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. 


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.

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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 radical 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.
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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 enhancement 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
TBTU- $O$-(benzotriazol-1-yl)$N,N',N''$-tetramethyluronium tetrafluoroborate

THF-tetrahydrofuran

THQ-tetrahydroquinoline

TLC – thin layer chromatography

$t_R$- residence time

UV – ultraviolet

V-volume

W - Watt

wt- weight
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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](image)

A study carried out in 2011 by Roughly and Jordan \textit{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 \(S_N\)Ar and Pd catalysed Buchwald-Hartwig cross coupling reactions.\(^3\) A similar review was also carried out by Carey, Williams and Laffan \textit{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.

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.

\[
\begin{align*}
2 \begin{array}{c}
\text{aryl halide} 4 \\
\text{Cu (2 eq)}
\end{array} & \xrightarrow{< 200 \degree C} \begin{array}{c}
\text{symmetrical biaryl} 5
\end{array}
\end{align*}
\]

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).\(^6,7\)

\[
\begin{align*}
\text{aryl} \begin{array}{c}
\text{NH}_2 \\
\text{Cl}
\end{array} + \begin{array}{c}
\text{acid}
\end{array} & \xrightarrow{[\text{Cu}] (1.1 \text{ eq})} \begin{array}{c}
\text{symmetrical product} 8
\end{array}
\end{align*}
\]

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).\(^8\)

\[
\begin{align*}
\text{amide} + \text{aryl bromide} & \xrightarrow{\text{cat}[\text{Cu}], NaOAc (1 eq.)} \text{arylamide}
\end{align*}
\]

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.\textsuperscript{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.\textsuperscript{10}

![Scheme 1.4](image)


\[ \text{Nu} = \text{HNRR'}, \text{HAc}, \text{HSR} \]

Modifications to the Ullmann reaction introduced by Buchwald \textit{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).\textsuperscript{11}

![Scheme 1.5](image)

Recent developments by Ma \textit{et al.} have shown the use of aryl chlorides and lower temperature reactions to carry out transformation (Scheme 1.6).\textsuperscript{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.
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. This methodology was investigated further by Buchwald and Hartwig in the 1990s (Scheme 1.7). 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.

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).
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).

Scheme 1.10

In 2016 Macmillian and Buchwald et al demonstrated together that a nickel catalyst could be used in conjunction with a photocatalyst to carry out the amination on an aromatic ring (Scheme 1.11). 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.
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.

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 \(N\)-heterocycles were synthesised using this method (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. 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).

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). They propose that the [Cu(OAc)]₂·2H₂O 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(III)OAc species 64 which is oxidised by O₂ and HX to regenerate the Cu(II) species 56. Through this study, improved reaction reliability has been shown due to the use of additives.
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. 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).  

![Scheme 1.15](image)

![Scheme 1.16](image)

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. These reactions utilised Cu(OAc)$_2$ as a stoichiometric co-oxidant in the reactions (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

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.
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.

**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$_2$SO$_4$ 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.$^{32}$
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. 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. Following this the nitrogen-centred radical readily undergoes an intermolecular 1,5-hydrogen atom transfer resulting in the alkyl radical then undergoes radical recombination to form the alkyl-halogen bond. Finally treatment with a base which deprotonates the salt, allowing the internal nucleophilic substitution reaction to occur yielding the pyrrolidine, with excellent regioselectivity observed.

In 1974, Oishi et al. demonstrated that the chloroamine could be generated in situ and irradiated directly under UV light to obtain under neutral conditions. 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.

![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).\(^\text{36}\) The alternative method involved reacting N-nitroamines, N-cyanamines or N-phosphoramides with hypervalent iodine species under neutral conditions, generating the nitrogen centred radicals.

![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.\(^\text{37}\) They found that lower catalyst loadings increased the yield of the desired product (Scheme 1.24).

![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
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). \(^{42}\)

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\(_2\)SO\(_4\) that had been successfully demonstrated by Day and Robinson (i.e. 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).

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\(_2\)SO\(_4\) or a mixture of H\(_2\)SO\(_4\) and AcOH.
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).

Minisci et al. have also developed an intramolecular variation of this reaction. The reaction of $N$-methyl-$N$-(phenylethyl)-$N$-chloroamine 107 and FeSO$_4$ in concentrated H$_2$SO$_4$ is an exothermic reaction that is very sensitive to temperature. When the reaction was carried out without cooling, once above 35 °C low yields of $N$-methylindoline 108 were observed, whereas when the reaction is cooled and kept at -5 °C 27% of $N$-methylindoline 108 is formed, with the formation of benzyl chloride 109 as a side product also (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)
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).

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.
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). 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.

Jiao et al has also investigated an alternative hydroxylamine derivative for the amination of aromatics (Scheme 1.36). 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.
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.

Leonori et al described the use of \(O\)-aryl hydroxylamines \(128\) to form aminium radicals in the presence of \(\text{Ru(bpy)}_3\) 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).\(^{50}\)
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 imidy1 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). 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.

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). 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](image)

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 phthalamides (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](image)

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-phthalamidyl radical 138, which then reacts with the arene 104. The radical species 142 is then oxidised by the iridium species 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.\(^{54}\)
In 2014 Baran et al. reported a metal mediated intermolecular N-arylation reaction between heteraromatics and N-succinimidyl derivatives. The first substrate imide 144 underwent decarboxylation/deformylation to generate the imidyl radical which was shown to react with methoxypyridines (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.
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. 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 nitrosoamide is considerably weaker than a nitrosamine and that these compounds underwent facile photochemical reactions (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.

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. 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).

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).
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-\textit{exo}-trig cyclisation in 35\% yield, however when N-chloroamide 158 was irradiated the major product was the amide 160 with no 6-\textit{exo} cyclisation occurring (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-\textit{exo}-trig or fused ring by 6-\textit{endo}-trig, however the only cyclised product obtained from the reaction was the spiro-lactam 162, showing preference for 5-\textit{exo} cyclisations (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).

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.\textsuperscript{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).

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.
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. 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)

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.
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.

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. 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.
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).

**1.7.3 PTOC (N-hydroxypyridine-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.\(^6\) is the PTOC imidate ester 184 which are structurally similar to the PTOC ester 183 used by Barton et al (Figure 1.5).\(^6\)

![Scheme 1.56](image)

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).

**Scheme 1.57**

\[
\begin{align*}
\text{dibenzoyl peroxide, dioxane, } & 80^\circ \text{C} \quad 0\% \\
\text{CrCl}_2 \text{ (1M in MeOH), CHCl}_3 / \text{MeOH, } & -78^\circ \text{C}, 100 \text{ h} \quad 80\%
\end{align*}
\]

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

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![Scheme 1.57](image)

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![Scheme 1.57](image)

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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).

\[ \text{Scheme 1.58} \]

Newcomb et al. also showed radical cascade reactions could be initiated to afford bi-cyclic systems (Scheme 1.59).\textsuperscript{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.

\[ \text{Scheme 1.59} \]
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).

\[
\text{Scheme 1.60}
\]

These compounds have been shown to undergo intramolecular cyclisation reactions to form five-membered rings. When amide 197 was treated with \( \text{Bu}_3\text{SnH} \) whilst heating in benzene it afforded 77\% of the desired compound (Scheme 1.61).

\[
\text{Scheme 1.61}
\]

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.
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.\(^{57} \) The first step in the radical initiation 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](image)

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, 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).
The radical by photolysis of the hydroxamic acid derivatives was further explored for the use in cyclisation reactions by Zard et al. in 1995. 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).

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.

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). 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.

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. 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.

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 C3 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 °C this was followed by a continuous quench with a third flow of 1M HCl at 25 °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).

![Scheme 2.1](image)

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.\(^7\) 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.

![Chemical reaction diagram]

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

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. 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.
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

\[
\text{STY (g L}^{-1} \text{h}^{-1}) \text{ = } \frac{\text{Mass of product (g)}}{\text{Reactor volume (L) x Residence time (h)}} \quad [1]
\]

The STY for each of the substrates synthesised in over investigations 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).

![Scheme 2.2](image)

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 MeSO₃H to be equal. 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.

\[ V = \pi r^2 h \] [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 mercury 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 1/32\textsuperscript{nd} 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.
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).

![Figure 2.1](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Flow rate (mL min$^{-1}$)</th>
<th>Yield (%)</th>
<th>Productivity (g h$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.33</td>
<td>66</td>
<td>0.45</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>62</td>
<td>1.25</td>
</tr>
</tbody>
</table>

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\textsubscript{3}H then flowed into the UV reactor for the \textit{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\textsubscript{3}H 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 \textbf{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).

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Entry & Substrate & Yield (%) & Productivity (g h\textsuperscript{-1}) & STY (g L\textsuperscript{-1} h\textsuperscript{-1}) \\
\hline
1 & & 34 & 0.29 & 9.6 \\
\hline
2 & & 25 & 0.165 & 5.5 \\
\hline
\end{tabular}
\caption{Table 2.4}
\end{table}

The postulated side-product was the \textit{\delta}-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 \textit{N}-arylation step in flow separately.
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 1/32\textsuperscript{nd} 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\textsuperscript{-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.
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.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Productivity (g h⁻¹)</th>
<th>STY (g L⁻¹ h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>73</td>
<td>0.92</td>
<td>180</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>72</td>
<td>1.13</td>
<td>221</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>61</td>
<td>0.97</td>
<td>129</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>61</td>
<td>0.95</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>51</td>
<td>0.78</td>
<td>91</td>
</tr>
</tbody>
</table>

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. 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$^{-1}$. 
<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Productivity (g h(^{-1}))</th>
<th>STY (g L(^{-1}) h(^{-1}))</th>
<th>Batch Yields (^{77})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>38</td>
<td>1.00</td>
<td>198</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>43</td>
<td>1.29</td>
<td>260</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>60</td>
<td>1.62</td>
<td>325</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td>35</td>
<td>0.76</td>
<td>152</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td>0.65</td>
<td>130</td>
</tr>
</tbody>
</table>

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.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction</th>
<th>Yield (%)</th>
<th>Productivity (g h⁻¹)</th>
<th>STY (g L⁻¹ h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chlorination</td>
<td>45</td>
<td>0.498</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>N-arylation</td>
<td>58</td>
<td>1.12</td>
<td>224</td>
</tr>
</tbody>
</table>

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
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).\textsuperscript{77}

It was decided to investigate whether the basic conditions detailed by Sarpong \textit{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.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure24.png}
\caption{Figure 2.4}
\end{figure}

\textbf{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.\textsuperscript{78} LiAlH\textsubscript{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.\textsuperscript{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](image)

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.\textsuperscript{43} This involved photolysis of the chloroamines 256a and 256b with Et\textsubscript{3}N 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 \textsuperscript{1}H 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$_3$H and conc. H$_2$SO$_4$ was attempted however, no product was observed in either reaction and only the dechlorinated amine was recovered (Table 2.8, Entries 3-5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-pyridine 256a</td>
<td>Et$_3$N, DCM, hv, RT, 5 h</td>
<td>Amine 259</td>
</tr>
<tr>
<td>2</td>
<td>4-pyridine 256b</td>
<td>Et$_3$N, DCM, hv, RT, 5 h</td>
<td>Amine 259</td>
</tr>
<tr>
<td>3</td>
<td>3-pyridine 256a</td>
<td>MeSO$_3$H, DCM, hv, RT, 5 h</td>
<td>Amine 259</td>
</tr>
<tr>
<td>4</td>
<td>4-pyridine 256b</td>
<td>MeSO$_3$H, DCM, hv, RT, 5 h</td>
<td>Amine 259</td>
</tr>
<tr>
<td>5</td>
<td>4-pyridine 256b</td>
<td>H$_2$SO$_4$, hv, RT, 5 h</td>
<td>Amine 259</td>
</tr>
</tbody>
</table>

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.

![Image](256a.png)

![Image](256b.png)

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). The reaction was
carried out exactly as described in Sarpong’s paper, however no desired product was observed by \(^1\text{H} \text{NMR or LC-MS analysis and only the amine 259 was recovered.}

![Scheme 2.6](image)

**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](image)

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](image)
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 LiAlH₄, 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.

![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 ¹H 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 H₂SO₄ or MeSO₃H (Table 2.9, Entries 2-3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₃N (6 eq), DCM, hυ, RT, 5 h</td>
<td>Amine 271</td>
</tr>
<tr>
<td>2</td>
<td>MeSO₃H (10 eq), DCM, hυ, RT 5 h</td>
<td>Amine 271</td>
</tr>
<tr>
<td>3</td>
<td>H₂SO₄ (80% soln. in H₂O), hυ, RT, 5 h</td>
<td>Amine 271</td>
</tr>
</tbody>
</table>

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.

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 methyamine to afford the desired amide 276 in a 72% yield.

![Scheme 2.9](image)

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](image)

With the unsuccessful attempts to brominate the amide, alternative conditions were found for chlorination. 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).
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).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalents of reagents</th>
<th>Yield of chloroamide 278</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOCl (1.00 eq), AcOH (1.00 eq), tBuOH (1.00 eq)</td>
<td>54 %</td>
</tr>
<tr>
<td>2</td>
<td>NaOCl (1.05 eq), AcOH (1.05 eq), tBuOH (1.05 eq)</td>
<td>66 %</td>
</tr>
<tr>
<td>3</td>
<td>NaOCl (1.50 eq), AcOH (1.50 eq), tBuOH (1.50 eq)</td>
<td>83 %</td>
</tr>
</tbody>
</table>

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. Neutral conditions which utilise a range of solvents of increasing polarity were chosen in line with what had been used previously in literature. 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$_2$SO$_4$ was used (Table 2.11, Entry 3).

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et$<em>3$N (6 eq), DCM, h$</em>\nu$, RT, 5 h</td>
<td>Amide 276 (90%)</td>
</tr>
<tr>
<td>2</td>
<td>MeSO$<em>3$H (10 eq), DCM, h$</em>\nu$, RT, 5 h</td>
<td>280 52% yield</td>
</tr>
<tr>
<td>3</td>
<td>H$_2$SO$_4$ (80% soln. in H$<em>2$O), h$</em>\nu$, RT, 5 h</td>
<td>Amide 276 (85%)</td>
</tr>
<tr>
<td>4</td>
<td>DCM, h$_\nu$, RT, 5 h</td>
<td>Amide 276 (93%)</td>
</tr>
<tr>
<td>5</td>
<td>Toluene, h$_\nu$, RT, 5 h</td>
<td>Amide 276 (84%)</td>
</tr>
<tr>
<td>6</td>
<td>CH$<em>3$CN, h$</em>\nu$, RT, 5 h</td>
<td>Amide 276 (89%)</td>
</tr>
<tr>
<td>7</td>
<td>$t$-Butanol, h$_\nu$, RT, 5 h</td>
<td>Amide 276 (88%)</td>
</tr>
<tr>
<td>8</td>
<td>2-Methyl but-2-ene (1 eq), DCM, RT, h$_\nu$, 5 h</td>
<td>Amide 276 (86%)</td>
</tr>
<tr>
<td>9</td>
<td>BF$_3$OEt$<em>2$ (5 eq), DCM, h$</em>\nu$, RT, 5 h</td>
<td>Amide 276 (85%)</td>
</tr>
</tbody>
</table>

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).
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.

\[
\text{Scheme 2.12}
\]
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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Products (isolated yields)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₃N (6 eq), DCM, hυ, RT, 5 h</td>
<td>Amide 282 (90%)</td>
</tr>
<tr>
<td>2</td>
<td>MeSO₃H (10 eq), DCM, hυ, RT, 5 h</td>
<td>Amide 282 (89%)</td>
</tr>
<tr>
<td>3</td>
<td>H₂SO₄ (80% soln. in H₂O), hυ, RT, 5 h</td>
<td>Amide 282 (87%)</td>
</tr>
<tr>
<td>4</td>
<td>DCM, hυ, RT, 5 h</td>
<td>Amide 282 (92%)</td>
</tr>
<tr>
<td>5</td>
<td>Toluene, hυ, RT, 5 h</td>
<td>Amide 282 (88%)</td>
</tr>
<tr>
<td>6</td>
<td>MeCN, hυ, RT, 5 h</td>
<td>Amide 282 (93%)</td>
</tr>
<tr>
<td>7</td>
<td>t-Butanol, hυ, RT, 5 h</td>
<td>Amide 282 (88%)</td>
</tr>
<tr>
<td>8</td>
<td>2-Methyl but-2-ene, DCM, hυ, RT, 5 h</td>
<td>Amide 282 (86%)</td>
</tr>
<tr>
<td>9</td>
<td>BF₃·OEt₂, DCM, hυ, RT, 5 h</td>
<td>Amide 282 (85%)</td>
</tr>
</tbody>
</table>

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

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.

![Figure 2.9](image)

**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).

![Scheme 2.14](image)

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.
The chloroamide 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product (isolated yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et$_3$N (6 eq), DCM, hu, RT 5 h</td>
<td>Amide 287 (88%)</td>
</tr>
<tr>
<td>2</td>
<td>MeSO$_3$H (10 eq), DCM, hu, RT, 5 h</td>
<td>Amide 287 (80%) + dihydroindolones 289 (trace)</td>
</tr>
<tr>
<td>3</td>
<td>H$_2$SO$_4$ (80% soln. in H$_2$O), hu, RT, 5 h</td>
<td>Amide 287 (85%)</td>
</tr>
<tr>
<td>4</td>
<td>Toluene, hu, RT, 5 h</td>
<td>Amide 287 (92%)</td>
</tr>
<tr>
<td>5</td>
<td>DCM, hu, RT, 5 h</td>
<td>Amide 287 (95%)</td>
</tr>
<tr>
<td>6</td>
<td>t-Butanol, hu, RT, 5 h</td>
<td>Amide 287 (96%)</td>
</tr>
<tr>
<td>7</td>
<td>BF$_3$OEt$_2$ (5 eq), DCM, hu, RT, 5 h</td>
<td>Dihydroindolones 289 (10% yield)</td>
</tr>
</tbody>
</table>

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.
entry cyclisation of the amidyl radical. The first step in the synthesis was the acetylation of
next step was the chlorination of the amide using the previously established conditions to afford
after cyclisation. This could also show whether having the sp
investigate the acetylated version where the amide would be in the
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 sp² 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.

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.
When the reaction was carried out using \( \text{AlCl}_3 \) DCM was also carried out in the dark. After 5 hours only the chloroamide was isolated after purification with impurities present. 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 \(^1\text{H} \) NMR or LC-MS analysis. However, when it was tested in hexane the product was observed by \(^1\text{H} \) NMR and 6% yield of the product was isolated after purification with impurities present. When the reaction was carried out using the \( \text{AlCl}_3 \) none of the desired product was isolated. As before, the reaction using BF\(_3\)OEt\(_2\) in DCM was also carried out in the dark. After 5 hours only the chloroamide 292 was present in the reaction mixture.

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 \(^1\text{H} \) NMR or LC-MS analysis. However, when it was tested in hexane the product was observed by \(^1\text{H} \) NMR and 6% yield of the product was isolated after purification with impurities present. When the reaction was carried out using the \( \text{AlCl}_3 \) none of the desired product was isolated. As before, the reaction using BF\(_3\)OEt\(_2\) in DCM was also carried out in the dark. After 5 hours only the chloroamide 292 was present in the reaction mixture.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et(_3)N (6 eq), DCM, hv, RT, 5h</td>
<td>Amide 291 (92%)</td>
</tr>
<tr>
<td>2</td>
<td>MeSO(_3)H (10 eq), DCM, hv, RT, 5h</td>
<td>Amide 291 (93%)</td>
</tr>
<tr>
<td>3</td>
<td>Toluene, hv, RT, 5h</td>
<td>Amide 291 (94%)</td>
</tr>
<tr>
<td>4</td>
<td>DCM, hv, RT, 5h</td>
<td>Amide 291 (88%)</td>
</tr>
<tr>
<td>5</td>
<td>MeCN, hv, RT, 5h</td>
<td>Amide 291 (90%)</td>
</tr>
<tr>
<td>6</td>
<td>( t)-Butanol, hv, RT, 5h</td>
<td>Amide 291 (94%)</td>
</tr>
<tr>
<td>7</td>
<td>BF(_3)OEt(_2) (5 eq), DCM, hv, RT, 5h</td>
<td>Amide 291 + product 293 (3% yield impure)</td>
</tr>
</tbody>
</table>

Table 2.15

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Products (isolated yields%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF(_3)OEt(_2) (5 eq), DCM, hv, RT, 5h</td>
<td>Amide 291 + D.P. 293 (3% yield impure)</td>
</tr>
<tr>
<td>2</td>
<td>BF(_3)OEt(_2), toluene, hv, RT, 5h</td>
<td>Amide 291 (95%)</td>
</tr>
<tr>
<td>3</td>
<td>BF(_3)OEt(_2), hexane, hv, RT, 5h</td>
<td>Amide 291 + D.P. 293 (6% yield impure)</td>
</tr>
<tr>
<td>4</td>
<td>AlCl(_3), DCM, hv, RT, 5h</td>
<td>Amide 291 (94%)</td>
</tr>
</tbody>
</table>

Table 2.16
2.3.5 Constraining 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 \textit{in situ} which then cyclised.\textsuperscript{61} The amide 165, was prepared by an amide coupling with biphenylcarboxylic acid 294 and methylamine in 72\% yield (Scheme 2.16).

\begin{equation}
\begin{array}{c}
\text{HO-} \\
\text{CHO}
\end{array}
\xrightarrow{TBTU, DIPEA, \text{MeNH}_2HCl, DCM, RT, 16h}
\begin{array}{c}
\text{HN-} \\
\text{NO}
\end{array}
\end{equation}

\text{Scheme 2.16}

The conditions to form the iodoamide \textit{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 \textsuperscript{1}H NMR.

\begin{equation}
\begin{array}{c}
\text{HN-} \\
\text{NO}
\end{array}
\xrightarrow{hv, ICl, KO'Bu, iodine, DCM, RT, 5h}
\begin{array}{c}
\text{N-} \\
\text{NO}
\end{array}
\end{equation}

\text{Scheme 2.17}

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

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.
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.

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, tBuBrettphos), 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).\(^{45}\)

\[ \text{Ph} + \text{Cl-N} \text{R} \xrightarrow{\text{FeSO}_4, \text{H}_2\text{SO}_4/\text{AcOH}} \text{Ph-N} \text{R} \]

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\(_3\)H in DCM (Scheme 3.2). Initial 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.
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). The chloroamines can be purified by column chromatography and most can be fully characterised, some decompose during LC-MS analysis to the parent amine.

The conditions used by Minisci et al. utilised H$_2$SO$_4$/AcOH (3:1) as the solvent. 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.
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 MeSO₃H, with all other acids affording the amine 236 or SM 115 after 1 hour (Table 3.2, entry 6).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield of 116 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FeSO₄•7H₂O (10 mol%), H₂SO₄, AcOH (3:1), 0 °C, 1 h</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>FeSO₄•7H₂O (10 mol%), H₂SO₄, AcOH (3:1), -5 °C, 1 h</td>
<td>80</td>
</tr>
</tbody>
</table>

Table 3.1
The reaction was carried out using MeSO\textsubscript{3}H 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.
Entries 6-7). The best yields were observed with 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 FeCl₃, the reactions using ferrocene, Fe(acac)₃ and Fe(OTf)₂ were used, only the amine 236 was obtained (Table 3.4, Entries 6-7). The best yields were observed with FeSO₄·7H₂O, 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 FeCl₃, 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)₃ and Fe(OTf)₂ suggesting that the iron(II) source was soluble in DCM giving a homogenous reaction mixture.

