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C-H Activation Studies Towards the Synthesis of Highly Functionalised Quinazolinones

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Abstract

A new synthetic strategy towards highly functionalised quinazolines and quinazolinones has been developed. The *C-H* amidation/cyclisation methodology allows for the conversion of simple benzoic acids into synthetically useful heterocyclic scaffolds.

Investigations revealed palladium, copper and ruthenium catalysis to be unsuitable for the *C-H* amidation transformation, whilst rhodium catalysis was found to be optimal in conjunction with sulfonamides and trifluoroacetamide. Additionally, in the case of the trifluoroacetamide, mild temperatures of 25 to 40 °C were sufficient to promote the reaction. Utilisation of these conditions allowed for the synthesis of a range of highly functionalised amino-substituted aromatic oxazolines. Transformation of these valuable motifs into the corresponding quinazolines could be readily achieved following a simple and efficient cyclisation procedure. Additionally, the corresponding quinazolinones could be rapidly afforded *via* an acid promoted reaction. Furthermore, the utility of the synthetic strategy was shown by the total synthesis of the tyrosine kinase inhibitor, Erlotinib, and the multi-gram scale synthesis of the Halofuginone quinazolinone.

Studies were extended towards the synthesis of 2-substituted quinazolinones. The use of methyl benzimidate hydrochloride allowed for the successful introduction of a phenyl substituent, however attempts to incorporate alternative groups were unsuccessful. Additionally, attempts to functionalise the 2-position of the quinazolinone after cyclisation using xanthate radical precursors were also unsuccessful.

Application of the *C-H* amidation/cyclisation strategy was successfully realised upon pyridine scaffolds. The presence of a 2-substituent on the pyridine heterocycle was found to be crucial to allow rhodium-catalysed *C-H* amidation to occur. Investigations revealed that a range of 2-substituents could be utilised to allow reactivity upon the pyridine motif. Whilst furans were not successfully aminated under the reaction conditions, thiophenes were found to be compatible. Post *C-H* amidation functionalisation was extensively explored. Transformation into the azaquinazolinone was readily achieved *via* utilisation of the previously established cyclisation conditions. Additionally, functionalisation of the 2-halo substituent allowed for the incorporation of amino, alcohol, aryl and alkyl functional groups in good yields, affording medicinally relevant pyridines.

Dedication

First of all, I would like to dedicate the entirety of my PhD to two people who sadly can't be with me to see it in its finished form.

Brian William Matthewman (1st March 1936 to 31st March 2014)

Uncle Brian, or Bri-Bri from my younger self, you're the man who taught me to read and write and helped me to fall in love with the beauty that is science. You encouraged me to keep that love going all the way to where I am now – no words can express my eternal gratitude, and no way would have I ever gotten this far without you. Thank you for the endless cups of tea, and for always being my best friend.

Tobi Leigh Hooper (21st Decemeber 1971 to 26th February 2015)

Tobi, Hoops, or my personal favourite 'big bruv', how I would love you to see this finished piece of work and ask me thousands of questions as to how or why it all works (or doesn't for part of it actually). You were always mesmerised by what I do, and I loved your curiosity.

I never had a biological brother, but I got better when Sally brought you home. You were better than I could have ever wished for. Thank you for all the love, support, and encouragement – it's what got me through your loss and gave me the strength to carry on and finish this.

Bri and Tobi, I will love you always – this is for you.

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Dad – You've always been a great dad, incredibly supportive, never saying something is too much (even when it is) and offering guidance, love and care along the way. I couldn't imagine any of my life without you. You've helped me right from day one in my education, always helping me to be the best I can possibly be. Thank you Dad – for everything.

Sally – Thank you for all your support and guidance throughout my life sis. You've been a wonderful role model to look up to and have always helped me to make the best choices. You've always been so kind and generous to me, and I can never thank you and Tobi enough.

We have some brilliant memories together and I'm sure we'll have time to make a lot more now this is done! I truly would be lost without you.

Andrewwwwwwwwwwwwwwwww! I only ever hoped that my time in Joe's group would turn me into a better scientist and help me to submit a good PhD thesis – I never in my dreams expected to be leaving with a fiancée! It's in all honesty an incredible feeling to have someone who is not only your best friend and other half, but is also your fellow lab member. I don't think there are or will ever be words to explain how much I have appreciated your support, friendship, belief in me, love, enthusiasm, knowledge, shoulder to cry on, humour (aka sarcasm) – basically just everything from these past years, I wouldn't change a single thing (except that toad stool maybe) – you have been my rock and I cannot wait to see where we go from here lovely. I love you.

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Friends – I simply have the best bunch of friends in the world. You have all been incredibly supportive of the path I've taken and it's only ever allowed our friendships to blossom. In particular, Nicola, you are essentially my sister from another mister and a truly wonderful best friend! Thank you for sticking by me through it all, sharing my worst days and helping me enjoy the best ones! Here's to many more years of friendship and more meet ups!

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"I began to realise how important it was to be an enthusiast in life. He taught me that if you are interested in something, no matter what it is, go at it full speed ahead. Embrace it with both arms, hug it, love it, and above all become passionate about it. Lukewarm is no good. Hot is no good either. White hot and passionate is the only thing to be."

Roald Dahl, 'My Uncle Oswald'

Abbreviations

α, α, α-TFT	α, α, α-Trifluorotoluene
1,2-DCE	1,2-Dichloroethane
1,2-DCB	1,2-Dichlorobenzene
Ac	Acetyl
acac	Acetylacetone
aq.	Aqueous
atm	Atmospheres
n-Bu	*normal*-Butyl
$BuPAd_2$	Beller's ligand, cataCXium®
cat.	Catalytic
CDI	1,1'-Carbonyldiimidazole
CMD	Concerted metallation deprotonation
DAST	Diethylaminosulfur trifluoride
D^{t}BPF	1,1'-Bis(di-*tert*-butylphosphino)ferrocene
DG	Directing group
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
dppb	1,4-Bis(diphenylphosphino)butane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
eq.	Equivalents

Et	Ethyl
EtOH	Ethanol
FG	Functional group
G-H II	Hoveyda-Grubbs catalyst 2nd generation, (1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium
h	Hour
HRMS	High Resolution Mass Spectrometry
IPA	*iso*-Propyl alcohol
IPr	1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene
Lauroyl peroxide	DiDodecanoyl peroxide
LCMS	Liquid Chromatography Mass Spectrometry
LiHMDS	Lithium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
MAD	(2,6-*tert*-Bu_2-4-Me-$C_6H_2O)_2AlMe$
Me	Methyl
MeOH	Methanol
m.p.	Melting point
NMO	*N*-Methylmorpholine *N*-oxide
NMP	*N*-Methyl-2-pyrrolidone
Ns	4-nitrobenzenesulfonyl
Ph	Phenyl
n-Pr	*normal*-Propyl
Red-Al®	Sodium bis(2-methoxyethoxy)aluminium hydride
RT	Room Temperature
SET	Single electron transfer

SM	Starting material
S_NAr	Nucleophilic aromatic substitution
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
tert	Tertiary
THF	Tetrahydrofuran
TPPMS	Sodium(diphenylphosphino)benzene-3-sulfonate
Ts	Tosyl, 4-Toluenesulfonyl
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
XPhosPdG2	2nd Generation XPhos Pre-catalyst, chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)

Contents

Chapter 1: Introduction

1.1 The quinazolinone heterocycle

Modern day synthetic organic chemistry involves the design and synthesis of complex molecules. Many of these complex molecules are employed as bioactive agents in the pharmaceutical, agrochemical and veterinary industries. These compounds are diverse in structure but commonly involve heterocyclic units, which are often vital to the activity of the molecule. In this context, quinazolinones are a class of fused heterocycle that are of considerable interest as components of such molecules (*figure 1*).

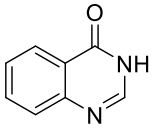


Figure 1 – Quinazolinone basic structure

Quinazolinones can be classified into different categories depending upon the substitution patterns of the ring system, as shown in *figure 2*. The 2-substituted-4(*3H*)quinazolinones **1** are amongst the most common, either as intermediates or as part of a larger scaffold in both non-natural and natural products.[1]

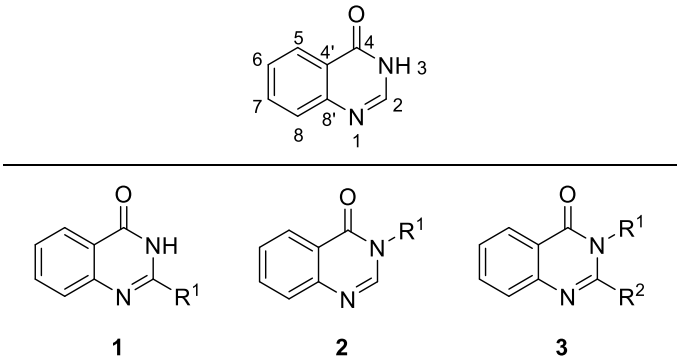
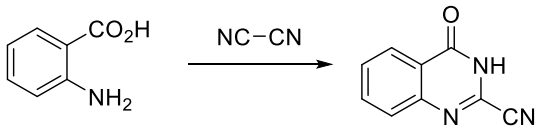


Figure 2 – Substitution of quinazolinones: 2-substituted-4(*3H*)quinazolinones **1**, 3-substituted-4(*3H*)quinazolinones **2** and 2,3-disubstituted-4(*3H*)quinazolinones **3**

The quinazolinone heterocycle is of significant interest in medicinal chemistry due to the broad and diverse range of biological properties which molecules containing the scaffold exhibit. Some of these noteworthy properties include anticancer, diuretic, anti-inflammatory, anticonvulsant and antihypertensive activities.[2, 3] The first documented synthesis of a quinazolinone was in the late 1860s by Griess who produced 2-cyanoquinazolinone **5** from a reaction between 2-aminobenzoic acid **4** and cyanogen, *scheme 1*.[4] However, it was not until a number of decades later in the 1950s that interest in the

medicinal chemistry of quinazolinones was stimulated by the discovery of a quinazolinone alkaloid natural product.[5]

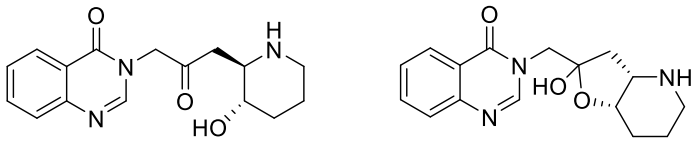


4 **5**

Scheme 1 – Synthesis of 2-cyanoquinazolinone **5**

1.2 Natural products containing the quinazolinone heterocycle

The fused heterocycle quinazolinone has been found as a building block for an array of synthetic and naturally occurring alkaloid structures.[5] For example, febrifugine **6** was isolated from a Chinese plant, *Dichroa febrifuga*, and was later found to be present in a popular garden plant, *hydrangea*.[6] For over 2000 years, decoctions involving *Dichroa febrifuga* have been used in Chinese traditional medicine for illnesses such as stomach cancer and malaria.[7] Recently, it has been demonstrated that febrifugine **6** and its isomer, isofebrifugine **7**, exhibit potent anti-malarial activity. Despite the interesting biological activity shown by these alkaloid structures, serious side effects including vomiting, nausea and liver toxicity have precluded their use as clinical candidates for the treatment of malaria.[8]



6 **7**

Figure 3 – Febrifugine **6** and isofebrifugine **7**

Fumiquinazoline A **8**, a natural product which exhibits moderate cytotoxicity against P-388 lymphocytic leukemia cells, consists of a quinazolinone core fused with a piperazine ring system. It was isolated from the mycelium of a strain of *Aspergillus fumigatus*, found in the gastrointestinal tract of the salt water fish *Pseudolabrus japonicus*.[9, 10] The first total synthesis of fumiquinazoline A was achieved by Snider *et al.* in 2000, in a total of 16 steps.[11]

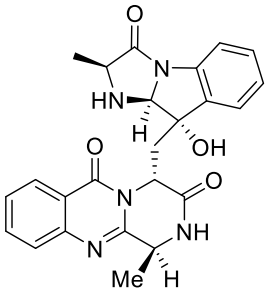


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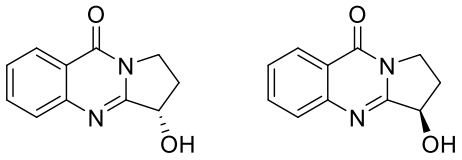
Figure 4 – Fumiquinazoline A **8**

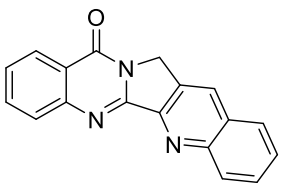
Vasicinone is a pyrrolo[2,1-*b*]quinazoline alkaloid, which was isolated from the leaves and inflorescence of *Adhatada vasica Nees*, an evergreen subherbaceus bush.[12] It has been traditionally used as a component of indigenous medicines, for the treatment of bronchitis and asthma.[13] Recently, Joshi and co-workers reversed the previously assigned 3*R* configuration of (-)-vasicinone **9** to the 3*S* configuration **10** on the basis of the X-ray crystallographic analysis of (+)-vasicinone hydrobromide.[14]



9 **10**

Figure 5 – (-)-Vasicinone **9** and (+)-vasicinone **10**

Luotonin A **11** is a unique structure compromising a quinoline and quinazoline skeleton.[15] It was isolated from the aerial parts of *Peganum nigellastrum*, which is a plant found in numerous areas of Asia and the northwestern region of China. Also known by the Chinese name *Luo-Tuo-Hao*, the plant from which Luotonin A was isolated has been used in Chinese traditional medicine to treat rheumatism and inflammation.[5] Similarly to fumiquinazoline A, it has been demonstrated that Luotonin A is cytotoxic towards the murine leukemia P-388 cell line, although its mechanism of action is still unknown. Luotonin A is currently of great interest as its structure resembles that of camptothecin **12**, the derivatives of which are clinically useful anti-cancer agents.[16]



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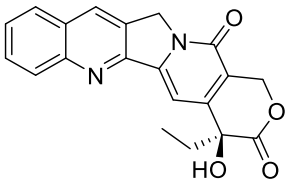

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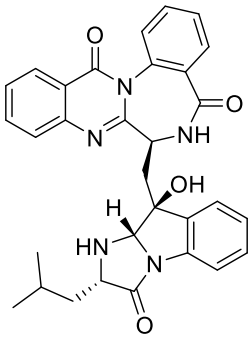
Figure 6 – Luotonin A **11** and camptothecin **12**

(-)-Asperlicin **13** is a competitive non-peptide cholecystokinin antagonist, isolated from the fungus *Aspergillus alliaceus*.[17] The natural product compromises of 4 stereocentres and a multi-cyclic framework including that of the quinazolinone. The first total synthesis of (-)-asperlicin was achieved by Snider *et al.* in 1998. They reported an efficient synthesis of asperlicin C **14**, and further extended their methodology to the successful synthesis of (-)-asperlicin in 15 steps.[18]



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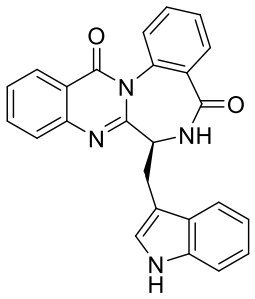

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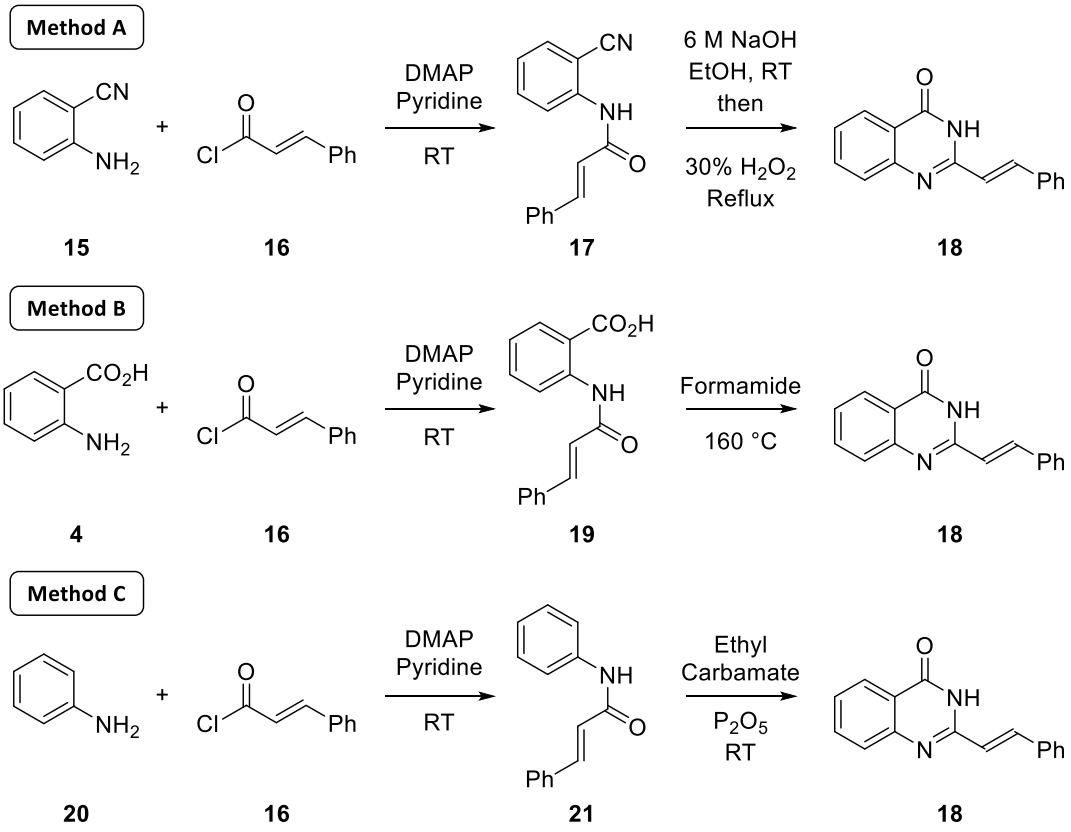
Figure 7 – (-)-Asperlicin **13** and asperlicin C **14**

1.3 Non-metal-catalysed routes to quinazolinones

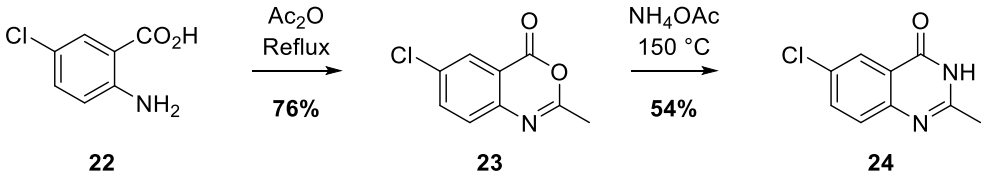
The most common and traditional method used in quinazolinone synthesis is *via* amidation and cyclisation of anthranilic acid derivatives. Bogert *et al.* reported initial results in this field in the early 1900's, however very little scope was demonstrated.[19, 20, 21] In 1990, Jiang and co-workers reported a selection of methodologies to access 2-substituted-4(*3H*)quinazolinones.[22] All of the routes involved the preparation of a benzamide intermediate that functioned as a precursor to a cyclocondensation reaction. As shown in method A, *scheme 2*, amidation of 2-aminobenzonitrile **15** to the amide intermediate **17**, followed by base promoted ring closure provided quinazolinone **18** under relatively mild conditions. Ring closure under acidic conditions was also explored and gave higher yields of the desired quinazolinone; with the advantage of shorter reaction times.[23] Another methodology used involved condensation of formamide with an amide intermediate,

generated in the amidation of anthranilic acid **4** (method B, *scheme 2*). Treatment of amide intermediate **21**, generated from aniline **20**, with urethane in the presence of P_2O_5 at elevated temperatures was also shown to yield the desired quinazolinone (method C, *scheme 2*). The scope demonstrated by these methods as a whole is limited, offering only a small variety of substituents on the aromatic ring of the quinazolinone (OMe, OEt, Cl, Br, I, H). A maximum yield of 61% was achieved *via* method A with a chloro substituted 2-aminobenzonitrile.



Scheme 2 – Methodologies demonstrated by Jiang and co-workers

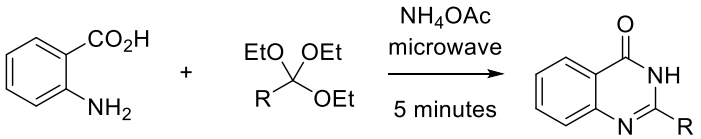
In related work, Jiang developed alternative synthetic routes to quinazolinones.[5, 22] A particularly interesting synthesis was *via* an initially generated benzoxazinone **23**. Preparation of benzoxazinone **23** was achieved in good yield from the reaction of 5-chloroanthranilic acid **22** with acetic anhydride. Further reaction of the benzoxazinone **23** in the presence of ammonium acetate at an elevated temperature gave 6-chloro-2-methylquinazolin-4(*3H*)-one **24** in 54% yield.



22 **23** **24**

Scheme 3 – Quinazolinone synthesis *via* initial preparation of benzoxazinone

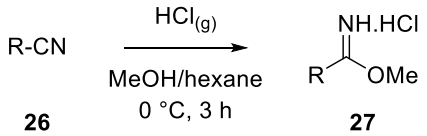
The synthesis of 2-substituted-4(*3H*)quinazolinones has also been reported to proceed successfully under microwave conditions by Rad-Moghadam and Mohseni.[24] The procedure involves the condensation of anthranilic acid with an orthoester **25** and ammonium acetate. Whilst the scope only consisted of varied substituents upon the orthoester (R= H, Me, Et, *n*-Pr, *n*-Bu, Ph), the advantages of the procedure included a short reaction time and solvent free conditions. High yields of the desired quinazolinones, ranging from 77 – 83%, were achieved.



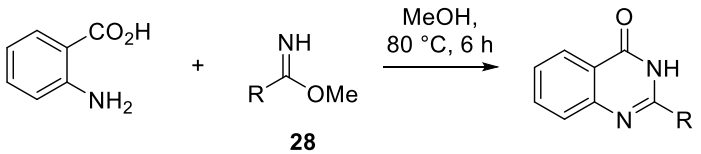
25

Scheme 4 – Synthesis of 2-substituted quinazolin-4(*3H*)-ones under microwave conditions

Another approach to the synthesis of 2-substituted-4(*3H*)quinazolinones is *via* the condensation reaction of imidates with anthranilic acids. A particularly effective illustration of this approach was reported by Connolly and Guiry, who prepared a range of 2-aryl and 2-alkylquinazolinones in satisfactory to good yields.[25] The methodology first involved the synthesis of imidate hydrochloride salts **27** from the corresponding nitriles **26**, all of which were achieved in good to excellent yields (62 – 97%). Following this, the imidate salts were then initially transformed to the equivalent imidates **28** *via* reaction with one equivalent of base. Subsequent condensation with anthranilic acid then led to the desired quinazolinone.



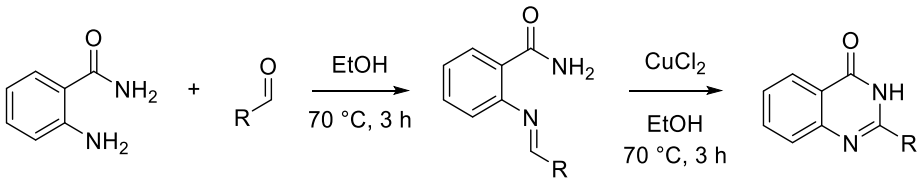
26 **27**



28

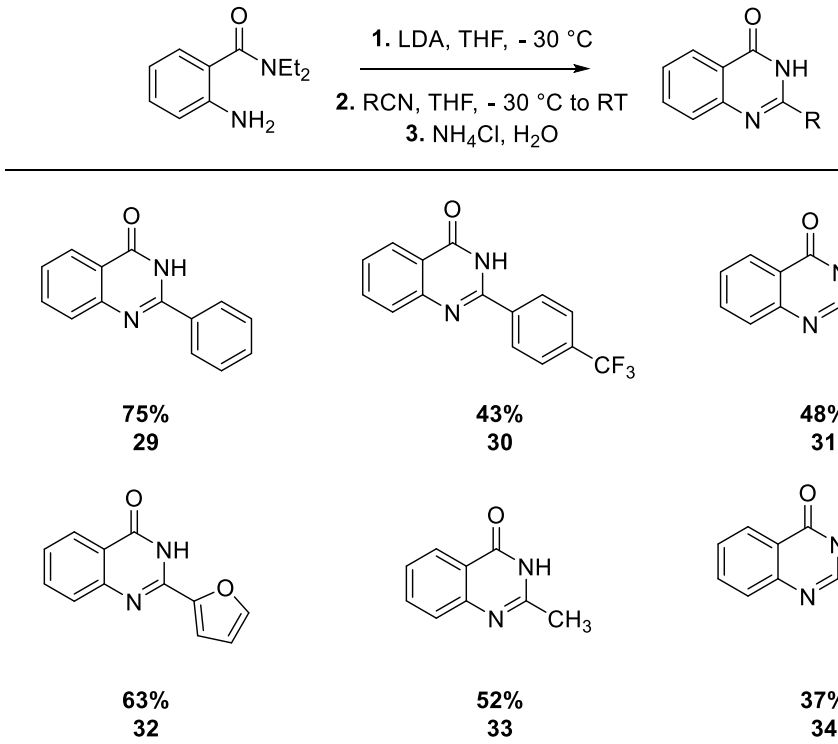
Scheme 5 – Condensation of imidate hydrochloride salts **27** with anthranilic acid

Abel-Jalil reported a copper-mediated condensation of 2-aminobenzamide with aryl, alkyl or heteroaryl aldehydes in refluxing ethanol as a means of accessing 2-substituted-4(*3H*)quinazolinones.[26] Stoichiometric quantities of the copper source were required to yield the quinazolinone in excellent yields. The procedure was demonstrated to be successful in a one-pot manner, or over two steps *via* isolation of the Schiff base. There was a seemingly negligible difference between the two approaches; the isolated yields of the quinazolinones were 79 – 88% and 82 – 91%, respectively. Despite the relative simplicity of the procedure, the overall scope of the reaction was extremely limited. Only 7 aldehydes were shown to couple with the 2-aminobenzamide starting material. In addition to the lack of aldehydes used, no derivatives of the 2-aminobenzamide were exemplified. The main versatility of the reaction is in its tolerance to alkyl, aryl and heteroaryl aldehydes.



Scheme 6 – Copper-mediated condensation by Abel-Jalil

Couture and co-workers demonstrated a novel route to quinazolinones *via* the reaction of nitriles with lithiated 2-aminobenzamides.[27] The procedure tolerated both aryl and heteroaryl nitriles, and was also extended to include alkyl nitriles, specifically those bearing a cyclohexyl and a methyl group. Quinazolinones were obtained in poor to good yields, 15 - 75%. The scope of the reaction was limited, but did show that different functional groups could be tolerated. Electron withdrawing aryl rings, and heteroaromatic compounds, which incorporated both a thiophene and a furan, were reported.

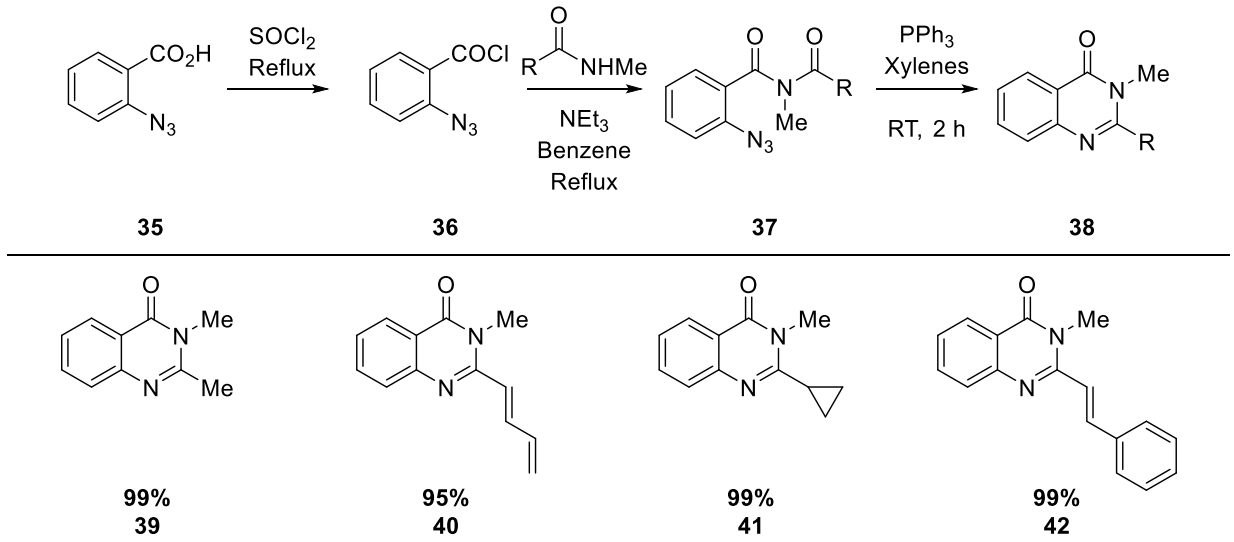


Scheme 7 – Procedure and examples of the scope demonstrated by Couture and co-workers

Azides have received much attention over the past few decades as key intermediates in synthetic organic chemistry.[28] As a consequence of their increased use, azides have also proven to be useful reactive functional groups as a means to synthesise quinazolinones. Azides have primarily been used in the synthesis of quinazolinones by means of intramolecular aza-Wittig type reactions. The aza-Wittig methodology has become an attractive procedure for the formation of the C=N bond, especially in the synthesis of *N*-heterocyclic molecules. It has been shown to be a powerful tool for the synthesis of 5 to 7 membered *N*-heterocycles, including those of natural products containing a 4(*3H*)-quinazolinone fragment.[29]

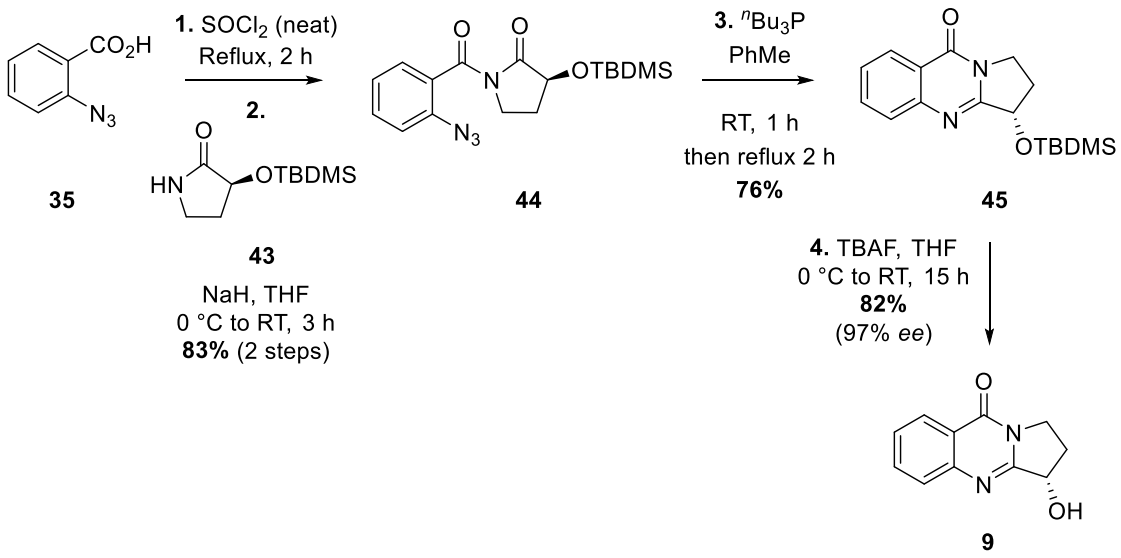
In 1989, Eguchi *et al.* demonstrated the first application of the aza-Wittig reaction for the synthesis of quinazolinones.[30] Azido-substituted imides were shown to react with triphenylphosphine or tributylphosphine to afford imidazolinones and quinazolinones *via* an intramolecular aza-Wittig reaction. The reaction sequence began with an organic azide bearing a pendant carboxylic acid group **35**; transformation to the acid chloride **36** was initially carried out *via* reaction with thionyl chloride. The acid chloride **36** was then reacted with the appropriate amide to give the necessary intermediate **37**. Cyclisation of intermediate **37** with triphenylphosphine then occurred to give the quinazolinone product **38**. The reaction offered advantages of high yields of the quinazolinone under relatively mild conditions, as well as the introduction of the aza-Wittig reaction as a promising synthetic

route to 5 and 6 membered nitrogen containing heterocycles. A drawback is that the reported reaction scope is narrow, with the entire range of the quinazolinones shown in *scheme 8*. The synthetic route also required 3 steps to give the quinazolinone product. In addition to this, the use of organic azides does present certain safety issues. It is important to note that organic azides are classified as toxic reagents and can be highly explosive under certain circumstances,[31] meaning appropriate safety measures must be taken at all times when handling these particular substrates.



Scheme 8 – Aza-Wittig route to quinazolinones by Eguchi *et al*.

Later, in 1996, Eguchi extended the application of the aza-Wittig methodology to the synthesis of a natural product, (-)-vasicinone **9**, which has been previously discussed.[12] Demonstrating the utility of the reaction conditions, the fused quinazolinone was synthesised by means of an intramolecular aza-Wittig reaction in 4 efficient steps.



Scheme 9 – (-)-Vasicinone synthesis

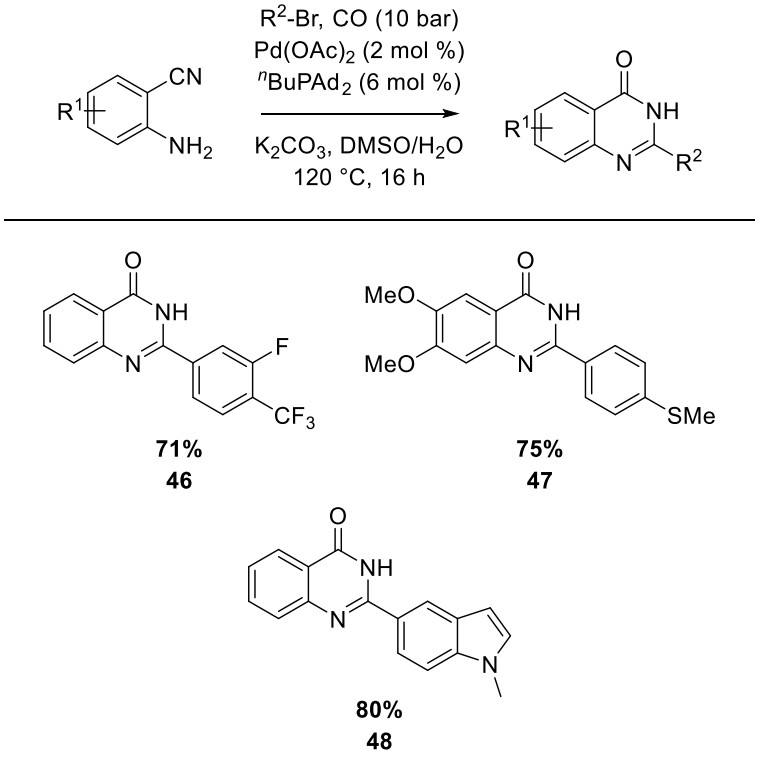
1.4 Metal-catalysed routes to quinazolinones

As described previously, classical methodologies used in the synthesis of quinazolinones rely primarily upon condensation pathways from 1,2-disubstituted aromatics such as anthranilic acid derivatives, and formamide equivalents.[2, 32] Whilst methods of this nature are well established and able to provide the desired scaffolds, they suffer from a multitude of drawbacks. For example, high temperatures and long reaction times are typically employed and these methods suffer particularly from displaying a very limited scope. Over recent years, attempts to improve upon classical syntheses have moved in the direction of catalytic methodologies in order to overcome these limitations. Indeed, catalysis offers numerous synthetic benefits including; shorter reaction times, extended scope and reduced reaction temperatures, as well as offering the opportunity to explore exciting new methodologies.

1.5 Catalytic-carbonylation towards quinazolinones

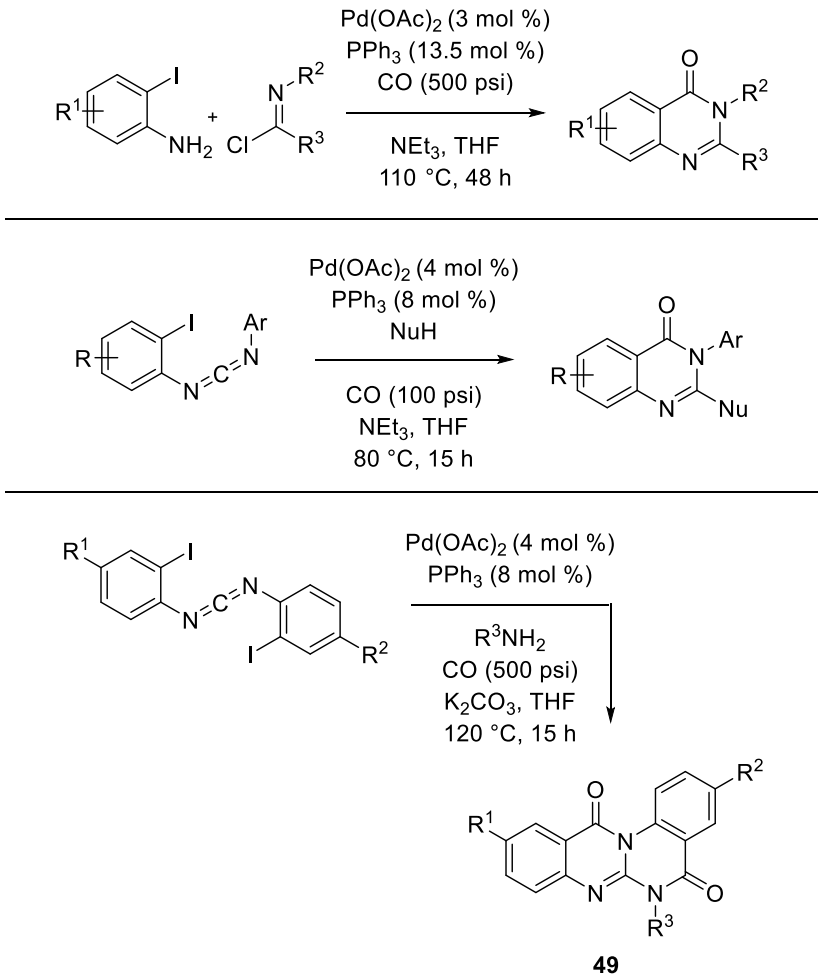
The palladium-catalysed carbonylation reaction offers a mild and general method to produce aromatic carboxylic acid derivatives.[33] This transformation typically consists of reaction between an arylhalide and carbon monoxide to form a acylpalladium intermediate, which in turn can be trapped by a variety of nucleophiles.[34] Over the past decade there have been many reports that demonstrate the application of this transformation to heterocycle synthesis, and quinazolinones in particular.

During ongoing research into the application of carbonylation reactions for heterocyclic synthesis, Beller described a cascade reaction that took place under palladium catalysis to build the quinazolinone framework, employing 2-aminobenzamides and aryl bromides.[35] Despite demonstrating a broad range of aryl bromides were compatible with the procedure, a narrow scope of the 2-aminobenzamides greatly limited the methodology. In an effort to improve upon their preliminary work and extend the methodology to more available reagents, it was decided to replace the limited 2-aminobenzamides with 2-aminobenzonitriles (*scheme 10*).[36] An *in situ* hydration of the nitrile group would in theory allow these more available starting materials to be used. After optimisation of the procedure, various quinazolinones were produced in moderate to excellent yields, and purified by the simple means of recrystallisation. With respect to reaction scope, a selection of aryl bromides and 2-aminobenzonitriles were shown to participate in the reaction, allowing for the production of some novel 2-aryl-4(3H)quinazolinones (**46** – **48**). Additionally, low palladium loadings were sufficient to promote the annulation reaction.



Scheme 10 – Beller's palladium-catalysed carbonylative cyclisation of 2-aminobenzonitriles

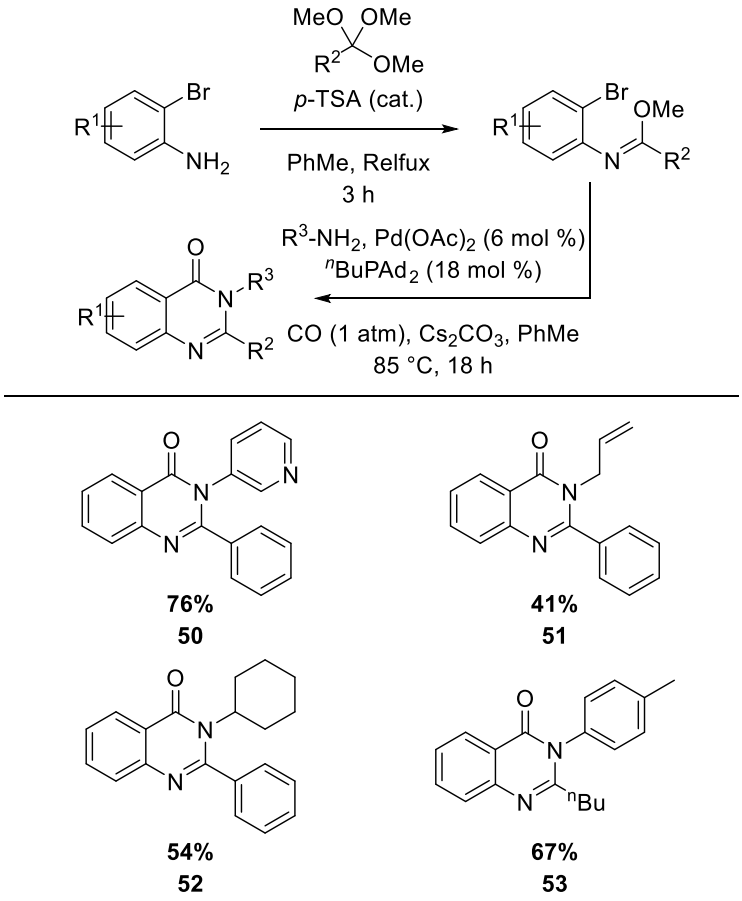
In 2008 Alper reported the use of imidoyl chlorides as a useful reagent for the synthesis of quinazolinones in conjunction with palladium catalysis and *ortho*-iodoanilines (*scheme 11*).[37] The reaction utilised a catalyst system of palladium acetate and triphenylphosphine. Despite an impressive reaction scope with respect to both synthetic partners, the method required reaction times of 48 – 72 h, with reaction temperatures of 150 °C and high pressures of up to 10 bar. In 2010, Alper extended this methodology to encompass a tandem palladium-catalysed addition/cyclocarbonylation reaction of *N*-(2-iodophenyl)-*N*'-arylcarbodiimide to access a 2-substituted quinazolinone scaffold.[38] In comparison to the initial report, a shorter reaction time, lower reaction temperature and lower pressure of carbon monoxide was required. However, whilst a variety of nucleophile sources were utilised, inclusive of secondary amines (both cyclic and linear) and phenols with good to excellent yields, the process was found to be incompatible with thiols. In addition, a limited scope of *N*-(2-iodophenyl)-*N*'-arylcarbodiimides was demonstrated, likely because of their scarce availability. Only the *N*-aryl substituent was varied to include phenyl, 4-Cl- and 4-MeO-phenyl as well as 1-naphthyl substituents. Further reaction scope was demonstrated later that year when the same reaction conditions were applied towards the synthesis of quinazolino[3,2-a]quinazolinones **49**.[39] As before, a variety of amino sources were shown to be successfully incorporated into this novel framework.



Scheme 11 – Alper's carbonylative cyclisation towards quinazolinone scaffolds

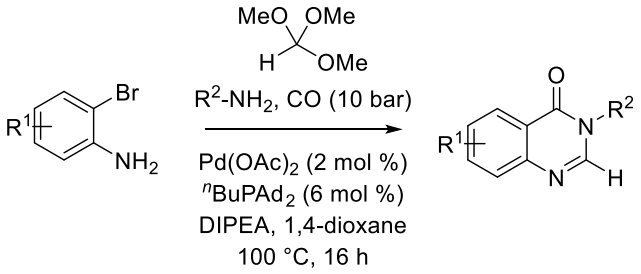
Willis and co-workers have developed an interesting palladium-catalysed route to biologically important benzimidazoles and quinazolinones from *N*-(*o*-halophenyl)imidoyl chlorides and their corresponding imidates, using a strategically related route to that described by Alper (*scheme 12*).[40] *N*-(*o*-Halophenyl)imidoyl chlorides were found to be successful substrates for the synthesis of benzimidazoles. However, for the synthesis of the corresponding quinazolinones, the imidate precursors was found to be more effective. Formation of the quinazolinone in this case is believed to occur after an initial palladium-catalysed aminocarbonylation of the aryl halide to form an amide intermediate which undergoes a base-induced cyclisation. Synthesis of the required imidate precursors could be achieved from 2-bromoanilines and orthoesters. Sodium *tert*-butoxide and potassium carbonate were successful bases for the cyclisation reaction, however caesium carbonate was found to be optimal, giving the quinazolinone in a 75% yield. Optimisation of the catalyst and the ligand highlighted palladium acetate and Beller's ligand to be the most suitable for the transformation. Overall, a diverse selection of quinazolinones were successfully synthesised in moderate to good yields under these optimised conditions (**50** – **53**). For

example, electron rich and deficient arylbromides were tolerated, and both aromatic and alkyl amines were successfully incorporated. Notably however, imidates derived from 2-chloroanilines were found to be unreactive.



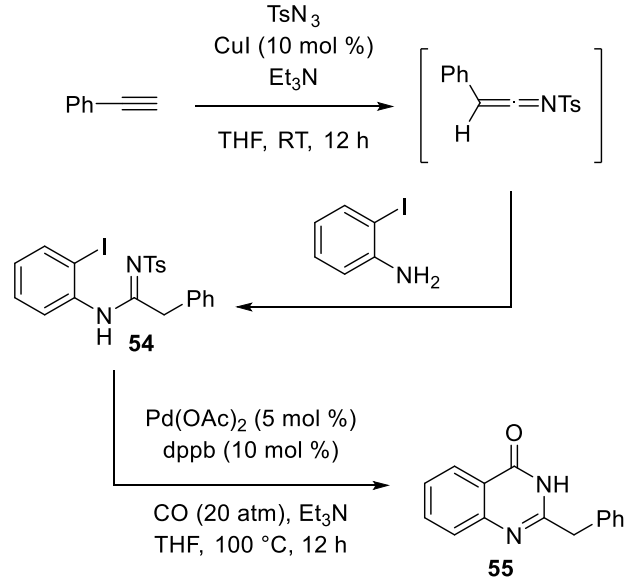
Scheme 12 – Willis' palladium-catalysed aminocarbonylation route

More recently, Beller developed a one-pot variant of the aminocarbonylation route to quinazolinones *via* an *in situ* generation of imidates.[41] In this instance, 2-bromoanilines, trimethyl orthoformate, a variety amines and CO were subjected to a multicomponent palladium-catalysed cyclisation reaction. In comparison to the stepwise process devised by Willis, this one-pot approach offers lower catalyst loading and shorter reaction times. Good yields of the quinazolinones were achieved, and a tolerance for various reactive functional groups was also demonstrated (*scheme 13*).



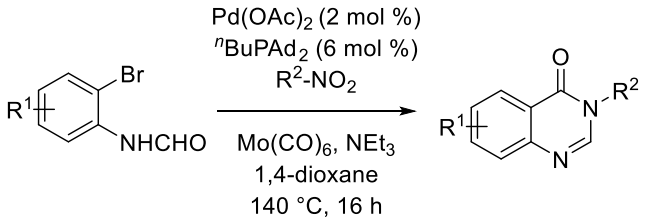
Scheme 13 – Beller's one-pot multicomponent palladium-catalysed reaction

In 2012, Lu and Wang reported a synthesis of 4(*3H*)quinazolinones by a combination of azides, alkynes, anilines and CO.[42] The procedure involved a three component copper-catalysed cascade reaction to yield an amidine intermediate **54**, which was subjected to a palladium-catalysed carbonylation leading to the desired quinazolinone **55** after hydrolysis of the sulfonamide. The formation of the amidine is proposed to proceed *via* a ketenimine intermediate. Ketenimines are a class of easily accessible intermediates which demonstrate high reactivity and tolerance to a wide range of substrates.[43] Moreover, palladium acetate is believed to have dual roles within the reaction; as well as catalysing the carbonylation, it is believed to function as a Lewis acid to promote the hydrolysis of the sulfonamide by trace water present in the solvent. While initial studies were devoted to developing a stepwise procedure that involved isolation of the amidine **54**, a more efficient one-pot transition metal-catalysed cascade process was realised that yielded the quinazolinone in an impressive yield of 74%. Having optimised this one-pot procedure, the substrate diversity was next investigated. A range of aromatic and aliphatic terminal alkynes were shown to be effective, in contrast, only a few 2-haloanilines were shown to be applicable in the reaction.



Scheme 14 – Lu and Wang's synthesis of quinazolinones

Whilst the aforementioned examples successfully afford the quinazolinone heterocycle, they all rely on the use of carbon monoxide gas, which due to its toxicity, raises practical challenges and safety concerns. In order to address the limitations associated with the use of carbon monoxide gas, Beller reported the use of $Mo(CO)_6$ as a safer source of CO (*scheme 15*).[44] Indeed, a reaction between 2-bromoformanilides and aryl- and alkyl-nitro compounds was found to be catalysed by palladium(II) in the presence of $Mo(CO)_6$ to generate a series *N*-substituted quinazolinones in good yields. In this case, $Mo(CO)_6$ is believed to play a number of key roles; it acts as a CO source, nitro reducing agent and cyclisation promoter. Mechanistic studies demonstrated the nitro compounds were initially reduced to the corresponding amines which, following addition to the *in situ* generated acylpalladium complex and subsequent cyclisation, formed the desired heterocycle.



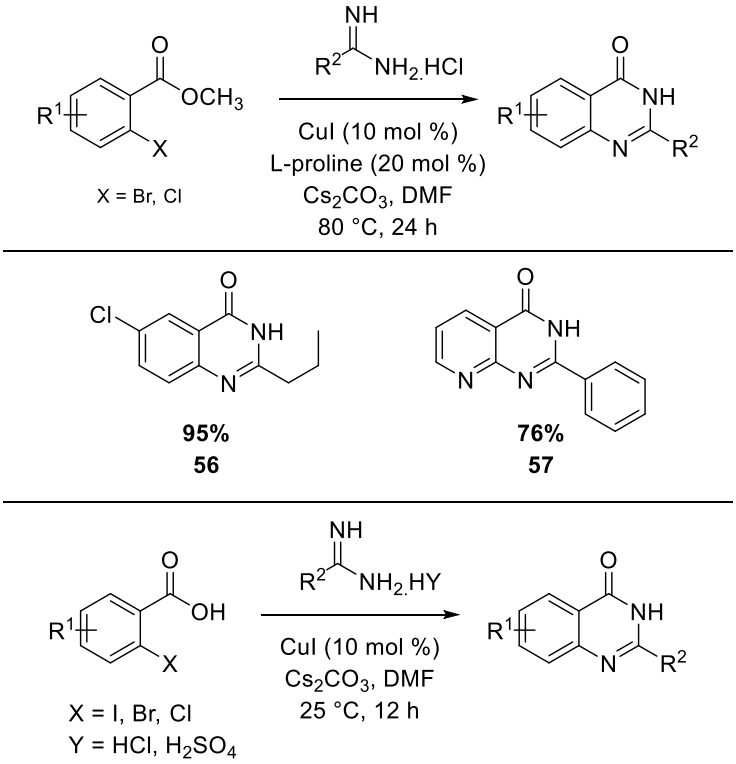
Scheme 15 – Beller's alternative palladium-catalysed carbonylative cyclisation using $Mo(CO)_6$

1.6 Catalytic-domino and multi-component processes towards quinazolinones

Domino and multi-component reaction processes are highly sought after within organic synthesis. Domino reactions are defined as chemical processes involving two or more bond-forming transformations which take place under the same reaction conditions, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step.[45] In terms of multi-component reactions, the ability to develop methodologies in which more than two molecules come together in a controlled and predictable manner to yield a single product encompassing part of each substrate represents an attractive strategy to build molecular diversity by a fast and efficient means.[46] Both reaction classes have been successfully applied to quinazolinone synthesis. Notably, in addition to reports described below, some of the carbonylative methods previously described embody the requirement of multi-component or domino reaction profiles.

In 2008, Fu reported a copper-catalysed cascade synthesis of quinazoline and quinazolinone derivatives *via* the reaction of amidine hydrochlorides with 2-halobenzene-aldehydes, -ketones and -esters (*scheme 16*).[47] Optimisation highlighted that a CuI catalyst in combination with L-proline as the ligand and Cs_2CO_3 as a base, afforded very good yields of

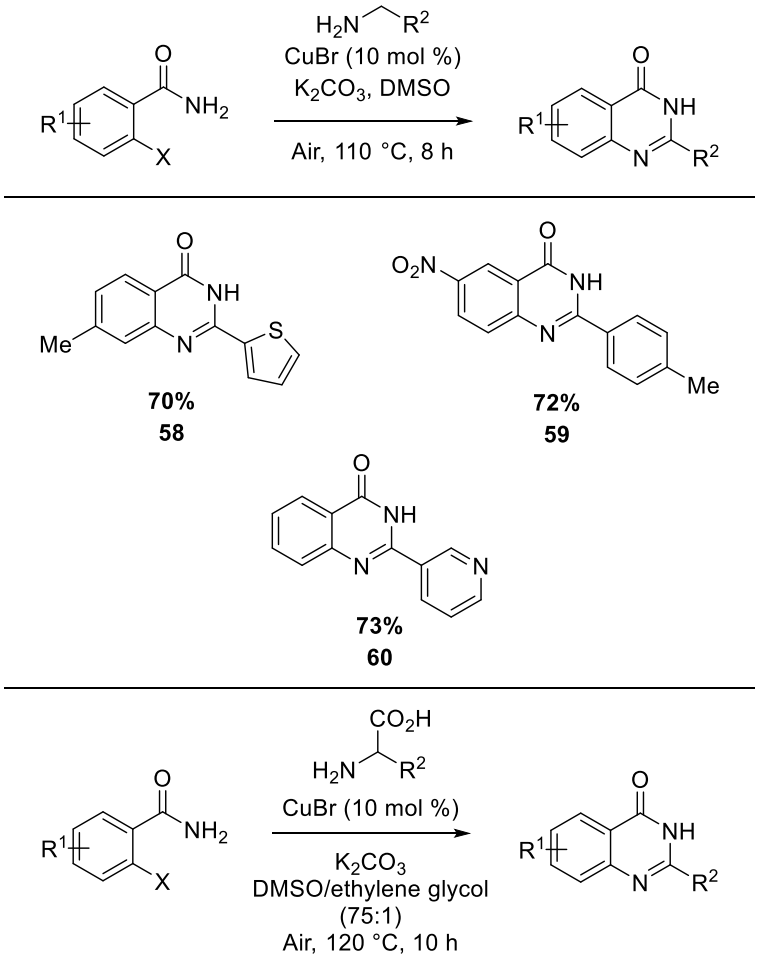
the desired quinazoline and quinazolinone derivatives, the latter being generated at relatively low temperatures (80 versus 110 °C). Both alkyl and aryl amidines were successfully employed, and heteroaromatic scaffolds could be utilised to afford the corresponding azaquinazolinone scaffolds. Furthermore, the work was extended to include 2-halobenzoic acid substrates.[48] Compared to the previous reaction conditions, when 2-halobenzoic acids were used, no ligand was required to promote the cascade and the reaction proceeded successfully at room temperature. Additionally, 2-iodo, 2-bromo and 2-chlorobenzoic acids were found to be effective substrates, although 2-chlorobenzoic acids typically required a higher temperature of 80 °C. With regard to the scope, functionalised chloro and dioxolane 2-bromobenzoic acid derivatives were found to be viable substrates. Switching from amidines to guanidines allowed 2-amino quinazolinones to be generated, albeit these reactions again required the use of elevated temperatures. Furthermore, the replacement of CuI catalyst with $FeCl_3$ for the conversion of 2-bromobenzoic acids to quinazolinones was described by Fu in 2009.[49] These reactions offered similar scope to the copper-catalysed process although they required an elevated temperature of 120 °C.



Scheme 16 – Fu's copper-catalysed synthesis of quinazolines and quinazolinones

Fu *et al.* further extended their investigations into the copper-catalysed domino synthesis of 2-substituted-4(3H)-quinazolinones by exploiting 2-halobenzamides (*scheme 17*).[50] The ring forming reaction involved a sequential Ullmann-type coupling under air, together with aerobic oxidative *C-H* amidation. The methodology is simple, practical and efficient, and uses

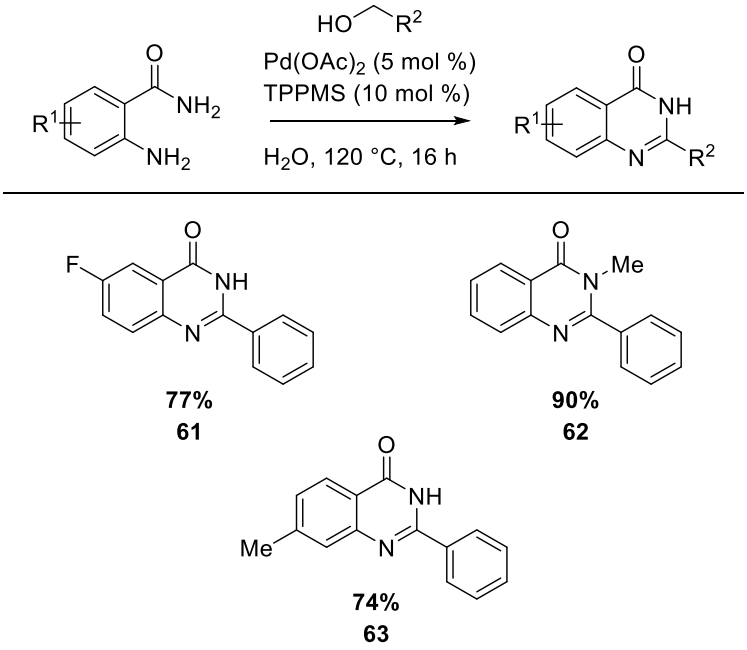
commercially available starting materials. Moreover, the procedure affords the product quinazolinones in good to excellent yields, without the need for ligands or additives. With regard to the reaction scope, 2-iodo, 2-bromo and 2-chlorobenzamides bearing both electron withdrawing and electron donating substituents were tolerated. An array of (aryl)methanamines were also successfully employed, including (heteroaryl)methanamines based on pyridine, furan and thiophene (**58** and **60**). This work was later extended at the quinazolinone *C*2 position *via* use of α-amino acids.[51] The ready availability of α-amino acids, along with their prevalence in nature, makes this class of compounds one of the most attractive sources of amines for organic synthesis. The optimal reaction conditions were found to be somewhat harsher than that required of (aryl)methanamine substrates with an increase in both reaction time (10 h) and temperature (120 °C). Nonetheless, a small selection of α-amino acids were found to be compatible with this transformation.



Scheme 17 – Fu's copper-catalysed domino process with (aryl)methanamines and α-amino acids

Yokoyama *et al.* reported a novel synthesis of 2,3-disubstituted-4(*3H*)quinazolinones *via* a palladium-catalysed reaction of 2-aminobenzamides with benzyl alcohols (*scheme 18*).[52] The

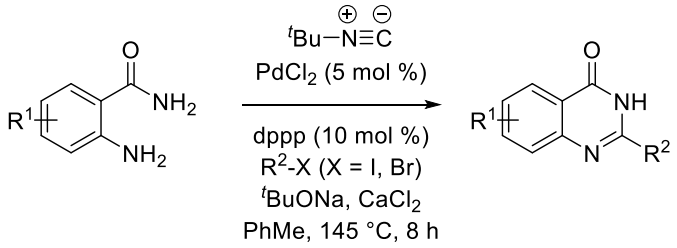
reaction is believed to involve *N*-benzylation, benzylic *C-H* amidation and dehydrogenation in a one-pot domino process. As well as being the first reported palladium-catalysed benzylic *C-H* amidation reaction, the preceding aniline benzylation step is also noteworthy. Examples of palladium-catalysed benzylation of amines with benzylic alcohols are scarce in the literature.[53] Optimisation showed $Pd(OAc)_2$ and TPPMS to give the best catalyst combination for the formation of the quinazolinone heterocycle. A small range of benzylic alcohols with electron donating substituents were shown to be applicable to the reaction conditions, producing the corresponding quinazolinones in yields of 65 to 96%. Substituents in all three of the *ortho*, *meta* and *para* positions were tolerated on the benzylic alcohol, although it is not clear whether or not the method is compatible with benzylic alcohols bearing electron withdrawing substituents. In addition, only a small range of 2-aminobenzamides were shown to take part in the reaction. Nonetheless, the methodology is effective and can produce quinazolinones in good yields of 72 to 90%.



Scheme 18 – Yokoyama's palladium-catalysed coupling of benzylic alcohols with 2-aminobenzamides

More recently in 2014, Ji disclosed a palladium-catalysed three-component reaction sequence to generate quinazolinones *via* the reaction of 2-aminobenzamides and aryl halides in the presence of an isocyanide (*scheme 19*).[54] A catalyst system consisting of $PdCl_2$ and DPPP was found to be optimal, promoting the reaction of *tert*-butyl isocyanide with a range of aryl iodides bearing electron donating and electron withdrawing substituents. In addition, aryl bromides could also be used with no significant change in product yield. A single heteroaromatic iodide was also demonstrated producing 2-(thiophene-2-yl)quinazoline-

4(3H)-one in a good yield of 65%. In comparison to the relatively large reaction scope of the aryl halide counterpart, only 4 examples of substituted anthranilamide substrates were disclosed.

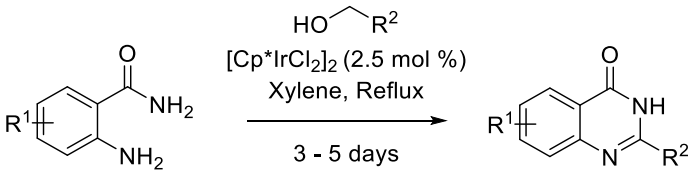


Scheme 19 – Ji's palladium-catalysed *tert*-butyl isocyanide insertion reaction to quinazolinones

1.7 Catalytic hydrogen transfer processes towards quinazolinones

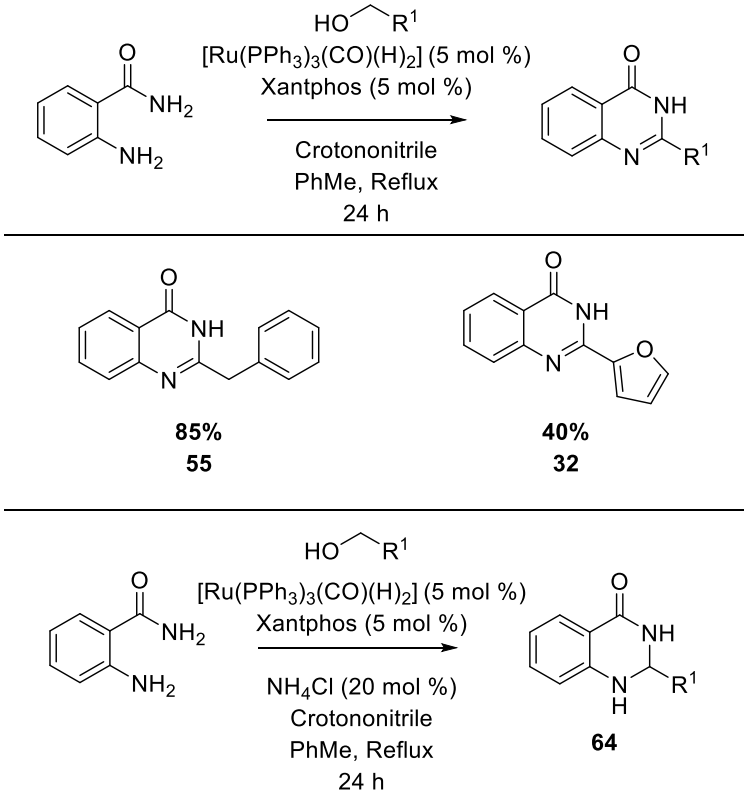
Hydrogen transfer methodologies have emerged in the literature as catalytic and green protocols that significantly enable organic synthesis. This process allows functional groups such as ketones and imines to be reduced, and alcohols and amines to be oxidised under relatively mild conditions.[55] The embodiment of this useful methodology in heterocycle synthesis has now been realised and reported upon in the context of quinazolinone synthesis.

An iridium-catalysed route to quinazolinones was reported by Zhou in 2011.[56] A one pot oxidative cyclisation of primary alcohols with 2-aminobenzamides to quinazolinones was demonstrated *via* use of $[Cp^*IrCl_2]_2$ as a catalyst under hydrogen transfer conditions (*scheme 20*). The reaction is believed to occur in a domino sequence in which initially the primary alcohol is oxidised to an aldehyde *via* catalytic hydrogen transfer. Condensation of the aldehyde with 2-aminobenzamide after loss of water leads to an aminal intermediate. The aminal intermediate is then further oxidised to the desired quinazolinone under the same hydrogen transfer catalysis. The procedure is tolerant of a range of aromatic alcohols, bearing electron withdrawing and electron donating substituents in *ortho*, *meta* and *para* positions. Heteroaromatic- and alkyl-substituted primary alcohols were also shown to be suitable substrates for the reaction, demonstrated by the reactions of 2-thiophenemethanol and 1-pentanol. A variety of substituted 2-aminobenzamides were also tolerated in the reaction. On the whole, this method offers generally good to excellent yields of the quinazolinone product, although the reaction times are rather long, taking generally 3 to 5 days to reach completion.



Scheme 20 – Zhou's iridium-catalysed hydrogen transfer conditions

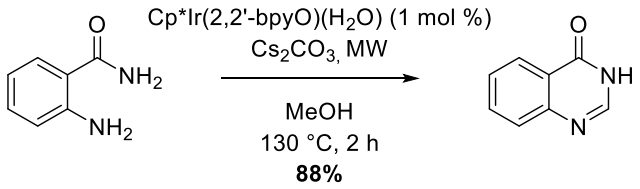
A similar process was reported by Watson and co-workers in 2012, who also used catalytic hydrogen transfer methodology as a means to access quinazolinone derivatives.[57] They reported a ruthenium-catalysed oxidation of a benzylic alcohol in a tandem process with 2-aminobenzamide to generate the quinazolinone heterocycle (*scheme 21*). Interestingly, they found that that the oxidation level of the product could be modulated by judicious choice of reaction conditions. Specifically, the inclusion of ammonium chloride as an additive led to the preferential production of the 2,3-dihydroquinazoline, whereas in the absence of this reagent the reaction generated the corresponding quinazolinone. A small selection of primary alcohols were shown to participate, including benzylic alcohols bearing methyl, methoxy and halide substituents. The scope of substituents upon the 2-aminobenzamide reagent was not demonstrated for this particular procedure.



Scheme 21 – Watson's catalytic hydrogen transfer methodology to quinazolinones

A very recent hydrogen transfer methodology was reported by Li in 2016, where methanol was demonstrated as a *C*1 source for the construction of quinazolinones.[58] After

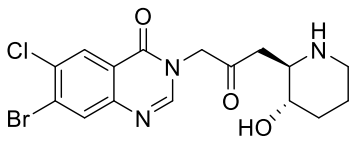
optimisation, it was found that *ortho*-aminobenzamide could be transformed into the corresponding quinazolinone under microwave conditions by utilisation of an iridium-based catalyst, [Cp*Ir(2,2'-bpyO)(H_2O)]. The ligands in this instance were found to be crucial to catalyst activity. Iridium catalysts based solely upon Cp* and COD were found to give low yields, whereas functionalised bipyridine motifs were more optimal. The scope of the *ortho*-aminobenzamide derivatives was broad; aromatic groups bearing both electron rich and electron poor substituents were found to participate, furthermore a *N*-substituted amide was shown to be viable, furnishing the corresponding heterocyclic product in a good yield of 66%. Moreover, alternative alcohol sources were found to be compatible, allowing for incorporation of substituents in the 2-position of the quinazolinone scaffold (*scheme 22*).[59]



Scheme 22 – Li's dehydrogenative coupling of *ortho*-aminobenzamide with alcohols

1.8 Introduction to project

As previously discussed, the natural product febrifugine **6** has been shown to display interesting biological properties. A synthetic analogue of febrifugine, which has also been shown to display noteworthy features is that of halofuginone **65**, shown in *figure 8*.[60] The replacement of the metabolically labile protons upon the quinazolinone by the two halogens makes halofuginone an interesting structure which has sparked much interest amongst medicinal chemists. Halofuginone is already used in veterinary medicine as an anti-parasitic treatment, in the marketed pharmaceutical drugs of Halocur ® and Sterenorol ®.[7]



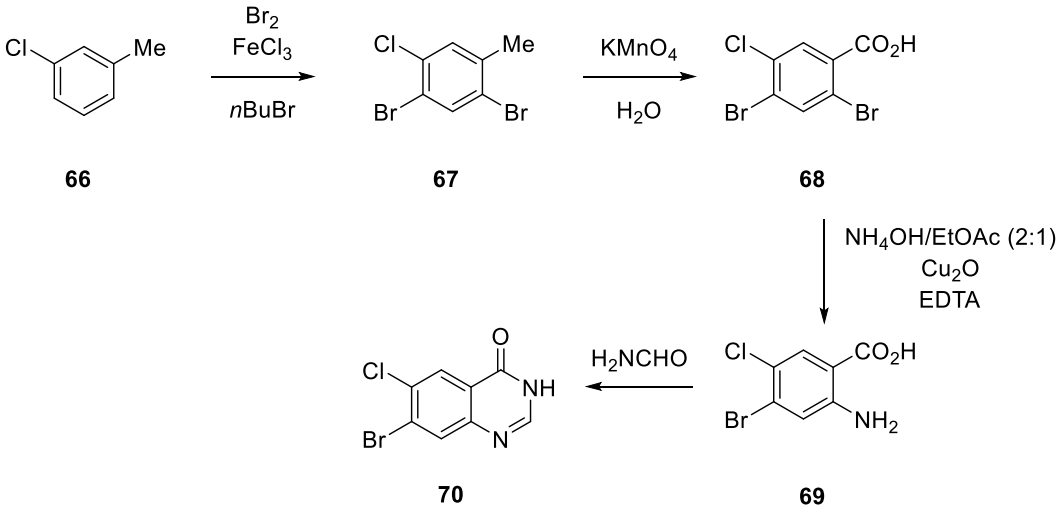
65

Figure 8 – Halofuginone

Whilst many synthetic routes to febrifugine and its analogues have already been reported in the literature, there are few reports on the synthesis and studies of halofuginone and its analogues. Indeed, there is only a single reported route to the halofuginone quinazolinone, shown in *scheme 23*.[61] With the use of toxic reagents, and an overall 6 step sequence, the

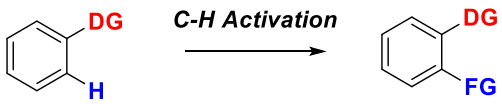
route shows much scope for optimisation. For research into the synthesis of halofuginone and its analogues to be carried out, the synthesis of the halofuginone quinazolinone **70** is first required, ideally from an alternative and more direct methodology.

The lack of synthetic routes to the halofuginone quinazolinone **70** arises from a key problem in quinazolinone synthesis as a whole. Many of the routes to quinazolinones described in literature start from 1,2-disubstituted aromatic rings. Whilst the use of these molecules as starting materials do lead to the succesful synthesis of quinazolinones, they also possess some disadvantages. Many of them are expensive to buy or prepare, especially the more highly-functionalised examples. The common 1,2-disubstituted aromatics are also restrictive in terms of reactivity, allowing for only certain methodologies to be used to access the desired quinazolinone.



Scheme 23 – Known route to the halofuginone quinazolinone **70**

A plausible route to broaden the scope of starting materials further, and to develop a new route to the halofuginone quinazolinone, is to use *C-H* activation chemistry. In this case, the substituent upon the molecule would be a directing group (DG). The directing group serves to help introduce the desired functionality to the aromatic ring (FG), as depicted in *scheme 24*.[62] Many examples of *C-H* activation have been reported in the literature, the majority over the last decade, where a variety of directing groups have been shown to succesfully introduce a range of functionalities.[63,64]



Scheme 24 – *C-H* Activation

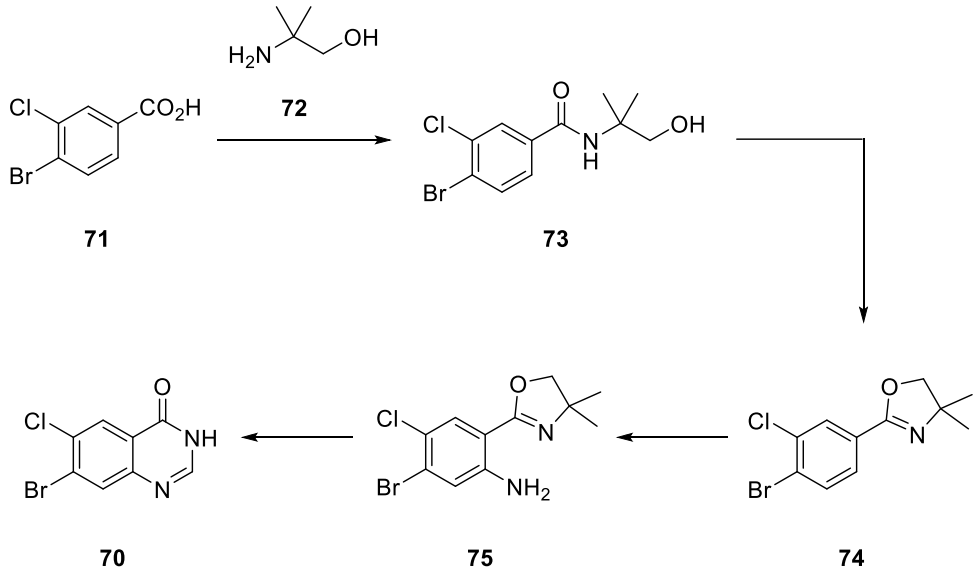
One particular aspect of *C-H* activation which has the potential for application to *N*-heterocycle synthesis is *ortho C-H* amination/amidation. Over the past few years, increasing numbers of both intramolecular and intermolecular *ortho C-H* amination/amidation

reactions have been reported.[65] Use of this increasingly popular methodology could provide a direct means to a new quinazolinone synthesis. If the directing group is already a component for the cyclisation to the heterocycle to occur, this would allow for a potentially shorter and novel route to quinazolinones from a readily avaliable starting material. This project explored the potential of this strategy to generate a range of highly functionalised quinazolinones, in particular that of the halofuginone quinazolinone.

Chapter 2: *C-H* Activation Towards Quinazolinone Synthesis

2.1 Synthesis of the oxazoline substrate

As previously shown in *scheme 23*, there has been only one reported synthetic route to the halofuginone quinazolinone. Whilst the route does provide a clear methodology to the desired material, it relies upon relatively harsh reaction conditions and a multi-step linear sequence. A novel and more appealing approach to the quinazolinone, which allows for the possibility of *C-H* activation by directed *ortho*-metallation chemistry and transition metal catalysis is shown in *scheme 25*.

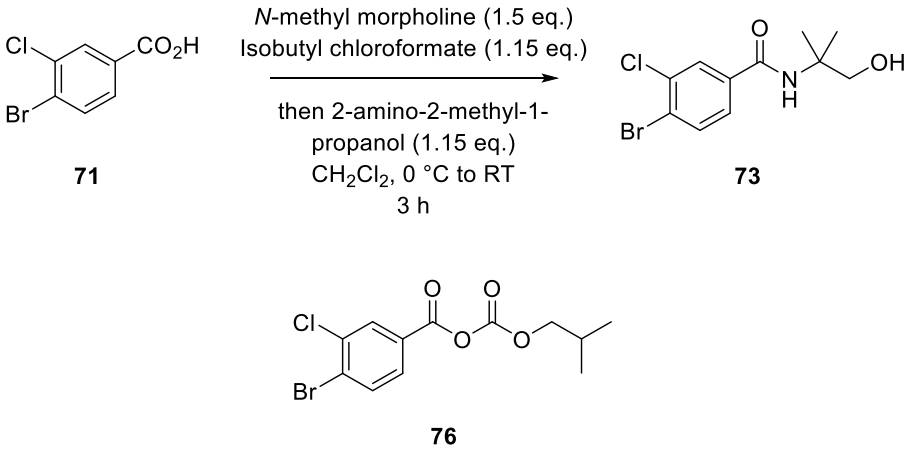


Scheme 25 – Proposed novel synthesis of halofuginone quinazolinone

The novel synthetic route primarily relies upon the synthesis of an aromatic oxazoline **74**, which is generated from the commercially avaliable parent benzoic acid **71** using 2-amino-2-methyl-1-propanol **72**. It was then envisaged that the generated oxazoline **74** would undergo direct *ortho*-metallation chemistry, allowing for the subsequent addition of DPPA for the formation of the key *C-N* bond. Subsequent reduction of the introduced azide functionality would yield **75**. From here cyclisation to the quinazolinone could then be carried out. A more interesting aspect of the proposed synthesis was that the directed *ortho*-metallation chemisty could be replaced by metal-catalysed *C-H* amination/amidation, a form of *C-H* activation, in which the use of the aromatic oxazoline as a directing group is scarcely reported. This approach would avoid the use of reactive main group bases.

Initial work began with the synthesis of the amide intermediate **73** shown in *scheme 26*. Many methodolgies are well documented for the synthesis of amides, but the chosen methodology was that reported by Sigman and co-workers in 2009.[66] The synthesis relied

upon the generation of an anhydride intermediate **76**, *via* the use of isobutyl chlorofomate, which was displaced by the chosen amino alcohol **72**.



Scheme 26 – Attempted synthesis of the amide using Sigman's conditions

Following the literature conditions, as shown in *scheme 26*, led to a crude yield of 94% of the anhydride intermediate **76**. Subjecting the isolated anhydride intermediate **76** to 1.15 equivalents of the amino alcohol in dichloromethane, did lead to a 40% yield of the desired material.

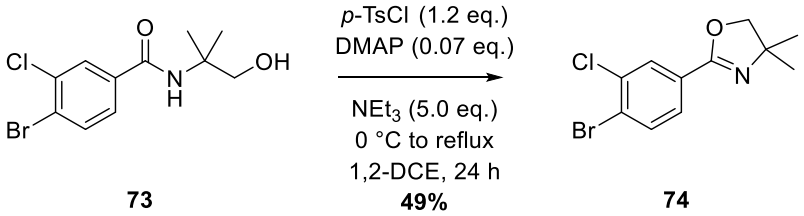
Entry	Time	Solvent	Temperature	Amine eq.	Yield
1	3 h	CH_2Cl_2	0 °C to RT	1.15	Trace
2	24 h	CH_2Cl_2	0 °C to RT	1.15	24%
3	30 h	CH_2Cl_2	0 to 40 °C	1.15	47%
4	30 h	CH_2Cl_2	0 to 40 °C	1.15 (x 2)	45%
5	30 h	1,2-DCE	0 to 40 °C	1.15	47%
6	24 h	1,2-DCE	0 °C to reflux	1.15	90%

Table 1 – Optimisation of amide formation

Following isolation of the desired material, a small optimisation of the reaction was then carried out (*table 1*). Use of the exact literature conditions only led to a trace amount of product, but almost quantitative yield of the anhydride intermediate **76** (entry 1). A longer reaction time led to an increase in yield (entry 2), as did an increase in temperature (entry 3). An additional portion of amino alcohol failed to change the outcome of the reaction (entry 4), however the reaction did prove to be successful in an alternative solvent of 1,2-dichloroethane (entry 5). Further increase in temperature to reflux following addition of all the reagents led to an excellent yield of the amide being obtained (entry 6).

Following successful synthesis of the amide **73**, conversion to the desired oxazoline **74** was then investigated. Sigman and co-workers also reported conditions for the cyclisation to the oxazoline, which involved the use of *p*-toluenesulfonyl chloride, dimethylamino pyridine and

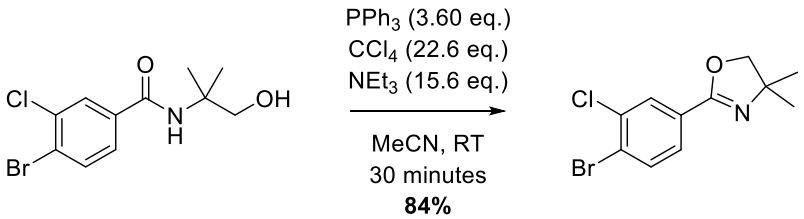
triethylamine.[66] Application of these conditions to the halogenated amide **73** led to a 49% yield of the desired material, as shown in *scheme 27*. Increasing the reaction scale to a 2.49 mmol led to a slightly lower isolated yield of 43%. Replacing *p*-toluenesulfonyl chloride with methane sulfonyl chloride led to only trace observation of the desired product.



73 **74**

Scheme 27 – Cyclisation to the oxazoline using *p*-toluenesulfonyl chloride

Following the consistently observed moderate yields, alternative conditions to generate the oxazoline in greater yields were considered. A well established route to generate oxazolines in the literature, relies upon the use of a mixture of carbon tetrachloride, triphenylphosphine and triethylamine.[67] Gratifyingly, subjection of the amide **73** to these reaction conditions gave an 84% yield of the desired oxazoline **74**, as shown in *scheme 28*. A scale up of the reaction to 2 mmol led to a lower isolated yield of 66%. Despite the unattractive use of the enviromentally unfriendly carbon tetrachloride, the methodology did allow access to good yields of the oxazoline substrate.

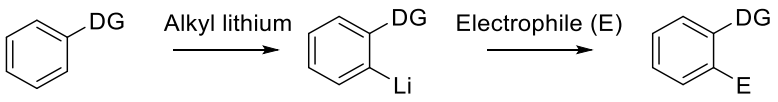


73 **74**

Scheme 28 – Alternative cyclisation to the oxazoline

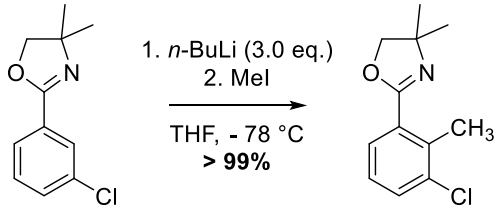
2.2 Directed *ortho*-metallation

With the oxazoline in hand, functionalisation of the aromatic moiety was then considered, firstly by the use of directed *ortho*-metallation chemistry. Directed *ortho*-metallation chemistry commonly comprises the addition of an alkyl lithium to deprotonate an aromatic ring in the position *ortho* to the directing group. Quenching with an electrophile leads to the introduction of a new functionality upon the aromatic ring, as depicted in *scheme 29*.[68] Directed *ortho*-metallation was initially discovered in 1939-1940 by Gilman and Wittig, where the successful metallation of anisole with *n*-BuLi was observed.[69, 70]



Scheme 29 – Directed *ortho*-metallation chemistry

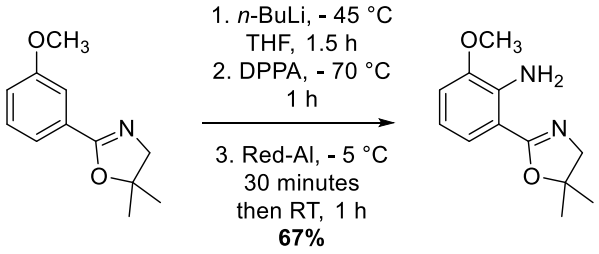
Following the observed reactivity with a methoxy group, more and more directing groups, with application to this chemistry were discovered. One protecting group which also served as a strong directing group was the oxazoline. Meyers exemplified this chemistry as shown in *scheme 30*.[71]



77 **78**

Scheme 30 – Oxazoline in directed *ortho*-metallation chemistry

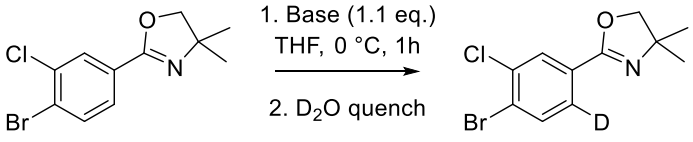
Many examples of directed *ortho*-metallation have been shown with various electrophile quenches. An example of relevance to this particular study is in the use of the electrophile DPPA, which following reduction allows the introduction of an amine on an aromatic ring.[72] This chemistry was reported by Shioiri in 1986, in which regioselective amination is achieved *via* the use of directed *ortho*-metallation chemistry, as shown in *scheme 31*.



79 **80**

Scheme 31– Regioselective amination using directed *ortho*-metallation chemistry [72]

It was anticipated that the employment of this strategy to compound **74** could be problematic due to competing Li-halogen exchange. Therefore, before the halogenated oxazoline **74** was subjected to the conditions reported by Shioiri, initial control reactions were carried out in order to investigate this issue. The control reactions involved subjecting the halogenated oxazoline **74** to base, then quenching with D_2O as shown in *scheme 32*.



74 **81**

Scheme 32 – Control reactions with the halogenated oxazoline **74**

Entry	Base	Result
1	*n*-BuLi	Deprotonation & Li/Halogen exchange
2	LDA	Recovered SM
3	LiHMDS	Recovered SM

Table 2 – Results from control reactions with the halogenated oxazoline **74**

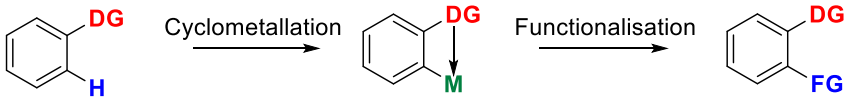
Results from the control reactions are listed above in *table 2*. Treatment of oxazoline **74** with *n*-BuLi (entry 1) led to a mixture of products which were inseperable *via* column chromatography. Analysis *via* LCMS showed successful deprotonation had occurred, however competing lithium-halogen was also observed, as evidenced by the identification of $[M^2H^{81}Br]$ and $[MH^{35}Cl]$. Slightly weaker bases such as LDA (entry 2) and LiHMDS (entry 3) were also used to test if deprotonation could occur without unwanted lithium-halogen exchange. However, in both cases only the oxazoline starting material was recovered, neither deprotonation nor lithium-halogen exchange were observed.

With these results in hand, it was decided to assess transition metal-catalysed *C-H* activation as an alternative methodology, as it was concluded that directed *ortho*-metallation chemistry would inevitably lead to a mixture of unwanted products.

2.3 Introduction to *ortho*-directed *C-H* activation

The conversion of carbon-hydrogen bonds into carbon-heteroatom and carbon-halogen bonds has always been a critical challenge in synthetic organic chemistry.[73] The formation of such bonds has traditionally relied upon pre-functionalised starting materials or strong bases as shown above. Pre-functionalised starting materials can be expensive to purchase or prepare, and can also add numerous steps to the synthesis of the required starting material. The use of strong bases can present limitations in terms of reaction scope. Direct *C-H* bond functionalisation reactions, whilst appealing to the organic chemist, are mostly limited in two ways. First of all, the unreactive nature of most carbon-hydrogen bonds, and secondly, the need to control site selectivity in molecules that contain multiple *C-H* groups. Many studies have now shown that the inert nature of carbon-hydrogen bonds can be overcome by the use of transition metals which are able to react with *C-H* bonds to produce *C-M* bonds in a process known as *C-H* activation (or cyclometallation). Cyclometallation, or mechanistically referred to as concerted metallation-deprotonation (CMD) has become the key process behind *C-H* activation.[74] The resulting *C-M* bonds have been found to be more reactive than their *C-H* counterparts, and have been demonstrated to have the potential to be successfully transformed into an array of new functional groups. Control of site selectivity has been

achieved using substrates which contain co-ordinating ligands, often termed as 'directing groups' (DG) in the literature. The use of a directing group allows for the successful binding of a molecule to a transition metal centre, selectively delivering the transition metal to a proximal *C-H* bond, enabling selective functionalisation (*scheme 33*).[75]



Scheme 33 – *C-H* Activation *via* cyclometallation

The ability of *C-H* activation to successfully and selectively achieve functionalisation of "inert" carbon-hydrogen bonds, makes the new and upcoming protocol an increasingly attractive methodology, as well as an alternative to the now well established cross-coupling procedures.

The field of *C-H* activation began to grow rapidly in the 1980s where it was found that numerous metal salts and complexes were able to initiate *C-H* activation *via* oxidative addition.[62] However, the main drawback of these early reports the requirement of stoichiometric amounts of transition metals, which in most circumstances made the procedures costly. In the past decade or so, synthetic organic chemists have achieved great developments by converting these initially stoichiometric reactions into catalytic methodologies. There are numerous reports of catalytic *C-H* activation using transition metals including Pd, Pt, Rh, Ru, Ni and Cu, amongst others.[76]

C-H activation has now been shown to be applicable to many types of bond formation as depicted in *figure 9*. Carbon-halogen bond formation *via C-H* activation has been shown to be viable on carbon sp^2 bearing substrates using *N*-halosuccinimides with Pd catalysis.[77] Carbon-oxygen bond formation has been extensively researched and achieved using palladium-catalysed *C-H* activation with the use of iodine, peroxide and dioxygen based oxidants.[78,79,80] Carbon-sulfur bond formation has also been shown to be viable *via* the use *C-H* activation, especially in terms of intramolecular bond formation towards the synthesis of benzothiopenes and benzothiazoles.[81,82] Carbon-carbon bond formation has also been successful using *C-H* activation methodologies, using both alkyl and aryl substrates.[83,84]

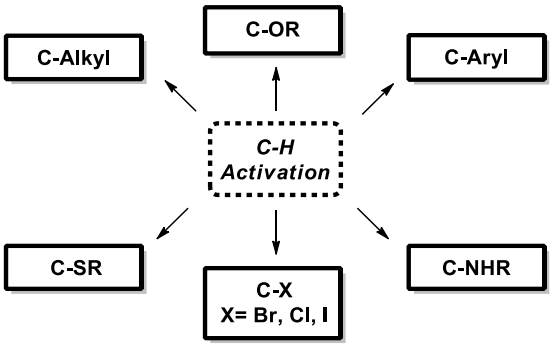


Figure 9 – C-X Bond formation *via C-H* activation

In addition to the range of transition metals used, and the variety of bonds which can be formed in *C-H* activation procedures, an array of directing groups have been shown to be successfully applicable (*figure 10*). The most prevalent in literature is by far the pyridine directing group. Many of the first reported *C-H* activation procedures are with the 2-phenyl pyridine substrate. Whilst its co-ordination ability is superior to many other examples, its weakness lies in limited options for further functionalisation and removal of the directing group. To avoid this problem, many *C-H* activation procedures have now been developed using directing groups that can be subsequently modified, to allow for further functionalisation following the *C-H* activation step. Examples of such directing groups include amides, oximes and esters.

