Investigations into direct *N*-arylation reactions

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The candidate confirms that the work submitted is their own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chapter 2 section 2.1 contains work from the jointly authored paper.

'Continous Flow for the Photochemical C-H Amination of Arenes', Sebastian C. Cosgrove, Gayle E. Douglas, Steven A. Raw, Stephen P. Marsden, ChemPhotoChem, 2018, 2, 851-854.

The Substrate scope for both the chloroamines and THQ's in flow were carried out by the candidate Gayle E. Douglas.

Initial optimisation of the reactors was carried out by Sebastian C. Cosgrove.

Abstract

This thesis details investigations and the optimisation of *N*-arylation reactions using precious-metal-free conditions. It is an important motif in several pharmaceutical and agrochemical molecules. In 1965 Bock *et al* described the use of concentrated sulfuric acid and acetic acid as the solvent in a modified version of the Hofmann-Löffler-Freytag to carry out direct amination of aromatics via *N*-haloamines.[1]

The first section looks at the UV irradiation chemistry where we utilised *N*-halo species which under photolytic conditions form the aminium radicals. Several examples of tetrahydroquinolines being synthesised in flow have been carried out**.**

Investigations into amination of electron-deficient heterocycles such as pyridines were also investigated. Unfortunately, no *N*-arylation was observed under the various conditions trialled.

Similar investigations have been carried out into the photolysis of *N*-chloroamides with varying degrees of chain length and position of the amide. Under neutral conditions in the presence of a Lewis acid some success in *N*-arylation reactions has been observed.

In the second section the use of iron(II) salts has been investigated towards the *N*-arylation reaction via the aminium radial generated from the *N*-halo species. A variety of substrates containing electron-poor and electron-rich aromatic rings have been synthesised under these conditions.

This methodology has been expanded to include an iron salt variant of the work with examples of intramolecular and intermolecular direct *N*-arylation described. Using our methodology some simple aromatics and the drug naproxen have now been aminated successfully. The use of hydroxylamines as alternative precursors to the aminium radical has also been investigated with some success in the synthesis of various substrates.

Acknowledgements

Firstly my thanks go to Professor Steve Marsden for his support and guidance throughout my PhD as well as for the opportunity to work within his group. Without his input and guidance I would not be where I am today.

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Abbreviations

°C- degrees Celsius

Δ - heat

δ – chemical shift

Ar – aryl

Acac- acetylacetone

Bn- benzyl

Bu- butyl

Br – broad

Cat,- catalytic

Conc – concentrated

COSY – correlation spectroscopy

d- doublet

DCM - dichloromethane

dd - doublet of doublets

DEPT – distortionless enchancement by polarization transfer

dFppy-2(4,6-difluorophenyl)pyridine

DIPEA-diisopropylethylamine

Dppf- 1,1'-bis(diphenylphosphino)ferrocene

eq – equivalents

ESI- electrospray ionisation

FEP- fluoroethylene propylene

FR- flow rate

FT-IR- fourier transform infrared

HLF- Hoffmann-Löffler-Freytag

HRMS- high resolution mass spectrometry

Hz- Hertz

I.D.- internal diameter

J – coupling constant

$LiAlH_4$- lithium aluminium hydride

LC-MS – Liquid chromatography mass spectrometry

M- molar

m- multiplet

Me - Methyl

mmol - millimole

M.p- melting point

MHz – megahertz

MTBE- methyl *tert*-butyl ether

NCS- *N*-chlorosuccinimide

NIS- *N*-iodosuccinimide

NMR- Nuclear Magnetic Resonance

NOSEY- nuclear overhauser effect spectroscopy

ppm- parts per million

PTFE-polytetrafluoroethylene

q- quartet

r- radius

RT- room temperature

R.V.- reactor volume

s- singlet

SET- single electron transfer

STAB- sodium triacetoxyborohydride

STY- Space Time Yield

t- triplet

t – tertiary

^{t}Bu – *tert*-butyl

TBTU- *O*-(benxotriazol-1-yl)*N*,*N*,*N*',*N*''-tetramethyluronium tetrafluoroborate

THF-tetrahydrofuran

THQ-tetrahydroquinoline

TLC – thin layer chromatography

t_R- residence time

UV – ultraviolet

V-volume

W - Watt

wt- weight

Contents

Chapter 1 Introduction

1.1 Importance of Aryl C-N Bond Formation in the Pharmaceutical Industry

Within the pharmaceutical industry there are many examples of drug molecules which contain an aryl C-N bond. A few examples of important drug molecules that contain this motif are shown in Figure 1.1. This makes research into the different ways this bond can be formed vital.[2]

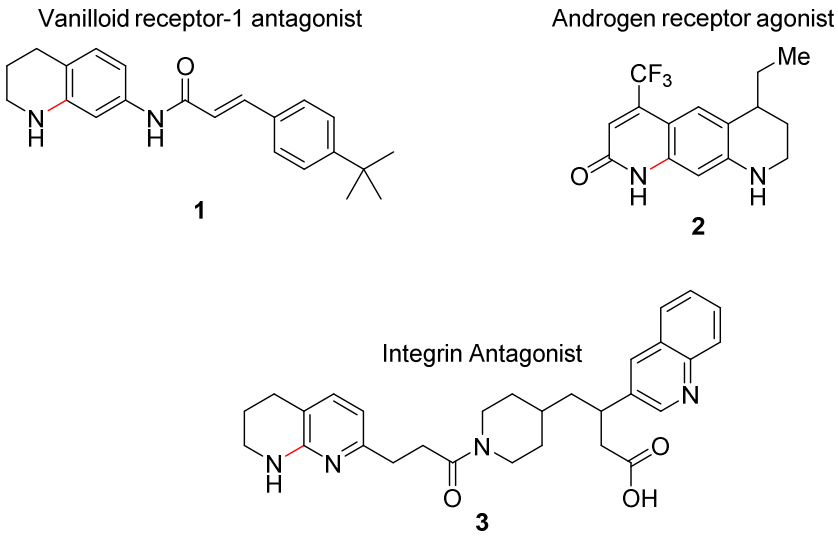


Figure 1.1

A study carried out in 2011 by Roughly and Jordan *et al* showed that *N*-arylation reactions made up 6.3% of the total reactions carried out by medicinal chemists in AstraZeneca, Pfizer and GlaxoSmithKline over the course of a year. The most common ways of carrying out this transformation were S_NAr and Pd catalysed Buchwald-Hartwig cross coupling reactions.[3] A similar review was also carried out by Carey, Williams and Laffan *et al* in 2006 who showed that in process chemistry 19% of the total reactions carried out were heteroaromatic alkylations and arylations, of which *N*-substitution made up 57%. *N*-arylation reactions made up 17% of these reactions with more examples of this being carried out due to the development of Buchwald and Hartwig's *N*-arylation methodology.[4]

1.2 Methods of C-N bond formation

There are different methods that can be undertaken to form an aryl C-N bond one of the traditional methods is nitration to install the nitro group then reduction of the nitro to afford the amine. This can then be alkylated as desired. Another method of C-N aryl bond formation is S_NAr although this has limitations as it requires electron-withdrawing groups in the *ortho* or *para* positions and a fluorine as a leaving group for the substitution, More modern methods involve the use of precious metals such as palladium complexes, require prefunctionalised aromatic rings such as a halogen and boronic acids. A more desirable method would be direct amination of the aromatic ring and developments in this area will be the focus of this discussion.

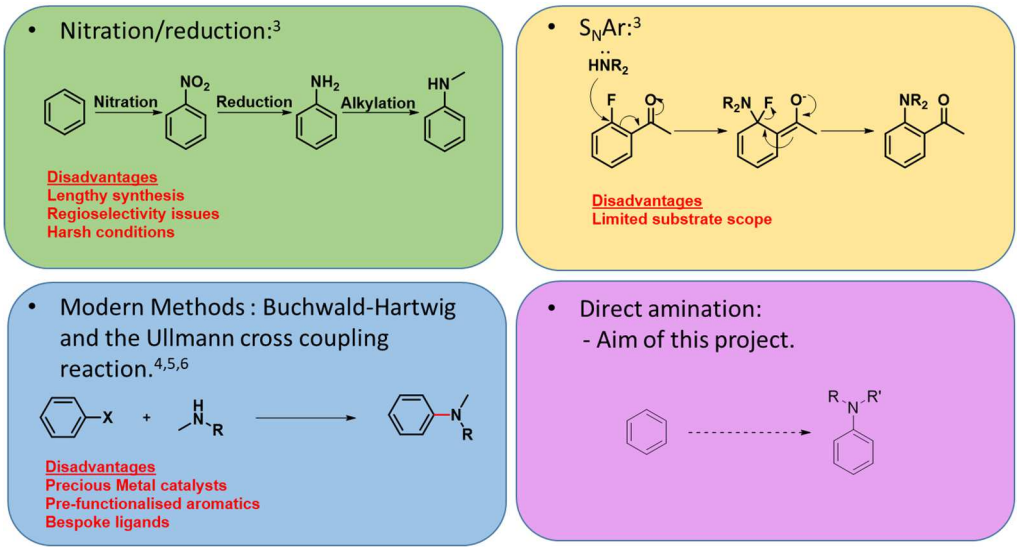


Figure 1.2

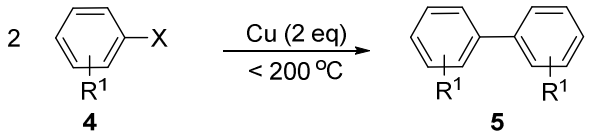
This chapter will contain a brief review that will look into the different reactions that have been used traditionally for such bond formations, focusing firstly on the formation of the aryl C-N bond by several different methods including a closer look into the applications of *N*-centred radicals in this area.

1.3 Transition Metal Catalysed Aryl C-N Bond Formation

There are many examples of metals being used as catalysts and initiators in the formation of aryl C-N bonds; this section will look at the different metals involved.

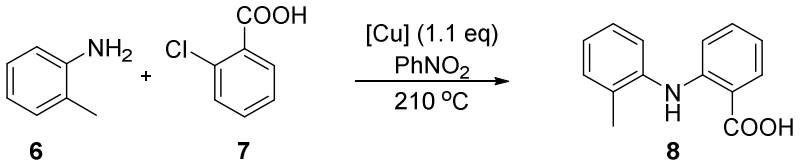
1.3.1 Ullmann Coupling

In 1901, Ullmann *et al*. first reported the coupling between 2 equivalents of aryl halide **4** using finely powdered copper which afforded a symmetrical biaryl **5** (Scheme 1.1).[5] This reaction is formally known as the Ullmann coupling.



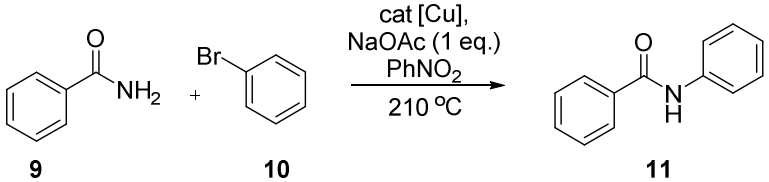
Scheme 1.1

Modifications to this methodology in subsequent years by Ullmann, expanded the scope of the reaction to allow copper to couple aryl halides to different oxygen, carbon and nitrogen nucleophiles (Scheme 1.2).[6,7]



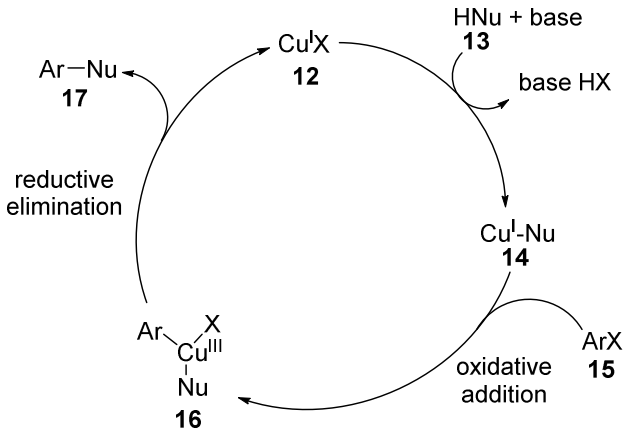
Scheme 1.2

The Ullmann coupling reaction requires harsh conditions with high temperatures and stoichiometric amounts of copper being used. In 1906 Goldberg demonstrated amide nucleophiles could be used, and later in the same year went on to show the first catalytic version of the reaction (Scheme 1.3).[8]



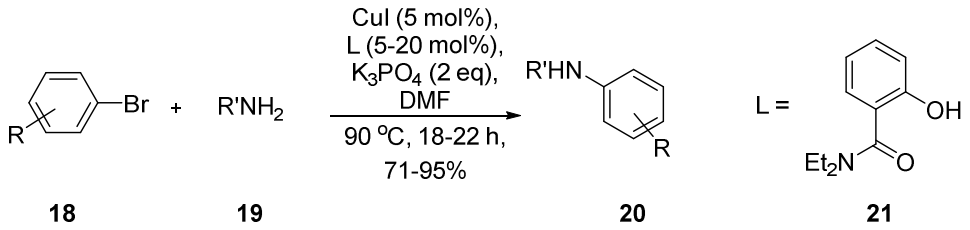
Scheme 1.3

The mechanism of the reaction has been widely disputed as it has been proposed to proceed through non-radical and radical pathways.[9] A proposed catalytic mechanism for amination of aryl halides is shown in Scheme 1.4. It involves the copper halide species **12** which reacts with the nucleophile and base to yield the copper-nucleophile species **14**. Oxidative addition of the aryl halide generates the copper species **16**. Reductive elimination affords the desired aryl compound **17** and regeneration of the catalyst.[10]



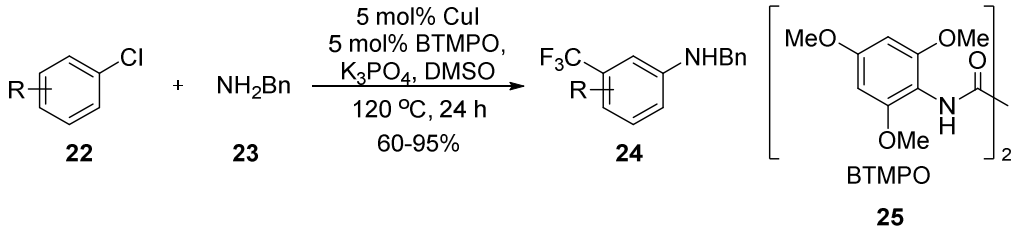
Scheme 1.4

Modifications to the Ullmann reaction introduced by Buchwald *et al*. have shown that aryl halides (iodide is required in most cases) can be coupled to amines using catalytic copper(I) salts at lower temperatures than previously used (Scheme 1.5).[11]



Scheme 1.5

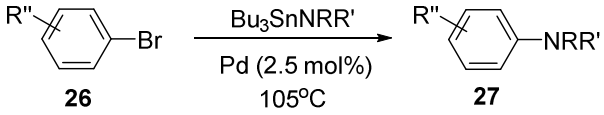
Recent developments by Ma *et al* have shown the use of aryl chlorides and lower temperature reactions to carry out transformation (Scheme 1.6).[12] The synthesis of a new ligand allowed these changes in conditions to be achieved. They observed that more electron-rich anilides and bulkier ligands gave the best yields. This has been shown to work on electron-rich as well as electron-poor aromatic rings and on heterocycles such as pyridine.



Scheme 1.6

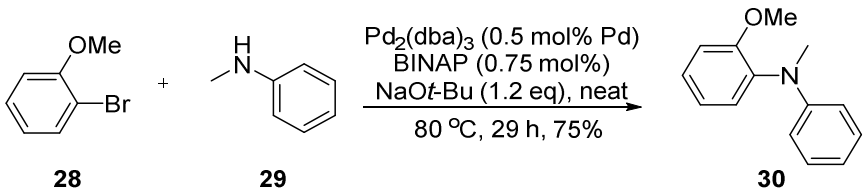
1.3.2 Buchwald-Hartwig Cross Coupling Reaction

In 1983 Migita *et al*. showed the first Pd-catalysed formation of aryl C-N bonds using aminostannanes and palladium catalysts.[13] This methodology was investigated further by Buchwald and Hartwig in the 1990s (Scheme 1.7).[14,15] These reactions however did have some issues due to the instability of some of the aminostannanes, thereby reducing the scope of the reaction. Some of the instability issues observed could be overcome by forming the aminostannane *in situ*.[16]



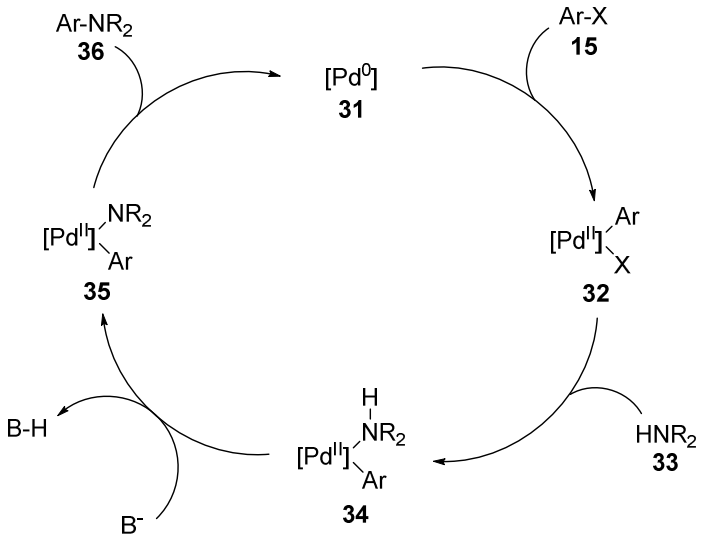
Scheme 1.7

Later both Buchwald and Hartwig went on to show that with the addition of an appropriate base and ligands, amines could be used directly and aminostannanes were not required, therefore relieving any issues of instability. The use of a strong base in these reactions allows for the formation of the aromatic amines from the corresponding halides and amines with it now being one of the most commonly used *N*-arylation reactions. There are many examples of these throughout the literature (Scheme 1.8).[17]



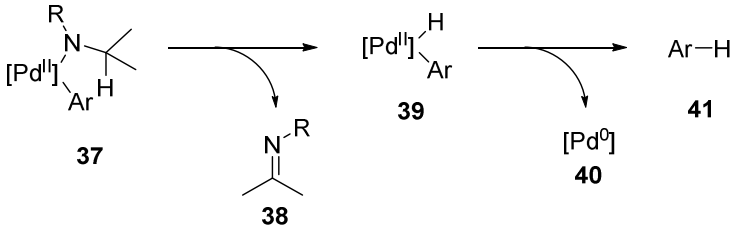
Scheme 1.8

The proposed mechanism of the reaction is shown in Scheme 1.9. The first step is the oxidative addition of the aryl halide **15** to the palladium(0) to form an arylpalladium(II) species **32**. Subsequently the amine group **33** then coordinates to the palladium centre **34**. The base then deprotonates the coordinated amine after which reductive elimination yields the desired product **36**.



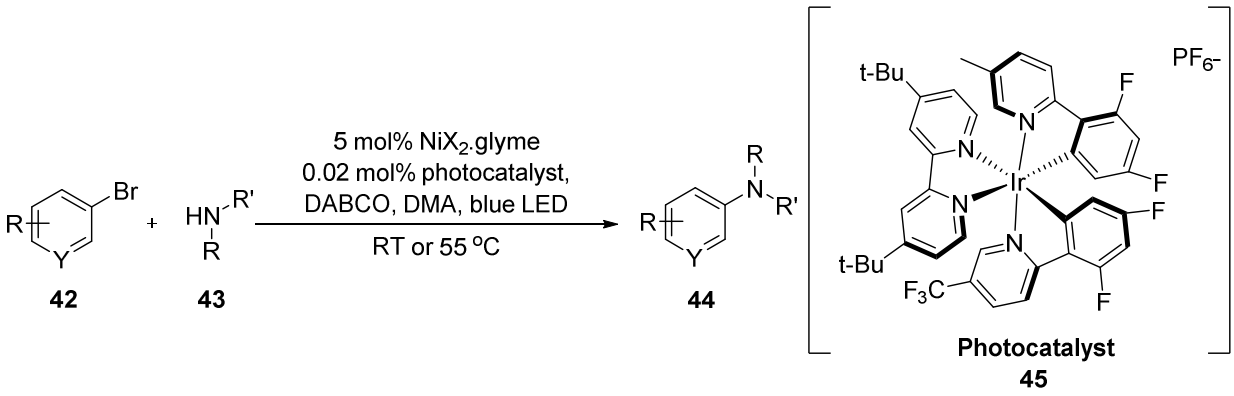
Scheme 1.9

There are some issues observed with the reductive elimination step when electron-rich aryl halides are employed (electron-deficient palladium species undergo reductive elimination more readily). The amide can instead undergo hydrodehalogenation which yields the reduced arene **41** as a side product of the reaction (Scheme 1.10). [17]



Scheme 1.10

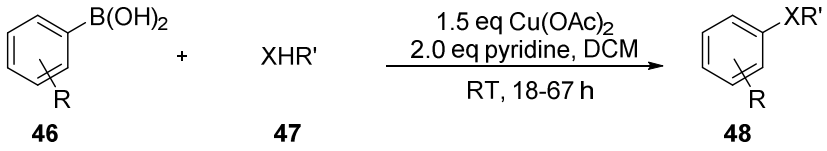
In 2016 Macmillian and Buchwald *et al* demonstrated together that a nickel catalyst could be used in conjuction with a photocatalyst to carry out the amination on an aromatic ring (Scheme 1.11).[18] A variety of aromatic rings could be aminated using aryl bromides under these conditions without the need for other ligands or high temperatures. The photocatalyst regenerates the nickel catalyst **45** through a single electron transfer.



Scheme 1.11

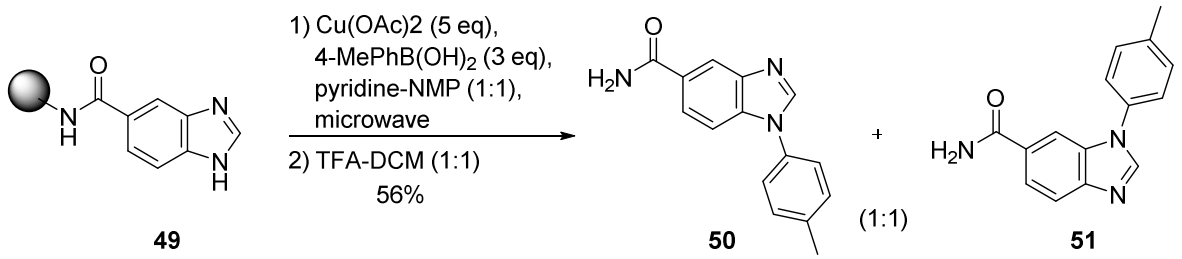
1.3.3 Chan-Evans-Lam cross coupling reaction

In 1998 Chan-Evans-Lam cross coupling was described which involves the cross-coupling between a boronic acid and a heteroatom (Scheme 1.12).[19,20,21] The initial reaction conditions required the use of stoichiometric copper salts and a tertiary amine base. It was shown to work on amines, amides, phenols and nitrogen containing heterocycles with a variety of arylboronic acids.



Scheme 1.12

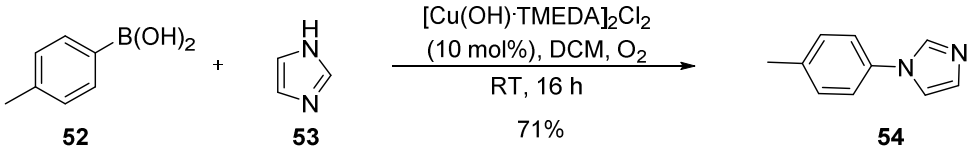
Several groups have investigated the reaction further and developed conditions that allow the use of catalytic copper and have reduced reaction times compared to the original conditions. Combs *et al* described the first polymer supported version of the reaction which dramatically decreased the reaction times through microwave irradiation.[22] A variety of *N*-heterocyles where synthesised using this method (Scheme 1.13).



49 **50** **51**

Scheme 1.13

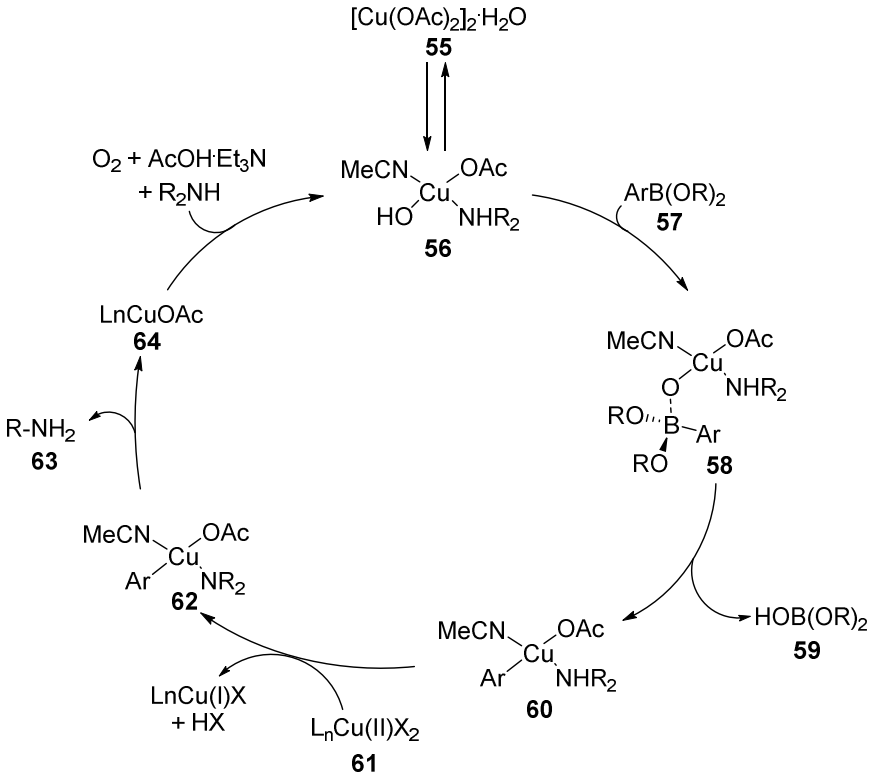
Collman *et al*. established a catalytic version of Chan-Evans-Lam reaction which used 10 mol% of a TMEDA complexed copper catalyst.[23] This was shown to work between several boronic acids and imidazoles, with air being the oxidant to return the copper to the original oxidation state (Scheme 1.14).



52 **53** **54**

Scheme 1.14

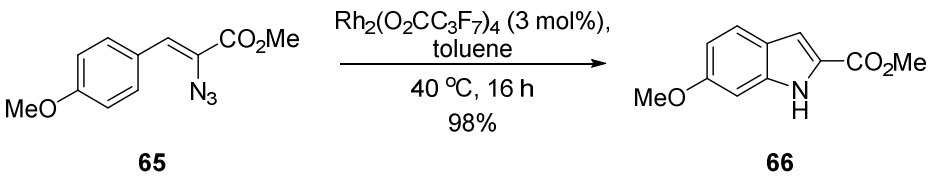
Several probes into the mechanism of the reaction have been made latterly by Watson *et al* who used 4-phenyl-phenylboronic acid and piperidine (Scheme 1.15).[24] They propose that the $[Cu(OAc)_2]_2 \cdot 2H_2O$ complex **55** is denucleated to a mononuclear Cu(II) complex **56** which then undergoes transmetallation with the organoboron reagent **57** to afford the Cu(II) species **58**. Oxidation of the Cu(II) species **60** to the Cu(III) species *via* disproportionation gives complex **62**. Reductive elimination then yields the desired product **63** and a Cu(I)OAc species **64** which is oxidised by O_2 and HX to regenerate the Cu(II) species **56**. Through this study, improved reaction reliability has been shown due to the use of additives.



Scheme 1.15

1.4 C-H activation amination reactions

In recent years C-H activation methodology has been expanded to include the formation of C-N aryl bonds under a variety of conditions, a few examples of which will be discussed in this section. There are other examples within the literature that heated azides to form nitrenes, however this is an undesirable method due to safety concerns.[25] Driver *et al*. established milder conditions which utilises rhodium catalysis to transform azides into various heterocycles focusing mainly on the synthesis of indoles (Scheme 1.16).[26]

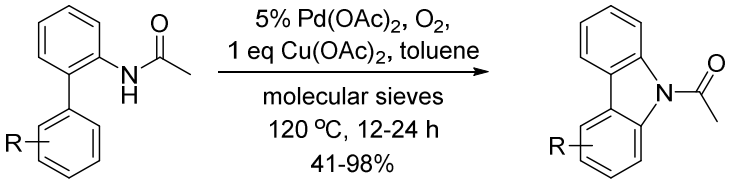


65 66

Scheme 1.16

In 2005 Buchwald *et al*. first described the C-H activation reaction that resulted in C-N bond formation, involving amide precursors **67**, using palladium as the catalyst towards the synthesis

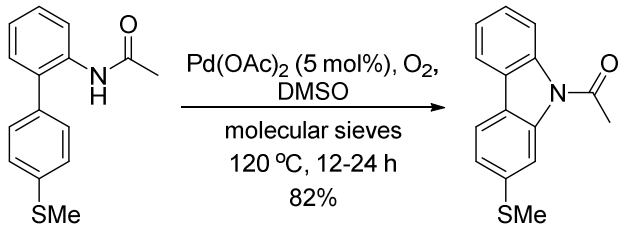
of carbazoles **68**.[27] These reactions utilised $Cu(OAc)_2$ as a stoichiometric co-oxidant in the reactions (Scheme 1.17).



67 **68**

Scheme 1.17

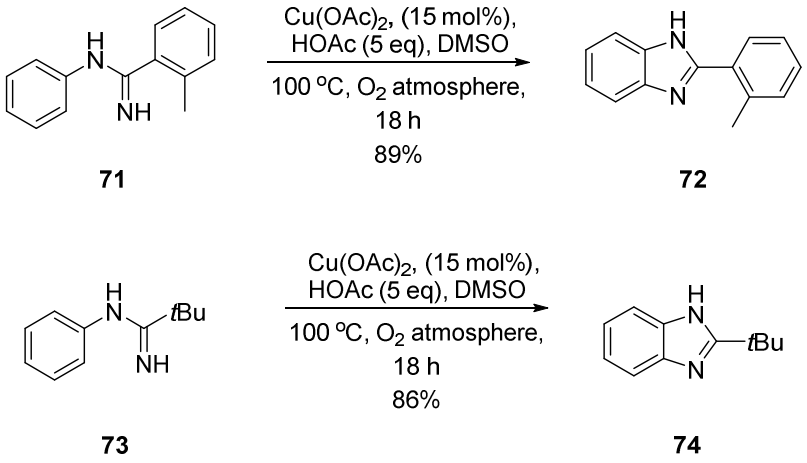
This reaction did have some disadvantages due to the incompatibility of some functional groups with $Cu(OAc)_2$. In subsequent years it was found by Buchwald *et al*. that when DMSO was used as the solvent $Cu(OAc)_2$ was not required as a co-oxidant. The scope of the reaction was increased due to the increase in the variety of functional groups that could be tolerated (Scheme 1.18).[28]



69 **70**

Scheme 1.18

In 2008, Buchwald *et al*. described a copper-mediated amination reaction involving amidines that proceeded via C-H activation to afford benzimidazoles (Scheme 1.19).[29] It was found that electron-donating and electron-withdrawing groups on the *N*-aryl ring were tolerated well within the reaction. Further investigations established that 2-alkylated instead of arylated benzimidazoles could also be afforded under these conditions, however, this was limited to amidines bearing the *tert*-butyl group only. When smaller alkyl groups were used only decomposition of the starting material was observed and no desired product was obtained.



Scheme 1.19

1.5 Amination reactions involving Aminyl and Iminyl Radicals

There are different types of *N*-centred radicals that can be formed, examples of which are shown in Figure 1.3.

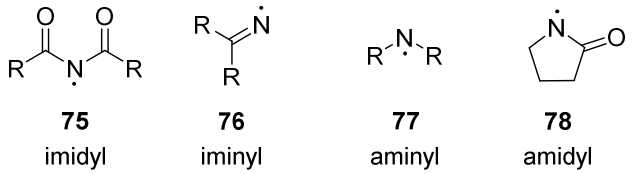
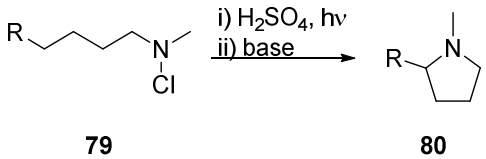


Figure 1.3

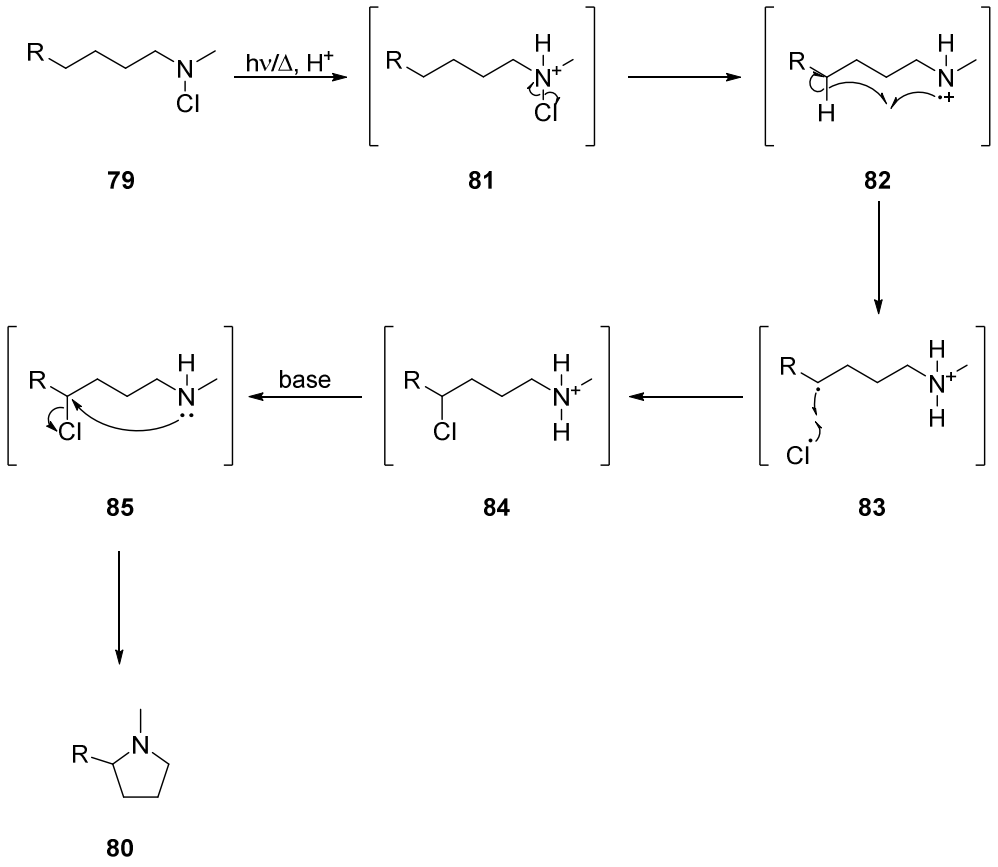
1.5.1 The Hofmann-Löffler-Freytag Reaction (HLF)

The HLF reaction was discovered in 1878 by Hofmann who observed that when secondary chloroamines containing alkyl chains with at least four carbons are treated with H_2SO_4 and photolysed the resulting product was a cyclic tertiary amine.[30,31] Following this, further work was carried out by Löffler and Freytag who demonstrated this could be applied to secondary amines as well. This method could be employed in the general synthesis of pyrrolidines **80** as shown in Scheme 1.20.[32]



Scheme 1.20

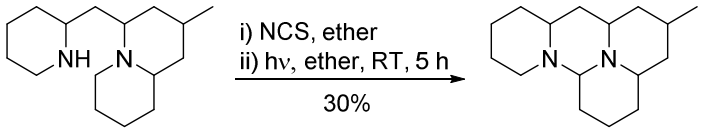
The mechanism of the HLF reaction was initially investigated by Wawzonek *et al*. who proposed that it proceeded *via* a radical reaction, which was later investigated thoroughly by Corey *et al* (Scheme 1.21).[33,34] The reaction is initiated *via* heating, external radical initiator or irradiation of the reaction mixture with UV light, which generates an aminium radical *via* homolytic cleavage of the *N*-halo bond of the protonated chloroamine **81**. Following this the nitrogen-centred radical readily undergoes an intermolecular 1,5-hydrogen atom transfer resulting in **83**. The alkyl radical then undergoes radical recombination to form the alkyl-halogen bond **84**. Finally treatment with a base which deprotonates the salt, allowing the internal nucleophilic substitution reaction to occur yielding the pyrrolidine **80**, with excellent regioselectivity observed.



Scheme 1.21

In 1974, Oishi *et al*. demonstrated that the chloroamine could be generated *in situ* and irradiated directly under UV light to obtain **87** under neutral conditions (Scheme 1.22).[35] This photocyclisation differs from the HLF reaction in three main aspects. One is that a six-membered ring is formed instead of the five-membered ring which shows that other pathways are possible even though 1,5- is usually favoured. The formation of the six-membered ring

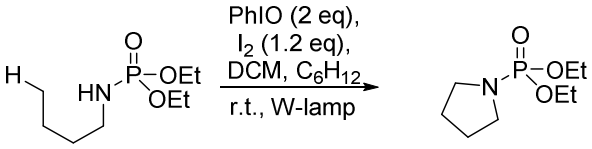
might be preferred as it would proceed *via* a carbon centred radical which is stabilised by the adjacent nitrogen lone pair. No strong acid was present in the reaction mixture and the cyclisation therefore occurred without any treatment with base.



86 **87**

Scheme 1.22

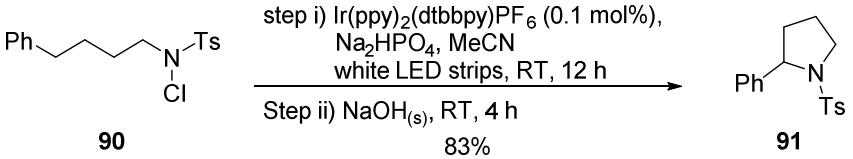
In 1983 Suarez *et al.* published another modified version of the HLF reaction that eliminates the need to use strongly acidic conditions, which are not suitable for all functional or protecting groups (Scheme 1.23).[36] The alternative method involved reacting *N*-nitroamines, *N*-cyanamines or *N*-phosphoramides with hypervalent iodine species under neutral conditions, generating the nitrogen centred radicals.



88 **89**

Scheme 1.23

An adapted HLF reaction that utilises an iridium photocatalyst to access the aminyl radicals, from *N*-chlorosulfonamides precursor **90** was published in 2015 by Yu *et al.*[37] They found that lower catalyst loadings increased the yield of the desired product (Scheme 1.24).

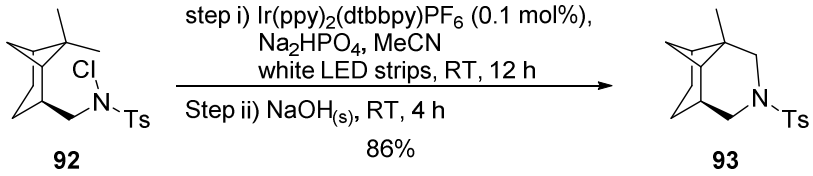


90 **91**

Scheme 1.24

They then went on to apply this methodology to late stage modifications of biologically important molecules. In one example the matrix-2 protein inhibitor (–)-*cis*-myrtanylamine derived *N*-chlorosulfonamide **92** was subjected to the newly established methodology and

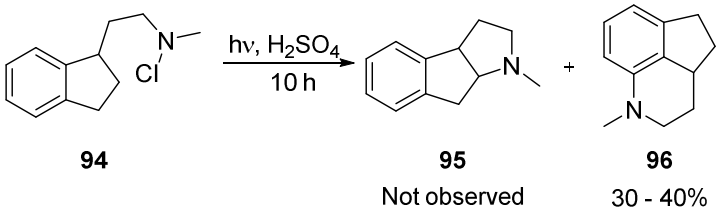
piperidine **93** was isolated as one isomer (Scheme 1.25). Due to the restricted conformation of the *N*-chlorosulfonamide **92** the six-membered ring was formed over the generally preferred five membered ring.



Scheme 1.25

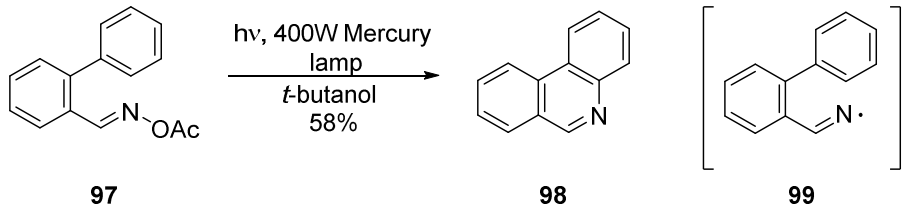
1.5.2 Arylation of aminyl and iminyl radicals

When attempting the synthesis of indenopyrrolidine **95**, Dey *et al*. and Robinson *et al*. both reported that instead of the expected hydrogen abstraction occurring for an HLF reaction, amination occurred on the aryl ring instead to yield the tricyclic compound **96** (Scheme 1.26). This result showed that amination on aryl rings could be achieved without the use of transition metals.[38, 39]



Scheme 1.26

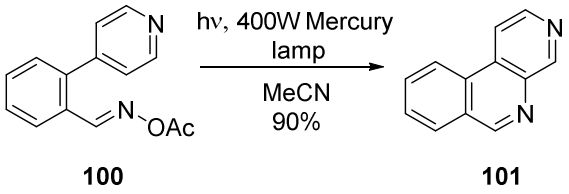
Interestingly, alternative groups to chlorine have been investigated. One example is *N*-alkyloximes **97** that are used to form iminyl radicals **99**, in the synthesis of heterocycles shown by Rodriguez *et al* (Scheme 1.27).[40] They have shown that this reaction can be carried out under neutral conditions and after a solvent screen, *t*-butanol was found to be optimal. It has been shown by Walton *et al*. through studies carried out using EPR spectroscopy, that the reaction proceeds *via* the iminyl radical.[41]



97 98 99

Scheme 1.27

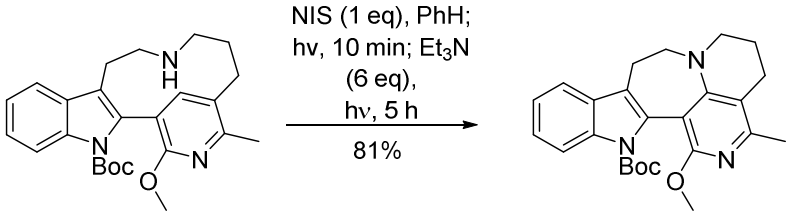
Rodriguez *et al*. have expanded on this work to show amination can occur on heterocyclic rings including pyridine and thiophene rings, again under neutral conditions (Scheme 1.28).[42]



100 101

Scheme 1.28

In 2012 Sarpong *et al*. demonstrated the use of aromatic amination *via* a modified HLF reaction under basic conditions in the total synthesis of arboflorine.[43] The acidic conditions using H_2SO_4 that had been successfully demonstrated by Day and Robinson (i.v. Scheme 1.26) gave no desired *N*-arylation product **103**, yielding starting material only. The reaction was also attempted under conditions described by Oishi *et al*. (c.f. Scheme 1.22), with irradiation of the chloroamine under neutral conditions, however these gave the desired product in a low 8% yield.[35] The reaction was then tried with a base and the desired product was afforded, with the best results seen through the presumed formation of the *N*-iodoamine *in situ* (Scheme 1.29).



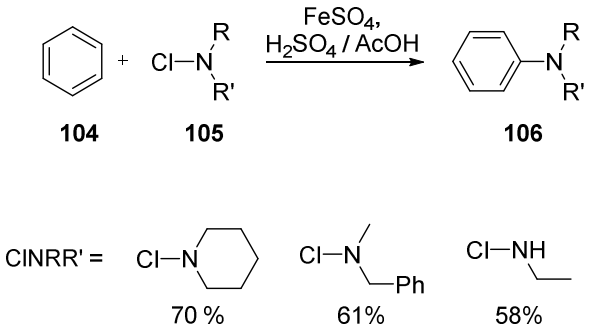
102 103

Scheme 1.29

1.5.3 Amination of Aryl rings by *N*-centred Radicals Generated by Transition Metals

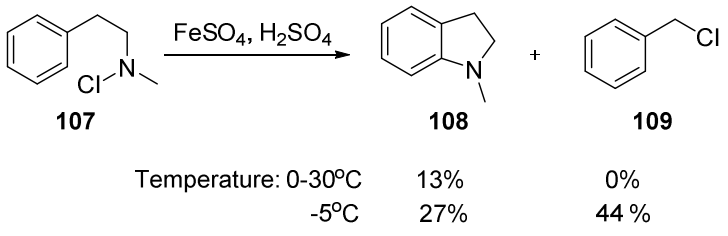
Minisci *et al*. described intermolecular examples of homolytic aromatic amination using Fe^{2+} salts as radical initiators in either concentrated H_2SO_4 or a mixture of H_2SO_4 and AcOH

(Scheme 1.30).[44] The reaction was shown to work with benzene and various amino substrates with alkyl chains, phenyl groups or primary amines. The yields of these reactions are dependent on various factors, one of which is the bulk of the substituents on the chloroamine (the bulkier the group the lower the yield).



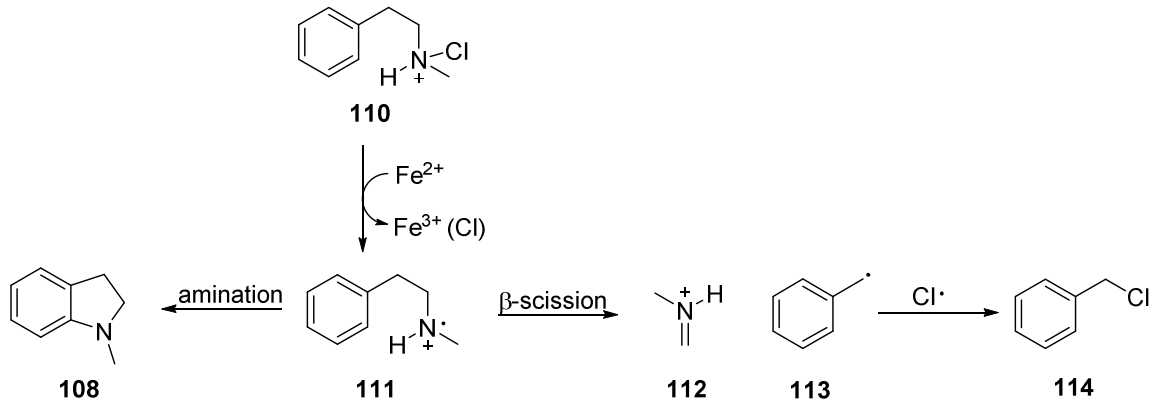
Scheme 1.30

Minisci *et al*. have also developed an intramolecular variation of this reaction. [45] The reaction of *N*-methyl-*N*-(phenylethyl)-*N*-chloroamine **107** and $FeSO_4$ in concentrated H_2SO_4 is an exothermic reaction that is very sensitive to temperature. When the reaction was carried out without cooling, once above 35 ^oC low yields of *N*-methylindoline **108** were observed, whereas when the reaction is cooled and kept at -5 ^oC 27% of *N*-methylindoline **108** is formed, with the formation of benzyl chloride **109** as a side product also (Scheme 1.31).



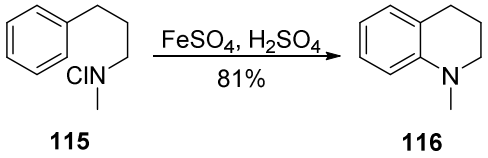
Scheme 1.31

N-Methylindoline **108** is formed by the intramolecular addition of the aminyl radical to the aromatic ring and then subsequent oxidation by the Fe^{2+} salt. An alternative mechanism that was proposed was a radical chain addition followed by the elimination of HCl to yield the product **114**. β-Scission to form the benzyl chloride product **114** is promoted due to the formation of a benzyl radical (Scheme 1.32)



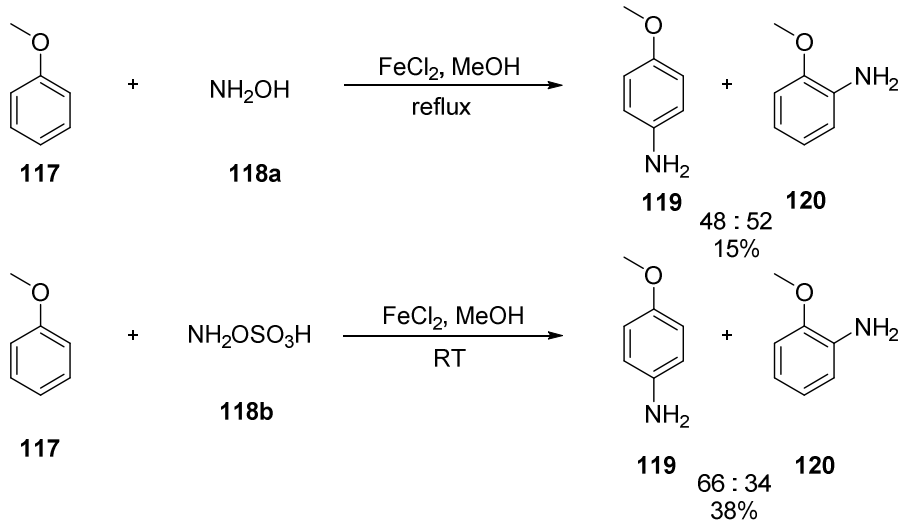
Scheme 1.32

When this reaction was attempted with methyl-3-phenylpropyl-*N*-chloroamine **115** the tetrahydroquinoline **116** was afforded in much higher yields (81%) as no β-scission was observed (Scheme 1.33).



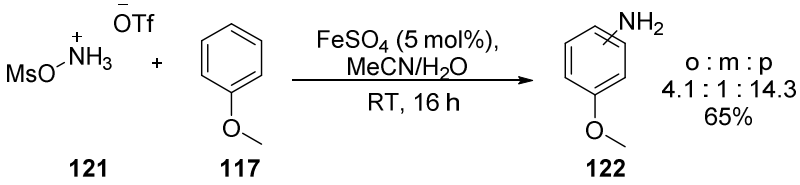
Scheme 1.33

Minisci *et al*. also investigated the use of different leaving groups to generate the protonated aminyl radical by using either hydroxylamine **118a** or hydroxylamine *O*-sulfonic acid **118b** for intermolecular *N*-arylation reactions.[44, 46] Either can be used to install an amine group on the aromatic ring. More electron-rich rings are favoured and higher yields are obtained. A higher yield is also obtained when using the hydroxylamine *O*-sulfonic acid although these are reportedly unstable (Scheme 1.34). When comparing the two hydroxylamines reacting with anisole it can been seen that a different ratio of *ortho* and *para* substitution is obtained this could be due to the different counter ions generated in the reaction.



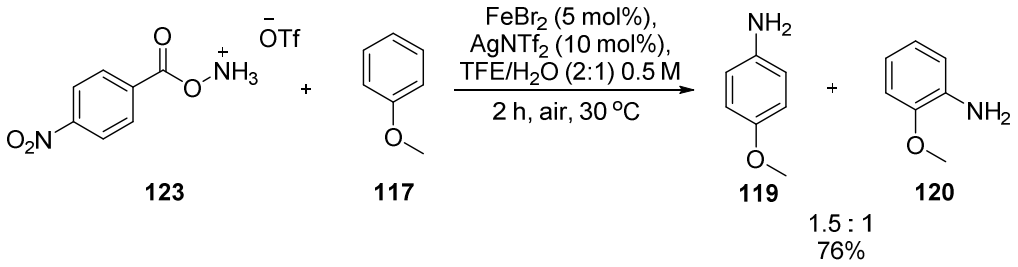
Scheme 1.34

In 2016 Morandi *et al* described the use of a different hydroxylamine derivative with mesylate on the oxygen **121** to install an amine group on the aromatic ring (Scheme 1.35).[47] A range of substrates with a variety of substituents have been shown to work again with the electron rich rings being preferred. The distribution of the isomers synthesised is again more in preference of the *ortho* and *para* positions.



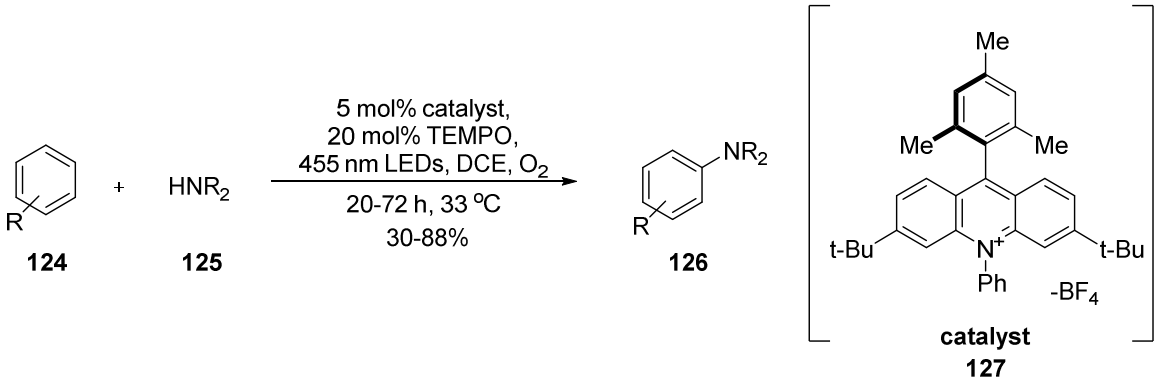
Scheme 1.35

Jiao *et al* has also investigated an alternative hydroxylamine derivative for the amination of aromatics (Scheme 1.36).[48] They carried out investigations into various substituents on the oxygen where they found the nitrobenzoate to be the best leaving group. Again slight selectivity for the para position over the *ortho* position was observed. A range of electron-rich aromatics were shown to work under these conditions along with a few unactivated arenes.



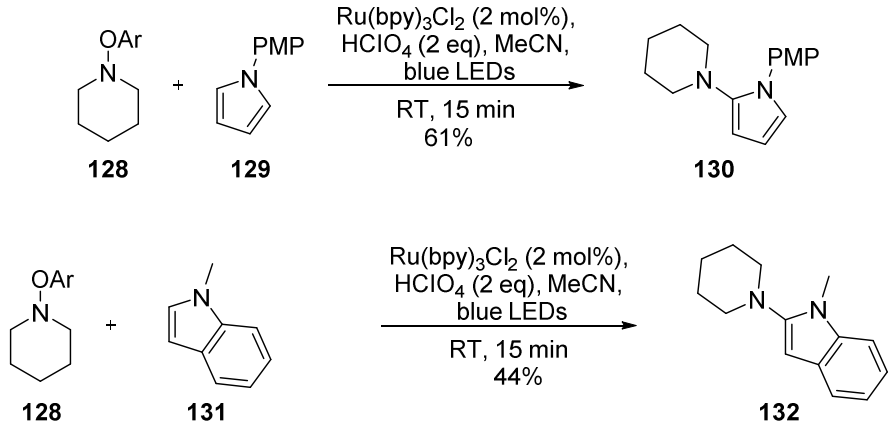
Scheme 1.36

There have been some examples within the literature that show the use of photoredox for the amination of aromatic rings (Scheme 1.37). Nicewicz *et al* described the amination of a variety of electron rich aromatics using nitrogen heterocycles such as pyrazole and triazoles.[49] It was found that increasing the mol% of TEMPO from 10 mol% to 20 mol% showed improved yields.



Scheme 1.37

Leonori *et al* described the use of *O*-aryl hydroxylamines **128** to form aminium radicals in the presence of $Ru(bpy)_3$ and visible light through a single electron transfer (SET) mechanism. Using the conditions established they have successfully aminated a variety of aromatic rings including pyrrole and indole (Scheme 1.38).[50]

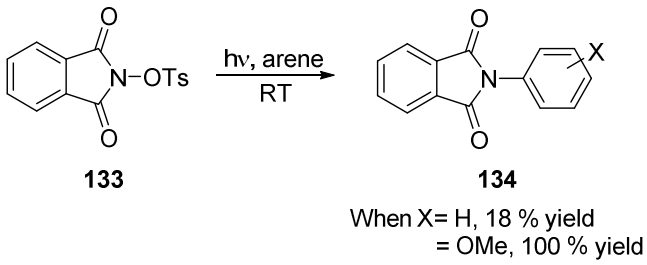


Scheme 1.38

Apart from the examples discussed there have been few *N*-arylation reactions *via* aminyl radicals described within the literature. In regard to aminating aromatic rings with hydroxylamines this work has been limited to just installing amine groups with no substituents on the amine present.

1.6 Arylation reactions of imidyl radicals

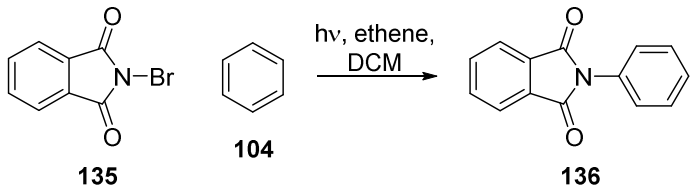
In 1976 Cadogan *et al*. demonstrated how *N*-tosyloxyphthalimides **133** readily underwent UV photolysis at room temperature in aromatic solvents to give *N*-arylphthalimides **134** *via* a proposed radical mechanism (Scheme 1.39).[51] The isomer ratios that were observed when carrying out the reaction under photolytic or thermolytic conditions suggests that it proceeds *via* an electrophilic phthalimido radical rather than a nitrenium ion (when compared to known radical reactions), which is supported by previous work carried out by Lidgett et al.[52]



Scheme 1.39

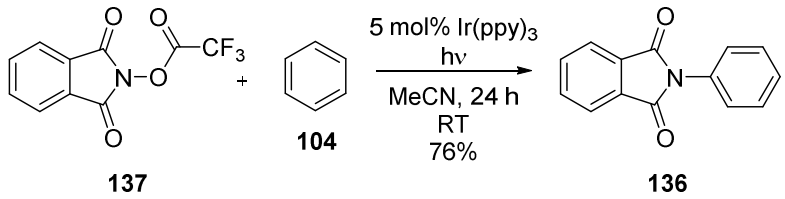
This work was later expanded upon by Skell *et al*. in 1986, who showed *N*-centred radicals could be generated from photolysis of *N*-bromophthalimide **135** (Scheme 1.40).[53] This *N*-centred radical could then be used for amination reactions on alkyl chains and aryl groups as

well. The problem that was encountered was the side reaction involving the bromo radical and the alkyl chain or aryl group, with bromination occurring on these groups. This was overcome through the addition of a sacrificial alkene into the reaction mixture.



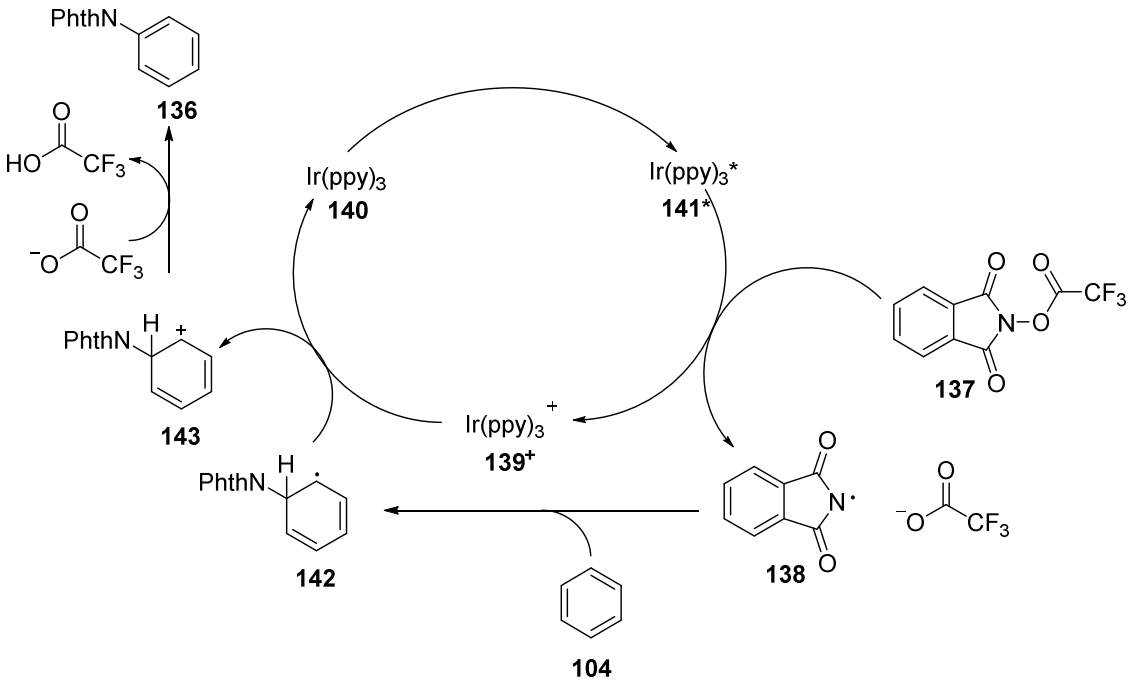
Scheme 1.40

Work carried out by Sanford *et al.* focused on iridium photoredox catalysts being used alongside visible light to activate *N*-oxyphthalimides **137**.[54] This work was based on the previous research carried out by Skell on arylation using phthalimides (Scheme 1.41). A wide range of mono-, di- and trisubstituted arene species were successfully aminated under the conditions developed by Sanford *et al*. Some substrates shown to work under these conditions were unstable under the high temperatures or strong oxidising conditions that were previously used. The conditions have also been shown to work on heterocycles.



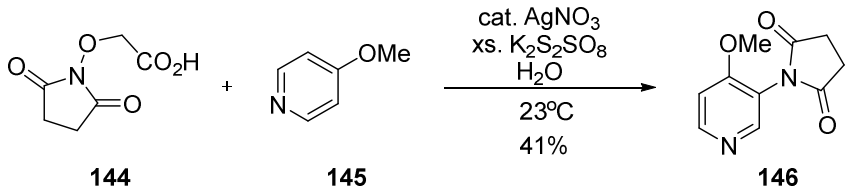
Scheme 1.41

The mechanism that was proposed for this reaction is shown in Scheme 1.42. Excitation of the $Ir(ppy)_3$ photocatalyst **140** with visible light forms the $Ir(ppy)_3^*$ species **141***. A single electron is transferred from the excited catalyst species **141*** to *N*-acyloxyphthalimide **137** which generates the *N*-phthalimidyl radical **138**, which then reacts with the arene **104**. The radical species **142** is then oxidised by the iridium species $\mathbf{139}^+$ to form **143** and regenerate the photocatalyst. The trifluoroacetate anion formed during the breaking of the N-O bond, deprotonates **143**, releasing the product **136** and TFA as a by-product.[54]



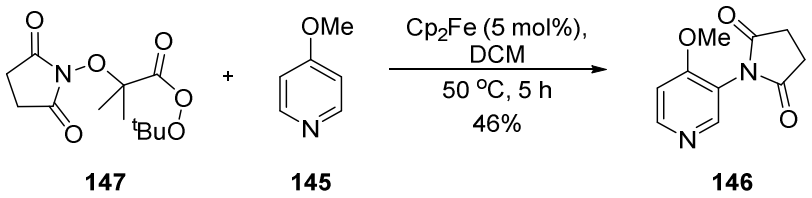
Scheme 1.42

In 2014 Baran *et al*. reported a metal mediated intermolecular *N*-arylation reaction between heteraromatics and *N*-succinimidyl derivatives.[55] The first substrate imide **144** underwent decarboxylation/deformylation to generate the imidyl radical which was shown to react with methoxypyridines (Scheme 1.43).



Scheme 1.43

Unfortunately, the scope of the reaction could not be increased with this set of imidyl radical precursors and so instead the *N*-succinimide perester radical precursors were investigated. This new system was shown to work on electron-rich and electron-poor heteraromatic/ aromatic systems an example of which is shown in Scheme 1.44.



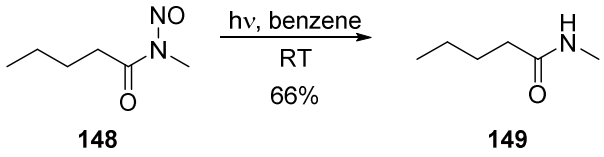
Scheme 1.44

1.7 C-N bond formation by amidyl radicals

In section 1.5 the formation of aminyl radicals for use in the formation of C-N bonds has been looked at in detail. In this section we will focus on the use on amidyl radicals in the formation of C-N bonds. A variety of different methods have been utilised for the formation of the amidyl radical ranging from alternative subunits to different initiators which will be described in this section.

1.7.1 Nitrosoamides

Following on from work by Barton *et al*. and the success of establishing conditions for the photolysis of nitrite esters as a useful synthetic method in the synthesis of the natural product aldosterone, investigations were carried out into the photolysis of nitrosamines.[56] However this did not lead to any improvement . It was hypothesised that this was due to the increased strength in the bond that was being broken, N-O (37 kcal/mol) to an N-N (43 kcal/mol). Kuhn *et al*. went on to show that the N-N bond of a nitrosamide is considerably weaker than a nitrosamine and that these compounds underwent facile photochemical reactions (Scheme 1.45).[57]



Scheme 1.45

They studied how the different structures of the nitrosoamides affected whether the amidyl radicals abstracted hydrogens intermolecularly or intramolecularly. The *N*-methylvaleramido radical **150** can only abstract hydrogens intramolecularly when it is in the *trans*- conformer, whereas the conformation of the *N*-pentylacetamido radical **151** can be either *cis*- or *trans*- and

the intramolecular hydrogen abstraction can still occur (Figure 1.4). To minimise intermolecular hydrogen abstraction non-polar solvents such as benzene can be used.

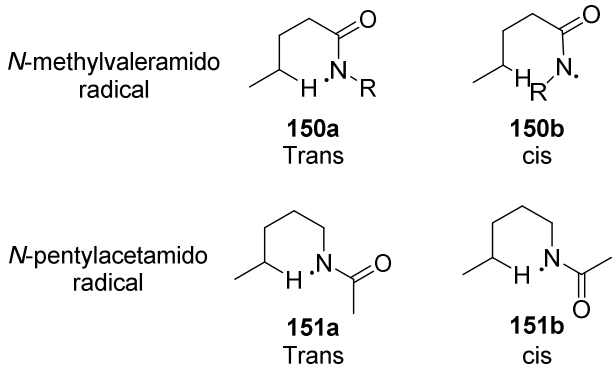
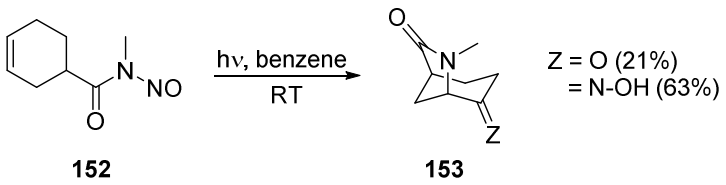


Figure 1.4

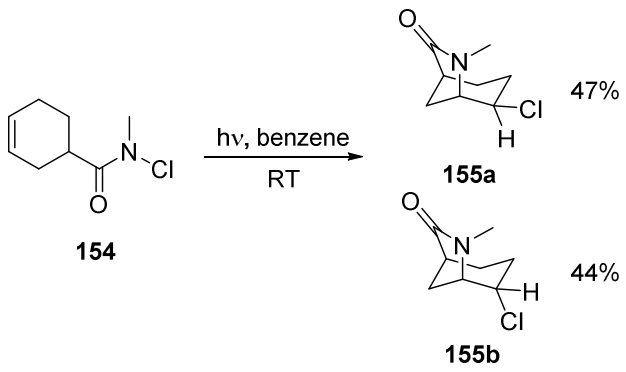
This work was investigated further and expanded upon by Perry *et al*. in 1972, who established an effective intramolecular cyclisation through the formation of an amidyl radical.[58] In their work they reported the successful formation of amidyl radicals *via* the homolytic cleavage of N-N. The photolysis of each compound was carried out in neutral conditions and the leaving group was incorporated into the cyclisation products. When the nitroso compound underwent photolysis a mixture of products containing the oxide or the hydroxylamine of which both the *syn*- and *anti*-geometric isomers were observed due to the incorporation of the N-OH group (Scheme 1.46).



Scheme 1.46

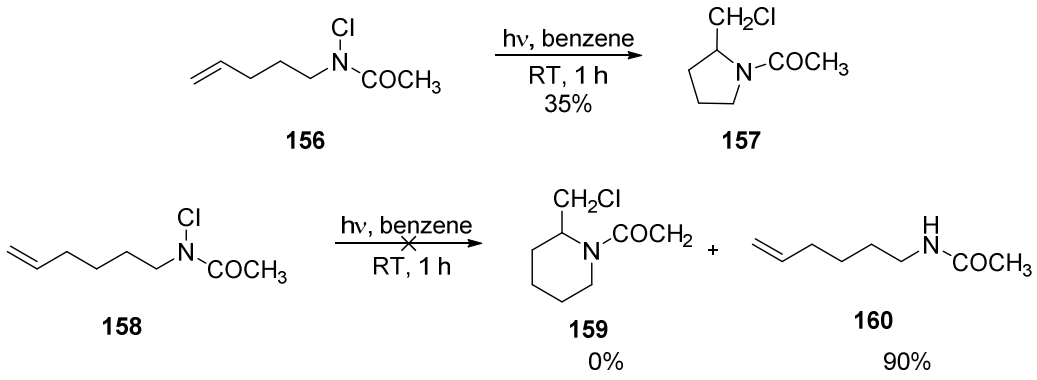
1.7.2 Halo-amides

Perry *et al*. not only showed the successful cyclisations of nitrosoamides but also chloroamides. They observed that when chloroamides underwent photolysis, chlorine was incorporated into the final product in either the *syn*- or *anti*- position (Scheme 1.47).[58]



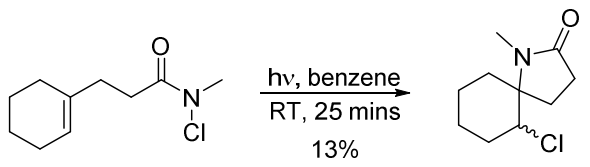
Scheme 1.47

In 1975 Kuehne *et al*. further investigations into whether the formation of the kinetically less favoured 6-membered ring, over the favoured 5-membered, could be forced were also carried out.[59] Irradiation of the *N*-chloroamide **156** lead to the 5-*exo*-trig cyclisation in 35% yield, however when *N*-chloroamide **158** was irradiated the major product was the amide **160** with no 6-*exo* cyclisation occurring (Scheme 1.48).



Scheme 1.48

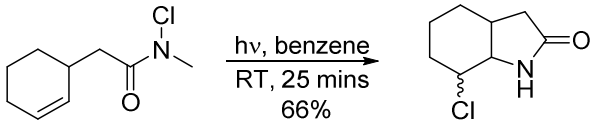
This methodology for the formation of the 5-membered rings was expanded to include bicyclic compounds. When the *N*-chloroamide **161** was subjected to irradiation it could form either a spirocycle by 5-*exo*-trig or fused ring by 6-*endo*-trig, however the only cyclised product obtained from the reaction was the spiro-lactam **162**, showing preference for 5-*exo* cyclisations (Scheme 1.49).



161 **162**

Scheme 1.49

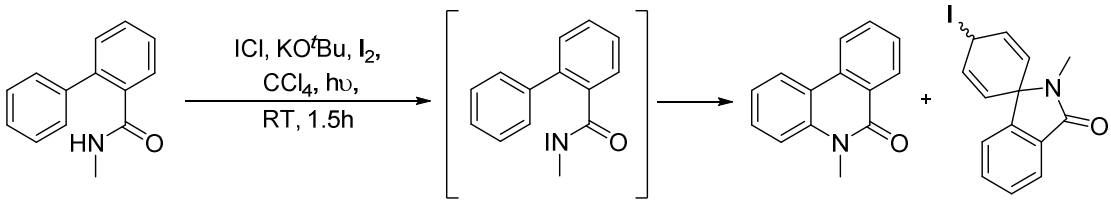
With the knowledge obtained of the preference for 5-*exo* cyclisations the synthesis of the perhydroindole skeleton which is prevalent in several alkaloid classes was successfully demonstrated (Scheme 1.50).



