UNIVERSITY OF Southampton
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Electrosynthesis in flow reactors. Part 1: Anodic deprotection of nitrogen containing compounds. Part 2: Cathodic cyclisation of aryl halides

by

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Abstract

Flow electrosynthesis is an important field of chemistry, with the ability to deliver improved selectivity, higher yields, and higher productivities compared to both batch electrochemistry and chemical oxidative and reductive processes, in a manner that satisfies the global need for sustainable production of materials.

Herein discusses the flow electrosynthesis carried out using a spiral, extended channel length microflow cell designed for routine and convenient application in an organic synthesis laboratory: The Ammonite 8 reactor. Specifically, two chemical transformations were explored in this work: the anodic deprotection of the 4-methoxybenzyl (PMB) protecting group from nitrogen containing compounds, and the cathodic cyclisation of aryl halides.

By the anodic process, the PMB group was successfully removed from seventeen substrates, including two biologically active β-lactams, with yields of up to 91%. The process could be scaled to operate in the Ammonite 15 reactor, where productivities of 43 mmol/hour could be achieved. As a continuation to this work, in collaboration with Dr Ana Folgueiras, a paired electrosynthesis was implemented using an oxidatively and reductively active molecule, 2-Iodo-*N*-(4-methoxybenzyl)benzamide in a parallel-plate divided electrolysis reactor developed in-house. Selective anodic removal of the PMB group, and cathodic dehalogenation of the aryl iodide were achieved, and the methodology was extended to further substrates.

By the cathodic process, heterocycles were furnished from their respective aryl iodides, bromides and chlorides in what is the first metal-free mediated reductive electrosynthesis of its kind. Thirteen substrates were cyclised successfully, in yields of up to 92% and productivities of 12 mmol/hour. The mediator used to induce cyclisation was found to operate catalytically, further providing merit to the sustainability criteria of the process.

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Finally, a big thank you to my family, friends, girlfriend Elen and most of all, my parents whose endless encouragement, love and support have helped me to where I am.

Dedicated to my late Grandpa, John Theodore Teuten,

for never ceasing to believe in and inspire me.

Definitions and Abbreviations

CAN	Ceric Ammonium Nitrate
CRD	Cambridge Reactor Design
CV	Cyclic Voltammetry
DDQ	2,3–Dichloro–5,6–dicyano–1,4–benzoquinone
DMB	1,3–dimethoxylbenzyl
DMF	Dimethylformamide
DNPH	2,4-dinitrophenylhydrazine
DoE	Design of Experiment
EA	Electroauxilliary
EI	Electron ionisation
ESI	Electrospray ionisation
FDA	Food and Drugs Administration
FFKM	Perfluoroelastomer (synthetic rubber)
GC	Gas Chromatography
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
LRMS	Low Resolution Mass Spectrometry
MeCN	Acetonitrile
NMP	*N*–Methylpyrrolidinone
NMR	Nuclear Magnetic Resonance
PEM	Polymer-Electrolyte Membrane or Proton-Exchange Membrane
PG	Protecting Group
PMB	Paramethoxybenzyl (IUPAC: 4–methoxybenzyl)

PPE	Personal Protective Equipment
PVDF	Polyvinylidenefluoride
RT	Room Temperature
SCE	Saturated Calomel Electrode
SET	Single Electron Transfer
SHE	Standard Hydrogen Electrode
SM	Starting Material
SS	Stainless Steel
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

Chapter 1 Introduction

1.1 Organic electrochemistry

1.1.1 Introduction to electrosynthesis

The process of organic electrochemistry, or electrosynthesis, is to create organic compounds in an electrochemical cell. Neutral substrates undergo redox processes through the application of a current (i.e. a flow of charge, by electrons or electrolyte ions), with reactions initiated through a single electron transfer (SET) to form radical species as intermediates (Figure 1.1).[1]

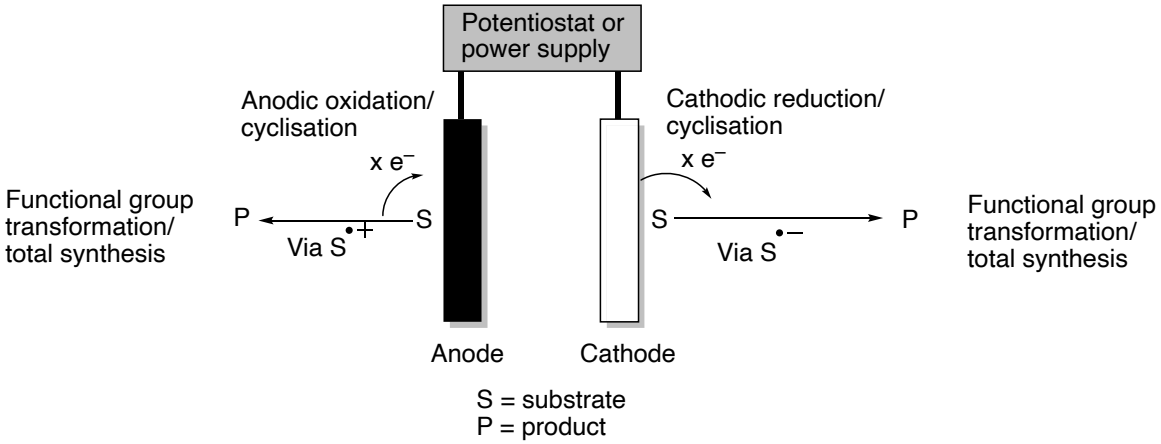


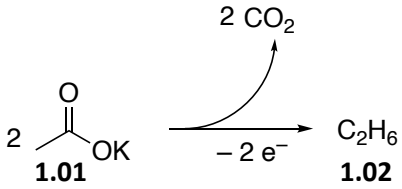
Figure 1.1: Anodic and cathodic processes in neutral substrates

Neutral substrates undergoing oxidation reactions react via the loss of an electron to form a radical cation species, with uncharged reduction substrates gaining an electron to form radical anions. This species is transformed to the final product by a series of bond forming or bond breaking steps, with further SET's possible. An electrochemical setup requires two electrodes: an anode and a cathode, both in contact with a solution with sufficient electrical conductivity that current can pass, through migration of ions. A power source is also required, which is able to deliver a direct current.[2]

1.1.2 History of organic electrochemistry

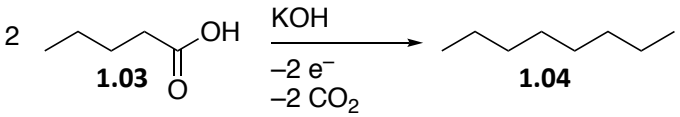
The first reported use of electricity to induce a chemical transformation was in 1789 by Troostwijk and Deiman. These were two Dutch merchants that used an electrostatic generator to produce a discharge between two gold electrodes immersed in water.[3] The next significant

development was not until 1800 however, when Alessandro Volta created the first electrochemical cell: the voltaic pile from copper and zinc stack electrodes.[4] Later that year, Anthony Carlisle and William Nicholson used the cell to split water into oxygen and hydrogen, thereby carrying out the first electrolysis.[5] However, the first organic electrosynthesis was not carried out until 1834 when Faraday electrolysed potassium acetate to form ethane with concomitant loss of CO_2 (Scheme 1.1).[6]



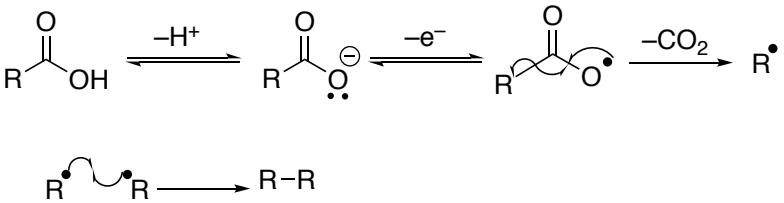
Scheme 1.1: The first organic electrosynthesis, reported by Faraday

Faraday's work also led to the coining of terms such as electrolysis, anode and cathode, and the understanding that an electric current induces the movement of ions through a solution, a concept that led to the use of ionic salts as electrolytes to improve the electrical conductivity of organic solvents. Following on from this, Kolbe established a method to synthesise dimeric alkanes through decarboxylation of carboxylic acids, a process known today as the Kolbe coupling (Scheme 1.2).[7]



Scheme 1.2: Kolbe coupling by anodic decarboxylation

The driving force of the reaction is the formation of CO_2, which being a gas represents a large increase in entropy. Formation of a stable product i.e., a hydrocarbon, with formation of a strong C–C bond is another driving force. The reaction mechanism (Scheme 1.3) includes the formation of the radical anion of the carboxylic acid, followed by decarboxylation to form an alkyl radical. Two of these couple together to afford the alkane product.

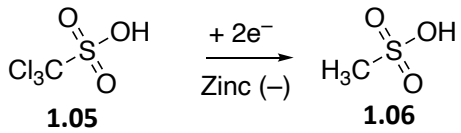


Scheme 1.3: Kolbe coupling mechanism

Redox processes (such as the first step in this reaction) are reversible in their nature up until the point when a chemical reaction occurs (in this case, decarboxylation in a C–C bond

cleaving step). The formation of a more stable compound (in this case the dimerisation of two alkyl radicals in a C–C bond forming step) prevents any reverse reaction occurring. Over the years there have been many modifications of the Kolbe coupling, including the Crum Brown–Walker reaction developed in 1891 that features the coupling of half-esters such as mono-ethyl malonate.[8]

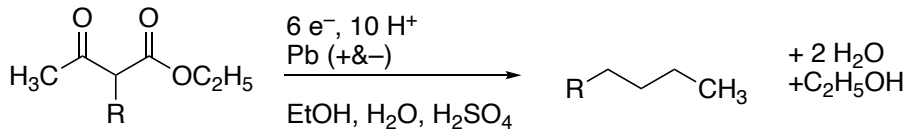
The first reductive organic process was thought to be the dehalogenation of Trichloromethylsulfonic acid to Methylsulfonic acid on a zinc cathode by Schöenbein (Scheme 1.4). [9]



1.05 **1.06**

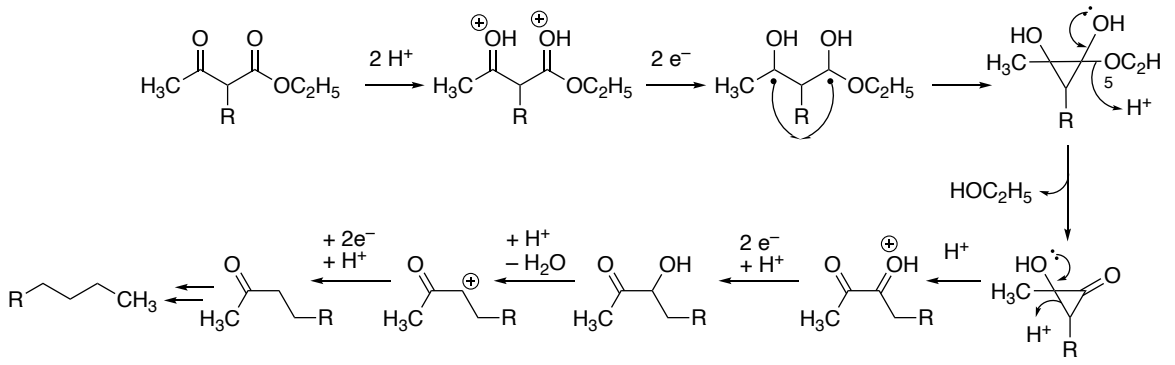
Scheme 1.4: Cathodic dehalogenation of Trichloromethylsulfonic acid to Methylsulfonic acid by Schöenbein

Another reductive process called the Tafel rearrangement, developed in 1907, is a widely used method to prepare hydrocarbons from alkylated acetoacetates (Scheme 1.5).[10]



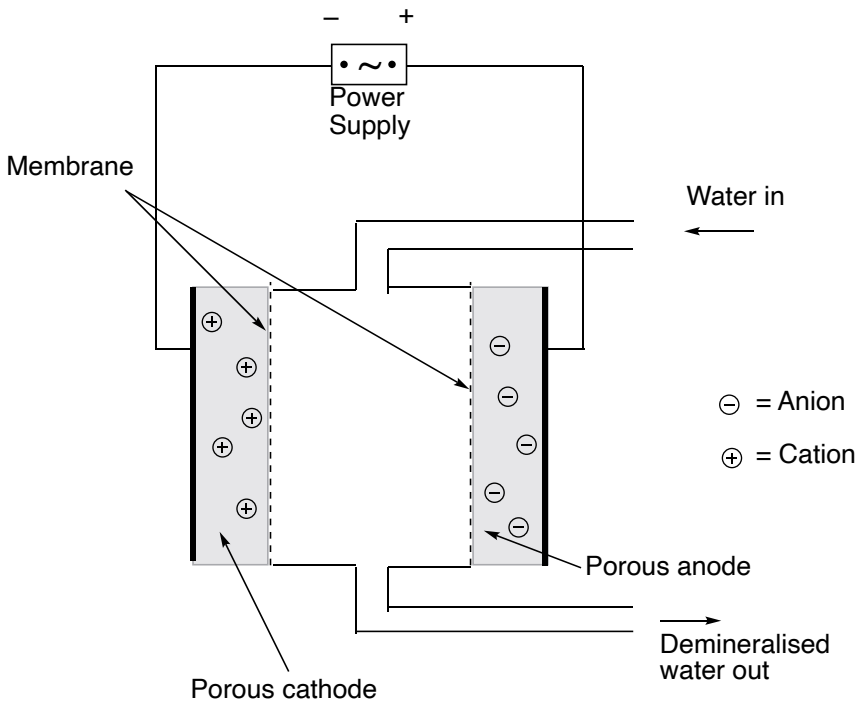
Scheme 1.5: Hydrocarbon preparation by Tafel rearrangement

The proposed mechanism for this unusual reaction features a two-electron reduction of the doubly protonated starting material (which is crucial: rearrangement is not observed in the absence of a nonacidic medium), followed by cyclisation of the diradical to form a cyclopropane. Collapse of the hemiacetal creates the cyclopropenone, and subsequent collapse of the cyclopropane affords the diketone. This can then further reduce (in a similar mechanism to that of the Clemmensen reduction[11]) to the hydrocarbon (Scheme 1.6).



Scheme 1.6: Proposed mechanism for the Tafel rearrangement

The first divided electrolysis was described in a 1889 German patent by Maigrot and Sabates, involving an electrodialysis process proposed for sugar syrup demineralisation with a non-selective separator.[12] Electrodialysis involves the removal of ions from a solution by transport through ion-permeable membranes under an applied electrical field. Demineralisation is an example of this, and is a common technique in waste water treatment works, along with the technique by which deionised water is made (Scheme 1.7)[13, 14]



Scheme 1.7: Water demineralisation process, adapted from Zhaoxiang Qi and Gary M. Koenig Jr's Review Article: "Flow battery systems with solid electroactive materials"

These processes indicated and underpinned the synthetic capabilities of electrochemistry and led to many more electrosynthetic reactions in years to come.

1.1.3 Fundamentals of electrosynthesis

1.1.3.1 Mass transfer and the electrical double layer

Electron transfer in the typical sense is a heterogeneous process, in that electrons are transferred from the cathode, enter the reaction solution and leave through the anode. As a result, an interface exists between the electrodes and the solution, which itself differs from the bulk solution and alters the course of the electrochemical process. This interface is known as the electrical double layer. This theory originated from the work of Helmholtz, and later Perrin who proposed that positively charged ions move toward cathode and negatively charged ions move toward anode creating external Helmholtz layers, leaving a hydrated sheet in the middle consisting of water molecules called the inner Helmholtz layer.[15] This theory has certain limitations as it considered the electrodes to be rigid and ignored factors like diffusion, mixing, and adsorption of ions on the electrode surfaces. Later, Gouy and Chapman observed that electrochemical capacitance (build-up of charge) depends on the applied potential and the ionic concentration of the solution. Hence, they used statistics deduced by Maxwell and Boltzmann to develop a model for capacitance accounting for the potential difference and temperature. Their proposal was a semi-infinite layer of anions and cations distributed unequally in obedience of Poisson and Boltzmann laws by which the potential gradient diminishes exponentially from the surface of the electrode.[16-18] Later Stern proposed what is generally considered to be an accurate model of the electrode surface in most instances for aqueous systems, although there is little evidence that the same model fits for organic solvent systems. Stern's model is a combination of the two models described above, proposing that some ions adhere to the electrode in the internal layer as suggested by Helmholtz, giving an internal Stern layer, while some form a Gouy-Chapman diffuse layer.[19-21]

The Stern model suggests that there is now a steep potential gradient over the double layer, which is not felt in the bulk phase (Figure 1.1). The double layer is typically between 1 and 10 nm and depending on the applied voltage, a potential gradient of the order of 10^6 V cm^{-1} can be achieved, which is an electrical field of considerable intensity. It is this that drives the electrochemical reaction at the electrode surface.

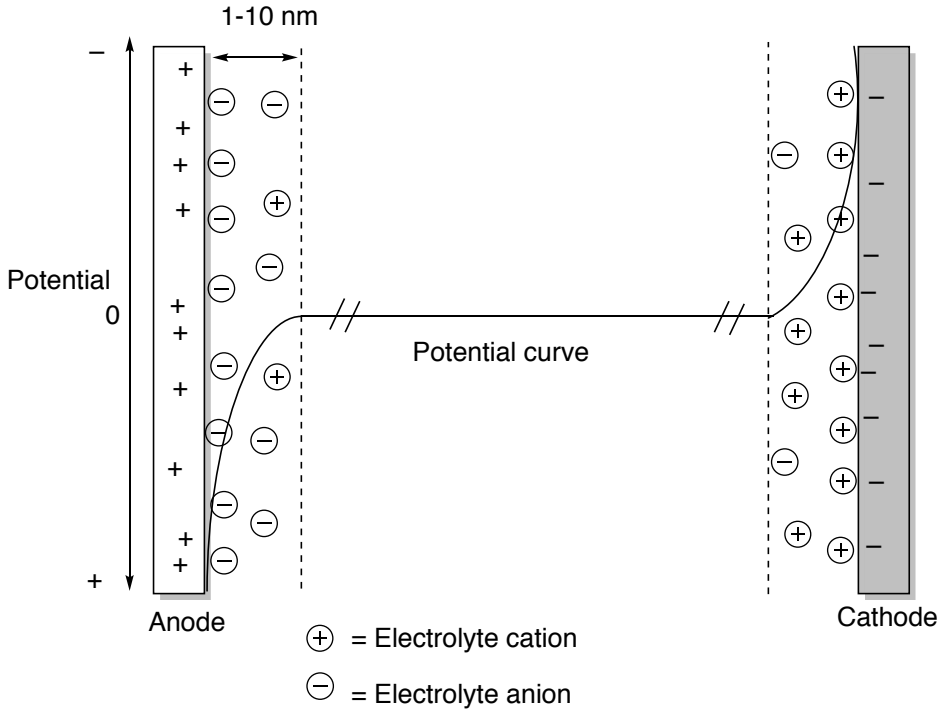


Figure 1.2: Model of the electrical double layer in aqueous systems, adapted from Fuchigami, T, Inagi, S and Atobe, M's "Fundamentals and Applications of Organic Electrochemistry"

Electron transfer from the electrode to the substrate creates a charge imbalance in the vicinity, and as such ions are transferred to the electrode interface to neutralise this, which propagates the movement of ions and hence current in the solution. The mechanism outlined in scheme 1.3 is a simplified illustration for the process that occurs during electrolysis. The electrochemical setup also needs to be considered. Figure 1.3 illustrates each elementary reaction step of substrate S forming product P via intermediate I.[2]

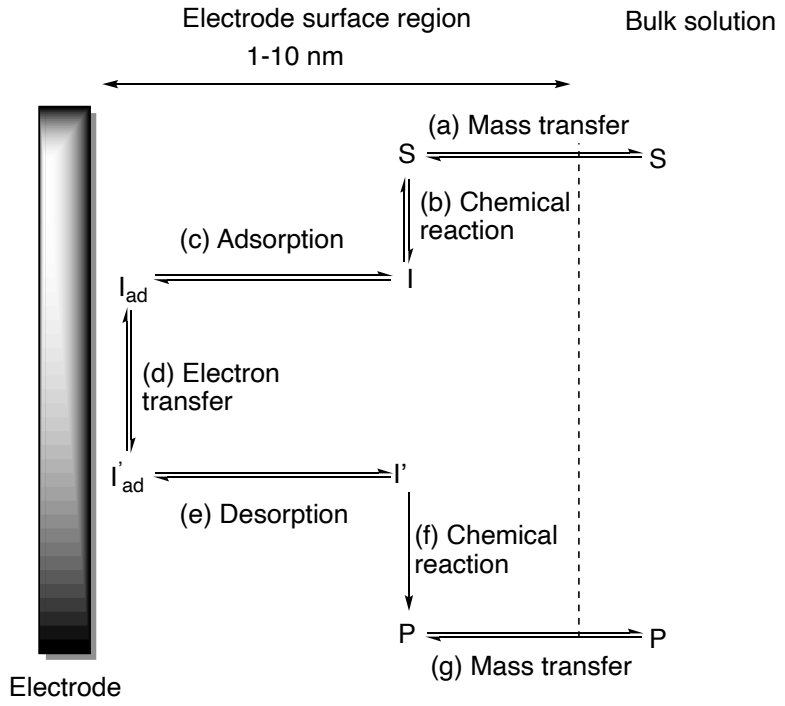


Figure 1.3: Elementary processes of electrode reactions, adapted from "Fuchigami, T, Inagi, S and Atobe, M's Fundamentals and Applications of Organic Electrochemistry"

Initially, a substrate molecule must approach the electrode surface from the bulk solution, which occurs in step (a). Next reversible chemical processes such as deprotonation, desolvation or dissociation in step (b) may occur to form intermediate I, which then adsorbs to the electrode surface in step (c). In step (d) intermediate I (or substrate S) will undergo electron transfer to create a radical species, which desorbs from the electrode in step (e). A subsequent chemical reaction (f) forms product O that then escapes the double layer to the bulk solution in step (g). During indirect electrolysis, electron transfer in I will occur without an adsorption process, furthermore steps (e) and (f) may be reversed i.e., I_{ad} undergoes a reaction at the electrode surface before desorption occurs. This reaction represents a one-electron electrochemical process, which occurs in coupling reactions such as the Kolbe electrolysis. However, many (most in fact) electrochemical reactions are two-electron processes, and as such a second electron transfer step will occur, either with or without adsorption to the electrode surface. Figure 1.2 illustrates nicely how much an electrochemical reaction differs to a conventional homogeneous chemical reaction.[2]

In terms of the relative rates of the processes described above, the electron transfer process and chemical steps are very fast, and in most cases the rate-limiting step in electrolysis is the rate of mass transfer from the bulk solution to the electrode. This process can be quantified through the mass transfer coefficient, which depends on theoretical factors such as mass transfer area, driving force concentration difference and mass transfer rate, and also practical factors such

as flow patterns in the electrochemical reactor and diffusivities of the substrates.

1.1.3.2 Redox potentials, orbitals and the effect of electroauxillaries

Redox potential is an intrinsic property of any substance, be it a material (e.g., electrode), organic molecule (either solvent or reagent) or inorganic salt (e.g., electrolyte). It is a measure of the tendency for a chemical species to gain or lose electrons, thereby being reduced or oxidised, respectively. Redox potential is measured in volts (V) and is determined relative to the redox potential of a reference reaction, since it is practically impossible to determine the absolute potential of a species. Common materials and reactions for the reference electrode will be discussed later. The relative magnitude for the redox potential of one species to another determines how readily that process will occur and the potential that needs to be applied for the reaction to proceed (assuming the potential for the redox couple is positive and thereby a potential is required).[22, 23]

In terms of molecular orbitals, a reduction is described as the transfer of an electron from the cathode to the lowest unoccupied molecular orbital (LUMO) of the substrate. An oxidation process is the transfer of an electron from the highest occupied molecular orbital (HOMO) of the substrate to the anode. The redox potential directly correlates with the LUMO energy of a reduction substrate, and the HOMO of an oxidation substrate i.e., a low energy LUMO means a substrate is easily reduced and a high energy HOMO means a substrate is easily oxidised. The Fermi level (which in the absence of an applied potential sits between the HOMO and LUMO in conductors) lowers and rises when a positive and negative potential is applied respectively: an oxidation occurs when the Fermi energy level of the electrode falls below the substrate's HOMO, and a reduction occurs when the Fermi level exceeds the substrate's LUMO (Figure 1.3).[2, 22, 24]

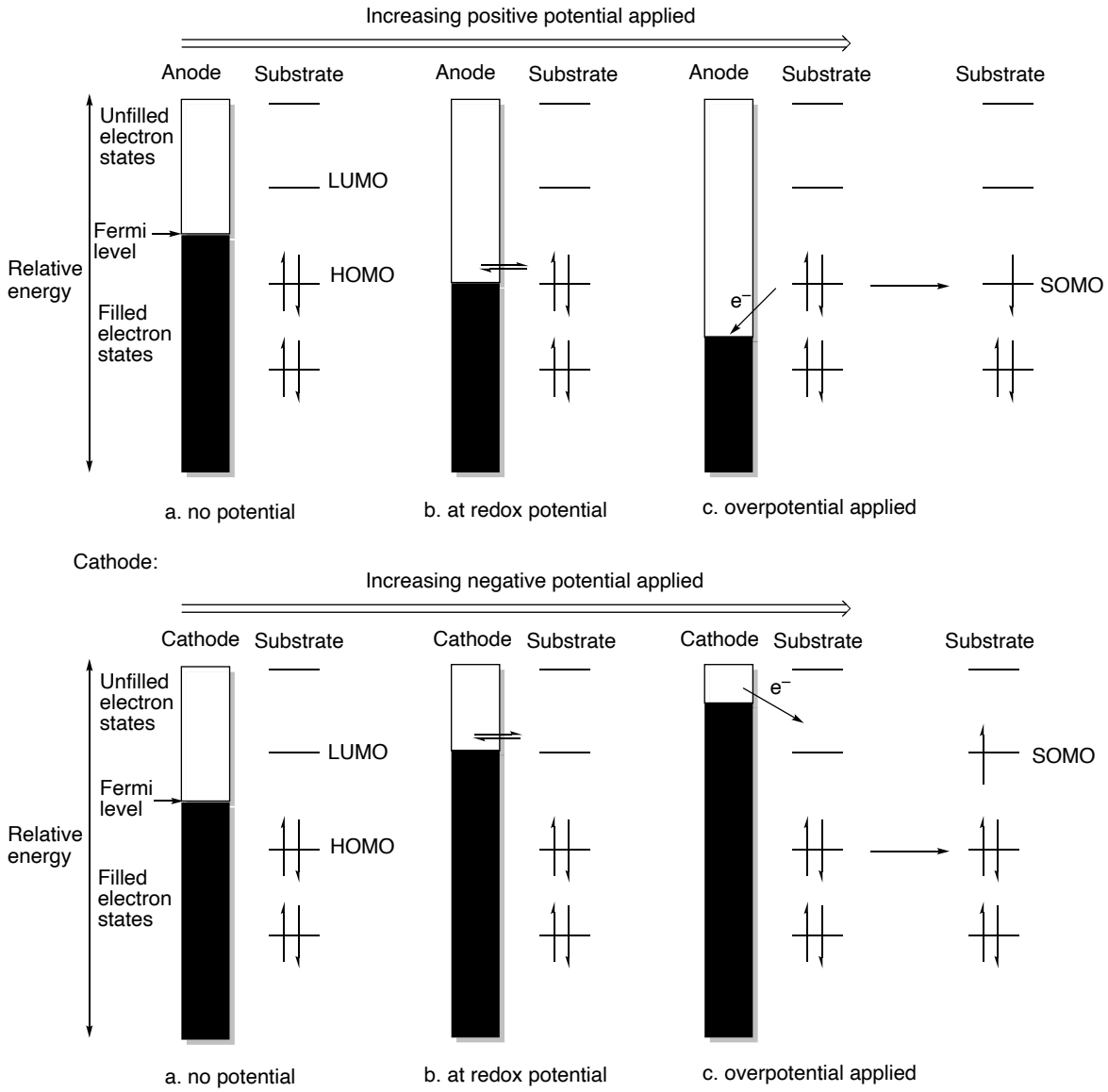
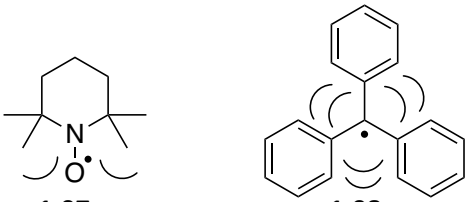


Figure 1.4: Orbital energy diagrams illustrating redox processes

The potential difference between the standard potential and the potential at which the redox event is experimentally observed is called the overpotential. The critical potential at which this electron-transfer process occurs identifies the standard potential, E_0, of the redox couple, relative to a reference potential. After electron transfer has taken place a radical species forms, whereby a singly occupied molecular orbital (SOMO) is formed.[2]

All organic molecules have a redox potential, and this is dependent on degree of radical stabilisation that is created by neighbouring groups. It is known that radicals are stabilised by both electron donating and withdrawing groups, but the extent of this varies.[25] Bulky groups which introduce steric hinderance also have a stabilising effect, for example in the TEMPO and triphenylmethyl radicals (**1.07** and **1.08**), which are (further) stabilised by four methyl groups and three phenyl groups respectively (Figure 1.5).[26]



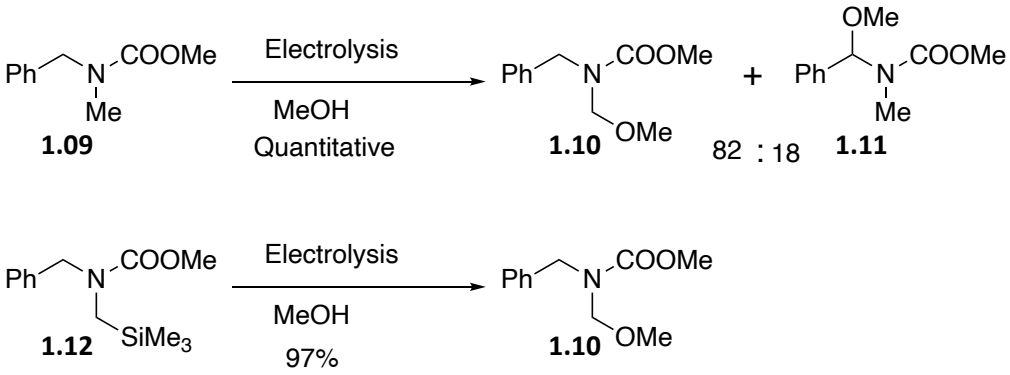
1.07 **1.08**

Figure 1.5: Stabilisation of TEMPO and triphenylmethyl radicals by steric hinderance

For a useful electrochemical reaction to occur in a selective manner, it is necessary that:

- Electron transfer should occur selectively at the position in the substrate molecule that is needed for a subsequent chemical process.
- The subsequent chemical process should occur selectively to cleave the specific bond or make a bond at that site.[27]

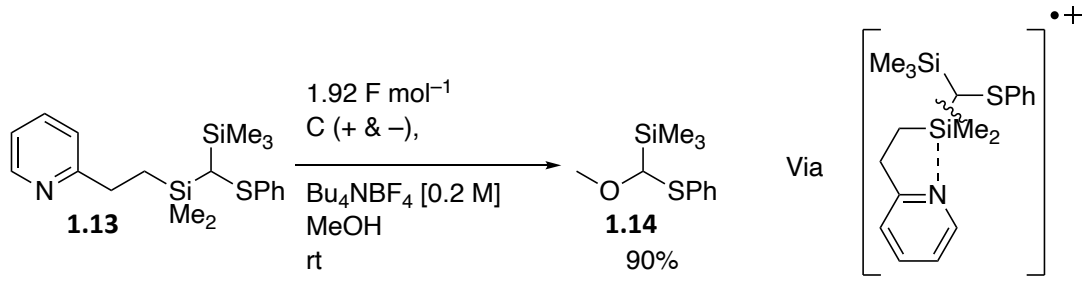
Functional groups that modify the redox potential for a specific site, and therefore control the electrochemical reactivity of a substrate are effective. Such a functional group is called an electroauxiliary (EA). Use of EA's enables regioselective electrochemical transformations that are difficult to achieve by conventional means. Reductive EA'S are rare and so only those of oxidative EA's are discussed. In orbital terms, the introduction of the EA increases the energy of the HOMO level, thereby decreasing the oxidative potential at the position which the EA is attached, namely the α-position carbon. Introduction of the EA results in a regioselective electron transfer at this position, where in its absence several sites on the substrate could oxidise readily (Scheme 1.8).[27] [28, 29]



Scheme 1.8: Impact of an electroauxiliary on the regioselectivity of the Shono oxidation

An example of an electroauxiliary is the trimethylsilyl group (Scheme 1.4), which lowers the oxidation potential at the methylene carbon such that regioselective methanolysis occurs. This effect is also brought about when using germanyl,[30] stannyl,[31, 32] and phenylthio[33] EA's. Similarly to protecting groups, the incorporation (removal is not required as the EA is cleaved as part of the reaction) of an EA requires an extra step in a synthesis, and so it is advantageous to use EA's that are easily and cleanly added. It is worth noting that if the EA has a specific coordinating site to stabilise the developing charge, the electron transfer can be assisted by a distant intramolecular

coordination. Such coordination also facilitates subsequent chemical processes such as fragmentation. The pyridyl group serves as an effective coordinating group for the oxidation of compounds containing heteroatoms and, therefore, functions as an additional electroauxiliary. For example, the pyridylethylsilyl group can confer electrochemical selectivity even over that of conventional EA's (Scheme 1.9). [34, 35]



Scheme 1.9: Yoshida's "super" EA

The ability to selectively remove the pyridylethylsilyl EA in the presence of other oxidatively electroactive groups is very desirable, especially where such groups are part of the final compound of interest or used to protect another functional group, which can then be oxidatively cleaved later on. The selectivity arises from the stabilisation of the emerging positive charge on silicon by donation of electron density from the pyridine nitrogen, which acts synergistically with the positive inductive effect of the silyl group to the attached carbon. Other peripheral groups containing heteroatoms can also be used in place of pyridine.[34]

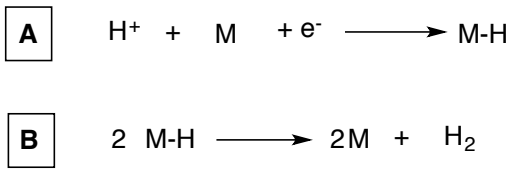
1.1.3.3 Counter-electrode processes

Any redox process, by definition, has two reactions occurring simultaneously, and so electrosynthesis is no exception to this rule. Where only one useful reaction occurs there will be a counter-reaction occurring that has no synthetic use, however this process must be robust and unlikely to interfere with the useful process. There are many counter-reactions known, both reductive and oxidative.

