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# Evolvable Process Design

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By

Hemal Parekh

A thesis submitted in partial fulfilment of the requirements for  
the degree of Doctor of Philosophy in Chemistry

University of Warwick

Department of Chemistry

September 2011



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are pleased with their investment and that this work and all that I can achieve in the future would make them proud of me as I am of them.

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## **Declaration**

The work presented in this thesis is the original work of the author. References to previous related results and ideas have been fully acknowledged. All work was performed in the Department of Chemistry at the University of Warwick between October 2007 and February 2011 and has not been submitted for a degree at any other institution.

Hemal Parekh

## Abstract

The aim of this project lied in the development of an Evolvable Process Design (EPD) reactor platform such that ‘evolved’ chemical reactions could be investigated for the first time. The development of this ‘machine’ would allow us to take small organic / inorganic building blocks and use them to prepare any theoretical compound with any theoretical property that is determined by the ‘machine’. One of the essential components required were building blocks that can reversibly react under various conditions until a product with a desired property has been evolved. As we were developing a proof-of-principle EPD, we at Warwick concentrated on synthesizing a library of uniquely coloured imine products to prove a desired coloured imine could be evolved in the ‘machine’.

For this we first required a suitable analytical method that could accurately detect multiple components in a mixture (three aldehydes, three amines resulting in nine imine products) so we could understand the reaction before placing into the ‘machine’. In chapter 2, we demonstrated that  $^{19}\text{F}$  NMR spectroscopy was sufficient to monitor in real time the equilibrium of a 3 x 3 matrix of fluorinated amine + aldehyde building blocks (nine imines). We also demonstrated that the system of our study was under a dynamic equilibrium and that by altering the acid or base concentrations, we can affect the dynamics of the reaction and monitor it quantitatively.

In chapter 3, we synthesized a library of highly conjugated aromatic imines from fluorinated aldehydes and non-fluorinated amines. These imines possessed unique UV / Vis profiles (and unique  $^{19}\text{F}$  NMR data) therefore could be monitored in our ‘machine’ equipped with a UV / Vis sensor.

In chapter 4, a reaction was ready to be trailed on the ‘machine’ as previously synthesized in chapter three but no such ‘machine’ had been developed by our collaborators and therefore we created our own mini-flow system to test *in situ* UV / Vis absorbance measurements of our library of imines.

In chapter 5 we focused on synthesizing imine ligands for metal mediated atom transfer radical cyclization reactions (ATRC) (extensively studied by the Clark group) as this ‘machine’ was still under development by our collaborators. We knew that once the ‘machine’ was developed, we could tweak the system in a way which would allow us to develop optimised imine catalysts for ATRC reactions.

In chapter 6 we demonstrated  $\text{KBH}_4$  to be the most efficient reducing agent for copper mediated AGET / ARGET – ATRC and by increasing the concentration of the reaction mixtures we significantly improved the efficiency of copper mediated AGET–ATRC of previously investigated reactions by the Clark group. We also demonstrated copper mediated AGET-ATRC in water at good conversions using ultrasound, replacing a toxic solvent and may now be considered as ‘green’ chemistry.

In chapter 7, we were able to demonstrate an alternative procedure to oxindoles via copper mediated cyclisation reaction. In the presence of 1.1 equiv. of  $\text{CuBr}$  / TPA in methanol at 50 °C we were able to show 100% conversions of substrates 2-Bromo-*N*-butyl-2-methyl-*N*-(*p*-tolyl)propanamide and 2-Bromo-*N*-butyl-2-methyl-*N*-(*m*-tolyl)propanamide. We then performed a series of reactions to reduce the transition metal and ligand loadings by using borohydride reducing agents but unfortunately, these reactions were not that efficient.

## Abbreviations

|                                     |   |
|-------------------------------------|---|
| Ac                                  | Acetyl                                      |
| acac                                | Acetoacetate                                |
| AcOH                                | Acetic Acid                                 |
| Ag                                  | Silver                                      |
| AIBN                                | Azabisisobutyronitrile                      |
| AGET-                               | Activators generated by electron transfer   |
| Ar                                  | Aryl  |
| ARGET-                              | Activators regenerated by electron transfer |
| ATRA                                | Atom transfer radical addition              |
| ATRC                                | Atom transfer radical cyclisation           |
| ATRP                                | Atom transfer radical polymerisation        |
| 9-BBN                               | 9-Borabicyclo[3.3.1]nonane                  |
| Bipy                                | Bipyridine                                  |
| Bn                                  | Benzyl                                      |
| Boc                                 | <i>tert</i> -Butylcarbamate                 |
| br                                  | Broad                                       |
| Bu                                  | Butyl                                       |
| <sup>t</sup> Bu                     | <i>tert</i> -Butyl                          |
| BuLi                                | Butyl Lithium                               |
| Bu <sub>3</sub> SnH                 | Tributyltin hydride                         |
| Bu <sub>3</sub> SnSnBu <sub>3</sub> | Hexabutylditin                              |
| CA                                  | Carbonic Anhydrase                          |
| CCl <sub>4</sub>                    | Carbon tetrachloride                        |
| CBr <sub>4</sub>                    | Carbon tetrabromide                         |
| CDCl <sub>3</sub>                   | Deuterated Chloroform                       |
| CDL                                 | Constitutional Dynamic Chemistry            |
| Co                                  | Cobalt                                      |
| Conv                                | Conversion                                  |
| Cr                                  | Chromium                                    |
| CSTR                                | Continuous Stirred-Tank Reactor             |
| Cu                                  | Copper                                      |

|                   |   |
|-------------------|---|
| d                 | Doublet                                 |
| DCC               | Dynamic Combinatorial Chemistry         |
| DCL               | Dynamic Combinatorial Library           |
| dd                | Doublet of doublets                     |
| ddd               | Doublet of doublet of doublets          |
| ddt               | Doublet of doublet of triplets          |
| dt                | Doublet of triplets                     |
| DCE               | Dichloroethane                          |
| DCM               | Dichloromethane                         |
| de                | Diastereomeric excess                   |
| DMAP              | Dimethylaminopyridine                   |
| DMF               | Dimethylformamide                       |
| DNA               | Deoxyribonucleic Acid                   |
| D <sub>2</sub> O  | Deuterium Oxide                         |
| ESI               | Electron Spray Ionisation               |
| EPD               | Evolvable Process Design                |
| Equiv             | Equivalents                             |
| ESI               | Electrospray Ionisation                 |
| Et                | Ethyl                                   |
| Et <sub>3</sub> B | Triethylborane                          |
| Et <sub>3</sub> N | Triethylamine                           |
| Et <sub>2</sub> O | Diethyl ether                           |
| EtOH              | Ethanol                                 |
| FAB-MS            | Fast Atom Bombardment Mass Spectrometry |
| Fe                | Iron                                    |
| GIST              | Gastrointestinal Stromal Tumor          |
| HBr               | Hydrogen Bromide                        |
| hCA               | Human Carbonic Anhydrase                |
| HEWL              | Hen Egg-White Lysosome                  |
| HPLC              | High Performance Liquid Chromatography  |
| HRMS              | High Resolution Mass Spectroscopy       |
| Hz                | Hertz                                   |
| IR                | Infra-red                               |

|                                |  |
|--------------------------------|--|
| K <sub>2</sub> CO <sub>3</sub> | Potassium Carbonate                                      |
| LLCT                           | Ligand to Ligand Charge Transfer                         |
| m                              | Multiplet  |
| MB                             | Mass Balance   |
| Me                             | Methyl   |
| MeCN                           | Acetonitrile   |
| MeOH                           | Methanol   |
| Me <sub>6</sub> -Tren          | <i>N,N,N',N',N'',N''</i> -hexamethyltriethylenetetramine |
| Mg                             | Magnesium  |
| MMA                            | Methyl Methacrylate                                      |
| Mo                             | Molybdenum   |
| mpt                            | Melting Point  |
| NA                             | Neuraminidase Inhibitors                                 |
| Ni                             | Nickel   |
| nm                             | Nanometers   |
| NMPI                           | Pyridine-imine ligand                                    |
| NMR                            | Nuclear magnetic resonance                               |
| OBR                            | Oscillatory Baffled Reactor                              |
| PEEK                           | Polyetheretherketone                                     |
| PFR                            | Plug Flow Reactor  |
| Ph                             | Phenyl   |
| PMDETA                         | <i>N,N,N',N',N''</i> -pentamethyldiethylenetriamine      |
| ppm                            | Parts per million  |
| PTFE                           | Polytetrafluoroethylene                                  |
| q                              | Quartet  |
| RCC                            | Renal Cell Carcinoma                                     |
| RNA                            | Ribonucleic Acid   |
| rt                             | Room temperature   |
| RTK                            | Receptor Tyrosine Kinases                                |
| Ru                             | Ruthenium  |
| s                              | Singlet  |
| SDS                            | Sodium Dodecyl Sulfonate                                 |
| Sept                           | Septet   |

|                  |  |
|------------------|--|
| SET              | Single electron transfer                               |
| SET-LRP          | Single electron transfer living radical polymerisation |
| SM               | Starting Material                                      |
| t                | Triplet  |
| t <sub>1/2</sub> | Half-life  |
| Temp             | Temperature  |
| THF              | Tetrahydrofuran  |
| TLC              | Thin Layer Chromatography                              |
| TMEDA            | Tetramethylethylenediamine                             |
| TMS              | Trimethylsilyl   |
| Tol              | Toluene  |
| TsOH             | Toluenesulfonic Acid                                   |
| TPA              | Tripyridylamine  |
| Ts               | Tosyl  |
| Ugi-4CR          | Ugi Four Component Reaction                            |
| UV               | Ultraviolet  |
| Vis              | Visible  |
| Zn               | Zinc   |

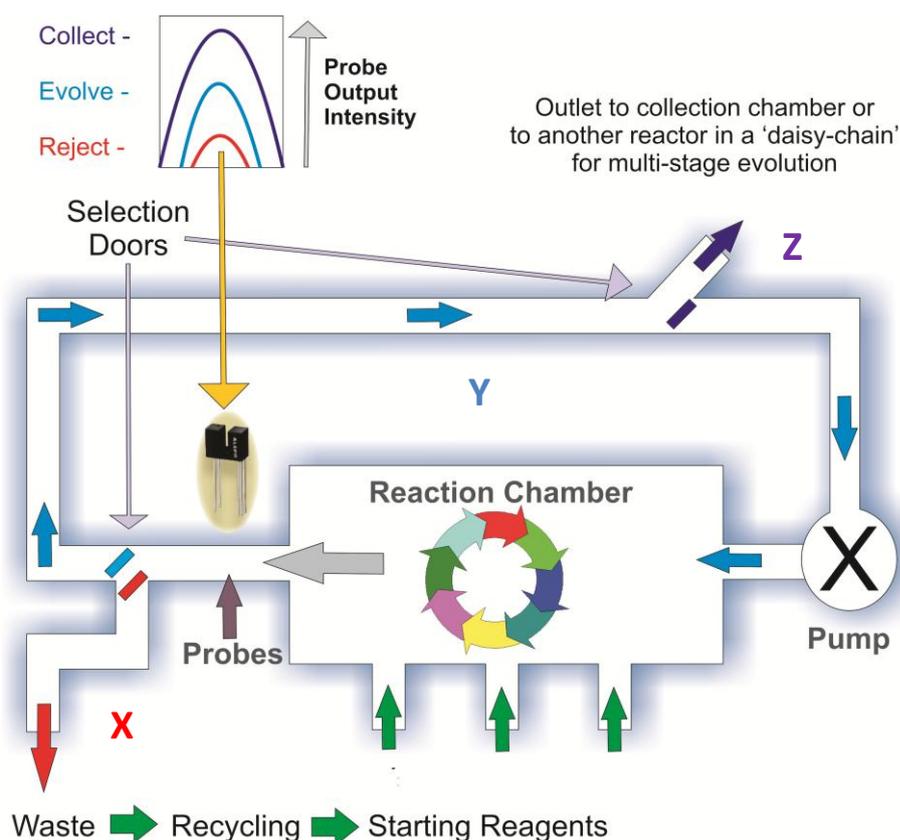
## 1.0 Introduction

### 1.1 Project Objectives

We are part of a large EPSRC funded consortium that wishes to engineer a ‘machine’ that will take small organic and/or inorganic building blocks and use them to prepare any theoretical compound with any theoretical property that has been determined by the ‘machine’.

This research lies in the development of an Evolvable Process Design (EPD) reactor platform (Figure 1) such that ‘evolved’ chemical reactions can be investigated for the first time. The research proposed here outlines a radical approach to the development of a system that allows molecular evolution; the evolutionary direction being dictated by the properties that form the fitness landscape (or selection criteria). Initially this system will allow these selection criteria to be imposed artificially, and thus allow the possibility of designing molecules and materials with desired function.

The realisation of the EPD concept platform will require: building blocks that can reversibly connect; a reactor / reaction to connect the blocks equipped with a range of sensors and feedback controllers; separators to isolate the product(s) for analysis; an integrated ‘property sensor’ and flow control system; a property to detect with the sensor; software control of the process.

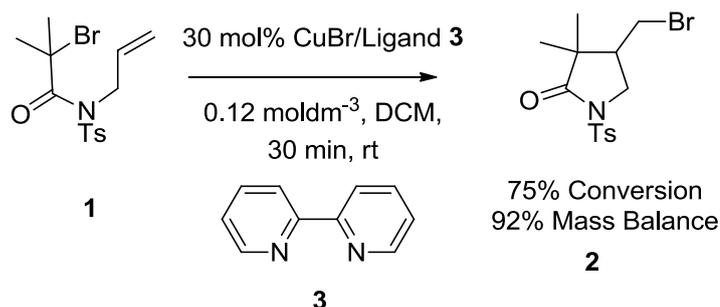


**Figure 1:** Schematic of the proposed reactor platform.

Organic building blocks that can reversibly react will be reacted under various conditions until a product with desired property (certain mass of product, UV / Vis absorbance, biological activity etc.) is evolved. This will be detected by a suitable probe (e.g. mass spectrometer, UV / Vis spectrometry or enzyme assay etc.). If the desired product cannot be evolved or the concentration is low then the products are rejected, recycled and re-introduced back into the reaction chamber with the addition of different building blocks (**X**). If the product is evolving (**Y**), the products flow back into the reaction chamber with slight change of conditions (pH, temperature, pressure etc.) until a suitable amount of desired product is evolved that can then be collected (**Z**). Our engineering partners will be working on the hardware and the software control of this reactor system.

At Warwick University, our goal was to create a dynamic combinatorial library of imine products using simple aldehyde and amine building blocks that would reversibly react under a variety of conditions. We were then to progress into creating a complex dynamic combinatorial library which would generate imine products of various colours that could be uniquely identified using a UV / Vis spectrometer in the ‘machine’. We are to collect these data for our engineer partners to aid them on the design of the ‘machine’, to prove that we can evolve a compound with a specific property. We will eventually be designing a range of building blocks that contain multiple functionalities and thus can undergo multiple reactions to achieve our goal of an almost unlimited combination of ‘evolvable products’.

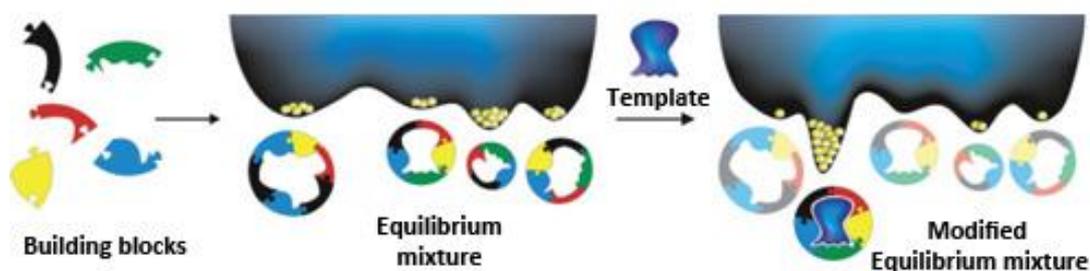
We also decided to synthesize imine ligands to improve the reaction efficiency for metal mediated atom transfer radical cyclization reactions (ATRC) (Scheme 1) which is extensively studied by the Clark group. We knew that once the ‘machine’ was developed, we could adapt the system in a way which would allow us to develop optimised imine catalysts for ATRC reactions.



**Scheme 1.** An example of ATRC reaction for the 5-*exo* cyclisation process of *N*-allyl-2-bromo-2-methyl-*N*-tosylpropanamide **1** to 4-(bromomethyl)-3,3-dimethyl-1-tosylpyrrolidin-2-one **2** using 30 mol% CuBr and bipyridine ligand **3**.

## 1.2 Dynamic Combinatorial Chemistry

Dynamic combinatorial chemistry (DCC) is a powerful tool which offers access to wide range of substances generated by a small library of molecules without having to individually synthesize each molecule. These are molecular systems that are able to self-replicate, or in which the most effective members become amplified. DCC requires inter-conversion of library members into one another through a reversible chemical process *via* covalent or non-covalent bonds including metal-ligand interaction, generating dynamic combinatorial libraries (DCL).<sup>1, 2</sup>



**Scheme 2:** Re-Equilibrium of a DCL upon Addition of a Template, Resulting with an Amplification of Molecules which Tightly Bind to the Target in the Expense of Non-Binders.

In chemistry, Le Châtelier's principle states that: *“If a chemical system at equilibrium experiences a change in concentration, temperature, volume, or partial pressure, then the equilibrium shifts to counteract the imposed change and a new equilibrium is established.”*<sup>3</sup>

Luckily, DCL relies on thermodynamic control and, therefore, this principle can be numerously exploited (Section 1.2.4). For example, upon addition of a template molecule, the equilibrium mixture is disturbed and the mixture re-

equilibrates to generate high concentration of new components based on its affinity for the template (Scheme 2). Such shift in equilibrium will lead to amplification of molecules with a high affinity for the template which can then be identified within the library of molecules and isolated with minimal separation.<sup>4</sup>

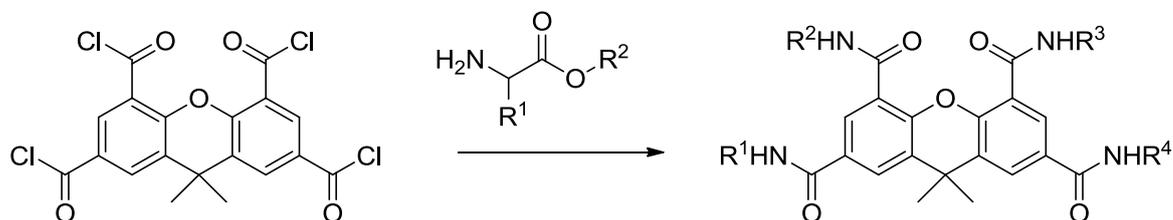
### 1.2.1 Origins of Dynamic Combinatorial Chemistry

The basic principle of dynamic combinatorial chemistry was first introduced by Paul Brady in 1996<sup>5</sup> from the realization that biological systems have been able to construct effective receptors that are capable of specific molecular recognition through millions of years of evolution, but constructing an effective molecule through a simple synthetic design approach had been an extremely difficult task. Therefore, a new, more efficient general approach was introduced consisting of combinatorial, selection and amplification elements shown by the mammalian immune system. Some of the elements were already present in two areas of chemistry; conventional combinatorial chemistry and supramolecular chemistry.<sup>6</sup>

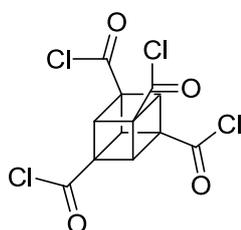
The concept of conventional combinatorial chemistry was first introduced in the 1990's to improve the probability of finding a desired product by generating larger numbers of small molecules.<sup>7</sup> These solution phase molecules were then screened for the affinity to a receptor and lead to a large library of molecules creating analytical and de-convolution problems.<sup>8</sup>

For example, The Rebek group reacted a range of amines with one of three core tri- or tetra-acid halides (compounds **4-6**, Figure 2) which resulted in a library of up to 97,461 members.<sup>9-11</sup> HPLC traces of those crude members showed that many compounds had been formed, but the real problem they came across was to

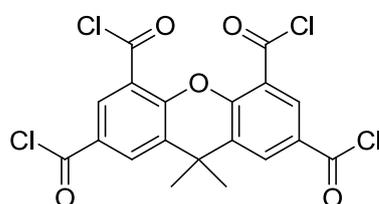
identify which of those components were biologically active. Compound **7** was later identified as the most effective trypsin inhibitor after repetitive deconvolution protocols.<sup>12</sup>



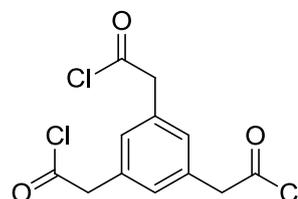
Scaffolds:



**4**

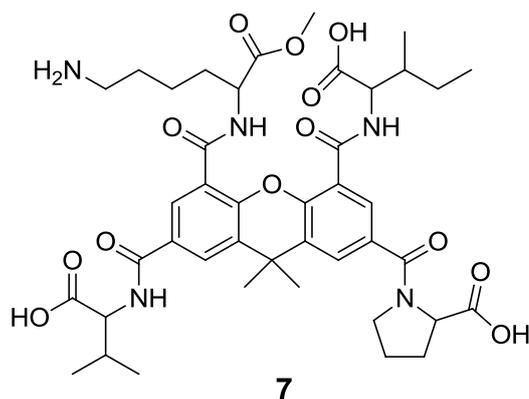


**5**



**6**

**Figure 2:** Reactive Scaffolds Used in the Preparation of Solution-Phase Mixture Libraries.

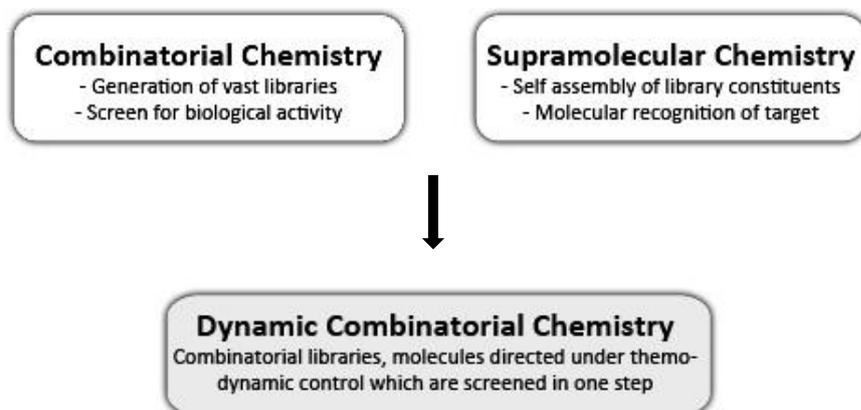


**7**

In parallel development, self-assembly processes directed by molecular recognition were also investigated in supramolecular chemistry<sup>13</sup>. Supramolecules are complexes that are associated by two or more chemical species which are held together by intermolecular forces such as hydrogen<sup>14</sup> bonding, metal to ligand attraction<sup>15</sup>,  $\pi$ - $\pi$  binding dispersion interactions<sup>16</sup>, and hydrophobic interactions.<sup>17</sup>

Supramolecular chemistry involves the study of complexes which have a cavity (the host or the molecular receptor) that enable smaller molecules (the guest or the substrate) to fit into the cavity of the host. For example, hosts are the receptor sites of enzymes and antibodies of the immune system, or ionophores and guests are the counterparts of the hosts such as substrates, antigens, cofactors, inhibitors or drugs.<sup>13</sup>

The concept of dynamic combinatorial chemistry (DCC) was created from combining these two areas of chemistry (Scheme 3).<sup>13, 18, 19</sup> The guest molecule can select its own, most effective host that it could strongly bind to, among a mixture of possible hosts. The most successful host from this equilibrium mixture of potential hosts would cause a shift in the equilibrium position and amplify the “best binder”. In principle, this minimizes the synthetic effort, in which a wide range of effective large, complex products can be evolved from a small number of simple building blocks.



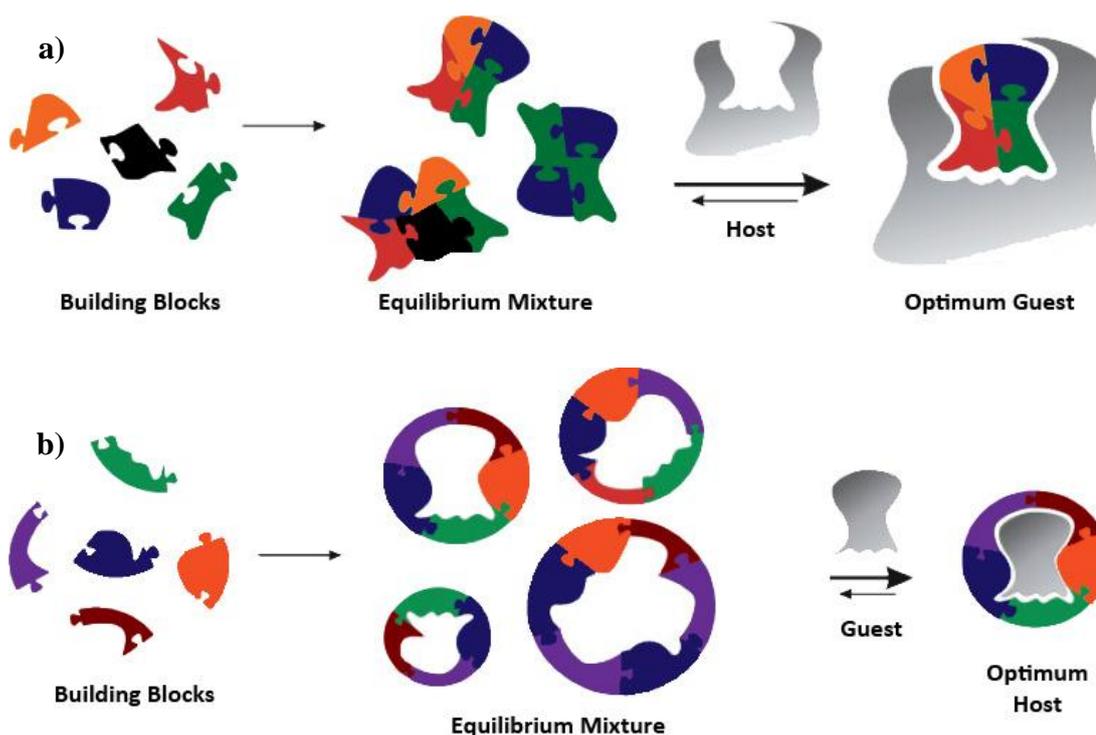
**Scheme 3:** Evolution of Dynamic Combinatorial Chemistry.

## 1.2.2 Stabilization of Library Components

As dynamic combinatorial chemistry is thermodynamically controlled, stable libraries can be generated in a number of different ways; chemical templates, self templating, external stimulus or by phase change.

### 1.2.2.1 Chemical Templates

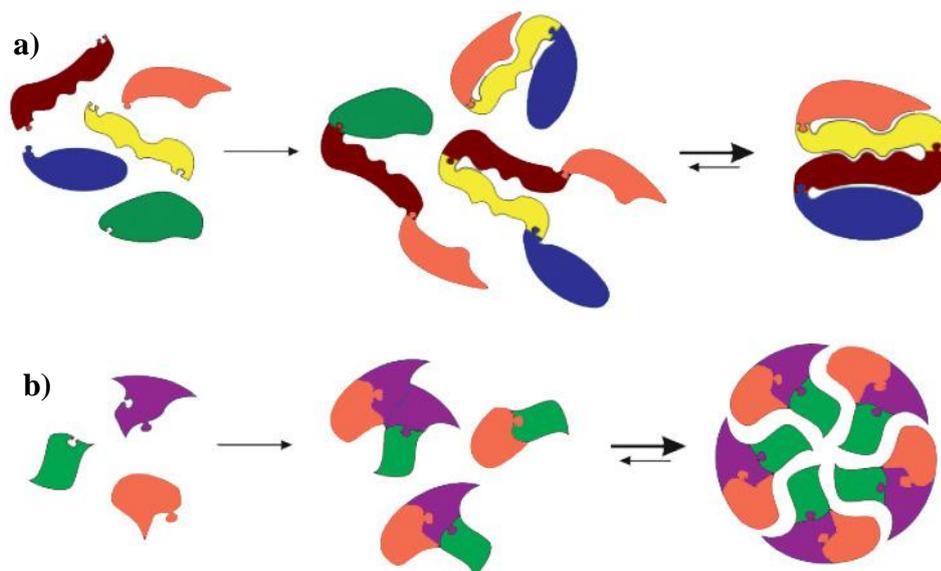
The concept of templating in the fashion of ‘casting’ and ‘moulding’ was first employed by Lehn and co-workers.<sup>20</sup> In ‘casting’, a macromolecule (host) provides a cavity within which the optimum ligand (guest) may be trapped *via* noncovalent interactions (Figure 3, a). The poor candidates remain in solution and are consumed by the equilibrium process. In ‘moulding’, the ligand collects the optimum receptor around itself also *via* noncovalent interactions (Figure 3, b). Examples of these used for imine DCL’s are discussed in detail in Sections 1.2.4.1 and 1.2.4.2.



**Figure 3:** Diagrammatic representation of (a) ‘casting’ and (b) ‘moulding’ in dynamic combinatorial libraries.<sup>21</sup>

### 1.2.2.2 Self templating

Stabilization of library components by self-assembly involves *intermolecular* noncovalent forces such as hydrophobic interactions, coordination around a metal ion or hydrogen bonding, generating libraries with stable assemblies or aggregates (Figure 4, b). Foldamers arrange themselves to the structural conformation with the most stable *intermolecular* noncovalent interactions, over those library members which lack such stabilization (Figure 4, a).<sup>21</sup> Examples of these used for imine DCL’s are discussed in detail in Sections 1.2.4.1 and 1.2.4.2.



**Figure 4:** Diagrammatic representation of a) ‘foldamers’ and b) ‘self-assembly’ in dynamic combinatorial libraries.<sup>21</sup>

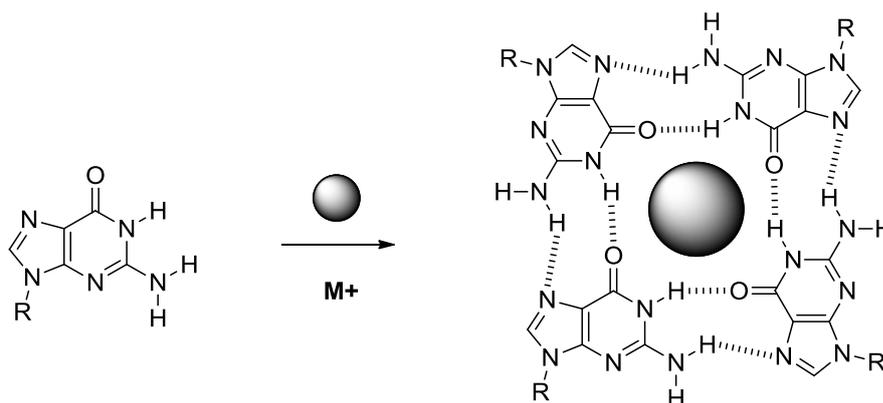
### 1.2.2.3 External Physical or Chemical Stimuli

Stabilization of library components shown by casting, moulding, self-assembly and foldamers are driven by molecular recognition that requires noncovalent bond interactions, but library components that are able to reorganise and amplify by purely covalent bond interactions in the presence of an external influence, in the form of physical (electric field, pressure, temperature) or chemical (molecules, ions, protons) triggers<sup>22, 23</sup> is known as constitutional dynamic chemistry (CDC).<sup>24</sup> Examples of these used for imine DCL’s are discussed in detail in Section 1.2.4.3.

### 1.2.2.4 Phase Change

This is a process of self-organisation by selection, where the formation of a structured phase (for example, a gel) drives the selection of the components, thus amplifying the highly organised and most stable assembly.

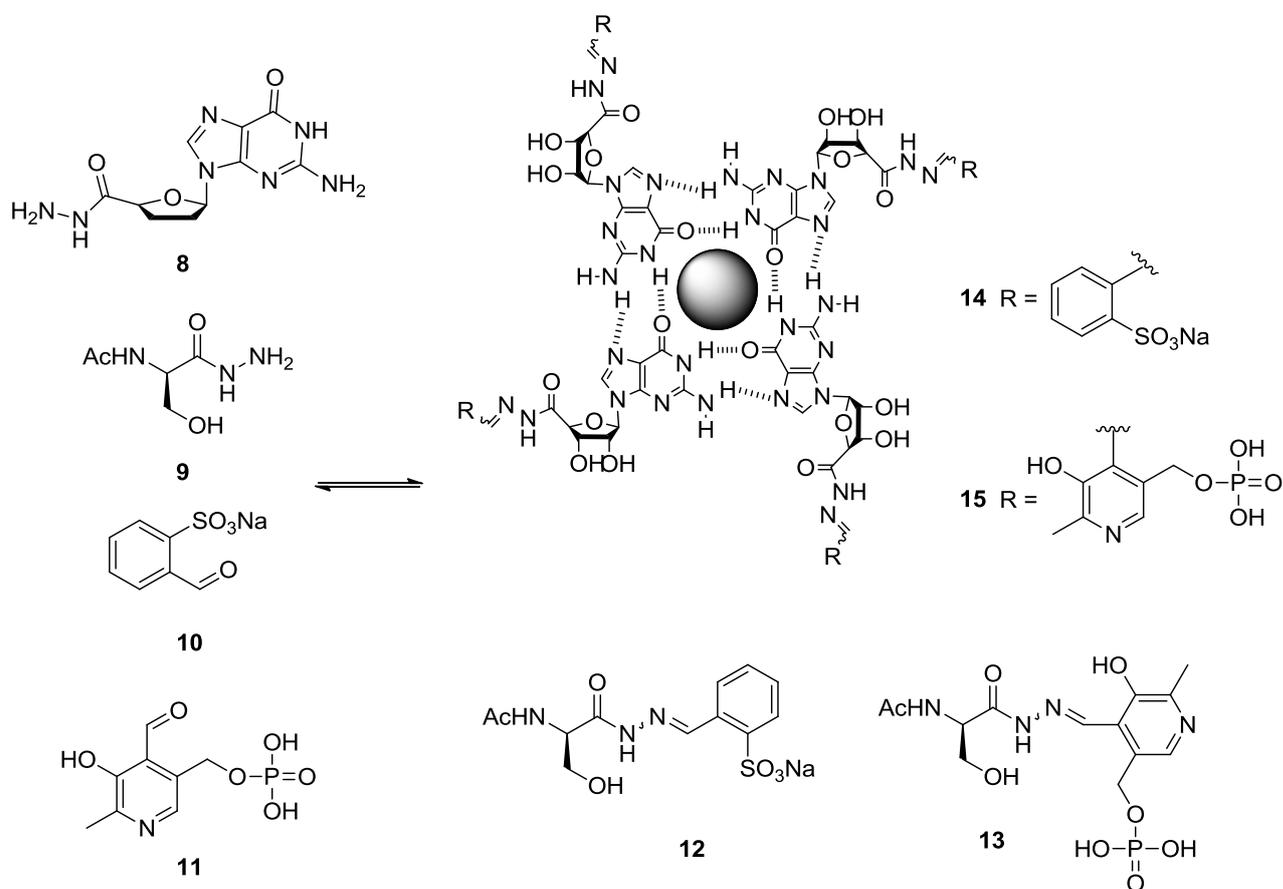
One of the early examples of phase change was reported by Lehn.<sup>25</sup> Guanosine hydrazine **8**, although not soluble in water itself was able to form stable free-standing gels. This is because it performs quadruple association into G-quartets through Hoogsteen type hydrogen bonding forming supramolecular macrocycles that stack into G4 assemblies in the presence of  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{NH}_4^+$  and  $\text{Me}_4\text{N}^+$  at neutral pH (Figure 5).



**Figure 5.** Guanine Derivatives Self-Assemble into G-Quartets in the Presence of Metal Ions.

Guanosine hydrazine **8** and its assemblies can be reversibly reacted with various aldehydes to form acylhydrazones (Scheme 4). When **8** and **9** were mixed with aldehydes **10** and **11** at 1:1:1:1 molar ratio, acylhydrazones **12** and **13** and acylhydrazone G-quartets **14** and **15** were formed. These hydrazones were thermoreversible, where at temperatures of  $80^\circ\text{C}$ , the distribution of acylhydrazones

was close to equal, but at cooler temperatures of 25°C, the equilibrium strongly favoured the formation of acylhydrazone **15** which formed the strongest gel.



**Scheme 4.** Generation of a Dynamic Library of Hydrazones **12-15**.

A further example of selection *via* phase change used for imine DCL is demonstrated in Section 1.2.4.4.

### 1.2.3 Exchange Reactions

The most important element of DCC is the requirement of building blocks that can reversibly react, thus allowing exchange between building blocks. These

building blocks must comply with certain standards for it to be effective for dynamic combinatorial libraries.<sup>21</sup>

- I) The reaction must be reversible within acceptable time scale. The equilibrium and selection occurs simultaneously and, therefore, the components must be suitable with the reaction conditions of the selection process (phase changes, templates and external physical or chemical influences).
- II) Noncovalent bonding interactions are weaker than covalent bonding interactions (Table 1) and therefore in the presence of noncovalent bonds, the reaction conditions (concentration, temperature and pressure) needs to be mild to prevent disturbances to the weak noncovalent bonds.
- III) At equilibrium, the reaction components should be soluble and there should be a way to freeze the reaction to isolate the library member(s).
- IV) The library member(s) are required to be of equal energy, this would prevent production of reaction mixtures that would strongly favour in producing a certain product which would result in high energy costs to return the products back to equilibrium.

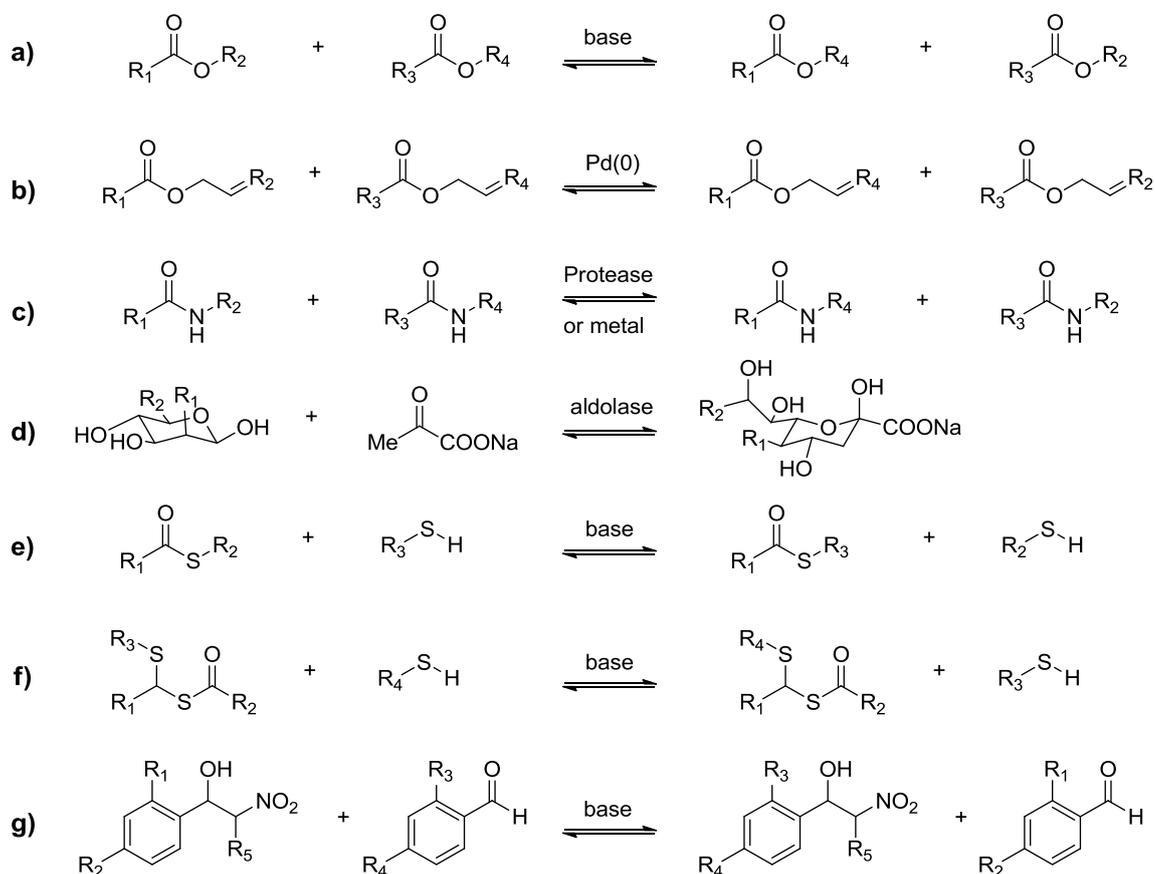
| interactions       |                                  | energy (kJ/mol)      | lability |
|--------------------|----------------------------------|----------------------|----------|
| covalent bonds     |                                  | 150-800 <sup>a</sup> | low      |
| coordinative bonds | 1 <sup>st</sup> row <sup>b</sup> | 80-350               | high     |
|                    | 2 <sup>nd</sup> row <sup>b</sup> | 80-350               | medium   |
|                    | 3 <sup>rd</sup> row <sup>b</sup> | 80-350               | low      |
| hydrogen bonds     |                                  | 0-20                 | high     |

<sup>a</sup> typical range for single and double bonds. <sup>b</sup> localization of the metal in the d block of the periodic table (3d-5d series)

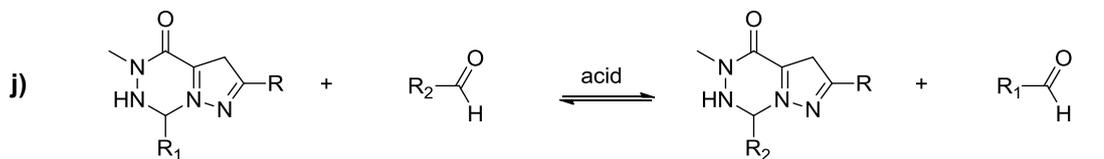
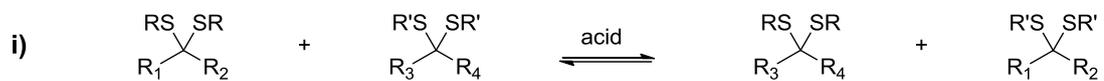
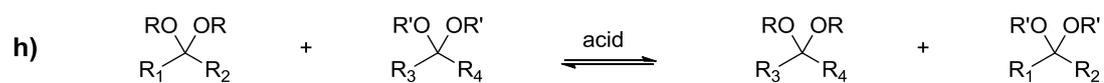
**Table 1**

There is a huge diversity of covalent and noncovalent bond types that have been shown in DCL generation which has been reviewed by Sanders and Otto (Figure 6).<sup>26</sup> We are only interested in looking at covalent bonds of imine exchange reactions, including molecular recognition of imine DCLs via noncovalent interactions used in DCC to aid the development of our ‘machine’. These reactions are discussed in Section 1.2.4.

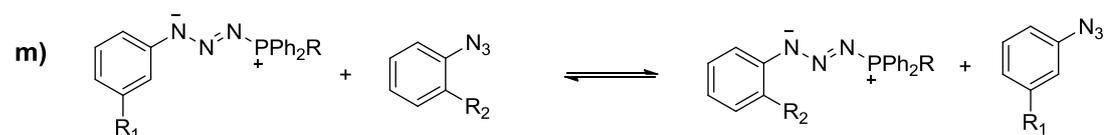
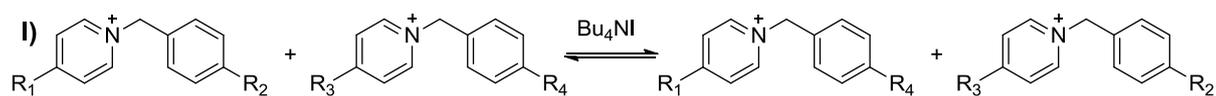
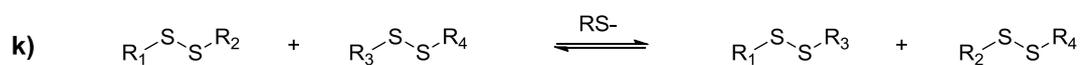
### Acyl transfer and related



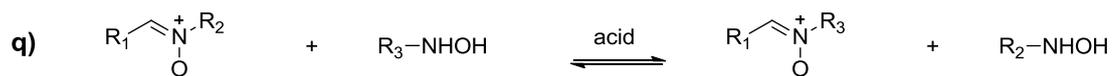
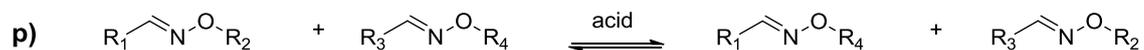
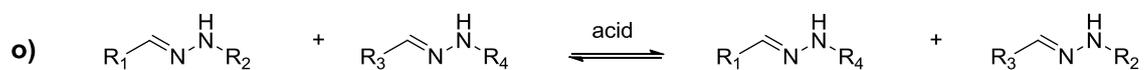
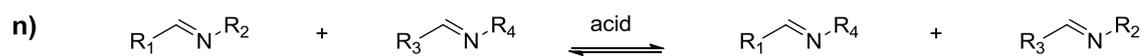
## Acetal exchange and related



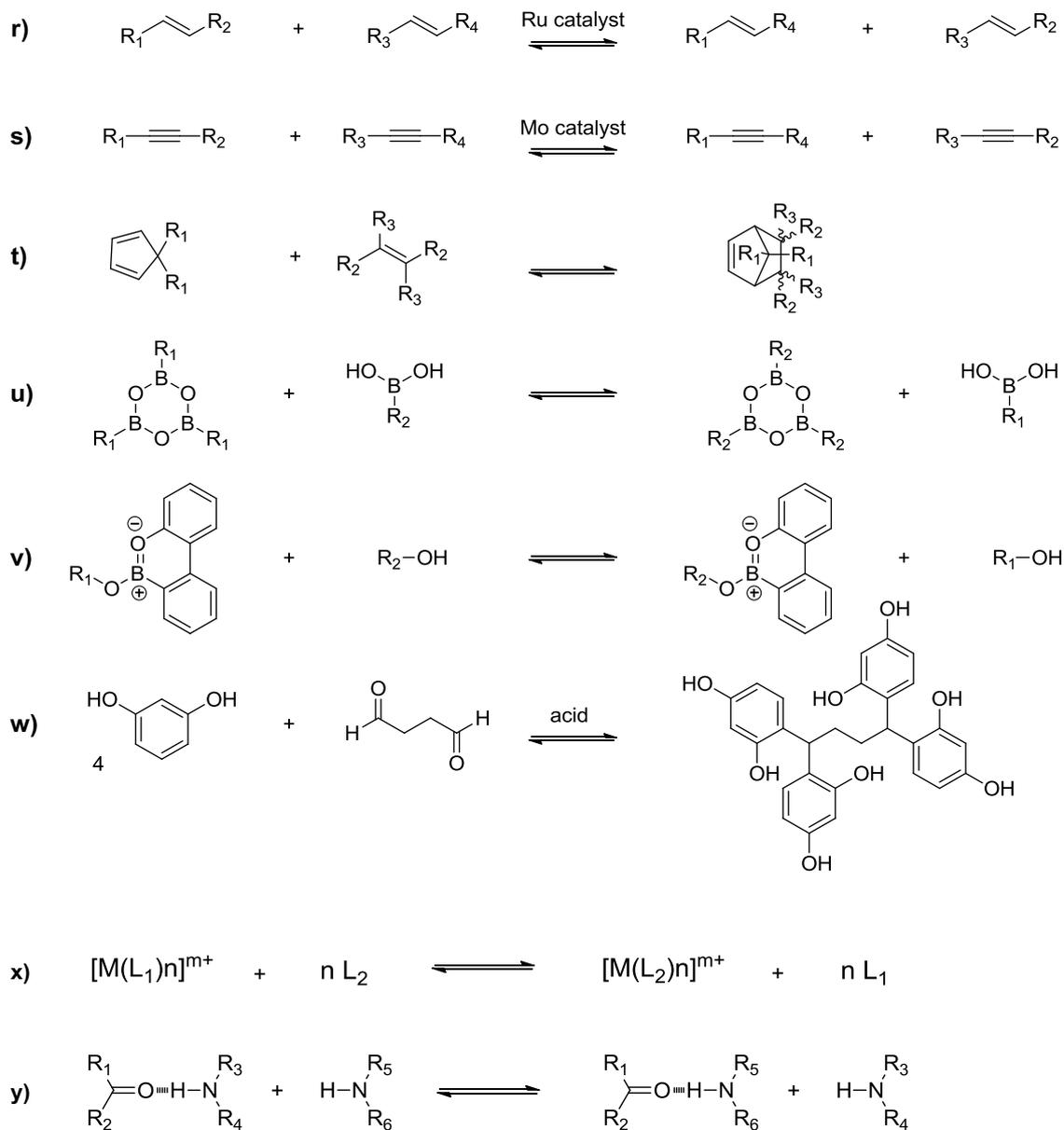
## Nucleophilic substitutions



## C=N exchange



## Other reversible covalent bonds

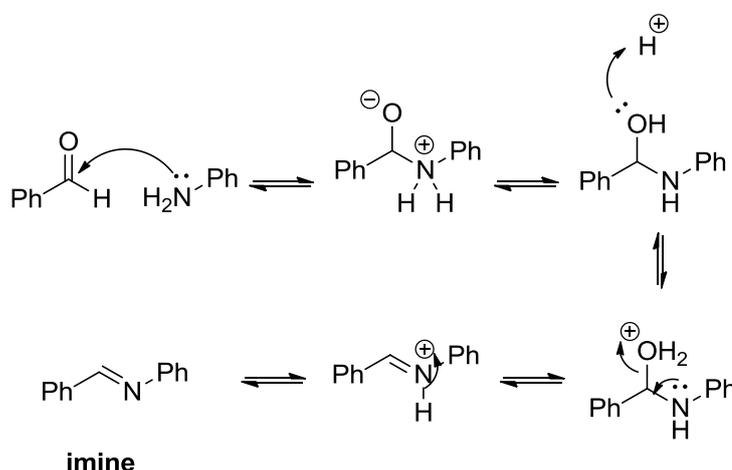


**Figure 6.** Various Reversible Reactions used in DCC; a) transesterification; b) transallylesterification; c) transamidation; d) aldol exchange; e) transthoesterification; f) Michael / retro-Michael reactions; g) nitroaldol exchange; h) acetal exchange; i) thioacetal exchange; j) pyrazolotriazone metathesis; k) disulfide exchange; l) reversible benzylic nucleophilic substitution; m) phosphazide exchange; n) imine exchange; o) hydrazine exchange; p) oxime exchange; q) nitron exchange; r) alkene metathesis; s) alkyne

metathesis; t) Diels-Alder / retro-Diels-Alder reactions; u) reversible boroxine formation; v) transboroxoaromatic esterification; w) reversible resorcinol and 1, 4-butanediol condensation; x) metal-ligand exchange; and y) hydrogen bond exchange.

### 1.2.4 Imine DCL

Imine bonds (azomethine linkage) are formed when reacting an aldehyde or ketone with a primary amine. This reaction is acid catalysed and was first discovered by Schiff<sup>27</sup> and the imines are, therefore, also known as Schiff bases.



**Scheme 5:** A Mechanism for Imine Formation.

Acid is not required for the first step of the mechanism (addition of the amine to the aldehyde) (Scheme 5), where, in the presence of strong acid, the amine will be protonated and slow down the reaction. Acid is however required to protonate the alcohol in step three to aid the removal of water. The optimum pH for imine formation is ~ 5-6 at room temperature. Either side of this pH and the reaction will

precede slowly, just like biological reactions, imine reactions precede fastest near neutral pH.<sup>28</sup>

Imines generated by reacting diaryl or arylalkyl ketones with primary amines require the removal of water from the reaction to drive the equilibrium towards product formation; this can be achieved by either 1) separating it physically using a Dean-Stark apparatus, or 2) by adding a drying agent that absorbs water from the reaction. Imine formation by reacting dialkyl ketone or aldehydes with primary amines can proceed without the removal of water from the reaction. Due to the fact that removing water from a reaction to synthesize imine bonds would create difficulties in DCC, there is only a limited number of papers reported to date that have used ketones and primary amines DCC's to generate imines.<sup>29</sup>

Once azomethine linkages have been generated in the reaction, the exchange of building blocks can be obtained *via* hydrolysis,<sup>28</sup> aminolysis (transamination or exchange)<sup>30, 31</sup> or metathesis reactions.<sup>21, 26</sup>

Hydrolysis reactions involve breaking the azomethine linkage in the presence of water and acid generating the aldehyde / ketone and primary amine starting material, but as imine reactions are reversible, the equilibrium can then be shifted back towards product formation by alteration of pH towards neutrality. In the presence of new building blocks, new imines can be generated.<sup>28</sup>

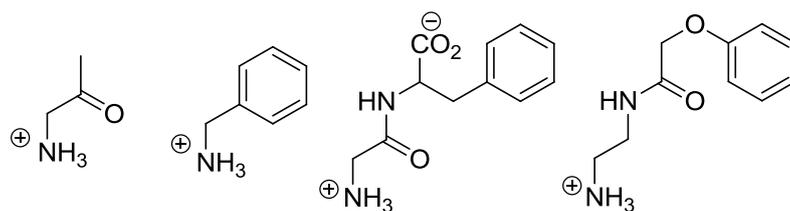
Aminolysis reaction is a direct replacement of the amine component of a Schiff base by another amine in the presence of acid. This reaction proceeds *via* a two-step reaction pathway involving a formation of *gem*-diamine as an intermediate (Scheme 6).<sup>30, 31</sup>



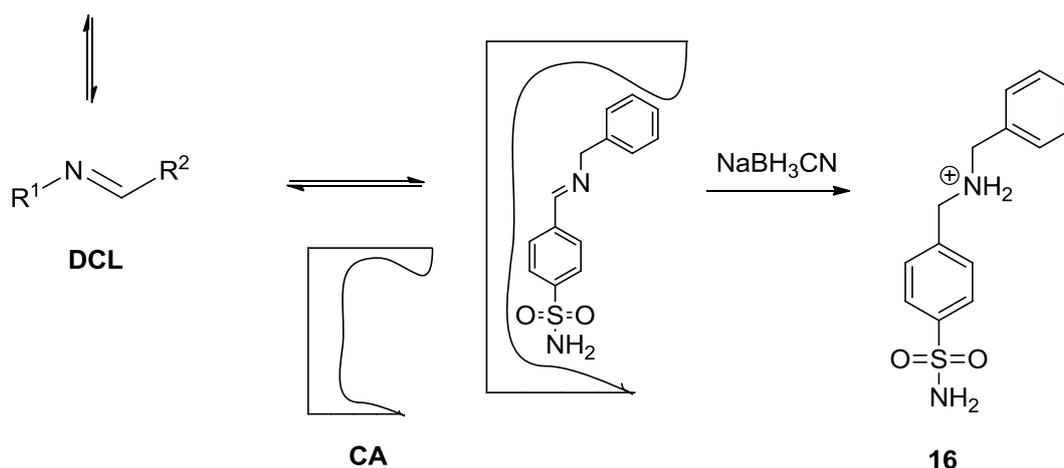
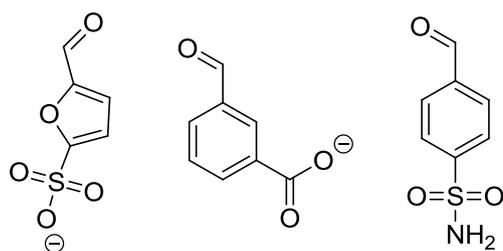
### 1.2.4.1 Selection *via* Casting

In 1997, Lehn and co-workers<sup>20</sup> demonstrated ligand ‘casting’ by creating a dynamic combinatorial library of imines generated from four amines and three aldehydes in an attempt to discover effective inhibitors for human carbonic anhydrase I (hCAI) (Scheme 8). The imine mixtures were allowed to reach equilibrium and with the addition of CA, there was a two-fold increase in concentration of compound **16** when compared to the control experiment. These imines were detected by HPLC, which required a fixed library composition. This was achieved by freezing the equilibrium by irreversible reduction of imines with  $\text{NaBH}_3\text{CN}$  to their resulting amine.

## Amines



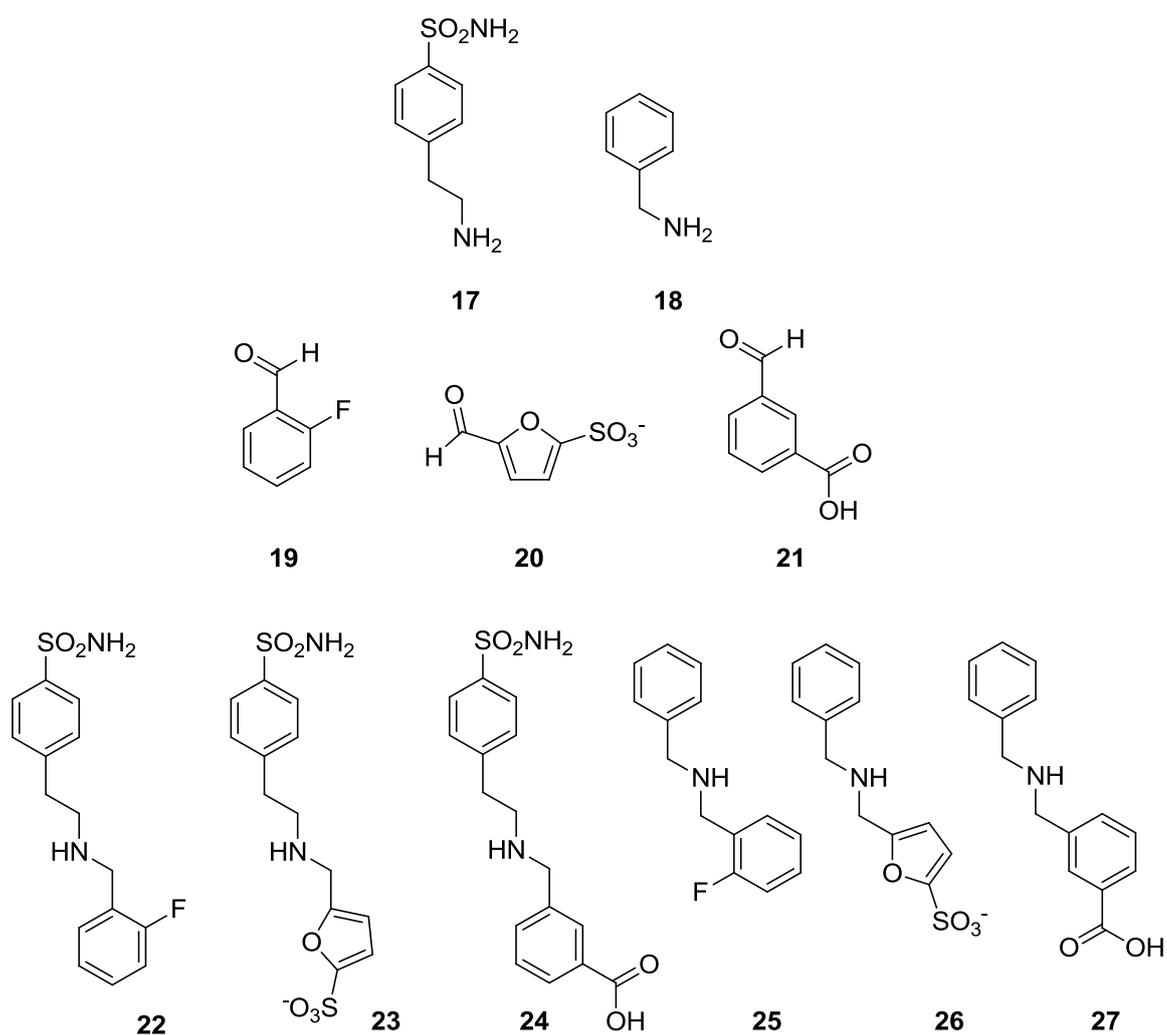
## Aldehydes



**Scheme 8.** Amplification of a Successful Binder to CA from a DCL of Imines.

Since then, much research has been carried out on CA and currently there are 13 catalytically active  $\alpha$ -CA isozymes, human carbonic anhydrases hCAI and hCAII are the most selective isoforms, selective inhibition of these could lead to effective antiglaucoma, antiepileptic, anti-obesity, or anticancer drugs.<sup>36</sup> By using DCC, a more selective inhibitor was discovered by Barboiu *et al.* using aminocarbonyl /

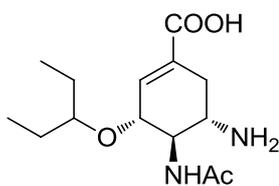
imine interconversion as reversible chemistry.<sup>36</sup> Two amines **17**, **18** and three aldehydes **19** - **21** were selected. Amine **17** was selected due to the presence of a sulfonamide group which are one of the best zinc binding groups (ZBG) present in hCAI and hCAII active sites allowing generation of potent CAIs. Aldehyde **20** and **21** contain weaker ZBG where **18** and **19** contained phenyl hydrophobic moieties to probe the hydrophobic interactions of the hydrophobic pocket above the active enzyme site (Figure 7).



**Figure 7.** A DCL of amines via reduction of imines.

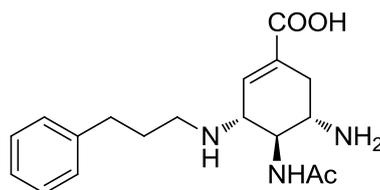
Placing amines **17**, **18** with aldehydes **19** – **21** resulted in six possible imine products in equilibrium with initial components. In the presence of hCAI and hCAII, the distribution of products was highly altered. After the reduction of imines by NaBH<sub>3</sub>CN to **22** – **27** and HPLC analysis, in the presence of hCAI, they found a significant amplification of amine **24** (350%) compared to no hCAI, which confirmed the strong inhibition power of the sulfonamide group combined to hydrophobic effects of the carboxylic acid group of component **21** in hydrophobic pockets. A minor amplification of **26** was also observed. When they exposed the imine library to a more active (selective) isoform of CA family (hCAII), a strong amplification of compounds **22** – **24** (250 – 420 %) was observed again confirming the strong inhibition power of the sulfonamide group. The dynamic screening of the imine library was successful in terms of identifying components **26** and **24** as a potent inhibitor of hCAI and sulfonamide inhibitors **22** – **24** for hCAII isozyme.

Apart from using imine DCL for effective inhibition of CA, work was also carried out on neuraminidase, which is a key enzyme responsible for influenza virus propagation.<sup>37</sup> Neuraminidase is a major target for drug action on influenza.<sup>38</sup> The

**28**

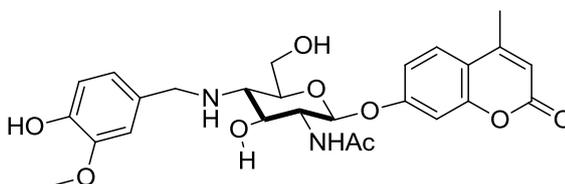
enzyme structure is well known and for the most important functionalities are the presences of carboxylate and acetamido groups for efficient inhibition. For example compound **28**, which is the active component of the commercially available influenza drug Tamiflu.<sup>39</sup>



**30**

Although ketones are rarely used in DCC, Eliseev and co-workers also worked on ketone components to discover a selective NA inhibitor.<sup>29</sup> Again diamine **29** was used to generate dynamic imine libraries by exposing with 20 various ketones, and then reduced to their corresponding amines for LC / MS analysis. Comparing the relative amounts of imines with or without the presence of NA target, they clearly observed amplification of selected amine peaks due to the interactions with the neuraminidase active site.

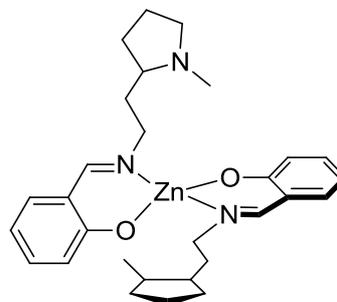
Another example of enzyme inhibition was shown by Beau and co-workers.<sup>41, 42</sup> They demonstrated the use of dynamic imine library as potential active site ligands comprising of an aryl group mimicking a carbohydrate group for the inhibition of hen egg-white lysosome (HEWL). They were able to identify amine **31** from its corresponding imine to be the most amplified product being around 100-fold more active than the previously known inhibitor *N*-acetyl-D-glucosamine.

**31**

Selective molecular recognition between synthetic oligonucleotide ligands and nucleic acid targets play an important role in molecular biology, biotechnology and molecular medicine.<sup>43</sup> With the introduction of a chemical modifier, the

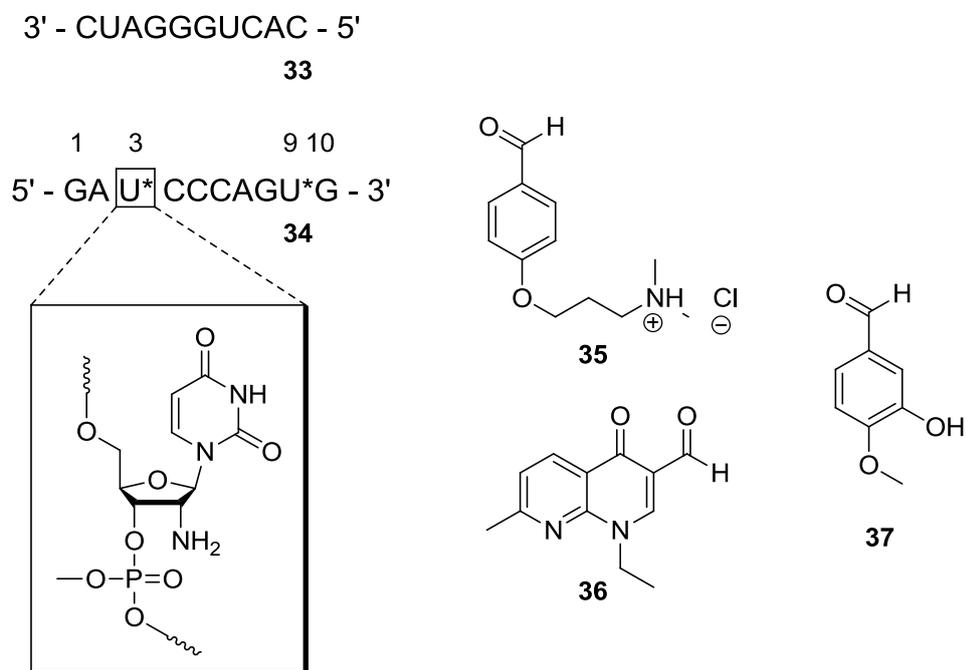
properties of natural DNA or RNA oligonucleotide can be altered (e.g. affinity, nuclease resistance, membrane permeability). Designing these chemical modifiers is not a simple task, but with the use of DCC, this effort can be greatly reduced.

Early work of Miller and Klekota<sup>44,45</sup> revealed that exposing salicylaldehyde with six different amines lead to a imine DCL, which in the presence of Zn(II) ions, amplified compound **32** as one of the highest binding affinity to an immobilised double-stranded DNA-cellulose resin used as the affinity target.

**32**

Bugart *et al.* used imine DCL for the identification of covalently appended small molecules that stabilize nucleic acid complexes.<sup>46</sup> They demonstrated that reversible exchange reaction between imine libraries formed from 2'-aminonucleotide, incorporated into an oligonucleotide ligand and a group of aldehydes can be influenced by the presence of a nucleic acid target, where the strongest binding conjugated products were amplified. In their experiment they used an oligonucleotide ligand **34**, incorporated by two 2'-deoxy-2'-aminouridine (U\*) in positions 3 and 9. This reactive ligand was then exposed to three aldehydes (**35** – **37**) both in the presence and without the presence of the complementary oligoribonucleotide **33** as the target, to observe which imine component successfully stabilizes the RNA duplex formed between **33** and **34** (Scheme 10). HPLC analysis of the corresponding amines reduced by NaBH<sub>3</sub>CN of the possible 15 imine products (six monoconjugated and nine biconjugated products) with and without the presence of the target had shown clear amplification of product consisting of aldehyde **36** at

position 3 of the ligand in the expense of other products, hence stabilizing the duplex formed with **33**.

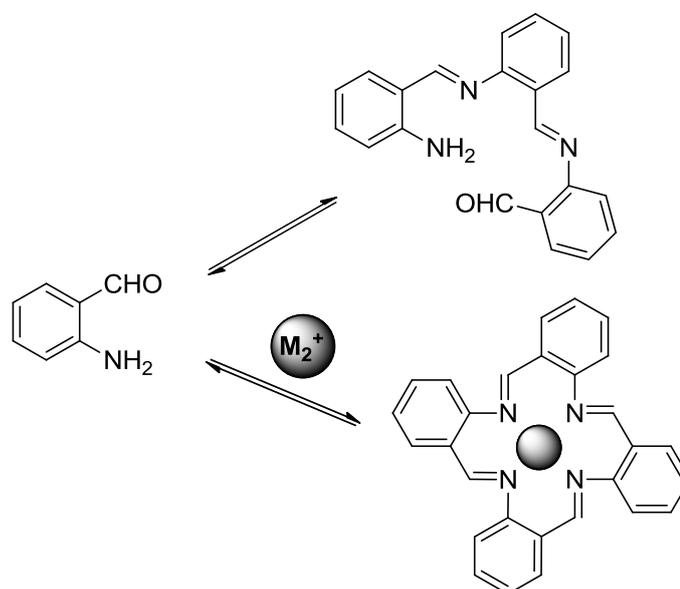


**Scheme 10.** Using DCC to Stabilize the RNA Duplex Formed Between Target **33** and Complementary **34** Incorporating 2'-deoxy-2'-aminouridine (U\*) in Positions 3 and 9.

#### 1.2.4.2 Selection *via* Moulding

Reversible imine chemistry has been used to form cyclic ligands for transition metals for several decades. Addition of a template would direct the synthesis of soluble cyclic adducts from insoluble polymers and shift the condensation equilibrium to completion. For example, in the absence of a metal template, *o*-aminobenzaldehyde self-condenses into a linear trimer (due to an incomplete condensation reaction), but under the influence of metal ions such as

Ni(II) and Co(II), a closed tri- or tetradentate macrocyclic ligands are formed (Scheme 11).<sup>47</sup>



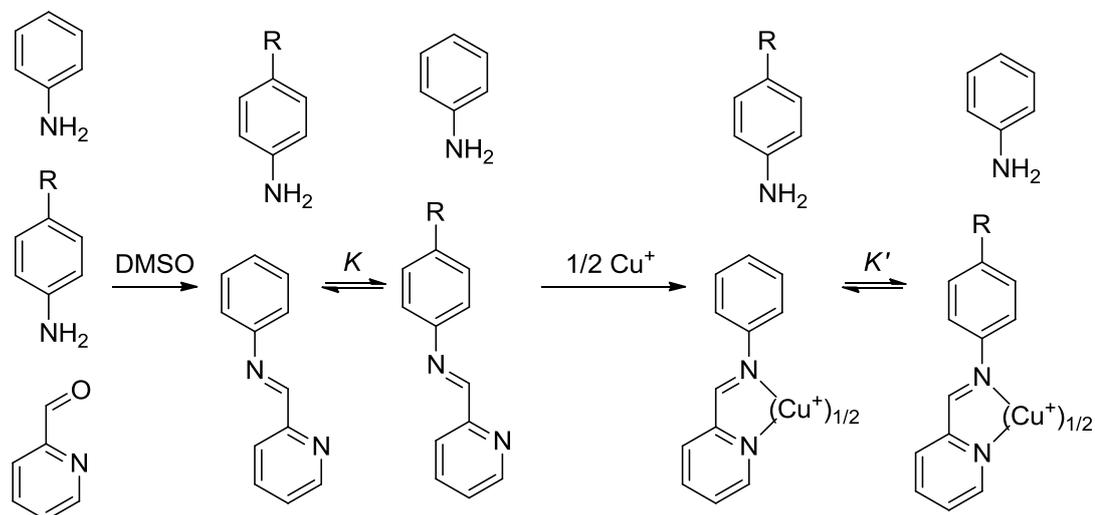
**Scheme 11:** One of the Earliest Examples of Thermodynamically Templated Imine Synthesis.

Lehn and co-workers have provided insight into the thermodynamic and kinetic feature of imine formation, using scandium and lanthanide cations as transimination catalysts in organic medium.<sup>48</sup> Sc(OTf)<sub>3</sub> is a powerful and general Lewis acid in organic media, it has shown acceleration of the reaction by up to 10<sup>5</sup>-fold, which is more effective compared to Brønsted acids at same concentrations. Catalysis by H<sup>+</sup> is less effective, especially with the most basic amines, as protonation reduces the reactivity of the amine. Scandium mediated catalysts are most effective in solvents with low dielectric constant, whereas coordinating solvents greatly reduces the catalytic effect. Lanthanide mediated catalysts have resulted in the most nucleophilic amines forming the thermodynamically most stable imines. The mechanism involves the formation of a termolecular amine-imine-metal

ion complex, resulting in a nucleophilic attack of the amine in the rate determining step. Amines which strongly coordinate will react most efficiently.

Various metal ions have been used in DCC to identify the most suitable imine ligand to synthesize the most efficient metal - ligand complex. Examples of some metals include B,<sup>49</sup> Zn,<sup>33, 34, 50, 51</sup> Cd<sup>34, 52</sup> and Ba.<sup>52</sup> Our primary interest is with Cu(I) and (II) ions, as the Clark group has been extensively working with this metal for many years to catalyse atom transfer radical cyclization (ATRC) reactions. Using our “machine” we may be able to develop an efficient ligand to improve ATRC reactions (Chapter 5).

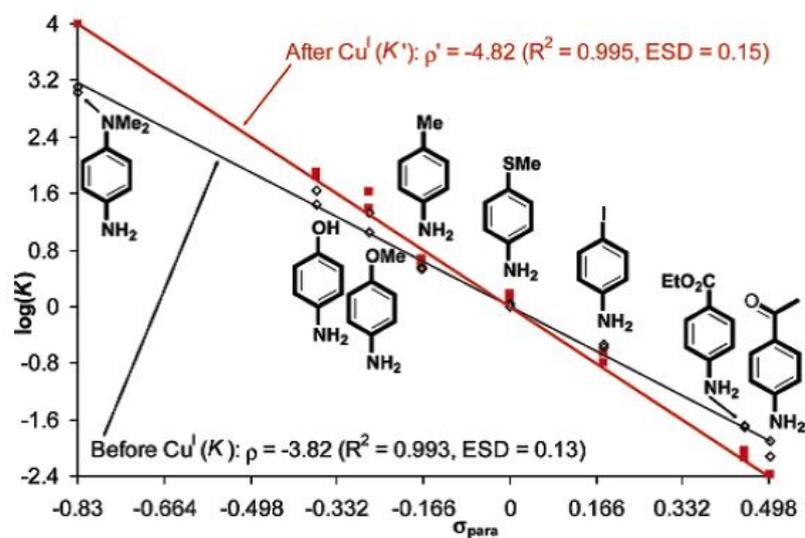
Nitschke and co-workers demonstrated the technique of subcomponent self-assembly, a process where intra-ligand (covalent (generally C=N)) bonds form at the same time as metal-ligand (non-covalent) bonds.<sup>53,54</sup> They examined how electronic effects may provide a thermodynamic driving force for imine exchange within Cu(I)-imine complexes.<sup>55</sup>



**Scheme 12.** Formation of Equilibrium Mixtures of Imines from Unsubstituted and 4-Substituted Anilines with Pyridine-2-carbaldehyde (left); Reactions of these Imines with Copper(I) to Form New Equilibrium Mixtures of Imine Complexes (right).

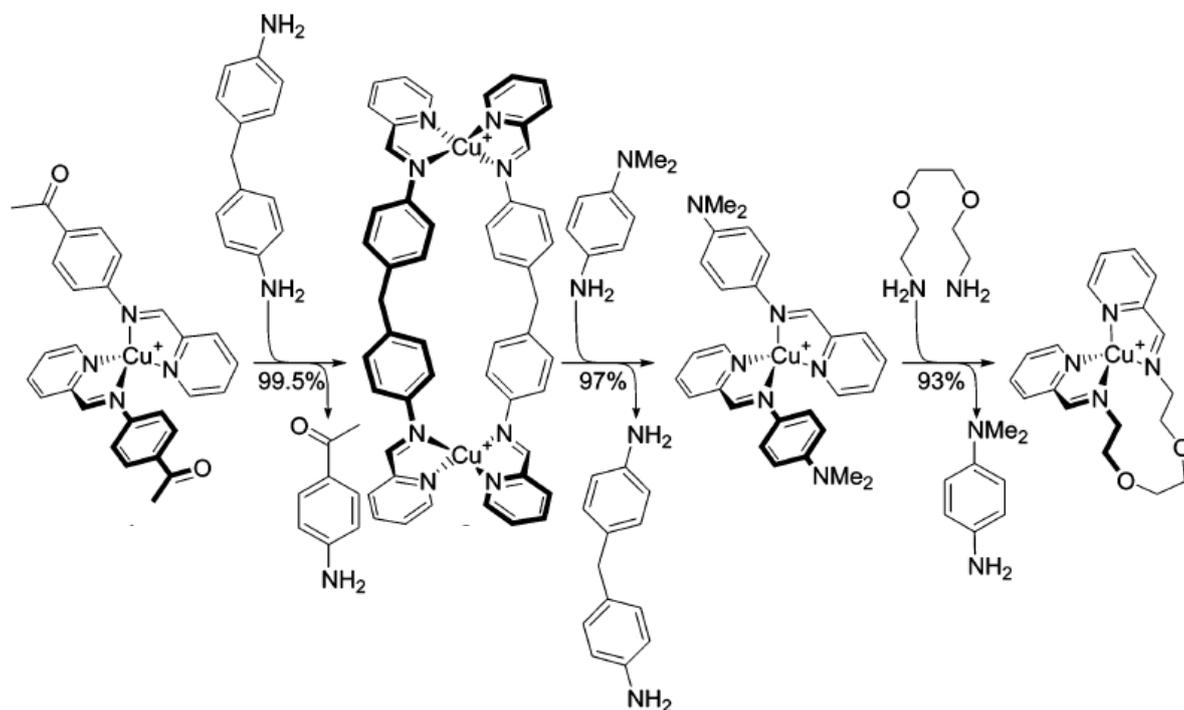
Working with unsubstituted and 4-substituted anilines, a relationship was found between the equilibrium constant of an imine exchange reactions and the electron-donating ability of the aniline's 4-substituent which was measured by Hammett  $\sigma_{\text{para}}$  parameter. This showed that electron rich anilines displace electron poor anilines, this transformation can be performed in the same reaction flask with imine exchange step generating more than 95% yield. Creating a wide range of electron poor aniline complexes and then adding one electron-rich aniline resulted in a quantitative displacement of all electron poor anilines giving just one imine complex.

The equilibrium constant  $K$  for the two imines and two amines shown in scheme 2 (left) were determined by integrating the  $^1\text{H}$  NMR resonances. The addition of copper (I) tetrafluoroborate resulted in quantitative formation of a mixture of imine complexes (Scheme 12, right) for which a new equilibrium was measured as equilibrium constant  $K'$ . These data were used to generate a Hammett plot (Figure 8). This showed that the incorporation of electron-rich aniline will strongly stabilize both imine ligands and copper (I) complexes. The cationic metal complex was more stabilized by the electron donating groups than the simple aniline.



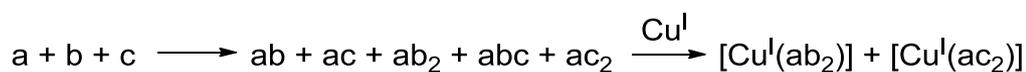
**Figure 8:** Hammett Plots for the Thermodynamic Competition of Anilines to Form Imines (Scheme 12) in the Presence and Absence of Copper(I), Including the Linear Regressions used to Obtain  $\rho$  and  $\rho'$ .

Structural complexity through subcomponents was introduced by incorporating substituted anilines into larger molecules shown by Scheme 13. In the same reaction vessel, three distinct subsequent transformations were carried out. The aniline  $\sigma$  values were used as driving forces for the first two substitutions. The last reaction was pushed forward by adding a more chelating ligand. Substituent electronic effects can be readily employed to drive ligand subcomponent substitution and may also be used to control and shape the constitution of dynamic combinatorial libraries.



**Scheme 13.** A One-Pot Synthesis of Transformations, Using Substituent Effects and the Chelate Effect to Provide Driving Forces for Imine Exchange.

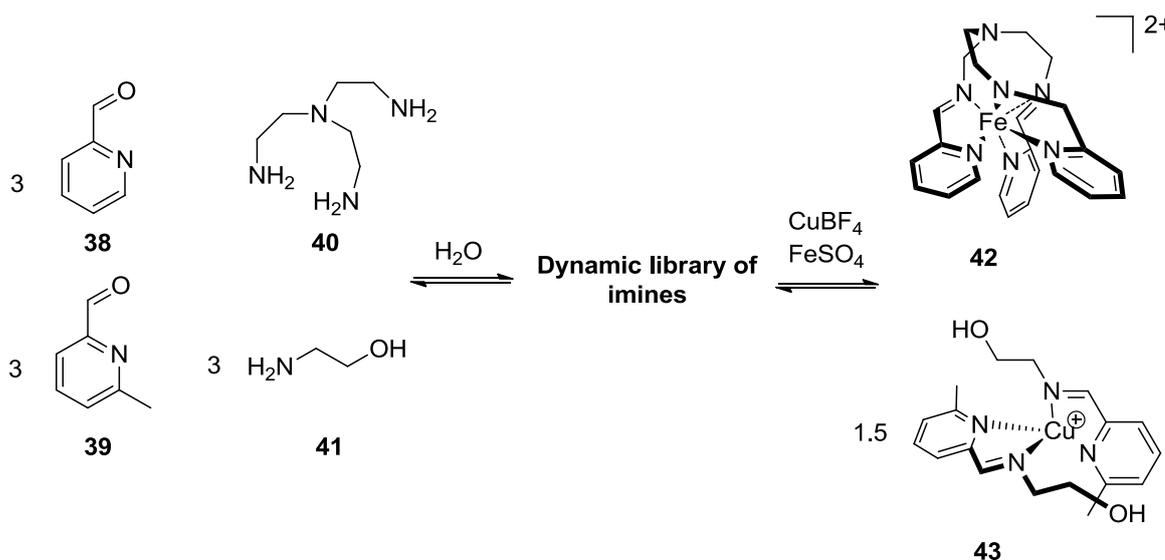
With the realization of copper(I)-imine complexes undergoing ligand substitution, they worked on a simple three component system of imine DCL, which combined to give five possible ligands in the absence of copper(I) ions (Equation 1).<sup>53</sup> In the presence of copper(I) ions, the ligands had performed thermodynamic self-sorting process amplifying the most successful ligand, and eliminating mixed ligands from the system.



**Equation 1**

In 2006, they presented a more complex self-organizing system, in which a larger dynamic combinatorial library of potential imine ligands self-assemble in the presence of copper(I) and iron(II) ions.<sup>56</sup> Mixing pyridine-2-carbaldehyde (**38**), 6-

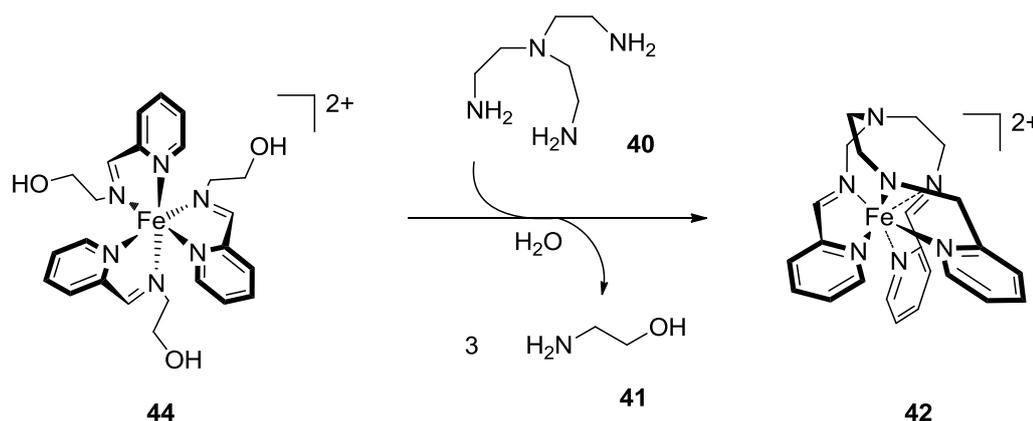
methyl-pyridine-2-carbaldehyde (**39**), tris(2-aminoethyl)amine (**40**) and ethanolamine (**41**) gave a dynamic library of imines (Scheme 14). With the addition of copper(I) tetrafluoroborate and iron(II) sulphate, the dynamic mixture of imines collapsed within 12 hours at 323K to give thermodynamically stable complexes of **42** and **43**.



**Scheme 14:** The Formation of a Dynamic Combinatorial Library of Ligands, and the Collapse of this Library Following the Addition of  $Cu^I$  and  $Fe^{II}$  ions.

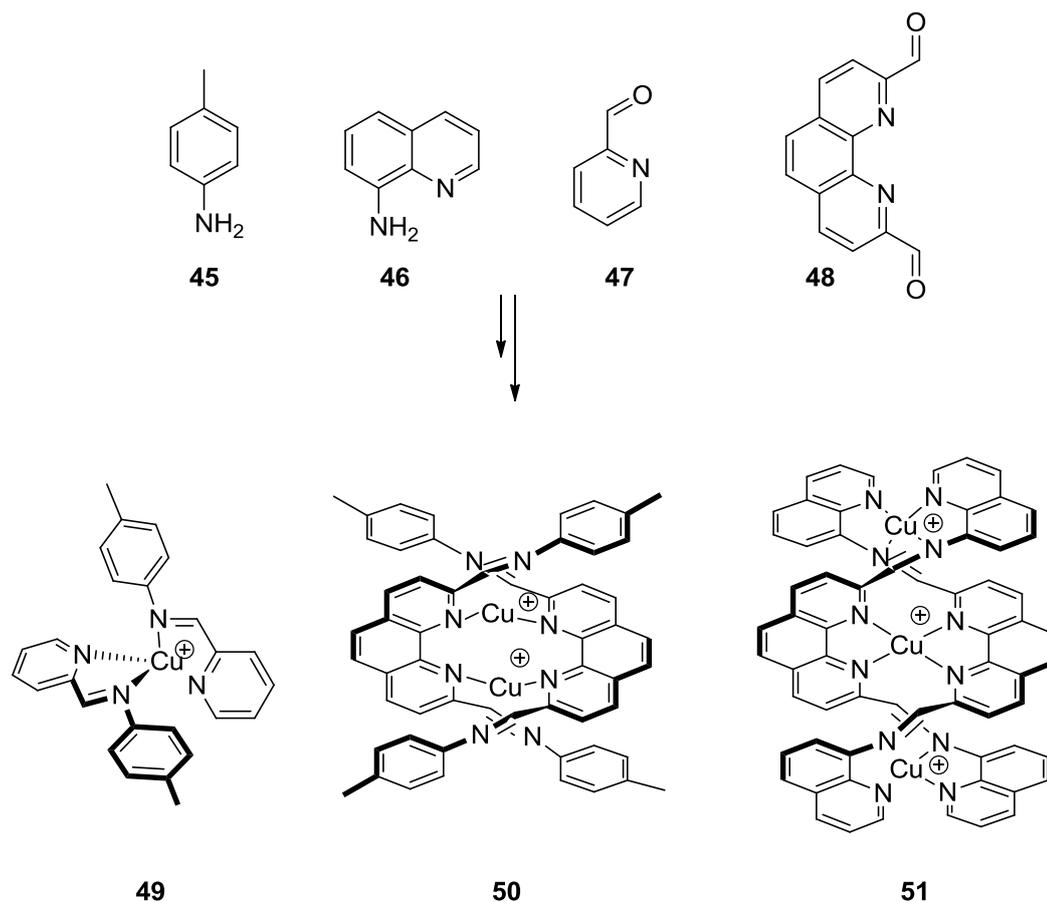
By further investigations, three distinct preferences observed by copper and iron were concluded; (1) Copper(I) ions preferred methylated aldehyde **39** than **38** in a pseudo-tetrahedral complex, this was due to the electron-donating methyl group on B, which would allow greater stabilization of the cationic copper(I) centre. (2) Iron(II) ions preferred triamine **40** pseudo-octahedral complexes over monoamine **41**. They managed to displace monoamine **41** by exposing compound **44** with an equimolar amount of triamine **40** in aqueous solution (Scheme 15). The displacement of three equivalents of **41** with one equivalent of **40** provided the entropic driving

force of greater than  $22 \text{ kJ mol}^{-1}$  resulting in the substitution of ligand **41**. It was later proved that the chelate effect plays an essential role in stabilizing complex **42** against subcomponent substitution.<sup>57</sup> (3) Iron(II) ions strong preference to incorporate **38** in preference to **39** was possibly due to the high energy penalty paid for the steric clash in iron(II) pseudo-octahedral type complexes.

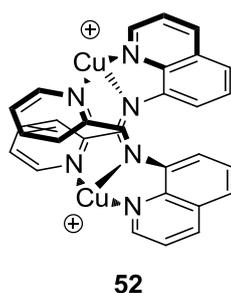


**Scheme 15.** The Choice of Iron: The Entropically Driven Displacement of Monoamine **41** by Triamine **40**.

By controlling the stoichiometry of the four subcomponents, Nitschke and co-workers were able to produce three products at any relative proportions, in which the synthesis of these products were directed by the rules of valence satisfaction (Scheme 16).<sup>58</sup> The smallest possible structures will be formed where all copper(I) ions tetracoordinate and all nitrogen atoms are bound to copper(I). Though imine products formed from dialdehyde subcomponent **48** generates di or trinuclear helicates, as they are poorly configured to chelate a single copper(I) ion pseudotetrahedrally.



**Scheme 16.** By changing the stoichiometry of **45**, **46**, **47** and **48**, any of complexes **49**, **50** and **51** can be amplified.