163 **164**

Scheme 1.50

Glover *et al*. extended the scope of the amidyl radical cyclisation to include examples of amination onto aromatic rings, shown to work with bi-aryl systems first.[60,61] They achieved this through photolysis of the iodoamide **166** which was formed *in situ*. The de-aromatised compound **168** was isolated in 19% yield alongside the desired product **167** (Scheme 1.51).

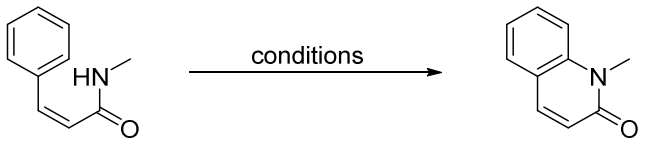


165 **166** **167** **168**

71% 19%

Scheme 1.51

Only slight success was observed for the thermal and photolysis conditions on the single aryl system **169** (Scheme 1.52) with isolated yields of the desired cyclised product much lower than for the bi-aryl system. This could be due to the system being less constrained and therefore not being held in the correct conformation to promote cyclisation.

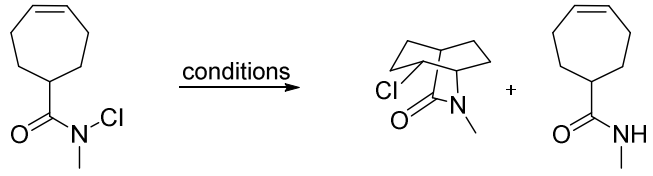


169 **170**

I_2, *t*-BuOCl, KO^{t}Bu, *t*-BuOH, 70 °C, 8.5 h, 24%
I_2, *t*-BuOCl, KO^{t}Bu, *t*-BuOH, hν, 6 h, 17%

Scheme 1.52

The activation of *N*-chloroamides can be achieved through methods other than photolysis one of which was described by Waegall *et al*. in 1978 who used dibenzoyl peroxide as a chemical initiator.[62] This has been shown to increase the yields of the cyclised product in reactions where the less favoured 6-membered ring is formed compared to results obtained under photolytic conditions (Scheme 1.53)

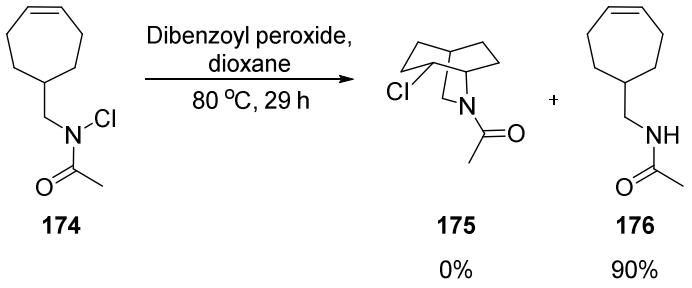


171 **172** **173**

Photolysis in DCM, RT, 1 h	55%	12%
Dibenzoyl peroxide in dioxane, 80 °C, 29 h	79%	18%

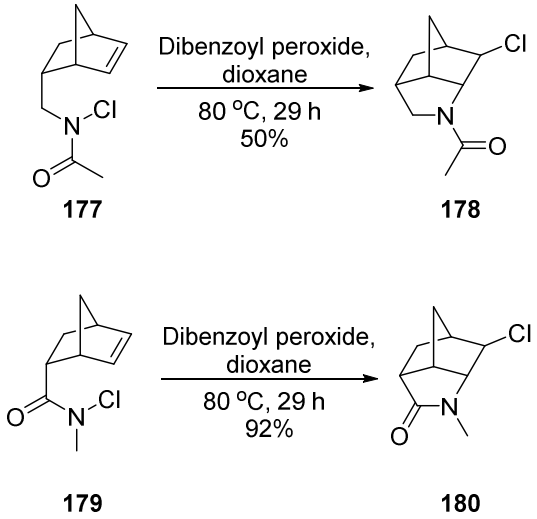
Scheme 1.53

The yields of the desired cyclised product from *N*-alkyl chloroacetamides were a lot lower than those of similar *N*-methyl chlorocarboxamides. *N*-Chloro carboxamide **171** when initiated with dibenzoyl peroxide affords 79% yield of the desired cyclised product (Scheme 1.53). However, when the same reaction is carried out using the corresponding *N*-chloroacetamide **174** none of the desired product is obtained, and instead 90% of the amide **176** is recovered. (Scheme 1.54). This can be explained in terms of steric interactions which is expected to be larger for *N*-alkyl chloroacetamido radical than for the *N*-methylcarboxamido radicals according to the models that they made.



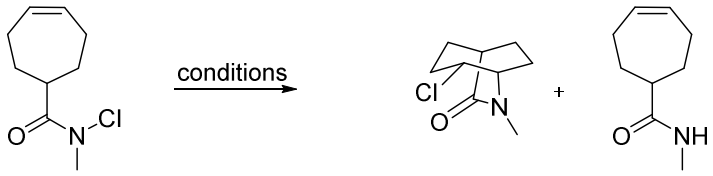
Scheme 1.54

Success was observed with the *N*-chloroacetamide **177** in the formation of the more favoured 5-membered ring **178** (Scheme 1.55). However, the desired product was afforded in lower yields than had been observed for the *N*-methyl chlorocarboxamide **179** with which 92% of the desired compound **180** was obtained. This could be due to the greater rotational freedom that *N*-chloroamide **177** experiences as a result of the CH_2 group, increasing the chance of hydrogen abstraction before the cyclisation occurs.



Scheme 1.55

In a subsequent paper by Lessard *et al*. another way was described to access the amidyl radicals from the chloroamides which used chromium(II) chloride.[63] It showed increased yields in the formation of the disfavoured 6-membered ring compared to when the reaction was carried out under photolytic or chemical initiation with dibenzoyl peroxide (Scheme 1.56). The disadvantage to this method is the long reaction times required for some of the substrates and the use of chromium (II) chloride.

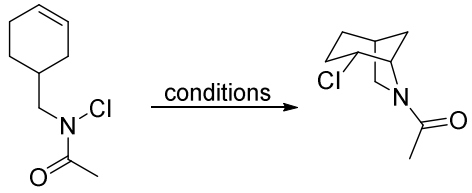


171 **172** **173**

hυ, DCM, RT, 1 h	55%	12%
dibenzoyl peroxide, dioxane, 80 °C, 29 h	79%	18%
$CrCl_2$ (1M in MeOH, 0.9 eq), $CHCl_3$/MeOH, -78 °C, 40 h	95%	trace

Scheme 1.56

When the chromium(II) chloride conditions were utilised in the reactions of the *N*-chloro acetamides **181** an improvement in the yields was observed. Interestingly, reactions that had failed previously under the dibenzoyl peroxide conditions, afforded good yields of the desired product when using chromium(II) chloride (Scheme 1.57).



181 **182**

dibenzoyl peroxide, dioxane, 80 °C	0%
$CrCl_2$ (1M in MeOH), $CHCl_3$/MeOH, -78 °C, 100 h	80%

Scheme 1.57

1.7.3 PTOC (*N*-hydrozypyridine-2-thione) imidate esters

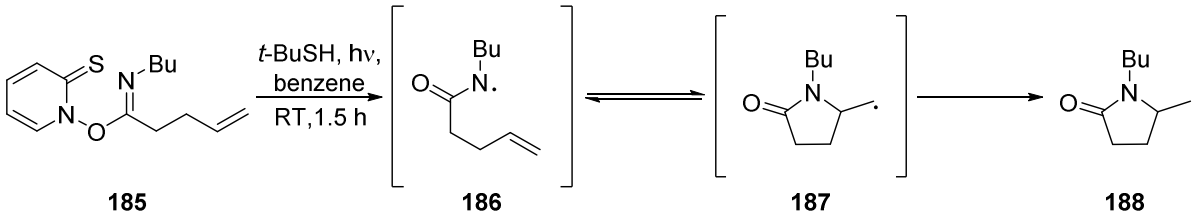
There has been some work to find alternative methods to generate the amidyl radical which would alleviate the limitations of functional groups. A class of radical precursors that has been developed by Newcomb *et al*.[64] is the PTOC imidate ester **184** which are structurally similar to the PTOC ester **183** used by Barton *et al* (Figure 1.5).[65]

183 **184**

PTOC ester PTOC imidate ester

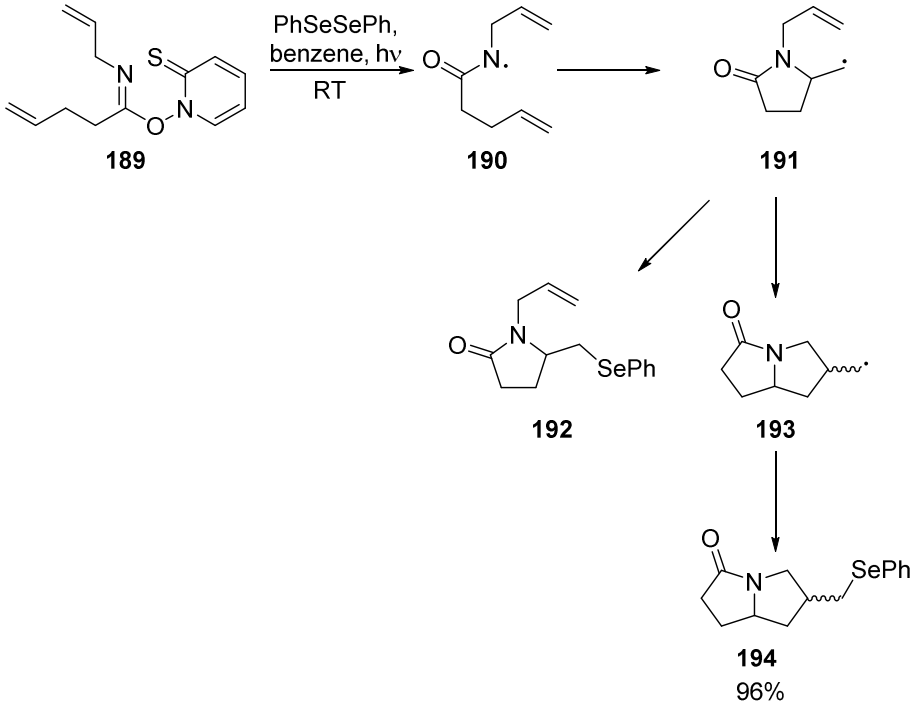
Figure 1.5

The use of *t*-BuSH with the amidyl radical was effective for the radical cyclisation chain process rather than a simple amidyl reduction taking place (Scheme 1.58).



Scheme 1.58

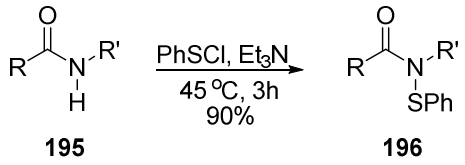
Newcomb *et al*. also showed radical cascade reactions could be initiated to afford bi-cyclic systems (Scheme 1.59).[64] The reaction can either proceed through the cascade pathway or the radical will be trapped after the first cyclisation. It can be forced to proceed *via* the cascade reaction when the reaction is carried out at a higher dilution.



Scheme 1.59

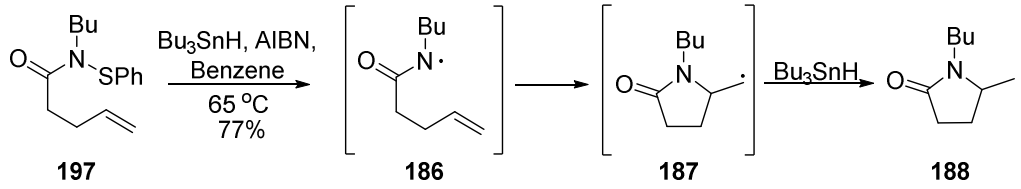
1.7.4 Sulfur amides

Newcomb *et al*. established an alternative class of radical precursors, *N*-(phenylthio)amides, as suitable sources of amidyl radicals.[66] The *N*-thioamides can be prepared easily through the reaction of amides with phenylsulfenyl chloride and triethylamine to yield the desired *N*-thioamide **196** (Scheme 1.60).



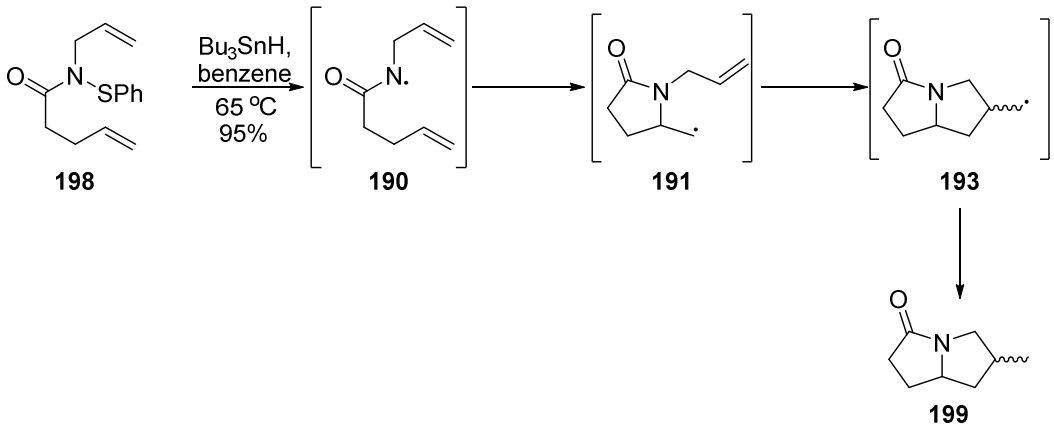
Scheme 1.60

These compounds have been shown to undergo intramolecular cyclisation reactions to form five-membered rings. When amide **197** was treated with Bu_3SnH whilst heating in benzene it afforded 77% of the desired compound (Scheme 1.61).



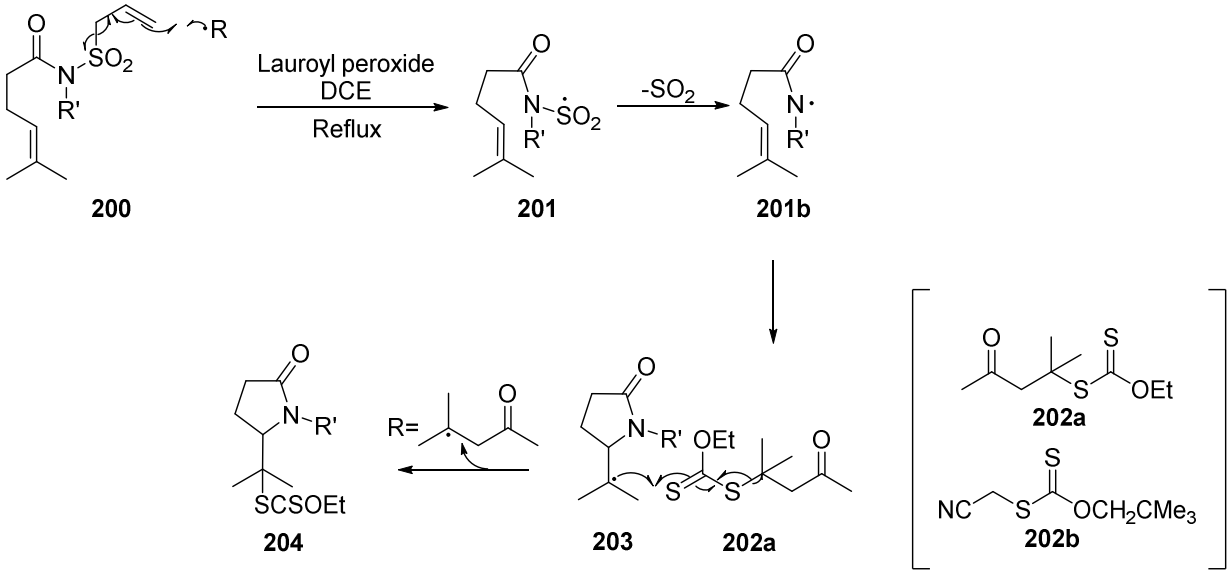
Scheme 1.61

Using these conditions tandem radical cyclisations have been shown to occur which form the bicyclic systems instead of trapping the radical after the first cyclisation (Scheme 1.62). The cyclisation of amide **198** gave the bi-cyclic amide **199** in a 95% yield and a 3:1 mixture of the diastereoisomers.



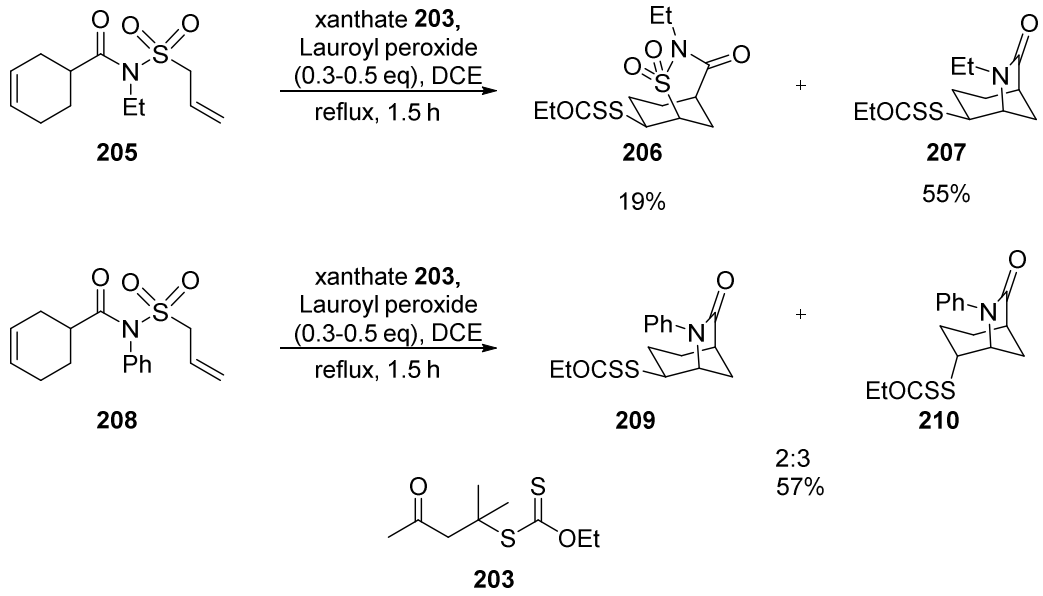
Scheme 1.62

In 2004 Zard *et al.* published a new method for the formation of amidyl radicals which involves the exclusion of sulfur dioxide from the *N*-amidosulfonimide.[67] The first step in the radical initation involves an addition-fragmentation to the allyl group which produces the *N*-sulfonyl radical **201a** (Scheme 1.63). The initiators used in the reaction were substiochiometric amounts of Lauroyl peroxide to generate the radical from xanthate **202a** or **202b**. Xanthate was chosen as the reversible transfer of the xanthate group to the product in the last step regenerates the initial radical (which reacts with the allyl group of the starting material) and also introduces useful functionality into the product. The desired amidyl radical **201b** is then formed *via* loss of sulfur dioxide. This last step is slow and could lead to the *N*-amidosulfonyl radicals abstracting a hydrogen from the solvent or cyclising onto the olefin. Careful selection of solvents with poor hydrogen-donating capabilities can prevent hydrogen abstraction from the solvent.



Scheme 1.63

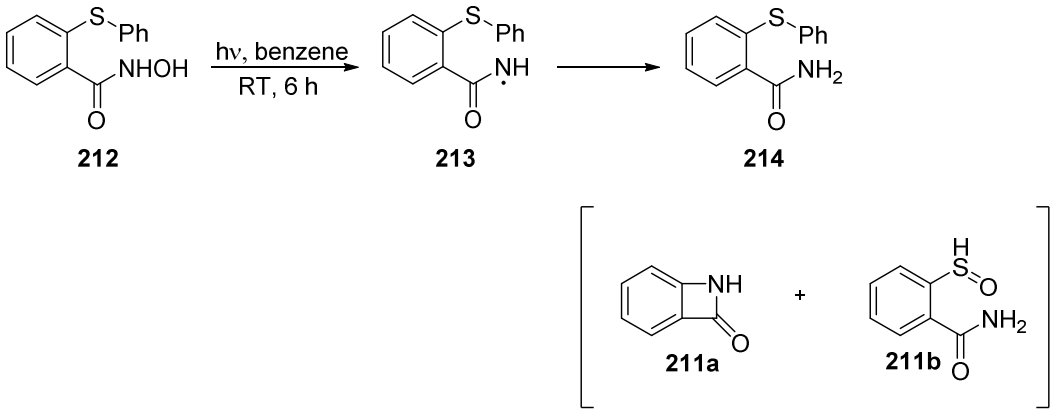
It was observed that when an alkyl group was present on the nitrogen, cyclisation of the *N*-amidosulfonyl radical onto the alkene occurred, whereas when the ethyl group was changed for a phenyl group none of the *N*-amidosulfonyl radical cyclisation products were observed: only an epimeric mixture of the desired lactam was observed (Scheme 1.64).



Scheme 1.64

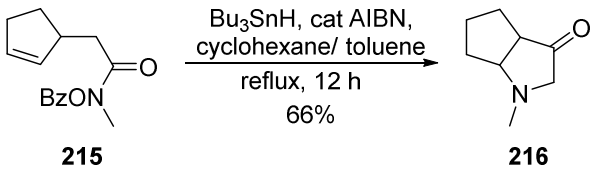
1.7.5 Hydroxamic acids

In 1978 Hosangadi *et al*. found that when they irradiated hydroxamic acid **212** instead of affording the expected lactam **211a** or 2-arylsulfinylbenzamide **211b**,[68] they instead obtained 2-arylthiobenzamide **214** as the product of the reaction which they believed to be formed through the amidyl radical intermediate (Scheme 1.65).



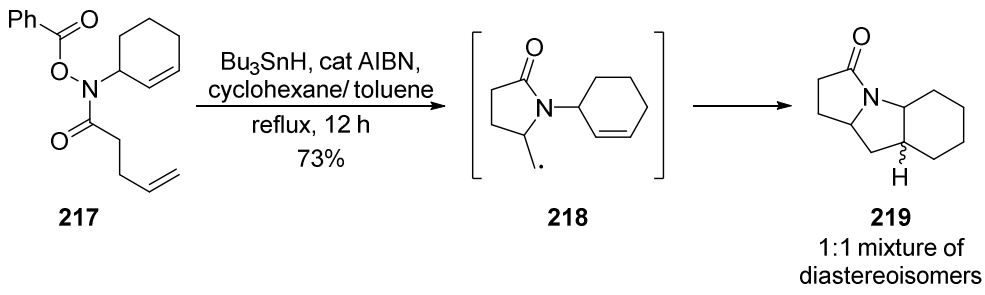
Scheme 1.65

The formation of the amidyl radical upon irradiation of the hydroxamic acid derivatives was further explored for the use in cyclisation reactions by Zard *et al*. in 1995.[69] Instead of forming the radical by photolysis of the *O*-benzoyl hydroxamic acid **215** its formation was initiated using tributyltinhydride and AIBN. This lead to successful cyclisations of the amidyl radicals onto olefins (Scheme 1.66).



Scheme 1.66

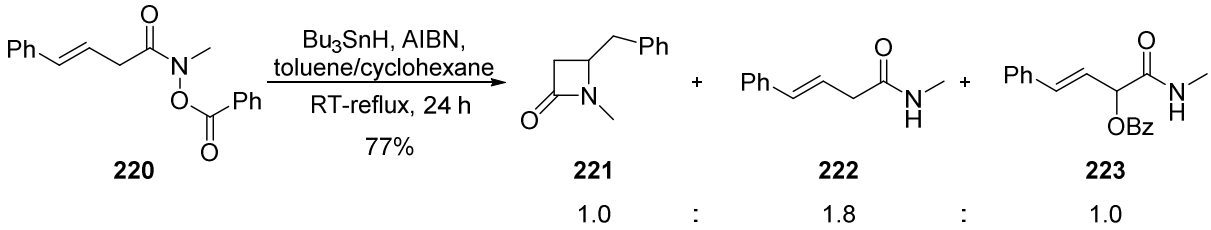
The amidyl radical precursors were incorporated into various cyclisation cascade reactions an example of which is shown in Scheme 1.67, in which tricyclic compound **219** was afforded.



Scheme 1.67

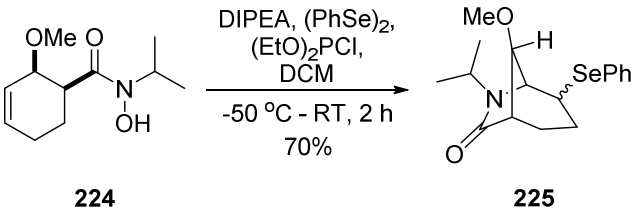
Application of Zard's conditions was demonstrated by Clark *et al.* in 1998 for the synthesis of lactams involving a 4-*exo*-trig cyclisation of the amidyl radical (Scheme 1.68). [70]Although the

lactam **221** was formed in the reaction there were issues with competition reactions, one of which formed the amide **222** (found to be the major product). The issues with the formation of the amide could be addressed through two methods, one of which was to carry out the reaction at a higher dilution. The other method was the addition of a group which would stabilise the carbon centred radical formed to form compound **223**.



Scheme 1.68

Following on from the success in the cyclisations of hydroxamic acid, milder conditions for the amidyl radical formation were shown by Weinreb *et al*., who used *tert*-butylsulfonyl chloride or diethyl chlorophosphite, Hunig's base and low temperatures.[71] Various radical trapping agents such as diphenyl diselenide, diphenyl disulfide and TEMPO were used to successfully yield the desired products (Scheme 1.69), with a preference shown for the formation of the 5-*endo* products. These conditions were applied to the synthesis of the key intermediate for the alkaloid (+/-)-peduncularine to synthesis the key intermediate **225**.



Scheme 1.69

1.8 Summary

There have been many advances in the different techniques that are used in the formation of C-N bonds which has expanded the scope of the reactions. Many of the reactions unfortunately use expensive metals such as palladium and iridium. Reactions such as the Buchwald-Hartwig reaction use expensive ligands in the synthesis.

There have also been advances in utilising UV and visible light in the formation of C-N bonds, many of which avoid the use of expensive metals and don't require the addition of other reagents. Although there have been advances in the area of light mediated reactions, there are only a few examples within the literature, detailing the formation of ring systems such as tetrahydroquinolines. The same can also be said for the metal-mediated versions of the reaction. With regards to amidyl radicals there are a very limited number of examples of *N*-arylation reactions.

Chapter 2 Intramolecular *N*-arylation reactions

2.1 Flow chemistry and benefits over batch reactions

Flow chemistry has been commonplace within the petrochemical and bulk chemical industry for many years, but only recently has it become the focus for the chemical development industry. A recent review by Hughes *et al* discussed the benefits gained from the use of flow in recent syntheses of API's, and included:[72]

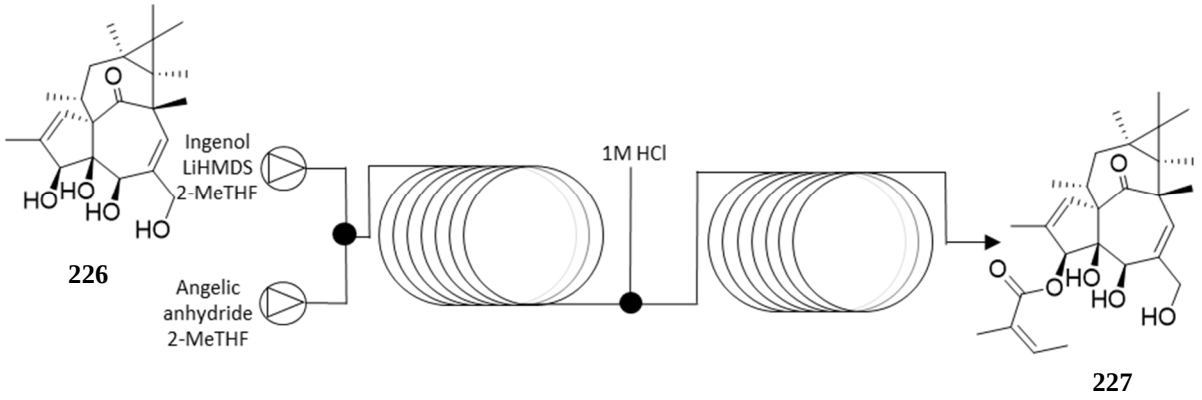
1) Enables chemistry that is difficult to scale in batch such as electrochemistry, microwave heating and photochemistry.
2) Can access extreme conditions such as high and low temperatures and high pressures readily.
3) Scale up is more straightforward as mixing and heat transfer are maintained as scale is increased.
4) Safer execution of hazardous chemistry as only a small number of unstable intermediates are generated at any one time. The high surface area to volume allows for excellent control of exothermic chemistry (helping to avoid reaction 'runaway').

This demonstrates the appeal for using these systems in API synthesis, however there are still challenges facing the progression of flow chemistry in chemical development. Some of the issues faced are the lack of knowledge and skill set required to implement such methodology along with chemists being traditionally trained in batch chemistry and therefore unaware of when flow chemistry could benefit their process.

2.1.1 Flow chemistry in the synthesis of API's

Within Patents submitted in 2016 and 2017 there are examples of drug molecules which have a continuous step described within the possible synthesis. Each of these have described a benefit of using flow over traditional batch methods. In the synthesis of ingenol mebutate there was improved regioselectivity reported in the acylation of the C_3 alcohol which also benefitted from avoiding the need for protection/deprotection steps used in the previous synthesis. In the optimised flow conditions, a flow of ingenol/LiHMDS was mixed with angelic anhydride at 0 ^{o}C this was followed by a continuous quench with a third flow of 1M HCl at 25 ^{o}C. This allowed

isolation of the desired compound **227** in a 40% yield and the starting material could be recovered. The previous batch reaction gave a 37% yield over three steps and had a very difficult final deprotection step which had to be carefully controlled to prevent isomerisation, which took 7 days to achieve (Scheme 2.1).



226 **227**

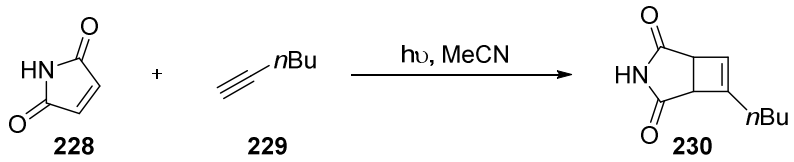
Scheme 2.1

This demonstrates one of the many advantages that flow chemistry can achieve over the corresponding batch reactions.

2.1.2 Continuous photochemistry

On a small-scale, UV-light-mediated reactions are commonly carried out in immersion well reactors. Larger scale versions of these batch reactors encounter a major drawback due to the uneven distribution of photons through the reaction obtained. This leads to poor translation of reactions in scale-up. In 2005, Booker-Milburn *et al* described how a standard immersion well reactor could be converted into a continuous photochemical reactor by wrapping UV-transparent fluorinated ethylene propylene (FEP) tubing around the outside of the immersion well.[73] This was either done with a mono-layer of tubing or a triple-layer of the tubing on the reactor to compare the yields of each reactor and the associated benefits of each. Several examples were then shown within the paper to demonstrate the benefits of the continuous flow system in comparison to the traditional batch methods, especially upon scale-up of the reactions. Using the reactor, the authors managed to obtain high yields with high projected productivities for the reactions of over a 24 h period. The intermolecular [2+2] cycloaddition between hexyne and maleimide afforded high levels of productivity with the mono-layer FEP reactor at 0.2 M with a 24 h projection of 363 g being achieved (Table 2.1, Entry 1). By

switching to the triple-layer FEP reactor and increasing the concentration to 0.3 M a projected productivity of 408 g was achieved (Table 2.1, Entry 2). The authors also demonstrated the benefits of using a more powerful lamp: by switching to a 600 W lamp from a 400 W lamp, the productivity increased to 685 g over the 24 h period (Table 2.1, Entry 3). The indicates that an increase in the flux of protons is a more effective way to increase the yield of the reaction over a change in the flow rate.

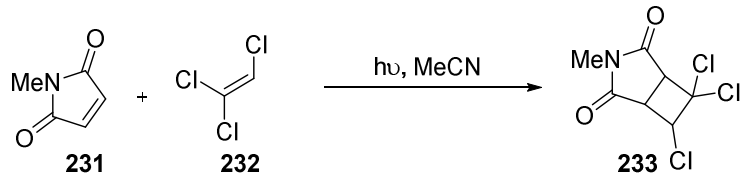


228 **229** **230**

Entry	Conc (M)	Lamp (W)	Layers of FEP	Flow rate (mL/min)	Conversion (%)	Projected 24 h yield of x (g)
1	0.2	400	1	8	88	363
2	0.3	400	3	6	88	408
3	0.4	600	3	8	83	685

Table 2.1

An example that highlights the benefits of flow over batch is the [2+2] cycloaddition shown in the scheme below. When comparing the batch conditions (Table 2.2, Entry 1) with flow we can see the productivity increases from 6.56 g to 8.55 g for the triple layer FEP flow reactor (Table 2.2, Entry 2). For the mono-layer flow reactor (Table 2.2, Entry 3) we can see the productivity is slightly lower than that of the batch reactions.[74] The lower yields for the mono-layer reactor over the triple-layer reactor could be attributed due to the fact light can escape between the gap in the tubes whereas in the triple-layer reactor the light would then interact with another tube, this increase absorption by the reaction mixture and in turn productivity.



Entry	Mode	Conditions	Yield (%)	Productivity at batch end (g)
1	Batch	0.096 M, 180 min	68	6.56
2	Flow[a]	0.096 M, 3 mL min^{-1}	68	8.55
3	Flow[b]	0.096 M, 2 mL min^{-1}	68	5.70

[a] triple layer FEP reactor, [b] mono layer FEP reactor

Table 2.2

Three trends can be observed from the comparison of these reactions:

1) Yields for batch and flow reactors in synthetic photochemistry are essentially the same at full conversion.
2) Triple-layer FEP reactors have on average 20% higher productivity compared to the same batch end point.
3) Mono-layer FEP reactors have on average 20% lower productivity compared to the same batch end point.

2.1.3 Space-Time Yield (STY) calculation

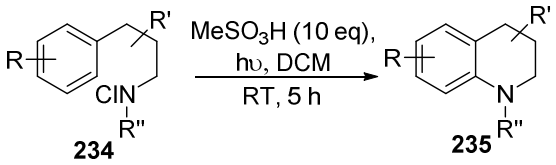
The space-time yield (STY) calculation is a useful way to determine the efficiency of a continuous reactor as well as allowing for comparisons between reactors of differing sizes. It gives the yield for the process as a unit of space-time. The STY is calculated using equation [1] and the units are g L^{-1} h^{-1}.[75]

$$\frac{Mass\ of\ product\ (g)}{(Reactor\ volume\ (L)\ x\ Residence\ time\ (h))} \quad [1]$$

The STY for each of the substrates synthesised in over investigatons was calculated to allow for comparison between them.

2.1.4 Previous work in the Marsden group

Previous work carried out within the Marsden group has established a modified HLF methodology that utilises UV light under acidic conditions in the formation of C-N bonds. This method avoids the need to use expensive metals (such as palladium) and ligands previously employed. The optimised conditions have been shown to work on a range of substrates with a variety of substitution on the aromatic ring, the alkyl chain and on the nitrogen (Scheme 2.2).[76]



Scheme 2.2

This methodology was shown to work in both batch and flow. A continuous photochemical reactor was built following the design described by Booker-Milburn *et al*, with a dual syringe pump attached to a T-junction to allow both flow rates of the chloroamine and the $MeSO_3H$ to be equal.[73] A reactor volume of 5 mL was chosen. The length of the UV-transparent FEP tubing (with an internal diameter of 2.7 mm) had been calculated using the equation [2] for the volume of a cylinder.

$$V = \pi r^2 h \qquad [2]$$

Inputting the values gave 87.4 cm of tubing for a 5mL reactor volume. An additional 50 cm of the tubing was added to either end of the reactor volume to allow the transportation of the reactants to and from the photochemical reactor. A 125W high pressure mecury lamp was used for these investigations. The FEP tubing was attached to the immersion well of the reactor using double-sided tape and Sellotape. One end of the reactor was attached to a T-junction to which two syringes in a dual syringe pump were connected using PTFE tubing with an I.D of 1/32nd of an inch. The photochemical reactor was contained in foil and directly attached to a water supply to cool the lamp. In the event of the flow of water failing the lamp automatically turns off. The reactor was additionally contained within a red box which blocked any stray UV radiation.

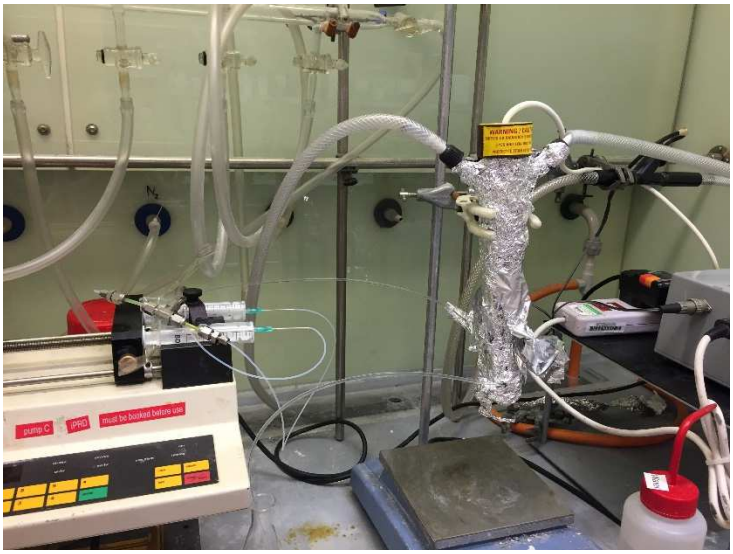
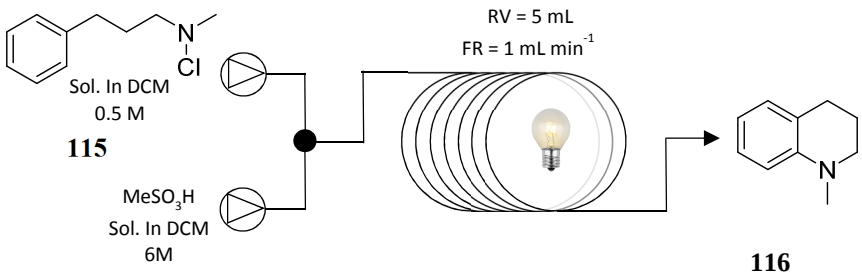


Figure 2.1

The first flow reactor built as described above, was used to carry out the *N*-arylation step depicted in Figure 2.1. The system was tested at two different flow rates to find the optimal conditions. Based on the overall productivity the flow rate was set at 1 mL min^{-1} for all future flow reactions, as there was no substantial increase in yield observed from slowing the flow rate down. The STY for the faster flow rate was calculated to be 248 g h^{-1} (Table 2.3).



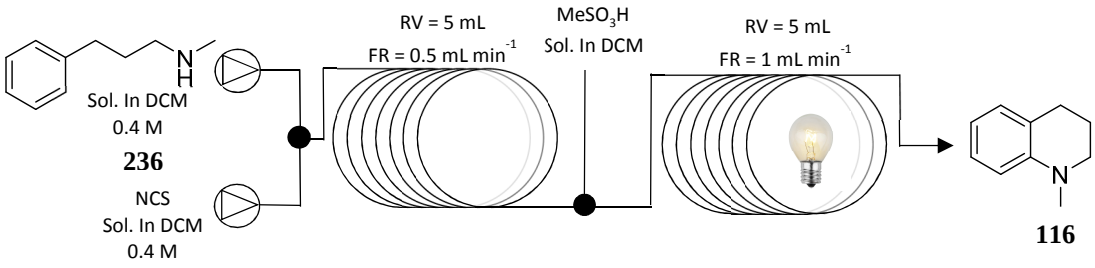
Entry	Flow rate (mL min^{-1})	Yield (%)	Productivity (g h^{-1})
1	0.33	66	0.45
2	1	62	1.25

Table 2.3

After the success of this methodology in flow it was then decided to telescope the chlorination reaction mixture to the *N*-arylation step. The chloroamine once formed was then mixed with

$MeSO_3H$ then flowed into the UV reactor for the *N*-arylation reaction to occur. An issue with the dual reactor setup was that the concentration of the reaction had to be lowered due to the limited solubility of NCS in DCM (maximum concentration 0.41 M). This meant that when the chloroamine was mixed with the solution of $MeSO_3H$ the concentration halved again to 0.1 M which lowers the overall concentration of the reactor by 2.5 times compared to the single step reactor.

Two substrates were synthesised using this dual reactor to show its overall benefits. The yield of the THQ **116** was lower when carried out in the dual reactor as opposed to the single step processes, nevertheless the dual flow reaction is more productive than the batch reactions (Table 2.4, entry 1). Cyclisations to yield the natural product angustureine did not afford the desired product cleanly instead a side product was observed, with a mass that was consistent with that of the chloroamine (Table 2.4, entry 2).



Entry	Substrate	Yield (%)	Productivity (g h^{-1})	STY (g L^{-1} h^{-1})
1		34	0.29	9.6
2		25	0.165	5.5

Table 2.4

The postulated side-product was the δ-chloroamine, arising from an intramolecular 1,5-hydride abstraction. It was hypothesised that the formation of this side product might be avoided or lowered by carrying out the chlorination step and the *N*-arylation step in flow separately.

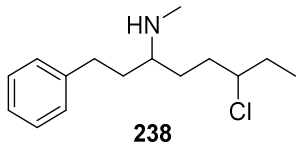


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Figure 2.2

The work detailed in this section is a continuation of this work to investigate other substrates to find the scope of this process. The investigations looked at carrying out the chlorination and the photolysis in separate steps due to the reduction in yield that was previously observed with the two-step flow reactor.

2.1.5 Chlorination in flow

Due to the issues with solubility of NCS in DCM which lead to lower concentrations for the dual flow reactor which in turn lead to lower yields of the desired cyclised product it was decided to carry out investigations into a single step chlorination flow reactor. When carried out in batch the large scale chlorination reactions gave relatively poor yields and therefore flow could be a way around this issue.

A flow reactor was built by connecting a dual syringe pump (to allow addition rates to be equal for both the amine and the NCS) to a T-junction using PTFE tubing with an I.D of 1/32nd of an inch. The other end of the T-junction was connected to 10 m of the same PTFE tubing which gave a reactor volume of 5 mL. The end of the PTFE tubing fed into a conical flask where the reactants were collected and the tubing itself was covered in tin foil to exclude light that may have resulted in product degradation.

The reaction was run at a rate of 0.5 mL min^{-1}, and after discarding the first reactor volume, which is just DCM, the rest was collected in a conical flask. The collected reactor volumes were concentrated and purified by column chromatography to afford the desired chloroamines.

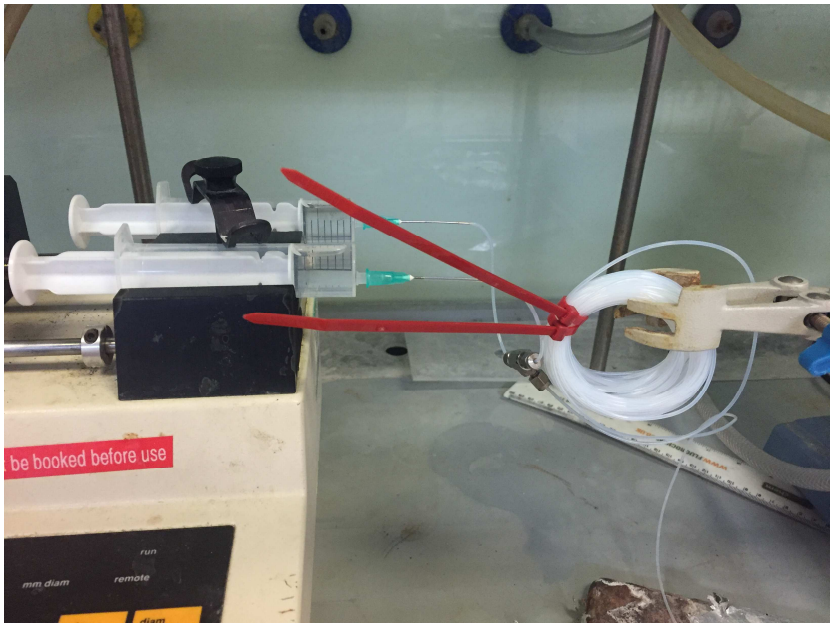
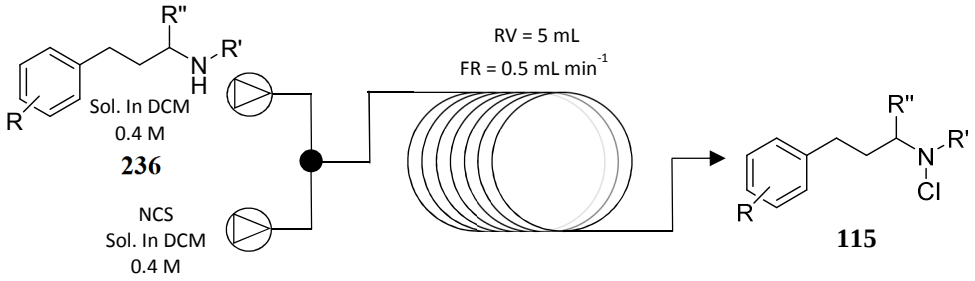


Figure 2.3

A variety of chloroamines were synthesised using the flow reactor as shown in Table 2.5. The synthesis of the amines used in the process will be discussed in chapter 3. The productivities and yields are higher than would be expected during batch reactions as when over ~750mg (5 mmol scale) of the starting material is used the yield of the chlorination decreases. This could be due to an exotherm in the reaction mixture which on a small scale the heat can be dissipated effectively but affects the chloroamine when the reaction is scaled up as there is a larger build-up of heat and the surface area:volume ratio is lower. The STY was calculated using the equation shown in section 2.1.3. The residence time for the reactor was 0.17 h and the reactor volume was 0.005 L, so for the allyl substrate (Table 2.5, entry 1) which yields 0.153g per reactor volume a STY of 180 g L^{-1} h^{-1}. Assuming for the batch reaction a 0.5 g scale and a 3 hour reaction time, the STY would be 142 mg L^{-1} h^{-1}, showing the benefits of the flow in regards to productivity.



Entry	Product	Yield (%)	Productivity (g h^{-1})	STY (g L^{-1} h^{-1})
1		73	0.92	180
2		72	1.13	221
3		61	0.97	129
4		61	0.95	100
5		51	0.78	91

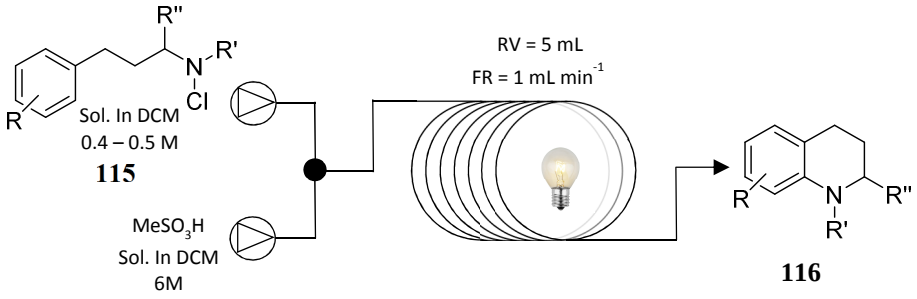
Table 2.5

With the successful synthesis of the chloroamines attention then turned to carrying out the *N*-arylation step in flow.

2.1.6 *N*-Arylation in flow

The chloroamines synthesised using the flow reactor were then subjected to the flow conditions for the *N*-arylation step. A reactor matching the one previously used within the group and described in Section 2.1.4, was built for this purpose. The mono-layer reactors have previously

been shown not to be as efficient as triple-layer reactors and could contribute to lower yields (20-30%) than observed in the batch reactions.[77] The flow reactions however do have a much higher productivity than the batch reactions which are limited to production of 0.5 g in 3-5 hours. During the reactions up to 7 column volumes (CV) were collected though the first two were discarded. The remaining CV were worked up individually and analysed by ^{1}H NMR, then these were combined and purified by column chromatography. The yields of the *N*-arylation reactions are all moderate with the exception of the bromo compound **246** (Table 2.6, Entry 4) for which a good yield of 60% was obtained. The natural product angusteriene (Table 2.6, Entry 5) had shown problems previously with the competing formation of the HLF side-products, this issue was not alleviated by carrying out the chlorination and the photolysis separately with a similar yield overall being obtained (20% over the two steps). For the STY calculation, the reactor volume is 0.005 L and the residence time is 0.083 h. In the case of the allyl substrate (Table 2.6, Entry 1) 0.084 g per reactor volume were isolated giving a STY of 198 g $L^{-1}h^{-1}$.



Entry	Starting material	Product	Yield (%)	Productivity (g h^{-1})	STY (g L^{-1} h^{-1})	Batch Yields[77]
1			38	1.00	198	40
2			43	1.29	260	82
3			60	1.62	325	72
4			35	0.76	152	72
5			40	0.65	130	50

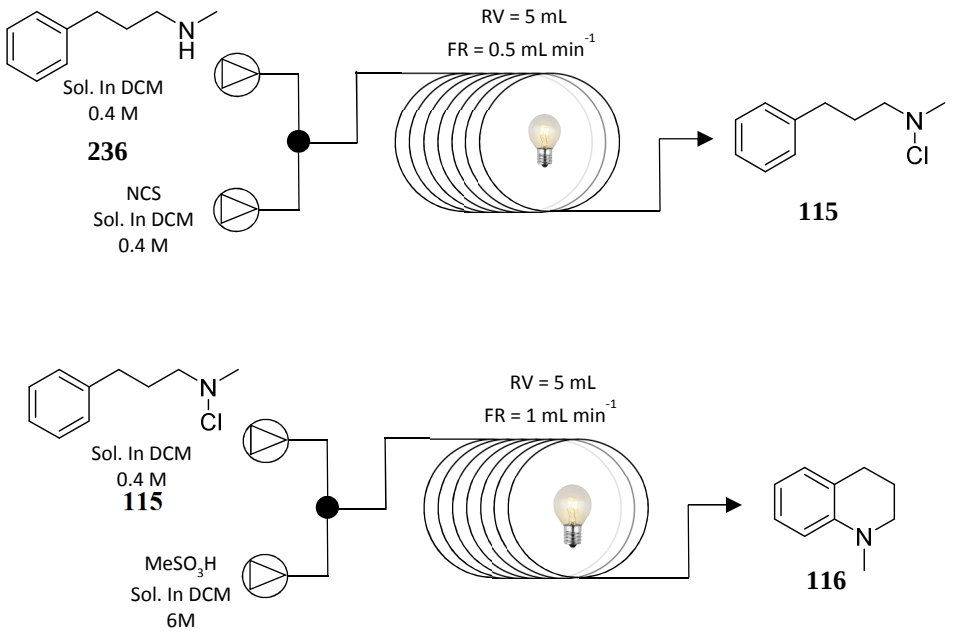
Table 2.6

The *N*-arylations yields in flow were slightly lower than the batch yields however the productivity is higher and the yields could also be potentially increased with multilayer reactors as previously described (Section xx) Due to the success of the reactions in flow in both the chlorination and the *N*-arylation step it was therefore decided to carry out the reaction on a larger scale.

2.1.7 Large scale chlorination and flow chemistry

With the success of the chlorination in flow and the *N*-arylation it was decided to see if it was possible to carry this out on a larger scale as previously the *N*-arylation was carried out on under a gram of material.

The chlorination step was carried out using a flow rate of 0.5 ml min^{-1} as before; overall 3 g of the amine **236** were used in the reaction which afforded a 45% yield of the desired chloroamine **115** which is lower than expected however still better than would have been achieved in batch on such a scale (40% yield obtained in a 1g batch reaction). The *N*-arylation was then carried out using the previously described reactor at a flow rate of 1 mL min^{-1}. The first two reactor volumes were discarded and the rest of the reactor volumes were collected in a conical flask. The productivity was slightly lower for the *N*-arylation than had previously been observed within the group on a smaller scale. The lower productivity of the chlorination step could be attributed to the issues with the solubility of the NCS in DCM and some solid was observed to have formed in the syringe. This issue could be avoided potentially through a faster flow rate or using alternative chlorination conditions. The slightly lower productivity for the *N*-arylation step could be caused by decomposition of the chloroamine before it entered the photochemical reactor.



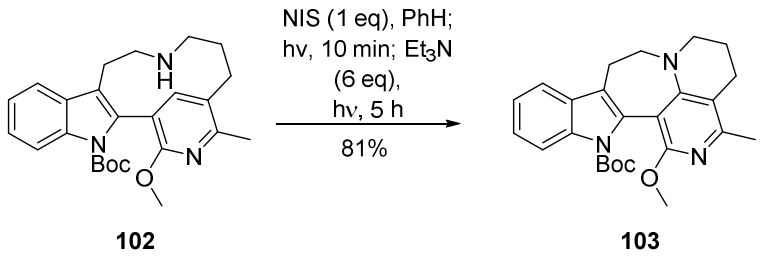
Entry	Reaction	Yield (%)	Productivity (g h^{-1})	STY (g L^{-1} h^{-1})
1	Chlorination	45	0.498	97
2	*N*-arylation	58	1.12	224

Table 2.7

A process has been successfully established for the scale up of both the chloroamines and the *N*-arylation to synthesis THQs, with the successful synthesis of a variety of substrates with various substitution problems.

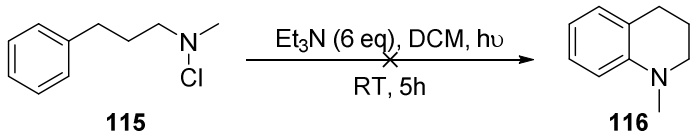
2.2 Investigation of potential heteroaromatic *N*-arylations

As stated previously the Marsden group has established a modified HLF methodology that utilises UV light under acidic conditions for the formation of C-N bonds. These results are consistent with the proposed reaction mechanism which states the intermediate involves a protonated aminyl radical. In contrast to these results as shown in Scheme 2.3, Sarpong *et al.* have shown that an *N*-arylation of a pyridine can be carried out under basic conditions under UV irradiation.[43]



Scheme 2.3

However when these basic conditions were applied to the substrates that worked under acidic conditions, in our group, no reactions were observed (Scheme 2.4).[77]



Scheme 2.4

It was decided to investigate whether the basic conditions detailed by Sarpong *et* al. could be utilised to *N*-arylate other heteroaromatic rings. With this in mind, similar compounds to those previously shown to work within the group were proposed, however this time with a pyridine ring instead of the phenyl ring, with substitution in the 3- and 4- positions of the pyridine being investigated (Figure 2.4). Once synthesised, the *N*-halo amines were irradiated with UV light under both basic and acidic conditions, to see what the effect the heterocyclic rings would have.

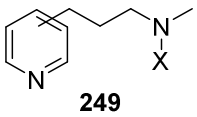
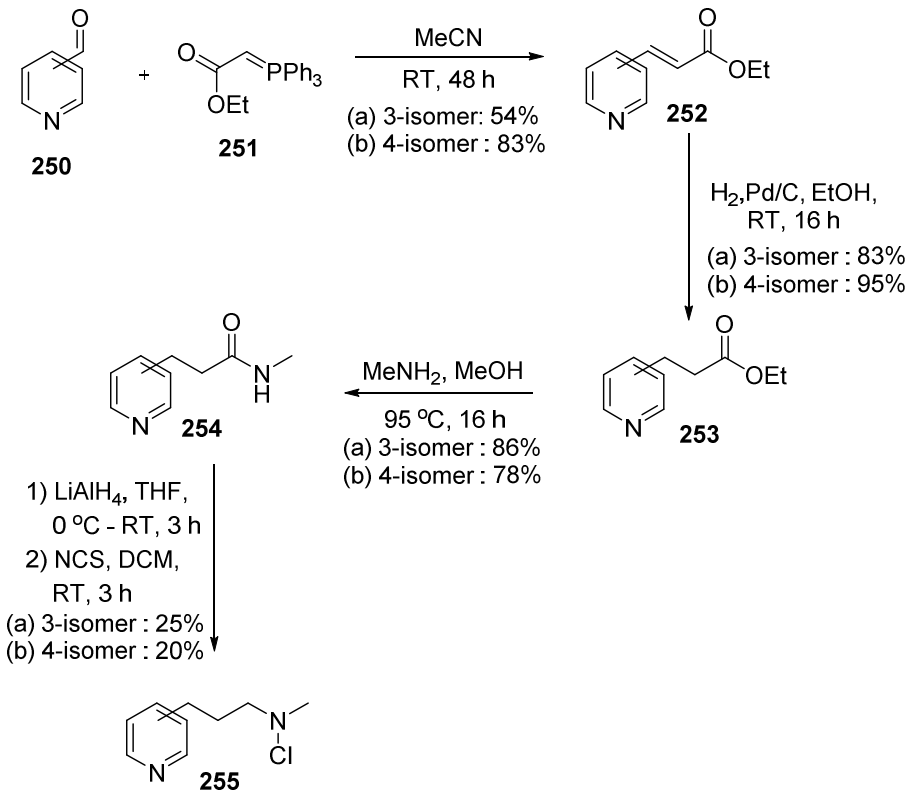


Figure 2.4

2.2.1 Substrate synthesis

The synthetic route used to afford the desired substrates is shown in Scheme 2.5. The first step was a Wittig reaction between pyridine carboxaldehyde **250** and the ester **251**. Both the 3- and the 4- substituted pyridinecarboxaldehydes were used. Hydrogenation of the alkenes **252** afforded the esters **253** in 83-95% yield. Following literature procedures for similar compounds the *N*-methyl amides **254** could be obtained by heating the esters with excess $MeNH_2$ solution,

achieving 78-86% yields.[78] $LiAlH_4$ reduction was used to obtain the *N*-methylamines, however due to the polarity of the products, isolation was difficult, resulting in low yields (crude yield 50%) and therefore the crude material was telescoped through to the next step. The final step in the synthesis was the formation of the chloroamine **255**. Following the conditions used by De Luca *et al*., the crude amine was stirred with *N*-chlorosuccinimide in DCM for 3 hours followed by purification by column chromatography to remove the succinimide by-product.[79] This unfortunately provided low yields over the two steps (20-25 %) but enough material was obtained to try the *N*-arylation reaction under various conditions.

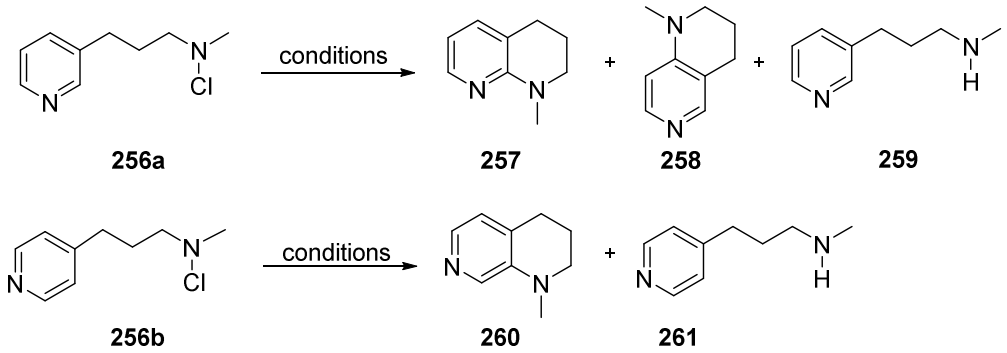


Scheme 2.5

2.2.2 Intramolecular *N*-arylation reactions on pyridine substrates

With the successful synthesis of the chloroamine derivatives achieved, investigations into the light-mediated *N*-arylation under conditions previously detailed by Sarpong *et al*. were attempted.[43] This involved photolysis of the chloroamines **256a** and **256b** with Et_3N in DCM (Table 2.8, Entries 1-2) Using a 125W high pressure mercury lamp. Unfortunately, when basic conditions were employed the product was not observed by LC-MS analysis or ^1H NMR and only amines **259** and **261** was isolated. The reaction was also attempted under the acidic

conditions that have previously been shown to work the best within the Marsden group (Table 2.8, Entries 3-4). The use of both $MeSO_3H$ and conc. H_2SO_4 was attempted however, no product was observed in either reaction and only the dechlorinated amine was recovered (Table 2.8, Entries 3-5).



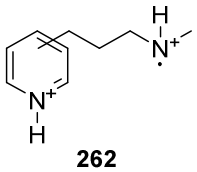
256a **257** **258** **259**

256b **260** **261**

Entry	Substrate	Conditions	Products
1	3-pyridine **256a**	Et_3N, DCM, hυ, RT, 5 h	Amine **259**
2	4-pyridine **256b**	Et_3N, DCM, hυ, RT, 5 h	Amine **261**
3	3-pyridine **256a**	$MeSO_3H$, DCM, hυ, RT, 5 h	Amine **259**
4	4-pyridine **256b**	$MeSO_3H$, DCM, hυ, RT, 5 h	Amine **261**
5	4-pyridine **256b**	H_2SO_4, hυ, RT, 5 h	Amine **261**

Table 2.8

Under the acidic conditions the pyridine nitrogen would be protonated, making the system more electron-deficient. Therefore, it is likely to show decreasing reactivity towards the electrophilic aminyl radical as it requires a more nucleophilic species to react with.

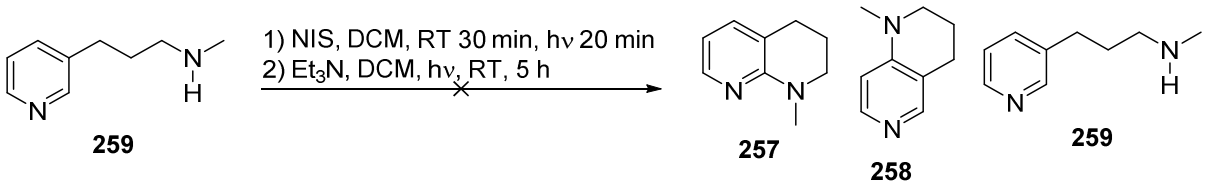


262

Figure 2.5

After a lack of success with the chloroamines it was proposed that the iodoamine could be formed *in situ* then photolysed as detailed by Sarpong *et al* (Scheme 2.6).[43] The reaction was

carried out exactly as described in Sarpong's paper, however no desired product was observed by ^{1}H NMR or LC-MS analysis and only the amine **259** was recovered.



Scheme 2.6

2.2.3 Methoxypyridine substrates

Due to the lack of success with the pyridyl series under a range of conditions, a new substrate was proposed. The structure was based on the core of arboflorine **103** which was constructed through metal-free *N*-arylation methodology by Sarpong *et al*.[43] The pyridine ring in this case is more electron rich due to the methoxy group, two alkyl substituents and the heteroaryl group.

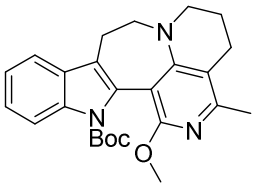


Figure 2.6

A methoxy group was added in the 2-position of the pyridine to make a more electron-rich system than the previous substrates with the hope of promoting the cyclisation. With the alkyl chain *para* to the methoxy this would then allow cyclisation to either the 4 or 6-position of the pyridine ring (compound **263**).

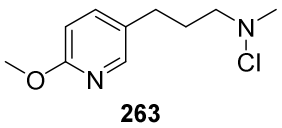
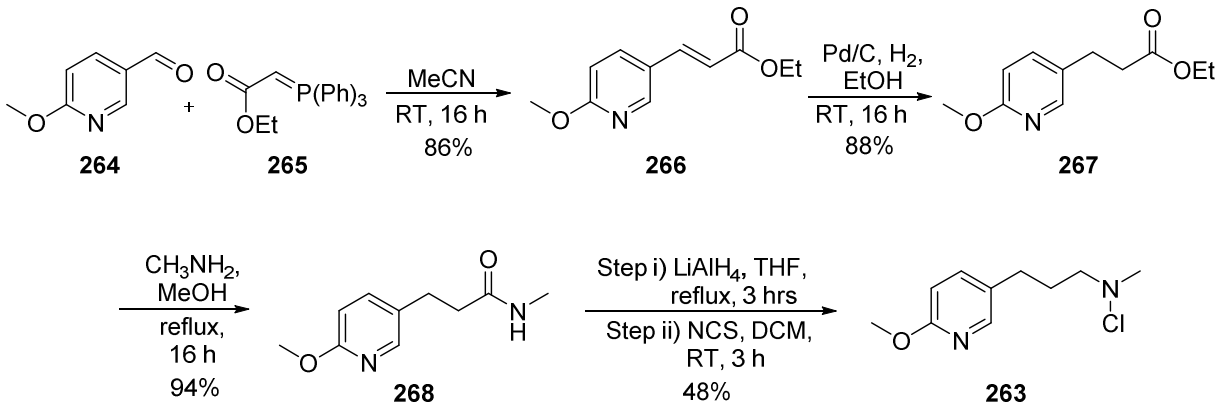


Figure 2.7

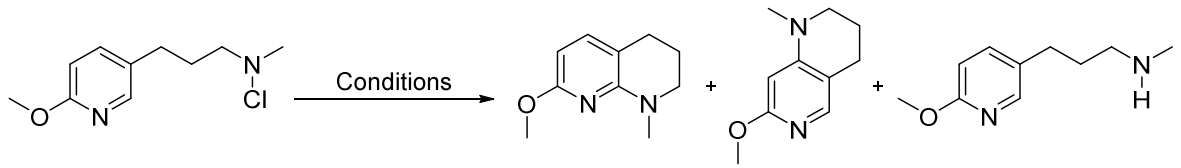
The synthesis of the methoxypyridine substrate **263** was carried out via the same synthetic route used for the previous substrates (Scheme 2.7). The Wittig reaction used to form ester **266** provided higher yields than previously seen in the pyridyl series. Hydrogenation afforded ester **267** in 88% yield, which was converted to the amide **268** in 94% yield. The amide **268** was reduced to the amine using $LiAlH_4$, which was directly converted to the chloroamine **263** in a 48% yield over 2 steps. The yield over these 2 steps was an improvement on the yields observed for the previous pyridyl substrates and it allowed us to access enough of the desired chloroamine **263** to test various *N*-arylation conditions.



264 **265** **266** **267** **268** **263**

Scheme 2.7

The substrate **263** was subjected to conditions already applied to previous substrates (Table 2.9). Under basic conditions none of the desired product was observed by LC-MS analysis or ^{1}H NMR with the amine being the major product of the reaction (Table 2.9, Entry 1). The acidic conditions that have been successful for other substrates within the Marsden group were applied, however no desired product was observed when using either H_2SO_4 or $MeSO_3H$ (Table 2.9, Entries 2-3).

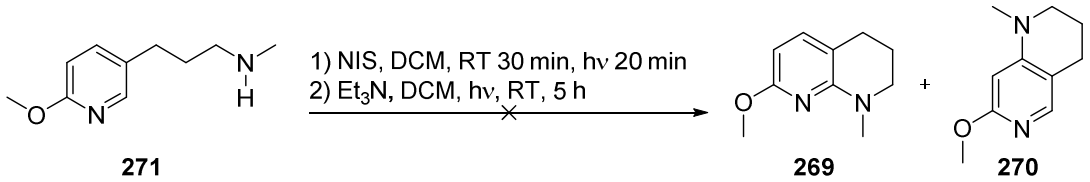


263 **269** **270** **271**

Entry	Conditions	Product
1	Et_3N (6 eq), DCM, hυ, RT, 5 h	Amine **271**
2	$MeSO_3H$ (10 eq), DCM, hυ, RT 5 h	Amine **271**
3	H_2SO_4 (80% soln. in H_2O), hυ, RT, 5 h	Amine **271**

Table 2.9

The last set of conditions that were trialled were Sarpong's (Scheme 2.8) which forms the iodoamine *in situ*, again however this did not yield any of the desired product and only amine **271** was obtained.



Scheme 2.8

In summary the intramolecular aromatic amination of the pyridine has been unsuccessful using the substrates that we have proposed both with and without the methoxy group present. Sarpong's conditions used in the synthesis of arboflorine were also applied however no desired products were obtained. These conditions could have been successful in Sarpong's case due to the enforced proximity of the reactive aminyl radical to the pyridine ring. In the pyridine substrates that we have investigated there is a higher degree of rotational freedom of the radical which is not held in close proximity to the pyridine ring. This decreases the likelihood of cyclisations and increasing the possibility of hydrogen abstraction before the radical can cyclise.

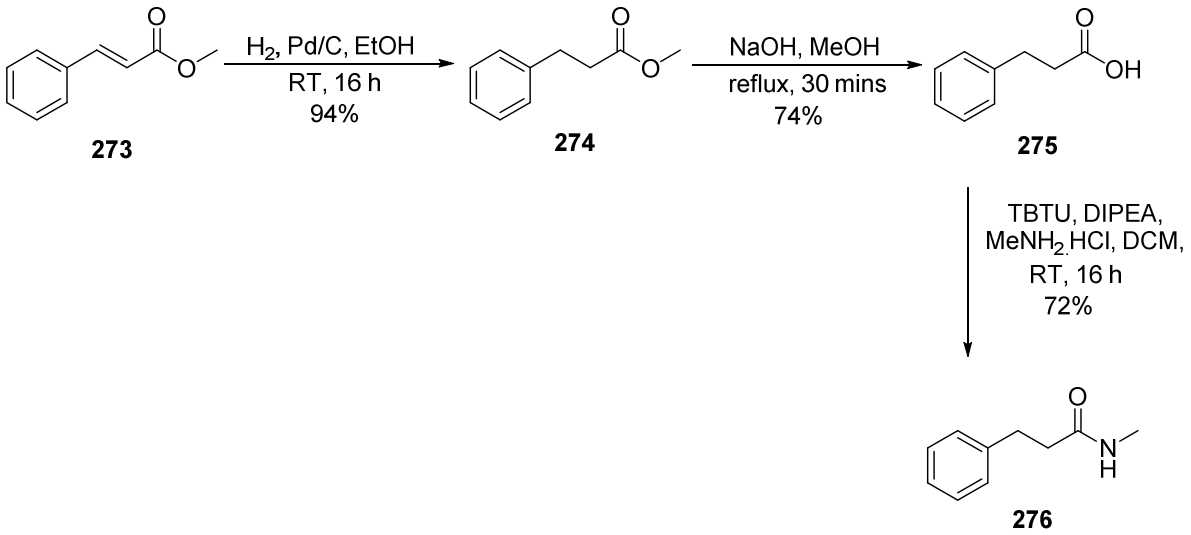
2.3 Amidyl radicals

To continue our investigations into *N*-arylation reactions of nitrogen-centred radicals and to expand the substrate scope, amidyl radicals were tested under various conditions.

2.3.1 Synthesis of substrates for tetrahydroquinolinones

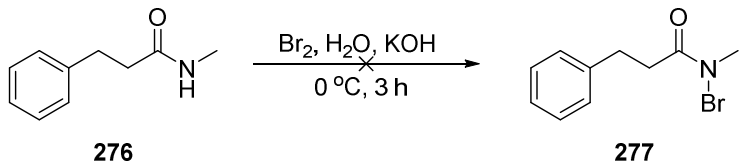
Due to previous success within the Marsden group with similar amine substrates, the amide **276** was proposed. The proposed synthesis for the amide **276** is shown in Scheme 2.9. The first step was a hydrogenation reaction to reduce the double bond which afforded the ester **274** in a 94% yield. Initial trials to convert ester **274** to amide **275** in one step by refluxing in methylamine as had been previously used in the pyridine substrate synthesis was not successful and gave a mixture of the starting ester **274**, ethyl ester and the amide **276**. Therefore, it was decided to proceed via saponification of ester **274** to yield the carboxylic acid **275** in a 74%

yield. The acid **275** was converted via an amide coupling reaction with methylamine to afford the desired amide **276** in a 72% yield.