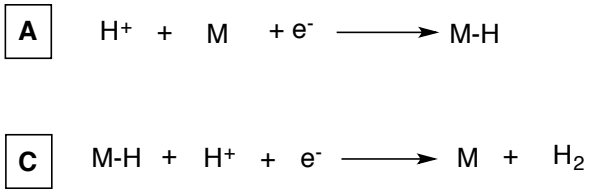
1.1.3.3.1 Reductive counter-electrode processes

The most common counter-electrode reaction in electrosynthesis is the reduction of a protic solvent, where the working electrode reaction is an oxidation. In the case of water electrolysis this is known as the hydrogen evolution reaction (HER), with an oxidation potential of –1.23V.[36] There are two commonly-accepted mechanisms for generic hydrogen evolution from protic solvents (Scheme 1.6).[37]

Mechanism 1



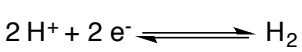
Mechansm 2



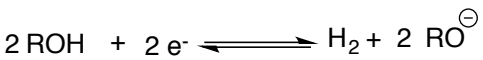
Scheme 1.10: Electrode processes leading to hydrogen gas evolution

M represents a site on the surface of the cathode material. The initial step A is the same in each case, but steps B and C will be in competition with each other, with the faster reaction dominating. The electrode surface clearly has an impact in the mechanism and therefore rate of hydrogen evolution. It is noteworthy to add that at different pH the overall hydrogen evolution reaction occurs through different species as shown:

In acidic solution:



In neutral or basic solution:

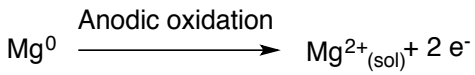


Scheme 1.11: Electrochemical hydrogen formation in acidic and basic conditions

In acidic solutions, protons have dissociated from the solvent prior to reduction. Literature mechanistic studies show that the counter-electrode reaction in many systems, including the Shono oxidation described in section 1.1.5.1.1, and in the deprotection of the PMB group from organic substrates in chapter 2 follow one of the two processes in Scheme 1.11.

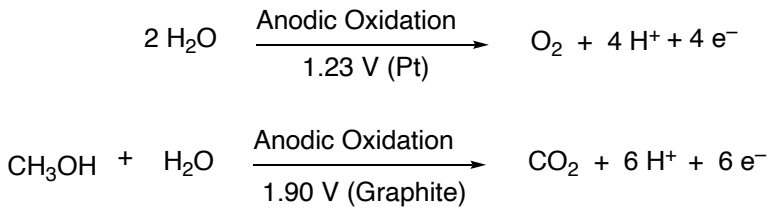
1.1.3.3.2 Oxidative counter-electrode processes

For reductive electrosynthesis, widely explored counter-electrode reaction mechanisms utilise a sacrificial metal (magnesium, aluminium, zinc or alloys of these) anode, whereby the metal anode is degraded and oxidised metal cations are allowed to escape (Scheme 1.12). [38]



Scheme 1.12: Counter-electrode anodic oxidation (sacrificial Mg electrode)

Alternatively, oxidation of a protic solvent (H_2O or MeOH) is also common:[36, 37]



Scheme 1.13: Anodic counter-electrode solvent oxidation mechanisms

Other counter-electrode processes (such as protic solvent oxidation above, or paired electrosynthesis) have largely superseded sacrificial metal anodes in recent years, for a number of reasons. The cationic metal species can interfere in the reaction (e.g. Mg^{2+} and other cationic metals can act as Lewis acids, which can have undesirable effects on the reaction), and frequently prevent recovery of catalysts and electrolytes from the reaction solution, although in some cases the cationic metal species can carry out either or both of these roles. Purification can also be affected: poor aqueous solubility of many sacrificial metals can complicate extractive workup. Furthermore, the FDA operates very low tolerability limits for metals within medicines, which makes the use of sacrificial anodes prohibitively restrictive in the synthesis of many pharmaceuticals.

1.1.3.4 Direct vs. indirect electrolysis

The method of electron transfer described in section 1.3.2 is a heterogeneous process whereby the substrate is oxidised or reduced at the electrode surface. This is referred to as a direct electrolysis. In Indirect electrolysis, the electron transfer step on the substrate is a homogeneous process that occurs away from the electrode, whereby an electrochemical mediator undergoes a redox process instead of the substrate. The mediator is an electrochemically generated reagent that will be part of a reversible redox couple starting at the electrode and then performing the reaction of interest. An illustration of an oxidative indirect electrolysis follows (Figure 1.6).[28]

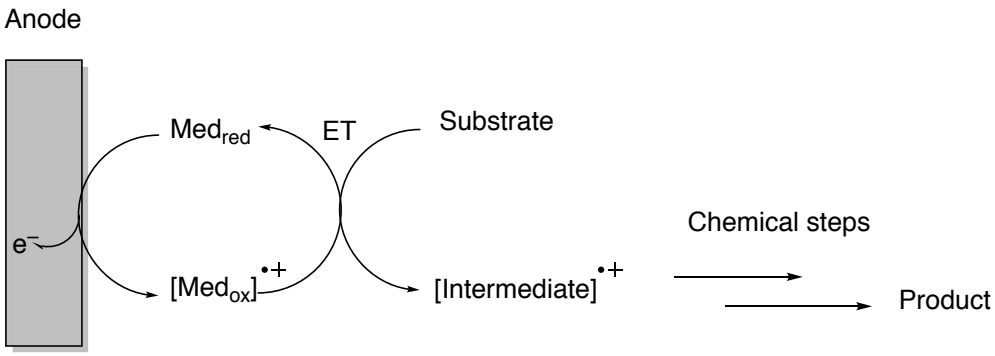
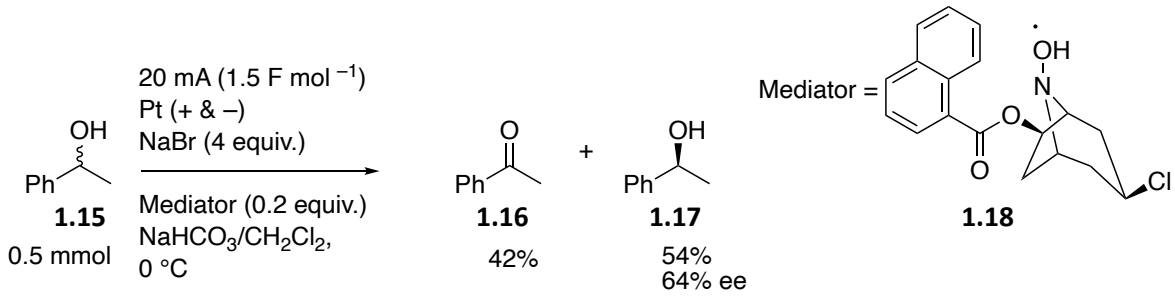


Figure 1.6: Indirect electrolysis schematic

In essence, indirect electrolysis is a combination of an electrochemical reaction and a homogeneous redox process (which would utilise a chemical redox reagent, and these are often employed as electrochemical mediators due to this). Indirect electrolysis exists in two formats: in-cell and ex-cell. For in-cell electrolysis, the substrate and mediator are both present in the same cell. The redox potential for the mediator is typically lower in magnitude (although not always, see Chapter 3 of this work) than that of the substrate. In ex-cell electrolysis, the mediator and substrate are in separate vessels, and the applied potential only serves to activate or regenerate the mediator.

Because the mediator for in-cell electrolysis has a lower potential, it can be used in catalytic amounts. The lower potential of the mediator allows electrolysis under milder conditions, as the substrate would not react, or react slowly under the applied potential. This can circumvent the formation of side-products, which is beneficial, especially when the substrate has complex functionality. In ex-cell electrolysis the redox potential of the mediator exceeds that of the substrate, and so a quantitative amount of the mediator is necessary. In this setup the activated mediator must be sufficiently stable to be transferred to the second reaction vessel. Purification can also be more difficult since the mediator is often present in larger quantities. The merit of ex-cell is that it represents a simpler approach, since the two processes (electrolysis of the mediator, and electron transfer/chemical reaction with the substrate) can be optimised separately. Nevertheless, in-cell represents the more desirable method of indirect electrolysis, both for economic and environmental factors. Mediators in electrosynthesis offer a different route to forming the product and often lead to improved selectivity for the target redox site, in the same way an EA would. Such selectivity may not be possible by direct electrolysis, or through the use of a chemical redox reagent. In addition, mediators often bypass common problems in electrosynthesis that is the passivation of the electrodes (which occurs when a polymer film partially or fully blocks an electrode surface and prevents current from passing), and

overoxidation/reduction of the substrate.[28] Mediators have other specific roles, such as inducing chirality[38] (Scheme 1.14)[39, 40]



Scheme 1.14: Use of chiral aminooxyl mediator in enantioselective alcohol oxidation

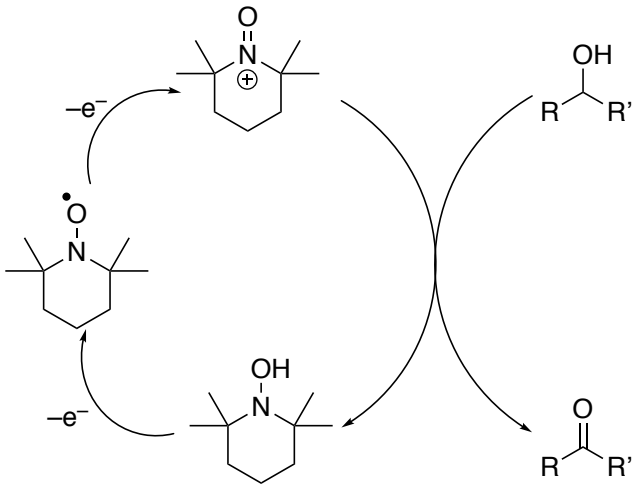
Cyclic voltammetry is particularly useful for the initial evaluation of an indirect electrosynthesis, since the redox potentials for substrate and mediator in the reaction solvent can be measured and hence the potential at which the catalytic step takes place can be determined. Studying the literature for similar transformations that have been carried out by a certain mediator is of course another sensible method for selecting a mediator, along with identifying a chemical redox reagent that could be used catalytically, being regenerated electrochemically.[2]

There are many commercial mediators available, which facilitate a variety of electrochemical reactions. Their structures and redox potentials generally mean that they are only effective at mediating specific processes, i.e. there isn't a "one size fits all" approach to indirect electrolysis. Mediators can be categorised by whether they mediate oxidative or reductive processes. Oxidative mediators include triarylamines, *N*-oxyl radicals, halide salts, iodobenzene derivatives, DDQ, triarylimidazoles, nitrate salts, and various transition metal salts (Cr^{VI}/Cr^{III}, Fe^{III}/Fe^{II}, V^{V}/V^{III}, Ce^{IV}/Ce^{III}, Co^{III}/Co^{II}, Ru^{VIII}/Ru^{IV}, Os^{VIII}/Os^{VI} and Mn^{III}/Mn^{II}). Common reductive redox mediators include aromatic hydrocarbons, fullerenes and o-carboranes, Ni and Co-salen complexes, highly-dispersed base metal particles (Zn^{II}/Zn^{0}, Cu^{II}/Cu^{0}, Sn^{II}/Sn^{0}, Fe^{II}/Fe^{0}), low–valent metal salts (Ti^{IV}/Ti^{III} and Cr^{III}/Cr^{II}) and various transition metal complexes (Ni^{0}/Ni^{II}, Ni^{I}/Ni^{II}, Co^{I}/Co^{III}, Pd^{0}/Pd^{II}, Rh^{I}/Rh^{III}). Important examples of oxidative, reductive and paired electrosynthesis using mediators will be discussed.[28]

1.1.3.4.1 Oxidative indirect electrolysis

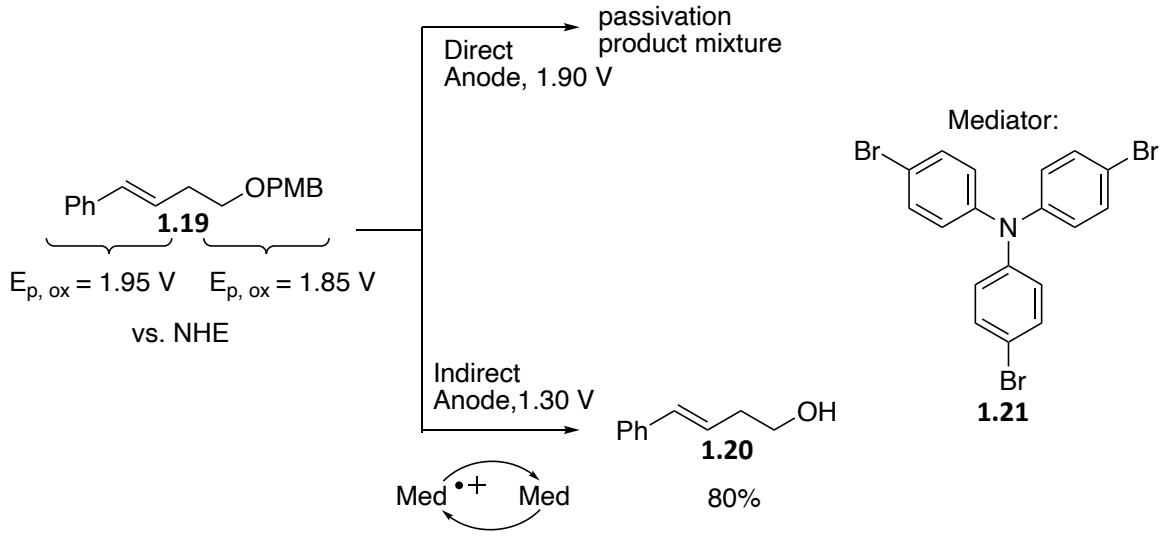
Brown *et al.* reported a flow method to electrochemically oxidise primary and secondary alcohols to form aldehydes and ketones respectively, using the aminooxyl radical 2,2,6,6,-tetramethylpiperidine-1-oxyl (TEMPO) as a mediator (Scheme 1.15).[41] The first alcohol oxidation by TEMPO was developed by Semmelhack, Choe and Cortes in 1983,[42] using stoichiometric TEMPO and as a mediator using electrochemistry. Conducting the reaction electrochemically

means it can be used in catalytic amounts, being turned over by the generated current. In the electrolysis TEMPO is oxidised at the anode to give the oxoammonium ion, which then oxidises the alcohol to form the corresponding aldehyde or ketone, and the hydroxylamine. This is rapidly oxidised at the anode through a single electrode transfer to regenerate the TEMPO radical. (Scheme 1.15).



Scheme 1.15: Electrochemical TEMPO–mediated alcohol oxidation

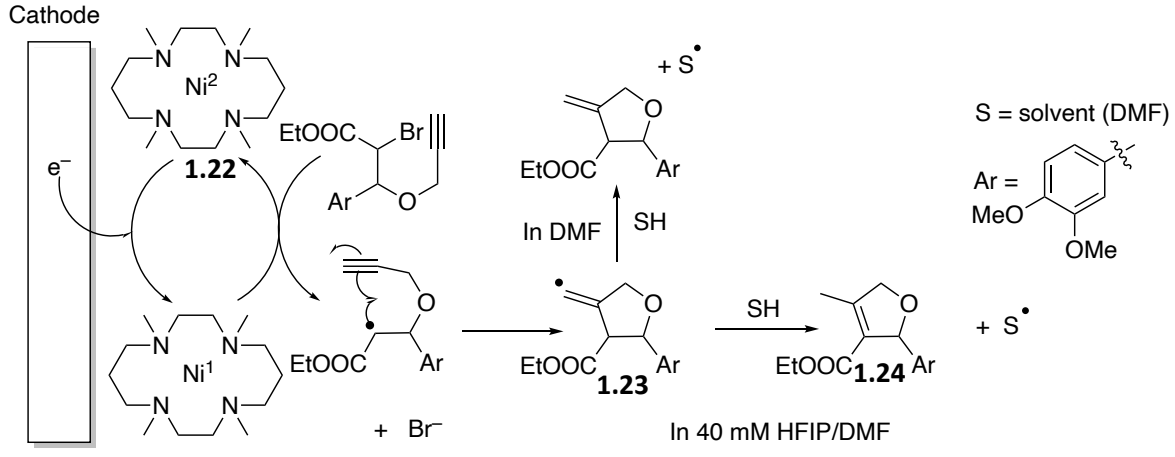
Another important example is the mediated electrochemical removal of the PMB group in the presence of an oxidatively active styrene moiety. The substrate contains two electrophores whose potentials differ by just 0.1 V. However, the indirect electrolysis demonstrates 100% selectivity. A reaction scheme follows (Scheme 1.16).[43]



Scheme 1.16: Indirect electrolysis utilised in the selective deprotection of PMB ether using a triarylamine mediator

1.1.3.4.2 Reductive indirect electrolysis

Radical cyclisation of unsaturated alkyl halides constitutes one of the key methodologies for the preparation of natural products containing heterocyclic rings. Traditionally they are accomplished with toxic Tri-n-butyltin hydride in the presence of a radical initiator such as azobisisobutyronitrile (AIBN). Peters *et al.* used an electrogenerated nickel(I) complex (**1.22**) as a mediator in the cyclisation of a bromo propargyloxy ester (Scheme 1.17).[28, 44] Similar work was also conducted by Little *et al*.[45]

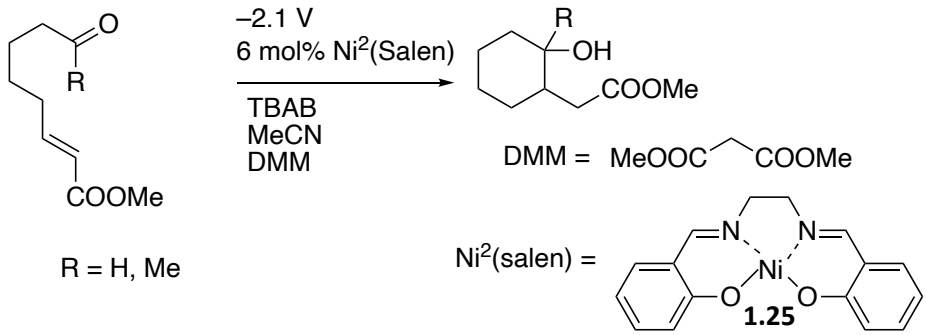


Scheme 1.17: Electrochemical reductive cyclisation using a Ni^1(TMC) mediator [44]

In the absence of a proton donor (HFIP), the exo-alkene **1.23** forms in 76% yield. When HFIP is added however, the endo dihydrofuran **1.24** is obtained in near-quantitative yield.[28, 44] It is proposed that in essence, the HFIP acts as a buffer in the electrolysed solution that facilitates isomerisation of the alkene products, a theory substantiated by the fact that the conjugate base

of HFIP will readily deprotonate the exo alkene. This methodology was similarly utilised in chapter 3 of this thesis wherein radical cyclisation was conducted with a polyaromatic hydrocarbon as mediator.

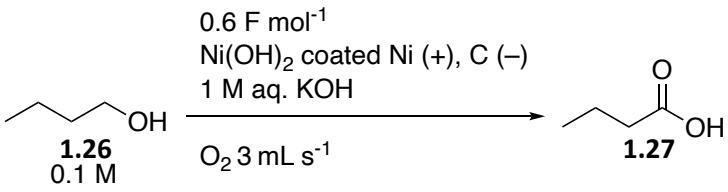
Using a similar Ni^1 complex (**1.25**), an indirect electrohydrocyclisation was achieved by Little *et al.* (Scheme 1.18).[45]



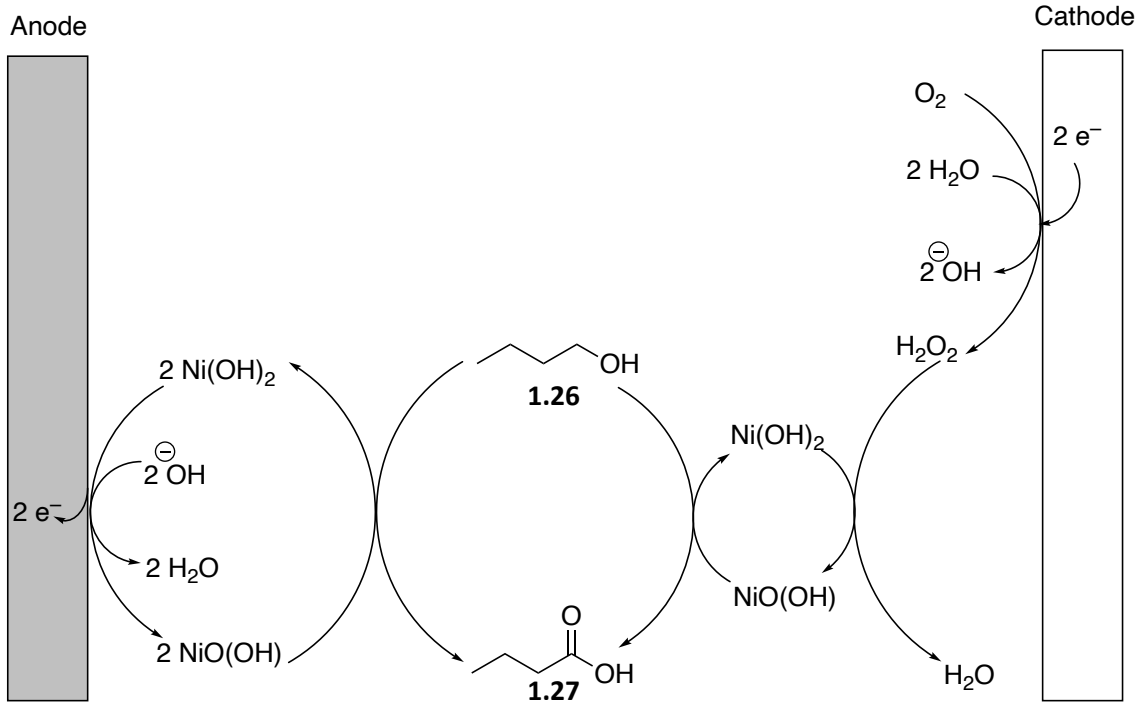
Scheme 1.18: Indirect EHC using Ni^2(salen) mediator by Little *et al.*

1.1.3.4.3 Paired indirect electrolysis

Chou *et al.* developed a paired convergent electrosynthesis of *n*-Butyric acid from *n*-Butanol. This means that both the anode and cathode reactions lead to product formation. The method uses a Ni^{III} source (NiO(OH) as the mediator for the anodic oxidation, which is oxidised from $Ni(OH)_2$, and H_2O_2 as a mediator for the cathodic reduction, which arises through the reduction of oxygen. Alcohols (excluding MeOH and benzylic alcohols) typically display a high oxidation potential, leading to a low current efficiency and passivation of the electrode surfaces, hence why Brown *et al.* required a mediator for their alcohol oxidation electrolysis method (Scheme 1.15).[41] The mediators also play an important role here, and thanks to efficient transfer of electrons between electrodes; this method provides current efficiencies of 175%, a remarkable result that can only be achieved under paired electrolysis. The $Ni(OH)_2$ mediator is supplied by the electrode (as a coating, or Ni can simply be used), which because it acts catalytically is not significantly consumed in the reaction. The reactions in the paired oxidation are expressed in Scheme 1.19 and Scheme 1.20:[46]



Scheme 1.19: Indirect paired electrolysis of *n*-Butanol to *n*-Butyric acid by Chou *et al.* using $Ni(OH)_2$ and H_2O_2 as mediators



Scheme 1.20: Schematic for the paired electrolysis of *n*–Butanol to *n*–Butyric acid by Chou *et al.*

Three moles of n-butyric acid are made for every mole of O_2 (the limiting reagent). Two moles are created directly by the Nickel^{III} species, and another by the regeneration of 1 equiv. of the Nickel^{III} species by reduction of H_2O_2 to H_2O. O_2 is delivered into the reactor through a stream of bubbles. The mediator reactions balance such that hydroxide anions created by cathodic oxygen reduction are used in the oxidation of the oxidation of $Ni(OH)_2$, so there is no change in pH during the reaction.

Nikishi *et al.* developed a paired indirect electrosynthesis to create *trans*-α,β-dicyanostilbenes from benzonitriles, with a sodium halide mediator (Scheme 1.21 and Scheme 1.22).[47]

Anode:

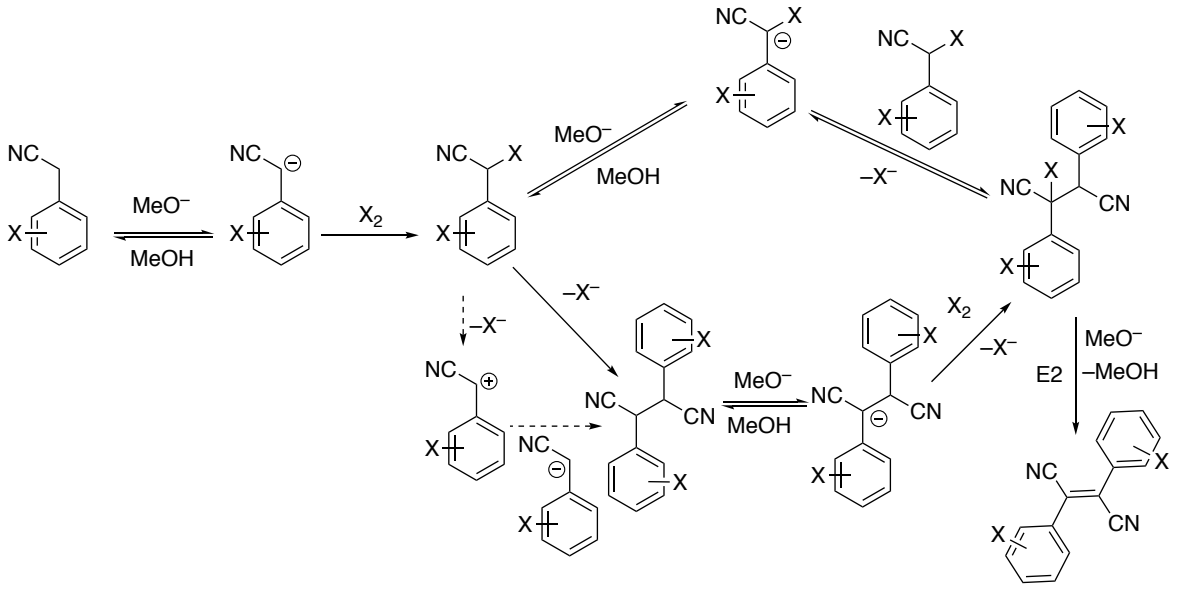
$$2\,X^- \longrightarrow X_2 + 2\,e^-$$

X = Br, I

Cathode:

$$2\,MeOH + 2\,e^- \longrightarrow 2\,MeO^- + H_2$$

Scheme 1.21: electrode processes in paired indirect benzonitrile coupling by Nikishin *et al.*



Scheme 1.22: Chemical steps involved in benzonitrile coupling

The organic reaction occurs through the cathodic electro-generation of base in the form of methoxide. The oxidation of the halide salt is the counter-electron reaction, which is common owing to its low oxidation potential. Formation of base enables a powerful transformation of the substrate through the series of steps shown. The two mechanisms were both shown to proceed in appreciable rates, with the final step an E2 elimination to give the *trans* product.

1.1.3.5 Cyclic voltammetry

Cyclic voltammetry is an experimental technique that allows electrochemical reactions to be investigated. It has been used during this work to acquire information, through understanding the electrochemical process. Both qualitative and quantitative information can be obtained within minutes, and that information directly applied to instruct the next experiments. The speed and ease of setup makes CV the method of choice to investigate electrochemical reactions.

In the CV experiment, the potential is swept through a potential range of interest, and then swept back to the starting potential. At the potential where an electrochemical reaction occurs, a response is observed which is measured by an increase in the current (i) or current density (j).

Current density is the current divided by the surface area of the working electrode. Differences in the peak shape are related to whether the electron transfer is electrochemically reversible or not and if any chemical steps are involved. Further mechanistic and kinetic information can be obtained by changing the scan rate, the number of scans, and the potential ranges used. Changing the concentration, temperature and pH of the solution can also provide useful information for the reaction under study.

Figure 1.4 shows how a CV experimental setup that was used in the work described in this thesis. A three-electrode system is employed, which is controlled by the potentiostat. The observed current response is measured at the glassy carbon working electrode, which for positive potentials acts as the anode and cathode where a negative potential is applied. The surface of the working electrode should be regularly polished between experiments, to remove any impurities from the electrode surface that can affect the results. A Platinum counter-electrode is present to balance the overall electrochemistry and allow current to flow. Finally a reference electrode (Saturated Calomel electrode, SCE) is used to standardise the potential. HPLC grade solvents should be used, and should also be degassed, as dissolved oxygen within the solvent can affect the results. Oxygen is electroactive (can be reduced at –1.0 V vs. SCE), the CV peak of which can obscure important reduction processes occurring at this potential.[37, 48]

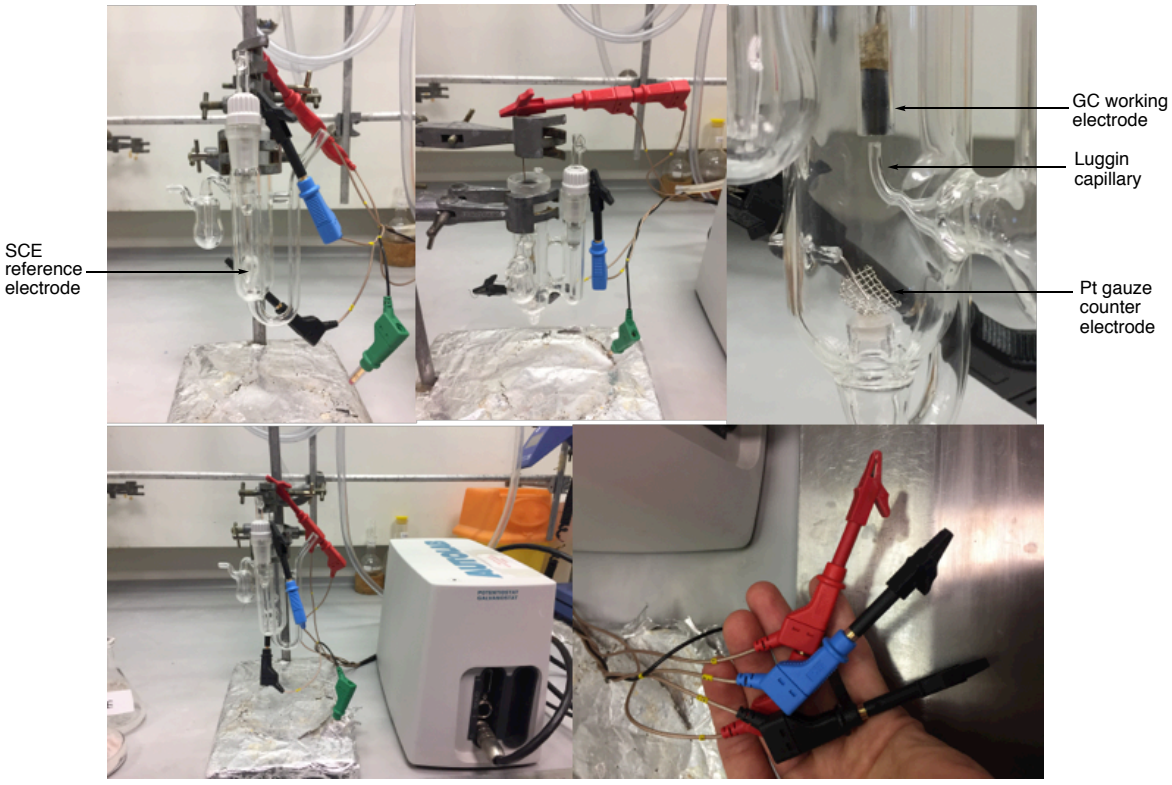


Figure 1.7: Photographs of the Cyclic Voltammetry apparatus setup

The working and counter electrodes are in close proximity to each other to make sure consistent data is achieved. The reference electrode is held in close proximity to these because of the Luggin capillary. The working electrode also needs to be fixed close to the Luggin capillary to achieve consistent data by reducing the experimental IR drop. This is the resistance in the cell, affecting the observed current, which is minimised in the setup shown.[37]

1.1.4 Interpreting CV results

Figure 1.8 shows a CV trace for the reversible, one-electron process of an unknown substrate:

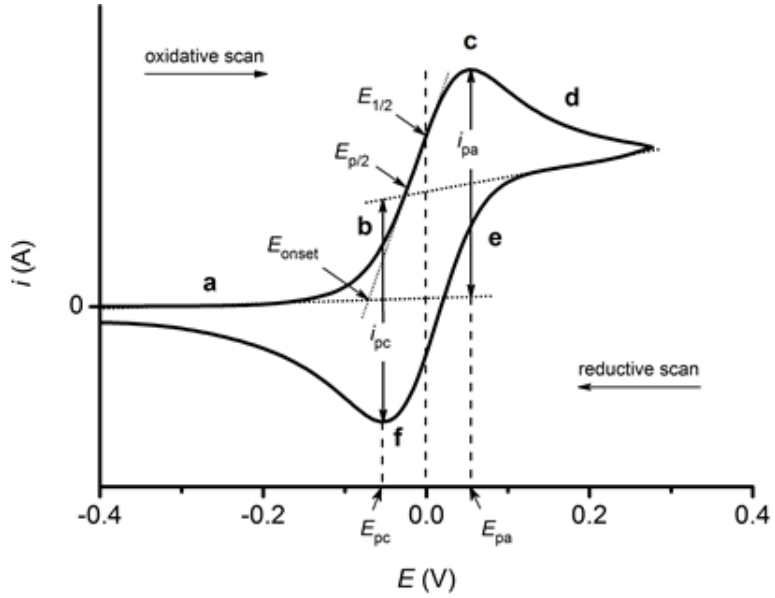


Figure 1.8: CV for a reversible, one-electron process

The potential is recorded on the x-axis in V. The current is occasionally recorded on the y-axis, although it is more accurate to record the current density as it accounts for the surface area of the electrode and therefore standardises the results. The initial increase in potential (point a) causes very little if any rise in current, since the potential is not sufficient to oxidise the substrate. At point b the current increases exponentially as the substrate close to the working electrode surface is oxidised. As this is consumed, mass transfer allows new substrate molecules to approach the electrode and react. The process is now under electrochemical control with the current linearly increasing with increasing voltage with a constant concentration gradient of the substrate near the electrode surface within the double layer. The current plateaus as the double layer increases in thickness. The current reaches peak maximum at point c, which is the redox potential for the substrate, at this point increased potential no longer induces an increase in current because of decreased flux of substrate from further and further distance from the electrode surface. The process is now rate-limited by mass transfer from the bulk solution to the

double layer. The current falls (point d) because the mass transfer rate is slower than the rate of electron transfer at redox potential. Eventually a steady state is reached where no further change in current is observed. Scan reversal to negative potentials (initially through less-positive values) sustains substrate oxidation until the applied potential reaches the value where the electrolysis product accumulated at the electrode surface can be reduced (point e). The reduction process mimics that of the oxidation, except with an opposite scan direction and a cathodic peak (i_{pc}) at the cathodic peak potential (E_{pc}) (point f). The equal magnitude of i_{pa} and i_{pc} indicate that the process is reversible. Conversely, an irreversible electrochemical process is confirmed by an absence of a reduction peak on the reverse sweep. The implication of this is that the intermediate formed during the forward scan undergoes a chemical reaction, at a rate that exceeds that of the scan.[23, 37, 48]

Diffusion is the dominant mode of mass transfer during a CV experiment. Whether this is the rate-limiting step for the reaction under investigation can be determined from the shape of the observed voltammograms, along with the peak area and height. It is important that CV experiments are conducted at two different scan rates, because it can inform as to whether the process is diffusion-controlled, or if the electron transfer is the rate-limiting step. For both reversible and irreversible electrochemical processes, where the reaction is diffusion controlled, the current density is proportional to the square root of the scan rate, although the constants vary in each case. For an irreversible process, the equation relating them is:

$$j = 3 \times 10^5 \, n(nx)^{1/2} D^{1/2} c v^{1/2}$$

Figure 1.9: Equation linking mass transfer coefficient to scan rate in CV

Where *j* is current density and *v* is scan rate. For convenience, a scale factor of four with respect to scan rate has been used during the CV experiments herein. Hence the current density for the two CV diagrams should vary by a factor of two. If this is not the case, then the electron transfer process will be the rate-limiting process. It is important that during a CV experiment the solution is not agitated or mixed because mass transfer will no longer be the rate-limiting process, and therefore i_{pa} or i_{pc} cannot be deduced. See Figure 1.10 for a comparison of a linear sweep for calm and stirred solutions:[37, 49]

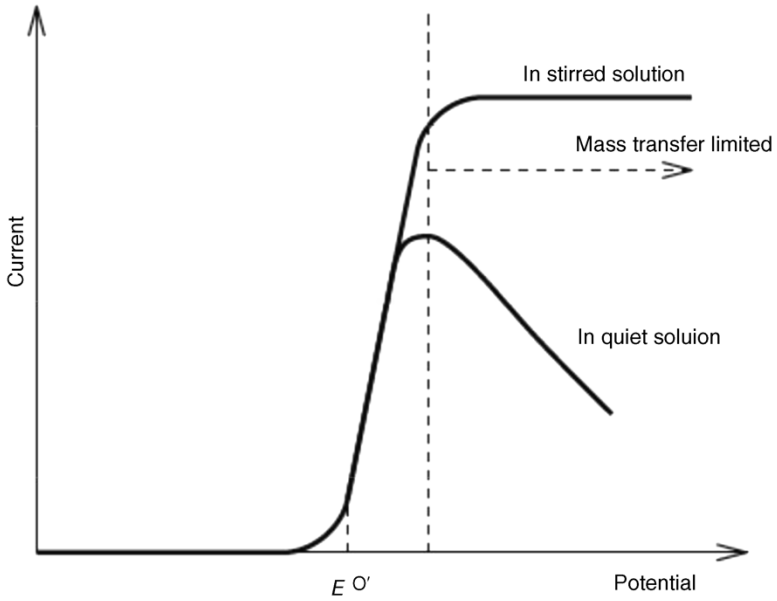


Figure 1.10: Linear sweep voltammograms of quiet and stirred solutions of an oxidation substrate adapted from Fuchigami, Inagi and Atobe's "Fundamentals and Applications of Organic Electrochemistry"

1.1.5 Selected electrosynthesis examples

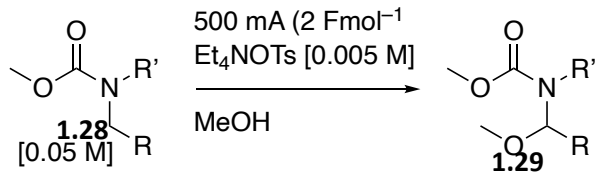
The examples described in this section represent a non-exhaustive list of the synthetic processes that can be carried out through electrochemistry. They are characterised by their redox nature i.e. oxidative, reductive or paired. The examples selected represent varied transformations that can be achieved, demonstrating that electrochemistry extends beyond simply the oxidation or reduction of a functional group. Some of these reactions illustrate that electrosynthesis can be recognised as a powerful toolkit to the synthetic chemist, both carrying out processes in a green and sustainable manner but also enabling transformations difficult or impossible by other means or by reducing processing.