### Table 3.3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product (isolated yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FeSO₄·7H₂O (10 mol%), MeSO₃H (10 eq.), RT, 1 h</td>
<td>THQ 116 (50%)</td>
</tr>
<tr>
<td>2</td>
<td>FeSO₄·7H₂O (10 mol%), MeSO₃H (10 eq.), 0 °C, 1 h</td>
<td>THQ 116 (73%)</td>
</tr>
<tr>
<td>3</td>
<td>FeSO₄·7H₂O (10 mol%), MeSO₃H (10 eq.), -5 °C, 1 h</td>
<td>THQ 116 (73%)</td>
</tr>
<tr>
<td>4</td>
<td>FeSO₄·7H₂O (10 mol%), 0 °C, 1 h</td>
<td>SM 115</td>
</tr>
<tr>
<td>5</td>
<td>MeSO₃H (10 eq.), 0 °C, 1 h</td>
<td>SM 115</td>
</tr>
</tbody>
</table>

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 FeSO₄·7H₂O, FeCl₂ or ferrocene (Table 3.4, Entries 1,2 and 4). When Fe(CO₂CH₃)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 FeSO₄·7H₂O, 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 FeCl₃, 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)₃ and Fe(OTf)₂ suggesting that the iron(II) source was soluble in DCM giving a homogenous reaction mixture.
Through each of these investigations it was shown that the best conditions were FeSO$_4$$\cdot$7H$_2$O (10 mol%) and MeSO$_3$H (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$_3$H 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Change in Iron Salt (10 mol%)</th>
<th>Products (isolated yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FeSO$_4$$\cdot$7H$_2$O</td>
<td>THQ <strong>116</strong> (73%)</td>
</tr>
<tr>
<td>2</td>
<td>FeCl$_2$</td>
<td>THQ <strong>116</strong> (63%)</td>
</tr>
<tr>
<td>3</td>
<td>FeCl$_3$</td>
<td>SM <strong>115</strong> (90%)</td>
</tr>
<tr>
<td>4</td>
<td>Ferrocene</td>
<td>THQ <strong>116</strong> (20%) and chlorinated THQ <strong>299</strong> (trace)</td>
</tr>
<tr>
<td>5</td>
<td>Fe(acac)$_2$</td>
<td>SM <strong>115</strong> (88%)</td>
</tr>
<tr>
<td>6</td>
<td>Fe(CO$_2$CH$_3$)$_2$</td>
<td>Amine <strong>236</strong> (88%)</td>
</tr>
<tr>
<td>7</td>
<td>Fe(OTf)$_2$</td>
<td>Amine <strong>236</strong> (85%)</td>
</tr>
</tbody>
</table>

**Table 3.4**
<table>
<thead>
<tr>
<th>Iron Salt (mol%)</th>
<th>2.5</th>
<th>5</th>
<th>7.5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0%</td>
<td>0%</td>
<td>70%</td>
<td>73%</td>
</tr>
<tr>
<td>7.5</td>
<td>0%</td>
<td>54%</td>
<td>68%</td>
<td>53%</td>
</tr>
<tr>
<td>5</td>
<td>0%</td>
<td>55%</td>
<td>53%</td>
<td>56%</td>
</tr>
<tr>
<td>2.5</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*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\(_3\)H 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.
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. 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Products (isolated yield%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>Amine 236 (85%)</td>
</tr>
<tr>
<td>2</td>
<td>EtOAc</td>
<td>SM 115 (90%)</td>
</tr>
<tr>
<td>3</td>
<td>2-methyl THF</td>
<td>Amine 236 (88%)</td>
</tr>
<tr>
<td>4</td>
<td>Dioxane</td>
<td>Trace THQ 116 and Amine 236 (50%)</td>
</tr>
<tr>
<td>5</td>
<td>DCM</td>
<td>THQ 116 (73%)</td>
</tr>
<tr>
<td>6</td>
<td>Toluene</td>
<td>THQ 116 (45%) and trace amine 236</td>
</tr>
</tbody>
</table>

Table 3.6
The desired products from the cyclisations were achieved in good yields (Table 3.8).

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).

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 1H 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.
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 desir© choroamine 311.

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.
bromides, but desired products were obtained in adequate yields.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-Me 308a</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>3,5-Me 308b</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>3-Cl 308c</td>
<td>99</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-Cl 308d</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>2-Cl 308e</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>4-Br 308f</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>4-OMe 308g</td>
<td>63</td>
</tr>
</tbody>
</table>

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.
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.\textsuperscript{80}
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.
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.
Previous work carried out within the group synthesised the amine 237 in one-pot via a Grignard reaction using 3-phenylpropionitrile and pentylmagnesium bromide, the product of which was trapped with ethyl chloroformate to form the imino-carbamate (Scheme 3.9). The imino-carbamate could be reduced using LiAlH₄ 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.

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.

![Figure 3.1](image)

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](image)

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).
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).

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).
It was therefore decided to investigate the substrate scope using the FeSO₄·7H₂O 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](image)

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).
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.

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).
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).

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.
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).

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.
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](image)

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.
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. The amide 363 was reduced using LiAlH₄ 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.

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.
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

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. 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](image-url)

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.
The amide 393a was then reduced using LiAlH₄ 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 LiAlH₄, which resulted in partial reduction of CF₃ group to CF₂H, 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.
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.
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](image)

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 FeCl₂ to generate FeCl₃ 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalents of NCS</th>
<th>Average yield of x (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.00</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>0.90</td>
<td>65</td>
</tr>
</tbody>
</table>

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.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R’</th>
<th>One-pot yield (%)</th>
<th>Two-pot yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>allyl</td>
<td>H</td>
<td>45</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>butyl</td>
<td>H</td>
<td>57</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>3-chloro</td>
<td>42</td>
<td>41</td>
</tr>
</tbody>
</table>

Table 3.14
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.

<table>
<thead>
<tr>
<th>One-pot process yield (%)</th>
<th>Two-pot process (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>44 (639 mg of THQ isolated)</td>
</tr>
</tbody>
</table>

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).
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).

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Concentration with respect to chloroamine</th>
<th>Isolated Yield of product 403 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.45 M</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>1 M</td>
<td>33</td>
</tr>
</tbody>
</table>

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.
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).

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

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.
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
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.\\n
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). 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.

Scheme 3.32
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. 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.

![Chemical structure](image)

Table 3.20

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Product yield (%)</th>
<th>Additive remaining (%)</th>
<th>SM remaining (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>89</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>82</td>
<td>85</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>0</td>
<td>81</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>10</td>
<td>0</td>
<td>36</td>
</tr>
</tbody>
</table>

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.

![Chemical structure](image)

\[ \text{FeSO}_4 \cdot 7\text{H}_2\text{O} (10 \text{ mol\%}), \text{MeSO}_3\text{H} (10 \text{ eq.}), \text{DCM}, \text{[Additive]} \rightarrow 0^\circ \text{C, 1 h} \]

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

**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.\(^2\)
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](image)

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](image)

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.
3.23). 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5 eq. chloroamine, 1 eq. pyridine $N$-oxide</td>
<td>Amine 429</td>
</tr>
<tr>
<td>2</td>
<td>1.5 eq. chloroamine, 1 eq. pyridine $N$-oxide, 13 eq. MeSO$_3$H</td>
<td>Amine 429</td>
</tr>
<tr>
<td>3</td>
<td>1 eq. chloroamine, 10 eq. pyridine $N$-oxide, 20 eq. MeSO$_3$H</td>
<td>Amine 429</td>
</tr>
<tr>
<td>4</td>
<td>1 eq. chloroamine, 10 eq. pyridine $N$-oxide, no acid</td>
<td>SM 401</td>
</tr>
</tbody>
</table>

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. As shown in table 3.23 under various reaction conditions none of the desired compound was observed by LC-MS analysis.
**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](image)

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).
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). Both examples showed improved yields compared to Minisci’s results.

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 1H NMR analysis.
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).
3.6.4 DOE with FeCl$_2$ and FeSO$_4$.7H$_2$O

The iron salts FeCl$_2$ and FeSO$_4$.7H$_2$O 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$_4\cdot7$H$_2$O.

![Reaction diagram]

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

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.

![Chemical structure](attachment:structure.png)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Area%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOAc</td>
<td>5.29</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>17.44</td>
</tr>
<tr>
<td>3</td>
<td>2-methyl THF</td>
<td>12.5</td>
</tr>
<tr>
<td>4</td>
<td>Dioxane</td>
<td>13.93</td>
</tr>
<tr>
<td>5</td>
<td>Isopropanol</td>
<td>67.50</td>
</tr>
<tr>
<td>6</td>
<td>MeCN</td>
<td>15.55</td>
</tr>
<tr>
<td>7</td>
<td>Ethanol</td>
<td>71.43</td>
</tr>
<tr>
<td>8</td>
<td>IPAC</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>MIBK</td>
<td>-</td>
</tr>
</tbody>
</table>

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).\textsuperscript{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.
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).

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 FeCl₃ 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 FeCl₃ into the system. This could be due to the FeCl₃ 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 ammonium radical or scavenge halides.
The catalyst screen showed that FeCl₂ in conjunction with FeCl₃ 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 FeCl₂ (5-20 mol%), FeCl₃ (5-60 mol%) and the equivalents of methylhydroxylamine HCl (1.1-2.9 eq) an increase in yield could be obtained. The mol% of FeCl₃ was calculated by multiplying the FeCl₂ mol% by either 1-3 depending on the factor being high, low or the middle control (2x). With the higher loadings of FeCl₂ (20 mol%) more impurities were observed after 24 hours, whereas with lower loading of FeCl₂ 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 FeCl₂. There is a slight increase in yield from reaction 5 to 7 in which the loading of FeCl₃ is higher.
To see whether this slight increase in yield between reaction 5 and 7 is due to the increase in FeCl₃, it was decided to carry out a reaction using FeCl₂ (5 mol%), FeCl₃ (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 FeCl₃ is increased from 5 mol% to 100 mol%.

![Image of chemical reaction and yield data table]

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

Table 3.27
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 methyamine.

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.
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 methyamine or water could be an issue after a certain level is reached.

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.
It has therefore been established that 5 mol% of FeCl₂ and 1 eq FeCl₃ is the best catalyst combination for the reaction. The addition of 5.8 eq of the methylhydroxylamine 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>% water in solvent</th>
<th>% Area uncorrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0%</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>5%</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>20%</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>35%</td>
<td>57</td>
</tr>
</tbody>
</table>

Table 3.28
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-methoxynaphthlene where the \textit{para} position (which is the more favoured position) we do observe some amination in the \textit{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.
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.\textsuperscript{44}

![Scheme 3.41](image)

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](image)

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](image)

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.
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. As they can help stabilise the negative charge generated on the oxygen when the N-O bond is cleaved.

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.
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 150F254). 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: Continuous 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 \textit{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\(_3\)H (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\(_2\)O 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\(_2\)SO\(_4\) 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**

![Chemical Structure]

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

Compound data can be found in section 4.5

**N-chloro-N-allyl-3-phenylpropan-1-amine 239**

![Chemical Structure]

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

Compound data can be found in section 4.5

**N-chloro-N-benzyl-3-phenylpropan-1-amine 240**

![Chemical Structure]

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: \(\left(\frac{1.88g}{20}\right) \times 12 = 1.13 \text{ g h}^{-1}\)
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.43 – 7.17 (10H, m, 10 × ArCH), 4.13 (2H, NClCH$_2$Ar), 3.00 (2H, t, $J = 6.7$, CH$_2$NCl), 2.72 (2H, t, $J = 7.7$, ArCH$_2$), 2.10 – 2.03 (2H, m, CH$_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 141.8 (C$_q$), 137.1 (C$_q$), 129.2 (2 × ArCH), 128.5 (2 × CH), 128.4 (2 × ArCH), 128.4 (2 × ArCH), 127.9 (ArCH), 125.8 (ArCH), 68.4 (NClCH$_2$Ar), 62.2 (CH$_2$NCl), 32.7 (ArCH$_2$), 29.5 (CH$_2$); IR $\nu_{max}$ (neat) / cm$^{-1}$ 3062, 3027, 2920, 2857, 1702, 1602, 1495, 1453; HRMS (ESI$^+$): C$_{16}$H$_{19}$ClN $[M + H]^+$: calculated 260.1201, found 260.1201, $\Delta = 0.0$ 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: $\left(\frac{1.10 g}{13.6}\right) \times 12 = 0.97$ 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)-N-methylpropan-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: $\left(\frac{0.89 g}{11.2}\right) \times 12 = 0.95$ g h$^{-1}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.63-7.22 (9H, m, 9 × ArCH), 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$_3$) $\delta$ ppm 141.2 (C$_q$), 140.9 (C$_q$), 139.0 (C$_q$), 129.0 (2 × ArCH), 128.9 (2 × ArCH), 127.3
(2 × ArCH), 127.2 (ArCH), 127.1 (2 × ArCH), 65.4 (NCH2), 53.2 (NCH3), 32.5 (ArCH2), 29.8 (CH2); IR $\nu_{\text{max}}$ (neat) / cm$^{-1}$: 3057, 3029, 2997, 2863, 1595, 1487, 1455, 1439; HRMS (ESI): C$_{16}$H$_{19}$ClN [M+H$^+$]: calculated 260.1201, found 260.1201, $\Delta = 0.0$ ppm.

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

![Chemical Structure](image)

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

Compound data can be found in section 4.5

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

![Chemical Structure](image)

General procedure B was followed, using *N*-chloroamine 115 (0.5 M solution in DCM) and MeSO$_3$H (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: $\left(\frac{0.81g}{7}\right) \times 12 = 1.39$ g h$^{-1}$

Compound data can be found in section 4.5
1-allyl-1,2,3,4-tetrahydroquinoline 244

![Structure](image1)

General procedure B was followed, using *N*-chloroamine 239 (0.5 M solution in DCM) and MeSO$_3$H (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: \( \left( \frac{0.58 g}{7} \right) \times 12 = 1.00 \text{ g h}^{-1} \)

Compound data can be found in section 4.5

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

![Structure](image2)

General procedure B was followed, using *N*-chloroamine 240 (0.45 M solution in DCM) and MeSO$_3$H (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: \( \left( \frac{0.65 g}{6} \right) \times 12 = 1.29 \text{ g h}^{-1} \)

$^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.38-7.17 (5H, m, 5 × ArCH), 7.05-6.89 (2H, m, 2 × ArCH), 6.61-6.48 (2H, m, 2 × ArCH), 4.48 (2H, s, NCH$_2$Ar), 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 (ArCH), 128.6 (2 × ArCH), 127.1 (ArCH), 126.7 (ArCH), 126.6 (2 × ArCH), 122.2 (C$_q$), 115.8 (ArCH), 110.9 (ArCH), 55.2 (NCH$_2$Ph), 49.9 (NCH$_2$), 28.2 (ArCH$_2$), 22.4 (CH$_2$); IR $\nu_{\text{max}}$ (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, $\Delta = 0.45$ 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 MeSO₂H (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: \( \left( \frac{0.95 g}{7} \right) \times 12 = 1.62 \text{ g h}^{-1} \)

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 MeSO₂H (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: \( \left( \frac{0.38 g}{6} \right) \times 12 = 0.76 \text{ g h}^{-1} \)

\(^1\text{H NMR}\) (400 MHz, CDCl₃) δ ppm 7.56-7.47 (2H, m, 2 × ArCH), 7.39-7.30 (2H, m, 2 × ArCH), 7.28-7.21 (1H, m, ArCH), 7.00-6.92 (1H, m, ArCH), 6.80-6.70 (2H, m, 2 × ArCH), 3.24-3.17 (2H, m, NC₂H₂), 2.89 (3H, s, NCH₃), 2.74 (2H, t, J = 6.5, ArCH₂), 2.01-1.89 (2H, m, C₂H₂); \(^{13}\text{C NMR}\) (101 MHz, CDCl₃) δ ppm 147.1 (Cₚ), 142.5 (Cₚ), 140.5 (Cₚ), 129.3 (ArCH), 128.7 (2 × ArCH), 127.3 (2 × ArCH), 127.0 (ArCH), 122.2 (Cₚ), 115.4 (ArCH), 110.0 (ArCH), 51.5 (NCH₂), 39.3 (NCH₃), 27.7 (ArCH₂), 22.6 (CH₂); \( \text{IR } \nu_{\text{max}} \) (neat) / cm\(^{-1}\): 3054, 3028, 2924, 2837, 1678, 1605, 1561, 1515; \( \text{HRMS (ESI\textsuperscript{+})} \): C₁₆H₁₄N [M+H\textsuperscript{+}]: calculated 224.1434, found 224.1434, \( \Delta = 0.0 \text{ ppm} \).
2-pentyl-1,2,3,4-tetrahydroquinoline 248

General procedure B was followed, using N-chloroamine 243 (0.25 M solution in DCM) and MeSO₃H (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: \( \frac{0.38 \text{g}}{7} \times 12 = 0.65 \text{ g h}^{-1} \)

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 CH₃CN (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 H₂O (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 NaHCO₃ (aq) to pH 7 and extracted using DCM (3 × 80 mL). The organic phases were dried over MgSO₄ 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 MeNH₂ (8 M solution in EtOH, 8 eq) 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**

\[
\text{Ar-}^\text{O} \xrightarrow{\text{i}} \text{Ar-}^\text{N} \xrightarrow{\text{ii}} \text{Ar-}^\text{N}^\text{Cl}
\]

**Step i:** Following a modified procedure by Williamson *et al.*,\(^9^7\) 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\(_2\)O (12.0 eq), 2M NaOH\(_{\text{aq}}\) (2.0 eq) and H\(_2\)O (2.0 eq). The resulting slurry was dried over Na\(_2\)SO\(_4\), 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.*,\(^7^9\) 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**

\[
\text{Ar-}^\text{C=O}^\text{Et} \xrightarrow{\text{H}_2} \text{Ar-}^\text{C=O}^\text{Et}
\]

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

\[
\begin{align*}
R \text{O} & \quad \rightarrow \quad R \text{O} \quad \text{N} \\
\text{COH} & \quad \rightarrow \quad \text{COHN}
\end{align*}
\]

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\textsubscript{3}. The two phases were separated and the aqueous phase was extracted with DCM (3 ×). The organic phases were combined, dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo}. Purification by column chromatography yielded the desired product.

General Procedure F N-Chlorination

\[
\begin{align*}
\text{Ar} \text{C} & \quad \rightarrow \quad \text{Ar} \text{N} \\
\text{O} & \quad \text{Cl}
\end{align*}
\]

Following a modified procedure by Zhong \textit{et al.}\textsuperscript{80} to a stirred solution of the amide (1.0 eq) and \textit{tert}-butanol (1.5 eq) in MTBE (0.2 M) at 0 °C, was added acetic acid (1.5 eq) and sodium hypochlorite (1.5 eq) dropwise. The reaction mixture was then stirred at 0 °C for 2 h. The organic phases were separated and the top phase was washed with H\textsubscript{2}O then brine, dried using MgSO\textsubscript{4} and concentrated \textit{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

\[
\begin{align*}
& \text{OEt} \\
& \text{OEt}
\end{align*}
\]

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\textsubscript{2}O in hexane, afforded the \textit{title compound} (1.81 g, 10.2 mmol, 54%) as a pale yellow
oil. The NMR data was in accordance with the literature.\textsuperscript{98} \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ ppm 8.67 (1H, d, J = 2.2, C\textsubscript{2}H), 8.60 (1H, dd, J = 4.8, 1.6, C\textsubscript{6}H), 7.83 (1H, dt, J = 7.9, 1.8, C\textsubscript{6}H), 7.67 (1H, d, J = 16.1, C\textsubscript{3}CH), 7.32 (1H, dd, J = 8.4, 4.4, C\textsubscript{5}H), 6.51 (1H, d, J = 16.1, CHCO), 4.28 (2H, q, J = 7.1, OCH\textsubscript{2}), 1.34 (3H, t, J = 7.1, CH\textsubscript{3}); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ ppm 166.3 (CO), 150.9 (C\textsubscript{2}), 149.7 (C\textsubscript{6}), 140.8 (C\textsubscript{3}CHCH), 134.2 (C\textsubscript{4}), 130.2 (C\textsubscript{3}), 123.7 (C\textsubscript{5}), 120.5 (CHCO), 60.8 (CH\textsubscript{2}), 14.3 (CH\textsubscript{3}) \textbf{IR} \textit{ν}_\text{max} (neat)/cm\textsuperscript{-1}: 3031, 2982, 2936, 1712 (CO), 1641, 1586, 1477 1342; HRMS (ESI\textsuperscript{*}): C\textsubscript{10}H\textsubscript{12}NO\textsubscript{2} [M + H]\textsuperscript{+}: calculated 178.0863, found 178.0867, Δ = +2.2 ppm.

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

![Chemical Structure](image)

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\textsubscript{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 °C by addition of 4 M HCl until the reaction mixture was at pH 2. The solution was then neutralised with saturated aqueous NaHCO\textsubscript{3} to pH 7 and extracted with Et\textsubscript{2}O (3 × 100 mL). The combined organic phases were dried over MgSO\textsubscript{4}, filtered through a pad of Celite and concentrated \textit{in vacuo} to afford the \textit{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.\textsuperscript{99} \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ ppm 8.53 – 8.44 (2H, m, includes 1H, m, C\textsubscript{2}H; and 1H, m, C\textsubscript{6}H), 7.55 (1H, dt, J = 7.8, 2.0, C\textsubscript{6}H), 7.23 (1H, dd, J = 7.8, 4.8, C\textsubscript{5}H), 4.14 (2H, q, J = 7.1, OCH\textsubscript{2}), 2.97 (2H, t, J = 7.6, CH\textsubscript{2}), 2.65 (2H, t, J = 7.6, CH\textsubscript{2}), 1.24 (3H, t, J = 7.1, CH\textsubscript{3}); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ ppm 172.3 (CO), 149.8 (C\textsubscript{2}), 147.7 (C\textsubscript{6}), 135.9 (C\textsubscript{3}), 135.8 (C\textsubscript{4}), 123.4 (C\textsubscript{5}), 60.6 (OCH\textsubscript{2}), 35.4 (CH\textsubscript{2}), 28.1 (CH\textsubscript{2}), 14.2 (CH\textsubscript{3}); \textbf{IR} \textit{ν}_\text{max} (neat)/cm\textsuperscript{-1}: 3032, 2982, 2935, 1731 (CO), 1642, 1575, 1422, 1371; HRMS (ESI\textsuperscript{*}): C\textsubscript{10}H\textsubscript{14}NO\textsubscript{2} [M + H]\textsuperscript{+}: calculated 180.1090, found 180.1021, Δ = -1.1 ppm.
Synthesis of N-methyl 3-pyridin-3-yl-propanamide 254a

![Chemical structure of 254a](image)

General procedure B was followed, using the ester 253a (1.30 g, 6.23 mmol) and MeNH₂ (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. **¹H NMR** (300 MHz, CDCl₃) δ ppm 8.50 - 8.44 (2H, m, includes 1H, m, C₂H; and 1H, m, C₆H), 7.55 (1H, dt, J = 7.8, 2.0, C₆H), 7.22 (1H, dd, J = 7.8, 4.8, C₅H), 5.66 (1H, br. s, NH), 2.99 (2H, t, J = 7.6, CH₂), 2.79 (3H, d, J = 4.8, CH₃), 2.48 (2H, t, J = 7.6, CH₂); **¹³C NMR** (75 MHz, CDCl₃) δ ppm 172.0 (CO), 149.7 (C₂), 147.7 (C₆), 136.4 (C₅), 136.1 (C₄), 123.4 (C₃), 37.7 (CH₂), 28.7 (CH₃); **IR** (νmax (neat)/cm⁻¹): 3294, 3085, 2921, 1649 (CO), 1562, 1479, 1413, 1371; **HRMS (ESI⁺)**: C₉H₁₃N₂O [M + H]⁺: calculated 165.1022, found 165.1017, Δ = +0.2 ppm.

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

![Chemical structure of 255a](image)

General procedure C was followed, step i, using amide 254a (430 mg, 2.64 mmol) and LiAlH₄ (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. **¹H NMR** (300 MHz, CDCl₃) δ ppm 8.50-8.46 (2H, m, includes 1H, m, C₂H; and 1H, m, C₆H), 7.54 (1H, dt, J = 7.8, 2.0, C₆H), 7.24 (1H, dd, J = 7.8, 4.8, C₅H), 2.96 (3H, s, CH₃), 2.92 – 2.87 (2H, m, CH₂), 2.71 (2H, t, J = 7.4, CH₂), 1.99 (2H, m, CH₂); **¹³C NMR** (75 MHz, CDCl₃) δ ppm 150.0 (C₂), 147.5 (C₆), 136.9 (C₅), 135.9 (C₄), 123.4 (C₃), 64.7 (CH₂N), 53.1 (CH₃), 29.8 (CH₂), 29.4 (CH₂); **IR** (νmax (neat)/cm⁻¹): 3028, 2941, 2856, 1773, 1710, 1665, 1427, 1348; **HRMS (ESI⁺)**: C₉H₁₄ClN₂ [M + H]⁺: calculated 185.0840, found 185.0840, Δ = -0.2 ppm.
Synthesis of 3-(pyridin-4-yl)prop-2-enoate 252b

![Chemical Structure](image)

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% Et3N), 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 °C, platelets, hexane. The NMR data was in accordance with the literature.100 1H NMR (300 MHz, CDCl3) δ ppm 8.65 (2H, dd, J = 4.5, 1.6, 2 × C2H), 7.59 (1H, d, J = 16.1, C4H), 7.36 (2H, dd, J = 4.6, 1.6, 2 × C3H), 6.59 (1H, d, J = 16.1, CHCO), 4.29 (2H, q, J = 7.1, C2H2), 1.35 (3H, t, J = 7.1, C3H3); 13C NMR (75 MHz, CDCl3) δ ppm 166.0 (CO), 150.6 (2 × C2), 149.7 (C4), 141.7 (CCH), 122.9 (CHCO), 121.8 (2 × C3), 61.0 (CH2), 14.2 (CH3); IR νmax (neat)/cm⁻¹ 3052, 2982, 1704 (CO), 1640, 1623, 1597, 1547, 1444; HRMS (ESI⁺): C10H12NO2 [M + H]⁺: calculated 178.0863, found 178.0864, ∆ = +0.8 ppm.

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

![Chemical Structure](image)

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 1H NMR: (300 MHz, CDCl3) δ ppm 8.51 (2H, dd, J = 4.4, 1.6, 2 × C2H), 7.14 (2H, dd, J = 4.4, 1.6, 2 × C3H), 4.13 (2H, q, J = 7.1, OCH2), 2.95 (2H, t, J = 7.6, CH2), 2.64 (2H, t, J = 7.6, CH2), 1.23 (3H, t, J = 7.1, CH3); 13C NMR (75 MHz, CDCl3) δ ppm 172.2 (CO), 149.9 (2 × C2), 149.4 (C4), 123.7 (2 × C3), 60.7 (OCH2), 34.5 (CH2), 30.1 (CH2), 14.2 (CH3); IR νmax (neat)/cm⁻¹ 3027, 2981, 2933, 1728 (CO), 1601, 1559, 1445, 1415; HRMS (ESI⁺): C10H14NO2 [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 MeNH₂ (8 M in EtOH, 13 mL). Purification by column chromatography eluting with 1% MeOH in DCM (1% Et₃N), 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 °C, platelets, hexane.