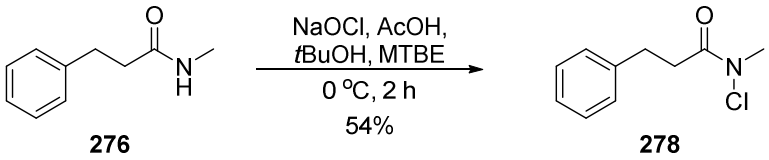
Scheme 2.9

Due to issues previously encountered within the group when attempting the chlorination of an amide using NCS, in which no chlorination was observed, it was decided to proceed with bromination instead. However, the conditions found within the literature did not yield the desired product and instead only the starting amide **276** was recovered (Scheme 2.10).



Scheme 2.10

With the unsuccessful attempts to brominate the amide, alternative conditions were found for chlorination.[80] This reaction involves the *in situ* formation of *tert*-butyl hypochlorite. This reaction proceeded well using one equivalent of each reagent and afforded the desired compound **278** in reasonable yields (Scheme 2.11).



276 278

Scheme 2.11

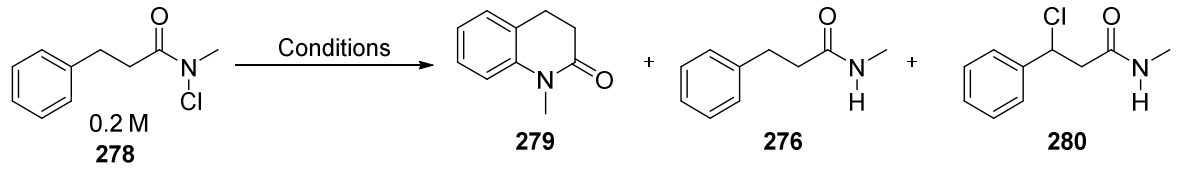
Different equivalents of the reagents were investigated to see if the yield could be increased (Table 2.10). Gratifyingly the yield was shown to improve with the best results being seen when using 1.5 equivalents of each reagent; no chlorination on the aryl ring was observed (Table 2.10, entry 3).

Entry	Equivalents of reagents	Yield of chloroamide 278
1	NaOCl (1.00 eq), AcOH (1.00 eq), *t*BuOH (1.00 eq)	54 %
2	NaOCl (1.05 eq), AcOH (1.05 eq), *t*BuOH (1.05 eq)	66 %
3	NaOCl (1.50 eq), AcOH (1.50 eq), *t*BuOH (1.50 eq)	83 %

Table 2.10

With the chloroamide **278** in hand, the compound was irradiated under UV light using a 125W high pressure mercury lamp under a range of conditions for the *N*-aryl cyclisation reaction. The acidic, basic and Lewis acid conditions were chosen due to previous work carried out within the Marsden group.[77] Neutral conditions which utilise a range of solvents of increasing polarity were chosen in line with what had been used previously in literature.[81] When the reaction was tried under basic conditions or neutral conditions this did not yield any of the desired product (Table 2.11). A similar result was seen when the reaction was carried out in the presence of a Lewis acid (Table 2.11, Entry 9). Only the dechlorinated amide **276** was isolated at the end of the reactions. An interesting result was observed when the reaction was carried out in 10 equivalents of methanesulfonic acid; the benzylic chloride **280** was isolated in a 52% yield (Table 2.11, Entry 2). One way in which the benzylic chloride product **280** could be formed is if after homolytic cleavage of the N-Cl bond the amidyl formed abstracts a hydrogen from another chloroamide. This would generate a benzylic radical which could then abstract a chlorine from another molecule of chloroamide. This reaction was repeated in the dark to establish if this reaction was photochemically mediated. Only the chloroamide was obtained after 5 hours showing that it is a light mediated process. The same result however was not

found in the stronger acidic conditions when concentrated H_2SO_4 was used (Table 2.11, Entry 3).



Entry	Conditions	Products
1	Et_3N (6 eq), DCM, hυ, RT, 5 h	Amide **276** (90%)
2	$MeSO_3H$ (10 eq), DCM, hυ, RT, 5 h	**280** 52% yield
3	H_2SO_4 (80% soln. in H_2O), hυ, RT, 5 h	Amide **276** (85%)
4	DCM, hυ, RT, 5 h	Amide **276** (93%)
5	Toluene, hυ, RT, 5 h	Amide **276** (84%)
6	CH_3CN, hυ, RT, 5 h	Amide **276** (89%)
7	*t*-Butanol, hυ, RT, 5 h	Amide **276** (88%)
8	2-Methyl but-2-ene (1 eq), DCM, RT, hυ, 5 h	Amide **276** (86%)
9	$BF_3{\cdot}OEt_2$(5 eq), DCM, hυ, RT, 5 h	Amide **276** (85%)

Table 2.11

The structure of **280** was assigned through the NOESY NMR spectrum to confirm which carbon the chlorine was on. It showed there was a long range correlation between H^2 and the amide proton but no correlation between H^1 and the amide proton. The signal for H^1 showed a correlation to H^2 but no long range correlation was observed between H^1 and H^3 (Figure 2.7).

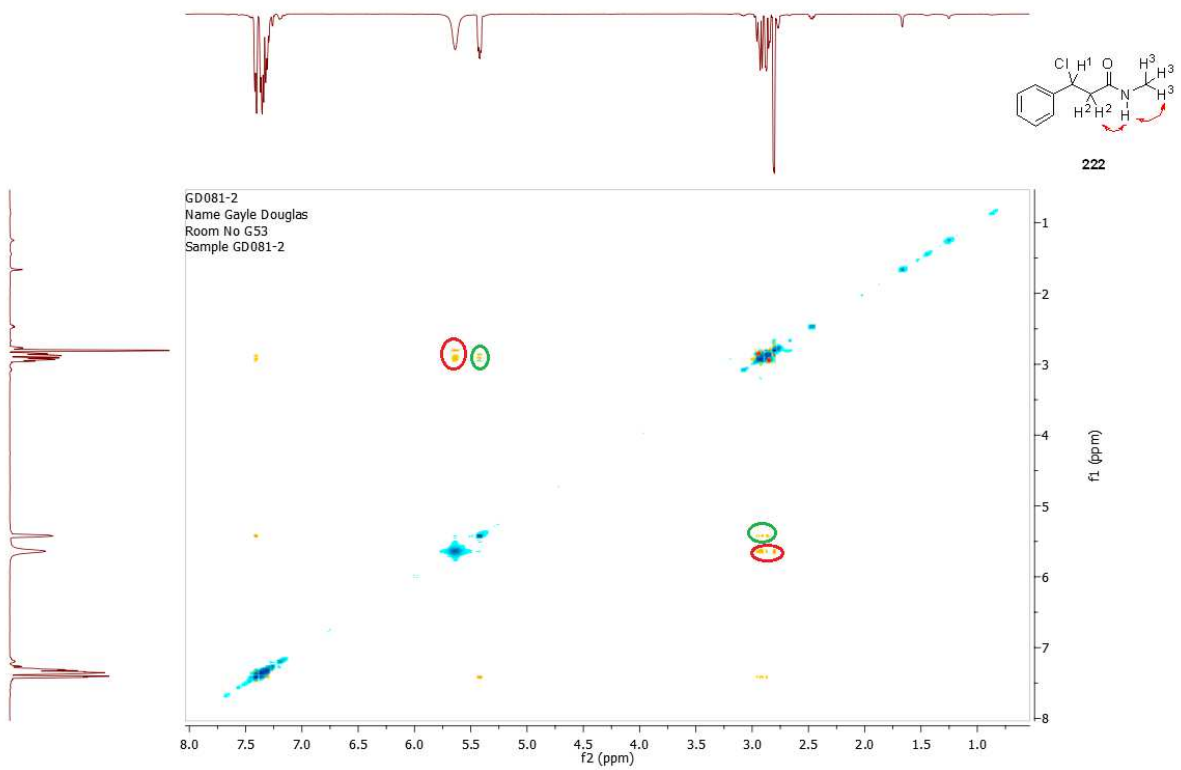
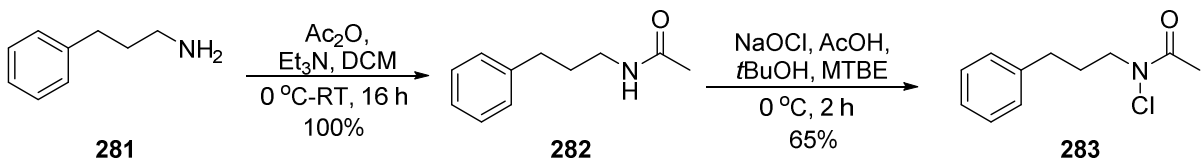


Figure 2.8

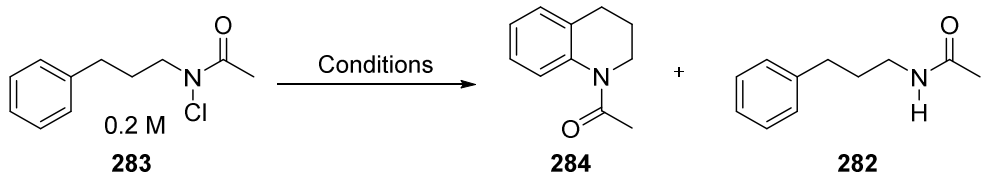
2.3.2 Synthesis of substrates for *N*-acetyltetrahydroquinolinones

Investigations within the literature into amidyl radicals looked at both the amide both in and outside of the ring. Therefore, the second substrate that we investigated for the formation of the six-membered rings *via* amidyl radicals, had the inverted amide bond so the carbonyl would be *exo*- to the forming ring. The first step in the synthesis of the chloroamide **283** was the acetylation of phenylpropylamine **281**, which proceeded in quantitative yield (Scheme 2.12). The chlorination of the amide **282** was carried out under the previously established conditions to afford chloroamide **283** in 65% yield.



Scheme 2.12

The same conditions for the *N*-arylation reaction were screened against the chloroamide **283** (Table 2.12). Unfortunately, none of the conditions afforded any of the desired product with the major product being the amide **282**.

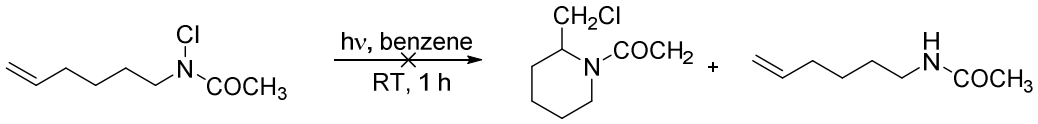


283 **284** **282**

Entry	Conditions	Products (isolated yields)
1	Et_3N (6 eq), DCM, hυ, RT, 5 h	Amide **282** (90%)
2	$MeSO_3H$ (10 eq), DCM, hυ, RT, 5 h	Amide **282** (89%)
3	H_2SO_4 (80% soln. in H_2O), hυ, RT, 5 h	Amide **282** (87%)
4	DCM, hυ, RT, 5 h	Amide **282** (92%)
5	Toluene, hυ, RT, 5 h	Amide **282** (88%)
6	MeCN, hυ, RT, 5 h	Amide **282** (93%)
7	*t*-Butanol, hυ, RT, 5 h	Amide **282** (88%)
8	2-Methyl but-2-ene, DCM, hυ, RT, 5 h	Amide **282** (86%)
9	$BF_3{\cdot}OEt_2$, DCM, hυ, RT, 5 h	Amide **282** (85%)

Table 2.12

Within the literature a control experiment was carried out by Kuehne *et al* to show whether the amidyl radical would carry out a 6-*exo* cyclisation, however this reaction only yielded the amide **160**.[59]

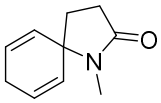


158 **159** 0% **160** 90%

Scheme 2.13

This could explain why the trials to form the tetrahydroquinolones under our conditions; even when a 6-membered ring could be formed, have been unsuccessful and no cyclisation product was observed. If the same stereoelectronic traits were at play then preference for the 5-membered ring formation would lead to the formation of the spiro compound **285.** This might

not be a facile process due to the inability of this compound to re-aromatise making this process unfavourable.

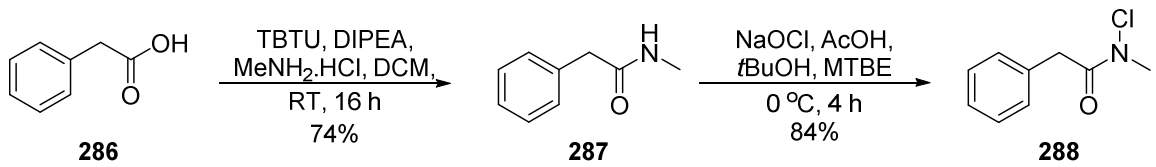


285

Figure 2.9

2.3.3 Synthesis of substrates for dihydroindolones

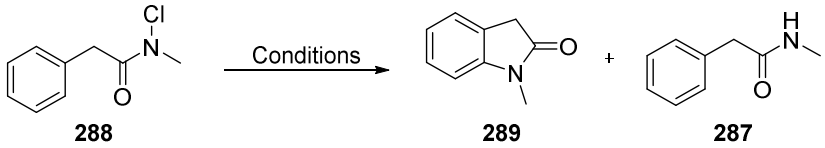
Due to the unsuccessful investigations into cyclisations to form 6-membered rings studies into the 5-membered ring formation were initiated. The amide **287** was constructed from phenylacetic acid **286** and methylamine *via* an amide coupling reaction in 74% yield. The next step was the chlorination of amide **287** which was carried out under the previously established conditions and afforded the desired chloroamide **288** in 84 % yield (Scheme 2.14).



286 **287** **288**

Scheme 2.14

Applying the neutral and basic conditions previously used did not yield any of the desired product (Table 2.13). Also, no product was observed in concentrated sulphuric acid, however when 10 equivalents of methanesulfonic acid was used, product **289** was observed by ^{1}H NMR and LC-MS analysis. Unfortunately, none of the desired product was isolated with only the amide **287** isolated. The conditions using the $BF_3.OEt_2$ in DCM yielded 10 % of the desired product **289** with the amide **287** being the major product.

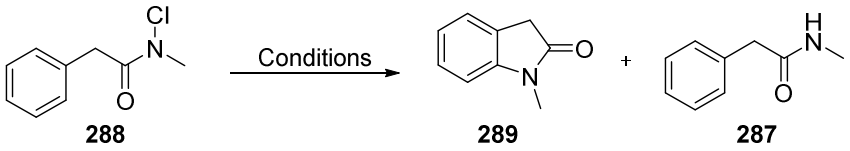


288 **289** **287**

Entry	Conditions	Product (isolated yield%)
1	Et_3N (6 eq), DCM, hυ, RT 5 h	Amide **287** (88%)
2	$MeSO_3H$ (10 eq), DCM, hυ, RT, 5 h	Amide **287** (80%) + dihydroindolones **289** (trace)
3	H_2SO_4 (80% soln. in H_2O), hυ, RT, 5 h	Amide **287** (85%)
4	Toluene, hυ, RT, 5 h	Amide **287** (92%)
5	DCM, hυ, RT, 5 h	Amide **287** (95%)
6	*t*-Butanol, hυ, RT, 5 h	Amide **287** (96%)
7	$BF_3{\cdot}OEt_2$ (5 eq), DCM, hυ, RT, 5 h	Dihydroindolones **289** (10% yield)

Table 2.13

With the initial success seen with the Lewis acid conditions in DCM a different Lewis acid was examined. It was also hoped that less polar solvents would force the Lewis acid to interact with the chloroamide **288** and promote the cyclisation to form the desired product **289** (Table 2.14). Toluene was chosen as the solvent and desired product was isolated in 9% yield, however a large amount could not be separated from an unidentified side product. Other solvents tried included anisole and chlorobenzene however the desired product was not isolated from either of these reactions. The other investigation that was carried out looked into changing the Lewis acid and for this aluminium trichloride was picked. This did not afford any of the desired product. The reaction was also carried out in the dark (as a control) to observe whether the dichlorination to form the free amide light mediated or not. After five hours only the chloroamide **288** was observed by ^{1}H NMR and LC-MS analysis showing that the light is a key factor in the reaction.



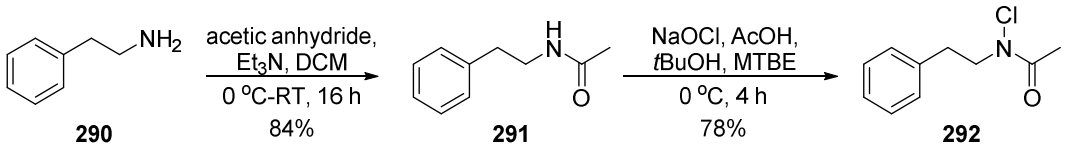
288 **289** **287**

Entry	Conditions	Products (isolated yield%)
1	$BF_3{\cdot}OEt_2$, DCM, hυ, RT, 5h	Amide **287** + product **289** (10% yield)
2	$BF_3{\cdot}OEt_2$, toluene, hυ, RT, 5h	Amide **287** + product. **289** (9% yield)
3	$BF_3{\cdot}OEt_2$, anisole, hυ, RT, 5h	Amide **287** (95%)
4	$BF_3{\cdot}OEt_2$, chlorobenzene, hυ, RT, 5h	Amide **287** (92%)
5	$AlCl_3$, DCM, hυ, RT, 5h	Amide **287** (93%)
6	$BF_3{\cdot}OEt_2$, DCM, dark, RT, 5h	Chloroamide **288** (98%)

Table 2.14

2.3.4 Synthesis of substrates for *N*-acetyldihydroindolones

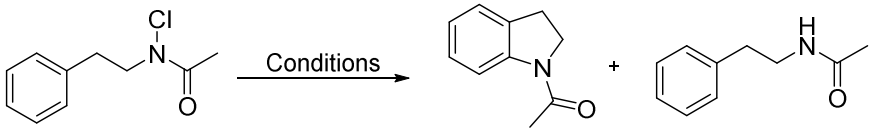
Following on from our previous investigations into amidyl radicals it was also decided to investigate the acetylated version where the amide would be in the *exo*- position to the ring after cyclisation. This could also show whether having the sp^2 internal or external has an effect on the cyclisation of the amidyl radical. The first step in the synthesis was the acetylation of phenylethylamine **290** which gave the desired product **291** in 84% yield (Scheme 2.15). The next step was the chlorination of the amide using the previously established conditions to afford chloroamide **292** in a 78% yield.



290 **291** **292**

Scheme 2.15

The same conditions that were tested previously were applied to the chloroamide **292** (Table 2.15). No desired product was observed under the basic conditions or acidic conditions with only the dechlorinated amide being isolated. The Lewis acid conditions yielded a more positive result with traces of the product being observed by ^1H NMR and LC-MS analysis. However, after purification only 3% yield of the desired compound were obtained with impurities.

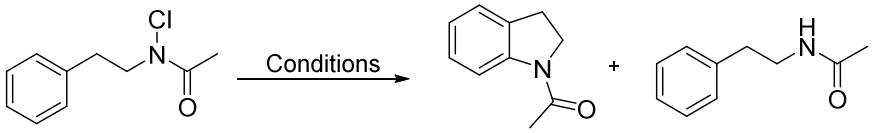


292 **293** **291**

Entry	Conditions	Result
1	Et_3N (6 eq), DCM, hυ, RT, 5h	Amide **291** (92%)
2	$MeSO_3H$ (10 eq), DCM, hυ, RT, 5h	Amide **291** (93%)
3	Toluene, hυ, RT, 5h	Amide **291** (94%)
4	DCM, hυ, RT, 5h	Amide **291 (**88%)
5	MeCN, hυ, RT, 5h	Amide **291** (90%)
6	*t*-Butanol, hυ, RT, 5h	Amide **291** (94%)
7	$BF_3{\cdot}OEt_2$ (5 eq), DCM, hυ, RT, 5h	Amide **291** + product **293** (3% yield impure)

Table 2.15

As a result of the success of the Lewis acid reaction, the compound was tested with an alternative Lewis acid and other non-polar solvents (Table 2.16). When toluene was used as solvent none of the desired product was observed by ^1H NMR or LC-MS analysis. However, when it was tested in hexane the product was observed by ^1H NMR and 6% yield of the product was isolated after purification with impurities present. When the reaction was carried out using the $AlCl_3$ none of the desired product was isolated. As before, the reaction using $BF_3{\cdot}OEt_2$ in DCM was also carried out in the dark. After 5 hours only the chloroamide **292** was present in the reaction mixture.



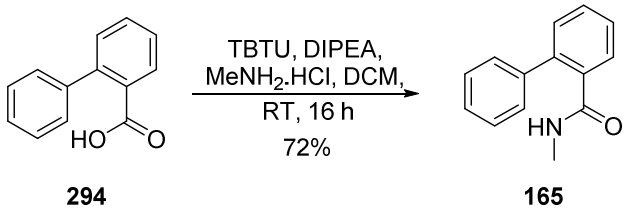
292 **293** **291**

Entry	Conditions	Products (isolated yields%)
1	$BF_3{\cdot}OEt_2$ (5 eq), DCM, hυ, RT, 5h	Amide **291** + D.P. **293** (3% yield impure)
2	$BF_3{\cdot}OEt_2$, toluene, hυ, RT, 5h	Amide **291** (95%)
3	$BF_3{\cdot}OEt_2$, hexane, hυ, RT, 5h	Amide **291** + D.P. **293** (6% yield impure)
4	$AlCl_3$, DCM, hυ, RT, 5h	Amide **291** (94%)

Table 2.16

2.3.5 Constrained systems

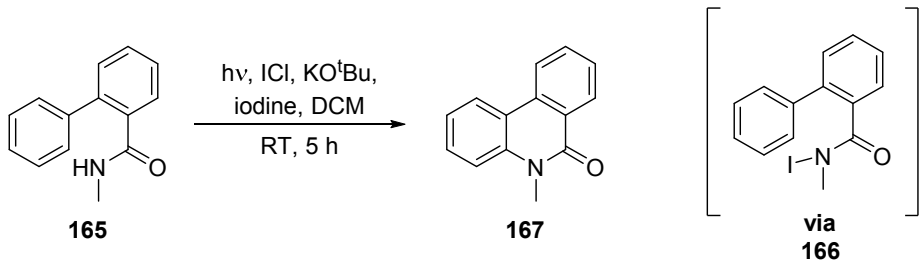
Due to success that had been seen previously in the group with less conformationally free substrates it was decided to try and see if this would have an effect for amidyl radicals. An example of a biaryl system was found within the literature in which they formed the iodoamide **166** *in situ* which then cyclised.[61] The amide **165**, was prepared by an amide coupling with biphenylcarboxylic acid **294** and methylamine in 72% yield (Scheme 2.16).



294 **165**

Scheme 2.16

The conditions to form the iodoamide *in situ* were then attempted with the only change made to the conditions was DCM used instead of carbon tetrachloride (Scheme 2.17). In the paper the reaction was irradiated under UV light for 1.5 hours, however in our hands this only yielded trace product. It was therefore decided to extend this time to 5 hours but again only trace product was observed by ^{1}H NMR.



165 **167** **via 166**

Scheme 2.17

The signals corresponding to the amide **165** were still observed as the major component of the reaction mixture in the crude ^{1}H NMR spectrum (Figure 2.9). The signals that are outlined in green in Figure 2.10 correspond to the desired product.[61] The same result is observed whether the reaction mixture is irradiated under UV light for 1.5 or 5 hours.

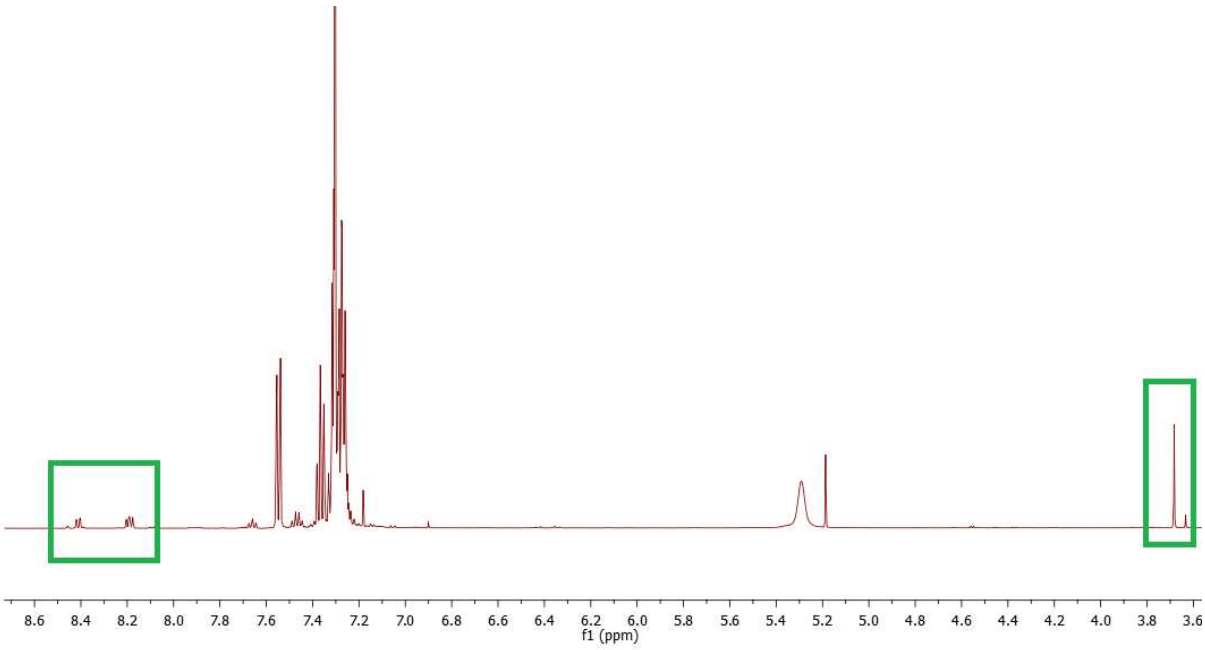
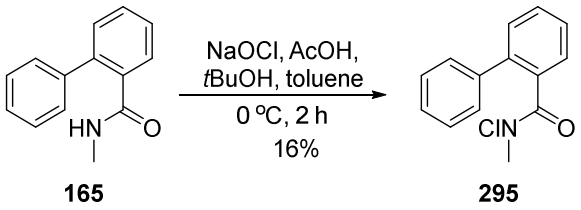


Figure 2.10

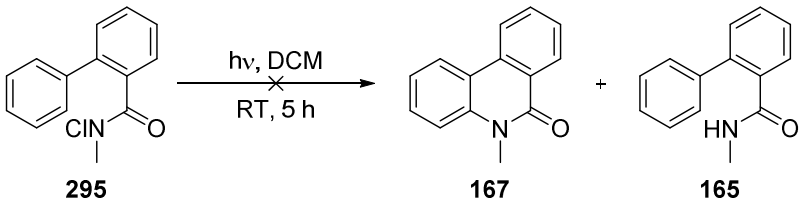
It was then decided to try and see if the chloroamide **295** might give better results. There were issues with the formation of the chloroamide for this compound due to solubility issues with the starting material. Better results were seen with toluene, as opposed to MTBE or EtOAc, and a small amount of the chloroamide **295** was obtained (Scheme 2.18).



165 **295**

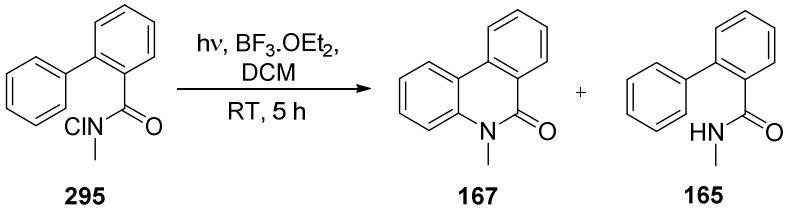
Scheme 2.18

The substrate **295** was subjected to the neutral conditions and photolysis with a Lewis acid. Unfortunately, no product was observed when the reaction was carried out under neutral conditions using DCM as solvent (Scheme 2.19). Only the amide **165** was isolated at the end of the reaction.



Scheme 2.19

Photolysis of the bi-aryl system was also attempted under the Lewis acid conditions that had previously shown success with a different substrate, trace product was observed by ^{1}H NMR (Scheme 2.20). A control experiment was also carried out in the dark after 5 hours only the chloroamide was present in the reaction mixture showing the irradiation under UV light is key to the formation of the product. There was no improvement under these conditions compared with the formation of the iodoamide *in situ*.



Scheme 2.20

The intramolecular aromatic amination reactions using the amidyl reactions to form the six-membered quinolone substrates has been unsuccessful under a range of conditions. This could be due to the preference for five membered rings.

With regards to the cyclisation to form five-membered rings some success with the addition of Lewis acids to the reaction mixture with the desired product isolated in 10% yield. These conditions have been applied to several substrates with limited success seen.

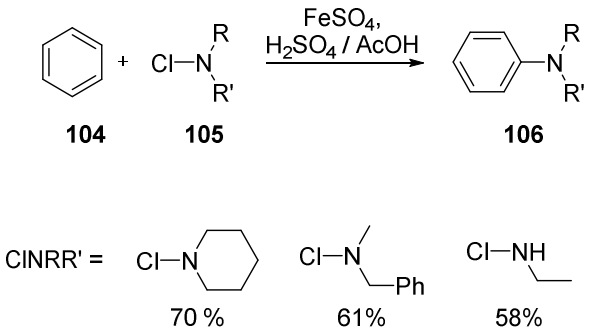
The conformationally restrained systems also showed limited success under the conditions found within the literature and under the conditions that had proved to be the most successful for our proposed substrates. There was also difficulty in chlorinating the bi-aryl systems due to solubility issues with the compound which also added to its limited success.

Chapter 3 *N*-arylation reactions using chloroamines and iron salts

3.1 Introduction

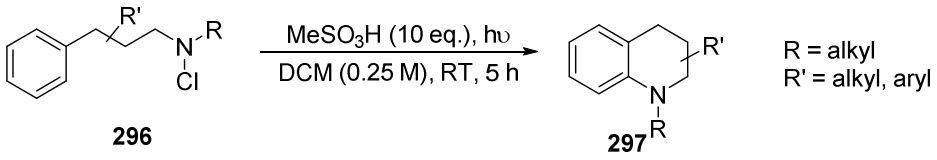
Current *N*-arylation techniques, such as the Buchwald-Hartwig cross-coupling reaction and the Ullmann coupling, often require expensive or bespoke ligands (eq xphos, *t*BuBrettphos), require pre-functionalised aryl species and precious-metal catalysts leading to high-cost synthetic routes.[7,11] An alternative method that can be used is direct aromatic amination of unfunctionalised aromatics with aminium radicals which can be generated through a variety of methods such as photolysis, single electron transfer and thermolysis.

A modified version of the HLF reaction was demonstrated by Minisci who showed that chloroamines could be used to aminate aromatic rings in either intermolecular or intramolecular reactions. The limited examples in the literature use Fe(II) and Ti(III) salts in concentrated acid (Scheme 3.1).[45]



Scheme 3.1

This process suffers from problems associated with using concentrated sulfuric acid as the reaction solvent, such as its highly corrosive nature, the viscosity of the reaction and the aqueous nature of it which leads to heterogenous reaction mixtures. It was therefore decided to investigate whether the iron salts could be used in conjunction with the homogenous organic media conditions that have been previously established within the Marsden group for use in photolysis, which utilise $MeSO_3H$ in DCM (Scheme 3.2). Intial investigations focused on the formation of THQs so a direct comparison with the photochemical approaches developed within the group can be carried out. There had also been one THQ example within the literature demonstrated by Minisci where R' = H and R = Me, which utilised the aqueous conditions.

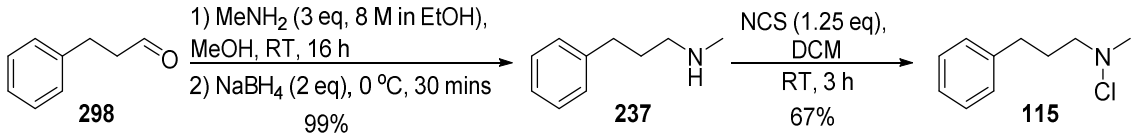


296 297

Scheme 3.2

3.2 Intramolecular amination

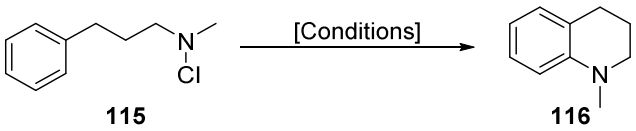
Initial investigations were carried out on the chloroamine substrate **115**, which Minisci *et al*. had shown was able to cyclise using concentrated sulfuric acid as the reaction medium; this was readily synthesised through reductive amination of hydrocinnamaldehyde **298** followed by chlorination of amine **237** using NCS (Scheme 3.3). [79] The chloroamines can be purified by column chromatography and most can be fully characterised, some decompose during LC-MS analysis to the parent amine.



298 237 115

Scheme 3.3

The conditions used by Minisci *et al*. utilised H_2SO_4/AcOH (3:1) as the solvent.[45] These conditions were initially tested upon chloroamine **115**; pleasingly, when the reaction was cooled to 0 °C, a 39% yield of the desired product **116** was obtained (Table 3.1, entry 1). Upon further cooling to -5 °C, the yield increased dramatically to 80%, as it eliminated the production of a resinous compound observed when the reaction is not cooled. Both of the reactions were carried out in the dark, which was ensured by wrapping the flask in tin foil, to ensure that light was not responsible for the breaking of the N-Cl bond to form the nitrogen centred radical. The reactions were also carried out open to light and the same yield for the products was obtained



115 116

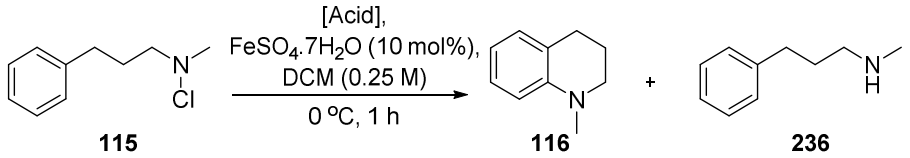
Entry	Conditions	Yield of 116 (%)
1	$FeSO_4 \cdot 7H_2O$ (10 mol%), H_2SO_4, AcOH (3:1), 0 °C, 1 h	39
2	$FeSO_4 \cdot 7H_2O$ (10 mol%), H_2SO_4, AcOH (3:1), -5 °C, 1 h	80

Table 3.1

Due to the success of this substrate under the aqueous conditions, it was chosen as a model substrate for optimisation of organic media-based conditions. Investigations into screening a variety of acids, iron salts and stoichiometries of both, were undertaken in DCM initially. The reason DCM was used before any solvent screen was carried out was due to previous studies carried out into the photochemical version of the reaction.

3.2.1 Acid screen

A variety of acids were investigated using 10 eq. of each in the attempted *N*-arylation reaction of the chloroamine **115** (Table 3.2). Investigations into the photochemical version of the reaction within the Marsden group demonstrated that 10 eq. of acid gave the best results therefore investigations began with 10 eq. of acid. The poor solubility of *p*-TsOH and camphorsulfonic acid in DCM could be the reason why no reaction occurred and only SM was observed after 1 hour (Table 3.2, entry 1-2). Test reactions with these acids were also carried out in methanol to improve the solubility of the acids, however again only SM was observed after 1 hour. When 3N HCl in MeOH was used the amine **236** was the only product of the reaction (Table 3.2, entry 4). The result with acetic acid (Table 3.2, entry 5) suggests that the pKa of the acid may also play a key role in whether the acid will aid the formation of the desired product. The pKa for methanesulfonic acid in water is -2.42 which is comparable to that of *p*-TsOH (-2.8), this suggests that it is the solubility of *p*-TsOH acid in DCM that could be hindering the reaction in this case rather than the strength of the acid. This is based on the pKa's of the acids being similar in DCM or following similar trends observed in water. The only acid screened that generated the desired THQ **116** was $MeSO_3H$, with all other acids affording the amine **236** or SM **115** after 1 hour (Table 3.2, entry 6).

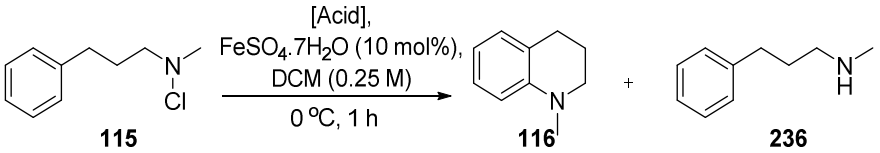


115 116 236

Entry	Acid (10 eq.)	Product (isolated yield%)
1	*p*-TsOH	Starting material **115**
2	Camphorsulfonic acid	Starting material **115**
3	TFA	Starting material **115**
4	3N HCl in MeOH	Amine **236** (90% recovery)
5	AcOH	Starting material **115**
6	$MeSO_3H$	THQ **116** (73%)

Table 3.2

The reaction was carried out using $MeSO_3H$ at RT, 0 °C and -5 °C with similar yields obtained at the lower temperatures, but at RT more of the dechlorinated starting material **236** was formed (Table 3.3). It was noted that the reaction is exothermic upon the addition of the acid which suggests higher temperatures are detrimental to the cyclisation of the aminium radical. The order of addition of the reagents doesn't affect the overall yield. Therefore, reactions were carried out at 0 °C from this point onwards. Control experiments were also carried out in the absence of acid or iron salt. In both cases only the SM **115** was observed after 1 hour, and no decomposition of the SM was observed.



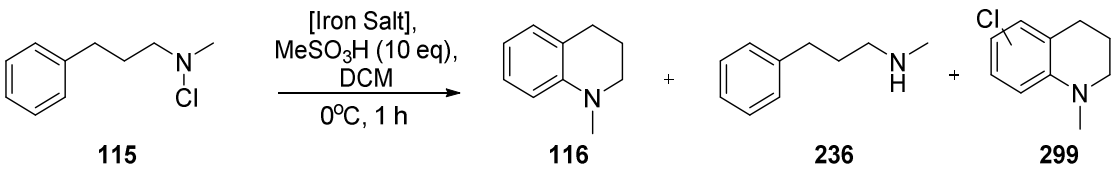
Entry	Conditions	Product (isolated yield%)
1	$FeSO_4 \cdot 7H_2O$ (10 mol%), $MeSO_3H$ (10 eq.), RT, 1 h	THQ **116** (50%)
2	$FeSO_4 \cdot 7H_2O$ (10 mol%), $MeSO_3H$ (10 eq.), 0 °C, 1 h	THQ **116** (73%)
3	$FeSO_4 \cdot 7H_2O$ (10 mol%), $MeSO_3H$ (10 eq.), -5 °C, 1 h	THQ **116** (73%)
4	$FeSO_4 \cdot 7H_2O$ (10 mol%), 0 °C, 1 h	SM **115**
5	$MeSO_3H$ (10 eq.), 0 °C, 1 h	SM **115**

Table 3.3

With the best acid for the reaction and the optimum temperature in hand, a range of iron salts were screened.

3.2.2 Iron salt screen

It was then decided to screen a variety of Fe(II) salts. The formation of the desired product **116** was observed when using either $FeSO_4 \cdot 7H_2O$, $FeCl_2$ or ferrocene (Table 3.4, Entries 1,2 and 4). When $Fe(CO_2CH_3)_2$ and $Fe(OTf)_2$ were used, only the amine **236** was obtained (Table 3.4, Entries 6-7). The best yields were observed with $FeSO_4 \cdot 7H_2O$, and therefore this was used for the further optimisation of the reaction conditions. Investigations were also carried out using an Fe(III) salt to demonstrate that the reaction is initiated by a single electron transfer from the iron salt to the N-Cl bond rather than by Lewis acid catalysis. When using $FeCl_3$, it was found that after an hour only the SM **115** was present, therefore supporting the theory of electron transfer from the iron salt (Table 3.4, Entry 3). Colourisation of the solutions was observed in the reactions using ferrocene, $Fe(acac)_2$ and $Fe(OTf)_2$ suggesting that the iron(II) source was soluble in DCM giving a homogenous reaction mixture.



115 116 236 299

Entry	Change in Iron Salt (10 mol%)	Products (isolated yield%)
1	$FeSO_4 \cdot 7H_2O$	THQ **116** (73%)
2	$FeCl_2$	THQ **116** (63%)
3	$FeCl_3$	SM **115** (90%)
4	Ferrocene	THQ **116** (20%) and chlorinated THQ **299** (trace)
5	$Fe(acac)_2$	SM **115** (88%)
6	$Fe(CO_2CH_3)_2$	Amine **236** (88%)
7	$Fe(OTf)_2$	Amine **236** (85%)

Table 3.4

Through each of these investigations it was shown that the best conditions were $FeSO_4 \cdot 7H_2O$ (10 mol%) and $MeSO_3H$ (10 eq.) in DCM. With these successful conditions in hand it was then decided to investigate the optimal number of equivalents of both the acid and the iron salt.

3.2.3 Iron salt and acid equivalents optimisation

A range of equivalents of acid and iron salt (2.5 – 10 eq.) were investigated, as shown in Table 3.5. The reactions are carried out at 0.2 M. As can be seen in Table 3.5, the number of equivalents cannot be lowered to below 2.5 mol% of iron or 2.5 eq. of acid, as this leads to none of the desired product **116** being formed, only the SM **115** is observed after 1 hour. The best yield is observed when 10 eq. of $MeSO_3H$ and 10 mol% of iron salt is used. There appears to be a correlation between the number of equivalents of acid and the loading of iron: a change in the balance is detrimental, leading to either the formation of amine **236** or only SM **115** being observed by LC-MS analysis after 1 hour.

	Equivalents of Acid			
Iron Salt (mol%)	**2.5**	**5**	**7.5**	**10**
10	0%	0%	70%	73%
7.5	0%	54%	68%	53%
5	0%	55%	53%	56%
2.5	0%	0%	0%	0%

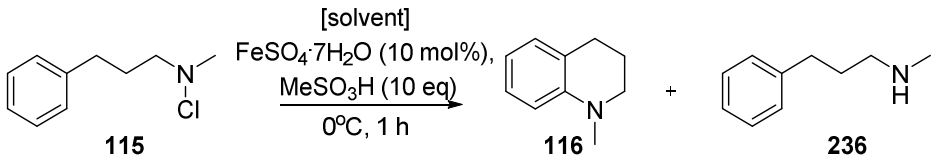
*Red = SM or free amine, Amber = d.p. yield less than 60%, Green = d.p. yield over 60%
** Average isolated yields shown in table for replicate runs of each reaction.

Table 3.5

With the optimised set of conditions in hand with regards to the iron salt and the acid, it was decided to screen a variety of solvents with differing degrees of polarity.

3.2.4 Solvent screen

Using the optimised reaction conditions established previously, a solvent screen was carried out to establish if DCM was the best solvent. The use of EtOAc stopped the reaction occurring and only the SM **115** was observed after 1 hour (Table 3.6). When the reaction was carried out using 2-methylTHF, the only compound observed after 1 hour was the amine **236**. A trace of the desired product **116** was observed by ^{1}H NMR analysis when using dioxane, however none was isolated. Both 2-methylTHF and dioxane can act as a source of hydrogen atom which can be readily abstracted by the electrophilic aminium radical, this could explain why the amine **236** is observed rather than the cyclised product.[82] When the reaction was carried out in toluene it was observed that the $MeSO_3H$ was immiscible and although the desired product **116** was isolated in a 45% yield, this could be a contributing factor to the decrease in yield observed compared to when DCM is used.



Entry	Solvent	Products (isolated yield%)
1	MeOH	Amine **236** (85%)
2	EtOAc	SM **115** (90%)
3	2-methyl THF	Amine **236** (88%)
4	Dioxane	Trace THQ **116** and Amine **236** (50%)
5	DCM	THQ **116** (73%)
6	Toluene	THQ **116** (45%) and trace amine **236**

Table 3.6

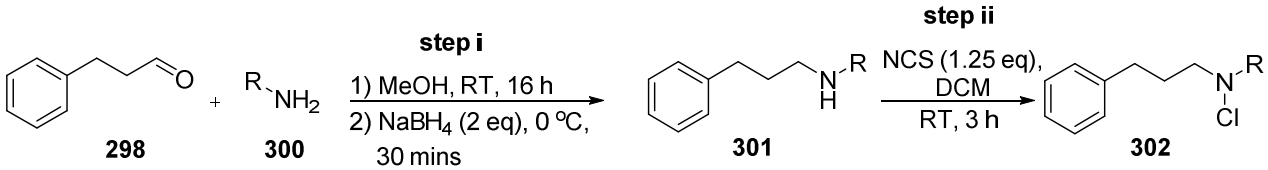
Through carrying out this solvent screen using a variety of polar to non-polar solvents it was shown that DCM is the optimal solvent in which to carry out this reaction. Therefore, with an optimised set of conditions in hand, the scope of the reaction could be investigated.

3.3 Substrate scope

Substrates possessing a variety of different substitution patterns were synthesised by altering the groups on the aromatic ring, the nitrogen and the alkyl chain, to investigate the scope of the reaction.

3.3.1 Nitrogen substitution

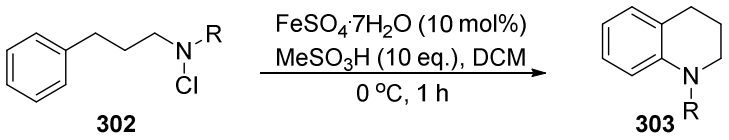
Different substitution patterns on the nitrogen can be achieved through changing the amine used during the reductive amination of hydrocinnamaldehyde **298**, which has been previously done within the group.[77] The synthesis of the allyl-, butyl- and hexyl-substituted chloroamines is shown in Table 3.7. The reductive amination with each of the corresponding amines proceeded well, however, purification issues with the hexyl substrate led to a lower yield. Chlorination of each of the amines using NCS afforded the desired chloroamines in good yields.



Entry	Substrate (R=)	Step (i) Yield (%)	Step (ii) Yield (%)
1	Allyl **a**	91	71
2	Butyl **b**	85	70
3	Hexyl **c**	31	70

Table 3.7

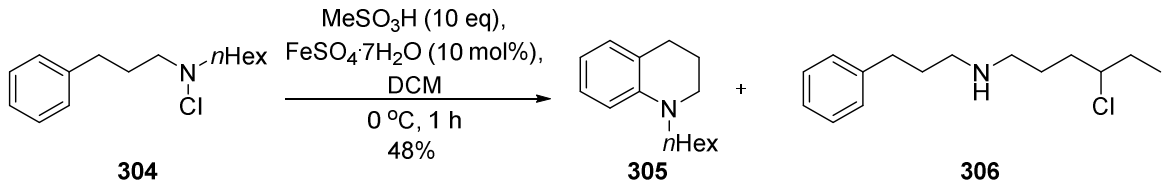
These substrates were subjected to the standard conditions for *N*-arylation. Pleasingly the desired products from the cyclisations were achieved in good yields (Table 3.8).



Entry	**Substrate**	**Yield (%)**
1	Allyl **a**	69
2	Butyl **b**	43
3	Hexyl **c**	48

Table 3.8

With regards to the hexyl substrate, previous work carried out within the group on the photolysis of chloroamine **302c** showed that there was a competition reaction between the HLF and the *N*-arylation reaction (Scheme 3.4). Due to the length of the chain, a 1,5-hydride abstraction followed by a radical recombination reaction to give the chloroalkylamine **306** is possible. However, none of chloroalkylamine **306** was observed by LC-MS or ^{1}H NMR analysis, when subjected to the standard *N*-arylation conditions developed within this work. The 1,5-hydride abstraction can occur, however, as no chlorine radical is generated in the breakdown of the chloroamines, the radical recombination step that forms the chloroalkylamine **306** cannot occur via that mechanism.

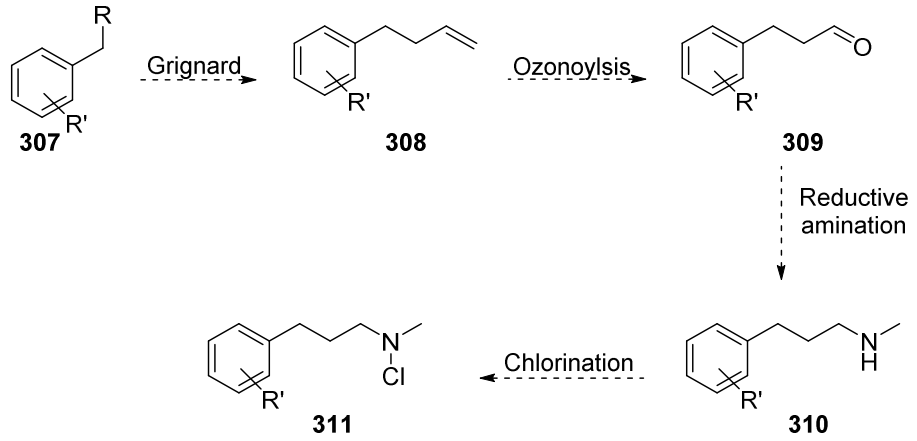


Scheme 3.4

Successful synthesis of these substrates has demonstrated that substitution on the nitrogen is tolerated for different groups.

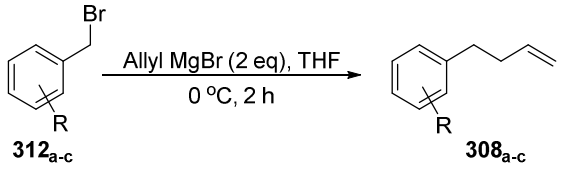
3.3.2 Substituted aromatics

It was then envisaged that a variety of substrates with different substituents and substitution patterns on the aromatic ring could be synthesised via the synthetic route shown in Scheme 3.5. The first step would involve substitution of a benzyl bromide or a benzyl mesylate with a Grignard reagent (allylmagnesium bromide) to afford the terminal alkene **308**. Compound **308** could then undergo an ozonolysis reaction to afford the corresponding aldehyde **309**. Reductive amination of compound **309** followed by chlorination would afford the desire chloroamine **311**.



Scheme 3.5

Depending on the availability of starting materials, either a benzyl bromide or a benzyl alcohol was chosen for the Grignard displacement reaction. The substrates synthesised using the corresponding benzyl bromide **312**, along with the yields, are shown in Table 3.9. All the corresponding terminal alkenes were obtained in excellent yields.

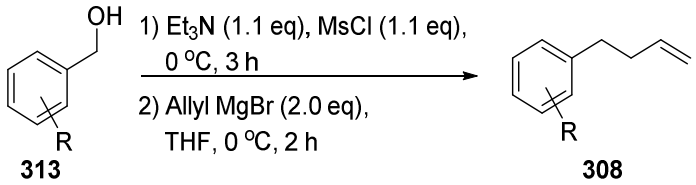


312_{a-c} 308_{a-c}

Entry	Substrate	Yield (%)
1	4-Me **308a**	93
2	3,5-Me **308b**	95
3	3-Cl **308c**	99

Table 3.9

The benzyl alcohols were converted to benzyl mesylates and the crude material was telescoped through to the next step (Table 3.10). Displacement of the mesylate by allylmagnesium bromide afforded the desired terminal alkenes **308**. The range of substrates synthesised using this method are shown in Table 3.10. The yields were slightly lower than those of the benzyl bromides, but desired products were obtained in adequate yields.

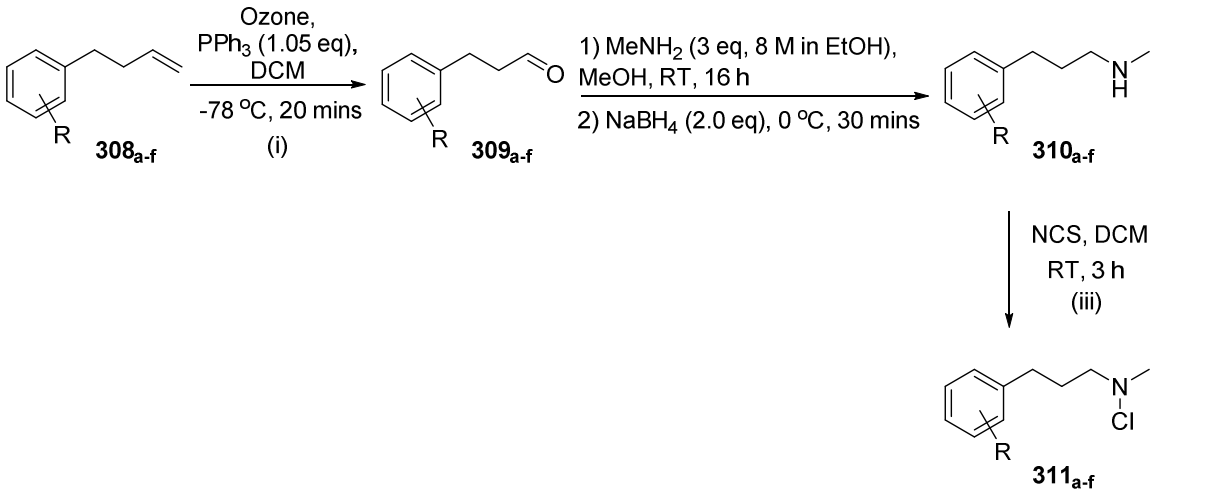


313 **308**

Entry	Substrate	Yield (%)
1	4-Cl **308d**	42
2	2-Cl **308e**	62
3	4-Br **308f**	68
4	4-OMe **308g**	63

Table 3.10

With the terminal alkenes **308** in hand, the rest of the synthetic route was carried out to afford the desired chloroamines. Ozonolysis of the terminal alkenes **308** afforded the aldehydes **309** in 60-87% yields. Reductive amination of aldehydes **309** generated the amines **310** in excellent yields. Chlorination of amines **310** yielded enough of the desired chloroamines **311** to proceed to the *N*-arylation reactions. The conditions and the yields of each step for the corresponding substrates is shown in Table 3.11.

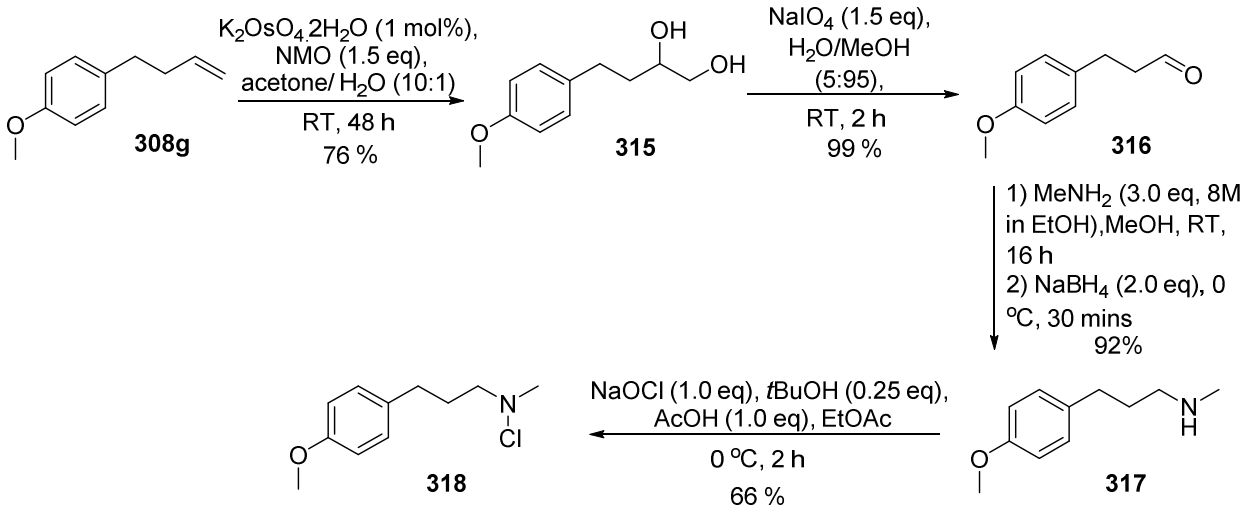


Entry	Substrate	Step (i)	Step (ii)	Step (iii)
1	4-Me **a**	72	97	73
2	3,5-Me **b**	73*	95	66
3	3-Cl **c**	76	88	85
4	4-Cl **d**	87	88	67
5	2-Cl **e**	68	72	59
6	4-Br **f**	80	86	75

*crude yield – material was telescoped through

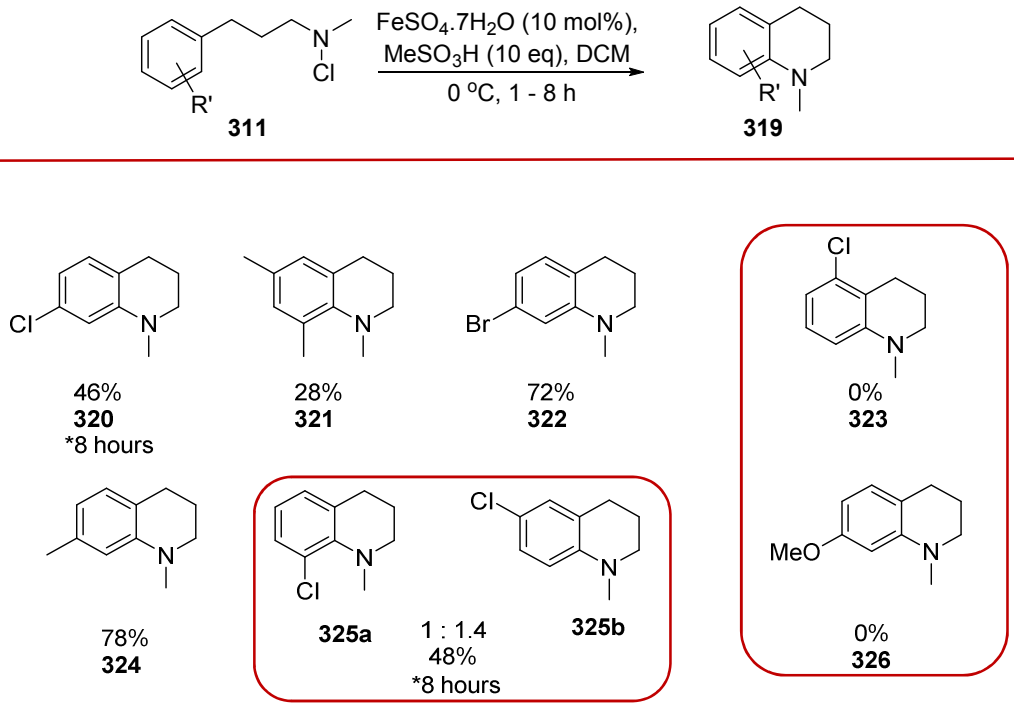
Table 3.11

Unfortunately, when the aromatic ring is substituted with a methoxy group the aldehyde cannot be formed through ozonolysis due to potential oxidation of the aromatic ring. When ozonolysis was trialled only trace of the desired product was isolated nothing else could successfully be isolated (myriad of spots by TLC). Therefore, an alternative step to obtain the aldehyde was proposed, as shown in Scheme 3.6. The diol **315** was formed from dihydroxylation of the alkene **308g** followed by oxidative cleavage using sodium periodate, which afforded the desired aldehyde **316** in quantitative yield. The aldehyde **316** was then converted to amine **317** *via* reductive amination. Another problem was encountered during the chlorination step. The conditions used previously, which utilise NCS in the chlorination step, cannot be used as they were found to chlorinate the electron-rich aromatic ring. Alternative conditions found involve the *in situ* formation of *tert*-butyl hypochlorite which allows the nitrogen to be selectively chlorinated.[80]



Scheme 3.6

With the desired chloroamines in hand, the key *N*-arylation reaction was then carried out for each of the substrates (Scheme 3.7). Pleasingly, the *p*-Me product **324** was obtained in a good yield (78%). The yield of the di-methyl product **321** was lower due to competing chlorination on the aromatic ring, which was observed by LC-MS analysis, and which may have occurred as a result of the aromatic being more electron-rich. The substrates which are more electron-poor, such as substrates with *p*-Br **322**, *m*-Cl **325** and *p*-Cl **320** substituents**,** did undergo *N*-arylation, however, the reaction time needed to be increased from 1 hour to 8 hours for complete conversion. The yields for the *m*-Cl **325** and *p*-Cl compounds **320** were lower which could be due to the increased electronegativity of chlorine rendering the aromatic ring more electron-poor and was accompanied by an increase in the formation of the dechlorinated starting material. Although the chlorine was tolerated in the *m*-position and *p*-position of the aromatic ring, it was not tolerated in the *o*-position, which led only to the formation of the amine **310e**. This could be due to blocking one of the positions for attack of the aminium radical on a substrate which has poor reactivity for *N*-arylation. The methoxy group was also not tolerated, with mainly the reduced amine observed. A product whose mass matched the chlorinated tetrahydroquinoline was observed by LC-MS analysis, however, it could not be isolated.

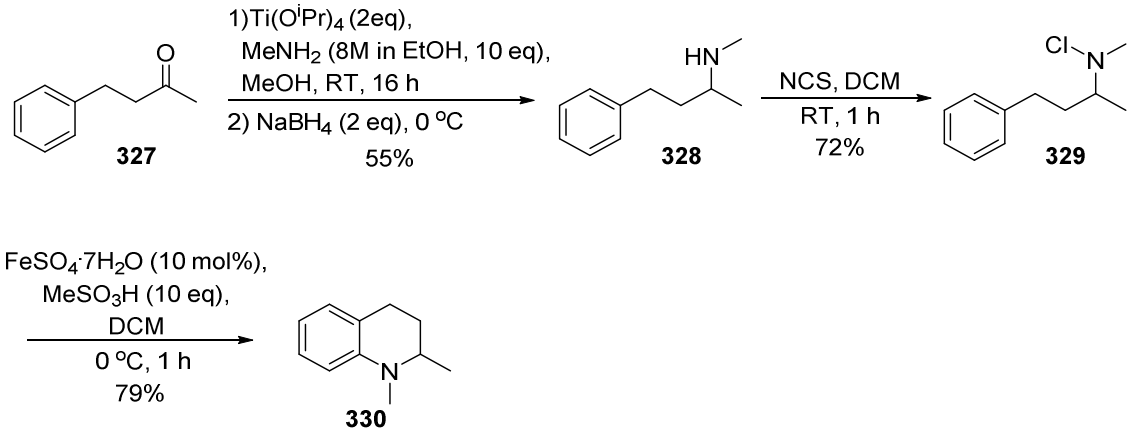


Scheme 3.7

There has been success with the synthesis of substrates with a variety of substitution patterns on the aromatic ring. Some problems have been observed with electron-withdrawing substituents, especially chlorine in the *o*-position which resulted in only SM being isolated from the RM. Similar yields are obtained when using the photochemical conditions. Chlorine in the 2-position is tolerated under the photochemical conditions.

3.3.3 Alkyl substitution

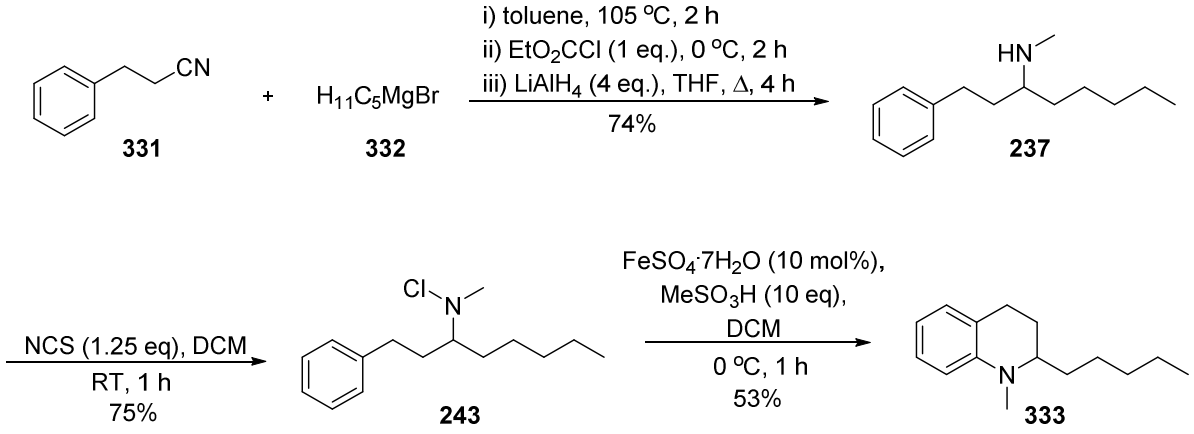
Substrates with different alkyl substituents were achieved through a variety of methods. The first method attempted involved the reductive amination of 4-phenyl-2-butanone **327** with methylamine to afford the amine **328** in excellent yields (Scheme 3.8). The amine **328** was then subjected to the standard chlorination conditions to afford the desired chloromine **329** in good yields. With the chloroamine **329**, in hand the *N*-arylation reaction was attempted, and pleasingly, the desired THQ **330** was afforded in a 79% yield.



327 **328** **329** **330**

Scheme 3.8

Previous work carried out within the group synthesised the amine **237** in one-pot *via* a Grignard reaction using 3-phenylpropionitrile and pentylmagnesnium bromide, the product of which was trapped with ethyl chloroformate to form the imino-carbamate (Scheme 3.9).[83] The imino-carbamate could be reduced using $LiAlH_4$ to form the desired amine **237**, which is a precursor to the natural product angustureine **333**, and could be chlorinated in a good yield to afford chloroamine **243**. A sample of the chloroamine **243** that was previously synthesised in the group using the described method was subjected to the established *N*-arylation conditions which afforded the desired racemic natural product angustureine **333** in reasonable yield.[84]



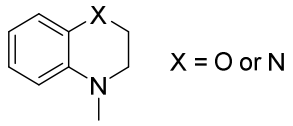
331 **332** **237** **243** **333**

Scheme 3.9

It has been demonstrated that variations in substitution on the alkyl chain are supported and that functional groups that could be used for functionalisation later are tolerated as well.

3.3.1 Benzomorpholines

To expand the substrate scope it was decided to investigate substrates which include another heteroatom in the saturated ring (Figure 3.1). It was hypothesised that substrates including oxygen and nitrogen could be synthesised.

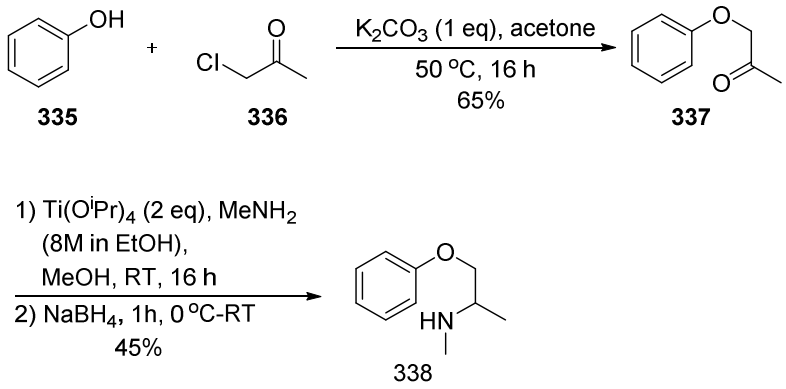


334

Figure 3.1

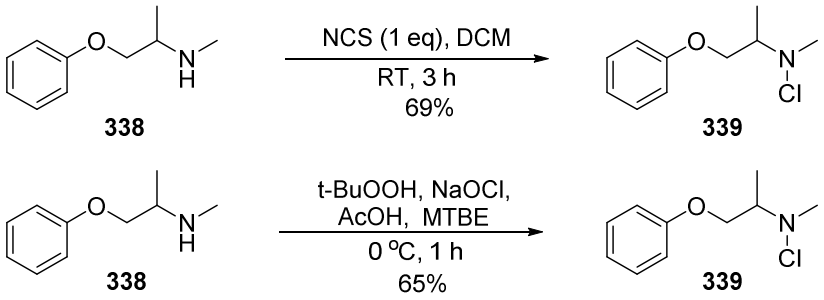
3.3.2 Substrate Synthesis

The required *N*-chloroamine could be synthesised in three steps. A substitution reaction involving phenol and chloroacetone afforded the ketone **337** in a moderate yield (60%). Reductive amination of ketone **337** yielded the desired amine **338** (Scheme 3.10).



Scheme 3.10

With the desired amine **338** in hand focus was turned to the formation of the corresponding chloroamine **339**. Previously we had observed issues with chlorination of amines in the presence of electron rich aromatic rings; this could be overcome using alternative conditions which utilised the formation of *tert*-butyl hypochlorite *in situ*. It was therefore decided to investigate chlorination of the amine using both sets of conditions. Pleasingly in this case chlorination of the amine proceeded well under both sets of conditions and chlorination on the aromatic ring was not an issue, with good yields of the desired chloroamine **339** obtained (Scheme 3.11).

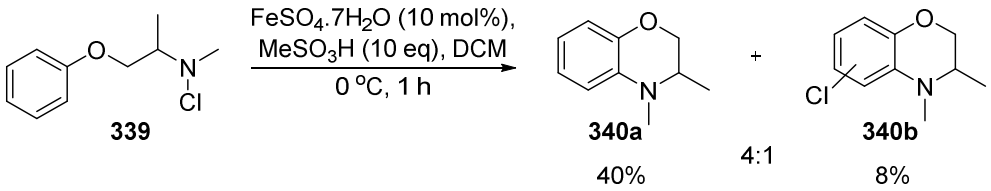


Scheme 3.11

With the desired chloroamine in hand the *N*-arylation reaction could be attempted.

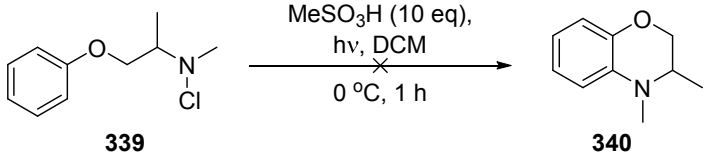
3.3.3 *N*-Arylation of the benzomorpholine precursors

When the *N*-chloroamine was subjected to the *N*-arylation conditions the desired compound alongside some of the chlorinated product was afforded in 4:1 ratio which were inseparable by column chromatography (Scheme 3.12).



Scheme 3.12

Conditions previously established within in the group utilise UV light to initiate the formation of the aminium radical. It was decided to trial these conditions and see if the yield obtained was comparable or an increase in yield was observed. However, when the *N*-chloroamine **339** was subjected to these conditions none of the desired product was observed and only the amine **338** was observed (Scheme 3.13).

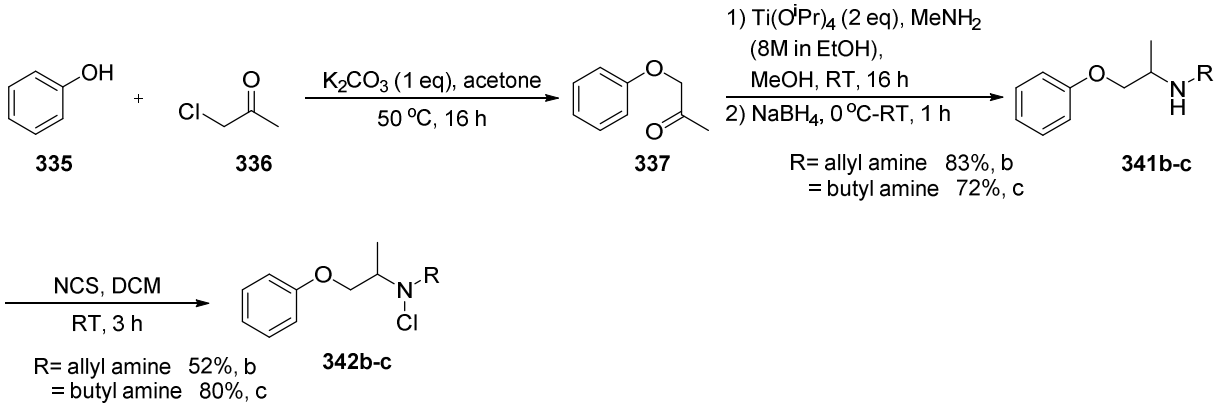


Scheme 3.13

It was therefore decided to investigate the substrate scope using the $FeSO_4.7H_2O$ *N*-arylation conditions as these afforded the desired product. Substitution on the nitrogen and the aromatic ring were investigated which have been shown to work on the carbon containing rings.

