Direct Photochemical Amination of Aromatics

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Abstract

The formation of aromatic carbon to nitrogen bonds is one of the most important processes used in the chemical industry. It is prevalent in many biologically-relevant molecules such as pharmaceuticals and agrochemicals. A modified Hofmann-Löffler-Freytag reaction, which allowed the direct functionalisation of aromatic C-H bonds using N-haloamines under UV-irradiation in highly acidic media, was first reported by Bock et al. in 1965.1 The reported conditions used concentrated sulfuric acid as solvent and demonstrated a minimal substrate scope.

Here, it has been shown that UV-irradiation of N-chloroamines with 10 equivalents of methanesulfonic acid in DCM allows for the intramolecular amination of unfunctionalised aryl C-H bonds to form tetrahydroquinolines. These novel conditions have been extended to 30 examples including in a concise synthesis of the alkaloid natural product angustureine. Furthermore, studies have helped elucidate a potential mechanism of the reaction and led to the discovery of a 1,2-alkyl migration reaction.

The reaction has also been shown to work in a continuous photochemical reactor. This was extended to work in a two-stage reactor where amines were chlorinated and reacted in situ to form tetrahydroquinolines directly.

Some of the substrates produced with the photochemical methodology have been tested in enzymatic deracemizations using genetically modified monoamine oxidase enzymes. Whilst modest activity was observed for a series of N-substituted tetrahydroquinolines, a group of natural products containing N-unsubstituted tetrahydroquinoline cores were successfully deracemized, with ee’s as high as 90% obtained.
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Abbreviations

°C - degree Celsius
Δ - heat
δ - chemical shift
μw - microwave
μs - mircosecond
6-HDNO - 6-hydroxy-D-nicotine oxidase
Ac - acetate
acac - acetylacetone
Alk - alkyl
API - active pharmaceutical ingredient
aq. - aqueous
Ar - aryl
BINAP - (±)-2,2'-bis(diphenylphosphino)-1,1'-binapthelene
Bn - benzyl
bpy - 2,2'-bipyridine
br - broad
Boc - tert-butyloxycarbonate
Bs - benzenesulfonyl
Bu - butyl
c/conc - concentration
cat. - catalytic
CBSA - p-chlorobenzenesulfonic acid
CHAO - cyclohexylamine oxidase
cm - centimetre
cod - cyclooctadiene
conv. - conversion
COSY - correlation spectroscopy
Cp - cyclopentadiene
Cp* - pentamethycyclopentadiene
Cy - cyclohexyl
d - doublet
DABCO - 1,4-diazabicyclo[2.2.2]octane
dba - dibenzylideneacetone
DCE - 1,2-dichloroethane
DCM - dichloromethane
de - diastereomeric excess
DEPT - distortionless enhancement by polarization transfer
dFppy - 2(4,6-difluorophenyl)pyridine
DERA - deoxyribose-5-phosphate aldolase
DFT - density functional theory
DG - directing group
DIPEA - diisopropylethylamine
DMA - N,N-dimethylacetamide
DMF - N,N-dimethylformamide
DMSO - dimethylsulfoxide
dppf - 1,1’-bis(diphenylphosphino)ferrocene
d.r. - diastereomeric ratio
dtbppy - 4,4’-di-t-butyl-2,2’bipyridyl
EA - electron acceptor
E. coli - Escherichia coli
ED - electron donor
ee - enantiomeric excess
eq - equivalents
ESI - electrospray ionisation
fac - facial
FEP - fluoroethylene propylene
FR - flow rate
FT-IR - fourier transform infrared
g - gram
GC - gas chromatography
h - hour
het - heterocyclic
HLF - Hofmann-Löffler-Freytag
HPLC - high performance liquid chromatography
HRMS - high resolution mass spectrometry
Hz - hertz
IBX - iodoxybenzoic acid
I.D. - internal diameter
IPA - isopropanol
IRED - imine reductase
J - coupling constant
kJ - kilojoule
KRED - ketoreductase
L - litre
LED - light emitting diode
L_n - ligand
LiHMDS - lithium hexamethyldisilazide
LC-MS - liquid chromatography mass spectrometry
M - molar
MAP - 4-methoxyacetophenone
MAO - monoamine oxidase
mg - milligram
MHz - megahertz
MLCT - metal-to-ligand charge transfer
mmol - millimole
mol - mole
Ms - mesylate
NBE - norbornene
NCS - N-chlorosuccinimide
NFSI - N-fluorobenzenesulfonylimide
NIS - N-iodosuccinimide
NMR - nuclear magnetic resonance
Ns - nosyl
NSP - N-succinimidyl perester
PC - photocatalyst
Phth - phthalimide
PIDA - (diacetoxyiodo)benzene
PIFA - [Bis(trifluoroacetoxy)iodo]benzene
pin - pinacolato
Piv - Pivaloyl
ppy - 2-phenylpyridine
PTFE - polytetrafluoroethylene
PyBROP - bromotripyrrolidinophosphonium hexfluorophosphate
q - quartet
r - radius
rt - room temperature
R.V - reactor volume
s - singlet

SET - single electron transfer

STAB - sodium trisacetoxyborohydride

STY - Space Time Yield

t - triplet

TBS - tert-butyldimethylsilyl

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

TEMPO – (2,2,6,6-tetramethylpiperidin-1-yl)-oxyl

tert – tertiary

Tf - triflate

TFA - trifluoroacetic acid

THQ - tetrahydroquinoline

TLC - thin layer chromatography

TMEDA - tetramethylethylenediamine

t_R - residence time

V - volume

Vis - visible

wt - wild type
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Chapter 1 Introduction

1.1 The Importance of Aryl C-N Bond Forming Reactions

Efficient reactions to form C-N bonds are essential to industry and academia due to the prevalence of the bond in biologically relevant molecules. In 2014, Njardarson et al. assembled a database containing all drugs approved for use by the FDA. Their analysis revealed that 59% of approved small-molecule drugs contained a nitrogen heterocycle of some kind, with 84% of all drugs containing at least one nitrogen atom. There is a vast amount of known pharmacologically relevant compounds that contain aromatic C-N bonds, including the anti-depressant drug Aripiprazole 1, which is one of the best-selling pharmaceuticals in America. The naturally occurring antibiotic virantmycin 2, first isolated in 1981, contains a tetrahydroquinoline (THQ) core and the alkaloid angustureine 3, comes from a family of natural products of which some have been demonstrated to have antimalarial activity (Figure 1.1).

![Chemical structures](image)

**Figure 1.1**

The importance of this type of reaction was highlighted by Roughley and co-workers in their analysis of all the published reactions that were performed by medicinal chemists at AstraZeneca, GlaxoSmithKline and Pfizer over the course of a year. Of 7315 documented reactions, it was found that 458 of them (roughly 6%) were amination of aryl halides, using SNAr chemistry and Pd-catalysed Buchwald-Hartwig reactions. This was the most used type of C-N bond forming reaction, and the fourth most common reaction discussed in the study.

As well as SNAr reactions and the Buchwald-Hartwig reaction, numerous other methods have been reported that can be used to aminate aromatic groups. These will be discussed in depth in the remainder of this section.
1.2 Classical Methods for N-Arylation

1.2.1 Metal Free Methods for Aryl C-N Bond Formation

1.2.1.1 Nitration of Aromatics

One of the most common ways of installing amino functionality on aromatic groups is by nitration of aromatics followed by reduction of the nitro group. There have been numerous methods described that can be used to reduce a nitro group to an amine. The most commonly employed techniques include hydrogenation with metal catalysts such as Pd/C, Pt or Raney nickel, or heterogeneous reduction with metals, for instance Fe with AcOH. The main problems with the nitration/reduction sequence are use of the highly corrosive medium in the nitration step, regioisomeric issues and a lack of functional group compatibility. There have been developments that mean the reduction can now be performed under conditions that are more tolerant of sensitive functional groups, however these reactions still frequently require precious-metal catalysts or specialist reagents. One issue that is hard to overcome is the regioselectivity of the nitration reaction. Olah and co-workers reported the distribution of products for the nitration of toluene with a range of nitrating agents. In all instances there were roughly a 2:1 ortho/para- distribution. New methods are required to improve efficiency and try to overcome the regioselectivity issues with this reaction.

1.2.1.2 Amination of Aryne Intermediates

Another method used for amination of aromatics is the formation of aryne intermediates then trapping with nucleophilic nitrogen species. Benzyne intermediates are reactive derivatives of aromatics that formally contain a strained triple bond. The lifetime of these species is extremely short-lived due to their high reactivity, and this has been exploited in the synthesis of arylamines. Classical methods involved the use of amide bases and aryl halides to generate the intermediate. This then reacted subsequently with the ammonia produced in the reaction (Scheme 1.1).

![Scheme 1.1](image)

The advent of aryne generation through the fluoride-mediated decomposition of o-silylaryl triflates has emerged as a milder method to produce these reactive intermediates. A fluoride source is used to generate the benzyne by reacting with the o-silyl group which
then eliminates the triflate. For example, Wang et al. showed that secondary N-haloamines generated in situ from amine precursors 7 could be added directly across an aryne to afford o-haloanilines 9. A range of cyclic haloamines were demonstrated, with several functionalities tolerated under the reaction conditions (Scheme 1.2).

![Scheme 1.2](image)

As with the nitration of the aromatics, there are regioselectivity issues with the reactivity of benzyne derivatives. There is little control with the position of reaction when the aromatic is not symmetrical, meaning mixtures of products are often obtained. Transition-metal catalysed techniques offer a more controlled way of aminating aromatic groups.

1.2.2 Precious-Metal Catalysed Aryl C-N Bond Forming Reactions: Pre-Functionalised Aromatic Groups

1.2.2.1 The Ullmann Coupling

The Ullmann coupling, first reported in 1903, is a Cu-mediated coupling between two aryl halides 10. The initial reported conditions required stoichiometric amounts of Cu and high temperatures, often in excess of 200 °C (Scheme 1.3).

![Scheme 1.3](image)

After the initial report, Ullmann also showed that the reaction could be used to form aryl ethers and anilines 14 under the same conditions (Scheme 1.4).
In 1906 the first catalytic variants were also reported, with Goldberg reporting catalytic N-arylation of amines and demonstrating that amides 15 could also be used as the nucleophile in the reaction (Scheme 1.5).[^18]

![Scheme 1.5](image)

Considerable work into the mechanism of the reaction in the latter half of the 20th Century led to the discovery and development of ligand systems that have greatly enhanced the usefulness of Ullmann-type couplings.[^19]^[^20] These discoveries have meant that the reactions can be run at much lower temperatures than those originally reported by Ullmann and Goldberg, so the scope of the reaction and feasibility of running them have increased as well.[^20]

In 2001, Buchwald et al. demonstrated that when using diamine ligands nitrogen nucleophiles 18 could be coupled to aryl iodides, bromides and chlorides 17.[^21] The different nitrogen coupling partners demonstrated included primary and secondary amides, primary and secondary amines, heterocyclic amines including pyrroles, indoles and pyrazole and hydrazine and hydrazone derivatives. The scope of aryl halides 17 used in the reaction included carbocyclic aromatics and heterocycles (Scheme 1.6).[^21]

![Scheme 1.6](image)

The same group later proposed a mechanism for the catalytic Goldberg coupling.[^22] They proposed that a Cu¹ species 22 was first formed through coordination to the amide coupling...
partner 21, and after this oxidative addition occurred between the aryl halide 23 and the Cu(I) intermediate 22 to give a Cu(III) species 24, then reductive elimination furnished the desired product 25 and regenerated the catalyst 20 (Scheme 1.7).22

Much development of the Ullmann-Goldberg catalyst/ligand systems has meant even less harsh conditions can be used, with reports of room temperature cross-couplings for certain substrates reported in the literature.23,24

1.2.2.2 The Chan-Lam Coupling

Another Cu-mediated N-arylation reaction is the Chan-Lam coupling, which is the coupling of a range of heteroatomic coupling partners with boronic acids.25-27 The initial reports used stoichiometric amounts of Cu, required a tertiary amine base and worked with amines, amides, phenols and nitrogen-containing heterocycles 27 and were coupled with several arylboronic acids 26 (Scheme 1.8).25-27

After the initial reports, several groups developed modifications that allowed the use of catalytic Cu.28 Initially, Collman et al. showed that 10 mol% catalyst loading of a TMEDA-complexed Cu-catalyst successfully mediated the arylation of imidazoles with several arylboronic acids.29 It was found that an oxidant was required to return the Cu to the original oxidation state, with many groups reporting the use of air being enough as an external oxidant (Scheme 1.9).28
Catalytic variants were also extended to include benzamides, imides, sulphonamides and primary amines. A review by Lam and work by Stahl et al. and recently by Watson et al. have helped put together a picture for the mechanism. Watson et al. used a model system of 4-phenyl-phenylboronic acid and piperidine for the study. The authors state the Cu(OAc)$_2$ exists as a dimeric paddlewheel complex [Cu(OAc)$_2$]$_2$·2H$_2$O in solution and this is denucleated by piperidine to give the mononuclear Cu$^{II}$ species. This undergoes a transmetallation with organoboron to give the organo-Cu$^{II}$ intermediate which is oxidised to the Cu$^{III}$ species by way of disproportionation with another Cu$^{II}$ molecule, then reductive elimination delivers the desired product along with the Cu$^{I}$ species. This is oxidised to the catalyst to complete the catalytic cycle with O$_2$ and acid (Scheme 1.10).

Developments of the Chan-Lam coupling have meant it can now be conducted under ligand- and base-free conditions, usually at lower temperatures than the Ullmann-Goldberg reactions; however it requires pre-functionalised aromatics as coupling partners. This can mean sensitive
functionality must be carried through several synthetic steps and it increases the amount of waste produced with every reaction. Ideally similar methodology that functionalises inert C-H bonds is preferable as C-H functionalisation reactions are more atom economical.

1.2.2.3 The Buchwald-Hartwig Cross-Coupling Reaction

In 1994 the groups of Buchwald and Hartwig independently published details describing a Pd-catalysed cross-coupling of aryl halides with aminostannanes, with heating at near reflux in toluene and no base required for the reaction.\(^{35,36}\) One year later, the Buchwald group found that the addition of NaOrBu as a base alleviated the need for a stannyl-amide species at the start of the reaction, and that amines could be reacted directly with aryl bromides.\(^{37}\) This study showed that whilst the catalyst system was effective for secondary amines and intramolecular amination, and also avoided the use of any stoichiometric tin reagents, it was limited in scope with only o-substituted aryl bromides providing consistently good yields as coupling partners for primary amines.\(^{37}\)

A greater understanding of the catalytic cycle led to a realisation of the importance of ligand selection to the reaction, which allowed for further development of the catalyst/ligand systems employed for the reactions.\(^{38}\) Buchwald et al. revealed that use of BINAP 46 increased the scope of the reaction and meant that a range of primary amines 44 could be arylated with a multitude of aryl bromides 43 (Scheme 1.11).\(^{38}\)

![Scheme 1.11](image)

Work by both the Buchwald and Hartwig groups has helped to elucidate the mechanism and propose a catalytic cycle for the reaction with reasonable confidence.\(^{36,38-40}\) Initial work by the group of Hartwig focussed on the mono-coordinating phosphine ligands P(o-tolyl)$_3$, that led to the initial discoveries of the reaction.\(^{36,39,40}\) With the advent of BINAP type ligands and their superiority as ligands for this reaction more work has shown how they affect the reactions.\(^{38,41}\)

A proposed catalytic cycle is shown below. Initially, an equilibrium is formed between the BINAP ligand 46 and the Pd$_2$(dba)$_3$ 47, which after ligand exchange gives rise to the chelated (BINAP)Pd(dba) species 48, and then elimination of the dba ligand releases the active Pd$^0$
species 49. This undergoes oxidative addition with the aryl halide 50 to give the four-coordinate complex 51 and, the authors argue, a five-coordinate complex 53 then reversibly forms from association with the amine 52. Deprotonation of the amine allows elimination of the halide to give the four-coordinate complex 54, which then undergoes rapid reductive elimination to afford the desired product 55 and reform the active catalyst 49. The use of the BINAP ligand 46 throughout stabilises the Pd centre as there is a permanent double coordination from the ligand. This helps to prevent bis-coordination of amine species 52 which would ultimately kill catalytic activity (Scheme 1.12). 38

![Scheme 1.12](image)

The authors noted several points of evidence to support this mechanistic pathway: 38,42

1. The (BINAP)Pd°(dba) 48 species was isolated as an orange crystalline solid.
2. The Pd° complex 51 arising from oxidative addition of the aryl halide was also isolated and fully characterised.
3. With no base in the reaction no aniline product 55 was observed. A large excess of amine 52 (5 eq.) was added to the reaction, however even with this excess no product 55 was observed by 1H NMR.

The introduction and further development of the biaryl phosphane ligands has revolutionised Pd-catalysed aryl C-N cross coupling reactions. 43,44 A novel ligand L2 first reported by Buchwald et al., which has subsequently given rise to many similar and related classes of ligands, allowed amination of aryl chlorides 56 to occur at rt (Scheme 1.13). 45
Recently, the groups of Buchwald and MacMillan published a collaborative study that merged the reactivity of photoredox catalysis with that of a Ni catalyst.\(^\text{46}\) Using a combination of a nickel halide pre-catalysts and extremely low loadings of the Ir photocatalyst \(\text{C}_1\), a range of amides and amines \(\text{60}\) were coupled to several aromatic bromides \(\text{59}\). Other than catalysts the only additive required was DABCO as base, with no ligands or external oxidants required for the reaction to occur (Scheme 1.14).\(^\text{46}\) The mechanism proceeds through the regeneration of the Ni catalyst using the Ir photocatalyst \(\text{C}_1\) through a single electron transfer pathway, however photoredox catalysis will be covered in a later section where there will be detailed discussions of related mechanisms.

The use of the bidentate ligands in C-N cross-coupling chemistry has advanced the field to the point where compounds that hitherto had been inaccessible, are now easily synthesised through these methods. Nevertheless, the necessity of pre-functionalised aromatic groups can lead to an increased number of synthetic steps and with this increases the amount of waste produced for each reaction. Also, even though ligands have enabled much lower catalyst loadings (regularly <0.1 mol\%) their use in reactions is not always trivial, with catalyst/ligand screens a frequent and often necessary feature of cross-coupling chemistry to give optimal conditions. A technology that looks to address the issues of increased waste and unnecessary pre-functionalisation of aromatic groups is C-H activation, where usually unreactive C-H bonds are reacted directly to avoid the need for extra synthetic steps.
1.3 C-H Activation Reactions

Within the last decade C-H activation has changed synthetic approaches to transition-metal catalysed bond forming reactions. Numerous methods have been disclosed for amination of unactivated aryl C-H bonds. C-H activation reactions catalysed by precious-metals generally proceed through two mechanistic pathways: 1) directed C-H activation, where a functional group directs insertion into the C-H bond, and 2) non-directed C-H activation, where arenes are reacted without the use of a directing-group for metal-insertion. Directing group assisted C-H activation usually employs heteroatomic coordination of a metal-centre, which allows for a facile intramolecular C-H insertion to give an activated metallo-carbon bond that can undergo amination. Non-directed C-H activation reactions do not require the sometimes bulky directing-groups, so there are fewer synthetic steps associated with installation and removal of the groups; however the selective activation and insertion into unreactive C-H bonds without any direction remains a difficult challenge for synthetic chemists.

1.3.1 Directing-Group Assisted C-H Amination

1.3.1.1 Intramolecular C-H Amination Using Directing Groups

One of the first reports of aryl C-H amination came from Buchwald et al., when they reported that a Pd catalyst with a Cu oxidant could allow for intramolecular C-H/N-H dehydrogenative coupling to give carbazoles 63 (Scheme 1.15).

\[ \text{Scheme 1.15} \]

The proposed mechanism proceeded though coordination of Pd to the amide 64 followed by electrophilic addition to the aromatic ring, then reductive elimination to afford the desired product 67 (Scheme 1.16).

\[ \text{Scheme 1.16} \]
In 2012, two groups reported the use of picolinamide directing groups in the intramolecular formation of indolines 69 from 2-phenylethylamines 68. Daugulis et al. reported that the bidentate chelating effect of the picolinamide directing group could be used to synthesise a range of indolines 69. Control experiments showed that the double-coordination of the directing group was essential to the reaction happening, with no cyclisation observed when a phenyl group replaced the pyridyl moiety. Instead of using a Cu oxidant however, the group reported the use of hypervalent iodine species PhI(OAc)₂ (PIDA) (Scheme 1.17). Chen and co-workers reported simultaneously near identical conditions, however only demonstrated one example of N-arylation. 51

Scheme 1.17

The group of Gaunt showed that amines 70 could also be used in intramolecular amination, in the synthesis of carbazoles 71 once again using PIDA as the oxidant. The use of the strong oxidant allowed the reaction to proceed at room temperature (Scheme 1.18). 52

Scheme 1.18

The proposed catalytic cycle involved oxidation of the Pd‰ species 74 to a PdIV species 75 rather than the Pd‰/Pd⁰ catalytic cycles previously reported. The smooth reductive elimination to reform the Pd‰ catalyst was stated as one of the key reasons that the reaction takes place at room temperature. The group reported the isolation of a trinuclear Pd complex, and suggested that reductive elimination is promoted by oxidation of the Pd‰ centre to PdIV. This was confirmed by smooth conversion of Pd complex 74 to the desired product upon treatment with the oxidant (Scheme 1.19).
The use of chelating ligands has also found use in the intermolecular amination of aromatics.

1.3.1.2 **Intermolecular C-H Amination Using Directing Groups**

The use of directing groups for intermolecular C-H activation has greatly expanded the amount of transformations available to synthetic chemists. In particular, Rh, Ru and Pd catalysis now have numerous applications for several types of transformations, including in C-H amination reactions.

Rh catalysis has received much attention in recent years. Glorius and co-workers reported that [Cp*RhCl₂]₂ catalysed the o-amination of O-pivaloyl hydroxamic esters 76 with several N-chloroamines 77 employed as the aminating agents (Scheme 1.20). N-Chloroamines are easily obtained from chlorination of amines with chlorinating agents such as NCS or NaOCl.

The proposed mechanism begins with a base-mediate dissociation of the dimeric Rh catalyst 79 to give the active species 80 which then forms the rhodacycle 82 in the rate-determining C-H activation step. The authors stated that the remaining steps were fast but were only presumed due to lack of experimental evidence. The N-chloroamine 83 electrophilically adds to the C-Rh bond to give the aminated Rh-amido species 84, then protodemetallation affords the desired product 85 and regenerates the active catalyst 80 (Scheme 1.21).
The Yu group have also used masked amine derivatives for directed C-H amination, employing cyclic $O$-benzoyl hydroxylamines $87$ for $m$-selective functionalisation.$^{54}$ The $m$-selectivity is gained through addition of norbornene (NBE) to the reaction which acts as a transient mediator; an initial Pd-insertion still occurs ortho- to the directing group however reacts through a Heck-type pathway with the NBE molecule to direct meta-amination (Scheme 1.22).$^{54}$

Several groups have reported sulfonamide derivatives for imidation in C-H activation reactions, including $N$-fluorobenzenesulfonylhydride $93$ (NFSI). Yang and Li found that it could be used for the Rh-catalysed amination of 1-pyridyl arenes $92$, with the pyridine acting as the directing group for the C-H insertion step (Scheme 1.23).$^{55}$
Using a combination of AgSbF\textsubscript{6} and PhI(OAc)\textsubscript{2} in conjunction with [Cp\textsuperscript{′}RhCl\textsubscript{2}] as catalyst, Su and co-workers showed that unactivated sulphonamides 96 could be coupled directly with a range of simple arenes 95\textsuperscript{,65} This constituted a dehydrogenative cross-coupling, with H\textsubscript{2} being the only formal by-product of the reaction. The reaction scope was demonstrated with over 30 examples, and the groups showed several directing groups could be used (Scheme 1.24).\textsuperscript{56}

Using Pd-catalysis and the NFSI reagent 93 discussed previously (see Scheme 1.23), Zhang et al. demonstrated that \textit{o}-methoxy anilides 98 led to formation of the \textit{p}-substituted products 99 under Pd catalysis (Scheme 1.25).\textsuperscript{57}
The authors suggested a possible catalytic cycle for the $p$-amination protocol. Initially after reduction of the Pd$^{II}$ catalyst $100$ to a Pd$^{0}$ species $101$, addition of a molecule of NFSI $93$ gives the Pd$^{II}$ species $102$ which then coordinates to the aromatic ring via direction from the oxygen of the anilide $103$, then electrophilic addition of Pd gives the spirocycle $105$ which undergoes attack by the amide anion. The de-aromatised product $106$ eliminates hydrogen to afford the desired product $107$ and give the catalyst $100$ which re-enters the catalytic cycles through reduction (Scheme 1.26). This mechanism seems highly unlikely due to the oxidising conditions that are employed: reduction of the resting catalyst $100$ will most likely not occur as the authors have stated it does.

Initial attempts to use Pd catalysts for intermolecular C-H amination saw the use of isolated palladacycle complexes that were synthesised and subsequently reacted with aminating reagents. Sanford and co-workers synthesised dimeric Pd-complexes $108$ that were subsequently reacted with hypervalent iodine reagents to give amidated products $109$ through nitrenoid intermediates (Scheme 1.27).

The authors proposed two possible mechanistic pathways: one proceeding through a stepwise process where a Pd$^{IV}$ intermediate $111$ is formed; and the second a concerted process with a three-centred interaction $113$ between the Pd$^{II}$, the carbon and the aminating agent (Scheme 1.28). The authors stated that they believed the stepwise pathway was more likely, and then computational studies by Cundari et al. supported this proposal. Both groups noted that
further reaction with HCl decomposed to the resulting palladacycle \( 112 \) to give the N-arylation products.

\[
\begin{align*}
\text{Stepwise Pathway} \\
\text{Concerted Pathway}
\end{align*}
\]

1.3.2 Directing-Group Free C-H Amination Reactions

1.3.2.1 Directing-Group Free Intramolecular C-H Amination

Directing-group free C-H activation reactions offer a more streamlined synthetic approach, and reduce the overall waste impact of synthetic routes with no directing groups that must be removed after they have fulfilled their requirements. One area that has received much attention recently is the use of nitrenes in transition-metal catalysed direct N-arylation. These reactive intermediates are generally obtained from the decomposition of azides and diazo compounds. Nitrenoid insertion for intramolecular aryl C-H amination was pioneered by Driver et al., with their report detailing the Rh\( ^{II} \)-catalysed degradation of azides \( 114 \) to give reactive nitrene intermediates \( 117 \) that reacted directly with a range of heteroaromatic groups.\(^6\) The use of a Rh\( ^{II} \) catalyst allowed formation of nitrenoid intermediates at much lower temperatures than was conventional in the thermal decomposition of azides. The reaction mechanism was said to proceed in a similar fashion to the insertion of Rh\( ^{II} \)-catalysts into \( \alpha \)-diazocarbonyls, with formation of the Rh-nitrenoid \( 117 \) followed by one of two pathways: concerted or stepwise mechanisms (Scheme 1.29).\(^6\)
Bolm and co-workers showed that the same transformation could be mediated by much cheaper Fe catalysts, with 16 examples demonstrated in consistently good yields.\(^6\) The report showed that the same starting materials 118 could be converted to the same indole products 119 but the use of Fe(OTf)\(_2\) instead of the dimeric Rh catalysts represents a more economically attractive procedure for industry (Scheme 1.30).\(^6\)

\[\text{Scheme 1.30}\]

One of the main issues associated with the use of azides in synthesis is their potential explosive properties, so there is often a reluctance to scale up reactions involving them. Several groups have addressed this issue by using alternative nitrene precursors. For example, Chiba et al. reported the Pd-catalysed intramolecular formation of indoles 121 using α-aryloximes 120 as starting materials.\(^6\) The reaction proceeded through a base-mediated formation of nitrenes, which were intercepted with a Pd-catalyst and subsequently reacted directly with the aromatic group (Scheme 1.31).\(^6\)

\[\text{Scheme 1.31}\]

The proposed mechanism proceeded in a similar manner to that of the Rh-catalysed examples discussed above (see Scheme 1.29), with formation of metallo-nitrene intermediate 124 that reacts with the aromatic group. Through the use of isotopic labelling experiments, the authors postulated that an electrophilic aromatic substitution pathway must be occurring, rather than a σ-bond metathesis (Scheme 1.32).\(^6\)
Several groups have also utilised the 2H-azirine moiety 129 as a safe nitrene precursor.\textsuperscript{48} Zheng \textit{et al.} for example demonstrated that FeCl\textsubscript{2} could be used as catalyst in the synthesis of indoles from azirines.\textsuperscript{63} The azirines 129 were easily prepared from α-arylketones 127 either via the hydrazone 128 or the oxime (Scheme 1.33).\textsuperscript{63}

These were then easily converted to the desired indole products 130 under Fe catalysis in refluxing THF (Scheme 1.34).\textsuperscript{63}

Limited work has been conducted in directing-group free C-H amination reactions that do not utilise nitrene precursors as starting materials. Yoshikai and co-workers demonstrated that acyl oximes 131 could react through a different intermediate, with an Fe-mediated C-N bond formation to produce phenanthridines 132 (Scheme 1.35).\textsuperscript{64}
The authors proposed a mechanism based on some of their experimental observations. The addition of TEMPO did not affect the reaction, ruling out the existence of any radical intermediates. They also observed that when an electron-rich aromatic was used as the cyclisation partner (4-OMe), a complex mixture of unidentifiable products was obtained. They stated the mechanistic pathway must be distinct from the work performed by Rodriguez (see Scheme 1.68) and Walton (see Scheme 1.70), where photochemical irradiation of $N$-acyloximes led to phenanthridine formation through an iminyl radical. The two proposed pathways were: 1) a Friedel-Crafts type pathway, and 2) a $6\pi$-electrocyclisation pathway. The Fe-catalyst was deemed to act as a Lewis-Acid catalyst in the reaction (Scheme 1.36).

Due to the unreactive nature of C-H bonds, non-directed activation of these bonds is an inherently hard task to achieve. This is more prominent in intermolecular reactions.

### 1.3.2.2 Directing-Group Free Intermolecular C-H activation

To enable directing-group free C-H activation between two molecules, many reports have relied on the innate reactivity of five-membered heterocycles for regioselective C-H amination reactions. One of the first groups to exploit this reactivity through Cu-catalysis were Mori and co-workers who coupled amines 136 with a range of azoles 135 using Cu(OAc)$_2$ as catalyst, with PPh$_3$ as ligand and NaOAc as base for the reaction. They found that an atmosphere of O$_2$ was essential to reaction proceeding, with no reaction observed under an inert atmosphere (Scheme 1.37).
Miura et al. reported a mild Cu-catalysed amination of azoles 138 with N-chloroamines 139. The key difference with their procedure was the amine was prefunctionalised as the N-chloroamine 139 which alleviated the need for high temperatures or superstoichiometric amounts of external oxidant (Scheme 1.38). A plausible mechanism could proceed through the formation of an organocopper(I) intermediate, followed by oxidative addition of the N-chloroamine then reductive elimination to afford the desired product.

Schreiber et al. reported similar conditions to those reported by Mori et al., however amides 142 were used as the nitrogen coupling partner instead of amines (Scheme 1.39). The authors proposed catalytic cycle proceeds through base-mediated ligand exchange to give the organocopper species 145, which undergoes further ligand exchange to afford the Cu-amido intermediate 147. This undergoes reductive elimination to yield the desired product 148 and a Cu species which is oxidised under the O₂ atmosphere to complete the catalytic cycle and give the active catalyst 149 again (Scheme 1.40). The authors give no details of the potential oxidation state of Cu throughout the catalytic cycle, but a Cu¹/Cu³ cycle is frequently proposed for these types of pathways and seems most likely.
The group of Che exploited the reactivity of nitrenes in their Ru-porphyrin 152 catalysed amidation of several heteroaromatics 150. As with some of the intramolecular examples of C-H activation discussed earlier this report exploited the reactivity of nitrene intermediates, but was also one of the first reports that made use of the reactivity of highly reactive five-membered heterocycles 150. Interestingly, the authors found that conversion was greatly enhanced when ultrasound was used in the reaction but gave no explanation as to why this was the case (Scheme 1.41).  

Falck and co-workers reported a general procedure for both inter- and intramolecular N-arylation of benzenes 153 using a dimeric Rh-catalyst that forms presumed nitrenoid intermediates in situ with hydroxylamine derivatives 154 as the aminating agent (Scheme 1.42). Through this method nine tetrahydroquinolines were synthesised and 21 anilines were produced, including in the late stage functionalisation of four drugs and natural products.
Several groups have demonstrated that nitrenoid species generated \textit{in situ} from the use of hypervalent iodine species can, in conjunction with precious-metal catalysis, aminate with reasonable levels of regioselectivity on simple aromatics. One of the earlier reports came from Chang \textit{et al.}, with the Cu-catalysed synthesis of carbazoles 157 using sulphonamides 156.\textsuperscript{72} In the same study they also demonstrated that similar results could be obtained using PhI(OAc)\textsubscript{2} alone, in a metal-free amination protocol (Scheme 1.43).

\begin{center}
\includegraphics[width=\textwidth]{Scheme1.43.png}
\end{center}

\textbf{Scheme 1.43}

The use of metal-free hypervalent iodine conditions has been pioneered by the groups of Chang and DeBoef.\textsuperscript{73,74} However, without mediation by precious-metal catalysts there is little regioselectivity observed in these reactions rendering them synthetically useless. Hartwig and co-workers were one of the first groups to develop the initial work by Chang and DeBoef by adding catalytic amounts of Pd(OAc)\textsubscript{2} and using the steric bias of the arene 158 to govern regioselectivity.\textsuperscript{75} Whilst there was complete regiocontrol obtained with 1,2,3-trisubstituted aromatics and higher levels of selectivity for mono- and di-substituted aryls, there was not complete control for every substrate. Also, to prevent the formation of Pd-black in the reaction multiple quantities of PIDA needed to be added to the reaction, resulting in six equivalents being the optimum amount (Scheme 1.44).\textsuperscript{75}

\begin{center}
\includegraphics[width=\textwidth]{Scheme1.44.png}
\end{center}

\textbf{Scheme 1.44}

Inspired by the work of Hartwig, the group of DeBoef employed Au-catalysis with an oxidant and obtained much higher selectivity for \textit{p}-substituted products then Hartwig.\textsuperscript{76} As with the previous work, this represented a C-H/N-H coupling and proceeded at 100 °C, considerably lower than the 140 °C that was required for the metal-free variants of this work. It did however require superstoichiometric amounts of the oxidant again, this time with a second addition of
four equivalents of PIDA to make a total of eight required for the reaction. In the absence of 
Au there were small amounts of product seen (<15% yield) but the selectivity was diminished, 
with the justification being that a competing non-metal catalysed radical pathway was also 
occurring that led to trace amounts of m-products in several of the products (Scheme 1.45).  

![Scheme 1.45]

The authors rationalised the high selectivity for p-amination through an electrophilic aromatic 
substitution mechanism-type pathway. They stated that the predominant p-selectivity lay with 
the fact that the Au atom’s size meant it would preferentially add away from o-positions. The 
proposed mechanism proceeds through oxidation of the resting AuI catalyst 163 with PIDA 
to produce the active AuIII species 164, which is added to an arene 165 through an electrophilic 
aromatic metalation step to give the metalloaryl intermediate 166. Concomitantly, another 
molecule of PIDA oxidatively adds to phthalimide to give the electrophilic iodane species 
167, which transmetallates with the Au species 166 to give the complex 168, and consequent 
reductive elimination affords the desired product 169 and regenerates the catalyst 163 
(Scheme 1.46).  

![Scheme 1.46]

Many advances have been made in C-H activation as a method for aromatic amination within 
the last 15 years. There are lots of of metals and ligands that can give diverse products, with 
mild conditions available for substrates that contain sensitive functionality. Nevertheless, 
there is often a requirement for directing-groups to ensure regiospecific reactions occur and
with this an increased number of synthetic steps from addition and removal of these groups. There are limited numbers of examples that do not require directing-groups but they sometimes suffer from bespoke catalyst/ligands, the necessity to have reactive intermediates in the starting materials (nitrene precursors for example) or involve high temperatures to ensure the reaction goes to completion. Recent work has explored the generation of nitrene precursors using hypervalent iodine species, however to attain acceptable levels of regioselectivity there is a necessity for precious-metal catalysts in the reaction. Furthermore, substantial amounts of the oxidant are required to ensure the reaction goes to completion meaning large amounts of waste are produced. These factors make the reaction type unattractive to industry.

1.4 Photoredox Catalysis

1.4.1 Modes of Reactivity of Photoredox Catalysts

Photoredox catalysis has emerged in recent years as an attractive technique for a wide variety of transformations. Rather than using UV irradiation of reaction mixtures photoredox catalysis uses transition-metal catalysts, most commonly Ir$^{III}$ and Ru$^{II}$ complexes (Figure 1.2), which can absorb energy in the visible light region then through metal-to-ligand charge transfer (MLCT) can be used to mediate SET processes.

![Figure 1.2](image)

These photocatalysts are attractive to synthetic organic chemists due to their ability to act as both oxidants and reductants when in the excited state, the fact they have long-lived excited states (~1.9 μs for Ir(ppy)$_3$) and the capacity to convert visible light energy into considerable amounts of chemical energy. A schematic demonstrating the dual nature of the photocatalyst is shown below. Irradiation of the ground state photocatalyst PC$^n$ generates the excited species PC$^{n*}$. This can either undergo oxidative quenching (acting as a reductant) to give the oxidized species PC$^{n+1}$ through transfer of an electron to an electron acceptor EA, and then be reduced again by an electron donor ED to regenerate the resting state catalyst. Or, the excited species
can act as in an oxidative manner, being reduced in the process to PC
. This then undergoes oxidation to give the initial catalyst (Scheme 1.47).\textsuperscript{77–79}

Scheme 1.47

Amongst the broad application of photoredox catalysis, it has been used in the mediation of aryl C-N bond forming reactions.

1.4.2 Use of Photoredox Catalysis in N-Arylation Reactions

1.4.2.1 Transition-Metal Photoredox Catalysts for N-Arylation

Even though photoredox catalysis is an emerging field in organic synthesis, there have been several advances in the area of N-arylation.\textsuperscript{80} One of the first reports of photoredox-mediated N-arylation came from the group of Sanford who, inspired by the work of Skell (see Scheme 1.64), showed that phthalimide radicals could be generated from N-acyloxyphthalimide derivatives 170 using Ir(ppy)\textsubscript{3} C3 as catalyst and reacted directly with unfunctionalized aromatics 171. The work greatly expanded on that by Skell,\textsuperscript{81} with numerous arenes and heteroarenes tolerated under the reaction conditions. It also avoided the liberation of bromide radicals in solution, so eliminated halogenated side-products being formed. The reaction did however require 10 equivalents of the arene 171 for the reactions to take place in consistently good yields and, perhaps due to the fact this was an early report in this field, the catalyst loading was particularly high at 5 mol% which is problematic considering the cost of the photocatalyst (~ £1000 per g) (Scheme 1.48).\textsuperscript{82}

Scheme 1.48
The proposed mechanism proceeds through the photo-excitation of the catalyst C3, followed by single electron transfer to the N-acyloxyphthalimide 170 generating the phthalimidyl radical intermediate 173. This is followed by radical attack of the arene 171, oxidation of 174 by the photocatalyst C3⁺ and re-aromatisation to give the desired product 176 and regeneration of the catalyst C3 (Scheme 1.49).  

Scheme 1.49

A few groups did still report the use of N-halophthalimides as precursors for N-imidation. Lee and co-workers coupled N-chlorophthalimide 177 with simple aromatics 178. As with some previous reports however, the method did not give complete regiocontrol, with mixtures of isomers obtained with several substrates. A 20 W fluorescent bulb was used as the visible light source, and the hexafluorinated Ir catalyst Ir(dFppy)₃ C4 (Scheme 1.50).  

Scheme 1.50

Xue et al. used N-chloroamine precursors 180 for the synthesis of aminated benzoxazoles 182. Cyclic and acyclic secondary amines which were converted to N-chloroamines in situ, or the isolated N-chloroamines themselves, were supposedly converted to the aminyl radical by irradiation with blue LEDs in the presence of [Ir(dtbbpy)(ppy)₂]PF₆ C5, which reacted with the benzoxazole 181 at the 2-position exclusively (Scheme 1.51).
The authors stated that in the absence of photocatalyst, if the light source was switched off, or if there was no Ph₃N in the reaction than the reaction did not work. They reasoned that Ph₃N was essential for the reduction of the excited catalyst to the active IrII species that is used to reduce the N-Cl bond to afford the intermediate aminyl radical.

The Yu group have been particularly productive in the area of N-arylation through N-centred radicals generated through photocatalysis. Inspired by the work of MacMillan, their first foray into these types of reactions was the cleavage of O-sulfonylhydroxylamine derivatives 183 which were reacted with indoles 184 and other electron-rich heterocycles. The radicals generated can be considered as amidyl type radicals as the groups attached to nitrogen were always methyl and benzenesulfonyl (Scheme 1.52).86

They developed this work further, showing that the tosylamide 186 could be used in conjunction with bleach to give a C-H/N-H coupling between the aromatic 187 and the sulphonamide 186.87 The group proposed that the bleach was necessary to oxidise the excited state photocatalyst which could then oxidise the sulphonamide 186 to the amidyl radical. This demonstrates that appropriate catalyst and substrate selection can avoid the need for any pre-functionalisation of the nitrogen species, allowing for an almost completely atom economic cross-coupling (Scheme 1.53).87
The group of Studer demonstrated an intermolecular amination of (hetero)aromatics \textbf{191} using $N$-aminopyridinium salts \textbf{190}, which were prepared easily from pyrylium salts \textbf{189} and could be stored at room temperature for months (Scheme 1.54).\textsuperscript{88}

\textbf{Scheme 1.54}

1.4.2.2 \textbf{Organic Molecule-Based Photoredox Catalysts for $N$-Arylation}

Some groups have addressed the costs of transition metal photocatalysts by using organic molecules that absorb in the visible light region instead. This has even been used for direct functionalisation of the C-H bonds of electron-rich aromatics \textbf{193} by the group of Nicewicz, who used an acridinium based catalyst C\textsubscript{6} in conjunction with TEMPO under irradiation from LEDs emitting at 455 nm. The group showed that nitrogen heterocycles \textbf{194} could be reacted directly with several aromatics to give the $N$-arylated products \textbf{195}. The group also showed that using the ammonia equivalent ammonium carbonate, $(\text{NH}_4)_2\text{CO}_3$ that primary anilines could also be synthesised in one step. This represents a great improvement upon the nitration/reduction techniques commonly employed in industry currently, as no toxic gas is produced and the reaction is run at room temperature. There were some regioselectivity issues however, with only two of the eight products not affording a mixture of isomers (Scheme 1.55).\textsuperscript{89} Even though this does avoid the use of transition metal photocatalysts, which is an obvious benefit, it suffers from extended reaction times that are on average at least a day.
Recently Lei and co-workers reported a similar transformation, however they avoided the use of an oxidant by using a Co co-catalyst C8 alongside a similar acridinium-based photocatalyst C7. The nitrogen coupling partners only included five-membered heterocycles including pyrazole, triazole, indazole and benzotriazole therefore showing a limited scope of amines compared with the work by Nicewicz et al. (Scheme 1.56).89,90

Both the papers discussed above have similar mechanistic proposals where oxidation of the arene occurred by the excited organophotocatalyst, which was then restored to the resting state catalyst by oxidation (either with TEMPO or C8). The second part of the catalytic depended on the co-oxidant used in the reaction.89,90

Leonori et al. recently reported the photocatalytic generation of amidyl radicals, which were derived from hydroxamic acid precursors 199 and were used in the intermolecular N-arylation of electron-rich (hetero)aromatics 200.91 The photosensitiser that was employed in this reaction was eosin Y C9, which meant that green LEDs could be used as the light source (Scheme 1.57).91
The report by Leonori seems to be the only one that employs amidyl radicals for the direct amidation of aromatics.

The area of photoredox catalysis has emerged as a promising method for formation of aryl C-N bonds. Using the reactivity of the photocatalysts has meant challenging bonds have been formed under ambient conditions that would usually require stoichiometric oxidants and high temperatures. The main issue is the cost of the Ir and Ru photocatalysts that are most commonly used in the reactions, with both usually costing in excess of £1k per g. Some groups have addressed this issue with the use of organic-based photocatalysts instead.

### 1.5 Radical Based C-N Bond Forming Reactions

The generation and subsequent reaction of nitrogen-centred radicals is an alternative method for the formation of C-N bonds. These intermediates are often generated from the homolytic cleavage of an N-X bond through photochemical or thermolytic means, or sometimes through single electron transfer processes. This section will discuss some of the ways that N-centred radicals have been generated and how they have been exploited in N-arylation reactions.

#### 1.5.1 Photolytic Generation of N-Centred Radicals

The use of light in synthetic organic chemistry stretches back to some of the earliest reports in the field. Originally, due to lack of suitable light sources, most photochemistry involved the solar irradiation of various substances. Development of light sources after 1900 led to synthetic organic photochemistry becoming a fruitful area of research, and is an important technology in the 21st century due to the growing importance of ‘green’ chemistry in research laboratories.
1.5.1.1 The Hofmann-Löffler-Freytag Reaction

One of the earliest reports of the use of light in synthetic organic chemistry was the Hofmann-Löffler-Freytag (HLF) reaction, first reported by Hofmann in 1881.\textsuperscript{95,96} He noted that after UV-irradiation, or heating, of \( \text{N-bromo-2-propylpiperidine}\) \(202\) in concentrated sulfuric acid a tertiary amine was obtained as the product, later identified as the pyrrolidine \(203\) (Scheme 1.58).

![Scheme 1.58](image)

A few decades after the initial discovery, Löffler and Freytag established the reaction as a general synthesis of pyrrolidines,\textsuperscript{97} and in the middle of the last century work by Wawzonek\textsuperscript{98} and then Corey\textsuperscript{99} established the proposed mechanism as a radical chain mechanism.

The proposed mechanism initially proceeds through the protonation of the \( \text{N-haloamine}\) species \(204\) to form the \( \text{N-haloammonium}\) \(205\). This undergoes radical cleavage of the nitrogen-halogen bond to afford the protonated aminyl radical intermediate \(206\). The cationic aminyl radical is essential for the reaction due to it being more reactive than the equivalent neutral aminyl radical. The protonated aminyl radical species \(206\) display electrophilic character which the neutral species do not due to repulsion by the lone pair on nitrogen, and it is this difference that gives rise to the different reactivity.\textsuperscript{100} The radical cation \(206\) undergoes a 1,5-hydride abstraction through a chair-like transition state, then a radical recombination affords the \( \delta\)-haloamine \(208\), which is transformed into the pyrrolidine \(209\) through a base-mediated cyclisation (Scheme 1.59).

![Scheme 1.59](image)

1.5.1.2 HLF Modifications: Direct Functionalisation of Aryl C-H Bonds

Several decades after the original discovery of the HLF reaction, Bock \textit{et al.} reported that under UV irradiation in the same highly acidic conditions, direct amination of aromatic C-H
bonds could occur with $N$-chloroamines 211 (Scheme 1.60).\(^1\) The report detailed that a range of aryl groups 210 could be aminated under the reaction conditions however with some acyclic alkyl chloroamines, such as $N$-chlorodibutylamine, intramolecular hydride abstraction was observed like in the HLF reaction. In addition to photolysis, thermal decomposition and reducing-metal salts (including Cu(I)Cl, Ni(II)Cl\(_2\) and Fe(II)SO\(_4\)) were used as alternative methods for homolysis of the $N$-chloroamine substrates.

\[ \text{Scheme 1.60} \]

One of the key differences between the reaction discussed above and the HLF reaction is the lack of a need for any base to affect the C-N bond forming reaction. Minisci discussed the mechanism for the reducing-metal mediated $N$-arylation reaction between $N$-chloroamines and aromatic groups, but stated that the mechanism was likely similar for both the photochemical and thermolytic equivalents with initiation of the reactions being the only real difference.\(^1\)\(^0\)

A proposed mechanism is discussed below.\(^1\)\(^0\) As with the HLF reactions, protonation of the $N$-chloroamine 213 occurs first to give the $N$-chloroammonium 214 which then undergoes cleavage to afford the electrophilic protonated aminyl radical intermediate 215. This species then reacts directly with the aromatic ring 216 to give the aminated substrate 217 which undergoes re-aromatisation to afford the desired product 218 (Scheme 1.61).

\[ \text{Scheme 1.61} \]

Separate reports from two groups, first the group of Dey in 1970\(^1\)\(^0\)\(^2\) and then the Anderson group a year later,\(^1\)\(^0\)\(^3\) both disclosed that whilst trying to synthesise pyrrole 221 under standard...
conditions for the HLF reaction that an intramolecular $N$-arylation reaction occurred giving the THQ 220 instead. The initial report by Dey et al. reported that low yields of 30-40% were obtained, however Anderson and co-workers stated that a recovery of 13.4 g of THQ 220 from 18 g of $N$-chloroamine 219 was obtained, which equates to a yield of 90% (Scheme 1.62).

The reactions did use conc. $\text{H}_2\text{SO}_4$ as the reaction solvent which leads to viscous non-homogenous reactions mixtures.

In both instances discussed above, neither group reported formation of the pyrrole product 221, nor did they state that any of the $\delta$-chloroamine was formed. This suggests that in the presence of aromatic groups, even when there is a $\delta$-H there is selectivity for the $N$-arylation reaction as opposed to the HLF pathway.

Despite reports of $N$-arylation reactions utilising other types of $N$-centred radicals (amidyl, imidyl, etc.) there has only been one report of the direct functionalisation of an arene with a supposed aminyl radical intermediate, in a report by Sarpong and co-workers of the synthesis of the natural product arboflorine.$^{104}$ The authors stated that numerous methods were attempted and failed in the formation of the heteroaryl C-N bond, and that after consulting the literature turned to the report by Anderson et al. (see Scheme 1.62) in the hope this would form the bond effectively. They had no luck, and instead trialled a set of modified conditions originally proposed by Oishi et al.,$^{105}$ which did lead to successful bond formation in 81% yield (Scheme 1.63).

Despite the report by Sarpong being an $N$-arylation involving an amine, the conditions that were used are distinctly different from the earlier reports of $N$-arylation, the key difference being the basic conditions as opposed to a highly acidic media. The report by Oishi discussed
the difference as well, stating that under those conditions the intermediates that would form would be different to those proposed by Wawzonek\textsuperscript{98} and Corey.\textsuperscript{99} Furthermore, the fact that a heteroarene was the coupling partner in the case of Sarpong could also be an explanation as to why those conditions were successful.\textsuperscript{104} There have been multiple reports of the intramolecular reactions of aminyl radicals (protonated and un-protonated) with alkenes, usually in 5-\textit{exo}-type cyclisations to afford pyrrolidines\textsuperscript{92} but cases of \textit{N}-arylation, aside from the aforementioned examples, are mainly limited to other types of \textit{N}-centred radicals.

1.5.1.3 \textit{N}-Arylation With Other Types of \textit{N}-Centred Radical Intermediates

\textbf{Imidyl Radicals}

The \textit{N}-centred radicals that have been described thus far were all derived from amine derivatives, giving aminyl-type radicals. There are many other types of \textit{N}-centred radicals, that due to the electronic nature of the nitrogen have varying levels of reactivity compared with aminyl radicals.

One type of \textit{N}-centred radical that has received a lot of attention is the phthalimide radical, and has been generated from numerous precursors. One of the earlier reports came from Cadogan and Rowley, where they reported the UV-photolysis of \textit{N}-tosyloxyphthalimide 224 to release the phthalimide radical which was then coupled with several unfunctionalised aromatic groups.\textsuperscript{106} For synthetic utility, the group demonstrated that the phthalimide products 225 could be cleaved \textit{via} hydrazinolysis to furnish the primary anilines 226 (Scheme 1.64). The authors stated that due to the product distribution that it indicated the reaction proceeded through a radical pathway.

![Scheme 1.64](image)

Skell \textit{et al}. demonstrated that similar imidyl radicals could be generated from the \textit{N}-bromo precursors 227 once again under UV-photolysis.\textsuperscript{81} There was a lack of details with regards to yields, and a low scope was reported as the study was more focussed on the analysis of the chemistry of several imidyl radicals, including succinimidyl, glutarimidyld, phthalimidyl and naphthalenedicarboximidyl. They reported the reactions of the radicals listed above with several cyclic and acyclic unsaturated systems, including benzene 228. The paper stated that
ethene was present in the reaction mixture as a radical scavenger, to prevent further reaction of the bromide radicals generated from photolysis of the starting materials (Scheme 1.65).

Scheme 1.65

Glover and co-workers demonstrated that under similar conditions intramolecular cyclisation of amidyl radicals could occur. The reactions used benzene as solvent, and the authors reported that as well as the phenanthridine products 231 that spirocycle adduct 232 was also obtained from the reactions (Scheme 1.66). The authors reported that similar results were also observed for the sulfonamidyl radicals, giving the equivalent sultam products.

Scheme 1.66

A more recent report came from the group of Luo, where they reported that irradiation of \( N \)-bromosaccharin 235 with a fluorescent lamp led to amination of aromatics 234. Despite the fact that direct amination of unfunctionalised aromatics was achieved, they encountered regioselectivity issues with mixtures of products obtained when unsymmetrical aromatics were used in the reactions (Scheme 1.67). One of the highlights of this method is the use of a low energy light source, with a fluorescent bulb having a much lower impact than a medium/high pressure Hg UV lamp.
Iminyl Radicals

More recently, Rodríguez and co-workers described the synthesis of phenanthridines 238 derived from acyloximes 237, with the reaction proceeding through the formation of iminyl radicals 239. UV photolysis of the acyloximes 237 afforded the intermediate iminyl radicals 239 which then reacted directly with the aromatic ring (Scheme 1.68).

![Scheme 1.68](image)

The same group extended this methodology to work with heterocycles 240 as well, incorporating thiofuran, pyridine and pyrazole heterocycles into the products 241. The group also reported that the natural product trispheridine 242 could be prepared efficiently with their methodology, and they also synthesised a precursor to the alkaloid vasconine 243 (Scheme 1.69).

![Scheme 1.69](image)

The group of Walton demonstrated that instead of acyloximes, oxime carbonates 244 could be used as precursors in the generation of iminyl radicals. They extended the scope of the reaction to also include furans and benzothiophenes, with 4-methoxyacetophenone (MAP) employed as a photosensitizer (Scheme 1.70). Further to the expansion of the scope of the reaction, Walton used EPR spectroscopy to prove the existence in solution of the intermediate iminyl radicals that were proposed by both his group and Rodriguez et al. (see Scheme 1.68).
He also stated that phenoxide radicals were observed at roughly the same concentration as the iminyl radical, suggesting that decarboxylation of the carbonate species 244 was virtually instantaneous.

![Scheme 1.70](image)

**Amidyl Radicals**

Amidyl radicals, the oxidised radical forms of amides, are not as reactive towards aromatic groups as protonated aminyl radicals but are more so than neutral aminyl radicals.\(^\text{110}\) As a consequence the only report which employs direct amidation of aromatics with amidyl radicals is that of Leonori et al. (see Scheme 1.57), a photoredox catalysis process that enables \(N\)-arylation with amidyl radicals.\(^\text{91}\)

1.5.2 Generation of \(N\)-Centred Radicals Through Single Electron Transfer (SET)

Another way of generating \(N\)-centred radical intermediates is through the use of reducing metal salts, giving the reactive intermediates through a proposed single electron transfer (SET) process.\(^\text{101}\) Metal salts that are typically used include \(\text{Fe}^{2+}\) salts, \(\text{Ti}^{3+}\) salts and \(\text{Cu}^{1+}\) salts. Minisci et al. reported one of the first uses of these types of reducing metal salts in the amination of aromatics.\(^\text{111}\) It was reported that mixing \(N\)-chloropiperidine 211 with anisole 248 and \(\text{FeSO}_4\) in methanol afforded the aminated aromatics 249, albeit in low yields. The main component obtained from the reaction mixture was piperidine 33 derived from reduction of the \(N\)-chloroamine starting material however no yield was given (Scheme 1.71).\(^\text{111}\)

![Scheme 1.71](image)
The authors stated that no reactions were observed with benzene or with any electron-deficient aromatics. This supports the assumption of the enhanced electrophilicity of aminyl radicals when they are protonated.

The same group later showed that running the same reactions in acid allowed for the intermolecular amination of several aromatics 250, including benzene, toluene and xylene. Much better yields were achieved when acidic conditions were used, which was to be expected due to change in nature of the aminyl radical (Scheme 1.72).

![Scheme 1.72]

The study by Bock and Kompa (see Scheme 1.60) that reported the photochemical intermolecular amination of aromatics with N-chloropiperidine, also reported that thermolysis of the N-chloroamines in conc. H2SO4 was accelerated by the addition of metal salts. The different salts listed as working included Na2SO4, CuCl, NiCl2, FeSO4·H2O and Hg2Cl2.

The group of Minisci showed that, as with the photochemical N-arylation of protonated aminyl radicals, intramolecular N-arylation could be achieved as well. Both methyl-2-phenylethyl-N-chloroamine 253 and methyl-3-phenylpropyl-N-chloroamine 255 could be cyclised in the presence of FeSO4 under highly acidic conditions, to afford N-methylindoline 254 and N-methylTHQ 256 respectively (Scheme 1.73).

![Scheme 1.73]

The aminyl radical is presumably formed by a single electron transfer from the Fe2+ salt, and subsequent reaction pathways are analogous to that of the photolysis pathways. However when the indoline precursor 253 was photolysed benzyl chloride 257 was also isolated in 44% yield. This was because of a radical decomposition pathway, a β-scission that could only occur with the indoline precursor and not the THQ precursor (Scheme 1.74).
Minisci et al. also showed an intermolecular variant of this reaction which also employed Fe\(^{2+}\) salt initiators as opposed to light.\(^{114}\) While yields were not reported, it was found that reducing the concentration of the sulfuric acid had a significant effect on the reaction outcome. With the concentration at 85\% or above only a small amount of imine \(262\) was formed, however, when 70\% \(\text{H}_2\text{SO}_4\) was used the imine \(262\) was the major product with only trace amounts of amination product \(261\) observed (Scheme 1.75).\(^{114}\)

\[
\begin{align*}
\text{C} & \quad \text{H} & \quad \text{N} & \quad \text{S} & \quad \text{O} \\
\text{228} & \quad + & \quad \text{260} & \quad \text{H}_2\text{SO}_4, [\text{Fe}^{2+}] & \quad \text{261} & \quad + & \quad \text{262}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Acid conc.</th>
<th>96%</th>
<th>90%</th>
<th>80%</th>
<th>70%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HN(N\text{Cl}^+) yield</td>
<td>98.4</td>
<td>98.2</td>
<td>84.9</td>
<td>Trace</td>
</tr>
<tr>
<td>HN(N\text{Cl}^+) yield</td>
<td>1.6</td>
<td>1.8</td>
<td>15.1</td>
<td>99.9</td>
</tr>
</tbody>
</table>

Scheme 1.75

The same group also reported an alternative precursor that could be used to generate aminyl radicals, namely hydroxyamino-\(O\)-sulfonic acid \(264\) which could be converted to the simple amino radical, \(\text{H}_3\text{N}^+\).\(^{115}\) This meant that the C-H bonds of some aromatic groups \(263\) could be converted directly to the free aniline \(265\), in one synthetic step. As with other studies, several aromatic groups were aminated, however all substrates gave mixtures of regioisomers, with no obvious trends observable (Scheme 1.76).\(^{115}\)

\[
\begin{align*}
\text{C} & \quad \text{H} & \quad \text{N} & \quad \text{N} \\
\text{263} & \quad + & \quad \text{264} & \quad \text{FeSO}_4\cdot7\text{H}_2\text{O} (3 \text{ mol\%}) & \quad \text{265} \\
\text{R} & \quad \text{H}_2\text{NO}_3\text{SO}_3 & \quad \text{AcOH}:\text{H}_2\text{O} (2:1), 40 ^\circ\text{C} & \quad \text{R} & \quad \text{NH}_2 \\
\text{5-60\%} & \quad & \quad & \quad & \quad & \quad
\end{align*}
\]

Scheme 1.76

Other than the work of Minisci, there are few reports exploring \(N\)-centred radicals generated from SET processes that do not fall into the classes of photochemical or photoredox. One of those reports came from the Baran group in 2014.\(^{116}\) The account detailed the design of a new
reagent, *N*-succinimidyl perester (NSP) \(267\), which was used to aminate a range of (hetero)arenes \(266\) in conjunction with ferrocene as catalyst (Scheme 1.77).\(^{116}\)

![Scheme 1.77](image)

One other similar report came from the lab of Morandi, where they used another novel reagent that allowed for the synthesis of primary anilines.\(^{117}\) The group reported a serendipitous discovery that when combined, FeSO\(_4\) as catalyst with MsONH\(_3\)OTf \(270\) (a novel aminating reagent they had discovered during another study) led to the formation of primary aniline derivatives \(271\) (Scheme 1.78).\(^{117}\) The reaction was shown to be tolerant to wide range of functionality, however there were regioselectivity issues with mixtures of products being obtained with over half of the examples reported.

![Scheme 1.78](image)

Aside from the last few reports, much of the work by Minisci employed conc. H\(_2\)SO\(_4\) as solvent, and frequently required non-catalytic amounts of the ferrous salts for the reactions to proceed efficiently.\(^{101}\) Whilst Baran addressed the problem partially with only requiring 5 mol% catalyst in DCM for the imidation of a range of aromatics, the NSP reagent \(267\) required three synthetic steps to be made and was only stable when stored at \(-20\) °C.\(^{116}\) The advent of catalytic procedures, such as C-H activation and photoredox methods has led to this area of research remaining underexplored.
1.6 Summary

The importance of $N$-arylation to industry is underlined by the vast amounts of techniques that can be used to form aryl C-N bonds. The most commonly used methods in industry are the transition-metal catalyzed amination of aryl halides such as the Buchwald-Hartwig cross-coupling reaction and the Cu-catalysed Ullmann coupling. Both reactions have been revolutionised by the advent of chelating ligands which have greatly expanded the scope of the transformations. More recently, C-H activation methods have emerged as more attractive procedures as there is no pre-requisite for functionalisation of the aromatic group therefore reducing the number of synthetic steps and the amount of waste produced. Photoredox catalysis has further advanced this field with the reported methods often proceeding under ambient conditions without the need for external oxidants. The use of precious-metal catalysis is a common theme with most of the methods mentioned here; however, this leads to expensive synthetic routes and makes these transformations unattractive for industrial scale-up. Some groups have used hypervalent iodine species to generate reactive nitrene intermediates and circumvent the need for precious-metal catalysts but these reactions often require super-heated solvents and large amounts of the highly oxidizing I$^{III}$ reagents.

The use of $N$-centered radicals in synthesis alleviates the need for any precious-metal catalysts as the reactive intermediates can often be generated from photolysis, thermolysis or SET reduction from cheap metals such as Fe. The Hofmann-Löffler-Freytag reaction was modified to allow for direct functionalisation of aromatic C-H bonds using $N$-chloroamines but required conc. sulfuric acid for the reactions to proceed and many of the reports stated a combination of heat and UV-irradiation was necessary. Nevertheless, these few reports did show that precious-metal free $N$-arylation was feasible under the right conditions with only acid and photolysis needed to form aromatic C-N bonds.