The NMR data was in accordance with the literature.¹⁰³ ¹H NMR (300 MHz, CDCl₃) δ ppm 8.50 (2H, dd, J = 4.4, 1.6, 2 × C₂H), 7.13 (2H, dd, J = 4.4, 1.6, 2 × C₂H), 5.37 (1H, br. s, NH), 2.98 (2H, t, J = 7.6, CH₂), 2.79 (3H, d, J = 4.9, CH₃), 2.47 (2H, t, J = 7.6, CH₂); ¹³C NMR (75 MHz, CDCl₃) δ ppm 172.7 (CO), 150.0 (C₄), 149.9 (2 × C₂), 123.8 (2 × C₃), 36.9 (CH₂), 30.7 (CH₂), 26.3 (CH₃); IR νmax (neat)/cm⁻¹: 3300, 3102, 3027, 2938, 1632 (CO), 1557, 1495, 1454; HRMS (ESI⁺): C₉H₁₃N₂O [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), LiAlH₄ (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. ¹H NMR (500 MHz, CDCl₃) δ ppm 8.55 - 8.52 (2H, m, 2 × C₂H), 7.20 - 7.16 (2H, m, 2 × C₂H), 2.97 (3H, s, CH₃), 2.89 (2H, t, J = 6.7, CH₂), 2.76 - 2.72 (2H, m, CH₂), 2.05 - 1.98 (2H, m, CH₂); ¹³C NMR (75 MHz, CDCl₃) δ ppm 149.8 (2 × C₂), 149.0 (C₄), 124.0 (2 × C₃), 64.7 (CH₂N), 53.1 (CH₃), 29.6 (CH₂), 28.5 (CH₂); IR νmax (neat) / cm⁻¹: 3029, 2949, 2856, 1773, 1702, 1637 1604, 1463; HRMS (ESI⁺): C₉H₁₄ClN₂ [M + H]⁺: calculated 185.0840, found 185.0837, Δ = +1.5 ppm.
Synthesis of ethyl (2E)-3-(6-methoxypyridin-3-yl)prop-2-enoate 266

[Chemical structure image]

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% Et3N), 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$_3$) $\delta$ ppm 8.27 (1H, d, $J$ = 2.4, C$_2$H), 7.77 (1H, dd, $J$ = 8.7, 2.5, C$_4$H), 7.63 (1H, d, $J$ = 16.0, CCH), 6.77 (1H, d, $J$ = 8.7, C$_5$H), 6.33 (1H, d, $J$ = 16.0, CHCO), 4.27 (2H, q, $J$ = 7.1, OCH$_2$), 3.97 (3H, s, OCH$_3$), 1.34 (3H, t, $J$ = 7.1, CH$_2$CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 166.8 (CO), 165.3 (OC$_4$), 148.3 (C$_2$), 140.9 (CCH), 136.3 (C$_4$), 123.9 (C$_6$), 117.2 (CHCO), 111.6 (C$_5$), 60.5 (OCH$_2$), 53.8 (OCH$_3$), 14.3 (CH$_2$CH$_3$); IR $\nu_{max}$ (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, $\Delta$ = -2.2 ppm

Synthesis of ethyl 3-(6-methoxypyridin-3-yl)propanoate 267

[Chemical structure image]

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$_3$) $\delta$ ppm 8.00 (1H, d, $J$ = 2.0, C$_2$H), 7.43 (1H, dd, $J$ = 8.5, 2.5, C$_4$H), 6.68 (1H, d, $J$ = 8.5, C$_5$H), 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$_3$) $\delta$ ppm 172.5 (CO), 163.0 (OC$_6$), 146.1 (C$_2$), 138.9 (C$_4$), 128.5 (C$_3$), 110.6 (C$_5$), 60.5 (OCH$_2$), 53.3 (OCH$_3$), 35.9 (CH$_2$), 27.3 (CH$_2$), 14.2 (CH$_2$CH$_3$); IR $\nu_{max}$ (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, $\Delta$ = +0.7 ppm.
Synthesis of 3-(6-methoxypyridin-3-yl)-N-methylpropanamide 268

General procedure B was followed, using the ester 267 (5.00 g, 23.9 mmol) and MeNH₂ (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°C, platelets, hexane. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.99 (1H, d, J = 2.4, C₃H), 7.43 (1H, dd, J = 8.5, 2.5, C₄H), 6.67 (1H, d, J = 8.5, C₅H), 5.38 (1H, s, NH), 3.91 (3H, s, OCH3), 2.90 (2H, t, J = 7.6, CH₂), 2.78 (3H, d, J = 4.9, NHCH₃), 2.42 (2H, t, J = 7.6, CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 172.2 (CO), 162.9 (OC₆), 146.0 (C₂), 139.0 (C₄), 128.9 (C₃), 110.6 (C₅), 53.3 (OCH₃), 38.2 (CH₂), 27.9 (CH₂), 26.3 (CH₃); IR νmax (neat)/cm⁻¹: calculated 3131, 3107, 2949, 2932, 1638, 1609, 1566, 1492; HRMS (ESI⁺): C₁₁H₁₄N₂NaO₂ [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 LiAlH₄ (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. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.98 (1H, d, J = 2.4, 0.5, C₃H), 7.42 (1H, dd, J = 8.5, 2.5, C₄H), 6.68 (1H, d, J = 8.5, C₅H), 3.91 (3H, s, CH₃), 2.93 (3H, s, CH₃), 2.90 – 2.82 (2H, m, CH₂), 2.65 – 2.58 (2H, m, CH₂), 1.99 – 1.86 (2H, m, CH₂); ¹³C NMR (75 MHz, CDCl₃) δ ppm 162.7 (OC₆), 146.1 (C₂), 138.9 (C₄), 129.5 (C₃), 110.5 (C₅), 64.8 (CH₂), 53.3 (CH₃), 53.1 (CH₃), 29.6 (CH₂), 28.8 (CH₂); IR νmax (neat)/cm⁻¹: calculated 2945, 2845, 2795, 1607, 1572, 1489, 1460, 1439; HRMS (ESI⁺): C₁₀H₁₆³⁵ClN₂O [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 \textit{trans}-cinnamate (4.00 g, 24.7 mmol) and 10\% Pd/C (400 mg, 10\% wt), affording the \textit{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.$^{105}$\textbf{\textit{H}} NMR \((300 \text{ MHz, CDCl}_3) \ \delta \ 7.37 \text{ – } 7.18 \ (5\text{H, m, 5 } \times \text{ ArCH}), \ 3.70 \ (3\text{H, s, C}_3\text{H}), \ 2.98 \ (2\text{H, t, } J = 7.8, \text{ ArCH}_2), \ 2.66 \ (2\text{H, t, } J = 7.8, \text{ CH}_2\text{CO}); \ \textbf{^{13}}\text{C} \text{ NMR} \ (75 \text{ MHz, CDCl}_3) \ \delta \ 173.3 \ (\text{CO}), \ 140.5 \ (\text{C}_q), \ 128.5 \ (\text{ArC}), \ 128.3 \ (\text{ArC}), \ 126.3 \ (\text{ArC}), \ 51.6 \ (\text{CH}_3), \ 35.7 \ (\text{CH}_2), \ 30.9 \ (\text{CH}_2); \ \textbf{IR} \ \nu_{\text{max}} \ (\text{neat}) / \text{cm}^{-1} \ 3063, \ 3028, \ 2951, \ 2848, \ 1734 \ (\text{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 \times 3), dried over Na$_2$SO$_4$ and concentrated \textit{in vacuo} to afford the \textit{title compound} (2.50 g, 16.6 mmol, 74\%) as a colourless solid which was recrystallized in hexane to yield colourless crystals. \textbf{M.p.} 43-44 °C, needles, hexane. The NMR data was in accordance with literature.$^{106}$\textbf{\textit{H}} NMR \((300 \text{ MHz, CDCl}_3) \ \delta \ 9.00 \ (1\text{H, s, O}_\text{H}), \ 7.35 \text{ – } 7.15 \ (5\text{H, m, 5 } \times \text{ ArCH}), \ 2.96 \ (2\text{H, t, } J = 7.8, \text{ CH}_2), \ 2.69 \ (2\text{H, t, } J = 7.8, \text{ CH}_2); \ \textbf{^{13}}\text{C} \text{ NMR} \ (75 \text{ MHz, CDCl}_3) \ \delta \ 178.7 \ (\text{CO}), \ 140.2 \ (\text{C}_q), \ 128.6 \ (2 \times \text{ ArC}), \ 128.3 \ (2 \times \text{ ArC}), \ 126.4 \ (\text{ArC}), \ 35.5 \ (\text{CH}_2), \ 30.6 \ (\text{CH}_2); \ \textbf{IR} \ \nu_{\text{max}} \ (\text{neat}) / \text{cm}^{-1} \ 3058, \ 3028 \ (\text{br OH}), \ 2952, \ 2932, \ 2625, \ 1692 \ (\text{CO}), \ 1601, \ 1495; \ \textbf{HRMS} \ (\text{ESI}): \text{C}_9\text{H}_9\text{Na}_2\text{O}_2 \ [M + \text{Na}_2 - \text{H}]: \text{calculated} \ 195.0392, \text{found} \ 195.0388, \Delta = -2.5 \text{ ppm}.
Synthesis of \textit{N}-methyl-3-phenylpropanamide \textit{276}

\begin{center}
\includegraphics[width=0.2\textwidth]{synthesis_n_methyl-3-phenylpropanamide_276}
\end{center}

General procedure \textit{E} was followed, using acid \textit{275} (2.21 g, 14.7 mmol), NH\textsubscript{2}Me.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 \textit{title compound} (1.74 g, 10.7 mmol, 72\%) as a colourless solid which was crystallised from hexane to yield colourless crystals. \textbf{M.p.} 54-55 \degree C, platelets, hexane. The NMR data was in accordance with literature.\textsuperscript{107} \textbf{\textit{1H NMR}} (300 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 7.36 - 7.16 (5H, m, 5 \times ArCH), 5.34 (1H, br. s, NH), 2.99 (2H, t, \(J = 7.6\), CH\textsubscript{2}), 2.79 (3H, d, \(J = 4.9\), CH\textsubscript{3}), 2.49 (2H, \(t, J = 7.7\), CH\textsubscript{2}); \textbf{\textit{13C NMR}} (75 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 172.7 (CO), 140.9 (\(C\textsubscript{q}\)), 128.5 (2 \times ArCH), 128.3 (2 \times ArCH), 126.2 (ArCH), 38.5 (CH\textsubscript{2}), 31.7 (CH\textsubscript{2}), 26.3 (CH\textsubscript{3}); \textbf{\textit{IR}} \(\nu\)\textsubscript{max (neat)} / \text{cm}^{-1} 3301, 3064, 3030, 2934, 2877, 1638, 1605, 1549; \textbf{HRMS (ESI\textsuperscript{+})}: \textit{C}_{10}\textit{H}_{14}\textit{NO} [M + H]\textsuperscript{+}: calculated 164.1070, found 164.1070, \(\Delta = -1.5\) ppm.

Synthesis of \textit{N}-chloro-\textit{N}-methyl-3-phenylpropanamide \textit{278}

\begin{center}
\includegraphics[width=0.2\textwidth]{synthesis_n_chloro_n_methyl-3-phenylpropanamide_278}
\end{center}

General procedure \textit{F}, using amide \textit{276} (670 mg, 4.10 mmol), \textit{ tert-}butanol (610 \text{\mu}L, 6.15 mmol), acetic acid (350 \text{\mu}L, 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 \textit{title compound} (671 mg, 3.39 mmol, 83\%) as a colourless oil. \textbf{\textit{1H NMR}} (300 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 7.35 - 7.17 (5H, m, 5 \times ArCH), 3.33 (3H, s, CH\textsubscript{3}), 3.01 - 2.93 (2H, m, CH\textsubscript{2}), 2.85 - 2.77 (2H, m, CH\textsubscript{2}); \textbf{\textit{13C NMR}} (126 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 174.0 (CO), 140.8 (\(C\textsubscript{q}\)), 128.5 (2 \times ArC), 128.4 (2 \times ArC), 126.3 (ArC), 40.9 (CH\textsubscript{3}), 35.2 (CH\textsubscript{2}), 31.1 (CH\textsubscript{2}); \textbf{\textit{IR}} \(\nu\)\textsubscript{max (neat)} / \text{cm}^{-1} 3085, 3062, 3027, 2936, 2873, 1667, 1603, 1495; \textbf{HRMS (ESI\textsuperscript{+})}: \textit{C}_{10}\textit{H}_{13}\textit{ClNO} [M + H]\textsuperscript{+}: calculated 198.0680, found 198.0680, \(\Delta = -0.3\) ppm.

150
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 MgSO₄ 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. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.44 – 7.28 (5H, m, 5 × ArCH), 5.54 (1H, br. s, NH), 5.42 (1H, dd, J = 9.1, 5.2, CH), 2.96 – 2.83 (2H, m, CH₂), 2.81 (3H, d, J = 4.9, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ ppm 169.4 (CO), 140.7 (ArC₆), 128.8 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 128.3 (ArCH), 126.8 (ArCH), 59.1 (CH), 47.3 (CH₂), 26.4 (CH₃); IR νmax (neat) / cm⁻¹ 3303 (NH), 3101, 3032, 2932, 2920, 1711 (CO), 1639, 1615; HRMS (ESI⁺): C₁₀H₁₂³⁵ClNNaO [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 NaHCO₃ until neutralised, dried over MgSO₄ 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. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.33 – 7.13 (5H, m, 5 × ArCH), 5.63 (1H, br. s, NH), 3.27 (2H, q, J = 6.5, NHCH₂), 2.68 – 2.61 (2H, t, J = 7.6, ArCH₂), 1.93 (3H, s, CH₃), 1.83 (2H, apparent quin, J = 7.3, CH₂); ¹³C NMR (75 MHz, CDCl₃) δ ppm 170.1 (CO), 141.5 (ArC₆), 128.5 (2 × ArCH), 128.3 (2 × ArCH), 126.0 (ArCH), 39.3 (NHCH₂), 33.3 (ArCH₂), 26.4 (CH₃).
HRMS (ESI\(^+\)): \( \text{C}_{11}\text{H}_{16}\text{NO} \ [\text{M} + \text{H}]^+ \): calculated 178.1226, found 178.1225, \( \Delta = -3.4 \text{ ppm} \).

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

![Chemical structure](image)

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. \(^1\text{H NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) ppm 7.35 – 7.15 (5H, m, 5 \( \times \) ArCH\(_2\)), 3.73 (2H, t, \( J = 7.1, \text{NCICH}_2 \)), 2.64 (2H, t, \( J = 7.4, \text{ArCH}_2 \)), 2.20 (3H, s, CH\(_3\)), 2.01 (2H, quartet, \( J = 7.4, \text{CH}_2 \)); \(^{13}\text{C NMR} \) (126 MHz, CDCl\(_3\)) \( \delta \) ppm 172.0 (CO), 141.0 (ArC\(_3\)), 128.5 (2 \( \times \) ArCH), 128.3 (2 \( \times \) ArCH), 126.1 (ArCH), 51.8 (CH\(_2\)), 32.4 (CH\(_2\)), 28.8 (CH\(_2\)), 21.8 (CH\(_3\)); IR \( \nu \text{max} \) (neat)/cm\(^{-1} \): calculated 3085, 3062, 2934, 2860, 1669, 1603, 1496, 1453; HRMS (ESI\(^+\)): \( \text{C}_{11}\text{H}_{15}\text{ClNO} \ [\text{M} + \text{H}]^+ \): calculated 212.0837, found 212.0830, \( \Delta = +3.4 \text{ ppm} \).

**Synthesis of \( N \)-methyl-2-phenylacetamide 287**

![Chemical structure](image)

General procedure E was followed, using phenylacetic acid (2.00 g, 14.7 mmol), NH\(_2\)Me.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°C, platelets, hexane. The NMR data was in accordance with the literature. \(^1\text{H NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) ppm 7.42 – 7.24 (5H, m, 5 \( \times \) ArCH), 5.43 (1H, br. s, NH), 3.59 (2H, s, CH\(_2\)), 2.77 (3H, d, \( J = 4.9, \text{CH}_3 \)). \(^{13}\text{C NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) ppm 171.6 (CO), 134.9 (ArC\(_3\)), 129.5 (2 \( \times \) ArCH), 129.1 (2 \( \times \) ArCH), 127.4 (ArCH), 43.8 (CH\(_2\)), 26.5 (CH\(_3\)); IR \( \nu \text{max} \) (neat)/cm\(^{-1} \): calculated 3301, 3087, 3064, 3030, 2934, 2877, 1638, 1549; HRMS (ESI\(^+\)): \( \text{C}_9\text{H}_{12}\text{NO} \ [\text{M} + \text{H}]^+ \): calculated 150.0913, found 150.0911, \( \Delta = +1.8 \text{ ppm} \).
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.\textsuperscript{110} \textbf{1H NMR} (300 MHz, CDCl$_3$) δ ppm 7.40 – 7.25 (5H, m, 5 × ArCH), 3.90 (2H, s, CH$_2$), 3.38 (3H, s, CH$_3$); \textbf{13C NMR} (126 MHz, CDCl$_3$) δ ppm 172.6 (CO), 129.2 (2 × ArCH), 128.6 (2 × ArCH), 127.1 (ArCH), 41.2 (CH$_3$), 40.2 (CH$_2$); \textbf{IR} $\nu_{\text{max}}$ (neat) / cm$^{-1}$: 3031, 3007, 2968, 2913, 1682, 1659 (CO), 1496, 1451; \textbf{HRMS (ESI$^+$)}: C$_9$H$_{11}$ClNO [M + H$^+$]: calculated 184.0524, found 184.0518, $\Delta$ = -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$_3$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.\textsuperscript{111} \textbf{1H NMR} (300 MHz, CDCl$_3$) δ ppm 7.34 – 7.23 (2H, m, 2 × ArCH), 7.06 (1H, td, $J$ = 7.6, 0.9, ArCH), 6.84 (1H, d, $J$ = 7.8, ArCH), 3.55 (2H, s, CH$_2$), 3.24 (3H, s, $J$ = 5.1, CH$_3$); \textbf{13C NMR} (126 MHz, CDCl$_3$) δ ppm 175.1 (CO), 145.3 (ArC$_6$H$_2$), 127.9 (ArCH), 124.5 (ArC$_6$N), 124.3 (ArCH), 122.3 (ArCH), 108.1 (ArCH), 35.7 (CH$_2$), 26.2 (CH$_3$); \textbf{IR} $\nu_{\text{max}}$ (neat) / cm$^{-1}$: 3056, 2920, 2850, 1711 (CO), 1615, 1494, 1470, 1370; \textbf{HRMS (ESI$^+$)}: C$_9$H$_{10}$NO [M + H$^+$]: calculated 148.0757, found 148.0751, $\Delta$ = +3.9 ppm.
Synthesis of N-(2-phenylethyl)acetamide 291

\[ \text{To a stirred solution of 3-phenylethylamine (2.00 g, 16.5 mmol) and triethylamine (2.65 mL 19.0 mmol) in DCM (12 mL) at 0 }^\circ\text{C was added a solution of acetic anhydride (1.80 mL, 19.0 mmol) in DCM (10 mL) dropwise. After 15 min the reaction was warmed to RT and stirred 16 hours. The RM was washed with 2 M HCl (pH 2). The aqueous phase was extracted with DCM (2 }\times\text{100 mL). The organic phases were combined and washed with a saturated aqueous solution of NaHCO}_3\text{ until neutralised, dried over MgSO}_4\text{ and concentrated in vacuo to afford the title compound (2.25 g, 13.8 mmols, 84%) as a pale yellow solid. This was crystallised from hexane to yield pale yellow crystals which were characterised without further purification. M.p. 46-47 }^\circ\text{C, platelets, hexane. The NMR data was in accordance with the literature.}^{112} \]

\[ \text{H NMR (300 MHz, CDCl}_3\text{) }\delta\text{ ppm 7.40 – 7.17 (5H, m, 5 }\times\text{ ArCH), 5.48 (1H, br. s, NH), 3.54 (2H, q, J = 6.8, NHCH}_2\text{), 2.84 (2H, t, J = 6.9, ArCH}_2\text{), 1.96 (3H, s, CH}_3\text{); C NMR (75 MHz, CDCl}_3\text{) }\delta\text{ ppm 170.0 (CO), 138.9 (ArC}_4\text{), 128.7 (2 }\times\text{ ArCH), 128.7 (2 }\times\text{ ArCH), 126.5 (ArCH), 40.6 (CH}_2\text{), 35.6 (CH}_2\text{), 23.3 (CH}_3\text{); IR }\nu\text{max (neat) }/\text{cm}^{-1}: 3285 (NH) 3086, 3065, 2930, 2871, 1642 (CO), 1539, 1496; HRMS (ESI\textsuperscript{+}): C}_{10}\text{H}_{14}\text{NO [M + H\textsuperscript{+}]: calculated 164.1069, found 164.1066, }\Delta = -2.4 \text{ ppm.} \]

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

\[ \text{General procedure F was followed, using amide 291 (500 mg, 3.06 mmol), tert-butanol (460 }\mu\text{L, 4.59 mmol), acetic acid (260 }\mu\text{L, 4.59 mmol) and sodium hypochlorite (0.75M, 6.12 mL, 4.59 mmol) stirred for 4 h. Purification by column chromatography 10% EtOAc in hexane afforded the title compound (472 mg, 2.39 mmol, 78%) as a colourless oil. The NMR data was in accordance with the literature.}^{113} \]

\[ \text{H NMR (300 MHz, CDCl}_3\text{) }\delta\text{ ppm 7.37 – 7.19 (5H, m, 5 }\times\text{ ArCH), 3.93 (2H, t, J = 7.3, CH}_2\text{), 3.00 (2H, t, J = 7.4, CH}_2\text{), 2.12 (3H, s, CH}_3\text{); C NMR (126 MHz, CDCl}_3\text{) }\delta\text{ ppm 170.3 (CO), 137.6 (ArC}_4\text{), 128.9 (2 }\times\text{ ArCH), 128.6 (2 }\times\text{ ArCH), 126.7 (ArCH), 53.6 (CH}_2\text{), 33.5 (CH}_2\text{), 21.5 (CH}_3\text{); IR }\nu\text{max (neat) }/\text{cm}^{-1}: 3086, 3065, 2934, 2860, 1668, 1539, 1496, 1429; HRMS (ESI\textsuperscript{+}): C}_{10}\text{H}_{13}\text{ClNO [M + H\textsuperscript{+}]: calculated 198.0680, found 198.0673, }\Delta = +3.5 \text{ ppm.} \]
Synthesis of N-methyl-2-phenylbenzamide 165

General procedure E was followed, using 2-biphenylcarboxylic acid (1.00 g, 5.04 mmol), NH₂Me.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 °C, needles, EtOAc. The NMR data was in accordance with literature. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.71 (1H, dd, J = 7.5, 1.5, ArCH), 7.52 - 7.33 (8H, m, 8 × ArCH), 5.15 (1H, br. s, NH), 2.68 (3H, d, J = 4.9, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ ppm 170.2 (CO), 140.2 (ArC₉), 139.3 (ArC₉), 135.7 (ArC₉), 130.2 (ArCH), 130.1 (2 × ArCH), 128.9 (ArCH), 128.7 (2 × ArCH), 127.8 (ArCH), 127.6 (ArCH), 26.7 (CH₃); IR νmax (neat) / cm⁻¹ 3306 (NH), 3077, 3055, 3024, 2977, 2944, 1656 (CO), 1592; HRMS (ESI⁺): C₁₄H₁₄NO [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. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.56 - 7.35 (9H, m, 9 × ArCH), 2.94 (3H, s, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm 171.1 (CO), 139.5 (ArC₉), 133.4 (ArC₉), 130.3 (ArC₉), 130.0 (ArC₉), 129.7 (ArC₉), 128.6 (ArC₉), 128.4 (ArC₉), 128.2 (ArC₉), 127.9 (ArC₉), 127.7 (ArC₉), 21.0 (CH₃); IR νmax (neat) / cm⁻¹ 3057, 3024, 2977, 2944, 1656 (CO), 1596, 1565, 1475; HRMS (ESI⁺): C₁₄H₁₃ClNO [M + H⁺]: calculated 246.0680, found 246.0680, Δ = 0.0 ppm.
4.5 Chapter 3 experimental

General Procedure A Reductive Amination

\[
\text{\textbf{R}H} \quad \rightarrow \quad \text{\textbf{R}N}^R
\]

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 °C and NaBH₄ (2 eq) was added portionwise. The RM was warmed to RT and stirred for 2 h then quenched with saturated aqueous NaHCO₃. The aqueous phase was extracted with EtOAc (3 ×). The combined organic extracts were dried over MgSO₄ and concentrated \textit{in vacuo}. Purification afforded the desired products.