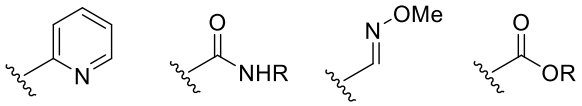
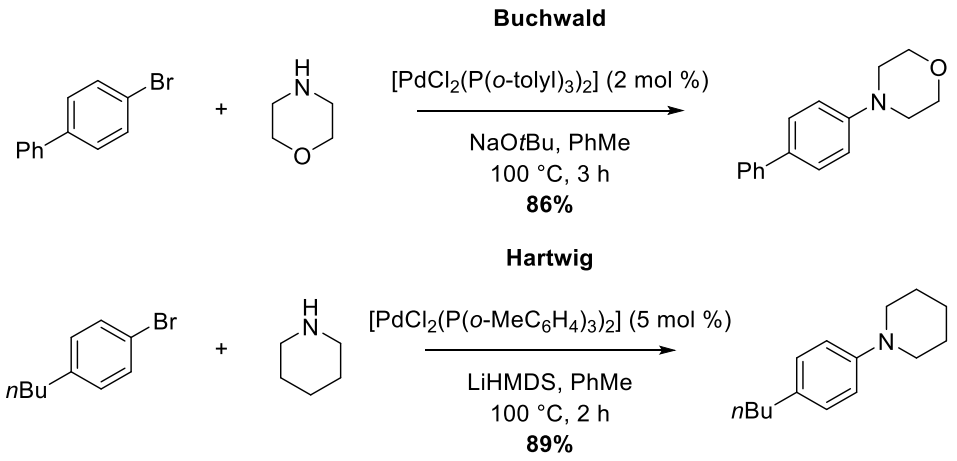


Figure 10 – Directing groups in *C-H* activation

2.4 *C-H* Amination/amidation introduction

Of particular interest, is the formation of carbon-nitrogen bonds *via C-H* activation. Buchwald-Hartwig coupling has become a well established cross-coupling methodology for the formation of carbon-nitrogen bonds. It was in 1995 that Buchwald and Hartwig independently reported the formation of carbon-nitrogen bonds *via* the use of palladium catalysis, *scheme 34*.[85,86] Since those early reports, an extensive amount of work on catalyst and ligand design has improved the methodology and helped it to become an established tool in organic synthesis and molecular design.[87]



Scheme 34 – Buchwald's and Hartwig's initial reports of palladium-catalysed carbon-nitrogen bond formation

Whilst Buchwald-Hartwig amination will always be a commonly used methodology, the obvious benefit of using *C-H* activation as a tool for the formation of carbon-nitrogen bonds again stems from avoiding the need for pre-functionalisation.

2.5 Classification of *C-H* amination/amidation reactions – External and internal oxidants

Significant progress has been made towards efficient *C-H* amination in recent years. Reports of carbon-nitrogen bond formation *via C-H* activation have become more and more popular within the general literature. Both intramolecular and intermolecular variants of *C-H* amination have been documented.[88] Much of what has been reported in terms of *C-H* amination, both in intra- and intermolecular modes, can be classified into two general methods. The first class involves the use of an external oxidant, often referred to as cross-dehydrogenative coupling, and the second class involves the use of pre-oxidised aminating reagents. Both classes of *C-H* amination are depicted in *figure 11*.[65]

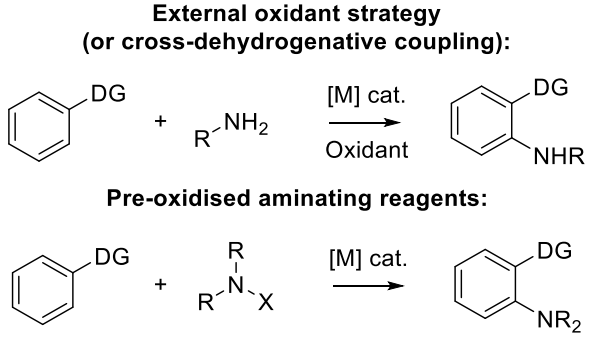
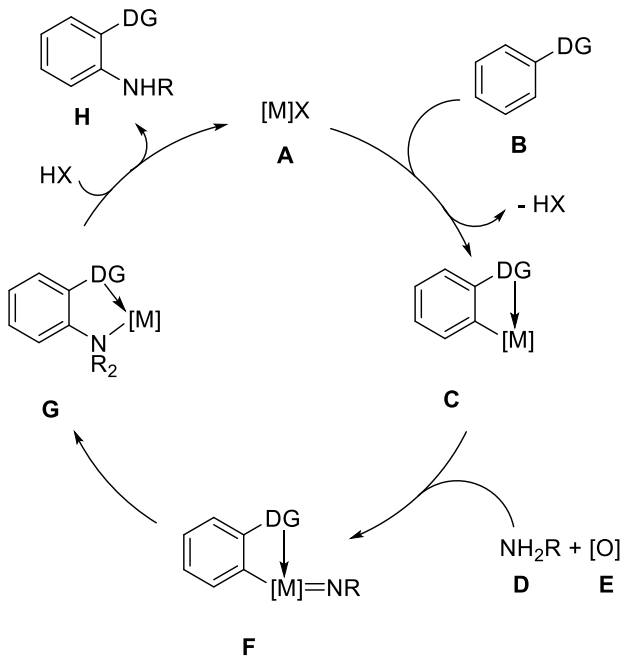


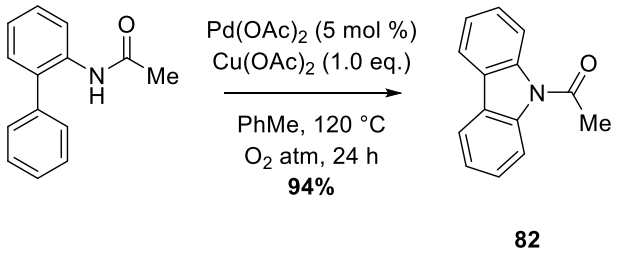
Figure 11 – The two classes of *C-H* amination

The external oxidant strategy shown above is very attractive because it avoids the need for pre-functionalised *C-H* and *N-H* coupling partners. The role of the external oxidant is to formally scavenge the H_2 by-product upon formation of the carbon-nitrogen bond. The by-product is not actually H_2, but the role of the oxidant is to abstract each hydrogen atom sequentially from each coupling partner.[65] Typical procedures which make use of the strategy involve taking an aromatic molecule **B**, with a suitable directing group, and a transition metal catalyst **A** to allow for generation of the cyclometallated intermediate **C**. Co-ordination of the oxidised amine coupling partner to the transition metal centre **F** is the next step in the catalytic pathway which, following insertion of the amine into the cyclometallated species **G**, gives the aminated product **H** and regenerates the catalytic species **A** (*scheme 35*).



Scheme 35 – External oxidant strategy reaction pathway

One of the very first examples of cross-dehydrogenative coupling was reported by Buchwald in 2005.[89] The intramolecular *C-H* amination reaction involved the use of palladium catalysis to synthesise acetylated carbazoles **82**, *scheme 36*. In this particular case, the reaction was facilitated in two ways. First of all, the amide directing group also served as the *N*-coupling partner. Secondly, the intramolecular character of the reaction helped to overcome the undoubtedly high energy barrier of the final carbon-nitrogen reductive elimination step. In 2008, Buchwald also showed the applicablity of Cu catalysis in cross-dehydrogenative coupling by the synthesis of benzimidazoles *via* copper-catalysed *C-H* amination.[90] The initial demonstration shown by Buchwald and co-workers of cross-dehydrogenative coupling impacted greatly amongst the scientific field, sparking the development of many other intramolecular *C-H* amination reports towards the synthesis of heterocycles.[91, 92]

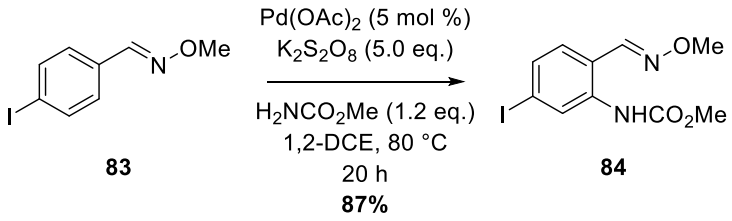


82

Scheme 36 – Buchwald's intramolecular *C-H* amination to carbazoles

Whilst less common in the general literature than the intramolecular variant, intermolecular reports of cross-dehydrogenative *C-H* amination are becoming more apparent. An initial and highly regarded example of this methodology was published by Wing-Yiu Yu in 2006.[93] 2-Phenylpyridine and imine derivatives **83** successfully underwent *C-H* amidation with amide coupling partners of carbamates and acetamides. The methodology involved the use of

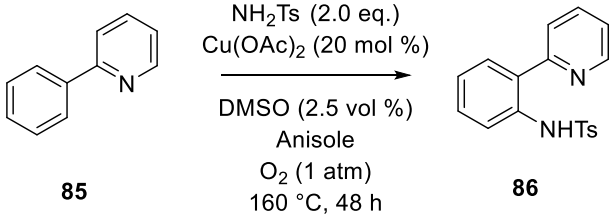
palladium catalysis, with postulated Pd^{IV} intermediates, and an external oxidant of potassium persulfate, *scheme 37*.



83 **84**

Scheme 37 – Yu's palladium-catalysed *C-H* amidation

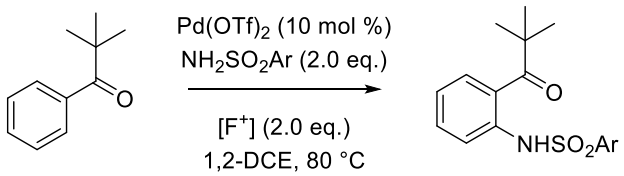
In 2011, the use of sulfonamides as amine coupling partners was established by both Nicholas and Liu.[94,95] Nicholas showed that sulfonamides could be successfully coupled to 2-phenylpyridine substrates **85** using copper catalysis with oxygen as the external oxidant (*scheme 38*).[95] The reaction scope only showed a total of seven amidating reagents which included both alkyl and aromatic sulfonamides, and electron withdrawing benzamides. High temperatures and long reaction times were required to obtain the products in good to moderate yields. In addition, all substrates used the pyridine directing group only.



85 **86**

Scheme 38 – Nicholas' copper-catalysed *C-H* amidation with sulfonamides

Palladium-catalysed intermolecular directed *C-H* amidation with aromatic ketones using a range of primary and secondary sulfonamides was shown by Liu. Similar to Nicholas, a handful of electron withdrawing benzamides were also shown to be viable substrates albeit in much lower yield (*scheme 39*).[94] Alkyl ketones were used as the directing group, where tertiary alkyl groups were found to give better yields than the primary and secondary counterparts. The applicability of the procedure was shown by the use of the amidated products towards the synthesis of alkyl-substituted indoles.

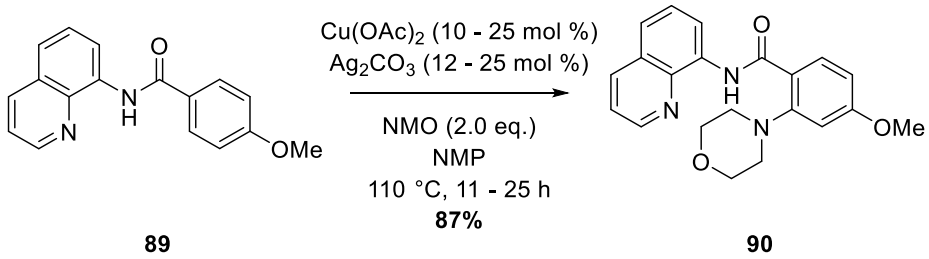


87 **88**

[F+] = *N*-fluoro-2,4,6-trimethyl-pyridinium triflate

Scheme 39 – Liu's palladium-catalysed *C-H* amidation with sulfonamides

Daugulis also reported intermolecular *C-H* amination with a Cu/Ag catalyst system as shown in *scheme 40*. Unlike many other reported *C-H* activation procedures, the directing group in this case was based upon an 8-aminoquinoline structure which could be readily cleaved with sodium hydroxide in ethanol to afford the parent carboxylic acid. In most cases, good to excellent yields were obtained over a range of cyclic and alkyl substituted secondary amines. A few primary amines were also shown to couple successfully, however in low to moderate yields. Despite the advantageous deprotectable directing group the procedure required a relatively high catalyst loading (25 mol %) in comparison to other *C-H* amination procedures previously described.



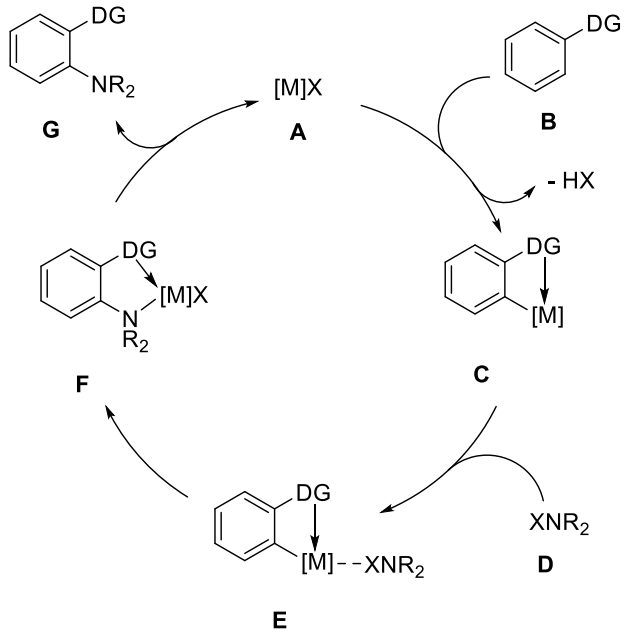
89 **90**

Scheme 40 – Daugulis' intermolecular *C-H* amination

The internal oxidant strategy, which makes use of pre-oxidised aminating reagents has become more apparent in literature as a successful strategy for *C-H* amination. The use of pre-oxidised aminating reagents essentially relies on reversing the reactivity of the amine partner. In the external oxidant strategy described above, the amine coupling partners are nucleophillic in character. In this case however, pre-functionalised aminating reagents make the nitrogen centre more electrophillic in character, which in theory better facilitates the attack of the nucleophillic *C-M* bond of the metallated intermediate. Many pre-oxidised aminating reagents are in the form of *N*-carboxylates, *N*-tosylates and *N*-halides; essentially the nitrogen atom contains a leaving group.[65] Advantages of using pre-functionalised aminating reagents include milder and more selective reaction conditions, as well as the exclusion of an external oxidant. The obvious disadvantage of the strategy as a whole is in the unavoidable synthesis of the pre-oxidised aminating reagents, which in some circumstances can be both rather tedious and time consuming.

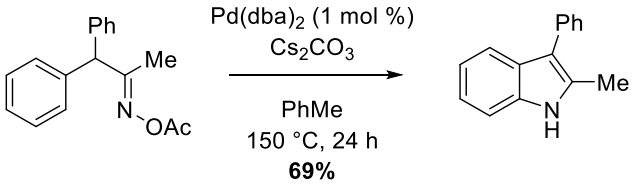
In a similar manner to the cross dehydrogenative methodologies described above, the initial step in the catalytic pathway is the formation of the cyclometallated intermediate **C**. Following reaction between the cyclometallated intermediate **C** and the pre-oxidised aminating reagent **D** to generate intermediate **E**, the internal oxidant fragment of the aminating reagent is displaced allowing for insertion of the amine functionality into the carbon-metal bond. Intermediate **F** then leads to the product **G** and the re-generation of the catalytic species **A** (*scheme 41*). Much ambiguity surrounds the insertion step in many of the

known and established *C-H* amination protocols, with both internal and external oxidants. The step is believed to occur in one of two possible ways. The first is a concerted migratory insertion, and the second a stepwise nitrenoid pathway *via* high-valent transition metal complexes.[96]



Scheme 41 – Pre-oxidised aminating reagent reaction pathway

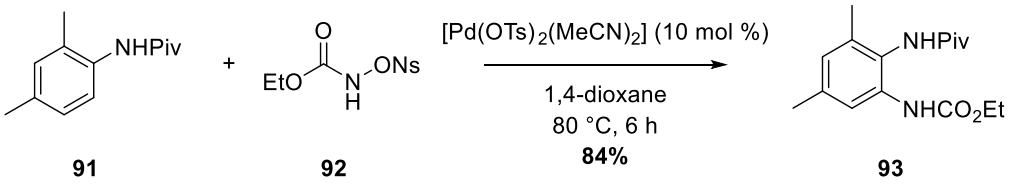
Intramolecular *C-H* amination using a pre-oxidised aminating reagent was exemplified by Hartwig in 2010, where the synthesis of substituted indoles was succesfully shown *via* the use of palladium catalysis.[97] As shown in *scheme 42*, the procedure used oxime ethers to aminate aromatic *C-H* bonds in overall redox neutral conditions. The advantages of the procedure included low catalyst loadings, applicability to a range of substrates as both electron withdrawing and electron donating functionalities were tolerated.



Scheme 42 – Hartwig's intramolecular *C-H* amination

The first example of intermolecular *C-H* amination using pre-oxidised aminating reagents was reported by Wing-Yiu Yu in 2010.[98] The reaction involved a palladium-catalysed *ortho C-H* amidation of anilides **91** with *N*-nosyloxycarbamates **92** as the pre-oxidised aminating reagents. The reaction showed a tolerance to a wide range of substrates, and proceeded in all cases in moderate to excellent yields. A drawback however, was that a significant proportion of the reaction scope was exemplified using substrates with only one avaliable

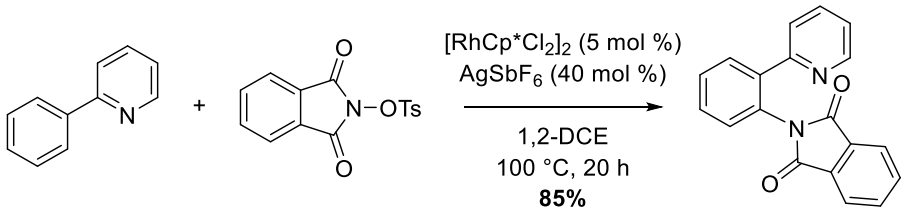
ortho position, which suggested that diamination was a side reaction observed when less substituted substrates were employed (*scheme 43*).



91 **92** **93**

Scheme 43 – Yu's intermolecular *C-H* amidation with *N*-nosyloxycarbamates

As well as palladium catalysis showing applicability to *C-H* amination with pre-oxidised aminating reagents, Cu, Rh and Ir have become common transition metal catalysts in this transformation.[99,100,101] Rhodium catalysis in particular has become more popular in the general literature as a means for carbon-nitrogen bond formation. For example Wan and Li showed the use of pre-oxidised aminating reagents and rhodium catalysis for the introduction of protected amines to 2-phenylpyridine derivatives (*scheme 44*).[102] Other directing groups including oxime methyl ether and pyrimidine were also shown to be successful directing groups.

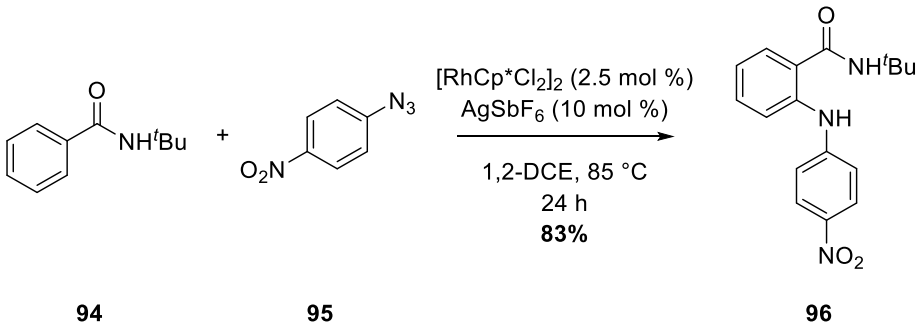


Scheme 44 – Wan and Li's rhodium-catalysed *C-H* amination

One class of pre-oxidised amination reagents which have received increasing amounts of attention amongst the scientific community are azides. With a wide synthetic utility, high reactivity within *C-H* activation methodologies and a single formal by-product of nitrogen gas, azides are very attractive coupling partners. The only disadvantage of azides as amination reagents is in regard to the safety of the substances, as previously mentioned azides can be hazardous reagents upon handling, storage and preparation. Despite safety concerns, azides have been shown to be very successful coupling partners for *C-H* amination protocols.

In 2012 Sukbok Chang and co-workers were amongst the first to report the intermolecular reaction of benzamides **94** with azide derivatives *via* the use of rhodium catalysis towards the synthesis of diaryl amines **96**, *scheme 45.*[103] The reaction was shown to tolerate both amides and ketoximes as directing groups, delivering products in generally moderate to excellent yields. Mechanistically, it was suggested that the metallacycle intermediate approaches the azide, liberating nitrogen gas, and generating a reactive nitrene intermediate which subsequently inserts into the carbon-rhodium bond leading to the desired product. As

a whole, despite the procedure being mostly limited to electron poor aryl azides, the reported reaction increased the interest around the reactivity of azides in intermolecular *C-H* amination.



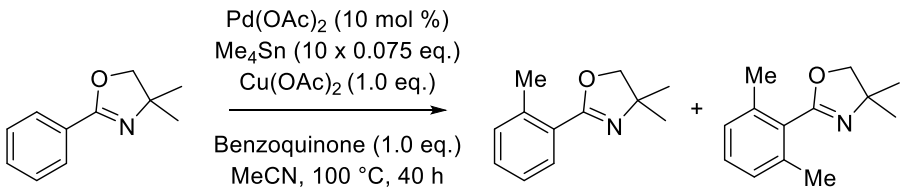
94 **95** **96**

Scheme 45 – Chang's rhodium-catalysed intermolecular *C-H* amination with azides

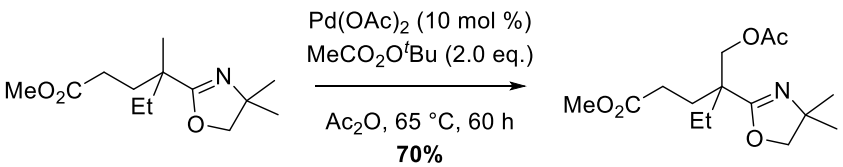
Further work reported by Chang in 2013 showed that the scope of the reaction could be extended to both benzyl and alkyl azides. Moreover, the use of an iridium-based catalyst showed the reaction could be carried out at room temperature, delivering *C-H* amination products in excellent yields.[104, 105]

2.6 Results and discussion: Intermolecular palladium-catalysed *C-H* activation towards quinazolinone synthesis

Inspired by the above reports and with the halogenated oxazoline **74** in hand, it was decided to attempt intermolecular *C-H* amination as a means of introducing the desired amine functionality. The oxazoline as a functional group has appeared scarcely in literature as a directing group for *C-H* activation. Two examples where the oxazoline serves as a directing group in palladium-catalysed *C-H* activation are shown in *scheme 46*. Both examples were demonstrated by Yu *et al.* in 2005. The first example in *scheme 46* involves *C-H* alkylation of the aromatic oxazoline with organotin reagents, and the second involves *C-H* acetoxylation of alkyl oxazoline substrates using lauroyl peroxide and acetic anhydride.[106, 107]



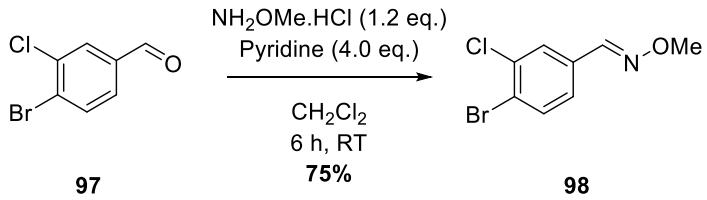
20% **64%**



Scheme 46 – The oxazoline directing group in palladium-catalysed *C-H* activation

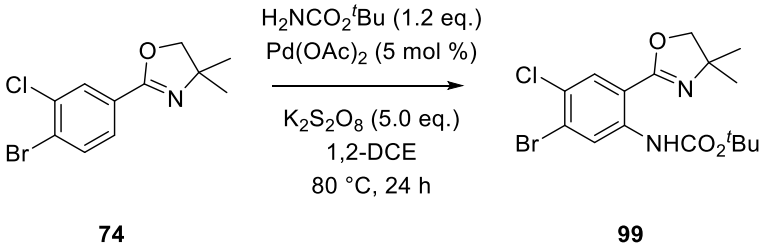
Intrigued by the apparent utility of oxazolines in palladium-catalysed *C-H* activation, it was hypothesised that palladium-catalysed *C-H* amination using the oxazoline would be a viable methodology towards the synthesis of the halofuginone quinazolinone. It was decided to consider the palladium-catalysed *C-H* amidation conditions previously described by Wing-Yi Yu upon the oxazoline substrate.[93] The external oxidant conditions shown previously in *scheme 37*, involve the use of a pyridine or oxime directing group, with a palladium acetate catalyst in the presence of an external oxidant of potassium persulfate. The amine sources shown within the publication were methyl and *tert*-butyl carbamate, a few examples using trifluoroacetamide were also shown.

In addition to using the above conditions on the halogenated oxazoline **74** it was decided to synthesise the halogenated oxime substrate **98** to ensure that the conditions were reproducible. The oxime was readily synthesised using established chemistry to afford the desired product in a good yield of 75%.[108]



Scheme 47 – Synthesis of the halogenated oxime

With the two substrates of interest in hand the conditions were tried initially upon the oxazoline.



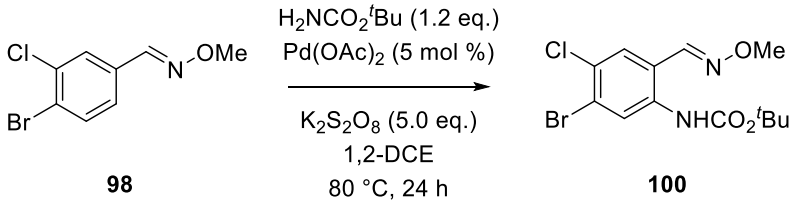
Scheme 48 – Initial attempt with Yu's conditions upon the halogenated oxazoline

Initial attempts unfortunately only resulted in the recovery of the starting material **74** as judged by ^{1}H NMR spectroscopic analysis. However, LCMS and HRMS suggested low conversion to the desired product had occured. Attempts to achieve higher conversion of the starting material by reaction optimisation was then undertaken, see *table 3*.

Entry	Amide	Pd cat. Loading	Time	Result
1	H_2NCO_2tBu	5 mol %	24 h	Trace[a]
2	H_2NCO_2Me	5 mol %	24 h	Trace[a]
3	H_2NCHO	5 mol %	24 h	Trace[a]
4	$H_2NCO_2{}^tBu$	5 mol %	72 h	Trace[a]
5	$H_2NCO_2{}^tBu$	50 mol %	24 h	Trace[a]
6	$H_2NCO_2{}^tBu$	50 mol %	24 h	Trace[b]

Table 3 – Reaction varitations with the halogenated oxazoline **74** [a] Oxidant, $K_2S_2O_8$, added portionwise in the reaction. [b] Oxidant, $K_2S_2O_8$, added at the start of the reaction only.

As described, the use of the literature conditions led to trace amounts of product formation (entry 1). Changing the amide source to methyl carbamate and formamide, again only led to trace amounts of product formation (entries 2 and 3). Leaving the reaction for a longer period of time, 72 hours, had no impact upon the result (entry 4). Increase in the palladium catalyst loading to 50 mol % was attempted to address the possibilty of catalyst degradation, however this also failed to affect the reaction conversion (entry 5). Increasing catalyst loading and portionwise addition of the oxidant, or addition of all the reagents in one step led only to the same observation (entry 6). At this stage it was decided to use the halogenated oxime **98** as opposed to the oxazoline to assess the effect of the directing group.



Scheme 49 – Initial attempt with Yu's conditions upon the halogenated oxime

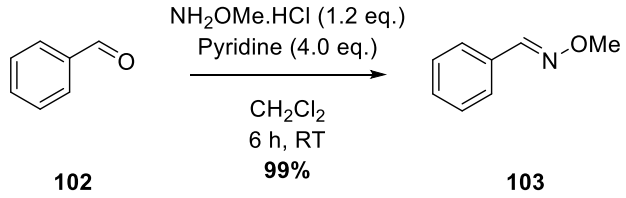
The use of the oxime directing group unfortunately only resulted in the recovery of the starting material. Similar to the halogenated oxazoline, various aspects of the reaction conditions were altered as shown in *table 4* below.

Entry	Amide	Time	Result
1	H_2NCO_2tBu	24 h	Recovered SM
2	H_2NCO_2Me	24 h	Recovered SM
3	H_2NCHO	24 h	Recovered SM
4	$H_2NCO_2{}^tBu$	72 h	Recovered SM

Table 4 – Reaction variations with the halogenated oxime **98**

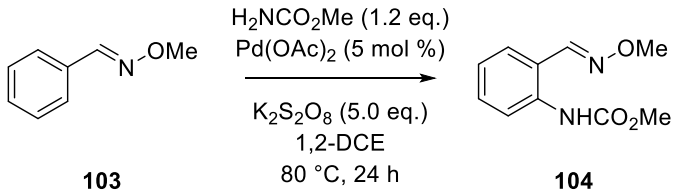
As described in *table 4*, the use of the literature conditions led to only the recovery of the starting materials (entry 1). Changing the amide reagent to methyl carbamate and formamide also failed to afford product (entries 2 and 3). Finally leaving the reaction for a longer time period, 72 hours, did not lead to product formation (entry 4).

Due to the lack of reactivity observed by both the halogenated oxazoline **74** and the halogenated oxime **98** it was postulated that the substituents on the aromatic ring could be affecting the efficiency of the reaction. It was decided to subject the commercially avaliable, parent un-functionalised oxazoline **101** to the literature conditions. The use of the unsubstituted aryl oxime and the use of 2-phenylpyridine would also allow assessment of the reproducibility of the reaction conditions, as these precise substrates had been reported to react efficiently.[93] Using the same methodology for the halogenated oxime formation, the unsubstituted oxime **103** was formed in almost quantitative yield, as shown in *scheme 50*.



Scheme 50 – Synthesis of the unsubstituted oxime

Having successfully synthesised the unsubstituted oxime, the substrate was then subjected to Yu's exact conditions with methyl carbamate as the amide coupling partner.



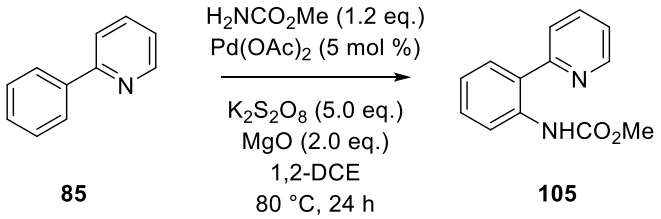
Scheme 51 – Yu's literature conditions with the unsubstituted oxime

Suprisingly, the use of the unsubstituted oxime **103** also failed to afford any product, despite being reported to be a viable substrate by Yu.

Entry	Temperature	Result
1	80 °C	Recovered SM[a]
2	80 °C	Recovered SM[b]
3	100 °C	Recovered SM[a]

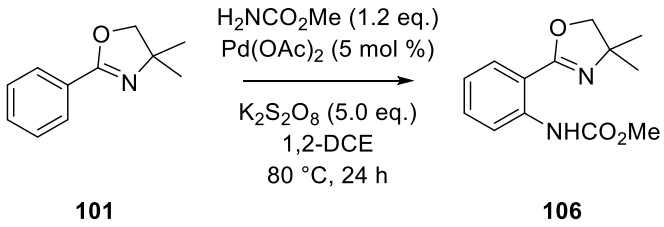
Table 5 – Attempts to amidate the unsubstituted oxime [a] Oxidant, $K_2S_2O_8$, added portionwise in the reaction. [b] Oxidant, $K_2S_2O_8$, added at the start of the reaction only.

As shown in *table 5* above, the exact literature conditions failed to afford any conversion of the starting material (entry 1). Adapting the procedure from portionwise addition of the oxidant, to addition of all the reagents in one step led to only recovery of the starting material (entry 2). Finally, an increase in temperature to 100 °C again had no impact upon the result (entry 3). An alternative substrate of 2-phenylpyridine **85**, again an exact example from the literature source, was subjected to the reaction conditions to assess their reproducibility. Unfortunately, in the presence and absence of a magnesium oxide additive no reaction occurred, leading only to the recovery of the starting material, *scheme 52*.



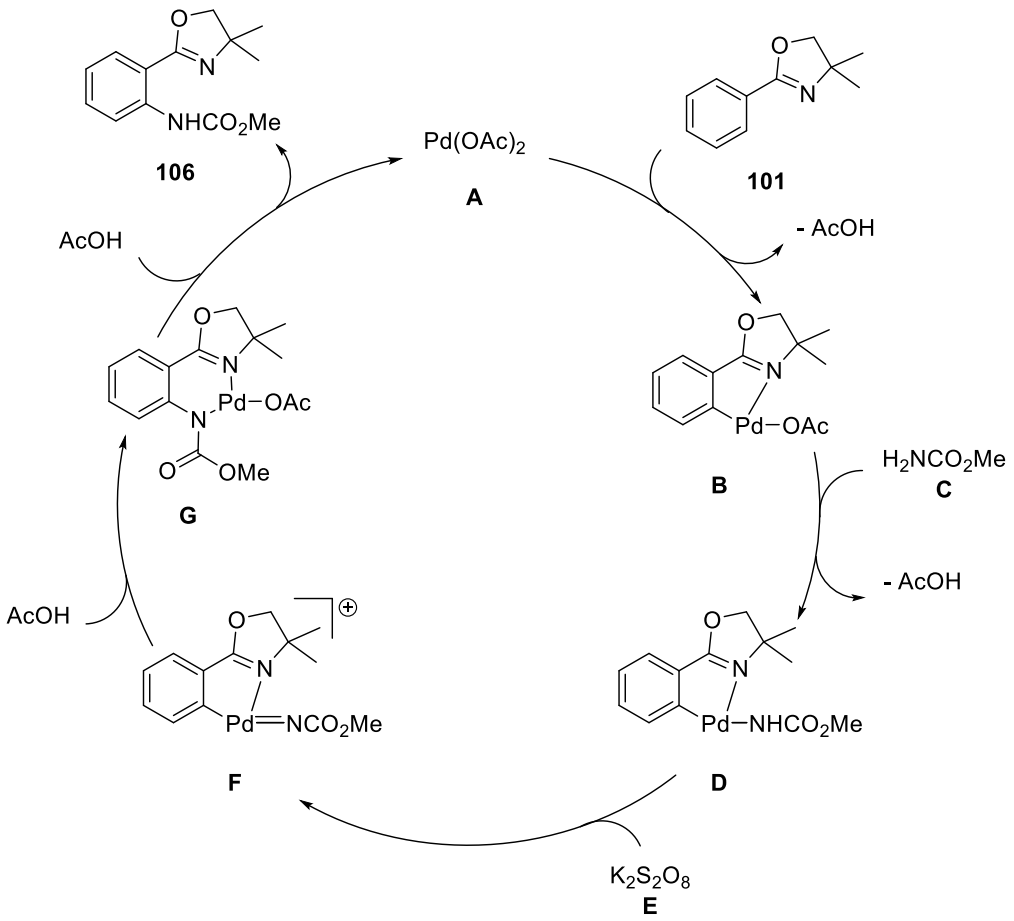
Scheme 52 – Yu's literature conditions with 2-phenyl pyridine

Despite the failure to reproduce Yu's conditions, it was decided to try the conditions upon the unsubstituted oxazoline to see if any reaction at all would occur.



Scheme 53 – Yu's conditions with the unsubstituted oxazoline

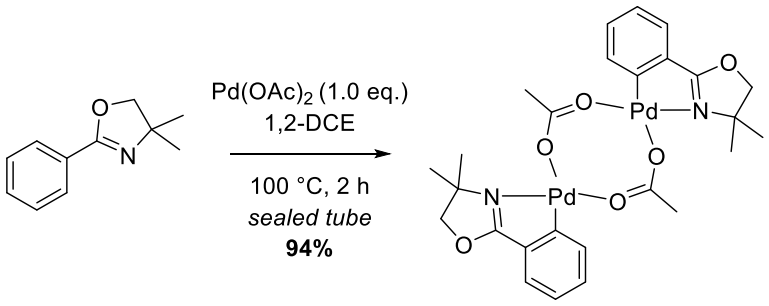
Similar to the results obtained with the halogenated oxazoline **74**, subjection of the unsubstituted oxazoline **101** to the reaction conditions with methyl carbamate led to trace amounts of product formation, identifiable by HRMS. To further probe why the reaction conditions with the oxazoline substrates **74** and **101** were consistently leading to low conversion, the reaction mechanism was considered.



Scheme 54 – Mechanism of Yu's intermolecular *C-H* amidation

Mechanistically the reaction, depicted in *scheme 54* with the unsubstituted oxazoline substrate, initally proceeds *via* formation of the palladacycle **B**. The palladacycle most likely forms *via* a CMD process, losing acetic acid from reaction between the palladium catalyst **A** and the substrate **101**. The amide source, methyl carbamate **C**, next displaces an acetate ligand to co-ordinate to the palladium centre **D**. The oxidant potassium persulfate **E** leads to the generation of a nitrene intermediate, which leads to a postulated palladium(IV) intermediate **F**. Addition of acetic acid causes insertion of the amide into palladacycle affording intermediate **G**. Further addition of acetic acid generates the product **106** and regenerates the catalyst **A**.

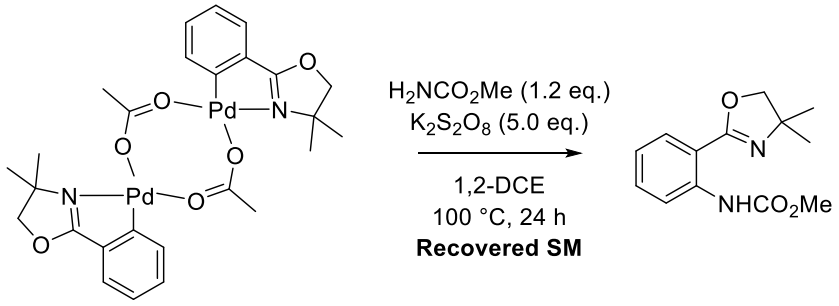
In an effort to understand why the reaction conditions were consistently giving low conversion, two hypotheses were made. Firstly, under the reaction conditions the palladacycle necessary for *C-H* activation to occur was not forming. Secondly, the palladacycle was forming under the reaction conditions, however the amide source was not reactive enough. To probe the hypothesis it was decided to synthesise the palladacycle by alternative means and subject it to the reaction conditions to see if product formation would be observed. The palladacycle was successfully synthesised in an excellent yield of 94%, *scheme 55*.[106]



101 **107**

Scheme 55 – Formation of the oxazoline palladacycle

Subjection of the oxazoline palladacycle **107** to the reaction conditions was then carried out as shown in *scheme 55*.

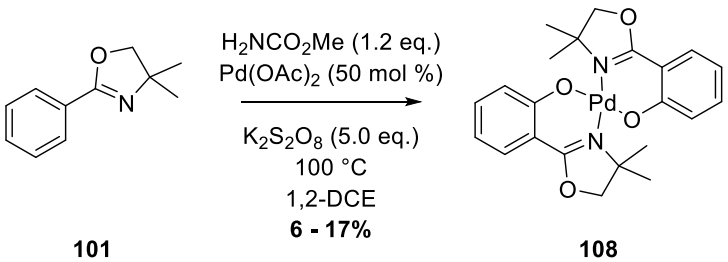


107 **106**

Scheme 56 – Subjection of the palladacycle to the reaction conditions

When the palladacycle **107** was subjected to the reaction conditions, only recovery of the starting palladacycle was observed. This led to the conclusions that the amine source in the reaction was potentially not reactive enough for the *C-H* amination to occur, or under the reaction conditions the palladacycle was very stable and unable to participate in any reaction leading to its recovery.

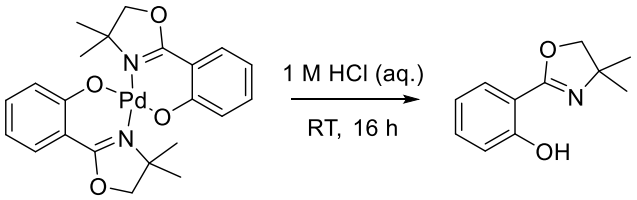
In further final efforts to increase conversion in the amination of the oxazoline substrate **101** using methyl carbamate under palladium catalysis, it was decided to conduct the reaction at 100 °C, increase the palladium loading to 50 mol % and add all of the external potassium persulfate oxidant at the start of the reaction. Interestingly, although no desired aminated product was observed, an alternative palladacycle was isolated in low yield **108** (*scheme 57*).



101 **108**

Scheme 57 – Isolation of the alternative oxazoline palladacycle

Formation of the oxidised palladacycle **108** was observed in the absence and presence of the carbamate source, in yields varying from 6 to 17%. Confirmation that the characterisation data obtained was indeed that of the oxidised palladacycle was found *via* reaction of **108** with 1 M HCl (aq.). Leaving the reaction to stir for 16 h afforded 2-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-phenol **109**, identifiable by ^{1}H NMR and ^{13}C NMR analysis confirming the formation of the oxidised palladacycle.

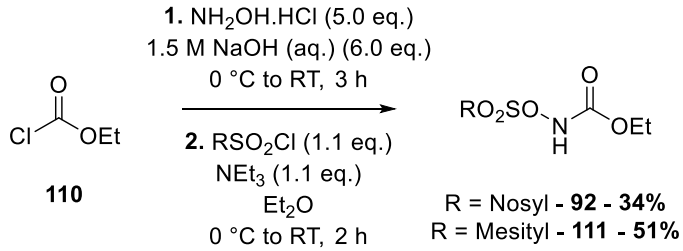


108 **109**

Scheme 58 – Formation of 2-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-phenol **109**

At this stage, it was apparent that Yu's conditions were not reproducible, and far from ideal for the oxazoline substrate. It was decided to consider alternative conditions for the desired *C-H* amination reaction.

As opposed to intermolecular palladium-catalysed *C-H* amination using an external oxidant, conditions using pre-oxidised aminating reagents were chosen given the lack of reactivity observed with Yu's conditions. As previously described, *N*-oxycarbamates have been successful coupling partners for *C-H* activation methodologies. It was decided to try the conditions described above in *scheme 43*, where *N*-nosyloxycarbamates were successfully used under palladium catalysis.[98] Synthesis of the *N*-nosyloxycarbamate and *N*-mesityloxycarbamate, which is also precedented in literature, were carried out from readily available starting materials of ethyl chloroformate and hydroxylamine hydrochloride (*scheme 59*).[109] Yields of 34% and 51% were obtained for the *N*-nosyl and *N*-mesityloxycarbamates respectively.

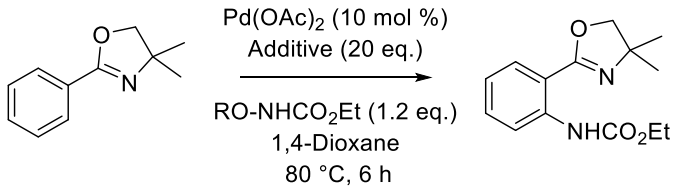


110

R = Nosyl - **92 - 34%**
R = Mesityl - **111 - 51%**

Scheme 59 – Synthesis of *N*-oxycarbamates

With the two internal oxidant substrates to hand, the reaction conditions were applied to the phenyl oxazoline substrate **101** (*scheme 60*), the results of which are shown in *table 6*.



101 **106**

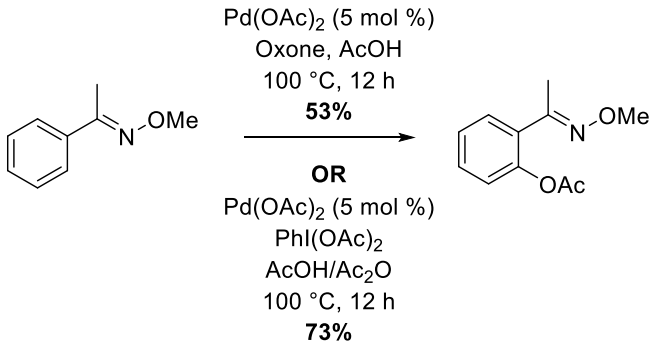
Scheme 60 – Internal oxidant methodology with the phenyl oxazoline **101**

Entry	Internal oxidant	Additive	Result
1	**92**	-	Recovered SM
2	**92**	AcOH	Recovered SM
3	**111**	-	Recovered SM
4	**111**	AcOH	Recovered SM

Table 6 – Internal oxidants with the phenyl oxazoline **101**

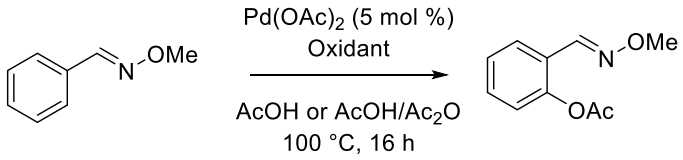
As shown in *table 6*, the use of both the synthesised internal oxidants failed to afford any of the desired products, in the presence and absence of an acetic acid additive (entries 1 to 4). In all cases only recovery of the starting material was observed.

Since both intermolecular *C-H* amination with external and internal oxidants were failing to deliver the desired products, it was questioned whether or not palladium-catalysed amidation on the oxazoline substrate was at all viable. As described earlier, many examples of *C-H* activation have been described in literature, one of the more common types being the formation of carbon-oxygen bonds. With this in mind, it was decided to investigate if subjection of the oxazoline substrate **101** to alternative *C-H* activation reaction conditions would result in any reaction at all. One well renowned example of carbon-oxygen bond formation was reported by Sanford in 2006, where palladium-catalysed intermolecular direct methoxylation and acetoxylation was described upon oxime substrates, see *scheme 61*.[79] Oxidants of oxone and $PhI(OAc)_2$ were employed to generate the products in good to excellent yield.



Scheme 61 – Sanford's palladium-catalysed direct acetoxylation

Since a similar phenyl oxime substrate **103** had already been previously prepared, it was decided to try the reaction conditions on this initially to ensure the conditions were reproducible, before subjecting the oxazoline substrate to them (*Scheme 62* and *Table 7*).



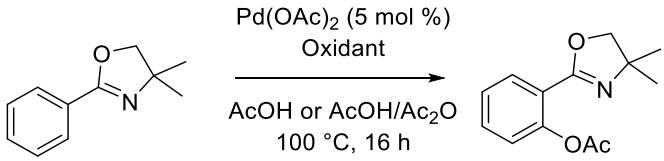
103 **112**

Scheme 62 – Sanfords conditions upon the phenyl oxime **103**

Entry	Oxidant	Oxidant eq.	Solvent	Result
1	Oxone	0.95	AcOH	5%
2	$PhI(OAc)_2$	1.10	$AcOH/Ac_2O$ (1:1)	44%

Table 7 – Sanfords conditions with the phenyl oxime substrate **103**

Gratifyingly, using both sets of Sanford's conditions for the direct acetoxylation reaction, the expected product was obtained. When using oxone in acetic acid as the solvent, a poor yield of 5% was obtained (entry 1), however when using an oxidant of $PhI(OAc)_2$ in a mixed solvent system of acetic acid and acetic anhydride the product was afforded in a moderate yield of 44% (entry 2). With successful *C-H* activation conditions in hand the oxazoline substrate **101** was subjected to oxidation conditions (*scheme 63*). The results are described below in *table 8*.



101 **113**

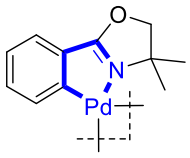
Scheme 63 – Sanfords conditions upon the phenyl oxazoline **101**

Entry	Oxidant	Oxidant eq.	Solvent	Result
1	Oxone	0.95	AcOH	Recovered SM
2	$PhI(OAc)_2$	1.10	$AcOH/Ac_2O$ (1:1)	Recovered SM

Table 8 – Sanford's conditions with the phenyl oxazoline substrate **101**

Unfortunately, reaction with the phenyl oxazoline substrate **101** failed to deliver product under either set of conditions (entries 1 and 2).

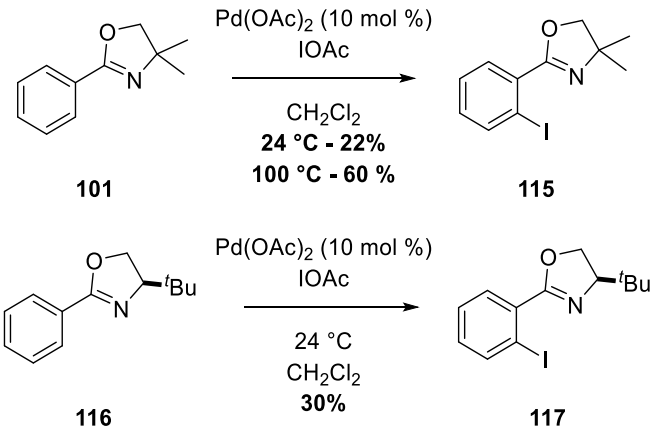
The consistently observed lack of reactivity of the oxazoline subtrates **74** and **101** prompted the conclusion that the substrates are not suitable for palladium-catalysed *C-H* activation. One plausible reason for the observation could be related to the stability of the palladacycle formed within the various reaction conditions, see *figure 12* below.



114

Figure 12 – Stable 5-membered oxazoline palladacycle **114**

The results and observations found from the attempts at palladium catalysis upon the oxazoline substrates **74** and **101** are in agreement with those made by Jin-Quan Yu.[110] Yu and co-workers reported in 2008 that attempts to functionalise the phenyl oxazoline **101** *via* direct-iodination with palladium catalysis were largely ineffective, see *scheme 64*. Attempts to iodinate the molecule with a reactive electrophilic iodine source of IOAc at room temperature led only to 22% yield of the product after reaction for a total of 72 hours. Increasing the temperature, led to an increase in yield, but the same extensive reaction time was required. Yu similarly attributes the lack of reactivity to the palladacycle *"… the five-membered palladacycle intermediate resulting from ortho-palladation could be very stable"*.[110] Their attempt to make the palladacycle more unstable and hence more reactive, was by increasing the steric bulk of the oxazoline substitutent from a *gem*-dimethyl unit to a *tert*-butyl group **116**, however this only led to a slight increase in yield again after a reaction time of 72 hours. In addition, they also reasoned that six- or seven-membered cyclometalated complexes could be more reactive as they make the palladium (IV) species less stable, and hence reductive elimation could proceed more quickly.[110] This was also further enforced in work done by Sanford upon the 2-phenylpyridine substrate **85**. They reported that five-membered palladacycles are very stable, and very reluctant to undergo catalytic reactions because of the stability of Pd(IV) intermediates.[111] Further evidence of the stability of five-membered palladacycles is in their ability to be successfully isolated.[112, 113]



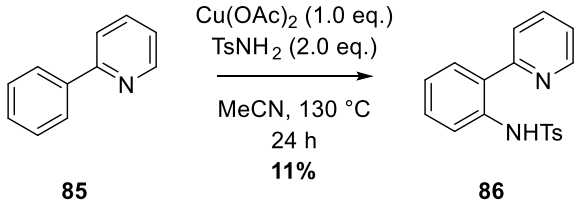
Scheme 64 – Yu's work upon phenyl oxazoline substrates

From these observations, it was clear that the necessary carbon-nitrogen bond formation required for the synthesis of the halofuginone quinazoline **70** could not be achieved using palladium-catalysed *C-H* amination with the aromatic oxazoline directing group.

2.7 Copper- and ruthenium-catalysed intermolecular *C-H* activation towards quinazolinone synthesis

Given the inability of the oxazoline to promote palladium-catalysed *C-H* activation, it was hypothesised that other transition metals would be able to functionalise the compounds of interest. As described previously, in addition to palladium, many other transition metals have now been shown to successfully catalyse *C-H* activation reactions.[76] Along with palladium, catalysts derived from copper, ruthenium and rhodium are commonly used. With this in mind, it was decided to first of all try copper and ruthenium *C-H* amination conditions upon the oxazoline substrate.

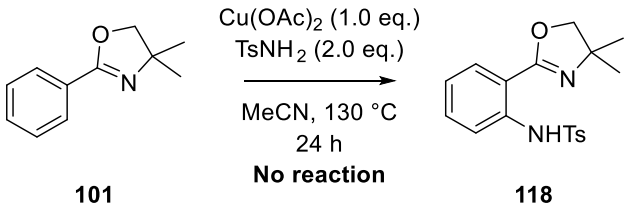
C-H amination *via* the use of copper was first reported in 2006 by Jin-Quan Yu.[114] Using a stoichiometric amount of copper (II) acetate, functionalisation of 2-phenylpyridine **85** was achieved using *p*-toluenesulfonamide in a good yield of 74%. Only this example of an amide was reported in the publication, however a range of other nucleophiles were shown such as CN, OH and Br.



Scheme 65 – Stoichiometric Cu *C-H* amination with 2-phenylpyridine

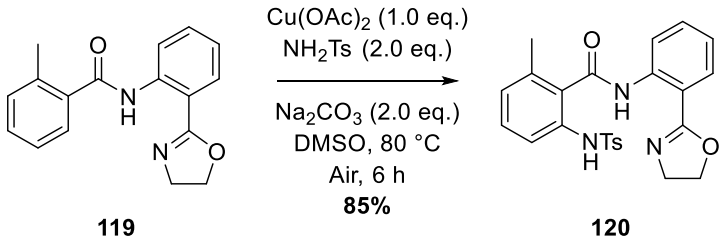
Repetition of the exact literature conditions, led to only a poor yield of 11% of **86** being obtained (*scheme 65*). Subjection of the reaction conditions upon the unsubstituted

oxazoline substrate **101**, as shown in *scheme 66*, unfortunately only led to the recovery of the starting material.



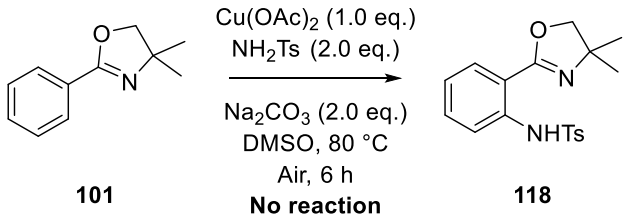
Scheme 66 – Stochiometric Cu *C-H* amiantion with the oxazoline

More recently, Yu also reported Cu(II)-mediated *C-H* amidation and amination conditions *via* the use of an alternative directing group.[99] As shown in *scheme 67*, a amide-tethered oxazoline directing group **119** is successfully used to introduce a range of amides and anilines in good to excellent yield. The methodology was also shown to be applicable to amidation of heterocycles.



Scheme 67 – Yu's Cu *C-H* amidation with amide-tethered oxazoline directing group

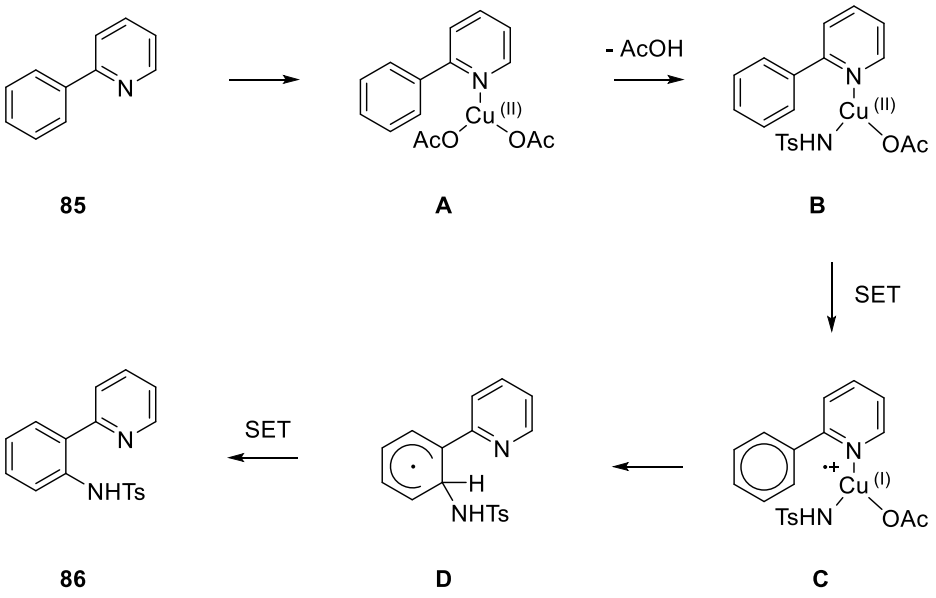
Despite the attractive nature of the reaction conditions, their application to oxazoline substrate **101**, unfortunately only led to recovery of the starting material, *scheme 68*.



Scheme 68 – Alternative Cu *C-H* amidation conditions with the oxazoline

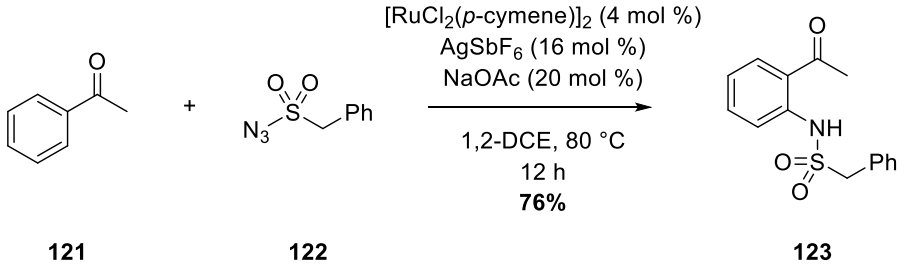
Both sets of the Cu-promoted *C-H* amidation conditions failed to deliver any conversion of the oxazoline **101** starting material. One potential reason for this could be due to the operation of a distinctly different mechanism. Unlike palladium, copper mediated *C-H* functionalisation reactions do not rely upon the formation of a metallacycle.[106] Instead, it is suggested that a radical-cation pathway is responsible.[114] This is shown in *scheme 69* where the amidation of 2-phenylpyridine is depicted. The initial step is co-ordination of the copper source to the pyridine **A** followed by replacement of the acetate ligand with *p*-toluenesulfonamide **B**. A single electron transfer (SET) then takes place from the aryl ring to the co-ordinated Cu(II) leading to a cation-radical intermediate **C**. Further SET leads to the product **86**. Mechanistic studies by Yu suggested that co-ordination of the Cu(II) to the

pyridine is necessary for the SET process.[114] Perhaps in the case of the oxazoline, the strength of co-ordination to the copper centre is less than that of the pyridine leading to the observed lack of reactivity.



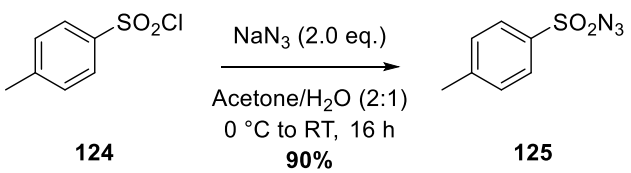
Scheme 69 – Mechanism of the Cu *C-H* amidation with *p*-toluenesulfonamide

With the use of copper also failing to functionalise the oxazoline, alternative conditions using ruthenium catalysis were sought. One interesting report of ruthenium-catalysed *C-H* amidation was shown using azides as coupling partners by Chang in 2013, as shown in *scheme 70*.[115] The methodology was shown to be applicable to a range of directing groups including aromatic ketones, benzamides and heterocyclic groups such as the pyrazole.



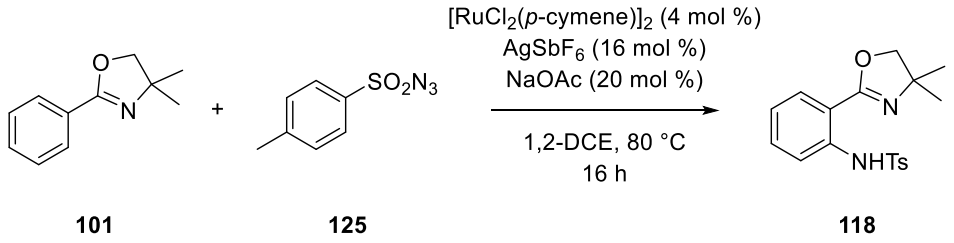
Scheme 70 – Chang's ruthenium-catalysed *C-H* amidation using azides

In order to try the ruthenium-catalysed conditions with the oxazoline substrate, the synthesis of the *p*-toluenesulfonyl azide was initially carried out. As shown in *scheme 71*, using *p*-toluenesulfonyl chloride and sodium azide led to synthesis of the desired azide **125** in an excellent yield of 90%.[116]



Scheme 71 – Synthesis of *p*-toluenesulfonyl azide

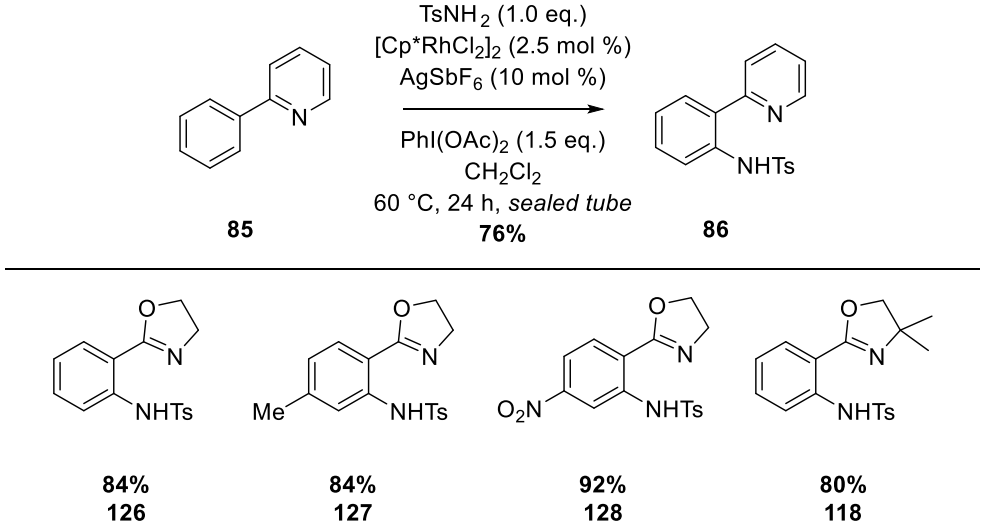
Subjecting the oxazoline substrate **101** to the reaction conditions, unfortunately only led to the recovery of the starting materials, suggesting that the oxazoline is an unsuitable directing group for ruthenium-catalysed *C-H* activation also (*scheme 72*).



Scheme 72 – Ruthenium-catalysed *C-H* amidation upon the oxazoline substrate

2.8 Rhodium-catalysed intermolecular *C-H* activation towards quinazolinone synthesis

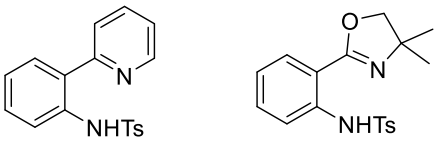
With copper and ruthenium catalysts also proving ineffective towards oxazoline functionalisation, it was decided to consider rhodium catalysis. Rhodium has become more apparent in the literature as a successful catalyst for *C-H* amination protocols in the past few years. One interesting report was shown in 2013 by Su, where catalytic Rh(III) was shown to successfully functionalise a range of substrates.[117] 2-Phenylpyridine **85** was used, but in addition four oxazoline substrates were shown to couple to *p*-toluenesulfonamide using a higher reaction temperature of 100 °C, *scheme 73*.



Scheme 73 – Su's rhodium-catalysed *C-H* amidation conditions

Intrigued by the reported reaction conditions, it was decided to try and repeat the literature using the 2-phenylpyridine **85** and the oxazoline **101**. Gratifyingly, use of the literature conditions led to amination of 2-phenylpyridine in a yield of 51%, and an initial yield of 47% with the oxazoline substrate. The yield of the oxazoline was likely affected by a challenging purification procedure, due to co-elution of the product and starting material on flash column chromatography with petroleum ether and ethyl acetate. However, purification using

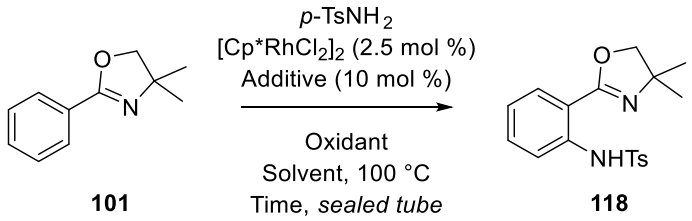
dichloromethane as the only elutent led to clean isolation of the product. When the reaction was repeated the yield of **118** was improved to 65% using the optimised purification conditions.



51% **65%**
86 **118**

Scheme 74 – Results obtained when repeating the literature conditions

With conditions in hand to form the crucial carbon-nitrogen bond required for the synthesis of the quinazolinone heterocycle, it was decided to further investigate the reaction. As the conditions described and exemplified by Su had been optimised using the pyridine directing group, it was decided that an optimisation should be investigated using the *gem*-dimethyl oxazoline directing group, *scheme 75* and *table 9*.



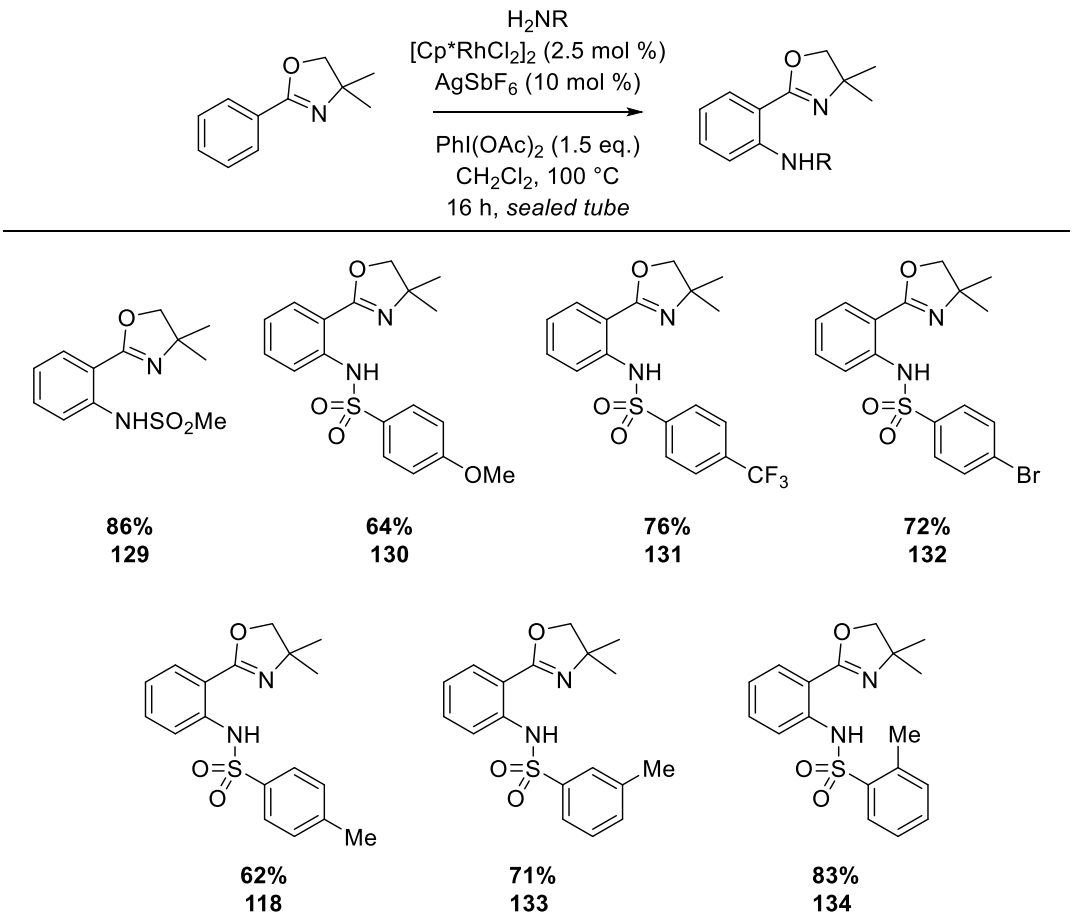
Scheme 75 – Optimisation upon the *gem*-dimethyl oxazoline directing group

Entry	Solvent	Additive	Oxidant	Oxidant eq.	Time	Result
1	CH_2Cl_2	$AgSbF_6$	$PhI(OAc)_2$	1.5	24 h	65%
2	CH_2Cl_2	$AgSbF_6$	$PhI(OAc)_2$	1.5	16 h	62%
3	1,2-DCE	$AgSbF_6$	$PhI(OAc)_2$	1.5	16 h	57%
4	1,2-DCB	$AgSbF_6$	$PhI(OAc)_2$	1.5	16 h	7%
5	α,α,α - TFT	$AgSbF_6$	$PhI(OAc)_2$	1.5	16 h	32%
6	CH_2Cl_2	$AgSbF_6$	$PhI(OAc)_2$	2.0	16 h	69%
7	CH_2Cl_2	$AgSbF_6$	$PhI(OCOCF_3)_2$	1.5	16 h	0%
8	CH_2Cl_2	AgOTs	$PhI(OAc)_2$	1.5	16 h	50%
9	CH_2Cl_2	$AgNTf_2$	$PhI(OAc)_2$	1.5	16 h	74%
10	CH_2Cl_2	-	$PhI(OAc)_2$	1.5	16 h	29%
11	CH_2Cl_2	-	$PhI(OAc)_2$	1.5	16 h	0%[a]
12	CH_2Cl_2	$AgSbF_6$	$PhI(OAc)_2$	1.5	16 h	0%[a]

Table 9 – Optimisation upon the *gem*-dimethyl oxazoline directing group. [a] Reactions performed in the absence of $[RhCp^*Cl_2]_2$

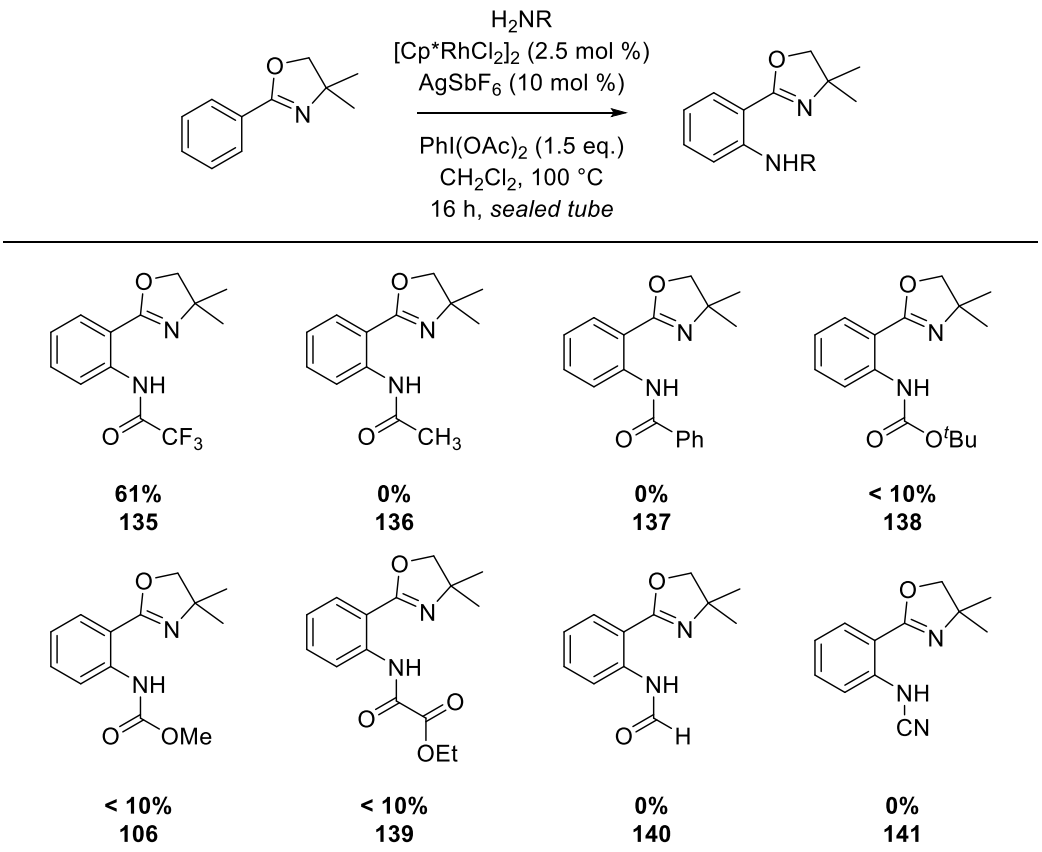
Using *p*-toluenesulfonamide and 4,4-dimethyl-2-phenyl-2-oxazoline **101** as the model substrates, various aspects of the reaction conditions were changed as shown in *scheme 75* and *table 9*. Using Su's conditions directly with $[RhCp^*Cl_2]_2$ and $AgSbF_6$ for a period of 24 hours led to a 65% yield of product (entry 1), leaving the reaction for the shorter period of 16 hours led only to a slight decrease in yield to 62% (entry 2), therefore all subsequent reactions were conducted for 16 hours. Varying the solvent of the reaction to higher boiling halogenated solvents failed to improve the result of the reaction; 1,2-dichloroethane led to a comparable yield of 57% (entry 3), whereas 1,2-dichlorobenzene and α, α, α-trifluorotoluene depleted the reaction yield (entries 4 and 5). In a different manner, increasing the equivalents of the oxidant led to a slight increase in yield to 69%, but it was felt this slight increase in yield did not warrant an extra 0.5 equivalents of oxidant (entry 6). Changing the oxidant to [bis(trifluoroacetoxy)iodo]benzene led to no observed reaction (entry 7). Switching the additive to silver *p*-toluenesulfonate led to a slightly lower yield of 50% (entry 8). However, when changing the additive to silver bis(trifluoromethyl-sulfonyl)imide, a slight increase in yield to 74% was noted (entry 9), despite this the original additive ($AgSbF_6$) was chosen due to the high commercial expense of the $AgNTf_2$ additive compared to that of $AgSbF_6$. Finally control reactions were performed to verify the catalytic nature of the conditions. In the absence of any silver additive the reaction proceeded, albeit in a much lower yield affording only 29% of product (entry 10). In the absence of the rhodium catalyst, both with and without silver additive, no reaction occurred (entries 11 and 12). Despite all attempts, Su's conditions were found to be optimial for the desired transformation.

Following on from the optimisation studies described above, the amide sources which could successfully participate in the reaction conditions were explored. As shown in *schemes 76* and *77*, a wide range of amide sources were investigated. Initially a range of sulfonamides, which are more commonly reported to be successful in the general literature, were considered (*scheme 76*). It was observed that both alkyl and aryl sulfonamides could be used under the reaction conditions. Methyl sulfonamide was found to couple in an excellent yield of 86% **129**. Aryl sulfonamides with both electron withdrawing and electron donating substituents were tolerated in the reaction in good yields, in addition aryl sulfonamides substituted in the *ortho*-, *meta*- and *para*-positions were also found to be applicable.



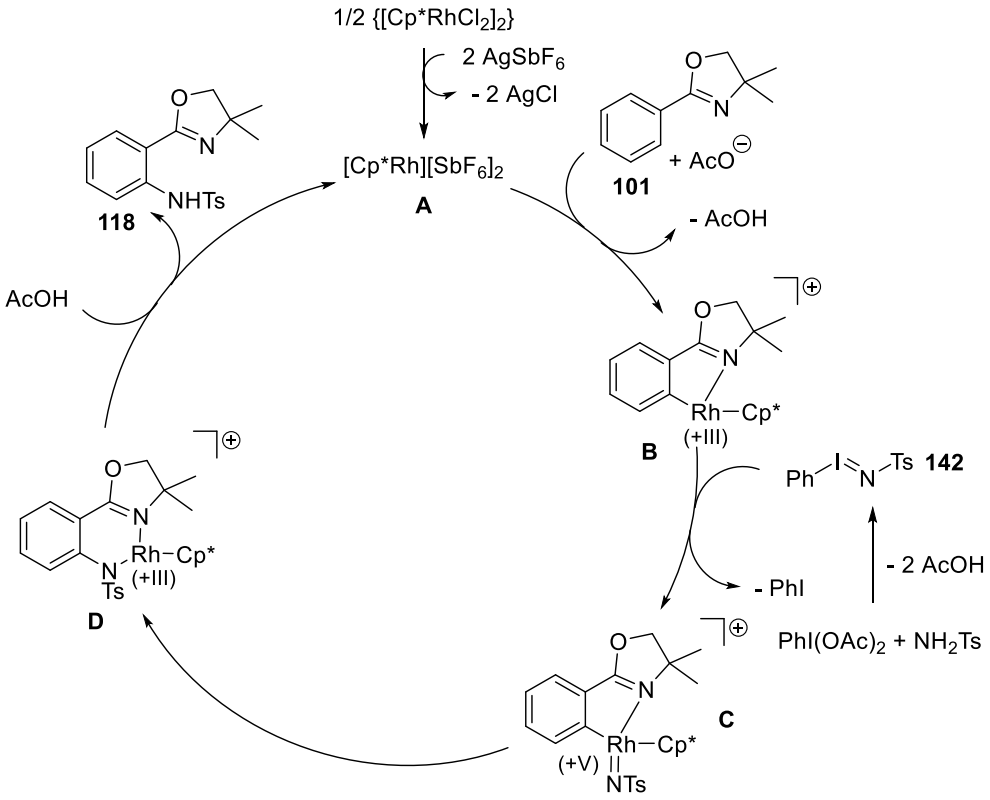
Scheme 76 – Sulfonamide scope

Following on from the success of a variety of sulfonamides participating in the *C-H* amidation, alternative amide sources were considered. Particular focus was given to amides which could be readily deprotected to the corresponding amine. Whilst the sulfonamides were proving to be efficient substrates, the deprotection of such substrates typically requires very harsh conditions and would potentially add limitations to the proposed quinazolinone synthetic strategy.[118] As shown in *scheme 77* a range of alternative amide sources were investigated. Using trifluoroacetamide, which has been reported to couple with the 2-phenylpyridine by Yu, Su and others, gratifyingly gave a 61% yield with the oxazoline substrate **135**.[117] However, when trying to extend the scope to amides including acetamide, benzamide, formamide and cyanamide no reaction was observed. In addition, attempting to use both methyl and *tert*-butyl carbamate and ethyl oxamate led to poor yields, less than 10% of the desired product was obtained in each case. Variation of the reaction conditions was attempted to help incorporate the unreactive amide sources; however no significant improvement was noticed.



Scheme 77 – Amide scope

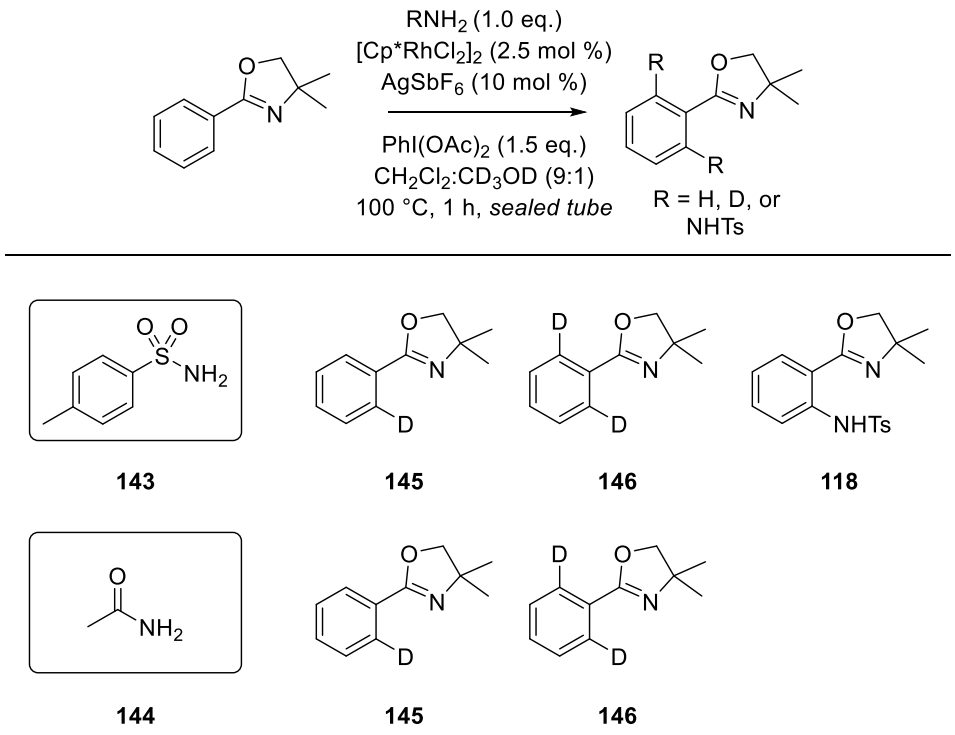
With a handful of different amidation substrates explored, it was contemplated as to why some of the amide and carbamate coupling partners were delivering recovery of the starting material, or only very low conversion to product. To further understand this observation, the reaction mechanism was considered, *scheme 78*.



Scheme 78 – Rhodium-catalysed *C-H* amination of aryl oxazoline with external oxidant

The reaction mechanism initially proceeds *via* formation of the active catalytic species **A**. Reaction of the oxazoline substrate **101** with the rhodium catalyst **A** leads to formation of a rhodacyclic intermediate **B**, which most likely occurs *via* a CMD process. Reaction of the amide with the hypervalent iodine reagent affords iminoiodane **142**, which following co-ordination to rhodium yields the rhodium (V) species **C**. Insertion of the nitrogen source then occurs to give intermediate **D**. Acetic acid then protonates the compound to deliver the product **118**, and re-generate the active catalytic species **A**.

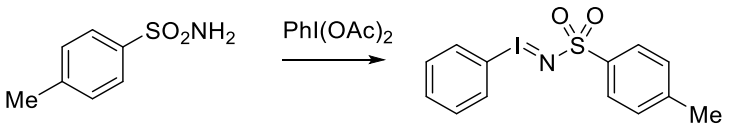
To probe if the problem with the amide and carbamate sources were to do with formation of the rhodacycle or the co-ordination and insertion of the amide source deuterium labelling experiments were run. As depicted in *scheme 79* below, reactions were conducted in the presence of deuterated methanol.



Scheme 79 – Deuterium labelling experiments

When deuterated methanol was added to the rhodium-catalysed coupling of *p*-toluenesulfonamide **143**, LCMS analysis suggested that deuterium incorporation had occurred upon the oxazoline substrate **101**. Despite unsuccessful attempts to isolate the deuterated products *via* column chromatography, from similar work done by Su with the 2-phenylpyridine substrate it was speculated that the most likely sites for deuterium incorporaton were in the two *ortho*-positions, **145** and **146**.[117] In addition, the product **118** was also observed *via* LCMS analysis. These observations showed that in the case of *p*-toluenesulfonamide the rhodacycle was forming, and co-ordination and insertion of the amide source was occuring. However, when deuterated methanol was added to the reaction with acetamide **144**, LCMS showed the deuterium incorporation had again occurred with the oxazoline substrate, **145** and **146**. In this case, it appeared that rhodacycle formation proceeded as planned, but that co-ordination and insertion of the amide substrates did not proceed.

As shown in the reaction mechanism above in *scheme 78*, the reaction is suggested to proceed *via* the formation of a nitrene species.[117] Nitrenes derived from sulfonamides are known in the general literature, and they are generated by reaction between a sulfonamide **143** and the (diacetoxy)iodobenzene oxidant, as shown in *scheme 80*.[119] The formation of the iminoiodane **142** was also shown in Su's report, and it was documented that subjection of the reaction conditions to the substrate **142** did lead to successful product formation.[117]

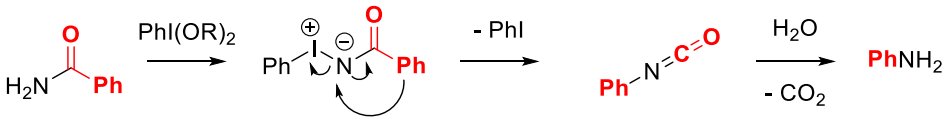


143 **142**

Scheme 80 – Formation of the iminoiodane **142**

If the reaction proceeded *via* the nitrene such as **142**, it was possible that substrates which were failing to react or only reacting in low conversion were unable to form the necessary iminoiodane. After an extensive search of the literature, a variety of iminoiodanes were found in which the amide partner was either a sulfonamide or trifluoroacetamide.[120] However, any other amides, such as benzamides or acetamide derivatives, were not found as iminoiodanes. Any reports of them in the literature were from a theoretical perspective only, alluding to their possible instability, or the inability to prepare them *via* known methodology.

Further analysis of the literature led to the finding of a documented Hoffmann rearrangement between benzamide **147** and hypervalent iodine reagents.[121] If the iminoiodane **148** undergoes Hoffmann rearrangement as depicted in *scheme 81*, the corresponding isocyanate **149** would be generated that would ultimately yield the aniline **150**, this would in theory shut down the reaction system with all potential amide source consumed in this unwanted side reaction.

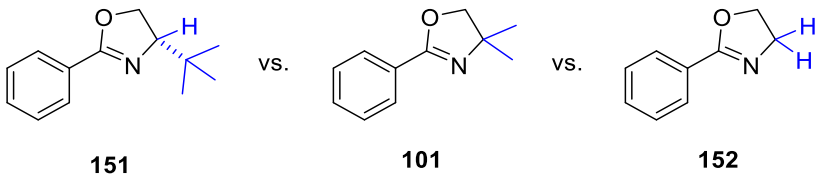


147 **148** **149** **150**

Scheme 81 – Hoffmann rearrangement

Despite the discovery that the reaction conditions were limiting the scope of the transformation, the range of sulfonamides and the trifluoroacetamide were attractive features of the conditions. With a further understanding of the reaction mechanism in place, it was decided to exemplify the reaction further, and to use the conditions as a key step in the generation of quinazolinone heterocycles, in particular that of the halofuginone quinazolinone.

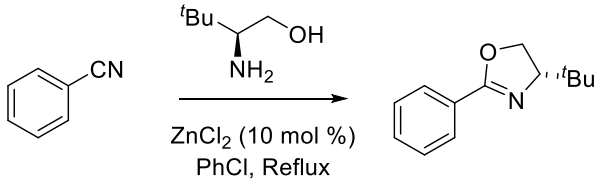
After reconsidering results from the investigation into amides which could be utilised by the conditions, it was considered if the *gem*-dimethyl moiety of the oxazoline could play a role in the *C-H* amidation efficiency.



151 **101** **152**

Scheme 82 – Plausible steric effects

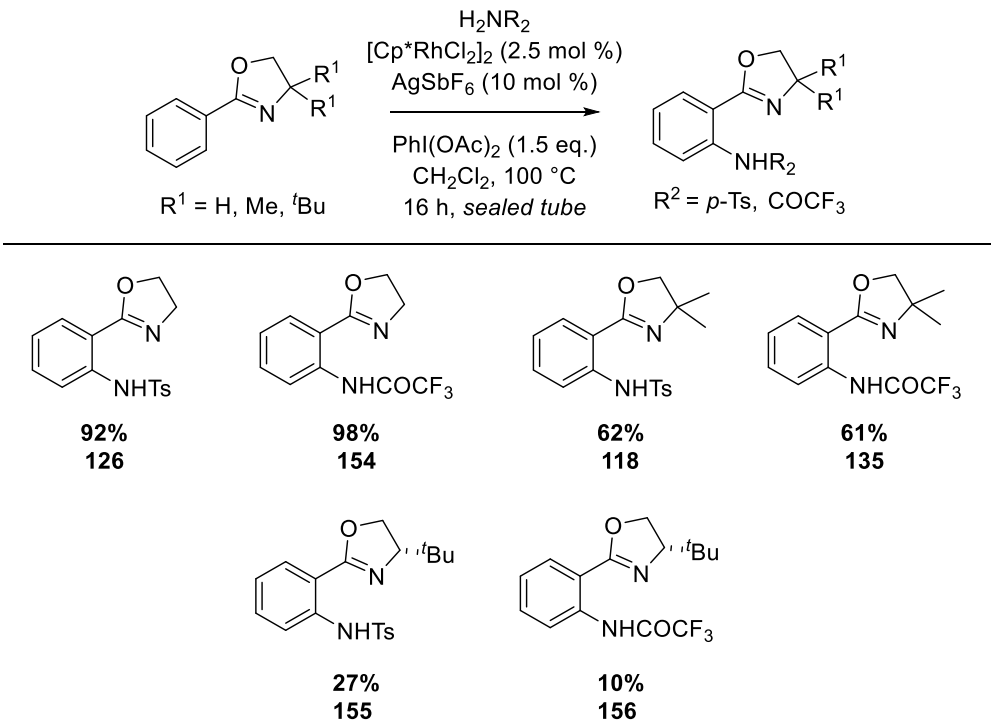
In order to establish if the *gem*-dimethyl unit was having an effect, comparative reactions were run with an example of a commercially avaliable un-substituted oxazoline **152** and also a *tert*-butyl substituted example **151**. The *tert*-butyl substituted oxazoline was prepared from reaction of benzonitrile **153** and L-*tert*-leucinol with catalytic $ZnCl_2$ in a moderate yield of 50%, *scheme 83.*[122]



153 **151**

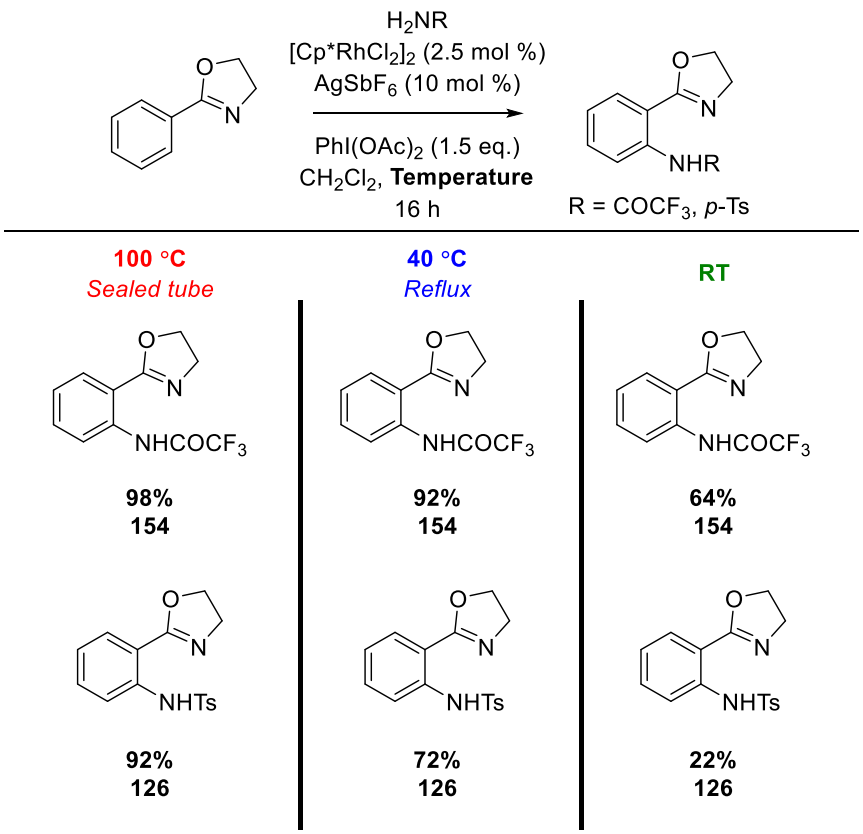
Scheme 83 – Preparation of *tert*-butyl substitued oxazoline

Interestingly, as shown in *scheme 84*, the substituents on the oxazoline were found to have an effect on the overall result of the reaction. As previously shown, the two *gem*-dimethyl substituted oxazolines proceeded to give good yields with the amide sources of *p*-toluenesulfonamide **118** and trifluoroacetamide **135**, 62% and 61% respectively. Most pleasingly, by decreasing the steric bulk of the oxazoline to the un-substituted variant an increase in yield with both amides was observed. This was most striking in the case of the trifluoroacetamide **154** which was afforded in an almost quantitative yield of 98%. Furthermore, when increasing the steric bulk of the oxazoline to the *tert*-butyl substituent it was found the reaction only proceeded in 27% yield in the case of *p*-toluenesulfonamide **155**, and 10% with the trifluoroacetamide **156**. From these results it can be concluded that the oxazoline substituents must be hindering the reaction to an extent, either *via* sluggish formation of the required rhodacycle or preventing co-ordination of the iminoiodane species which eventually leads to the key nitrogen insertion. From here on, it was decided to focus upon the un-substituted oxazoline as to aid the overall yield of the *C-H* amidation procedure.