A method that exploits the reactivity of $N$-centered radicals but avoids the use of concentrated acid, expensive precious-metal catalysts and large amounts of oxidizing agents in high temperatures would be beneficial to synthetic chemists.
1.7 Thesis Aims

The aims of the work described in this thesis were:

1. To find a suitable set of conditions that allow for direct $N$-arylation to occur using $N$-haloamines (Chapter 2).
2. To use experimental insights and computational studies to help elucidate the mechanism of the reaction (Chapter 2).
3. To construct a photochemical reactor that can be used to scale up the $N$-arylation methodology described in Chapter 2 (Chapter 3).
4. To use enzymatic deracemization reactions to convert racemic samples produced using the photochemical reaction into single enantiomers (Chapter 4).
Chapter 2  Photochemical $N$-Arylation

2.1  Results and Discussion

2.1.1  Optimisation of the Reaction Conditions

2.1.1.1  Starting Material Synthesis and Apparatus Set-Up

We began with the synthesis of a model substrate for optimisation studies to be carried out on. Minisci et al. reported the metal-initiated aromatic amination of $N$-chloroamine 255 as a precursor to $N$-methyltetrahydroquinoline (N-MeTHQ) 256 (Scheme 2.1). This reaction was chosen as the model reaction for optimisation.

\[
\begin{align*}
\text{Ph} & \quad \text{Cl} \quad \text{Me} \quad \text{H}_2\text{SO}_4, \text{FeSO}_4 \text{(cat.)} \quad -5 \degree \text{C} \\
\text{255} & \quad \rightarrow \quad \text{256} \quad 81\%
\end{align*}
\]

\textit{Scheme 2.1}

Methylation of commercial 3-phenylpropylamine 272 by carbamate formation with ethyl chloroformate then reduction with lithium aluminium hydride proceeded smoothly, giving the desired $N$-methylamine 273 in a 98% yield. The chlorination of amine 273 using NCS\textsuperscript{118} gave the desired $N$-chloroamine 255 in a 92% yield, with the compound stable to flash chromatography. $N$-Chloroamine 255 could be stored under an inert atmosphere at low temperatures (< 0 \degree C) for long periods of time (>1 year) without decomposition. One observed issue with the chlorination reaction was the limited scale it could be performed on. When the reaction was scaled up to anything over ~750 mg there was a sharp decrease in the isolated yield (<50%). This may have been due to the scale of the reaction: small exotherms on less material may not have affected the $N$-chloroamines however when the same reaction was performed on a larger scale there may have been a larger build-up of heat. This did not change our approach, as large amounts of material were not necessary for the optimisation. This would have been an issue if looking to increase the reaction size to a process scale (Scheme 2.2). Chloramine-T was also used to successfully chlorinate amine 273, affording the desired product in 72% yield. Due to slightly lower yield and necessity for aqueous work up, NCS was chosen instead as the reagent to be used for chlorination.
With a suitable starting material in hand, the reaction apparatus was then assembled. Initial studies were to be performed in a batch reactor. The batch set-up was chosen first as it was thought it would be easier to optimise the reaction in this format, as opposed to using a continuous reactor immediately.

The requirement was for a small scale photochemical reactor. The immersion-well reactors that are commonly used for photochemical reactions are made from housing for the UV bulb which is surrounded by a jacket for the reaction to take place in. The initial reaction set-up employed a 125 W medium-pressure Hg lamp, produced by Photochemical Reactors Ltd. The lamps emit broad spectrum UV light with energy predominantly emitted at 365 nm, but also throughout the UV region at 254, 265, 270, 289, 297, 302, 313 and 334 nm. Due to the size of the bulb, these jacketed reactors are often large and require relatively large volumes (>100 mL) as a minimum for the reactions to take place. Instead of using the immersion-well jacket, small PYREX reaction vials were placed in a carousel holder around the housing for the bulb (Figure 2.1). This allowed for multiple small reactions to take place simultaneously, with consistent distances from the light source in each reaction vessel. The carousel was placed inside a 3 L beaker that was filled with water to cool the reactions, otherwise the reaction could have been effected by excess heat from the UV lamp. The bulb which was housed in the immersion well was then lowered into the water bath.
The beaker and bulb housing were wrapped in aluminium foil to reflect back light, then surrounded by a red Perspex box to prevent any stray UV irradiation escaping into the lab area. The light was connected to the power source through a water-flow trip device, that would cut power to the light should the water source required for cooling the lamp stop (Figure 2.2).

**Figure 2.2**

2.1.1.2 Optimisation of Conditions For N-Arylation

With the N-chloroamine 255 in hand and a suitable reaction set-up, the substrate was subjected to irradiation under a range of conditions. Firstly, the substrate was irradiated using the 125 W medium-pressure Hg lamp, which emits broad-spectrum UV light, in concentrated sulfuric acid. This afforded the desired N-MeTHQ 256 in 81% yield (Table 2.1, entry 1). Despite this reaction proceeding in high yield, the initial problems with dissolving the substrate in the reaction mixture meant this was not a favourable set of reaction conditions. Upon addition of sulfuric acid to the N-chloroamine, a heterogeneous reaction mixture was obtained, and proved hard to agitate even with magnetic stirring. The reaction was repeated in concentrated HCl. The desired product 256 was observed by LC-MS analysis; however, after attempted work-up no product was isolated (Table 2.1, entry 2). This may have been due to the aqueous conditions of the reaction mixture. To alleviate solubility issues 3M methanolic HCl was used as reaction solvent but only de-chlorination of the starting material was observed (Table 2.1, entry 3). Acetic acid led to the same outcome (Table 2.1, entry 4). Trifluoroacetic acid (TFA) was then used. While some of the desired product 256 was observed, it was isolated as a 6:2:1 mixture with the chlorinated side products 274. (Table 2.1, entry 5). The by-products were
identified through analysis of the $^1$H NMR spectrum and LC-MS analysis (Figure 2.3). The signals at δ 7.17, 7.00, 6.91, 6.83 and 6.48 in the $^1$H NMR spectrum shown below are that of 6-chloro and 8-chloroTHQ.*

![NMR spectrum](image)

*The assignment of the by-products was later confirmed by independent synthesis.

The use of methanesulfonic acid in DCM as a 1:1 mixture afforded exclusively the desired product 256 in 80% yield, approximately equivalent to the original conditions when using sulfuric acid (Table 2.1, entry 6). Decreasing the amount of acid used, we found that 10 equivalents of MeSO$_3$H in DCM afforded the desired product 256 in even greater yield (Table 2.1, entry 7). The use of 10 equivalents in the volume of solvent used was approximately 3 M. Lowering to five equivalents of acid still yielded some formation of product 256, however this was obtained as a 3:1 mixture with the dechlorinated starting material 273, showing that the optimal amounts of acid remained above five equivalents (Table 2.1, entry 8). This hypothesis was confirmed when only 2.5 equivalents of acid were used, with just the dechlorinated starting material 273 observed after photolysis (Table 2.1, entry 9). Applying the most successful conditions under irradiation from visible light afforded the desired product 256 in 17% yield, however the de-chlorinated starting amine 273 was the main component recovered from the reaction (Table 2.1, entry 10). Whilst this is not as effective as UV irradiation, this shows the visible light region may also provide energy to some extent to cleave the N-Cl bond. In the absence of any light, after one hour the N-chloroamine was observed by TLC analysis however the mass for the amine 273 was also observed by LC-MS analysis. After five hours the LC-MS trace showed the mass for the amine 273 as well as multiple other masses, but none of the N-chloroamine 255 nor the THQ 256 were seen by
either TLC analysis or in the MS trace, with a complex mixture of products seen by inspection of the $^1$H NMR spectrum of the reaction mixture (Table 2.1, entry 11). The degradation of the N-chloroamine in the absence of light is an interesting outcome under these conditions. With no base or reducing agent the de-chlorination is hard to fully explain: degradation through alpha elimination could lead to several by-products explaining the complex mixture of products. Different solvents were then investigated. The use of EtOAc did lead to some of the desired product formation, however this was as a complex mixture which, by analysis of the LC-MS, also included a large amount of the de-chlorinated amine 273 and the chlorinated side product 274 (Table 2.1, entry 12). A similar outcome was observed with MeOH, however none of the desired product was obtained, with only the chlorinated side product 274 alongside the dechlorinated amine 273 in roughly a 1:1 mixture (Table 2.1, entry 13) observed by analysis of the LC-MS. 2-MeTHF was chosen next due to its popularity in industry as a green alternative to many solvents commonly used in industrial processes. It has been used in place of DCM in several processes, due to its apparent similar properties. Nevertheless, upon photolysis in 2-MeTHF, only the mass for the dechlorinated amine 273 was observed in the reaction mixture by LC-MS (Table 2.1, entry 14). Diethyl ether returned similar results, with the masses for numerous other unidentified products observed as well (Table 2.1, entry 15).

The results seem to show a qualitative correlation between the conversion from N-chloroamine 255 to THQ 256, and the pKa of the acid used. Acids that have pKas (in water) greater than four (acetic acid) seem to lead to no conversion, with only de-chlorination of the starting material 255 observed. Trifluoroacetic acid, which has a pKa of 0.23 in water, gave a mixture of the desired product and the chlorinated side-products but switching to MeSO$_3$H (pKa = −2.6 in water) supressed any side-product formation and gave the desired product. The pKa of these acids in DCM could be different due to the solvation effects of an organic medium compared with aqueous conditions, however the general trend seems to stand in this instance.

Another observation that can be made is the strength of the acid in solution has a major effect on the outcome of the reaction. This is seen with concentrated hydrochloric acid (approx. 12 M), where by LC-MS analysis of the reaction mixture showed that the desired product had been formed, however when hydrochloric acid in an organic solvent was used at lower concentrations (3 M), no conversion to the desired product was observed with only dechlorinated starting material obtained. The same trend was seen with MeSO$_3$H. When used at anything above 3 M (when 10 equivalents of acid were used) there was full conversion to the desired product. Decreasing the amount of MeSO$_3$H to anything less than 3 M (or 10 equivalents) led to a lower conversion to the desired product 256, with more amine 274 obtained the lower the concentration of acid.
Table 2.1 a Recovered as ammonium salts b Light excluded completely with aluminium foil c Mass for 273 was observed by LC-MS analysis

In comparison to the literature precedent that employed concentrated sulfuric acid as solvent our optimal conditions used MeSO$_3$H which gives a homogeneous reaction medium, avoiding the difficulties of handling highly corrosive and viscous concentrated acid. The conditions were also amenable to continuous photochemical processing, an effective way of scaling up lab-based photochemical reactions.

2.1.1.3 UV-Vis Experiments

The reaction vessels that were used were made from PYREX glass. PYREX’s visible light transmittance cuts off at around 280 nm, however this has been disputed with some claims that it transmits through to around 260 nm. Therefore it was important to measure the absorbance spectra of both the N-chloroamine 255 and the protonated N-chloroammonium species that will be formed in the presence of acid. The absorption spectrum of the N-chloroamine 255 in DCM at a concentration of 5 × 10$^{-3}$ mM was recorded first. The sample was too concentrated and the signal obtained was not useful. This was diluted by a factor of 10 to give a 5 × 10$^{-4}$ mM solution in DCM, which gave a useful signal. The $\lambda_{\text{max}}$ for this
compound was measured at 262 nm with another maximum at 268 nm. Despite the wavelengths being below the cut-off point for PYREX there were still strong absorbance readings from 330 nm through to 240 nm (Figure 2.4).

![Absorbance vs Wavelength](image)

**Figure 2.4**

The *N*-chloroamine 255 was then made up to the same concentration of $5 \times 10^{-4}$ mM in a 3 M solution of MeSO$_3$H in DCM and the absorption spectrum was measured again. In the acidic solution, stronger absorbances were observed. The $\lambda_{\text{max}}$ for the *N*-chloroammonium was observed at a slightly lower wavelength of 253 nm, with another at 259 nm. There was a second maxima around 370 nm, with strong absorbance seen throughout the UV region. (Figure 2.5). The absorbance at ~370 nm corresponds to the main wavelengths of light emitted by the lamp that was used in the optimisation of the reaction (see section 2.1.1.1).

![Absorbance vs Wavelength](image)

**Figure 2.5**
Despite both the $N$-chloroamine and $N$-chloroammonium substrates having maxima below the supposed "cut-off" for PYREX they still showed strong absorbance from around 300 to 240 nm, which was within the emission range of the bulbs that were used.

### 2.1.1.4 One-Pot Process Development

Whilst $N$-chloroamine 255 could be isolated in good yields and was stable for long periods when stored cold under $N_2$, we wondered if a ‘one-pot’ procedure could be applied, whereby no intermediate $N$-chloroamine would have to be isolated therefore improving the efficiency of the reaction and avoid the handling of $N$-chloroamines that could be unstable or potentially hazardous. Using the amine 273, one equivalent of NCS was added to the reaction vial and the reaction mixture stirred for 30 minutes. After this, MeSO$_2$H was added directly to the reaction mixture and then the mixture was irradiated for 5 h. After purification the desired product 256 was obtained in 60% yield. This was lower than the individual reactions but required no isolation of the $N$-chloroamine 255 and converted the free amine 273 directly to the THQ 256 in one-pot (Scheme 2.3).

#### Scheme 2.3

### 2.1.2 Substrate Scope

#### 2.1.2.1 N-Substituted Derivatives

To fully explore the potential of the reaction, a range of substrates were chosen. A simple synthetic route was identified to test the substitution of groups on the nitrogen of the THQ. Amines 277a-d could be obtained from reductive amination of hydrocinnamaldehyde 275. Further chlorination using the standard conditions would afford the $N$-chloroamines 278a-d (Table 2.2). The four amines chosen were benzylamine 276a, $n$-butylamine 276b, allylamine 276c and $n$-hexylamine 276d. All the substrates gave good yields in the reductive amination step using STAB, except for the $n$-hexylamine substrate 277d where purification issues led to the lower yield. Subsequent chlorination with NCS gave the desired precursors 278a-d (Table 2.2).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine (eq.)</th>
<th>Step (i)</th>
<th>Step (ii)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzylamine 276a (3.0)</td>
<td>54% (277a)</td>
<td>82% (278a)</td>
</tr>
<tr>
<td>2</td>
<td>n-Butylamine 276b (5.0)</td>
<td>72% (277b)</td>
<td>73% (278b)</td>
</tr>
<tr>
<td>3</td>
<td>n-Hexylamine 276c (5.0)</td>
<td>16% (277c)</td>
<td>81% (278c)</td>
</tr>
<tr>
<td>4</td>
<td>Allylamine 276d (5.0)</td>
<td>48% (277d)</td>
<td>87% (278d)</td>
</tr>
</tbody>
</table>

Table 2.2

The $N$-chloroamines 278a-d were photolyzed under the standard conditions. The benzyl substrate 278a afforded the $N$-benzylTHQ 279 in 82% yield. The $n$-butyl substrate 278b afforded product 280 in 59% yield. This was lower than those observed for both the $N$-Me and $N$-benzyl substrates, however by LC-MS analysis and inspection of the crude $^1$H NMR the de-chlorinated starting material 277b was the only other observable product. Pleasingly none of the $\delta$-chloroalkylamine that would occur from a HLF reaction was observed by either LC-MS or $^1$H NMR analysis. The $n$-hexyl-$N$-chloroamine 278c afforded the desired product 281 in a lower 28% yield. The THQ 282 derived from allylchloroamine was obtained in 40% yield, with several unidentified side products also isolated from the crude reaction mixture. These were most likely derivatives that had reacted radically through the allylamine, for example radically chlorinated substrates (Scheme 2.4).

![Scheme 2.4](image)

The lower yield observed with $N$-hexyl substrate 281 was due to the formation of the $\delta$-chloroalkylamine 283, which was isolated from the crude mixture of the reaction. It was isolated as an inseparable mixture with the de-chlorinated starting material 277c (~2:1 in favour of 277c) and had to be converted to the $N$-Ns derivative 284 to achieve separation by chromatography (Scheme 2.5).

![Scheme 2.5](image)
This intermediate would have formed through the 6-membered transition state that is proposed for the HLF mechanism (see Scheme 1.59). This evidence supports a radical-based mechanism for the reaction as the abstraction product would only arise via a radical pathway.

2.1.2.2 Aryl Group Variation – 3,3-Diarylalkylamine Substrates & Competition Experiments

The scope to vary the aromatic portion of the THQ was then investigated. A series of 3,3-diarylalkylamine substrates were proposed to see if selectivity could arise between different aryl groups. A synthesis for the starting materials using cinnamaldehyde derivatives 285 in a Rh(I)-catalysed conjugate addition to introduce the second aromatic group was proposed. Rh(I)-catalysed conjugate additions of boronic acids 286 to enones 285 were first reported by Miyaura et al. (Scheme 2.6).

Studies began using cinnamaldehyde 288 with no base added to the reaction. This yielded only a trace amount of the desired product by analysis of the \(^1\)H NMR spectrum however no product was isolated after purification of the crude reaction mixture (Table 2.3, entry 1). Addition of one equivalent of triethylamine yielded a small amount of the desired product, but it could not be separated from several unidentified impurities (Table 2.3, entry 2). Fortunately, when methyl \textit{trans}-cinnamate 289 was used instead of cinnamaldehyde the desired product 290 was obtained in 87% yield (Table 2.3, entry 3). Decreasing the catalyst loading to 1 mol% afforded the desired product in an excellent 96% yield. This could be due to an increase in the scale of the reaction (7.50 mmol from 1.00 mmol scale) or due to the fact that with less catalyst in the reaction less protodeboronation would occur (Table 2.3, entry 4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H (288)</td>
<td>([\text{Rh}] (3 \text{ mol%}), 1.5 \text{ eq. PhB(OH)}_2, \text{aq. dioxane, 50 °C})</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>H (288)</td>
<td>([\text{Rh}] (3 \text{ mol%}), 1.5 \text{ eq. PhB(OH)}_2, \text{Et}_3\text{N (1 eq.), aq. dioxane, 50 °C})</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 2.3

<table>
<thead>
<tr>
<th></th>
<th>OMe (289)</th>
<th>[Rh] (3 mol%), 1.5 eq. PhB(OH)₂, Et₃N (1 eq.), aq. dioxane, 50 °C</th>
<th>87%</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>OMe (289)</td>
<td>[Rh] (1 mol%), 1.25 eq. PhB(OH)₂, Et₃N (1 eq.), aq. dioxane, 50 °C</td>
<td>96%</td>
</tr>
</tbody>
</table>

Hydrolysis of the ester 290 afforded the acid 291 in quantitative yield. The acid was then converted to the amide 292 in 90% yield. LiAlH₄ reduction gave the amine 293 in 61% yield which was converted to the N-chloroamine 294 using NCS (Scheme 2.7).

Scheme 2.7

The optimised conditions for the N-arylation reaction were applied to the N-chloroamine 294. This afforded the 4-phenylTHQ 295 in 67% yield (Scheme 2.8).

Scheme 2.8

The same route was followed to make further 3,3-diarylalkylamines bearing different aryl groups (Scheme 2.9). Aryl groups bearing m-CF₃ and p-Me substitution were chosen. The conjugate additions afforded the desired 3,3-diarylalkyl compounds 297a and 297b in 66% and 99% yield respectively. Hydrolysis furnished the acids 298a and 298b both in 96% yield, then amide formation provided 299a and 299b in 77% and 69% yields respectively.
Reduction of the \( p\)-Me amide 299b using LiAlH\(_4\) afforded the desired amine 300 and subsequent chlorination using NCS afforded the \( N\)-chloroamine 301 in 81% yield (Scheme 2.10).

Applying the same reduction conditions to the \( m\)-CF\(_3\) amide 299a afforded the desired product 302; however, a small impurity was also present that could not be separated from the sample. The mass spectrum and a signal in the \(^1\)H NMR spectrum were consistent with a partial reduction of the CF\(_3\) group to the CF\(_2\)H group (Figure 2.6). The signal, a triplet present at 6.60 ppm in the \(^1\)H NMR spectrum, has a coupling constant of 56.6 Hz which is representative of the CF\(_2\)H group.\(^\text{123}\)
To alleviate this problem, BH$_3$•THF was used as an alternative reductant. This yielded exclusively the desired product 302, albeit in a lower yield. The reduction in yield could be attributed to the problematic work-up associated with the borane reaction. By LC-MS analysis masses that equated to boron adducts of the product were observed. After purification these were not isolated, hence perhaps the lower yield. The standard chlorination conditions afforded the N-chloroamine 303 in 90% yield (Scheme 2.11).

With N-chloroamines 301 and 303 in hand the standard photolysis conditions were applied (Scheme 2.12). High levels of selectivity towards the more electron-rich aromatic groups were observed for both compounds. For $p$-Me substrate 304a-b a 10.4:1 selectivity, determined by ratios in the $^1$H NMR spectrum, was shown towards the tolyl group and with the CF$_3$ substrate 305 total selectivity was shown towards the phenyl group.
These results demonstrate that a preference will be shown towards a more electron-rich aromatic group, displaying that the protonated aminyl radical is electrophilic in nature.

2.1.2.3 Aryl Group Variation – 3-Arylamine Substrates

To ensure a wide variety of aromatic moieties could be tested under the standard conditions, two different routes to synthesise the starting materials were chosen. The first route used N-methyl crotonamide and applied the Rh(I)-catalysed conjugate addition chemistry described previously. The diversity would be derived from the boronic acids that could be used in this reaction. The second route employed the displacement of a (pseudo)halide on a benzyl bromide derivative with allylmagnesium chloride the oxidative cleavage and reductive amination to afford the amines which could then be chlorinated. The benzyl bromide derivative would be the variable for this series of substrates.

Synthesis of Boronic Acid Derived Substrates

We envisaged that by applying the Rh(I)-catalysed conjugate addition chemistry a range of aromatic substrates could be made, using N-methyl crotonamide 307 as the α,β-unsaturated carbonyl compound. Amide 307 was prepared based on literature precedence from crotonyl chloride 306 and methylamine. This gave desired product 307 in 70% yield (Scheme 2.13).

\[
\begin{align*}
  \text{Me} & \quad \text{Cl} & \quad \text{NH}_2\text{Me} & (40\% \text{ w/w in H}_2\text{O}, 1.1 \text{ eq.}) \\
  \text{DCM, 0 °C} & \rightarrow \text{rt, 24 h} & \text{Et}_3\text{N} & (1 \text{ eq.}) \\
  \text{Me} & \quad \text{O} & \quad \text{N} & \quad \text{Me} \\
  \text{Cl} & \quad & 307 & \quad 70\%
\end{align*}
\]

*Scheme 2.13*

A short synthesis was envisaged using the amide products of the conjugate addition followed by reduction of the amides to yield the amines, which would then be converted to the N-chloroamines. With most substrates LiAlH₄ was used as the reducing agent and for more sensitive substrates, such as the p-Br substrate, BH₃•THF was used. Methyl groups at the o-, m- and p-positions were chosen to test the steric demands of the reaction. p-Bromophenylboronic acid 308e and p-methoxyphenylboronic acid 308f were the other starting materials chosen. With the phenylboronic acid 308a and all three tolylboronic acid substrates 308b-d good yields were obtained over the three steps (Table 2.4, entries 1, 2, 3 & 4). The Rh(I)-catalysed conjugate addition with p-Br substrate 309e gave a slightly lower yield. BH₃•THF gave the amine 310e in 74% yield and the N-chloroamine 311e was obtained under the standard chlorination conditions (Table 2.4, entry 5). When applied to the p-OMe substrate, the product 309f from the conjugate addition could not be separated from the starting material 307. To circumvent this issue, the whole mixture was reduced using LiAlH₄ and after purification amine 310f was obtained in 14% over two steps (Table 2.4, entry 6).
Earlier studies in the group had shown that upon mixing with NCS chlorination occurred on the ring of highly electron-rich aromatic groups, including anisoles and anilines. Consequently, the NCS chlorination conditions were not applied to this substrate.

Different conditions for the chlorination of amines in the presence of electron-rich aromatic groups were found, with the in situ generation of tert-butyl hypochlorite as the chlorinating agent. Pleasingly when these conditions were applied to the amine 310f the desired product 311f was isolated in a 94% yield (Scheme 2.14).

**Synthesis of Benzyl Bromide Derived Substrates**

Two di-aryl substrates 316a-b, the m-chloro and p-chloro substrates 316c-d, the p-trifluoromethyl substrate 316e and the p-pinacolboronic ester substrate 320 were chosen as the derivatives that would be synthesised from an alternative synthetic route due to availability of commercial starting materials.
Depending on starting material availability, two starting points were used: 1) a mesylation and displacement of benzyl alcohol derivatives with allylmagnesium chloride, or 2) displacement of benzyl bromide derivatives with allylmagnesium chloride. The o-phenyl, p-phenyl, p-chloro and p-trifluoromethyl substrates 313a-e were all derived from the benzyl alcohol derivatives. Both phenyl derivatives afforded the desired 1-arylbutene substrates 313a-b in good yields of 85% and 72% respectively, however the p-chloro 313c and p-trifluoromethyl 313e derivatives were obtained in lower yields of 42% and 45% respectively. This could be due to the electron-poor nature of the aromatic groups giving less stabilisation of the intermediate charge in the S_N2 reaction. The m-chloro and p-bromo substrates 313d,f were formed from benzyl bromide derivatives, and afforded both the desired products in quantitative yields. Details in the literature for oxidative cleavage of terminal double bonds using O_3 to afford aldehydes were found.\textsuperscript{126} Ozonolysis of these substrates afforded the aldehydes 314a-f in good yields and reductive amination with MeNH_2 afforded the methylamines 315a-f, also in high yields. Chlorination with NCS gave the desired N-chloroamines 316a-e in good yields, however the p-bromo substrate was not converted to the N-chloroamine (Table 2.5).

![Chemical structures](https://example.com/structures)

**Table 2.5** X = OH, \(^b\)X = Br

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Step (i)</th>
<th>Step (ii)</th>
<th>Step (iii)</th>
<th>Step (iv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>o-Ph</td>
<td>85% (313a)(^a)</td>
<td>79% (314a)</td>
<td>99% (315a)</td>
<td>75% (316a)</td>
</tr>
<tr>
<td>2</td>
<td>p-Ph</td>
<td>72% (313b)(^a)</td>
<td>84% (314b)</td>
<td>94% (315b)</td>
<td>75% (316b)</td>
</tr>
<tr>
<td>3</td>
<td>p-Cl</td>
<td>42% (313c)(^a)</td>
<td>87% (314c)</td>
<td>88% (315c)</td>
<td>67% (316c)</td>
</tr>
<tr>
<td>4</td>
<td>m-Cl</td>
<td>99% (313d)(^b)</td>
<td>76% (314d)</td>
<td>88% (315d)</td>
<td>85% (316d)</td>
</tr>
<tr>
<td>5</td>
<td>p-CF_3</td>
<td>45% (313e)(^a)</td>
<td>85% (314e)</td>
<td>83% (315e)</td>
<td>86% (316e)</td>
</tr>
<tr>
<td>6</td>
<td>p-Br</td>
<td>99% (313f)(^b)</td>
<td>88% (314f)</td>
<td>99% (315f)</td>
<td>-</td>
</tr>
</tbody>
</table>

Details were found in the literature for conversion of aryl bromides to aryl boronic esters using PdCl_2(dppf)-DCM and B_3(Pin)$_2$.\textsuperscript{127} First, Boc-protection of the amine moiety afforded the carbamate 317 in 80% yield, then applying the conditions detailed in the literature afforded
the desired product 318 in 62% yield. The dimerisation product arising from a Suzuki reaction between the starting material and desired product was also observed by LC-MS analysis. Deprotection of the Boc group yielded the desired methylamine 319, followed by chlorination with NCS to afford N-chloroamine 320 in 82% yield (Scheme 2.15).

The N-chloroamines 311a-f, 316a-e and 320 were then subjected to the standard photolysis conditions. The phenyl substrate 311a, the o-tolyl 311b and p-tolyl 311d substrates afforded the desired products 321-323 with yields in the range of 66-73%. The m-methyl substrate 311c afforded a mixture of regioisomers 324 obtained in a ratio of 2.5:1 in favour of the p-substituted product. This was determined by the signal patterns in the ^1H NMR spectrum. Photolysis of the p-bromo N-chloroamine 311e afforded the 7-bromoTHQ 325 in a 53% yield, the 7-chloroTHQ 330 was obtained in 39% yield and the m-chloro substrate 316d afforded an inseparable 1.1:1 mixture of regioisomers 326 in 57% yield, once again in favour of the p-substituted product. Unfortunately, the p-OMe compound 311f yielded none of the desired product, with a small amount of the side products 327 being isolated in a 1.2:1 mixture in favour of the 6-chloroTHQ derivative. The ratio of products was determined by the aromatic signals in the ^1H NMR spectrum. The highly electron-rich product, with contributions from both the oxygen and the nitrogen if it was not protonated, may undergo chlorination with the N-chloroammonium salt of the starting material. Carr et al. demonstrated that under acidic conditions electrophilic aromatic chlorination of phenol occurred in the presence of N-chloromorpholine, which is presumably the same mechanism through which the observed chlorination of the desired THQ could proceed. Both di-aryl substrates 316a-b afforded the desired products 328 and 329 in good yields. The p-trifluoromethyl substrate 316e gave the desired THQ 331 but in a much lower yield of 30%. Pleasingly the p-pinacolboronic ester substrate 320 was converted to the THQ 332 in a yield of 47% (Scheme 2.16).
As discussed previously with the competition reactions (see Scheme 2.12), the more electron-poor a substrate is the less reactive it is towards the protonated aminyl radical intermediate. This reactivity is the likely explanation for the lower yields observed with several of the substrates discussed. The trifluoromethyl substrate 331, the p-Cl substrate 330 and the pinacolboronic ester substrate 332 all contain electron-withdrawing groups. In these instances, dechlorinated starting material was also observed in the mass spectra and by analysis the 1H NMR spectra of the crude reaction mixture.

**2.1.2.4 Substitution at the 2-Position**

Substrates with substitution at other positions around the saturated ring were also targeted, starting with 2-substituted substrates. One of the main points of interest in the synthesis of 2-substituted THQs is that the core is present in a family of alkaloids that were isolated and reported by Jacquemind-Collet and co-workers in 1999 (Figure 2.7). The natural products and some of their derivatives have been shown to have anti-malarial activity, making them an interesting target for total synthesis.

\[\text{(-)-Angustureine, 3} \quad R = \text{Me}, \text{(-)-Cuspareine, 333} \]

\[\text{R = -CH}_2-, \text{(-)-Galipinine, 334}\]
These natural products were identified as suitable targets to exemplify our chemistry in a targeted synthesis. It was envisaged that a vinyl moiety installed at the 2-position would give an intermediate that could be used in the synthesis in several of the natural products. The 2-Me and 2-Ph substrates were also synthesised.

A common intermediate \( \text{336} \) was identified that could be used in the synthesis of the enantiopure target compounds.\(^{129}\) This was easily prepared from hydrocinnamaldehyde \( \text{275} \) and \( \text{tert-} \)butylsulfimide \( \text{335} \) and was obtained in quantitative yield (Scheme 2.17).

![Scheme 2.17](image)

The stereoselective addition of Grignard reagents to sulfinimines is well documented.\(^{130,131}\) The proposed mechanism proceeds through a 6-membered chair transition state with the Grignard reagent (Figure 2.8).

![Figure 2.8](image)

The sulfinamide products from the Grignard additions were alkylated and de-protected to yield the amines, which underwent chlorination using the standard conditions. The Grignard reagents chosen were phenylmagnesium bromide and methylmagnesium bromide, as well as vinylmagnesium bromide. Unfortunately, with the phenyl and vinyl products \( \text{337a-b} \) diastereomeric ratios of just 3.2:1 and 2:1 were obtained (Table 2.6 entries 1 & 2). This could be due to the \( sp^2 \) nature of the Grignard reagents meaning their reduced steric demands lower the selectivity. With the methyl Grignard however a much better \( d.r \) of 93:7 was obtained (Table 2.6, entry 3). With all three substrates it was hoped the diastereoisomers would be separable by chromatography, however no separation was achieved. The diastereomeric ratios of the mixtures were determined by comparing the signals in the \( ^1H \) NMR spectrum for the \( \text{tert-} \)butyl groups of each isomer. Methylation was achieved using LiHMDS and MeI, and then de-protection of the crude products to the amine was easily achieved using methanolic HCl for the phenyl \( \text{338a} \) and methyl \( \text{338c} \) derivatives in yields of 82% and 85% respectively. The vinyl substrate \( \text{338b} \) was isolated from the reaction with an unidentified impurity. Attempts to remove the impurity, including flash chromatography and SCX cartridge, all
failed. This compound was taken straight through to the chlorination step, where the N-chloroamine 339b was successfully isolated with no impurities in a 50% yield over the 3 steps. Both the phenyl 339a and methyl 339c derivatives were converted to the N-chloroamines in high yields (Table 2.6).

![Chemical structure and reaction scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>RMgBr</th>
<th>Step (i)</th>
<th>d.r step (i)</th>
<th>Step (ii)</th>
<th>Step (iii)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>55% (337a)</td>
<td>3.2:1</td>
<td>82% (338a)</td>
<td>96% (339a)</td>
</tr>
<tr>
<td>2</td>
<td>Vinyl</td>
<td>85% (337b)</td>
<td>2.1</td>
<td>-</td>
<td>50%* (339b)</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>68% (337c)</td>
<td>93:7</td>
<td>85% (338c)</td>
<td>82% (339c)</td>
</tr>
</tbody>
</table>

*amine carried forward crude to chlorination and purified, yield quoted over 3 steps

The three substrates were then subjected to UV irradiation under the standard conditions. Both the 2-Ph 340 and 2-Me 342 products were obtained in 50% and 55% yields respectively. Photolysis of the 2-vinyl substrate 341 was performed on a 500 mg scale and proceeded in a 51% yield, providing enough material to attempt subsequent reactions (Scheme 2.18).

![Scheme 2.18]

To test further the steric limitations of the photochemical reaction, a 1,2-disubstituted THQ precursor was proposed. Using benzylacetone 343 and a Ti(OiPr)₄-mediated reductive amination procedure that was detailed in the literature, the amine 345 was obtained in quantitative yield, then easily converted into the N-chloroamine 346 under the standard conditions. Photolysis of the substrate proceeded in 54% yield, however, a small amount of the dechlorinated starting material was also observed, likely due to the increased steric demands in the position alpha to the nitrogen (Scheme 2.19).
2.1.2.5 Substitution at the 3-Position

Using two simple nitrile starting materials, a concise synthetic route was devised to give suitable precursors for 3-substituted THQs. Benzyl cyanide 348a and propionitrile 348b were chosen to give 3-phenyl- and 3-methylTHQ. Interestingly, the precursor for the 3-phenylTHQ would also allow for the 5-membered ring formation to form an indoline. As shown (see Scheme 1.73), decomposition through a $\beta$-scission pathway can occur with $\beta$-arylaminyln radicals. Should we have observed this decomposition, this would have given further evidence of a radical mechanism.

The alkylation of benzyl cyanide 348a proceeded in 88% yield. Applying the same conditions to propionitrile 348b however only yielded the bis-alkylated product 351. Increasing the amount of propionitrile 348b from 2.5 equivalents to 10 equivalents afforded exclusively the desired product 350b in 81% yield (Scheme 2.20).

The nitrile compounds 350a-b were then reduced with LiAlH$_4$ to the amines 352a-b. In both instances low yields were obtained from the reactions. This was due to what appeared to be formation of dimerisation products as well as the desired products of the reaction. Dimerisation of primary nitriles to form diamines during reduction with LiAlH$_4$ is documented, with Soffer and Katz reporting that varying the amount of reducing agent can influence the amount of by-product that is formed in the reaction. What was isolated from our reduction was the monoamine 353 shown below. Whelan and co-workers described the hydrogenolysis of $\beta$-cyanoamines under LiAlH$_4$ reducing conditions, a possible decomposition route for the formation of the by-product 353 from the diamine formed through dimerisation (Scheme 2.21).
Carbamate formation and reduction afforded the methylamines 354a-b, with chlorination under the standard conditions affording the desired N-chloroamines 355a-b in good yields (Scheme 2.22).

The 3-methylTHQ 356b was obtained in a yield of 77%, consistent with previous results. As expected, a much lower yield of 23% was obtained for the 3-Ph derivative 356a. This is likely due to decomposition through the radical β-scission pathway, further supporting our assumption of a radical based mechanism (Scheme 2.23).

There are multiple natural products and drug molecules that are known to contain heteroatoms on the aliphatic ring of the THQ, such as the natural product helquinoline 357 or the antimalarial drug 358 both shown in Figure 2.9.136

A target was proposed that would contain heteroatomic substitution on the aliphatic chain of the THQ. A base-mediated ring opening of (2,3-epoxypropyl)benzene 359 and MeNH₂·HCl afforded the amino alcohol 360 in 47% yield, which was converted to N-chloroamine 361.
Photolysis of the substrate gave a complex mixture of products, with the desired THQ 362 observed by LC-MS analysis along with the de-chlorinated starting material 360 also identified. The mass for the de-chlorinated starting material plus chlorine was also observed by analysis of the LC-MS data. Analysis of the $^1$H NMR spectrum of the crude reaction mixture indicated the de-chlorinated amine 360 was the main component, and after purification by flash chromatography no desired product was isolated (Scheme 2.24).

With this lack of success, it was thought a protected alcohol may fare better in the photolysis reaction. Using the same reaction as previously described, N-benzylmethylamine was chosen as starting material to allow for a selective alkylation of the free hydroxyl to occur. When the starting materials were subjected to the same reaction conditions previously described, repeated over-pressurising within the microwave reactor occurred upon heating. Consequently, the base-mediated ring-opening was carried out under thermal conditions and afforded the desired product 363 exclusively in 91% yield. Alkylation with NaH and MeI gave the ether 364 in 47% yield, and hydrogenolysis of the benzyl group with Pd/C afforded the amino ether 365 in good yield. This was converted to the N-chloroamine 366 in quantitative yield. Pleasingly photolysis of this substrate did give the desired THQ 367, in 40% yield. The lower yield may have been due to the stabilising effect the oxygen atom could have on an α-radical, leading to decomposition of the intermediate aminyl radical that is formed through a possible radical β-scission pathway (Scheme 2.25).
2.1.2.6 Efforts Towards Natural Products Bearing the THQ Motif

A family of natural products isolated from the bark of the South American plant Galipea officinalis all contained a THQ core (see Figure 2.7). A Heck coupling was seen as the most straightforward way to install the aromatic moiety on the vinyl group. Conditions were found detailing Heck reactions specifically with allylic amines. When applied to our substrate 341 using aryl bromide 368 the desired product 369 was observed by LC-MS analysis of the reaction mixture, however multiple other masses were also observed and no desired product was isolated upon work-up (Scheme 2.26).

Scheme 2.26

A second set of conditions were also applied, employing Pd⁰ instead of Pd¹ as a pre-catalyst, however once again only a complex mixture of products was obtained from the reaction. With this lack of success an alternative route to the natural products was sought.

A report from Senanayake et al. detailed the one-pot formation of aldimes arising from the addition of a Grignard reagent to a nitrile. We thought a modified procedure using pentylmagnesium bromide then instead of reducing the intermediate first trapping with ethyl chloroformate then reducing globally with LiAlH₄ could lead to a potential N-methylamine precursor 373 to the natural product angustureine 3. Addition of pentylmagnesium bromide to 3-phenylpropionitrile 370 gave a presumed metalloimine intermediate 371. This was trapped with ethyl chloroformate and the resulting imino-carbamate 372 was then reduced with LiAlH₄ to afford the desired methylamine 373 in 74% yield (Scheme 2.27).

Scheme 2.27
To ensure a concise synthesis, the one-pot chlorination/photolysis procedure was employed to reduce the number of synthetic steps. Pleasingly, this step proceeded in a 50% yield, giving an overall yield of 37% in a two-pot sequence for (±)-angustureine 3 (Scheme 2.28). As with the other examples, the N-chloroamine 374 was synthesised and fully characterised as well. The chlorination of the amine 373 proceeded in a 75% yield, and photolysis of the N-chloroamine 374 afforded the desired product 3 in 69% yield. Pleasingly, no δ-chloroamine was observed by either LC-MS analysis or upon inspection of the 1H NMR spectrum of the crude reaction mixture. Individually the three-step sequence involving the isolation of the N-chloroamine gives a slightly higher overall yield of 38% however an extra purification was required, therefore reducing the efficiency when compared with the two-step sequence.

![Scheme 2.28](image)

To complete a stereoselective synthesis of the natural product 3, Ellman chemistry was applied using the sulfinimine precursor 336 and pentylmagnesium bromide. This afforded the desired sulfinimide 375 in 78% yield, although only with a d.r of 6:1. Unfortunately the diastereoisomers could not be separated at this stage, as was seen with other the other hydrocinnamaldehyde derivatives (see Table 2.6), so were taken forward as a mixture. This was converted to the amine 373 and the one-pot procedure afforded the non-racemic product 3 in a 52% yield, giving an overall yield of 25%. Analysis by chiral HPLC showed the ee to be 70%. Despite this being low, it demonstrated that the photochemical reaction was not stereoablative, with this figure matching the observed d.r from the Grignard addition. The [α]D23 was measured at -5.2 (c 0.1, DCM) which is in accordance with the literature value of [α]D25 -7.7 (c 0.65, CHCl3) (Scheme 2.29).
Different structural topologies were targeted to exemplify the methodology. The first were based around cyclohexanone.

Preparation of the first compound began with alkylation of cyclohexanone 376 with benzyl bromide 349 to give the β-arylketone 377 in 75% yield. The transformation of the ketone 377 to the amine 378 was achieved using the Ti(OiPr)_4-mediated reductive amination conditions described earlier. This proceeded in 44% yield and gave an inseparable 5:1 mixture of the diastereoisomers 378. The diastereomeric ratio was determined using the signals from the NCH in the 1H NMR. The amines were then taken forward to the chlorination step using NCS, where the N-chloroamine diastereoisomers 379 and 380 were successfully separated by flash chromatography (Scheme 2.30).

The relative configuration of the diastereoisomers was determined through the coupling constants and multiplicity of the protons on the cyclohexyl ring. Using the Karplus relationship, it can be determined what the relative configuration a proton has to its neighbouring protons. The closer the dihedral angle to 90°, the smaller the coupling constant.
will be so axial-equatorial relationships have a smaller coupling than axial-axial relationships. The signal for proton H₆ of the syn-diastereoisomer 379 displays a doublet of triplets due to the large coupling constant of 11.4 Hz to the axial proton shown in blue in the ¹H NMR spectrum. The signal for proton H₆ of the anti-diastereoisomer 380 appears as a triplet of doublets instead, due to the coupling constant of 10.4 Hz to two equivalent axial protons also shown in blue. The smaller coupling constants of 3.4 and 3.5 Hz arise due to the equatorial relationship with the protons shown in green (Figure 2.10).

![NMR Spectra](image)

**Figure 2.10**

The N-chloroamine 379 was subjected to the standard photolysis conditions. Surprisingly no reaction occurred, with just the amine recovered 378 recovered. Changing the solvent to toluene alleviated this issue, giving the desired product 381 in 57% yield. The amine 378 was also recovered in a 31% yield. Toluene and MeSO₃H proved to be immiscible. This could explain why the reaction didn’t work with DCM. In toluene the reaction will be taking place in ‘pseudo-concentrated’ conditions, with the N-chloroammonium formation likely meaning
the reaction will be taking place in the acidic phase of the reaction. With DCM, however, it was a homogenous reaction mixture with a lower concentration of acid, and perhaps this N-chloroamine 379 was not reactive enough for the less acidic conditions of the DCM/MeSO₂H reaction. This reaction was repeated in concentrated H₂SO₄ and the desired product was isolated in 52% yield, demonstrating that highly acidic conditions are required for this reaction to proceed (Scheme 2.31).

![Scheme 2.31](image)

A more challenging structure was the bridged compound 387 shown below. We envisaged a short synthesis applying the Rh(I)-catalysed conjugate addition reaction to cyclohexenone 382. This reaction proceeded as expected, with the desired β-arylketone 383 obtained in a quantitative yield. The ketone was converted to an inseparable mixture of diastereomeric amines 384 under the Ti(OIPr)₄ conditions employed previously, and the crude amine mixture was chlorinated and separated to afford the N-chloroamine diastereomers 385 and 386 in 69% and 27% yield respectively (Scheme 2.32).

![Scheme 2.32](image)

Both N-chloroamines 385 and 386 were irradiated under the standard conditions. As expected the anti-diastereoisomer 386, which cannot cyclise to the pendant aromatic, only afforded the de-chlorinated starting material 384, however the syn-compound 385 afforded the desired product 387 in 40% yield (Scheme 2.33).
2.1.2.8 Pyrrolidine and Piperidine Derivatives

Polycyclic alkaloids make up a major class of natural products. Gephyrotoxin 388 is a natural product that was isolated from skin extracts of the Columbian frog *Dendrobates histrionicus*, and exhibits several neurological activities. The structure contains a saturated quinoline core that could be derived from the reduction of a THQ such as 389 shown below (Scheme 2.34).

We envisaged that N-chloroamine 390 could be obtained from a short synthesis using readily available starting materials. A Wittig reaction between benzyltriphenylphosphonium chloride 391 and rac-prolinal 392 using LiHMDS afforded the alkene 393. This was taken crude and reduced then de-protected to yield the amine 394 in 71% yield over two steps. Chlorination with NCS proceeded in a high yield when performed on a scale less than one mmol, however the desired N-chloroamine 390 quickly decomposed and efforts to isolate the product from any larger scale reactions afforded mixtures of the starting material 394 and unidentified side-products. Fortunately, applying the ‘one-pot’ procedure alleviated this issue, affording the desired THQ 395 in 73% yield (Scheme 2.35).
Applying the same chemistry, the piperidine derivative was also synthesised. The Wittig reaction afforded the alkene 397 and once again this was reduced and de-protected to afford the amine 398 in 81% yield. The piperidine N-chloroamine 399 was stable and could be isolated and stored, however the compound decomposed after being left in solvent so could not be fully characterised. Nonetheless it was successfully converted to the THQ 400 in high yield upon photolysis (Scheme 2.36).

With this success it is envisaged that derivatives of gephyrotoxin intermediates can be accessed from this short synthetic route.

### 2.1.3 Mechanistic Studies and Insights

#### 2.1.3.1 5- vs 6-Membered Ring Formation

When given two options a radical cyclisation will proceed through the kinetically favourable (faster) pathway, sometimes almost exclusively. Newcomb et al. studied the difference in rates of reactions between 5-exo and 6-exo cyclisations of dialkylamanyl radicals using laser flash photolysis. The observed rate constants of 5-exo cyclisations of two different aminyl radicals were measured at $1.9 \times 10^5$ s$^{-1}$ and $3.2 \times 10^5$ s$^{-1}$ respectively (Table 2.7, entries 1 and 2). The authors stated that the equivalent 6-exo cyclisation was so slow that they couldn’t accurately measure it using this technique (Table 2.7, entry 3).

<table>
<thead>
<tr>
<th>Entry</th>
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<th>$k_{2(20)}$ (s$^{-1}$) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>H</td>
<td>$1.9 \times 10^5$</td>
</tr>
<tr>
<td>Entry</td>
<td>n</td>
<td>$k_{200}$ (s$^{-1}$)$^a$</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>---</td>
<td>-----------------</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>$9 \times 10^7$</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>$1 \times 10^{10}$</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.8 $^a$The rate constant as measured at 20 °C

5-exo cyclisations proceed in a faster manner than 6-exo cyclisations because the overlap of the orbitals in the transition state is perfect for a 5-membered ring formation. The radical can attack the LUMO of the alkene at the perfect angle of 109° (Bürgi-Dunitz angle) in the transition state for a 5-membered ring formation, whereas this is not the case with a 6-membered ring formation.

A substrate was designed to test and see if the photolysis reaction would proceed through a 5-membered intermediate, formed through a kinetically favourable 5-exo cyclisation, that would then migrate to form the 6-membered ring. By blocking both $\alpha$-positions of the aromatic ring we wondered if this would trap an intermediate arising from a 5-exo cyclisation. The 2,6-dimethyl substrate 404 was chosen. Using 2,6-dimethylphenylboronic acid 401 and N-methylcrotonamide 307, a Rh(I)-catalysed conjugate addition gave the amide 402 in 47% yield, LiAlH$_4$ reduction then afforded the amine 403 and the N-chloroamine 404 was obtained through chlorination with NCS in 86% yield (Scheme 2.37).
The *N*-chloroamine 404 was then irradiated under the standard conditions. Surprisingly, the main product isolated from the reaction was migration product 405 in 41% yield. The product was identified through analysis of the signals in the aromatic region of the $^1$H NMR spectrum. There were only two doublets present, and coupled with analysis of the high resolution-MS the mass was correct for the given structure. A small amount of another unidentified product was also isolated, however this decomposed before it could be fully characterised (Scheme 2.38).

Due to the unexpected nature of this result, Density Functional Theory (DFT) calculations were then used to try to explain the experimental outcome.

2.1.3.2 DFT Calculations

Using DFT calculations it is possible to investigate the electronic structure of reactive intermediates in reactions. The calculations were run by Professor John Plane at the University of Leeds. Using these techniques, the energy of intermediates forming 5- and 6-membered rings were investigated first, then the energy difference between the protonated and non-protonated aminyl radical species.

For the 5-membered ring formation, the energy difference between that of the open-chain structure A and the final spirocyclic structure E is $+33 \text{ kJ mol}^{-1}$. This would suggest that the ring-closure to form the 5-membered spirocycle is an endothermic process and so is not energetically favourable (Figure 2.11).
Comparison with the 6-membered ring formation shows a more favourable process. The energy of the 6-membered ring product H compared with the open-chain structure A is only +12 kJ mol\(^{-1}\). The uncertainty at the level of theory used is ±20 kJ mol\(^{-1}\), meaning that the 6-membered ring formation could be a thermoneutral process (Figure 2.12).
Further calculations looked at the energy differences between protonated and non-protonated aminyl radicals. Photolysis in DCM alone yields exclusively the de-chlorinated amine starting material, and DFT calculations demonstrated that to form the 5- or even 6-membered ring in a neutral solvent would be too endothermic. It was calculated that formation of a 6-membered ring with a neutral aminyl radical was +41 kJ mol\(^{-1}\) higher in energy than the open chain structure. Furthermore, the 5-membered formation ring was +57 kJ mol\(^{-1}\) above the open chain structure.

These DFT calculations have not only demonstrated that the reaction likely proceeds through a direct 6-membered ring formation, but that acid is also essential to the reaction, with the neutral species being too high in energy to react.

### 2.1.3.3 Chloride Migration Investigation

After the intriguing migratory result further experiments were planned to try and ascertain the generality of the migration reaction. There was precedence for radical-based halide migrations: Everly and Traynham reported that chlorination of \(p\)-bromonitrobenzene \(406\) led to 2-bromo-4-nitro-chlorobenzene \(410\), arising from ipso-attack of the chloride then 1,2-migration of bromide radical.\(^{146, 147}\) The report states that there were only trace amounts of the migratory compound \(410\) observed by GC analysis, however products \(407\) and \(408\) arising from further reactions of the migration compound \(410\) are present in relatively high amounts in the product distribution (Scheme 2.39).

![Scheme 2.39](image)

A series of substrates were synthesised to test this theory. These substrates were synthesised using the same (pseudo)-halide displacement at a benzylic position with allylmagnesium chloride that was used in earlier syntheses (see Table 2.5). Starting with 2,6-dichlorobenzyl bromide \(411\), the halide was displaced using allylmagnesium chloride to afford the alkene \(412\) in a 93% yield. The alkene \(412\) was then oxidatively cleaved under ozonolysis conditions with \(PPh_3\) as the reductant, affording the desired aldehyde \(413\) in a 63% yield. The aldehyde \(413\) was then converted to the methylamine \(414\) using the reductive amination conditions employed previously (see Table 2.2) in 74% yield, which was converted to the \(N\)-chloroamine \(415\) in a 92% yield (Scheme 2.40).
For a direct comparison, substrates bearing a chloride at one ortho-position and a methyl or a proton at the other were synthesised. The benzyl alcohols 416a-b were converted to the terminal alkenes 417a-b in 85% and 52% yields respectively. Both aldehydes 418a-b were obtained in good yields and were converted to the amines 419a-b via reductive amination with NaBH₄ in 49% and 99% yield respectively. Chlorination with NCS furnished the N-chloroamines 420a-b in good yields (Scheme 2.41).

The chloro-methyl substrate 420a gave a mixture of products. The migratory product 423 was only isolated in 5% yield, and the chloride substitution product 424 was obtained in 14% yield.
with the de-chlorinated amine starting material the main component of the reaction mixture (Scheme 2.43).

![Scheme 2.43](image)

The mono-chloro compound 420b gave an inseparable 2:1 mixture of the ipso-substitution product and the direct amination product in a combined yield of 45%. The ratio of products was determined using the $^1$H NMR spectrum (Scheme 2.44).

![Scheme 2.44](image)

These substrates showed that despite some consistency with the first migration reaction, the yields were not useful and investigations into the migration reactions were stopped.

### 2.1.3.4 Mechanistic Proposal

With the different experimental results and considering the DFT calculations, mechanistic proposals are shown below. Some of the key points relating to the mechanism include:

1. Formation of the $N$-chloroammonium species occurs under acidic conditions before the reaction takes place (see Figure 2.4 and Figure 2.5).
2. The $N$-hexyl substrate 278c (see Scheme 2.5) undergoes a 1,5-hydride abstraction and recombination to form the $\delta$-chloroalkylamine which indicates a radical nature as this would only occur through this pathway, like seen in the HLF reaction. Furthermore, ipso-radical substitution of the aryl-chloride species 415 occurred at RT (see Scheme 2.42), a transformation that would also only proceed through a radical pathway at these temperatures.
3. The protonated aminyl radical intermediate is an electrophilic species, as shown with the competition reactions (see Scheme 2.12) where high levels of selectivity were shown for more electron-rich aromatic moieties.
4. DFT calculations, spurred by the unexpected migratory reaction (see Scheme 2.38), have shown that: a) there is most likely a direct 6-membered ring formation, with a 5-exo type cyclisation energetically unfavourable; b) that acid is essential to the reaction as the neutral aminyl radical species are too high in energy to react directly with the aromatic ring.

With these considerations, some proposed mechanisms are shown below. First, protonation of the N-chloroamine 255 occurs to give the N-chloroammonium species 425, which then undergoes photolysis to yield the protonated aminyl radical species 426. This then directly couples with the aromatic ring to form the new 6-membered ring 427. There have been several reports that the HLF reactions proceeds through a radical chain mechanism, where the reaction is propagated by reaction of the intermediate with the starting material.\textsuperscript{98,99} In this instance, propagation of the starting material would give the aryl chloride intermediate 428 that would then eliminate HCl to give the re-aromatised product 429. This would be neutralised on workup to give the desired product. The mechanism could also proceed by oxidation of intermediate 427, with loss of an electron to give aryl cation 430. Elimination of H\textsuperscript{+} would afford the re-aromatised product 429 (Scheme 2.45).

\begin{center}
\textbf{Scheme 2.45}
\end{center}

With double ortho-substitution of the aromatic group a different mechanism will proceed depending on the substituent. Cyclisation will proceed through the same pathway, forming the 6-membered ring as seen previously. In the case of the aryl chloride species, radical elimination of chloride will afford the re-aromatised product 432. In the case of X = methyl, radical capture of the alkyl group and cleavage of the bond will allow the methyl group to undergo the 1,2-aryl shift then elimination of HCl will afford the desired product 434 (Scheme 2.46).
Whilst there have been no direct reports of 1,2-alkyl radical migration on aromatic rings, Nevado and co-workers described in 2015 the expulsion of methyl radicals from 2,6-dimethyl anilines.\textsuperscript{148} Whilst investigating cascade cyclisations involving amidyl radicals, the unusual expulsion of a radical group was seen (product 438, Scheme 2.47).

The authors reasoned the loss of the methyl group from 435 was through a radical pathway. After the formation of intermediate 441 a radical coupling caused a de-aromatisation, then to re-aromatise a methyl radical was expelled (Scheme 2.48). The mechanism may not be likely as there is an excess of hypervalent iodine reagent which could oxidise the intermediate 442 to give an aryl cation, and result in the loss of an alkyl cation as opposed to the alkyl radical that is proposed.
This is not the same as what was seen in the case of our substrates, however if it was proceeding through a radical would support the existence of methyl radical formation and movement within molecules.
2.2 Conclusion

In summary, an efficient synthesis of tetrahydroquinolines starting from N-chloroamines and using only MeSO$_3$H in DCM under photolysis from a medium-pressure mercury lamp has been developed. It has been shown that improved yields are obtained compared with using concentrated sulfuric acid. The optimal conditions now use a minimal amount of an organic acid that is soluble in organic solvent leading to a more practical procedure that avoids the use of highly corrosive acidic conditions.

Over 30 substrates have so far been shown to work, with several functionalities and topologies demonstrated. The synthetic utility of the methodology has been demonstrated in the synthesis of the natural product angustureine, which was synthesised in a concise three-step synthesis.

The reaction is shown to be selective for more electron-rich aromatic groups in preference to electron-deficient aromatic groups, however highly electron-rich groups, such as anisoles, suffer from direct chlorination of the aryl ring preventing further reaction.

Attempts to probe the mechanism of the key reaction led to a surprise result, with a 1,2-alkyl migration around the ring resulting in a contiguously tetrasubstituted aromatic-ring. Along with this result DFT calculations have likely ruled out the formation of a 5-membered spirocyclic intermediate, with the direct formation of 6-membered ring a more energetically favourable process.

Evidence for a radical-based mechanism has been supported by the isolation of a product that arises from a 1,5-hydride abstraction with the $n$-hexyl substrate 281. Further to this, during the investigation of the migratory reaction, a chloride substitution occurred that would not have occurred through a cationic pathway under the mild conditions employed in the reaction.
2.3 Future work

The advances made have shown that the modified reaction can be used in place of some traditional methods. However, the limitations lie in the fact that more electron-rich substrates suffer from chlorination on the ring, which consequently stops the reaction from proceeding. There have been several reports of $N$-centred radicals being initiated from hydroxylamine based derivatives, where cleavage of an N-O bond triggers the generation of the $N$-centred radical.

As discussed in the introduction chapter (see Scheme 1.57), Leonori et al. recently reported that amidyl radicals generated from the photochemical cleavage of hydroxamic ester derivative could be coupled directly with unfunctionalised (hetero)aromatics. Applying this type of radical precursor to the substrates described above could lead to electron rich aromatics being aminated without the problem of over-reaction once the THQ has formed.

One of the limitations of the reaction is the scale on which it can be performed. A way to address this problem is the use of continuous photochemical processing, which allows for the production of material in a continuous manner using a flow reactor (see Chapter 3). Products produced using this methodology bearing chiral centres can only be produced as racemic samples (unless chiral information is imparted from another reaction). An efficient method to produce chiral amines would be desirable, with enzymatic deracemization reactions a potential route to such non-racemic samples (see Chapter 4).
Chapter 3  Continuous Photochemistry

3.1  Introduction to Flow Chemistry

3.1.1  Why Choose Flow?

The use of continuous reactors in the production of biologically relevant molecules, such as natural products\textsuperscript{149} or pharmaceutical intermediates,\textsuperscript{150} has attracted much attention in recent years. This has been attributed to the fact that flow reactors can offer numerous advantages over the equivalent batch processes, such as improved mixing of reagents and better control of the reaction conditions.\textsuperscript{151} There still seems to be a reluctance amongst the academic community to switch fully to flow-based research laboratories, and this is often due to the perceived cost of the specialist equipment that is required.\textsuperscript{152}

3.1.2  Batch vs Flow: Which is Better?

There have been many studies that compare the cost efficiencies of flow processes versus the equivalent batch process. Trout \textit{et al.} performed a full cost analysis of the production of 2000 tons of tablets per year of an active pharmaceutical ingredient (API) comparing a novel continuous process with the batch process.\textsuperscript{153} They found, when altering numerous costing parameters relating to the price of key ingredients, that the flow process was almost always the more cost-effective process. Numerous process scenarios were compared, such as the continuous process with recycling of materials and without, and with a novel direct formation of the tablets at the end of the process compared with roller compaction, which is a well-established technology for pharmaceutical formulation processes. The Authors stated that overall savings ranged from 9 to 40% if the appropriate flow processes were selected, when compared with equivalent batch processes. This is only one case study, but shows that flow chemistry has huge potential in the synthesis of important pharmaceutical intermediates.

3.1.3  Applications of Flow Chemistry

There have been many examples of the applications of continuous processes in the synthesis of important molecules such as APIs or natural products.\textsuperscript{149,150} Jamison and co-workers described the continuous production of diphenhydramine 445, an antihistamine of which over 100 tons per year in produced.\textsuperscript{154} The process that was developed utilised the smaller volumes of a microfluidic continuous reactor to avoid the use of any solvent, and careful selection of reagents and conditions meant that 100\% atom economy was achieved (where all atoms of the starting material are part of the product). To attain this the product was produced as the hydrochloride salt in molten form, meaning the reaction is above the melting point of the salt, then quenched after with an in-line addition of aqueous NaOH. Addition of hexane then separation in an in-house built separation membrane afforded the desired product in a solution
of hexane. This was then crystallised using 5 M HCl in IPA. To further reduce the waste, it was also demonstrated that, with a slight compromise in yield, direct crystallisation could be achieved by adding IPA directly to the reaction mixture, avoiding the need for any extraction and reducing the amount of waste solvent from the process (Table 3.1).

![Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. 444</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
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<td>88</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>93</td>
<td>92</td>
</tr>
</tbody>
</table>

*Table 3.1*<sup>a</sup> <sup>1</sup>H NMR yield obtained with internal standard<sup>b</sup> Isolated yield after recrystallization

The key findings from this study highlight several techniques that improve the efficiency that would not be reproducible in batch:

1) The formation of a molten salt would not be achievable under batch conditions, which allowed for solvent free conditions leading to reductions in the waste stream.

2) No additional additives (i.e. base, which is used in the batch process) were required, once again decreasing the environmental footprint of the process.

In 2006, Ley *et al.* demonstrated the first synthesis of a natural product under continuous conditions. One of the more impressive elements associated with this synthesis is that all the apparatus was built and assembled in-house, due to a lack of suitable commercially available equipment. The first step of the synthesis involved passing ferulic acid solution with PyBROP and DIPEA over supported hydroxybenzotriazole to form an activated ester species. Once the column was loaded, an amine was pumped through to allow for amide formation. This was performed with a switching valve and carried out over two columns, so whilst one of the solutions was being passed through one column, the other would be pumped through the other to ensure a continuous reaction. The solution was then passed over sulfonic acid residues in a second cartridge to scavenge any unreacted amine. The resultant amide was fed into a third reactor, at the same time as a hydrogen peroxide-urea buffered solution, that contained silica supported Horseradish Peroxidase and underwent an enzyme-mediated
dimerization to afford the desired product 449. There were multiple in-line analytical instruments incorporated, including LC-MS and UV-Vis, which allowed self-optimisation of the system through feedback loops that could alter flow rate, dilution etc. to give the optimal conditions for product formation (Scheme 3.1).

The two previous examples demonstrate just a few of the advantages flow chemistry can offer over conventional laboratory methods. The next section will discuss how continuous photochemical reactors can give much improved results for photochemical reactions against the standard batch reactors that were discussed and used in the previous chapter.

3.1.4 Continuous Photochemistry

Photochemical reactions, specifically UV-mediated transformations, are hard to scale up. One of the main problems is the poor penetration of light into reaction mixtures, with large scale reactors often suffering from an uneven distribution of photons amongst reactions. This often makes optimisation of photochemical reactions for industrial scale hard, as the conditions for small-scale batch reactions do not translate well to bigger reactors. In 2005 Booker-Milburn and co-workers demonstrated that by wrapping UV-transparent fluorinatedethylene propylene (FEP) tubing around the flask that houses a UV-bulb in a typical immersion-well reactor, they were able to convert the conventional glassware into a continuous photochemical reactor. The authors were able to demonstrate that using this set-up, which fit into a normal fumehood in a research lab, they could obtained productivities of >500 g of material per 24 h. Two different examples were demonstrated in the paper, an intramolecular [5+2] cycloaddition of N-alkylmaleimide 450, and the intermolecular [2+2] cycloaddition between maleimide 452 and 1-hexyne 453.