General procedure B Reductive amination with ketones

\[
\text{\textbf{R}H} \quad \rightarrow \quad \text{\textbf{R}N}^R
\]

Following a modified procedure by Williamson \textit{et al}, to a stirred solution of ketone (1 eq) in MeOH (0.2 M) was added amine (3–10 eq) and Ti(O'Pr)₄ (2 eq).⁹⁷ The RM was stirred for 16 h. The RM was cooled to 0 °C and NaBH₄ (2 eq) was added portionwise. The RM was warmed to RT and stirred for 2 h then concentrated \textit{in vacuo}. The residue was taken up in EtOAc and ammonium hydroxide (2M, 6.0 eq) was added. The resulting mixture was dried over MgSO₄, the filtered through Celite and concentrated \textit{in vacuo}. Purification afforded the desired product.

General procedure C Chlorination using NCS

\[
\text{\textbf{R}H}^R \quad \rightarrow \quad \text{\textbf{R}N}^R
\]

Following a modified procedure by De Luca \textit{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**

\[
\begin{align*}
\text{R}'' + \text{R}^{' \text{N.R}} \quad &\rightarrow \quad \text{R}'' \text{N.R}'
\end{align*}
\]

To a stirred solution of the amine (1.0 eq) in DCM (0.2 M) at 0 °C was added MeSO₃H (10 eq) and FeSO₄·7H₂O (10 mol%). 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 ×). The organic phases were combined, dried over MgSO₄ and concentrated in vacuo. Purification by column chromatography yielded the desired product.

**General Procedure E Amide coupling**

\[
\begin{align*}
\text{R} \text{O.H} \quad &\rightarrow \quad \text{R} \text{O.NH}
\end{align*}
\]

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 NaHCO₃. The two phases were separated and the aqueous phase was extracted with DCM (3 ×). The organic phases were combined, dried over MgSO₄ 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)Cl₂] (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 Et₃N (1 eq.) simultaneously. The reaction mixture was heated at 50 °C 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. Chloroacetone (1.1 eq) was then added and the RM was heated at 50 °C for 16 h. The RM was filtered and concentrated in vacuo. The residue was then taken up in H₂O and basified to pH 9 using 2 M NaOH. The aqueous phase was extracted using EtOAc (3 ×). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. Purification by column chromatography afforded the desired product.
General Procedure H N-arylation using hydroxylamines

\[
\begin{align*}
&\text{A stirred solution of the aromatic (1 eq), hydroxylamine (3 eq), FeCl}_2 (5 \text{ mol\%}) \text{ and FeCl}_3 (1 \text{ eq}) \text{ in MeOH was heated at 60 °C for 4 h. Hydroxylamine (3 eq) was then added to the reaction mixture and the reaction was heated at 60 °C for 16 h. The RM was cooled to RT and partitioned between H}_2\text{O and EtOAc. The mixture was basified to pH 9 using 2M NaOH and the phases separated. The aqueous phase was extracted with EtOAc (3 ×). The combined organic extracts were dried over MgSO}_4, \text{ filtered and concentrated in vacuo. Purification by column chromatography afforded the desired product.}
\end{align*}
\]

General Procedure I One pot process

\[
\begin{align*}
\text{Following a modified procedure by De Luca et al.}^{79}, \text{ to a stirred solution of the amine (1.0 eq) in DCM (0.5 M) in the dark was added NCS (0.9 eq) portionwise over 10 min at RT. The RM was stirred for 1 h at RT. The RM was cooled to 0 °C. MeSO}_3\text{H (10 eq) and FeSO}_4\cdot7\text{H}_2\text{O (10 mol\%) were added to the RM. The RM was stirred at 0 °C for 1 h. The RM was basified using 2 M NaOH (pH 9). The two phases were separated and the aqueous phase was extracted with DCM (3 ×). The organic phases were combined, dried over MgSO}_4 \text{ and concentrated in vacuo. Purification by column chromatography yielded the desired product.}
\end{align*}
\]

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4.6 Experimental Data

Synthesis of methyl(3-phenylpropyl)amine 237

General Procedure A was followed, using hydrocinnamaldehyde (4.00 g, 29.8 mmol), MeNH₂ (8 M solution in EtOH, 5.0 ml, 1.3 eq), NaBH₄ (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.¹¹⁶¹¹⁶ H NMR (500 MHz, CDCl₃) δ ppm 7.33 – 7.28 (2H, m, 2 × ArCH), 7.24 – 7.19 (3H, m, 3 × ArCH), 2.72 – 2.62 (4H, m, include ArCH₂ and CH₂N), 2.47 (3H, s, CH₃), 1.91 – 1.82 (2H, m, CH₂); ¹³C NMR (126 MHz, CDCl₃) δ ppm 142.1 (Cq), 128.4 (2 × ArCH), 128.4 (2 × ArCH), 125.8 (ArCH), 51.5 (CH₂NH), 36.3 (CH₃), 33.6 (ArCH₂), 31.3 (CH₂); IR v_max (neat) / cm⁻¹ 3061, 3025, 2932, 2855, 2792, 1659, 1548, 1495; HRMS (ESI⁺): C₁₀H₁₆N [M + H]⁺ : calculated 150.1277, found 150.1278, ∆ = + 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.⁷⁷¹¹⁷¹¹⁷ H NMR (500 MHz, CDCl₃) δ ppm 7.31 – 7.25 (2H, m, 2 × ArCH), 7.21 – 7.17 (3H, m, 3 × ArCH), 2.93 (3H, s, CH₃), 2.88 (2H, t, J = 7.0, NCH₂), 2.69 (2H, t, J = 7.7, ArCH₂), 2.01 – 1.93 (2H, m, CH₂); ¹³C NMR (101 MHz, CDCl₃) δ ppm 141.7 (Cq), 128.5 (2 × ArCH), 128.4 (2 × ArCH), 125.9 (ArCH), 65.3 (NCH₂), 53.1 (CH₃), 32.8 (ArCH₂), 29.8 (CH₂); IR v_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), MeSO₃H (350 µL, 5.40 mmol) and FeSO₄·7H₂O (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

¹H NMR (500 MHz, CDCl₃) δ ppm 7.11 (1H, t, J = 7.7, ArCH), 6.99 (1H, d, J = 7.1, ArCH), 6.65 – 6.62 (2H, m, 2 × ArCH), 3.28 – 3.24 (2H, m, NC₂H₂), 2.92 (3H, s, CH₃), 2.81 (2H, t, J = 6.4, ArCH₂), 2.05 – 2.00 (2H, m, CH₂C₂H₂N); ¹³C NMR (126 MHz,CDCl₃) 146.8 (Cq), 128.8 (ArCH), 127.0 (ArCH), 116.2 (ArCH), 111.0 (ArCH), 51.3 (NCH₂), 39.1 (CH₃), 27.8 (ArCH₂), 22.5 (CH₂); IR νmax (neat) / cm⁻¹ 3075, 3032, 2998, 2931, 2834, 1639, 1611, 1583; HRMS (ESI⁺): C₁₀H₁₄N [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 NaBH₄ (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

¹H NMR (300 MHz, CDCl₃) δ ppm 7.35 – 7.16 (5H, m, 5 × ArCH), 5.86 – 5.99 (1H, m, ArCH), 5.18 (1H, ddd, J = 17.2, 3.3, 1.6, CHCH₂), 5.10 (1H, ddd, J = 10.2, 3.3, 1.6, CHCH₂), 3.27 (2H, dt, J = 6.0, 1.4, NCH₂CH), 2.72 – 2.65 (4H, m, ArCH₂ and CH₂CH₂N), 1.91 – 1.79 (2H, m, CH₂CH₂CH₂); ¹³C NMR (75 MHz, CDCl₃) δ ppm 142.2 (Cq), 137.0 (CH), 128.4 (2 × ArCH), 128.3 (2 × ArCH), 125.8 (ArCH), 115.7 (CHCH₂), 52.5 (NCH₂CH), 49.0 (ArCH₂), 33.7 (CH₂N), 31.8 (CH₂CH₂CH₂); IR νmax (neat) / cm⁻¹ 3082, 3062, 2928, 2857, 2814, 1642, 1603, 1495; HRMS (ESI⁺): C₁₂H₁₈N [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.\(^7\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.36 – 7.27 (2H, m, 2 × ArCH), 7.25 – 7.21 (3H, m, 2 × ArCH), 6.02 – 5.92 (1H, m, CHC\(_2\)H), 5.34 – 5.24 (2H, m, CHC\(_2\)H), 3.62 (2H, d, \(J = 6.4\), NClC\(_2\)H), 2.99 – 2.92 (2H, m, CHC\(_2\)H), 2.75 – 2.67 (2H, m, ArC\(_2\)H), 2.07 – 2.00 (2H, m, ArCHC\(_2\)H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 141.7 (C\(_q\)), 133.6 (CHC\(_2\)H), 128.4 (2 × ArC\(_2\)H), 128.3 (2 × ArC\(_2\)H), 125.9 (ArCH), 119.2 (CHC\(_2\)H), 66.9 (NClC\(_2\)H), 62.2 (CHC\(_2\)H), 32.8 (ArCH), 29.4 (ArCHC\(_2\)H); IR \(\nu_{\max}\) (neat) / cm\(^{-1}\) 3017, 3084, 2982, 2948, 1602, 1495, 1438, 1417; HRMS (ESI\(^+\)): C\(_{12}\)H\(_{17}\)ClN \([\text{M} + \text{H}]^+\) : calculated 210.1044, found 210.1042, \(\Delta = +0.9\) 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\(_3\)H (315 \(\mu\)L, 4.80 mmol) and FeSO\(_4\).7H\(_2\)O (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.\(^7\)

General Procedure I was followed using amine 301a (100 mg, 0.57 mmol), NCS (68 mg, 0.51 mmol), MeSO\(_3\)H (331 \(\mu\)L, 5.10 mmol) and FeSO\(_4\).7H\(_2\)O (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\(_3\)) \(\delta\) ppm 7.02 (1H, t, \(J = 7.8\), ArCH), 6.94 (1H, d, \(J = 7.5\), ArCH), 6.58 – 6.54 (2H, m, 2 × ArCH), 5.89 – 5.80 (1H, m, CHC\(_2\)H), 5.24 – 5.10 (2H, m, CHC\(_2\)H), 3.89 – 3.82 (2H, m, NCH\(_2\)CH), 3.31 – 3.23 (2H, m, NCH\(_2\)H), 2.76 (2H, t, \(J = 6.3\), ArCH), 2.02
−1.90 (2H, m, CH₂); ¹³C NMR (101 MHz, CDCl₃) δ 145.4 (C₆), 133.6 (ArCH), 129.0 (ArCH), 127.1 (ArCH), 122.4 (C₆), 115.9 (CHCH₂), 115.7 (ArCH), 111.0 (CHCH₂), 53.9 (NCH₂CH), 49.2 (NCH₂), 28.2 (ArCH₂), 22.4 (CH₂); IR υmax (neat) / cm⁻¹ 3065, 3022, 2928, 2841, 1725, 1675, 1642, 1601; HRMS (ESI⁺): C₁₂H₁₆N [M + H]⁺: calculated 174.1277, found 174.1272, Δ = -2.9 ppm.

**Synthesis of butyl(3-phenylpropyl)amine 301b**

![Diagram](image)

General procedure A was followed, using hydrocinnamaldehyde (500 mg, 3.73 mmol), butylamine (1.40 mL, 18.7 mmol) and NaBH₄ (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 ¹H NMR (300 MHz, CDCl₃) δ ppm 7.32 − 7.23 (2H, m, 2 × ArCH), 7.22 − 7.12 (3H, m, 3 × ArCH), 2.71 − 2.54 (6H, m, include ArCH₂, C₆H₂ and C₆H₂), 1.89 − 1.75 (2H, m, C₆H₂), 1.54 − 1.39 (2H, m, C₆H₂), 1.39 − 1.26 (2H, m, CH₂CH₃), 0.91 (3H, t, J = 7.2, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ ppm 142.3 (C₆), 128.4 (2 × ArCH), 128.3 (2 × ArCH), 125.7 (ArCH), 49.8 (C₆), 49.7 (ArCH₂), 33.8 (C₆), 32.4 (C₆), 31.8 (C₆), 20.5 (CH₂CH₃), 14.0 (CH₃); IR υmax (neat) / cm⁻¹ 3084, 3062, 3000, 2954, 2926, 2858, 1603, 1495; HRMS (ESI⁺): C₁₃H₂₆N [M + H]⁺: calculated 192.1747, found 192.1753, Δ = +3.4 ppm.

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

![Diagram](image)

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 ¹H NMR (300 MHz, CDCl₃) δ ppm 7.32 − 7.24 (2H, m, 2 × ArCH), 7.22 − 7.14 (3H, m, 3 × ArCH), 2.96 − 2.87 (4H, m, includes C₆H and C₆H), 2.68 (2H, t, J = 7.7, ArCH₂), 2.07 − 1.94 (2H, m, C₆H), 1.69 − 1.59 (2H, m, C₆H), 1.37 (2H, dq, J = 14.5, 7.3, CH₂CH₃), 0.93 (3H, t, J
= 7.3, CH₃); \(^{13}\)C NMR (75 MHz, CDCl₃) δ ppm 141.8 (C₉), 128.5 (ArCH), 128.3 (ArCH), 125.8 (ArCH), 64.1 (C₈), 63.3 (C₇), 32.8 (ArCH₂), 30.0 (C₇), 29.5 (C₆), 20.0 (CH₂CH₃), 13.9 (CH₃); IR \(\nu_{\text{max}}\) (neat) / cm\(^{-1}\) 3026, 2955, 2933, 2864, 1495, 1454, 1366, 1352; HRMS (ESI⁺): C₁₃H₂₁N [M + H]⁺; calculated 226.1357, found 226.1360, \(\Delta = -1.1\) ppm.

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

General Procedure D was followed, using chloroamine 302b (100 mg, 0.44 mmol), MeSO₃H (285 µL, 4.40 mmol) and FeSO₄·7H₂O (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), MeSO₃H (305 µL, 4.70 mmol) and FeSO₄·7H₂O (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, CDCl₃) δ ppm 7.08 – 6.98 (1H, m, ArCH), 6.98 – 6.86 (1H, m, ArCH), 6.60 – 6.49 (2H, m, 2 × ArCH), 3.34 – 3.15 (4H, m, C₆H₂ and C₇H₂), 2.80 – 2.68 (2H, m, ArCH₂), 2.02 – 1.86 (2H, m, C₆H₂), 1.64 – 1.48 (2H, m, C₇H₂), 1.42 – 1.26 (2H, m, CH₂CH₃), 0.95 (3H, \(t, J = 7.3, CH₃\)); \(^{13}\)C NMR (75 MHz, CDCl₃) δ ppm 145.4 (C₉), 129.1 (ArCH), 127.0 (ArCH), 122.1 (C₈), 115.1 (ArCH), 110.5 (ArCH), 51.2 (NCH₂), 49.5 (NCH₂), 28.4 (C₆), 28.2 (ArCH₂), 22.3 (C₇), 20.5 (CH₂CH₃), 14.1 (CH₃); IR \(\nu_{\text{max}}\) (neat) / cm\(^{-1}\) 3064, 3020, 2954, 2929, 2860, 1676, 1601, 1503; HRMS (ESI⁺): C₁₃H₂₀N [M + H]⁺; calculated 190.1590, calculated 190.1593, \(\Delta = +1.5\) 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 NaBH₄ (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

¹H NMR (300 MHz CDCl₃) δ ppm 7.32-7.23 (2H, m, 2 × ArCH), 7.21-7.16 (3H, m, 3 × ArCH), 2.70-2.54 (6H, m, includes ArCH₂, C₆H₂ and C₆H₂), 1.88-1.74 (2H, m, C₆H₂), 1.51-1.41 (2H, m, C₆H₂), 1.37-1.21 (6H, m, includes CH₂CH₃, C₆H₂ and C₆H₂), 0.93-0.83 (3H, m, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ ppm 142.2 (Cₐ), 128.4 (2 × ArCH), 128.3 (2 × ArCH), 125.7 (ArCH), 50.1 (Cₐ), 49.6 (Cₐ), 33.7 (Cₐ), 31.8 (ArCH₂ and Cₐ), 30.2 (Cₐ), 27.1 (Cₐ), 22.6 (CH₂), 14.0 (CH₃); IR vₘₐₓ (neat)/cm⁻¹: 3026, 2925, 2855, 1603, 1495, 1454, 1129, 687; HRMS (ESI⁺): C₁₅H₂₆N [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

¹H NMR (300 MHz, CDCl₃) δ ppm 7.30 (2H, m, 2 × ArCH), 7.25-7.13 (3H, m, 3 × ArCH), 2.92 (4H, m, includes 2H, m, C₆H₂ and C₆H₂), 2.75-2.61 (2H, m, ArCH₂), 2.09-1.95 (2H, m, C₆H₂), 1.75-1.60 (2H, m, C₆H₂), 1.43-1.22 (6H, m, includes C₆H₂, C₆H₂ and CH₂CH₃), 0.91 (3H, t, J = 6.8, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ ppm 142.0 (Cₐ), 128.6 (2 × ArCH), 128.5 (2 × ArCH), 126.0 (ArCH), 64.6 (CH₂), 63.4 (CH₂), 32.9 (CH₂), 31.8 (CH₂), 29.6 (CH₂), 28.0 (CH₂), 26.7 (CH₂), 22.7 (CH₂), 14.2 (CH₃); IR vₘₐₓ (neat)/cm⁻¹: 3085, 3027, 2928, 1063, 1496, 1454, 1347, 1302; HRMS (ESI⁺): C₁₅H₂₅ClN [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\textsubscript{3}H (255 µL, 3.90 mmol) and FeSO\textsubscript{4}.7H\textsubscript{2}O (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.\textsuperscript{77}

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ ppm 7.09-6.99 (1H, m, ArCH), 6.97-6.89 (1H, m, ArCH), 6.63-6.47 (2H, m, includes 2 × ArCH), 3.34-3.15 (4H, m, includes CH\textsubscript{2c} and CH\textsubscript{2d}), 2.75 (2H, t, J = 6.4, ArCH\textsubscript{2}), 2.02-1.88 (2H, m, CH\textsubscript{2a}), 1.66-1.51 (2H, m, CH\textsubscript{2d}), 1.40-1.24 (6H, m, includes CH\textsubscript{2c}, CH\textsubscript{2f} and CH\textsubscript{2f}CH\textsubscript{3}), 0.98-0.81 (3H, m, CH\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ ppm 145.5 (C\textsubscript{o}), 129.3 (ArCH), 127.2 (ArCH), 122.3 (C\textsubscript{o}), 115.3 (ArCH), 110.6 (ArCH), 51.7 (C\textsubscript{e}), 49.6 (C\textsubscript{e}), 31.9 (C\textsubscript{o}), 28.4 (ArCH\textsubscript{2}), 27.1 (C\textsubscript{o}), 26.3 (C\textsubscript{e}), 22.8 (C\textsubscript{e}), 22.4 (CH\textsubscript{2}), 14.2 (CH\textsubscript{3}); IR \textnu_{\text{max}} (neat)/cm\textsuperscript{-1}: 3066, 2925, 2855, 1601, 1574, 1504, 1456, 1369; HRMS (ESI): C\textsubscript{15}H\textsubscript{24}N [M+H]\textsuperscript{+}: 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\textsubscript{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\textsubscript{4}Cl. The aqueous phase was extracted using EtOAc (3 × 70 mL). The combined organic layers were dried over MgSO\textsubscript{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.\textsuperscript{117}

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ ppm 7.12 (4H, s, 4 × ArCH), 5.96 – 5.83 (1H, m, CH\textsubscript{CH\textsubscript{2}}), 5.10 – 4.99 (2H, m, CH\textsubscript{CH\textsubscript{2}}), 2.70 (2H, t, J = 7.6, ArCH\textsubscript{2}), 2.40 (2H, t, J = 7.6, CH\textsubscript{2}), 2.35 (3H, s, CH\textsubscript{3}); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ 138.8 (C\textsubscript{o}), 138.2 (CH), 135.2 (C\textsubscript{o}), 128.9 (2 × ArCH), 166
128.3 (2 × ArCH), 114.8 (CHCH₂), 35.6 (ArCH₂CH₂), 34.9 (ArCH₂), 21.0 (CH₃); IR νmax (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 °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 °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.

1H NMR (400 MHz, CDCl₃) δ ppm 9.86 (1H, t, J = 1.3, CHO), 7.40 – 7.35 (1H, m, ArCH), 7.28 – 7.25 (1H, m, ArCH), 7.24 – 7.15 (2H, m, ArCH), 3.09 (2H, t, J = 7.5, ArCH₂), 2.83 (2H, td, J = 7.6, 1.2, CH₃CHO), 2.35 (3H, s, CH₃); 13C NMR (126 MHz, CDCl₃) δ ppm 201.8 (CHO), 137.2 (C₉), 135.9 (C₉), 129.3 (2 × ArCH), 128.2 (2 × ArCH), 45.4 (CH₂), 27.7 (ArCH₂), 21.0 (CH₃). IR νmax (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), MeNH₂ (8M solution in EtOH, 300 µL) and NaBH₄ (153 mg, 4.04 mmol). Purification by SCX cartridge afforded the title compound (320 mg, 1.96 mmol, 97%) as a yellow oil. The 1H NMR data is in accordance with the literature.

1H NMR (500 MHz, CDCl₃) δ ppm 7.08 (4H, s, 4 × ArCH), 2.62 (4H, t, J = 7.3, include ArCH₂ and CH₂NH), 2.43 (3H, s, NHCH₃), 2.31 (3H, s, ArCH₃), 1.85 – 1.79 (2H, m, CH₂); 13C NMR
(126 MHz, CDCl₃) δ ppm 138.9 (C₄), 135.3 (C₄), 129.1 (2 × ArCH), 128.3 (2 × ArCH), 51.4 (CH₂NH), 36.2 (NHCH₃), 33.1 (ArCH₂), 31.3 (CH₂), 21.0 (ArCH₃); IR νmax (neat) / cm⁻¹ 3046, 3016, 2925, 2853, 2789, 1514, 1470, 1445; HRMS (ESI⁺): C₁₁H₁₈N [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.

**1H NMR** (300 MHz, CDCl₃) δ ppm 7.09 (4H, s, ArCH), 2.92 (3H, s, NCIClH₃), 2.87 (2H, t, J = 6.8, CH₂N), 2.64 (2H, t, J = 7.8, ArCH₂), 2.32 (3H, s, ArCH₃), 2.00 – 1.89 (2H, m, ArCH₂CH₂); **13C NMR** (75 MHz, CDCl₃) δ 138.6 (C₆), 135.3 (C₄), 129.1 (2 × ArCH), 128.3 (2 × ArCH), 65.3 (CH₂N), 53.0 (NCH₃), 32.3 (ArCH₂), 29.8 (CH₂), 21.0 (ArCH₃); **IR** νmax (neat) / cm⁻¹ 3046, 3018, 2995, 2948, 1514, 1437, 1375, 1169; HRMS (ESI⁺): C₁₁H₁₇₃ClN [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), MeSO₃H (335 µL, 5.10 mmol) and FeSO₄·7H₂O (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.²

**1H NMR** (400 MHz, CDCl₃) δ ppm 6.76 (1H, d, J = 7.3, ArCH), 6.36 (2H, m, 2 × ArCH), 3.16 – 3.08 (2H, m, NCH₂), 2.80 (3H, s, NCH₃), 2.65 (2H, t, J = 6.5, ArCH₂), 2.20 (3H, s, ArCH₃), 1.93 – 1.84 (2H, m, CH₂); **13C NMR** (101 MHz, CDCl₃) δ 146.6 (C₆), 136.6 (C₄), 128.7 (ArCH), 112.0 (C₄), 117.0 (ArCH), 111.8 (ArCH), 51.4 (NCH₂), 39.2 (NCH₃), 27.5 (ArCH₂), 22.7 (CH₂), 21.6 (ArCH₃); **IR** νmax (neat) / cm⁻¹ 3041, 3022, 2924, 2856, 2839, 2812, 1611, 1575; *HRMS* (ESI⁺): C₁₁H₁₇ClN [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 N₂ 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 NH₄Cl. The solution was extracted using EtOAc (3 × 70 mL). The combined organic extracts were dried over MgSO₄ and concentration in vacuo afforded the title compound (613 mg, 3.83 mmol, 95%) as a yellow oil without further purification being required.