1.1.5.1 Oxidative processes

Oxidative electrochemical reactions form the majority of those achieved.

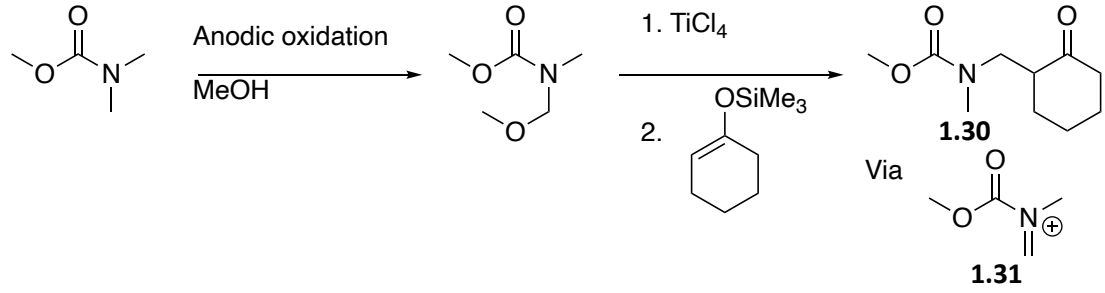
1.1.5.1.1 Shono oxidation

In 1975 Tatsuya Shono *et al.* introduced a method for oxidising at the α position to an amide or carbamate, providing an easy way to functionalise this position (Scheme 1.23).[50]



Scheme 1.23: Shono anodic methoxylation

There are a huge array of anodic oxidation reactions that can be traced back to this process, including a later method by Shono himself; using the methoxylated product of his reaction to create a new carbon-carbon bond α to nitrogen (Scheme 1.24).[51] The PMB deprotection detailed in chapter 2 is a variant of this process, along with the Yoshida cation flow method that utilises low-temperature electrolysis to form the iminium cation **1.31** *in situ*, which subsequently reacts with an introduced nucleophile.

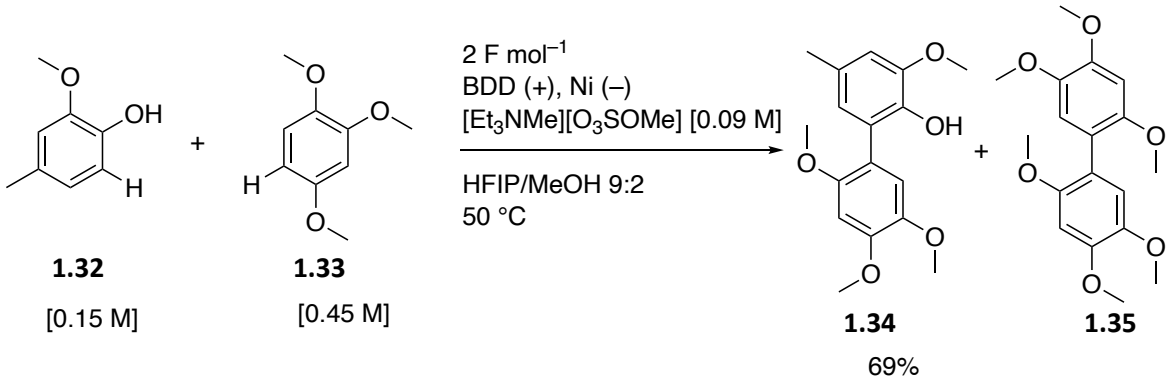


Scheme 1.24: Shono oxidation and subsequent application in Mannich-type reaction

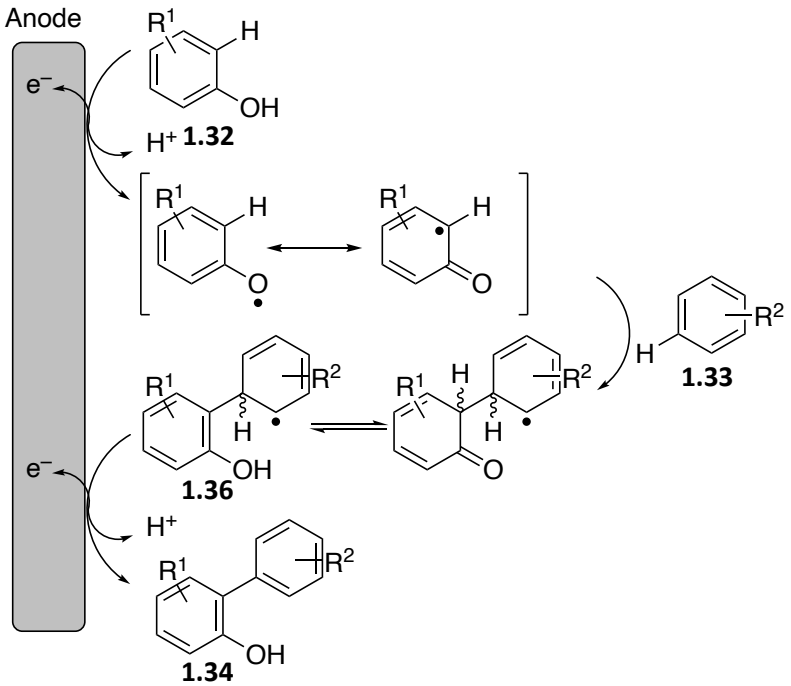
1.1.5.1.2 Electrochemical biaryl coupling

Cross-coupling chemistry has been widely utilised as a powerful synthetic method, and was the subject of the Nobel Prize for Chemistry in 2010 (through the works of Suzuki and Negishi).[52, 53] Biaryls especially are the subject of much interest, as these structures are widely used in catalysis[54], pharmaceuticals[55] and polymers[56], and feature in many natural products.[57] The methods proposed by Suzuki and Negishi to make these molecules was through transition metal catalysis (Pd, with others used in subsequent years). However, the concept of carrying out such coupling reactions without the need for such catalysts (which are non-renewable, expensive and often laborious to remove from the product) remains desirable.

Waldvogel has contributed significantly to the field of metal free, electrochemical aromatic cross-couplings, both practically and theoretically. Him and Atobe developed an electrochemical phenol-aryl coupling by oxidation of functionalised phenols (Scheme 1.25), together with a proposed mechanism (Scheme 1.26).[58]



Scheme 1.25: Electrochemical oxidative aryl-aryl cross coupling

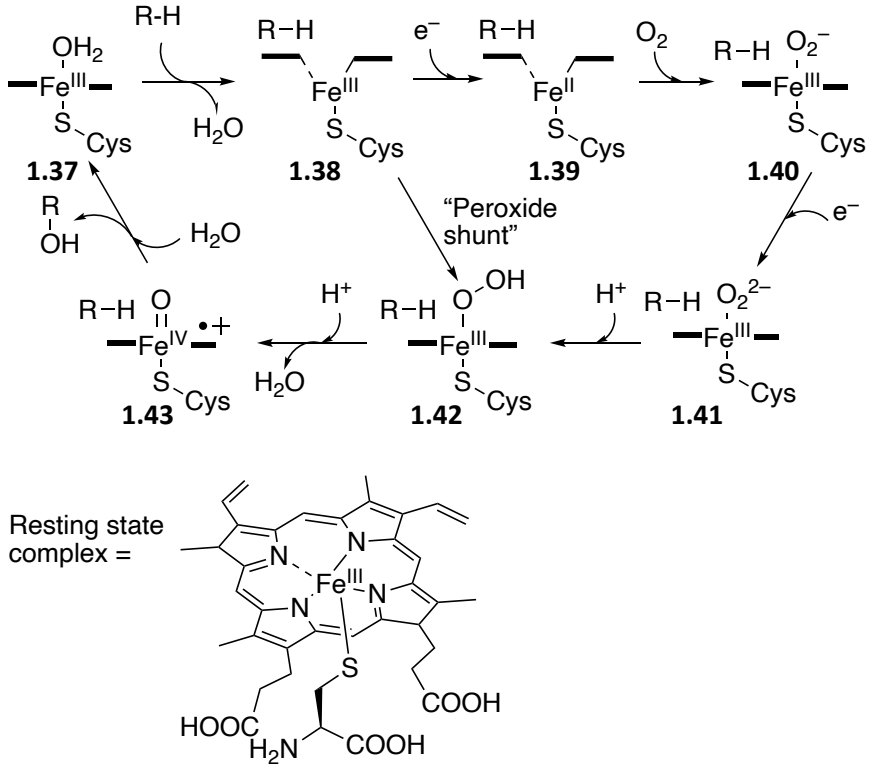


Scheme 1.26: Mechanistic Rationale for the Anodic Aryl–Aryl Coupling Reaction of Phenols with Arenes: adapted from "Electrochemical Arylation Reaction by Siegfried R. Waldvogel, Sebastian Lips, Maximilian Selt *et al.*"

The homo-dimerisation reaction of arene **1.33** competes with the desired asymmetrical aryl-phenol coupling between **1.32** and **1.33**, because the oxidation potential of the arene is lower than that of the phenol. The use of methanol as a co-solvent reduces the oxidation potential of the phenol under specific concentrations, or rather it acts as a weak base to deprotonate the phenol with a lower oxidative potential. The anodically generated phenoxyl radical is stabilised by the solvent (HFIP) via hydrogen bonding, before being displaced by the electron-rich coupling aromatic. The intermediate **1.36** can be oxidised directly at the anode or indirectly, followed by proton abstraction to furnish the biaryl product **1.34**. [59] The cross-coupled product **1.34** could be obtained in 69% yield.[58]

1.1.5.1.3 Mimicking *in-vivo* metabolic processes through electrochemistry

Electrochemistry can be a quick and convenient way to mimic redox reactions that occur *in-vivo*, which can identify possible metabolites from a drug compound.[60-62] It can also be used to make these metabolites on a preparative scale such that further tests can be conducted on them, e.g. toxicity, bioactivity etc.[63] In this way electrosynthesis can provide a new tool to complement pharmacokinetic studies. Drug metabolism is normally divided into phases 1, 2 and 3. Phase 1 metabolism involves functionalisation, typically enzyme-catalysed oxidative processes (although reduction, hydrolysis and isomerisation also occur),[64] the most significant of which are by Cytochrome P450 enzymes. Phase 2 metabolism is often related to conjugation, including glucuronidation, sulfation, glutathione conjugation, methylation, acetylation and condensation. The term phase 3 metabolism is used to describe transport processes, such as excretion.[65] Cytochrome P450 enzymes proceed through the general mechanism illustrated in Scheme 1.27.

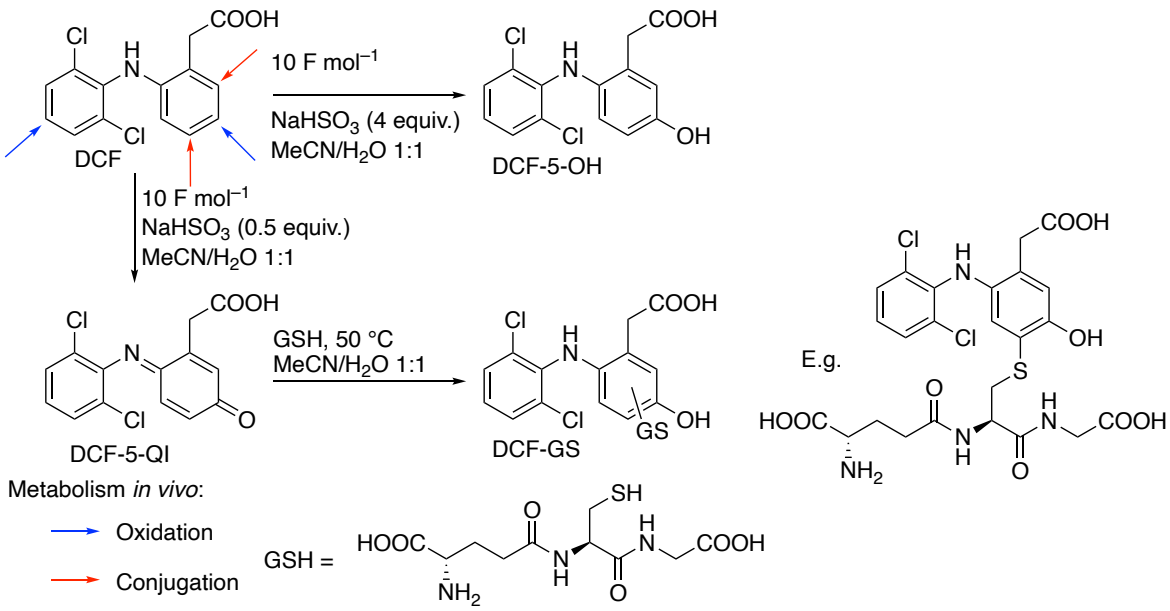


Scheme 1.27: Mechanism of action of Cytochrome P450 enzymes

The mechanism illustrated in Scheme 1.27 represents the oxidation of a hydrocarbon to an alcohol; the Cytochrome P450 enzymes carry out many more oxidative processes than this. In the resting, substrate-free state, cytochrome P450 contains a six-coordinate low-spin ferric state **1.37** with water as the displaceable distal ligand. The binding of substrate to the resting state generates a five-coordinate high-spin ferric state, **1.38**, which now has a vacant coordination site for dioxygen binding. Conversion of the low-spin ferric haem to the high-spin ferric haem shifts

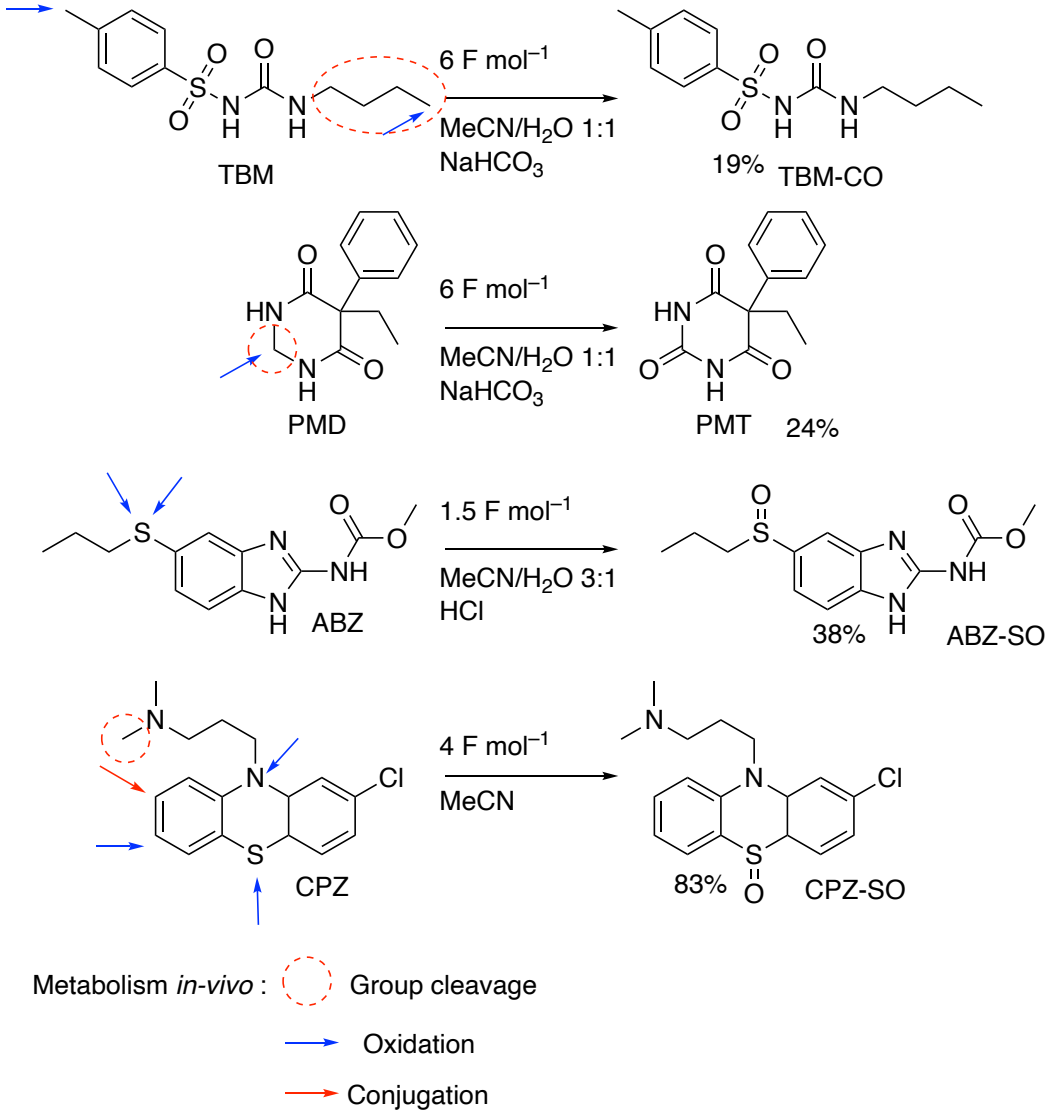
the redox potential from −300 mV to 170 mV, thus facilitating the reduction of the ferric haem to generate a five-coordinate high-spin ferrous haem, **1.39**. It is proposed that Oxygen then binds to the ferrous haem to form complex **1.40** (although this is subject to discussion). Addition of a second electron, presumed to be the rate-limiting step in the catalytic cycle, yields **1.41** which is then protonated to give a ferric-hydroperoxo complex, **1.42**. The delivery of a second proton to this results in heterolytic O-O bond cleavage to release a water molecule and generate the oxoiron (IV) porphyrin π-cation radical intermediate **1.43**. The final step of the cycle is the transfer of an oxygen atom from **1.43** to the substrate to give the alcohol product followed by the regeneration of the resting, water-bound state **1.37**. In a reaction known as the "peroxide shunt," single oxygen atom donors such as hydrogen peroxide, alkyl hydroperoxides, peracids, and iodosylbenzenes can also be used to generate oxygenated products by bypassing intermediates **1.39** to **1.41**.

Studies to determine the products of phase 1 and 2 metabolism have been conducted on many drug compounds,[66] some of which are good candidates to confirm whether the electrochemical oxidation suitably mimics the *in-vivo* process. An example of this was reported by Roth *et al.*,[61] who have prepared 5 phase 1 drug metabolites on a preparative scale by electrosynthesis (Scheme 1.28). Diclofenac (DCF), an anti-inflammatory drug, metabolised in the liver by aromatic hydroxylation, was treated under electrochemical conditions. Sodium sulfate was used as electrolyte, although this is also a mild reducing agent, and so the concentration of this determined whether DCF-5-OH (4 equivalents) or the quinone imine DCF-5-QI (0.5 equivalents) were formed. The phase 2 metabolite was also formed under continuous flow, by combining the electrolysed solution with a solution of glutathione in a microfluidic reactor.[61]



Scheme 1.28: Electrosynthetic preparation of DCF-5-OH, DCF-5-QI and DCF-GS, products of metabolism of Diclofenac

Through optimisation of the process, the products of the electrochemical process closely mimicked those that would form *in-vivo*. These conditions were then tested on four other marketed drugs: Tolbutamide (TMB), Primidone (PMD), Albendazole (ABZ), and Chlorpromazine (CPZ), and the products compared to those formed *in-vivo*. The products are illustrated in Scheme 1.29.

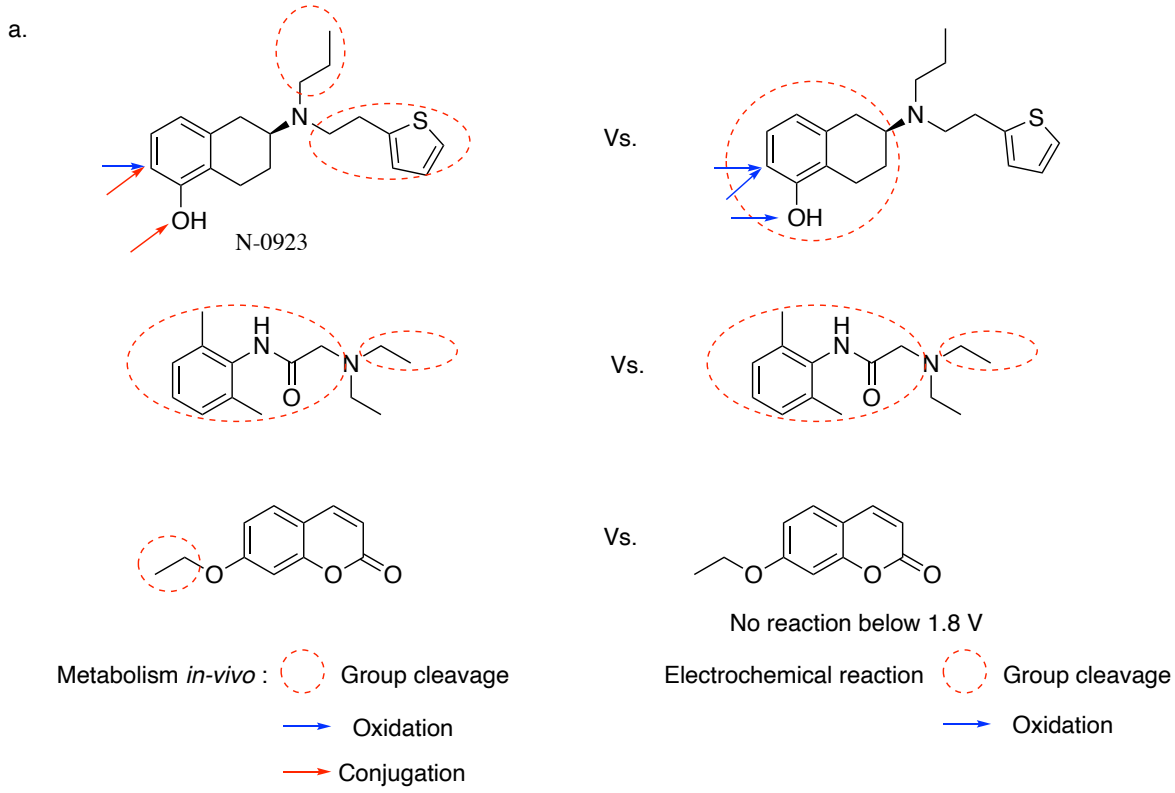


Scheme 1.29: Anodic oxidation products of the drugs Tolbutamide (TBM), Primidone (PMD), Albendazole (ABZ) and Chlorpromazine (CPZ).

In vivo, TMB undergoes a number of oxidative processes including benzylic oxidation, alkyl C–H oxidation and cleavage of the *N*-butyl chain (Scheme 1.23). The electrolysis product (TBM-CO, isolated in 19% yield) is not reported as a known metabolite of TBM, although such reactivity is common in electrosynthesis (e.g. ?-position substitution displayed in the Shono oxidation in Scheme 1.23). Under the applied electrolysis conditions, PMT was formed in 24% yield, and so electrochemical oxidation of PMD closely mimicked the outcome of one *in vivo* metabolic pathway, the other being to phenylethylmalonamide (PEMA) by methylene cleavage. ABZ is oxidised *in vivo* to the sulfoxide and sulfone products, and both could be formed electrochemically by controlling the current in the cell (although multiple side-products meant the sulfone was not isolated). Metabolism of the sulfinyl ether present in CPZ was also successfully mimicked electrochemically by sulfur oxidation, producing CPZ-SO in 83% yield. Although there are limitations to the scope of electrolysis in terms of mimicking drug metabolism (demonstrated

by different products formed in the electrolysis cell compared to the body), the concept that that drug metabolites can be synthesised electrochemically on a preparative scale at higher productivities than existing methods has been demonstrated.[61, 63]

Bruins *et al.* have also investigated the potential of electrochemistry as a metabolism-mimicking tool (Figure 1.11). Three compounds with previously reported *in vitro* and *in vivo* metabolism:[67] the dopamine agonist 2-(*N*-Propyl-*N*-2-thienylethylamino)-5-hydroxytetralin (N-0923),[60] the anaesthetic lidocaine and sun-screen 7-Ethoxycoumarin were examined in an electrolysis/mass spectrometry system. Lidocaine and 7-Ethoxycoumarin are exclusively metabolised by Cytochrome P450 enzymes (3A4 and 1A2/2E1 respectively), and so indicates the ability of the system to mimic these enzymes. [62]



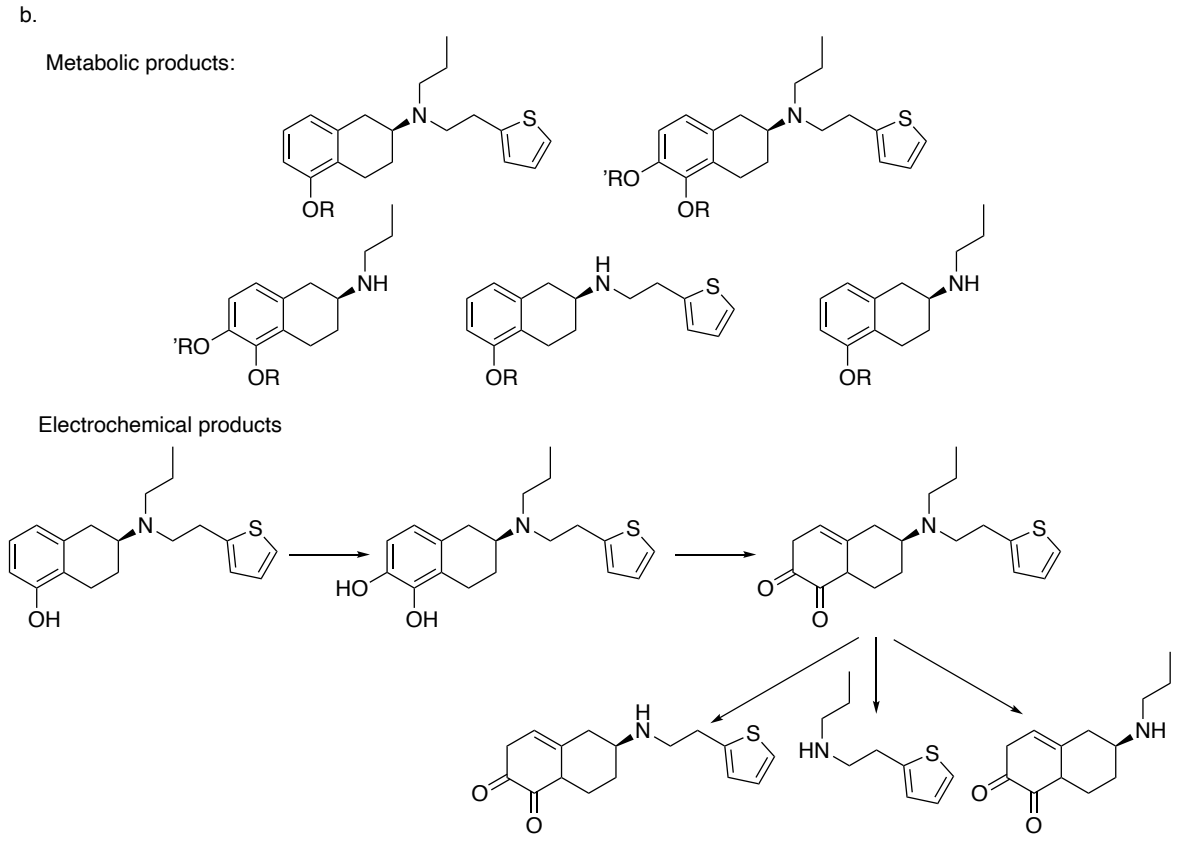


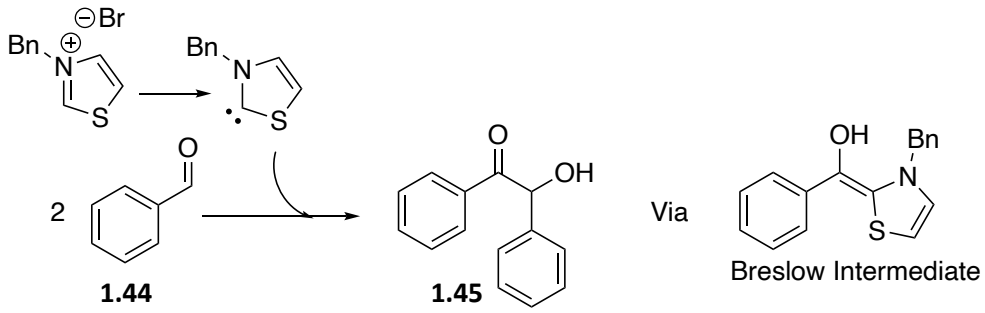
Figure 1.11: a. Comparison of in-vivo metabolism to electrochemical oxidation methods in drug compounds N-0923, Lidocaine and 7-Ethoxycoumarin. b. products of electrolysis and metabolism of N-0923.

The reported metabolism of the tertiary amino group in N-0923 was mimicked by N-dealkylation in the electrochemical reactor. Oxidation of the phenol moiety in the EC/MS system, unsurprisingly, afforded quinones, which went on to dealkylate. Metabolism is a more controlled process and so oxidation stopped at the catechol, although the process of glutathione conjugation proceeds through the quinone as shown in Scheme 1.28, and so it is plausible that the electro-generated products would react in the same way. The *in-vivo N*-dealkylation of lidocaine provided another example of how the electrolysis approach can closely mimic outcomes of metabolism of alkylamino functional groups. Unsurprisingly, *O*-dealkylation of 7-Ethoxycoumarin could not be replicated electrochemically under the conditions applied. This was to be expected as alkyl ethers are not readily oxidised, and only activated (benzylic, phenolic, or allylic) ethers readily dealkylate.[62, 68]

In summary, electrosynthesis cannot replace analytical biosynthetic techniques such as microsomal incubations for complete drug metabolism pathway studies, but it has been demonstrated that electrosynthesis performed in flow can complement biosynthetic studies through convenient synthesis and isolation of drug oxidation products that match those of *in vivo* metabolism.