The intramolecular [5+2] cycloaddition was first run using a reactor which used a Pyrex filter, which as discussed (see Figure 2.4 and Figure 2.5) cuts off transmission around 280 nm, and

Scheme 3.1
this gave a yield of 79% with a projected 24 h yield of 44 g (Table 3.2, entry 1). Changing the filter to a Vycor filter allowed transmission of light to 220 nm instead, and increasing the number of layers of FEP tubing to three increased the yield to 80%, but more importantly increased the projected yield after 24 h to 178 g (Table 3.2, entry 2).158

![Chemical structure](image)

**Table 3.2** Isolated yield after purification of 50 mL of photosylate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conc. (M)</th>
<th>Flow rate (mL min⁻¹)</th>
<th>Filter</th>
<th>Layers FEP</th>
<th>Yield (%)</th>
<th>24 h proj. (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>2</td>
<td>Pyrex</td>
<td>1</td>
<td>79</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>8</td>
<td>Vycor</td>
<td>3</td>
<td>80</td>
<td>178</td>
</tr>
</tbody>
</table>

The intermolecular [2+2] reaction between maleimide 452 and hexyne 453 afforded even higher levels of productivity when using the triple-layered Vycor reactor. The initial run using one layer of FEP gave a conversion of 88% with a 24 h projection of 363 g at a concentration of 0.2 M (Table 3.3, entry 1). Changing the parameters to a concentration of 0.3 M and three layers of FEP increased the projected yield to 408 g (Table 3.3, entry 2). To assess power versus conversion, a 600 W lamp was used instead and showed a remarkable increase to 685 g productivity in a 24 h period (Table 3.3, entry 3).158

![Chemical structure](image)

**Table 3.3**

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

Booker-Milburn et al. further demonstrated the application of the photochemical reactor with the synthesis of several complex tricyclic aziridines 456.159 The substrates were constructed from N-alkylpyrroles 455 with an electron-withdrawing group at the 2-position, initially in batch. The reaction proceeded through a [2+2] cycloaddition to give intermediate 457.
followed by radical fragmentation and recombination to afford the desire aziridine products (Scheme 3.2).

![Scheme 3.2](image)

The scalability of these reactions were tested with a few of the substrates being synthesised in a continuous photochemical reactor similar to those described previously. Three substrates were chosen, as these were then subjected to further reactions to give a library of complex products derived from the aziridine as starting materials. Using a continuous photochemical reactor, the authors could obtain multigram quantities of the three desired products in a short space of time. The amide derivative gave the highest yield and was obtained in the shortest amount of time (Table 3.4, entry 1). A slower flow rate was used for the ketone derivative to give over 2.5 g of material after 7.7 h (Table 3.4, entry 2). Finally, when R = CN the substrate gave the lowest yield and took the longest time (Table 3.4, entry 3). There was no reasoning given for the variations seen in the yields.

![Table 3.4](image)

A comprehensive analysis of batch and flow photochemical reactions drew several conclusions about the two ways of running the reactions:

1. When conversion is full, yields for both flow and batch photochemical reactions are usually the same.
2. Triple-layered FEP reactors are on average 20% more productive when compared with the equivalent batch reaction.
3. Mono-layered FEP reactors are on average 20% less productive when compared with the equivalent batch reaction.
The reasoning for the productivity differences between the mono- and triple-layered FEP reactors was to do with how light could and could not escape from the immersion well. Whilst the light could escape directly from between the FEP tubes in the mono-layer it would encounter another layer of tubing in the triple-layer increasing absorption by the reaction mixture and therefore productivity.

Recently, Booker-Milburn, Elliott and co-workers described the design and production of a lab-scale reactor that could attain productivities well in excess of 1kg d\(^{-1}\) for several different substrates.\(^{162}\) ‘The Firefly’ is a compact, low footprint photochemical reactor. To increase its durability, compared with the FEP reactors that were described previously, an array of quartz tubing was used instead. The housing for the light source that was used in the reactor meant different light sources could be used, including mercury lamps and LEDs. A variable power source was installed as well, which allowed for powers ranging from 1.5 to 5 kW to be set. One of the most impressive outputs was the isomerisation of ene-dione 458 to afford Cookson’s dione 459. Several conditions were tested, with the optimal conditions showing that a productivity of >8 kg d\(^{-1}\) could be obtained with the power set to only 3 kW (Table 3.5).\(^{162}\)

\[
\begin{array}{ccccccc}
\text{Run time (h)} & \text{Conc. (M)} & \text{Power (kW)} & \text{Flow rate (mL min}^{-1}\text{)} & \text{Yield} & \text{Amount (g)} & \text{24 h proj. (g)} \\
3.47 & 1.0 & 3 & 36 & 89 & 1,165 & 8,058 \\
\end{array}
\]

\textit{Table 3.5}
3.2 Aims

Based around the design of Booker-Milburn’s original FEP reactor we aimed to design and build a continuous photochemical reactor that would tolerate our optimised N-arylation reaction conditions described earlier (see Table 2.1). The limitations of the scale of our reactions were the main reason for the desire to optimise the reaction for continuous conditions. The largest scale the photochemical reaction could feasibly be carried out on was around 500 mg, and with a reaction time of 3-5 h depending on the substrates this rendered productivity low.

A two-step reactor that would incorporate the chlorination of secondary amines to form N-chloroamines in situ would also be explored, as this would allow for a further streamlined synthesis of THQs directly from the amine starting materials. This would also avoid the isolation of N-chloroamines that were potentially hazardous or unstable, such as the pyrrolidine derivative 395, which decomposed when the reaction was scaled up in batch.
3.3 Continuous Photochemical Processing Results

3.3.1 Construction of the Continuous Photochemical Reactor

The first task was build a suitable reactor, closely based on the design of Booker-Milburn.\textsuperscript{158} The use of an HPLC pump for the reaction was one option, but this was not chosen as the use of MeSO$_3$H solutions in DCM may have caused damage to the interior of the pump. Consequently, dual syringe pumps were instead chosen as the pressure source for the reactors, with syringes used to house the solutions as they could be regularly replaced should any corrosion or fouling occur.

Initially, the FEP tubing that had an internal diameter (I.D) of 2.7 mm was chosen for the whole system. Issues with the size of the tubing when attached directly to the syringe however meant that when the system was pressurised, the solvent began to leak (Figure 3.1).

![Figure 3.1 Leak caused by using FEP tubing directly with syringe](image1)

One solution was to attach a stretchable Marprene adapter between the syringe and the tubing, however the material was not resistant to MeSO$_3$H and dissolved immediately upon testing (Figure 3.2).

![Figure 3.2 Dissolved Marprene tubing upon use of MeSO$_3$H solution](image2)
To solve this issue, smaller PTFE tubing was used. The tubing had an I.D of 1/32\textsuperscript{nd} of an inch, so also could not be directly connected to the syringes, however use of needles alleviated this (Figure 3.3).

![Figure 3.3](image)

The PTFE tubing could not be used as the tubing for the photochemical reaction as this was not UV transparent. The small size of the tubing also meant it was much harder to wrap around the immersion well, a problem that Booker-Milburn \textit{et al}. reported in the construction of the first generation FEP reactors.\textsuperscript{158} A stainless steel junction piece was used to connect two tubes with the \textit{N}-chloroamine solutions and the MeSO\textsubscript{3}H solutions to the UV-transparent FEP tubing that would be wrapped around the immersion well flask.

A small initial reactor volume of 5 mL was chosen. The length of the tubing required for this volume can be calculated using the equation for the volume of a cylinder (eq. [1]), where \( V \) is the volume in mL, \( r \) is radius in cm and \( h \) is the height in cm:

\[
V = \pi r^2 h \tag{1}
\]

Rearranging for \( h \) gives (eq. [2]):

\[
h = \frac{V}{\pi r^2} \tag{2}
\]

Inputting the values gave a length of 87.4 cm of tubing with an internal diameter of 2.7 mm and a reactor volume of 5 mL. Either side of the reactor volume an extra 50 cm of tubing was added for transport of the solutions to and from the photochemical reactor itself. Using a double-sided adhesive tape, along with masking tape the tubing was assembled around the immersion well reactor. This proved problematic, as the tubing was prone to bending causing kinks which could lead to blockages during the reaction. Several attempts were made before the tubing was successfully attached (Figure 3.4).
The whole reaction setup fitted in a standard fumehood. As with the batch reactors, before the UV light was switched on the reactor was completely wrapped in aluminium foil, and round this a red Perspex box was placed to capture any stray UV light. As was used previously, a water-flow trip device was attached if the water source required for cooling the bulb had cut out (Figure 3.5).

3.3.2 N-Arylation Reaction in a Continuous Photochemical Reactor

The N-chloroamine \textbf{255} which was used for the optimisation of the $N$-arylation reaction, was also chosen for the optimisation of the photochemical reaction in flow. The reaction when run in batch was run at 0.25 M with respect to the $N$-chloroamine. The ratio of the MeSO$_3$H to DCM in batch was approximately 1:7 v/v every time, which worked out at around 3 M. Consequently, the initial reactions were run with double these concentrations as the concentration would half when mixed with the other solution at the junction. A 0.5 M solution of $N$-chloroamine \textbf{255} was made up in DCM and a 6.0 M solution of MeSO$_3$H in DCM also made up. At the junction, when the concentration would half, the flow rate would double as there was twice the amount of solvent passing through the same diameter tubing. Initially, a
residence time of 15 minutes was chosen. This amount of time was chosen because as the solution would be much lower in volume and in much closer proximity to the light source, it was thought this would mean there would be a much quicker reaction time compared with the batch process. Therefore, the required flow rate was 0.33 mL min\(^{-1}\) for a 15 minute residence time in the 5 mL reactor. To enable this, the syringe pump was set at half the desired flow rate of 0.17 mL min\(^{-1}\), as this would double at the point of mixing.

First, DCM was passed through the reactor to ensure no leaks occurred. With the reactor being confirmed as secure, the syringes were loaded and the pump switched on. To allow the reactor to reach steady state, the point at which the parameters of the reaction don’t change with time, the first two reactor volumes were discarded. After this the reaction mixture was collected in 5 mL aliquots every 15 minutes, each being one reactor volume. LC-MS analysis of every three reactor volumes showed that the reaction contained the mass for the desired product 256. In total, nine reactor volumes were run through (not including the initial two that were discarded). They were combined, worked up and purified to afford the desired product 256 in 66% yield. The amount of material produced also worked out as a productivity of 0.45 g h\(^{-1}\), which was considerably higher than what was attainable with the equivalent batch reactions that were limited to 0.5 g scale reactions and 3-5 h reaction times (Table 3.6, entry 1).

To try and test the limits of the reactor, the flow rate was then increased to 1.0 mL min\(^{-1}\), meaning the syringe pump was changed to 0.5 mL min\(^{-1}\). This gave the reaction a residence time of 5 minutes. Pleasingly, after reaching steady state, LC-MS analysis of the reaction mixture once again showed that the mass for the desired product 256 was present. After running through 9 reactor volumes again, the reaction mixture was worked up and afforded the desired product 256 in a 62% yield. More importantly this gave a productivity of 1.24 g h\(^{-1}\), a three-fold increase when compared with the first run and a massive increase in productivity compared with the batch equivalents for this reaction (Table 3.6, entry 2).
Comparing these results with the equivalent batch reaction shows an increase in the productivity in the reaction, displaying an obvious advantage over the small-scale batch reactors in that respect. Nevertheless, the yields in both cases, 66% and 62%, are considerably lower than those seen in the batch reaction, which gave a yield of 91% under the standard conditions. This could be rationalised by applying the observations of Booker-Milburn and co-workers in their comparative study of photochemical batch and flow reactions. One of the key points they made was that a mono-layer FEP reactor is on average 20% lower yielding than the equivalent batch reactor. The reactions here have seen a 20-30% decrease in yield in comparison with the equivalent batch reactions. This concurs with the observations that was made in their study. To increase this yield, perhaps a triple-layer FEP reactor would have provided an increase in yield. Another key difference between the work described here and much of that discussed by Booker-Milburn, is the addition of MeSO₃H. Much of the work described by the Booker-Milburn group only requires solvent, so is effectively ‘reagent-free’. MeSO₃H does absorb in the UV region, although at a lower wavelength to that of the N-chloroamine and N-chloroammonium compounds (see Figure 2.4 and Figure 2.5). This additional factor may contribute to a lower efficiency of the FEP reactor described here. Comparison with the batch however does show the increased productivity of the reactor: The limit of the batch reactor was 0.5 g per reaction, and these require photolysis for 3-5 h depending on the substrate. Assuming a 3 h reaction time in batch, the productivity attained for a yield of 80% would be 107 mg h⁻¹.

3.3.2.1 Space-Time Yield

A useful calculation to determine efficiency of a continuous reactor is the space-time yield (STY). The STY gives the yield for a process as a unit of space-time, which is...
independent of the reactor scale, so more useful for a comparison between different sized reactors. The STY yield is calculated by equation [3], with the units given as g L⁻¹ h⁻¹:

\[
\frac{\text{Mass of Product (g)}}{(\text{Reactor Volume (L)}) \times (\text{Residence Time (h)})} \quad [3]
\]

For the photochemical transformation described above (see Table 3.6), one reactor volume gave on average 0.103 g, with a reactor volume of 0.005 L and a residence time of 0.083 h. This gives a STY of 248 g L⁻¹ h⁻¹. As stated, this measure of productivity is useful as a comparison between different reactors that vary in size.

3.3.3 In-Line Chlorination and Photolysis Reactions in Flow

As discussed in (see Scheme 2.3), a ‘one-pot’ procedure was devised to allow for potentially unstable and toxic N-chloroamines to be telescoped directly from formation into the photolysis reaction. This was shown to work with several substrates, including the pyrrolidine substrate 395 of which the respective N-chloroamine was unstable, and the natural product angustureine 3 (Scheme 3.3).

The same conditions were attempted in flow. If the chlorination could work in flow this would allow for a more efficient reaction, where no N-chloroamine would have to be isolated and could be produced continuously. The first task was to establish the actual time it took for chlorination of the secondary amines to take, so a suitable residence time could be established for the continuous reactor. A ¹H NMR time course experiment was set up, with intervals set up to establish how long the reaction took however by the time the first spectrum was collected the reaction had gone to completion. This meant that the reaction took less than the 7 minutes between the NCS being added to the reaction mixture in the NMR tube and the acquisition of the ¹H NMR spectrum. The chlorination reaction was then run to establish if the reaction would proceed in flow.
Initially the reaction was going to be run at 1.0 M with respect to both the amine 273 and NCS, as this would then halve in the first reactor, then halve again in the second reactor to give a final desired concentration of 0.25 M. It transpired that NCS did not dissolve in DCM at rt to give a concentration of 1.0 M. After adding to a flask with DCM, it remained undissolved at the bottom. By adding an excess amount to 10 mL of DCM and stirring for ten minutes, then filtering off and concentrating the mixture it was established that the maximum concentration of NCS in DCM was around 0.41 M. Consequently, the reaction was run with both the amine 273 and the NCS as 0.4 M solutions in DCM. A 5 mL reactor volume was chosen as this would keep the amount of ‘active’ N-chloroamine to a minimum. Using the PTFE tubing that was described before, with an I.D of 1/32\textsuperscript{nd} of an inch, over 10 m of tubing was required to give a reactor volume of 5 mL. As with the previous reactor, an extra meter of tubing was added to give 50 cm at each end for transport to and from the reactor.

Once connected the reaction was run at a rate of 1 mL min\(^{-1}\), and after discarding the first two reactor volumes, the reaction mixture was collected in 5 mL aliquots. Pleasingly, the reaction had gone to full conversion by TLC analysis after the first reactor volume. Only five reactor volumes were run in total, giving a yield of 61% and a productivity of 2.69 g h\(^{-1}\). When compared with the individual batch process, this was a massive improvement as the batch chlorinations when scaled above ~750 mg tended to have much lower yields (see Scheme 2.2) (Table 3.7).

![Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conc. (M)</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>0.2</td>
<td>5</td>
<td>61%</td>
<td>2.69</td>
</tr>
</tbody>
</table>

*Table 3.7*

The STY for the chlorination reaction above was calculated. The average mass of the product for one reactor volume of 0.005 L was 0.224 g and with a residence time of 0.083 h the STY was 540 g L\(^{-1}\) h\(^{-1}\).

With conditions established for N-chlorination in flow, a two-step reactor was then designed. As there was an excess 50 cm of tubing from both reactors (photochemical and chlorination) at the end, the two previous reactors were combined. Additionally, a second syringe pump
was required to pump the MeSO$_3$H solution in DCM into the reaction. To enable this, another stainless steel junction would be used to connect to it to the chlorination solution, and then these combined into the photochemical reactor made of FEP tubing.

As was seen with the chlorination reaction, the concentration limit of NCS in DCM was 0.4 M. If this was used in the combined reactor, this would limit the total concentration of N-chloroamine 255 to 0.1 M, as the solution would double in volume twice, therefore limiting productivity by 2.5 times compared with the individual reactor. To try and avoid this, several co-solvent mixtures were used to try and dissolve NCS. The first solvent tried was EtOAc, as conversion was seen when it tested during the optimisation of the batch reaction (see Table 2.1). This however made no difference, and NCS proved to be even less soluble in EtOAc then in DCM. Toluene was also tried, but led to the same results. It was found that NCS was soluble in MeCN, a solvent that had not been tried in the photochemical reaction. A 40% solution by volume of MeCN in DCM completely solubilised NCS. With a 1.0 M solution of NCS, the reactor was then set up.

As with the previous reactor, a 6.0 M solution of MeSO$_3$H in DCM was used and placed on the second syringe pump. The initial flow rate of the first syringe pump was set to 0.25 mL min$^{-1}$, as this would double after the first junction, leaving the first reactor with a flow rate of 0.5 mL min$^{-1}$ and a residence time of 10 minutes. This would then double again when the MeSO$_3$H solution was added at the second, giving a final flow rate of 1 mL min$^{-1}$ in the photochemical reactor, with a residence time of 5 minutes. Unfortunately, no desired product was obtained from this reaction. This was most likely due to the MeCN that was present as a solubilising agent for the NCS (Table 3.8, entry 1). After this initial result, it was decided to proceed without a solubilising agent and to just run the reaction at 0.1 M final concentration in the photochemical reactor. Due to the predicted concentration in the final reactor, it was decided that a 2.0 M solution of MeSO$_3$H would be used as this would give a 1.0 M solution in the final reactor, equalling 10 equivalents with respect to the N-chloroamine 255 which was equivalent to that used in the batch reactions. Running these conditions did lead to some product formation, however after reaching steady state was obtained as approximately a 1:1.5 mixture with the starting material 273, which was determined by analysis of the $^1$H NMR spectrum (Table 3.8, entry 2). This could have been due to several factors. First, the acidity of the MeSO$_3$H solution may have been too low to fully protonate the N-chloroamine 255, thereby photolysis of the N-chloroamine 255 would just lead to amine formation and no reaction. Secondly, there may not have been enough NCS to fully chlorinate the amine 273 in the first place meaning no reaction would take place anyway. The first, and only, parameter that was changed was the concentration of the MeSO$_3$H solution. This was doubled to a 4.0 M solution in DCM which would therefore give a concentration of 2.0 M in the photochemical
reactor. This did increase the conversion to a 2:1 ratio in favour of the desired product 256, according to the $^1$H NMR spectrum (Table 3.8, entry 3). The concentration of MeSO$_3$H was once again increased, this time to a 6.0 M solution in DCM and half this in the final reactor. The conversion increased again, this time giving a 4:1 conversion in favour of the desired product 256 (Table 3.8, entry 4). Finally, increasing the concentration of MeSO$_3$H again to 8.0 M, and 4.0 M in the photochemical reactor, gave a conversion of >10:1 by analysis of the $^1$H NMR spectrum. From this run, eight reactor volumes were collected and combined then purified. This gave an isolated yield of 34%, which equated to a productivity of 0.29 g h$^{-1}$ (Table 3.8, entry 5).

The productivity was around four times lower than that seen for the isolated photochemical reactor where $N$-chloroamine 255 was introduced directly into the instrument, but there are a few considerations. First, the second reactor was limited by the maximum concentration of NCS in DCM being 0.4 M and with no suitable co-solvent found, the concentration of the $N$-chloroamine 255 in the final reactor was 2.5 times lower. Had this been at the same concentration, arguably the productivity could have been up to 2.5 times higher, which would have been around 0.75 g h$^{-1}$. Secondly, in comparison to the batch equivalent, the ‘one-pot’ process gave a yield of 60% and the combined two-stage reactor a yield of 34%. Referring to the reasoning again that a mono-layered FEP reactor reduces yield, on average by 20%, this could potentially have been improved with a triple-layered FEP reactor, and an increased absorbance of the UV light. Nonetheless, a production of nearly 300 mg h$^{-1}$ is still much more

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent$^a$</th>
<th>Amine (M)</th>
<th>NCS (M)</th>
<th>MeSO$_3$H (M)</th>
<th>Conversion$^b$</th>
<th>Yield (%)$^c$</th>
<th>Prod. (g h$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40% MeCN/DCM</td>
<td>1.0</td>
<td>1.0</td>
<td>6.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>DCM</td>
<td>0.4</td>
<td>0.4</td>
<td>2.0</td>
<td>1:2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>DCM</td>
<td>0.4</td>
<td>0.4</td>
<td>4.0</td>
<td>2:1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>DCM</td>
<td>0.4</td>
<td>0.4</td>
<td>6.0</td>
<td>4:1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>DCM</td>
<td>0.4</td>
<td>0.4</td>
<td>8.0</td>
<td>&gt;10:1</td>
<td>34</td>
<td>0.29</td>
</tr>
</tbody>
</table>

$^a$ Percentage mix of solvent in second reactor
$^b$ Conversion determined by $^1$H NMR
$^c$ Isolated yield after purification

Table 3.8
efficient than the two individual batch processes and shows promise for this technology, with some optimisation.

As this was a two-stage flow reactor the STY had to take this into consideration for the calculation. The volumes of both the ‘dark’ and ‘light’ reactors were combined, and the residence times were also combined. The mass of the product was taken from the second reactor as no product was isolated after the chlorination reaction. The average mass per reactor volume was 0.024 g, the combined reactor volume was 0.01 L and the residence time was 0.25 h. This gave a STY of 9.6 g L\(^{-1}\) h\(^{-1}\). This productivity is much lower than the two individual reactors (chlorination reactor STY, 540 g L\(^{-1}\) h\(^{-1}\); photochemical reactor STY, 248 g L\(^{-1}\) h\(^{-1}\)), however as already discussed there were factors that lowered the productivity of the two-stage reactor, primarily the reduced operating concentration due to limited NCS solubility.

3.3.4 Natural Product Synthesis in Flow: Angustureine

To test the application of the two-stage photochemical flow reactor, an attempt to synthesise the alkaloid natural product angustureine was attempted. As shown previously (see Scheme 3.3), the THQ 3 had been formed using the one-pot process and was obtained in 50% yield. This was slightly lower than the individual steps, involving isolation of the N-chloroamine (chlorination = 75%, photolysis = 69%, combined = 52%), but as stated earlier this still removed an isolation and purification step improving the overall efficiency of the reaction.

Using the same photochemical reactor described above, the natural product synthesis was attempted in flow. The same optimised conditions that were used for the synthesis of the THQ 256 in flow were applied directly to the synthesis of angustureine 3. The mass for the desired product was observed by LC-MS analysis, however multiple other products were also observed, including the mass for starting material, the mass for the starting material plus chlorine and the desired product plus chlorine was also observed amongst other unidentified side-products. Ten reactor volumes were run through, with the first two discarded again and the next eight combined, worked up and purified by flash chromatography. This led to only 65 mg of desired product being isolated, which was equivalent to a 15% yield and a productivity of 98 mg h\(^{-1}\) (Table 3.9, entry 1). Retrospective analysis of the starting material showed several impurities, probably from degradation of the product over a long period. A new sample of the precursor amine 373 was synthesised and the reaction was run again. As with the previous runs, the first two reactor volumes were discarded and a subsequent eight were collected. Despite the synthesis of fresh starting material, the LC-MS analysis displayed the same number of impurities. After ten reactor volumes were run through the system, the last eight were once again combined, worked up and purified by flash chromatography to give
110 mg of desired product, which was an isolated yield of 25% with the respective productivity for this process 165 mg h\(^{-1}\) (Table 3.9, entry 2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Yield (%)(^a)</th>
<th>Productivity (g h(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>0.098</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>0.165</td>
</tr>
</tbody>
</table>

Table 3.9 *Isolated yield after purification*

The yield obtained for the two-stage flow synthesis of angustureine was considerably lower than the equivalent one-pot batch process, with the yield for the flow reaction being half that of the batch. Despite there being no evidence of the HLF product seen in the batch reaction (see Scheme 2.28), one of the masses observed by LC-MS analysis was the mass for the HLF 1,5-hydride abstraction product 460 (Scheme 3.4).

The conditions for the flow reaction may have helped to promote the side reaction, which could be a possible explanation for the considerable reduction in yield.

The space time yield for this reaction was calculated. An average yield of 0.014 g per reactor volume, a total reactor volume of 0.01 L and a residence time of 0.25 h gave a STY of 5.5 g L\(^{-1}\) h\(^{-1}\).
3.4 Conclusion

The photochemical reaction that was described and optimised in Chapter 2 was shown to work in a continuous photochemical reactor. The reactor was built with an immersion well reactor that housed the medium-pressure Hg lamp and FEP tubing, with an I.D of 2.7 mm, was wrapped around the immersion well and used as the reactor. Syringe pumps were used to create the pressurised system, and the N-arylation was optimised to give a productivity of 1.24 g h\(^{-1}\), with a STY of 248 g L\(^{-1}\) h\(^{-1}\).

The chlorination of the secondary amine was also shown to work in a ‘dark’ reactor. The reactor was constructed from PTFE tubing this time with an I.D of 1/32\(^{nd}\) of an inch and allowed for a highly efficient continuous synthesis of N-chloroamine 255, giving a productivity of 2.69 g h\(^{-1}\) and a STY of 540 g L\(^{-1}\) h\(^{-1}\).

The two reactors were then combined to allow for direct formation of the THQ 256 in a two-stage continuous reactor, which required no isolation of the N-chloroamine 255. The productivity of the process was limited by the solubility of NCS in DCM not being able to be higher than 0.41 M. Nevertheless, a productivity of 0.29 g h\(^{-1}\) was obtained, with the STY being calculated as 9.6 g L\(^{-1}\) h\(^{-1}\).

The natural product angustureine 3 was then synthesised in the two-stage flow reactor, however the productivity was much lower than the previous reactions with the highest productivity obtained being 0.165 g h\(^{-1}\), and the corresponding STY being 5.5 g L\(^{-1}\) h\(^{-1}\). The lower yield may have been due to the formation of a side product 460 arising from the HLF reaction.
3.5 Future Work

Despite the efficiency of the continuous photochemical reaction compared with the batch processes, some of the waste streams were still quite high. For example, there is one molar equivalent of succinimide produced for every mole of \( N \)-chloroamine that is produced. Looking at more environmentally benign chlorination methods, that are compatible with the \( N \)-arylation reaction conditions, could decrease the environmental impact of this process. Blacker et al. demonstrated that a range of dialkylamines could be chlorinated in a biphasic static mixer flow reactor.\(^{166}\) This particular example employed bleach as the chlorinating agent so would not be compatible directly with the acidic reaction mixture employed in the photochemical reactor, but something similar could be applied.

Moody and co-workers showed that polymer supported iodamine-T could be used in the flow synthesis of diazo compounds from the respective hydrazone.\(^{167}\) As demonstrated (see Scheme 2.2), chloramine-T can be employed in the chlorination of dialkylamines. Using a polymer supported chloramine-T, this could be used in a continuous chlorination reactor to produce \( N \)-chloroamines, which would produce the desired precursors to the \( N \)-arylation reactions with no by-products from the previous reaction and wouldn’t be limited by the chlorinating agent’s solubility. Chloramine-T can also be regenerated using bleach, which would give a recyclable reagent.

Purification of the reaction was still required with the flow system. Despite being a streamlined synthetic process, having to work up the reaction mixture to remove the acid residues adds more labour and makes the process less attractive to industry. The Gaunt group have used an ion exchange resin, similar to the SCX cartridges that were used in some of the purifications described earlier (see experimental), to purify amines produced in a continuous reactor.\(^{165}\) After passing the reaction mixture over the supported sulfonic acid residues, methanolic ammonia was used to collect the desired amines. Applying a similar set up could alleviate the need for a work up.

As with the batch reactions, compounds that contain chiral centres produced by this methodology are produced as racemic samples. Being able to convert these samples to single enantiomers would mean high-value enantiopure samples could be obtained; for example the natural product angustureine 3. Enzyme-mediated deracemizations are a common method that can been used in the production of chiral amines (see Chapter 4).
Chapter 4  Biotransformations

4.1  Introduction to Biotransformations

4.1.1  Biotransformations in Industrial Processes

Biotransformations are reactions that use enzymes as catalysts instead of using conventional chemicals. This class of reactions is attractive to synthetic chemists as they offer frequently unrivalled levels of chemo- and stereoselectivity and can often allow remote functionalisation in one step of bonds that are usually unreactive. Two examples of the use of biocatalysis in industry are shown below. Atorvastatin 461 is a cholesterol-lowering drug and aprepitant 462 is a NK1 receptor antagonist which helps with chemotherapy-induced nausea. Both compounds use biotransformations in the synthesis of key intermediates (Figure 4.1).

![Figure 4.1](image)

Intermediates for atorvastatin 461 were synthesised using biocatalytic transformations. Burk, Greenberg and co-workers used deoxyribose-5-phosphate aldolase (DERA) in a one-pot tandem aldol process to form a 6-membered lactol intermediate 465 from acetaldehyde 463 and chloroacetaldehyde 464 achieving an ee of >99.9% and de of 99.8%. This was then oxidised chemically to the lactone intermediate 466 that was used in the next step (Scheme 4.1).

![Scheme 4.1](image)

An alcohol dehydrogenase from *Rhodococcus erythropolis* (ADH RE) was used to achieve the stereoselective reduction of ketone 467 to alcohol 468 in the synthesis of aprepitant 462. The alcohol 468 was obtained with ee of >99%, with the other enantiomer accessible by
switching to ketoreductase 101 (KRED) instead. The Space Time Yield of this reaction is quoted as being 260 g L\(^{-1}\) d\(^{-1}\) (Scheme 4.2).\(^{170}\)

![Scheme 4.2]

Despite these examples of biocatalytic methods being used in industry,\(^{171}\) the uptake of these has been slow and this has been attributed to limited number of enzymes that are commercially available and a lack of operational simplicity.\(^{172}\)

### 4.1.2 Directed Evolution of Enzymes

Recent advances in genomics has enabled directed evolution of biocatalysts, which has increased the toolkit which chemists can choose from when designing enzyme-mediated chemical reactions.\(^{173}\)

Random mutagenesis is a technique that can be used to randomly alter vast amounts of the genetic code of an organism then using assays determine which mutant is the most active, then repeat this until high activity and selectivity is obtained. Reetz and Jaeger demonstrated one of the earliest examples of this, with the improvement in the activity of a wild-type (wt) lipase which was isolated from the bacteria *Pseudomonas aeruginosa*. The wt enzyme gave an \(ee\) of 2% in the hydrolysis of \(p\)-Ns-2-methyldecanoate 469; however after four rounds of mutations the fourth generation mutant gave an \(ee\) of 81% (Scheme 4.3).\(^{174}\)

![Scheme 4.3]

Site-directed mutagenesis is another useful genetic engineering technique which allows specific point changes in a sequenced genome of an organism. These kinds of procedures mean large libraries of mutant enzymes can be produced through a variety of methods that increases the activity of the enzyme to the substrate.
Monoamine oxidase (MAO) is from a class of enzymes called oxidoreductases, and can be used specifically for the selective oxidation of a range of simple amine molecules. MAO-N was isolated from *Aspergillus niger* and subsequently cloned and expressed in *E. coli*.[175,176] The wt enzyme was able to oxidise simple amines such as *n*-butylamine and benzylamine but had low activity towards chiral amines.[168]

In 2002 Turner *et al.* detailed an *in vitro* evolution of this wt enzyme to increase activity towards chiral amines, with α-methylbenzylamine 471 being the model substrate chosen.[177] The mutant enzymes were determined by a colourimetric assay that was developed to detect hydrogen peroxide, which is produced as a by-product from the oxidation of the amine to the imine by the enzyme. Using peroxidase to capture the peroxides being released and coupling them with 3,3′-diaminobenzidine, the product was an insoluble pink compound that could be easily identified on the colony agar plates. In this first sequence the authors stated from around 150,000 clones that were produced, 35 clones were identified that had improved activity against the model substrate, so they were grown on a small scale and assayed against α-methylbenzylamine. Of these 35 the best 27 clones were further studied, and this subsequent investigation revealed that two of these clones (which happened to be identical) were superior to the others produced with this technique. The mutant enzyme was used and led to racemic α-methylbenzylamine 471 being deracemized to give exclusively the (R)-enantiomer, using NH₃-BH₃ as a non-selective reducing agent in an iterative process of selective oxidation of the (S)-enantiomer then non-selective reduction, halving the amount of substrate that will react with the enzyme with every turnover. This resulted in an *ee* of 93% and 77% isolated yield after 24 h (Scheme 4.4).

![Scheme 4.4](image)

The deracemization reaction works in a counter-intuitive manner. Using an enzyme that is selective for one enantiomer will result in enrichment of the other. Using the above reaction as an example, MAO-N is an (S)-selective enzyme, so will selectively oxidise (S)-enantiomers to the imines which results in the (R)-enantiomer becoming enriched (Scheme 4.5).
Turner and co-workers demonstrated the usefulness of directed evolution with another round of mutations to the enzyme obtained from the previous study, which increased the substrate specificity and retained the high levels of enantioselectivity. This allowed cyclic secondary amines to be deracemized, such as 2-methyltetrahydroisoquinoline shown below (Scheme 4.6). The reactions were only performed on an analytical scale so no yields or conversions were reported.

Further development of this strain of enzyme by the Turner group allowed for a wide range of amines to be deracemized. The variant called MAO-N D5 demonstrated good activity towards a range of nitrogen-containing functional groups, including O-alkyl-N-hydroxylamines and tertiary amines. The oxidation of tertiary amines proceeded through the formation of an iminium intermediate, and was exemplified with the complete deracemization of nicotine in 24 h. Preparative deracemization (0.4 g scale) of this substrate was also carried out, affording (R)-nicotine in 75% yield with ee of >99% after 24 h (Scheme 4.7).

In 2008 Brzozowski and Grogan solved the structure of the MAO-N D5 variant enzyme. They discovered that the D5 variant exists as a functional dimer of two proteins. They found that compared with the wt enzyme there were five mutations. Specifically, most of the mutations seemed to be in active sites where the reactions would take place (Figure 4.2).
As a result of these studies multiple strains have been engineered, using directed mutagenesis and the knowledge of the active site. Turner et al. have mutated the D5 enzyme further with rational structure-guided engineering that has allowed for specific mutations in the enzyme to give rise to more active enzymes. Benzhydrylamines was a substrate class that was not tolerated by the D5 variant. The group reasoned that increasing the volume of the active site would allow larger substrates with two aryl groups such as benzhydrylamine to fit. Modelling of α-methylbenzylamine 471 into the active site of the MAO-N D5 variant led to the identification of two residues that could increase the active site volume. The result of this was the production of the D10 variant, which had a single mutation which changed a residue within the active site. The mutations from another variant, D9, were combined with the single mutation in D10 to give the optimal mutant D11. The D11 mutant was applied in the full deracemization of benzhydrylamine derivative 474 and for 2-phenyltetrahydroisoquinoline 476 as well. Interestingly, the enzyme was (S)-selective for the tetrahydroisoquinoline, whereas all previous reported substrates with MAO-N had (R)-selectivity. Both these products are intermediates for the drugs levocetirizine 475 and solifenacin 477 respectively (Scheme 4.8).
The variants of the MAO-N enzyme allowed for a broad range of 1˚, 2˚ and 3˚ amines to be deracemized with high stereoselectivity but all were (S)-selective. This means that the enzymes would only oxidise the (S)-enantiomers and would not oxidise the (R)-enantiomer, resulting in enantiopure samples of the (R)-enantiomer. Further development of other classes of amine oxidases allowed access to complimentary enantiomers and also increased the substrate scope.

4.1.4 Other Amine Oxidases: 6-Hydroxy-α-nicotine Oxidase (6-HDNO) and Cyclohexylamine Oxidase (CHAO)

Some other amine oxidases that have been identified and used in enzyme-mediated deracemizations include 6-hydroxy-α-nicotine oxidase (6-HDNO), which gives opposite selectivity to MAO-N and is (R)-selective, and cyclohexylamine oxidase (CHAO) which is (S)-selective like MAO-N.

4.1.4.1 6-Hydroxy-α-nicotine Oxidase (6-HDNO)

6-HDNO was identified as a key enzyme in the metabolism of nicotine to myosmine by Decker and Dai. The pathway for metabolism was initially thought to proceed through the formation of an intermediate enamine species and not an iminium; however Turner et al. used deuterium labelling to prove the pathway must proceed through an iminium intermediate in the oxidation step. With the suitability of the enzyme for deracemization reactions established, mutagenesis was used to produce mutant strains of the enzyme. The wt and mutant were screened against 34 amines, and activity increased from eight hits with the wt enzyme to 19 with the mutant. This gave access to a synthetically useful amine oxidase that was enantiocomplementary to MAO-N variants, being (R)-selective.

The utility of the 6-HDNO mutant was demonstrated in a one-pot two-enzyme sequence combining the oxidase with an imine reductase (IRED) for full conversion of 2-substituted...
pyrrolidines, piperidines and other saturated \(N\)-heterocycles to single enantiomers (Scheme 4.9).\(^{185}\)

![Chemical structure](image)

**Scheme 4.9**

4.1.4.2 **Cyclohexylamine Oxidase (CHAO)**

CHAO, first isolated by Hasegawa et al. when identified in the biodegradation of cyclohexylamine by *Brevibacterium oxydans* IH-35A,\(^{186}\) was engineered for activity towards a range of substituted alkyl and aryl amines by Lau and co-workers.\(^{187}\) This was further shown to work on a wide range of amines, with 38 substrates tested on the wt CHAO and five strains of mutated CHAO.\(^{188}\) One of the key results of the study was deracemization of 1-aminotetraline \(478\), an intermediate in the synthesis of norsertraline \(479\) (a structurally similar compound to the anti-depressant sertraline) which is currently undergoing clinical trials for treatment of central nervous system disorders. The previous route employed *Candida* lipase CAL-B and a Ru catalyst with heating at 90 °C for 72 h necessary to obtain full deracemization. Using the mutant CHAO variant the same results were obtained after 12 h at 30 °C (Scheme 4.10).

![Chemical structure](image)

**Scheme 4.10**

Further work by this group demonstrated that THQs were also tolerated by the CHAO enzyme, where further genetic modifications of the previously described enzymes gave novel biocatalysts with activity towards several 2-substituted THQs.\(^{189}\) The substitution included 2-Me, 2-allyl, 2-benzyl and 2-Ph residues. Whilst there was very little activity observed for any of the enzymes with phenyl at the 2-position, better activity was observed with all three other substrates (Scheme 4.11).
Scheme 4.11

Preliminary work by both the Turner group and the Marsden group had shown that some other THQ substrates could be tolerated by the enzymes. Repetition of the above literature (see Scheme 4.11) gave equivalent results, with deracemization of the 2-Me and 2-benzyl substrates observed by the CHAO enzyme. 2-EthylTHQ was partially deracemized with both 6-HDNO and MAO-N D6 to afford ee’s of 69% and 78% respectively. No activity was observed with 2-PhTHQ. Interestingly the homobenzyl substrate 481 was partially deracemized after 48 h by the CHAO enzyme, giving an ee of 68% (Scheme 4.12). This molecule has the same core structure as several of the natural products that were isolated by Jacquemond-Collet et al. in 1999. The absolute stereochemistry of the final product was not assigned.

Scheme 4.12
4.2 Aims

Despite many examples of 2-substituted saturated $N$-heterocycles being deracemized under enzymatic conditions, to the best of our knowledge the above examples are the only known resolutions of THQs using biocatalysts.$^{189}$

Several of the substrates produced from the photochemical methodology described earlier (Chapter 2) were deemed suitable for testing against the mutant amine oxidase enzymes produced by the Turner group at the University of Manchester. Through the photochemical $N$-arylation reaction a range of 1,2-disubstituted THQs had been synthesised, as well as the tricyclic pyrrolidine and piperidine derivatives (Scheme 4.13).

![Scheme 4.13](image)

Primarily, the $N$-substituted series would be tested in the deracemization reactions to establish whether they would be tolerated by the enzymes. Turner et al. had demonstrated that iminium formation could be achieved by the MAO-N enzymes in the deracemization of nicotine derivatives (see Scheme 4.7).$^{180}$ Once activity had been established on an analytical scale, a key substrate would be scaled up to a preparative scale.
4.3 Biotransformation Results

4.3.1 N-Substituted THQ Series

The substrates were screened under the standard conditions used within the Turner group for the deracemization reactions. In the case of the 2-PhTHQ 340 and 2-VinylTHQ 341 racemic samples were not available so enantiomeric samples were used in the hope of seeing a change in ee. Previous studies in the Turner group had determined that MAO-N D9 was the most active variant towards THQ substrates so was chosen for these studies. CHAO and 6-HDNO were also tested against the substrates. The initial reactions were run on analytical scales, meaning only enough material was obtained for a HPLC sample. Using these analytical scale reactions would establish whether there were any substrates for the enzymes, and promising results would be identified and scaled up to a preparative scale.

Disappointingly, no activity was observed with any enzyme for most of the substrates. The 2-PhTHQ 340 (Table 4.1, entry 1), 2-vinylTHQ 341 (Table 4.1, entry 2), 2-pentylTHQ 3 (the natural product angustureine; Table 4.1, entry 3) and 1-benzyl-2-methylTHQ 347 (Table 4.1, entry 4) remained unchanged after 48 h deracemization with all three enzymes. The 2-MeTHQ 342 did undergo some deracemization with an ee of 33% obtained using CHAO and trace activity with both MAO-N D9 and 6-HDNO (Table 4.1, entry 5). These results follow with the previously observed results, in that 2-MeTHQ was the most active towards the amine oxidases whereas no activity was observed with 2-PhTHQ. The best results were observed with the tricyclic molecules 395 and 400. The piperidine derivative 400 had an ee of 41% with CHAO, however this was after being left for 96 h as opposed to 48 h. An ee of 31% was obtained for the same substrate using 6-HDNO also after 48 h. No activity was observed for MAO-N D9 (Table 4.1, entry 6). The pyrrolidine derivative 395 however had undergone full deracemization after only 24 h with both CHAO and 6-HDNO. After 48 h an ee of 78% was recorded with MAO-N D9 (Table 4.1, entry 7).
The pyrrolidine substrate \(395\) was chosen as the most promising substrate for scaling up to preparative scale from the initial screen. As stated earlier (see Scheme 2.34) this substrate is an intermediate in the synthesis of the natural product gephyrotoxin. Using enzymatic deracemization of this substrate could allow for a synthesis of enantiopure gephyrotoxin and analogues of the molecule.

The preparative scale reaction of the pyrrolidine substrate \(395\) was run using the CHAO enzyme as this had given the most promising results of the analytical scale reactions. The reaction was run on a 125 mg scale, and despite the fact the product was enantiopure, a yield of only 26% was obtained. Enough material was obtained to record the specific rotation of the molecule and assign it as the \((R)\)-enantiomer, with an \([\alpha]_D^{25}\) of +24.2 (c 0.80, THF). This is in

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*Table 4.1* Reaction conditions: Amine (5 mM), KPO<sub>4</sub> buffer (1 M, pH 7.4), NH<sub>3</sub>·BH<sub>4</sub> (50 mM), cells containing oxidase (100 mg mL<sup>-1</sup>), incubated at 30 °C with 250 rpm agitation. *ee determined by chiral HPLC*<sup>3</sup>Starting ee of 66% *Starting ee of 28%*<sup>4</sup>After 96 h

The pyrrolidine substrate \(395\) was chosen as the most promising substrate for scaling up to preparative scale from the initial screen. As stated earlier (see Scheme 2.34) this substrate is an intermediate in the synthesis of the natural product gephyrotoxin. Using enzymatic deracemization of this substrate could allow for a synthesis of enantiopure gephyrotoxin and analogues of the molecule.

The preparative scale reaction of the pyrrolidine substrate \(395\) was run using the CHAO enzyme as this had given the most promising results of the analytical scale reactions. The reaction was run on a 125 mg scale, and despite the fact the product was enantiopure, a yield of only 26% was obtained. Enough material was obtained to record the specific rotation of the molecule and assign it as the \((R)\)-enantiomer, with an \([\alpha]_D^{25}\) of +24.2 (c 0.80, THF). This is in
accordance with the recorded literature \([\alpha]_D^{25}\) of +75.2 (c 0.88, THF) (Scheme 4.14). The lower yield suggests that despite selectivity for the (S)-enantiomer that some other mechanism may have been oxidising the (R)-enantiomer, as if there was only selectivity for the (S)-enantiomer then the yield would have been 50%. Studies by Voorman et al. stated that there are several modes of metabolism of THQs leading ultimately to quinoline and quinolinium species.\(^{192}\) If proceeding through one of these metabolic pathways the product would have been lost in the aqueous layer explaining the poor mass recovery. If a second oxidation is occurring at a faster rate than the reduction with ammonia-borane this would be why the aromatised side-product is formed rather than the desired THQ. The oxidation to the quinolinium could be a highly favourable process that occurs in air, or could also be another enzyme-mediated oxidation.

Scheme 4.14

4.3.2 \(N\)-Unsubstituted THQ Series

With the lack of activity shown towards the \(N\)-substituted THQs it was decided that several \(N\)-unsubstituted substrates would be prepared and tested under biocatalytic conditions. From the preliminary enzymatic studies performed by Marsden and Turner,\(^{190,191}\) one of the key results was the 2-homobenzyl substrate \(481\) which was partially deracemized after 48 h by the CHAO enzyme (see Scheme 4.12). As this has the same core structure as some members of a family of natural products, the de-methylated analogues of these substrates were identified as suitable targets to expand the scope of the enzymatic deracemizations. The natural product angustureine 3 was one of the substrates that was tested and gave no activity in the \(N\)-substituted series described earlier. (Figure 4.3).

Figure 4.3

The photochemical methodology could not be used to make the de-methylated analogues of these natural products for two reasons:
1. Only secondary $N$-chloroamines could be used in the reactions.
2. The sidechains of three of the substrates contained electron-rich aromatic groups, meaning they would chlorinate during the $N$-arylation photolysis reactions.

In 2008 Marsden et al. reported the synthesis of quinolines 486 from $o$-aminophenylboronates 483 in a Rh(I)-catalysed conjugate addition-condensation-oxidation process proceeding through dihydroquinoline 485.193 The group also later demonstrated that the dihydroquinoline intermediates 485 formed in this reaction could be reduced in a diastereoselective manner to afford 2,4-disubstituted THQs 487 (Scheme 4.15).194

![Scheme 4.15](image)

Despite numerous examples of substituted enones being described by the authors, there was only one unsubstituted vinyl ketone example discussed. Use of vinyl ketones 488 would give access to racemic 2-substituted THQs 489. Unpublished work from the Marsden group has extended this methodology to several other vinyl ketones.191 It was found that heating the reaction mixture at 50 °C was more effective for vinyl ketones, and also running the reaction at a higher dilution to prevent polymerisation of the vinyl ketone starting materials. The reaction was optimised using the commercially available ethyl vinyl ketone (Scheme 4.16).191

![Scheme 4.16](image)

This was an appropriate way to construct the $N$-unsubstituted precursors of the family of natural products identified as suitable substrates for the biotransformations.
4.3.2.1 Substrate Synthesis

Firstly, the vinyl ketone starting materials needed to be synthesised. The vinyl ketones 490 were envisaged as coming from the oxidation of an allylic alcohol, which could be obtained from the Grignard addition of vinylmagnesium chloride to hydrocinnamaldehyde derivatives 491. These substrates could be obtained from oxidative cleavage of the butene 492, which in turn could be synthesised from the benzaldehyde 493 with a subsequent reduction of the benzyl alcohol (Scheme 4.17). The precursor for angustureine 3 could be obtained using hexanal as a starting material.

The suitable starting materials were all commercially available, with the TBS-protected phenol chosen in place of the free phenol for galipeine as the use of an unprotected hydroxyl group would not be compatible with Grignard reagents. The chosen route began with addition of allylmagnesium chloride to the benzaldehyde derivatives 494a–c (Table 4.2, step (i)). All three of these reactions proceeded in near quantitative yields giving the homoallylic alcohols 495a–c. The next step was reduction of the benzyl alcohol to yield the butene derivatives 496a–c. The first set of conditions trialled, using two equivalents of TFA and Et3SiH at 0 °C gave a complex mixture of products. This was likely due to the addition of TFA first at the relatively high temperature used in the reaction. The carbocation intermediates formed will have been highly stabilised due to the electron-rich aromatic groups, therefore upon addition of acid could have reacted through the benzylic position. A procedure by Salomon et al.195 used the same reagents, however the temperature was lowered to −50 °C and a dropwise addition of TFA to a solution of the alcohol and silane ensured the reaction proceeded smoothly to afford the desired products 496a–c in yields of 90%, 70% and 90% respectively (Table 4.2, step (ii)). An attempt to convert the alkene 496a directly to aldehyde 497a through ozonolysis failed, with a complex mixture of products obtained. This may have been due to the electron-rich nature of the aromatic ring as ozone is known to oxidise electron-rich aromatics. An alternate route using OsO4 and NaIO4 was used instead. Dihydroxylation afforded the diols 497a–c in excellent yields of 91%, 89% and 87% respectively (Table 4.2, step (iii)). Oxidative cleavage to furnish the aldehyde also proceeded in high yields for the
dimethoxy derivative, 93%, and the methylenedioxy derivative, 88%, but a lower yield of 52% was obtained for the TBSO substrate (Table 4.2, step (iv)). The lower yield for the TBSO substrate 498c was attributed to material lost on purification. All three substrates were easily converted to the allylic alcohols 499a-c through addition of vinylmagnesium chloride in good yields (Table 4.2, step (v)). A procedure was found for the oxidation of allylic alcohols 499a-c to vinyl ketones 500a-c using IBX. Simply refluxing in EtOAc for 16 h was enough to convert the substrates completely to the desired products by analysis by TLC. Lower yields were observed for both the dimethoxy substrate 500a and the methylenedioxy substrate 500b of 55% and 49% respectively. This was due to issues with benzoic acid, which is used as a stabiliser for commercial IBX, co-eluting with the product during purification by flash chromatography. It was found that washing the organic phase with aqueous 2 M NaOH removed the benzoic acid impurities. An improved yield of 82% was obtained for the OTBS substrate 500c (Table 4.2, step (vi)).

The synthesis of the precursor for angustureine 3 was simpler with a pentyl chain all that was required. Addition of vinylmagnesium chloride to hexanal 501 afforded the allylic alcohol 502 in a yield of 69%. Despite complete conversion by TLC, the slightly lower yield was observed due to volatility of the product and as a consequence some being lost during
concentration after purification. Oxidation with IBX afforded pentyl vinyl ketone 503 in a good yield of 79\% (Scheme 4.18).

\[ \text{VinyMgCl (1.5 eq.) THF, 0 °C, 1 h} \rightarrow \begin{array}{c} \text{O} \\ \text{OH} \end{array} \text{IBX (1.2 eq.)} \rightarrow \begin{array}{c} \text{OH} \\ \text{IBX (1.2 eq.)} \end{array} \rightarrow \begin{array}{c} \text{O} \\ \text{501} \end{array} \rightarrow \begin{array}{c} \text{502} \\ 69\% \end{array} \rightarrow \begin{array}{c} \text{503} \\ 79\% \end{array} \]

\[ \text{Scheme 4.18} \]

With the four starting materials in hand they were subjected to the Rh(I)-catalysed conjugate addition reaction with 2-aminophenylboronic acid. Analysis of all the reaction mixtures by LC-MS after 16 h showed full conversion of the starting materials to the dihydroquinoline intermediate. At this point, STAB was added and the mixture was stirred for a further 1 h. The work up was simply concentration in vacuo, followed by purification by flash chromatography. Unfortunately, the three substrates with aromatic functionality appended were obtained with what appeared to be the same impurity in each sample after purification by flash chromatography, so were further purified by SCX cartridge. This did remove the impurity, which could not be identified by LC-MS analysis. Pleasingly all three substrates were obtained in adequate to good yields after this. The cuspareine precursor 506 was obtained in 51\% yield, the galipinine precursor 507 in 32\% and the OTBS protected galipeine precursor 508 in 64\% yield. The lower yields observed are most likely due to the increased amount of purification steps that were required, with a second chromatographic step applied to 506 and 507. The angustureine precursor 509 was obtained in 65\% yield, and was performed on a 400 mg scale (Scheme 4.19).

\[ \begin{array}{c} \text{R} \\ \text{B(OH)_2} \end{array} + \begin{array}{c} \text{NH}_2 \\ +\text{Cl} \end{array} \rightarrow \begin{array}{c} \text{KOH (5 eq.)} \\ \text{toluene (0.1 M), 50 °C, 16 h} \end{array} \rightarrow \begin{array}{c} \text{N} \\ \text{504} \end{array} \rightarrow \begin{array}{c} \text{505} \\ 2 \text{eq.} \end{array} \rightarrow \begin{array}{c} \text{506} \\ 51\% \end{array} \rightarrow \begin{array}{c} \text{507} \\ 32\% \end{array} \rightarrow \begin{array}{c} \text{508} \\ 64\% \end{array} \rightarrow \begin{array}{c} \text{509} \\ 65\% \end{array} \]

\[ \text{Scheme 4.19} \]

These reactions provided ample material for trials with the biocatalysts.
4.3.2.2 Biotransformation Results

The substrates were once again screened under the standard conditions for deracemization reactions using amine oxidase on analytical scales. The three enzymes chosen were CHAO, 6-HDNO and MAO-N D9. Based on the homobenzyl derivative 481 having an ee of 68% after 48 h reaction time (Scheme 4.12), this set of reactions was run for 96 h instead of 48 h to allow for full reaction to take place. Of the four substrates, the angustureine derivative was also chosen to be scaled up to a preparative scale using the CHAO enzyme. CHAO was chosen due to the fact it was deemed the most active in the N-substituted derivatives study.

The precursor of galipinine 507 saw no activity with both 6-HDNO and MAO-N D9 returning racemic samples after 96 h. CHAO did deracemize the substrate, with an ee of 70% obtained after 96 h (Table 4.3, entry 1). Similar results were seen with cuspareine 506 with no deracemization with either of 6-HDNO or MAO-N D9 after 96 h, but almost full deracemization observed for CHAO, with an ee of 90% obtained (Table 4.3, entry 2). Much lower conversion was observed for the OTBS protected precursor of galipeine 508, however once again CHAO was the most active enzyme towards the substrate with a low ee of 15% obtained after 96 h (Table 4.3, entry 3). The angustureine precursor 509 saw deracemization with all three of the enzymes but the most active towards the substrate was MAO-N D9 as opposed to CHAO. With MAO-N D9 an ee of 85% was achieved after 96 h, but with CHAO the ee was only 47%. 6-HDNO gave a modest ee of 13%, with the HPLC trace showing that it was selective for the opposite enantiomer (Table 4.3, entry 4).

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*Table 4.3* Reaction conditions: Amine (5 mM), KPO4 buffer (1 M, pH 7.8), NH3·BH3 (50 mM), cells containing oxidase (100 mg mL⁻¹), incubated at 30 °C with 250 rpm agitation 'ee determined by chiral HPLC' *Significant amount of another unidentified product observed in HPLC trace*
Analysis of the HPLC trace of the angustureine precursor 509 showed a significant amount of another product forming, a retention time of around nine minutes, alongside the two enantiomers. This was tentatively suggested to be the fully oxidised quinoline 510 (Figure 4.4).

If the CHAO enzyme was oxidising the substrate to the quinoline 510, this could also lend support to the theory that the N-substituted derivatives were being oxidised fully to the quinolinium derivatives in the biotransformations.

The preparative scale reaction with CHAO led to a similar result. The main component obtained from the reaction was the fully oxidised quinoline 510 in a 37% yield, with only a 5% recovery of the THQ (Scheme 4.20).

The quinoline 510 was identified by comparison of the ¹H NMR data with an authentic sample from the literature, and was confirmed by analysis of the LC-MS showing the mass for the fully oxidised product. The signals present at δ 8.07, 7.78, 7.68, 7.48 and 7.31 correspond to 2-pentylquinoline,¹⁹⁷ with the three signals at δ 6.95, 6.59 and 6.47 representative of 2-pentylTHQ (Figure 4.5).
This suggests that if the extra peak observed in the HPLC is the quinoline 510, then CHAO could be involved in an extra oxidation step to form the fully aromatic species after formation of the dihydroquinoline. In the HPLC traces for 6-HDNO and MAO-N there was trace amounts of the same peak but not any appreciable amount compared with CHAO. This demonstrates that under the right conditions, ammonia-borane could be a suitable reducing agent for the reduction of the imine intermediate so long as it is faster than a second oxidation step. The low recovery could be associated with the problematic work up associated with this reaction.

4.3.2.3 Completion of Natural Product Syntheses

The precursors for galipinine, cuspareine and angustureine were also N-methylated to give the natural products and complete the total syntheses. Details were found in the literature for the N-methylation of the angustureine precursor using K₂CO₃ and MeI, so these conditions were applied to all three substrates. The reactions were heated at 70 °C in sealed vials for 20 h, with all three proceeding in good yields and completing the synthesis of the three natural products (Scheme 4.21).
The completion of these natural product syntheses means that should a suitable set of preparative conditions be found for the biotransformations that an asymmetric synthesis of these substrates could be achieved.
4.4 Conclusions

Two sets of substrates were tested against the mutant amine oxidase enzymes that were developed in the Turner lab at the University of Manchester: the first class were $N$-substituted THQs synthesised using the photochemical methodology described in Chapter 2 and the second $N$-unsubstituted THQs synthesised using a Rh(I)-catalysed conjugate addition/reduction previously described by Marsden et al.

The first set of substrates, the $N$-substituted derivatives, demonstrated minimal activity with most of the compounds however the tricyclic pyrrolidine derivative 395 was fully deracemized by both the CHAO and 6-HDNO enzymes after 48 h, and partially deracemized by MAO-N D9 after 48 h. This substrate was scaled up to a preparative scale however a low yield of 26% was obtained. The material was enantiopure but the low yield may have been due to over-oxidation of the dihydroquinolinium intermediate to yield the aromatised quinolinium product, which would have been lost in the aqueous layer.

The second set of substrates, the $N$-unsubstituted derivatives, were more successful, with three of the natural products deracemized to give ee as high as 90%. CHAO proved to be the most successful with two of the substrates, giving an ee of 70% for the galipinine precursor 507 and 90% for the cuspareine precursor 506. The angustureine precursor 509 had the best results with MAO-N D9, achieving an ee of 85% after 96 h reaction time. This substrate was also scaled up with CHAO as the enzyme, however primarily yielded the fully oxidised 2-pentylquinoline 510.
4.5 Future Work

Despite good activity towards several substrates of both classes when tested on an analytical scale, numerous issues were found when the biotransformations were scaled up to a preparative scale. The observed problem with the pyrrolidine substrate 395 was with mass recovery being too low with only a 26% yield from the reaction. The angustureine precursor 509 observed almost full oxidation to 2-pentylquinoline 510, something that may also have been observed on an analytical scale with a new peak appearing in the HPLC trace. In both instances this occurred with the CHAO enzyme. Promisingly, activity was observed towards both substrates with the other two enzymes that were tested, MAO-N D9 and the enantiocomplimentary 6-HDNO.

Further mutagenesis of the enzymes would be a way to increase activity towards the substrates. Using the crystal structures of the enzyme alongside a program such as PyMol, the substrates can be modelled in the active site and from this, key residues can be identified that could be influencing the reactivity of the biocatalysts. The genome of the biocatalysts has been fully mapped meaning directed mutagenesis can be used to alter specific genes that coordinate to the desired residues for manipulation in the active site. This is an iterative process that can be repeated, until a broad substrate scope is attained along with high levels of stereoselectivity. Once optimised on an analytical scale, this can be scaled up to a preparative scale to ensure practical usefulness.

With activity established, the substrate scope would have to be expanded. There are numerous THQ-containing natural products and biologically-relevant compounds that are 2-substituted. Establishing a large scope would increase the industrial relevance of the biocatalysts.

Another class of substrates that could be tested to see if they were tolerated by the oxidase enzymes would be 3-substituted THQs 513. Oxidation would presumably lead to tautomerization of the double bond to form the enamine species 515, and then non-selective reduction and repeated iterations could lead to deracemization of such substrates (Scheme 4.22).

As already discussed, there has been a recent interest in continuous flow chemical reactors as a suitable way to scale up lab-based reactions (Chapter 3). There has also been limited interest in the transfer of biotransformations into continuous reactors as well.\textsuperscript{199} Jamison and co-
workers demonstrated that immobilised *E. coli* cells containing ω-Transaminase could catalyse the production of multiple chiral amines. Ley *et al.* demonstrated that a multi-step reactor with two in-line biotransformations could be used in the production of chiral *O*-acetylcyanohydrins.

To improve efficiency of the biotransformations discussed here, use of a continuous reactor could be implemented. Immobilisation and use of heterogeneous systems allows for the recycling of the enzymes, decreasing the environmental impact and increasing the reaction efficiency.
Chapter 5  Conclusions

5.1  Photochemical Methodology

In conclusion, a novel set of conditions has been found that allows for the functionalisation of usually unreactive aromatic C-H bonds. Under UV irradiation in an acidic organic medium N-chloroamines can undergo intramolecular N-arylation to afford tetrahydroquinolines. This is an improvement on the original conditions which employed conc. sulfuric acid as the reaction solvent. Some of the most common methods that are currently used for N-arylation reactions are precious-metal catalysed methodologies such as the Buchwald-Hartwig reaction, or Ullmann-style Cu-catalysed reactions. The necessity for precious-metal catalysis coupled with the wide range of catalysts available means that no one set of conditions are usually suitable from one substrate class to the next. This often leads to large optimisation studies where high volumes of both catalysts and ligands need to be screened to find the best conditions. The methodology described here is much simpler, with only acid and organic solvent required along with UV irradiation for the reaction to proceed. Furthermore, the photochemical methodology does not require inert conditions with the reactions being run open to air with no anhydrous solvents. This makes the process operationally simple compared with many transition-metal catalysed procedures where exclusion of oxygen and moisture is essential for the reaction to work. One drawback from an industrial perspective is the use of DCM as the reaction solvent. DCM is a toxic solvent of which use has been slowly reduced in industrial settings. This was attempted to be addressed with a solvent screen of more environmentally benign solvents including EtOAc, 2-MeTHF and MeOH. All the other solvents that were tried did not yield any improved results, however this was a limited solvent screen. Use of a design of experiment (DoE) screen could indicate solvents with comparable properties to DCM that are classed as being ‘green’.

The substrate scope was extended to over 30 examples, including in a concise synthesis of the alkaloid natural product angustureine 3. This demonstrates that even under the acidic conditions there was a broad substrate tolerance. Also, the more challenging topologies that were constructed under the reaction conditions, such as the tricyclic compounds 381, 387, 395 and 400, demonstrate that scaffolds that are challenging to build using other methodologies can obtained in relatively short reaction sequences from readily available starting materials. The limitation of the substrate scope lay in the fact that electron-rich aromatic groups suffer from chlorination on the ring, which reduces the amount of desired product that can be formed. An alternative strategy could be to investigate alternative radical precursors to N-chloroamines, such as hydroxylamine derivatives.
5.2 Continuous Photochemical Processing

To address the issues encountered with scaling up photochemical reactions a two-stage continuous photochemical reactor was built that allowed for the chlorination of amines and the subsequent photochemical reaction of \textit{in situ} generated \textit{N}-chloroamines. The reactor was used to demonstrate a continuous synthesis of angustureine 3. The final reactor that was built combined both the chlorination of the amines and then the subsequent cyclisation of the \textit{in situ} generated \textit{N}-chloroamine. The productivity of the individual processes was much higher than the equivalent batch reactions. When combined the productivity did fall, however this may have been limited:

1) The size of the reactor, with a reactor volume of only 5 mL meaning a limited amount of material could only be passed through the reactor in a set time.
2) The solubility of NCS in DCM, which was limited to around 0.4 M and consequently meant the amount of amine that could be passed through the reactor was limited as well.

As a proof of concept reactor this design has shown that the reaction can be transferred into a continuous reactor, but more optimisation would need to be done to ensure that it was efficient enough for industrial uptake.