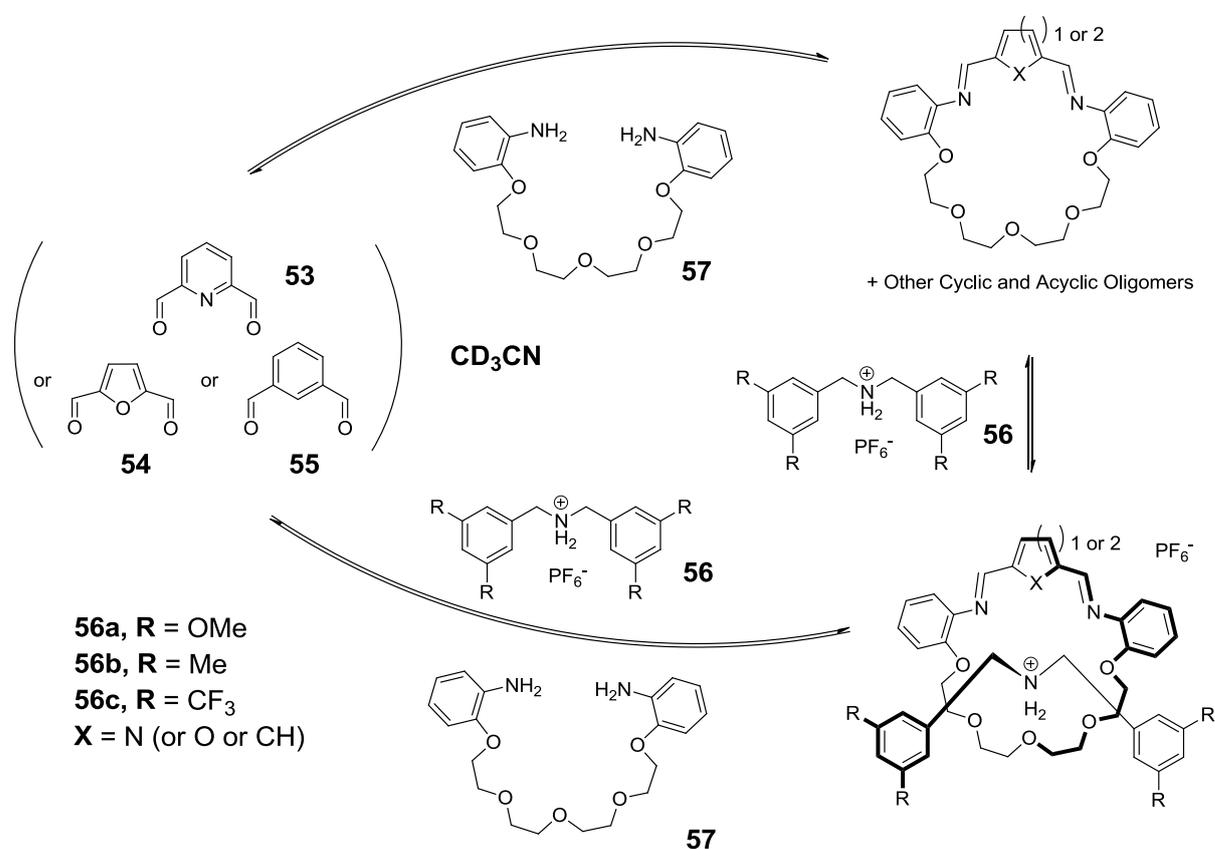
Theoretically, a reaction of two aldehydes and two amines in stoichiometric amounts would result in four possible imine products, but with the addition of Cu(I) ions, complexes **49**, **50** and **51** were generated, only synthesizing three of the possible imines. The imine product formed by reacting **46** with **47** which would generate structure **52** was forbidden as the Cu(I) centres were not tetrahedrally coordinated. Overall, their results demonstrated that the observed products cannot be predicted by the thermodynamic stability of individual imine

products, as it largely relies on the rules of valence satisfaction which must be applied to the system as whole.

Using DCC to synthesize macrocycles such as rotaxanes has been of great interest. Macrocycles are a subclass of cyclic compounds, and only a small number of macrocycles exist in nature, therefore, it is very important to develop efficient routes to synthesize these molecules. The synthesis of most macrocycles are unstrained, therefore their enthalpy of formation is comparable to that of five- or six-membered rings. There are no thermodynamic arguments against the formation of unstrained macrocycles, but the kinetics is different. The synthesis of a large macrocycle is difficult, as the remote ends have to connect. Formation of a macrocycle is an intramolecular process which competes with the intermolecular process of oligo- or polymerization, hence most cyclization mixtures will contain macrocycles, oligomers and polymers in a dynamic library, but by molecular recognition, the macrocycles can be amplified, as macrocycles possess a well-defined cavity, and with the correct guest that binds complementary into this cavity, amplification of that macrocycle can be achieved.<sup>59</sup>

Rotaxanes can be formed in several ways, such as clipping and threading followed by stoppering. Syntheses of macrocycles are at low priority to this project. Meyer *et al.* presented a detailed review on macrocycles.<sup>60</sup> But an example of the first thermodynamic synthesis of rotaxanes by imine DCL's was demonstrated by Glink *et al.* in 2001 by the clipping method (Scheme 17).<sup>61</sup> A library of macrocycles along with linear products were synthesized by the condensation reaction between tetraethylene glycol bis(1-amino-phenyl)ether (**57**) and 2,6-diformylpyridine (**53**). Analysis by <sup>1</sup>H NMR spectroscopy revealed 50% of starting components condensing into a 1:1 reaction to form the [24]crown-8-macrocycle while the other 50% resulted

in high order macrocycles and other linear product. Addition of one equivalent of dumbbell bis(3,5-dimethoxybenzyl)ammonium hexafluorophosphate (**56a**) resulted in a sharp increase in [2]rotaxane shown by  $^1\text{H}$  NMR and fast atom bombardment mass spectrometry (FAB-MS). This amplification of [2]rotaxane was observed because the ammonium centre of the dumbbell acts as a template to aid the formation of [24]crown-8 derivative using weak acid catalysis and bringing stability to the structure through hydrogen bonding. The reaction was frozen using a slight excess of  $\text{BH}_3 \cdot 2,6\text{-lutidine}$  in  $\text{CD}_3\text{CN}$ .



**Scheme 17:** Synthesis of [2]Rotaxanes by Clipping Process.

Soon after, they repeated the experiment,<sup>62</sup> generating a total of nine [2]rotaxanes (Scheme 17). Further studies on these nine compounds revealed that

using dumbbell **56c**, [2]rotaxanes were the most stable. **56a** resulted in [2]rotaxanes to be the least stable. This demonstrated that a more  $\pi$ -electron deficient dumbbell is the most efficient. [2]Rotaxane formed from **55** was the least stable, followed by **53**, while **54** resulted in the most stable macrocycle due to the enhanced basicity of the  $\pi$ -electron stabilized imino and phenoxy units acting as better hydrogen bond acceptors.

So far we have shown the selection of molecules *via* casting and moulding techniques in DCC. In the early stage of this project, implementing selection through casting would be difficult in our ‘machine’, but we could use the idea of moulding in DCC in our ‘machine’ to identify successful imine ligands for ATRC reactions by exposing copper salts to a dynamic library of imines to identify which imines would bind efficiently to the copper metal forming the most stable complexes (see Chapter 5). However, the casting and moulding technique would be difficult to implement in our ‘machine’ for the evolution of a desired coloured imine compound from a DCL of coloured imines; therefore we would be looking at a simpler external physical or chemical stimulus to drive amplification of a desired product.

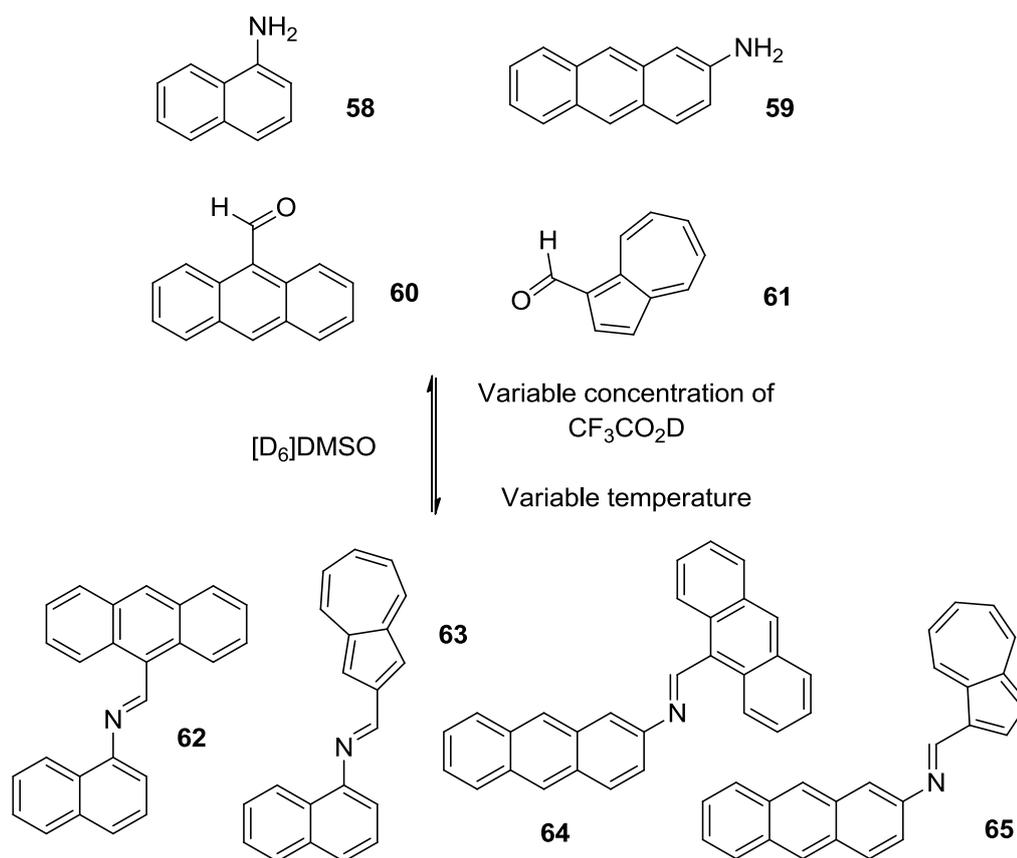
#### 1.2.4.3 Selection through External Physical or Chemical Stimulus

Guiseppe and Lehn had first shown constituent reorganisation and amplification / selection by means of component exchange in a DCL by means of external physical (temperature) and chemical ( $H^+$ ) influence.<sup>63</sup>

In one of their experiments, they took a dynamic set of aromatic imines **62** - **65** which were synthesized by stoichiometric mixtures of amines **58** - **59** and

aldehydes **60** – **61** building blocks (Scheme 18). **58** - **61** possessed different emission properties and, therefore, resulted in imine products with a dynamic emissive library. The equilibrium mixture was treated with variable concentrations of  $\text{CF}_3\text{CO}_2\text{D}$  ( $6.29 \times 10^{-6}$  –  $4.99 \times 10^{-1}$  M) and temperature (298 to 368 K) to observe the selectivity of the system in terms of relative amounts of imine products.

The library was analysed by  $^1\text{H}$  NMR spectroscopy and it was discovered that **62** and **64** predominate in the localised low  $[\text{H}^+]$  / high temperature region, **63** and then **62** predominate towards moderate  $[\text{H}^+]$  as temperature increases, **62** and then **65** predominate over the whole temperature range at moderate and high  $[\text{H}^+]$  respectively.



**Scheme 18.** Dynamic Library of the Four Components **58** – **61** and the Four Constituents **62**

The complexity of the effects had not allowed for a detailed quantitative explanation in terms of structure and mechanism, but their study had successfully shown constitutional recombination of a dynamic library under the effect of acidity, temperature and also the possibility of modulating a given functional property (in this case optical) induced by a specific trigger. Our studies would be expanding on this research and determine a method for detailed quantitative analysis of our imine DCL's. We would be using external physical or chemical stimulus in our 'machine' to evolve an imine of a desired colour from our imine DCL each with a unique UV / Vis absorption spectrum.

Constitutional dynamic polymers, dynamers, are polymeric entities based on monomeric components connected through reversible bonds.<sup>64, 65</sup> Amplification of a given dynamer of DCL can be achieved by stabilizing its microscopic structures. Lehn had shown amplification of a given dynamer of a DCL synthesized using reversible imine bonds under the pressure of self-organization process favouring the dynamer that formed the most stable phase. These dynamers would stabilize or destabilize influenced by an external physical stimuli (neat or solvent).<sup>66</sup>

Polymers **70** – **73** were connected through imine bonds and were synthesized using amines (**66** and **67**) and aldehydes (**68** and **69**) (Scheme 19). The dynamic behaviour of these polymers was demonstrated by the occurrence of ligand exchange and recombination. They had blended together homopolymers **70** and **71** in CDCl<sub>3</sub> with equal molar ratio and 1% pentadecafluorooctanoic acid (catalyst). Analysis of the mixture after 24h by <sup>1</sup>H NMR spectroscopy had shown the formation of two new connections, **72** and **73** that had resulted from recombination of all four polymers with polymer ratio of **70** : **71** : **72** : **73**; 3 : 3 : 2 : 2. When **70** and **71** were blended together in neat conditions for 24h at 80°C, two new connections of **72** and **73** were

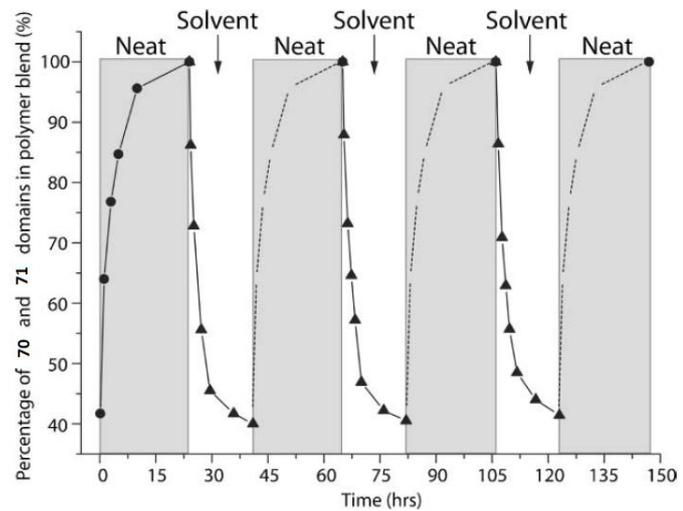
observed, but **71** and **72** were not observed with polymer ratio of **70 : 71 : 72 : 73**; 0 : 0 : 5 : 5. Successive solvent and neat cycles of the blended mixture **70** and **71** by evaporation had shown

continuous reversible switching of mixtures at expected ratios without apparent fatigue (Figure 9).

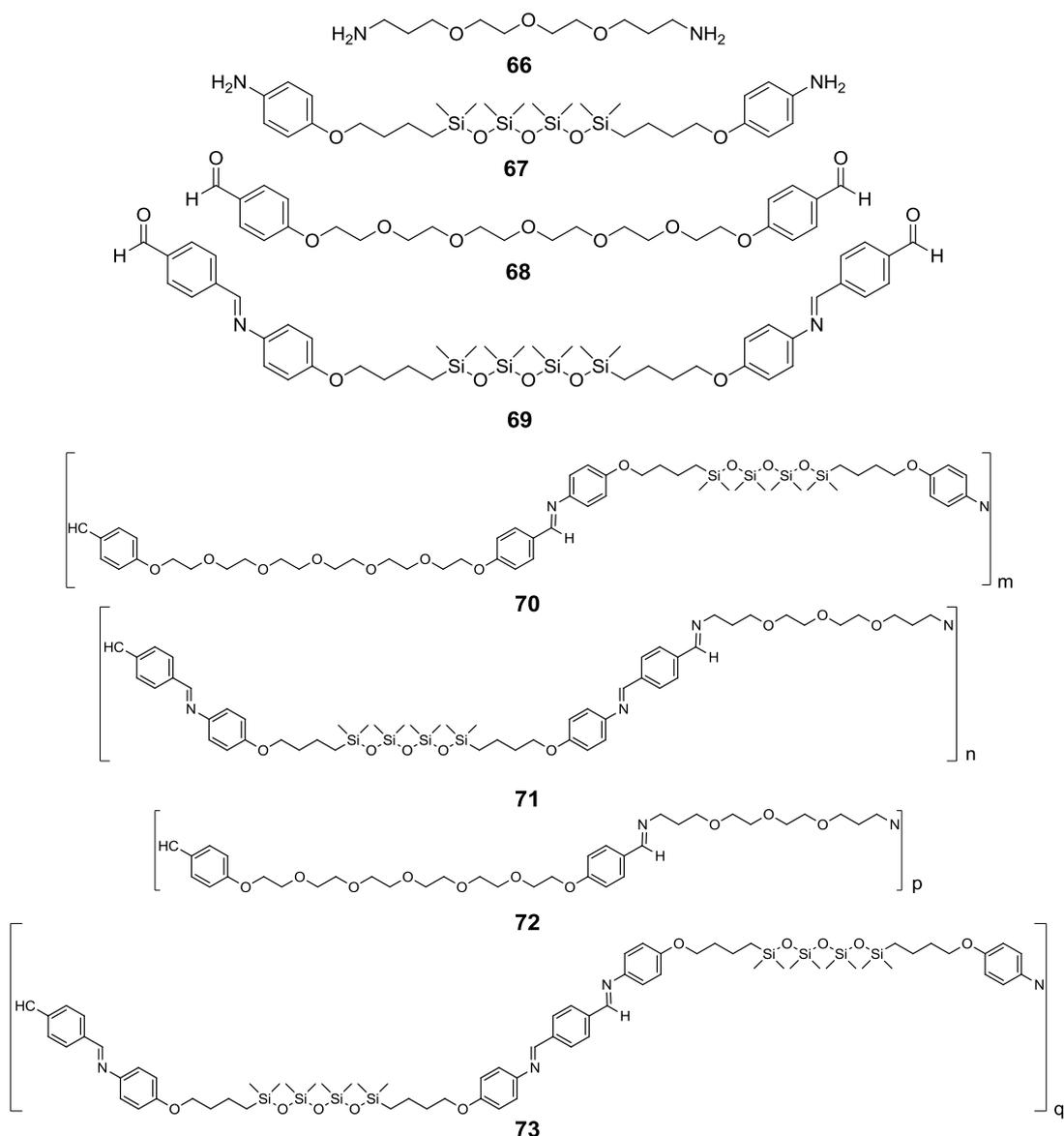
Therefore under neat conditions the dynamic system had reshuffled and

exchanged to components in a different way from the solution condition. This was due to the

strong driving force of the only crystalline polymer **73** which had shifted the equilibrium of the CDL towards itself in neat conditions and, as a consequence, generated also agonistically the copolymer **72**.



**Figure 9:** Constitutional Dynamic Interconversion between the Polymer Blends in Solution and in Neat Conditions.

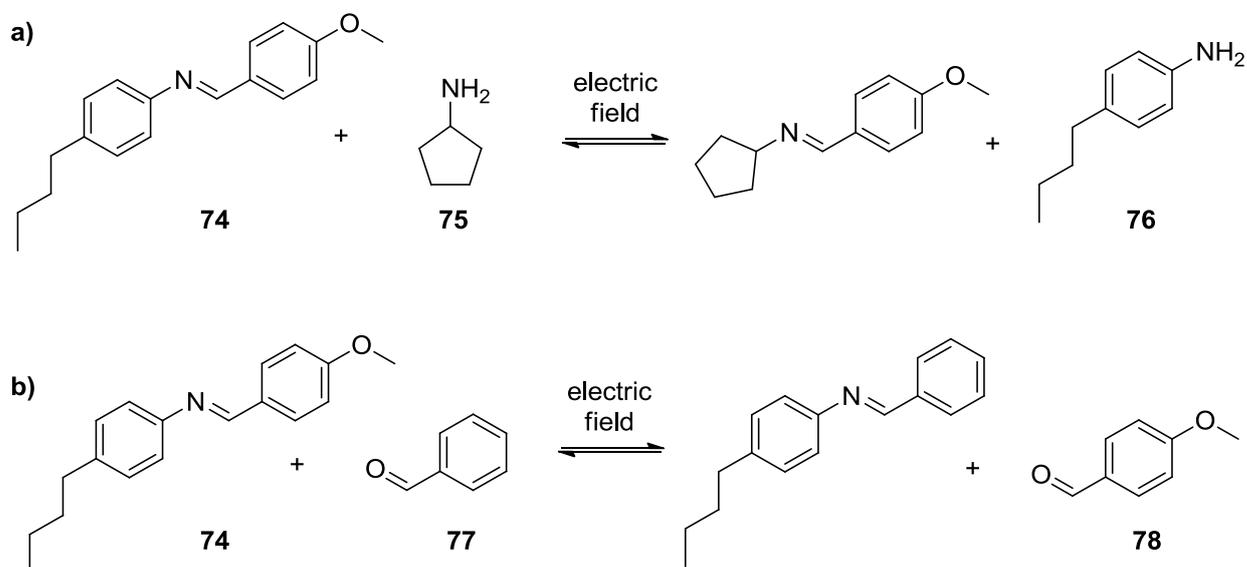


**Scheme 19:** Structure of Diamines **66** and **67**, of the Dialdehydes **68** and **69** and of the Polymers Obtained by Polycondensation: **70** (**68** + **67**), **71** (**69** + **66**), **72** (**68** + **66**) and **73** (**69** and **67**).

Fujii and Lehn had also shown that dynamers generated by condensation polymerisation through the reversible formation of imine bonds can undergo driven evolution under the double effect of donor-acceptor stacking and metal ion binding with response to external factors. In the presence of alkaline metal ions, they were

able to show adaptation behaviour associated with specific constitutional changes with different optical signals showing specific positioning of donor and acceptor units within the folded dynamer.<sup>67</sup>

Constituent reorganisation and amplification/selection by means of component exchange in a DCL with the influence of an electric field was recently shown by Guiseppone and Lehn.<sup>68, 69</sup> An electric field was applied to liquid crystalline type imines with a negative dielectric anisotropy such as *N*-(4-methoxybenzylidene)-4-butylaniline (**MBBA**, **74**) (Scheme 20). In the presence of compounds that do not participate in the liquid crystalline phase formation of the imine (e.g. an alcohol such as cyclopentanol) are expelled from the liquid crystal with the treatment of an electric field.



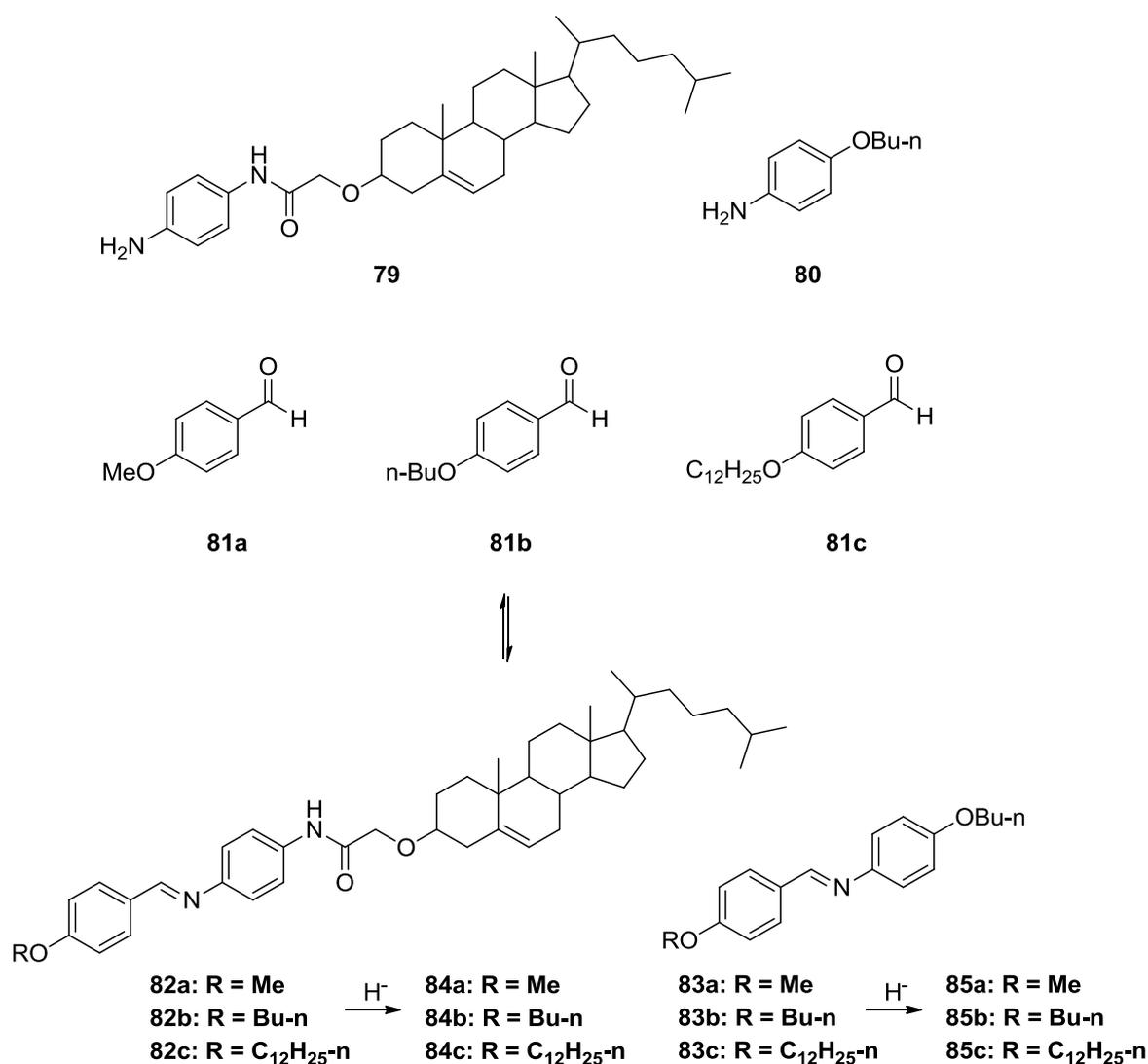
**Scheme 20.** Principle of Constitutional Reorganisation by Component Exchange of MBBA (**74**) with Cyclopentylamine (**75**) or Benzaldehyde (**77**) in the Presence of an Electric Field.

Whereas in the presence of compounds such as cyclopentylamine **75** that react reversibly with the liquid crystalline phase forming an imine, component exchange by transamination and the release of **76** was observed. They also investigated whether an exchange and release of an aldehyde / ketone part of the imine reaction was possible as amines are less interesting as bioactive compounds to be released. In the presence of an electric field and trace amounts of water, aldehyde component exchange **77** was observed releasing **78**, while exchange of ketone component failed. Component exchange of a DCL with the influence of an electric field could one day allow construction of devices that would allow accurate release of components in response to the strength of the electric field, hence allow efficient release of a broad variety of biologically active compounds in the area of life sciences.<sup>70</sup>

#### 1.2.4.4 Selection through Phase Change

Work carried out on selection through phase change using a dynamic imine library is very limited. An example was shown by Li and co-workers.<sup>71</sup> They demonstrated gelation-driven component selection of cholesterol moieties that were connected to an aromatic or other rigid unit by a flexible linker. They exposed cholesterol-appended aniline **79** and cholesterol-free aniline **80** to aldehydes **81a** – **81c** to form a dynamic library of imines **82a** – **82c** and **83a** – **83c** in protic solvents (Scheme 21). Individual studies of these imines had shown that cholesterol-free aniline based imines (**83a** – **83c**) did not gelate, while cholesterol-appended aniline based imines (**82a** – **83c**) gelled at room temperature. For quantitative analysis, the imines were reduced to amines by NaBH<sub>3</sub>CN generating **84a** – **84c** and **85a** – **85c**. The different self-assembly behaviours of the two sets of imines (**82a** – **82c** and **83a**

– **83c**) allowed them to investigate their expression in gel and solution phases. In a five component system **79**, **80** and **81a** – **81c**, they observed that even though the electron rich butoxyl group of **80** was stronger than the amide group **79** in promoting the condensation reaction to the corresponding imines, the formation of the gel phase of products **82a** and **82b** were favoured. Products **82c** and **83c** were absent due to the precipitation of **82c** during the reaction. Kinetically imines **83** were more favoured, but enrichment of **82** over time had confirmed the amplification of **82** by the reversible feature of the imine bond through the gelation process.



**Scheme 21.** Gelation-Driven Component Selection of Cholesterol Moieties.

### 1.3 Summary

The development of our ‘machine’ would allow us to take small organic / inorganic building blocks and use them to prepare any theoretical compound with any theoretical property that is determined by the ‘machine’. For this ‘machine’ to work, one of the essential components required are organic building blocks that can reversibly react under various conditions until a product with a desired property has been evolved.

We here at Warwick are to use DCC to generate a library of imine components with a specific property that would allow us to prove that such ‘machine’ can be developed. The beauty of DCC is that it allows us to access a wide range of substances generated by a small library of molecules without having to synthesize each molecule individually, which are in equilibrium with each other. We have shown that imine DCL’s have been developed where in the addition of a suitable target, such as a biological enzyme, metal ions, or by external or physical triggers, the most effective members of the library can be amplified. As these are products of reversible reactions, if not satisfied, the product can be recycled back to starting components.

As a proof of concept, we will use this same approach by designing a dynamic imine library for our ‘machine’. The machine will have a sensor to measure a UV / Vis absorbance of the components. With subject to external physical stimulus, compounds which are amplified with the desired absorbance would be isolated, whereas products that fail to have the correct absorbance are recycled and resubmitted to the process under different conditions.

While the ‘machine’ is being developed, we also aim to develop new imine ligands which have been used with Cu(I) to catalyse well known atom transfer radical cyclisations. This has been studied by the Clark group for several years.

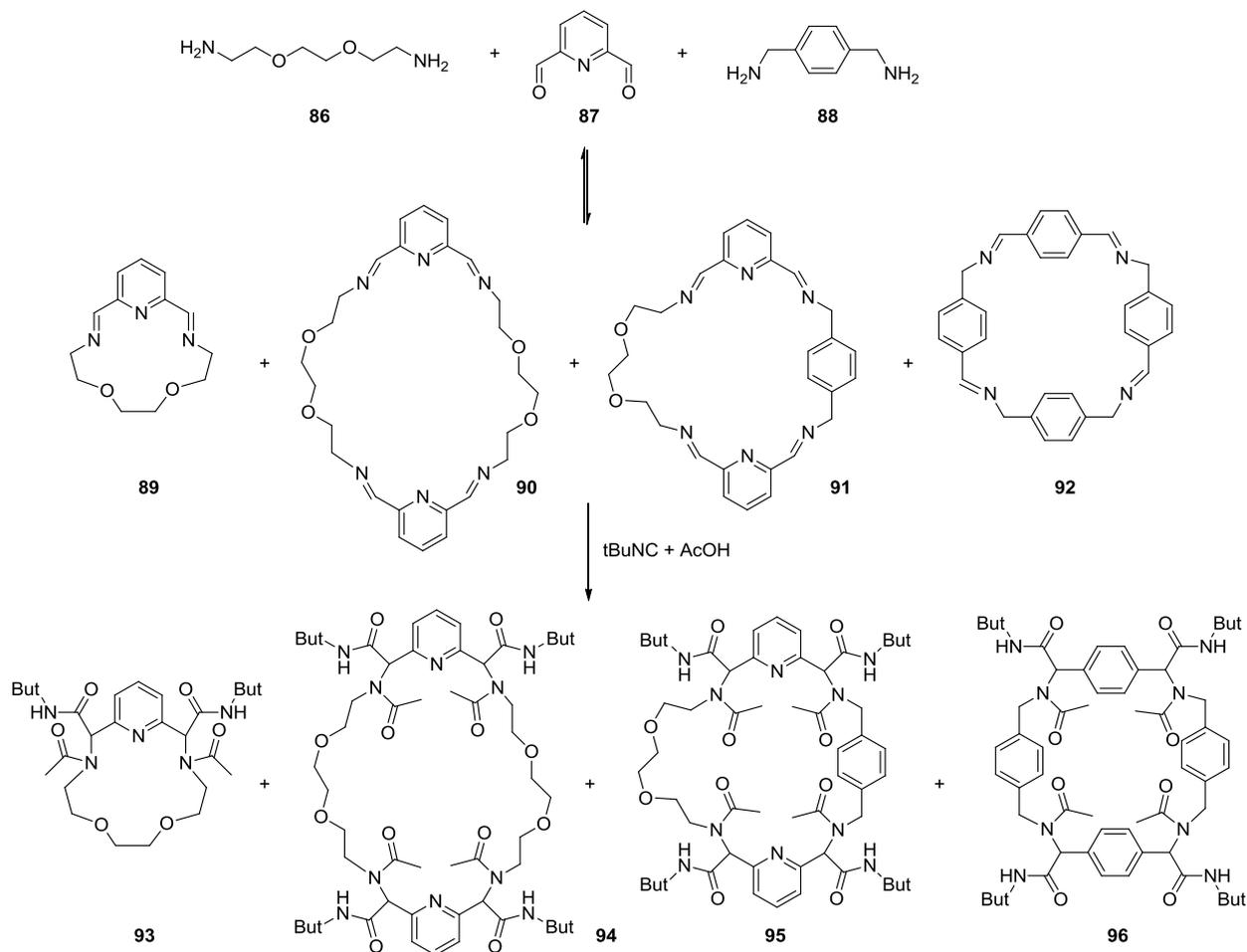
## 2.0 Determining a Suitable Analytical Method for our Imine DCLs

### 2.1 Introduction

Imine bonds are unstable under the conditions of many standard purification techniques and therefore most commonly the imine library components are reduced to amines then analysed by HPLC (previously shown in chapter 1). An alternative method is to stabilize the library by using the Ugi freezing method.<sup>72</sup> Leon and co-workers had developed a novel approach to freezing the imine exchange reactions in a DCL by using acid and isocyanide components. They demonstrated freezing the imine exchange process by Ugi four component reaction (Ugi-4CR). Ugi-4CR is the one pot condensation of a primary amine, an oxo component, a carboxylic acid and a isocyanide to afford a *N*-substituted peptide backbone, a multicomponent reaction (MCR) type II which involves a sequence of reversible steps followed by irreversible steps.

Dialdehyde **87** was exposed to diamine **86** and **88** with or without the presence of Mg<sup>II</sup> or Ba<sup>II</sup> ions (Table 2). The relative formation of macrocycles **89** – **92** was then examined. They discovered that exposing these macrocycles to metal ions at room temperature for long periods resulted in formation of some precipitates, and due to these instabilities of imine bonds, a quantitative and qualitative analysis of this DCL by HPLC would not be possible. Therefore, with the addition of a threefold excess of isocyanide and carboxylic acid, the imine DCL was frozen to amine based macrocycles **93** – **96** and then was able to analyse the mixtures by HPLC (Table 2). This process is highly efficient to switch off the imine exchange

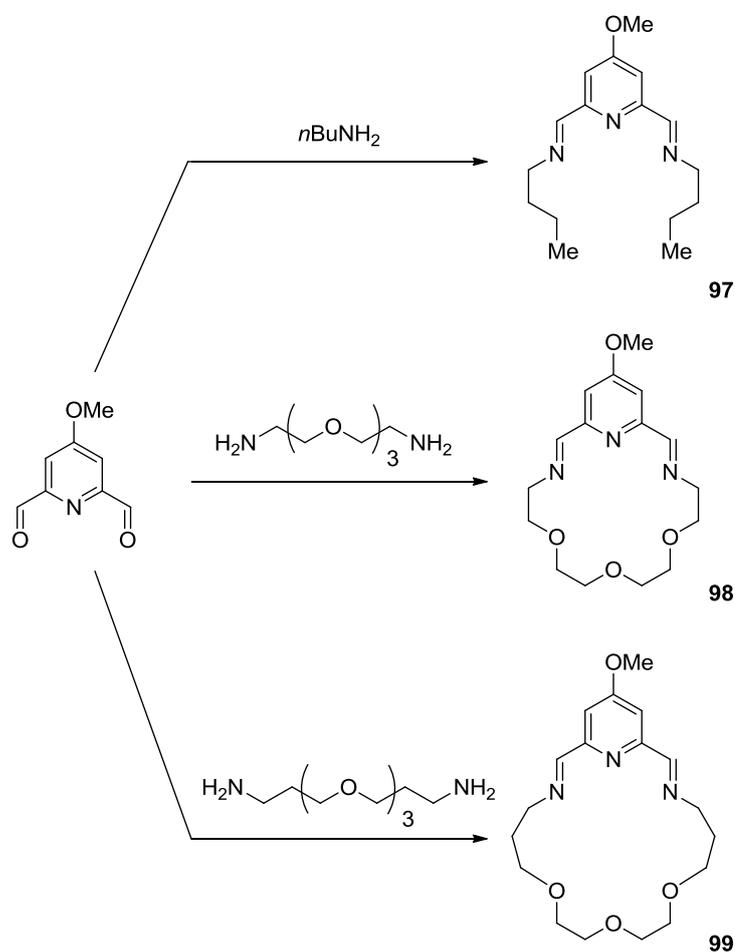
and further investigations proved successful in even complex macro(multi)cycles although its scope is not limited to macrocycles.<sup>72</sup>



| Product            | Yields (%) |    |    |    | Total |
|--------------------|------------|----|----|----|-------|
|                    | 93         | 94 | 95 | 96 |       |
| <b>No template</b> | 16         | 6  | 2  | 13 | 37    |
| <b>MgII</b>        | 69         | 7  | 6  | 3  | 85    |
| <b>BaII</b>        | 8          | 23 | 29 | 26 | 86    |

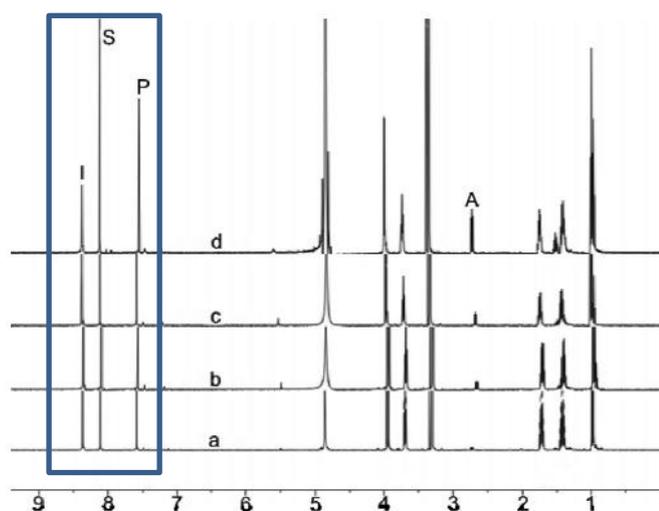
**Table 2.** Results of the Ugi-4CR-Based Quenching Approach of DCLs Equilibrated without and with Metal Ions.

The concept of our project involves multiple quantitative and qualitative analysis of the DCL while maintaining the imine exchange process and the reversibility step of the components. This means that freezing the imine DCL would not be suitable for our system. By using HPLC, we may lose quantitative and qualitative analysis of our imine DCL and, therefore, one direct analytical method that could be used is  $^1\text{H}$  nuclear magnetic resonance (NMR) spectroscopy.



**Scheme 22.** Stability Study of Imino Macrocycles **97** – **99** in Water.

Saggiomo and Lüning studied the stability of imino macrocycles **97**, **98** and **99** in water (Scheme 22), during their research, one of their tasks was to determine a suitable analytical method to analyse their imine DCL.<sup>73</sup> They discovered that components **98** and **99** could be detected by ESI mass spectroscopy but **97** remained undetected in addition the inability to carry out quantitative measurements by ESI mass spectrometry was unfavourable. This forced them to look for a different analytical method and chose to analyse their imine library by <sup>1</sup>H NMR spectroscopy. Analysis of the imine library by <sup>1</sup>H NMR spectroscopy had shown clearly distinguishable sharp singlet imine peaks of each individual product between 7.5 – 8.5 ppm. Also quantitative measurements were possible with the use of an internal



Spectra 1

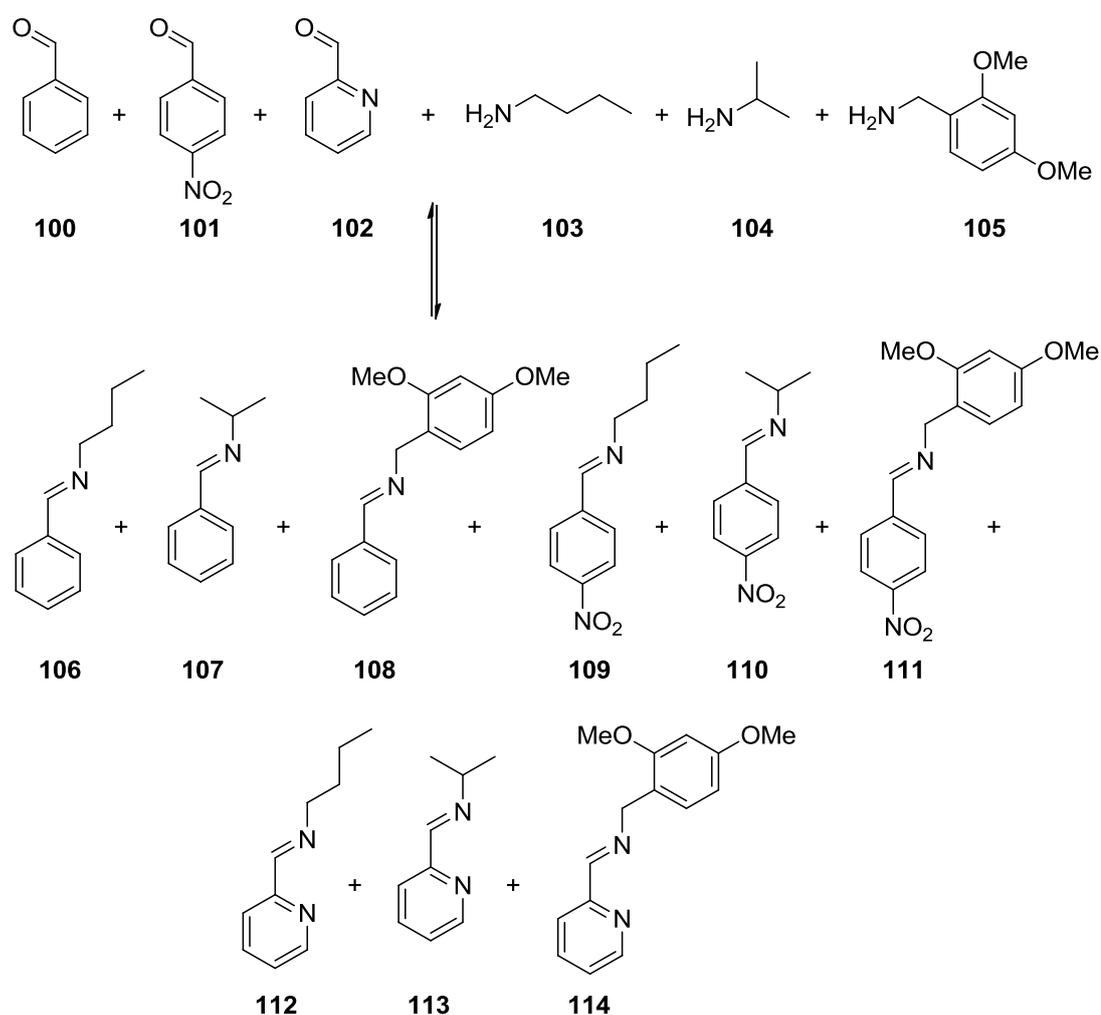
standard added to a library of manageable number of products (Spectra 1).

As previously stated, we have chosen to look at imine DCLs. Reacting multiple aldehydes and amines in one-pot will create a DCL of imines. We will be looking at changing conditions of this DCL to enhance the concentration of one product based on the desired property. Our ultimate aim is to evolve a selected imine of desired colour from a DCL, in a ‘machine’ equipped with a UV / Vis sensor to

prove such system can be developed. But, before we add various aldehydes and amines in one-pot and hope for the desired colour to evolve, we need to first analyse this DCL outside the 'machine' to understand the reaction. For this we require a suitable analytical method that could accurately detect 15 components in a mixture (three aldehydes, three amines resulting in nine imine products). For our method of characterisation and monitoring of the reaction outside the 'machine', we chose NMR spectroscopy. Before we work on synthesizing a DCL of complex coloured imines, we need to test out if  $^1\text{H}$  NMR spectroscopy would be suitable to characterise mixtures of multiple components.

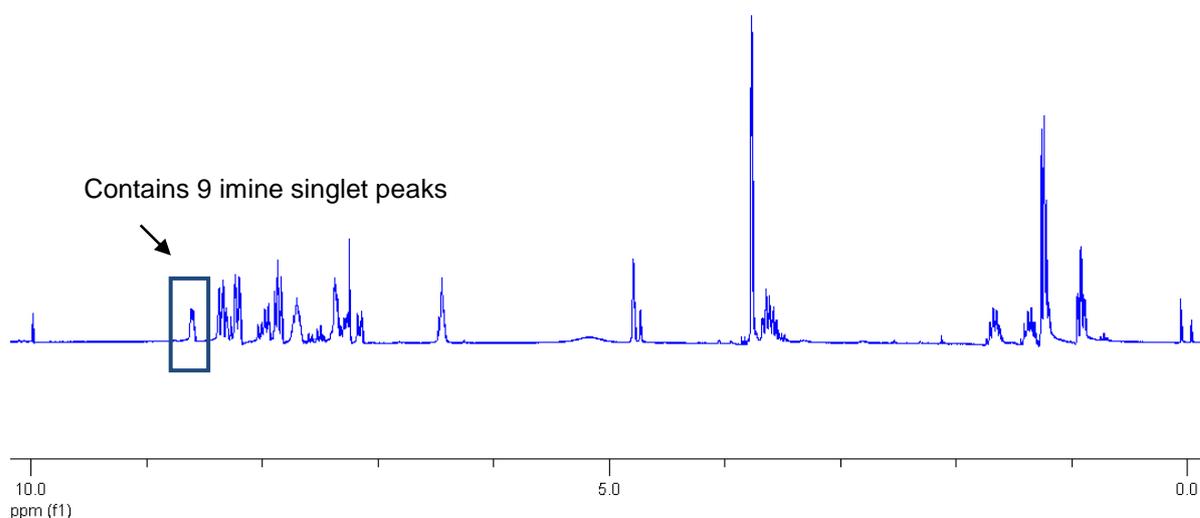
## 2.2 Results and Discussion

An imine can be synthesised by the nucleophilic addition of an amine to a ketone or aldehyde giving a hemiaminal followed by an elimination of water to yield the imine. Three aromatic aldehydes and three primary amines were chosen to synthesize a combination of nine imines. Benzaldehyde is the simplest representation of an aromatic aldehyde (**100**), 4-nitrobenzaldehyde (**101**) contains an electron withdrawing nitro group and 2-pyridinecarboxyaldehyde is a heterocyclic compound (**102**). *N*-butylamine (**103**) and *i*-propylamine (**104**) were chosen, the latter being more sterically hindered and 2,4-dimethoxybenzylamine (**105**) was chosen as an aromatic amine with two electron donating methoxy groups making the nitrogen more nucleophilic (Scheme 23).



Scheme 23. A Library of Simple Imines 106 - 114.

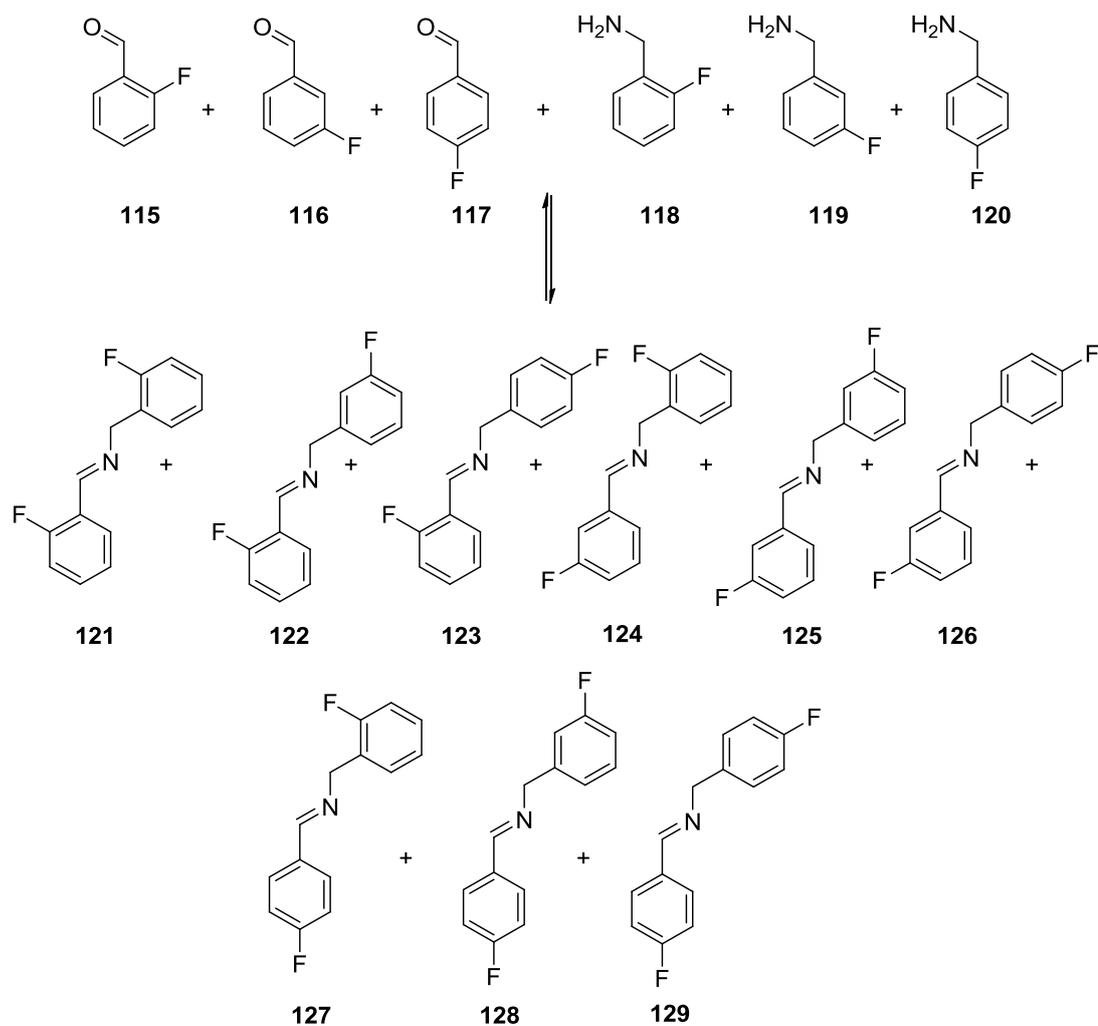
Our initial aims here were to see if NMR spectroscopy would allow us to characterise the mixtures of multiple imine products in one-pot. While analysis by NMR was satisfactory when following a 2 x 2 matrix (100, 101, 103 and 104), it was not sufficient to follow a 3 x 3 reaction matrix due to the multiple overlapping of imine and aromatic peaks (Spectra 2). Of course we could redesign the components so that each had a distinct  $^1\text{H}$  NMR but this would defeat the purpose of utilising ‘any’ imine in our ‘machine’.



### Spectra 2. $^1\text{H}$ NMR Spectra of Imines **106** - **114** in One-Pot

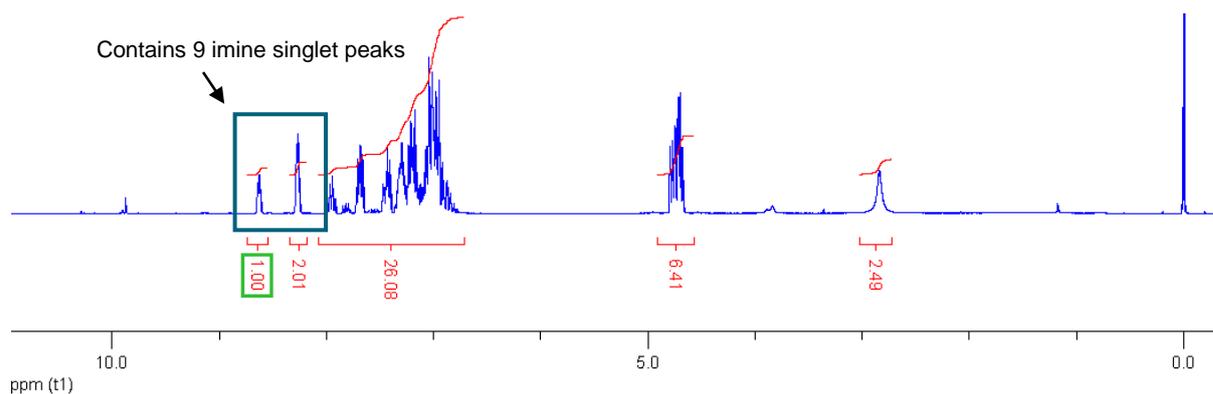
The most unique signals for imines prepared from aldehydes and amines are the imine signals themselves. However, with the 3 x 3 matrix, identification of multiple imines using proton NMR spectroscopy was not possible due to the clustering of the imine peaks and interference from the aromatic peaks in the same region. To see whether it is possible to identify each of the nine imine products and six starting materials, we decided to synthesize various imines containing fluorine atoms and screen the reaction mixture using  $^{19}\text{F}$  NMR spectroscopy. This required aldehydes and amines to contain a fluorine atom. The starting materials were purposely chosen so that the imines would have similar structures and therefore being able to distinguish each of them from their products by  $^{19}\text{F}$  NMR spectra would suggest that using more complex and varied starting materials would be even easier to distinguish. We chose to work with fluorobenzaldehydes and fluorobenzylamines, varying the positions of each fluorine atom (Scheme 24). These

starting materials are very similar and therefore being able to distinguish each of the products by  $^{19}\text{F}$  NMR spectroscopy would be a good starting point.



**Scheme 24.** A Library of Fluorinated Imines **121 - 129**.

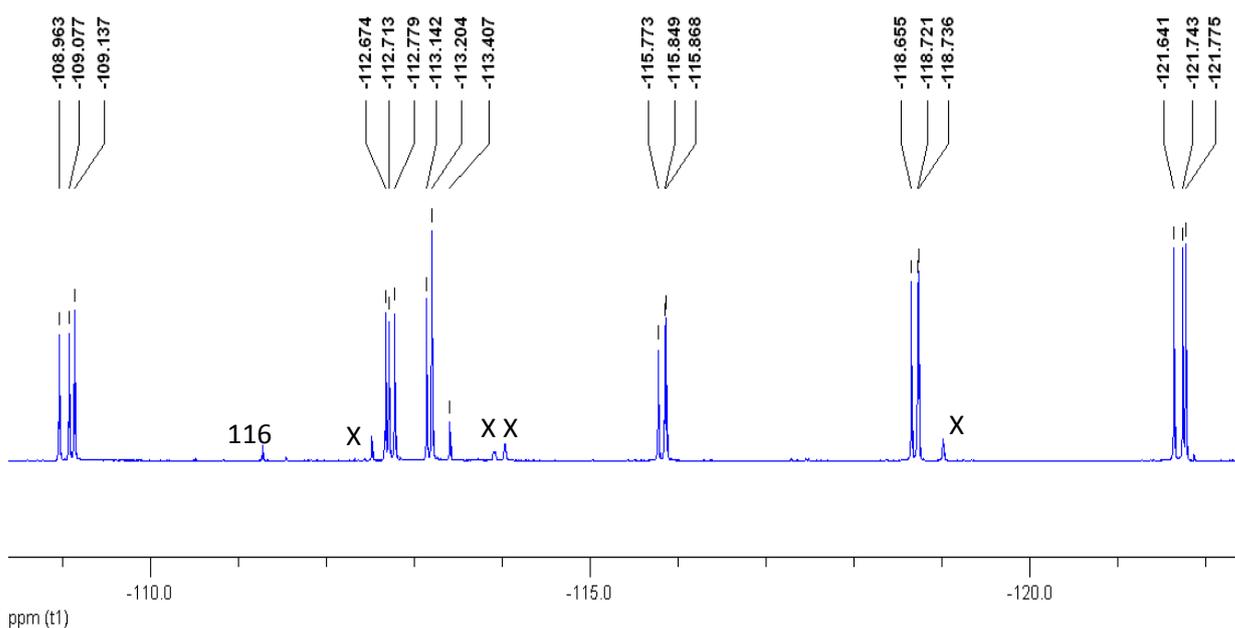
Aldehydes **115**, **116**, **117** were reacted with amines **118**, **119**, **120** in one pot resulting in  $^1\text{H}$  NMR Spectra 3. As expected, the nine imine singlet peaks are all clustered together making it impossible to identify ratios of each product formed.



**Spectra 3:**  $^1\text{H}$  NMR Spectra of Imines **121** – **129** in One-Pot.

The sample was then submitted for  $^{19}\text{F}$  NMR spectroscopy with the addition of hexafluorobenzene as the standard. A maximum of six fluorine singlets from starting materials and 18 singlet peaks from the nine imine products can be observed (Spectra 4).  $^{19}\text{F}$  NMR spectra showed a clear singlet peaks for the fluorine atoms present in each of the products formed. Each peak can unambiguously be identified by comparison to authentic standards prepared by parallel synthesis.

## Chapter 2: Determining a Suitable Analytical Method for our Imine DCLs



Starting materials were present (**116**)

X = minor impurities (SM's not 100% pure from Sigma-Aldrich)

|            | <b>115</b>    | <b>116</b>    | <b>117</b>    |
|------------|---------------|---------------|---------------|
|            | -121.89       | -111.28       | -102.29       |
| <b>118</b> | (115) -121.64 | (116) -112.78 | (117) -109.14 |
| -119.90    | (118) -118.66 | (118) -118.74 | (118) -118.72 |
| <b>119</b> | (115) -121.74 | (116) -112.67 | (117) -108.96 |
| -113.29    | (119) -113.20 | (119) -113.14 | (119) -113.41 |
| <b>120</b> | (115) -121.78 | (116) -112.71 | (117) -109.08 |
| -116.33    | (120) -115.85 | (120) -115.78 | (120) -115.87 |

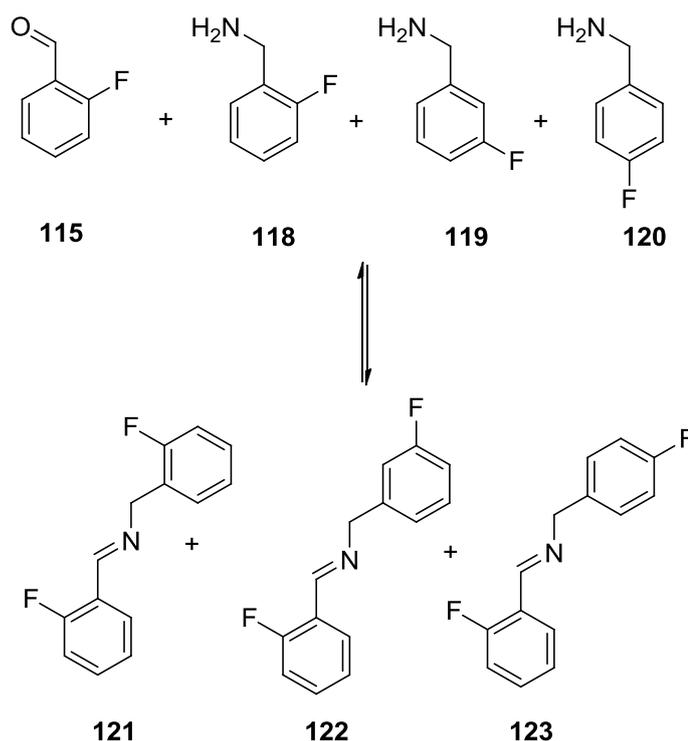
Values are in ppm.

**Spectra 4:**  $^{19}\text{F}$  NMR spectra of the reaction between **115**, **116**, **117** and **118**, **119**, **120** in one-pot with the peaks in ppm identified in the table. The numbers in brackets are NMR shifts from the fluorine atom that was previously a part of aldehyde or an amine.

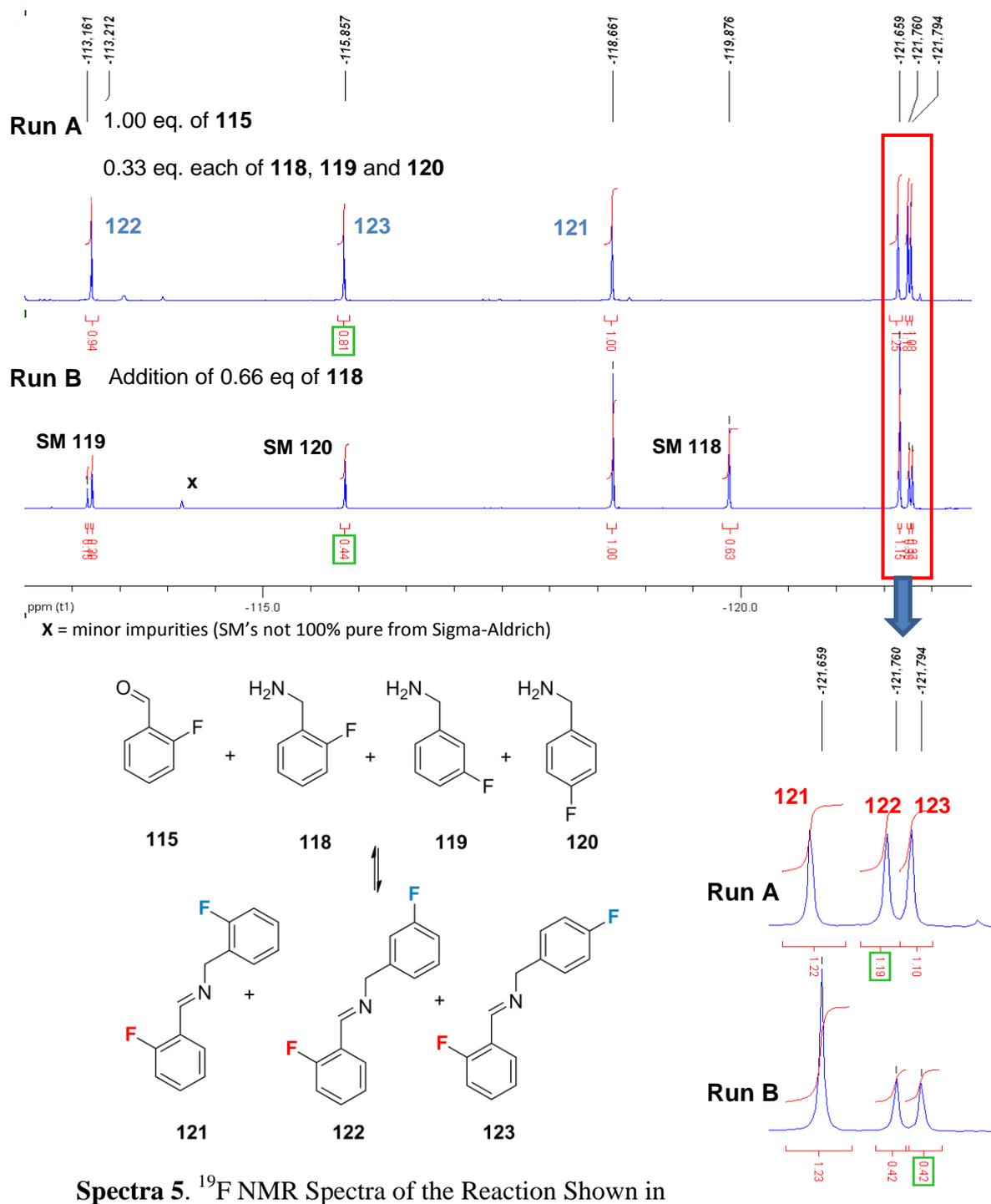
Now that we had a monitoring system that allowed us to easily identify the 15 components of the reaction, our aims were a) to show that the reaction was an equilibrium process that could be shifted and b) in the proposed 'machine' after the

'reaction' it is necessary to transform the products back to starting material to be recycled. Thus we needed to prove that this was possible.

Firstly, we investigated if the reaction was under equilibrium, therefore to prove this, an aldehyde, in this case 2-fluorobenzaldehyde (**115**) at 1.00 mol equiv. was reacted with amines **118**, **119**, and **120** at 0.33 mol equiv. each and stirred for an hour (Scheme 25). The products were then analysed by  $^{19}\text{F}$  NMR spectroscopy. After an hour, 0.66 mol equiv. of 2-fluorobenzylamine (**118**) was added to the reaction, stirred for an hour and then again analysed by  $^{19}\text{F}$  NMR spectroscopy (Spectra 5).



**Scheme 25.** The reaction of **115** with **118**, **119** and **120** in One-Pot Generating Three Imines **121**, **122** and **123**.



**Spectra 5.**  $^{19}\text{F}$  NMR Spectra of the Reaction Shown in Scheme 25.

The region of -121.6 to -121.9 ppm belongs to the imine products **121** - **123** and corresponding to the fluorine atom which was originally on the corresponding an aldehyde before the reaction, whereas fluorine peaks from the region of -112.0 to -

120.0 ppm belongs to the fluorine atom on the products which were originally on the amine before the reaction. Spectra 5 (Run A) showed that by adding three amines **118**, **119** and **120** at 0.33 mol equiv. each to 1.00 mol equiv. of **115**, the reaction produced imines **121**, **122** and **123** in an almost 1 : 1 : 1 ratio, and this was expected as the imines would have similar stabilities. Although the different basicity of the amines might mean that the imines were formed at different rates, we are observing the thermodynamic ratio at equilibrium. Addition of 2-fluorobenzylamine (**118**) to the dynamic library at 0.66 mol equiv. (Run B) shifted the equilibrium in favour of **121** and resulted in a 3 : 1 : 1 ratio of **121**: **122**: **123**, hence an amplification of product **121** as expected. This, of course, decreased the concentration of imines **122** and **123** due to the increase in concentration of **118** which displaces and competes with **119** and **120** (starting materials **119** and **120** are also seen on the NMR). This showed that the reaction is reversible and that  $^{19}\text{F}$  NMR allows accurate quantification of the change of concentration of products at equilibrium. Any one of the imines can be amplified by adding more of that amine starting material. This pattern was observed with all fluorobenzaldehydes and fluorobenzylamines as expected (NMR's not shown).

There are two possible mechanisms for the imine exchange process towards the increasing concentration of one imine by adding its corresponding amine; this is by a) a hydrolysis b) an aminolysis reaction. The hydrolysis mechanism would involve the imine products being broken down to starting reagents and reformed with an increased concentration of the imine derived from the excess amine. This mechanism requires water and acid. Whereas the aminolysis reaction is a direct replacement of the amine component of a Schiff base by another amine in the

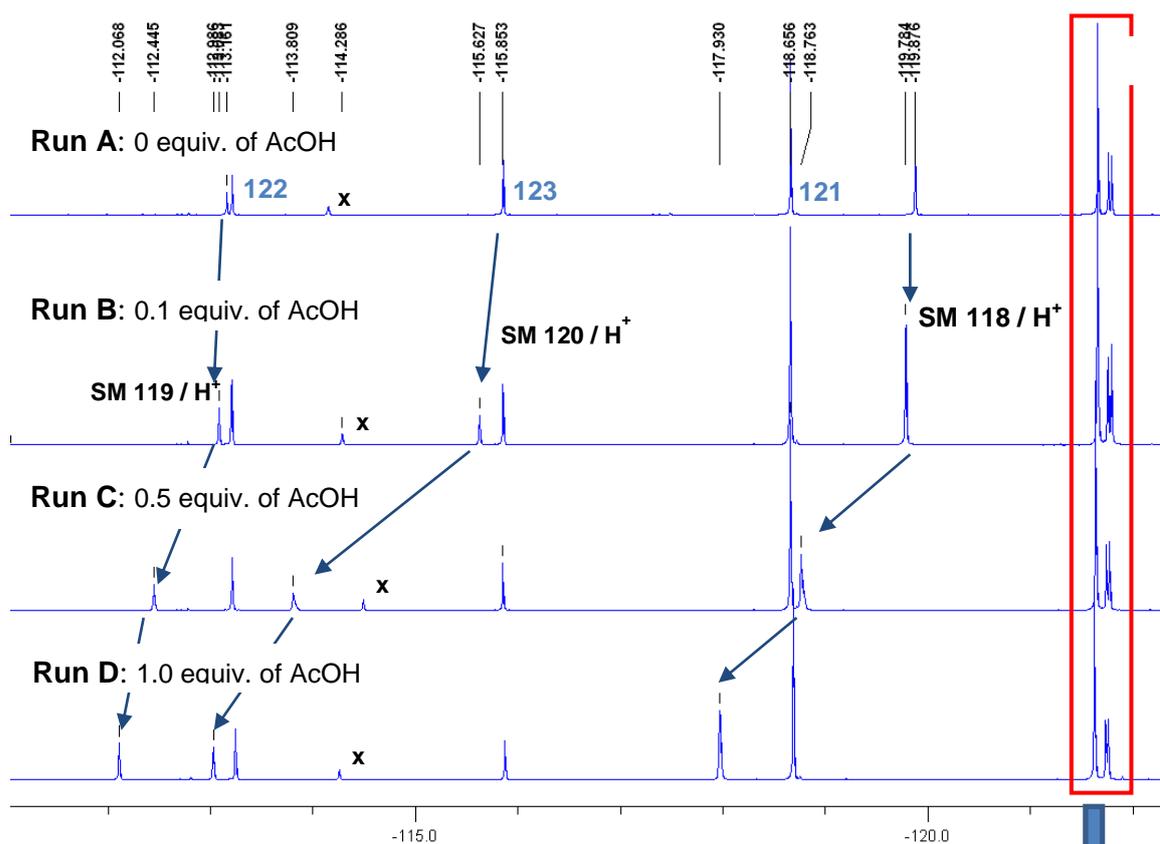
presence of acid and requires no water. The reaction conditions we used to mix the amine + aldehyde components in  $\text{CDCl}_3$  without added acid or the removal of water because deuterated chloroform overtime becomes acidic if not refrigerated and stored in the dark.<sup>74</sup> The solvent used was slightly acidic and therefore addition of any excess acid was not required. In addition no attempt to remove the  $\text{H}_2\text{O}$  formed in the condensation reactions was undertaken so clearly either mechanisms (a) or (b) or a mix could be occurring. One way to distinguish the mechanisms was to repeat the experiment under anhydrous conditions in the presence of a drying agent. Repeating the reaction using anhydrous deuterated chloroform in the presence of magnesium sulfate resulted in identical results, therefore with the addition of excess amine, under these conditions a shift in the reaction equilibrium is likely to occur *via* an aminolysis reaction.

At this point it is worth reminding ourselves of what is required in our 'machine'. We require:

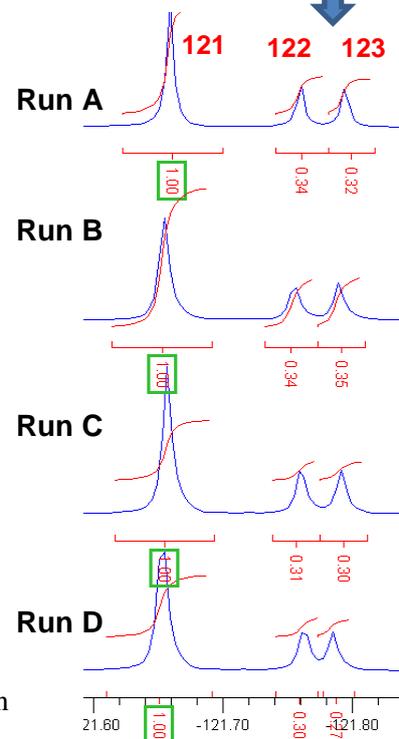
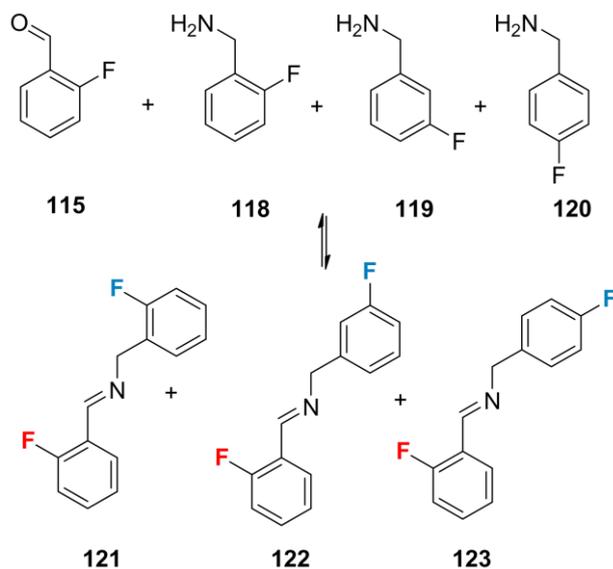
1. A dynamic equilibrium which can be characterised.
2. A product ratio that can be evolved (changed) by changing reaction parameters (e.g. pH, stoichiometry, solvent, temperature or pressure etc.).
3. A process where all the products can be broken back into starting materials if the product distribution doesn't lead to a desired physical property (e.g. colour).
4. Once broken down into starting materials the ability to once again set up a dynamic equilibrium with the addition of further building blocks in different conditions.

5. All of this is to occur in a flow system with no purification between stirs.

Having demonstrated one of the first aims (Aim 1) the next step was to add acetic acid to the reaction to see whether the product equilibrium could be changed by changing pH and that the products could be broken back to starting materials (Aims 2 / 3). The ratio 3 : 1 : 1 of imine products previously prepared was then subjected to 0.1, 0.5, 1.0 mol equiv. of acetic acid (AcOH) stirred for an hour and analysed by  $^{19}\text{F}$  NMR spectra (Spectra 6).



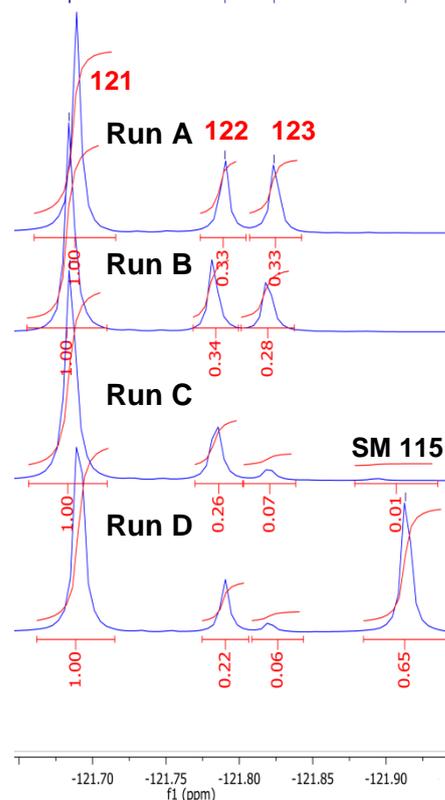
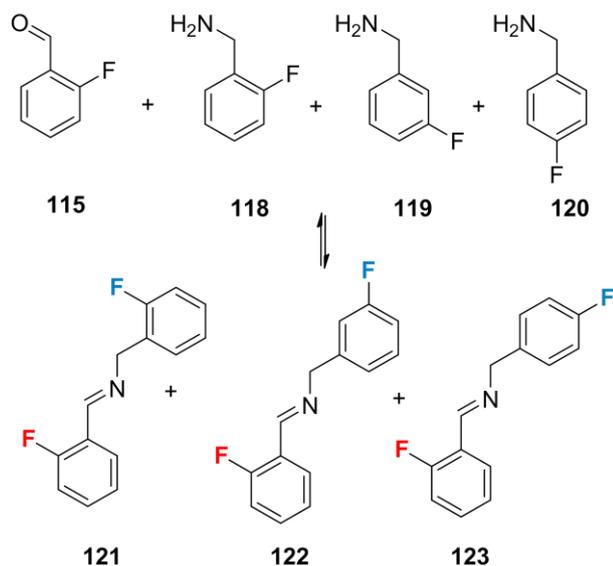
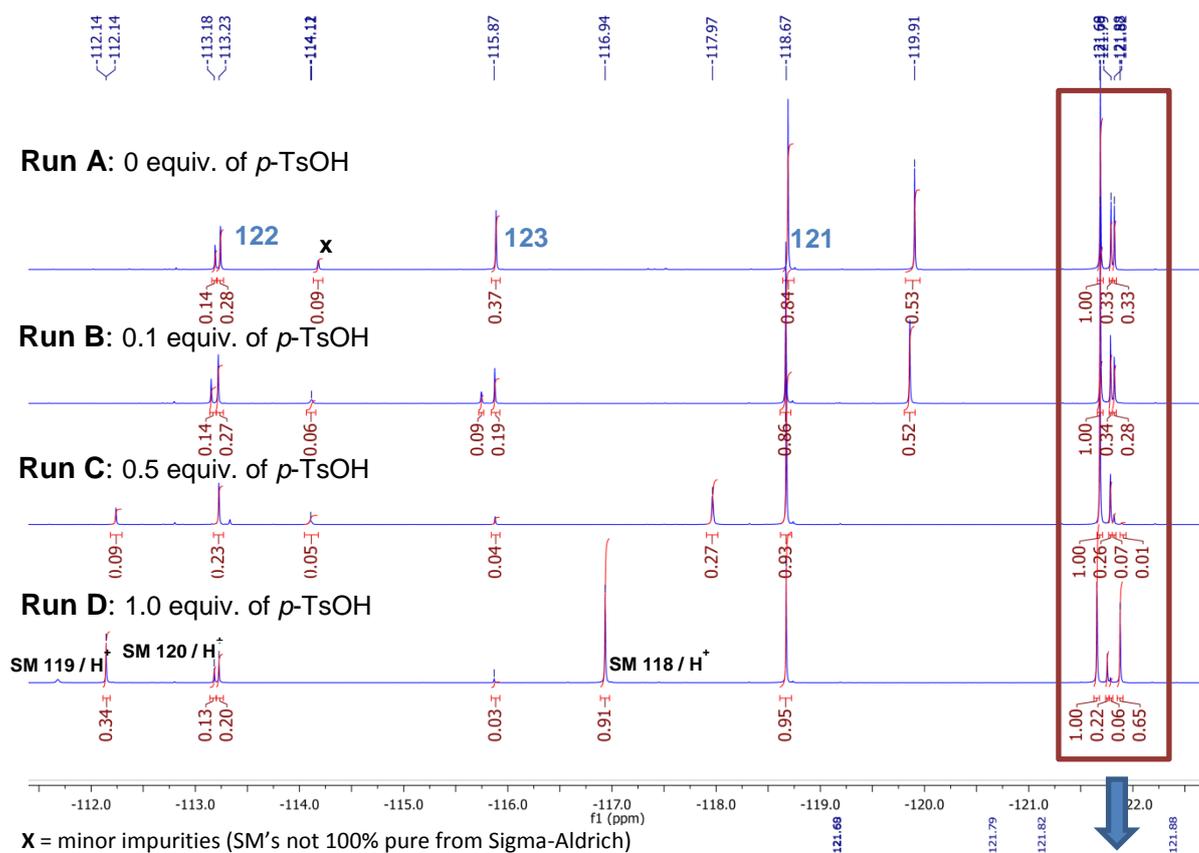
ppm (t1)  
 X = minor impurities (SM's not 100% pure from Sigma-Aldrich)



**Spectra 6.**  $^{19}\text{F}$  NMR spectra, showing the changes in reaction observed when reacting **115**, **118**, **119**, and **120** in 0.1, 0.5, 1.0 mol equiv. of acetic acid.

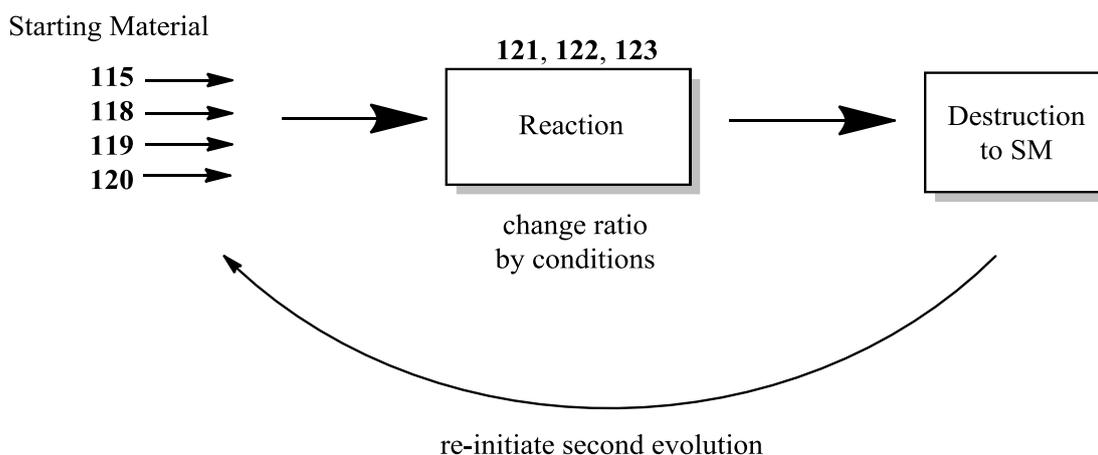
The results showed that there had been no effect on imine ratios (**121** : **122** : **123**) with the presence of varying concentrations of acetic acid. The ratios of imines were unchanged and no aldehyde starting material was present indicating that break down of products hadn't occurred. Instead, acetic acid (pKa 4.76) had protonated the amine **118** starting material (and **119** / **120**) which had shifted the peak of  $^{19}\text{F}$  NMR up-field from -119.87 to -117.93 ppm depending. This shifting of peaks was also observed with amines **119** and **120** where there was a shift of peak from approx. -115.62 to -112.89 and -113.10 to -112.09 ppm. Of course the imine formation has been shown to be catalysed by  $\text{AcOH}^{75}$  and so the reaction was then repeated with a stronger organic acid *p*-TsOH (pKa -2.8).

## Chapter 2: Determining a Suitable Analytical Method for our Imine DCLs



**Spectra 7.** <sup>19</sup>F NMR spectra, showing the changes in reaction observed when reacting **115** with **118**, **119**, and **120** in 0.1, 0.5, 1.0 mol equiv. of *p*-TsOH.

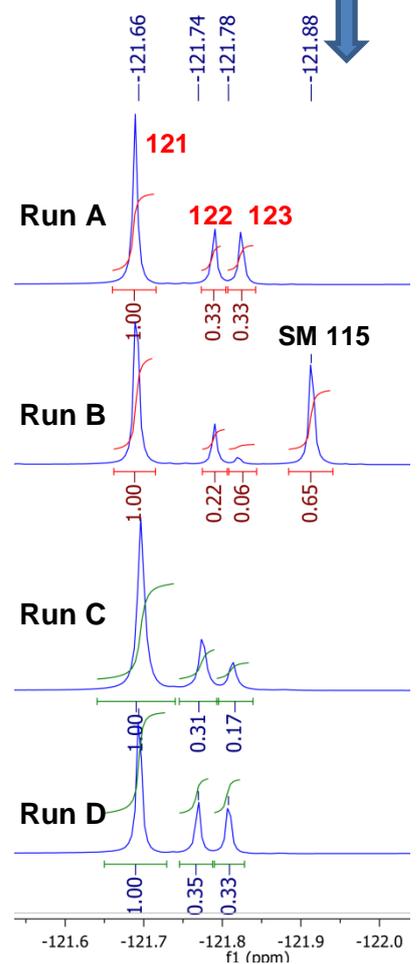
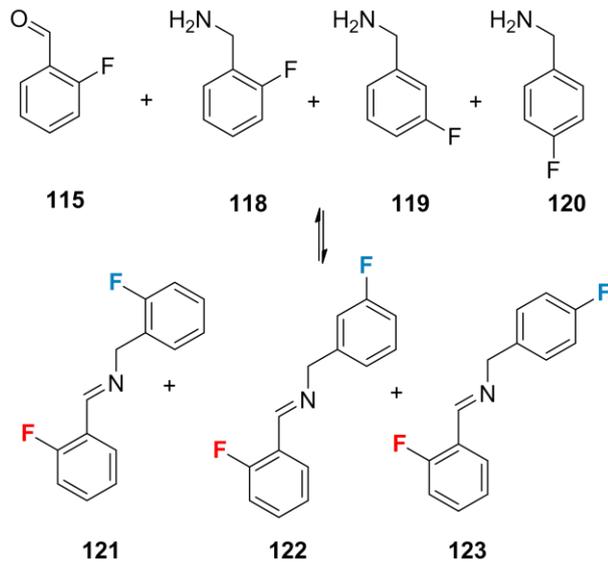
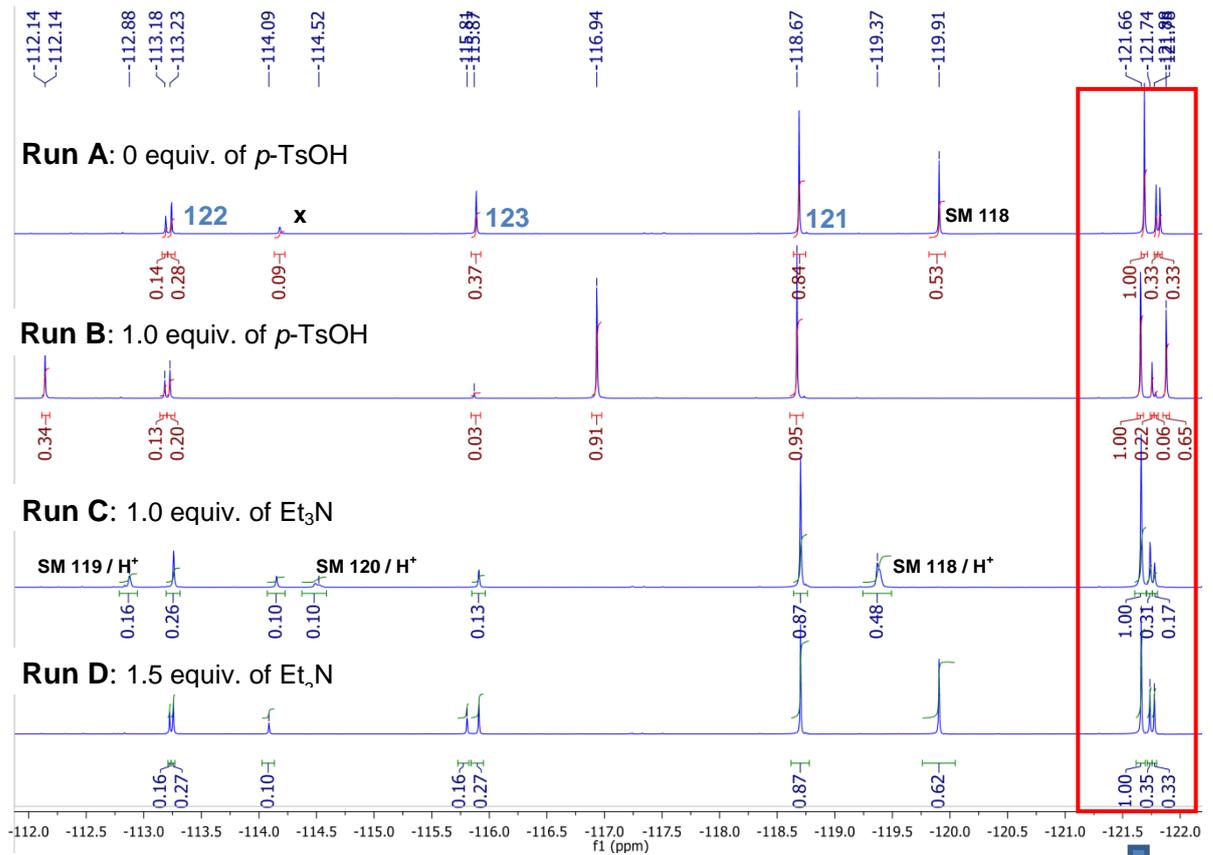
Spectra 7 showed that addition of 0.1 mol equiv. of *p*-TsOH selectively decreased the concentration of imine **123** more compared to imine **122** (Run B), whereas there was a decrease in amine **118** and an increase in imine **121**. By adding 0.5 mol equiv. of *p*-TsOH, it was clearly shown that the concentration of **123** had decreased (Run C). Addition of 1.0 mol equiv. of *p*-TsOH shifted the equilibrium towards starting materials, the peak for the **115** starting material began to appear at -121.87 ppm and there was also an increase in **118** starting material at -116.93 ppm (Run D). The peak for **123** had almost disappeared at -121.79 and -115.86 ppm. This showed that by adding 1.0 mol equiv. of *p*-TsOH, we start to reverse the reaction to the original building blocks. However, quantitative analysis of the breakdown of imine products by measuring the integrations of the appearing protonated amines **119** and **120** on the NMR spectrum should not be used as the amines precipitate in chloroform. Having shown that it was possible to alter the ratio of products by changing the acidity of the medium and monitoring the reversal of the reaction and break up the imines into their respected starting materials, we next need to demonstrate that we could form the imines again in a second cycle (so we can alter the conditions in the 'reaction chamber' or add an extra component in the reaction (Scheme 26)). It also should be highlighted that under these conditions we have demonstrated the 'evolved' removal (death) of the 'weakest' imine (**123**) showing that the thesis of evolution of DCL is easily monitored using  $^{19}\text{F}$  NMR.



Scheme 26

In order to re-initiate the reaction we investigated adding a base to the final reaction mixture containing 1.0 mol equiv. of *p*-TsOH. As before 2-fluorobenzaldehyde **115** was reacted with amines **118**, **119**, and **120** at 0.33 mol equiv. each and stirred for an hour. The 1 : 1 : 1 ratio of **121**, **122**, **123** was disrupted by the addition of 0.66 mol equiv. of 2-fluorobenzylamine **118** stirred for an hour and analysed again by  $^{19}\text{F}$  NMR spectroscopy. Thirdly 1.0 mol equiv. of *p*-TsOH was added, then after an hour the mixture was analysed by  $^{19}\text{F}$  NMR spectroscopy. Finally this mixture was treated with 1.0 and 1.5 mol equiv. of triethylamine ( $\text{Et}_3\text{N}$ ), stirred for an hour and again analysed by  $^{19}\text{F}$  NMR spectroscopy (Spectra 8).

Chapter 2: Determining a Suitable Analytical Method for our Imine DCLs



**Spectra 8:** <sup>19</sup>F NMR spectra, showing the changes in reaction observed when reacting **115** with **118**, **119**, and **120** in 1.0 mol equiv. of *p*-TsOH then neutralizing with 1.0, 1.5 mol equiv. of

Et<sub>3</sub>N.

As can be seen from Spectra 8, the addition of 1.0 equiv. of Et<sub>3</sub>N to the mixture observed in Run B re-initiates the dynamic equilibrium to give imine **121** / **122** and **123** as expected due to the neutralisation of the *p*-TsOH (Run C). However, with one equiv. of Et<sub>3</sub>N we have not reached the equilibrium level of Run A instead it takes a further 0.5 equiv. to restore the ratios observed in Run A (Run D). This would now set us up to re-initiate a second evolution cycle where we could add additional building blocks or alter the reaction conditions (Aim 4).

### 2.3 Conclusion

We have demonstrated that <sup>19</sup>F NMR spectroscopy is sufficient to monitor in real time the equilibrium of a 3 x 3 matrix of amine + aldehyde building blocks. The building blocks were chosen to have similar structure so that the fluorine NMR resolution would be severely tested. We have demonstrated that the system of our study is under a dynamic equilibrium and that we have shown that by altering the acid or base concentrations, we can affect the dynamics of the reaction and monitor it quantitatively. The nature of the acid used (e.g. AcOH or TsOH) is crucial in determining the equilibrium mixture and suggests that it is possible to selectively evolve or destroy an individual product by changing the conditions of the reaction. Now we need to synthesize a complex library of coloured fluorinated imines each resulting in a unique UV / Vis absorbance property to test in our 'machine'.