Scheme 84 – Comparative experiments with various substituted oxazolines

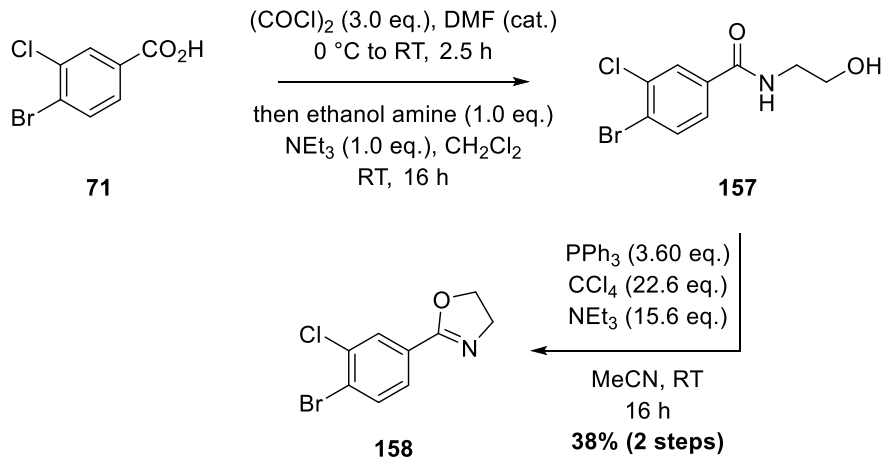
An additional aspect of the process which had not yet been considered was that of the reaction temperature. Typically *C-H* activation protocols, *C-H* amidation procedures especially, require reaction temperatures of 100 °C as a minimum, but keen to move away from sealed tube apparatus, particularly for scale up purposes, it was considered to conduct the reaction at lower temperatures. Using the un-substituted parent oxazoline **152** with both trifluoroacetamide and *p*-toluenesulfonamide comparative experiments were conducted at 100 °C in sealed tube apparatus, 40 °C in traditional reflux apparatus and at room temperature, *scheme 85*. Most surprisingly, reactivity was observed in all cases. Pleasingly, diminishing the temperature to 40 °C in more conventional reflux conditions led to only a slight decrease in yield. For example, when using trifluoroacetamide as the amide source, the oxazoline substrate **152** underwent amidation smoothly in an excellent yield of 92% versus 98% at the more elevated temperature. Moreover, reactions conducted at room temperature also afforded the desired product; trifluoroacetmaide gave a good yield of 64%, whereas in the case of *p*-toluenesulfonamide, the yield was somewhat lower at 22%. The above results contradict those reported by Su who stated that a temperature of 100 °C were required to afford reactivity upon the oxazoline substrates.[117] In addition, the results support the oxazoline and trifluoroacetamide's apparent unique combination of reactivity. As can be seen below the trifluoroacetamide appears supperior to that of the *p*-toluenesulfonamide.



Scheme 85 – Temperature studies

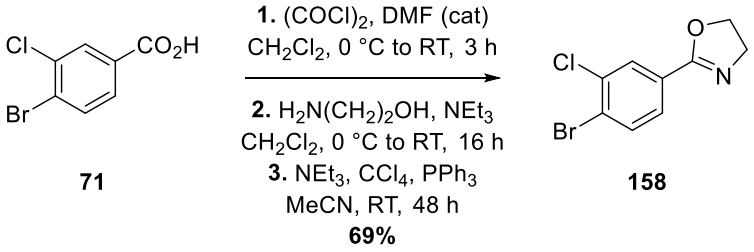
With all optimisation studies conducted, the optimal reaction system for rhodium-catalysed carbon-nitrogen bond formation was found to be *via* use of the parent un-substituted oxazoline directing group and the trifluoroacetamide amide source at a reaction temperature of 40 °C. Prior to the investigation of scope of the amidation conditions, a small library of functionalised un-substituted oxazolines were prepared. Preliminary attempts at synthesising the un-substituted oxazoline substrates were conducted upon the halofuginone substrate.

Initial attempts to prepare the substrate using the earlier optimised conditions going through an anhydride intermediate with an amine source of ethanolamine failed to lead to complete conversion to the desired product. Isolation of inseperable mixtures of the amide and anhydride were consistently observed. Attempts to make the amide *via* an acid chloride intermediate were proving more successful, however the amide of interest **157** was found to be very insoluble in many organic solvents and was difficult to purify, *scheme 86*. However, subjection of the crude amide **157** to the conditions previously used for cyclisation did lead to the formation of product, albeit in a 38% yield.



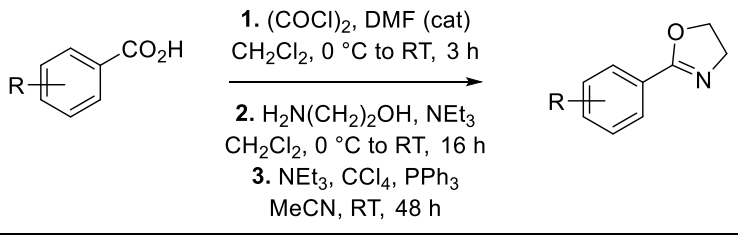
Scheme 86 – Attempts towards the synthesis of the un-substituted halofuginone oxazoline

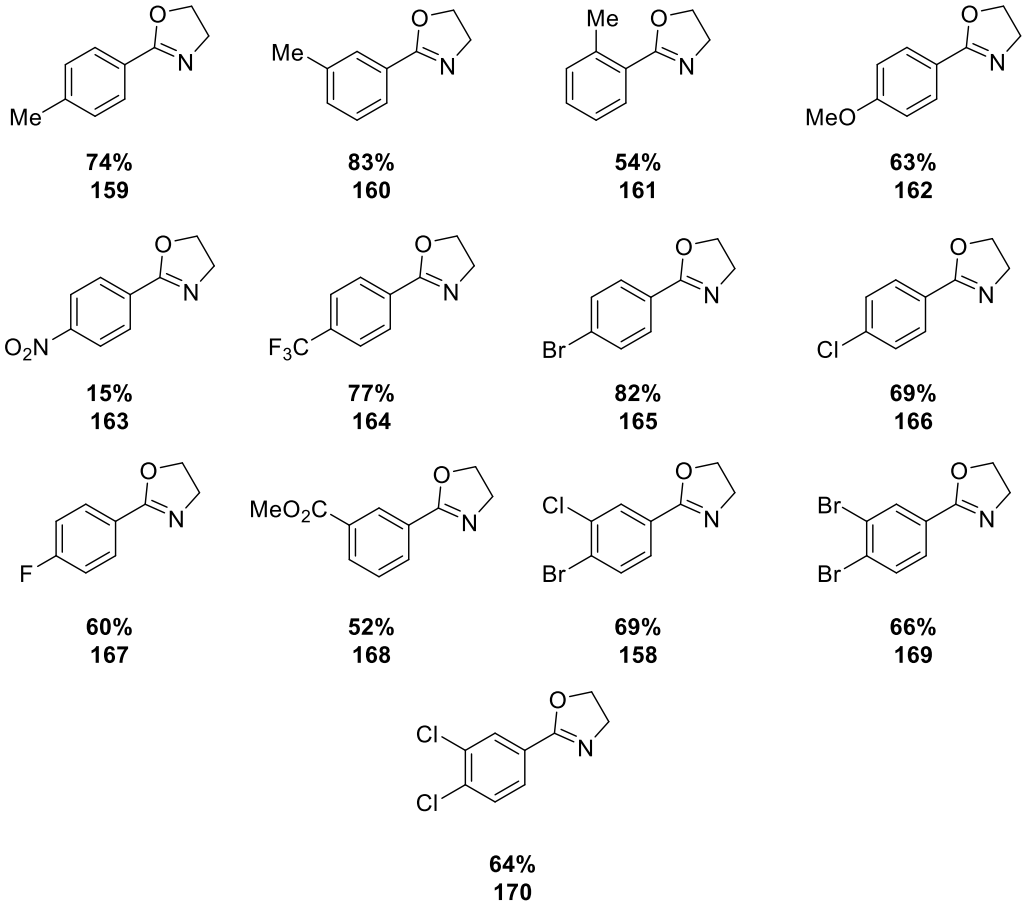
Gratifyingly, attempting a one pot reaction and avoiding work-up following amidation starting from the parent benzoic acid **71** and avoiding work-up following amidation, the oxazoline could be afforded in a good overall yield of 69%, *scheme 87*.



Scheme 87 – One-pot reaction of the un-substituted halofuginone oxazoline

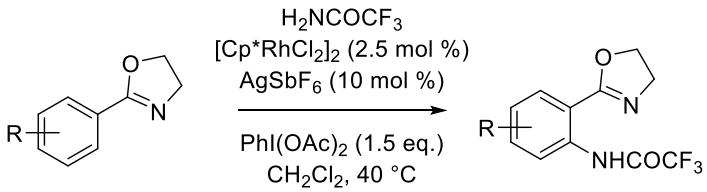
Using the above one-pot procedure a selection of functionalised oxazoline substrates were prepared successfully, *scheme 88*. As can be seen a variety of *ortho*-, *meta*- and *para*-substituted substrates were synthesised, in addition to substrates with different electronic properties. Cases to particularly note are those of the *para*-methoxy **162** and the *para*-nitro **163**, both of which co-eluted with the triphenyl phosphine oxide by-product during purification. It was found an aqueous acid wash during work-up aided their isolation, although in the case of the nitro substituted aromatic **163** the yield is very poor even after this isolation procedure. In the case of the *meta*-methyl ester example **168**, it was noted that thionyl chloride afforded cleaner reactivity than that of oxalyl chloride and yielded the oxazoline in 52% after the one-pot procedure.

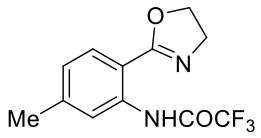




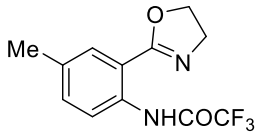
Scheme 88 – Synthesis of a variety of functionalised oxazolines

With a selection of substrates in hand, the oxazolines were subjected to the rhodium-catalysed direct amidation conditions, *scheme 89*. In all cases *C-H* amidation proceeded smoothly and efficiently to afford the amidated products in good to excellent yields. All steric and electronic factors of the substrates examined were well tolerated. In addition, only mono-amidation was observed upon each substrate and insertion was always found to occur into the least sterically hindered position. Most pleasingly, it was found the halofuginone substrate underwent the reaction protocol to afford the quinazolinone precursor in a very good yield of 76%.[123]

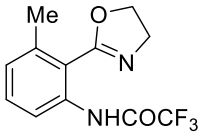




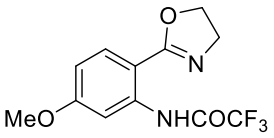
84%
171



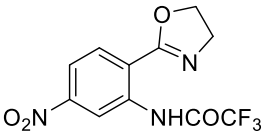
72%
172



74%
173



100%
174



100%
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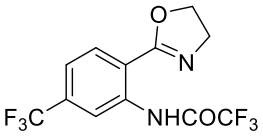

100%
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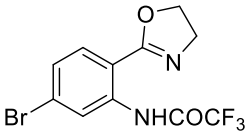
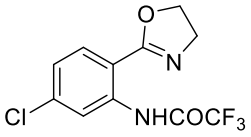
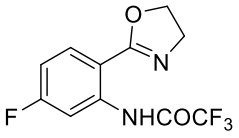


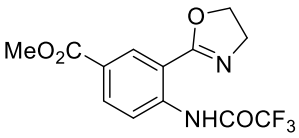
96%
177



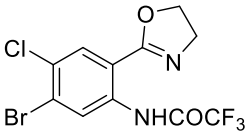
92%
178



97%
179



77%
180



72%
181

95%
182

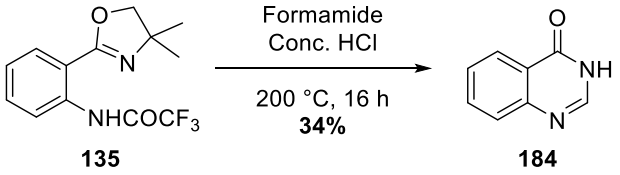
75%
183

Scheme 89 – C-H Amidation scope

Chapter 3: Application and Utility of the *C-H* Amidation Strategy Towards the Synthesis of Quinazolinones

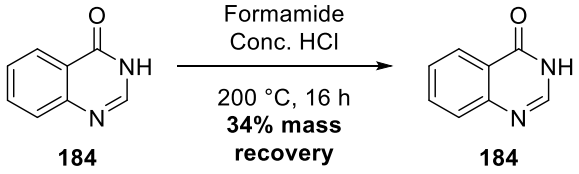
3.1 Cyclisation to the quinazolinone

With a selection of functionalised oxazoline scaffolds in hand, cyclisation to the quinazolinone heterocycle was considered. Initial attempts to implement this strategy involved treatment of substrate **135** with excesses hydrochloric acid and formamide. It was envisaged that the deprotection of both trifluoroacetamide and oxazoline functionalities simultaneously followed by a condensation reaction with formamide would afford the corresponding quinazolinone. A moderate yield of 34% was obtained of the desired quinazolinone scaffold through employment of this strategy (*scheme 90*).



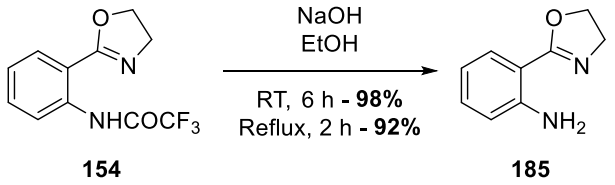
Scheme 90 – Initial result of quinazolinone formation

Despite isolation of the desired heterocycle, and a proof of principle, attempts to improve upon the overall outcome were unsuccessful. Moreover, subjection of the target material to the reaction conditions led to incomplete mass recovery, suggesting the product was not stable to the relatively harsh reaction conditions (*scheme 91*).



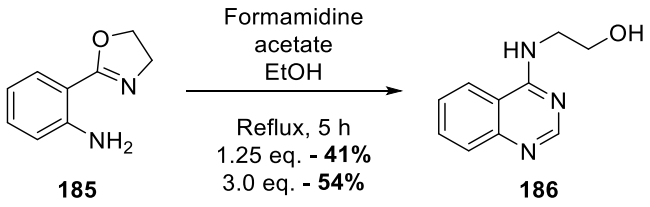
Scheme 91 – Control reaction with quinazolinone

Given the harsh conditions leading to the low mass recovery of the target material, a milder methodology was sought. It was hoped that considering the cyclisation in a stepwise manner would lead to cleaner and improved conversion to the heterocycle of interest. Utilising this strategy, deprotection of the trifluoroacetamide was initially explored. Gratifyingly, treatment of substrate **154** with sodium hydroxide in ethanol afforded the corresponding aniline in excellent yield (*scheme 92*).[124] It was found that an excess of hydroxide was required to avoid sluggish reactivity. In addition, heating the reaction mixture at reflux as opposed to stirring at room temperature shortened the reaction time from 6 h to 2 h.



Scheme 92 – Deprotection of trifluoroacetamide functionality

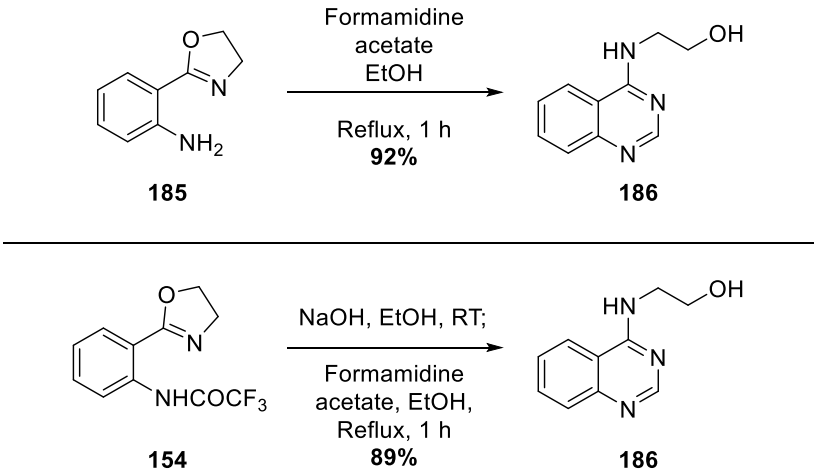
With the required aniline substrate in hand, the next step of the sequence was considered. Previous results indicated that the use of excess strong acid, along with the potential decomposition of formamide at high temperatures to CO and NH_3 were leading to product decomposition.[125] With this in mind, it was hoped the use of milder acid and a formamide derivative could avoid potential product degradation. Formamidine acetate has been previously shown to be a successful partner for the synthesis of quinazolinones with 2-aminobenzamides.[126] Intrigued by the low excess of reagent required, short reaction time and mild temperatures required in comparison to previous methods, the reaction conditions were attempted on substrate **185**. Most interestingly, complete conversion of the starting material was observed when using 1.25 equivalents of formamidine acetate in refluxing ethanol. However, the quinazolinone was not isolated. All characterisation analysis was suggestive of ethanolamine functionalised quinazoline **186** being the major product from the reaction, which was isolated in a moderate yield of 41% (*scheme 93*). Increasing the equivalents of formamidine acetate from 1.25 to 3.0 gave a slight increase in yield to 54%.



Scheme 93 – Formamidine acetate synthesis of quinazolinone

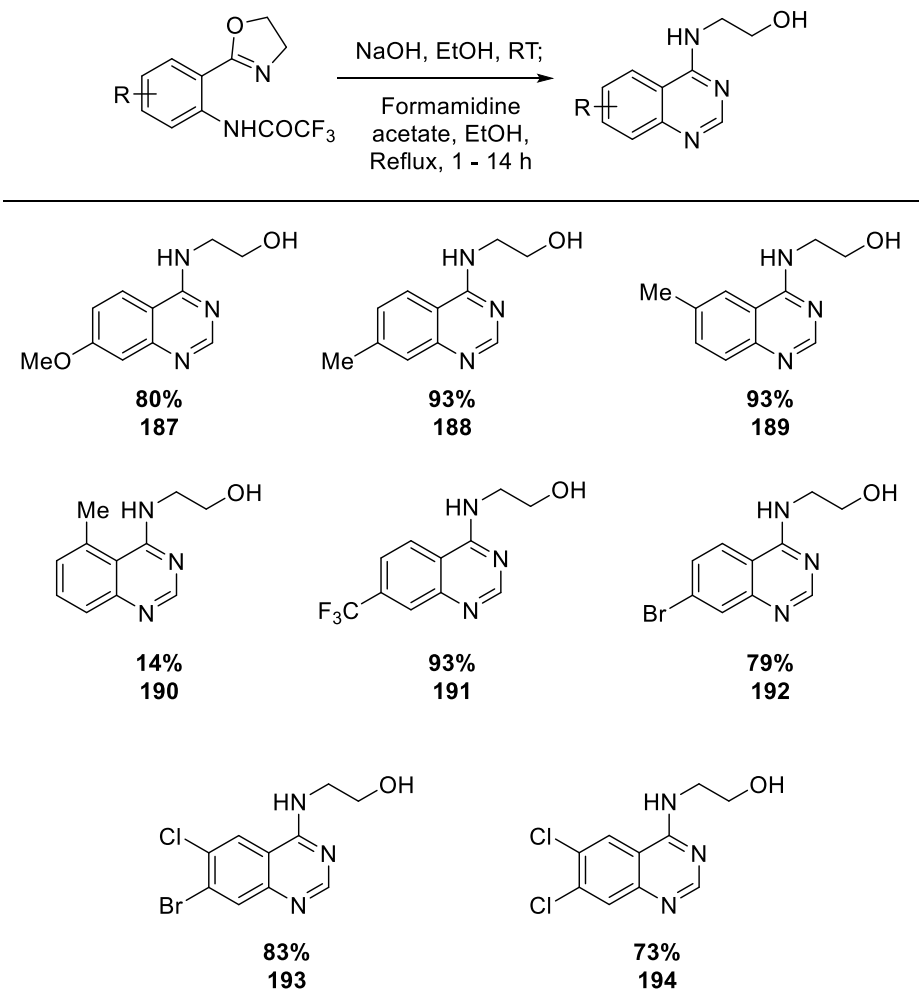
At this stage isolation of the quinazoline scaffold was carried out after aqueous work up. As full conversion was observed by TLC analysis of the reaction mixture, it was believed that the low yield was arising due to the products significant water solubility. In order to avoid an aqueous work up as means of isolation, an alternative protocol was attempted. Upon complete conversion by TLC analysis, after 1 hour only, the reaction was allowed to cool to room temperature and the mixture directly dry-loaded on to silica gel. Pleasingly, purification of the dry-loaded material by flash column chromatography resulted in an excellent yield of 92% of the quinazoline heterocycle (*scheme 94*). When the procedure was instead applied to trifluoroacetamide substrate **154,** deprotection followed by aqueous work up and subjection

of the crude material to the optimum cyclisation conditions and isolation by dry-loading upon silica gel afforded an excellent yield of 89% over the two steps as depicted in *scheme 94*.



Scheme 94 – Alternative isolation results

Pleased that the parent *C-H* amidated product was a viable precursor to the quinazoline scaffold, an investigation of scope was then carried out (*scheme 95*). Substrates previously synthesised by the rhodium-catalysed *ortho C-H* amidation methodology were subjected to the optimum deprotection and cyclisation strategy. Gratifyingly, methoxy-substituted analogue gave rise to an excellent yield of 80% of the cyclised material **187**. Similarly, methyl-substituted examples **188** and **189** were also afforded in excellent yield. Interestingly, synthesis of 5-methyl substituted quinazoline **190** was remarkably low yielding in comparison, affording only 14% of the desired material. In this instance the recovery of the trifluoroacetamide starting material was also observed. Switching to the electron withdrawing examples, it was found that a longer period of time was required for full conversion to the cyclised heterocycle to be achieved, typically 14 hours opposed to 1 hour with the electron donating examples. Despite the extended cyclisation time frame, both trifluoromethyl- **191** and bromo-substituted **192** examples were found to be applicable to the reaction conditions. Delightfully, the further functionalised examples of the halofuginone precursor and analogous dichloro-substituted example were successful under the reaction conditions affording the corresponding quinazolines, **193** and **194** in 83% and 73%.[123]



Scheme 95 – Scope of quinazoline synthesis

At this stage, there was a potential ambiguity as to the nature of the amino alcohol chain in the structure. Specifically, the heteroaromatic ring could be *N*- or *O*-linked to the amino alcohol chain, and this was not easy to discern by NMR spectroscopy. Pleasingly however, 7-methoxy-substituted quinazoline **187** was found to undergo slow recrystallisation from DMF to allow for structural confirmation by X-ray crystallography. As can be seen in *figure 13*, the amino alcohol chain is in the open form and appended to the quinazoline *via* the nitrogen atom.

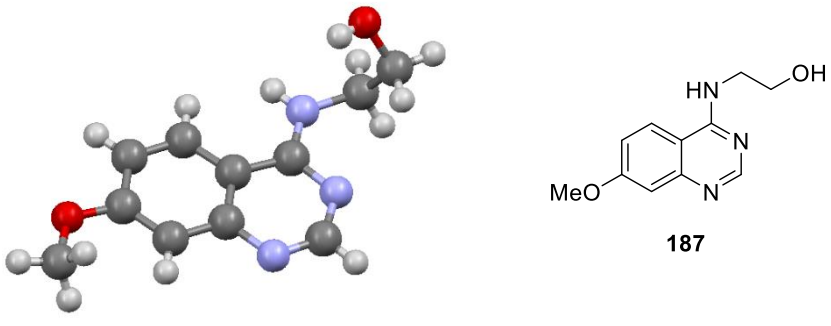
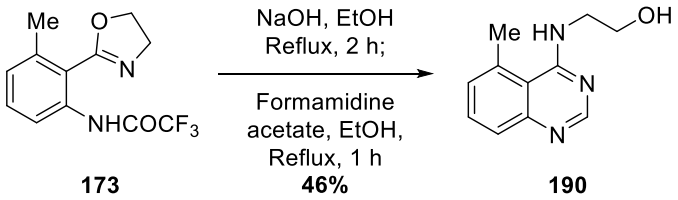


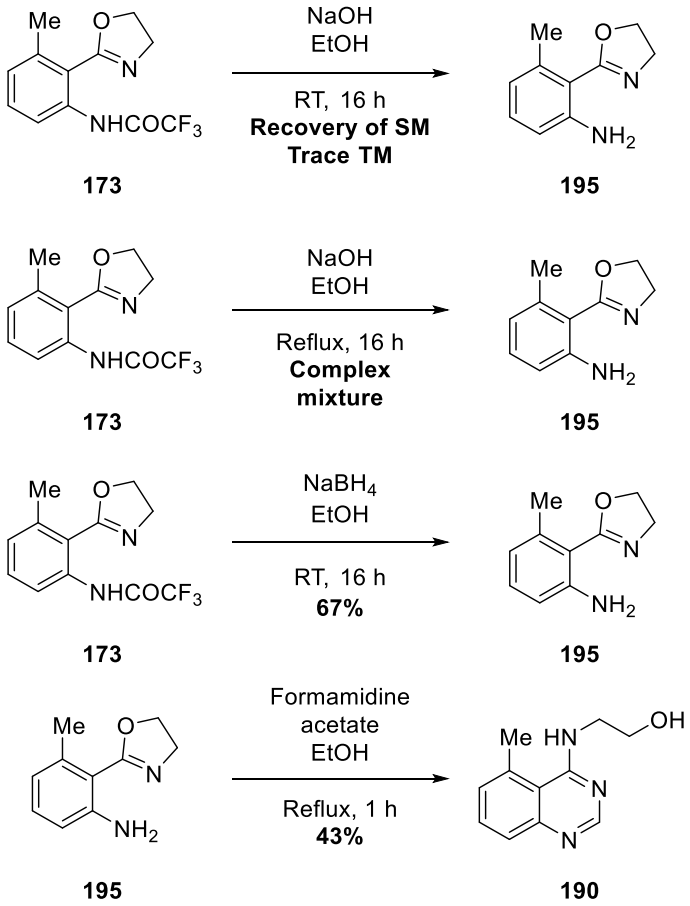
Figure 13 – X-Ray crystal structure of **187**

Having explored the scope of the quinazoline forming methodology, the low yield obtained with methyl substituted analogue **190** was further considered. Given the use of the optimum conditions led to only a 14% yield of the desired quinazoline **190**, and a 67% yield of recovered trifluoroacetamide **173** it was assumed the low yield was arising as a result of incomplete deprotection. Alternatively, the deprotection step of the sequence was performed at reflux for 2 h - when the crude mixture was subjected to the cyclisation conditions an improved yield of 46% of the quinazoline was obtained (*scheme 95*).



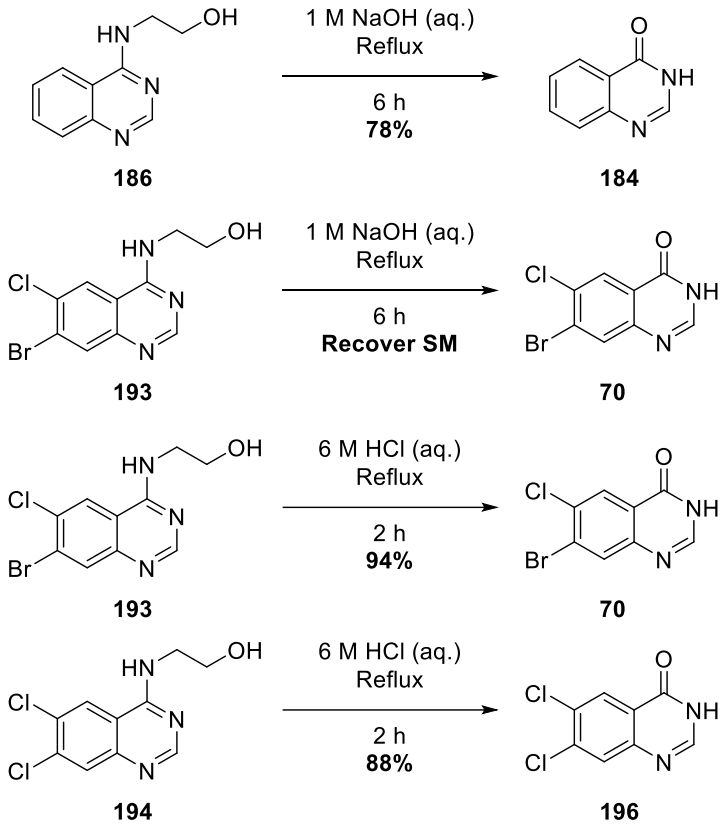
Scheme 95 – Further investigation with substrate **173**

In order to understand the potential challenges in this reaction more clearly, it was decided to perform the transformation in a stepwise manner. When taking substrate **173** under the standard deprotection conditions for an extended time period of 16 h, analysis of the crude reaction mixture suggested mainly the recovery of the starting material and only trace conversion to the desired product (*scheme 96*). Performing the same reaction except at reflux for 16 h unfortunately led only to the observation of a complex mixture (*scheme 96*). The results confirmed that the *ortho*-methyl substituent hinders hydrolysis of the trifluoroacetamide by sodium hydroxide in ethanol. Alternative conditions were attempted to hydrolyse the amide. Treatment of substrate **173** with sodium borohydride in ethanol pleasingly led to an improved deprotection yield of 67% (*scheme 96*).[127] Following on from this result, cyclisation was considered. Unfortunately, subjecting substrate **195** to the standard conditions led only to an isolated yield of 43% of the quinazoline substrate **190** (*scheme 96*). These results indicated that both the hydrolysis and cyclisation reactons are impeded by the inclusion of substituents adjacent to the oxazoline. Despite all attempts to enhance the yield of the reaction in this case, the best isolated yield remained at 46% over both the deprotection and cyclisation steps.



Scheme 96 – Stepwise investigations with substrate **173**

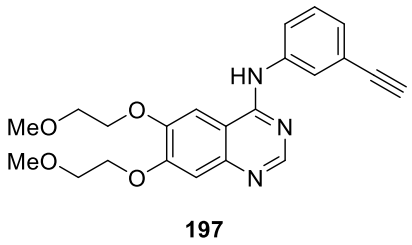
With methodology in hand to access highly-functionalised quinazoline scaffolds, conversion of these valuable intermediates to quinazolinones was next considered. Utilising conditions from the literature it was found that the amino alcohol chain of the parent substrate **186** could be readily cleaved under basic conditions to afford quinazolinone **184** in a good yield of 78% (*scheme 97*).[128] Interestingly, when using the same conditions on the halofuginone quinazolinone precursor **193** only recovery of the starting material was observed. This lack of reactivity was attributed to the apparent insolubility of substrate **193** in basic media. Most gratifyingly, when substrate **193** was instead subjected to acidic cleavage conditions, refluxing 6 M HCl (aq.) for a period of 2 hours, complete conversion to the quinazolinone was observed (*scheme 97*). An excellent yield of 94% of the halofuginone quinazolinone **70** was isolated by simple means of basification and filtration upon cooling the reaction to room temperature.[123] Pleasingly, application of the same acidic cleavage conditions to dichloro-substituted analogue **194** also afforded the corresponding quinazolinone **196** in a very good yield of 88% (*scheme 97*).



Scheme 97 – Cleavage of amino alcohol chain

3.2 Application and utility of strategy - Synthesis of Erlotinib

Erlotinib (Tarceva®), the reversible tyrosine kinase inhibitor, is a marketed pharmaceutical used for the treatment of pancreatic and non-small cell lung cancer, *figure 14*.[129] With a synthetic strategy in hand to rapidly access highly-functionalised quinazoline scaffolds, it was decided to apply the developed synthetic methodology towards the total synthesis of the biologically important motif, Erlotinib **197**.

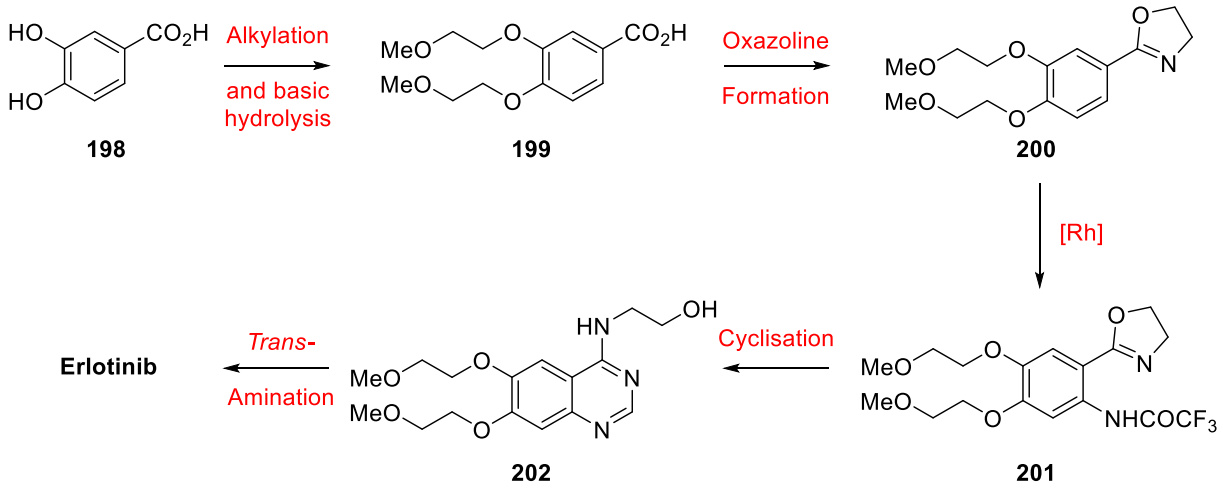


197

Figure 14 – Erlotinib (Tarceva®)

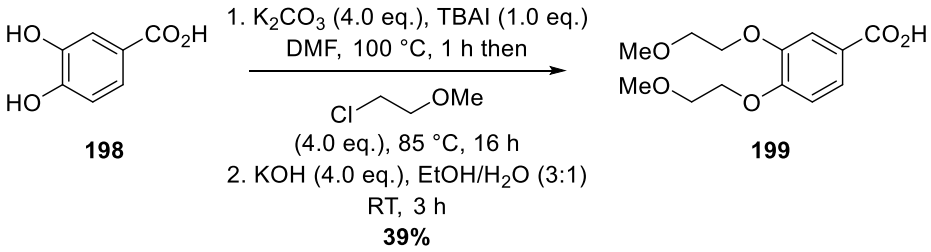
A hypothesised synthetic strategy towards the target is summarised below in *scheme 98*. The sequence begins *via* alkylation/hydrolysis of 3,4-dihydroxybenzoic acid **198** to afford the poly-ether functionalised benzoic acid **199**. Oxazoline formation under standard conditions previously discussed would afford the necessary substrate **200** for the *C-H* amidation

chemistry. Following insertion and subsequent cyclisation intermediate **202** would be afforded, in which a *trans*-amination reaction was envisaged to afford the final molecule.



Scheme 98 – Proposed synthetic strategy

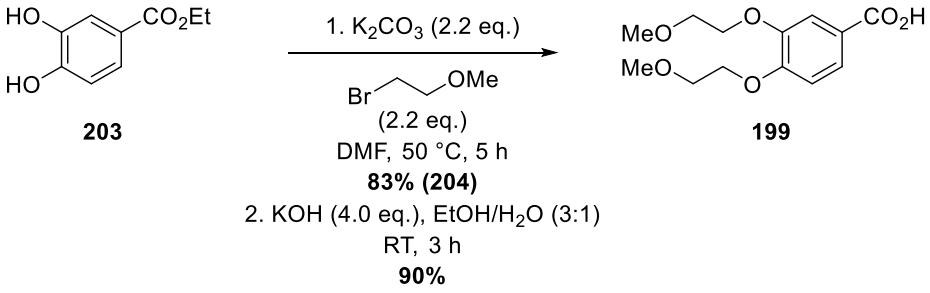
Preliminary work began upon the generation of functionalised benzoic acid **199**. Literature methodology by Asgari and co-workers shown in *scheme 99* was initially adopted.[130] The methodology involved a 3 stage process. The substrate 3,4-dihydroxybenzoic acid **198** was subjected to potassium carbonate and TBAI in DMF at 100 °C for 1 h, 2-chloroethyl methyl ether was then added after cooling to 50 °C. The mixture was then heated at 85 °C for a period of 16 h, which was followed by subsequent basic hydrolysis with potassium hydroxide in an ethanol/water mix. Despite the reported yield of 99%, only a 39% yield was obtained in our hands following the exact protocol. Attempts to repeat and scale up the alkylation/hydrolysis methodology led only to unclean mixtures of the desired product, primarily contaminated with TBAI. Attempts to replace the iodide source with potassium iodide led only to impure isolated samples of the desired product.



Scheme 99 – Asgari's methodology for the formation of **199**

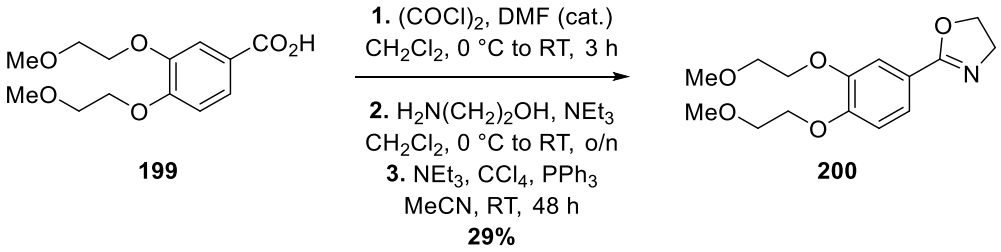
An alternative means of synthesis of the necessary benzoic acid **199** was reported by Löwe in 2008.[131] Instead of starting from 3,4-dihydroxybenzoic acid, ethyl-3,4-dihyroxybenzoate **203** was used with the more reactive 2-bromoethyl methyl ether to afford the alkylated ester in a very good yield of 84%. Gratifyingly, Löwe's exact protocol afforded the desired product

in 83% yield **204**, which was of high enough purity to use directly after work-up. Scale up of the procedure led to consistent yields of 74 – 83%. The subsequent hydrolysis of the ethyl ester proceeded smoothly to afford the functionalised benzoic acid **199** in excellent yield (*scheme 100*). The hydrolysis was also amenable to scale.



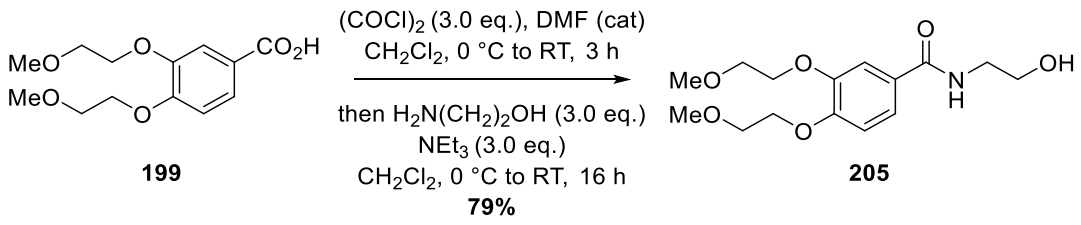
Scheme 100 – Löwe's methodology for the formation of **199**

With methodology in hand to afford large quantities of the required benzoic acid, attention was turned to the synthesis of the oxazoline moiety. Unfortunately, the use of the previously described 'one-pot' procedure consistently led to the isolation of the desired oxazoline product contaminated with the by-product triphenylphosphine oxide. Attempts to further purify *via* diethyl ether trituration led to the isolation of 29% of the desired oxazoline substrate **200**. Attempts to switch the phosphorus source to tributylphosphine, with a view to washing out the by-product more readily, failed to improve this step.



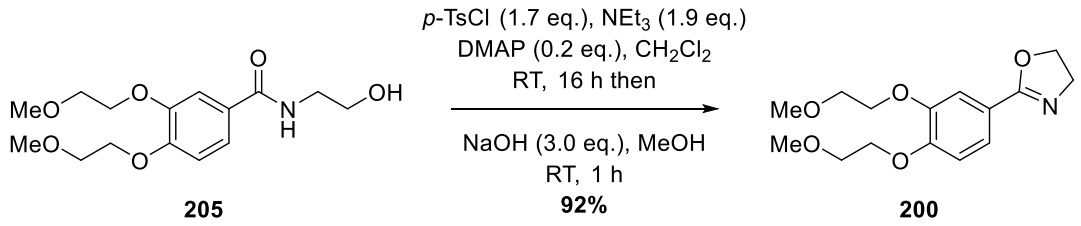
Scheme 101 – Oxazoline formation *via* 'one-pot' procedure

In light of the triphenylphosphine oxide contamination leading to low isolated yields, it was decided to consider alternative conditions. Synthesis of the amide **205** was achieved using activation *via* the acid chloride as in previous oxazoline syntheses. An initial attempt using only one equivalent of both ethanolamine and triethylamine led to a low isolated yield of 32% following flash column chromatography. Increasing the equivalents of both amines gratifyingly led to a yield of 79% of the desired product (*scheme 102*).



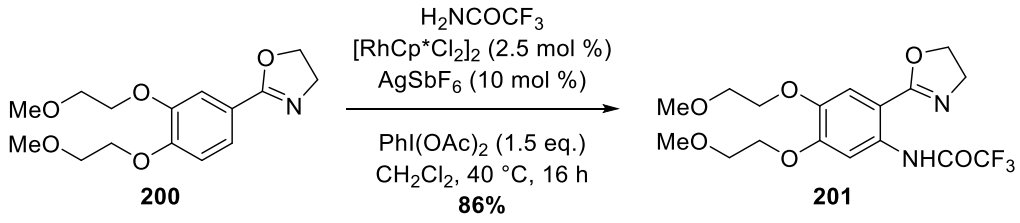
Scheme 102 – Formation of amide **205**

With the necessary amide in hand, oxazoline formation was again considered. As discussed previously, *p*-toluenesulfonyl chloride can be used to cyclise amino alcohol amides to the corresponding oxazolines by enhancing the leaving group ability of the terminal hydroxyl group. A literature report towards unsubstituted oxazolines described the use of *p*-toluenesulfonyl chloride followed by treatment with sodium hydroxide to further induce cyclisation.[132] Delightfully, application of these conditions to the Erlotinib amide **205** led to the synthesis of the Erlotinib oxazoline **200** in an excellent yield of 92%.



Scheme 103 – Synthesis of Erlotinib oxazoline **200**

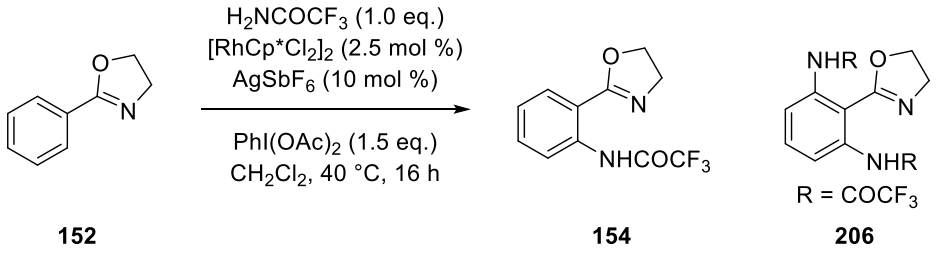
Following synthesis of the Erlotinib oxazoline, the *C-H* insertion step was considered. Pleasingly subjecting the oxazoline to the optimised *C-H* amidation conditions, using two equivalents of compound **200**, afforded the mono-amidated product **201** in an excellent yield of 86% as shown in *scheme 104*.



Scheme 104 – *C-H* Amidation with Erlotinib oxazoline

Being mindful of scaling up the *C-H* amidation chemistry, both for the purpose of Erlotinib and the halofuginone quinazolinone, it was considered if the stoichiometry of the oxazoline substrate could be reduced from the required two equivalents. It was previously hypothesised that the two equivalents helped prevent formation of the di-aminated product **206**, a problem which many *C-H* activation protocols suffer from. In order to assess this

further, attention was turned to the parent oxazoline **152**, conducting reactions with varying equivalents of the substrate.



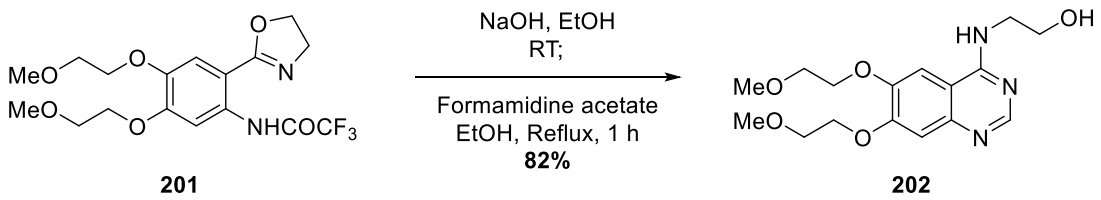
Scheme 105 – Parent oxazoline in equivalent studies

Entry	Oxazoline (eq.)	Mono-amidated 154	Di-amidated 206
1	1.0	80%	7%
2	1.2	97%	Trace
3	1.5	96%	Trace
4	2.0	92%	0%

Table 10 – Equivalent studies

As shown above in *scheme 105* and *table 10*, the *C-H* amidation was found to proceed with less than two equivalents of the oxazoline substrate. However as hypothesised, in these cases the formation di-amidation product **206** was observed. When the stoichiometry of the oxazoline and trifluoroacetamide were exactly 1:1 (entry 1), an 80% yield of mono-amidated product **154** and a 7% yield of di-amidated **206** product was observed. Gratifyingly when increasing equivalents of the oxazoline to 1.2 and 1.5, entries 2 and 3 respectively, the formation of the di-amidated product **206** could be supressed to the point where the compound was observed in the crude reaction mixture, but in only trace amounts. The yield of the di-amidated material was believed to be negligible in most cases due to the change in electronic nature of the ring following the initial insertion, making a second *C-H* amidation more difficult. From these studies, the optimal oxazoline equivalents was determined to be 1.2. When using the newly defined stoichiometry upon the Erlotinib substrate, the desired amidated product could be afforded in a good yield of 66% and upon gram scale quantities.

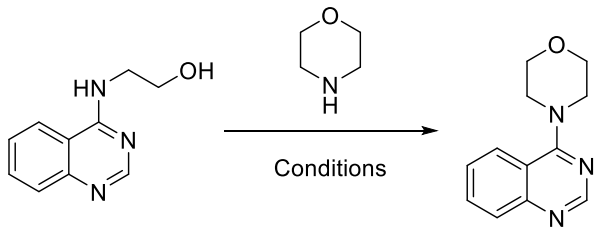
Conversion to the quinazoline was then considered. Pleasingly, subjection of the oxazoline to the standard conditions of sodium hydroxide cleavage of the trifluoroacetamide followed by cyclisation with formamidine acetate yielded the cyclised adduct in excellent yield of 82% (*scheme 106*). Notably, due to the electronic properties of the ring the cyclisation proceeded quickly, reaching full conversion in 1 h.



201 **202**

Scheme 106 – Cyclisation to the Erlotinib quinazoline

With intermediate **202** in hand, exploration of the envisaged *trans*-amination was considered *via* a simple S_NAr reaction. A model substrate **186** was chosen over the Erlotinib quinazoline, along with an amine source of morpholine.



186 **207**

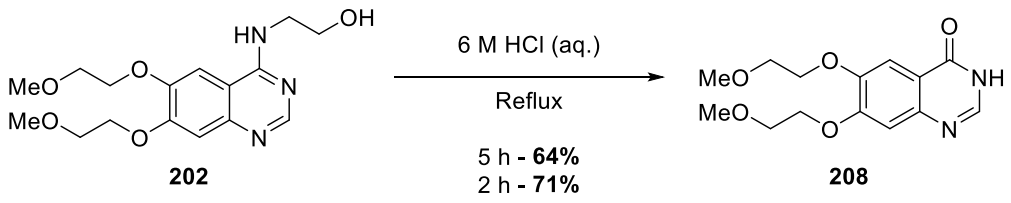
Scheme 107 – Envisaged *trans*-amidation

Entry	Conditions	Result
1	Morpholine (20 eq.), 1,4-Dioxane, Reflux, 24 h	Recovered SM
2	Morpholine (50 eq.), Reflux, 24 h	Recovered SM
3	Morpholine (50 eq.), 4.0 M HCl in 1,4-Dioxane (10 eq.), Reflux, 24 h	Recovered SM

Table 11 – Attempts at *trans*-amidation

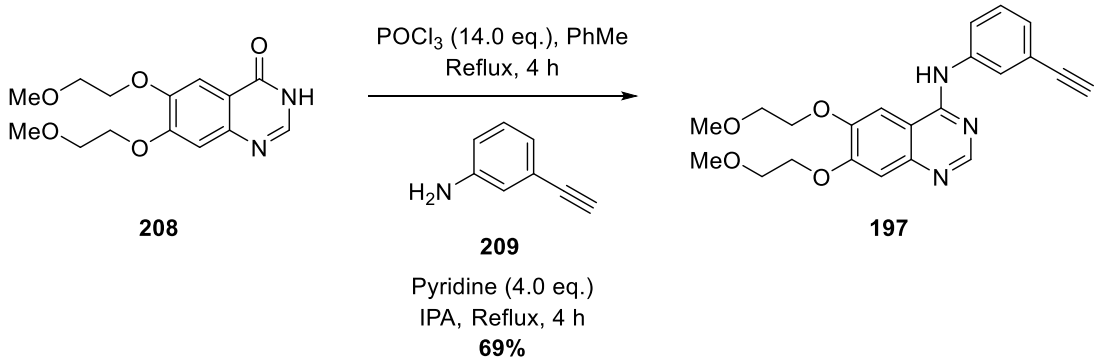
As depicted above in *scheme 107* and *table 11*, all attempts at *trans*-amidation were unsuccessful. Heating substrate **186** with an excess of morpholine in 1,4-dioxane failed to afford any product (entry 1). Removing dioxane from the system (entry 2), and introducing acid into the system (entry 3) led to no improvement. With these disappointing initial results, it was decided to switch approach towards the synthesis of Erlotinib. Specifically, it was decided to use more established chemistry of hydrolysis of the amino alcohol chain to the quinazolinone followed by activation with $POCl_3$ and amine substitution.

The hydrolysis of the Erlotinib quinazoline was conducted using the previously described optimum conditions of aqueous 6 M HCl at reflux. Pleasingly 64% of the desired material **208** was obtained using the optimum conditions for a period of 5 hours, however running the reaction for a slightly shorter period of time led to an improved yield of 71%.



Scheme 108 – Hydrolysis to the Erlotinib Quinazolinone

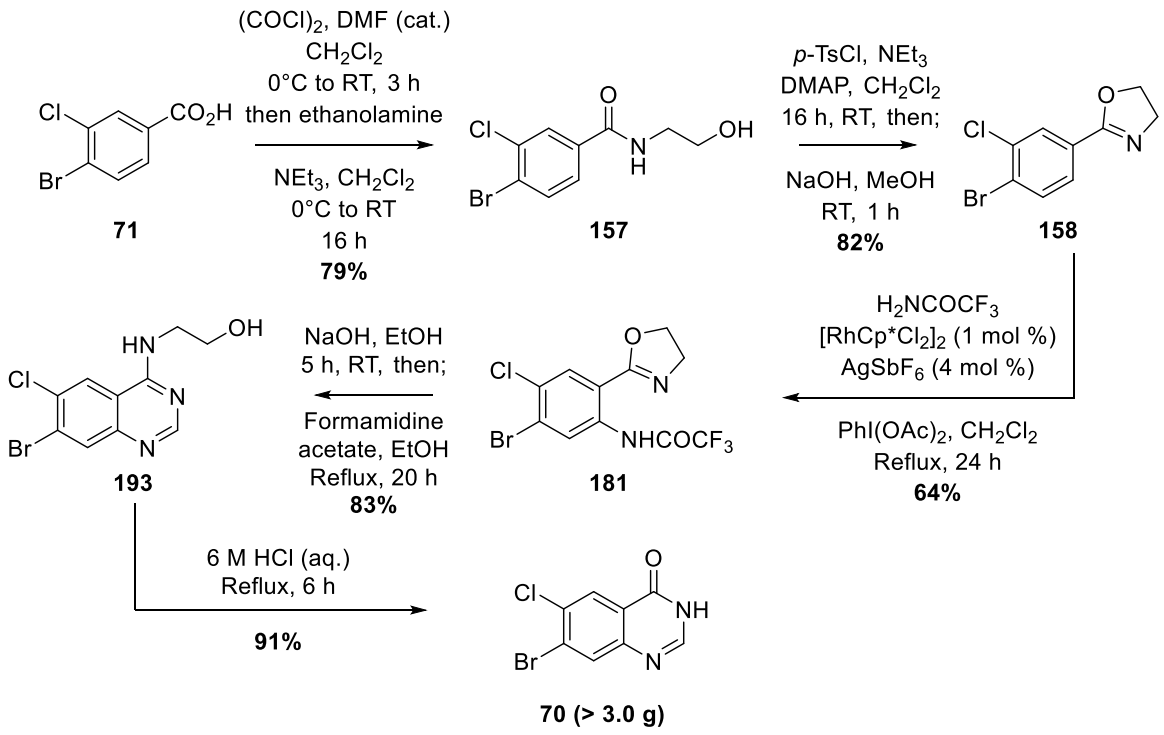
Having successfully synthesised quinazolinone **208**, the final steps of the synthetic sequence were considered. Utilising established methodology, the quinazolinone was treated with $POCl_3$ in PhMe followed by treatment with 3-ethynyl aniline with pyridine in *iso*-propanol.[133] Using this methodology Erlotinib **197** was afforded in a very good yield of 69% over the chlorination and substitution steps (*scheme 109*).[123] All characterisation of Erlotinib was in accordance with previously reported data from the literature.[133]



Scheme 109 – Synthesis of Erlotinib **197**

3.3 Application and utility of strategy - Scale-up of halofuginone quinazolinone synthesis

Having demonstrated ability of the *C-H* amidation/cyclisation strategy towards the synthesis of the halofuginone quinazolinone, it was considered how amenable the synthetic sequence would be to scale-up. Previous attempts utilising the developed route had at best afforded a few hundred milligrams of the desired compound. Delightfully starting from the 4-bromo-3-chloro benzoic acid **71** as in previous cases, the route could be scaled up to produce gram quantities the halofuginone quinazolinone **70**, as depicted in *scheme 110*.



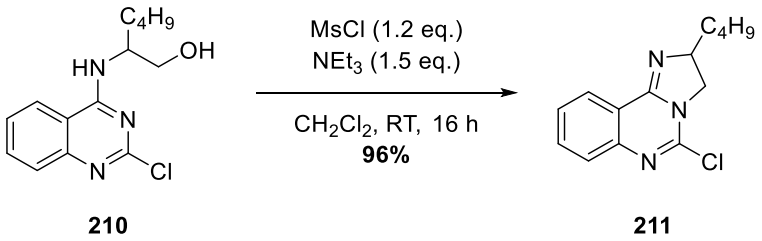
Scheme 110 – Scale up synthesis of Halofuginone Qunazolinone

Mindful of the previous success synthesising reasonable quantities of the Erlotinib oxazoline, it was decided to apply the same conditions upon the halofuginone starting material. Pleasingly using the same conditions, on a fifteen-gram scale, the amino alcohol amide **157** was synthesised in a 79% yield. Following isolation of the amide, cyclisation to the oxazoline **158** was achieved using again *p*-toluenesulfonyl chloride in an excellent yield of 82%. *C-H* amidation was conducted using 1 mol % of the rhodium catalyst, but for an extended period of 24 hours which afforded the amidated product **181** in a good yield of 64%. It is noteworthy that the reaction here is conducted with 1.2 equivalents of oxazoline and affords the amidated product in comparable yield to when conducted with 2.0 equivalents of oxazoline. Treatment with sodium hydroxide in ethanol afforded the free aniline, which following condensation with formamidine acetate afforded the cyclised material **193** after overnight reflux. Finally, hydrolysis of the compound proceeded as expected yielding the halofuginone quinazolinone **70** in a 91% yield. The route afforded just over three grams of the desired product, in an overall yield of 31%.

3.4 Application and utility of strategy - Further cyclisation and application to an enantioenriched heterocycle

An aspect of the developed synthetic route which had not yet been contemplated was the further exploitation of the amino alcohol substituted quinazolines. As described above in the synthesis of the halofuginone quinazolinone, the amino alcohol chain is cleaved from the

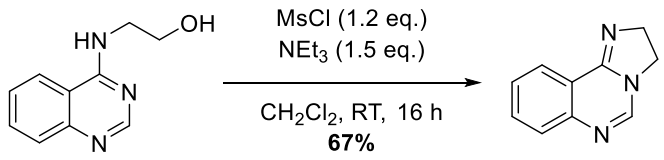
molecule to afford the key heterocycle of interest. It was considered if a further application could be developed that made more use of the amino alcohol. An interesting report published in 2014 demonstrated that amino alcohol substituted quinazolines, such as **210** depicted in *scheme 111*, could undergo a further cyclisation to generate the imidazoline fused quinazoline **211** in excellent yield.[134]



210 **211**

Scheme 111 – Fused imidazoline quinazoline synthesis[134]

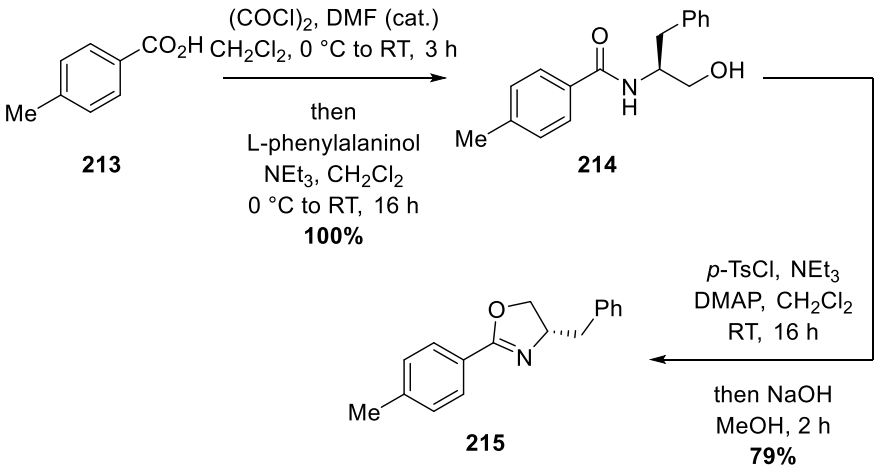
Intrigued by the report, the reaction as described within the literature was conducted upon the parent amino alcohol quinazoline **186** (*scheme 112*). As can be seen below, the desired product **212** could be afforded in a very good yield of 67%, slightly lower than that described within the literature.



186 **212**

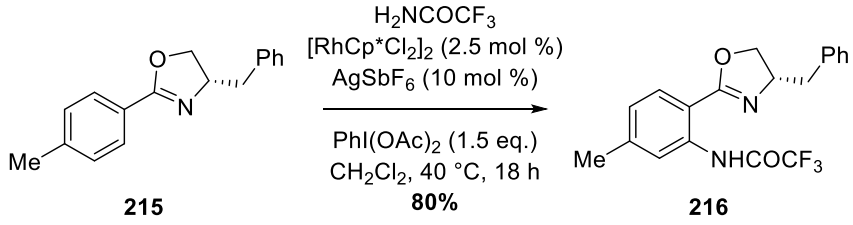
Scheme 112 – Further cyclisation on the parent substrate

With this additional cyclisation proving successful, application to an enantioenriched example was considered. It was contemplated that using an enantiomerically pure amino alcohol at the start of the reaction sequence could allow for the synthesis of enantiomerically pure imidazoline fused quinazolines. However, it was also considered that a substituent on the oxazoline directing group which would arise from the use of an enantiomerically pure amino alcohol could hinder the *C-H* amidation sequence as discussed previously with the use of the *gem*-dimethyl substituted oxazoline. With this in mind, L-phenylalaninol was chosen as the enantiomerically pure amino alcohol. Synthesis of the necessary oxazoline was carried out using *p*-toluic acid *via* isolation of the amide followed by corresponding cyclisation with *p*-toluenesulfonyl chloride. Both steps proceeded in good to excellent yield (*scheme 113*).



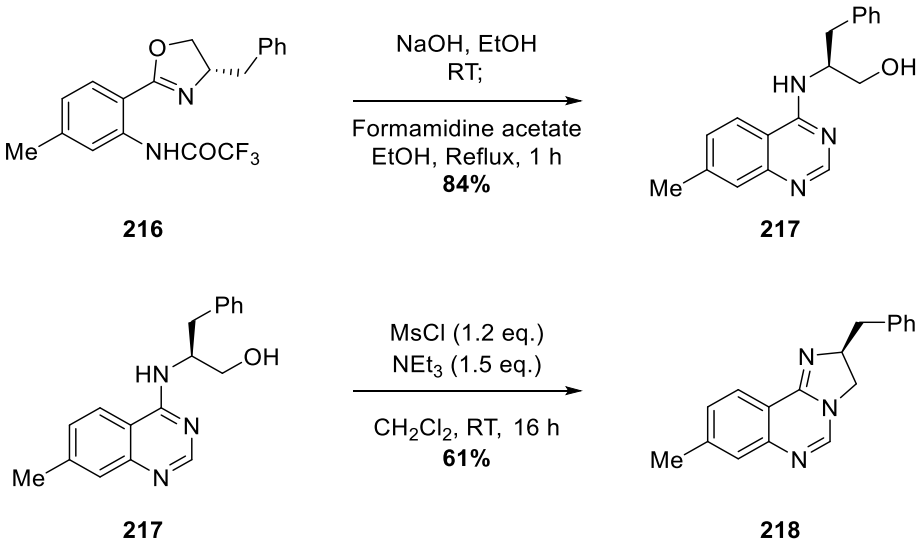
Scheme 113 – Synthesis of enantiomerically pure oxazoline **215**

Enantiomerically pure oxazoline **215** was then subjected to the *C-H* amidation conditions, which pleasingly proceeded very well, affording the product in a very good yield of 80% (*scheme 114*). In comparison to the substituted oxazolines previously shown, the L-phenylalaninol derived variant proves to be superior which is believed to be due to decreased steric bulk when compared to the *gem*-dimethyl and *tert*-butyl oxazolines explored previously within this chemistry.



Scheme 114 – *C-H* amidation of enantiomerically pure oxazoline **215**

Following the amidation, the two subsequent cyclisations were considered. The first cyclisation to form the quinazoline core afforded the desired product **217** in a very good yield of 82%. The reaction proceeded to full conversion within an hour. The next cyclisation to form the fused imidazoline ring proceeded well, giving rise to the fused enantiomerically pure heterocycle in a good yield of 62%. Despite the reaction reaching full conversion, a yield of 62% was afforded due to tedious purification. An eventual trituration with dichloromethane led to isolation of the pure product. These studies highlighted that the oxazoline can both promote *C-H* amidation, but also provide further value in the generation of complex heterocyclic products.



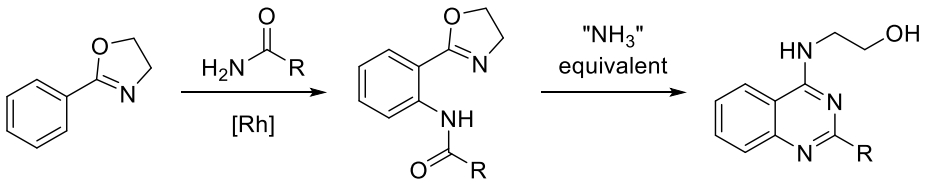
216 **217**

217 **218**

Scheme 115 – Cyclisations with enantiomerically pure substrate

Chapter 4: Access to 2-Substituted Quinazolines and Quinazolinones

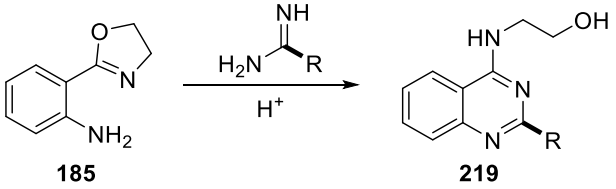
Having developed a strategy to highly-functionalised quinazolines and quinazolinones, the ability of the route to access 2-substituted analogues was yet to be fully explored. Attempts to alter the amine source in the *C-H* amidation to variants such as acetamide or benzamide were unsuccessful, suggesting that 2-substituted scaffolds could not be accessed in this particular manner. In order to overcome this limitation, it was considered if the incorporation of a substituent in the 2-position could be achieved at alternative stages of the developed *C-H* amidation/cyclisation sequence.



Scheme 116 – *C-H* amidation followed by cyclocondensation towards 2-substituted quinazolinones

4.1 Incorporation of a 2-substituent during the cyclisation

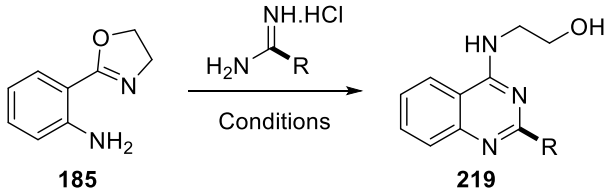
Initially, it was envisaged that a 2-substituent could be incorporated on the heterocyclic scaffold by replacement of formamidine acetate during the cyclisation step (*scheme 117*). It was hypothesised that through alteration of the cyclisation fragment both alkyl and aryl substituents could be successfully introduced.



Scheme 117 – Incorporation of substituent by replacement of formamidine acetate

The corresponding phenyl and methyl amidines were unavaliable as the acetic acid salts, however the hydrochloric acid salts were commercially avaliable and were chosen for initial investigation. Unfortunately, taking substrate **185** with benzamidine hydrochloride and acetamidine hydrochloride led to no observed reactivity when refluxing for 5 h in ethanol (*scheme 118* and *table 11*, entries 1 and 2). Attempts to free base acetamidine hydrochloride with sodium hydroxide prior to the cyclisation also led to no reaction (entry 3). Assuming that acid was required for the transformation to occur, the reacton with acetamidine

hydrochloride was attempted by pre-stirring the salt in the presence of sodium acetate for 30 minutes, followed by addition of substrate **185**. However, again in this instance there was no observed reactivity (entry 4). Additionally instead of using benzamidine hydrochloride, substrate **185** was subjected to reaction with benzamide and acetic acid in refluxing ethanol, however no improvement in reaction outcome was afforded (entry 5). The lack of reactivity observed was attributed to the potentially slow nucleophillic addition of the aniline substrate **185** to the more sterically encumbered salts. In order to aid the reaction, it was decided to look for reagents which had successfully been used in quinazolinone synthesis which proceeded *via* similar mechanistic pathways.

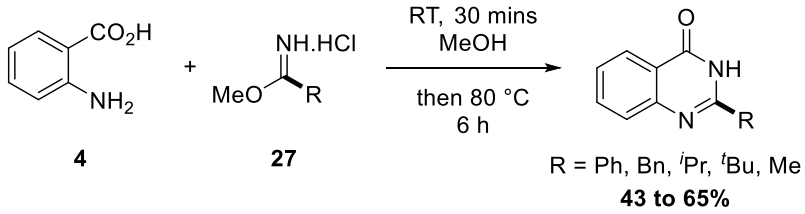


Scheme 118 – Alternative salts

Entry	R	Conitions	Result
1	Ph	Benzamidine hydrochloride (3.0 eq.), EtOH, reflux, 5 h	Recovered SM
2	Me	Acetamidine hydrochloride (3.0 eq.), reflux, 5 h	Recovered SM
3	Me	Acetamidine hydrochloride (3.0 eq.), pre-stir with NaOH (3.0 eq.), RT, EtOH 30 mins then **185**, reflux, 5 h	Recovered SM
4	Me	Acetamidine hydrochloride (3.0 eq.), pre-stir with NaOAc (3.0 eq.), RT, EtOH 30 mins then **185**, reflux, 5 h	Recovered SM
5	Ph	Benzamide (3.0 eq.), AcOH (3.0 eq.), EtOH, reflux 5 h	Recovered SM

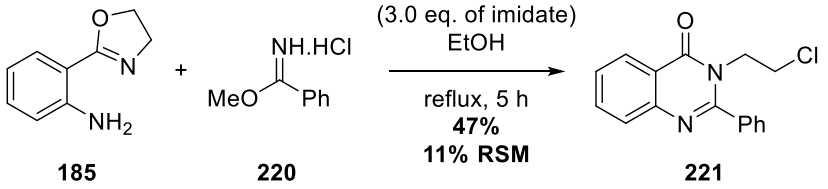
Table 11 – Alternative salts

As previously described, a report by Guiry in 2004 demonstrated the use of imidate salts **27** in conjunction with anthranilic acid **4** to yield quinazolinones functionalised in the 2-position (*scheme 119*).[135] A small selection of alkyl and aryl substituents were shown to be incorporated. It was therefore decided to exploit this chemistry within the cyclisation step of the *C-H* amidation/cyclisation sequence.



Scheme 119 – Guiry's use of imidate salts in quinazolinone synthesis

Commercially avaliable salt, methyl benzenecarboximidoate hydrochloride **220** was used with substrate **185** under the standard conditions of refluxing in ethanol for 5 h. Pleasingly in this instance, reactivity was observed (*scheme 120*). Quinazolinone **221** was isolated in a moderate yield of 47%. The recovery of starting material was also observed in a yield of 11%. In contrast to the previous chemistry however, the *N*-substituted quinazolinone was afforded instead of the amino substituted quinazoline, suggesting a different mechanistic pathway for this process. All characterisation data was in agreement with reported data for quinazolinone **221**. [136]



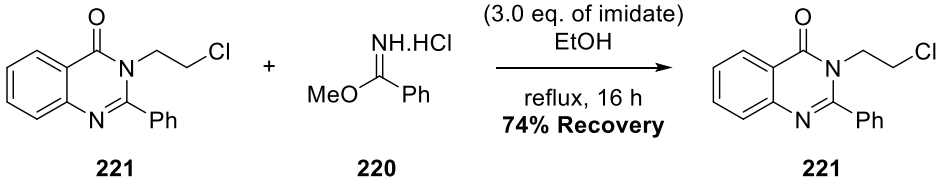
Scheme 120 – Reaction of methyl benzenecarboximidoate hydrochloride **221** with **185**

Following on from the synthesis of substrate **221** in moderate yield, optimisation of the reaction conditions was investigated. As shown in *table 12*, preparation of the free base of imidate salt **220** with NaOH prior to condensation afforded only trace reactivity (entry 1). Returning to the original conditions and carrying out the reaction for an extended period of time, 16 h, yielded the quinazolinone in a similar yield of 45% (entry 2). Basifying the reaction during work-up with $NaHCO_3$ (entry 3) and NaOH (entry 4) afforded increased isolation yields of 64% and 59%, respectively. In a similar manner to formamidine acetate, it was considered if the product yielded was difficult to extract, therefore upon cooling the reaction the crude material was dry-loaded onto silica gel and purified by flash column chromatography directly. In this instance, no significant improvement in reaction yield was observed (entry 5). Changing the reaction solvent to methanol showed no increase in reaction yield (entry 6). Repetition of the highest yielding reaction conditions, entry 3, unfortuantely afforded a lower yield of 42% versus the previously isolated 64%, indicating poor reproducibility (entry 7).

Entry	Conitions	Result
1	**220** (3.0 eq.) and NaOH (3.0 eq.) pre-stir, 30 mins, EtOH then **185** reflux, 5 h	Trace product
2	**220** (3.0 eq.), EtOH, reflux, 16 h	45%
3	**220** (3.0 eq.), EtOH, reflux, 16 h ($NaHCO_3$ work-up)	64%
4	**220** (3.0 eq.), EtOH, reflux, 16 h (NaOH work-up)	59%
5	**220** (3.0 eq.), EtOH, reflux, 16 h (dry-loaded on silicia)	52%
6	**220** (3.0 eq.), MeOH, reflux, 16 h ($NaHCO_3$ work-up)	47%
7	**220** (3.0 eq.), EtOH, reflux, 16 h ($NaHCO_3$ work-up)	42%

Table 12 – Optimisation with methyl benzenecarboximidoate hydrochloride **220**

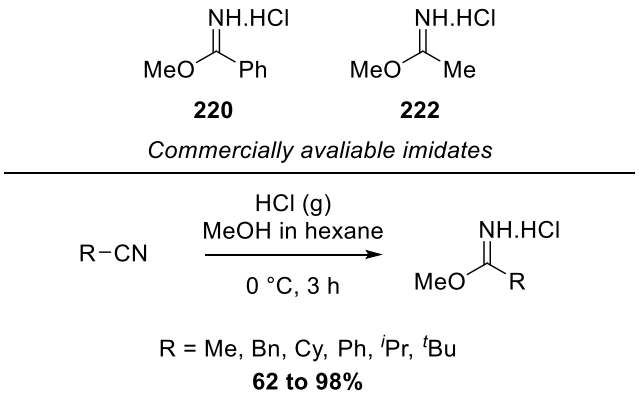
Following the observation that the optimum reaction conditions utilising a $NaHCO_3$ work-up (*table 12*, entry 3) could not be reproduced, investigation into the stability of the product under the reaction conditions was considered. Unfortunately when subjecting quinazolinone **221** to the reaction conditions, only 74% mass recovery was observed following purification by flash column chromatography, indicating the target material may be unstable under the conditions of its formation. Furthermore, it was noted that in the work disclosed by Guiry, only a moderate yield of 46% is reported suggesting that further improvements were unlikely.[135]



221 **220** **221**

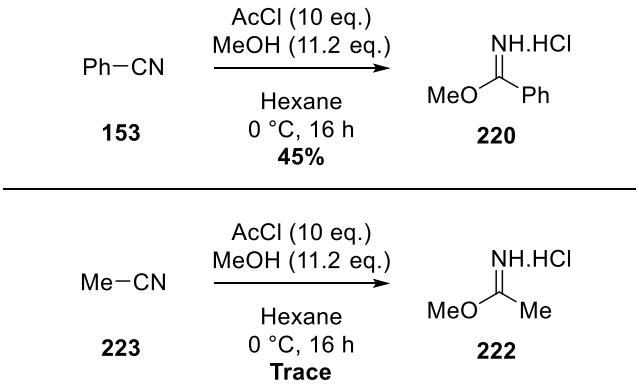
Scheme 121 – Control reaction with quinazolinone **221** and Guiry's result with methyl benzenecarboximidoate hydrochloride

After exploring the condensation reaction with methyl benzenecarboximidoate hydrochloride, alteration of the imidate salt was considered. As previously mentioned, imidate salt **220** can be obtained from commercial sources, as can the corresponding methyl imidate salt **222**. However, other substrates with alternative aryl or alkyl substituents required their synthesis from the corresponding nitriles (*scheme 122*).



Scheme 122 – Commercially avaliable imidate salts and the traditional synthesis

As shown in *scheme 122*, the traditional synthesis of imidate salts of this nature is by reaction of a substututed nitrile compound in the presence of gaseous hydrochloric acid and methanol.[25] Using this methodology a variety of functionalised imidates can readily be afforded in good yields. However, the necessity for the use of gaseous hydrochloric acid is a significant drawback and greatly limits the methodology. In order to overcome this limitation, it was considered if their synthesis could be achieved in a manner which did not require the use of gaseous hydrochloric acid. Specifically, it was considered if substituted nitrile would react in the presence of dry hydrochloric acid, generated *in situ* from the reaction of acetyl chloride in a slight excess of methanol, to afford the corresponding imidate salts (*scheme 123*). Initially this methodology was attempted upon benzonitrile and acetonitrile. Pleasingly, when taking benzonitrile in the presence of acetyl chloride (10 eq.) and methanol (11.2 eq.) at 0 °C for 16 h in hexane, methyl benzenecarboximidoate hydrochloride **220** was afforded in a moderate yield of 48% (*scheme 123*). However in the case of acetonitrile, precipitation of **222** only occurred in trace amounts. Stirring for extended periods of time (ca. 60 h) and cooling the reaction further afforded no improvement, concluding imidate salts could not generally be prepared by this means.



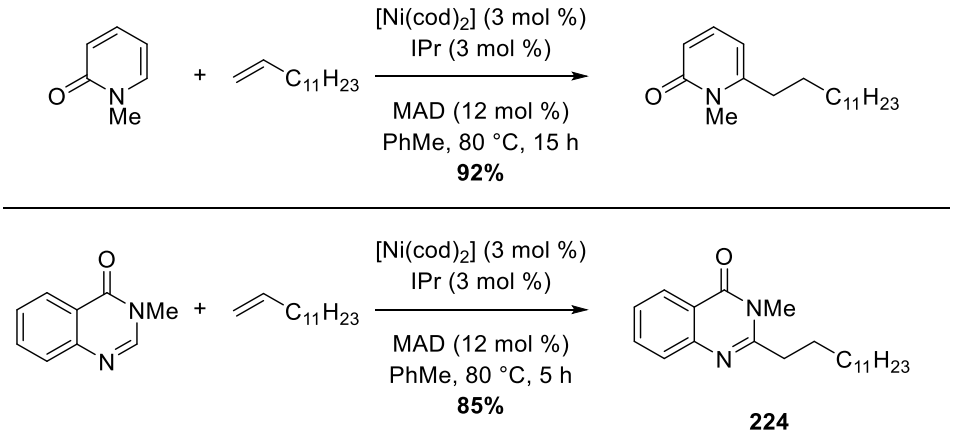
Scheme 123 – Attempts to synthesise imidate salts *via* the *in situ* generation of HCl

Overall, from the moderate yields of cyclisation and a significant limitation in the synthesis of the imidate salts required for condensation to the quinazolinone heterocycle, it was concluded that this strategy did not provide a general methodology for the incorporation of a 2-substituent on quinazoline products.

4.2 Post cyclisation incorporation of a 2-substituent

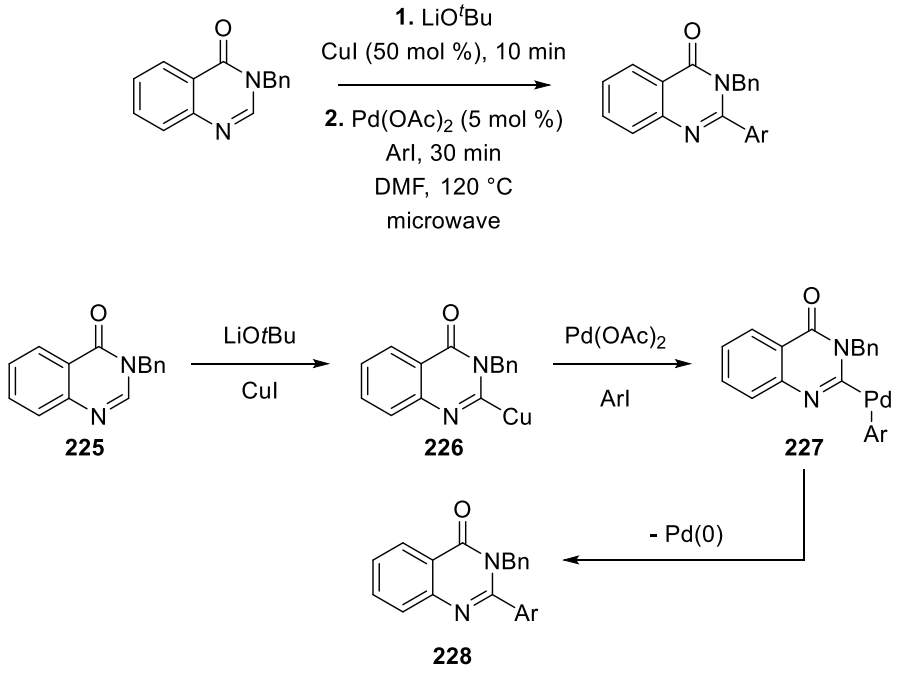
Consideration of the potential incorporation of a 2-substituent on the quinazoline or quinazolinone directly after cyclisation was next investigated. In this context, the general literature contained some interesting reports which disclosed the direct functionalisation of quinazolinones in the 2 position.

Nickel- and Lewis acid catalysed direct alkylation of *N*-heterocycles was previously reported in 2012 by Nakao and Hiyama.[137] Primarily the report discloses the alkylation of a variety of pyridone derivatives with a range of alkenes. One example of a quinazolinone scaffold was described, with the corresponding alkylated scaffold **224** afforded in an excellent yield of 85% (*scheme 124*).



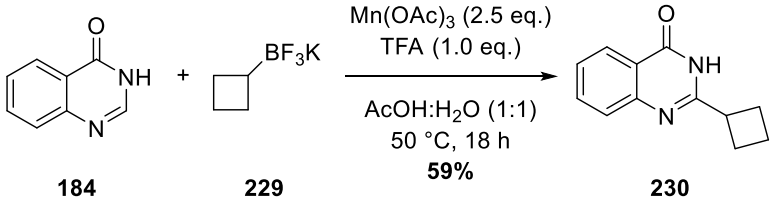
Scheme 124 – Nakao and Hiyama's direct alkylation of heterocycles

More recently in 2015, the palladium-catalysed direct arylation reaction of quinazolinone derivatives was described.[138] The reaction utilised a two-step procedure. Initially treatment with copper(I) iodide and lithium *tert*-butoxide afforded copper species **226**, which upon subsequent treatment with palladium acetate and corresponding aryl iodide yields the functionalised quinazolinone **228**. A wide variety of aryl iodides were shown to successfully participate under the reaction conditions.



Scheme 125 – Direct arylation of quinazolinones

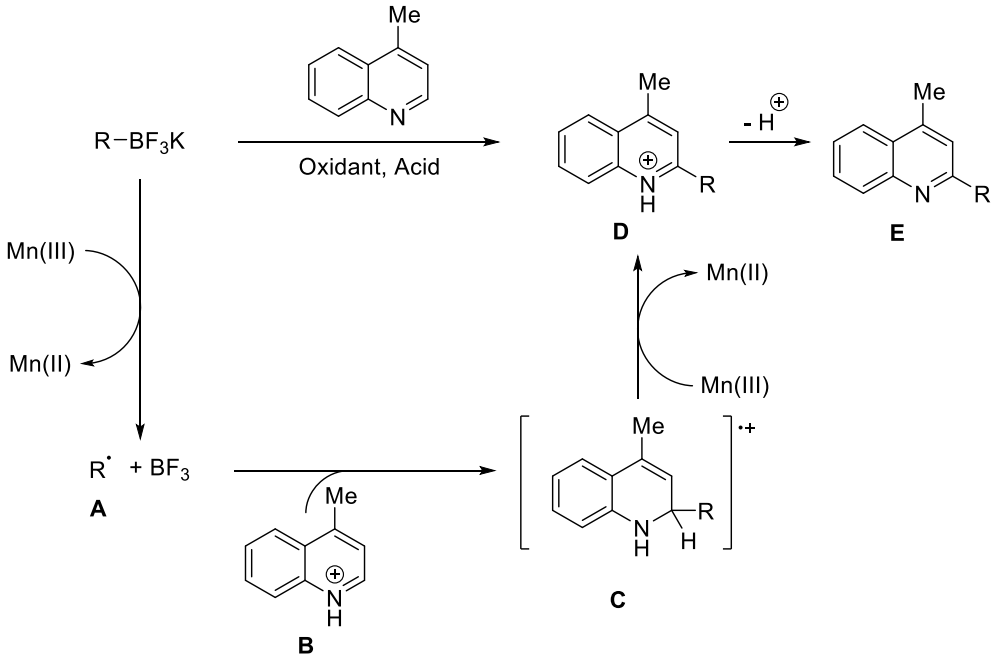
An additional example of quinazolinone functionalisation was reported by Molander in 2011.[139] The report disclosed the direct alkyl functionalisation of quinolines and isoquinolines, amongst other heterocycles, with potassium alkyl- and alkoxymethyltrifluoroborates. The reaction was found to proceed successfully using an oxidant of $Mn(OAc)_3$ and a range of highly-functionalised trifluoroborates. As in the case of Nakao and Hiyama, only a single example of a quinazolinone was demonstrated. Successful functionalisation with cyclobutyltrifluoroborate **229** was achieved in this case in a good yield of 59% **230** (*scheme 126*).



Scheme 126 – Molander's heterocycle functionalisation with potassium alkyl- and alkoxymethyltrifluoroborates

Interestingly, the reaction described by Molander is believed to proceed *via* a radical mechanism.[139] As depicted in *scheme 127*, the reaction begins by the homolytic cleavage of the C-B Bond using one equivalent of $Mn(OAc)_3$. The generated radical **A** then adds to the protonated heterocyclic scaffold **B** forming a radical cation intermediate **C**. Further oxidation

by $Mn(OAc)_3$ affords the protonated heterocycle **D** which upon basic work-up yields the product **E**.

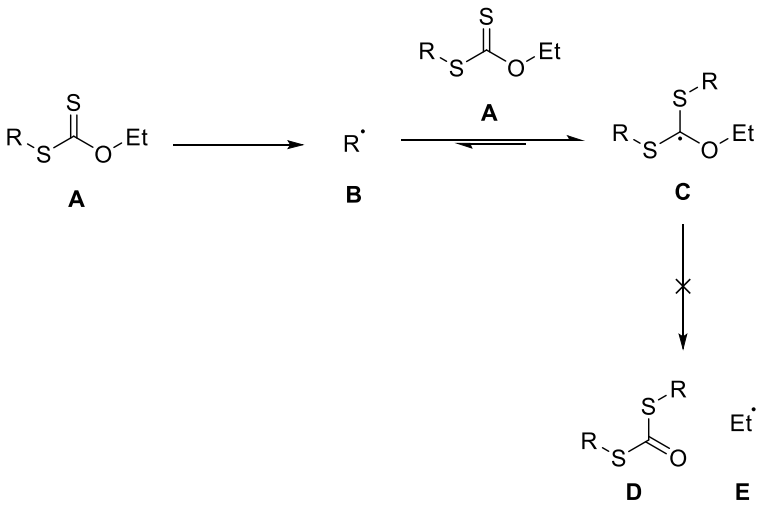


Scheme 127 – Molanders direct alkylation mechanism

Intrigued by the apparent ability of radicals to functionalise quinazolinone scaffolds in the 2-position, as disclosed by Molander, it was wondered if radical addition could comprise a general solution to the formation of 2-substituted quinazolines and quinazolinones.

Xanthates are a very important class of radical precursors. Pioneering work by Zard and co-workers has shown how these substrates address many of the long established drawbacks of radical centred reactions.[140] The well-established limitation of radical reactions is the propensity of radicals to interact with themselves *via* dimerisation and/or disproportionation mechanisms, both of which can proceed very quickly. In order to prevent these problems arising, the steady-state concentration of the radical species needs to be kept as low as possible. A potential way to achieve this is by forcing the reactive radical into a desired direction with the use of redundant or degenerate loops - in this regard Zard and co-workers have extensively studied the addition/transfer of xanthates to alkenes.[141] To understand the success of xanthates in this instance, the mechanism must be considered.[140] As shown in *scheme 128*, xanthate **A** is able to undergo chemical or photochemical initiation to yield radical **B**. In this case the radical is captured by another xanthate molecule affording adduct **C**. In this state, **C** is unable to undergo scission to give symmetrical dithiocarbonate **D** and high energy ethyl centred radical **E**. Instead, it is easier for the system to return to its original state yielding again radical **B** which can then propagate the reaction forwards. This very fast

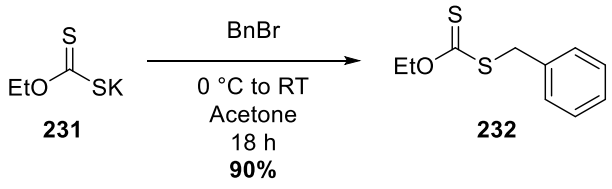
addition/fragmentation mechanism is a degenerate process with doesn't cause macroscopic change to the reaction system and allows for the constant generation of radical **B**, dramatically increasing its lifetime.