5.3 Biotransformations

Some of the 2-substituted tetrahydroquinolines that were synthesised using the methodology described in chapter 2 were subjected to enzyme-mediated deracemization reactions using monoamine oxidases. This resulted in full deracemization of the pyrrolidine-containing substrate 395 in only 24 h, which was scaled up to 125 mg scale as well but did not give a good recovery with only a 26% yield of the enantiopure product. This may have been due to several reasons, but shows that some of the THQ substrates are substrates for the MAO class of enzymes. Coupled with the photochemical methodology, if the biotransformations could be optimised then a transition-metal free route would exist that could be used to produce enantiopure THQ substrates from the respective amine precursors. At the moment the activity of the enzyme has limited this, but perhaps the use of rational site-selective mutagenesis could lead to the generation of more active mutants.

Following on from the results that had already been published, a family of natural product precursors were also deracemized on an analytical scale using the MAO enzymes with ee’s up to 90% obtained. The N-H THQs turned out to be substrates for deracemization using several of the MAO enzymes. CHAO gave the best results with the 2-(2-aryl)-ethyl-THQs, however the substrate that was scaled up (2-pentyl THQ) delivered almost exclusively the fully aromatised quinoline instead of enantiopure THQ. As with the \textit{N}-substituted THQs,
mutagenesis of the enzymes could give a more selective mutant that does not lead so heavily to the side-product formation.
Chapter 6 Thesis Experimental

6.1 General Experimental

Water-sensitive reactions were performed in oven- or flame-dried glassware cooled under nitrogen before use. Solvents were removed under reduced pressure using a Büchi rotary evaporator and a Vacuubrand PC2001 Vario diaphragm pump.

All other solvents and reagents were of analytical grade and used as supplied. Commercially available starting materials were obtained from Sigma–Aldrich, Alfa Aesar and Fluorochem. Flash column chromatography was carried out using silica (35-70 µm particles). Thin layer chromatography was carried out on commercially available pre-coated aluminium plates (Merck silica 2 8 8 0 Kieselgel 60F254).

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 + 0.1% Formic acid or MeCN/H₂O.

Proton and carbon NMR spectra were recorded on a Bruker Avance DPX 300, Avance 500, AV-3 400 or DRX 500 or JEOL ECA600II spectrometer using an internal deuterium lock. Carbon NMR spectra were recorded with composite pulse decoupling using the watts 16 pulse sequence. DEPT, COSY, HMQC and HMBC pulse sequences were routinely used to aid the assignment of spectra. Chemical shifts are quoted in parts per million downfield of tetramethylsilane, and coupling constants (J) are given in Hz. NMR spectra were recorded at 300 K unless otherwise stated.

Melting points were determined on a Reichert hot stage microscope and are uncorrected.

Infrared spectra were recorded on a Bruker alpha FT-IR spectrometer using a “platinum ATR” accessory and are reported in wavenumbers (cm⁻¹).

Nominal mass spectrometry was routinely performed on a Bruker HCT Ultra spectrometer using electrospray (+) ionization. Nominal and accurate mass spectrometry using electrospray ionisation was carried in the School of Chemistry at the University of Leeds, using a Bruker MaXis Impact spectrometer.

Photochemical reactions were conducted using a quartz immersion well reactor and 125 W medium pressure mercury lamp supplied by Photochemical Reactors Ltd.
6.2 Photochemistry Experimental Data

6.2.1 General Procedures

**General Procedure A: Chlorination reaction**

Following a procedure by De Luca *et al.*,\(^{118}\) to a stirred solution of amine (1.0 eq.) in DCM (0.20 M) at RT in a flask covered by aluminium foil was added NCS (1-1.50 eq.) portionwise and the reaction mixture was stirred for 3 h then concentrated *in vacuo*. Purification by column chromatography afforded the desired product.

**General Procedure B: N-arylation reaction**

A PYREX glass test tube (total vol. = 7 mL) was placed in a carousel holder that was placed in a water bath with the water at 18 °C, all above a stirrer hotplate. A solution of the N-chloroamine (1.0 eq.) in DCM (0.25 M) was added to the vial and stirred with a magnetic stirrer bar, then methanesulfonic acid (10 eq.) was added portionwise. The reactor was covered in aluminium foil and a red Perspex box was placed around it, then the reaction mixture was irradiated under UV light with a 125 W medium pressure mercury lamp at rt for 5 h. The reaction was either worked up by SCX cartridge (workup A) or by basic aqueous work up (workup B). Purification afforded the desired product.

**General Procedure C: Reductive amination**

To a stirred solution of aldehyde (1.0 eq.) in DCM (1.0 M) at 0 °C was added amine (3-10 eq.) and the reaction mixture was stirred for 15 mins. To this was added sodium trisacetoxyborohydride (2.0 eq.) or NaBH₄ (2.0 eq.) portionwise, and the reaction mixture was warmed to RT, stirred for 3 h then the reaction was quenched with sat. aqueous NaHCO₃. The aqueous phase was extracted with EtOAc (× 3) and the combined organics were dried over Na₂SO₄ and concentrated *in vacuo*. Purification afforded the desired product.

**General Procedure D: Rh(I)-catalysed 1,4-conjugate addition**

Following a procedure by Miyaura *et al.*,\(^{122}\) to a stirred solution of [Rh(cod)Cl]₂ (1 mol%) and ArB(OH)₂ (1.25-1.50 eq.) in degassed aqueous dioxane (6:1, 0.33 M) was added a solution of α,β-unsaturated carbonyl compound (1.0 eq.) in aqueous dioxane and distilled degassed Et₃N (1.0 eq.) simultaneously. The reaction mixture was heated at 50 °C under an atmosphere of N₂ for 6 h, after which it was cooled to RT, concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the desired product.
General Procedure E: LiAlH$_4$ reduction

To a stirred suspension of LiAlH$_4$ (2.0-4.0 eq.) in anhydrous THF (1.0 M) at 0 °C was added a solution of reactant in anhydrous THF (0.5 M) dropwise. The reaction mixture was then heated at reflux under an atmosphere of N$_2$ for 2-6 h. The reaction mixture was cooled to 0 °C the quenched with H$_2$O (1.0 eq.), 2 M aqueous NaOH (1.0 eq.) and H$_2$O (5.0 eq.) then stirred for 1 h at RT until the reaction mixture had turned white. The resultant slurry was dried over Na$_2$SO$_4$, filtered through a pad of Celite and the pad of Celite was washed with EtOAc. The filtrate was concentrated in vacuo. Purification afforded the desired products.

General Procedure F: Grignard addition to benzyl bromide

To a stirred solution of benzyl bromide (1.0 eq.) in anhydrous THF (0.5 M) at 0 °C was added a solution of Grignard reagent (1.1 eq.) dropwise. The reaction mixture was stirred at 0 °C under an atmosphere of N$_2$ for 30 min then warmed to RT and stirred for 1.5 h after which the reaction was quenched with sat. aqueous NH$_4$Cl. The aqueous phase was extracted with EtOAc (× 3) and the combined organic extracts were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification afforded the desired product.

General Procedure G: Formation of benzyl mesylate and Grignard addition

To a stirred solution of benzyl alcohol (1.0 eq.) in anhydrous DCM (0.33 M) at 0 °C was added Et$_3$N (1.1 eq.) and then MsCl (1.1 eq.) dropwise. The reaction mixture was left to stir for 2 h under an atmosphere of N$_2$, was warmed to RT then the reaction was quenched with sat. aqueous NaHCO$_3$ and the phases were separated. The aqueous phase was extracted with DCM (× 2) and the combined organic extracts were washed with brine, dried over Na$_2$SO$_4$ and then concentrated in vacuo. The crude residue was then flushed with N$_2$ and taken up in THF. The reaction mixture was cooled to 0 °C and a solution of Grignard reagent (2.0 eq.) was added dropwise. After 2 h the reaction mixture was warmed to RT and the reaction was quenched with sat. aqueous NH$_4$Cl, then the aqueous phase was extracted with EtOAc (× 3). The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification afforded the desired product.

General Procedure H: Ozonolysis reaction

A stream of O$_2$ gas was bubbled through a solution of alkene (1.0 eq.) in DCM (0.2 M) at -78 °C for 5 min. After, O$_3$ gas was bubbled through the solution until the solution turned blue. O$_2$ was then bubbled through the reaction mixture until the solution turned colourless and then PPh$_3$ (1.05 eq.) was added and the reaction mixture was stirred until no peroxides
remained (starch/I₂ test). The reaction mixture was warmed to RT and concentrated in vacuo. Purification afforded the desired products.

**Workup A: SCX cartridge**

TfOH (0.5 M in MeOH/5 g SPE-SCX) was washed through the SPE-SCX cartridge prior to use. The crude residue was loaded (3.5 mmol/5 g SPE-SCX silica) in the minimum amount of MeOH. The cartridge was washed with MeOH and the filtrate was collected. The cartridge was then washed with sat. methanolic NH₃ and the filtrate was collected and concentrated in vacuo.

**Workup B: Basic aqueous workup**

The crude reaction mixture was taken up in H₂O 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 Na₂SO₄ and concentrated in vacuo.

6.2.2  **Experimental Data**

**Synthesis of N-methyl-3-phenylpropan-1-amine 273**

![Chemical structure](image)

To a stirred solution of 3-phenylpropylamine 272 (2.10 mL, 14.7 mmol, 1.0 eq.) in Et₂O (20 mL) at 0 °C, was added Et₃N (2.05 mL, 14.7 mmol, 1.0 eq.) and ethyl chloroformate (1.41 mL, 14.7 mmol, 1.0 eq.). The reaction mixture was warmed to RT, stirred for 16 h then the reaction was quenched with H₂O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organics extracts were washed with brine (25 mL), dried over Na₂SO₄ and concentrated in vacuo. To a stirred suspension of LiAlH₄ (911 mg, 24.0 mmol, 2.0 eq.) in THF (24 mL) at 0 °C was added a solution of the crude reaction mixture (2.50 g, 12.0 mmol, 1.0 eq.) in THF (12 mL) dropwise. The reaction mixture was heated at reflux for 2 h, then cooled to 0 °C and the reaction was quenched with H₂O (5.0 mL), 1 M aqueous NaOH (2.5 mL) and H₂O (2.5 mL) then stirred for 1 h at RT until the reaction mixture had turned white. The resultant slurry was dried over Na₂SO₄, filtered through a pad of Celite and the pad of Celite was washed with EtOAc (200 mL). The filtrate was concentrated in vacuo to afford the title compound 273 (1.76 g, 11.7 mmol, 98%) as a colourless oil with no further purification required. The data is in accordance with the literature.²⁰²¹H NMR (300 MHz, CDCl₃) δ 7.32-7.24 (2H, m, ArH), 7.22-7.15 (3H, m, ArH), 2.70-2.57 (4H, m, includes 2H, m, propyl H₂-C₃; and 2H, m, propyl H₂-C1), 2.43 (3H, s, NCH₃), 1.87-1.76 (2H, m, propyl H₂-C2);¹³C NMR (75 MHz, CDCl₃) δ 142.2 (C₀), 128.3 (2 × C, ArC), 128.3 (2 × C, ArC), 125.7 (ArC),
51.7 (propyl C1), 36.5 (NCH3), 33.6 (propyl C3), 31.6 (propyl C2); IR \( \nu_{\text{max}} \) (neat)/cm\(^{-1} \): 3308 (N-H), 2932, 2854, 1603, 1495, 1472, 1453, 1112; HRMS (ESI): C\(_{10}\)H\(_{16}\)N [M+H\(^{+}\)]: calculated 150.1277, found 150.1289.

**Synthesis of N-chloro-N-methyl-3-phenylpropan-1-amine 255**

Following general procedure A, using amine 273 (500 mg, 3.35 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 255 (565 mg, 3.08 mmol, 92%) as a colourless oil. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.32-7.25 (2H, m, ArH), 7.22-7.14 (3H, m, ArH), 2.93 (3H, s, NCH\(_3\)), 2.88 (2H, t, \( J = 6.9 \) propyl H\(_2\)-C1), 2.68 (2H, t, \( J = 7.7 \) propyl H\(_2\)-C3), 2.03-1.90 (2H, m, propyl H\(_2\)-C2); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 141.7 (C\(_q\)), 128.4 (2 × C, ArC), 128.4 (2 × C, ArC), 125.9 (ArC), 65.2 (propyl C1), 53.0 (NCH\(_3\)), 32.7 (propyl C3), 29.7 (propyl C2); IR \( \nu_{\text{max}} \) (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 256**

Following general procedure B, using chloroamine 255 (100 mg, 0.54 mmol). Workup A afforded the title compound 256 (72 mg, 0.49 mmol, 91%) as a yellow oil. The data is in accordance with the literature. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.11-7.04 (1H, m, ArH-C7), 6.98-6.92 (1H, m, ArH-C5), 6.65-6.56 (2H, m, includes 1H, m, ArH-C6; and 1H, m, ArH-C8), 3.25-3.18 (2H, m, H\(_2\)-C2), 2.89 (3H, s, NCH\(_3\)), 2.81-2.73 (2H, m, H\(_2\)-C4), 2.03-1.92 (2H, m, H\(_2\)-C3); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 146.8 (C\(_q\)), 128.4 (2 × C, ArC), 128.4 (2 × C, ArC), 125.9 (ArC), 65.2 (propyl C1), 53.0 (NCH\(_3\)), 32.7 (propyl C3), 29.7 (propyl C2); IR \( \nu_{\text{max}} \) (neat)/cm\(^{-1} \): 2929, 2838, 1602, 1505, 1464, 1321, 1305, 1189; HRMS (ESI): C\(_{10}\)H\(_{14}\)N [M+H\(^{+}\)]: calculated 148.1121, found 148.1118.

**Synthesis of N-benzyl-3-phenylpropan-1-amine 277a**

Following general procedure C, using hydrocinnamaldehyde 275 (1.00 mL, 7.45 mmol) and benzylamine 276a (2.44 mL, 22.4 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 25-100% EtOAc in hexane afforded the title compound 277a (899 mg, 3.99 mmol, 54%) as a yellow oil. The data is in accordance with the literature. \(^1\)H NMR
(300 MHz, CDCl₃) δ 7.50-7.14 (10H, m, ArH), 3.85 (2H, s, NCH₂Ph), 2.82-2.65 (4H, m, includes 2H, m, propyl H₂-C1; and 2H, m, propyl H₂-C3), 1.99-1.85 (2H, m, propyl H₂-C2);

¹³C NMR (75 MHz, CDCl₃) δ 142.2 (Cₗ), 140.5 (Cₗ), 128.4 (4 × C, ArC), 128.3 (4 × C, ArC), 128.1 (ArC), 126.9 (ArC), 54.0 (NCH₂Ph), 33.6 (propyl C₃), 31.7 (propyl C₂);

IR νmax (neat)/cm⁻¹: 3025, 2927, 2856, 2813, 1602, 1494, 1452, 1171;


Synthesis of N-benzyl-N-chloro-3-phenylpropan-1-amine 278a

Following general procedure A, using amine 277a (500 mg, 2.22 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc afforded the title compound 278a (471 mg, 1.81 mmol, 82%) as a colourless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.48-7.05 (10H, m, ArH), 4.12 (2H, s, NC₄H₂Ph), 2.99 (2H, t, J = 6.7, propyl H₂-C1), 2.71 (2H, t, J = 7.5, propyl H₂-C3), 2.12-2.00 (2H, m, propyl H₂-C₂);

¹³C NMR (75 MHz, CDCl₃) δ 141.8 (Cₗ), 137.1 (Cₗ), 129.2 (2 × C, ArC), 128.5 (2 × C, ArC), 128.4 (2 × C, ArC), 128.3 (2 × C, ArC), 127.8 (ArC), 125.8 (ArC), 68.4 (NCH₂Ph), 62.1 (propyl C₁), 32.6 (propyl C₃), 29.4 (propyl C₂);

IR νmax (neat)/cm⁻¹: 3027, 2946, 2838, 1602, 1495, 1453, 1101, 1029;


Synthesis of 1-benzyl-1,2,3,4-tetrahydroquinoline 279

Following general procedure B, using chloroamine 278a (100 mg, 0.38 mmol). Work up A afforded the title compound 279 (69 mg, 0.31 mmol, 82%) as a yellow oil. The data is in accordance with the literature. ²⁰⁵ ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.17 (5H, m, ArH), 7.05-6.89 (2H, m, includes 1H, m, ArH-C7; and 1H, m, ArH-C5), 6.61-6.48 (2H, m, includes 1H, m, ArH-C6; and 1H, m, ArH-C8), 4.48 (2H, s, NCH₂Ph), 3.37 (2H, t, J = 5.6, H₂-C2), 2.82 (2H, t, J = 6.3, H₂-C4), 2.10-1.92 (2H, m, H₂-C3);

¹³C NMR (125 MHz, CDCl₃) δ 145.6 (Cₗ), 138.9 (Cₗ), 129.0 (ArC), 128.6 (2 × C, ArC), 127.1 (ArC), 126.7 (ArC), 126.6 (2 × C, ArC), 122.2 (Cₗ), 115.8 (ArC), 110.9 (ArC), 55.2 (NCH₂Ph), 49.9 (C₂), 28.2 (C₄), 22.4 (C₃);

IR νmax (neat)/cm⁻¹: 3061, 3024, 2924, 2839, 1600, 1494, 1449, 1343; HRMS (ESI): C₁₆H₁₈N [M+H⁺]: calculated 224.1434, found 224.1435.
Synthesis of \(N\)-(3-phenylpropyl)butan-1-amine 277b

Following general procedure C, using hydrocinnamaldehyde 275 (0.98 mL, 7.45 mmol) and \(n\)-butylamine 276b (3.69 mL, 37.3 mmol). Purification by SCX cartridge afforded the title compound 277b (1.02 g, 5.33 mmol, 72%) as a yellow oil. The data is in accordance with the literature.\(^{206}\) \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.32-7.23 (2H, m, ArH), 7.22-7.15 (3H, m, ArH), 2.69-2.61 (4H, m, includes 2H, m, propyl H\(_2\)-C\(_3\); and 2H, m, propyl H\(_2\)-C\(_1\)), 2.59 (2H, t, \(J = 7.6\), butyl H\(_2\)-C\(_1\)), 1.87-1.77 (2H, m, butyl H\(_2\)-C\(_2\)), 1.50-1.42 (2H, m, butyl H\(_2\)-C\(_2\)), 1.38-1.29 (2H, m, butyl H\(_2\)-C\(_3\)), 0.91 (3H, t, \(J = 7.3\), butyl H\(_3\)-C\(_4\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 142.2 (C\(_q\)), 128.4 (2 \(\times\) C, ArC), 128.3 (2 \(\times\) C, ArC), 125.7 (ArC), 49.8 (butyl C\(_1\)), 49.6 (propyl C\(_1\)), 33.7 (propyl C\(_3\)), 32.4 (butyl C\(_2\)), 31.8 (propyl C\(_2\)), 20.5 (butyl C\(_3\)), 14.0 (butyl C\(_4\)); IR \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 3026, 2955, 2927, 2858, 1496, 1454, 1128, 697; HRMS (ESI): C\(_{13}\)H\(_{22}\)N [M+H\(^+\)]: calculated 192.1747, found 192.1750.

Synthesis of \(N\)-chloro-\(N\)-(3-phenylpropyl)butan-1-amine 278b

Following general procedure A, using amine 277b (500 mg, 2.61 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 278b (429 mg, 1.90 mmol, 73%) as a yellow oil. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.35-7.26 (2H, m, ArH), 7.26-7.16 (3H, m, ArH), 2.98-2.89 (4H, m; includes 2H, m, propyl H\(_2\)-C\(_1\); and 2H, m, butyl H\(_2\)-C\(_1\)), 2.71 (2H, t, \(J = 7.6\), propyl H\(_2\)-C\(_3\)), 2.09-1.97 (2H, m, propyl H\(_2\)-C\(_2\)), 1.73-1.60 (2H, m, butyl H\(_2\)-C\(_2\)), 1.47-1.32 (2H, m, butyl H\(_2\)-C\(_3\)), 0.95 (2H, t, \(J = 7.3\), butyl H\(_3\)-C\(_4\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 141.8 (C\(_q\)), 128.5 (2 \(\times\) C, ArC), 128.3 (2 \(\times\) C, ArC), 125.8 (ArC), 64.1 (butyl C\(_1\)), 63.3 (propyl C\(_1\)), 32.8 (propyl C\(_3\)), 30.0 (butyl C\(_2\)), 29.5 (propyl C\(_2\)), 20.0 (butyl C\(_3\)), 13.9 (butyl C\(_4\)); IR \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 3027, 2955, 2864, 2835, 1496, 1453, 745, 697; HRMS (ESI): C\(_{13}\)H\(_{21}\)ClN [M+H\(^+\)]: calculated 226.1357, found 226.1358.

Synthesis of 1-butyl-1,2,3,4-tetrahydroquinoline 280

Following general procedure B, using chloroamine 278b (100 mg, 0.44 mmol). Workup A afforded the title compound 280 (49 mg, 0.26 mmol, 59%) as a brown oil. \(^1\)H NMR (300
Following general procedure A, using amine 275 (1.00 mL, 7.45 mmol) and n-hexylamine 276c (4.92 mL, 37.3 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 25-100% EtOAc in hexane afforded the title compound 277c (260 mg, 1.19 mmol, 16%) as a colourless oil. \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.32-7.23 (2H, m, ArH), 7.21-7.16 (3H, m, ArH), 2.70-2.54 (6H, m, includes 2H, m, propyl H\(_2\)-Cl; 2H, m, propyl H\(_2\)-C3; and 2H, m, hexyl H\(_2\)-C1), 1.88-1.74 (2H, m, propyl H\(_2\)-C2), 1.51-1.41 (2H, m, hexyl H\(_2\)-C2), 1.37-1.21 (6H, m, hexyl H\(_2\)-C3-5), 0.93-0.83 (3H, m, hexyl H\(_3\)-C6); \( ^{13}C \) NMR (75 MHz, CDCl\(_3\)) \( \delta \) 142.2 (C\(_q\)), 128.4 (2 \times C, ArC), 128.3 (2 \times C, ArC), 125.7 (ArC), 50.1 (CH\(_2\)), 49.6 (CH\(_2\)), 33.7 (CH\(_2\)), 31.8 (2 \times C, CH\(_2\)), 30.2 (CH\(_2\)), 27.1 (CH\(_2\)), 22.6 (CH\(_2\)), 14.0 (CH\(_3\)); IR \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\): 3026, 2925, 2855, 1603, 1495, 1454, 1129, 687; HRMS (ESI): C\(_{15}\)H\(_{30}\)N [M+H\(^+\)]; calculated 220.2060, found 220.2063.

**Synthesis of N-chloro-N-(3-phenylpropyl)hexan-1-amine 278c**

Following general procedure A, using amine 277c (225 mg, 1.03 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in pentane afforded the title compound 278c (209 mg, 0.83 mmol, 81%) as a colourless oil. \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.30 (2H, m, ArH), 7.25-7.13 (3H, m, ArH), 2.92 (4H, m, includes 2H, m, propyl H\(_2\)-Cl; and 2H, m, hexyl H\(_2\)-C1), 2.75-2.61 (2H, m, propyl H\(_2\)-C3), 2.09-1.95 (2H, m, propyl H\(_2\)-C2), 1.75-1.60 (2H, m, hexyl H\(_2\)-C2), 1.43-1.22 (6H, m, hexyl H\(_2\)-C3-5), 0.91 (3H, t, \( J = 6.8 \), hexyl H\(_3\)-C6); \( ^{13}C \) NMR (75 MHz, CDCl\(_3\)) \( \delta \) 142.0 (C\(_q\)), 128.6 (2 \times C, ArC), 128.5 (2 \times C, ArC), 126.0 (ArC), 64.6 (CH\(_2\)), 63.4 (CH\(_2\)), 32.9 (CH\(_2\)), 31.8 (CH\(_2\)), 29.6 (CH\(_2\)), 28.0 (CH\(_2\)), 26.7 (CH\(_2\)), 22.7 (CH\(_2\)), 14.2 (CH\(_3\)); IR \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\): 3085, 3027, 2928, 1063, 1496, 1454, 1347, 1302; HRMS (ESI): C\(_{15}\)H\(_{35}\)ClN [M+H\(^+\)]; calculated 254.1670, found 254.1675.
Synthesis of 1-hexyl-1,2,3,4-tetrahydroquinoline 281

Following general procedure B, using chloroamine 278c (100 mg, 0.39 mmol). Workup B then purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 281 (23 mg, 0.11 mmol, 28%) as a colourless oil. 

\[ ^1H \text{NMR} (300 MHz, CDCl}_3 \delta 7.09-6.99 (1H, m, ArH-C7), 6.97-6.89 (1H, m, ArH-C5), 6.63-6.47 (2H, m, includes 1H, m, ArH-C6; and 1H, m, ArH-C8), 3.34-3.15 (4H, m, includes: 2H, m, H-2-C2; and 2H, m, hexyl H-2-C1), 2.75 (2H, t, J = 6.4, H-2-C4), 2.02-1.88 (2H, m, H-2-C3), 1.66-1.51 (2H, m, hexyl H-2-C2), 1.40-1.24 (6H, m, hexyl H-2-C3-5), 0.98-0.81 (3H, m, hexyl H-3-C6); 

\[ ^13C \text{NMR} (125 MHz, CDCl}_3 \delta 145.5 (Cq), 129.3 (ArC), 127.2 (ArC), 122.3 (Cq), 115.3 (ArC), 110.6 (ArC), 51.7 (CH2), 49.6 (CH2), 31.9 (CH2), 28.4 (CH2), 27.1 (CH2), 26.3 (CH2), 22.8 (CH2), 22.4 (CH2), 14.2 (CH3); 

IR \nu_{\text{max}} \text{(neat)/cm}^{-1}: 3066, 2925, 2855, 1601, 1574, 1504, 1456, 1369; 

HRMS (ESI): C_{15}H_{24}N [M+H]^+: calculated 218.1903, found 218.1902.

Synthesis of N-(4-chlorohexyl)-4-nitro-N-(3-phenylpropyl)benzene-1-sulfonamide 284

To a stirred solution of the crude amine mixture (24 mg, 0.10 mmol, 1.0 eq.) in DCM (0.5 mL) at 0 °C was added Et3N (15 µL, 0.11 mmol, 1.1 eq.) and p-NsCl (24 mg, 0.11 mmol, 1.1 eq.). The reaction mixture was warmed to RT and stirred for 2 h, after which it was diluted with H2O (2 mL) and the aqueous phase was extracted with DCM (3 × 5 mL). The combined organic extracts were dried over Na2SO4 and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with 5% EtOAc in hexane afforded the title compound 284 (12 mg, 0.03 mmol, 30%) as a colourless gum. 

\[ ^1H \text{NMR} (400 MHz, CDCl}_3 \delta 8.34 (2H, d, J = 8.9, ArH), 7.94 (2H, d, J = 8.9, ArH), 7.34-7.13 (5H, m, ArH), 3.89-3.75 (1H, m, hexyl H-1-C4), 3.28-3.11 (4H, m, includes 2H, m, propyl H-2-C1; and 2H, m, hexyl H-2-C1), 2.63 (2H, t, J = 7.5, propyl H-2-C3), 1.98-1.60 (8H, m, includes 2H, m, propyl H-2-C2; and 2H, m, hexyl H-2-C2; 2H, m, hexyl H-2-C3, and 2H, m, hexyl C5), 1.04 (3H, t, J = 7.3, hexyl H-3-C6); 

\[ ^13C \text{NMR} (125 MHz, CDCl}_3 \delta 150.1 (Cq), 145.8 (Cq), 140.8 (Cq), 128.7 (2 × C, ArC), 128.5 (2 × C, ArC), 128.4 (2 × C, ArC), 126.4 (ArC), 124.5 (2 × C, ArC), 65.0 (hexyl C4), 48.0 (CH2), 30.7 (CH2), 28.4 (CH2), 27.1 (CH2), 25.9 (CH2), 25.0 (CH2), 14.2 (CH3); 

IR \nu_{\text{max}} \text{(neat)/cm}^{-1}: 3066, 2925, 2855, 1601, 1574, 1504, 1456, 1369; 

HRMS (ESI): C_{15}H_{24}N [M+H]^+: calculated 218.1903, found 218.1902.
47.8 (CH₂), 34.9 (CH₂), 33.0 (CH₂), 31.8 (CH₂), 30.2 (CH₂), 25.6 (CH₂), 11.1 (hexyl C₆); HRMS data could not be obtained.

Synthesis of N-(3-phenylpropyl)prop-2-en-1-amine 277d

Following general procedure C, using hydrocinnamaldehyde 275 (0.98 mL, 7.45 mmol) and allylamine 276d (2.79 mL, 37.3 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 50-100% EtOAc in hexane afforded the title compound 277d (624 mg, 3.56 mmol, 48%) as a colourless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.23 (2H, m, ArH), 7.23-7.15 (3H, m, ArH), 5.91 (1H, ddt, J = 16.8, 10.3, 6.0, propenyl H₁-C2), 5.17 (1H, dd, J = 16.8, 1.5, propenyl H₁-C3), 5.09 (1H, dd, J = 10.3, 1.5, propenyl H₂-C3), 3.25 (2H, dt, J = 6.0, 1.3, propenyl H₂-C1), 2.70-2.61 (4H, m, includes 2H, m, propyl H₂-C1; and 2H, m, propyl H₂-C3), 1.88-1.80 (2H, m, propyl H₂-C2); ¹³C NMR (125 MHz, CDCl₃) δ 142.3 (C_q), 137.1 (propenyl C₂), 128.5 (2 × C, ArC), 125.9 (ArC), 115.9 (propenyl C₃), 52.6 (propenyl C₁), 49.1 (propyl C₁), 31.9 (propyl C₃); IR νₘₐₓ (neat)/cm⁻¹: 3063, 3026, 2927, 2857, 2812, 1643 (C=C), 1603, 1453; HRMS (ESI): C₁₂H₁₈N [M+H⁺]: calculated 176.1434, found 176.1432.

Synthesis of N-chloro-N-(3-phenylpropyl)prop-2-en-1-amine 278d

Following general procedure A, using amine 278d (500 mg, 2.85 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 278d (523 mg, 2.49 mmol, 87%) as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.34-7.27 (2H, m, ArH), 7.24-7.17 (3H, m, ArH), 6.02-5.91 (1H, m, propenyl H₁-C2), 5.32-5.22 (2H, m, propenyl H₂-C3), 3.61 (2H, dd, J = 6.4, 0.9, propenyl H₂-C1), 2.94 (2H, t, J = 6.9, propyl H₂-C1), 2.70 (2H, t, J = 7.7, propyl H₂-C3), 2.07-1.97 (2H, m, propyl H₂-C2); ¹³C NMR (125 MHz, CDCl₃) δ 141.7 (propenyl C₂), 133.6 (C_q), 128.4 (2 × C, ArC), 128.3 (2 × C, ArC), 125.8 (ArC), 119.2 (propenyl C₃), 66.9 (propenyl C₁), 62.1 (propyl C₁), 32.7 (propyl C₃), 29.4 (propyl C₂); IR νₘₐₓ (neat)/cm⁻¹: 3084, 3063, 3026, 2948, 2840, 1645, 1603, 1496; HRMS (ESI): C₁₂H₁₇ClN [M+H⁺]: calculated 210.1044, found 210.1039.
Following general procedure B, using chloroamine 278d (100 mg, 0.48 mmol). Workup A then purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 282 (33 mg, 0.19 mmol, 40%) as a colourless oil. The data is in accordance with the literature.\(^{207}\)

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.06-7.00 (1H, m, ArH), 6.97-6.93 (1H, m, ArH), 6.60-6.53 (2H, m, includes 1H, m, ArH-C6; and 1H, m, ArH-C8), 5.86 (1H, ddt, \(J = 17.1, 10.1, 5.0\), propenyl H\(_1\)-C2), 5.24 (1H, dd, \(J = 17.1, 1.7\), propenyl H\(_3\)-C3), 5.18 (1H, dd, \(J = 10.1, 1.7\), propenyl H\(_4\)-C3), 3.87 (2H, dt, \(J = 4.9, 1.6\), propenyl H\(_2\)-C1), 3.31-3.24 (2H, m, H\(_2\)-C2), 2.77 (2H, t, \(J = 6.3\), H\(_2\)-C4), 2.01-1.93 (2H, m, H\(_2\)-C3); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 145.3 (C\(_q\)), 133.6 (propenyl C2), 129.0 (ArC), 127.0 (ArC), 122.4 (C\(_q\)), 115.9 (ArC), 115.7 (propenyl C3), 111.0 (ArC), 53.8 (propenyl C1), 49.1 (C2), 28.1 (C4), 22.3 (C3); IR \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 3036, 3018, 2927, 2840, 1641, 1601, 1574, 1502; HRMS (ESI): C\(_{12}\)H\(_{16}\)N [M+H\(^+\)]: calculated 174.1277, found 174.1272.

**Synthesis of methyl 3,3-diphenylpropanoate 290**

Following general procedure D, using methyl trans-cinnamate 289 (1.22 g, 7.5 mmol) and PhB(OH)\(_2\) 29 (1.14 g, 9.38 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 290 (1.73 g, 7.20 mmol, 96%) as a bright yellow oil. The data is in accordance with the literature.\(^{208}\)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.35-7.15 (10H, m, ArH), 4.57 (1H, t, \(J = 8.0\), propyl H\(_1\)-C3), 3.59 (3H, s, OCH\(_3\)), 3.08 (2H, d, \(J = 8.0\), propyl H\(_2\)-C2); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 143.5 (2 \(\times\) C, C\(_q\)), 128.6 (4 \(\times\) C, ArC), 127.6 (4 \(\times\) C, ArC), 126.5 (2 \(\times\) C, ArC), 51.7 (OCH\(_3\)), 47.0 (propyl C3), 40.6 (propyl C2); IR \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 3340, 3018, 2927, 2840, 1641, 1601, 1574, 1502; HRMS (ESI): C\(_{16}\)H\(_{16}\)O\(_2\)Na [M+Na\(^+\)]: calculated 263.1043, found 263.1045.
Synthesis of 3,3-diphenylpropanoic acid 291

To a stirred solution of ester 290 (1.50 g, 6.24 mmol, 1.0 eq.) in MeOH (20 mL) was added 2 M aqueous NaOH (20 mL). The reaction mixture was heated to reflux for 30 min then cooled to RT and diluted with 2 M aqueous HCl (20 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organics were washed with brine (20 mL), dried over Na₂SO₄ and concentrated in vacuo to afford the title compound 291 (1.41 g, 6.23 mmol, 99%) as a colourless solid, which was used without further purification. A small quantity was crystallised from 9:1 hexane-EtOAc. The data is in accordance with the literature.²⁰⁹ M.p 155-158 °C, colourless needles, hexane-EtOAc; ¹H NMR (300 MHz, MeOD) δ 7.31-7.23 (8H, m, ArH), 7.20-7.12 (2H, m, ArH), 4.50 (1H, t, J = 8.0, propyl H₁-C₃), 3.04 (2H, d, J = 8.0, propyl H₂-C₂); ¹³C NMR (75 MHz, MeOD) δ 175.6 (propyl C₁), 145.3 (2 × C, C₉), 129.5 (4 × C, ArC), 128.8 (4 × C, ArC), 127.4 (2 × C, ArC), 126.5 (2 × C, ArC), 124.0 (2 × C, ArC), 119.6 (2 × C, ArC), 48.5 (propyl C₃), 41.5 (propyl C₂); IR νmax (neat)/cm⁻¹: 3027 (O-H), 2910, 1695 (C=O), 1597, 1493, 1427, 1268, 919; HRMS (ESI): C₁₅H₁₄O₂Na [M+Na⁺]: calculated 249.0886, found 249.0886.

Synthesis of N-methyl-3,3-diphenylpropanamide 292

To a stirred solution of acid 291 (1.25 g, 5.52 mmol, 1.0 eq.) in DCM (20 mL) was added TBTU (2.84 g, 8.83 mmol, 1.6 eq.), DIPEA (3.85 mL, 22.1 mmol, 4.0 eq.) and NH₂Me·HCl (559 mg, 8.28 mmol, 1.5 eq.). The reaction mixture was stirred at RT for 20 h and then the reaction was quenched with sat. aqueous NaHCO₃ (20 mL). The aqueous phase was extracted with DCM (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried over Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with 50% EtOAc in hexane afforded the title compound 292 (1.27 g, 5.31 mmol, 96%) as an amorphous solid. ¹H NMR (300 MHz, CDCl₃) δ 7.26-7.06 (10H, m, ArH), 5.16 (1H, br. s, NH), 4.50 (1H, t, J = 7.8, propyl H₁-C₃), 2.80 (2H, d, J = 7.8, propyl H₂-C₂), 2.56 (3H, d, J = 4.9, NCH₃); ¹³C NMR (75 MHz, CDCl₃) δ 171.7 (propyl C₁), 143.7 (2 × C, C₉), 128.6 (4 × C, ArC), 127.7 (4 × C, ArC), 126.5 (2 × C, ArC), 124.0 (2 × C, ArC), 47.3 (propyl C₃), 43.3 (propyl
C2), 26.3 (NCH3); IR νmax (neat)/cm−1: 3341 (N-H), 3030, 2941, 1638 (C=O), 1601, 1550, 1492, 745; HRMS (ESI): C16H17NONa [M+Na+] : calculated 262.1202, found 262.1203.

**Synthesis of N-methyl-3,3-diphenylpropan-1-amine 293**

![Chemical structure of N-methyl-3,3-diphenylpropan-1-amine 293](image)

To a stirred suspension of LiAlH4 (317 mg, 8.36 mmol, 2.0 eq.) in THF (16 mL) at 0 °C was added a solution of amide 292 (1.00 g, 4.18 mmol, 1.0 eq.) in THF (4 mL) dropwise. The reaction mixture was heated at reflux for 4 h, then cooled to 0 °C and the reaction was quenched with H2O (2.0 mL), 1 M aqueous NaOH (1.0 mL) and H2O (1.0 mL) then stirred for 1 h at RT until the reaction mixture had turned white. The resultant slurry was dried over Na2SO4, filtered through a pad of Celite and the pad of Celite was washed with EtOAc (200 mL), then the filtrate was concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with EtOAc then 5% MeOH in DCM, afforded the title compound 293 (574 mg, 2.55 mmol, 61%) as a colourless gum. The data is in accordance with the literature.210 1H NMR (300 MHz, CDCl3) δ 7.32-7.23 (8H, m, ArH), 7.21-7.14 (2H, m, ArH), 4.01 (1H, t, J = 7.8, propyl H1-C3), 2.55 (2H, t, J = 7.4, propyl H2-C1), 2.39 (3H, s, NCH3), 2.26 (2H, app. dd, J = 14.9, 7.4, propyl H2-C2); 13C NMR (75 MHz, CDCl3) δ 144.7 (2 × C, Cq), 128.5 (4 × C, ArC), 127.8 (4 × C, ArC), 126.2 (2 × C, ArC), 126.2 (2 × C, ArC), 50.4 (propyl C1), 49.0 (propyl C3), 36.3 (NCH3), 35.5 (propyl C2); IR νmax (neat)/cm−1: 3060, 2931 (N-H), 2843, 2791, 1599, 1493, 1469, 1030; HRMS (ESI): C16H20N [M+H+] : calculated 226.1590, found 226.1590.

**Synthesis of N-chloro-N-methyl-3,3-diphenylpropan-1-amine 294**

![Chemical structure of N-chloro-N-methyl-3,3-diphenylpropan-1-amine 294](image)

Following general procedure A, using amine 293 (500 mg, 2.22 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in pentane afforded the title compound 294 (269 mg, 1.04 mmol, 47%) as a colourless gum. 1H NMR (300 MHz, CDCl3) δ 7.34-7.23 (8H, m, ArH), 7.21-7.14 (2H, m, ArH), 4.08 (1H, t, J = 7.9, propyl H1-C3), 2.88 (3H, s, NCH3) 2.81 (2H, t, J = 6.8, propyl H2-C1), 2.46-2.36 (2H, m, propyl H2-C2); 13C NMR (75 MHz, CDCl3) δ 144.4 (2 × C, Cq), 128.5 (4 × C, ArC), 127.9 (4 × C, ArC), 126.3 (2 × C, ArC), 64.2 (propyl C1), 53.2 (NCH3), 48.1 (propyl C3), 34.0 (propyl C2); IR νmax (neat)/cm−1: 3062, 3025,
2938, 1595, 1492, 1451, 777, 747; **HRMS** (ESI): C_{16}H_{19}^{35}ClN [M+H^+]: calculated 260.1201, found 260.1203.

**Synthesis of 1-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 295**

Following general procedure B, using chloroamine 294 (100 mg, 0.39 mmol). Workup A then purification by flash chromatography on silica gel, eluting with 5% EtOAc in pentane afforded the title compound 295 (57 mg, 0.26 mmol, 67%) as a colourless gum. The ^1^H NMR data is in accordance with the literature.\(^\text{211}\) ^1^H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.34–7.09 (6H, m, Ar\(\text{H}\)), 6.79–6.67 (2H, m, Ar\(\text{H}\)), 6.62–6.53 (1H, m, Ar\(\text{H}\)), 4.14 (1H, t, \(J = 6.2\), H\(\text{1-C4}\)), 3.28–3.12 (2H, m, H\(\text{2-C2}\)), 2.95 (3H, s, NC\(\text{H}_3\)), 2.33–2.21 (1H, m, H\(\text{a-C3}\)), 2.17–2.05 (1H, m, H\(\text{b-C3}\)); ^13^C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 146.5 (2 \(\times\) C, C\(\text{q}\)), 129.9 (ArC), 128.7 (2 \(\times\) C, ArC), 128.3 (2 \(\times\) C, ArC), 127.6 (ArC), 126.1 (C\(\text{q}\)), 124.9 (ArC), 116.3 (ArC), 111.1 (ArC), 48.5 (C2), 43.4 (C4), 39.3 (NCH\(_3\)), 31.0 (C3); ^IR\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 3023, 2922, 2862, 2820, 1600, 1502, 1450, 1207; **HRMS** (ESI): C\(_{16}\)H\(_{18}\)N [M+H^+]: calculated 224.1434, found 224.1438.

**Synthesis of methyl 3-phenyl-3-(3-(trifluoromethyl)phenyl)propanoate 297a**

Following general procedure D, using methyl trans-cinnamate 289 (1.22 g, 7.50 mmol) and ArB(OH)$_2$ 296a (1.78 g, 9.38 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 25-50% DCM in hexane afforded the title compound 297a (1.01 g, 3.28 mmol, 44%) as a colourless gum. ^1^H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.52–7.38 (4H, m, Ar\(\text{H}\)), 7.35–7.27 (2H, m, Ar\(\text{H}\)), 7.25–7.19 (3H, m, Ar\(\text{H}\)), 4.62 (1H, t, \(J = 8.0\), propyl H\(\text{1-C3}\)), 3.59 (3H, s, OCH\(_3\)), 3.08 (2H, d, \(J = 7.9\), propyl H\(\text{2-C2}\)); ^13^C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 171.8 (propyl C1), 144.4 (ArC), 142.5 (ArC), 131.1 (ArC), 130.9 (q, \(J = 32.1\), C\(\text{q}\)), 129.0 (ArC), 128.8 (2 \(\times\) C, ArC), 127.6 (2 \(\times\) C, ArC), 126.9 (ArC), 124.4 (q, \(J = 3.8\), ArC), 124.1 (q, \(J = 272.4\), CF\(_3\)), 123.5 (q, \(J = 3.8\), ArC), 51.7 (CH\(_3\)), 46.8 (propyl C3), 40.4 (propyl C2); ^IR\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 3030, 2954, 1736 (C=O), 1600, 1495, 1438, 1326, 1119; **HRMS** (ESI): C\(_{17}\)H\(_{15}\)F\(_3\)O\(_2\)Na [M+Na^+] : calculated 331.0916, found 331.0920.
Synthesis of 3-phenyl-3-(3-(trifluoromethyl)phenyl)propanoic acid 298a

To a stirred solution of ester 296a (900 mg, 2.92 mmol, 1.0 eq.) in MeOH (10 mL) was added 2 M aqueous NaOH (10 mL). The reaction mixture was heated at 95 °C for 8 h then cooled to RT and diluted with 2 M aqueous HCl (10 mL). The aqueous phase was extracted with EtOAc (2 × 15 mL) and the combined organics were dried over Na₂SO₄ and concentrated in vacuo. Crystallisation from hexane:EtOAc (9:1) afforded the title compound 298a (551 mg, 1.87 mmol, 64%) as a colourless crystalline solid. M.p 88-90 °C, crystalline solid, hexane-EtOAc; ¹H NMR (300 MHz, CDCl₃) δ 7.55-7.16 (9H, m, ArH), 4.58 (1H, t, J = 7.9, propyl H₁-C₃), 3.10 (2H, dd, J = 7.9, 1.2, propyl H₂-C₂); ¹³C NMR (125 MHz, CDCl₃) δ 177.5 (propyl C₁), 144.2 (ArC), 142.2 (ArC), 131.0 (ArC), 131.0 (q, J = 32.1, C₉), 129.1 (ArC), 128.9 (2 × C, ArC), 127.5 (2 × C, ArC), 127.0 (ArC), 124.4 (q, J = 3.8, ArC), 124.0 (q, J = 272.4, CF₃), 123.6 (q, J = 3.8, ArC), 46.4 (propyl C₃), 40.2 (propyl C₂); IR νmax (neat)/cm⁻¹: 3064 (O-H), 2910, 1704 (C=O), 1598, 1498, 1449, 1429, 1406; HRMS (ESI): C₁₆H₁₃F₃O₂Na [M+Na⁺]: calculated 317.0760, found 317.0759.

Synthesis of N-methyl-3-phenyl-3-(3-(trifluoromethyl)phenyl)propanamide 299a

To a stirred solution of acid 298a (940 mg, 3.21 mmol, 1.0 eq.) in DCM (15 mL) was added TBTU (1.65 g, 5.14 mmol, 1.6 eq.), DIPEA (2.24 mL, 12.9 mmol, 4.0 eq.) and NH₂Me·HCl (325 mg, 4.82 mmol, 1.5 eq.). The reaction mixture was stirred at RT for 24 h and then the reaction was quenched with sat. aqueous NaHCO₃ (20 mL). The phases were separated and the aqueous phase was extracted with DCM (2 × 15 mL). The combined organic extracts were washed with H₂O (20 mL), dried over Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with 25% EtOAc in pentane afforded the title compound 299a (648 mg, 2.11 mmol, 66%) as a colourless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.51-7.36 (4H, m, ArH), 7.33-7.27 (2H, m, ArH), 7.24-7.17 (3H, m, ArH), 5.42 (1H, s, NH), 4.68 (1H, t, J = 7.7, propyl H₁-C₃), 2.88 (2H, dd, J = 7.7, 3.3, propyl H₂-C₂), 2.66 (3H, d, J = 4.8, NCH₃); ¹³C NMR (125 MHz, CDCl₃) δ 171.1 (propyl C₁), 144.8 (C₉), 142.8 (C₉), 131.4 (ArC), 130.8 (q, J = 32.0, C₉), 129.0 (ArC), 128.7 (2 × C, ArC), 127.7 (2 × C, ArC), 126.9
(ArC), 124.2 (q, J = 3.8, ArC), 124.1 (q, J = 272.4, CF₃), 123.4 (q, J = 3.8, ArC), 47.0 (propyl C3), 42.9 (propyl C2), 26.2 (NCH₃); IR ν max (neat)/cm⁻¹: 3285 (N-H), 3090, 3030, 2945, 1640 (C=O), 1562, 1495, 1411; HRMS (ESI): C₁₇H₁₆F₃NO [M+H⁺]: calculated 308.1257, found 308.1244.

**Synthesis of N-methyl-3-phenyl-3-(3-(trifluoromethyl)phenyl)propan-1-amine 302**

![Chemical Structure](image)

To a stirred solution of amide 299a (640 mg, 2.08 mmol, 1.0 eq.) in THF (8 mL) at 0 °C was added a solution of BH₃ (8.3 mL of 1 M solution in THF, 4.0 eq) dropwise. The reaction mixture was stirred at 0 °C for 15 mins, then heated to reflux and stirred for 6 h, after which it was cooled to 0 °C and the reaction was quenched with the addition of 4 M aqueous NaOH (10 mL) dropwise. The phases were then separated, and the aqueous phase was extracted with EtOAc (3 × 15 mL) then the combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄ and concentrated in vacuo. Purification by SCX cartridge afforded the title compound 302 (201 mg, 0.69 mmol, 33%) as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.21-7.10 (4H, m, ArH), 7.07-6.92 (5H, m, ArH), 3.85 (1H, t, J = 7.8, propyl H₁-C₃), 2.28 (2H, t, J = 7.2, propyl H₂-C₁), 2.14 (3H, s, NC₃H₃), 2.05-1.95 (2H, m, propyl H₂-C₂); ¹³C NMR (125 MHz, CDCl₃) δ 145.8 (C₉), 143.7 (C₈), 131.2 (ArC), 130.7 (q, J = 32.0, C₇), 128.9 (ArC), 128.7 (2 × C, ArC), 127.8 (2 × C, ArC), 126.6 (ArC), 124.4 (q, J = 3.8, ArC), 124.2 (q, J = 272.1, CF₃), 123.1 (q, J = 3.5, ArC), 50.1 (propyl C1), 48.8 (propyl C3), 36.3 (NCH₃), 35.4 (propyl C2); IR ν max (neat)/cm⁻¹: 3028, 2934, 2850, 2797, 1599, 1494, 1474, 1325; HRMS (ESI): C₁₇H₁₆F₃N [M+H⁺]: calculated 294.1464, found 294.1463.

**Synthesis of N-chloro-N-methyl-3-phenyl-3-(3-(trifluoromethyl)phenyl)propan-1-amine 303**

Following general procedure A, using amine 302 (150 mg, 0.51 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 303 (151 mg, 0.46 mmol, 90%) as a colourless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.52 (1H, s, ArH), 7.48-7.37 (3H, m, ArH), 7.34-7.29 (2H, m, ArH), 7.27-7.19 (3H, m, ArH), 4.18 (1H,
t, J = 7.9, propyl H1-C3), 2.89 (3H, s, NCH3), 2.79 (2H, t, J = 6.8, propyl H2-C1), 2.47-2.35 (2H, m, propyl H2-C2); 13C NMR (125 MHz, CDCl3) δ 145.5 (Cq), 143.3 (Cq), 131.3 (ArC), 130.8 (q, J = 31.9, Cq), 129.0 (ArC), 128.7 (2 × C, ArC), 127.9 (2 × C, ArC), 126.7 (ArC), 124.6 (q, J = 3.8, ArC), 124.2 (q, J = 72.4, CF3), 123.2 (q, J = 3.8, ArC), 63.7 (propyl C1), 53.2 (NCH3), 47.7 (propyl C3), 33.8 (propyl C2); IR νmax (neat)/cm⁻¹: 3062, 3028, 2952, 2881, 1599, 1494, 1445, 1326; HRMS (ESI): C17H18F3N [M+H⁺]: calculated 328.1074, found 328.1069.

**Synthesis of 1-methyl-4-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline 305**

Following general procedure B, using chloroamine 303 (100 mg, 0.31 mmol). Workup A afforded the title compound 305 (67 mg, 0.23 mmol, 74%) as a brown gum. 1H NMR (500 MHz, CDCl3) δ 7.50-7.35 (3H, m, ArH), 7.31-7.24 (1H, m, ArH), 7.18-7.11 (1H, m, ArH), 6.76-6.67 (2H, m, ArH), 6.62-6.54 (1H, m, ArH), 4.20 (1H, dd, J = 12.8, 6.6, H1-C4), 3.28-3.21 (1H, m, Hα-C2), 3.19-3.12 (1H, m, Hb-C2), 2.96 (1H, s, NCH3), 2.33-2.24 (1H, m, Hα-C3), 2.15-2.07 (1H, m, Hb-C3); 13C NMR (100 MHz, CDCl3) δ 147.7 (Cq), 147.0 (Cq), 132.3 (ArC), 130.8 (q, J = 32.0, Cq), 129.9 (ArC), 128.9 (ArC), 128.1 (ArC), 125.4 (q, J = 3.7, ArC), 124.4 (q, J = 72.4, CF3), 123.9 (Cq), 123.2 (q, J = 3.7, ArC), 116.5 (ArC), 111.4 (ArC), 48.5 (C2), 43.5 (C4), 39.3 (NCH3), 31.2 (C3); IR νmax (neat)/cm⁻¹: 3027, 2946, 2824, 1504, 1445, 1324, 1207; HRMS (ESI): C17H15ClF3N [M+H⁺]: calculated 292.1308, found 292.1310.

**Synthesis of methyl 3-phenyl-3-(p-tolyl)propanoate 297b**

Following general procedure D, using methyl trans-cinnamate 289 (1.22g, 7.50 mmol) and ArB(OH)2 296b (1.28 g, 9.38 mmol). Purification by flash chromatography on silica gel, eluting with 25% DCM in pentane afforded the title compound 297b (625 mg, 2.46 mmol, 33%) as a pale yellow oil. The data is in accordance with the literature. 1H NMR (300 MHz, CDCl3) δ 7.31-7.06 (9H, m, ArH), 4.52 (1H, t, J = 8.0, propyl H1-C3), 3.58 (3H, s, OCH3), 2.46 (3H, s, OCH3), 1.63 (3H, s, OCH3), 1.36 (3H, s, OCH3), 1.34 (3H, s, OCH3), 1.24 (3H, s, OCH3), 1.21 (3H, s, OCH3).
3.05 (2H, d, J = 8.0, propyl H$_2$-C2), 2.29 (3H, s, ArCH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 172.3 (propyl C1), 143.7 (C$q$), 140.5 (C$q$), 136.1 (C$q$), 129.2 (2 × C, ArC), 128.5 (2 × C, ArC), 127.6 (2 × C, ArC), 127.5 (2 × C, ArC), 126.5 (ArC), 51.6 (OCH$_3$), 46.6 (propyl C3), 40.6 (propyl C2), 21.0 (ArCH$_3$); IR ν$_{max}$ (neat)/cm$^{-1}$: 3026, 2951, 2921, 1734 (C=O), 1601, 1494, 1434, 1254; HRMS (ESI): calculated 277.1199, found 277.1203.

**Synthesis of 3-phenyl-3-(p-tolyl)propanoic acid 298b**

![Chemical structure](image)

To a stirred solution of ester 297b (2.00 g, 7.86 mmol, 1.0 eq.) in MeOH (20 mL) was added 2 M aqueous NaOH (20 mL). The reaction mixture was heated at 95 °C for 8 h then cooled to RT and diluted with 4 M aqueous HCl (20 mL). The aqueous phase was extracted with EtOAc (2 × 25 mL) and the combined organics were dried over Na$_2$SO$_4$ and concentrated in vacuo to afford the title compound 298b (1.82 g, 7.57 mmol, 96%) as a colourless solid. No further purification was required. A small sample was crystallised from hexane:EtOAc (19:1). M.p 141-145 °C, colourless microcrystalline solid, hexane-EtOAc; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.31-7.05 (9H, m, ArH), 4.49 (1H, t, J = 7.9, propyl H$_1$-C3), 3.07 (2H, d, J = 7.9, propyl H$_2$-C2), 2.30 (3H, s, ArCH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 177.0 (propyl C1), 143.5 (C$q$), 140.2 (C$q$), 136.2 (C$q$), 129.3 (2 × C, ArC), 128.6 (2 × C, ArC), 127.5 (2 × C, ArC), 127.4 (2 × C, ArC), 126.5 (ArC), 46.3 (propyl C3), 40.3 (propyl C2), 21.0 (ArCH$_3$); IR ν$_{max}$ (neat)/cm$^{-1}$: 3272 (O-H), 3094, 3019, 2929, 1636 (C=O), 1567, 1492, 1435; HRMS (ESI): C$_{16}$H$_{16}$O$_2$Na [M+Na$^+$]: calculated 263.1043, found 263.1045.

**Synthesis of N-methyl-3-phenyl-3-(p-tolyl)propanamide 299b**

![Chemical structure](image)

To a stirred solution of acid 298b (1.35 g, 5.62 mmol, 1.0 eq.) in DCM (20 mL) was added TBTU (2.89 g, 8.99 mmol, 1.6 eq.), DIPEA (3.92 mL, 22.5 mmol, 4.0 eq.) and NH$_2$Me·HCl (569 mg, 8.43 mmol, 1.5 eq.). The reaction mixture was stirred at RT for 16 h and then the reaction was quenched with sat. aqueous NaHCO$_3$ (20 mL). The phases were separated and the aqueous phase was extracted with DCM (2 × 25 mL). The combined organic extracts were washed with H$_2$O (20 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash
chromatography on silica gel, eluting with 50% EtOAc in pentane afforded the **title compound 299b** (975 mg, 3.85 mmol, 69%) as an amorphous solid. **1H NMR** (500 MHz, CDCl₃) δ 7.29-7.15 (5H, m, ArH), 7.12 (2H, d, J = 8.1, ArH), 7.08 (2H, d, J = 8.1, ArH), 5.38 (1H, br. s, NH), 4.54 (1H, t, J = 7.8, propyl C3), 2.87 (2H, d, J = 8.1, propyl C2), 2.64 (3H, d, J = 4.7, NCH₃), 2.29 (3H, s, ArCH₃); **13C NMR** (125 MHz, CDCl₃) δ 171.8 (propyl C1), 144.0 (C₉), 140.7 (C₈), 136.0 (C₇), 129.2 (2 × C, ArC), 128.5 (2 × C, ArC), 127.6 (2 × C, ArC), 127.5 (2 × C, ArC), 126.4 (ArC), 46.9 (propyl C3), 43.3 (propyl C2), 26.2 (NCH₃), 20.9 (ArCH₃); **IR** ν_max (neat)/cm⁻¹: 3272, 3094, 3062, 3020, 2929, 1636 (C=O), 1567, 1512; **HRMS** (ESI): C_{17}H_{20}NO [M+H⁺]: calculated 254.1539, found 254.1534.

**Synthesis of N-methyl-3-phenyl-3-(p-tolyl)propan-1-amine 300**

![Image of amine 300]

To a stirred suspension of LiAlH₄ (449 mg, 11.8 mmol, 4.0 eq.) in THF (12 mL) at 0 °C was added a solution of amide 299b (750 mg, 2.96 mmol, 1.0 eq.) in THF (3 mL) dropwise. The reaction mixture was heated at reflux for 4 h, then cooled to 0 °C and the reaction was quenched with H₂O (1.5 mL), 2 M aqueous NaOH (0.5 mL) and H₂O (1.0 mL) then stirred for 1 h at RT until the reaction mixture had turned white. The resultant slurry was dried over MgSO₄, filtered through a pad of Celite and the pad of Celite was washed with EtOAc (100 mL). The filtrate was concentrated **in vacuo** to afford the **title compound 300** (684 mg, 2.86 mmol, 97%) as a yellow oil. No further purification required was required. **1H NMR** (500 MHz, CDCl₃) δ 7.32-7.22 (4H, m, ArH), 7.19-7.06 (5H, m, ArH), 3.99 (1H, t, J = 7.8, propyl H₁-C3), 2.58-2.52 (2H, m, propyl H₂-C1), 2.40 (3H, s, NCH₃), 2.31 (3H, s, ArCH₃), 2.28-2.22 (2H, m, propyl H₂-C2); **13C NMR** (125 MHz, CDCl₃) δ 145.0 (C₉), 141.8 (C₈), 135.6 (C₇), 129.1 (2 × C, ArC), 128.4 (2 × C, ArC), 127.7 (2 × C, ArC), 127.6 (2 × C, ArC), 126.1 (ArC), 50.5 (propyl C1), 48.7 (propyl C3), 36.4 (propyl C2), 35.7 (NCH₃), 20.9 (ArCH₃); **IR** ν_max (neat)/cm⁻¹: 3024, 2925, 2862, 2792, 1600, 1512, 1493, 1450; **HRMS** (ESI): C₁₇H₂₂N [M+H⁺]: calculated 240.1747, found 240.1743.

**Synthesis of N-chloro-N-methyl-3-phenyl-3-(p-tolyl)propan-1-amine 301**

![Image of amine 301]
Following general procedure A, using amine 300 (500 mg, 2.09 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 301 (465 mg, 1.70 mmol, 81%) as a colourless oil. 

**^1H NMR** (500 MHz, CDCl₃) δ 7.32-7.22 (4H, m, ArH), 7.20-7.08 (5H, m, ArH), 4.04 (1H, t, J = 7.9, propyl H₁-C₃), 2.89 (3H, s, NCH₃), 2.85-2.78 (2H, m, propyl H₂-C₁), 2.42-2.36 (2H, m, propyl H₂-C₂), 2.31 (3H, s, ArCH₃) 

**¹³C NMR** (125 MHz, CDCl₃) δ 144.7 (Cq), 141.4 (Cq), 135.8 (Cq), 129.2 (2 × C, ArC), 128.5 (2 × C, ArC), 127.8 (2 × C, ArC), 127.7 (2 × C, ArC), 126.2 (ArC), 64.3 (propyl C1), 53.2 (NCH₃), 47.7 (propyl C3), 34.0 (propyl C2), 21.0 (ArCH₃) 

**IR** νmax (neat)/cm⁻¹: 3023, 2981, 2938, 2920, 2890, 2852, 1597, 1581 

HRMS (ESI): C₁₇H₂₁N [M+H⁺]: calculated 274.1357, found 274.1354.

**Synthesis of 1,7-dimethyl-4-phenyl-1,2,3,4-tetrahydroquinoline and 1-methyl-4-(p-tolyl)-1,2,3,4-tetrahydroquinoline 304**

![Image of two chemical structures](image-url)

Following general procedure B, using chloroamine 301 (100 mg, 0.37 mmol). Workup A then purification by flash chromatography on silica gel, eluting with a gradient of 2-10% EtOAc in pentane afforded an inseparable mixture of the regioisomeric title compounds 304 (57 mg, 0.24 mmol, 65%) as a colourless gum. 

**¹H NMR** signals for major product reported (500 MHz, CDCl₃) δ 7.34-7.27 (2H, m, ArH), 7.24-7.18 (1H, m, ArH), 7.15-7.19 (2H, m, ArH), 6.64 (1H, d, J = 7.5, ArH), 6.51 (1H, s, ArH), 6.41 (1H, d, J = 7.5, ArH), 4.11 (1H, t, J = 6.2, H₁-C₄), 3.25-3.12 (2H, m, H₂-C₂), 2.95 (3H, s, NCH₃), 2.31 (3H, s, ArCH₃), 2.29-2.21 (1H, m, H₂-C₃), 2.14-2.04 (1H, m, H₆-C₃); 

**¹³C NMR** signals for major product reported (125 MHz, CDCl₃) δ 146.7 (2 × C, Cq), 137.1 (Cq), 129.8 (ArC), 128.6 (2 × C, ArC), 128.2 (2 × C, ArC), 126.0 (ArC), 122.1 (Cq), 117.1 (ArC), 111.8 (ArC), 48.6 (C2), 43.1 (C4), 39.3 (NCH₃), 31.3 (C3), 21.6 (ArCH₃); 

**IR** νmax (neat)/cm⁻¹: 3024, 2918, 2853, 2813, 1610, 1567, 1507, 1490 

HRMS (ESI): C₁₇H₂₀N [M+H⁺]: calculated 238.1590, found 238.1585.

**Synthesis of (E)-N-methylbut-2-enamide 307**

![Image of chemical structure](image-url)
Following a procedure by Greaney et al., to a stirred solution of methylamine (5.50 mL of a 40% w/w in H$_2$O, 1.1 eq.) and Et$_3$N (7.67 mL, 50 mmol, 1 eq.) in DCM (100 mL) at 0 °C, was added crotonyl chloride (4.79 mL, 50 mmol, 1 eq.) dropwise. The reaction mixture was stirred at 0 °C for 30 min, then warmed to RT and stirred for 24 h. The reaction was quenched with sat. aqueous NaHCO$_3$ (50 mL) and the phases separated. The organic phase was dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with EtOAc afforded the title compound 307 (3.46 g, 34.9 mmol, 70%) as a colourless solid. A small sample was crystallised from hexane. The data is in accordance with the literature. M.p 72-75 °C, colourless microcrystalline solid, hexane; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.83 (1H, dq, $J = 15.1$, 6.9, butenyl H$_1$-C), 5.78 (1H, dq, $J = 15.1$, 1.6, butenyl H$_1$-C), 5.41 (1H, s, NH), 2.86 (3H, d, $J = 3.9$, NCH$_3$), 1.84 (3H, dd, $J = 6.9$, 1.6, butenyl H$_3$-C4); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.9 (C=O), 139.5 (C3), 125.1 (C2), 26.3 (NCH$_3$), 17.7 (C4); IR $\nu$$_{\text{max}}$ (neat)/cm$^{-1}$: 3269 (N-H), 3092, 2961, 2943, 2916, 1666 (C=O), 1625, 1563; HRMS (ESI): C$_5$H$_{10}$ON [M+H$^+$]: calculated 100.0757, found 100.0754.