## Chapter 3.0 Synthesis of Highly Conjugated Fluorinated Imines

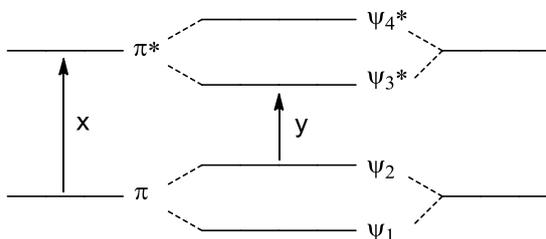
### 3.1 Introduction

In chapter two, we looked at finding a suitable method to analyse an imine DCL of 15 components. We discovered that using  $^1\text{H}$  NMR spectroscopy resulted in an overlap of several key peaks, therefore, quantitative and qualitative analysis of this library was impossible. To overcome this problem we created a library of imines which contained a fluorine atom on each of the building blocks then analysed these using  $^{19}\text{F}$  NMR spectroscopy, this proved successful. Now that we have a suitable analytical method, we need to create a library of imines which are ultraviolet / visibly active, so we could evolve a compound based on a colour property on our ‘machine’. For this we require conjugated building blocks that give rise to unique UV / Vis spectrum when synthesized into an imine, and also we require these building blocks to contain a fluorine atom, so we already know what to expect before we place the components in the ‘machine’.

#### 3.1.1 Highly Conjugated Aromatics

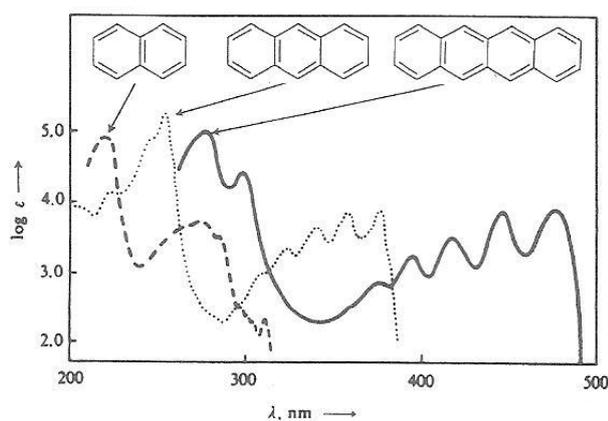
In our quest to synthesize an imine library giving rise to a variety of absorptions in the visible region, we require chromophores in which a high degree of conjugation is present. In the presence of an isolated double bond or lone pairs, a strong absorption maximum at 190 nm, corresponding to transition  $\pi \rightarrow \pi^*$  is observed (Figure 10). This results in a wavelength too short to be observed, therefore, when two or more double bonds are brought into conjugation, the  $\pi$ -bonding orbitals overlap causing the energy of the highest occupied orbital to be raised and the lowest

unoccupied anti-orbital lowered. The  $\pi \rightarrow \pi^*$  is now associated with a small  $y$  value, resulting in absorption at a longer wavelength.<sup>76</sup>



**Figure 10**

Fusing aromatic rings together results in a high degree of conjugation pushing the wavelength of maximum absorption to the visible region resulting in complex absorption spectra (Figure 11).<sup>77</sup> These compounds are useful as fingerprints and would be a useful backbone for our building blocks, but obtaining these components containing a fluorine atom are either not commercially available or are very expensive, therefore, we would have to devise synthetic procedures to include a fluorine atom.



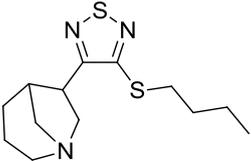
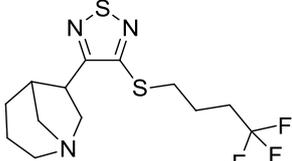
**Figure 11.** UV / Vis absorbance of Conjugated Aromatics.

### 3.1.2 The Fluorine Atom

Fluorine is unique in that it is possible to replace hydrogen with fluorine in vast hydrocarbon systems without much distortion of the geometry. Fluorine compounds are rarely found in nature;<sup>78</sup> in fact it is only recently that a fluorinase enzyme, a biological catalyst which bonds carbon to fluorine was discovered by Professor David O'Hagan.<sup>79</sup> Fluorocarbon chemistry dates back to 1890 when Moissan claimed to have isolated carbon tetrafluoride from the reaction of fluorine with carbon,<sup>80</sup> which was then proved to be false. Later in 1890's, Swarts, a Belgian chemist, began studies on fluorocarbon compounds by exchange reactions and prepared the first organofluorine system in 1922.<sup>81</sup> Simons and Block discovered that mercury promotes the reaction between carbon and fluorine and prepared the first liquid perfluorocarbons<sup>82</sup> in 1937 and were also able to isolate  $\text{CF}_4$ ,  $\text{C}_2\text{F}_6$ ,  $\text{C}_3\text{F}_8$ ,  $\text{C}_4\text{F}_{10}$ , cyclo- $\text{C}_6\text{F}_{12}$  and  $-\text{C}_6\text{F}_{14}$ . Due to rapid progress in fluorocarbon chemistry, in 1971, the *Journal of Fluorine Chemistry* was established.

Fluorocarbons possess high thermal stability, as they form very strong bonds with other elements including carbon due to the high electronegativity of fluorine. The volatilities of hydrocarbon and fluorocarbon systems are very similar (boiling point of benzene,  $80.1^\circ\text{C}$  and hexafluorobenzene,  $80.5^\circ\text{C}$ ) even though analogous fluorocarbons have significantly increased molecular weight. Fluorine-19 has a nuclear spin quantum number of  $\frac{1}{2}$  which allows the application of NMR in an analogous way.<sup>78</sup> Due to great similarities between hydrocarbon and fluorocarbon systems, the powerful techniques of isolation, purification and identifications are similar to that of hydrocarbon systems.

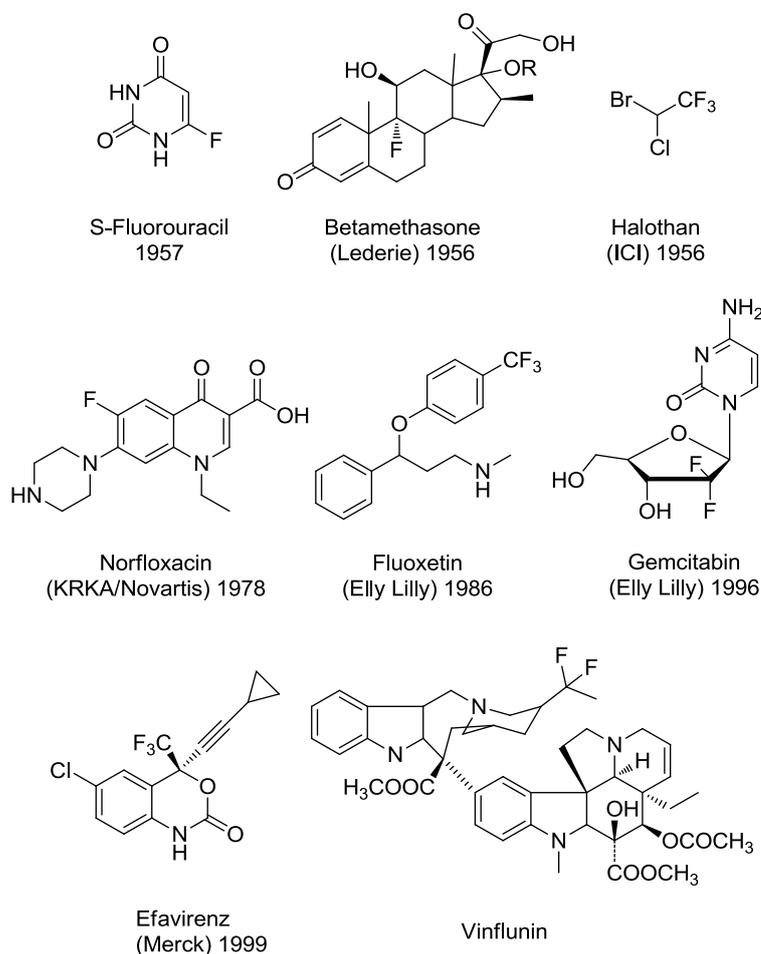
Fluorocarbons exhibit unique properties, which are being exploited in medicinal chemistry. Fluorine adds desirable characteristics to drugs by adapting the pharmacokinetics characteristics of a drug. One of the most important is the metabolic stability observed by fluorine compounds; rapid oxidative metabolism by the liver enzymes (P450 cytochrome enzymes) and / or stomach acidity may prematurely decompose the drug, but the addition of fluorine prevents the decomposition of the drug through proteolysis, therefore make the drug more resistant (Figure 12).<sup>83</sup> Insertion of fluorine or fluorine derivatives into a drug also improves the lipophilicity and enhances absorption into biological membranes.

|  | Ki (nM)<br>(M receptor) | Plasmic Concentration<br>(ng/Kg)<br>(after 1h, 30 mg/Kg p.o.) |
|--|-------------------------|---|
| <br>(5S,6S)exo             | 0.45                    | 21  |
| <br>(5S,6S)exo (LY316108) | 0.40                    | 805   |

**Figure 12.** Protective Effects of Fluorine Substitution on Oxidative Metabolisms: Effect of Fluorination on Plasmatic Concentration of the Muscarinic Analgesic LY316108.

Fluorouracil, halothane and fluorocorticoids were the first class of important fluorocarbon drugs developed (Figure 13). One of the most important uses of fluorocarbon has been fluothane, discovered by Imperial Chemical Industries, which was said to be the best general anaesthetic ever. Today, fluorine based drugs are

widely used as antiparasitic agents (especially antimalarial), antibacterial, anticancer compounds (such as kinases), and phosphodiesterase inhibitors.<sup>83</sup>

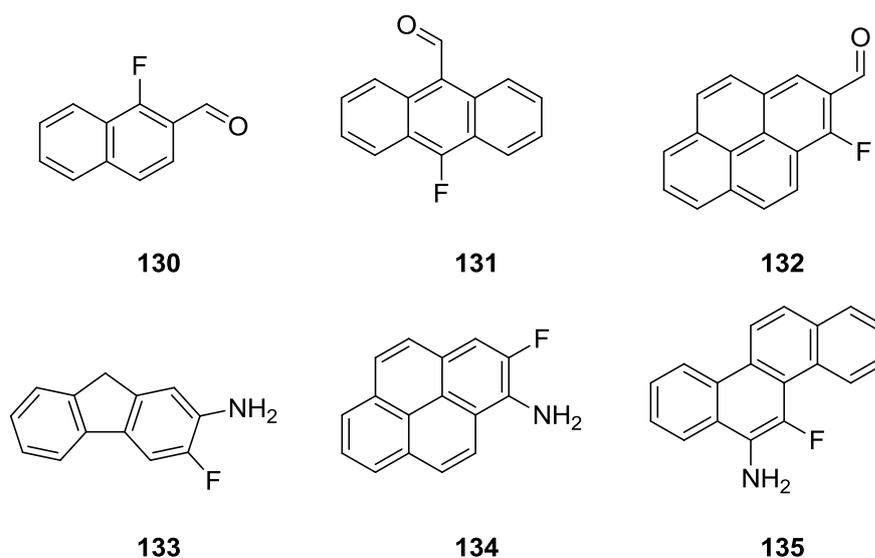


**Figure 13.** Milestones in Fluorine Medicinal Chemistry, Examples of Fluorine Containing Drugs.

Fluorine is a very useful atom but our aim is not to add fluorine atom to improve the bioavailability of our complex conjugated imines but to use its nuclear spin quantum number of  $\frac{1}{2}$  which allows the application of  $^{19}\text{F}$  NMR spectroscopy.

### 3.2 Results and Discussion

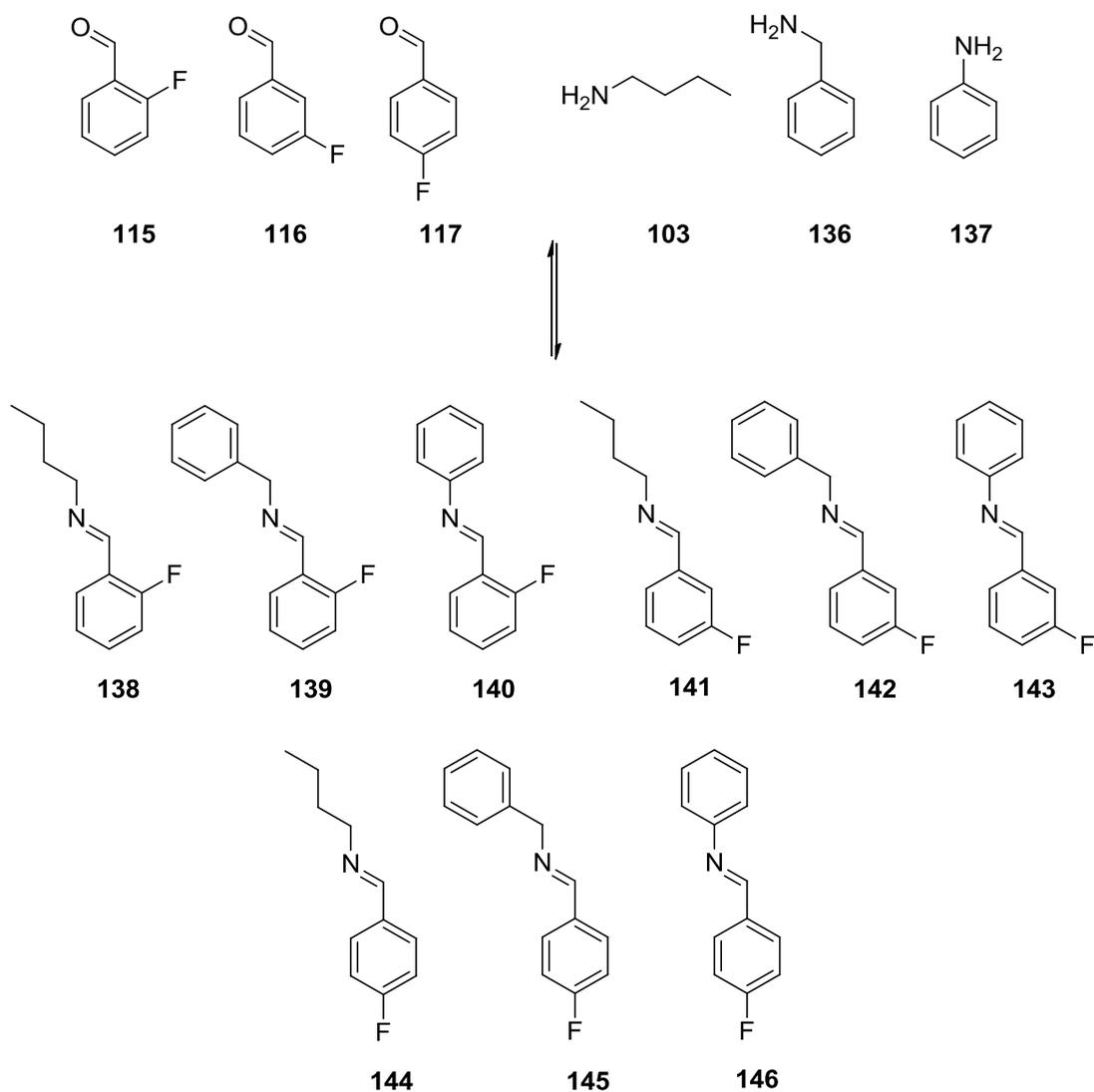
As previously stated, including a fluorine atom in our building blocks and monitoring the reaction using  $^{19}\text{F}$  NMR spectroscopy is sufficient to distinguish multiple fluorinated products in a reaction. Now we need to use this to generate complex building blocks. We decided to place fluorine atoms in highly conjugated aromatic systems which are UV / Vis and / or fluorescence active (Figure 14). The compounds we initially aimed to synthesize were; 1-fluoro-2-naphthaldehyde<sup>84</sup> (**130**), 10-fluoroanthracene-9-carbaldehyde (**131**), 1-fluoropyrene-2-carbaldehyde (**132**), 3-fluoro-9*H*-fluoren-2-amine (**133**), 2-fluoropyren-1-amine (**134**), and 5-fluorochrysen-6-amine (**135**).



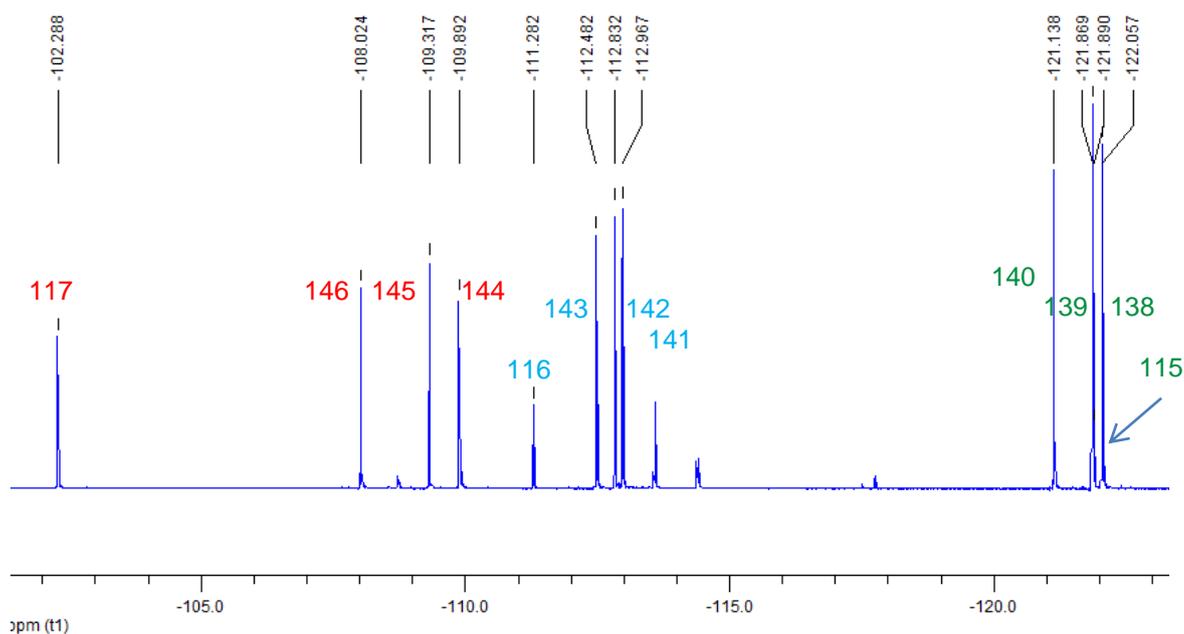
**Figure 14.** Complex Fluorinated Aldehydes and Amines We Aim to Synthesize.

Addition of a fluorine atom is not an easy task especially when we are looking to synthesize large amounts of products for our flow system; therefore we went a step back. We observed a reaction that contained a fluorine atom on only one functional group, this would be the aldehyde. Three fluorinated benzaldehydes **115**,

**116 and 117**, with three non-fluorinated amines **103, 136 and 137** were reacted together in chloroform for 24 hours at room temperature, which could lead to nine possible products **138 - 146** in one pot (Scheme 27). A fluorine NMR spectrum was obtained (Spectra 9)



**Scheme 27.** A Library of Simple Imines Synthesized From Fluorinated Aldehyde and Non-Fluorinated Amines.

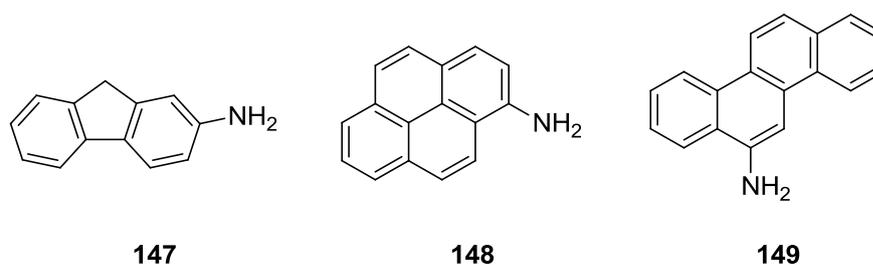


|       |         |         |         |
|-------|---------|---------|---------|
|       | (115)   | (116)   | (117)   |
|       | -121.89 | -111.28 | -102.29 |
| (103) | -122.06 | -112.97 | -109.89 |
| (136) | -121.87 | -112.83 | -109.32 |
| (137) | -121.14 | -112.48 | -108.02 |

Values in parts per million (ppm)

### Spectra 9. $^{19}\text{F}$ NMR Data for Imines **138** – **146**.

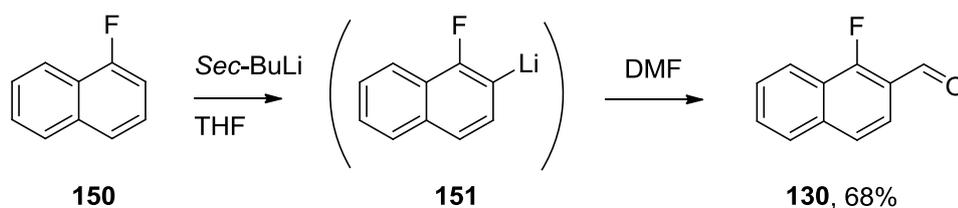
The fluorine NMR spectrum shows that by having three fluorinated aldehydes and three different non-fluorinated amines, we are still able to distinguish the nine different fluorinated products formed. With this result, we decided to synthesize highly conjugated aromatic amines with no fluorine atoms attached (**147** - **149**) to partner highly conjugated aldehydes in which the fluorine atom would be present (Figure 15).



**Figure 15.** The Three Non-Fluorinated Amines We Aim to Synthesize.

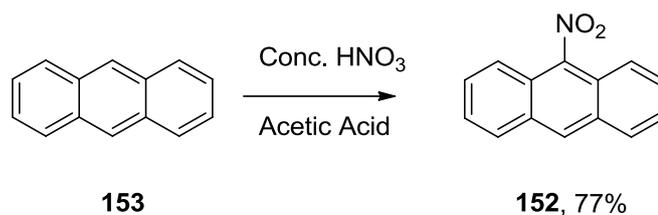
### 3.2.1 Synthesis of Conjugated Building Blocks

The first highly conjugated fluorinated aromatic aldehyde we synthesized was 1-fluoro-2-naphthaldehyde<sup>84</sup> (**130**). This was synthesized by reacting 1-fluoronaphthalene (**150**) with *sec*-butyl lithium at  $-75^{\circ}\text{C}$  generating the 1-fluoro-2-naphthyllithium intermediate (**151**), which was treated with dimethylformamide resulting in yellow crystals of **130** in 68% yield (Scheme 28). The structure was confirmed by  $^1\text{H}$  NMR spectroscopy and accurate mass spectrometry.



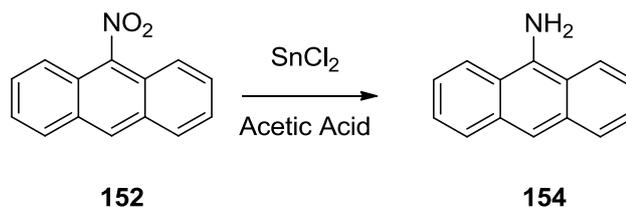
**Scheme 28.** Synthesis of our First Fluorinated Conjugated Building Block **130**.

With the successful synthesis of fluorinated naphthalene, we moved onto synthesizing our second fluorinated aldehyde, which is based on an anthracene backbone. Our first attempt was to synthesize 10-fluoroanthracene-9-carbaldehyde (**131**), for this we first need to synthesize 9-nitroanthracene<sup>85</sup> (**152**) (Scheme 29).



Scheme 29. Nitration of Anthracene.

Compound **152** can easily be synthesized by reacting anthracene (**153**) with concentrated nitric and hydrochloric acid in glacial acetic acid. This resulted in a pale yellow precipitate of 9-nitro-10-chloro-9,10-dihydroanthracene which was treated with sodium hydroxide and re-crystallized from acetic acid to obtain orange needles of **152** in 77% yield.

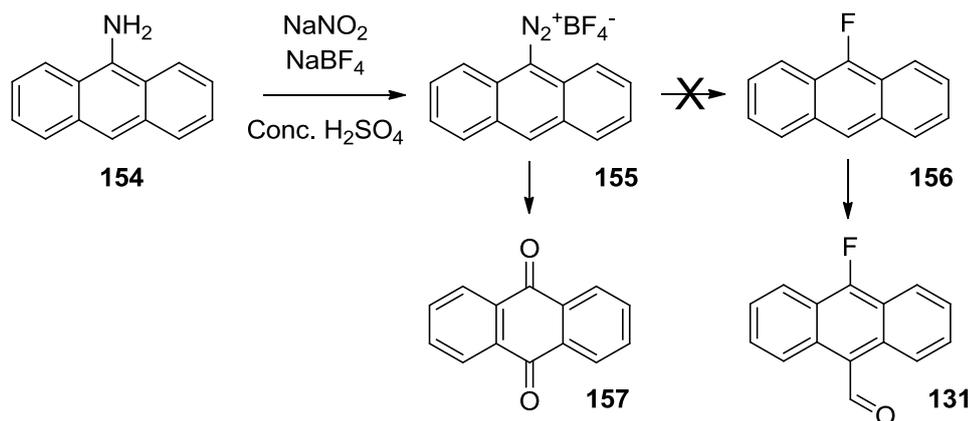


Scheme 30. Reduction of 9-Nitroanthracene.

Compound **152** was reduced to 9-aminoanthracene<sup>86</sup> (**154**) by reacting with tin (II) chloride (Scheme 30). This resulted in a pale yellow precipitate. After washing with concentrated hydrochloric acid and treatment with sodium hydroxide, crude orange crystals of **154** were obtained. Attempts to purify **154** by chromatography failed due to partial decomposition of the compound and, therefore, we utilised it without further purification.

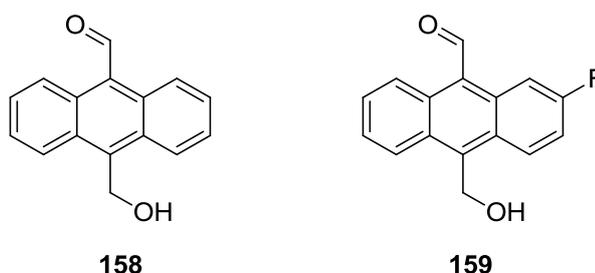
Our next step was to replace the amine with a tetrafluoroborate salt. Compound **154** was reacted with sodium nitrite for three and half hours and poured into an aqueous solution of sodium tetrafluoroborate. This resulted in a greenish-grey

precipitate which was collected. The next step was to decompose **155** which would result in 9-fluoroanthracene **156**. Sublimation and decomposition in xylene were the two methods attempted and after many attempts, both failed and only resulted in the formation of anthraquinone **157** (Scheme 31). This was possibly due to the moisture sensitivity of the reaction.

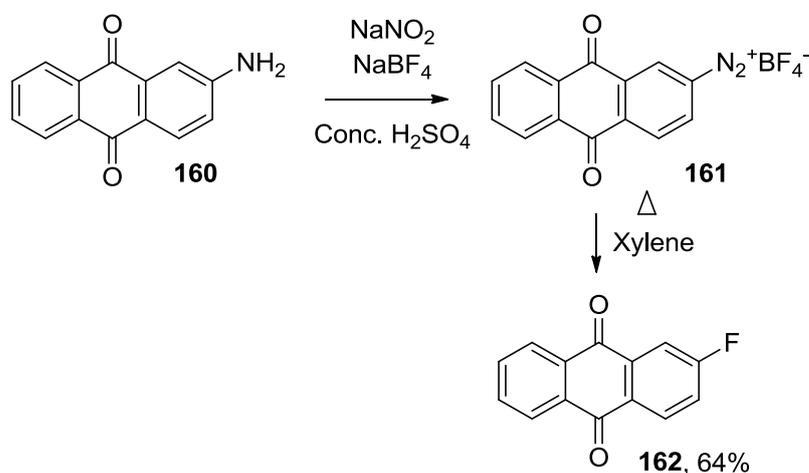


**Scheme 31.** Attempted Synthesis of **131**.

A search on Scifinder for an alternative method for the synthesis of 9-fluoroanthracene **156** gave no results. For my research, a specific position of the fluorine atom on anthracene was not relevant. Literature search showed that the diketone functionality on anthraquinone (**157**) could be converted to an aldehyde and an alcohol functional group **158**.<sup>87</sup> Therefore we decided to use this method to synthesize **159**.

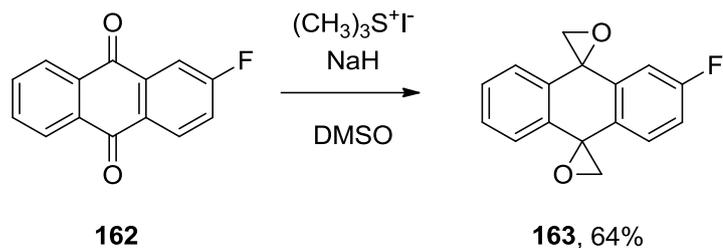


We first started with cheap, commercially available 2-aminoanthraquinone (**160**). Compound **160** was reacted with sodium nitrite overnight and poured into an aqueous solution of sodium tetrafluoroborate. This gave a dark orange / brown precipitate of **161** which was collected. Compound **161** was then suspended in xylene and heated under reflux overnight, resulting in crude black crystals. The product was extracted with ethyl acetate, evaporated and purified by column chromatography, resulting in isolation of pale yellow crystals of 2-fluoroanthracene-9,10-dione<sup>88</sup> (**162**) in 64% yield (Scheme 32).



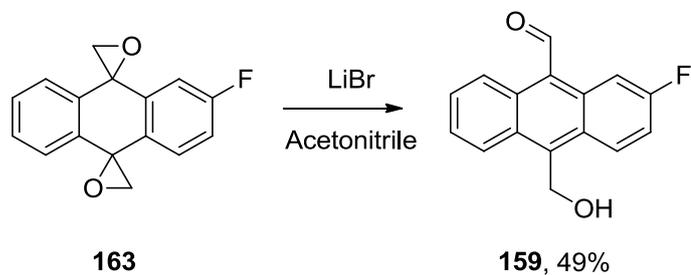
**Scheme 32.** Conversion of an Amine Functional Group to a Fluorine Atom.

Compound **162** was then reacted with sodium hydride and trimethylsulfonium iodide in anhydrous dimethylsulfoxide at room temperature for five hours under nitrogen. After filtration to remove excess sodium hydride, the filtrate was poured into cold water where a pale yellow precipitate was observed. This was filtered, resulting in fluorinated *trans*-dispiro[oxirane-2,9'[10'*H*]-anthracene-10',2''-oxirane] (**163**) in 64% yield (Scheme 33).



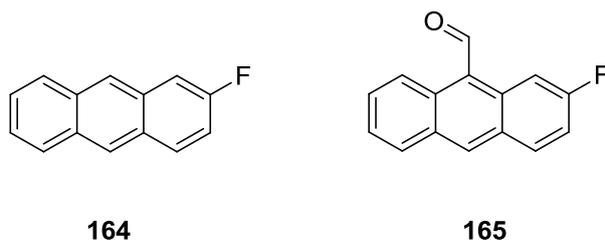
**Scheme 33.** Conversion of Ketones into Oxirane Rings.

This next reaction involved breaking open the two strained three-membered rings into an alcohol and aldehyde functional groups respectively, while re-aromatizing the central ring. Compound **163** was reacted with lithium bromide in anhydrous acetonitrile for 72 hours. The mixture was then cooled to  $-70^\circ\text{C}$  and the resulting orange precipitate was collected. The crude product was purified by column chromatography resulting in 3-fluoro-10-(hydroxymethyl)anthracene-9-carbaldehyde (**164**) in 49% yield (Scheme 34).

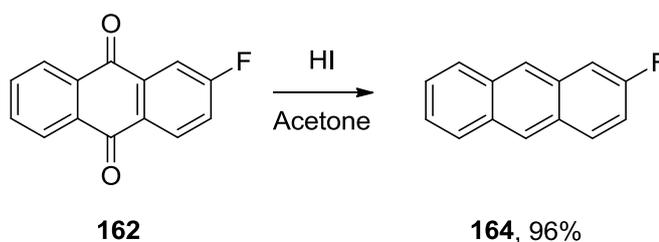


**Scheme 34.** Oxirane Ring Opening using LiBr.

While the synthesis of **159** was straight forward and amenable on a small scale reaction, reaction to **163** and **159** was quite difficult on a large scale, in particular we found difficulty in purifying side products. This project requires large amounts (10 – 100 g) of highly conjugated fluorinated aldehydes and conjugated amines. Therefore, an alteration in the procedure was required.



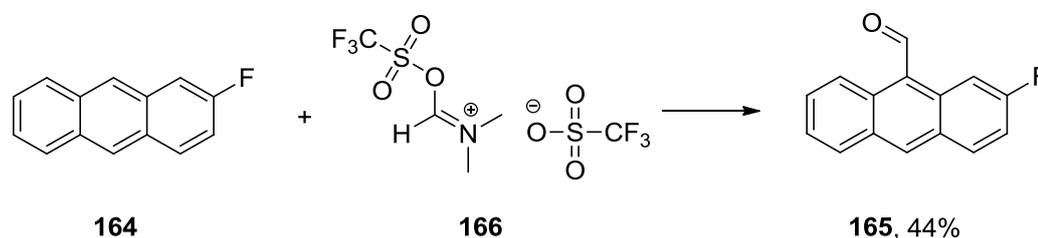
Instead of forming two oxirane rings with compound **162**, we decided to reduce the two ketone groups directly to an anthracene to obtain **164** and then formylate to obtain compound **165**. Compound **162** was dissolved in acetone, treated with 15 equivalents of hydriodic acid and heated under reflux for 7 days. TLC showed the reaction was still incomplete even after a week. However, the mixture was poured into water, resulting in a dark green precipitate, which was collected. The precipitate was dissolved in toluene and treated with excess solid iodine. The mixture was heated under reflux until no starting material was present. After workup, a yellow crude solid was obtained which was re-crystallized from acetone, resulting in off-white crystals of 2-fluoroanthracene<sup>88</sup> (**164**) in 96% yield (Scheme 35).



**Scheme 35.** Reduction of Ketones using Hydriodic Acid.

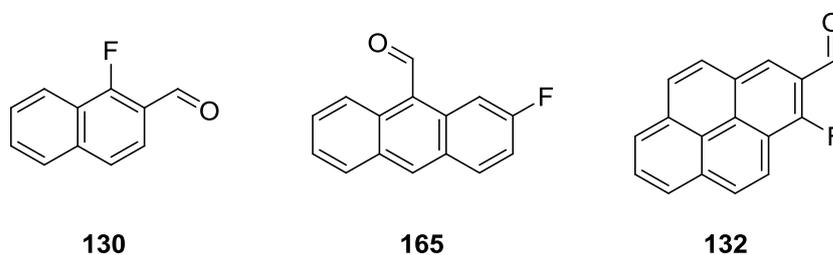
Compound **164** was then formylated by reacting with trifluoromethanesulfonyloxy-methylen-*N,N*-dimethyliminiumtrifluoromethane sulfonate (**166**). Compound **166** is not commercially available and was synthesized by reacting trifluoromethanesulfone anhydride with dimethylformamide at 0°C.<sup>89</sup> Reaction of **164** with the iminium salt **166** at 37°C for 48 hours followed by

purification by column chromatography resulted in bright yellow crystals of 2-fluoroanthracene-9-carbaldehyde (**165**) in 44% yield (Scheme 36).

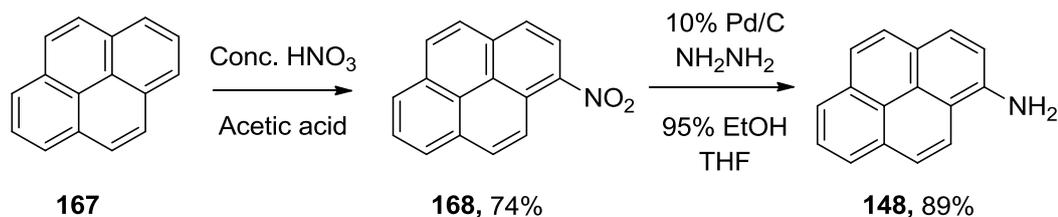


**Scheme 36.** Formylation of 2-Fluoroanthracene.

Now that the second fluorinated aldehyde had been synthesized, we moved onto synthesizing the third fluorinated aldehyde for a 3 x 3 matrix. We have fluorinated naphthalene (**130**) and anthracene (**165**); therefore, we chose a pyrene backbone (**132**) which contains four fused aromatic rings. Our aim was to synthesize 1-fluoropyrene-2-carbaldehyde (**132**).

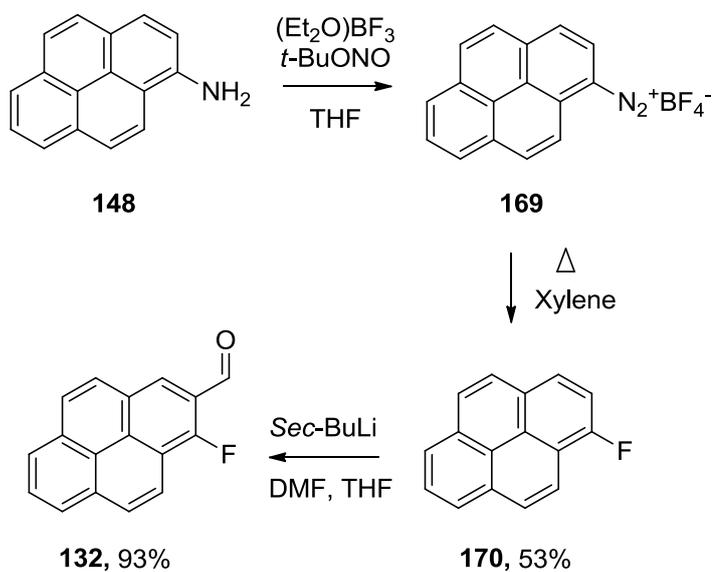


The first step was a simple nitration reaction. Reaction of **167** with concentrated nitric acid in acetic acid resulted in 1-nitropyrene<sup>90</sup> **168** in 74% yield. This was then reduced with 10% Pd/C catalyst and hydrazine hydrate as a hydrogen source in ethanol and THF. After 24 hours and filtration through celite, pure greenish/grey crystals of 1-aminopyrene<sup>90</sup> (**148**) were obtained in 89% yield (Scheme 37).



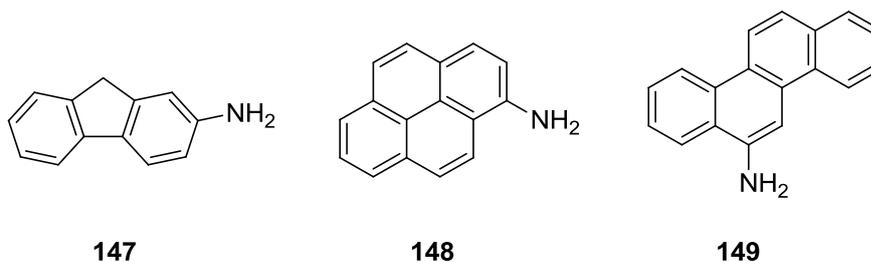
Scheme 37. Amination of Pyrene.

We then made the tetrafluoroborate salt **169** by reacting **148** with trifluoroborate diethyletherate and tert-butyl nitrite in THF. This was thermally decomposed in xylene and purified by column chromatography to give colorless crystals of **170** in 53% yield. Compound **170** was then easily formylated by reaction with *sec*-butyl lithium + DMF at  $-75^\circ\text{C}$ , purified to give the desired product **132** as yellow crystals in 93% yield (Scheme 38).

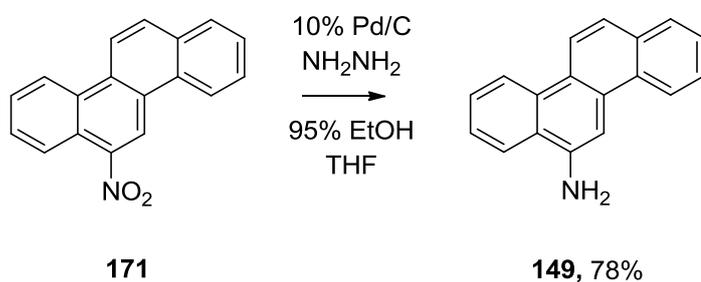


Scheme 38. Fluorination and Formylation of 1-Aminopyrene.

With the synthesis of our three complex fluorinated aldehydes (**130**, **165** and **132**) completed, we next turned our attention to the three complex amines **147**, **148** and **149**.

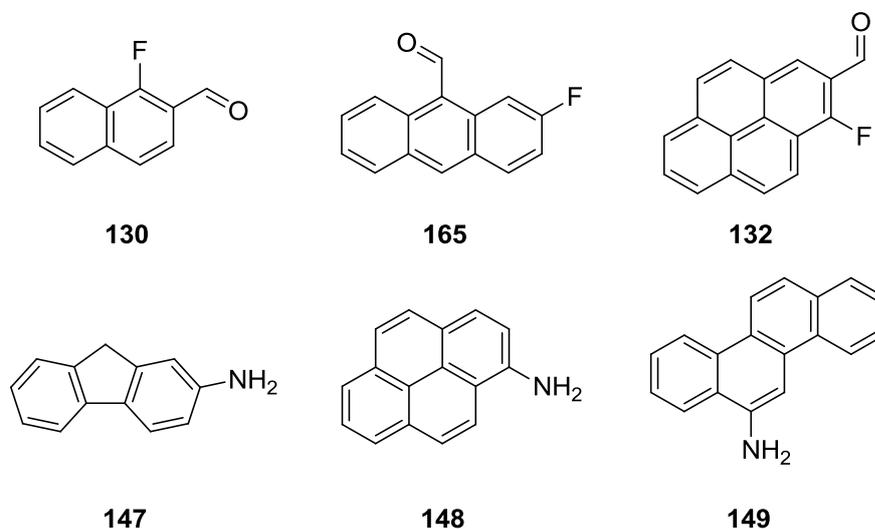


Amine **147** is cheap and commercially available and, therefore, we did not need to make it. Amine **148** had previously been synthesized in the synthesis of **132** (See Scheme 37). Amine **149** was synthesized by simple reduction of commercially available 6-nitrochrysenes (**171**) with 10% Pd/C catalyst and hydrazine hydrate in ethanol and THF. After 24 hours and filtration through celite, pure orange / red crystals of **149** were obtained in 78% yield (Scheme 39).

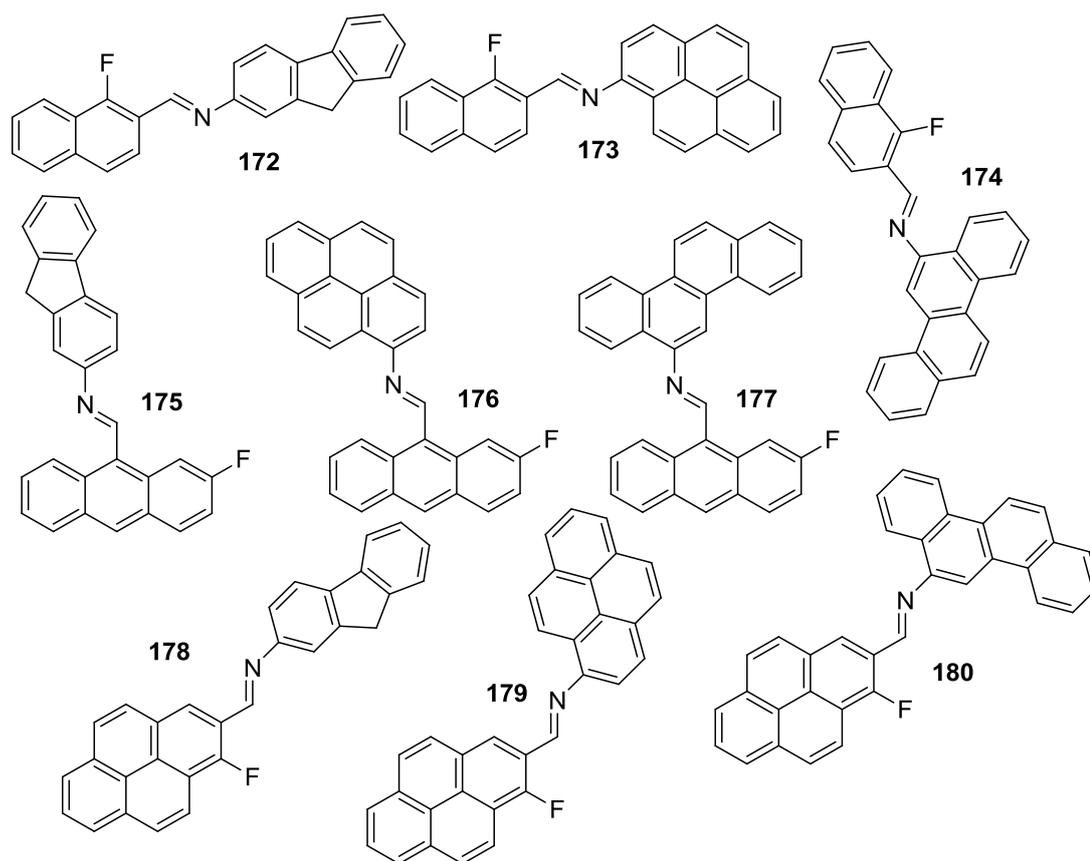


**Scheme 39.** Reduction of 6-Nitrochrysenes to 6-Aminochrysenes.

## 3.2.2 Synthesis of Complex Imines



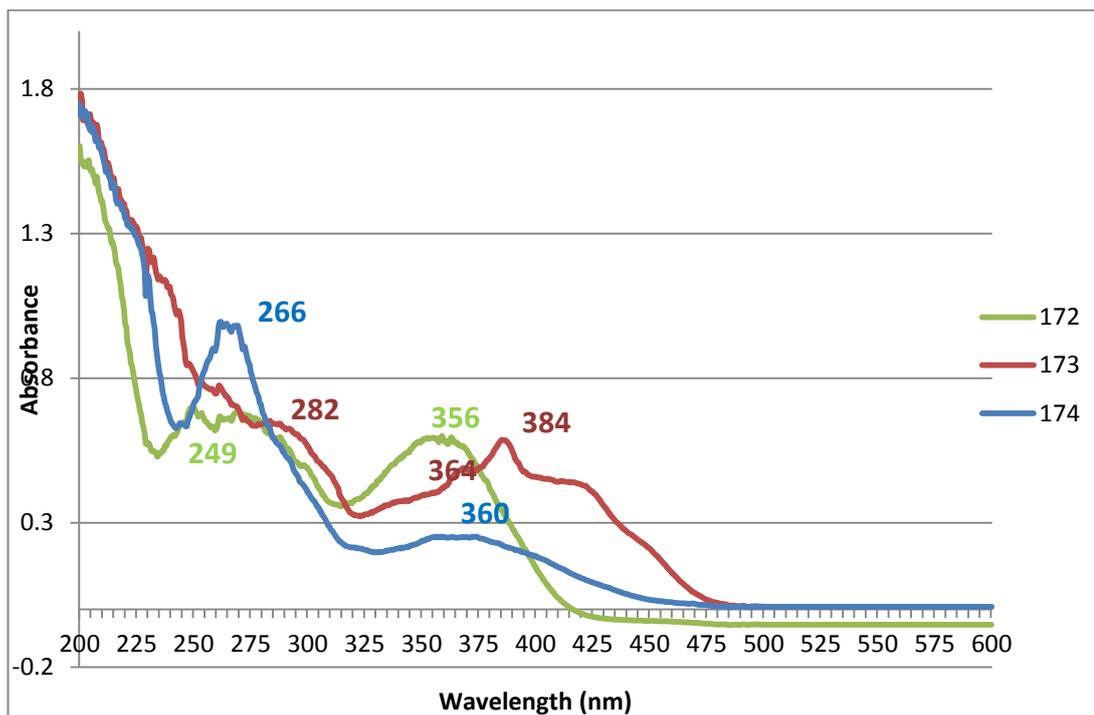
We now had our three complex fluorinated aldehydes **130**, **165**, **132** and three complex non-fluorinated amines **147**, **148**, **149**. The next step was to synthesize a library of imines from these aldehydes and amines and obtain their UV / Vis absorbance and  $^{19}\text{F}$  NMR data. The imines **172** – **180** (Figure 16) were individually synthesized by exposing the aldehyde to the amine in methanol, and heating under reflux for 72 hours. The starting components were soluble in methanol and the imines were insoluble, therefore the products precipitated out. The imines were then purified by recrystallization using toluene / methanol. Our library of complex imines were then analysed by  $^{19}\text{F}$  NMR and UV / Vis spectroscopy (Table 3) (**Spectra 10 – 13**).



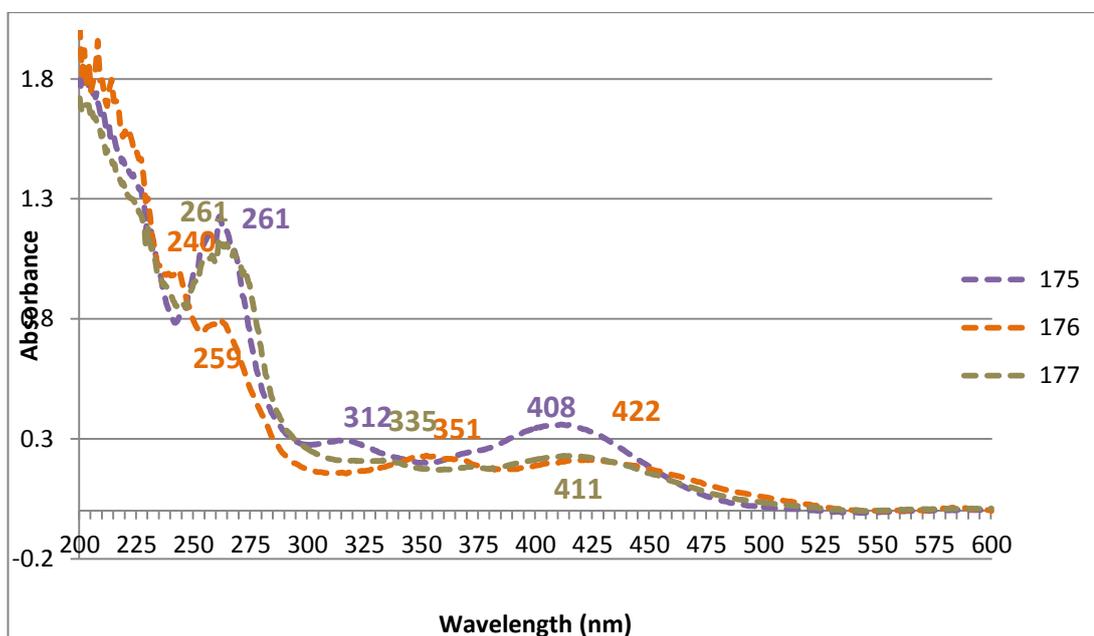
**Figure 16.** Library of Complex Imines **172 - 180**.

| Imine      | $^{19}\text{F}$ NMR (ppm) | UV / Vis Absorption (nm) |
|------------|---------------------------|--------------------------|
| <b>172</b> | -130.17                   | 249, 356                 |
| <b>173</b> | -130.05                   | 282, 364, 384            |
| <b>174</b> | -129.90                   | 266, 360                 |
| <b>175</b> | -109.96                   | 261, 312, 408            |
| <b>176</b> | -109.64                   | 240, 259, 351, 422       |
| <b>177</b> | -109.52                   | 261, 353, 411            |
| <b>178</b> | -132.61                   | 260, 288, 353, 339, 356  |
| <b>179</b> | -132.14                   | 289, 324, 339, 384, 415  |
| <b>180</b> | -131.70                   | 265, 280, 323, 339       |

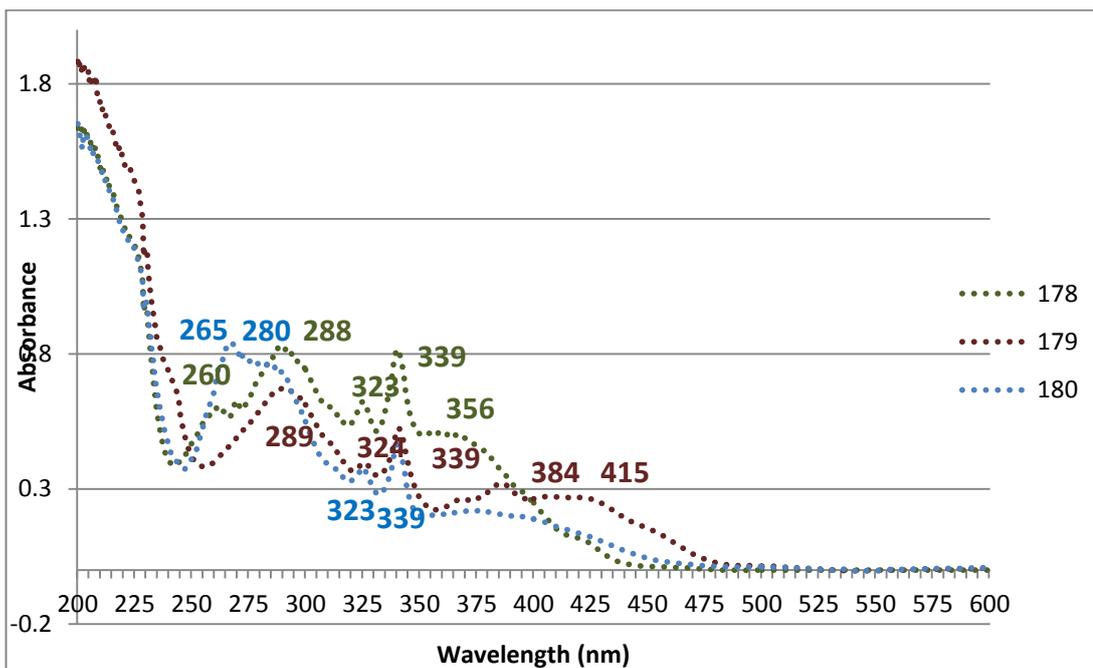
**Table 3.** A Table to Show the Unique  $^{19}\text{F}$  NMR and UV / Vis Spectroscopic Data for Our Nine Complex Imines **172 - 180**.



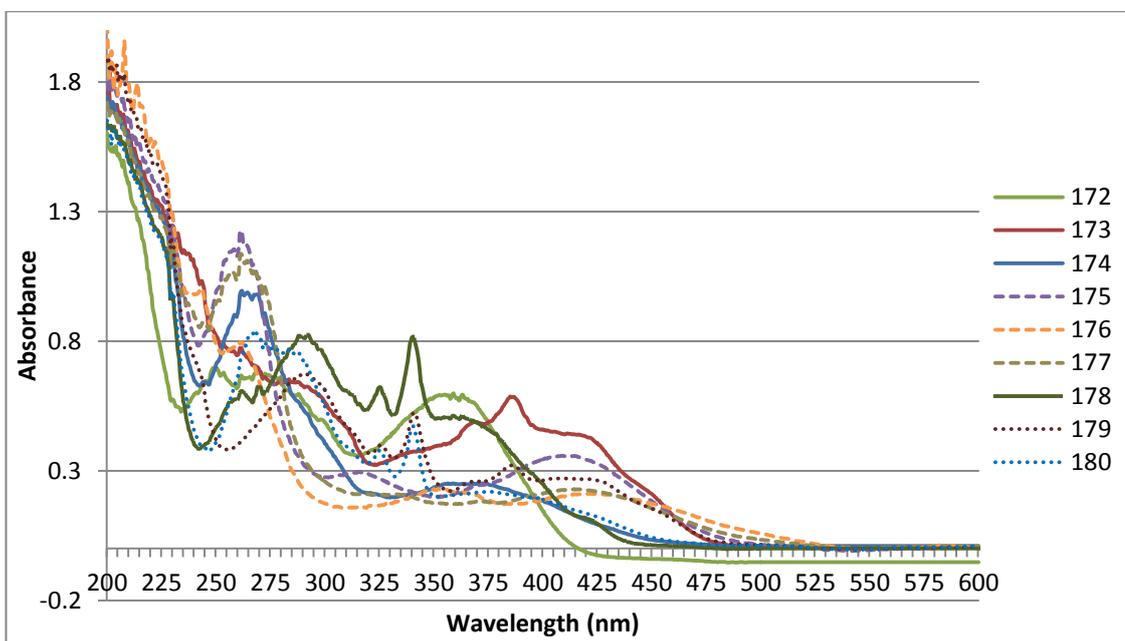
**Spectra 10.** UV / Vis Absorbance Spectra of Three Complex Imines **172 - 174**.



**Spectra 11.** UV / Vis Absorbance Spectra of Three Complex Imines **175 - 177**.



**Spectra 12.** UV / Vis Absorbance Spectra of Three Complex Imines **178 - 180**.



**Spectra 13.** UV / Vis Absorbance Spectra for Our Nine Complex Imines **172 - 180**.

As predicted, our complex synthesized imines resulted in unique  $^{19}\text{F}$  NMR and UV / Vis spectra for each product. We now had a library of complex imines ready.

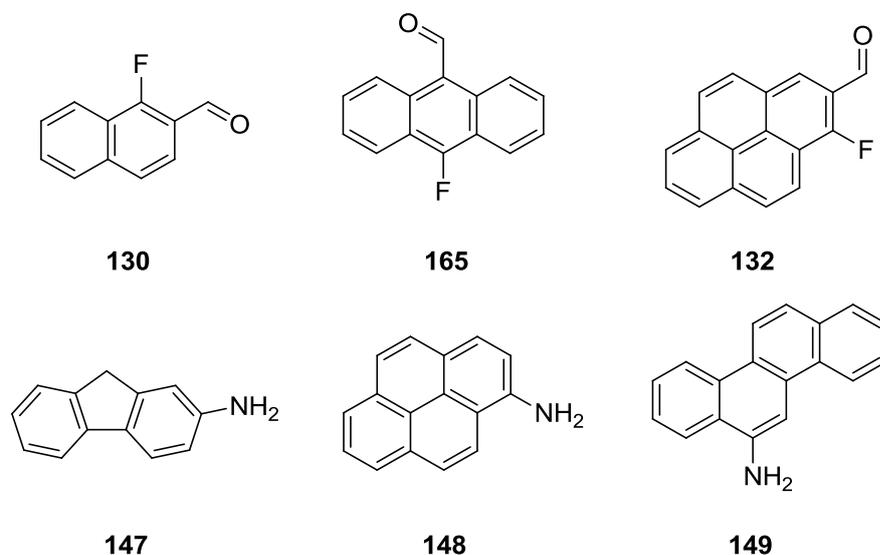
### 3.3 Conclusion

In chapter two, we concluded that we could identify a library of nine imine products individually if we add a fluorine atom to our aldehyde and amine building blocks and then analyse the imines by  $^{19}\text{F}$  NMR spectroscopy. In this chapter we presented work where we were able to prepare and individually identify nine imine products by having a fluorine atom only on one component (the aldehyde building blocks) and leaving the amine component non-fluorinated. This ultimately saved us time and money in preparing building blocks for the next stage of the research. We then successfully synthesized three complex fluorinated aldehydes and three complex non-fluorinated amines, which resulted in formation of nine coloured imine products with unique  $^{19}\text{F}$  NMR and UV / Vis absorbance spectrums that would enable us to monitor this reaction *in situ* in our ‘machine’ containing a UV / Vis sensor.

## Chapter 4.0 Development of the 'Machine'

### 4.1 Introduction

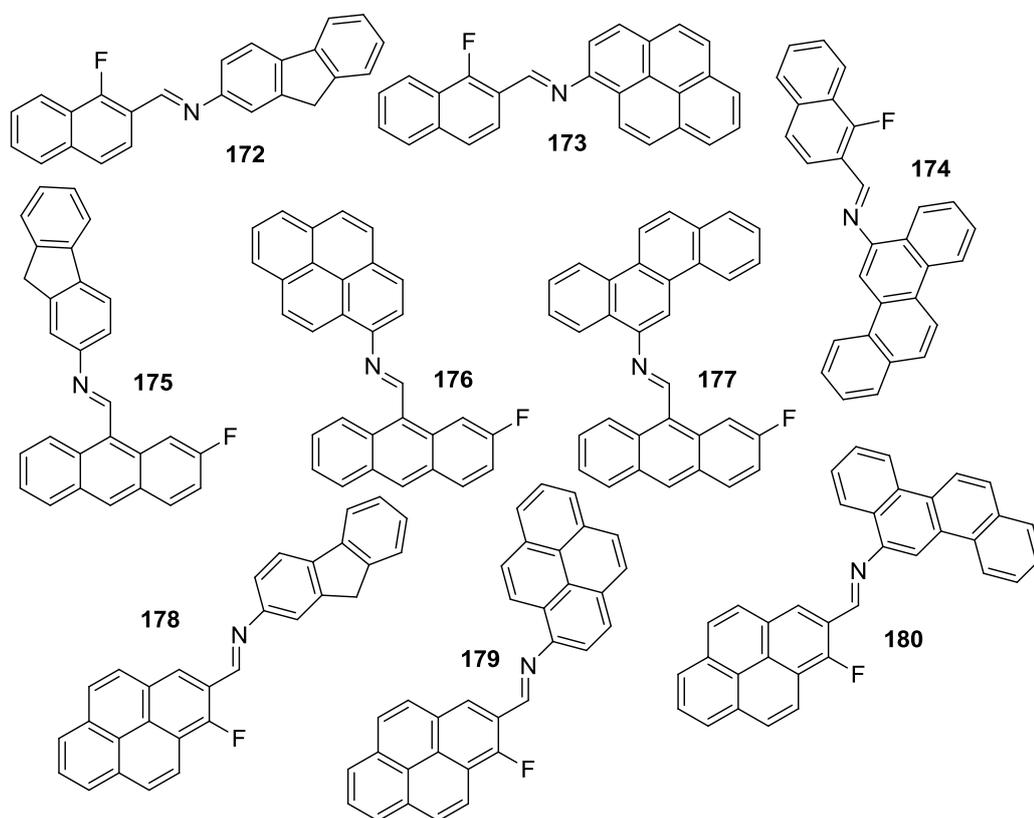
In chapter three, we decided to synthesize a library of highly conjugated aromatic imines. These imines were active in the UV / Vis region of the spectrum, therefore, could be monitored in our 'machine' equipped with a UV / Vis sensor, once completed. A fluorine atom had to be inserted to the building blocks, so we could accurately monitor the reaction using  $^{19}\text{F}$  NMR spectroscopy, but due to time and cost effectiveness, we decided to insert one fluorine atom to the highly conjugated aldehydes and have non-fluorinated highly conjugated amines as building blocks (Figure 17).



**Figure 17.** Highly Conjugated Fluorinated Aldehyde (**130**, **132**, **165**) and Highly Conjugated Non-Fluorinated Amine (**147**, **148**, **149**) Building Blocks which were Synthesized in Chapter

## 4.2 Results and Discussion

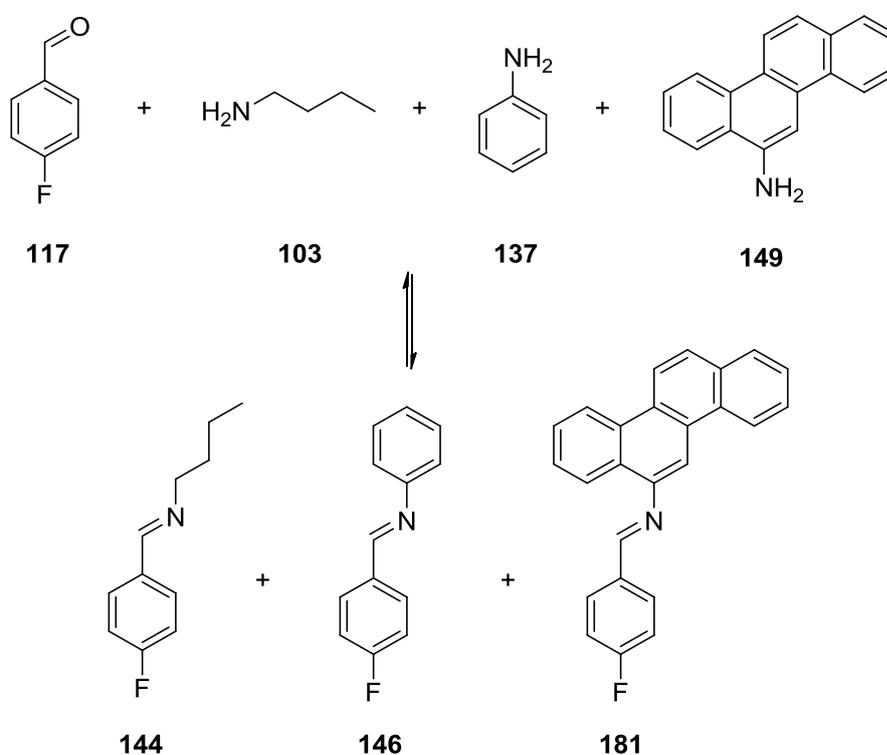
### 4.2.1 Preparing a Trial Reaction for the 'Machine'



**Figure 18.** Highly Conjugated Fluorinated Imines (**172 - 180**) which were Synthesized in Chapter 3.

Complex building blocks (Figure 17) and their imine products (Figure 18, **172 - 180**) had been synthesized and characterised, but using all these complex compounds straight away in a developing 'machine' would be very time consuming and expensive, therefore, we decided to pick one complex amine (**149**), one cheap aldehyde (**117**) and two amines (**103** and **137**) that were commercially available, just

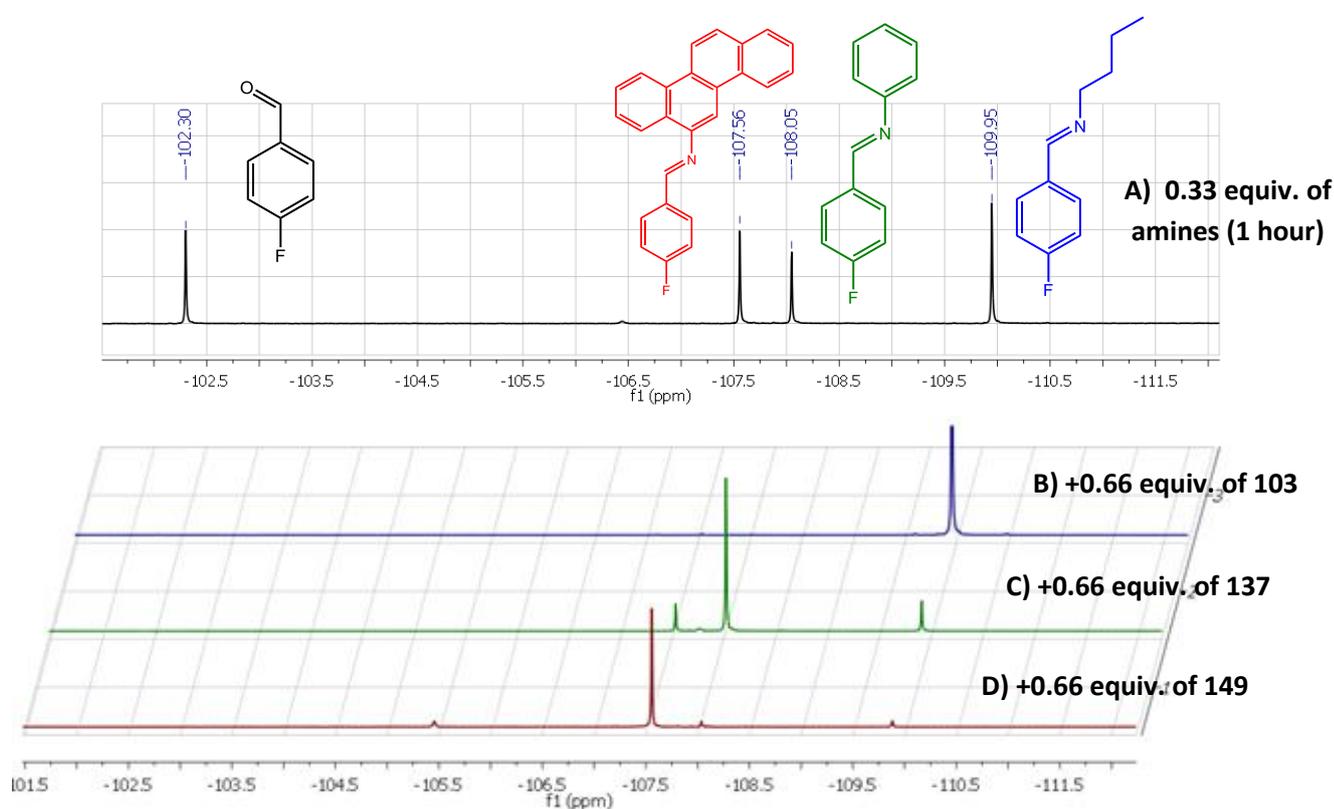
to see if we could cheaply control the formation of a specific imine monitored using  $^{19}\text{F}$  NMR spectroscopy and UV / Vis spectroscopy (Scheme 40). We do know that the accuracy of identification of imines by UV / Vis spectroscopy is poor compared to NMR spectroscopy, therefore we picked building blocks where only one imine, imine **181** would be uniquely coloured in the visible region of the spectrum compared to the alternative imines **144** and **146**. We first would still like to see if increasing the concentration of one product in a mixture could affect the absorbance spectrum and the whole system be automated in a computer controlled system.



**Scheme 40.** A DCL of Imines to be tested in our 'Machine'.

Aldehyde **117** at 1.00 mol equiv. was exposed to three amines **103**, **137** and **149** at 0.33 mol equiv. each in deuterated chloroform. A  $^{19}\text{F}$  NMR spectrum was taken within 10 min of the reaction, showed a reaction still under progress, and with

this spectrum we could see a peak for **117** at -102.1 ppm, **144** at -109.9 ppm, **146** at -108.1 ppm and **181** at -107.6 ppm (NMR not shown). Eventually after one hour (Spectra 14, A), starting material **117** disappears resulting in **144**, **146** and **181** in equilibrium at approx. 1 : 1 : 1 product ratio. With this ratio preserved, 0.66 mol equiv. of **103** was added, stirred for an hour then analysed by  $^{19}\text{F}$  NMR spectroscopy (Spectra 14, B). This experiment was repeated with excess of **137** (Spectra 14, C) and **149** (Spectra 14, D). The NMR spectra showed a shift in equilibrium in favour of the amines added in excess, which from our previous studies were expected.

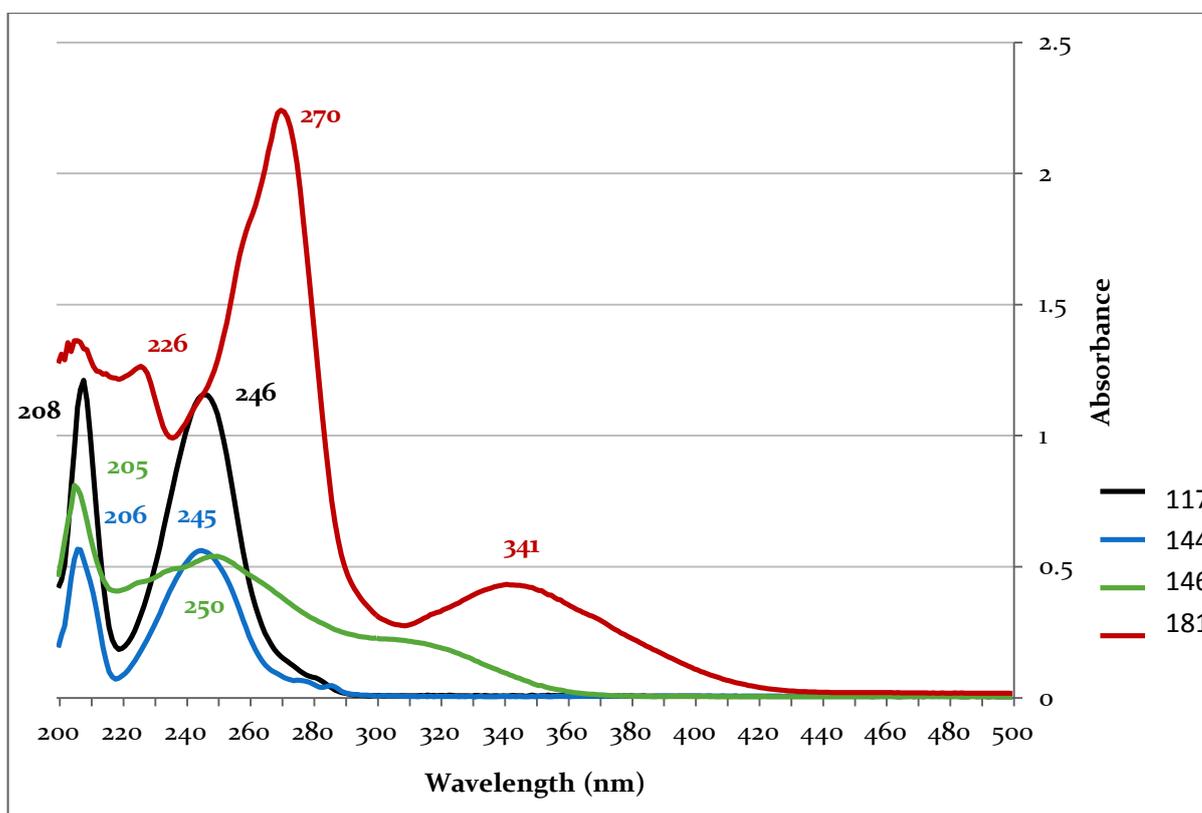


**Spectra 14.** NMR Spectra Showing the Effect on the Reaction Equilibrium by Adding Excess Amine.

This time we had products that varied in UV / Vis absorptions, therefore the above samples were also analysed by UV / Vis spectroscopy to see if an increase in

absorption was observed when compared to the standard 1 : 1 : 1 ratio of **144**, **146** and **181**.

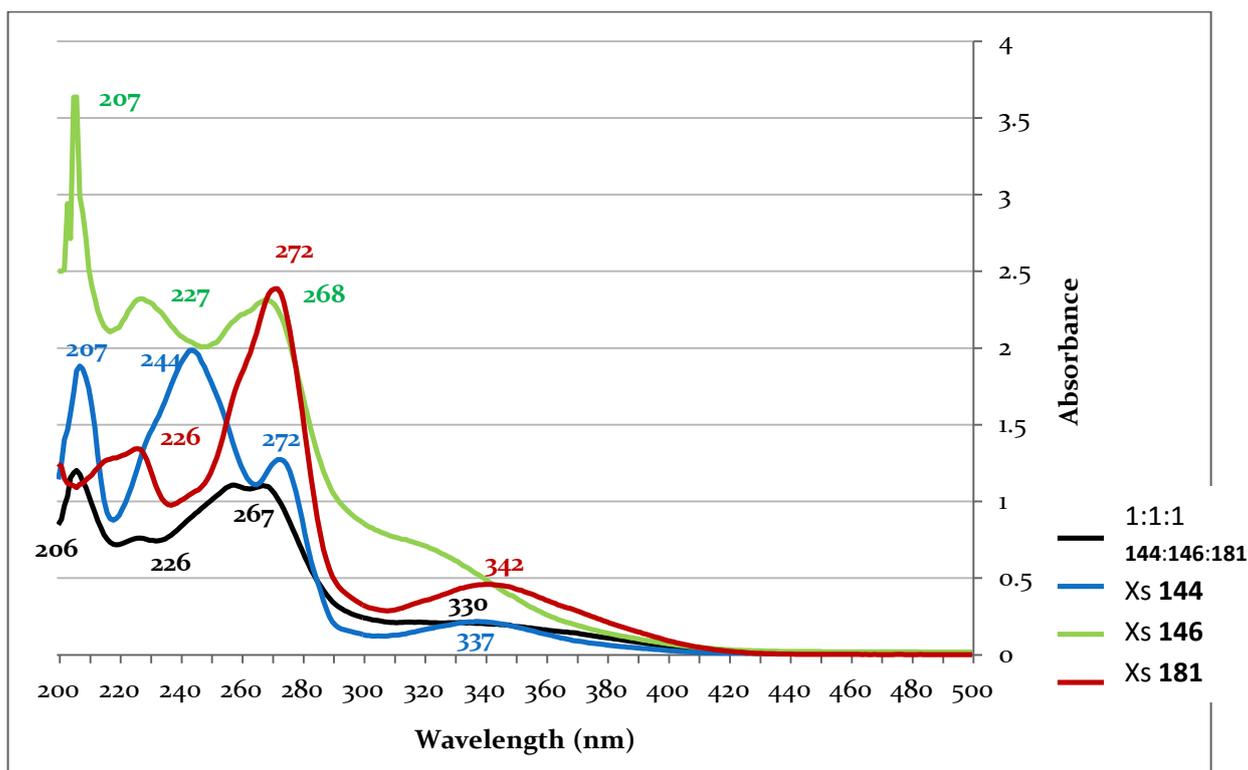
Spectra 15 showed the individual absorbance spectra of aldehyde **117** and the imine products **144**, **146** and **181**. We have products **144** and **146** which strongly absorb in the ultraviolet region of the spectrum and product **181** which absorbs further towards the visible region. We aimed to have a compound **181** absorbing in the visible region for easier identification purpose.



**Spectra 15.** UV / Vis Absorbance Spectra of Aldehyde **117** and Imine Products **144**, **146** and **181**.

Spectra 16 showed the UV / Vis absorbance spectrums of the approx. 1 : 1 : 1 mixture of imine products **144**, **146** and **181** (black line) (Spectra 14, A) and three

absorption lines containing the excess of each amine, the same mixture representing the  $^{19}\text{F}$  NMR spectrum - Spectra 14; B, C and D. Spectrum 16 clearly showed that the shift in equilibrium caused by the addition of excess amine could also be seen in a UV / Vis absorbance spectrum. We could clearly compare the shift of the standard (black line) with the excess product of **144** (blue line), **146** (green line) and **181** (red line).



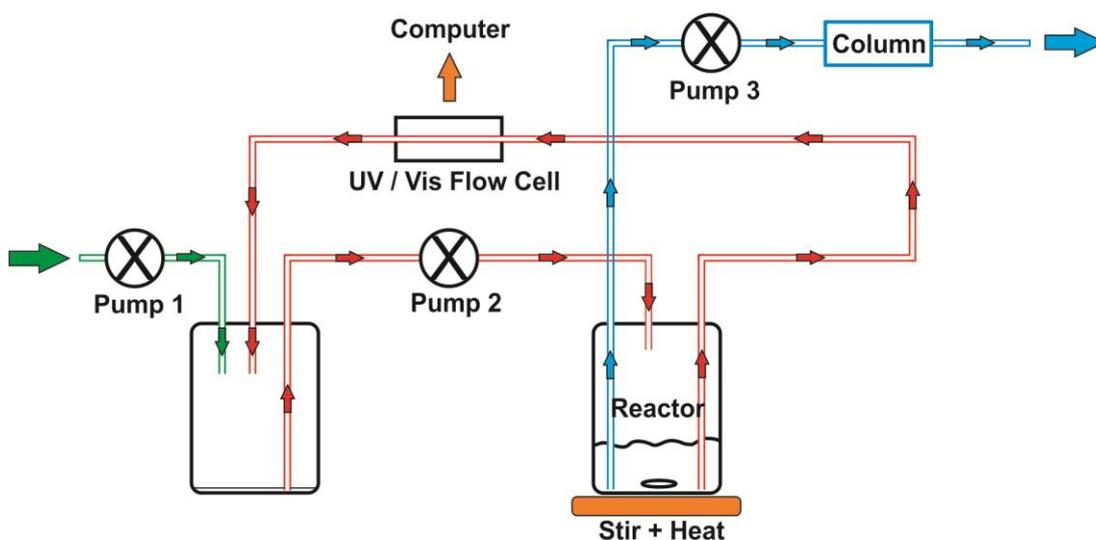
**Spectra 16.** The UV / Vis Absorbance Spectra of the Approx. 1 : 1 : 1 Mixture of Imine Products **144**, **146** and **181** (Spectra 14, A) (Black Line) and Three Absorption Lines Containing the Excess of each Amine, the same Mixture Representing the  $^{19}\text{F}$  NMR Spectrum (Spectra 14; B, C and D).

We have a reaction ready to be trailed in the 'machine', our aim was to replicate this reaction in our machine to see if the UV / Vis sensor built with an

automated software system could detect such increase in product concentrations and perform new commands accordingly. No such 'machine' had yet been developed by our collaborators while nearing the end of my PhD, therefore, further reactions on the complex building blocks were suspended. Instead, we here at Warwick University decided to create our own mini reactor flow system with the help of our collaborators at Brunel and Glasgow University working towards evolving a desired product.

#### 4.2.2 Designing a Mini-Flow System.

We first designed a preliminary flow system to see whether we could measure real-time UV / Vis absorbance of a mixture in a flow environment (Scheme 41). In this design we had pump 1 which would transfer building blocks into a non-sealed storage tank (green channel). Pump 2 would then transfer the building blocks into a sealed reactor which could be stirred and heated. As the reactor is sealed, any pumping action from pump 2 would create pressure in the reactor and to release this pressure, the reaction mixture would flow out *via* the red channel through the UV / Vis flow cell into the non-sealed storage tank. The reaction mixture would continually be flowed through the flow cell and the absorbance measured on the computer. We would also have the ability to transfer the contents of the reactor through a column to be collected by activating pump 3 (blue channel), if we have the desired UV / Vis absorbance spectra.



**Scheme 41.** Preliminary Design of our Mini-Flow System.

With the design ready, we had to build this system. Vigorous research and help from our collaborators allowed us to gather the parts and accessories required to build a flow system (Figure 19). We bought three syringe pumps from Tricontinent (Part A).<sup>91</sup> These pumps contain a RS-232 port and can be controlled by a computer using HyperTerminal or a custom build LabView<sup>92</sup> application (supplied by Dr Leonid Paramonov from Brunel University). Two 100 ml bottles and three port Omnifit bottle cap were bought from Kinesis<sup>93</sup> which would be our reactor and storage tank. We obtained a UV / Vis flow cell built by Dr Hien Nguyen at City College London. This flow cell was built from a highly resistant PEEK (polyetheretherketone) cross assembly containing optical fibre cables pointing at 180° to each other with the flow travelling perpendicularly (Part C). Other parts / accessories obtained included highly resistant PTFE (polytetrafluoroethylene) tubing (Part D), a custom built SolventPlus Omnifit column purchased from Kinesis (Part E), Ocean Optics USB 2000+ UV / Vis absorbance spectrometer with light source,<sup>94</sup> a computer, and high definition webcam (Figure 20 - 23). Using these parts, the system was constructed.

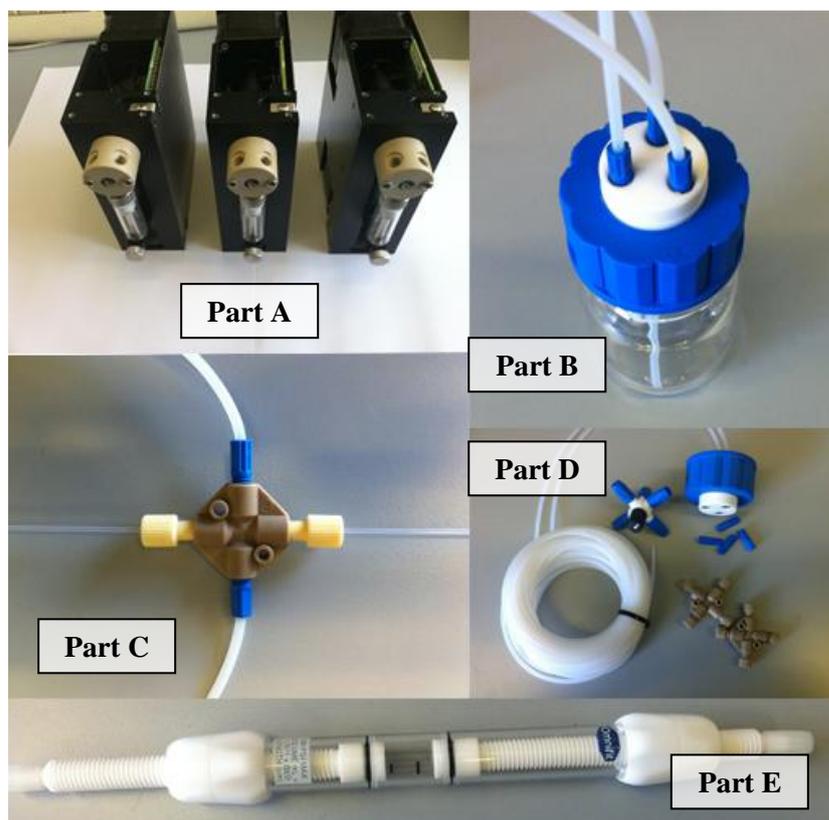


Figure 19. Pictures of Various Parts Used to Build Our Flow System.

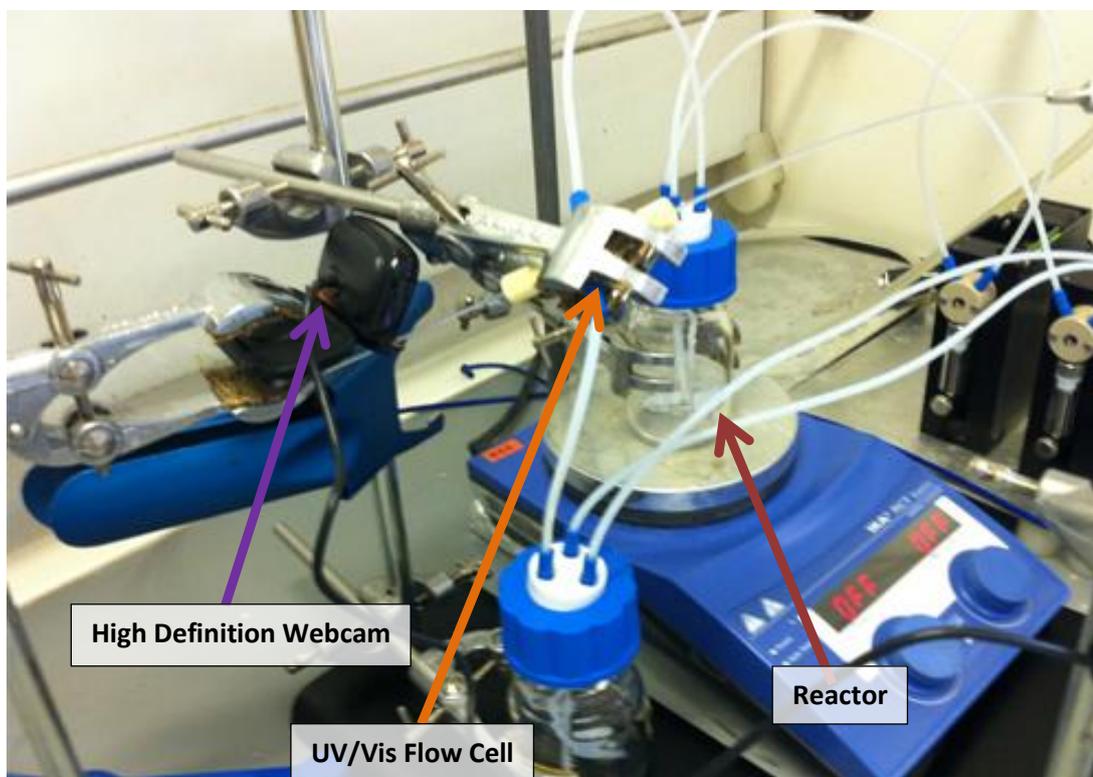


Figure 20. Picture of Our Flow System.

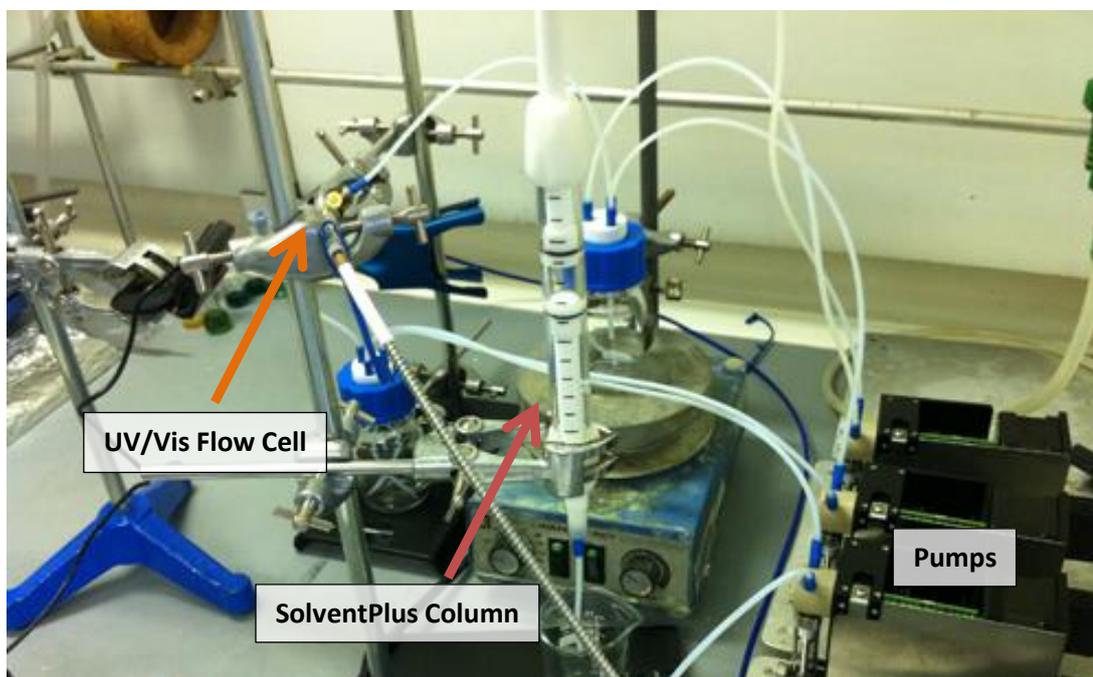


Figure 21. Picture of Our Flow System.