Scheme 128 – Xanthates as long-lived radical species

Furthermore, the simple preparation of *O*-ethyl xanthates by the reaction of an alkylating agent with cheap and commercially available potassium *O*-ethyl xanthate enhances their popularity as effective radical precursors.

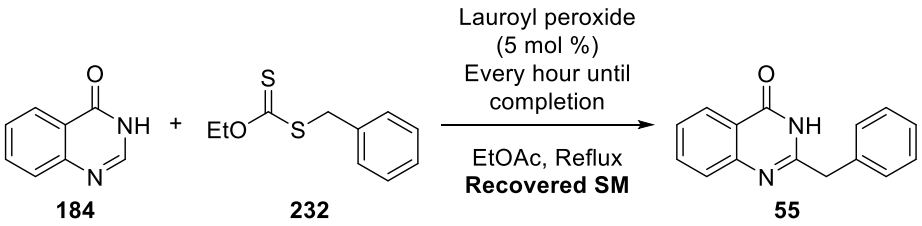
With the radical functionalisation of quinazolinones in mind, it was envisaged that xanthates could function as successful radical precursors as a means to functionalise these heterocycles. In order to investigate this hypothesis, the synthesis of a xanthate was first required. Pleasingly, benzyl analogue **232** could be readily prepared in excellent yield using established methodology with benzyl bromide and potassium *O*-ethyl xanthate **231** (*scheme 129*).[142]



Scheme 129 – Preparation of benzyl xanthate **232**

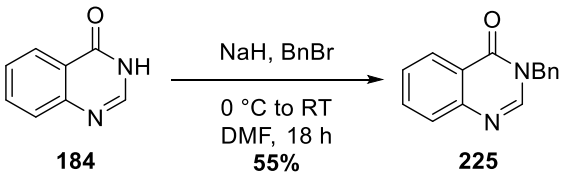
With xanthate **232** in hand, attention was turned to the use of the reagent in conjunction with quinazolinone **184**. The reaction was performed with two equivalents of xanthate and portionwise addition of lauroyl peroxide (5 mol %) every hour until complete consumption of the starting material was observed (*scheme 130*). Unfortunately, monitoring the reaction by TLC analysis only indicated the presence starting material. In this instance, it was believed

the lack of reactivity could be a result of poor solubility of the unprotected quinazolinone **184** in ethyl acetate as full dissolution was not observed during the reaction.



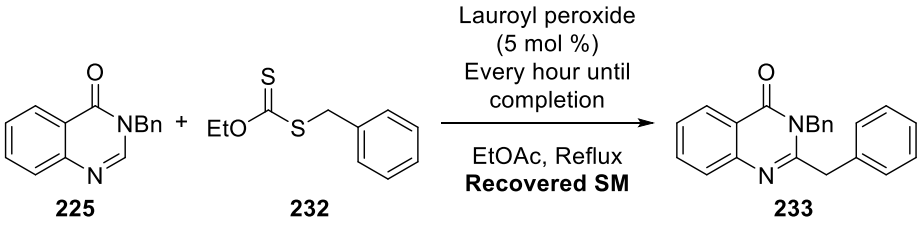
Scheme 130 - Reaction of quinazolinone with xanthate **232**

To aid solubility of the quinazolinone heterocycle it was decided to protect it as the benzyl derivative. Benzylation was readily achieved using conventional conditions of sodium hydride and benzyl bromide to afford the quinazolinone **225** in good yield, following isolation by recrystallisation (*scheme 131*).



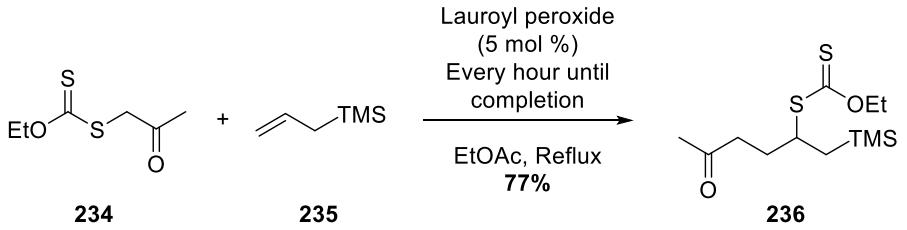
Scheme 131 – Synthesis of benzyl protected quinazolinone **225**

With benzyl protected quinazolinone in hand, the reaction with xanthate **232** was again investigated (*scheme 132*). However, as in previous attempts the reaction was found to be unsuccessful, yielding only the recovery of the starting material. In this instance, it is noteworthy that benzyl protected quinazolinone **225** was soluble throughout the reaction.



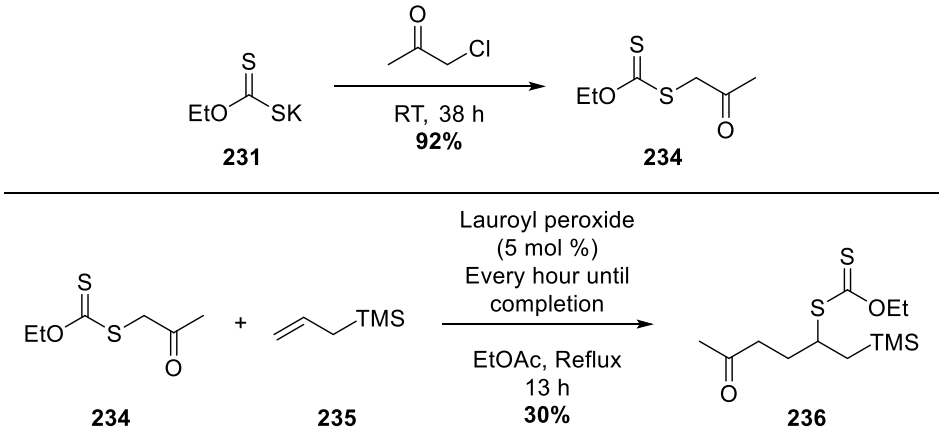
Scheme 132 – Reaction of quinazolinone **225** with xanthate **232**

Given the lack of reactivity observed between xanthate **232** and quinazolinones **184** and **225**, it was decided to reproduce a literature example of Zard's to ensure that the reactions were performed in the correct manner, and that the xanthate was a successful radical precursor. In order to do this, a reported example was chosen (*scheme 133*).[143]



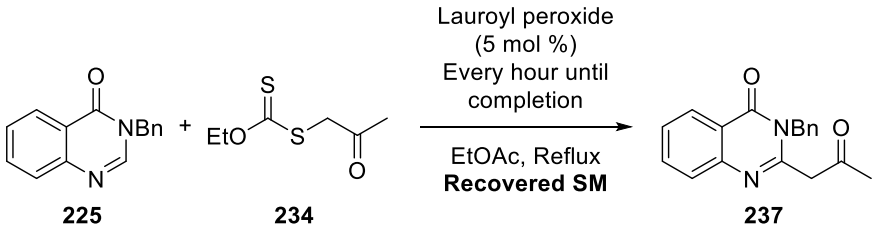
Scheme 133 – Literature example of Zard's chemistry

The required xanthate **234** was prepared using the same procedure previously discussed in an excellent yield of 92% (*scheme 134*). Pleasingly upon reaction with allyltrimethylsilane, the addition product was successfully afforded, albeit in a low yield of 30% **236** (*scheme 134*). In this instance the low yield in comparison to the reported example can be explained due to the reaction stoichiometry. The reaction was performed using two equivalents of xanthate **234** and one equivalent of allyltrimethylsilane **235** – as in all previous attempts with this chemistry. However, Zard's procedure uses one equivalent of xanthate **234** and four equivalents of allyltrimethylsilane **235** – presumably due to the volatility of the silane.



Scheme 134 – Reproducing Zard's chemistry

Having successfully performed a reaction using a xanthate radical precursor **234**, it was decided to attempt the analogous reaction with benzyl protected quinazolinone **225** to assess whether the nature of the xanthate was important. Unfortunately, the use of alternative xanthate **234** again led to no reactivity in conjunction with quinazolinone **225**. The results gathered suggest the quinazolinone heterocycle is not a viable substrate for functionalisation by radical addition using xanthates.



225 234 237

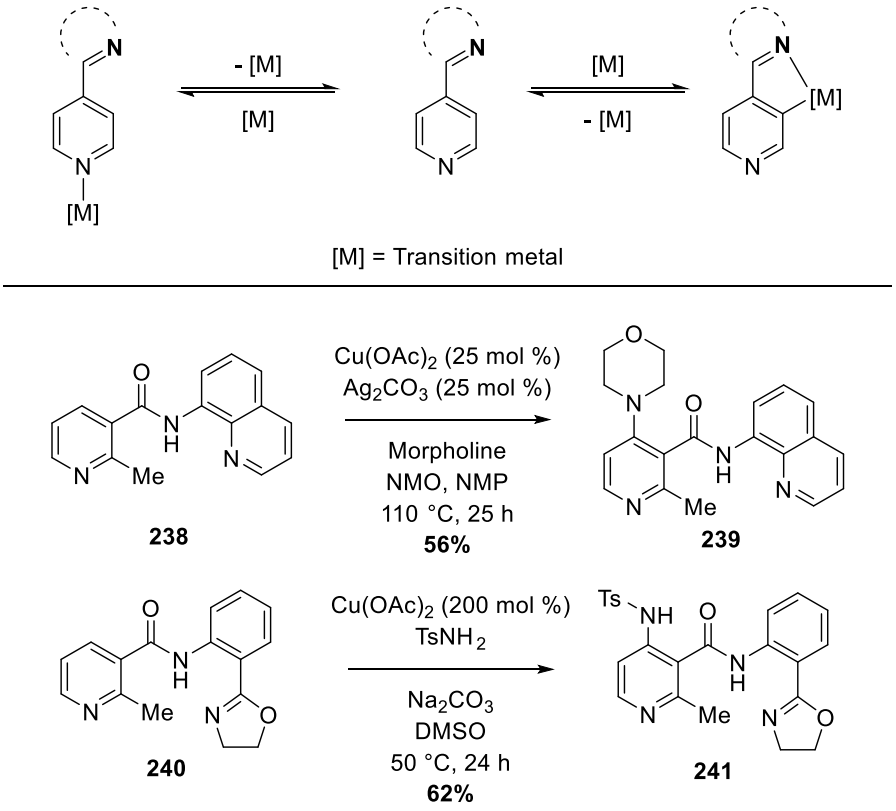
Scheme 135 – Reaction of quinazolinone **225** with xanthate **237**

The *C-H* amidation methodology provides an efficient means for constructing quinazoline derivatives that are unsubstituted at *C*2. Attempts to-date to extend this chemistry to 2-substituted derivatives by use of alternative cyclocondensation sequences or by direct functionalisation have been unsuccessful, and require further study.

Chapter 5: Application to Heterocyclic Scaffolds

5.1 Heterocyclic scaffolds in *C-H* activation

Whilst many advances in *C*-H activation have been achieved, an area which remains relatively underdeveloped in comparison is *C-H* activation of heterocycles, particularly pyridine derivatives. In the context of *C-H* amidation, impressive advances have been made upon heterocycles including the likes of indole,[144] pyrrole,[145] furan[146] and thiophene,[147] yet examples of pyridine functionalisation remain somewhat rare in comparison. Indeed, the success of pyridine itself as a directing group within *C-H* activation chemistry highlights the important role that the Lewis basic nitrogen atom plays in coordinating to a transition metal catalyst. Therefore, *C-H* activation of the pyridine ring raises an inherent challenge in competitive chelation, which can hinder the reaction pathway by preventing the required concerted metallation deprotonation step, as depicted in *scheme 136*. Nonetheless, key contributions by Yu and Daugulis have allowed significant advances in this challenging area. Elegant stoichiometric and catalytic copper-mediated *C-H* amidations have been achieved upon pyridine scaffolds by utilising bidentate directing groups such as the 8-aminoquinoline or oxazoline tethered secondary amides (*scheme 136*).[99, 148]

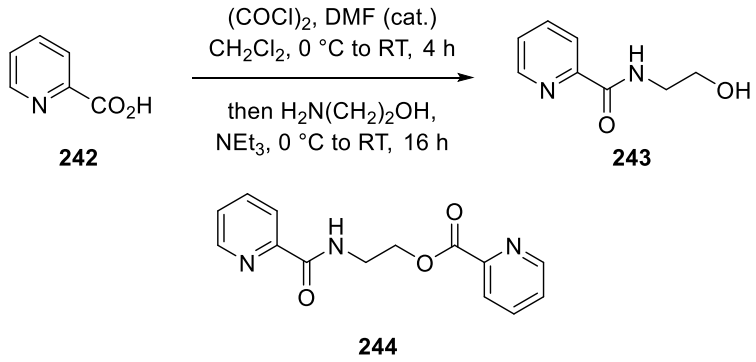


Scheme 136 – Limitation of pyridine substrates in *C-H* activation, and examples by Yu and Daugulis

Given the limited number of examples and methodologies within the literature to access aminated pyridine motifs by *C-H* activation methodology, it was hypothesised that application of the mild and efficient rhodium-catalysed conditions previously developed could be of value - allowing for the potential development of a general strategy for the functionalisation of pyridines by means of *C-H* activation.

5.2 Pyridine oxazoline synthesis

In order to explore the hypothesis, the parent pyridine oxazoline scaffolds were initially prepared. First attempts at the preparation of these structures began with utilisation of previously described methodologies. In the first instance 2-picolinic acid **242** was treated with oxalyl chloride and catalytic DMF to generate the acid chloride intermediate, followed by subjection to ethanolamine (*scheme 137* and *table 13*).



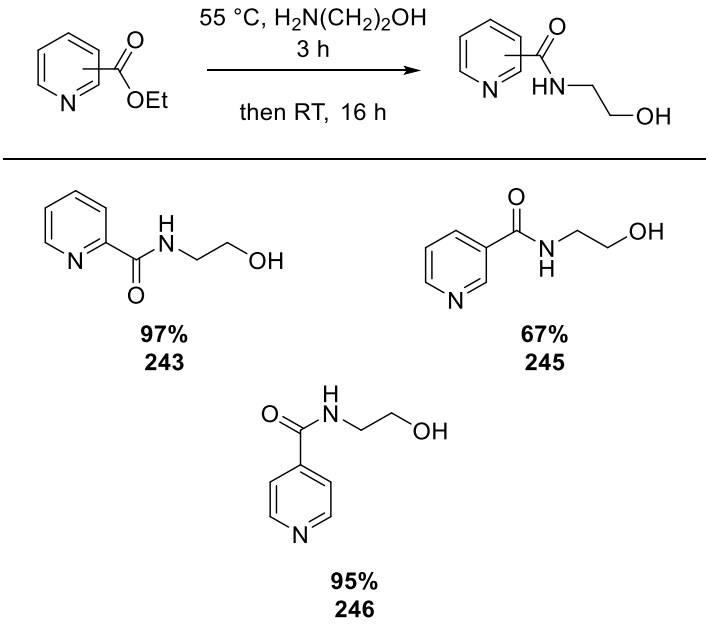
Scheme 137 – Oxalyl chloride attempts with 2-picolinic acid

Entry	NEt_3 eq.	Amine eq.	Yield of 243	Yield of 244
1	0	1.2	18%	-
2	1.2	1.2	-	48%
3	3.0	3.0	51%	21%

Table 13 - Oxalyl chloride attempts with 2-picolinic acid

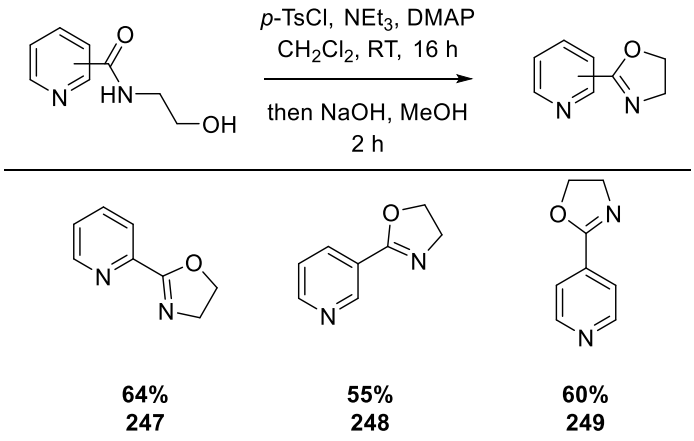
Treatment with only 1.2 equivalents of ethanolamine in the absence of triethylamine led to a poor yield of **243** (entry 1). Addition of triethylamine led only to the isolation of reaction by-product **244** in a moderate yield of 48% (entry 2). Increasing equivalents of both the amine and triethylamine, and avoiding an aqueous work-up led to improved isolation yields (entry 3). Despite achieving a useful yield of the desired substrate, formation of the reaction by-product was unavoidable and so an alternative methodology was sought. A report by Fátima in 2014 demonstrated the use of the corresponding pyridine ester opposed to the use of 2-picolinic acid towards the synthesis of the desired amino alcohol amide.[149] Pleasingly,

utilisation of the described literature conditions led to the successful synthesis of the desired amide **243** in an excellent yield of 97%. It is worth noting that no by-product formation was observed in this instance. Application of the reaction conditions to ethyl nicotinate and ethyl isonicotinate led to the synthesis of the respective amides, **245** and **246**, again in good to excellent yields.



Scheme 138 – Synthesis of pyridine amino alcohol amides

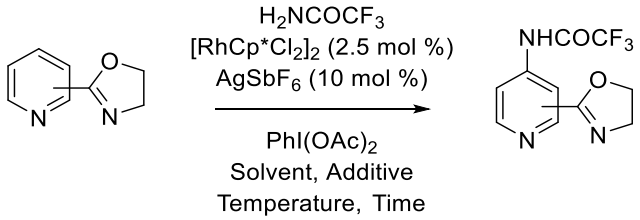
With the pyridine amides in hand, conversion to the oxazoline was then considered. Utilising the conditions used for the synthesis of the Erlotinib oxazoline **200**, the three parent oxazoline substituted pyridines were afforded in yields of 55 – 64% on preparative scale, as shown in *scheme 139*.



Scheme 139 - Synthesis of oxazoline substituted pyridines

5.3 *C-H* Amidation of oxazoline substituted pyridines

With the successful synthesis of substrates **247** – **249**, subjection to the rhodium-catalysed *C-H* amidation conditions was then considered. Using the optimised conditions of oxazoline substrate (1.2 eq.) with $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), trifluoroacetamide (1.0 eq.) as the amide source and (diacetoxyiodo)benzene (1.5 eq.) as the oxidant in dichloromethane at reflux (40 – 45 °C), no reaction was observed with any of the three parent substrates (*table 14*, entries 1 – 3). Efforts were made to promote reactivity by variation of the reaction conditions. Changing the reaction solvent to the higher boiling 1,2-dichloroethane alongside an increase in reaction temperature to 100 °C led to no observed improvement in the case of substrates **247** and **248** (entries 4 and 5). However, substrate **249** displayed trace reactivity, judged by analysis of ^1H NMR and LCMS samples (entry 6). Unfortunately, attempts to isolate the trace product formation were unsuccessful. Further attempts to optimise were then carried out upon substrate **249**, yet both further increase in time and temperature offered no advantage (entries 7 and 8). It was hypothesised the lack of reactivity was arising due to the co-ordination between the pyridine nitrogen and the rhodium catalyst, hence shutting down the reaction pathway. In order to circumvent this problematic path, it was decided to introduce a copper source into the reaction, due to the known affinity of pyridines for copper salts. It was hoped that this additive would block the undesired co-ordination between the heteroaromatic motif and the rhodium catalyst. However, when attempting to introduce $CuSO_4$ into the reaction system no conversion to the desired product was observed with substrate **249** (entries 9 and 10).



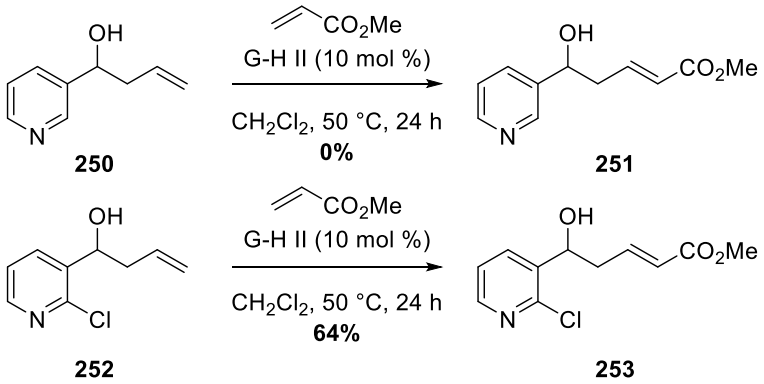
Scheme 140 – Subjection of oxazoline substituted pyridines to the optimum *C-H* amidation conditions

Entry	Substrate	Solvent	Temperature	Time	Additive	Result
1	**247**	CH_2Cl_2	40 °C	18 h	-	0%
2	**248**	CH_2Cl_2	40 °C	18 h	-	0%
3	**249**	CH_2Cl_2	40 °C	18 h	-	0%
4	**247**	1,2-DCE	100 °C	18 h	-	0%
5	**248**	1,2-DCE	100 °C	18 h	-	0%
6	**249**	1,2-DCE	100 °C	18 h	-	Trace
7	**249**	1,2-DCE	100 °C	48 h	-	Trace
8	**249**	1,2-DCE	120 °C	18 h	-	Trace
9	**249**	1,2-DCE	100 °C	22 h	$CuSO_4$ (1.2 eq.)	0%
10	**249**	1,2-DCE	100 °C	22 h	$CuSO_4$ (1.2 eq.)[a]	0%

Table 14 - Subjection of oxazoline substituted pyridines to the optimum *C-H* amidation conditions ([a] $CuSO_4$ and substrate pre-stirred for 10 minutes prior to reaction)

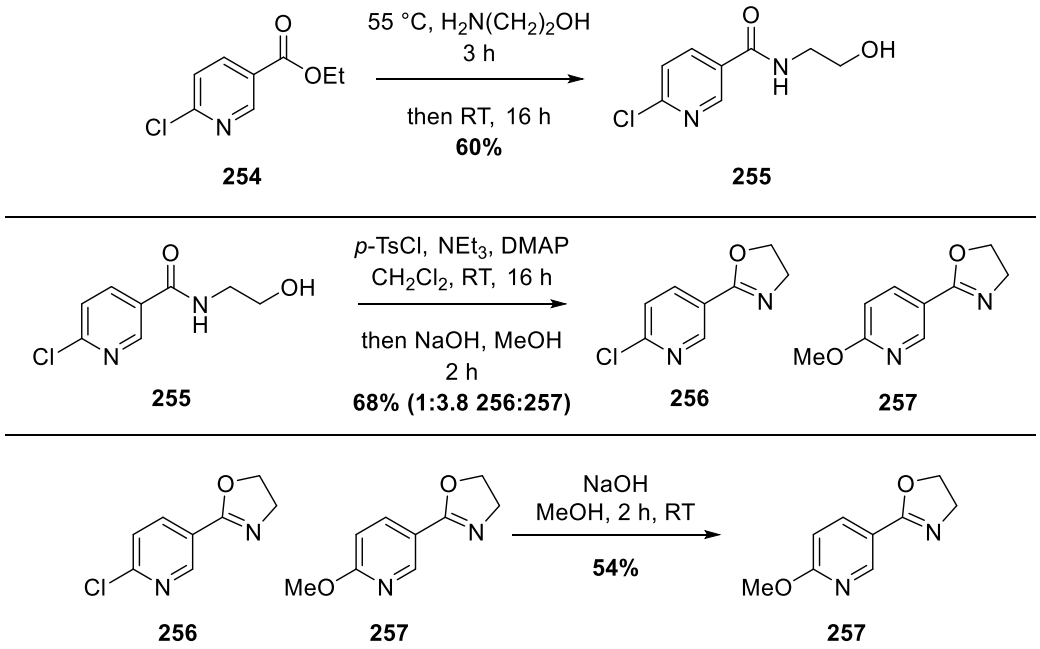
5.4 Modulation of pyridine basicity

Intrigued by the idea that the lack of observed reactivity could be as a result of the previously discussed competing Lewis basic site, ways to modulate the basicity of the pyridine nitrogen were considered. A report by Cossy in 2014 demonstrated that the incorporation of a 2-substituent upon the pyridine ring allowed for successful cross-metathesis to occur, whereby the parent pyridine ring was found to be inert, as demonstrated in *scheme 141*.[150] Attracted to the idea that the incorporation of a 2-substituent upon the oxazoline substituted pyridine could modulate basicity in order for *C-H* amidation to occur, and to also potentially provide a platform for derivatisation post *C-H* amidation, synthesis of the required substrate for trial of the hypothesis was investigated.



Scheme 141 – Cossy's modulation of pyridine basicity for cross-metathesis

Using ethyl-6-chloro nicotinate **254** and the previous amidation conditions, amide **255** was afforded in good yield. However, utilising the *p*-toluenesulfonyl chloride methodology to achieve synthesis of the oxazoline led to an observed mixture of products, identified by both ^{1}H NMR and LCMS. Interestingly, when treating the reaction mixture with sodium hydroxide in methanol, not only was the desired oxazoline synthesised but a reaction by-product **257** arising from S_NAr with *in situ* generated sodium methoxide was observed. Gratifyingly, re-subjection of the reaction mixture to sodium hydroxide and methanol allowed for full conversion to the methoxy substituted pyridine **257**, however access to the required 2-chloro substituted pyridine required further optimisation.



Scheme 142 – Amide and attempted oxazoline synthesis with ethyl-6-chloro nicotinate

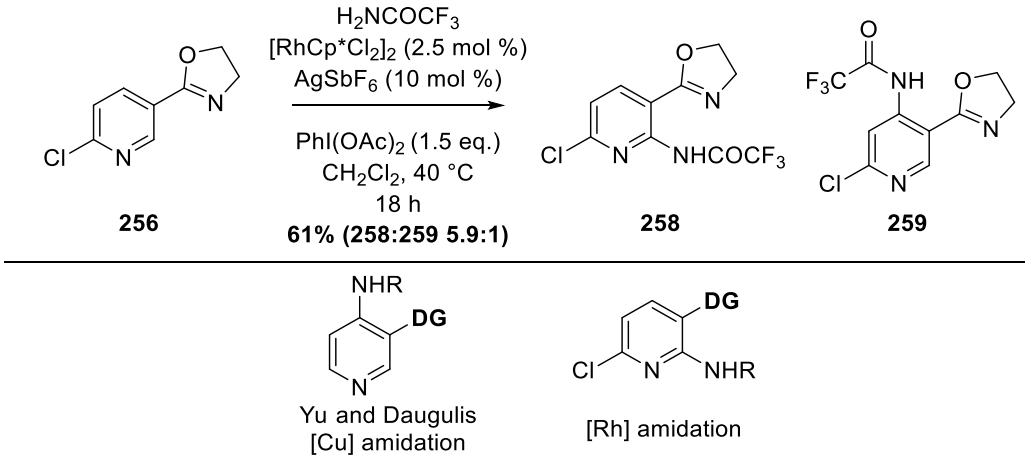
With the observed by-product in hand, attempts were made to optimise the reaction conditions to successfully yield only the oxazoline substrate **256**. The initial reaction conditions led to a low yield of 68% and a 1.0 to 3.8 mixture of the desired material to the reaction by-product (entry 1). Lowering the equivalents of sodium hydroxide led to an observable increase in yield and a change in reaction selectivity, with only a trace amount of methoxy incorporated oxazoline present following purification (entry 2). Attempts to change the reaction solvent to *iso*-propyl alcohol or *tert*-butyl alcohol removed all traces of S_NAr by-product and resulted in moderate yields of the oxazoline substituted pyridine (entries 3 and 4). Alternative reaction conditions, utilising the electrophilic fluorination reagent DAST led to a good yield of 63% of the target material (entry 5). However, due to the exothermic nature of DAST mediated reactions and the required safety precautions alternative methods were sought. Changing the cyclisation conditions to potassium carbonate in acetonitrile at reflux

for 2 h led to an isolated yield of 35% (entry 6), yet it was found leaving the cyclisation reaction for a longer period of time, 5 h, an excellent yield of the desired oxazoline substrate could be achieved, 88% (entry 7). Additionally, the optimised reaction conditions could be used on preparative scale to provide gram quantities of substrate **256**.

Entry	Conditions	Result
1	*p*-TsCl (1.7 eq.), NEt_3 (1.9 eq.), DMAP (0.2 eq.), CH_2Cl_2, 16 h, RT then NaOH (3.0 eq.), MeOH, 2 h, RT	68% (1:3.8 **256**:**257**)
2	*p*-TsCl (1.7 eq.), NEt_3 (1.9 eq.), DMAP (0.2 eq.), CH_2Cl_2, 16 h, RT then NaOH (1.0 eq.), MeOH, 2 h, RT	56% (50:1 **256**:**257**)
3	*p*-TsCl (1.7 eq.), NEt_3 (1.9 eq.), DMAP (0.2 eq.), CH_2Cl_2, 16 h, RT then NaOH (3.0 eq.), IPA, 2 h, RT	44%
4	*p*-TsCl (1.7 eq.), NEt_3 (1.9 eq.), DMAP (0.2 eq.), CH_2Cl_2, 16 h, RT then NaOH (3.0 eq.), *t*-BuOH, 2 h, RT	33%
5	DAST (1.1 eq.), CH_2Cl_2, 1.5 h, - 78 °C	63%
6	*p*-TsCl (1.7 eq.), NEt_3 (1.9 eq.), DMAP (0.2 eq.), CH_2Cl_2, 16 h, RT then K_2CO_3 (3.0 eq.), MeCN, 2 h, Reflux	35%
7	*p*-TsCl (1.7 eq.), NEt_3 (1.9 eq.), DMAP (0.2 eq.), CH_2Cl_2, 16 h, RT then K_2CO_3 (3.0 eq.), MeCN, 5 h, Reflux	88%

Table 15 – Optimisation on oxazoline synthesis

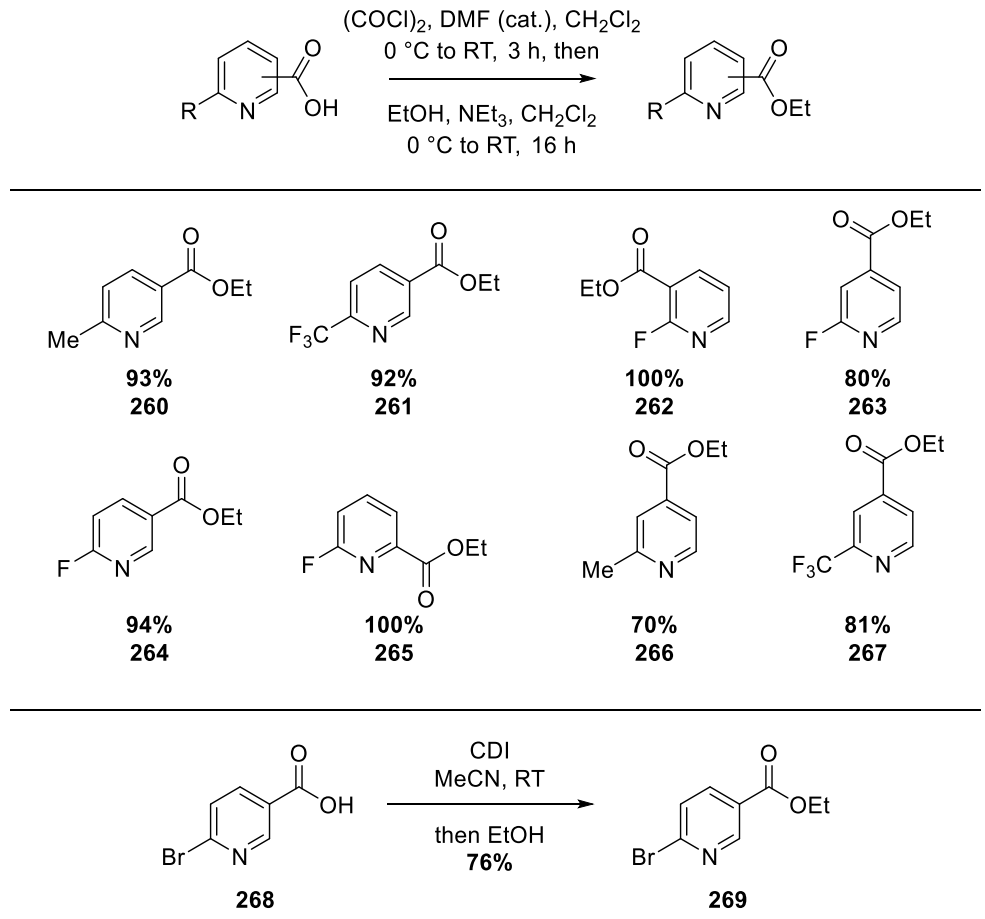
With the required oxazoline substrate in hand subjection to the *C-H* amidation conditions was then considered. Delightfully, when **256** was reacted in the presence of the optimum reaction conditions conversion to the *C-H* aminated products was achieved in good yield*, scheme 143*. Interestingly, the reaction displayed respectable regioselectivity with **258** being the observed major regioisomer. Contrary to the work displayed by Yu and Daugulis, the major regioisomer isolated by this method is the 2-aminopyridine, rather than the 4-aminopyridine observed by their Cu-promoted technique.[99, 148b]



Scheme 143 – *C-H* amidation of 2-chloro substituted pyridine

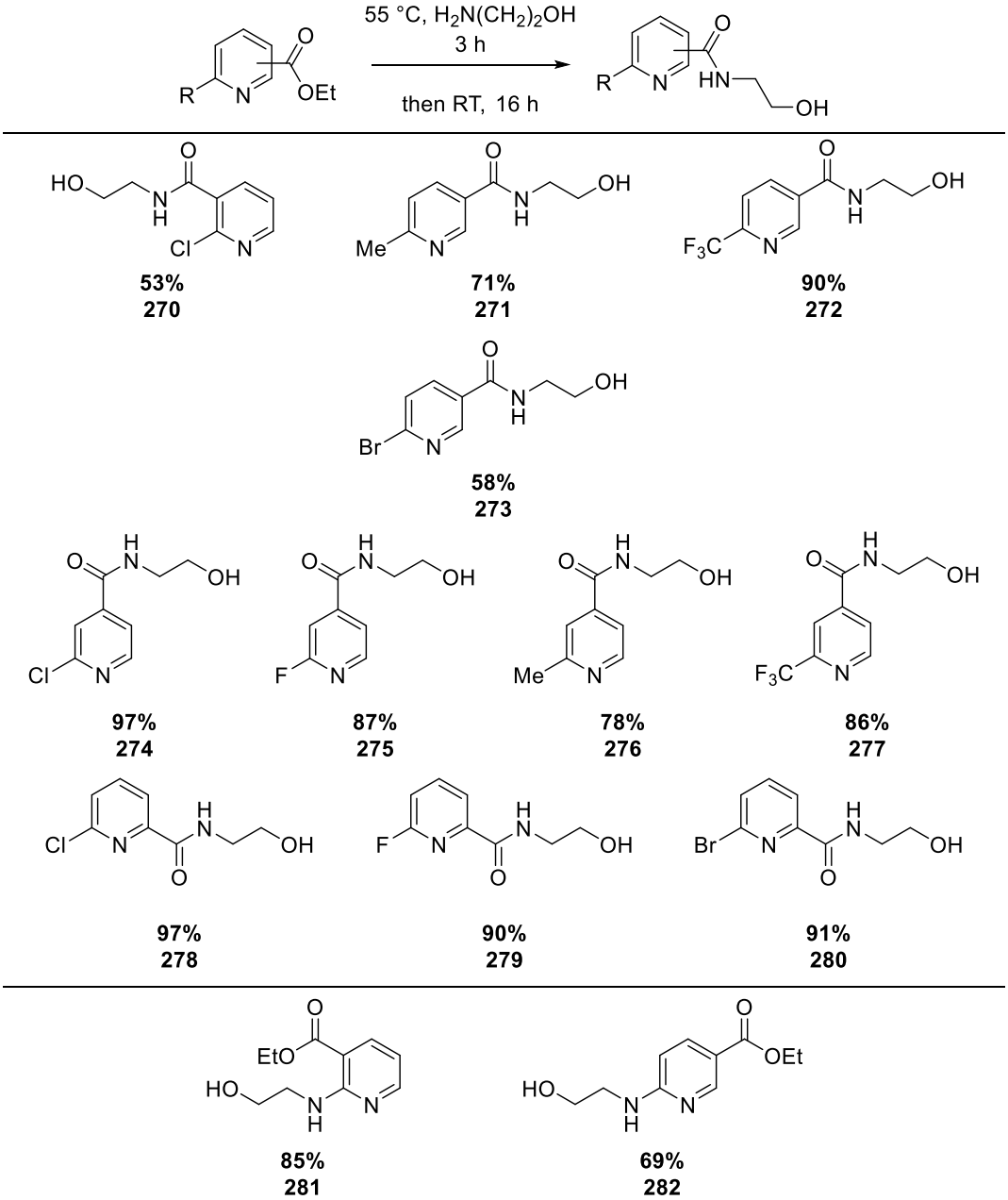
5.5 Synthesis of 2-substituted pyridine oxazolines

Intrigued by the unique observed reactivity, further exploration of the observed benefit of incorporation of a 2-substituent upon a pyridine motif was considered. In order to probe the nature of the substituent effect, a large variety of oxazoline substituted pyridines were synthesised. Initially, synthesis of the requisite oxazolines began by utilising commercially available substrates and the previously demonstrated oxazoline synthesis methodology. In some cases, the required ester was unavailable, but these could be accessed from the corresponding acid in these cases. Depending upon the nature of the substrate, esterification was achieved using either oxalyl chloride methodology or CDI coupling. Pleasingly the chemistry performed well in all cases to generate the corresponding esters in good to excellent yields and in good quantities, as demonstrated in *scheme 144*. In all cases the esterification products were isolated from the reaction mixture and used in the subsequent step without further purification or full characterisation.



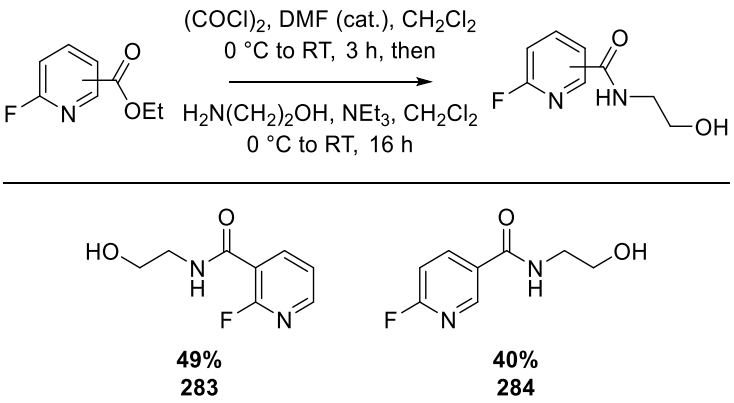
Scheme 144 – Esterification of substituted pyridines

With a range of pyridine esters in hand, the amidation with ethanolamine was then considered. Pleasingly using the previously described amidation conditions, the required 2-hydroxyethyl amides were readily afforded, *scheme 145*. However, in the cases of the fluoro-substituted pyridines, S_NAr side reactivity prevailed over the desired amide formation when the ester was present in the 3- or 5-positions, affording substrates **281** and **282** as the major reaction products in good to excellent yield.



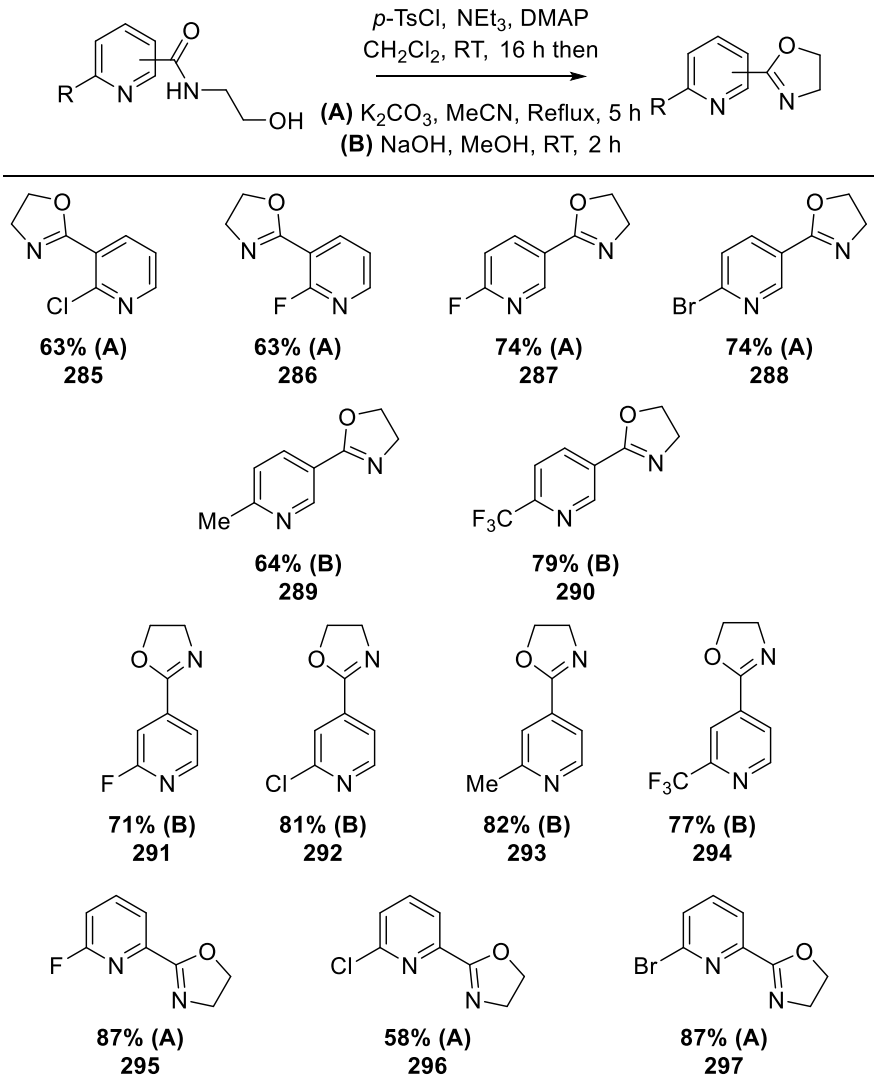
Scheme 145 – Amidation of substituted pyridines

Nonetheless, the problematic 2-fluoropyridines could be accessed *via* the corresponding acid chlorides. However, while the reaction with ethanolamine allowed access to the amide intermediates, in both cases the resulting amides could not be purified and so were used directly in the synthesis of the oxazoline without further purification or full characterisation.



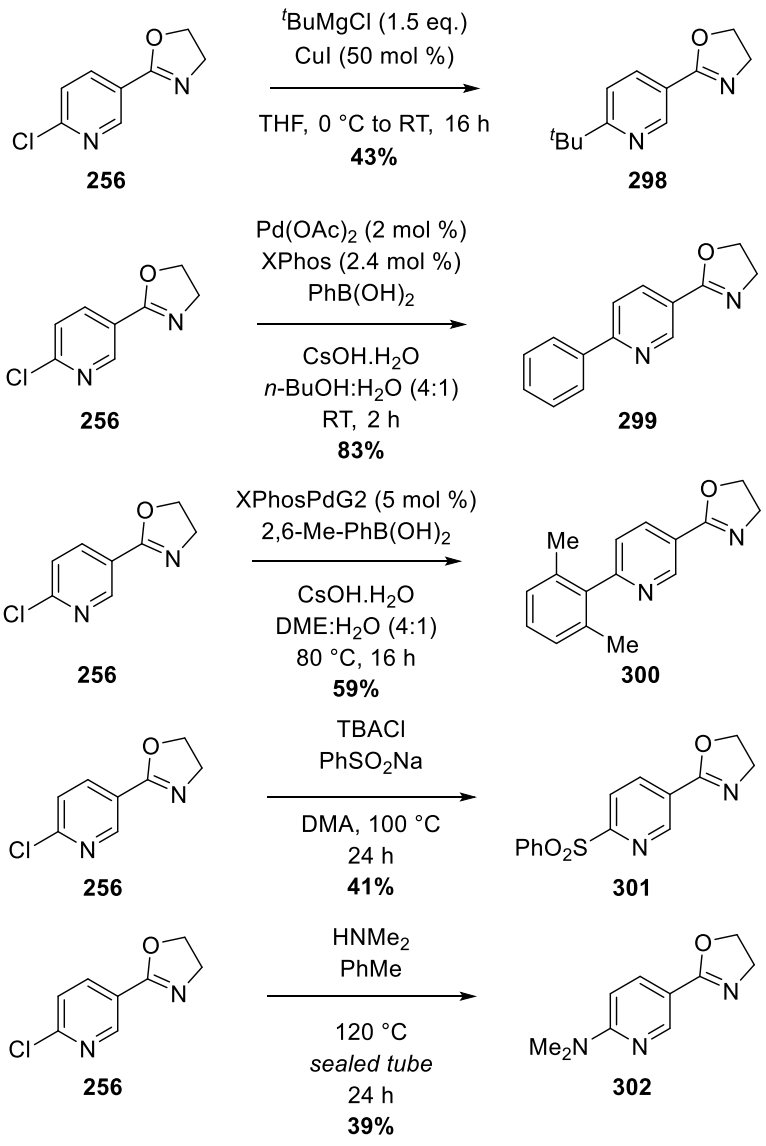
Scheme 146 – Amidation of 2-fluoro pyridines

Oxazoline synthesis was carried out upon all amide substrates utilising the *p*-toluenesulfonyl chloride methodology. Cyclisation was carried out using either sodium hydroxide in methanol or potassium carbonate in refluxing acetonitrile depending upon the nature of the functionality on the pyridine ring (*scheme 147*).



Scheme 147 – Oxazoline synthesis of substituted pyridines

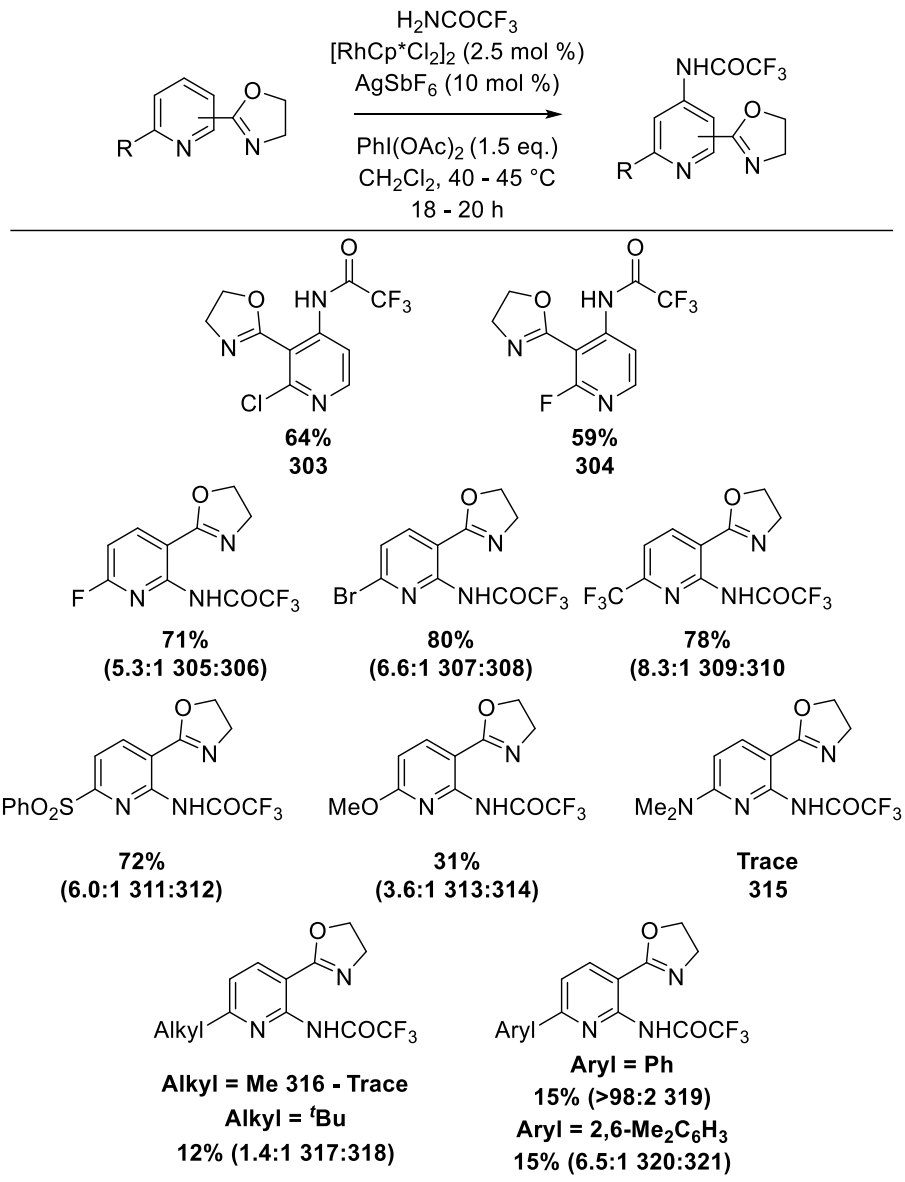
Pyridines substituted with alternate functionalities were also attractive for the exploration of the *C-H* amidation scope, hence in order to synthesise some oxazoline substituted pyridines the parent chloro-substituted pyridine **256** was used as a common starting point. In this regard, alkyl, aromatic, sulfonyl and amino functional groups were introduced successfully, as displayed in *scheme 148*. It was found utilising copper-catalysed chemistry, the *tert*-butyl substituent could be introduced, albeit in a moderate yield **298**. Suzuki-Miyaura coupling was achieved in excellent yield with phenyl boronic acid using reported literature conditions **299**.[151] However, the sterically hindered 2,6-dimethyl phenyl boronic acid showed much lower reactivity. The use of more forceful conditions did however lead to the successful synthesis of the desired substrate in a good yield of 59% **300**. Using phase-transfer conditions the chloro-substituent could readily be substituted with a sulfonyl moiety in an acceptable yield of 41% **301**.[152] Finally, synthesis of the dimethylamino-substituted pyridine was achieved with dimethylamine in refluxing toluene, again only a moderate yield of the desired material was afforded **302**.



Scheme 148 – Further synthesis of substituted pyridine scaffolds

5.6 *C-H* Amidation scope

Following isolation of the desired oxazoline substrates, subjection to the *C-H* amidation reaction conditions was then addressed. Initially the 3-oxazoline substituted pyridine scaffolds were examined as depicted in *scheme 149*.



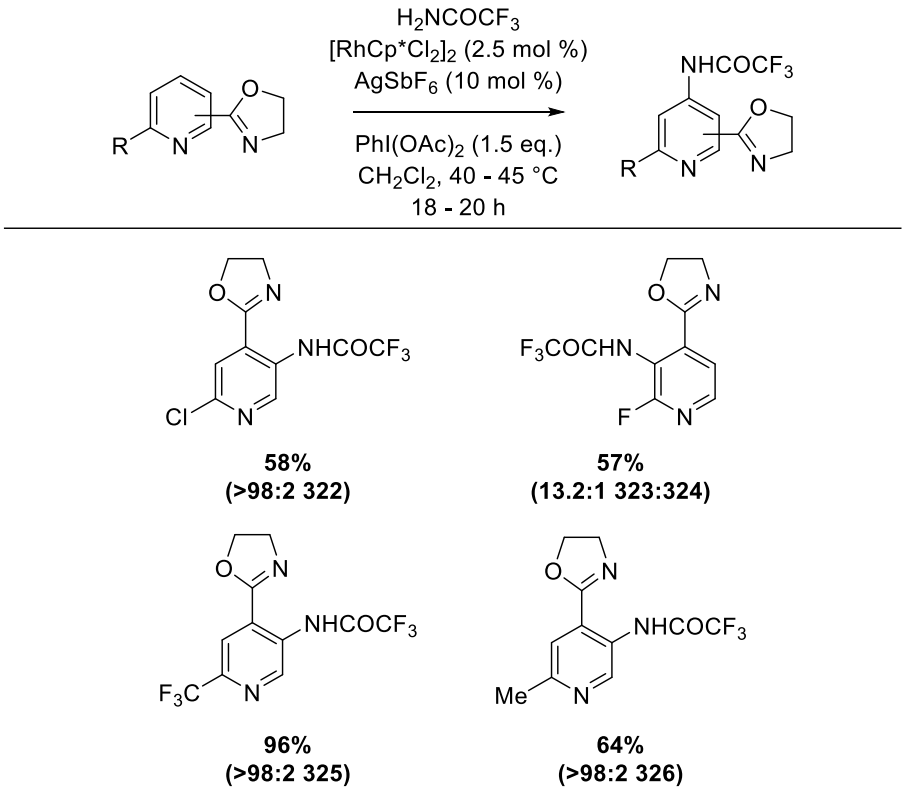
Scheme 149 – *C-H* amidation of 3-oxazoline substituted pyridines (major regioisomer shown where mixtures were observed)

Pleasingly, utilising the standard reaction conditions in refluxing dichloromethane a range of *C-H* amidated products were successfully afforded.[153] When oxazolines **285** and **286** were subjected the corresponding products, **303** and **304** were isolated in good yields. Examining the 3-oxazoline substituted pyridines in which regioisomers were possible, insertion *ortho* to the pyridine nitrogen was consistently observed as the major isomers – in agreement with the initial result upon the chloro substrate **256**. Interestingly, in cases with halide substituents, similar regioisomeric ratios were observed, **305** and **307**, typically in the region of 6:1. Additional electron withdrawing substituents in the form of the trifluoromethyl and the sulfone again worked well, affording the products in very good yields of 72% and 78% respectively, **309** and **311**. Furthermore, in the case of the trifluoromethyl example a very good regioselectivity was observed, 8.3:1.0. When subjecting the electron donating

substituent examples of the methoxy and the dimethylamino, a drop in reactivity was observed. In the case of the methoxy-substituted pyridine a poor yield of 31% was observed, and a much lower regioisomeric ratio of 3.6:1 **313**. The dimethylamino-substituted pyridine demonstrated only trace reactivity, most likely due to its Lewis basic nature. Interestingly, when subjecting alkyl and aryl functionalised pyridines, again a lack of reactivity was observed. In the case of the methyl substituted example **316** only trace conversion was observed. The potential for insertion of the rhodium catalyst upon the sp^3 *C-H* bond cannot be ruled out in this instance as an undesired reaction pathway. Moving to the sterically enhanced *tert*-butyl substituent, a slight increase in reactivity was observed. An overall yield of 12% of substrates **317** and **318** and a regioisomeric ratio of 1.4:1 was noted. Similarly, in the case of the un-functionalised phenyl ring only substrate **319** was isolated following purification in a low yield of 15%. Unfortunately, attempts to isolate other possible insertion products were unsuccessful. The propensity of the pyridine to act as a directing group, allowing for insertion upon the aromatic ring, could not be ruled out. However, in order to further probe this potential side reaction, the sterically encumbered substrate **300** was used, however in agreement with previous observations a low yield was observed **320**. The above observations suggest the beneficial effect of the 2-substituent upon pyridine reactivity in *C-H* functionalisation is primarily electronic rather than steric in nature. Electron withdrawing groups greatly reduced pyridine basicity preventing it from competing with the oxazoline in directing *C-H* activation. Moving to electron donating substituents, reaction yield decreased drastically, and in cases of sterically hindered substrates with alkyl or aromatic functionalities, little reaction is observed. In these instances, it is assumed the pyridine nitrogen atom has little modification of its basicity and again competes with the oxazoline for co-ordination to the rhodium catalyst, hence explaining the lack of reactivity.

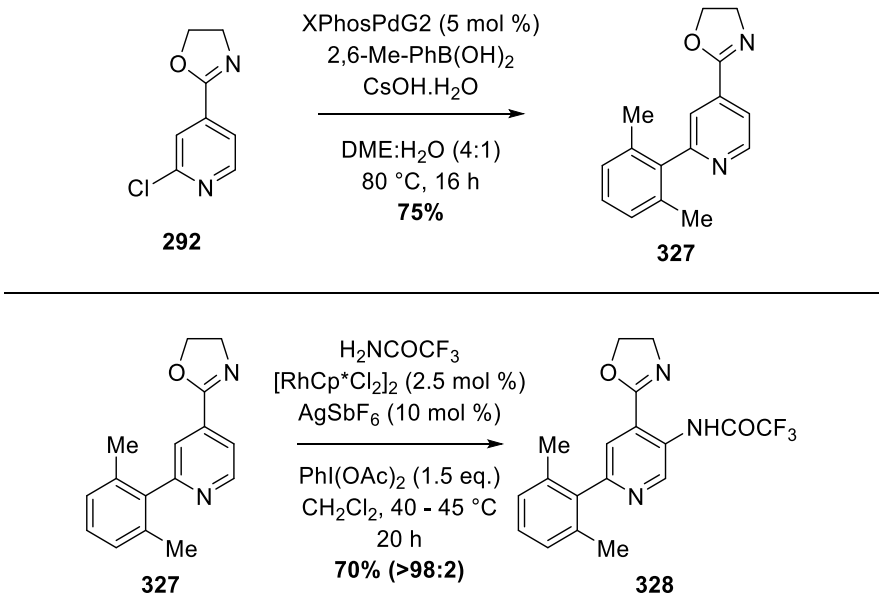
The 4-oxazoline substituted pyridines were then subjected to the reaction conditions, as depicted in *scheme 150*.[153] As expected when 2-chloro-subtituted pyridine was used, **322** was isolated as the only product from the reaction mixture in a good yield of 58%. Surprisingly, when the analogous 2-fluoro-substituted pyridine was subjected to the optimum reaction conditions, the opposite insertion product **323** was isolated as the major isomer with excellent regioselectivity – pleasingly in this instance the regioisomers were separable by flash column chromatography. *C-H* insertion into the alternative position is believed to arise from the electronegativity of fluorine, and its effect upon *C-H* acidity of the *ortho*-protons. Additionally, 2-trifluoromethyl substituted pyridine afforded a single product **325** in excellent yield, following the same insertion pattern as the 2-chloro substituted pyridine. Most unexpectedly, when 2-methyl substituted pyridine was subjected to the amidation

conditions, reactivity occurred affording a single product **326** in a good yield of 64%. When compared to the analogous 3-oxazoline substituted pyridine in which the methyl group had no effect upon the reaction, this particular result highlights the profound effect the oxazoline directing group can have upon the substrate reactivity by acting as an electron withdrawing group and reducing the Lewis basicity of the pyridine nitrogen.



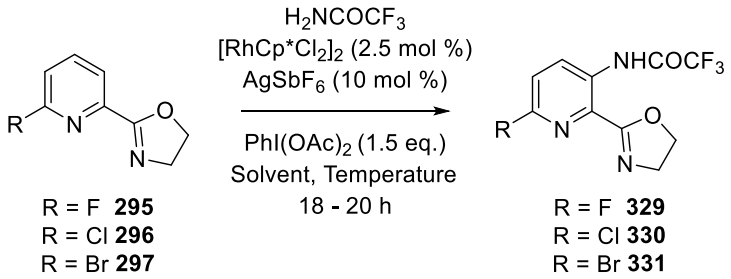
Scheme 150 – *C-H* amidation of 4-oxazoline substituted pyridines (major regioisomer shown where mixtures were observed)

Intrigued by the observed reactivity with substrate **293**, it was decided to prepare an analogous aryl example. Utilising Suzuki-Miyaura reaction conditions with substrate **292** and 2,6-dimethylphenyl boronic acid in the presence of Buchwald pre-catalyst afforded the desired product **327** in a good yield of 75% (*scheme 151*). Pleasingly, when subjected to the optimal *C-H* amidation conditions a single product was isolated **328** in a very good yield of 70% - again this result highlights the effect of the oxazoline directing group.



Scheme 151 – Synthesis of substrate **327** and subjection to the amidation conditions

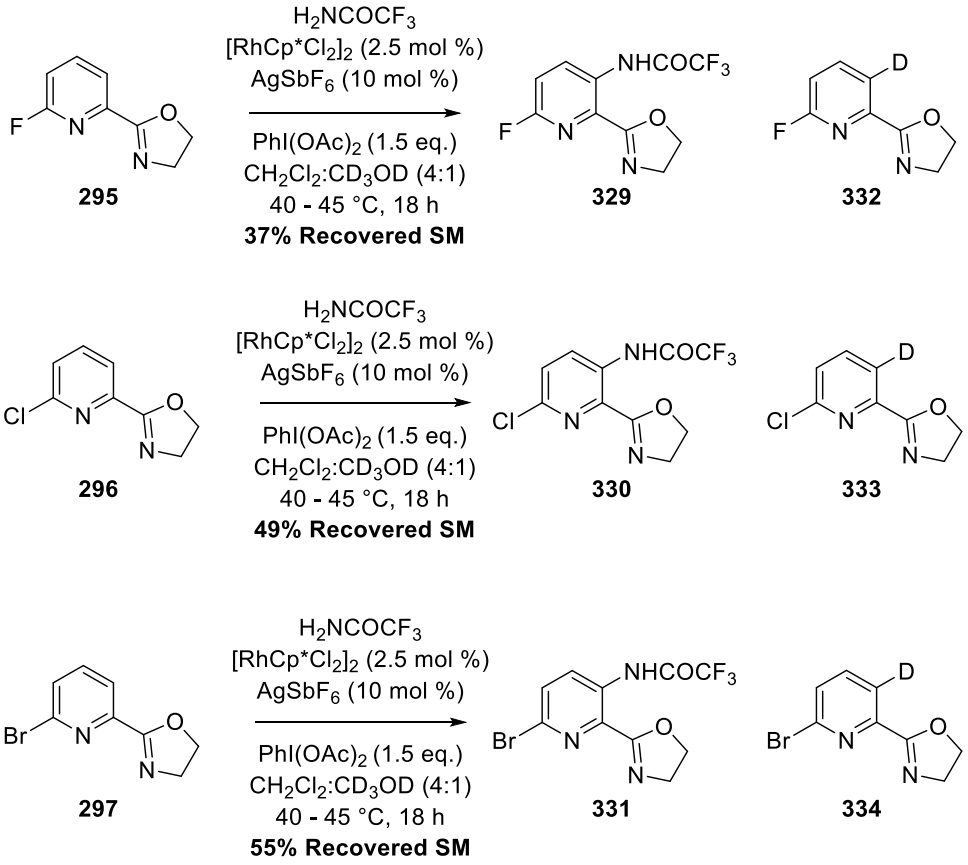
Finally, attention was turned to the 2-oxazoline substituted pyridine scaffolds. Disappointingly when subjecting substrates **295**, **296** and **297** to the standard reaction conditions, no reactivity was observed (*table 16,* entries 1 – 3). When increasing the reaction temperature, only complex mixtures were observed in each case (*table 16, e*ntries 4 – 6). In order to probe the observed lack of reactivity, deuterium incorporation experiments were considered. As in previous cases, if deuterium incorporation was observed then it could be concluded rhodacycle formation was occurring under the reaction conditions, and the lack of reactivity was arising from the subsequent steps. If no deuterium incorporation was detected, then the required rhodacycle formation was somehow being prevented under the reaction conditions.



Scheme 152 – *C-H* amidation attempts with substrates **295**, **296** and **297**

Entry	Substrate	Solvent	Temperature	Result
1	**295**	CH_2Cl_2	40 °C	Recovered SM
2	**296**	CH_2Cl_2	40 °C	Recovered SM
3	**297**	CH_2Cl_2	40 °C	Recovered SM
4	**295**	1,2-DCE	100 °C	Complex mixture
5	**296**	1,2-DCE	100 °C	Complex mixture
6	**297**	1,2-DCE	100 °C	Complex mixture

Table 16 – *C-H* amidation attempts with substrates **295**, **296** and **297**



Scheme 153 – Deuterium incorporation experiment results

Unfortunately, in all three cases, no deuterium incorporation was observed suggesting the required rhodacycle formation was not taking place under the reaction conditions. Interestingly, in each case starting material was re-isolated from the reaction mixtures in less than quantitative yields, however in all cases no by-products were isolated from the crude reaction mixtures. Given the propensity of substrates of this nature to undergo S_NAr reactions, it is important to highlight that there was no evidence for S_NAr attack by the deuterated methanol solvent. The lack of reactivity observed with 2-oxazoline substituted

pyridines is believed to arise from their potential ability to act as ligands. The ability of 2-oxazoline substituted pyridines to act as successful ligands for rhodium is well documented within the literature.[154] In this instance, if the substrates ligate strongly to the rhodium centre, the required cyclometallation pathway is inhibited, shutting down any possible reaction.

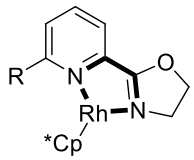
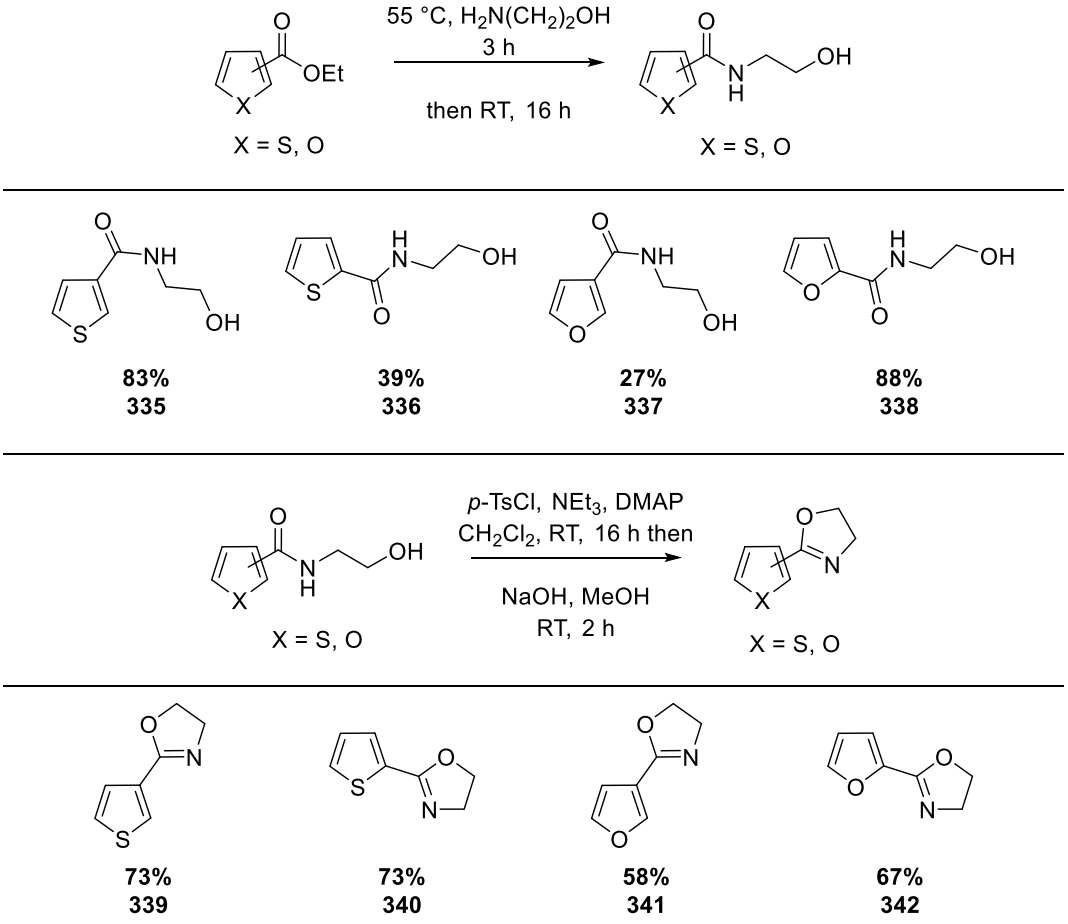


Figure 15 – Ligative nature of 2-oxazoline substituted pyridines

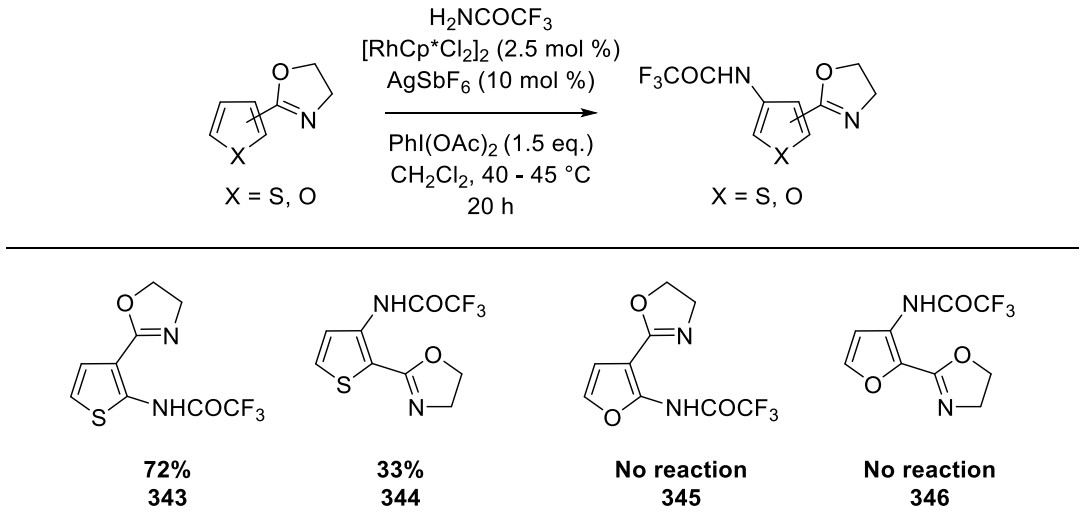
5.7 Heterocycles other than pyridine

Having thoroughly explored the pyridine *C-H* activation scope, attention was then turned to alternative heterocycles, in particular those of thiophene and furan. Utilising commercially available starting materials, the required substrates were synthesised *via* previously described methodologies in two steps, as shown in *scheme 154*. Pleasingly the amidation with ethanolamine followed by the *p*-toluenesulfonyl chloride induced cyclisation affording the four oxazoline substituted heterocycles in good yields.



Scheme 154 – Synthesis of thiophene and furan substituted oxazolines

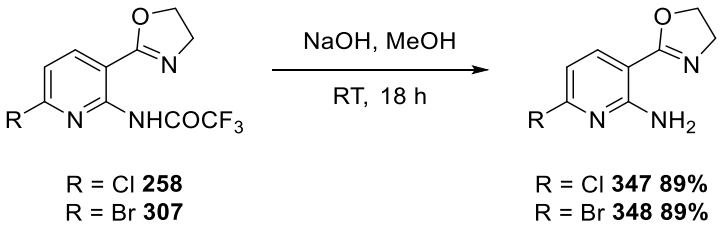
With the azole substrates in hand, subjection to the standard *C-H* amidation conditions were then carried out, as depicted in *scheme 155*. When 3-oxazoline thiophene **339** was subjected to the rhodium-catalysed amidation, major product **343** was isolated in a very good yield of 72%. Traces of the alternative regioisomer were also observed in this instance. Interestingly, when 2-oxazoline thiophene **340** was used, the reaction proceeded in a much lower yield of 33%. However, most surprisingly when both furan substrates **341** and **342** were subjected to the reaction conditions no reaction occurred. By analysis of the crude ^{1}H NMR spectra, only recovered starting material was observed. The lack of reactivity observed with the two furan substrates is somewhat contradictory to the general literature. Furans have been demonstrated to successfully participate in *C-H* amidation protocols by Glorius and Yu.[99, 144] Finally, attempts to aid reactivity of the furan substrates by alteration of reaction solvent and increase in reaction temperature – afforded no observable difference.



Scheme 155 – Thiophene and furan *C-H* amidations

5.8 Post *C-H* amidation functionalisation

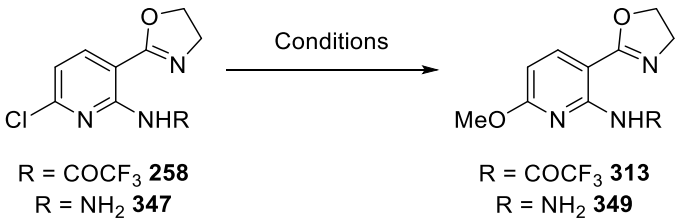
With a selection of amidated 2-substituted pyridines in hand, post *C-H* amidation functionalisation was then considered. In particular, the 2-halo substituted pyridines offered a platform for elegant elaboration to highly functionalised intermediates, along with potential to be transformed into heterocyclic quinazolinone scaffolds. Deprotection of the trifluoroacetamide was initially investigated. Pleasingly, utilising the previously discussed sodium hydroxide in methanol protocol, deprotection of both 2-chloro and 2-bromo substituted pyridines was successfully achieved in excellent yield **347** and **348**, *scheme 156*.



Scheme 156 – Deprotection of the trifluoroacetamide functionality

Moving on, S_NAr reactions were considered to allow for the introduction of alcohol and amine functionalities. First of all, the introduction of an alcohol was considered. As shown in *scheme 157* and *table 17*, utilising sodium hydroxide in methanol on the trifluoroacetamide substrate led only to amide hydrolysis in almost quantitative yield (entry 1). Switching to the parent aniline and sodium hydride as the base led to no improvement (entry 2). Reverting back to sodium hydroxide and methanol but conducting the reaction at reflux pleasingly led to a 2:1 mixture of target material to starting material (entry 3). In order to shift the ratio in the favour of the product, the equivalents of sodium hydroxide were increased from 5.0 to 10.0 and the

reaction was heated at reflux for a slightly longer period of 24 hours which gratifyingly afforded the alcohol substituted product in an excellent yield of 98% (entry 4).



R = $COCF_3$ **258**
R = NH_2 **347**

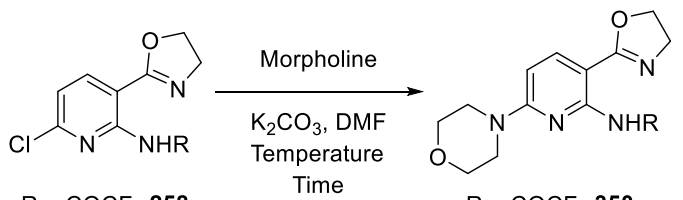
R = $COCF_3$ **313**
R = NH_2 **349**

Scheme 157 – Alcohol incorporation by S_NAr

Entry	Substrate	Conditions	Result
1	**258**	NaOH, MeOH, RT, 18 h	95% of **347**
2	**347**	NaH, MeOH, THF, RT, 18 h	Recovered SM
3	**347**	NaOH (5.0 eq.), MeOH, Reflux, 18 h	97% (2:1 TM:SM **349**:**347**)
4	**347**	NaOH (10.0 eq.), MeOH, Reflux, 24 h	98%

Table 17 – Alcohol incorporation by S_NAr

The introduction of an amine was then considered (*scheme 158* and *table 18*). Using morpholine as the amine source in conjunction with potassium carbonate in DMF unfortunately led only to a mixture of recovered starting material and partial removal of the trifluoroacetamide group (entry 1). Performing the reaction on the parent aniline again led only to the recovery of the starting material (entry 2). However, increasing the reaction temperature to 120 °C led to a mixture of starting material and target material, 38% and 39% respectively (entry 3). Leaving the reaction for an extended period of time, 48 h, gratifyingly afforded the desired product in a good yield of 63%, with only minimal recovery of the starting material observed (entry 4).



R = $COCF_3$ **258**
R = NH_2 **347**

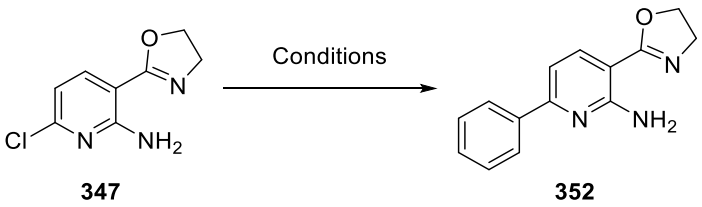
R = $COCF_3$ **350**
R = NH_2 **351**

Scheme 158 – Amine incorporation by S_NAr

Entry	Substrate	Temperature	Time	Result
1	**258**	80 °C	16 h	72% (5.0:1.0 **258:347**)
2	**347**	80 °C	16 h	Recovered SM
3	**347**	120 °C	16 h	38% of **347** & 39% of **351**
4	**347**	120 °C	48 h	3% of **347** & 63% of **351**

Table 18 – Amine incorporation by S_NAr

Notably, the S_NAr reactions described above help to address the previously identified limitations of 3-oxazoline directed *C-H* amidation. In order to further address the scope limitations and utilise the 2-halo functionality, cross-coupling chemistry was then explored with the aim to introduce both phenyl and alkyl substituents. Initially introduction of the phenyl group was considered by Suzuki-Miyaura cross-coupling upon the parent aniline substrate **347** (*scheme 159* and *table 19*). Initially, the previously discussed Suzuki-Miyaura conditions, which were successful for the synthesis of substrates **299** and **300** were considered, however no product formation resulted in this instance (entry 1). Utilising conditions reported by Buchwald led to product formation, albeit in a low yield and delivering impure material (entry 2).[155] Increasing the palladium loadings from 2 to 5 mol %, in conjunction with the loadings of SPhos, 4 to 10 mol %, offered no improvement (entry 3). Altering the reaction system to include the sterically encumbered ligand D^{t}BPF unfortunately led to no conversion to the target material (entry 4).[156]



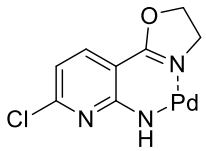
347 **352**

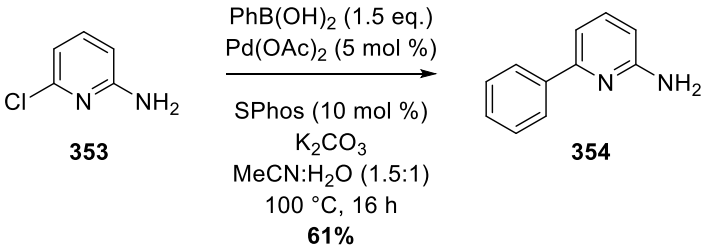
Scheme 159 – Initial Suzuki-Miyaura Optimisation

Entry	Substrate	Conditions	Result
1	**347**	XPhosPdG2 (5 mol %), $PhB(OH)_2$ (1.5 eq.), $CsOH.H_2O$, 1,2-DME:H_2O (4:1), 80 °C, 16 h	Recovered SM
2	**347**	$Pd(OAc)_2$ (2 mol %), SPhos (4 mol %), $PhB(OH)_2$ (1.5 eq.), K_2CO_3, MeCN:H_2O (1.5:1), 100 °C, 16 h	13%
3	**347**	$Pd(OAc)_2$ (5 mol %), SPhos (10 mol %), $PhB(OH)_2$ (1.5 eq.), K_2CO_3, MeCN:H_2O (1.5:1), 100 °C, 16 h	32% (1:2.6 **352:347**)
4	**347**	$Pd(OAc)_2$ (10 mol %), D^tBPF (10 mol %), $PhB(OH)_2$ (1.5 eq.), K_3PO_4, 1,4-Dioxane, Reflux, 16 h	Recovered SM

Table 19 – Initial Suzuki-Miyaura Optimisation

Due to the observed lack of reactivity, it was hypothesised the substrate **347** could potentially be ligating to the palladium catalyst and inhibiting the reaction (*scheme 160*). In order to uncover conditions which were more likely to be successful, a direct example from Buchwald's report was repeated. Using 2-amino-6-chloropyridine **353** the corresponding cross-coupled product was afforded in a 61% yield (*scheme 160*). The result suggested the sluggish reactivity was arising due to the nature of the oxazoline substituted substrate.





Scheme 160 – Potential problem of substrate **347** and control reaction

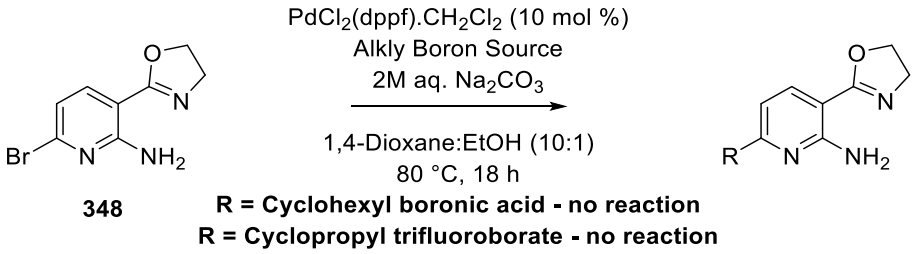
Attention was then turned to alternative conditions. A similar example was reported in 2014, in which a catalytic system of $PdCl_2(dppf).CH_2Cl_2$ was utilised in conjunction with an aqueous solution of sodium carbonate in a refluxing mixture of dioxane and ethanol.[157] Gratifyingly when substrate **347** was subjected to these conditions with $PdCl_2(dppf).CH_2Cl_2$ an increase in yield was observed, however the product was isolated as a mixture of starting material and target material (*table 20*, entry 1). Leaving the reaction for a longer period of time, 24 h,

resulted in full conversion, however only a moderate yield of 36% was obtained (entry 2). Switching to the corresponding bromide **348** gave a similar result of 39% (entry 3). Pleasingly, when both 2-chloro and 2-bromo substrates were subjected to the reaction conditions with an extra equivalent of boronic acid, full conversion was achieved and the cross-coupled product was obtained in increased yields of 47% and 58% respectively (entries 4 and 5).

Entry	Substrate	Conditions	Result
1	**347**	$PdCl_2(dppf).CH_2Cl_2$ (10 mol %), $PhB(OH)_2$ (1.6 eq.), 2M aq. Na_2CO_3, 1,4-Dioxane:EtOH (10:1), 80 °C, 18 h	48% (6.3:1 **352**:**347**)
2	**347**	$PdCl_2(dppf).CH_2Cl_2$ (10 mol %), $PhB(OH)_2$ (1.6 eq.), 2M aq. Na_2CO_3, 1,4-Dioxane:EtOH (10:1), 80 °C, 24 h	36%
3	**348**	$PdCl_2(dppf).CH_2Cl_2$ (10 mol %), $PhB(OH)_2$ (1.6 eq.), 2M aq. Na_2CO_3, 1,4-Dioxane:EtOH (10:1), 80 °C, 18 h	39%
4	**347**	$PdCl_2(dppf).CH_2Cl_2$ (10 mol %), $PhB(OH)_2$ (2.6 eq.), 2M aq. Na_2CO_3, 1,4-Dioxane:EtOH (10:1), 80 °C, 18 h	47%
5	**348**	$PdCl_2(dppf).CH_2Cl_2$ (10 mol %), $PhB(OH)_2$ (2.6 eq.), 2M aq. Na_2CO_3, 1,4-Dioxane:EtOH (10:1), 80 °C, 18 h	58%

Table 20 – Further Suzuki-Miyaura Optimisation

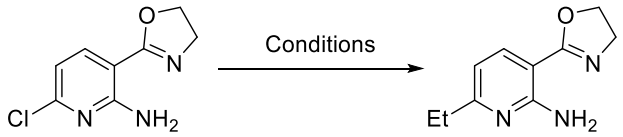
Following on from the successful Suzuki-Miyaura coupling of the *C-H* amidated product, introduction of an alkyl substituent was then considered. Initial attempts involved utilisation of the optimal Suzuki-Miyaura cross-coupling conditions with substrate **348** and two different alkyl boron sources (*scheme 161*). Unfortunately, with both cyclopropyl trifluoroborate and cyclohexyl boronic acid no conversion to the desired product was observed. Due to the observed lack of reactivity alternative methodologies were sought.



Scheme 161 – Suzuki-Miyaura with alkyl boron sources

Attention was turned to utilising the previously reported organocopper and Grignard chemistry which afforded substrate **298**. It was hoped that using the same conditions upon the post *C-H* amidation substrate **347** would allow for successful incorporation of an alkyl

substituent at the 2-position of the pyridine. Unfortunately, when subjecting substrate **347** to ethyl magnesium bromide and copper (I) iodide, a complex mixture was afforded (entry 1, *table 21*). Turning to reported Negishi cross-coupling conditions with diethylzinc offered no improvement (entry 2).[158] Excitingly, when switching to Fürstner's Iron-catalysed cross-coupling conditions with ethyl magnesium bromide, clean reactivity was observed furnishing the alkyl substituted product **355** in a good yield of 57% (entry 3).[158-159]



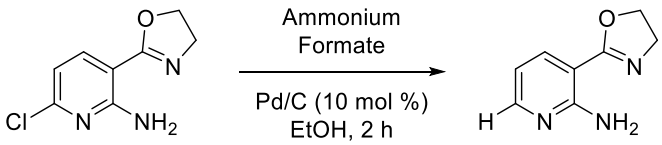
347 **355**

Scheme 162 – Post *C-H* amidation introduction of alkyl substituent

Entry	Conditions	Result
1	EtMgBr (3.3 eq.), CuI (1.0 eq.), THF, 0 °C to RT, 24 h	Complex mixture
2	$ZnEt_2$ (1.8 eq.), $Pd(PPh_3)_4$ (10 mol %), NMP, 100 °C, 20 h	Complex mixture
3	EtMgBr (3.3 eq.), $Fe(acac)_3$ (15 mol %), THF:NMP (10:1), RT, 2 h	57%

Table 21 – Post *C-H* amidation introduction of alkyl substituent

With successful achievement of both aryl and alkyl incorporation, removal of the halide substituent to afford the parent unsubstituted pyridine was next explored. Again, this product could not be accessed previously because the corresponding substrate was inert to the *C-H* amidation conditions. Initially taking substrate **347** with ammonium formate and catalytic Pd/C only afforded the recovery of the starting material. This was believed to be due to the low solubility of substrate **347**.[160] It was found however, utilising the same reaction conditions, except at reflux for 2 h afforded better reactivity, yielding the pyridine **356** in a very good yield of 69% following purification (*scheme 163*).

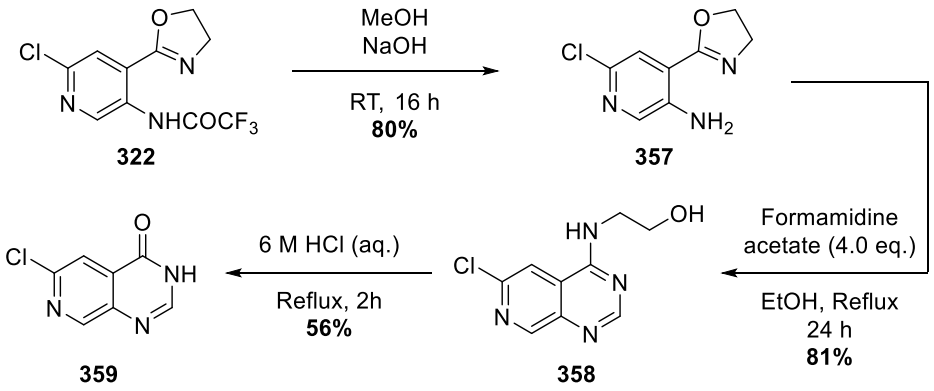


347 **356**

Scheme 163 – Removal of the 2-chloro substituent

Attention was then turned to conversion of the amidated intermediates into the quinazolinone scaffold (*scheme 164*). Subjection of substrate **322** to sodium hydroxide in

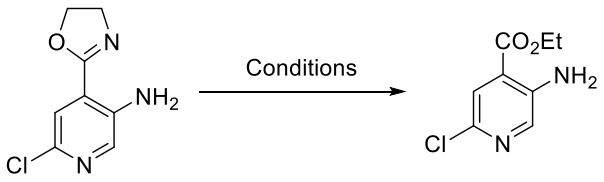
methanol afforded the deprotected aniline **357** in an excellent yield of 80%. Pleasingly, the aza-quinazoline scaffold **358** could be generated in excellent yield, 81%. It was found an additional equivalent of formamidine acetate and an extended reaction time of 24 h, when compared to the previously discussed aryl examples, was required to achieve full conversion. Finally, subjection of quinazoline **358** to aqueous acid afforded the aza-quinazolinone **359** in a good yield of 56% and upon practical scale (*scheme 164*).



Scheme 164 – Conversion to the azaquinazolinone

Finally, having thoroughly exemplified post *C-H* amidation functionalisation chemistry and conversion to the quinazolinone, deprotection of the oxazoline to a carboxylic acid derivative was considered. It was decided to employ reported conditions in which the deprotected oxazoline was converted to the corresponding ester (*scheme 165*).[161] Utilising sulphuric acid in ethanol at reflux, cleavage of the oxazoline was observed in a moderate yield of 40% (*table 22*, entry 1). Running the reaction at a higher concentration unfortunately led to a slight decrease in yield, suggesting that high dilution was important (entry 2). Altering the ratio of sulphuric acid to ethanol from (1:9) to (1:4) led a similar isolated yield, 42%, of the desired ester product (entry 3). Leaving the reaction for a shorter period of time, 14 h versus 20 h, again led to no significant improvement (entry 4). Finally, increasing the scale of the deprotection afforded a similar yield (entry 5).

Despite many attempts, only a moderate yield of oxazoline deprotection could be afforded. In spite of the low deprotection yield, the successful removal of the directing group does add value to the overall *C-H* amidation chemistry – highlighting it as a highly useful route to affording functionalised amino-pyridine scaffolds.