Synthesis of N-methyl-3-phenylbutanamide 309a

Following general procedure D, using N-methylcrotonamide 307 (500 mg, 5.04 mmol) and PhB(OH)$_2$ 29 (768 mg, 6.30 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 25-50% EtOAc in hexane afforded the title compound 309a (461 mg, 2.60 mmol, 52%) as a colourless solid. A small sample was crystallised from hexane-EtOAc (9:1). The data is in accordance with the literature. M.p 60-62 °C, colourless crystalline solid, hexane-EtOAc; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.36-7.27 (2H, m, ArH), 7.24-7.16 (3H, m, ArH), 5.22 (1H, br. s, NH), 3.37-3.24 (1H, m, butyl H$_1$-C3), 2.71 (3H, d, $J = 4.8$, NCH$_3$), 2.49-2.32 (2H, m, butyl H$_2$-C2), 1.31 (3H, d, $J = 7.0$, butyl H$_3$-C4); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 172.3 (butyl C1), 146.0 (C$_q$), 128.6 (2 × C, ArC), 126.7 (2 × C, ArC), 126.4 (ArC), 45.8 (butyl C2), 36.9 (butyl C3), 26.2 (NCH$_3$), 21.6 (butyl C4); IR $\nu$$_{\text{max}}$ (neat)/cm$^{-1}$: 3298 (N-H), 3029, 2961, 2919, 1639 (C=O), 1564, 1494, 1298; HRMS (ESI): C$_{11}$H$_{16}$NO [M+H$^+$]: calculated 178.1226, found 178.1225.

Synthesis of N-methyl-3-phenylbutan-1-amine 310a
To a stirred suspension of LiAlH₄ (343 mg, 9.04 mmol, 4.0 eq.) in THF (9 mL) at 0 °C was added a solution of amide 309a (400 mg, 2.26 mmol, 1.0 eq.) in THF (3 mL) dropwise. The reaction mixture was heated at reflux for 4 h, then cooled to 0 °C and the reaction was quenched with H₂O (1.5 mL), 2 M aqueous NaOH (0.5 mL) and H₂O (1.0 mL) then stirred for 1 h at RT until the reaction mixture had turned white. The resultant slurry was dried over MgSO₄, filtered through a pad of Celite and the pad of Celite was washed with EtOAc (100 mL). The filtrate was concentrated in vacuo to afford the title compound 310a (275 mg, 1.68 mmol, 74%) as a yellow oil. No further purification was required.

**1H NMR (300 MHz, CDCl₃)** δ 7.34-7.26 (2H, m, ArH), 7.22-7.14 (3H, m, ArH), 2.85-2.70 (1H, m, butyl H₁-C₃), 2.57-2.42 (2H, m, butyl H₂-C₁), 2.37 (3H, s, NC₃H₃), 1.83-1.72 (2H, m, butyl H₂-C₂), 1.26 (3H, d, J = 7.0, butyl H₃-C₄);

**13C NMR (75 MHz, CDCl₃)** δ 147.2 (Cₚ), 128.4 (2 × C, ArC), 126.9 (2 × C, ArC), 126.0 (ArC), 50.4 (butyl C₁), 38.3 (butyl C₂), 38.0 (N₃C₃H₃), 36.5 (butyl C₃), 22.5 (butyl C4);

**IR νmax (neat)/cm⁻¹**: 3026, 2958 (N-H), 2925, 1603, 1543, 1493, 1473, 1376;

**HRMS (ESI):** C₁₁H₁₈N [M+H⁺]: calculated 164.1434, found 164.1432.

**Synthesis of N-chloro-N-methyl-3-phenylbutan-1-amine 311a**

Following general procedure A, using amine 310a (250 mg, 1.53 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 311a (230 mg, 1.16 mmol, 76%) as a pale yellow oil.

**1H NMR (300 MHz, CDCl₃)** δ 7.35-7.27 (2H, m, ArH), 7.23-7.15 (3H, m, ArH), 2.87 (2H, s, NCH₃), 2.85-2.71 (3H, m, includes 1H, m, butyl H₁-C₃; and 2H, m, butyl H₂-C₁), 2.00-1.86 (2H, m, butyl H₂-C₂), 1.28 (3H, d, J = 7.0, butyl H₃-C₄);

**13C NMR (75 MHz, CDCl₃)** δ 146.7 (Cₚ), 128.5 (2 × C, ArC), 127.0 (2 × C, ArC), 126.1 (ArC), 64.3 (butyl C₁), 53.1 (NCH₃), 37.3 (butyl C₃), 36.5 (butyl C₂), 22.5 (butyl C4);

**IR νmax (neat)/cm⁻¹**: 3027, 2958, 2871, 1602, 1493, 1452, 1374, 761;

**HRMS (ESI):** C₁₁H₁₇ClN [M+H⁺]: calculated 198.1044, found 198.1040.

**Synthesis of 1,4-dimethyl-1,2,3,4-tetrahydroquinoline 321**

Following general procedure B, using chloroamine 311a (100 mg, 0.51 mmol). Workup A afforded the title compound 321 (59 mg, 0.37 mmol, 73%) as a brown oil. The data is in accordance with the literature.

**1H NMR (300 MHz, CDCl₃)** δ 7.13-7.02 (2H, m, ArH), 6.69-6.58 (2H, m, ArH), 3.31-3.14 (2H, m, H₂-C₂), 2.95-2.84 (4H, m, includes 3H, s, NCH₃;
and 1H, m, butyl H-1-C4), 2.10-1.97 (1H, m, H-2-C3), 1.75-1.64 (1H, m, H-6-C3), 1.29 (3H, d, J = 7.0, CH3); 13C NMR (75 MHz, CDCl3) δ 145.9 (Cq), 127.8 (Cq), 127.0 (2 × C, ArC), 116.2 (ArC), 111.0 (ArC), 48.2 (C2), 39.2 (C4), 30.8 (NCH3), 29.9 (C3), 22.7 (CH3); IR νmax (neat)/cm^-1: 3028, 2956, 2926, 2864, 2818, 1602, 1501, 1447; HRMS (ESI): C11H16N [M+H]^+: calculated 162.1277, found 162.1274.

Synthesis of N-methyl-3-(o-tolyl)butanamide 309b

Following general procedure D, using N-methylcrotonamide 307 (500 mg, 5.04 mmol) and ArB(OH)2 308b (857 mg, 6.30 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 25-50% EtOAc in hexane afforded the title compound 309b (422 mg, 2.21 mmol, 44%) as a yellow gum. 1H NMR (500 MHz, CDCl3) δ 7.20-7.06 (4H, m, ArH), 5.35 (1H, s, NH), 3.62-3.53 (1H, m, butyl H-1-C3), 2.72 (1H, d, J = 4.8, NCH3), 2.45 (1H, dd, J = 14.0, 6.6, butyl H-2-C2), 2.39-2.29 (4H, m, includes 3H, s, ArCCH3; and 1H, m, butyl H-3-C4), 1.26 (3H, d, J = 6.9, butyl H-3-C4); 13C NMR (125 MHz, CDCl3) δ 172.4 (butyl C1), 144.2 (Cq), 135.5 (Cq), 130.5 (ArC), 126.2 (ArC), 126.0 (ArC), 124.9 (ArC), 44.8 (butyl C2), 31.8 (butyl C3), 26.2 (NCH3), 21.2 (butyl C4), 19.4 (ArCH3); IR νmax (neat)/cm^-1: 3303 (N-H), 3062, 2965, 2877, 1638 (C=O), 1559, 1458, 1363; HRMS (ESI): C12H17NONa [M+Na]^+: calculated 214.1202, found 214.1207.

Synthesis of N-methyl-3-(o-tolyl)butan-1-amine 310b

To a stirred suspension of LiAlH4 (278 mg, 7.32 mmol, 4.0 eq.) in THF (7 mL) at 0 °C was added a solution of amide 309b (350 mg, 1.83 mmol, 1.0 eq.) in THF (3 mL) dropwise. The reaction mixture was heated at reflux for 4 h, then cooled to 0 °C and the reaction was quenched with H2O (1.0 mL), 2 M aqueous NaOH (0.5 mL) and H2O (1.0 mL) then stirred for 1 h at RT until the reaction mixture had turned white. The resultant slurry was dried over MgSO4, filtered through a pad of Celite and the pad of Celite was washed with EtOAc (100 mL), then the filtrate was concentrated in vacuo. Purification by SCX cartridge afforded the title compound 310b (270 mg, 1.52 mmol, 83%) as a yellow oil. 1H NMR (300 MHz, CDCl3) δ 7.24-7.04 (4H, m, ArH), 3.13-2.99 (1H, m, butyl H-1-C3), 2.59-2.43 (2H, m, butyl H-2-C1), 2.39 (3H, s, NCH3), 2.33 (3H, s, ArCH3), 1.90-1.68 (2H, m, butyl H-2-C2), 1.22 (3H, d, J = 6.9, butyl H-3-C4); 13C NMR (75 MHz, CDCl3) δ 145.4 (Cq), 135.2 (Cq), 130.2 (ArC), 126.2
(ArC), 125.6 (ArC), 125.2 (ArC), 50.4 (butyl C1), 37.8 (butyl C2), 36.5 (NCH3), 32.5 (butyl C3), 21.8 (butyl C4), 19.6 (ArCH3); IR νmax (neat)/cm⁻¹: 3018, 2959 (N-H), 2927, 2788, 1489, 1456, 1375, 1123; HRMS (ESI): C12H20N [M+H⁺]: calculated 178.1590, found 178.1587.

**Synthesis of N-chloro-N-methyl-3-(o-tolyl)butan-1-amine 311b**

Following general procedure A, using amine 310b (200 mg, 1.13 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 311b (187 mg, 0.88 mmol, 77%) as a colourless oil. ¹H NMR (300 MHz, CDCl3) δ 7.24-7.04 (4H, m, ArH), 3.18-3.05 (1H, m, butyl H1-C3), 2.88 (3H, s, NCH3), 2.78 (2H, t, J = 7.1, butyl H2-C1), 2.34 (3H, s, ArCH3), 2.01-1.87 (2H, m, ArCH2), 1.24 (3H, d, J = 6.9, butyl H3-C4); ¹³C NMR (75 MHz, CDCl3) δ 144.9 (Cq), 135.5 (Cq), 130.3 (ArC), 126.3 (ArC), 125.7 (ArC), 125.2 (ArC), 64.3 (butyl C1), 53.1 (NCH3), 36.0 (butyl C2), 31.8 (butyl C3), 21.8 (butyl C4), 19.5 (ArCH3); IR νmax (neat)/cm⁻¹: 3063, 3018, 2959, 2869, 1490, 1458, 1438, 1375; HRMS (ESI): C12H19ClN [M+H⁺]: calculated 212.1201, found 212.1196.

**Synthesis of 1,4,5-trimethyl-1,2,3,4-tetrahydroquinoline 322**

Following general procedure B, using chloroamine 311b (100 mg, 0.47 mmol). Workup A afforded the title compound 322 (58 mg, 0.33 mmol, 70%) as a brown oil. ¹H NMR (300 MHz, CDCl3) δ 6.99 (1H, dd, J = 8.1, 7.6, ArH-C7), 6.50 (2H, app. d, J = 7.7, ArH), 3.42 (1H, ddd, J = 13.0, 11.4, 3.7, Hα-C2), 3.20-3.05 (2H, m, includes 1H, m, Hβ-C2; and 1H, m, H1-C4), 2.93 (3H, s, NCH3), 2.29 (3H, s, ArCH3), 1.98 (1H, tt, J = 13.0, 5.0, Hα-C3), 1.72 (1H, ddt, J = 13.1, 3.7, 2.4, Hβ-C3), 1.17 (3H, d, J = 7.0, CH3); ¹³C NMR (125 MHz, CDCl3) δ 145.4 (Cq), 135.5 (Cq), 126.5 (ArC), 125.6 (Cq), 118.3 (ArC), 108.8 (ArC), 45.9 (C2), 39.3 (NCH3), 28.3 (C3), 27.3 (C4), 20.7 (CH3), 19.0 (ArCH3); IR νmax (neat)/cm⁻¹: 2926, 2861, 2813, 1617, 1509, 1463, 1412, 1373; HRMS (ESI): C12H19N [M+H⁺]: calculated 176.1434, found 176.1432.

**Synthesis of N-methyl-3-(m-tolyl)butanamide 309c**

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Following general procedure D, using N-methylcrotonamide 307 (500 mg, 5.04 mmol) and ArB(OH)$_2$ 308c (1.03 g, 7.56 mmol). Purification by flash chromatography on silica gel, eluting with 50% EtOAc in pentane afforded the title compound 309c (598 mg, 3.13 mmol, 62%) as a yellow gum. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.21 (1H, t, $J$ = 7.5, ArH), 7.08-7.01 (3H, m, ArH), 5.36 (1H, s, NH), 3.28 (1H, h, $J$ = 7.1, butyl H$_1$-C3), 2.74 (3H, d, $J$ = 4.8, NCH$_3$), 2.46 (1H, dd, $J$ = 13.9, 7.2, butyl H$_a$-C2), 2.39 (1H, dd, $J$ = 14.0, 7.7, butyl H$_b$-C2), 2.36 (3H, s, ArCH$_3$), 1.32 (3H, d, $J$ = 7.0, butyl H$_3$-C4); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.3 (butyl C1), 146.1 (C$_q$), 138.1 (C$_q$), 128.5 (ArC), 127.6 (ArC), 127.1 (ArC), 123.7 (ArC), 45.8 (butyl C2), 36.9 (butyl C3), 26.1 (NCH$_3$), 22.5 (butyl C4), 21.4 (ArCH$_3$); IR $\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3302 (N-H), 2961, 2905, 1637 (C=O), 1608, 1586, 1554, 1489; HRMS (ESI): C$_{12}$H$_{18}$NO [M+H$^+$]: calculated 192.1383, found 192.1381.

**Synthesis of N-methyl-3-(m-tolyl)butan-1-amine 310c**

![Structure of N-methyl-3-(m-tolyl)butan-1-amine 310c]

To a stirred suspension of LiAlH$_4$ (357 mg, 9.40 mmol, 4.0 eq.) in THF (9 mL) at 0 °C was added a solution of amide 309c (450 mg, 2.35 mmol, 1.0 eq.) in THF (3 mL) dropwise. The reaction mixture was heated at reflux for 4 h, then cooled to 0 °C and the reaction was quenched with H$_2$O (1.0 mL), 2 M H$_2$O (0.5 mL) and H$_2$O (1.0 mL) then stirred for 1 h at RT until the reaction mixture had turned white. The resultant slurry was dried over MgSO$_4$, filtered through a pad of Celite and the pad of Celite was washed with EtOAc (100 mL), then the filtrate was concentrated in vacuo. Purification by SCX cartridge afforded the title compound 310c (399 mg, 2.25 mmol, 96%) as a yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.21-7.15 (1H, m, ArH), 7.04-6.96 (3H, m, ArH), 2.77-2.69 (1H, m, butyl H$_1$-C3), 2.55-2.42 (2H, m, butyl H$_2$-C1), 2.38 (3H, s, NCH$_3$), 2.34 (3H, s, ArCH$_3$), 1.83-1.72 (2H, m, butyl H$_2$-C2), 1.25 (3H, d, $J$ = 7.0, butyl H$_3$-C4); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 147.1 (C$_q$), 137.8 (C$_q$), 128.2 (ArC), 127.6 (ArC), 126.7 (ArC), 123.9 (ArC), 50.3 (butyl C1), 38.2 (butyl C2), 37.9 (butyl C3), 36.3 (NCH$_3$), 22.5 (butyl C4), 21.4 (ArCH$_3$); IR $\nu_{\text{max}}$ (neat)/cm$^{-1}$: 2958, 2923, 2869, 2792, 1606, 1454, 1375, 1306; HRMS (ESI): C$_{12}$H$_{20}$N [M+H$^+$]: calculated 178.1590, found 178.1588.

**Synthesis of N-chloro-N-methyl-3-(m-tolyl)butan-1-amine 311c**

![Structure of N-chloro-N-methyl-3-(m-tolyl)butan-1-amine 311c]
Following general procedure A, using amine 310c (250 mg, 1.41 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 311c (249 mg, 1.18 mmol, 84%) as a colourless oil. \(^1H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.24-7.15 (1H, m, ArH), 7.05-6.98 (3H, m, ArH), 2.89 (3H, s, NCH\(_3\)), 2.84-2.71 (3H, m, includes 2H, butyl H\(_2\)-C1; and 1H, m, butyl H\(_1\)-C3), 2.35 (3H, s, ArCH\(_3\)), 1.99-1.86 (2H, m, butyl H\(_2\)-C2), 1.28 (3H, d, \(J = 7.0\), butyl H\(_3\)-C4); \(^13C\) NMR (125 MHz, CDCl\(_3\)) \(\delta\) 146.7 (C\(_q\)), 137.9 (C\(_q\)), 128.3 (ArC), 127.7 (ArC), 126.8 (ArC), 123.9 (ArC), 64.4 (butyl C1), 53.1 (NCH\(_3\)), 37.2 (butyl C3), 36.5 (butyl C2), 22.5 (butyl C4), 21.5 (ArCH\(_3\)); IR \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 3022, 2957, 2924, 2870, 1606, 1589, 1489, 1455; HRMS (ESI): C\(_{12}\)H\(_{19}\)ClN [M+H\(^+\)] calculated 212.1201, found 212.1195.

**Synthesis of 1,4,6-trimethyl-1,2,3,4-tetrahydroquinoline and 1,4,8-trimethyl-1,2,3,4-tetrahydroquinoline 324**

Following general procedure B, using chloroamine 311c (100 mg, 0.47 mmol). Workup A afforded an inseparable mixture of the regioisomeric title compounds 324 (57 mg, 0.33 mmol, 70\%, 2.5:1) as a brown oil. \(^1H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.06 (0.30H, d, \(J = 7.6\), ArH, minor), 7.02 (0.30H, d, \(J = 7.3\), ArH, minor), 6.94-6.86 (1.7H, m, includes 1.4H, m, ArH, major; and 0.3H, m, ArH, minor), 6.56 (0.70H, d, \(J = 7.9\), ArH, major), 3.24-3.06 (2H, m, includes 1.4H, m, H\(_2\)-C2, major; and 0.6H, m, H\(_2\)-C2, minor), 2.99-2.85 (3.1H, m, includes 2.1H, s, NCH\(_3\), major; 0.7H, m, H\(_1\)-C4, major; and 0.3H, m, H\(_1\)-C4, minor), 2.74 (0.9H, s, NCH\(_3\), minor), 2.33 (0.9H, s, ArCH\(_3\), minor), 2.26 (2.1H, s, ArCH\(_3\), major), 2.10-1.96 (1H, m, includes 0.7H, m, H\(_2\)-C3, major; and 0.3H, m, H\(_2\)-C3, minor), 1.76-1.67 (0.7H, m, H\(_5\)-C3, major), 1.63-1.55 (0.3H, m, H\(_5\)-C3, minor), 1.32 (0.9H, d, \(J = 7.1\), CH\(_3\), minor), 1.30 (2.1H, d, \(J = 7.0\), CH\(_3\), major); \(^13C\) NMR (125 MHz, CDCl\(_3\)) \(\delta\) 147.5 (C\(_q\)), 144.1 (C\(_q\)), 134.3 (C\(_q\)), 131.1 (C\(_q\)), 128.9 (ArC), 128.6 (ArC), 128.2 (C\(_q\)), 127.4 (ArC), 126.5 (ArC), 125.3 (C\(_q\)), 121.5 (ArC), 111.32 (ArC), 49.3 (CH\(_2\)), 48.4 (CH\(_2\)), 42.9, 39.5, 31.1, 30.7, 30.3 (CH\(_2\)), 25.1 (CH\(_2\)), 23.4, 22.9, 20.3, 18.8; IR \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 2959, 2923, 2862, 2820, 1589, 1492, 1467, 1449; HRMS (ESI): C\(_{12}\)H\(_{18}\)N [M+H\(^+\)] calculated 176.1434, found 176.1428.

**Synthesis of N-methyl-3-(p-tolyl)butanamide 309d**
Following general procedure D, using N-methylcrotonamide 307 (500 mg, 5.04 mmol) and ArB(OH)$_2$ 308d (1.03 g, 7.56 mmol). Purification by flash chromatography on silica gel, eluting with 50% EtOAc in pentane afforded the title compound 309d (564 mg, 2.95 mmol, 59%) as a colourless solid. A sample was crystallised from hexane. M.p 86-87 °C, colourless needles, hexane; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.11 (4H, s, ArH), 5.19 (1H, s, NH), 3.26 (1H, h, J = 7.1, butyl H$_1$-C3), 2.71 (3H, d, J = 4.9, NCH$_3$), 2.42 (1H, dd, J = 14.0, 7.3, butyl H$_2$-C2), 2.36 (1H, dd, J = 14.0, 7.5, butyl H$_1$-C2), 2.32 (3H, s, ArCH$_3$), 1.29 (3H, d, J = 7.0, butyl H$_3$-C4); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 172.4 (butyl C1), 142.9 (C$_q$), 135.9 (C$_q$), 129.2 (2 × C, ArC), 126.6 (2 × C, ArC), 45.9 (butyl C2), 36.5 (butyl C3), 26.2 (NCH$_3$), 21.7 (ArCH$_3$), 21.0 (butyl C4); IR $\nu_{max}$ (neat)/cm$^{-1}$: 3306 (N-H), 2972, 2960, 2916, 2875, 1637 (C=O), 1550, 1514; HRMS (ESI): C$_{12}$H$_{17}$NaNO [M+Na$^+$]: calculated 214.1202, found 214.1210.

**Synthesis of N-methyl-3-(p-tolyl)butan-1-amine 310d**

![Chemical Structure](image)

To a stirred suspension of LiAlH$_4$ (357 mg, 9.40 mmol, 4.0 eq.) in THF (9 mL) at 0 °C was added a solution of amide 309d (450 mg, 2.35 mmol, 1.0 eq.) in THF (3 mL) dropwise. The reaction mixture was heated at reflux for 4 h, then cooled to 0 °C and the reaction was quenched with H$_2$O (1.0 mL), 2 M aqueous NaOH (0.5 mL) and H$_2$O (1.0 mL) then stirred for 1 h at RT until the reaction mixture had turned white. The resultant slurry was dried over MgSO$_4$, filtered through a pad of Celite and the pad of Celite was washed with EtOAc (100 mL), then the filtrate was concentrated in vacuo. Purification by SCX cartridge afforded the title compound 310d (399 mg, 2.17 mmol, 92%) as a yellow gum. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.15-7.04 (4H, m, ArH), 2.78-2.70 (1H, m, butyl H$_1$-C3), 2.56-2.42 (2H, m, butyl H$_2$-C1), 2.38 (3H, s, NCH$_3$), 2.32 (3H, s, ArCH$_3$), 1.82-1.70 (2H, m, butyl H$_3$-C2), 1.24 (3H, d, J = 7.0, butyl H$_3$-C4); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 144.2 (C$_q$), 135.4 (C$_q$), 129.0 (2 × C, ArC), 126.7 (2 × C, ArC), 50.4 (butyl C1), 38.3 (butyl C2), 37.5 (butyl C3), 36.4 (NCH$_3$), 22.6 (butyl C4), 20.9 (ArCH$_3$); IR $\nu_{max}$ (neat)/cm$^{-1}$: 2957, 2923, 2869, 2790, 1514, 1451, 1373, 1114; HRMS (ESI): C$_{12}$H$_{20}$N [M+H$^+$]: calculated 178.1590, found 178.1592.

**Synthesis of N-chloro-N-methyl-3-(p-tolyl)butan-1-amine 311d**

![Chemical Structure](image)
Following general procedure A, using amine 310d (250 mg, 1.41 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the *title compound* 311d (227 mg, 1.07 mmol, 76%) as a colourless gum. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.15-7.08 (4H, m, ArH), 2.89 (3H, s, NCH$_3$), 2.85-2.71 (3H, m, includes 2H, m, butyl H$_2$-C1; and 1H, m, butyl H$_1$-C3), 2.34 (3H, s, ArCH$_3$), 2.00-1.85 (2H, m, butyl H$_2$-C2), 1.28 (3H, m, butyl H$_1$-C4); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 143.6 (C$q$), 135.5 (C$q$), 129.1 (2 × C, ArC), 126.8 (2 × C, ArC), 64.4 (butyl C1), 53.1 (NCH$_3$), 36.8 (butyl C3), 36.5 (butyl C2), 22.6 (butyl C4), 21.0 (ArCH$_3$); IR $\nu$$_{max}$ (neat)/cm$^{-1}$: 2956, 2924, 2870, 1514, 1455, 1438, 1374, 1349; HRMS (ESI): C$_{12}$H$_{19}$ClN [M+H$^+$]: calculated 212.1201, found 212.1194.

**Synthesis of 1,4,7-trimethyl-1,2,3,4-tetrahydroquinoline 323**

Following general procedure B, using chloroamine 311d (100 mg, 0.47 mmol). Workup A afforded the *title compound* 323 (54 mg, 0.31 mmol, 66%) as a brown oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.97 (1H, d, $J$ = 7.6, ArH-C5), 6.49 (1H, d, $J$ = 7.6, ArH-C6), 6.45 (1H, s, ArH-C8), 3.29-3.16 (2H, m, H$_2$-C2), 2.93-2.85 (4H, m, includes 3H, s, NC$_3$H; and 1H, m, H$_1$-C4), 2.31 (3H, s, ArCH$_3$), 2.09-2.00 (1H, m, H$_a$-C3), 1.70 (1H, ddt, $J$ = 10.3, 6.4, 4.0, H$_b$-C3), 1.29 (3H, d, $J$ = 7.0, CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 146.0 (C$q$), 136.5 (C$q$), 127.7 (ArC), 125.2 (C$q$), 117.0 (ArC), 111.7 (ArC), 48.3 (C2), 39.2 (NCH$_3$), 30.4 (C3), 30.2 (C4), 22.7 (CH$_3$), 21.5(ArCH$_3$); IR $\nu$$_{max}$ (neat)/cm$^{-1}$: 2954, 2921, 2855, 2812, 1611, 1572, 1507, 1484; HRMS (ESI): C$_{12}$H$_{18}$N [M+H$^+$]: calculated 176.1434, found 176.1428.

**Synthesis of 3-(4-bromophenyl)-N-methylbutanamide 309e**

Following general procedure D, using N-methylcrotonamide 307 (500 mg, 5.04 mmol) and ArB(OH)$_2$ 308e (1.52 g, 7.56 mmol). Purification by automated flash chromatography on silica gel, eluting with a gradient 25-100% EtOAc in hexane afforded the *title compound* 309e (536 mg, 2.09 mmol, 42%) as a colourless solid. A sample was crystallised from hexane-EtOAc (9:1). M.p 108-111 °C, colourless microcrystalline solid, hexane-EtOAc; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.41 (2H, d, $J$ = 8.4, ArH), 7.09 (2H, d, $J$ = 8.4, ArH), 5.26 (1H, s, NH), 3.34-3.23 (1H, m, butyl H$_1$-C3), 2.72 (3H, d, $J$ = 4.8, NCH$_3$), 2.36 (2H, d, $J$ = 7.4, butyl H$_2$-C2), 1.28 (3H, d, $J$ = 7.0, butyl H$_3$-C4); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.8 (butyl C1), 157
145.0 (C_2), 131.6 (2 × C, ArC), 128.5 (2 × C, ArC), 120.0 (C_2), 45.5 (butyl C2), 36.3 (butyl C3), 26.2 (NCH_3), 21.4 (butyl C4); IR v_{max} (neat)/cm^{-1}: 3299 (N-H), 2962, 2931, 2874, 1634 (C=O), 1556, 1487, 1402; HRMS (ESI): C_{11}H_{15}BrNO [M+H^+] calculated 256.0332, found 256.0330.

**Synthesis of 3-(4-bromophenyl)-N-methylbutan-1-amine 310e**

![Structure of 310e](image)

To a stirred solution of amide 309e (400 mg, 1.56 mmol, 1.0 eq.) in THF (6 mL) at 0 °C was added a solution of BH_3 (3.1 mL of a 1.0 M solution in THF, 2.0 eq) dropwise. The reaction mixture was stirred at 0 °C for 15 mins, then heated to reflux and stirred for 6 h, after which it was cooled to 0 °C and the reaction was quenched with 4 M aqueous NaOH (10 mL) dropwise. The phases were then separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL) then the combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification by SCX cartridge afforded the title compound 310e (281 mg, 1.16 mmol, 74%) as a colourless oil. ^1H NMR (500 MHz, CDCl_3) δ: 7.40 (2H, d, J = 8.4, ArH), 7.06 (2H, d, J = 8.4, ArH), 2.79-2.70 (1H, m, butyl H_1-C3), 2.51-2.40 (2H, m, butyl H_2-C1), 2.37 (3H, s, NC_3H_3), 1.77-1.69 (2H, m, butyl H_2-C2), 1.23 (3H, d, J = 7.0, butyl H_3-C4); ^13C NMR (125 MHz, CDCl_3) δ: 146.2 (C_q), 131.4 (2 × C, ArC), 128.7 (2 × C, ArC), 119.5 (C_2), 50.2 (butyl C1), 38.2 (butyl C2), 37.4 (butyl C3), 36.5 (NCH_3), 22.4 (butyl C4); IR v_{max} (neat)/cm^{-1}: 2959, 2925, 2871, 2792, 1621, 1548, 1486, 1454; HRMS (ESI): C_{11}H_{17}BrNO [M+H^+] calculated 242.0539, found 242.0537.

**Synthesis of 3-(4-bromophenyl)-N-chloro-N-methylbutan-1-amine 311e**

![Structure of 311e](image)

Following general procedure A, using amine 310e (250 mg, 1.03 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 311e (251 mg, 0.91 mmol, 88%) as a pale yellow gum. ^1H NMR (500 MHz, CDCl_3) δ: 7.41 (2H, d, J = 8.4, ArH), 7.08 (2H, d, J = 8.4, ArH), 2.87 (3H, s, NCH_3), 2.81 (1H, dd, J = 15.3, 6.8, butyl H_1-C3), 2.75-2.67 (2H, m, butyl H_2-C1), 1.99-1.90 (1H, m, butyl H_2-C2), 1.90-1.80 (1H, m, butyl H_3-C2), 1.25 (3H, d, J = 7.0, butyl H_3-C4); ^13C NMR (125 MHz, CDCl_3) δ: 145.7 (C_q), 131.5 (2 × C, ArC), 128.8 (2 × C, ArC), 119.7 (C_2), 64.0 (butyl C1), 53.1 (NCH_3), 36.7 (butyl C3), 36.3 (butyl C2), 22.3 (butyl C4); IR v_{max} (neat)/cm^{-1}: 2958, 2872, 2795, 1591,
1488, 1455, 1437, 1407; **HRMS** (ESI): C$_{11}$H$_{16}^{35}$Cl$_{5}^{79}$BrN [M+H$^+$]: calculated 276.1049, found 276.1045.

**Synthesis of 7-bromo-1,4-dimethyl-1,2,3,4-tetrahydroquinoline 325**

Following general procedure B, using chloroamine 311e (100 mg, 0.36 mmol). Workup A then purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 325 (46 mg, 0.19 mmol, 53%) as a brown oil. **$^1$H NMR** (500 MHz, CDCl$_3$) $\delta$ 6.88 (1H, d, $J$ = 8.0, ArH-C5), 6.73 (1H, dd, $J$ = 8.0, 1.9, ArH-C6), 6.67 (1H, d, $J$ = 1.9, ArH-C8), 3.30-3.17 (2H, m, H$_2$-C2), 2.88 (3H, s, NC$_3$H$_3$), 2.82 (1H, dt, $J$ = 13.1, 6.5, H$_1$-C4), 1.99 (1H, ddt, $J$ = 13.2, 8.6, 4.8, H$_b$-C3), 1.25 (3H, d, $J$ = 7.0, CH$_3$); **$^{13}$C NMR** (125 MHz, CDCl$_3$) $\delta$ 147.1 (C$_q$), 128.8 (ArC), 126.6 (C$_q$), 120.7 (C$_q$), 118.5 (ArC), 113.2 (ArC), 47.9 (C2), 38.9 (NCH$_3$), 30.5 (C4), 29.5 (C3), 22.2 (CH$_3$); **IR** $\nu_{\text{max}}$ (neat)/cm$^{-1}$: 2956, 2923, 2852, 1593, 1557, 1498, 1408, 1303; **HRMS** (ESI): C$_{11}$H$_{15}^{81}$BrN [M+H$^+$]: calculated 242.0362, found 242.0355.

**Synthesis of [3-(4-methoxyphenyl)butyl][methyl]amine 310f**

Following general procedure D, using N-methylcrotonamide 307 (1.00 g, 10.1 mmol) and ArB(OH)$_2$ 308f (2.31 g, 15.2 mmol). Purification by flash chromatography on silica gel, eluting with 50% EtOAc in hexane afforded an inseparable mixture of the desired product and starting material (490 mg). To a stirred suspension of LiAlH$_4$ (358 mg, 9.44 mmol, 4.0 eq.) in THF (9 mL) at 0 °C was added a solution of the mixture (490 mg) in THF (4 mL) dropwise. The reaction mixture was heated to reflux and left to stir, after which it was cooled to 0 °C and the reaction was quenched with H$_2$O (1 mL), 2 M aqueous NaOH (0.5 mL) and H$_2$O (0.5 mL) then stirred for 1 h at RT until the reaction mixture had turned white. The resultant slurry was dried over Na$_2$SO$_4$. The slurry was filtered through a pad of Celite and the pad of Celite washed with EtOAc (150 mL). The filtrate was then concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with EtOAc then a gradient of 0-10% MeOH in DCM afforded the title compound 310f (275 mg, 1.42 mmol, 14%) as a yellow oil. **$^1$H NMR** (500 MHz, CDCl$_3$) $\delta$ 7.11 (2H, d, $J$ = 8.6, ArH), 6.84 (2H, d, $J$ = 8.6, ArH), 3.79 (3H, s, OCH$_3$), 2.77-2.69 (1H, m, CH$_2$), 2.52 (1H, dt, $J$ = 11.5, 7.5, NCH$_3$H$_b$), 2.46 (1H, dt, $J$ = 11.6, 7.3, NCH$_3$H$_b$), 2.38 (3H, s, NCH$_3$), 1.77 (2H, app. q, $J$ = 7.5, CH$_2$), 1.23 (3H, d, $J$ = 6.9, CH$_3$);
\[ ^{13}\text{C NMR} (75 \text{ MHz, CDCl}_3) \delta 157.8 (\text{ArC}_q), 138.7 (\text{ArC}_q), 127.6 (2 \times \text{C, ArC}), 113.8 (2 \times \text{C, ArC}), 55.1 (\text{OCH}_3), 49.8 (\text{NCH}_2), 37.5 (\text{CH}_2), 37.0 (\text{CH}), 35.6 (\text{NCH}_2), 22.6 (\text{CH}_3); \text{IR } \nu_{\text{max}} \text{(neat)/cm}^{-1}: 2955, 2928, 2871, 2835, 2794, 1611, 1583, 1511; \text{HRMS} \text{(ESI): } \text{C}_{12}\text{H}_{20}\text{NO} [\text{M+H}^+]\text{: calculated 194.1539, found 194.1537.}

**Synthesis of chloro[3-(4-methoxyphenyl)butyl]methylamine 311f**

To a stirred solution of amine 310f (200 mg, 1.03 mmol, 1.0 eq.) in EtOAc (5.2 mL) and tBuOH (25 µL, 0.26 mmol, 0.25 eq.) at 0 °C was added simultaneously a solution of NaOCl (1.37 mL of a 0.75 M aqueous solution, 1.03 mmol, 1.0 eq.) and AcOH (59 µL, 1.03 mmol, 1.0 eq.) dropwise. The reaction mixture was stirred at 0 °C for 2 h then the phases were separated and the organic phase was washed with H₂O (10 mL), dried over Na₂SO₄ and concentrated in vacuo to afford the title compound 311f (222 mg, 0.97 mmol, 94%) as a brown oil. \[ ^1\text{H NMR} (500 \text{ MHz, CDCl}_3) \delta 7.11 (2\text{H, d}, J = 8.6, \text{ArH}), 6.84 (2\text{H, d}, J = 8.6, \text{ArH}), 3.79 (3\text{H, s}, \text{OC}_3\text{H}_3), 2.87 (3\text{H, s}, \text{NC}_3\text{H}_2), 2.81-2.68 (3\text{H, m}, \text{includes } 2\text{H, m, NC}_2\text{H}; \text{and } 1\text{H, m, CH}); \] \[ ^{13}\text{C NMR} (125 \text{ MHz, CDCl}_3) \delta 157.9 (\text{ArC}_q), 138.7 (\text{ArC}_q), 127.8 (2 \times \text{C, ArC}), 113.8 (2 \times \text{C, ArC}), 64.4 (\text{NCH}_2), 55.2 (\text{OCH}_3), 53.0 (\text{NCH}_2), 36.6 (\text{CH}_2), 36.4 (\text{CH}), 22.7 (\text{CH}_3); \text{IR } \nu_{\text{max}} \text{(neat)/cm}^{-1}: 2994, 2955, 2870, 2835, 1611, 1583, 1511, 1457; \text{HRMS} \text{(ESI): } \text{C}_{12}\text{H}_{19}\text{ClNO} [\text{M+H}^+]\text{: calculated 228.1150, found 228.1144.}

**Synthesis of 1-(but-3-en-1-yl)-2-phenylbenzene 313a**

Following general procedure G, using (2-biphenyl)methanol 312a (1.00 g, 5.43 mmol) and allylmagnesium chloride (5.43 mL of a 2.0 M solution in THF). Purification by flash chromatography on silica gel, eluting with 20% DCM in hexane afforded the title compound 313a (956 mg, 4.59 mmol, 85%) as a colourless oil. \[ ^1\text{H NMR} (500 \text{ MHz, CDCl}_3) 7.48-7.22 (9\text{H, m, ArH}), 5.75 (1\text{H, ddt, } J = 16.9, 10.2, 6.6, \text{butenyl H}_1-\text{C}3), 4.98-4.88 (2\text{H, m, butenyl H}_2-\text{C}4), 2.77-2.68 (2\text{H, m, butenyl H}_2-\text{C}1), 2.29-2.21 (2\text{H, m, butenyl H}_2-\text{C}2); ^{13}\text{C NMR} (125 \text{ MHz, CDCl}_3) \delta 142.1 (\text{C}_3), 142.0 (\text{C}_4), 139.4 (\text{C}_q), 138.3 (\text{butenyl C}3), 130.2 (\text{ArC}), 129.4 (2 \times \text{C, ArC}), 128.2 (2 \times \text{C, ArC}), 127.5 (\text{ArC}), 126.9 (\text{ArC}), 125.9 (\text{ArC}), 114.8 (\text{butenyl C}4), 35.3 (\text{butenyl C}2), 32.7 (\text{butenyl C}1); \text{IR } \nu_{\text{max}} \text{(neat)/cm}^{-1}: 3060, 3021, 2926, 1640, 1598, 1500, 1478, 1450;\]
Synthesis of 3-(2-phenylphenyl)propanal 314a

Following general procedure H, using alkene 313a (750 mg, 3.60 mmol). Purification by flash chromatography on silica gel, eluting with 10% Et₂O in hexane afforded the *title compound* 314a (596 mg, 2.83 mmol, 79%) as a colourless oil. 

<table>
<thead>
<tr>
<th>Spectroscopy</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>¹H NMR</td>
<td>δ 9.63 (1H, t, J = 1.4, propyl H₁-C₁), 7.49-7.17 (9H, m, ArH), 2.96 (2H, t, J = 7.8, propyl H₂-C₃), 2.55 (2H, td, J = 7.8, 1.4, propyl H₂-C₂)</td>
</tr>
<tr>
<td>¹³C NMR</td>
<td>δ 201.7 (propyl C₁), 142.1 (C₉), 141.5 (C₈), 137.8 (C₇), 130.5 (ArC), 129.24 (ArC), 129.17 (2 × C, ArC), 128.4 (2 × C, ArC), 127.8 (ArC), 127.2 (ArC), 126.5 (ArC), 45.0 (propyl C2), 25.8 (propyl C3)</td>
</tr>
</tbody>
</table>

IR νₘₐₓ (neat)/cm⁻¹: 3059, 3022, 2891, 2822, 2722, 1719 (C=O), 1598, 1500;

Synthesis of N-methyl[3-(2-phenylphenyl)propyl]amine 315a

Following general procedure C, using aldehyde 314a (450 mg, 2.14 mmol) and MeNH₂ (3.00 mL of an 8.0 M solution in EtOH) afforded the *title compound* 315a (480 mg, 2.13 mmol, 99%) as a clear yellow oil.

<table>
<thead>
<tr>
<th>Spectroscopy</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>¹H NMR</td>
<td>δ 7.47-7.18 (9H, m, ArH), 2.68-2.58 (2H, m, propyl H₂-C₁), 2.51-2.42 (2H, m, propyl H₂-C₁), 2.33 (3H, s, NCH₃), 1.71-1.60 (2H, m, propyl H₂-C₂), 1.35 (1H, br. s, NH)</td>
</tr>
<tr>
<td>¹³C NMR</td>
<td>δ 142.02 (C₉), 142.00 (C₈), 139.8 (C₇), 130.2 (ArC), 129.4 (2 × C, ArC), 128.1 (2 × C, ArC), 127.6 (ArC), 126.9 (ArC), 125.9 (ArC), 51.8 (propyl C1), 36.4 (NCH₃), 31.5 (propyl C3), 30.9 (propyl C2)</td>
</tr>
</tbody>
</table>

IR νₘₐₓ (neat)/cm⁻¹: 3057, 3022, 2891, 2822, 2722, 1719 (C=O), 1598, 1500;


Synthesis of N-chloro(methyl)[3-(2-phenylphenyl)propyl]amine 316a

Following general procedure A, using amine 315a (250 mg, 1.11 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the *title compound* 316a (215 mg, 0.83 mmol, 75%) as a pale yellow oil.

<table>
<thead>
<tr>
<th>Spectroscopy</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>¹H NMR</td>
<td>δ 7.37-7.09 (9H, m, ArH), 2.74 (3H, s, NCH₃), 2.69-2.64 (2H, m, propyl H₂-C₁), 2.60-2.54 (2H, m, propyl H₂-C₃), 1.75-1.65 (2H, m, propyl H₂-C₂)</td>
</tr>
<tr>
<td>¹³C NMR</td>
<td>δ 142.1 (C₉), 141.9 (C₈), 139.3 (C₇), 130.3 (ArC), 129.5 (ArC), 129.3 (2 × C, ArC), 128.3 (2 × C, ArC)</td>
</tr>
</tbody>
</table>

127.6 (ArC), 127.0 (ArC), 126.0 (ArC), 65.7 (propyl C1), 53.0 (NCH3), 30.3 (propyl C3), 29.8 (propyl C2); IR νmax (neat)/cm−1: 3059, 3021, 2991, 2950, 2867, 2794, 1598, 1500; HRMS (ESI): C16H35ClN [M+H]+: calculated 260.1201, found 260.1199.

**Synthesis of 1-methyl-5-phenyl-1,2,3,4-tetrahydroquinoline 328**

Following general procedure B, using chloroamine 316a (100 mg, 0.39 mmol). Work up B then purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 328 (65 mg, 0.29 mmol, 74%) as a clear yellow gum.

1H NMR (500 MHz, CDCl3) δ 7.41–7.35 (2H, m, ArH), 7.34–7.29 (3H, m, ArH), 7.16–7.10 (1H, m, ArH), 6.64 (1H, d, J = 8.2, ArH), 6.58 (1H, d, J = 7.5, ArH), 3.28–3.22 (2H, m, H2-C2), 2.96 (3H, s, NC3H7), 2.62 (2H, t, J = 6.4, H2-C4), 1.91–1.83 (2H, m, H2-C3);

13C NMR (125 MHz, CDCl3) δ 147.0 (Cq), 142.6 (Cq), 141.9 (Cq), 129.3 (2 × C, ArC), 128.0 (2 × C, ArC), 126.7 (ArC), 126.6 (ArC), 120.8 (Cq), 118.3 (ArC), 110.2 (ArC), 51.3 (C2), 39.7 (NCH3), 26.4 (C4), 22.7 (C3); IR νmax (neat)/cm−1: 3055, 2921, 2850, 2818, 2786, 1579, 1483, 1461; HRMS (ESI): C16H18N [M+H]+: calculated 224.1434, found 224.1434.

**Synthesis of 1-(but-3-en-1-yl)-4-phenylbenzene 313b**

Following general procedure G, using (4-phenylphenyl)methanol 312b (1.00 g, 5.43 mmol) and allylmagnesium chloride (5.43 mL of a 2.0 M solution in THF). Purification by flash chromatography on silica gel, eluting with 5% DCM in hexane afforded the title compound 313b (816 mg, 3.92 mmol, 72%) as a colourless oil.

1H NMR (400 MHz, CDCl3) δ 7.67–7.17 (9H, m, ArH), 5.88 (1H, ddt, J = 16.9, 10.2, 6.6, butenyl H1-C3), 5.07 (1H, dd, J = 17.1, 1.6, butenyl Htrans-C4), 5.02–4.97 (1H, m, butenyl Hcis-C4), 2.81–2.69 (2H, m, butenyl H2-C1), 2.46–2.36 (2H, m, butenyl H2-C2); 13C NMR (100 MHz, CDCl3) δ 141.3 (Cq), 141.1 (Cq), 138.9 (Cq), 138.2 (butenyl C3), 129.0 (2 × C, ArC), 128.9 (2 × C, ArC), 127.2 (2 × C, ArC), 127.1 (2 × C, ArC), 115.2 (butenyl C4), 35.6 (butenyl C2), 35.2 (butenyl C1) one 13C signal missing; IR νmax (neat)/cm−1: 3077, 3027, 2924, 2853, 1639, 1601, 1519, 1486;

**Synthesis of 3-(4-phenylphenyl)propanal 314b**
Following general procedure H, using alkene 313b (750 mg, 3.60 mmol). Purification by flash chromatography on silica gel, eluting with 5% EtO in hexane afforded the title compound 314b (640 mg, 3.04 mmol, 84%) as a colourless oil. The data is in accordance with the literature.\textsuperscript{21} \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 9.86 (1H, s, propyl H\textsubscript{1}-C1), 7.64-7.51 (4H, m, ArH), 7.48-7.22 (5H, m, ArH), 3.01 (2H, t, J = 7.5, propyl H\textsubscript{2}-C3), 2.83 (2H, t, J = 7.4, propyl H\textsubscript{2}-C2); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 201.6 (propyl C1), 141.0 (C\textsubscript{q}), 139.6 (C\textsubscript{q}), 139.5 (C\textsubscript{q}), 128.89 (2 × C, ArC), 128.87 (2 × C, ArC), 127.5 (2 × C, ArC), 127.3 (ArC), 127.2 (2 × C, ArC), 45.4 (propyl C2), 27.9 (propyl C3); IR \(\nu_{\text{max}}\) (neat)/cm\textsuperscript{-1}: 3029, 2944, 2821, 2725, 1709 (C=O), 1597, 1582, 1563;

Synthesis of \(N\)-methyl[3-(4-phenylphenyl)propyl]amine 315b

Following general procedure C, using aldehyde 314b (550 mg, 2.62 mmol) and MeNH\textsubscript{2} (3.00 mL of an 8.0 M solution in EtOH) afforded the title compound 315b (554 mg, 2.46 mmol, 94%) as a colourless amorphous solid. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.60-7.23 (9H, m, ArH), 2.74-2.60 (4H, m, includes 2H, m, propyl H\textsubscript{2}-C1; and 2H, m, propyl H\textsubscript{2}-C3), 2.44 (3H, s, NCH\textsubscript{3}), 1.94-1.77 (3H, m, includes 1H, br. s, NH; and 2H, m, propyl H\textsubscript{2}-C2); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 141.4 (C\textsubscript{q}), 141.2 (C\textsubscript{q}), 138.9 (C\textsubscript{q}), 128.9 (2 × C, ArC), 128.8 (2 × C, ArC), 127.2 (2 × C, ArC), 127.14 (ArC), 127.11 (2 × C, ArC), 51.7 (propyl C1), 36.5 (NCH\textsubscript{3}), 33.4 (propyl C3), 31.5 (propyl C2); IR \(\nu_{\text{max}}\) (neat)/cm\textsuperscript{-1}: 3314, 3055, 3027, 2930, 2852, 2789, 1601, 1563; HRMS (ESI): C\textsubscript{16}H\textsubscript{20}N [M+H\textsuperscript{+}]: calculated 226.1590, found 226.1586.

Synthesis of \(N\)-chloro(methyl)[3-(4-phenylphenyl)propyl]amine 316b

Following general procedure A, using amine 315b (350 mg, 1.55 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 316b (302 mg, 1.16 mmol, 75%) as a pale yellow oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.63-7.22 (9H, m, ArH), 2.96 (3H, s, NCH\textsubscript{3}), 2.95-2.90 (2H, m, propyl H\textsubscript{2}-C1), 2.77-2.71 (2H, m, propyl H\textsubscript{2}-C3), 2.07-1.97 (2H, m, propyl H\textsubscript{2}-C2); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 141.2 (C\textsubscript{q}), 140.9 (C\textsubscript{q}), 139.0 (C\textsubscript{q}), 129.0 (2 × C, ArC), 128.9 (2 × C, ArC), 127.3 (2 × C, ArC), 127.2 (ArC), 127.1 (2 × C, ArC), 65.4 (propyl C1), 53.2 (NCH\textsubscript{3}), 32.5 (propyl C3), 29.8 (propyl C2); IR \(\nu_{\text{max}}\) (neat)/cm\textsuperscript{-1}: 3057, 3029, 2997, 2863, 1595, 1487, 1455, 1439; HRMS (ESI): C\textsubscript{16}H\textsubscript{19}ClN [M+H\textsuperscript{+}]: calculated 260.1201, found 260.1201.
Synthesis of 1-methyl-7-phenyl-1,2,3,4-tetrahydroquinoline 329

Following general procedure B, using chloroamine 316b (100 mg, 0.39 mmol). Work up B then purification by flash chromatography on silica gel, eluting with 20% DCM in hexane afforded the title compound 329 (63 mg, 0.28 mmol, 72%) as a colourless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.56-7.47 (2H, m, ArH), 7.39-7.30 (2H, m, ArH), 7.28-7.21 (1H, m, ArH), 7.00-6.92 (1H, m, ArH), 6.80-6.70 (2H, m, ArH), 3.24-3.17 (2H, m, H$_2$-C$_2$), 2.89 (3H, s, NCH$_3$), 2.74 (2H, t, J = 6.5, H$_2$-C4), 2.01-1.89 (2H, m, H$_2$-C3); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 147.1 (C$q$), 142.5 (C$q$), 140.5 (C$q$), 129.3 (ArC), 128.7 (2 × C, ArC), 127.3 (2 × C, ArC), 127.0 (ArC), 122.2 (C$q$), 115.4 (ArC), 110.0 (ArC), 51.5 (C2), 39.3 (NCH$_3$), 27.7 (C4), 22.6 (C3); IR $\nu_{\text{max}}$(neat)/cm$^{-1}$: 3054, 3028, 2924, 2837, 1678, 1605, 1561, 1515; HRMS (ESI): C$_{16}$H$_{18}$N [M+H$^+$]: calculated 224.1434, found 224.1434.

Synthesis of 1-(but-3-en-1-yl)-4-chlorobenzene 313c

Following general procedure G, using 4-chlorobenzyl alcohol 312c (1.30 g, 9.12 mmol) and allylmagnesium bromide (9.10 mL of 2.0 M solution in THF). Purification by flash chromatography on silica gel with 10% EtOAc in hexane afforded the title compound 313c (640 mg, 3.84 mmol, 42%) as a colourless oil. The NMR data is in accordance with the literature.$^{218}$ $^1$H NMR (400 MHz, CDCl$_3$) δ 7.24 (2H, d, J = 8.6, ArH), 7.11 (2H, d, J = 8.6, ArH), 5.88-5.77 (1H, m, butenyl H$_1$-C3), 5.06-4.95 (2H, m, butenyl H$_2$-C4), 2.68 (2H, t, J = 7.7, butenyl H$_2$-C1), 2.39-2.30 (2H, m, butenyl H$_2$-C2); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 140.3 (C$q$), 137.6 (butenyl C2), 131.5 (C$q$), 129.8 (2 × C, ArC), 128.4 (2 × C, ArC), 115.3 (butenyl C1), 35.4 (butenyl C3), 34.7 (butenyl C4); IR $\nu_{\text{max}}$(neat)/cm$^{-1}$: 3078, 3027, 2978, 2928, 2837, 1678, 1605, 1561, 1515.

Synthesis of 3-(4-chlorophenyl)propanal 314c

Following general procedure H, using alkene 313c (550 mg, 3.30 mmol). Purification by flash chromatography on silica gel, eluting with 10% diethyl ether in hexane afforded the title compound 314c (481 mg, 2.85 mmol, 87%) as a colourless oil. The NMR data is in accordance with the literature.$^{219}$ $^1$H NMR (500 MHz, CDCl$_3$) δ 9.84 (1H, t, J = 1.2, propyl H$_1$-C1), 7.29
(2H, d, J = 8.2, ArH), 7.16 (2H, d, J = 8.2, ArH), 2.96 (2H, t, J = 7.5, propyl H₂-C3), 2.83-2.78 (2H, m, propyl H₂-C2); ¹³C NMR (126 MHz, CDCl₃) δ ppm 201.0 (propyl C₁), 138.8 (C₉), 132.1 (C₈), 129.7 (2 × ArC), 128.7 (2 × ArC), 45.1 (propyl C₂), 27.4 (propyl C₃); IR ν_max (neat) / cm⁻¹: 3028, 2929, 2894, 2725, 1720, 1492, 1447, 1408.

**Synthesis of [3-(4-chlorophenyl)propyl](methyl)amine 315c**

Following general procedure C, using aldehyde 314c (300 mg, 1.78 mmol) and MeNH₂ (0.5 mL of an 8 M solution in EtOH). Work-up A afforded the title compound 315c (288 mg, 1.57 mmol, 88%) as a yellow oil no further purification was required. The ¹H NMR data is in accordance with the literature.²²⁰ ¹H NMR (400 MHz, CDCl₃) δ 7.30-7.22 (2H, m, ArH), 7.17-7.10 (2H, m, ArH), 2.69-2.60 (2H, m, propyl H₂-C₁), 2.45 (3H, s, NCH₃), 2.16-1.96 (2H, m, propyl H₂-C₃), 1.90-1.76 (2H, m, propyl H₂-C₂); ¹³C NMR (100 MHz, CDCl₃) δ 140.5 (C₉), 131.5 (C₈), 129.8 (2 × C, ArC), 128.5 (2 × C, ArC), 51.3 (propyl C₁), 36.3 (NCH₃), 32.9 (propyl C₃), 31.2 (propyl C₂); IR ν_max (neat) / cm⁻¹: 3025, 2933, 2857, 2793, 1632, 1538, 1490, 1383; HRMS (ESI): C₁₀H₁₅ClN [M+H⁺]: calculated 184.0888, found 184.0892.

**Synthesis of N-chloro[3-(4-chlorophenyl)propyl]methylamine 316c**

Following general procedure A, using amine 315c (200 mg, 1.09 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 316c (160 mg, 0.73 mmol, 67%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.25 (2H, d, J = 8.3, ArH), 7.12 (2H, d, J = 8.3, ArH), 2.92 (3H, s, NCH₃), 2.85 (2H, t, J = 6.8, propyl H₂-C₁), 2.64 (2H, t, J = 7.6, propyl H₂-C₃), 1.98-1.90 (2H, m, propyl H₂-C₂); ¹³C NMR (100 MHz, CDCl₃) δ 140.1 (C₉), 131.6 (C₈), 129.8 (2 × C, ArC), 128.5 (2 × C, ArC), 65.0 (propyl C₁), 53.1 (NCH₃), 32.0 (propyl C₃), 29.6 (propyl C₂); IR ν_max (neat) / cm⁻¹: 2950, 2866, 1491, 1455, 1437, 1407, 1365, 1129; HRMS could not be obtained.

**Synthesis of 1-methyl-7-chloro-1,2,3,4-tetrahydroquinoline 326**

Following general procedure B, using chloroamine 316c (100 mg, 0.46 mmol). Work-up B, followed by purification by flash chromatography on silica gel, eluting with a gradient of 10% EtOAc in hexane afforded the title compound 326 (33 mg, 0.18 mmol, 39%) as a colourless
oil. ¹H NMR (400 MHz, CDCl₃) δ 6.83 (1H, d, J = 7.8, ArH-C5), 6.57-6.50 (2H, m, includes 1H, m, ArH-C6; and 1H, m, ArH-C8), 3.26-3.17 (2H, m, H₂-C2), 2.87 (3H, s, NCH₃), 2.70 (2H, t, J = 6.4, H₂-C4), 1.99-1.91 (2H, m, H₂-C3); ¹³C NMR (100 MHz, CDCl₃) δ 147.6 (C₉), 132.6 (C₉), 129.6 (ArC), 121.2 (C₉), 115.7 (ArC), 110.6 (ArC), 51.0 (C₂), 39.1 (NCH₃), 27.4 (C₄), 22.3 (C₃); IR ν_max (neat) / cm⁻¹: 3022, 2929, 2890, 2840, 1599, 1564, 1502, 1466; HRMS (ESI): C₁₀H₁₃ClN [M+H⁺]: calculated 182.0731, found 182.0723.

Synthesis of 1-(but-3-en-1-yl)-3-chlorobenzene 313d

Following general procedure F, using 3-chlorobenzyl bromide 312d (1.50 g, 7.30 mmol) and allylmagnesium chloride (7.30 mL of 2.0 M solution in THF). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 313d (1.20 g, 7.20 mmol, 99%) as a colourless oil. The data is in accordance with the literature. ²¹⁸ ¹H NMR (400 MHz, CDCl₃) δ 7.26-7.17 (3H, m, ArH), 7.09 (1H, d, J = 7.2, ArH), 5.92-5.80 (1H, m, butenyl H₁-C₃), 5.12-4.98 (2H, m, butenyl H₂-C₄), 2.72 (2H, t, J = 7.7, butenyl H₂-C₁), 2.39 (2H, m, butenyl H₂-C₂); ¹³C NMR (100 MHz, CDCl₃) δ 143.9 (C₉), 137.5 (butenyl C₃), 134.1 (C₉), 129.5 (ArC), 128.6 (ArC), 126.7 (ArC), 126.0 (ArC), 115.3 (butenyl C₄), 35.2 (butenyl C₂), 35.0 (butenyl C₁); IR ν_max (neat) / cm⁻¹: 3077, 2978, 2928, 2857, 1640, 1598, 1573, 1476;

Synthesis of 3-(3-chlorophenyl)propanal 314d

Following general procedure H, using alkene 313d (1.00 g, 6.00mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 314d (766 mg, 4.54 mmol, 76%) as a colourless oil. The data is in accordance with the literature. ²¹⁹ ¹H NMR (400 MHz, CDCl₃) δ 9.84 (1H, s, propyl H₁-C₁), 7.30-7.18 (3H, m, ArH), 7.10 (1H, d, J = 7.1, ArH), 2.96 (2H, t, J = 7.4, propyl H₂-C₂), 2.81 (2H, t, J = 7.5, propyl H₂-C₁); ¹³C NMR (100 MHz, CDCl₃) δ 200.9 (propyl C₁), 142.4 (C₉), 134.3 (C₉), 129.9 (ArC), 128.5 (ArC), 126.5 (ArC), 126.5 (ArC), 45.0 (propyl C₂), 27.7 (propyl C₃); IR ν_max (neat) / cm⁻¹: 3019, 2928, 2894, 2824, 2724, 1721 (C=O), 1598, 1573;

Synthesis of [3-(3-chlorophenyl)propyl](methyl)amine 315d
Following general procedure C, using aldehyde 314d (700 mg, 4.15 mmol) and MeNH₂ (1.50 mL of a 8.0 M solution in EtOH). Work-up A afforded the **title compound** 315d (672 mg, 3.66 mmol, 88%) as a colourless oil. **¹H NMR** (400 MHz, CDCl₃) δ 7.26-7.15 (3H, m, ArH), 7.08 (1H, d, J = 7.2, ArH), 2.70-2.61 (4H, m, including 2H, m, propyl H₂-C₁; and 2H, m, propyl H₂-C₃), 2.47 (3H, s, NC₃H₃), 1.91-1.80 (2H, m, propyl H₂-C₂); **¹³C NMR** (100 MHz, CDCl₃) δ 144.0 (C₉), 134.1 (C₈), 129.6 (ArC), 128.5 (ArC), 126.6 (ArC), 126.1 (ArC), 51.1 (propyl C₁), 36.1 (NCH₃), 33.2 (propyl C₃), 30.8 (propyl C₂); **IR** ν_{max} (neat) / cm⁻¹: 3059, 2935, 2858, 2796, 1596, 1571, 1536, 1473; **HRMS** (ESI): C₁₀H₁₅ClN [M+H⁺]: calculated 184.0888, found 184.0886.

**Synthesis of N-chloro[3-(3-chlorophenyl)propyl]methylamine 316d**

Following general procedure A, using amine 315d (300 mg, 1.64 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the **title compound** 316d (300 mg, 1.38 mmols, 85%) as a colourless oil. **¹H NMR** (400 MHz, CDCl₃) δ 7.26-7.17 (3H, m, ArH), 7.10 (1H, d, J = 7.2, ArH), 2.96 (3H, s, NCH₃), 2.89 (2H, t, J = 6.8, propyl H₂-C₁), 2.69 (2H, t, J = 7.7, propyl H₂-C₃), 2.01-1.94 (2H, m, propyl H₂-C₂); **¹³C NMR** (100 MHz, CDCl₃) δ 143.8 (C₉), 134.1 (C₈), 129.7 (ArC), 128.6 (ArC), 126.7 (ArC), 126.1 (ArC), 64.9 (propyl C₁), 53.1 (NCH₃), 32.4 (propyl C₃), 29.5 (propyl C₂); **IR** ν_{max} (neat) / cm⁻¹: 3061, 2992, 2950, 2919, 2867, 1597, 1572, 1475; **HRMS** (ESI): C₁₀H₁₄Cl₂N [M+H⁺]: calculated 218.0498, found 218.0492.

**Synthesis of 1-methyl-6-chloro-1,2,3,4-tetrahydroquinoline and 1-methyl-8-chloro-1,2,3,4-tetrahydroquinoline 330**

Following general procedure B, using chloroamine 316d (100 mg, 0.46 mmol). Work-up B, followed by purification by flash chromatography on silica gel, eluting with a gradient of 10% EtOAc in hexane afforded an inseparable mixture of regioisomeric title compounds 330 (47 mg, 0.26 mmol, 57%, 1:1:1). **¹H NMR** (400 MHz, CDCl₃) δ 7.20-7.15 (0.52H, m, ArH, **major**), 6.97-6.94 (0.48H, m, ArH, **minor**), 6.82 (0.52H, t, J = 7.7, ArH, **major**), 6.48 (0.48H, d, J = 8.7, ArH, **minor**), 3.22-3.18 (0.96H, m, H₂-C₂, **minor**), 3.16-3.12 (1.04H, m, H₂-C₂, **major**), 2.89 (1.56H, s, NCH₃, **major**), 2.86 (1.44H, s, NCH₃, **minor**), 2.80 (1.04H, t, J = 6.7, H₂-C₄, **major**), 167
2.73 (0.96H, t, J = 6.5, H-2-C4, minor), 1.96 (0.96H, ddd, J = 12.8, 9.1, 4.6, H-2-C3, minor),
1.86 (1.04H, ddd, J = 12.8, 9.1, 4.6, H-2-C3, major); 13C NMR (100 MHz, CDCl3) δ 146.1 (Cq),
145.4 (Cq), 131.4 (Cq), 128.5 (ArC), 128.4 (ArC), 128.3 (ArC), 127.6 (Cq), 126.8 (ArC), 124.6
(Cq), 122.2 (ArC), 120.8 (Cq), 112.0 (ArC), 52.1 (CH2), 51.2 (CH2), 43.0 (CH3), 39.3 (CH3),
28.0 (CH2), 27.8 (CH2), 22.3 (CH2), 17.3 (CH2); IR νmax (neat)/cm⁻¹: 2935, 2861, 1596, 1561,
1501, 1464, 1443, 1416; HRMS (ESI): H10C13F35N [M+H⁺]: calculated 182.0731, found 182.0728.