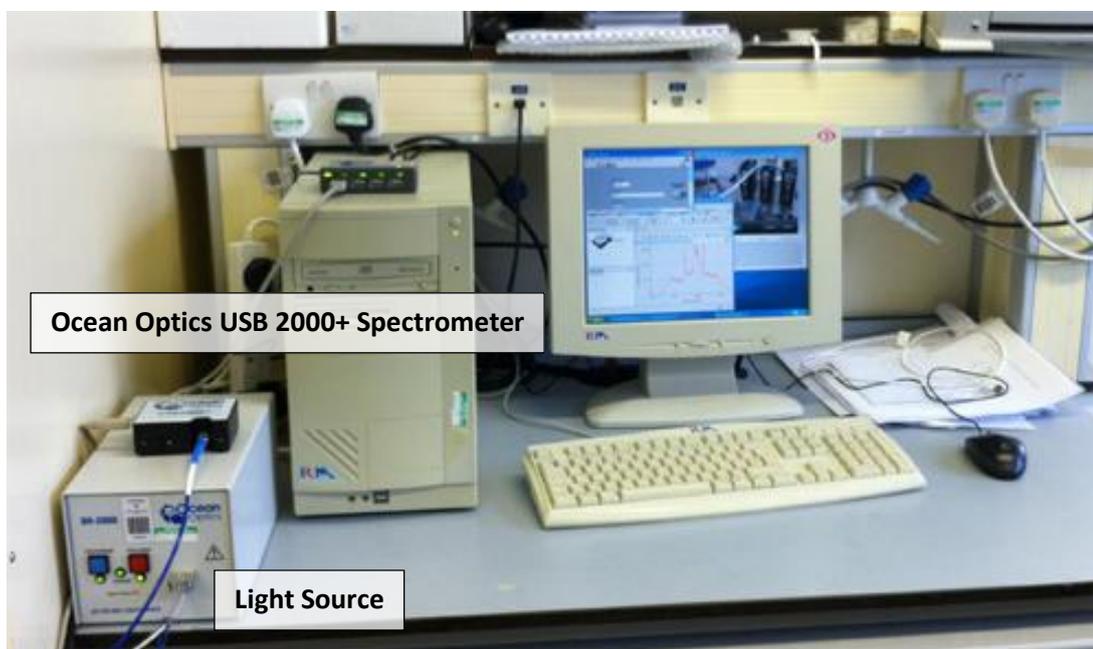
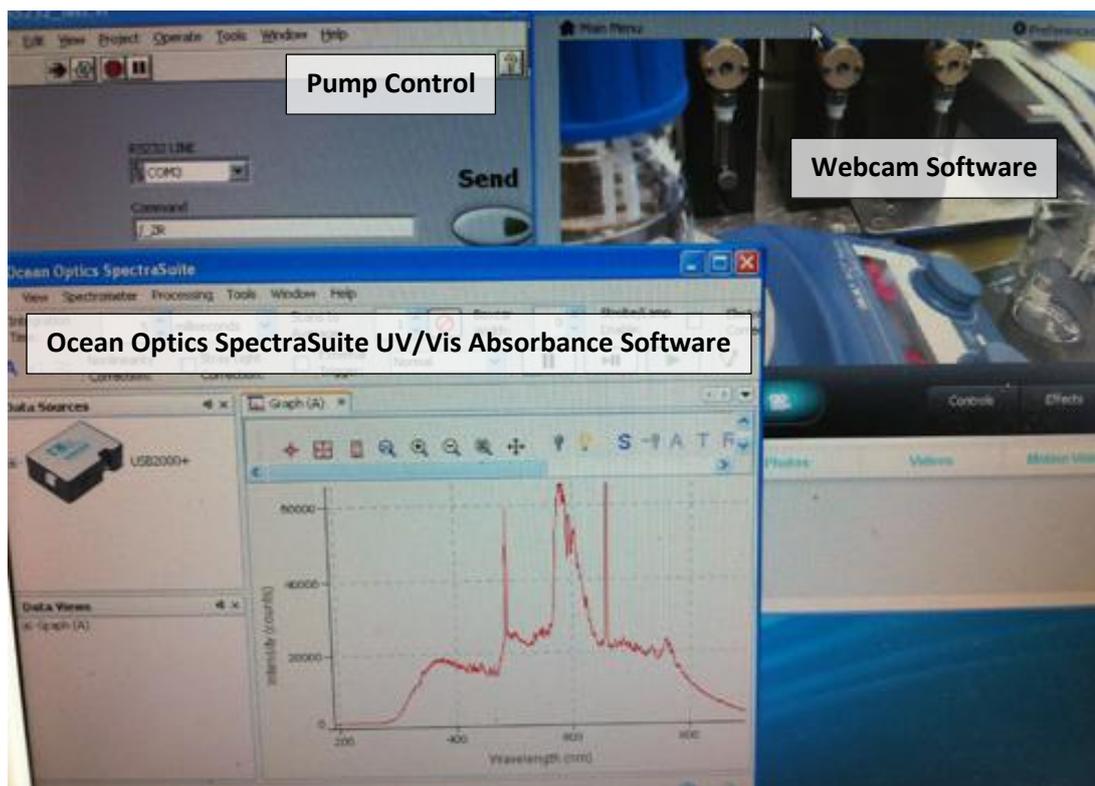


Figure 22. Picture of the Spectrometer, Light Source and Computer Hardware.



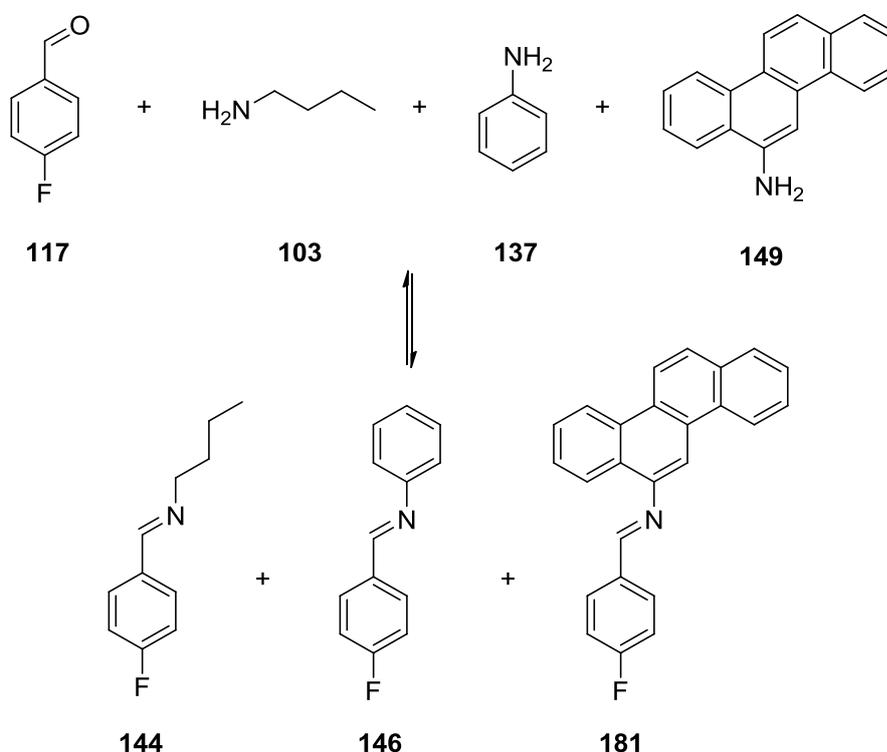
**Figure 23.** Picture of the Software Used to Control the Flow System.

The reaction presented in Scheme 40 was then tested in this mini-flow system, but we instantly came across concentration problems where the too much light is absorbed and measurements would read off the chart. The mixture was running too concentrated to be detected by our UV / Vis spectrometer. The initial concentrations of our building blocks were  $0.1 \text{ mol dm}^{-3}$  and to obtain a useful absorbance spectrum we had to reduce the concentration of our building blocks to  $0.0001 \text{ mol dm}^{-3}$ . However the rate of reaction at this ultra-low concentration was now too slow! At this concentration the reactants did not synthesize the imines even after 72 hours. We had to think of alternate ways of obtaining real-time UV / Vis absorbance spectrums while keeping the concentration of the building blocks high enough to allow the synthesis of imines in a reasonable time scale of about 12 - 24 hours.

$$A = \epsilon lc$$

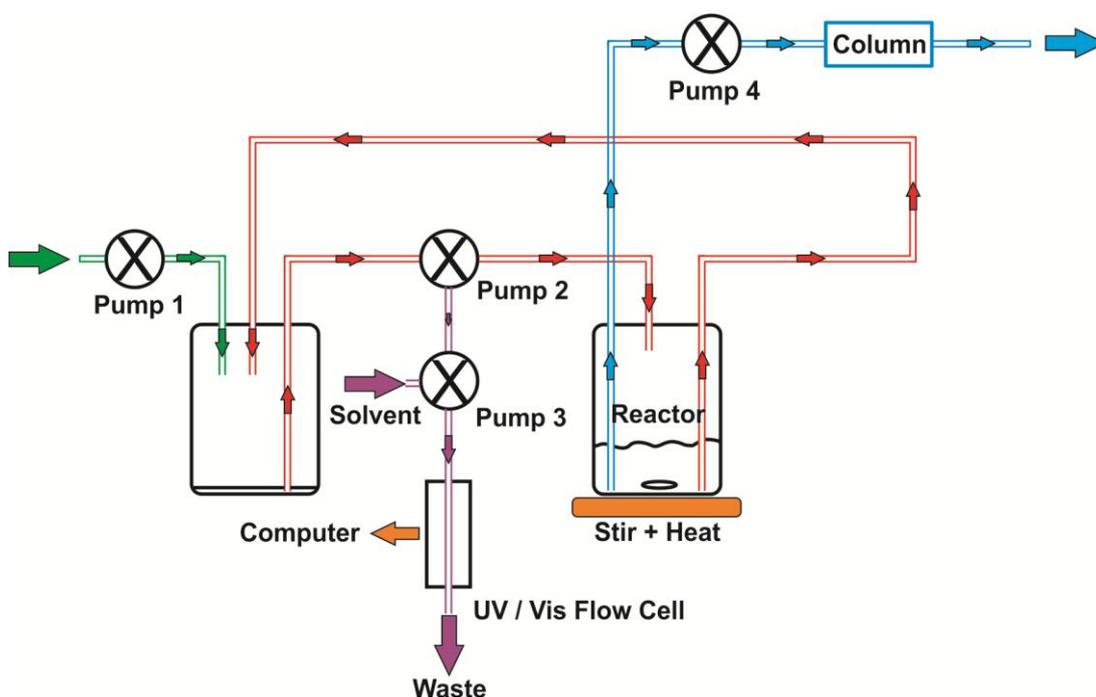
**Equation 2.** Beer-Lambert Law; where  $A$  = absorbance,  $\epsilon$  = molar absorptivity,  $l$  = the path length and  $c$  = concentration.

According to the Beer-Lambert law (Equation 2),<sup>76</sup> absorbance is directly proportional to  $\epsilon lc$ , therefore we can reduce the absorbance by selecting compounds with low molar absorptivity, by reducing the path length of the flow cell or by reducing the concentration of the mixture. Controlling the molar absorptivity would be very difficult, therefore, the simplest variable to change would be path length of the flow cell or the concentration of the mixture. As previously tested, reducing the concentration by 1000 times resulted in very slow reaction times and, therefore, we decided to alter the path length.



**Scheme 40.** A Dynamic Library of Imines.

We redesigned our flow system to reduce the path length from 10 mm to 1 mm, repeated the reaction in Scheme 40 which again resulted in too high a light absorbance due to the high concentration of the mixture. However, this was expected as absorbance is directly proportional to  $\epsilon lc$  and we would've had to reduce the path length by 1000 times to obtain absorbance spectra for concentrations of our building blocks at  $0.1 \text{ mol dm}^{-3}$ . But reducing the path length by 1000 times would disrupt the flow and, therefore, we went back to the drawing board and proposed an alternative flow design where now we would use a reduced path length flow cell (1 mm) and also dilute the reaction mixture before passing through the UV / Vis flow cell (Scheme 42).



**Scheme 42.** Improved Design of Our Mini-Flow System

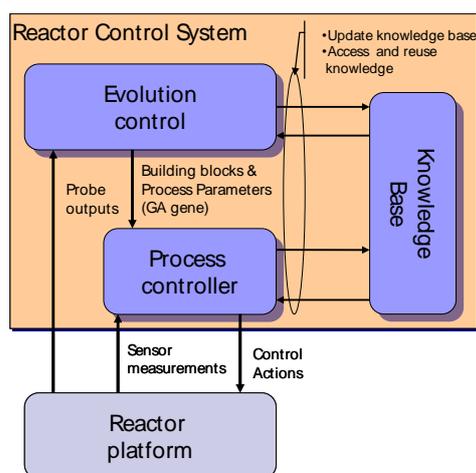
In this new and improved system, we introduced a three way valve system on pumps 2 and 3. Now, a desired amount of reaction mixture could be transferred from pump 2 to pump 3 and this amount of mixture could then be diluted by adding a

desired amount of solvent. This mixture would then be forced through the UV / Vis flow cell into a waste container (purple channel). We understood that by using this method we would lose chemical components from the reaction which diminishes the original idea of recycling all components leaving no waste, but with the accuracy of these pumps, we are talking about transferring microliters of reaction mixture per given time.

The reaction in scheme 40 was repeated in this new improved system and we were now able to see UV / Vis absorbance spectrum using concentrations of building blocks at  $0.1 \text{ mol dm}^{-3}$ . A video of this system is present with the thesis. With a suitable in-flow UV / Vis absorbance monitoring system in place, we progressed into developing a more complex automated flow system.

### 4.2.3 Development of a more Complex Flow System.

The software control system in development at Brunel University will ultimately comprise of three levels: (i) evolution control; (ii) process controller; (iii) feedback from probe and sensors.



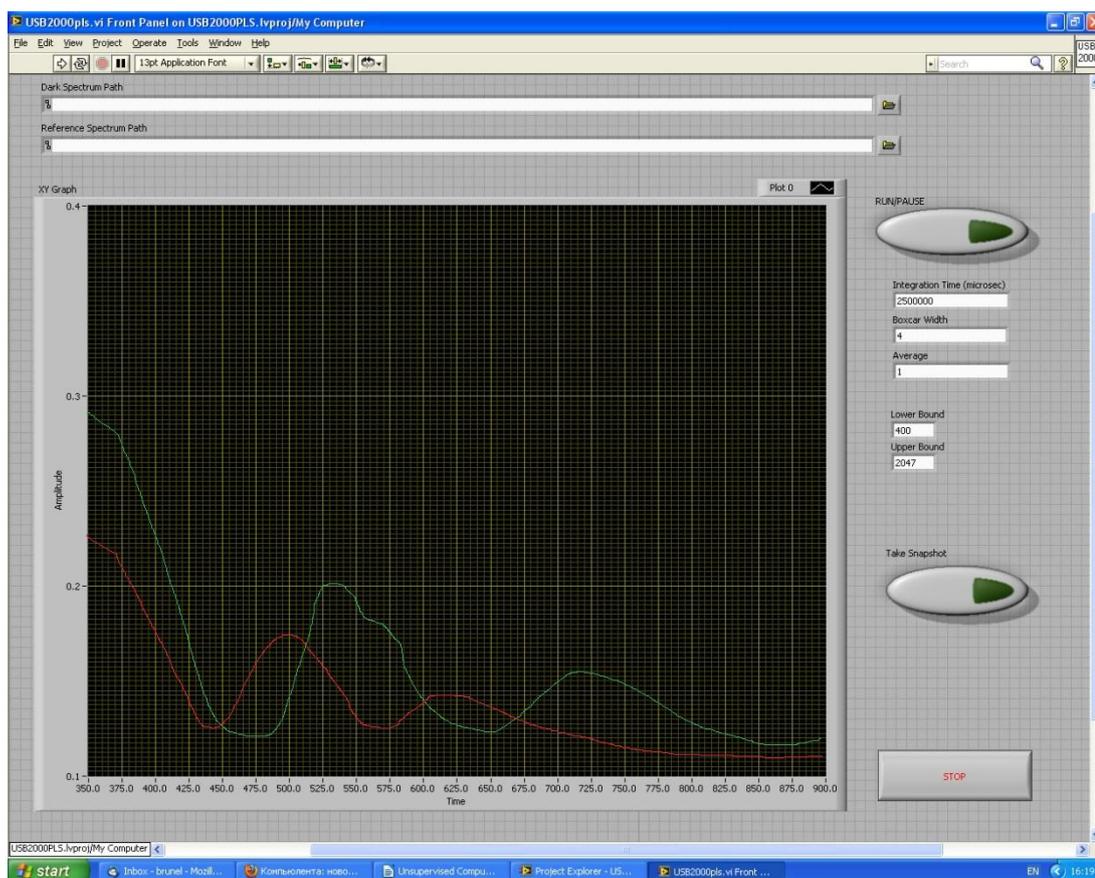
**Figure 24.** Schematic of the EPD Software Control System.

(i) The control system (Figure 24) would drive our reactor system using an evolutionary process, which systematically determines and tracks combinations of building blocks. Potentially these are the chemical systems with the required properties and will be produced by the reactor platform, in our case, evolving an imine with a desired colour. This evolution process would be controlled by a Genetic Algorithm which is a probabilistic search algorithm that iteratively transforms a set of objects (genes), called a population, each with an associated fitness value, into a new population of offspring objects using the Darwinian principle of natural selection. It will follow operations that are modelled after natural genetic operations, such as crossover and mutation. A combination of building blocks would be subjected to several processing parameters (temperature, pressure, flow rates etc.) to drive the reactor system for its production.

(ii) A constrained predictive control strategy will be employed to control physical processing in the reactor. This will be based on feedback from the sensors (such as UV / Vis, temperature, pressure) at particular sampling stages, and optimal control actions would be performed when a desired product is detected. The model is used to predict the behaviour of dependent variables (i.e., outputs) of the system with respect to changes in the process independent variables (i.e., inputs).

(iii) Outputs of the reactor will be interrogated by the probe monitoring the colour of the imine product. Probe outputs will be the values against which fitness is determined by the genetic algorithm. Based on that, the evolution controller would make a decision to channel those outputs for collection or recycling. The evolution controller progresses to the next iteration until the desired colour has been achieved or a stopping criterion has been satisfied. If the desired coloured product fails to

synthesize at a particular initial condition, then a breakdown of products to starting materials and a restart of the system would occur. Finally, if the desired product is successfully synthesized, then the combinations of building blocks, parameters and reactor system configurations that achieved desired properties, will be logged into a knowledge base for reuse and to direct evolution of potentially similar chemical systems.



**Figure 25.** Front Panel of the Customised LabView Program.

During thesis preparation, the software created by Dr Leonid Paramonov at Brunel University would currently allow us to automatically control the reaction based on the feedback from the UV / Vis absorbance spectrometer. We could now set a desired UV / Vis absorbance spectrum on the software (Figure 25, green line),

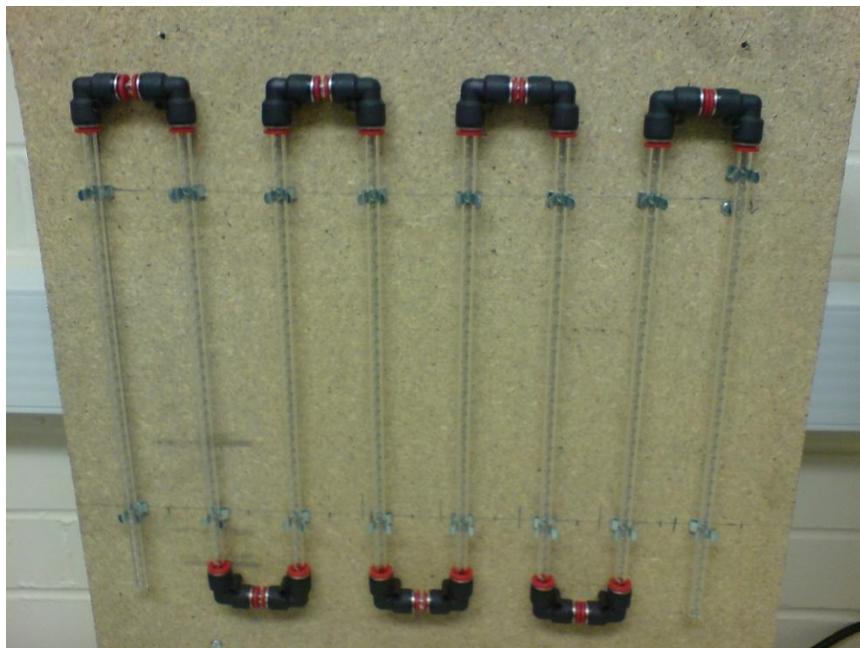
run a reaction and when the initial dynamic library mixture (Figure 25, red line) eventually synthesizes a product to the same green absorbance spectrum (or similar to a desired proximity), the computer would detect this and perform the next desired task such as filtering the mixture through a column and be collected. Basic elements of (i) evolution control; (ii) process controller; and (iii) feedback from probe and sensors have been developed but further improvements and vigorous testing was still required. At this point I had run out of time to continue with this project.

With a complex software system being developed at Brunel University, we also required a complex reactor platform. Unlike our current simple flow system which monitors one but crucial UV / Vis absorbance of our imine products, the complex reactor platform being developed at Newcastle University will include multiple probes monitoring multiple reaction variables such as concentration, temperature, pH, pressure, etc.

Instead of having a 'reaction chamber' which is essentially a Continuous Stirred-Tank Reactor (CSTR), they have been developing a continuous system which operates in plug flow. Plug Flow Reactor (PFR) allows tight control of residence time which would ensure that all chemical elements within the reactor experience the same processing conditions. This is crucial because if the residence time is correct and there is 'good' plug flow then no portion of the reactants will be "undercooked" (not reaching the desired conversion) or "overcooked" (leading to undesired by-products). This would ensure that the correct product is synthesized while minimising the time lag between input change and output response (i.e. the system is 'responsive'), thereby giving a clear step-change between steady states. This is an efficient mode of operation and would result in no wasted volume within the reactor.

One of the main challenges in designing such a reactor system would be its ability to cope with a wide range of conditions.

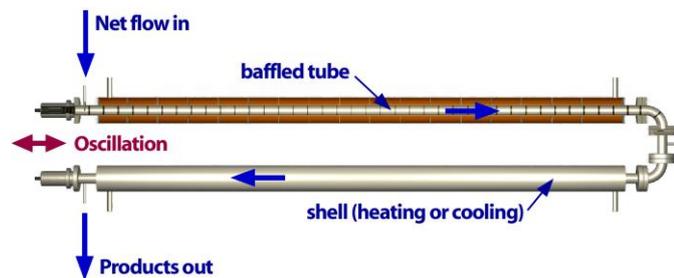
CSTR are usually designed for specific route rather than general applications. The plug flow operation is designed to have a wide operating window, for example, simply by changing the flow rate, we could vary the online residence time. We would also be able to set a desired temperature profile along the length of tubular unit operations, and other profiles such as agitation, if required.



**Figure 26.** Small Scale Baffled PFR Developed by Newcastle University.

Conventional PFRs are simply tubes (or tubes containing flow improvers) in which high a degree of mixing and plug flow are achieved by creating turbulence. One such example has been developed by Newcastle University (Figure 26). For chemical reactions with a long duration time, it would be difficult to design a practical, scaleable, laboratory-scale plug flow reactor. Longer reactions would require an extremely long and narrow PFR, as the fluid must have a certain velocity

for a long period of time. There are many associated disadvantages to this conventional PFR design, hence the oscillatory baffled reactor (OBR) is likely to be the best solution for these longer reactions. OBRs would be practical as unlike conventional plug flow reactors the mixing is decoupled from the net flow velocity, hence allowing relatively long reactions continuously, without requiring impractically long, narrow reactor designs. (Figure 27).



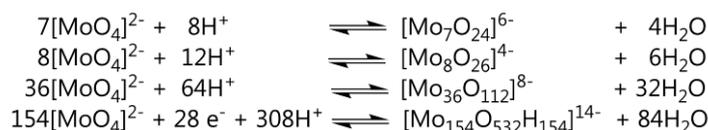
**Figure 27:** A Schematic of the Oscillatory Baffled Reactor (OBR).

Mixing in an OBR is achieved by oscillating fluid through orifice plate baffles, each baffle acting as a small CSTR therefore would behave as having multiple CSTRs (typically  $>100$ ) in series. A conventional PFR can easily be turned into an OBR simply by activating the oscillation of the fluid and therefore it would be sensible to use a conventional PFR (halting oscillation) for chemical reactions with a short duration and OBR (activating oscillation) for longer reactions. The main alternative solution to use of the OBR / conventional PFR system is to use a series of CSTRs. This option will be evaluated in the future against the OBR system. Currently, we have been using a single CSTR, while no baffled PFR / OBR has been available to us to be incorporated into our flow system. The ultimate EPD may incorporate aspects of both solutions as there are certain kinetic profiles which are best suited to sequential CSTR-PFR systems.

#### 4.2.4 Inorganic Building Blocks for the 'Machine'.

We at The University of Warwick had concentrated on developing **organic building blocks** as previously shown in chapters 2 and 3 while our collaborator at Glasgow University had been developing **inorganic building blocks** for the 'machine'.

There are a huge number of potential inorganic and ligand / metal combinations that could be used including redox active metal complexes, photoactive complexes and magnetic systems where the connection of building blocks in diverse ways using an evolutionary algorithm would yield interesting results. Our collaborator at Glasgow University focused on the polymerisation of molybdenum oxide building blocks  $[\text{MoO}_4]^{2-}$  which have shown to undergo an extraordinary range of growth processes to polyoxomolybdate-based clusters. This polymerisation to nanoscale cluster molecules can be controlled and the polymerisation process is reversible (Figure 28).



**Figure 28.** Reversible Formation of Small Molecule and Nanoscale Mo-Clusters.

Polyoxomolybdate-based cluster formation can occur on a range of timescales from sub-millisecond to several hour timescales and the breakdown to starting reagents can be achieved by addition of water and electrolyte and moderate

temperatures. The massive different in length scales between the different molecules formed mean that both mass spectrometry, NMR, and X-ray structural analysis can be used to determine the molecular products. Variable reaction parameters include concentration, temperature, ionic strength, reducing agent, pH, additional ligands / metals. Different cluster types and sizes are also different colours and this could also be used as a marker.

### 4.3 Conclusion

Our work from chapters two and three allowed us to create a library of complex imines which we could uniquely detect using  $^{19}\text{F}$  NMR spectroscopy and UV / Vis absorbance spectroscopy. A reaction was ready to be trailed on the 'machine' but no such 'machine' had been developed by our collaborators, while nearing the end of my PhD, therefore we created our own simple system to test *in situ* UV / Vis absorbance measurements of our library of imines. Initially we had problems with the concentrations of our building blocks as they were too concentrated to be detected by UV / Vis spectroscopy, but with further work, since writing this thesis we were successful in modifying the system to carry out such measurements using high concentration of components in the reactor. My time on this project is complete and the development of the 'machine' is still in early stages, concentration may not be just one issue, and more may come up as we develop this into a more complex system.

## Pre-Chapter 5 Summary

The development of our ‘machine’ would allow us to take small organic / inorganic building blocks and use them to prepare any theoretical compound with any theoretical property that is determined by the ‘machine’. For this ‘machine’ to work, one of the essential components required were organic building blocks that can reversibly react under various conditions until a product with a desired property had been evolved.

Our goal was to create a dynamic combinatorial library of imine products using simple aldehyde and amine building blocks that would reversibly react under a variety of conditions. We were then to progress into creating a complex dynamic combinatorial library which would generate imine products of various colours that could be uniquely identified using a UV / Vis spectrometer in the ‘machine’. We are to collect these data for our engineer partners to aid them on the design of the ‘machine’, to prove that we could evolve a compound with a specific colour. But, before we combine various aldehydes and amines in one-pot and hope for the desired colour to evolve, we had to first analyse these imines outside the ‘machine’ to understand the reaction. For this we required a suitable analytical method that could accurately detect multiple components in a mixture (three aldehydes, three amines resulting in nine imine products).

In chapter two, we demonstrated that  $^{19}\text{F}$  NMR spectroscopy was sufficient to monitor in real time the equilibrium of a 3 x 3 matrix of fluorinated amine + aldehyde building blocks. We also demonstrated that the system of our study was

under a dynamic equilibrium and that by altering the acid or base concentrations, we can affect the dynamics of the reaction and monitor it quantitatively. With a suitable analytical method ready, we needed to create a library of imines which were ultraviolet / visibly active, so we could evolve a compound based on a colour property on our ‘machine’.

In chapter three, we presented work where we were able to prepare and individually identify nine imine products by having a fluorine atom only on one component (the aldehyde building blocks) and leaving the amine component non-fluorinated. This ultimately saved us time and money in preparing building blocks for the next stage of the research. From this result, we decided to synthesize a library of highly conjugated aromatic imines. These imines could be uniquely detected in the UV / Vis region of the spectrum (and using  $^{19}\text{F}$  NMR spectroscopy) therefore could be monitored in our ‘machine’ equipped with a UV / Vis sensor, once completed.

In chapter four, a reaction was ready to be trailed on the ‘machine’ but no ‘machine’ had been developed by our collaborators, therefore, we created our own mini-flow system to test *in situ* UV / Vis absorbance measurements of our library of imines, as we were running out of time and nearing the end of my PhD.

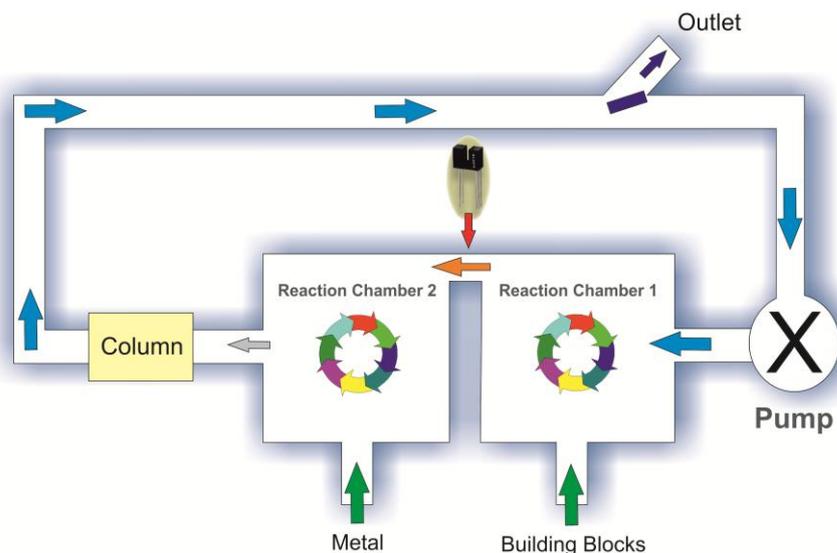
While this ‘machine’ was under development we also decided to synthesize imine ligands for metal mediated atom transfer radical cyclization reactions (ATRC) which is extensively studied by the Clark group. We knew that once the ‘machine’ was developed, we could modify the system in a way which would allow us to develop optimised imine catalysts for ATRC reactions (further explained in the next chapter).

## Chapter 5 Developing Efficient Catalysts for ATRC

### 5.1 Introduction

In Chapter four, we created our own mini-flow system as we were running out of time and no ‘machine’ was delivered to us in time as promised. Halfway through my PhD, we knew that there would be delay with the development of the ‘machine’ to experiment with our complex coloured imines. For this reason we decided to synthesize imine ligands for metal mediated atom transfer radical cyclization reactions (ATRC) which is extensively studied by the Clark group.

This move was made as we knew that once the ‘machine’ was developed, we could modify the system in a way which would allow us to develop optimised imine catalysts for ATRC reactions. We could use the idea of moulding in DCC by exposing copper salts to a dynamic library of imines to identify which imines would bind efficiently to the copper metal forming the most stable complexes. The most efficient imine ligand for ATRC may not be the strongest binder to the copper metal, therefore the idea was to create a flow system where we would be able to identify the most stable complexes to the least stable complexes.



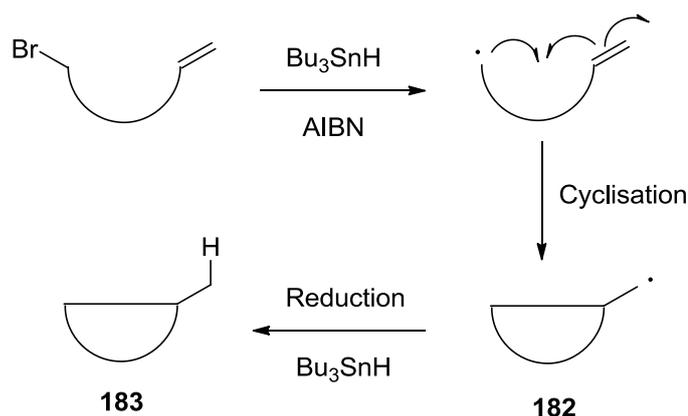
**Figure 29.** Schematic of the Proposed Preliminary Reactor Platform to Discover Efficient Ligands for Metal Mediated ATRC.

This could be achieved by modifying the existing flow design. In this new design (**Figure 29**) we would have two reaction chambers and an inline silica plug (column). The idea here would be to insert various aldehyde and amine building blocks into the reaction chamber 1 and allow the imines to reach equilibrium. This mixture would then be analysed and transferred to reaction chamber 2 where a small amount of metal salt would be added. After a given time reaction time, the mixture would then be filtered through an inline silica plug which would trap the most stable metal / ligand complex and allow the non-metal coordinated ligands back into reaction chamber 1, then analysed to determine the declining / missing imine before repeating this process. This process would be automated and run several times mopping up the most stable metal / ligand complexes each time. With the resulting metal / ligand stability data we could identify the possible reactivity of these imine ligands towards ATRC reactions.

Our ‘machine’ should allow us to categorise various metal – ligand complexes relative to their stability and their reactivity, but before we develop a tweaked system to do this job in the ‘machine’ it would be necessary to obtain data on the relative efficiency of various novel imine ligands compared to those currently used in ATRC.

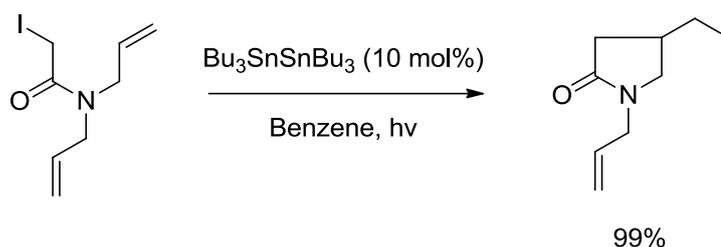
### 5.1.1 Atom Transfer Radical Cyclization (ATRC)

Traditionally, formation of a carbon - carbon bond to form cyclic systems are performed using stoichiometric amounts of tributyltin hydride ( $\text{Bu}_3\text{SnH}$ ) or related triorganostannanes.<sup>95, 96, 97</sup> Common problems arising from the use of tin compounds are its high toxicity,<sup>98, 99</sup> expense<sup>98</sup> and difficulty with purification.<sup>99</sup> But the main disadvantage is that they are reductive by nature, for example, the formation of the radical **182** after cyclisation is ‘quenched’ by the addition of hydrogen atom generating product **183** and losing a functional group (Scheme 43).



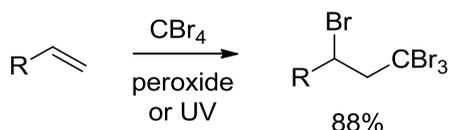
**Scheme 43.** Reductive Cyclisations using  $\text{Bu}_3\text{SnH}$ .

In 1993, Curran came up with an improved method to retain the functionality by replacing stoichiometric amounts of  $\text{Bu}_3\text{SnH}$  with catalytic amounts of hexabutylditin ( $\text{Bu}_3\text{SnSnBu}_3$ ) (Scheme 44).<sup>100, 101</sup> While the disadvantage of this reaction still lay with the use of an organostannane reagent, nevertheless, the reaction was terminated by an iodine atom transfer (instead of reduction). These kinds of reactions are commonly known as atom transfer radical cyclisations (ATRC).



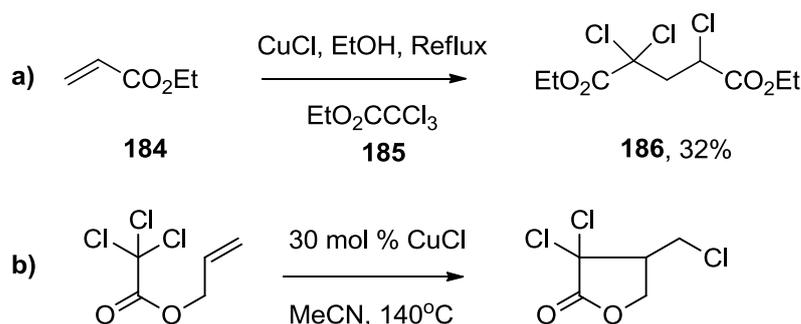
**Scheme 44.** Cyclisation using Hexabutylditin.

ATRC is similar to atom transfer radical addition (ATRA) which was first demonstrated by Kharasch in 1945.<sup>102-104</sup> He demonstrated the addition of carbon tetrahalides or haloforms across an olefin when heated to 70 – 90 °C in the presence of 1 – 5 mol % of diacyl peroxide (Scheme 45). Carbon tetrabromide was different from other carbon tetrahalides as the addition could also be initiated by visible light. Kharasch proposed the commonly known initiation, propagation and termination mechanism for this reaction.



**Scheme 45.** Kharasch Addition Reaction.

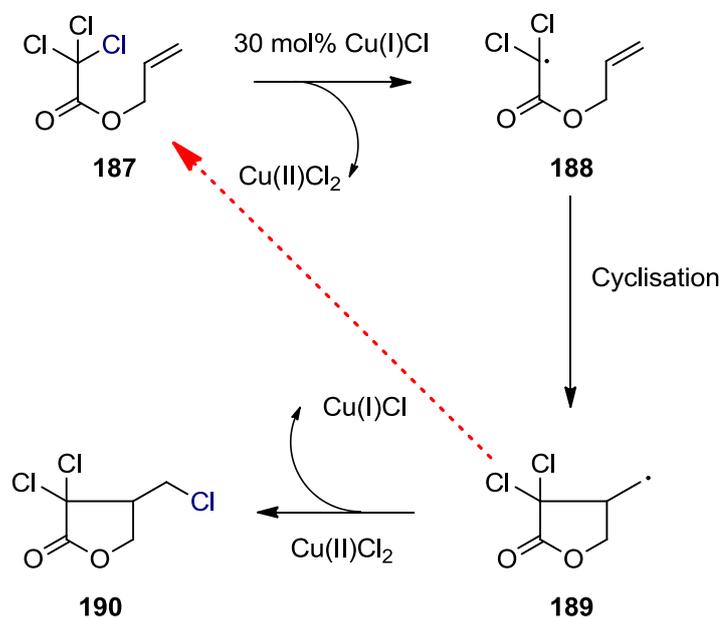
In 1964, Murai and co-workers introduced ATRA using catalytic transition metals which did not require the use of toxic tetrabromomethane or reactive peroxides.<sup>105</sup> After screening various metals, they discovered copper to be the most efficient and synthesized diethyl 2,2,4-trichloroglutarate (**186**) from ethyl acrylate (**184**) and ethyl trichloroacetate (**185**) using cuprous chloride as catalyst (Scheme 46, a).



**Scheme 46.** a) Copper Mediated Intermolecular Addition; b) Copper Mediated Intramolecular Addition.

In 1983, Nagashima and co-workers had developed the reaction further by demonstrating an intramolecular system leading to the copper mediated ATRC reaction (Scheme 46, b).<sup>106</sup> He also proposed a catalytic redox mechanism for this 5-*exo-trig* ATRC reaction (Scheme 47). Treating **187** with CuCl in MeCN at 140°C in a pressure bottle would initiate the reaction by the homolysis of C-Cl bond generating radical **188** and CuCl<sub>2</sub>. Cyclisation of **188** would result in a 5-membered ring with a more reactive radical **189**. Radical **189** would then abstract chlorine from CuCl<sub>2</sub>, resulting in the termination product **190**, and regenerating CuCl. But this catalytic cycle has a major flaw, the more reactive radical **189** can also abstract chlorine from **187**, in this case there would be a build up the inactive CuCl<sub>2</sub>,

eventually leaving no CuCl for initiation, reducing the efficiency of the reaction (see chapter 5.1.3).



**Scheme 47.** Catalytic Redox Mechanism for ATRC.

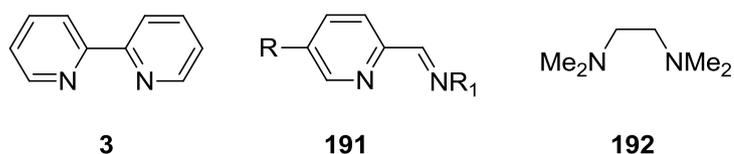
There are many factors that influence the efficiency of copper mediated ATRC. Three important factors arise from the substrate itself. The ease / difficulty of homolysis of the C-X (halogen) bond to initiate the reaction (stronger bonds such as C-F are difficult to homolyse).<sup>107</sup> The presence of adjacent electron withdrawing groups generally weakens the bond. The stability of the initial radical formed, where  $3^\circ > 2^\circ > 1^\circ$ . The presence of electron withdrawing groups can further stabilise the radical and lead to faster initiation. The conformation of radical precursors; where a close proximity between the initial radical and the unsaturated carbon bond is required for successful cyclisation.<sup>108</sup>

Other factors include the type of solvent used (toluene or DCM) which control the solubility of the copper halides as well as the addition of ligands to

further improve solubility and / or modify the redox potential of the catalytic system,<sup>109, 110</sup> and the use of additives which could reduce any accumulated inactive Cu(II) species back to the active Cu(I) complex (Chapter 6). We will investigate these latter two aspects of the reaction.

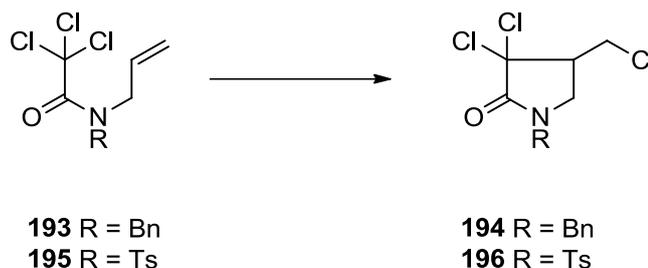
### 5.1.2 Ligands used in Copper-Mediated ATRC

Ligands have been shown to accelerate copper mediated ATRC reactions possibly by solubilising the copper metal or by altering the redox potential of the catalytic system, or by both. One of the early classes of ligands investigated in the field of copper mediated ATRC were the nitrogen containing bidentate ligands such as bipyridine **3** (bipy),<sup>109, 110</sup> pyridineimines **191** (NPMI)<sup>111 - 116</sup> and *N,N,N',N'*-tetramethylethyl ethylenediamine **192** (TMEDA)<sup>117 - 120</sup> (Figure 30).



**Figure 30.** Bidentate Ligands used in ATRC.

Cyclisation of substrates **193** and **195** to form compounds **194** and **196** in the presence of **3** was faster and could be conducted at lower temperature compared to that when no **3** was present (Table 4).<sup>110</sup>

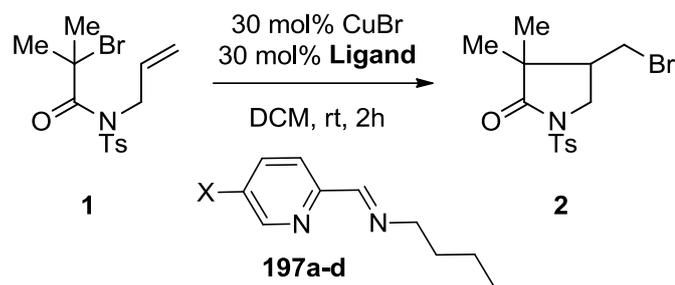


| Substrate  | Catalyst (mol%)     | Solvent | Temp / °C | Time / h | Yield (%) |
|------------|---------------------|---------|-----------|----------|-----------|
| <b>193</b> | CuCl (30)           | MeCN    | 80        | 18       | 68        |
| <b>193</b> | CuCl- <b>3</b> (30) | DCM     | rt        | 1        | 98        |
| <b>195</b> | CuCl (30)           | MeCN    | rt        | 24       | 97        |
| <b>195</b> | CuCl- <b>3</b> (5)  | DCM     | rt        | 0.2      | 91        |

**Table 4.** The Effect of Bipy Ligand (**3**) in ATRC.

The role of the bipyridine ligand was primarily to increase the solubility of the copper halide as a  $[\text{Cu}(\text{I})\text{bipy}_2]\text{X}$  complex. In addition the ligand stabilises the  $\text{Cu}^{\text{I}}$  state due to the low lying LUMO  $\pi^*$  orbital present in the conjugated  $\pi$  system of bipy. This allows the ligand to easily accept electron density from the copper, stabilising the  $\text{Cu}(\text{I})$  oxidation state and improving the efficiency of the last step of the ATRC reaction.

In 2001, Clark and co-workers investigated structurally similar NPMI's. They looked at the electronic effects of various NPMI's on the rates of copper mediated ATRC reaction (Table 5).<sup>115</sup>

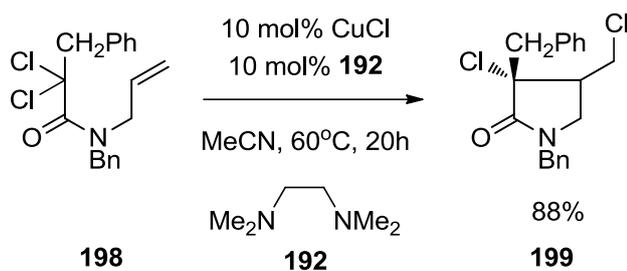


| Ligand      | X group         | Ratio 1 : 2 |
|-------------|-----------------|-------------|
| <b>197a</b> | H               | 41 : 59     |
| <b>197b</b> | Me              | 34 : 66     |
| <b>197c</b> | OMe             | 73 : 27     |
| <b>197d</b> | NO <sub>2</sub> | 98 : 2      |

**Table 5.** The Effect of Various NPMI Ligands in ATRC.

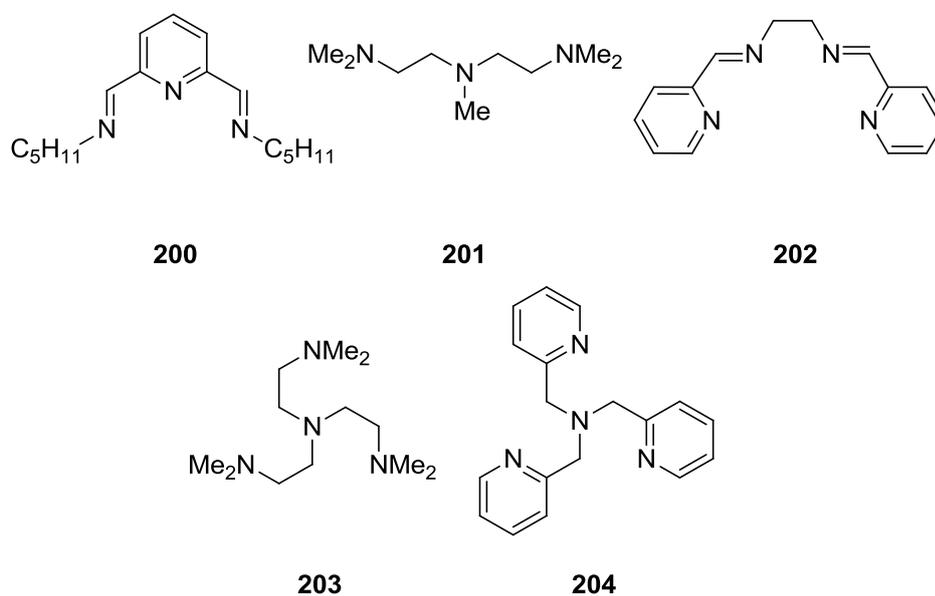
Ligand **197b** with a mildly inductive electron donating group (Me) was proven to be the most efficient and it was concluded that the inductive effect on the pyridine nitrogen is a more dominant feature than the resonance effect on the imine nitrogen. **The electronic effect of substituents at the imine nitrogen has not been investigated.**

Unfortunately, ATRC with either bipyridine or NPMI's generally require high catalyst loadings of up to 30 mol %. The catalyst loadings were reduced with the introduction of a more reactive CuCl-TMEDA complex system.<sup>117</sup>



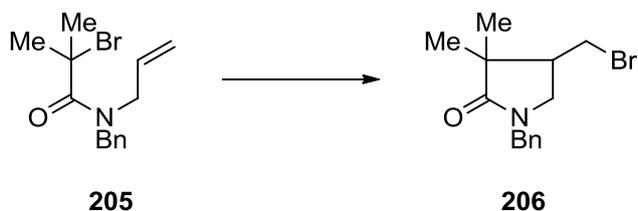
**Scheme 48.** A More Reactive CuCl-TMEDA Complex System.

Using the optimum 2 : 1 ratio of bidentate TMEDA ligand to CuCl,<sup>117</sup> substrate **198** was cyclised to **199** in 88 % yield (Scheme 48), whereas attempts to cyclise the same substrate with bipyridine failed. This may be due to the greater redox potential of amine ligand compared to pyridine ligand. With the realisation that the most active metal-ligand system consisted of 2 : 1 ratio of bidentate ligand to copper, a new class of multidentate ligands were introduced which allowed 1 : 1 ratio of ligand to copper (Figure 31).



**Figure 31.** Multidentate Ligands used in ATRC.

Bidentate ligand **3**, tridentate ligands (*N,N'E,N,N'E*)-*N,N'*-(pyridine-2,6-diylbis(methanylylidene))bis(pentan-1-amine) (**200**)<sup>121</sup> and *N,N,N',N',N''*-pentamethyldiethylenetriamine (PMDETA, **201**),<sup>122</sup> branched tetradentate ligands (*N<sup>1</sup>E,N<sup>2</sup>E*)-*N<sup>1</sup>,N<sup>2</sup>*-bis(pyridin-2-ylmethylene)ethane-1,2-diamine (**202**),<sup>121</sup> *N,N,N',N',N'',N''*-hexamethyltriethylenetetramine (Me<sub>6</sub>-Tren, **203**),<sup>111, 112, 116, 121</sup> and tripyridylamine (TPA, **204**)<sup>123</sup> were investigated head to head to compare their activity in converting allyl-*N*-benzyl-2-bromo-2-methylpropanamide (**205**) to 1-benzyl-4-(bromomethyl)-3,3-dimethylpyrrolidin-2-one (**206**) using copper mediated 5-*exo-trig* ATRC reactions.<sup>123</sup>



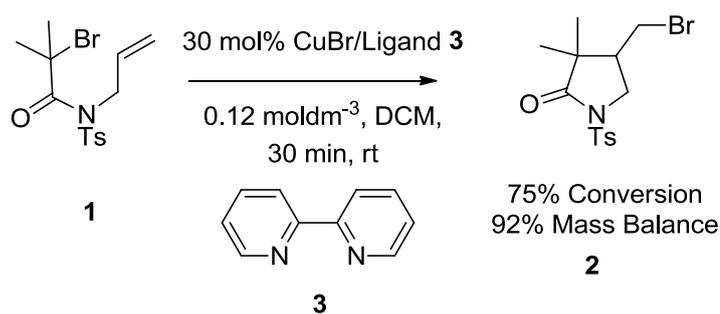
Both Me<sub>6</sub>-Tren (**203**) and TPA (**204**) proved superior to **3** and **201**, while the imine based ligands **200** and **202** performed extremely poorly. Reducing the time to 2 hours proved **204** to be a more superior ligand than **203**.

Currently ligands based on tetradentate amines and pyridines are used in ATRC, our aim is to identify more reactive imine ligands that would eventually give us leads to the evolution of more efficient imine ligands for ATRC in our ‘machine’.

## 5.2 Results and Discussion

### 5.2.1 Screening Bidentate Imine Ligands for ATRC.

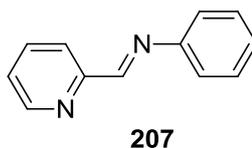
Imines have been used as ligands for various metals to generate complexes which can be used as catalysts in ATRC reactions, but limited work has been published. There have been reports of bidentate pyridineimines (NPMI) ligands used for 5-*exo* ATRC, but these have performed poorly compared to tetradentate amines or pyridines.<sup>111 - 116</sup> We decided to re-investigate imines because we would use our ‘machine’ to evolve the most successful binder to the copper metal from a dynamic library of compounds and / or an imine profile that is more efficient at mediating ATRC than existing ligands. Our plan was to screen various imine bidentate ligands to identify any such ligand that can be compared to the currently successful bipyridine ligand. We will initially screen the cyclisation process of *N*-allyl-2-bromo-2-methyl-*N*-tosylpropanamide **1** to 4-(bromomethyl)-3,3-dimethyl-1-tosylpyrrolidin-2-one **2**. The use of 30 mol% bipyridine ligand results in a conversion of 75% (Scheme 49) at RT in 30 min.<sup>124</sup>



**Scheme 49.** 5-*exo trig* ATRC of **1** using CuBr / Bipy (**3**) Reagent System.

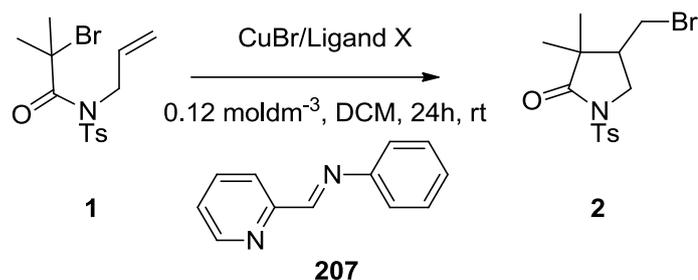
The pyridine imine functional groups accept electron density from copper, stabilising the Cu(I) oxidation state, they also increase the solubility of the Cu<sup>I</sup> and

Cu<sup>II</sup> complex. No study on the effect of the electronic nature of the imine substituent on the rate of ATRC has been published. Consequently, we decided to examine pyridineimines where an aromatic ring was attached at the imine nitrogen by changing the aryl group. A reagent system with different solubility, steric and electronic features could be studied.



First, our aim was to optimise the conversion of **1** using the simplest imine structure (*E*)-*N*-(pyridin-2-ylmethylene)aniline **207** to identify the conditions required to yield approx. 25 - 75% conversion. This was necessary because we could then use these conditions in screening other ligands and easily determine if the new ligands were better or worse in the reaction. One of the first points observed using ligand **207** was the difficulty in solubilising the CuBr / ligand complex in DCM when compared to bipyridine.

Substrate **1** was exposed to various amounts of CuBr and ligand **207** in DCM and reacted for 24 hours at room temperature. The mixture was then filtered through silica plug and washed with DCM. After evaporation of the volatiles, the conversions were measured by <sup>1</sup>H NMR spectroscopy. Where partial conversions were observed, the only other product present in the crude NMR was the starting material. This suggests that starting material to product ratios are satisfactory in determining ligand effectiveness (Table 6).



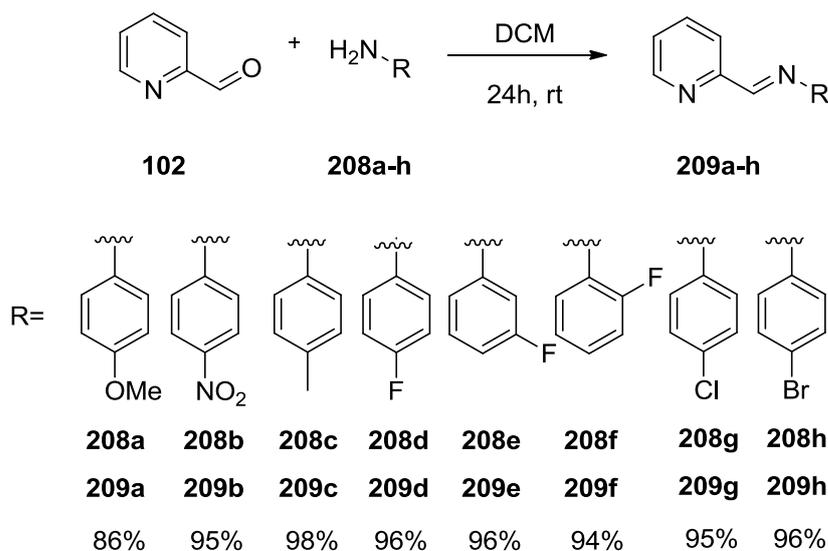
| Entry | Time (h) | CuBr (mol%) | Ligand <b>207</b> (mol%) | Conversion (%) | Mass Balance (%) |
|-------|----------|-------------|--------------------------|----------------|------------------|
| 1     | 24       | 10          | 20                       | 0              | 78               |
| 2     | 24       | 25          | 50                       | 2              | 81               |
| 3     | 24       | 35          | 70                       | 2              | 77               |
| 4     | 24       | 45          | 90                       | 70             | 72               |
| 5     | 24       | 50          | 100                      | 90             | 70               |
| 6     | 24       | 100         | 200                      | 94             | 68               |
| 7     | 0.2      | 100         | 200                      | 0              | 76               |
| 8     | 1        | 100         | 200                      | 0              | 70               |
| 9     | 48       | 100         | 200                      | 96             | 72               |

**Table 6.** Optimising 5-*exo trig* ATRC of **1** using CuBr / **207** Reagent System to Achieve 25 – 75% Conversion.

In the presence of 10 – 35 mol% CuBr and 20 – 70 mol% **207** the conversion to product **2** was extremely poor (Table 6, entry 1-3), whereas conversion of our control reaction using 30 mol% CuBr / **207** resulted in 75% conversion. Increasing the catalyst loadings to 45 / 90 mol% of CuBr / **207**, caused a sharp increase in conversion to 70% (Table 6, entry 4). Increasing the loadings further resulted in conversion of >90% (Table 6, entry 5 and 6). The loadings required were fairly high indicating that the ligand was quite ineffective, possibly due to the poor solubility of the reagent system. To optimise the reaction time, substrate **1** was treated with 100 /

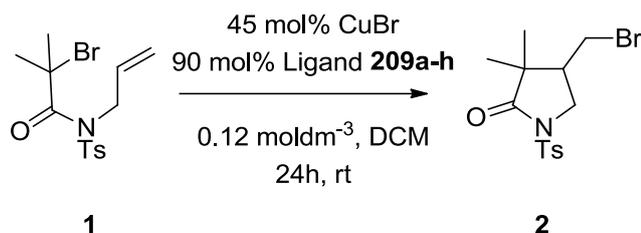
200 mol% of CuBr / **207** at various time lengths (Table 6, entry 7 - 9). Reaction times of 10 min and 1 hour resulted in no conversion of **1** to **2** while 100% conversion was not obtained by increasing the reaction time to 48 hours. We chose 45 / 90 mol% of CuBr / **207** in DCM, 24 hour at room temp as the optimum conditions to test the efficiency of various imine ligands compared to this control ligand.

Imine ligands **208a-h** were synthesised by reacting 2-pyridinecarboxy aldehyde **102** with substituted anilines **209a-h** in DCM at room temperature for 24 hours. After evaporating the solvent, the crude products were purified by vacuum distillation resulting in high yields (Scheme 50).



**Scheme 50.** Synthesis of Pyridineimines **209a-h**.

The ligands contained a mix of electron donating groups (e.g. methoxy and methyl groups) and electron withdrawing groups such as NO<sub>2</sub> and various halogens. The efficiency of ligands **209a-h** was then screened by observing the conversion of **1** to **2** (Table 7).

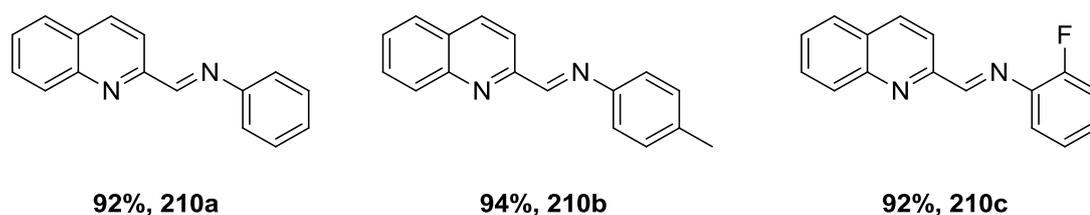


| Entry | Ligand      | Conversion (%) | Mass Balance (%) |
|-------|-------------|----------------|------------------|
| 1     | <b>209a</b> | 0              | 71               |
| 2     | <b>209b</b> | 0              | 69               |
| 3     | <b>209c</b> | 11             | 67               |
| 4     | <b>209d</b> | 0              | 79               |
| 5     | <b>209e</b> | 0              | 60               |
| 6     | <b>209f</b> | 88             | 19               |
| 7     | <b>209g</b> | 0              | 68               |
| 8     | <b>209h</b> | 0              | 58               |

**Table 7.** 5-*exo trig* ATRC of **1** using CuBr / **209a-h** Reagent Systems.

While carrying out these reactions, it was determined that the solubility of these reagent systems were very poor in DCM. One way to improve the solubility would be to heat the reaction or use a different solvent all together, but as we were comparing like to like with ligand **207** it was important to keep the same conditions at this point. The results showed zero conversion rates for most of these ligands except **12c** and **209f** (Table 7). Ligand **209c** with a mild electron donating group showed signs of conversion but these were low compared to ligand **207**, while surprisingly the 2-fluoroaniline based ligand **209f** showed high conversion (loss of SM) but resulted with an extremely poor mass balance.

The pyridine ring was then replaced with a quinoline nucleus for the three active ligands **207**, **209c** and **209f**. It was hoped the extra aromatic ring would help solubilise the complexes in DCM. Ligands **210a-c** was easily synthesized by reacting quinoline-2-carboxy aldehyde with the corresponding anilines in DCM, 24 hour at room temperature. The volatiles were then evaporated and the crude products purified by vacuum distillation obtaining yields of >90% (Figure 32).



**Figure 32.** Synthesis of More Conjugated Pyridineimines **210a-h**.

The efficiency of ligands **210a-c** was then screened by observing the conversion of **1** to **2** (Table 8) as before.



| Entry | Ligand (mol%) | Conversion (%) | Mass Balance (%) |
|-------|---------------|----------------|------------------|
| 1     | <b>210a</b>   | 0              | 94               |
| 2     | <b>210b</b>   | 0              | 91               |
| 3     | <b>210c</b>   | 0              | 93               |

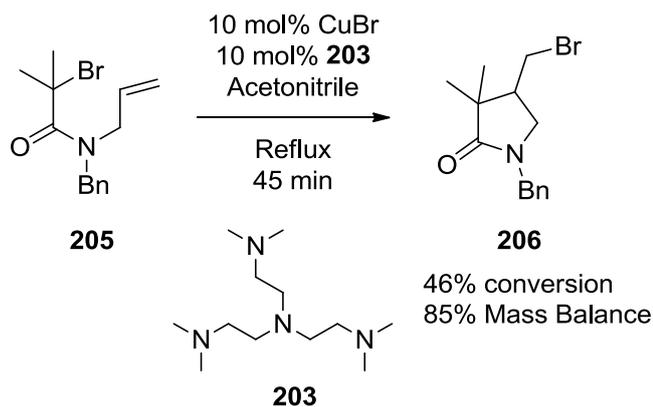
**Table 8.** 5-*exo trig* ATRC of **1** using CuBr / **210a-c** Reagent Systems.

The results showed that by replacing the pyridine with the quinoline nucleus in these types of ligands, the conversion of **1** failed miserably (Table 8). The reason for this is uncertain, the  $pK_a$  of pyridine (4.9) and quinoline (5.2) are very similar hence the ability to stabilise the Cu(I) oxidation state should be very similar. On the other hand the difference in the steric effects of the two ring systems may indicate that the reaction is very sensitive to the steric effects. Further evidence for this is that the conversion of **1** to **2** for ligand **207** vs **210a** has been shown to be much slower.

The currently screened bidentate pyridine imine ligands proved to perform more poorly than bipyridine, but we knew that bidentate ligands are not the most efficient ligands for ATRC. Therefore, without investing too much time expanding boundaries to screen various other bidentate imine ligands, we decided to screen various multidentate imine ligands.

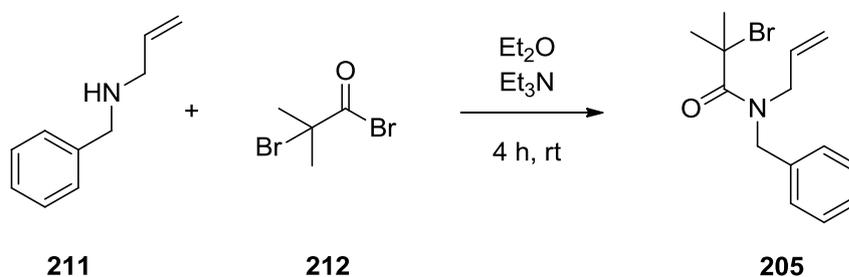
### 5.2.2 Screening Multidentate Imine Ligands for ATRC.

The cyclisation process of allyl-*N*-benzyl-2-bromo-2-methylpropanamide (**205**) to 1-benzyl-4-(bromomethyl)-3,3-dimethylpyrrolidin-2-one (**206**) using CuBr is very slow compared to *N*-tosyl **1**. Previously, branched tetradentate ligand  $N^1, N^1$ -bis(2-(dimethylamino)ethyl)- $N^2, N^2$ -dimethylethane-1,2-diamine **203** has been reported as the next most efficient ligand after TPA for ATRC reactions.<sup>125</sup> Using 10 mol% CuBr / **203** in acetonitrile, under reflux for 45 min resulted in 46% conversion of **205** (Scheme 51). We decided to use this as our control reaction when screening various tetradentate imine ligands to compare their efficiency.



**Scheme 51.** ATRC of **205** to **206** using 10 mol% of CuBr and **203**.

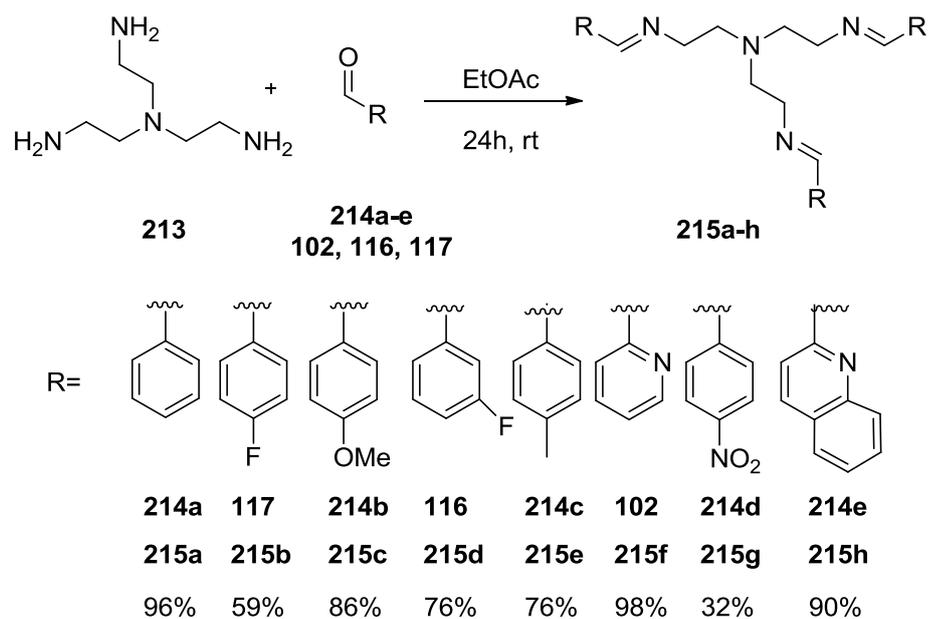
We chose to synthesize imine based ligands based upon the branched tetradentate structure of **203** to see if they would be a good target for an evolvable ‘machine.’ Firstly, substrate **205** was synthesized in large scale. This was prepared by a known literature procedure (Scheme 52).<sup>126, 127</sup>



**Scheme 52.** Synthesis of **205** by Reacting *N*-benzylprop-2-en-1-amine (**211**) with 2-Bromoisobutyryl Bromide (**212**).

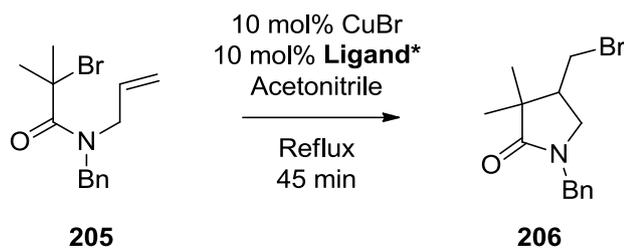
Next, a set of tetradentate ligands were prepared. *N*<sup>1</sup>,*N*<sup>1</sup>-bis(2-aminoethyl)ethane-1,2-diamine (**213**) was reacted with benzaldehyde (**214a**), 4-fluorobenzaldehyde (**117**), 4-methoxybenzaldehyde (**214b**), 3-fluorobenzaldehyde

(**116**), tolualdehyde (**214c**), 2-pyridinecarboxyaldehyde (**102**), 4-nitrobenzaldehyde (**214d**) and 2-quinolinecarboxyaldehyde (**214e**). These reactions were carried out in ethyl acetate at room temperature stirring for 24 hours, resulting in formation of imines **215a-h** in the yields shown below (Scheme 53).



**Scheme 53.** Synthesis of Multidentate Imine Ligands **215a-h**.

Ligands **215a-h** (10 mol %) was added to 10 mol% of CuBr in acetonitrile and then exposed to substrate **205**. The reaction was heated under reflux for 45 min. The reaction was quenched by filtering the reaction through silica and percentage conversion of **206** was obtained by  $^1\text{H}$  NMR spectroscopy (Table 9).



| Entry | Ligand      | Conversion (%) | Mass Balance (%) |
|-------|-------------|----------------|------------------|
| 1     | <b>203</b>  | 46             | 85               |
| 2     | <b>215a</b> | 17             | 85               |
| 3     | <b>215b</b> | 13             | 94               |
| 4     | <b>215c</b> | 15             | 89               |
| 5     | <b>215d</b> | 10             | 81               |
| 6     | <b>215e</b> | 7              | 91               |
| 7     | <b>215f</b> | 22             | 92               |
| 8     | <b>215g</b> | 3              | 83               |
| 9     | <b>215h</b> | 3              | 75               |

**Table 9.** 5-*exo trig* ATRC of **205** using CuBr / **215a-h** Reagent Systems.

The control reaction using Me<sub>6</sub>-Tren (**203**) resulted in 46% conversion. The results in Table 9 show that none of the synthesized imine ligands **215a-h** performed better than **203**. Although the pyridine imine ligand (**215f**) is the most efficient ligand of those prepared. Thus the strategy to use this scaffold to ‘evolve’ a better ligand than **203** may not be optimal, however it did show that the reaction was sensitive to the nature of the imine ligand. Thus evolution of better imine ligands using the ‘machine’ once developed may be possible.

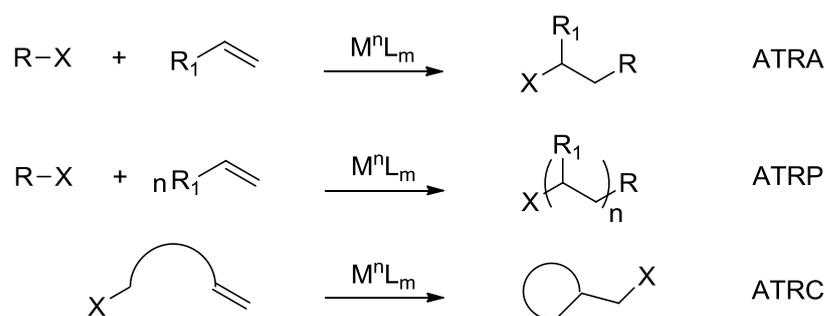
### 5.3 Conclusion

Currently, bidentate and multidentate imine ligands have performed poorly compared to their more basic amine and pyridine counterparts. Screening various imine ligands individually was time consuming as we had to individually prepare them. With the introduction of our ‘machine’ we would be able to insert various commercially available aldehyde and amines into the reactor, generate a dynamic library of imines and with the insertion of our metal, amplify the most successful binder or the most active catalyst combination. While the ‘machine’ was being developed, we decided to invest time in improving the efficiency of copper mediated *5-exo trig* ATRC by the use of additives as explained in chapter 6.

## Chapter 6 Additives used in Copper-Mediated ATRC

## 6.1 Introduction

In chapter 5 we showed that imine ligands performed poorly for copper mediated ATRC reactions. Branched tetradentate ligands such as Me<sub>6</sub>-Tren (**203**) or TPA (**204**) are more efficient at mediating cyclisations at catalyst loadings of 30 mol%. While this amount of catalyst is acceptable for laboratory scale reactions, it is undesirable for industrial scale reactions. Such high catalyst loadings would be environmentally unfriendly and expensive, therefore, catalyst loadings must be reduced further to make ATRC industrially friendly.

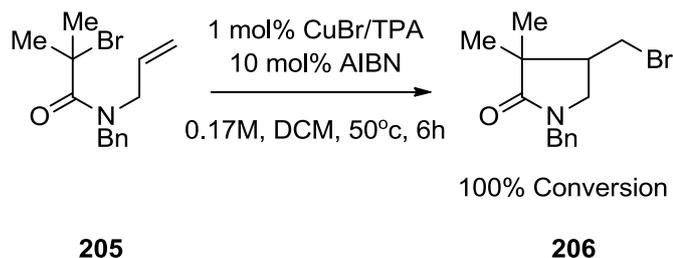


**Scheme 54.** Basic Types of Atom Transfer Radical Reactions.

In 1995, Matyjaszewski and Sawamoto discovered a new class of controlled radical polymerisation named atom transfer radical polymerisation (ATRP) which originated from ATRA (Scheme 54).<sup>128</sup> The mechanism of ATRP<sup>129-131</sup> is similar to ATRA<sup>102-104</sup> except it involves more than one addition step. A sufficiently stable and active ATRP catalyst can be used at very low concentrations, however due to unavoidable radical termination reaction, the deactivator Cu(II) from the active Cu(I) will accumulate in the reaction which would slow down the polymerisation rate

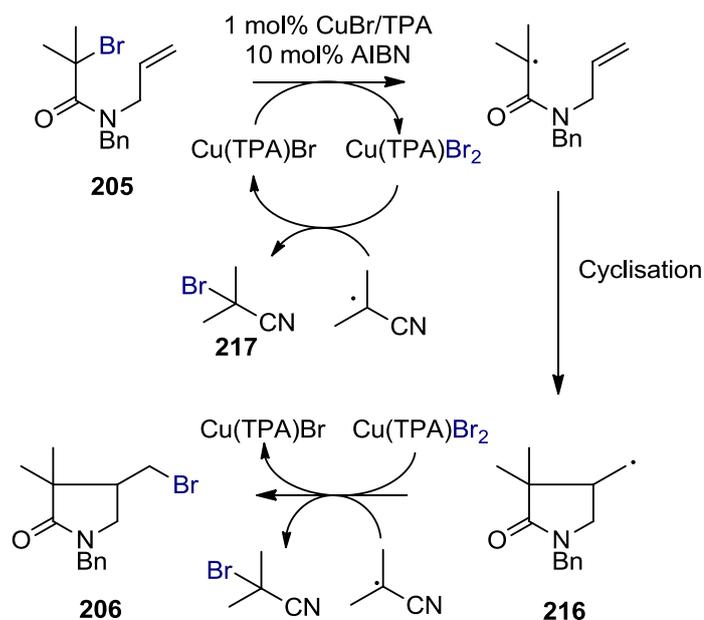


the catalyst loadings by up to 300 fold for reactive substrates and 30 fold for less reactive substrates. For example, substrate **205** was cyclised to product **206** using 1 mol % of CuBr / TPA (**204**) and 10 mol % AIBN, achieving 100% conversion (Scheme 55), reducing catalyst loadings by a factor of 30 from previously reported method.<sup>123</sup>



**Scheme 55.** ATRC of **205** with AIBN as Additive.

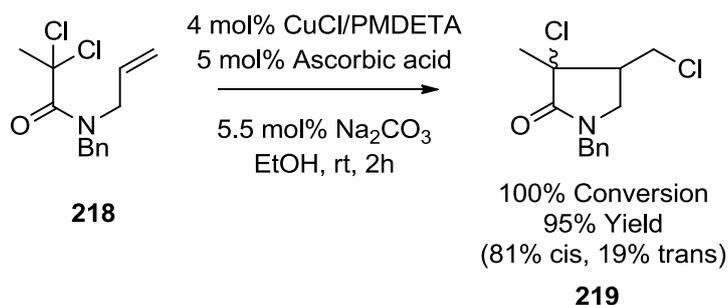
The mechanism (Scheme 56) follows the same general steps of ATRC, but now the addition of AIBN mediates regeneration of the activator Cu(TPA)Br, the reactive radical **216** can now abstract bromine from Cu(TPA)Br<sub>2</sub>, substrate **205** or by AIBN by-product **217** to terminate the reaction.



**Scheme 56.** ARGET-ATRC Mechanism.

A common drawback with this method was the use of AIBN, it has to be heated to at least 50°C to decompose the molecule to its radical components, and AIBN is also toxic,<sup>138</sup> while DCM is a possible carcinogen,<sup>138</sup> TPA is quite expensive and the reaction times were fairly high.

Casolari *et al.* were able to carry out efficient green 5-*exo* ARGET-ATRC reactions with catalytic system CuCl[PMDETA]/ascorbic acid/Na<sub>2</sub>CO<sub>3</sub>. An example was the cyclisation of *N*-allyl-*N*-benzyl-2,2-dichloropropanamide **218** to **219** (Scheme 57) using 4 mol% of CuCl, 4 mol% of cheap PMDETA, 5 mol% of safe natural reductant ascorbic acid, 5.5 mol% of Na<sub>2</sub>CO<sub>3</sub>, in safe biodegradable ethanol at room temperature in 2 hours resulting in 100% conversion.<sup>139</sup>



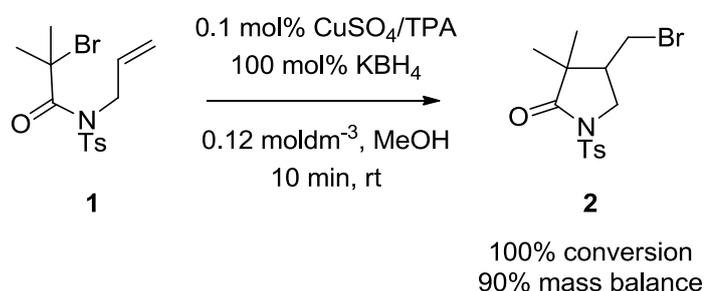
**Scheme 57.** An Efficient CuCl/PMDETA Mediated ARGET-ATRC.

Casolari *et al.* had demonstrated an efficient copper mediated 5-*exo*-trig ATRC reaction. Our aim was to improve this reaction by identifying an efficient additive which would enable us to reduce catalyst loadings and hopefully allow us to perform reactions in a non-toxic solvent.

## 6.2 Results and Discussion

### 6.2.1 Borohydrides as Additives for ATRC.

Currently unpublished work carried out in our group had shown borohydrides to be very useful additives for copper mediated AGET-ATRC reactions. Borohydrides are used in traditional organic chemistry for selective reductions of carbonyl compounds, but in this chapter we will be using borohydride reducing agents to reduce the Cu(II) deactivator to Cu(I) activator. Before completing his PhD, Dr Paul Wilson from the Clark group recently demonstrated 100% conversion to product **2** by exposing the monobromide substrate **1** to 0.1 mol% CuSO<sub>4</sub> / TPA and 100 mol% potassium borohydride in methanol at room temp for 10 min (Scheme 58).<sup>Unpublished work</sup>



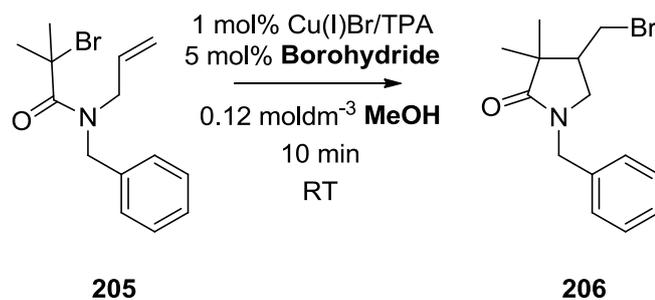
**Scheme 58.** ARGET-ATRC Reaction of **1** with KBH<sub>4</sub> as Additive

Our aim was to further improve the efficiency of this reaction by screening various reducing agents, ligands and changing reaction conditions such as solvent and concentration. A range of reducing agents were obtained from Sigma-Aldrich. These included metal borohydrides (such as sodium / potassium borohydride), organoborohydrides (such as tetrabutylammonium borohydride, tetramethylammonium triacetoxymborohydride, and benzyltriethylammonium

borohydride) and non-borohydrides (such as borane and triethylsilane) reducing agents. The amide carbonyl of the monobromide substrate **1** should be inert to all the reducing agents used.

In previous chapter we employed DCM as the choice of solvent for copper mediated ATRC reactions, but due to the insolubility of borohydrides in DCM, the solvent preferred for these reactions was MeOH. Generally organic borohydride reactions are carried out in protic solvents. Note, theoretically EtOH (a greener choice) can also be used.

Substrate **205** was treated with 1 mol% CuBr / TPA and 5 mol% of various reducing agents in methanol at room temperature for 10 min. The reaction mixture was then filtered through a silica plug, the solvent evaporated and the conversions were obtained from the crude  $^1\text{H}$  NMR spectrum (Table 10).



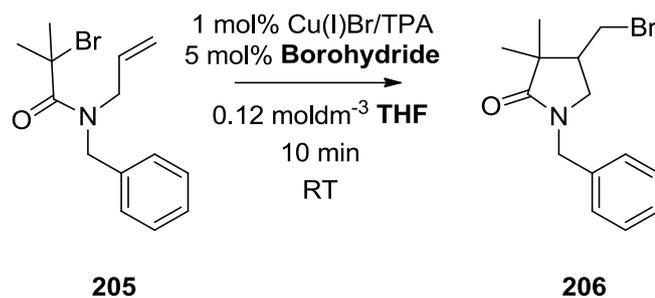
| Entry | Borohydride                                   | Conversion (%) | Mass Balance (%) |
|-------|---|----------------|------------------|
| 1     | -   | 0              | 95               |
| 2     | Sodium borohydride                            | 46             | 98               |
| 3     | Sodium aluminium hydride                      | 0              | 91               |
| 4     | Sodium bis(2-methoxy)aluminium hydride        | 0              | 85               |
| 5     | Diisobutyl aluminium hydride                  | 0              | 81               |
| 6     | Lithium tri-tert-butoxy aluminium borohydride | 0              | 91               |
| 7     | Lithium dimethylamino borohydride             | 1              | 82               |
| 8     | Potassium borohydride                         | 73             | 86               |
| 9     | Calcium borohydride- THF                      | 88             | 86               |
| 10    | 9-BBN   | 0              | 87               |
| 11    | Borane- THF                                   | 0              | 90               |
| 12    | Triethylsilane                                | 0              | 80               |
| 13    | Bis(triphenylphosphine)copper(I) borohydride  | 0              | 93               |
| 14    | Tetrabutylammonium borohydride                | 36             | 87               |
| 15    | Tetramethylammonium triacetoxyborohydride     | 0              | 93               |
| 16    | Benzyltriethylammonium borohydride            | 3              | 85               |

**Table 10.** Screening Various Reducing Agents as Additives for ATRC in MeOH.

The general procedure involved dissolving substrate **205** in MeOH at room temperature at a concentration of 0.12 M. A solution of Cu(TPA)Br was prepared at a concentration of 0.01 M and added to the substrate. This resulted in a dark green solution indicative of Cu(I). The reducing agents were then added. Upon addition of either NaBH<sub>4</sub>, KBH<sub>4</sub>, Ca(BH<sub>4</sub>)<sub>2</sub>·2THF, (Bu)<sub>4</sub>N(BH<sub>4</sub>), borane-THF or BnN(BH<sub>4</sub>)(Et)<sub>3</sub> there was a colour change of the reaction mixture from dark green to brown and

eventually back to dark green (within 10 min). The reaction was stirred at room temperature for 10 min. The results showed that without the presence of a reducing agent, no conversion of **205** is obtained (entry 1), while reasonable conversions of 36% and 46% were obtained using  $(\text{Bu})_4\text{N}(\text{BH}_4)$  and  $\text{NaBH}_4$  (entry 2 and 14). Good conversion of 73% and 88% were observed using  $\text{KHB}_4$  and  $\text{Ca}(\text{BH}_4)_2 \cdot 2\text{THF}$  (entry 8 and 9). The remaining reducing agents performed extremely poorly. The surprise here was observing 36% conversion using organoborohydride  $(\text{Bu})_4\text{N}(\text{BH}_4)$ , this is a promising reducing agent to consider as it is soluble in many solvents (unlike  $\text{NaBH}_4$  /  $\text{KBH}_4$ ) and contains no metals.

The most efficient reducing agent - calcium borohydride was purchased as a complex with THF, therefore we investigated the conversion of **205** using various reducing agents, replacing the solvent to a polar aprotic solvent – THF while preserving all other conditions previously used (Table 11).

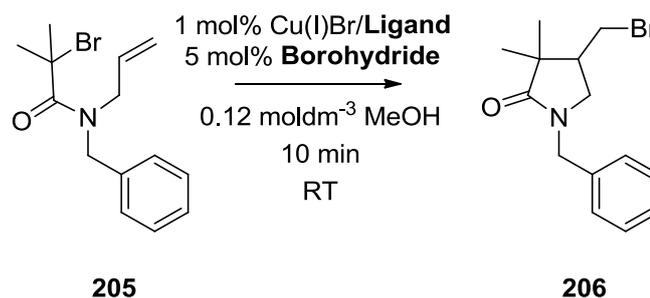


| Entry | Borohydride                                   | Conversion (%) | Mass Balance (%) |
|-------|---|----------------|------------------|
| 1     | -   | 0              | 94               |
| 2     | Sodium borohydride                            | 0              | 84               |
| 3     | Sodium aluminium hydride                      | 0              | 81               |
| 4     | Sodium bis(2-methoxy)aluminium hydride        | 0              | 82               |
| 5     | Diisobutyl aluminium hydride                  | 0              | 82               |
| 6     | Lithium tri-tert-butoxy aluminium borohydride | 0              | 86               |
| 7     | Lithium dimethylamino borohydride             | 0              | 86               |
| 8     | Potassium borohydride                         | 0              | 94               |
| 9     | Calcium borohydride- THF                      | 0              | 89               |
| 10    | 9-BBN   | 0              | 80               |
| 11    | Borane- THF                                   | 0              | 92               |
| 12    | Triethylsilane                                | 0              | 81               |
| 13    | Bis(triphenylphosphine)copper(I) borohydride  | 0              | 89               |
| 14    | Tetrabutylammonium borohydride                | 2              | 83               |
| 15    | Tetramethylammonium triacetoxyborohydride     | 0              | 95               |
| 16    | Benzyltriethylammonium borohydride            | 0              | 90               |

**Table 11.** Screening Various Reducing Agents as Additives for ATRC in THF.

The reducing agents used were all soluble in THF, but resulted in 0% conversion except for  $(\text{Bu})_4\text{N}(\text{BH}_4)$  which showed a trace reactivity. The previously successful  $\text{NaBH}_4$ ,  $\text{KBH}_4$ ,  $\text{Ca}(\text{BH}_4)_2$  in MeOH showed no signs of activity in THF which suggested that even though these metal borohydrides were soluble in THF, they resulted in 0% conversion pointing out the importance of the protic solvent in the copper mediated ARGET-ATRC.

The general order of reactivity for nitrogen based ligands in copper mediated ATRC for 5-*exo* cyclisations was stated in chapter 5. The order was TPA (**204**) > Me<sub>6</sub>-Tren (**203**) > PMDETA (**201**) > Bipy (**3**).<sup>123, chapter 5</sup> We exposed substrate **205** to two of these ligands **201** and **3** with the four most efficient borohydrides discovered with the Cu(TPA)Br reagent system. Unsurprisingly, ligands **201** and **3** performed poorly (Table 12).

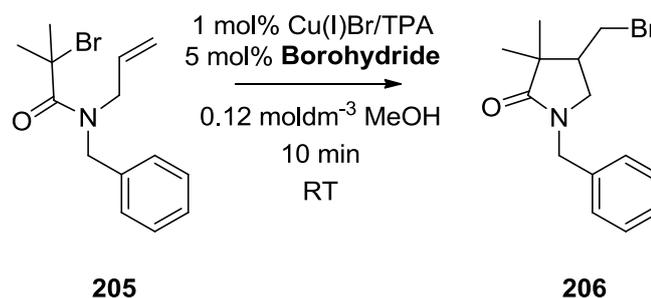


| Entry | Ligand | Borohydride                              | Conversion (%) | Mass Balance (%) |
|-------|--------|--|----------------|------------------|
| 1     | bipy   | -  | 0              | 96               |
| 2     | PMDETA | -  | 0              | 95               |
| 3     | bipy   | NaBH <sub>4</sub>                        | 2              | 87               |
| 4     | PMDETA | NaBH <sub>4</sub>                        | 0              | 83               |
| 5     | bipy   | KBH <sub>4</sub>                         | 0              | 74               |
| 6     | PMDETA | KBH <sub>4</sub>                         | 0              | 91               |
| 7     | bipy   | Ca(BH <sub>4</sub> ) <sub>2</sub> · 2THF | 0              | 77               |
| 8     | PMDETA | Ca(BH <sub>4</sub> ) <sub>2</sub> · 2THF | 0              | 84               |
| 9     | bipy   | (Bu) <sub>4</sub> N(BH <sub>4</sub> )    | 0              | 87               |
| 10    | PMDETA | (Bu) <sub>4</sub> N(BH <sub>4</sub> )    | 0              | 90               |

**Table 12.** Screening Four Most Efficient Borohydrides in CuBr / bipy and CuBr / PMDETA Reagent System.

The general procedure for these copper mediated ARGET-ATRC reactions involved making a stock solution of Cu<sup>I</sup>(TPA)Br at a concentration of 0.01 M. We generally prepared this stock solution in large quantities and then stored and used

when required. While repeating the 5-*exo* cyclisation of substrate **205** with NaBH<sub>4</sub>, KBH<sub>4</sub>, Ca(BH<sub>4</sub>)<sub>2</sub> and (Bu)<sub>4</sub>N(BH<sub>4</sub>), we obtained inconsistent conversions. Therefore we decided to prepare a fresh stock solution of Cu<sup>I</sup>(TPA)Br, perform the cyclisation of **205** using NaBH<sub>4</sub>, KBH<sub>4</sub>, Ca(BH<sub>4</sub>)<sub>2</sub> and (Bu)<sub>4</sub>N(BH<sub>4</sub>), then we would store the stock solution for six days and repeat the cyclisation reactions to see if the age of the complex was the cause of the inconsistency (Table 13).

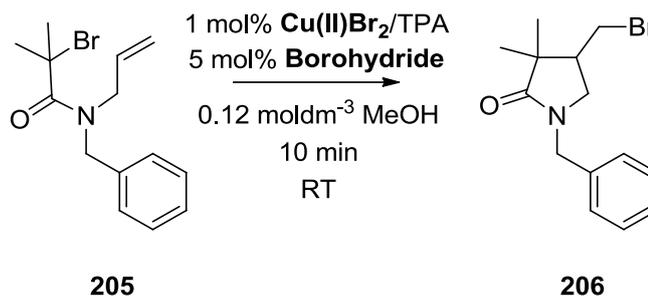


| Entry | Age of Cu(TPA)Br Stock Solution | Borohydride                              | Conversion (%) | Mass Balance (%) |
|-------|---------------------------------|--|----------------|------------------|
| 1     | 0                               | NaBH <sub>4</sub>                        | 15             | 82               |
| 2     | 6                               | NaBH <sub>4</sub>                        | 40             | 77               |
| 3     | 0                               | KBH <sub>4</sub>                         | 62             | 81               |
| 4     | 6                               | KBH <sub>4</sub>                         | 73             | 83               |
| 5     | 0                               | Ca(BH <sub>4</sub> ) <sub>2</sub> · 2THF | 96             | 82               |
| 6     | 6                               | Ca(BH <sub>4</sub> ) <sub>2</sub> · 2THF | 44             | 75               |
| 7     | 0                               | (Bu) <sub>4</sub> N(BH <sub>4</sub> )    | 2              | 82               |
| 8     | 6                               | (Bu) <sub>4</sub> N(BH <sub>4</sub> )    | 26             | 79               |

**Table 13.** The Effect on ATRC Using Fresh or Aged Cu(I)Br / TPA Reagent System.

The results showed variations in conversions of substrate **205** by copper mediated ARGET-ATRC reaction using a fresh stock solution and a stock solution that was six days old. Ca(BH<sub>4</sub>)<sub>2</sub> was the only reducing agent which showed a decrease in conversion rate as the stock solution aged (entry 6), while the remaining

three borohydrides improved while aging, more importantly  $(\text{Bu})_4\text{N}(\text{BH}_4)$  (entry 2, 4 and 8). The reason behind this is not clear therefore we decided to monitor the UV / Vis absorbance of the  $\text{Cu}^{\text{I}}(\text{TPA})\text{Br}$  stock solution over six days to observe any changes to the spectrum, but first we investigated if using  $\text{Cu}^{\text{II}}(\text{TPA})\text{Br}_2$  had the same varied effect on the conversion rate (Table 14).