357 **360**

Scheme 165 – Deprotection of the oxazoline

Entry	Conditions	Result
1	H_2SO_4:EtOH (1:9) (0.035 M), Reflux, 20 h	40%
2	H_2SO_4:EtOH (1:9) (0.07 M), Reflux, 20 h	30%
3	H_2SO_4:EtOH (1:4) (0.035 M), Reflux, 20 h	42%
4	H_2SO_4:EtOH (1:4) (0.035 M), Reflux, 14 h	44%
5	H_2SO_4:EtOH (1:9) (0.035 M), Reflux, 20 h (1.0 mmol scale)	42%

Table 22 – Deprotection of the oxazoline

Chapter 6: Conclusions and Future Outlook

In conclusion, a new methodology for the synthesis of highly functionalised quinazolines and quinazolinones has been successfully achieved. Rhodium-catalysed *C-H* amidation was found to be most optimal for the desired transformation. In comparison, palladium catalysis was found to be unsuccessful. In the latter case, results indicated that the five membered palladacyclic-intermediate was too stable to undergo amidation. Furthermore, copper and ruthenium catalysis were also found to be ineffective. Examination of the rhodium-catalysed conditions led to a number of interesting observations. The steric bulk of the oxazoline directing group was found to have an effect upon reaction outcome, whereby smaller analogues were found to be more reactive. Pleasingly, it was found that the reaction could be performed at room temperature although slightly elevated temperatures were optimal. Additionally, a limitation of amide source was discovered, with the trifluoroacetamide and sulfonamides being amongst only a few successful substrates. The reaction was also found to show significant functional group tolerance, with mono-amidation and insertion into the least sterically hindered position observed in virtually all cases. Transformation of the highly functionalised amino substituted aromatic oxazolines into the corresponding quinazolines was established by a deprotection/cyclisation sequence. Overall, the new methodology alleviates the previous requisite for a 1,2-disubstituted aromatic starting material, and allows readily available benzoic acids to be used instead. The methodology also allows for rapid access to medicinally relevant quinazolinones as established by the synthesis of the halofuginone and Erlotinib quinazolinones.

The *C-H* amidation methodology provides an efficient means for constructing quinazoline derivatives that are unsubstituted at *C*2. Efforts were made to functionalise the 2-position of the quinazolinone scaffold both during and after the cyclisation step. Within the cyclisation step, the use of methyl benzimidate hydrochloride allowed for the incorporation of the phenyl moiety in moderate yield. However, attempts to further expand the reaction scope and increase the reaction yield were unsuccessful. Alternative attempts at functionalisation involved the use of the xanthate radical precursors. Despite efforts with a small selection of the xanthate precursors no incorporation of a 2-substituent was observed. In summary, efforts to-date have led to little progress towards the introduction of a 2-substituent upon the heteroaromatic scaffold, and therefore require further study.

Application of the rhodium-catalysed *C-H* amidation chemistry upon pyridine scaffolds was successful. Initial investigations upon the parent pyridine-oxazoline scaffolds were disappointing; poor reactivity was observed due to the competing complexation to the metal

(pyridine nitrogen versus oxazoline nitrogen). However, modulation of the Lewis basic pyridine nitrogen was successfully achieved *via* the incorporation of a 2-substituent upon the heteroaromatic motif. Investigations revealed that a wide variety of 2-substituted pyridine scaffolds could be successfully subjected to the reaction conditions. Attempts to expand the scope to alternative heterocyclic scaffolds showed that thiophenes could readily undergo the rhodium-catalysed *C-H* amidation, however furans were found to be incompatible. To demonstrate the synthetic potential of the *C-H* amidation of 2-substituted pyridines, post *C-H* functionalisation was investigated. Pleasingly, the pyridine ring could undergo the same cyclisation and cleavage conditions as the previously discussed aryl examples to afford a valuable azaquinazolinone scaffold. Additionally, functionalisation of the 2-chloro- and 2-bromopyridine scaffolds could be readily achieved to incorporate alcohol and amine functionalities by S_NAr reactions, and aromatic groups by Suzuki-Miyaura coupling. Furthermore, the 2-chloropyridine substrate was found to readily undergo iron-catalysed cross-coupling to introduce alkyl groups. Synthesis of the parent pyridine could also be achieved by hydrogenation methodologies.

Future work within the scope of this project is likely to deal with the replacement of the precious transition metal rhodium catalyst with an alternative and more sustainable source. Additionally, further research in the incorporation of a 2-substituent upon the quinazolinone scaffold would further establish the value of the method within organic synthesis. Finally, the *C-H* activation/cyclisation sequence could be explored with a view towards the synthesis of other heterocycles by the use of alternative directing groups and the introduction of different functionalities.

Chapter 7: Experimental

7.1 General considerations

All reactions were conducted in flame-dried glassware under ambient conditions unless otherwise stated.

Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer, ν_{max} in cm^{-1}. Samples were recorded neat or as thin films using sodium chloride plates as a dichloromethane solution. Bands are characterised as broad (br), strong (s), medium (m), or weak (w).

^{1}H NMR spectra were recorded on a Bruker AVIII HD 400 (400 MHz), Bruker AVI 400 (400 MHz), Bruker AMX-400 (400 MHz) or DPX-400 (400 MHz) supported by an Aspect 3000 data system. Chemical shifts are reported in parts per million (ppm) from tetramethylsilane with the residual protic solvent resonance as the internal standard ($CHCl_3$: δ 7.26, DMSO: δ 2.50, MeOH: δ 3.31) unless otherwise stated. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), assignments).

^{13}C NMR spectra were recorded on a Bruker AVIII HD 400 (100.6 MHz), Bruker AVI 400 (100.6 MHz), Bruker AMX-400 (100.6 MHz) or DPX-400 (100.6 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ($CHCl_3$: δ 77.16, DMSO: δ 39.52, MeOH: δ 49.00) unless otherwise stated.

^{19}F NMR spectra were recorded on a Bruker AVIII HD 400 (235.1 MHz) or Bruker AMX-400 (235.1 MHz).

High-resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on either a MicroMass LCT operating in Electrospray mode (TOF ES^+) or a MicroMass Prospec operating in FAB (FAB^+), EI (EI^+) or CI (CI^+) mode.

Thin layer chromatography (TLC) was performed on aluminium backed plates pre-coated with silica (0.2 mm, Merck DC-alufolien Kieselgel 60 F254) which were developed using standard visualizing agents: UV light or potassium permanganate. Flash chromatography was performed on silica-gel (BDH Silica Gel 60 43-60). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. All solvents and reagents were purified using standard laboratory techniques according to methods published in "Purification of Laboratory Chemicals" by Perrin, Armarego and Perrin (Pergamon Press, 1966).

7.2 General Procedures

General Procedure A: Rhodium-Catalysed C-H Amidation Procedure (Schlenk Tube)

To a dried Schlenk tube was added oxazoline (1.2 – 2.0 eq.), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $PhI(OAc)_2$ (1.5 eq.) and trifluoroacetamide (1.0 eq.). The tube was fitted with a rubber septum, and placed under an atmosphere of nitrogen, followed by the addition of dry dichloromethane *via* syringe (0.1 M with respect to trifluoroacetamide). The septum was replaced by a Teflon screwcap under nitrogen flow. The reaction mixture was stirred at 40 – 45 °C for 16 – 20 h. After cooling to room temperature the solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) followed by dichloromethane to afford the aminated products.

General Procedure B: One-Pot Oxazoline Synthesis via Appel Methodology

To a stirred solution of benzoic acid (1.0 eq.) in dry dichloromethane (0.3 M with respect to benzoic acid) at 0 °C was added oxalyl chloride (3.0 eq.) and DMF (few drops). The reaction was allowed to warm to room temperature and stirred for a period of 3 hours before removing the solvent *in vacuo*. The crude residue was then dissolved in dry dichloromethane (0.14 M with respect to benzoic acid) and cooled to 0 °C using an ice bath. Triethylamine (1.0 eq.) was added, followed by the slow addition of ethanolamine over 5 minutes (1.0 eq.). The reaction was allowed to warm to room temperature and stir overnight before removing the solvent *in vacuo*. To the crude residue was added dry acetonitrile (0.085 M with respect to benzoic acid), triethylamine (15.6 eq.) and carbon tetrachloride (22.6 eq.). Triphenylphosphine (3.6 eq.) was then added in one portion, and the reaction was allowed to stir at room temperature for 48 hours. The reaction was diluted with ethyl acetate and washed with saturated $NaHCO_3$ (aq.). The organic phase was dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) and ethyl acetate to afford the oxazoline products.

General Procedure C: Rhodium-Catalysed C-H Amidation Procedure (Reflux Apparatus)

To a dried round bottomed flask equipped with a stirrer bar and reflux condenser was added oxazoline (1.2 – 2.0 eq.), $[RhCp^*Cl_2]_2$ (1 – 2.5 mol %), $AgSbF_6$ (1 – 4 mol %), $PhI(OAc)_2$ (1.5 eq.) and trifluoroacetamide (1.0 eq.). The system was evacuated and refilled with nitrogen (3 times), followed by the addition of dry dichloromethane *via* syringe (0.1 M with respect to trifluoroacetamide). The reaction mixture was stirred at reflux (40 – 45 °C) for 16 – 20 h. After cooling to room temperature the solvent was removed *in vacuo* and the residue was purified

by flash column chromatography on silica gel eluting with petroleum ether (40/60) followed by dichloromethane to afford the aminated products.

General Procedure D: Cyclisation to the Quinazoline

Trifluoroacetamide substrate (1.0 eq.) was dissolved in ethanol (0.1 M with respect to trifluoroacetamide substrate), NaOH pellets (20 eq.) were added and the reaction mixture was allowed to stir at room temperature. The reaction was monitored by TLC analysis until complete conversion of the starting material was observed (typically 5 – 6 h); upon completion the solvent was removed *in vacuo*. The residue was dissolved in water and ethyl acetate, and transferred to a separating funnel. The layers were partitioned, followed by further extraction of the aqueous layer with ethyl acetate. The combined organics were then washed with brine, followed by drying over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue was then dissolved in ethanol (0.1 M with respect to trifluoroacetamide substrate) and formamidine acetate (3.0 eq.) was added, and the mixture heated at reflux for 1 hour. After cooling to room temperature, the reaction mixture was dry loaded onto silica gel and purified by flash column chromatography eluting with dichloromethane and methanol (1% MeOH to 20% MeOH) to afford the quinazoline products.

General Procedure E: Cleavage of the Amino-Alcohol Chain to the Quinazolinone

Quinazoline substrate (1.0 eq.) was suspended in 6 M HCl aq. in a round bottomed flask equipped with reflux condenser, and heated to 100 – 105 °C for a period of 2 hours. The reaction was then allowed to cool to room temperature, and further cooled to 0 °C with an ice/water bath. The reaction mixture was basified to pH 11 with aqueous ammonia solution (35%) or aqueous NaOH solution (10% w/v) and allowed to stir for 15 minutes. The resulting precipitate was filtered and washed with ice cold water to afford the quinazolinone products. In cases where precipitate was not observed the reaction mixture was concentrated under reduced pressure, dried overnight before suspended in dichloromethane and methanol and dry-loaded onto silica gel. Purification was then achieved by flash column chromatography on silica gel eluting with dichloromethane and methanol (1% MeOH to 20% MeOH) to afford the quinazolinone products.

General Procedure F: Oxazoline Synthesis via p-TsCl and NaOH

To a dried round bottomed flask was added amide (1.0 eq.) and dry dichloromethane (0.6 M with respect to amide). With stirring NEt_3 (1.9 eq.) was then added, followed by DMAP (0.2 eq.) and *p*-TsCl (1.7 eq.). The reaction mixture was allowed to stir at room temperature overnight, before being diluted with dichloromethane and water. The mixture was then

transferred to a separating funnel and the layers partitioned. The aqueous layer was further extracted with dichloromethane. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude residue was dissolved in MeOH (0.5 M with respect to amide) and NaOH pellets (3.0 eq.) were added in one portion. The reaction mixture was stirred at room temperature for 1 – 3 h before removing the solvent *in vacuo*. The residue was dissolved in dichloromethane and water, and transferred to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with dichloromethane and ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) and ethyl acetate (0% ethyl acetate to 100% ethyl acetate) to afford the oxazoline products.

General Procedure G: Amide Synthesis

To a dried round bottomed flask was added ester (1.0 eq.) and heated to 55 °C with stirring. Upon reaching the desired temperature ethanolamine (1.5 eq.) was added slowly *via* syringe and the reaction was stirred for 3 h before cooling to room temperature, and stirring for a further 18 hours. The crude reaction mixture was then purified by recrystallisation or flash column chromatography on silica gel eluting with dichloromethane and methanol (1% MeOH to 20% MeOH) or ethyl acetate (100%) to afford the amide products.

NB: When the required ester was not commercially available, esterification was carried out to the ethyl ester from the parent carboxylic acid using one of the following procedures. The products were used directly without characterisation or purification.

Esterification procedure 1: To a stirred solution of carboxylic acid (1.0 eq.) in dry dichloromethane (0.2 M with respect to carboxylic acid) at 0 °C was added oxalyl chloride (3.0 eq.) and DMF (few drops). The reaction was allowed to warm to room temperature and stirred for a period of 3 hours before removing the solvent *in vacuo*. The crude residue was then dissolved in dry dichloromethane (0.2 M with respect to carboxylic acid) and cooled to 0 °C using an ice bath. Triethylamine (3.0 eq.) was then added, followed by ethanol (3.0 eq.) *via* syringe. The reaction was allowed to warm to room temperature and stir overnight. The reaction was then diluted with a saturated solution of $NaHCO_3$ (aq.) and dichloromethane, and transferred to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the crude ester product.

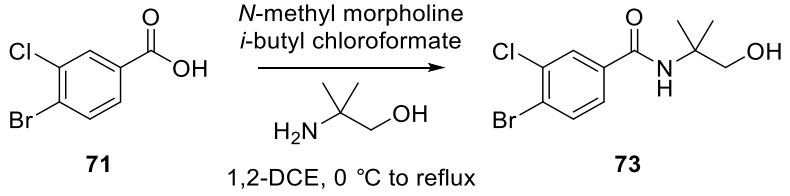
Esterification procedure 2: To a stirred solution of carboxylic acid (1.0 eq.) in MeCN (0.6 M with respect to carboxylic acid) was added CDI (1.1 eq.). The reaction mixture was allowed to stir for a period of 2 hours at room temperature before ethanol (2.5 eq.) was added *via* syringe. The reaction was then stirred overnight at room temperature, before diluting with dichloromethane and transferring to a separating funnel. The organic phase was then subsequently washed with a saturated solution of $NaHCO_3$ (aq.) and deionised water. The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the crude ester product.

General Procedure H: Oxazoline Synthesis via p-TsCl and K_2CO_3

To a dried round bottomed flask was added amide (1.0 eq.) and dry dichloromethane (0.6 M with respect to amide). With stirring NEt_3 (1.9 eq.) was then added, followed by DMAP (0.2 eq.) and *p*-TsCl (1.7 eq.). The reaction mixture was allowed to stir at room temperature overnight, before being diluted with dichloromethane and water. The mixture was then transferred to a separating funnel and the layers partitioned. The aqueous layer was further extracted with dichloromethane. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude residue was dissolved in MeCN (0.5 M with respect to amide) and K_2CO_3 (3.0 eq.) was added in one portion. The reaction mixture was stirred at 85 °C for 5 h before cooling to room temperature and removing the solvent *in vacuo*. The residue was dissolved in dichloromethane and water, and transferred to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with dichloromethane and ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) and ethyl acetate (0% ethyl acetate to 100% ethyl acetate) to afford the oxazoline products.

7.3 Characterisation data and additional procedures

Synthesis of 4-bromo-3-chloro-N-(1-hydroxy-2-methylpropan-2-yl)benzamide **73**

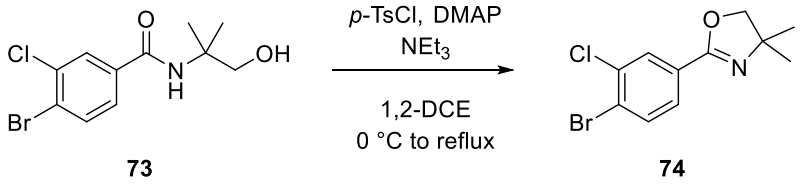


71 73

4-Bromo-3-chlorobenzoic acid **71** (0.59 g, 2.5 mmol) was dissolved in 1,2-dichloroethane (25 mL) and cooled to 0 °C using an ice/water bath. *N*-Methyl morpholine (0.38 g, 3.8 mmol) and isobutyl chloroformate (0.39 g, 2.9 mmol) were added to the reaction followed by stirring for 10 minutes. 2-Amino-2-methyl-1-propanol (0.25 g, 2.9 mmol) was added dropwise, and the reaction was allowed to slowly warm to room temperature. The reaction was then heated at reflux 24 hours and monitored *via* TLC analysis until completion. The reaction was quenched with HCl (aq.) (1 M, 15 mL) and transferred to a separating funnel. Dichloromethane was added and the layers were partitioned. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether (40/60)/ethyl acetate (2:1) to afford product **73** as a colourless solid (0.69 g, 90%).

M.p.: 79 – 81 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3314 (m), 3083 (w), 2998 (w), 1638 (m), 1465 (m), 1323 (m), 1055 (m), 1018 (m); ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.80 (1H, d, *J* = 2.0 Hz, C*H*$_{ar}$), 7.69 – 7.65 (1H, m, C*H*$_{ar}$), 7.47 – 7.43 (1H, m, C*H*$_{ar}$), 3.68 (2H, s, C*H*$_2$), 1.41 (6H, s, C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$); δ 166.2, 135.6, 135.2, 134.1, 129.0, 126.3, 126.2, 70.5, 56.8, 24.6; HRMS: *m/z* $[MH]^+$ $C_{11}H_{14}NO_2{}^{35}Cl^{79}Br$ calcd. 305.9896, found 305.9893.

Synthesis of 2-(4-bromo-3-chlorophenyl)-4,4-dimethyl-4,5-dihydrooxazole **74**



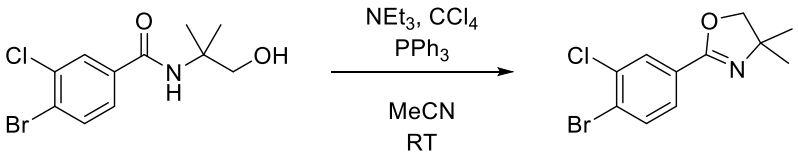
73 74

p-Toluene sulfonyl chloride (0.08 g, 0.4 mmol) and *N*,*N*-dimethylaminopyridine (0.002 g, 0.02 mmol) were dissolved in 1,2-dichloroethane (2.5 mL), and the mixture cooled to 0 °C using an ice/water bath, followed by the addition of triethylamine (0.17 g, 1.7 mmol). 4-Bromo-3-chloro-*N*-(1-hydroxy-2-methylpropan-2-yl)benzamide **73** (0.10 g, 0.33 mmol) was dissolved in 1,2-dichloroethane (2.5 mL) and the solution added dropwise to the cooled mixture *via* syringe. The reaction was stirred at 0 °C for 15 minutes before being heated at reflux for 16 h. The reaction was allowed to cool to room temperature before being transferred to a

separating funnel and diluted with dichloromethane. The organic phase was washed with saturated $NaHCO_3$ (aq.), H_2O and brine, dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) and ethyl acetate (2:1) to afford product **74** as a pale yellow solid (0.05 g, 49%).

M.p.: 139 – 141 °C (decomp.); FTIR: ν_{max}/ cm^{-1} (neat) 2966 (m), 1650 (s), 1352 (s), 1308 (s), 1070 (s), 1020 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 – 8.02 (1H, m, CH_{ar}), 7.68 – 7.62 (2H, m, CH_{ar}), 4.11 (2H, s, CH_2), 1.38 (6H, s, (CH_3)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 160.0, 134.5, 133.4, 129.7, 128.4, 127.1, 125.5, 79.2, 67.7, 28.0; HRMS: *m/z* $[MH]^+$ $C_{11}H_{12}NO^{35}Cl^{79}Br$ calcd. 287.9791, found 287.9799.

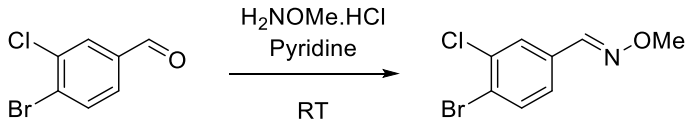
Synthesis of 2-(4-bromo-3-chlorophenyl)-4,4-dimethyl-4,5-dihydrooxazole **74**



73 **74**

4-Bromo-3-chloro-*N*-(1-hydroxy-2-methylpropan-2-yl)benzamide **73** (0.10 g, 0.33 mmol) was dissolved in dry MeCN. Triethylamine (0.52 g, 5.2 mmol), carbon tetrachloride (1.15 g, 7.45 mmol) and triphenylphosphine (0.34 g, 1.3 mmol) were added, and the mixture was allowed to stir at room temperature. Once full conversion was visible *via* TLC analysis, the reaction was diluted with ethyl acetate and washed with saturated $NaHCO_3$ (aq.). The organic phase was dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60)/ethyl acetate (2:1) to afford product **74** as a pale yellow solid (0.08 g, 84%). *See above for characterisation data*.

Synthesis of O-methyloxime 4-bromo-3-chlorobenzaldehyde **98**



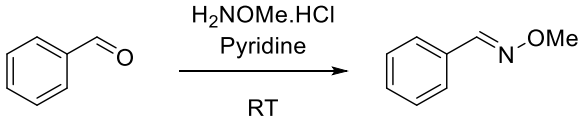
97 **98**

4-Bromo-3-chlorobenzaldehyde **97** (0.25 g, 1.1 mmol) was added to a stirring solution of *O*-methylhydroxylamine hydrochloride (0.11 g, 1.4 mmol) and pyridine (0.36 g, 4.6 mmol) in dichloromethane (3 mL). The reaction was stirred at room temperature for 6 hours and the volatiles were removed *in vacuo*. The remaining residue was dissolved in dichloromethane,

filtered through a short pad of silica gel, and volatiles removed *in vacuo*. The crude product was recrystallised from dichloromethane/petroleum ether (40/60) to afford product **98** as a colourless crystalline solid (0.22 g, 75%). (The product was isolated as a mixture of oxime isomers in a ratio of >20:1).

FTIR: ν_{max}/ cm^{-1} (neat) 3078 (w), 1645 (w), 1019 (s), 725 (m), 555 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (1H, s, *H*C=NOMe), 7.68 (1H, d, *J* = 2.0 Hz, C*H*$_{ar}$), 7.61 (1H, m, C*H*$_{ar}$), 7.31 (1H, dd, *J* = 2.0, 8.5 Hz, C*H*$_{ar}$), 3.98 (3H, s, OC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): 146.1, 134.9, 133.4, 132.4, 128.1, 126.0, 123.5, 62.2; HRMS: *m/z* $[MH]^+$ $C_8H_8NO^{35}Cl^{79}Br$ calcd. 247.9478, found 247.9488.

Synthesis of O-methyloxime benzaldehyde **103**[108]

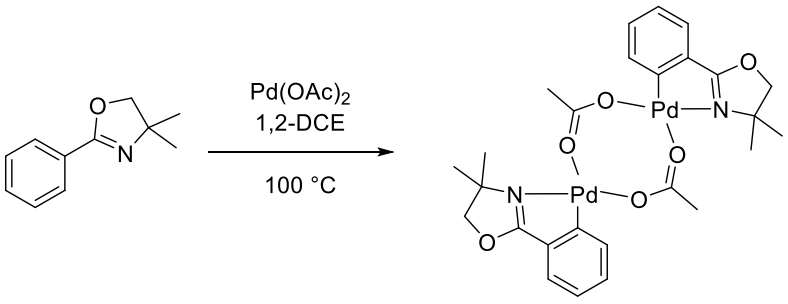


102 **103**

Benzaldehyde **102** (0.53 g, 5.0 mmol) was added to a stirring solution of *O*-methylhydroxylamine hydrochloride (0.50 g, 6.0 mmol) and pyridine (1.6 g, 20 mmol) in dichloromethane (15 mL). The reaction was stirred at room temperature overnight and evaporated *in vacuo*. The remaining residue was dissolved in dichloromethane, filtered through a short pad of silica gel, and evaporated *in vacuo* to afford product **103** as a clear oil (0.68 g, 99%). (The product was isolated as a mixture of oxime isomers in a ratio of >20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (1H, s, *H*C=NOMe), 7.63 – 7.56 (2H, m, C*H*$_{ar}$), 7.61 (3H, m, C*H*$_{ar}$), 3.99 (3H, s, OC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 148.3, 132.1, 129.7, 128.6, 126.9, 61.9.

Synthesis of di-μ-acetato-bis[2-(4',4'-dimethyl-2'-oxazolinyl)phenyl, 1-C, 3'-N]dipalladium **107**[106, 162]



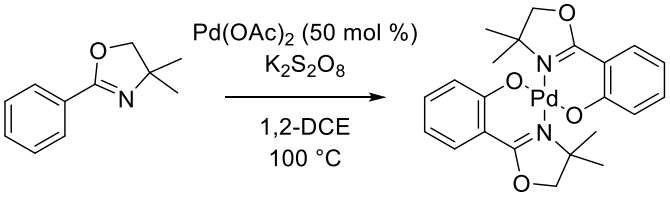
101 **107**

4,4-Dimethyl-2-phenyl-2-oxazoline **101** (35 mg, 0.22 mmol) and $Pd(OAc)_2$ (45 mg, 0.20 mmol) were dissolved in 1,2-dichloroethane (2 mL) in a 10 mL microwave vial. The vial was sealed

with a Teflon lined cap and heated at 100 °C for 2 hours. After cooling to room temperature, the mixture was filtered through a pad of Celite® and the filtrate was concentrated under vacuum to afford the product **107** as a yellow solid (63 mg, 94%).

M.p.: 136 – 137 °C (lit.,[162] 135 – 137 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 – 7.06 (2H, m, CH_{ar}), 7.03 – 6.93 (6H, m, CH_{ar}), 4.25 (2H, d, *J* = 8.5 Hz, OCH_2), 4.06 (2H, d, *J* = 8.5 Hz, OCH_2), 2.15 (6H, s, Acetate CH_3), 1.40 (6H, s, (CH_3)$_2$), 0.77 (6H, s, (CH_3)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 181.5, 172.7, 146.6, 132.6, 131.5, 130.2, 125.1, 123.7, 81.5, 65.2, 27.4, 24.7.

Synthesis of palladacycle **108**

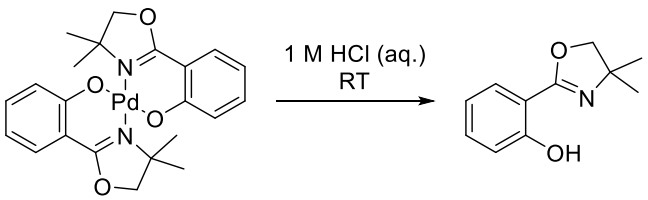


101 **108**

4,4-Dimethyl-2-phenyl-2-oxazoline **101** (53 mg, 0.30 mmol) and $Pd(OAc)_2$ (34 mg, 0.15 mmol) were combined in a 10 mL microwave vial with 1,2-dichloroethane (2 mL). The vial was sealed with a Teflon lined cap and heated at 100 °C. Potassium persulfate was added to the reaction mixture portionwise at time intervals of 1 and 4 hours (2 x 2.5 eq, 203 mg, 0.0751 mmol). After a further 3 hours, the reaction was allowed to cool to room temperature, and filtered through a short pad of silica, and washed with dichloromethane. The solvent was removed *in vacuo*, and residue was purified by flash column chromatography on silica gel eluting with dichloromethane to afford the product **108** as a yellow solid (10 mg, 13%).

M.p.: 179 – 180 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3058 (w), 2917 (w), 1608 (s), 1074 (s); ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.57 (1H, dd, *J* = 8.0, 2.0 Hz, CH_{ar}), 7.18 (1H, ddd, *J* = 8.5, 7.0, 2.0 Hz, CH_{ar}), 6.82 (1H, dd, *J* = 8.5, 1.0 Hz, CH_{ar}), 6.55 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, CH_{ar}), 4.21 (2H, s, CH_2), 1.72 (6H, s, (CH_3)$_2$); ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 166.7, 161.8, 133.4, 129.3, 119.9, 114.5, 110.7, 81.4, 68.6, 27.2; HRMS: *m/z* $[MH]^+$ $C_{22}H_{25}N_2O_4{}^{106}Pd$ calcd. 487.0849, found 487.0857.

Synthesis of 2-(4,4-dimethyl)-4,5-dihydrooxazol-2-yl)phenol **109**[163]

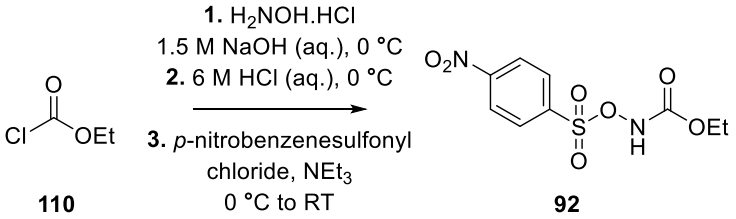


108 **109**

1 M HCl (aq.) (1 mL) was added to palladacycle **108** (8 mg, 0.02 mmol) and the mixture was stirred at room temperature for 16 hours. The reaction was diluted with dichloromethane and transferred to a separating funnel. The layers were partitioned, and the organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the product **109** as a colourless oil (2 mg, 32%). Due to the low isolated sample mass, structural confirmation was assessed by comparison of only ^{1}H NMR data to the reported literature data.[163]

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.72 – 7.60 (1H, m, CH_{ar}), 7.41 (1H, s, CH_{ar}), 7.07 (1H, d, *J* = 7.0 Hz, CH_{ar}), 6.88 (1H, s, CH_{ar}), 4.19 (2H, s, CH_2), 1.45 (6H, s, (CH_3)$_2$).

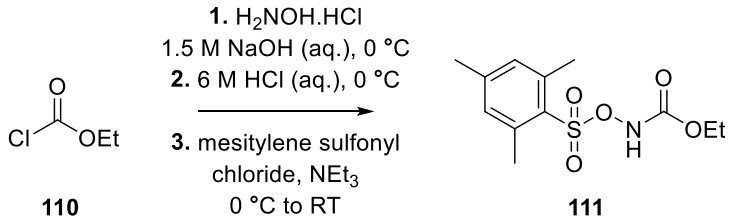
Synthesis of ethyl N-nosyloxycarbamate **92**[98]



Hydroxylamine hydrochloride (13.9 g, 200 mmol) was added to a 1.5 M aqueous solution of sodium hydroxide (160 mL, 240 mmol). The solution was then cooled to 0 °C, and ethyl chloroformate **110** (3.40 g, 38.0 mmol) was added dropwise. After complete addition, the reaction mixture was warmed to room temperature and stirred for 3 hours. The reaction mixture was then acidified to pH 4 – 5 with 6 M HCl (aq.). The mixture was then extracted with diethyl ether, and ethyl acetate. The organic layers were combined washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was used directly in the next step without further purification. Crude *N*-hydroxycarbamate (2.68 g, 25.5 mmol) was dissolved in diethyl ether (250 mL), and the solution was cooled to 0 °C. *p*-Nitrobenzenesulfonyl chloride (6.20 g, 28.0 mmol) was added, followed by the dropwise addition of triethylamine (2.83 g, 28.0 mmol). The resulting suspension was warmed to room temperature, and stirred for 2 hours. Water was then added until a clear solution was obtained. The two layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude yellow solid was then recrystallised from chloroform/hexane to afford product **92** as a pale yellow solid (2.49 g, 34%).

M.p.: 109 – 111 °C (lit.,[98] 115 – 116.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 – 8.39 (2H, m, C*H*$_{ar}$), 8.25 – 8.19 (2H, m, C*H*$_{ar}$), 7.96 (1H, s, N*H*), 4.09 (2H, q, *J* = 7.0 Hz, C*H*$_2$), 1.16 (3H, t, *J* = 7.0 Hz, C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 155.3, 151.4, 139.2, 131.2, 124.3, 63.9, 14.2.

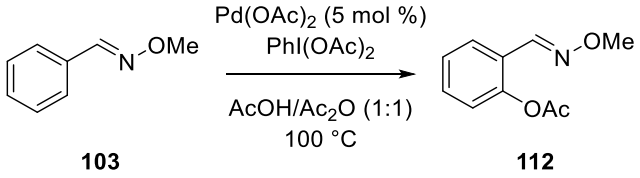
Synthesis of ethyl N-mesityloxycarbamate **111**



Hydroxylamine hydrochloride (13.9 g, 200 mmol) was added to a 1.5 M aqueous solution of sodium hydroxide (160 mL, 240 mmol). The solution was then cooled to 0 °C, and ethyl chloroformate **110** (3.40 g, 38.0 mmol) was added dropwise. Upon complete addition, the reaction mixture was warmed to room temperature and stirred for 3 hours. The reaction mixture was then acidified to pH 4 – 5 with 6 M HCl (aq.). The mixture was then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude material was used directly in the next step without further purification. Crude *N*-hydroxycarbamate (2.01 g, 19.1 mmol) was dissolved in diethyl ether (190 mL), and the solution was cooled to 0 °C. 2-Mesitylene sulfonyl chloride (4.59 g, 21.0 mmol) was added, followed by the dropwise addition of triethylamine (2.11 g, 21.0 mmol). The resulting suspension was warmed to room temperature, and stirred for 2 hours. Water was then added until a clear solution was obtained. The two layers were separated, and the aqueous layer extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude yellow solid was then recrystallised from dichloromethane/petroleum ether (40/60) to give product **111** as a colourless solid (2.77 g, 51%).

M.p.: 105 – 107 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3275 (m), 2984 (w), 1770 (s), 1357 (s), 1176 (s); ^{1}H NMR (400 MHz, d_6-DMSO): δ 11.46 (1H, s, N*H*), 7.13 (2H, s, C*H*$_{ar}$), 3.97 (2H, q, *J* = 7.0 Hz, C*H*$_2$), 2.57 (6H, s, C*H*$_3$), 2.30 (3H, s, C*H*$_3$), 1.05 (3H, t, *J* = 7.0 Hz, C*H*$_3$); ^{13}C NMR (100.6 MHz, d_6-DMSO): δ 156.2, 144.4, 141.0, 131.8, 128.6, 62.1, 22.5, 20.7, 14.1; HRMS: *m/z* $[MH]^+$ $C_{12}H_{18}NO_5S$ calcd. 288.0906, found 288.0910.

Synthesis of 1-(O-methyloxime)-2-(acetyloxy) benzaldehyde **112**

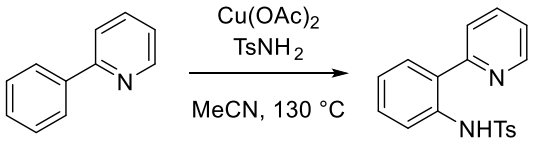


103 **112**

O-Methyloxime benzaldehyde **103** (46 mg, 0.34 mmol) and $Pd(OAc)_2$ (5 mg, 0.02 mmol) were combined in a 10 mL microwave vial with acetic acid (1.4 mL) and acetic anhydride (1.4 mL). To this was added (diacetoxyiodo)benzene (119 mg, 0.369 mmol), and the vial was sealed with a Teflon lined cap and heated at 100 °C for 17 hours. The reaction was then allowed to cool to room temperature, before diluting with ethyl acetate and transferring to a separating funnel. The organic phase was washed with H_2O, saturated $NaHCO_3$ (aq.) and brine. The organic phase was dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with hexane/ethyl acetate (4:1) to afford product **112** as a clear oil (29 mg, 44%).

FTIR: ν_{max}/ cm^{-1} (neat) 2939 (w), 1766 (m), 1607 (w), 1048 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (1H, s, C*H*=NOCH$_3$), 7.76 (1H, dd, *J* = 8.0, 1.5 Hz, CH_{ar}) , 7.42 – 7.36 (1H, m, CH_{ar}), 7.29 – 7.22 (1H, m, CH_{ar}), 7.10 (1H, dd, *J* = 8.0, 1.0 Hz, CH_{ar}), 3.98 (3H, s, OCH_3), 2.34 (3H, s, O*Ac*); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 169.3, 148.7, 144.2, 130.8, 128.0, 126.4, 124.6, 123.1, 62.3, 21.1; HRMS: *m/z* $[MH]^+$ $C_{10}H_{12}NO_3$ calcd. 194.0817, found 194.0821.

Synthesis of 4-methyl-N-[2-(2-pyridinyl)phenyl]-benzenesulfonamide **86**[114]

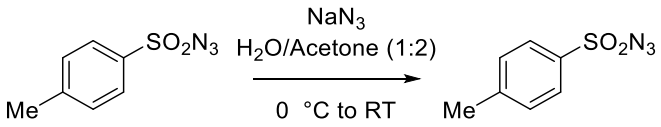


85 **86**

In a 10 mL microwave vial, 2-phenyl pyridine **85** (47 mg, 0.30 mmol), $Cu(OAc)_2$ (55 mg, 0.30 mmol) and *p*-toluenesulfonamide (103 mg, 0.602 mmol) were dissolved in acetonitrile (1 mL) under air. The vial was sealed with a Teflon lined cap and heated at 130 °C for a period of 24 hours. After cooling to room temperature, the mixture was diluted with dichloromethane followed by the addition of aqueous ammonium hydroxide. The mixture was then filtered through a short pad of Celite®, and the residue was washed with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60)/ethyl acetate (6:4) to afford product **86** as a colourless solid (11 mg, 11%).

M.p.: 90 – 91 °C (lit.,[164] (106 – 108 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.15 (1H, s ,N*H*), 8.68 – 8.56 (1H, m, CH_{ar}), 7.80 – 7.65 (2H, m, CH_{ar}), 7.61 – 7.49 (1H, m, CH_{ar}), 7.48 – 7.31 (4H, m, CH_{ar}), 7.27 – 7.21 (1H, m, CH_{ar}), 7.16 (1H, dd, *J* = 11.0, 4.5 Hz, CH_{ar}), 6.96 (2H, *J* = 8.5 Hz, CH_{ar}), 2.27 (3H, s, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 157.1, 147.4, 142.9, 137.4, 136.8, 136.5, 130.2, 129.1, 128.5, 127.4, 126.8, 124.6, 123.4, 122.2, 122.1, 21.4.

Synthesis of p-toluenesulfonyl azide **125**[116]

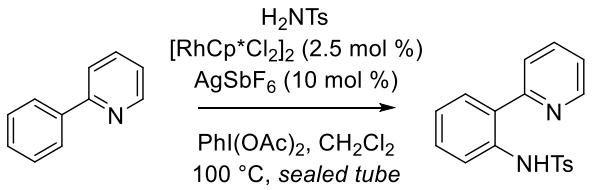


124 **125**

To a solution of sodium azide (0.49 g, 7.5 mmol) in water (2.5 mL) was added dropwise a solution of *p*-toluenesulfonyl chloride **124** (0.95 g, 5.0 mmol) in acetone (5 mL) at 0 °C. The reaction was allowed to slowly warm to room temperature and stir overnight. The solvent was removed *in vacuo*, and the residue was extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$ (aq.) and dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford product **125** as a clear oil (0.89 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (2H, d, *J* = 8.5 Hz, C*H*ar), 7.41 (2H, d, *J* = 8.5 Hz, CH_{ar}), 2.48 (3H, s, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 146.1, 135.0, 129.8, 127.1, 21.5.

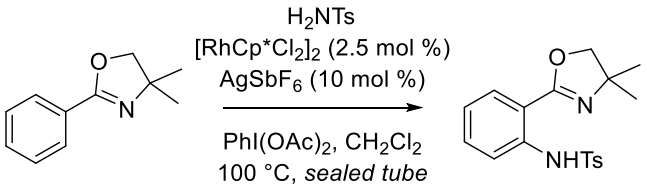
Synthesis of 4-methyl-N-[2-(2-pyridinyl)phenyl]-benzenesulfonamide **86**[117]



85 **86**

Following general procedure A, using *p*-toluenesulfonamide (34 mg, 0.20 mmol) and 2-phenylpyridine **85** (62 mg, 0.40 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 100 °C for 16 h, product **86** was isolated as a colourless solid (33 mg, 51%). *See above for characterisation data*.

Synthesis of N-[2-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)phenyl]-4-methyl-benzenesulfonamide **118**[117]

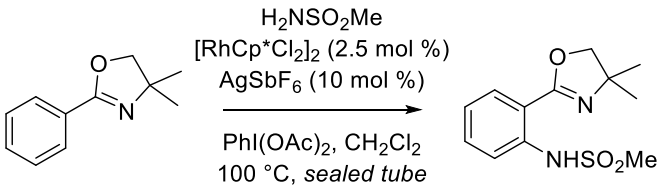


101 **118**

Following general procedure A, using *p*-toluenesulfonamide (34 mg, 0.20 mmol) and 4,4-dimethyl-2-phenyl-2-oxazoline **101** (70 mg, 0.40 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 100 °C for 16 h, product **118** was isolated as a colourless solid (43 mg, 62%).

M.p.: 104 – 106 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.29 (1H, s, N*H*), 7.71 (4H, m, CH_{ar}), 7.42 – 7.31 (1H, m, CH_{ar}), 7.17 (2H, d, *J* = 8.5 Hz, CH_{ar}), 7.07 – 6.96 (1H, m, CH_{ar}), 4.02 (2H, s, CH_2), 2.33 (3H, s, CH_3), 1.42 (6H, s, (CH_3)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 161.6, 143.3, 139.1, 136.9, 132.2, 129.4, 129.1, 127.1, 122.6, 118.6, 114.1, 77.9, 67.9, 28.3, 21.5.

Synthesis of N-[2-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)phenyl]-4-methanesulfonamide **129**

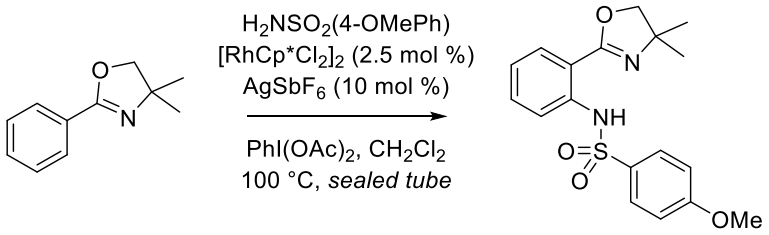


101 **129**

Following general procedure A, using methane sulfonamide (19 mg, 0.20 mmol) and 4,4-dimethyl-2-phenyl-2-oxazoline **101** (70 mg, 0.40 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 100 °C for 16 h, product **129** was isolated as a colourless solid (46 mg, 86%).

M.p.: 86 – 88 °C; FTIR: ν_{max}/ cm^{-1} (neat) 2971 (w), 2872 (w), 1322 (m), 1142 (s), 1047 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.01 (1H, s, N*H*), 7.85 (1H, dd, *J* = 8.0 and 1.5 Hz, CH_{ar}), 7.72 (1H, dd, *J* = 8.5 and 1.0 Hz, CH_{ar}), 7.50 – 7.40 (1H, m, CH_{ar}), 7.16 – 7.06 (1H, m, CH_{ar}), 4.07 (2H, s, CH_2), 3.01 (3H, s, CH_3), 1.39 (6H, s, (CH_3)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 161.9, 139.4, 132.7, 129.7, 122.8, 118.1, 114.1, 78.2, 68.1, 39.9, 28.6; HRMS: *m/z* $[MH]^+$ $C_{12}H_{17}N_2O_3S$ calcd. 269.0960, found 269.0959.

Synthesis of N-[2-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)phenyl]-4-methoxy-benzenesulfonamide **130**

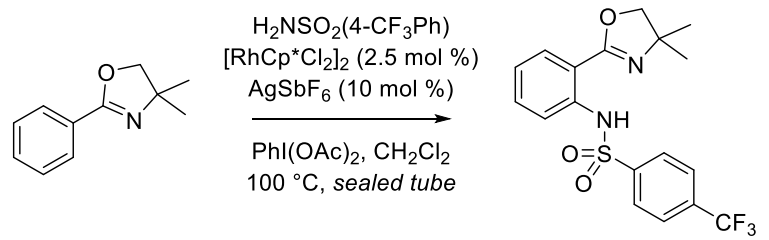


101 **130**

Following general procedure A, using 4-methoxybenzene sulfonamide (37 mg, 0.20 mmol) and 4,4-dimethyl-2-phenyl-2-oxazoline **101** (70 mg, 0.40 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 100 °C for 16 h, product **130** was isolated as a colourless solid (46 mg, 64%).

M.p.: 106 – 108 °C; FTIR: ν_{max}/ cm^{-1} (neat) 2974 (w), 2849 (w), 1336 (s), 1157 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 12.22 (1H, s, N*H*), 7.79 – 7.68 (4H, m, CH_{ar}), 7.39 – 7.31 (1H, m, CH_{ar}), 7.04 – 6.97 (1H, m, CH_{ar}), 6.87 – 6.80 (2H, m, CH_{ar}), 4.02 (2H, s, CH_2), 3.79 (3H, s, OCH_3), 1.40 (6H, s, $(CH_3)_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.1, 161.6, 139.1, 132.4, 131.7, 129.4, 129.3, 122.7, 118.8, 114.3, 114.1, 78.1, 68.1, 55.6, 28.6; HRMS: *m/z* $[MH]^+$ $C_{18}H_{21}N_2O_4S$ calcd. 361.1222, found 361.1237.

Synthesis of N-(2-(4,4-dimethyl-1,5-dihydrooxazol-2-yl)phenyl)-4-(trifluoromethyl)benzenesulfonamide **131**



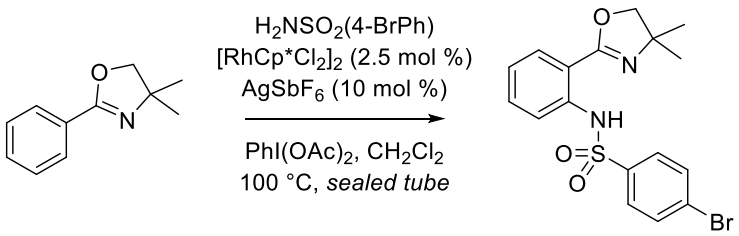
101 **131**

Following general procedure A, using 4-trifluoromethylbenzene sulfonamide (45 mg, 0.20 mmol) and 4,4-dimethyl-2-phenyl-2-oxazoline **101** (70 mg, 0.40 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 100 °C for 16 h, product **131** was isolated as a colourless solid (46 mg, 76%).

M.p.: 80 – 81 °C; FTIR: ν_{max}/ cm^{-1} (neat) 2980 (w), 1628 (m), 1506 (m), 1340 (m), 1321 (s), 1161 (s), 1129 (s), 1059 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 12.50 (1H, s, N*H*), 7.94 (2H, d, *J* = 8.0 Hz, CH_{ar}), 7.77 – 7.72 (2H, m, CH_{ar}), 7.65 (2H, d, *J* = 8.0 Hz, CH_{ar}), 7.39 (1H, ddd, *J* = 8.5, 7.5,

1.5 Hz, CH_{ar}), 7.06 (1H, td, *J* = 8.0, 1.0 Hz, CH_{ar}), 4.03 (2H, s, CH_2), 1.39 (6H, s, C(CH_3)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.0, 143.6, 138.6, 134.5 (q, *J* = 33.0 Hz), 132.6, 129.5, 127.7, 126.1 (q, *J* = 3.5 Hz), 123.4, 123.3 (q, *J* = 273.0 Hz), 118.9, 114.5, 78.2, 68.1, 28.6; ^{19}F NMR (376.5 MHz; $CDCl_3$): δ – 63.1; HRMS: *m/z* $[MH]^+$ $C_{18}H_{18}N_2O_3F_3S$ calcd. 399.0990, found 361.0986.

Synthesis of N-[2-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)phenyl]-4-bromo-benzenesulfonamide **132**

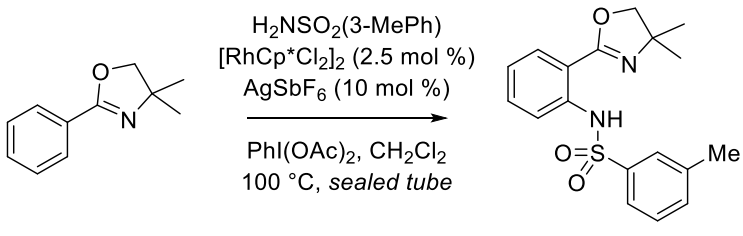


101 **132**

Following general procedure A, using 4-bromobenzene sulfonamide (47 mg, 0.20 mmol) and 4,4-dimethyl-2-phenyl-2-oxazoline **101** (70 mg, 0.40 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 100 °C for 16 h, product **132** was isolated as a colourless solid (59 mg, 72%).

M.p.: 111 – 114 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3099 (w), 2961 (w), 2890 (w), 1336 (s), 1160 (s), 1064 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.37 (1H, s, N*H*), 7.76 – 7.65 (4H, m, CH_{ar}), 7.55 – 7.49 (2H, m, CH_{ar}), 7.41 – 7.34 (1H, m, CH_{ar}), 7.08 – 7.01 (1H, m, CH_{ar}), 4.03 (2H, s, CH_2), 1.39 (6H, s, (CH_3)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 161.9, 139.0, 138.8, 132.5, 132.2, 129.5, 128.8, 127.7, 123.2, 118.8, 114.5, 78.2, 68.1, 28.6; HRMS: *m/z* $[MH]^+$ $C_{17}H_{18}N_2O_3S^{79}Br$ calcd. 409.0222, found 409.0216.

Synthesis of N-(2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl)-3-methylbenzenesulfonamide **133**

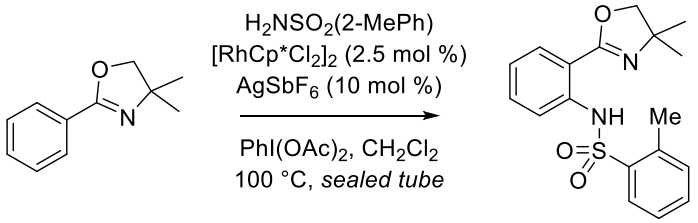


101 **133**

Following general procedure A, using 3-methylbenzene sulfonamide (39 mg, 0.20 mmol) and 4,4-dimethyl-2-phenyl-2-oxazoline **101** (70 mg, 0.20 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 100 °C for 16 h, product **133** was isolated as a colourless solid (49 mg, 71%).

M.p.: 98 – 99 °C; FTIR: ν_{max}/ cm^{-1} (neat) 2971 (w), 1631 (m), 1500 (m), 1340 (s), 1280 (m), 1161 (s), 1062 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.30 (1H, s, N*H*), 7.76 – 7.69 (2H, m, C*H*$_{ar}$), 7.65 – 7.63 (1H, m, C*H*$_{ar}$), 7.62 – 7.59 (1H, m, C*H*$_{ar}$), 7.36 (1H, ddd, *J* = 8.5, 7.5, 1.5 Hz, C*H*$_{ar}$), 7.29 – 7.23 (2H, m, C*H*$_{ar}$), 7.01 (1H, ddd, *J* = 8.5, 7.5, 1.0 Hz, C*H*$_{ar}$), 4.02 (2H, s, C*H*$_2$), 2.32 (3H, s, C*H*$_3$), 1.39 (6H, s, (C*H*$_3$)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 161.9, 139.9, 139.2, 139.0, 133.6, 132.4, 129.3, 128.7, 127.5, 124.4, 122.8, 118.8, 114.4, 78.1, 68.1, 28.6, 21.4; HRMS: *m/z* $[MH]^+$ $C_{18}H_{21}N_2O_3$ calcd. 345.1273, found 345.1288.

Synthesis of N-(2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl)-2-methylbenzenesulfonamide **134**

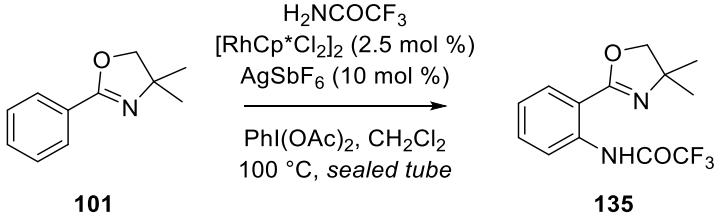


101 **134**

Following general procedure A, using 2-methylbenzene sulfonamide (34 mg, 0.20 mmol) and 4,4-dimethyl-2-phenyl-2-oxazoline **101** (70 mg, 0.20 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 100 °C for 16 h, product **134** was isolated as a colourless solid (57 mg, 83%).

M.p.: 96 – 97 °C; FTIR: ν_{max}/ cm^{-1} (neat) 2967 (w), 1631 (m), 1500 (m), 1337 (s), 1270 (s), 1158 (s), 1136 (s), 1056 (s), 1043 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.64 (1H, s, N*H*), 8.12 (1H, dd, *J* = 8.0, 1.5 Hz, C*H*$_{ar}$), 7.74 (1H, dd, *J* = 8.0, 1.5 Hz, C*H*$_{ar}$), 7.56 (1H, dd, *J* = 8.5, 1.0 Hz, C*H*$_{ar}$), 7.39 (1H, td, *J* = 7.5, 1.5 Hz, C*H*$_{ar}$), 7.33 – 7.24 (2H, m, C*H*$_{ar}$), 7.21 (1H, d, *J* = 7.5 Hz), 6.95 (1H, ddd, *J* = 8.5, 7.5, 1.0 Hz, C*H*$_{ar}$), 4.06 (2H, s, C*H*$_2$), 2.66 (3H, s, C*H*$_3$), 1.41 (6H, s, C(C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.0, 139.1, 137.8, 137.6, 133.0, 132.7, 132.5, 130.3, 129.4, 126.0, 121.8, 116.3, 112.8, 78.1, 68.1, 28.6, 20.2; HRMS: *m/z* $[MH]^+$ $C_{18}H_{21}N_2O_3S$ calcd. 345.1273, found 345.1270.

Synthesis of 2,2,2-trifluoro-N-[2-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)phenyl] acetamide **135**

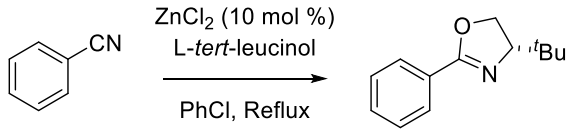


101 **135**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 4,4-dimethyl-2-phenyl-2-oxazoline **101** (70 mg, 0.40 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 100 °C for 16 h, product **135** was isolated as a colourless solid (24 mg, 61%).

M.p.: 81 – 84 °C; FTIR: ν_{max}/ cm^{-1} (neat) 2969 (w), 1717 (m), 1611 (m), 1148 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.88 (1H, s, N*H*), 8.66 (1H, d, *J* = 8.0 Hz, CH_{ar}), 7.88 (1H, d, *J* = 8.0, CH_{ar}), 7.53 (1H, t, *J* = 8.0 Hz, CH_{ar}), 7.22 (1H, t, *J* = 8.0 Hz, CH_{ar}), 4.11 (2H, s, CH_2), 1.40 (6H, s, (CH_3)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 161.9, 155.6 (q, *J* = 37.5 Hz), 137.7, 132.8, 129.2, 124.4, 120.3, 117.5 (q, *J* = 288.5 Hz), 114.7, 78.3, 68.0, 28.5; ^{19}F NMR (376.5 MHz; $CDCl_3$): δ – 76.1; HRMS: *m/z* $[MH]^+$ $C_{13}H_{14}N_2O_2F_3$ calcd. 287.1007, found 287.1009.

Synthesis of (S)-4-(tert-butyl)-2-phenyl-4,5-dihydrooxazole **151**[165]

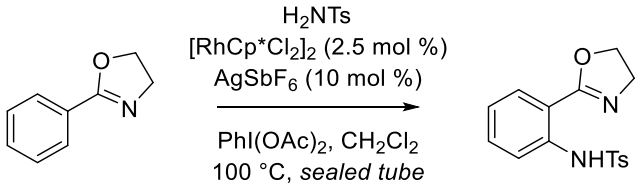


153 **151**

To a flame dried round bottomed flask was added zinc dichloride (68 mg, 0.50 mmol) and chlorobenzene (15 mL). Benzonitrile **153** (516 mg, 5.00 mmol) and *L-tert*-leucinol (762 mg, 6.50 mmol) were then added sequentially, followed by heating the mixture at reflux for 48 h. The reaction was then allowed to cool to room temperature, and the solvent was removed *in vacuo*. The residue was redissolved in dichloromethane and transferred to a separating funnel. The organic phase was washed with water, followed by further extraction with dichloromethane and ethyl acetate. The combined organics were dried over anhydrous Na_2SO_4, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60)/ethyl acetate (6:4) to afford product **151** as a colourless oil (510 mg, 50%).

$[\alpha]_D^{23}$ = - 90° (c 0.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 – 7.94 (2H, m, CH_{ar}), 7.49 – 7.37 (3H, m, CH_{ar}), 4.34 (1H, dd, *J* = 10.0, 8.5 Hz, C*H*), 4.24 (1H, dd, *J* = 8.5, 7.5 Hz, C*H*), 4.05 (1H, dd, *J* = 10.0, 7.5 Hz, C*H*), 0.95 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.4, 131.1, 128.4, 128.3, 128.1, 76.3, 68.9, 34.2, 26.0.

Synthesis of N-[2-(4,5-dihydro-2-oxazolyl)phenyl]-4-methyl-benzenesulfonamide **126**[117]

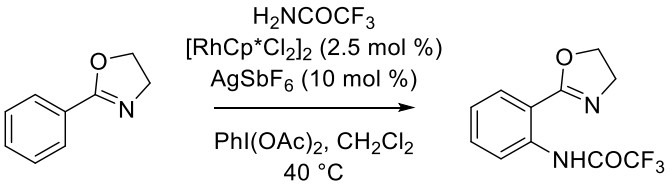


152 **126**

Following general procedure A, using *p*-toluenesulfonamide (34 mg, 0.20 mmol) and 2-phenyl-2-oxazoline **152** (59 mg, 0.40 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 100 °C for 16 h, product **126** was isolated as a colourless solid (58 mg, 92%).

M.p.: 191 – 193 °C (lit.,[166] 195 – 199 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.36 (1H, s, N*H*), 7.78 – 7.70 (3H, m, CH_{ar}), 7.64 (1H, dd, *J* = 8.0 and 1.0 Hz, CH_{ar}), 7.37 – 7.29 (1H, m, CH_{ar}), 7.20 (2H, d, *J* = 8.0 Hz, CH_{ar}), 6.99 (1H, td, *J* = 8.0 and 1.0 Hz, CH_{ar}), 4.39 – 4.31 (2H, m, CH_2), 4.16 – 4.08 (2H, m, CH_2), 2.34 (3H, s, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.5, 143.5, 139.1, 136.9, 132.4, 129.5, 129.4, 127.2, 122.3, 117.8, 113.5, 66.5, 54.5, 21.5.

Synthesis of 2,2,2-trifluoro-N-[2-(4,5-dihydro-2-oxazolyl)phenyl]-acetamide **154**

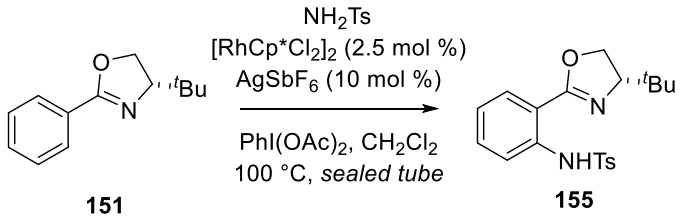


152 **154**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-phenyl-2-oxazoline **152** (59 mg, 0.40 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 16 h, product **154** was isolated as a colourless solid (48 mg, 92%).

M.p.: 74 – 75 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3054 (w), 2915 (w), 1734 (s), 1260 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.69 (1H, s, N*H*), 8.68 (1H, dd, *J* = 8.5 and 1.0 Hz, CH_{ar}), 7.90 (1H, dd, *J* = 8.5 and 1.0 Hz, CH_{ar}), 7.52 (1H, t, *J* = 8.5 Hz, CH_{ar}), 7.21 (1H, t, *J* = 8.5 Hz, CH_{ar}), 4.43 (2H, t, *J* = 9.5 Hz, CH_2), 4.16 (2H, t, *J* = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.7, 155.7 (q, *J* = 37.5 Hz), 137.7, 132.9, 129.4, 124.5, 120.3, 116.1 (q, *J* = 288.5 Hz), 114.5, 66.8, 54.5; ^{19}F NMR (376.5 MHz, $CDCl_3$); δ – 76.0; HRMS: *m*/*z* $[MH]^+$ $C_{11}H_{10}N_2O_2F_3$ calcd. 259.0694, found 259.0704.

Synthesis of (S)-N-(2-(4-(tert-butyl)-4,5-dihydrooxazol-2-yl)phenyl)-4-methylbenzenesulfonamide **155**

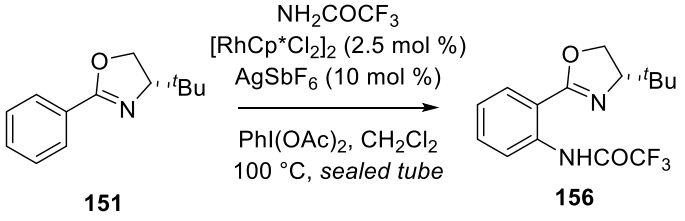


151 **155**

Following general procedure A, using *p*-toluenesulfonamide (34 mg, 0.20 mmol) and (*S*)-4-(*tert*-butyl)-2-phenyl-4,5-dihydrooxazole **151** (81 mg, 0.40 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 100 °C for 16 h, product **155** was isolated as a colourless oil (20 mg, 27%).

$[\alpha]_D^{23}$ = - 21° (c 0.01, $CHCl_3$); FTIR: ν_{max}/ cm^{-1} (neat) 3067 (w), 2958 (w), 1633 (s), 1336 (s), 1156 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.60 (1H, s, N*H*), 7.78 – 7.74 (2H, m, CH_{ar}), 7.73 – 7.68 (2H, m, CH_{ar}), 7.37 – 7.31 (1H, m, CH_{ar}), 7.22 – 7.17 (2H, m, CH_{ar}), 7.02 – 6.96 (1H, m, CH_{ar}), 4.34 – 4.26 (1H, m, C*H*), 4.18 – 4.11 (2H, m, C*H*), 2.34 (3H, s, CH_3), 0.97 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.5, 143.6, 139.6, 137.2, 132.5, 129.6, 129.4, 127.3, 122.3 117.6, 113.4, 76.0, 67.8, 34.0, 26.0, 21.6; HRMS: *m/z* $[MH]^+$ $C_{20}H_{25}N_2O_3$ calcd. 373.1586, found 373.1602.

Synthesis of (S)-N-(2-(4-(tert-butyl)-4,5-dihydrooxazol-2-yl)phenyl)-2,2,2-trifluoroacetamide **156**



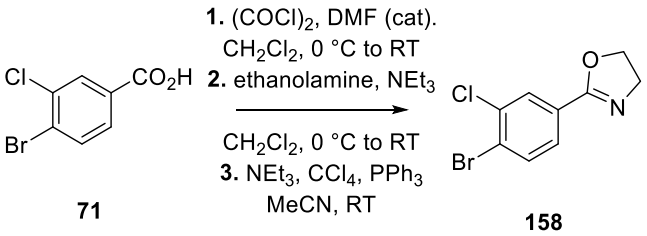
151 **156**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and (*S*)-4-(*tert*-butyl)-2-phenyl-4,5-dihydrooxazole **151** (81 mg, 0.40 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 100 °C for 16 h, product **156** was isolated as a colourless oil (6 mg, 10%).

$[\alpha]_D^{23}$ = + 5° (c 0.01, $CHCl_3$); FTIR: ν_{max}/ cm^{-1} (neat) 3113 (w), 2972 (w), 1721 (m), 1640 (m), 1149 (s), 1124 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.74 (1H, s, N*H*), 8.71 (1H, dd, *J* = 8.5, 1.0 Hz, CH_{ar}), 7.90 (1H, dd, *J* = 8.0, 1.5 Hz, CH_{ar}), 7.57 – 7.50 (1H, m, CH_{ar}), 7.22 (1H, td, *J* = 8.0, 1.0 Hz, CH_{ar}), 4.41 – 4.32 (1H, m, C*H*), 4.23 – 4.15 (2H, m, C*H*), 0.96 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100.6

MHz, $CDCl_3$): δ 163.5, 155.7 (q, *J* = 37.5 Hz), 137.9, 132.9, 129.5, 124.5, 120.3, 116.1 (q, *J* = 288.5 Hz), 114.5, 76.2, 68.0, 33.8, 25.9; ^{19}F NMR (376.5 MHz, $CDCl_3$); δ – 75.6; HRMS: *m/z* $[MH]^+$ $C_{15}H_{18}N_2O_2F_3$ calcd. 315.1320, found 315.1324.

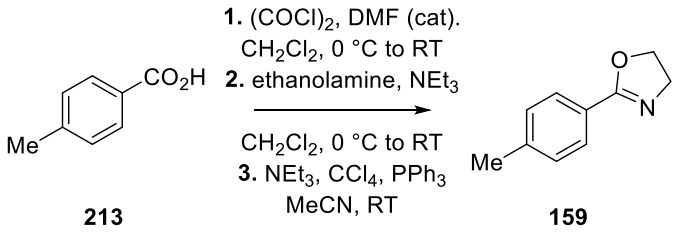
Synthesis of 2-(3-chloro-4-bromo-phenyl)-4,5-dihydro-oxazole **158**



Following general procedure B, using 4-bromo-3-chlorobenzoic acid **71** (1.00 g, 4.25 mmol) with oxalyl chloride (1.65 g, 13.0 mmol) and DMF (few drops) in dichloromethane (14 mL) the respective acid chloride was synthesised. The amide was then generated using ethanolamine (263 mg, 4.25 mmol), triethylamine (428 mg, 4.25 mmol) in dichloromethane (30 mL). Cyclisation of the amide with carbon tetrachloride (14.8 g, 96.0 mmol), triethylamine (6.71 g, 66.4 mmol) and triphenylphosphine (4.00 g, 15.3 mmol) in dry acetonitrile (50 mL) afforded the oxazoline product **158** (760 mg, 69%) as a pale orange solid.

M.p.: 66 – 68 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3054 (w), 2981 (w), 1650 (s), 1390 (m), 1268 (s), 1074 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (1H, d, *J* = 1.5 Hz, C*H*$_{ar}$), 7.68 – 7.61 (m, 2H, C*H*$_{ar}$), 4.42 (1H, t, *J* = 9.5 Hz, C*H*$_2$), 4.04 (1H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.1, 134.9, 133.9, 130.0, 128.5, 127.5, 126.0, 68.1, 55.1; HRMS: *m/z* $[MH]^+$ $C_9H_8NO^{35}Cl^{79}Br$ calcd. 259.9478, found 259.9485.

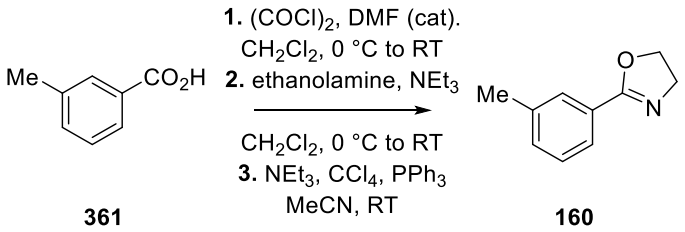
Synthesis of 2-(4-methylphenyl)-4,5-dihydro-oxazole **159**[167]



Following general procedure B, using *p*-toluic acid **213** (580 mg, 4.25 mmol) with oxalyl chloride (1.65 g, 13.0 mmol) and DMF (few drops) in dichloromethane (14 mL) the respective acid chloride was synthesised. The amide was then generated using ethanolamine (263 mg, 4.25 mmol), triethylamine (428 mg, 4.25 mmol) in dichloromethane (30 mL). Cyclisation of the amide with carbon tetrachloride (14.8 g, 96.0 mmol), triethylamine (6.71 g, 66.4 mmol) and triphenylphosphine (4.00 g, 15.3 mmol) in dry acetonitrile (50 mL) afforded the oxazoline product **159** (510 mg, 74%) as a pale orange solid.

M.p.: 78 – 79 °C (lit.,[167] 65 – 67 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (2H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 7.21 (2H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 4.41 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.04 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 2.39 (3H, s, C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.9, 141.7, 129.2, 128.2, 125.1, 67.6, 55.0, 21.7.

Synthesis of 2-(3-methylphenyl)-4,5-dihydro-oxazole **160**[168]

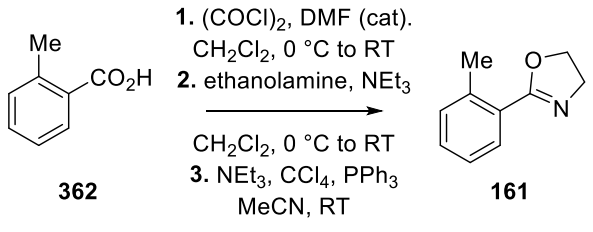


361 **160**

Following general procedure B, using *m*-toluic acid **361** (580 mg, 4.25 mmol) with oxalyl chloride (1.65 g, 13.0 mmol) and DMF (few drops) in dichloromethane (14 mL) the respective acid chloride was synthesised. The amide was then generated using ethanolamine (263 mg, 4.25 mmol), triethylamine (428 mg, 4.25 mmol) in dichloromethane (30 mL). Cyclisation of the amide with carbon tetrachloride (14.8 g, 96.0 mmol), triethylamine (6.71 g, 66.4 mmol) and triphenylphosphine (4.00 g, 15.3 mmol) in dry acetonitrile (50 mL) afforded the oxazoline product **160** (570 mg, 83%) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (1H, s, C*H*$_{ar}$), 7.76 – 7.72 (1H, m, C*H*$_{ar}$), 7.33 – 7.27 (2H, m, C*H*$_{ar}$), 4.42 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.05 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 2.38 (3H, s, C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.9, 138.2, 132.2, 128.9, 128.4, 127.7, 125.4, 67.7, 55.0, 21.4.

Synthesis of 2-(2-methylphenyl)-4,5-dihydro-oxazole **161**[169]



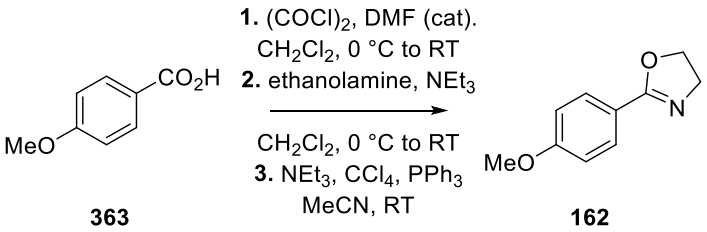
362 **161**

Following general procedure B, using *o*-toluic acid **362** (580 mg, 4.25 mmol) with oxalyl chloride (1.65 g, 13.0 mmol) and DMF (few drops) in dichloromethane (14 mL) the respective acid chloride was synthesised. The amide was then generated using ethanolamine (263 mg, 4.25 mmol), triethylamine (428 mg, 4.25 mmol) in dichloromethane (30 mL). Cyclisation of the amide with carbon tetrachloride (14.8 g, 96.0 mmol), triethylamine (6.71 g, 66.4 mmol) and triphenylphosphine (4.00 g, 15.3 mmol) in dry acetonitrile (50 mL) afforded the oxazoline product **161** (370 mg, 54%) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (1H, dd, *J* = 7.5, 1.5 Hz, C*H*$_{ar}$), 7.33 (1H, td, *J* = 7.5, 1.5 Hz, C*H*$_{ar}$), 7.25 – 7.18 (2H, m, C*H*$_{ar}$), 4.38 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.09 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 2.59

(3H, s, C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.2, 138.8, 131.3, 130.6, 129.9, 127.3, 125.7, 66.9, 55.5, 21.9.

Synthesis of 2-(4-methoxyphenyl)-4,5-dihydro-oxazole **162**[167]

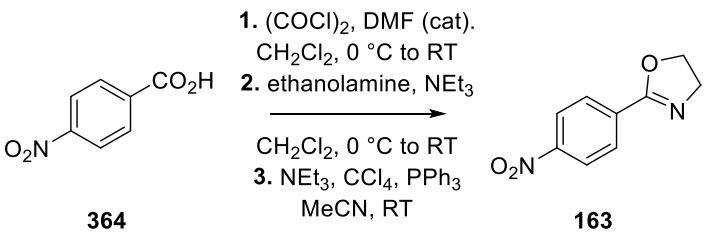


363 **162**

Following general procedure B, using 4-methoxybenzoic acid **363** (647 mg, 4.25 mmol) with oxalyl chloride (1.65 g, 13.0 mmol) and DMF (few drops) in dichloromethane (14 mL) the respective acid chloride was synthesised. The amide was then generated using ethanolamine (263 mg, 4.25 mmol), triethylamine (428 mg, 4.25 mmol) in dichloromethane (30 mL). Cyclisation of the amide with carbon tetrachloride (14.8 g, 96.0 mmol), triethylamine (6.71 g, 66.4 mmol) and triphenylphosphine (4.00 g, 15.3 mmol) in dry acetonitrile (50 mL) afforded the oxazoline product **162** (474 mg, 63%) as a colourless solid. (NB: An alternative work-up procedure was adopted following the cyclisation. Upon completion, the reaction was poured into a mixture of dichloromethane and water, followed by acidifying to pH ~2-3 with aq. 2 M HCl. The mixture was then transferred to a separating funnel, and the layers partitioned. The organic layer was disregarded and the aqueous layer was basified with $NaHCO_3$ to pH 8. The aqueous layer was then extracted with ethyl acetate, followed by drying over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*.)

M.p.: 56 – 57 °C (lit.,[167] 56 – 58 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (2H, d, *J* = 9.0 Hz, C*H*$_{ar}$), 6.88 (2H, d, *J* = 9.0 Hz, C*H*$_{ar}$), 4.36 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 3.99 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 3.80 (3H, s, OC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.4, 162.0, 129.9, 120.3, 113.7, 67.5, 55.3, 54.9.

Synthesis of 2-(4-nitrophenyl)-4,5-dihydro-oxazole **163**[167]



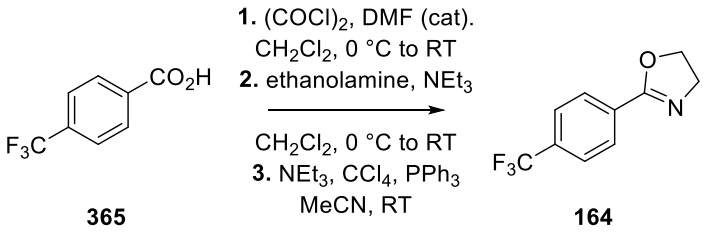
364 **163**

Following general procedure B, using 4-nitrobenzoic acid **364** (710 mg, 4.25 mmol) with oxalyl chloride (1.65 g, 13.0 mmol) and DMF (few drops) in dichloromethane (14 mL) the respective acid chloride was synthesised. The amide was then generated using ethanolamine (263 mg, 4.25 mmol), triethylamine (428 mg, 4.25 mmol) in dichloromethane (30 mL). Cyclisation of

the amide with carbon tetrachloride (14.8 g, 96.0 mmol), triethylamine (6.71 g, 66.4 mmol) and triphenylphosphine (4.00 g, 15.3 mmol) in dry acetonitrile (50 mL) afforded the oxazoline product **163** (122 mg, 15%) as a pale yellow solid. (NB: An alternative work-up procedure was adopted following the cyclisation. Upon completion, the reaction was poured into a mixture of dichloromethane and water, followed by acidifying to pH ~2-3 with aq. 2 M HCl. The mixture was then transferred to a separating funnel, and the layers partitioned. The organic layer was disregarded and the aqueous layer was basified with $NaHCO_3$ to pH 8. The aqueous layer was then extracted with ethyl acetate, followed by drying over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*.)

M.p.: 183 – 184 °C (lit.,[167] 173 – 174 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (2H, d, *J* = 9.0 Hz, C*H*$_{ar}$), 8.12 (2H, d, *J* = 9.0 Hz, C*H*$_{ar}$), 4.50 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.12 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.0, 149.6, 133.7, 129.3, 123.7, 68.3, 55.4.

Synthesis of 2-(4-trifluoromethylphenyl)-4,5-dihydro-oxazole **164**

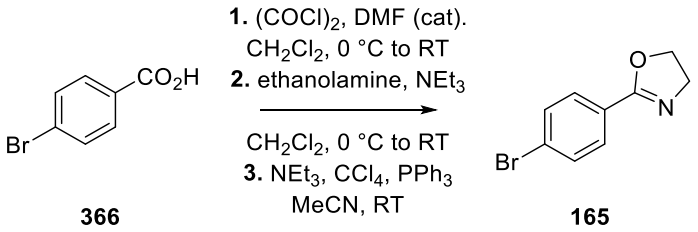


365 **164**

Following general procedure B, using 4-trifluoromethylbenzoic acid **365** (808 mg, 4.25 mmol) with oxalyl chloride (1.65 g, 13.0 mmol) and DMF (few drops) in dichloromethane (14 mL) the respective acid chloride was synthesised. The amide was then generated using ethanolamine (263 mg, 4.25 mmol), triethylamine (428 mg, 4.25 mmol) in dichloromethane (30 mL). Cyclisation of the amide with carbon tetrachloride (14.8 g, 96.0 mmol), triethylamine (6.71 g, 66.4 mmol) and triphenylphosphine (4.00 g, 15.3 mmol) in dry acetonitrile (50 mL) afforded the oxazoline product **164** (700 mg, 77%) as a pale orange solid.

M.p.: 134 – 135 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3064 (w), 2983 (w), 1654 (m), 1326 (s), 1121 (s), 1107 (s), 1068 (s), 856 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (2H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 7.65 (2H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 4.45 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.07 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.8, 133.1 (q, *J* = 30.0 Hz), 131.1, 128.7, 125.5 (q, *J* = 3.5 Hz), 124.7 (q, *J* = 239.0 Hz), 68.1, 55.0; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 63.0; HRMS: *m/z* $[MH]^+$ $C_{10}H_9NOF_3$ calcd. 216.0636, found 216.0636.

Synthesis of 2-(4-bromophenyl)-4,5-dihydro-oxazole **165**[170]

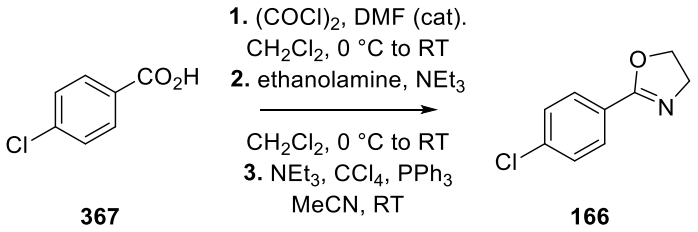


366 **165**

Following general procedure B, using 4-bromobenzoic acid **366** (855 mg, 4.25 mmol) with oxalyl chloride (1.65 g, 13.0 mmol) and DMF (few drops) in dichloromethane (14 mL) the respective acid chloride was synthesised. The amide was then generated using ethanolamine (263 mg, 4.25 mmol), triethylamine (428 mg, 4.25 mmol) in dichloromethane (30 mL). Cyclisation of the amide with carbon tetrachloride (14.8 g, 96.0 mmol), triethylamine (6.71 g, 66.4 mmol) and triphenylphosphine (4.00 g, 15.3 mmol) in dry acetonitrile (50 mL) afforded the oxazoline product **165** (790 mg, 82%) as a pale orange solid.

M.p.: 101 – 102 °C (lit.,[170] 95 – 97 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (2H, d, *J* = 8.5 Hz, C*H*$_{ar}$), 7.55 (2H, d, *J* = 8.5 Hz, C*H*$_{ar}$), 4.43 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.05 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.0, 131.8, 129.9, 126.9, 126.1, 67.9, 55.1.

Synthesis of 2-(4-chlorophenyl)-4,5-dihydro-oxazole **166**[169]

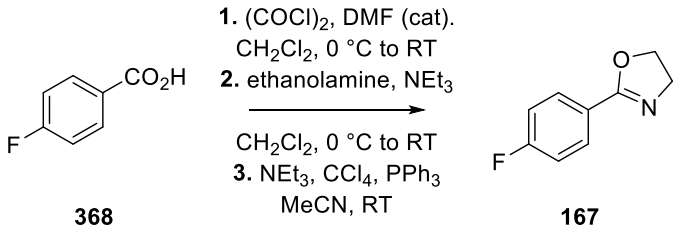


367 **166**

Following general procedure B, using 4-chlorobenzoic acid **367** (665 mg, 4.25 mmol) with oxalyl chloride (1.65 g, 13.0 mmol) and DMF (few drops) in dichloromethane (14 mL) the respective acid chloride was synthesised. The amide was then generated using ethanolamine (263 mg, 4.25 mmol), triethylamine (428 mg, 4.25 mmol) in dichloromethane (30 mL). Cyclisation of the amide with carbon tetrachloride (14.8 g, 96.0 mmol), triethylamine (6.71 g, 66.4 mmol) and triphenylphosphine (4.00 g, 15.3 mmol) in dry acetonitrile (50 mL) afforded the oxazoline product **166** (530 mg, 69%) as a pale orange solid.

M.p.: 140 – 141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (2H, d, *J* = 9.0 Hz, C*H*$_{ar}$), 7.35 (2H, d, *J* = 9.0 Hz, C*H*$_{ar}$), 4.39 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.02 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.8, 137.5, 129.6, 128.7, 126.3, 67.8, 55.0.

Synthesis of 2-(4-fluorophenyl)-4,5-dihydro-oxazole **167**

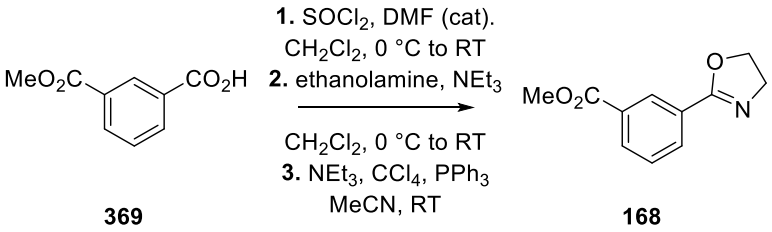


368 **167**

Following general procedure B, using 4-fluorobenzoic acid **368** (595 mg, 4.25 mmol) with oxalyl chloride (1.65 g, 13.0 mmol) and DMF (few drops) in dichloromethane (14 mL) the respective acid chloride was synthesised. The amide was then generated using ethanolamine (263 mg, 4.25 mmol), triethylamine (428 mg, 4.25 mmol) in dichloromethane (30 mL). Cyclisation of the amide with carbon tetrachloride (14.8 g, 96.0 mmol), triethylamine (6.71 g, 66.4 mmol) and triphenylphosphine (4.00 g, 15.3 mmol) in dry acetonitrile (50 mL) afforded the oxazoline product **167** (420 mg, 60%) as a pale orange solid.

M.p.: 139 – 140 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3060 (w), 2958 (w), 1651 (s), 1506 (s), 1068 (s), 725 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 – 7.91 (2H, m, C*H*$_{ar}$), 7.12 – 7.04 (2H, m, C*H*$_{ar}$), 4.42 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.04 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 166.0, 163.7 (d, *J* = 34.0 Hz), 130.5 (d, *J* = 9.0 Hz), 124.1 (d, *J* = 3.0 Hz), 115.6 (d, *J* = 22.0 Hz), 67.9, 55.1; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 108.4; HRMS: *m/z* $[MH]^+C_9H_9NOF$ calcd. 166.0668, found 166.0667.

Synthesis of 3-(4,5-dihydro-2-oxazolyl)-methyl ester benzoic acid **168**



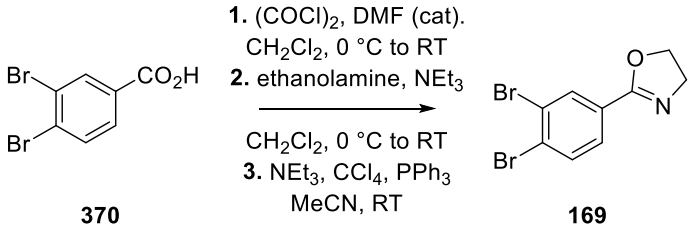
369 **168**

Following general procedure B, using 3-(methoxycarbonyl) benzoic acid **369** (766 mg, 4.25 mmol) with thionyl chloride (1.01 g, 8.50 mmol) and DMF (few drops) in dichloromethane (25 mL) the respective acid chloride was synthesised. The amide was then generated using ethanolamine (263 mg, 4.25 mmol), triethylamine (428 mg, 4.25 mmol) in dichloromethane (30 mL). Cyclisation of the amide with carbon tetrachloride (14.8 g, 96.0 mmol), triethylamine (6.71 g, 66.4 mmol) and triphenylphosphine (4.00 g, 15.3 mmol) afforded the oxazoline product **168** (450 mg, 52 %) as a colourless solid.

M.p.: 91 – 92 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3039 (w), 2982 (w), 2949 (w), 1724 (s), 1652 (s), 1233 (s), 700 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (1H, t, *J* = 1.5 Hz, C*H*$_{ar}$), 8.09 – 8.06 (2H, m, C*H*$_{ar}$), 7.43 (1H, t, *J* = 8.0 Hz, C*H*$_{ar}$), 4.39 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.01 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR

(100.6 MHz, $CDCl_3$): δ 166.5, 164.1, 132.6, 132.4, 130.6, 129.5, 128.7, 128.2, 68.0, 55.0, 52.4; HRMS: *m/z* $[MH]^+$ $C_{11}H_{12}NO_3$ calcd. 206.0817, found 206.0824.

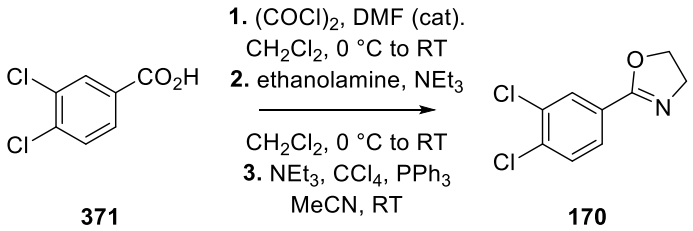
Synthesis of 2-(3,4-dibromophenyl)-4,5-dihydro-oxazole **169**



Following general procedure B, using 3,4-dibromobenzoic acid **370** (500 mg, 1.79 mmol) with oxalyl chloride (0.70 g, 5.48 mmol) and DMF (few drops) in dichloromethane (6 mL) the respective acid chloride was synthesised. The amide was then generated using ethanolamine (111 mg, 1.79 mmol), trimethylamine (182 mg, 1.79 mmol) in dichloromethane (13 mL). Cyclisation of the amide with carbon tetrachloride (6.22 g, 40.4 mmol), triethylamine (2.83 g, 28.0 mmol) and triphenylphosphine (1.70 g, 6.43 mmol) in dry acetonitrile (17 mL) afforded the oxazoline product **169** (360 mg, 66%) as a pale orange solid.

M.p.: 99 – 100 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3057 (w), 2986 (w), 1644 (m), 1319 (m), 1068 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (1H, d, *J* = 2.0 Hz, CH_{ar}), 7.70 (1H, dd, *J* = 8.0, 2.0 Hz, CH_{ar}), 7.63 (1H, d, *J* = 8.0 Hz, CH_{ar}), 4.42 (2H, t, *J* = 9.5 Hz, CH_2), 4.03 (2H, t, *J* = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.8, 133.7, 133.3, 128.4, 128.3, 128.0, 125.0, 68.1, 55.1; HRMS: *m/z* $[MH]^+$ $C_9H_8NO^{79}Br_2$ calcd. 303.8973, found 303.8986.

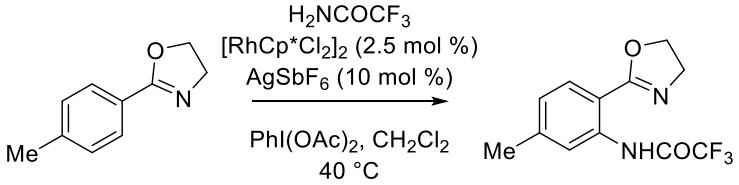
Synthesis of 2-(3,4-dichlorophenyl)-4,5-dihydro-oxazole **170**



Following general procedure B, using 3,4-dichlorobenzoic acid **371** (812 mg, 4.25 mmol) with oxalyl chloride (1.65 g, 13.0 mmol) and DMF (few drops) in dichloromethane (14 mL) the respective acid chloride was synthesised. The amide was then generated using ethanolamine (263 mg, 4.25 mmol), trimethylamine (428 mg, 4.25 mmol) in dichloromethane (30 mL). Cyclisation of the amide with carbon tetrachloride (14.8 g, 96.0 mmol), triethylamine (6.71 g, 66.4 mmol) and triphenylphosphine (4.00 g, 15.3 mmol) in dry acetonitrile (50 mL) afforded the oxazoline product **170** (590 mg, 64%) as a pale orange solid.

M.p.: 95 – 96 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3082 (w), 2983 (w), 1647 (s), 1241 (s), 1071 (s), 714 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (1H, d, *J* = 2.0 Hz, C*H*$_{ar}$), 7.77 (1H, dd, *J* = 8.5, 2.0 Hz, C*H*$_{ar}$), 7.49 (1H, d, *J* = 8.5 Hz, C*H*$_{ar}$), 4.45 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.07 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.0, 135.7, 132.9, 130.6, 130.3, 127.8, 127.4, 68.1, 55.1; HRMS: *m/z* $[MH]^+$ $C_9H_8NO^{35}Cl_2$ calcd. 215.9983, found 215.9977.

*Synthesis of 2,2,2-trifluoro-N-[*2-(4-methylphenyl)-4,5-dihydro-oxazole]-*acetamide* **171**

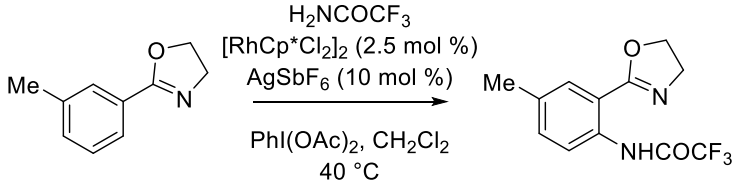


159 **171**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 4,5-dihydro-2-(4-methylphenyl)-oxazole **159** (65 mg, 0.40 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 16 h, product **171** was isolated as a colourless solid (46 mg, 84%).

M.p.: 120 – 121 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3046 (w), 2958 (w), 1721 (s), 1637 (s), 1153 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.66 (1H, s, N*H*), 8.52 (1H, s, C*H*$_{ar}$), 7.77 (1H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 7.02 (1H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 4.41 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.14 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 2.42 (3H, s, C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): 164.8, 155.6 (q, *J* = 37.5 Hz), 143.8, 137.5, 129.2, 125.3, 120.8, 116.1 (q, *J* = 289.0 Hz), 112.0, 66.7, 54.4, 22.1; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.0; HRMS: *m/z* $[MH]^+$ $C_{12}H_{12}N_2O_2F_3$ calcd. 273.0851, found 273.0861.