**Synthesis of 1-(but-3-en-1-yl)-4-trifluoromethylbenzene 313e**

Following general procedure G, using 4-trifluoromethylbenzyl alcohol 312e (700 mg, 3.96
mmol) and allylmagnesium bromide (3.96 mL of 2.0 M solution in THF). Purification by flash
chromatography on silica gel with 10% EtOAc in hexane afforded the title compound 313e
(354 mg, 1.77 mmol, 45%) as a colourless oil. The data is in accordance with the literature.²²¹

1H NMR (400 MHz, CDCl3) δ 7.54 (2H, d, J = 8.1, ArH), 7.30 (2H, d, J = 8.1, ArH), 5.84
(1H, ddt, J = 16.9, 10.2, 6.6, butenyl H-1-C3), 5.09-4.98 (2H, m, butenyl H-2-C4), 2.78 (2H, t,
J = 7.5, butenyl H-2-C1), 2.40 (2H, ddt, J = 14.7, 7.5, butenyl H-2-C2); 13C NMR (100 MHz,
CDCl3) δ 146.1 (Cq), 137.5 (butenyl C3), 128.9 (2 × C, Ar C2), 128.3 (q, J = 32.2, Cq), 125.4
(2 × C, q, J = 3.7, Ar C3), 124.5 (q, J = 271.7, CF3), 115.6 (butenyl C4), 35.3 (butenyl C1),
35.2 (butenyl C2); IR νmax (neat)/cm⁻¹: 3082, 2982, 2932, 2861, 1642, 1619, 1418, 1322.

**Synthesis of 3-(4-trifluoromethylphenyl)propanal 314e**

Following general procedure H, using alkene 313e (300 mg, 1.50 mmol). Purification by flash
chromatography on silica gel, eluting with 10% diethyl ether in hexane afforded the title compound 314e
(256 mg, 1.27 mmol, 85%) as a colourless oil. The data is in accordance with the literature.²²²

1H NMR (500 MHz, CDCl3) δ 9.82 (1H, s, propyl H-1-C1), 7.55 (2H, d, J = 8.1, ArH), 7.31 (2H, d, J = 8.1, ArH), 3.01 (2H, t, J = 7.4, propyl H-2-C3), 2.82 (2H, t, J = 7.4, propyl H-2-C2); 13C NMR (100 MHz,
CDCl3) δ 200.8 (propyl C1), 144.7 (Cq), 128.9 (q, J = 32.3, Cq), 128.8 (2 × C, Ar C2), 125.7 (2 × C, q, J = 3.6, Ar C3), 124.9 (q, J = 271.8, CF3), 45.0 (propyl C2), 27.9 (propyl C3); IR νmax (neat)/cm⁻¹: 2936, 2829, 2730, 1723 (C=O), 1619,
1585, 1419, 1322.

**Synthesis of [3-(4-trifluoromethylphenyl)propyl](methyl)amine 315e**
Following general procedure C, using aldehyde 314e (200 mg, 0.99 mmol) and MeNH₂ (1.25 mL of an 8 M solution in EtOH). Work-up A afforded the title compound 315e (180 mg, 0.83 mmol, 83%) as a yellow oil no further purification was required. The ¹H NMR data is in accordance with the literature.²²⁰ ¹H NMR (400 MHz, CDCl₃) (400 MHz, CDCl₃) δ 7.52 (2H, d, J = 8.0, ArH), 7.28 (2H, d, J = 8.0, ArH), 2.71 (2H, t, J = 7.7, propyl H₂-C3), 2.60 (2H, t, J = 7.1, propyl H₂-C1), 2.42 (3H, s, NCH₃), 1.85-1.77 (2H, m, propyl H₂-C2); ¹³C NMR (100 MHz, CDCl₃) δ 146.4 (Cₗq), 128.8 (2 × C, Ar C₂), 128.30 (q, Jₗq = 32.3, Ar C₃), 125.4 (2 × C, q, Jₗq = 3.9, Ar C₃), 124.3 (q, J = 271.7, CF₃), 51.5 (propyl C₁), 36.5 (NCH₃), 33.5 (propyl C₃), 31.3 (propyl C₂);

IR νₘₐₓ (neat) / cm⁻¹: 3294, 2938, 2862, 1619, 1537, 1476, 1418, 1322; HRMS (ESI): C₁₁H₁₅F₃N [M+H⁺]: calculated 218.1151, found 218.1151.

Synthesis of N-chloro[3-(4-trifluoromethylphenyl)propyl]methylamine 316e

Following general procedure A, using amine 315e (150 mg, 0.69 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 316e (148 mg, 0.59 mmol, 86%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.54 (2H, d, J = 8.1, ArH), 7.31 (2H, d, J = 8.1, ArH), 2.94 (3H, s, NCH₃), 2.87 (2H, t, J = 6.8, propyl H₂-C1), 2.75 (2H, t, J = 7.7, propyl H₂-C3), 2.02-1.94 (2H, m, propyl H₂-C₂); ¹³C NMR (100 MHz, CDCl₃) δ 146.0 (Cₗq), 128.9 (2 × C, Ar C₂), 128.47 (d, J = 32.3, Cₗq), 125.5 (2 × C, q, J = 3.7, Ar C₃), 124.5 (q, J = 271.8, CF₃), 65.0 (propyl C₁), 53.2 (NCH₃), 32.6 (propyl C₃), 29.6 (propyl C₁); IR νₘₐₓ (neat) / cm⁻¹: 2953, 2872, 2798, 1619, 1537, 1476, 1418, 1322; HRMS could not be obtained.

Synthesis of 1-methyl-7-trifluoromethyl-1,2,3,4-tetrahydroquinoline 331

Following general procedure B, using chloroamine 316e (100 mg, 0.40 mmol). Work-up B, followed by purification by flash chromatography on silica gel, eluting with a gradient of 10% EtOAc in hexane afforded the title compound 331 (26 mg, 0.12 mmol, 30%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.01 (1H, d, J = 7.6, Ar-H-C₅), 6.82 (1H, d, J = 7.6, Ar-H-C₆), 6.74 (1H, s, Ar-H-C₈), 3.30-3.25 (2H, m, H₂-C₂), 2.92 (3H, s, NCH₃), 2.78 (2H, t, J = 6.3, H₂-C₄), 2.02-1.95 (2H, m, H₂-C₃); ¹³C NMR (100 MHz, CDCl₃) δ 146.8 (Cₗq), 129.5 (q,
$J = 31.5, C_q, 128.9 \text{ (C5)}, 126.4 \text{ (C6)}, 124.8 \text{ (d, } J = 272.0, \text{ CF}_3), 112.5 \text{ (q, } J = 3.9, \text{ C6)}, 106.9 \text{ (q, } J = 3.8, \text{ C8)}, 51.1 \text{ (C2)}, 39.0 \text{ (NCH}_3, 27.9 \text{ (C4)}, 22.1 \text{ (C3)}; \text{ IR } \nu_{\text{max}} \text{ (neat) / cm}^{-1}: 2933, 2843, 1615, 1582, 1510, 1488, 1467, 1445; \text{ HRMS (ESI): } C_{22}H_{25}F_6N [2M+H]^+: \text{ calculated 431.1916, found 431.1903.}

**Synthesis of 1-(but-3-en-1-yl)-4-bromobenzene 313f**

Following general procedure F, using benzyl bromide 312f (10.0 g, 40.0 mmol) and allyl magnesium chloride (20 mL of 2.0 M solution in THF) afforded the title compound 313f (8.52 g, 40.0 mmol, quant.) as a colourless oil. The data is in accordance with the literature.

$^1H$ NMR (500 MHz, CDCl$_3$) $\delta$ 7.40 (2H, d, $J = 8.4$, ArH), 7.06 (2H, d, $J = 8.5$, ArH), 5.83 (1H, ddt, $J = 17.0, 10.2, 6.6$, butenyl $H_{1-C3}$), 5.04 (1H, ddd, $J = 17.0, 3.4$, butenyl $H_{\text{trans-C4}}$), 4.99 (1H, dd, $J = 10.2, 1.9$, butenyl $H_{\text{cis-C4}}$), 2.71 - 2.61 (2H, m, butenyl $H_{2-C1}$), 2.35 (2H, app. dtt, $J = 9.0, 7.8, 1.3$, butenyl $H_{2-C2}$);

$^{13}C$ NMR (125 MHz, CDCl$_3$) $\delta$ 140.9 (C$\text{q}$), 137.7 (butenyl C3), 131.5 (2 × C, ArC), 130.4 (2 × C, ArC), 119.7 (C$\text{q}$), 115.4 (butenyl H$_2$-C4), 35.4 (butenyl C2), 34.9 (butenyl C1); IR $\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3078, 3024, 2978, 2929, 2857, 1641, 1487, 1439.

**Synthesis of 3-(4-bromophenyl)propanal 314f**

Following general procedure H, using alkene 313f (8.10 g, 38.1 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 20–40% Et$_2$O in hexane afforded the title compound 314f (7.13 g, 33.5 mmol, 88%) as a pale yellow oil. The data is in accordance with the literature.

$^1H$ NMR (400 MHz, CDCl$_3$) $\delta$ 9.80 (1H, s, propyl $H_{1-C1}$), 7.40 (2H, d, $J = 8.3$, ArH), 7.07 (2H, d, $J = 8.3$, ArH), 2.90 (2H, t, $J = 7.4$, propyl H$_2$-C3), 2.76 (2H, t, $J = 7.4$, propyl H$_2$-C2); $^{13}C$ NMR (100 MHz, CDCl$_3$) $\delta$ 201.1 (propyl C1), 139.5 (C$\text{q}$), 131.8 (2 × C, ArC), 130.2 (2 × C, ArC), 120.2 (C$\text{q}$), 45.1 (propyl C3), 27.6 (propyl C2); IR $\nu_{\text{max}}$ (neat)/cm$^{-1}$: 2930, 2823, 2724, 1719 (C=O), 1591, 1487, 1438, 1404;

**Synthesis of [3-(4-bromophenyl)propyl](methyl)amine 315f**

Following general procedure C, using aldehyde 314f (5.00 g, 23.5 mmol) and methylamine (30.0 mL of a 8.0 M solution in EtOH, 235 mmol) afforded the title compound 315f (5.31 g, 23.3 mmol, 99%) as a yellow oil. The data is in accordance with the literature.
(400 MHz, CDCl₃) δ 7.38 (2H, d, J = 8.3, ArH), 7.05 (2H, d, J = 8.3, ArH), 2.64-2.55 (4H, m, includes 2H, m, propyl H₂-C₁; and 2H, m, propyl H₂-C₃), 2.41 (3H, s, NC₃H₃), 1.83-1.73 (2H, m, propyl H₂-C₂);

**13C NMR** (101 MHz, CDCl₃) δ 141.1 (C=O), 131.5 (2 × C, ArC), 130.2 (2 × C, ArC), 119.6 (Cₚ), 51.3 (propyl C₁), 36.4 (N₃C₃H₉), 33.1 (propyl C₃), 31.2 (propyl C₂);

**IR** νmax (neat)/cm⁻¹: 3310 (N-H), 3023, 2932, 2857, 2798, 1537, 1487, 1452;

**HRMS** (ESI): C₁₀H₁₅₇9BrN [M+H⁺]: calculated 228.0382, found 228.0376.

**Synthesis of tert-butyl-N-[3-{4-bromophenyl}propyl]-N-methylcarbamate 317**

To a stirred solution of amine 315f (5.00 g, 21.9 mmol, 1.0 eq.) in DCM (60 mL) was added Et₃N (6.11 mL, 43.8 mmol, 2.0 eq.), Boc₂O (5.26 g, 24.1 mmol, 1.1 eq.) and DMAP (269 mg, 2.20 mmol, 0.1 eq.). The reaction mixture was stirred at RT for 1 h then was diluted with H₂O (100 mL) and the aqueous phase was extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with H₂O (100 mL), dried over Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with a gradient of 0-40% EtOAc in hexane afforded the title compound 317 (5.74 g, 17.5 mmol, 80%) as a colourless oil.

**1H NMR** (400 MHz, CDCl₃) δ 7.38 (2H, d, J = 8.2, ArH), 7.05 (2H, d, J = 8.3, ArH), 3.27 (2H, br. s, propyl H₂-C₁), 2.83 (3H, br. s, NC₃H₃), 2.59-2.47 (2H, m, propyl H₂-C₃), 1.43 (9H, s, OC(CH₃)₃); **13C NMR** (100 MHz, CDCl₃) δ 155.9 (C=O), 140.8 (Cₚ), 131.5 (2 × C, ArC), 130.2 (2 × C, ArC), 119.7 (Cₚ), 79.4 (Cₚ), 48.4 (propyl C₁), 34.2 (NCH₃), 32.6 (propyl C₃), 29.4 (propyl C₂), 28.6 (3 × C, OC(CH₃)₃); **IR** νmax (neat)/cm⁻¹: 2974, 2930, 2863, 1688 (C=O), 1487, 1453, 1423, 1391; **HRMS** (ESI): C₁₅H₂₂₁⁷BrNO₂Na [M+Na⁺]: calculated 350.0726, found 350.0721.

**Synthesis of tert-butyl-N-methyl-N-{3-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]propyl}carbamate 318**

To a stirred solution of aryl bromide 317 (750 mg, 2.28 mmol, 1.0 eq.) in DMSO (9.2 mL) was added PdCl₂(dppf)•DCM (73 mg, 0.09 mmol, 0.05 eq.), B₂(pin)₂ (580 mg, 2.28 mmol, 1.0 eq.) and KOAc (538 mg, 5.49 mmol, 3.0 eq.). The reaction mixture was heated at 90 °C for 18 h then cooled to RT and diluted with H₂O (75 mL). The aqueous phase was extracted with hexane (2 × 50 mL) then hexane:Et₂O (1:1 v/v, 2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na₂SO₄ and concentrated in vacuo.
Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the **title compound** 318 (532 mg, 1.42 mmol, 62%) as a colourless solid. **1H NMR** (400 MHz, CDCl$_3$) $\delta$ 7.73 (2H, d, $J = 7.8$, ArH), 7.19 (2H, d, $J = 7.8$, ArH), 3.23 (2H, br. s, propyl H$_2$-C1), 2.83 (3H, br. s, NCH$_3$), 2.61 (2H, t, $J = 7.7$, propyl H$_2$-C3), 1.88-1.77 (2H, m, propyl H$_2$-C2), 1.44 (9H, s, OC(C$_3$H$_7$)$_3$), 1.33 (12H, s, 2 $\times$ OC(C$_3$H$_7$)$_2$); **13C NMR** (100 MHz, CDCl$_3$) $\delta$ 156.0 (C=O), 145.3 (C$q$), 135.1 (2 $\times$ C, ArC), 127.9 (2 $\times$ C, ArC), 83.8 (2 $\times$ C, OC(CH$_3$)$_3$), 79.4 (OC(CH$_3$)$_3$), 48.7 (propyl C1), 34.3 (NCH$_3$), 33.4 (propyl C3), 29.5 (propyl C2), 1.81 (2H, dt, $J = 14.5$, 7.4, propyl H$_2$-C2), 1.33 (12H, s, 2 $\times$ OC(CH$_3$)$_3$); **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2980, 2970, 2934, 2862, 1681 (C=O), 1611, 1483, 1458; **HRMS** (ESI): C$_{21}$H$_{34}$BNO$_4$Na [M+Na$^+$]: calculated 398.2473, found 398.2475.

**Synthesis of methyl([3-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]propyl])amine 319**

To a stirred solution of carbamate 318 (400 mg, 1.07 mmol, 1.0 eq.) in DCM (3 mL) at 0 °C was added TFA (3 mL) portionwise. The reaction mixture was warmed to RT at stirred for 1 h then concentrated. The residue was then dissolved in DCM (5 mL) and K$_2$CO$_3$ (663 mg, 4.80 mmol, 5 eq.) was added portionwise. The reaction mixture was stirred at RT for 1 h, then diluted with H$_2$O (10 mL) and the aqueous phase was extracted with EtOAc (2 $\times$ 20 mL). The combined organic extracts were washed with brine (10 mL), dried over Na$_2$SO$_4$ and concentrated *in vacuo*. Purification by SCX-cartridge afforded the **title compound** 319 (253 mg, 0.92 mmol, 86%) as a yellow oil. **1H NMR** (400 MHz, CDCl$_3$) $\delta$ 7.73 (2H, d, $J = 7.9$, ArH), 7.20 (2H, d, $J = 7.8$, ArH), 2.72-2.63 (2H, m, propyl H$_2$-C1), 2.63-2.57 (2H, m, propyl H$_2$-C3), 2.42 (3H, s, NCH$_3$), 1.81 (2H, dt, $J = 14.5$, 7.4, propyl H$_2$-C2), 1.33 (12H, s, 2 $\times$ OC(CH$_3$)$_3$); **13C NMR** (100 MHz, CDCl$_3$) $\delta$ 156.1 (C$q$), 135.1 (2 $\times$ C, ArC), 128.0 (2 $\times$ C, ArC), 83.8 (2 $\times$ C, OC(CH$_3$)$_3$), 51.8 (propyl C1), 36.6 (NCH$_3$), 34.0 (propyl C3), 31.5 (propyl C2), 25.0 (4 $\times$ C, OC(CH$_3$)$_2$) one ArC$q$ signal missing; **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3305 (N-H), 2977, 2932, 2861, 1678, 1611, 1518, 1460; **HRMS** (ESI): C$_{16}$H$_{27}$BNO$_2$ [M+H$^+$]: calculated 276.2129, found 276.2131.
Synthesis of \(N\)-chloro(methyl){3-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]propyl}amine 320

Following general procedure A, using amine 319 (250 mg, 0.91 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 320 (232 mg, 0.75 mmol, 82%) as a clear yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.74 (2H, d, \(J = 7.9, \text{ArH}\)), 7.21 (2H, d, \(J = 7.9, \text{ArH}\)), 2.92 (3H, s, NC\(_3\)H), 2.86 (2H, t, \(J = 7.4, \text{propyl H}_2\)) \(\text{C}1\)), 2.70 (2H, t, \(J = 7.4, \text{propyl H}_2\)) \(\text{C}3\)), 2.02-1.93 (2H, m, propyl \(\text{H}_2\)) \(\text{C}2\)), 1.34 (12H, s, OC(CH\(_3\))\(_2\)) \(\text{one ArC}_q\) signal missing; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 145.2 (C \(\text{q}\)), 135.1 (2 \times C, phenyl C3), 128.1 (2 \times C, phenyl C-2), 83.8 (2 \times C, OC(CH\(_3\))\(_2\)), 65.3 (propyl C1), 53.2 (propyl C3), 29.7 (propyl C2), 25.0 (4 \times C, OC(CH\(_3\))\(_2\)) one ArC\(_q\) signal missing; IR \(\nu_{\text{max}}\) (neat) / cm\(^{-1}\): 2972, 2877, 2802, 1611, 1559, 1520, 1460, 1439; HRMS (ESI): \(\text{C}_{16}\text{H}_{26}\text{B}_{35}\text{ClNO} [\text{M+H}^+]\): calculated 310.1740, found 310.1739.

Synthesis of 1-methyl-7-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydroquinoline 332

To a stirred solution of chloroamine 320 (100 mg, 0.32 mmol) in DCM (1.07 mL) was added MeSO\(_3\)H (0.21 mL, 3.23 mmol, 10.0 eq.). The reaction mixture was irradiated with a high pressure 125 W Hg lamp for 3 h, after which it was diluted with DCM (5 mL) and extracted with H\(_2\)O (5 mL). The layers were separated and the aqueous layer was basified with sat. NaHCO\(_3\) solution (10 mL), then extracted with EtOAc (3 \times 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na\(_2\)SO\(_4\) and concentrated. Purification by flash chromatography on silica gel, eluting with a gradient of 10% EtOAc in hexane afforded the title compound 332 (41 mg, 0.15 mmol, 47%) as a yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.08 (1H, d, \(J = 7.3, \text{ArH}\)), 7.03 (1H, s, \text{ArH}), 6.97 (1H, d, \(J = 7.3, \text{ArH}\)), 3.24-3.18 (2H, m, NCH\(_2\)), 2.93 (3H, s, NCH\(_3\)), 2.77 (2H, t, \(J = 6.5, \text{PhCH}_2\)), 1.97 (2H, app. dt, \(J = 12.0, 6.3, \text{CH}_2\)), 1.33 (12H, s, OC(CH\(_3\))\(_2\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 146.4 (Ar\(_q\)), 128.5 (ArC), 126.7 (Ar\(_q\)), 123.2 (ArC), 117.0 (ArC), 83.6 (2 \times C, OC(CH\(_3\))\(_2\)), 51.5 (NCH\(_2\)), 39.4 (NCH\(_3\)), 28.2 (PhCH\(_2\)), 25.0 (4 \times C, OC(CH\(_3\))\(_2\)) one Ar\(_q\) signal missing; IR
\[ \nu_{\text{max}} \ (\text{neat})/\text{cm}^{-1}: \ 2976, \ 2930, \ 2838, \ 1695, \ 1605, \ 1561, \ 1510, \ 1480; \ \text{HRMS} \ (\text{ESI}): \ \text{C}_{16}\text{H}_{25}\text{BNO}_2 \ [\text{M+H}^+]: \ \text{calculated} \ 274.1973, \ \text{found} \ 274.1980. \]

**Synthesis of (S,E)-2-methyl-N-(3-phenylpropyldene)propane-2-sulfinamide 336**

To an oven-dried flask flushed with N\(_2\) was added anhydrous CuSO\(_4\) (7.98 g, 50.0 mmol, 2.0 eq.) and (S)-(−)-tert-butylsulfinamide (3.03 g, 25.0 mmol, 1.0 eq.). A solution of hydrocinnamaldehyde \(275\) (3.62 mL, 27.5 mmol, 1.1 eq.) in DCM (30 mL) was added and the reaction mixture was stirred at RT for 16 h. The reaction mixture was filtered through celite and washed with DCM (400 mL) and the filtrate was concentrated in vacuo to afford the title compound \(336\) (5.93 g, 25.0 mmol, quant.) as a yellow oil. The data is in accordance with the literature.\(^{225}\)

**1H NMR** (500 MHz, CDCl\(_3\)) \(\delta \ 8.12 \ (1\ H, \ t, \ J = 4.3, \ \text{propylidyl H}_{1-1} - \text{C}1), \ 7.31-7.25 \ (2\ H, \ m, \ \text{ArH}), \ 7.23-7.16 \ (3\ H, \ m, \ \text{ArH}), \ 3.01-2.94 \ (2\ H, \ m, \ \text{propylidyl H}_{2-2} - \text{C3}), \ 2.90-2.84 \ (2H, m, propylidyl H_{2-2} - \text{C2}), \ 1.13 \ (9H, s, \ C(CH_{3})_{3}); \ **13C NMR** (125 MHz, CDCl\(_3\)) \(\delta \ 168.6 \ (\text{propylidyl C1}), \ 140.5 \ (C_q), \ 128.7 \ (2 \times C, \ \text{ArC}), \ 128.5 \ (2 \times C, \ \text{ArC}), \ 126.4 \ (\text{ArC}), \ 56.7 \ (C_q), \ 37.6 \ (\text{propylidyl C3}), \ 31.5 \ (\text{propylidyl C2}), \ 22.4 \ (3 \times C, \ (CH_{3})_{3}); \ **IR** \(\nu_{\text{max}} \ (\text{neat})/\text{cm}^{-1}: \ 3027, \ 2959, \ 2926, \ 2867, \ 1622 \ (\text{N=C}), \ 1497, \ 1455, \ 1391; \ **HRMS** \ (ESI): \ \text{C}_{13}\text{H}_{20}\text{NOS} \ [\text{M+H}^+]: \ \text{calculated} \ 238.1260, \ \text{found} \ 238.1258. \]

**Synthesis of (S)-N-(1,3-diphenylpropyl)-2-methylpropane-2-sulfinamide 337a**

To a stirred solution of sulfinamide \(336\) (1.00 g, 4.21 mmol, 1 eq.) in THF (8 mL) at −78 °C was added a solution of phenylmagnesium bromide (6.32 mL of of 1.0 M solution in THF, 1.5 eq.) dropwise and the reaction mixture was stirred for 2 h, after which it was the reaction was quenched with sat. aqueous NH\(_4\)Cl (20 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were dried over Na\(_2\)SO\(_4\) then concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with 20% EtOAc in hexane afforded an inseparable mixture of the diastereoisomeric title compounds \(337a\) (729 mg, 2.31 mmol, 55%, 3:1) as a colourless gum.\(^{1H NMR} \ (500 MHz, \text{CDCl}_3) \delta \ 7.40-7.24 \ (7H, m, \text{includes } 5.25H, \ m, \text{ArH}, \ \text{major}; \text{and } 1.75H, \ m, \text{ArH}, \ \text{minor}), \ 7.19-7.09 \ (3H, m, \text{includes } 2.25H, \ m, \text{ArH}, \ \text{major}; \text{and } 0.75H, \ m, \text{ArH}, \ \text{minor}), \ 4.45-4.37 \ (1H, m, \text{includes } 0.75H, \ m, \text{propyl H}_{1-1} - \text{C1}, \ \text{major}; \text{and } 0.25H, \ m, \text{propyl H}_{1-1} - \text{C1}, \ \text{minor}), \ 3.45-3.36 \ (1H, m,
includes 0.75H, m, NH, major; and 0.25H, m, NH, minor), 2.62–2.51 (1 H, m), 2.51 – 2.42 (1 H, m), 2.37 (1 H, ddt, J 13.4, 10.9, 5.6), 2.21 – 2.12 (1 H, m), 2.12 – 2.02 (1 H, m), 1.23 (6.75H, s, C(CH₃)₃, major), 1.14 (2.25H, s, C(CH₃)₃, minor); ^1H NMR (125 MHz, CDCl₃) δ 142.1 (s), 141.7 (m), 141.4 (s), 141.1 (m), 128.8 (s), 128.5 (s), 128.4 (s), 128.4 (s), 128.3 (s), 128.0 (s), 127.7 (s), 127.7 (s), 127.3 (s), 126.1 (s), 125.9 (s), 59.0 (s), 58.7 (s), 55.7 (s), 55.5 (s), 40.2 (s), 38.2 (s), 32.2 (s), 31.9 (s), 22.6 (s), 22.5 (s); IR ν_max (neat)/cm⁻¹: 3240 (N-H), 3215, 3087, 3027, 2954, 1603, 1495, 1452; HRMS (ESI): C₁₉H₂₆NOS [M+H⁺]: calculated 316.1730, found 316.1736.

Synthesis of N-methyl-1,3-diphenylpropan-1-amine 338a

To a stirred solution of sulfinamide 337a (700 mg, 2.22 mmol, 1.0 eq.) in THF (10 mL) at 0 °C was added a solution of LiHMDS (2.22 mL of a 1.0 M solution in THF, 1.0 eq.) dropwise. After 1 h neat MeI (0.28 mL, 4.44 mmol, 2.0 eq.) was added portionwise and the reaction mixture was warmed to RT and stirred for 2 h. The reaction was quenched with H₂O (10 mL) and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na₂SO₄, concentrated in vacuo and the crude gum was taken up in 3 N methanolic HCl (10 mL) and stirred for 3 h. The reaction mixture was concentrated in vacuo then taken up in EtOAc (10 mL). This was extracted with 2 M aqueous HCl (10 mL) then the aqueous phase was basified with 2 M aqueous NaOH (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. Purification by SCX cartridge afforded the title compound 338a (413 mg, 1.83 mmol, 82%) as a yellow oil. ^1H NMR (500 MHz, CDCl₃) δ 7.39-7.32 (2H, m, ArH), 7.32-7.24 (5H, m, ArH), 7.20-7.10 (3H, m, ArH), 3.49 (1H, dd, J = 7.8, 6.0, propyl H₁-C1), 2.60-2.48 (2H, m, propyl H₂-C3), 2.27 (3H, s, NCH₃), 2.14-2.04 (1H, m, propyl H₆-C2), 2.03-1.92 (1H, m, propyl H₇-C2); ^13C NMR (125 MHz, CDCl₃) δ 143.4 (C₉), 142.0 (ArC), 128.4 (2 × C, ArC), 128.3 (2 × C, ArC), 127.4 (2 × C, ArC), 127.13 (ArC), 125.7 (C₉), 64.9 (propyl C1), 39.2 (propyl C2), 34.3 (NCH₃), 32.5 (propyl C3); IR ν_max (neat)/cm⁻¹: 3061, 2935, 2850, 2789, 1602, 1493, 1475, 1452; HRMS (ESI): C₁₇H₁₇NOS [M+H⁺]: calculated 266.1590, found 226.1592.

Synthesis of N-chloro-N-methyl-1,3-diphenylpropan-1-amine 339a

![Diagram](attachment:diagram.png)
Following general procedure A, using amine 338a (350 mg, 1.55 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 339a (386 mg, 1.49 mmol, 96%) as a pale yellow gum. 

**1H NMR** (500 MHz, CDCl₃) δ 7.45-7.34 (5H, m, ArH), 7.34-7.27 (2H, m, ArH), 7.25-7.15 (3H, m, ArH), 3.76 (1H, dd, J = 8.7, 4.4, propyl H₁-C1), 2.79 (3H, s, NC₂H₃), 2.61-2.50 (3H, m, includes 2H, m, propyl H₂-C₃; and 1H, m, propyl H₃-C₂), 2.25-2.13 (1H, m, propyl H₆-C₃); **13C NMR** (125 MHz, CDCl₃) δ 141.6 (C₉), 138.5 (C₉), 128.9 (2 × C, ArC), 128.4 (2 × C, ArC), 128.3 (2 × C, ArC), 128.1 (ArC), 125.9 (ArC), 75.2 (propyl C₁), 49.7 (NC₂H₃), 35.6 (propyl C₂), 32.3 (propyl C₃); **IR** ν max (neat)/cm⁻¹: 3061, 3027, 2953, 2858, 1602, 1583, 1494, 1452; **HRMS** (ESI): C₁₆H₁₉ClN [M+H⁺]: calculated 260.1201, found 260.1197.

**Synthesis of 1-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 340**

Following general procedure B, using chloroamine 339a (250 mg, 0.96 mmol). Workup B then purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 340 (96 mg, 0.43 mmol, 50%) as a yellow oil. The data is in accordance with the literature. **1H NMR** (500 MHz, CDCl₃) δ 7.34-7.28 (2H, m, ArH), 7.21-7.14 (3H, m, ArH), 6.99 (1H, d, J = 7.2, ArH), 6.68 (1H, d, J = 8.2, ArH), 6.67-6.62 (1H, m, ArH), 4.49 (1H, t, J = 4.8, H₁-C₂), 2.88 (3H, s, NCH₃), 2.66-2.54 (2H, m, H₂-C₄), 2.25-2.16 (1H, m, H₃-C₃), 2.06-1.99 (1H, m, H₆-C₃); **13C NMR** (125 MHz, CDCl₃) δ 146.1 (C₉), 144.3 (C₉), 128.4 (2 × C, ArC), 127.3 (ArC), 126.8 (ArC), 126.5 (2 × C, ArC), 122.6 (C₉), 115.6 (ArC), 109.9 (ArC), 63.3 (C₂), 37.7 (NCH₃), 30.2 (C₃), 24.2 (C₄); **IR** ν max (neat)/cm⁻¹: 3024, 2930, 2894, 2838, 1600, 1502, 1448, 1379; **HRMS** (ESI): C₁₆H₁₉N [M+H⁺]: calculated 224.1434, found 224.1429.

**Synthesis of (S)-2-methyl-N-(5-phenylpent-1-en-3-yl)propane-2-sulfinamide 337b**

To a stirred solution of sulfinamide 336 (2.50 g, 10.5 mmol, 1 eq.) in THF (20 mL) at −78 °C was added a solution of vinylmagnesium bromide (15.8 mL of a 1.0 M solution in THF, 1.5 eq.) dropwise and the reaction mixture was stirred for 2 h, after which it was the reaction was quenched with sat. aqueous NH₄Cl (50 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were dried over Na₂SO₄ then concentrated in
vacuo. Purification by flash chromatography on silica gel, eluting with 20% EtOAc in hexane afforded an inseparable mixture of the diastereoisomeric title compounds 337b (2.38 g, 8.97 mmol, 85%, 2:1) as a pale yellow oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.38-7.31 (2H, m, includes 1.34H, m, ArH, major; and 0.66H, m, ArH minor), 7.28-7.20 (3H, m, includes 2H, m, ArH, major; and 1H, m, ArH, minor), 5.95 (0.33H, ddd, \(J = 17.3, 10.3, 7.0\), pentenyl H\(_{1-C2}\), minor), 5.78 (0.67H, ddd, \(J = 17.5, 10.2, 7.6\), pentenyl H\(_{1-C2}\), major), 5.39-5.24 (2H, m, includes 1.34H, m, pentenyl H\(_2-C1\), major; and 0.66H, m, pentenyl H\(_2-C1\), minor), 3.95-3.82 (1H, m, includes 0.67H, m, pentenyl H\(_{1-C3}\), major; and 0.33H, m, pentenyl H\(_{1-C3}\), minor), 3.27-3.18 (1H, m, includes 0.67H, m, NH, major; and 0.33H, m, NH, minor), 2.83-2.66 (2H, m, includes 1.34H, m, pentenyl H\(_2-C5\), major; and 0.66H, m, pentenyl H\(_2-C5\), minor), 2.10-1.86 (2H, m, includes 1.34H, m, pentenyl H\(_2-C4\), major; and 0.66H, m, pentenyl H\(_2-C4\), minor), 1.29 (2.97H, s, C(CH\(_3\))\(_3\), minor), 1.25 (6.03H, s, C(CH\(_3\))\(_3\), major); \(^1\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 141.5 (C\(_o\)), 141.2 (C\(_o\)), 139.5 (CH), 138.8 (CH), 128.4 (ArC), 128.4 (ArC), 128.3 (ArC), 126.0 (ArC), 125.9 (ArC), 117.4 (CH\(_2\)), 116.8 (CH\(_2\)), 58.2 (CH), 58.0 (CH), 55.8 (C\(_o\)), 55.4 (C\(_o\)), 37.9 (CH\(_2\)), 37.0 (CH\(_2\)), 31.8 (CH\(_2\)), 31.7 (CH\(_2\)), 22.6 (CH\(_3\)), 22.5 (CH\(_3\)); IR \(\nu\) (max) (neat)/cm\(^{-1}\): 3212 (N-H), 3026, 2979, 2949, 2864, 1642, 1603, 1496; HRMS (ESI): C\(_{15}\)H\(_{26}\)NOS [M+H\(^+\)]: calculated 266.1573, found 266.1574.

**Synthesis of N-chloro-N-methyl-5-phenylpent-1-en-3-amine 339b**

![N-chloro-N-methyl-5-phenylpent-1-en-3-amine 339b](image)

To a stirred solution of sulfanilamide 337b (2.00 g, 7.54 mmol, 1.0 eq.) in THF (30 mL) at 0 °C was added a solution of LiHMDS (7.54 mL of a 1.0 M solution in THF, 1 eq.) dropwise. After 1 h neat MeI (0.94 mL, 15.1 mmol, 2.0 eq.) was added portionwise and the reaction mixture was warmed to RT and stirred for 2 h. The reaction was quenched with H\(_2\)O (30 mL) and the aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried over Na\(_2\)SO\(_4\), concentrated in vacuo and the crude gum was taken up in 3 N methanolic HCl (30 mL) and stirred for 3 h. The reaction mixture was concentrated in vacuo then taken up in EtOAc (20 mL). This was extracted with 2 M aqueous HCl (20 mL) then the aqueous phase was basified with 2 M aqueous NaOH (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. The crude gum (824 mg) was taken up in DCM (10 mL) and NCS (628 mg, 4.70 mmol, 1 eq.) was added. The reaction mixture was stirred in the dark for 3 h, then concentrated in vacuo and purified by flash chromatography on silica gel, eluting with 30% DCM in hexane to afford the title compound 339b (791 mg, 3.77 mmol, 50%) as a colourless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.33-7.27 (2H, m, ArH), 7.24-7.18 (3H, m,
(ArH), 5.94-5.84 (1H, m, pentenyl H₁-C₂), 5.37 (1H, d, J = 10.3, pentenyl H₂-C₁), 5.23-5.16 (1H, m, pentenyl H₂-C₁), 3.13 (1H, dd, J = 14.6, 7.4, pentenyl H₁-C₃), 2.87 (3H, s, NCH₃), 2.75-2.64 (2H, m, pentenyl H₂-C₅), 2.18-2.09 (1H, m, pentenyl Hₐ-C₄), 1.92-1.81 (1H, m, pentenyl Hₐ-C₄); 1³C NMR (125 MHz, CDCl₃) δ 141.8 (C₉), 135.1 (pentenyl C₂), 128.5 (2 × C, ArC), 128.3 (2 × C, ArC), 125.8 (ArC), 119.9 (pentenyl C₁), 72.8 (pentenyl C₃), 49.2 (NCH₃), 34.9 (pentenyl C₄), 31.9 (pentenyl C₅); IR νmax (neat)/cm⁻¹: 3063, 3027, 2949, 2923, 2882, 2859, 1639, 1496; HRMS (ESI): C₁₂H₁₇ClN [M+H⁺]: calculated 210.1044, found 210.1039.

**Synthesis of 1-methyl-2-vinyl-1,2,3,4-tetrahydroquinoline 341**

![Structure of 1-methyl-2-vinyl-1,2,3,4-tetrahydroquinoline](image)

Following general procedure B, using chloroamine 339b (500 mg, 2.38 mmol). Workup B then purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound (209 mg, 1.21 mmol, 51%) as a colourless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.12 (1H, t, J = 7.8, ArH-C₇), 6.98 (1H, d, J = 7.1, ArH-C₅), 6.65-6.59 (2H, m, ArH), 5.80 (1H, ddd, J = 16.9, 10.2, 6.5, vinyl H₁-C₁), 5.13 (2H, ddt, J = 29.4, 17.1, 1.4, vinyl H₂-C₂), 3.82 (1H, ddd, J = 10.4, 5.2, 0.9, H₁-C₂), 2.91 (3H, s, NCH₃), 2.83-2.74 (1H, m, Hₐ-C₄), 2.68 (1H, dt, J = 15.8, 4.7, Hₐ-C₄), 2.02 (1H, ddt, J = 12.9, 11.4, 4.9, H₂-C₃), 1.95-1.86 (1H, m, Hₐ-C₃); ¹³C NMR (125 MHz, CDCl₃) δ 145.6 (C₉), 138.9 (vinyl C₁), 128.4 (ArC), 127.2 (ArC), 122.4 (C₉), 115.6 (ArC), 115.5 (vinyl C₂), 110.2 (ArC), 61.7 (C₂), 37.3 (NCH₃), 27.1 (C₃), 24.3 (C₄); IR νmax (neat)/cm⁻¹: 3019, 2976, 2929, 2894, 1639, 1601, 1575, 1498; HRMS data could not be obtained.

**Synthesis of (S)-2-methyl-N-(4-phenylbutan-2-yl)propane-2-sulfinamide 337c**

To a stirred solution of sulfinamide 336 (1.00 g, 4.21 mmol, 1.0 eq.) in THF (8 mL) at −78 °C was added a solution of methylmagnesium bromide (2.11 mL of 3.0 M solution in Et₂O, 1.5 eq.) dropwise and the reaction mixture was stirred for 2 h, after which the reaction was quenched with sat. aqueous NH₄Cl (20 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were dried over Na₂SO₄ then concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with a gradient of 20-40% EtOAc in pentane afforded an inseparable mixture of the diastereoisomeric title compounds 337c (726 mg, 2.87 mmol, 68%, dr 93:7) as a colourless solid. The data is in accordance with
the literature.\textsuperscript{226} \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.30-7.25 (2H, m, ArH), 7.21-7.14 (3H, m, ArH), 3.39 (1H, dt, \(J = 13.2, 6.7\), butyl H\textsubscript{1-2}), 2.92 (1H, d, \(J = 7.0, \text{NH}\)), 2.75-2.60 (2H, m, butyl H\textsubscript{2-4}), 1.90 - 1.70 (2H, m, butyl H\textsubscript{2-3}), 1.31 (3H, d, \(J = 6.5\), butyl H\textsubscript{3-1}), 1.22 (9H, s, C(CH\textsubscript{3})\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 141.8 (C\textsubscript{q}), 128.4 (2 \times C, ArC), 128.3 (2 \times C, ArC), 125.9 (ArC), 55.7 (C\textsubscript{q}), 52.1 (butyl C\textsubscript{2}), 39.9 (butyl C\textsubscript{3}), 32.1 (butyl C\textsubscript{4}), 23.2 (butyl C\textsubscript{1}), 22.6 (3 \times C, (CH\textsubscript{3})\textsubscript{3}); IR \(\nu_{\text{max}}\) (neat)/cm\textsuperscript{-1}: 3255 (N-H), 3062, 3025, 2965, 2923, 2862, 1493, 1454; HRMS (ESI): C\textsubscript{14}H\textsubscript{24}NOS [M+H\textsuperscript{+}]: calculated 254.1573, found 254.1574.

**Synthesis of \textit{N}-methyl-4-phenylbutan-2-amine 338c**

\[\text{HN} \]

To a stirred solution of sulfinamide 337c (700 mg, 2.75 mmol, 1.0 eq.) in THF (11 mL) at 0 °C was added a solution of LiHMDS (4.13 mL of a 1.0 M solution in THF, 1.5 eq.) dropwise. After 30 mins neat MeI (0.34 mL, 5.50 mmol, 2.0 eq.) was added portionwise and the reaction mixture was warmed to RT and stirred for 2 h. The reaction mixture was quenched with H\textsubscript{2}O (15 mL) and the aqueous phase was extracted with EtOAc (3 \times 10 mL). The combined organic extracts were dried over Na\textsubscript{2}SO\textsubscript{4}, concentrated in vacuo and the crude gum was taken up in 3 N methanolic HCl (20 mL) and stirred for 2 h. The reaction mixture was concentrated in vacuo then taken up in EtOAc (10 mL). This was extracted with 2 M aqueous HCl (10 mL) then the aqueous phase was basified with 2 M aqueous NaOH (15 mL) and extracted with EtOAc (3 \times 10 mL). The combined organic extracts were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo to afford the title compound 338c (382 mg, 2.34 mmol, 85%) as a pale brown oil. The data is in accordance with the literature.\textsuperscript{227} \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.32-7.24 (2H, m, ArH), 7.22-7.14 (3H, m, ArH), 2.72-2.50 (3H, m, includes 2H, m, butyl H\textsubscript{2-4}; and 1H, m, butyl H\textsubscript{1-2}), 2.40 (3H, s, NCH\textsubscript{3}), 1.84-1.72 (1H, m, butyl H\textsubscript{2-3}), 1.68-1.54 (1H, m, butyl H\textsubscript{3-1}), 1.09 (3H, d, \(J = 6.2\), butyl H\textsubscript{3-1}); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 142.4 (C\textsubscript{q}), 128.3 (2 \times C, ArC), 128.3 (2 \times C, ArC), 125.7 (ArC), 54.4 (butyl C2), 38.5 (butyl C3), 33.8 (NCH\textsubscript{3}), 32.3 (butyl C4), 19.9 (butyl C1); IR \(\nu_{\text{max}}\) (neat)/cm\textsuperscript{-1}: 3304 (N-H), 3062, 2930, 2857, 2792, 1541, 1495, 1453; HRMS (ESI): C\textsubscript{14}H\textsubscript{18}N [M+H\textsuperscript{+}]: calculated 164.1434, found 164.1432.

**Synthesis of \textit{N}-chloro-\textit{N}-methyl-4-phenylbutan-2-amine 339c**

Following general procedure A, using amine 338c (500 mg, 3.06 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the \textit{title compound}
339c (350 mg, 1.77 mmol, 58%) as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.31-7.26 (2H, m, ArH), 7.23-7.16 (3H, m, ArH), 2.93-2.84 (4H, m, includes 3H, s, NCH₃; and 1H, m, butyl H₁-C2), 2.73-2.66 (2H, m, butyl H₂-C4), 1.98 (1H, ddt, J = 13.6, 8.8, 6.8, butyl H₃-C3), 1.73-1.63 (1H, m, butyl H₂-C3), 1.16 (3H, d, J = 6.3, butyl H₃-C1); ¹³C NMR (125 MHz, CDCl₃) δ 142.1 (Cₗ), 128.4 (2 × C, ArC), 128.3 (2 × C, ArC), 125.8 (ArC), 64.5 (butyl C₂), 48.1 (NCH₃), 36.3 (butyl C₃), 32.3 (butyl C₄), 14.2 (butyl C₁); IR ν max (neat)/cm⁻¹: 3026, 2973, 2947, 2863, 1603, 1495, 1453, 1433; HRMS (ESI): C₁₁H₁₇ClN [M+H⁺]: calculated 198.1044, found 198.1938.

Synthesis of 1,2-dimethyl-1,2,3,4-tetrahydroquinoline 342

Following general procedure B, using chloroamine 339c (300 mg, 1.52 mmol). Workup B then purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 342 (194 mg, 1.20 mmol, 79%) as a yellow oil. The data is in accordance with the literature.¹²⁸ ¹H NMR (500 MHz, CDCl₃) δ 7.13 (1H, t, J = 7.7, ArH-C₇), 7.02 (1H, d, J = 7.3, ArH-C₅), 6.64 (1H, t, J = 7.3, ArH-C₆), 6.60 (1H, d, J = 8.2, ArH-C₈), 3.52-3.44 (1H, m, H₁-C₂), 2.94 (3H, s, NCH₃), 2.93-2.84 (1H, m, Hₐ-C₄), 2.73 (1H, dt, J = 16.1, 4.6, H₃-C₄), 2.07-1.99 (1H, m, H₃-C₃), 1.84-1.76 (1H, m, H₃-C₃), 1.18 (3H, d, J = 6.5, H₃-Me); ¹³C NMR (125 MHz, CDCl₃) δ 145.4 (Cₗ), 128.5 (ArC), 127.1 (ArC), 122.1 (Cₗ), 115.4 (ArC), 110.6 (ArC), 53.8 (C₂), 37.0 (NCH₃), 28.1 (C₃), 23.8 (C₄), 17.6 (CH₃); IR ν max (neat)/cm⁻¹: 3066, 3019, 2964, 2928, 2846, 2792, 1601, 1575; HRMS (ESI): C₁₁H₁₆N [M+H⁺]: calculated 162.1277, found 162.1270.

Synthesis of benzyl(4-phenylbutan-2-yl)amine 345

To a stirred solution of 4-phenylbutan-2-one (1.01 mL, 6.48 mmol, 1.0 eq.) in EtOH (20 mL) was added benzyamine (1.42 mL, 13.0 mmol, 2.0 eq.). The reaction mixture was stirred for 5 h at rt then cooled to 0 °C and NaBH₄ (492 mg, 13.0 mmol, 2.0 eq.) was added portionwise. The reaction mixture was warmed to rt, then after 30 min was concentrated, then taken up in EtOAc (25 mL) and aqueous NH₄OH (20 mL of a 2 M solution) was added to this. Na₂SO₄ was added and the crude mixture was filtered through a pad of celite, then the celite washed with EtOAc (200 mL) and the filtrate was collected and concentrated. Purification by automated flash chromatography on silica gel,
eluting with a gradient of 20-50% afforded the title compound 345 (1.54 g, 6.43 mmol, 99%) as a colourless oil. The data is in accordance with the literature.\(^\text{229}\) \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.39-7.16 (10H, m, ArH), 3.85 (1H, d, \(J = 13.0\), NCH\(_2\)H\(_b\)), 3.75 (1H, d, \(J = 13.0\), NCH\(_2\)H\(_b\)), 2.81-2.70 (1H, m, butyl H\(_1\)-C2), 2.68 (2H, ddd, \(J = 9.4, 6.4, 4.9\), butyl H\(_2\)-C4), 1.83 (1H, ddt, \(J = 13.0, 9.4, 6.4\), butyl H\(_a\)-C3), 1.69 (1H, ddt, \(J = 13.0, 9.4, 6.4\), butyl H\(_b\)-C3), 1.16 (3H, d, \(J = 6.3\), butyl H\(_3\)-C1) \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 142.6 (C\(_q\)), 141.0 (C\(_q\)), 128.6 (2× C, ArC), 128.3 (2× C, ArC), 127.0 (ArC), 125.8 (ArC), 52.2 (butyl C2), 51.5 (NCH\(_2\)), 38.9 (butyl C3), 32.2 (butyl C4), 20.5 (butyl C1); IR \(\nu_{\text{max}}\) (neat) / cm\(^{-1}\): 3084, 3061, 3026, 2923, 2859, 1602, 1495, 1453; HRMS (ESI): C\(_{17}\)H\(_{22}\)N \([M+H]^+\): calculated 240.1747, found 240.1740.

**Synthesis of benzyl(chloro)(4-phenylbutan-2-yl)amine 346**

Following general procedure A, using amine 345 (500 mg, 2.09 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 346 (554 mg, 2.02 mmol, 97%) as a colourless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.42-7.14 (10H, m, ArH), 4.15 (1H, d, \(J = 13.7\), NCH\(_2\)H\(_b\)), 4.03 (1H, d, \(J = 13.7\), NCH\(_2\)H\(_b\)), 3.12-3.00 (1H, m, butyl H\(_1\)-C2), 2.86-2.74 (1H, m, butyl H\(_a\)-C4), 2.74-2.65 (1H, m, butyl H\(_b\)-C4), 2.15-2.02 (1H, m butyl H\(_a\)-C3), 1.78-1.65 (1H, m, butyl H\(_b\)-C3), 1.24 (3H, d, \(J = 6.2\), butyl H\(_3\)-C1); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 142.4 (C\(_q\)), 137.9 (C\(_q\)), 129.0 (2× C, ArC), 128.7 (2× C, ArC), 128.51 (2× C, ArC), 128.48 (2× C, ArC), 128.47 (2× C, ArC), 127.8 (ArC), 125.9 (ArC), 64.0 (NCH\(_2\)), 62.3 (butyl C2), 36.6 (butyl C3), 32.6 (butyl C4), 14.5 (butyl C1); IR \(\nu_{\text{max}}\) (neat) / cm\(^{-1}\): 3086, 3062, 3027, 2970, 2931, 2860, 1603, 1495; HRMS (ESI): C\(_{17}\)H\(_{22}\)N \([M+H]^+\]: calculated 274.1357, found 274.1353.

**Synthesis of 1-benzyl-2-methyl-1,2,3,4-tetrahydroquinoline 347**

Following general procedure B, using chloroamine 346 (100 mg, 0.37 mmol). Work-up B, followed by purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 347 (47 mg, 0.20 mmol, 54%) as a clear yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.39-7.23 (5H, m, ArH), 7.05 (1H, d, \(J = 7.3\), ArH-C5), 6.98 (1H, app. t, \(J = 7.7\), ArH-C7), 6.61 (1H, app. t, \(J = 7.3\), ArH-C6), 6.44 (1H, d, \(J = 8.2\), ArH-C8), 181
4.60 (1H, d, J = 17.3, NCH₆H₆), 4.50 (1H, d, J = 17.3, NCH₆H₆), 3.67-3.57 (1H, m, H₁-C₂), 3.02-2.91 (1H, m, H₁-C₄), 2.80 (1H, dt, J = 16.0, 4.5, H₅-C₄), 2.14-2.03 (1H, m, H₂-C₃), 1.88 (1H, ddd, J = 13.0, 8.6, 4.3, H₃-C₁), 1.23 (3H, d, J = 6.4, methyl H₃-C₁); ¹³C NMR (100 MHz, CDCl₃) δ 144.9 (Cₗ), 139.6 (Cₙ), 128.9 (2 × C, ArC), 127.2 (C₅), 126.8 (C₇), 126.5 (2 × C, ArC), 121.9 (Cₙ), 115.6 (C₆), 111.6 (C₈), 53.5 (NCH₂), 53.2 (C₂), 28.3 (C₃), 24.2 (C₄), 19.1 (methyl C₁); IR ν max (neat)/cm⁻¹: 3062, 3024, 2964, 2926, 2848, 1600, 1574, 1494; HRMS (ESI): C₁₇H₂₀N [M+H⁺]: calculated 238.1590, found 238.1586.

**Synthesis of 2,3-diphenylpropanenitrile 350a**

![Structure of 350a](image)

To a stirred solution of benzyl cyanide 348a (2.93 g, 25 mmol, 2.5 eq.) in THF (25 mL) at −78 °C was added a solution of LiHMDS in THF (10 mL of a 1.0 M solution in THF, 1.0 eq.) dropwise. The reaction mixture was stirred for 1 h and then a solution of benzyl bromide (1.19 mL, 10 mmol, 1.0 eq.) in THF (10 mL) was added dropwise. This was stirred at −78 °C for 0.5 h and then warmed to RT and stirred for 4 h, before being concentrated in vacuo and taken up in H₂O (25 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with 4% EtOAc in hexane afforded the title compound 350a (1.83 g, 8.82 mmol, 88%) as a colourless solid. A sample was crystallised from hexane. The data is in accordance with the literature. M.p 55-58 °C, colourless crystalline solid, hexane; ¹H NMR (300 MHz, CDCl₃) δ 7.41-7.23 (8H, m, ArH), 7.17-7.12 (2H, m, ArH), 4.01 (1H, dd, J = 8.2, 6.6, propyl H₁-C₂), 3.26-3.08 (2H, m, propyl H₂-C₃); ¹³C NMR (75 MHz, CDCl₃) δ 136.4 (Cₗ), 135.4 (Cₙ), 129.3 (2 × C, ArC), 129.2 (2 × C, ArC), 128.8 (2 × C, ArC), 128.3 (ArC), 127.6 (2 × C, ArC), 127.5 (ArC), 120.5 (Cₙ), 42.3 (propyl C₃), 39.9 (propyl C₂); IR ν max (neat)/cm⁻¹: 3062, 3030, 2964, 2926, 2848, 1598, 1495, 1455.

**Synthesis of 2,3-diphenylpropan-1-amine 352a**

![Structure of 352a](image)

To a stirred suspension of LiAlH₄ (687 mg, 18.1 mmol, 2.5 eq.) in THF (18 mL) at 0 °C was added a solution of nitrile 350a (1.50 g, 7.24 mmol, 1.0 eq.) in THF (7 mL) dropwise. The
reaction mixture was stirred at 0 °C for 15 minutes then heated at reflux and left to stir for 2 h. The reaction mixture was then cooled to 0 °C and the reaction was quenched with H₂O (2 mL), 2 M aqueous NaOH (1 mL) and H₂O (1 mL), then stirred for 1 h at RT until the reaction mixture had turned white. The resultant slurry was dried over MgSO₄, filtered through a pad of Celite and the pad of Celite was washed with EtOAc (150 mL). The filtrate was concentrated in vacuo and purified by SCX cartridge then flash chromatography on silica gel, eluting with a gradient of 75 – 100% EtOAc in hexane then 20% MeOH in DCM afforded the title compound 352a (489 mg, 2.31 mmol, 32%) as a colourless oil. The data is in accordance with the literature.\(^ {231}\)

### 1H NMR (300 MHz, CDCl₃) δ 7.36-7.11 (8H, m, ArH), 7.11-7.02 (2H, m, ArH), 3.12-2.72 (5H, m, includes 1H, m, propyl H₁-C₂; 2H, m, propyl H₂-C₁; and 2H, m, propyl H₂-C₃), 1.70 (2H, br. s, NH₂); 13C NMR (75 MHz, CDCl₃) δ 142.9 (Cq), 140.2 (Cq), 129.1 (2 × C, ArC), 128.6 (2 × C, ArC), 128.3 (2 × C, ArC), 128.1 (2 × C, ArC), 126.7 (ArC), 126.0 (ArC), 51.4 (propyl C₂), 46.9 (CH₂), 40.9 (CH₂); IR ν max (neat)/cm⁻¹: 3084, 3060, 3026, 2920, 1601, 1494, 1452, 1384; HRMS (ESI): C₁₅H₁₈N [M+H⁺]: calculated 212.1434, found 212.1432.

### Synthesis of (2,3-diphenylpropyl)(methyl)amine 354a

To a stirred solution of amine 352a (400 mg, 1.89 mmol, 1.0 eq.) in THF (8 mL) at 0 °C was added Et₃N (0.26 mL, 1.89 mmol, 1.0 eq.) and then ethyl chloroformate (0.18 mL, 1.89 mmol, 1.0 eq.) dropwise. The reaction mixture was warmed to RT and stirred for 16 h, after which it was filtered through a pad of Celite and the pad of Celite washed with Et₂O (100 mL). The filtrate was concentrated in vacuo to give the carbamate (480 mg) as an oil. To a stirred suspension of LiAlH₄ (161 mg, 4.23 mmol, 2.5 eq.) in THF (4.5 mL) at 0 °C was added a solution of the carbamate (460 mg, 1.69 mmol, 1.0 eq.) in THF (3 mL) dropwise. The reaction mixture was heated at reflux and left to stir for 6 h, after which it was cooled to 0 °C and the reaction was quenched with H₂O (1 mL), 2 M aqueous NaOH (1 mL) and H₂O (0.5 mL), then stirred for 1 h at RT until the reaction mixture had turned white. The resultant slurry was dried over MgSO₄, filtered through a pad of Celite and the pad of Celite was washed with EtOAc (100 mL). The filtrate was concentrated in vacuo to afford the title compound 354a (359 mg, 1.59 mmol, 84%) as a yellow oil. The data is in accordance with the literature.\(^ {231}\)

### 1H NMR (300 MHz, CDCl₃) δ 7.40-7.05 (10H, m, ArH), 3.22-3.09 (1H, m, propyl H₁-C₂), 3.02-2.91 (2H, m, propyl H₂-C₁), 2.87 (2H, d, J = 7.1, propyl H₂-C₃), 2.38 (3H, s, NCH₃); 13C NMR (75 MHz, CDCl₃) δ 143.3 (Cq), 140.3 (Cq), 129.2 (2 × C, ArC), 128.6 (2 × C, ArC), 128.2 (2
Synthesis of chloro(2,3-diphenylpropyl)methylamine 355a

Following general procedure A, using amine 354a (300 mg, 1.33 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 355a (313 mg, 1.21 mmol, 91%) as a colourless gum. 

1H NMR (300 MHz, CDCl3) δ 7.35-7.11 (8H, m, ArH), 7.08-7.00 (2H, m, ArH), 3.45-3.32 (1H, m, propyl H1-C2), 3.24-3.10 (3H, m, includes 1H, m, propyl H-a-C3; and 2H, m, propyl H2-C1), 2.98 (3H, s, NC3H3), 2.90 (1H, dd, J = 13.6, 8.9, propyl Hb-C3); 

13C NMR (75 MHz, CDCl3) δ 142.4 (Cq), 139.9 (Cq), 129.3 (2 × C, ArC), 128.5 (2 × C, ArC), 128.2 (2 × C, ArC), 128.1 (2 × C, ArC), 126.7 (ArC), 126.0 (ArC), 70.8 (propyl C1), 53.6 (NC3H3), 46.5 (propyl C2), 40.3 (propyl C3); 

IR νmax (neat)/cm⁻¹: 3085, 3062, 3027, 2909, 2817, 1678, 1602, 1575, 1497; 


Synthesis of 1-methyl-3-phenyl-1,2,3,4-tetrahydroquinoline 356a

Following general procedure B, using chloroamine 355a (100 mg, 0.39 mmol). Workup B then purification by flash chromatography on silica gel, eluting with 20% DCM in hexane afforded the title compound 356a (21 mg, 0.09 mmol, 23%) as a pale yellow gum. The data is in accordance with the literature. 

1H NMR (500 MHz, CDCl3) δ 7.31-7.23 (2H, m, ArH), 7.19 (3H, m, ArH), 7.06 (1H, app. t, J = 7.7, ArH-C7), 6.95 (1H, d, J = 7.2, ArH-C5), 6.62-6.54 (2H, m, includes 1H, m, ArH-C6; and 1H, m, ArH-C8), 3.26 (2H, d, J = 7.8, H2-C4), 3.20-3.11 (1H, m, H1-C3), 3.01-2.91 (2H, m, H2-C2), 2.87 (3H, s, NCH3); 

13C NMR (100 MHz, CDCl3) δ 146.2 (Cq), 143.9 (Cq), 129.1 (ArC), 128.8 (2 × C, ArC), 127.4 (2 × C, ArC), 127.3 (ArC), 126.8 (Cq), 122.8 (Cq), 116.5 (ArC), 111.1 (ArC), 57.8 (C4), 39.2 (NCH3), 39.0 (C3), 35.5 (C2); 

IR νmax (neat)/cm⁻¹: 3062, 3026, 2909, 2817, 1678, 1602, 1575, 1497; 

HRMS (ESI): C16H18N [M+H⁺]: calculated 224.1434, found 224.1429.
Synthesis of 2-methyl-3-phenylpropanenitrile 350b

To a stirred solution of propionitrile 348b (7.10 mL, 100 mmol, 10 eq.) in THF (100 mL) at –78 °C was added a solution of LiHMDS (10 mL of a 1.0 M solution in THF, 1.0 eq.) dropwise. The reaction mixture was stirred for 1 h and then a solution of benzyl bromide (10 mL of a 1.0 M solution in THF, 1.0 eq.) was added drop wise. This was stirred at –78 °C for 0.5 h and then warmed to RT and stirred for 4 h, before being concentrated in vacuo and taken up in H2O (25 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were dried over Na2SO4 and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with a gradient of 2-10% EtOAc in hexane afforded the title compound 350b (1.18 g, 8.13 mmol, 81%) as a colourless oil. The data is in accordance with the literature.

1H NMR (300 MHz, CDCl3) δ 7.30-7.12 (5H, m, ArH), 2.93-2.70 (3H, m, includes 1H, m, propyl H1-C2; and 2H, m, propyl H2-C3), 1.25 (3H, d, J = 6.7, CH3); 13C NMR (75 MHz, CDCl3) δ 137.0 (Cq), 129.2 (2 × C, ArC), 128.8 (2 × C, ArC), 127.4 (ArC), 122.7 (propyl C1), 40.1 (propyl C3), 27.7 (propyl C2), 17.7 (CH3); IR νmax (neat)/cm⁻¹: 3030, 2983, 2938, 2238 (C≡N), 1496, 1454, 1083, 699.

Synthesis of 2-methyl-3-phenylpropan-1-amine 352b

To a stirred suspension of LiAlH4 (816 mg, 21.5 mmol, 2.5 eq.) in THF (22 mL) at 0 °C was added a solution of nitrile 350b (1.25 g, 8.61 mmol, 1.0 eq.) in THF (8 mL) dropwise. The reaction mixture was heated at reflux and left to stir for 4 hours, after which it was cooled to 0 °C and the reaction was quenched with H2O (4 mL), 2 M aqueous NaOH (2 mL) and H2O (2 mL), then stirred for 1 h at RT until the reaction mixture had turned white. The resultant slurry was dried over MgSO4, filtered through a pad of Celite and the pad of Celite was washed with EtOAc (150 mL). The filtrate was concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with a gradient of 2-10% EtOAc in hexane afforded the title compound 352b (331 mg, 2.22 mmol, 26%) as a yellow oil. The data is in accordance with the literature.

1H NMR (500 MHz, CDCl3) δ 7.31-7.24 (2H, m, ArH), 7.21-7.13 (3H, m, ArH), 2.70 (1H, dd, J = 13.4, 6.2, propyl Hα-C3), 2.67-2.64 (1H, m, propyl Hα-C1), 2.53 (1H, dd, J = 12.5, 6.9, propyl Hβ-C1), 2.38 (1H, dd, J = 13.4, 8.2, propyl Hβ-C3), 2.00-1.72 (3H, m, includes 2H, br. s, NH2; and 1H, m, propyl H1-C2), 0.89 (3H, d, J = 6.7, CH3); 13C NMR (125 MHz, CDCl3) δ 140.9 (Cq), 129.1 (2 × C, ArC), 128.2 (2 × C, ArC), 127.4 (ArC), 122.7 (propyl C1), 40.1 (propyl C3), 27.7 (propyl C2), 17.7 (CH3); IR νmax (neat)/cm⁻¹: 3030, 2983, 2938, 2238 (C≡N), 1496, 1454, 1083, 699.
ArC), 125.8 (ArC), 48.0 (propyl C1), 41.0 (propyl C3), 38.3 (propyl C2), 17.4 (CH3); HRMS (ESI): C10H16N [M+H+]: calculated 150.1277, found 150.1275.