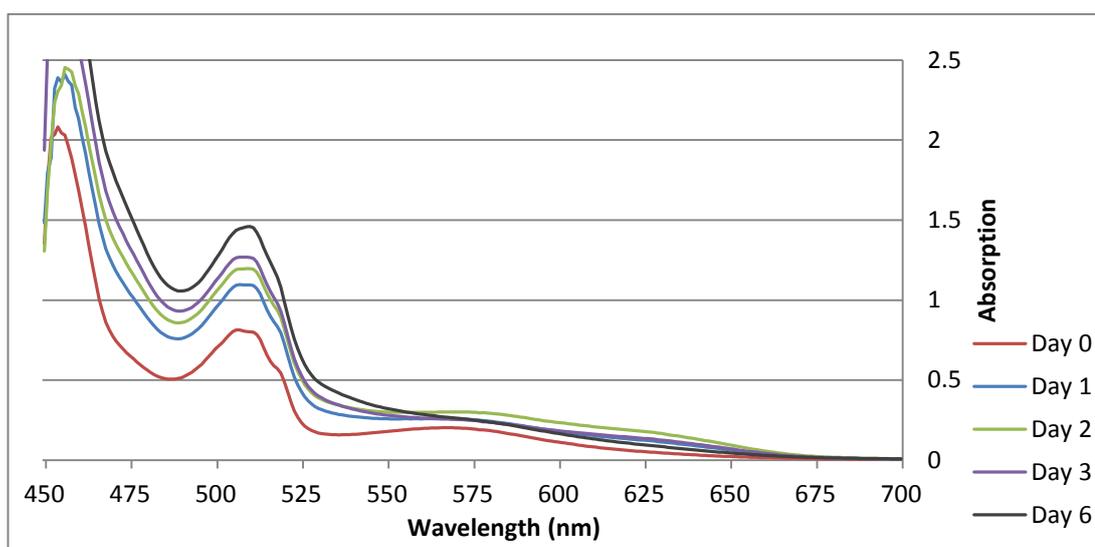
| Entry | Age of $\text{Cu(II)Br}_2/\text{TPA}$ (Day) | Borohydride     | Conversion (%) | Mass Balance (%) |
|-------|---|-----------------|----------------|------------------|
| 1     | 0   | -               | 0              | 93               |
| 2     | 3   | -               | 0              | 94               |
| 3     | 0   | $\text{NaBH}_4$ | 47             | 88               |
| 4     | 3   | $\text{NaBH}_4$ | 55             | 88               |

**Table 14.** The Effect on ATRC Using Fresh or Aged  $\text{Cu(II)Br} / \text{TPA}$  Reagent System.

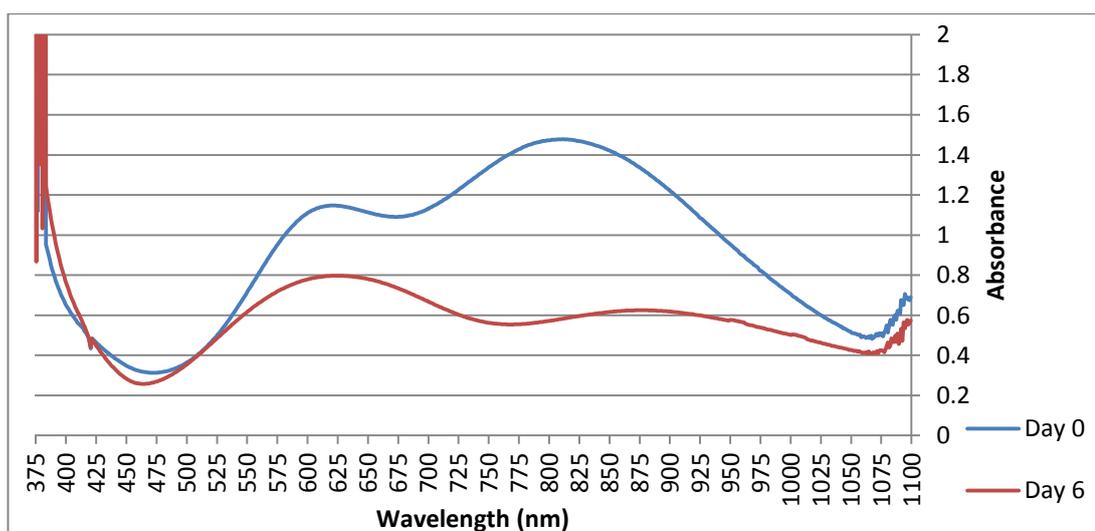
By replacing  $\text{Cu(I)}$  with  $\text{Cu(II)}$  the conversion rates appeared to be fairly stable. We could account for the minor differences (7 %) by experimental and NMR spectroscopy integration errors, but to be fairly sure we also observed  $\text{Cu}^{\text{II}}(\text{TPA})\text{Br}_2$  stock solution by UV / Vis absorbance over a period of three days to determine whether a change in absorbance is observed.

### 6.2.2 UV / Vis Experiments

We have observed significant variations on conversions of substrate **205** depending on the age of the  $\text{Cu}^{\text{I}}(\text{TPA})\text{Br}$  stock solution.  $\text{Cu}^{\text{I}}(\text{TPA})\text{Br}$  solution appears dark green to the naked eye, but to the visible eye, we failed to observe any changes in the colour of the solution overtime and therefore observed this solution by UV / Vis spectroscopy over a period of six days (Spectra 17 and 18).



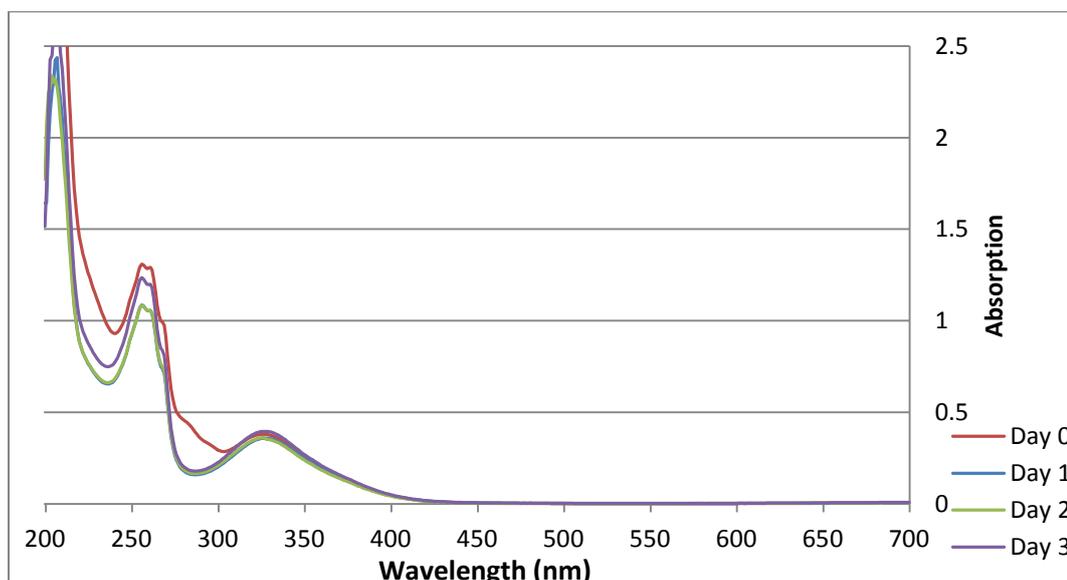
**Spectra 17.** Observing  $\text{Cu}^{\text{I}}(\text{TPA})\text{Br}$  Solution Over 6 Days in the Ultraviolet Region.



**Spectra 18.** Observing  $\text{Cu}^{\text{I}}(\text{TPA})\text{Br}$  Solution Over 6 Days in the Visible Region.

Absorbance measurements in the ultraviolet region of the spectrum showed changes in the spectrum profile. We could observe the peak at 325nm smoothing as the days progressed, but the major change was observed in the visible region of the spectrum. We could clearly see a decline and shift in peak at 800 nm to 875 nm as the days progressed.  $\text{Cu}^{\text{I}}(\text{TPA})\text{Br}$  is known to undergo disproportionation forming  $\text{Cu}(0)$  metal and  $\text{Cu}^{\text{II}}(\text{TPA})\text{Br}_2$  in polar solvents such as MeOH. The presence of  $\text{Cu}^{\text{II}}(\text{TPA})\text{Br}_2$  would result in a peak at 900 – 950 nm, therefore what we may be observing is a slow disproportionation of  $\text{Cu}(\text{I})$  to  $\text{Cu}(0)$  and  $\text{Cu}(\text{II})$ , although no metal  $\text{Cu}(0)$  was observed.

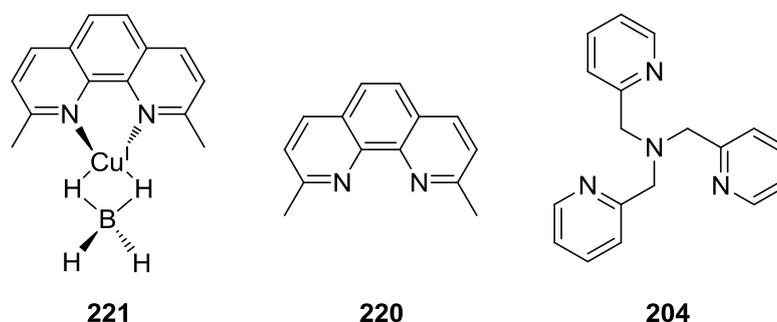
We compared Spectra 17 with the ultraviolet region of  $\text{Cu}^{\text{II}}(\text{TPA})\text{Br}_2$  stock solution spectrum (Spectra 19).



**Spectra 19.** Observing  $\text{Cu}^{\text{II}}(\text{TPA})\text{Br}_2$  Solution Over 3 Days in the Ultraviolet Region.

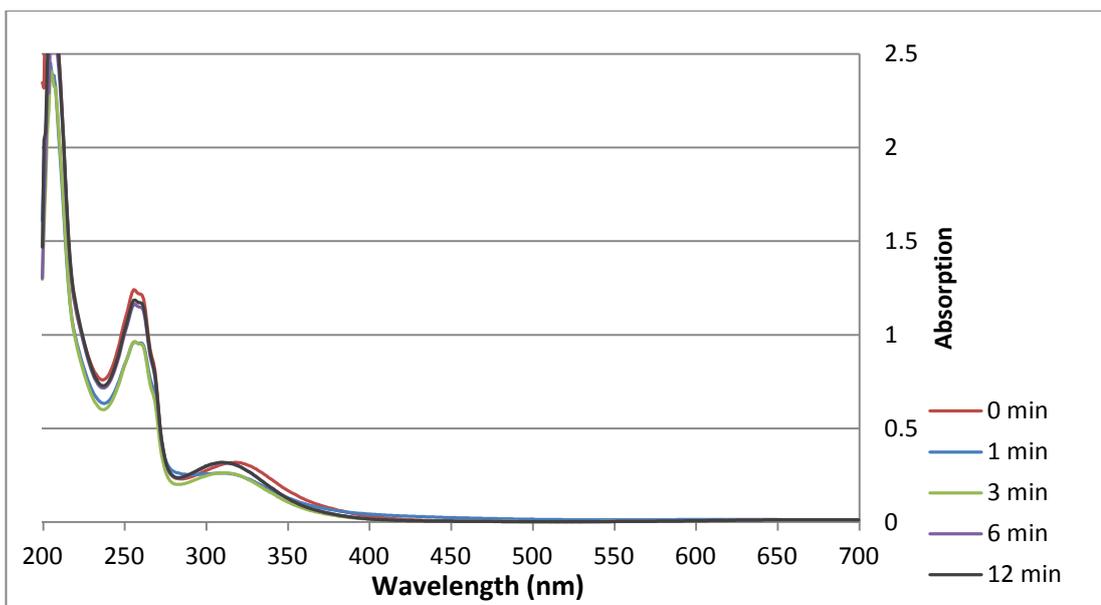
After the initial day 0 result, the absorbance measurements were consistent, indicating no change with  $\text{Cu}^{\text{II}}(\text{TPA})\text{Br}_2$  stock solution in the ultraviolet region.

Previously Kunkely and Volger<sup>140, 141</sup> have been able to synthesize a  $\text{CuBH}_4$  complex stabilised by phenanthroline **220** ligand (Figure 34). The ligand to ligand charge transfer (LLCT) between the coordinated borohydride and the phenanthroline ligand in complex **221** resulted with UV absorbance at 465 nm. Considering TPA and phenanthroline ligands are fairly similar, it would be fair to suggest that the addition of  $\text{NaBH}_4$  should result in an absorbance peak at approx. 460 nm responsible for borohydride-TPA LLCT.

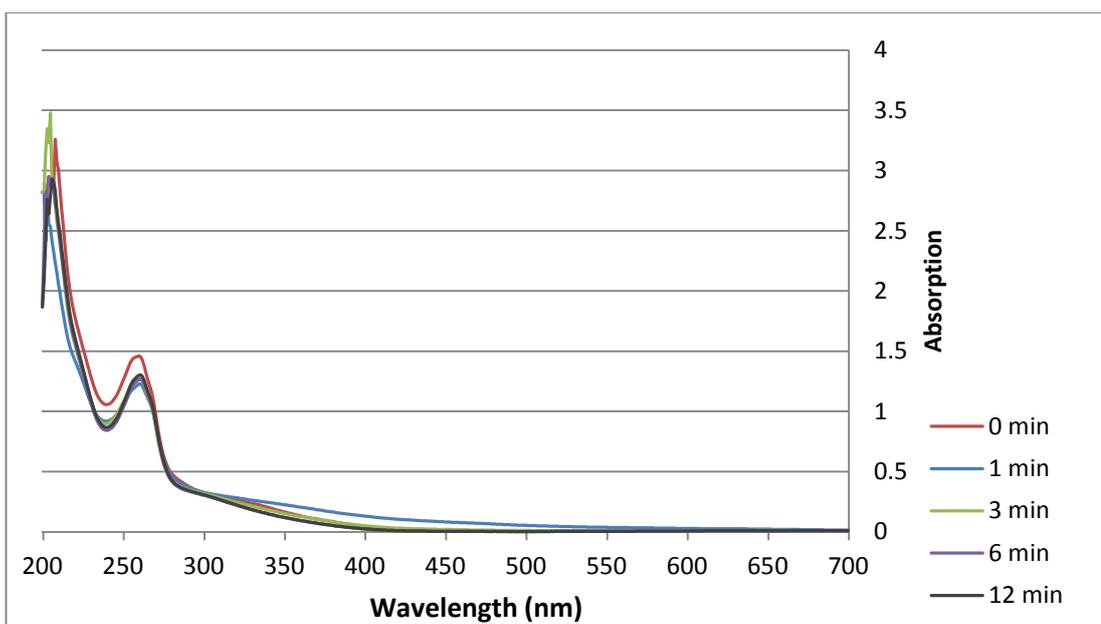


**Figure 34.** The Ligand to Ligand Charge Transfer (LLCT) Between the Coordinated Borohydride and the Phenanthroline Ligand in Complex **221**.

The effect of  $\text{NaBH}_4$  addition was first examined for both new and aged stock solutions of  $\text{Cu}^{\text{I}}(\text{TPA})\text{Br}$  in the ultraviolet region of the spectrum (Spectra 20 and 21) .

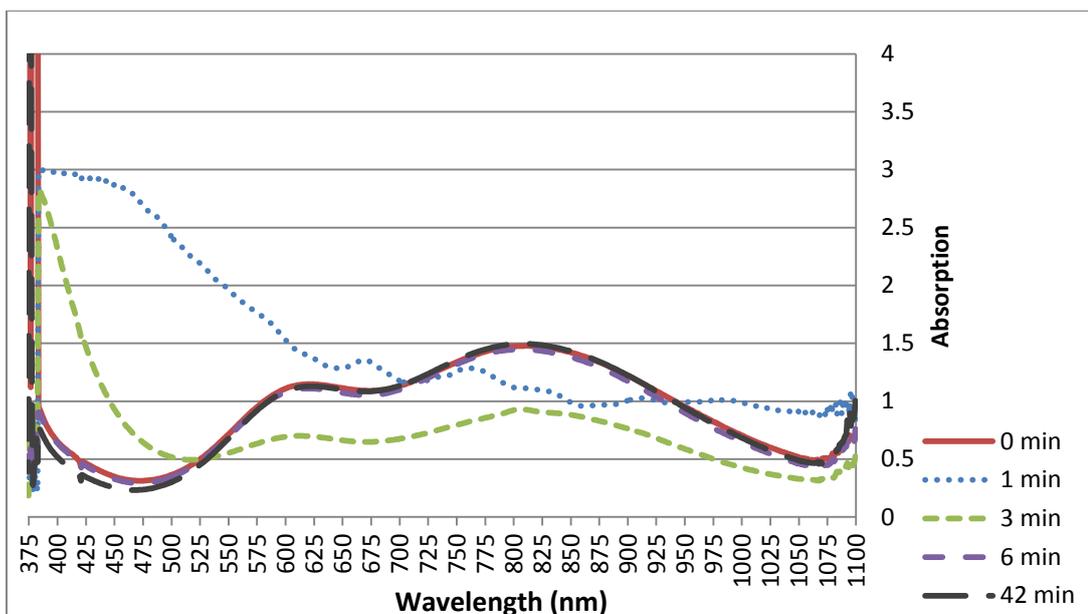


**Spectra 20.** Day 0 -  $\text{Cu}^{\text{I}}(\text{TPA})\text{Br}$  Solution With the Addition of  $\text{NaBH}_4$ .

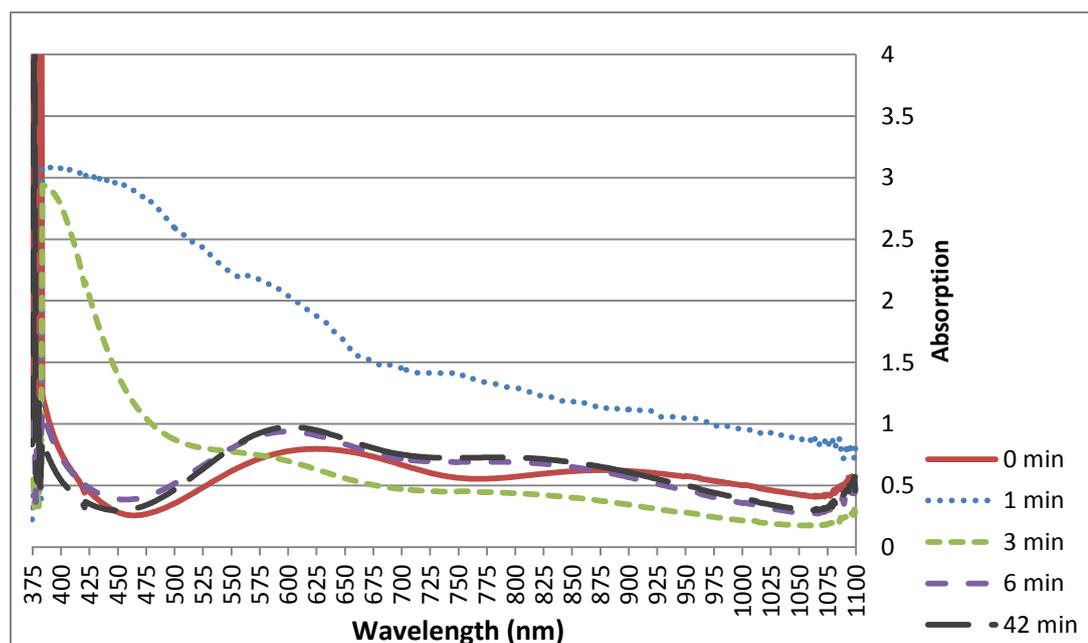


**Spectra 21.** Day 6 -  $\text{Cu}^{\text{I}}(\text{TPA})\text{Br}$  Solution with the Addition of  $\text{NaBH}_4$ .

Addition of  $\text{NaBH}_4$  to the catalytic species had little effect on the spectrum in the ultraviolet region, therefore we focused on the visible region. As from previous visual experience of this reaction, a colour change from dark green to brown and back to dark green was observed (Spectra 22 and 23).



**Spectra 22.** Day 0 -  $\text{Cu}^{\text{I}}(\text{TPA})\text{Br}$  Solution with the Addition of  $\text{NaBH}_4$ .



**Spectra 23.** Day 6 -  $\text{Cu}^{\text{I}}(\text{TPA})\text{Br}$  Solution with the Addition of  $\text{NaBH}_4$ .

Upon addition of the borohydride at  $t = 0$ , there was no evidence of  $\text{CuBH}_4$ -TPA coordination, but as the reaction proceeded, we saw an appearance of peak at approx. 450 nm, which we assume was the  $\text{CuBH}_4$  complex stabilised by TPA.

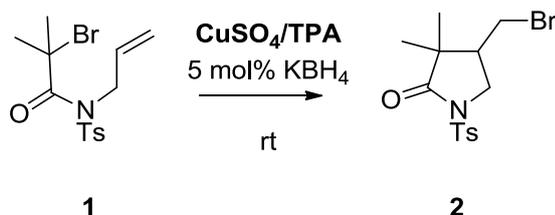
Within six minutes, the peak responsible for  $\text{CuBH}_4\text{-TPA}$  disappeared for both new and aged  $\text{Cu}^{\text{I}}(\text{TPA})\text{Br}$  stock solutions and the absorbance spectrum returned back to  $t = 0$  suggesting a short lifetime of  $\text{CuBH}_4\text{-TPA}$ . The new and aged  $\text{Cu}^{\text{I}}(\text{TPA})\text{Br}$  stock solutions both followed a similar pattern upon addition of the borohydride, therefore the reason why such variations in conversion observed is still unclear, however, the decline and shift in peak at 800 nm to 875 nm as the days progressed for aged  $\text{CuBr}(\text{TPA})$  (Spectra 18) (due to slow disproportionation of  $\text{Cu}(\text{I})$  to  $\text{Cu}(\text{0})$  and  $\text{Cu}(\text{II})$  may indicate that  $\text{Cu}(\text{II})$  and  $\text{Cu}(\text{0})$  are necessary for an efficient catalytic cycle). Due to the instability of  $\text{Cu}(\text{I})$  species, we decided to continue the copper mediated ATRC studies using  $\text{Cu}(\text{II})\text{SO}_4$  species and  $\text{KBH}_4$ , which has proved successful for ATRC reactions within the Clark group (unpublished results).

### 6.2.3 The Effect of Reaction Concentration on Copper-Mediated ATRC

Looking back at the UV / Vis absorbance results we concluded that the supposed 'active'  $\text{CuBH}_4\text{-TPA}$  species are relatively short lived (approx. six minutes). After six minutes, the borohydride stops regenerating the oxidised inactive  $\text{Cu}(\text{II})$  species back to the active  $\text{Cu}(\text{I})$  species. One complication of this short lived 'active' catalyst is that slow reactions may not be efficiently catalysed. Our aim was now to make the most of this short lived  $\text{CuBH}_4\text{-TPA}$  species by increasing the concentration of the reaction mixture to increase reaction rates. In most 'radical' reactions, increasing the concentration of the reaction has detrimental effects on the yield (due to its radical dimerization, disproportionation etc.).

The conversion of substrate **1** to product **2** was observed at increased concentrations of the reaction mixture, exposed to  $\text{CuSO}_4/\text{TPA}$  and  $\text{KBH}_4$  in MeOH

or EtOH at room temperature (Table 15). Although *N*-tosyl substrates are more reactive than their *N*-benzyl counterparts, it was observed that **1** was only sparingly soluble in methanol, therefore a few drops of DCM was added as a co-solvent to assist dissolution.



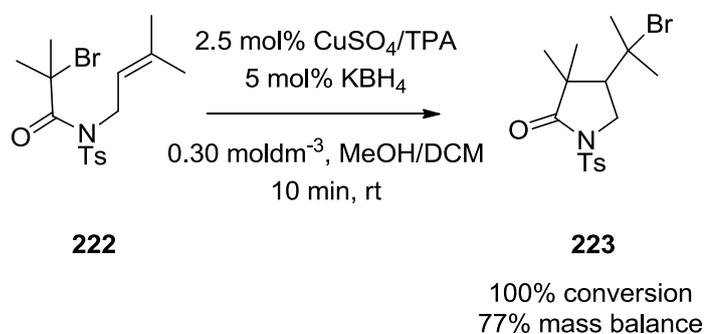
| Entry | Solvent + DCM | Concentration (mol dm <sup>-3</sup> ) | CuSO <sub>4</sub> /TPA (mol%) | Time (min) | Conversion (%) | Mass Balance (%) |
|-------|---------------|---------------------------------------|-------------------------------|------------|----------------|------------------|
| 1     | MeOH          | 0.12                                  | 2.5                           | 10         | 41             | 87               |
| 2     | MeOH          | 0.16                                  | 2.5                           | 10         | 69             | 88               |
| 3     | MeOH          | 0.30                                  | 2.5                           | 10         | 100            | 85               |
| 4     | MeOH          | 0.30                                  | 1.0                           | 10         | 58             | 87               |
| 5     | EtOH          | 0.30                                  | 1.0                           | 10         | 46             | 95               |
| 6     | EtOH          | 0.30                                  | 1.0                           | 60         | 45             | 91               |
| 7     | MeOH          | 0.51                                  | 1.0                           | 10         | 100            | 90               |
| 8     | MeOH          | 0.82                                  | 0.5                           | 10         | 76             | 92               |
| 9     | MeOH          | 1.55                                  | 0.1                           | 10         | 0              | 91               |

**Table 15.** The Effect on Conversion of **1** to **2** by Increasing Concentration.

The results showed that by increasing the concentration of the reaction mixture from 0.12 M to 0.30 M, we observed an increase in conversion from 41% to 100% of product **2** after 10 min (Table 15, entry 1 and 3). Achieving 100% conversion using 2.5 mol% CuSO<sub>4</sub> / TPA, we pushed the reaction further by decreasing the catalyst loading to 1 mol%. This resulted in a 58% conversion at 0.30 M (entry 4), while repeating this reaction in EtOH resulted in 46% conversion (entry 5), suggesting MeOH to be the dominant solvent. Further increasing the

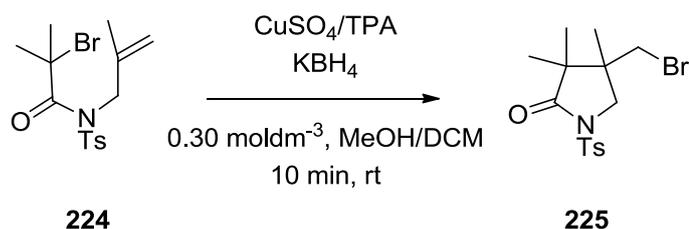
concentration to 0.51 M, we were able to achieve 100% conversion using 1 mol% catalyst (entry 7). We pushed the reaction further by reducing the catalyst loadings to 0.5 and 0.1 mol% at 0.82 and 1.55 M concentration. This resulted in a 76% and 0% conversion to product **2** respectively (entry 8 and 9). Increasing the reaction time to 60 min failed to improve the conversion (entry 5 and 6) as expected due to the short lived  $\text{CuBH}_4\text{-TPA}$  species. Any further increase in concentration failed to solubilise the substrate and so we couldn't conduct the experiment. These results proved that we could significantly improve the conversion of **1** by moving from 0.1 mol%  $\text{CuSO}_4 / \text{TPA}$  and 100 mol%  $\text{KBH}_4$  (Scheme 58) to 1.0 mol%  $\text{CuSO}_4 / \text{TPA}$  and 5 mol%  $\text{KBH}_4$  (Table 15) by increasing the concentration of the reaction mixture. More importantly the mass balance for the cyclised product remained good indicating that there was no detrimental effect on yield by increasing the concentration.

The technique of increasing the concentration of the reaction mixture and improving the conversion were then tested on various *5-exo trig* and *5-exo dig* substrates. The solubility of these substrates in MeOH varied therefore we chose to initially expose these compounds to standard conditions of 2.5 mol%  $\text{CuSO}_4 / \text{TPA}$ , 5 mol% at 0.30 M concentration in MeOH/DCM at room temperature for 10 min.



**Scheme 59.** Using Our Optimised Reagent System to Cyclise **222**.

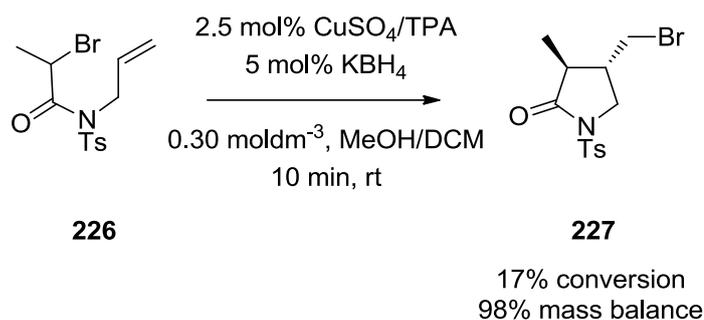
Substrate **222** resulted in a complete conversion to *5-exo trig* cyclised product **223** (Scheme 59), this was predicted as the two methyl groups on the alkene would efficiently stabilize the terminal radical after the cyclisation. However, with substrate **224**, only 44% conversion was achieved using the standard conditions. Increasing borohydride loading to 10 mol% almost doubled the conversion to 81% resulting in product **225** (Table 16).



| Entry | CuSO <sub>4</sub> /TPA (mol%) | KBH <sub>4</sub> (mol%) | Conversion (%) | Mass Balance (%) |
|-------|-------------------------------|-------------------------|----------------|------------------|
| 1     | 2.5                           | 5                       | 44             | 90               |
| 2     | 2.5                           | 10                      | 81             | 89               |

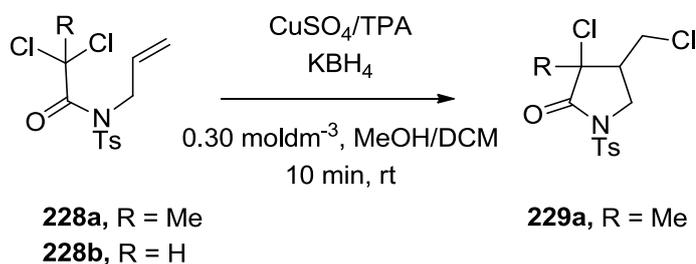
**Table 16.** Using Our Optimised Reagent System to Cyclise **224**.

When a more challenging *5-exo trig* cyclisation of secondary bromide **226** was attempted (Scheme 60), only 17% conversion to product **227** was achieved. The rates of secondary bromide cyclisations are known to be slower than those of tertiary bromides, possibly due to the removal of Thorpe-Ingold effect.<sup>112</sup>



**Scheme 60.** Using Our Optimised Reagent System to Cyclise **226**.

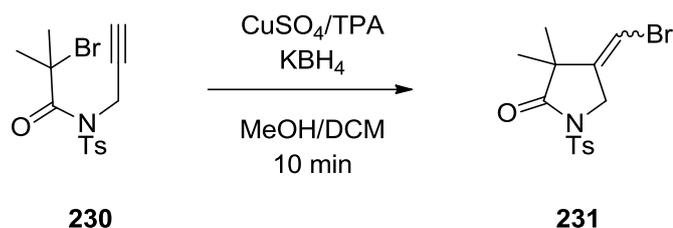
At standard conditions, substrate **228a** resulted in 54% conversion to 5-*exo* trig cyclised product **229a** (Table 17), while increasing the borohydride loading to 10 mol% resulted in 83% conversion, while an attempt to cyclise a more challenging secondary chloride **228b** failed.



| Entry | Substrate   | CuSO <sub>4</sub> /TPA (mol%) | KBH <sub>4</sub> (mol%) | Conversion (%)                      | Mass Balance (%) |
|-------|-------------|-------------------------------|-------------------------|-------------------------------------|------------------|
| 1     | <b>228a</b> | 2.5                           | 5                       | 54%<br>(1.58 : 1 <i>cis:trans</i> ) | 91               |
| 2     | <b>228a</b> | 2.5                           | 10                      | 83%<br>(1.96 : 1 <i>cis:trans</i> ) | 89               |
| 3     | <b>228b</b> | 2.5                           | 5                       | 0%                                  | 99               |

**Table 17.** Using Our Optimised Reagent System to Cyclise **228a** and **228b**.

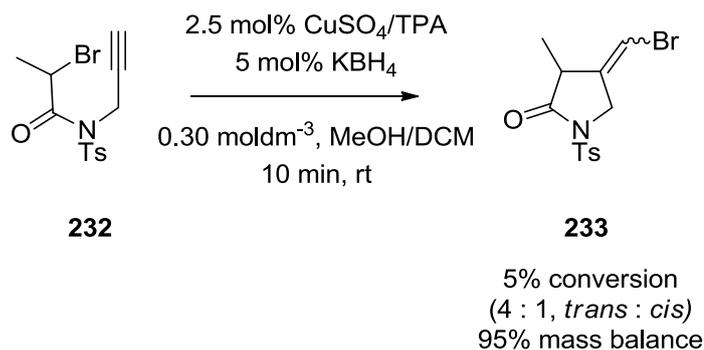
ATRC onto alkynes have been reported to be more difficult than with alkenes,<sup>111</sup> and under conventional conditions (30 mol%, DCM, rt) are up to 100 times slower than *5-exo trig* reactions. In addition the products obtained are often solvent, ligand and *N*-protecting group dependent. Substrate **230**, when treated to the standard conditions, resulted in 16% conversion to **231** (Table 18, entry 1).



| Entry | Concentration (mol dm <sup>-3</sup> ) | CuSO <sub>4</sub> /TPA (mol%) | KBH <sub>4</sub> (mol%) | Temp | Conversion (%)                               | Mass Balance (%) |
|-------|---------------------------------------|-------------------------------|-------------------------|------|--|------------------|
| 1     | 0.30                                  | 2.5                           | 5                       | RT   | 16%<br>(7 : 1 <i>trans</i> : <i>cis</i> )    | 92               |
| 2     | 0.51                                  | 2.5                           | 5                       | RT   | 16%<br>(7 : 1 <i>trans</i> : <i>cis</i> )    | 96               |
| 3     | 0.51                                  | 2.5                           | 5                       | 50°C | 16%<br>(7 : 1 <i>trans</i> : <i>cis</i> )    | 81               |
| 4     | 0.51                                  | 2.5                           | 10                      | RT   | 19%<br>(3.75 : 1 <i>trans</i> : <i>cis</i> ) | 88               |

**Table 18.** Using Our Optimised Reagent System to Perform ATRC onto Alkyne **230**.

An increase in concentration to 0.51 M gave no improvement on conversion, while increasing the concentration to 0.51 M and temperature to 50°C also failed to improve the conversion to **231**. Increasing the borohydride loading to 10 mol% resulted in slight improvement of 19% conversion to **231**. When a more challenging *5-exo dig* cyclisation of secondary bromide **232** was attempted (Scheme 61), only 5% conversion to product **233** was achieved.



**Scheme 61.** Using Our Optimised Reagent System to Perform ATRC onto Alkyne **232**.

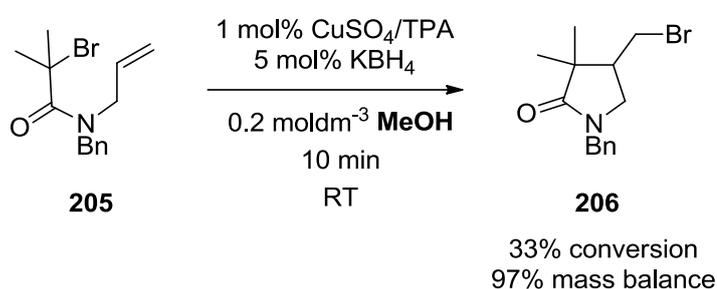
### 6.2.4 Sonication

Ultrasound comprises sonic waves with frequencies of  $2 \times 10^4$  to  $10^7$  Hz. Transmittance of these waves through water results in cavitation, resulting in extremely high local temperatures of approx. 5000 K inside the bubble and its surroundings, with pressures of about  $10^8 \text{ Pa}^2$  in the collapsed microbubbles.<sup>142</sup> The treatment of ultrasound to water and an immiscible organic co-solvent would create an emulsion, while this emulsion would be short lived, the timespan can be increased with the addition of a surfactant such as sodium dodecyl sulfonate (SDS) which aids association to form organised structures by aggregation of molecules and additionally provides stability to the hydrophobic components in the reaction.<sup>142, 143,</sup>

144

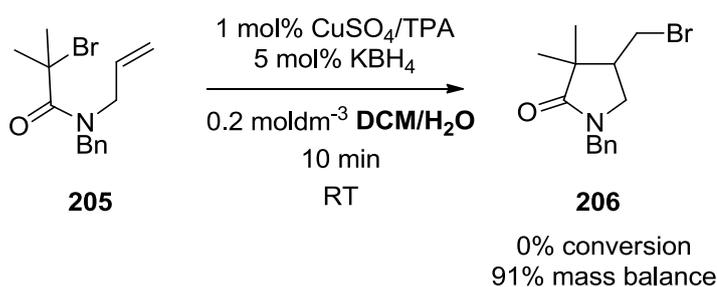
Ultrasound initiated emulsion radical polymerisation has been performed on methyl methacrylate (MMA) in water which resulted in high polymer yield.<sup>142, 145</sup> We aimed to use this ultrasound technique to preform copper mediated AGET-

ATRC of tertiary bromide **205** in water and an immiscible organic solvent to dissolve the substrate to eventually reduce the amount of toxic solvents used in ATRC. As previously stated, metal borohydrides require protic solvents to be able to reduce the inactive Cu(II) to active Cu(I), here we would assume water to be a great solvent.  $\text{CuSO}_4$  / TPA readily dissolve in water. In the absence of the ultrasonic device, substrate **205** was treated with 1 mol%  $\text{CuSO}_4$  / TPA, 5 mol%  $\text{KBH}_4$  in MeOH for 10 min at room temperature (Scheme 62).



**Scheme 62.** 5-*exo trig* AGET-ATRC of **205** in MeOH.

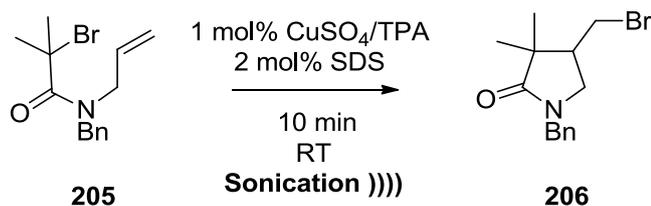
This resulted with a 33% conversion to product **206**. Repeating the reaction with water / DCM (Scheme 63) resulted in 0% conversion due to the biphasic nature of the reaction.



**Scheme 63.** Failed 5-*exo trig* AGET-ATRC of **205** in DCM/ $\text{H}_2\text{O}$ .

The same reaction was now repeated and treated with ultrasound (Table 19, entry 1 – 4) varying only the concentration of the solvent. The general procedure involved dissolving  $\text{CuSO}_4$  / TPA in water, while dissolving substrate **205** in

minimum amount of DCM and transferred to water / catalyst. The surfactant (SDS) was then added and the reaction mixture was treated to ultrasound for 2 min to form an emulsion.  $\text{KBH}_4$  was then added and the reaction was further treated to ultrasound for 8 min, after which the emulsion was allowed to settle overnight, resulting in a DCM /  $\text{H}_2\text{O}$  layer, where DCM was extracted, washed, dried and analysed by  $^1\text{H}$  NMR spectroscopy.



| Entry | Solvent                    | Concentration (mol dm <sup>-3</sup> ) | $\text{KBH}_4$ | Conversion (%) | Mass Balance (%) |
|-------|----------------------------|---------------------------------------|----------------|----------------|------------------|
| 1     | DCM / $\text{H}_2\text{O}$ | 0.2                                   | -              | 0              | 90               |
| 2     | DCM / $\text{H}_2\text{O}$ | 0.2                                   | 5              | 23             | 76               |
| 3     | DCM / $\text{H}_2\text{O}$ | 0.4                                   | 5              | 40             | 85               |
| 4     | DCM / $\text{H}_2\text{O}$ | 0.8                                   | 5              | 56             | 93               |
| 5     | $\text{H}_2\text{O}$       | 0.8                                   | 5              | 72             | 92               |

**Table 19.** 5-*exo trig* AGET-ATRC of **205** using Sonication at Increased Concentrations in DCM/ $\text{H}_2\text{O}$  or  $\text{H}_2\text{O}$ .

Treating substrate **205** to the reagent / solvent system used in Scheme 63 resulted in 23% conversion to **206**, while in the absence of  $\text{KBH}_4$ , no conversion was observed (Table 19, entry 1 and 2). Even though the conversion is lower than using just MeOH, this suggested that the borohydride is active in water and efficiently generated the active Cu(I) species, while the emulsion allowed interaction between the substrate and the catalyst. Increasing the concentration of the reaction mixture to 0.4 and 0.8 M resulted in an increased conversion to 40% and 56% (entry 3 and 4).

At this point we thought if we really needed DCM as substrate **205** was an oil, therefore a major surprise was observed when removing the toxic DCM and performing the reaction in just water, resulting in 72% conversion to **206** (entry 5).

Further reactions will be carried out using this technique by the group as we were able to demonstrate copper mediated AGET-ATRC in water at good conversions, replacing all toxic solvents. This could be considered as 'green' chemistry, besides the fact the ultrasonic devices use high energy. There is energy saving alternatives to ultrasonic devices which are used to create emulsions used by the industry<sup>142</sup> which do a similar job, which we need test in the future.

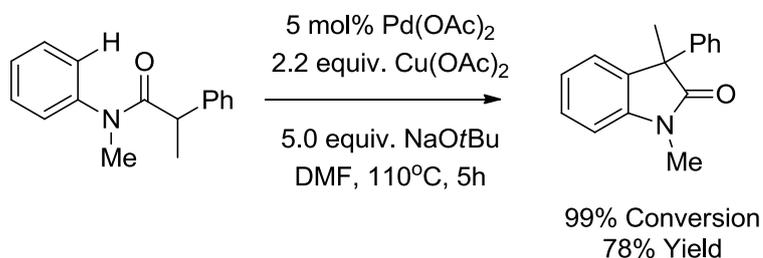
### 6.3 Conclusion

In this chapter we have demonstrated  $\text{KBH}_4$  to be the most efficient reducing agent for copper mediated AGET / ARGET – ATRC. We discovered inconsistent conversion rates when using  $\text{Cu}^{\text{I}}(\text{TPA})\text{Br}$  catalyst solution of varying age, but the reasons are not yet fully understood. By increasing the concentration of the reaction mixtures we significantly improved the efficiency of copper mediated AGET–ATRC, for example the conversion of **1** to **2** from 0.1 mol%  $\text{CuSO}_4$  / TPA and 100 mol%  $\text{KBH}_4$  (Scheme 58) was improved to 1.0 mol%  $\text{CuSO}_4$  / TPA and 5 mol%  $\text{KBH}_4$  (Table 15). While Casolari<sup>139</sup> previously demonstrated full conversion of substrates *via* 5-exo-trig cyclisation using 4 mol% metal / ligand and 5 mol% additives, we performed these types of reaction using 1 mol% metal / ligand and 5 mol% additive. Using ultrasound, we were able to demonstrate copper mediated AGET-ATRC in water at a good conversion, replacing toxic solvent which could be considered as 'green' chemistry.

7.0 Synthesizing Oxindoles *via* Copper-Mediated Cyclisation

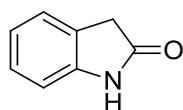
## 7.1 Introduction

In chapter 6, we were able to improve the efficiency of 5-*exo* AGET-ATRC reactions using  $\text{CuSO}_4/\text{TPA}$  and  $\text{KBH}_4$  at an increased concentration. We next investigated whether we could improve the efficiency of the currently known synthesis of oxindoles *via* copper mediated radical cyclisation of anilides (Scheme 64).



**Scheme 64.** An Example Synthesis of Oxindole by Direct Coupling of C-H and Aryl-H.

Oxindoles (Figure 35, **234**) are a unique class of heterocyclic compounds. The structure is present in a number of natural products and medicinal agents or is an important intermediate for the synthesis of medicinal agents.



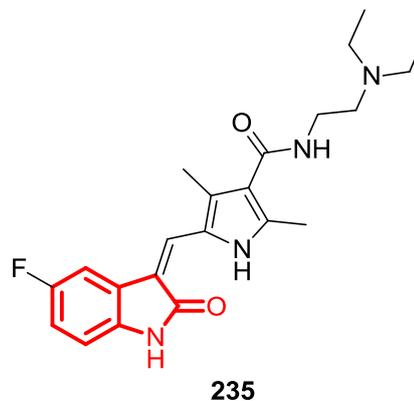
**234**

**Figure 35**

Oxindoles are of great interest in medicinal chemistry due to their biological properties that include activities as protein kinase inhibitors<sup>146, 147</sup>, phosphodiesterase inhibitors<sup>148</sup> and anti-rheumatic agents.<sup>149</sup> An example of an oxindole based drug is (*Z*)-*N*-(2-(diethylamino)ethyl)-5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxamide (Figure 36, **235**), marketed by Pfizer as Sutent®. This drug is a multi-kinase inhibitor targeting several receptor tyrosine kinases (RTK) for the

treatment of renal cell carcinoma (RCC) and gastrointestinal stromal tumor (GIST).<sup>150</sup>

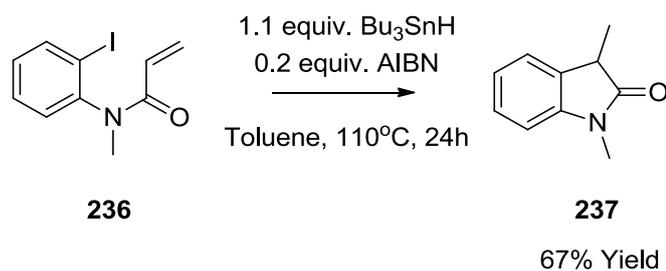
There are many ways to synthesize oxindoles. The most common methods providing the most efficient entry to oxindoles are the 5-*exo* radical cyclisation reactions,<sup>151-157</sup> Heck reactions,<sup>158-162</sup> palladium-catalysed Buchwald-Hartwig-type amidation,<sup>163-167</sup> direct coupling of C-H's<sup>169-173</sup> and direct photolysis.<sup>175-177</sup>



**Figure 36**

### 7.1.1 Radical Cyclisation Reaction

Intramolecular *ortho*-aryl radical cyclisation reactions have extensively been used to synthesize oxindoles. One of the early examples was the addition of such radicals to the  $\alpha$ -position of  $\alpha$ - $\beta$ -unsaturated *N*-alkylamides using  $\text{Bu}_3\text{SnH}$  and AIBN (Scheme 65).<sup>151</sup>



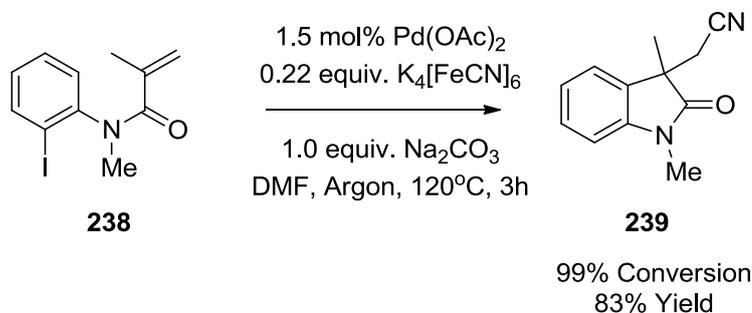
**Scheme 65.** Oxindole Synthesis via 5-*exo* Radical Cyclisation using  $\text{Bu}_3\text{SnH}$ .

Ever since, further examples 5-*exo* radical cyclisation using  $\text{Bu}_3\text{SnH}$  have appeared for the synthesis of oxindoles<sup>152, 153, 154</sup> but using stoichiometric amounts of

highly toxic tin hydride and AIBN at elevated temperatures were a major disadvantage hence transition metals such as In(II),<sup>155</sup> Sm(II),<sup>156</sup> Co(II)<sup>157</sup> and Cu(II) (see 7.1.3) have been used to prepare oxindoles in redox processes. These transition-metal-mediated radical cyclisation reactions still require large amounts of metal with excess additives.

### 7.1.2 Palladium-Catalysed Oxindole Synthesis 1) Heck Reaction.

Palladium-catalysed carbopalladation, especially domino Heck reactions have played a prominent role in synthesizing oxindoles.<sup>158-162</sup> An example was demonstrated by Zhu *et al*, where they performed a domino intramolecular Heck-cyanation sequence. Reaction of *ortho*-iodoanilide **238** with potassium ferro(II)cyanide, dissolved in DMF in the presence of palladium acetate and sodium carbonate afforded oxindole **239** in 83% yield (Scheme 66).<sup>158</sup>



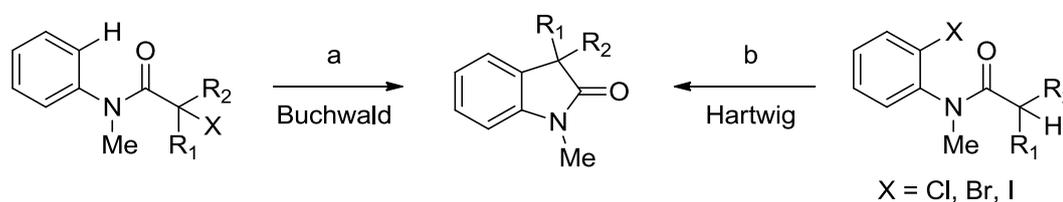
**Scheme 66.** Oxindole Synthesis *via* Palladium-Catalysed Domino Heck-Cyanation Reaction.

Although domino palladium-catalysed intramolecular Heck reactions are advantageous in that they allow the formation of multiple chemical bonds in a single synthetic operation, the use of expensive palladium, high temperatures and the requirement of inert conditions may prove expensive for industrial scale reactions.

## 7.1.3 Palladium-Catalysed Oxindole Synthesis 2) via Buchwald and Hartwig

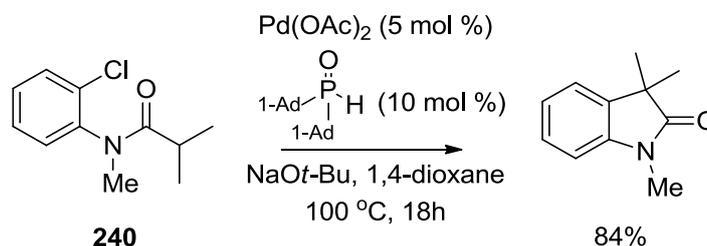
## Method.

Palladium-catalysed oxindole syntheses via Buchwald and Hartwig methods have also provided a useful access to oxindoles. The Buchwald method<sup>163</sup> (Scheme 67, a) requires an  $\alpha$ -halogen or  $\alpha$ -hydroxy group precursor, but only limited work has been published as the Hartwig method<sup>164, 165, 166</sup> (Scheme 67, b) has proved to be more successful. The Hartwig method requires an *ortho*-halogen precursor for successful cyclisation.



**Scheme 67.** Buchwald and Hartwig Method to Oxindoles.

Recently, oxindoles were synthesized using a palladium catalyst and an air-stable secondary phosphine oxide [(1-Ad)<sub>2</sub>P(O)H] which enabled efficient intramolecular  $\alpha$ -arylation of amides with aryl chloride **240** (Scheme 68).<sup>167</sup>



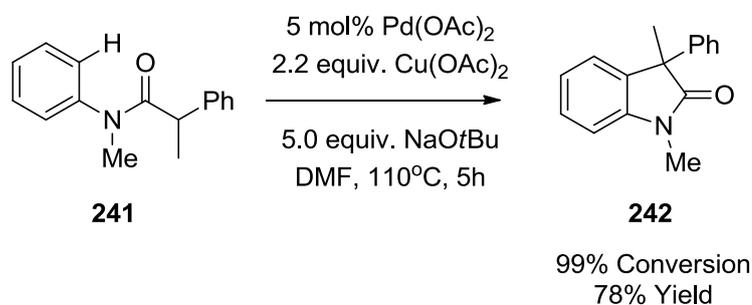
**Scheme 68.** Oxindole Synthesis via Palladium-Catalysed Hartwig Reaction.

Although the amounts of palladium catalyst and ligand used were fairly low (5 – 10 mol%), the use of expensive palladium and custom designer ligands often prove to be expensive industrial scale reactions.

#### 7.1.4 Direct Coupling of C-H and Aryl-H

Considerable attention has been directed to the development of transition metal catalysed methodologies that directly functionalise arene C-H bonds.<sup>168</sup> In particular, palladium catalysed aromatic C-H functionalization / C-C bond formations.<sup>169, 170, 171</sup>

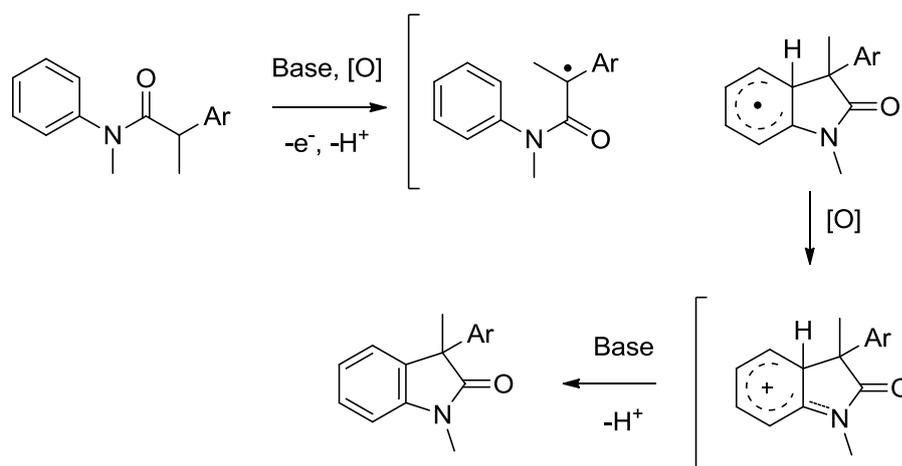
Recently, Kündig and co-workers demonstrated the synthesis of oxindole **242** from *N*-methyl-*N*-2-diphenylpropanamide (**241**) by using 5 mol% of Pd(OAc)<sub>2</sub>, 2.2 equiv of Cu(OAc)<sub>2</sub> oxidant and 5.0 equiv. of *t*BuONa as a base obtaining **1a** in 99% conversion and 85% (Scheme 69).<sup>172</sup>



**Scheme 69.** Synthesis of Oxindole by Direct Coupling of C-H and Aryl-H

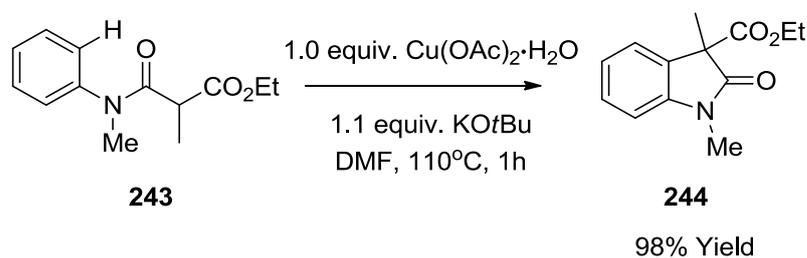
They soon realised that the expensive Pd(OAc)<sub>2</sub> catalyst was not necessary and that **242** could be synthesized with the same yield without it. As the presence of palladium did not play a significant role, the initially hypothesized Heck-type pathway was revised and a new radical mechanism for direct C-H coupling reaction was proposed (Scheme 70).<sup>172</sup>

## 7.0: Synthesizing Oxindoles *via* Copper Mediated Cyclisation



**Scheme 70.** Proposed Pathway for the Direct C-H Coupling Reaction.

Taylor and co-workers also reported a non-palladium route to oxindoles by direct C-X, Ar-H coupling of **243** using 1.0 equiv. of  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ , and 1.1 equiv. KOtBu in DMF resulting in 98% yield of **244** in 1h (Scheme 71).<sup>173</sup>



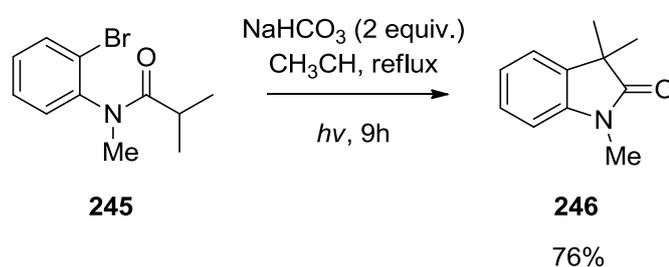
**Scheme 71.** Non-palladium Route to Oxindoles by Direct C-X, Ar-H Coupling.

Although the amount of transition metal required was significantly reduced compared to Kündig's approach, it still required stoichiometric amounts of metal, DMF as solvent and high temperatures.

7.1.5 Direct Photolysis of *ortho*-Substituted Aniline Precursors.

The photoinduced cyclisation of mono- or dianions of *N*-acyl-*o*-chloroanilines have resulted in oxindoles via a S<sub>RN</sub>1 mechanism.<sup>174</sup> Aryl C-X (X = halogen) bonds have been known to homocleave upon UV photolysis to give the corresponding aryl radicals.<sup>175, 176</sup> Chaozhong and co-workers used this to their advantage and replaced the commonly used mediators Bu<sub>3</sub>SnH or diethyl phosphine for the synthesis of oxindoles.<sup>177</sup>

They demonstrated the synthesis of oxindole **246** from *N*-(2-bromophenyl)-*N*-methylisobutyramide **245**. This was achieved when the mixture of **245** and NaHCO<sub>3</sub> (2 equiv.) in acetonitrile was irradiated with a high pressure mercury lamp (125 W) at reflux for 9 h (Scheme 72).

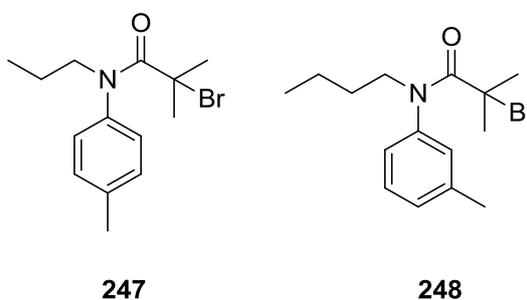


**Scheme 72.** Synthesis of Oxindole *via* Direct Photolysis.

In a lab-scale reaction this method would be useful, but photo-induced homolysis of a C-X bond on an industrial scale might be impractical.<sup>178</sup> Also Bu<sub>3</sub>SnH reactions are not very practical due to the high toxicity and expense of the reagent. Alternative transition metal-mediated radical cyclisation reactions and palladium catalysed reactions are more efficient than Bu<sub>3</sub>SnH mediated processes, but the common drawbacks include the relatively large amounts of transition metals and additives required. Palladium catalysed reactions require expensive palladium

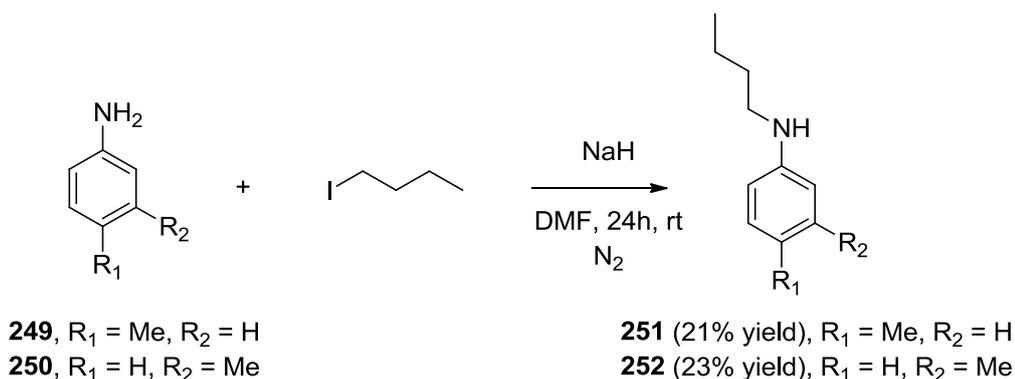
catalysts and expensive designer ligands. The copper-mediated direct coupling reactions still require stoichiometric amounts of transition-metals and bases, unfavourable solvents and high temperatures. Our aim is to develop an alternative and possibly an efficient route to oxindoles by using the reagent system that proved successful in 5-*exo*-AGET-ATRC reactions in chapter 6.

## 7.2 Results and Discussion



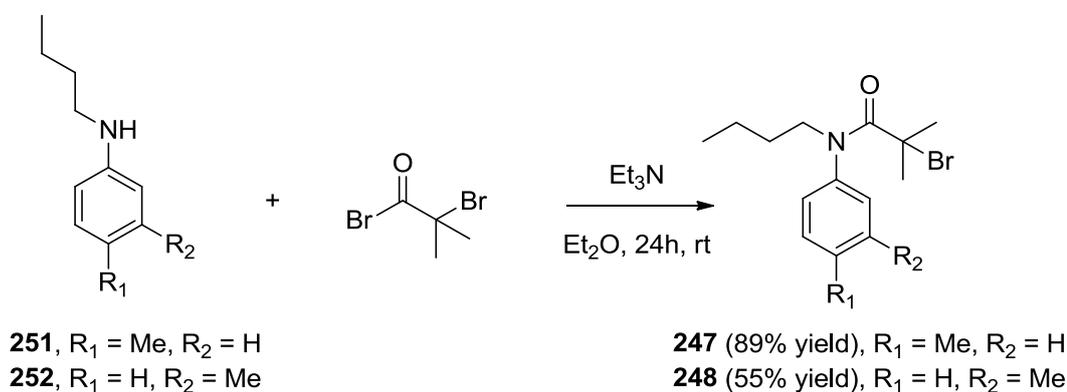
**Figure 37.** Oxindole Precursors we First Synthesized.

To investigate copper mediated cyclisations using borohydride as an additive for the synthesis of oxindoles, we first synthesised halogenated precursors, 2-bromo-*N*-butyl-2-methyl-*N*-(*p*-tolyl)propanamide (Figure 37, **247**) and 2-bromo-*N*-butyl-2-methyl-*N*-(*m*-tolyl)propanamide (Figure 37, **248**). These precursors contain a bromine atom at the  $\alpha$ -position of the amide. To make these compounds the anilines **249** and **250** were deprotonated using NaH followed by the addition of iodobutane with stirring for 24 h under nitrogen. After workup and purification by column chromatography, intermediates **251** and **252** were successfully synthesized (Scheme 73).



**Scheme 73.** Synthesis of the Intermediates for Oxindole Precursors **247** and **248**.

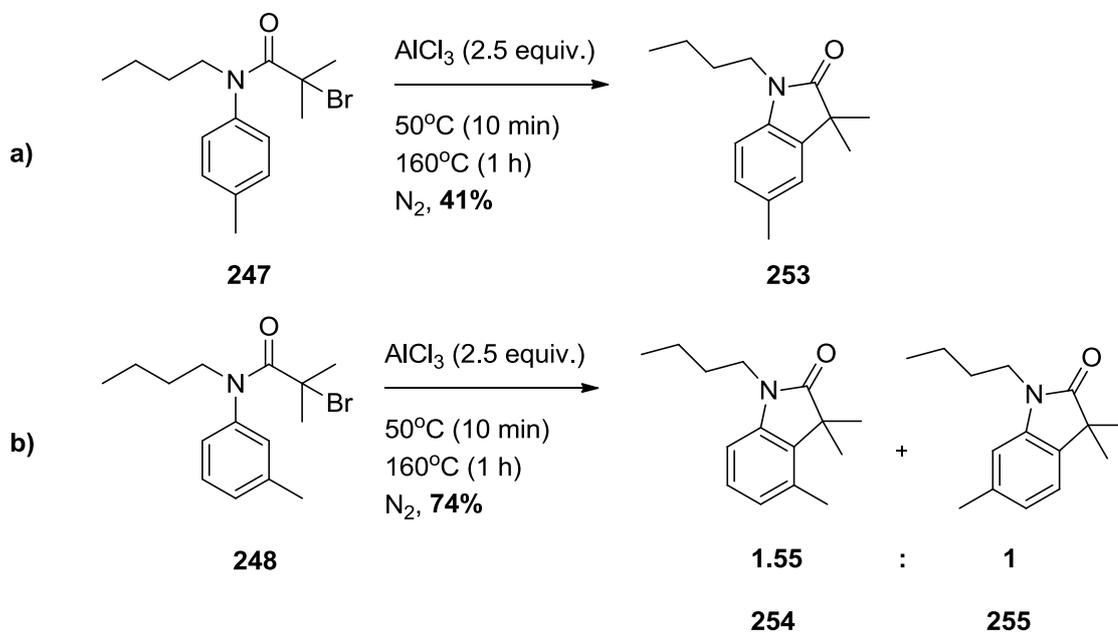
The next step to synthesize the oxindole precursors **247** and **248** required acylation of the intermediate **251** and **252** with 2-bromoisobutyryl bromide in the presence of  $\text{Et}_3\text{N}$  as a base. After 24 h, and with standard organic reaction work-up, pure products **247** and **248** were obtained (Scheme 74).



**Scheme 74.** Synthesis of Oxindole Precursors **247** and **248**.

As previously described, there are various ways to synthesize oxindoles. Before we tried to cyclise these precursors using our copper / ligand and borohydride reagent system, we attempted to cyclise these substrates using two alternative methods a) intramolecular Friedel-Crafts acylation and b) conventional radical cyclisation using  $\text{Bu}_3\text{SnH}$  / AIBN. From these results we could compare the efficiency of our copper mediated cyclisations with these standard processes.

We can perform an intramolecular Friedel-Crafts reaction by treating our substrates **247** and **248** with 2.5 equiv. aluminium trichloride at elevated temperatures under nitrogen (Scheme 75, a and b).

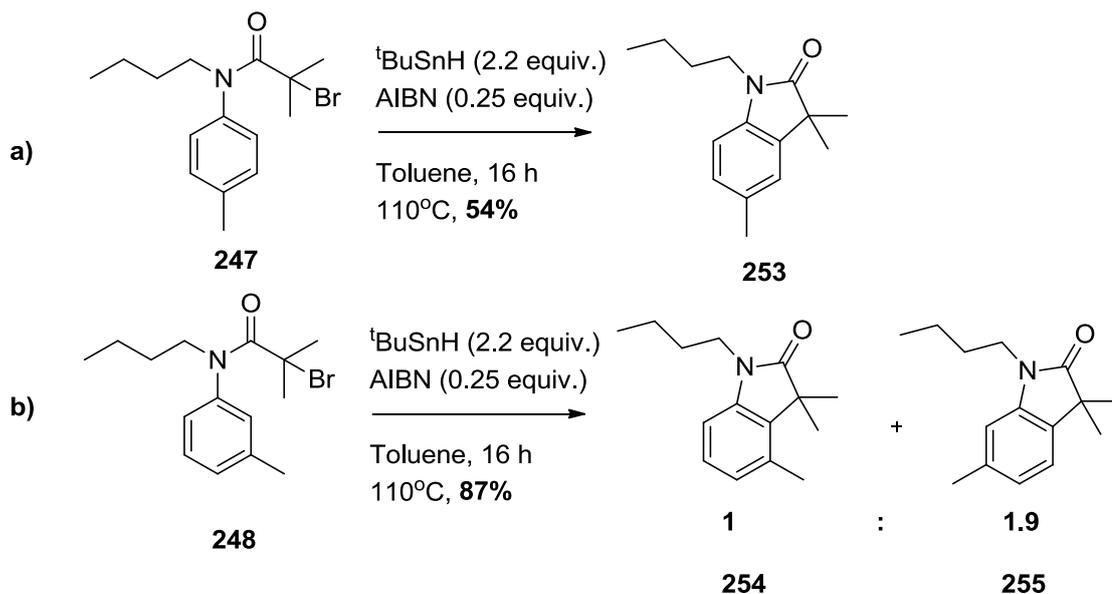


**Scheme 75.** Synthesis of Oxindoles *via* Friedel-Crafts Acylation Reaction.

Treating substrate **247** under Friedel-Crafts conditions provided **253** in 41% yield after purification by column chromatography (Scheme 75, a), while substrate **248** provided regio-isomers **254** and **255** in a ratio of 1.55 : 1 (**254** : **255**) (74% combined yield) (Scheme 75, b).

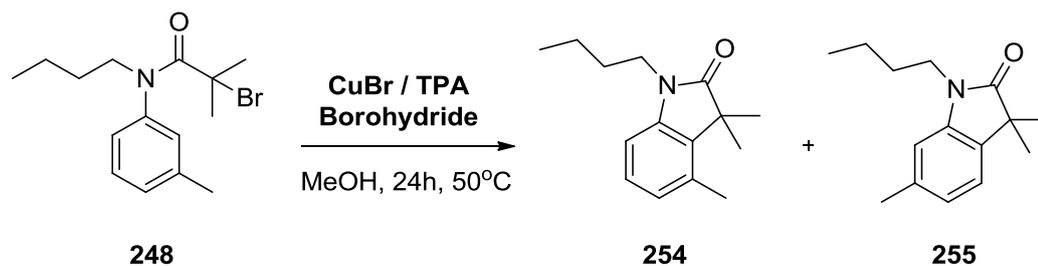
Substrates **247** and **248** were also cyclised using 2.20 / 0.25 equiv. of  $\text{Bu}_3\text{SnH}$  / AIBN, refluxed in toluene for 16 h (Scheme 76). This resulted in a higher 54% yield for product **253** (Scheme 76, a) and a higher combined 87% yield for products **254** and **255** in a ratio of 1.9 : 1 (**255** : **254**) (Scheme 76, b). Evidently, Friedel-Crafts reaction favours the synthesis of the more hindered oxindole **254**. The

reason for this may possibly be a more efficient electrophilic substitution mechanism in the presence of an adjacent inductive electron donating methyl group. While with a radical approach using  $t\text{BuSnH}$  / AIBN, the steric hindrance and electron donation from the adjacent methyl group to the aromatic may have a negative effect towards 5-*exo* radical cyclisation reaction, hence favouring oxindole **255**.



**Scheme 76.** Synthesis of Oxindoles *via* Radical Cyclisation Reactions.

The first reagent system we used for copper mediated cyclisation of substrate **X** was an aged solution of  $\text{CuBr}$  / TPA alone. Substrate **248** was dissolved in methanol and heated to 50°C, then  $\text{CuBr}$  / TPA was added. After 24h the reaction mixture was filtered through silica plug and washed with water to remove any metal / ligand and borohydride. The organic layer was evaporated and the crude material was then analysed by  $^1\text{H}$  NMR spectroscopy (Table 20).

7.0: Synthesizing Oxindoles *via* Copper Mediated Cyclisation

| Entry | CuBr / TPA (mol%) | KBH <sub>4</sub> (mol%) | Conversion (%)                    | Yield (%) |
|-------|-------------------|-------------------------|-----------------------------------|-----------|
| 1     | 10                | -                       | 13<br>(2.3:1.0, <b>254:255</b> )  | 12        |
| 2     | 30                | -                       | 19<br>(1.7:1.0, <b>254:255</b> )  | 15        |
| 3     | 110               | -                       | 100<br>(2.2:1.0, <b>254:255</b> ) | 90        |
| 4     | 30                | 300                     | 87<br>(1.9:1.0, <b>254:255</b> )  | 76        |

**Table 20.** The Effect of varied CuBr / TPA Loadings and a Reducing Agent.

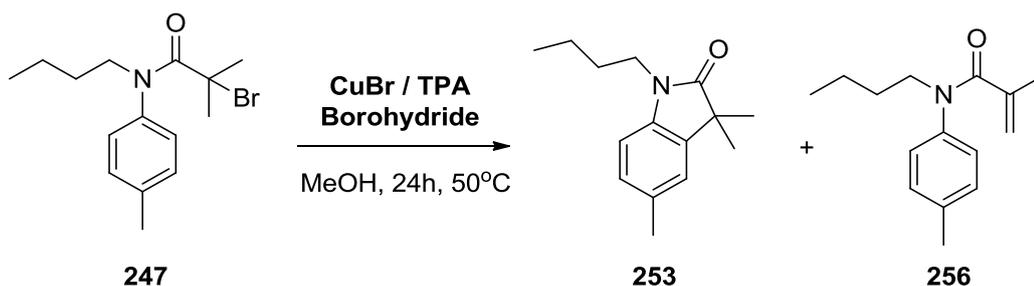
In the presence of 10 mol% CuBr / TPA, substrate **248** cyclised to products **254** and **255** with a combined yield of 12% (Table 20, entry 1). If the reaction required stoichiometric amounts of copper we would expect a yield of 10% or less. (12% is within the experimental error). In the presence of 30 mol% CuBr / TPA we observed a 15% yield of combined products **254** and **255** (entry 2) which was disappointing. Increasing the CuBr / TPA loading to 110 mol%, we observed 100% conversion and 90% yield (entry 3). The data seemed to indicate that stoichiometric quantities of copper / ligand were required.

Our previous work in chapter 6 allowed us to greatly improve the efficiency of copper mediated ATRC reactions with the addition of borohydride reducing agents. By reducing the CuBr / TPA loading to 30 mol% and adding 300 mol%

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KBH<sub>4</sub> we were able to achieve an 87% conversion and 76% yield of combined products **254** and **255** (entry 4), suggesting regeneration of an active Cu(I) form from inactive Cu(II).

Similarly, substrate **247** was also treated with varying quantities of CuBr / TPA and KBH<sub>4</sub> (Table 21).



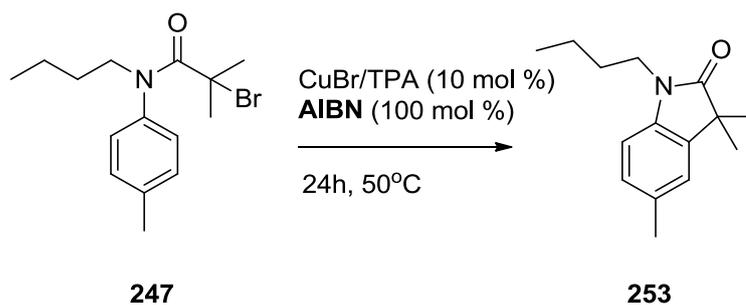
| Entry | CuBr / TPA (mol%) | KBH <sub>4</sub> (mol%) | Conversion (%) | Yield ( <b>253</b> ) (%) | Yield ( <b>256</b> ) (%) |
|-------|-------------------|-------------------------|----------------|--------------------------|--------------------------|
| 1     | 10                | -                       | 12             | 11                       | 1                        |
| 2     | 110               | -                       | 100            | 87                       | 8                        |
| 3     | 30                | 300                     | 64             | 54                       | 27                       |
| 4     | 10                | 100                     | 69             | 48                       | 15                       |

**Table 21.** The Effect of varied CuBr / TPA Loadings and a Reducing Agent.

In the presence of 10 mol% CuBr / TPA, 12% conversion of substrate **247** was observed, again suggesting a stoichiometric requirement of the reagent system. Increasing the CuBr / TPA loading to 110 mol% resulted in 100% conversion and 87% yield as anticipated (Table 21, entry 1 and 2). By reducing the CuBr / TPA loading to 30 mol% and adding 300 mol% KBH<sub>4</sub> we were able to achieve 64% conversion and 54% yield of product **253** (entry 3). The conversion of **247** was fairly low as in the presence of 300 mol% KBH<sub>4</sub>, a large amount of alkene **256** was

observed. We therefore attempted to reduce the amount of  $\text{KBH}_4$  added. Thus by reducing  $\text{CuBr}$  / TPA loading to 10 mol% and adding 100 mol%  $\text{KBH}_4$  we were able to achieve a marginally higher conversion of 69% conversion and 48% yield of product **253** (entry 4) with a decreased amount of alkene **256** formed.

As previously indicated, the synergistic effect of  $\text{CuBr}$  / TPA and AIBN has been previously reported. We chose to briefly look at whether replacing  $\text{KBH}_4$  with AIBN would be beneficial. The reaction was repeated with AIBN in three different solvents - DCM, acetonitrile and toluene at elevated temperatures. The reactions proved extremely inefficient (Table 22), pointing out the greater efficiency of borohydrides rather than AIBN in this system.



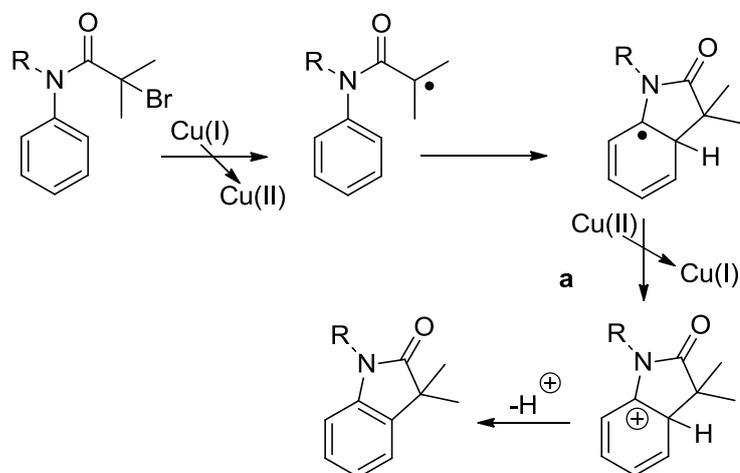
| Entry | Solvent (Dry) | Yield (%) |
|-------|---------------|-----------|
| 1     | DCM           | 0         |
| 2     | Acetonitrile  | 2         |
| 3     | Toluene       | 4         |

**Table 22.** The Effect of Changing Solvents.

Possible mechanism(s) for the reaction in the absence of  $\text{KBH}_4$  is shown in scheme 77. However, the mechanism (a) indicates that the metal should be catalytic (it is regenerated in the oxidation step). Observations indicated the mechanism to require stoichiometric amount of  $\text{CuBr}$  which may indicate the reaction proceeds via

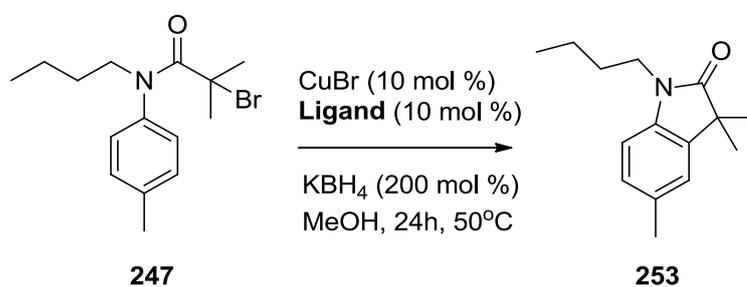
an alternative mechanism (possibly an organocopper or Friedel-Crafts type process).

The addition of  $\text{KBH}_4$  improves matters.



**Scheme 77**

In order to try and improve the  $\text{CuBr}$  /  $\text{TPA}$  /  $\text{KBH}_4$  protocol we tried to optimise the reagent system by screening various ligands (Table 23).



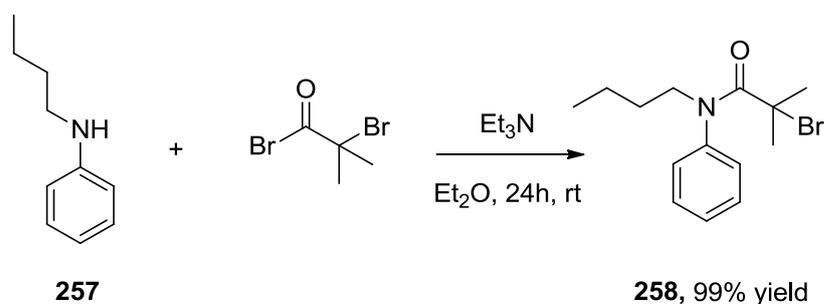
| Entry | Ligand                  | Conversion (%) | Yield (%) |
|-------|-------------------------|----------------|-----------|
| 1     | Bipyridine <sup>a</sup> | 24             | 18        |
| 2     | TMEDA <sup>a</sup>      | 32             | 23        |
| 3     | PMDETA                  | 32             | 23        |
| 4     | TETEDA                  | 25             | 19        |
| 5     | TREN                    | 59             | 42        |
| 6     | TPA                     | 69             | 48        |

<sup>a</sup> (20 mol%) used.

**Table 23.** The Effect of Changing Ligands.

In chapter 5, we carried out extensive screening of various ligands for copper in ATRC reactions, and from those results we found that in this study, the relative efficiencies of the ligands were identical with the bidentate and tridentate ligands such as bipyridine, TMEDA, TETEDA and PMDETA proving less efficient than the branched tetradentate ligands such as TREN and TPA. TPA was the most efficient and therefore chosen as the ligand of choice for future copper mediated cyclisation reactions towards the formation of oxindoles.

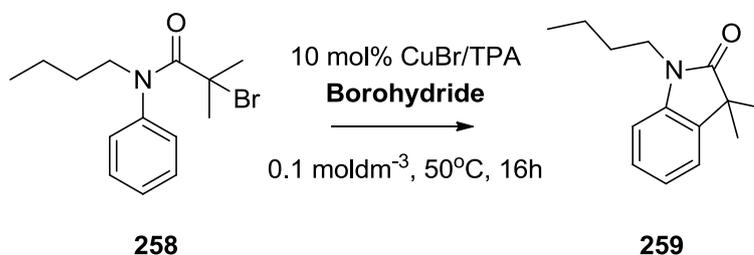
We decided to investigate further optimisation of the reaction using the unsubstituted aniline substrate **258**. This was synthesized by reacting commercially available **257** with 2-bromo-2-methylpropanoic acid bromide in the presence of Et<sub>3</sub>N. After 24 h, and with standard organic reaction work-up, the pure orange oil **258** was obtained (Scheme 78).



**Scheme 78.** Synthesis of Oxindole Precursors **258**.

Work from chapter 5 revealed that for a successful reduction of Cu(II) to Cu(I) by metal borohydrides, the reaction must be carried out in protic solvents such as methanol, ethanol or water. Nevertheless we performed a copper mediated

cyclisation in an aprotic solvent to determine if the solubility of the reagents might affect the outcome of the reaction (1,2-dichloroethane) (Table 24).



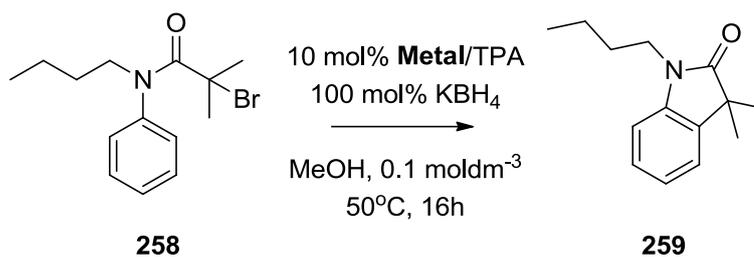
| Entry | Solvent | Borohydride (mol%)     | Conversion (%) | Yield (%) |
|-------|---------|------------------------|----------------|-----------|
| 1     | 1,2-DCE | -                      | 0              | 0         |
| 2     | 1,2-DCE | KBH <sub>4</sub> (100) | 0              | 0         |
| 3     | MeOH    | KBH <sub>4</sub> (100) | 30             | 24        |

**Table 24.** The Effect of Changing Protic MeOH to an Alternative Aprotic Solvent.

An attempt to cyclise substrate **258** in 1,2-DCE failed both in the presence and absence of borohydride reducing agent, while in methanol, 30% conversion and 24% yield was observed.

Screening different copper salts offered improved conversions for substrate **258** (Table 25). Cu(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O and Cu(acac)<sub>2</sub> proved marginally better than Cu(I)Br. CuSO<sub>4</sub> being the cheapest commercially available salt showed the best improvement on the conversion of substrate **258** from 30% to 49%. Hereon we replaced our CuBr / TPA reagent system with CuSO<sub>4</sub> / TPA.

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| Entry | Metal   | Conversion (%) | Yield (%) |
|-------|---|----------------|-----------|
| 1     | CuBr  | 30             | 24        |
| 2     | CuSO <sub>4</sub>                                     | 49             | 39        |
| 3     | Cu(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O | 32             | 32        |
| 4     | Cu(acac) <sub>2</sub>                                 | 34             | 32        |

**Table 25.** The Effect of Alternative Copper Salts.

In chapter 6, after screening various reducing agents, we came to the conclusion that NaBH<sub>4</sub>, KBH<sub>4</sub>, Ca(BH<sub>4</sub>)<sub>2</sub> and (Bu)<sub>4</sub>N(BH<sub>4</sub>) were the most efficient additives in ATRC reactions. We picked three of these additives to compare their efficiency towards cyclisation of substrate **258** (Table 26) and observe if they follow the ATRC efficiency pattern KBH<sub>4</sub> > Ca(BH<sub>4</sub>)<sub>2</sub> > (Bu)<sub>4</sub>N(BH<sub>4</sub>).

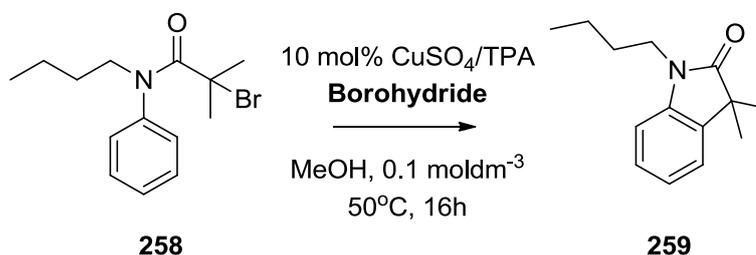
## 7.0: Synthesizing Oxindoles *via* Copper Mediated Cyclisation



| Entry | Borohydride                                  | Conversion (%) | Yield (%) |
|-------|--|----------------|-----------|
| 1     | $\text{KBH}_4$                               | 49             | 39        |
| 2     | $\text{Ca}(\text{BH}_4)_2 \cdot 2\text{THF}$ | 25             | 19        |
| 3     | $(\text{Bu})_4\text{N}(\text{BH}_4)$         | 31             | 23        |

**Table 26.** The Effect of Alternative Reducing Agents.

The results showed  $\text{KBH}_4$  to be the most efficient additive, followed by  $(\text{Bu})_4\text{N}(\text{BH}_4)$  while  $\text{Ca}(\text{BH}_4)_2$  proved to be the least efficient (Table 26).

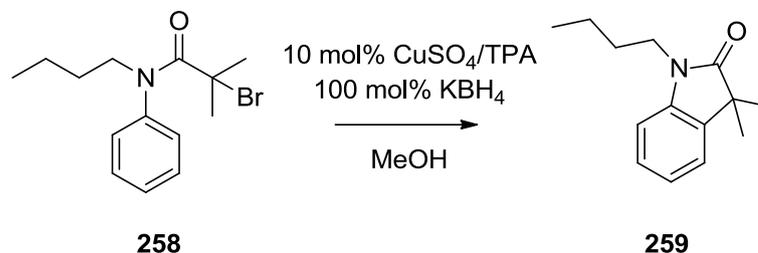


| Entry | $\text{KBH}_4$ (mol%) | Conversion (%) | Yield (%) |
|-------|-----------------------|----------------|-----------|
| 1     | 100                   | 49             | 39        |
| 2     | 50                    | 17             | 16        |
| 3     | 10                    | 10             | 10        |

**Table 27.** The Effect of Reducing  $\text{KBH}_4$  Loadings.

Reducing borohydride loadings also reduced the conversion of substrate **258**, therefore 100 mol% is currently the optimum borohydride loading (Table 27). With 10 mol%  $\text{CuSO}_4$  / TPA, 100 mol%  $\text{KBH}_4$  and MeOH currently being the preferred reagent system, we now optimised the reaction time, temperature and concentration

(Table 28). A known amount of DMF (used as a standard) was added to a known amount of crude material. This mixture was analysed by NMR and the conversion to product **259** was measured relative to the standard.



| Entry | Concentration (mol dm <sup>-3</sup> ) | Time (hours) | Temp (°C) | Conversion (%) | Yield (%) |
|-------|---------------------------------------|--------------|-----------|----------------|-----------|
| 1     | 0.1                                   | 0.2          | 50        | 18             | 14        |
| 2     | 0.1                                   | 1            | 50        | 25             | 19        |
| 3     | 0.1                                   | 16           | 50        | 49             | 39        |
| 4     | 0.1                                   | 48           | 50        | 47             | 41        |
| 5     | 0.2                                   | 16           | 50        | 41             | 36        |
| 6     | 0.05                                  | 16           | 50        | 8              | 7         |
| 7     | 0.1                                   | 16           | rt        | 42             | 32        |
| 8     | 0.1                                   | 16           | 50        | 63             | 47*       |

\*Slow addition of aliquots of KBH<sub>4</sub> 20mol% h<sup>-1</sup>

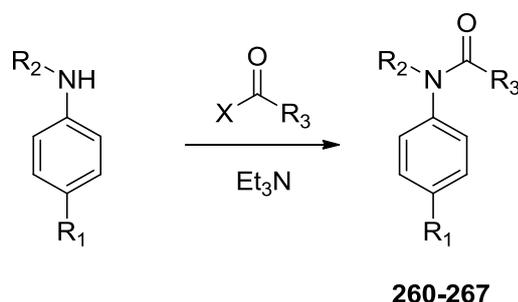
**Table 28.** Optimising Reaction Conditions.

The results show that by reducing the reaction time from 16 h to 10 min the conversion decreased from 49% to 18%, while only 25% conversion was observed after 1 hour. Increasing the reaction time to 48 hours resulted in no significant improvement in conversion; the minor 2% increase could be accounted for experimental or spectroscopic errors (Table 28, entries 1 – 4). Increasing the concentration of the reaction from 0.1 M to 0.2 M reduced the conversion from 47% to 41%, while reducing the concentration to 0.05 M significantly reduced the conversion to 8% suggesting 0.1 M to be the optimum concentration (entries 3, 5 and 6). Performing the reaction at room temperature marginally decreased the conversion to 42%, nevertheless a good conversion rate (entry 7). Good improvement from 47%

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to 63% conversion was observed when  $\text{KBH}_4$  was added slowly at 20 mol% quantity per hour (entry 8). This suggests the optimum conditions to be 10 mol%  $\text{CuSO}_4$  / TPA, 100 mol%  $\text{KBH}_4$ , in MeOH at 0.1 M for 16 h at  $50^\circ\text{C}$ , with slow addition of the borohydride to the reaction mixture.

These conditions were then tested on a range of other oxindole precursors; i) we investigated a range of *para*-aromatic substituents (electron donating / withdrawing), ii) the effect of the N-protecting groups, and iii) the effect of the acyl group. Oxindole precursors **260** - **267** were synthesized by reacting the appropriate amine with the relevant acid halide in the presence of  $\text{Et}_3\text{N}$ . After 24 h, and with standard organic reaction work-up, pure products **260** - **267** were obtained with average to excellent yields (Table 29).