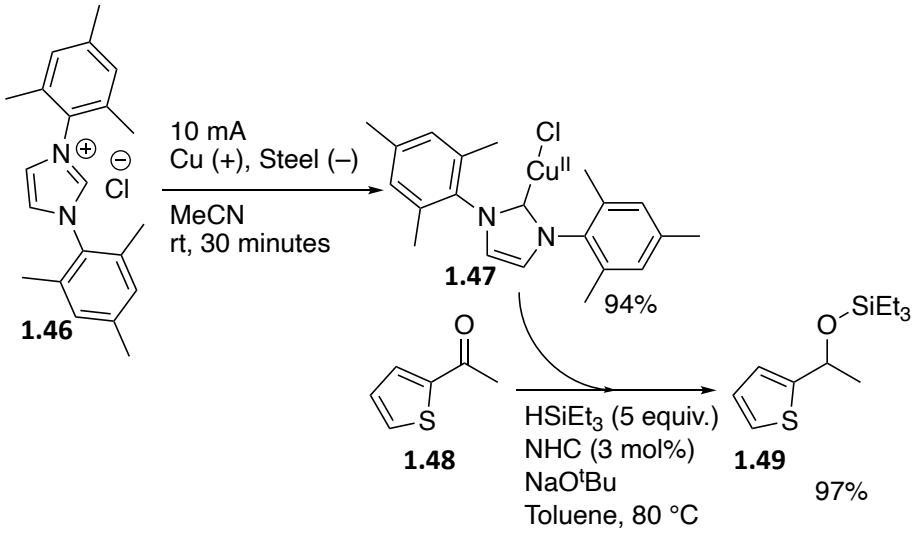
1.1.5.1.4 NHC-mediated couplings

N-Heterocyclic carbenes (NHCs) are powerful organocatalysts for a number of reactions, including hydrosilylations, olefin metathesis, hydrogenation and cross-coupling reactions.[69] The first example of this kind of transformation was 1943 when Ukai *et al.* reported the homo-dimerisation of aldehydes to benzoins catalysed by a thiazolium salt (Scheme 1.30).[70] Breslow later confirmed the mechanism for the process,[71] and hence the Breslow intermediate (Scheme 1.30) is named after him.



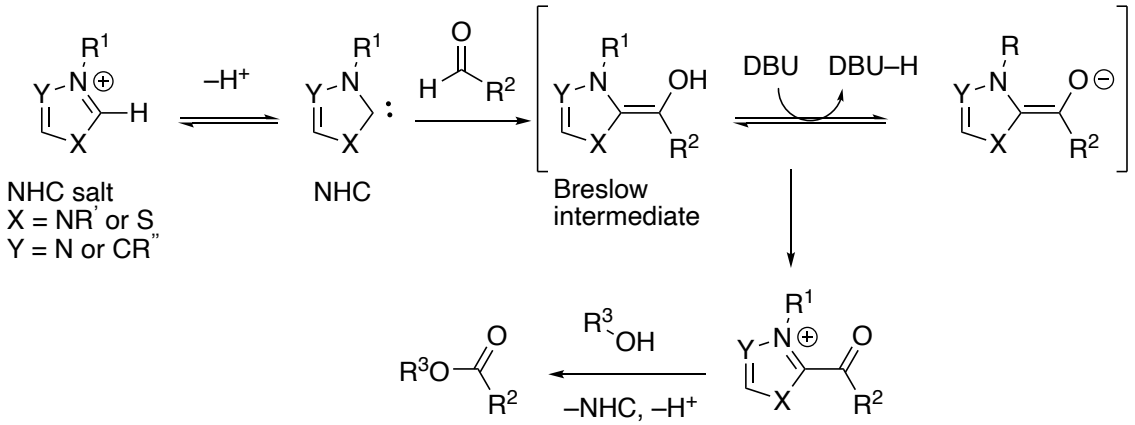
Scheme 1.30: NHC-mediated benzoin coupling by Ukai (featuring the intermediate proposed by Breslow)

Among many other NHC- mediated syntheses, Willans *et al.* reported a synthesis of NHC's using electrochemistry in flow (Scheme 1.31)[72]



Scheme 1.31: Willans NHC electrochemical hydrosilylation

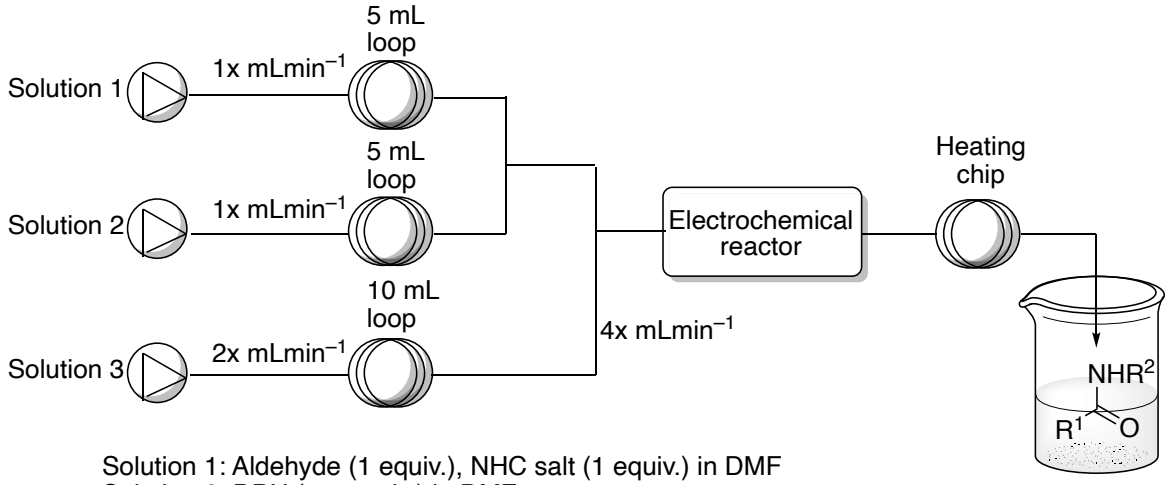
Brown *et al.* developed a method to synthesise esters via anodic oxidation mediated by *N*-heterocyclic carbenes using the Syrris electrochemical flow reactor (Scheme 1.32).



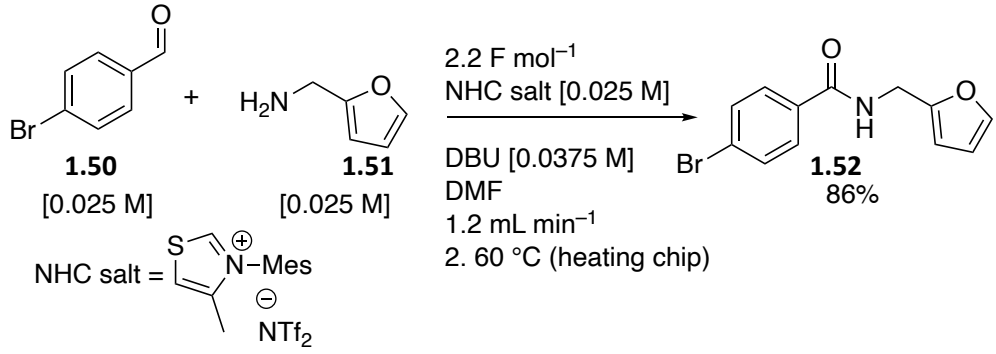
Scheme 1.32: NHC mediated oxidative esterification

Reactive species, known as Breslow intermediates, were generated by mixing two different flow streams, connected using a simple T-piece. One reservoir contained a solution of the aldehyde, the alcohol, and the thiazolium salt in dimethyl sulfoxide and tetrahydrofuran; the other contained the base 1,8-Diazabicyclo[5.4.0]undec- 7-ene (DBU) in tetrahydrofuran. Upon mixing, the Breslow intermediate was formed, which fed into the undivided electrochemical cell where the oxidation takes place to afford the acylthiazolium cation. Rapid reaction with the alcohol gave the corresponding ester in yields of up to 99%, productivities from 1.5 to 4 g hr^{-1} and current efficiencies between 80 and 100%.[73]

The setup for ester synthesis was not applicable for amide synthesis, due to the potential for side-reactions and slow formation of the amide. This issue was resolved by controlling the order of mixing using three reservoirs instead of two, and a heating chip to accelerate the reaction of the amine with the activated acyl thiazolium (Scheme 1.33).[74] This method was applied to a range of amines and aldehydes to give the desired amides in good to excellent yields (up to 99%). Chemically oxidisable functionalities are tolerated in the process such as furan, phenol and indole.



Solution 1: Aldehyde (1 equiv.), NHC salt (1 equiv.) in DMF
Solution 2: DBU (1.5 equiv.) in DMF
Solution 3: Amine (1 equiv.) in DMF



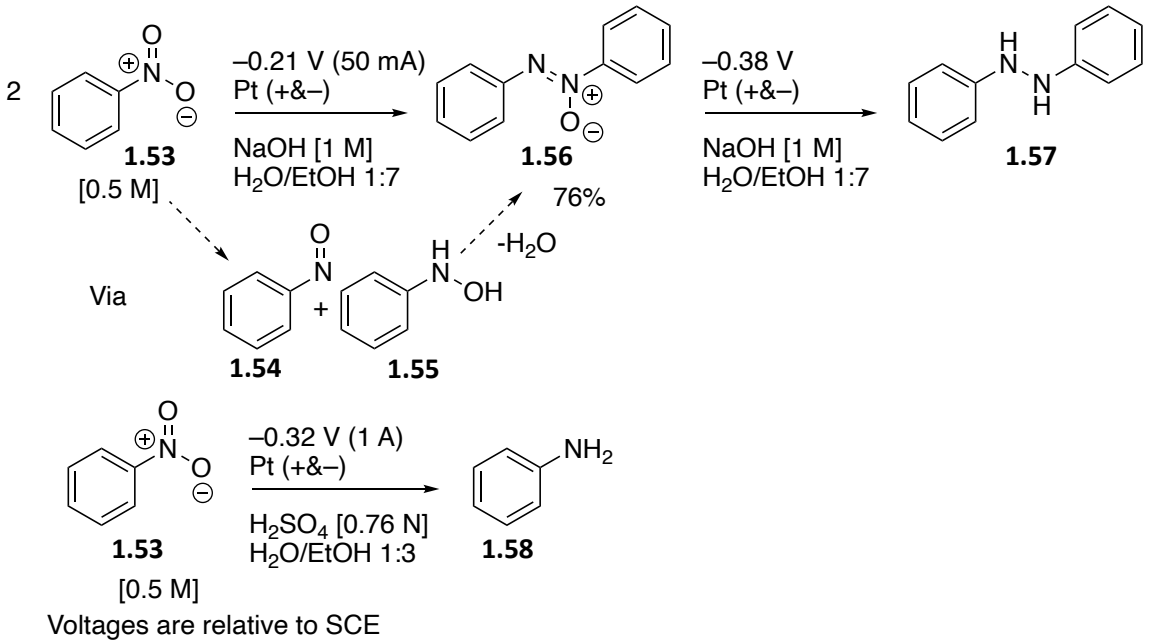
Scheme 1.33: a. Flow setup for NHC mediated electrochemical oxidative amidation. b. Reaction scheme for NHC mediated amidation by Brown *et al.*

1.1.5.2 Reductive processes

Historically at least, reductive electrochemical processes were considered more uncommon than oxidative, owing to the difficulty in excluding oxygen (which is susceptible to reduction) in the reaction mixture. Furthermore, the synthetic utility of many reductive processes (such as the dehalogenation are limited.

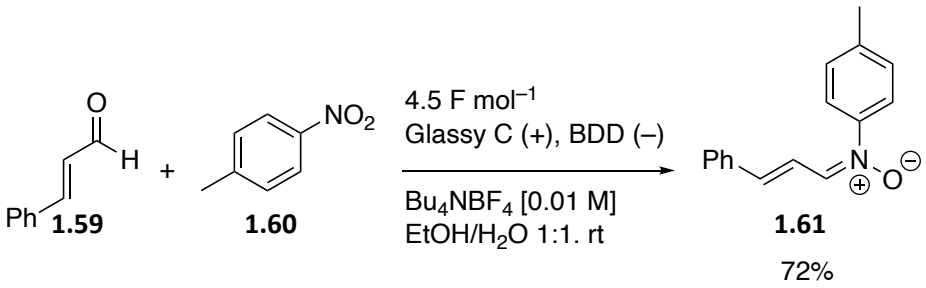
1.1.5.2.1 Haber's Nitrobenzene reduction

In 1898 Haber reduced nitrobenzene sequentially to (Z)-1,2-diphenyldiazene 1-oxide, 1,2-diphenylhydrazine and aniline.[75] He observed that selectivity towards each product could be achieved by controlling the potential applied to the working electrode (Scheme 1.34) . Later work by Hofmann and Bugge,[76] would lead to the isolation of these compounds (since at the time Haber was working the compounds could not be isolated).[77]



Scheme 1.34: Haber's selective reduction of nitrobenzene by controlled potential electrolysis

Haber demonstrated through dye analysis that partial reduction of Nitrobenzene led to the formation of Nitrosobenzene **1.54** (in a 2 e^- reduction) and *N*-Phenylhydroxylamine **1.55** (in a 4 e^- reduction), which condensed together to form diazo compound **1.56**. A further 4 e^- reduction on this compound led to the formation of 1,2-Diphenylhydrazine **1.57**, which was resistant to further reduction. Conversely, in acidic conditions and a lower reduction potential, Nitrobenzene **1.53** would reduce (in a 6 e^- reduction) to Aniline **1.58**. Since this discovery there have been many developments in the field of partial nitrobenzene reduction, including a method for nitrone synthesis by Waldvogel *et al.* (Scheme 1.35).[78]

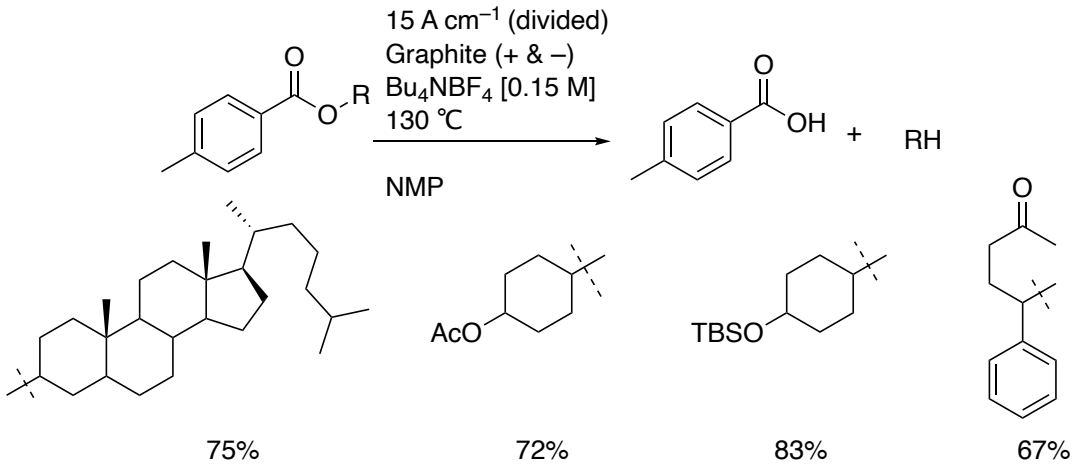


Scheme 1.35: Nitrone synthesis from nitrobenzene analogues by Waldvogel

1.1.5.2.2 Marko-Lam deoxygenation

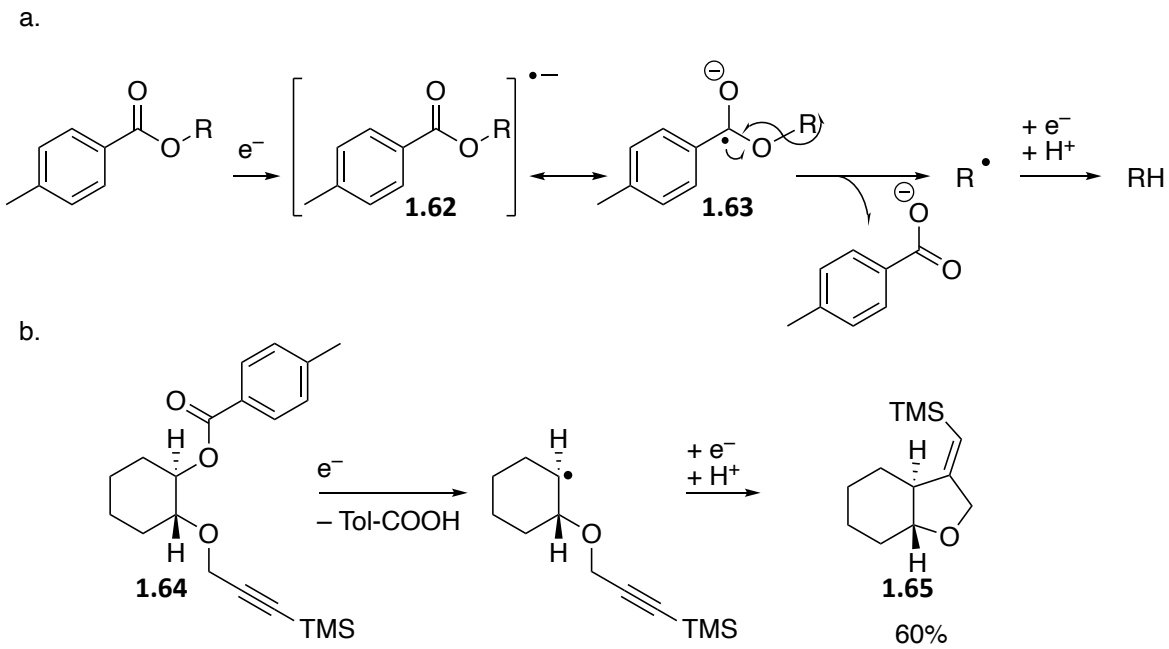
In 2009 Kevin Lam and István E. Markó reported a reductive deoxygenation method from aromatic esters, representing an alternative to the Barton-McCombie method (Scheme 1.36).[79] Toluate esters have the advantage of being easier to synthesise and handle than xanthates used in the Barton procedure, and the electrochemical method also avoids the use of toxic and

hazardous AIBN and tin reagents. The conditions for the Marko-Lam deoxygenation require high temperatures and a divided cell.[80]



Scheme 1.36: Markó-Lam electrochemical deoxygenation

The proposed mechanism is illustrated (Scheme 1.37).



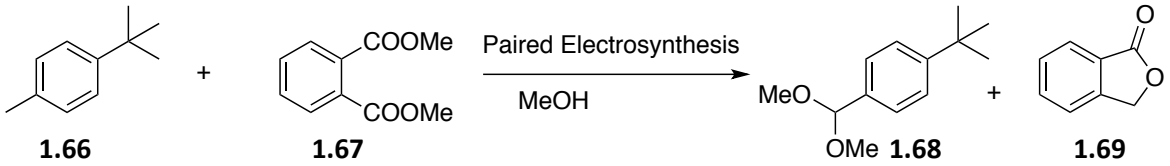
Scheme 1.37: a. Proposed electrochemical deoxygenation mechanism by Markó and Lam. b. Radical cyclisation reaction to confirm mechanism

The reaction is proposed to proceed through the radical anion species **1.62**, which collapses to the toluate anion and the alkyl radical **1.63**, which forms the hydrocarbon following a second SET and protonation. To confirm the formation of the radical intermediate, alkyne **1.64** was assembled and subjected to electrolysis to determine if cyclisation occurred. This was indeed the reaction outcome, with the cyclised tetrahydrofuran **1.65** formed in 60% yield.

1.1.6 Industrial electrochemical processes

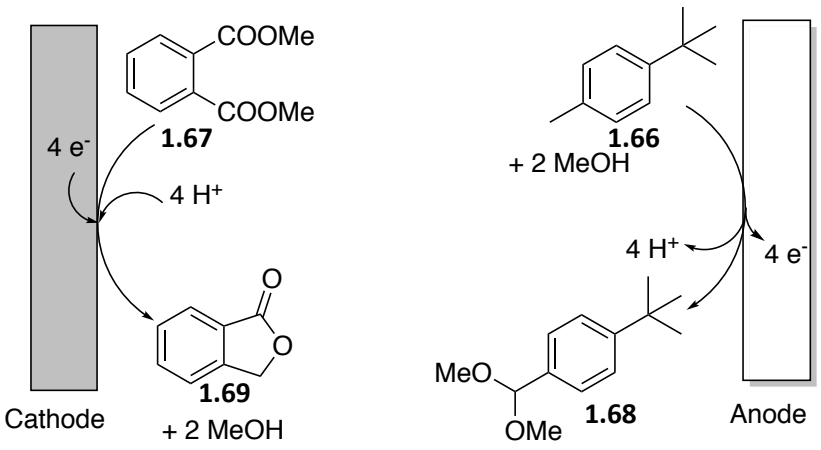
Due to advances in understanding of electrosynthesis, development of technology such as continuous flow chemistry, and a need to develop more sustainable methods to make fine chemicals and pharmaceuticals, there are large and growing numbers of electrochemical processes occurring on an industrial scale.[81, 82]

In 1999 BASF developed an industrial-scale paired electrosynthesis for the concomitant synthesis of Phthalide and 4-(*t*-Butyl)benzaldehyde dimethylacetal from methyl phthalate and 4-(*t*-butyl)toluene. The former is reduced at the cathode, with the latter oxidised at the anode, both in 90% yield. The setup utilises an undivided reactor with methanol as both solvent and reagent. In contrast to many electro-oxidative processes, hydrogen gas is not formed during the reaction at the counter electrode, and protons generated at the anode are consumed at the cathode. This increases the process safety as well as the efficiency and 1000 tons of each product is made each year using this method.[83, 84]



1.66 **1.67** **1.68** **1.69**

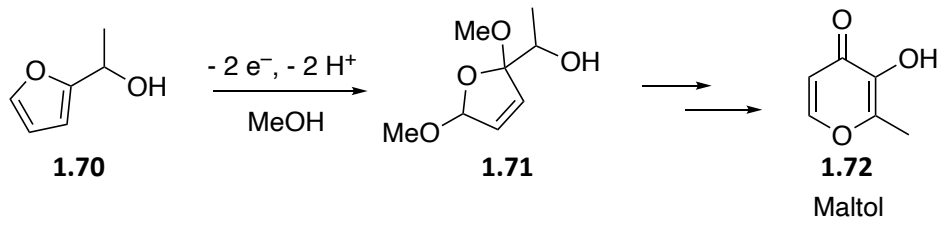
Scheme 1.38: Industrial scale preparation of Phthalide and 4-(*t*-Butyl)benzaldehyde dimethylacetal



Scheme 1.39: Diagram illustrating paired electrosynthesis of Phthalide and 4-(*t*-Butyl)benzaldehyde dimethylacetal

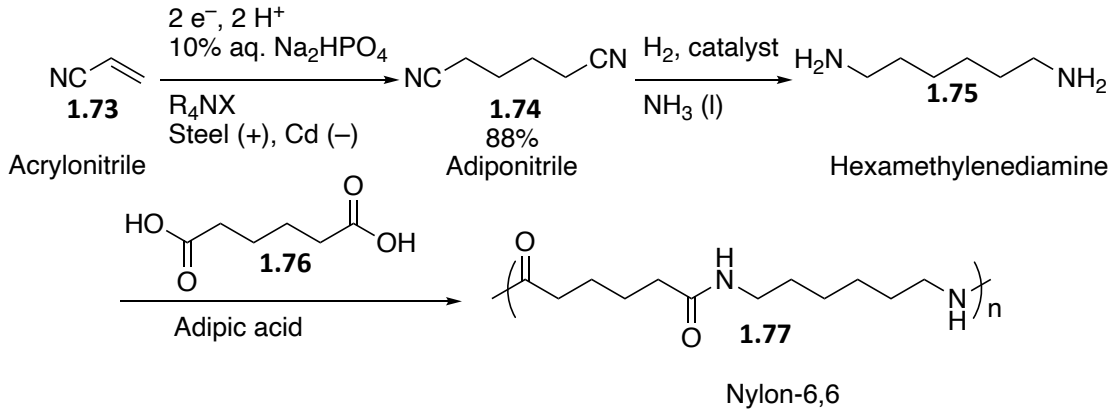
Another industrial electrosynthesis process is the methoxylation of 1-(Furan-2-yl)ethan-1-ol, established by Otsuka pharmaceutical in Japan (Scheme 1.31). 150 tons of the intermediate is

produced per year, and it is a precursor for the production of the food additive maltol. A carbon cylinder anode and steel pipe cathode are used.[84]



Scheme 1.40: Electrochemical methoxylation of 1-(Furan-2-yl)ethan-1-ol, leading to the synthesis of Maltol

In 1960 the Baizer process was developed, in which Adiponitrile is made by hydrodimerisation of Acrylonitrile (Scheme 1.41).[85-87] Around 200 000 tons were made in 2018 through this process. The counter electrode reaction involves oxidation of hydrogen gas at the anode producing protons that combine with the reduced dimer in an undivided biphasic system, and so the process can be considered an example of paired electrosynthesis. Small amounts (0.5% and 2% by moles respectively) of the tetra sodium salt of ethylenediaminetetraacetic acid (Na_4(EDTA)) and Borax ($Na_2B_4O_7$) are added to the electrolyte to avoid passivation of the electrodes.



Scheme 1.41: Electrosynthesis of Adiponitrile for the synthesis of Nylon-6,6 polymer

Yields of up to 88% are observed in the undivided setup, with the aqueous part of the emulsion recycled through the reactor to fully convert Acrylonitrile **1.73**. The Acrylonitrile is saturated in the aqueous phase (7%), with Adiponitrile extracted into the organic phase of which a fraction is continuously removed from the reactor for product extraction. The simplified design of the new reactor (Figure 1.12) allowed operation in undivided mode, reducing the cost to less than 10% of the original divided cell. Further modifications the energy consumption could be reduced from 6700 to 2500 kW hr ton^{-1}, owing to reduced cell resistance.

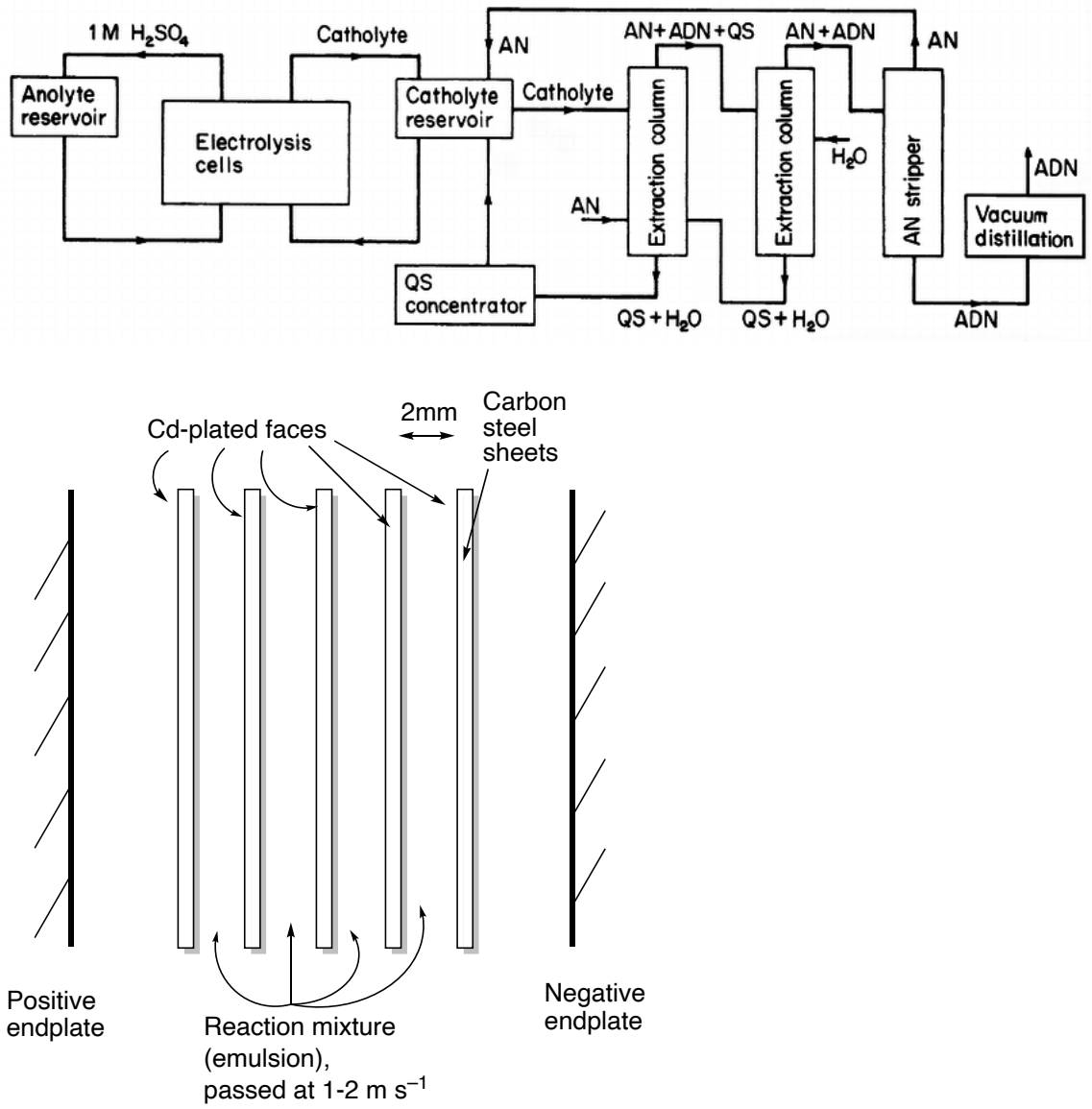
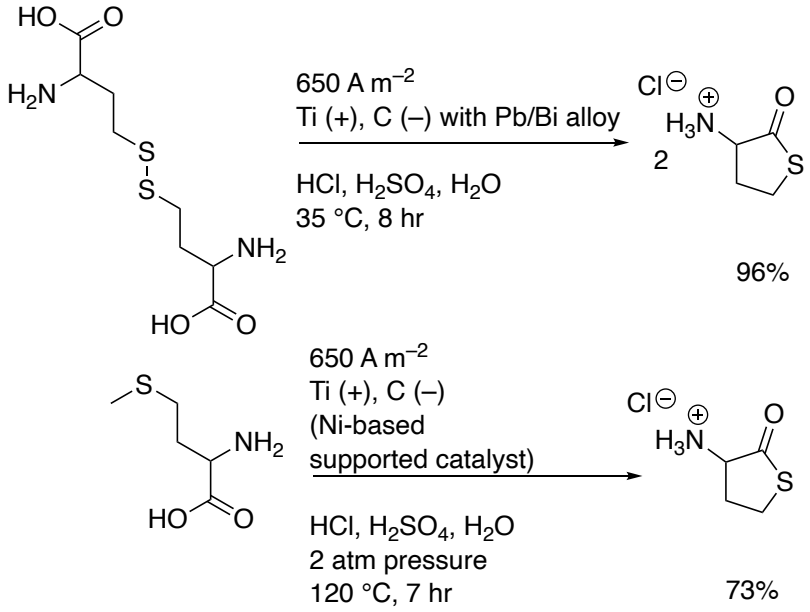


Figure 1.12: Above, flow sheet for Baizer process[85]. Below, schematic for reactor

Recently, Wuhan BJM Pharm Inc. developed a process for electrochemical reduction of DL-homocysteine thiolactone hydrochloride from DL-homocysteine on a 200 kg scale (Scheme 1.42). The compound of interest has previously been synthesised on ton scale by the reduction of the DL-homocysteine with a zinc/H^+ (Clemmensen) reduction. The method has drawbacks however: the formation of large quantities of zinc salts that are produced and its hazardous nature as the reaction is exothermic and hydrogen is formed thus requiring rigorous safety measures.[88] The Wuhan BJM Pharm Inc. process utilises a carbon electrode covered by a lead/bismuth alloy to increase service lifetime, and a titanium anode in a batch electrolysis reactor. Using DL-homocysteine as a reagent, the product was furnished in 96% yield. However, in order the reduce the cost of synthesis as DL-homocysteine is more costly to produce than DL-methionine, a method was produced to furnish the cyclised product from DL-methionine, in 73% yield (Scheme 1.42). DL-homocysteine thiolactone hydrochloride is a biochemical reagent and a pharmaceutical

building block used in the preparation of the drugs citiolone and ersteine.[89]



Scheme 1.42: DL-homocysteine thiolactone hydrochloride electrosynthesis from DL-homocysteine or DL-methionine by Wuhan BJM Pharm Inc.

1.1.7 Merits and limitations of electrosynthesis

Electrosynthesis offers a number of advantages over conventional organic synthesis methods. The use of electrons as a reagent bypasses the use of chemical redox reagents, which are costly and laborious to synthesise and associated with problems of storage and transfer safety. Unstable and hazardous reagents can be produced *in situ* and directly reacted. Electrosynthesis in the purest sense is a "reagentless" technique, since in direct electrolysis no reagents are required to create the product. Whilst supporting electrolytes are frequently required to improve conductivity of the solution, these can often be recovered and reused. Electrolysis solvents used in the reaction can also be recovered, a process frequently employed in industry. In these respects electrochemistry meets a number of the guidelines essential in a "green" chemistry process, a concept discussed in section 1.2.3.[90] Many electrosynthesis are performed at atmospheric pressure and ambient temperature, which can be considered to be mild and energy efficient. These mild conditions, combined with the avoidance of using costly reagents and recycling of electrolyte, ensures low running costs.[73, 91-94]

Electrosynthesis, like any process, has some drawbacks. As the reaction only proceeds at the electrode surface, the rate of electron transfer is limited by mass transfer. The setup of the electrochemical reactor, along with what has often been bespoke manufactured equipment, and the electrode materials, such as precious Nobel metals like platinum, are costly. The scale-up can also be problematic due to the faradaic losses caused by high current (necessary for high

productivity) passing in the cell. In addition, the removal of supporting electrolytes is a time-consuming step, in which additional solvent is usually necessary. In a convenient reactor setup such as a beaker cell, a high supporting electrolyte concentration is required due to a low mass transfer coefficient. On a related point, the setup for an electrosynthesis is far from routine in the way a conventional reaction is. An investment in time is required in order to consider the counter-electrode process of the reaction, and some reactions are simply impossible to carry out through electrosynthesis. For example, metal cations are easily reduced at the cathode to zero-valent metals, so the use of metal catalysts in electrosynthesis is relatively limited. In divided cell electrosynthesis, expensive ion exchange membranes are necessary for dividing anode and cathode compartments, which need to be carefully selected so as to meet the requirements of the reaction. Furthermore, there are cases where electrosynthesis fails on a number of green metrics, which will be discussed in section 1.2.3. However, as more and more literature is being written on the practice of electrosynthesis, and through new techniques such as electrosynthesis in flow, a number of these limitations have been addressed.[29, 95]

1.1.8 Electrochemical reactors

1.1.8.1 Divided vs. undivided

A divided electrochemical cell is used to prevent the product from reacting at the counter electrode, which can occur where it contains functional groups that are electroactive under reaction conditions. The solution that is retained in the anodic chamber is called the anolyte, which is oxidised, and that in the cathodic chamber is the catholyte, which is reduced. A separator is kept in place, which is only permeable to ionic species. The separator must have thermal, chemical and mechanical stability, and in specialist examples such as polymer electrolyte membrane (PEM) electrolysis it can eliminate the need for electrolyte in the solution. Many materials are now employed as separators, and can be classified into two types:

- Ion-exchange membranes selectively transport ions. There are examples of anionic and cationic species that can selectively transfer anions and cations between reaction chambers respectively. The PEM is the most widely explored and is utilised in many reactors such as fuel cells.