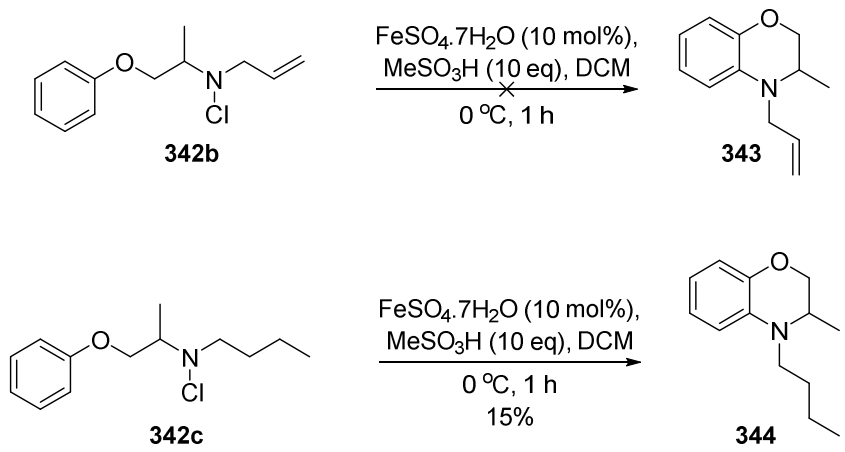
3.3.4 Substitution on the Nitrogen

Initial investigations used allylamine and butylamine as these were shown to give the best results previously. The synthesis of these could be achieved through the already established route with the substitution reaction between phenol and chloroacetone to generate ketone **337** (Scheme 3.14). This was followed by reductive amination with the corresponding amine **341**. Both amines were synthesised in good yields and were chlorinated using NCS to afford the desired *N*-chloroamines **342** in good yields.



Scheme 3.14

With the chloroamines in hand they were then subjected to the *N*-arylation conditions. The butylamine substrate cyclised to afford the desired benzomorpholine **344** in a 11% yield (Scheme 3.15). However, the allyl amine substrate did not cyclise and the amine **341b** was instead recovered from the reaction mixture (60% yield of recovered amine).



Scheme 3.15

3.3.5 Substitution on the aromatic ring

Substrates with bromine on the aromatic ring had shown good yields before so this was selected as one to try for the benzomorpholine substrates (Figure 3.2). The 4-chloro substrate was also chosen to establish whether the oxygen being attached to the aromatic ring makes it more electron rich and therefore allow *N*-arylation on electron poor rings. A decrease in yield and a more sluggish reaction has been observed previously due to chloro- substitution on the ring.

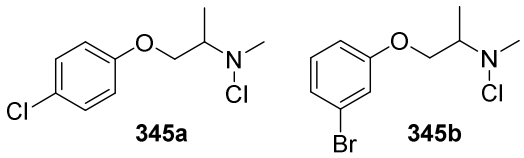
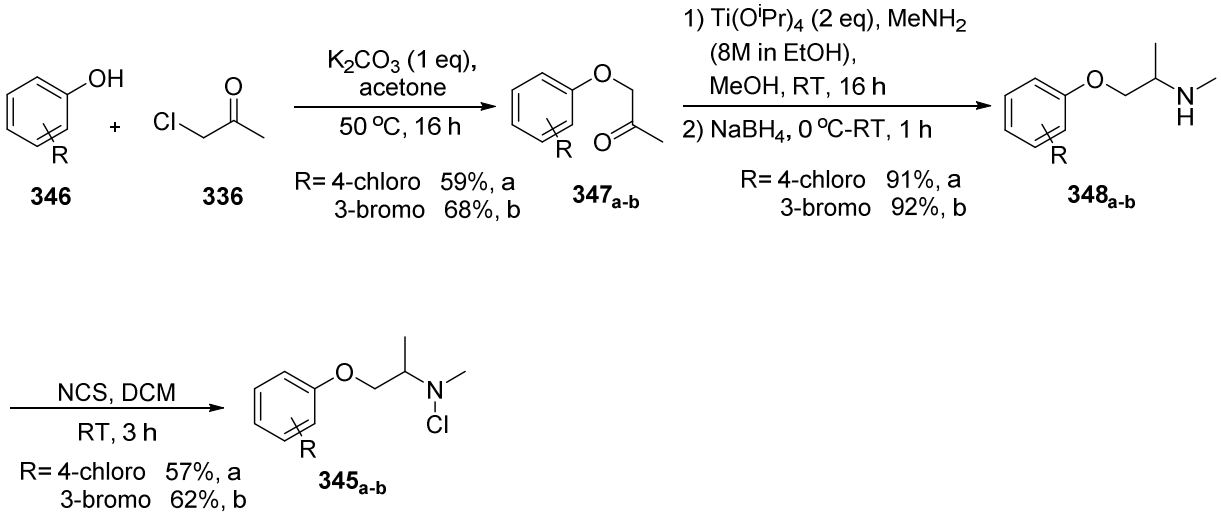


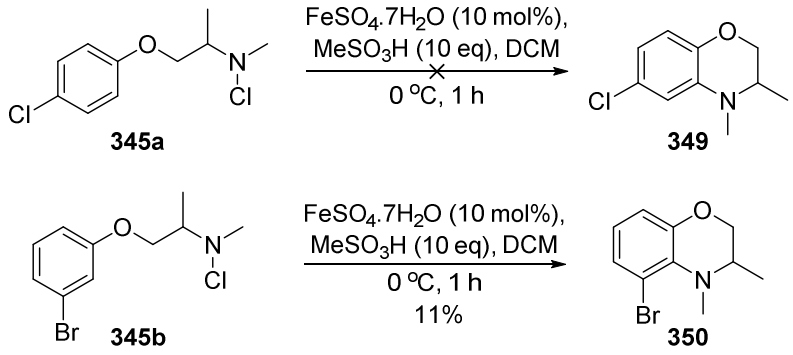
Figure 3.2

The synthesis of the substrates was achieved through a substitution reaction of the corresponding phenol with chloroacetone. The corresponding ketones then underwent reductive amination followed by chlorination to afford the desired chloroamines (Scheme 3.16).



Scheme 3.16

The corresponding chloroamines were then subjected to the *N*-arylation conditions (Scheme 3.17). The 3-bromo substrate **345b** cyclised to afford the desired compound **350** in a 15% yield. Unfortunately, the 4-chloro substrate **345a** did not afford the desired product and instead the amine **348a** was isolated at the end of the reaction (65% recovery of the amine).

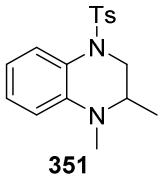


Scheme 3.17

With some examples of the benzomorpholine substrates successfully synthesised but in moderate yields, it was decided to investigate the synthesis of the nitrogen compounds to form benzopiperazines.

3.3.6 Synthesis of benzopiperazine substrates

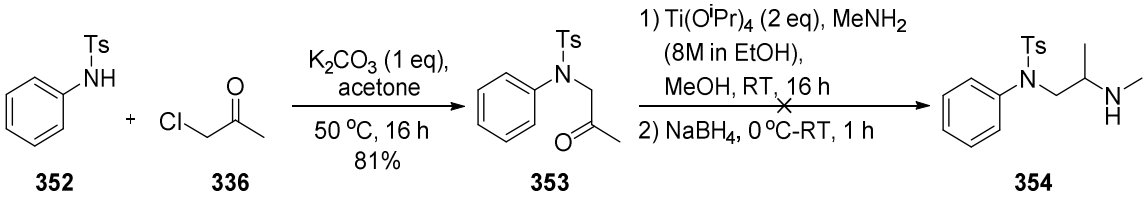
It was hypothesised benzopiperidine **351** version could be synthesised in the same way as the benzomorpholine precursors.



351

Figure 3.3

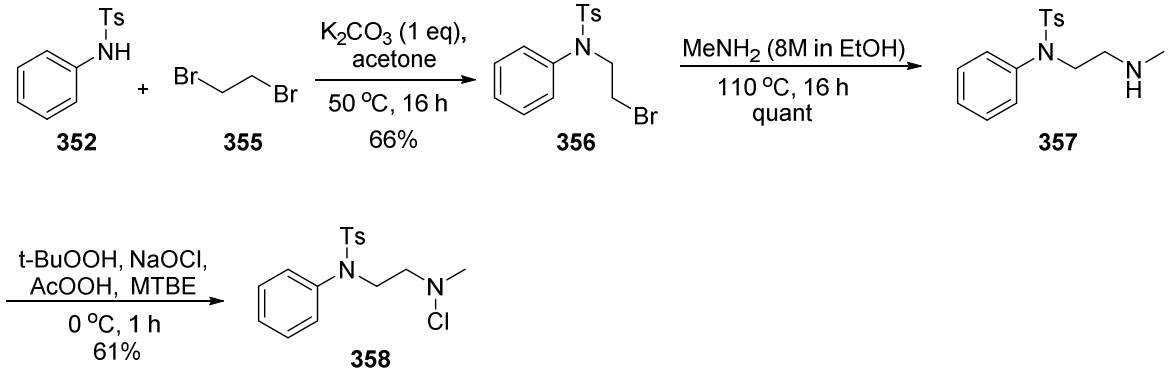
The substitution reaction between the tosylprotected aniline proceeded well. Unfortunately, the reductive amination of ketone **353** was unsuccessful and therefore an alternative route had to be found (Scheme 3.18).



352 **336** **353** **354**

Scheme 3.18

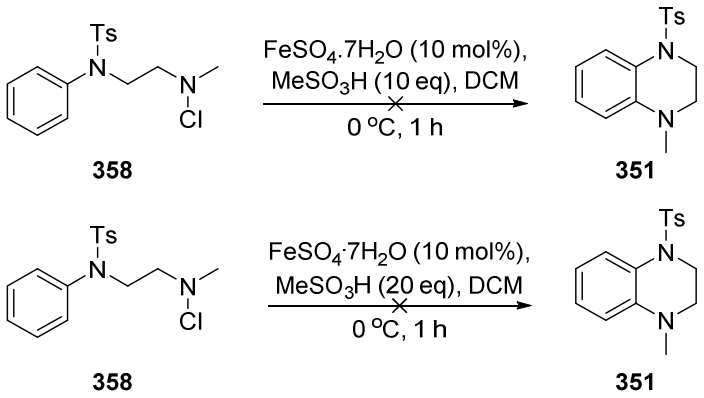
It was found that a substitution reaction between dibromoethane **355** and the tosyl-protected aniline **352** afforded the bromoalkane **356** (Scheme 3.19). Heating the bromo compound **356** in methylamine afforded the desired amine **357** in excellent yields. To avoid any potential chlorination on the aromatic ring the conditions which utilise the formation of *tert*-butyl hypochlorite was used. The desired chloroamine **358** was synthesised in a moderate yield but enough of the *N*-chloroamine was obtained to attempt the *N*-arylation reaction.



352 **355** **356** **357** **358**

Scheme 3.19

Two *N*-arylation reactions were attempted, one under the standard conditions and another with double the equivalents of acid were used due to the presence of the second nitrogen in the substrate to ensure that the *N*-chloroamine was fully protonated (Scheme 3.20). Unfortunately, only the amine **357** was recovered at the end of the reaction (over 55% amine).



Scheme 3.20

It was therefore decided to stop further investigations due to unsuccessful attempts to synthesis the benzopiperizine under both the iron salt and UV irradiation *N*-arylation conditions.

3.3.7 Mechanistic investigation

Radical reactions frequently proceed through the kinetically more favourable cyclisation pathway which more often than not generates the 5-membered ring over the 6-membered ring.[85] 5-membered-spiro cyclisations are more favoured due to a better orbital overlap in the transition state which is not the case for 6-membered-ortho cyclisations.[86,87] In an attempt to probe the mechanism as to whether within our systems the 5-membered ring was formed initially before a migration occurred to form the observed THQ, a substrate with both *o*-positions blocked was proposed. It was hypothesised that this would allow us to observe alternative dearomatised products arising from either the 5-*exo* or 6-*exo* intermediates giving an insight into the mechanism of the reaction (Figure 3.4). This has previously been carried out within the group in the UV-initiated reactions.

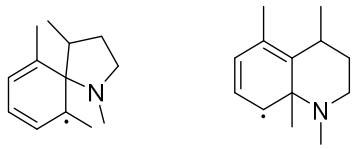
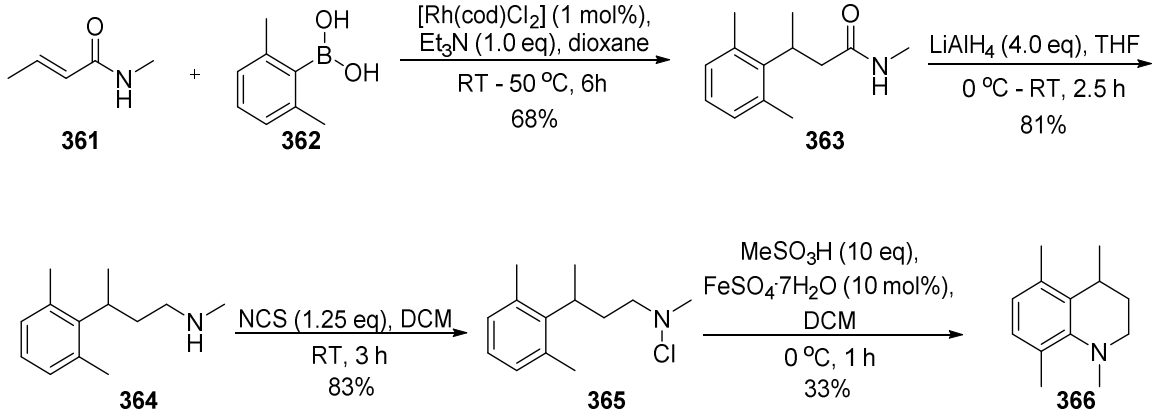


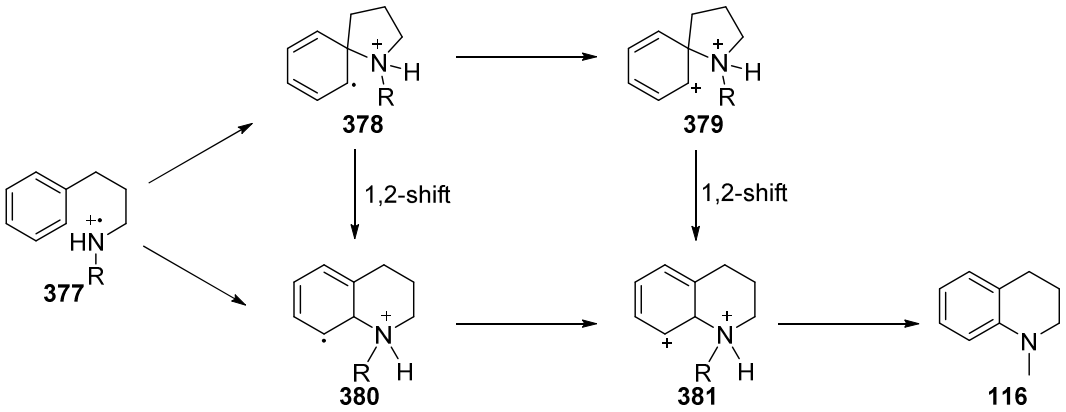
Figure 3.4

The desired chloroamine **365** was synthesised in three steps from the crotonamide **361** (Scheme 3.21). The crotonamide **361** underwent a rhodium-catalysed 1,4-conjugate addition which afforded the corresponding amide **363**.[88] The amide **363** was reduced using $LiAlH_4$ which worked in excellent yield to afford the desired amine **364**. Chlorination of amine **364** was carried out in good yield using NCS to afford chloroamine **365**. Compound **366**, which has undergone migration of a methyl group, was isolated in a reasonable yield, in accordance with the previous work carried out in the group using photolysis.



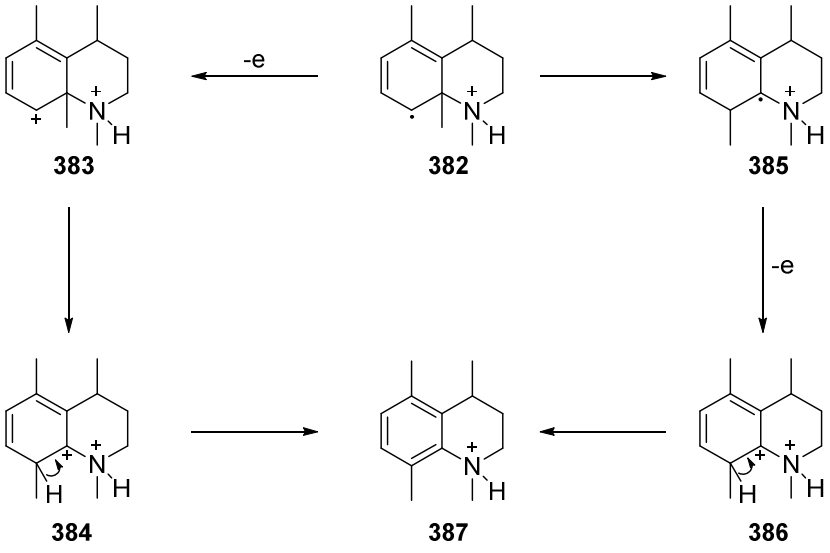
Scheme 3.21

A possible mechanism for the formation of a tetrahydroquinoline is shown in Scheme 3.22. The required six-membered ring intermediate **381** could either be formed directly or from migration of the spiro cyclisation product either at the radical **380** or cation **379** stage. DFT calculations that have previously been carried out within the group have shown that for the cyclisation of an unsubstituted aromatic the 6-membered ring is favoured.



Scheme 3.22

The cyclisation of the aminium radical onto the aromatic ring would form the intermediate **382** this could then proceed via two different pathways to generate the migratory product **387** (Scheme 3.23). In one pathway the radical species **382** could then be oxidised by the iron(III) or chloroamine to give the cation **383**. This means that the methyl group could migrate to form the more stable cation **384**. Rearomatisation can then occur to afford the observed compound **387**. In the second pathway the methyl can migrate via a radical mechanism before rearomatisation occurs.[89]



Scheme 3.23

Previous work in the group has shown that this migration does not occur for other substrates such as 2,6-dichlorophenyl where substitution of one of the *ipso*-chloro atoms occurs instead, therefore this was not investigated further.

3.3.8 Reactivity studies

The proposed aminium radical intermediate is a highly electrophilic species and therefore should react with more electron-rich aromatic rings preferentially.[44] The mechanism of the reaction can therefore be probed as far as showing that it proceeds through a highly electrophilic intermediate. With this in mind, two substrates were designed in which a phenyl ring competes with either an electron-rich (green) or electron-poor aromatic ring (red) (Figure 3.5).

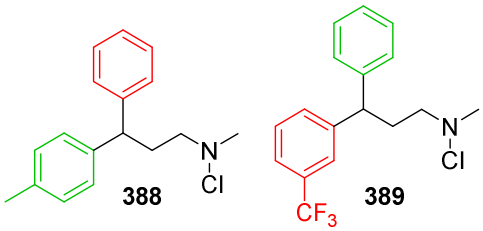
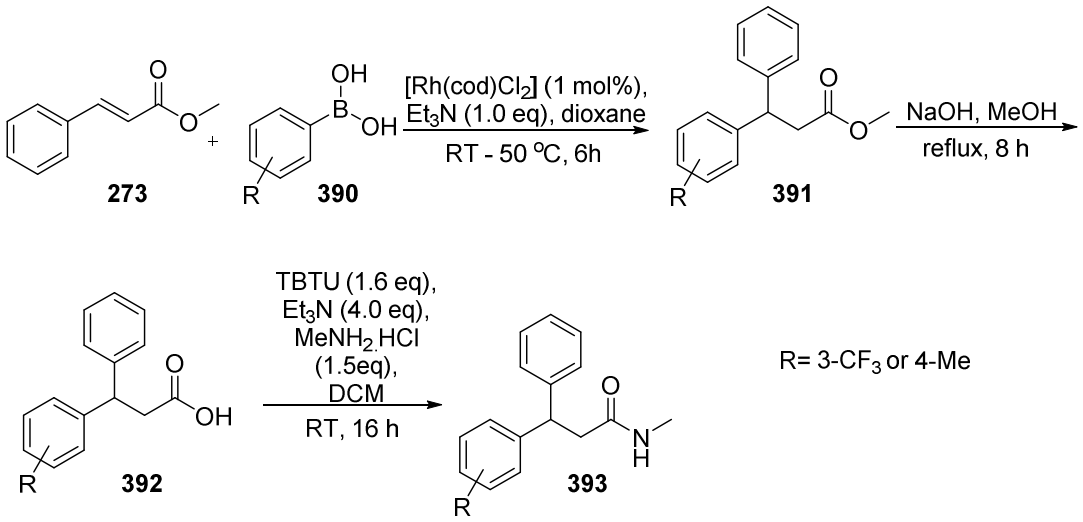


Figure 3.5

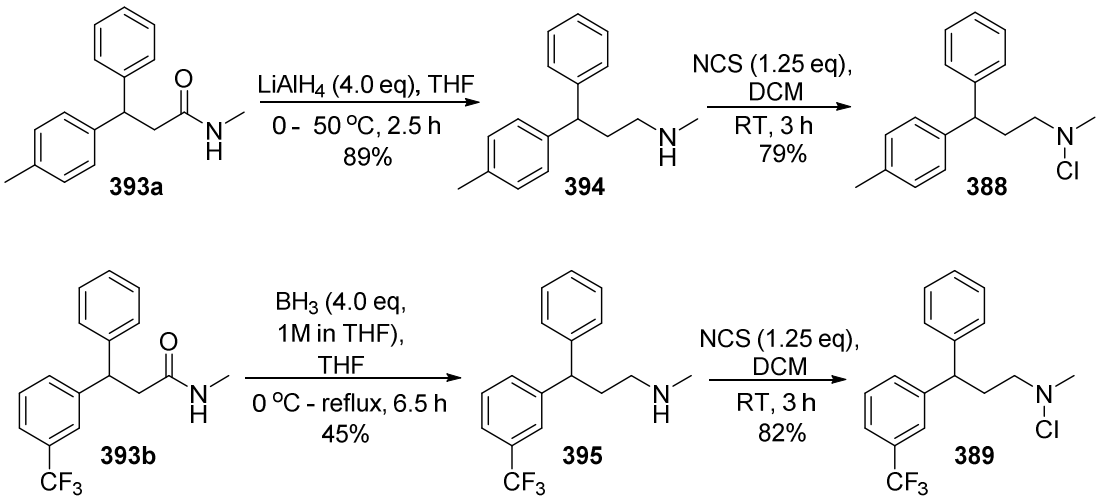
A rhodium-catalysed 1,4-conjugate addition of tolylboronic acid or (trifluoromethyl)boronic acid to methyl cinnamate afforded the esters **391** in excellent yields. Saponification of the resulting esters **391** afforded the acids **392** in good yields. Amide coupling of acids **392** with methylamine yielded amides **393** (Table 3.12). The yield of the amide coupling for the CF_3 compound **393b** was lower due to purification issues.



Entry	R group	Step i	Step ii	Step iii
1	4-Me **a**	91	79	78
2	3-CF_3 **b**	96	73	34

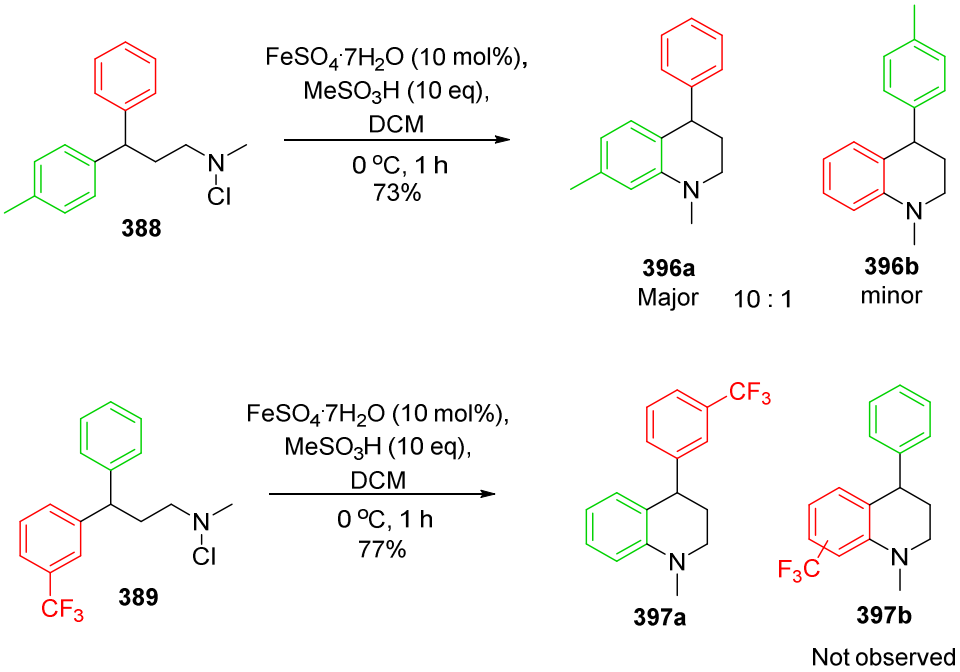
Table 3.12

The amide **393a** was then reduced using $LiAlH_4$ to afford the desired amine **394** in high yields. Chlorination of amine **394** using NCS afforded the desired chloroamine **388** in a good yield (Scheme 3.24). Due to issues previously found within the group in regards to the reduction of the amide **393b** with $LiAlH_4$, which resulted in partial reduction of CF_3 group to CF_2H, it was decided to carry out the reduction using borane.[90] The yields for the reduction were lower however enough material was obtained to carry on to the next step. The chlorination of amine **395** to afford chloroamine **389** proceeded in excellent yields, and enough material was obtained to test the *N*-arylation reaction.



Scheme 3.24

With the chloroamines in hand, the *N*-arylation reactions were carried out (Scheme 3.25). In both cases there was high selectivity for the more electron-rich ring. In the case of the tolyl compound there was a 10:1 selectivity, which was determined by ^{1}H NMR analysis, in favour of the tolyl aromatic ring over the phenyl. In the case of the CF_3 compound **389**, there was complete selectivity for reaction at the unsubstituted phenyl ring. The same results were observed when the study was carried out under the photochemical conditions established within the group.

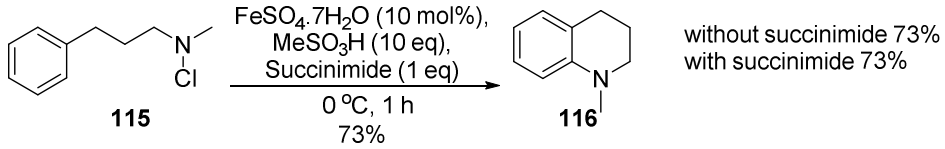


Scheme 3.25

The selectivity observed for the more electron-rich ring in each of the cyclisations supports the hypothesis that this reaction proceeds through a highly electrophilic intermediate.

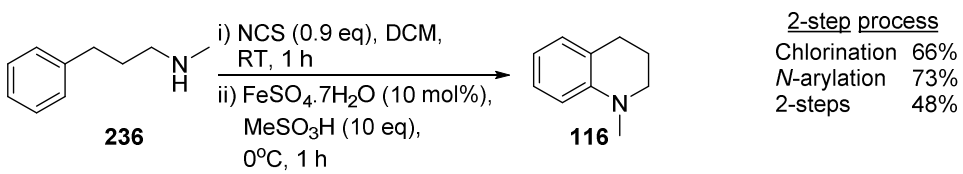
3.3.9 One-pot procedure

To alleviate the need to isolate potentially unstable chloramines, and to reduce the number of individual steps required, it was envisaged that the chlorination and *N*-arylation could be carried out in a one-pot process. The number of equivalents of NCS was decreased from a slight excess (1.25 eq.) to one equivalent to avoid any chlorination of the aromatic ring in the product. A control experiment was carried out using succinimide, which is the by-product from the chlorination reaction, to ensure its presence during the *N*-arylation reaction was not detrimental. Pleasingly, the presence of succinimide did not affect the reaction (Scheme 3.26).



Scheme 3.26

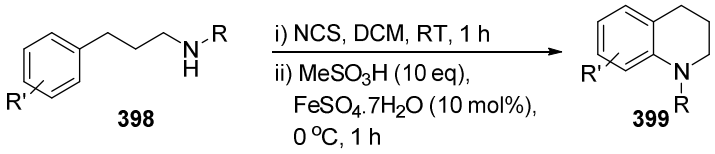
Unfortunately, when 1 eq. of NCS was used to form the chloramine *in situ* there was only a trace amount of product observed by LC-MS analysis at the end of the reaction (Table 3.13). The issue may have been due to a slight excess of the NCS reacting with the Fe(II) which prevented the *N*-arylation step – for example by reacting with $FeCl_2$ to generate $FeCl_3$ which is inactive in the reaction conditions. By decreasing the number of equivalents of NCS to 0.9 eq. (to ensure there was no excess chlorinating reagent), the yield over the two steps increased to 65% (yield calculated relative to NCS). The reaction was repeated for both table entries and the same result was observed each time



Entry	Equivalents of NCS	Average yield of x (%)
1	1.00	<5
2	0.90	65

Table 3.13

Pleasingly, we have established a one-pot process which alleviates the need to isolate potentially unstable chloroamines. It was therefore decided to investigate this process with regards to some of the substrates previously synthesised in order to compare the results (Table 3.14). The first substrate tried was the *N*-substituted butyl compound; although there was a slight decrease in the yield when the one-pot process was carried out it alleviates the need for a purification step and isolation of the chloroamine itself. When the 3-Cl amine (Table 3.14, Entry 3) was subjected to the one-pot process a similar yield was obtained to that which was observed for the overall two-pot process. Again, an increased reaction time was required due to the more electron-poor ring.



Entry	R	R’	One-pot yield (%)	Two-pot yield (%)
1	allyl	H	45	49
2	butyl	H	57	30
3	Me	3-chloro	42	41

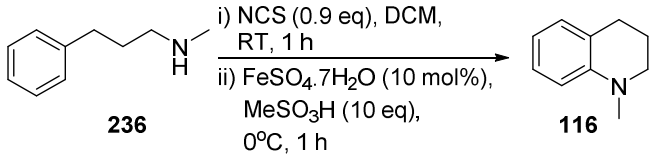
Table 3.14

An alternative one-pot process has been established which alleviates the need to isolate the chloroamine and therefore eliminates a purification step. This could be beneficial when working with less stable chloroamines and would hopefully avoid decomposition issues.

3.3.10 Scale up

It was decided to see whether a large batch reaction was possible under the optimised conditions using both the one-pot and two-pot processes (Table 3.15). The one-pot process was carried out on 1g of the amine **236**; the yield obtained of the desired product however was very low. It has been previously noted that the chlorination process using NCS can produce lower yields at higher scales. This could lead to NCS being present still in the reaction mixture which has been shown to decrease the yields of the desired product. For the two-pot process the

chlorination step achieved a 67% yield and to avoid the lower yields observed on scale-up of the chlorination this was carried out on a 3 x 500 mg scale. Pleasingly for the *N*-arylation step carried out on a 1g scale a 65% yield was achieved showing that this process can be scaled up successfully.



One-pot process yield (%)	Two-pot process (%)
9	44 (639 mg of THQ isolated)

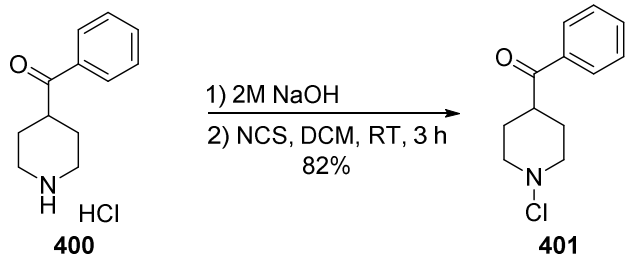
Table 3.15

3.4 Intermolecular reactions

With the success of the intramolecular reactions it was envisaged that the developed reaction conditions could be applied to intermolecular reactions with the ultimate goal of using the protocol in late stage amination reactions. It was previously discussed in Chapter 1 section 1.5.3 how Minisci had shown examples of intermolecular amination using chloroamines with the aromatic being used in excess. Using the aromatics in large excess is not favourable when it comes to late stage functionalisation of drug molecules.

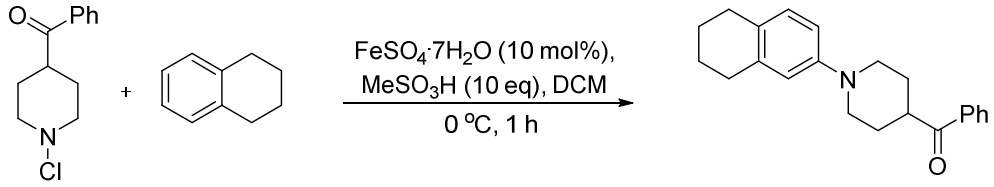
3.4.1 Initial substrate investigations

Initial investigations were carried out into the substitution with tetralin and chloroamine **401**. The chloroamine **401** could be synthesised by free-basing the 4-benzoylpiperidine HCl salt and then chlorination with NCS to afford the desired chloroamine in good yields (Scheme 3.27).



Scheme 3.27

The concentration of the reaction and the equivalents of the aromatic were varied to find the optimum conditions. The initial experiments investigated how increasing the concentration of the reaction affects the yield. Pleasingly when increasing the concentration to 1M the yield improved dramatically (Table 3.16).

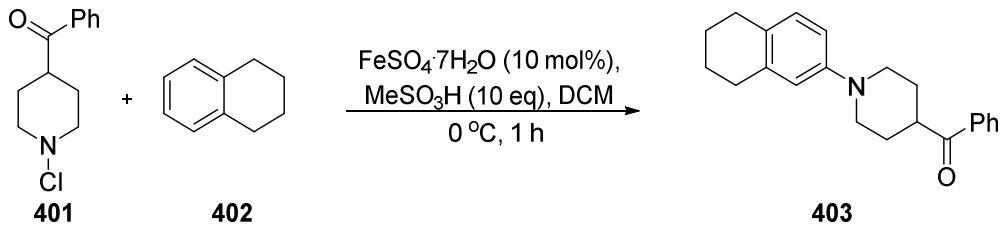


1 eq **401** 10 eq **402** **403**

Entry	Concentration with respect to chloroamine	Isolated Yield of product 403 (%)
1	0.45 M	14
2	1 M	33

Table 3.16

It was then decided to see how varying the equivalents of tetralin **402** would affect the yield. It was found that with 5 eq. of tetralin, there was a significant decrease in the yield of the desired product (Table 3.17). By increasing to 15 eq. no further increase in the yield was observed. However, inversion of the reagents such that the chloroamine was in excess resulted in a vast increase in yield. The use of 1.5eq. proved to be optimum, further increasing the equivalents of chloroamine to 2 eq. and 3 eq. resulted in a decrease in yield. This result is favourable for our goal of late stage functionalisation of drug molecules.



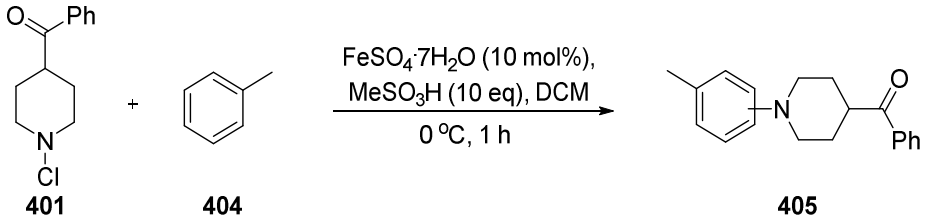
401 **402** **403**

Entry	Eq. of chloroamine	Eq. of tetralin	Average isolated yield of product 403 (%)*
1	1	5	19
2	1	10	33
3	1	15	30
4	1.5	1	78
5	2	1	51
6	3	1	30

***average yield of two reactions**

Table 3.17

However, the results of an increase in yield observed through having the chloroamine in excess with respect to the aromatic seem to be substrate specific, as when this was tried with toluene no increase in yield was observed (Table 3.18).

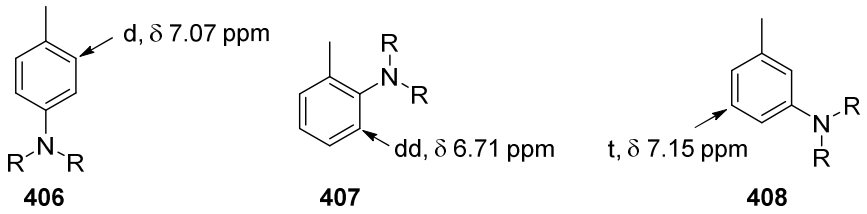


401 **404** **405**

Entry	Equivalents	Combined yield, ratio (*o* : *m* : *p*)
1	1 eq. chloroamine, 10 eq. toluene	29%, (3.6 : 7.2 : 5.5)
2	1.5 eq. chloroamine, 1 eq. toluene	28%, (3.6 : 7.2 : 5.5)

Table 3.18

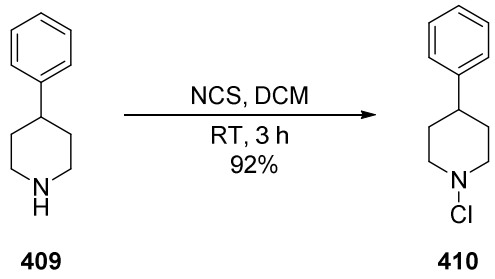
The regioisomers can be identified through characteristic peaks for the *para*-isomer (the doublet at 7.07), *ortho*- the double doublet at 6.71 and *meta*- through the triplet at 7.15 (Scheme 3.28).



Scheme 3.28

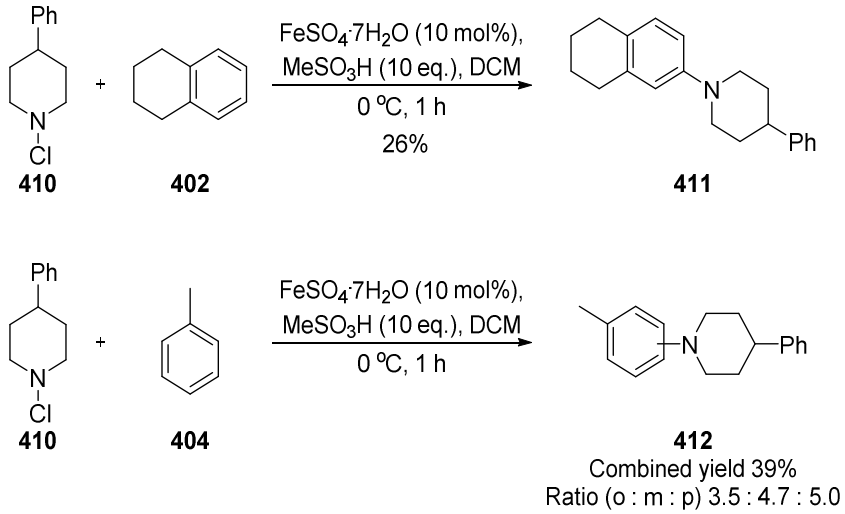
Therefore, from this point onwards all new substrates were tried using the optimal conditions with either the chloroamine in excess or the aromatic in excess. In the case of toluene the aminated products were obtained as an inseparable mixture of the *ortho*, *meta* and *para* regioisomers which were identified by ^{1}H NMR through which the ratio of each could be calculated.

With the reaction conditions in hand, another *N*-chloroamine **410** was trialled. This could be synthesised through the chlorination of the commercially available 4-phenylpiperidine **409** (Scheme 3.29).



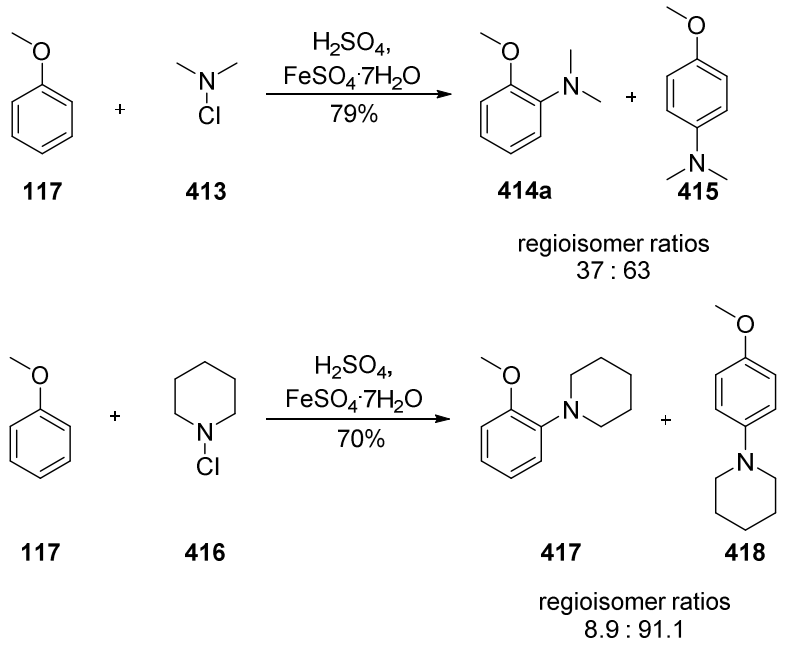
Scheme 3.29

In the case of tetralin, only a trace of the *ortho* substitution product was observed by LC-MS analysis, and it could not be isolated (Scheme 3.30). The *meta* product was isolated in a 26% yield. Again, in the case of toluene the aminated product was obtained, in a 39% yield, as an inseparable mixture of the *ortho*, *meta* and *para* regioisomers.



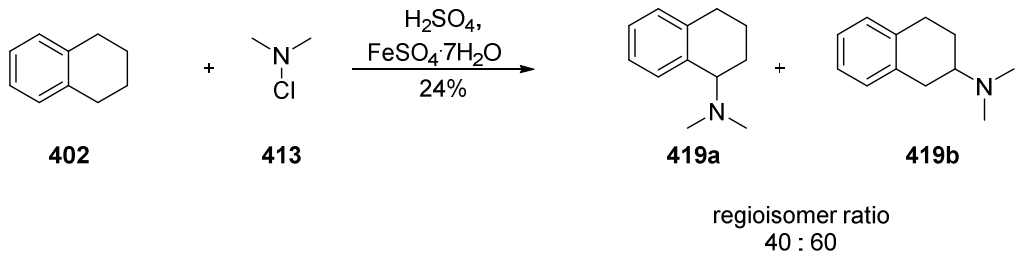
Scheme 3.30

In the reaction between both chloroamines and tetralin we observe selectivity for the *meta* position, where as in the case of toluene a mixture of *ortho meta* and *para* products is observed. Minisci *et al* observed similar results in their investigations of chloroamines reacting with aromatics they suggested this was caused due to two factors: the bulk of the chloroamine being used and the reaction medium. With regards to steric bulk it was noted that the regioselectivity was lower in the case of dimethylchloroamine **413** when compared to piperidine chloroamine **416**. In the case shown in Scheme 3.31 the methoxy group also has an electronic influence that installs the amine either in the *ortho* or *para* position.[44]



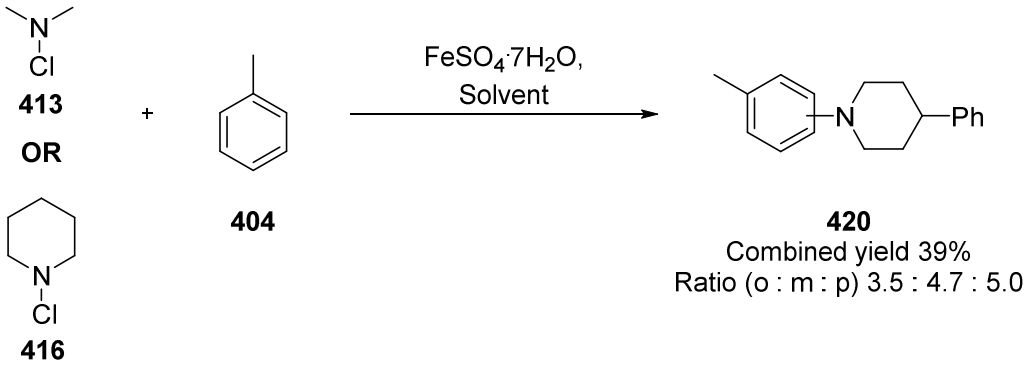
Scheme 3.31

Minisci *et al* also showed when tetralin was reacted with dimethylchloroamine **413** the 6-regioisomer was favoured in a 60:40 ratio with the 5-regioisomer (Scheme 3.32). Therefore, in our case since the steric bulk is increased the favoured amination in the 6-position can be rationalised.[44]



Scheme 3.32

Minisci *et al* also noted that changing the reaction medium had an effect on the regioisomers obtained when reacting toluene and chloroamines. When the ratio of acetic acid increased in the reaction medium the regiochemistry switched from favouring the *para* substitution to *meta* substitution (Table 3.19).[44] Although the distribution of the regioisomers changed between meta and para the *ortho* substitution products remaining low. This could be due to the differing solvation of the aminium radical with the different counter ions.



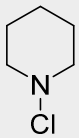
Entry	*N*-chloroamines	Solvent (H_2SO_4 : CH_3COOH)	% Toluidines		
			o-	m-	p-
1	 **413**	100 : 0	9.6	43.6	46.8
		90 : 10	10.2	47.6	42.2
		85 : 15	9.6	54.2	36.2
		80 : 20	10.8	59.7	29.5
		70 : 30	10.2	59.4	30.4
2	 **416**	100 : 0	4.6	39.2	56.2
		80 : 20	4.6	58.0	37.4
		60 : 40	3.6	61.7	34.7
		40 : 60	3.6	61.7	34.8

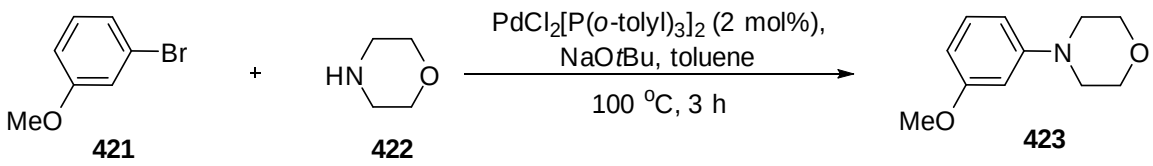
Table 3.19

Our results observed with the reaction of toluene and the chloroamine show a similar trend with the *ortho* product being the minor one observed. The distribution between the meta and para products differs but this could be due to the different steric bulk of the chloroamines. With an optimised set of conditions in hand for the intermolecular reactions it was decided to carry out a catalyst poisoning screening test to establish which functional groups are tolerated within the reaction. This was due to the unsuccessful attempts to aminate *N*-methylindole and benzoxazole.

3.4.2 Catalyst poisoning reaction

It has been shown by Glorius *et al*. that the scope of a reaction, with regards to functional group tolerance, can be carried out through using the highest yielding reaction and the addition of additives to it.[91] The additives would contain a variety of functional groups to test the reactions

robustness to the presence of them within the reaction mixture. Using the optimal reaction conditions, 1 equivalent of the additive would be spiked into the reaction to see its effects on the yields an example of which is shown in Table 3.20. It can be seen that the presence of terminal alkynes and nitrogen containing heterocycles are not tolerated by the reaction.

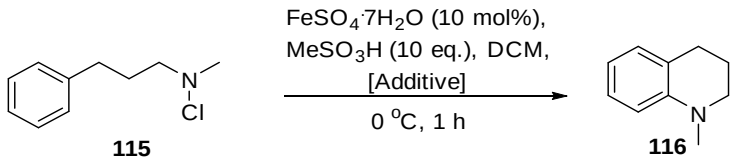


Entry	Additive	Product yield (%)	Additive remaining (%)	SM remaining (%)
1	None	89	-	-
2		0	100	100
3		82	85	0
4		0	81	99
5		10	0	36

Table 3.20

Initial investigations focused on a catalyst poisoning screens using the best reaction from the intramolecular substrates (as the yields were better than with the intermolecular version) with a variety of additives. Each trial was carried out with 10 mol% and 1 eq. of the additives relative to the substrate (Table 3.21). The table has been colour coded: green refers to a yield of 58-73%, amber refers to a yield of 43-58% and red refers to a yield of 0-43%. There was a slight decrease in the yield when benzaldehyde, benzyl alcohol, benzoic acid, methyl benzoate, chlorobenzene and pyridine were added to the reaction. There was a large decrease in the yield of the desired product when 1 eq. of piperidine was added. Only a few compounds poisoned the reaction to the extent that no desired product was afforded. In the cases of the heteroaromatic rings it could be due to side reactions hindering the reaction which could be the

additive abstracting the chlorine from the chloroamine therefore preventing the formation of the aminium radical.



115 116

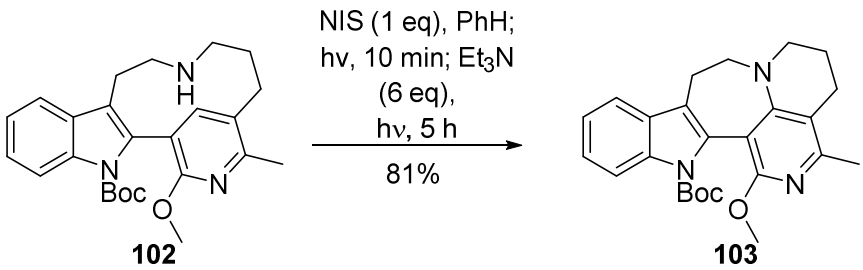
Entry	Additive	10 mol%-Yield of 116 (%)	1 eq. – Yield of 116 (%)
1	No additive	73	73
2	Benzaldehyde	53	50
3	Benzyl alcohol	57	57
4	Benzoic acid	62	59
5	Methyl benzoate	50	53
6	Chlorobenzene	68	70
7	*N*-Methylindole	44	0
8	Benzothiophene	34	0
9	Benzofuran	38	0
10	Piperidine	58	9
11	Pyridine	58	56

Table 3.21

With an insight into what functional groups are tolerated by the reaction, it was decided to investigate the *N*-arylation of tolerated heteroaromatic rings and late stage functionalisation of drug compounds. Late stage functionalisation has become more important in recent years as the number of drug molecules being approved has declined and a renewed interest in exploiting the structural diversity of natural products has occurred. This has largely been underexplored due to the synthetic challenges that accompany the structural complexity and diverse functionality of natural products. This shows the importance of developing new methodologies to allow the exploration and optimisation of natural product scaffolds.[92]

3.4.3 Heteroaromatic ring *N*-arylation

In 2012 Sarpong *et al.* demonstrated the use of aromatic amination of a pyridine ring *via* a modified HLF reaction under basic conditions in the total synthesis of arboflorine (Scheme 3.33).[43]



Scheme 3.33

The previously described catalyst poisoning experiments have shown that the presence of pyridine does not inhibit the reaction. Previous work carried out within this project which was discussed in chapter 2 section 2.2, had screened a variety of conditions with no success in the cyclisation of the aminium radical onto the pyridine ring. A hypothesis of why this was unsuccessful was that the nitrogen of the pyridine is protonated under the acidic conditions, therefore the system is more electron-poor and the cyclisation of the electrophilic aminium radical is disfavoured. Therefore, it was decided to attempt the *N*-arylation reaction using the optimised conditions on pyridine *N*-oxide. The electrons from the oxygen are delocalised around the aromatic ring and therefore the 2- and the 4- position are more susceptible to electrophilic attack (Figure 3.6).

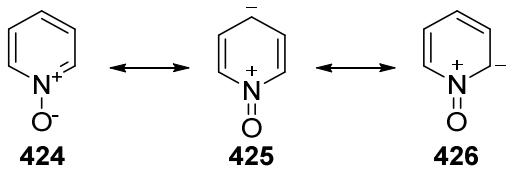
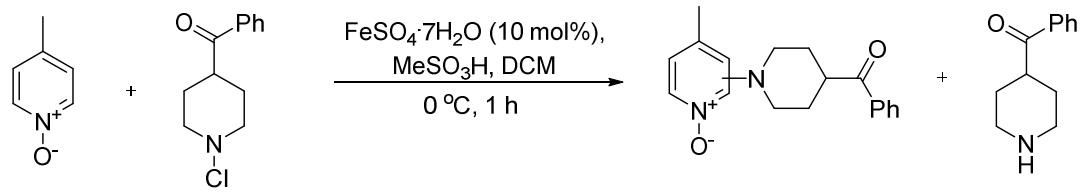


Figure 3.6

Unfortunately, none of the desired product was observed by LC-MS analysis when using pyridine *N*-oxide at various equivalents with respect to the chloroamine (Table 3.22), with only the chloroamine **401** and the declorinated amine **429** being observed.

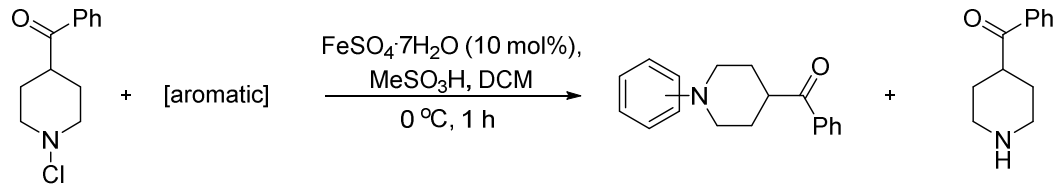


427 **401** **428** **429**

Entry	Conditions	Result
1	1.5 eq. chloroamine, 1 eq. pyridine *N*-oxide	Amine **429**
2	1.5 eq. chloroamine, 1 eq. pyridine *N*-oxide, 13 eq. $MeSO_3H$	Amine **429**
3	1 eq. chloroamine, 10 eq. pyridine *N*-oxide, 20 eq. $MeSO_3H$	Amine **429**
4	1 eq. chloroamine, 10 eq. pyridine *N*-oxide, no acid	SM **401**

Table 3.22

It was then decided to try 2- or 4- quinoline along with their respective *N*-oxides to see whether this slight change in electronics was enough to allow the amination to occur. The benzene ring of the quinoline is favoured for electrophilic substitution in the C-5 and C-8 position (Table 3.23). The *N*-oxide of quinoline can be used so that electrophilic substitution occurs on the pyridine ring of the quinoline. The energy required for dearomatisation of quinoline is lower than that required for pyridine due to stabilisation from the second aromatic ring. As shown in table 3.23 under various reaction conditions none of the desired compound was observed by LC-MS analysis.



aromatic = quinoline, quinoline N-oxide, isoquinoline or isoquinoline N-oxide

Entry	Equivalents	Result
1	1 eq. quinoline, 1.5 eq. chloroamine	Amine **429**
2	10 eq. quinolone, 1 eq. chloroamine	Amine **429**
3	1 eq. quinoline *N*-oxide, 1.5 eq. chloroamine	Amine **429**
4	10 eq. quinoline *N*-oxide, 1 eq. chloroamine	Amine **429**
5	1 eq. Isoquinoline, 1.5 eq. chloroamine	Amine **429**
6	10 eq. Isoquinoline, 1 eq. chloroamine	Amine **429**
7	1 eq. Isoquinoline *N*-oxide, 1.5 eq. chloroamine	Amine **429**
8	10 eq. Isoquinoline *N*-oxide, 1 eq. chloroamine	Amine **429**

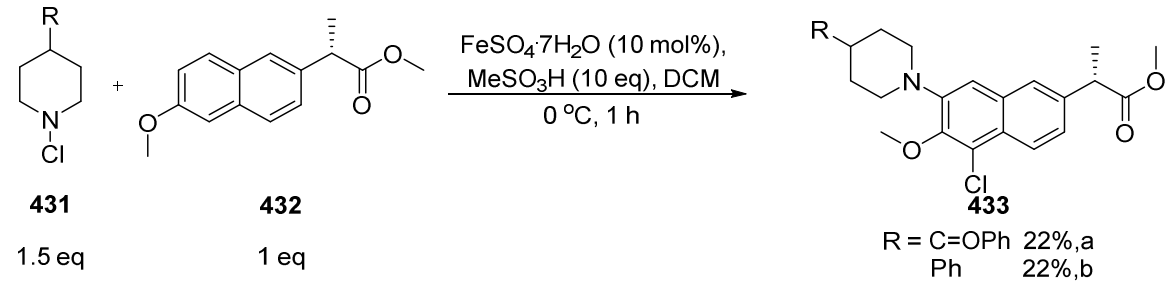
Table 3.23

Under the developed reaction conditions amination of heteroaromatic rings proved not to be possible, we therefore decided to move on and investigate the late stage functionalisation of drug compounds.

3.5 Late-stage functionalisation

It was then decided to see whether late-stage functionalisation of a drug could be achieved. The first drug chosen was the methyl ester of naproxen **432** which is a non-steroidal anti-inflammatory. It was found that at the reaction concentration of 1M, with naproxen in excess (10 eq.) the drug compound could not be fully solubilised. This led to only trace amounts of the aminated product being observed by LC-MS analysis but unfortunately it could not be isolated. By using the chloroamine in slight excess (1.5 eq.) with regards to the naproxen the aminated product could be isolated. In both cases it was the over-chlorinated product that was isolated which was identified by LC-MS and ^{1}H NMR (Scheme 3.34). Only one regioisomer

was isolated. This product could be formed by the aminated product abstracting a chlorine from a molecule of chloroamine and could explain the lower yield.



Scheme 3.34

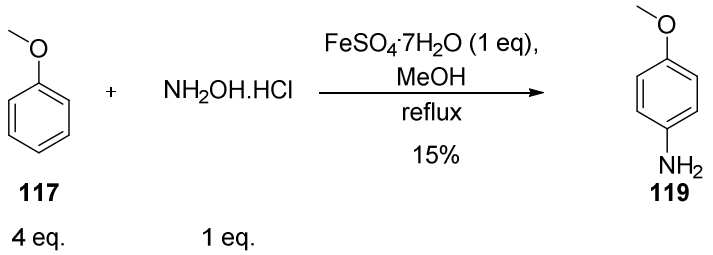
It has been shown that late stage functionalisation of simple drug molecules is feasible however care needs to be taken regarding acid labile groups within the molecule. Preferentially they would be installed in the compound after the *N*-arylation step.

3.6 Hydroxylamine amination reactions

One of the problems encountered when using chloroamines for intermolecular *N*-arylation reactions was chlorination of the desired product. It was therefore decided to investigate the use of a different nitrogen radical source precursor to avoid this undesirable side reaction.

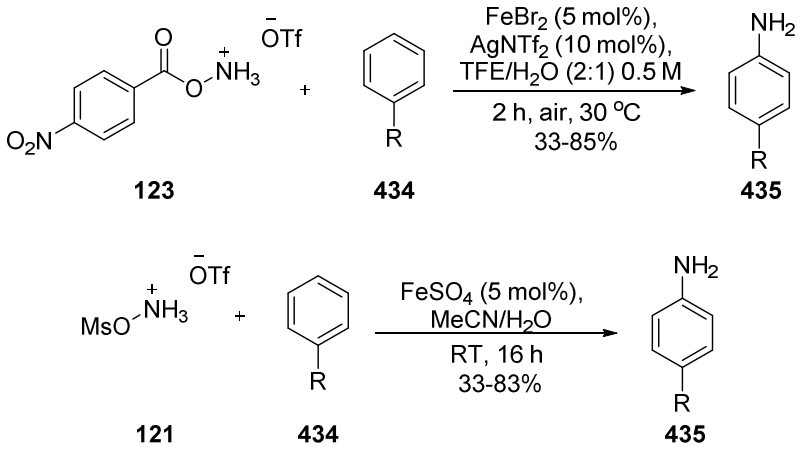
3.6.1 Amination using hydroxylamines

It has been shown by Minisci that hydroxylamine HCl can be used to aminate a variety of aromatic rings (Scheme 3.35).[44]



Scheme 3.35

Recent work by Jiao *et al* and Morandi *et al* has also demonstrated amination of aromatic rings with alternative hydroxylamine derivatives which stabilise the negative charge generated on the O when the N-O bond is cleaved (Scheme 3.36).[47,48] Both examples showed improved yields compared to Minisci's results.

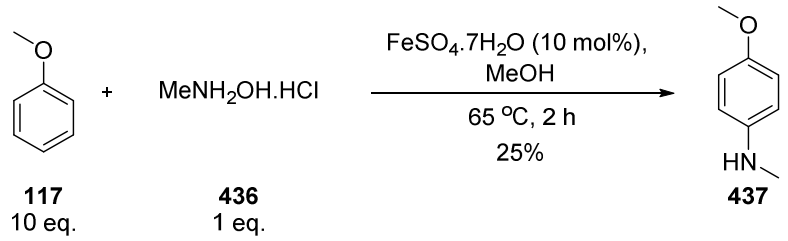


Scheme 3.36

To date within the literature, no example of substitution on the nitrogen has been shown. This section will detail investigations carried out into intermolecular *N*-arylation reactions using *N*-substituted hydroxylamines.

3.6.2 Initial trial

It was decided to use hydroxylamines with no activating substitution on the oxygen as this is a more atom economical route, with the by-product of the reaction being water. Initial investigations, with the conditions based on previous work and the reactions carried out by Minisci *et al*, were carried out using methylhydroxylamine HCl **436** and pleasingly the desired product **437** was obtained in a 25% yield (Scheme 3.37). One regioisomer was obtained which could be determined through ^{1}H NMR analysis.



Scheme 3.37

Although the desired product was synthesised successfully it was decided if this methodology was to be utilised in the late stage functionalisation of drug molecules then the aromatic should be the limiting reagent. Therefore, a design of experiment was carried out to optimise the reaction with anisole as the limiting reagent.

3.6.3 Design of Experiment (DOE)

Design of experiment is a methodology developed by the statistician Ronald Fisher in 1958 which has the objective of getting as much information as possible from the minimum number of experiments.[93] Traditional methods of optimising a reaction look at individual factors against the reaction yield and therefore the optimal conditions might be missed or take a long time to establish. Design of experiment can be used to screen several factors at the same time to identify which of the factors are critical within the reaction. For our investigations, a three-factorial system was used; for this 2 values for each of the 3 reaction conditions are investigated which leads to 8 reactions and 2 control experiments (Figure 3.7).

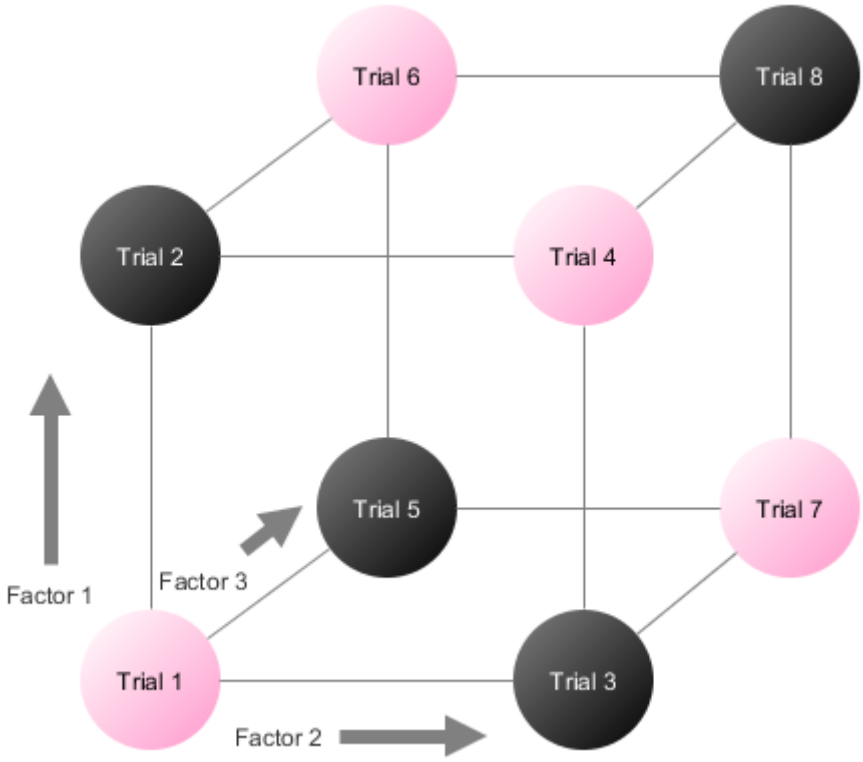
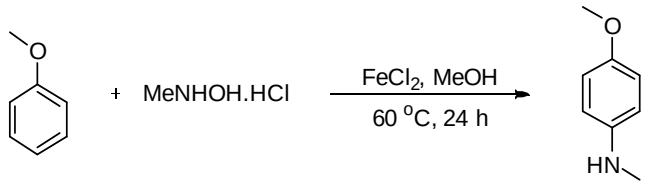


Figure 3.7[94]

3.6.4 DOE with $FeCl_2$ and $FeSO_4.7H_2O$

The Iron salts $FeCl_2$ and $FeSO_4.7H_2O$ were selected for the DOE as they had previously shown the best results in our investigations into *N*-arylation using chloroamines. For the investigations into the *N*-arylation with hydroxylamine a three-factorial system was used which investigated the loading of iron salt (3-25 mol%), equivalents of methylhydroxylamine HCl (1.1-2.9 eq) and the concentration of the reaction (0.1-2.1 M). The amounts were decided upon based on the current reaction conditions and a random order was generated of the reaction conditions to carry out the DoE (whether the high or low value was used). The reactions were monitored by HPLC analysis which was uncorrected at this stage (75% area product peak correlates to a 10% isolated yield of the desired product). When comparing Entry 1 and Entry 5 where the concentration of the reaction is increased from 0.1 M to 2.1 M the percentage area of the product observed increases from 2.8% to 72.0%. This shows how important the concentration of the reaction is (Table 3.24, Entries 1 and 5). In the case of catalyst loading the lower catalyst loading in reaction 7 gives an area% of 75.0 whereas the higher catalyst loading in reaction 8 only achieves an area% of 10.2 for the product this demonstrates the benefits of lower catalyst

loading (Table 3.24, Entries 7 and 8). In both cases lower catalyst loading and higher concentration of the reaction gave the better yields. The reaction profile was cleaner with $FeCl_2$ and gave the same conversion as $FeSO_4 \cdot 7H_2O$.



117 **436** **437**

Entry	Catalyst charge (mol% vs RNHOH)	MeNHOH.HCl charge (mol eq vs Anisole)	Conc (Anisole, mol/L)	HPLC, Product Area %	HPLC, SM Area %
1	3	1.1	0.1	2.8	78.6
2	25	1.1	0.1	12.1	68.3
3	3	2.9	0.1	15.5	73.3
4	14	2	1.1	62.8	21.4
5	3	1.1	2.1	72.0	24.9
6	25	2.9	0.1	58.9	35.4
7	3	2.9	2.1	75.2	20.8
8	25	2.9	2.1	10.6	22.5
9	14	2	1.1	62.9	22.0
10	25	1.1	2.1	32.8	23.8

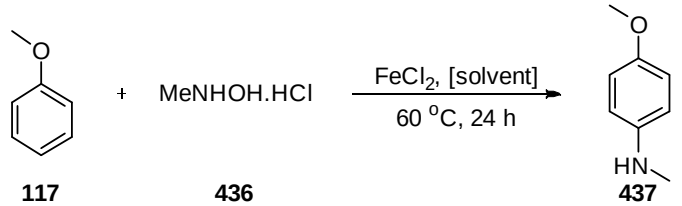
Table 3.24

Due to the improved reaction profile and the similar yields obtained it was decided to continue with $FeCl_2$.

3.6.5 Solvent screen

Using the optimised conditions established in the DOE a solvent screen was carried out to ensure methanol was the best solvent. A range of polar solvents were tried with the best results being observed with ethanol and isopropanol. Analysis was carried out using HPLC analysis with uncorrected Area% (75% equates to a 10% isolated yield). Good solubility of the hydroxylamine was observed when using isopropanol, ethanol and methyl isobutyl ketone

(MIBK) (Table 3.25 entries 5, 7 and 9). This could explain the increased conversions of the alcohols compared to the other solvents trialled.



117 **436** **437**

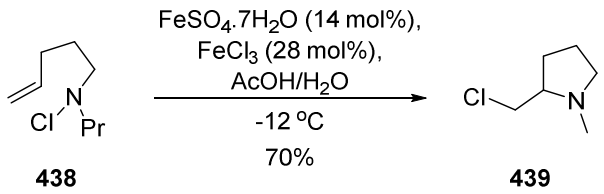
Entry	Solvent	Area%
1	EtOAc	5.29
2	THF	17.44
3	2-methyl THF	12.5
4	Dioxane	13.93
5	Isopropanol	67.50
6	MeCN	15.55
7	Ethanol	71.43
8	IPAC	-
9	MIBK	-

Table 3.25

It was therefore decided to continue using methanol as the solvent of choice for the reaction and if problems with solubility arose then ethanol or isopropanol could be used instead.

3.6.6 Mixed catalyst system

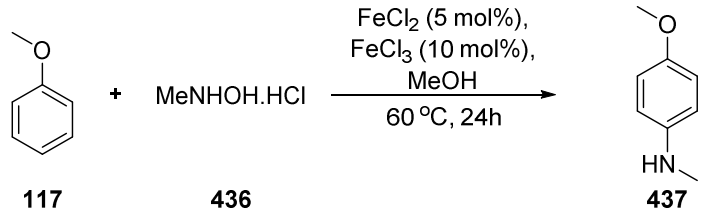
Despite our best efforts to optimise the system only a maximum of a 10% isolated yield of the desired product was obtained when the aromatic was used as the limiting reagent. Within the literature Tordo *et al*. describe the use of a mixed catalyst system which utilises Fe(II) and Fe(III) sources (Scheme 3.38).[95] An increase in yield was observed when the mixed catalyst system in the reaction between *N*-chloroamines and alkenes. In the reaction double the amount of Fe(III) catalyst was used in comparison to Fe(II) catalyst. The benefit of this could be the Fe(III) can accept an electron from the pyrrolidine and therefore regenerate the Fe(II) catalyst.



438 **439**

Scheme 3.38

It was therefore decided to see whether this could be applied to our system to increase the yield. Initial results showed only a slight increase in yield from 10% to 13% which is within experimental error (Scheme 3.39).

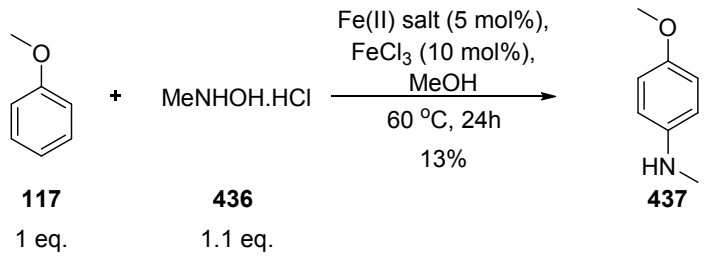


117 **436** **437**

1 eq. 1.1 eq.

Scheme 3.39

To ensure this was the best combination of iron salts for the reaction, a variety of Fe(II) salts were tested. Analysis was carried out using HPLC with the percentage areas corresponding to the actual yield of the product formed. It can be seen from this table that the addition of $FeCl_3$ to the reaction does increase the yield of the desired product being formed. The best example of this can be seen when using ferrocene: the yield goes from 0.3% (Table 3.26, entry 1) after 24 hours to 7% (Table 3.26, Entry 2) just through the addition of $FeCl_3$ into the system. This could be due to the $FeCl_3$ accepting the electron from the aromatic allowing it to rearomatize and in turn regenerating Fe(II) catalyst which can then go on to generate more of the protonated amiunium radical or scavenge halides.