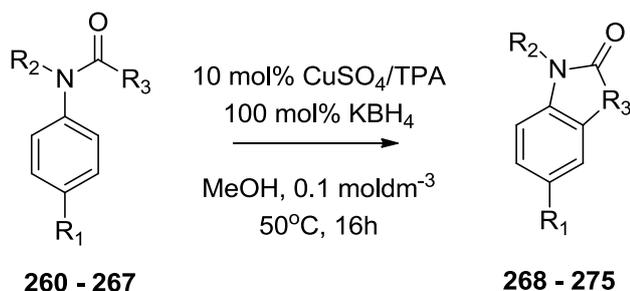


| Product    | R <sub>1</sub>  | R <sub>2</sub> | R <sub>3</sub>        | Yield (%) |
|------------|-----------------|----------------|-----------------------|-----------|
| <b>260</b> | H               | Me             | C(Me) <sub>2</sub> Br | 82        |
| <b>261</b> | Cl              | Me             | C(Me) <sub>2</sub> Br | 82        |
| <b>262</b> | OMe             | Me             | C(Me) <sub>2</sub> Br | 89        |
| <b>263</b> | NO <sub>2</sub> | Me             | C(Me) <sub>2</sub> Br | 48        |
| <b>264</b> | H               | <i>i</i> -pr   | C(Me) <sub>2</sub> Br | 79        |
| <b>265</b> | H               | Bn             | C(Me) <sub>2</sub> Br | 87        |
| <b>266</b> | H               | Bu             | C(Me)(H)Br            | 98        |
| <b>267</b> | H               | Bu             | C(Cl) <sub>2</sub> H  | 99        |

**Table 29.** Synthesis of Oxindole Precursors **260** – **267**.

## 7.0: Synthesizing Oxindoles *via* Copper Mediated Cyclisation

These various oxindole precursors **260** - **267** were then exposed to the optimum conditions of 10 mol% CuSO<sub>4</sub> / TPA, 100 mol% KBH<sub>4</sub>, in MeOH at 0.1 M for 16 h at 50°C, with slow addition of the borohydride to the reaction mixture (Table 30).



| Entry | Product    | R <sub>1</sub>  | R <sub>2</sub> | R <sub>3</sub>     | Conversion (%) | Yield (%) |
|-------|------------|-----------------|----------------|--------------------|----------------|-----------|
| 1     | <b>247</b> | Me              | Bu             | C(Me) <sub>2</sub> | 38             | 35        |
| 2     | <b>268</b> | H               | Me             | C(Me) <sub>2</sub> | 43             | 40        |
| 3     | <b>269</b> | Cl              | Me             | C(Me) <sub>2</sub> | 50             | 50        |
| 4     | <b>270</b> | OMe             | Me             | C(Me) <sub>2</sub> | 24             | 23        |
| 5     | <b>271</b> | NO <sub>2</sub> | Me             | C(Me) <sub>2</sub> | 37             | 35        |
| 6     | <b>272</b> | H               | <i>i</i> -pr   | C(Me) <sub>2</sub> | 45             | 41        |
| 7     | <b>273</b> | H               | Bn             | C(Me) <sub>2</sub> | 44             | 39        |
| 8     | <b>274</b> | H               | Bu             | C(Me)(H)           | 0              | 0         |
| 9     | <b>275</b> | H               | Bu             | C(Cl)H             | 0              | 0         |

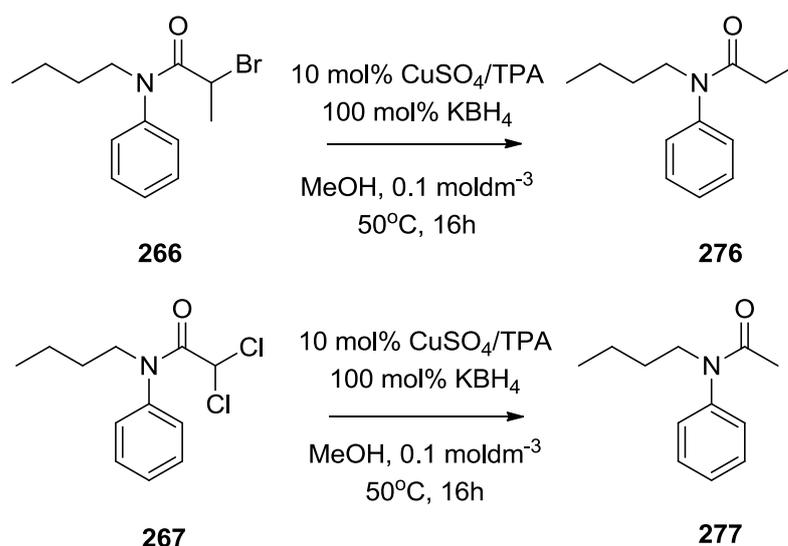
**Table 30.** Synthesis of Oxindoles **268** – **275**.

On average most of the reactions gave similar yields (35 – 50%) with the exception of run 4 containing the strongly electron donating (OMe). The best conversions were observed with unsubstituted aromatic rings or in the presence of the mild electron withdrawing Cl group on R<sup>1</sup> (Table 30, entry 2 and 3).

Replacing the methyl group on the nitrogen with a more sterically hindered isopropyl group or benzyl group showed no difference in conversion or yields within

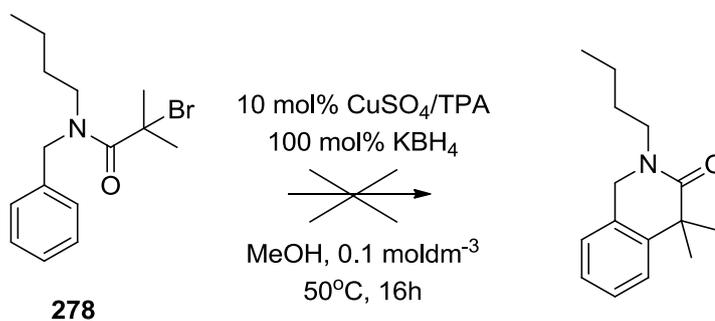
experimental error indicating the steric nature of the allyl group is not important (Table 30, entry 2, 6 and 7).

Replacing the tertiary bromide group  $R^3$  to a secondary bromide (**266**) resulted in no oxindole formation, instead analysis by  $^1H$  NMR and mass spectroscopy showed that the bromine had been reduced resulting in the product **276**. Identical results were observed when using secondary dichloride (**267**) resulting in product **277** (Scheme 79). It is known that the rate of cyclisation of  $3^\circ$   $\alpha$ -amine radicals are faster than  $2^\circ$  derived radicals due to the Thorpe-Ingold effect. Thus under these conditions, reduction of the initial radical is faster than cyclisation.



**Scheme 79.** Unsuccessful Cyclisations.

After limited success with the copper mediated 5-*exo* cyclisations to give oxindoles, we briefly attempted a 6-*exo* cyclisation on substrate **278** using our optimised conditions. Unfortunately the reaction failed with no cyclised product being detected, instead numerous side products were observed which were not characterised (Scheme 80).



**Scheme 80.** Unsuccessful 6-*exo* cyclisation on substrate **278**.

### 7.3 Conclusion

Oxindoles are a unique class of heterocyclic compounds and are of great interest in medicinal chemistry due to their useful biological properties. There are numerous ways to synthesize oxindoles, but most methods are either expensive, very toxic, require large amount of metals, harsh conditions or are impractical for an industrial scale. In this chapter, we were able to demonstrate an alternative procedure to oxindoles. In the presence of 1.1 equiv. of CuBr / TPA in methanol at 50 °C we were able to show 100% conversions of substrates **247** and **248**. We then performed a series of reactions to reduce the transition metal and ligand loading by using borohydride reducing agents to regenerate active Cu(I) species from deactivated Cu(II) species. We were then able to reduce the transition metal loading to 10 mol% CuSO<sub>4</sub> / TPA, while using 100 mol% KBH<sub>4</sub>, in MeOH at 0.1 M for 16 h at 50°C achieving a reasonable 63% conversion to oxindole **259**. We still believe the conversion can be further increased by optimising the rate of borohydride addition and by performing the reaction in water using the sonication method described in chapter 6, but due to the limited time available, this was not investigated.

## 7.0: Synthesizing Oxindoles *via* Copper Mediated Cyclisation

Unfortunately, the reactions were not that efficient; with relative to low average yields and stoichiometric amounts of  $\text{KBH}_4$  required, thus it is unlikely to find favour as a general method for oxindole synthesis.

## 8.0 Experimental

### 8.1 General Information

All reactions were performed using commercially available anhydrous solvents. Reactions were followed by TLC, performed on silica coated aluminium plates (Merck Kieselgel 60F<sub>254</sub> 230-400 mesh) developed either from UV fluorescence (254 nm) or potassium permanganate. Flash chromatography was carried out using Merck 9385 Kieselgel 60 SiO<sub>2</sub> (230-400 mesh).

Infrared Spectrums were obtained using a Perkin-Elmer 1720X Fourier transform spectrometer. Solids were compressed into a very thin tablet and non-volatile liquids were analysed as films over a diamond sensor. Ultraviolet/Visible spectrums were obtained using Perkin-Elmer Lambda 25 and Ocean Optics USB2000+ spectrophotometers. Measurements were performed in methanol, DCM or toluene.

<sup>1</sup>H, <sup>13</sup>C and <sup>19</sup>F NMR were recorded on a 300MHz, 400MHz and 500MHz Bruker instruments using internal residual protio solvent resonances and TMS as standards. Hexafluorobenzene was used as an internal standard for <sup>19</sup>F NMR spectroscopy. Chemical shifts are reported in ppm and coupling constant *J* is quoted in hertz (Hz).

Mass spectrometry was achieved using either electron, chemical or electrospray ionisation techniques. Most low resolution analysis was performed on a Bruker Esquire 200 machine. Accurate mass spectrometry was available through in house mass spectroscopy service using either Bruker HCT or Bruker HCT Ultra

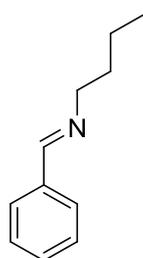
machines to perform accurate mass ESI analysis. Elemental analysis was performed by Warwick Analytical Service using a CE440 Elemental Analyser.

## 8.2 Substrates Synthesized In Chapter 2

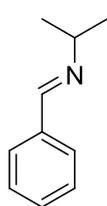
### 8.2.1 General Procedure for the Synthesis of Imines 106 - 114:

Aldehyde was dissolved in ethyl acetate (25 ml) in a 100 ml round bottom flask equipped with a magnetic stirrer bar. Amine was also dissolved in ethyl acetate (25 ml) and added to the aldehyde mixture followed by magnesium sulphate (5.0 g). The reaction mixture was stirred at room temperature for two hours, filtered and the solvent evaporated. Crude products were purified by vacuum distillation.

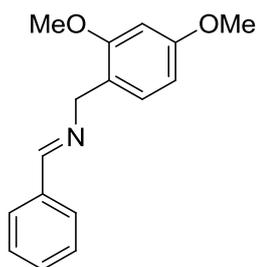
#### (*E*)-*N*-benzylidenebutan-1-amine (106)<sup>179</sup>



Benzaldehyde (1.59 g, 15.0 mmol) and *n*-butylamine (1.46 g, 20.0 mmol) was subject to the general procedure for the synthesis of imines (8.2.1). Purification by vacuum distillation resulted in formation of a pale yellow oil (1.50 g, 9.5 mmol, 62 %); spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 2954 (C-H), 1644 (C=N, imine);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.30 (1H, s,  $\text{CH}=\text{N}$ ), 7.75 (2H, m, Ar), 7.43 (3H, m, Ar), 3.64 (2H, t,  $J_{\text{HH}}$  7.0 Hz, N- $\text{CH}_2$ ), 1.74 (2H, m,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 1.41 (2H, sextuplet,  $J_{\text{HH}}$  7.3 Hz,  $\text{CH}_2\text{CH}_3$ ), 0.98 (3H, t,  $J_{\text{HH}}$  7.3 Hz,  $\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 160.5 ( $\text{HC}=\text{N}$ ), 136.4 (Ar, quaternary), 130.4 (Ar), 128.6 (Ar), 128.0 (Ar), 61.5 (N- $\text{CH}_2$ ), 33.0 ( $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 20.3 ( $\text{CH}_2\text{CH}_3$ ), 13.9 ( $\text{CH}_2\text{CH}_3$ ).

**(E)-N-benzylidenepropan-2-amine (107)**<sup>180</sup>

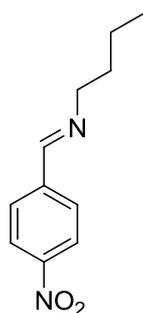
Benzaldehyde (1.59 g, 15.0 mmol) and *i*-propylamine (1.18 g, 20.0 mmol) was subject to the general procedure for the synthesis of imines (8.2.1). Purification by vacuum distillation resulted in formation of a pale yellow oil (1.74 g, 11.7 mmol, 79 %); spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 2965 (C-H), 1646 (C=N, imine);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.30 (1H, s,  $\text{CH}=\text{N}$ ), 7.73 (2H, m, Ar), 7.39 (3H, m, Ar), 3.53 (1H, septuplet,  $J_{\text{HH}}$  6.3 Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.26 (6H, d,  $J_{\text{HH}}$  6 Hz,  $\text{CH}(\text{CH}_3)_2$ );  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 158.3 ( $\text{HC}=\text{N}$ ), 136.5 (Ar, quaternary), 130.4 (Ar), 128.6 (Ar), 128.1 (Ar), 61.7 ( $\text{CH}(\text{CH}_3)_2$ ), 24.2 ( $\text{CH}(\text{CH}_3)_2$ ).

**Benzylidene-(2,4-dimethoxy-benzyl)-amine (108)**<sup>181</sup>

Benzaldehyde (0.53 g, 5.0 mmol) and 2,4-dimethoxybenzylamine (0.84 g, 5.0 mmol) was subject to the general procedure for the synthesis of imines (8.2.1). Purification by vacuum distillation resulted in formation of a pale orange oil (0.85 g, 3.3 mmol, 67 %); spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 2833 (O- $\text{CH}_3$ ), 1640 (C=N, imine);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.26 (1H, s,  $\text{CH}=\text{N}$ ), 7.69 (2H, m, Ar), 7.33 (3H, m, Ar), 7.13 (1H, m, Ar), 6.40 (2H, m, Ar), 4.59 (2H, s, N- $\text{CH}_2$ ), 3.73 (6H, d,  $J_{\text{HH}}$  2.5 Hz,  $\text{OCH}_3$ );  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 161.8 ( $\text{HC}=\text{N}$ ), 160.1 ( $\text{Ar-OCH}_3$ , quaternary), 158.3 ( $\text{Ar-OCH}_3$ , quaternary), 136.5 ( $\text{Ar-HC}=\text{N}$ , quaternary), 130.6 (Ar), 130.1 (Ar), 128.6 (Ar), 128.2

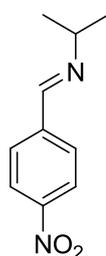
(Ar), 120.0 (N-CH<sub>2</sub>-Ar, quaternary), 104.1 (Ar), 98.5 (Ar), 59.0 (N-CH<sub>2</sub>), 55.4 (6H, OCH<sub>3</sub>).

**(E)-N-(4-nitrobenzylidene)butan-1-amine (109)**<sup>182</sup>



4-Nitrobenzaldehyde (1.51 g, 10.0 mmol) and *n*-butylamine (1.09 g, 15.0 mmol) was subject to the general procedure for the synthesis of imines (8.2.1). Purification by vacuum distillation resulted in formation of an orange oil (1.62 g, 7.9 mmol, 79 %); spectral details match these reported;  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 2927 (C-H), 1643 (C=N, imine), 1518 (NO<sub>2</sub>);  $\delta_{\text{H}}$  (300MHz, CDCl<sub>3</sub>) 8.36 (1H, s, CH=N), 8.26 (2H, d,  $J_{\text{HH}}$  8.9 Hz, Ar), 7.89 (2H, d,  $J_{\text{HH}}$  8.9 Hz, Ar), 3.68 (2H, t,  $J_{\text{HH}}$  7.0 Hz, N-CH<sub>2</sub>), 1.71 (2H, m, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.41 (2H, sextuplet,  $J_{\text{HH}}$  7.3 Hz, CH<sub>2</sub>CH<sub>3</sub>), 0.96 (3H, t,  $J_{\text{HH}}$  7.3 Hz, CH<sub>2</sub>CH<sub>3</sub>);  $\delta_{\text{C}}$  (75MHz, CDCl<sub>3</sub>) 158.4 (HC=N), 148.9 (Ar-NO<sub>2</sub>, quaternary), 141.9 (Ar, quaternary), 128.7 (Ar), 124.0 (Ar), 61.6 (N-CH<sub>2</sub>), 32.8 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 20.5 (CH<sub>2</sub>CH<sub>3</sub>), 13.9 (CH<sub>2</sub>CH<sub>3</sub>).

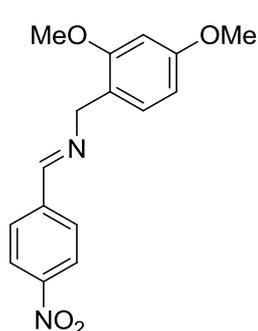
**(E)-N-(4-nitrobenzylidene)propan-2-amine (110)**<sup>183</sup>



4-Nitrobenzaldehyde (1.51 g, 10.0 mmol) and *i*-propylamine (0.89 g, 15.0 mmol) was subject to the general procedure for the synthesis of imines (8.2.1). Purification by vacuum distillation resulted in formation of dark orange crystals (1.24 g, 6.5 mmol, 64 %); spectral details match these reported;  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 2963 (s, Ar), 1642 (C=N, imine), 1517 (NO<sub>2</sub>);  $\delta_{\text{H}}$  (300MHz, CDCl<sub>3</sub>) 8.39 (1H, s, CH=N), 8.25 (2H, d,  $J_{\text{HH}}$  8.9 Hz, Ar), 7.90 (2H, d,

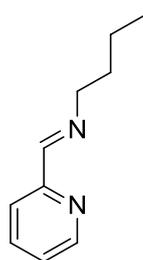
$J_{\text{HH}}$  8.9 Hz, Ar), 3.63 (1H, septuplet,  $J_{\text{HH}}$  6.3 Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.30 (6H, d,  $J_{\text{HH}}$  6 Hz,  $\text{CH}(\text{CH}_3)_2$ );  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 155.4 ( $\text{HC}=\text{N}$ ), 148.2 ( $\text{Ar}-\text{NO}_2$ , quaternary), 141.5 (Ar, quaternary), 128.5 (Ar), 123.2 (Ar), 61.3 ( $\text{N}-\text{CH}(\text{CH}_3)_2$ ), 23.4 ( $\text{CH}(\text{CH}_3)_2$ ).

#### 4-Nitrobenzylidene-(2,4-dimethoxy-benzyl)-amine (111)<sup>184</sup>



4-Nitrobenzaldehyde (0.76 g, 5.0 mmol) and 2,4-dimethoxybenzylamine (0.84 g, 5.0 mmol) was subject to the general procedure for the synthesis of imines (8.2.1). Purification by vacuum distillation resulted in formation of dark orange crystals (1.10 g, 3.7 mmol, 73 %); spectral details match these reported;  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 2971 (C-H), 2837 (O-CH<sub>3</sub>), 1643 (C=N, imine), 1519 (NO<sub>2</sub>);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.41 (1H, s,  $\text{CH}=\text{N}$ ), 8.28 (2H, d,  $J_{\text{HH}}$  8.9 Hz, Ar), 7.94 (2H, d,  $J_{\text{HH}}$  8.9 Hz, Ar), 7.20 (1H, m, Ar), 6.52 (2H, m, Ar), 4.85 (2H, s, Ar-CH<sub>2</sub>-N), 3.84 (6H, s, OCH<sub>3</sub>);  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 160.4 (C-OCH<sub>3</sub>, quaternary), 159.2 ( $\text{HC}=\text{N}$ ), 158.4 (Ar-OCH<sub>3</sub>, quaternary), 148.9 (Ar-NO<sub>2</sub>), 142.0 (Ar-HC=N, quaternary), 130.4 (Ar), 128.6 (Ar), 123.7 (Ar), 118.9 (N-CH<sub>2</sub>-Ar, quaternary), 104.2 (Ar), 98.6 (Ar), 59.2 (Ar-CH<sub>2</sub>-N), 55.4 (6H, OCH<sub>3</sub>).

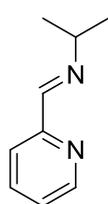
#### (E)-N-(pyridin-2-ylmethylene)butan-1-amine (112)<sup>185</sup>



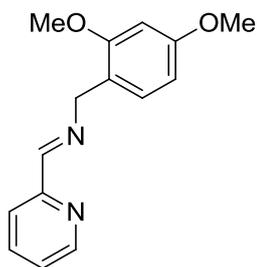
2-Pyridinecarboxyaldehyde (1.61 g, 15.0 mmol) and *n*-butylamine (1.46 g, 20.0 mmol) was subject to the general procedure for the synthesis of imines (8.2.1). Purification by vacuum distillation resulted

with dark orange oil (1.98 g, 12.2 mmol, 82 %); spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 1687 (C=N), 1550 (pyridine).  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.60 (1H, d,  $J_{\text{HH}}$  4.8 Hz, Ar), 8.34 (1H, s,  $\text{CH}=\text{N}$ ), 7.95 (1H, d,  $J_{\text{HH}}$  7.9 Hz, Ar), 7.69 (1H, td,  $J_{\text{HH}}$  7.9, 1.6 Hz, Ar), 7.26 (1H, ddd,  $J_{\text{HH}}$  7.9, 4.8, 1.6 Hz, Ar), 3.68 (2H, t,  $J_{\text{HH}}$  7.1 Hz, N- $\text{CH}_2$ ), 1.71 (2H, m,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 1.41 (2H, sextuplet,  $J_{\text{HH}}$  7.3 Hz,  $\text{CH}_2\text{CH}_3$ ), 0.92 (3H, t,  $J_{\text{HH}}$  7.3 Hz,  $\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 161.7 ( $\text{HC}=\text{N}$ ), 154.6 (Ar, quaternary), 149.4 (Ar), 136.5 (Ar), 124.6 (Ar), 121.2 (Ar), 61.2 (N- $\text{CH}_2$ ), 32.7 ( $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 20.3 ( $\text{CH}_2\text{CH}_3$ ), 13.8 ( $\text{CH}_2\text{CH}_3$ ).

**(E)-N-(pyridin-2-ylmethylene)propan-2-amine (113)**<sup>186</sup>



2-Pyridinecarboxaldehyde (1.61 g, 15.0 mmol) and *i*-propylamine (1.18 g, 15.0 mmol) was subject to the general procedure for the synthesis of imines (8.2.1). Purification by vacuum distillation resulted in formation of an orange oil (1.44 g, 9.7 mmol, 65 %); spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 1643 (C=N, imine), 1521 (pyridine);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.64 (1H, d,  $J_{\text{HH}}$  5 Hz, Ar), 8.40 (1H, s,  $\text{CH}=\text{N}$ ), 8.00 (1H, d,  $J_{\text{HH}}$  8 Hz, Ar), 7.72 (1H, td,  $J_{\text{HH}}$  8, 2 Hz, Ar), 7.30 (1H, ddd,  $J_{\text{HH}}$  8, 5, 1 Hz, Ar), 3.64 (1H, septuplet,  $J_{\text{HH}}$  6 Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.28 (6H, d,  $J_{\text{HH}}$  6 Hz,  $\text{CH}(\text{CH}_3)_2$ );  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 158.6 ( $\text{HC}=\text{N}$ ), 154.1 (Ar, quaternary), 148.7 (Ar), 136.3 (Ar), 123.9 (Ar), 120.9 (Ar), 60.6 (N- $\text{CH}$ ), 23.3 ( $\text{CH}(\text{CH}_3)_2$ ).

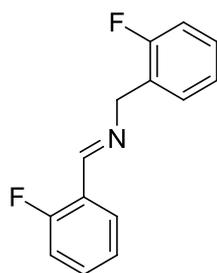
**(2,4-Dimethoxyphenyl)-*N*-(pyridin-2-ylmethylene)methanamine (114)**<sup>184</sup>

2-Pyridinecarboxyaldehyde (0.54 g, 5.0 mmol) and 2,4-dimethoxybenzylamine (0.84 g, 5.0 mmol) was subject to the general procedure for the synthesis of imines (8.2.1).

Purification by vacuum distillation resulted in formation of an orange oil (0.82 g, 3.2 mmol, 64 %); spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 2971 (C-H), 2900 (O-CH<sub>3</sub>), 1645 (C=N, imine);  $\delta_{\text{H}}$  (300MHz, CDCl<sub>3</sub>) 8.65 (1H, d,  $J_{\text{HH}}$  4.8 Hz, Ar), 8.43 (1H, s,  $\text{CH}=\text{N}$ ), 8.09 (1H, d,  $J_{\text{HH}}$  7.9 Hz, Ar), 7.75 (1H, td,  $J_{\text{HH}}$  7.9, 1.6 Hz, Ar), 7.32 (1H, ddd,  $J_{\text{HH}}$  7.9, 4.8, 1.6 Hz, Ar), 7.22 (1H, m, Ar), 6.50 (2H, m, Ar), 4.85 (2H, s, Ar-CH<sub>2</sub>-N), 3.83 (6H, d,  $J_{\text{HH}}$  2.5, OCH<sub>3</sub>).

**8.2.2 General Procedure for the Synthesis of Fluorinated Imines 121 – 129**

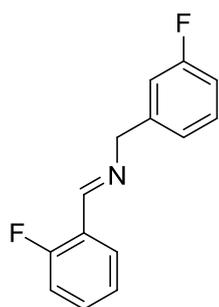
Aldehyde was dissolved in ethyl acetate (25 ml) in a 100 ml round bottom flask equipped with a magnetic stirrer bar. Amine was also dissolved in ethyl acetate (25 ml) and added to the aldehyde mixture followed by magnesium sulphate (10 g). The reaction mixture was stirred at room temperature for 24 hours, filtered and the solvent evaporated. Crude products were purified by vacuum distillation.

**(*E*)-*N*-(2-fluorobenzylidene)-1-(2-fluorophenyl)methanamine (121)**<sup>187</sup>

2-Fluorobenzylaldehyde (1.0 g, 8.1 mmol) and 2-fluorobenzylamine (1.21 g, 9.7 mmol) was subject to the general procedure for the synthesis of imines (8.2.2). Purification by

vacuum distillation resulted in formation of a colourless oil (1.75 g, 7.7 mmol, 94 %); spectral details as these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3045 (C-H, Aromatic), 2892 (C-H, Alkane), 1640 (C=N, Imine), 1614, 1584, 1485, 1456 (C=C, Aromatic), 1379 (C-N), 1230 (Ar-F);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 8.73 (1H, s, CH=N), 8.03 (1H, td,  $J$  7.7, 1.2 Hz, Ar), 7.44 – 7.35 (2H, m, Ar), 7.30 – 7.22 (1H, m, Ar), 7.21 - 7.01 (4H, m, Ar), 4.88 (2H, s,  $\text{CH}_2$ );  $\delta_{\text{C}}$  (101MHz,  $\text{CDCl}_3$ ) 162.3 (d,  $J_{\text{CF}}$  252.3 Hz, Ar), 160.8 (d,  $J_{\text{CF}}$  246.4 Hz, Ar), 156.1 (d,  $J_{\text{CF}}$  4.8 Hz,  $\text{HC}=\text{N}$ ), 132.5 (d,  $J_{\text{CF}}$  8.6 Hz, Ar), 130.2 (d,  $J_{\text{CF}}$  4.4 Hz, Ar), 128.8 (d,  $J_{\text{CF}}$  8.1 Hz, Ar), 127.9 (d,  $J_{\text{CF}}$  2.6 Hz, Ar), 126.1 (d,  $J_{\text{CF}}$  15.0 Hz, Ar, quaternary), 124.4 (d,  $J_{\text{CF}}$  3.5 Hz, Ar), 124.2 (d,  $J_{\text{CF}}$  3.5 Hz, Ar), 123.7 (d,  $J_{\text{CF}}$  9.5 Hz, Ar, quaternary), 115.8 (d,  $J_{\text{CF}}$  21.1 Hz, Ar), 115.3 (d,  $J_{\text{CF}}$  21.5 Hz, Ar), 58.5 (d,  $J_{\text{CF}}$  2.8 Hz,  $\text{CH}_2$ );  $\delta_{\text{F}}$  (376MHz,  $\text{CDCl}_3$ ) -118.66 (1F, s, C-F), -121.64 (1F, s, C-F);  $m/z$  (ESI) 232 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 232.0942,  $\text{C}_{14}\text{H}_{12}\text{F}_2\text{N}$  requires, 232.0932].

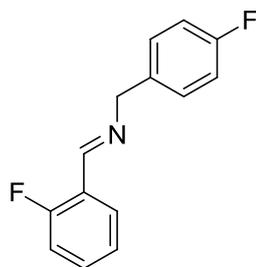
**(E)-N-(2-fluorobenzylidene)-1-(3-fluorophenyl)methanamine (122)**



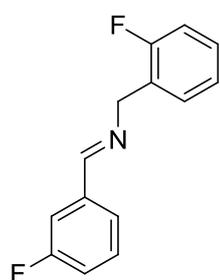
2-Fluorobenzylaldehyde (1.0 g, 8.1 mmol) and 3-fluorobenzylamine (1.21 g, 9.7 mmol) was subject to the general procedure for the synthesis of imines (8.2.2). Purification by vacuum distillation resulted in formation of a colourless oil (1.71 g, 7.4 mmol, 92 %);  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3068 (C-H, Aromatic), 2850 (C-H, Alkane), 1645 (C=N, Imine), 1614, 1585, 1488, 1449 (C=C, Aromatic), 1378 (C-N), 1264, 1229 (Ar-F);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 8.69 (1H, s, CH=N), 8.04 (1H, td,  $J$  7.7, 1.2 Hz, Ar), 7.38 (1H, td,  $J$  7.7, 1.2 Hz, Ar), 7.32 – 7.24 (1H, m, Ar), 7.15 (1H, t,  $J$  7.7 Hz, Ar), 7.06 (3H, m, Ar), 6.93 (1H, td,  $J$  8.5, 2.0 Hz, Ar), 4.80 (2H, s,  $\text{CH}_2$ );  $\delta_{\text{C}}$  (101MHz,  $\text{CDCl}_3$ ) 163.1 (d,  $J_{\text{CF}}$  245.7 Hz, Ar), 162.4 (d,  $J_{\text{CF}}$  252.4 Hz, Ar), 155.8

(d,  $J_{CF}$  4.7 Hz,  $\underline{HC=N}$ ), 141.9 (d,  $J_{CF}$  7.2 Hz, Ar, quaternary), 132.6 (d,  $J_{CF}$  8.6 Hz, Ar), 129.9 (d,  $J_{CF}$  8.2 Hz, Ar), 127.9 (d,  $J_{CF}$  2.6 Hz, Ar), 124.4 (d,  $J_{CF}$  3.4 Hz, Ar), 123.7 (d,  $J_{CF}$  9.2 Hz, Ar, quaternary), 123.5 (d,  $J_{CF}$  2.7 Hz, Ar), 115.8 (d,  $J_{CF}$  21.1 Hz, Ar), 114.8 (d,  $J_{CF}$  21.7 Hz, Ar, quaternary), 113.9 (d,  $J_{CF}$  21.1 Hz, Ar), 64.7 (d,  $J_{CF}$  1.4 Hz,  $\underline{CH_2}$ );  $\delta_F$  (376MHz,  $CDCl_3$ ) -113.20 (1F, s, C-F), -121.74 (1F, s, C-F);  $m/z$  (ESI) 232 ( $[M]^+H$ ); [Found: ( $[M]^+H$ ) 232.0932,  $C_{14}H_{12}F_2N$  requires, 232.0932].

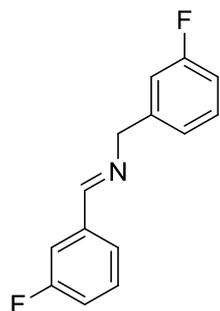
**(E)-N-(2-fluorobenzylidene)-1-(4-fluorophenyl)methanamine (123)**



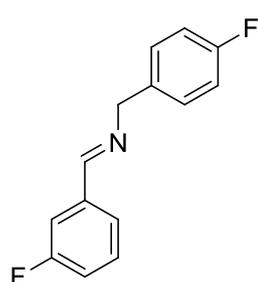
2-Fluorobenzylaldehyde (1.0 g, 8.1 mmol) and 4-fluorobenzylamine (1.21 g, 9.7 mmol) was subject to the general procedure for the synthesis of imines (8.2.2). Purification by vacuum distillation resulted in formation of a colourless oil (1.82 g, 7.8 mmol, 98 %);  $\nu_{max}$  (neat,  $cm^{-1}$ ) 3047 (C-H, Aromatic), 2844 (C-H, Alkane), 1646 (C=N, Imine), 1598, 1507, 1489, 1455 (C=C, Aromatic), 1377 (C-N), 1226 (Ar-F);  $\delta_H$  (400MHz,  $CDCl_3$ ) 8.30 (1H, s,  $\underline{CH=N}$ ), 7.73 (2H, m, Ar), 7.36 (1H, t,  $J$  7.7 Hz, Ar), 7.24 – 7.17 (1H, m, Ar), 7.12 – 6.98 (4H, m, Ar), 4.80 (2H, s,  $\underline{CH_2}$ );  $\delta_C$  (101MHz,  $CDCl_3$ ) 164.45 (d,  $J_{CF}$  250.9 Hz, Ar), 161.2 (d,  $J_{CF}$  4.7 Hz,  $\underline{HC=N}$ ), 160.9 (d,  $J_{CF}$  246.1 Hz, Ar), 132.5 (d,  $J_{CF}$  2.9 Hz, Ar, quaternary), 130.2 (2C, d,  $J_{CF}$  5.2 Hz, Ar), 130.3 (d,  $J_{CF}$  3.2 Hz, Ar), 128.8 (d,  $J_{CF}$  8.1 Hz, Ar), 126.3 (d,  $J_{CF}$  14.9 Hz, Ar, quaternary), 124.3 (d,  $J_{CF}$  3.5 Hz, Ar), 115.7 (2C, d,  $J_{CF}$  21.9 Hz, Ar), 115.3 (d,  $J_{CF}$  21.5 Hz, Ar), 58.1 (d,  $J_{CF}$  2.7 Hz,  $\underline{CH_2}$ );  $\delta_F$  (376MHz,  $CDCl_3$ ) -115.85 (1F, s, C-F), -121.78 (1F, s, C-F);  $m/z$  (ESI) 232 ( $[M]^+H$ ); [Found: ( $[M]^+H$ ) 232.0930,  $C_{14}H_{12}F_2N$  requires, 232.0932].

**(E)-N-(3-fluorobenzylidene)-1-(2-fluorophenyl)methanamine (124)**

3-Fluorobenzylaldehyde (1.0 g, 8.1 mmol) and 2-fluorobenzylamine (1.21 g, 9.7 mmol) was subject to the general procedure for the synthesis of imines (8.2.2). Purification by vacuum distillation resulted in formation of a colourless oil (1.78 g, 7.7 mmol, 96 %);  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3070 (C-H, Aromatic), 2850 (C-H, Alkane), 1645 (C=N, Imine), 1585, 1488, 1450 (C=C, Aromatic), 1378 (C-N), 1264, 1229 (Ar-F);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 8.34 (1H, s, CH=N), 7.52 (1H, d,  $J$  9.2 Hz, Ar), 7.48 (1H, d,  $J$  7.7 Hz, Ar), 7.40 – 7.31 (2H, m, Ar), 7.28 – 7.20 (1H, m, Ar), 7.14 – 7.07 (2H, m, Ar), 7.04 (1H, d,  $J$  9.2 Hz, Ar), 4.84 (2H, s,  $\text{CH}_2$ );  $\delta_{\text{C}}$  (101MHz,  $\text{CDCl}_3$ ) 163.1 (d,  $J_{\text{CF}}$  246.6 Hz, Ar), 161.3 (d,  $J_{\text{CF}}$  2.7 Hz,  $\text{HC}=\text{N}$ ), 160.9 (d,  $J_{\text{CF}}$  246.2 Hz, Ar), 138.5 (d,  $J_{\text{CF}}$  7.3 Hz, Ar, quaternary), 130.3 (d,  $J_{\text{CF}}$  6.9 Hz, Ar), 130.2 (d,  $J_{\text{CF}}$  10.5 Hz, Ar), 128.9 (d,  $J_{\text{CF}}$  8.1 Hz, Ar), 126.0 (d,  $J_{\text{CF}}$  14.9 Hz, Ar, quaternary), 124.5 (d,  $J_{\text{CF}}$  2.7 Hz, Ar), 124.3 (d,  $J_{\text{CF}}$  3.5 Hz, Ar), 117.8 (d,  $J_{\text{CF}}$  21.6 Hz, Ar), 115.3 (d,  $J_{\text{CF}}$  21.5 Hz, Ar), 114.4 (d,  $J_{\text{CF}}$  22.2 Hz, Ar), 58.0 (d,  $J_{\text{CF}}$  2.7 Hz,  $\text{CH}_2$ );  $\delta_{\text{F}}$  (376MHz,  $\text{CDCl}_3$ ) -112.78 (1F, s, C-F), -118.74 (1F, s, C-F);  $m/z$  (ESI) 232 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 232.0932,  $\text{C}_{14}\text{H}_{12}\text{F}_2\text{N}$  requires, 232.0932].

**(E)-N-(3-fluorobenzylidene)-1-(3-fluorophenyl)methanamine (125)**<sup>188</sup>

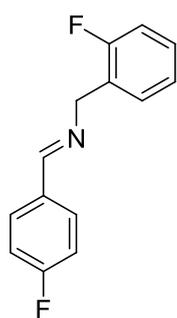
3-Fluorobenzylaldehyde (1.0 g, 8.1 mmol) and 3-fluorobenzylamine (1.21 g, 9.7 mmol) was subject to the general procedure for the synthesis of imines (8.2.2). Purification by vacuum distillation resulted in formation of a colourless oil (1.62 g, 7.0 mmol, 87 %); spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3071 (C-H, Aromatic), 2852 (C-H, Alkane), 1646 (C=N, Imine), 1586, 1486, 1449 (C=C, Aromatic), 1376 (C-N), 1251 (Ar-F);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.35 (1H, s, CH=N), 7.58 – 7.44 (2H, m, Ar), 7.43 – 7.23 (2H, m, Ar), 7.17 – 7.01 (3H, m, Ar), 6.95 (1H, td,  $J$  8.4, 2.5 Hz, Ar), 4.80 (2H, s,  $\text{CH}_2$ );  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 162.5 (d,  $J_{\text{CF}}$  246.8 Hz, Ar), 162.4 (d,  $J_{\text{CF}}$  245.7 Hz, Ar), 160.4 (d,  $J_{\text{CF}}$  2.7 Hz,  $\text{HC}=\text{N}$ ), 141.1 (d,  $J_{\text{CF}}$  7.4 Hz, Ar, quaternary), 137.7 (d,  $J_{\text{CF}}$  7.1 Hz, Ar, quaternary), 129.6 (d,  $J_{\text{CF}}$  8.0 Hz, Ar), 129.4 (d,  $J_{\text{CF}}$  8.2 Hz, Ar), 123.8 (d,  $J_{\text{CF}}$  2.7 Hz, Ar), 122.8 (d,  $J_{\text{CF}}$  2.7 Hz, Ar), 117.3 (d,  $J_{\text{CF}}$  21.6 Hz, Ar), 114.2 (d,  $J_{\text{CF}}$  21.7 Hz, Ar), 113.7 (d,  $J_{\text{CF}}$  22.2 Hz, Ar), 113.3 (d,  $J_{\text{CF}}$  21.1 Hz, Ar), 63.6 (d,  $J_{\text{CF}}$  1.4 Hz,  $\text{CH}_2$ );  $\delta_{\text{F}}$  (282MHz,  $\text{CDCl}_3$ ) -112.67 (1F, s, C-F), -113.14 (1F, s, C-F);  $m/z$  (ESI) 232 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 232.0931,  $\text{C}_{14}\text{H}_{12}\text{F}_2\text{N}$  requires, 232.0932].

**(E)-N-(3-fluorobenzylidene)-1-(4-fluorophenyl)methanamine (126)**

3-Fluorobenzylaldehyde (1.0 g, 8.1 mmol) and 4-fluorobenzylamine (1.21 g, 9.7 mmol) was subject to the general procedure for the synthesis of imines (8.2.2).

Purification by vacuum distillation resulted in formation of a colourless oil (1.77 g, 7.7 mmol, 95 %);  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3071 (C-H, Aromatic), 2843 (C-H, Alkane), 1645 (C=N, Imine), 1586, 1508, 1487, 1449 (C=C, Aromatic), 1375 (C-N), 1264, 1219 (Ar-F);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.31 (1H, s, CH=N), 7.56 – 7.45 (2H, m, Ar), 7.35 (1H, td,  $J$  8.0, 5.6 Hz, Ar), 7.28 (2H, dt,  $J$  8.5, 5.5 Hz, Ar), 7.10 (1H, td,  $J$  8.0, 2.3 Hz, Ar), 7.01 (2H, t,  $J$  8.5 Hz, Ar), 4.75 (2H, s,  $\text{CH}_2$ );  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 162.5 (d,  $J_{\text{CF}}$  246.6 Hz, Ar), 161.4 (d,  $J_{\text{CF}}$  244.9 Hz, Ar), 160.0 (d,  $J_{\text{CF}}$  2.7 Hz,  $\text{HC}=\text{N}$ ), 137.8 (d,  $J_{\text{CF}}$  7.3 Hz, Ar, quaternary), 134.2 (d,  $J_{\text{CF}}$  3.1 Hz, Ar, quaternary), 129.6 (d,  $J_{\text{CF}}$  8.0 Hz, Ar), 128.9 (2C, d,  $J_{\text{CF}}$  8.0 Hz, Ar), 123.8 (d,  $J_{\text{CF}}$  2.7 Hz, Ar), 117.2 (d,  $J_{\text{CF}}$  21.6 Hz, Ar), 114.7 (2C, d,  $J_{\text{CF}}$  21.3 Hz, Ar), 113.7 (d,  $J_{\text{CF}}$  22.2 Hz, Ar), 63.5 (s,  $\text{CH}_2$ );  $\delta_{\text{F}}$  (282MHz,  $\text{CDCl}_3$ ) -112.71 (1F, s, C-F), -115.78 (1F, s, C-F);  $m/z$  (ESI) 232 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 232.0931,  $\text{C}_{14}\text{H}_{12}\text{F}_2\text{N}$  requires, 232.0932].

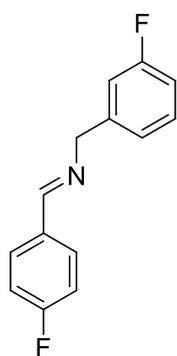
**(E)-N-(4-fluorobenzylidene)-1-(2-fluorophenyl)methanamine (127)**



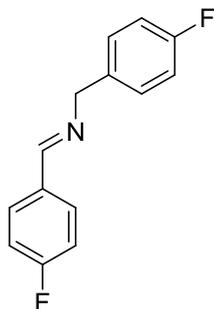
4-Fluorobenzylaldehyde (1.0 g, 8.1 mmol) and 2-fluorobenzylamine (1.21 g, 9.7 mmol) was subject to the general procedure for the synthesis of imines (8.2.2). Purification by vacuum distillation resulted in formation of a colourless oil (1.79 g, 7.7 mmol, 96 %);  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3071 (C-H, Aromatic), 2845 (C-H, Alkane), 1646 (C=N, Imine), 1598, 1507, 1489, 1455 (C=C, Aromatic), 1378 (C-N), 1226 (Ar-F);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.33 (1H, s, CH=N), 7.80 – 7.69 (2H, m, Ar), 7.37 (1H, td,  $J$  7.5, 1.6 Hz, Ar), 7.29 – 7.18 (1H, m, Ar), 7.14 – 6.99 (4H, m, Ar), 4.82 (2H, s,  $\text{CH}_2$ );  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 164.5 (d,  $J_{\text{CF}}$  250.8 Hz, Ar), 161.3 (s,  $\text{HC}=\text{N}$ ), 160.9 (d,  $J_{\text{CF}}$  246.1 Hz, Ar), 132.5 (d,  $J_{\text{CF}}$  2.8 Hz, Ar, quaternary), 130.2 (2C, d,  $J_{\text{CF}}$  5.3 Hz, Ar),

130.3 (d,  $J_{CF}$  3.1 Hz, Ar), 128.9 (d,  $J_{CF}$  8.1 Hz, Ar), 126.3 (d,  $J_{CF}$  14.9 Hz, Ar, quaternary), 124.3 (d,  $J_{CF}$  3.5 Hz, Ar), 115.8 (2C, d,  $J_{CF}$  21.9 Hz, Ar), 115.3 (d,  $J_{CF}$  21.5 Hz, Ar), 58.1 (d,  $J_{CF}$  2.6 Hz,  $\underline{CH}_2$ );  $\delta_F$  (282MHz,  $CDCl_3$ ) -109.14 (1F, s, C-F), -118.72 (1F, s, C-F);  $m/z$  (ESI) 232 ( $[M]^+H$ ); [Found: ( $[M]^+H$ ) 232.0930,  $C_{14}H_{12}F_2N$  requires, 232.0932].

**(E)-N-(4-fluorobenzylidene)-1-(3-fluorophenyl)methanamine (128)**



4-Fluorobenzylaldehyde (1.0 g, 8.1 mmol) and 3-fluorobenzylamine (1.21 g, 9.7 mmol) was subject to the general procedure for the synthesis of imines (8.2.2). Purification by vacuum distillation resulted in formation of a colourless oil (1.75 g, 7.7 mmol, 94 %);  $\nu_{max}$  (neat,  $cm^{-1}$ ) 3072 (C-H, Aromatic), 2842 (C-H, Alkane), 1645 (C=N, Imine), 1596, 1508, 1486, 1448 (C=C, Aromatic), 1376 (C-N), 1228 (Ar-F);  $\delta_H$  (300MHz,  $CDCl_3$ ) 8.33 (1H, s, CH=N), 7.82 – 7.72 (2H, m, Ar), 7.34 – 7.22 (1H, m, Ar), 7.14 – 7.01 (4H, m, Ar), 6.94 (1H, td,  $J$  8.5, 2.2 Hz, Ar), 4.77 (2H, s,  $\underline{CH}_2$ );  $\delta_C$  (75MHz,  $CDCl_3$ ) 164.5 (d,  $J_{CF}$  251.0 Hz, Ar), 163.1 (d,  $J_{CF}$  245.7 Hz, Ar), 161.0 (d,  $J_{CF}$  2.7 Hz,  $\underline{HC=N}$ ), 142.0 (d,  $J_{CF}$  7.2 Hz, Ar, quaternary), 132.4 (d,  $J_{CF}$  3.0 Hz, Ar, quaternary), 130.3 (2C, d,  $J_{CF}$  8.7 Hz, Ar), 130.0 (d,  $J_{CF}$  8.2 Hz, Ar), 123.5 (d,  $J_{CF}$  2.7 Hz, Ar), 115.8 (2C, d,  $J_{CF}$  21.9 Hz, Ar), 114.9 (d,  $J_{CF}$  21.6 Hz, Ar), 113.9 (d,  $J_{CF}$  21.1 Hz, Ar), 64.3 (d,  $J_{CF}$  1.4 Hz,  $\underline{CH}_2$ );  $\delta_F$  (282MHz,  $CDCl_3$ ) -108.96 (1F, s, C-F), -113.41 (1F, s, C-F);  $m/z$  (ESI) 232 ( $[M]^+H$ ); [Found: ( $[M]^+H$ ) 232.0934,  $C_{14}H_{12}F_2N$  requires, 232.0932].

**(E)-N-(4-fluorobenzylidene)-1-(4-fluorophenyl)methanamine (129)**<sup>189</sup>

4-Fluorobenzylaldehyde (1.0 g, 8.1 mmol) and 4-fluorobenzylamine (1.21 g, 9.7 mmol) was subject to the general procedure for the synthesis of imines (8.2.2). Purification by vacuum distillation resulted in formation of a colourless oil (1.81 g, 7.8 mmol, 97 %); spectral details match these reported;  $\nu_{\max}$

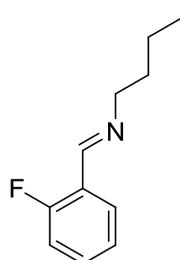
(neat,  $\text{cm}^{-1}$ ) 3044 (C-H, Aromatic), 2841 (C-H, Alkane), 1646 (C=N, Imine), 1600, 1506 (C=C, Aromatic), 1219 (Ar-F);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.32 (1H, s, CH=N), 7.80 – 7.70 (2H, m, Ar), 7.32 – 7.24 (2H, m, Ar), 7.13 – 6.97 (4H, m, Ar), 4.74 (2H, s,  $\text{CH}_2$ );  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 164.5 (d,  $J_{\text{CF}}$  251.0 Hz, Ar), 162.1 (d,  $J_{\text{CF}}$  244.7 Hz, Ar), 160.6 (s,  $\text{HC}=\text{N}$ ), 135.1 (d,  $J_{\text{CF}}$  3.0 Hz, Ar, quaternary), 132.5 (d,  $J_{\text{CF}}$  2.9 Hz, Ar, quaternary), 130.3 (2C, d,  $J_{\text{CF}}$  8.7 Hz, Ar), 129.6 (2C, d,  $J_{\text{CF}}$  8.0 Hz, Ar), 115.8 (2C, d,  $J_{\text{CF}}$  21.9 Hz, Ar), 115.4 (2C, d,  $J_{\text{CF}}$  21.2 Hz, Ar), 64.2 (s,  $\text{CH}_2$ );  $\delta_{\text{F}}$  (282MHz,  $\text{CDCl}_3$ ) -109.08 (1F, s, C-F), -115.87 (1F, s, C-F);  $m/z$  (ESI) 232 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 232.0933,  $\text{C}_{14}\text{H}_{12}\text{F}_2\text{N}$  requires, 232.0932].

**8.3 Substrates Synthesized In Chapter 3****8.3.1 General Procedure for the Synthesis of Fluorinated Imines 138 - 146**

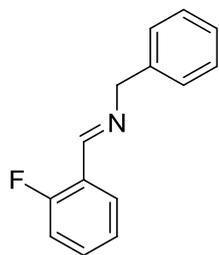
Aldehyde was dissolved in ethyl acetate (25 ml) in a 100 ml round bottom flask equipped with a magnetic stirrer bar. Amine was also dissolved in ethyl acetate (25 ml) and added to the aldehyde mixture followed by magnesium sulphate (5 g). The

reaction mixture was stirred at room temperature for 24 hours, gravity filtered and the solvent evaporated. Crude products were then purified by vacuum distillation.

**(*E*)-*N*-(2-fluorobenzylidene)butan-1-amine (138)**<sup>190</sup>

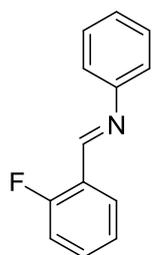


2-Fluorobenzaldehyde (1.0 g, 8.1 mmol) and *n*-butylamine (0.71 g, 9.7 mmol) was subject to the general procedure for the synthesis of imines (8.3.1). Purification by vacuum distillation resulted in formation of a pale yellow oil (1.40 g, 7.8 mmol, 97 %); spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 2930 (C-H), 1642 (C=N, Imine), 1584, 1484, 1457 (C=C, Aromatic), 1376 (C-N), 1232 (Ar-F);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.55 (1H, s,  $\text{HC}=\text{N}$ ), 7.94 (1H, td,  $J$  7.6, 1.8 Hz, Ar), 7.40 – 7.30 (1H, m, Ar), 7.14 (1H, t,  $J$  7.6 Hz, Ar), 7.09 – 6.98 (1H, m, Ar), 3.62 (2H, td,  $J_{\text{HH}}$  7.1, 1.1 Hz, N- $\text{CH}_2$ ), 1.74 – 1.60 (2H, m,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 1.44 – 1.30 (2H, m,  $\text{CH}_2\text{CH}_3$ ), 0.93 (3H, t,  $J_{\text{HH}}$  7.3 Hz,  $\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 162.1 (d,  $J_{\text{CF}}$  251.9 Hz, Ar), 154.1 (d,  $J_{\text{CF}}$  4.6 Hz,  $\text{HC}=\text{N}$ ), 131.9 (d,  $J_{\text{CF}}$  8.6 Hz, Ar), 127.7 (d,  $J_{\text{CF}}$  2.8 Hz, Ar), 124.3 (d,  $J_{\text{CF}}$  3.5 Hz, Ar), 124.0 (d,  $J_{\text{CF}}$  9.1 Hz, Ar, quaternary), 115.7 (d,  $J_{\text{CF}}$  21.2 Hz, Ar), 61.8 (s, N- $\text{CH}_2$ ), 33.0 (s,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 20.5 (s,  $\text{CH}_2\text{CH}_3$ ), 13.9 (s,  $\text{CH}_2\text{CH}_3$ );  $\delta_{\text{F}}$  (282MHz,  $\text{CDCl}_3$ ) -122.06 (1F, s, C-F);  $m/z$  (ESI) 180.1 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 180.1181,  $\text{C}_{11}\text{H}_{15}\text{FN}$  requires, 180.1183].

**(E)-N-(2-fluorobenzylidene)-1-phenylmethanamine (139)**<sup>36</sup>

2-Fluorobenzylaldehyde (1.0 g, 8.1 mmol) and benzylamine (1.04 g, 9.7 mmol) was subject to the general procedure for the synthesis of imines (8.3.1). Purification by vacuum distillation resulted in formation of a colourless oil (1.59 g, 7.5 mmol, 92 %);

spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3028 (C-H, Aromatic), 2889 (C-H, Alkane), 1639 (C=N, Imine), 1613, 1582, 1484, 1453 (C=C, Aromatic), 1378 (C-N), 1232 (Ar-F);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.61 (1H, s,  $\text{HC}=\text{N}$ ), 7.96 (1H, td,  $J$  7.7, 1.8 Hz, Ar), 7.32 – 7.21 (5H, m, Ar), 7.20 – 7.12 (1H, m, Ar), 7.05 (1H, t,  $J$  7.7 Hz, Ar), 7.01 – 6.90 (1H, m, Ar), 4.73 (2H, s,  $\text{CH}_2$ );  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 161.8 (d,  $J_{\text{CF}}$  252.2 Hz, Ar), 154.6 (d,  $J_{\text{CF}}$  4.7 Hz,  $\text{HC}=\text{N}$ ), 138.6 (s, Ar, quaternary), 131.8 (d,  $J_{\text{CF}}$  8.6 Hz, Ar), 128.0 (2C, s, Ar), 127.5 (2C, s, Ar), 127.3 (d,  $J_{\text{CF}}$  2.7 Hz, Ar), 126.5 (s, Ar), 123.8 (d,  $J_{\text{CF}}$  3.4 Hz, Ar, quaternary), 123.3 (d,  $J_{\text{CF}}$  9.3 Hz, Ar, quaternary), 115.2 (d,  $J_{\text{CF}}$  21.1 Hz, Ar), 64.9 (s,  $\text{CH}_2$ );  $\delta_{\text{F}}$  (282MHz,  $\text{CDCl}_3$ ) -121.87 (1F, s, C-F);  $m/z$  (ESI) 214.1 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 214.1031,  $\text{C}_{14}\text{H}_{13}\text{FN}$  requires, 214.1027].

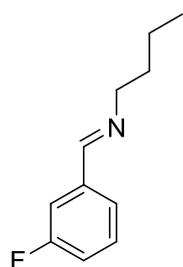
**(E)-N-(2-fluorobenzylidene)aniline (140)**<sup>191</sup>

2-Fluorobenzylaldehyde (1.0 g, 8.1 mmol) and aniline (0.90 g, 9.7 mmol) was subject to the general procedure for the synthesis of imines (8.3.1). Purification by vacuum distillation resulted in formation of a pale yellow oil (1.44 g, 7.2 mmol, 90 %); spectral details match these

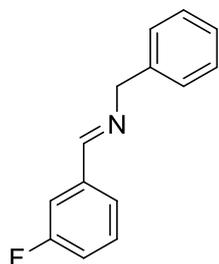
reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3063 (C-H, Aromatic), 1622 (C=N, Imine), 1590, 1578, 1480, 1457 (C=C, Aromatic), 1367 (C-N), 1205 (Ar-F);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.76

(1H, s,  $\underline{\text{HC}}=\text{N}$ ), 8.18 (1H, td,  $J$  7.8, 1.5 Hz, Ar), 7.45 – 7.33 (3H, m, Ar), 7.28 – 7.15 (4H, m, Ar), 7.14 – 7.04 (1H, m, Ar);  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 162.3 (d,  $J_{\text{CF}}$  253.5 Hz, Ar), 152.9 (d,  $J_{\text{CF}}$  4.9 Hz,  $\underline{\text{HC}}=\text{N}$ ), 151.4 (s, Ar, quaternary), 132.4 (d,  $J_{\text{CF}}$  8.7 Hz, Ar), 128.6 (2C, s, Ar), 127.3 (d,  $J_{\text{CF}}$  2.3 Hz, Ar), 125.8 (s, Ar), 123.9 (d,  $J_{\text{CF}}$  3.4 Hz, Ar), 123.4 (d,  $J_{\text{CF}}$  9.0 Hz, Ar, quaternary), 120.5 (2C, s, Ar), 115.3 (d,  $J_{\text{CF}}$  21.0 Hz, Ar);  $\delta_{\text{F}}$  (282MHz,  $\text{CDCl}_3$ ) -121.14 (1F, s, C-F);  $m/z$  (ESI) 200 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 200.0874,  $\text{C}_{13}\text{H}_{11}\text{FN}$  requires, 200.0870].

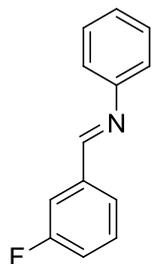
**(*E*)-*N*-(3-fluorobenzylidene)butan-1-amine (141)**



3-Fluorobenzylaldehyde (1.0 g, 8.1 mmol) and *n*-butylamine (0.71 g, 9.7 mmol) was subject to the general procedure for the synthesis of imines (8.3.1). Purification by vacuum distillation resulted in formation of a pale yellow oil (1.32 g, 7.4 mmol, 92 %);  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 2931 (C-H), 1648 (C=N, Imine), 1586, 1449 (C=C, Aromatic), 1376 (C-N), 1265 (Ar-F);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.22 (1H, d,  $J$  1.1 Hz,  $\underline{\text{HC}}=\text{N}$ ), 7.48 – 7.40 (2H, m, Ar), 7.34 (1H, td,  $J$  8.1, 5.6 Hz, Ar), 7.07 (1H, tdd,  $J$  8.1, 2.6, 1.0 Hz, Ar), 3.59 (2H, td,  $J_{\text{HH}}$  7.0, 1.1 Hz, N- $\underline{\text{CH}}_2$ ), 1.73 – 1.58 (2H, m,  $\text{CH}_2\underline{\text{CH}}_2\text{CH}_2$ ), 1.36 (2H, sextuplet,  $J_{\text{HH}}$  7.3 Hz,  $\underline{\text{CH}}_2\text{CH}_3$ ), 0.93 (3H, t,  $J_{\text{HH}}$  7.3 Hz,  $\text{CH}_2\underline{\text{CH}}_3$ );  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 163.1 (d,  $J_{\text{CF}}$  246.4 Hz, Ar), 159.4 (d,  $J_{\text{CF}}$  2.7 Hz,  $\underline{\text{HC}}=\text{N}$ ), 138.7 (d,  $J_{\text{CF}}$  7.3 Hz, Ar, quaternary), 130.7 (d,  $J_{\text{CF}}$  8.0 Hz, Ar), 124.1 (d,  $J_{\text{CF}}$  2.7 Hz, Ar), 117.4 (d,  $J_{\text{CF}}$  21.6 Hz, Ar), 114.1 (d,  $J_{\text{CF}}$  22.2 Hz, Ar), 61.4 (s, N- $\underline{\text{C}}\text{H}_2$ ), 32.9 (s,  $\text{CH}_2\underline{\text{C}}\text{H}_2\text{CH}_2$ ), 20.5 (s,  $\underline{\text{C}}\text{H}_2\text{CH}_3$ ), 13.9 (s,  $\text{CH}_2\underline{\text{C}}\text{H}_3$ );  $\delta_{\text{F}}$  (282MHz,  $\text{CDCl}_3$ ) -112.97 (1F, s, C-F);  $m/z$  (ESI) 180.1 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 180.1179,  $\text{C}_{11}\text{H}_{15}\text{FN}$  requires, 180.1183].

**(E)-N-(3-fluorobenzylidene)-1-phenylmethanamine (142)**<sup>192</sup>

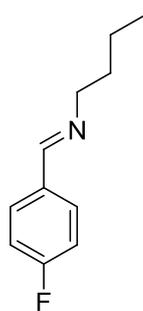
3-Fluorobenzylaldehyde (1.0 g, 8.1 mmol) and benzylamine (1.04 g, 9.7 mmol) was subject to the general procedure for the synthesis of imines (8.3.1). Purification by vacuum distillation resulted in formation of a colourless oil (1.61 g, 7.6 mmol, 94 %); spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3029 (C-H, Aromatic), 2843 (C-H, Alkane), 1645 (C=N, Imine), 1585, 1485, 1449 (C=C, Aromatic), 1375 (C-N), 1264 (Ar-F);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.31 (1H, s,  $\text{HC}=\text{N}$ ), 7.57 – 7.50 (1H, m, Ar), 7.48 (1H, d,  $J$  7.9 Hz, Ar), 7.41 – 7.20 (6H, m, Ar), 7.08 (1H, td,  $J$  7.9, 2.7 Hz, Ar), 4.79 (2H, s,  $\text{CH}_2$ );  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 162.5 (d,  $J_{\text{CF}}$  246.5 Hz, Ar), 160.0 (d,  $J_{\text{CF}}$  2.7 Hz,  $\text{HC}=\text{N}$ ), 138.5 (s, Ar, quaternary), 138.0 (d,  $J_{\text{CF}}$  7.3 Hz, Ar, quaternary), 129.6 (d,  $J_{\text{CF}}$  8.0 Hz, Ar), 128.0 (2C, s, Ar), 127.4 (2C, s, Ar), 126.6 (s, Ar), 123.8 (d,  $J_{\text{CF}}$  2.7 Hz, Ar), 117.1 (d,  $J_{\text{CF}}$  21.6 Hz, Ar), 113.8 (d,  $J_{\text{CF}}$  22.2 Hz, Ar), 64.4 (s,  $\text{CH}_2$ );  $\delta_{\text{F}}$  (282MHz,  $\text{CDCl}_3$ ) -112.83 (1F, s, C-F);  $m/z$  (ESI) 214.1 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 214.1025,  $\text{C}_{14}\text{H}_{13}\text{FN}$  requires, 214.1027].

**(E)-N-(3-fluorobenzylidene)aniline (143)**

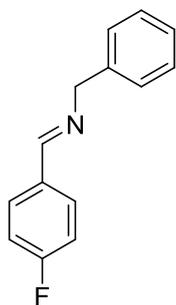
4-Fluorobenzylaldehyde (1.0 g, 8.1 mmol) and aniline (0.90 g, 9.7 mmol) was subject to the general procedure for the synthesis of imines (8.3.1). Purification by vacuum distillation resulted in formation of a pale yellow oil (1.52 g, 7.6 mmol, 95 %);  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3066 (C-H, Aromatic), 1628 (C=N, Imine), 1583, 1487, 1448 (C=C, Aromatic), 1366 (C-N), 1203 (Ar-F);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 8.37 (1H, s,  $\text{HC}=\text{N}$ ), 7.64 (1H, d,  $J$

9.4 Hz, Ar), 7.59 (1H, d,  $J$  8.0 Hz, Ar), 7.42 – 7.34 (3H, m, Ar), 7.24 – 7.17 (3H, m, Ar), 7.13 (1H, td,  $J$  8.0, 2.5 Hz, Ar);  $\delta_C$  (101MHz,  $CDCl_3$ ) 163.2 (d,  $J_{CF}$  246.9 Hz, Ar), 158.8 (d,  $J_{CF}$  2.9 Hz,  $HC=N$ ), 151.6 (s, Ar, quaternary), 138.6 (d,  $J_{CF}$  7.4 Hz, Ar, quaternary), 130.4 (d,  $J_{CF}$  7.4 Hz, Ar), 129.3 (2C, s, Ar), 126.4 (s, Ar), 125.1 (d,  $J_{CF}$  2.7 Hz, Ar), 121.0 (2C, s, Ar), 118.4 (d,  $J_{CF}$  21.6 Hz, Ar), 114.7 (d,  $J_{CF}$  22.3 Hz, Ar);  $\delta_F$  (376MHz,  $CDCl_3$ ) -112.48 (1F, s, C-F);  $m/z$  (ESI) 200 ( $[M]^+H$ ); [Found: ( $[M]^+H$ ) 200.0871,  $C_{13}H_{11}FN$  requires, 200.0870].

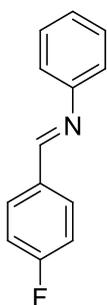
**(*E*)-*N*-(4-fluorobenzylidene)butan-1-amine (144)**<sup>193</sup>



4-Fluorobenzylaldehyde (1.0 g, 8.1 mmol) and *n*-butylamine (0.71 g, 9.7 mmol) was subject to the general procedure for the synthesis of imines (8.3.1). Purification by vacuum distillation resulted in formation of a pale yellow oil (1.39 g, 7.8 mmol, 96 %); spectral details match these reported;  $\nu_{max}$  (neat,  $cm^{-1}$ ) 2930 (C-H), 1646 (C=N, Imine), 1600, 1507 (C=C, Aromatic), 1377 (C-N), 1228 (Ar-F);  $\delta_H$  (300MHz,  $CDCl_3$ ) 8.23 (1H, 2,  $HC=N$ ), 7.77 – 7.65 (2H, m, Ar), 7.14 – 7.04 (2H, m, Ar), 3.59 (2H, t,  $J_{HH}$  6.8 Hz, N- $CH_2$ ), 1.75 – 1.60 (2H, m,  $CH_2CH_2CH_2$ ), 1.38 (2H, sextuplet,  $J_{HH}$  7.3 Hz,  $CH_2CH_3$ ), 0.93 (3H, t,  $J_{HH}$  7.3 Hz,  $CH_2CH_3$ );  $\delta_C$  (75MHz,  $CDCl_3$ ) 164.2 (d,  $J_{CF}$  250.3 Hz, Ar), 159.3 (s,  $HC=N$ ), 132.7 (d,  $J_{CF}$  2.9 Hz, Ar, quaternary), 129.8 (2C, d,  $J_{CF}$  8.6 Hz, Ar), 115.6 (2C, d,  $J_{CF}$  21.8 Hz, Ar), 61.4 (s, N- $CH_2$ ), 33.0 (s,  $CH_2CH_2CH_2$ ), 20.5 (s,  $CH_2CH_3$ ), 13.9 (s,  $CH_2CH_3$ );  $\delta_F$  (282MHz,  $CDCl_3$ ) -109.89 (1F, s, C-F);  $m/z$  (ESI) 180.1 ( $[M]^+H$ ); [Found: ( $[M]^+H$ ) 180.1180,  $C_{11}H_{15}FN$  requires, 180.1183].

**(E)-N-(4-fluorobenzylidene)-1-phenylmethanamine (145)**<sup>194</sup>

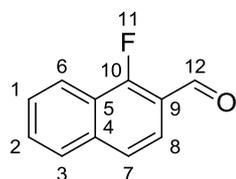
4-Fluorobenzylaldehyde (1.0 g, 8.1 mmol) and benzylamine (1.04 g, 9.7 mmol) was subject to the general procedure for the synthesis of imines (8.3.1). Purification by vacuum distillation resulted in formation of a colourless oil (1.54 g, 7.2 mmol, 90 %); spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3028 (C-H, Aromatic), 2840 (C-H, Alkane), 1643 (C=N, Imine), 1597, 1507, 1496 (C=C, Aromatic), 1376 (C-N), 1227 (Ar-F);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.30 (1H, s,  $\text{HC}=\text{N}$ ), 7.80 – 7.66 (2H, m, Ar), 7.37 – 7.28 (4H, m, Ar), 7.27 – 7.19 (1H, m, Ar), 7.11 – 7.00 (2H, m, Ar), 4.78 (2H, s,  $\text{CH}_2$ );  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 163.8 (d,  $J_{\text{CF}}$  250.7 Hz, Ar), 159.9 (s,  $\text{HC}=\text{N}$ ), 138.7 (s, Ar, quaternary), 131.9 (d,  $J_{\text{CF}}$  2.9 Hz, Ar, quaternary), 129.6 (2C, d,  $J_{\text{CF}}$  8.6 Hz, Ar), 128.0 (2C, s, Ar), 127.4 (2C, s, Ar), 126.5 (s, Ar), 115.1 (2C, d,  $J_{\text{CF}}$  21.9 Hz, Ar), 64.4 (s,  $\text{CH}_2$ );  $\delta_{\text{F}}$  (282MHz,  $\text{CDCl}_3$ ) -109.32 (1F, s, C-F);  $m/z$  (ESI) 214.1 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 214.1034,  $\text{C}_{14}\text{H}_{13}\text{FN}$  requires, 214.1027].

**(E)-N-(4-fluorobenzylidene)aniline (146)**<sup>194</sup>

4-Fluorobenzylaldehyde (1.0 g, 8.1 mmol) and aniline (0.90 g, 9.7 mmol) was subject to the general procedure for the synthesis of imines (8.3.1). Purification by vacuum distillation resulted in formation of a pale yellow oil (1.56 g, 7.8 mmol, 97 %);  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3065 (C-H, Aromatic), 1625 (C=N, Imine), 1585, 1504 (C=C, Aromatic), 1358 (C-N), 1217 (Ar-F);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 8.35 (1H, s,  $\text{HC}=\text{N}$ ), 7.85 (2H, dd,  $J$  8.6, 5.6 Hz, Ar), 7.36 (2H, t,  $J_{\text{HH}}$  7.7 Hz, Ar), 7.21 (1H, t,  $J_{\text{HH}}$  7.7 Hz, Ar), 7.17 (2H, d,  $J_{\text{HH}}$

7.7 Hz, Ar), 7.10 (1H, t,  $J$  8.6 Hz, Ar);  $\delta_{\text{C}}$  (101MHz,  $\text{CDCl}_3$ ) 164.8 (d,  $J_{\text{CF}}$  252.2 Hz, Ar), 158.8 (s,  $\text{HC}=\text{N}$ ), 151.9 (s, Ar, quaternary), 132.7 (d,  $J_{\text{CF}}$  2.9 Hz, Ar, quaternary), 130.9 (2C, d,  $J_{\text{CF}}$  8.8 Hz, Ar), 129.3 (2C, s, Ar), 126.1 (s, Ar), 121.0 (2C, s, Ar), 116.0 (2C, d,  $J_{\text{CF}}$  22.0 Hz, Ar);  $\delta_{\text{F}}$  (376MHz,  $\text{CDCl}_3$ ) -108.02 (1F, s, C-F);  $m/z$  (ESI) 200 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 200.0871,  $\text{C}_{13}\text{H}_{11}\text{FN}$  requires, 200.0870].

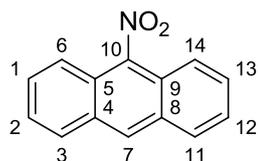
### 1-Fluoro-2-naphthaldehyde (130)<sup>84</sup>



1-Fluoronaphthalene (10.0 g, 68.0 mmol, 1 equiv.) was added to a solution of sec-butyllithium (48.6 ml, 68 mmol, 1 equiv.) in THF (200 ml) cooled in an acetone/ dry ice bath. After 2 hours at  $-75^\circ\text{C}$ , the mixture was treated with DMF (4.77 g, 68.0 mmol, 1 equiv.). The mixture was poured into water (500 ml) and extracted with diethyl ether (3 x 50 ml). After evaporation of the volatiles, the residue was crystallized with ethanol, resulted in formation of yellow crystals (8.1 g, 46.6 mmol, 68 %); spectral details match these reported;  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 3064 (C-H, Aromatic), 2846, 2749 (=C-H, Aldehyde), 1697 (C=O, Aldehyde), 1578 (C=C, Aromatic);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 10.54 (1H, s,  $\text{H}_{12}$ ), 8.17 (1H, d,  $J_{\text{HH}}$  8.3 Hz,  $\text{H}_6$ ), 7.85 - 7.81 (1H, m,  $\text{H}_3$ ), 7.81 - 7.76 (1H, m,  $\text{H}_8$ ), 7.64 (1H, t,  $J_{\text{HH}}$  7.4 Hz,  $\text{H}_2$ ), 7.61-7.55 (2H, m,  $\text{H}_1\text{H}_7$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 187.0 (d,  $J_{\text{CF}}$  8.5 Hz,  $\text{C}_{12}$ ), 163.0 (d,  $J_{\text{CF}}$  267.6 Hz,  $\text{C}_{10}$ ), 137.9 (d,  $J_{\text{CF}}$  6.1 Hz,  $\text{C}_4$ , quaternary), 130.0 (s,  $\text{C}_2$ ), 127.8 (d,  $J_{\text{CF}}$  2.8 Hz,  $\text{C}_3$ ), 127.3 (d,  $J_{\text{CF}}$  1.6 Hz,  $\text{C}_1$ ), 124.3 (d,  $J_{\text{CF}}$  4.2 Hz,  $\text{C}_7$ ), 123.2 (d,  $J_{\text{CF}}$  15.4 Hz,  $\text{C}_5$ , quaternary), 121.9 (d,  $J_{\text{CF}}$  6.4 Hz,  $\text{C}_6$ ), 121.9 (d,  $J_{\text{CF}}$  2.1 Hz,  $\text{C}_8$ ), 118.9 (d,  $J_{\text{CF}}$  5.7 Hz,  $\text{C}_9$ , quaternary);  $\delta_{\text{F}}$

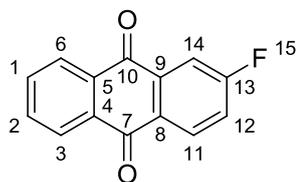
(376MHz, CDCl<sub>3</sub>) -130.23 (1F, s, F<sub>11</sub>); *m/z* (ESI) 197 ([M]<sup>+</sup>Na); [Found: ([M]<sup>+</sup>Na) 197.0377, C<sub>11</sub>H<sub>7</sub>FNaO requires, 197.0373].

### 9-Nitroanthracene (152)<sup>86</sup>

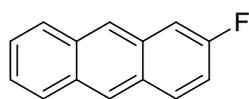


Concentrated nitric acid (4 ml, 90 mmol) was added drop wise to a suspension of anthracene (10 g, 56.0 mmol) in glacial acetic acid (40 ml) maintaining the temperature below 30°C.

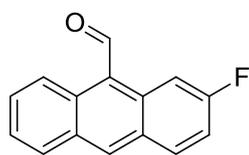
This was stirred vigorously for 1 hour to form a clear solution. A mixture of concentrated hydrochloric acid (50 ml) and glacial acetic acid (50 ml) was added slowly resulting in a pale yellow precipitate of 9-nitro-10-chloro-9, 10-dihydroanthracene. This was filtered, washed with glacial acetic acid (3 x 30 ml) and thoroughly with water until the washings were neutral. The resulting yellow solid was treated with a warm solution (60-70°C) of 10 % sodium hydroxide (250 ml), filtered, washed with water until washings were neutral, air dried and re-crystallized from glacial acetic acid, resulting in fluffy yellow crystals (9.66 g, 43.3 mmol, 77 %); spectral details match these reported;  $\delta_{\text{H}}$  (400MHz, CDCl<sub>3</sub>) 8.52 (1H, s, H<sub>7</sub>), 7.99 (2H, d,  $J_{\text{HH}}$  8.8 Hz, H<sub>3</sub>H<sub>11</sub>), 7.90 (2H, d,  $J_{\text{HH}}$  8.9 Hz, H<sub>6</sub>H<sub>14</sub>), 7.60 (2H, m, H<sub>1</sub>H<sub>13</sub>), 7.50 (2H, m, H<sub>2</sub>H<sub>12</sub>);  $\delta_{\text{C}}$  (100MHz, CDCl<sub>3</sub>) 144.3 (C<sub>10</sub>, quaternary), 130.7 (2C, C<sub>4</sub>C<sub>8</sub>, quaternary), 130.4 (C<sub>7</sub>), 128.9 (2C, C<sub>1</sub>C<sub>13</sub>), 128.4 (2C, C<sub>3</sub>C<sub>11</sub>), 126.2 (2C, C<sub>2</sub>C<sub>12</sub>), 122.6 (2C, C<sub>3</sub>C<sub>9</sub>, quaternary), 121.4 (2C, C<sub>6</sub>C<sub>14</sub>).

**2-Fluoroanthracene-9,10-dione (162)**<sup>88</sup>

To a solution of 2-aminoanthraquinone (20 g, 89.6 mmol, 1 equiv.) in 98% H<sub>2</sub>SO<sub>4</sub> (260 ml) at 0°C, NaNO<sub>2</sub> (7.6 g, 110.0 mmol, 1.2 equiv.) was added portion wise with stirring. The solution was stirred at room temp for 3.5 h, then poured into an aqueous solution (300 ml) of NaBF<sub>4</sub> (13.6 g, 124 mmol, 1.4 equiv.) at 0°C, a greenish-grey precipitate was formed and the mixture was stirred for an additional 1 h. the precipitate was filtered, washed consecutively with cold water, cold methanol and diethyl ether then dried at room temp resulting in greenish-grey diazonium salt. Diazonium salt (14.0 g, 43.5 mmol) was suspended in toluene (500 ml) and refluxed for 24 h. Toluene was then evaporated and the product was extracted using diethyl ether (6 x 150 ml). The crude was then purified by column chromatography, resulted in formation of yellow crystals (3.58 g, 15.8 mmol, 36 %); spectral details match these reported; mpt 204 - 205°C, (lit: 204°C);  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 3076 (C-H, Aromatic), 1678 (C=O), 1588 (C=C, Aromatic), 1287 (Ar-F);  $\delta_{\text{H}}$  (300MHz, CDCl<sub>3</sub>) 8.39 - 8.25 (3H, m, H<sub>1</sub>H<sub>2</sub>H<sub>11</sub>), 7.93 (1H, dd, *J* 8.7, 2.6 Hz, H<sub>14</sub>), 7.86 - 7.76 (2H, m, H<sub>3</sub>H<sub>6</sub>), 7.45 (1H, td, *J* 8.3, 2.6 Hz, H<sub>12</sub>);  $\delta_{\text{C}}$  (75MHz, CDCl<sub>3</sub>) 181.6 – 181.1 (2C, C<sub>7</sub>C<sub>10</sub>, quaternary), 165.7 (d, *J*<sub>CF</sub> 257.7 Hz, C<sub>13</sub>), 135.6 (d, *J*<sub>CF</sub> 8.2 Hz, C<sub>9</sub>, quaternary), 133.8 – 133.5 (2C, C<sub>3</sub>C<sub>6</sub>), 130.2 – 129.8 (2C, C<sub>4</sub>C<sub>5</sub>, quaternary), 129.5 (s, *J*<sub>CF</sub> 3.2 Hz, C<sub>11</sub>), 126.7 (d, *J*<sub>CF</sub> 2.1 Hz, C<sub>8</sub>, quaternary), 120.8 (d, *J*<sub>CF</sub> 22.5 Hz, C<sub>12</sub>), 113.1 (d, *J*<sub>CF</sub> 23.3 Hz, C<sub>14</sub>).

**2-Fluoroanthracene (164)**<sup>88</sup>

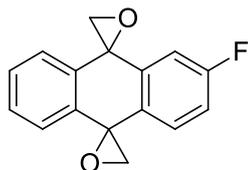
To a solution of 2-fluoroanthracene-9,10-dione (**162**) (0.60 g, 2.6 mmol, 1 equiv.) in AcOH (75 ml) was refluxed in 57 % HI (5.16 ml, 39 mmol, 15 equiv.) for 60h. The mixture was cooled to room temp and poured into water (150 ml). The precipitate that formed was filtered and dried. According to TLC, small amounts of starting material were present therefore excess Iodine was added to the solid in refluxing toluene (75 ml) until the starting material disappeared according to TLC. The mixture was cooled to room temp, washed successively with 5 % NaHCO<sub>3</sub> (150 ml), saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (150 ml) and water (150 ml) and the organic evaporated to dryness under reduced pressure. The yellow crude was recrystallized from AcOH, resulting in off-white crystals (0.50 g, 2.5 mmol, 96 %); mp 211 – 213 °C (lit. 212°C); Spectral details match these reported;  $\delta_{\text{H}}$  (300MHz, CDCl<sub>3</sub>) 8.43 (1H, s, Ar), 8.35 (1H, s, Ar), 7.99 (3H, m, Ar), 7.57 (1H, dd, *J* 9.6, 2.3 Hz, Ar), 7.47 (2H, m, Ar), 7.27 (1H, ddd, *J* 10.2, 9.6, 2.3 Hz, Ar).

**2-Fluoroanthracene-9-carbaldehyde (165):**

Trifluoromethanesulfonic anhydride (0.72 g, 2.55 mmol, 1 equiv.) was added drop-wise to DMF (0.19 g, 2.55 mmol, 1 equiv.) at 0°C, whereby a white precipitate was formed. A solution of 2-fluoroanthracene (**164**) (0.50 g, 2.55 mmol, 1 equiv.) in DCM (15 ml) was added to the mixture and heated in a sealed ampoule at 37°C for 48 h. After cooling, the mixture was hydrolysed with 5 % NaOH (15 ml) and extracted with

DCM (3 x 15 ml). The combined DCM layers were washed with water (2 x 20 ml) and dried over MgSO<sub>4</sub>, filtered and evaporated, resulting in bright yellow crystals (0.25 g, 1.11 mmol, 44 %);  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 3060 (C-H, stretch), 1662 (C=O), 1620 (C=C, stretch), 1042 (C-F, stretch);  $\delta_{\text{H}}$  (400MHz, CDCl<sub>3</sub>) 11.42 (1H, s, CHO), 8.90 (1H, d,  $J_{\text{HH}}$  9.0 Hz, Ar), 8.76 (1H, dd,  $J$  12.5, 2.4 Hz, Ar), 8.67 (1H, s, Ar), 8.08 - 8.02 (2H, m, Ar), 7.70 (1H, dt,  $J_{\text{HH}}$  8.6, 1.2 Hz, Ar), 7.55 (1H, t,  $J_{\text{HH}}$  8.6 Hz, Ar), 7.35 (1H, dt,  $J$  9.6, 2.4 Hz, Ar);  $\delta_{\text{C}}$  (100MHz, CDCl<sub>3</sub>) 192.2 (CHO), 164.3 (d,  $J_{\text{CF}}$  251.2 Hz, ArCF, quaternary), 135.7 (Ar), 133.4 (C, quaternary), 131.9 (d,  $J_{\text{CF}}$  9.9 Hz, Ar), 129.6 (Ar), 129.6 (Ar), 128.5 (C, quaternary), 125.6 (Ar), 123.7 (C, quaternary), 123.6 (C, quaternary), 123.5 (C, quaternary), 122.5 (Ar), 117.7 (d,  $J_{\text{CF}}$  24.3 Hz, Ar), 107.1 (d,  $J_{\text{CF}}$  27.7 Hz, Ar);  $\delta_{\text{F}}$  (376MHz, CDCl<sub>3</sub>) -106.79 (1F, s, C-F);  $m/z$  (ESI) 225.3 ([M]<sup>+</sup>H); [Found: ([M]<sup>+</sup>H) 225.0704, C<sub>15</sub>H<sub>10</sub>FO requires, 225.0710].

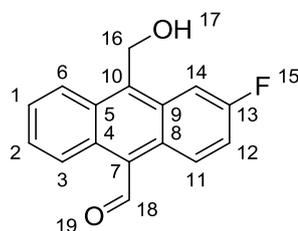
### Fluorinated *trans*-dispiro[oxirane-2,9'[10'*H*]-anthracene-10',2''-oxirane] (**163**)



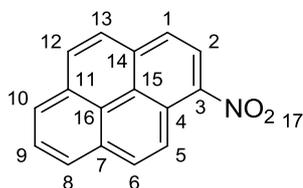
To a stirred mixture of sodium hydride (0.14 g, 5.65 mmol, 2.2 equiv.) and 2-fluoroanthracene-9,10-dione (**162**) (0.58 g, 2.56 mmol, 1 equiv.) in dry DMSO (56 ml) at room temperature in dark and under nitrogen was added drop-wise a solution of trimethylsulfonium iodide (1.15 g, 5.65 mmol, 2.2 equiv.) in dry DMSO (34 ml) over a period of 30 min. The reaction mixture was stirred for an additional hour and filtered through a sintered glass funnel. The filtrate was poured into ice water (200 ml) and allowed to stand for 30 min. The yellow crystals were collected and washed with water (0.42 g, 1.65 mmol, 64 %);  $\delta_{\text{H}}$  (300MHz, CDCl<sub>3</sub>) 7.23 - 7.18 (2H, m, Ar), 7.12 (1H, s, Ar), 6.98 - 6.87 (4H, m, Ar), 2.47 (4H, s, CH<sub>2</sub>);  $\delta_{\text{C}}$  (75MHz, CDCl<sub>3</sub>) 162.3 (d,  $J_{\text{CF}}$  252.6

Hz, ArCF, quaternary), 144.9 (C, quaternary), 142.8 (C, quaternary), 142.7 (C, quaternary), 134.2 (C, quaternary), 128.5 (Ar), 128.5 (Ar), 124.6 (d,  $J_{CF}$  8.5 Hz, Ar), 122.3 (Ar), 122.30 (Ar), 115.7 (d,  $J_{CF}$  22.1 Hz, Ar), 109.4 (d,  $J_{CF}$  23.8 Hz, Ar), 63.7 (CH<sub>2</sub>), 63.6 (CH<sub>2</sub>), 65.1 (2C, quaternary);  $\delta_F$  (282MHz, CDCl<sub>3</sub>) -113.44 (1F, s, C-F);  $m/z$  (ESI) Found 255.1 ([M]<sup>+</sup>H), C<sub>16</sub>H<sub>11</sub>FO<sub>2</sub> requires, 255.1.

### 3-Fluoro-10-(hydroxymethyl)anthracene-9-carbaldehyde (**159**)



To a solution of lithium bromide (0.32 g, 3.6 mmol, 4.6 equiv.) in dry acetonitrile (50 ml) was added to **163** (0.20 g, 0.8 mmol, 1 equiv.). The reaction mixture was stirred at 60°C in the dark for 16 h and then cooled to -40°C in a dry ice-acetone bath. The resulting crystals were collected by filtration and washed with water giving yellow crystals (0.098 g, 0.39 mmol, 49%); 3415 (OH), 3020 (C-H, Aromatic), 2919 (C-H, Alkane), 1669 (C=O), 1588 (C=C, Aromatic), 1287 (Ar-F), 1027 (C-O);  $\delta_H$  (500MHz, CDCl<sub>3</sub>) 10.41 (1H, s, H<sub>18</sub>), 8.03 (1H, dd,  $J_{HH}$  9.7, 6.1 Hz, H<sub>11</sub>), 7.89 (1H, d,  $J_{HH}$  8.4 Hz, H<sub>3</sub>), 7.57 (1H, d,  $J_{HH}$  8.4 Hz, H<sub>6</sub>), 7.23 (1H, dd,  $J_{HH}$  12.0, 2.5 Hz, H<sub>14</sub>), 6.68 - 6.76 (2H, m, H<sub>5</sub>H<sub>6</sub>), 6.69 - 6.64 (1H, m, H<sub>12</sub>), 4.66 (1H, s, H<sub>17</sub>), 4.41 (2H, s, H<sub>16</sub>),  $\delta_C$  (125MHz, CDCl<sub>3</sub>) 194.9 (s, C<sub>18</sub>), 159.5 (d,  $J_{CF}$  246.2 Hz, C<sub>13</sub>, quaternary), 140.2 (d,  $J_{CF}$  7.6 Hz, C<sub>10</sub>, quaternary), 130.4 (s, C<sub>4</sub>, quaternary), 130.1 (d,  $J_{CF}$  9.8 Hz, C<sub>9</sub>, quaternary), 129.7 (s, C<sub>5</sub>, quaternary), 128.1 (s, C<sub>1</sub>), 127.6 (s, C<sub>8</sub>, quaternary), 127.5 (d,  $J_{CF}$  8.8 Hz, C<sub>11</sub>), 126.4 (s, C<sub>2</sub>), 126.0 (s, C<sub>7</sub>, quaternary), 125.3 (s, C<sub>6</sub>), 123.7 (s, C<sub>3</sub>), 119.4 (d,  $J_{CF}$  26.8 Hz, C<sub>12</sub>), 108.0 (d,  $J_{CF}$  21.8 Hz, C<sub>14</sub>), 55.6 (s, C<sub>16</sub>);  $\delta_F$  (470MHz, CDCl<sub>3</sub>) -111.64 (1F, s, C-F);  $m/z$  (ESI) 277.0633 (100%) (Found: (M + Na)<sup>+</sup>, C<sub>16</sub>H<sub>11</sub>FNaO<sub>2</sub> requires 277.0633).

**1-Nitropyrene (168)**<sup>90</sup>

Concentrated nitric acid (3.52 ml, 60 mmol, 1.2 equiv.)

was added drop wise to a suspension of pyrene (10.0 g, 50

mmol, 1.0 equiv.) in acetic acid (70 ml). The mixture was

stirred at room temp for 1 h. The mixture was partitioned

using dichloromethane and saturated sodium bicarbonate. The organic was dried,

filtered and evaporated, leading to orange crystals. The product was recrystallized

using acetic acid, resulting in orange/brown crystals (9.0 g, 33.3 mmol, 74%);

spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3044 (C-H, Aromatic), 1591

(N-O), 1498 (C=C, Aromatic), 1306 (N-O);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 8.66 (1H, d,  $J_{\text{HH}}$

9.5 Hz, H<sub>5</sub>), 8.48 (1H, d,  $J_{\text{HH}}$  8.5 Hz, H<sub>1</sub>), 8.16 (1H, d,  $J_{\text{HH}}$  7.6 Hz, H<sub>8</sub>), 8.13 (1H, d,

$J_{\text{HH}}$  7.6 Hz, H<sub>10</sub>), 8.06 (1H, d,  $J_{\text{HH}}$  9.5 Hz, H<sub>6</sub>), 8.03 (1H, d,  $J_{\text{HH}}$  8.9 Hz, H<sub>13</sub>), 8.00

(1H, t,  $J_{\text{HH}}$  7.6 Hz, H<sub>9</sub>), 7.91 (1H, d,  $J_{\text{HH}}$  8.5 Hz, H<sub>2</sub>), 7.86 (1H, d,  $J_{\text{HH}}$  8.9 Hz, H<sub>12</sub>);

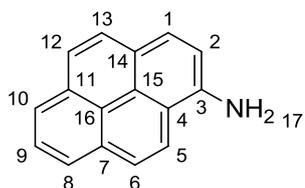
$\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 142.5 (C<sub>3</sub>, quaternary), 134.8 (C<sub>14</sub>, quaternary), 131.3 (C<sub>6</sub>),

130.6 (C<sub>11</sub>, quaternary), 130.5 (C<sub>13</sub>), 129.8 (C<sub>4</sub>, quaternary), 127.5 (C<sub>8</sub>), 127.0 (C<sub>10</sub>),

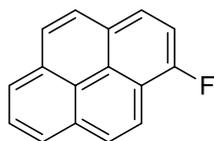
126.9 (C<sub>9</sub>), 126.6 (C<sub>12</sub>), 124.5 (C<sub>15</sub>, quaternary), 124.4 (C<sub>16</sub>, quaternary), 123.9 (C<sub>2</sub>),

123.3 (C<sub>7</sub>, quaternary), 122.5 (C<sub>1</sub>), 121.5 (C<sub>5</sub>);  $m/z$  (ESI) 248.1 ( $[\text{M}]^+\text{H}$ ); [Found:

( $[\text{M}]^+\text{Na}$ ) 270.0732,  $\text{C}_{16}\text{H}_9\text{NNaO}_2$  requires, 270.0525].