*Synthesis of 2,2,2-trifluoro-N-[*2-(3-methylphenyl)-4,5-dihydro-oxazole]-*acetamide* **172**



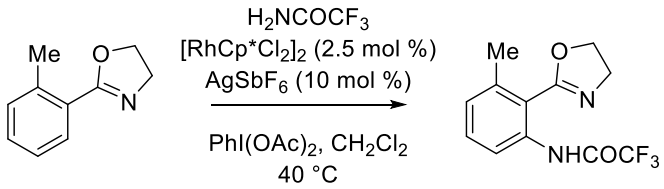
160 **172**

Following general procedure A, using trifluoroacetamide (65 mg, 0.20 mmol) and 2-(3-methylphenyl)-4,5-dihydro-oxazole **160** (104 mg, 0.400 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 16 h, product **172** was isolated as a colourless solid (39 mg, 72%).

M.p.: 145 – 146 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3096 (w), 2993 (w), 2887 (w), 1714 (m), 1615 (m), 1138 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.56 (1H, s, N*H*), 8.55 (1H, d, *J* = 8.5 Hz, C*H*$_{ar}$), 7.70 (1H, d, *J* = 2.0 Hz, C*H*$_{ar}$), 7.32 (1H, dd, *J* = 8.5, 2.0 Hz, C*H*$_{ar}$), 4.42 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.15 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 2.36 (3H, s, C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.7, 155.4 (q, *J* = 37.5 Hz),

135.3, 134.3, 133.4, 129.7, 120.3, 116.9 (q, *J* = 288.5 Hz), 114.4, 66.7, 54.5, 20.9; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.0; HRMS: *m/z* $[MH]^+$ $C_{12}H_{12}N_2O_2F_3$ calcd. 273.0851, found 273.0859.

*Synthesis of 2,2,2-trifluoro-N-[*2-(2-methylphenyl)-4,5-dihydro-oxazole]-*acetamide* **173**

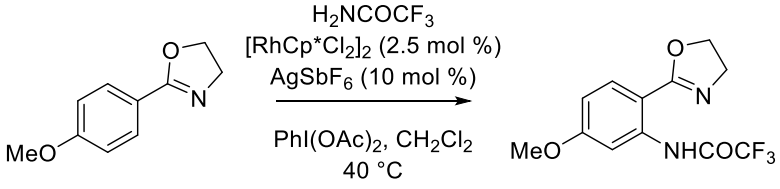


161 **173**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(2-methylphenyl)-4,5-dihydro-oxazole **161** (65 mg, 0.400 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 16 h, product **173** was isolated as a colourless solid (40 mg, 74%).

M.p.: 105 – 106 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3117 (w), 2983 (w), 2944 (w), 1707 (m), 1612 (m), 1145 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.25 (1H, s, N*H*), 8.43 (1H, d, *J* = 8.0 Hz, CH_{ar}), 7.36 (1H, t, *J* = 8.0 Hz, CH_{ar}), 7.05 (1H, d, *J* = 8.0 Hz, CH_{ar}), 4.46 (2H, t, *J* = 9.5 Hz, CH_2), 4.12 (2H, t, *J* = 9.5 Hz, CH_2), 2.54 (3H, s, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.8, 155.3 (q, *J* = 37.5 Hz), 140.2, 137.4, 131.6, 128.4, 118.7, 116.2 (q, *J* = 288.5 Hz), 115.4, 67.1, 53.5, 23.3; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.0; HRMS: *m/z* $[MH]^+$ $C_{12}H_{12}N_2O_2F_3$ calcd. 273.0851, found 273.0847.

*Synthesis of 2,2,2-trifluoro-N-[*2-(4-methoxyphenyl)-4,5-dihydro-oxazole]-*acetamide* **174**



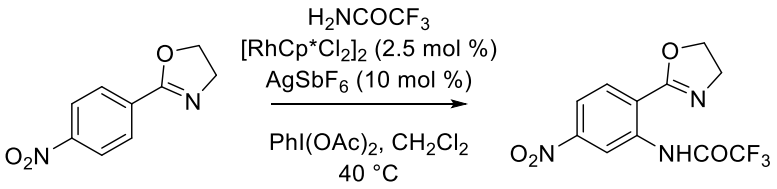
162 **174**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(4-methoxyphenyl)-4,5-dihydro-oxazole **162** (71 mg, 0.400 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 16 h, product **174** was isolated as a colourless solid (57 mg, 100%).

M.p.: 103 – 104 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3117 (w), 2979 (w), 1714 (m), 1637 (m), 1181 (s), 1145 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.84 (1H, s, N*H*), 8.31 (1H, d, *J* = 2.5 Hz, CH_{ar}), 7.79 (1H, d, *J* = 8.5 Hz, CH_{ar}), 6.73 (1H, dd, *J* = 8.5, 2.5 Hz, CH_{ar}), 4.39 (2H, t, *J* = 9.5 Hz, CH_2), 4.12 (2H, t, *J* = 9.5 Hz, CH_2), 3.87 (3H, s, OCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): 164.7, 162.9, 155.8 (q, *J* = 37.5 Hz), 139.4, 130.6, 116.0 (q, *J* = 288.5 Hz), 111.0, 107.4, 105.3, 66.6, 55.7, 54.3; ^{19}F NMR

(376.5 MHz, $CDCl_3$): δ – 76.0; HRMS: *m/z* $[MH]^+$ $C_{12}H_{12}N_2O_3F_3$ calcd. 289.0800, found 289.0799.

*Synthesis of 2,2,2-trifluoro-N-[*2-(4-nitrophenyl)-4,5-dihydro-oxazole]-*acetamide* **175**

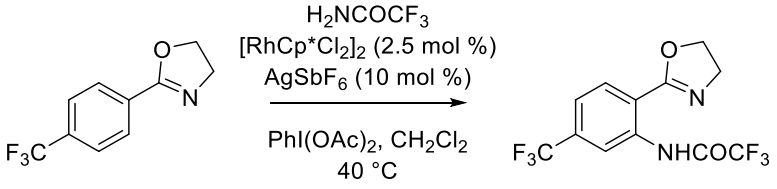


163 **175**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(4-nitrophenyl)-4,5-dihydro-oxazole **163** (77 mg, 0.40 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 16 h, product **175** was isolated as a colourless solid (52 mg, 100%).

M.p.: 152 – 153 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3124 (w), 2990 (w), 1725 (m), 1153 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 13.82 (1H, s, N*H*), 9.53 (1H, s, CH_{ar}), 8.05 (2H, q, *J* = 8.5 Hz, CH_{ar}), 4.52 (2H, t, *J* = 9.5 Hz, CH_2), 4.25 (2H, t, *J* = 9.6 Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.6, 156.1 (q, *J* = 38.5 Hz), 149.9, 138.6, 130.5, 119.1, 118.9, 116.8 (q, *J* = 288.5 Hz), 115.2, 67.3, 54.7; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.1; HRMS: *m/z* $[MH]^+$ $C_{11}H_9N_3O_4F_3$ calcd. 304.0545, found 304.0546.

*Synthesis of 2,2,2-trifluoro-N-[*2-(4-trifluoromethylphenyl)-4,5-dihydro-oxazole]-*acetamide* **176**



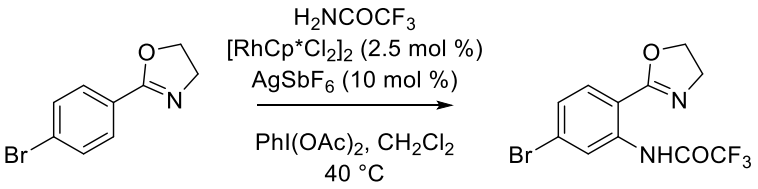
164 **176**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(4-trifluoromethylphenyl)-4,5-dihydro-oxazole **164** (86 mg, 0.40 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 16 h, product **176** was isolated as a colourless solid (65 mg, 100%).

M.p.: 130 – 131 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3007 (w), 2901 (w), 1728 (m), 1326 (s), 1128 (s), 683 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 13.78 (1H, s, N*H*), 9.01 (1H, d, *J* = 1.0 Hz, CH_{ar}), 8.01 (1H, d, *J* = 8.0 Hz, CH_{ar}), 7.46 (1H, dd, *J* = 8.0, 1.0 Hz, CH_{ar}), 4.48 (2H, t, *J* = 9.5 Hz, CH_2), 4.21 (2H, t, *J* = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.0, 156.0 (q, *J* = 38.0 Hz), 138.2, 134.4 (q, *J* = 33.0 Hz), 130.0, 123.6 (q, *J* = 232.0 Hz), 121.1 (q, *J* = 3.5 Hz), 117.3 (q, *J* = 3.5 Hz), 117.2,

115.6 (q, *J* = 288.5 Hz), 67.1, 54.6; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 63.4, – 76.1; HRMS: *m/z* $[MH]^+$ $C_{12}H_9N_2O_2F_6$ calcd. 327.0568, found 327.0562.

*Synthesis of 2,2,2-trifluoro-N-[*2-(4-bromophenyl)-4,5-dihydro-oxazole]-*acetamide* **177**

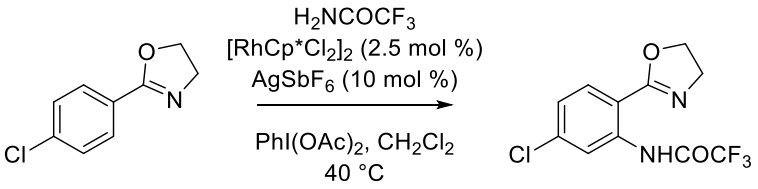


165 **177**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(4-bromophenyl)-4,5-dihydro-oxazole **165** (91 mg, 0.40 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 16 h, product **177** was isolated as a colourless solid (65 mg, 96%).

M.p.: 169 – 170 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3117 (w), 2993 (w), 1718 (m), 1637 (m), 1153 (s), 1064 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.75 (1H, s, N*H*), 8.93 (1H, s, CH_{ar}), 7.76 (1H, d, *J* = 8.5 Hz, CH_{ar}), 7.38 (1H, d, *J* = 8.5, 2.0 Hz, CH_{ar}), 4.46 (2H, t, *J* = 9.5 Hz, CH_2), 4.18 (2H, t, *J* = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.3, 155.8 (q, *J* = 38.0 Hz), 138.5, 130.4, 127.8, 127.3, 123.3, 115.9 (q, *J* = 288.5 Hz), 113.3, 66.9, 54.5; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.0; HRMS: *m/z* $[MH]^+$ $C_{11}H_9N_2O_2{}^{79}BrF_3$ calcd. 336.9799, found 336.9790.

*Synthesis of 2,2,2-trifluoro-N-[*2-(4-chlorophenyl)-4,5-dihydro-oxazole]-*acetamide* **178**

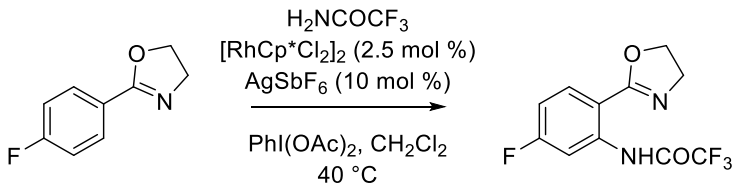


166 **178**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(4-chlorophenyl)-4,5-dihydro-oxazole **166** (73 mg, 0.400 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 16 h, product **178** was isolated as a colourless solid (54 mg, 92%).

M.p.: 151 – 152 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3117 (w), 2993 (w), 1718 (m), 1600 (m), 1149 (s), 750 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.75 (1H, s, N*H*), 8.73 (1H, d, *J* = 2.0 Hz, CH_{ar}), 7.80 (1H, d, *J* = 8.5 Hz, CH_{ar}), 7.18 (1H, dd, *J* = 2.0, 8.5 Hz, CH_{ar}), 4.43 (2H, t, *J* = 9.5 Hz, CH_2), 4.16 (2H, d, *J* = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.1, 155.8 (q, *J* = 38.0 Hz), 138.9, 138.5, 130.4, 124.7, 120.4, 115.9 (q, *J* = 288.5 Hz), 112.9, 66.9, 54.4; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.0; HRMS: *m/z* $[MH]^+$ $C_{11}H_9N_2O_2{}^{35}ClF_3$ calcd. 293.0305, found 293.0307.

*Synthesis of 2,2,2-trifluoro-N-[*2-(4-fluorophenyl)-4,5-dihydro-oxazole]-*acetamide* **179**

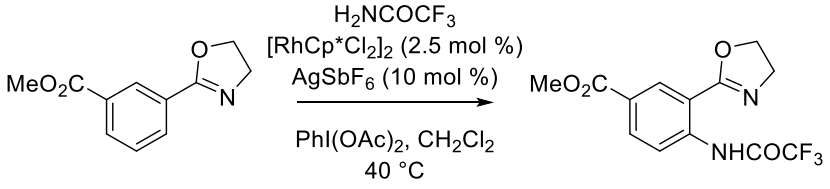


167 **179**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(4-fluorophenyl)-4,5-dihydro-oxazole **167** (66 mg, 0.400 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 16 h, product **179** was isolated as a colourless solid (54 mg, 97%).

M.p.: 121 – 122 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3124 (w), 2993 (w), 1721 (m), 1637 (m), 1142 (s), 757 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.86 (1H, s, N*H*), 8.47 (1H, dd, *J* = 11.0, 2.5 Hz, CH_{ar}), 7.89 (1H, dd, *J* = 9.0, 7.0 Hz, CH_{ar}), 6.91 (1H, ddd, *J* = 9.0, 7.0, 2.5 Hz, CH_{ar}), 4.43 (2H, t, *J* = 9.5 Hz, CH_2), 4.15 (2H, t, *J* = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 166.1, 163.9 (d, *J* = 57. 0 Hz), 155.9 (q, *J* = 37.5 Hz), 139.5 (d, *J* = 12.0 Hz), 131.3 (d, *J* = 10.5 Hz), 115.1 (q, *J* = 288.5 Hz), 111.7 (d, *J* = 22.0 Hz), 110.9, 108.2 (d, J = 28.5 Hz), 66.9, 54.4; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.1, – 103.3; HRMS: *m/z* $[MH]^+$ $C_{11}H_9N_2O_2F_4$ calcd. 277.0600, found 277.0601.

*Synthesis of 2,2,2-trifluoro-N-[*3-(4,5-dihydro-2-oxazolyl)-methyl ester *benzoic acid*]-*acetamide* **180**



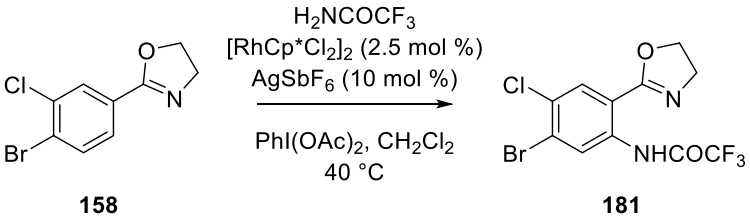
168 **180**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 3-(4,5-dihydro-2-oxazolyl)-methyl ester benzoic acid **168** (104 mg, 0.400 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 16 h, product **180** was isolated as a colourless solid (49 mg, 77%).

M.p.: 212 – 213 °C; FTIR: ν_{max}/ cm^{-1} (neat) 2961 (w), 2891 (w), 1715 (s), 1646 (m), 1594 (m), 1155 (s), 1139 (s), 767 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.90 (1H, s, N*H*), 8.74 (1H, d, *J* = 9.0 Hz, CH_{ar}), 8.57 (1H, d, *J* = 2.0 Hz, CH_{ar}), 8.17 (1H, dd, *J* = 9.0, 2.0 Hz, CH_{ar}), 4.47 (2H, t, *J* = 9.5 Hz, CH_2), 4.19 (2H, t, *J* = 9.5 Hz, CH_2), 3.93 (3H, s, OCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.8, 164.3, 156.0 (q, *J* = 38.0 Hz), 141.3, 134.0, 131.1, 126.2, 120.1, 116.4 (q, *J* = 288.5 Hz), 114.5,

67.0, 54.6, 52.4; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.0; HRMS: *m/z* $[MH]^+$ $C_{13}H_{12}N_2O_4F_3$ calcd. 317.0744, found 317.0743.

*Synthesis of 2,2,2-trifluoro-N-[*2-(3-chloro-4-bromophenyl)-4,5-dihydro-oxazole]-*acetamide* **181**

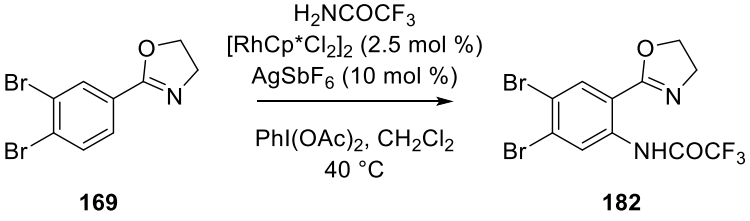


158 **181**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(3-chloro-4-bromophenyl)-4,5-dihydro-oxazole **158** (104 mg, 0.400 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 16 h, product **181** was isolated as a colourless solid (54 mg, 72%).

M.p.: 110 – 111 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3054 (w), 2990 (w), 1725 (s), 1265 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.60 (1H, s, N*H*), 9.02 (1H, s, CH_{ar}), 7.93 (1H, s, CH_{ar}), 4.46 (2H, t, *J* = 9.5 Hz, CH_2), 4.17 (2H, t, *J* = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.4, 155.7 (q, *J* = 38.0 Hz), 136.4, 130.3, 127.2, 125.3, 120.1, 115.8 (q, *J* = 288.5 Hz), 114.8, 67.2, 54.6; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.0; HRMS: *m/z* $[MH]^+$ $C_{11}H_8N_2O_2F_3{}^{35}Cl^{79}Br$ calcd. 370.9410, found 370.9421.

Synthesis of 2,2,2-trifluoro-N-[2-(3,4-dibromophenyl)-4,5-dihydro-oxazole]-acetamide **182**



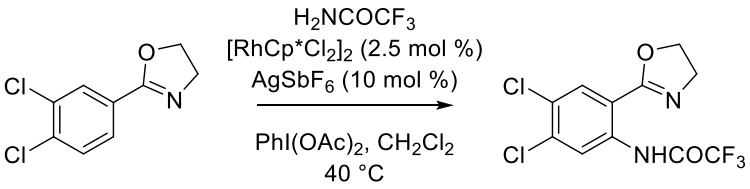
169 **182**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(3,4-dibromophenyl)-4,5-dihydro-oxazole **169** (122 mg, 0.400 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 16 h, product **182** was isolated as a colourless solid (79 mg, 95%).

M.p.: 140 – 141 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3067 (w), 2979 (w), 1714 (m), 1145 (s), 750 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.60 (1H, s, N*H*), 9.00 (1H, s, CH_{ar}), 8.07 (1H, s, CH_{ar}), 4.45 (2H, t, *J* = 9.5 Hz, CH_2), 4.17 (2H, t, *J* = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.3, 155.7 (q, *J* = 38.0 Hz), 136.9, 133.5, 129.6, 125.1, 119.9, 115.8 (q, *J* = 288.5 Hz), 114.8, 67.1, 54.6; ^{19}F NMR

(376.5 MHz, $CDCl_3$): δ – 76.0; HRMS: *m/z* $[MH]^+$ $C_{11}H_8N_2O_2F_3{}^{79}Br_2$ calcd. 414.8905, found 414.8907.

Synthesis of 2,2,2-trifluoro-N-[2-(3,4-dichlorophenyl)-4,5-dihydro-oxazole]-acetamide **183**

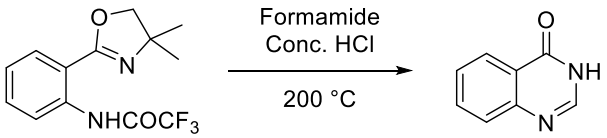


170 **183**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(3,4-dichlorophenyl)-4,5-dihydro-oxazole **170** (86 mg, 0.40 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 16 h, product **183** was isolated as a colourless solid (49 mg, 75%).

M.p.: 135 – 136 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3117 (w), 2887 (w), 1711 (s), 1145 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 13.64 (1H, s, N*H*), 8.87 (1H, s, CH_{ar}), 7.94 (1H, s, CH_{ar}), 4.47 (2H, t, *J* = 9.5 Hz, CH_2), 4.20 (2H, t, *J* = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.3, 155.8 (q, *J* = 38.5 Hz), 137.0, 136.6, 130.6, 128.2, 122.0, 115.8 (q, *J* = 288.5 Hz), 114.2, 67.1, 54.6; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.2; HRMS: *m/z* $[MH]^+$ $C_{11}H_8N_2O_2F_3{}^{35}Cl_2$ calcd. 326.9915, found 326.9931.

Synthesis of quinazoline-4(3H)-one **184**[171]



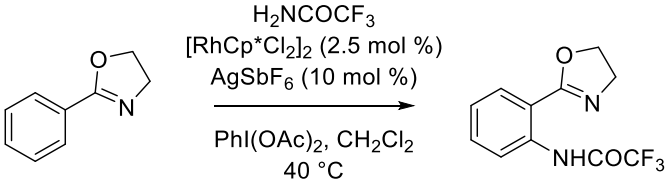
135 **184**

To a round bottomed flask equipped with a reflux condenser was added 2,2,2-trifluoro-*N*-[2-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)phenyl] acetamide **135** (143 mg, 0.500 mmol), formamide (1.13 g, 25.0 mmol) and concentrated hydrochloric acid (1.5 mL, 50 mmol). The reaction mixture was heated at 200 °C for a period of 16 h. The reaction was then allowed to cool to room temperature, diluted with H_2O and transferred to a separating funnel. The aqueous phase was extracted with ethyl acetate. The combined organics were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60)/ethyl acetate (0% ethyl acetate to 100% ethyl acetate) to afford product **184** as a colourless solid (25 mg, 34%).

M.p.: 189 – 190 °C; ^1H NMR (400 MHz, d_6-DMSO): δ 12.24 (1H, br s, N*H*), 8.12 (1H ddd, *J* = 8.0, 1.5 and 0.5 Hz, CH_{ar}), 8.09 (1H, s, N=C*H*), 7.82 (1H, ddd, *J* = 8.0, 7.0 and 1.5 Hz, CH_{ar}), 7.67

(1H, dd, *J* = 8.0 and 0.5 Hz, C*H*$_{ar}$), 7.52 (1H, ddd, *J* = 8.0, 7.0 and 1.0 Hz, C*H*$_{ar}$); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 160.8, 148.7, 145.4, 134.3, 127.2, 126.7, 125.8, 122.6.

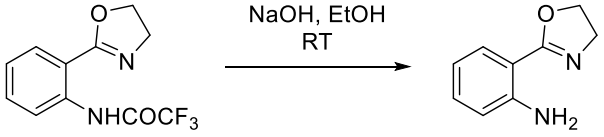
Synthesis of 2,2,2-trifluoro-N-[2-(4,5-dihydro-2-oxazolyl)phenyl]-acetamide **154**



152 **154**

Following general procedure C, using trifluoroacetamide (500 mg, 4.42 mmol) and 2-phenyl-2-oxazoline **152** (1.30 g, 8.84 mmol) with $[Cp^*RhCl_2]_2$ (27 mg, 0.044 mmol), $AgSbF_6$ (61 mg, 0.17 mmol) and $PhI(OAc)_2$ (2.14 g, 6.63 mmol) in dichloromethane (44 mL) at 40 °C for 16 h, product **154** was isolated as a colourless solid (861 mg, 76%). *See above for characterisation data.*

Synthesis of 2-(4,5-dihydrooxazol-2-yl)aniline **185**[172]

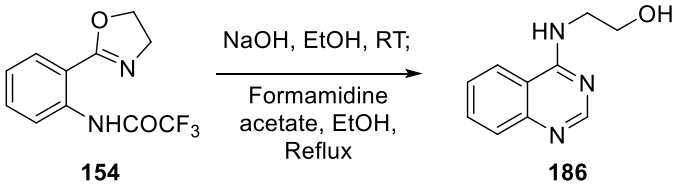


154 **185**

To a solution of 2,2,2-trifluoro-*N*-[2-(4,5-dihydro-2-oxazolyl)phenyl]-acetamide **154** (130 mg, 0.500 mmol) in ethanol (5 mL) was added sodium hydroxide pellets (400 mg, 10.0 mmol). The reaction mixture was stirred at room temperature and monitored by TLC analysis until complete conversion of the starting material was indicated (6 h). The solvent was then removed *in vacuo* followed by dissolving the residue in ethyl acetate and H_2O. The mixture was transferred to a separating funnel and the layers were partitioned. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the desired product **185** as a colourless solid (80 mg, 98%).

M.p.: 54 – 55 °C (lit.,[166] 54 – 57 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (1H, dd, *J* = 8.0, 1.5 Hz, C*H*$_{ar}$), 7.24 – 7.15 (1H, m C*H*$_{ar}$), 6.72 – 6.60 (2H, m, C*H*$_{ar}$), 6.07 (2H, br s, N*H*$_2$), 4.31 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.09 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.9, 148.6, 132.0, 129.7, 116.1, 115.8, 190.3, 65.8, 55.0.

Synthesis of 2-(4-quinazolinylamino)-ethanol **186**

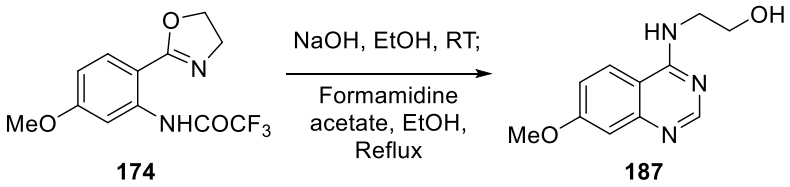


154 **186**

Following general procedure D, using trifluoroacetamide substrate **154** (103 mg, 0.400 mmol), NaOH pellets (320 mg, 8.00 mmol) in ethanol (4.0 mL) generated the crude aniline. Cyclisation with formamidine acetate (125 mg, 1.20 mmol) in ethanol (4.0 mL) for 1 hour afforded product **186** as a colourless solid (67 mg, 89%).

M.p.: 157 – 158 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3233 (m), 3021 (w), 2961 (w), 1584 (s), 1319 (s), 1064 (s), 771 (s); ^{1}H NMR (400 MHz, d^{6}-DMSO): δ 8.44 (1H, s, N=C*H*), 8.27 (1H, s, N*H*), 8.24 (1H, dd, *J* = 8.5, 1.0 Hz, C*H*$_{ar}$), 7.75 (1H, ddd, *J* = 8.5, 7.0, 1.0 Hz, C*H*$_{ar}$), 7.67 (1H, dd, *J* = 8.5, 1.0 Hz, C*H*$_{ar}$), 7.50 (1H, ddd, *J* = 8.5, 7.0, 1.0 Hz, C*H*$_{ar}$), 4.81 (1H, t, *J* = 5.5 Hz, O*H*), 3.67 – 3.57 (4H, m, (C*H*$_2$)$_2$); ^{13}C NMR (100.6 MHz, d^{6}-DMSO): δ 159.5, 155.0, 149.1, 132.5, 127.5, 125.5, 122.7, 115.0, 59.2, 43.3; HRMS: *m*/*z* [MH]$^+$ $C_{10}H_{12}N_3O$ calcd. 190.0980, found 190.0973.

Synthesis of 2-((7-methoxy-4-quinazolinylamino)-ethanol **187**

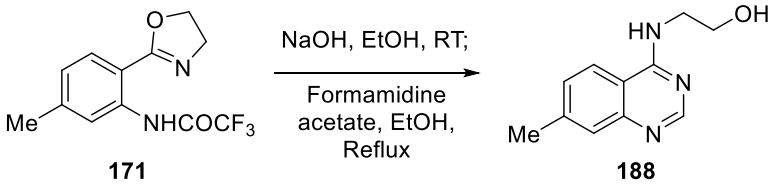


174 **187**

Following general procedure D, using trifluoroacetamide substrate **174** (115 mg, 4.00 mmol), NaOH pellets (320 mg, 8.00 mmol) in ethanol (4.0 mL) generated the crude aniline. Cyclisation with formamidine acetate (125 mg, 1.20 mmol) in ethanol (4.0 mL) for 1 hour afforded product **187** as a colourless solid (71 mg, 80%).

M.p.: 192 – 193 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3237 (m), 3118 (m), 3057 (w), 2943 (w), 1583 (s), 1333 (s), 1237 (s), 1040 (s), 780 (s); ^{1}H NMR (400 MHz, d^{6}-DMSO): δ 8.38 (1H, s, N=C*H*), 8.16 (1H, d, *J* = 9.0 Hz, C*H*$_{ar}$), 8.12 (1H, t, *J* = 4.5 Hz, C*H*$_{ar}$), 7.13 – 7.04 (2H, m, C*H*$_{ar}$), 4.84 (1H, s, O*H*), 3.87 (3H, s, OC*H*$_3$), 3.64 – 3.55 (4H, m, (C*H*$_2$)$_2$); ^{13}C NMR (100.6 MHz, d^{6}-DMSO): δ 162.3, 159.2, 155.6, 151.4, 124.4, 116.6, 109.2, 106.8, 59.4, 55.5, 43.2; HRMS: *m*/*z* [MH]$^+$ $C_{11}H_{14}N_3O_2$ calcd. 220.1086, found 220.1087.

Synthesis of 2-((7-methyl-4-quinazolinylamino)-ethanol **188**

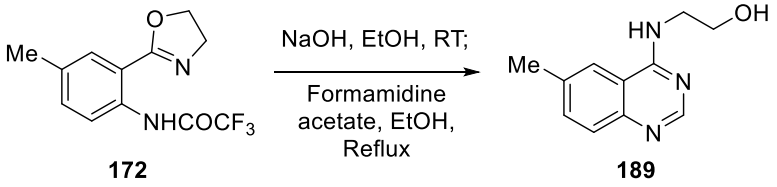


171 **188**

Following general procedure D, using trifluoroacetamide substrate **171** (109 mg, 0.400 mmol), NaOH pellets (320 mg, 8.00 mmol) in ethanol (4.0 mL) generated the crude aniline. Cyclisation with formamidine acetate (125 mg, 1.20 mmol) in ethanol (4.0 mL) for 1 hour afforded product **188** as a colourless solid (76 mg, 93%).

M.p.: 155 – 156 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3330 (m), 3220 (m), 2963 (w), 1580 (s), 1323 (s), 1053 (s), 787 (s); ^{1}H NMR (400 MHz, d^{6}-DMSO): δ 8.40 (1H, s, N=C*H*), 8.16 (1H, s, N*H*), 8.13 (1H, d, *J* = 8.5 Hz, CH_{ar}), 7.46 (1H, d, *J* = 1.5 Hz, CH_{ar}), 7.33 (1H, dd, *J* = 8.5, 1.5 Hz, CH_{ar}), 4.81 (1H, t, *J* = 5.0 Hz, O*H*), 3.66 – 3.56 (4H, m, (CH_2)$_2$), 2.45 (3H, s, CH_3); ^{13}C NMR (100.6 MHz, d^{6}-DMSO): δ 159.4, 155.1, 149.3, 142.5, 127.2, 126.7, 122.5, 112.9, 59.3, 43.3, 21.3; HRMS: *m/z* [MH]$^{+}$ $C_{11}H_{14}N_3O$ calcd. 204.1137, found 204.1140.

Synthesis of 2-((6-methyl-4-quinazolinylamino)-ethanol **189**

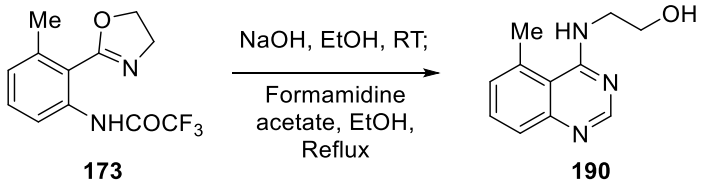


172 **189**

Following general procedure D, using trifluoroacetamide substrate **172** (109 mg, 0.400 mmol), NaOH pellets (320 mg, 8.00 mmol) in ethanol (4.0 mL) generated the crude aniline. Cyclisation with formamidine acetate (125 mg, 1.20 mmol) in ethanol (4.0 mL) for 1 hour afforded product **189** as a colourless solid (76 mg, 93%).

M.p.: 125 – 126 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3307 (m), 3170 (m), 2937 (w), 1587 (s), 1540 (s), 1357 (s), 1320 (s), 1063 (s), 833 (s); ^{1}H NMR (400 MHz, d^{6}-DMSO): δ 8.40 (1H, s, N=C*H*), 8.13 (1H, s, N*H*), 8.05 (1H, s, CH_{ar}), 7.58 (2H, s, CH_{ar}), 4.82 (1H, s, O*H*), 3.68 – 3.56 (4H, m, (CH_2)$_2$), 2.46 (3H, s, CH_3); ^{13}C NMR (100.6 MHz, d^{6}-DMSO): δ 159.2, 154.3, 147.3, 134.9, 134.1, 127.2, 121.8, 114.8, 59.3, 43.3, 21.2; HRMS: *m/z* [MH]$^{+}$ $C_{11}H_{14}N_3O$ calcd. 204.1137, found 204.1140.

Synthesis of 2-((5-methyl-4-quinazolinylamino)-ethanol **190**

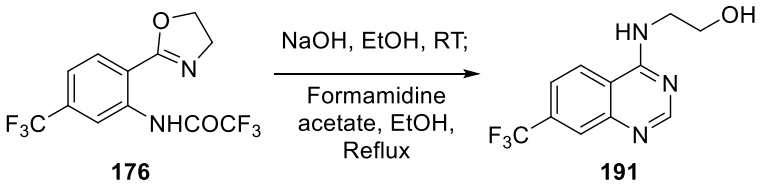


173 **190**

Following general procedure D, using trifluoroacetamide substrate **173** (109 mg, 0.400 mmol), NaOH pellets (320 mg, 8.00 mmol) in ethanol (4.0 mL) generated the crude aniline (NB: The hydrolysis for this particular substrate was conducted at reflux for 2 hours). Cyclisation with formamidine acetate (125 mg, 1.20 mmol) in ethanol (4.0 mL) for 1 hour afforded product **190** as a colourless solid (37 mg, 46%).

M.p.: 174 – 175 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3467 (w), 3033 (m), 2953 (w), 2887 (m), 1583 (s), 1523 (s), 1347 (s), 1098 (s), 820 (s); ^{1}H NMR (400 MHz, d^{6}-DMSO): δ 8.37 (1H, s, C=N*H*), 7.62 – 7.56 (1H, m, C*H*$_{ar}$), 7.50 (1H, d, *J* = 9.0 Hz, C*H*$_{ar}$), 7.27 (1H, d, *J* = 7.0 Hz, C*H*$_{ar}$), 6.99 (1H, s, N*H*), 4.90 (1H, s, O*H*), 3.66 – 3.61 (4H, m, (C*H*$_2$)$_2$), 2.86 (3H, s, C*H*$_3$); ^{13}C NMR (100.6 MHz, d^{6}-DMSO): δ 160.3, 154.0, 151.1, 134.2, 131.8, 128.6, 125.8, 115.1, 59.0, 43.7, 23.3; HRMS: *m*/*z* [MH]$^+$ $C_{11}H_{14}N_3O$ calcd. 204.1137, found 204.1138.

Synthesis of 2-((7-trifluoromethyl-4-quinazolinylamino)-ethanol **191**

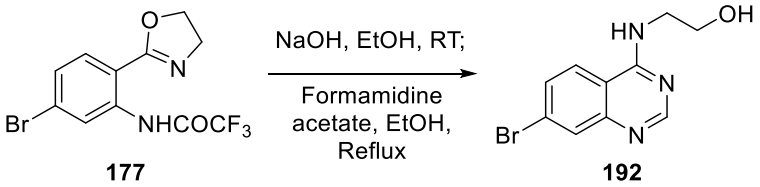


176 **191**

Following general procedure D, using trifluoroacetamide substrate **176** (131 mg, 0.400 mmol), NaOH pellets (320 mg, 8.00 mmol) in ethanol (4.0 mL) generated the crude aniline. Cyclisation with formamidine acetate (125 mg, 1.20 mmol) in ethanol (4.0 mL) for 14 hours afforded product **191** as a colourless solid (95 mg, 93%).

M.p.: 154 – 155 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3317 (m), 3217 (m), 2943 (w), 1580 (s), 1317 (s), 1120 (s), 1047 (s), 890 (m); ^{1}H NMR (400 MHz, d^{6}-DMSO): δ 8.61 (1H, s, N*H*), 8.55 (1H, s, N=C*H*), 8.49 (1H, d, *J* = 8.5 Hz, C*H*$_{ar}$), 7.97 (1H, s, C*H*$_{ar}$), 7.81 (1H, dd, *J* = 8.5, 2.0 Hz, C*H*$_{ar}$), 4.83 (1H, t, *J* = 5.5 Hz, O*H*), 3.68 – 3.59 (4H, m, (C*H*$_2$)$_2$); ^{13}C NMR (100.6 MHz, d^{6}-DMSO): δ 159.4, 156.5, 148.8, 132.4 (q, *J* = 32.0 Hz), 124.9, 124.7 (q, *J* = 4.0 Hz), 123.7 (q, *J* = 273.0 Hz), 120.9 (q, *J* = 3.0 Hz), 117.2, 58.9, 43.5; ^{19}F NMR (376.5 MHz, d^{6}-DMSO): δ – 61.7; HRMS: *m*/*z* [MH]$^+$ $C_{11}H_{11}N_3OF_3$ calcd. 258.0854, found 258.0859.

Synthesis of 2-((7-bromo-4-quinazolinylamino)-ethanol **192**

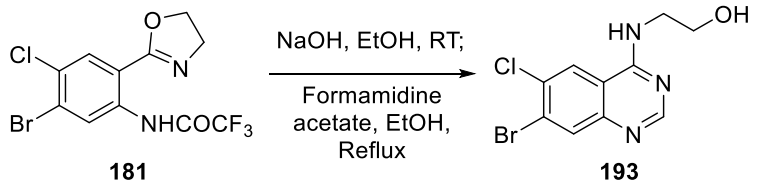


177 **192**

Following general procedure D, using trifluoroacetamide substrate **177** (135 mg, 0.400 mmol), NaOH pellets (320 mg, 8.00 mmol) in ethanol (4.0 mL) generated the crude aniline. Cyclisation with formamidine acetate (125 mg, 1.20 mmol) in ethanol (4.0 mL) for 14 hours afforded product **192** as a colourless solid (84 mg, 79%).

M.p.: 185 – 186 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3320 (m), 3123 (m), 2913 (m), 1588 (s), 1423 (s), 1320 (s), 1060 (s), 877 (s); ^{1}H NMR (400 MHz, d^{6}-DMSO): δ 8.45 (1H, s, C=N*H*), 8.43 (1H, s, N*H*), 8.21 (1H, d, *J* = 9.0 Hz, CH_{ar}), 7.86 (1H, d, *J* = 2.0 Hz, CH_{ar}), 7.67 (1H, dd, *J* = 9.0, 2.0 Hz, CH_{ar}), 4.82 (1H, s, O*H*), 3.66 – 3.55 (4H, m, (CH_2)$_2$); ^{13}C NMR (100.6 MHz, d^{6}-DMSO): δ 159.5, 156.2, 150.3, 129.4, 128.5, 126.0, 125.1, 113.9, 59.0, 43.4; HRMS: *m*/*z* [MH]$^+$ $C_{10}H_{11}N_3O^{79}Br$ calcd. 268.0085, found 268.0091.

Synthesis of 2-((7-bromo-6-chloro-4-quinazolinylamino)-ethanol **193**

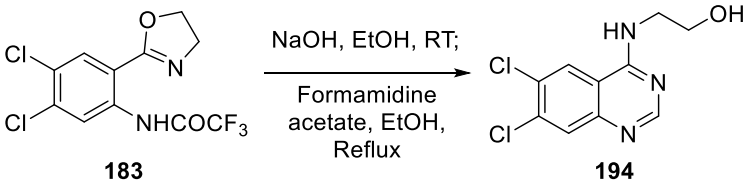


181 **193**

Following general procedure D, using trifluoroacetamide substrate **181** (149 mg, 0.400 mmol), NaOH pellets (320 mg, 8.00 mmol) in ethanol (4.0 mL) generated the crude aniline. Cyclisation with formamidine acetate (125 mg, 1.20 mmol) in ethanol (4.0 mL) for 14 hours afforded product **193** as a colourless solid (100 mg, 83%).

M.p.: 229 – 230 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3309 (m), 3180 (m), 2976 (w), 2876 (w), 1578 (s), 1351 (s), 1054 (s); ^{1}H NMR (400 MHz, d^{6}-DMSO): δ 8.63 (1H, s, C=N*H*), 8.52 (1H, s, N*H*), 8.47 (1H, s, CH_{ar}), 8.07 (1H, s, CH_{ar}), 4.81 (1H, t, *J* = 5.5 Hz, O*H*), 3.65 – 3.56 (4H, m, (CH_2)$_2$); ^{13}C NMR (100.6 MHz, d^{6}-DMSO): δ 158.7, 156.4, 148.6, 132.1, 129.4, 126.0, 124.3, 115.0, 58.9, 43.5; HRMS: *m*/*z* [MH]$^+$ $C_{10}H_{10}N_3O^{35}Cl^{79}Br$ calcd. 301.9696, found 301.9686.

Synthesis of 2-((6,7-dichloroquinazolin-4-yl)amino)ethanol **194**

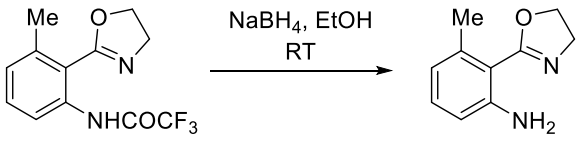


183 **194**

Following general procedure D, using trifluoroacetamide substrate **183** (495 mg, 1.51 mmol), NaOH pellets (1.21 g, 30.3 mmol) in ethanol (15.1 mL) generated the crude aniline. Cyclisation with formamidine acetate (472 mg, 4.53 mmol) in ethanol (15.1 mL) for 14 hours afforded product **194** as a colourless solid (283 mg, 73%).

M.p.: 204 - 205 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3315 (m), 3006 (w), 2981 (w), 1580 (s), 1362 (m), 1059 (s), 913 (s), 873 (s); ^{1}H NMR (400 MHz, d^{6}-DMSO): δ 8.66 (1H, s, C=N*H*), 8.52 (1H, br s, N*H*), 8.48 (1H, s, CH_{ar}), 7.93 (1H, s, CH_{ar}), 4.82 (1H, br s, O*H*), 3.66 – 3.55 (4H, m, (CH_2)$_2$); ^{13}C NMR (100.6 MHz, d^{6}-DMSO): δ 158.6, 156.5, 148.6, 135.3, 128.7, 127.7, 124.9, 114.6, 58.9, 43.3; HRMS: *m/z* [MH]$^+$ $C_{10}H_{10}N_3O^{35}Cl_2$ calcd. 258.0195, found 258.0198.

Synthesis of 2-(4,5-dihydrooxazol-2-yl)-3-methylaniline **195**



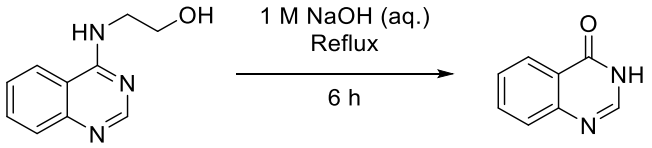
173 **195**

To a stirred solution of trifluoroacetamide substrate **173** (110 mg, 0.400 mmol) in ethanol (4 mL) was added sodium borohydride (76 mg, 2.0 mmol). The reaction mixture was stirred at room temperature for 16 h under air. Upon completion, the reaction mixture was cooled to 0 °C using an ice/water bath, followed by the careful addition of 1 M HCl (aq.) to pH 1. The reaction mixture was then basified with an aqueous NaOH solution (10% w/v.) solution to pH 11 and transferred to a separating funnel with ethyl acetate. The layers were partitioned and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue was then purified by flash column chromatography on silica gel eluting with dichloromethane and methanol (0% to 5% methanol) to afford the product **195** as a colourless oil (47 mg, 67%).

FTIR: ν_{max}/ cm^{-1} (neat) 3381 (m), 3290 (m), 2965 (w), 1609 (s), 1594 (s), 1451 (m), 1245 (m), 1056 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (1H, t, *J* = 8.0 Hz, CH_{ar}), 6.53 (2H, app. t, *J* = 8.0 Hz, CH_{ar}), 5.38 (2H, br s, NH_2), 4.34 (2H, t, *J* = 9.5 Hz, CH_2), 4.07 (2H, t, *J* = 9.5 Hz, CH_2), 2.42 (3H,

s, C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.6, 148.2, 139.7, 130.8, 120.1, 113.9, 111.1, 66.2, 54.3, 22.5; HRMS: *m/z* $[MH]^+$ $C_{10}H_{13}N_2O$ calcd. 177.1022, found 177.1025.

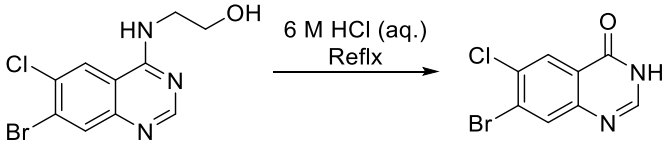
Synthesis of quinazoline-4(3H)-one **184**



186 **184**

To a round bottomed flask was added 2-(4-quinazolinylamino)-ethanol **186** (68 mg, 0.36 mmol) and an aqueous solution of 1 M NaOH (5.0 mL). The reaction mixture was heated at reflux for a period of 5 h. After cooling to room temperature the reaction mixture was acidified to pH 6 using 1 M HCl (aq.) and transferred to a separating funnel with ethyl acetate. The layers were partitioned and the aqueous layer was further extracted with ethyl acetate. The aqueous layer was then further acidified to pH 1 using 1 M HCl (aq.) and transferred to a separating funnel with ethyl acetate. The layers were partitioned and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo* to afford the product **184** as a colourless solid (41 mg, 78%). *The compound showed satisfactory analytical data, and characterisation data is reported earlier in this section.*

Synthesis of 7-bromo-6-chloro-4(3H)-quinazolinone **70**

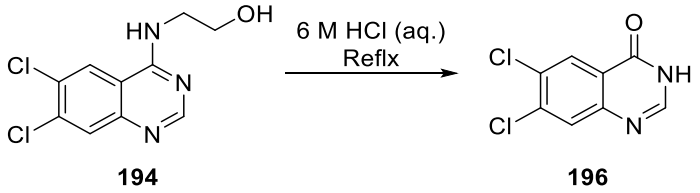


193 **70**

Following general procedure E, using 2-((7-Bromo-6-chloro-4-quinazolinylamino)-ethanol **193** (226 mg, 0.76 mmol) and 6 M HCl aq. (6.0 mL), the quinazolinone product **70** was afforded as a colourless solid (182 mg, 94%).

M.p.: > 300 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3193 (m), 3043 (m), 2887 (w), 1677 (s), 1640 (s), 1607 (s), 1373 (s), 1217 (s), 893 (s); ^{1}H NMR (400 MHz, d^6-DMSO): δ 12.25 (1H, s, N*H*), 8.18 (1H, s, C=N*H*), 8.15 (1H, s, CH_{ar}), 8.09 (1H, s, CH_{ar}); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 160.0, 148.7, 147.7, 132.8, 131.6, 128.5, 127.2, 123.6; HRMS: *m/z* $[MH]^+$ $C_8H_5N_2O^{35}Cl^{79}Br$ calcd. 258.9274, found 258.9285.

Synthesis of 6,7-dichloroquinazolin-4(3H)-one **196**

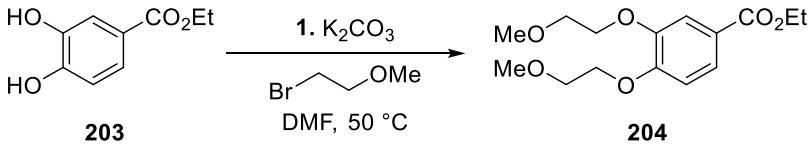


194 **196**

Following general procedure E, using 2-((6,7-dichloroquinazolin-4-yl)amino)ethanol **194** (181 mg, 0.70 mmol)) and 6 M HCl aq. (5.0 mL), the quinazolinone product **196** was afforded as a colourless solid (132 mg, 88%).

M.p.: > 300 °C; FTIR: ν_{max} 3047 (m), 3012 (m), 1665 (s), 1611 (s), 1444 (s), 1254 (s), 1122 (m), 910 (s), 866 (m); ^{1}H NMR (400 MHz, d^{6}-DMSO): δ 12.18 (1H, br s), 8.21 (1H, s), 8.16 (1H, s), 7.95 (1H, s); ^{13}C NMR (101 MHz, d^{6}-DMSO) δ 159.3, 148.3, 147.3, 137.1, 129.3, 128.9, 127.2, 122.7; HRMS: m/z [MH]$^{+}$ $C_8H_5{}^{35}Cl_2N_2O$ calcd. 214.9773, found 214.9772.

Synthesis of 3,4-bis(2-methoxyethoxy)-ethyl ester benzoic acid **204**[131]

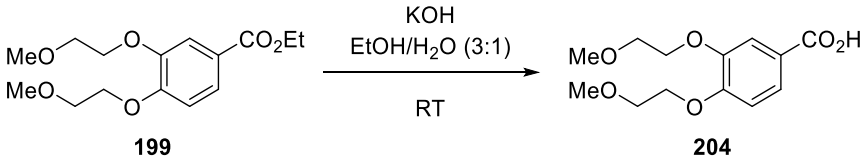


203 **204**

To a round bottomed flask equipped with a reflux condenser was dissolved ethyl-3,4-dihydroxybenzoate **203** (1.41 g, 7.74 mmol) in DMF (13 mL). Potassium carbonate (2.35 g, 17.03 mmol) was then added followed by 2-bromoethyl methyl ether (2.37 g, 17.03 mmol). The reaction was then heated at 50 °C for 5 hours. The reaction was then cooled to room temperature, followed by the addition of ethyl acetate and water. The resulting mixture was transferred to a separating funnel, where the layers were partitioned. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were then washed with an aqueous NaOH solution (10% w/v), brine and an aqueous solution of LiCl (5% w/v), which was followed by drying over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo* to afford the desired product **204** as pale green solid (1.91 g, 83%).

M.p.: 57 – 58 °C (lit.,[131] 53 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (1H, dd, *J* = 8.5, 2.0 Hz, C*H*$_{ar}$), 7.58 (1H, d, *J* = 2.0 Hz, C*H*$_{ar}$), 6.90 (1H, d, *J* = 8.5 Hz, C*H*$_{ar}$), 4.33 (2H, q, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 4.22 – 4.17 (4H, m, O(C*H*$_2$)$_2$OMe), 3.81 – 3.75 (4H, m, O(C*H*$_2$)$_2$OMe), 3.45 (3H, s, OC*H*$_3$), 3.44 (3H, s, OC*H*$_3$), 1.37 (3H, t, *J* = 7.0 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 166.4, 153.0, 148.4, 124.1, 123.6, 115.2, 112.8, 71.1, 71.0, 69.0, 68.6, 60.9, 59.4, 59.3, 14.5.

Synthesis of 3,4-bis(2-methoxyethoxy)-benzoic acid **199**[130]

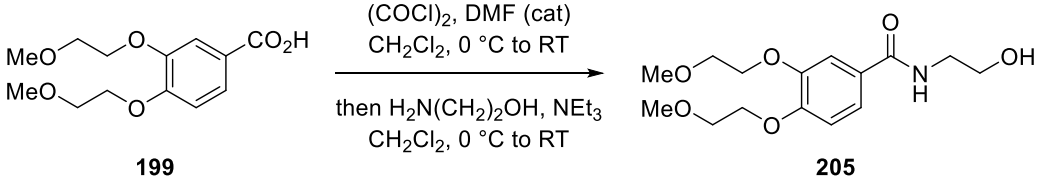


199 **204**

3,4-Bis(2-methoxyethoxy)-ethyl ester benzoic acid **204** (1.18 g, 3.96 mmol) was dissolved in ethanol (9 mL). Water (3 mL) was then added followed by the addition of KOH pellets (888 mg, 15.8 mmol). The reaction was stirred at room temperature for a period of 3 hours, before removing the volatiles *in vacuo*. The remaining residue was cooled to 0 °C with an ice/water bath and acidified to pH 2 with 2M HCl aq., ethyl acetate was then added and the mixture was transferred to a separating funnel. The layers were partitioned and the aqueous was further extracted with ethyl acetate. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo* to afford the desired product **199** as a colourless solid (966 mg, 90%).

M.p.: 108 – 109 °C (lit.,[130] 101 – 103 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (1H, dd, *J* = 8.5, 2.0 Hz, C*H*$_{ar}$), 7.63 (1H, d, *J* = 2.0 Hz, C*H*$_{ar}$), 6.94 (1H, d, *J* = 8.5 Hz, C*H*$_{ar}$), 4.26 – 4.18 (4H, m, O(C*H*$_2$)$_2$OMe), 3.83 – 3.77 (4H, m, O(C*H*$_2$)$_2$OMe), 3.47 (3H, s, OC*H*$_3$), 3.46 (3H, s, OC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 171.3, 153.8, 148.5, 125.1, 122.2, 115.5, 112.8, 71.1, 70.9, 68.9, 68.7, 59.5, 59.4.

Synthesis of N-(3-hydroxypropyl)-3,4-bis(2-methoxyethoxy)-benzamide **205**



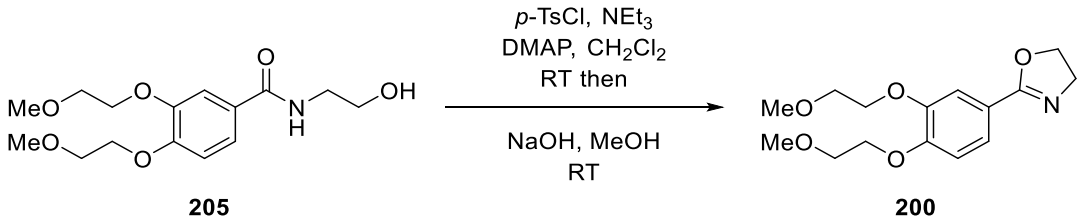
199 **205**

3,4-Bis(2-methoxyethoxy)-benzoic acid **199** (1.03 g, 3.80 mmol) was dissolved in dry dichloromethane (19 mL) and cooled to 0 °C using an ice/water bath. Oxalyl chloride (1.45 g, 11.4 mmol) was added followed by DMF (few drops). The reaction was then warmed to room temperature and allowed to stir for 3 hours before removing the solvent *in vacuo*. The crude residue was re-dissolved in dry dichloromethane (19 mL) and cooled to 0 °C using an ice/water bath. Triethylamine (1.15 g, 11.4 mmol) was then added followed by the slow addition of ethanolamine (0.696 g, 11.4 mmol). The reaction was then warmed to room temperature and allowed to stir overnight. Water was then added and the mixture was transferred to a separating funnel, where the layers were partitioned. The aqueous layer was further extracted with dichloromethane. The combined organic extracts were then dried

over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo* to afford the crude product. The crude residue was purified by flash column chromatography on silica gel, eluting with 2.5% methanol in dichloromethane to afford the purified product **205** as a colourless solid (940 mg, 79%).

M.p.: 82 – 83 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3265 (m), 2937 (w), 2819 (w), 1633 (m), 1510 (s), 1129 (s), 1022 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (1H, d, *J* = 2.0 Hz, C*H*$_{ar}$), 7.30 (1H, dd, *J* = 8.5, 2.0 Hz, C*H*$_{ar}$), 7.08 (1H, t, *J* = 5.5 Hz, N*H*), 6.80 (1H, d, *J* = 8.5 Hz, C*H*$_{ar}$), 4.15 – 4.08 (4H, m, C*H*$_2$), 3.75 – 3.68 (6H, m, C*H*$_2$), 3.54 – 3.48 (2H, m, C*H*$_2$), 3.39 (3H, s, OC*H*$_3$), 3.38 (3H, s, OC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 168.1, 151.7, 148.5, 127.3, 120.6, 113.5, 113.0, 71.0, 70.9, 68.8, 68.6, 62.1, 59.3, 59.2, 43.0; HRMS: *m/z* $[MH]^+$ $C_{15}H_{24}NO_6$ calcd. 314.1604, found 314.1616.

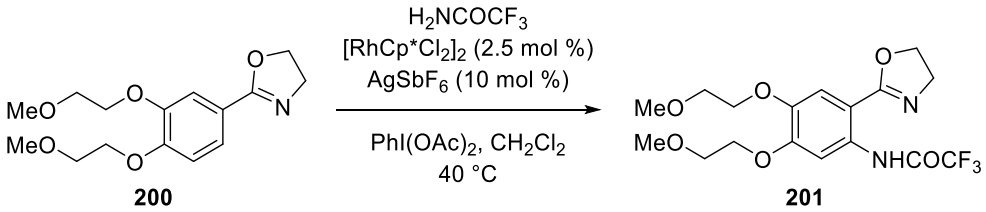
Synthesis of 2-(3,4-bis(2-methoxyethoxy))-4,5-dihydro-oxazole **200**



Following general procedure F, using *of N*-(3-hydroxypropyl)-3,4-bis(2-methoxyethoxy)-benzamide **205** (795 mg, 2.54 mmol), *p*-TsCl (824 mg, 4.32 mmol), NEt_3 (489 mg, 4.83 mmol), DMAP (70 mg, 0.57 mmol) and dichloromethane (4.0 mL), then using NaOH pellets (305 mg, 7.62 mmol) and methanol (16.0 mL), the oxazoline product **200** was afforded as a colourless solid (690 mg, 92%).

M.p.: 44 – 45 °C; FTIR: ν_{max}/ cm^{-1} (neat) 2933 (w), 2880 (w), 1647 (m), 1507 (s), 1433 (s), 1267 (s), 1197 (s), 1120 (s), 703 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.48 (2H, m, C*H*$_{ar}$), 6.89 (1H, d, *J* = 9.0 Hz, C*H*$_{ar}$), 4.39 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.20 – 4.15 (4H, m, O(C*H*$_2$)$_2$OMe), 4.01 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 3.79 – 3.74 (4H, m, O(C*H*$_2$)$_2$OMe), 3.43 (6H, s, OC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.6, 151.7, 148.6, 122.2, 120.9, 113.7, 113.3, 71.0, 70.9, 68.8, 68.7, 67.7, 59.4, 59.3, 54.8; HRMS: *m/z* $[MH]^+$ $C_{15}H_{22}NO_5$ calcd. 296.1498, found 296.1502.

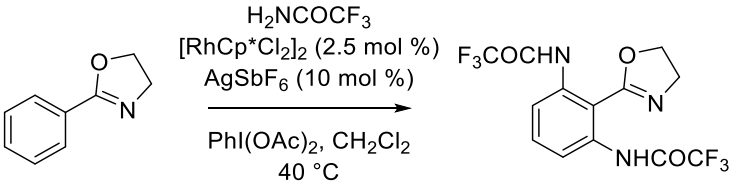
Synthesis of 2,2,2-trifluoro-N-[2-(3,4-bis(2-methoxyethoxy))-4,5-dihydro-oxazole]-acetamide **201**



Following general procedure C, using trifluoroacetamide (447 mg, 3.95 mmol) and 2-(3,4-bis(2-methoxyethoxy))-4,5-dihydro-oxazole **200** (1.40 g, 4.74 mmol) with $[Cp^*RhCl_2]_2$ (61 mg, 0.030 mmol), $AgSbF_6$ (136 mg, 0.110 mmol) and $PhI(OAc)_2$ (1.91 g, 5.93 mmol) in dichloromethane (40 mL) at 40 °C for 16 h, product **201** was isolated as a colourless solid (1.06 g, 66%).

M.p.: 137 – 138 °C; FTIR: ν_{max}/ cm^{-1} (neat) 2930 (w), 2883 (w), 1707 (m), 1613 (m), 1133 (s), 1043 (w), 877 (m); ^1H NMR (400 MHz, $CDCl_3$): δ 13.65 (1H, s, N*H*), 8.37 (1H, s, CH_{ar}), 7.40 (1H, s, CH_{ar}), 4.38 (2H, t, *J* = 9.5 Hz, CH_2), 4.26 – 4.22 (2H, m, CH_2), 4.19 – 4.14 (2H, m, CH_2), 4.12 (2H, t, *J* = 9.5 Hz, CH_2), 3.82 – 3.74 (4H, m, O(CH_2)$_2$OMe), 3.45 (6H, s, OCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.4, 155.4 (q, *J* = 37.5 Hz), 152.3, 144.9, 133.2, 116.1 (q, *J* = 288.5 Hz), 114.9, 107.1, 106.5, 71.1, 70.7, 69.4, 68.5, 66.7, 59.4, 59.3, 54.4; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.0; HRMS: *m*/*z* $[MH]^+$ $C_{17}H_{22}N_2O_6F_3$ calcd. 407.1430, found 407.1432.

Synthesis of trifluoromethyl N-(2-(4,5-dihydrooxazol-2-yl)-3-(2,2,2-trifluoroacetamido)phenyl)formimidate **206**

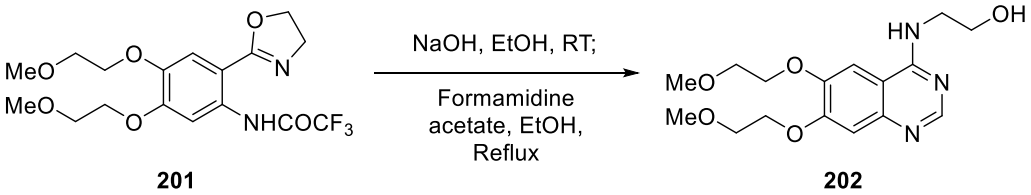


152 **206**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-phenyl-2-oxazoline **152** (29 mg, 0.20 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 16 h, product **206** was isolated as a colourless solid (5 mg, 7%). The mono-amidated product **154** was also isolated (41 mg, 80%).

M.p.: 152 – 153 °C; FTIR: ν_{max}/ cm^{-1} (neat) 2964 (w), 2919 (w), 1721 (m), 1606 (m), 1471 (m), 1257 (m), 1142 (s), 1056 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 12.12 (2H, s, 2 x N*H*), 8.43 (2H, d, *J* = 8.5 Hz, CH_{ar}), 7.58 (1H, t, *J* = 8.5 Hz, CH_{ar}), 4.60 (2H, t, *J* = 9.5 Hz, CH_2), 4.23 (2H, t, *J* = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.5, 155.3 (q, *J* = 37.5 Hz), 137.5, 133.5, 118.4, 115.9 (d, *J* = 289.0 Hz), 104.9, 67.6, 53.1; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.1; HRMS: *m*/*z* $[MH]^+$ $C_{13}H_{10}F_6N_3O_3$ calcd. 370.0621, found 370.0627.

Synthesis of 2-((6,7-bis(2-methoxyethoxy))-4-quinazolinylamino)-ethanol **202**

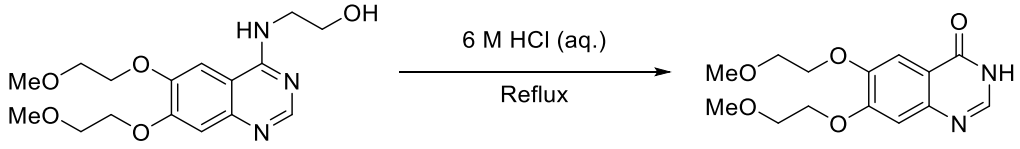


201 **202**

Following general procedure D, using trifluoroacetamide substrate **201** (43 mg, 0.11 mmol), NaOH pellets (88 mg, 2.2 mmol) in ethanol (1.0 mL) generated the crude aniline. Cyclisation with formamidine acetate (34 mg, 0.33 mmol) in ethanol (1.0 mL) for 1 hour afforded product **202** as a colourless solid (31 mg, 82%).

M.p.: 139 – 140 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3480 (m), 2927 (m), 2882 (m), 1581 (s), 1441 (s), 1113 (s), 1035 (s); ^{1}H NMR (400 MHz, d^{6}-DMSO): δ 8.31 (1H, s, N=C*H*), 7.96 (1H, t, *J* = 5.0 Hz, N*H*), 7.66 (1H, s, CH_{ar}), 7.09 (1H, s, CH_{ar}), 4.84 (1H, s, O*H*), 4.26 – 4.18 (4H, m, O(CH_2)$_2$OMe), 3.78 – 3.70 (4H, m, O(CH_2)$_2$OMe), 3.64 – 3.55 (4H, m, HN(CH_2)$_2$OH), 3.36 (3H, s, OMe), 3.34 (3H, s, OMe); ^{13}C NMR (100.6 MHz, d^{6}-DMSO): δ 158.4, 153.5, 153.0, 147.3, 146.0, 108.6, 108.1, 103.5, 70.1, 70.0, 68.1, 67.8, 59.5, 58.4, 58.3, 43.3; HRMS: *m/z* [MH]$^+$ $C_{16}H_{24}N_3O_5$ calcd. 338.1716, found 338.1727.

Synthesis of 6,7-bis(2-methoxyethoxy)-4(3H)-Quinazolinone **208**[133]



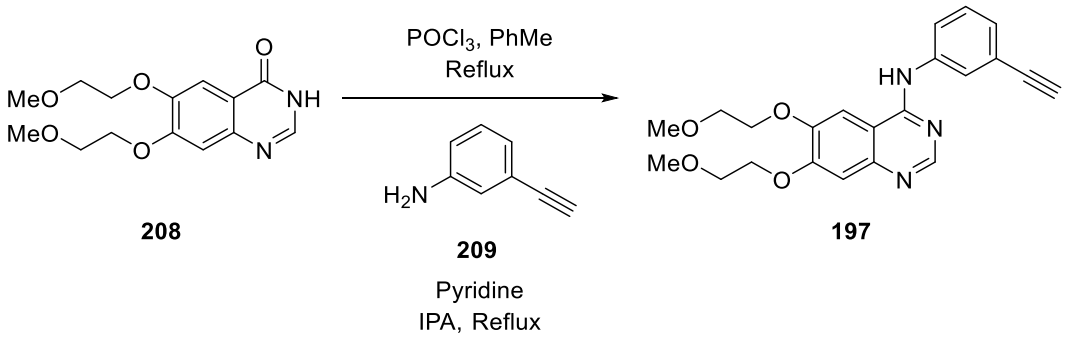
202 **208**

Following general procedure E, using 2-((6,7-bis(2-methoxyethoxy))-4-quinazolinylamino)-ethanol **202** (100 mg, 0.290 mmol) and 6 M HCl aq. (2.4 mL), the quinazolinone product **208** was afforded as a colourless solid (62 mg, 71%). *In this particular case the product was isolated by alternative means:* The reaction mixture was then cooled to 0 °C with an ice/water bath, followed by neutralisation with aqueous ammonia solution (35%). The reaction mixture was then concentrated to remove H_2O. The reaction mixture was then dry loaded onto silica and purified by flash column chromatography, eluting with dichloromethane and 10% methanol to afford the product.

M.p.: 193 – 194 °C (lit.,[133] 183 – 184 °C); ^{1}H NMR (400 MHz, d^{6}-DMSO): δ 12.06 (1H, s, N*H*), 7.97 (1H, s, N=C*H*), 7.46 (1H, s, CH_{ar}), 7.15 (1H, s, CH_{ar}), 4.27 – 4.23 (2H, m, CH_2), 4.21 – 4.18 (2H, m, CH_2), 3.71 (4H, dd, *J* = 9.0, 4.5 Hz, CH_2), 3.33 (6H, s, OCH_3); ^{13}C NMR (100.6 MHz, d^{6}-

DMSO): δ 160.0, 153.9, 147.8, 144.9, 143.9, 115.7, 109.1, 106.5, 70.2, 70.1, 68.2, 68.1, 58.3, 58.2.

Synthesis of Erlotinib **197**[133]

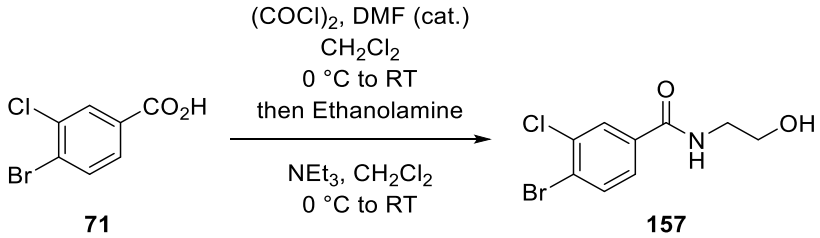


6,7-Bis(2-methoxyethoxy)-4(3H)-quinazolinone **208** (52 mg, 0.18 mmol) was added to toluene (1 mL) with $POCl_3$ (380 mg, 2.48 mmol). The reaction mixture was heated at reflux for a period of 4 hours before cooling to room temperature and removing the volatiles *in vacuo*. The residue was then dissolved in dichloromethane and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was then dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo* to afford the crude chloro-quinazoline. The crude residue was then dissolved in IPA (1.3 mL) and added dropwise to a stirred solution of pyridine (16 mg, 0.20 mmol) and 3-ethnyl aniline (24 mg, 0.20 mmol) in IPA (0.7 mL) at room temperature. The resulting mixture was then heated to reflux for a period of 4 hours before cooling to room temperature and removing the volatiles *in vacuo*. The residue was then dissolved in dichloromethane and an aqueous solution of NaOH (10% w/v) was added. The mixture was transferred to a separating funnel and the layers partitioned. The aqueous was then further extracted with dichloromethane. The combined organics were then dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane and 5% methanol to afford purified Erlotinib **197** as a yellow solid (48 mg, 69%). The product was further purified by recrystallisation from dichloromethane/hexane.

M.p.: 94 – 95 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3532 (w), 3271 (w), 2917 (w), 2881 (w), 1623 (m), 1577 (m), 1427 (s), 1212 (s), 1116 (s), 1023 (s), 780 (s), 687 (s), 587 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (1H, s, N=C*H*), 7.86 – 7.84 (1H, m, CH_{ar}), 7.74 (1H, ddd, *J* = 8.0, 2.0, 1.0 Hz, CH_{ar}), 7.44 (1H, s, N*H*), 7.34 (1H, t, *J* = 8.0 Hz, CH_{ar}), 7.26 (1H, dt, *J* = 7.5, 1.0 Hz, CH_{ar}), 7.21 (1H, s, CH_{ar}), 7.19 (1H, s, CH_{ar}), 4.27 – 4.20 (4H, m, CH_2), 3.80 (4H, td, *J* = 5.0, 1.5 Hz, CH_2), 3.44 (3H, s, OCH_3), 3.43 (3H, s, OCH_3), 3.09 (1H, s, alkyne C*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 156.4, 154.7, 153.8, 149.0, 147.8, 139.0, 129.2, 127.9, 125.1, 123.0, 122.4, 109.3, 109.0, 102.6, 83.5,

77.6, 71.1, 70.6, 69.4, 68.4, 59.5, 59.4; HRMS: *m/z* $[MH]^+$ $C_{22}H_{24}N_3O_4$ calcd. 394.1767, found 394.1749.

Synthesis of 4-bromo-3-chloro-N-(2-hydroxyethyl)benzamide **157**

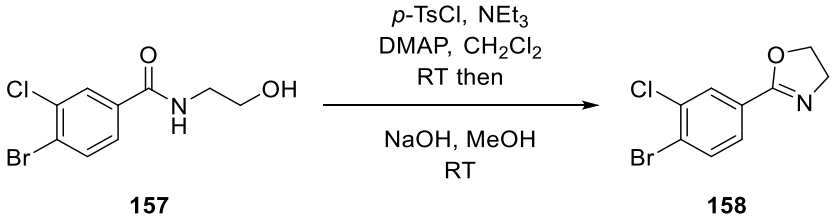


71 **157**

To a stirred solution of 4-bromo-2-chlorobenzoic acid **71** (15.0 g, 63.7 mmol) in dry dichloromethane (318 mL) at 0 °C was added oxalyl chloride (24.25 g, 191.1 mmol) and DMF (few drops). The reaction was allowed to warm to room temperature and stirred for a period of 3 hours before removing the solvent *in vacuo*. The crude residue was then dissolved in dry dichloromethane (318 mL) and cooled to 0 °C using an ice bath. Triethylamine (19.33 g, 191.1 mmol) was added, followed by the slow addition of ethanolamine over 5 minutes (19.33 g, 191.1 mmol). The reaction was allowed to warm to room temperature and stir for 16 h. The observable colourless precipitate was collected by vacuum filtration, and purified by recrystallisation (hot filtration to remove insoluble solids) with ethyl acetate. The filtrate was purified by flash column chromatography on silica gel eluting with dichloromethane and methanol (0 to 10 % methanol) to afford the product **157** as a colourless solid (14.00 g, 79%).

M.p.: 121 – 122 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3360 (m), 3294 (m), 2927 (w), 1629 (s), 1535 (s), 1458 (s), 1423 (s), 1052 (s); ^{1}H NMR (400 MHz, d^6-DMSO): δ 8.63 (1H, t, *J* = 5.5 Hz, N*H*), 8.07 (1H, d, *J* = 2.0 Hz, CH_{ar}), 7.87 (1H, d, *J* = 8.5 Hz, CH_{ar}), 7.73 (1H, dd, *J* = 8.5, 2.0 Hz, CH_{ar}), 4.74 (1H, t, *J* = 5.5 Hz, O*H*), 3.54 – 3.48 (2H, m, CH_2), 3.35 – 3.29 (2H, m, CH_2); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 164.1, 135.5, 133.9, 133.2, 129.0, 127.6, 124.6, 59.5, 42.3; HRMS: *m/z* $[MH]^+$ $C_9H_{10}{}^{81}Br^{35}ClNO_2$ calcd. 279.9556, found 279.9560.

Synthesis of 2-(3-chloro-4-bromo-phenyl)-4,5-dihydro-oxazole **158**

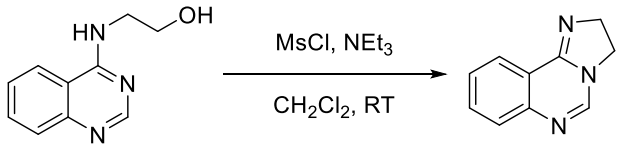


157 **158**

Following general procedure F, 4-bromo-3-chloro-*N*-(2-hydroxyethyl)benzamide **157** (15.22 g, 54.62 mmol), *p*-TsCl (17.70 g, 92.85 mmol), NEt_3 (10.50 g, 103.8 mmol), DMAP (1.33 g, 10.9

mmol) and dichloromethane (90 mL), then using NaOH pellets (6.60 g, 163 mmol) and methanol (110 mL), the oxazoline product was afforded as a colourless solid **158** (11.7 g, 82%). *See above for characterisation data.*

Synthesis of 2,3-dihydroimidazo[1,2-c]quinazoline **212**

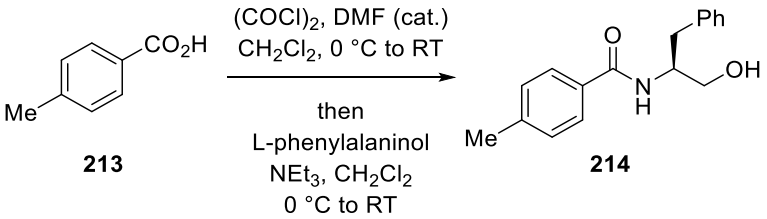


186 **212**

2-(4-Quinazolinylamino)-ethanol **186** (34 mg, 0.18 mmol) was dissolved in dichloromethane (2 mL). Triethylamine (27 mg, 0.27 mmol) was then added followed by the slow addition of methane sulfonyl chloride (25 mg, 0.22 mmol). The reaction mixture was allowed to stir at room temperature for 16 h. Upon completion the reaction mixture was diluted with dichloromethane, and the colourless precipitate was collected *via* filtration, washing with dichloromethane. The filtrate was concentrated followed by trituration with dichloromethane to afford a colourless solid. The colourless solids were combined to afford the product **212** (41 mg, 67%).

M.p.: 119 – 120 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3005 (w), 2976 (w), 1659 (m), 1200 (s), 1155 (s), 1035 (s); ^{1}H NMR (400 MHz, d^6-DMSO): δ 8.71 (1H, s, C=N*H*), 8.57 (1H, br s, C*H*$_{ar}$), 8.13 – 8.02 (1H, m, C*H*$_{ar}$), 7.91 (1H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 7.80 (1H, t, *J* = 8.0 Hz, C*H*$_{ar}$), 4.73 – 4.64 (2H, m, C*H*$_2$), 4.21 – 4.12 (2H, m, C*H*$_2$); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 156.7, 147.5, 143.6, 137.2, 128.9, 128.2, 126.3, 111.9, 47.9, 44.5; HRMS: *m*/*z* [MH]$^+$ $C_{10}H_{10}N_3$ calcd. 172.0875, found 172.0882.

Synthesis of (S)-N-(1-hydroxy-3-phenylpropan-2-yl)-4-methylbenzamide **214**



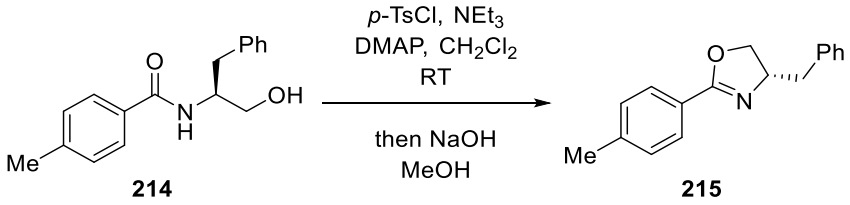
213 **214**

p-Toluic acid **213** (500 mg, 3.67 mmol) in dichloromethane (19 mL) was cooled to 0 °C using an ice/water bath. Oxalyl chloride (1.40 g, 11.0 mmol) was then added followed by DMF (few drops). The reaction was then warmed to room temperature and allowed to stir. After a period of 3 hours, the solvent was removed *in vacuo*. The crude acid chloride residue was then dissolved in dichloromethane (5 mL) and added slowly to a solution of L-phenylalaninol (1.67 g, 11.0 mmol) and triethylamine (1.12 g, 11.0 mmol) in dichloromethane (14 mL) at 0

°C. Upon complete addition, the reaction mixture was then warmed to room temperature and allowed to stir overnight. Following dilution with dichloromethane and water, the reaction mixture was transferred to a separating funnel and the layers were partitioned. The aqueous layer was then further extracted with dichloromethane. The combined organics were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel, eluting with 5% MeOH in dichloromethane to afford the amide product **214** as a colourless solid (1.00 g, 100%).

$[\alpha]_D^{24}$ = - 104 (c 0.01, MeOH); M.p.: 159 – 160 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3297 (m), 3022 (w), 2958 (w), 1633 (s), 1540 (s), 1330 (m), 1030 (m), 701 (s), 683 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (2H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 7.35 – 7.21 (5H, m, C*H*$_{ar}$), 7.19 (2H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 6.39 (1H, d, *J* = 7.0 Hz, N*H*), 4.42 – 4.30 (1H, m, CONHC*H*(CH_2Ph)), 3.84 – 3.64 (2H, m, C*H*$_2$OH), 3.02 – 2.96 (2H, m, C*H*$_2$Ph), 2.37 (3H, s, C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 168.2, 142.3, 137.8, 131.5, 129.4, 129.3, 128.9, 127.1, 126.9, 64.5, 53.5, 37.2, 21.6; HRMS: *m*/*z* $[MH]^+$ $C_{17}H_{20}NO_2$ calcd. 270.1489, found 270.1485.

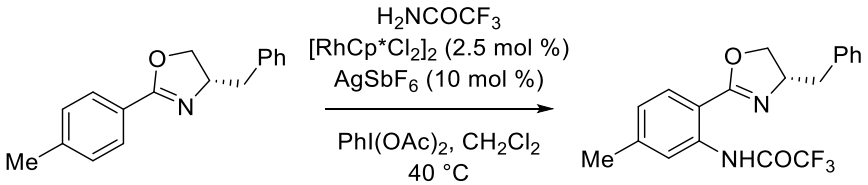
Synthesis of (S)-4-benzyl-2-(p-tolyl)-4,5-dihydrooxazole **215**



Following general procedure F, using (*S*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-4-methylbenzamide **214** (518 mg, 1.92 mmol), *p*-TsCl (622 mg, 3.26 mmol), NEt_3 (369 mg, 3.65 mmol), DMAP (47 mg, 0.38 mmol) and dichloromethane (4.0 mL), then using NaOH pellets (230 mg, 5.76 mmol) and methanol (12.0 mL), the oxazoline product **215** was afforded as a colourless solid (384 mg, 79%).

$[\alpha]_D^{24}$ = - 0.6 (c 0.05, CH_2Cl_2); M.p.: 85 – 86 °C; FTIR: ν_{max}/ cm^{-1} (neat) 2979 (w), 2954 (w), 1651 (m), 1351 (m), 1065 (s), 826 (s), 705 (s), 673 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (2H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 7.35 – 7.21 (7H, m, C*H*$_{ar}$), 4.64 – 4.54 (1H, m, C*H*CH_2Ph), 4.33 (1H, dd, *J* = 9.0, 8.5 Hz, C*H*$_2$O), 4.14 (1H, dd, *J* = 8.5, 7.5 Hz, C*H*$_2$O), 3.27 (1H, dd, *J* = 14.0, 5.0 Hz, C*H*$_2$Ph), 2.74 (1H, dd, *J* = 14.0, 9.0 Hz, C*H*$_2$Ph), 2.41 (3H, s, C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.1, 141.7, 138.1, 129.3, 129.1, 128.6, 128.3, 126.5, 125.1, 71.8, 67.9, 41.9, 21.6; HRMS: *m*/*z* $[MH]^+$ $C_{17}H_{18}NO$ calcd. 252.1383, found 252.1379.

Synthesis of (S)-N-(2-(4-benzyl-4,5-dihydrooxazol-2-yl)-5-methylphenyl)-2,2,2-trifluoroacetamide **216**

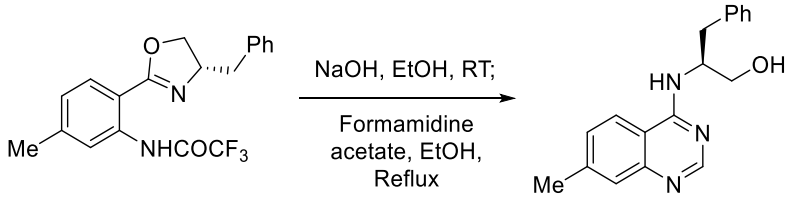


215 **216**

Following general procedure C, using trifluoroacetamide (150 mg, 1.33 mmol) and (*S*)-4-benzyl-2-(p-tolyl)-4,5-dihydrooxazole **215** (400 mg, 1.59 mmol) with $[Cp^*RhCl_2]_2$ (21 mg, 0.03 mmol), $AgSbF_6$ (46 mg, 0.13 mmol mmol) and $PhI(OAc)_2$ (643 mg, 1.99 mmol) in dichloromethane (13 mL) at 40 °C for 18 h, product **216** was isolated as a colourless solid (383 mg, 80%).

$[\alpha]_D^{24}$ = + 40 (c 0.01, CH_2Cl_2); M.p.: 61 – 62 °C; FTIR: ν_{max}/ cm^{-1} (neat) 2961 (w), 2897 (w), 1719 (m), 1637 (m), 1144 (s), 1130 (s), 694 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.68 (1H, s, N*H*), 8.56 (1H, s, CH_{ar}), 7.77 (1H, d, *J* = 8.0 Hz, CH_{ar}), 7.38 – 7.20 (5H, m, CH_{ar}), 7.04 (1H, d, *J* = 8.0 Hz, CH_{ar}), 4.78 – 4.67 (1H, m, C*H*CH_2Ph), 4.40 (1H, dd, *J* = 9.0, 8.5 Hz, CH_2O), 4.14 (1H, dd, *J* = 8.5, 7.0 Hz, CH_2O), 3.16 (1H, dd, *J* = 14.0, 6.0 Hz, CH_2Ph), 2.86 (1H, dd, *J* = 14.0, 8.0 Hz, CH_2Ph), 2.45 (3H, s, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.0, 155.6 (q, *J* = 37.5 Hz), 144.0, 137.7, 137.4, 129.3, 129.2, 128.8, 126.8, 125.4, 120.9, 116.0 (q, *J* = 288.5 Hz), 111.9, 71.0, 67.5, 41.8, 22.2; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.0; HRMS: *m/z* $[MH]^+$ $C_{19}H_{18}F_3N_2O_2$ calcd. 363.1315, found 363.1309.

Synthesis of (S)-2-((7-methylquinazolin-4-yl)amino)-3-phenylpropan-1-ol **217**



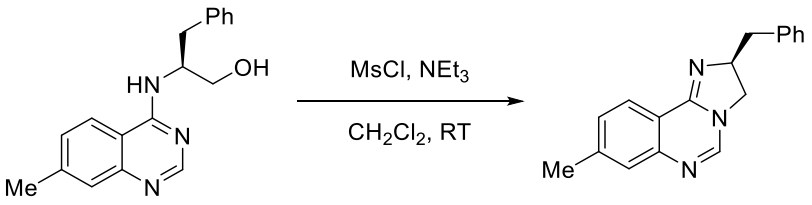
216 **217**

Following general procedure D, using trifluoroacetamide substrate **216** (383 mg, 1.06 mmol), NaOH pellets (848 mg, 21.2 mmol) in ethanol (10 mL) generated the crude aniline. Cyclisation with formamidine acetate (331 mg, 3.18 mmol) in ethanol (10 mL) for 1 hour afforded product **217** as a colourless solid (262 mg, 84%).

$[\alpha]_D^{24}$ = - 1 (c 0.01, EtOH); M.p.: 202 – 203 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3247 (w), 3025 (w), 2915 (w), 1622 (m), 1569 (m), 1490 (m), 1033 (s), 694 (s); ^{1}H NMR (400 MHz, d^6-DMSO): δ 8.35 (1H,

s, N=C*H*), 8.21 (1H, d, *J* = 8.0 Hz, CH_{ar}), 7.81 (1H, d, *J* = 8.0 Hz, CH_{ar}), 7.44 (1H, s, CH_{ar}), 7.35 – 7.26 (3H, m, CH_{ar} and N*H*), 7.21 (2H, t, *J* = 7.5 Hz, CH_{ar}), 7.15 – 7.08 (1H, m, CH_{ar}), 4.90 (1H, t, *J* = 5.5 Hz, O*H*), 4.64 – 4.54 (1H, m, C*H*OH), 3.63 – 3.47 (2H, m, CH_2O), 3.06 – 2.90 (2H, m, CH_2Ph), 2.44 (3H, s, CH_3); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 159.1, 155.1, 149.4, 142.5, 139.5, 129.1, 128.1, 127.1, 126.6, 125.9, 122.7, 112.8, 62.3, 54.1, 36.3, 21.3; HRMS: *m*/*z* [MH]$^+$ $C_{18}H_{20}N_3O$ calcd. 294.1606, found 294.1597.

Synthesis of (S)-2-benzyl-8-methyl-2,3-dihydroimidazo[1,2-c]quinazoline **218**

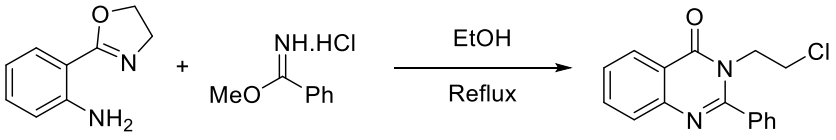


217 **218**

To a stirred solution of (*S*)-2-((7-methylquinazolin-4-yl)amino)-3-phenylpropan-1-ol **217** (80 mg, 0.27 mmol) in dichloromethane (3 mL), was added triethylamine (41 mg, 0.41 mmol) followed by methane sulfonyl chloride (37 mg, 0.32 mmol). The reaction mixture was allowed to stir at room temperature for a period of 24 hours. The resulting colourless precipitate was collected by vacuum filtration, and washed with ice cold dichloromethane to afford the desired product as a colourless solid **218** (45 mg, 61%).

$[\alpha]_D^{24}$ = + 7 (c 0.014, MeOH); M.p.: > 250 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3061 (w), 2917 (w), 1656 (s), 1374 (m), 1290 (m), 700 (s); ^{1}H NMR (400 MHz, d^6-DMSO): δ 8.58 (1H, s, C=N*H*), 8.54 (1H, d, *J* = 8.5 Hz, CH_{ar}), 7.70 (1H, s, CH_{ar}), 7.65 (1H, d, *J* = 8.5 Hz, CH_{ar}), 7.37 (2H, d, *J* = 7.0 Hz, CH_{ar}), 7.30 (2H, t, *J* = 7.0 Hz, CH_{ar}), 7.23 (1H, t, *J* = 7.0 Hz, CH_{ar}), 4.95 – 4.85 (1H, m, C*H*CH$_2$Ph), 4.63 (1H, t, *J* = 11.0 Hz, CH_2O), 4.44 (1H, dd, *J* = 11.0, 6.5 Hz, CH_2O), 3.24 – 3.05 (2H, m, CH_2Ph), 2.54 (3H, s, CH_3); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 155.5, 148.8, 147.6, 143.5, 135.5, 130.5, 129.6, 128.6, 127.6, 127.0, 126.3, 109.1, 57.8, 51.6, 39.2, 21.7; HRMS: *m*/*z* [MH]$^+$ $C_{18}H_{18}N_3$ calcd. 276.1501, found 276.1504.

Synthesis of 3-(2-chloroethyl)-2-phenylquinazolin-4(3H)-one **219**[136]



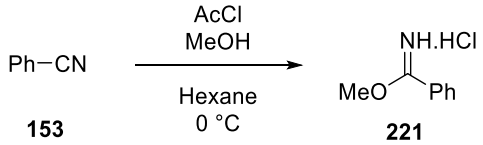
185 **221** **219**

2-(4,5-Dihydrooxazol-2-yl)aniline **185** (50 mg, 0.31 mmol) and methyl benzimidate hydrochloride **221** (159 mg, 0.924 mmol) were combined in ethanol (3 mL) and heated at

reflux for a period of 16 h. The reaction was allowed to cool to room temperature followed by neutralisation to pH 6/7 with a saturated aqueous solution of $NaHCO_3$. Ethyl acetate and H_2O were then added followed by transferring the reaction mixture to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was dry-loaded onto silica gel and purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) and ethyl acetate (0% to 30% ethyl acetate) to afford the product as a colourless solid **219** (38 mg, 42%).