- Porous membranes are not selective towards species but can delay the movement of molecules between the chambers. They are normally used when an ion-exchange membrane is not suitable e.g. when using an aprotic solvent. They are typically made of inexpensive materials such as sintered glass or ceramic and can be designed with a specific pore size. In order to achieve a sufficient barrier to the

molecules of interest this type of separator is substantially thicker than ion-exchange membranes, which increases electrical resistance in the cell and means high voltages are often required.[22, 96]

1.1.8.2 Batch reactors

In a batch reactor, a solution of the substrates and reagents is subjected to electric current. The reaction is carried out for the time required to reach completion i.e. consume all the starting material. Stirring is desirable as it ensures even distribution of substances in the reactor. A separator (membrane or diaphragm) can be used to segregate the reactor into anodic and cathodic chambers.

1.1.8.2.1 Undivided cell

This is the simplest reactor to setup, requiring very little if any specialist equipment. The cell consists of a single compartment containing a solution of reagents and supporting electrolyte in a compatible solvent. The working and counter electrodes are inserted into the solution and connected to a power supply, or the vessel can be made of a conductive material that doubles as one of the electrodes. A reference electrode can also be used if required. The vessel is typically constructed with a rigid, unreactive material such PTFE or glass. Common laboratory glassware such as a beaker can suffice. Ideally, the distance between the working and counter electrodes is small to minimise resistance. The rate of reaction is dependent on the surface area of the electrodes, and so connecting multiple in parallel will improve reaction rates. An undivided setup is used when the product from the reaction is not susceptible to reaction at the counter electrode, or with products formed in the counter electrode reaction. A typical setup is shown in

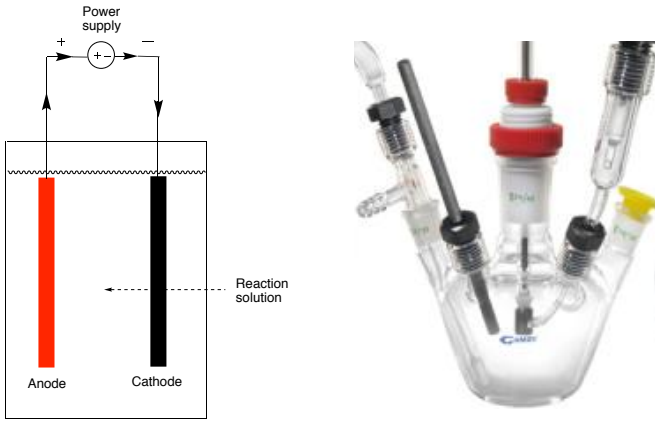


Figure 1.13.

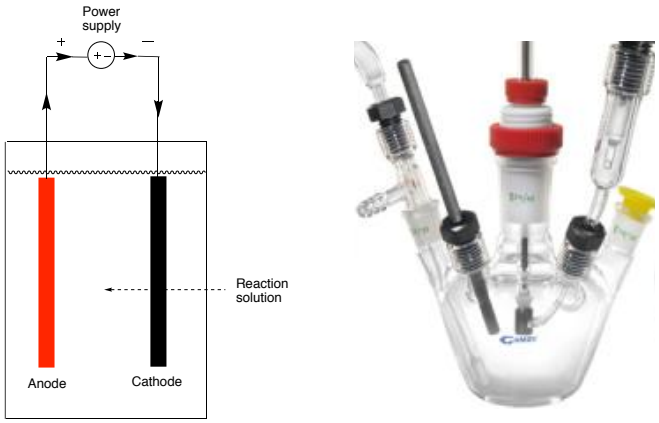


Figure 1.13: Diagram (left) and experimental setup (right) of undivided batch reactor

1.1.8.2.2 Divided batch cell

The H-cell is similarly easy to setup, provided the glassware is available. A typical setup is shown in Figure 1.14.

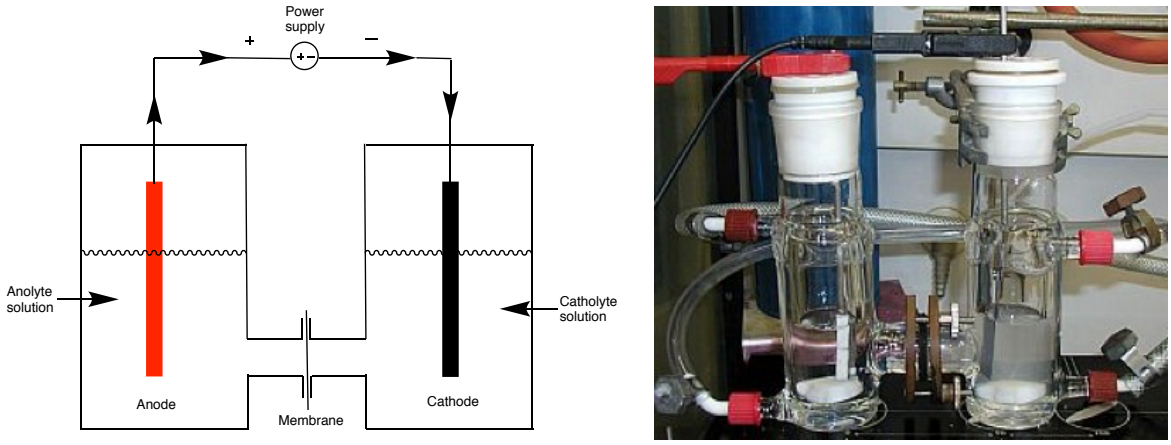


Figure 1.14: Diagram (left) and experimental setup (right) of a divided H-Cell reactor

The setup shown contains additional features including a water-jacketing system for temperature control, but essentially two pieces of glassware that can be clamped together with a suitable membrane between them will suffice.

1.1.8.3 Flow electrolysis cells

This section is an introduction to some of the flow electrolysis cells either manufactured for commercial (academic or industrial) use or developed in-house by researchers with the objective of developing electrosynthetic processes. It is a non-exhaustive list of those published but illustrate how their designs differ and are often developed with a particular reaction in mind.

1.1.8.3.1 Willans Electrochemical flow reactor

The flow reactor designed for the synthesis of the Cu-NHC complex in section 1.1.5.1.4 (Scheme 1.31) consists of six square copper plates (50 x 50 x 1 mm), which are separated by five Teflon® spacers (1 mm thick). These spacers are cut with the shape of the channel used for the reaction (4 mm wide and 200 mm long). This design provides a total reactor volume of 4 mL and a surface area of 40 cm^2.[72]

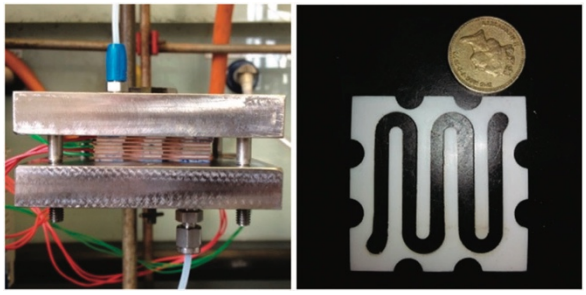


Figure 1.15: Electrochemical reactor developed by Willans *et al.*

1.1.8.3.2 Wirth electrochemical reactor

Wirth *et al.* designed a microflow electrochemical reactor that consists of two platinum electrodes that are separated by a fluorinated ethylene propylene (FEP) foil of varying thickness, into which a channel is cut for the reaction solution (Figure 1.16). The reactor was initially used to carry out the synthesis of diaryliodonium salts (Scheme 1.43).[97]

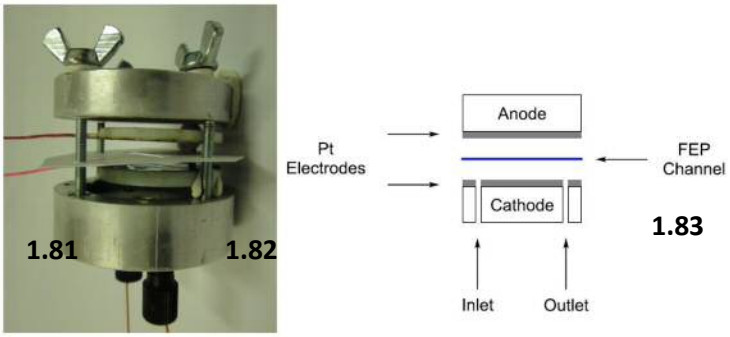
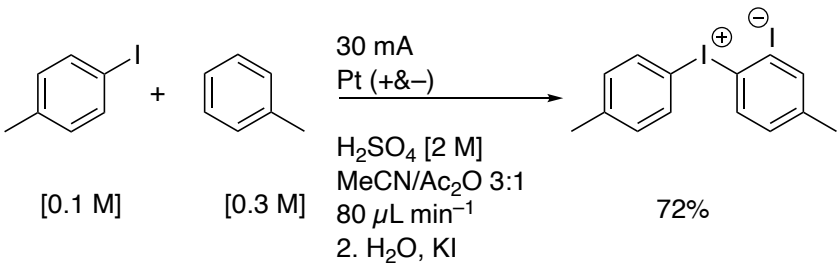


Figure 1.16: Electrochemical reactor designed by Wirth *et al.*



Scheme 1.43: Electrochemical synthesis of diaryliodonium salts

1.1.8.3.3 Syrris Flux reactor

The Syrris Flux reactor is a commercially available flow electrolysis cell designed for routine electrosynthesis. A diagram of the reactor and schematic for its assembly is shown in Figure 1.17.[93]

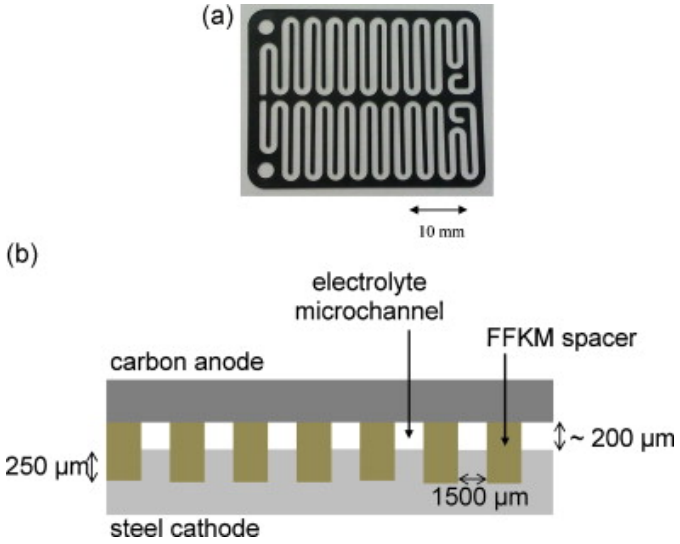
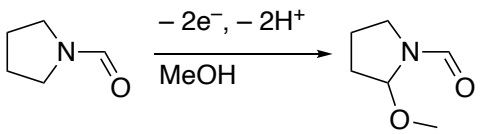


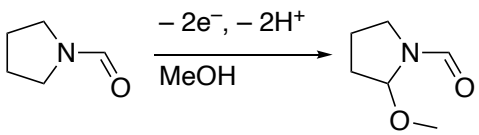
Figure 1.17: (a) Cell spacer for the Syrris Flux module, (b) schematic for assembly. Reproduced from ref.[93]

Pletcher, Brown *et al.* developed the reactor in collaboration with Syrris with the objective of enabling convenient routine laboratory electrosynthesis on a preparative scale. They and others reported a number of electrosynthesis using the Syrris cell contributing to the development of flow electrosynthesis. The electrochemical methoxylation of *N*-Formylpyrrolidine **1.84** was used as a test reaction for investigating the efficacy of this and other electrochemical reactors (Table 1.1).[91-94, 98]



1.84 **1.85**

Entry	Reactor/description	Flow rate/ mL min^{-1}	Conversion/ %	Productivity /g hr	Ref
1	Star-shaped reactor (600 x 1 x 0.5 mm channel)	0.1 3.5	96 33	0.08 1.0	94
2	Syrris reactor 700 x 1.5 x 0.2 mm channel)	3	80	1.8	93



1.84 **1.85**

Entry	Reactor/description	Flow rate/ mL min^{-1}	Conversion/ %	Productivity /g hr	Ref
3	Ammonite 8 (1000 x 2 x 0.5 mm channel)	1	93	3.2	[99]
4	Ammonite 15 (2000 x 5 x 0.5 mm channel)	16	88	20.7	[92]
5	Wirth reactor (120 x 20 x 0.5 mm)	0.5	94	1.6	[97]
6	Parallel plate cell (30 x 20 x 10 mm)	36[a]	95	0.6	[98]

a. Operates in recycling mode

Table 1.1: Methoxylation of *N*-Formylpyrrolidine in electrolysis reactors

1.1.8.3.4 Waldvogel modular electrochemical cell

Waldvogel *et al.* reported a modular electrochemical flow cell (Figure 1.18), consisting of two Teflon blocks (100 x 40 x 16 mm) with an opening (60 x 20 x 3 mm) where the electrode can be placed. A gasket/spacer with variable thickness (between 0.12 and 2.0 mm) is used to separate both electrodes and it will serve as reaction channel and can be employed as a divided cell if a Nafion® membrane is used. The electrode material can be selected according to the reaction of interest. The cell was used to successfully furnish nitriles from aldoximines using a graphite anode and lead cathode in a domino oxidative/reductive sequence (Scheme 1.44).

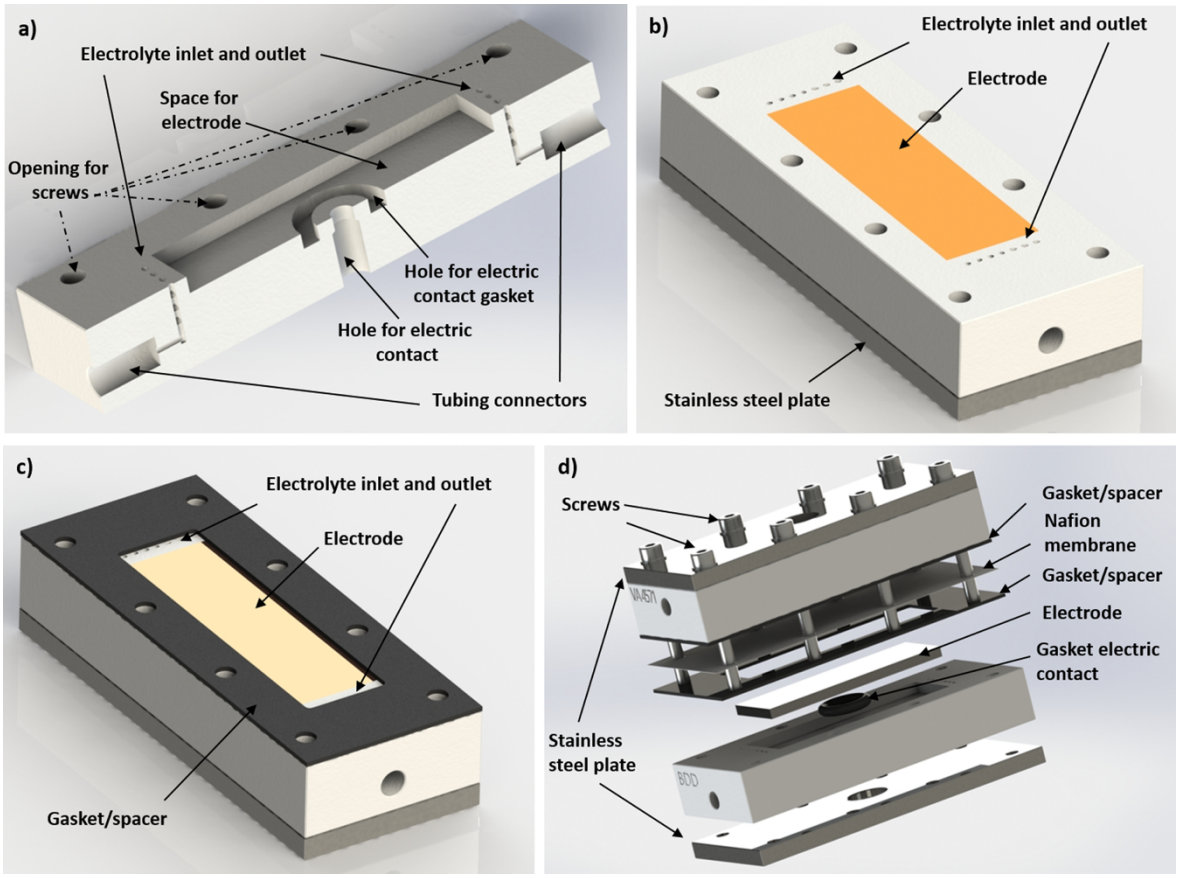
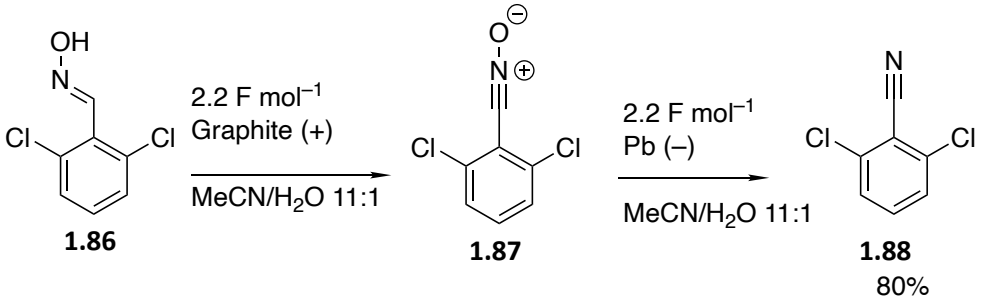


Figure 1.18 Modular electrochemical flow cell developed by Waldvogel *et al.* (a) Cross-section of the Teflon piece with connection for tubing, inlet, outlet, and free space for electrode. (b) Complete half-cell containing the Teflon piece, the electrode, and a stainless-steel plate. (c) Half-cell with gasket/spacer on top. (d) Exploded drawing of a complete divided cell.



Scheme 1.44: Domino Oxidation-reduction sequence in nitrile synthesis

1.1.8.3.5 Ammonite 8 reactor (undivided flow cell)

The majority of reactions that form the basis of the work described in this thesis were carried out in the Ammonite 8 reactor developed in collaboration with Cambridge Reactor Design (CRD).[91] The reactor is essentially a spiral flow channel between two electrodes, separated by an insulating polymer gasket made from the perfluoroelastomer FFKM (Figure 1.19).[91]

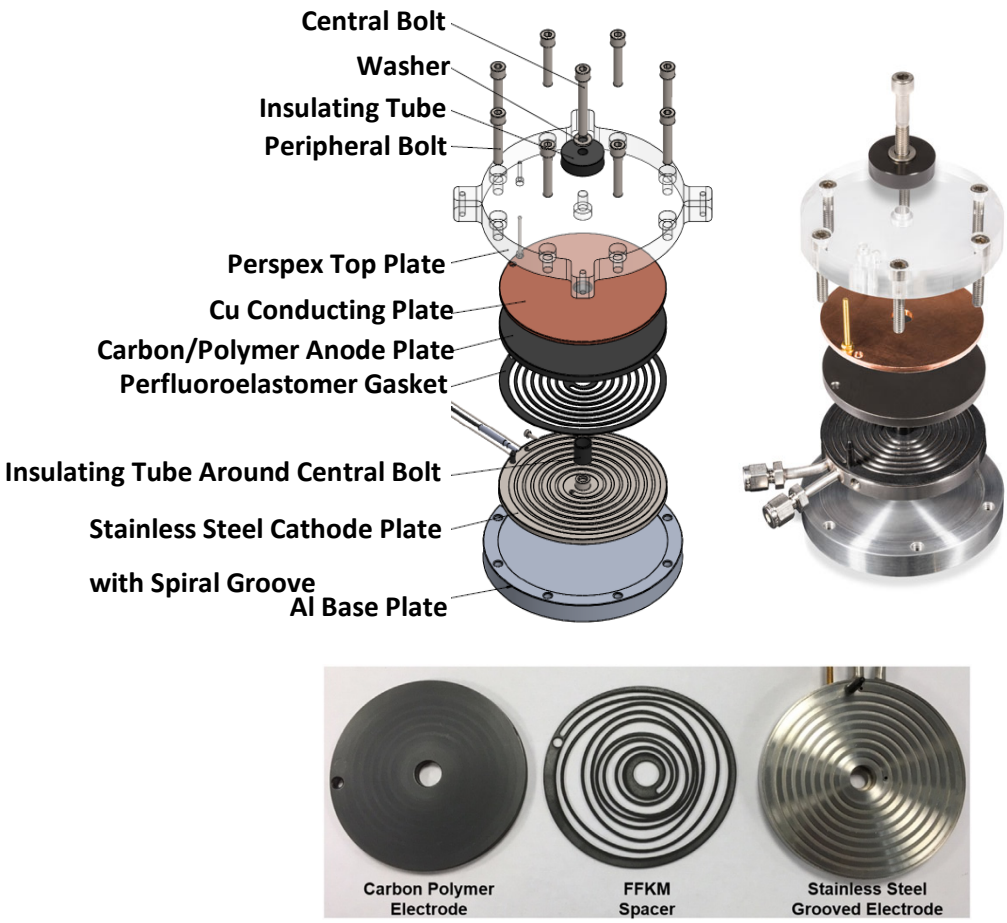
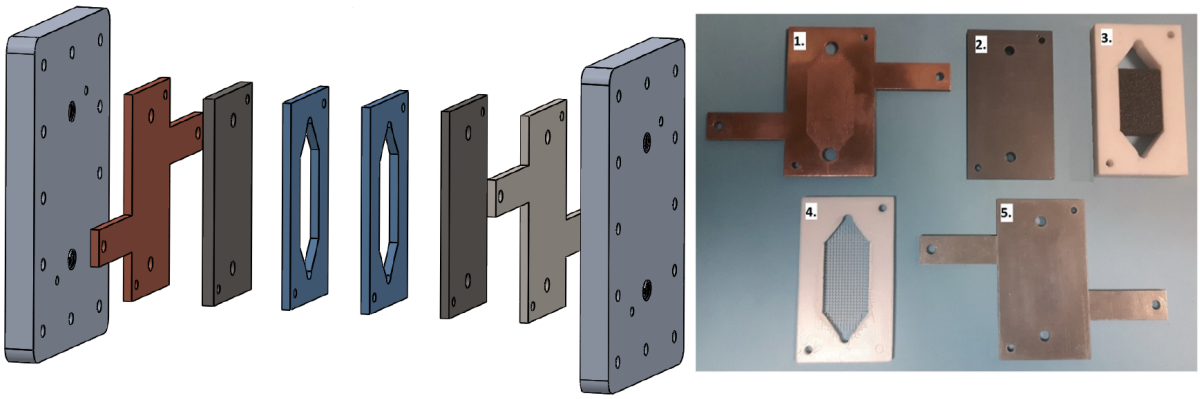


Figure 1.19: Photographs and images of the Ammonite 8 reactor

The Ammonite 8 reactor has been designed for routine laboratory electrolysis and has a number of important design considerations. The coiled channel creates a long (1m) path length, which aims to facilitate high conversion in one pass through the reactor. In addition to this, the coiled reactor design may introduce turbulent flow in the cell, which improves the mass transfer coefficient and thereby improves the reaction efficiency. The narrow interelectrode gap means that a low concentration of electrolyte is required in the reaction solution, and for some reactions electrolyte is not required.

1.1.8.3.6 Parallel-plate reactor (divided flow cell)

Another key reactor utilised in this work is a parallel-plate cell, designed and manufactured at the University of Southampton by Dr Ana Folgueiras (Figure 1.20).[98] The idea was to create a simple reactor that would enable electrolysis in both divided and undivided modes. In contrast, the Ammonite 8 was designed operate in undivided mode (a prototype divided Ammonite is under development). The design is simple to enable easy reproduction in a typical university or company workshop, and it is also scalable with modest modifications.



1. 2. 3. 4. 4. 3. 5. 1.

1. Aluminium body to hold the cell
2. Copper plate for electrical contact
3. Carbon electrode
4. PTFE gasket (reaction channel and sealing)
5. Stainless steel plate/electrode for electrical contact

Figure 1.20: Photographs and images of the parallel-plate reactor

The ability to carry out reactions in a divided flow electrolysis cell provided the opportunity to explore processes that are not practical in undivided reactors. As outlined in the section on divided batch cells (1.8.1.2), products at the counter-electrode reaction can interfere with the reaction at the working electrode, or the product can react at the counter-electrode. The membrane utilised in this reactor is Nafion® 438 (Figure 1.21), which consists of a hydrophobic fluorocarbon backbone and perfluoroether side chains containing a hydrophilic sulfonic acid group.

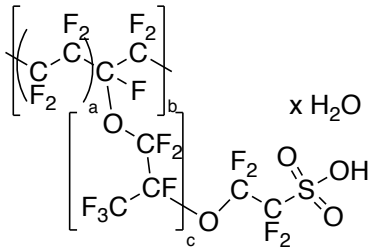


Figure 1.21: Chemical structure of Nafion®

Nafion® is a widely used in PEM's because of its excellent thermal, mechanical and electrochemical properties, resisting high and low temperatures, high tensile forces and oxidative conditions. In aqueous media, or when exposed to water the hydrolysed form of the sulfonate group ($SO_3^-H_3O^+$) allows protons to pass freely through the membrane through two potential mechanisms. One is the of "proton hopping" proposed by Grotthuss,[100] where protons are transferred, or "hop" from one hydrolysed ionic state to another across the membrane using the sulfonate groups. Another is a process called electroosmotic drag, where hydrated protons

$(H+(H_2O)_x$ drag one or more water molecules across the membrane. Nafion® 438 used in the current work is a specific composition, whereby it is bound to a PTFE mesh for additional mechanical strength.[101, 102]

1.1.8.3.7 Yoshida cation flow cell

Yoshida *et al.* designed a divided flow electrolysis reactor that could operate at low temperature (Figure 1.22). This was crucial for the development of a procedure for the generation of highly reactive carbocations by electrolysis, which enables direct oxidative C–C bond formation in a process known as the "cation flow" method. The cation flow method has been utilised to make a wide range of compounds in high yield, including biaryls,[78] THP rings,[103] C–N[103] and C–I[104] bonds. One example is the anodic generation of iminium species **1.87** by oxidation of pyrrolidine **1.86**, followed by reaction with nucleophiles such as allyl silanes either in batch or flow to furnish **1.88** in a C-C bond formation (Scheme 1.45).[105]

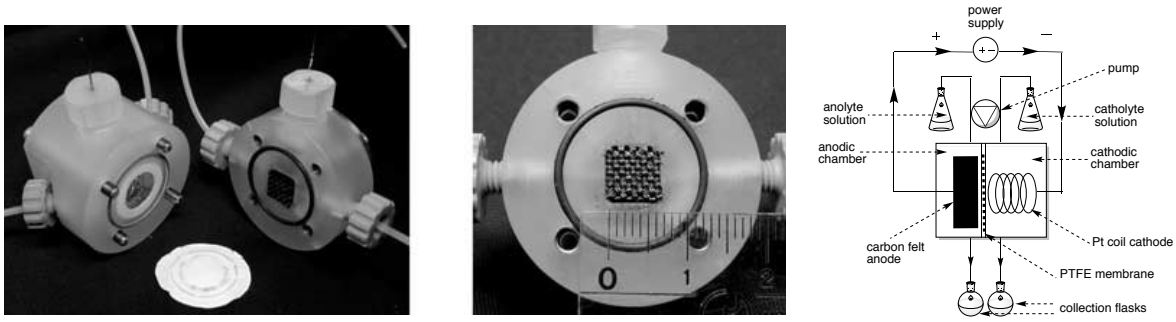
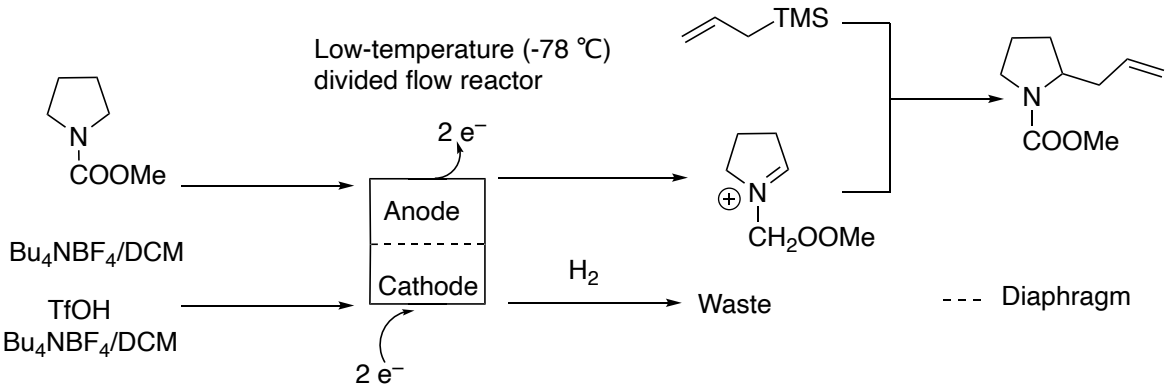


Figure 1.22: Photographs and a schematic of a cation flow system in Yoshida's cell, reproduced from Ref.[106]



Scheme 1.45: Schematic for the cation flow system.

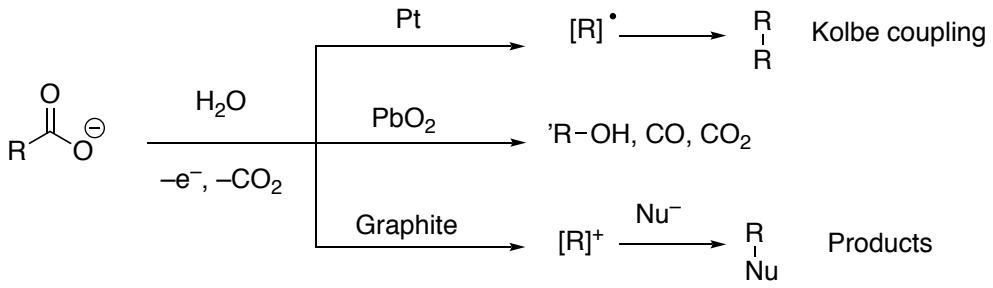
1.1.9 Electrode materials

The electrodes are a very significant aspect of an electrochemical cell; they often determine outcome of the electrochemical synthesis. A wide review on different electrode materials and

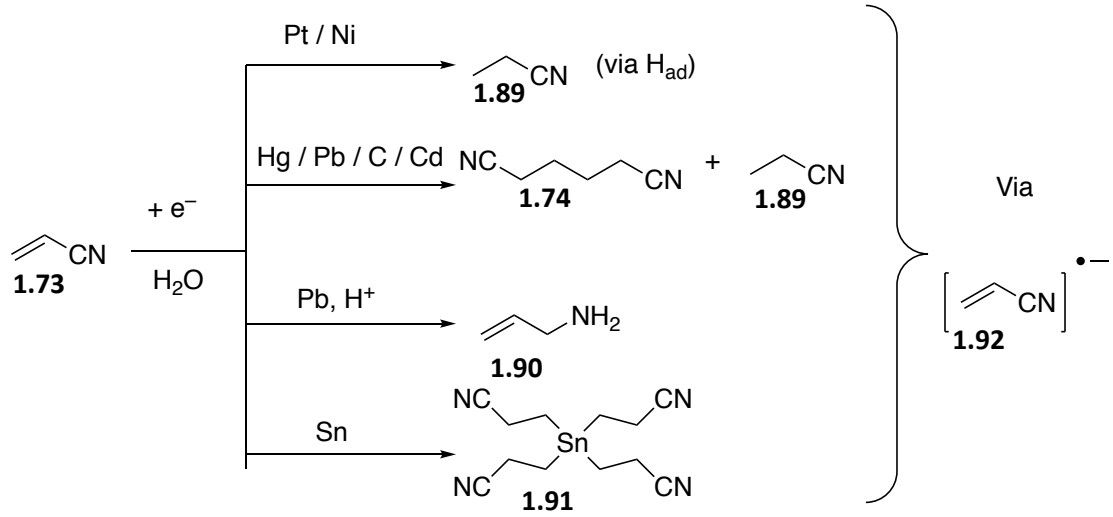
their reactivity has been published by Pletcher.[107] The electrode of choice must have the following characteristics:

- Electrical conductivity: this should be high throughout the electrode system including connections and entire surface exposed to reaction solution, to allow current to pass efficiently in the cell and avoid voltage losses leading to energy inefficiencies.
- Chemical stability: it must be resistant to corrosion, unwanted oxide or hydride formation, and the deposition of inhibiting organic films, i.e. it must be inert to the solvent, substrates and intermediates formed in the course of the reaction.
- Physical stability: must have adequate mechanical strength, and not prone to erosion by the electrolyte, reagents or products, and must be resistant to damage during the setup and reaction.
- Physical form: must be of a format that can be incorporated into the cell, facilitating sound electrical connections and permit easy installation and removal (for cleaning). The shape and size must be considered, the former to allow separation of products, namely gasses, and the latter in order to optimise the current density for the reaction of interest. They can take many forms such as flat plates, coils, 3D foams, rods and foils.
- Selective electrocatalytic activity: The electrode material must promote the desired chemical change (ideally at a high rate and low overpotential) whilst inhibiting competing chemical changes.
- Cost/durability, displaying reproducible performance including a suitable lifetime (several years ideally) to avoid costly replacement of the electrode.

The electrode material has a clear influence on the reaction, even forming a different product from the same substrate and reaction conditions (Scheme 1.46 and Scheme 1.47).[108]



Scheme 1.46: Impact of electrode material on anodic decarboxylation



Scheme 1.47: impact of electrode material on cathodic Acrylonitrile reduction

When selecting electrode materials, the overpotentials for oxygen and hydrogen evolution reactions need to be considered because they determine the electrochemical window for the reaction in many cases. Overpotential is the potential difference between a half-reaction's thermodynamically determined potential and the potential at which the redox event is experimentally observed. It is necessary for an anode material to have a high activation overpotential for oxygen evolution (i.e. the oxygen evolution reaction from water has a high redox potential on it), such that the substrate preferentially oxidises. Similarly, a cathode material needs a high activation overpotential for hydrogen evolution such that the selective reaction is substrate reduction. Poisoning (deposition of a different material) of the electrode surfaces can reduce the activation overpotential for these processes, thereby reducing current efficiency for the reaction and introduce unwanted side effects caused by the reactivity of oxygen and hydrogen.[108]

Along with the anode and cathode materials discussed next, there are a number of miscellaneous electrodes:

- Coated electrodes: they normally consist of an inexpensive metal coated with an expensive metal, the one of interest to use as electrode. For example, platinum coated onto carbon or titanium is less costly than a solid platinum electrode.

- Porous/3D electrodes: they can be used to increase the working surface area, and therefore current density, which can be crucial to a successful electrolysis.