**1-Aminopyrene (148)**<sup>90</sup>

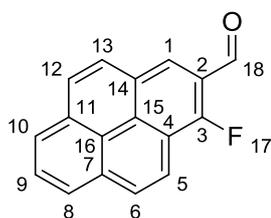
To a solution of 1-nitropyrene (**168**) (20.0 g, 74 mmol, 1 equiv.) in 95% ethanol (500 ml) was added 10% Pd/C (2.0 g) and 50% hydrazine in water (50.0 ml, 1.0 mol, 14 equiv.). The mixture was heated under reflux and nitrogen for 16 h. The solution was filtered through a celite bed and evaporated under reduced pressure. The residue was dissolved in diethyl ether, washed with water and dried over anhydrous MgSO<sub>4</sub> to give a crude 1-aminopyrene (15.6 g, 72.0 mmol, 89 %); spectral details match these reported;  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 3461, 3386, 3324 (N-H), 3028 (C-H, Aromatic), 1617 (C-N, Amine), 1599, 1506 (C=C, Aromatic);  $\delta_{\text{H}}$  (400MHz, CDCl<sub>3</sub>) 8.03 – 7.97 (2H, m, H<sub>8</sub>H<sub>10</sub>), 7.99 (1H, d,  $J_{\text{HH}}$  8.2 Hz, H<sub>1</sub>), 7.98 (1H, d,  $J_{\text{HH}}$  9.4 Hz, H<sub>6</sub>), 7.89 – 7.83 (3H, m, H<sub>5</sub>H<sub>9</sub>H<sub>13</sub>), 7.84 (1H, d,  $J_{\text{HH}}$  8.9 Hz, H<sub>12</sub>), 7.34 (1H, d,  $J_{\text{HH}}$  8.2 Hz, H<sub>2</sub>), 4.42 (2H, s, H<sub>17</sub>);  $\delta_{\text{C}}$  (100MHz, CDCl<sub>3</sub>) 140.1 (C<sub>3</sub>, quaternary), 132.2 (C<sub>11</sub>, quaternary), 131.7 (C<sub>7</sub>, quaternary), 127.6 (C<sub>13</sub>), 126.1 (C<sub>6</sub>), 126.0 (C<sub>1</sub>), 126.0 (C<sub>9</sub>), 125.6 (C<sub>15</sub>, quaternary), 125.5 (C<sub>16</sub>, quaternary), 124.3 (C<sub>14</sub>, quaternary), 124.1 (C<sub>8</sub>), 123.7 (C<sub>12</sub>), 123.6 (C<sub>10</sub>), 120.2 (C<sub>5</sub>), 116.9 (C<sub>4</sub>, quaternary), 113.9 (C<sub>2</sub>);  $m/z$  (ESI) 218 ([M]<sup>+</sup>H); [Found: ([M]<sup>+</sup>H) 218.0973, C<sub>16</sub>H<sub>12</sub>N requires, 218.0964].

**1-Fluoropyrene (170)**<sup>195</sup>

To a solution of 1-aminopyrene (**148**) (15.6 g, 72.0 mmol, 1 equiv.) in (Et<sub>2</sub>O)BF<sub>3</sub> (22.45 g, 160 mmol, 2.2 equiv.) and THF (500 ml) was added t-BuONO (16.3 g, 160 mmol, 2.2 equiv.) at -8°C. After stirring for 1 h, pentane was added to the mixture. The solid material

formed was filtered and washed with ether to give a crude tetrafluoroboron-diazonium salt. The dried salt was heated in xylene at reflux for 24 h and purified by silica gel by column chromatography, resulting in colourless crystals (8.4 g, 38.2 mmol, 53 %); spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3039 (C-H, stretch), 1599 (C=C, stretch), 1245 (C-F, stretch);  $\delta_{\text{H}}$  (500MHz,  $\text{CDCl}_3$ ) 8.28 (1H, d,  $J_{\text{HH}}$  9.1 Hz, Ar), 8.18 (1H, dd,  $J_{\text{HH}}$  7.5, 2.9 Hz, Ar), 8.16 (1H, dd,  $J_{\text{HH}}$  7.5, 2.9 Hz, Ar), 8.11 (1H, d,  $J$  9.1 Hz, Ar), 8.11 (1H, d,  $J$  10.0 Hz, Ar), 8.02 (1H, t,  $J_{\text{HH}}$  7.5 Hz, Ar), 8.00 (2H, m, Ar), 7.74 (1H, dd,  $J$  10.0, 1.4 Hz, Ar);  $\delta_{\text{C}}$  (125MHz,  $\text{CDCl}_3$ ) 156.7 (d,  $J_{\text{CF}}$  251.0 Hz, ArCF), 131.2 (d,  $J_{\text{CF}}$  4.1 Hz, C, quaternary), 127.8 (d,  $J_{\text{CF}}$  2.7 Hz, C, quaternary), 127.7 (C, quaternary), 127.0 (Ar), 126.5 (Ar), 126.4 (d,  $J_{\text{CF}}$  2.8 Hz, Ar), 125.9 (C, quaternary), 125.3 (Ar), 125.0 (d,  $J_{\text{CF}}$  2.0 Hz, C, quaternary), 125.0 (Ar), 124.5 (C, quaternary), 124.5 (C, quaternary), 119.3 (d,  $J_{\text{CF}}$  4.2 Hz, Ar), 118.8 (d,  $J_{\text{CF}}$  14.7 Hz, C, quaternary), 112.6 (d,  $J_{\text{CF}}$  22.1 Hz, Ar);  $\delta_{\text{F}}$  (470MHz,  $\text{CDCl}_3$ ) -122.92 (1F, s, C-F).

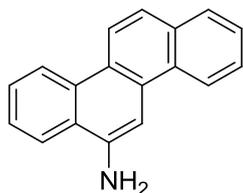
### 1-Fluoropyrene-2-carbaldehyde (132)



1-Fluoropyrene (**170**) (5.0 g, 22.7 mmol, 1 equiv.) was added to a solution of 1.4 M *sec*-butyllithium (16.2 ml, 22.7 mmol, 1 equiv.) in THF (100 ml) cooled in acetone/dry ice bath. After 2 hours at  $-75^{\circ}\text{C}$ , the mixture was treated with DMF (2.1 ml, 27.2 mmol, 1.2 equiv.). The mixture was poured into water and extracted with diethyl ether. After evaporation of the volatiles, the residue was purified by column chromatography, resulting in pale yellow crystals (5.2 g, 19.2 mmol, 93 %);  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3045 (C-H, stretch), 1687 (C=O, stretch), 1589 (C=C, stretch), 1162 (C-

F, stretch);  $\delta_{\text{H}}$  (500MHz,  $\text{CDCl}_3$ ) 10.66 (1H, s,  $\text{H}_{18}$ ), 8.33 (1H, d,  $J_{\text{HF}}$  5.6 Hz,  $\text{H}_1$ ), 8.13 (1H, d,  $J_{\text{HH}}$  9.1 Hz,  $\text{H}_5$ ), 8.11 (1H, d,  $J_{\text{HH}}$  7.6 Hz,  $\text{H}_{10}$ ), 8.10 (1H, d,  $J_{\text{HH}}$  7.6 Hz,  $\text{H}_8$ ), 8.02 (1H, t,  $J_{\text{HH}}$  7.6 Hz,  $\text{H}_9$ ), 8.00 (1H, d,  $J_{\text{HH}}$  9.1 Hz,  $\text{H}_6$ ), 7.88 (1H, d,  $J_{\text{HH}}$  9.2 Hz,  $\text{H}_{12}$ ), 7.85 (1H, d,  $J_{\text{HH}}$  9.2 Hz,  $\text{H}_{13}$ );  $\delta_{\text{C}}$  (126MHz,  $\text{CDCl}_3$ ) 187.7 (d,  $J_{\text{CF}}$  7.6 Hz,  $\text{C}_{18}$ ), 158.0 (d,  $J_{\text{CF}}$  262.7 Hz,  $\text{C}_3$ ), 131.8 (s,  $\text{C}_7$ , quaternary), 131.6 (s,  $\text{C}_{11}$ , quaternary), 128.8 (d,  $J_{\text{CF}}$  6.5 Hz,  $\text{C}_{15}$ , quaternary), 128.5 (d,  $J_{\text{CF}}$  2.3 Hz,  $\text{C}_6$ ), 127.8 (s,  $\text{C}_9$ ), 127.4 (d,  $J_{\text{CF}}$  2.3 Hz,  $\text{C}_{13}$ ), 127.3 (s,  $\text{C}_{12}$ ), 127.1 (d,  $J_{\text{CF}}$  3.1 Hz,  $\text{C}_{14}$ , quaternary), 125.6 (s,  $\text{C}_{10}$ ), 125.0 (s,  $\text{C}_8$ ), 123.8 (d,  $J_{\text{CF}}$  3.3 Hz,  $\text{C}_{16}$ , quaternary), 122.8 (s,  $\text{C}_1$ ), 120.3 (d,  $J_{\text{CF}}$  8.8 Hz,  $\text{C}_2$ , quaternary), 119.2 (d,  $J_{\text{CF}}$  5.6 Hz,  $\text{C}_5$ ), 118.9 (d,  $J_{\text{CF}}$  14.6 Hz,  $\text{C}_4$ , quaternary);  $\delta_{\text{F}}$  (470MHz,  $\text{CDCl}_3$ ) -133.25 (1F, s, C-F);  $m/z$  (ESI) 271 ( $[\text{M}]^+\text{Na}$ ); [Found: ( $[\text{M}]^+\text{Na}$ ) 271.0525,  $\text{C}_{17}\text{H}_9\text{FNaO}$  requires, 271.0530].

### 6-Aminochrysene (149)<sup>196</sup>



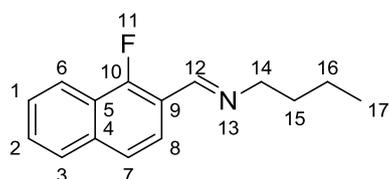
To a solution of 6-nitrochrysene (0.5 g, 1.8 mmol, 1 equiv.) in 95% ethanol (40 ml) was added 10% Pd/C (0.1 g) and 50% hydrazine in water (1.6 ml, 25.6 mmol, 10 equiv.). The mixture was heated under reflux and nitrogen for 16 h. The solution was filtered through a celite bed and evaporated under reduced pressure. The residue was dissolved in diethyl ether, washed with water and dried over anhydrous  $\text{MgSO}_4$  to give pure green crystals of 6-aminochrysene (0.43 g, 1.7 mmol, 98 %); mp 208 - 210°C (lit. 209 - 211°C); spectral details match these reported;  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 3433, 3364 (N-H), 3050 (C-H, Aromatic), 1622 (C-N, Amine), 1573, 1440 (C=C, Aromatic);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 8.78 (1H, d,  $J_{\text{HH}}$  8.3 Hz, Ar), 8.62 (1H, d,  $J_{\text{HH}}$  8.3 Hz, Ar), 8.58 (1H, d,  $J_{\text{HH}}$  9.1 Hz, Ar), 7.98 (1H, d,  $J_{\text{HH}}$  8.3 Hz, Ar), 7.94 (1H, s, Ar), 7.90 (1H, dd,

$J_{\text{HH}}$  7.0, 1.2 Hz, Ar), 7.78 (1H, d,  $J_{\text{HH}}$  9.1 Hz, Ar), 7.70 (1H, td,  $J_{\text{HH}}$  7.0, 1.2 Hz, Ar), 7.55 - 7.66 (3H, m, Ar), 4.32 (2H, s, NH<sub>2</sub>);  $\delta_{\text{C}}$  (100MHz, CDCl<sub>3</sub>) 140.9 (C-NH<sub>2</sub>), 132.6 (C, quaternary), 131.5 (C, quaternary), 129.6 (C, quaternary), 129.5 (C, quaternary), 128.5 (Ar), 126.8 (Ar), 126.3 (Ar), 126.0 (Ar), 125.6 (Ar), 124.5 (C, quaternary), 123.9 (Ar), 123.2 (Ar), 122.9 (C, quaternary), 121.3 (Ar), 121.2 (2C, Ar), 103.4 (Ar);  $m/z$  (ESI) 244.1 ([M]<sup>+</sup>H); [Found: ([M]<sup>+</sup>H) 244.1129, C<sub>18</sub>H<sub>14</sub>N requires, 244.1121].

### 8.3.2 General Procedure for the Synthesis of Imines 172 – 180.

Aldehyde was dissolved in methanol in a round bottom flask equipped with a magnetic stirrer bar. Amine was also dissolved in methanol, added to the aldehyde mixture and heated under reflux for 24 hours. The resulting precipitate was then filtered and washed with cold methanol. The crude product was then purified by recrystallization using hot methanol / toluene mixture. The resulting pure product was then dried in a vacuum oven for 24 hours.

#### (*E*)-*N*-((1-fluoronaphthalen-2-yl)methylene)butan-1-amine.

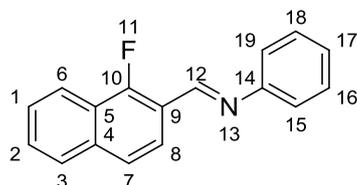


1-Fluoro-2-naphthaldehyde (**130**) (0.16 g, 0.92 mmol, 1.0 equiv.), *n*-butylamine (0.18 g, 1.84 mmol, 2.0 equiv.) and methanol (25 ml) was subject to the

general procedure (8.3.2) with no requirement to recrystallize, resulted with pure yellow oil (0.19 g, 0.83 mmol, 87 %);  $\nu_{\text{max}}$  (neat, cm<sup>-1</sup>) 3070 (C-H, Aromatic), ~2900

(C-H, Alkane), 1640 (C=N, Imine), 1577, 1434 (C=C, Aromatic), 1379 (C-N), 1065 (Ar-F);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 8.76 (1H, s,  $\text{H}_{12}$ ), 8.18 - 8.08 (1H, m,  $\text{H}_6$ ), 8.02 (1H, m,  $\text{H}_8$ ), 7.87 - 7.78 (1H, m,  $\text{H}_3$ ), 7.61 (1H, d,  $J_{\text{HH}}$  8.7 Hz,  $\text{H}_7$ ), 7.58 - 7.51 (2H, m,  $\text{H}_1\text{H}_2$ ), 3.70 (2H, t,  $J_{\text{HH}}$  7.0 Hz,  $\text{H}_{14}$ ), 1.73 (2H, m,  $\text{H}_{15}$ ), 1.42 (2H, m,  $\text{H}_{16}$ ), 0.97 (3H, t,  $J_{\text{HH}}$  7.4 Hz,  $\text{H}_{17}$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 158.60 (d,  $J_{\text{CF}}$  259.2 Hz,  $\text{C}_{10}$ , quaternary), 154.10 (d,  $J_{\text{CF}}$  5.5 Hz,  $\text{C}_{12}$ ), 135.85 (d,  $J_{\text{CF}}$  5.4 Hz,  $\text{C}_4$ , quaternary), 127.88 (s,  $\text{C}_2$ ), 127.64 (d,  $J_{\text{CF}}$  2.9 Hz,  $\text{C}_3$ ), 126.60 (d,  $J_{\text{CF}}$  1.5 Hz,  $\text{C}_1$ ), 123.77 (d,  $J_{\text{CF}}$  4.1 Hz,  $\text{C}_7$ ), 123.54 (d,  $J_{\text{CF}}$  16.1 Hz,  $\text{C}_5$ , quaternary), 123.23 (d,  $J_{\text{CF}}$  3.4 Hz,  $\text{C}_8$ ), 121.11 (d,  $J_{\text{CF}}$  6.2 Hz,  $\text{C}_6$ ), 118.50 (d,  $J_{\text{CF}}$  7.6 Hz,  $\text{C}_9$ , quaternary), 61.95 (s,  $\text{C}_{14}$ ), 33.08 (s,  $\text{C}_{15}$ ), 20.51 (s,  $\text{C}_{16}$ ), 13.94 (s,  $\text{C}_{17}$ );  $\delta_{\text{F}}$  (376MHz,  $\text{CDCl}_3$ ) -131.69 (1F, s,  $\text{F}_{11}$ );  $m/z$  (ESI) 230.1 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 230.1338,  $\text{C}_{15}\text{H}_{17}\text{FN}$  requires, 230.1340].

**(E)-N-((1-fluoronaphthalen-2-yl)methylene)aniline.**

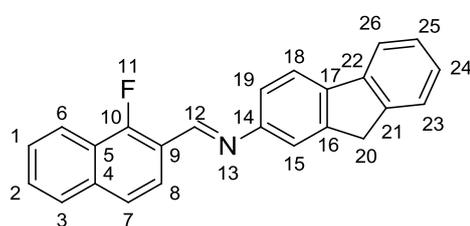


1-Fluoro-2-naphthaldehyde (**130**) (0.16 g, 0.92 mmol, 1.0 equiv.), aniline (0.084 ml, 0.92 mmol, 1.0 equiv.) and methanol (25 ml) was subject to the general

procedure (8.3.2), resulted in formation of pale yellow crystals (0.18 g, 0.72 mmol, 78 %); mpt. 52 – 54 °C;  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) ~3000 (C-H, Aromatic), 1614 (C=N, Imine), 1587, 1483 (C=C, Aromatic), 1377 (C-N), 1067 (Ar-F);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 8.99 (1H, s,  $\text{H}_{12}$ ), 8.27 – 8.13 (2H, m,  $\text{H}_6\text{H}_8$ ), 7.87 (1H, d,  $J_{\text{HH}}$  7.6 Hz,  $\text{H}_3$ ), 7.67 (1H, d,  $J_{\text{HH}}$  8.7 Hz,  $\text{H}_7$ ), 7.63 - 7.54 (2H, m,  $\text{H}_1\text{H}_2$ ), 7.46 - 7.39 (2H, m,  $\text{H}_{15}\text{H}_{19}$ ), 7.34-7.21 (3H, m,  $\text{H}_{16}\text{H}_{17}\text{H}_{18}$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 159.8 (d,  $J_{\text{CF}}$  261.5 Hz,  $\text{C}_{10}$ ), 153.5 (d,  $J_{\text{CF}}$  5.9 Hz,  $\text{C}_{12}$ ), 152.2 (s,  $\text{C}_{14}$ , quaternary), 136.4 (d,  $J_{\text{CF}}$  5.7 Hz,  $\text{C}_4$ , quaternary), 129.2 (2C, s,  $\text{C}_{15}\text{C}_{19}$ ), 128.4 (s,  $\text{C}_1$ ), 127.8 (d,  $J_{\text{CF}}$  2.8 Hz,  $\text{C}_3$ ), 126.8 (s,

C<sub>2</sub>), 126.3 (s, C<sub>17</sub>), 124.0 (d,  $J_{CF}$  4.0 Hz, C<sub>7</sub>), 123.5 (d,  $J_{CF}$  16.3 Hz, C<sub>5</sub>, quaternary), 123.1 (d,  $J_{CF}$  2.9 Hz, C<sub>8</sub>), 121.4 (d,  $J_{CF}$  6.2 Hz, C<sub>6</sub>), 121.1 (2C, s, C<sub>16</sub>C<sub>18</sub>), 118.7 (d,  $J_{CF}$  7.5 Hz, C<sub>9</sub>, quaternary);  $\delta_F$  (376MHz, CDCl<sub>3</sub>) -130.11 (1F, s, F<sub>11</sub>);  $m/z$  (ESI) 250.1 ([M]<sup>+</sup>H); [Found: ([M]<sup>+</sup>H) 250.1035, C<sub>17</sub>H<sub>13</sub>FN requires, 250.1027].

**(E)-N-((1-fluoronaphthalen-2-yl)methylene)-9H-fluoren-2-amine (172)**

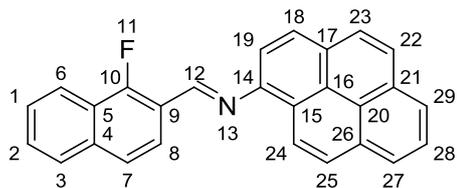


1-Fluoro-2-naphthaldehyde (**130**) (0.087 g, 0.50 mmol, 1.0 equiv.), 2-aminofluorene (**147**) (0.091 g, 0.50 mmol, 1.0 equiv.) and methanol (10 ml) was subject to the general

procedure (8.3.2), resulted in formation of pale yellow crystals (0.14 g, 0.40 mmol, 81 %); mpt. 184 – 186 °C;  $\lambda_{max}$  249, 356;  $\nu_{max}$  (neat, cm<sup>-1</sup>) 3053 (C-H, Aromatic), ~2900 (C-H, Alkane), 1600 (C=N, Imine), 1572, 1453 (C=C, Aromatic), 1379 (C-N), 1066 (Ar-F);  $\delta_H$  (500MHz, CDCl<sub>3</sub>) 9.12 (1H, s, H<sub>12</sub>), 8.34 - 8.28 (1H, m, H<sub>8</sub>), 8.23 (1H, d,  $J_{HH}$  7.4 Hz, H<sub>6</sub>), 7.90 (1H, d,  $J_{HH}$  7.4 Hz, H<sub>3</sub>), 7.85 (1H, d,  $J_{HH}$  8.0 Hz, H<sub>18</sub>), 7.82 (1H, d,  $J_{HH}$  7.5 Hz, H<sub>26</sub>), 7.72 (1H, d,  $J_{HH}$  8.6 Hz, H<sub>7</sub>), 7.67-7.61 (2H, m, H<sub>1</sub>, H<sub>2</sub>), 7.59 (1H, d,  $J_{HH}$  7.5 Hz, H<sub>23</sub>), 7.54 (1H, s, H<sub>15</sub>), 7.43 (1H, t,  $J_{HH}$  7.5 Hz, H<sub>25</sub>), 7.40 (1H, d,  $J_{HH}$  8.0 Hz, H<sub>19</sub>), 7.35 (1H, t,  $J_{HH}$  7.5 Hz, H<sub>24</sub>), 3.98 (1H, s, H<sub>20</sub>);  $\delta_C$  (126MHz, CDCl<sub>3</sub>) 159.7 (d,  $J_{CF}$  261.3 Hz, C<sub>10</sub>), 152.5 (d,  $J_{CF}$  5.6 Hz, C<sub>12</sub>), 150.9 (C<sub>14</sub>, quaternary), 144.5 (C<sub>17</sub>, quaternary), 143.5 (C<sub>22</sub>, quaternary), 141.4 (C<sub>21</sub>, quaternary), 140.3 (C<sub>16</sub>, quaternary), 136.3 (d,  $J_{CF}$  5.6 Hz, C<sub>4</sub>, quaternary), 128.4 (C<sub>2</sub>), 127.8 (C<sub>3</sub>), 126.9 (C<sub>1</sub>), 126.8 (C<sub>25</sub>), 126.6 (C<sub>24</sub>), 125.1 (C<sub>23</sub>), 124.0 (d,  $J_{CF}$  3.8 Hz, C<sub>7</sub>), 123.5 (d,  $J_{CF}$  16.4 Hz, C<sub>5</sub>, quaternary), 123.1 (d,  $J_{CF}$  2.6 Hz, C<sub>8</sub>), 121.3 (d,  $J_{CF}$  6.1 Hz, C<sub>6</sub>), 120.5 (C<sub>18</sub>), 120.4 (C<sub>26</sub>), 119.8 (C<sub>19</sub>), 118.9 (d,  $J_{CF}$  7.3 Hz, C<sub>9</sub>,

quaternary), 117.7 (C<sub>15</sub>), 37.0 (2H, C<sub>20</sub>);  $\delta_F$  (470MHz, CDCl<sub>3</sub>) -130.17 (1F, s Ar-F<sub>11</sub>);  $m/z$  (ESI) 338.1 ([M]<sup>+</sup>H); [Found: ([M]<sup>+</sup>H) 338.1348, C<sub>24</sub>H<sub>17</sub>FN requires, 338.1340].

**(E)-N-((1-fluoronaphthalen-2-yl)methylene)pyren-1-amine (173)**

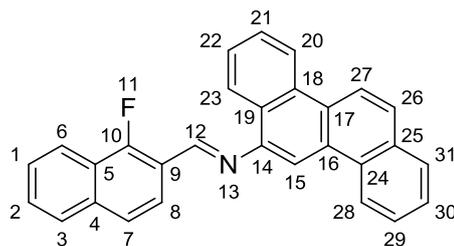


1-Fluoro-2-naphthaldehyde (**130**) (0.040 g, 0.23 mmol, 1.0 equiv.), 1-aminopyrene (**148**) (0.050 g, 0.23 mmol, 1.0 equiv.) and methanol (10 ml) was subject to the general procedure

(8.3.2), resulted in formation of dark yellow crystals (0.044 g, 0.12 mmol, 51 %); mpt. 172 – 174 °C;  $\lambda_{\max}$  282, 364, 384;  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 3042 (C-H, Aromatic), ~2900 (C-H, Alkane), 1615 (C=N, Imine), 1577 (C=C, Aromatic), 1377 (C-N), 1064 (Ar-F);  $\delta_H$  (500MHz, CDCl<sub>3</sub>) 9.26 (1H, s, H<sub>12</sub>), 8.76 (1H, d,  $J_{HH}$  9.1 Hz, Ar), 8.56 - 8.48 (1H, m, H<sub>8</sub>), 8.23 (1H, d,  $J_{HH}$  7.3 Hz, H<sub>3</sub>), 8.21 – 8.16 (3H, m, Ar), 8.13 (1H, d,  $J_{HH}$  9.1 Hz, Ar), 8.09 – 7.96 (3H, m, Ar), 7.92 (1H, d,  $J_{HH}$  7.3 Hz, H<sub>6</sub>), 7.83 (1H, d,  $J_{HH}$  8.1 Hz, Ar), 7.77 (1H, d,  $J_{HH}$  8.6 Hz, H<sub>7</sub>), 7.67 – 7.58 (2H, m, H<sub>1</sub>, H<sub>2</sub>);  $\delta_C$  (126MHz, CDCl<sub>3</sub>) 159.9 (d,  $J_{CF}$  261.8 Hz, C<sub>10</sub>), 153.6 (d,  $J_{CF}$  5.7 Hz, C<sub>12</sub>), 145.6 (s, C<sub>14</sub>, quaternary), 136.4 (d,  $J_{CF}$  5.5 Hz, C<sub>4</sub>, quaternary), 131.6 (s, Ar, quaternary), 131.5 (s, Ar, quaternary), 129.9 (s, Ar, quaternary), 128.5 (s, C<sub>2</sub>), 127.8 (d,  $J_{CF}$  2.6 Hz, C<sub>6</sub>), 127.3 (s, C<sub>1</sub>), 127.2 (s, Ar), 126.8 (2H, s, Ar), 126.1 (s, Ar), 125.8 (s, Ar, quaternary), 125.6 (s, Ar), 125.3 (s, Ar, quaternary), 125.1 (s, Ar), 125.0 (s, Ar), 124.9 (s, Ar, quaternary), 124.1 (d,  $J_{CF}$  3.8 Hz, C<sub>7</sub>), 123.6 (d,  $J_{CF}$  15.9 Hz, C<sub>5</sub>, quaternary), 123.3 (s, Ar), 123.27 (d,  $J_{CF}$  2.8 Hz, C<sub>8</sub>), 121.4 (d,  $J_{CF}$  6.1 Hz, C<sub>3</sub>), 119.2 (d,  $J_{CF}$  7.2 Hz, C<sub>9</sub>, quaternary), 115.3 (s, Ar);  $\delta_F$  (470MHz, CDCl<sub>3</sub>) -130.05 (1F, s

Ar-F<sub>11</sub>);  $m/z$  (ESI) 374.1 ( $[M]^+H$ ); [Found: ( $[M]^+H$ ) 374.1334, C<sub>27</sub>H<sub>17</sub>FN requires, 374.1340].

**(*E*)-*N*-((1-fluoronaphthalen-2-yl)methylene)chrysen-6-amine (174)**

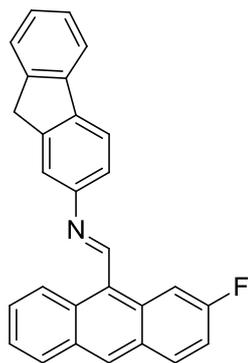


1-Fluoro-2-naphthaldehyde (**130**) (0.040 g, 0.23 mmol, 1.0 equiv.), 6-aminochrysen-6-amine (**149**) (0.056 g, 0.23 mmol, 1.0 equiv.) and methanol (10 ml) was subject to the general procedure (8.3.2), resulted in formation of bright yellow

crystals (0.048 g, 0.12 mmol, 52 %); mpt. 225 – 227 °C;  $\lambda_{\max}$  266, 360;  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 3068 (C-H, Aromatic), ~2900 (C-H, Alkane), 1611 (C=N, Imine), 1572 (C=C, Aromatic), 1378 (C-N), 1069 (Ar-F);  $\delta_H$  (500MHz, Tol) 9.20 (1H, s, H<sub>12</sub>), 8.80 (1H, dd,  $J$  6.3, 3.2 Hz, Ar), 8.63 – 8.58 (2H, m, Ar), 8.52 (1H, d,  $J$  9.0 Hz, Ar), 8.48 (1H, dd,  $J$  6.0, 3.4 Hz, H<sub>6</sub>), 8.17 (1H, s, H<sub>15</sub>), 8.14 – 8.08 (1H, m, Ar), 7.81 (1H, dd,  $J_{HH}$  6.0, 3.4 Hz, H<sub>3</sub>), 7.79 (1H, d,  $J$  9.0 Hz, Ar), 7.60 – 7.56 (2H, m, Ar), 7.55 – 7.50 (1H, m, Ar), 7.45 (3H, m, H<sub>1</sub>, H<sub>2</sub>, H<sub>7</sub>), 7.27 – 7.23 (2H, m, Ar);  $\delta_C$  (126MHz, Tol) 159.9 (d,  $J_{CF}$  261.0 Hz, C<sub>10</sub>), 152.8 (d,  $J_{CF}$  5.2 Hz, C<sub>12</sub>), 148.9 (s, Ar, quaternary), 136.5 (d,  $J_{CF}$  5.3 Hz, C<sub>4</sub>, quaternary), 132.6 (s, Ar, quaternary), 131.3 (s, Ar, quaternary), 131.0 (s, Ar, quaternary), 129.0 (s, Ar, quaternary), 128.8 (s, Ar), 128.2 (s, Ar), 128.0 (s, Ar, quaternary), 127.8 (s, Ar), 127.1 (s, Ar), 126.7 (s, Ar), 126.5 (s, Ar), 126.3 (s, Ar), 126.2 (s, Ar), 126.1 (s, Ar), 125.0 (s, Ar), 124.1 (d,  $J_{CF}$  3.5 Hz, C<sub>7</sub>), 123.7 (d,  $J_{CF}$  16.4 Hz, C<sub>5</sub>, quaternary), 123.5 (d,  $J_{CF}$  2.0 Hz, C<sub>8</sub>), 123.3 (s, Ar), 123.1 (s, Ar), 121.2 (2C, m, Ar), 119.3 (d,  $J_{CF}$  7.4 Hz, C<sub>9</sub>, quaternary), 111.2 (s, Ar,

quaternary), 107.2 (s, Ar);  $\delta_F$  (470MHz,  $CDCl_3$ ) -129.90 (1F, s Ar-F<sub>11</sub>);  $m/z$  (ESI) 422.1 ( $[M]^+Na$ ); [Found: ( $[M]^+Na$ ) 422.1308,  $C_{29}H_{18}FNNa$  requires, 422.1315].

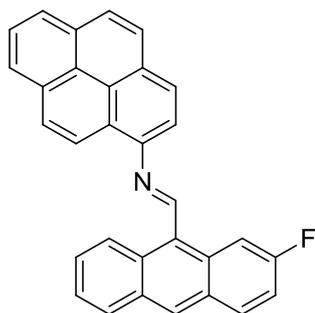
**(E)-N-((2-fluoroanthracen-9-yl)methylene)-9H-fluoren-2-amine (175)**



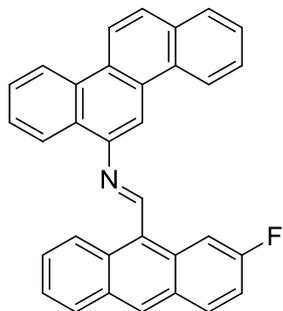
2-Fluoroanthracene-9-carbaldehyde (**165**) (0.06 g, 0.26 mmol, 1.0 equiv.), 2-aminofluorene (**147**) (0.048 g, 0.26 mmol, 1.0 equiv.) and methanol (10 ml) was subject to the general procedure (8.3.2), resulted in formation of orange crystals (0.06 g, 0.15 mmol, 58 %); mpt. 211 – 213 °C;  $\lambda_{max}$  261, 312, 408;  $\nu_{max}$  (neat,  $cm^{-1}$ ) ~3000 (C-H, Aromatic), 1623 (C=N, Imine), 1577, 1487 (C=C, Aromatic), 1364 (C-N), 1062 (Ar-F);  $\delta_H$  (500MHz,  $CDCl_3$ ) 9.71 (1H, s, imine), 8.71 (1H, d,  $J$  8.9 Hz, Ar), 8.65 (1H, dd,  $J$  12.3, 2.1 Hz, Ar), 8.55 (1H, s, Ar), 8.06 (1H, d,  $J$  9.1 Hz, Ar), 8.04 (1H, d,  $J$  8.7 Hz, Ar), 8.77 (1H, d,  $J$  8.0 Hz, Ar), 7.83 (1H, d,  $J$  7.5 Hz, Ar), 7.64 – 7.56 (3H, m, Ar), 7.55 – 7.50 (1H, m, Ar), 7.47 (1H, d,  $J$  8.7 Hz, Ar), 7.41 (1H, t,  $J$  7.5 Hz, Ar), 7.36 – 7.31 (2H, m, Ar), 4.00 (2H, s,  $CH_2$ );  $\delta_C$  (126MHz,  $CDCl_3$ ) 161.7 (d,  $J_{CF}$  248.5 Hz, C-F), 158.4 (s, imine), 151.4 (s, Ar, quaternary), 144.6 (s, Ar, quaternary), 143.5 (s, Ar, quaternary), 141.4 (s, Ar, quaternary), 140.4 (s, Ar, quaternary), 131.8 (d,  $J_{CF}$  9.4 Hz, Ar), 131.6 (s, Ar, quaternary), 131.1 (s, Ar), 131.0 (s, Ar, quaternary), 130.8 (d,  $J_{CF}$  1.3 Hz, Ar, quaternary), 129.3 (s, Ar), 128.9 (s, Ar, quaternary), 127.9 (s, Ar), 126.9 (s, Ar), 126.7 (s, Ar), 126.5 (d,  $J_{CF}$  7.8 Hz, Ar, quaternary), 125.4 (s, Ar), 125.1 (s, Ar), 124.1 (s, Ar), 120.5 (s, Ar), 120.4 (s, Ar), 119.9 (s, Ar), 117.7 (s, Ar), 117.4 (d,  $J_{CF}$  27.8 Hz, Ar), 107.9 (d,  $J_{CF}$  23.5 Hz, Ar), 37.1 (s,  $CH_2$ );  $\delta_F$  (470MHz,  $CDCl_3$ ) -109.96

(1F, s Ar-F);  $m/z$  (ESI) 388 ( $[M]^+H$ ); [Found: ( $[M]^+H$ ) 388.1503,  $C_{28}H_{19}FN$  requires, 388.1496].

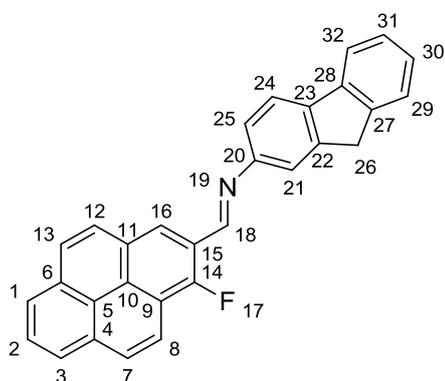
**(E)-N-((2-fluoroanthracen-9-yl)methylene)-4,6-dihydropyren-1-amine (176)**



2-Fluoroanthracene-9-carbaldehyde (**165**) (0.06 g, 0.26 mmol, 1.0 equiv.), 1-aminopyrene (**148**) (0.058 g, 0.26 mmol, 1.0 equiv.) and methanol (10 ml) was subject to the general procedure (8.3.2), resulted in formation of dark green crystals (0.049 g, 0.12 mmol, 45 %); mpt. 200 – 202 °C;  $\lambda_{max}$  240, 259, 351, 422;  $\nu_{max}$  (neat,  $cm^{-1}$ ) ~3000 (C-H, Aromatic), 1644 (C=N, Imine), ~1500 (C=C, Aromatic), 1355 (C-N), 1056 (Ar-F);  $\delta_H$  (500MHz,  $CDCl_3$ ) 9.69 (1H, s, imine), 9.09 (1H, dd,  $J$  12.6, 1.9 Hz, Ar), 8.87 (2H, t,  $J$  8.7 Hz, Ar), 8.16 (1H, s, Ar), 8.00 (1H, d,  $J$  8.1 Hz, Ar), 7.95 (1H, d,  $J$  7.6 Hz, Ar), 7.94 – 7.87 (3H, m, Ar), 7.84 (1H, d,  $J$  8.7 Hz, Ar), 7.77 (2H, t,  $J$  7.6 Hz, Ar), 7.67 – 7.65 (2H, m, Ar), 7.40 – 7.36 (1H, m, Ar), 7.30 – 7.26 (1H, m, Ar), 7.12 – 7.08 (1H, m, Ar);  $\delta_C$  (126MHz,  $CDCl_3$ ) 158.9 (s, imine), 131.6 (s, Ar), 131.5 (s, Ar), 131.2 (s, Ar), 129.1 (s, Ar), 127.8 (s, Ar), 127.5 (s, Ar), 127.3 (s, Ar), 127.1 (s, Ar), 126.7 (s, Ar), 125.8 (s, Ar), 125.4 (s, Ar), 124.9 (s, Ar), 124.7 (s, Ar), 124.3 (s, Ar), 123.5 (s, Ar), 116.9 (d,  $J_{CF}$  28.1 Hz, Ar), 108.4 (d,  $J_{CF}$  23.8 Hz, Ar);  $\delta_F$  (470MHz,  $CDCl_3$ ) -109.64 (1F, s Ar-F);  $m/z$  (ESI) 424.1 ( $[M]^+H$ ); [Found: ( $[M]^+H$ ) 424.1495,  $C_{31}H_{19}FN$  requires, 424.1496].

**(E)-N-((2-fluoroanthracen-9-yl)methylene)chrysen-6-amine (177)**

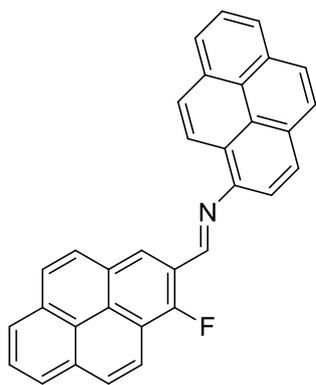
2-Fluoroanthracene-9-carbaldehyde (**165**) (0.06 g, 0.26 mmol, 1.0 equiv.), 6-aminochrysen (**149**) (0.065 g, 0.26 mmol, 1.0 equiv.) and methanol (10 ml) was subject to the general procedure (8.3.2), resulted in formation of brick red crystals (0.063 g, 0.14 mmol, 54 %); mpt. 279 – 281 °C;  $\lambda_{\max}$  261, 353, 411;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3020 (C-H, Aromatic), 1634 (C=N, Imine), 1580, 1488 (C=C, Aromatic), 1380 (C-N), 1072 (Ar-F);  $\delta_{\text{H}}$  (500MHz,  $\text{CDCl}_3$ ) 9.75 (1H, s, imine), 9.09 (1H, dd,  $J$  12.6, 2.2 Hz, Ar), 8.85 (1H, d,  $J$  9.0 Hz, Ar), 8.68 (1H, d,  $J$  7.8 Hz, Ar), 8.61 (1H, d,  $J$  8.4 Hz, Ar), 8.58 (1H, d,  $J$  8.4 Hz, Ar), 8.52 (1H, d,  $J$  9.0 Hz, Ar), 8.25 (1H, s, Ar), 8.16 (1H, s, Ar), 7.83 – 7.73 (3H, m, Ar), 7.63 (1H, dd,  $J$  9.2, 6.2 Hz, Ar), 7.52 (1H, t,  $J$  7.8 Hz, Ar), 7.48 – 7.38 (3H, m, Ar), 7.35 – 7.30 (1H, m, Ar), 7.26 – 7.22 (1H, m, Ar), 7.08 – 7.05 (1H, m, Ar);  $\delta_{\text{C}}$  (126MHz,  $\text{CDCl}_3$ ) 161.9 (d,  $J_{\text{CF}}$  248.9 Hz, C-F), 158.4 (s, imine), 149.7 (s, Ar, quaternary), 137.1 (s, Ar, quaternary), 132.6 (s, Ar, quaternary), 132.2 (s, Ar, quaternary), 131.7 (s, Ar, quaternary), 131.6 (s, Ar, quaternary), 131.5 (s, Ar, quaternary), 131.4 (d,  $J_{\text{CF}}$  10.0 Hz, Ar), 131.4 (s, Ar, quaternary), 130.9 (s, Ar, quaternary), 130.8 (s, Ar, quaternary), 128.9 (s, Ar), 128.7 (s, Ar), 128.5 (s, Ar), 128.3 (s, Ar), 127.5 (s, Ar, quaternary), 127.5 (s, Ar), 127.0 (s, Ar, quaternary), 126.8 (s, Ar), 126.2 (s, Ar), 126.1 (s, Ar), 126.0 (s, Ar), 125.9 (s, Ar), 124.8 (s, Ar), 124.1 (s, Ar), 123.0 (s, Ar), 122.9 (s, Ar), 121.0 (s, Ar), 116.8 (d,  $J_{\text{CF}}$  27.9 Hz, Ar), 108.2 (d,  $J_{\text{CF}}$  23.9 Hz, Ar), 106.8 (s, Ar);  $\delta_{\text{F}}$  (470MHz,  $\text{CDCl}_3$ ) -109.52 (1F, s Ar-F);  $m/z$  (ESI) 450 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 450.1654,  $\text{C}_{33}\text{H}_{21}\text{FN}$  requires, 450.1653].

**(E)-N-((1-fluoropyren-2-yl)methylene)-9H-fluoren-2-amine (178)**

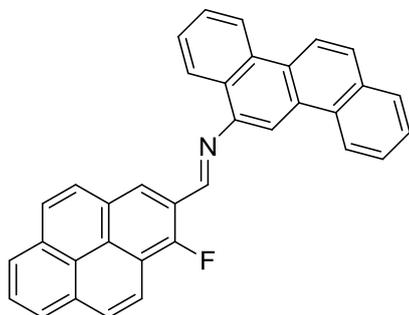
1-Fluoropyrene-2-carbaldehyde (**132**) (0.10 g, 0.40 mmol, 1.0 equiv.), 2-aminofluorene (**147**) (0.072 g, 0.40 mmol, 1.0 equiv.) and methanol (10 ml) was subject to the general procedure (8.3.2), resulted in formation of greenish crystals (0.15 g, 0.36 mmol, 91 %); mpt. 240 – 242 °C;  $\lambda_{\max}$  260, 288, 353, 339, 356;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3043 (C-H, Aromatic), 2899 (C-H, Alkane), 1620 (C=N, Imine), 1586, 1478 (C=C, Aromatic), 1376 (C-N), 1200 (Ar-F);  $\delta_{\text{H}}$  (500MHz, Tol) 9.26 (1H, s, H<sub>18</sub>), 9.04 (1 H, d,  $J_{\text{HF}}$  6.8 Hz, H<sub>16</sub>), 8.21 (1 H, d,  $J_{\text{HH}}$  9.0 Hz, Ar), 7.83 (2 H, m, H<sub>1</sub>, H<sub>3</sub>), 7.79 (1H, d,  $J_{\text{HH}}$  9.0 Hz, Ar), 7.77 (1H, d,  $J_{\text{HH}}$  9.0 Hz, Ar), 7.70 (1 H, t,  $J_{\text{HH}}$  7.6 Hz, H<sub>2</sub>), 7.67 (1 H, d,  $J_{\text{HH}}$  9.0 Hz, Ar), 7.64 (1 H, d,  $J_{\text{HH}}$  8.0 Hz, H<sub>24</sub>), 7.61 (1 H, d,  $J_{\text{HH}}$  7.5 Hz, H<sub>32</sub>), 7.41 (1 H, d,  $J_{\text{HH}}$  0.9 Hz, H<sub>21</sub>), 7.37 (1 H, dd,  $J_{\text{HH}}$  8.0, 1.9 Hz, H<sub>25</sub>), 7.29 (1 H, d,  $J_{\text{HH}}$  7.5 Hz, H<sub>29</sub>), 7.22 (1 H, td,  $J_{\text{HH}}$  7.5, 1.0 Hz, H<sub>31</sub>), 7.13 (1 H, td,  $J_{\text{HH}}$  7.5, 1.0 Hz, H<sub>30</sub>), 3.60 (2 H, s, H<sub>26</sub>);  $\delta_{\text{C}}$  (126MHz, Tol) 156.8 (d,  $J_{\text{CF}}$  257.5 Hz, C<sub>14</sub>), 151.9 (d,  $J_{\text{CF}}$  5.6 Hz, C<sub>18</sub>), 151.3 (s, Ar, quaternary), 144.5 (s, Ar, quaternary), 143.4 (s, Ar, quaternary), 141.6 (s, Ar, quaternary), 140.5 (s, Ar, quaternary), 136.8 (d,  $J_{\text{CF}}$  9.8 Hz, Ar, quaternary), 131.8 (s, Ar, quaternary), 131.7 (s, Ar, quaternary), 128.0 (d,  $J_{\text{CF}}$  2.3 Hz, Ar), 127.9 (d,  $J_{\text{CF}}$  2.7 Hz, Ar, quaternary), 127.7 (s, Ar), 126.8 (d,  $J_{\text{CF}}$  2.4 Hz, Ar), 126.7 (s, Ar), 126.6 (s, Ar), 126.3 (s, Ar), 125.2 (d,  $J_{\text{CF}}$  1.7 Hz, Ar), 125.0 (d,  $J_{\text{CF}}$  0.9 Hz, Ar), 124.7 (s, Ar), 124.1 (d,  $J_{\text{CF}}$  4.1 Hz, Ar, quaternary), 123.2 (d,  $J_{\text{CF}}$  2.7 Hz, Ar), 121.6 (d,  $J_{\text{CF}}$  9.9 Hz, Ar, quaternary), 120.4 (s, Ar), 120.2 (s, Ar), 119.6 (s, Ar), 119.2 (d,  $J_{\text{CF}}$  15.2 Hz, Ar, quaternary), 119.0 (d,  $J_{\text{CF}}$  5.7 Hz, Ar), 117.6 (s, Ar), 36.7 (s, C<sub>26</sub>);  $\delta_{\text{F}}$  (470MHz,

CDCl<sub>3</sub>) -132.61 (1F, s Ar-F<sub>17</sub>); *m/z* (ESI) 412.1 ([M]<sup>+</sup>H); [Found: ([M]<sup>+</sup>H) 412.1510, C<sub>30</sub>H<sub>19</sub>FN requires, 412.1496].

**(E)-N-((1-fluoropyren-2-yl)methylene)-4,6-dihydropyren-1-amine (179)**



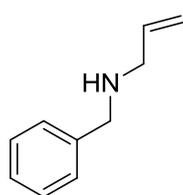
1-Fluoropyrene-2-carbaldehyde (**132**) (0.057 g, 0.23 mmol, 1.0 equiv.), 1-aminopyrene (**148**) (0.050 g, 0.23 mmol, 1.0 equiv.) and methanol (10 ml) was subject to the general procedure (8.3.2), resulted in formation of dark green crystals (0.053 g, 0.12 mmol, 53 %) difficulty with further purification, NMR showed minor aldehyde SM; mpt. 252 – 254 °C;  $\lambda_{\max}$  289, 324, 339, 384, 415;  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 3043 (C-H, Aromatic), 1615 (C=N, Imine), 1583, 1476 (C=C, Aromatic), 1378 (C-N), 1195 (Ar-F);  $\delta_{\text{H}}$  (500MHz, Tol) 9.35 (1H, s, imine), 9.17 (1 H, d, *J* 6.8 Hz, Ar), 8.95 (1 H, d, *J* 9.2 Hz, Ar), 8.23 (1 H, d, *J* 9.0 Hz, Ar), 7.97 (1 H, d, *J* 9.2 Hz, Ar), 7.95 – 7.91 (3 H, m, Ar), 7.88 – 7.78 (6 H, m, Ar), 7.76 (1 H, d, *J* 7.6 Hz, Ar), 7.74 – 7.70 (2 H, m, Ar), 7.64 (1 H, d, *J* 8.1 Hz, Ar);  $\delta_{\text{C}}$  (126MHz, Tol) 156.9 (d, *J*<sub>CF</sub> 257.7 Hz), 153.5 (d, *J*<sub>CF</sub> 5.4 Hz, Imine), 128.6 (s, Ar), 127.7 (s, Ar), 127.1 (s, Ar), 127.0 (s, Ar), 126.9 (d, *J*<sub>CF</sub> 2.0 Hz, Ar), 126.8 (s, Ar), 126.7 (s, Ar), 125.8 (s, Ar), 125.4 (s, Ar), 125.3 (s, Ar), 125.1 (s, Ar), 124.9 (s, Ar), 124.8 (s, Ar), 123.5 (s, Ar), 123.2 (d, *J*<sub>CF</sub> 2.5 Hz, Ar), 119.1 (d, *J*<sub>CF</sub> 5.6 Hz, Ar), 115.0 (s, Ar);  $\delta_{\text{F}}$  (470MHz, CDCl<sub>3</sub>) -132.14 (1F, s Ar-F); [Found: C, 87.35; H, 4.07; N, 3.25, C<sub>33</sub>H<sub>18</sub>FN requires: C, 88.57; H, 4.05; N, 3.13].

**(E)-N-((1-fluoropyren-2-yl)methylene)chrysen-6-amine (180)**

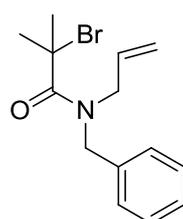
1-Fluoropyrene-2-carbaldehyde (**132**) (0.10 g, 0.40 mmol, 1.0 equiv.), 6-aminochrysene (**149**) (0.098 g, 0.40 mmol, 1.0 equiv.) and methanol (10 ml) was subject to the general procedure (8.3.2), resulted in formation of bright yellow crystals

(0.12 g, 0.25 mmol, 62 %) difficulty with further purification, NMR showed minor aldehyde SM;  $\lambda_{\max}$  265, 280, 323, 339;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3043 (C-H, Aromatic), 1617 (C=N, Imine), 1583, 1477 (C=C, Aromatic), 1378 (C-N), 1195 (Ar-F);  $\delta_{\text{H}}$  (500MHz, Tol) 9.40 (1H, s, imine), 9.17 (1H, d,  $J$  6.7 Hz, Ar), 8.81 – 8.77 (1H, m, Ar), 8.63 – 8.59 (1H, m, Ar), 8.56 (1H, d,  $J$  8.1 Hz, Ar), 8.51 (1H, d,  $J$  9.1 Hz, Ar), 8.26 (1H, s, Ar), 8.25 (1H, d,  $J$  9.8 Hz, Ar), 7.86 (2H, d,  $J$  7.6 Hz, Ar), 7.83 (1H, d,  $J$  8.7 Hz, Ar), 7.82 (1H, d,  $J$  8.7 Hz, Ar), 7.80 – 7.75 (2H, m, Ar), 7.73 (2H, t,  $J$  8.1 Hz, Ar), 7.58 – 7.53 (2H, m, Ar), 7.47 – 7.38 (2H, m, Ar);  $\delta_{\text{C}}$  (126MHz, Tol) 153.5 (d,  $J_{\text{CF}}$  5.4 Hz, imine), 128.7 (2C, s, Ar), 127.7 (2C, s, Ar), 127.0 (s, Ar), 126.9 (s, Ar), 126.8 (s, Ar), 126.4 (s, Ar), 126.2 (s, Ar), 126.1 (s, Ar), 126.0 (s, Ar), 125.3 (d,  $J_{\text{CF}}$  28.6 Hz, Ar), 124.9 (s, Ar), 123.4 (d,  $J_{\text{CF}}$  2.7 Hz, Ar), 123.2 (s, Ar), 123.1 (s, Ar), 121.1 (s, Ar), 119.1 (d,  $J_{\text{CF}}$  5.8 Hz, Ar), 107.1 (s, Ar);  $\delta_{\text{F}}$  (470MHz,  $\text{CDCl}_3$ ) -131.70 (1F, s Ar-F); [Found: C, 87.68; H, 4.36; N, 2.79,  $\text{C}_{35}\text{H}_{20}\text{FN}$  requires: C, 88.77; H, 4.26; N, 2.96].

## 8.4 Substrates Synthesized In Chapter 5

***N*-benzylprop-2-en-1-amine (211)**<sup>126</sup>

Allyl amine (3.34 g, 58.5 mmol) and  $K_2CO_3$  (8.08 g, 58.5 mmol) was placed in dry dichloromethane (150 ml) in a 250 ml round bottom flask. The mixture was cooled to  $0^\circ C$  under nitrogen. Benzyl bromide (10.0 g, 58.5 mmol) was added drop wise to the mixture and stirred overnight at room temperature under nitrogen. The mixture was filtered through celite, washed with dichloromethane, evaporated and purified by column chromatography, eluting in 10% EtOAc in petroleum ether to yield pale yellow oil (1.09 g, 7.4 mmol, 13%).  $R_f$  (50% EtOAc/petrol) 0.90; spectral details match these reported;  $\delta_H$  (300MHz,  $CDCl_3$ ) 7.24 - 7.37 (5H, m, Ar), 5.97 (1H, ddt,  $J_{HH}$  17.0, 10.2, 6.0 Hz,  $\underline{CH=CH_2}$ ), 5.23 (1H, ddt,  $J_{HH}$  17.0, 1.5, 1.2 Hz,  $CH=\underline{CH_2}$ ), 5.15 (1H, ddt,  $J_{HH}$  10.2, 1.5, 1.2 Hz,  $CH=\underline{CH_2}$ ), 3.83 (2H, s, Ar- $\underline{CH_2}$ ), 3.32 (2H, dt,  $J_{HH}$  6.0, 1.2 Hz, N- $\underline{CH_2}CH$ ), 1.49 (1H, s,  $\underline{NH}$ );  $\delta_C$  (75MHz,  $CDCl_3$ ) 139.5 (Ar, quaternary), 135.8 ( $\underline{CH=CH_2}$ ), 128.6 (Ar), 128.0 (Ar), 126.7 (Ar), 117.2 ( $CH=\underline{CH_2}$ ), 57.7 (N- $\underline{CH_2}CH$ ), 56.2 ( $CH=\underline{CH_2}$ ).

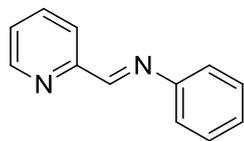
***N*-allyl-*N*-benzyl-2-bromo-2-methylpropanamide (205)**<sup>127</sup>

*N*-benzylprop-2-en-1-amine (1.09 g, 7.41 mmol) was dissolved in diethyl ether (100 ml) and cooled to  $0^\circ C$ . Triethylamine (0.81 g, 8.00 mmol) was added to the reaction and stirred for 30 min. 2-

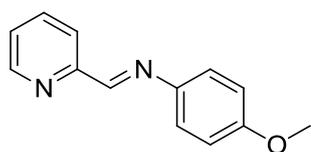
Bromoisobutyryl bromide (1.84 g, 8.00 mmol) was added drop wise to the reaction mixture and stirred for 4 hours at room temperature. The reaction was quenched with saturated  $\text{NH}_4\text{Cl}$  (20 ml), washed with water (3 x 50 ml), dilute HCl (2 x 20 ml), 1 mol  $\text{NaHCO}_3$  solution (2 x 20 ml). The organic layer was dried over magnesium sulphate, filtered and evaporated. Pale yellow oil was obtained (2.01 g, 6.8 mmol, 92%); spectral details match these reported;  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 3000 (C-H), 1632 (C=O, ketone), ~700 (C-Br);  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.35 (5H, m, Ar), 5.83 (1H, br,  $\text{CH}$ ), 5.25 (1H, dd,  $J_{\text{HH}}$  10.3, 1.4 Hz,  $\text{CH}=\text{CH}_2$ ), 5.16 (1H, br d,  $J_{\text{HH}}$  17.9 Hz,  $\text{CH}=\text{CH}_2$ ), 4.92 (2H, br, Ar- $\text{CH}_2$ ), 4.24 (2H, br, N- $\text{CH}_2$ ), 2.08 (6H, s,  $\text{C}(\text{CH}_3)_2\text{Br}$ );  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ), 170.0 ( $\text{C}=\text{O}$ ), 136.3 (Ar, quaternary), 132.3 ( $\text{CH}=\text{CH}_2$ ), 128.1 (Ar), 127.8 (Ar), 126.7 (Ar), 115.6 ( $\text{CH}=\text{CH}_2$ ), 65.2 ( $\text{C}(\text{CH}_3)_2\text{Br}$ ), 56.6 (N- $\text{CH}_2$ ), 48.3 (Ar- $\text{CH}_2$ ), 32.0 ( $\text{CH}_3$ ), 31.8 ( $\text{CH}_3$ ).

#### 8.4.1 General Procedure for the Synthesis of Bi-dentate Imine Ligands for ATRC Reactions

Amine was dissolved in dichloromethane in a round bottom flask equipped with a magnetic stirrer bar. Aldehyde was also dissolved in dichloromethane and slowly added to the amine mixture followed by magnesium sulphate (5.0 g). The reaction mixture was stirred at room temperature for 24 hours, filtered and the solvent evaporated. Crude products were then purified by vacuum distillation.

**(E)-N-(pyridin-2-ylmethylene)aniline (207)**<sup>197</sup>

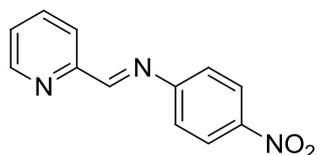
2-Pyridinecarboxyaldehyde (0.32 g, 3.0 mmol, 1.2 equiv.), aniline (0.23 g, 2.5 mmol, 1.0 equiv.) and dichloromethane (20 ml) was subject to the general procedure for the synthesis of imines (8.4.1). Purification by vacuum distillation resulted in formation of a dark orange oil (0.45 g, 2.5 mmol 99 %); spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3053 (C-H, aromatic), 1627 (C=N, imine), 1591, 1485 (C=C, Aromatic);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 8.72 (1H, d,  $J_{\text{HH}}$  4.8 Hz, Ar), 8.61 (1H, s,  $\text{HC}=\text{N}$ ), 8.21 (1H, d,  $J_{\text{HH}}$  7.7 Hz, Ar), 7.82 (1H, td,  $J_{\text{HH}}$  7.7, 1.6 Hz, Ar), 7.45 – 7.40 (2H, m, Ar), 7.37 (1H, ddd,  $J_{\text{HH}}$  7.7, 4.8, 1.0 Hz, Ar), 7.32 – 7.24 (3H, m, Ar);  $\delta_{\text{C}}$  (101MHz,  $\text{CDCl}_3$ ) 160.7 ( $\text{HC}=\text{N}$ ), 154.6 (Ar, quaternary), 151.0 (Ar, quaternary), 149.7 (Ar), 136.7 (Ar), 129.3 (2C, Ar), 126.8 (Ar), 125.2 (Ar), 121.9 (Ar), 121.1 (2C, Ar);  $m/z$  (ESI) 183.1 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 183.0919,  $\text{C}_{12}\text{H}_{11}\text{N}_2$  requires, 183.0917].

**(E)-4-methoxy-N-(pyridin-2-ylmethylene)aniline (209a)**<sup>197</sup>

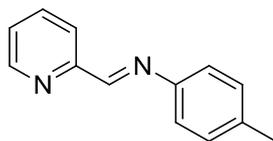
2-Pyridinecarboxyaldehyde (0.32 g, 3.0 mmol, 1.2 equiv.), *p*-anisidine (0.31 g, 2.5 mmol, 1.0 equiv.) and dichloromethane (20 ml) was subject to the general procedure for the synthesis of imines (8.4.1). Purification by vacuum distillation resulted in formation of a dark orange oil (0.45 g, 2.12 mmol, 86 %); spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3051 (C-H, aromatic), 2834 (C-H), 1624 (C=N, imine), 1579, 1503 (C=C, Aromatic), 1242 (C-O);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.62 (1H, d,  $J_{\text{HH}}$  4.7 Hz, Ar), 8.55 (1H, s,  $\text{HC}=\text{N}$ ), 8.10 (1H, d,  $J_{\text{HH}}$  7.8 Hz, Ar), 7.71 (1H,

td,  $J_{\text{HH}}$  7.8, 1.6 Hz, Ar), 7.31 – 7.21 (3H, m, Ar), 6.94 – 6.81 (2H, m, Ar), 3.76 (3H, s, OCH<sub>3</sub>);  $\delta_{\text{C}}$  (75MHz, CDCl<sub>3</sub>) 158.3 (Ar, quaternary), 157.6 (Ar), 154.3 (Ar, quaternary), 149.0 (Ar), 143.1 (Ar, quaternary), 136.0 (Ar), 124.2 (Ar), 122.1 (2C, Ar), 121.0 (Ar), 113.8 (2C, Ar), 54.9 (CH<sub>3</sub>);  $m/z$  (ESI) 213.1 ([M]<sup>+</sup>H); [Found: ([M]<sup>+</sup>H) 213.1019, C<sub>13</sub>H<sub>13</sub>N<sub>2</sub>O requires, 213.1022].

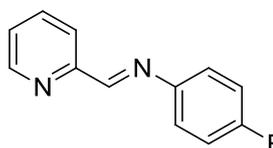
**(E)-4-nitro-N-(pyridin-2-ylmethylene)aniline (209b)**



2-Pyridinecarboxyaldehyde (0.32 g, 3.0 mmol, 1.2 equiv.), 4-nitroaniline (0.35 g, 2.5 mmol, 1.0 equiv.) and dichloromethane (20 ml) was subject to the general procedure for the synthesis of imines (8.4.1). Purification by vacuum distillation resulted in formation of yellow crystals (0.54 g, 2.37 mmol, 95 %); mpt 166 – 168 °C;  $\nu_{\text{max}}$  (neat, cm<sup>-1</sup>) 3060 (C-H, aromatic), 1629 (C=N, imine), 1583, 1469 (C=C, Aromatic), 1504 (N-O), 1339 (N-O);  $\delta_{\text{H}}$  (300MHz, CDCl<sub>3</sub>) 8.76 (1H, d,  $J_{\text{HH}}$  4.8 Hz, Ar), 8.56 (1H, s, HC=N), 8.33 – 8.24 (2H, m, Ar), 8.20 (1H, d,  $J_{\text{HH}}$  7.8 Hz, Ar), 7.87 (1H, td,  $J_{\text{HH}}$  7.8, 1.6 Hz, Ar), 7.45 (1H, ddd,  $J_{\text{HH}}$  7.8, 4.8, 1.0 Hz, Ar), 7.36 – 7.24 (2H, m, Ar);  $\delta_{\text{C}}$  (75MHz, CDCl<sub>3</sub>) 162.7 (HC=N), 156.2 (Ar, quaternary), 153.0 (Ar, quaternary), 149.4 (Ar), 145.3 (Ar, quaternary), 136.3 (Ar), 125.3 (Ar), 124.5 (2C, Ar), 121.9 (Ar), 120.8 (2C, Ar);  $m/z$  (ESI) 228 ([M]<sup>+</sup>H); [Found: ([M]<sup>+</sup>H) 228.0768, C<sub>12</sub>H<sub>10</sub>N<sub>3</sub>O<sub>2</sub> requires, 228.0768].

**(E)-4-methyl-N-(pyridin-2-ylmethylene)aniline (209c)**<sup>198</sup>

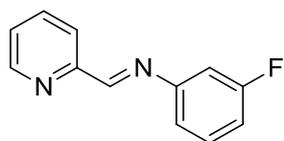
2-Pyridinecarboxyaldehyde (0.32 g, 3.0 mmol, 1.2 equiv.), *p*-toluidine (0.27 g, 2.5 mmol, 1.0 equiv.) and dichloromethane (20 ml) was subject to the general procedure for the synthesis of imines (8.4.1). Purification by vacuum distillation resulted in formation of an orange crystals (0.48 g, 2.44 mmol, 98 %); mpt 62 – 64 °C; spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3047 (C-H, aromatic), 2919 (C-H), 1626 (C=N, imine), 1584, 1504 (C=C, Aromatic);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.69 (1H, d,  $J_{\text{HH}}$  4.8 Hz, Ar), 8.62 (1H, s,  $\text{HC}=\text{N}$ ), 8.18 (1H, d,  $J_{\text{HH}}$  7.8 Hz, Ar), 7.78 (1H, td,  $J_{\text{HH}}$  7.8, 1.6 Hz, Ar), 7.33 (1H, ddd,  $J_{\text{HH}}$  7.8, 4.8, 1.0 Hz, Ar), 7.25 – 7.16 (4H, m, Ar), 2.37 (3H, s,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 159.1 ( $\text{HC}=\text{N}$ ), 154.1 (Ar, quaternary), 149.1 (Ar), 147.7 (Ar, quaternary), 136.1 (Ar, quaternary), 136.1 (Ar), 129.3 (2C, Ar), 124.4 (Ar), 121.1 (Ar), 120.5 (2C, Ar), 20.5 ( $\text{CH}_3$ );  $m/z$  (ESI) 197.1 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 197.1083,  $\text{C}_{13}\text{H}_{13}\text{N}_2$  requires, 197.1073].

**(E)-4-fluoro-N-(pyridin-2-ylmethylene)aniline (209d)**<sup>198</sup>

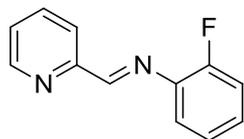
2-Pyridinecarboxyaldehyde (0.32 g, 3.0 mmol, 1.2 equiv.), 4-fluoroaniline (0.28 g, 2.5 mmol, 1.0 equiv.) and dichloromethane (20 ml) was subject to the general procedure for the synthesis of imines (8.4.1). Purification by vacuum distillation resulted in formation of an orange crystals (0.48 g, 2.4 mmol, 96 %); mpt 56 – 58 °C; spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3056 (C-H, aromatic), 1627 (C=N, imine), 1582, 1499 (C=C, Aromatic), 1216 (C-F);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.66

(1H, d,  $J_{\text{HH}}$  4.7 Hz, Ar), 8.55 (1H, s,  $\underline{\text{HC}}=\text{N}$ ), 8.13 (1H, d,  $J_{\text{HH}}$  7.8 Hz, Ar), 7.75 (1H, t,  $J_{\text{HH}}$  7.8 Hz, Ar), 7.35 – 7.29 (1H, m, Ar), 7.28 – 7.19 (2H, m, Ar), 7.11 – 7.00 (2H, m, Ar);  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 161.1 (d,  $J_{\text{CF}}$  245.9 Hz, Ar), 159.6 (s,  $\underline{\text{HC}}=\text{N}$ ), 153.8 (s, Ar, quaternary), 149.1 (s, Ar), 146.3 (d,  $J_{\text{CF}}$  2.8 Hz, Ar, quaternary), 136.0 (s, Ar), 124.5 (s, Ar), 122.1 (2C, d,  $J_{\text{CF}}$  8.4 Hz, Ar), 121.2 (s, Ar), 121.8 (2C, d,  $J_{\text{CF}}$  22.6 Hz, Ar);  $m/z$  (ESI) 201 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 201.0823,  $\text{C}_{12}\text{H}_{10}\text{FN}_2$  requires, 201.0823].

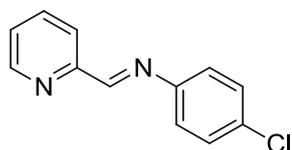
**(E)-3-fluoro-N-(pyridin-2-ylmethylene)aniline (209e)**



2-pyridinecarboxyaldehyde (0.32 g, 3.0 mmol, 1.2 equiv.), 3-fluoroaniline (0.28 g, 2.5 mmol, 1.0 equiv.) and dichloromethane (20 ml) was subject to the general procedure for the synthesis of imines (8.4.1). Purification by vacuum distillation resulted in formation of an orange oil (0.48 g, 2.4 mmol, 96 %);  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 3055 (C-H, aromatic), 1633 (C=N, imine), 1582, 1477 (C=C, Aromatic), 1223 (C-F);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 8.71 (1H, d,  $J_{\text{HH}}$  4.7 Hz, Ar), 8.57 (1H, s,  $\underline{\text{HC}}=\text{N}$ ), 8.18 (1H, d,  $J_{\text{HH}}$  7.8 Hz, Ar), 7.80 (1H, t,  $J_{\text{HH}}$  7.8 Hz, Ar), 7.40 – 7.30 (2H, m, Ar), 7.05 (1H, d,  $J_{\text{HH}}$  8.0 Hz, Ar), 7.03 – 6.92 (2H, m, Ar);  $\delta_{\text{C}}$  (101MHz,  $\text{CDCl}_3$ ) 163.3 (d,  $J_{\text{CF}}$  246.7 Hz, Ar), 161.6 (s,  $\underline{\text{HC}}=\text{N}$ ), 154.2 (s, Ar, quaternary), 152.8 (d,  $J_{\text{CF}}$  8.8 Hz, Ar, quaternary), 149.8 (s, Ar), 136.7 (s, Ar), 130.4 (d,  $J_{\text{CF}}$  9.2 Hz, Ar), 125.4 (s, Ar), 122.1 (s, Ar), 116.8 (d,  $J_{\text{CF}}$  2.8 Hz, Ar), 113.4 (d,  $J_{\text{CF}}$  21.4 Hz, Ar), 108.4 (d,  $J_{\text{CF}}$  22.6 Hz, Ar);  $m/z$  (ESI) 201 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 201.0821,  $\text{C}_{12}\text{H}_{10}\text{FN}_2$  requires, 201.0823].

**(E)-2-fluoro-N-(pyridin-2-ylmethylene)aniline (209f)**<sup>200</sup>

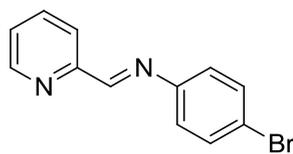
2-pyridinecarboxyaldehyde (0.32 g, 3.0 mmol, 1.2 equiv.), 2-fluoroaniline (0.28 g, 2.5 mmol, 1.0 equiv.) and dichloromethane (20 ml) was subject to the general procedure for the synthesis of imines (8.4.1). Purification by vacuum distillation resulted in formation of an orange oil (0.47 g, 2.35 mmol, 94 %); spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3055 (C-H, aromatic), 1629 (C=N, imine), 1584, 1491 (C=C, Aromatic), 1224 (C-F);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 8.72 (1H, d,  $J_{\text{HH}}$  4.7 Hz, Ar), 8.67 (1H, s,  $\underline{\text{H}}\text{C}=\text{N}$ ), 8.26 (1H, d,  $J_{\text{HH}}$  7.8 Hz, Ar), 7.82 (1H, t,  $J_{\text{HH}}$  7.8 Hz, Ar), 7.42 – 7.35 (1H, m, Ar), 7.25 - 7.12 (4H, m, Ar);  $\delta_{\text{C}}$  (101MHz,  $\text{CDCl}_3$ ) 163.1 (d,  $J_{\text{CF}}$  2.6 Hz, Ar), 155.4 (d,  $J_{\text{CF}}$  250.0 Hz, Ar), 154.4 (s, Ar, quaternary), 149.7 (s, Ar), 139.0 (d,  $J_{\text{CF}}$  10.2 Hz, Ar, quaternary), 136.7 (s, Ar), 127.6 (d,  $J_{\text{CF}}$  7.7 Hz, Ar), 125.5 (s, Ar), 124.6 (d,  $J_{\text{CF}}$  3.9 Hz, Ar), 122.0 (s, Ar), 121.8 (s, Ar), 116.4 (d,  $J_{\text{CF}}$  20.1 Hz, Ar);  $m/z$  (ESI) 201 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 201.0827,  $\text{C}_{12}\text{H}_{10}\text{FN}_2$  requires, 201.0823].

**(E)-4-chloro-N-(pyridin-2-ylmethylene)aniline (209g)**<sup>198</sup>

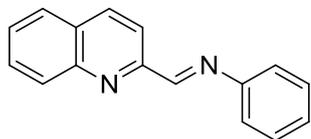
2-pyridinecarboxyaldehyde (0.32 g, 3.0 mmol, 1.2 equiv.), 4-chloroaniline (0.32 g, 2.5 mmol, 1.0 equiv.) and dichloromethane (20 ml) was subject to the general procedure for the synthesis of imines (8.4.1). Purification by vacuum distillation resulted in formation of an orange crystals (0.51 g, 2.35 mmol, 95 %); spectral details match these reported; mpt 70 – 72 °C;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3050 (C-H, aromatic),

1619 (C=N, imine), 1566, 1486 (C=C, Aromatic), 695 (C-Cl);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.59 (1H, d,  $J_{\text{HH}}$  4.6 Hz, Ar), 8.46 (1H, s,  $\text{HC}=\text{N}$ ), 8.06 (1H, d,  $J_{\text{HH}}$  7.8 Hz, Ar), 7.69 (1H, td,  $J_{\text{HH}}$  7.8, 1.6 Hz, Ar), 7.28 – 7.21 (3H, m, Ar), 7.14 – 7.07 (2H, m, Ar);  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 160.3 ( $\text{HC}=\text{N}$ ), 153.7 (Ar, quaternary), 149.2 (Ar), 148.9 (Ar, quaternary), 136.1 (Ar), 131.7 (Ar, quaternary), 128.7 (2C, Ar), 124.7 (Ar), 121.8 (2C, Ar), 121.4 (Ar).  $m/z$  (ESI) 217 ( $[\text{M}]^+\text{H}$ ).

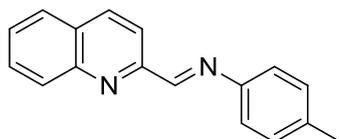
**(E)-4-bromo-N-(pyridin-2-ylmethylene)aniline (209h)**<sup>198</sup>



2-pyridinecarboxyaldehyde (0.27 g, 2.5 mmol, 1.0 equiv.), 4-bromoaniline (0.52 g, 3.0 mmol, 1.2 equiv.) and dichloromethane (20 ml) was subject to the general procedure for the synthesis of imines (8.4.1). Purification by vacuum distillation resulted in formation of orange / brown crystals (0.62 g, 2.4 mmol, 96 %); spectral details match these reported; mpt 69 – 71 °C;  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 3049 (C-H, aromatic), 1622 (C=N, imine), 1562, 1476 (C=C, Aromatic), 681 (C-Br);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 8.71 (1H, d,  $J_{\text{HH}}$  4.8 Hz, Ar), 8.57 (1H, s,  $\text{HC}=\text{N}$ ), 8.17 (1H, d,  $J_{\text{HH}}$  7.7 Hz, Ar), 7.81 (1H, td,  $J_{\text{HH}}$  7.7, 1.6 Hz, Ar), 7.55 – 7.50 (2H, m, Ar), 7.37 (1H, ddd,  $J_{\text{HH}}$  7.7, 4.8, 0.9 Hz, Ar), 7.19 – 7.13 (2H, m, Ar);  $\delta_{\text{C}}$  (101MHz,  $\text{CDCl}_3$ ) 161.1 ( $\text{HC}=\text{N}$ ), 154.3 (Ar, quaternary), 149.9 (Ar, quaternary), 149.8 (Ar), 136.7 (Ar), 132.3 (2C, Ar), 125.3 (Ar), 122.8 (2C, Ar), 122.0 (Ar), 120.3 (Ar, quaternary);  $m/z$  (ESI) 261 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 261.0022,  $\text{C}_{12}\text{H}_{10}^{79}\text{BrN}_2$  requires, 261.0022].

**(E)-N-(quinolin-2-ylmethylene)aniline (210a)**<sup>200</sup>

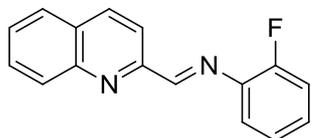
2-quinolinecarboxyaldehyde (0.47 g, 3.0 mmol, 1.00 equiv.), Aniline (0.33 g, 3.5 mmol, 1.15 equiv.) and dichloromethane (25 ml) was subject to the general procedure for the synthesis of imines (8.4.1). Purification by vacuum distillation resulted in formation of pale orange crystals (0.64 g, 2.75 mmol, 92 %); spectral details match these reported; mpt 76 – 78 °C;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3060 (C-H, aromatic), 1624 (C=N, imine), 1595, 1586, 1502 (C=C, Aromatic);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.80 (1H, s,  $\text{HC}=\text{N}$ ), 8.37 (1H, d,  $J_{\text{HH}}$  8.6 Hz, Ar), 8.25 (1H, d,  $J_{\text{HH}}$  8.6 Hz, Ar), 8.17 (1H, d,  $J_{\text{HH}}$  8.0 Hz, Ar), 7.87 (1H, d,  $J_{\text{HH}}$  8.0 Hz, Ar), 7.78 (1H, td,  $J_{\text{HH}}$  8.0, 1.2 Hz, Ar), 7.60 (1H, t,  $J_{\text{HH}}$  8.0 Hz, Ar), 7.51 – 7.24 (5H, m, Ar);  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 161.1 ( $\text{HC}=\text{N}$ ), 155.0 (Ar, quaternary), 151.0 (Ar, quaternary), 148.1 (Ar, quaternary), 136.8 (Ar), 130.0 (Ar), 129.8 (Ar), 129.4 (2C, Ar), 129.0 (Ar, quaternary), 127.9 (Ar), 127.8 (Ar), 127.1 (Ar), 121.4 (2C, Ar), 118.8 (Ar);  $m/z$  (ESI) 255 ( $[\text{M}]^+\text{Na}$ ); [Found: ( $[\text{M}]^+\text{Na}$ ) 255.0894,  $\text{C}_{16}\text{H}_{12}\text{N}_2\text{Na}$  requires, 255.0893].

**(E)-4-methyl-N-(quinolin-2-ylmethylene)aniline (210b)**<sup>200</sup>

2-quinolinecarboxyaldehyde (0.47 g, 3.0 mmol, 1.00 equiv.), *p*-toluidine (0.37 g, 3.5 mmol, 1.15 equiv.) and dichloromethane (25 ml) was subject to the general procedure for the synthesis of imines (8.4.1). Purification by vacuum distillation resulted in formation of dark orange crystals (0.70 g, 2.84 mmol, 94 %); spectral

details match these reported; mpt 83 – 85 °C;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3057 (C-H, aromatic), 2916 (C-H, Alkane), 1624 (C=N, imine), 1594, 1557, 1503 (C=C, Aromatic);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.79 (1H, s,  $\text{HC}=\text{N}$ ), 8.35 (1H, d,  $J_{\text{HH}}$  8.6 Hz, Ar), 8.22 (1H, d,  $J_{\text{HH}}$  8.6 Hz, Ar), 8.15 (1H, d,  $J_{\text{HH}}$  8.0 Hz, Ar), 7.85 (1H, d,  $J_{\text{HH}}$  8.0 Hz, Ar), 7.76 (1H, td,  $J_{\text{HH}}$  8.0, 1.1 Hz, Ar), 7.59 (1H, t,  $J_{\text{HH}}$  8.0 Hz, Ar), 7.34 – 7.18 (4H, m, Ar), 2.38 (3H, s,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 160.0 ( $\text{HC}=\text{N}$ ), 155.2 (Ar, quaternary), 148.3 (Ar, quaternary), 148.1 (Ar, quaternary), 137.2 (Ar, quaternary), 136.7 (Ar), 130.0 (3C, Ar), 129.8 (Ar), 129.0 (Ar, quaternary), 127.9 (Ar), 127.8 (Ar), 121.4 (2C, Ar), 118.8 (Ar), 21.2 ( $\text{CH}_3$ );  $m/z$  (ESI) 247.1 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 247.1232,  $\text{C}_{17}\text{H}_{15}\text{N}_2$  requires, 247.1230].

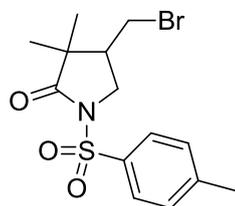
**(E)-2-fluoro-N-(quinolin-2-ylmethylene)aniline (210c)**



2-quinolinecarboxyaldehyde (0.47 g, 3.0 mmol, 1.00 equiv.), 2-fluoroaniline (0.39 g, 3.5 mmol, 1.15 equiv.) and dichloromethane (25 ml) was subject to the general procedure for the synthesis of imines (8.4.1). Purification by vacuum distillation resulted in formation of dark orange crystals (0.69 g, 2.76 mmol, 92 %); mpt 78 – 80 °C;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 3055 (C-H, aromatic), 1622 (C=N, imine), 1597, 1503, 1488 (C=C, Aromatic);  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 8.85 (1H, s,  $\text{HC}=\text{N}$ ), 8.40 (1H, d,  $J_{\text{HH}}$  8.6 Hz, Ar), 8.26 (1H, d,  $J_{\text{HH}}$  8.6 Hz, Ar), 8.17 (1H, d,  $J_{\text{HH}}$  8.6 Hz, Ar), 7.87 (1H, d,  $J_{\text{HH}}$  8.6 Hz, Ar), 7.77 (1H, td,  $J_{\text{HH}}$  8.6, 1.2 Hz, Ar), 7.61 (1H, t,  $J_{\text{HH}}$  7.2 Hz, Ar), 7.36 – 7.13 (4H, m, Ar);  $\delta_{\text{C}}$  (75MHz,  $\text{CDCl}_3$ ) 163.3 (d,  $J_{\text{CF}}$  2.5 Hz, Ar), 155.7 (d,  $J_{\text{CF}}$  250.6 Hz, Ar), 154.8 (s, Ar, quaternary), 148.1 (s, Ar, quaternary), 139.0 (d,  $J_{\text{CF}}$  10.2 Hz, Ar, quaternary), 136.7 (s, Ar), 130.1 (s, Ar), 129.9 (s, Ar), 129.2 (s, Ar, quaternary),

128.0 (d,  $J_{CF}$  7.9 Hz, Ar), 127.9 (2C, s, Ar), 124.8 (d,  $J_{CF}$  3.8 Hz, Ar), 121.8 (s, Ar), 118.8 (s, Ar), 116.6 (d,  $J_{CF}$  20.1 Hz, Ar);  $m/z$  (ESI) 251.1 ( $[M]^+H$ ); [Found: ( $[M]^+H$ ) 251.0981,  $C_{16}H_{12}FN_2$  requires, 251.0979].

#### 8.4.2 General Procedure for the Cyclisation of *N*-allyl-2-bromo-2-methyl-*N*-tosylpropanamide (**1**) to 4-(Bromomethyl)-3,3-dimethyl-1-tosylpyrrolidin-2-one (**2**)<sup>201</sup>



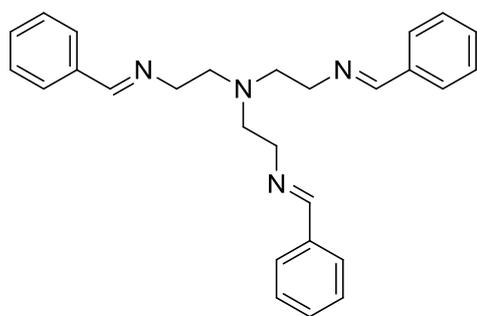
CuBr (10 – 100 mol%) and ligand (**209a-h** and **210a-c**) (20 – 200 mol%) was dissolved in DCM. *N*-allyl-2-bromo-2-methyl-*N*-tosylpropanamide (**1**) (72 mg, 0.2 mmol, 1.0 equiv.) was also dissolved in DCM and added to the mixture to generate a

concentration of 0.12 M. The reaction mixture was stirred at room temperature for 24 hours. The mixture was filtered through silica, washed with dichloromethane (50 ml) and solvent evaporated. The resulting filtrate was washed with water (30 ml). The organic layer was dried over  $MgSO_4$ , filtered and concentrated under reduced pressure to isolate the crude product. The conversion rates were identified by  $^1H$  NMR spectroscopy. Spectral details match these reported;  $\delta_H$  (400 MHz,  $CDCl_3$ ) 7.92 (2H, d,  $J_{HH}$  8.3 Hz, Ar), 7.34 (2H, d,  $J_{HH}$  8.3 Hz, Ar), 4.15 (1H, dd,  $J_{HH}$  10.3, 7.4 Hz, N- $\underline{CH}_2$ ), 3.47 (1H, dd,  $J_{HH}$  10.2, 8.7 Hz,  $\underline{CH}_2$ Br), 3.44 (1H, dd,  $J_{HH}$  10.2, 4.8 Hz,  $\underline{CH}_2$ Br), 3.21 (1H, t,  $J_{HH}$  10.3 Hz, N- $\underline{CH}_2$ ), 2.46 (1H, m,  $\underline{CH}$ ), 2.44 (3H, s, Ar- $\underline{CH}_3$ ), 1.17 (3H, s, C( $\underline{CH}_3$ )<sub>2</sub>), 0.90 (3H, s, C( $\underline{CH}_3$ )<sub>2</sub>);  $\delta_C$  (100 MHz,  $CDCl_3$ ) 177.1 ( $\underline{C=O}$ ), 145.5 (Ar, quaternary), 135.0 (Ar, quaternary), 129.9 (2C, Ar), 128.1 (2C, Ar), 48.9 ( $\underline{C}(\underline{CH}_3)_2$ , quaternary), 45.6 ( $\underline{CH}$ ), 45.2 (N- $\underline{CH}_2$ ), 30.1 ( $\underline{CH}_2$ Br), 23.5 (Ar- $\underline{CH}_3$ ), 21.8 ( $\underline{CH}_3$ ), 18.0 ( $\underline{CH}_3$ ).

### 8.4.3 General Procedure for the Synthesis of Tetra-dentate Imine Ligands for ATRC Reactions

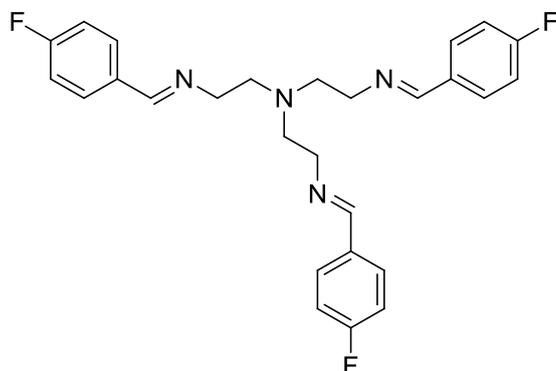
Tris-(2-aminoethyl)-amine (1.00 g, 3.42 mmol, 1 equiv.) was dissolved in ethyl acetate (50 ml) in a 100 ml round bottomed flask. Aldehyde (10.94 mmol, 3.2 equiv.) was slowly added to the amine followed by magnesium sulphate (10 g). The reaction mixture was stirred at room temperature for 24 hours. The mixture was then filtered and the filtrate evaporated. The crude products were purified by vacuum distillation.

#### *(E)*-*N*<sup>1</sup>-benzylidene-*N*<sup>2</sup>,*N*<sup>2</sup>-bis(2-((*E*)-benzylideneamino)ethyl)ethane-1,2-diamine (215a)<sup>202</sup>



Tris-(2-aminoethyl)-amine, benzaldehyde and ethyl acetate (25 ml) was subject to the general procedure for the synthesis of imines (8.4.3). Purification by vacuum distillation resulted in formation of a yellow oil (1.35 g, 3.29 mmol, 96 %); spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 2953 (C-H), 1645 (C=N, imine);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 8.01 (3H, s, CH=N), 7.42 (6H, d,  $J_{\text{HH}}$  7.8 Hz, Ar), 7.45 - 7.30 (9H, m, Ar), 3.63 (6H, t,  $J_{\text{HH}}$  6.1 Hz,  $\text{CH}_2$ ), 2.85 (6H, t,  $J_{\text{HH}}$  6.1 Hz,  $\text{CH}_2$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 161.9 (3C, imine), 136.3 (3C, quaternary), 130.4 (6C, Ar), 128.6 (6C, Ar), 128.0 (3C, Ar), 60.2 (3C,  $\text{CH}_2$ ), 55.7 (3C,  $\text{CH}_2$ );  $m/z$  (ESI) 411.2 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 411.2542,  $\text{C}_{27}\text{H}_{31}\text{N}_4$  requires, 411.2543].

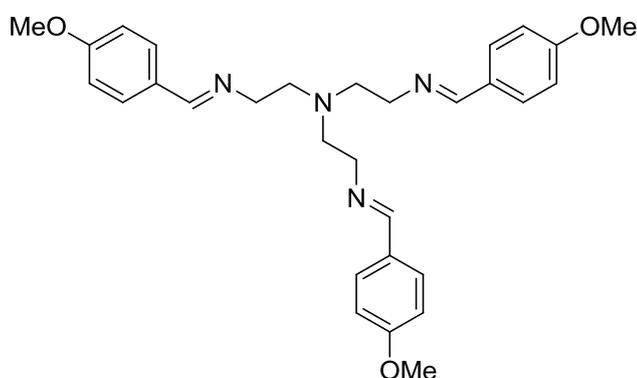
**(*E*)-*N*<sup>1</sup>-(4-fluorobenzylidene)-*N*<sup>2</sup>,*N*<sup>2</sup>-bis(2-((*E*)-4-fluorobenzylideneamino)ethyl)ethane-1,2-diamine (215b)**



Tris-(2-aminoethyl)-amine, 4-fluorobenzaldehyde and ethyl acetate (25 ml) was subject to the general procedure for the synthesis of imines (8.4.3). Purification by vacuum distillation resulted in formation of a

dark orange oil (0.94 g, 2.0 mmol, 59 %);  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 2838 (C-H), 1644 (C=N, imine), 1506 (Ar), ~1330 (C-F);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 8.01 (3H, s, CH=N), 7.55 - 7.45 (6H, m, Ar), 6.98 (6H, t,  $J_{\text{HH}}$  8.6 Hz, Ar), 3.60 (6H, t,  $J_{\text{HH}}$  6.3 Hz,  $\text{CH}_2$ ), 2.85 (6H, t,  $J_{\text{HH}}$  6.3 Hz,  $\text{CH}_2$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 165.4 (3C, Ar, quaternary), 160.3 (3C, imine), 132.6 (3C, Ar, quaternary), 129.8 (6C, Ar), 115.7 (6C, Ar), 60.0 (3C,  $\text{CH}_2$ ), 55.6 (3C,  $\text{CH}_2$ );  $m/z$  (ESI) 464.2 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 465.2266,  $\text{C}_{27}\text{H}_{28}\text{F}_3\text{N}_4$  requires, 465.2294].