^{1}H NMR (400 MHz, $CDCl_3$); δ 8.33 (1H, dd, *J* = 8.0, 1.0 Hz, C*H*$_{ar}$), 7.95 – 7.66 (2H, m, C*H*$_{ar}$), 7.69 – 7.42 (6H, m, C*H*$_{ar}$), 4.37 (2H, t, *J* = 6.5 Hz, C*H*$_2$), 3.74 (2H, t, *J* = 6.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$); δ 162.3, 156.1, 147.2, 135.1, 134.8, 130.2, 129.1, 128.3, 127.7, 127.4, 126.8, 120.7, 47.2, 40.4.

Synthesis of methyl benzimidate hydrochloride **221**[135]

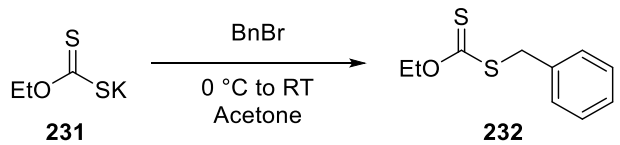


153 **221**

To a round bottomed flask was added benzonitrile **153** (1.0 g, 9.7 mmol) followed by dry hexane (2.8 mL). The stirred mixture was cooled to 0 °C using an ice bath, followed by the addition of methanol (684 mg, 21.3 mmol). Acetyl chloride (761 mg, 9.70 mmol) was then added slowly *via* syringe. Upon complete addition the reaction was allowed to stir at room temperature for 16 h. The resulting precipitate was collected by filtration, washed with hexanes, to afford the product **221** as a pale yellow solid (741 mg, 45%).

M.p. 95 – 96 °C (lit.,[135] 94 – 96 °C); ^{1}H NMR (400 MHz, $CDCl_3$); δ 12.75 (1H, br s, N*H*), 12.01 (1H, br s, N*H*), 8.39 (2H, d, *J* = 7.5 Hz, C*H*$_{ar}$), 7.70 (1H, t, *J* = 7.5 Hz, C*H*$_{ar}$), 7.56 (2H, t, *J* = 7.5 Hz, C*H*$_{ar}$), 4.56 (3H, s, OC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$); δ 172.0, 135.9, 129.8, 129.4, 125.0, 61.6.

Synthesis of S-benzyl O-ethyl carbonodithioate **232**[142]



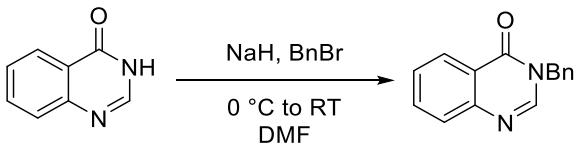
231 **232**

To a stirred solution of benzyl bromide (4.27 g, 25.0 mmol) in acetone (12 mL) at 0 °C was slowly added a solution of potassium *O*-ethyl dithiocarbonate **231** (4.00 g, 25.0 mmol) in acetone (25 mL) – both solutions were stirred at 0 °C using an ice bath prior to mixing. Upon

complete addition the reaction mixture was warmed to room temperature and allowed to stir for 18 h. The solvent was then removed *in vacuo* followed by dissolving the residue in H_2O and chloroform. The reaction mixture was then transferred to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with chloroform. The combined organics were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the product **232** as a yellow oil (4.78 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.38 – 7.25 (5H, m, CH_{ar}), 4.66 (2H, q, *J* = 7.0 Hz, OCH_2CH$_3$), 4.37 (2H, s, CH_2Ph), 1.43 (3H, t, *J* = 7.0 Hz, OCH$_2$CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$); δ 214.2, 135.8, 129.2, 128.6, 127.7, 70.2, 40.5, 13.9.

Synthesis of 3-benzylquinazolin-4(3H)-one **225**[171]

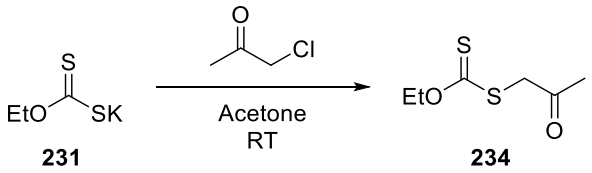


184 **225**

A solution of 4-hydroxyquinazolinone **184** (1.00 g, 6.84 mmol) in DMF (60 mL) was added slowly to a solution of NaH (263 mg, 10.9 mmol - 60% dispersion in mineral oil) in DMF (40 mL) at 0 °C. Upon complete addition the mixture was allowed to stir for 30 minutes at 0 °C followed by the addition of benzyl bromide (2.34 g, 13.7 mmol) slowly *via* syringe. The reaction was then warmed to room temperature and stirred for 18 h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. Ethyl acetate and H_2O were then added followed by transferring the reaction mixture to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were washed with an aqueous solution of NaOH (10 % w/v) and brine, dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the crude product. The crude residue was recrystallised using ethanol to afford the product **225** as a colourless solid (883 mg, 55%).

M.p. 115 – 116 °C (lit.,[171] 117 – 119 °C): ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.33 (1H, dd, *J* = 8.0, 1.0 Hz, CH_{ar}), 8.11 (1H, s, N=C*H*), 7.78 – 7.69 (2H, m, CH_{ar}), 7.51 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, CH_{ar}), 7.37 – 7.28 (5H, m, CH$_2$*Ph*), 5.20 (2H, s, CH_2Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$); δ 161.3, 148.2, 146.5, 135.9, 134.5, 129.3, 128.5, 128.1, 127.7, 127.5, 127.0, 122.3, 49.7.

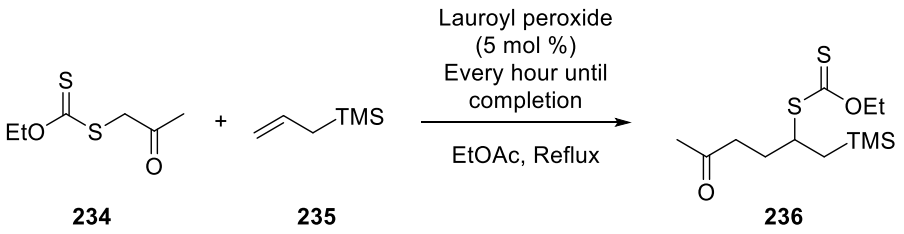
Synthesis of O-ethyl S-(2-oxopropyl) carbonodithioate **234**[142]



To a stirred solution of chloroacetone (2.31 g, 25.0 mmol) in acetone (25 mL) at room temperature was slowly added potassium *O*-ethyl dithiocarbonate **231** (4.00 g, 25.0 mmol). Upon complete addition the reaction mixture was warmed to room temperature and allowed to stir for 38 h. The solvent was then removed *in vacuo* followed by dissolving the residue in H_2O and dichloromethane. The reaction mixture was then transferred to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with dichloromethane. The combined organics were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the product **234** as an orange oil (4.09 g, 92%).

^{1}H NMR (400 MHz, $CDCl_3$); δ 4.62 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 3.98 (2H, s, $SCH_2C(O)$), 2.31 (3H, s, $C(O)CH_3$), 1.40 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$); δ 213.4, 201.3, 71.0, 46.1, 29.3, 13.8.

Synthesis of O-ethyl S-(5-oxo-1-(trimethylsilyl)-hexan-2-yl) carbonodithioate **236**[143]

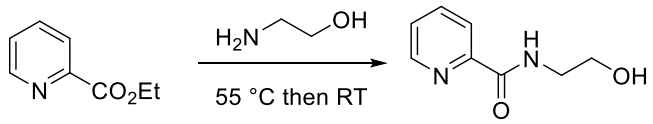


To a solution of *O*-ethyl *S*-(2-oxopropyl) carbonodithioate **234** (303 mg, 1.70 mmol) in ethyl acetate (0.85 mL) was added allyltrimethylsilane **235** (97 mg, 0.85 mmol) under an atmosphere of nitrogen. The reaction mixture was heated at reflux for 10 minutes prior to the addition of the first portion of lauroyl peroxide (17 mg, 0.0042 mmol). The reaction was monitored by TLC analysis, with additional portions of lauroyl peroxide added every hour, until complete conversion of the starting material was observed (5 portions of lauroyl peroxide, 13 hours). The reaction mixture was allowed to cool to room temperature followed by the addition of a saturated aqueous solution of sodium thiosulfate. The reaction was stirred for 10 minutes at room temperature before transferring to a separating funnel, washing with ethyl acetate. The layers were partitioned and the aqueous layer was further extracted with ethyl acetate. The combined organics were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the crude product. Purification by

flash column chromatography on silica gel eluting with petroleum ether (40/60) and ethyl acetate (0% to 7.5% ethyl acetate) to afford the product **236** as a colourless oil (75 mg, 30%).

^{1}H NMR (400 MHz, $CDCl_3$); δ 4.65 – 4.57 (2H, app m, C*H*$_2$CH$_3$), 3.84 (1H, tdd, *J* = 8.5, 7.0, 4.5 Hz, C*H*), 2.64 – 2.48 (2H, m, C*H*$_2$), 2.11 (3H, s, C*H*$_3$), 2.09 – 2.02 (1H, m, C*H*$_2$), 1.78 (1H, dtd, *J* = 14.0, 8.5, 5.5 Hz, C*H*$_2$), 1.39 (3H, t, *J* = 7.0 Hz, CH$_2$C*H*$_3$), 1.14 – 1.07 (1H, m, C*H*$_2$), 1.00 – 0.93 (1H, m, C*H*$_2$), 0.06 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$); δ 214.3, 207.9, 69.7, 48.3, 40.7, 30.4, 30.0, 23.7, 13.6, -0.5.

Synthesis of N-(2-hydroxyethyl)picolinamide **243**[149]

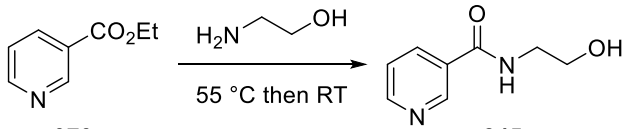


372 **243**

Following general procedure G, using ethyl-2-picolinate **372** (1.00 g, 6.62 mmol) and ethanolamine (607 mg, 9.93 mmol) the amide product **243** was afforded as a colourless oil (1.11 g, 97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (1H, ddd, *J* = 5.0, 1.5, 1.0 Hz, C*H*$_{ar}$), 8.44 (1H, s, N*H*), 8.10 (1H, dt, *J* = 8.0, 1.0 Hz, C*H*$_{ar}$), 7.77 (1H, td, *J* = 8.0, 1.5 Hz, C*H*$_{ar}$), 7.36 (1H, ddd, *J* = 8.0, 5.0, 1.0 Hz, C*H*$_{ar}$), 3.89 (1H, s, O*H*), 3.78 (2H, app. q, *J* = 10.0 Hz, C*H*$_2$), 3.59 (2H, app. q, *J* = 10.0 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.4, 149.7, 148.2, 137.5, 126.3, 122.3, 61.9, 42.4.

Synthesis of N-(2-hydroxyethyl)nicotinamide **245**[149]

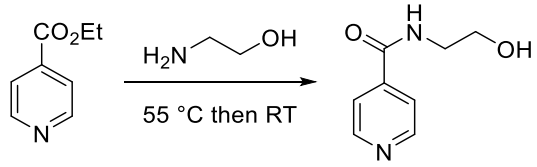


373 **245**

Following general procedure G, using ethyl nicotinate **373** (1.00 g, 6.62 mmol) and ethanolamine (607 mg, 9.93 mmol) the amide product **245** was afforded as a colourless solid (732 mg, 67%).

M.p.: 92 – 93 °C (lit.,[149] 88 °C); ^{1}H NMR (400 MHz, d^6-DMSO): δ 9.01 (1H, dd, *J* = 2.0, 1.0 Hz, C*H*$_{ar}$), 8.69 (1H, dd, *J* = 5.0, 1.5 Hz, C*H*$_{ar}$), 8.66 (1H, t, *J* = 5.0 Hz, N*H*), 8.19 (1H, ddd, *J* = 8.0, 2.0, 1.5 Hz, C*H*$_{ar}$), 7.49 (1H, ddd, *J* = 8.0, 5.0, 1.0 Hz, C*H*$_{ar}$), 3.52 (2H, t, *J* = 6.0 Hz, C*H*$_2$), 3.37 – 3.32 (3H, m, C*H*$_2$ and O*H*); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 164.9, 151.7, 148.4, 134.9, 130.0, 123.4, 59.6, 42.2.

Synthesis of N-(2-hydroxyethyl)isonicotinamide **246**[149]

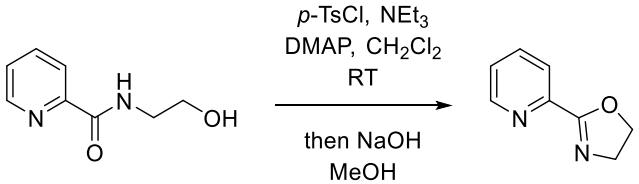


374 **246**

Following general procedure G, using ethyl isonicotinate **374** (1.00 g, 6.62 mmol) and ethanolamine (607 mg, 9.93 mmol) the amide product **246** was afforded as a colourless solid (1.04 g, 95%).

M.p.: 131 – 132 °C (lit.,[149] 135 °C); ^{1}H NMR (400 MHz, d^{6}-DMSO); δ 8.75 (1H, s, N*H*), 8.72 (2H, dd, *J* = 4.5, 1.5 Hz, CH_{ar}), 7.76 (2H, dd, *J* = 4.5, 1.5 Hz, CH_{ar}), 4.77 (1H, s, O*H*), 3.53 (2H, t, *J* = 5.5 Hz, CH_2), 3.35 (2H, app. q, *J* = 5.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, d^{6}-DMSO)): δ 164.8, 150.2, 141.5, 121.3, 59.5, 42.3.

Synthesis of 2-(pyridine-2-yl)-4,5-dihydrooxazole **247**[170]

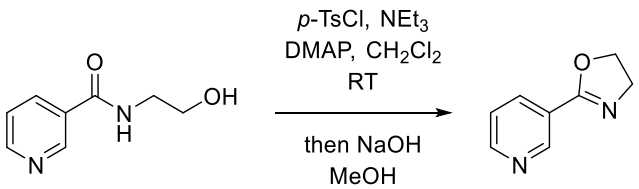


243 **247**

Following general procedure F, using *N*-(2-hydroxyethyl)picolinamide **243** (1.10 g, 6.62 mmol), *p*-TsCl (2.15 g, 11.3 mmol), NEt_3 (1.27 g, 12.6 mmol), DMAP (162 mg, 1.32 mmol) and dichloromethane (11.0 mL), then using NaOH pellets (800 mg, 19.9 mmol) and methanol (13.5 mL), the oxazoline product **247** was afforded as a yellow oil (625 mg, 64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (1H, ddd, *J* = 5.0, 1.5, 1.0 Hz, CH_{ar}), 7.82 (1H, dd, *J* = 8.0, 1.0 Hz, CH_{ar}), 7.56 (1H, td, *J* = 8.0, 1.5 Hz, CH_{ar}), 7.17 (1H, ddd, *J* = 8.0, 5.0, 1.0 Hz, CH_{ar}), 4.30 (2H, t, *J* = 9.5 Hz, CH_2), 3.90 (2H, t, *J* = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.4, 149.3, 146.3, 136.3, 125.2, 123.4, 67.8, 54.7.

Synthesis of 2-(pyridin-3-yl)-4,5-dihydrooxazole **248**[169]

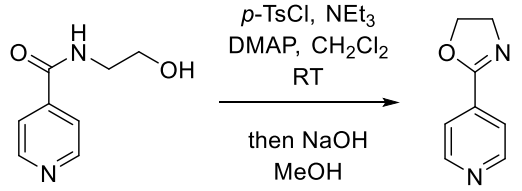


245 **248**

Following general procedure F, using *N*-(2-hydroxyethyl)nicotinamide **245** (687 mg, 4.13 mmol), *p*-TsCl (1.34 g, 7.03 mmol), NEt_3 (794 mg, 7.85 mmol), DMAP (101 mg, 0.826 mmol) and dichloromethane (7.0 mL), then using NaOH pellets (500 mg, 12.4 mmol) and methanol (8.3 mL), the oxazoline product **248** was afforded as a tan solid (338 mg, 55%).

M.p.: 66 – 67 °C (lit.,[169] 66 - 68 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.02 (1H, dd, *J* = 2.0, 1.0 Hz, C*H*$_{ar}$), 8.56 (1H, dd, *J* = 5.0, 2.0 Hz, C*H*$_{ar}$), 8.07 (1H, dt, *J* = 8.0, 2.0 Hz, C*H*$_{ar}$), 7.21 (1H, ddd, *J* = 8.0, 5.0, 1.0 Hz, C*H*$_{ar}$), 4.31 (2H, t, *J* = 9.5 Hz, CH_2), 3.94 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.5, 151.8, 149.3, 135.3, 123.7, 123.0, 67.6, 54.8.

Synthesis of 2-(pyridine-4-yl)-4,5-dihydrooxazole **249**[173]

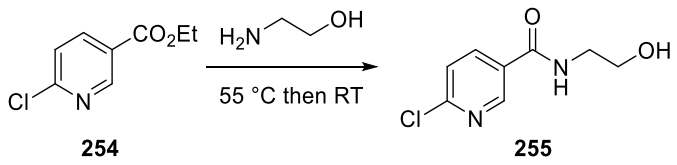


246 **249**

Following general procedure F, using *N*-(2-hydroxyethyl)isonicotinamide **246** (1.0 g, 6.02 mmol), *p*-TsCl (1.95 g, 10.2 mmol), NEt_3 (1.16 g, 11.4 mmol), DMAP (147 mg, 1.20 mmol) and dichloromethane (10 mL), then using NaOH pellets (722 mg, 18.1 mmol) and methanol (12 mL), the oxazoline product **249** was afforded as a pale yellow solid (533 mg, 60%).

M.p.: 109 – 110 °C (lit.,[173] 109-111 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (2H, dd, *J* = 4.5, 1.5 Hz, C*H*$_{ar}$), 7.76 (2H, dd, *J* = 4.5, 1.5 Hz, C*H*$_{ar}$), 4.45 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.08 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.3, 150.4, 135.2, 122.0, 68.1, 55.1.

Synthesis of 6-chloro-N-(2-hydroxyethyl)nicotinamide **255**



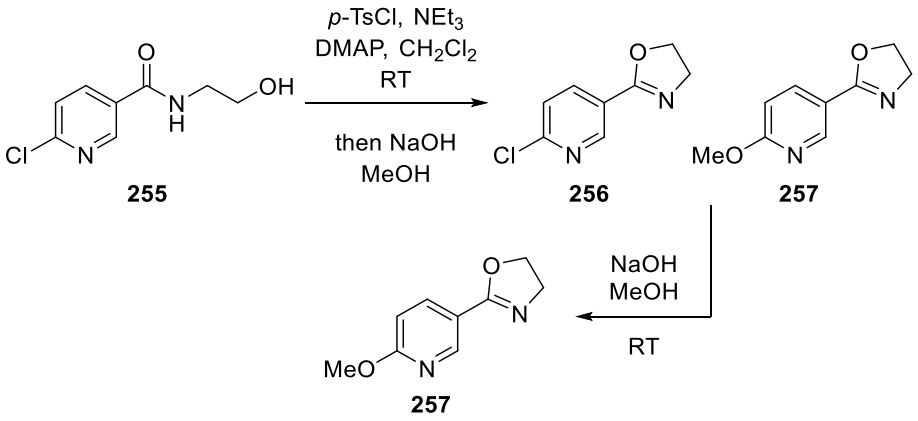
254 **255**

Following general procedure G, using ethyl 6-chloro nicotinate **254** (4.00 g, 21.6 mmol) and ethanolamine (1.97 g, 32.3 mmol) the amide product **255** was afforded as a colourless solid (2.60 g, 60%).

M.p.: 100 – 101 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3363 (m), 3277 (m), 3044 (w), 2930 (w), 2873 (w), 1640 (s), 1586 (m), 1542 (s), 1456 (s), 1371 (m), 1169 (m), 1109 (s), 1059 (m), 1034 (s), 1018 (s), 851 (s); ^{1}H NMR (400 MHz, d^6-DMSO): δ 8.83 (1H, dd, *J* = 2.5, 0.5 Hz, C*H*$_{ar}$), 8.72 (1H, t, *J* =

5.0 Hz, N*H*), 8.24 (1H, dd, *J* = 8.0, 2.5 Hz, CH_{ar}), 7.63 (1H, dd, *J* = 8.0, 0.5 Hz, CH_{ar}), 4.76 (1H, t, *J* = 5.5 Hz, O*H*), 3.52 (2H, app. q, *J* = 6.0 Hz, CH_2), 3.34 (2H, app. q, *J* = 6.0 Hz, CH_2); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 163.8, 152.4, 149.0, 138.6, 129.4, 124.1, 59.5, 42.0; HRMS: *m/z* [MH]$^+$ $C_8H_{10}{}^{35}ClN_2O_2$ calcd. 201.0425, found 201.0426.

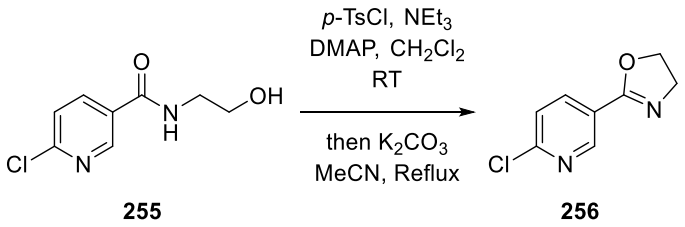
Synthesis of 2-(6-methoxypyridin-3-yl)-4,5-dihydrooxazole **257**



Following general procedure F, using 6-chloro-*N*-(2-hydroxyethyl)nicotinamide **255** (1.50 g, 8.76 mmol), *p*-TsCl (2.84 g, 14.9 mmol), NEt_3 (1.68 g, 16.6 mmol), DMAP (214 mg, 1.75 mmol) and dichloromethane (14.6 mL), then using NaOH pellets (1.05 g, 26.3 mmol) and MeOH (17.5 mL), a crude mixture of oxazolines **257** and **256** was afforded in a 7.6:1 ratio, respectively. The crude oxazoline mixture was then re-subjected with NaOH pellets (717 mg, 17.9 mmol) and methanol (12 mL). The reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was then concentrated, dissolved in dichloromethane and water, and transferred to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with dichloromethane. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the oxazoline product **257** as a colourless amorphous solid (845 mg, 54%).

FTIR: ν_{max}/ cm^{-1} (neat) 2944 (w), 1655 (m), 1600 (m), 1495 (s), 1284 (s), 1072 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (1H, app. d, *J* = 2.0 Hz, CH_{ar}), 7.97 (1H, dd, *J* = 8.5, 2.0 Hz, CH_{ar}), 6.64 (1H, dd, *J* = 8.5, 1.0 Hz, CH_{ar}), 4.29 (2H, t, *J* = 9.5 Hz, CH_2), 3.91 (2H, t, *J* = 9.5 Hz, CH_2), 3.86 (3H, s, O*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.7, 162.7, 147.5, 138.1, 117.3, 110.6, 67.5, 54.8, 53.7; HRMS: *m/z* [MH]$^+$ $C_9H_{11}N_2O_2$ calcd. 179.0821, found 179.0814.

Synthesis of 2-(6-chloropyridin-3-yl)-4,5-dihydrooaxole **256**

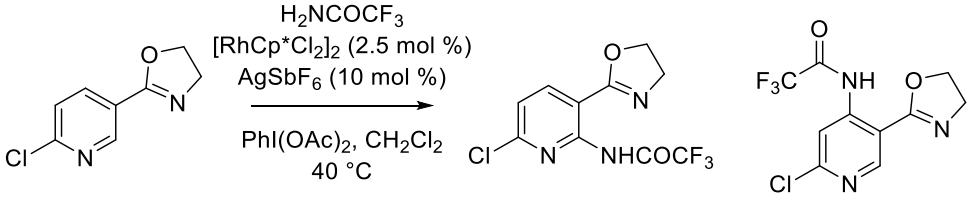


255 **256**

Following general procedure H, using 6-chloro-*N*-(2-hydroxyethyl)nicotinamide **255** (2.51 g, 12.5 mmol), *p*-TsCl (4.05 g, 21.3 mmol), NEt_3 (2.41 g, 23.8 mmol), DMAP (306 mg, 2.50 mmol) and dichloromethane (21 mL), then using K_2CO_3 (5.19 g, 37.5 mmol) and MeCN (25 mL), the oxazoline product **256** was afforded as a colourless solid (2.01 g, 88%).

M.p.: 81 – 82 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3039 (w), 2878 (w), 1655 (s), 1581 (m), 1455 (m), 1350 (m), 1120 (s), 1069 (s), 737 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (1H, app. d, *J* = 2.0 Hz, C*H*$_{ar}$), 8.16 (1H, dd, *J* = 8.0, 2.0 Hz, C*H*$_{ar}$), 7.37 (1H, dd, *J* = 8.0, 1.0 Hz, C*H*$_{ar}$), 4.46 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.07 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.0, 154.1, 149.6, 138.3, 124.2, 123.0, 68.1, 55.1; HRMS: *m/z* $[M]^+$ $C_8H_7{}^{35}ClN_2O$ calcd. 182.0241, found 182.0239.

Synthesis of N-(6-chloro-3-(4,5-dihydrooxazol-2-yl)pyridine-2-yl)-2,2,2-trifluoroacetamide **258** *and N-(2-chloro-5-(4,5-dihydrooxazol-2-yl)pyridine-4-yl)-2,2,2-trifluoroacetamide* **259**



256

258 Major

259 Minor

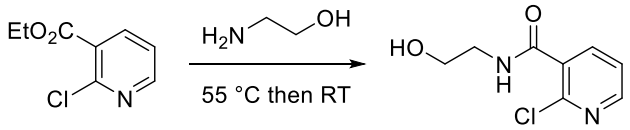
Mixture of Regioisomers (5.93:1)

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(2-chloropyridin-3-yl)-4,5-dihydrooxazole **256** (44 mg, 0.24 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 20 h, products **258** and **259** were isolated in a regioisomeric mixture of 5.93:1 and as a colourless solid (36 g, 61%).

FTIR: ν_{max}/ cm^{-1} 1753 (m), 1598 (m), 1570 (m), 1400 (m), 1264 (m), 1135 (s), 1056 (m), 920 (m), 828 (m); ^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ 13.43 (1H, s, N*H*), 8.10 (1H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 7.20 (1H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 4.49 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.19 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{1}H NMR (400 MHz, $CDCl_3$) minor isomer: δ 13.79 (1H, s, N*H*), 8.81 (1H, s, C*H*$_{ar}$), 8.60 (1H, s, C*H*$_{ar}$), 4.50 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.16 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{19}F NMR (376.5 MHz, $CDCl_3$)

major isomer: δ – 76.3; ^{19}F NMR (376.5 MHz, $CDCl_3$) minor isomer: δ – 76.2; ^{13}C NMR (100.6 MHz, $CDCl_3$) major isomer: δ 162.7, 154.1 (q, *J* = 38.5 Hz), 152.8, 149.7, 140.0, 120.3, 115.5 (q, *J* = 282.0 Hz), 108.9, 67.7, 54.5; HRMS: *m/z* $[MH]^+$ $C_{10}H_8{}^{35}ClF_3N_3O_2$ calcd. 294.0252, found 294.0252.

Synthesis of 2-chloro-N-(2-hydroxyethyl)nicotnamide **270**

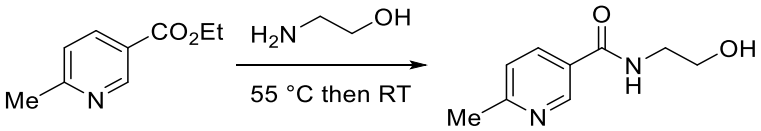


375 **270**

Following general procedure G, using ethyl 2-chloro nicotinate **375** (2.00 g, 10.8 mmol) and ethanolamine (987 mg, 16.2 mmol) the amide product **270** was afforded as a colourless solid (1.14 g, 53%).

M.p.: 75 – 76 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3261 (m), 3070 (w), 2941 (w), 1640 (s), 1589 (s), 1546 (s), 1401 (s), 1057 (s), 740 (m); ^{1}H NMR (400 MHz, d^6-DMSO): δ 8.58 (1H, br s, N*H*), 8.45 (1H, dd, *J* = 5.0, 2.0 Hz, CH_{ar}), 7.89 (1H, dd, *J* = 7.5, 2.0 Hz, CH_{ar}), 7.48 (1H, dd, *J* = 7.5, 5.0 Hz, CH_{ar}), 4.76 (1H, t, *J* = 5.5 Hz, O*H*), 3.52 (2H, app. q, *J* = 6.0 Hz, CH_2), 3.31 (2H, app. q, *J* = 6.0 Hz, CH_2); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 165.3, 150.2, 146.6, 138.1, 133.3, 123.0, 59.6, 42.0; HRMS: *m/z* $[MH]^+$ $C_8H_{10}{}^{35}ClN_2O_2$ calcd. 201.0425, found 201.0428.

Synthesis of N-(2-hydroxyethyl)-6-methylnicotinamide **271**



260 **271**

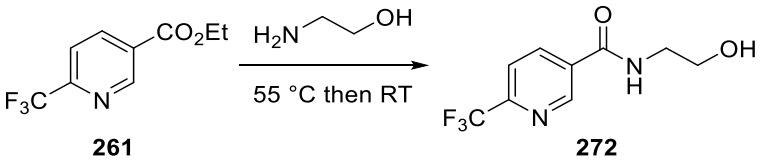
Following general procedure G, using ethyl 6-methyl nicotinate **260** (1.30 g, 7.69 mmol) and ethanolamine (704 mg, 11.5 mmol) the amide product **271** was afforded as an amorphous colourless solid (988 mg, 71%).

NB: Ethyl 6-methyl nicotinate was synthesised from the corresponding carboxylic acid using esterification procedure 2

FTIR: ν_{max}/ cm^{-1} (neat) 3304 (m), 3070 (m), 2972 (m), 1632 (s), 1604 (s), 1554 (s), 1292 (s), 1214 (m), 1053 (s), 877 (m), 862 (m), 655 (s); ^{1}H NMR (400 MHz, d^6-DMSO): δ 8.88 (1H, d, *J* = 2.0 Hz, CH_{ar}), 8.55 (1H, t, *J* = 5.0 Hz, N*H*), 8.07 (1H, dd, *J* = 8.0, 2.0 Hz, CH_{ar}), 7.33 (1H, d, *J* = 8.0 Hz, CH_{ar}), 4.74 (1H, br s, O*H*), 3.50 (2H, app. d, *J* = 3.5 Hz, CH_2), 3.31 (2H, m, CH_2 – peak cannot be fully resolved due to overlap with H_2O signal); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 164.9,

160.7, 147.9, 135.2, 127.2, 122.6, 59.7, 42.1, 24.0; HRMS: *m/z* $[MH]^+$ $C_9H_{13}N_2O_2$ calcd. 181.0972, found 181.0974.

Synthesis of N-(2-hydroxyethyl)-6-(trifluoromethyl)nicotinamide **272**



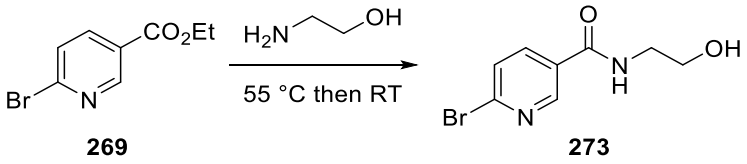
261 **272**

Following general procedure G, using ethyl 6-(trifluoromethyl) nicotinate **261** (1.50 g, 6.84 mmol) and ethanolamine (627 mg, 10.3 mmol) the amide product **272** was afforded as a colourless solid (1.45 g, 90%).

NB: Ethyl 6-(trifluoromethyl) nicotinate was synthesised from the corresponding carboxylic acid using esterification procedure 1

M.p.: 113 – 114 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3426 (m), 3277 (m), 3101 (w), 2946 (w), 1646 (s), 1542 (m), 1450 (m), 1330 (s), 1185 (m), 1166 (s), 1125 (s), 1087 (s), 1059 (s), 1046 (m), 857 (m); ^{1}H NMR (400 MHz, d^6-DMSO): δ 9.15 (1H, app. s, C*H*$_{ar}$), 8.89 (1H, s, N*H*), 8.46 (1H, dd, *J* = 8.0, 1.5 Hz, C*H*$_{ar}$), 8.05 (1H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 4.79 (1H, s, O*H*), 3.54 (2H, m, C*H*$_2$), 3.37 (2H, app. dd, *J* = 11.5, 6.0 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 164.2, 149.5, 148.4 (q, *J* = 34.0 Hz), 137.8, 133.6, 121.9 (q, *J* = 274.0 Hz), 121.0, 59.9, 42.8; ^{19}F NMR (376.5 MHz, d^6-DMSO): δ – 66.6; HRMS: *m/z* $[MH]^+$ $C_9H_{10}F_3N_2O_2$ calcd. 235.0689, found 235.0692.

Synthesis of 6-bromo-N-(2-hydroxyethyl)nicotinamide **273**



269 **273**

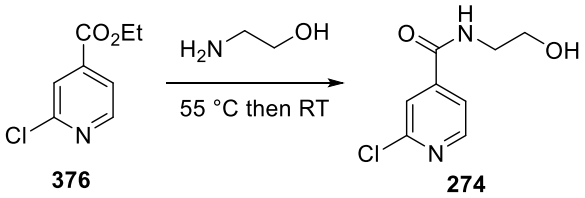
Following general procedure G, using ethyl 6-bromo nicotinate **269** (1.29 g, 5.60 mmol) and ethanolamine (513 mg, 8.41 mmol) the amide product **273** was afforded as a colourless solid (795 mg, 58%).

NB: Ethyl 6-bromo nicotinate was synthesised from the corresponding carboxylic acid using esterification procedure 2

M.p.: 118 – 119 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3360 (m), 3273 (m), 3042 (w), 2942 (w), 2871 (w), 1638 (s), 1578 (s), 1541 (s), 1458 (m), 1370 (m), 1086 (s), 1036 (s), 848 (s), 660 (s); ^{1}H NMR (400 MHz, d^6-DMSO): δ 8.80 (1H, d, *J* = 2.5 Hz, C*H*$_{ar}$), 8.73 (1H, t, *J* = 5.0 Hz, N*H*), 8.12 (1H, dd, *J* = 8.0, 2.5 Hz, C*H*$_{ar}$), 7.78 (1H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 4.75 (1H, t, *J* = 5.5 Hz, O*H*), 3.51 (2H, app.

q, *J* = 6.0 Hz, C*H*$_2$), 3.33 (2H, app. q, *J* = 6.0 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 163.9, 149.4, 143.8, 138.2, 129.7, 127.8, 59.5, 42.3; HRMS: *m/z* [MH]$^+$ $C_8H_{10}{}^{79}BrN_2O_2$ calcd. 244.9920, found 244.9922.

Synthesis of 2-chloro-N-(2-hydroxyethyl)isonicotinamide **274**

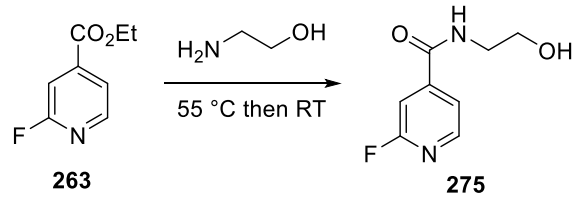


376 **274**

Following general procedure G, using ethyl 2-chloro isonicotinate **376** (5.00 g, 26.9 mmol) and ethanolamine (2.47 g, 40.4 mmol) the amide product **274** was afforded as a colourless solid (5.23 g, 97%).

M.p.: 138 – 139 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3416 (m), 3281 (m), 3069 (m), 2946 (w), 1652 (s), 1557 (s), 1539 (s), 1327 (s), 1305 (s), 1207 (m), 1119 (m), 1059 (s), 1027 (m), 882 (s); ^{1}H NMR (400 MHz, d^6-DMSO): δ 8.85 (1H, t, *J* = 5.0 Hz, N*H*), 8.56 (1H, dd, *J* = 5.0, 1.0 Hz, C*H*$_{ar}$), 7.88 (1H, dd, *J* = 1.5, 1.0 Hz, C*H*$_{ar}$), 7.78 (1H, dd, *J* = 5.0, 1.5 Hz, C*H*$_{ar}$), 4.77 (1H, t, *J* = 5.5 Hz, O*H*), 3.52 (2H, app. q, *J* = 6.0 Hz, C*H*$_2$), 3.41 – 3.29 (2H, m, C*H*$_2$ – signal not resolved due to overlap with residual H_2O); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 163.3, 150.8, 150.7, 145.1, 122.0, 120.9, 59.4, 42.4; HRMS: *m/z* [MH]$^+$ $C_8H_{10}{}^{35}ClN_2O_2$ calcd. 201.0425, found 201.0426.

Synthesis of 2-fluoro-N-(2-hydroxyethyl)isonicotinamide **275**



263 **275**

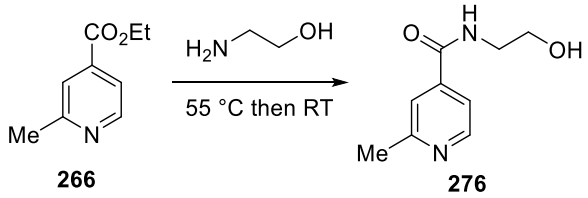
Following general procedure G, using ethyl 2-fluoro isonicotinate **263** (1.40 g, 8.28 mmol) and ethanolamine (759 mg, 12.4 mmol) the amide product **275** was afforded as a colourless solid (1.33 g, 87%).

NB: Ethyl 2-fluoro isonicotinate was synthesised from the corresponding carboxylic acid using esterification procedure 1

M.p.: 99 – 100 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3336 (m), 3093 (w), 2945 (w), 1640 (m), 1550 (s), 1401 (s), 1315 (s), 1237 (m), 1073 (s), 764 (s), 651 (s); ^{1}H NMR (400 MHz, d^6-DMSO): δ 8.82 (1H, br s, N*H*), 8.38 (1H, d, *J* = 5.0 Hz, C*H*$_{ar}$), 7.73 (1H, d, *J* = 5.0 Hz, C*H*$_{ar}$), 7.53 (1H, s, C*H*$_{ar}$), 4.77 (1H, t, *J* = 5.5 Hz, O*H*), 3.53 (2H, app. q, *J* = 6.0 Hz, C*H*$_2$), 3.34 (2H, app. q, *J* = 6.0 Hz, C*H*$_2$);

^{13}C NMR (100.6 MHz, d^6-DMSO): δ 163.5 (d, *J* = 236.0 Hz), 163.4 (d, *J* = 3.5 Hz), 148.4 (d, *J* = 15.0 Hz), 147.7 (d, *J* = 7.5 Hz), 119.9 (d, *J* = 4.0 Hz), 107.6 (d, *J* = 39.0 Hz), 59.4, 42.4; ^{19}F NMR (376.5 MHz, d^6-DMSO): δ – 68.0; HRMS: *m/z* [MH]$^+$ $C_8H_{10}FN_2O_2$ calcd. 185.0721, found 185.0720.

Synthesis of N-(2-hydroxyethyl)-2-methylisonicotinamide **276**



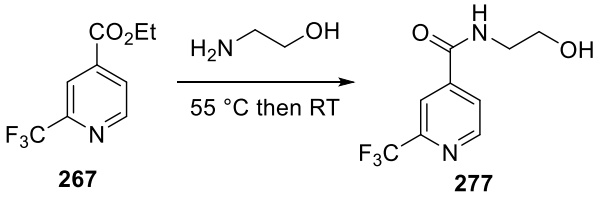
266 **276**

Following general procedure G, using ethyl 2-methyl isonicotinate **266** (857 mg, 5.07 mmol) and ethanolamine (460 mg, 7.60 mmol) the amide product **276** was afforded as a yellow amorphous solid (714 mg, 78%).

NB: Ethyl 2-methyl isonicotinate was synthesised from the corresponding carboxylic acid using esterification procedure 1

FTIR: ν_{max}/ cm^{-1} (neat) 3258 (m), 3076 (w), 2941 (w), 1635 (s), 1546 (s), 1314 (s), 1076 (s), 894 (m), 858 (m); ^{1}H NMR (400 MHz, d^6-DMSO): δ 8.66 (1H, t, *J* = 5.0 Hz, N*H*), 8.56 (1H, d, *J* = 5.0 Hz, C*H*$_{ar}$), 7.63 (1H, app. s, C*H*$_{ar}$), 7.55 (1H, dd, *J* = 5.0, 1.0 Hz, C*H*$_{ar}$), 4.75 (1H, t, *J* = 5.5 Hz, O*H*), 3.52 (2H, app. q, *J* = 6.0 Hz, C*H*$_2$), 3.41 – 3.27 (2H, m, C*H*$_2$), 2.53 (3H, s, C*H*$_3$); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 165.0, 158.6, 149.5, 141.8, 120.6, 118.4, 59.5, 42.2, 24.1; HRMS: *m/z* [MH]$^+$ $C_9H_{13}N_2O_2$ calcd. 181.0972, found 181.0972.

Synthesis of N-(2-hydroxyethyl)-2-(trifluoromethyl)isonicotinamide **277**



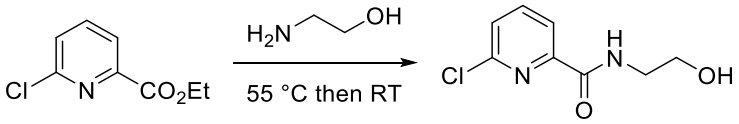
267 **277**

Following general procedure G, using ethyl 2-(trifluoromethyl) isonicotinate **267** (924 mg, 4.22 mmol) and ethanolamine (386 mg, 6.33 mmol) the amide product **277** was afforded as a colourless solid (846 mg, 86%).

NB: Ethyl 2-(trifluoromethyl) isonicotinate was synthesised from the corresponding carboxylic acid using esterification procedure 1

M.p.: 126 - 127 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3369 (w), 3276 (w), 3091 (w), 2980 (w), 1646 (m), 1550 (m), 1304 (m), 1143 (s), 1086 (s), 1061 (s), 904 (m), 854 (m); ^{1}H NMR (400 MHz, d^{6}-DMSO): δ 9.00 (1H, br s, N*H*), 8.92 (1H, d, *J* = 5.0 Hz, C*H*$_{ar}$), 8.26 (1H, app. s, C*H*$_{ar}$), 8.09 (1H, dd, *J* = 5.0, 1.0 Hz, C*H*$_{ar}$), 4.79 (1H, br s, O*H*), 3.58 – 3.52 (2H, m, C*H*$_2$), 3.41 – 3.34 (2H, m, C*H*$_2$); ^{13}C NMR (100.6 MHz, d^{6}-DMSO): δ 163.4, 151.1, 147.1 (q, *J* = 34.0 Hz), 143.6, 125.1, 121.6 (q, *J* = 274.0 Hz), 118.3, 59.4, 42.5; ^{19}F NMR (376.5 MHz, d^{6}-DMSO): δ – 66.6; HRMS: *m/z* [MH]$^{+}$ $C_9H_{10}F_3N_2O_2$ calcd. 235.0689, found 235.0691.

Synthesis of 6-chloro-N-(2-hydroxyethyl)picolinamide **278**

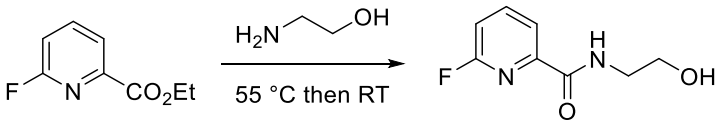


377 **278**

Following general procedure G, using ethyl 6-chloro picolinate **377** (1.00 g, 5.39 mmol) and ethanolamine (494 mg, 8.09 mmol) the amide product **278** was afforded as a colourless solid (1.05 g, 97%).

M.p.: 55 – 56 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3416 (m), 3296 (m), 2955 (m), 1646 (s), 1567 (s), 1529 (s), 1431 (s), 1311 (m), 1217 (m), 1147 (m), 1131 (m), 1068 (s), 1049 (s), 816 (s); ^{1}H NMR (400 MHz, d^{4}-MeOD): δ 8.04 (1H, dd, *J* = 7.5, 1.0 Hz, C*H*$_{ar}$), 7.95 (1H, t, *J* = 7.5 Hz, C*H*$_{ar}$), 7.59 (1H, dd, *J* = 7.5, 1.0 Hz, C*H*$_{ar}$), 3.73 (1H, t, *J* = 5.5 Hz, C*H*$_2$), 3.54 (1H, t, *J* = 5.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, d^{4}-MeOD): δ 165.3, 151.6, 151.4, 141.8, 128.4, 122.0, 61.5, 43.0; HRMS: *m/z* [MH]$^{+}$ $C_8H_{10}{}^{35}ClN_2O_2$ calcd. 201.0425, found 201.0427.

Synthesis of 6-fluoro-N-(2-hydroxyethyl)picolinamide **279**



265 **279**

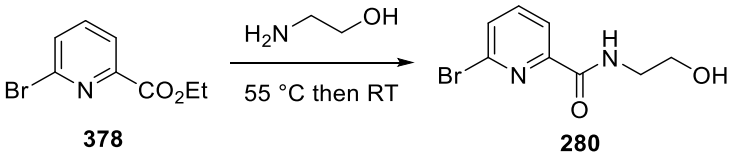
Following general procedure G, using ethyl 6-fluoro picolinate **265** (2.40 g, 14.2 mmol) and ethanolamine (1.30 g, 21.3 mmol) the amide product **279** was afforded as a yellow amorphous solid (2.36 g, 90%).

NB: Ethyl 6-fluoro picolinate was synthesised from the corresponding carboxylic acid using esterification procedure 1

FTIR: ν_{max}/ cm^{-1} (neat) 3397 (m), 3274 (m), 3082 (w), 2959 (s), 1646 (s), 1535 (s), 1447 (s), 1330 (m), 1239 (s), 1068 (s), 1049 (s), 942 (s); ^{1}H NMR (400 MHz, d^{6}-DMSO): δ 8.55 (1H, br s,

N*H*), 8.18 (1H, dd, *J* = 16.0, 8.0 Hz, C*H*$_{ar}$), 7.97 (1H, dd, *J* = 7.5, 2.5 Hz, C*H*$_{ar}$), 7.41 (1H, dd, *J* = 8.0, 2.5 Hz, C*H*$_{ar}$), 4.78 (1H, t, *J* = 5.5 Hz, O*H*), 3.52 (2H, app. q, *J* = 6.0 Hz, C*H*$_2$), 3.36 (2H, app. q, *J* = 6.0 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 161.7 (d, *J* = 240.0 Hz), 160.5, 148.6 (d, *J* = 11.5 Hz), 143.8 (d, *J* = 8.0 Hz), 120.0, 112.7 (d, *J* = 36.5 Hz), 59.5, 41.7; ^{19}F NMR (376.5 MHz, d^6-DMSO): δ – 68.2; HRMS: *m/z* [MH]$^+$ $C_8H_{10}FN_2O_2$ calcd. 185.0721, found 185.0718.

Synthesis of 6-bromo-N-(2-hydroxyethyl)picolinamide **280**[174]

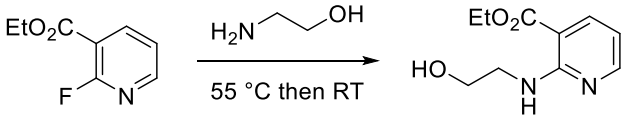


378 **280**

Following general procedure G, using ethyl 6-bromo 2-pyridine carboxylate **378** (1.00 g, 4.35 mmol) and ethanolamine (398 mg, 6.52 mmol) the amide product **280** was afforded as a beige solid (967 mg, 91%).

M.p.: 79 – 80 °C; ^{1}H NMR (400 MHz, d^6-DMSO): δ 8.52 (1H, app. s, N*H*), 8.04 (1H, dd, *J* = 7.5, 1.0 Hz, C*H*$_{ar}$), 7.94 (1H, t, *J* = 7.5 Hz, C*H*$_{ar}$), 7.85 (1H, dd, *J* = 7.5, 1.0 Hz, C*H*$_{ar}$), 4.81 (1H, br s, O*H*), 3.53 (2H, app. br s, C*H*$_2$), 3.38 (2H, app. q, *J* = 6.0 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 162.4, 151.3, 141.0, 140.2, 130.8, 121.4, 59.5, 41.7.

Synthesis of ethyl 2-((2-hydroxyethyl)amino)nicotinate **281**



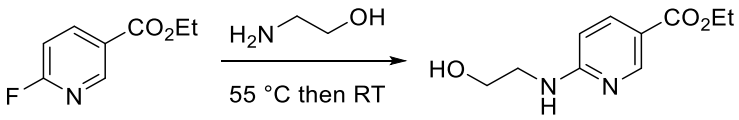
262 **281**

Following general procedure G, using ethyl 2-fluoronicotinate **262** (2.40 g, 14.2 mmol) and ethanolamine (1.30 g, 21.3 mmol) the amine product **281** was afforded as a yellow solid (2.23 g, 85%).

NB: Ethyl 2-fluoronicotinate was synthesised from the corresponding carboxylic acid using esterification procedure 1

M.p.: 52 – 53 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3356 (m), 3201 (m), 2987 (m), 1693 (s), 1580 (s), 1513 (s), 1251 (s), 1059 (s); ^{1}H NMR (400 MHz, d^6-DMSO): δ 8.26 (1H, dd, *J* = 4.5, 2.0 Hz, C*H*$_{ar}$), 8.14 – 8.02 (2H, m, C*H*$_{ar}$ and N*H*), 6.60 (1H, dd, *J* = 7.5, 4.5 Hz, C*H*$_{ar}$), 4.81 (1H, t, *J* = 5.0 Hz, O*H*), 4.27 (2H, q, *J* = 7.0 Hz, C*H*$_2$), 3.61 – 3.47 (4H, m, 2 x C*H*$_2$), 1.30 (3H, t, *J* = 7.0 Hz, C*H*$_3$); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 166.7, 158.0, 153.6, 139.7, 111.0, 105.3, 60.5, 59.6, 42.9, 14.1; HRMS: *m/z* [MH]$^+$ $C_{10}H_{15}N_2O_3$ calcd. 211.1077, found 211.1081.

Synthesis of ethyl 6-((2-hydroxyethyl)amino)nicotinate **282**



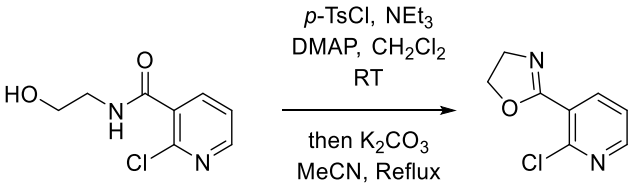
264 **282**

Following general procedure G, using ethyl 6-fluoronicotinate **264** (2.25 g, 13.3 mmol) and ethanolamine (1.22 g, 19.9 mmol) the amine product **282** was afforded as a yellow solid (1.94 g, 69%).

NB: Ethyl 6-fluoronicotinate was synthesised from the corresponding carboxylic acid using esterification procedure 1

M.p.: 39 – 40 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3466 (m), 3287 (m), 2984 (w), 1677 (s), 1608 (s), 1519 (s), 1270 (s), 1103 (s); ^{1}H NMR (400 MHz, d^{6}-DMSO): δ 8.55 (1H, d, *J* = 2.0 Hz, C*H*$_{ar}$), 7.79 (1H, dd, *J* = 9.0, 2.0 Hz, C*H*$_{ar}$), 7.41 (1H, br s, N*H*), 6.53 (1H, d, *J* = 9.0 Hz, C*H*$_{ar}$), 4.76 (1H, br s, O*H*), 4.22 (2H, q, *J* = 7.0 Hz, C*H*$_2$), 3.53 (2H, t, *J* = 6.0 Hz, C*H*$_2$), 3.39 (2H, app. q, *J* = 6.0 Hz, C*H*$_2$), 1.27 (3H, t, *J* = 7.0 Hz, C*H*$_3$); ^{13}C NMR (100.6 MHz, d^{6}-DMSO): δ 165.3, 161.1, 150.8, 139.2, 136.8, 113.1, 59.8, 59.7, 43.3, 14.3; HRMS: *m/z* [MH]$^+$ $C_{10}H_{15}N_2O_3$ calcd. 211.1077, found 211.1079.

Synthesis of 2-(2-chloropyridin-3-yl)-4,5-dihydrooxazole **285**

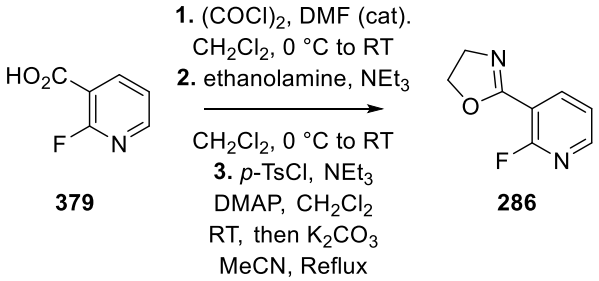


270 **285**

Following general procedure H, using 6-chloro-*N*-(2-hydroxyethyl)nicotinamide **270** (300 mg, 1.50 mmol), *p*-TsCl (486 mg, 2.55 mmol), NEt_3 (288 mg, 2.85 mmol), DMAP (37 mg, 0.30 mmol) and dichloromethane (2.5 mL), then using K_2CO_3 (622 mg, 4.50 mmol) and MeCN (3 mL), the oxazoline product **285** was afforded as a yellow solid (172 mg, 63%).

M.p.: 90 – 91 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3072 (w), 2981 (w), 1658 (m), 1633 (m), 1586 (m), 1400 (s), 1368 (m), 1270 (m), 1119 (s), 1030 (s), 936 (s), 901 (s), 819 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (1H, dd, *J* = 5.0, 2.0 Hz, C*H*$_{ar}$), 8.09 (1H, dd, *J* = 7.5, 2.0 Hz, C*H*$_{ar}$), 7.28 (1H, dd, *J* = 7.5, 5.0 Hz, C*H*$_{ar}$), 4.44 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.10 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 161.7, 151.0, 149.8, 140.1, 124.4, 122.0, 67.9, 55.5; HRMS: *m/z* [M]$^+$ $C_8H_7{}^{35}ClN_2O$ calcd. 182.0241, found 182.0239.

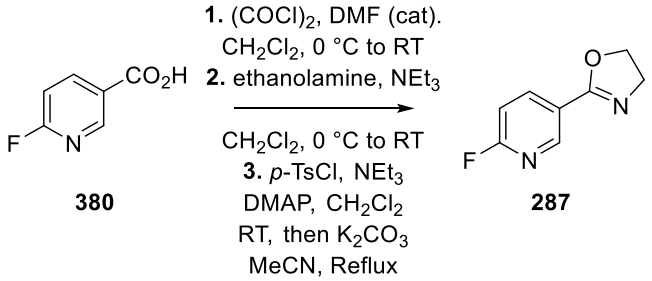
Synthesis of 2-(2-fluoropyridin-3-yl)-4,5-dihydrooxazole **286**



To a stirred solution of 2-fluoro-3-pyridine carboxylic acid **379** (500 mg, 3.54 mmol) in dry dichloromethane (17 mL) at 0 °C was added oxalyl chloride (1.35 g, 10.6 mmol) and DMF (few drops). The reaction was allowed to warm to room temperature and stirred for a period of 3 hours before removing the solvent *in vacuo*. The crude residue was then dissolved in dry dichloromethane (17 mL) and cooled to 0 °C using an ice bath. Triethylamine (1.07 g, 10.6 mmol) was then added, followed by ethanolamine (260 mg, 4.25 mmol) *via* syringe. The reaction was allowed to warm to room temperature and stir overnight. The reaction was then dry loaded onto silica gel and purified by flash column chromatography on silica gel eluting with dichloromethane and methanol (0 to 2% methanol) to afford the amide product (316 mg, 1.72 mmol). Without further purification or characterisation, the amide was carried forward to yield the oxazoline. Following general procedure H, using *p*-TsCl (557 mg, 2.92 mmol), NEt_3 (331 mg, 3.27 mmol), DMAP (42 mg, 0.34 mmol) and dichloromethane (2.9 mL), then using K_2CO_3 (713 mg, 5.16 mmol) and MeCN (3.5 mL), the oxazoline product **286** was afforded as a colourless solid (181 mg, 31% over two steps).

M.p.: 60 – 61 °C; FTIR: ν_{max}/ cm^{-1} 3072 (w), 2987 (w), 1646 (m), 1608 (m), 1447 (m), 1434 (m), 1264 (m), 1040 (s), 942 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 – 8.27 (2H, m, CH_{ar}), 7.29 – 7.24 (1H, m, CH_{ar}), 4.44 (2H, t, *J* = 9.5 Hz, CH_2), 4.12 (2H, t, *J* = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 161.1 (d, *J* = 248.0 Hz), 160.1 (d, *J* = 9.5 Hz), 150.1 (d, *J* = 15.0 Hz), 141.9 (d, *J* = 2.0 Hz), 121.4 (d, *J* = 5.0 Hz), 111.6 (d, *J* = 25.5 Hz), 55.5, 67.7; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 62.4; HRMS: *m/z* $[MH]^+$ $C_8H_8FN_2O$ calcd. 167.0615, found 167.0613.

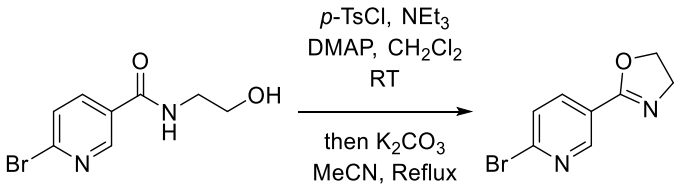
Synthesis of 2-(6-fluoropyridin-3-yl)-4,5-dihydrooaxole **287**



To a stirred solution of 2-fluoro-5-pyridine carboxylic acid **380** (500 mg, 3.54 mmol) in dry dichloromethane (17 mL) at 0 °C was added oxalyl chloride (1.35 g, 10.6 mmol) and DMF (few drops). The reaction was allowed to warm to room temperature and stirred for a period of 3 hours before removing the solvent *in vacuo*. The crude residue was then dissolved in dry dichloromethane (17 mL) and cooled to 0 °C using an ice bath. Triethylamine (1.07 g, 10.6 mmol) was then added, followed by ethanolamine (260 mg, 4.25 mmol) *via* syringe. The reaction was allowed to warm to room temperature and stir overnight. The reaction was then dry loaded onto silica gel and purified by flash column chromatography on silica gel eluting with dichloromethane and methanol (0 to 5% methanol) to afford the amide product (287 mg, 1.56 mmol). Without further purification or characterisation, the amide was carried forward to yield the oxazoline. Following general procedure H, using *p*-TsCl (506 mg, 2.65 mmol), NEt_3 (300 mg, 2.96 mmol), DMAP (38 mg, 0.31 mmol) and dichloromethane (2.6 mL), then using K_2CO_3 (647 mg, 4.68 mmol) and MeCN (3.1 mL), the oxazoline product **287** was afforded as a colourless solid (191 mg, 32% over two steps).

M.p.: 72 – 73 °C; FTIR: ν_{max}/ cm^{-1} 3052 (w), 2967 (w), 1653 (m), 1594 (m), 1383 (s), 1079 (s), 935 (s), 853 (m), 834 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (1H, d, *J* = 2.5 Hz, C*H*$_{ar}$), 8.32 (1H, ddd, *J* = 8.5, 7.0, 2.5 Hz, C*H*$_{ar}$), 6.97 (1H, dd, *J* = 8.5, 2.5 Hz, C*H*$_{ar}$), 4.46 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.07 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.1 (d, *J* = 244.0 Hz), 161.2, 148.3 (d, *J* = 16.0 Hz), 141.2 (d, *J* = 9.0 Hz), 122.3, 109.6 (d, *J* = 37.5 Hz), 68.1, 55.1; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 63.7; HRMS: *m/z* $[MH]^+$ $C_8H_8FN_2O$ calcd. 167.0615, found 167.0615.

Synthesis of 2-(6-bromopyridin-3-yl)-4,5-dihydrooaxole **288**



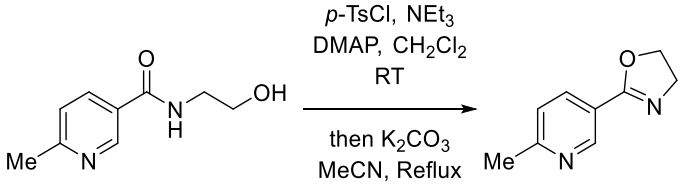
273 **288**

Following general procedure H, using 6-bromo-*N*-(2-hydroxyethyl)nicotinamide **273** (458 mg, 1.87 mmol), *p*-TsCl (606 mg, 3.18 mmol), NEt_3 (360 mg, 3.55 mmol), DMAP (46 mg, 0.37 mmol) and dichloromethane (3.2 mL), then using K_2CO_3 (775 mg, 5.61 mmol) and MeCN (3.8 mL), the oxazoline product **288** was afforded as a yellow solid (314 mg, 74%).

M.p.: 114 – 115 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3079 (w), 2955 (w), 1652 (m), 1578 (m), 1448 (m), 1253 (m), 1096 (s), 1069 (s), 935 (s), 737 (s), 680 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (1H, d, *J* = 2.0 Hz, C*H*$_{ar}$), 8.04 (1H, dd, *J* = 8.5, 2.0 Hz, C*H*$_{ar}$), 7.53 (1H, d, *J* = 8.5 Hz, C*H*$_{ar}$), 4.44 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.05 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 161.9, 149.8,

144.9, 137.8, 127.9, 123.3, 68.0, 55.1; HRMS: *m/z* $[M]^+$ $C_8H_8{}^{79}BrN_2O$ calcd. 226.9815, found 226.9816.

Synthesis of 2-(6-methylpyridin-3-yl)-4,5-dihydrooxazole **289**

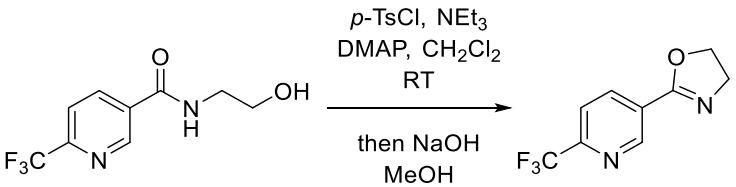


271 **289**

Following general procedure H, using *N*-(2-hydroxyethyl)-6-methylnicotinamide **271** (695 mg, 3.86 mmol), *p*-TsCl (1.25 g, 6.56 mmol), NEt_3 (742 mg, 7.33 mmol), DMAP (94 mg, 0.77 mmol) and dichloromethane (6.5 mL), then using K_2CO_3 (463 mg, 11.6 mmol) and MeCN (8 mL), the oxazoline product **289** was afforded as a beige solid (400 mg, 64%).

M.p.: 56 – 57 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3035 (w), 2933 (w), 1640 (s), 1597 (m), 1378 (s), 1261 (s), 1077 (s), 940 (s), 842 (m), 733 (s), 690 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (1H, d, *J* = 2.0 Hz, C*H*$_{ar}$), 7.98 (1H, dd, *J* = 8.0, 2.0 Hz, C*H*$_{ar}$), 7.10 (1H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 4.33 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 3.95 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 2.50 (3H, s, C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.8, 161.3, 148.8, 135.7, 122.8, 121.0, 67.6, 54.8, 24.6; HRMS: *m/z* $[MH]^+$ $C_9H_{10}N_2O$ calcd. 162.0788, found 162.0785.

Synthesis of 2-(6-(trifluoromethyl)pyridine-3-yl)-4,5-dihydrooxazole **290**



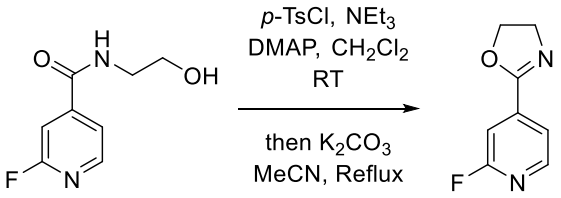
272 **290**

Following general procedure F, using *N*-(2-hydroxyethyl)-6-(trifluoromethyl)nicotinamide **272** (500 mg, 2.14 mmol), *p*-TsCl (694 mg, 3.64 mmol), NEt_3 (411 mg, 4.07 mmol), DMAP (52 mg, 0.43 mmol) and dichloromethane (3.6 mL), then using NaOH pellets (257 mg, 6.42 mmol) and MeOH (4.3 mL), the oxazoline product **290** was afforded as a colourless solid (363 mg, 79%).

M.p.: 72 – 73 °C; FTIR: ν_{max}/ cm^{-1} 3054 (w), 2988 (w), 1655 (m), 1335 (m), 1116 (s), 1092 (s), 1073 (s), 1014 (m), 936 (m), 858 (m), 686 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22 (1H, s, CH$_{ar}$), 8.37 (1H, dd, *J* = 8.0, 1.0 Hz, C*H*$_{ar}$), 7.72 (1H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 4.48 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.10 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 161.6, 150.0 (q, *J* = 35.0 Hz), 149.7,

137.1, 126.6, 121.4 (q, *J* = 274.0 Hz), 120.2, 68.2, 55.2; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 68.2; HRMS: *m/z* $[MH]^+$ $C_9H_8F_3N_2O$ calcd. 217.0583, found 217.0582.

Synthesis of 2-(2-fluoropyridin-4-yl)-4,5-dihydrooxazole **291**

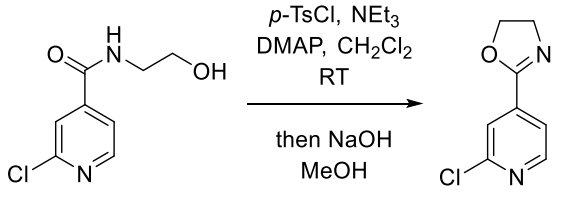


275 **291**

Following general procedure H, using 2-fluoro-*N*-(2-hydroxyethyl)isonicotinamide **275** (200 mg, 1.09 mmol), *p*-TsCl (352 mg, 1.85 mmol), NEt_3 (209 mg, 2.06 mmol), DMAP (27 mg, 0.22 mmol) and dichloromethane (1.8 mL), then using K_2CO_3 (450 mg, 3.26 mmol) and MeCN (2.2 mL), the oxazoline product **291** was afforded as a colourless solid (128 mg, 71%).

M.p.: 99 – 100 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3058 (w), 2980 (w), 1651 (m), 1604 (m), 1550 (m), 1413 (s), 1389 (s), 1194 (m), 1081 (m), 945 (m), 854 (s), 702 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (1H, d, *J* = 5.0 Hz, C*H*$_{ar}$), 7.72 – 7.64 (1H, m, C*H*$_{ar}$), 7.41 (1H, *J* = 1.0 Hz, C*H*$_{ar}$), 4.48 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.11 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.1 (d, *J* = 239.0 Hz), 162.0 (d, *J* = 4.0 Hz), 148.3 (d, *J* = 15.0 Hz), 140.5 (d, *J* = 8.5 Hz), 119.9 (d, *J* = 4.5 Hz), 108.5 (d, *J* = 40.0 Hz), 68.3, 55.2; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 66.9; HRMS: *m/z* $[M]^+$ $C_8H_7FN_2O$ calcd. 166.0537, found 166.0535.

Synthesis of 2-(2-chloropyridin-4-yl)-4,5-dihydrooxazole **292**[175]

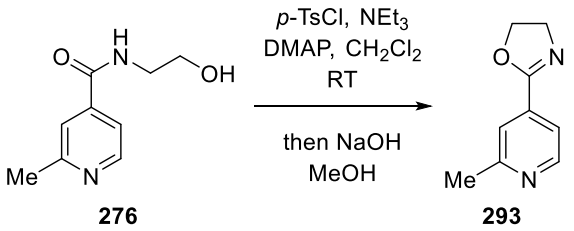


274 **292**

Following general procedure F, using 2-chloro-*N*-(2-hydroxyethyl)isonicotinamide **274** (5.0 g, 24.9 mmol), *p*-TsCl (8.07 g, 42.4 mmol), NEt_3 (4.79 g, 47.4 mmol), DMAP (610 mg, 4.98 mmol) and dichloromethane (42 mL), then using NaOH pellets (3.0 g, 74.8 mmol) and MeOH (50 mL), the oxazoline product **292** was afforded as a colourless solid (3.69 g, 81%).

M.p.: 89 – 90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (1H, dd, *J* = 5.0, 1.0 Hz, C*H*$_{ar}$), 7.76 (1H, s, C*H*$_{ar}$), 7.65 (1H, dd, *J* = 5.0, 1.0 Hz, C*H*$_{ar}$), 4.42 (2H, t, *J* = 10.0 Hz, C*H*$_2$), 4.05 (2H, t, *J* = 10.0 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 161.9, 152.1, 150.1, 138.1, 122.9, 120.7, 68.2, 55.2.

Synthesis of 2-(2-methylpyridin-4-yl)-4,5-dihydrooxazole **293**

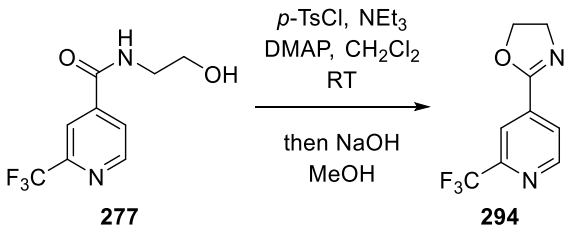


276 **293**

Following general procedure F, using *N*-(2-hydroxyethyl)-2-methylisonicotinamide **276** (507 mg, 2.81 mmol), *p*-TsCl (912 mg, 4.78 mmol), NEt_3 (540 mg, 5.34 mmol), DMAP (69 mg, 0.56 mmol) and dichloromethane (4.7 mL), then using NaOH pellets (337 mg, 8.43 mmol) and MeOH (5.6 mL), the oxazoline product **293** was afforded as a tan solid (373 mg, 82%).

M.p.: 58 – 59 °C; FTIR: ν_{max}/ cm^{-1} (neat) 2984 (w), 2919 (w), 1650 (m), 1610 (m), 1479 (m), 1375 (s), 1211 (s), 1083 (s), 954 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (1H, d, *J* = 5.0 Hz, C*H*$_{ar}$), 7.65 (1H, app. s, C*H*$_{ar}$), 7.56 (1H, dd, *J* = 5.0, 1.0 Hz, C*H*$_{ar}$), 4.45 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.08 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 2.59 (3H, s, C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.4, 159.3, 149.7, 135.4, 121.6, 119.1, 68.0, 55.2, 24.5; HRMS: *m/z* $[MH]^+$ $C_9H_{11}N_2O$ calcd. 163.0866, found 163.0866.

Synthesis of 2-(2-(trifluoromethyl)pyridine-4-yl)-4,5-dihydrooxazole **294**

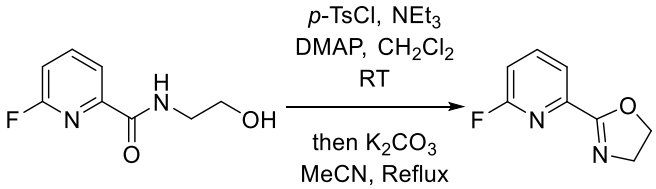


277 **294**

Following general procedure F, using *N*-(2-hydroxyethyl)-2-(trifluoromethyl)isonicotinamide **277** (626 mg, 2.67 mmol), *p*-TsCl (866 mg, 4.54 mmol), NEt_3 (513 mg, 5.07 mmol), DMAP (65 mg, 0.53 mmol) and dichloromethane (4.5 mL), then using NaOH pellets (320 mg, 8.01 mmol) and MeOH (5 mL), the oxazoline product **294** was afforded as a colourless solid (444 mg, 77%).

M.p.: 49 – 50 °C; FTIR: ν_{max}/ cm^{-1} (neat) 2991 (w), 2905 (w), 1653 (m), 1607 (m), 1314 (m), 1250 (m), 1111 (s), 1079 (s), 940 (s), 879 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (1H, d, *J* = 5.0 Hz, C*H*$_{ar}$), 8.19 (1H, app. s, C*H*$_{ar}$), 7.98 (1H, dd, *J* = 5.0, 1.0 Hz, C*H*$_{ar}$), 4.52 (2H, t, *J* = 9.5 Hz, C*H*$_{ar}$), 4.14 (2H, t, *J* = 9.5 Hz, C*H*$_{ar}$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.1, 150.7, 149.1 (q, *J* = 35.0 Hz), 137.0, 124.7, 121.4 (q, *J* = 274.0 Hz), 119.2 (app d, *J* = 2.5 Hz), 68.5, 55.4; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 68.1; HRMS: *m/z* $[MH]^+$ $C_9H_8F_3N_2O$ calcd. 217.0583, found 217.0584.

Synthesis of 2-(6-fluoropyridin-2-yl)-4,5-dihydrooxazole **295**

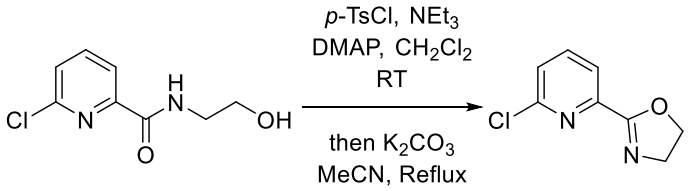


279 **295**

Following general procedure H, using 6-fluoro-*N*-(2-hydroxyethyl)picolinamide **279** (1.24 g, 6.73 mmol), *p*-TsCl (2.18 g, 11.5 mmol), NEt_3 (1.29 g, 12.8 mmol), DMAP (164 mg, 1.35 mmol) and dichloromethane (1.8 mL), then using K_2CO_3 (2.79 g, 20.2 mmol) and MeCN (13.5 mL), the oxazoline product **295** was afforded as a tan solid (970 mg, 87%).

M.p.: 59 – 60 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3083 (w), 3057 (w), 2971 (w), 1649 (m), 1460 (m), 1365 (m), 1236 (s), 1111 (s), 978 (s), 824 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 – 7.79 (2H, m, CH_{ar}), 7.04 (1H, ddd, *J* = 7.5, 3.0, 1.0 Hz, CH_{ar}), 4.50 (2H, t, *J* = 9.5 Hz, CH_2), 4.11 (2H, t, *J* = 9.5 Hz, CH_2); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 65.3; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.5 (d, *J* = 148.0 Hz), 161.8, 145.2 (d, *J* = 13.5 Hz), 141.8 (d, *J* = 7.5 Hz), 121.3 (d, *J* = 4.0 Hz), 112.2 (d, *J* = 36.5 Hz), 68.5, 55.3; HRMS: *m/z* $[MH]^+$ $C_8H_8FN_2O$ calcd. 167.0615, found 167.0612.

Synthesis of 2-(6-chloropyridin-2-yl)-4,5-dihydrooxazole **296**

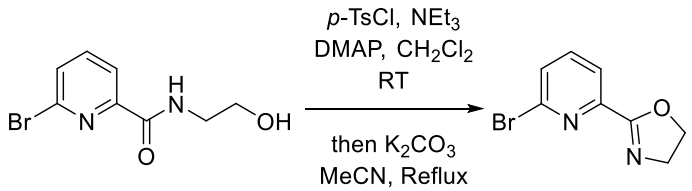


278 **296**

Following general procedure H, using 6-chloro-*N*-(2-hydroxyethyl)picolinamide **278** (300 mg, 1.50 mmol), *p*-TsCl (486 mg, 2.55 mmol), NEt_3 (288 mg, 2.85 mmol), DMAP (37 mg, 0.30 mmol) and dichloromethane (2.5 mL), then using K_2CO_3 (622 mg, 4.50 mmol) and MeCN (3 mL), the oxazoline product **296** was afforded as a colourless solid (160 mg, 58%).

M.p.: 79 – 80 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3050 (w), 2875 (w), 1631 (m), 1561 (m), 1432 (m), 1370 (m), 1104 (s), 1069 (s), 807 (s), 737 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (1H, d, *J* = 7.5 Hz, CH_{ar}), 7.75 (1H, t, *J* = 7.5 Hz, CH_{ar}), 7.45 (1H, d, *J* = 7.5 Hz, CH_{ar}), 4.54 (2H, t, *J* = 10.0 Hz, CH_2), 4.13 (2H, t, *J* = 10.0 Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.9, 151.6, 147.2, 139.3, 126.6, 122.4, 68.6, 55.2; HRMS: *m/z* $[MH]^+$ $C_8H_8N_2O^{35}Cl$ calcd. 183.0325, found 183.0322.

Synthesis of 2-(6-bromopyridin-2-yl)-4,5-dihydrooxazole **297**

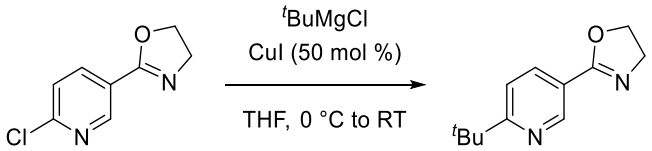


280 **297**

Following general procedure H, using 6-bromo-*N*-(2-hydroxyethyl)picolinamide **280** (200 mg, 0.816 mmol), *p*-TsCl (264 mg, 1.39 mmol), NEt_3 (157 mg, 1.55 mmol), DMAP (20 mg, 0.16 mmol) and dichloromethane (1.4 mL), then using K_2CO_3 (338 mg, 2.45 mmol) and MeCN (1.6 mL), the oxazoline product **297** was afforded as a tan solid (970 mg, 87%).

M.p.: 104 – 105 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3043 (w), 2929 (w), 1640 (m), 1554 (m), 1436 (m), 1362 (m), 1245 (m), 1096 (s), 1065 (s), 944 (s), 799 (s), 733 (s), 639 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (1H, dd, *J* = 7.5, 1.0 Hz, C*H*$_{ar}$), 7.67 – 7.57 (2H, m, C*H*$_{ar}$), 4.53 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.13 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.8, 147.6, 142.1, 139.0, 130.4, 122.8, 69.0, 55.2; HRMS: *m/z* $[MH]^+$ $C_8H_8{}^{79}BrN_2O$ calcd. 226.9820, found 226.9824.

Synthesis of 2-(6-(tert-butyl)pyridine-3-yl)-4,5-dihydrooxazole **298**



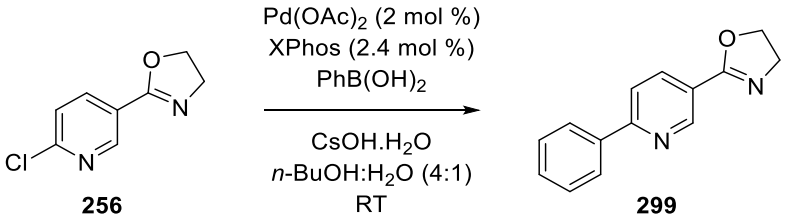
256 **298**

To a round bottomed flask was added 2-(2-chloropyridin-3-yl)-4,5-dihydrooxazole **256** (700 mg, 3.83 mmol) and copper (I) iodide (365 mg, 1.92 mmol). The flask was then placed under an atmosphere of nitrogen followed by the addition of THF (6.4 mL). The reaction was stirred and cooled to 0 °C using an ice/water bath. *Tert*-butyl magnesium chloride (4.0 mL, 1.42 M in THF, 5.75 mmol) was then added dropwise, upon complete addition the ice/water bath was removed and the reaction mixture was stirred at room temperature overnight. The reaction was quenched by the addition of saturated NH_4Cl (aq.) solution (approx. 10 mL) and stirred for 10 – 15 mins. The reaction mixture was then transferred to a separating funnel where ethyl acetate and aqueous ammonia solution (35 %) were added. The layers were partitioned and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with

petroleum ether (40/60) and ethyl acetate (0% ethyl acetate to 60% ethyl acetate) to afford the oxazoline product **298** as a yellow amorphous solid (334 mg, 43%).

FTIR: ν_{max}/ cm^{-1} (neat) 2966 (w), 2912 (w), 1639 (s), 1593 (m), 1486 (m), 1368 (m), 1261 (s), 1129 (m), 1076 (s), 940 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.05 (1H, dd, *J* = 2.0, 0.5 Hz, CH_{ar}), 8.11 (1H, dd, *J* = 8.0, 2.0 Hz, CH_{ar}), 7.36 (1H, dd, *J* = 8.0, 0.5 Hz, CH_{ar}), 4.42 (2H, t, *J* = 9.5 Hz, CH_2), 4.04 (2H, t, *J* = 9.5 Hz, CH_2), 1.36 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 172.4, 163.1, 148.4, 135.9, 121.0, 118.7, 67.7, 55.0, 37.9, 30.2; HRMS: *m/z* $[MH]^+$ $C_{12}H_{17}N_2O$ calcd. 205.1335, found 205.1338.

Synthesis of 2-(6-phenylpyridin-3-yl)-4,5-dihydrooxazole **299**

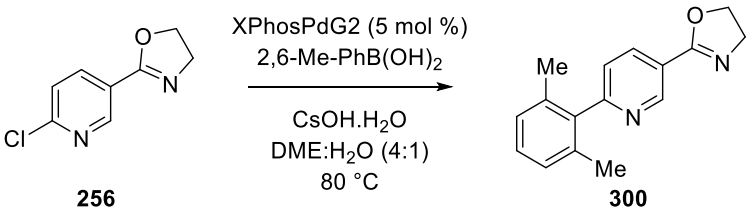


256 **299**

A round bottomed flask equipped with a stirrer bar was added 2-(2-chloropyridin-3-yl)-4,5-dihydrooxazole **256** (183 mg, 1.00 mmol), $PhB(OH)_2$ (146 mg, 1.2 mmol), $Pd(OAc)_2$ (5 mg, 0.02 mmol), XPhos (12 mg, 0.024 mmol) and $CsOH.H_2O$ (285 mg, 1.7 mmol). The flask was sealed and placed under an atmosphere of nitrogen, followed by the addition of the degassed solvents, *n*-BuOH (5.6 mL) and H_2O (1.36 mL). The reaction mixture was then stirred at room temperature for a period of 2 hours. The reaction mixture was then transferred to a separating funnel and the layers were partitioned. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) and ethyl acetate (0% ethyl acetate to 100% ethyl acetate) to afford the oxazoline product **299** as a colourless solid (185 mg, 83%).

M.p.: 131 – 132 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3086 (w), 2982 (w), 1649 (m), 1595 (w), 1558 (w), 1370 (m), 1263 (m), 1079 (m), 935 (m), 744 (s), 690 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (1H, d, *J* = 2.0 Hz, CH_{ar}), 8.25 (1H, dd, *J* = 8.5, 2.0 Hz, CH_{ar}), 8.07 – 8.01 (2H, m, CH_{ar}), 7.77 (1H, dd, *J* = 8.5 Hz, 1.0 Hz, CH_{ar}), 7.52 – 7.40 (3H, m, CH_{ar}), 4.45 (2H, t, *J* = 9.5 Hz, CH_2), 4.08 (2H, t, *J* = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.9, 159.6, 149.5, 138.6, 136.4, 129.7, 129.0, 127.3, 122.2, 119.9, 67.8, 55.1; HRMS: *m/z* $[MH]^+$ $C_{14}H_{13}N_2O$ calcd. 225.1022, found 225.1021.

Synthesis of 2-(6-(2,6-dimethylphenyl)pyridine-3-yl)-4,5-dihydrooxazole **300**

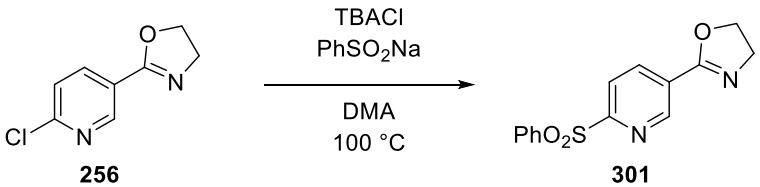


256 **300**

A round bottomed flask equipped with a stirrer bar was added 2-(2-chloropyridin-3-yl)-4,5-dihydrooxazole **256** (120 mg, 0.660 mmol), 2,6-dimethylphenyl boronic acid (148 mg, 0.990 mmol), XPhosPdG2 (26 mg, 0.033 mmol) and $CsOH.H_2O$ (188 mg, 1.12 mmol). The flask was sealed and placed under an atmosphere of nitrogen, followed by the addition of the degassed solvents, 1,2-DME (3.73 mL) and H_2O (0.91 mL). The reaction mixture was then stirred at 80 °C for a period of 18 hours. The reaction mixture was then cooled to room temperature, and transferred to a separating funnel. Ethyl acetate was added and the layers were partitioned. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) and ethyl acetate (0% ethyl acetate to 80% ethyl acetate) to afford the oxazoline product **300** as a colourless oil (99 mg, 59%).

FTIR: ν_{max}/ cm^{-1} 3016 (w), 2966 (w), 2909 (w), 1646 (s), 1600 (m), 1461 (m), 1375 (s), 1257 (s), 1083 (s), 1018 (s), 936 (s), 765 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.25 (1H, dd, *J* = 2.0, 1.0 Hz, C*H*$_{ar}$), 8.28 (1H, dd, *J* = 8.0, 2.0 Hz, C*H*$_{ar}$), 7.29 (1H, dd, *J* = 8.0, 1.0 Hz, C*H*$_{ar}$), 7.19 (1H, t, *J* = 7.0 Hz, C*H*$_{ar}$), 7.09 (2H, d, *J* = 7.0 Hz, C*H*$_{ar}$), 4.48 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.10 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 2.03 (6H, s, C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.0, 162.7, 149.5, 139.9, 135.9, 135.7, 128.3, 127.7, 124.2, 122.0, 67.9, 55.1, 20.3; HRMS: *m/z* $[MH]^+$ $C_{16}H_{17}N_2O$ calcd. 253.1335, found 253.1337.

Synthesis of 2-(6-(phenylsulfonyl)pyridine-3-yl)-4,5-dihydrooxazole **301**



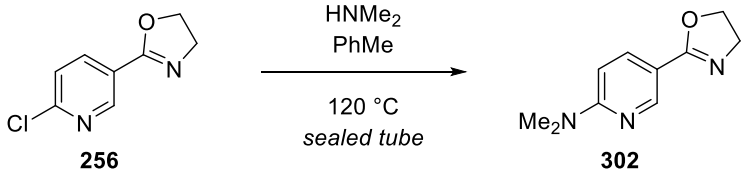
256 **301**

To a round bottomed flask was added 2-(2-chloropyridin-3-yl)-4,5-dihydrooxazole **256** (200 mg, 1.10 mmol), benzenesulfinic acid sodium salt (271 mg, 1.65 mmol), tetrabutyl ammonium chloride (92 mg, 0.33 mmol) and DMA (1.60 mL). The reaction mixture was stirred and heated at 100 °C for a period of 24 hours. After cooling to room temperature, deionised

water was added (4 mL) and the mixture was stirred for 10 minutes. The observable thick colourless slurry was collected by vacuum filtration, washing with a little deionised water. After drying under vacuum the oxazoline product **301** was afforded as a colourless solid (131 mg, 41%).

M.p.: 189 – 190 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3096 (w), 3062 (w), 2908 (w), 1645 (m), 1578 (w), 1307 (m), 1173 (m), 1076 (m), 1019 (w), 761 (s), 687 (s), 607 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 – 9.18 (1H, m, CH_{ar}), 8.42 (1H, dd, *J* = 8.0, 2.0 Hz, CH_{ar}), 8.24 (1H, dd, *J* = 8.0, 0.5 Hz, CH_{ar}), 8.09 – 8.06 (2H, m, CH_{ar}), 7.69 – 7.59 (1H, m, CH_{ar}), 7.59 – 7.49 (2H, m, CH_{ar}), 4.47 (2H, t, *J* = 9.5 Hz, CH_2), 4.10 (2H, t, *J* = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 161.3, 160.4, 150.1, 138.6, 137.6, 134.0, 129.2, 129.1, 126.8, 121.8, 68.1, 55.2; HRMS: *m/z* [MH]$^+$ $C_{14}H_{13}N_2O_3S$ calcd. 289.0641, found 289.0645.

Synthesis of 5-(4,5-dihydrooxazol-2-yl)-N,N-dimethylpyridin-2-amine **302**

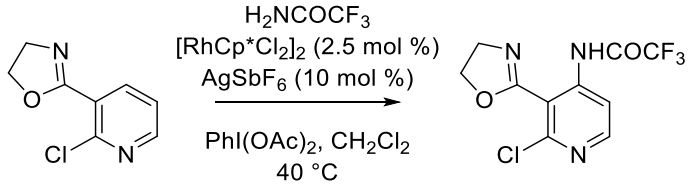


256 **302**

To a sealed tube equipped with a stirrer bar was added 2-(2-chloropyridin-3-yl)-4,5-dihydrooxazole **256** (85 mg, 0.47 mmol) and PhMe (3.88 mL). Dimethylamine (3.95 mL, 2.0 M in THF, 7.90 mmol) was then added *via* syringe, followed by sealing the tube with a Teflon lined cap. The reaction mixture was stirred and heated to 120 °C for a period of 36 hours. After cooling to room temperature, the reaction mixture was concentrated and the residue was dry loaded onto silica gel and purified by flash column chromatography on silica gel, eluting with 20% methanol in dichloromethane to afford the oxazoline product **302** as a yellow solid (35 mg, 39%).

M.p.: 138 – 139 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3044 (w), 2971 (w), 1643 (m), 1598 (s), 1516 (s), 1311 (s), 1254 (s), 1077 (m), 933 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (1H, app. s, CH_{ar}), 7.94 (1H, dd, *J* = 9.0, 2.0 Hz, CH_{ar}), 6.48 (1H, d, *J* = 9.0 Hz, CH_{ar}), 4.37 (2H, t, *J* = 9.0 Hz, CH_2), 3.99 (2H, t, *J* = 9.0 Hz, CH_2), 3.13 (6H, s, NMe_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.9, 160.3, 148.9, 136.9, 111.6, 104.9, 67.4, 54.8, 38.2; HRMS: *m/z* [MH]$^+$ $C_{10}H_{14}N_3O$ calcd. 192.1121, found 192.1133.