**¹H NMR** (500 MHz, CDCl₃) δ ppm 6.84 – 6.81 (3H, m, 3 × ArCH), 5.96 – 5.79 (1H, m, CH), 5.08 – 4.96 (2H, m, CHCH₂), 2.66 – 2.61 (2H, m, CH₂), 2.41 – 2.32 (2H, m, CH₂), 2.30 (6H, s, CH₃); **¹³C NMR** (126 MHz, CDCl₃) δ ppm 141.9 (C₉), 138.4 (CHCH₂), 137.8 (2 × C₉), 127.5 (ArCH), 126.3 (2 × ArCH), 114.7 (CHCH₂), 35.6 (CH₂), 35.3 (CH₂), 21.3 (2 × ArCH₃); **IR** νmax (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), MeNH₂ (8M solution in EtOH, 300 µL) and NaBH₄ (140 mg, 3.70 mmol). Purification by SCX cartridge afforded the title compound (311 mg, 1.75 mmol, 95%) as a pale yellow oil.
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), MeSO₃H (305 mL, 4.70 mmol) and FeSO₄.7H₂O (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, CDCl₃) δ ppm 6.81 – 6.83 (1H, s, ArCH), 6.72 (1H, s, ArCH), 3.14 – 3.06 (2H, m, NCH₂), 2.75 (2H, t, J = 6.7, ArCH₂), 2.68 (3H, s, CH₃), 2.27 (3H, s, ArCH₃), 2.22 (3H, s, ArCH₃), 1.88 – 1.78 (2H, m, CH₂); \(^{13}\)C NMR (101 MHz, CDCl₃) δ ppm 131.3 (C₉), 131.1 (C₉), 130.5 (C₉), 129.7 (ArCH), 128.8 (C₉), 127.9 (ArCH), 52.2 (NCH₂), 43.0 (CH₃), 27.7 (ArCH₂), 25.8 (CH₂), 23.7 (CH₃). IR \(\nu_{\text{max}}\) (neat) / cm⁻¹: 2948, 2917, 2858, 1605, 1456, 1375, 1191; HRMS (ESI⁺): C₁₂H₁₉N [M + H]⁺: calculated 212.1205, found 212.1205, Δ = +1.2 ppm.
20.6 (ArCH₃), 18.4 (ArCH₃), 16.7 (CH₂); **IR** νₘₐₓ (neat) / cm⁻¹: 2997, 2933, 2853, 1722, 1678, 1605, 1479, 1439; **HRMS (ESI⁺)**: C₁₂H₁₈N [M + H]⁺: calculated 176.1453, found 176.1455, ∆ = +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 N₂ and THF (18 mL) was added. The solution was cooled to 0 °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 °C for 2 h, it was then quenched with NH₄Cl. The solution was extracted using EtOAc (3 x 100 mL) The combined organic layers were dried over MgSO₄ 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.

**¹H NMR** (400 MHz, CDCl₃) δ ppm 7.26 – 7.17 (3H, m, 3 × ArCH), 7.09 (1H, d, J = 7.2, ArCH), 5.92 – 5.80 (1H, m, CHCH₃), 5.12 – 4.98 (2H, m, CHCH₂), 2.72 (2H, t, J = 7.7, ArCH₂), 2.39 (2H, m, CH₂); **¹³C NMR** (101 MHz, CDCl₃) δ ppm 143.9 (C_q), 137.5 (CH), 134.1 (C_q), 129.5 (ArCH), 128.6 (ArCH), 126.7 (ArCH), 126.0 (ArCH), 115.3 (CHCH₂), 35.2 (CH₂), 35.0 (ArCH₂); **IR** νₘₐₓ (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 °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 °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.\textsuperscript{122}

\textbf{1H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 9.84 (1H, s, CHO), 7.30 – 7.18 (3H, m, 3 ArCH), 7.10 (1H, d, \(J = 7.1\), ArCH), 2.96 (2H, t, \(J = 7.4\), CH\textsubscript{2}), 2.81 (2H, t, \(J = 7.5\), ArCH\textsubscript{2}); \textbf{13C NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 200.9 (\(C\text{q}\)), 142.4 (\(C_q\)), 134.3 (\(C_q\)), 129.9 (ArCH), 128.5 (ArCH), 126.6 (ArCH), 126.5 (ArCH), 45.0 (CH\textsubscript{2}), 27.7 (ArCH\textsubscript{2}); \textbf{IR} \(\nu_{\text{max}}\) (neat) / cm\textsuperscript{-1} 3019, 2928, 2894, 2824, 2724, 1721 (CO), 1598, 1573; \textbf{HRMS} data could not be obtained.

\textbf{Synthesis of [3-(3-chlorophenyl)propyl](methyl)amine 310c}

General Procedure A was followed, using aldehyde 309c (700 mg, 4.15 mmol), MeNH\textsubscript{2} (8M in EtOH, 1.50 mL, 12.0 mol) and NaBH\textsubscript{4} (236 mg, 6.23 mmol). Purification by SCX cartridge afforded the \textit{title compound} (672 mg, 3.66 mmol, 88%) as a colourless oil.

\textbf{1H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 7.26 – 7.15 (3H, m, 3 \times ArCH), 7.08 (1H, d, \(J = 7.2\), ArCH), 2.70 – 2.61 (4H, m, includes ArCH\textsubscript{2} and CH\textsubscript{2}NH), 2.47 (3H, s, CH\textsubscript{3}), 1.91 – 1.80 (2H, m, CH\textsubscript{2}); \textbf{13C NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 144.0 (\(C_q\)), 134.1 (\(C_q\)), 129.6 (ArCH), 128.6 (ArCH), 126.6 (ArCH), 126.1 (ArCH), 51.1 (CH\textsubscript{2}N), 36.1 (CH\textsubscript{3}), 33.2 (ArCH\textsubscript{2}), 30.8 (CH\textsubscript{2}); \textbf{IR} \(\nu_{\text{max}}\) (neat) / cm\textsuperscript{-1} 3059, 2935, 2858, 2796, 1596, 1571, 1536, 1473; \textbf{HRMS (ESI\textsuperscript{+})}: \(\text{C}_{10}\text{H}_{15}\text{ClN} [M + H]\textsuperscript{+}\): calculated 184.0888, found 184.0886, \(\Delta = + 1.0\) ppm.

\textbf{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 \textit{title compound} (300 mg, 1.38 mmols, 85%) as a colourless oil.

\textbf{1H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 7.26 – 7.17 (3H, m, 3 \times ArCH), 7.10 (1H, d, \(J = 7.2\), ArCH), 2.96 (3H, s, CH\textsubscript{3}), 2.89 (2H, t, \(J = 6.8\), CH\textsubscript{2}), 2.69 (2H, t, \(J = 7.7\) CH\textsubscript{2}), 2.01 – 1.94 (2H, m, CH\textsubscript{2}); \textbf{13C NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 143.8 (\(C_q\)), 134.1 (\(C_q\)), 129.7 (ArCH), 128.6 (ArCH), 126.7 (ArCH), 126.1 (ArCH), 64.9 (CH\textsubscript{2}N), 53.1 (CH\textsubscript{3}), 32.4 (ArCH\textsubscript{2}), 29.5
(CH₂): IR $\nu_{\text{max}}$ (neat) / cm$^{-1}$ 3061, 2992, 2950, 2919, 2867, 1597, 1572, 1475; HRMS (ESI$^+$): C$_{10}$H$_{14}$Cl$_2$N [M + H]$^+$: calculated 218.0498, found 218.0492, $\Delta = -2.5$ 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](image)

![325b](image)

General Procedure D was followed, using chloroamine 311c (100 mg, 0.46 mmol), MeSO$_3$H (300 µL, 4.60 mmol) and FeSO$_4$·7H$_2$O (13 mg, 0.046 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the regioisomeric 325a and 325b as an inseparable 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$_3$H (318 µL, 4.90 mmol) and FeSO$_4$·7H$_2$O (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) $\delta$ ppm 7.02 (1H, dd, $J = 8.7$, 2.6, ArCH), 6.93 (1H, d, $J = 2.6$, ArCH), 6.50 (1H, d, $J = 8.7$, ArCH), 3.25 – 3.19 (2H, m, CH$_2$NMe), 2.88 (3H, s, CH$_3$), 2.75 (2H, t, $J = 6.5$, ArCH$_2$), 1.99 (2H, m, CH$_2$)$_2$; $^{13}$C NMR (101 MHz, CDCl$_3$, peaks for 325a) $\delta$ ppm 145.3 (C$_q$), 131.2 (C$_q$), 128.4 (ArCH), 126.6 (ArCH), 124.4 (C$_q$), 111.9 (ArCH), 51.1 (CH$_2$NMe), 39.2 (CH$_3$), 27.7 (ArCH$_2$), 22.2 (CH$_2$)$_2$; $^1$H NMR (400 MHz, CDCl$_3$, peaks for 325b) $\delta$ ppm 7.19 (1H, d, $J = 7.8$, ArCH), 6.97 (1H, d, $J = 7.8$), 6.85 (1H, t, $J = 7.8$, ArCH), 3.19 – 3.14 (2H, m, CH$_2$NMe), 2.91 (3H, s, CH$_3$), 2.82 (2H, t, $J = 6.7$, ArCH$_2$), 1.91 – 1.85 (2H, m, CH$_2$)$_2$; $^{13}$C NMR (101 MHz, CDCl$_3$, peaks for 325b) $\delta$ ppm 146.0 (C$_q$), 128.3 (ArCH), 128.2 (ArCH), 127.5 (C$_q$), 122.0 (ArCH), 120.7 (C$_q$), 52.0 (CH$_2$NMe), 42.8 (CH$_3$), 27.9 (ArCH$_2$), 17.2 (CH$_2$); IR $\nu_{\text{max}}$ (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 Et₃N (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 NaHCO₃. The two phases were separated and the aqueous phase was extracted with DCM (2 × 60 mL). The combined organic phases were dried over MgSO₄ and concentrated to afford the desired crude mesylate as a yellow oil.

Step ii) The crude oil was flushed with N₂ 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 NH₄Cl. The phases were separated and the aqueous phase was extracted using EtOAc (3 × 60 mL), the combined organic layers were dried over MgSO₄ 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. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.24 (2H, d, J = 8.6, 2 × ArCH), 7.11 (2H, d, J = 8.6, 2 × ArCH), 5.88 – 5.77 (1H, m, CHCH₂), 5.06 – 4.95 (2H, m, CHCH₂), 2.68 (2H, t, J = 7.7, ArCH₂), 2.39 – 2.30 (2H, m, ArCH₂CH₂); ¹³C NMR (75 MHz, CDCl₃) δ ppm 140.3 (C₃), 137.6 (CHCH₂), 131.5 (C₄), 129.8 (2 × ArCH), 128.4 (2 × ArCH), 115.3 (CHCH₂), 35.4 (CH₂), 34.7 (CH₂); IR νmax (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.\textsuperscript{77}

\textbf{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}) $\delta$ ppm 9.84 (1H, t, $J = 1.2$, CHO), 7.32 – 7.26 (2H, m, 2 $\times$ ArCH), 7.16 (2H, d, $J = 8.2$, 2 $\times$ ArCH), 2.96 (2H, t, $J = 7.5$, ArCH\textsubscript{2}), 2.83 – 2.78 (2H, m, C\textsubscript{H}\textsubscript{2}CHO); \textbf{\textsuperscript{13}C NMR} (126 MHz, CDCl\textsubscript{3}) $\delta$ ppm 201.0 (C\textsubscript{HO}), 138.8 (C\textsubscript{q}), 132.1 (C\textsubscript{q}), 129.7 (2 $\times$ ArCH), 128.7 (2 $\times$ ArCH), 45.1 (CH\textsubscript{2}CHO), 27.4 (ArCH\textsubscript{2}); \textbf{IR} $\nu_{\text{max}}$ (neat) / cm$^{-1}$ 3028, 2929, 2894, 2725, 1720, 1492, 1447, 1408. HRMS data could not be obtained.

\textbf{Synthesis of [3-(4-chlorophenyl)propyl](methyl)amine 310d}

General procedure A was followed, using aldehyde 309d (300 mg, 1.78 mmol), MeNH\textsubscript{2} (8 M solution in EtOH, 500 $\mu$L) and NaBH\textsubscript{4} (101 mg, 2.67 mmol). 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.\textsuperscript{77}

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) $\delta$ ppm 7.30 – 7.22 (2H, m, 2 $\times$ ArCH), 7.17 – 7.10 (2H, m, 2 $\times$ ArCH), 2.69 – 2.60 (2H, m, ArCH\textsubscript{2}), 2.45 (3H, s, CH\textsubscript{3}), 2.16 – 1.96 (2H, m, NHCH\textsubscript{2}), 1.90 – 1.76 (2H, m, CH\textsubscript{2}); \textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) $\delta$ ppm 140.5 (C\textsubscript{q}), 131.5 (C\textsubscript{q}), 129.7 (2 $\times$ ArCH), 128.5 (2 ArCH), 51.3 (ArCH\textsubscript{2}), 36.3 (CH\textsubscript{3}), 32.9 (NHCH\textsubscript{2}), 31.2 (CH\textsubscript{2}); \textbf{IR} $\nu_{\text{max}}$ (neat) / cm$^{-1}$ 3025, 2933, 2857, 2793, 1632, 1538, 1490, 1383; HRMS (ESI\textsuperscript{+}): C\textsubscript{10}H\textsubscript{15}ClN [M + H]\textsuperscript{+}: calculated 184.0888, found 184.0892, $\Delta$ = -2.4 ppm.

\textbf{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.\textsuperscript{77}
1H NMR (400 MHz, CDCl₃) δ ppm 7.25 (2H, d, J = 8.3, 2 × ArCH), 7.12 (2H, d, J = 8.3, 2 × ArCH), 2.92 (3H, s, CH₃), 2.85 (2H, t, J = 6.8, CH₂NCl), 2.64 (2H, t, J = 7.6, ArCH₂), 1.98 – 1.90 (2H, m, CH₂); 

13C NMR (101 MHz, CDCl₃) δ ppm 140.1 (Cₚ), 131.6 (Cₚ), 129.8 (2 × ArCH), 128.5 (2 × ArCH), 65.0 (CH₂NCl), 53.1 (CH₃), 32.0 (ArCH₂), 29.6 (CH₂); 

IR νmax (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), MeSO₃H (300 µL, 4.40 mmol) and FeSO₄.7H₂O (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

1H NMR (400 MHz, CDCl₃) δ ppm 6.83 (1H, d, J = 7.8, ArCH), 6.56 – 6.49 (2H, m, 2 × ArCH), 3.25 – 3.19 (2H, m, NCH₃CH₂), 2.86 (3H, s, CH₃), 2.70 (2H, t, J = 6.4, ArCH₂), 1.99 – 1.90 (2H, m, CH₂); 

13C NMR (101 MHz, CDCl₃) δ ppm 147.5 (Cₚ), 132.5 (Cₚ), 129.5 (ArCH), 121.0 (Cₚ), 115.5 (ArCH), 110.5 (ArCH), 50.9 (NCH₃CH₂), 38.9 (CH₃), 27.3 (ArCH₂), 22.2 (CH₂); IR νmax (neat) / cm⁻¹ 3022, 2929, 2890, 2840, 1599, 1564, 1502, 1466; 

HRMS (ESI⁺): C₁₀H₁₃ClN [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 Et₃N (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 NaHCO₃. The two phases were separated and the aqueous phase was extracted with DCM (2
× 60 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo to afford the desired crude mesylate as a yellow oil.

**Step ii)** The crude oil was flushed with N₂ 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 NH₄Cl. The phases were separated and the aqueous phase was extracted using EtOAc (3 × 60 mL). The combined organic extracts were dried over MgSO₄ 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.

1H NMR (400 MHz, CDCl₃) δ ppm 7.33 (1H, m, ArCH), 7.17 (3H, m ArCH), 5.95 – 5.80 (1H, m, CH₂CH₂), 5.11 – 4.96 (2H, m, CH₂CH₂), 2.86 – 2.79 (2H, m, ArCH₂), 2.42 – 2.33 (2H, m, CH₂); 13C NMR (101 MHz, CDCl₃) δ ppm 139.4 (Cq), 137.8 (Cq), 134.0 (Cq), 130.4 (ArCH), 129.5 (ArCH), 127.3 (ArCH), 126.7 (ArCH), 115.2 (CH₂CH₂), 33.7 (ArCH₂), 33.1 (CH₂); IR νmax (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.

1H NMR (500 MHz, CDCl₃) δ ppm 9.86 (1H, t, J = 1.2, CHO), 7.37 – 7.33 (1H, m, ArCH), 7.31 – 7.26 (1H, m, ArCH), 7.25 – 7.17 (2H, m, 2 × ArCH), 3.10 (2H, t, J = 7.6, ArCH₂), 2.83 (2H, td, J = 7.6, 1.2, CH₂); 13C NMR (126 MHz, CDCl₃) δ 201.1 (CO), 138.0 (Cq), 133.9 (Cq), 115.2 (ArCH), 126.7 (ArCH), 121.9 (CH₂CH₂), 33.7 (ArCH₂), 33.1 (CH₂).
130.5 (ArCH), 129.7 (ArCH), 127.9 (ArCH), 127.0 (ArCH), 43.5 (CH₂CHO), 26.2 (ArCH₂); IR \( \nu_{\text{max}} \) (neat) \( \text{cm}^{-1} \) 3069, 2935, 2896, 2823, 2723, 1722 (CO), 1474, 1444. HRMS data could not be obtained.

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

![Structure of 310e]

General procedure A was followed, using aldehyde 309e (300 mg, 1.78 mmol), MeNH₂ (8M solution in EtOH, 500 \( \mu \)L) and NaBH₄ (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 \( ^1\text{H} \) NMR data is in accordance with the literature.\(^{119} \)

\( ^1\text{H} \) NMR (300 MHz, CDCl₃) \( \delta \) ppm 7.37 – 7.29 (1H, m, ArCH), 7.24 – 7.06 (3H, m, 3 × ArCH), 2.80 – 2.72 (2H, m, CH₂NH), 2.69 – 2.60 (2H, m, ArCH₂), 2.45 (3H, s, CH₃), 1.89 – 1.73 (2H, m, CH₂); \( ^1\text{C} \) NMR (75 MHz, CDCl₃) \( \delta \) ppm 139.8 (Cₐr), 133.9 (Cₐr), 130.3 (ArCH), 129.5 (ArCH), 127.3 (ArCH), 126.8 (ArCH), 51.6 (ArCH₂), 36.5 (CH₃), 31.4 (CH₂NH), 29.9 (CH₂); IR \( \nu_{\text{max}} \) (neat) / \( \text{cm}^{-1} \) 2948, 2871, 2791, 1567, 1451, 1379, 1304, 1263; HRMS (ESI⁺): C₁₀H₁₅Cl₂N [M+H]⁺: calculated 218.0498, found 218.0494.

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

![Structure of 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.

\( ^1\text{H} \) NMR (400 MHz, CDCl₃) \( \delta \) ppm 7.34 (1H, dd, \( J = 7.7, 1.5, \) ArCH), 7.25 – 7.12 (3H, m, 3 × ArCH), 2.95 (3H, s, CH₃), 2.92 (2H, t, \( J = 6.9, \) CH₂NCl), 2.80 (2H, t, \( J = 7.8, \) ArCH₂), 2.02 – 1.93 (2H, m, CH₂); \( ^1\text{C} \) NMR (101 MHz, CDCl₃) \( \delta \) ppm 139.3 (Cₐr), 134.0 (Cₐr), 130.5 (ArCH), 129.5 (ArCH), 127.4 (ArCH), 126.8 (ArCH), 65.3 (CH₂NCl), 53.0 (CH₃), 30.6 (ArCH₂), 28.1 (CH₂); IR \( \nu_{\text{max}} \) (neat) \( \text{cm}^{-1} \) 3063, 2952, 2868, 2844, 1473, 1439, 1365, 1274; HRMS (ESI⁺): C₁₀H₁₄Cl₂N [M+H]⁺: calculated 218.0498, found 218.0494.

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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 Et₃N (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 NaHCO₃. The two phases were separated and the aqueous phase was extracted with DCM (2 × 60 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo to afford the desired crude mesylate as a yellow oil.

Step ii) The crude oil was flushed with N₂ 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 NH₄Cl. The phases were separated and the aqueous phase was extracted using EtOAc (3 × 60 mL). The combined organic extracts were dried over MgSO₄ 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

¹H NMR (500 MHz, CDCl₃) δ ppm 7.40 (2H, d, J = 8.4, 2 × ArCH), 7.06 (2H, d, J = 8.4, 2 × ArCH), 5.83 (1H, ddt, J = 17.0, 10.2, 6.6, CH=CH₂), 5.04 (1H, ddd, J = 17.0, 3.4, trans-CHCH₂), 4.99 (1H, dd, J = 10.2, 1.9, cis-CHCH₂), 2.71-2.61 (2H, m, ArCH₂), 2.35 (2H, app. dtt, J = 9.0, 7.8, 1.3, CH₂); ¹³C NMR (125 MHz, CDCl₃) δ ppm 140.9 (Cq), 137.7 (CH=CH₂), 131.5 (2 × ArCH), 130.4 (2 × ArCH), 119.7 (Cq), 115.4 (CH=CH₂), 35.4 (CH₂), 34.9 (ArCH₂); IR νmax (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.\textsuperscript{127}

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 9.80 (1H, t, $J = 1.4$, CHO), 7.40 (2H, d, $J = 8.3$, 2 $\times$ ArCH), 7.07 (2H, d, $J = 8.3$, 2 $\times$ ArCH), 2.90 (2H, t, $J = 7.4$, ArCH$_2$), 2.78 – 2.74 (2H, m, ArCH$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 201.1 (C=O), 139.5 (C$q$), 131.8 (2 $\times$ ArCH), 130.2 (2 $\times$ ArCH), 120.2 ($C_q$), 45.1 (CH$_2$), 27.6 (ArCH$_2$); IR \(\nu_{\max}\) (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**

![Chemical structure of 310f](image)

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.\textsuperscript{128}

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.38 (2H, d, $J = 8.3$, 2 $\times$ ArCH), 7.05 (2H, d, $J = 8.3$, 2 $\times$ ArCH), 2.64-2.55 (4H, m, includes ArCH$_2$ and CH$_2$N), 2.41 (3H, s, NCH$_3$), 1.83-1.73 (2H, m, CH$_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 141.1 ($C_q$), 131.5 (2 $\times$ ArCH), 130.2 (2 $\times$ ArCH), 119.6 ($C_q$), 51.3 (CH$_2$N), 36.4 (NCH$_3$), 33.1 (ArCH$_2$), 31.2 (CH$_2$); IR \(\nu_{\max}\) (neat)/cm$^{-1}$: 3310 (NH), 3023, 2932, 2857, 2798, 1537, 1487, 1452; HRMS (ESI)$^+$: C$_{10}$H$_{15}$BrN [M+H]$^+$: calculated 228.0382, found 228.0376.

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

![Chemical structure of 311f](image)

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 × ArCH), 7.10 – 7.04 (2H, m, 2 × ArCH), 2.93 (3H, s, CH$_3$), 2.85 (2H, t, $J = 6.9$, CH$_2$NCI), 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 × ArC), 130.2 (2 × ArC), 119.7 (C$q$), 64.9 (CH$_2$NCI), 53.1 (CH$_3$), 32.1 (ArCH$_2$), 29.6 (CH$_2$); IR $\nu_{max}$ (neat) cm$^{-1}$: 2991, 2949, 2919, 2864, 1487, 1455, 1437, 1403; HRMS (ESI$^+$): C$_{10}$H$_{14}$Br$_3$ClN [M + H]$^+$ calculated 261.9992, found 261.9989, $\Delta = +1.0$ ppm.

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

[Diagram]

General Procedure D was followed, using [3-(4-bromo phenyl)propyl](chloro)methylamine 311f (100 mg, 0.38 mmol), MeSO$_3$H (250 µL, 3.80 mmol) and FeSO$_4$.7H$_2$O (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, $J = 7.7$, ArCH), 6.70 – 6.65 (2H, m, 2 × ArCH), 3.26 – 3.18 (2H, m, CH$_2$NMe), 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 (ArC), 121.5 (C$q$), 120.6 (C$q$), 118.5 (ArCH), 113.2 (ArCH), 50.9 (CH$_2$NMe), 38.9 (CH$_3$), 27.4 (ArCH$_2$), 22.1 (CH$_2$); IR $\nu_{max}$ (neat) / cm$^{-1}$: 3015, 2928, 2886, 2837, 1593, 1557, 1497, 1464; HRMS (ESI$^+$): C$_{10}$H$_{14}$Br$_3$ClN [M + H]$^+$ calculated 226.1583, found 226.1583, $\Delta = 0$ ppm.