**Synthesis of methyl(2-methyl-3-phenylpropyl)amine 354b**

To a stirred solution of amine 352b (300 mg, 2.01 mmol, 1.0 eq.) in THF (8 mL) at 0 °C was added Et3N (0.28 mL, 2.01 mmol, 1.0 eq.) and then ethyl chloroformate (0.19 mL, 2.01 mmol, 1.0 eq.) dropwise. The reaction mixture was warmed to RT and stirred for 2 h, after which it was filtered through a pad of Celite and the pad of Celite washed with THF (75 mL). The filtrate was concentrated in vacuo. The crude oil was taken up in THF (3 mL) and was added dropwise to a stirred suspension of LiAlH4 (129 mg, 3.40 mmol, 2.5 eq.) in THF (7 mL) at 0 °C. The reaction mixture was heated at reflux and left to stir for 6 h, after which it was cooled to 0 °C and the reaction was quenched with H2O (1 mL), 2 M aqueous NaOH (1 mL) and H2O (0.5 mL), then stirred for 1 h at RT until the reaction mixture had turned white. The resultant slurry was dried over MgSO4, filtered through a pad of Celite and the pad of Celite was washed with EtOAc (150 mL). The filtrate was collected and concentrated in vacuo to afford the title compound 354b (224 mg, 1.36 mmol, 99%) as a colourless oil.

1H NMR (500 MHz, CDCl3) δ 7.30-7.24 (2H, m, ArH), 7.21-7.13 (3H, m, ArH), 2.72 (1H, dd, J = 13.4, 6.0, propyl Hα-C3), 2.54 (1H, dd, J = 11.6, 5.9, propyl Hα-C1), 2.45-2.35 (5H, m, includes 3H, s, NCH3; 1H, m, propyl Hb-C3; and 1H, m, propyl Hb-C1), 1.94 (1H, td, J = 13.1, 6.5, propyl H1-C2), 1.84-1.73 (5H, m, propyl H1-C2), 1.65 (3H, d, J = 6.7, CH3); 13C NMR (125 MHz, CDCl3) δ 141.1 (Cq), 129.3 (2 × C, ArC), 128.3 (2 × C, ArC), 125.9 (ArC), 58.5 (propyl C1), 41.7 (propyl C3), 35.4 (propyl C2), 18.1 (CH3); IR νmax (neat)/cm⁻¹: 3062, 3026, 2954, 2922, 1603, 1542, 1493, 1453; HRMS (ESI): C11H18N [M+H+]: calculated 164.1434, found 164.1439.

**Synthesis of N-chloro(methyl)(2-methyl-3-phenylpropyl)amine 355b**

Following general procedure A, using amine 354b (200 mg, 1.23 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 355b (198 mg, 1.00 mmol, 81%) as a pale yellow oil. 1H NMR (500 MHz, CDCl3) δ 7.31-7.25 (2H, m, ArH), 7.22-7.15 (3H, m, ArH), 2.95 (3H, s, NCH3), 2.83 (1H, dd, J = 13.4, 5.0, propyl Hα-C3), 2.76 (1H, dd, J = 12.7, 7.0, propyl Hα-C1), 2.67 (1H, dd, J = 12.7, 7.0, propyl Hα-C1), 2.38 (1H, dd, J = 13.4, 8.6, propyl Hb-C3), 2.24-2.15 (1H, m, propyl H1-C2), 0.90 (3H, d, J = 6.7, CH3); 13C NMR (125 MHz, CDCl3) δ 140.5 (Cq), 129.5 (2 × C, ArC), 128.3 (2 × C, ArC), 126.0 (ArC), 72.1 (propyl C1), 53.5 (NCH3), 40.7 (propyl C3), 34.1 (propyl...
C2), 17.4 (CH3); IR νmax (neat)/cm⁻¹: 3062, 3027, 2954, 2922, 2873, 1602, 1495, 1454; HRMS data could not be obtained.

**Synthesis of 1,3-dimethyl-1,2,3,4-tetrahydroquinoline 356b**

Following general procedure B, using chloroamine 355b (100 mg, 0.51 mmol). Workup B then purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 356b (62 mg, 0.39 mmol, 77%) as a clear yellow oil. The ¹H NMR data was in accordance with the literature. ³¹C NMR (125 MHz, CDCl₃) δ 146.4 (Cq), 129.0 (ArC), 127.2 (ArC), 122.6 (Cq), 116.3 (ArC), 110.9 (ArC), 58.5 (C2), 36.4 (C4), 19.3 (CH3); IR νmax (neat)/cm⁻¹: 3021, 2952, 2905, 2870, 2830, 1603, 1500, 1432; HRMS (ESI): C₁₁H₁₆N [M+H⁺]: calculated 162.1277, found 162.1273.

**Synthesis of 1-[benzyl(methyl)amino]-3-phenylpropan-2-ol 363**

To a stirred solution of (2,3-epoxypropyl)benzene (1.00 g, 7.50 mmol, 1.0 eq.) in MeOH (15 mL) was added K₂CO₃ (5.18 g, 37.5 mmol, 5.0 eq.) and BnMeNH (4.84 mL, 37.5 mmol, 5.0 eq.). The reaction mixture was heated at reflux for 16 h and then the reaction mixture was cooled to RT and concentrated. The crude mixture was taken up in H₂O (30 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with EtOAc (+ 1% Et₃N) afforded the title compound 363 (1.75 g, 6.85 mmol, 91%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.19 (10 H, m, ArH), 4.01-3.91 (1H, m, propyl H₁-C2), 3.66 (1H, d, J = 13.1, NCH₃), 3.45 (1H, d, J = 13.1, NCH₃), 2.83 (1H, dd, J = 13.7, 7.1, propyl H₃-C1), 2.67 (1H, dd, J = 13.7, 5.6, propyl H₅-C1), 2.47 (1H, dd, J = 12.1, 10.3, propyl H₅-C3), 2.37 (1H, dd, J = 12.2, 3.3, propyl H₅-C3), 2.21 (3H, s, NCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 138.54 (C₃), 138.52 (C₀), 129.4 (2 × C, ArC), 129.1 (2 × C, ArC), 128.5 (4 × C, ArC), 127.4 (ArC), 126.4 (ArC), 68.2 (propyl C2), 63.0 (propyl C3), 62.5 (NCH₂), 42.1 (NCH₃), 41.5 (propyl C1); IR νmax (neat)/cm⁻¹: 3425 (O-H), 3061,
3027, 2931, 2843, 2793, 1602, 1495; HRMS (ESI): C_{17}H_{22}NO [M+H^+] : calculated 256.1696, found 256.1696.

**Synthesis of benzyl(2-methoxy-3-phenylpropyl)methylamine 364**

To a stirred suspension of NaH (156 mg of a 60% dispersion in mineral oil, 3.90 mmol, 1.0 eq.) in THF (5 mL) at 0 °C was added a solution of alcohol 363 (1.00 g, 3.90 mmol, 1.0 eq.) in THF (5 mL) dropwise. The reaction mixture was stirred at 0 °C for 30 minutes then MeI (0.24 mL, 3.90 mmol, 1.0 eq.) was added portionwise. The reaction mixture was warmed to RT and stirred for 3 h, after which H₂O (20 mL) was added and the phases separated. The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed with brine (20 mL), dried over Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with 25% EtOAc in hexane afforded title compound 364 (494 mg, 1.83 mmol, 47%) as a colourless oil.

**1H NMR** (400 MHz, CDCl₃) δ 7.38-7.16 (10H, m, ArH), 3.63-3.53 (3H, m, includes 1H, m, propyl H₁-C2; and 2H, m, NCH₂), 3.39 (3H, s, OCH₃), 2.93 (1H, dd, J = 13.9, 5.4, propyl H₉-C1), 2.82 (1H, dd, J = 13.9, 6.6, propyl H₆-C1), 2.54 (1H, dd, J = 13.0, 6.1, propyl H₆-C3), 2.47 (1H, dd, J = 13.0, 5.4, propyl H₆-C3), 2.26 (3H, s, NCH₃); 

**13C NMR** (100 MHz, CDCl₃) δ 139.3 (C₉₁), 139.2 (C₉₂), 129.6 (2 × C, ArC), 129.1 (2 × C, ArC), 128.3 (4 × C, ArC), 127.1 (ArC), 126.1 (ArC), 81.0 (NCH₂), 63.0 (propyl C2), 60.4 (propyl C3), 57.5 (OCH₃), 43.2 (NCH₃), 39.0 (propyl C1); 

**IR** ν<sub>max</sub> (neat)/cm⁻¹: 3085, 3062, 3027, 2976, 2928, 2823, 1703, 1602; HRMS (ESI): C₁₈H₂₄NO [M+H^+] : calculated 270.1852, found 270.1849.

**Synthesis of (2-methoxy-3-phenylpropyl)(methyl)amine 365**

To a stirred solution of benzylamine 364 (400 mg, 1.49 mmol, 1.0 eq.) in degassed EtOH (6 mL) was added Pd/C (159 mg, 0.15 mol, 0.1 eq., 10% wt Pd). The solution was evacuated and flushed with N₂ (× 3) and then flushed with H₂ and left to stir under an atmosphere of H₂ for 48 h. The reaction mixture was filtered through a pad of Celite and the pad of Celite was washed with EtOAc (200 mL). The filtrate was concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with a gradient of 0-10% MeOH in DCM (+1% Et₃N) afforded the title compound 365 (187 mg, 1.04 mmol, 70%) as a yellow oil. 

**1H NMR** (400 MHz, CDCl₃) δ 7.35-7.21 (5H, m, ArH), 3.69-3.58 (1H, m, propyl H₁-C2), 3.42 (3H, s, OCH₃), 2.95 (1H, dd, J = 13.8, 5.6, propyl H₆-C1), 2.76 (1H, dd, J = 13.8, 7.0, propyl H₆-C1), 2.67 (1H, dd, J = 12.3, 3.5, propyl H₆-C3), 2.60 (1H, dd, J = 12.3, 7.8, propyl H₆-C3), 2.46
(3H, s, NCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 138.2 (C₉), 129.5 (2 × C, ArC), 128.5 (2 × C, ArC), 126.4 (ArC), 81.1 (propyl C2), 57.5 (OCH₃), 54.5 (propyl C1), 38.3 (propyl C3), 36.2 (NCH₃); IR νₘₐₓ (neat)/cm⁻¹: 3334 (N-H), 3027, 2930, 2826, 2794, 1603, 1495, 1454; HRMS (ESI): C₁₁H₁₈NO [M+H⁺]: calculated 180.1383, found 180.1383.

**Synthesis of N-chloro(2-methoxy-3-phenylpropyl)methylamine 366**

Following general procedure A, using amine 365 (150 mg, 0.84 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 366 (179 mg, 0.84 mmol, quant.) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.20 (5H, m, ArH), 3.82-3.73 (1H, m, propyl H₁-C2), 3.43 (3H, s, OCH₃), 3.04-2.95 (4H, m, includes 3H, s, NCH₃; and 1H, m, propyl H₁-C1), 2.94-2.80 (3H, m, includes 2H, m, propyl H₂-C3; and 1H, m, propyl H₃-C1); ¹³C NMR (100 MHz, CDCl₃) δ 138.3 (C₉), 129.7 (2 × C, ArC), 128.4 (2 × C, ArC), 126.4 (ArC), 80.0 (propyl C2), 69.1 (propyl C1), 58.0 (OCH₃), 53.9 (NCH₃), 38.4 (propyl C3); IR νₘₐₓ (neat)/cm⁻¹: 3062, 3028, 2927, 2885, 2828, 1681, 1603, 1495; HRMS (ESI): C₁₁H₁₆ClNOS [M+Na⁺]: calculated 236.0813, found 236.0806.

**Synthesis of 3-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline 367**

Following general procedure B, using chloroamine 366 (100 mg, 0.47 mmol). Work-up B, followed by purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 367 (34 mg, 0.19 mmol, 40%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.10 (1H, app. t, J = 7.5, ArH-C7), 7.00 (1H, d, J = 7.3, ArH-C5), 6.69-6.60 (2H, m, ArH), 3.84-3.75 (1H, m, H₁-C3), 3.46 (3H, s, OCH₃), 3.37 (1H, app. ddd, J = 11.1, 3.8, 1.8, H₃-C2), 3.15 (1H, app. ddd, J = 11.1, 7.1, 0.8, H₃-C2), 3.06 (1H, dd, J = 15.5, 4.3, H₃-C4), 2.92 (3H, s, NCH₃), 2.82 (1H, dd, J = 5.7, 7.6, H₄-C4); ¹³C NMR (100 MHz, CDCl₃) δ 146.2 (C₉), 129.6 (ArC), 127.5 (ArC), 120.5 (C₉), 117.1 (ArC), 111.1 (ArC), 73.3 (C3), 56.4 (OCH₃), 54.8 (C4), 39.2 (NCH₃), 33.5 (C2); IR νₘₐₓ (neat)/cm⁻¹: 2929, 2894, 2823, 1675, 1628, 1602, 1579, 1499; HRMS (ESI): C₁₁H₁₆NO [M+H⁺]: calculated 178.1226, found 178.1233.

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Synthesis of methyl(1-phenyloctan-3-yl)amine 373

To a stirred solution of nitrile 370 (1.00 g, 7.51 mmol, 1.0 eq.) in toluene (15 mL) at 0 °C was added pentylmagnesium bromide (3.75 mL of a 2.0 M solution in Et₂O, 1.0 eq.) dropwise. The reaction mixture was heated at reflux for 2 h, then cooled to 0 °C and EtO₂CCl (0.72 mL, 7.51 mmol, 1.0 eq.) was added dropwise. The reaction mixture was warmed to RT and stirred for 2 h, after which it was transferred by canular to a suspension of LiAlH₄ (1.14 g, 30.0 mmol, 4.0 eq.) in THF (30 mL) at 0 °C. The reaction mixture was then heated at reflux for 4 h, after which it was cooled to 0 °C and the reaction was quenched with H₂O (4 mL), 2.0 M aqueous NaOH (2 mL) and H₂O (2 mL), then stirred for 1 h at RT until the reaction mixture had turned white. The resultant slurry was dried over MgSO₄, filtered through a pad of Celite and the pad of Celite was washed with EtOAc (100 mL). The filtrate was concentrated in vacuo to afford the title compound 373 (1.22 g, 5.56 mmol, 74%) as a clear yellow oil.

1H NMR (400 MHz, CDCl₃) δ 7.31-7.14 (5H, m, ArH), 2.63 (2H, dd, J = 9.7, 6.7, octyl H₂-C₁), 2.49-2.42 (1H, m, octyl H₁-C₃), 2.39 (3H, s, NCH₃), 1.75-1.66 (2H, m, octyl H₂-C₄), 1.36-1.24 (6H, m, octyl H₂-C₅-7), 0.94-0.83 (3H, m, octyl H₃-C₈); 13C NMR (100 MHz, CDCl₃) δ 142.9 (Cₙ), 128.5 (4 × C, ArC), 125.8 (ArC₄), 58.9 (octyl C₃), 35.5 (octyl C₁), 33.7 (octyl C₄), 33.5 (NCH₃), 32.3 (octyl C₂), 32.2 (CH₃), 25.5 (CH₂), 22.8 (CH₂), 14.2 (octyl C₈); IR νmax (neat)/cm⁻¹: 3062, 3026, 2926, 2856, 2788, 1603, 1495, 1454; HRMS (ESI): C₁₅H₂₆N [M+H⁺]: calculated 220.2060, found 220.2064.

Synthesis of N-chloro(methyl)(1-phenyloctan-3-yl)amine 374

Following general procedure A, using amine 373 (500 mg, 2.28 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound (432 mg, 1.70 mmol, 75%) as a pale yellow oil. 1H NMR (400 MHz, CDCl₃) δ 7.34-7.27 (2H, m, ArH), 7.25-7.17 (3H, m, ArH), 2.89 (3H, s, NCH₃), 2.79-2.62 (3H, m, includes 1H, m, octyl H₁-C₃; and 2H, m, octyl H₂-C₁), 2.01-1.89 (1H, m, octyl H₃-C₂), 1.81-1.66 (2H, m, includes 1H, m, octyl H₆-C₂; and 1H, m, octyl H₃-C₄), 1.51-1.39 (1H, m, octyl H₆-C₄), 1.39-1.24 (6H, m, octyl H₂-C₅-7), 0.91 (3H, t, J = 6.9, octyl H₃-C₈); 13C NMR (100 MHz, CDCl₃) δ 142.4 (C₄), 128.6 (2 × C, ArC₂), 128.5 (2 × C, ArC₃), 125.9 (ArC₄), 69.5 (octyl C₃), 48.0 (NCH₃), 32.90 (octyl C₂), 32.86 (octyl C₁), 32.1 (CH₃), 30.0 (octyl C₄), 26.5 (CH₂), 22.7
(CH₂), 14.2 (octyl C8); IR νmax (neat)/cm⁻¹: 3062, 3026, 2930, 2858, 1603, 1495, 1454, 1433; HRMS (ESI): C₁₅H₂₅ClN [M+H⁺]: calculated 254.1670, found 254.1663.

**Synthesis of 1-methyl-2-pentyl-1,2,3,4-tetrahydroquinoline 3**

Following general procedure B, using chloroamine 374 (100 mg, 0.39 mmol). Work up B then purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 3 (59 mg, 0.27 mmol, 69%) as a clear yellow oil. The data is in accordance with the literature.²²⁸¹H NMR (400 MHz, CDCl₃) δ 7.09 (1H, app. t, J = 7.7, ArH-C7), 6.98 (1H, d, J = 7.2, ArH-C5), 6.59 (1H, app. t, J = 7.3, ArH-C6), 6.54 (1H, d, J = 8.2, ArH-C8), 3.24 (1H, td, J = 8.4, 4.1, H₁-C2), 2.94 (3H, s, NCH₃), 2.87-2.76 (1H, m, ArH-C5), 2.67 (1H, dt, J = 16.2, 4.1, H₆-C₄), 1.95-1.86 (2H, m, H₂-C₃), 1.67-1.52 (1H, m, pentyl H₄-C1), 1.48-1.20 (7H, m, includes 1H, m, pentyl H₅-C1; and 6H, m, H₂-C₅-7), 0.91 (3H, t, J = 6.8, pentyl H₃-C5); ¹³C NMR (100 MHz, CDCl₃) δ 145.5 (C₉), 128.8 (C5), 127.2 (C7), 122.0 (C₆), 115.3 (C6), 110.5 (C8), 59.1 (C2), 38.1 (NCH₃), 32.2 (CH₂), 31.3 (pentyl C1), 25.9 (CH₂), 24.6 (C3), 23.7 (C4), 22.8 (CH₂), 14.2 (pentyl C5); IR νmax (neat)/cm⁻¹: 3020, 2926, 2856, 1602, 1498, 1479, 1455; HRMS (ESI): C₁₅H₂₅N [M+H⁺]: calculated 218.1903, found 218.1903; [α]²³D -5.2 (0.1 DCM).

**Synthesis of 2-benzylcyclohexan-1-one 377**

To a stirred solution of cyclohexanone (2.08 mL, 20.0 mmol, 1.0 eq.) in THF (20 mL) at -78 °C was added a solution of LiHMDS (20 mL of 1.0 M solution in THF, 1.0 eq.) dropwise. After 0.5 h a solution of benzyl bromide (2.62 mL, 20.0 mmol, 1.0 eq.) in THF (20 mL) was added via syringe pump at a rate of 1 drop per second, then the reaction mixture was warmed to RT and stirred for 4 h. After concentration in vacuo the residue was taken up in H₂O (40 mL) and extracted with EtOAc (3 × 30 mL) and the combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with 50% DCM in hexane afforded the title compound 377 (2.83 g, 15.0 mmol, 75%) as a colourless oil. The data is in accordance with the literature.²³⁶¹H NMR (500 MHz, CDCl₃) δ 7.28 (2H, m, ArH), 7.22-7.11 (3H, m, ArH), 3.24 (1H, dd, J = 13.9, 4.8, benzyl H₆-C1), 2.60-2.50 (1H, m, cyclohexyl H-C₂), 2.47-2.38 (2H, m, includes 1H, m, cyclohexyl H₃-C₆, and 1H, dd, J = 13.8, 8.7, benzyl H₅-C1), 2.33 (1H, td, J
= 12.9, 5.8, cyclohexyl H₀-C6), 2.12-1.97 (2H, m, includes 1H, m, cyclohexyl H₀-C3, and 1H, m, cyclohexyl H₀-C5), 1.88-1.78 (1H, m, cyclohexyl H₀-C4), 1.73-1.52 (2H, m, includes 1H, m, cyclohexyl H₀-C4, and 1H, m, cyclohexyl H₀-C5), 1.36 (1H, app. qd, J = 12.4, 3.6, cyclohexyl H₀-C3); ¹³C NMR (75 MHz, CDCl₃) δ ppm 212.2 (C₁), 140.1 (C₉), 128.9 (2 × C, ArC), 128.0 (2 × C, ArC), 125.7 (ArC), 52.2 (C₂), 41.9 (C₆), 35.2 (benzyl C₁), 33.1 (C₅), 27.8 (C₅), 24.8 (C₄); IR νmax (neat)/cm⁻¹: 3025, 2933, 2859, 1705 (C=O), 1495, 1448, 1312, 1127;

Synthesis of (1R,2S)-2-benzyl-N-chloro-N-methylcyclohexan-1-amine 379

To a stirred solution of ketone 377 (2.80 g, 14.9 mmol, 1.0 eq.) in MeOH (30 mL) at RT was added NH₂Me (12 mL of an 8.0 M solution in EtOH, 10 eq.) and Ti(OiPr)₄ (9.04 mL, 29.8 mmol, 2.0 eq.). The reaction mixture was stirred for 16 h at RT, then it was cooled to 0 °C and NaBH₄ (845 mg, 22.4 mmol, 1.5 eq.) was added portionwise then the reaction mixture was warmed to RT and stirred for 1 h. The reaction mixture was concentrated in vacuo then the crude gum was taken up in EtOAc (50 mL) and a 2 M aqueous NH₄OH (40 mL) and Na₂SO₄ were added. The resultant slurry was filtered through a pad of Celite, the pad of Celite washed with EtOAc (400 mL) and concentrated in vacuo to afford the crude amine 378 as an inseparable mixture of diastereoisomers (confirmation by LC-MS analysis).

Following general procedure B, using the crude amine mixture 378 (350 mg, 1.72 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 20-40% DCM in hexane afforded the title compound 379 (280 mg, 1.18 mmol, 69%) as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.28-7.13 (5H, m, ArH), 3.05 (3H, s, NCH₃), 2.97-2.88 (1H, m, benzyl Hα-C₁), 2.69 (1H, dt, J = 11.6, 3.3, cyclohexyl H-C₁), 2.55-2.45 (2H, m, includes 1H, m, benzyl Hβ-C₁; and 1H, m, cyclohexyl H-C₂), 2.04-1.94 (1H, m, cyclohexyl H-C₆), 1.91-1.82 (1H, m, cyclohexyl H-C₅), 1.60 (1H, d, J = 14.0, cyclohexyl H-C₃), 1.57-1.45 (2H, m, cyclohexyl H-C₄), 1.45-1.36 (1H, m, cyclohexyl H₀-C₆), 1.35-1.24 (1H, m, cyclohexyl H₀-C₅), 1.23-1.16 (1H, m, cyclohexyl H₀-C₃); ¹³C NMR (75 MHz, CDCl₃) δ 141.6 (C₉), 128.9 (2 × C, ArC), 127.9 (2 × C, ArC), 125.3 (ArC), 73.8 (cyclohexyl C₁), 49.7 (NCH₃), 39.0 (cyclohexyl C₂), 29.7 (PhCH₂), 26.4 (cyclohexyl C₃), 25.9 (cyclohexyl C₅), 25.2 (cyclohexyl C₆), 19.0 (cyclohexyl C₄); IR νmax (neat)/cm⁻¹: 3025, 2928, 2855, 1601, 1494, 1448, 1367, 1338; HRMS (ESI): C₁₅H₂₃ClN [M+H⁺]: calculated 238.1363, found 238.1357.
Synthesis of \((4aR^*,9aR^*)-10\text{-}methyl\text{-}1,2,3,4,4a,9,9a,10\text{-}octahydroacridine 381\)

Following general procedure O, using chloroamine \(\text{379} (150 \text{ mg}, 0.63 \text{ mmol})\). Work-up A then purification by flash chromatography on silica gel, eluting with 10\% DCM in hexane afforded the title compound \(\text{381} (73.0 \text{ mg}, 0.36 \text{ mmol}, 57\%) \) as a yellow gum. The data is in accordance with the literature.\(^{203}\) \(^{1}\text{H NMR} (500 \text{ MHz, CDCl}_3) \delta 7.06 (1\text{H, t, } J = 7.7, \text{ ArH-C6}), 6.95 (1\text{H, d, } J = 7.3, \text{ ArH-C8}), 6.57 (1\text{H, t, } J = 7.2, \text{ ArH-C7}), 6.50 (1\text{H, d, } J = 8.2, \text{ ArH-C5}), 3.16 (1\text{H, app. dt, } J = 10.7, 3.7, \text{ H-C4a}), 2.97 (1\text{H, dd, } J = 16.1, 12.3, \text{ H-C9a}), 2.90 (3\text{H, s, NCH}_3), 2.51 (1\text{H, dd, } J = 16.2, 5.2, \text{ H-C9}), 2.32-2.23 (1\text{H, m, H-C9a}), 1.81-1.61 (4\text{H, m, includes 1H, m, H-C4, and 1H, m, H-C2, and 2H, m, H-C3}); \(^{13}\text{C NMR} \delta (125 \text{ MHz, CDCl}_3) 144.8 (\text{Cq}), 128.9 (\text{ArC}), 127.0 (\text{ArC}), 115.2 (\text{ArC}), 109.8 (\text{ArC}), 61.0 (\text{C9a}), 36.9 (\text{NCH}_3), 31.7 (\text{C4a}), 29.9 (\text{C9}), 28.5 (\text{C4}), 25.7 (\text{C1}), 24.9 (\text{C2}), 20.6 (\text{C3}); \text{IR} \nu_{\text{max}} (\text{neat/cm}^{-1}): \text{2917, 2851, 2829, 1602, 1572, 1491, 1287, 1198}; \text{HRMS (ESI): C}_{14}\text{H}_{20}\text{N [M+H}^+]\): calculated 202.1596, found 202.1597.

Synthesis of 3-phenylcyclohexan-1-one 383

Following general procedure D, using 2-cyclohexene-1-one \(\text{382} (0.73 \text{ mL}, 7.5 \text{ mmol})\) and PhB(OH)\(_2\) \(\text{29} (1.37 \text{ g}, 11.3 \text{ mmol})\). Purification by flash chromatography on silica gel, eluting with 20\% EtOAc in hexane afforded the title compound \(\text{383} (1.30 \text{ g}, 7.46 \text{ mmol}, 99\%) \) as a colourless oil. The data is in accordance with the literature.\(^{237}\) \(^{1}\text{H NMR} (400 \text{ MHz, CDCl}_3) \delta 7.40-7.33 (2\text{H, m, ArH}), 7.30-7.22 (3\text{H, m, ArH}), 3.04 (1\text{H, tt, } J = 11.7, 3.9, \text{ cyclohexyl H$_1$-C3}), 2.67-2.52 (2\text{H, m, cyclohexyl H$_2$-C2}), 2.52-2.36 (2\text{H, m, cyclohexyl H$_2$-C6}), 2.23-2.07 (2\text{H, m, contains 1H, m, cyclohexyl H$_2$-C4}; \text{and 1H, m, cyclohexyl H$_2$-C5}), 1.95-1.73 (2\text{H, m, contains 1H, m, cyclohexyl H$_2$-C4}; \text{and 1H, m, cyclohexyl H$_2$-C5}); \(^{13}\text{C NMR} (100 \text{ MHz, CDCl}_3) \delta 211.1 (\text{Cq}), 144.5 (\text{Cq}), 128.8 (2 \times \text{ C, ArC}), 126.8 (\text{ArC}), 126.7 (2 \times \text{ C, ArC}), 49.0 (\text{cyclohexyl C2}), 44.8 (\text{cyclohexyl C3}), 41.3 (\text{cyclohexyl C6}), 32.9 (\text{cyclohexyl C4}), 25.6 (\text{cyclohexyl C5}); \text{IR} \nu_{\text{max}} (\text{neat/cm}^{-1}): 3061, 3028, 2937, 2865, 1707 (\text{C=O}), 1603, 1496, 1450.

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Synthesis of (1R*,3S*)-N-chloro-N-methyl-3-phenylcyclohexan-1-amine 385 and (1S*,3S*)-N-chloro-N-methyl-3-phenylcyclohexan-1-amine 386

To a stirred solution of ketone 383 (1.00 g, 5.74 mmol, 1.0 eq.) in MeOH (11.5 mL) at RT was added NH₂Me (7.0 mL of an 8.0 M solution in EtOH, 10 eq.) and Ti(OiPr)₄ (3.41 mL, 11.5 mmol, 2.0 eq.). The reaction mixture was stirred for 16 h at RT, then it was cooled to 0 °C and NaBH₄ (326 mg, 8.61 mmol, 1.5 eq.) was added portionwise then the reaction mixture was warmed to RT and stirred for 1 h. The reaction mixture was concentrated in vacuo then the crude gum was taken up in EtOAc (25 mL) and a 2 M aqueous NH₄OH (20 mL) and Na₂SO₄ were added. The resultant slurry was filtered through a pad of Celite, the pad of Celite washed with EtOAc (250 mL) and concentrated in vacuo to afford the crude amine 384 as an inseparable mixture of diastereoisomers (confirmation by LC-MS analysis). Following general procedure A, using the crude amine mixture 384 (1.00 g, 5.28 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 20-40% DCM in hexane afforded the syn-diastereoisomer 385 (817 mg, 3.65 mmol, 69%) as a yellow oil and the anti-diastereoisomer 386 (325 mg, 1.45 mmol, 27%) as a brown gum.

**Syn-diastereoisomer 385:**

**¹H NMR** (500 MHz, CDCl₃) δ 7.34-7.17 (5H, m, ArH), 2.95 (3H, s, NCH₃), 2.84 (1H, tt, J = 11.0, 3.5, cyclohexyl H₁-C₁), 2.59 (1H, tt, J = 12.1, 3.3, cyclohexyl H₁-C₃), 2.27-2.22 (1H, m, cyclohexyl H₂-C₂), 2.17-2.10 (1H, m, cyclohexyl H₂-C₆), 1.99 (1H, ddd, J = 9.1, 6.5, 3.1, cyclohexyl H₂-C₅), 1.87 (1H, dd, J = 9.1, 3.9, cyclohexyl H₂-C₄), 1.59-1.33 (4H, m, includes 1H, m, cyclohexyl H₀-C₂; 1H, m, cyclohexyl H₀-C₄; 1H, m, cyclohexyl H₀-C₆; and 1H, m, cyclohexyl H₀-C₅); **¹³C NMR** (125 MHz, CDCl₃) δ 146.5 (C₉), 128.6 (2 × C, ArC), 127.0 (2 × C, ArC), 126.4 (ArC), 70.2 (cyclohexyl C₁), 48.6 (NCH₃), 37.4 (cyclohexyl C₂), 33.7 (cyclohexyl C₄), 29.3 (cyclohexyl C₆), 25.3 (cyclohexyl C₅); **IR** νₘₐₓ (neat)/cm⁻¹: 3027, 2931, 2857, 1668, 1602, 1494, 1449, 1408; **HRMS** (ESI): C₁₃H₁₉₃ClN [M+H⁺]: calculated 224.1201, found 224.1192.

**Anti-diastereoisomer 386:**

**¹H NMR** (400 MHz, CDCl₃) δ 7.37-7.19 (5H, m, ArH), 3.10-2.95 (5H, m, includes 3H, s, NCH₃; 1H, m, cyclohexyl H₁-C₁; and 1H, m, cyclohexyl H₁-C₃), 2.30 (1H, d, J = 14.0, cyclohexyl H₂-C₂), 2.21-2.11 (1H, m, cyclohexyl H₂-C₆), 1.99-1.92 (1H, m, cyclohexyl H₂-C₄), 1.86-1.73 (2H, m, includes 1H, m, cyclohexyl H₀-C₂; and 1H, m, cyclohexyl H₀-C₅), 1.67-1.53 (3H, m, includes 1H, m, cyclohexyl H₀-C₆; 1H, m, cyclohexyl H₀-C₄; and 1H, m, cyclohexyl H₀-C₅); **¹³C NMR** (100 MHz, CDCl₃) δ 146.8 (C₉), 128.5 (2 × C, ArC), 127.0 (2 × C, ArC), 126.1 (ArC), 67.6 (cyclohexyl C₁), 50.1 (NCH₃), 37.4 (cyclohexyl C₂), 37.2 (cyclohexyl C₃), 33.9
(cyclohexyl C4), 30.0 (cyclohexyl C6), 20.6 (cyclohexyl C4); IR \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\): 3059, 3026, 2932, 2858, 1601, 1493, 1443, 1407; HRMS could not be obtained.

**Synthesis of (1\(S^*,9S^*\))-8-methyl-8-azatricyclo[7.3.1.0\(^2,7\)]trideca-2(7),3,5-triene 387**

Following general procedure B, using chloroamine 385 (100 mg, 0.45 mmol). Workup B then purification by flash chromatography on silica gel, eluting with 10% DCM in hexane afforded the title compound 387 (26 mg, 0.14 mmol, 31%) as a colourless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 7.13-7.06 (1H, m, ArH-C5), 6.94 (1H, d, \( J = 7.2 \), ArH-C3), 6.59-6.52 (2H, m, includes 1H, m, ArH-C4; and 1H, m, ArH-C6), 3.44 (1H, s, H-1-C9), 3.01-2.92 (4H, m, includes 3H, s, NCH\(_3\); and 1H, s, H-1-C1), 1.99 (1H, d, \( J = 12.8 \), H-1-C10), 1.87 (2H, s, H-2-C13), 1.76-1.67 (2H, m, H-2-C12), 1.50-1.37 (2H, m, includes 1H, m, H-2-C10; and 1H, m, H-\(_a\)-C11), 1.30-1.19 (1H, m, H-\(_b\)-C11); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \): 147.5 (C\(_q\)), 128.1 (ArC), 127.3 (ArC), 126.3 (C\(_q\)), 114.8 (ArC), 108.6 (ArC), 54.9 (C9), 37.1 (C1), 34.9 (C12), 34.1 (NCH\(_3\)), 31.1 (C10), 30.0 (C13), 17.7 (C11); IR \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\): 3065, 3016, 2925, 2899, 2844, 1600, 1571, 1498; HRMS (ESI): C\(_{13}\)H\(_{18}\)N [M+H\(^+\)]: calculated 188.1434, found 188.1428.

**Synthesis of N-(tert-butoxycarbonyl)-2-(2-phenylethenyl)pyrrolidine 393**

To a stirred solution of Wittig reagent 391 (2.17 g, 5.00 mmol, 4.0 eq.) in THF at 0 °C was added a solution of LiHMDS in THF (3.75 mL of a 1.0 M solution in THF, 3.0 eq.) dropwise. The reaction mixture turned bright orange upon addition. After 15 mins, a solution of prolinal 392 (250 mg, 1.25 mmol, 1.0 eq.) in THF (2.5 mL) was added dropwise then the reaction mixture was warmed to RT and stirred for 16 h. The reaction was quenched with H\(_2\)O (10 mL) and the aqueous phase was extracted with Et\(_2\)O (3 × 15 mL). The combined organic extracts were washed with H\(_2\)O (20 mL), dried over Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. The crude mixture was dissolved in ether (20 mL) and filtered through a pad of celite and the celite washed with ether (20 mL). The filtrate was collected and concentrated \textit{in vacuo} to afford the title compound 393 (306 mg, 1.12 mmol, 90%) as a pale yellow gum. This was taken forward with no further purification.
Synthesis of 2-phenethylpyrrolidine 394

To a stirred solution of alkene 393 (300 mg, 1.10 mmol, 1 eq.) in degassed EtOH (6 mL) was added Pd/C (117 mg, 0.11 mol, 0.1 eq., 10% wt Pd). The solution was evacuated and flushed with N₂ (× 3) and then flushed with H₂ and left to stir under an atmosphere of H₂ for 2 h. The reaction mixture was filtered through a pad of Celite and the pad of Celite was washed with EtOAc (100 mL). The filtrate was concentrated in vacuo. The crude residue was taken up in DCM (6 mL) and the reaction mixture was cooled to 0 °C and TFA (5 mL) was added slowly. The reaction mixture was warmed to RT and stirred for 16 h, after which it was concentrated in vacuo and taken up in sat. aqueous K₂CO₃ (10 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried over Na₂SO₄ then concentrated in vacuo. Purification by SCX cartridge afforded the title compound 394 (137 mg, 0.78 mmol, 71%) as a brown oil. The data is in accordance with the literature.

1H NMR (300 MHz, MeOD) δ 7.30-7.10 (5H, m, ArH), 3.02-2.87 (2H, m, includes 1H, m, pyrrolidinyl H₁-C₂; and 1H, m, ethyl Hₐ-C₂), 2.82-2.72 (1H, m, ethyl Hₐ-C₂), 2.72-2.62 (2H, m, pyrrolidinyl H₂-C₅), 2.00-1.87 (1H, m, ethyl Hₐ-C₁), 1.87-1.64 (4H, m, includes 2H, m, pyrrolidinyl H₂-C₃; and 2H, m, pyrrolidinyl H₂-C₄), 1.40-1.23 (1H, m, ethyl Hₐ-C₁); 13C NMR (75 MHz, MeOD) δ 143.4 (Cₗ), 129.4 (2 × C, ArC), 129.4 (2 × C, ArC), 126.8 (ArC), 59.9 (pyrrolidinyl C₂), 46.9 (ethyl C₂), 38.7 (pyrrolidinyl C₃), 34.8 (pyrrolidinyl C₅), 32.6 (ethyl C₁), 26.1 (pyrrolidinyl C₄); IR νmax (neat)/cm⁻¹: 3061, 3025, 2935, 2858, 1603, 1495, 1454, 1365; HRMS (ESI): C₁₂H₁₈N [M+H⁺]: calculated 176.1434, found 176.1437.

Synthesis of 1H,2H,3H,3aH,4H,5H-pyrrolo[1,2-a]quinoline 395

To a stirred solution of amine 394 (100 mg, 0.57 mmol, 1.0 eq.) in DCM (1.9 mL) was added NCS (76 mg, 0.57 mmol, 1.0 eq.) and the reaction mixture was stirred for 0.5 h. After this MeSO₃H (0.37 mL, 5.70 mmol, 10 eq.) was added and the reaction mixture was irradiated for 3 h. The reaction mixture was extracted with H₂O (10 mL) and the aqueous phase was basified with 2M aqueous NaOH (10 mL) then extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄ then concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with a gradient of 10% EtOAc in hexane afforded the title compound 395 (73 mg, 0.42 mmol, 73%) as a yellow oil. The data is in accordance with the literature.

1H NMR (500 MHz, CDCl₃) δ 7.09 (1H, t, J
= 7.7, ArH-C8), 7.00 (1H, d, J = 7.3, ArH-C6), 6.57 (1H, t, J = 7.3, ArH-C7), 6.42 (1H, d, J = 8.0, ArH-C9), 3.44 (1H, tdd, J = 10.7, 5.1, 3.1, H1-C3a), 3.34 (1H, td, J = 9.0, 2.1, H2-C5), 3.24 (1H, dd, J = 16.6, 9.1, H5-C5), 2.94-2.84 (3H, m, includes 2H, m, H2-C2; and 1H, m, H2-C4), 2.01-1.88 (1H, m, H3-C4), 1.56-1.40 (2H, m, H2-C3); \( ^{13}C\) NMR (125 MHz, CDCl_3) \( \delta \): 144.8 (s), 128.4 (s), 127.1 (s), 121.2 (s), 114.7 (s), 109.9 (s), 58.0 (s), 46.9 (s), 33.2 (s), 28.2 (s), 27.4 (s), 23.9 (s); IR \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\): 3019, 2933, 2837, 1602, 1573, 1502, 1458, 1386; HRMS (ESI): C_{12}H_{16}N [M+H\(^+\)]: calculated 174.1277, found 174.1270.

**Synthesis of 2-(2-phenethyl)-piperidine 398**

![Image of a molecule](image)

To a stirred solution of Wittig reagent 391 (3.05 g, 7.04 mmol, 1.5 eq.) in THF (14 mL) at 0 ºC was added a solution of LiHMDS in THF (6.1 mL of a 1.0 M solution in THF, 1.3 eq.) dropwise. The reaction mixture turned bright orange upon addition. After 15 mins, a solution of piperinal derivative 396 (1 g, 4.69 mmol, 1.0 eq.) in THF (4 mL) was added dropwise then the reaction mixture was warmed to RT and stirred for 2 h. The reaction was quenched with H_2O (30 mL) and the aqueous phase was extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with H_2O (3 × 20 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude gum was dissolved in hexane/Et_2O (9:1, 10 mL) and filtered through a pad of celite to give a pale yellow gum 397. The crude gum (1.00 g) was taken up in MeOH (30 mL) and Pd/C (369 mg, 0.11 mol, 0.1 eq., 10% wt Pd) was added. The solution was evacuated and flushed with N_2 (× 3) and then flushed with H_2 and left to stir under an atmosphere of H_2 for 16 h. The reaction mixture was filtered through a pad of Celite and the pad of Celite was washed with EtOAc (200 mL). The filtrate was concentrated in vacuo. The crude residue was taken up in DCM (6 mL) and the reaction mixture was cooled to 0 ºC and TFA (5 mL) was added slowly. The reaction mixture was warmed to RT and stirred for 1 h, after which it was concentrated in vacuo and taken up in DCM (10 mL) and K_2CO_3 (2.22 g, 16.0 mmol, 5.0 eq.) was added and the reaction mixture stirred for 1 h. The reaction mixture was diluted with H_2O (30 mL) and the phases separated. The aqueous phase was extracted with DCM (2 × 25 mL) and the combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4 and concentrated in vacuo to afford the **title compound 398** (536 mg, 2.83 mmol, 60%) as a brown oil. \(^1H\) NMR (400 MHz, CDCl_3) \( \delta \): 7.35-7.13 (5H, m, ArH), 3.14-3.05 (1H, m, piperidinyl H1-C6), 2.76-2.60 (3H, m, includes 2H, m, ethyl H2-C2; and 1H, m, piperidinyl H2-C6), 2.56-2.47 (1H, m, piperidinyl H1-C2), 1.96 (1H, br. s, NH), 1.85-1.77 (1H, m, piperidinyl H2-C5), 1.77-1.65 (3H, m, includes 2H, m, ethyl H2-C1; and 1H, m, piperidinyl H2-C3) 1.65-1.58 (1H,
m, piperidinyl H2-C4) 1.50-1.29 (2H, m, includes 1H, m, piperidinyl H2-C4; and 1H, m, piperidinyl H2-C5), 1.22-1.08 (1H, m, piperidinyl H6-C3); 13C NMR (100 MHz, CDCl3) δ 142.5 (Cq), 128.5 (ArC), 128.4 (ArC), 125.9 (ArC), 56.6 (piperidinyl C2), 47.2 (piperidinyl C6), 39.3 (ethyl C1), 33.0 (piperidinyl C3), 32.4 (ethyl C2), 26.7 (piperidinyl C4), 24.9 (piperidinyl C5); IR νmax (neat)/cm⁻¹: 3303 (N-H), 3061, 3025, 2925, 2852, 2798, 2738, 1602; HRMS (ESI): C13H20N [M+H⁺]: calculated 190.1590, found 190.1587.

Synthesis of 1-chloro-2-(2-phenylethyl)piperidine 399

Following general procedure A, using amine 398 (150 mg, 0.79 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound (154 mg, 0.69 mmol, 87%) as a yellow gum. The sample degraded upon dissolution in chloroform so full data was not obtained.

Synthesis of 1H,2H,3H,4H,4aH,5H,6H-pyrido[1,2-a]quinoline 400

Following general procedure B, using chloroamine 399 (100 mg, 0.45 mmol). Workup B then purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 400 (70 mg, 0.37 mmol, 82%) as a pale yellow oil. The data is in accordance with the literature. 1H NMR (500 MHz, CDCl3) δ 7.08 (1H, td, J = 8.2, 1.5, Ar-H-C9), 6.97 (1H, dd, J = 7.3, 0.5, Ar-H-C7), 6.83 (1H, d, J = 8.3, Ar-H-C10), 6.66 (1H, td, J = 7.3, 0.9, Ar-H-C8), 3.99-3.90 (1H, m, H6-C6), 2.93-2.79 (2H, m, includes 1H, m, H1-C4a, and 1H, m, H7-C1), 2.73-2.63 (2H, m, includes 1H, m, H5-C6, and 1H, m, H6-C1), 1.95 (1H, dt, J = 13.2, 5.2, 4.0, H5-C4), 1.88-1.55 (5H, m, includes 1H, H5-C4; 2H, m, H2-C2; 1H, m, H1-C3, and 1H, m, H7-C5), 1.50-1.38 (2H, m, includes 1H, H5-C3, and 1H, m, H6-C5); 13C NMR (125 MHz, CDCl3) δ 147.1 (Cq), 129.2 (ArC), 127.1 (ArC), 125.1 (Cq), 117.4 (ArC), 112.9 (ArC), 57.1 (C4a), 48.3 (C6), 33.5 (C5), 30.5 (C4), 27.2 (C1), 26.0 (C2), 24.7 (C3); IR νmax (neat)/cm⁻¹: 3067, 3016, 2927, 2846, 2795, 1602, 1576, 1492; HRMS (ESI): C13H18N [M+H⁺]: calculated 188.1434, found 188.1434.
Synthesis of 3-(2,6-dimethylphenyl)-N-methylbutanamide 402

Following general procedure D, using N-methylcrotonamide 307 (500 mg, 5.04 mmol) and ArB(OH)2 401 (1.13 g, 7.56 mmol). Purification by flash chromatography on silica gel, eluting with 50% EtOAc in hexane afforded the title compound 402 (490 mg, 2.39 mmol, 47%) as a colourless gum. 1H NMR (500 MHz, CDCl3) δ 6.98 (3H, s, ArH), 5.33 (1H, br. s, NH), 3.87 (1H, app. h, J = 7.3, CH), 2.73 (3H, d, J = 4.8, NCH3), 2.56 (2H, d, J = 7.3, CH2), 2.40 (6H, s, ArCH3), 1.36 (3H, d, J = 7.3, CH3); 13C NMR (125 MHz, CDCl3) δ 172.9 (C=O), 141.8 (ArC), 136.5+135.8 (ArCq), 130.3 (ArCq), 128.5 (ArCq), 126.0 (2 × C, ArC), 42.3 (CH2), 31.9 (CH), 26.2 (NCH3), 21.5 (2 × C, ArCH3), 18.9 (CH3); IR νmax (neat)/cm−1: 3267 (N-H), 3087, 2961, 2876, 1637 (C=O), 1570, 1462, 1411; HRMS (ESI): C13H20NO [M+H]+: calculated 206.1539, found 206.1539.

Synthesis of [3-(2,6-dimethylphenyl)butyl](methyl)amine 403

To a stirred suspension of LiAlH₄ (296 mg, 7.80 mmol, 4.0 eq.) in THF (8 mL) at 0 °C was added a solution of amide 402 (375 mg, 1.83 mmol, 1.0 eq.) in THF (2 mL) dropwise. The reaction mixture was heated at reflux and left to stir for 4 hours, after which it was cooled to 0 °C and the reaction was quenched with H₂O (2 mL), 2 M aqueous NaOH (1 mL) and H₂O (1 mL). then stirred for 1 h at RT until the reaction mixture had turned white. The resultant slurry was dried over MgSO₄, filtered through a pad of Celite and the pad of Celite was washed with EtOAc (150 mL). The filtrate was concentrated in vacuo. Purification by SCX cartridge afforded the title compound 403 (283 mg, 1.48 mmol, 81%) as a pale yellow oil. 1H NMR (500 MHz, CDCl3) δ 6.97 (3H, s, ArH), 3.37-3.29 (1H, m, butyl H1-C3), 2.60-2.53 (1H, m, butyl H2-C1), 2.52-2.30 (10H, m, includes 3H, s, NCH3; 6H, br. m, ArCH3; and 1H, m, butyl H3-C1), 2.06-1.95 (1H, m, butyl H4-C2), 1.93-1.83 (1H, m, butyl H5-C2), 1.32 (3H, d, J = 7.3, butyl H7-C4); 13C NMR (125 MHz, CDCl3) δ 142.7 (ArC), 136.2 (Cq), 130.4 (Cq), 128.3 (Cq), 125.6 (2 × C, ArC), 51.2 (butyl C1), 36.5 (butyl C2), 35.6 (NCH3), 33.0 (butyl C3), 21.6 (2 × C, ArCH3), 19.1 (butyl C4); IR νmax (neat)/cm−1: 3017, 2957, 2872, 2788, 1544, 1467, 1380, 1308; HRMS (ESI): C13H22N [M+H]+: calculated 192.1747, found 192.1745.
Synthesis of N-chloro[3-(2,6-dimethylphenyl)butyl]methylamine 404

Following general procedure A, using amine 403 (250 mg, 1.31 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the *title compound 404* (256 mg, 1.13 mmol, 86%) as a colourless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.00 (3H, s, ArH), 3.44-3.34 (1H, m, butyl H$^-_{C3}$), 2.89 (3H, s, NCH$_3$), 2.83-2.71 (2H, m, butyl H$^-_{C1}$), 2.49-2.30 (6H, br. m, 2 × ArCH$_3$), 2.21-2.12 (1H, m, butyl H$^-_{a-C2}$), 2.08-2.00 (1H, m, butyl H$^-_{b-C2}$), 1.34 (3H, d, J = 7.3, butyl H$^-_{3-C4}$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 142.0 (ArC), 136.4 (C$q$), 130.4 (C$q$), 128.3 (C$q$), 125.7 (2 × C, ArC), 64.8 (butyl C1), 53.1 (NCH$_3$), 33.6 (butyl C2), 32.1 (butyl C3), 21.5 (2 × C, ArCH$_3$), 17.0 (butyl C4); IR $\nu_{\text{max}}$ (neat)/cm$^{-1}$: 2956, 2873, 2794, 1580, 1462, 1438, 1262, 1176; HRMS (ESI): C$_{13}$H$_{21}$ClN $[\text{M}+\text{H}]^+$: calculated 226.1357, found 226.1353.

Synthesis of 1,4,5,8-tetramethyl-1,2,3,4-tetrahydroquinoline 405

Following general procedure B, using chloroamine 404 (100 mg, 0.44 mmol). Workup B then purification by flash chromatography on silica gel, eluting with 50% DCM in hexane afforded the *title compound 405* (34 mg, 0.18 mmol, 41%) as a colourless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 6.93 (1H, d, J = 7.6, ArH), 6.72 (1H, d, J = 7.6, ArH), 3.23 (1H, td, J = 12.9, 2.8, H$_a$-C2), 3.14-3.08 (1H, m, H$_b$-C2), 3.08-3.03 (1H, m, H$_1$-C4), 2.73 (3H, s, NCH$_3$), 2.30 (3H, s, ArCH$_3$), 2.29 (3H, s, ArCH$_3$), 2.06 (1H, tdd, J = 13.0, 5.3, 4.0, H$_a$-C3), 1.52 (1H, ddd, J = 13.3, 5.3, 2.9, H$_b$-C3), 1.19 (3H, d, J = 7.0, CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 147.3 (C$q$), 133.6 (C$q$), 132.5 (C$q$), 128.8 (ArC), 128.1 (C$q$), 123.4 (ArC), 47.3 (C2), 43.9 (NCH$_3$), 28.1 (C4), 25.1 (C3), 21.3 (CH$_3$), 19.2 (ArCH$_3$), 18.9 (ArCH$_3$); IR $\nu_{\text{max}}$ (neat)/cm$^{-1}$: 2929, 2864, 2787, 1737, 1578, 1460, 1397, 1370; HRMS (ESI): C$_{13}$H$_{20}$N [M+H$^+$]: calculated 190.1590, found 190.1586.

Synthesis of 2-(but-3-en-1-yl)-1,3-dichlorobenzene 412

200
Following general procedure F, using 2,6-dichlorobenzyl bromide 411 (1.00 g, 4.18 mmol) and allylmagnesium chloride (2.30 mL of a 2.0 M solution in THF) afforded the title compound 412 (827 mg, 4.11 mmol, 98%) as a colourless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.29-7.22 (2H, m, ArH), 7.10-6.99 (1H, m, ArH), 5.96 (1H, ddt, $J = 16.9, 10.2, 6.7$, butenyl H$_{1-3}$C3), 5.07 (1H, ddt, $J = 16.9, 1.1$, butenyl H$_{trans}$-C4), 5.04-4.97 (1H, m, butenyl H$_{cis}$-C4); $^1$C NMR (100 MHz, CDCl$_3$) $\delta$ 137.9 (C$_q$), 137.6 (butenyl C3), 135.5 (2 × C, C$_q$), 128.3 (2 × C, ArC), 127.7 (ArC), 115.3 (butenyl C4), 32.3 (butenyl C3), 30.9 (butenyl C1); IR $\nu_{max}$ (neat)/cm$^{-1}$: 3078, 2978, 2942, 2872, 1641, 1582, 1561, 1490.

**Synthesis of 3-(2,6-dichlorophenyl)propanal 413**

![Chemical structure](image)

Following general procedure H, using alkene 412 (827 mg, 4.11 mmol). Purification by flash chromatography on silica gel, eluting with 10% Et$_2$O in hexane afforded the title compound 413 (528 mg, 2.60 mmol, 63%) as a colourless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.86 (1H, s, propyl H$_1$-C1), 7.32-7.26 (2H, m, ArH), 7.14-7.06 (1H, m, ArH), 3.26 (2H, t, $J = 8.1$, propyl H$_2$-C3), 2.73 (2H, t, $J = 8.1$, propyl H$_2$-C2); $^1$C NMR (100 MHz, CDCl$_3$) $\delta$ 200.9 (propyl C1), 136.4 (C$_q$), 135.4 (2 × C, C$_q$), 128.4 (2 × C, ArC), 128.3 (ArC), 42.1 (propyl C2), 24.2 (propyl C3); IR $\nu_{max}$ (neat)/cm$^{-1}$: 2953, 2857, 1699 (C=O), 1582, 1561, 1433, 1409, 1395.

**Synthesis of [3-(2,6-dichlorophenyl)propyl](methyl)amine 414**

To a stirred solution of aldehyde 413 (400 mg, 1.97 mmol, 1.0 eq.) in DCM (10 mL) was added a solution of MeNH$_2$ (3.5 mL of an 8.0 M solution in EtOH, 10 eq.). This was stirred for 0.5 h then cooled to 0 °C and sodium trisacetoxyborohydride (835 mg, 3.94 mmol, 2.0 eq.) was added portionwise. The reaction mixture was stirred for 4 h then the reaction was quenched with H$_2$O (20 mL). The organic phase was separated and the aqueous phase was extracted with DCM (1 × 20 mL) and the combined organic extracts were then washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Due to the presence of residual imine the residue was re-dissolved in MeOH (10 mL) and NaBH$_4$ (149 mg, 3.94 mmol, 2.0 eq.) was added portionwise. After 20 minutes the reaction mixture was diluted with H$_2$O (30 mL) and then extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by SCX cartridge afforded
the title compound 414 (319 mg, 1.46 mmol, 74%) as a pale yellow oil. \( ^1H \text{NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) 7.28-7.22 (2H, m, ArH), 7.08-7.00 (1H, m, ArH), 2.99-2.92 (2H, m, propyl H\(_2\)-C1), 2.70 (2H, t, \( J = 7.2 \), propyl H\(_2\)-C3), 2.46 (3H, s, NCH\(_3\)), 1.84-1.74 (2H, m, propyl H\(_2\)-C2); \( ^13C \text{NMR} \) (100 MHz, CDCl\(_3\)) \( \delta \) 138.1 (C\(_q\)), 135.4 (2 × C, C\(_q\)), 128.3 (2 × C, ArC), 127.7 (ArC), 51.6 (propyl C1), 36.3 (NCH\(_3\)), 2.70 (2H, t, \( J = 7.2 \), propyl H\(_2\)-C3), 2.46 (3H, s, NCH\(_3\)), 1.84-1.74 (2H, m, propyl H\(_2\)-C2); IR \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\): 3283, 3057, 2933, 2870, 2790, 1582, 1561, 1434; HRMS (ESI): C\(_{10}\)H\(_{14}\)Cl\(_2\)N [M+H\(^{+}\)]: calculated 218.0498, found 218.0493.

**Synthesis of N-chloro[3-(2,6-dichlorophenyl)propyl]methylamine 415**

Following general procedure A, using amine 414 (250 mg, 1.15 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 415 (268 mg, 1.06 mmol, 92%) as a pale yellow oil. \( ^1H \text{NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) 7.30-7.23 (2H, m, ArH), 7.10-7.04 (1H, m, ArH), 3.03-2.93 (7H, m, includes 3H, s, NCH\(_3\); 2H, m, propyl H\(_2\)-C1; and 2H, m, propyl H\(_2\)-C3), 1.98-1.87 (2H, m, propyl H\(_2\)-C2); \( ^13C \text{NMR} \) (100 MHz, CDCl\(_3\)) \( \delta \) 137.9 (C\(_q\)), 135.5 (2 × C, C\(_q\)), 128.3 (2 × C, ArC), 127.8 (ArC), 53.1 (NCH\(_3\)), 28.7 (propyl C3), 26.9 (propyl C2); IR \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\): 2950, 2873, 2845, 2794, 1582, 1561, 1455, 1434; HRMS (ESI): C\(_{16}\)H\(_{13}\)Cl\(_3\)N [M+H\(^{+}\)]: calculated 252.0108, found 252.0104.

**Synthesis of 5-chloro-1-methyl-1,2,3,4-tetrahydroquinoline 421**

Following general procedure B, using chloroamine 415 (100 mg, 0.40 mmol). Work up B then purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 421 (37 mg, 0.20 mmol, 50%) as a clear yellow oil. \( ^1H \text{NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) 7.02-6.94 (1H, m, ArH), 6.71-6.65 (1H, m, ArH), 3.03-2.93 (7H, m, includes 3H, s, NCH\(_3\); 2H, m, propyl H\(_2\)-C1; and 2H, m, propyl H\(_2\)-C3), 1.98-1.87 (2H, m, propyl H\(_2\)-C2); \( ^13C \text{NMR} \) (100 MHz, CDCl\(_3\)) \( \delta \) 148.4 (C\(_q\)), 134.5 (2 × C, C\(_q\)), 128.3 (2 × C, ArC), 127.8 (ArC), 65.8 (propyl C1), 53.1 (NCH\(_3\)), 28.7 (propyl C3), 26.9 (propyl C2); IR \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\): 2950, 2873, 2845, 2794, 1582, 1561, 1455, 1434; HRMS (ESI): C\(_{16}\)H\(_{13}\)Cl\(_3\)N [M+H\(^{+}\)]: calculated 182.0731, found 182.0731.
Synthesis of 2-(but-3-en-1-yl)-1-chloro-3-methylbenzene 417a

Following and general procedure G, using (2-chloro-6-methylphenyl)methanol 416a (900 mg, 5.76 mmol) and allylmagnesium chloride (5.76 mL of a 2.0 M solution in THF). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 417a (880 mg, 4.87 mmol, 85%) as a colourless oil. 1H NMR (400 MHz, CDCl3) δ 7.23-7.19 (1H, m, ArH), 7.08-6.99 (2H, m, ArH), 5.93 (1H, ddt, J = 16.9, 10.2, 6.6, butenyl H1-C3), 5.09 (1H, dd, J = 17.1, 1.5, butenyl Htrans-C4), 5.02 (1H, dd, J = 10.1, 1.5, butenyl Hcis-C4), 2.91-2.81 (2H, m, butenyl H2-C1), 2.36 (3H, s, ArCH3), 2.34-2.25 (2H, m, butenyl H2-C2); 13C NMR (100 MHz, CDCl3) δ 138.3 (Cq), 138.13 (butenyl C3), 138.10 (Cq), 134.6 (Cq), 128.9 (ArC), 127.4 (ArC), 126.9 (ArC), 115.0 (butenyl C4), 32.8 (butenyl C2), 30.0 (butenyl C1), 20.3 (ArCH3); IR νmax (neat)/cm⁻¹: 3064, 2951, 2916, 1640, 1594, 1568, 1452, 1415;

Synthesis of 3-(2-chloro-6-methylphenyl)propanal 418a

Following general procedure H, using alkene 417a (800 mg, 4.43 mmol). Purification by flash chromatography on silica gel, eluting with 20% Et2O in hexane afforded the title compound 418a (605 mg, 3.31 mmol, 75%) as a colourless oil. 1H NMR (400 MHz, CDCl3) δ 9.86 (1H, s, propyl H1-C1), 7.24-7.17 (1H, m, ArH), 7.10-7.01 (2H, m, ArH), 3.16-3.03 (2H, m, propyl H2-C3), 2.75-2.65 (2H, m, propyl H2-C2), 2.34 (3H, s, ArCH3); 13C NMR (100 MHz, CDCl3) δ 201.4 (propyl C1), 138.2 (Cq), 136.5 (Cq), 134.5 (Cq), 129.1 (ArC), 127.5 (ArC), 127.4 (ArC), 42.6 (propyl C2), 22.9 (propyl C3), 20.3 (ArCH3); IR νmax (neat)/cm⁻¹: 3023, 2964, 2914, 2699, 1698 (C=O), 1568, 1449, 1427;

Synthesis of [3-(2-chloro-6-methylphenyl)propyl](methyl)amine 419a

To a stirred solution of aldehyde 418a (500 mg, 2.74 mmol, 1.0 eq.) in DCM (10 mL) was added a solution of MeNH2 (6.0 mL of an 8.0 M solution in EtOH, 20 eq.). This was stirred for 0.5 h then cooled to 0 °C and sodium trisacetoxyborohydride (1.16 g, 5.48 mmol, 2.0 eq.) was added portionwise. The reaction mixture was stirred for 3 h then the reaction was...
quenched with H$_2$O (20 mL). The organic phase was separated and the aqueous phase was extracted with DCM (1 × 20 mL) and the combined organic extracts were then washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Due to the presence of residual imine the residue was re-dissolved in MeOH (10 mL) and NaBH$_4$ (104 mg, 2.74 mmol, 1.0 eq.) was added portionwise. After 20 minutes the reaction mixture was diluted with H$_2$O (30 mL) and then extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo.

Due to the presence of residual imine the residue was re-dissolved in MeOH (10 mL) and NaBH$_4$ (104 mg, 2.74 mmol, 1.0 eq.) was added portionwise. After 20 minutes the reaction mixture was diluted with H$_2$O (30 mL) and then extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with a gradient of 5-100% MeOH in DCM afforded the title compound 419a (264 mg, 1.34 mmol, 49%) as a pale yellow oil.

**1H NMR** (400 MHz, CDCl$_3$) δ 7.23-7.16 (1H, m, ArH), 7.07-6.96 (2H, m, ArH), 2.86-2.76 (2H, m, propyl H$_2$-C1), 2.69 (2H, t, J = 7.1, propyl H$_2$-C3), 2.46 (3H, s, NCH$_3$), 2.35 (3H, s, ArCH$_3$), 1.79-1.66 (2H, m, propyl H$_2$-C2), 1.18 (1H, s, NH); **13C NMR** (100 MHz, CDCl$_3$) δ 138.5 (C$q$), 138.2 (C$q$), 134.6 (C$q$), 128.9 (ArC), 127.4 (ArC), 126.8 (ArC), 52.3 (propyl C3), 36.7 (NCH$_3$), 29.0 (propyl C1), 28.3 (propyl C2), 20.2 (ArCH$_3$); **IR** $\tilde{\nu}_{\text{max}}$ (neat)/cm$^{-1}$: 3061, 2932, 2872, 2791, 1594, 1568, 1451, 1380; **HRMS** (ESI): C$_{11}$H$_{17}$ClN [M+H$^+$]: calculated 198.1044, found 198.1043.