**(*E*)-*N*<sup>1</sup>-(4-methoxybenzylidene)-*N*<sup>2</sup>,*N*<sup>2</sup>-bis(2-((*E*)-4-methoxybenzylideneamino)ethyl)ethane-1,2-diamine (215c)**

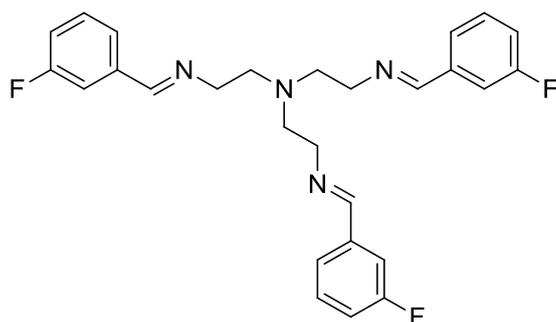


Tris-(2-aminoethyl)-amine, 4-methoxybenzaldehyde and ethyl acetate (25 ml) was subject to the general procedure for the synthesis of imines (8.4.3). Purification by vacuum

distillation resulted in formation of a yellow oil (1.47 g, 2.9 mmol, 86 %);  $\nu_{\max}$  (neat,

cm<sup>-1</sup>) 2834 (C-H), 1642 (C=N, imine), 1510 (Ar);  $\delta_{\text{H}}$  (400MHz, CDCl<sub>3</sub>) 8.05 (3H, s, CH=N), 7.50 (6H, d,  $J_{\text{HH}}$  8.7 Hz, Ar), 6.88 (6H, d,  $J_{\text{HH}}$  8.7 Hz, Ar), 3.85 (9H, s, CH<sub>3</sub>), 3.67 (6H, t,  $J_{\text{HH}}$  6.5 Hz, CH<sub>2</sub>), 2.95 (6H, t,  $J_{\text{HH}}$  6.5 Hz, CH<sub>2</sub>);  $\delta_{\text{C}}$  (100MHz, CDCl<sub>3</sub>) 161.5 (3C, Ar, quaternary), 161.2 (3C, imine), 129.6 (6C, Ar), 129.4 (3C, Ar, quaternary), 114.0 (6C, Ar), 60.1 (3C, CH<sub>2</sub>), 55.8 (3C, CH<sub>3</sub>), 55.3 (3C, CH<sub>2</sub>);  $m/z$  (ESI) 501.3 ([M]<sup>+</sup>H); [Found: ([M]<sup>+</sup>H) 501.2860, C<sub>30</sub>H<sub>37</sub>N<sub>4</sub>O<sub>3</sub> requires, 501.2865].

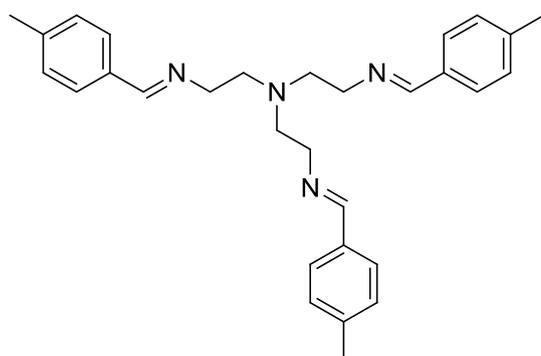
**(*E*)-N<sup>1</sup>-(3-fluorobenzylidene)-N<sup>2</sup>,N<sup>2</sup>-bis(2-((*E*)-3-fluorobenzylideneamino)ethyl) ethane-1,2-diamine (215d)**



Tris-(2-aminoethyl)-amine and 3-fluorobenzaldehyde and ethyl acetate (25 ml) was subject to the general procedure for the synthesis of imines (8.4.3). Purification by vacuum distillation resulted in formation of a

yellow oil (1.20 g, 2.6 mmol, 76 %);  $\nu_{\text{max}}$  (neat, cm<sup>-1</sup>) 2828 (C-H), 1644 (C=N, imine), 1511 (Ar), ~1330 (C-F);  $\delta_{\text{H}}$  (300MHz, CDCl<sub>3</sub>) 7.96 (3H, s, CH=N), 7.25 – 7.20 (3H, m, Ar), 7.17 - 7.10 (6H, m, Ar), 7.05 – 7.00 (3H, m, Ar), 3.59 (6H, t,  $J_{\text{HH}}$  6.0 Hz, CH<sub>2</sub>), 2.84 (6H, t,  $J_{\text{HH}}$  6.0 Hz, CH<sub>2</sub>);  $\delta_{\text{C}}$  (75MHz, CDCl<sub>3</sub>) 164.3 (3C, Ar, quaternary), 160.5 (3C, imine), 138.6 (3C, Ar, quaternary), 130.1 (3C, Ar), 124.0 (3C, Ar), 117.4 (3C, Ar), 114.0 (3C, Ar), 59.9 (3C, CH<sub>2</sub>), 55.5 (3C, CH<sub>2</sub>);  $m/z$  (ESI) 464.2 ([M]<sup>+</sup>H); [Found: ([M]<sup>+</sup>H) 465.2260, C<sub>27</sub>H<sub>28</sub>F<sub>3</sub>N<sub>4</sub> requires, 465.2294].

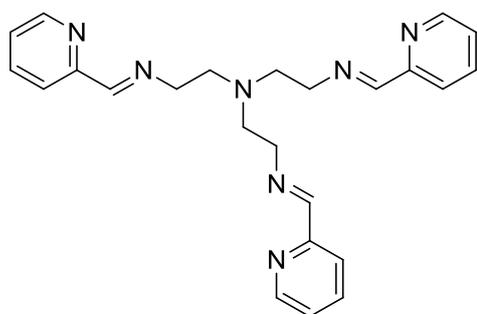
**(E)-N<sup>1</sup>-(4-methylbenzylidene)-N<sup>2</sup>,N<sup>2</sup>-bis(2-((E)-4-methylbenzylideneamino)ethyl) ethane-1,2-diamine (215e)**



Tris-(2-aminoethyl)-amine, tolualdehyde and ethyl acetate (25 ml) was subject to the general procedure for the synthesis of imines (8.4.3). Purification by vacuum distillation resulted in formation of a yellow oil (1.17 g, 2.6 mmol, 76 %);

$\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 2840 (C-H), 1643 (C=N, imine);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 8.07 (3H, s, CH=N), 7.43 (6H, d,  $J_{\text{HH}}$  8.0 Hz, Ar), 7.15 (6H, d,  $J_{\text{HH}}$  8.0 Hz, Ar), 3.68 (6H, t,  $J_{\text{HH}}$  6.4 Hz,  $\text{CH}_2$ ), 2.95 (6H, t,  $J_{\text{HH}}$  6.4 Hz,  $\text{CH}_2$ ), 2.38 (9H, s,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 161.8 (3C, imine), 140.7 (3C, Ar, quaternary), 133.7 (3C, Ar, quaternary), 129.3 (6C, Ar), 128.1 (6C, Ar), 60.2 (3C,  $\text{CH}_2$ ), 55.8 (3C,  $\text{CH}_2$ ), 21.5 (3C,  $\text{CH}_3$ );  $m/z$  (ESI) 453.3 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 453.3013,  $\text{C}_{30}\text{H}_{37}\text{N}_4$  requires, 453.3013].

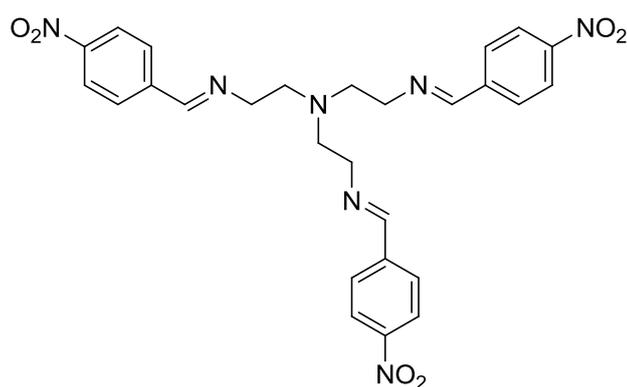
**(E)-N<sup>1</sup>-(pyridin-2-ylmethylene)-N<sup>2</sup>,N<sup>2</sup>-bis(2-((E)-pyridin-2-ylmethyleneamino)ethyl) ethane-1,2-diamine (215f)<sup>203</sup>**



Tris-(2-aminoethyl)-amine, 2-pyridinecarboxyaldehyde and ethyl acetate (25 ml) was subject to the general procedure for the synthesis of imines (8.4.3). Purification by vacuum distillation resulted in formation of a dark orange oil (1.38 g, 3.3 mmol, 98 %); spectral details match these

reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 2842 (C-H), 1644 (C=N, imine), 1467 (pyridine);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 8.61 (3H, d,  $J_{\text{HH}}$  4.7 Hz, Ar), 8.34 (3H, s, CH=N), 7.91 (3H, d,  $J_{\text{HH}}$  7.9 Hz, Ar), 7.69 (3H, td,  $J_{\text{HH}}$  7.8, 1.5 Hz, Ar), 7.27 (3H, dd,  $J_{\text{HH}}$  4.9, 1.5 Hz, Ar), 3.79 (6H, t,  $J_{\text{HH}}$  6.5 Hz,  $\text{CH}_2$ ), 3.01 (6H, t,  $J_{\text{HH}}$  6.5 Hz,  $\text{CH}_2$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 162.1 (3C, imine), 153.8 (3C, Ar, quaternary), 148.8 (3C, Ar), 135.9 (3C, Ar), 124.0 (3C, Ar), 120.7 (3C, Ar), 59.2 (3C,  $\text{CH}_2$ ), 54.6 (3C,  $\text{CH}_2$ );  $m/z$  (ESI) Found 413.2 ( $[\text{M}]^+\text{H}$ ).

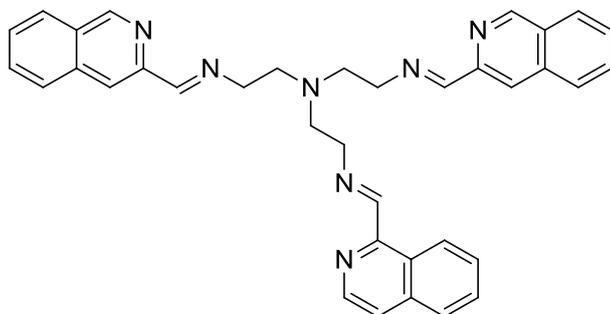
**(*E*)- $N^1$ -(4-nitrobenzylidene)- $N^2,N^2$ -bis(2-((*E*)-4-nitrobenzylideneamino)ethyl)ethane-1,2-diamine (215g)<sup>204</sup>**



Tris-(2-aminoethyl)-amine, 4-nitrobenzaldehyde and ethyl acetate (25 ml) was subject to the general procedure for the synthesis of imines (8.4.3). Purification by vacuum

distillation resulted in formation of orange crystals (0.59 g, 1.1 mmol, 32 %); spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 2828 (C-H), 1643 (C=N, imine), 1599 (Ar), 1511 (Ar);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 8.28 (3H, s, CH=N), 8.22 (6H, d,  $J_{\text{HH}}$  8.6 Hz, Ar), 7.78 (6H, d,  $J_{\text{HH}}$  8.6 Hz, Ar), 3.77 (6H, t,  $J_{\text{HH}}$  6.2 Hz,  $\text{CH}_2$ ), 3.00 (6H, t,  $J_{\text{HH}}$  6.2 Hz,  $\text{CH}_2$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 159.5 (3C, imine), 149.0 (3C, Ar, quaternary), 141.5 (3C, Ar, quaternary), 128.6 (6C, Ar), 123.9 (6C, Ar), 60.3 (3C,  $\text{CH}_2$ ), 55.3 (3C,  $\text{CH}_2$ );  $m/z$  (ESI) Found 546.2 ( $[\text{M}]^+\text{H}$ ).

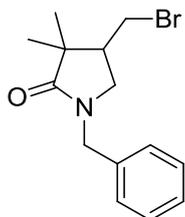
**(*E*)-*N*<sup>1</sup>-(isoquinolin-1-ylmethylene)-*N*<sup>2</sup>,*N*<sup>2</sup>-bis(2-(*E*)-isoquinolin-3-ylmethyleneamino)ethyl)ethane-1,2-diamine (215h)**



Tris-(2-aminoethyl)-amine (0.25 g, 1.71 mmol, 1 equiv.) was dissolved in ethyl acetate (100 ml) in a 100 ml round bottomed flask. 2-Quinolinecarboxyaldehyde (0.861 g, 5.47 mmol, 3.2 equiv.) was

slowly added to the amine followed by magnesium sulphate (10 g). The reaction mixture was stirred at room temperature for 24 hours. The mixture was then filtered and the filtrate evaporated. The imine was purified by recrystallization. Orange crystals were observed (0.87 g, 1.5 mmol, 90 %);  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 2845 (C-H), 1641 (C=N, imine), 1595 (Ar), 1502 (Ar);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 8.51 (3H, s, CH=N), 8.04 (6H, s, Ar), 8.02 (3H, d,  $J_{\text{HH}}$  8.5 Hz, Ar), 7.73 (3H, d,  $J_{\text{HH}}$  8.1 Hz, Ar), 7.74 – 7.69 (3H, m, Ar), 7.51 (3H, t,  $J_{\text{HH}}$  7.4 Hz, Ar), 3.89 (6H, t,  $J_{\text{HH}}$  6.6 Hz,  $\text{CH}_2$ ), 3.09 (6H, t,  $J_{\text{HH}}$  6.6 Hz,  $\text{CH}_2$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 163.4 (3C, imine), 154.7 (3C, Ar), 147.7 (3C, Ar, quaternary), 136.5 (3C, Ar), 129.6 (3C, Ar), 128.7 (3C, Ar, quaternary), 127.6 (3C, Ar), 127.2 (3C, Ar), 118.3 (3C, Ar), 59.9 (3C,  $\text{CH}_2$ ), 55.3 (3C,  $\text{CH}_2$ );  $m/z$  (ESI) Found 563.3 ( $[\text{M}]^+\text{H}$ ).

**8.4.4 General Procedure for the Cyclisation of *N*-allyl-*N*-benzyl-2-bromo-2-methylpropanamide (205) to 1-Benzyl-4-(bromomethyl)-3,3-dimethylpyrrolidin-2-one (206)<sup>205</sup>**



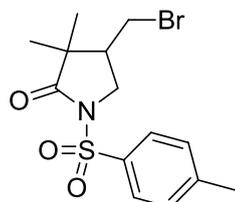
CuBr (0.0048 g, 0.0338 mmol, 0.1 equiv.) and ligand (**215a-h**) (0.0338 mmol, 0.1 equiv.) was dissolved in dry acetonitrile (2 ml) and stirred under nitrogen for 5 min. *N*-allyl-*N*-benzyl-2-bromo-2-methylpropanamide (**205**) (0.1 g, 0.338 mmol, 1.0 equiv.) was dissolved in dry acetonitrile (1 ml) and added to the mixture. The reaction mixture was stirred under reflux and nitrogen for 45 min. The mixture was filtered through silica, washed with dichloromethane and solvent evaporated. The resulting filtrate was washed with water (30 ml). The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to isolate the crude product. The conversion rates were identified by <sup>1</sup>H NMR spectroscopy. Spectral details match these reported;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.28 (5H, m, Ar), 4.51 (1H, d,  $J_{\text{HH}}$  14.0 Hz, Ar-CH<sub>2</sub>), 4.34 (1H, d,  $J_{\text{HH}}$  14.0 Hz, Ar-CH<sub>2</sub>), 3.45 (1H, dd,  $J_{\text{HH}}$  10.1, 4.7 Hz, CH<sub>2</sub>Br), 3.34 (1H, dd,  $J_{\text{HH}}$  10.1, 7.5 Hz, N-CH<sub>2</sub>), 3.21 (1H, t,  $J_{\text{HH}}$  10.1 Hz, CH<sub>2</sub>Br), 2.86 (1H, t,  $J_{\text{HH}}$  10.1 Hz, CH<sub>2</sub>), 2.38 (1H, m, CHCH<sub>2</sub>Br), 1.23 (3H, s, CH<sub>3</sub>), 0.98 (3H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 178.4 (C=O), 136.2 (Ar, quaternary), 128.7 (Ar), 128.0 (Ar), 127.6 (Ar), 48.7 (C(CH<sub>3</sub>)<sub>2</sub>, quaternary), 46.5 (Ar-CH<sub>2</sub>), 46.0 (N-CH<sub>2</sub>), 39.8 (CH(CH<sub>2</sub>Br), 31.4 (CH<sub>2</sub>Br), 24.2 (CH<sub>3</sub>), 19.5 (CH<sub>3</sub>).

## 8.5 Substrates Synthesized In Chapter 6

### 8.5.1 General Procedure for Copper Mediated ATRC Using $\text{KBH}_4$

A solution (0.01 M) of  $\text{CuSO}_4$  / TPA was added to the precursor dissolved in preferred amount of methanol and DCM to make up a desired concentration at room temperature, followed by the addition of  $\text{KBH}_4$ . The reaction mixture was then stirred at room temperature for 10 minutes. The mixture was filtered through a silica plug using DCM (50 ml) and the resulting filtrate was washed with water (30 ml). The organic layer was dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to isolate the crude product.

#### 4-(Bromomethyl)-3,3-dimethyl-1-tosylpyrrolidin-2-one (2)<sup>201</sup>

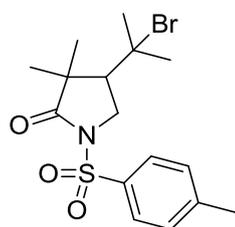


*N*-allyl-2-bromo-2-methyl-*N*-tosylpropanamide (145.0 mg, 0.40 mmol, 1.000 equiv.) was subject to the general procedure for copper mediated atom transfer radical cyclisation (8.5.1) using  $\text{CuSO}_4$  (1.00 mg, 0.004 mmol, 0.004 equiv.), TPA (1.20 mg,

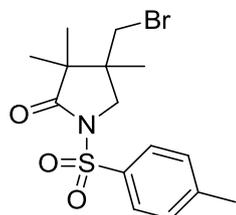
0.004 mmol, 0.004 equiv.),  $\text{KBH}_4$  (1.1 mg, 0.02 mmol, 0.050 equiv.) in methanol (0.58 ml) and DCM (0.2 ml). Resulted in formation of white crystalline solid of 4-(bromomethyl)-3,3-dimethyl-1-tosylpyrrolidin-2-one (130.3 mg, 0.36 mmol, 90 %); spectral details match these reported;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.92 (2H, d,  $J_{\text{HH}}$  8.3 Hz, Ar), 7.34 (2H, d,  $J_{\text{HH}}$  8.3 Hz, Ar), 4.15 (1H, dd,  $J_{\text{HH}}$  10.3, 7.4 Hz, N- $\text{CH}_2$ ), 3.47 (1H, dd,  $J_{\text{HH}}$  10.2, 8.7 Hz,  $\text{CH}_2\text{Br}$ ), 3.44 (1H, dd,  $J_{\text{HH}}$  10.2, 4.8 Hz,  $\text{CH}_2\text{Br}$ ), 3.21 (1H, t,  $J_{\text{HH}}$  10.3 Hz, N- $\text{CH}_2$ ), 2.46 (1H, m,  $\text{CH}$ ), 2.44 (3H, s, Ar- $\text{CH}_3$ ), 1.17 (3H, s,

C(CH<sub>3</sub>)<sub>2</sub>), 0.90 (3H, s, C(CH<sub>3</sub>)<sub>2</sub>); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 177.1 (C=O), 145.5 (Ar, quaternary), 135.0 (Ar, quaternary), 129.9 (2C, Ar), 128.1 (2C, Ar), 48.9 (C(CH<sub>3</sub>)<sub>2</sub>, quaternary), 45.6 (CH), 45.2 (N-CH<sub>2</sub>), 30.1 (CH<sub>2</sub>Br), 23.5 (Ar-CH<sub>3</sub>), 21.8 (CH<sub>3</sub>), 18.0 (CH<sub>3</sub>).

#### 4-(2-Bromopropan-2-yl)-3,3-dimethyl-1-tosylpyrrolidin-2-one (223)<sup>206</sup>

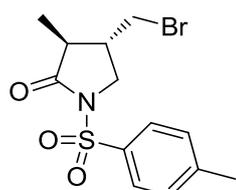


2-Bromo-2-methyl-*N*-(3-methylbut-2-en-1-yl)-*N*-tosylpropanamide (155 mg, 0.40 mmol, 1.000 equiv.) was subject to the general procedure for copper mediated atom transfer radical cyclisation (8.5.1) using CuSO<sub>4</sub> (2.50 mg, 0.01 mmol, 0.025 equiv.), TPA (2.90 mg, 0.01 mmol, 0.025 equiv.), KBH<sub>4</sub> (1.1 mg, 0.02 mmol, 0.050 equiv.) in methanol (1.12 ml) and DCM (0.2 ml). Resulted in formation of white crystalline solid of 4-(2-Bromopropan-2-yl)-3,3-dimethyl-1-tosylpyrrolidin-2-one (118.9 mg, 0.31 mmol, 77 %); spectral details match these reported. δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 7.94 (2H, d, *J*<sub>HH</sub> 8.5 Hz, Ar), 7.36 (2H, d, *J*<sub>HH</sub> 8.5 Hz, Ar), 4.16 (1H, dd, *J*<sub>HH</sub> 10.0, 7.6 Hz, N-CH<sub>2</sub>), 3.81 (1H, t, *J*<sub>HH</sub> 10.0 Hz, N-CH<sub>2</sub>), 2.44 (3H, s, Ar-CH<sub>3</sub>), 2.28 (1H, dd, *J*<sub>HH</sub> 10.0, 7.6 Hz, CH), 1.88 (3H, s, C(CH<sub>3</sub>)<sub>2</sub>Br), 1.86 (3H, s, C(CH<sub>3</sub>)<sub>2</sub>Br), 1.29 (3H, s, C(CH<sub>3</sub>)<sub>2</sub>), 1.07 (3H, s, C(CH<sub>3</sub>)<sub>2</sub>); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 177.2 (C=O), 145.6 (Ar, quaternary), 135.1 (Ar, quaternary), 130.0 (2C, Ar), 128.2 (2C, Ar), 65.4 (C(CH<sub>3</sub>)<sub>2</sub>Br, quaternary), 55.0 (N-CH<sub>2</sub>), 47.9 (CH), 46.9 (C(CH<sub>3</sub>)<sub>2</sub>, quaternary), 36.1 (CH<sub>3</sub>), 33.1 (CH<sub>3</sub>), 26.3 (CH<sub>3</sub>), 22.0 (CH<sub>3</sub>), 19.1 (CH<sub>3</sub>).

**4-(Bromomethyl)-3,3,4-trimethyl-1-tosylpyrrolidin-2-one (225)**<sup>206</sup>

2-Bromo-2-methyl-*N*-(2-methylallyl)-*N*-tosylpropanamide (150 mg, 0.40 mmol, 1.000 equiv.) was subject to the general procedure for copper mediated atom transfer radical cyclisation (8.5.1) using CuSO<sub>4</sub> (2.50 mg, 0.01 mmol, 0.025 equiv.), TPA

(2.90 mg, 0.01 mmol, 0.025 equiv.), KBH<sub>4</sub> (2.2 mg, 0.04 mmol, 0.100 equiv.) in methanol (1.12 ml) and DCM (0.2 ml). Resulted in the formation of 4-(bromomethyl)-3,3,4-trimethyl-1-tosylpyrrolidin-2-one (96.0 mg, 0.26 mmol, 66 %); spectral details match these reported;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.91 (2H, d,  $J_{\text{HH}}$  8.2 Hz, Ar), 7.34 (2H, d,  $J_{\text{HH}}$  8.2 Hz, Ar), 3.85 (1H, d,  $J_{\text{HH}}$  10.6 Hz, N-CH<sub>2</sub>), 3.57 (1H, d,  $J_{\text{HH}}$  10.6 Hz, N-CH<sub>2</sub>), 3.28 (1H, d,  $J_{\text{HH}}$  10.5 Hz, CH<sub>2</sub>Br), 3.22 (1H, d,  $J_{\text{HH}}$  10.5 Hz, CH<sub>2</sub>Br), 2.44 (3H, s, Ar-CH<sub>3</sub>), 1.09 (3H, s, C(CH<sub>3</sub>)<sub>2</sub>), 1.07 (3H, s, C(CH<sub>3</sub>)<sub>2</sub>), 0.97 (3H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 165.2 (C=O), 145.3 (Ar, quaternary), 135.0 (Ar, quaternary), 129.7 (2C, Ar), 128.0 (2C, Ar), 54.1 (N-CH<sub>2</sub>), 48.5 (C(CH<sub>3</sub>)<sub>2</sub>, quaternary), 48.2 (C(CH<sub>3</sub>)CH<sub>2</sub>Br, quaternary), 38.5 (CH<sub>2</sub>Br), 21.7 (Ar-CH<sub>3</sub>), 20.0 (C(CH<sub>3</sub>)<sub>2</sub>), 19.1 (C(CH<sub>3</sub>)<sub>2</sub>), 18.5 (CH<sub>3</sub>).

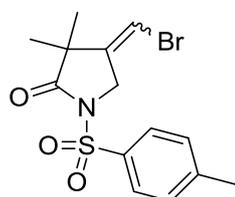
**(S,S)-4-(bromomethyl)-3-methyl-1-tosylpyrrolidin-2-one (227)**<sup>112</sup>

*N*-allyl-2-bromo-*N*-tosylpropanamide tosylpropanamide (146.0 mg, 0.40 mmol, 1.000 equiv.) was subject to the general procedure for copper mediated atom transfer radical cyclisation

(8.5.1) using CuSO<sub>4</sub> (1.00 mg, 0.004 mmol, 0.004 equiv.), TPA (1.20 mg, 0.004

mmol, 0.004 equiv.),  $\text{KBH}_4$  (1.1 mg, 0.02 mmol, 0.050 equiv.) in methanol (1.12 ml) and DCM (0.2 ml). Resulted in formation of (S,S)-4-(bromomethyl)-3-methyl-1-tosylpyrrolidin-2-one (23.1 mg, 0.07 mmol, 17 %); spectral details match these reported;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.88 (2H, d,  $J_{\text{HH}}$  8.2 Hz, Ar), 7.30 (2H, d,  $J_{\text{HH}}$  8.2 Hz, Ar), 4.06 (1H, dd,  $J_{\text{HH}}$  10.2, 7.4 Hz,  $\text{CH}_2\text{Br}$ ), 3.48 (2H, m,  $\text{CH}_2\text{Br}$ , N- $\text{CH}_2$ ), 3.31 (1H, dd,  $J_{\text{HH}}$  10.5, 7.1 Hz, N- $\text{CH}_2$ ), 2.39 (3H, m, Ar- $\text{CH}_3$ ), 2.28 (2H, br,  $\text{CH}$ ), 1.12 (3H, d,  $J_{\text{HH}}$  6.6 Hz,  $\text{CHCH}_3$ );  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 173.9 ( $\text{C}=\text{O}$ ), 145.3 (Ar, quaternary), 134.8 (Ar, quaternary), 129.7 (2C, Ar), 128.0 (2C, Ar), 49.5 ( $\text{CHCH}_3$ ), 42.7 ( $\text{CHCH}_2$ ), 41.7 ( $\text{CH}_2\text{Br}$ ), 32.7 (N- $\text{CH}_2$ ), 21.6 (Ar- $\text{CH}_3$ ), 12.9 ( $\text{CH}_3$ ).

#### 4-(Bromomethylene)-3,3-dimethyl-1-tosylpyrrolidin-2-one (231)<sup>206</sup>



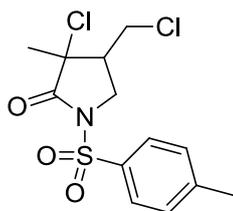
2-Bromo-2-methyl-*N*-(prop-2-yn-1-yl)-*N*-tosylpropanamide

(143 mg, 0.40 mmol, 1.000 equiv.) was subject to the general procedure for copper mediated atom transfer radical cyclisation (8.5.1) using  $\text{CuSO}_4$  (2.50 mg, 0.01 mmol, 0.025 equiv.), TPA

(2.90 mg, 0.01 mmol, 0.025 equiv.),  $\text{KBH}_4$  (2.2 mg, 0.04 mmol, 0.100 equiv.) in methanol (1.12 ml) and DCM (0.2 ml). Resulted in formation of 4-(Bromomethylene)-3,3-dimethyl-1-tosylpyrrolidin-2-one (25.3 mg, 0.07 mmol, 18 %); spectral details match these reported;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.88 (2H, m, Ar), 7.29 (2H, m, Ar), 6.12 (1H, t,  $J_{\text{HH}}$  2.5 Hz,  $\text{CHBr}$ ), 4.39 (2H, m, N- $\text{CH}_2$ ), 2.39 (3H, s, Ar- $\text{CH}_3$ ), 1.16 (3H, s,  $\text{C}(\text{CH}_3)_2$ ), 1.10 (3H, s,  $\text{C}(\text{CH}_3)_2$ );  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 175.8 ( $\text{C}=\text{O}$ ), 145.6 (Ar, quaternary), 142.5 (Ar, quaternary), 134.6 ( $\text{C}=\text{CH}$ , quaternary),

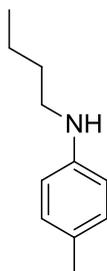
129.7 (2C, Ar), 127.9 (2C, Ar), 102.3 ( $\underline{\text{C}}\text{HBr}$ ), 50.0 (N- $\underline{\text{C}}\text{H}_2$ ), 47.6 ( $\underline{\text{C}}(\text{CH}_3)_2$ , quaternary), 25.0 ( $\underline{\text{C}}\text{H}_3$ ), 24.2 ( $\underline{\text{C}}\text{H}_3$ ), 21.6 (Ar- $\underline{\text{C}}\text{H}_3$ ).

### 3-Chloro-4-(chloromethyl)-3-methyl-1-tosylpyrrolidin-2-one (229a)<sup>112</sup>

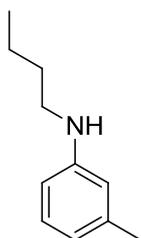


*N*-allyl-2,2-dichloro-*N*-tosylpropanamide (133 mg, 0.40 mmol, 1.000 equiv.) was subject to the general procedure for copper mediated atom transfer radical cyclisation (8.5.1) using  $\text{CuSO}_4$  (2.50 mg, 0.01 mmol, 0.025 equiv.), TPA (2.90 mg, 0.01 mmol, 0.025 equiv.),  $\text{KBH}_4$  (2.2 mg, 0.04 mmol, 0.100 equiv.) in methanol (1.12 ml) and DCM (0.2 ml). Resulted in formation of white crystalline solid of 3-chloro-4-(chloromethyl)-3-methyl-1-tosylpyrrolidin-2-one (87.8 mg, 0.26 mmol, 66 %) as inseparable mixture of diastereoisomers (ratio 1.96 : 1.00 *cis* : *trans*); spectral details match these reported;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) *cis* 7.92 (2H, d,  $J_{\text{HH}}$  8.4 Hz, Ar), 7.35 (2H, d,  $J_{\text{HH}}$  8.4 Hz, Ar), 4.21 (1H, dd,  $J_{\text{HH}}$  10.0, 7.0 Hz, N- $\underline{\text{C}}\text{H}_2$ ), 3.77 (1H, dd,  $J_{\text{HH}}$  11.5, 5.5 Hz, N- $\underline{\text{C}}\text{H}_2$ ), 3.63 (1H, dd,  $J_{\text{HH}}$  11.5, 9.0 Hz,  $\underline{\text{C}}\text{H}_2$ -Cl), 3.44 (1H, t,  $J_{\text{HH}}$  10.0 Hz,  $\underline{\text{C}}\text{H}_2$ -Cl), 2.61 (1H, m,  $\underline{\text{C}}\text{HCH}_2\text{Cl}$ ), 2.45 (3H, s,  $\underline{\text{C}}\text{H}_3$ ), 1.72 (3H, s,  $\underline{\text{C}}\text{H}_3\text{CCl}$ ); *trans* 7.91 (2H, d,  $J_{\text{HH}}$  8.4 Hz, Ar), 7.35 (2H, d,  $J_{\text{HH}}$  8.4 Hz, Ar), 4.14 (1H, dd,  $J_{\text{HH}}$  10.6, 6.6 Hz, N- $\underline{\text{C}}\text{H}_2$ ), 3.87 (1H, dd,  $J_{\text{HH}}$  10.6, 3.6 Hz, N- $\underline{\text{C}}\text{H}_2$ ), 3.65 (1H, dd,  $J_{\text{HH}}$  11.5, 4.3 Hz,  $\underline{\text{C}}\text{H}_2$ -Cl), 3.37 (1H, dd,  $J_{\text{HH}}$  11.5, 8.5 Hz,  $\underline{\text{C}}\text{H}_2$ -Cl), 2.89 (1H, m,  $\underline{\text{C}}\text{HCH}_2\text{Cl}$ ), 2.45 (3H, s,  $\underline{\text{C}}\text{H}_3$ ), 1.60 (3H, s,  $\underline{\text{C}}\text{H}_3\text{CCl}$ );  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) *mixture* 169.3 (C=O), 169.1 (C=O), 146.3 (2C, Ar, quaternary), 134.4 (Ar), 134.1 (Ar), 130.3 (2C, Ar), 130.2 (2C, Ar), 128.6 (2C, Ar), 128.5 (2C, Ar, quaternary), 71.4 ( $\underline{\text{C}}\text{H}_3\text{CCl}$ ), 69.4 ( $\underline{\text{C}}\text{H}_3\text{CCl}$ ), 47.7 ( $\underline{\text{C}}\text{H}_2$ -Cl), 47.6 ( $\underline{\text{C}}\text{H}_2$ -Cl), 47.4 ( $\underline{\text{C}}\text{HCH}_2\text{Cl}$ ), 47.2 ( $\underline{\text{C}}\text{HCH}_2\text{Cl}$ ), 42.3 (N- $\underline{\text{C}}\text{H}_2$ ), 41.4 (N- $\underline{\text{C}}\text{H}_2$ ), 24.2 (2C,  $\underline{\text{C}}\text{H}_3\text{CCl}$ ), 22.2 (2C, Ar- $\underline{\text{C}}\text{H}_3$ ).

## 8.6 Substrates Synthesized In Chapter 7

***N*-butyl-4-methylaniline (251)**<sup>207</sup>

In a 250 ml RBF under nitrogen, sodium hydride (6.72 g, 140 mmol, 1 equiv.) was washed with diethyl ether to remove mineral oil. Amine (15.00 g, 140 mmol, 1 equiv.) was dissolved in DMF (100 ml), added to sodium hydride and allowed to stir for 1 hour. Iodobutane (25.80 g, 140 mmol, 1 equiv.) was then added and the reaction stirred overnight. The reaction was quenched with 90% ethanol and strong effervescing was observed, followed by addition of saturated ammonium chloride. Diethyl ether (200 ml) was added and the organic was washed with water (5 x 50 ml) and brine (5 x 50 ml). The organic was then dried over magnesium sulphate and evaporated. The crude was then purified by column chromatography resulting in formation of an orange oil (4.80 g, 29.4 mmol, 21 %); spectral details match these reported;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 6.98 (2H, d,  $J_{\text{HH}}$  8.1 Hz, Ar), 6.53 (2H, d,  $J_{\text{HH}}$  8.1 Hz, Ar), 3.44 (1H, s, NH), 3.08 (2H, t,  $J_{\text{HH}}$  7.2 Hz, NHCH<sub>2</sub>), 2.23 (3H, s, Ar-CH<sub>3</sub>), 1.59 (2H, quintet,  $J_{\text{HH}}$  7.2 Hz, NH-CH<sub>2</sub>), 1.42 (2H, sextuplet,  $J_{\text{HH}}$  7.2 Hz, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.95 (3H, t,  $J_{\text{HH}}$  7.2 Hz, CH<sub>2</sub>CH<sub>3</sub>).

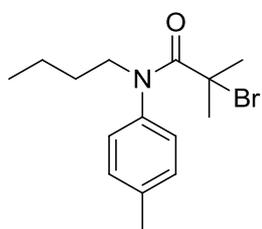
***N*-butyl-3-methylaniline (252)**<sup>207</sup>

In a 250 ml RBF under nitrogen, sodium hydride (6.72 g, 140 mmol, 1 equiv.) was washed with diethyl ether to remove mineral oil. Amine

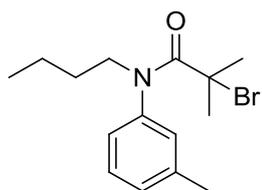
(15.00 g, 140 mmol, 1 equiv.) was dissolved in DMF (100 ml), added to sodium hydride and allowed to stir for 1 hour. Iodobutane (25.80 g, 140 mmol, 1 equiv.) was then added and the reaction stirred overnight. The reaction was quenched with 90% ethanol and strong effervescing was observed, followed by addition of saturated ammonium chloride. Diethyl ether (200 ml) was added and the organic was washed with water (5 x 50 ml) and brine (5 x 50 ml). The organic was then dried over magnesium sulphate and evaporated. The crude was then purified by column chromatography resulting in formation of a yellow oil (5.15 g, 31.5 mmol, 23 %); spectral details match these reported;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.14 – 6.98 (1H, m, Ar), 6.56 – 6.37 (3H, m, Ar), 3.53 (1H, s,  $\text{NH}$ ), 3.10 (2H, t,  $J_{\text{HH}}$  7.2 Hz,  $\text{NHCH}_2$ ), 2.29 (3H, s, Ar- $\text{CH}_3$ ), 1.67 – 1.50 (2H, m,  $\text{NHCH}_2\text{CH}_2$ ), 1.42 (2H, sextuplet,  $J_{\text{HH}}$  7.2 Hz,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.96 (3H, t,  $J_{\text{HH}}$  7.2 Hz,  $\text{CH}_2\text{CH}_3$ ).

### 8.6.1 General Procedure for the Synthesis of Oxindole Precursors 247, 248, 258 and 260 – 265.

Amine and 2-bromoisobutyryl bromide was dissolved in diethyl ether and the mixture was cooled to 0°C. Triethylamine was added drop wise to the mixture and then stirred at room temperature for 24 hours. The organic was then transferred to a separating funnel, washed with water (5 x 50 ml), dilute hydrochloric acid (5 x 50 ml) and 1 M sodium hydrogen carbonate solution (5 x 50 ml). The organic was separated and dried over magnesium sulphate, filtered and evaporated under reduced pressure. No further purification was required.

**2-Bromo-*N*-butyl-2-methyl-*N*-(*p*-tolyl)propanamide (247)**

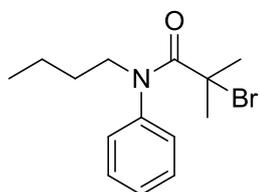
*N*-butyl-4-methylaniline (4.30 g, 26.0 mmol, 1.0 equiv.), 2-bromoisobutyryl bromide (7.28 g, 32.0 mmol, 1.2 equiv.), triethylamine (3.23 g, 32.0 mmol, 1.2 equiv.) and diethyl ether (200 ml) was subject to the general procedure (8.6.1), resulted in formation of a pure dark orange oil (7.19 g, 23.0 mmol, 89 %);  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 2959 (C-H), 1738 (C=O, Amide), 1642 (C=C, Aromatic), 826 (C-Br);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 7.35 – 7.15 (4H, m, Ar), 3.65 (2H, t,  $J_{\text{HH}}$  7.3 Hz, N- $\text{CH}_2$ ), 2.39 (3H, s, Ar- $\text{CH}_3$ ), 1.79 (6H, s, C( $\text{CH}_3$ ) $_2$ Br), 1.55 (2H, quintet,  $J_{\text{HH}}$  7.3 Hz,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 1.30 (2H, sextuplet,  $J_{\text{HH}}$  7.3 Hz,  $\text{CH}_2\text{CH}_3$ ), 0.90 (3H, t,  $J_{\text{HH}}$  7.3 Hz,  $\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 170.0 (C=O, quaternary), 139.9 (Ar- $\text{CH}_3$ , quaternary), 138.2 (Ar-N, quaternary), 129.6 (2C, Ar), 129.4 (2C, Ar), 58.5 (C( $\text{CH}_3$ ) $_2$ Br, quaternary), 53.5 (N- $\text{CH}_2$ ), 33.4 (C( $\text{CH}_3$ ) $_2$ Br), 29.2 ( $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 21.2 (Ar- $\text{CH}_3$ ), 20.0 ( $\text{CH}_2\text{CH}_3$ ), 13.9 ( $\text{CH}_2\text{CH}_3$ );  $m/z$  (ESI) 334 ( $[\text{M}]^+\text{Na}$ ); [Found: ( $[\text{M}]^+\text{Na}$ ) 334.0777,  $\text{C}_{15}\text{H}_{22}^{79}\text{BrNNaO}$  requires, 334.0777].

**2-Bromo-*N*-butyl-2-methyl-*N*-(*m*-tolyl)propanamide (248)**

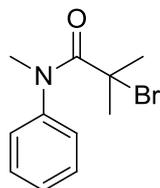
*N*-butyl-3-methylaniline (2.38 g, 14.6 mmol, 1.0 equiv.) 2-bromoisobutyryl bromide (4.03 g, 17.5 mmol, 1.2 equiv.), triethylamine (1.77 g, 17.5 mmol, 1.2 equiv.) and diethyl ether (120 ml) was subject to the general procedure (8.6.1), resulted in formation of a pure dark orange oil (2.49 g, 8.0 mmol, 55 %);  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ )

2965 (C-H), 1719 (C=O, Amide), 1634 (C=C, Aromatic), 833 (C-Br);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 7.28 (1H, t,  $J_{\text{HH}}$  7.7 Hz, Ar), 7.20 – 7.10 (3H, m, Ar), 3.65 (2H, t,  $J_{\text{HH}}$  7.4 Hz, N- $\text{CH}_2$ ), 2.38 (3H, s, Ar- $\text{CH}_3$ ), 1.71 (6H, s,  $\text{C}(\text{CH}_3)_2\text{Br}$ ), 1.56 (2H, quintet,  $J_{\text{HH}}$  7.4 Hz,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 1.31 (2H, sextuplet,  $J_{\text{HH}}$  7.4 Hz,  $\text{CH}_2\text{CH}_3$ ), 0.90 (3H, t,  $J_{\text{HH}}$  7.4 Hz,  $\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 169.7 ( $\text{C}=\text{O}$ , quaternary), 142.5 (Ar-N, quaternary), 139.0 (Ar, quaternary), 130.2 (Ar), 128.9 (Ar), 128.7 (Ar), 126.6 (Ar), 58.6 ( $\text{C}(\text{CH}_3)_2\text{Br}$ , quaternary), 53.4 (N- $\text{CH}_2$ ), 33.4 ( $\text{C}(\text{CH}_3)_2\text{Br}$ ), 29.2 ( $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 21.3 (Ar- $\text{CH}_3$ ), 20.0 ( $\text{CH}_2\text{CH}_3$ ), 13.9 ( $\text{CH}_2\text{CH}_3$ );  $m/z$  (ESI) 334 ( $[\text{M}]^+\text{Na}$ ); [Found: ( $[\text{M}]^+\text{Na}$ ) 334.0771,  $\text{C}_{15}\text{H}_{22}^{79}\text{BrNNaO}$  requires, 334.0777].

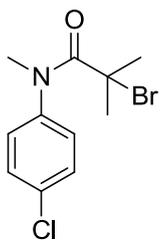
### 2-Bromo-*N*-butyl-2-methyl-*N*-phenylpropanamide (258)



*N*-butylaniline (2.00 g, 13.4 mmol, 1.0 equiv.) 2-bromoisobutyryl bromide (3.69 g, 16.0 mmol, 1.2 equiv.), triethylamine (1.62 g, 16.0 mmol, 1.2 equiv.) and diethyl ether (100 ml) was subject to the general procedure (8.6.1), resulted in the formation of a pure dark orange oil (3.98 g, 13.3 mmol, 99 %);  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 2958 (C-H), 1641 (C=O, Amide), 1593 (C=C, Aromatic), 698 (C-Br);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 7.37 - 7.25 (5H, m, Ar), 3.61 (2H, t,  $J_{\text{HH}}$  7.7 Hz, N- $\text{CH}_2$ ), 1.63 (6H, s,  $\text{C}(\text{CH}_3)_2\text{Br}$ ), 1.53 - 1.44 (2H, m,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 1.24 (2H, sextuplet,  $J_{\text{HH}}$  7.4 Hz,  $\text{CH}_2\text{CH}_3$ ), 0.83 (3H, t,  $J_{\text{HH}}$  7.4 Hz,  $\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 169.7 ( $\text{C}=\text{O}$ , quaternary), 142.7 (Ar-N, quaternary), 129.7 (2C, Ar), 129.0 (Ar), 128.2 (2C, Ar), 58.5 ( $\text{C}(\text{CH}_3)_2\text{Br}$ , quaternary), 53.4 (N- $\text{CH}_2$ ), 33.4 ( $\text{C}(\text{CH}_3)_2\text{Br}$ ), 29.2 ( $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 20.0 ( $\text{CH}_2\text{CH}_3$ ), 13.9 ( $\text{CH}_2\text{CH}_3$ );  $m/z$  (ESI) 320 ( $[\text{M}]^+\text{Na}$ ); [Found: ( $[\text{M}]^+\text{Na}$ ) 320.0623,  $\text{C}_{15}\text{H}_{22}^{79}\text{BrNNaO}$  requires, 320.0620].

**2-Bromo-*N*,2-dimethyl-*N*-phenylpropanamide (260)**<sup>208</sup>

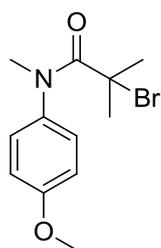
*N*-methylaniline (1.43 g, 13.4 mmol, 1.0 equiv.) 2-bromoisobutyryl bromide (3.69 g, 16.0 mmol, 1.2 equiv.), triethylamine (1.62 g, 16.0 mmol, 1.2 equiv.) and diethyl ether (100 ml) was subject to the general procedure (8.6.1), resulted in formation of pure light yellow crystals (2.82 g, 11.0 mmol, 82 %);  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 2977 (C-H), 1635 (C=O, Amide), 1593 (C=C, Aromatic), 778 (C-Br);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 7.45 - 7.35 (5H, m, Ar), 3.35 (3H, s, N- $\text{CH}_3$ ), 1.76 (6H, s,  $\text{C}(\text{CH}_3)_2\text{Br}$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 170.4 ( $\text{C}=\text{O}$ , quaternary), 144.4 (Ar-N, quaternary), 129.2 (2C, Ar), 128.5 (Ar), 128.1 (2C, Ar), 57.9 ( $\text{C}(\text{CH}_3)_2\text{Br}$ , quaternary), 41.9 (N- $\text{CH}_3$ ), 33.3 ( $\text{C}(\text{CH}_3)_2\text{Br}$ );  $m/z$  (ESI) 278 ( $[\text{M}]^+\text{Na}$ ); [Found: ( $[\text{M}]^+\text{Na}$ ) 278.0153,  $\text{C}_{11}\text{H}_{14}^{79}\text{BrNNaO}$  requires, 278.0151].

**2-Bromo-*N*-(4-chlorophenyl)-*N*,2-dimethylpropanamide (261)**<sup>208</sup>

4-Chloro-*N*-methylaniline (1.90 g, 13.4 mmol, 1.0 equiv.) 2-bromoisobutyryl bromide (3.69 g, 16.0 mmol, 1.2 equiv.), triethylamine (1.62 g, 16.0 mmol, 1.2 equiv.) and diethyl ether (100 ml) was subject to the general procedure (8.6.1), resulted in formation of pure light orange crystals (3.18 g, 10.9 mmol, 82 %);  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 2970 (C-H), 1632 (C=O, Amide), 1591 (C=C, Aromatic), 834 (C-Br), 723 (C-Cl);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 7.39 (2H, dd,  $J_{\text{HH}}$  8.7, 1.9 Hz, Ar), 7.31 (2H, dd,  $J_{\text{HH}}$  8.7, 1.9 Hz, Ar), 3.35 (3H, s, N- $\text{CH}_3$ ), 1.80 (6H, s,  $\text{C}(\text{CH}_3)_2\text{Br}$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 170.3 ( $\text{C}=\text{O}$ , quaternary), 142.9 (Ar-N, quaternary), 133.8 (Ar-Cl, quaternary), 129.9 (2C, Ar), 129.5 (2C, Ar), 57.5 ( $\text{C}(\text{CH}_3)_2\text{Br}$ , quaternary), 41.8 (N- $\text{CH}_3$ ), 33.2 ( $\text{C}(\text{CH}_3)_2\text{Br}$ );

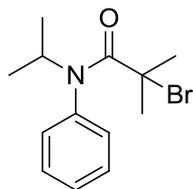
$m/z$  (ESI) 312 ( $[M]^+Na$ ); [Found: ( $[M]^+Na$ ) 311.9759,  $C_{11}H_{13}^{79}BrClNNaO$  requires, 311.9761].

### 2-Bromo-*N*-(4-methoxyphenyl)-*N*,2-dimethylpropanamide (262)



4-Methoxy-*N*-methylaniline (0.75 g, 5.5 mmol, 1.0 equiv.) 2-bromoisobutyryl bromide (1.51 g, 6.5 mmol, 1.2 equiv.), triethylamine (0.66 g, 6.5 mmol, 1.2 equiv.) and diethyl ether (50 ml) was subject to the general procedure (8.6.1), resulted in the formation of a pure brown oil (1.40 g, 4.9 mmol, 89 %);  $\nu_{max}$  (neat,  $cm^{-1}$ ) 2973 (C-H), 1737 (C=O, Amide), 1639 (C=C, Aromatic), 662 (C-Br);  $\delta_H$  (400MHz,  $CDCl_3$ ) 7.22 (2H, d,  $J_{HH}$  8.8 Hz, Ar), 6.83 (2H, dd,  $J_{HH}$  8.8, 1.4 Hz, Ar), 3.76 (3H, s,  $OCH_3$ ), 3.23 (3H, s, N- $CH_3$ ), 1.68 (6H, s,  $C(CH_3)_2Br$ );  $\delta_C$  (100MHz,  $CDCl_3$ ) 170.8 ( $C=O$ , quaternary), 159.1 ( $Ar-OCH_3$ , quaternary), 136.9 (Ar-N, quaternary), 129.7 (2C, Ar), 114.3 (2C, Ar), 58.0 ( $C(CH_3)_2Br$ , quaternary), 55.5 (Ar- $OCH_3$ ), 42.1 (N- $CH_3$ ), 33.3 ( $C(CH_3)_2Br$ );  $m/z$  (ESI) 308 ( $[M]^+Na$ ); [Found: ( $[M]^+Na$ ) 308.0270,  $C_{15}H_{24}^{79}BrNNaO_2$  requires, 308.0257].

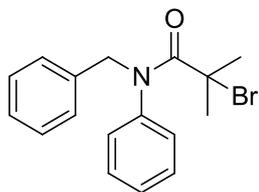
### 2-Bromo-*N*-isopropyl-2-methyl-*N*-phenylpropanamide (264)



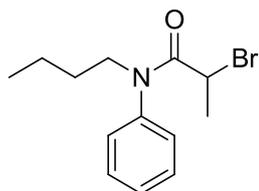
*N*-isopropylaniline (0.50 g, 3.7 mmol, 1.0 equiv.) 2-bromoisobutyryl bromide (1.02 g, 4.4 mmol, 1.2 equiv.), triethylamine (0.45 g, 4.4 mmol, 1.2 equiv.) and diethyl ether (50 ml) was subject to the general procedure (8.6.1), resulted with pure yellow crystals (0.83 g, 2.9 mmol, 79 %); mpt 58 – 60 °C;  $\nu_{max}$  (neat,  $cm^{-1}$ ) 2976 (C-

H, Alkane), 1629 (C=O, Amide), 1588 (C=C, Aromatic), 1322 (C-N), 708 (C-Br);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 7.43 - 7.35 (3H, m, Ar), 7.32 - 7.24 (2H, br m, Ar), 4.98 (1H, septuplet,  $J_{\text{HH}}$  6.7 Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.69 (6H, br s,  $\text{C}(\text{CH}_3)_2\text{Br}$ ), 1.06 (6H, d,  $J_{\text{HH}}$  6.7 Hz,  $\text{CH}(\text{CH}_3)_2$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 169.5 ( $\text{C}=\text{O}$ , quaternary), 137.8 (Ar-N, quaternary), 131.9 (Ar), 128.5 (Ar), 128.3 (Ar), 59.3 ( $\text{C}(\text{CH}_3)_2\text{Br}$ , quaternary), 49.3 ( $\text{CH}(\text{CH}_3)_2$ ), 33.5 ( $\text{C}(\text{CH}_3)_2\text{Br}$ ), 20.6 ( $\text{CH}(\text{CH}_3)_2$ );  $m/z$  (ESI) 284 ( $[\text{M}]^+\text{H}$ ); [Found: ( $[\text{M}]^+\text{H}$ ) 284.0646,  $\text{C}_{13}\text{H}_{19}^{79}\text{BrNO}$  requires, 284.0645].

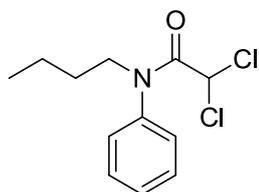
***N*-benzyl-2-bromo-2-methyl-*N*-phenylpropanamide (265)<sup>208</sup>**



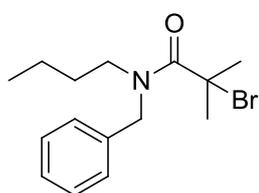
*N*-benzylaniline (2.75 g, 15.0 mmol, 1.0 equiv.) 2-bromoisobutyryl bromide (4.14 g, 18.0 mmol, 1.2 equiv.), triethylamine (1.82 g, 18.0 mmol, 1.2 equiv.) and diethyl ether (120 ml) was subject to the general procedure (8.6.1), resulted in formation of a pure yellow oil (4.33 g, 13.0 mmol, 87 %);  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 2973 (C-H), 1639 (C=O, Amide), 1593 (Aromatic), 1493 (Aromatic), 680 (C-Br);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 7.33 - 7.24 (6H, m, Ar), 7.22 - 7.16 (4H, m, Ar), 4.90 (2H, s, N- $\text{CH}_2$ ), 1.72 (6H, s,  $\text{C}(\text{CH}_3)_2\text{Br}$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 170.1 ( $\text{C}=\text{O}$ , quaternary), 142.2 (Ar-N, quaternary), 137.0 (Ar, quaternary), 130.0 (Ar), 128.9 (Ar), 128.8 (Ar), 128.4 (Ar), 128.3 (Ar), 127.5 (Ar), 58.4 ( $\text{C}(\text{CH}_3)_2\text{Br}$ , quaternary), 57.0 (N- $\text{CH}_2$ ), 33.5 ( $\text{C}(\text{CH}_3)_2\text{Br}$ );  $m/z$  (ESI) 354 ( $[\text{M}]^+\text{Na}$ ); [Found: ( $[\text{M}]^+\text{Na}$ ) 354.0466,  $\text{C}_{17}\text{H}_{18}^{79}\text{BrNNaO}$  requires, 354.0464].

**2-Bromo-*N*-butyl-*N*-phenylpropanamide (266)**

*N*-butylaniline (1.50 g, 10.0 mmol, 1.0 equiv.) and 2-bromopropionyl bromide (2.61 g, 12.0 mmol, 1.2 equiv.) was dissolved in diethyl ether and the mixture was cooled to 0°C. Triethylamine (1.22 g, 12.0 mmol, 1.2 equiv.) was added dropwise to the mixture and then stirred at room temperature for 24 hours. The organic was then transferred to a separating funnel, washed with water (5 x 50 ml), dilute hydrochloric acid (5 x 50 ml) and 1 M sodium hydrogen carbonate solution (5 x 50 ml). The organic was separated and dried over magnesium sulphate, filtered and evaporated under reduced pressure. No further purification was required and resulted in formation of a pure dark orange oil (2.79 g, 9.8 mmol, 98 %);  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 2929 (C-H, Alkane), 1662 (C=O, Amide), 1594 (C=C, Aromatic), 1404 (C-N), 700 (C-Br);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 7.48 - 7.39 (3H, m, Ar), 7.30 - 7.25 (2H, br m, Ar), 4.19 (1H, q,  $J_{\text{HH}}$  6.6 Hz,  $\text{CH}(\text{CH}_3)\text{Br}$ ), 3.81 - 3.71 (1H, m, N- $\text{CH}_2$ ), 3.68 - 3.59 (1H, m, N- $\text{CH}_2$ ), 1.72 (3H, d,  $J_{\text{HH}}$  6.6 Hz,  $\text{CH}(\text{CH}_3)\text{Br}$ ), 1.57 - 1.45 (2H, m,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 1.32 (2H, sextuplet,  $J_{\text{HH}}$  7.3 Hz,  $\text{CH}_2\text{CH}_3$ ), 0.90 (3H, t,  $J_{\text{HH}}$  7.3 Hz,  $\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 169.3 ( $\text{C}=\text{O}$ , quaternary), 141.5 (Ar-N, quaternary), 129.8 (Ar), 128.5 (Ar), 128.2 (Ar), 49.8 (N- $\text{CH}_2$ ), 39.6 ( $\text{CH}$ ), 29.5 ( $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 21.8 ( $\text{CH}(\text{CH}_3)\text{Br}$ ), 20.0 ( $\text{CH}_2\text{CH}_3$ ), 13.8 ( $\text{CH}_2\text{CH}_3$ );  $m/z$  (ESI) 306 ( $[\text{M}]^+\text{Na}$ ); [Found: ( $[\text{M}]^+\text{Na}$ ) 306.0470,  $\text{C}_{13}\text{H}_{18}^{79}\text{BrNNaO}$  requires, 306.0464].

***N*-butyl-2,2-dichloro-*N*-phenylacetamide (267)**

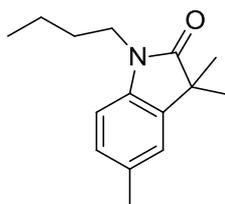
*N*-butylaniline (1.50 g, 10.0 mmol, 1.0 equiv.) and 2,2-dichloroacetyl chloride (1.78 g, 12.0 mmol, 1.2 equiv.) was dissolved in diethyl ether and the mixture was cooled to 0°C. Triethylamine (1.22 g, 12.0 mmol, 1.2 equiv.) was added dropwise to the mixture and then stirred at room temperature for 24 hours. The organic was then transferred to a separating funnel, washed with water (5 x 50 ml), dilute hydrochloric acid (5 x 50 ml) and 1 M sodium hydrogen carbonate solution (5 x 50 ml). The organic was separated and dried over magnesium sulphate, filtered and evaporated under reduced pressure. No further purification was required and resulted in formation of a dark orange oil (2.56 g, 9.8 mmol, 99 %);  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 2958 (C-H, Alkane), 1682 (C=O, Amide), 1594 (C=C, Aromatic), 669 (C-Cl);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 7.52 – 7.44 (3H, m, Ar), 7.29 – 7.23 (2H, m, Ar), 5.80 (1H, s,  $\text{CHCl}_2$ ), 3.74 (2H, t,  $J_{\text{HH}}$  7.6 Hz, N- $\text{CH}_2$ ), 1.59 – 1.49 (2H, m,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 1.34 (2H, sextuplet,  $J_{\text{HH}}$  7.4 Hz,  $\text{CH}_2\text{CH}_3$ ), 0.91 (3H, t,  $J_{\text{HH}}$  7.4 Hz,  $\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 169.7 ( $\text{C}=\text{O}$ , quaternary), 140.22 (Ar-N, quaternary), 130.0 (Ar), 129.2 (Ar), 128.0 (Ar), 64.6 ( $\text{CH}$ ), 50.4 (N- $\text{CH}_2$ ), 29.3 ( $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 20.0 ( $\text{CH}_2\text{CH}_3$ ), 13.7 ( $\text{CH}_2\text{CH}_3$ );  $m/z$  (ESI) 282 ( $[\text{M}]^+\text{Na}$ ); [Found: ( $[\text{M}]^+\text{Na}$ ) 282.0422,  $\text{C}_{12}\text{H}_{15}^{35}\text{Cl}_2\text{NNaO}$  requires, 282.0423].

***N*-benzyl-2-bromo-*N*-butyl-2-methylpropanamide (278)**

*N*-benzylbutan-1-amine (1.63 g, 10.0 mmol, 1.0 equiv.) 2-bromoisobutyryl bromide (2.76 g, 12.0 mmol, 1.2 equiv.),

triethylamine (1.22 g, 12.0 mmol, 1.2 equiv.) and diethyl ether (100 ml) was subject to the general procedure (8.6.1), resulted in formation of a orange oil (2.99 g, 9.6 mmol, 96 %);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 7.45 - 7.10 (5H, m, Ar), 5.20 - 4.56 (2H, br m, Bn- $\text{CH}_2$ ), 3.76 - 3.15 (2H, m, N- $\text{CH}_2$ ), 2.01 (6H, s,  $\text{C}(\text{CH}_3)_2\text{Br}$ ), 1.71 - 1.46 (2H, m,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 1.36 - 1.21 (2H, m,  $\text{CH}_2\text{CH}_3$ ), 0.95 - 0.85 (3H, m,  $\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 170.5 ( $\text{C}=\text{O}$ , quaternary), 136.9 (Ar, quaternary), 128.7 (2C, Ar), 127.3 (2C, Ar), 126.8 (C, Ar), 57.3 ( $\text{C}(\text{CH}_3)_2\text{Br}$ , quaternary), 52.6 (Bn- $\text{CH}_2$ ), 47.1 (N- $\text{CH}_2$ ), 32.9 ( $\text{C}(\text{CH}_3)_2\text{Br}$ ), 30.8 ( $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 20.1 ( $\text{CH}_2\text{CH}_3$ ), 13.9 ( $\text{CH}_2\text{CH}_3$ ).

### 1-Butyl-3,3,5-trimethylindolin-2-one (253)<sup>209</sup>



#### Intramolecular Friedel-Crafts Method

Anhydrous aluminium chloride (1.62 g, 12.1 mmol, 2.5 equiv.) was kept under a stream of nitrogen in a round bottomed flask. 2-bromo-*N*-butyl-2-methyl-*N*-p-tolylpropanamide (1.50 g, 4.8 mmol, 1 equiv.) was added to the stirring aluminium chloride without solvent. An air condenser was attached and the mixture was heated to 50°C for 10 min and then maintained at 160°C for 1 hour. A purple/brown solid was obtained upon cooling. The mixture was washed with water (5 x 50 ml) resulting in a dark yellow solution. The organic product was extracted by diethyl ether, dried over  $\text{MgSO}_4$ , filtered and evaporated, resulting in dark yellow/brown

crude (0.84 g). Crude was purified by column chromatography and resulted with colourless oil (0.45 g, 41%).

### **Bu<sub>3</sub>SnH / AIBN Radical Cyclisation Method**

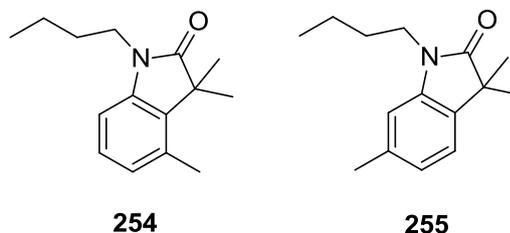
To a solution of 2-bromo-*N*-butyl-2-methyl-*N*-*p*-tolylpropanamide (0.62 g, 2.0 mmol, 1 equiv.) in toluene (60 ml) was added drop-wise a solution of Bu<sub>3</sub>SnH (0.64 g, 2.2 mmol, 1.1 equiv.), and AIBN (0.04 g, 0.25 mmol, 0.13 equiv.) in toluene (20 ml) over 2 hours via syringe pump. The mixture was then heated under reflux for 6 hours. Then additional solution of Bu<sub>3</sub>SnH (0.64 g, 2.2 mmol, 1.1 equiv.), and AIBN (0.04 g, 0.25 mmol, 0.13 equiv.) in toluene (20 ml) was added over an hour and the mixture further refluxed for 8 hours. The solvent was then evaporated, ethyl acetate (40 ml) and 10 % aq. KF solution (100 ml) was added to the residue and the mixture stirred for an hour, washed with water (3 x 40 ml) and brine (3 x 40 ml). The organic phase was separated, dried over magnesium sulfate, concentrated and purified by column chromatography resulting with colourless oil (0.25 g, 54 %).

### **Copper Mediated Radical Cyclisation Method**

Tris(pyridin-2-ylmethyl)amine (TPA) (0.100 g, 0.34 mmol, 1.1 equiv.) and CuBr (0.051g, 0.34 mmol, 1.1 equiv.) was dissolved in methanol (8 ml). 2-bromo-*N*-butyl-2-methyl-*N*-*p*-tolylpropanamide (0.10 g, 0.32 mmol, 1 equiv.) was dissolved in methanol (2 ml), added to the copper complex and stirred for 24 hour under reflux. The mixture was then filtered through silica and washed with dichloromethane. The filtrate was the evaporated, dissolved in diethyl ether, transferred to separating funnel and washed with water (3 x 25 ml). The organic was dried over magnesium sulphate, filtered and evaporated. Colourless oil was obtained (0.064 g, 87%);  $\nu_{\max}$

(neat,  $\text{cm}^{-1}$ ) 2929 (C-H), 1705 (C=O, Amide), 1599 (C=C, Aromatic), 1351 (C-N);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 7.04 (1H, d,  $J_{\text{HH}}$  8.6 Hz, Ar), 7.02 (1H, s, Ar), 6.75 (1H, d,  $J_{\text{HH}}$  8.6 Hz, Ar), 3.68 (2H, t,  $J_{\text{HH}}$  7.3 Hz, N- $\text{CH}_2$ ), 2.35 (3H, s, Ar- $\text{CH}_3$ ), 1.65 (2H, quintet,  $J_{\text{HH}}$  7.3 Hz,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 1.38 – 1.34 (2H, m,  $\text{CH}_2\text{CH}_3$ ), 1.35 (6H, s,  $\text{C}(\text{CH}_3)_2$ ), 0.95 (3H, t,  $J_{\text{HH}}$  7.3 Hz,  $\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 181.3 ( $\text{C}=\text{O}$ , quaternary), 139.7 (Ar-N, quaternary), 136.2 (Ar, quaternary), 131.7 (Ar, quaternary), 127.7 (Ar), 123.3 (Ar), 108.1 (Ar), 44.1 ( $\text{C}(\text{CH}_3)_2$ , quaternary), 39.6 (N- $\text{CH}_2$ ), 29.5 ( $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 24.5 ( $\text{C}(\text{CH}_3)_2$ ), 21.1 (Ar- $\text{CH}_3$ ), 20.1 ( $\text{CH}_2\text{CH}_3$ ), 13.8 ( $\text{CH}_2\text{CH}_3$ );  $m/z$  (ESI) 254.1 ( $[\text{M}]^+\text{Na}$ ); [Found: ( $[\text{M}]^+\text{Na}$ ) 254.1515,  $\text{C}_{15}\text{H}_{21}\text{NNaO}$  requires, 254.1522].

**1-Butyl-3,3,4-trimethylindolin-2-one (254),<sup>209</sup> 1-Butyl-3,3,6-trimethylindolin-2-one (255)<sup>209</sup>**



### Intramolecular Friedel-Crafts Method

Anhydrous aluminium chloride (1.08 g, 8.09 mmol, 2.5 equiv.) was kept under a stream of nitrogen in a round bottomed flask. 2-Bromo-*N*-butyl-2-methyl-*N*-(*m*-tolyl)propanamide (1.00 g, 3.2 mmol, 1 equiv.) was added to the stirring aluminium chloride without solvent. An air condenser was attached and the mixture was heated to 50°C for 10 min and then maintained at 160°C for 1 hour. A purple/brown solid

was obtained upon cooling. The mixture was washed with water (5 x 50 ml) resulting in a dark yellow solution. The organic product was extracted by diethyl ether, dried over MgSO<sub>4</sub>, filtered and evaporated, resulting in dark yellow/brown crude (0.84 g). Crude was purified by column chromatography and resulted with inseparable mixture of 254 and 255 (1.55 : 1.00) (0.55 g, 74%).

### **Bu<sub>3</sub>SnH / AIBN Radical Cyclisation Method**

To a solution of 2-Bromo-*N*-butyl-2-methyl-*N*-(*m*-tolyl)propanamide (0.62 g, 2.0 mmol, 1 eq) in toluene (60 ml) was added drop-wise a solution of Bu<sub>3</sub>SnH (0.64 g, 2.2 mmol, 1.1 equiv.), and AIBN (0.04 g, 0.25 mmol, 0.13 equiv.) in toluene (20 ml) over 2 hours via syringe pump. The mixture was then heated under reflux for 6 hours. Then additional solution of Bu<sub>3</sub>SnH (0.64 g, 2.2 mmol, 1.1 equiv.), and AIBN (0.04 g, 0.25 mmol, 0.13 equiv.) in toluene (20 ml) was added over an hour and the mixture further refluxed for 8 hours. The solvent was then evaporated, ethyl acetate (40 ml) and 10 % aq. KF solution (100 ml) was added to the residue and the mixture stirred for an hour, washed with water (3 x 40 ml) and brine (3 x 40 ml). The organic phase was separated, dried over magnesium sulfate, concentrated and the crude mixture was purified by column chromatography and resulted with inseparable mixture of 254 and 255 (1.00 : 1.90) (0.40 g, 87 %).

### **Copper Mediated Cyclisation Method**

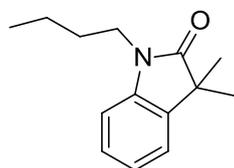
Tris(pyridin-2-ylmethyl)amine (TPA) (0.100 g, 0.34 mmol, 1.1 equiv.) and CuBr (0.051g, 0.34 mmol, 1.1 equiv.) was dissolved in methanol (8 ml). 2-Bromo-*N*-butyl-2-methyl-*N*-(*m*-tolyl)propanamide (0.10 g, 0.32 mmol, 1 equiv.) was dissolved in methanol (2 ml), added to the copper complex and stirred for 24 hour under reflux.

The mixture was then filtered through silica and washed with dichloromethane. The filtrate was the evaporated, dissolved in diethyl ether, transferred to separating funnel and washed with water (3 x 25 ml). The organic was dried over magnesium sulphate, filtered and evaporated. Inseparable mixture of 254 and 255 (2.2 : 1. 0) was obtained (0.066 g, 90%); **1-butyl-3,3,4-trimethylindolin-2-one**;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 2931 (C-H), 1706 (C=O, Amide), 1606 (C=C, Aromatic);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 7.14 (1H, t,  $J_{\text{HH}}$  7.8 Hz, Ar), 6.81 (1H, d,  $J_{\text{HH}}$  7.8 Hz, Ar), 6.71 (1H, d,  $J_{\text{HH}}$  7.8 Hz, Ar), 3.70 (2H, t,  $J_{\text{HH}}$  7.3 Hz, N- $\text{CH}_2$ ), 2.40 (3H, s, Ar- $\text{CH}_3$ ), 1.65 (2H, quintet,  $J_{\text{HH}}$  7.3 Hz,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 1.45 (6H, s,  $\text{C}(\text{CH}_3)_2$ ), 1.38 – 1.34 (2H, m,  $\text{CH}_2\text{CH}_3$ ), 0.95 (3H, t,  $J_{\text{HH}}$  7.3 Hz,  $\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 181.3 (C=O, quaternary), 142.3 (Ar-N, quaternary), 134.2 (C, quaternary), 132.8 (C, quaternary), 127.4 (Ar), 124.7 (Ar), 106.1 (Ar), 44.9 (C, quaternary), 39.6 (N- $\text{CH}_2$ ), 29.5 ( $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 22.4 ( $\text{CH}_3$ ), 20.1 ( $\text{CH}_2\text{CH}_3$ ), 18.2 ( $\text{CH}_3$ ), 13.8 ( $\text{CH}_2\text{CH}_3$ ); **1-butyl-3,3,6-trimethylindolin-2-one**;  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 7.08 (1H, d,  $J_{\text{HH}}$  7.5 Hz, Ar), 6.86 (1H, d,  $J_{\text{HH}}$  7.5 Hz, Ar), 6.68 (1H, s, Ar), 3.69 (2H, t,  $J_{\text{HH}}$  7.3 Hz, N- $\text{CH}_2$ ), 2.38 (3H, s, Ar- $\text{CH}_3$ ), 1.65 (2H, quintet,  $J_{\text{HH}}$  7.3 Hz,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 1.38 – 1.34 (2H, m,  $\text{CH}_2\text{CH}_3$ ), 1.34 (6H, s,  $\text{C}(\text{CH}_3)_2$ ), 0.95 (3H, t,  $J_{\text{HH}}$  7.3 Hz,  $\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 181.3 (C=O, quaternary), 142.2 (Ar-N, quaternary), 137.6 (C, quaternary), 133.2 (C, quaternary), 122.6 (Ar), 122.1 (Ar), 109.2 (Ar), 43.8 ( $\text{C}(\text{CH}_3)_2$ , quaternary), 39.5 (N- $\text{CH}_2$ ), 29.6 ( $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 24.6 ( $\text{C}(\text{CH}_3)_2$ ), 21.8 (Ar- $\text{CH}_3$ ), 20.1 ( $\text{CH}_2\text{CH}_3$ ), 13.8 ( $\text{CH}_2\text{CH}_3$ );  $m/z$  (ESI) 254.1 ( $[\text{M}]^+\text{Na}$ ); [Found: ( $[\text{M}]^+\text{Na}$ ) 254.1519,  $\text{C}_{15}\text{H}_{21}\text{NNaO}$  requires, 254.1522].

### 8.6.2 General Procedure for the Synthesis of Oxindoles

Oxindole precursor, copper metal and TPA was placed in a RBF and dissolved in methanol. The mixture was stirred for 5 min and  $\text{KBH}_4$  was added and continued stirring for 24 hours at 50 °C. The mixture was then filtered through silica plug and washed with DCM (50 ml). The solvent was evaporated, the crude was dissolved in diethyl ether (50 ml), transferred to a separating funnel and washed with water (3 x 25 ml). The organic was then dried over  $\text{MgSO}_4$ , filtered and evaporated. Crude was purified by column chromatography.

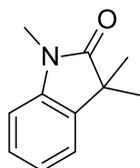
#### 1-Butyl-3,3-dimethylindolin-2-one (259)



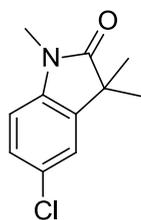
2-Bromo-*N*-butyl-2-methyl-*N*-phenylpropanamide (287.0 mg, 0.96 mmol, 1.0 equiv.) was subject to the general procedure (8.6.2) for copper mediated cyclisation using  $\text{CuBr}$  (15.0 mg, 0.096 mmol, 0.1 equiv.), TPA (27.0 mg, 0.096 mmol, 0.1 equiv.),  $\text{KBH}_4$  (102.0 mg, 1.92 mmol, 2.0 equiv.) in methanol (10 ml). Purified by column chromatography resulting in formation of pale yellow oil of 1-butyl-3,3-dimethylindolin-2-one (67.3 mg, 0.31 mmol, 32 %);  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 2963 (C-H), 1704 (C=O, Amide), 1611 (C=C, Aromatic);  $\delta_{\text{H}}$  (400MHz,  $\text{CDCl}_3$ ) 7.17 (1H, t,  $J_{\text{HH}}$  7.6 Hz, Ar), 7.13 (1H, d,  $J_{\text{HH}}$  7.6 Hz, Ar), 6.97 (1H, t,  $J_{\text{HH}}$  7.6 Hz, Ar), 6.78 (1H, d,  $J_{\text{HH}}$  7.6 Hz, Ar), 3.64 (2H, t,  $J_{\text{HH}}$  7.4 Hz, N- $\text{CH}_2$ ), 1.58 (2H, quintet,  $J_{\text{HH}}$  7.4 Hz,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 1.32 – 1.28 (2H, m,  $\text{CH}_2\text{CH}_3$ ), 1.29 (6H, s,  $\text{C}(\text{CH}_3)_2$ ), 0.87 (3H, t,  $J_{\text{HH}}$  7.4 Hz,  $\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (100MHz,  $\text{CDCl}_3$ ) 181.3 ( $\text{C}=\text{O}$ , quaternary), 142.1 (Ar-N,

quaternary), 136.1 (Ar, quaternary), 127.5 (Ar), 122.4 (Ar), 122.2 (Ar), 108.3 (Ar), 44.1 (C, quaternary), 39.6 (N-CH<sub>2</sub>), 29.5 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 24.5 (C(CH<sub>3</sub>)<sub>2</sub>), 20.1 (CH<sub>2</sub>CH<sub>3</sub>), 13.0 (CH<sub>2</sub>CH<sub>3</sub>); *m/z* (ESI) 240.1 ([M]<sup>+</sup>Na); [Found: ([M]<sup>+</sup>Na) 240.1362, C<sub>14</sub>H<sub>19</sub>NNaO requires, 240.1359].

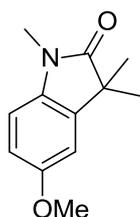
### 1,3,3-Trimethylindolin-2-one (268)<sup>210</sup>



2-Bromo-*N*,2-dimethyl-*N*-phenylpropanamide (246.0 mg, 0.96 mmol, 1.0 equiv.) was subject to the general procedure (8.6.2) for copper mediated cyclisation using CuBr (15.0 mg, 0.096 mmol, 0.1 equiv.), TPA (27.0 mg, 0.096 mmol, 0.1 equiv.), KBH<sub>4</sub> (102.0 mg, 1.92 mmol, 2.0 equiv.) in methanol (10 ml). Purified by column chromatography resulting in formation of pale yellow oil of 1,3,3-trimethylindolin-2-one (26.2 mg, 0.15 mmol, 16 %); spectral details match these reported;  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 2968 (C-H), 1703 (C=O, Amide), 1612 (C=C, Aromatic);  $\delta_{\text{H}}$  (400MHz, CDCl<sub>3</sub>) 7.26 (1H, td,  $J_{\text{HH}}$  7.7, 1.0 Hz, Ar), 7.20 (1H, d,  $J_{\text{HH}}$  7.7 Hz, Ar), 7.06 (1H, td,  $J_{\text{HH}}$  7.7, 1.0 Hz, Ar), 6.84 (1H, d,  $J_{\text{HH}}$  7.7 Hz, Ar), 3.20 (3H, s, N-CH<sub>3</sub>), 1.35 (6H, s, C(CH<sub>3</sub>)<sub>2</sub>);  $\delta_{\text{C}}$  (100MHz, CDCl<sub>3</sub>) 181.4 (C=O, quaternary), 142.7 (Ar-N, quaternary), 135.9 (Ar, quaternary), 127.7 (Ar), 122.5 (Ar), 122.3 (Ar), 108.0 (Ar), 44.2 (C(CH<sub>3</sub>)<sub>2</sub>, quaternary), 26.2 (N-CH<sub>3</sub>), 24.4 (C(CH<sub>3</sub>)<sub>2</sub>); *m/z* (ESI) 176.1 ([M]<sup>+</sup>H); [Found: ([M]<sup>+</sup>H) 176.1070, C<sub>11</sub>H<sub>14</sub>NO requires, 176.1070].

**5-Chloro-1,3,3-trimethylindolin-2-one (269)**<sup>208</sup>

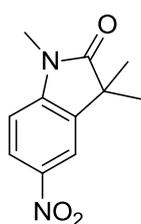
2-Bromo-*N*-(4-chlorophenyl)-*N*,2-dimethylpropanamide (186.0 mg, 0.64 mmol, 1.0 equiv.) was subject to the general procedure (8.6.2) for copper mediated cyclisation using CuBr (9.0 mg, 0.064 mmol, 0.1 equiv.), TPA (18.0 mg, 0.064 mmol, 0.1 equiv.), KBH<sub>4</sub> (54.0 mg, 0.64 mmol, 1.0 equiv.) in methanol (10 ml). Purified by column chromatography resulting in pale yellow crystals of 5-chloro-1,3,3-trimethylindolin-2-one (57.0 mg, 0.27 mmol, 42 %); mpt 92 – 94 °C;  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 2977 (C-H), 1706 (C=O, Amide), 1610 (C=C, Aromatic), 813 (C-Cl);  $\delta_{\text{H}}$  (400MHz, CDCl<sub>3</sub>) 7.16 (1H, dd,  $J_{\text{HH}}$  8.2, 2.1 Hz, Ar), 7.10 (1H, d,  $J_{\text{HH}}$  2.1 Hz, Ar), 6.69 (1H, d,  $J_{\text{HH}}$  8.2 Hz, Ar), 3.13 (3H, s, N-CH<sub>3</sub>), 1.30 (6H, s, C(CH<sub>3</sub>)<sub>2</sub>);  $\delta_{\text{C}}$  (100MHz, CDCl<sub>3</sub>) 180.8 (C=O, quaternary), 141.2 (Ar-N, quaternary), 137.5 (Ar, quaternary), 127.9 (Ar-Cl, quaternary), 127.6 (Ar), 122.9 (Ar), 108.9 (Ar), 44.5 (C(CH<sub>3</sub>)<sub>2</sub>, quaternary), 26.3 (N-CH<sub>3</sub>), 24.3 (C(CH<sub>3</sub>)<sub>2</sub>);  $m/z$  (ESI) 232 ([M]<sup>+</sup>Na); [Found: ([M]<sup>+</sup>Na) 232.0506, C<sub>11</sub>H<sub>12</sub><sup>35</sup>ClNNaO requires, 232.0500].

**5-Methoxy-1,3,3-trimethylindolin-2-one (270)**<sup>211</sup>

2-Bromo-*N*-(4-methoxyphenyl)-*N*,2-dimethylpropanamide (275.0 mg, 0.96 mmol, 1.0 equiv.) was subject to the general procedure (8.6.2) for copper mediated cyclisation using CuBr (15.0 mg, 0.096 mmol, 0.1 equiv.), TPA (27.0 mg, 0.096 mmol, 0.1 equiv.), KBH<sub>4</sub> (102.0 mg, 1.92 mmol, 2.0

equiv.) in methanol (10 ml). Purified by column chromatography resulting in formation of pale yellow crystals of 5-methoxy-1,3,3-trimethylindolin-2-one (41.8 mg, 0.20 mmol, 22 %);  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 2968 (C-H), 2835 (O-CH<sub>3</sub>), 1699 (C=O, Amide), 1601 (C=C, Aromatic);  $\delta_{\text{H}}$  (400MHz, CDCl<sub>3</sub>) 6.81 (1H, d,  $J_{\text{HH}}$  2.4 Hz, Ar), 6.77 (1H, dd,  $J_{\text{HH}}$  8.4, 2.4 Hz, Ar), 6.72 (1H, d,  $J_{\text{HH}}$  8.4 Hz, Ar), 3.78 (3H, s, OCH<sub>3</sub>), 3.17 (3H, s, N-CH<sub>3</sub>), 1.34 (6H, s, C(CH<sub>3</sub>)<sub>2</sub>);  $\delta_{\text{C}}$  (100MHz, CDCl<sub>3</sub>) 181.1 (C=O, quaternary), 156.1 (Ar-OCH<sub>3</sub>, quaternary), 137.3 (Ar-N, quaternary), 136.2 (Ar, quaternary), 111.6 (Ar), 110.1 (Ar), 108.2 (Ar), 55.3 (O-CH<sub>3</sub>), 44.6 (C(CH<sub>3</sub>)<sub>2</sub>, quaternary), 26.3 (N-CH<sub>3</sub>), 24.4 (C(CH<sub>3</sub>)<sub>2</sub>);  $m/z$  (ESI) 206.1 ([M]<sup>+</sup>H); [Found: ([M]<sup>+</sup>H) 206.1175, C<sub>12</sub>H<sub>16</sub>NO<sub>2</sub> requires, 206.1176].

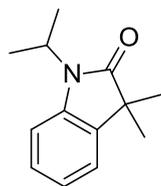
### 1,3,3-Trimethyl-5-nitroindolin-2-one (271)<sup>212</sup>



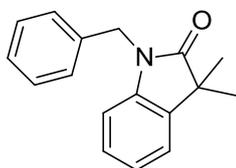
2-Bromo-*N*,2-dimethyl-*N*-(4-nitrophenyl)propanamide (289.0 mg, 0.96 mmol, 1.0 equiv.) was subject to the general procedure (8.6.2) for copper mediated cyclisation using CuBr (15.0 mg, 0.096 mmol, 0.1 equiv.), TPA (27.0 mg, 0.096 mmol, 0.1 equiv.), KBH<sub>4</sub> (102.0 mg, 1.92 mmol, 2.0 equiv.) in methanol (10 ml). Purified by column chromatography resulting in formation of orange crystals of 1,3,3-trimethyl-5-nitroindolin-2-one (74.2 mg, 0.34 mmol, 35 %); spectral details match these reported;  $\nu_{\max}$  (neat,  $\text{cm}^{-1}$ ) 2976 (C-H), 1721 (C=O, Amide), 1613 (C=C, Aromatic), 1508, 1350 (NO<sub>2</sub>);  $\delta_{\text{H}}$  (400MHz, CDCl<sub>3</sub>) 8.26 (1H, dd,  $J_{\text{HH}}$  8.6, 2.3 Hz, Ar), 8.10 (1H, d,  $J_{\text{HH}}$  2.3 Hz, Ar), 6.94 (1H, d,  $J_{\text{HH}}$  8.6 Hz, Ar), 3.30 (3H, s, N-CH<sub>3</sub>), 1.40 (6H, s, C(CH<sub>3</sub>)<sub>2</sub>);  $\delta_{\text{C}}$

(100MHz, CDCl<sub>3</sub>) 181.3 (C=O, quaternary), 148.4 (Ar-N, quaternary), 145.0 (Ar-NO<sub>2</sub>, quaternary), 136.5 (Ar, quaternary), 125.2 (Ar), 118.3 (Ar), 107.6 (Ar), 44.2 (C(CH<sub>3</sub>)<sub>2</sub>, quaternary), 26.6 (N-CH<sub>3</sub>), 24.2 (C(CH<sub>3</sub>)<sub>2</sub>); *m/z* (ESI) 221.1 ([M]<sup>+</sup>H); [Found: ([M]<sup>+</sup>H) 221.0922, C<sub>11</sub>H<sub>13</sub>N<sub>2</sub>O<sub>3</sub> requires, 221.0921].

### 1-Isopropyl-3,3-dimethylindolin-2-one (272)



2-Bromo-*N*-isopropyl-2-methyl-*N*-phenylpropanamide (273.0 mg, 0.96 mmol, 1.0 equiv.) was subject to the general procedure (8.6.2) for copper mediated cyclisation using CuBr (15.0 mg, 0.096 mmol, 0.1 equiv.), TPA (27.0 mg, 0.096 mmol, 0.1 equiv.), KBH<sub>4</sub> (102.0 mg, 1.92 mmol, 2.0 equiv.) in methanol (10 ml). Purified by column chromatography resulting in formation of colourless crystals of 1-isopropyl-3,3-dimethylindolin-2-one (59.0 mg, 0.29 mmol, 30 %);  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 3053 (C-H, Aromatic), 2970 (C-H, Alkane), 1692 (C=O, Amide), 1607, 1486 (C=C, Aromatic), 1358 (C-N);  $\delta_{\text{H}}$  (400MHz, CDCl<sub>3</sub>) 7.22 (1H, t,  $J_{\text{HH}}$  7.8 Hz, Ar), 7.21 (1H, d,  $J_{\text{HH}}$  7.8 Hz, Ar), 7.04 (1H, d,  $J_{\text{HH}}$  7.8 Hz, Ar), 7.02 (1H, d,  $J_{\text{HH}}$  7.8 Hz, Ar), 4.65 (1H, septuplet,  $J_{\text{HH}}$  7.0 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 1.48 (6H, d,  $J_{\text{HH}}$  7.0 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 1.31 (6H, s, C(CH<sub>3</sub>)<sub>2</sub>);  $\delta_{\text{C}}$  (100MHz, CDCl<sub>3</sub>) 181.0 (C=O, quaternary), 141.2 (Ar-N, quaternary), 136.4 (Ar, quaternary), 127.3 (Ar), 122.5 (Ar), 121.9 (Ar), 109.9 (Ar), 43.8 (C(CH<sub>3</sub>)<sub>2</sub>, quaternary), 43.4 (CH(CH<sub>3</sub>)<sub>2</sub>), 24.5 (C(CH<sub>3</sub>)<sub>2</sub>), 19.4 (CH(CH<sub>3</sub>)<sub>2</sub>); *m/z* (ESI) 204.1 ([M]<sup>+</sup>H).

**1-Benzyl-3,3-dimethylindolin-2-one (273)**<sup>211</sup>

*N*-benzyl-2-bromo-2-methyl-*N*-phenylpropanamide (319.0 mg, 0.96 mmol, 1.0 equiv.) was subject to the general procedure (8.6.2) for copper mediated cyclisation using CuBr (15.0 mg, 0.096 mmol, 0.1 equiv.), TPA (27.0 mg, 0.096 mmol, 0.1 equiv.), KBH<sub>4</sub> (102.0 mg, 1.92 mmol, 2.0 equiv.) in methanol (10 ml). Purified by column chromatography resulting in formation of pale yellow crystals of 1-benzyl-3,3-dimethylindolin-2-one (60.1 mg, 0.24 mmol, 25 %); spectral details match these reported; mpt 79 – 81 °C;  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 2970 (C-H), 1708 (C=O, Amide), 1612 (C=C, Aromatic);  $\delta_{\text{H}}$  (400MHz, CDCl<sub>3</sub>) 7.28 – 7.24 (5H, m, Ar), 7.20 (1H, d,  $J_{\text{HH}}$  7.4 Hz, Ar), 7.12 (1H, td,  $J_{\text{HH}}$  7.7, 1.0 Hz, Ar), 7.01 (1H, t,  $J_{\text{HH}}$  7.4 Hz, Ar), 6.72 (1H, d,  $J_{\text{HH}}$  7.7 Hz, Ar), 4.91 (2H, s, N-CH<sub>2</sub>), 1.43 (6H, s, C(CH<sub>3</sub>)<sub>2</sub>);  $\delta_{\text{C}}$  (100MHz, CDCl<sub>3</sub>) 181.0 (C=O, quaternary), 141.7 (Ar-N, quaternary), 136.1 (Ar, quaternary), 135.8 (Ar, quaternary), 128.8 (Ar), 127.6 (Ar), 127.5 (Ar), 127.2 (Ar), 122.5 (Ar), 122.4 (Ar), 109.1 (Ar), 44.2 (C(CH<sub>3</sub>)<sub>2</sub>, quaternary), 43.6 (N-CH<sub>2</sub>), 24.8 (C(CH<sub>3</sub>)<sub>2</sub>);  $m/z$  (ESI) 252.1 ([M]<sup>+</sup>H); [Found: ([M]<sup>+</sup>H) 252.1384, C<sub>17</sub>H<sub>18</sub>NO requires, 252.1383].

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