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

[Diagram]

Step i: To a stirred solution of 4-methoxybenzyl alcohol (1.00 g, 7.24 mmol) in DCM (18 mL) at 0 ºC was added Et$_3$N (1.10 mL, 7.96 mmol) then MsCl (0.60 mL, 7.96 mmol) was added dropwise and the RM was stirred at 0 ºC 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\textsubscript{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\textsubscript{4}Cl. The aqueous phase was extracted with EtOAc (3 × 100 mL), the combined organic extracts were dried over MgSO\textsubscript{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\textsuperscript{117}.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ ppm 7.10 (2H, d, J = 8.4, 2 × ArCH), 6.83 (2H, d, J = 8.5, 2 × ArCH), 5.90 – 5.80 (1H, m, CH), 5.05 – 4.95 (2H, m, CHC\textsubscript{2}H\textsubscript{2}), 3.78 (3H, s, C\textsubscript{H}\textsubscript{3}), 2.65 (2H, t, J = 7.8 ArCH\textsubscript{2}), 2.37 – 2.31 (2H, m, CH\textsubscript{2}); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ ppm 157.8 (C\text{q}), 138.2 (C\text{H}), 134.0 (C\text{q}), 129.3 (2 × ArCH), 114.8 (CH\textsubscript{2}CH), 113.7 (2 × ArCH), 55.3 (CH\textsubscript{3}), 35.8 (CH\textsubscript{2}), 34.5 (ArCH\textsubscript{2}); \textbf{IR} v\textsubscript{max} (neat) / cm\textsuperscript{-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\textsuperscript{130}.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ ppm 7.16 – 7.13 (2H, m, 2 × ArCH), 6.89 – 6.83 (2H, m, 2 × ArCH), 3.81 (3H, s, CH\textsubscript{3}), 3.77 – 3.65 (2H, m, CH\textsubscript{2}OH), 3.53 – 3.45 (1H, m, CHO\textsubscript{H}), 2.81 – 2.59 (2H, m, ArCH\textsubscript{2}), 1.85 – 1.72 (2H, m, ArCH\textsubscript{2}CH\textsubscript{2}); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ ppm 157.9 (C\text{q}), 133.7 (C\text{q}), 129.3 (2 × ArCH), 113.9 (2 × ArCH), 71.5 (CH\textsubscript{2}OH), 66.9 (CHO\textsubscript{H}), 55.3 (CH\textsubscript{3}), 34.9 (CH\textsubscript{2}), 30.9 (ArCH\textsubscript{2}); \textbf{IR} v\textsubscript{max} (neat) / cm\textsuperscript{-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 H₂O/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 MgSO₄ 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.¹¹³

¹H NMR (400 MHz, CDCl₃) δ ppm 9.81 (1H, t, J = 1.4, CHO), 7.11 (2H, d, J = 8.6, ArCH), 6.83 (2H, d, J = 8.6, ArCH), 3.79 (3H, s, CH₃), 2.91 (2H, t, J = 7.4, ArCH₂), 2.77 – 2.72 (2H, m, CH₂); ¹³C NMR (101 MHz, CDCl₃) δ ppm 201.8 (CO), 158.1 (C₅), 132.3 (C₄), 129.2 (2 × ArCH), 114.0 (2 × ArCH), 55.3 (CH₃), 45.5 (CH₂), 27.3 (ArCH₂); IR ʋ 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), MeNH₂ (8 M solution in EtOH, 300 µL, 1.3 eq.) and NaBH₄ (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

¹H NMR (500 MHz, CDCl₃) δ ppm 7.10 (2H, d, J = 8.6, 2 × ArCH), 6.85 – 6.80 (2H, m, 2 × ArCH), 3.78 (3H, s, OCH₃), 2.65 – 2.57 (4H, m, includes ArCH₂ and CH₂NH), 2.44 (3H, s, CH₃), 1.85 – 1.80 (2H, m, CH₂); ¹³C NMR (126 MHz, CDCl₃) δ ppm 157.8 (C₅), 133.9 (C₄), 129.2 (2 × ArCH), 113.8 (2 × ArCH), 55.3 (OCH₃), 51.2 (CH₂NH), 36.0 (NCH₃), 32.6 (ArCH₂), 31.2 (CH₂); IR ʋ max (neat) / cm⁻¹ 3040, 2996, 2933, 2855, 2799, 1611, 1510, 1463; HRMS (ESI⁺): C₁₁H₁₈NO [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 H₂O (10 mL) then brine (10 mL), dried over MgSO₄ 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.

1H NMR (400 MHz, CDCl₃) δ ppm 7.06 – 7.01 (2H, m, 2 × ArCH), 6.78 – 6.73 (2H, m, 2 × ArCH), 3.72 (3H, s, OC₃H₃), 2.85 (3H, s, CH₃), 2.83 (2H, t, J = 6.9, CH₂N), 2.58 (2H, t, J = 7.6, ArCH₂), 1.91 – 1.81 (2H, m, CH₂); 13C NMR (101 MHz, CDCl₃) δ ppm 157.8 (Cq), 133.7 (Cq), 129.3 (2 × ArCH), 113.8 (2 × ArCH), 65.2 (ArCH₂), 55.3 (OC₃H₃), 53.0 (CH₃), 31.8 (CH₂N), 29.9 (CH₂); IR νmax (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), MeNH₂ (8 M solution in EtOH, 8.00 mL, 26.0 mmol), Ti(OiPr)₄ (2.00 mL, 6.75 mmol) and NaBH₄ (255 mg, 6.25 mmol). Purification by SCX cartridge afforded the title compound (300 mg, 1.84 mmol, 55%) as a pale yellow oil.

1H NMR (500 MHz, CDCl₃) δ ppm 7.32 – 7.24 (2H, m, 2 × ArCH), 7.22 – 7.14 (3H, m, 3 × ArCH), 2.72 – 2.50 (3H, m, includes ArCH₂ and NCH), 2.40 (3H, s, NCH₃), 1.84 – 1.72 (1H, m, CH₂), 1.68 – 1.54 (1H, m, CH₂), 1.09 (3H, d, J = 6.2, CHCH₃); 13C NMR (125 MHz, CDCl₃) δ ppm 142.4 (Cq), 128.3 (2 × ArCH), 128.2 (2 × ArCH), 125.7 (ArCH), 54.4 (CH), 38.5 (ArCH₂), 33.8 (NCH₃), 32.3 (CH₂) 19.9(CHCH₃); IR νmax (neat)/cm⁻¹: 3304, 3062, 2930, 2857, 2792, 1541, 1495, 1453; HRMS (ESI⁺):C₁₁H₁₈N [M + H]⁺ : calculated 164.1434, found 164.1432, Δ = - 1.2 ppm.
Synthesis of [3-(4-bromophenyl)propyl](chloro)methylamine 329

![Chemical structure of [3-(4-bromophenyl)propyl](chloro)methylamine](image)

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\(_3\)) \(\delta\) ppm 7.31 – 7.26 (2H, m, 2 × ArCH), 7.23 – 7.16 (3H, m, 3 × ArCH), 2.93 – 2.84 (4H, m, includes NCH\(_3\) and CH), 2.73 – 2.66 (2H, m, ArCH\(_2\)), 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\(_3\)) \(\delta\) ppm 142.1 (C\(_\alpha\)), 128.4 (2 × ArCH), 128.3 (2 × ArCH), 125.8 (ArCH), 64.5 (CH), 48.1 (NCH\(_3\)), 36.3 (ArCH\(_2\)), 32.3 (CH\(_2\)) 14.2 (CHCH\(_3\)) ; IR \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 3026, 2970, 2951, 1762, 1605, 1496, 1453, 1442; HRMS (ESI\(^+\)): C\(_{11}\)H\(_{17}\)Cl\(_3\) [M + H\(^+\)]\(^+\) : calculated 198.1044, found 198.1038, \(\Delta = -3.0\) ppm.

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

![Chemical structure of 7-bromo-1-methyl-1,2,3,4-tetrahydroquinoline](image)

General Procedure D was followed, using [3-(4-bromophenyl)propyl](chloro)methylamine 330 (100 mg, 0.50 mmol), MeSO\(_3\)H (330 µL, 5.10 mmol) and FeSO\(_4\).7H\(_2\)O (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\(_3\)) \(\delta\) ppm 7.13 (1H, t, \(J = 7.7\), ArCH), 7.02 (1H, d, \(J = 7.3\), ArCH), 6.64 (1H, t, \(J = 7.3\), ArCH), 6.60 (1H, d, \(J = 8.2\), ArCH), 3.52 – 3.44 (1H, m, CH), 2.94 (3H, s, NCH\(_3\)), 2.93 – 2.84 (1H, m, ArCH\(_2\)), 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\(_3\)) \(\delta\) ppm 145.4 (C\(_\alpha\)), 128.5 (ArCH), 127.1 (ArCH), 122.1 (C\(_\beta\)), 115.4 (ArCH), 110.6 (ArCH), 53.8 (CH), 37.0 (NCH\(_3\)), 28.1 (CH\(_2\)), 23.8 (ArCH\(_2\)) 17.6 (CHCH\(_3\)) ; IR \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 3068, 3021, 2962,
2925, 2843, 2790, 1603, 1575; HRMS (ESI⁺):C₁₁H₁₆N [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.¹⁶

¹H NMR (400 MHz, CDCl₃) δ ppm 7.33 – 7.26 (2H, m, 2 × ArC₆H), 7.24 – 7.16 (3H, m, includes ArC₆H₂ and CH₃), 2.89 (3H, s, CH₃), 2.79 – 2.61 (3H, m, includes ArC₆H₂ and CH₃), 2.01 – 1.89 (1H, m, CH₂), 1.81 – 1.65 (2H, m, includes CH₂ and C₆H₂), 0.91 (3H, t, J = 6.9, CH₃) ; ¹³C NMR (100 MHz, CDCl₃) δ ppm 142.9 (C₉), 128.5 (4 × ArCH), 125.8 (ArCH), 58.9 (CH), 35.5 (ArCH₂), 33.7 (C₆H₂), 32.3 (ArCH₂CH₂), 32.2 (CH₂), 25.5 (CH₂), 22.8 (CH₂), 14.2 (CH₃) ; IR νmax (neat)/cm⁻¹: 3062, 3026, 2926, 2856, 2788, 1603, 1495, 1454; HRMS (ESI⁺):C₁₅H₂₆ClN [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), MeSO₃H (260 µL, 3.90 mmol) and FeSO₄.7H₂O (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.¹⁶

¹H NMR (400 MHz, CDCl₃) δ ppm 7.07 (1H, t, J = 7.7, ArCH), 6.96 (1H, d, J = 7.3, ArCH), 6.57 (1H, t, J = 7.3, ArCH), 6.51 (1H, d, J = 8.2, ArCH), 3.29 – 3.17 (1H, m, CH), 2.92 (3H, s, CH₃), 2.86 – 2.73 (1H, m, ArCH₂), 2.71 – 2.58 (1H, m, ArCH₂) 1.94 – 1.82 (2H, m, CH₂),
1.65 – 1.53 (1H, m, C₆H₅), 1.44 – 1.19 (7H, m, includes C₆H₅, C₆H₅, C₆H₂ and C₆H₂) 0.98 – 0.81 (3H, m, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm 145.7 (C₆), 128.8 (ArCH), 127.2 (ArCH), 122.0 (C₆), 115.3 (ArCH), 110.5 (CH), 59.1 (NCH₃), 32.2 (ArCH₂), 31.3 (C₆H₅), 25.9 (CH₂), 24.6 (ArCH₂CH₂), 23.7 (CH₂), 22.8 (CH₂), 14.2 (CH₃); IR νₘₚ₅ (neat) / cm⁻¹: 3020, 2926, 2856, 1602, 1575, 1498, 1479, 1455; HRMS (ESI⁺): C₁₅H₂₄N [M + H]⁺: calculated 218.1903, found 218.1903, Δ = 0.0 ppm.

**Synthesis of 1-phenoxypropan-2-one 337**

![Chemical structure](image)

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.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.36 – 7.30 (2H, m, 2 × ArCH), 7.03 (1H, t, J = 7.4 Hz, ArCH), 6.91 (2H, d, J = 7.8 Hz, 2 × ArCH), 4.56 (2H, s, CH₂), 2.31 (3H, s, NHC₆H₅); ¹³C NMR (75 MHz, CDCl₃) δ ppm 206.0 (C₆), 157.7 (C₆), 129.7 (2 × ArCH), 121.8 (ArCH), 114.5 (2 × ArCH), 73.1 (CH₂), 26.7 (CH₃); IR νₘₚ₅ (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**

![Chemical structure](image)

General procedure B was followed, using ketone 337 (1.50 g, 9.99 mmol), MeNH₂ (8 M solution in EtOH, 12.0 mL, 94.0 mmol), Ti(OiPr)₄ (5.90 mL, 20.0 mmol) and NaBH₄ (567 mg, 15.0 mmol). Purification by SCX cartridge afforded the *title compound* (743mg, 4.50 mmol, 45%) as a pale yellow oil.

¹H NMR (300 MHz, CDCl₃) δ ppm 7.34 – 7.26 (2H, m, 2 × ArCH), 7.00 – 6.89 (3H, m, 3 × ArCH), 3.88 (2H, m, CH₂), 3.02 (1H, m, CH), 2.50 (3H, s, NHCH₃), 1.16 (3H, d, J = 6.5, CHCH₃); ¹³C NMR (101 MHz, CDCl₃) δ ppm 158.9 (C₆), 129.5 (2 × ArCH), 120.8 (ArCH), 114.6 (2 × ArCH), 71.6 (CH₂), 54.1 (CH), 33.8 (NHCH₃), 16.8 (CH₃); IR νₘₚ₅ (neat) / cm⁻¹: 3063, 3043, 2903, 1720, 1589, 1493, 1432, 1357. HRMS data could not be obtained.
3062, 3039, 2968, 2930, 2872, 2795, 1676, 1599; HRMS (ESI⁺): C₁₀H₁₅NO [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 H₂O (20 mL) then brine (20 mL), dried over MgSO₄ 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.

**1H NMR** (300 MHz, CDCl₃) δ ppm 7.37 – 7.24 (2H, m, 2 × ArCH), 7.05 – 6.91 (3H, m, 3 × ArCH), 4.24 (1 H, dd, J = 9.8, 5.6, CH₂), 3.93 (1H, dd, J = 9.8, 5.6, CH₂), 3.46 – 3.30 (1H, m, CH), 3.04 (3H, s, NHCH₃), 1.32 (3H, d, J = 6.5, CH₃); **13C NMR** (101 MHz, CDCl₃) δ ppm 158.6 (C₉), 129.5 (2 × ArCH), 121.0 (ArCH), 114.7 (2 × ArCH), 69.9 (CH₂), 64.7 (CH), 49.5 (NHCH₃), 13.1 (CH₃); **IR** ν 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**

General Procedure D was followed, using chloroamine 339 (150 mg, 0.75 mmol), MeSO₃H (490 µL, 7.50 mmol) and FeSO₄·7H₂O (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.³¹⁴

**1H NMR** signals for the major product reported 340a (300 MHz, CDCl₃) δ ppm 6.92 – 6.84 (1H, m, ArCH), 6.83 – 6.77 (1H, m, ArCH), 6.69 – 6.61 (2H, m, 2 × ArCH), 4.21 (1H, dd, J = 10.5, 2.6, CH₂), 4.04 (1H, dd, J = 10.5, 2.6, CH₂), 3.44 – 3.33 (1H, m, CH), 2.89 (3H, s, NCH₃), 1.22 (3H, d, J = 6.5, CH₃); **13C NMR** signals for the major product reported 340a (101 MHz,
Synthesis of \((\text{ArC})_2\)δ ppm 144.2 (Cₙ), 126.6 (Cₙ), 121.8 (ArCH), 116.6 (ArCH), 116.4 (ArCH), 111.7 (ArCH), 69.2 (CH₂), 52.1 (CH), 36.1 (NCH₃), 14.1 (CH₃); IR \(\nu_{\text{max}}\) (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 \(N-(1\text{-phenoxypropan-2-yl})\text{-prop-2-en-1-amine 341b}\)**

![Chemical structure of 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 NaBH₄ (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 × ArCH), 7.00 – 6.89 (3H, m, 3 × ArCH), 5.95 (1H, ddt, \(J = 16.2, 10.2, 6.0, \text{CH}=\text{CH}_2\)), 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, CHNH), 1.19 (3H, d, \(J = 6.5, \text{CH}_3\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) δ ppm 158.9 (Cₙ), 137.0 (CH=CH\(_2\)), 129.5 (2 × ArCH), 120.8 (ArCH), 115.9 (CH=CH\(_2\)), 114.6 (2 × ArCH), 72.0 (OCH\(_2\)), 51.8 (CHNH), 49.8 (NHCH\(_2\)), 17.4 (CH\(_3\)); IR \(\nu_{\text{max}}\) (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, \(\Delta = -0.6\) ppm.

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

![Chemical structure of 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 × ArCH), 7.02 – 6.91 (3H, m, 3 × ArCH), 5.97 (1H, ddt, \(J = 16.7, 10.2, 6.4, \text{CH}=\text{CH}_2\)), 5.39 – 5.21 (2H, m, CH=CH\(_2\)), 4.29 (1H, ddt, \(J = 9.8, 5.9, \text{CH}_2\)), 3.95 (1H, ddt, \(J = 9.8, 5.9, \text{CH}_2\)), 3.85 – 3.66 (2H, m, CH\(_2\)), 3.62 – 3.44 (1H, m, CHNHCl), 1.33 (3H, d, \(J = 6.4, \text{CH}_3\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) δ ppm 158.6 (Cₙ), 134.1 (CH=CH\(_2\)), 129.5 (2 × ArCH), 121.0 (ArCH), 119.0 (CH=CH\(_2\)), 114.7 (2 × ArCH), 69.9 (OCH\(_2\)), 63.7 (CHNHCl), 62.2 (NClCH\(_2\)), 13.3 (CH\(_3\)); IR \(\nu_{\text{max}}\) (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-phenoxyp propane-2-yl)butan-1-amine 341c**

![Chemical Structure](image)

General procedure B was followed, using ketone 337 (500 mg, 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 (500 mg, 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 × ArCH), 7.00 – 6.88 (3H, m, 2 × ArCH), 3.96 – 3.80 (2H, m, CH$_2$), 3.17 – 3.04 (1H, m, CH), 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 × ArCH), 120.8 (ArCH), 114.6 (2 × ArCH), 72.0 (OCH$_2$), 52.5 (CH), 47.1 (NHCH$_2$), 32.6 (NHCH$_2$CH$_2$), 20.6 (CH$_2$CH$_3$), 17.5 (CH$_3$CH), 14.3 (CH$_3$CH$_2$); **IR** $\nu_{\text{max}}$ (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-phenoxyp propane-2-yl)butan-1-amine 342c**

![Chemical Structure](image)

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 × ArCH), 7.03 – 6.89 (3H, m, 3 × ArCH), 4.32 – 4.25 (1H, m, CH$_2$), 4.00 – 3.91 (1H, m, CH$_2$), 3.54 – 3.41 (1H, m, CH), 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 × ArCH), 120.9 (ArCH), 114.7 (2 × ArCH), 70.0 (OCH$_2$), 63.3 (CH), 60.7 (NCI=CH$_2$), 30.3 (NCI=CH$_2$CH$_2$), 20.0 (CH$_2$CH$_3$), 14.0 (CH$_3$CH), 13.3 (CH$_3$CH$_3$); **IR** $\nu_{\text{max}}$ (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\textsubscript{3}H (270 µL, 4.10 mmol) and FeSO\textsubscript{4}.7H\textsubscript{2}O (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.

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ ppm 6.93 – 6.77 (2H, m, 2 × ArC\textsubscript{H}), 6.68 – 6.55 (2H, m, 2 × ArC\textsubscript{H}), 4.13 – 3.97 (2H, m, OC\textsubscript{H}\textsubscript{2}), 3.54 – 3.41 (1H, m, C\textsubscript{H}), 3.40 – 3.27 (1H, m, C\textsubscript{H}\textsubscript{2}), 3.21 – 3.04 (1H, m, C\textsubscript{H}\textsubscript{2}), 1.71 – 1.52 (2H, m, CH\textsubscript{2}), 1.47 – 1.32 (2H, m, CH\textsubscript{2}), 1.22 (3H, d, J = 6.5, CHC\textsubscript{H}\textsubscript{3}), 1.04 – 0.94 (3H, m, C\textsubscript{H}\textsubscript{3}); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ ppm 143.4 (C\textsubscript{q}), 134.5 (C\textsubscript{q}), 121.8 (ArCH), 116.3 (ArCH), 116.1 (ArCH), 111.8 (ArCH), 69.1 (OCH\textsubscript{2}), 50.9 (CH), 48.7 (NCH\textsubscript{2}), 29.5 (CH\textsubscript{2}), 20.4 (CH\textsubscript{2}), 15.9 (CH\textsubscript{3}), 14.0 (CHCH\textsubscript{3}); IR ν\textsubscript{max} (neat) / cm\textsuperscript{-1} 3065, 3039, 2958, 2930, 2872, 1605, 1578, 1502; HRMS (ESI\textsuperscript{+}): C\textsubscript{13}H\textsubscript{20}NO [M + H] \textsuperscript{+}: 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, 12.8 mmol). 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.\textsuperscript{135}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ ppm 7.28 (2H, d, J= 9.0, 2 × ArCH), 6.84 (2H, d, J = 9.0, 2 ArCH), 4.54 (2H, s, CH\textsubscript{2}), 2.30 (3H, s, CH\textsubscript{3}); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ ppm 205.1 (CO), 156.4 (C\textsubscript{q}), 129.6 (2 × ArCH), 126.8 (C\textsubscript{q}), 115.9 (2 × ArCH), 73.3 (CH\textsubscript{2}), 26.6 (CH\textsubscript{3}); IR ν\textsubscript{max} (neat) / cm\textsuperscript{-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), MeNH₂ (8 M solution in EtOH, 7.00 mL, 56.0 mmol), Ti(OiPr)₄ (3.20 mL, 10.8 mmol) and NaBH₄ (308 mg, 8.13 mmol). Purification by SCX cartridge afforded the title compound (986mg, 4.94 mmol, 91%) as a pale yellow oil.

^1H NMR (300 MHz, CDCl₃) δ ppm 7.23 (2H, d, J = 9.0, 2 × ArCH), 6.85 (2H, d, J = 9.0, 2 × ArCH), 3.97 – 3.8 (2H, m, OCH₂), 3.19 – 3.03 (1H, m, CH), 2.53 (3H, s, NCH₃), 1.22 (3H, d, J = 6.5, CH₃); ^13C NMR (101 MHz, CDCl₃) δ ppm 156.9 (C), 129.4 (2 × ArCH), 116.9 (C), 116.0 (2 × ArCH), 70.0 (OCH₂), 53.9, 32.0, 14.9 (CHCH₃); IR ν max (neat) / cm⁻¹ 3061, 2962, 2930, 2872, 1596, 1493, 1380, 1274; HRMS (ESI⁺): C₁₀H₁₅ClNO [M + H]^⁺: calculated 234.0447, found 234.0442, ∆ = 2.0 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.