**Synthesis of N-chloro[3-(2-chloro-6-methylphenyl)propyl]methylamine 420a**

Following general procedure A, using amine 419a (200 mg, 1.01 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 420a (213 mg, 0.92 mmol, 91%) as a pale yellow oil. **1H NMR** (400 MHz, CDCl$_3$) δ 7.24-7.18 (1H, m, ArH), 7.09-6.98 (2H, m, ArH), 3.03-2.94 (5H, m, includes 3H, s, NCH$_3$; and 2H, m, propyl H$_2$-C1), 2.88-2.80 (2H, m, propyl H$_2$-C3), 2.38 (3H, s, ArCH$_3$), 1.94-1.81 (2H, m, propyl H$_2$-C2); **13C NMR** (100 MHz, CDCl$_3$) δ 138.4 (C$q$), 138.1 (C$q$), 134.6 (C$q$), 128.9 (ArC), 127.4 (ArC), 126.9 (ArC), 65.9 (propyl C1), 53.2 (NCH$_3$), 27.6 (propyl C3), 27.3 (propyl C2), 20.2 (ArCH$_3$); **IR** $\tilde{\nu}_{\text{max}}$ (neat)/cm$^{-1}$: 3063, 2951, 2875, 2845, 2794, 1594, 1568, 1451, 1380; **HRMS** (ESI): C$_{11}$H$_{16}$Cl$_2$N [M+H$^+$]: calculated 232.0654, found 232.0651.

**Synthesis of 1,5-dimethyl-1,2,3,4-tetrahydroquinoline 424**

Following general procedure B, using chloroamine 420a (100 mg, 0.43 mmol). Work up B then purification by flash chromatography on silica gel, eluting with 15% DCM in hexane afforded the title compound 424 (10 mg, 0.06 mmol, 14%) as a colourless oil. **1H NMR** (400 MHz, CDCl$_3$) δ 7.24-7.18 (1H, m, ArH), 7.09-6.98 (2H, m, ArH), 3.03-2.94 (5H, m, includes 3H, s, NCH$_3$; and 2H, m, propyl H$_2$-C1), 2.88-2.80 (2H, m, propyl H$_2$-C3), 2.38 (3H, s, ArCH$_3$), 1.94-1.81 (2H, m, propyl H$_2$-C2); **13C NMR** (100 MHz, CDCl$_3$) δ 138.4 (C$q$), 138.1 (C$q$), 134.6 (C$q$), 128.9 (ArC), 127.4 (ArC), 126.9 (ArC), 65.9 (propyl C1), 53.2 (NCH$_3$), 27.6 (propyl C3), 27.3 (propyl C2), 20.2 (ArCH$_3$); **IR** $\tilde{\nu}_{\text{max}}$ (neat)/cm$^{-1}$: 3063, 2951, 2875, 2845, 2794, 1594, 1568, 1451, 1380; **HRMS** (ESI): C$_{11}$H$_{16}$Cl$_2$N [M+H$^+$]: calculated 232.0654, found 232.0651.
MHz, CDCl$_3$) $\delta$ 7.03-6.95 (1H, ArH), 6.56-6.49 (2H, ArH), 3.21-3.14 (2H, H$_2$-C2), 2.88 (3H, s, NCH$_3$), 2.70-2.62 (2H, H$_2$-C4), 2.19 (3H, s, ArCH$_3$), 2.07-1.97 (2H, H$_2$-C3); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 147.3 (C$q$), 136.5 (C$q$), 126.4 (ArC), 121.6 (C$q$), 118.7 (ArC), 109.6 (ArC), 51.2 (C$_2$), 40.0 (NCH$_3$), 24.8 (C$_4$), 22.6 (C$_3$), 20.0 (ArCH$_3$);

**Synthesis of 1-(but-3-en-1-yl)-2-chlorobenzene 417b**

![Chemical Structure](image)

Following general procedure G, using (2-chlorophenyl)methanol 416b (900 mg, 5.76 mmol) and allylmagnesium chloride (5.76 mL of a 2.0 M solution in THF). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 417b (880 mg, 4.87 mmol, 85%) as a colourless oil. The data is in accordance with the literature.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37-7.31 (1H, m, ArH), 7.24-7.09 (3H, m, ArH), 5.88 (1H, ddt, $J$ = 17.0, 10.2, 6.6, butenyl H$_1$-C3), 5.06 (1H, dd, $J$ = 17.0, 1.6, butenyl H$_{trans}$-C4), 5.00 (1H, ddt, $J$ = 10.1, 1.6, 1.1, butenyl H$_{cis}$-C4), 2.87-2.80 (2H, m, butenyl H$_2$-C1), 2.43-2.33 (2H, m, butenyl H$_2$-C2); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 139.5 (C$q$), 137.9 (butenyl C$_3$), 134.1 (C$_q$), 130.6 (ArC), 129.6 (ArC), 127.5 (ArC), 126.8 (ArC), 115.30 (butenyl H$_2$-C4), 33.8 (butenyl H$_2$-C2), 33.2 (butenyl H$_2$-C1); IR $\nu_{max}$ (neat)/cm$^{-1}$: 3075, 2978, 2930, 2861, 1641, 1595, 1572, 1474;

**Synthesis of 3-(2-chlorophenyl)propanal 418b**

![Chemical Structure](image)

Following general procedure H, using alkene 417b (500 mg, 3.00 mmol). Purification by flash chromatography on silica gel, eluting with 10% Et$_2$O in hexane afforded the title compound 418b (301 mg, 1.79 mmol, 60%) as a colourless oil. The data is in accordance with the literature.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.84 (1H, s, propyl H$_1$-C1), 7.40-7.34 (1H, m, ArH), 7.34-7.11 (3H, m, ArH), 3.08 (2H, t, $J$ = 7.5, propyl H$_2$-C3), 2.81 (2H, t, $J$ = 7.5, propyl H$_2$-C2); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 201.2 (propyl C1), 138.1 (C$q$), 134.0 (C$_q$), 130.7 (ArC), 129.8 (ArC), 128.0 (ArC), 127.1 (ArC), 43.7 (propyl C2), 26.4 (propyl C3); IR $\nu_{max}$ (neat)/cm$^{-1}$: 3025, 2962, 2919, 2700, 1698 (C=O), 1429, 1408, 1354;
Synthesis of [3-(2-chlorophenyl)propyl](methyl)amine 419b

Following general procedure C, using aldehyde 418b (295 mg, 1.75 mmol) and MeNH₂ (2.00 mL of an 8.0 M solution in EtOH) afforded the title compound 419b (318 mg, 1.73 mmol, 99%) as a pale yellow oil. The ¹H NMR data is in accordance with the literature.²²⁰ ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.29 (1H, m, ArH), 7.24-7.09 (3H, m, ArH), 2.82-2.74 (2H, m, propyl H₂-C1), 2.65 (2H, t, J = 7.2, propyl H₂-C3), 2.45 (3H, s, NCH₃), 1.95 (1H, br. s, NH), 1.88-1.77 (2H, m, propyl H₂-C2); ¹³C NMR (100 MHz, CDCl₃) δ 139.8 (Cₗ), 134.1 (Cₗ), 130.5 (ArC), 129.6 (ArC), 127.4 (ArC), 126.9 (ArC), 51.6 (propyl C1), 36.4 (NCH₃), 31.4 (propyl C3), 29.8 (propyl C2); IR νₘₐₓ (neat)/cm⁻¹: 3062, 2933, 2862, 2792, 1594, 1572, 1473, 1442; HRMS (ESI): C₁₀H₁₅Cl₃N⁺ [M+H⁺]: calculated 184.0888, found 184.0885.

Synthesis of N-chloro[3-(2-chlorophenyl)propyl]methylamine 420b

Following general procedure A, using amine 419b (200 mg, 1.08 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 420b (157 mg, 0.72 mmol, 66%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.32 (1H, m, ArH), 7.27-7.11 (3H, m, ArH), 3.00-2.88 (5H, m, includes 3H, s, NCH₃; and 2H, m, propyl H₂-C1), 2.85-2.77 (2H, m, propyl H₂-C1), 2.03-1.92 (2H, m, propyl H₂-C2); ¹³C NMR (100 MHz, CDCl₃) δ 139.4 (Cₗ), 134.1 (Cₗ), 130.6 (ArC), 129.7 (ArC), 127.6 (ArC), 126.9 (ArC), 65.4 (propyl C1), 53.2 (NCH₃), 30.7 (propyl C3), 28.2 (propyl C2); IR νₘₐₓ (neat)/cm⁻¹: 3063, 2992, 2952, 2869, 2795, 1594, 1572, 1474; HRMS (ESI): C₁₀H₁₄Cl₂N⁺ [M+H⁺]: calculated 218.0498, found 218.0494.

6.3 Continuous Photochemical Processors

6.3.1 One-Stage Photochemical Reactor

A photochemical reactor was designed based on the reactor described by Booker-Milburn et al.¹⁵⁸ The photochemical reactor was constructed using FEP tubing (internal diameter 2.7 mm, external diameter 3.1 mm) that was wrapped around a 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 outlet of a stainless steel T-junction. Adapters were placed in the inlets of the T-junction that allowed PTFE tubing (internal diameter 1/32\textsuperscript{nd} inch, external diameter 1/16\textsuperscript{th} 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. 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).

6.3.2 Two-Stage Photochemical Reactor

The two-stage photochemical reactor was constructed using the one-stage photochemical reactor as the ‘light’ reactor. To one of the inlets in the stainless steel T-junction of the light reactor was attached tubing that led to a single syringe housed a mono-syringe pump. To the other inlet of the stainless steel T-junction of the light reactor was attached 10 m of PTFE tubing (internal diameter 1/32\textsuperscript{nd} inch, external diameter 1/16\textsuperscript{th} inch, 5 mL reactor volume) which would make up the ‘dark’ reactor element. The other end of PTFE tubing was attached to the outlet of another stainless steel T-junction and to the inlets PTFE tubing (internal diameter 1/32\textsuperscript{nd} inch, external diameter 1/16\textsuperscript{th} 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. The single syringe pump was set to go at twice the speed so the solution of acid was added at the same rate as the flow from the dark reactor. 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).

6.4 Biocatalysis Experimental Data

6.4.1 General Procedures

General Procedure I: Grignard Addition

To a stirred solution of aldehyde (1.0 eq.) in anhydrous THF (1.0 M) at 0 °C under an atmosphere of N\textsubscript{2} was added a solution of Grignard reagent (1.5 eq.) dropwise. The reaction
mixture was warmed to rt then stirred for 1 h, after which it was quenched with sat. aqueous NH₄Cl (2 vol) and the aqueous phase was then extracted with EtOAc (× 3). The combined organic extracts were washed with brine (2 vol), dried over Na₂SO₄ and concentrated in vacuo. Purification afforded the desired products.

**General Procedure J: Et₃SiH Reduction of Benzylic Alcohols**

Following a procedure by Salomon et al.,¹⁹⁵ to a stirred solution of alcohol (1.0 eq.) in DCM (0.33 M) at -50 °C was added Et₃SiH (2.5 eq.) and then TFA (6.0 eq.) dropwise. The reaction mixture was warmed to rt then stirred for 1 h, after which it was quenched with sat. aqueous NaHCO₃ (2 vol). The phases were separated and the aqueous phase was then extracted with EtOAc (× 3). The combined organic extracts were washed with brine (2 vol), dried over Na₂SO₄ and concentrated in vacuo. Purification afforded the desired products.

**General Procedure K: Dihydroxylation**

To a stirred solution of alkene (1.0 eq.) in Acetone:H₂O (9:1, 0.2 M) at rt was added NMO (1.5 eq.) then K₂OsO₄·2H₂O (1 mol%). The reaction mixture was stirred at rt for 3 h then Na₂S₂O₄ (5 eq.) was added portionwise and the reaction mixture was then filtered through a pad of Celite, the Celite washed with Acetone (10 vol) and the filtrate collected and then concentrated in vacuo. Purification afforded the desired products.

**General Procedure L: Periodate Oxidative Cleavage**

To a stirred solution of diol (1.0 eq.) in MeOH:H₂O (9:1, 0.2 M) at rt was added NaIO₄ (1.5 eq.). The reaction mixture was stirred at rt for 1 h after which brine (5 vol) was added and the aqueous phase was then extracted with EtOAc (× 3). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. Purification afforded the desired products.

**General Procedure M: IBX Oxidation**

Following a procedure by Loh et al.,¹⁹⁶ to a stirred solution of vinyl alcohol (1.0 eq.) in EtOAc (0.05 M) was added IBX (45% wt, 1.2 eq.) portionwise. The reaction mixture was heated at reflux for 16 h then was cooled to rt, filtered through a pad of Celite and the Celite was washed with EtOAc (10 vol). The organic phase was washed with aqueous 2M NaOH (× 2), brine (2 vol), dried over Na₂SO₄ and concentrated in vacuo. Purification afforded the desired products.
6.4.2 Experimental Data

**Synthesis of 1-(3,4-dimethoxyphenyl)but-3-en-1-ol 495a**

Following general procedure I, using 3,4-dimethoxybenzaldehyde 494a (2.00 g, 12.0 mmol) and allylmagnesium chloride (9 mL of a 2.0 M in THF, 18.0 mmol) afforded the title compound 495a (2.47 g, 11.9 mmol, 99%) as a colourless amorphous solid. The data is in accordance with the literature.\(^{243}\)

\[ ^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \delta 6.97-6.76 (3\text{H, m, ArH}), 5.79 (1\text{H, ddt, } J = 17.2, 10.1, 6.8, \text{ butenyl H}_1-\text{C3}), 5.21-5.10 (2\text{H, m, butenyl H}_2-\text{C4}), 4.66 (1\text{H, t, } J = 6.8, \text{ butenyl H}_1-\text{C1}), 3.88 (3\text{H, s, OCH}_3), 3.86 (3\text{H, s, OCH}_3), 2.49 (2\text{H, t, } J = 6.8, \text{ butenyl H}_2-\text{C2}), 2.13 (1\text{H, br. s, OH}); ^{13}\text{C NMR} \ (100 \text{ MHz, CDCl}_3) \delta 149.4 (\text{C}_q), 148.8 (\text{C}_q), 137.0 (\text{C}_q), 135.0 (\text{butenyl C3}), 118.6 (\text{ArC}), 118.5 (\text{ArC}), 111.37 (\text{butenyl C4}), 109.4 (\text{ArC}), 73.6 (\text{butenyl C1}), 56.33 (\text{OCH}_3), 55.9 (\text{OCH}_3), 44.2 (\text{butenyl C2}); ^\text{IR} \ \nu_{\text{max}} \ (\text{neat})/\text{cm}^{-1}: 3396 (\text{O-H}), 2996, 2963, 2939, 2916, 2892, 1640, 1593, 1521, 1508. \]

**Synthesis of 4-(but-3-en-1-yl)-1,2-dimethoxybenzene 496a**

Following general procedure J, using alcohol 495a (1.50 g, 7.20 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 0-40% DCM in hexane afforded the title compound 496a (1.25 g, 6.50 mmol, 90%) as a colourless oil. \( ^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \delta 6.85-6.69 (3\text{H, m, ArH}), 5.86 (1\text{H, ddt, } J = 16.9, 10.2, 6.6, \text{ butenyl H}_1-\text{C3}), 5.05 (1\text{H, dd, } J = 17.1, 1.6, \text{ butenyl H}_{\text{trans}}-\text{C4}), 4.98 (1\text{H, d, } J = 10.2, \text{ butenyl H}_{\text{cis}}-\text{C4}), 3.87 (3\text{H, s, OCH}_3), 3.86 (3\text{H, s, OCH}_3), 2.73-2.58 (2\text{H, m, butenyl H}_2-\text{C1}), 2.46-2.30 (2\text{H, m, butenyl H}_2-\text{C2}); ^{13}\text{C NMR} \ (100 \text{ MHz, CDCl}_3) \delta 148.9 (\text{C}_q), 147.3 (\text{C}_q), 138.3 (\text{butenyl C3}), 134.7 (\text{C}_q), 120.3 (\text{ArC}), 115.0 (\text{butenyl C4}), 111.9 (\text{ArC}), 111.3 (\text{ArC}), 56.0 (\text{OCH}_3), 55.9 (\text{OCH}_3), 35.8 (\text{butenyl C2}), 35.1 (\text{butenyl C1}); ^\text{IR} \ \nu_{\text{max}} \ (\text{neat})/\text{cm}^{-1}: 3075, 2998, 2933, 2834, 1639, 1607, 1590, 1513. \]

**Synthesis of 4-(3,4-dimethoxyphenyl)butane-1,2-diol 497a**

}\]
Following general procedure K, using alkene 496a (850 mg, 4.42 mmol). Purification by flash chromatography on silica gel, eluting with EtOAc afforded the title compound 497a (911 mg, 4.03 mmol, 91%) as a colourless gum. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.82-6.70 (3H, m, ArH), 3.87 (3H, s, OCH$_3$), 3.85 (3H, s, OCH$_3$), 3.78-3.69 (1H, m, butyl H$_1$-C2), 3.69-3.61 (1H, m, butyl H$_a$-C1), 3.51-3.42 (1H, m, butyl H$_b$-C1), 2.81-2.70 (1H, m, butyl H$_a$-C4), 2.70-2.59 (1H, m, butyl H$_b$-C4), 2.23 (1H, d, $J$ = 2.9, C2OH), 2.00 (1H, s, C1OH), 1.84-1.69 (2H, m, butyl H$_2$-C3).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 149.1 (C$_q$), 147.5 (C$_q$), 134.4 (C$_q$), 120.3 (ArC), 111.9 (ArC), 111.5 (ArC), 71.7 (butyl C$_2$), 67.0 (butyl C1), 56.1 (OCH$_3$), 55.9 (OCH$_3$), 35.0 (butyl C3), 31.6 (butyl C4); IR $\nu_{max}$ (neat)/cm$^{-1}$: 3378 (O-H), 2999, 2934, 2863, 2835, 1607, 1590, 1513.

Synthesis of 3-(3,4-dimethoxyphenyl)propanal 498a

Following general procedure L, using diol 497a (850 mg, 3.76 mmol). Purification by flash chromatography on silica gel, eluting with 20% EtOAc in hexane afforded the title compound 498a (680 mg, 3.50 mmol, 93%) as a colourless oil. The data is in accordance with the literature. $^2$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.81 (1H, t, $J$ = 1.4, propyl H$_1$-C1), 6.85-6.64 (3H, m, ArH), 3.86 (3H, s, OCH$_3$), 3.84 (3H, s, OCH$_3$), 2.90 (2H, t, $J$ = 7.5, propyl H$_2$-C3), 2.79-2.72 (2H, m, propyl H$_2$-C2); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 149.1 (C$_q$), 147.5 (C$_q$), 134.4 (C$_q$), 120.3 (ArC), 111.8 (ArC), 111.5 (ArC), 56.1 (OCH$_3$), 55.9 (OCH$_3$), 45.6 (propyl C2), 27.9 (propyl C3); IR $\nu_{max}$ (neat)/cm$^{-1}$: 3001, 2936, 2835, 1720 (C=O), 1607, 1591, 1513, 1464.

Synthesis of 5-(3,4-dimethoxyphenyl)pent-1-en-3-ol 499a

Following general procedure I, using aldehyde 498a (600 mg, 3.09 mmol) and vinylmagnesium chloride (4.7 mL of a 1.0 M solution in THF, 4.63 mmol). Purification by flash chromatography on silica gel, eluting with 20% EtOAc in hexane afforded the title compound 499a (467 mg, 2.10 mmol, 68%) as a colourless oil. The data is in accordance with the literature. $^2$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.87-6.66 (3H, m, ArH), 5.91 (1H, ddd, $J$ = 16.9, 10.4, 6.2, pentenyl H$_1$-C2), 5.24 (1H, dd, $J$ = 17.2, 1.2, pentenyl H$_{trans}$-C1), 5.14 (1H, d, $J$ = 10.4, pentenyl H$_{cis}$-C1), 4.13 (1H, dd, $J$ = 12.7, 6.2, pentenyl H$_1$-C3), 3.86 (3H, s, OCH$_3$), 3.85 (3H, s, OCH$_3$), 2.75-2.58 (2H, m, pentenyl H$_2$-C5), 1.87-1.78 (2H, m, pentenyl H$_2$-C4);
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 149.0 (C$_q$), 147.4 (C$_q$), 141.2 (pentenyl C2), 134.6 (C$_q$), 120.3 (ArC), 115.0 (pentenyl C1), 111.9 (ArC), 111.4 (ArC), 72.6 (pentenyl C3), 56.1 (OCH$_3$), 56.0 (OCH$_3$), 38.8 (pentenyl C4), 31.4 (pentenyl C5); IR $\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3414 (O-H), 3000, 2935, 2835, 1643, 1607, 1590, 1513.

Synthesis of 5-(3,4-dimethoxyphenyl)pent-1-en-3-one 500a

Following general procedure M, using allylic alcohol 499a (400 mg, 1.80 mmol) afforded the title compound 500a (219 mg, 0.99 mmol, 55%) as a colourless oil. The data is in accordance with the literature.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.83-6.69 (3H, m, ArH), 6.35 (1H, dd, $J$ = 17.7, 10.5, pentenyl H$_{\text{trans}}$-C1), 6.21 (1H, dd, $J$ = 17.7, 0.9, pentenyl H$_{\text{cis}}$-C1), 5.82 (1H, dd, $J$ = 10.5, 0.9, pentenyl H$_1$-C2), 3.86 (3H, s, OCH$_3$), 3.85 (3H, s, OCH$_3$), 2.90 (4H, app. s, includes 2H, m, pentenyl H$_2$-C4; and 2H, m, pentenyl H$_2$-C5); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 200.0 (pentenyl C3), 149.0 (C$_q$), 147.6 (C$_q$), 136.7 (pentenyl C2), 133.8 (pentenyl C1), 128.4 (C$_q$), 120.3 (ArC), 111.9 (ArC), 111.5 (ArC), 56.1 (OCH$_3$), 56.0 (OCH$_3$), 41.6 (CH$_2$), 29.6 (CH$_2$); IR $\nu_{\text{max}}$ (neat)/cm$^{-1}$: 2998, 2935, 2834, 1698 (C=O), 1677, 1611, 1590, 1513.

Synthesis of 1-(2H-1,3-benzodioxol-5-yl)but-3-en-1-ol 495b

Following general procedure I, using piperonal 494b (1.50 g, 10.0 mmol) and allylmagnesium chloride (5.5 mL of a 2.0 M in THF, 11.0 mmol) afforded the title compound 495b (1.89 g, 9.83 mmol, 98%) as a colourless oil. The $^1$H NMR data is in accordance with the literature.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.89 (1H, d, $J$ = 1.3, aryl H-C6), 6.84-6.75 (2H, m, ArH), 5.94 (2H, s, (O)$_2$CH$_2$), 5.78 (1H, ddt, $J$ = 17.2, 10.2, 6.8, butenyl H$_1$-C3), 5.19-5.09 (2H, m, butenyl H$_2$-C4), 4.64 (1H, t, $J$ = 6.8, butenyl H$_1$-C1), 2.47 (2H, t, $J$ = 6.8, butenyl H$_2$-C2), 2.08 (1H, br. s, OH); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 147.9 (C$_q$), 147.0 (C$_q$), 138.1 (C$_q$), 134.6 (butenyl H$_1$-C3), 119.3 (ArC), 118.5 (butenyl C4), 108.2 (ArC), 106.5 (ArC), 101.1 ((O)$_2$CH$_2$), 73.3 (butenyl C1), 43.9 (butenyl C2); IR $\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3370 (O-H), 3075, 2978, 2896, 1640, 1609, 1503, 1486.

Synthesis of 5-(but-3-en-1-yl)-2H-1,3-benzodioxole 496b
Following general procedure J, using alcohol 495b (1.50 g, 7.80 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 0-20% DCM in hexane afforded the title compound 496b (965 mg, 5.48 mmol, 70%) as a colourless oil. The data is in accordance with the literature.\textsuperscript{218} \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 6.79-6.59 (3H, m, ArH), 5.92 (2H, s, (O\textsubscript{2}CH\textsubscript{2}), 5.84 (1H, ddt, \(J = 17.0, 10.2, 6.6\)), butenyl H\textsubscript{1}-C3), 5.04 (1H, ddd, \(J = 17.0, 3.4, 1.6\), butenyl H\textsubscript{trans}-C4), 4.98 (1H, ddt, \(J = 10.2, 2.0, 1.1\), butenyl H\textsubscript{cis}-C4), 2.71-2.59 (2H, m, butenyl H\textsubscript{2}-C1), 2.39-2.29 (2H, m, butenyl H\textsubscript{1}-C2); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 147.6 (C\textsubscript{q}), 145.7 (C\textsubscript{q}), 138.1 (butenyl C3), 135.9 (C\textsubscript{q}), 121.3 (ArC), 115.1 (butenyl C4), 109.0 (ArC), 108.2 (ArC), 100.9 ((O\textsubscript{2}CH\textsubscript{2}), 35.9 (OCH\textsubscript{3}), 35.3 (OCH\textsubscript{3}); IR \(\nu_{\max}\) (neat)/cm\textsuperscript{-1}: 3076, 2978, 2776, 1640, 1608, 1502, 1487.

**Synthesis of 4-(2H-1,3-benzodioxol-5-yl)butane-1,2-diol 497b**

Following general procedure K, using alkene 496b (850 mg, 4.82 mmol). Purification by flash chromatography on silica gel, eluting with 75% EtOAc in hexane afforded the title compound 497b (899 mg, 4.28 mmol, 89%) as a colourless oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 6.77-6.60 (3H, m, ArH), 5.91 (1H, s, (O\textsubscript{2}CH\textsubscript{2}), 3.78-3.70 (1H, m, butyl H\textsubscript{1}-C2), 3.69-3.64 (1H, m, butyl H\textsubscript{a}-C1) 3.53-3.39 (1H, m, butyl H\textsubscript{b}-C1), 2.79-2.54 (2H, m, butyl H\textsubscript{2}-C4), 2.30 (1H, s, C2OH), 2.09 (1H, s, C1OH), 1.81-1.61 (2H, m, butyl H\textsubscript{2}-C3); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 147.8 (C\textsubscript{q}), 145.9 (C\textsubscript{q}), 135.6 (C\textsubscript{q}), 121.3 (ArC), 109.0 (ArC), 108.4 (ArC), 100.9 ((O\textsubscript{2}CH\textsubscript{2}), 71.5 (butyl C2), 67.0 (butyl C1), 35.0 (butyl C3), 31.7 (butyl C4); IR \(\nu_{\max}\) (neat)/cm\textsuperscript{-1}: 3377 (O-H), 3241 (O-H), 2972, 2953, 2918, 2778, 1498, 1484.

**Synthesis of 3-(2H-1,3-benzodioxol-5-yl)propanal 498b**

Following general procedure L, using diol 497b (850 mg, 4.04 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 498b (637 mg, 3.57 mmol, 88%) as a colourless oil. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 9.80 (1H, t, \(J = 1.4\), propyl H\textsubscript{1}-C1), 6.80-6.54 (3H, m, ArH), 5.92 (2H, s, (O\textsubscript{2}CH\textsubscript{2}), 2.89-2.80 (2H, m, propyl H\textsubscript{2}-C3), 2.81-2.68 (2H, m, propyl H\textsubscript{2}-C2); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 201.7 (propyl C1), 147.9 (C\textsubscript{q}), 146.1 (C\textsubscript{q}), 134.2 (C\textsubscript{q}), 121.2 (ArC), 108.9 (ArC), 108.4 (ArC), 101.0 ((O\textsubscript{2}CH\textsubscript{2}), 45.7 (propyl C2), 28.0 (propyl C3); IR \(\nu_{\max}\) (neat)/cm\textsuperscript{-1}: 2894, 2726, 1720 (C=O), 1608, 1503, 1488, 1442, 1408.
Synthesis of 5-(2H-1,3-benzodioxol-5-yl)pent-1-en-3-ol 499b

Following general procedure I, using aldehyde 498b (600 mg, 3.37 mmol) and vinylmagnesium chloride (5.1 mL of a 1.0 M solution in THF, 5.05 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 499b (565 mg, 2.74 mmol, 81%) as a colourless gum.

\[
\begin{align*}
\delta & = 6.77-6.60 (3\text{H, m, ArH}), 5.97-5.82 (3\text{H, m, includes 2H, s, (O)CH}_2; \text{ and 1H, m, pentenyl H}_1\text{-C2}), 5.24 (1\text{H, d, } J = 17.2, \text{ pentenyl H}_{\text{trans}}\text{-C1}), 5.13 (1\text{H, d, } J = 10.4, \text{ pentenyl H}_{\text{cis}}\text{-C1}), 4.11 (1\text{H, dd, } J_1 = 12.6, 6.2, \text{ pentenyl H}_1\text{-C3}), 2.71-2.55 (2\text{H, m, pentenyl H}_2\text{-C5}), 1.87-1.76 (2\text{H, m, pentenyl H}_2\text{-C4});
\end{align*}
\]

\[
\begin{align*}
\text{IR } & \nu_{\text{max}} \text{(neat)/cm}^{-1}: 3388 (\text{O-H}), 3077, 2923, 2776, 1644, 1608, 1503, 1489.
\end{align*}
\]

Synthesis of 5-(2H-1,3-benzodioxol-5-yl)pent-1-en-3-one 500b

Following general procedure M, using allylic alcohol 499b (400 mg, 1.94 mmol) afforded the title compound 500b (192 mg, 0.94 mmol, 49%) as a colourless oil.

\[
\begin{align*}
\delta & = 6.74-6.62 (3\text{H, m, ArH}), 6.35 (1\text{H, dd, } J = 17.7, 10.6, \text{ pentenyl H}_1\text{-C2}), 6.21 (1\text{H, dd, } J = 17.7, 1.0, \text{ pentenyl H}_{\text{trans}}\text{-C1}), 5.91 (2\text{H, s, (O)CH}_2), 5.83 (1\text{H, dd, } J = 10.6, 1.0, \text{ pentenyl H}_{\text{cis}}\text{-C1}), 2.87 (4\text{H, app. s, includes 2H, m, pentenyl H}_2\text{-C4; and 2H, m, pentenyl H}_2\text{-C5});
\end{align*}
\]

\[
\begin{align*}
\text{IR } & \nu_{\text{max}} \text{(neat)/cm}^{-1}: 2896, 1699 (\text{C=O}), 1678, 1612, 1502, 1489, 1443, 1402.
\end{align*}
\]

Synthesis of 1-3-[(tert-butyldimethylsilyl)oxy]-4-methoxyphenylbut-3-en-1-ol 495c

Following general procedure M, using allylic alcohol 499b (400 mg, 0.94 mmol) afforded the title compound 500b (192 mg, 0.94 mmol, 49%) as a colourless oil.
Following general procedure I, using aldehyde 494c (2.50 g, 9.38 mmol) and allylmagnesium chloride (7.05 mL of a 2.0 M in THF, 14.1 mmol) afforded the title compound 495c (2.87 g, 9.30 mmol, 99%) as a pale yellow oil. \( ^1\)H NMR (400 MHz, CDCl\(_3\)) δ 6.93-6.77 (3H, m, ArH), 5.78 (1H, ddt, J = 17.2, 10.2, 7.1, butenyl H\(_1\)-C3), 5.19-5.06 (2H, m, butenyl H\(_2\)-C4), 4.63 (1H, t, J = 6.5, butenyl H\(_1\)-C1), 3.79 (3H, s, OCH\(_3\)), 2.47 (2H, t, J = 6.8, butenyl H\(_2\)-C2), 1.97 (1H, br. s, OH), 1.00 (9H, s, SiC(CH\(_3\))\(_3\)), \( ^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 150.5 (C\(_q\)), 145.1 (C\(_q\)), 136.8 (C\(_q\)), 134.8 (butenyl C3), 119.2 (ArC), 118.8 (ArC), 118.2 (butenyl C4), 112.0 (ArC), 73.1 (butenyl C1), 55.7 (OCH\(_3\)), 43.9 (butenyl C2), 25.9 (3 × C, SiC(CH\(_3\))\(_3\)), 18.6 (C\(_q\)), -4.45 (SiCH\(_3\)), -4.47 (SiCH\(_3\)); IR \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\): 3397 (O-H), 3076, 2954, 2930, 2898, 2857, 1641, 1606, 1586, 1509.

**Synthesis of 5-(but-3-en-1-yl)-2-methoxyphenoxy(tert-butyl)dimethylsilane 496c**

Following general procedure J, using alcohol 495c (2.70 g, 8.75 mmol). Purification by flash chromatography on silica gel, eluting with 20% DCM in hexane afforded the title compound 496c (2.30 g, 7.86 mmol, 90%) as a colourless oil. \( ^1\)H NMR (400 MHz, CDCl\(_3\)) δ 6.80-6.67 (3H, m, ArH), 5.84 (1H, ddt, J = 17.0, 10.2, 7.3, butenyl H\(_1\)-C3), 5.03 (1H, dd, J = 17.0, 1.6, butenyl H\(_{\text{trans}}\)-C4), 4.97 (1H, dd, J 10.2, 0.8, butenyl H\(_{\text{cis}}\)-C4), 3.78 (3H, s, OCH\(_3\)), 2.64-2.57 (2H, m, butenyl H\(_2\)-C1), 2.33 (2H, dt, J = 7.3, 6.8, butenyl H\(_2\)-C2), 1.00 (9H, s, SiC(CH\(_3\))\(_3\)), 0.16 (6H, s, Si(CH\(_3\))\(_2\)); \( ^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 149.3 (C\(_q\)), 144.9 (C\(_q\)), 138.4 (butenyl C3), 134.8 (C\(_q\)), 121.5 (ArC), 121.4 (ArC), 114.9 (butenyl C4), 112.3 (ArC), 55.8 (OCH\(_3\)), 35.8 (butenyl C2), 34.7 (butenyl C1), 25.9 (3 × C, SiC(CH\(_3\))\(_3\)), 18.6 (C\(_q\)), -4.5 (2 × C, SiCH\(_3\)); IR \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\): 3078, 2953, 2929, 2857, 1640, 1608, 1583, 1511.

**Synthesis of 4-{3-[(tert-butyldimethylsilyl)oxy]-4-methoxyphenyl}butane-1,2-diol 497c**

Following general procedure K, using alkene 496c (1.50 g, 5.13 mmol). Purification by flash chromatography on silica gel, eluting with 50% EtOAc in hexane afforded the title compound 497c (1.45 g, 4.44 mmol, 87%) as a colourless oil. \( ^1\)H NMR (400 MHz, CDCl\(_3\)) δ 6.82-6.62 (3H, m, ArH), 3.77 (3H, s, OCH\(_3\)), 3.74-3.66 (1H, m, butyl H\(_1\)-C2), 3.63 (1H, dd, J = 11.0, 2.8, butyl H\(_2\)-C1), 3.45 (1H, dd, J = 11.0, 7.6, butyl H\(_3\)-C1), 2.76-2.52 (2H, m, butyl H\(_2\)-C4), 2.29 (1H, s, OH), 2.17 (1H, s, OH), 1.85-1.59 (2H, m, butyl H\(_2\)-C3), 0.99 (9H, s, SiC(CH\(_3\))\(_3\)), 0.16 (6H, s, Si(CH\(_3\))\(_2\)); IR \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\): 3078, 2953, 2929, 2857, 1640, 1608, 1583, 1511.
0.15 (6H, s, Si(CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 149.36 (s), 145.07 (s), 134.45 (s), 121.45 (s), 121.31 (s), 112.38 (s), 71.73 (s), 66.94 (s), 55.74 (s), 34.90 (s), 31.15 (s), 25.88 (s), 18.58 (s), -4.48 (s); IR <sub>ν</sub><sub>max</sub> (neat)/cm<sup>-1</sup>: 3363 (O−H), 2929, 2857, 1607, 1583, 1509, 1463, 1442; HRMS (ESI): C<sub>17</sub>H<sub>30</sub>O<sub>4</sub>Si [M+Na<sup>+</sup>]: calculated 349.1806, found 349.1802.

**Synthesis of 3-[[tert-butyldimethylsilyl]oxy]-4-methoxyphenylpropanal 498c**

Following general procedure L, using diol 497c (1.30 g, 3.98 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 498c (613 mg, 2.08 mmol, 52%) as a colourless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.80 (1H, t, <sub>J</sub> = 1.3, propyl H<sub>1</sub>-C1), 6.79-6.64 (3H, m, ArH), 3.77 (3H, s, OCH<sub>3</sub>), 2.85 (2H, t, <sub>J</sub> = 7.5, propyl H<sub>2</sub>-C3), 2.72 (2H, t, <sub>J</sub> = 7.5, propyl H<sub>2</sub>-C2), 0.99 (9H, s, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.15 (6H, s, Si(CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 202.0 (propyl C1), 149.6 (C<sub>q</sub>), 145.2 (C<sub>q</sub>), 133.1 (C<sub>q</sub>), 121.3 (ArC), 121.2 (ArC), 112.4 (ArC), 55.7 (OCH<sub>3</sub>), 45.6 (propyl C2), 27.6 (propyl C3), 25.9 (3 × C, SiC(CH<sub>3</sub>)<sub>3</sub>), 18.9 (C<sub>q</sub>), -4.5 (2 × C, Si(CH<sub>3</sub>)<sub>2</sub>); IR <sub>ν</sub><sub>max</sub> (neat)/cm<sup>-1</sup>: 2953, 2930, 2896, 2857, 2715, 1725 (C=O), 1608, 1584, 1510.

**Synthesis of 5-[[tert-butyldimethylsilyl]oxy]-4-methoxyphenylpent-1-en-3-ol 499c**

Following general procedure I, using aldehyde 498c (550 mg, 1.87 mmol) and vinylmagnesium chloride (2.80 mL of a 1.0 M solution in THF, 2.80 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 0-10% EtOAc in hexane afforded the title compound 499c (442 mg, 1.37 mmol, 73%) as a colourless oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.81-6.67 (3H, m, ArH), 5.90 (1H, ddd, <sub>J</sub> = 16.9, 10.4, 6.2, pentenyl H<sub>1</sub>-C2), 5.23 (1H, dt, <sub>J</sub> = 17.2, 1.3, pentenyl H<sub>trans</sub>-C1), 5.13 (1H, dt, <sub>J</sub> = 10.4, 1.2, pentenyl H<sub>cis</sub>-C1), 4.11 (1H, app. q, <sub>J</sub> = 6.6, pentenyl H<sub>1</sub>-C3), 3.77 (3H, s, OCH<sub>3</sub>), 2.70-2.52 (2H, m, pentenyl H<sub>2</sub>-C5), 1.87-1.73 (2H, m, pentenyl H<sub>2</sub>-C4), 1.53 (1H, s, OH), 1.00 (9H, s, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.15 (6H, s, Si(CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 149.3 (C<sub>q</sub>), 145.0 (C<sub>q</sub>), 141.2 (pentenyl C2), 134.6 (C<sub>q</sub>), 121.5 (ArC), 121.4 (ArC), 115.0 (pentenyl C1), 112.4 (ArC), 72.6 (pentenyl C3), 55.8 (OCH<sub>3</sub>), 38.8 (pentenyl C4), 30.1 (pentenyl C5), 25.9 (3 × C, SiC(CH<sub>3</sub>)<sub>3</sub>), 18.6 (C<sub>q</sub>), -4.5 (2 × C, Si(CH<sub>3</sub>)<sub>2</sub>); IR <sub>ν</sub><sub>max</sub> (neat)/cm<sup>-1</sup>: 3396 (O−H), 2929, 2857, 2896, 2857, 2715, 1725 (C=O), 1608, 1584, 1510.
Synthesis of 5-{3-[(tert-butyldimethylsilyl)oxy]-4-methoxyphenyl}pent-1-en-3-one 500c

Following general procedure M, using allylic alcohol 499c (400 mg, 1.24 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 500c (327 mg, 1.02 mmol, 82%) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.79-6.67 (3H, m, ArH), 6.35 (1H, dd, $J = 17.7$, 10.5, pentenyl H$_1$-C2), 6.20 (1H, dd, $J = 17.7$, 1.0, pentenyl H$_{trans}$-C1), 5.81 (1H, dd, $J = 10.5$, 1.0, pentenyl H$_{cis}$-C1), 3.77 (3H, s, OCH$_3$), 2.85 (4H, app. s, includes 2H, m, pentenyl H$_2$-C4; and 2H, m, pentenyl H$_2$-C5), 0.99 (9H, s, SiC(CH$_3$)$_3$), 0.15 (6H, s, Si(CH$_3$)$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 200.2 (pentenyl C3), 149.5 (C$_q$), 145.1 (C$_q$), 136.7 (pentenyl C2), 133.4 (C$_q$), 128.3 (pentenyl C1), 121.4 (ArC), 121.3 (ArC), 112.4 (ArC), 55.7 (OCH$_3$), 41.6 (CH$_2$), 29.3 (CH$_2$), 25.8 (3 × C, SiC(CH$_3$)$_3$), 18.6 (C$_q$), -4.5 (2 × C, Si(CH$_3$)$_2$); IR $\nu_{max}$ (neat)/cm$^{-1}$: 2953, 2930, 2897, 2857, 1701 (C=O), 1682, 1613, 1583, 1510.

Synthesis of Oct-1-en-3-ol 502

Following general procedure I, using hexanal 501 (1.23 mL, 9.98 mmol) and vinylmagnesium chloride (15.0 mL of a 1.0 M solution in THF, 15.0 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 10% EtOAc in hexane afforded the title compound 502 (883 mg, 6.89 mmol, 69%) as a colourless oil. The data is in accordance with the literature. $^{248}$ $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.86 (1H, ddd, $J = 17.1$, 10.4, 6.3, octenyl H$_1$-C2), 5.21 (1H, dd, $J = 17.1$, octenyl H$_{trans}$-C1), 5.09 (1H, d, $J = 10.4$, octenyl H$_{cis}$-C1), 4.09 (1H, q, $J = 6.3$, octenyl H$_1$-C3), 1.67-1.21 (8H, m, octenyl H$_2$-C4-7), 0.88 (3H, t, $J = 6.8$, octenyl H$_3$-C8); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 141.5 (octenyl C2), 114.7 (octenyl C1), 73.4 (octenyl C3), 37.2 (CH$_2$), 31.9 (CH$_2$), 25.1 (CH$_2$), 22.7 (CH$_2$), 14.16 (octenyl C8); IR $\nu_{max}$ (neat)/cm$^{-1}$: 3425 (O-H), 2955, 2929, 2859, 1671, 1639, 1506, 1490.

Synthesis of Oct-1-en-3-one 503

Following general procedure M, using allylic alcohol 502 (800 mg, 6.24 mmol). Purification by flash chromatography on silica gel, eluting with 50% DCM in pentane afforded the title
compound 503 (626 mg, 4.96 mmol, 79%) as a colourless oil. The data is in accordance with the literature. \(^{249}\) \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 6.34 (1H, dd, J = 17.7, 10.5, \text{octenyl H}_1-\text{C}2), 6.20 (1H, d, J = 17.7, \text{octenyl H}_\text{trans-C}1), 5.80 (1H, d, J = 10.5, \text{octenyl H}_\text{cis-C}1), 2.56 (2H, t, J = 7.4, \text{octenyl H}_2-\text{C}4), 1.65-1.56 (2H, m, \text{octenyl H}_2-\text{C}5), 1.36-1.21 (4H, m, includes 2H, m, \text{octenyl H}_2-\text{C}6; and 2H, m, \text{octenyl H}_2-\text{C}7), 0.88 (3H, t, J = 6.8, \text{octenyl H}_3-\text{C}8); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta \) 201.2 (octenyl C3), 136.7 (octenyl C2), 127.9 (octenyl C1), 39.8 (octenyl C4), 31.6 (CH\(_2\)), 23.8 (octenyl C5), 22.6 (CH\(_2\)), 14.0 (octenyl C8); \(^{1}\)R v\(_{\text{max}}\) (neat)/cm\(^{-1}\): 2957, 2931, 2861, 1700 (C=O), 1682, 1615, 1459, 1401.

6.4.3 \(^{N}\)-Unsubstituted THQ synthesis

General Procedure N: Rh(I)-catalysed conjugate addition/reduction

Following a procedure by Marsden \textit{et al.} \(^{194}\), a flask was evacuated and back-filled with N\(_2\) (× 3). To this flask was added 2-aminophenylboronic acid HCl salt (2.0 eq.), [Rh(cod)Cl]\(_2\) (3 mol%) then de-gassed toluene (0.1 M). To the stirred solution was added vinyl ketone (1.0 eq.) then de-gassed aqueous KOH (5.0 eq. of a 3.8 M aqueous solution). The reaction mixture was heated at 50 °C for 18 h, then cooled to RT and STAB (8.0 eq.) was added portionwise. After 30 minutes the reaction mixture was concentrated \textit{in vacuo}, then purification afforded the desired products.

Synthesis of 2-[2-(3,4-dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline 506

Following general procedure N, using vinyl ketone 500a (200 mg, 0.91 mmol). Purification by flash chromatography on silica gel, eluting with 20% EtOAc in hexane, then SCX cartridge afforded the title compound 506 (136 mg, 0.46 mmol, 51%) as a yellow gum. The data is in accordance with the literature. \(^{250}\) \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 6.97 (2H, m, including 1H, m, \text{ArH-C}6; and 1H, m, \text{ArH-C}7), 6.84-6.66 (3H, m, ArH), 6.64-6.57 (1H, m, ArH), 6.49-6.40 (1H, m, ArH), 3.88 (3H, s, OCH\(_3\)), 3.87 (3H, s, OCH\(_3\)), 3.36-3.26 (1H, m, H\(_1-\text{C}2\)), 2.87-2.65 (4H, m, includes 2H, m, ethyl H\(_2-\text{C}2\); and 2H, m, H\(_2-\text{C}4\)), 2.00 (2H, ddt, J = 9.8, 8.5, 4.3, ethyl H\(_a-\text{C}1\)), 1.87-1.78 (2H, m, H\(_2-\text{C}3\)), 1.68 (1H, dtd, J = 12.9, 10.3, 5.6, ethyl H\(_b-\text{C}1\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 149.1 (\text{C}_q), 147.5 (\text{C}_q), 144.6 (\text{C}_q), 134.6 (\text{C}_q), 129.4 (\text{ArC}), 126.9
(ArC), 121.5 (Cq), 120.3 (ArC), 117.2 (ArC), 114.3 (ArC), 111.8 (ArC), 111.5 (ArC), 56.1 (OCH3), 56.0 (OCH3), 51.4 (C2), 38.6 (C3), 32.0 (C4), 28.2 (ethyl C1), 26.3 (ethyl C2); IR νmax (neat)/cm⁻¹: 3379 (N-H), 3001, 2932, 2835, 1605, 1586, 1513, 1497; HRMS (ESI): C₁₉H₂₃NO₂ [M+H⁺]: calculated 298.1802, found 298.1799.

**Synthesis of 2-[2-(2H-1,3-benzodioxol-5-yl)ethyl]-1,2,3,4-tetrahydroquinoline 507**

Following general procedure N, using vinyl ketone 500b (200 mg, 0.98 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane, then SCX cartridge afforded the title compound 507 (87 mg, 0.31 mmol, 32%) as a colourless oil. The data is in accordance with the literature.²⁵¹ ¹H NMR (400 MHz, CDCl₃) δ 7.01-6.92 (2H, m, ArH), 6.78-6.58 (4H, m, ArH), 6.47 (1H, d, J = 7.7, ArH), 5.93 (2H, s, (O)₂CH₂), 3.34-3.24 (1H, m, H₁-C₂), 2.87-2.63 (4H, m, includes 2H, m, ethyl H₂-C₂; and 2H, m, H₂-C₄), 2.04-1.93 (1H, m, ethyl Hₐ-C₁), 1.84-1.76 (2H, m, H₂-C₃), 1.73-1.61 (1H, m, ethyl Hₐ-C₁); ¹³C NMR (100 MHz, CDCl₃) δ 147.8 (Cq), 145.9 (Cq), 144.6 (Cq), 135.8 (Cq), 129.4 (ArC), 126.9 (ArC), 121.4 (Cq), 121.2 (ArC), 117.2 (ArC), 114.3 (ArC), 108.9 (ArC), 108.4 (ArC), 101.0 ((O)₂CH₂), 51.1 (C₂), 38.6 (C₃), 32.0 (C₄), 28.1 (ethyl C₁), 26.3 (ethyl C₂); IR νmax (neat)/cm⁻¹: 3389 (N-H), 2968, 2914, 2890, 2852, 2838, 1602, 1584; HRMS (ESI): C₁₈H₁₉NO₂ [M+H⁺]: calculated 282.1484, found 282.1489.

**Synthesis of 2-[2-([3-[(tert-butyldimethylsilyl)oxy]-4-methoxyphenyl]ethyl)-1,2,3,4-tetrahydroquinoline 508**

Following general procedure N, using vinyl ketone 500c (280 mg, 0.87 mmol). Purification by flash chromatography on silica gel, eluting with 5% EtOAc in hexane, then SCX cartridge afforded the title compound 508 (223 mg, 0.56 mmol, 64%) as a colourless gum. ¹H NMR (400 MHz, CDCl₃) δ 6.96 (2H, t, J = 7.3, ArH), 6.81-6.69 (3H, m, ArH), 6.60 (1H, t, J = 7.3, ArH), 6.46 (1H, d, J = 7.8, ArH), 3.79 (3H, s, OCH₃), 3.33-3.24 (1H, m, H₁-C₂), 2.87-2.69 (2H, m, ethyl H₂-C₂), 2.68-2.59 (2H, m, H₂-C₄), 1.99 (1H, ddd, J = 12.7, 8.0, 4.9, ethyl Hₐ-C₁), 1.85-1.75 (2H, m, H₂-C₃), 1.66 (1H, dtd, J = 12.8, 10.2, 5.6, ethyl Hₐ-C₁), 1.01 (9H, s, SiC(CH₃)₃), 0.16 (6H, s, Si(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 149.4 (Cq), 145.1 (Cq), 144.7 (Cq), 134.6 (Cq), 129.4 (ArC), 126.9 (ArC), 121.5 (Cq), 121.4 (ArC), 121.3 (ArC), 117.1
(ArC), 114.3 (ArC), 112.4 (ArC), 55.8 (OCH$_3$), 51.3 (C2), 38.5 (C3), 31.5 (C4), 28.2 (ethyl C1), 26.4 (ethyl C2), 25.9 (3 × C, Si(C$_3$H$_3$)$_3$), 18.6 (C$_q$), -4.5 (2 × C, Si(CH$_3$)$_2$); IR $\nu_{\text{max}}$(neat)/cm$^{-1}$: 3404 (N-H), 2928, 2855, 1607, 1584, 1509, 1485, 1442; HRMS (ESI): C$_{24}$H$_{35}$NO$_2$Si [M+H$^+$]: calculated 398.2510, found 398.2509.

**Synthesis of 2-pentyl-1,2,3,4-tetrahydroquinoline 509**

![Chemical Structure](image)

Following general procedure N, using vinyl ketone 503 (400 mg, 3.17 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 0-25% DCM in pentane afforded the title compound 509 (417 mg, 2.05 mmol, 65%) as a yellow oil. The data is in accordance with the literature.$^{252}$

$^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.05-6.93 (2H, m, ArH), 6.66-6.59 (1H, m, ArH), 6.48 (1H, d, $J$ = 7.5, ArH), 3.76 (1H, br. s, NH), 3.24 (1H, dt, $J$ = 9.4, 6.3, 2.9, H$_1$-C2), 2.89-2.68 (2H, m, H$_2$-C4), 1.97 (1H, ddt, $J$ = 6.9, 5.6, 4.0, H$_a$-C3), 1.69-1.57 (1H, m, H$_b$-C3), 1.55-1.26 (8H, m, pentyl H$_2$-C1-4), 0.92 (3H, t, $J$ = 6.8, pentyl H$_3$-C5); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 144.9 (C$_q$), 129.4 (ArC), 126.8 (ArC), 121.5 (C$_q$), 117.0 (ArC), 114.2 (ArC), 51.7 (C2), 36.8 (CH$_2$), 32.1 (CH$_3$), 28.3 (C3), 26.6 (C4), 25.5 (CH$_3$), 22.7 (CH$_2$), 14.2 (pentyl C5); IR $\nu_{\text{max}}$(neat)/cm$^{-1}$: 3404 (N-H), 3051, 3015, 2953, 2924, 2852, 1606, 1585; HRMS (ESI): C$_{14}$H$_{21}$N [M+H$^+$]: calculated 204.1747, found 204.1744.

### 6.4.4 N-Methylation Procedure

$\xrightarrow{\text{Mel (5 eq.), } \text{K$_2$CO$_3$ (2 eq.)}}$

![Chemical Structure](image)

**General Procedure O: N-Methylation of THQ**

Following a procedure by Davies et al., a vial was flushed with N$_2$ then charged with THQ (1.0 eq.), MeI (2.0 eq.), K$_2$CO$_3$ (5.0 eq.) and THF (0.2 M) and the reaction mixture was sealed, stirred and heated at 70 °C for 20 h. The reaction mixture was cooled to rt then H$_2$O (5 vol.) was added and the aqueous phase was extracted with EtOAc ($\times$ 3). The combined organic extracts were washed with brine (3 vol.), dried over Na$_2$SO$_4$ then concentrated in vacuo. Purification afforded the desired products.
Synthesis of 2-[2-(3,4-dimethoxyphenyl)ethyl]-1-methyl-1,2,3,4-tetrahydroquinoline 333

Following general procedure O, using THQ 506 (50 mg, 0.17 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 10% EtOAc in hexane afforded the title compound 333 (37 mg, 0.12 mmol, 71%) as a yellow oil. The data is in accordance with the literature.\textsuperscript{253} \textbf{1H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.09 (1H, app. t, \(J = 7.7\), ArH), 6.99 (1H, d, \(J = 7.3\), ArH), 6.80 (1H, d, \(J = 8.0\), ArH), 6.76-6.70 (2H, m, ArH), 6.63-6.58 (1H, m, ArH), 6.54 (1H, d, \(J = 8.2\), ArH), 3.88 (3H, s, OCH\textsubscript{3}), 3.87 (3H, s, OCH\textsubscript{3}), 3.30 (1H, td, \(J = 8.5, 4.2\), H\textsubscript{1}-C2), 2.93 (3H, s, NCH\textsubscript{3}), 2.90-2.80 (1H, m, ethyl H\textsubscript{2}-C1; and 1H, m, H\textsubscript{a}-C4), 2.69 (2H, m, includes 1H, m, ethyl H\textsubscript{b}-C2; and 1H, m, H\textsubscript{b}-C4), 2.54 (1H, ddd, \(J = 14.0, 10.1, 6.5\), H\textsubscript{b}-C4), 2.00-1.85 (3H, m, includes 2H, m, ethyl H\textsubscript{2}-C1; and 1H, m, H\textsubscript{a}-C3), 1.84-1.68 (1H, m, H\textsubscript{b}-C3); \textbf{13C NMR} (100 MHz, CDCl\textsubscript{3}) \(\delta\) 149.0 (C\textsubscript{q}), 147.4 (C\textsubscript{q}), 145.4 (C\textsubscript{q}), 134.8 (C\textsubscript{q}), 128.8 (ArC), 127.3 (ArC), 121.9 (C\textsubscript{q}), 120.2 (ArC), 115.5 (ArC), 111.4 (ArC), 110.7 (ArC), 58.5 (C2), 56.1 (OCH\textsubscript{3}), 38.2 (NCH\textsubscript{3}), 33.2 (C3), 32.1 (C4), 24.5 (ethyl C1), 23.7 (ethyl C2); \textbf{IR} \(\nu_{\text{max}}\) (neat)/cm\textsuperscript{-1}: 2995, 2930, 2833, 1601, 1575, 1513, 1498, 1479; \textbf{HRMS} (ESI): C\textsubscript{20}H\textsubscript{26}NO\textsubscript{2} [M+H\textsuperscript{+}]: calculated 312.1958, found 312.1957.

Synthesis of 2-[2-(2H-1,3-benzodioxol-5-yl)ethyl]-1-methyl-1,2,3,4-tetrahydroquinoline 334

Following general procedure O, using THQ 507 (15 mg, 0.05 mmol). Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound 334 (13 mg, 0.044 mmol, 88%) as a yellow oil. The data is in accordance with the literature.\textsuperscript{251} \textbf{1H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.08 (1H, app. t, \(J = 7.7\), ArH), 6.97 (1H, d, \(J = 7.0\), ArH), 6.75-6.50 (5H, m, ArH), 5.92 (2H, s, (O)\textsubscript{2}CH\textsubscript{2}), 3.27 (1H, td, \(J = 8.4, 4.1\), H\textsubscript{1}-C2), 2.91 (3H, s, NCH\textsubscript{3}), 2.87-2.78 (1H, m, ethyl H\textsubscript{b}-C2), 2.73-2.57 (2H, m, includes 1H, m, ethyl H\textsubscript{b}-C2; and 1H, m, H\textsubscript{b}-C4), 2.50 (1H, ddd, \(J = 13.9, 9.9, 6.6\), H\textsubscript{b}-C4), 1.98-1.82 (3H, m, includes 2H, m, ethyl H\textsubscript{2}-C1; and 1H, m, H\textsubscript{a}-C3), 1.76-1.63 (1H, m, H\textsubscript{b}-C3); \textbf{13C NMR} (100 MHz, CDCl\textsubscript{3}) \(\delta\) 147.8 (C\textsubscript{q}), 145.8 (C\textsubscript{q}), 145.5 (C\textsubscript{q}), 136.0 (C\textsubscript{q}), 128.8 (ArC), 127.3 (ArC), 121.9 (C\textsubscript{q}), 121.1 (ArC), 115.6 (ArC), 110.8 (ArC), 108.9 (ArC), 108.3 (ArC), 100.9 ((O)\textsubscript{2}CH\textsubscript{2}), 58.4 (C2), 38.20 (NCH\textsubscript{3}), 33.3 (C3), 32.2 (C4), 24.5 (ethyl C1), 23.7 (ethyl C2); \textbf{IR} \(\nu_{\text{max}}\) (neat)/cm\textsuperscript{-1}:
3018, 2925, 2855, 1601, 1499, 1487, 1441; HRMS (ESI): C_{19}H_{22}NO_{2} [M+H^{+}]: calculated 296.1645, found 296.1647.

6.4.5 Biotransformation Procedures

General procedure for analytical-scale biotransformations

Reactions were carried out in 2 mL Eppendorf tubes with a total reaction volume of 500 µL. The *E. coli* cells containing the expressed monoamine oxidase protein were resuspended in 1 M potassium phosphate buffer (pH 7.4) to a final cell concentration of 100 mg/mL. A stock solution of NH\textsubscript{3}·BH\textsubscript{3} (1 M) was prepared by dissolving NH\textsubscript{3}·BH\textsubscript{3} complex in 1 M pH 7.4 potassium phosphate buffer. Substrate stock solutions (250 mM) were prepared by dissolving the amines in DMSO. Biotransformations were started by addition of NH\textsubscript{3}·BH\textsubscript{3} (25 µL of a 1 M stock solution, final concentration 50 mM) and the substrate stock solution (10 µL of a 250 mM stock solution, final concentration 5 mM) to the cell suspension in buffer. The reaction tubes were incubated at 30 °C, 250 rpm for 48 or 96 h, after which the pH of the reaction mixture was adjusted to pH 12.0 with 10 M sodium hydroxide. The aqueous mixture was extracted into MTBE (1 mL) before the layers were separated by centrifugation (16100 rpm, 10 min). The organic layer was separated, dried over MgSO\textsubscript{4} and then added to sample tubes for analysis. Enantioselectivities were determined by normal phase chiral HPLC.

HPLC Conditions

**1,2-dimethyl-1,2,3,4-tetrahydroquinoline 342**

Following the general procedure described above using the CHAO enzyme, after 48 h HPLC analysis showed 33% ee. The enantiomeric excess was determined was determined by HPLC using a chiral phase column: CHIRALCEL® DAICEL OJ-H column; flowrate 1 mL min\textsuperscript{-1}; UV 254 nm; eluent hexane/iPrOH 98/2; Rt (1) = 8.02 min, (2) = 9.64 min.
1H,2H,3H,4H,4aH,5H,6H-pyrido[1,2-a]quinoline 400

Following the general procedure described above using the CHAO enzyme, after 96 h HPLC analysis showed 41% ee. The enantiomeric excess was determined by HPLC using a chiral phase column: CHIRALCEL® DAICEL OJ-H column; flow rate 0.5 mL min⁻¹; UV 254 nm; eluent hexane/iPrOH 90/10; Rt (1) = 13.44 min, (2) = 15.03 min.

1H,2H,3H,4H,4aH,5H,6H-pyrido[1,2-a]quinoline 400

Following the general procedure described above using the HDNO enzyme, after 96 h HPLC analysis showed 31% ee. The enantiomeric excess was determined by HPLC using a chiral phase column: CHIRALCEL® DAICEL OJ-H column; flow rate 0.5 mL min⁻¹; UV 254 nm; eluent hexane/iPrOH 90/10; Rt (1) = 13.44 min, (2) = 15.03 min.
Following the general procedure described above using the CHAO enzyme, after 48 h HPLC analysis showed >99% ee. The enantiomeric excess was determined by HPLC using a chiral phase column: CHIRALCEL® DAICEL OD-H column; flowrate 1 mL min\(^{-1}\); UV 254 nm; eluent hexane/iPrOH 98/2; Rt (1) = 11.07 min, (2) = 17.04 min.
**1H,2H,3H,3aH,4H,5H-pyrrolo[1,2-a]quinoline 395**

Following the general procedure described above using the HDNO enzyme, after 48 h HPLC analysis showed >99\% ee. The enantiomeric excess was determined by HPLC using a chiral phase column: CHIRALCEL® DAICEL OJ-H column; flowrate 1 mL min\(^{-1}\); UV 254 nm; eluent hexane/iPrOH 98/2; Rt (1) = 11.07 min, (2) = 17.04 min.

![HPLC chromatogram for HDNO enzyme](image)

**1H,2H,3H,3aH,4H,5H-pyrrolo[1,2-a]quinoline 395**

Following the general procedure described above using the MAO-N D9 enzyme, after 48 h HPLC analysis showed 90\% ee. The enantiomeric excess was determined by HPLC using a chiral phase column: CHIRALCEL® DAICEL OJ-H column; flowrate 1 mL min\(^{-1}\); UV 254 nm; eluent hexane/iPrOH 98/2; Rt (1) = 11.07 min, (2) = 17.04 min.

![HPLC chromatogram for MAO-N D9 enzyme](image)
2-[2-(3,4-dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline 506

Following the general procedure described above using the CHAO enzyme, after 96 h HPLC analysis showed 90% ee. The enantiomeric excess was determined by HPLC using a chiral phase column: CHIRALCEL® DAICEL OD-H column; flow rate 1 mL min⁻¹; UV 254 nm; eluent hexane/iPrOH 80/20; Rt (1) = 17.39 min, (2) = 18.93 min.

2-[2-(2H-1,3-benzodioxol-5-yl)ethyl]-1,2,3,4-tetrahydroquinoline 507

Following the general procedure described above using the CHAO enzyme, after 96 h HPLC analysis showed 70% ee. The enantiomeric excess was determined by HPLC using a chiral phase column: CHIRALCEL® DAICEL OD-H column; flow rate 1 mL min⁻¹; UV 254 nm; eluent hexane/iPrOH 80/20; Rt (1) = 12.08 min, (2) = 14.97 min.
2-pentyl-1,2,3,4-tetrahydroquinoline 509

Following the general procedure described above using the MAO-N D9 enzyme, after 96 h HPLC analysis showed 86% ee. The enantiomeric excess was determined by HPLC using a chiral phase column: CHIRALCEL® DAICEL OJ-H column; flowrate 0.5 mL min⁻¹; UV 254 nm; eluent hexane/iPrOH 90/10; Rt (1) = 13.78 min, (2) = 15.14 min.
Chapter 7 Bibliography

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