Synthesis of N-(2-chloro-3-(4,5-dihydrooxazol-2-yl)pyridine-4-yl)-2,2,2-trifluoroacetamide **303**

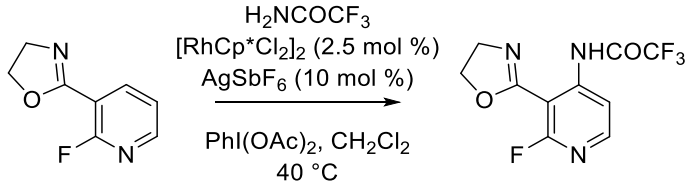


285 **303**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(2-chloropyridin-3-yl)-4,5-dihydrooxazole **285** (44 mg, 0.24 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 20 h, product **303** was isolated as a colourless solid (38 mg, 64%).

M.p.: 92 – 93 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3151 (w), 2981 (w), 2896 (w), 1731 (s), 1573 (s), 1355 (s), 1296 (m), 1191 (m), 1144 (s), 936 (m), 885 (m), 844 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.64 (1H, s, N*H*), 8.49 (1H, d, *J* = 5.5 Hz, CH_{ar}), 8.40 (1H, d, *J* = 5.5 Hz, CH_{ar}), 4.55 (2H, t, *J* = 9.5 Hz, CH_2), 4.15 (2H, t, *J* = 9.5 Hz, CH_2); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.2; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.2, 156.0 (q, *J* = 38.5 Hz), 151.6, 151.4, 146.5, 115.5 (q, *J* = 288.5 Hz), 113.2, 110.5, 67.9, 53.4; HRMS: *m/z* $[MH]^+$ $C_{10}H_8{}^{35}ClF_3N_3O_2$ calcd. 294.0252, found 294.0250.

Synthesis of N-(3-(4,5-dihydrooxazol-2-yl)-2-fluoropyridin-4-yl)-2,2,2-trifluoroacetamide **304**

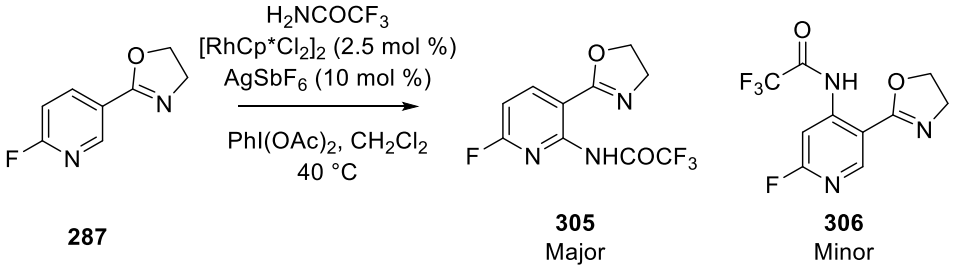


286 **304**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(2-fluoropyridin-3-yl)-4,5-dihydrooxazole **286** (40 mg, 0.24 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 20 h, product **304** was isolated as a colourless solid (33 mg, 59%).

M.p.: 102 – 103 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3242 (m), 3097 (m), 2968 (w), 1633 (s), 1567 (s), 1207 (s), 1157 (s), 1056 (s), 876 (s), 844 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.35 (1H, s, N*H*), 8.50 (1H, d, *J* = 6.0 Hz, CH_{ar}), 8.27 (1H, d, *J* = 6.0 Hz, CH_{ar}), 4.54 (2H, t, *J* = 10.0 Hz, CH_2), 4.13 (2H, t, *J* = 10.0 Hz, CH_2); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 57.8, – 76.1; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.9 (d, *J* = 7.0 Hz), 160.5, 156.3 (q, *J* = 39.0 Hz), 150.9 (d, *J* = 18.0 Hz), 148.4 (d, *J* = 5.0 Hz), 115.6 (q, *J* = 288.5 Hz), 112.6 (d, *J* = 4.5 Hz), 97.6 (d, *J* = 29.0 Hz), 67.8, 53.1; HRMS: *m/z* $[MH]^+$ $C_{10}H_8F_4N_3O_2$ calcd. 278.0547, found 278.0551.

Synthesis of N-(3-(4,5-dihydrooxazol-2-yl)-6-fluoropyridin-2-yl)-2,2,2-trifluoroacetamide **305** *and N-(5-(4,5-dihydrooxazol-2-yl)-2-fluoropyridin-4-yl)-2,2,2-trifluoroacetamide* **306**

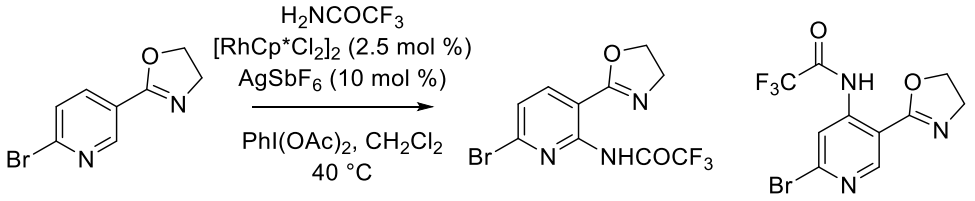


Mixture of Regioisomers (5.3:1)

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(6-fluoropyridin-3-yl)-4,5-dihydrooxazole **287** (40 mg, 0.24 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 20 h, products **305** and **306** were isolated in a regioisomeric mixture of 5.3:1 and as a colourless solid (39 mg, 71%).

FTIR: ν_{max}/ cm^{-1} (neat) 3246 (m), 3132 (m), 3097 (m), 2968 (w), 1633 (s), 1570 (s), 1551 (s), 1333 (s), 1204 (s), 1154 (s), 1056 (s), 1008 (s), 876 (s), 835 (s); ^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ 13.55 (1H, s, N*H*), 8.27 (1H, t, *J* = 8.0 Hz, CH_{ar}), 6.80 (1H, dd, *J* = 8.0 Hz, 3.0 Hz, CH_{ar}), 4.49 (2H, t, *J* = 9.5 Hz, CH_2), 4.19 (2H, t, *J* = 9.5 Hz, CH_2); ^{1}H NMR (400 MHz, $CDCl_3$) minor isomer: δ 13.89 (1H, s, N*H*), 8.71 (1H, s, CH_{ar}), 8.19 (1H, s, CH_{ar}), 4.49 (2H, t, *J* = 9.5 Hz, CH_2), 4.19 (2H, t, *J* = 9.5 Hz, CH_2); ^{19}F NMR (376.5 MHz, $CDCl_3$) major isomer: δ – 59.3, – 76.3; ^{19}F NMR (376.5 MHz, $CDCl_3$) minor isomer: δ – 59.5, – 76.2; ^{13}C NMR (100.6 MHz, $CDCl_3$) major and minor isomers: δ 167.3, 164.8, 164.4, 163.0, 162.6, 162.0, 154.0, 149.6, 149.5, 149.3, 142.9 (d, *J* = 9.0 Hz), 140.0, 120.3, 119.8, 117.0, 116.8, 114.1, 114.0, 111.2, 107.8 (d, *J* = 5.0 Hz), 105.2 (d, *J* = 37.0 Hz), 99.9 (d, *J* = 44.0 Hz), 67.7, 67.4, 54.4, 54.1 – complex ^{13}C due to mixture of regioisomers and ^{19}F coupling; HRMS: *m/z* $[MH]^+$ $C_{10}H_8F_4N_3O_2$ calcd. 278.0547, found 278.0549.

Synthesis of N-(6-bromo-3-(4,5-dihydrooxazol-2-yl)pyridine-2-yl)-2,2,2-trifluoroacetamide **307** *and N-(2-bromo-5-(4,5-dihydrooxazol-2-yl)pyridine-4-yl)-2,2,2-trifluoroacetamide* **308**



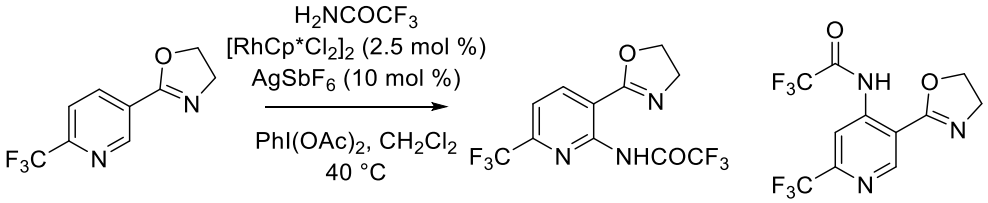
288 **307** Major **308** Minor

Mixture of Regioisomers (6.6:1)

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(6-bromopyridin-3-yl)-4,5-dihydrooxazole **288** (55 mg, 0.24 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 20 h, products **307** and **308** were isolated in a regioisomeric mixture of 6.6:1 and as a colourless solid (55 mg, 80%).

FTIR: ν_{max}/ cm^{-1} (neat) 3101 (w), 2991 (w), 2887 (w), 1750 (m), 1639 (m), 1607 (m), 1568 (m), 1268 (m), 1193 (m), 1125 (s), 1054 (m), 911 (m), 833 (m); ^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ 13.39 (1H, s, N*H*), 7.97 (1H, d, *J* = 8.0 Hz, CH_{ar}), 7.36 (1H, d, *J* = 8.0 Hz, CH_{ar}), 4.49 (2H, t, *J* = 9.5 Hz, CH_2), 4.17 (2H, t, *J* = 9.5 Hz, CH_2); ^{1}H NMR (400 MHz, $CDCl_3$) minor isomer: δ 13.76 (1H, s, N*H*), 8.76 (1H, s, CH_{ar}), 8.75 (1H, s, CH_{ar}), 4.50 (2H, t, *J* = 9.5 Hz, CH_2), 4.16 (2H, t, *J* = 9.5 Hz, CH_2); ^{19}F NMR (376.5 MHz, $CDCl_3$) major isomer: δ – 76.4; ^{19}F NMR (376.5 MHz, $CDCl_3$) minor isomer: δ – 76.2; ^{13}C NMR (100.6 MHz, $CDCl_3$) major isomer: δ 162.8, 154.1 (q, *J* = 38.5 Hz), 149.6, 143.4, 139.5, 124.2, 115.5 (q, *J* = 289.5 Hz), 109.2, 67.7, 54.5; HRMS: *m/z* $[MH]^+$ $C_{10}H_8{}^{79}BrF_3N_3O_2$ calcd. 337.9747, found 337.9747.

Synthesis of N-(3-(4,5-dihydrooxazol-2-yl)-6-(trifluoromethyl)pyridine-2-yl)-2,2,2-trifluoroacetamide **309** *and N-(5-(4,5-dihydrooxazol-2-yl)-2-(trifluoromethyl)pyridine-4-yl)-2,2,2-trifluoroacetamide* **310**



290 **309** Major **310** Minor

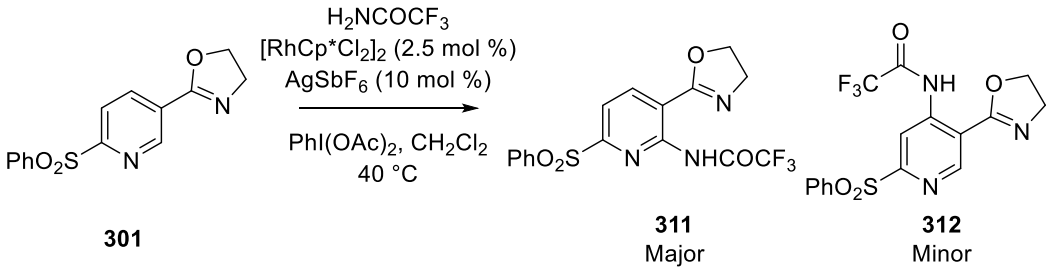
Mixture of Regioisomers (8.3:1)

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(6-(trifluoromethyl)pyridine-3-yl)-4,5-dihydrooxazole **290** (52 mg, 0.24 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in

dichloromethane (2 mL) at 40 °C for 20 h, products **309** and **310** were isolated in a regioisomeric mixture of 8.3:1 and as a colourless solid (51 mg, 78%).

FTIR: ν_{max}/ cm^{-1} (neat) 3242 (m), 3126 (m), 3097 (m), 2968 (w), 2927 (w), 1633 (s), 1567 (s), 1551 (s), 1337 (s), 1311 (s), 1204 (s), 1150 (s), 1053 (s), 1034 (s), 1008 (s), 876 (s), 838 (s); ^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ 13.42 (1H, s, N*H*), 8.36 (1H, d, *J* = 8.0 Hz, CH_{ar}), 7.55 (1H, d, *J* = 8.0 Hz, CH_{ar}), 4.53 (2H, t, *J* = 9.5 Hz, CH_2), 4.24 (2H, t, *J* = 9.5 Hz, CH_2); ^{1}H NMR (400 MHz, $CDCl_3$) minor isomer: δ 13.88 (1H, s, N*H*), 9.14 (1H, s, CH_{ar}), 8.96 (1H, s, CH_{ar}), 4.53 (2H, t, *J* = 9.5 Hz, CH_2), 4.24 (2H, t, *J* = 9.5 Hz, CH_2); ^{19}F NMR (376.5 MHz, $CDCl_3$) major isomer: δ – 68.5, – 76.4; ^{19}F NMR (376.5 MHz, $CDCl_3$) minor isomer: δ – 68.5, – 76.2; ^{13}C NMR (100.6 MHz, $CDCl_3$) major and minor isomers: δ 162.5, 154.3, 153.9, 150.9, 150.1, 149.2, 148.8, 145.5, 139.6, 131.1, 130.2, 128.9, 124.9, 122.1, 119.9, 119.4, 117.0, 116.3, 116.2, 114.1, 112.9, 110.9, 67.9, 67.6, 54.7, 54.3 – complex ^{13}C due to mixture of regioisomers and ^{19}F coupling; HRMS: *m/z* $[MH]^+$ $C_{11}H_8F_6N_3O_2$ calcd. 328.0515, found 328.0516.

Synthesis of N-(3-(4,5-dihydrooxazol-2-yl)-6-(phenylsulfonyl)pyridine-2-yl)-2,2,2-trifluoroacetamide **311** *and N-(5-(4,5-dihydrooxazol-2-yl)-2-(phenylsulfonyl)pyridine-4-yl)-2,2,2-trifluoroacetamide* **312**

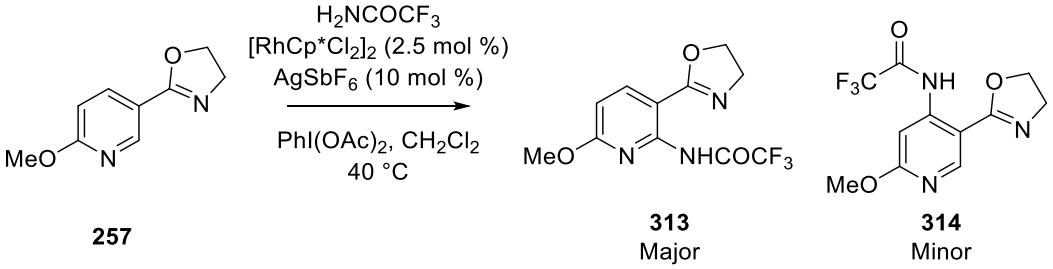


Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(6-(phenylsulfonyl)pyridine-3-yl)-4,5-dihydrooxazole **301** (69 mg, 0.24 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 20 h, products **311** and **312** were isolated in a regioisomeric mixture of 6.0:1 and as a colourless solid (57 mg, 72%).

FTIR: ν_{max}/ cm^{-1} (neat) 3073 (w), 2987 (w), 2919 (w), 1750 (m), 1643 (m), 1568 (m), 1411 (m), 1318 (m), 1257 (m), 1190 (m), 1133 (s), 1051 (s); ^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ 13.37 (1H, s, N*H*), 8.36 (1H, d, *J* = 8.0 Hz, CH_{ar}), 8.29 – 8.24 (2H, m, CH_{ar}), 8.01 (1H, d, *J* = 8.0 Hz, CH_{ar}), 7.66 – 7.49 (3H, m, CH_{ar}), 4.50 (2H, t, *J* = 9.5 Hz, CH_2), 4.20 (2H, t, *J* = 9.5 Hz, CH_2); ^{1}H NMR (400 MHz, $CDCl_3$) minor isomer: δ 13.87 (1H, s, N*H*), 9.35 (1H, s, CH_{ar}), 9.05 (1H, s, CH_{ar}), 8.10 – 8.06 (2H, m, CH_{ar}), 7.66 – 7.49 (3H, m, CH_{ar}), 4.50 (2H, t, *J* = 9.5 Hz, CH_2), 4.20 (2H, t, *J*

= 9.5 Hz, CH_2); ^{19}F NMR (376.5 MHz, $CDCl_3$) major isomer: δ – 76.4; ^{19}F NMR (376.5 MHz, $CDCl_3$) minor isomer: δ – 76.2; ^{13}C NMR (100.6 MHz, $CDCl_3$) major and minor isomers: δ 162.3, 159.2, 153.8 (q, *J* = 38.5 Hz), 151.2, 150.0, 145.9, 140.0, 139.8, 138.4, 137.8, 134.3, 134.2, 133.7, 130.1, 129.4, 129.3, 129.1, 129.0, 116.9, 114.0, 113.0, 112.4, 111.8, 110.2, 67.9, 67.7, 54.7, 54.3 –complex ^{13}C due to mixture of regioisomers; HRMS: *m/z* $[MH]^+$ $C_{16}H_{13}F_3N_3O_4S$ calcd. 400.0573, found 400.0574.

Synthesis of N-(3-(4,5-dihydrooxazol-2-yl)-6-methoxypyridin-2-yl)-2,2,2-trifluoroacetamide **313** *and N-(5-(4,5-dihydrooxazol-2-yl)-2-methoxypyridin-4-yl)-2,2,2-trifluoroacetamide* **314**



257

313 Major

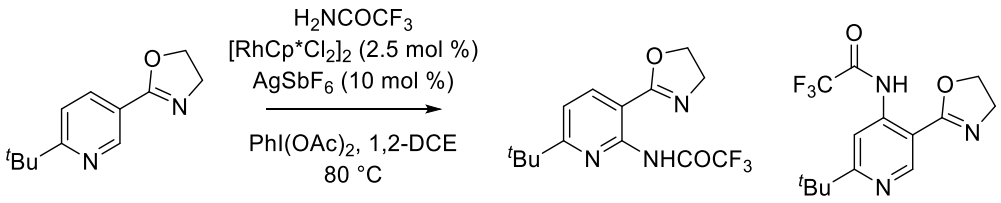
314 Minor

Mixture of Regioisomers (3.6:1)

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(6-methoxypyridin-3-yl)-4,5-dihydrooxazole **257** (43 mg, 0.24 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 20 h, products **313** and **314** were isolated in a regioisomeric mixture of 3.6:1 and as a colourless solid (18 mg, 31%).

FTIR: ν_{max}/ cm^{-1} (neat) 2987 (w), 2952 (w), 1737 (m), 1627 (m), 1479 (m), 1371 (m), 1318 (m), 1138 (s), 1131 (s), 1034 (s), 933 (m), 826 (s); ^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ 13.45 (1H, s, N*H*), 8.00 (1H, d, *J* = 8.5 Hz, CH_{ar}), 6.56 (1H, d, *J* = 8.5 Hz, CH_{ar}), 4.42 (2H, t, *J* = 9.0 Hz, CH_2), 4.13 (2H, t, *J* = 9.0 Hz, CH_2), 4.05 (3H, s, CH_3); ^{1}H NMR (400 MHz, $CDCl_3$) minor isomer: δ 13.70 (1H, s, N*H*), 8.64 (1H, s, CH_{ar}), 7.95 (1H, s, CH_{ar}), 4.45 (2H, t, *J* = 9.0 Hz, CH_2), 4.14 – 4.08 (2H, m, CH_2), 3.99 (3H, s, CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$) major isomer: δ – 76.3; ^{19}F NMR (376.5 MHz, $CDCl_3$) minor isomer: δ – 76.2; ^{13}C NMR (100.6 MHz, $CDCl_3$) major isomer: δ 164.8, 163.5, 154.3 (q, *J* = 37.5 Hz), 149.4, 139.9, 115.7 (q, *J* = 289.5 Hz), 106.6, 102.7, 67.3, 54.5, 54.3; HRMS: *m/z* $[MH]^+$ $C_{11}H_{11}F_3N_3O_3$ calcd. 290.0747, found 290.0747.

Synthesis of N-(6-(tert-butyl)-3-(4,5-dihydrooxazol-2-yl)pyridine-2-yl)-2,2,2-trifluoroacetamide **317** *and N-(2-(tert-butyl)-5-(4,5-dihydrooxazol-2-yl)pyridine-4-yl)-2,2,2-trifluoroacetamide* **318**



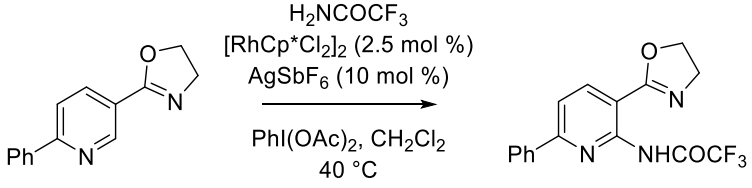
298 **317** **318**

Following general procedure C, using trifluoroacetamide (154 mg, 1.36 mmol) and 2-(6-*tert*-butyl-pyridin-3-yl)-4,5-dihydrooxazole **298** (333 mg, 1.63 mmol) with $[Cp^*RhCl_2]_2$ (21 mg, 0.034 mmol), $AgSbF_6$ (47 mg, 0.14 mmol) and $PhI(OAc)_2$ (657 mg, 2.04 mmol) in 1,2-DCE (13.6 mL) at 80 °C for 20 h, products **317** and **318** were isolated as colourless solids. (**317**, 28 mg, 7% and **318**, 23 mg, 5%).

317: M.p.: 103 – 104 °C; FTIR: ν_{max}/ cm^{-1} (neat) 2941 (m), 2855 (m), 1643 (s), 1543 (s), 1322 (s), 1079 (s), 857 (m), 762 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.17 (1H, s, N*H*), 8.07 (1H, d, *J* = 8.0 Hz, CH_{ar}), 7.19 (1H, d, *J* = 8.0 Hz, CH_{ar}), 4.45 (2H, t, *J* = 9.5 Hz, CH_2), 4.16 (2H, t, *J* = 9.5 Hz, CH_2), 1.39 (9H, s, C(CH_3)$_3$); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.3; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 172.4, 163.4, 154.1 (q, *J* = 37.5 Hz), 149.0, 138.0, 115.8 (q, *J* = 290.0 Hz), 115.1, 107.4, 67.3, 54.5, 38.4, 29.9; HRMS: *m/z* $[MH]^+$ $C_{14}H_{17}F_3N_3O_2$ calcd. 316.1267, found 316.1269.

318: M.p.: 111 – 112 °C; FTIR: ν_{max}/ cm^{-1} (neat) 2966 (w), 2912 (w), 2862 (w), 1643 (s), 1603 (m), 1543 (s), 1275 (s), 1147 (s), 1076 (s), 890 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.65 (1H, s, N*H*), 9.00 (1H, s, CH_{ar}), 8.63 (1H, s, CH_{ar}), 4.47 (2H, t, *J* = 9.5 Hz, CH_2), 4.15 (2H, t, *J* = 9.5 Hz, CH_2), 1.39 (9H, s, C(CH_3)$_3$); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.2; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 174.8, 163.8, 156.4 (q, *J* = 38.0 Hz), 149.6, 144.3, 115.6 (q, *J* = 288.5 Hz), 109.4, 107.5, 67.2, 54.2, 38.4, 30.0; HRMS: *m/z* $[MH]^+$ $C_{14}H_{17}F_3N_3O_2$ calcd. 316.1267, found 316.1267.

Synthesis of N-(3-(4,5-dihydrooxazol-2-yl)-6-phenylpyridin-2-yl)-2,2,2-trifluoroacetamide **319**

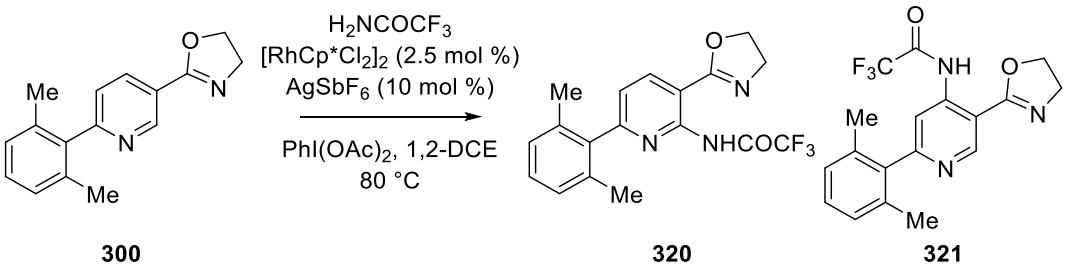


299 **319**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(6-phenylpyridin-3-yl)-4,5-dihydrooxazole **299** (54 mg, 0.24 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 20 h, product **319** was isolated as a colourless amorphous solid (11 mg, 15%).

FTIR: ν_{max}/ cm^{-1} (neat) 2976 (w), 2959 (w), 2916 (w), 1643 (m), 1607 (m), 1546 (s), 1318 (m), 1272 (s), 1143 (m), 1079 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.38 (1H, s, N*H*), 8.26 – 8.10 (3H, m, CH_{ar}), 7.66 (1H, d, *J* = 8.0 Hz, CH_{ar}), 7.53 – 7.42 (3H, m, CH_{ar}), 4.48 (2H, t, *J* = 9.5 Hz, CH_2), 4.20 (2H, t, *J* = 9.5 Hz, CH_2); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.3; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.3, 158.5, 154.4 (q, *J* = 37.5 Hz),149.9, 138.7, 137.5, 130.5, 129.1, 127.6, 115.8 (q, *J* = 289.5 Hz), 115.5, 108.6, 67.5, 54.6; HRMS: *m/z* $[MH]^+$ $C_{16}H_{13}F_3N_3O_2$ calcd. 336.0954, found 336.0953.

Synthesis of N-(3-(4,5-dihydrooxazol-2-yl)-6-(2,6-dimethylphenyl)pyridine-2-yl)-2,2,2-trifluoracetamide **320** *and N-(5-(4,5-dihydrooxazol-2-yl)-2-(2,6-dimethylphenyl)pyridine-4-yl)-2,2,2-trifluoroacetamide* **321**



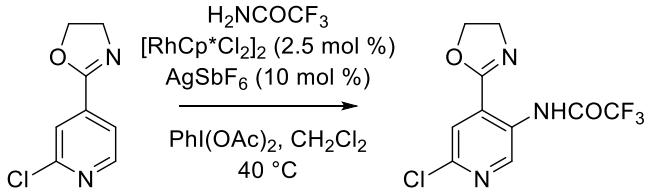
300 **320** **321**

Following general procedure C, using trifluoroacetamide (36 mg, 0.32 mmol) and 2-(6-(2,6-dimethylphenyl)pyridine-3-yl)-4,5-dihydrooxazole **300** (98 mg, 0.39 mmol) with $[Cp^*RhCl_2]_2$ (5 mg, 0.008 mmol), $AgSbF_6$ (11 mg, 0.032 mmol) and $PhI(OAc)_2$ (155 mg, 0.48 mmol) in dichloromethane (3 mL) at 40 °C for 20 h, products **320** and **321** were isolated as colourless solids. (**320**, 15 mg, 13% and **321**, 3 mg, 2%).

320: M.p.: 121 – 122 °C; FTIR: ν_{max}/ cm^{-1} (neat) 1731 (m), 1646 (m), 1614 (m), 1557 (m), 1361 (m), 1150 (s), 1140 (s), 1054 (m), 783 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.23 (1H, s, N*H*), 8.24 (1H, d, *J* = 8.0 Hz, CH_{ar}), 7.21 – 7.15 (2H, m, CH_{ar}), 7.10 (2H, d, *J* = 8.0 Hz, CH_{ar}), 4.50 (2H, t, *J* = 9.5 Hz, CH_2), 4.21 (2H, t, *J* = 9.5 Hz, CH_2), 2.18 (6H, s, CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.3; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.3, 161.7, 154.4 (q, *J* = 38.0 Hz), 149.6, 139.0, 137.8, 136.2, 128.5, 128.1, 121.4, 115.8 (q, *J*= 290.0 Hz), 108.9, 67.5, 54.7, 20.7; HRMS: *m/z* $[MH]^+$ $C_{18}H_{17}F_3N_3O_2$ calcd. 364.1267, found 364.1273.

321: M.p.: 155 – 156 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3008 (w), 2969 (w), 2923 (w), 1735 (m), 1635 (m), 1603 (m), 1571 (s), 1368 (m), 1222 (m), 1143 (s), 1076 (s), ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.76 (1H, s, N*H*), 9.16 (1H, s, CH_{ar}), 8.50 (1H, s, CH_{ar}), 7.21 (1H, dd, *J* = 8.0, 7.0 Hz, CH_{ar}), 7.12 (1H, app. s, CH_{ar}), 7.10 (1H, app. s, CH_{ar}), 4.52 (2H, t, *J* = 9.5 Hz, CH_2), 4.20 (2H, t, *J* = 9.5 Hz, CH_2), 2.07 (6H, s, CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.1; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.7, 163.8, 156.4 (q, *J* = 38.5 Hz), 150.6, 144.2, 139.7, 135.6, 128.5, 127.8, 115.6 (q, *J* = 290.0 Hz), 114.6, 108.4, 67.3, 54.3, 20.3; HRMS: *m/z* [MH]$^+$ $C_{18}H_{17}F_3N_3O_2$ calcd. 364.1267, found 364.1274.

Synthesis of N-(6-chloro-4-(4,5-dihydrooxazol-2-yl)pyridine-3-yl)-2,2,2-trifluoroacetamide **322**

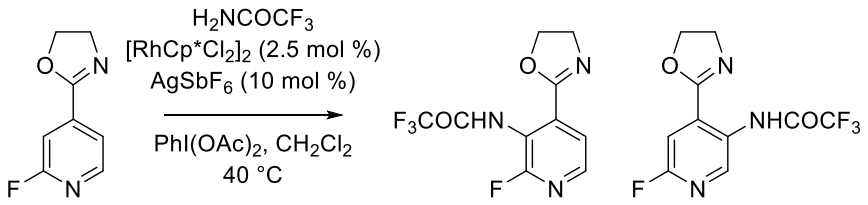


292 **322**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(2-chloropyridin-4-yl)-4,5-dihydrooxazole **292** (44 mg, 0.24 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 20 h, product **322** was isolated as a colourless solid (34 mg, 58%).

M.p.: 98 – 99 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3097 (w), 2921 (w), 2882 (w), 1726 (s), 1589 (m), 1565 (m), 1522 (m), 1307 (s), 1143 (s), 1123 (s), 944 (s), 741 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.18 (1H, s, N*H*), 9.73 (1H, s, CH_{ar}), 7.75 (1H, s, CH_{ar}), 4.51 (2H, t, *J* = 9.5 Hz, CH_2), 4.24 (2H, t, *J* = 9.5 Hz, CH_2); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 75.8; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.6, 155.5 (q, *J* = 38.5 Hz), 147.1, 142.4, 132.2, 123.4, 122.9, 115.7 (q, *J* = 288.5 Hz), 67.6, 54.8; HRMS: *m/z* [MH]$^+$ $C_{10}H_8{}^{35}ClF_3N_3O_2$ calcd. 294.0252, found 294.0252.

Synthesis of N-(4-(4,5-dihydrooxazol-2-yl)-2-fluoropyridin-3-yl)-2,2,2-trifluoroacetamide **323** *and Synthesis of N-(4-(4,5-dihydrooxazol-2-yl)-6-fluoropyridin-3-yl)-2,2,2-trifluoroacetamide* **324**



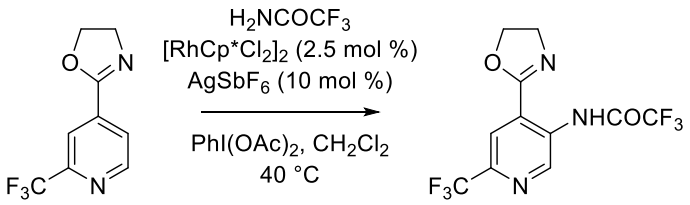
291 **323** **324**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(2-fluoropyridin-4-yl)-4,5-dihydrooxazole **291** (40 mg, 0.24 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 20 h, products **323** and **324** were isolated as colourless solids. (**323**, 30 mg, 53% and **324**, 3 mg, 4%).

323: M.p.: 94 – 95 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3242 (m), 3094 (m), 2971 (w), 1633 (s), 1570 (s), 1554 (s), 1340 (s), 1207 (s), 1154 (s), 1053 (s), 869 (s), 838 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.53 (1H, s, N*H*), 8.20 (1H, dd, *J* = 5.0, 1.0 Hz, CH_{ar}), 7.62 (1H, app. d, *J* = 5.0 Hz, CH_{ar}), 4.50 (2H, t, *J* = 10.0 Hz, CH_2), 4.20 (2H, t, *J* = 10.0 Hz, CH_2); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 64.2, – 75.6; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.2 (d, *J* = 4.5 Hz), 156.7 (d, *J* = 244.5 Hz), 154.8 (q, *J* = 38.5 Hz), 144.6 (d, *J* = 14.5 Hz), 129.0 (d, *J* = 4.5 Hz), 120.3 (d, *J* = 4.5 Hz), 118.7 (d, *J* = 30.5 Hz), 115.8 (q, *J* = 288.5 Hz), 67.7 (s), 55.0 (s); HRMS: *m/z* $[MH]^+$ $C_{10}H_8F_4N_3O_2$ calcd. 278.0547, found 278.0549.

324: M.p.: 71 – 72 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3038 (m), 2987 (m), 1725 (s), 1611 (m), 1542 (s), 1321 (m), 1289 (m), 1150 (s), 970 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.10 (1H, s, N*H*), 9.59 (1H, s, CH_{ar}), 7.40 (1H, d, *J* = 3.0 Hz, CH_{ar}), 4.52 (2H, t, *J* = 10.0 Hz, CH_2), 4.25 (2H, t, *J* = 10.0 Hz, CH_2); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 70.4, – 75.8; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.5 (d, *J* = 3.5 Hz), 160.0 (d, *J* = 237.5 Hz), 155.4 (q, *J* = 38.0 Hz), 140.4 (d, *J* = 15.5 Hz), 131.3 (d, *J* = 5.0 Hz), 125.9 (d, *J* = 8.0 Hz), 115.8 (q, *J* = 288.5 Hz), 108.7 (d, *J* = 42.0 Hz), 67.6, 54.9; HRMS: *m/z* $[MH]^+$ $C_{10}H_8F_4N_3O_2$ calcd. 278.0547, found 278.0546.

Synthesis of N-(4-(4,5-dihydrooxazol-2-yl)-6-(trifluoromethyl)pyridine-3-yl)-2,2,2-trifluoroacetamide **325**

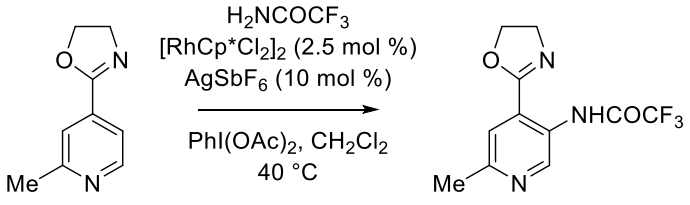


294 **325**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(2-(trifluoromethyl)pyridine-4-yl)-4,5-dihydrooxazole **294** (52 mg, 0.24 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 20 h, product **325** was isolated as a colourless solid (63 mg, 96%).

M.p.: 52 – 53 °C; FTIR: ν_{max}/ cm^{-1} (neat); 3012 (w), 2991 (w), 2916 (w), 1729 (m), 1575 (m), 1322 (m), 1200 (m), 1125 (s), 1100 (s), 947 (s), 915 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.45 (1H, s, N*H*), 10.07 (1H, s, CH_{ar}), 8.11 (1H, s, CH_{ar}), 4.55 (2H, t, *J* = 9.5 Hz, CH_2), 4.27 (2H, t, *J* = 9.5 Hz, CH_2); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 67.7, – 75.8; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.8, 155.9 (q, *J* = 38.5 Hz), 144.2 (q, *J* = 35.5 Hz), 142.7, 135.4, 121.3 (q, *J* = 274.0 Hz), 119.9, 119.4 (app d, *J* = 2.5 Hz), 115.6 (q, *J* = 285.5 Hz), 67.7, 54.9; HRMS: *m/z* $[MH]^+$ $C_{11}H_8F_6N_3O_2$ calcd. 328.0515, found 328.0514.

Synthesis of N-(4-(4,5-dihydrooxazol-2-yl)-6-methylpyridin-3-yl)-2,2,2-trifluoroacetamide **326**

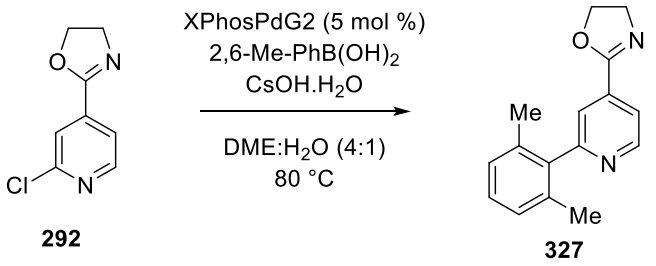


293 **326**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(2-methylpyridin-4-yl)-4,5-dihydrooxazole **293** (39 mg, 0.24 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 20 h, product **326** was isolated as a colourless solid (35 mg, 64%).

M.p.: 101 – 102 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3016 (w), 2966 (w), 1714 (m), 1603 (m), 1525 (m), 1318 (m), 1275 (s), 1147 (s), 954 (m), 754 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.11 (1H, s, N*H*), 9.82 (1H, s, CH_{ar}), 7.58 (1H, s, CH_{ar}), 4.48 (2H, t, *J* = 9.5 Hz, CH_2), 4.20 (2H, t, *J* = 9.5 Hz, CH_2), 2.59 (3H, s, CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 75.8; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.5, 155.3 (q, *J* = 38.0 Hz), 155.1, 141.9, 130.6, 121.4, 121.0, 115.9 (q, *J* = 288.5 Hz), 67.3, 54.8, 24.1; HRMS: *m/z* $[MH]^+$ $C_{11}H_{11}F_3N_3O_2$ calcd. 274.0798, found 274.0801.

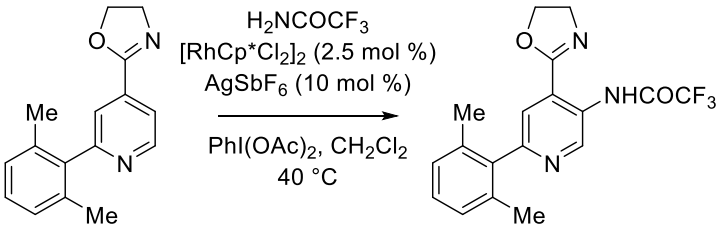
Synthesis of 2-(2-(2,6-dimethylphenyl)pyridine-4-yl)-4,5-dihydrooxazole **327**



A round bottomed flask equipped with a stirrer bar was added 2-(2-chloropyridin-4-yl)-4,5-dihydrooxazole **292** (120 mg, 0.660 mmol), 2,6-dimethylphenyl boronic acid (148 mg, 0.990 mmol), XPhosPdG2 (26 mg, 0.033 mmol) and $CsOH.H_2O$ (188 mg, 1.12 mmol). The flask was sealed and placed under an atmosphere of nitrogen, followed by the addition of the degassed solvents, 1,2-DME (3.73 mL) and H_2O (0.91 mL). The reaction mixture was then stirred at 80 °C for a period of 18 hours. The reaction mixture was then cooled to room temperature, and transferred to a separating funnel. Ethyl acetate was added and the layers were partitioned. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) and ethyl acetate (0% ethyl acetate to 80% ethyl acetate) to afford the oxazoline product **327** as a colourless oil (125 mg, 75%).

FTIR: ν_{max}/ cm^{-1} 3019 (w), 2980 (w), 1650 (m), 1596 (m), 1400 (m), 1225 (m), 1079 (m), 947 (s), 772 (s), 751 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (1H, dd, *J* = 5.0, 1.0 Hz, CH_{ar}), 7.75 (1H, dd, *J* = 5.0, 1.5 Hz, CH_{ar}), 7.74 – 7.73 (1H, m, CH_{ar}), 7.18 (1H, dd, *J* = 8.0, 7.0 Hz, CH_{ar}), 7.10 (1H, app. s, CH_{ar}), 7.08 (1H, app. s, CH_{ar}), 4.46 (2H, t, *J* = 9.5 Hz, CH_2), 4.09 (2H, t, *J* = 9.5 Hz, CH_2), 2.03 (6H, s, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.2, 160.8, 150.3, 140.0, 135.8, 135.6, 128.1, 127.7, 122.8, 120.0, 68.0, 55.2, 20.3; HRMS: *m/z* $[MH]^+$ $C_{16}H_{17}N_2O$ calcd. 253.1335, found 253.1337.

Synthesis of N-(4-(4,5-dihydrooxazol-2-yl)-6-(2,6-dimethylphenyl)pyridine-3-yl)-2,2,2-trifluoroacetamide **328**

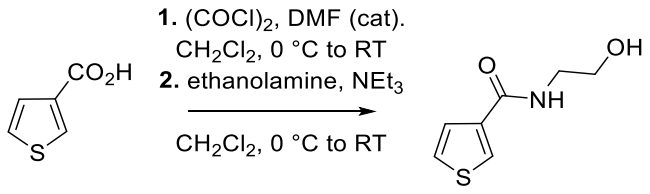


327 **328**

Following general procedure C, using trifluoroacetamide (30 mg, 0.26 mmol) and 2-(2-(2,6-dimethylphenyl)pyridine-4-yl)-4,5-dihydrooxazole **327** (80 mg, 0.32 mmol) with $[Cp^*RhCl_2]_2$ (4 mg, 0.007 mmol), $AgSbF_6$ (9 mg, 0.03 mmol) and $PhI(OAc)_2$ (128 mg, 0.40 mmol) in dichloromethane (2 mL) at 40 °C for 20 h, product **328** was isolated as a colourless solid (67 mg, 70%).

M.p.: 149 – 150 °C; FTIR: ν_{max}/ cm^{-1} (neat) 2995 (w), 2887 (w), 1728 (s), 1607 (m), 1489 (m), 1286 (s), 1193 (s), 1150 (s), 940 (s), 755 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.30 (1H, s, N*H*), 10.07 (1H, s, CH_{ar}), 7.70 (1H, s, CH_{ar}), 7.21 (1H, dd, *J* = 8.0, 7.0 Hz, CH_{ar}), 7.12 (1H, app. s, CH_{ar}), 7.10 (1H, app. s, CH_{ar}), 4.48 (2H, t, *J* = 9.5 Hz, CH_2), 4.24 (2H, t, *J* = 9.5 Hz, CH_{ar}), 2.05 (6H, s, CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 75.8; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.6, 156.5, 155.5 (q, *J* = 38.0 Hz), 142.5, 139.3, 136.1, 131.3, 128.4, 127.8, 122.8, 121.0, 115.9 (q, *J* = 288.5 Hz), 67.3, 54.8, 20.4; HRMS: *m/z* $[MH]^+$ $C_{18}H_{17}F_3N_3O_2$ calcd. 364.1267, found 364.1271.

Synthesis of N-(2-hydroxyethyl)thiophene-3-carboxamide **335**



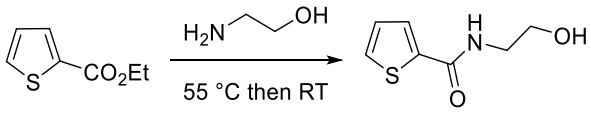
381 **335**

To a round bottomed flask was added 3-thiophene carboxylic acid **381** (500 mg, 3.90 mmol) and dry dichloromethane (20 mL). The reaction was cooled to 0 °C using an ice bath, followed by the addition of oxalyl chloride (1.49 g, 11.7 mmol) and DMF (few drops). The reaction was warmed to room temperature and stirred for 3 h, concentrated and re-suspended in dry dichloromethane (20 mL). After cooling to 0 °C using an ice bath, triethylamine (1.18 g, 11.7 mmol) was added followed by ethanolamine (715 mg, 11.7 mmol). The reaction mixture was then warmed to room temperature and allowed to stir for 16 h. The reaction was then filtered and the filtrate was dry loaded onto silica gel and purified directly by flash column

chromatography on silica gel eluting with dichloromethane and methanol (0% to 10% methanol) to afford the amide product **335** as a colourless oil (555 mg, 83%).

FTIR: ν_{max}/ cm^{-1} (neat) 3297 (m), 3101 (m), 2937 (m), 2859 (m), 1604 (s), 1554 (s), 1507 (s), 1409 (m), 1289 (s), 1057 (s), 823 (s), 745 (s); ^{1}H NMR (400 MHz, d^{6}-DMSO): δ 8.28 (1H, t, *J* = 5.0 Hz, N*H*), 8.12 (1H, dd, *J* = 3.0, 1.0 Hz, C*H*$_{ar}$), 7.57 (1H, dd, *J* = 5.0, 3.0 Hz, C*H*$_{ar}$), 7.50 (1H, dd, *J* = 5.0, 1.0 Hz, C*H*$_{ar}$), 4.73 (1H, t, *J* = 5.5 Hz, O*H*), 3.49 (2H, app. q, *J* = 6.0 Hz, C*H*$_2$), 3.29 (2H, app. q, *J* = 6.0 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, d^{6}-DMSO): δ 162.2, 137.9, 128.5, 126.8, 126.6, 59.8, 41.8; HRMS: *m/z* [MH]$^+$ $C_7H_9NO_2S$ calcd. 172.0427, found 172.0425.

Synthesis of N-(2-hydroxyethyl)thiophene-2-carboxamide **336**[176]

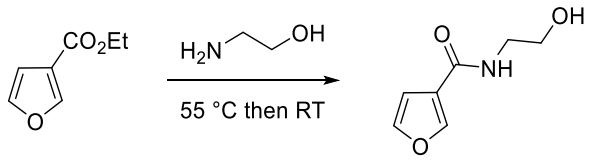


382 **336**

Following general procedure G, using ethyl 2-thiophene carboxylate **382** (2.00 g, 12.8 mmol) and ethanolamine (1.17 g, 19.2 mmol) the amide product **336** was afforded as a colourless solid (845 mg, 39%).

M.p.: 80 – 81 °C; ^{1}H NMR (400 MHz, d^{6}-DMSO): δ 8.47 (1H, s, N*H*), 7.74 (1H, ddd, *J* = 6.0, 4.0, 1.0 Hz, C*H*$_{ar}$), 7.15 – 7.11 (2H, m, C*H*$_{ar}$), 4.74 (1H, t, *J* = 5.5 Hz, O*H*), 3.50 (2H, app. q, *J* = 6.0 Hz, C*H*$_2$), 3.29 (2H, app. q, *J* = 6.0 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, d^{6}-DMSO): δ 161.2, 140.2, 130.6, 127.9, 127.8, 59.8, 42.0.

Synthesis of N-(2-hydroxyethyl)furan-3-carboxamide **337**



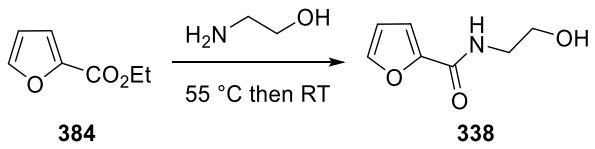
383 **337**

Following general procedure G, using ethyl-3-furoate **383** (1.50 g, 10.7 mmol) and ethanolamine (980 mg, 16.1 mmol) the amide product **337** was afforded as an amorphous colourless solid (442 mg, 27%).

FTIR: ν_{max}/ cm^{-1} (neat) 3246 (m), 3126 (m), 3100 (m), 2974 (w), 1636 (s), 1570 (s), 1551 (s), 1340 (s), 1201 (s), 1157 (s), 1056 (s), 1037 (s), 1008 (s), 876 (s), 838 (s); ^{1}H NMR (400 MHz, d^{6}-DMSO): δ 8.16 (2H, s, N*H* and C*H*$_{ar}$), 7.77 – 7.59 (1H, m, C*H*$_{ar}$), 6.95 – 6.75 (1H, m, C*H*$_{ar}$), 4.73 (1H, s, O*H*), 3.52 – 3.43 (2H, m, C*H*$_2$), 3.26 (2H, app. q, *J* = 6.0 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz,

d^6-DMSO): δ 161.8, 145.1, 143.9, 122.9, 109.0, 59.9. 41.6; HRMS: *m/z* $[MH]^+$ $C_7H_{10}NO_3$ calcd. 156.0655, found 156.0656.

Synthesis of N-(2-hydroxyethyl)furan-2-carboxamide **338**[176]

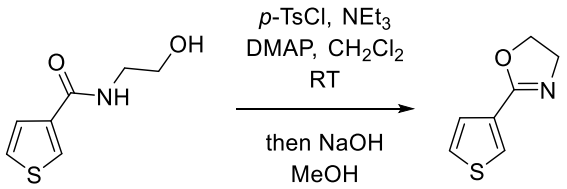


384 **338**

Following general procedure G, using ethyl-2-furoate **384** (1.00 g, 7.13 mmol) and ethanolamine (654 mg, 10.7 mmol) the amide product **338** was afforded as an orange oil (979 mg, 88%).

^{1}H NMR (400 MHz, d^6-DMSO): δ 8.25 (1H, s, N*H*), 7.81 – 7.79 (1H, m, CH_{ar}), 7.08 (1H, dd, *J* = 3.5, 1.0 Hz, CH_{ar}), 6.60 (1H, dd, *J* = 3.5, 1.5 Hz, CH_{ar}), 4.75 (1H, t, *J* = 5.5 Hz, O*H*), 3.48 (2H, app. q, *J* = 6.0 Hz, CH_2), 3.28 (2H, app. q, *J* = 6.0 Hz, CH_2); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 158.0, 148.1, 144.9, 113.3, 111.9, 59.8, 41.4.

Synthesis of 2-(thiophen-3-yl)-4,5-dihydrooxazole **339**

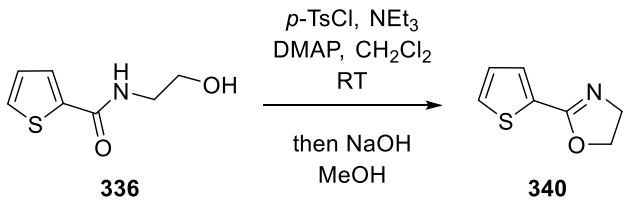


335 **339**

Following general procedure F, using *N*-(2-hydroxyethyl)thiophene-3-carboxamide **335** (327 mg, 1.91 mmol), *p*-TsCl (620 mg, 3.25 mmol), NEt_3 (367 mg, 3.63 mmol), DMAP (47 mg, 0.38 mmol) and dichloromethane (3.2 mL), then using NaOH pellets (229 mg, 5.73 mmol) and MeOH (3.8 mL), the oxazoline product **339** was afforded as a colourless amorphous solid (213 mg, 73%).

FTIR: ν_{max}/ cm^{-1} (neat) 3107 (w), 3067 (w), 2981 (w), 2943 (w), 2902 (w), 1649 (s), 1532 (m), 1516 (m), 1419 (m), 1318 (m), 1251 (s), 1198 (m), 1062 (s), 951 (s), 851 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.83 (1H, dd, *J* = 3.0, 1.0 Hz, CH_{ar}), 7.48 (1H, dd, *J* = 5.0, 1.0 Hz, CH_{ar}), 7.27 (1H, dd, *J* = 5.0, 3.0 Hz, CH_{ar}), 4.33 (2H, t, *J* = 9.5 Hz, CH_2), 3.97 (2H, t, *J* = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 161.0, 130.0, 128.5, 127.2, 126.1, 67.4, 54.8; HRMS: *m/z* $[M]^+$ C_7H_7NOS calcd. 153.0243, found 153.0244.

Synthesis of 2-(thiophen-2-yl)-4,5-dihydrooxazole **340**[177]

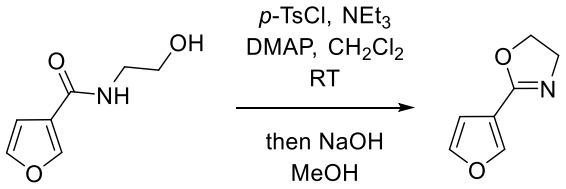


336 **340**

Following general procedure F, using *N*-(2-hydroxyethyl)thiophene-2-carboxamide **336** (300 mg, 1.75 mmol), *p*-TsCl (568 mg, 2.98 mmol), NEt_3 (336 mg, 3.33 mmol), DMAP (43 mg, 0.35 mmol) and dichloromethane (3 mL), then using NaOH pellets (210 mg, 5.25 mmol) and MeOH (3.5 mL), the oxazoline product **340** was afforded as a colourless solid (196 mg, 73%).

M.p.: 59 – 60 °C (lit.,[177] 58 – 60 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (1H, dd, *J* = 3.5, 1.0 Hz, C*H*$_{ar}$), 7.35 (1H, dd, *J* = 5.0, 1.0 Hz, C*H*$_{ar}$), 6.98 (1H, dd, *J* = 5.0, 3.5 Hz, C*H*$_{ar}$), 4.31 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 3.93 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 160.2, 130.3, 130.0, 129.6, 127.5, 67.9, 54.9.

Synthesis of 2-(furan-3-yl)-4,5-dihydrooxazole **341**

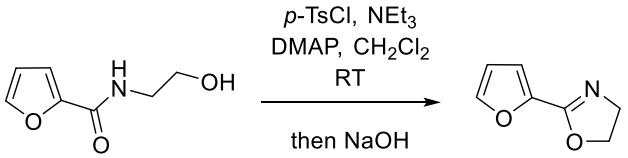


337 **341**

Following general procedure F, using *N*-(2-hydroxyethyl)furan-3-carboxamide **337** (328 mg, 2.11 mmol), *p*-TsCl (685 mg, 3.59 mmol), NEt_3 (406 mg, 4.01 mmol), DMAP (52 mg, 0.42 mmol) and dichloromethane (3.5 mL), then using NaOH pellets (253 mg, 6.33 mmol) and MeOH (4.2 mL), the oxazoline product **341** was afforded as a beige solid (167 mg, 58%).

M.p.: 59 – 60 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3097 (m), 2988 (w), 1667 (m), 1565 (m), 1483 (m), 1167 (s), 1096 (s), 1010 (s), 955 (s), 768 (s), 709 (s), 616 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (1H, s, C*H*$_{ar}$), 7.41 (1H, t, *J* = 1.5 Hz, C*H*$_{ar}$), 6.84 – 6.67 (1H, m, C*H*$_{ar}$), 4.34 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 3.97 (2H, t, *J* = 9.4 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 160.0, 144.8, 143.8, 115.7, 109.5, 67.4, 54.7; HRMS: *m/z* $[MH]^+$ $C_7H_8NO_2$calcd. 138.0550, found 138.0551.

Synthesis of 2-(furan-2-yl)-4,5-dihydrooxazole **342**[178]

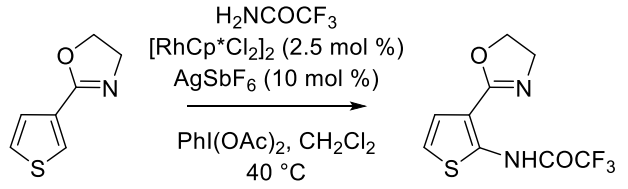


338 **342**

Following general procedure F, using *N*-(2-hydroxyethyl)furan-2-carboxamide **338** (510 mg, 3.29 mmol), *p*-TsCl (1.07 g, 5.59 mmol), NEt_3 (633 mg, 6.25 mmol), DMAP (80 mg, 0.66 mmol) and dichloromethane (5.5 mL), then using NaOH pellets (395 mg, 9.87 mmol) and MeOH (6.6 mL), the oxazoline product **342** was afforded as a colourless solid (303 mg, 67%).

M.p.: 79 – 80 °C (lit.,[178] 78 – 80 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (1H, dd, *J* = 1.5, 1.0 Hz, C*H*$_{ar}$), 6.93 (1H, d, *J* = 3.5 Hz, C*H*$_{ar}$), 6.46 (1H, dd, *J* = 3.5, 1.5 Hz, C*H*$_{ar}$), 4.39 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.04 (2H, t, *J* = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 157.1, 145.2, 143.2, 114.2, 111.6, 67.8, 55.9.

Synthesis of N-(3-(4,5-dihydrooxazol-2-yl)thiophen-2-yl)-2,2,2-trifluoroacetamide **343**

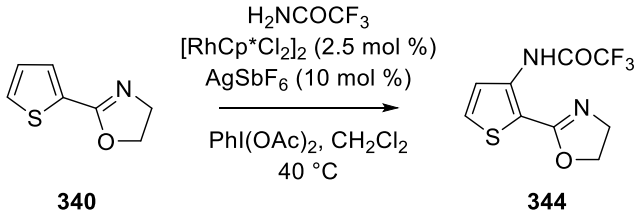


339 **343**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(thiophen-3-yl)-4,5-dihydrooxazole **339** (37 mg, 0.24 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 20 h, product **343** was isolated as a colourless solid (38 mg, 72%).

M.p.: 169 – 170 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3069 (m), 2937 (m), 1639 (s), 1610 (s), 1539 (s), 1314 (s), 1079 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.26 (1H, s, N*H*), 7.18 (1H, d, *J* = 5.5 Hz, C*H*$_{ar}$), 6.94 (1H, d, *J* = 5.5 Hz, C*H*$_{ar}$), 4.43 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.09 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.8, 154.3 (q, *J* = 39.0 Hz), 142.3, 123.4, 118.5, 115.9 (q, *J* = 286.5 Hz), 113.1, 67.4, 53.7; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 75.3; HRMS: *m/z* $[MH]^+$ $C_9H_8F_3N_2O_2S$ calcd. 265.0253, found 265.0253.

Synthesis of N-(3-(4,5-dihydrooxazol-2-yl)thiophen-2-yl)-2,2,2-trifluoroacetamide **344**

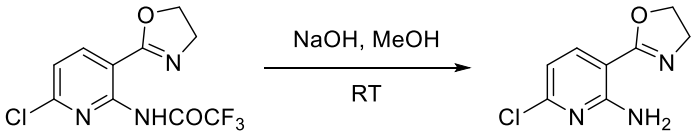


340 **344**

Following general procedure A, using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(thiophen-2-yl)-4,5-dihydrooxazole **340** (37 mg, 0.24 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL) at 40 °C for 20 h, product **344** was isolated as a colourless solid (17 mg, 33%).

M.p.: 121 – 122 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3122 (w), 2955 (w), 1718 (s), 1627 (s), 1248 (m), 1150 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.23 (1H, s, N*H*), 8.07 (1H, d, *J* = 5.5 Hz, CH_{ar}), 7.45 (1H, d, *J* = 5.5 Hz, CH_{ar}), 4.42 (2H, t, *J* = 9.0 Hz, CH_{ar}), 4.12 (2H, t, *J* = 9.0 Hz, CH_{ar}); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 161.1, 154.5 (q, *J* = 38.0 Hz), 138.7, 128.9, 122.1, 116.0 (q, *J* = 288.0 Hz), 111.4, 67.6, 54.5; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 75.8; HRMS: *m/z* $[MH]^+$ $C_9H_8F_3N_2O_2S$ calcd. 265.0253, found 265.0253.

Synthesis of 6-chloro-3-(4,5-dihydrooxazol-2-yl)pyridin-2-amine **347**



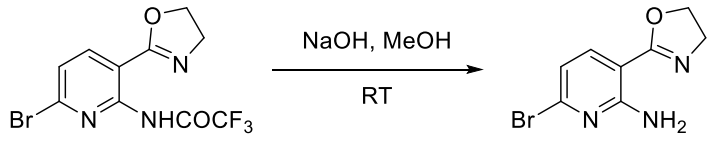
258 **347**

To a round bottomed flask was added *N*-(6-chloro-3-(4,5-dihydrooxazol-2-yl)pyridine-2-yl)-2,2,2-trifluoroacetamide **258** (2.22 g, 7.56 mmol) and methanol (76 mL). NaOH pellets (907 mg, 22.7 mmol) were then added and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated, dissolved in ethyl acetate and deionised water and transferred to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the aniline product **347** as a colourless solid (1.33 g, 89%). (NB: Trace amounts of the regioisomer were present in the isolated sample).

FTIR: ν_{max}/ cm^{-1} (neat) 3330 (m), 3144 (m), 2984 (w), 2944 (w), 1643 (s), 1550 (s), 1440 (m), 1464 (m), 1357 (m), 1068 (s), 1029 (s), 929 (s), 765 (s); ^{1}H NMR (400 MHz, d^6-DMSO): δ 8.25 (1H, br s, N*H*), 7.85 (1H, d, *J* = 8.0 Hz, CH_{ar}), 7.59 (1H, br s, N*H*), 6.64 (1H, d, *J* = 8.0 Hz, CH_{ar}),

4.34 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.02 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 162.1, 158.0, 151.2, 140.3, 110.5, 102.2, 66.3, 54.4; HRMS: *m/z* [MH]$^+$ $C_8H_9{}^{35}ClN_3O$ calcd. 198.0429, found 198.0426.

Synthesis of 6-bromo-3-(4,5-dihydrooxazol-2-yl)pyridin-2-amine **348**

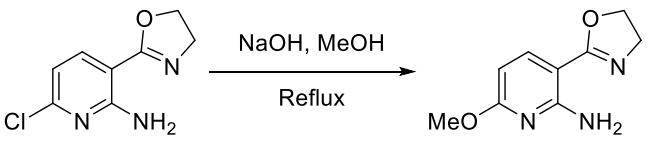


307 **348**

To a round bottomed flask was added *N*-(6-bromo-3-(4,5-dihydrooxazol-2-yl)pyridine-2-yl)-2,2,2-trifluoroacetamide **307** (1.03 g, 3.01 mmol) and methanol (31 mL). NaOH pellets (369 mg, 9.22 mmol) were then added and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated, dissolved in ethyl acetate and deionised water and transferred to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the aniline product **348** as colourless solid (664 mg, 89%). (NB: Trace amounts of the regioisomer were present in the isolated sample).

FTIR: ν_{max}/ cm^{-1} (neat) 3340 (m), 3266 (w), 3149 (m), 2928 (w), 2878 (w), 1645 (m), 1608 (m), 1551 (s), 1461 (m), 1424 (m), 1370 (m), 1283 (s), 1260 (s), 1072 (s), 915 (s), 767 (s); ^{1}H NMR (400 MHz, d^6-DMSO): δ 7.74 (1H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 6.78 (1H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 4.34 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.02 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 162.2, 158.0, 142.6, 139.9, 114.4, 102.4, 66.3, 54.5; HRMS: *m/z* [MH]$^+$ $C_8H_9{}^{79}BrN_3O$ calcd. 241.9924, found 241.9925.

Synthesis of 3-(4,5-dihydrooxazol-2-yl)-6-methoxypyridin-2-amine **349**



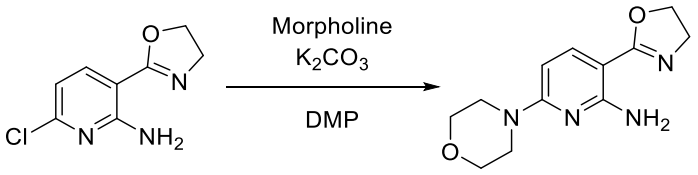
347 **349**

To a round bottomed flask was added 6-chloro-3-(4,5-dihydrooxazol-2-yl)pyridin-2-amine **347** (50 mg, 0.25 mmol) and methanol (2.5 mL). NaOH pellets (101 mg, 2.50 mmol) were added in one portion. The reaction was stirred and heated at reflux for a period of 24 hours. The reaction mixture was allowed to cool to room temperature, and ethyl acetate and

deionised water were added. The mixture was transferred to a separating funnel and the layers were partitioned. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the product **349** as a colourless solid (47 mg, 98%). (NB: Trace amounts of the regioisomer were present in the isolated sample).

FTIR: ν_{max}/ cm^{-1} (neat) 3330 (w), 3148 (w), 2984 (w), 1639 (m), 1589 (m), 1553 (m), 1460 (m), 1297 (s), 1261 (s), 1061 (m), 1022 (m), 765 (s); ^{1}H NMR (400 MHz, d^6-DMSO): δ 7.75 (1H, d, *J* = 8.5 Hz, C*H*$_{ar}$), 5.99 (1H, d, *J* = 8.5 Hz, C*H*$_{ar}$), 4.28 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 3.97 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 164.5, 162.9, 157.9, 140.1, 97.3, 95.7, 65.9, 54.2, 53.0; HRMS: *m/z* $[MH]^+$ $C_9H_{12}N_3O_2$ calcd. 194.0924, found 194.0923.

Synthesis of 3-(4,5-dihydrooxazol-2-yl)-6-morpholinopyridin-2-amine **351**

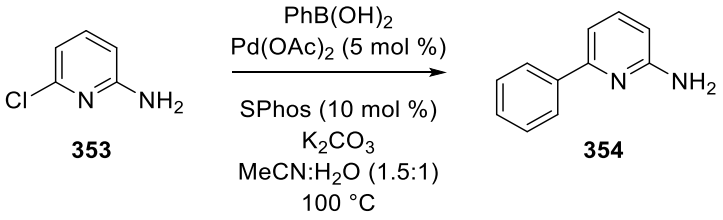


347 **351**

To a round bottomed flask containing 6-chloro-3-(4,5-dihydrooxazol-2-yl)pyridin-2-amine **347** (50 mg, 0.25 mmol) and K_2CO_3 (173 mg, 1.25 mmol). The flask was placed under an atmosphere of nitrogen followed by the addition of DMF (2.5 mL) and morpholine (44 mg, 0.50 mmol). The reaction mixture was then stirred and heated at 120 °C for a period of 48 hours. The reaction mixture was cooled to room temperature and concentrated. The reaction mixture was dry loaded onto silica gel and purified by flash column chromatography eluting with petroleum ether (40/60) and ethyl acetate (0% to 40% ethyl acetate) to afford the product **351** as a colourless solid (39 mg, 63%).

FTIR: ν_{max}/ cm^{-1} (neat) 3461 (w), 3376 (w), 3258 (w), 2980 (w), 2883 (w), 1632 (m), 1603 (s), 1368 (m), 1278 (s), 1111 (m), 1061 (w), 765 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (1H, d, *J* = 8.5 Hz, C*H*$_{ar}$), 5.94 (1H, d, *J* = 8.5 Hz, C*H*$_{ar}$), 4.28 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.03 (2H, t, *J* = 9.5 Hz, C*H*$_{ar}$), 3.82 – 3.70 (4H, m, C*H*$_2$), 3.63 – 3.49 (4H, m, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.2, 157.9, 151.0, 139.5, 108.4, 95.2, 66.9, 66.2, 54.8, 45.1; HRMS: *m/z* $[MH]^+$ $C_{12}H_{17}N_4O_2$ calcd. 249.1346, found 249.1349.

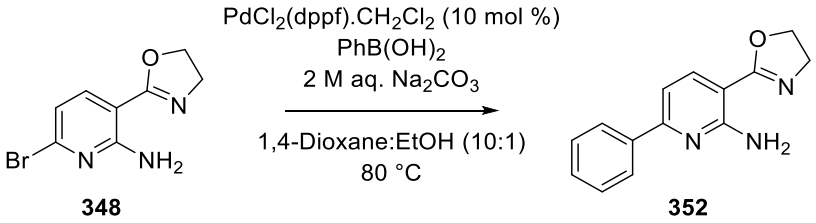
Synthesis of 6-phenylpyridin-2-amine **354**[155]



To a Schlenk tube was added 2-amino-6-chloropyridine **353** (32 mg, 0.25 mmol), phenyl boronic acid (46 mg, 0.38 mmol), $Pd(OAc)_2$ (3 mg, 0.01 mmol), SPhos (10 mg, 0.025 mmol) and K_2CO_3 (104 mg, 0.75 mmol). The tube was fitted with a rubber septum, and placed under an atmosphere of nitrogen, followed by the addition of the degassed solvents MeCN (0.38 mL) and H_2O (0.25 mL). The septum was replaced by a Teflon screwcap under nitrogen flow. The reaction mixture was stirred at 100 °C for 16 h, followed by cooling to room temperature. The reaction mixture was then diluted by the addition of ethyl acetate and H_2O and transferred to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was then purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) and ethyl acetate (0% to 60% ethyl acetate) to afford the cross-coupled product **354** as a colourless oil (26 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 – 7.90 (2H, m, C*H*$_{ar}$), 7.54 – 7.34 (4H, m, C*H*$_{ar}$), 7.10 (1H, dd, *J* = 7.5, 0.5 Hz, C*H*$_{ar}$), 6.46 (1H, dd, *J* = 7.5, 0.5 Hz, C*H*$_{ar}$), 4.53 (2H, s, N*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 158.4, 156.3, 139.8, 138.5, 128.7, 128.7, 126.9, 111.1, 107.2.

Synthesis of 3-(4,5-dihydrooxazol-2-yl)-6-phenylpyridin-2-amine **352**

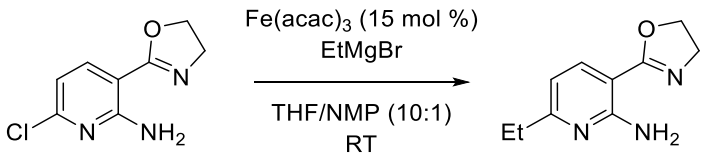


To a round bottomed flask equipped with a reflux condenser was added 6-bromo-3-(4,5-dihydrooxazol-2-yl)pyridin-2-amine **348** (61 mg, 0.25 mmol), phenyl boronic acid (79 mg, 0.65 mmol) and $PdCl_2(dppf).CH_2Cl_2$ (21 mg, 0.025 mmol). The reaction system was evacuated and refilled with nitrogen (3 cycles) followed by the addition of the degassed solvents ethanol (0.5 mL) and 1,4-dioxane (5 mL). Degassed aqueous Na_2CO_3 (2M, 0.76 mL) was then added. The reaction mixture was then stirred and heated at 80 °C for a period of 18 hours. The

reaction mixture was then cooled to room temperature and concentrated. The residue was dissolved in NaOH aqueous solution (10% (w/v)) and ethyl acetate (sonication was necessary to completely dissolve the residue). The mixture was transferred to a separating funnel and the layers were partitioned. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography eluting with petroleum ether (40/60) and ethyl acetate (0% to 30% ethyl acetate) to afford the product **352** as a yellow solid (35 mg, 58%).

M.p.: 131 – 132 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3354 (m), 3280 (w), 3159 (w), 3019 (w), 2972 (w), 2908 (w), 2871 (w), 1638 (s), 1615 (s), 1575 (s), 1555 (s), 1454 (s), 1364 (s), 1253 (s), 1059 (s), 1029 (s), 942 (m), 918 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 – 7.96 (3H, m, CH_{ar}), 7.51 – 7.34 (3H, m, CH_{ar}), 7.08 (1H, d, *J* = 8.0 Hz, CH_{ar}), 4.36 (2H, t, *J* = 9.5 Hz, CH_2), 4.12 (2H, t, *J* = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.8, 158.7, 158.0, 139.1, 138.8, 129.4, 128.7, 127.2, 109.4, 103.4, 66.5, 55.1; HRMS: *m/z* $[MH]^+$ $C_{14}H_{14}N_3O$ calcd. 240.1131, found 240.1130.

Synthesis of 3-(4,5-dihydrooxazol-2-yl)-6-ethylpyridin-2-amine **355**

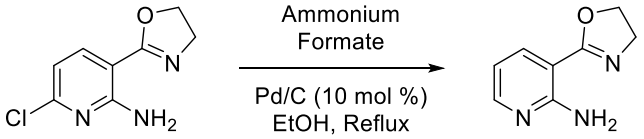


347 **355**

To a round bottomed flask was added 6-chloro-3-(4,5-dihydrooxazol-2-yl)pyridin-2-amine **347** (50 mg, 0.25 mmol) and $Fe(acac)_3$ (13 mg, 0.038 mmol). The flask was placed under an atmosphere of nitrogen followed by the addition of dry THF (2.27 mL) and NMP (0.23 mL). Ethylmagnesium bromide (0.28 mL, 2.7 M in diethyl ether, 0.75 mmol) was added to the stirred solution dropwise, resulting in colour changes of red to brown to violet. Upon complete addition the reaction mixture was stirred at room temperature for a period of 2 hours. The reaction was then quenched by the addition of saturated NH_4Cl aq. solution. NaOH aqueous solution (10% (w/v)) was then added followed by ethyl acetate, and the mixture was transferred to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography eluting with petroleum ether (40/60) and ethyl acetate (0% to 40% ethyl acetate) to afford the product **355** as a yellow solid (27 mg, 57%).

M.p.: 102 – 103 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3323 (w), 3263 (w), 3132 (w), 2972 (w), 1638 (s), 1615 (m), 1585 (s), 1454 (s), 1364 (s), 1257 (s), 1066 (s), 1032 (s), 935 (s), 814 (s), 798 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (1H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 6.48 (1H, d, *J* = 8.0 Hz, C*H*$_{ar}$), 4.32 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.07 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 2.64 (2H, q, *J* = 7.5 Hz, C*H*$_2$), 1.25 (3H, t, *J* = 7.5 Hz, C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.9, 163.0, 157.9, 138.4, 110.7, 102.3, 66.4, 55.0, 31.6, 13.7; HRMS: *m/z* [MH]$^+$ $C_{10}H_{14}N_3O$ calcd. 192.1131, found 192. 1131.

Synthesis of 3-(4,5-dihydrooxazol-2-yl)pyridine-2-amine **356**

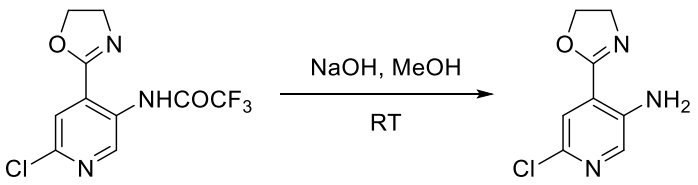


347 **356**

To a round bottomed flask equipped with a stirrer bar and a reflux condenser was added 6-chloro-3-(4,5-dihydrooxazol-2-yl)pyridin-2-amine **347** (50 mg, 0.25 mmol), ammonium formate (315 mg, 5.0 mmol) and ethanol (2.5 mL). The flask was placed under an atmosphere of nitrogen followed by the addition of Pd/C (3 mg, 0.03 mmol). The reaction was then stirred and heated at 100 C for a period of 2 hours. The reaction was then cooled to room temperature and filtered through a plug of Celite, rinsing with methanol. The filtrate was concentrated and the residue was purified by flash column chromatography on silica gel eluting wit petroleum ether (40/60) and ethyl acetate (0% to 60% ethyl acetate) to afford the product **356** as a colourless solid (28 mg, 69%).

M.p.: 116 – 117 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3317 (m), 3260 (m), 3129 (m), 2978 (w), 2871 (w), 1645 (m), 1618 (m), 1571 (m), 1478 (m), 1451 (m), 1374 (m). 1257 (s), 1069 (s), 1032 (s), 945 (s), 774 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (1H, dd, *J* = 5.0, 2.0 Hz, C*H*$_{ar}$), 7.92 (1H, dd, *J* = 7.5, 2.0 Hz, C*H*$_{ar}$), 6.60 (1H, dd, *J* = 7.5, 5.0 Hz, C*H*$_{ar}$), 4.34 (2H, t, *J* = 9.5 Hz, C*H*$_2$), 4.09 (2H, t, *J* = 9.5 Hz, C*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.7, 158.2, 151.2, 138.1, 112.4, 104.9, 66.5, 55.0; HRMS: *m/z* [MH]$^+$ $C_8H_{10}N_3O$ calcd. 164.0818, found 164.0819.

Synthesis of 6-chloro-4-(4,5-dihydrooxazol-2-yl)pyridin-3-amine **357**

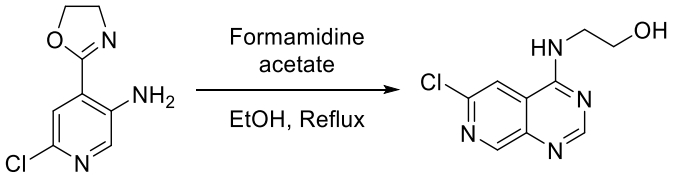


322 **357**

To a round bottomed flask was added *N*-(6-chloro-4-(4,5-dihydrooxazol-2-yl)pyridine-3-yl)-2,2,2-trifluoroacetamide **322** (680 mg, 2.31 mmol) and methanol (23 mL). NaOH pellets (277 mg, 6.93 mmol) were then added and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated, dissolved in ethyl acetate and deionised water and transferred to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the aniline product **357** as colourless solid (364 mg, 80%).

M.p.: 184 – 185 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3347 (w), 3151 (w), 2980 (w), 1643 (m), 1614 (m), 1475 (s), 1364 (s), 1290 (m), 1247 (m), 1111 (m), 951 (s), 869 (s); ^{1}H NMR (400 MHz, d^6-DMSO): δ 8.02 (1H, s, CH_{ar}), 7.37 (1H, s, CH_{ar}), 7.11 (2H, s, NH_2), 4.36 (2H, t, *J* = 9.5 Hz, CH_2), 4.07 (2H, t, *J* = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 162.0, 144.0, 138.8, 135.0, 121.6, 115.6, 66.7, 55.3; HRMS: *m/z* $[MH]^+C_8H_9{}^{35}ClN_3O$ calcd. 198.0429, found 198.0428.

Synthesis of 2-((6-chloropyrido[3,4-d]pyrimidin-4-yl)amino)ethanol **358**

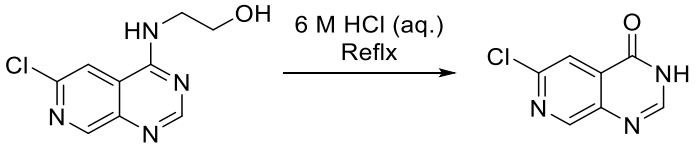


357 **358**

6-Chloro-4-(4,5-dihydrooxazol-2-yl)pyridin-3-amine **357** (67 mg, 0.34 mmol) was dissolved in ethanol (3.4 mL) and formamidine acetate (141 mg, 1.36 mmol) was added, and the mixture heated at reflux for 24 hours. After cooling to room temperature, the reaction mixture was dry loaded onto silica gel and purified by flash column chromatography eluting with dichloromethane and methanol (0% to 15% methanol) to afford the quinazoline product **358** as a colourless solid (62 mg, 81%).

M.p.: 179 – 180 °C; FTIR: ν_{max}/ cm^{-1} (neat) 3433 (m), 3233 (m), 2898 (m), 1617 (s), 1593 (s), 1560 (s), 1425 (s), 1332 (s), 1279 (s), 1084 (s), 865 (s), 751 (s); ^{1}H NMR (400 MHz, d^6-DMSO): δ 8.90 (1H, s, CH_{ar}), 8.72 (1H, app d, *J* = 4.5 Hz, N*H*), 8.56 (1H, s, CH_{ar}), 8.38 (1H, s, CH_{ar}), 4.85 (1H, s, O*H*), 3.77 – 3.52 (4H, m, (CH_2)$_2$); ^{13}C NMR (100.6 MHz, d^6-DMSO): δ 158.1, 156.9, 152.0, 144.1, 143.2, 121.6, 115.8, 58.7, 43.4; HRMS: *m/z* $[MH]^+$ $C_9H_{10}{}^{35}ClN_4O$ calcd. 225.0538, found 225.0538.

Synthesis of 6-chloropyrido[3,4-d]pyrimidin-4(3H)-one **359**[179]

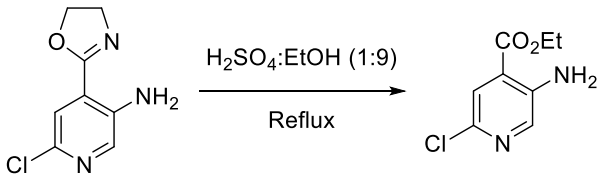


358 **359**

Following general procedure E, using 2-((6-chloropyrido[3,4-d]pyrimidin-4-yl)amino)ethanol **358** (750 mg, 3.34 mmol) and 6 M HCl aq. (25 mL), the quinazolinone product **359** was afforded as a colourless solid (342 mg, 56%).

M.p.: > 300 °C; ^{1}H NMR (400 MHz, d^{6}-DMSO): δ 12.75 (1H, s, N*H*), 8.90 (1H, d, *J* = 0.5 Hz, CH_{ar}), 8.24 (1H, s, N=C*H*), 7.97 (1H, d, *J* = 0.5 Hz, CH_{ar}); ^{13}C NMR (100.6 MHz, d^{6}-DMSO): δ 158.9, 151.0, 147.7, 146.2, 142.9, 130.6, 118.5.

Synthesis of ethyl 5-amino-2-chloroisonicotinate **360**



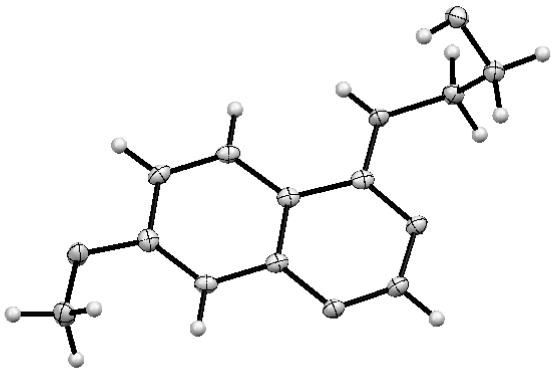
357 **360**

To a round bottomed flask equipped with a reflux condenser was added 6-chloro-4-(4,5-dihydrooxazol-2-yl)pyridin-3-amine **357** (50 mg, 0.25 mmol) followed by ethanol (6.3 mL) and concentrated H_2SO_4 (0.7 mL). The reaction mixture was stirred and heated at reflux for 20 h. The reaction was then allowed to cool to room temperature and diluted with water. The reaction mixture was then neutralised to pH 6 using a saturated aqueous solution of $NaHCO_3$ and transferred to a separating funnel with ethyl acetate. The layers were partitioned and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were then dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether (40/60) and ethyl acetate (0% to 40% ethyl acetate) to afford the ester product **360** as an orange amorphous solid (20 mg, 40%).

FTIR: ν_{max}/ cm^{-1} (neat) 2989 (w), 1701 (m), 1274 (m), 767 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 – 7.96 (1H, m, CH_{ar}), 7.66 – 7.65 (1H, m, CH_{ar}), 5.12 (2H, br s, NH_2), 4.37 (2H, q, *J* = 7.0 Hz, CH_2), 1.40 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 166.0, 143.9, 139.9, 137.9, 123.5, 119.0, 61.7, 14.3; HRMS: *m/z* $[MH]^+$ $C_8H_{10}{}^{35}ClN_2O_2$ calcd. 201.0425, found 201.0429.

Appendices

Appendix One: Crystallographic Data for 187



Identification code	**187**	
Empirical formula	C11 H13 N3 O2	
Formula weight	219.24	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 13.1709(3) Å	α = 90°.
	b = 7.4238(2) Å	β = 90°.
	c = 20.8269(6) Å	γ = 90°.
Volume	2036.42(9) $Å^3$	
Z	8	
Density (calculated)	1.430 Mg/m^3	
Absorption coefficient	0.835 mm^{-1}	
F(000)	928	
Crystal size	0.12 x 0.10 x 0.05 mm^3	
Theta range for data collection	4.25 to 66.65°.	
Index ranges	-15<=h<=15, -8<=k<=8, -24<=l<=24	
Reflections collected	26383	
Independent reflections	1800 [R(int) = 0.0364]	
Completeness to theta = 66.65°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9595 and 0.9065	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1800 / 0 / 147	
Goodness-of-fit on F^2	0.891	
Final R indices [I>2sigma(I)]	R1 = 0.0354, wR2 = 0.0878	

R indices (all data)	R1 = 0.0396, wR2 = 0.0919
Largest diff. peak and hole	0.133 and -0.275 e.Å^{-3}

Table 23 – Crystal data and structure refinement for **187**

x	y	z	U(eq)
O(1)	2000(1)	1688(1)	4558(1)	19(1)
O(2)	3856(1)	2721(1)	796(1)	20(1)
N(1)	666(1)	4442(2)	2638(1)	16(1)
N(2)	1822(1)	5458(2)	1821(1)	15(1)
N(3)	3551(1)	5057(2)	1898(1)	15(1)
C(1)	998(1)	1213(2)	4760(1)	21(1)
C(2)	2093(1)	2492(2)	3975(1)	16(1)
C(3)	3104(1)	2694(2)	3759(1)	16(1)
C(4)	3295(1)	3442(2)	3173(1)	15(1)
C(5)	2490(1)	4043(2)	2777(1)	14(1)
C(6)	1485(1)	3852(2)	2998(1)	14(1)
C(7)	1291(1)	3070(2)	3603(1)	15(1)
C(8)	904(1)	5209(2)	2092(1)	16(1)
C(9)	2627(1)	4864(2)	2156(1)	14(1)
C(10)	3729(1)	5749(2)	1252(1)	17(1)
C(11)	3394(1)	4443(2)	730(1)	18(1)

Table 24 – Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **187**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

O(1)-C(2)	1.3577(17)
O(1)-C(1)	1.4298(16)
O(2)-C(11)	1.4226(16)
O(2)-H(2)	0.8400
N(1)-C(8)	1.3100(18)
N(1)-C(6)	1.3861(17)
N(2)-C(9)	1.3444(17)
N(2)-C(8)	1.3473(17)
N(3)-C(9)	1.3379(17)
N(3)-C(10)	1.4592(17)
N(3)-H(3N)	0.8800
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(2)-C(7)	1.3781(19)
C(2)-C(3)	1.4140(18)
C(3)-C(4)	1.3636(19)
C(3)-H(3)	0.9500
C(4)-C(5)	1.4150(19)
C(4)-H(4)	0.9500
C(5)-C(6)	1.4087(18)
C(5)-C(9)	1.4408(19)
C(6)-C(7)	1.4098(19)
C(7)-H(7)	0.9500
C(8)-H(8)	0.9500
C(10)-C(11)	1.5226(19)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900

C(2)-O(1)-C(1)	117.05(10)
C(11)-O(2)-H(2)	109.5
C(8)-N(1)-C(6)	114.90(11)
C(9)-N(2)-C(8)	116.44(11)
C(9)-N(3)-C(10)	123.65(11)
C(9)-N(3)-H(3N)	118.2
C(10)-N(3)-H(3N)	118.2
O(1)-C(1)-H(1A)	109.5

O(1)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
O(1)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
O(1)-C(2)-C(7)	124.76(12)
O(1)-C(2)-C(3)	114.58(11)
C(7)-C(2)-C(3)	120.66(12)
C(4)-C(3)-C(2)	120.07(12)
C(4)-C(3)-H(3)	120.0
C(2)-C(3)-H(3)	120.0
C(3)-C(4)-C(5)	120.83(12)
C(3)-C(4)-H(4)	119.6
C(5)-C(4)-H(4)	119.6
C(6)-C(5)-C(4)	118.74(12)
C(6)-C(5)-C(9)	117.02(12)
C(4)-C(5)-C(9)	124.24(12)
N(1)-C(6)-C(5)	121.50(12)
N(1)-C(6)-C(7)	118.21(11)
C(5)-C(6)-C(7)	120.28(12)
C(2)-C(7)-C(6)	119.42(12)
C(2)-C(7)-H(7)	120.3
C(6)-C(7)-H(7)	120.3
N(1)-C(8)-N(2)	129.69(12)
N(1)-C(8)-H(8)	115.2
N(2)-C(8)-H(8)	115.2
N(3)-C(9)-N(2)	118.28(12)
N(3)-C(9)-C(5)	121.31(12)
N(2)-C(9)-C(5)	120.41(12)
N(3)-C(10)-C(11)	112.83(11)
N(3)-C(10)-H(10A)	109.0
C(11)-C(10)-H(10A)	109.0
N(3)-C(10)-H(10B)	109.0
C(11)-C(10)-H(10B)	109.0
H(10A)-C(10)-H(10B)	107.8
O(2)-C(11)-C(10)	112.29(11)
O(2)-C(11)-H(11A)	109.1
C(10)-C(11)-H(11A)	109.1
O(2)-C(11)-H(11B)	109.1
C(10)-C(11)-H(11B)	109.1

H(11A)-C(11)-H(11B) 107.9

Symmetry transformations used to generate equivalent atoms.

Table 25 – Bond lengths [Å] and angles [°] for **187**

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	14(1)	26(1)	18(1)	6(1)	-1(1)	-2(1)
O(2)	19(1)	19(1)	20(1)	0(1)	4(1)	1(1)
N(1)	12(1)	17(1)	18(1)	0(1)	-1(1)	0(1)
N(2)	12(1)	15(1)	18(1)	0(1)	-1(1)	0(1)
N(3)	10(1)	19(1)	15(1)	1(1)	-1(1)	0(1)
C(1)	16(1)	28(1)	19(1)	5(1)	1(1)	-3(1)
C(2)	18(1)	14(1)	16(1)	-1(1)	-1(1)	-2(1)
C(3)	14(1)	15(1)	20(1)	-1(1)	-4(1)	1(1)
C(4)	12(1)	14(1)	19(1)	-3(1)	0(1)	-1(1)
C(5)	14(1)	12(1)	17(1)	-3(1)	-1(1)	-1(1)
C(6)	12(1)	12(1)	18(1)	-3(1)	-1(1)	0(1)
C(7)	12(1)	15(1)	18(1)	-2(1)	1(1)	-2(1)
C(8)	13(1)	16(1)	19(1)	0(1)	-1(1)	1(1)
C(9)	14(1)	11(1)	17(1)	-4(1)	-1(1)	0(1)
C(10)	13(1)	19(1)	18(1)	3(1)	1(1)	-1(1)
C(11)	17(1)	21(1)	17(1)	3(1)	0(1)	1(1)

Table 26 – Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **187**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

x	y	z	U(eq)
H(2)	3543	2121	1075	29
H(3N)	4081	4751	2131	18
H(1A)	606	2310	4843	32
H(1B)	1036	493	5153	32
H(1C)	665	510	4422	32
H(3)	3652	2308	4022	20
H(4)	3976	3560	3029	18
H(7)	614	2942	3753	18
H(8)	346	5655	1851	19
H(10A)	4462	6005	1200	20
H(10B)	3356	6898	1200	20
H(11A)	2647	4304	747	22
H(11B)	3572	4950	305	22

Table 27 – Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **187**

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