^1H NMR (300 MHz, CDCl₃) δ ppm 7.27 – 7.22 (2H, m, 2 × ArCH), 6.93 – 6.77 (2H, m, 2 × ArCH), 4.20 (1H, dd, J = 9.8, 5.8, CH₂), 3.89 (1H, dd, J = 9.8, 5.8, CH₂), 3.42 – 3.29 (1H, m, CH), 3.03 (3H, s, NCH₃), 1.30 (3H, d, J = 6.5, CH₃); ^13C NMR (75 MHz, CDCl₃) δ ppm 156.1 (C), 129.5 (2 × ArCH), 125.9 (C), 116.1 (2 × ArCH), 70.3 (OCH₂), 64.6 (CH), 49.5 (NCH₃), 12.9 (CH₃); IR ν max (neat) / cm⁻¹ 2979, 2935, 2882, 1596, 1491, 1471, 1285, 1241; HRMS (ESI⁺): C₁₀H₁₄Cl₂NO [M + H]^⁺: calculated 234.0447, found 234.0442, ∆ = 2.0 ppm.
Synthesis of 1-(3-bromophenoxy)propan-2-one 347b

![Chemical structure of 1-(3-bromophenoxy)propan-2-one 347b](image)

General procedure G was followed, using 3-bromophenol (1.50 g, 8.67 mmol), potassium carbonate (1.20 g, 8.67 mmol) and chloroacetonitrile (0.76 mL, 9.54 mmol). 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\(_3\)) \(\delta\) ppm 7.23 – 7.12 (2H, m, 2 × ArCH\(_2\)), 7.10 – 7.05 (1H, m, ArCH), 6.88 – 6.81 (1H, m, ArCH\(_2\)), 4.55 (2H, s, CH\(_2\)N), 2.30 (3H, s, CH\(_3\)). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) ppm 204.8 (C\(_q\)), 158.5 (C\(_q\)), 130.8 (ArCH\(_2\)), 125.0 (ArCH), 123.0 (C\(_q\)), 118.1 (ArCH), 113.4 (ArCH), 73.1 (CH\(_2\)), 26.6 (CH\(_3\)). IR \(\nu_{\text{max}}\) (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

![Chemical structure of 1-(3-bromophenoxy)-N-methylpropan-2-amine 348b](image)

General procedure B was followed, using ketone 347b (1.00 g, 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 (983 mg, 4.04 mmol, 92%) as a pale yellow oil.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) ppm 7.20 – 6.98 (3H, m, 3 × ArCH\(_2\)), 6.88 – 6.82 (1H, m, ArCH), 3.93 – 3.73 (2H, m, CH\(_2\)), 3.06 – 2.97 (1H, m, CH), 2.49 (3H, s, NCH\(_3\)), 1.17 (3H, d, \(J = 6.5\), CH\(_3\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm 159.6 (C\(_q\)), 130.6 (ArCH), 124.0 (ArCH), 122.8 (C\(_q\)), 117.9 (ArCH), 113.5 (ArCH), 71.7 (OCH\(_2\)), 53.9 (CH), 33.6 (NCH\(_3\)), 16.5 (CH\(_3\)). IR \(\nu_{\text{max}}\) (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, \(\Delta = 1.0\) 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 × ArCH), 6.88 (1H, ddd, $J = 7.9$, 2.4, 1.5, ArCH), 4.24 − 4.17 (1H, m, CH$_2$), 3.94 − 3.88 (1H, m, CH$_2$), 3.43 − 3.29 (1H, m, CH), 3.03 (3H, s, NCH$_3$), 1.31 (3H, d, $J = 6.5$, CH$_3$); $^1$C NMR (101 MHz, CDCl$_3$) δ ppm 159.4 (C$_q$), 130.6 (ArCH), 124.1 (ArCH), 122.8 (C$_q$), 118.0 (ArCH), 113.7 (ArCH), 70.1 (OCH$_2$), 64.5 (CH), 49.5 (NCH$_3$), 12.9 (CH$_3$); IR $\nu_{\text{max}}$ (neat) / cm$^{-1}$ 3067, 2979, 2937, 2884, 2791, 1589, 1574, 1470; HRMS (ESI$^+$): C$_{10}$H$_{13}$Br$_3$ClNaO [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$_3$H (240 µL, 3.60 mmol) and FeSO$_4$$\cdot$7H$_2$O (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 × ArCH), 6.38 (1H, d, $J = 8.4$, ArCH), 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, CH), 2.76 (3H, s, CH$_3$), 1.10 (3H, d, $J = 6.5$, CH$_3$); IR $\nu_{\text{max}}$ (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$_2$CO$_3$ (558 mg, 4.04 mmol) and dibromoethane (350 µL, 4.04 mmol) in MeCN (4 mL) was heated at reflux for 16 h. 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 (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 × ArCH), 7.39 – 7.32 (3H, m, 3 × ArCH), 7.27 (2H, d, $J = 8.0$, 2 × ArCH), 7.13 – 7.04 (2H, m, 2 × ArCH), 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 × ArCH), 129.3 (2 × ArCH), 129.0 (2 × ArCH), 128.4 (ArCH), 127.7 (2 × ArCH), 52.6 (NCH$_2$), 28.8 (CH$_2$Br), 21.6 (CH$_3$); IR $\nu_{\text{max}}$ (neat) / cm$^{-1}$ 3065, 3979, 2963, 2923, 2870, 1593, 1490, 1453; HRMS (ESI$^+$): C$_{15}$H$_{16}$BrNNaO$_2$S [M + Na]$^+$: calculated 375.9977, found 375.9973, $\Delta = 1.0$ 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 × ArCH), 7.28 – 7.22 (3H, m, 3 × ArCH), 7.19 (2H, d, $J = 8.5$, 2 × ArCH), 7.10 – 7.02 (2H, m, 2 × ArCH), 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 × ArCH), 129.5 (2 × ArCH), 128.8 (2 × ArCH), 128.7 (ArCH), 128.1 (2 × ArCH), 48.1 (NCH$_2$), 47.5 (CHNH), 33.8 (NCH$_3$), 21.6 (CH$_3$); IR $\nu_{\text{max}}$ (neat) / cm$^{-1}$ 2962, 2920, 2875, 2859, 2719, 2423, 1593, 1490; HRMS (ESI$^+$): C$_{16}$H$_{21}$N$_2$O$_2$S [M + H]$^+$: calculated 305.1318, found 305.1315, $\Delta = 0.3$ 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\(_3\)) \(\delta\) ppm 7.53 – 7.47 (4H, m, 4 × ArCH), 7.46 – 7.41 (1H, m, ArCH), 7.34 – 7.29 (1H, m, ArCH), 7.08 (1H, m, ArCH), 6.99 – 6.93 (2H, m, 2 × ArCH), 3.85 – 3.74 (2H, m, CH\(_2\)), 3.06 – 3.00 (2H, m, NCICH\(_2\)), 2.90 (3H, s, CH\(_3\)), 2.44 (3H, s, CH\(_3\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm 144.4 (C\(_q\)), 132.3 (C\(_q\)), 130.4 (C\(_q\)), 129.6 (2 × ArCH), 129.5 (2 × ArCH), 129.1 (2 × ArCH), 128.8 (ArCH\(_3\)), 127.8 (2 × ArCH), 64.1 (NCICH\(_2\)), 53.3 (NCH\(_2\)), 49.4 (NCICH\(_3\)), 22.7 (ArCH\(_3\)); IR \(\nu_{\text{max}}\) (neat) / cm\(^{-1}\): 3059, 3024, 2998, 2967, 2916, 1597, 1487, 1439; HRMS (ESI\(^+\)): \(C_{16}H_{19}^{35}\)ClN\(_2\)O\(_2\)S [M + Na]\(^+\): calculated 361.0748, found 361.0747, \(\Delta = 0.1\) 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\(_3\)N (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\(_3\)) \(\delta\) ppm 7.00 – 6.97 (3H, m, 3 × ArCH), 5.21 (1H, s, NH), 3.93 – 3.81 (1H, m, CH\(_2\)CH\(_2\)), 2.73 (3H, d, \(J = 4.9\), NHCH\(_3\)), 2.56 (2H, d, \(J = 7.3\), CH\(_2\)CO), 2.40 (6H, s, 2 × ArCH\(_3\)), 1.36 (3H, d, \(J = 7.3\), CHCH\(_3\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) ppm 172.8 (CO), 143.1 (ArCH), 136.5 (C\(_q\)), 130.3 (C\(_q\)), 128.5 (C\(_q\)) 126.1 (2 × ArCH), 42.4 (CH\(_2\)), 31.9 (CHCH\(_2\)), 26.3
(NH\textsubscript{3}), 21.6 (Ar\textsubscript{2}CH\textsubscript{3}), 19.1 (CH\textsubscript{2}CH\textsubscript{3}); IR \( \nu_{\text{max}} \) (neat) / cm\textsuperscript{-1} 3091, 2961, 2938, 2912, 2877, 1636, 1569, 1510; HRMS (ESI\textsuperscript{+}): C\textsubscript{13}H\textsubscript{20}NO [M + H]\textsuperscript{+}: calculated 206.1539, found 206.1547, \( \Delta = +3.4 \) ppm.

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

Following a modified procedure by Williamson et al.\textsuperscript{97} to a stirred suspension of LiAlH\textsubscript{4} (443 mg, 11.7 mmol) in THF (12 mL) at 0 °C was added a solution of amide 363 (600 mg, 2.92 mmol) in THF (3 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\textsubscript{2}O (12.0 eq), aqueous NaOH (2 M, 2.0 eq) and H\textsubscript{2}O (2.0 eq). The resulting slurry was dried over Na\textsubscript{2}SO\textsubscript{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.

\( \textsuperscript{1}H \text{ NMR} \) (300 MHz, CDCl\textsubscript{3}) \( \delta \) ppm 6.99 – 6.95 (3H, m, 3 \( \times \) Ar\textsubscript{2}CH), 3.39 – 3.26 (1H, m, CH\textsubscript{2}CH\textsubscript{2}), 2.69 – 2.26 (10H, m, includes 2 \( \times \) Ar\textsubscript{2}CH\textsubscript{3}, NHC\textsubscript{3}H\textsubscript{3} and CH\textsubscript{2}NH), 2.11 – 1.83 (2H, m, CH\textsubscript{2}NH\textsubscript{2}), 1.37 – 1.28 (3H, d, \( J = 7.36 \), CHC\textsubscript{3}H\textsubscript{3}); \( \textsuperscript{13}C \text{ NMR} \) (75 MHz, CDCl\textsubscript{3}) \( \delta \) ppm 142.5 (Ar\textsubscript{2}C\textsubscript{2}H), 136.2 (C\textsubscript{q}), 128.3 (C\textsubscript{q}) 125.7 (3 \( \times \) ArCH), 50.9 (NCH\textsubscript{2}), 36.2 (CH\textsubscript{2}), 35.2 (NCH\textsubscript{3}), 33.0 (CH), 21.6 (2 \( \times \) ArCH\textsubscript{3}), 19.1 (CHCH\textsubscript{3}); IR \( \nu_{\text{max}} \) (neat) / cm\textsuperscript{-1} 3017, 2930, 2871, 2790, 1466, 1369, 1309, 1256; HRMS (ESI\textsuperscript{+}): C\textsubscript{13}H\textsubscript{21}NNa [M + Na]\textsuperscript{+}: calculated 214.1566, found 214.1564, \( \Delta = +1.0 \) 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.

\( \textsuperscript{1}H \text{ NMR} \) (300 MHz, CDCl\textsubscript{3}) \( \delta \) ppm 6.98 (3H, d, \( J = 4.2 \), 3 \( \times \) ArCH), 3.47 – 3.31 (1H, m, CH), 2.87 (3H, s, NCH\textsubscript{3}), 2.80 – 2.69 (2H, m, NCH\textsubscript{2}), 2.49 – 2.30 (6H, br.s, 2 \( \times \) ArCH\textsubscript{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 × ArCH), 125.6, 64.9 (NCH$_2$), 53.2 (NCH$_3$), 33.7 (CH$_2$), 32.2 (CH), 21.6 (2 × ArCH$_3$), 19.1 (CH$_3$); IR $\nu_{max}$ (neat) / cm$^{-1}$ 3017, 2954, 2930, 1463, 1437, 1368, 1175, 1076; HRMS (ESI)$^+$: C$_{13}$H$_{21}$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**

![Image of 1,4,5,8-tetramethyl-1,2,3,4-tetrahydroquinoline](image)

General Procedure D was followed, using chloroamine 365 (100 mg, 0.44 mmol), MeSO$_3$H (285 µL, 4.40 mmol) and FeSO$_4$$\cdot$7H$_2$O (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, $J = 7.6$, ArCH), 6.70 (1H, d, $J = 7.6$, ArCH), 3.24 – 3.18 (2H, m, NCH$_2$), 3.12 – 3.02 (1H, m, CH), 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 (ArCH), 128.1 (C$q$), 123.5 (ArCH), 47.4 (NCH$_2$), 44.0 (NCH$_3$), 28.2 (CH), 25.1 (CH$_2$), 21.3 (CHCH$_3$), 19.2 (ArCH$_3$), 19.0 (ArCH$_3$); IR $\nu_{max}$ (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**

![Image of methyl 3-(4-methylphenyl)-3-phenylpropanoate](image)

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$_3$N (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\(_3\)) \(\delta\) ppm 7.31 – 7.16 (5H, m, 5 \(\times\) ArCH), 7.12 – 7.07 (4H, m, 4 \(\times\) ArCH), 4.52 (1H, t, \(J = 8.0,CHCH_2\)), 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\(_3\)) \(\delta\) ppm 172.4 (CO), 143.7 (C\(_q\)), 140.5 (C\(_q\)), 136.1 (C\(_q\)), 129.3 (2 \(\times\) ArCH), 128.6 (2 \(\times\) ArCH), 127.6 (2 \(\times\) ArCH), 127.5 (2 \(\times\) ArCH), 126.5 (ArCH), 51.7 (OCH\(_3\)), 46.6 (CHCH\(_2\)), 40.7 (CHCH\(_2\)), 21.0 (ArCH\(_3\)); IR \(\nu_{\text{max}}\) (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, \(\Delta = 0.0\) ppm.

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

\[
\begin{align*}
\text{To a stirred solution of ester } &391a \text{ (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 \(\times\) 3). The combined organic phases were dried over Na\(_2\)SO\(_4\) 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}
\end{align*}
\]

\(^{1}H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.16– 6.96 (9H, m, 9 \(\times\) ArCH), 4.35 (1H, t, \(J = 7.6,CH\)), 2.81 (2H, s, CH\(_2\)), 2.21 (3 H, s, ArCH\(_3\)); \(^{13}C\) NMR (126 MHz, CDCl\(_3\)) \(\delta\) ppm 177.0 (CO), 144.3 (C\(_q\)), 141.1 (C\(_q\)), 135.8 (C\(_q\)), 129.2 (2 \(\times\) ArCH), 128.5 (2 \(\times\) ArCH), 127.6 (2 \(\times\) ArCH), 127.5 (2 \(\times\) ArCH), 126.3 (ArCH), 46.8 (CH), 41.7 (CH\(_2\)), 21.0 (CH\(_3\)); IR \(\nu_{\text{max}}\) (neat) / cm\(^{-1}\) 3055, 3025, 3003, 2920, 2858, 1697, 1577, 1512; HRMS (ESI\(^{+}\)): C\(_{16}\)H\(_{15}\)Na\(_2\)O\(_2\) [M + Na\(_2\)]\(^{+}\): calculated 285.0862, found 285.0867, \(\Delta = +1.6\) ppm.
Synthesis of \(N\)-methyl-3-(4-methylphenyl)-3-phenylpropanamide 393a

General procedure E was followed, using acid 392a (800 mg, 3.33 mmol), \(\text{NH}_2\text{Me.HCl}\) (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.\(^\text{76}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.30 – 7.14 (5H, m, 5 × ArCH), 7.13 – 7.06 (4H, m, 4 × ArCH), 5.19 (1H, s, NCH), 4.53 (1H, t, \(J = 7.8\), CH), 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\(_3\)) \(\delta\) ppm 171.8 (CO), 144.0 (C\(_q\)), 140.8 (C\(_q\)), 136.1 (C\(_q\)), 129.3 (2 × ArCH), 128.6 (2 × ArCH), 127.7 (2 × ArCH), 127.6 (2 × ArCH), 126.5 (ArCH), 47.0 (CH), 43.4 (CH\(_2\)), 26.3 (NCH\(_3\)), 21.0 (ArCH\(_3\)); IR \(\nu_{\text{max}}\) (neat) / cm\(^{-1}\) 3271, 3097, 3061, 2966, 2929, 1635, 1566, 1512; HRMS (ESI\(^+\)): \(\text{C}_{17}\text{H}_{20}\text{NO} [\text{M + H}]^+:\) calculated 254.1539, found 254.1548, \(\Delta = -3.4\) ppm.

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

Following a modified procedure by Williamson et al.,\(^\text{97}\) 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\(_2\)O (12.0 eq.), aqueous NaOH (2 M, 2.0 eq.) and H\(_2\)O (2.0 eq.). The resulting slurry was dried over Na\(_2\)SO\(_4\), filtered through a pad of Celite and was washed with EtOAc. Concentration \(\text{in vacuo}\) afforded the title compound (420 mg, 1.75 mmol, 89%) as a pale yellow oil. The data is in accordance with the literature.\(^\text{76}\)
**1H NMR** (300 MHz, CDCl₃) δ ppm 7.31 – 7.20 (4H, m, 4 × ArCH), 7.19 – 7.05 (5H, m, 5 × ArCH), 3.97 (1H, t, J = 7.8, CHCH₂), 2.56 (2H, t, J = 7.3, CH₂NH), 2.39 (3H, s, NHCH₃), 2.30 (3H, s, ArCH₃), 2.26 – 2.14 (2H, m, CHCH₂); ¹³C NMR (75 MHz, CDCl₃) δ ppm 145.0 (Cq), 141.7 (Cq), 135.7 (Cq), 129.2 (2 × ArCH), 128.5 (2 × ArCH), 127.7 (2 × ArCH), 126.1 (ArCH), 50.4 (CH₂NH), 48.7 (CHCH₂), 36.3 (NHCH₃), 35.5 (CH₂), 21.0 (ArCH₃); IR νmax (neat) / cm⁻¹ 3083, 3056, 2925, 2861, 2792, 1599, 1511, 1493; HRMS (ESI⁺): C₁₇H₂₁NNa [M + Na]⁺: calculated 262.1566, found 262.1568, Δ = -0.8 ppm.

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

![Chemical Structure](image)

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

**1H NMR** (400 MHz, CDCl₃) δ ppm 7.30 – 7.22 (4H, m, 4 × ArCH), 7.19 – 7.06 (5H, m, 5 × ArCH), 4.03 (1H, t, J = 7.9, CHCH₂), 2.88 (3H, s, NCH₃), 2.83 – 2.77 (2H, m, CH₂N), 2.40 – 2.35 (2H, m, CHCH₂), 2.29 (3H, s, ArCH₃); ¹³C NMR (101 MHz, CDCl₃) δ ppm 144.7 (Cq), 141.4 (Cq), 135.8 (Cq), 129.2 (2 × ArCH), 128.5 (2 × ArCH), 127.8 (2 × ArCH), 127.7 (2 × ArCH), 126.2 (ArCH), 64.3 (CH₂N), 53.2 (NCH₃), 47.7 (CH), 34.0 (CHCH₂), 21.0 (ArCH₃); IR νmax (neat) / cm⁻¹ 3058, 3024, 2983, 2952, 2920, 1598, 1511, 1493; HRMS (ESI⁺): C₁₇H₂₁⁵⁵ClN [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

General Procedure D was followed, using chloroamine 388 (100 mg, 0.37 mmol), MeSO\textsubscript{3}H (240 µL, 3.70 mmol) and FeSO\textsubscript{4}\cdot 7H\textsubscript{2}O (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.\textsuperscript{76}

\textsuperscript{1}H NMR signals for the major product reported 396a (400 MHz, CDCl\textsubscript{3}) δ ppm 7.30 - 7.25 (2H, m, 2 × ArCH), 7.21 - 7.17 (1H, m, ArCH), 7.12 - 7.09 (2H, m, 2 × ArCH), 6.62 (1H, d, J = 7.6, ArCH), 6.49 (1H, s, ArCH), 6.39 (1H, d, J = 7.6, ArCH), 4.09 (1H, t, J = 6.2, CHCH\textsubscript{2}), 3.23 - 3.11 (2H, m, NCCH\textsubscript{2}), 2.93 (3H, s, NCCH\textsubscript{3}), 2.29 (3H, s, ArCH\textsubscript{3}), 2.26 - 2.19 (1H, m, CHCH\textsubscript{2}), 2.12 - 2.02 (1H, m, CHCH\textsubscript{2}); \textsuperscript{13}C NMR signals for the major product reported 396a (101 MHz, CDCl\textsubscript{3}) δ ppm 146.8 (2 × C\textsubscript{q}), 137.2 (C\textsubscript{q}), 129.8 (ArCH), 128.7 (2 × ArCH), 128.3 (2 × ArCH), 126.1 (ArCH), 122.1 (C\textsubscript{q}), 117.1 (ArCH), 111.8 (ArCH), 48.7 (NCH\textsubscript{2}), 43.2 (NCH\textsubscript{3}), 39.3 (CHCH\textsubscript{2}), 31.3 (CHCH\textsubscript{2}), 21.7 (ArCH\textsubscript{3}); IR \textit{v}_{\text{max}} \text{ (neat) / cm}^{-1} \text{ 3076, 3063, 2975, 2950, 1640, 1568, 1452, 1415; HRMS (ESI\textsuperscript{+})}: C\textsubscript{17}H\textsubscript{20}N [M + H]\textsuperscript{+}: calculated 238.1590, found 238.1585, \textit{Δ} = -2.1 ppm.

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

General procedure F was followed, using methyl \textit{trans}-cinnamate (1.50 g, 9.25 mmol), 3-(trifluoromethyl)phenylboronic acid (2.20 g, 11.6 mmol, 1.25 eq.), [Rh(cod)Cl\textsubscript{2}] (46 mg, 0.093
mmol) and Et$_3$N (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$_3$) $\delta$ ppm 7.52 – 7.36 (4H, m, 4 × ArCH), 7.34 – 7.18 (5H, m, 5 × ArCH), 4.62 (1H, t, J = 8.0, CHCH$_2$), 3.59 (3H, s, CH$_3$), 3.07 (2H, d, J = 8.0, CH$_2$CO); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.9 (CO), 144.4 (C$q$), 142.5 (C$q$), 131.2 (ArC$_H$), 130.9 (q, J = 32.1, C$q$CF$_3$), 129.1 (ArCH), 128.8 (2 × ArCH), 127.6 (2 × ArCH), 127.0 (ArCH), 124.4 (q, J = 3.7, ArCHC$_q$CF$_3$), 124.1 (q, J = 272.4, CF$_3$), 123.6 (q, J = 3.7, ArCHC$_q$CF$_3$), 51.8 (CH$_3$), 46.8 (CH), 40.4 (CH$_2$); IR $\nu_{\text{max}}$ (neat) / cm$^{-1}$ 3064 (Br.OH), 3027, 2958, 2910, 1696, 1628, 1496, 1448; HRMS (ESI$^+$): C$_{17}$H$_{15}$F$_3$NaO$_2$ [M + Na]$^+$: calculated 331.0916, found 331.0916, $\Delta$ = +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$_2$SO$_4$ and concentrated in vacuo. Crystalisation from hexane : EtOAc (9:1) 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$_3$) $\delta$ ppm 7.58 – 7.36 (4H, m, 4 × ArCH), 7.35 – 7.17 (5H, m, 5 × ArCH), 4.59 (1H, t, J = 7.9, CHCH$_2$), 3.12 (2H, dd, J = 7.9, 2.0, CH$_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 176.5 (CO), 147.2 (C$q$), 144.2 (C$q$), 142.2 (C$q$), 131.1 (ArCH), 131.0 (q, J = 32.1, C$q$), 129.2 (ArCH), 128.9 (2 × ArCH), 127.6 (2 × ArCH), 127.1 (ArCH), 124.4 (q, J = 3.8, ArCHC$_q$CF$_3$), 124.1 (q, J = 272.3, CF$_3$), 123.7 (q, J = 3.8, ArCHC$_q$CF$_3$), 46.5 (CH), 40.1 (CH$_2$); IR $\nu_{\text{max}}$ (neat) / cm$^{-1}$ 3064(Br.OH), 3027, 2958, 2910, 1696, 1628, 1496, 1448; HRMS (ESI$^+$): C$_{16}$H$_{13}$F$_3$NaO$_2$ [M + Na]$^+$: calculated 317.0760, found 317.0759, $\Delta$ = -0.2 ppm.
Synthesis of N-methyl-3-phenyl-3-[3-(trifluoromethyl)phenyl]propanamide 393b

![Chemical structure of 393b](image)

General procedure E was followed, using acid 392b (800 mg, 2.72 mmol), NH₂Me.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

¹H NMR (300 MHz, CDCl₃) δ ppm 7.57 – 7.34 (4H, m, 4 × ArCH), 7.34 – 7.12 (5H, m, 5 × ArCH), 5.27 (1H, s, NH), 4.68 (1H, t, J = 7.7, CH₂CH₂), 2.88 (2H, d, J = 7.8, CH₂CO), 2.67 (3H, d, J = 4.8, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 171.0 (CO), 144.8 (C₆), 142.8 (C₄), 131.4 (ArCH), 130.8 (q, J = 32.1, C₅CF₃), 129.0 (ArCH), 128.8 (2 × ArCH), 127.7 (2 × ArCH), 126.9 (ArCH), 124.2 (q, J = 3.8, ArCHCCF₃), 124.1 (q, J = 272.4, CF₃), 123.5 (q, J = 3.7, ArCHCCF₃), 47.0 (CH), 43.1 (CH₂), 26.3 (CH₃); IR vₘₐₓ (neat) / cm⁻¹ 3296, 3088, 3066, 2942, 1642, 1562, 1494, 1446; HRMS (ESI⁺): C₁₇H₁₆F₃NNaO [M + Na]⁺: calculated 330.1076, found 330.1087, Δ = +3.3 ppm.

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

![Chemical structure of 395](image)

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 BH₃ (4 mL of a 1 M solution in THF, 4.0 eq.) dropwise. The reaction mixture 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 MgSO₄ 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.\(^\text{76}\)

**\(^1\)H NMR** (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.50 (1H, s, ArCH), 7.46 – 7.34 (3H, m, 3 × ArCH), 7.33 – 7.16 (5H, m, 5 × ArCH), 4.09 (1H, t, \(J = 7.8\), CHCH\(_2\)), 2.54 (2H, t, \(J = 7.3\), CH\(_2\)NH), 2.39 (3H, s, CH\(_3\)), 2.31 – 2.21 (2H, m, CHCH\(_2\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 145.6 (C\(_q\)), 143.4 (C\(_q\)), 131.3 (ArCH), 130.8 (q, \(J = 32.0\), C\(_q\)CF\(_3\)), 129.0 (ArCH), 128.8 (2 × ArCH), 127.9 (2 × ArCH), 126.7 (ArCH), 124.4 (q, \(J = 3.7\), ArCHC\(_q\)CF\(_3\)), 124.2 (q, \(J = 272.3\), CF\(_3\)) 123.2 (q, \(J = 3.8\), ArCHC\(_q\)CF\(_3\)), 49.7 (NCH\(_2\)), 36.3 (NCH\(_3\)), 34.6 (CH\(_2\)); IR \(\nu\)\text{max} (neat) / cm\(^{-1}\) 3062, 3028, 2952, 2881, 1599, 1494, 1445, 1326; HRMS (ESI\(^+\)): C\(_{17}\)H\(_{18}\)F\(_3\)NNa [M + Na]\(^+\): calculated 294.1391, found 294.1492, \(\Delta = -0.8\) ppm.