- Gas evolving electrodes: oxygen, hydrogen or carbon dioxide can often be evolved at the electrode surface, and this gas formation can be either of interest in the reaction or used as sacrificial counter reaction. These bubbles can also improve the mass transfer within the electrolyte.

1.1.9.1 Anodes

Corrosion is a common problem with regards to anodes and is the main factor to consider when choosing the anode material. The degradation of an anode material can negatively impact a reaction by producing unwanted side reactions and can be expensive to replace. Corrosion is accelerated under certain conditions such as high potentials and temperatures,[109] and in the presence of certain ions such as hydroxide (HO^-)[110] and chloride (Cl^-).[111, 112] Corrosion has even been reported to occur at undesirable rates on common carbon-based anode materials such as graphite[113] and glassy carbon.[114] However the effect of corrosion is a desirable process when using a sacrificial anode, such as magnesium, aluminium, zinc or copper, as it constitutes the counter-electrode process.

Common non-sacrificial materials for anode electrodes are Noble metals such as platinum, gold and alloys of these with cheaper metals. In addition, plated electrodes are common, whereby a cheap conductive material is plated (through various deposition methods) with a precious metal. This represents a cheaper method to use a specific anode material where it would be costly to use in bulk. However extensive cleaning of the surface layer can quickly erode the coating. Nickel, lead and lead oxide are also sometimes used as bulk electrodes, since they are protected by a metal oxide layer (with Nickel this has been used to good effect in the indirect synthesis of *n*-butyric acid described in section 1.3.5.3). Carbon anodes are very typical in different forms, such as graphite, glassy carbon or reticulated vitreous carbon (RVC). Recently boron doped diamond (BDD) electrodes have been developed; they possess the highest known overvoltage for oxygen evolution, giving a wide electrochemical window. The high overpotential for formation of side products (such as oxygen in a useful oxidation reaction), and a low overpotential for the counter-electrode reaction are both integral to a successful electrosynthesis. For example, oxidation of alcohol substrates is frequently conducted on platinum electrodes as

the overpotential for oxygen evolution (which is a side-reaction) on this material is very high. Conversely, carbon-based electrodes are common for reactions featuring C-H activation as a relatively low overpotential exists for these substrates on this electrode.[22]

1.1.9.2 Cathodes

Corrosive effects are not common in cathode materials; therefore there are a wider variety of materials to choose. Mercury was a cathode material often used historically as a liquid pool, otherwise known as the dropping mercury electrode (DME). Due to its acute toxicity however its use has rapidly diminished. BDD electrodes are frequently used since they have the highest known overvoltage for hydrogen evolution. Other common materials to be used as cathodes include platinum, nickel, stainless steel, copper, lead, tin, and bronze alloys containing mixtures of the latter three materials. Platinum and palladium offer low overpotentials for hydrogen formation, meaning hydrogen evolution occurs at a low potential on these materials. Therefore they are useful in the electrochemical reduction of substrates by hydrogenation.

1.1.9.3 Reference electrodes

The standard hydrogen electrode (SHE) is the reference from which standard redox potentials are determined and has been assigned an arbitrary half-cell potential of 0.0 mV. The half-cell reaction is shown in Scheme 1.48:

$$2H^+_{(aq)} + 2e^- \rightleftharpoons H_{2\,(g)} \qquad E^o\,(V) = 0.00\ V$$

Scheme 1.48: Redox half-cell reaction for SHE

The SHE is fragile and impractical for routine laboratory use. Therefore, other more stable reference electrodes such as silver chloride and Saturated Calomel Electrode (SCE) are commonly used because of their more reliable performance. The potential for Ag^+/Ag is +0.222 V, vs. SHE at 25°C, but in practice the addition of KCl used to stabilise the silver chloride concentration this changes the potential to +0.198 V. The equations for the equilibrium between Ag and AgCl are illustrated in Scheme 1.49:[115]

Half-equations:

$$Ag^{+}_{(aq)} + e^{-} \rightleftharpoons Ag_{(s)}$$

$$AgCl_{(s)} + e^{-} \rightleftharpoons Ag_{(s)} + Cl^{-}_{(aq)}$$

Full:

$$AgCl_{(s)} \rightleftharpoons Ag^{+}_{(aq)} + Cl^{-}_{(aq)} \quad E^{o}\ (V) = +0.222\ V$$

Scheme 1.49: Redox cell and half-cell equations for Ag^{+}/Ag electrode

The SCE electrode redox potential is based on two redox processes, but also the contributions of the saturated KCl solution (which must be considered when comparing different reference potentials) alters the experimental value to +0.244 V. Scheme 1.50 illustrates the redox processes:[116, 117]

Half-equations:

$$Hg_2^{2+}{}_{(aq)} + 2e^{-} \rightleftharpoons Hg_{(l)} \quad E^{o}\ (V) = +0.80\ V$$

$$HgCl_{2\,(s)} + 2e^{-} \rightleftharpoons Hg_{(l)} + 2Cl^{-}_{(aq)} \quad E^{o}\ (V) = +0.27\ V$$

Full:

$$Hg_2^{2+} + 2Cl^{-} + 2\,Hg_{(l)} \rightleftharpoons Hg_2Cl_{2\,(s)} + 2Hg_{(l)} \quad E^{o}\ (V) = +0.53\ V$$

Scheme 1.50: Redox cell and half-cell equations for SCE electrode

The temperature, pressure and concentration of the solution are significant and standard conditions are required in order to accurately determine the redox potential (1 mol L^{-1} concentration, 298 K, 1 atm pressure). Reference electrodes are used to establish the standard redox potential for substrates, for CV experiments, and for preparative electrolysis where a fixed potential is required (for example the Haber reduction of nitrobenzene in Scheme 1.34).

1.1.10 Electrolytes

In most electrochemical processes organic solvents are not sufficiently conductive i.e. they fail to allow current to pass through them except when exceptionally high voltages are applied. As such a supporting electrolyte is needed to conduct charge in the reaction solution. If an acid or base is necessary to enhance the desired transformation, this can sometimes be sufficient to increase the conductivity of the solution. The process is cheaper and easier than a procedure to

remove electrolyte; neutralisation is sufficient. Unfortunately, many electrochemical reactions are sensitive to pH, and will not proceed smoothly under these conditions; hence an ionic salt is usually required. Several factors need to be considered when selecting an electrolyte for an electrochemical reaction:

- Good solubility and conductivity in the solvent
- Stable to redox processes, both oxidative and reductive. It should be inert to chemical reactions between any intermediate species formed.
- Low toxicity and price
- Easily separable from the crude, and ideally can be recovered and reused after purification.

Some of the cations and anions used in electrolytes will be discussed. Starting with cations:

- Sodium and lithium cations are highly stable to both oxidative and reductive conditions, although will discharge in highly reducing conditions (E= –2.70 and –3.04 vs. SHE for sodium and lithium cations respectively). Magnesium is occasionally used. Their solubility is low in aprotic solvents, which limits their application.
- Quaternary ammonium cations are popular due to their solubility in a range of protic and aprotic solvents. They have a broad electrochemical window, although can be reductively dealkylated (reduction potentials range from –2.2 to –2.9 V depending on anion, length of alkyl chain and whether there is a protic solvent present, which would inhibit any dealkylation),[118] with the longer alkyl chain salts more resistant to reduction owing to weak interaction with the cathode. The products of dealkylation are alkanes and alkenes. No oxidation decomposition reactions have been reported.[119-121]

The selection of the anion is more relevant for anodic oxidations. Common anions utilised are:

- Perchlorates are widely used, despite posing a risk of explosion (it has been reported that this can occur through heating of an organic solution containing perchlorate salts). They have a good electrochemical window, although perchlorates have also been reported to both oxidise and reduce in acetonitrile (which has an exceptionally wide electrochemical window) and reduce in other

solvents. They are soluble in protic solvents and some polar aprotic ones where the cation is a tetraalkylammonium species.[122-126 127]

- Nitrates are occasionally used as electrolytes, although their narrow electrochemical window means their scope is limited. More often they are used as mediators since they display reversible redox behaviour.[128] Nitrate salts also dissociate into ion pairs better than many electrolytes, including perchlorates in acetonitrile.[129] Metal nitrates oxidise (+1.92 V on Pt vs. Ag/AgCl)[130] and reduce at relatively low potentials in acetonitrile (between –1.5 and –2.0 V on various electrodes vs. Ag/AgCl).[131]

- Tetrafluoroborate is very widely used in electrochemistry. Its tetraalkylammonium salts are soluble in most solvents, non-hygroscopic, and has an excellent electrochemical window, with an oxidation potential of +2.91 V vs. Ag/Ag^+ in MeCN.[132] Reduction of the anion appears to be impossible in most solvents, with reduction of the cation occurring instead.[120] The main limitation of tetrafluoroborate salts is their cost, which is significantly more than halide, nitrate or perchlorate salts. However, the electrolyte can be recovered in many cases.

- Hexafluorophosphate is classified as an exotic electrolyte, and shares many of the properties of tetrafluoroborate, although oxidises even less readily (+3.02 V vs. Ag/Ag+ in MeCN).[132] It can also be used at low temperature, a characteristic not shared by many electrolytes. It is considerably more expensive however, and so is largely surplus to requirement except where high electrode potentials are required.[22, 122]

- Trifluoromethanesulfonate (triflate) and fluorosulfonamides such as bis[(trifluoromethyl)sulfonyl]imide (bistriflimide) are sometimes used, as they share the oxidative-resistant properties of fluoroborates, but dissolve more readily in organic solvents to produce electrolytes with high conductivity. They are cheap to synthesise as well, although they are susceptible to reducing conditions so a divided setup is recommended.[122]

Flow electrosynthesis utilising reactors with a narrow interelectrode gap has demonstrated that reactions can proceed without supporting electrolyte in some circumstances (see section 1.2.2). In addition, Fuchigami *et al.* developed a method where a solid-supported base can act as supporting electrolyte in methanol, carrying out α-methoxylation in a wide range of substrates.[133]

1.1.10.1 Room temperature ionic liquids

The use of room temperature ionic liquids (RTIL) in organic electrochemistry has increased significantly in recent years, thanks to their unique properties. RTILs consist of an ion pair material that exists as a liquid at rt. They present inherent ionic conductivity, low volatility, and the broad structural variety available permits the tuning of their physical properties, such as solubility and water miscibility. Mismatched ion pairs with low symmetry are often used to create ionic liquids at room temperature. In general, this can be achieved using asymmetric bulky organic cations and practically any anion. Some frequently used ions in ionic liquids are illustrated in Figure 1.23.

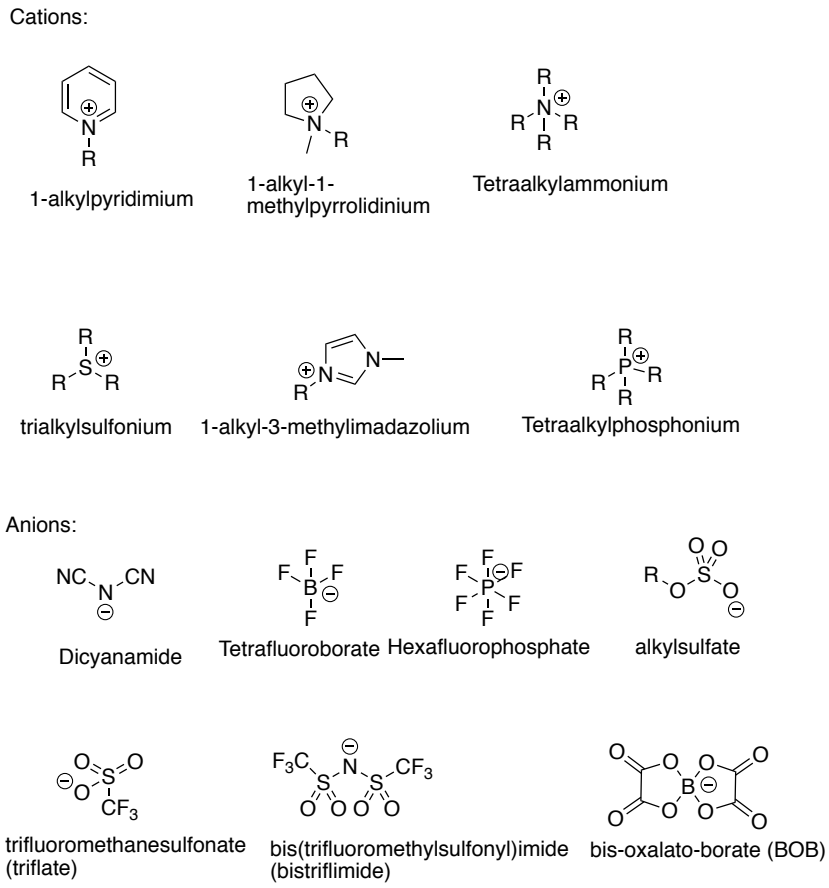


Figure 1.23: Commonly used anions and cations in ionic liquids

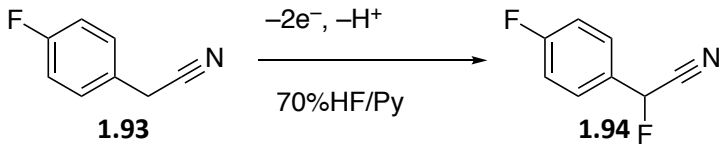
Although RTILs are typically good conductors due to their ionic nature, they usually have high viscosity, which can lead to poor mass transport and sometimes even to limited ionic conductivity when compared to some organic solvents. To overcome this problem, co-solvents or dissolved gasses have been employed, providing a higher rate of diffusion. RTIL's can also be susceptible to hydrolysis, and/or moisture sensitivity. Those that contain the anion $[BF_4]^-$, $[PF_6]^-$, $[SbF_6]^-$ and $[C_nSO_4]^-$ that were thought to be resistant have been shown to hydrolyse, in the case of the fluoride-based anions toxic and corrosive HF is produced.[134] To this end RTIL's require

protecting from water in most cases. They are however resistant to air-oxidation, owing to their design whereby the ions are not readily oxidised, and that their oxygen solubility is low and can be easily removed under vacuum or gas purging.

One of many merits of the use of RTIL's is their environmental benefit, i.e. they are typically non-volatile and represent a lower exposure risk than volatile solvents. Furthermore they are resistant to environmental photochemistry and are non-flammable. They are usually easily recovered, display excellent conductivity and have tuneable physical properties. Whilst they can be expensive, this can be offset by good recovery after the reaction, and this facilitates purification of the product. RTIL's have been shown to improve a large number of electrochemical reactions; a few of these are outlined next.

1.1.10.1.1 Oxidative processes in RTIL's

Electrochemical fluorination has been greatly facilitated by using ionic liquids instead of traditional solvents. Middleton *et al.* used ionic liquids to great effect, vastly improving the yield in the fluorination of **1.93** (Scheme 1.51) to **1.94**. Conducting the reaction in a co-solvent of the ionic liquid and MeCN led to multiple side-products forming.[135]



1.93 **1.94**

17% in MeCN, 87% in Ionic liquid

Scheme 1.51: Electrochemical fluorination using ionic liquid HF/Py

Later developments by Momota *et al.* led to the use of quaternary fluoride salts of formula $R_4N{\bullet}nHF$ (n > 3.5, R = Me, Et, *n*-pr), which are again non-viscous liquids and display greater anodic stability than commercial reagents $Et_3N{\cdot}3HF$ and 70% HF/py, and also did not lead to anode passivation by formation of non-conducting polymer films, when the latter salts often did. Reduced passivation of electrodes led to improved current efficiencies. Figure 1.24 illustrates the enhanced potential window for these salts.[136]

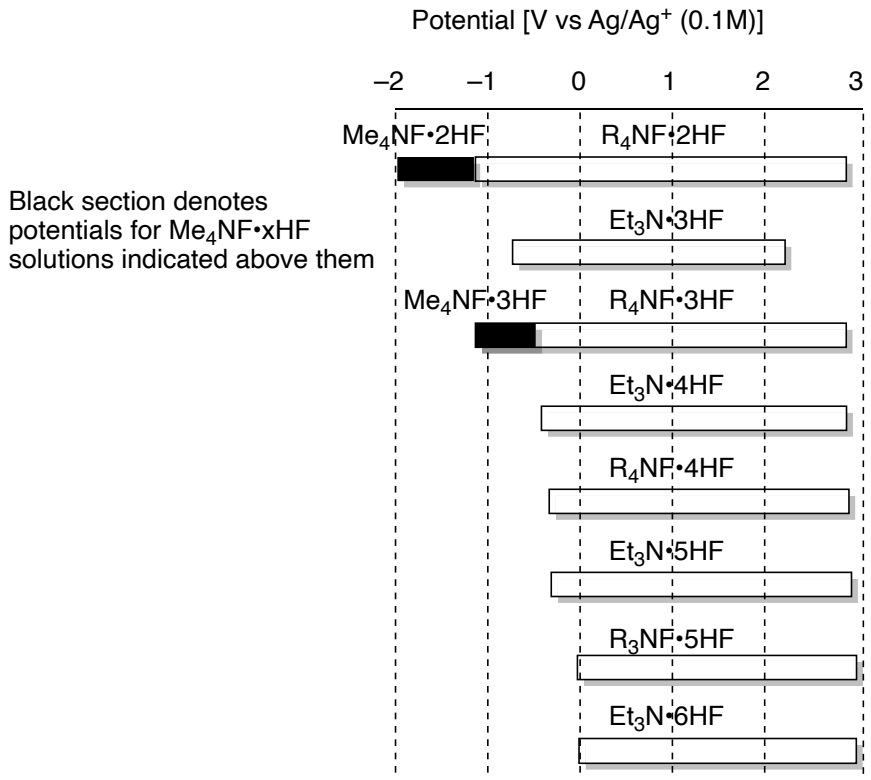
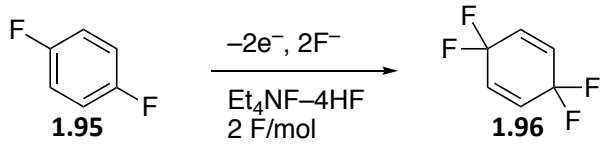


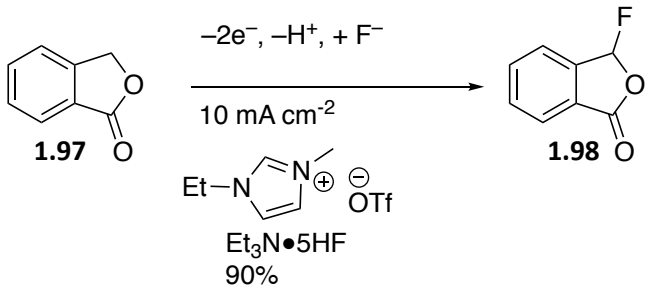
Figure 1.24: Potential window for fluoride ionic liquids

Momota demonstrated the capability of the ionic liquid Et_4NF-4HF (one of the commercial RTIL's available) on a number of substrates, including 1,4-difluorobenzene (Scheme 1.17), with a yield and current efficiency of 90%.[137] The use of the ammonium salt instead of alternatives even allowed the use of normal glassware instead of HF-resistant materials such as PTFE.[138]



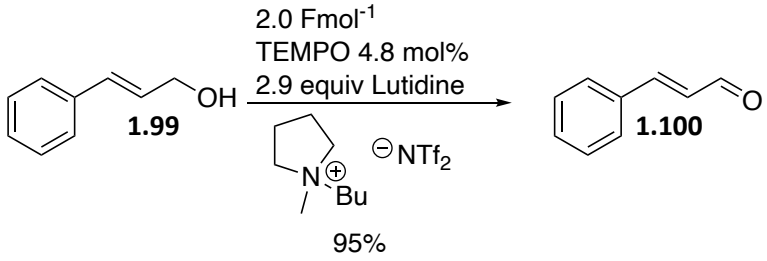
Scheme 1.52: Momota's electrochemical fluorination of difluorobenzene using quaternary ammonium ionic liquid

Similarly, Fuchigami *et al.* observed that using [Emim][OTf] as an RTIL with Et_3N-nHF as the fluoride source led to superior yields for the fluorination of phthalides compared to using acetonitrile or the fluoride source as solvents, as illustrated in Scheme 1.53. It is believed that the RTIL increases the nucleophilicity of the fluoride anion and stabilises the electro-generated cationic intermediate.[136, 139]



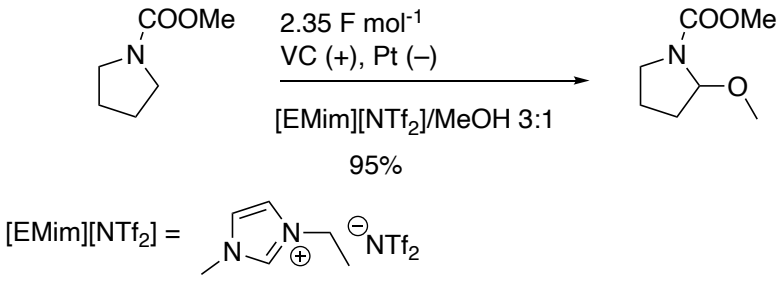
Scheme 1.53: Electrochemical fluorination of phthalides using RTIL's

A TEMPO-mediated electrochemical oxidation of alcohols has been conducted in RTIL, using TEMPO as a mediator. Alongside the environmental benefit of using an RTIL over acetonitrile, the method also demonstrates a higher kinetic peak current to anodic peak current ratio (1.4 vs. 1.2 for MeCN), which is corrected for mass transfer and viscosity and indicates that a lowering of viscosity would lead to a faster reaction rate, with comparable yields in both methods on similar substrates (Scheme 1.54).[140]



Scheme 1.54: Electrochemical oxidation of alcohols in RTIL's with TEMPO mediator

In addition to this, a Shono-type methoxylation was also successfully conducted in the RTIL [Emim][NTf_2] in high yield with recovery of the ionic liquid on purification. The process is illustrated in Scheme 1.55:[141]

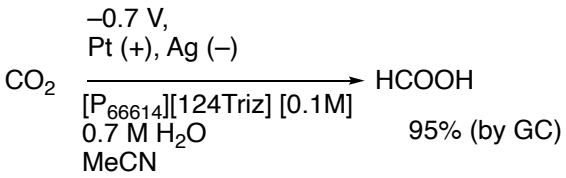


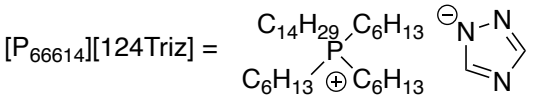
Scheme 1.55: Shono-type methoxylation in RTIL

1.1.10.1.2 Reductive electrosynthesis in RTIL's

RTIL's have been utilised in CO_2 fixation processes, demonstrating that the overpotential for CO_2 lowers from 1 V to less than 0.2 V. This is likely due to formation of a complex between the

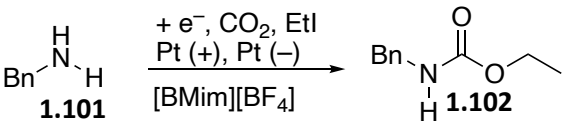
CO_2 and [Emim] cation of the RTIL.[142] Furthermore, the use of superbase IL's such as $[P_{66614}][124Triz]$ increase CO_2 solubility and also minimise the competing hydrogen evolution reaction (Scheme 1.56).[143] These processes could find use in the field of carbon trapping, and also demonstrate useful application in electrosynthesis (Scheme 1.56 and Scheme 1.57).

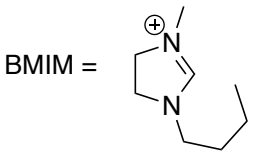




Scheme 1.56: Formate synthesis by Hardacre *et al.*

A similar carbon trapping process using CO_2 to form carbamates, was carried out by Inesi *et al.* (Scheme 1.57).[144]

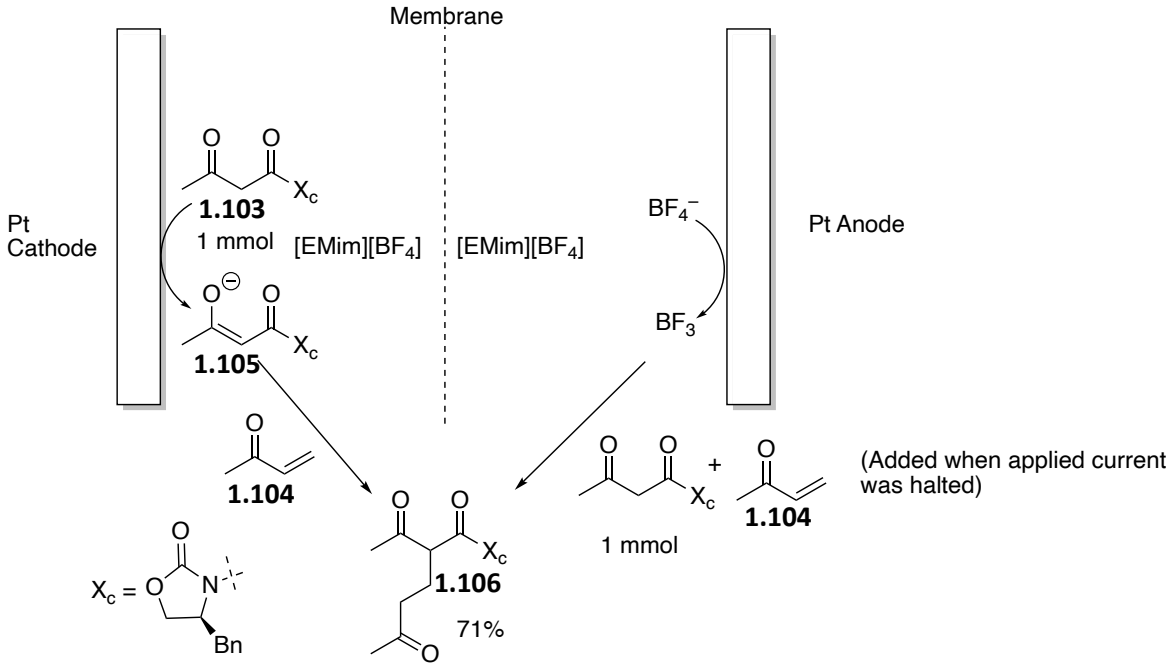




Scheme 1.57: Electrochemical reductive carbamate synthesis in RTIL by Inesi *et al.*

1.1.10.1.3 Paired electrosynthesis in RTIL's

Palombi *et al.* used a divided flow cell to carry out a Michael addition reaction under paired conditions, utilising a catalytic quantity of current. Anodic and cathodic processes both contribute to product formation (Scheme 1.58).[145] At the cathode a small quantity of the acetocarbamate **1.105** is reductively deprotonated, and then proceeds to react with the electrophile **1.104**. At the anode, oxidation of the RTIL anion (reportedly at least) produces Lewis acid BF_3 in catalytic quantities, which catalyses the Michael addition reaction. The use of the RTIL dramatically increases the current efficiency, with only 0.1 F mol^{-1} of charge used in the reaction. Whilst oxidation of the BF_4^- anion seems unlikely, there does not appear to be another substance which could be readily oxidised in the anodic chamber, and other electrolytes in which BF_3 cannot be formed did not lead to product formation.



Scheme 1.58: Paired electrolysis for a Michael addition in a RTIL (reproduced from Ref.[145])

RTIL's were not utilised in the work conducted in this PhD, despite their enormous potential. Reasons for this range from cost (the use of RTIL's as solvents is more expensive than common solvents), to engineering problems (RTIL's typically have a high viscosity) which can limit productivity where a high resistance occurs when passing solutions at high flow rates through the reactors.

1.1.11 Solvents

Solvents are equally significant in electrochemistry as they are in organic chemistry. Several additional factors need to be considered, beyond the usual features such as suitable temperature range, viscosity and cost, and environmental concerns such as toxicity and ease of waste disposal. These features follow:

- Usable potential window – this is such that the redox potential for the substrate is lower in magnitude than the solvent, and as such the substrate will react and not the solvent. The solvent needs to be compatible with the electrode and not corrode it or react with it, and not interact with intermediate substrate species, unless this is necessary for the reaction.

- Electrolyte and substrate solvation ability – the solvent needs to be able to solvate both the organic substrate and a supporting electrolyte. This can prove tricky, especially where the substrate is not readily soluble in polar solvents. Co-solvents can be used to promote dissolution. Inorganic (ionic) electrolytes readily dissolve in

water, and so this is commonly mixed with acetonitrile or methanol which typically solvate organic molecules. Tetraalkylammonium salts discussed previously are commonly used electrolytes because they are soluble in protic and even polar aprotic organic solvents, which is helpful as water can interfere with many electrochemical processes. The ability of the solvent to promote dissociation of the electrolyte ions and not simply solvate them as pairs is also significant, as dissolution improves the conductivity of the solution and promotes electron transfer.

- Dielectric constant – this oppositely correlates with the ohmic resistance of a solution, and so a high dielectric constant is desired, required even in order to dissociate ions in the solution.

- Proton availability – The availability of protons is an important characteristic of a solvent. In electrochemistry, the presence of protons is more important in reductions, although it can also help to stabilise cation radicals in anodic oxidations. In cathodic reductions, if there is high proton activity in the solution the substrate can be protonated prior to electron transfer, which often facilitates the process.[22, 108]

Individual solvents that are commonly used for electrolysis will be discussed, starting with protic solvents:

- Water is without a doubt the preferred solvent for electrolysis, combining an excellent green chemistry profile with a high dielectric constant (ε = 80) and a reasonable electrochemical window, especially for reductions (–2.5 to 2.0 V vs. SCE). Furthermore, supporting electrolyte is often surplus to requirement, if the experimental setup allows for this. Limitations of the solvent include poor solubility to many organic molecules (especially non-polar ones), competition for the substrate to adsorb to the electrode surface, and a modest potential window for anodic oxidation. Solubility can be enhanced through the use of emulsions[146] or hydrotropic salts.[147]

- Methanol is also a good solvent for electrochemistry, it's properties are similar to those of water, with a high dielectric constant (33), a convenient liquid temperature range (especially when most electrochemistry is conducted at rt) of –98 to 64 °C, making removal after the reaction facile. Many electrolytes are soluble in methanol, including NH4Cl, LiCl, HCl, KOH, KOMe, NaClO4 and

tetraalkylammonium salts. Methanolic HCl is a common solvent/electrolyte combination for cathodic reductions due to high conductance and ease of removal on purification. The electrochemical window is similar to that of water, which can limit the choice of substrates for anodic oxidations. Many of the processes discussed in this chapter utilise methanol as a solvent, and so too is it used in chapter 2 for the deprotection of PMB groups from nitrogen-containing compounds.

- Acetic acid is useful where acidic conditions are needed, or where an acetoxylation is the required reaction. It has a modest dielectric constant (6.2) and so supporting electrolyte, or a catalytic amount of another acid such as perchloric acid are also required. Care should be applied when choosing electrolytes with AcOH however, as they can lead to different reaction outcomes. For example, the Kolbe acetoxylation requires a basic electrolyte e.g. NaOAc[148]

- TFA can be used for many of the same processes as AcOH, and has been shown to stabilise cationic radical species well.[149]

- HFIP (hexafluoroisopropanol) has a number of desirable characteristics in electrochemistry, including physical properties (low bp, miscible with other solvents including water, recoverable from substrates), enhanced acidity vs. IPA, reduced nucleophilicity (which can inhibit counter-electrode side reactions), excellent H-bond donating ability, a high potential window (–1.75 to 2.85 V vs. Ag/AgCl), and significant cation stabilisation.[150] It is used in many electrolyses, especially in work conducted by Waldvogel et al.[59, 151] A setback however is that it is rated poorly on green metric analysis.

The use of aprotic solvents is of interest when aqueous or protic conditions lead to undesirable reaction outcomes. Aprotic solvents generally adsorb poorly to the electrode surfaces, which if this is one of the key mechanistic steps for the substrate then it is a desirable outcome. Some key aprotic solvents are now described:

- Acetonitrile is the most widely used aprotic solvent, with many of the desirable properties key to electrosynthesis. It solubilises organic substrates and electrolytes well and has a high dielectric constant (37). Furthermore it has an excellent electrochemical window and is in fact limited by that of the supporting electrolyte. It is a very poor proton donor, which is a useful property if protonation of the intermediate is undesired, for example in coupling reactions. It does however have

the disadvantage of being mildly toxic. Many of the processes in this chapter utilise MeCN as a solvent, and furthermore it is the solvent of choice for the reductive cyclisation process described in chapter 3.[119, 122, 152]

- Dimethylformamide (DMF) has similar properties to acetonitrile, however its use has seen a decline in recent years owing to its low volatility, toxicity, and stability (can be hydrolysed to dimethylamine which is readily oxidised).

- Dichloromethane (DCM) has some specific uses in electrosynthesis. It can stabilise certain cation radical species well and can solubilise non-polar organic molecules and larger tetraalkylammonium electrolytes well. It has a low reduction potential and the chloride ions that form can interfere with the anodic process, even in a divided cell. Adding MeOH or AcOH in order to change the counter-electrode reaction will counter this.

- Ethers are rarely used in electrosynthesis, in part because of their low dielectric constant and poor electrolyte solvation ability, but also because they display a narrow electrochemical window, especially to oxidation whereby polymerisation can occur, which can passivate the anode, or peroxides can form which are explosive.[22]

1.2 Organic electrochemistry under continuous flow

1.2.1 Flow chemistry introduction

Flow Chemistry has emerged as a useful method for organic chemists, because it offers a number of advantages over batch synthesis. The ability to carry out synthesis on a very small scale means that the efficiency of a synthesis step can be explored without the loss of large amounts of precious substrates.[153] On the other hand, flow chemistry can greatly facilitate the scale-up of reaction processes, with many reactors demonstrating high productivity (see Table 1.1).

Efficient heat transfer is a key feature in the growth of flow chemistry techniques. Flow chemistry has this advantage because low reaction volumes make heat transfer far more efficient, which leads to lower energy costs and ultimately a lower environmental impact.[95] Efficient heat transfer also has benefits in safety, since a potential runaway reaction can be avoided or controlled through cooling.[153, 154] With this in mind, scaling up of certain reactions can be carried out with fewer complications (thermal runaway more easily avoided, and the stoichiometric mixing of substrates. which offers improved yield by avoiding “hot spots” of reagents in solution).

Flow chemistry can be applied to a range of chemical reactions, including electrochemical, photochemical, thermal routes, or even harnessing the intrinsic reactivity of compounds through combining them under flow conditions from separate inlet streams, meeting at a T-piece of tubing. These methods can be combined in what is informally known as “daisy-chaining”, in order to produce highly functionalised, diverse products from simple substrates that would otherwise require multiple separate batch steps, or a one-pot, multiple-step batch approach.