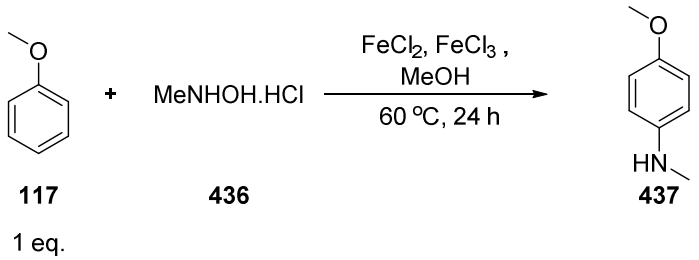
117 1 eq. **436** 1.1 eq. **437**

Entry	Reaction	30 mins	1 hour	2 hours	4 hours	22 hours
1	Ferrocene	-	-	-	-	0.30
2	Ferrocene, Iron(III) chloride	0.22	0.44	0.81	1.27	7.00
3	Iron acetate	0.84	1.16	1.99	2.76	9.63
4	Iron acetate, Iron(III) chloride	2.29	2.84	4.71	5.80	10.41
5	Iron phthalocyanine,	-	-	-	-	-
6	Iron phthalocyanine, Iron(III) chloride	0.56	0.91	0.93	0.96	3.99

*values represent conversion to product on HPLC trace

Table 3.26

The catalyst screen showed that $FeCl_2$ in conjunction with $FeCl_3$ gave the best results and this would be the catalyst system that would be used from now on. It was hypothesised that by carrying out a DOE this time investigating the loading of the $FeCl_2$ (5-20 mol%), $FeCl_3$ (5-60 mol%) and the equivalents of methylhydroxylamine HCl (1.1-2.9 eq) an increase in yield could be obtained. The mol% of $FeCl_3$ was calculated by multiplying the $FeCl_2$ mol% by either 1-3 depending on the factor being high, low or the middle control (2x). With the higher loadings of $FeCl_2$ (20 mol%) more impurities were observed after 24 hours, whereas with lower loading of $FeCl_2$ a much cleaner reaction profile was observed (Table 3.27). The best results were observed in reactions 5 and 7, this showed that the higher loading of the methylhydroxylamine HCl was important as well as the lower loading of $FeCl_2$. There is a slight increase in yield from reaction 5 to 7 in which the loading of $FeCl_3$ is higher.



Experiment	Fe(II) mol%	Fe(III) mol%	MeNHOH.HCl (eq)	Conversion by HPLC
1	5	5	1.1	9
2	20	20	1.1	7
3	5	15	1.1	11
4	12.5	25	2.0	18
5	5	5	2.9	20
6	20	60	1.1	7 (many impurities)
7	5	15	2.9	24
8	20	60	2.9	24 (impurity at 23%)
9	12.5	25	2.0	18
10	20	20	2.9	20

Table 3.27

To see whether this slight increase in yield between reaction 5 and 7 is due to the increase in $FeCl_3$, it was decided to carry out a reaction using $FeCl_2$ (5 mol%), $FeCl_3$ (100 mol%) and methylhydroxylamine HCl (2.9 eq) (Figure 3.8). The graph below shows that there is in fact an increase in the yield when the loading of $FeCl_3$ is increased from 5 mol% to 100 mol%.

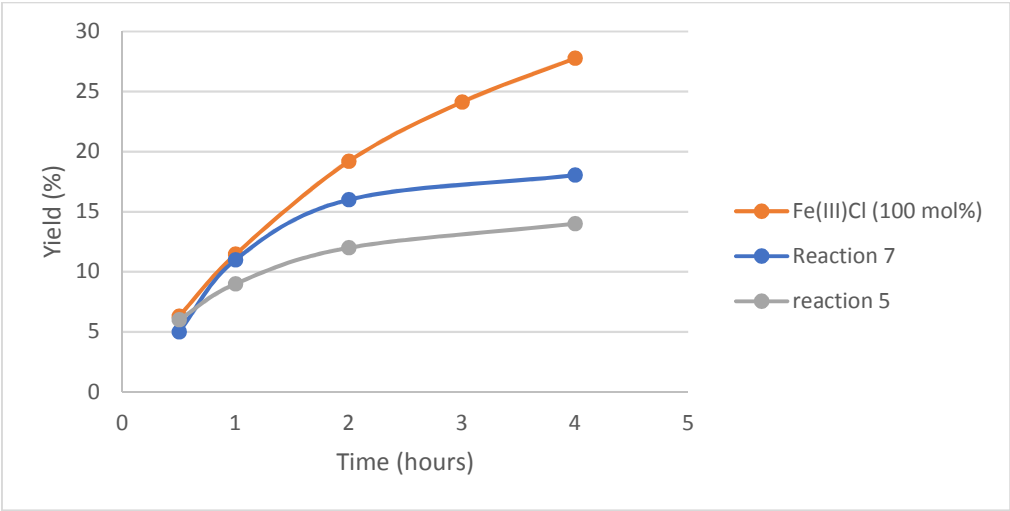


Figure 3.8

It was observed from the reaction profiling that the conversion of the SM to the desired product appears to stop after four hours (Figure 3.9). This could be due to the methylhydroxylamine HCl being reduced to methylamine.

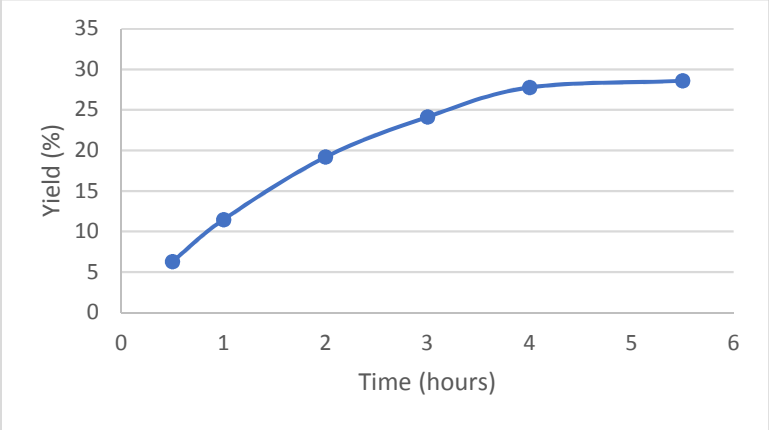


Figure 3.9

To establish whether this was the case a second loading of 2.9 eq of methylhydroxylamine HCl was added at four hours (Figure 3.10). As can be seen from the reaction profile below the yield of the desired product continued to increase due to the second addition therefore supporting the hypothesis that the hydroxylamine is limiting the formation of the product. The second addition is highlighted by the green arrow. The reaction was left to stir for 16 h in total and a 40% yield was obtained at the end.

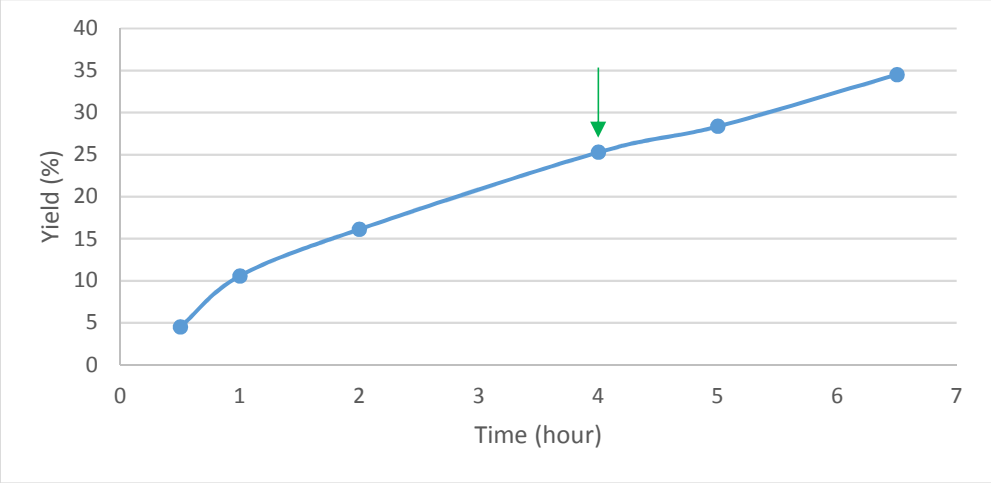
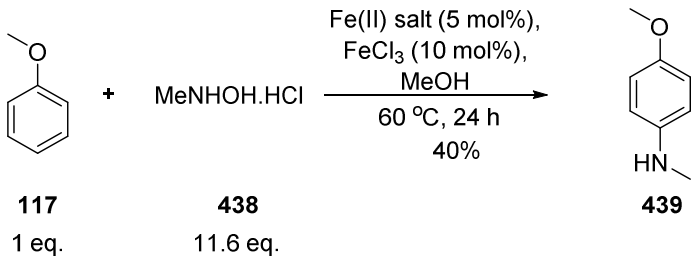


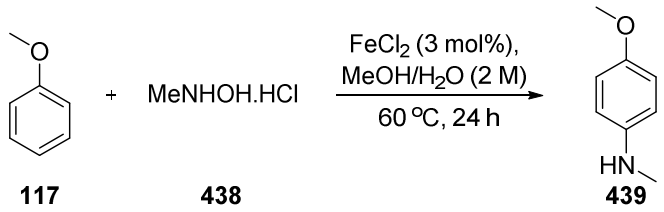
Figure 3.10

An additional experiment was carried out in which 4 additions of 2.9 eq methylhydroxylamine HCl was carried out to see whether a higher yield would be obtained (Scheme 3.40). It was found however that only a 40% yield was obtained despite double the amount of hydroxylamine being added to previous reactions. This suggests there are other limiting factors of the reaction, potentially the formation of methylamine or water could be an issue after a certain level is reached.



Scheme 3.40

Control reactions carried out on the single component catalyst system previously showed that increasing amounts of water in the reaction did decrease the overall yield of the reaction. Analysis of the reaction mixture was carried out using HPLC the values at this time are uncorrected and 75% equates to a 10% yield. Small amounts of water such as 5-20% of the solvent is not detrimental to the reaction (Table 3.28, Entry 2-3). When the solvent was made up of 35% water a decrease in the conversion was observed (Table 3.28, Entry 4). This supports the hypothesis that the build up of water in the reaction over time is hindering the overall yield.



117 438 439

Entry	%water in solvent	%Area uncorrected
1	0%	75
2	5%	75
3	20%	73
4	35%	57

Table 3.28

It has therefore been established that 5 mol% of $FeCl_2$ and 1 eq $FeCl_3$ is the best catalyst combination for the reaction. The addition of 5.8 eq of the methylhydroxlamine HCl in two portions 4 hours apart gives the best isolated yields of 40%.

3.6.7 Slow addition experiments

Due to the success of the second addition of MeNHOH.HCl after 4 hours, it was decided to investigate slow addition of the hydroxylamine into the reaction mixture. The addition was carried out over 3 hours, 6 hours and 9 hours to compare the yields. Additional samples were taken after addition had stopped was submitted for HPLC analysis to confirm the reaction had finished one hour after the addition finished. The graphs in Figure 3.11 show that the yields obtained over 6 hours and 9 hours give very similar. Further slow addition experiments would be carried out over the 6 hours period as there was no substantial benefit of addition over 9 hours.

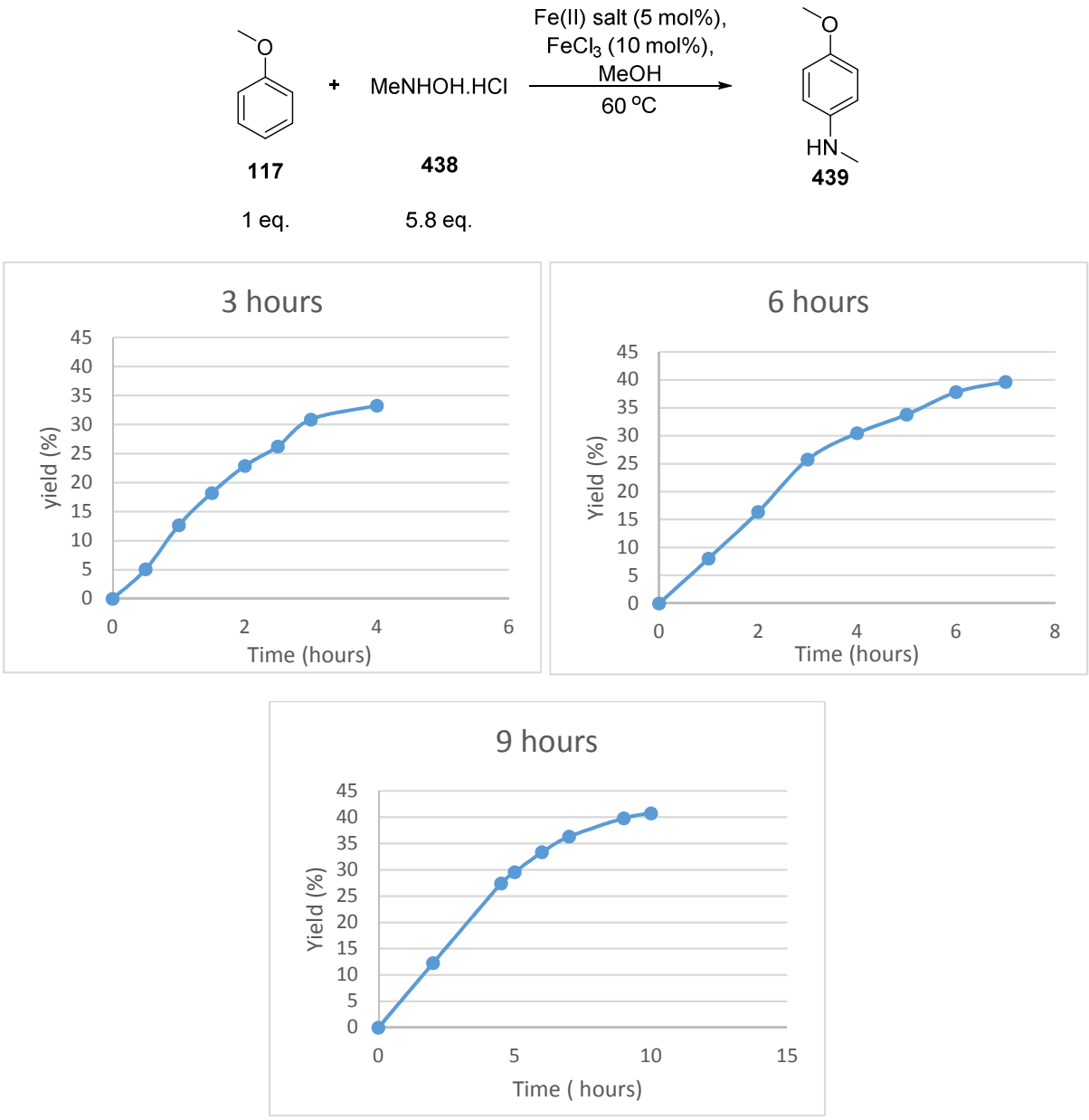
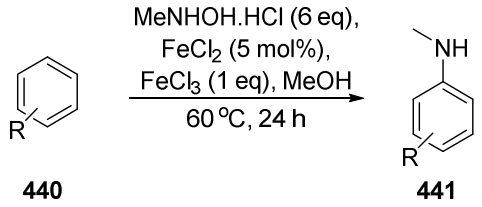


Figure 3.11

With the optimised conditions in hand and the option for slow addition reactions to decrease the reaction time from 16 hours to 6 hours it was decided to investigate the substrate scope of the reaction.

3.6.8 Substrate screening experiments

A variety of aromatics were chosen ranging from heteraromatics to polar and non-polar substituted aromatics (Table 3.29). It can be seen from the results that nitrogen containing heteroaromatics such as pyridine, *N*-methylindole and imidazole are not tolerated which agrees with findings in our previous studies. The aminium radical is highly electrophilic and the substrates that have failed are all electron poor or can be in the acidic conditions. In the case of 2-methoxynapthlene where the *para* position (which is the more favoured position) we do observe some amination in the *ortho* position, it was due to this it was believed naproxen could be aminated successfully. When using chloroamines to *N*-arylate the methyl ester of naproxen, chlorination on the aromatic ring was observed whereas with the hydroxylamines we avoid this issue and can successfully aminate the aromatic ring selectively. Again in this case selectivity for the more electron rich ring is observed.



440 **441**

Table 3.29

Successful products	**Unsuccessful substrates**
	N-methylindole
442 25%	Imidazole
443 11%	Benzofuran
444 8%	Chlorobenzene
445 13%	Pyridine
446 22%	Benzene pinacol boronate

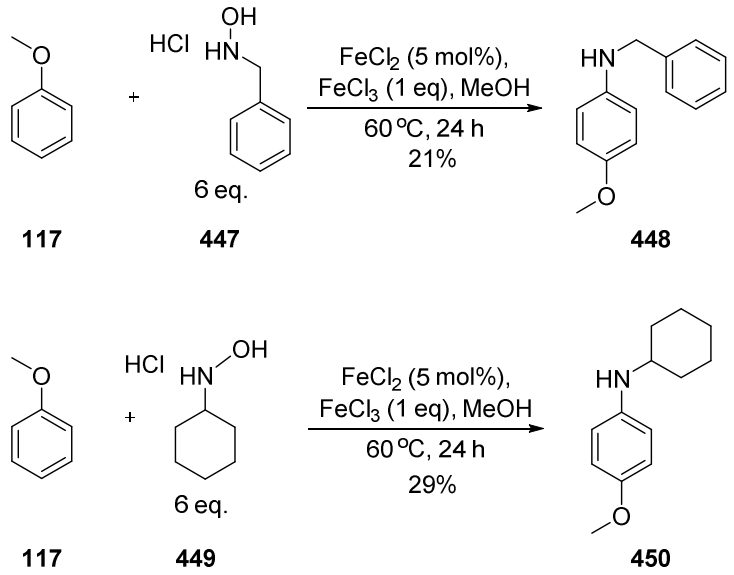
Table 3.30

With the scope of the aromatic substrates established, investigations then focussed on different hydroxylamines.

3.6.9 Hydroxylamine screening experiments

The two hydroxylamines chosen were *N*-benzylhydroxylamine and *N*-cyclohexylhydroxylamine both of which gave slightly lower yields with anisole than had previously been obtained with methylhydroxylamine (Scheme 3.41). Complete regioselectivity is observed for substitution in the *para* position, this agrees with results previously observed by Minisci *et al* that a mix of steric and electronic factors play a key role so in this case the

ortho and *para* positions would be preferred. Also due to the bulk of the amine the para position would be preferred over the *ortho* position.[44]



Scheme 3.41

Further investigations are required to optimise the yields obtained and screen other substrates.

3.7 Conclusions

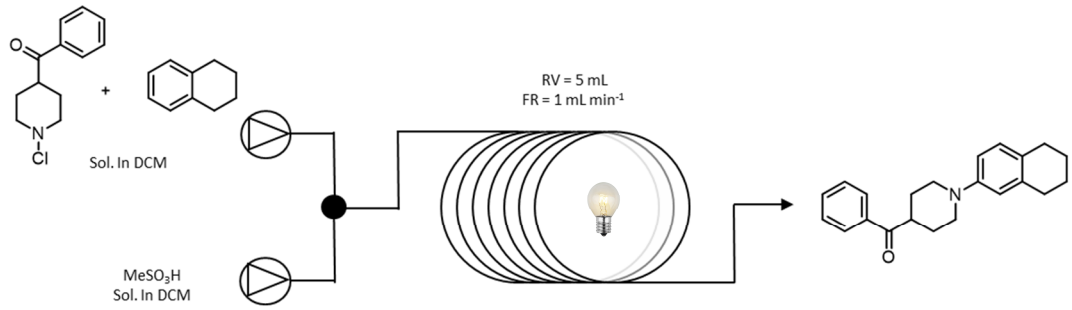
A methodology has been developed and optimised which utilises *N*-chloroamines and iron salts as the initiator in the amination of aromatic rings. The scope has been explored with variations in the substitution on the nitrogen, alkyl chain and the aromatic ring. A one-pot process has been established for the chlorination and *N*-arylation which alleviates the need to isolate the chloroamines.

Some probes into the mechanism of the reaction have been carried out, and the competition reactions support the hypothesis that this reaction proceeds through a highly electrophilic species.

With regards to the intermolecular reactions two sets of conditions which use either chloroamines or hydroxylamines have been established and trialled with a variety of aromatics. Late stage functionalisation of a couple of drug molecules has been achieved. There is still some optimisation to be carried out in regards to the yields obtained via these methodologies.

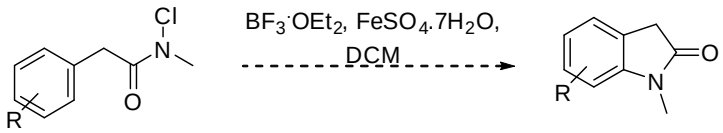
3.83.8 Future Work

With regards to the work carried out using UV light to initiate the *N*-arylation reaction in flow an intermolecular variant of the flow *N*-arylation reaction should be investigated. Initial trials would focus on tetralin and one of the chloroamines used in the iron salt study. Investigations into the equivalents of each substrate that is required and whether the concentrations would be suitable for flow could be carried out.



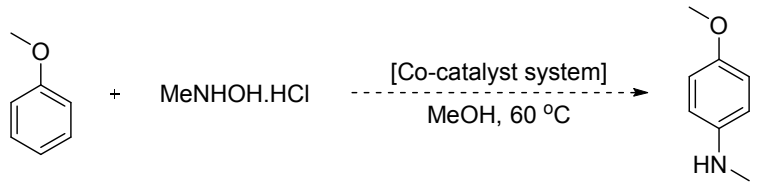
Scheme 3.42

Due to the conditions established using iron salts for the *N*-arylation of chloroamines investigations into whether this would be successfully with the chloroamides could be carried out. If successful and the yields improved compared to the photochemical example alternative substitution patterns could be investigated. It has been shown with the iron salts that substrates with different substituents work compared to when the UV light conditions are used when *N*-arylation is carried out using *N*-chloroamines.



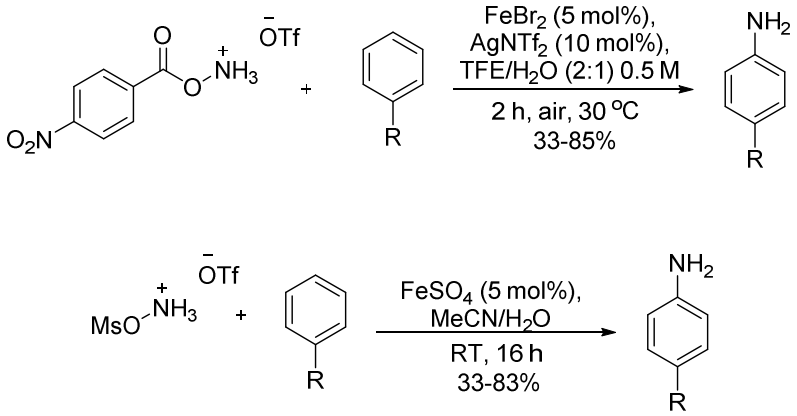
Scheme 3.43

The hydroxylamine work has shown some initial interesting results alternative metal co-systems could be investigated such as titanium(III) and iron(III) to investigate whether this would increase the yield at all.



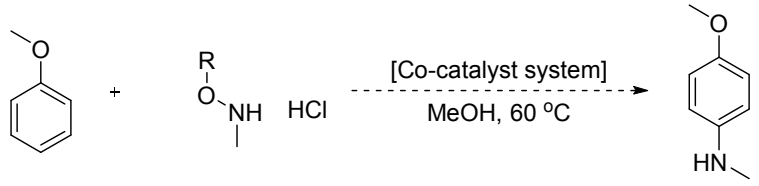
Scheme 3.434

It has been shown by Jiao *et al* and Morandi *et al* that different groups on the oxygen can increase the yields of amination products.[1,2] As they can help stablise the negative charge generated on the oxygen when the N-O bond is cleaved.



Scheme 3.45

Once the best co-catalyst system has been established investigations into different substituents on the oxygen starting with the groups shown by Jiao and Morandi could be trialled to see whether this improves the yields and the range of substrates.



Scheme 3.46

Chapter 4 Experimental

4.1 General Experimental

All reactions were carried out under an inert, dry nitrogen atmosphere, unless otherwise stated. Anhydrous solvents were purified by the solvent purification system. All reagents were obtained from commercial suppliers and used without further purification, unless otherwise stated.

Flash column chromatography was carried out using Merck silica gel (40 - 63 µm particles). Thin phase chromatography was carried out using pre-coated silica plates (Merck silica Kieselgel 150F_{254}). They were analysed using UV fluorescence (λ_{max} = 254 nm) and developed using potassium permanganate solution. All chromatography eluents were BDH GPR grade and used without further purification.

IR spectra were obtained on a Perkin Elmer Spectrum one FT-IR spectrometer, with absorption reported in wavenumbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 300, a Bruker DRX 500 or a Bruker Advance 500 spectrometer with an internal deuterium lock. ^{1}H chemical shifts reported in parts per million (ppm) and coupling constants (*J*) are reported in hertz (Hz). $^{13}C\{^{1}H\}$ NMR spectra were recorded with band proton decoupling at 75 MHz or 126 MHz. Assignments were made on the basis of chemical shifts and coupling data using COSY and DEPT where necessary. High resolution mass spectra were recorded on a Waters-Micromass ZMD spectrometer fitted with ES ion source. Melting points were obtained (uncorrected) on a Reichert hot stage apparatus.

Analytical LC-MS was performed using a system comprising of a Bruker HCT Ultra ion trap mass spectrometer equipped with electrospray ionization and an Agilent 1200 series LC made up of, a high vacuum degasser, a binary pump, a high performance autosampler, an autosampler thermostat, a thermostated column compartment and diode array detector. The system used a Phenomenex Luna C18 50 × 2 mm 5 micron column and elution was effected with a binary gradient of two solvent systems: MeCN/H2O + 1% TFA or MeCN/H2O.

HPLC spectra were recorded on an Agilent C100 series HPLC using an agilent C18 column (4.6 x 50 mm, 1.8 µm) with a binary gradient of two solvents: MeCN/H2O + 0.1% Formic acid.

4.2 Flow Chemistry Experimental

4.2.1 Chlorination flow reactor

A stainless steel T-junction was attached 10 m of PTFE tubing (internal diameter 1/32nd inch, external diameter 1/16th inch, 5 mL reactor volume) and to the inlets PTFE tubing (internal diameter 1/32nd inch, external diameter 1/16th inch) was attached to connect to syringes that contained the reactants to the dark reactor. The flow was controlled using a dual syringe pump that allowed both flows to go at equal rates (0.25 mL min^{-1}). DCM was then passed through the reactor (3 reactor volumes). Assuming no leaks, the reactor was covered in aluminium foil. The reaction mixture was collected in a conical flask and analysed appropriately. After the reaction was finished, DCM was passed through the reactor (5 reactor volumes) followed by IPA (5 reactor volumes).

4.2.2 Photochemical reactor

A photochemical reactor was designed based on the reactor described by Booker-Milburn *et al*.[73] The photochemical reactor was constructed using FEP tubing (internal diameter 2.7 mm, external diameter 3.1 mm) that was wrapped around a 125W high pressure mercury quartz immersion well reactor (overall length 390 mm, internal diameter 38 mm, external diameter 58 mm), with the tubing attached to the well using double-sided sticky tape and masking tape (184 cm of FEP tubing, to give a 5 mL reactor volume + 100 cm of excess tubing). There was 50 cm of excess tubing attached at each end of the reactor tubing, with one being placed in a conical flask to collect the reaction mixture and the other attached to the outlet of a stainless steel T-junction. Adapters were placed in the inlets of the T-junction that allowed PTFE tubing (internal diameter 1/32nd inch, external diameter 1/16th inch) to connect to syringes that contained the reactants. The flow was controlled using a dual syringe pump that allowed both flows to go at equal rates (0.50 mL min^{-1}). The quickfit joint of the immersion well was clamped in a stand, then DCM was passed through the reactor (3 reactor volumes). Assuming no leaks, the reactor was covered in aluminium foil and placed in a water bath with a temperature of 18 ˚C and then reaction was run, with the first three column volumes discarded. The reaction mixture was collected in 5 mL aliquots and analysed appropriately. After the reaction was finished, DCM was passed through the reactor (5 reactor volumes) followed by IPA (5 reactor volumes).

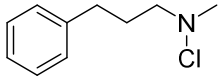
General procedure A: Continous chlorination of secondary amines

Using the continuous reactor described above, a solution of amine (0.4 M in DCM) in one syringe and a solution of NCS (0.4 M in DCM) in the other were pumped at a rate of 0.25 mL min^{-1}. The first 10 mL of eluent was discarded, then subsequently the rest was collected in a conical flask. The reaction mixture was concentrated *in vacuo* and purified by column chromatography to afford the desired products. The theoretical maximum yield was calculated by working out the amount of substrate that would have been present in one 5 mL column volume, then multiplying by the collected number of column volumes. This was then compared to the obtained product to give the percentage yield. Reactor productivity was calculated by dividing the amount of purified desired product by the number of reactor volumes collected in, then multiplying the result by 12 to give the amount of purified material that would be obtained per hour.

General procedure B: Continuous photochemical amination

Using the continuous reactor described above, a solution of N-chloroamine (0.4-0.5 M in DCM) in one syringe and a solution of $MeSO_3H$ (6 M in DCM) in the other were pumped at a rate of 0.5 mL min^{-1}. The first three reactor volumes were discarded, then subsequently collected in 5 mL fractions and analysed by LC-MS separately. The separate reactor volumes were taken up in H_2O and washed with EtOAc. The aqueous phase was then basified with 2 M aqueous NaOH and extracted with EtOAc (× 3). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography afforded the desired products. The theoretical maximum yield was calculated by working out the amount of substrate that would have been present in one 5 mL column volume, then multiplying by the collected number of column volumes. This was then compared to the obtained product to give the percentage yield. Reactor productivity was calculated by dividing the amount of purified desired product by the number of reactor volumes collected, then multiplying the result by 12 to give the amount of purified material that would be obtained per hour.

_N_-chloro-_N_-methyl-3-phenylpropan-1-amine 115

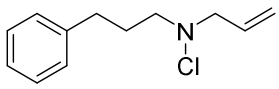


General procedure A was followed, using N-methyl-3-phenylpropan-1- amine (0.4 M in DCM) and running at 0.5 mL min^{-1}. 50 mL of eluent was collected, then purification column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (1.12 g, 6.09 mmol, 61%) as a yellow gum.

Productivity: $\left(\frac{1.12g}{5}\right) \times 12 = 2.69$ g h^{-1}

Compound data can be found in section 4.5

_N_-chloro-_N_-allyl-3-phenylpropan-1-amine 239

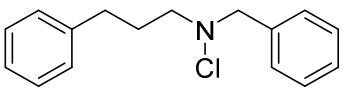


General procedure A was followed, using *N*-allyl-3-phenylpropan-1- amine (0.4 M in DCM). 50 mL of eluent was collected, purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (1.53 g, 7.29 mmol, 73%) as a yellow gum.

Productivity: $\left(\frac{1.53g}{20}\right) \times 12 = 0.92$ g h^{-1}

Compound data can be found in section 4.5

_N_-chloro-_N_-benzyl-3-phenylpropan-1-amine 240

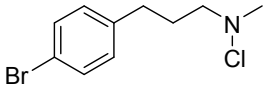


General procedure A was followed, using *N*-benzyl-3-phenylpropan-1- amine (0.4 M in DCM). 50 mL of eluent was collected, purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (1.88 g, 7.24 mmol, 72%) as a yellow gum.

Productivity: $\left(\frac{1.88g}{20}\right) \times 12 = 1.13$ g h^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.43 – 7.17 (10H, m, 10 × ArC*H*), 4.13 (2H, NClCH_2Ar), 3.00 (2H, t, *J* = 6.7, CH_2NCl), 2.72 (2H, t, *J* = 7.7, ArCH_2), 2.10 – 2.03 (2H, m, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 141.8 (C_q), 137.1 (C_q), 129.2 (2 × Ar*C*H), 128.5 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 127.9 (Ar*C*H), 125.8 (Ar*C*H), 68.4 (NClCH_2Ar), 62.2 (CH_2NCl), 32.7 (ArCH_2), 29.5 (CH_2); **IR** υ_{max} (neat) / cm^{-1} 3062, 3027, 2920, 2857, 1702, 1602, 1495, 1453; **HRMS (ESI$^+$)**: $C_{16}H_{19}{}^{35}ClN$ $[M + H]^+$: calculated 260.1201, found 260.1201, Δ = 0.0 ppm.

3-(4-bromophenyl)-*N*-chloro-*N*-methylpropan-1-amine 241

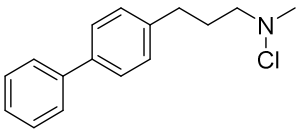


General procedure A was followed, using 3-(4-bromophenyl)-*N*-methylpropan-1-amine (0.4 M in DCM). 34 mL of eluent was collected, purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (1.10 mg, 4.19 mmol, 61%) as a yellow gum.

Productivity: $\left(\frac{1.10g}{13.6}\right)$ × 12 = 0.97 g h^{-1}

Compound data can be found in section 4.5

3-([1,1'-biphenyl]-4-yl)-*N*-chloro-*N*-methylpropan-1-amine 242



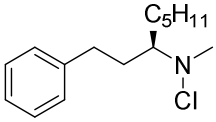
General procedure A was followed, using 3-([1,1'-biphenyl]-4-yl)-Nmethylpropan-1-amine (0.4 M in DCM). 28 mL of eluent was collected, purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (885 mg, 3.39 mmol, 61%) as a yellow gum.

Productivity: $\left(\frac{0.89g}{11.2}\right)$ × 12 = 0.95 g h^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.63-7.22 (9H, m, 9 × ArC*H*), 2.96 (3H, s, NCH_3), 2.95-2.90 (2H, m, NCH_2), 2.77-2.71 (2H, m, ArCH_2), 2.07-1.97 (2H, m, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 141.2 (C_q), 140.9 (C_q), 139.0 (C_q), 129.0 (2 × Ar*C*H), 128.9 (2 × Ar*C*H), 127.3

(2 × Ar*C*H), 127.2 (Ar*C*H), 127.1 (2 × Ar*C*H), 65.4 (NCH_2), 53.2 (NCH_3), 32.5 (ArCH_2), 29.8 (CH_2); **IR** υ_{max} (neat) / cm^{-1}: 3057, 3029, 2997, 2863, 1595, 1487, 1455, 1439; **HRMS (ESI)**: $C_{16}H_{19}{}^{35}ClN$ [M+H^+]: calculated 260.1201, found 260.1201, Δ = 0.0 ppm.

(*R*)-*N*-chloro-*N*-methyl-1-phenyloctan-3-amine 243

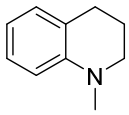


General procedure A was followed, using (*R*)-*N*-methyl-1-phenyloctan-3- amine (0.4 M in DCM). 30 mL of eluent was collected, purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (777 mg, 3.06 mmol, 51%) as a yellow gum.

Productivity: $\left(\frac{0.78g}{12}\right)$ × 12 = 0.78 g h^{-1}

Compound data can be found in section 4.5

1-methyl-1,2,3,4-tetrahydroquinoline 116

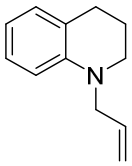


General procedure B was followed, using *N*-chloroamine **115** (0.5 M solution in DCM) and $MeSO_3H$ (6 M solution in DCM). In total, nine column volumes were collected. After work-up, purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (930 mg, 6.32 mmol, 56%) as a pale yellow oil.

Productivity: $\left(\frac{0.81g}{7}\right)$ × 12 = 1.39 g h^{-1}

Compound data can be found in section 4.5

1-allyl-1,2,3,4-tetrahydroquinoline 244

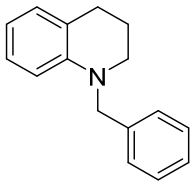


General procedure B was followed, using *N*-chloroamine **239** (0.5 M solution in DCM) and $MeSO_3H$ (6 M solution in DCM). In total, seven column volumes were collected. After work-up, purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (581 mg, 3.36 mmol, 38%) as a colourless oil.

Productivity: $\left(\frac{0.58g}{7}\right) \times 12 = 1.00$ g h^{-1}

Compound data can be found in section 4.5

1-benzyl-1,2,3,4-tetrahydroquinoline 245

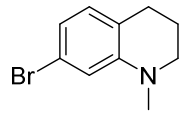


General procedure B was followed, using *N*-chloroamine **240** (0.45 M solution in DCM) and $MeSO_3H$ (6 M solution in DCM). In total, six column volumes were collected. After work-up, purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (648 mg, 2.90 mmol, 43%) as a colourless gum.

Productivity: $\left(\frac{0.65g}{6}\right) \times 12 = 1.29$ g h^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.38-7.17 (5H, m, 5 × ArC*H*), 7.05-6.89 (2H, m, 2 × ArC*H*), 6.61-6.48 (2H, m, 2 x ArC*H*), 4.48 (2H, s, NCH_2Ar), 3.37 (2H, t, *J* = 5.6, NCH_2), 2.82 (2H, t, J = 6.3, $ArCH_2$), 2.10-1.92 (2H, m, CH_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 145.6 (C_q), 138.9 (C_q), 129.0 (Ar*C*H), 128.6 (2 × Ar*C*H), 127.1 (Ar*C*H), 126.7 (Ar*C*H), 126.6 (2 × Ar*C*H), 122.2 (C_q), 115.8 (Ar*C*H), 110.9 (Ar*C*H), 55.2 (NCH_2Ph), 49.9 (NCH_2), 28.2 ($ArCH_2$), 22.4 (CH_2); **IR** υ_{max} (neat) / cm^{-1}: 3061, 3024, 2924, 2839, 1600, 1494, 1449, 1343; **HRMS (ESI$^+$)**: $C_{16}H_{18}N$ [$M+H^+$]: calculated 224.1434, found 224.1435, Δ = 0.45 ppm.

7-bromo-1,2,3,4-tetrahydroquinoline 246

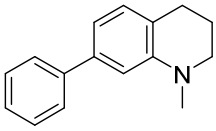


General procedure B was followed, using *N*-chloroamine **241** (0.4 M solution in DCM) and $MeSO_3H$ (6 M solution in DCM). In total, seven column volumes were collected. After work-up, purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (947 mg, 4.21 mmol, 60%) as a colourless oil.

Productivity: $\left(\frac{0.95g}{7}\right) \times 12 = 1.62$ g h^{-1}

Compound data can be found in section 4.5

7-phenyl-1,2,3,4-tetrahydroquinoline 247

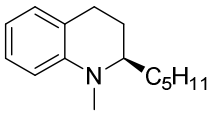


General procedure B was followed, using *N*-chloroamine **242** (0.4 M solution in DCM) and $MeSO_3H$ (6 M solution in DCM). In total, six column volumes were collected. After work-up, purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (378 mg, 1.69 mmol, 28%) as a colourless oil

Productivity: $\left(\frac{0.38g}{6}\right) \times 12 = 0.76$ g h^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.56-7.47 (2H, m, 2 × ArC*H*), 7.39-7.30 (2H, m, 2 × ArC*H*), 7.28-7.21 (1H, m, ArC*H*), 7.00-6.92 (1H, m, ArC*H*), 6.80-6.70 (2H, m, 2 × ArC*H*), 3.24-3.17 (2H, m, NCH_2), 2.89 (3H, s, NCH_3), 2.74 (2H, t, *J* = 6.5, ArCH_2), 2.01-1.89 (2H, m, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 147.1 (C_q), 142.5 (C_q), 140.5 (C_q), 129.3 (Ar*C*H), 128.7 (2 × Ar*C*H), 127.3 (2 × Ar*C*H), 127.0 (Ar*C*H), 122.2 (C_q), 115.4 (Ar*C*H), 110.0 (Ar*C*H), 51.5 (N*C*H_2), 39.3 (N*C*H3), 27.7 (Ar*C*H_2), 22.6 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1}: 3054, 3028, 2924, 2837, 1678, 1605, 1561, 1515; **HRMS (ESI$^+$)**: $C_{16}H_{18}N$ [M+H$^+$]: calculated 224.1434, found 224.1434, Δ = 0.0 ppm.

2-pentyl-1,2,3,4-tetrahydroquinoline 248



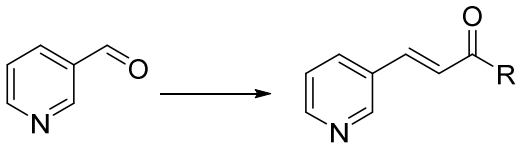
General procedure B was followed, using *N*-chloroamine **243** (0.25 M solution in DCM) and $MeSO_3H$ (6 M solution in DCM). In total, seven column volumes were collected. After workup, purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (378 mg, 1.74 mmol, 40%) as a yellow oil.

Productivity: $\left(\frac{0.38g}{7}\right) \times 12 = 0.65$ g h^{-1}

Compound data can be found in section 4.5

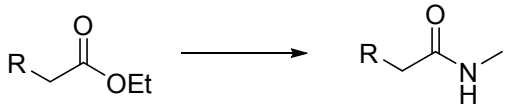
4.3 Photochemical Chapter experimental

General Procedure A: Wittig reaction



Following a modified procedure by Chatfield *et al*,[96] to a stirred solution of pyridinecarboxaldehyde (1.0 eq) in CH_3CN (0.2 M) was added the Wittig reagent (1.1 eq) and the reaction mixture was stirred for 48 h at RT. The reaction mixture was concentrated *in vacuo* and the residue diluted in H_2O (60 mL). The solution was acidified to pH 3 using 4 M HCl and extracted using DCM (3 × 80 mL). The water phase was then basified using $NaHCO_{3\,(aq)}$ to pH 7 and extracted using DCM (3 × 80 mL). The organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography afforded the desired product.

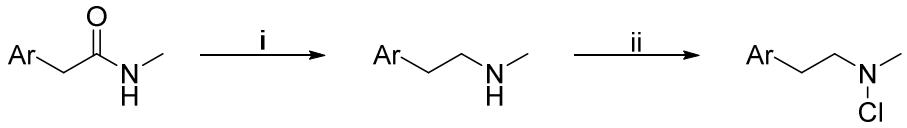
General Procedure B: Amide formation



Following a modified procedure by Juaristi *et al*,[78] to a stirred solution of pyridinyl ester (1.0 eq) in MeOH (0.40 M) was added $MeNH_2$ (8 M solution in EtOH, 8eq) and the reaction mixture

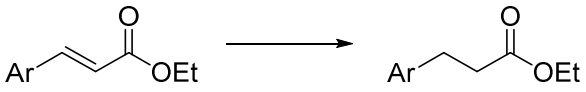
was heated at reflux for 16 h and then concentrated *in vacuo*. Purification by column chromatography afforded the desired products.

General Procedure C: Reduction – chlorination sequence



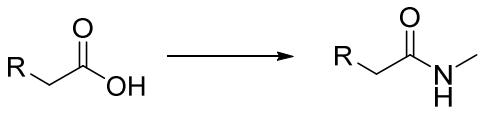
Step i: Following a modified procedure by Williamson *et al*,[97] to a stirred suspension of $LiAlH_4$ (2.0 eq) in THF (1 M) at 0 °C was added a solution of pyridinyl amide (1.0 eq) in THF (1 M) dropwise. The reaction mixture was stirred for 5 min at 0 °C before warming to RT and then heated at reflux for 3 h. The reaction mixture was cooled to 0 °C and the reaction was quenched through the dropwise addition of H_2O (12.0 eq), 2M $NaOH_{(aq)}$ (2.0 eq) and H_2O (2.0 eq). The resulting slurry was dried over Na_2SO_4, filtered through a pad of Celite and was washed with EtOAc. Concentration *in vacuo* afforded the crude amine product which was used without further purification. Desired product formation was confirmed by LC-MS analysis.
Step ii: Following a modified procedure by De Luca *et al*.[79] To a stirred solution of the amine (1.0 eq) in DCM (0.5 M) in the dark was added NCS (1.0 eq) portionwise over 10 mins at RT and the reaction mixture was stirred for 3 h then concentrated *in vacuo*. Purification by column chromatography afforded the desired products.

General Procedure D Hydrogenation



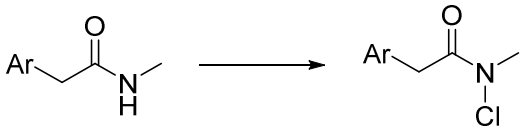
To a stirred solution of ester (1.0 eq) in EtOH (0.2 M) was added 10% Pd/C (10% wt) and the flask was evacuated and flushed with N_2 (3 ×). The flask was then evacuated and flushed with H_2 and stirred at RT for 16 h. The flask was then evacuated and flushed with nitrogen. The reaction mixture was filtered through a pad of Celite and washed with EtOAc. Concentrated *in vacuo* afforded the desired product without further purification being required.

General Procedure E Amide coupling



To a stirred solution of the acid (1 eq) and methylamine hydrochloride (1.5 eq) in DCM (0.2 M), was added TBTU (1.6 eq) and DIPEA (4 eq). The reaction mixture was stirred at RT for 16 hours. The reaction was quenched with saturated aqueous $NaHCO_3$. The two phases were separated and the aqueous phase was extracted with DCM (3 ×). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography yielded the desired product.

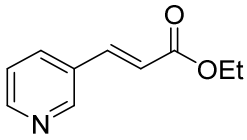
General Procedure F *N*-Chlorination



Following a modified procedure by Zhong *et al*,[80] to a stirred solution of the amide (1.0 eq) and *tert*-butanol (1.5 eq) in MTBE (0.2 M) at 0 ^oC, was added acetic acid (1.5 eq) and sodium hypochlorite (1.5 eq) dropwise. The reaction mixture was then stirred at 0 ^oC for 2 h. The organic phases were separated and the top phase was washed with H_2O then brine, dried using $MgSO_4$ and concentrated *in vacuo*. The crude material was then purified using column chromatography using to yield the desired product.

4.4 Experimental Data

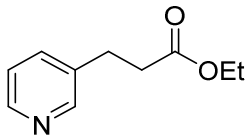
Synthesis of ethyl 3-(pyridin-3-yl)prop-2-enoate 252a



General procedure A was followed, using 3-pyridinecarboxaldehyde (2.00 g, 18.7 mmol) and Wittig reagent **251** (7.16 g, 20.5 mmol). Purification by column chromatography eluting with 70% Et_2O in hexane, afforded the *title compound* (1.81 g, 10.2 mmol, 54%) as a pale yellow

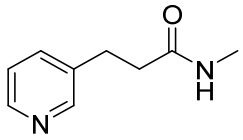
oil. The NMR data was in accordance with the literature.[98] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.67 (1H, d, *J* = 2.2, C_2H), 8.60 (1H, dd, *J* = 4.8, 1.6, C_6H), 7.83 (1H, dt, *J* = 7.9, 1.8, C_4H), 7.67 (1H, d, *J* = 16.1, C_3CH), 7.32 (1H, dd, *J* = 8.4, 4.4, C_5H), 6.51 (1H, d, *J* = 16.1, C*H*CO), 4.28 (2H, q, *J* = 7.1, OCH_2), 1.34 (3H, t, *J* = 7.1, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 166.3 (*C*O), 150.9 (C_2), 149.7 (C_6), 140.8 (C_3CHCH), 134.2 (C_4), 130.2 (C_3), 123.7 (C_5), 120.5 (*C*HCO), 60.8 (CH_2), 14.3 (CH_3) **IR** V_{max} (neat)/cm^{-1}: 3031, 2982, 2936, 1712 (CO), 1641, 1586, 1477 1342; **HRMS (ESI$^+$)**: $C_{10}H_{12}NO_2$ $[M + H]^+$: calculated 178.0863, found 178.0867, Δ = +2.2 ppm.

Synthesis of ethyl 3-(pyridin-3-yl)propanoate 253a



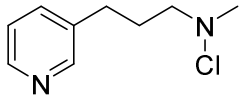
To a stirred solution of ester **252a** (1.81 g, 12.1 mmol, 1.00 eq) in toluene (0.2 M) was added 10% Pd/C (181 mg, 10% wt). To the reaction mixture AcOH (1.40 mL, 24.3 mmol, 2.00 eq) and then $NaBH_4$ (1.84 g, 48.5 mmol, 4.00 eq) were added. The reaction mixture was then warmed to RT and stirred for 8 h. The reaction mixture was quenched at 0 ^oC by addition of 4 M HCl until the reaction mixture was at pH 2. The solution was then neutralised with saturated aqueous $NaHCO_3$ to pH 7 and extracted with Et_2O (3 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered through a pad of Celite and concentrated *in vacuo* to afford the *title compound* (1.80 g, 10.1 mmol, 83%) as a yellow oil which was used without further purification. The NMR data was in accordance with literature.[99] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.53 – 8.44 (2H, m, includes 1H, m, C_2H; and 1H, m, C_6H), 7.55 (1H, dt, *J* = 7.8, 2.0, C_4H), 7.23 (1H, dd, *J* = 7.8, 4.8, C_5H), 4.14 (2H, q, *J* = 7.1, OCH_2), 2.97 (2H, t, *J* = 7.6, CH_2), 2.65 (2H, t, *J* = 7.6, CH_2), 1.24 (3H, t, *J* = 7.1, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 172.3 (*C*O), 149.8 (C_2), 147.7 (C_6), 135.9 (C_3), 135.8 (C_4), 123.4 (C_5), 60.6 (OCH_2), 35.4 (CH_2), 28.1 (CH_2), 14.2 (CH_3); **IR** υ_{max} (neat)/cm^{-1}; 3032, 2982, 2935, 1731 (CO), 1642, 1575, 1422, 1371; **HRMS (ESI$^+$)**: $C_{10}H_{14}NO_2$ $[M + H]^+$: calculated 180.1090, found 180.1021, Δ = -1.1 ppm.

Synthesis of *N*-methyl 3-pyridin-3-yl-propanamide 254a



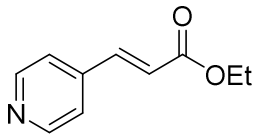
General procedure B was followed, using the ester **253a** (1.30 g, 7.25 mmol) and $MeNH_2$ (8 M in EtOH, 7.5 mL). Purification by column chromatography eluting with 2% MeOH in DCM, afforded the *title compound* (1.02 g, 6.23 mmol, 86%) as a pale yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.50 - 8.44 (2H, m, includes 1H, m, C_2H; and 1H, m, C_6H), 7.55 (1H, dt, J = 7.8, 2.0, C_4H), 7.22 (1H, dd, J = 7.8, 4.8, C_5H), 5.66 (1H, br. s, N*H*), 2.99 (2H, t, J = 7.6, CH_2), 2.79 (3H, d, J = 4.8, CH_3), 2.48 (2H, t, J = 7.6, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 172.0 (*C*O), 149.7 (C_2), 147.7 (C_6), 136.4 (C_3), 136.1 (C_4), 123.4 (C_5), 37.7 (CH_2), 28.7 (CH_2), 26.3 (CH_3); **IR** υ_{max} (neat)/cm^{-1}; 3294, 3085, 2921, 1649 (CO), 1562, 1479, 1413, 1371; **HRMS (ESI$^+$)**: $C_9H_{13}N_2O$ [M + H] $^+$: calculated 165.1022, found 165.1017, Δ = +3.1 ppm.

Synthesis of *N*-chloro(*N*-methyl)[3-(pyridin-3-yl)propyl]amine 255a



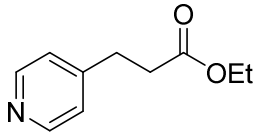
General procedure C was followed, step i, using amide **254a** (430 mg, 2.64 mmol) and $LiAlH_4$ (200 mg, 2.28 mmol) affording the crude amine **259**. Following step ii, using the crude amine **259** (397 mg, 2.64 mmol) and NCS (180 mg, 1.35 mmol). Purification by column chromatography, eluting with (30% EtOAc in hexane), afforded the *title compound* (50 mg, 0.27 mmol, 25%) as a brown oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.50-8.46 (2H, m, includes 1H, m, C_2H; and 1H, m, C_6H), 7.54 (1H, dt, J = 7.8, 2.0, C_4H), 7.24 (1H, dd, J = 7.8, 4.8, C_5H), 2.96 (3H, s, CH_3), 2.92 – 2.87 (2H, m, CH_2), 2.71 (2H, t, J = 7.4, CH_2), 1.99 (2H, m, CH_2), **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 150.0 (C_2), 147.5 (C_6), 136.9 (C_3), 135.9 (C_4), 123.4 (C_5), 64.7 (CH_2N), 53.1 (CH_3), 29.8 (CH_2), 29.4 (CH_2); **IR** υ_{max} (neat)/cm^{-1}: 3028, 2941, 2856, 1773, 1710, 1665, 1427, 1348, **HRMS (ESI$^+$)**: $C_9H_{14}{}^{35}ClN_2$ [M + H] $^+$: calculated 185.0840, found 185.0840, Δ = -0.2 ppm.

Synthesis of 3-(pyridin-4-yl)prop-2-enoate 252b



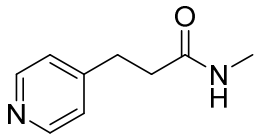
General procedure A was followed, using 4-pyridinecarboxaldehyde (2.00 g, 18.7 mmol) and Wittig reagent **251** (7.16 g, 20.5 mmol). Purification by column chromatography, eluting with 30% EtOAc in hexane (1% Et_3N), afforded *title compound* (2.77 g, 15.6 mmol, 83% yield) as a colourless solid. A sample was crystallised from hexane to yield colourless crystals. **M.p.** 67-68 ºC, platelets, hexane. The NMR data was in accordance with the literature.[100] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.65 (2H, dd, *J* = 4.5, 1.6, 2 × C_2H), 7.59 (1H, d, *J* = 16.1, C_4CH), 7.36 (2H, dd, *J* = 4.6, 1.6, 2 × C_3H), 6.59 (1H, d, *J* = 16.1, C*H*CO), 4.29 (2H, q, *J* = 7.1, CH_2), 1.35 (3H, t, *J* = 7.1, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 166.0 (*C*O), 150.6 (2 × C_2), 149.7 (C_4), 141.7 (C*C*H), 122.9 (*C*HCO), 121.8 (2 × C_3), 61.0 (CH_2), 14.2 (CH_3); **IR** υ_{max} (neat)/cm^{-1} 3052, 2982, 1704 (CO), 1640, 1623, 1597, 1547, 1444; **HRMS (ESI$^+$)**: $C_{10}H_{12}NO_2$ [M + H] $^+$: calculated 178.0863, found 178.0864, Δ = +0.8 ppm.

Synthesis of ethyl 3-(pyridin-4-yl)propanoate 253b



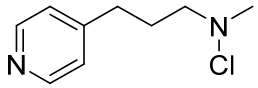
General procedure D was followed, using ester **252b** (2.50 g, 14.1 mmol) and 10% Pd/C (250 mg, 10% wt), affording the *title compound* (2.41 g, 13.4 mmol, 95%) as a colourless oil, which was characterised without further purification. The NMR data was in accordance with the literature.[101,102] **^{1}H NMR**: (300 MHz, $CDCl_3$) δ ppm 8.51 (2H, dd, *J* = 4.4, 1.6, 2 × C_2H), 7.14 (2H, dd, *J* = 4.4, 1.6, 2 × C_3H), 4.13 (2H, q, *J* = 7.1, OCH_2), 2.95 (2H, t, *J* = 7.6, CH_2), 2.64 (2H, t, *J* = 7.6, CH_2), 1.23 (3H, t, *J* = 7.1, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 172.2 (*C*O), 149.9 (2 × C_2), 149.4 (C_4), 123.7 (2 × C_3), 60.7 (OCH_2), 34.5 (CH_2), 30.1 (CH_2), 14.2 (CH_3); **IR** υ_{max} (neat)/cm^{-1} 3027, 2981, 2933, 1728 (CO), 1601, 1559, 1445, 1415; **HRMS (ESI$^+$)**: $C_{10}H_{14}NO_2$ [M + H] $^+$: calculated 180.1019, found 180.1017, Δ = -0.9 ppm.

Synthesis of *N*-methyl-3-(pyridin-4-yl)propanamide 254b



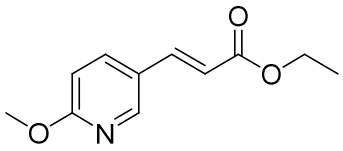
General procedure B was followed, using ester **253b** (2.30 g, 12.8 mmol) and $MeNH_2$ (8 M in EtOH, 13 mL). Purification by column chromatography eluting with 1% MeOH in DCM (1% Et_3N), afforded *title compound* (1.65 g, 10.1 mmol 78%) as a colourless solid. A small sample was crystallized from hexane to yield colourless crystals. **M.p.** 61- 62 ^oC, platelets, hexane. The NMR data was in accordance with the literature.[103] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.50 (2H, dd, *J* = 4.4, 1.6, 2 × C_2H), 7.13 (2H, dd, *J* = 4.4, 1.6, 2 × C_3H), 5.37 (1H, br. s, N*H*), 2.98 (2H, t, *J* = 7.6, CH_2), 2.79 (3H, d, *J* = 4.9, CH_3), 2.47 (2H, t, *J* = 7.6, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 172.7 (*C*O), 150.0 (C_4), 149.9 (2 × C_2), 123.8 (2 × C_3), 36.9 (CH_2), 30.7 (CH_2), 26.3 (CH_3); **IR** υ_{max} (neat)/cm^{-1} 3300, 3102, 3027, 2938, 1632 (CO), 1557, 1495, 1454; **HRMS (ESI$^+$)**: $C_9H_{13}N_2O$ $[M + H]^+$: calculated 165.1022, found 165.1019, Δ = +1.9 ppm.

Synthesis of *N*-chloro(*N*-methyl)[3-(pyridin-4-yl)propyl]amine 255b



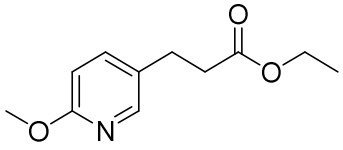
General procedure C was followed, step i, using amide **254b** (1.52 g, 9.28 mmol), $LiAlH_4$ (704 mg, 18.6 mmol) affording the crude amine **261**. Following step ii, using the crude amine **261** (1.39 g, 8.50 mmol) and NCS (1.55 g, 11.6 mmol). Purification by column chromatography, eluting with 30% EtOAc in hexane, afforded the *title compound* (350 mg, 1.90 mmol, 20%) as a brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.55 - 8.52 (2H, m, 2 × C_2H), 7.20 - 7.16 (2H, m, 2 × C_3H), 2.97 (3H, s, CH_3), 2.89 (2H, t, *J* = 6.7, CH_2), 2.76 - 2.72 (2H, m, CH_2), 2.05 - 1.98 (2H, m, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 149.8 (2 × C_2), 149.0 (C_4), 124.0 (2 × C_3), 64.7 (CH_2N), 53.1 (CH_3), 29.6 (CH_2), 28.5 (CH_2); **IR** υ_{max} (neat) / cm^{-1} : 3029, 2949, 2856, 1773, 1702, 1637 1604, 1463; **HRMS (ESI$^+$)**: $C_9H_{14}{}^{35}ClN_2$ $[M + H]^+$: calculated 185.0840, found 185.0837, Δ = +1.5 ppm.

Synthesis of ethyl (2*E*)-3-(6-methoxypyridin-3-yl)prop-2-enoate 266



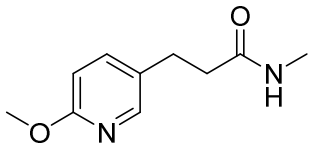
General procedure A was followed, using 5-formyl-2-methoxypyridine (5.00 g, 36.5 mmol) and Wittig reagent **265** (14.0 g, 40.1 mmol) followed by purification by column chromatography, eluting with 30% EtOAc in hexane (1% Et_3N), affording the *title compound* (6.49 g, 31.3 mmol, 86% yield) as a colourless gum. The ^{1}H NMR was in accordance with the literature.[104] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.27 (1H, d, *J* = 2.4, C_2H), 7.77 (1H, dd, *J* = 8.7, 2.5, C_4H), 7.63 (1H, d, *J* = 16.0, C*CH*), 6.77 (1H, d, *J* = 8.7, C_5H), 6.33 (1H, d, *J* = 16.0, C*H*CO), 4.27 (2H, q, *J* = 7.1, OCH_2), 3.97 (3H, s, OCH_3), 1.34 (3H, t, *J* = 7.1, CH_2CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 166.8 (*C*O), 165.3 (OC_q), 148.3 (C_2), 140.9 (C*C*H), 136.3 (C_4), 123.9 (C_q), 117.2 (*C*HCO), 111.6 (C_5), 60.5 (O*C*H_2), 53.8 (O*C*H_3), 14.3 (CH_2CH_3); **IR** υ_{max} (neat)/cm^{-1} 3036, 2984, 2948, 1708, 1633, 1600, 1567, 1497; **HRMS (ESI$^+$)**: $C_{11}H_{14}NO_3$ [M + H]$^+$: calculated 208.0968, found 208.0964, Δ = -2.2 ppm

Synthesis of ethyl 3-(6-metho×ypyridin-3-yl)propanoate 267



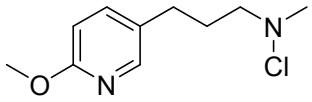
General procedure D was followed, using ester **266** (6.00 g, 29.0 mmol) and 10% Pd/C (600 mg, 10% wt), affording the *title compound* (5.32 g, 25.4 mmol, 88%) as a colourless oil, which was characterised without further purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.00 (1H, d, *J* = 2.0, C_2H), 7.43 (1H, dd, *J* = 8.5, 2.5, C_4H), 6.68 (1H, d, *J* = 8.5, C_5H), 4.13 (2H, q, *J* = 7.1, OCH_2), 3.91 (3H, s, OCH_3), 2.87 (2H, t, *J* = 7.6, CH_2), 2.58 (2H, t, *J* = 7.6, CH_2), 1.24 (3H, t, *J* = 7.1, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 172.5 (*C*O), 163.0 (OC_6), 146.1 (C_2), 138.9 (C_4), 128.5 (C_3), 110.6 (C_5), 60.5 (O*C*H_2), 53.3 (O*C*H_3), 35.9 (*C*H_2), 27.3 (*C*H_2), 14.2 (CH_2CH_3); **IR** υ_{max} (neat)/cm^{-1} 2980, 2945, 2906, 1730, 1609, 1572, 1491, 1445; **HRMS (ESI$^+$)**: $C_{11}H_{16}NO_3$ [M + H]$^+$: calculated 210.1125, found 210.1124, Δ = +0.7 ppm.

Synthesis of 3-(6-metho×ypyridin-3-yl)-*N*-methylpropanamide 268



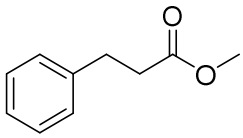
General procedure B was followed, using the ester **267** (5.00 g, 23.9 mmol) and $MeNH_2$ (8 M in EtOH, 30 mL). Purification by crystallization from hexane, afforded the *title compound* (4.36 g, 22.5 mmol, 94%) as a pale yellow crystals. **M.p.** 79-80 ºC, platelets, hexane. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.99 (1H, d, *J* = 2.4, C_2H), 7.43 (1H, dd, *J* = 8.5, 2.5, C_4H), 6.67 (1H, d, *J* = 8.5, C_5H), 5.38 (1H, s, N*H*), 3.91 (3H, s, OCH_3), 2.90 (2H, t, *J* = 7.6, CH_2), 2.78 (3H, d, *J* = 4.9, $NHCH_3$), 2.42 (2H, t, *J* = 7.6, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.2 (*C*O), 162.9 (OC_6), 146.0 (C_2), 139.0 (C_4), 128.9 (C_3), 110.6 (C_5), 53.3 (OCH_3), 38.2 (CH_2), 27.9 (CH_2), 26.3 (CH_3); **IR** υ_{max} (neat)/cm^{-1} 3311, 3107, 2949, 2932, 1638, 1609, 1566, 1492; **HRMS (ESI$^+$)**: $C_{10}H_{14}N_2NaO_2$ $[M + Na]^+$: calculated 217.0947, found 217.0939, Δ = +1.7 ppm.

Synthesis of chloro[3-(6-methoxypyridin-3-yl)propyl]methylamine 263



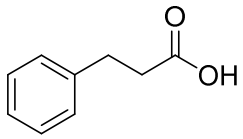
General procedure C was followed, step i, using amide **268** (2.00 g, 10.3 mmol) and $LiAlH_4$ (782 mg, 20.6 mmol) afforded the crude amine **271**. Following step ii, using the crude amine **271** (1.26 g, 6.97 mmol) and NCS (1.16 g, 8.71 mmol), purification by column chromatography, eluting with (10% EtOAc in hexane), afforded the *title compound* (712 mg, 3.33 mmol, 48%) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.98 (1H, dd, *J* = 2.4, 0.5, C_2H), 7.42 (1H, dd, *J* = 8.5, 2.5, C_4H), 6.68 (1H, d, *J* = 8.5, C_5H), 3.91 (3H, s, CH_3), 2.93 (3H, s, CH_3), 2.90 – 2.82 (2H, m, CH_2), 2.65 – 2.58 (2H, m, CH_2), 1.99 – 1.86 (2H, m, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 162.7 (OC_6), 146.1 (C_2), 138.9 (C_4), 129.5 (C_3), 110.5 (C_5), 64.8 (CH_2), 53.3 (CH_3), 53.1 (CH_3), 29.6 (CH_2), 28.8 (CH_2); **IR** υ_{max} (neat)/cm^{-1} 2945, 2845, 2795, 1607, 1572, 1489, 1460, 1439; **HRMS (ESI$^+$)**: $C_{10}H_{16}{}^{35}ClN_2O$ $[M+H]^+$: calculated 215.0946, found 215.0950, Δ = -2.1 ppm.

Synthesis of methyl 3-phenylpropanoate 274



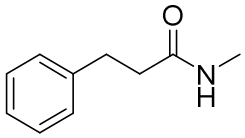
General procedure D was followed, using methyl *trans*-cinnamate (4.00 g, 24.7 mmol) and 10% Pd/C (400 mg, 10% wt), affording the *title compound* (3.80 g, 23.1 mmol, 94%) as a colourless oil, characterised without further purification. The NMR data was in accordance with the literature.[105] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37 – 7.18 (5H, m, 5 × ArC*H*), 3.70 (3 H, s, CH_3), 2.98 (2H, t, *J* = 7.8, ArCH_2), 2.66 (2H, t, *J* = 7.8, CH_2CO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.3 (*C*O), 140.5 (C_q), 128.5 (Ar*C*), 128.3 (Ar*C*), 126.3 (Ar*C*), 51.6 (*C*H_3), 35.7 (*C*H_2), 30.9 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3063, 3028, 2951, 2848, 1734 (CO), 1604, 1496, 1435.

Synthesis of 3-phenylpropanoic acid 275



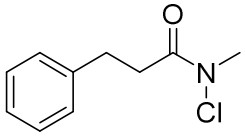
To a stirred solution of ester **274** (3.70 g, 22.5 mmol) in MeOH (50 mL, 0.45 M) was added NaOH (50 mL, 0.45 M). The reaction mixture was then heated to reflux and stirred for 2 h. The reaction mixture was cooled to RT and quenched with 4M HCl to pH 7 and the aqueous phase was extracted with EtOAc (50 mL × 3), dried over Na_2SO_4 and concentrated *in vacuo* to afford the *title compound* (2.50 g, 16.6 mmol, 74%) as a colourless solid which was recrystallized in hexane to yield colourless crystals. **M.p.** 43-44 ^{o}C, needles, hexane. The NMR data was in accordance with literature.[106] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 9.00 (1H, s, O*H*), 7.35 – 7.15 (5H, m, 5 × ArC*H*), 2.96 (2H, t, *J* = 7.8, CH_2), 2.69 (2H, t, *J* = 7.7, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 178.7 (*C*O), 140.2 (C_q), 128.6 (2 × Ar*C*), 128.3 (2 × Ar*C*), 126.4 (Ar*C*), 35.5 (*C*H_2), 30.6 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3058, 3028 (br OH), 2952, 2932, 2625, 1692 (CO), 1601, 1495; **HRMS (ESI^{+})**: $C_9H_9Na_2O_2$ [M + Na_2 - H]: calculated 195.0392, found 195.0388, Δ = -2.5 ppm.

Synthesis of *N*-methyl-3-phenylpropanamide 276



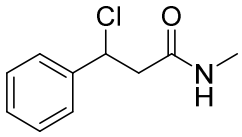
General procedure E was followed, using acid **275** (2.21 g, 14.7 mmol), $NH_2Me.HCl$ (1.49 g, 22.1 mmol), TBTU (7.57 g, 23.6 mmol) and DIPEA (5.14 mL, 29.5 mmol). Purification by column chromatography, eluting with 30-40% EtOAc in hexane, afforded the *title compound* (1.74 g, 10.7 mmol, 72%) as a colourless solid which was crystallised from hexane to yield colourless crystals. **M.p.** 54-55 ^oC, platelets, hexane. The NMR data was in accordance with literature.[107] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.36 – 7.16 (5H, m, 5 × ArC*H*), 5.34 (1H, br. s, N*H*), 2.99 (2H, t, *J* = 7.6, CH_2), 2.79 (3H, d, *J* = 4.9, CH_3), 2.49 (2H, t, *J* = 7.7, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 172.7 (*C*O), 140.9 (C_q), 128.5 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 126.2 (Ar*C*H), 38.5 (*C*H_2), 31.7 (*C*H_2), 26.3 (*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3301, 3064, 3030, 2934, 2877, 1638, 1605, 1549; **HRMS (ESI$^+$)**: $C_{10}H_{14}NO$ $[M + H]^+$: calculated 164.1070, found 164.1070, Δ = -1.5 ppm.

Synthesis of *N*-chloro-*N*-methyl-3-phenylpropanamide 278



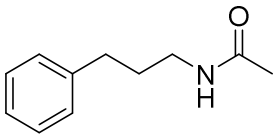
General procedure F, using amide **276** (670 mg, 4.10 mmol), *tert*-butanol (610 µL, 6.15 mmol), acetic acid (350 µL, 6.15 mmol) and sodium hypochlorite (0.75 M) (8.20 mL, 6.15 mmol), followed by purification by column chromatography, eluting with 20% EtOAc in hexane afforded the *title compound* (671 mg, 3.39 mmol, 83%) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.35 – 7.17 (5H, m, 5 × ArC*H*), 3.33 (3H, s, CH_3), 3.01 – 2.93 (2H, m, CH_2), 2.85 – 2.77 (2H, m, CH_2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 174.0 (*C*O), 140.8 (C_q), 128.5 (2 × Ar*C*), 128.4 (2 × Ar*C*), 126.3 (Ar*C*), 40.9 (*C*H_3), 35.2 (*C*H_2), 31.1 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3085, 3062, 3027, 2936, 2873, 1667, 1603, 1495; **HRMS (ESI$^+$)**: $C_{10}H_{13}{}^{35}ClNO$ $[M + H]^+$: calculated 198.0680, found 198.0680, Δ = -0.3 ppm.

Synthesis of 3-chloro-*N*-methyl-3-phenylpropanamide 280



To a stirred solution of chloroamide **278** (100 mg, 0.51 mmol) in DCM (1.70 mL) was added methanesulfonic acid (330 µL, 5.10 mmol) and the reaction mixture was stirred and irradiated under UV light using a 125 W high pressure mercury lamp for 5 h. The reaction mixture was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography eluting with 20% EtOAc in hexane affording the title compound (52 mg, 0.26 mmol, 52%) as colourless solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.44 – 7.28 (5H, m, 5 × ArC*H*), 5.54 (1H, br. s, N*H*), 5.42 (1H, dd, *J* = 9.1, 5.2, C*H*), 2.96 – 2.83 (2H, m, CH_2), 2.81 (3H, d, *J* = 4.9, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 169.4 (*C*O), 140.7 (ArC_q), 128.8 (Ar*C*H), 128.6 (Ar*C*H), 128.5 (Ar*C*H), 128.3 (Ar*C*H), 126.8 (Ar*C*H), 59.1 (*C*H), 47.3 (*C*H_2), 26.4 (*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3303 (NH), 3101, 3032, 2932, 2920, 1711 (CO), 1639, 1615; **HRMS (ESI$^+$)**: $C_{10}H_{12}{}^{35}ClNNaO$ $[M + Na]^+$: calculated 220.0499, found 220.0502, Δ = -0.9 ppm.