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

![Chemical structure of N-chloro(methyl)[3-phenyl-3-[3-(trifluoromethyl)phenyl]propyl]amine](image)

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.\(^\text{76}\)

**\(^1\)H NMR** (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.51 (1H, s, ArCH), 7.46 – 7.37 (3H, m, 3 × ArCH), 7.32 – 7.19 (5H, m, 5 × ArCH), 4.20 – 4.10 (1H, t, \(J = 7.9\), CH), 2.88 (3H, s, CH\(_3\)), 2.78 (2H, t, \(J = 6.8\), CH\(_2\)NCl), 2.46 – 2.36 (2H, m, CHCH\(_2\)); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 145.5 (C\(_q\)), 143.3 (C\(_q\)), 131.3 (ArCH), 130.8 (q, \(J = 32.0\), C\(_q\)CF\(_3\)), 129.0 (ArCH), 128.8 (ArCH), 127.9 (ArCH), 126.7 (ArCH), 124.6 (q, \(J = 3.8\), ArCHCCF\(_3\)), 124.2 (q, \(J = 272.4\), CF\(_3\)). 123.3 (q, \(J = 3.8\), ArCHCCF\(_3\)), 63.7 (NCH\(_2\)), 53.2 (NCH\(_3\)), 47.7 (CH), 33.8 (CH\(_2\)); IR \(\nu\)\text{max} (neat) / cm\(^{-1}\) 3062, 3028, 2952, 2881, 1599, 1494, 1445, 1326; HRMS (ESI\(^+\)): C\(_{17}\)H\(_{18}\)F\(_3\)ClNa [M + H]\(^+\): calculated 328.1074, found 338.1069, \(\Delta = -2.1\) 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$_3$H (200 µL, 3.10 mmol) and FeSO$_4$.7H$_2$O (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 × ArCH), 7.25 (1H, d, J = 7.6, ArCH), 7.18 – 7.10 (1H, m, ArCH), 6.70 – 6.67 (2H, m, 2 × ArCH), 6.57 (1H, td, J = 7.3, 1.1, ArCH), 4.24 – 4.15 (1H, m, CHCH$_2$), 3.31 – 3.07 (2H, m, CH$_2$N), 2.94 (3H, s, CH$_3$), 2.35 – 2.01 (2H, m, CHCH$_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm 147.5 (C$_q$, Ar), 146.8 (C$_q$, Ar), 132.2 (ArCH), 130.7 (q, J = 32.0, C$_q$CF$_3$), 129.8 (ArCH), 128.8 (ArCH), 128.0 (ArCH), 125.3 (q, J = 3.8, ArCHCCF$_3$), 124.3 (q, J = 272.3, CF$_3$), 123.8 (C$_q$), 123.1 (q, J = 3.8, ArCHCCF$_3$), 116.5 (ArCH), 111.3 (ArCH), 48.4 (NCH$_2$), 43.4 (CHCH$_2$), 39.2 (CH$_3$), 31.1 (CH$_2$); IR $\nu_{\text{max}}$ (neat) / cm$^{-1}$ 3066, 3026 2945, 2927, 1602, 1503, 1444, 1322; HRMS (ESI$^+$): C$_{17}$H$_{17}$F$_3$N [M + H]$^+$: calculated 292.1308, found 292.1313, $\Delta = -1.7$ppm.

Synthesis of 4-benzoyl-1-chloropiperidine 401

A solution of benzoyl piperidine HCl (1.00 g, 4.33 mmol) was dissolved in H$_2$O (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.

**H NMR** (500 MHz, CDCl₃) δ ppm 7.95 (2H, dd, J = 8.3, 1.1, 2 × ArCH), 7.64 - 7.58 (1H, m, ArCH), 7.51 (2H, t, J = 7.7, 2 × ArCH), 3.56 (2H, d, J = 9.5, NCH₂), 3.37 (1H, t, J = 10.7, CH), 3.11 - 3.00 (2H, m, NCH₂), 2.14 - 2.02 (2H, m, CHCH₂), 1.97 (2H, d, J = 14.1, CHCH₂); **C NMR** (101 MHz, CDCl₃) δ 201.5 (CO), 135.7 (C₉), 133.2 (ArCH), 128.8 (2 × ArCH), 128.3 (2 × ArCH), 62.0 (2 × NCH₂), 42.0 (CH), 29.8 (2 × CH₂CH); **IR** νmax (neat) / cm⁻¹ 3047, 2960, 2940, 2921, 2836, 1679, 1609, 1597; **HRMS (ESI⁺)**: C₁₂H₁₅ClNO [M + H]⁺: calculated 224.0835, found 224.0835, Δ = +0.6 ppm.

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

![Structure of 4-benzoyl-1-(5,6,7,8-tetrahydroanaphthalen-2-yl)piperidine](structure.png)

To a stirred solution of the chloroamine 401 (100 mg, 0.45 mmol) in DCM (0.45 mL) at 0 °C was added tetralin (610 μL, 4.50 mmol) MeSO₃H (295 μL, 4.50 mmol) and FeSO₄·7H₂O (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 MgSO₄ 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.

**H NMR** (500 MHz, CDCl₃) δ ppm 8.00 - 7.93 (2H, m, 2 × ArCH), 7.60 - 7.54 (1H, m, ArCH), 7.48 (2H, t, J = 7.6, 2 × ArCH), 6.97 (1H, d, J = 8.3, ArCH), 6.76 (1H, d, J = 7.7, ArCH), 6.68 (1H, s, ArCH), 3.69 (2H, d, J = 6.1, 2.8, NCH₂), 3.42 - 3.31 (1H, m, CHCO), 2.88 - 2.77 (2H, m, NCH₂), 2.73 - 2.68 (4H, m, 2 × CH₂H₂), 2.04 - 1.91 (4H, m, 2 × CH₂CH₂), 1.82 - 1.74 (4H, m, 2 × CH₂H₂); **C NMR** (126 MHz, CDCl₃) δ ppm 202.5 (CO), 137.6 (C₉), 136.1 (2 × C₈), 133.0 (ArCH), 129.7 (2 × ArCH), 128.9 (C₉), 128.8 (2 × ArCH), 128.3 (ArCH), 117.4 (ArCH), 115.1 (ArCH), 50.2 (2 × NCH₂), 43.6 (CH), 29.9 (2 × CH₂CH₂), 28.7 (CH₃), 28.6 (CH₂), 23.5 (CH₂), 23.4 (C₃H₂); **IR** νmax (neat) / cm⁻¹ 3057, 3013, 2854, 2834, 2801, 1679, 1609, 1597; **HRMS (ESI⁺)**: C₂₂H₂₅N₃NaO [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) MeSO₂H (295 µL, 4.50 mmol) and FeSO₄·7H₂O (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 and dried over MgSO₄ 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.

**¹H NMR** (400 MHz, CDCl₃) 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, ArCH, o), 7.15 (0.44H, t, J = 7.7, ArCH, m), 7.07 (0.68H, d, J = 8.2, 2 × ArCH, p), 6.88 (0.68H, d, J = 8.2, 2 × ArCH,p), 6.83 – 6.65 (2 × ArCH, o and m), 3.79 – 3.65 (2H, m, NCH₂), 3.43 – 3.32 (1H, m, CH), 2.85 (2H, m, NCH₂), 2.33 (0.66H, s, CH₃, o), 2.32 (1.32H, s, CH₃, m), 2.27 (1.02H, s, CH₃, p), 2.01 – 1.92 (4H, m, 2 × CH₃CH); **¹³C NMR** (101 MHz, CDCl₃) δ ppm 202.5 (CO), 151.7 (Cq), 150.3 (Cq), 149.6 (Cq), 138.8 (Cq), 136.3 (Cq), 136.1 (ArCH), 136.0 (Cq), 133.1 (ArCH), 133.0 (ArCH), 129.7 (ArCH), 129.4 (Cq), 129.0 (ArCH), 128.8 (ArCH), 128.3 (ArCH), 120.6 (ArCH), 119.2 (ArCH), 117.6 (ArCH), 117.1 (ArCH), 115.5 (ArCH), 113.8 (ArCH), 50.1 (NCH₂), 49.6 (NCH₂), 43.6 (CH), 28.7 (ArCH₃, o), 28.7 (ArCH₃, m), 28.5 (ArCH₃, p), 21.8 (CH₂CH), 20.5 (CH₂CH); **IR** νmax (neat) / cm⁻¹ 3057, 3026, 2948, 2921, 2807, 2748, 1678, 1595 **LCMS (ESI⁺):** C₁₉H₂₂NO [M + H]⁺; calculated 279.2, found 280.4.
Synthesis of 1-chloro-4-phenylpiperidine 410

![Structure of 1-chloro-4-phenylpiperidine]

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$_3$) $\delta$ ppm 7.35 (2H, dd, $J = 10.5, 4.5, 2 \times$ ArCH), 7.28 – 7.21 (3H, m, 3 $\times$ ArCH), 3.60 (2H, d, $J = 11.2$, NCH$_2$), 3.04 (2H, t, $J = 11.2$, NCH$_2$), 2.71 – 2.60 (1H, m, CH), 2.12 – 1.98 (2H, m, CH$_2$CH), 1.92 (2H, d, $J = 13.1$, CH$_2$CH); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ ppm 144.9 ($C_q$), 128.6 (2 $\times$ ArCH), 126.8 (2 $\times$ ArCH), 126.5 (ArCH), 63.4 (2 $\times$ NCH$_2$), 41.2 (CH), 35.0 (2 $\times$ CH$_2$CH); IR $\nu_{max}$ (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, $\Delta$ -1.3 ppm.

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

![Structure of 4-phenyl-1-(5,6,7,8-tetrahydronaphthalen-2-yl)piperidine]

To a stirred solution of the chloroamine 410 (100 mg, 0.51 mmol) in DCM (0.51 mL) at 0 °C was added tetralin (695 µL, 5.10 mmol) MeSO$_3$H (330 µL, 5.10 mmol) and FeSO$_4$·7H$_2$O (14 mg, 0.051). 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 $\times$ 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$_3$) $\delta$ ppm 7.38 – 7.15 (5H, m, 5 $\times$ ArCH), 6.97 (1H, d, $J = 8.1$, ArCH), 6.78 (1H, d, $J = 8.1$, ArCH), 6.70 (1H, s, ArCH), 3.72 (2H, d, $J = 11.4, 2 \times$ NCH$_2$), 2.79 – 2.66 (7H, m, includes CH, 2 $\times$ C$_6$H$_2$, 2 CH$_2$CH), 1.92 (4H, s, 2 $\times$ CHCH$_2$), 1.77 (4H, s, $J = 2.0, 2 \times$ C$_6$H$_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 149.9 ($C_q$), 146.3 ($C_q$), 137.6 ($C_q$), 129.7 (ArCH), 128.7 ($C_q$), 128.5 (2 $\times$ ArCH), 126.9 (2 $\times$ ArCH), 126.3 (ArCH), 117.4 (ArCH), 209
115.1 (ArCH), 51.3 (2 × NCH₂), 42.6 (CH), 33.5 (2 × CH₂CH), 29.9 (C₆H₂), 28.6 (C₆H₂), 23.6 (C₆H₂), 23.4 (C₆H₂); IR ʋmax (neat) / cm⁻¹ 3058, 3025, 2923, 2852, 2798, 1736, 1681, 1609; LCMS C₂₁H₂₆N [M+H]⁺ calculated 292.2, measured 292.2.

Synthesis of 412

![Diagram of molecule]

To a stirred solution of the chloroamine 410 (100 mg, 0.51 mmol) in DCM (0.45 mL) at 0 °C was added toluene (545 µL, 5.10 mmol) MeSO₃H (330 µL, 5.10 mmol) and FeSO₄.7H₂O (14 mg, 0.051). 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 MgSO₄ and concentrated in vacuo. Purification by column chromatography, eluting with DCM in hexane afforded the title compound as inseparable 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.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.30 – 7.10 (5H, m, 5 × ArCH), 7.09 – 7.04 (0.36H, m, ArCH, m), 7.02 – 6.99 (0.76H, m, 2 × ArCH, p), 6.85 – 6.82 (0.76H, m, 2 × ArCH, p), 6.78 – 6.70 (1.5H, m,5H includes o and m ArCH), 6.67 (0.36H, dd, J = 8.8, 3.0, ArCH, m), 6.61 (0.26H, d, J = 7.4, ArCH, o), 3.77 – 3.62 (2H, m, NCH₂), 3.52 – 3.46 (2H, m, NCH₂), 2.78 – 2.49 (5H, m, include 2 × CH₂CH and CH), 2.26 (0.78H, s, CH₃, o), 2.25 (1.08H, s, CH₃, m), 2.20 (1.14H, s, CH₃, p); ¹³C NMR (101 MHz, CDCl₃) δ ppm 151.7 (C₉), 150.3 (C₉), 149.6 (C₉), 144.9 (C₉), 136.3 (C₉), 136.1 (ArCH), 136.0 (C₉), 133.0 (ArCH), 129.7 (ArCH), 129.4 (C₉), 129.0 (ArCH), 128.6 (2 × ArCH) 126.8 (2 × ArCH), 126.5 (ArCH), 120.6 (ArCH), 119.2 (ArCH), 117.6 (ArCH), 117.1 (ArCH), 115.5 (ArCH), 113.8 (ArCH), 51 (2 × NCH₂), 43.6 (CH), 28.7 (ArCH₃, o), 28.6 (ArCH₃, m), 28.5 (ArCH₃, p), 22.0 (2 × CH₂CH); IR ʋmax (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 °C was added (2S)-2-(6-methoxynaphthalen-2-yl)propanoate (100 mg, 0.41 mmol) MeSO₄·H₂O (535 µL, 8.20 mmol) and FeSO₄·7H₂O (23 mg, 0.082 mmol). 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 MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃) δ ppm 8.17 (1H, d, J = 8.8, ArCH), 8.04 – 7.97 (3H, m, 3 × ArCH), 7.63 – 7.56 (1H, m, ArCH), 7.50 (3H, m, 3 × ArCH), 6.93 (1H, s, ArCH), 4.01 (3H, s, COOCH₃), 3.95 – 3.86 (1H, m, CH₃CH), 3.67 (3H, s, OCH₃), 3.55-3.45 (3H, m, includes CH and NCH₂), 2.95 (2 H, dd, J = 15.9, 6.9, NCH₂), 2.27 – 2.05 (4H, m, 2 × NCH₂CH₂), 1.59 (3H, d, J = 7.2, CH₂CH); ¹³C NMR (125 MHz, CDCl₃) δ ppm 204.8 (CO), 177.9 (CO), 157.1 (C₄), 144.1 (C₆), 140.6 (C₅), 136.5 (C₄), 131.2 (C₆), 128.8 (2 × ArCH), 127.4 (C₆), 127.3 (2 × ArCH), 126.4 (ArCH), 125.1 (ArCH), 124.3 (ArCH), 124.1 (ArCH), 110.0 (C₆) 105.5 (ArCH), 54.6 (OCH₃), 45.6 (2 × NCH₂CH₂), 45.3 (COOCH₃), 42.7 (CHCO), 41.0 (CH), 28.6 (2 × CH₂CH₂N), 17.4 (CHCH₃); IR νmax (neat) / cm⁻¹ 3055, 2947, 2850, 2808, 1731, 1678, 1593, 1461; HRMS (ESI⁺): C₂₇H₂₅ClINaO₄ [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 °C was added (2S)-2-(6-methoxynaphthalen-2-yl)propanoate (100 mg, 0.41 mmol) MeSO\(_3\)H (535 μL, 8.20 mmol) and FeSO\(_4\).7H\(_2\)O (23 mg, 0.082). 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 (36 mg, 0.09, 22%)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) δ ppm 7.99 (1H, d, J = 1.7, ArCH), 7.94 (1H, d, J = 8.7, ArCH), 7.44 (1H, dd, J = 8.7, 1.7, ArCH), 7.33 – 7.25 (4H, m, ArCH), 7.21 – 7.15 (1H, m, ArCH), 6.83 (1H, s, ArCH), 3.95 (3H, s, COOCH\(_3\)), 3.91 – 3.78 (1H, m, CH\(_3\)CH), 3.60 (3H, s, OCH\(_3\)), 3.50 – 3.37 (2H, m, CH\(_2\)), 2.85 – 2.59 (3H, m, includes CH, CH\(_2\)), 2.13 – 1.90 (4H, m, 2 × CHCH\(_2\)), 1.54 (3H, d, J = 7.2, CH\(_3\)CH); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) δ ppm 175.0 (CO), 149.4 (C\(_q\)), 145.9 (C\(_q\)), 137.4 (C\(_q\)), 135.8 (C\(_q\)), 131.0 (C\(_q\)), 128.8 (2 × ArCH), 127.4 (C\(_q\)), 127.0 (2 × ArCH), 126.4 (ArCH), 125.1 (ArCH), 123.7 (ArCH), 123.0 (ArCH), 112.4 (C\(_q\)) 106.5 (ArCH), 54.5 (OCH\(_3\)), 52.1 (2 × NCH\(_2\)), 45.5 (2 × NCH\(_2\)CH\(_2\)), 45.3 (COOCH\(_3\)), 42.5 (CHCO), 41.9 (CH) 33.6 (2 × CH\(_2\)CH\(_2\)), 17.8 (CH\(_3\)CH); IR \(\nu_{max}\) (neat) / cm\(^{-1}\) 3060, 3027, 2977, 2934, 2847, 1733, 1599, 1574; HRMS (ESI\(^+\)): C\(_{26}\)H\(_{35}\)ClO\(_3\) [M + H]\(^+\): calculated 438.1689, found 438.1690, \(\Delta = +0.5\) 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 accordance with the literature.\(^{138}\)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) δ ppm 6.82 (2H, d, J = 8.9, 2 × ArCH), 6.62 (2H, d, J = 8.9, 2 × ArCH), 3.77 (3H, s, C\(_3\)H\(_3\)), 2.83 (3H, s, C\(_3\)H\(_3\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) δ ppm 152.6 (C\(_q\)), 142.8 (C\(_q\)), 115.0 (2 × ArC\(_H\)), 114.3 (2 × ArC\(_H\)), 55.9 (OCH\(_3\)), 32.1 (NH\(_2\)C\(_3\)H\(_3\)); IR \(\nu_{\text{max}}\) (neat) / cm\(^{-1}\) 3042, 2989, 2934, 2899, 2831, 2809, 1509, 1464; HRMS (ESI\(^+\)): C\(_8\)H\(_{12}\)NO [M + H]\(^+\): calculated 138.0913, found 138.0911, ∆ = +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, ArCH), 6.36 (1H, dd, J = 8.2, 2.6, ArCH), 6.27 (1H, d, J = 2.6, ArCH), 2.74 (3H, s, NHCH\(_3\)), 2.66 – 2.55 (4H, m, 2 × C\(_b\)H\(_2\)), 1.72 – 1.65 (4H, m, 2 × C\(_a\)H\(_2\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) δ ppm 150.0 (ArC\(_H\)), 136.4 (C\(_q\)), 126.1 (ArCH), 120.8 (C\(_q\)), 118.9 (C\(_q\)), 106.5 (ArCH), 30.6 (CH\(_3\)), 27.4 (ArCH\(_2\)), 24.2 (ArCH\(_2\)), 22.5 (CH\(_2\)), 22.3 (CH\(_2\)); IR \(\nu_{\text{max}}\) (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, ∆ = 3.6 ppm.

**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$_3$) $\delta$ ppm 7.60 – 7.54 (2H, m, 2 $\times$ ArCH), 7.49 (2H, d, J = 8.6, 2 $\times$ ArCH), 7.46 – 7.38 (2H, m, 2 $\times$ ArCH), 7.32 – 7.23 (1H, m, ArCH), 6.72 (2H, d, J = 8.6, 2 $\times$ ArCH), 2.91 (3H, s, CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 148.8 (C$_{q}$), 141.3 (C$_{q}$), 130.2 (C$_{q}$), 128.7 (2 $\times$ ArCH), 127.9 (2 $\times$ ArCH), 126.3 (2 $\times$ ArCH), 126.1 (ArCH), 112.7 (2 $\times$ ArCH), 30.8 (CH$_3$); IR $\nu_{\text{max}}$ (neat) / cm$^{-1}$ 3414, 3054, 2926, 2812, 1609, 1524, 1489; HRMS (ESI$^+$): C$_{13}$H$_{14}$N [M+H]$^+$: calculated 188.1070, found 184.1067, $\Delta$ = 1.6ppm.

**Synthesis of 2-methoxy-N-methylnaphthalen-1-amine 444**

![Chemical structure of 2-methoxy-N-methylnaphthalen-1-amine 444](image)

General procedure x was followed, using 2-methoxynaphthalene (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$_3$) $\delta$ ppm 8.11 (1H, d, J = 8.5, ArCH), 7.79 (1H, d, J = 8.5, ArCH), 7.52 (1H, d, J = 8.9, ArCH), 7.47 (1H, ddd, J = 8.5, 6.8, 1.3, ArCH), 7.35 (1H, ddd, J = 8.5, 6.8, 1.3, ArCH), 7.28 (1H, d, J = 8.9, ArCH), 3.98 (3H, s, OCH$_3$), 3.00 (3H, s, NHCH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 148.4 (C$_{q}$), 129.7 (C$_{q}$), 128.4 (2 $\times$ ArCH), 127.8 (C$_{q}$), 126.4 (ArCH), 125.2 (C$_{q}$), 124.0 (ArCH), 122.3 (ArCH), 113.4 (ArCH), 57.0 (OCH$_3$), 37.1 (NHCH$_3$); IR $\nu_{\text{max}}$ (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, $\Delta$ = 1.6ppm.

**Synthesis of methyl 2-(6-methoxy-5-(methylamino)naphtalen-2-yl)propanoate 445**

![Chemical structure of methyl 2-(6-methoxy-5-(methylamino)naphtalen-2-yl)propanoate 445](image)

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.
1H NMR (300 MHz, CDCl3) δ ppm 7.97 (1H, d, J = 8.8, ArCH), 7.58 (1H, d, J = 1.8, ArCH), 7.39 (1H, d, J = 8.9, ArCH), 7.32 (1H, dd, J = 8.8, 1.8, ArCH), 7.17 (1H, d, J = 8.9, ArCH), 3.91 – 3.83 (4H, m, includes OCH3 and CH), 3.60 (3H, s, OCH3). 2.90 (3H, s, NHCH3), 1.51 (3H, d, J = 7.2, CHCH3); 13C NMR (75 MHz, CDCl3) δ ppm 175.1 (Cq), 135.7 (Cq), 133.5 (Cq), 130.0 (Cq), 127.3 (Cq), 126.5 (ArCH), 125.3 (ArCH), 123.4 (ArCH), 122.6 (ArCH), 113.9 (ArCH), 56.9 (OCH3), 52.1 (COOCH3), 45.3 (CHCH3), 37.2 (NHCH3), 18.5 (CH3); IR νmax (neat) / cm⁻¹ 3365, 2975, 2946, 2839, 1730, 1653, 1599, 1573; HRMS (ESI⁺): C16H15NNaO3 [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), FeCl2 (2 mg, 0.013 mmol) and FeCl3 (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.

1H NMR (300 MHz, CDCl3) δ ppm 7.38 (2H, d, J = 8.3 Hz, 2 × ArCH), 7.08 (2H, d, J = 8.3 Hz, 2 × ArCH), 6.54 (1H, d, J = 8.0, ArCH), 6.35 (1H, dd, J = 8.0, 2.0, ArCH), 6.25 (1H, d, J = 2.0, ArCH), 4.83 (1H, dd, J = 8.6, 7.0, CH), 3.75 (3H, s, OCH3), 3.48 (3H, s, COOCH3), 3.07 (1H, dd, J = 14.0, 7.0, CH2), 2.81 (3H, s, NCH3), 2.72 (3H, s, NHCH3), 2.71 – 2.62 (1H, m, CH2), 2.31 (3H, s, ArCH3); 13C NMR (75 MHz, CDCl3) δ ppm 171.0 (CO), 146.0 (Cq), 143.0 (Cq), 139.2 (Cq), 136.2 (Cq), 129.2 (2 × ArCH), 129.1 (Cq), 127.3 (2 × ArCH), 116.7 (ArCH), 110.0 (ArCH), 109.1 (ArCH), 60.5 (CHCO), 55.5 (OCH3), 52.0 (OCH3), 35.5 (CH2), 30.4 (NCH3), 30.1 (NCH3), 21.5 (ArCH3); IR νmax (neat) / cm⁻¹ 3432, 2950, 2923, 2852, 1737, 1599, 1523, 1449; HRMS (ESI⁺): C20H26N2O5S [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.

$^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.48 – 7.21 (5H, m, 5 × ArCH), 6.81 (2H, d, J = 9.0, 2 × ArCH), 6.64 (2H, d, J = 9.0, 2 × ArCH), 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 × ArCH), 128.0 (2 × ArCH), 127.0 (ArCH), 115.0 (2 × ArCH), 114.2 (2 × ArCH), 55.9 (OCH$_3$), 49.3 (NHCH$_3$); IR $\nu_{\text{max}}$ (neat) / cm$^{-1}$ 3408, 3061, 3028, 2996, 2931, 2831, 1509; HRMS (ESI$^+$): C$_{14}$H$_{16}$NO [M + H]$^+$: calculated 214.1226, found 214.1226, $\Delta$ = 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.

$^1$H NMR (300 MHz, CDCl$_3$) δ ppm 6.79 (2H, d, J = 8.9, 2 × ArCH), 6.59 (2H, d, J = 8.9, 2 × ArCH), 3.76 (3H, s, CH$_3$), 3.18 (1H, m, CH), 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}); \textbf{^{13}C NMR} (101 MHz, CDCl_{3}) \delta ppm 151.9 (C_q), 141.6 (C_q), 114.9 (2 × ArCH), 114.9 (2 × ArCH), 55.9 (OCH_{3}), 52.9 (NCH), 33.6 (2 × CH_{2}), 26.0 (CH_{2}), 25.1 (2 × CH_{2}); \textbf{IR} \nu_{\text{max}} \text{ (neat) / cm}^{-1} 3389, 2989, 2993, 2926, 2851, 2831, 1509, 1450; \textbf{HRMS (ESI^+)}: C_{13}H_{20}NO \quad [M + H]^+: \text{calculated 206.1539, found 206.1544, } \Delta = -2.2 \text{ ppm.}
Chapter 5 References

3523.


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