1.2.2 Fundamentals of flow electrochemistry

Flow electrochemistry has seen a rapid rate of development in the last 30 years in the synthetic organic laboratory, having advantages over conventional batch electrochemistry, such as high electrode surface-to-reactor volume ratio, short residence time, zero or low concentration of supporting electrolyte, and easier scale-up. The same principles of flow chemistry also apply to electrosynthesis in that a small amount of material is exposed to the reaction conditions, thereby minimising risks associated with overheating, loss of selectivity etc.[155]

The electrode gap in flow electrochemical reactors is typically very small, normally below 500 µm,[29] which significantly reduces the ohmic resistance and avoids the presence of large current gradients through the solution compared to conventional cells. The mass transfer coefficient in flow reactors is typically superior to batch reactors, which along with the previous point offers improved reaction selectivity and current efficiencies.[2] Due to improved conductivity of the reaction solution, electrochemical reactions can be carried out using very low concentrations of supporting electrolyte, or even in its absence (where the interelectrode gap is sufficiently narrow)[133, 156-158] since the diffusion layers of anode and cathode overlap with each other.[159]

Electrolysis in flow differs practically to the batch process because controlled current electrolysis is the most common method employed. A batch process is often limited by mass transfer, the implications of which are that for a given applied voltage an upper ceiling is reached, and as the reaction is left under those conditions the current decreases until the substrate is consumed. The amount of charge the solution is exposed to is determined by time, and the same is true for a flow reactor operating in recycling mode (where conversion is achieved through multiple passes of the reactor), such as the parallel plate reactor described in section 1.1.8.3.6. Reaction progress can be monitored in this mode because the solution does not reside in the reactor for the full duration of the reaction, and so the current applied is somewhat less relevant (although the expected length of time for the reaction can be determined by the amount of charge transferred to the solution). Many flow reactors operate by aiming to achieve full

conversion in a single pass, and the applied current in these reactors is very important. The residence time in the reactor is controlled by the flow rate of the solution, and therefore the charge transferred. To this end the amount of charge, and therefore the amount of current (I_{cell}) that is required to achieve theoretical full conversion must be calculated. I_{cell} is determined using the following equation:[160]

$$I_{cell} = nFQ_vC$$

Figure 1.25: Equation determining theoretical current for full conversion from cell parameters

Where n is the number of electrons involved in conversion of reactant to product, F is the Faraday constant (96485 C mol^{-1}), Q_v is the volumetric flow rate of the reaction solution and C is the concentration of the substrate in the reaction solution. As in conventional synthesis where an excess of a reagent is required, in an electrolysis a higher current than the theoretical might be needed, therefore using a number of electron equivalents (F mol^{-1}) > n. This might occur when a competing reaction is present e.g. solvent oxidation. Similarly, there might be cases where a sub-stoichiometric current is required due to the sensitivity of a reagent, which whilst not achieving full conversion, might offer a higher yield for the product.

1.2.3 Sustainability and Green chemistry

Green chemistry is a concept that encourages chemistry to be more sustainable and have a lower environmental impact. The term was coined in 1991 by Paul Anastas,[161] and focuses on the following:

- Designing of products and processes that minimise or eliminate the use and generation of toxic and/or hazardous substances.
- The environmental impact of chemistry, including reducing consumption of non-renewable resources and using technological approaches to prevent pollution.
- Efficient utilisation of raw materials, including energy resources in the manufacture and application of chemicals.

Anastas, together with John Warner formulated the following guidelines to promote the implementation of Green chemistry:[162]

- Waste prevention: prevent waste from the start rather than treating or cleaning it up afterwards.

- Atom economy: Design synthetic methods to maximise the incorporation of intermediate materials into the final product.
- Safer syntheses: Design synthetic methods to minimise the use and generation of toxic substances.
- Safer products: Design chemical products to carry out their function while minimising their toxicity.
- Safer auxiliaries: Minimise the use of solvents and other auxiliary substances, and make them as innocuous as possible
- Energy efficient: Minimise the energy used in chemical processes, and if possible, carry them out at ambient temperature and pressure.
- Renewable feedstocks: Use biomass and other renewable raw materials whenever practical.
- Derivative reduction: Minimise the potentially wasteful use of blocking groups and other temporary modifications of intermediates.
- Catalysis: Prefer catalytic reagents, as selective as possible to stoichiometric reagents.
- Degradability: Design chemical products for eventual disposal, so that they break down into innocuous compounds that do not persist in the environment.
- Pollution prevention: Develop methods for real-time monitoring and control of chemical processes that might form hazardous substances.
- Accident prevention: Choose processes and practices that minimise the potential for chemical accidents, including releases, explosions and fires.

A unified metrics toolkit has been developed by Clark *et al.* (although other methods exist) to evaluate sustainability of reactions, including a comprehensive range of criteria for measuring how green a reaction is, covering quantitative and qualitative criteria both upstream and downstream of the reaction itself. It assesses the hazards of chemicals according to their H-labels, the sustainability of reagents according to abundance of the earth's resource of elements, a pre-assessed solvent guide, catalyst use in the reaction and various standardised metrics to evaluate the green properties of the reaction under consideration.[163] The toolkit is available as an excel document, and has been utilised for the main reactions conducted in this work.

Solvents have come under particular scrutiny following the pursuit of green chemistry. This is largely because they have been overlooked historically in reactions, with the majority of optimisation centred on the reagents and catalysts employed. Historically, large volumes of solvent are often used in reactions (especially at the purification stage) or in formulation. Despite this, the solvent rarely contributes to the product structure (unless it is a reagent), nor is it the active component of a formulation. Therefore, the use of toxic, flammable, or environmentally damaging solvents is unnecessary where a safer option can be effectively used instead. Industrial companies have noticed this and make assessments as to the suitability of solvents used in reactions, considering factors such as:

- Water hazard
- Air hazard
- Persistency
- Chronic toxicity
- Irritation
- Acute toxicity
- Reaction/decomposition
- Fire/explosion
- Release potential

The impact of the solvent on each of these factors creates a cumulative score, which determines its overall environmental impact. Solvents with a high score on this assessment are restricted, and as such are not used unless essential to the process. Some solvents, such as benzene or CCl_4 are banned outright by industry because of their score.[164-166]

Electrosynthesis is seen as a desirable method for organic synthesis in many respects. A number of reasons for this have already been discussed (see section 1.7). Alongside reagent-free synthesis, mild and safe conditions and recovery of electrolyte, many of the solvents utilised in electrosynthesis have a low environmental health and safety (EHS) score, such as water and methanol. These solvents are typically used because they solubilise supporting electrolytes well, but the environmental benefit of using them is obviously desirable. There are however ways that electrosynthesis falls down on a green chemistry assessment. For example, hazardous electrolytes such as perchlorates are employed in many organic electrolyses, although their use is thankfully

diminishing. Toxic, flammable, or corrosive solvents may also be chosen for certain electrochemical reactions where low EHS scoring solvents fail, which negatively impacts on the safety features of the overall process. Environmentally unfriendly additives in the form of mediators are essential in some electrolysis reactions and contribute to the production of waste. In these cases, electro-organic synthesis fails to comply with crucial guidelines of green chemistry, and so more needs to be done to find ways to circumvent these, either through research into alternative solvents, mediators (or removing entirely), or through alternative electrosynthesis methodologies.[164, 166]

1.3 Application of flow electrosynthesis for use in contemporary organic synthesis

One of the main limitations to electrosynthesis is not the methodology itself, rather the ease of setup. It is true that an electrochemical flow apparatus requires a certain degree of expertise to setup and maintain. To this end the author would like to provide some assistance, commenting on such options as scale, safety features, reaction compatibility and other important features when carrying out organic electrosynthesis in flow.

To carry out electrosynthesis, the following pieces of equipment are mandatory:

- Electrochemical reactor: can be built in-house, or from a commercial supplier. Components of this are two electrodes, in contact with the reaction vessel, and two points where the electrodes can be connected to cables leading to the powerpack.
- Powerpack (preferably able to deliver current to within 1 mA), complete with conductive cables. It would be advantageous for the powerpack to deliver current via a fixed voltage, as a number of electrosyntheses are conducted in this way.
- Pump to transfer the reaction solution through the reactor (or to circulate). This can be HPLC derived or peristaltic. Tubing and adapters between the inlet solution flask, the pump, the reactor and the outlet flask are also required. N.b. in recirculation mode the inlet and outlet flasks are the same. A pump setup can be bought commercially (e.g. through Syrris), or developed in-house, although care should be taken to ensure good fittings between tubing.

In addition to the above, other equipment can also improve the process:

- Regulation of the pressure in the reactor (where this is approved) can be achieved by using a back pressure regulator.
- Heating equipment is common, and this can be used to facilitate the electrolysis where temperature is an important variable in the reaction.
- Other reactors can be linked to the outlet tubing in a “daisy-chain” setup, enabling multiple transformations to occur in tandem.
- Tube-in-tube technology can allow for the release of gases from the effluent reaction solution which can otherwise disrupt the isolation or subsequent reaction.

The current that should be applied to the reactor during electrolysis can be determined through the equation in 1.2.2. The accuracy with respect to the concentration of the reaction solution is of high importance because the current (and therefore the number of electrons

transferred) is controlled. Electrons are highly reactive: an excess of current might lead to formation of side-products or consume the product. Deficient current will mean complete consumption of starting material is not possible.

The scale of the reaction is conditional on the reactor used. Reactors are designed such that a wide range of reaction productivity is possible. For example, the Syrris reactor outlined in 1.1.8.3.3 has a productivity of 1.8 g hr^{-1} for the methoxylation of *N*-formylpyrrolidine,[93] whereas the Ammonite 15 reactor has a productivity of more than 10 times this for the same transformation.[92] Hence a realistic scale must be considered for the capabilities for the reactor used. For many electrolysis reactions in the literature a scale of 1 mmol is used.

Safety is of paramount importance in chemistry and within electrosynthesis this is no different. There are various safety features to consider when conducting an electrolysis, such as electrical insulation (to prevent dangerous electric discharge), temperature control, and formation of hazardous substances. Electrical discharge can be avoided by ensuring the electrical cables are fully insulated, are securely fitted to the reactor and the reactor is setup in accordance with the user guide. Raising the reactor off the base of the fume cupboard is also a good idea in case of a solvent leak that might pool around the reactor and increase risk of discharge. The powerpack should not be applying current except when electrolysis is being carried out, and the switch should be in the open position (i.e. disconnected) when connecting to the reactor.

During electrolysis heating can occur which could lead to uncontrolled reaction, especially if the products are unknown. The passing of current through the reactor leads to faradaic heat loss, which is more pronounced at current densities exceeding 50mA cm^{-1}. As such cooling measures might be necessary. Specialist equipment is available for this role, such as the Polar Bear Cub™ device used in this work, or a cooling jacket can be applied to the reactor. There must however be no risk that the cooling device can leak as this will increase risk of electrical discharge.

As with any reaction, the products and their state of matter must be considered prior to carrying out electrosynthesis; in particular the formation of solids under flow conditions and the counter-electrode reaction products. Under flow conditions, precipitation of substances can lead to reactor fouling and blocking of the tubing, both highly inconvenient and impractical. Hence, for example, a sacrificial anode cannot be used in conjunction with an organic solvent as the metal salts will be insoluble. Similarly, the oxidation of a protic solvent to CO_2 or O_2 (in the case of water oxidation) requires a gas outlet to allow the release of these products. Many electrolysis reactors are not tested or designed for use under pressure and so this should be avoided at all costs. Gases can also form by reduction of a protic solvent, for example the counter-electrode reaction for the electrolysis conducted in chapter 2 of this work releases H_2 gas, and in fact the reaction can arise

opportunistically if water is present in the reaction solution. H_2 is an extremely flammable gas, which can ignite spontaneously in certain concentrations. As such, any electrolysis where this is a known or suspected reaction product should be conducted in a fume cupboard, and if necessary, the airflow should be increased in order to sufficiently dilute the outlet gases. A final consideration is the disassembly and cleaning of the reactor and tubing, which might contain reagents and products. This process should be carried out with PPE in a fume cupboard.

Before carrying out an electrosynthesis, it is well-worth exploring the literature for a similar process that is achieved using a chemical redox reagent. Such processes are common, and include using reagents such as DDQ, CAN, TEMPO, various transition metal complexes, bleach, hypervalent iodine reagents for oxidations, and SmI_2, alkylated tin, boron, germanium and gallium hydrides for reductions. The choice of chemical redox agent can give an indication of the ease by which the reaction is carried out, depending on the redox potential for the reagent. In some circumstances, where a stoichiometric quantity of the redox reagent is used, it can be beneficial to use the same reagent in electrochemistry but in catalytic quantities, i.e. mediating the electrolysis. Using the chemical redox process as a template can bypass the need for extensive optimisation of the reaction as a number of parameters can be effectively transferred, such as reagent concentration, temperature, solvent choice and reagent stoichiometry.

Chapter 2 Anodic deprotection of nitrogen containing compounds

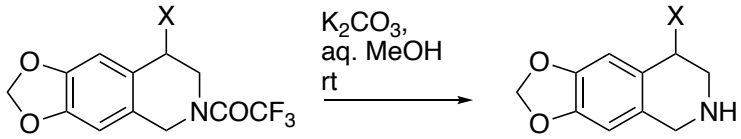
2.1 Introduction:

2.1.1 Protecting groups

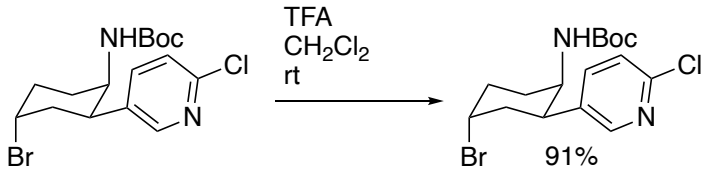
Protecting groups (PG) are widely employed in organic synthesis and are integral to preserving functionality within a complex molecule, to enable a selective transformation.[167] Whilst the use of protecting groups is undesirable in synthesis, it is of importance to make the process of protection and deprotection of these groups as and environmentally green as possible.

There are a wide variety of protecting groups and are typically classified by the conditions required to cleave them. These extend to:

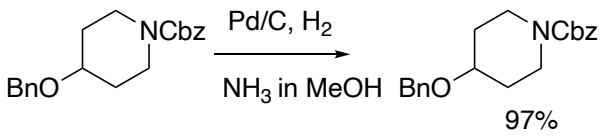
- Basic solvolysis:[168]



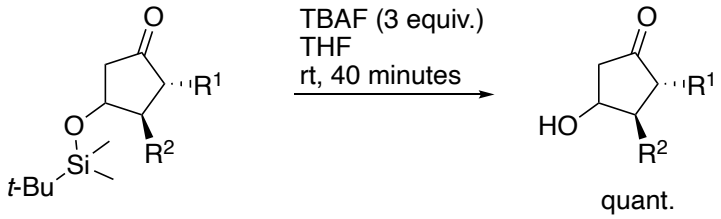
- Acid:[169]



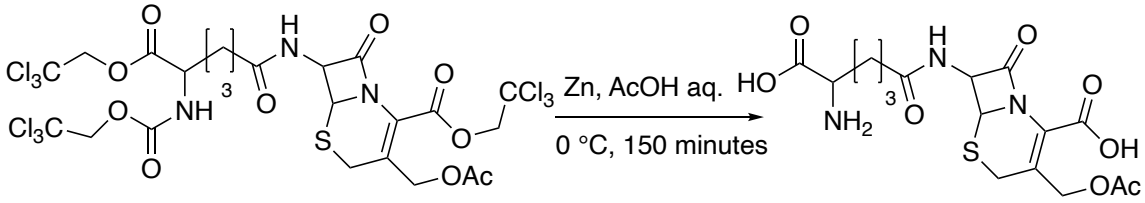
- Heavy metal:[170]



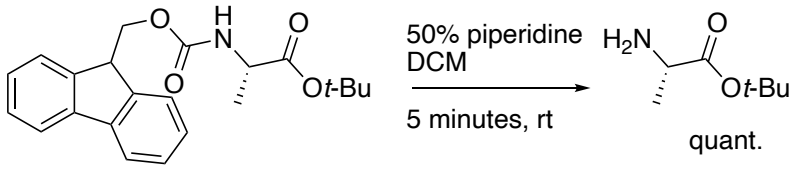
- Fluoride (anion)[171]



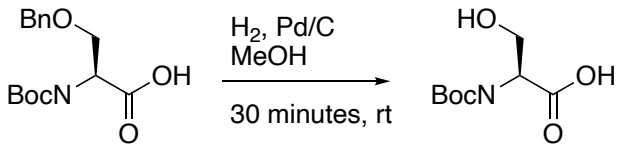
- Reductive elimination[172]



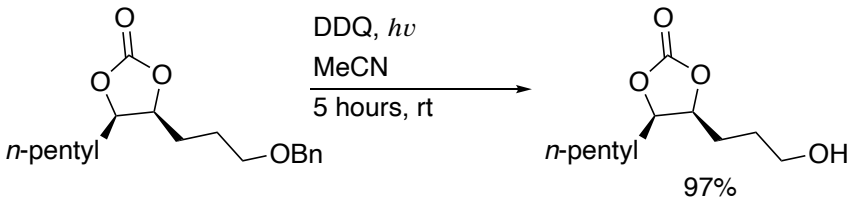
- β–Elimination[173]



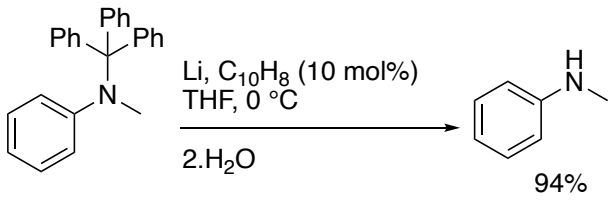
- Hydrogenolysis[170]



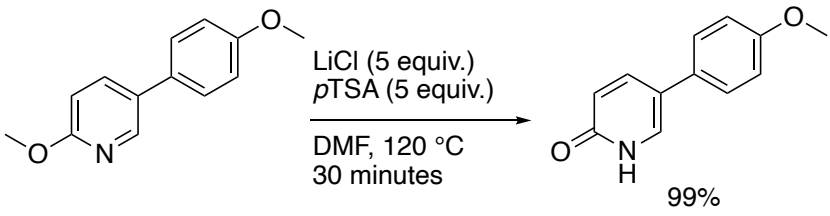
- Oxidation[174]



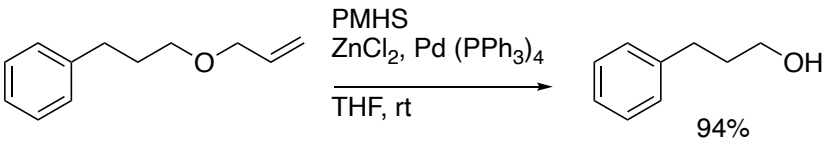
- Dissolving metal reduction[175]



- Nucleophilic substitution[176]

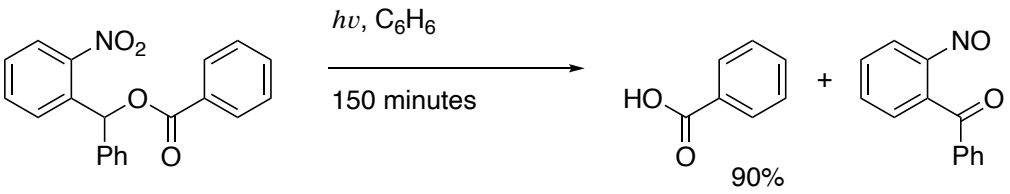


- Transition metal catalysis[177]

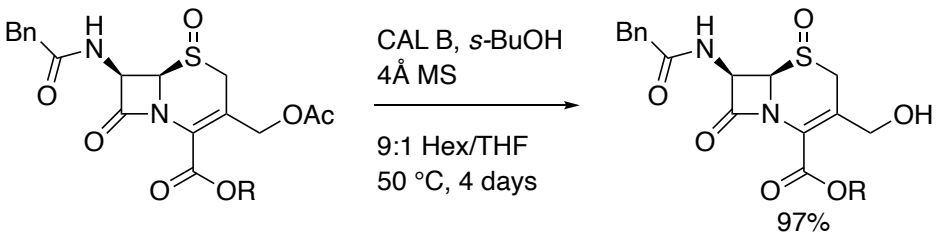


PMHS = Polymethylhydrosiloxane

- Light (UV/Vis typically)[178]



- Enzymes[179]



The different conditions for deprotection give rise to the term called orthogonal sets; a synthetic strategy where protecting groups are introduced in such a way that a group can be selectively removed in one step. This can be useful when a reactive functional group requires unmasking after other groups within the molecule. As part of this strategy, a protecting group must be stable to the conditions required to remove other types of protecting groups. Other key characteristics of a protecting group include:[167]

- Facile and efficient introduction
- Cheap and readily available
- Easy to characterise and avoid such complications as the creation of new stereogenic centres

- Stable to chromatography
- High atom economy
- Stable to a wide range of reaction conditions
- Selective and efficient removal under specific conditions
- Facile separation of by-product from substrate after deprotection

With respect to nitrogen containing compounds, common protecting groups include Boc[169], Fmoc,[173] Cbz,[170] Ts,[180] Ph_3C,[175] phthalimide,[181] benzyl (and derivatives)[182] and amides.[183, 168]

The benzyl (Bn) PG is versatile and widely utilised, however the range of specific deprotection conditions for it are limited and selectivity (within the field of electrosynthesis) can be poor. Alternative PG's of this type are the Cbz (carboxybenzyl) and the NAP (2-naphthylmethyl) groups, which offer selectivity over the benzyl PG[170] and can be deprotected under several conditions, including oxidation in the latter case by DDQ.[184] The PG's of interest in this project are those that can be deprotected electrochemically, and these are covered in more detail below.

2.1.2 4-methoxybenzyl (PMB) and 2,4-dimethoxybenzyl (DMB) protecting groups

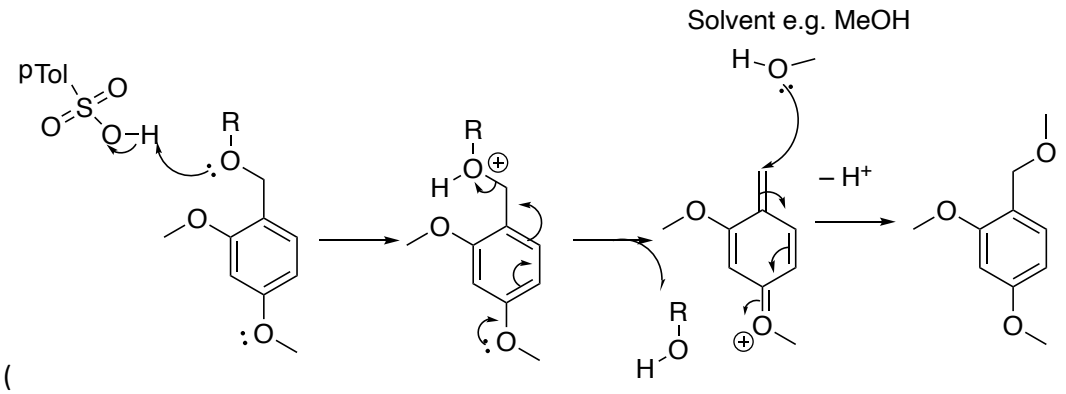
2.1.2.1 Background

PMB and DMB are widely employed protecting groups for a range of functional groups e.g. alcohols[185], thiols[186], amines[187], amides[188], carboxylic acids[189] and sulfonamides[190]. They are largely analogous to the Bn, Cbz and NAP protecting groups (and indeed for the most part the protection procedures are the same), with a key difference that the deprotection of PMB and DMB groups can be achieved through a wider range of conditions.

2.1.2.2 Electronic effects

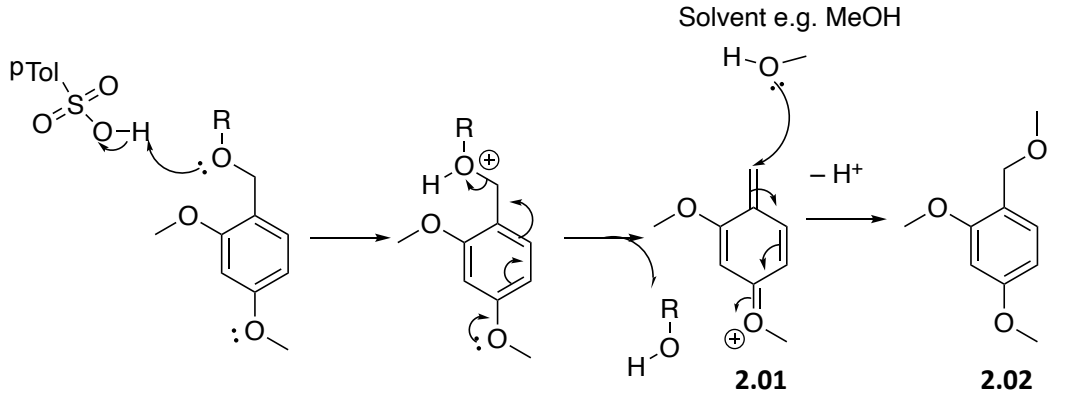
The strong electron donating ability (positive mesomeric effect) of the methoxy substituent/s make the PMB and DMB ring structures electron rich. This makes for more facile

deprotection; in the case of DMB strong acid at RT will often be sufficient



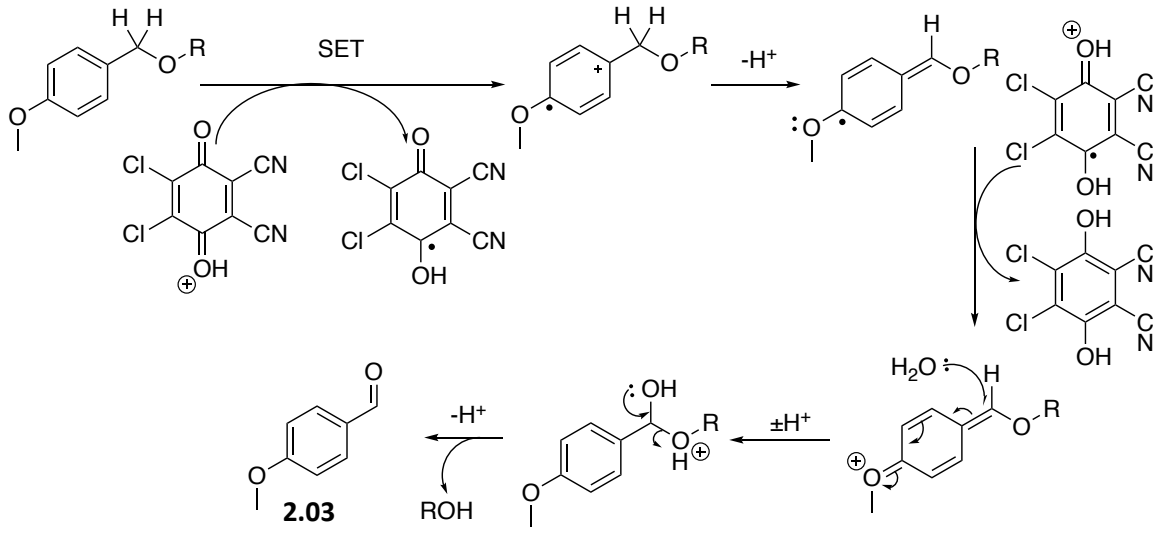
(

Scheme 2.1). Furthermore, these groups are both labile to oxidative and reducing (H_2) conditions.[167]



Scheme 2.1: Mechanism for acid deprotection of DMB ethers

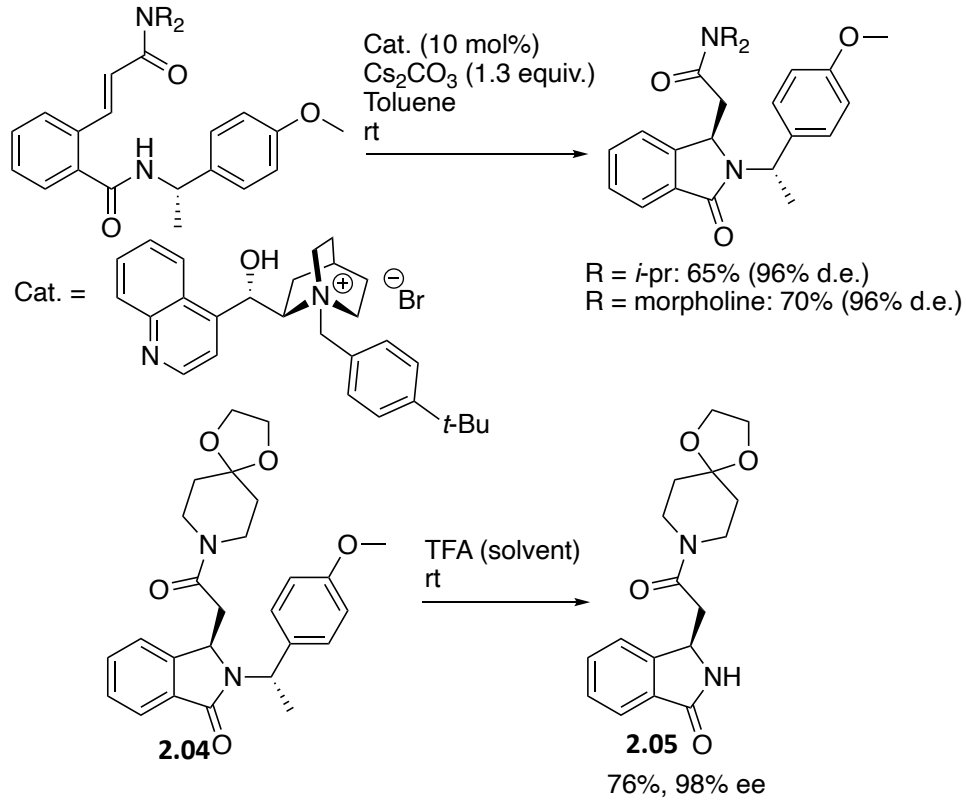
These mild deprotection conditions are available to the DMB group as the cation intermediate formed (**2.01**) is stabilised by two methoxy substituents. Contrary to this, the benzyl group may be cleaved by heating in acid (rarely used, as this offers very poor selectivity to many functional groups, protected or not), or catalytic hydrogenation, which has safety and sustainability issues and has poor tolerance to certain functional groups[191]. The PMB and DMB groups can also be cleaved by chemical oxidants e.g. ceric ammonium nitrate (CAN) or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). A proposed mechanism for oxidative cleavage of a PMB ether by DDQ follows a single electron transfer process (Scheme 2.2).



Scheme 2.2: Proposed SET mechanism for deprotection of PMB ethers by DDQ

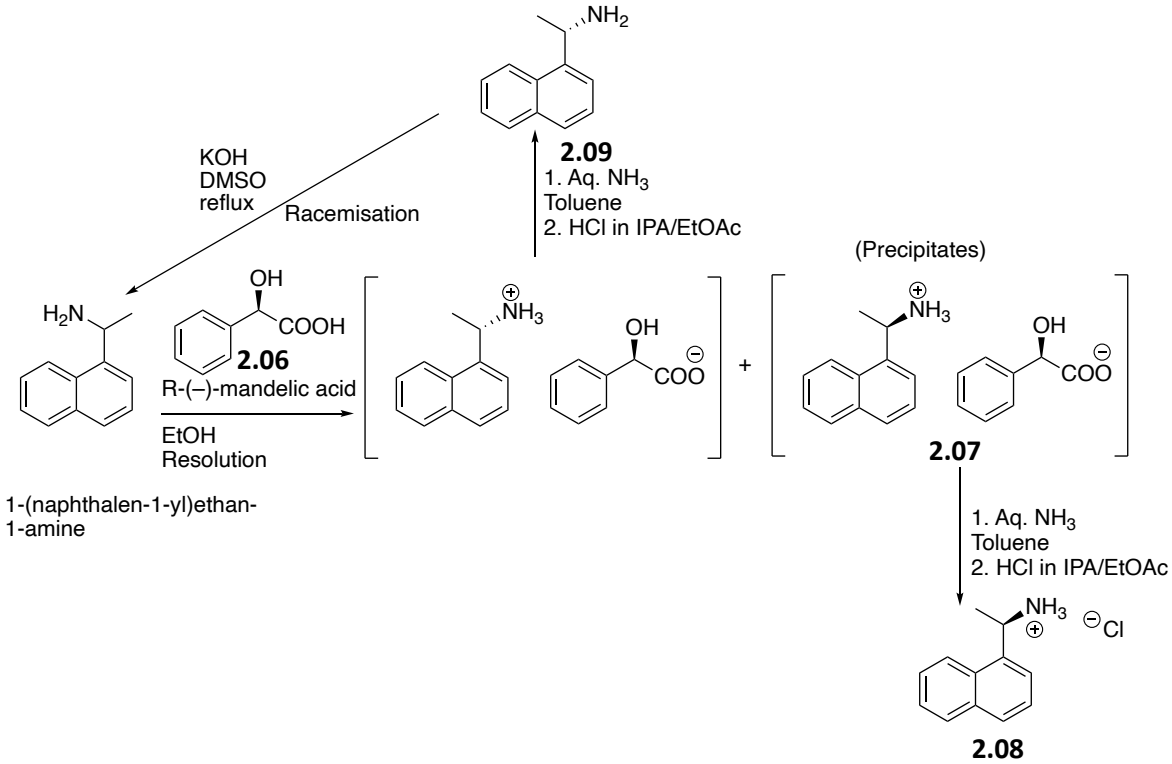
2.1.2.3 Chiral PMB protecting group

The standard PMB protecting group is common for synthesis where stereochemical control is not required. However, the presence of a methyl substituent at the benzylic position, (abbreviated as *m*-PMB), possessing a chiral centre, offers the potential to induce stereoselectivity in the molecule upon further modification. One such example of this has been conducted by Sallio *et al.*,[192] who devised the synthesis of optically active isoindolinones by a diastereoselective intramolecular Michael addition using a selected catalytic cinchoninium salt, combined with the effects of the *m*-PMB auxiliary. Removal of the chiral auxiliary furnished the enantiopure isoindolinone (Scheme 2.3).