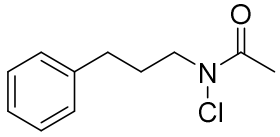
Synthesis of *N*-(3-phenylpropyl)acetamide 282



To a stirred solution of 3-phenylpropylamine (1.00 g, 7.40 mmol) and triethylamine (1.20 mL, 8.51 mmol) in DCM (8 mL) at 0 °C was added a solution of acetic anhydride (800 µL, 8.51 mmol) in DCM (2 mL) dropwise. After 15 min the reaction was warmed to RT and stirred for 16 h. The reaction was washed with an aqueous 2M HCl solution (pH 2). The aqueous phase was extracted with DCM (2 × 50 mL). The organic phases were combined and washed with a saturated aqueous solution of $NaHCO_3$ until neutralised, dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound (1.31g, 7.40 mmols, 100%) as a colourless oil, characterised without further purification. The NMR data was in accordance with the literature.[108] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.33 – 7.13 (5H, m, 5 × ArC*H*), 5.63 (1H, br. s, N*H*), 3.27 (2H, q, *J* = 6.5, NHCH_2), 2.68 – 2.61 (2H, t, *J* = 7.6, ArCH_2), 1.93 (3H, s, CH_3), 1.83 (2H, apparent quin, *J* = 7.3, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 170.1 (*C*O), 141.5 (ArC_q), 128.5 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 126.0 (Ar*C*H), 39.3 (NH*C*H_2), 33.3 (Ar*C*H_2),

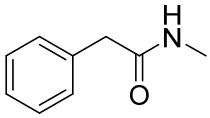
31.2 (*C*H_2), 23.3 (*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3282, 3084, 3063, 3026, 2931, 2860, 1645, 1549; **HRMS (ESI$^+$)**: $C_{11}H_{16}NO$ $[M + H]^+$: calculated 178.1226, found 178.1225, Δ = -3.4 ppm.

Synthesis *N*-chloro-*N*-(3-phenylpropyl)acetamide 283



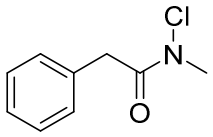
General procedure F was followed, using amide **282** (2.55 g, 14.4 mmol), *tert*-butanol (2.15 mL, 21.6 mmol), acetic acid (1.25 mL, 21.6 mmol) and sodium hypochlorite (0.75 M, 29.0 mL, 21.6 mmol). Purification by column chromatography, eluting with 20% EtOAc in hexane afforded the *title compound* (1.98 g, 9.35 mmol, 65%) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.35 – 7.15 (5H, m, 5 × ArC*H*), 3.73 (2H, t, *J* = 7.1, NClCH_2), 2.64 (2H, t, *J* = 7.4, ArCH_2), 2.20 (3H, s, CH_3), 2.01 (2H, quartet, *J* = 7.4, CH_2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 172.0 (CO), 141.0 (ArC_q), 128.5 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 126.1 (Ar*C*H), 51.8 (*C*H_2), 32.4 (*C*H_2), 28.8 (*C*H_2), 21.8 (*C*H_3); **IR** υ_{max} (neat)/cm^{-1} 3085, 3062, 2934, 2860, 1669, 1603, 1496, 1453; **HRMS (ESI$^+$)**: $C_{11}H_{15}{}^{35}ClNO$ $[M + H]^+$: calculated 212.0837, found 212.0830, Δ = -3.4 ppm.

Synthesis of *N*-methyl-2-phenylacetamide 287



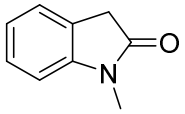
General procedure E was followed, using phenylacetic acid (2.00 g, 14.7 mmol), $NH_2Me.HCl$ (1.49 g, 22.0 mmol), TBTU (7.54 g, 23.5 mmol) and DIPEA (10.2 mL, 58.7 mmol). Purification by column chromatography, eluting with 45-55% EtOAc in hexane, afforded the *title compound* (1.62 g, 10.9 mmol, 74%) as a yellow solid which was crystallised from hexane to yield colourless crystals. **M.p.** 54-55 ^oC, platelets, hexane. The NMR data was in accordance with the literature.[109] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.42 – 7.24 (5H, m, 5 × ArC*H*), 5.43 (1H, br. s, N*H*), 3.59 (2H, s, CH_2), 2.77 (3H, d, *J* = 4.9, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 171.6 (*C*O), 134.9 (ArC_q), 129.5 (2 × Ar*C*H), 129.1 (2 × Ar*C*H), 127.4 (Ar*C*H), 43.8 (*C*H_2), 26.5 (*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3301, 3087, 3064, 3030, 2934, 2877, 1638, 1549; **HRMS (ESI$^+$)**: $C_9H_{12}NO$ $[M + H]^+$: calculated 150.0913, found 150.0911, Δ = +1.8 ppm.

Synthesis of *N*-chloro-*N*-methyl-2-phenylacetamide 288



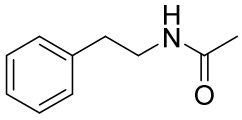
General procedure F was followed, using amide **287** (1.00 g, 6.70 mmol), *tert*-butanol (1.00 mL, 10.1 mmol), acetic acid (580 µL, 10.1 mmol) and sodium hypochlorite (0.75 M, 13.4 mL, 10.1 mmol) stirred for 4 h instead of 2 h. Purification by column chromatography (20% EtOAc in hexane) afforded the *title compound* (1.04 g, 5.64 mmol, 84%) as a colourless oil which upon storage in the freezer formed a colourless solid. The NMR data was in accordance with the literature.[110] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.40 – 7.25 (5H, m, 5 × ArC*H*), 3.90 (2H, s, CH_2), 3.38 (3H, s, CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 172.6 (*C*O), 134.1 (ArC_q), 129.2 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 127.1 (Ar*C*H), 41.2 (*C*H_3), 40.2 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3031, 3007, 2968, 2913, 1682, 1659 (CO), 1496, 1451; **HRMS (ESI$^+$)**: $C_9H_{11}{}^{35}ClNO$ [M + H^+]: calculated 184.0524, found 184.0518, Δ = -3.2 ppm.

Synthesis of 1-methyl-2,3-dihydro-1H-indol-2-one 289



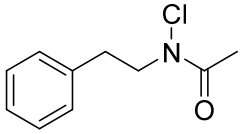
To a stirred solution of chloroamide **288** (100 mg, 0.54 mmol) in DCM (1.70 mL) was added $BF_3{\cdot}OEt_2$ (330 µL, 2.7 mmol) and the reaction mixture was stirred and irradiated under UV light with a 125W high pressure mercury lamp for 5 h. The reaction mixture was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography eluting with 25-30% EtOAc in hexane to afford the title compound (8 mg, 0.05 mmol, 10%) as a colourless oil. The NMR data was in accordance with literature.[111] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.34 – 7.23 (2H, m, 2 × ArC*H*), 7.06 (1H, td, *J* = 7.6, 0.9, ArC*H*), 6.84 (1H, d, *J* = 7.8, ArC*H*), 3.55 (2H, s, CH_2), 3.24 (3H, s, *J* = 5.1, CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 175.1 (*C*O), 145.3 (Ar$C_q$$CH_2$), 127.9 (Ar*C*H), 124.5 (ArC_qN), 124.3 (Ar*C*H), 122.3 (Ar*C*H), 108.1 (Ar*C*H), 35.7 (*C*H_2), 26.2 (*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3056, 2920, 2850, 1711 (CO), 1615, 1494, 1470, 1370; **HRMS (ESI$^+$)**: $C_9H_{10}NO$ $[M + H]^+$: calculated 148.0757, found 148.0751, Δ = +3.9 ppm.

Synthesis of *N*-(2-phenylethyl)acetamide 291



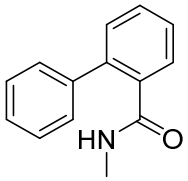
To a stirred solution of 3-phenylethylamine (2.00 g, 16.5 mmol) and triethylamine (2.65 mL 19.0 mmol) in DCM (12 mL) at 0 °C was added a solution of acetic anhydride (1.80 mL, 19.0 mmol) in DCM (10 mL) dropwise. After 15 min the reaction was warmed to RT and stirred 16 hours. The RM was washed with 2 M HCl (pH 2). The aqueous phase was extracted with DCM (2 × 100 mL). The organic phases were combined and washed with a saturated aqueous solution of $NaHCO_3$ until neutralised, dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound (2.25 g, 13.8 mmols, 84%) as a pale yellow solid. This was crystallised from hexane to yield pale yellow crystals which were characterised without further purification. **M.p.** 46-47 °C, platelets, hexane. The NMR data was in accordance with the literature.[112] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.40 – 7.17 (5H, m, 5 × ArC*H*), 5.48 (1H, br. s, N*H*), 3.54 (2H, q, *J* = 6.8, NHCH_2), 2.84 (2H, t, *J* = 6.9, ArC*H*2), 1.96 (3H, s, C*H*3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 170.0 (*C*O), 138.9 (ArC_q), 128.7 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 126.5 (Ar*C*H), 40.6 (CH_2), 35.6 (CH_2), 23.3 (CH_3); **IR** υ_{max} (neat) / cm^{-1}: 3285 (NH) 3086, 3065, 2930, 2871, 1642 (CO), 1539, 1496; **HRMS (ESI$^+$)**: $C_{10}H_{14}NO$ $[M + H]^+$: calculated 164.1069, found 164.1066, Δ = -2.4 ppm.

Synthesis of *N*-chloro-*N*-(2-phenylethyl)acetamide 292



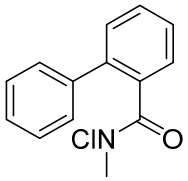
General procedure F was followed, using amide **291** (500 mg, 3.06 mmol), *tert*-butanol (460 µL, 4.59 mmol), acetic acid (260 µL, 4.59 mmol) and sodium hypochlorite (0.75M, 6.12 mL, 4.59 mmol) stirred for 4 h. Purification by column chromatography 10% EtOAc in hexane afforded the *title compound* (472 mg, 2.39 mmol, 78%) as a colourless oil. The NMR data was in accordance with the literature.[113] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.37 – 7.19 (5H, m, 5 × ArC*H*), 3.93 (2H, t, *J* = 7.3, CH_2), 3.00 (2H, t, *J* = 7.4, CH_2), 2.12 (3H, s, CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 170.3 (*C*O), 137.6 (ArC_q), 128.9 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 126.7 (Ar*C*H), 53.6 (CH_2), 33.5 (CH_2), 21.5 (CH_3); **IR** υ_{max} (neat) / cm^{-1}: 3086, 3065, 2934, 2860, 1668, 1539, 1496, 1429; **HRMS (ESI$^+$)**: $C_{10}H_{13}{}^{35}ClNO$ $[M + H^+]$: calculated 198.0680, found 198.0673, Δ = +3.5 ppm.

Synthesis of *N*-methyl-2-phenylbenzamide 165



General procedure E was followed, using 2-biphenylcarboxylic acid (1.00 g, 5.04 mmol), $NH_2Me.HCl$ (510 mg, 7.56 mmol), TBTU (2.59 g, 20.2 mmol) and DIPEA (2.61 mL, 20.2 mmol). Purification by column chromatography, eluting with 35-45% EtOAc in hexane afforded the *title compound* (765 mg, 3.62 mmol, 72%) as a colourless solid which was crystallized from EtOAc to form colourless needles. **M.p.** 171-172 ^oC, needles, EtOAc. The NMR data was in accordance with literature.[114] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.71 (1H, dd, *J* = 7.5, 1.5, ArC*H*), 7.52 – 7.33 (8H, m, 8 × ArC*H*), 5.15 (1H, br. s, N*H*), 2.68 (3H, d, *J* = 4.9, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 170.2 (*C*O), 140.2 (ArC_q), 139.3 (ArC_q), 135.7(ArC_q), 130.2 (Ar*C*H), 130.1 (2 × Ar*C*H), 128.9 (Ar*C*H), 128.7 (Ar*C*H), 128.6 (2 × Ar*C*H), 127.8 (Ar*C*H), 127.6 (Ar*C*H), 26.7 (*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3306 (NH), 3077, 3055, 3020, 2931, 2894, 1623 (CO), 1592; **HRMS (ESI$^+$)**: $C_{14}H_{14}NO$ [M + H^+]: calculated 212.1069, found 212.1066, Δ = +1.6 ppm.

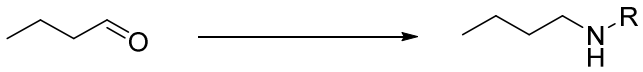
Synthesis of *N*-chloro-*N*-methyl-2-phenylbenzamide 295



General procedure F was followed, using amide **165** (700 mg, 3.32 mmol), *tert*-butanol (0.50 mL, 5.00 mmol), acetic acid (0.30 mL, 5.00 mmol) and sodium hypochlorite (0.75 M, 6.60 mL, 5.00 mmol) in toluene (17 mL). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (130 mg, 0.53 mmol, 16%) as a pale yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.56 – 7.35 (9 H, m, 9 × ArC*H*), 2.94 (3 H, s, CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 171.1 (CO), 139.5 (ArC_q), 133.4 (ArC_q), 130.3 (ArC_q), 130.0 (ArC_q), 129.7 (ArC_q), 128.6 (ArC_q), 128.4 (ArC_q), 128.2 (ArC_q), 127.9 (ArC_q), 127.7 (ArC_q), 21.0 (*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3057, 3024, 2977, 2944, 1656 (CO), 1596, 1565, 1475; **HRMS (ESI$^+$)**: $C_{14}H_{13}{}^{35}ClNO$ [M + H]$^+$: calculated 246.0680, found 246.0680, Δ = 0.0 ppm.

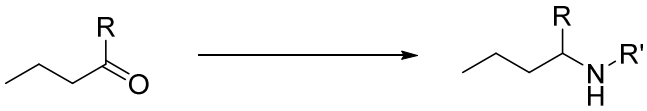
4.5 Chapter 3 experimental

General Procedure A Reductive Amination



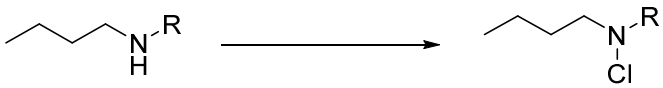
To a stirred solution of aldehyde (1 eq) in MeOH (0.2 M) was added amine (3−10 eq) and the RM was stirred for 2 h. The RM was cooled to 0 ^{o}C and $NaBH_4$ (2 eq) was added portionwise. The RM was warmed to RT and stirred for 2 h then quenched with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc (3 ×). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification afforded the desired products.

General procedure B Reductive amination with ketones



Following a modified procedure by Williamson *et al*, to a stirred solution of ketone (1 eq) in MeOH (0.2 M) was added amine (3−10 eq) and $Ti(O^iPr)_4$ (2 eq).[97] The RM was stirred for 16 h. The RM was cooled to 0 ^{o}C and $NaBH_4$ (2 eq) was added portionwise. The RM was warmed to RT and stirred for 2 h then concentrated *in vacuo*. The residue was taken up in EtOAc and ammonium hydroxide (2M, 6.0 eq) was added. The resulting mixture was dried over $MgSO_4$, the filtered through Celite and concentrated *in vacuo*. Purification afforded the desired product.

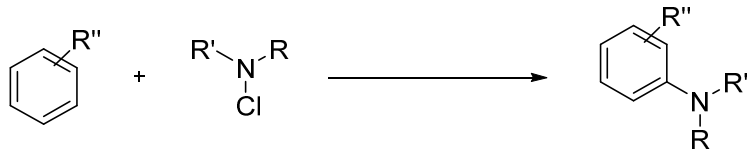
General procedure C Chlorination using NCS



Following a modified procedure by De Luca *et al*.[79], to a stirred solution of the amine (1.0 eq) in DCM (0.5 M) in the dark was added NCS (1.0 eq) portionwise over 10 min at RT. The RM

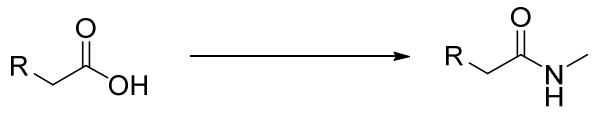
was stirred for 3 h then concentrated *in vacuo*. Purification by column chromatography afforded the desired products.

General procedure D *N*-Arylation



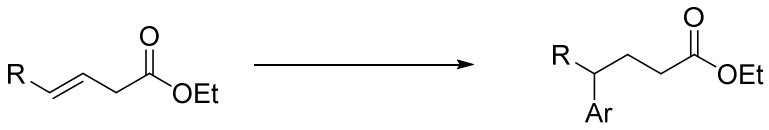
To a stirred solution of the amine (1.0 eq) in DCM (0.2 M) at 0 ^{o}C was added $MeSO_3H$ (10 eq) and $FeSO_4.7H_2O$ (10 mol%). The RM was stirred at 0 ^{o}C for 1 h. The RM was basified using 2 M NaOH (pH 9). The two phases were separated and the aqueous phase was extracted with DCM (3 ×). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography yielded the desired product.

General Procedure E Amide coupling



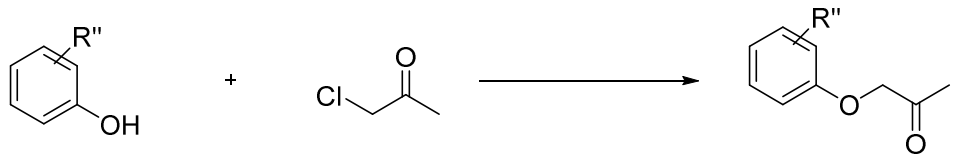
To a stirred solution of the acid (1.0 eq) and methylamine hydrochloride (1.5 eq) in DCM (0.2 M), was added TBTU (1.6 eq) and DIPEA (4.0 eq). The reaction mixture was stirred at RT for 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The two phases were separated and the aqueous phase was extracted with DCM (3 ×). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography afforded the desired product.

General Procedure F Rh(I)- catalysed 1,4-conjugate addition



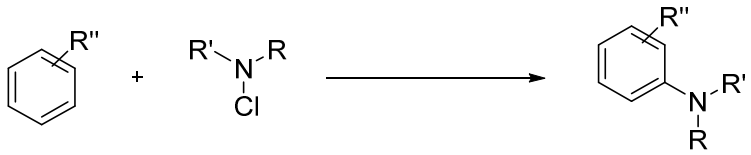
Following a modified procedure by Miyaura *et al*, to a stirred solution of [Rh(cod)Cl_2] (1 mol%) and $ArB(OH)_2$ (1.25 eq.) in degassed aqueous dioxane (0.33 M) was added a solution of 1,4-unsaturated carbonyl compound (1.0 eq.) in aqueous dioxane and distilled Et_3N (1 eq.) simultaneously.[88] The reaction mixture was heated at 50 ^oC for 6 h, after which it was cooled to RT, concentrated and purified by column chromatography afforded the desired product.

General Procedure G Alkylation of phenols



Following a modified procedure by Cuerva *et al*, to a stirred solution of phenol (1 eq) in acetone was added potassium carbonate (1 eq) and the RM was stirred at RT for 30 mins.[115] Chloroacetone (1.1 eq) was then added and the RM was heated at 50 ^oC for 16 h. The RM was filtered and concentrated *in vacuo*. The residue was then taken up in H_2O and basified to pH 9 using 2 M NaOH. The aqueous phase was extracted using EtOAc (3 ×). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography afforded the desired product.

General Procedure H *N*-arylation using hydroxylamines



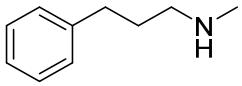
A stirred solution of the aromatic (1 eq), hydroxylamine (3 eq), $FeCl_2$ (5 mol%) and $FeCl_3$ (1 eq) in MeOH was heated at 60 ^oC for 4 h. Hydroxylamine (3 eq) was then added to the reaction mixture and the reaction was heated at 60 ^oC for 16 h. The RM was cooled to RT and partitioned between H_2O and EtOAc. The mixture was basified to pH 9 using 2M NaOH and the phases separated. The aqueous phase was extracted with EtOAc (3 ×). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography afforded the desired product

General Procedure I One pot process

Following a modified procedure by De Luca *et al.*[79], to a stirred solution of the amine (1.0 eq) in DCM (0.5 M) in the dark was added NCS (0.9 eq) portionwise over 10 min at RT. The RM was stirred for 1 h at RT. The RM was cooled to 0 ^oC. $MeSO_3H$ (10 eq) and $FeSO_4 \cdot 7H_2O$ (10 mol%) were added to the RM. The RM was stirred at 0 ^oC for 1 h. The RM was basified using 2 M NaOH (pH 9). The two phases were separated and the aqueous phase was extracted with DCM (3 ×). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography yielded the desired product.

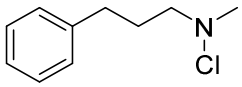
4.6 Experimental Data

Synthesis of methyl(3-phenylpropyl)amine 237



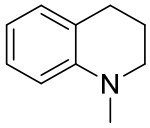
General Procedure A was followed, using hydrocinnamaldehyde (4.00 g, 29.8 mmol), $MeNH_2$ (8 M solution in EtOH, 5.0 ml, 1.3 eq), $NaBH_4$ (1.35 g, 35.8 mmol) Purification by SCX cartridge afforded the desired amine (4.42 g, 29.6 mmol, 99%) as a pale yellow oil. The NMR data was in accordance with the literature.[116] **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.33 – 7.28 (2H, m, 2 × ArC*H*), 7.24 – 7.19 (3H, m, 3 × ArC*H*), 2.72 – 2.62 (4H, m, include ArCH_2 and CH_2N), 2.47 (3H, s, CH_3), 1.91 – 1.82 (2H, m, CH_2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 142.1 (C_q), 128.4 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 125.8 (Ar*C*H), 51.5 (CH_2NH), 36.3 (CH_3), 33.6 (ArCH_2), 31.3 (CH_2); **IR** υ_{max} (neat) / cm^{-1} 3061, 3025, 2932, 2855, 2792, 1659, 1548, 1495; **HRMS (ESI$^+$)**: $C_{10}H_{16}N$ $[M + H]^+$: calculated 150.1277, found 150.1278, Δ = + 0.3 ppm.

Synthesis of chloro(methyl)(3-phenylpropyl)amine 115



General procedure C was followed, using amine **237** (500 mg, 3.35 mmol) and NCS (559 mg, 4.19 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (414 mg, 2.25 mmol, 67%) as a colourless oil. The data was in accordance with the literature.[77] **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.31 – 7.25 (2H, m, 2 × ArC*H*), 7.21 – 7.17 (3H, m, 3 × ArC*H*), 2.93 (3H, s, CH_3), 2.88 (2H, t, *J* = 7.0, NCH_2), 2.69 (2H, t, *J* = 7.7, ArCH_2), 2.01 – 1.93 (2H, m, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 141.7 (C_q), 128.5 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 125.9 (Ar*C*H), 65.3 (NCH_2), 53.1 (CH_3), 32.8 (ArCH_2), 29.8 (CH_2); **IR** υ_{max} (neat) / cm^{-1} 3027, 2949, 2866, 1603, 1496, 1454, 1439, 1172. **HRMS** data could not be obtained.

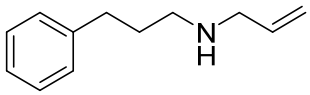
Synthesis of 1-methyl-1,2,3,4-tetrahydroquinoline 116



General Procedure D was followed, using chloroamine **115** (100 mg, 0.54 mmol), $MeSO_3H$ (350 µL, 5.40 mmol) and $FeSO_4.7H_2O$ (15 mg, 0.050 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (58 mg, 0.39 mmol, 73%) as a colourless oil. The data was in accordance with the literature.[77]

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.11 (1H, t, *J* = 7.7, ArC*H*), 6.99 (1H, d, *J* = 7.1, ArC*H*), 6.65 – 6.62 (2H, m, 2 × ArC*H*), 3.28 – 3.24 (2H, m, NCH_2), 2.92 (3H, s, CH_3), 2.81 (2H, t, *J* = 6.4, ArCH_2), 2.05 – 2.00 (2H, m, CH_2); **^{13}C NMR** (126 MHz,$CDCl_3$) 146.8 (C_q), 128.8 (Ar*C*H), 127.0 (Ar*C*H), 122.9 (C_q), 116.2 (Ar*C*H), 110.9 (Ar*C*H), 51.3 (N*C*H_2), 39.1 (*C*H_3), 27.8 (Ar*C*H_2), 22.5 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3075, 3032, 2998, 2931, 2834, 1639, 1611, 1583; **HRMS (ESI$^+$)**: $C_{10}H_{14}N$ [M+H$^+$]: calculated 148.1121, found 148.1118.

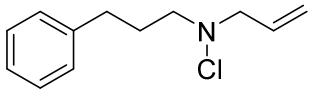
Synthesis of (3-phenylpropyl)(prop-2-en-1-yl)amine 301a



General procedure A was followed, using hydrocinnamaldehyde (500 mg, 3.73 mmol), allyl amine (2.13 g, 37.3 mmol) and $NaBH_4$ (282 mg, 7.46 mmol). Purification by SCX cartridge afforded the *title compound* (645 mg, 3.41 mmol, 91%) as a yellow oil. The data was in accordance with the literature.[77]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.35 – 7.16 (5H, m, 5 × ArC*H*), 5.86 – 5.99 (1H, m, C*H*), 5.18 (1H, ddd, *J* = 17.2, 3.3, 1.6, CHCH_2), 5.10 (1H, ddd, *J* = 10.2, 3.3, 1.6, CHCH_2), 3.27 (2H, dt, *J* = 6.0, 1.4, NCH_2CH), 2.72 – 2.65 (4H, m, ArCH_2 and CH_2CH_2N), 1.91 – 1.79 (2H, m, CH_2C$H_2$$CH_2$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 142.2 (C_q), 137.0 (*C*H), 128.4 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 125.8 (Ar*C*H), 115.7 (CH*C*H_2), 52.5 (N*C*H_2CH), 49.0 (Ar*C*H_2), 33.7 (*C*H_2N), 31.8 (CH_2*C*$H_2$$CH_2$); **IR** υ_{max} (neat) / cm^{-1} 3082, 3062, 2928, 2857. 2814, 1642, 1603, 1495; **HRMS (ESI$^+$)**: $C_{12}H_{18}N$ [M + H]$^+$: calculated 176.1434, found 176.1436, Δ = +1.4 ppm.

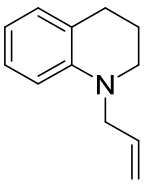
Synthesis of *N*-chloro(3-phenylpropyl)(prop-2-en-1-yl)amine 302a



General procedure C was followed, using amine **301a** (500 mg, 2.85 mmol) and NCS (476 mg, 3.57 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (426 mg, 2.03 mmol, 71%) as a colourless oil. The data was in accordance with the literature.[77]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.36 – 7.27 (2H, m, 2 × ArC*H*), 7.25 – 7.21 (3H, m, 2 × ArC*H*), 6.02 – 5.92 (1H, m, CH_2CH), 5.34 – 5.24 (2H, m, CH_2CH), 3.62 (2H, d, *J* = 6.4, $NClCH_2CH$), 2.99 – 2.92 (2H, m, CH_2CH_2NCl), 2.75 – 2.67 (2H, m, $ArCH_2$), 2.07 – 2.00 (2H, m, $ArCH_2CH_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.7 (C_q), 133.6 (CH_2CH), 128.4 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 125.9 (Ar*C*H), 119.2 ($CHCH_2$), 66.9 ($NClCH_2CH$), 62.2 (CH_2CH_2NCl), 32.8 ($ArCH_2$), 29.4 ($ArCH_2CH_2$); **IR** υ_{max} (neat) / cm^{-1} 3017, 3084, 2982, 2948, 1602, 1495, 1438, 1417; **HRMS (ESI$^+$)**: $C_{12}H_{17}{}^{35}ClN$ $[M + H]^+$: calculated 210.1044, found 210.1042, Δ = +0.9 ppm.

Synthesis of 1-(prop-2-en-1-yl)-1,2,3,4-tetrahydroquinoline 303a



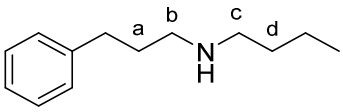
General procedure D was followed, using chloroamine **302a** (100 mg, 0.48 mmol), $MeSO_3H$ (315 µL, 4.80 mmol) and $FeSO_4.7H_2O$ (13 mg, 0.05 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (57 mg, 0.33 mmol, 69%) as a colourless oil. The data was in accordance with the literature.[77]

General Procedure I was followed using amine **301a** (100 mg, 0.57 mmol), NCS (68 mg, 0.51 mmol), $MeSO_3H$ (331 µL, 5.10 mmol) and $FeSO_4{\cdot}7H_2O$ (14 mg, 0.05 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (40 mg, 0.23 mmol, 45%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.02 (1H, t, *J* = 7.8, ArC*H*), 6.94 (1H, d, *J* = 7.5, ArC*H*), 6.58 – 6.54 (2H, m, 2 × ArC*H*), 5.89 – 5.80 (1H, m, $CHCH_2$), 5.24 – 5.10 (2H, m, $CHCH_2$), 3.89 – 3.82 (2H, m, NCH_2CH), 3.31 – 3.23 (2H, m, NCH_2), 2.76 (2H, t, *J* = 6.3, $ArCH_2$), 2.02

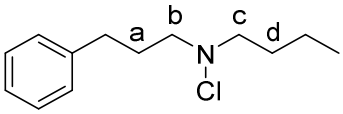
– 1.90 (2H, m, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.4 (C_q), 133.6 (Ar*C*H), 129.0 (Ar*C*H), 127.1 (Ar*C*H), 122.4 (C_q), 115.9 (CH*C*H_2), 115.7 (Ar*C*H), 111.0 (*C*HCH$_2$), 53.9 (N*C*H_2CH), 49.2 (N*C*H_2), 28.2 (Ar*C*H_2), 22.4 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3065, 3022, 2928, 2841, 1725, 1675, 1642, 1601; **HRMS (ESI$^+$)**: $C_{12}H_{16}N$ $[M + H]^+$: calculated 174.1277, found 174.1272, Δ = -2.9 ppm.

Synthesis of butyl(3-phenylpropyl)amine 301b



General procedure A was followed, using hydrocinnamaldehyde (500 mg, 3.73 mmol), butylamine (1.40 mL, 18.7 mmol) and $NaBH_4$ (282 mg, 7.46 mmol). Purification by column chromatography, eluting with 20% - 100% EtOAc in hexane afforded the *title compound* (607 mg, 3.17 mmol, 85%) as a yellow oil. The data was in accordance with the literature.[77] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.32 – 7.23 (2H, m, 2 × ArC*H*), 7.22 – 7.12 (3H, m, 3 × ArC*H*), 2.71 – 2.54 (6H, m, include ArCH_2, C_bH_2 and C_cH_2), 1.89 – 1.75 (2H, m, C_aH_2), 1.54 – 1.39 (2H, m, C_dH_2), 1.39 – 1.26 (2H, m, CH_2CH$_3$), 0.91 (3H, t, *J* = 7.2, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 142.3 (C_q), 128.4 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 125.7 (Ar*C*H), 49.8 (C_c), 49.7 (Ar*C*H_2), 33.8 (C_b), 32.4 (C_d), 31.8 (C_a), 20.5 (*C*H_2CH$_3$), 14.0 (*C*H$_3$); **IR** υ_{max} (neat) / cm^{-1} 3084, 3062, 3000, 2954, 2926, 2858, 1603, 1495; **HRMS (ESI$^+$)**: $C_{13}H_{22}N$ $[M + H]^+$: calculated 192.1747, found 192.1753, Δ = +3.4 ppm.

Synthesis of butyl(*N*-chloro)(3-phenylpropyl)amine 302b

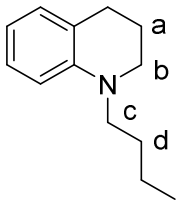


General procedure C was followed, using amine **301b** (500 mg, 2.61 mmol) and NCS (435 mg, 3.26 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (410 mg, 1.82 mmol, 70%) as a colourless oil. The data was in accordance with the literature.[77]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.32 – 7.24 (2H, m, 2 × ArC*H*), 7.22 – 7.14 (3H, m, 3 × ArC*H*), 2.96 – 2.87 (4H, m, includes C_bH and C_cH), 2.68 (2H, t, *J* = 7.7, ArCH_2), 2.07 – 1.94 (2H, m, C_aH), 1.69 – 1.59 (2H, m, C_dH), 1.37 (2H, dq, *J* = 14.5, 7.3, CH_2CH$_3$), 0.93 (3H, t, *J*

= 7.3, C*H*$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 141.8 (*C*$_q$), 128.5 (Ar*C*H), 128.3 (Ar*C*H), 125.8 (Ar*C*H), 64.1 (*C*$_c$), 63.3 (*C*$_b$), 32.8 (Ar*C*H$_2$), 30.0 (*C*$_d$), 29.5 (*C*$_a$), 20.0 (*C*H$_2$CH$_3$), 13.9 (*C*H$_3$); **IR** υ_{max} (neat) / cm^{-1} 3026, 2955, 2933, 2864, 1495, 1454, 1366, 1352; **HRMS (ESI$^+$)**: $C_{13}H_{21}{}^{35}ClN$ [M + H]$^+$: calculated 226.1357, found 226.1360, Δ = -1.1 ppm.

Synthesis of 1-butyl-1,2,3,4-tetrahydroquinoline 303b

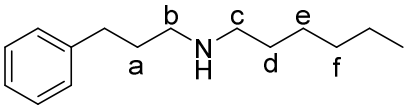


General Procedure D was followed, using chloroamine **302b** (100 mg, 0.44 mmol), $MeSO_3H$ (285 µL, 4.40 mmol) and $FeSO_4.7H_2O$ (12 mg, 0.04 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (36 mg, 0.19 mmol, 43%) as a pale yellow oil. The data was in accordance with the literature.[77]

General Procedure I was followed using amine (100 mg, 0.52 mmol), NCS (63 mg, 0.47 mmol), $MeSO_3H$ (305 µL, 4.70 mmol) and $FeSO_4{\cdot}7H_2O$ (14 mg, 0.05 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (51 mg, 0.27 mmol, 57%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.08 – 6.98 (1H, m, ArC*H*), 6.98 – 6.86 (1H, m, ArC*H*), 6.60 – 6.49 (2H, m, 2 × ArC*H*), 3.34 – 3.15 (4H, m, C$_b$*H*$_2$ and C$_c$*H*$_2$), 2.80 – 2.68 (2H, m, ArC*H*$_2$), 2.02 – 1.86 (2H, m, C$_a$*H*$_2$), 1.64 – 1.48 (2H, m, C$_d$*H*$_2$), 1.42 – 1.26 (2H, m, C*H*$_2$CH$_3$), 0.95 (3H, t, *J* = 7.3, C*H*$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 145.4 (*C*$_q$), 129.1 (Ar*C*H), 127.0 (Ar*C*H), 122.1 (*C*$_q$), 115.1 (Ar*C*H), 110.5 (Ar*C*H), 51.2 (N*C*H$_2$), 49.5 (N*C*H$_2$), 28.4 (*C*$_d$), 28.2 (Ar*C*H$_2$), 22.3 (*C*$_a$), 20.5 (*C*H$_2$CH$_3$), 14.1 (*C*H$_3$); **IR** υ_{max} (neat) / cm^{-1} 3064, 3020, 2954, 2929, 2860, 1676, 1601, 1503; **HRMS (ESI$^+$)**: $C_{13}H_{20}N$ [M + H]$^+$: calculated 190.1590, calculated 190.1593, Δ = +1.5 ppm.

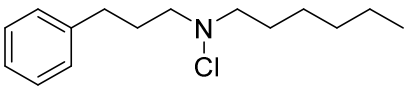
Synthesis of *N*-(3-phenylpropyl)hexan-1-amine 301c



General Procedure A was followed using hydrocinnamaldehyde (1.00 g, 7.45 mmol), hexylamine (4.90 mL, 37.3 mmol) and $NaBH_4$ (423 mg, 11.2 mmol). Purification by column chromatography, eluting with 20-100% EtOAc in hexane afforded the title compound (512 mg, 2.33 mmol,31 %) as a colourless oil. The data was in accordance with the literature.[77]

^{1}H NMR (300 MHz $CDCl_3$) δ ppm 7.32-7.23 (2H, m, 2 × ArC*H*), 7.21-7.16 (3H, m, 3 × ArC*H*), 2.70-2.54 (6H, m, includes ArCH_2, C_bH_2 and C_cH_2), 1.88-1.74 (2H, m, C_aH_2), 1.51-1.41 (2H, m, C_dH_2), 1.37-1.21 (6H, m, includes CH_2CH_3, C_eH_2 and C_fH_2), 0.93-0.83 (3H, m, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 142.2 (C_q), 128.4 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 125.7 (Ar*C*H), 50.1 (C_c), 49.6 (C_b), 33.7 (C_d), 31.8 (ArCH_2 and C_a), 30.2 (C_e), 27.1 (C_f), 22.6 (CH_2), 14.0 (CH_3); **IR** υ_{max} (neat)/cm-1: 3026, 2925, 2855, 1603, 1495, 1454, 1129, 687; **HRMS (ESI$^+$):** $C_{15}H_{26}N$ $[M+H]^+$: calculated 220.2060, found 220.2063, Δ = +1.4 ppm.

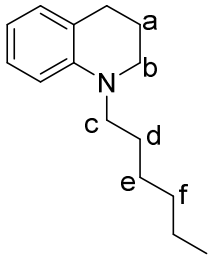
Synthesis of *N*-chloro-*N*-(3-phenylpropyl)hexan-1-amine 302c



General procedure C was followed, using amine **301c** (500 mg, 2.61 mmol) and NCS (435 mg, 3.26 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (410 mg, 1.82 mmol, 70%) as a colourless oil. The data was in accordance with the literature.[77]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.30 (2H, m, 2 x ArC*H*), 7.25-7.13 (3H, m, 3 x ArC*H*), 2.92 (4H, m, includes 2H, m, C_bH_2 and C_cH_2), 2.75-2.61 (2H, m, ArCH_2), 2.09-1.95 (2H, m, C_aH_2), 1.75-1.60 (2H, m, C_dH_2), 1.43-1.22 (6H, m, includes C_eH_2, C_fH_2 and CH_2CH_3), 0.91 (3H, t, *J* = 6.8, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 142.0 (C_q), 128.6 (2 × Ar*C*H), 128.5 (2 × Ar*C*H), 126.0 (Ar*C*H), 64.6 (CH_2), 63.4 (CH_2), 32.9 (CH_2), 31.8 (CH_2), 29.6 (CH_2), 28.0 (CH_2), 26.7 (CH_2), 22.7 (CH_2), 14.2 (CH_3); **IR** υ_{max} (neat)/cm^{-1}: 3085, 3027, 2928, 1063, 1496, 1454, 1347, 1302; **HRMS (ESI$^+$):** $C_{15}H_{25}{}^{35}ClN$ $[M+H]^+$: calculated 254.1670, found 254.1675, Δ = +2.0 ppm.

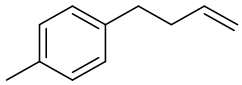
Synthesis of 1-hexyl-1,2,3,4-tetrahydroquinoline 303c



General Procedure D was followed, using chloroamine **302c** (100 mg, 0.39 mmol), $MeSO_3H$ (255 µL, 3.90 mmol) and $FeSO_4.7H_2O$ (11 mg, 0.04 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (41 mg, 0.19 mmol, 48%) as a colourless oil. The data was in accordance with the literature.[77]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.09-6.99 (1H, m, ArC*H*), 6.97-6.89 (1H, m, ArC*H*), 6.63-6.47 (2H, m, includes 2 × ArC*H*), 3.34-3.15 (4H, m, includes CH_{2c} and CH_{2b}), 2.75 (2H, t, *J* = 6.4, ArCH_2), 2.02-1.88 (2H, m, CH_{2a}), 1.66-1.51 (2H, m, CH_{2d}), 1.40-1.24 (6H, m, includes C$H_{2e,}$ CH_{2f} and CH_2CH_3), 0.98-0.81 (3H, m, CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 145.5 (C_q), 129.3 (Ar*C*H), 127.2 (Ar*C*H), 122.3 (C_q), 115.3 (Ar*C*H), 110.6 (Ar*C*H), 51.7 (C_c), 49.6 (C_b), 31.9 (C_d), 28.4 (Ar*C*H_2), 27.1 (C_a), 26.3 (C_e), 22.8 (C_f), 22.4 (*C*H_2), 14.2 (*C*H_3); **IR** υ_{max} (neat)/cm^{-1}: 3066, 2925, 2855, 1601, 1574, 1504, 1456, 1369; **HRMS** (ESI): $C_{15}H_{24}N$ $[M+H]^+$: calculated 218.1903, found 218.1902, Δ = -0.5 ppm.

Synthesis of 1-(but-3-en-1-yl)-4-methylbenzene 308a

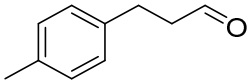


4-Methylbenzyl bromide (800 mg, 4.32 mmol) was flushed with N_2 and THF (11 mL) was added. The solution was cooled to 0 °C and allylmagnesium bromide (2.0 M in THF, 4.3 mL, 8.64 mmol) was added dropwise. The RM was stirred at 0 °C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted using EtOAc (3 × 70 mL). The combined organic layers were dried over $MgSO_4$ and concentration *in vacuo* afforded the *title compound* x (588 mg, 4.02 mmol, 93%) as a colourless oil without further purification being required. The NMR data is in accordance with the literature.[117]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.12 (4H, s, 4 × ArC*H*), 5.96 – 5.83 (1H, m, C*H*CH_2), 5.10 – 4.99 (2H, m, CHCH_2), 2.70 (2H, t, *J* = 7.6, ArCH_2), 2.40 (2H, t, *J* = 7.6, CH_2), 2.35 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.8 (C_q), 138.2 (*C*H), 135.2 (C_q), 128.9 (2 × Ar*C*H),

128.3 (2 × Ar*C*H), 114.8 (CH*C*H$_2$), 35.6 (ArCH$_2$*C*H$_2$), 34.9 (Ar*C*H$_2$), 21.0 (*C*H$_3$); **IR** υ_{max} (neat) / cm^{-1} 3077, 3048, 3003, 2978, 2923, 2856, 1640, 1515. **HRMS** data could not be obtained.

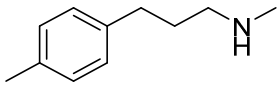
Synthesis of 3-(4-methylphenyl)propanal 309a



A stirred solution of alkene **308a** (500 mg, 3.42 mmol) in DCM (17 mL) was cooled to -78 ^{o}C and a flow of oxygen was bubbled through the solution for 5 min. Ozone was then bubbled through the RM for 20 min (colour change observed from colourless to bright blue). Oxygen was then bubbled through the RM for a further 5 min and triphenylphosphine (943 mg, 3.59 mmol) was added. The reaction was stirred at -78 ^{o}C for 10 min and the starch iodine test showed no peroxides were present. The reaction mixture was warmed to RT and concentrated *in vacuo*. Purification by column chromatography 10% EtOAc in hexane afforded the *title compound* (364 mg, 2.46 mmol, 72%) as a colourless oil. The NMR data is in accordance with the literature.[118]

^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 9.86 (1H, t, *J* = 1.3, C*H*O), 7.40 – 7.35 (1H, m, ArC*H*), 7.28 – 7.25 (1H, m, ArC*H*), 7.24 – 7.15 (2H, m, Ar*C*H), 3.09 (2H, t, *J* = 7.5, ArC*H*$_2$), 2.83 (2H, td, *J* = 7.6, 1.2, C*H*$_2$CHO), 2.35 (3H, s, C*H*$_3$).; **^{13}C NMR** (126 MHz, CDCl$_3$) δ ppm 201.8 (*C*HO), 137.2 (*C*$_q$), 135.9 (*C*$_q$), 129.3 (2 × Ar*C*H), 128.2 (2 × Ar*C*H), 45.4 (C*H*$_2$), 27.7 (Ar*C*H$_2$), 21.0 (*C*H$_3$). **IR** υ_{max} (neat) / cm^{-1} 3050, 3011, 2923, 2862, 1722, 1515, 1435, 1407. **HRMS** data could not be obtained.

Synthesis of methyl[3-(4-methylphenyl)propyl]amine 310a

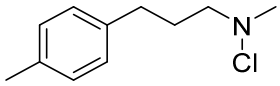


General procedure A was followed, using aldehyde **309a** (300 mg, 2.02 mmol), MeNH$_2$ (8M solution in EtOH, 300 µL) and NaBH$_4$ (153 mg, 4.04 mmol). Purification by SCX cartridge afforded the *title compound* (320 mg, 1.96 mmol, 97%) as a yellow oil. The ^{1}H NMR data is in accordance with the literature.[119]

^{1}H NMR (500 MHz, CDCl$_3$) δ ppm 7.08 (4H, s, 4 × ArC*H*), 2.62 (4H, t, *J* = 7.3, include ArC*H*$_2$ and C*H*$_2$NH), 2.43 (3H, s, NHC*H*$_3$), 2.31 (3H, s, ArC*H*$_3$), 1.85 – 1.79 (2H, m, C*H*$_2$); **^{13}C NMR**

(126 MHz, $CDCl_3$) δ ppm 138.9 (C_q), 135.3 (C_q), 129.1 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 51.4 (*C*H_2NH), 36.2 (NH*C*H_3), 33.1 (Ar*C*H_2), 31.3 (*C*H_2), 21.0 (Ar*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3046, 3016, 2925, 2853, 2789, 1514, 1470, 1445; **HRMS (ESI$^+$)**: $C_{11}H_{18}N$ $[M + H]^+$: calculated 164.1434, found 164.1432, Δ = +1.0 ppm.

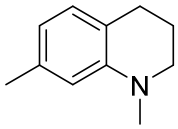
Synthesis of *N*-chloro(methyl)[3-(4-methylphenyl)propyl]amine 311a



General procedure C was followed, using amine **310a** (250 mg, 1.53 mmol) and NCS (255 mg, 1.91 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (219 mg, 1.11 mmol, 73%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.09 (4H, s, ArC*H*), 2.92 (3H, s, NClCH_3), 2.87 (2H, t, *J* = 6.8, CH_2N), 2.64 (2H, t, *J* = 7.8, ArCH_2), 2.32 (3H, s, ArCH_3), 2.00 – 1.89 (2H, m, ArCH_2CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.6 (C_q), 135.3 (C_q), 129.1 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 65.3 (*C*H_2N), 53.0 (N*C*H_3), 32.3 (Ar*C*H_2), 29.8 (*C*H_2), 21.0 (Ar*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3046, 3018, 2995, 2948, 1514, 1437, 1375, 1169; **HRMS (ESI$^+$)**: $C_{11}H_{17}{}^{35}ClN$ $[M + H]^+$: calculated 198.1044, found 198.1042, Δ = -0.8 ppm.

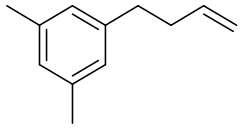
Synthesis of 1,7-dimethyl-1,2,3,4-tetrahydroquinoline 324



General Procedure D was followed, using chloroamine **311a** (100 mg, 0.51 mmol), $MeSO_3H$ (335 µL, 5.10 mmol) and $FeSO_4.7H_2O$ (14 mg, 0.051 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (64 mg, 0.40 mmol, 78%) as a colourless oil. The NMR data was in accordance with the literature.[120]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.76 (1H, d, *J* = 7.3, ArC*H*), 6.36 (2H, m, 2 × ArC*H*), 3.16 – 3.08 (2H, m, NCH_2), 2.80 (3H, s, NCH_3), 2.65 (2H, t, *J* = 6.5, ArCH_2), 2.20 (3H, s, ArCH_3), 1.93 – 1.84 (2H, m, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.6 (C_q), 136.6 (C_q), 128.7 (Ar*C*H), 112.0 (C_q), 117.0 (Ar*C*H), 111.8 (Ar*C*H), 51.4 (N*C*H_2), 39.2 (N*C*H_3), 27.5 (Ar*C*H_2), 22.7 (*C*H_2), 21.6 (Ar*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3041, 3022, 2924, 2856, 2839, 2812, 1611, 1575; **HRMS (ESI$^+$)**: $C_{11}H_{16}N$ $[M + H]^+$: calculated 162.1277, found 162.1280, Δ = -1.9 ppm.

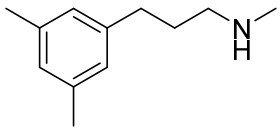
Synthesis of 1-(but-3-en-1-yl)-3,5-dimethylbenzene 308b



3,5-Methylbenzyl bromide (800 mg, 4.02 mmol) was flushed with N_2 in a round bottom flask and THF (10 mL) was added. The solution was cooled to 0 °C and allylmagnesium bromide (2.0 M in THF, 4.0 mL, 8.04 mmol) was added dropwise. The RM was stirred at 0 °C for 2 h The reaction was quenched with saturated aqueous NH_4Cl. The solution was extracted using EtOAc (3 × 70 mL). The combined organic extracts were dried over $MgSO_4$ and concentration *in vacuo* afforded the *title compound* (613 mg, 3.83 mmol, 95%) as a yellow oil without further purification being required.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.84 – 6.81 (3H, m, 3 × Ar*C*H), 5.96 – 5.79 (1H, m, C*H*), 5.08 – 4.96 (2H, m, CHCH_2), 2.66 – 2.61 (2H, m, CH_2), 2.41 – 2.32 (2H, m, CH_2), 2.30 (6H, s, CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 141.9 (C_q), 138.4 (*C*HCH$_2$), 137.8 (2 × C_q), 127.5 (Ar*C*H), 126.3 (2 × Ar*C*H), 114.7 (CHCH_2), 35.6 (CH_2), 35.3 (CH_2), 21.3 (2 × ArCH_3); **IR** υ_{max} (neat) / cm^{-1} 3026, 2955, 2933, 2864, 2835, 1495, 1454, 1366. **HRMS** data could not be obtained.

Synthesis of [3-(3,5-dimethylphenyl)propyl](methyl)amine 309b

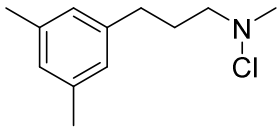


Step i) A stirred solution of alkene **308b** (500 mg, 3.12 mmol) in DCM (16 mL) was cooled to -78 °C and oxygen was bubbled through the solution for 5 min. Ozone was bubbled through the reaction mixture for 20 min (colour change observed from colourless to bright blue). Oxygen was then bubbled through the mixture for a further 5 min after which triphenylphosphine (862 mg, 3.28 mmol) was added. The reaction was stirred at -78 °C for 10 min and the starch iodine test showed no peroxides were present. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography 10% EtOAc in hexane afforded the *title compound* (370 mg, 2.28 mmol, 73%) as a colourless oil.

Step ii) General procedure A was followed, using aldehyde x (300 mg, 1.85 mmol), $MeNH_2$ (8M solution in EtOH, 300 µL) and $NaBH_4$ (140 mg, 3.70 mmol). Purification by SCX cartridge afforded the *title compound* (311 mg, 1.75 mmol, 95%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.84 – 6.80 (3H, m, 3 × ArC*H*), 2.66 – 2.54 (4H, m, ArCH_2, CH_2NH), 2.43 (3H, s, NCH_3), 2.28 (6H, s, 2 × ArCH_3), 1.86 – 1.76 (2H, m, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 142.0 (C_q), 137.8 (2 × C_q), 127.4 (Ar*C*H), 126.2 (2 × Ar*C*H), 51.6 (*C*H_2), 36.3 (*C*H_3), 33.5 (*C*H_2), 31.4 (*C*H_2), 21.3 (2 × Ar*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3300, 3012, 2918, 2855, 2788, 1605, 1545, 1469; **HRMS (ESI$^+$)** $C_{12}H_{19}N$ $[M + H]^+$: calculated 178.1590, found 178.1592, Δ = +1.2 ppm.

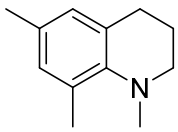
Synthesis of *N*-chloro[3-(3,5-dimethylphenyl)propyl]methylamine 310b



General procedure C was followed, using amine **309b** (250 mg, 1.41 mmol) and NCS (235 mg, 1.76 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (196 mg, 0.93 mmol, 66%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.95 – 6.80 (3H, m, ArC*H*), 2.97 – 2.95 (3H, s, CH_3), 2.91 (2H, t, *J* = 7.0, CH_2NCl), 2.66 – 2.60 (2H, t, *J* = 7.3, ArCH_2), 2.32 (6H, s, 2 × CH_3), 2.01 – 1.90 (2H, m, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 141.6 (C_q), 137.9 (2 × C_q), 127.5 (Ar*C*H), 126.3 (2 × Ar*C*H), 65.4 (*C*H_2NCl), 53.1 (*C*H_3), 32.6 (Ar*C*H_2), 29.8 (*C*H_2), 21.3 (2 × Ar*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 2948, 2917, 2858, 1605, 1456, 1437, 1375, 1191; **HRMS (ESI$^+$)**: $C_{12}H_{19}{}^{35}ClN$ $[M + H]^+$: calculated 212.1201, found 212.1205, Δ = +2.1 ppm.

Synthesis of 1,6,8-trimethyl-1,2,3,4-tetrahydroquinoline 321

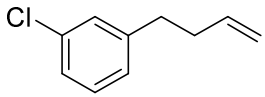


General Procedure D was followed, using chloroamine **310b** (100 mg, 0.47 mmol), $MeSO_3H$ (305 mL, 4.70 mmol) and $FeSO_4.7H_2O$ (13 mg, 0.047 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (22 mg, 0.13 mmol, 28%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.81 (1H, s, ArC*H*), 6.72 (1H, s, ArC*H*), 3.14 – 3.06 (2H, m, NCH_2), 2.75 (2H, t, *J* = 6.7, ArCH_2), 2.68 (3H, s, CH_3), 2.27 (3H, s, ArCH_3), 2.22 (3H, s, ArCH_3), 1.88 – 1.78 (2H, m,CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 131.3 (C_q), 131.1 (C_q), 130.5 (C_q), 129.7 (Ar*C*H), 128.8 (C_q), 127.9 (Ar*C*H), 52.2 (N*C*H_2), 43.0 (*C*H_3), 27.7 (Ar*C*H_2),

20.6 (Ar*C*H$_3$), 18.4 (Ar*C*H$_3$), 16.7 (*C*H$_2$); **IR** υ_{max} (neat) / cm^{-1} 2997, 2933, 2853, 1722, 1678, 1605, 1479. 1439; **HRMS (ESI$^+$)**: $C_{12}H_{18}N$ $[M + H]^+$: calculated 176.1453, found 176.1455, Δ = +2.0 ppm.

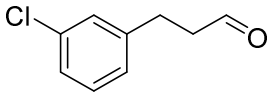
Synthesis of 1-(but-3-en-1-yl)-3-chlorobenzene 308c



3-chlorobenzyl bromide (1.50 g, 7.30 mmol) was flushed with N_2 and THF (18 mL) was added. The solution was cooled to 0 ^{o}C and the allyl Grignard (2.0 M in THF, 7.30 mL, 14.6 mmol) was added dropwise. The reaction mixture was stirred at 0^{o}C for 2 h, it was then quenched with NH_4Cl. The solution was extracted using EtOAc (3 x 100 mL) The combined organic layers were dried over $MgSO_4$ and concentrated. Purification by column chromatography 10% EtOAc in hexane afforded the *title compound* (1.20 g, 7.20 mmol, 99%) as a colourless oil. The NMR data was in accordance with the literature.[121]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.26 – 7.17 (3H, m, 3 × Ar*CH*), 7.09 (1H, d, *J* = 7.2, Ar*CH*), 5.92 – 5.80 (1H, m, *CH*CH$_2$), 5.12 – 4.98 (2H, m, CHC*H*$_2$), 2.72 (2H, t, *J* = 7.7, ArC*H*$_2$), 2.39 (2H, m, C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 143.9 (*C*$_q$), 137.5 (*C*H), 134.1 (*C*$_q$), 129.5 (Ar*C*H), 128.6 (Ar*C*H), 126.7 (Ar*C*H), 126.0 (Ar*C*H), 115.3 (CH*C*H$_2$), 35.2 (*C*H$_2$), 35.0 (Ar*C*H$_2$); **IR** υ_{max} (neat) / cm^{-1} 3077, 2978, 2928, 2857, 1640, 1598, 1573, 1476; **HRMS** data could not be obtained.

Synthesis of 3-(3-chlorophenyl)propanal 309c

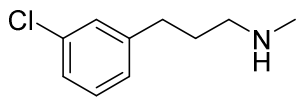


A stirred solution of alkene **308c** (1.00 g, 6.00 mmol) in DCM (30 mL) was cooled to -78 ^{o}C and oxygen was bubbled through it for 5 mins after which ozone was bubbled through the reaction mixture for 20 mins (colour change observed colourless to bright blue). Oxygen was then bubbled through the mixture for a further five mins after which triphenylphosphine (1.66 g, 6.30 mmol) was added. The reaction was stirred at -78 ^{o}C for 10 mins and the starch iodine test showed no peroxides were present. The reaction mixture was concentrated in vacuo. Purification by column chromatography 10% EtOAc in hexane afforded the *title compound*

(766 mg, 4.54 mmol, 76%) as a colourless oil. The NMR data was in accordance with the literature.[122]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.84 (1H, s, C*H*O), 7.30 – 7.18 (3H, m, 3 ArC*H*), 7.10 (1H, d, *J* = 7.1, ArC*H*), 2.96 (2H, t, *J* = 7.4, CH_2), 2.81 (2 H, t, *J* = 7.5, ArCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 200.9 (*C*HO), 142.4 (C_q), 134.3 (C_q), 129.9 (Ar*C*H), 128.5 (Ar*C*H), 126.6 (Ar*C*H), 126.5 (Ar*C*H), 45.0 (*C*H_2), 27.7 (Ar*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3019, 2928, 2894, 2824, 2724, 1721 (CO), 1598, 1573; **HRMS** data could not be obtained.

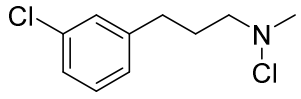
Synthesis of [3-(3-chlorophenyl)propyl](methyl)amine 310c



General Procedure A was followed, using aldehyde **309c** (700 mg, 4.15 mmol), $MeNH_2$ (8M in EtOH, 1.50 mL, 12.0 mol) and $NaBH_4$ (236 mg, 6.23 mmol). Purification by SCX cartridge afforded the *title compound* (672 mg, 3.66 mmol, 88%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.26 – 7.15 (3H, m, 3 × ArC*H*), 7.08 (1H, d, *J* = 7.2, ArC*H*), 2.70 – 2.61 (4H, m, includes ArCH_2 and CH_2NH), 2.47 (3H, s, CH_3), 1.91 – 1.80 (2H, m, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 144.0 (C_q), 134.1 (C_q), 129.6 (Ar*C*H), 128.5 (Ar*C*H), 126.6 (Ar*C*H), 126.1 (Ar*C*H), 51.1 (*C*H_2N), 36.1 (*C*H_3), 33.2 (Ar*C*H_2), 30.8 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3059, 2935, 2858, 2796, 1596, 1571, 1536, 1473; **HRMS (ESI$^+$)**: $C_{10}H_{15}{}^{35}ClN$ $[M + H]^+$: calculated 184.0888, found 184.0886, Δ = + 1.0 ppm.

Synthesis of *N*-chloro[3-(3-chlorophenyl)propyl]methylamine 311c

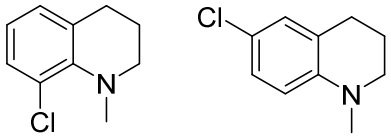


General procedure C was followed, using chloroamine **310c** (300 mg, 1.64 mmol), NCS (274 mg, 2.05 mmol). Purification by column chromatography eluting with 10% EtOAc in hexane afforded the *title compound* (300 mg, 1.38 mmols, 85%) as a colourless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.26 – 7.17 (3H, m, 3 × ArC*H*), 7.10 (1H, d, *J* = 7.2, ArC*H*), 2.96 (3H, s, CH_3), 2.89 (2H, t, *J* = 6.8, CH_2), 2.69 (2H, t, *J* = 7.7 CH_2), 2.01 – 1.94 (2H, m, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 143.8 (C_q), 134.1 (C_q), 129.7 (Ar*C*H), 128.6 (Ar*C*H), 126.7 (Ar*C*H), 126.1 (Ar*C*H), 64.9 (*C*H_2N), 53.1 (*C*H_3), 32.4 (Ar*C*H_2), 29.5

(CH_2): **IR** υ_{max} (neat) / cm^{-1} 3061, 2992, 2950, 2919, 2867, 1597, 1572, 1475; **HRMS (ESI$^+$)**: $C_{10}H_{14}{}^{35}Cl_2N$ $[M + H]^+$: calculated 218.0498, found 218.0492, Δ = - 2.5 ppm.

Synthesis of 6-chloro-1-methyl-1,2,3,4-tetrahydroquinoline and 8-chloro-1-methyl-1,2,3,4-tetrahydroquinoline 325a and 325b



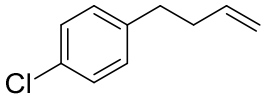
325a **325b**

General Procedure D was followed, using chloroamine **311c** (100 mg, 0.46 mmol), $MeSO_3H$ (300 µL, 4.60 mmol) and $FeSO_4.7H_2O$ (13 mg, 0.046 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the regioisomeric **325a** and **325b** as an inseperable mixture (1.4 : 1, 40 mg, 0.22 mmol, 48%) as a colourless oil. The NMR data for **325b** was in accordance with the literature.[123]

General Procedure I was followed using amine **310c** (100 mg, 0.54 mmol), $MeSO_3H$ (318 µL, 4.90 mmol) and $FeSO_4{\cdot}7H_2O$ (14 mg, 0.05 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (37 mg, 0.20 mmol, 42%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$, peaks for **325a**) δ ppm 7.02 (1H, dd, *J* = 8.7, 2.6, ArC*H*), 6.93 (1H, d, *J* = 2.6, ArC*H*), 6.50 (1H, d, *J* = 8.7, ArC*H*), 3.25 – 3.19 (2H, m, CH_2NMe), 2.88 (3H, s, CH_3), 2.75 (2H, t, *J* = 6.5, ArCH_2), 1.99 (2H, m, CH_2), **^{13}C NMR** (101 MHz, $CDCl_3$, peaks for **325a**) δ ppm 145.3 (C_q), 131.2 (C_q), 128.4 (Ar*C*H), 126.6 (Ar*C*H), 124.4 (C_q), 111.9 (Ar*C*H), 51.1 (*C*H_2NMe), 39.2 (*C*H_3), 27.7 (Ar*C*H_2), 22.2 (*C*H_2); **^{1}H NMR** (400 MHz, $CDCl_3$, peaks for **325b**) δ ppm 7.19 (1H, d, *J* = 7.8, ArC*H*), 6.97 (1H, d, *J* = 7.8), 6.85 (1 H, t, *J* = 7.8, ArC*H*), 3.19 – 3.14 (2H, m, CH_2NMe), 2.91 (3H, s, CH_3), 2.82 (2H, t, *J* = 6.7, ArCH_2), 1.91 – 1.85 (2H, m, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$, peaks for **325b**) δ ppm 146.0 (C_q), 128.3 (Ar*C*H), 128.2 (Ar*C*H), 127.5 (C_q), 122.0 (Ar*C*H), 120.7 (C_q), 52.0 (*C*H_2NMe), 42.8 (*C*H_3), 27.9 (Ar*C*H_2), 17.2 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3040, 2934, 2861, 2841, 1596, 1560, 1499, 1463; **HRMS** data could not be obtained.

Synthesis of 1-(but-3-en-1-yl)-4-chlorobenzene 308d

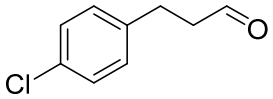


Step i) To a stirred solution of 4-chlorobenzyl alcohol (1.30 g, 9.12 mmol) in DCM (23 mL) at 0 °C was added Et_3N (1.40 mL, 10.0 mmol). MsCl (770 mL, 7.96 mmol) was added dropwise and the RM was stirred at 0 °C for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The two phases were separated and the aqueous phase was extracted with DCM (2 × 60 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to afford the desired crude mesylate as a yellow oil.

Step ii) The crude oil was flushed with N_2 and THF (23 mL) was added. The solution was cooled to 0 °C and allylmagnesium bromide (2.0 M in THF, 9.10 mL, 18.2 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl. The phases were separated and the aqueous phase was extracted using EtOAc (3 × 60 mL), the combined organic layers were dried over $MgSO_4$ and concentrated. Purification by column chromatography with 10% EtOAc in hexane afforded the *title compound* (640 mg, 3.84 mmol, 42%) as a colourless oil. The data was in accordance with the literature.[77]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.24 (2H, d, *J* = 8.6, 2 × ArC*H*), 7.11 (2H, d, *J* = 8.6, 2 × ArC*H*), 5.88 – 5.77 (1H, m, C*H*CH$_2$), 5.06 – 4.95 (2H, m, CHC*H*$_2$), 2.68 (2H, t, *J* = 7.7, ArC*H*$_2$), 2.39 – 2.30 (2H, m, ArCH$_2$C*H*$_2$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 140.3 (*C*$_q$), 137.6 (*C*HCH$_2$), 131.5 (*C*$_q$), 129.8 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 115.3 (CH*C*H$_2$), 35.4 (*C*H$_2$), 34.7 (*C*H$_2$); **IR** υ_{max} (neat) / cm^{-1} 3078, 3027, 2978, 2928, 2856, 1641, 1491, 1439. **HRMS** data could not be obtained.

Synthesis of 3-(4-chlorophenyl)propanal 309d

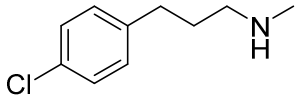


A stirred solution of alkene **308d** (550 mg, 3.30 mmol) in DCM (17 mL) was cooled to -78 °C and oxygen was bubbled through the solution for 5 min. Ozone was bubbled through the RM for 20 min (colour change observed from colourless to bright blue). Oxygen was then bubbled through the mixture for a further 5 min after which triphenylphosphine (912 mg, 3.47 mmol) was added. The reaction was stirred at -78 °C for 10 mins and the starch iodine test showed no

peroxides were present. The RM was concentrated *in vacuo*. Purification by column chromatography 10% diethyl ether in hexane afforded the *title compound* (481 mg, 2.85 mmol, 87%) as a colourless oil. The data was in accordance with the literature.[77]

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 9.84 (1H, t, *J* = 1.2, C*H*O), 7.32 – 7.26 (2H, m, 2 × ArC*H*), 7.16 (2H, d, *J* = 8.2, 2 × ArC*H*), 2.96 (2H, t, *J* = 7.5, ArCH_2), 2.83 – 2.78 (2H, m, CH_2CHO); **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 201.0 (*C*HO), 138.8 (C_q), 132.1 (C_q), 129.7 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 45.1 (*C*H_2CHO), 27.4 (Ar*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3028, 2929, 2894, 2725, 1720, 1492, 1447, 1408. **HRMS** data could not be obtained.

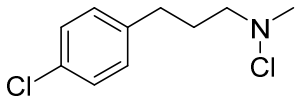
Synthesis of [3-(4-chlorophenyl)propyl](methyl)amine 310d



General procedure A was followed, using aldehyde **309d** (300 mg, 1.78 mmol), $MeNH_2$ (8 M solution in EtOH, 500 µL) and $NaBH_4$ (101 mg, 2.67mmol). Purification by SCX cartridge, afforded the *title compound* (288 mg, 1.57 mmol, 88%) as a yellow oil no further purification was required. The data was in accordance with the literature.[77]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.30 – 7.22 (2H, m, 2 × ArC*H*), 7.17 – 7.10 (2H, m, 2 × ArC*H*), 2.69 – 2.60 (2H, m, ArCH_2), 2.45 (3H, s, CH_3), 2.16 – 1.96 (2H, m, NHCH_2), 1.90 – 1.76 (2H, m, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 140.5 (C_q), 131.5 (C_q), 129.7 (2 × Ar*C*H), 128.5 (2 Ar*C*H), 51.3 (Ar*C*H_2), 36.3 (*C*H_3), 32.9 (NH*C*H_2), 31.2 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3025, 2933, 2857, 2793, 1632, 1538, 1490, 1383; **HRMS (ESI$^+$)**: $C_{10}H_{15}ClN$ $[M + H]^+$: calculated 184.0888, found 184.0892, Δ = -2.4 ppm.

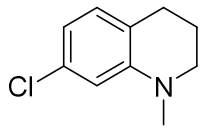
Synthesis of *N*-chloro[3-(4-chlorophenyl)propyl]methylamine 311d



General procedure C was followed, using amine **310d** (200 mg, 1.09 mmol) and NCS (182 mg, 1.36 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (160 mg, 0.73 mmol, 67%) as a colourless oil. The data was in accordance with the literature.[77]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.25 (2H, d, *J* = 8.3, 2 × ArC*H*), 7.12 (2H, d, *J* = 8.3, 2 × ArC*H*), 2.92 (3H, s, CH_3), 2.85 (2H, t, *J* = 6.8, CH_2NCl), 2.64 (2H, t, *J* = 7.6, ArCH_2), 1.98 – 1.90 (2H, m, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 140.1 (C_q), 131.6 (C_q), 129.8 (2 × Ar*C*H), 128.5 (2 × Ar*C*H), 65.0 (*C*H_2NCl), 53.1 (*C*H_3), 32.0 (Ar*C*H_2), 29.6 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 2950, 2866, 1491, 1455, 1437, 1407, 1365, 1129. **HRMS** data could not be obtained.

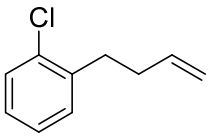
Synthesis of 7-chloro-1-methyl-1,2,3,4-tetrahydroquinoline 320



General Procedure D was followed, using chloroamine **311d** (100 mg, 0.46 mmol), $MeSO_3H$ (300 µL, 4.40 mmol) and $FeSO_4.7H_2O$ (13 mg, 0.046 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (37 mg, 0.20 mmol, 42%) as a colourless oil. The data was in accordance with the literature.[77]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.83 (1H, d, *J* = 7.8, ArC*H*), 6.56 – 6.49 (2H, m, 2 × ArC*H*), 3.25 – 3.19 (2H, m, NCH_3CH_2), 2.86 (3H, s, CH_3), 2.70 (2H, t, *J* = 6.4, ArCH_2), 1.99 – 1.90 (2H, m, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 147.5 (C_q), 132.5 (C_q), 129.5 (Ar*C*H), 121.0 (C_q), 115.5 (Ar*C*H), 110.5 (Ar*C*H), 50.9 (NCH_3CH_2), 38.9 (*C*H_3), 27.3 (Ar*C*H_2), 22.2 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3022, 2929, 2890, 2840, 1599, 1564, 1502, 1466; **HRMS** (ESI^+): $C_{10}H_{13}{}^{35}ClN$ $[M+H]^+$: calculated 182.0731, found 182.0723. **HRMS** data could not be obtained.

Synthesis of 1-(but-3-en-1-yl)-2-chlorobenzene 308e



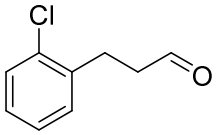
Step i) To a stirred solution of 2-chlorobenzyl alcohol (1.30 g, 9.12 mmol) in DCM (23 mL) at 0 °C was added Et_3N (1.40 mL, 10.0 mmol) then MsCl (780 µL, 10.0 mmol) was added dropwise and the RM was stirred at 0 °C for 2 h. The RM was quenched with saturated aqueous $NaHCO_3$. The two phases were separated and the aqueous phase was extracted with DCM (2

× 60 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford the desired crude mesylate as a yellow oil.

Step ii) The crude oil was flushed with N_2 in a round bottom flask and THF (23 mL) was added. The solution was cooled to 0 °C and allylmagnesium bromide (2.0 M in THF, 9.10 mL, 18.2 mmol) was added dropwise. The RM was stirred at 0 °C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl. The phases were separated and the aqueous phase was extracted using EtOAc (3 × 60 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. Purification by column chromatography with 10% EtOAc in hexane afforded the *title compound* (940 mg, 5.64 mmol, 62%) as a colourless oil. The NMR data is in accordance with the literature.[124]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.33 (1H, m, ArC*H*), 7.17 (3H, m ArC*H*), 5.95 – 5.80 (1H, m, C*H*CH_2), 5.11 – 4.96 (2H, m, CHC*H*$_2$), 2.86 – 2.79 (2H, m, ArC*H*$_2$), 2.42 – 2.33 (2H, m, C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 139.4 (C_q), 137.8 (C*H*CH_2), 134.0 (C_q), 130.4 (ArC*H*), 129.5 (Ar*C*H), 127.3 (Ar*C*H), 126.7 (Ar*C*H), 115.2 (CH*C*H_2), 33.7 (Ar*C*H_2), 33.1 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3075, 2999, 2978, 2931, 1640, 1572, 1473, 1442. **HRMS** data could not be obtained.

Synthesis of 3-(2-chlorophenyl)propanal 309e

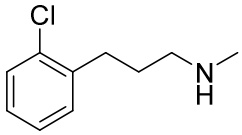


A stirred solution of alkene **308e** (550 mg, 3.30 mmol) in DCM (17 mL) was cooled to -78 °C and oxygen was bubbled through the solution for 5 min. Ozone was bubbled through the reaction mixture for 20 min (colour change observed from colourless to bright blue). Oxygen was then bubbled through the mixture for a further 5 min after which triphenylphosphine (912 mg, 3.47 mmol) was added. The reaction was stirred at -78 °C for 10 min and the starch iodine test showed no peroxides were present. The RM was concentrated *in vacuo*. Purification by column chromatography 10% diethyl ether in hexane afforded the *title compound* (377 mg, 2.24 mmol, 68%) as a colourless oil. The NMR data is in accordance with the literature.[125]

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 9.86 (1H, t, *J* = 1.2, C*H*O), 7.37 – 7.33 (1H, m, ArC*H*), 7.31 – 7.26 (1H, m, ArC*H*), 7.25 – 7.17 (2H, m, 2 × ArC*H*), 3.10 (2H, t, *J* = 7.6, ArC*H*$_2$), 2.83 (2 H, td, *J* = 7.6, 1.2, C*H*$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 201.1 (*C*O), 138.0 (C_q), 133.9 (C_q),

130.5 (Ar*C*H), 129.7 (Ar*C*H), 127.9 (Ar*C*H), 127.0 (Ar*C*H), 43.5 (*C*H_2CHO), 26.2 (Ar*C*H_2); **IR** υ_{max} (neat) cm^{-1} 3069, 2935, 2896, 2823, 2723, 1722 (CO), 1474, 1444. **HRMS** data could not be obtained.

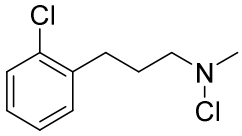
Synthesis of [3-(2-chlorophenyl)propyl](methyl)amine 310e



General procedure A was followed, using aldehyde **309e** (300 mg, 1.78 mmol), $MeNH_2$ (8M solution in EtOH, 500 µL) and $NaBH_4$ (101 mg, 2.67 mmol). Purification by SCX cartridge afforded the *title compound* (273 mg, 1.49 mmol, 72%) as a yellow oil no further purification was required. The ^{1}H NMR data is in accordance with the literature.[119]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.37 – 7.29 (1H, m, ArC*H*), 7.24 – 7.06 (3H, m, 3 × ArC*H*), 2.80 – 2.72 (2H,m, C*H*$_2$NH), 2.69 – 2.60 (2H, m, ArC*H*$_2$), 2.45 (3H, s, C*H*$_3$), 1.89 – 1.73 (2H, m, C*H*$_2$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 139.8 (*C*$_q$), 133.9 (*C*$_q$), 130.3 (Ar*C*H), 129.5 (Ar*C*H), 127.3 (Ar*C*H), 126.8 (Ar*C*H), 51.6 (Ar*C*H_2), 36.5 (*C*H_3), 31.4 (*C*H_2NH), 29.9 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 2948, 2871, 2791, 1567, 1451, 1379, 1304, 1263; **HRMS (ESI$^+$)**: $C_{10}H_{15}{}^{35}ClN$ $[M+H]^+$: calculated 184.0888, found 184.0885.

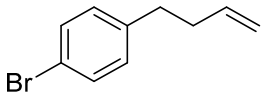
Synthesis of *N*-chloro[3-(2-chlorophenyl)propyl]methylamine 311e



General procedure C was followed, using amine **310e** (200 mg, 1.09 mmol) and NCS (182 mg, 1.36 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (141 mg, 0.65 mmol, 59%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.34 (1H, dd, *J* = 7.7, 1.5, ArC*H*), 7.25 – 7.12 (3H, m, 3 × ArC*H*), 2.95 (3H, s, C*H*$_3$), 2.92 (2H, t, *J* = 6.9, C*H*$_2$NCl), 2.80 (2H, t, *J* = 7.8, ArC*H*$_2$), 2.02 – 1.93 (2H, m, C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.3 (*C*$_q$), 134.0 (*C*$_q$), 130.5 (Ar*C*H), 129.5 (Ar*C*H), 127.4 (Ar*C*H), 126.8 (Ar*C*H), 65.3 (*C*H_2NCl), 53.0 (*C*H_3), 30.6 (Ar*C*H_2), 28.1 (*C*H_2); **IR** υ_{max} (neat) cm^{-1} 3063, 2952, 2868, 2844, 1473, 1439, 1365, 1274; **HRMS (ESI)$^+$**: $C_{10}H_{14}{}^{35}Cl_2N$ $[M+H]^+$: calculated 218.0498, found 218.0494.

Synthesis of 1-(but-3-en-1-yl)-4-bromobenzene 308f

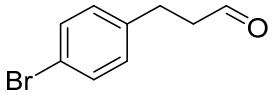


Step i) To a stirred solution of 4-bromobenzyl alcohol (3.00 g, 16.0 mmol) in DCM (40 mL) at 0 °C was added Et_3N (2.50 mL, 17.6 mmol) then MsCl (1.40 mL, 17.6 mmol) was added dropwise and the RM was stirred at 0 °C for 2 h. The RM was quenched with saturated aqueous $NaHCO_3$. The two phases were separated and the aqueous phase was extracted with DCM (2 × 60 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford the desired crude mesylate as a yellow oil.

Step ii) The crude oil was flushed with N_2 in a round bottom flask and THF (40 mL) was added. The solution was cooled to 0 °C and allylmagnesium bromide (2.0 M in THF, 16.1 mL, 32.1 mmol) was added dropwise. The RM was stirred at 0 °C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl. The phases were separated and the aqueous phase was extracted using EtOAc (3 × 60 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. Purification by column chromatography with 10% EtOAc in hexane afforded the *title compound* (2.31 g, 10.9 mmol, 68%) as a colourless oil. The data was in accordance with the literature.[126]

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.40 (2H, d, *J* = 8.4, 2 × ArC*H*), 7.06 (2H, d, *J* = 8.4, 2 × ArC*H*), 5.83 (1H, ddt, *J* = 17.0, 10.2, 6.6, C*H*=CH_2), 5.04 (1H, ddd, *J* = 17.0, 3.4, *trans*-CHC*H*$_2$), 4.99 (1H, dd, J = 10.2, 1.9, *cis*- CHC*H*$_2$), 2.71-2.61 (2H, m, ArC*H*$_2$), 2.35 (2H, app. dtt, J = 9.0, 7.8, 1.3, C*H*$_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 140.9 (C_q), 137.7 (*C*H=CH_2), 131.5 (2 × ArCH), 130.4 (2 × Ar*C*H), 119.7 (C_q), 115.4 (CH=*C*H$_2$), 35.4 (*C*H$_2$), 34.9 (Ar*C*H$_2$); **IR** υ_{max} (neat)/cm^{-1}: 3078, 3024, 2978, 2929, 2857, 1641, 1487, 1439. **HRMS** data could not be obtained.

Synthesis of 3-(4-bromophenyl)propanal 309f

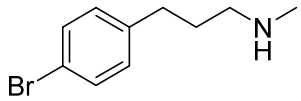


A stirred solution of alkene **308f** (2.00 g, 9.47 mmol) in DCM (47 mL) was cooled to -78 °C and oxygen was bubbled through the solution for 5 min. Ozone was bubbled through the reaction mixture for 20 min (colour change observed from colourless to bright blue). Oxygen was then bubbled through the mixture for a further 5 min after which triphenylphosphine (2.61

g, 9.94 mmol) was added. The reaction was stirred at -78 °C for 10 min and the starch iodine test showed no peroxides were present. The RM was concentrated *in vacuo*. Purification by column chromatography 10% diethyl ether in hexane afforded the *title compound* (1.60 g, 7.55 mmol, 80%) as a colourless oil. The data was in accordance with the literature.[127]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.80 (1H, *t*, *J* = 1.4, C*H*O), 7.40 (2H, d, *J* = 8.3, 2 × ArC*H*), 7.07 (2H, d, *J* = 8.3, 2 × ArC*H*), 2.90 (2H, t, *J* = 7.4, ArCH_2), 2.78 – 2.74 (2H, m, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 201.1 (*C*O), 139.5 (C_q), 131.8 (2 × Ar*C*H), 130.2 (2 × Ar*C*H), 120.2 (C_q), 45.1 (*C*H_2), 27.6 (Ar*C*H_2); **IR** υ_{max} (neat)/cm^{-1}: 2930, 2823, 2724, 1719 (C=O), 1591, 1487, 1438, 1404. **HRMS** data could not be obtained.

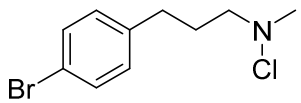
Synthesis of [3-(4-bromophenyl)propyl](methyl)amine 310f



General procedure A was followed, using aldehyde **309f** (1.60 g, 7.50 mmol), $MeNH_2$ (8M solution in EtOH, 4.70 mL) and $NaBH_4$ (426 mg, 11.3 mmol). Purification by SCX cartridge afforded the *title compound* (1.47 g, 6.47 mmol, 86%) as a yellow oil no further purification was required. The data was in accordance with the literature.[128]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.38 (2H, d, *J* = 8.3, 2 × ArC*H*), 7.05 (2H, d, *J* = 8.3, 2 × ArC*H*), 2.64-2.55 (4H, m, includes ArCH_2 and CH_2N), 2.41 (3H, s, NCH_3), 1.83-1.73 (2H, m, CH_2); **^{13}C NMR** (101 MHz, CDCl3) δ 141.1 (C_q), 131.5 (2 × Ar*C*H), 130.2 (2 × Ar*C*H), 119.6 (C_q), 51.3 (*C*H_2N), 36.4 (N*C*H_3), 33.1 (Ar*C*H_2), 31.2 (*C*H_2); **IR** υ_{max} (neat)/cm^{-1}: 3310 (NH), 3023, 2932, 2857, 2798, 1537, 1487, 1452; **HRMS (ESI)$^+$** : $C_{10}H_{15}{}^{79}BrN$ $[M+H]^+$: calculated 228.0382, found 228.0376.

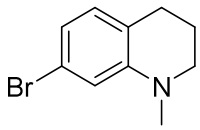
Synthesis of [3-(4-bromophenyl)propyl](chloro)methylamine 311f



General procedure C was followed, using [3-(4-bromophenyl)propyl](methyl)amine **310f** (300 mg, 1.32 mmol) and NCS (220 mg, 1.65 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (260 mg, 0.99 mmol, 75%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.43 – 7.37 (2H, m, 2 × ArC*H*), 7.10 – 7.04 (2H, m, 2 × ArC*H*), 2.93 (3H, s, CH_3), 2.85 (2H, t, *J* = 6.9, CH_2NCl), 2.64 (2H, t, *J* = 7.6, ArCH_2), 2.00 – 1.88 (2H, m, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 140.6 (C_q), 131.5 (2 × Ar*C*H), 130.2 (2 × Ar*C*H), 119.7 (C_q), 64.9 (*C*H_2NCl), 53.1 (*C*H_3), 32.1 (Ar*C*H_2), 29.6 (*C*H_2); **IR** υ_{max} (neat) cm^{-1} 2991, 2949, 2919, 2864, 1487, 1455, 1437, 1403; **HRMS (ESI$^+$)**: $C_{10}H_{14}{}^{79}Br^{35}ClN$ [M + H]$^+$ calculated 261.9992, found 261.9989, Δ = +1.0 ppm.

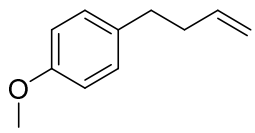
Synthesis of 7-bromo-1-methyl-1,2,3,4-tetrahydroquinoline 322



General Procedure D was followed, using [3-(4-bromophenyl)propyl](chloro)methylamine **311f** (100 mg, 0.38 mmol), $MeSO_3H$ (250 µL, 3.80 mmol) and $FeSO_4.7H_2O$ (11 mg, 0.038 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (62 mg, 0.27 mmol, 72%) as a colourless oil. The NMR data is in accordance with literature.[129]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.78 (1H, d, *J* = 7.7, ArC*H*), 6.70 – 6.65 (2H, m, 2 × ArC*H*), 3.26 – 3.18 (2H, m, CH_2NMe), 2.86 (3H, s, CH_3), 2.68 (2H, t, *J* = 6.4, ArCH_2), 2.00 – 1.88 (2H, m, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 147.7 (C_q), 129.8 (Ar*C*H), 121.5 (C_q), 120.6 (C_q), 118.5 (Ar*C*H), 113.2 (Ar*C*H), 50.9 (*C*H_2NMe), 38.9 (*C*H_3), 27.4 (Ar*C*H_2), 22.1 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3015, 2928, 2886, 2837, 1593, 1557, 1497, 1464; **HRMS (ESI$^+$)**: $C_{10}H_{13}{}^{79}Br^{35}ClN$ [M + H]$^+$ calculated 226.1583, found 226.1583, Δ = 0 ppm.

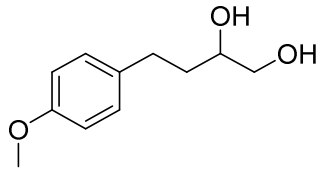
Synthesis of 1-(but-3-en-1-yl)-4-methoxybenzene 308g



Step i: To a stirred solution of 4-methoxybenzyl alcohol (1.00 g, 7.24 mmol) in DCM (18 mL) at 0 °C was added Et_3N (1.10 mL, 7.96 mmol) then MsCl (0.60 mL, 7.96 mmol) was added dropwise and the RM was stirred at 0 °C for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The two phases were separated, and the aqueous phase was extracted with DCM (2 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to afford the desired crude mesylate as a yellow oil.

Step ii: The crude oil was flushed with N_2 in a round bottom flask and THF (18 mL) was added. The solution was cooled to 0 °C and allylmagnesium bromide (2.0 M in THF, 7.25 mL, 14.48 mmol) was added dropwise. The RM was stirred at 0 °C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with EtOAc (3 × 100 mL), the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (744 mg, 4.59 mmol, 63%) as a colourless oil. The NMR data is in accordance with literature.[117] **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.10 (2H, d, *J* = 8.4, 2 × ArC*H*), 6.83 (2H, d, *J* = 8.5, 2 × ArC*H*), 5.90 – 5.80 (1H, m, *CH*), 5.05 – 4.95 (2H, m, CHCH_2), 3.78 (3H, s, CH_3), 2.65 (2H, t, *J* = 7.8 ArCH_2), 2.37 – 2.31 (2H, m, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 157.8 (C_q), 138.2 (*C*H), 134.0 (C_q), 129.3 (2 × Ar*C*H), 114.8 (*C*H_2CH), 113.7 (2 × Ar*C*H), 55.3 (*C*H_3), 35.8 (*C*H_2), 34.5 (Ar*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3075, 3031, 2997, 2931 1639, 1611, 1583, 1510. **HRMS** data could not be obtained.

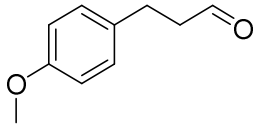
Synthesis of 4-(4-methoxyphenyl)butane-1,2-diol 315



To a stirred solution of alkene **308g** (500 mg, 3.08 mmol) in acetone/water (10:1, 15 mL) was added NMO (542 mg, 4.62 mmol) and potassium osmate (IV) dihydrate (57 mg, 0.15 mmol). The RM was stirred at RT for 48 h. The reaction was quenched using solid sodium hydrosulfate and the mixture was filtered through a pad of Celite, washed with acetone and concentrated *in vacuo*. Purification by column chromatography, eluting with 4% MeOH in DCM afforded the *title compound* (604 mg, 3.08 mmol, 76%) as a white solid. The NMR data was in accordance with the literature.[130]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.16 – 7.13 (2H, m, 2 × ArC*H*), 6.89 – 6.83 (2H, m, 2 × ArC*H*), 3.81 (3H, s, CH_3), 3.77 – 3.65 (2H, m, CH_2OH), 3.53 – 3.45 (1H, m, C*H*OH), 2.81 – 2.59 (2H, m, ArCH_2), 1.85 – 1.72 (2H, m, ArCH$_2$CH_2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 157.9 (C_q), 133.7 (C_q), 129.3 (2 × ArC*H*), 113.9 (2 × ArC*H*), 71.5 (*C*H_2OH), 66.9 (*C*HOH), 55.3 (*C*H_3), 34.9 (*C*H_2), 30.9 (Ar*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3317 (br. OH), 3003, 2922, 2857, 1610, 1510, 1453, 1419. **HRMS** data could not be obtained.

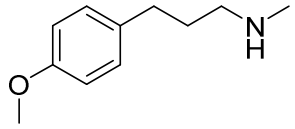
Synthesis of 3-(4-methoxyphenyl)propanal 316



To a stirred solution of diol **315** (400 mg, 2.04 mmol) in H_2O/MeOH (10:1, 10 mL) was added sodium periodate (654 mg, 3.06 mmol). The RM was stirred at RT for 2 h. The RM was diluted with brine and extracted with DCM (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to afford the *title compound* (330 mg, 2.01 mmol, 99%) as a colourless oil without further purification being required. The NMR data is in accordance with the literature.[131]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.81 (1H, t, *J* = 1.4, C*H*O), 7.11 (2H, d, *J* = 8.6, ArC*H*), 6.83 (2H, d, *J* = 8.6, ArC*H*), 3.79 (3H, s, CH_3), 2.91 (2H, t, *J* = 7.4, ArCH_2), 2.77 – 2.72 (2H, m, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 201.8 (*C*O), 158.1 (C_q), 132.3 (C_q), 129.2 (2 × Ar*C*H), 114.0 (2 × Ar*C*H), 55.3 (*C*H_3), 45.5 (*C*H_2), 27.3 (Ar*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3031, 2996, 2934, 2834, 1719, 1611, 1510, 1463. **HRMS** data could not be obtained.

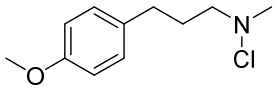
Synthesis of [3-(4-methoxyphenyl)propyl](methyl)amine 317



General procedure A was followed, using aldehyde **316** (300 mg, 1.83 mmol), $MeNH_2$ (8 M solution in EtOH, 300 µL, 1.3 eq.) and $NaBH_4$ (83 mg, 2.20 mmol). Purification by SCX cartridge afforded the *title compound* (303 mg, 1.69 mmol, 92%) as a yellow oil. The NMR data was in accordance with the literature.[132]

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.10 (2H, d, *J* = 8.6, 2 × ArC*H*), 6.85 – 6.80 (2H, m, 2 × ArC*H*), 3.78 (3H, s, OCH_3), 2.65 – 2.57 (4H, m, includes ArCH_2 and CH_2NH), 2.44 (3H, s, CH_3), 1.85 – 1.80 (2H, m, CH_2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 157.8 (C_q), 133.9 (C_q), 129.2 (2 × Ar*C*H), 113.8 (2 × Ar*C*H), 55.3 (O*C*H_3), 51.2 (*C*H_2NH), 36.0 (N*C*H_3), 32.6 (Ar*C*H_2), 31.2 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3040, 2996, 2933, 2855, 2799, 1611, 1510, 1463; **HRMS (ESI$^+$)**: $C_{11}H_{18}NO$ $[M + H]^+$: calculated 180.1383, found 180.1383, Δ = + 0.2 ppm.

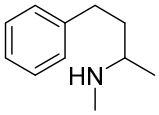
Synthesis of chloro[3-(4-methoxyphenyl)propyl]methylamine 317



Following a modified procedure by Zhong *et al*,[80] to a stirred solution of the amine **316** (200 mg, 1.12 mmol) and *tert*-butanol (28 µL, 0.28 mmol) in MTBE (6 mL) at 0 °C, was added acetic acid (65 µL, 1.12 mmol) and sodium hypochlorite (0.75 M, 1.5 mL, 1.12 mmol) dropwise. The reaction mixture was then stirred at 0 °C for 2 h. The phases were separated and the etheral phase was washed with H_2O (10 mL) then brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (157 mg, 0.73 mmol, 66%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.06 – 7.01 (2H, m, 2 × ArC*H*), 6.78 – 6.73 (2H, m, 2 × ArC*H*), 3.72 (3H, s, OCH_3), 2.85 (3H, s, CH_3), 2.83 (2H, t, *J* = 6.9, CH_2N), 2.58 (2H, t, *J* = 7.6, ArCH_2), 1.91 – 1.81 (2H, m, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 157.8 (C_q), 133.7 (C_q), 129.3 (2 × Ar*C*H), 113.8 (2 × Ar*C*H), 65.2 (Ar*C*H_2), 55.3 (O*C*H_3), 53.0 (*C*H_3), 31.8 (*C*H_2N), 29.9 (*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 2994, 2955, 2870, 2835, 1611, 1583, 1511, 1457. **HRMS** data could not be obtained.

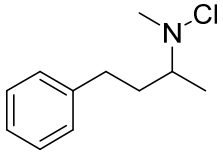
Synthesis of *N*-methyl-1-phenoxypropan-2-amine 328



General procedure B was followed, using ketone **327** (0.50 g, 3.37 mmol), $MeNH_2$ (8 M solution in EtOH, 8.00 mL, 26.0 mmol), $Ti(OiPr)_4$ (2.00 mL, 6.75 mmol) and $NaBH_4$ (255 mg, 6.25 mmol). Purification by SCX cartridge afforded the *title compound* (300 mg, 1.84 mmol, 55%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.32 – 7.24 (2H, m, 2 × ArC*H*), 7.22 – 7.14 (3H, m, 3 × ArC*H*), 2.72 – 2.50 (3H, m, includes ArCH_2 and NC*H*), 2.40 (3H, s, NCH_3), 1.84 – 1.72 (1H, m, CH_2), 1.68 – 1.54 (1H, m, CH_2), 1.09 (3H, d, *J* = 6.2, CHCH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 142.4 (C_q), 128.3 (2 × Ar*C*H), 128.2 (2 × Ar*C*H), 125.7 (Ar*C*H), 54.4 (*C*H), 38.5 (Ar*C*H_2), 33.8 (N*C*H_3), 32.3 (*C*H_2) 19.9(CH*C*H_3) ; **IR** ν_{max} (neat)/cm^{-1}: 3304, 3062, 2930, 2857, 2792, 1541, 1495, 1453; **HRMS** (ESI$^+$):$C_{11}H_{18}N$ $[M + H]^+$: calculated 164.1434, found 164.1432, Δ = - 1.2 ppm.

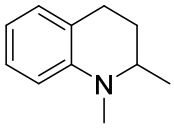
Synthesis of [3-(4-bromophenyl)propyl](chloro)methylamine 329



General procedure C was followed, using [3-(4-bromophenyl)propyl](methyl)amine **328** (200 mg, 1.23 mmol) and NCS (204 mg, 1.53 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (176 mg, 0.99 mmol, 72%) as a colourless oil. The data was in accordance with the literature.[76]

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.31 – 7.26 (2H, m, 2 × ArC*H*), 7.23 – 7.16 (3H, m, 3 × ArC*H*), 2.93 – 2.84 (4H, m, includes NCH_3 and C*H*), 2.73 – 2.66 (2H, m, Ar*C*H_2), 1.98 (1H, m, CH_2) 1.73 – 1.63 (1H, m, CH_2), 1.16 (3H, d, *J* = 6.3, CHCH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 142.1 (C_q), 128.4 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 125.8 (Ar*C*H), 64.5 (*C*H), 48.1 (N*C*H_3), 36.3 (Ar*C*H_2), 32.3 (*C*H_2) 14.2 (CH*C*H_3) ; **IR** ν_{max} (neat)/cm^{-1}: 3026, 2970, 2951, 2865, 1605, 1496, 1453, 1442; **HRMS** (ESI$^+$):$C_{11}H_{17}{}^{35}ClN$ $[M + H]^+$: calculated 198.1044, found 198.1038, Δ = - 3.0 ppm.

Synthesis of 7-bromo-1-methyl-1,2,3,4-tetrahydroquinoline 329

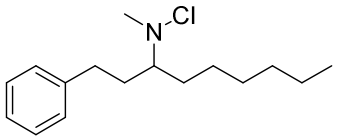


General Procedure D was followed, using [3-(4-bromophenyl)propyl](chloro)methylamine **330** (100 mg, 0.50 mmol), $MeSO_3H$ (330 µL, 5.10 mmol) and $FeSO_4.7H_2O$ (14 mg, 0.051 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (65 mg, 0.40 mmol, 79%) as a colourless oil. The NMR data is in accordance with literature.[76]

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.13 (1H, t, *J* = 7.7, ArC*H*), 7.02 (1H, d, *J* = 7.3, ArC*H*), 6.64 (1H, t, *J* = 7.3, ArC*H*), 6.60 (1H, d, *J* = 8.2, ArC*H*), 3.52 – 3.44 (1H, m, C*H*), 2.94 (3H, s, NCH_3), 2.93 – 2.84 (1H, m, Ar*C*H_2), 2.75 – 2.72 (1H, m, ArCH_2) 2.07 – 1.99 (1H, m, CH_2), 1.84 – 1.76 (1H, m, CH_2), 1.18 (3H, d, *J* = 6.5, CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 145.4 (C_q), 128.5 (Ar*C*H), 127.1 (Ar*C*H), 122.1 (C_q), 115.4 (Ar*C*H), 110.6 (Ar*C*H), 53.8 (*C*H), 37.0 (N*C*H_3), 28.1 (*C*H_2), 23.8 (Ar*C*H_2) 17.6 (CH*C*H_3) ; **IR** ν_{max} (neat)/cm^{-1}: 3068, 3021, 2962,

2925, 2843, 2790, 1603, 1575; **HRMS** (ESI^+):$C_{11}H_{16}N$ $[M + H]^+$: calculated 162.1277, found 162.1273, Δ = - 2.5 ppm.

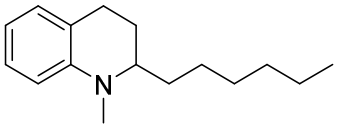
Synthesis of [3-(4-bromophenyl)propyl](chloro)methylamine 329



General procedure C was followed, using [3-(4-bromophenyl)propyl](methyl)amine **328** (300 mg, 1.32 mmol) and NCS (220 mg, 1.65 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (260 mg, 0.99 mmol, 75%) as a colourless oil. The data was in accordance with the literature.[76]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.33 – 7.26 (2H, m, 2 × ArC*H*), 7.24 – 7.16 (3H, m, 3 × ArC*H*), 2.89 (3H, s, CH_3), 2.79 – 2.61 (3H, m, includes ArCH_2 and C*H*), 2.01 – 1.89 (1H, m, *C*H_2), 1.81 – 1.65 (2H, m, includes CH_2 and C_aH_2) 1.51 – 1.38 (1H, m, C_aH_2), 1.37 – 1.23 (6H, m, includes C_bH_2 and C_cH_2), 0.91 (3H, t, *J* = 6.9, CH_3) ; **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 142.9 (C_q), 128.5 (4 × Ar*C*H), 125.8 (Ar*C*H), 58.9 (*C*H), 35.5 (Ar*C*H_2), 33.7 (C_aH_2), 32.3 (ArCH_2*C*H_2), 32.2 (*C*H_2), 25.5 (*C*H_2), 22.8 (*C*H_2), 14.2 (*C*H_3) ; **IR** ν_{max} (neat)/cm^{-1}: 3062, 3026, 2926, 2856, 2788, 1603, 1495, 1454; **HRMS** (ESI^+):$C_{15}H_{26}{}^{35}ClN$ $[M + H]^+$: calculated 254.1670, found 254.1674, Δ = 1.8 ppm.

Synthesis of 7-bromo-1-methyl-1,2,3,4-tetrahydroquinoline 329

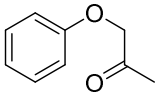


General Procedure D was followed, using [3-(4-bromophenyl)propyl](chloro)methylamine **330** (100 mg, 0.39 mmol), $MeSO_3H$ (260 µL, 3.90 mmol) and $FeSO_4.7H_2O$ (11 mg, 0.039 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (45 mg, 0.21 mmol, 53%) as a colourless oil. The NMR data is in accordance with literature.[76]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.07 (1H, t, *J* = 7.7, ArC*H*), 6.96 (1H, d, *J* = 7.3, ArC*H*), 6.57 (1H, t, *J* = 7.3, ArC*H*), 6.51 (1H, d, *J* = 8.2, ArC*H*), 3.29 – 3.17 (1H, m, C*H*), 2.92 (3H, s, CH_3), 2.86 – 2.73 (1H, m, Ar*C*H_2), 2.71 – 2.58 (1H, m, ArCH_2) 1.94 – 1.82 (2H, m, CH_2),

1.65 – 1.53 (1H, m, C_aH_2), 1.44 – 1.19 (7H, m, includes C_aH_2, C_bH_2, C_cH_2 and C_dH_2) 0.98 – 0.81 (3H, m, CH_3) ; **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 145.7 (C_q), 128.8 (Ar*C*H), 127.2 (Ar*C*H), 122.0 (C_q), 115.3 (Ar*C*H), 110.5 (Ar*C*H), 59.1 (*C*H), 38.1 (N*C*H$_3$), 32.2 (Ar*C*H$_2$), 31.3 (C_aH_2), 25.9 (*C*H$_2$), 24.6 (ArCH$_2$*C*H$_2$), 23.7 (*C*H$_2$), 22.8 (*C*H$_2$), 14.2 (*C*H$_3$) ; **IR** ν_{max} (neat)/cm^{-1}: 3020, 2926, 2856, 1602, 1575, 1498, 1479, 1455; **HRMS** (ESI$^+$):$C_{15}H_{24}N$ [M + H]$^+$: calculated 218.1903, found 218.1903, Δ = 0.0 ppm.

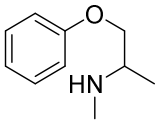
Synthesis of 1-phenoxypropan-2-one 337



General procedure G was followed, using phenol (1.50 g, 15.9 mmol), potassium carbonate (2.20 g, 15.9 mmol) and chloroacetone (1.40 mL, 17.5 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (1.56 g, 10.4 mmol, 65%) as a colourless oil. The NMR data was in accordance with the literature.[133]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.36 – 7.30 (2H, m, 2 × ArC*H*), 7.03 (1H, t, *J* = 7.4 Hz, ArC*H*), 6.91 (2H, d, *J* = 7.8 Hz, 2 × ArC*H*), 4.56 (2H, s, C*H*$_2$), 2.31 (3H, s, C*H*$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 206.0 (C_q), 157.7 (C_q), 129.7 (2 × Ar*C*H), 121.8 (Ar*C*H), 114.5 (2 × Ar*C*H), 73.1 (*C*H$_2$), 26.7 (*C*H$_3$); **IR** υ_{max} (neat) / cm^{-1}3063, 3043, 2903, 1720, 1589, 1493, 1432, 1357. **HRMS** data could not be obtained.

Synthesis of *N*-methyl-1-phenoxypropan-2-amine 338

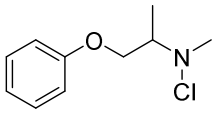


General procedure B was followed, using ketone **337** (1.50 g, 9.99 mmol), $MeNH_2$ (8 M solution in EtOH, 12.0 mL, 94.0 mmol), $Ti(OiPr)_4$ (5.90 mL, 20.0 mmol) and $NaBH_4$ (567 mg, 15.0 mmol). Purification by SCX cartridge afforded the *title compound* (743mg, 4.50 mmol, 45%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.34 – 7.26 (2H, m, 2 × ArC*H*), 7.00 – 6.89 (3H, m, 3 × ArC*H*), 3.88 (2H, m, C*H*$_2$), 3.02 (1H, m, C*H*), 2.50 (3H, s, NHC*H*$_3$), 1.16 (3H, d, *J* = 6.5, CHC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 158.9 (C_q), 129.5 (2 × Ar*C*H), 120.8 (Ar*C*H), 114.6 (2 × Ar*C*H), 71.6 (*C*H$_2$), 54.1 (*C*H), 33.8 (NH*C*H$_3$), 16.8 (*C*H$_3$); **IR** υ_{max} (neat) / cm^{-1}

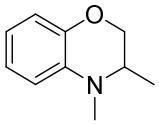
3062, 3039, 2968, 2930, 2872, 2795, 1676, 1599; **HRMS (ESI$^+$)**: $C_{10}H_{16}NO$ $[M + H]^+$: calculated 166.1226, found 166.1220, Δ = 3.8 ppm.

Synthesis of *N*-chloro-*N*-methyl-1-phenoxypropan-2-amine 339

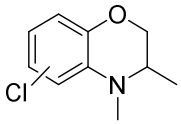


Following a modified procedure by Zhong *et al*, to a stirred solution of the amine **338** (300 mg, 1.82 mmol) and *tert*-butanol (44 µL, 0.46 mmol) in MTBE (9 mL) at 0 °C, was added acetic acid (105 µL, 1.82 mmol) and sodium hypochlorite (0.75 M, 2.45 mL, 1.82 mmol) dropwise simultaneously. The reaction mixture was stirred at 0 °C for 2 h. the organic phases were separated and the top phase was washed with H_2O (20 mL) then brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (250 mg, 1.25 mmol, 69%) as a pale yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.37 – 7.24 (2H, m, 2 × ArC*H*), 7.05 – 6.91 (3H, m, 3 × ArC*H*), 4.24 (1 H, dd, *J* = 9.8, 5.6, CH_2), 3.93 (1H, dd, *J* = 9.8, 5.6, CH_2), 3.46 – 3.30 (1H, m, C*H*), 3.04 (3H, s, NHCH_3), 1.32 (3H, d, *J* = 6.5, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 158.6 (C_q), 129.5 (2 × Ar*C*H), 121.0 (Ar*C*H), 114.7 (2 × Ar*C*H), 69.9 (*C*H_2), 64.7 (*C*H), 49.5 (NH*C*H_3), 13.1 (*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3063, 3040, 2960, 2940, 2872, 1599, 1585, 1495; **HRMS** data could not be obtained.

Synthesis of 3,4-dimethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine 340



340a



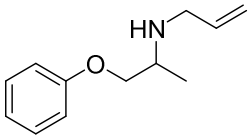
340b

General Procedure D was followed, using chloroamine **339** (150 mg, 0.75 mmol), $MeSO_3H$ (490 µL, 7.50 mmol) and $FeSO_4.7H_2O$ (21 mg, 0.075 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (25 mg, 0.15 mmol, 20%) as a colourless oil. The NMR data is in accordance with the literature.[134]

^{1}H NMR signals for the major product reported **340a** (300 MHz, $CDCl_3$) δ ppm 6.92 – 6.84 (1H, m, ArC*H*), 6.83 – 6.77 (1H, m, ArC*H*), 6.69 – 6.61 (2H, m, 2 × ArC*H*), 4.21 (1H, dd, *J* = 10.5, 2.6, CH_2), 4.04 (1H, dd, *J* = 10.5, 2.6, CH_2), 3.44 – 3.33 (1H, m, C*H*), 2.89 (3H, s, NCH_3), 1.22 (3H, d, *J* = 6.5, CH_3); **^{13}C NMR** signals for the major product reported **340a** (101 MHz,

$CDCl_3$) δ ppm 144.2 (C_q), 126.6 (C_q), 121.8 (Ar*C*H), 116.6 (Ar*C*H), 116.4 (Ar*C*H), 111.7 (Ar*C*H), 69.2 (*C*H_2), 52.1 (*C*H), 36.1 (N*C*H_3), 14.1 (*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3065, 3039, 2972, 2929, 2875, 2820, 1604, 1499; **LCMS (ESI$^+$)**: $C_{10}H_{14}NO$ $[M+H]^+$; calculated 164.22, measured 164.41. **HRMS** data could not be obtained.

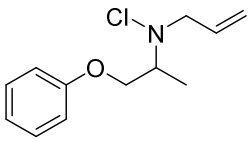
Synthesis of *N*-(1-phenoxypropan-2-yl)prop-2-en-1-amine 341b



General procedure B was followed, using ketone **337** (500mg, 3.33 mmol), allylamine (2.50 mL, 33.3 mmol), $Ti(OiPr)_4$ (2.00 mL, 6.66 mmol) and $NaBH_4$ (189 mg, 5.00 mmol). Purification by SCX cartridge afforded the *title compound* (705mg, 3.69 mmol, 83%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) ppm δ 7.35 – 7.25 (2H, m, 2 × Ar*CH*), 7.00 – 6.89 (3H, m, 3 × Ar*CH*), 5.95 (1H, ddt, *J* = 16.2, 10.2, 6.0, *CH*=CH_2), 5.36 – 5.04 (2H, m, CH=*CH*$_2$), 3.98 – 3.80 (2H, m, *CH*$_2$), 3.48 – 3.24 (2H, m, *CH*$_2$), 3.22 – 3.09 (1H, m, *CH*NH), 1.19 (3H, d, *J* = 6.5, *CH*$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 158.9 (C_q), 137.0 (*C*H=CH_2), 129.5 (2 × Ar*C*H), 120.8 (Ar*C*H), 115.9 (CH=*C*H_2), 114.6 (2 × Ar*C*H), 72.0 (O*C*H_2), 51.8 (*C*HNH), 49.8 (NH*C*H_2), 17.4 (*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3071, 3039, 2975, 2926, 2872, 2833, 1587, 1496; **HRMS (ESI$^+$)**: $C_{12}H_{18}NO$ $[M + H]^+$: calculated 192.1383, found 192.1384, Δ = -0.6 ppm.

Synthesis of *N*-chloro-*N*-(1-phenoxypropan-2-yl)prop-2-en-1-amine 342b

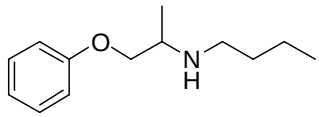


General Procedure C was followed, using amine **341b** (200 mg, 1.05 mmol) and NCS (140 mg, 1.05 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (123 mg, 0.54 mmol, 52%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.35 – 7.27 (2H,m, 2 × Ar*CH*), 7.02 – 6.91 (3H, m, 3 × Ar*CH*), 5.97 (1H, ddt, *J* = 16.7, 10.2, 6.4, *CH*=CH_2), 5.39 – 5.21 (2H, m, CH=*CH*$_2$), 4.29 (1H, dd, *J* = 9.8, 5.9, *CH*$_2$), 3.95 (1H, dd, *J* = 9.8, 5.9, *CH*$_2$), 3.85 – 3.66 (2H, m, *CH*$_2$), 3.62 – 3.44 (1H, m, *CH*NCl), 1.33 (3H, d, *J* = 6.4, *CH*$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 158.6 (C_q), 134.1 (*C*H=CH_2), 129.5 (2 × Ar*C*H), 121.0 (Ar*C*H), 119.0 (CH=*C*H_2), 114.7 (2 × Ar*C*H), 69.9 (O*C*H_2), 63.7 (*C*HNCl), 62.2 (NCl*C*H_2), 13.3 (*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3078, 3040, 2979,

2935, 2881, 1598, 1587, 1495; **HRMS (ESI$^+$)**: $C_{12}H_{16}{}^{35}ClNNaO$ [M + Na] $^+$: calculated 248.0813, found 248.0810, Δ = 1.3 ppm.

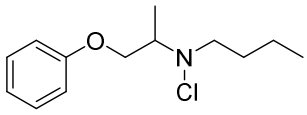
Synthesis of *N*-(1-phenoxypropan-2-yl)butan-1-amine 341c



General procedure B was followed, using ketone **337** (500mg, 3.33 mmol), butylamine (2.20 mL, 16.7 mmol), $Ti(OiPr)_4$ (2.00 mL, 6.66 mmol) and $NaBH_4$ (189 mg, 5.00 mmol). Purification by column chromatography eluting with 90% EtOAc in hexane, afforded the *title compound* (500mg, 2.41 mmol, 72%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.34 – 7.25 (2H, m, 2 × ArC*H*), 7.00 – 6.88 (3H, m, 2 × ArC*H*), 3.96 – 3.80 (2H, m, CH_2), 3.17 – 3.04 (1H, m, C*H*), 2.79 – 2.59 (2H, m, CH_2), 1.58 – 1.30 (4H, m, 2 × CH_2), 1.18 (3H, d, *J* = 6.5, CHCH_3), 0.99 – 0.91 (3H, m, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 158.9 (C_q), 129.5 (2 × Ar*C*H), 120.8 (Ar*C*H), 114.6 (2 × Ar*C*H), 72.0 (O*C*H_2), 52.5 (*C*H), 47.1 (NH*C*H_2), 32.6 (NHCH$_2$*C*H_2), 20.6 (*C*H_2CH$_3$), 17.5 (*C*H_3CH), 14.3 (*C*H_3CH$_2$); **IR** υ_{max} (neat) / cm^{-1} 3062, 3039, 2958, 2927, 2871, 1667, 1599, 1495; **HRMS (ESI$^+$)**: $C_{13}H_{22}NO$ [M + H] $^+$: calculated 208.1696, found 208.1695, Δ = 0.5 ppm.

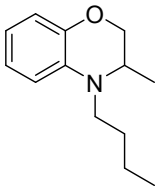
Synthesis of *N*-chloro-*N*-(1-phenoxypropan-2-yl)butan-1-amine 342c



General Procedure C was followed, using amine **341c** (100 mg, 0.52 mmol) and NCS (69 mg, 0.52 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (100 mg, 0.41 mmol, 80%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.35 – 7.25 (2H, m, 2 × ArC*H*), 7.03 – 6.89 (3H, m, 3 × ArC*H*), 4.32 – 4.25 (1H, m, CH_2), 4.00 – 3.91 (1H, m, CH_2), 3.54 – 3.41 (1H, m, C*H*), 3.18 – 2.96 (2H, m, CH_2), 1.67 (2H, dt, *J* = 14.6, 7.2, CH_2), 1.48 – 1.34 (2H, m, CH_2), 1.32 (3H, d, *J* = 6.5, CH_3), 1.01 – 0.91 (3H, m, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 158.7 (C_q), 129.5 (2 × Ar*C*H), 120.9 (Ar*C*H), 114.7 (2 × Ar*C*H), 70.0 (O*C*H_2), 63.3 (*C*H), 60.7 (NCl*C*H_2), 30.3 (NClCH$_2$*C*H_2), 20.0 (*C*H_2CH$_3$), 14.0 (C*H*$_3$CH), 13.3 (*C*H_3CH$_2$); **IR** υ_{max} (neat) / cm^{-1} 3063, 3040, 2958, 2934, 2872, 1599, 1587, 1495; **HRMS (ESI$^+$)**: $C_{13}H_{21}{}^{35}ClNO$ [M + H] $^+$: calculated 242.1306, found 242.1302, Δ = 1.8 ppm.

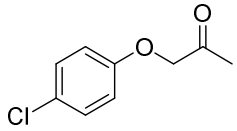
Synthesis of 4-butyl-3-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine 344



General Procedure D was followed, using chloroamine **342c** (100 mg, 0.41 mmol), $MeSO_3H$ (270 µL, 4.10 mmol) and $FeSO_4.7H_2O$ (11 mg, 0.04 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (13 mg, 0.06 mmol, 15%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.93 – 6.77 (2H, m, 2 × ArC*H*), 6.68 – 6.55 (2H, m, 2 × ArC*H*), 4.13 – 3.97 (2H, m, OCH_2), 3.54 – 3.41 (1H, m, C*H*), 3.40 – 3.27 (1H, m, CH_2), 3.21 – 3.04 (1H, m, CH_2), 1.71 – 1.52 (2H, m, CH_2), 1.47 – 1.32 (2H, m, CH_2), 1.22 (3H, d, *J* = 6.5, CHCH_3), 1.04 – 0.94 (3H, m, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 143.4 (C_q), 134.5 (C_q), 121.8 (Ar*C*H), 116.3 (Ar*C*H), 116.1 (Ar*C*H), 111.8 (Ar*C*H), 69.1 (O*C*H_2), 50.9 (*C*H), 48.7 (N*C*H_2), 29.5 (*C*H_2), 20.4 (*C*H_2), 15.9 (*C*H_3), 14.0 (CH*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3065, 3039, 2958, 2930, 2872, 1605, 1578, 1502; **HRMS (ESI$^+$)**: $C_{13}H_{20}NO$ $[M + H]^+$: calculated 206.1539, found 206.1538, Δ = +0.7 ppm.

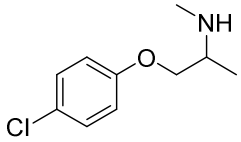
Synthesis of 1-(4-chlorophenoxy)propan-2-one 347a



General procedure G was followed, using 4-chlorophenol (1.50 g, 11.7 mmol), potassium carbonate (1.61 g, 11.7 mmol) and chloroacetone (1.02 mL, 12.8mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (1.26 g, 6.82 mmol, 59%) as a colourless oil. The NMR data is in accordance with the literature.[135]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.28 (2H, d, *J*= 9.0, 2 × ArC*H*), 6.84 (2H, d, *J* = 9.0, 2 ArC*H*), 4.54 (2H, s, CH_2), 2.30 (3H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 205.1 (*C*O), 156.4 (C_q), 129.6 (2 × Ar*C*H), 126.8 (C_q), 115.9 (2 × Ar*C*H), 73.3 (*C*H_2), 26.6 (*C*H_3); **IR** $\upsilon_{ma\times}$ (neat) / cm^{-1} 3099, 3071, 3011, 2914, 2839, 1721, 1584, 1488. **HRMS** data could not be obtained.

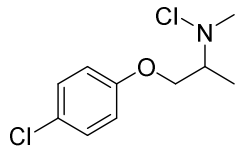
Synthesis of 1-(4-chlorophenoxy)-*N*-methylpropan-2-amine 348a



General procedure B was followed, using ketone **347a** (1.00g, 5.42 mmol), $MeNH_2$ (8 M solution in EtOH, 7.00 mL, 56.0 mmol), $Ti(OiPr)_4$ (3.20 mL, 10.8 mmol) and $NaBH_4$ (308 mg, 8.13 mmol). Purification by SCX cartridge afforded the *title compound* (986mg, 4.94 mmol, 91%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.23 (2H, d, *J* = 9.0, 2 × ArC*H*), 6.85 (2H, d, *J* = 9.0, 2 × ArC*H*), 3.97 – 3.84 (2H, m, OCH_2), 3.19 – 3.03 (1H, m, C*H*), 2.53 (3H, s, NCH_3), 1.22 (3H, d, *J* = 6.5, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 156.9 (C_q), 129.4 (2 × Ar*C*H), 116.9 (C_q), 116.0 (2 × Ar*C*H), 70.0 (O*C*H_2), 53.9, 32.0, 14.9 (CH*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3061, 2962, 2930, 2872, 1596, 1493, 1380, 1274; **HRMS (ESI$^+$)**: $C_{10}H_{15}{}^{35}ClNO$ $[M + H]^+$: calculated 200.0837, found 200.0835, Δ = 1.0 ppm.

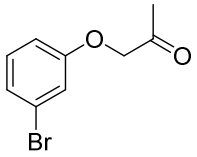
Synthesis of *N*-chloro-1-(4-chlorophenoxy)-*N*-methylpropan-2-amine 345a



General Procedure C was followed, using amine **348a** (300 mg, 1.50 mmol) and NCS (220 mg, 1.65 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (200 mg, 0.85 mmol, 57%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.27 – 7.22 (2H, m, 2 × ArC*H*), 6.93 – 6.77 (2H, m, 2 × ArC*H*), 4.20 (1H, dd, *J* = 9.8, 5.8, CH_2), 3.89 (1H, dd, *J* = 9.8, 5.8, CH_2), 3.42 – 3.29 (1H, m, C*H*), 3.03 (3H, s, NCH_3), 1.30 (3H, d, *J* = 6.5, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 156.1 (C_q), 129.5 (2 × Ar*C*H), 125.9 (C_q), 116.1 (2 × Ar*C*H), 110.2 (C_q), 70.3 (O*C*H_2), 64.6 (*C*H), 49.5 (N*C*H_3), 12.9 (*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 2979, 2935, 2882, 1596, 1491, 1471, 1285, 1241; **HRMS (ESI$^+$)**: $C_{10}H_{14}{}^{35}Cl_2NO$ $[M + H]^+$: calculated 234.0447, found 234.0442, Δ = 2.0 ppm.

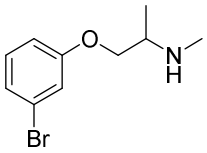
Synthesis of 1-(3-bromophenoxy)propan-2-one 347b



General procedure G was followed, using 3-bromophenol (1.50 g, 8.67 mmol), potassium carbonate (1.20 g, 8.67 mmol) and chloroacetone (0.76 mL, 9.54mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (1.35 g, 5.89 mmol, 68%) as a colourless oil. The NMR data is in accordance with the literature.[135]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.23 – 7.12 (2H, m, 2 × ArC*H*), 7.10 – 7.05 (1H, m, ArC*H*), 6.88 – 6.81 (1H, m, ArC*H*), 4.55 (2H, s, CH_2), 2.30 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 204.8 (C_q), 158.5 (C_q), 130.8 (Ar*C*H), 125.0 (Ar*C*H), 123.0 (C_q), 118.1 (Ar*C*H), 113.4 (Ar*C*H), 73.1 (*C*H_2), 26.6 (*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3066, 2970, 2919, 2897, 1732, 2589, 1575, 1475. **HRMS** data could not be obtained.

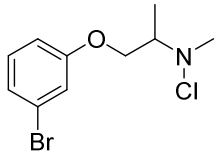
Synthesis of 1-(3-bromophenoxy)-*N*-methylpropan-2-amine 348b



General procedure B was followed, using ketone **347b** (1.00g, 4.37 mmol), $MeNH_2$ (8 M solution in EtOH, 5.50 mL, 44 mmol), $Ti(OiPr)_4$ (2.50 mL, 8.74 mmol) and $NaBH_4$ (248 mg, 6.56 mmol). Purification by SCX cartridge afforded the *title compound* (983mg, 4.04 mmol, 92%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.20 – 6.98 (3H, m, 3 × ArC*H*), 6.88 – 6.82 (1H, m, ArC*H*), 3.93 – 3.73 (2H, m, CH_2), 3.06 – 2.97 (1H, m, C*H*), 2.49 (3H, s, NCH_3), 1.17 (3H, d, *J* = 6.5, CH_3);**^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 159.6 (C_q), 130.6 (Ar*C*H), 124.0 (Ar*C*H), 122.8 (C_q), 117.9 (Ar*C*H), 113.5 (Ar*C*H), 71.7 (O*C*H_2), 53.9 (*C*H), 33.6 (N*C*H_3), 16.5 (*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3065, 2970, 2930, 2876, 2795, 1671, 1574, 1473; **HRMS (ESI$^+$)**: $C_{10}H_{15}BrNO$ $[M + H]^+$: calculated 244.0332, found 244.0329, Δ = 1.0 ppm.

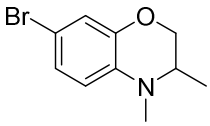
Synthesis of 1-(3-bromophenoxy)-*N*-chloro-*N*-methylpropan-2-amine 345b



General Procedure C was followed, using amine **348b** (300 mg, 1.23 mmol) and NCS (180 mg, 1.35 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (214 mg, 0.77 mmol, 62%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.20 – 7.08 (3H, m, 3 × ArC*H*), 6.88 (1H, ddd, *J* = 7.9, 2.4, 1.5, ArC*H*), 4.24 – 4.17 (1H, m, CH_2), 3.94 – 3.88 (1H, m, CH_2), 3.43 – 3.29 (1H, m, C*H*), 3.03 (3H, s, NCH_3), 1.31 (3H, d, *J* = 6.5, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 159.4 (C_q), 130.6 (Ar*C*H), 124.1 (Ar*C*H), 122.8 (C_q), 118.0 (Ar*C*H), 113.7 (Ar*C*H), 70.1 (OCH_2), 64.5 (*C*H), 49.5 (NCH_3), 12.9 (CH_3); **IR** υ_{max} (neat) / cm^{-1} 3067, 2979, 2937, 2884, 2791, 1589, 1574, 1470; **HRMS (ESI$^+$)**: $C_{10}H_{13}Br^{35}ClNNaO$ [M + Na] $^+$: calculated 299.9761, found 299.9762, Δ = -0.1 ppm.

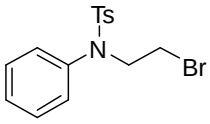
Synthesis of 7-bromo-3,4-dimethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine 350



General Procedure D was followed, using chloroamine **345b** (100 mg, 0.36 mmol), $MeSO_3H$ (240 µL, 3.60 mmol) and $FeSO_4.7H_2O$ (10 mg, 0.036 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (10 mg, 0.040 mmol, 11%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.90 – 6.80 (2H, m, 2 × ArC*H*), 6.38 (1H, d, *J* = 8.4, ArC*H*), 4.09 (1H, dd, *J* = 10.5, 2.5, CH_2), 3.93 (1H, dd, *J* = 10.6, 3.2, CH_2), 3.33 – 3.21 (1H, m, C*H*), 2.76 (3H, s, CH_3), 1.10 (3H, d, *J* = 6.5, CH_3); **IR** υ_{max} (neat) / cm^{-1} 3429, 3074, 2975. 2934, 2877, 2809, 1588, 1467; **HRMS** data could not be obtained.

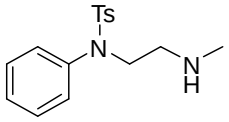
Synthesis of *N*-(2-bromoethyl)-4-methyl-*N*-phenylbenzenesulfonamide 356



Following a modified procedure by Barluenga *et al*, a stirred solution of 4-methyl-*N*-phenylbenzenesulfonamide (500 mg, 2.02 mmol), K_2CO_3 (558 mg, 4.04 mmol) and dibromoethane (350 µL, 4.04 mmol) in MeCN (4 mL) was heated at reflux for 16 h.[136] The RM was cooled to RT. The RM was partitioned between ethyl acetate (30 mL) and water (40 mL). The two phases were separated and the aqueous phase was re-extracted with EtOAc (2 × 30 mL). The organic extracts were combined and dried over $MgSO_4$. Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* x (476 mg, 1.34 mmol, 66%) as an amorphous white solid

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.51 (2H, d, *J* = 8.3, 2 × ArC*H*), 7.39 – 7.32 (3H, m, 3 × ArC*H*), 7.27 (2H, d, *J* = 8.0, 2 × ArC*H*), 7.13 – 7.04 (2H, m, 2 × ArC*H*), 3.90 (2H, t, *J* = 7.5, CH_2), 3.42 (2H, t, *J* = 7.5, CH_2), 2.45 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 143.8 (C_q), 139.0 (C_q), 135.2 (C_q), 129.5 (2 × Ar*C*H), 129.3 (2 × Ar*C*H), 129.0 (2 × Ar*C*H), 128.4 (Ar*C*H), 127.7 (2 × Ar*C*H), 52.6 (N*C*H_2), 28.8 (*C*H_2Br), 21.6 (*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3065, 3979, 2963, 2923, 2870, 1593, 1490, 1453; **HRMS (ESI$^+$)**: $C_{15}H_{16}BrNNaO_2S$ [M + Na] $^+$: calculated 375.9977, found 375.9973, Δ = 1.0 ppm.

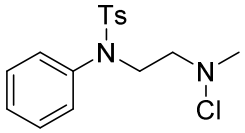
Synthesis of 4-methyl-*N*-(2-(methylamino)ethyl)-*N*-phenylbenzenesulfonamide 357



A stirred solution of alkylbromo compound **356** (200 mg, 0.57 mmol) in $MeNH_2$ (8M in EtOH, 2.8 mL) was heated at 100 °C in a sealed tube for 16 h. The RM was concentrated *in vacuo* to afforded *title compound* (174 mg, 0.57 mmol, quant) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.43 (2H, d, *J* = 8.3, 2 × ArC*H*), 7.28 – 7.22 (3H, m, 3 × ArC*H*), 7.19 (2H, d, *J* = 8.3, 2 × ArC*H*), 7.10 – 7.02 (2H, m, 2 × ArC*H*), 3.87 (2H, t, *J* = 5.9, CH_2), 2.95 (2H, t, *J* = 5.9, CH_2), 2.62 (3H, s, CH_3), 2.36 (3H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 144.4 (C_q), 138.8 (C_q), 133.6 (C_q), 129.8 (2 × Ar*C*H), 129.5 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 128.7 (Ar*C*H), 128.1 (2 × Ar*C*H), 48.1 (N*C*H_2), 47.5 (*C*HNH), 33.8 (N*C*H_3), 21.6 (*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 2962, 2920, 2875, 2859, 2719, 2423, 1593, 1490; **HRMS (ESI$^+$)**: $C_{16}H_{21}N_2O_2S$ [M + H] $^+$: calculated 305.1318, found 305.1315, Δ = 0.3 ppm.

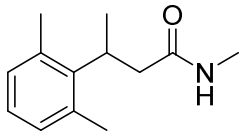
Synthesis of *N*-(2-(chloro(methyl)amino)ethyl)-4-methyl-*N*-phenylbenzenesulfonamide 358



Following a modified procedure by Zhong *et al*, to a stirred solution of the amine **357** (100 mg, 0.33 mmol) and *tert*-butanol (10 µL, 0.08 mmol) in MTBE (2 mL) at 0 °C, was added acetic acid (20 µL, 0.33 mmol) and sodium hypochlorite (0.75 M, 0.50 mL, 0.33 mmol) dropwise simultaneously. The reaction mixture was stirred at 0 °C for 2 h. the organic phases were separated and the top phase was washed with H_2O (20 mL) then brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (68 mg, 0.20 mmol, 61%) as a pale yellow oil.

^{1}H NMR (501 MHz, $CDCl_3$) δ ppm 7.53 – 7.47 (4H, m, 4 × Ar*C*H), 7.46 – 7.41 (1H, m, Ar*C*H), 7.34 – 7.29 (1H, m, ArC*H*), 7.08 (1H, m, Ar*C*H), 6.99 – 6.93 (2H, m, 2 × Ar*C*H), 3.85 – 3.74 (2H, m, CH_2), 3.06 – 3.00 (2H, m, NClCH_2), 2.90 (3H, s, CH_3), 2.44 (3H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 144.4 (C_q) 132.3 (C_q), 130.4 (C_q), 129.6 (2 × Ar*C*H), 129.5 (2 × Ar*C*H), 129.1 (2 × Ar*C*H), 128.8 (Ar*C*H_3), 127.8 (2 × Ar*C*H), 64.1 (NCl*C*H_2), 53.3 (N*C*H_2), 49.4 (NCl*C*H_3), 22.7 (Ar*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3059, 3024, 2998, 2967, 2916, 1597, 1487, 1439; **HRMS (ESI$^+$)**: $C_{16}H_{19}{}^{35}ClN_2NaO_2S$ [M + Na]$^+$: calculated 361.0748, found 361.0747, Δ = 0.1 ppm.

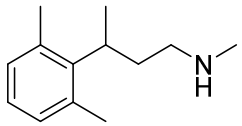
Synthesis of 3-(2,6-dimethylphenyl)-N-methylbutanamide 363



General procedure F was followed, using crotonamide (700 mg, 7.06 mmol), 2,6-dimethylboronic acid (1.32 g, 8.83 mmol, 1.25 eq.), [Rh(cod)Cl_2] (35 mg, 0.071 mmol) and Et_3N (990 µL, 7.06 mmol). Purification by column chromatography, eluting with 50% EtOAc in hexane afforded the *title compound* (990 mg, 4.82 mmol, 68%) colourless solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.00 – 6.97 (3H, m, 3 × ArC*H*), 5.21 (1H, s, N*H*), 3.93 – 3.81 (1H, m, C*H*CH_2), 2.73 (3H, d, *J* = 4.9, NHCH_3), 2.56 (2H, d, *J* = 7.3, CH_2CO), 2.40 (6H, s, 2 × ArCH_3), 1.36 (3H, d, *J* = 7.3, CHCH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 172.8 (*C*O), 143.1 (*ArC*H), 136.5 (C_q), 130.3 (C_q), 128.5 (C_q) 126.1 (2 × Ar*C*H), 42.4 (CH_2), 31.9 (*C*HCH_2), 26.3

(NH*C*H$_3$), 21.6 (Ar*C*H$_3$), 19.1 (CH*C*H$_3$); **IR** υ_{max} (neat) / cm^{-1} 3091, 2961, 2938, 2912, 2877, 1636, 1569, 1510; **HRMS (ESI$^+$)**: $C_{13}H_{20}NO$ $[M + H]^+$: calculated 206.1539, found 206.1547, Δ = +3.4 ppm.

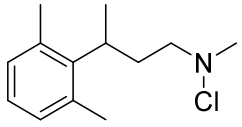
Synthesis of [3-(2,6-dimethylphenyl)butyl](methyl)amine 364



Following a modified procedure by Williamson *et al*,[97] to a stirred suspension of $LiAlH_4$ (443 mg, 11.7 mmol) in THF (12 mL) at 0 ºC was added a solution of amide **363** (600 mg, 2.92 mmol) in THF (3 mL) dropwise. The reaction mi×ture was stirred for 5 min at 0 ºC before warming to RT and then heated at reflux for 3 h. The reaction mixture was cooled to 0 ºC and the reaction was quenched through the dropwise addition of H_2O (12.0 eq), aqueous NaOH (2 M, 2.0 eq) and H_2O (2.0 eq). The resulting slurry was dried over Na_2SO_4, filtered through a pad of Celite and was washed with EtOAc. Concentration *in vacuo* afforded the *title compound* (452 mg, 2.36 mmol, 81%) as a colourless oil

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.99 – 6.95 (3H, m, 3 × ArC*H*), 3.39 – 3.26 (1H, m, C*H*CH$_2$), 2.69 – 2.26 (10H, m, includes 2 × ArC*H*$_3$, NHC*H*$_3$ and C*H*$_2$), 2.11 – 1.83 (2H, m, C*H*$_2$NH), 1.37 – 1.28 (3H, d, *J* = 7.36, CHC*H*$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 142.5 (Ar*C*H), 136.2 (*C*$_q$), 128.3 (*C*$_q$) 125.7 (3 × Ar*C*H), 50.9 (N*C*H$_2$), 36.2 (*C*H$_2$), 35.2 (N*C*H$_3$), 33.0 (*C*H), 21.6 (2 × Ar*C*H$_3$), 19.1 (CH*C*H$_3$); **IR** υ_{max} (neat) / cm^{-1} 3017, 2930, 2871, 2790, 1466, 1369, 1309, 1256; **HRMS (ESI$^+$)**: $C_{13}H_{21}NNa$ $[M + Na]^+$: calculated 214.1566, found 214.1564, Δ = +1.0 ppm.

Synthesis of *N*-chloro[3-(2,6-dimethylphenyl)butyl]methylamine 365

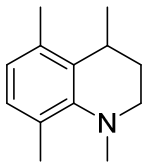


General procedure C was followed, using amine **364** (200 mg, 1.05 mmol) and NCS (175 mg, 1.31 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (200 mg, 0.89 mmol, 85%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.98 (3H, d, *J* = 4.2, 3 × ArC*H*), 3.47 – 3.31 (1H, m, C*H*), 2.87 (3H, s, NC*H*$_3$), 2.80 – 2.69 (2H, m, NC*H*$_2$), 2.49 – 2.30 (6H, br.s, 2 × ArC*H*$_3$), 2.22 – 1.95

(2H, m, CH_2), 1.37 – 1.27 (3H, m, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 142.1 (C_q), 136.4 (C_q), 130.4 (C_q), 128.1 (C_q), 125.6 (2 × Ar*C*H), 125.6, 64.9 (N*C*H_2), 53.2 (N*C*H_3), 33.7 (*C*H_2), 32.2 (*C*H), 21.6 (2 × Ar*C*H_3), 19.1 (*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3017, 2954, 2930, 1463, 1437, 1368, 1175, 1076; **HRMS (ESI)$^+$**: $C_{13}H_{21}{}^{35}ClN$ $[M+H]^+$: calculated 226.1357, found 226.1353, Δ = -1.8 ppm.

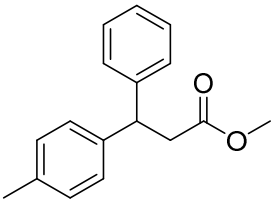
Synthesis of 1,4,5,8-tetramethyl-1,2,3,4-tetrahydroquinoline 366



General Procedure D was followed, using chloroamine **365** (100 mg, 0.44 mmol), $MeSO_3H$ (285 μL, 4.40 mmol) and $FeSO_4.7H_2O$ (12 mg, 0.44 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (27 mg, 0.14 mmol, 33%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.91 (1H, d, *J* = 7.6, ArC*H*), 6.70 (1H, d, *J* = 7.6, ArC*H*), 3.24 – 3.18 (2H, m, NCH_2), 3.12 – 3.02 (1H, m, C*H*), 2.71 (3H, s, NCH_3), 2.28 (3H, s, ArCH_3), 2.27 (3H, s, ArCH_3), 2.10 – 1.99 (1H, m, CHCH_2), 1.56 – 1.46 (1H, m, CHCH_2), 1.17 (3H, d, *J* = 7.0, CHCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 147.3 (C_q), 133.7 (C_q), 132.5 (C_q), 128.9 (Ar*C*H), 128.1 (C_q), 123.5 (Ar*C*H), 47.4 (N*C*H_2), 44.0 (N*C*H_3), 28.2 (*C*H), 25.1 (*C*H_2), 21.3 (CH*C*H_3), 19.2 (Ar*C*H_3), 19.0 (Ar*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 2929, 2864, 2787, 1737, 1578, 1460, 1397, 1370; **HRMS (ESI$^+$)**: $C_{13}H_{20}N$ $[M + H]^+$: calculated 190.1590, found 190.1593, Δ = +1.3 ppm.

Synthesis of methyl 3-(4-methylphenyl)-3-phenylpropanoate 391a

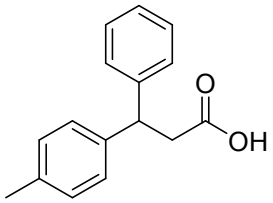


General procedure F was followed, using methyl *trans*-cinnamate (1.50 g, 9.25 mmol), *p*-tolylboronic acid (1.57 g, 11.6 mmol, 1.25 eq.), $[Rh(cod)Cl_2]$ (46 mg, 0.093 mmol) and Et_3N (1.30 mL, 9.25 mmol). Purification by column chromatography, eluting with 10% EtOAc in

hexane afforded the *title compound* (2.15 g, 8.44 mmol, 91%) pale yellow oil. The NMR data is in accordance with the literature.[137]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.31 – 7.16 (5H, m, 5 × ArC*H*), 7.12 – 7.07 (4H, m, 4 × ArC*H*), 4.52 (1H, t, *J* = 8.0, C*H*CH_2), 3.57 (3H, s, OCH_3), 3.04 (2H, d, *J* = 8.0, CHCH_2), 2.29 (3H, s, ArCH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 172.4 (*C*O), 143.7 (C_q), 140.5 (C_q), 136.1 (C_q), 129.3 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 127.6 (2 × Ar*C*H), 127.5 (2 × Ar*C*H), 126.5 (Ar*C*H), 51.7 (O*C*H_3), 46.6 (*C*HCH$_2$), 40.7 (CH*C*H_2), 21.0 (Ar*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3057, 3026, 2950, 2920, 1734 (CO), 1637, 1600, 1513; **HRMS (ESI$^+$)**: $C_{17}H_{19}O_2$ $[M + H]^+$: calculated 255.1380, found 255.1380, Δ = 0.0 ppm.

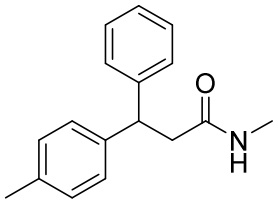
Synthesis of 3-(4-methylphenyl)-3-phenylpropanoic acid 392a



To a stirred solution of ester **391a** (2.00 g, 7.86 mmol) in MeOH (26 mL, 0.3 M) was added aqueous 2 M NaOH (26 mL, 0.3 M). The RM was then heated to reflux and stirred for 2 h. The RM was cooled to RT and the reaction was quenched with 4 M HCl to pH 7. The aqueous phase was extracted with EtOAc (50 mL × 3). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to afford the *title compound* (1.50 g, 6.24 mmol, 79%) as a colourless solid which was crystallized in 19 : 1 (EtOAc : hexane) to yield colourless micro-crystals. The NMR data is in accordance with the literature.[137]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.16– 6.96 (9H, m, 9 × ArC*H*), 4.35 (1H, t, *J* = 7.6, C*H*), 2.81 (2H, s, CH_2), 2.21 (3 H, s, ArCH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 177.0 (*C*O), 144.3 (C_q), 141.1 (C_q), 135.8 (C_q), 129.2 (2 × Ar*C*H), 128.5 (2 × Ar*C*H), 127.6 (2 × Ar*C*H), 127.5 (2 × Ar*C*H), 126.3 (Ar*C*H), 46.8 (*C*H), 41.7 (CH_2), 21.0 (CH_3); **IR** υ_{max} (neat) / cm^{-1} 3055, 3025, 3003, 2920, 2858, 1697, 1577, 1512; **HRMS (ESI$^+$)**: $C_{16}H_{15}Na_2O_2$ $[M + Na_2]^+$: calculated 285.0862, found 285.0867, Δ = +1.6 ppm.

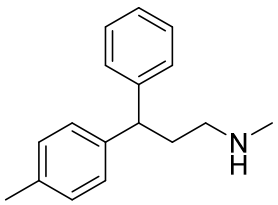
Synthesis of *N*-methyl-3-(4-methylphenyl)-3-phenylpropanamide 393a



General procedure E was followed, using acid **392a** (800 mg, 3.33 mmol), $NH_2Me.HCl$ (338 mg, 5.00 mmol), TBTU (1.71 g, 5.33 mmol) and DIPEA (1.72 mL, 13.3 mmol). Purification by column chromatography, eluting with 50-60% EtOAc in hexane, afforded the *title compound* (640 mg, 2.53 mmol, 78%) as a colourless solid which was crystallised from EtOAc to yield colourless crystals. The data is in accordance with the literature.[76]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.30 – 7.14 (5H, m, 5 × ArC*H*), 7.13 – 7.06 (4H, m, 4 × ArC*H*), 5.19 (1H, s, N*H*), 4.53 (1H, t, *J* = 7.8, C*H*), 2.86 (2H, d, *J* = 7.8, CH_2), 2.65 (3H, d, *J* = 4.9, NCH_3), 2.29 (3H, s, ArCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 171.8 (*C*O), 144.0 (C_q), 140.8 (C_q), 136.1 (C_q), 129.3 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 127.7 (2 × Ar*C*H), 127.6 (2 × Ar*C*H), 126.5 (Ar*C*H), 47.0 (*C*H), 43.4 (*C*H_2), 26.3 (N*C*H_3), 21.0 (Ar*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3271, 3097, 3061, 2966, 2929, 1635, 1566, 1512; **HRMS (ESI$^+$)**: $C_{17}H_{20}NO$ $[M + H]^+$: calculated 254.1539, found 254.1548, Δ = -3.4 ppm.

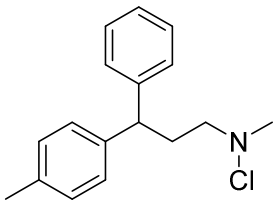
Synthesis of methyl[3-(4-methylphenyl)-3-phenylpropyl]amine 394



Following a modified procedure by Williamson *et al*,[97] to a stirred suspension of $LiAlH_4$ (299 mg, 7.88 mmol) in THF (8 mL) at 0 °C was added a solution of amide **393a** (500 mg, 1.97 mmol) in THF (2 mL) dropwise. The reaction mixture was stirred for 5 min at 0 °C before warming to RT and then heated at reflux for 3 h. The reaction mixture was cooled to 0 °C and the reaction was quenched through the dropwise addition of H_2O (12.0 eq.), aqueous NaOH (2 M, 2.0 eq.) and H_2O (2.0 eq.). The resulting slurry was dried over Na_2SO_4, filtered through a pad of Celite and was washed with EtOAc. Concentration *in vacuo* afforded the *title compound* (420 mg, 1.75 mmol, 89%) as a pale yellow oil. The data is in accordance with the literature.[76]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.31 – 7.20 (4H, m, 4 × ArC*H*), 7.19 – 7.05 (5H, m, 5 × ArC*H*), 3.97 (1H, t, *J* = 7.8, C*H*CH_2), 2.56 (2H, t, *J* = 7.3, CH_2NH), 2.39 (3H, s, NHCH_3), 2.30 (3H, s, ArCH_3), 2.26 – 2.14 (2H, m, CHCH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 145.0 (C_q), 141.7 (C_q), 135.7 (C_q), 129.2 (2 × Ar*C*H), 128.5 (2 × Ar*C*H), 127.7 (2 × Ar*C*H), 127.7 (2 × Ar*C*H), 126.1 (Ar*C*H), 50.4 (CH_2NH), 48.7 (*C*HCH_2), 36.3 (NH*C*H_3), 35.5 (*C*H_2), 21.0 (Ar*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3083, 3056, 2925, 2861, 2792, 1599, 1511, 1493; **HRMS (ESI$^+$)**: $C_{17}H_{21}NNa$ $[M + Na]^+$: calculated 262.1566, found 262.1568, Δ = -0.8 ppm.

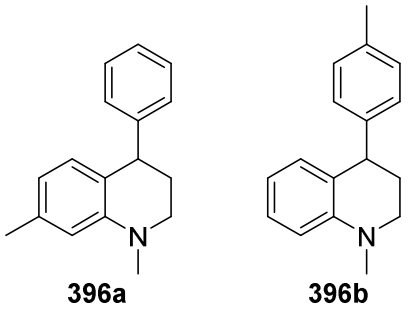
Synthesis of *N*-chloro(methyl)[3-(4-methylphenyl)-3-phenylpropyl]amine 388



General procedure C was followed, using amine **394** (200 mg, 0.84 mmol) and NCS (140 mg, 1.05 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (181 mg, 0.66 mmol, 79%) as a colourless oil. The data is in accordance with the literature.[76]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.30 – 7.22 (4H, m, 4 × ArC*H*), 7.19 – 7.06 (5H, m, 5 × ArC*H*), 4.03 (1H, t, *J* = 7.9, C*H*CH_2), 2.88 (3H, s, NCH_3), 2.83 – 2.77 (2H, m, CH_2N), 2.40 – 2.35 (2H, m, CHCH_2), 2.29 (3H, s, ArCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 144.7 (C_q), 141.4 (C_q), 135.8 (C_q), 129.2 (2 × Ar*C*H), 128.5 (2 × Ar*C*H), 127.8 (2 × Ar*C*H), 127.7 (2 × Ar*C*H), 126.2 (Ar*C*H), 64.3 (*C*H_2N), 53.2 (N*C*H_3), 47.7 (*C*H), 34.0 (CH*C*H_2), 21.0 (Ar*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3058, 3024, 2983, 2952, 2920, 1598, 1511, 1493; **HRMS (ESI$^+$)**: $C_{17}H_{21}{}^{35}ClN$ $[M + H]^+$: calculated 274.1357, found 274.1359, Δ = -0.2 ppm.

Synthesis of 1,7-dimethyl-4-phenyl-1,2,3,4-tetrahydroquinoline 396a and 396b



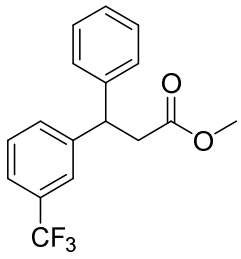
396a **396b**

10.4 : 1

General Procedure D was followed, using chloroamine 388 (100 mg, 0.37 mmol), $MeSO_3H$ (240 µL, 3.70 mmol) and $FeSO_4.7H_2O$ (10 mg, 0.037 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded an inseperable mixture of the regioisomeric *title compounds* (64 mg, 0.27 mmol, 73%) as a colourless oil. The data is in accordance with the literature.[76]

^{1}H NMR signals for the major product reported **396a** (400 MHz, $CDCl_3$) δ ppm 7.30 – 7.25 (2H, m, 2 × ArC*H*), 7.21 – 7.17 (1H, m, ArC*H*), 7.12 – 7.09 (2H, m, 2 × ArC*H*), 6.62 (1H, d, *J* = 7.6, ArC*H*), 6.49 (1H, s, ArC*H*), 6.39 (1H, d, *J* = 7.6, ArC*H*), 4.09 (1H, t, *J* = 6.2, C*H*CH_2), 3.23 – 3.11 (2H, m, NCH_2), 2.93 (3H, s, NCH_3), 2.29 (3H, s, ArCH_3), 2.26 – 2.19 (1H, m, CHCH_2), 2.12 – 2.02 (1H, m, CHCH_2); **^{13}C NMR** signals for the major product reported **396a** (101 MHz, $CDCl_3$) δ ppm 146.8 (2 × C_q), 137.2 (C_q), 129.8 (Ar*C*H), 128.7 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 126.1 (Ar*C*H), 122.1 (C_q), 117.1 (Ar*C*H), 111.8 (Ar*C*H), 48.7 (NCH_2), 43.2 (NCH_3), 39.3 (*C*HCH_2), 31.3 (CH*C*H_2), 21.7 (Ar*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3076, 3063, 2975, 2950, 1640, 1568, 1452, 1415; **HRMS (ESI$^+$)**: $C_{17}H_{20}N$ $[M + H]^+$: calculated 238.1590, found 238.1585, Δ = -2.1 ppm.

Synthesis of methyl 3-phenyl-3-[3-(trifluoromethyl)phenyl]propanoate 391b

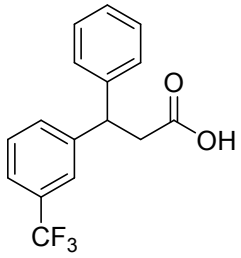


General procedure F was followed, using methyl *trans*-cinnamate (1.50 g, 9.25 mmol), 3-(trifluoromethyl)phenylboronic acid (2.20 g, 11.6 mmol, 1.25 eq.), $[Rh(cod)Cl_2]$ (46 mg, 0.093

mmol) and Et_3N (1.30 mL, 9.25 mmol). Purification by column chromatography, eluting with EtOAc in hexane afforded the *title compound* (2.74 g, 8.88 mmol, 96%) as a pale yellow oil. The data is in accordance with the literature.[76]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.52 – 7.36 (4H, m, 4 × ArC*H*), 7.34 – 7.18 (5H, m, 5 × ArC*H*), 4.62 (1H, t, *J* = 8.0, C*H*CH_2), 3.59 (3H, s, CH_3), 3.07 (2H, d, *J* = 8.0, CH_2CO); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.9 (*C*O), 144.4 (C_q), 142.5 (C_q), 131.2 (Ar*C*H), 130.9 (q, *J* = 32.1, C_qCF_3), 129.1 (Ar*C*H), 128.8 (2 × Ar*C*H), 127.6 (2 × Ar*C*H), 127.0 (Ar*C*H), 124.4 (q, *J* = 3.7, Ar*C*HC_qCF_3), 124.1 (q, *J* = 272.4, *C*F_3), 123.6 (q, *J* = 3.7, Ar*C*HC_qCF_3), 51.8 (*C*H_3), 46.8 (*C*H), 40.4 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3063, 3029, 2953, 2922, 1735 (CO), 1637, 1495, 1436; **HRMS (ESI$^+$)**: $C_{17}H_{15}F_3NaO_2$ $[M + Na]^+$: calculated 331.0916, found 331.0916, Δ = +0.1 ppm.

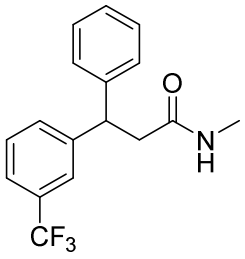
Synthesis of 3-phenyl-3-[3-(trifluoromethyl)phenyl]propanoic acid 392b



To a stirred solution of ester **391b** (2.00 g, 6.49 mmol) in MeOH (22 mL) was added aqueous 2 M NaOH (22 mL, 0.30 M). The RM was then heated to reflux and stirred for 2 h. The RM was cooled to RT and the reaction was quenched with addition of 4 M HCl until pH 7. The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Crystalisation from hexane : EtOAc (9:1) to to afford the *title compound* (1.40 g, 4.77 mmol, 73%) as a colourless crystalline solid. The data is in accordance with the literature.[76]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.58 – 7.36 (4H, m, 4 × ArC*H*), 7.35 – 7.17 (5H, m, 5 × ArC*H*), 4.59 (1H, t, *J* = 7.9, C*H*CH_2), 3.12 (2H, dd, *J* = 7.9, 2.0, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 176.5 (*C*O), 147.2 (C_q), 144.2 (C_q), 142.2 (C_q), 131.1 (Ar*C*H), 131.0 (q, *J* = 32.1, C_q), 129.2 (Ar*C*H), 128.9 (2 × Ar*C*H), 127.6 (2 × Ar*C*H), 127.1 (Ar*C*H), 124.4 (q, *J* = 3.8, Ar*C*HC_qCF_3), 124.1 (q, *J* = 272.3, *C*F_3), 123.7 (q, *J* = 3.8, Ar*C*HC_qCF_3), 46.5 (*C*H), 40.1 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3064(Br.OH), 3027, 2958, 2910, 1696, 1628, 1496, 1448; **HRMS (ESI$^+$)**: $C_{16}H_{13}F_3NaO_2$ $[M + Na]^+$: calculated 317.0760, found 317.0759, Δ = -0.2ppm.

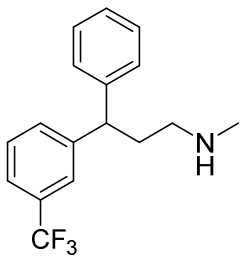
Synthesis of *N*-methyl-3-phenyl-3-[3-(trifluoromethyl)phenyl]propanamide 393b



General procedure E was followed, using acid **392b** (800 mg, 2.72 mmol), $NH_2Me.HCl$ (275 mg, 4.08 mmol), TBTU (1.40 g, 4.35 mmol) and DIPEA (1.90 mL, 10.9 mmol). Purification by column chromatography, eluting with 30-40% EtOAc in hexane, afforded the *title compound* (430 mg, 1.40 mmol, 34%) as a colourless oil. The data is in accordance with the literature.[76]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.57 – 7.34 (4H, m, 4 × ArC*H*), 7.34 – 7.12 (5H, m, 5 × ArC*H*), 5.27 (1H, s, N*H*), 4.68 (1H, t, *J* = 7.7, C*H*CH_2), 2.88 (2H, d, *J* = 7.8, C*H*$_2$CO), 2.67 (3H, d, *J* = 4.8, C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.0 (*C*O), 144.8 (C_q), 142.8 (C_q), 131.4 (Ar*C*H), 130.8 (q, *J* = 32.1, C_qCF_3), 129.0 (Ar*C*H), 128.8 (2 × Ar*C*H), 127.7 (2 × Ar*C*H), 126.9 (Ar*C*H), 124.2 (q, *J* = 3.8, Ar*C*HCCF_3), 124.1 (q, *J* = 272.4, *C*F_3), 123.5 (q, *J* = 3.7, Ar*C*HCCF_3), 47.0 (*C*H), 43.1 (*C*H_2), 26.3 (*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3296, 3088, 3066, 2942, 1642, 1562, 1494, 1446; **HRMS (ESI$^+$)**: $C_{17}H_{16}F_3NNaO$ $[M + Na]^+$: calculated 330.1076, found 330.1087, Δ = +3.3 ppm.

Synthesis of methyl({3-phenyl-3-[3-(trifluoromethyl)phenyl]propyl})amine 395

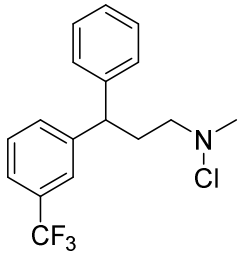


To a stirred solution of amide **393b** (310 mg, 1.01 mmol) in THF (5 mL) at 0 °C was added dropwise a solution of BH_3 (4 mL of a 1 M solution in THF, 4.0 eq.) dropwise. The reaction mi×ture was stirred at 0 °C for 15 min, then heated to reflux and stirred for 6 h. The reaction mixture was cooled to 0 °C and the reaction was quenched with 4 M NaOH (6 mL) dropwise. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by

SCX cartridge afforded the *title compound* (134 mg, 0.46 mmol, 45%) as a yellow oil. The data is in accordance with the literature.[76]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.50 (1H, s, ArC*H*), 7.46 – 7.34 (3H, m, 3 × ArC*H*), 7.33 – 7.16 (5H, m, 5 × ArC*H*), 4.09 (1H, t, *J* = 7.8, C*H*CH_2), 2.54 (2H, t, *J* = 7.3, C*H*$_2$NH), 2.39 (3H, s, C*H*$_3$), 2.31 – 2.21 (2H, m, CHC*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.6 (*C*$_q$), 143.4 (*C*$_q$), 131.2 (Ar*C*H), 130.7 (d, *J* = 32.0, *C*$_q$$CF_3$), 129.0 (Ar*C*H), 128.8 (2 × Ar*C*H), 127.9 (2 × Ar*C*H), 126.7 (Ar*C*H), 124.4 (q, *J* = 3.7, Ar*C*H*C*$_q$$CF_3$), 124.2 (q, *J* = 272.3, *C*F_3) 123.2 (q, *J* 3.8, Ar*C*H*C*$_q$$CF_3$), 49.7 (N*C*$H_2$), 48.6 (*C*H), 36.3 (N*C*H_3), 34.6 (*C*H_2) ; **IR** υ_{max} (neat) / cm^{-1} 3062,3029, 2936, 2850, 2797, 1599, 1493, 1473; **HRMS (ESI$^+$)**: $C_{17}H_{18}F_3NNa$ $[M + Na]^+$: calculated 294.1391, found 294.1492, Δ = -0.8 ppm.

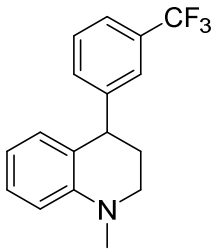
Synthesis of *N*-chloro(methyl){3-phenyl-3-[3-(trifluoromethyl)phenyl]propyl}amine 389



General procedure C was followed, using amine **395** (120 mg, 0.41 mmol) and NCS (68 mg, 0.51 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (110 mg, 0.34 mmol, 82%) as a colourless oil. The data is in accordance with the literature.[76]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.51 (1H, s, ArC*H*), 7.46 – 7.37 (3H, m, 3 × ArC*H*), 7.32 – 7.19 (5H, m, 5 × ArC*H*), 4.20 – 4.10 (1H, t, *J* = 7.9, C*H*), 2.88 (3H, s, C*H*$_3$), 2.78 (2H, t, *J* = 6.8, C*H*$_2$NCl), 2.46 – 2.36 (2H, m, CHC*H*$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.5 (*C*$_q$), 143.3 (*C*$_q$), 131.3 (Ar*C*H), 130.8 (q, *J* = 32.0, *C*$_q$$CF_3$), 129.0 (Ar*C*H), 128.8 (Ar*C*H), 127.9 (Ar*C*H), 126.7 (Ar*C*H), 124.6 (q, *J* = 3.8, Ar*C*H*C*CF_3), 124.2 (q, *J* = 272.4, *C*F_3). 123.3 (q, *J* = 3.8, Ar*C*H*C*CF_3), 63.7 (N*C*H_2), 53.2 (N*C*H_3), 47.7 (*C*H), 33.8 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3062, 3028, 2952, 2881, 1599, 1494, 1445, 1326; **HRMS (ESI$^+$)**: $C_{17}H_{18}{}^{35}ClF_3N$ $[M + H]^+$: calculated 328.1074, found 338.1069, Δ = -2.1 ppm.

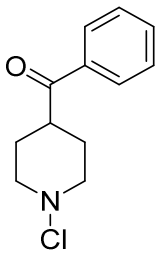
Synthesis of 1-methyl-4-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydroquinoline 397b



General procedure D was followed, using chloroamine **389** (100 mg, 0.31 mmol), $MeSO_3H$ (200 µL, 3.10 mmol) and $FeSO_4.7H_2O$ (9 mg, 0.031 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (69 mg, 0.24 mmol, 77%) as a colourless oil. The data is in accordance with the literature.[76]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.50 – 7.35 (3H, m, 3 × Ar*C*H), 7.25 (1H, d, *J* = 7.6, Ar*CH*), 7.18 – 7.10 (1H, m, Ar*CH*), 6.70 – 6.67 (2H, m, 2 × Ar*CH*), 6.57 (1H, td, *J* =7.3, 1.1, Ar*CH*), 4.24 – 4.15 (1H, m, C*H*CH_2), 3.31 – 3.07 (2H, m, C*H*$_2$N), 2.94 (3H, s, C*H*$_3$), 2.35 – 2.01 (2H, m, CHC*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 147.5 (*C*$_q$), 146.8 (*C*$_q$), 132.2 (Ar*C*H), 130.7 (q, *J* = 32.0, *C*$_q$$CF_3$), 129.8 (Ar*C*H), 128.8 (Ar*C*H), 128.0 (Ar*C*H), 125.3 (q, *J* = 3.8, Ar*C*HCCF_3), 124.3 (q, *J* = 272.3, *C*F_3), 123.8 (*C*$_q$), 123.1 (q, *J* = 3.8, Ar*C*HCCF_3), 116.5 (Ar*C*H), 111.3 (Ar*C*H), 48.4 (N*C*H_2), 43.4 (*C*HCH_2), 39.2 (*C*H_3), 31.1 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3066, 3026 2945, 2927, 1602, 1503, 1444, 1322; **HRMS (ESI$^+$)**: $C_{17}H_{17}F_3N$ $[M + H]^+$: calculated 292.1308, found 292.1313, Δ = -1.7ppm.

Synthesis of 4-benzoyl-1-chloropiperidine 401

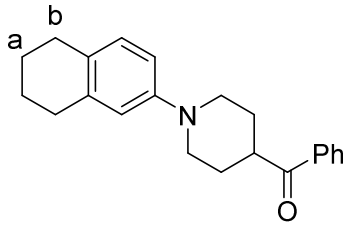


A solution of benzoyl piperidine HCl (1.00 g, 4.33 mmol) was dissolved in H_2O (10 mL) and basified to pH 9 using aqueous NaOH (2 M, 15 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* which afforded the crude amine. To a solution of the crude amine in DCM (22 mL) was added NCS (722 mg, 5.41 mmol) and the RM was stirred for 3 h at RT. Purification by

column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (790 mg, 3.53 mmol, 82%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.95 (2H, dd, *J* = 8.3, 1.1, 2 × ArC*H*), 7.64 – 7.58 (1H, m, ArC*H*), 7.51 (2H, t, *J* = 7.7, 2 × ArC*H*), 3.56 (2H, d, *J* = 9.5, NCH_2), 3.37 (1H, t, *J* = 10.7, C*H*), 3.11 – 3.00 (2H, m, NCH_2), 2.14 – 2.02 (2H, m, CHCH_2), 1.97 (2H, d, *J* = 14.1, CHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 201.5 (*C*O), 135.7 (C_q), 133.2 (Ar*C*H), 128.8 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 62.0 (2 × N*C*H_2), 42.0 (*C*H), 29.8 (2 × *C*H_2CH); **IR** υ_{max} (neat) / cm^{-1} 3047, 2960, 2940, 2921, 2836, 1673, 1593, 1577; **HRMS (ESI$^+$)**: $C_{12}H_{15}ClNO$ $[M + H]^+$: calculated 224.0837, found 224.0835, Δ = +0.6 ppm.

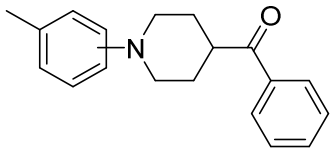
Synthesis of 4-benzoyl-1-(5,6,7,8-tetrahydronaphthalen-2-yl)piperidine 403



To a stirred solution of the chloroamine **401** (100 mg, 0.45 mmol) in DCM (0.45 mL) at 0 ºC was added tetralin (610 µL, 4.50 mmol) $MeSO_3H$ (295 µL, 4.50 mmol) and $FeSO_4.7H_2O$ (12 mg, 0.045). The RM was stirred at 0 ºC for 1 h. The RM was basified using 2 M NaOH (pH 9). The two phases were separated and the aqueous phase was extracted with DCM (3 × 15 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography, eluting with DCM in hexane afforded the *title compound* x (48 mg, 0.15 mmol, 33%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.00 – 7.93 (2H, m, 2 × ArC*H*), 7.60 – 7.54 (1H, m, ArC*H*), 7.48 (2H, t, *J* = 7.6, 2 × Ar*C*H), 6.97 (1H, d, *J* = 8.3, ArC*H*), 6.76 (1H, d, *J* = 7.7, Ar*C*H), 6.68 (1H, s, Ar*C*H), 3.69 (2H, dt, *J* = 6.1, 2.8, NCH_2), 3.42 – 3.31 (1H, m, C*H*CO), 2.88 – 2.77 (2H, m, NCH_2), 2.73 – 2.68 (4H, m, 2 × C_bH_2), 2.04 – 1.91 (4H, m, 2 × CH_2CH), 1.82 – 1.74 (4H, m, 2 × C_aH_2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 202.5 (*C*O), 137.6 (C_q), 136.1 (2 × C_q), 133.0 (Ar*C*H), 129.7 (2 × Ar*C*H), 128.9 (C_q), 128.8 (2 × Ar*C*H), 128.3 (Ar*C*H), 117.4 (Ar*C*H), 115.1 (Ar*C*H), 50.2 (2 × N*C*H_2), 43.6 (*C*H), 29.9 (2 × *C*H_2CH), 28.7 (C_bH_2), 28.6 (C_bH_2), 23.5 (C_aH_2), 23.4 (C_aH_2); **IR** υ_{max} (neat) / cm^{-1} 3057, 3013, 2854, 2834, 2801, 1679, 1609, 1597; **HRMS (ESI$^+$)**: $C_{22}H_{25}NNaO$ $[M + Na]^+$: calculated 342.1828, found 342.1825, Δ = -0.9 ppm.

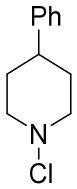
Synthesis of 405



To a stirred solution of the chloroamine **401** (100 mg, 0.45 mmol) in DCM (0.45 mL) at 0 °C was added toluene (480 µL, 4.50 mmol) $MeSO_3H$ (295 µL, 4.50 mmol) and $FeSO_4.7H_2O$ (12 mg, 0.045). The RM was stirred at 0 °C for 1 h. The RM was basified using 2 M NaOH (pH 9). The two phases were separated and the aqueous phase was extracted with DCM (3 × 15 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography, eluting with DCM in hexane afforded the *title compound* as inseparable regioisomers, o : m : p, 3.6 : 7.2 : 5.5 (42 mg, 0.13 mmol, 29%) as a colourless oil. NMRs reported as a mixture of the three regioisomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.99 – 7.93 (2H, m), 7.57 (1H, ddd, *J* = 7.9, 2.3, 1.1), 7.48 (2H, dd, *J* 11.6, 4.2), 7.18 (0.22H, d, *J* = 8.8, ArC*H*, o), 7.15 (0.44H, t, *J* = 7.7, Ar*C*H, m), 7.07 (0.68H, d, *J* = 8.2, 2 × ArC*H*, p), 6.88 (0.68H, d, *J* = 8.2, 2 × Ar*C*H,p), 6.83 – 6.65 (1.98H, m, 6 ArC*H, o* and *m*), 3.79 – 3.65 (2H, m, NCH_2), 3.43 – 3.32 (1H, m, C*H*), 2.85 (2H, m, NCH_2), 2.33 (0.66H, s, CH_3, *o*), 2.32 (1.32H, s, CH_3, *m*), 2.27 (1.02H, s, CH_3, *p*), 2.01 – 1.92 (4H, m, 2 × CH_2CH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 202.5 (*C*O), 151.7 (C_q), 150.3 (C_q), 149.6 (C_q), 138.8 (C_q), 136.3 (C_q), 136.1 (Ar*C*H), 136.0 (C_q), 133.1 (Ar*C*H), 133.0 (Ar*C*H), 129.7 (Ar*C*H), 129.4 (C_q), 129.0 (Ar*C*H), 128.8 (Ar*C*H), 128.3 (Ar*C*H), 120.6 (Ar*C*H), 119.2 (Ar*C*H), 117.6 (Ar*C*H), 117.1 (Ar*C*H), 115.5 (Ar*C*H), 113.8 (Ar*C*H), 50.1 (N*C*H_2), 49.6 (N*C*H_2), 43.6 (*C*H), 28.7 (Ar*C*H_3, *o*), 28.7 (Ar*C*H_3, *m*), 28.5 (Ar*C*H_3, *p*), 21.8 (*C*H_2CH), 20.5 (*C*H_2CH); **IR** υ_{max} (neat) / cm^{-1} 3057, 3026, 2948, 2921, 2807, 2748, 1678, 1595 **LCMS (ESI$^+$)**: $C_{19}H_{22}NO$ $[M + H]^+$: calculated 279.2, found 280.4.

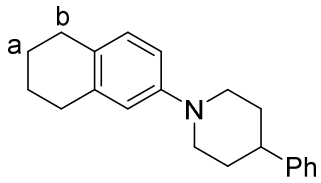
Synthesis of 1-chloro-4-phenylpiperidine 410



General procedure B was followed, using 4-phenylpiperidine (190 mg, 1.18 mmol) and NCS (198 mg, 1.48 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the *title compound* (212 mg, 1.08 mmol, 92%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.35 (2H, dd, *J* = 10.5, 4.5, 2 × ArC*H*), 7.28 – 7.21 (3H, m, 3 × ArC*H*), 3.60 (2H, d, *J* = 11.2, N*C*H$_2$), 3.04 (2 H, t, *J* = 11.2, N*C*H$_2$), 2.71 – 2.60 (1H, m, C*H*), 2.12 – 1.98 (2H, m, C*H*$_2$CH), 1.92 (2 H, d, *J* = 13.1, C*H*$_2$CH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 144.9 (*C*$_q$), 128.6 (2 × Ar*C*H), 126.8 (2 × Ar*C*H), 126.5 (Ar*C*H), 63.4 (2 × N*C*H$_2$), 41.2 (*C*H), 35.0 (2 × *C*H$_2$CH); **IR** υ_{max} (neat) / cm^{-1} 3026, 2936, 2918, 2902, 2826, 1493, 1468, 1451; **HRMS (ESI$^+$)**: $C_{11}H_{15}ClN$ $[M + H]^+$: calculated 196.0888, found 196.0890, Δ -1.3 ppm.

Synthesis of 4-phenyl-1-(5,6,7,8-tetrahydronaphthalen-2-yl)piperidine 411

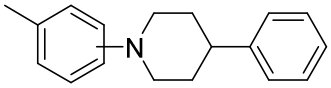


To a stirred solution of the chloroamine **410** (100 mg, 0.51 mmol) in DCM (0.51 mL) at 0 ºC was added tetralin (695 µL, 5.10 mmol) $MeSO_3H$ (330 µL, 5.10 mmol) and $FeSO_4.7H_2O$ (14 mg, 0.051). The RM was stirred at 0 ºC for 1 h. The RM was basified using 2 M NaOH (pH 9). The two phases were separated and the aqueous phase was extracted with DCM (3 × 15 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography, eluting with DCM in hexane afforded the *title compound* xx (39 mg, 0.13 mmol, 26%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.38 – 7.15 (5H, m, 5 × ArC*H*), 6.97 (1H, d, *J* = 8.1, ArC*H*), 6.78 (1H, d, *J* = 8.1, ArC*H*), 6.70 (1H, s, ArC*H*), 3.72 (2H, d, *J* = 11.4, 2 × NC*H*$_2$), 2.79 – 2.66 (7H, m, includes C*H*, 2 × C$_b$*H*$_2$, 2 C*H*$_2$CH), 1.92 (4 H, s, 2 × CHC*H*$_2$), 1.77 (4H, s, *J* = 2.0, 2 × C$_a$H$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 149.9 (*C*$_q$), 146.3 (*C*$_q$), 137.6 (*C*$_q$), 129.7 (Ar*C*H), 128.7 (*C*$_q$), 128.5 (2 × Ar*C*H), 126.9 (2 × Ar*C*H), 126.3 (Ar*C*H), 117.4 (Ar*C*H),

115.1 (Ar*C*H), 51.3 (2 × N*C*H_2), 42.6 (*C*H), 33.5 (2 × *C*H_2CH), 29.9 (*C*$_b$$H_2$), 28.6 (*C*$_b$$H_2$), 23.6 (*C*$_a$$H_2$), 23.4 (*C*$_a$$H_2$); **IR** υ_{max} (neat) / cm^{-1} 3058, 3025, 2923, 2852, 2798, 1736, 1681, 1609; **LCMS** $C_{21}H_{26}N$ $[M+H]^+$ calculated 292.2, measured 292.2.

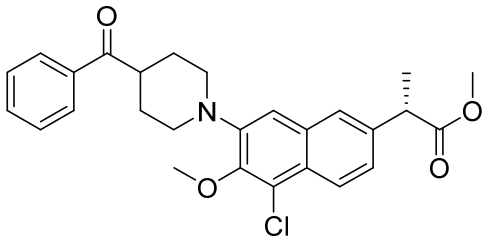
Synthesis of 412



To a stirred solution of the chloroamine **410** (100 mg, 0.51 mmol) in DCM (0.45 mL) at 0 ºC was added toluene (545 µL, 5.10 mmol) $MeSO_3H$ (330 µL, 5.10 mmol) and $FeSO_4.7H_2O$ (14 mg, 0.051). The RM was stirred at 0 ºC for 1 h. The RM was basified using 2 M NaOH (pH 9). The two phases were separated and the aqueous phase was extracted with DCM (3 × 15 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography, eluting with DCM in hexane afforded the *title compound* as inseperable regioisomers, o : m : p, 3.5 : 4.7 : 5.0 (39 mg, 0.14 mmol, 39%) as a colourless oil. All data reported as a mixture of the three regioisomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.30 – 7.10 (5H, m, 5 × ArC*H*), 7.09 – 7.04 (0.36H, m, ArC*H*, *m*), 7.02 – 6.99 (0.76H, m, 2 × ArC*H*, *p*), 6.85 – 6.82 (0.76H, m, 2 × ArC*H*, *p*), 6.78 – 6.70 (1.5H, m,5H includes *o* and *m* ArC*H*), 6.67 (0.36H, dd, *J* = 8.8, 3.0, ArC*H*, *m*), 6.61 (0.26H, d, *J* = 7.4, ArC*H*, *o*), 3.77 – 3.62 (2H, m, NCH_2), 3.52 – 3.46 (2H, m, NCH_2), 2.78 – 2.49 (5H, m, include 2 × CH_2CH and C*H*), 2.26 (0.78H, s, CH_3, *o*), 2.25 (1.08H, s, CH_3, *m*), 2.20 (1.14H, s, CH_3, *p*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 151.7 (*C*$_q$), 150.3 (*C*$_q$), 149.6 (*C*$_q$), 144.9 (*C*$_q$), 136.3 (*C*$_q$), 136.1 (Ar*C*H), 136.0 (*C*$_q$), 133.0 (Ar*C*H), 129.7 (Ar*C*H), 129.4 (*C*$_q$), 129.0 (Ar*C*H), 128.6 (2 × Ar*C*H) 126.8 (2 × Ar*C*H), 126.5 (Ar*C*H), 120.6 (Ar*C*H), 119.2 (Ar*C*H), 117.6 (Ar*C*H), 117.1 (Ar*C*H), 115.5 (Ar*C*H), 113.8 (Ar*C*H), 51 (2 × N*C*H_2), 43.6 (*C*H), 28.7 (Ar*C*H_3, *o*), 28.6 (Ar*C*H_3, *m*), 28.5 (Ar*C*H_3, *p*), 22.0 (2 × *C*H_2CH) ; **IR** υ_{max} (neat) / cm^{-1} 3060, 3028, 2948, 2923, 2810, 2748, 1595, 1425; **HRMS** data could not be obtained

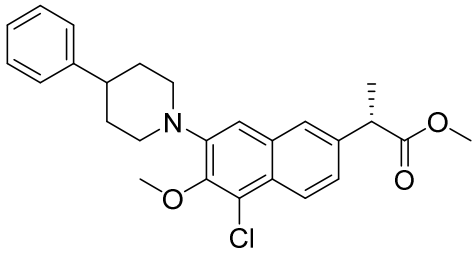
Synthesis of methyl (S)-2-(8-(4-benzoylpiperidin-1-yl)-5-chloro-6-methoxynaphthalen-2-yl)propanoate 433a



To a stirred solution of the chloroamine **401** (183 mg, 0.82 mmol) in DCM (0.45 mL) at 0 ºC was added (2S)-2-(6-methoxynaphthalen-2-yl)propanoate (100 mg, 0.41 mmol) $MeSO_3H$ (535 µL, 8.20 mmol) and $FeSO_4.7H_2O$ (23 mg, 0.082 mmol). The RM was stirred at 0 ºC for 1 h. The RM was basified using 2 M NaOH (pH 9). The two phases were separated and the aqueous phase was extracted with DCM (3 × 15 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography, eluting with DCM in hexane afforded the *title compound* (40 mg, 0.09 mmol, 22%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.17 (1H, d, *J* = 8.8, ArC*H*), 8.04 – 7.97 (3H, m, 3 × ArC*H*), 7.63 – 7.56 (1H, m, ArC*H*), 7.50 (3H, m, 3 × ArC*H*), 6.93 (1H, s, ArC*H*), 4.01 (3H, s, COOCH_3), 3.95 – 3.86 (1H, m, CH_3C*H*), 3.67 (3H, s, OCH_3), 3.55-3.45 (3H, m, includes C*H* and NCH_2), 2.95 (2 H, dd, *J* = 15.9, 6.9, NCH_2), 2.27 – 2.05 (4H, m, 2 × NCH_2CH_2), 1.59 (3H, d, *J* = 7.2, CH_3CH); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 204.8 (*C*O), 177.9 (*C*O), 157.1 (C_q), 144.1 (C_q), 140.6 (C_q), 136.5 (C_q), 131.2 (C_q), 128.8 (2 × Ar*C*H), 127.4 (C_q), 127.3 (2 × Ar*C*H), 126.4 (Ar*C*H), 125.1 (Ar*C*H), 124.3 (Ar*C*H), 124.1 (Ar*C*H), 110.0 (C_q) 105.5 (Ar*C*H), 54.6 (O*C*H_3), 45.6 (2 × NCH_2CH_2), 45.3 (COO*C*H_3), 42.7 (*C*HCO), 41.0 (*C*H), 28.6 (2 × *C*H_2CH_2N), 17.4 (CH*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3055, 2947, 2850, 2808, 1731, 1678, 1593, 1461; **HRMS (ESI$^+$)**: $C_{27}H_{28}ClNNaO_4$ $[M + Na]^+$: calculated 488.1599, found 488.1597, Δ = +0.5 ppm.

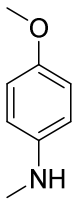
Synthesis of methyl (S)-2-(5-chloro-6-methoxy-8-(4-phenylpiperidin-1-yl)naphthalen-2-yl)propanoate 433b



To a stirred solution of the chloroamine **410** (160 mg, 0.82 mmol) in DCM (0.45 mL) at 0 ºC was added (2S)-2-(6-methoxynaphthalen-2-yl)propanoate (100 mg, 0.41 mmol) $MeSO_3H$ (535 µL, 8.20 mmol) and $FeSO_4.7H_2O$ (23 mg, 0.082). The RM was stirred at 0 ºC for 1 h. The RM was basified using 2 M NaOH (pH 9). The two phases were separated and the aqueous phase was e×tracted with DCM (3 × 15 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography, eluting with DCM in hexane afforded the *title compound* (36 mg, 0.09, 22%)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.99 (1H, d, *J* = 1.7, ArC*H*), 7.94 (1H, d, *J* = 8.7, ArC*H*), 7.44 (1H, dd, *J* = 8.7, 1.7, ArC*H*), 7.33 – 7.25 (4H, m, ArC*H*), 7.21 – 7.15 (1H, m, ArC*H*), 6.83 (1H, s, ArC*H*), 3.95 (3H, s, COOCH_3), 3.91 – 3.78 (1H, m, CH_3C*H*), 3.60 (3H, s, OCH_3), 3.50 – 3.37 (2H, m, CH_2), 2.85 – 2.59 (3H, m, includes C*H*, CH_2), 2.13 – 1.90 (4H, m, 2 × CH*C*H_2), 1.54 (3H, d, *J* = 7.2, CH_3CH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 175.0 (*C*O), 149.4 (C_q), 145.9 (C_q), 137.4 (C_q), 135.8 (C_q), 131.0 (C_q), 128.8 (2 × Ar*C*H), 127.4 (C_q), 127.0 (2 × Ar*C*H), 126.4 (Ar*C*H), 125.1 (Ar*C*H), 123.7 (Ar*C*H), 123.0 (Ar*C*H), 112.4 (C_q) 106.5 (Ar*C*H), 54.5 (O*C*H_3), 52.1 (2 × N*C*H_2), 45.5 (2 × NCH_2*C*H_2), 45.3 (COO*C*H_3), 42.5 (*C*HCO), 41.9 (*C*H) 33.6 (2 x *C*H_2CH_2N), 17.8 (*C*H_3CH); **IR** υ_{max} (neat) / cm^{-1} 3060, 3027, 2977, 2934, 2847, 1733, 1599, 1574; **HRMS (ESI$^+$)**: $C_{26}H_{29}{}^{35}ClO_3$ $[M + H]^+$: calculated 438.1689, found 438.1690, Δ = +0.5 ppm.

Synthesis of 4-methoxy-*N*-methylaniline 439

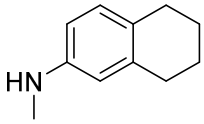


General procedure H was followed, using anisole (1.14 mL, 10.5 mmol), MeNHOH.HCl (2.54 g, 30.5 mmol), $FeCl_2$ (67 mg, 0.53 mmol) and $FeCl_3$ (1.70 g, 10.5 mmol). Purification by

column chromatography, eluting with 20% EtOAc in hexane afforded the *title compound* (580 mg, 4.23 mmol, 40%) as a colourless oil. The NMR data is in accordace with the literature.[138]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.82 (2H, d, *J* = 8.9, 2 × ArC*H*), 6.62 (2H, d, *J* = 8.9, 2 × ArC*H*), 3.77 (3H, s, CH_3), 2.83 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 152.6 (C_q), 142.8 (C_q), 115.0 (2 × Ar*C*H), 114.3 (2 × Ar*C*H), 55.9 (O*C*H_3), 32.1 (NH*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3042, 2989, 2934, 2899, 2831, 2809, 1509, 1464; **HRMS (ESI$^+$)**: $C_8H_{12}NO$ $[M + H]^+$: calculated 138.0913, found 138.0911, Δ = +2.0 ppm.

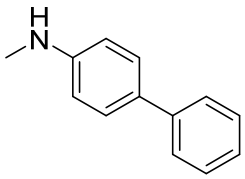
Synthesis of *N*-methyl-5,6,7,8-tetrahydronaphthalen-2-amine 442



General procedure x was followed, using tetralin (100 mg, 0.76 mmol), MeNHOH.HCl (381 mg, 4.56 mmol), $FeCl_2$ (5 mg, 0.058 mmol) and $FeCl_3$ (123 mg, 0.76 mmol). Purification by column chromatography, eluting with 20% EtOAc in hexane afforded the *title compound* (30 mg, 0.19 mmol, 25%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.82 (1H, d, *J* = 8.2, ArC*H*), 6.36 (1H, dd, *J* = 8.2, 2.6, ArC*H*), 6.27 (1H, d, *J* = 2.6, ArC*H*), 2.74 (3H, s, NHCH_3), 2.66 – 2.55 (4H, m, 2 × C_bH_2), 1.72 – 1.65 (4H, m, 2 × C_aH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 150.0 (Ar*C*H), 136.4 (C_q), 126.1 (Ar*C*H), 120.8 (C_q), 118.9 (C_q), 106.5 (Ar*C*H), 30.6 (*C*H_3), 27.4 (Ar*C*H_2), 24.2 (Ar*C*H_2), 22.5 (*C*H_2), 22.3 (*C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3430, 2927, 2858, 2825, 1590, 1512, 1448, 1435; **HRMS (ESI$^+$)**: $C_{11}H_{16}N$ $[M+H]^+$: calculated 162.1278, found 162.1271, Δ = 3.6ppm.

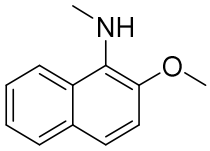
Synthesis of 4,4'-di-N-methylbiphenyl 443



General procedure x was followed, using biphenyl (100 mg, 0.65 mmol), MeNHOH.HCl (326 mg, 3.90 mmol), $FeCl_2$ (7 mg, 0.033 mmol) and $FeCl_3$ (105 mg, 0.65 mmol). Purification by column chromatography, eluting with 20% EtOAc in hexane afforded the *title compound* (15 mg, 0.071 mmol, 11%) as a colourless oil. The NMR data is in accordance with the literature.[139]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.60 – 7.54 (2H, m, 2 × ArC*H*), 7.49 (2H, d, *J* = 8.6, 2 × ArC*H*), 7.46 – 7.38 (2H, m, 2 × ArC*H*), 7.32 – 7.23 (1H, m, ArC*H*), 6.72 (2H, d, *J* = 8.6, 2 × ArC*H*), 2.91 (3H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 148.8 (C_q), 141.3 (C_q), 130.2 (C_q), 128.7 (2 × Ar*C*H), 127.9 (2 × Ar*C*H), 126.3 (2 × Ar*C*H), 126.1 (Ar*C*H), 112.7 (2 × Ar*C*H), 30.8 (*C*H_3); **IR** υ_{maX} (neat) / cm^{-1} 3414, 3054, 3022, 2926, 2812, 1609, 1524, 1489; **HRMS (ESI$^+$)**: $C_{13}H_{14}N$ $[M+H]^+$: calculated 184.1121, found 184.1119, Δ = 1.2ppm.

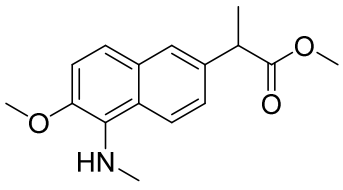
Synthesis of 2-methoxy-N-methylnaphthalen-1-amine 444



General procedure x was followed, using 2-methoxynapthlene (100 mg, 0.63 mmol), MeNHOH.HCl (316 mg, 3.78 mmol), $FeCl_2$ (6 mg, 0.032 mmol) and $FeCl_3$ (102 mg, 0.63 mmol). Purification by column chromatography, eluting with 20% EtOAc in hexane afforded the *title compound* (10 mg, 0.053 mmol, 8%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.11 (1H, d, *J* = 8.5, ArC*H*), 7.79 (1H, d, *J* = 8.5, ArC*H*), 7.52 (1H, d, *J* = 8.9, ArC*H*), 7.47 (1H, ddd, *J* = 8.5, 6.8, 1.3, ArC*H*), 7.35 (1H, ddd, *J* = 8.5, 6.8, 1.3, ArC*H*), 7.28 (1H, d, *J* = 8.9, ArC*H*), 3.98 (3H, s, OCH_3), 3.00 (3H, s, NHCH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 148.4 (C_q), 129.7 (C_q), 128.4 (2 × Ar*C*H), 127.8 (C_q), 126.4 (Ar*C*H), 125.2 (C_q), 124.0 (Ar*C*H), 122.3 (Ar*C*H), 113.4 (Ar*C*H), 57.0 (O*C*H_3), 37.1 (NH*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3364, 3053, 2937, 2837, 1639, 1594, 1574, 1512; **HRMS (ESI$^+$)**: $C_{12}H_{14}NO$ $[M+H]^+$: calculated 188.1070, found 184.1067, Δ = 1.6ppm.

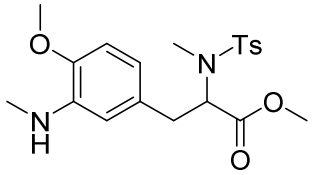
Synthesis of methyl 2-(6-methoxy-5-(methylamino)naphthalen-2-yl)propanoate 445



General procedure x was followed, using naproxen methyl ester (100 mg, 0.41 mmol), MeNHOH.HCl (205 mg, 2.46 mmol), $FeCl_2$ (3 mg, 0.021 mmol) and $FeCl_3$ (67 mg, 0.41 mmol). Purification by column chromatography, eluting with 15% EtOAc in hexane afforded the *title compound* (14 mg, 0.05 mmol, 13%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.97 (1H, d, *J* = 8.8, ArC*H*), 7.58 (1H, d, *J* = 1.8, ArC*H*), 7.39 (1H, d, *J* = 8.9, ArC*H*), 7.32 (1H, dd, *J* = 8.8, 1.8, ArC*H*), 7.17 (1H, d, *J* = 8.9, ArC*H*), 3.91 – 3.83 (4H, m, includes OCH_3 and C*H*), 3.60 (3H, s, OCH_3). 2.90 (3H, s, NHCH_3), 1.51 (3H, d, *J* = 7.2, CHCH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 175.1 (*C*O), 147.6 (C_q), 135.7 (C_q), 133.5 (C_q), 130.0 (C_q), 127.3 (C_q), 126.5 (Ar*C*H), 125.3 (Ar*C*H), 123.4 (Ar*C*H), 122.6 (Ar*C*H), 113.9 (Ar*C*H), 56.9 (O*C*H_3), 52.1 (COOCH_3), 45.3 (*C*HCH$_3$), 37.2 (NH*C*H_3), 18.5 (*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3365, 2975, 2946, 2839, 1730, 1653, 1599, 1573; **HRMS (ESI$^+$)**: $C_{16}H_{19}NNaO_3$ [M+Na]$^+$: calculated 296.1257, found 296.1252, Δ = 1.7ppm.

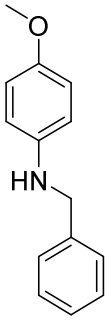
Synthesis of methyl 2-((*N*,4-dimethylphenyl)sulfonamido)-3-(4-methoxy-3-(methylamino)phenyl)propanoate 446



General procedure H was followed, using protected tyrosine (100 mg, 0.26 mmol), MeNHOH.HCl (108 mg, 1.56 mmol), $FeCl_2$ (2 mg, 0.013 mmol) and $FeCl_3$ (42 mg, 0.26 mmol). Purification by column chromatography, eluting with 20% EtOAc in hexane afforded the *title compound* (23 mg, 0.057 mmol, 22%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.38 (2H, d, *J* = 8.3 Hz, 2 × ArC*H*), 7.08 (2H, d, *J* = 8.3 Hz, 2 × ArC*H*), 6.54 (1H, d, *J* = 8.0, ArC*H*), 6.35 (1H, dd, *J* = 8.0, 2.0, ArC*H*), 6.25 (1H, d, *J* = 2.0, ArC*H*), 4.83 (1H, dd, *J* = 8.6, 7.0, C*H*), 3.75 (3H, s, OCH_3), 3.48 (3H, s, COOCH_3), 3.07 (1H, dd, *J* = 14.0, 7.0, CH_2), 2.81 (3H, s, NCH_3), 2.72 (3H, s, NHCH_3), 2.71 – 2.62 (1H, m, CH_2), 2.31 (3H, s, ArCH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 171.0 (*C*O), 146.0 (C_q), 143.0 (C_q), 139.2 (C_q), 136.2 (C_q), 129.2 (2 × Ar*C*H), 129.1 (C_q), 127.3 (2 × Ar*C*H), 116.7 (Ar*C*H), 110.0 (Ar*C*H), 109.1 (Ar*C*H), 60.5 (*C*HCO), 55.5 (O*C*H$_3$), 52.0 (O*C*H_3), 35.5 (*C*H_2), 30.4 (N*C*H$_3$), 30.1 (N*C*H_3), 21.5 (Ar*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3432, 2950, 2923, 2852, 1737, 1599, 1523, 1449; **HRMS (ESI$^+$)**: $C_{20}H_{26}N_2NaO_5S$ [M+Na]$^+$: calculated 429.1455, found 492.1451, Δ = 0.9ppm.

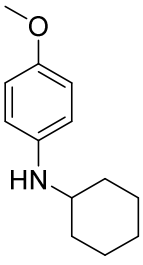
Synthesis of *N*-benzyl-4-methoxyaniline 448



General procedure H was followed, using anisole (100 mg, 0.92 mmol), *N*-benzylhydroxylamine.HCl (881 mg, 5.52 mmol), $FeCl_2$ (6 mg, 0.050 mmol) and $FeCl_3$ (149 mg, 0.92 mmol). Purification by column chromatography, eluting with 20% EtOAc in hexane afforded the *title compound* (30 mg, 0.14 mmol, 21%) as a colourless oil. The NMR data is in accordance with the literature.[140]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.48 – 7.21 (5H, m, 5 × ArC*H*), 6.81 (2H, d, *J* = 9.0, 2 × ArC*H*), 6.64 (2H, d, *J* = 9.0, 2 × ArC*H*), 4.32 (2H, s, CH_2), 3.77 (3H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 152.2 (C_q), 142.5 (C_q), 139.7 (C_q), 128.6 (2 × Ar*C*H), 128.0 (2 × Ar*C*H), 127.0 (Ar*C*H), 115.0 (2 × Ar*C*H), 114.2 (2 × Ar*C*H), 55.9 (O*C*H_3), 49.3 (NH*C*H_3); **IR** υ_{max} (neat) / cm^{-1} 3408, 3061, 3028, 2996, 2931, 2904, 2831, 1509; **HRMS (ESI$^+$)**: $C_{14}H_{16}NO$ [M + H]$^+$: calculated 214.1226, found 214.1226, Δ = 0.1 ppm.

Synthesis of *N*-cyclohexyl-4-methoxyaniline 450



General procedure H was followed, using anisole (118 µL, 1.09 mmol), N-cyclohydroxylamine.HCl (992 mg, 6.54 mmol), $FeCl_2$ (7 mg, 0.055 mmol) and $FeCl_3$ (177 mg, 1.09 mmol). Purification by column chromatography, eluting with 20% EtOAc in hexane afforded the *title compound* (65 mg, 0.32 mmol, 29%) as a colourless oil. The NMR data is in accordance with the literature.[141]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.79 (2H, d, *J* = 8.9, 2 × ArC*H*), 6.59 (2H, d, *J* = 8.9, 2 × ArC*H*), 3.76 (3H, s, CH_3), 3.18 (1H, m, C*H*), 2.14 – 2.00 (2H, m, CH_2), 1.87 – 1.72 (2H, m,

CH_2), 1.72 – 1.56 (1H, m, 1H of CH_2), 1.51 – 1.02 (5H, m, 2 × CH_2 and 1H of CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 151.9 (C_q), 141.6 (C_q), 114.9 (2 × Ar*C*H), 114.9 (2 × Ar*C*H), 55.9 (O*C*H_3), 52.9 (N*C*H), 33.6 (2 × *C*H_2), 26.0 (*C*H_2), 25.1 (2 × *C*H_2); **IR** υ_{max} (neat) / cm^{-1} 3389, 2989, 2993, 2926, 2851, 2831, 1509, 1450; **HRMS (ESI$^+$)**: $C_{13}H_{20}NO$ $[M + H]^+$: calculated 206.1539, found 206.1544, Δ = -2.2 ppm.

Chapter 5 References

1 H. Bock and K. L. Kompa, *Chem. Commun.*, 1965, **4**, 783.

2 V. Sridharan, P. A. Suryavanshi and J. C. Menendez, *Chem. Rev.*, 2011, **111**, 7157–7259.

3 S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451.

4 J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, **4**, 2337–2347.

5 F. Ullmann and J. Bielecki, *Chem. Ber.*, 1901, **34**, 2174–2185.

6 F. Ullmann, *Chem. Ber.*, 1903, **36**, 2382–2384.

7 F. Ullmann and P. Sponagel, *Chem. Ber.*, 1905, **38**, 2211–2212.

8 I. Goldberg, *Chem. Ber.*, 1906, **39**, 1691–1692.

9 C. Sambiagio, S. P. Marsden, A. J. Blacker and P. C. McGowan, *Chem. Soc. Rev.*, 2014, **43**, 3525–3550.

10 D. Scawen, N. Regional, T. Cohen and I. Cristea, *J. Am. Chem. Soc.*, 1975, **98**, 748–753.

11 F. Y. Kwong and S. L. Buchwald, *Org. Lett.*, 2003, **5**, 793–796.

12 W. Zhou, M. Fan, J. Yin, Y. Jiang and D. Ma, *J. Am. Chem. Soc.*, 2015, **137**, 11942–11945.

13 M. Kosugi, M. Kameyama and T. Migita, *Chem. Lett.*, 1983, **12**, 927–928.

14 F. Paul, J. Patt and J. F. Hartwig, *J. Am. Chem. Soc.*, 1994, **116**, 5969–5970.

15 J. Louie and J. F. Hartwig, *Tetrahedron*, 1995, **36**, 3609–3612.

16 S. L. Buchwald, *J. Am. Chem. Soc.*, 1994, **116**, 7901–7902.

17 B. H. Yang and S. L. Buchwald, *J. Organomet. Chem.*, 1999, **576**, 125–146.

18 E. B. Corcoran, M. T. Pirnot, S. Lin, S. D. Dreher, D. A. Dirocco, I. W. Davies, S. L. Buchwald and D. W. C. Macmillan, *Science (80-.).*, 2016, **353**, 279–283.

19 P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan and A. Combs, *Tetrahedron Lett.*, 1998, **39**, 2941–2944.

20 D. M. T. Chan, K. L. Monaco, R. P. Wang and M. P. Winters, *Tetrahedron Lett.*, 1998, **39**, 2933–2936.

21 K. Sanjeeva Rao and T. S. Wu, *Tetrahedron*, 2012, **68**, 7735–7754.

22 A. P. Combs, S. Saubern, M. Rafalski and P. Y. S. Lam, *Tetrahedron Lett.*, 1999, **40**, 1623–1626.

23 J. P. Collman and M. Zhong, *Org. Lett.*, 2000, **2**, 1233–1236.

24 J. C. Vantourout, H. N. Miras, A. Isidro-Llobet, S. Sproules and A. J. B. Watson, *J. Am. Chem. Soc.*, 2017, **139**, 4769–4779.

25 S. Bräse, C. Gil, K. Knepper and V. Zimmermann, *Angew. Chem. Int. Ed.*, 2005, **44**, 5188–5240.

26 B. J. Stokes, H. Dong, B. E. Leslie, A. L. Pumphrey and T. G. Driver, *J. Am. Chem. Soc.*, 2007, **129**, 7500–7501.

27 W. C. P. Tsang, N. Zheng and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 14560–14561.

28 W. C. P. Tsang, R. H. Munday, G. Brasche, N. Zheng and S. L. Buchwald, *J. Org. Chem.*, 2008, **73**, 1932–1934.

29 G. Brasche and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2008, **47**, 1932–1934.

30 A. W. Hofmann, *Chem. Ber.*, 1881, **14**, 2725–2736.

31 A. W. Hofmann, *Chem. Ber.*, 1883, **16**, 558–560.

32 C. Freytag and K. Loffler, *Chem. Ber.*, 1909, **42**, 3427–3431.

33 S. Wawzonek and T. Culbertson, *J. Am. Chem. Soc.*, 1959, **81**, 3367–3369.

34 E. J. Corey and W. R. Hertler, *J. Am. Chem. Soc.*, 1960, **2118**, 1657–1668.

35 Y. Ban, M. Kimura and O. Oishi, *Heterocycles*, 1974, **2**, 323–328.

36 C. Betancor, J. I. Concepcion, R. Hernandez, J. A. Salazar and E. Suarez, *J. Org. Chem.*, 1983, **48**, 4430–4432.

37 Q. Qin and S. Yu, *Org. Lett.*, 2015, **17**, 1894–1897.

38 A. U. Dey and B. Pathak, *J. Med. Chem.*, 1970, **13**, 152–153.

39 P. S. Anderson, G. F. Lundell, J. L. Ciss and F. M. Robinson, *Tetrahedron Lett.*, 1971, 2787–2790.

40 R. Alonso, P. J. Campos, B. García and M. A. Rodríguez, *Org. Lett.*, 2006, **8**, 3521–

3523.

41 R. T. McBurney, A. M. Z. Slawin, L. A. Smart, Y. Yu and J. C. Walton, *Chem. Commun.*, 2011, **47**, 7974–7976.

42 R. Alonso, A. Caballero, P. J. Campos and M. A. Rodríguez, *Tetrahedron*, 2010, **66**, 8828–8831.

43 R. A. Leal, D. R. Beaudry, S. K. Alzghari and R. Sarpong, *Org. Lett.*, 2012, **14**, 5350–5353.

44 F. Minisci, *Synthesis (Stuttg).*, 1973, 1–24.

45 F. Minisci and R. Galli, *Tetrahedron Lett.*, 1966, 2531–2533.

46 F. Minisci, R. Galli and M. Cecere, *Tetrahedron Lett.*, 1965, **6**, 4663–4667.

47 L. Legnani, G. Prina Cerai and B. Morandi, *ACS Catal.*, 2016, **6**, 8162–8165.

48 J. Liu, K. Wu, T. Shen, Y. Liang, M. Zou, Y. Zhu, X. Li, X. Li and N. Jiao, *Chem. - A Eur. J.*, 2017, **23**, 563–567.

49 N. A. Romero, K. A. Margrey, N. E. Tay and D. A. Nicewicz, *Science (80-.).*, 2015, **349**, 1326–1330.

50 T. D. Svejstrup, A. Ruffoni, F. Juliá, V. M. Aubert and D. Leonori, *Angew. Chemie - Int. Ed.*, 2017, **56**, 14948–14952.

51 J. Cadogan and A. Rowley, *J. Chem. Soc., Perkin. Trans 1*, 1975, 1069–1071.

52 R. A. Lidgett, E. R. Lynch and E. B. McCall, *J. Chem. Soc.*, 1965, 3754–3759.

53 I. Meyers, J. C. Day, N. Govindaraj, P. S. Skell and M. Tanko, *J. Org. Chem.*, 1986, **51**, 4959–4963.

54 L. J. Allen, P. J. Cabrera, M. Lee and M. S. Sanford, *J. Am. Chem. Soc.*, 2014, **136**, 5607–5610.

55 K. Foo, E. Sella, I. Thome, M. D. Eastgate and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 5279–5282.

56 D. H. R. Barton, M. Akhtar, J. M. Beaton and A. G. Hortmann, *J. Am. Chem. Soc.*, 1963, **85**, 1512–1519.

57 L. P. Kuhn, G. G. Kleinspehn and A. C. Duckworth, *J. Am. Chem. Soc.*, 1967, **89**, 3858.

58 Y. L. Chow and R. A. Perry, *Tetrahedron Lett.*, 1972, 531.

59 M. E. Kuehne and D. A. Horne, *J. Org. Chem.*, 1975, **40**, 1287–1292.

60 S. A. Glover and P. Elizabeth, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2353–2356.

61 S. A. Glover and A. Goosen, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1348–1356.

62 P. Mackiewicz, R. Furstoss, B. Waegell, C. No, M. Cedex, R. Cote and J. Lessard, *J. Org. Chem.*, 1978, **43**, 3746–3750.

63 J. Lessard, R. Cote, P. Mackiewicz, R. Furstoss and B. Waegell, *J. Org. Chem.*, 1978, **43**, 3750–3756.

64 J. L. Esker and M. Newcomb, *J. Org. Chem.*, 1993, **58**, 4933–4940.

65 D. H. R. Barton, D. Crich and W. B. Motherwell, *Tetrahedron*, 1985, **41**, 3901–3924.

66 J. L. Esker and M. Newcomb, *Tetrahedron Lett.*, 1993, **34**, 6877–6880.

67 C. Moutrille and S. Z. Zard, *Chem. Commun.*, 2004, 1848–1849.

68 B. D. Hosangadi, M. M. Chhaya, M. M. Nimbalkar and N. R. Patel, *Tetrahedron*, 1987, **43**, 5375–5380.

69 J. Boivin, A. Schiano, A. Callier-Dublanchet, B. Quiclet-Sire and S. Z. Zard, *Tetrahedron*, 1995, **51**, 6517–6528.

70 A. J. Clark and J. L. Peacock, *Tetrahedron Lett.*, 1998, **39**, 1265–1268.

71 X. Lin, G. D. Artman, D. Stien and S. M. Weinreb, *Tetrahedron*, 2001, **57**, 8779–8791.

72 D. L. Hughes, *Org. Process Res. Dev.*, 2017, acs.oprd.7b00363.

73 B. D. A. Hook, W. Dohle, P. R. Hirst, M. Pickworth, M. B. Berry and K. I. Booker-Milburn, *J. Org. Chem.*, 2005, **70**, 7558–64.

74 L. D. Elliott, J. P. Knowles, P. J. Koovits, K. G. Maskill, M. J. Ralph, G. Lejeune, L. J. Edwards, R. I. Robinson, I. R. Clemens, B. Cox, D. D. Pascoe, G. Koch, M. Eberle, M. B. Berry and K. I. Booker-Milburn, *Chem. - A Eur. J.*, 2014, **20**, 15226–15232.

75 J. P. Knowles, L. D. Elliott and K. I. Booker-Milburn, *Beilstein J. Org. Chem.*, 2012, **8**, 2025–2052.

76 S. C. Cosgrove, J. M. C. Plane and S. P. Marsden, *Chem. Sci.*, 2018.

77 S. Cosgrove, 2017.

78 J. Escalante and E. Juaristi, *Tetrahedron Lett.*, 1995, **36**, 4397–4400.

79 R. Cadoni, A. Porcheddu, G. Giacomelli, L. De Luca and V. Vienna, *Org. Lett.*, 2012, **14**, 1383–1386.

80 Y.-L. Zhong, H. Zhou, D. R. Gauthier, J. Lee, D. Askin, U. H. Dolling and R. P. Volante,

Tetrahedron Lett., 2005, **46**, 1099–1101.

81 S. Z. Zard, *Chem. Soc. Rev.*, 2008, **37**, 1603–1618.

82 T. Hokamp, A. Dewanji, M. Lübbesmeyer, C. Mück-Lichtenfeld, E. U. Würthwein and A. Studer, *Angew. Chemie - Int. Ed.*, 2017, **56**, 13275–13278.

83 Z. Han, D. Krishnamurthy, D. Pflum, Q. K. Fang, H. Butler, T. S. Cameron, A. Wald and C. H. Senanayake, *Tetrahedron: Asymmetry*, 2002, **13**, 107–109.

84 I. Jacquemond-Collet, S. Hannedouche, N. Fabre, I. Fourasté and C. Moulis, *Phytochemistry*, 1999, **51**, 1167–1169.

85 O. M. Musa, J. H. Homer, H. Shahin and M. Newcomb, *J. Am. Chem. Soc.*, 1996, **118**, 3862–3868.

86 J. H. Horner, F. N. Martinez, O. M. Musa, M. Newcomb and H. E. Shahin, *J. Am. Chem. Soc.*, 1995, **117**, 11124–11133.

87 D. J. Newcomb, M., Deeb, T. M., Marquardt, *Tetrahedron*, 1990, **46**, 2317–2328.

88 M. Sakai, H. Hayashi and N. Miyaura, *Organometallics*, 1997, **16**, 4229–4231.

89 N. Fuentes, W. Kong, L. Fern??ndez-S??nchez, E. Merino and C. Nevado, *J. Am. Chem. Soc.*, 2015, **137**, 964–973.

90 L. Xu and D. A. Vicic, *J. Am. Chem. Soc.*, 2016, **138**, 2536–2539.

91 K. D. Collins and F. Glorius, *Nat. Chem.*, 2013, **5**, 597–601.

92 J. He, L. G. Hamann, H. M. L. Davies and R. E. J. Beckwith, *Nat. Commun.*, 2015, **6**, 5943.

93 R. Fisher, *Design of Experiments*, 1972.

94 Https://sixsigmastudyguide.com/wp-content/uploads/2015/09/trial_distribution2.png, .

95 P. T. 1. M. Surzur, L. Stella, *Bull. SOC. Chim. Fr.*, 1970, 115.

96 E. Lewandowska and D. C. Chatfield, *Eur. J. Org. Chem.*, 2005, 3297–3303.

97 B. Miriyala, S. Bhattacharyya and J. S. Williamson, *Tetrahedron*, 2004, **60**, 1463–1471.

98 J. Lu and P. Toy, *Synlett*, 2011, 1723–1726.

99 C. Salomé and H. Kohn, *Tetrahedron Lett.*, 2009, **65**, 456–460.

100 M. Ye, G. Gao and J. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 6964–6967.

101 H. Yoshizawa, T. Kubota, H. Itani, K. Minami, H. Miwa and Y. Nishitani, *Bioorg. Med.*

Chem., 2004, **12**, 4221–4231.

102 C. A. Hunter, M. C. Misuraca and S. M. Turega, *J. Am. Chem. Soc.*, 2011, **133**, 582–594.

103 D. Capaldo, Luca; Fagnoni, Maurizio; Ravelli, *Chem. Eur. J.*, 2017, **23**, 6527–6530.

104 J. H. Hutchinson, W. Halczenko, K. M. Brashear, M. J. Breslin, P. J. Coleman, L. T. Duong, C. Fernandez-metzler, M. A. Gentile, J. E. Fisher, G. D. Hartman, J. R. Huff, D. B. Kimmel, C. Leu, R. S. Meissner, K. Merkle, R. Nagy, B. Pennypacker, J. J. Perkins, T. Prueksaritanont, G. A. Rodan, S. L. Varga, G. A. Wesolowski, A. E. Zartman, S. B. Rodan and M. E. Duggan, *J. Med. Chem.*, 2003, **46**, 4790–4798.

105 A. S. Kleinke and T. F. Jamison, *Org. Lett.*, 2013, **15**, 710–713.

106 Y. Monguchi, Y. Fujita, S. Hashimoto, M. Ina, T. Takahashi, R. Ito, K. Nozaki, T. Maegawa and H. Sajiki, *Tetrahedron*, 2011, **67**, 8628–8634.

107 L. Guo, Y. Liu, W. Yao, X. Leng and Z. Huang, *Org. Lett.*, 2013, **15**, 1144–1147.

108 D. Gao, F. Scholz, H. Nothofer, W. E. Ford, U. Scherf and J. M. Wessels, *J. Am. Chem. Soc.*, 2011, **133**, 5921–5930.

109 D. G. Pintori and M. F. Greaney, *Org. Lett.*, 2011, **13**, 5713–5715.

110 Y. Kawase, Masami; Kitamura, Takahiro; Kikugawa, *J. Org. Chem.*, 1989, **54**, 3394–3403.

111 B. Liégault, I. Petrov, S. I. Gorelsky and K. Fagnou, *J. Org. Chem.*, 2010, **75**, 1047–1060.

112 T. B. Nguyen, J. Sorres, M. Q. Tran, L. Ermolenko and A. Al-Mourabit, *Org. Lett.*, 2012, **14**, 3202–3205.

113 2004, WO2004/110982.

114 J. Zeng, K. M. Liu and X. F. Duan, *Org. Lett.*, 2013, **15**, 5342–5345.

115 Á. Martínez-Peragón, A. Millán, A. G. Campaña, I. Rodríguez-Márquez, S. Resa, D. Miguel, L. Álvarez De Cienfuegos and J. M. Cuerva, *European J. Org. Chem.*, 2012, 1499–1503.

116 A. E. Strom and J. F. Hartwig, *J. Org. Chem.*, 2013, **78**, 8909–14.

117 Y. Li, Y.-Y. Hu and S.-L. Zhang, *Chem. Commun.*, 2013, **49**, 10635–7.

118 H. Takakura, R. Kojima, M. Kamiya, E. Kobayashi, T. Komatsu, T. Ueno, T. Terai, K.

Hanaoka, T. Nagano and Y. Urano, *J. Am. Chem. Soc.*, 2015, **137**, 4010–3.

119 B. R. Henke, T. G. Consler, N. Go, R. L. Hale, D. R. Hohman, S. a. Jones, A. T. Lu, L. B. Moore, J. T. Moore, L. a. Orband-Miller, R. G. Robinett, J. Shearin, P. K. Spearing, E. L. Stewart, P. S. Turnbull, S. L. Weaver, S. P. Williams, G. B. Wisely and M. H. Lambert, *J. Med. Chem.*, 2002, **45**, 5492–5505.

120 B. He, Zhenhong; Liu, Huizhen; Qian, Qingli; Lu, Lu; Guo, Weiwei; Zhang, Lujun; Han, *Sci. China Chem.*, 2017, **60**, 927–933.

121 S.-L. Li, Ying; Hu, Yuan-yuan; Zhang, *Chem. Commun.*, 2013, **49**, 10635–10637.

122 A. D. Konopacki, Donald B,; Shortsleeves, Kelley C.; Turnbull, Mark M.; Wikairi, Jan L.; Hobson, *Eur. J. Org. Chem.*, 2015, **24**, 5453–5463.

123 Y. Minakawa, Maki; Watanabe, Kouchi; Toyoda, Satoru; Uozumi, *Synlett*, 2018, **29**, 2385–2389.

124 H. Huang, C. Yu, Y. Zhang, Y. Zhang, P. S. Mariano and W. Wang, *J. Am. Chem. Soc.*, 2017, **139**, 9799–9802.

125 M. Yus and J. Gomis, *European J. Org. Chem.*, 2002, 1989.

126 C.-J. Zhu, Dianhu; Lv, Leiyang; Li, Chen-Chen; Ung, Sosthene; Gao, Jian; Li, *Angew. Chem. Int. Ed.*, 2018, **57**, 16520–16524.

127 B. C. Frost, Christopher G; Hartley, *J. Org. Chem.*, 2009, **74**, 3599–3602.

128 D.-L. Chan, Daniel Shiu-Hin; Yang, Hui; Kwan, Maria Hiu-Tung; Cheng, Zhen; Lee, Paul; Bai, Li-Ping; Jiang, Zhi-Hong; Wong, Chun-Yuen; Fong, Wang-Fun;Laung, Chung-Hang; Ma, *Biochimie*, 2011, **93**, 1055–1064.

129 Y. Koide, Y. Urano, K. Hanaoka, W. Piao, M. Kusakabe, N. Saito, T. Terai, T. Okabe and T. Nagano, *J. Am. Chem. Soc.*, 2012, **134**, 5029–31.

130 C.-J. Zhou, Zhong-Zhen; Liu, Mingxin; Lv, Leiyang; Li, *Angew. Chem. Int. Ed.*, 2018, **57**, 2616–2620.

131 C. G. Frost and B. C. Hartley, *J. Org. Chem.*, 2009, **74**, 6689–6692.

132 S. Bielefeld, Jens; Doye, *Angew. Chem. Int. Ed.*, 2017, **56**, 15352–15355.

133 S. K. R. C. A. R. Reddy, *Tetrahedron Lett.*, 2018, **59**, 33–37.

134 R. A. Bunce, D. M. Herron and L. Y. Hale, *J. Heterocycl. Chem.*, 2003, **40**, 1031–1039.

135 J. Qu, Zhaohui; Shi, Weifeng; Wang, *J. Org. Chem.*, 2004, **69**, 217–219.

136 F. J. Fañanãs, A. Granados, R. Sanz, J. M. Ignacio and J. Barluenga, *Chem. - A Eur. J.*, 2001, **7**, 2896–2907.

137 P. Prediger, A. R. da Silva and C. R. D. Correia, *Tetrahedron*, 2014, **70**, 3333–3341.

138 L. Huang, R. Yu, X. Zhu and Y. Wan, *Tetrahedron*, 2013, **69**, 8974–8977.

139 H. Seo, A. C. Bédard, W. P. Chen, R. W. Hicklin, A. Alabugin and T. F. Jamison, *Tetrahedron*, 2018, **74**, 3124–3128.

140 D. Wei, A. Bruneau-Voisine, D. A. Valyaev, N. Lugan and J. B. Sortais, *Chem. Commun.*, 2018, **54**, 4302–4305.

141 R. Mamidala, V. Mukundam, K. Dhanunjayarao and K. Venkatasubbaiah, *Tetrahedron*, 2017, **73**, 2225–2233.