Scheme 2.3: Diastereoselective reaction utilising the m-PMB chiral auxiliary group followed by deprotection

The methylated PMB group can be deprotected in the same ways as the PMB; Sallio utilised acidic conditions using TFA as a solvent for this process. The chiral amine (*R*)-1-(4-methoxyphenyl)ethan-1-amine or (*S*)-1-(4-methoxyphenyl)ethan-1-amine can be synthesised through various methods, through the use of ω-transaminase enzymes in reductive amination,[193] resolution of the racemic amine using a chiral resolving agent such as *R* or *S* forms of mandelic acid[194] (e.g. Scheme 2.4), or hydrogen-transfer reductive amination utilising transition metal catalysis with chiral ligands.[195]

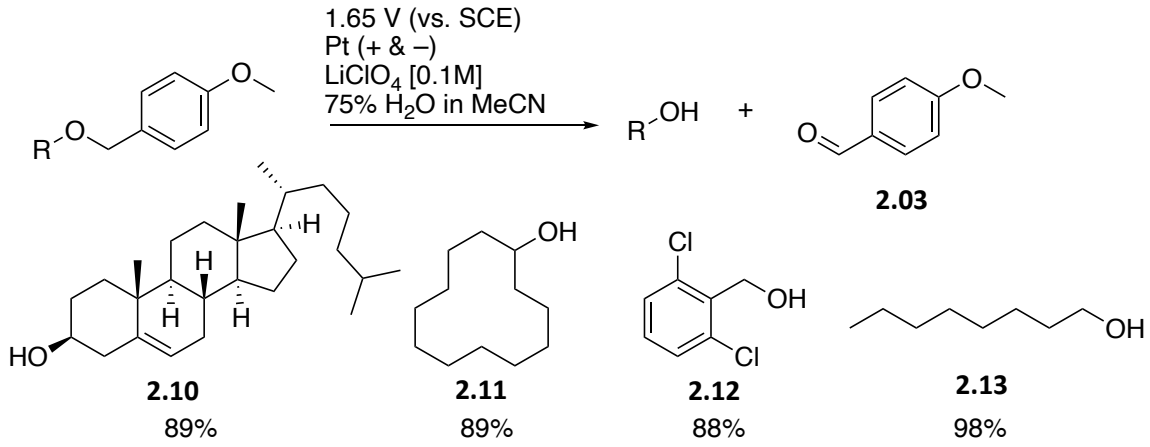


Scheme 2.4: Chiral resolution of 1-(4-methoxyphenyl) ethan-1-amine by Mathad *et al.*

Mathad discovered that heating the racemic amine with *R*-(–)-mandelic acid (**2.06**) to 60 °C followed by cooling to 25 °C caused precipitation of the mandelate salt of the *R* form (**2.07**). [194]Recrystallisation of this compound gave an e.e. of 99.8%, without loss of enantiomeric purity when transformed to the HCl salt. The mother liquor containing mostly the *S* enantiomer could be racemised and the process repeated to give the desired *R* enantiomer (**2.08**) in high yield. The same process can be carried out using the *S* enantiomer of mandelic acid to give the *S* enantiomer **2.09** selectively, as confirmed by Rajendra *et al.*[196]

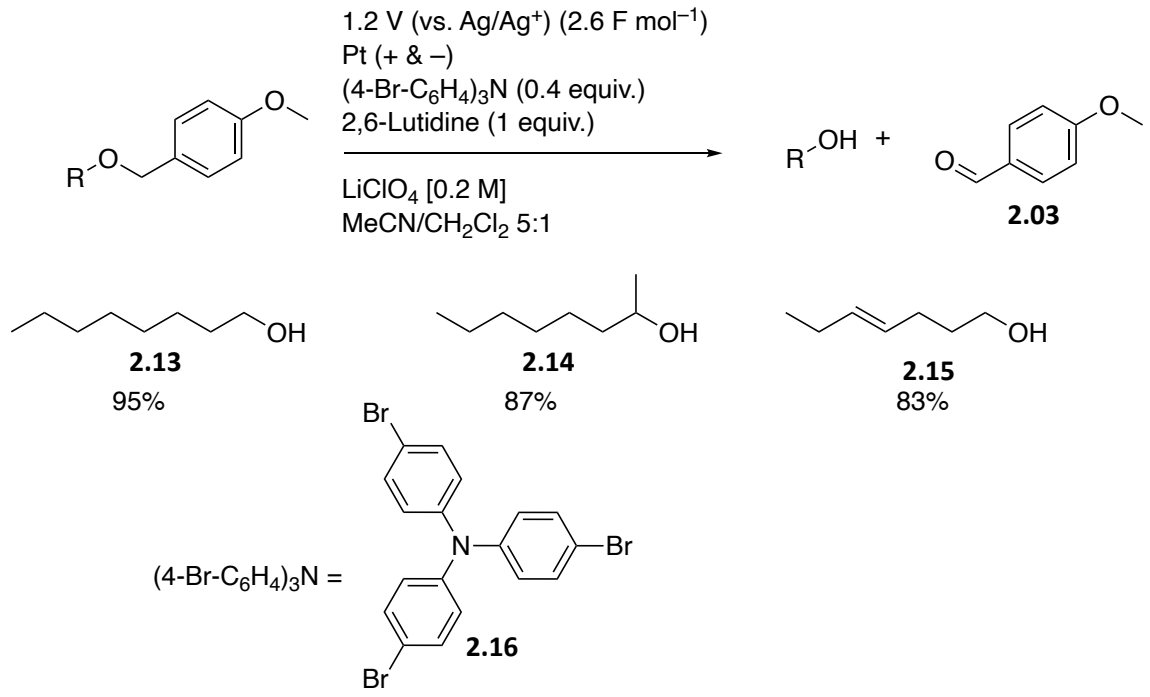
2.1.3 Electrochemical deprotection of PMB ethers

Removal of the 4-methoxybenzyl group in ethers by electrosynthesis was reported in 1974 by Weinreb *et al.* [197] using a divided batch cell with platinum electrodes and methyl cellulose membrane (Scheme 2.5):



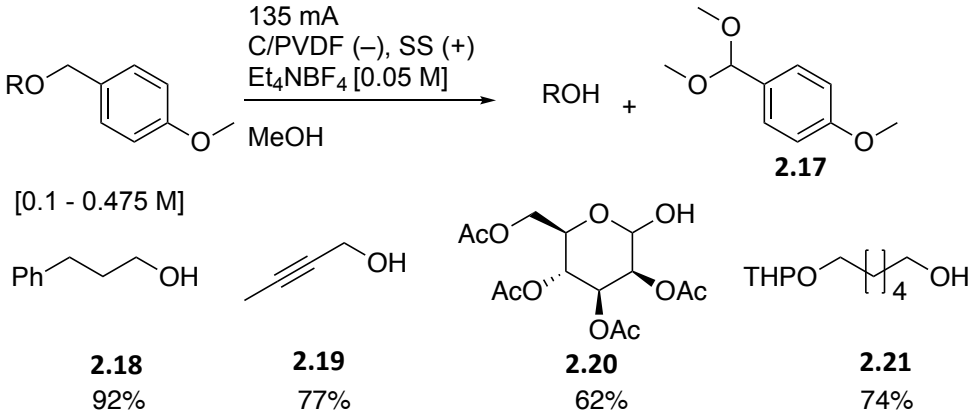
Scheme 2.5: Electrochemical deprotection of PMB ethers in a divided cell by Weinreb

Following this, in 1987 Steckhan reported the use of tris(*p*-bromophenyl)amine (**2.15**) as an electrochemical mediator to cleave PMB and benzyl protected alcohols, also in a divided batch cell[43] (Scheme 2.6):



Scheme 2.6: Mediated electrochemical PMB ether deprotection by Steckhan

In 2017 Brown *et al.* published an electrochemical deprotection of 4-methoxybenzyl ethers (PMB) to form the respective free alcohols (Scheme 2.7).[198] Seventeen PMB ether substrates were successfully deprotected with yields of up to 92%. Productivities of 7.6 g / hour were possible by increasing the substrate concentration to 0.475 M and a flow rate of 4 mL / min. The electrolyte used (Et_4NBF_4) could be recovered and reused. Some other common alcohol protecting groups tolerated these electrochemical conditions, with selective PMB group removal.



Scheme 2.7: Electrochemical deprotection of PMB ethers in an undivided flow reactor by Brown *et al.*

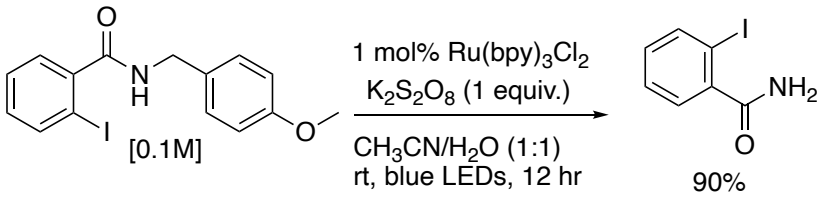
The optimised current was found to be 135 mA for the illustrated substrate **2.17** (for the flow rate illustrated and concentration of [0.1 M]) following a design of experiment. The specification for the Ammonite 8 reactor in section 1.1.8.3.2 gave these results. A C/PVDF anode and SS cathode were used; platinum was inefficient as an anode material. The conditions reported in this work and flow setup were applied to the current project described in this thesis, except for initially reducing the current to the theoretical value as calculated previously.

2.1.4 Research proposal

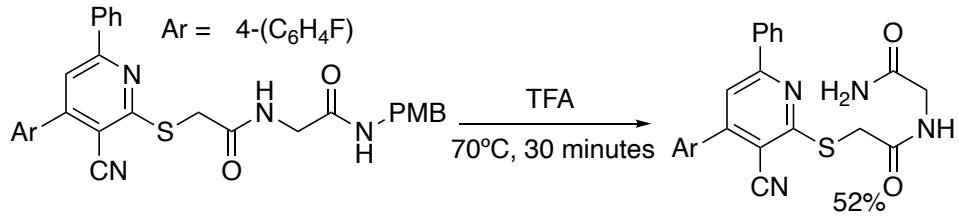
The concept of anodic deprotection of nitrogen containing compounds was proposed as a follow-up to the work published on anodic deprotection of PMB ethers by Brown *et al.*,[198] in order to increase the scope and therefore synthetic use of the deprotection strategy. The specialist equipment was on-hand to facilitate the optimisation and implementation of the methodology.

The removal of the PMB group from nitrogen containing compounds is widely reported in the literature through a range of conditions. These include:

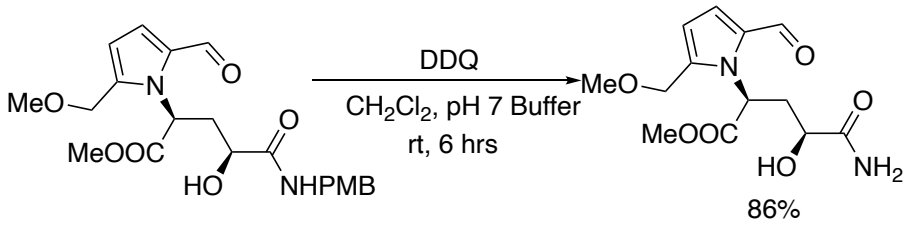
- Photo-redox[199]



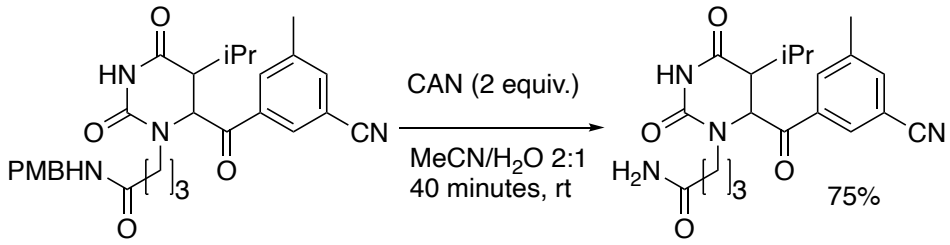
- Acid (TFA)[200]



- Oxidation
  - DDQ[201]



  - CAN[202]



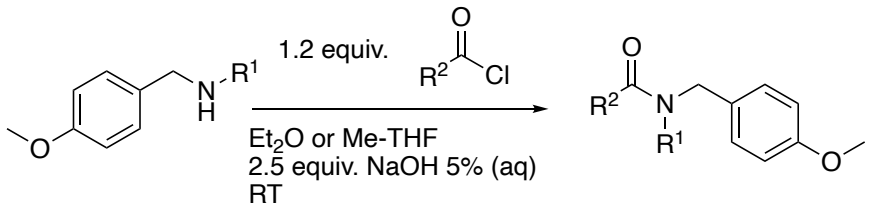
At the time of inception, there was no literature method for the electrochemical removal of the PMB group from nitrogen containing compounds. This was of surprise considering the wide usage of the protecting group; however it could be rationalised by the proposed difficulty in achieving reaction selectivity. Nitrogen in organic substrates features a lone pair that itself is prone to oxidation, which can lead to by-product formation. Contrast this to ethers; the lone pair that exists on oxygen is more tightly held by the nucleus and so is less readily oxidised, thereby the robustness of these compounds for electrochemical deprotection is more applicable. Nitrogen however features widely in natural products and pharmaceuticals, and an electrochemical method of unmasking it would prove desirable in many settings.

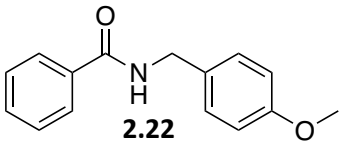
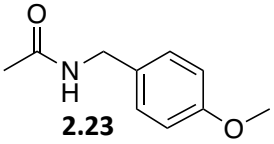
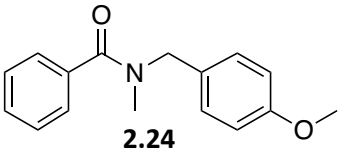
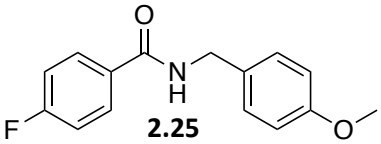
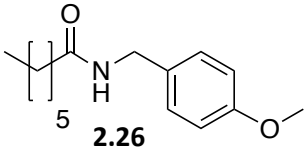
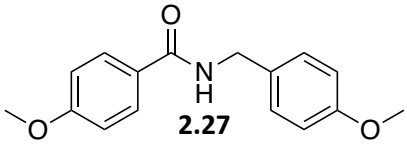
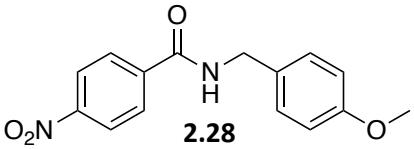
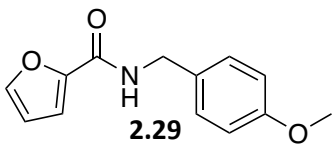
2.2 PMB functional group incorporation in simple substrates

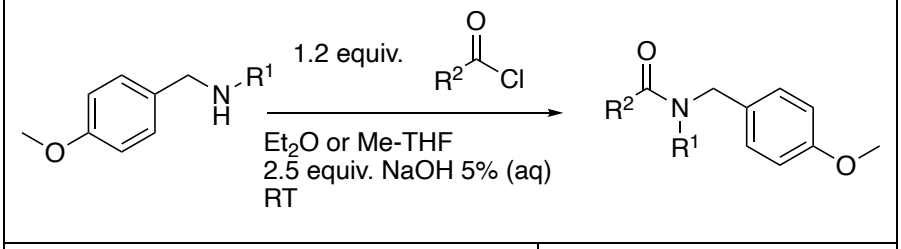
2.2.1 Amide coupling

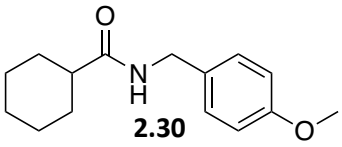
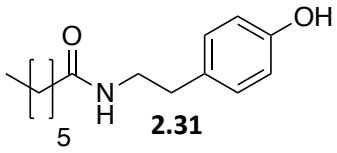
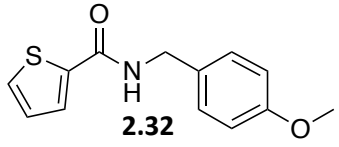
2.2.1.1 Schotten–Baumann conditions

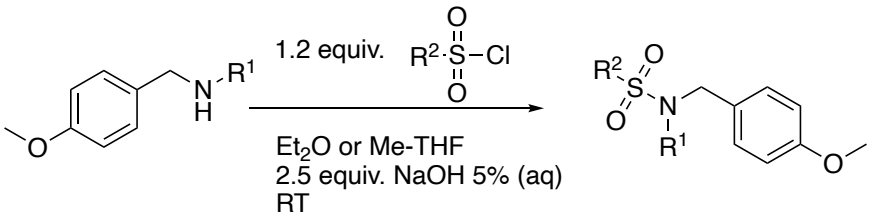
For the majority of substrates in this work, the PMB protecting group was introduced by coupling acid chlorides and amines under Schotten–Baumann biphasic conditions.[203, 204] The literature preparation followed was an industry-approved method[205], the conditions (with different substrates) of which are illustrated in Table 2.1.



Product	% Yield
 **2.22**	86
 **2.23**	74
 **2.24**	73
 **2.25**	75
 **2.26**	97
 **2.27**	99
 **2.28**	98
 **2.29**	75



Product	% Yield
 **2.30**	89
 **2.31**	93
 **2.32**	100



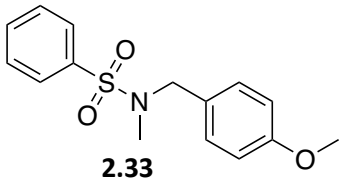
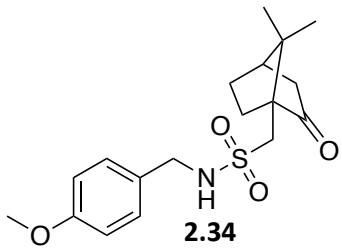
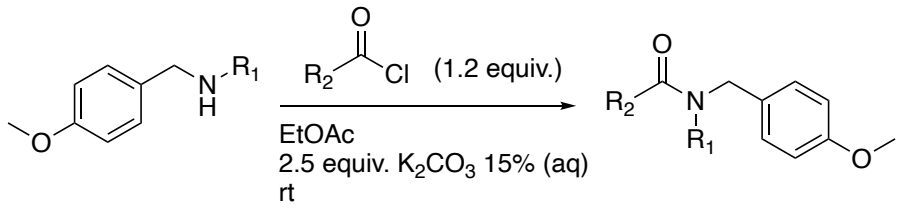
Product	% Yield
 **2.33**	73
 **2.34**	28

Table 2.1: Synthesis of PMB-protected amides and sulfonamides under Schotten–Baumann conditions

An assessment as to the environmental impact of this synthesis was later explored and it was deemed necessary to modify the preparation so as to utilise a less hazardous solvent than Et_2O. Fortunately, two other industry methods for preparation of amides under Schotten–Baumann conditions were reported, one utilising Me-THF as a solvent and NaOH as inorganic base[206], another with EtOAc as a solvent and K_2CO_3 as base.[207] The latter was utilised for the remaining substrates, owing to the better rating of the solvent and base according to green metrics. The conditions for the process are outlined in Table 2.2.



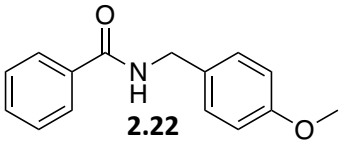
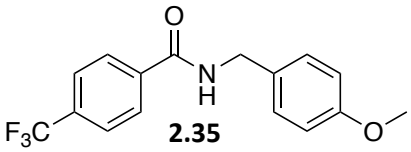
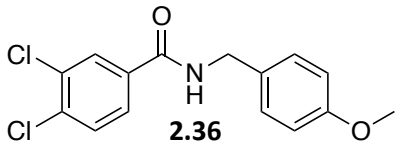
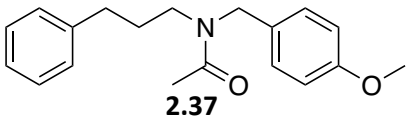
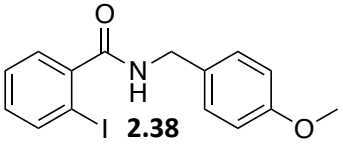
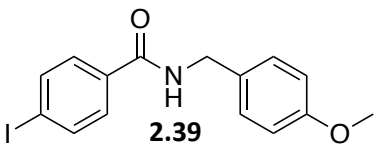
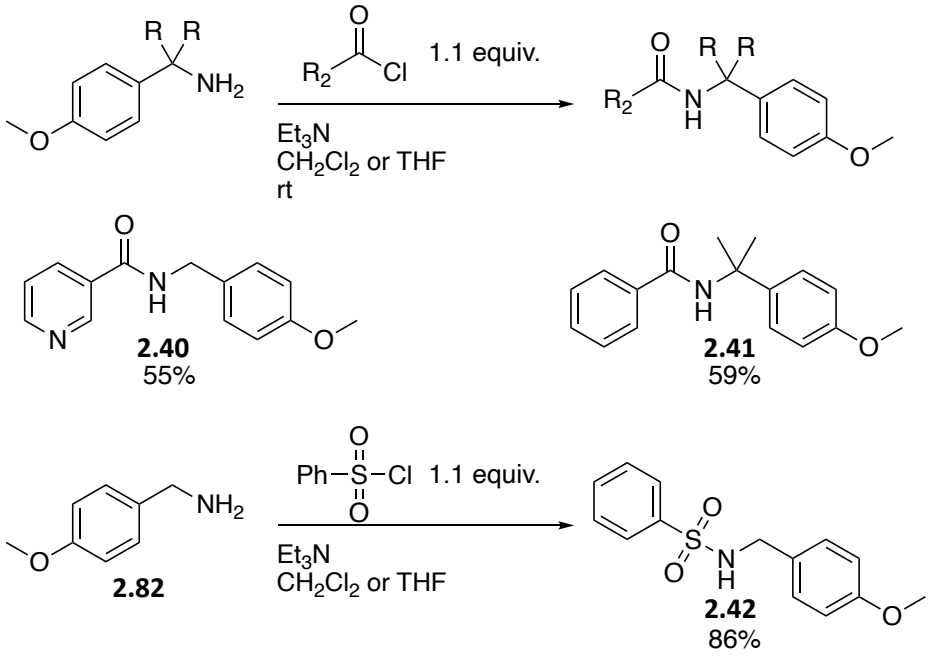
Product	% Yield
 **2.22**	96
 **2.35**	94
 **2.36**	91
 **2.37**	95
 **2.38**	100
 **2.39**	100

Table 2.2: Synthesis of PMB-protected amides under improved Schotten–Baumann conditions

2.2.1.2 Monophasic amide couplings

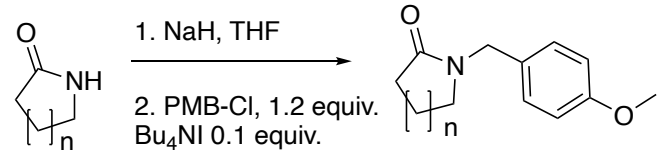
Owing to functional group sensitivity in some substrates, and also in order to follow literature procedures where the same substrate had been synthesised (thereby minimising the chance that the Schotten–Baumann conditions illustrated in Table 2.1 would not work on specific new substrates), a handful of substrates were made by monophasic amide coupling. Conditions of this are illustrated in Scheme 2.8.

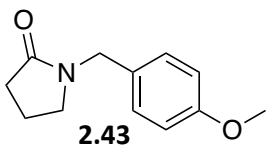


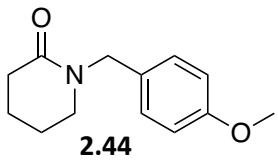
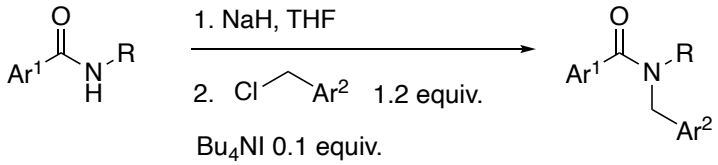
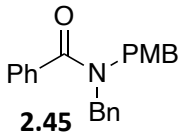
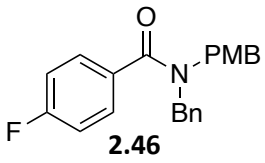
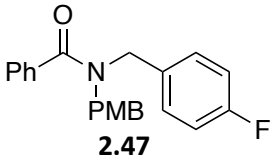
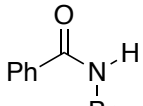
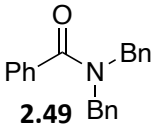
Scheme 2.8: Synthesis of protected amides and sulfonamides under monophasic conditions

2.2.2 PMB-protected lactam and tertiary amide synthesis

The PMB group was introduced into cyclic lactam and tertiary amide substrates through an alkylation reaction obtained from literature (Table 2.3).[208]



Product	% Yield
 **2.43**	69

 **2.44**	70
 1. NaH, THF; 2. Cl–Ar^2 1.2 equiv.; Bu_4NI 0.1 equiv.	
 **2.45**	72
 **2.46**	59
 **2.47**	79
 **2.48**	55[a]
 **2.49**	30[a]

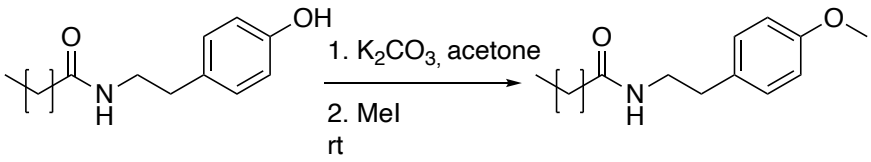
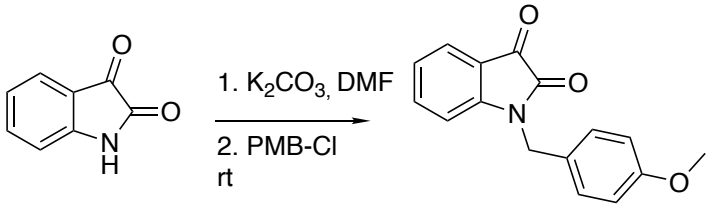
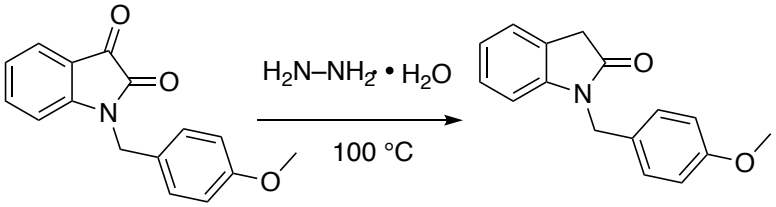
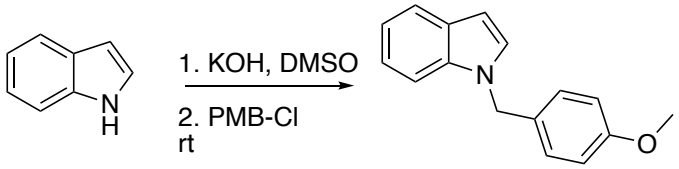
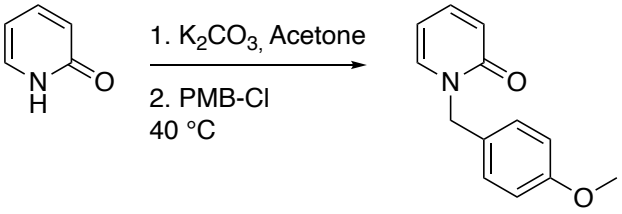
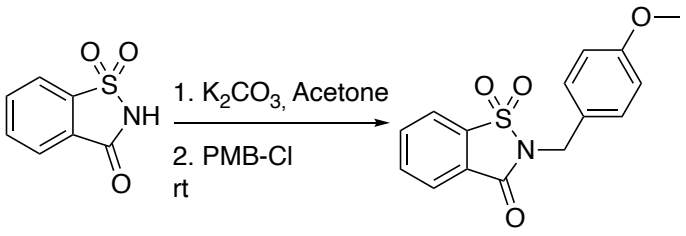
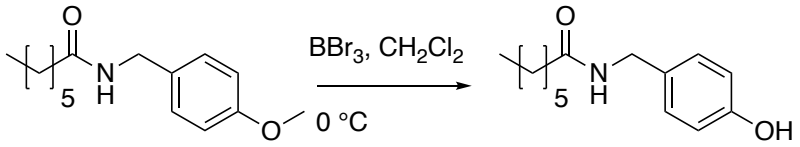
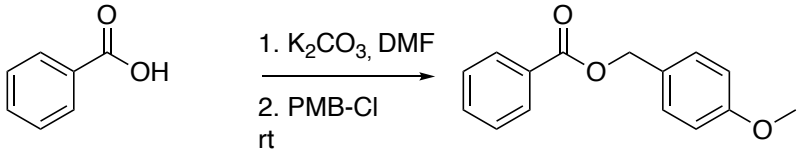
a. Products of the same reaction

Table 2.3: Synthesis of tertiary PMB-protected amides by alkylation

The yields for tertiary amide formation were moderate, with incomplete conversion seen in most cases. The starting material could be recovered following flash chromatography. The tertiary amides typically displayed low melting points compared to the secondary amides, and displayed a mixture of rotamers by NMR, which were resolved by VT NMR in some cases. Compounds **2.48** and **2.49** are products of the same reaction: it was expected that overalkylation of benzamide would occur however both the mono and di-substituted amide compounds were desired.

2.2.3 Miscellaneous protected substrates

Some substrates could not be prepared using the methods illustrated above, and so specific conditions were used for protection. These syntheses are illustrated in

Entry	Reaction	Product yield %
1		73
2		85
3		88
4		71
5		83
6		80
7		55
8		97

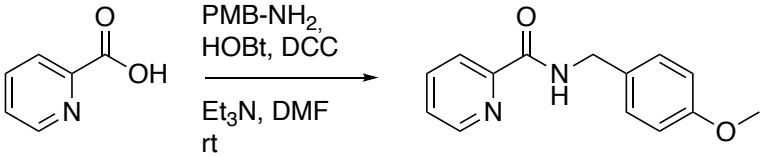
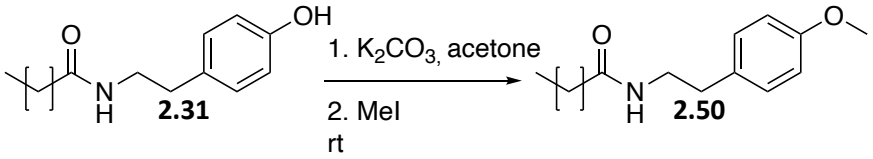
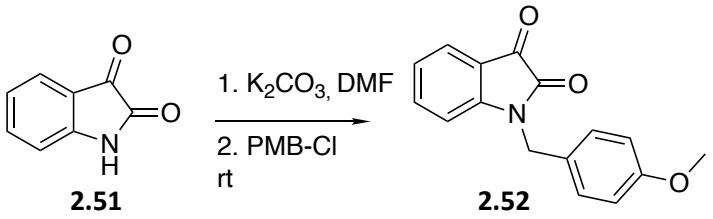
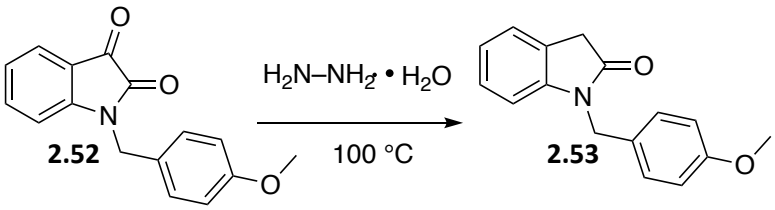
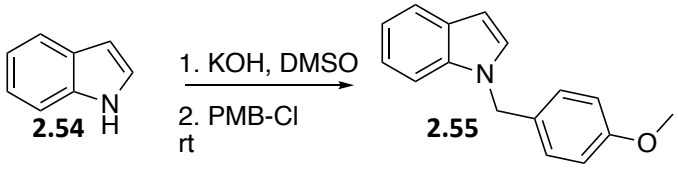
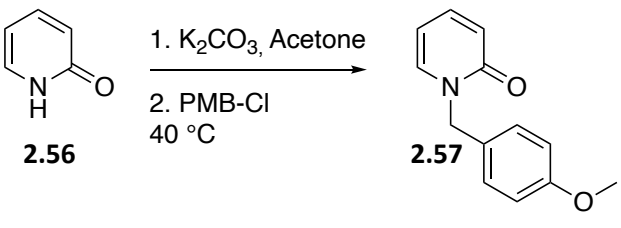
Entry	Reaction	Product yield %
9		95

Table 2.4.

Entry	Reaction	Product yield %
1		73
2		85
3		88
4		71
5		83

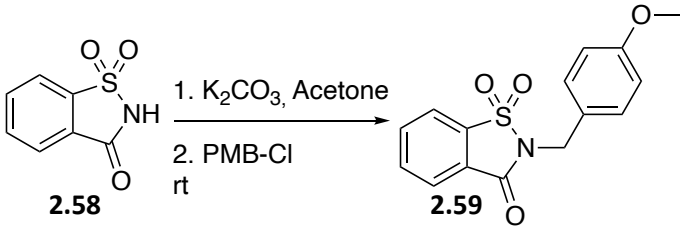
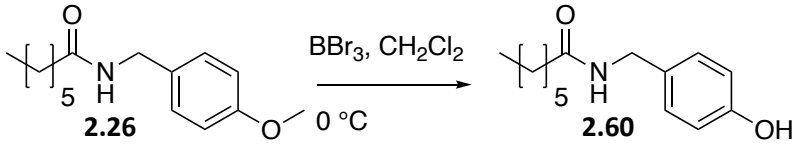
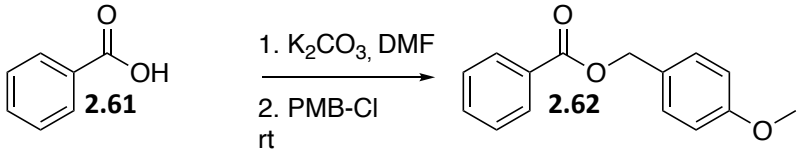
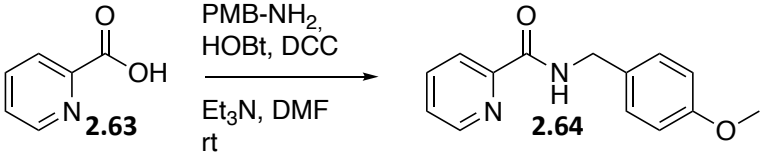
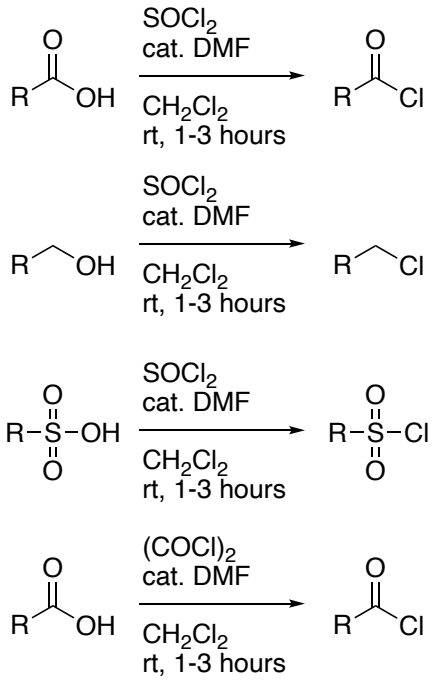
Entry	Reaction	Product yield %
6		80
7		55
8		97
9		95

Table 2.4: Synthesis of miscellaneous protected compounds

2.2.4 Acid and alkyl chlorides

Acid and alkyl chlorides are highly reactive and often have a limited shelf life before decomposition. As such, the majority of sulfonyl, acid and alkyl chlorides were synthesised from their sulfonic acids, carboxylic acids or alcohols. Conditions for the synthesis of these are illustrated in Scheme 2.9.



Scheme 2.9: Preparation of sulfonyl, acid and alkyl chlorides by thionyl or oxalyl chloride

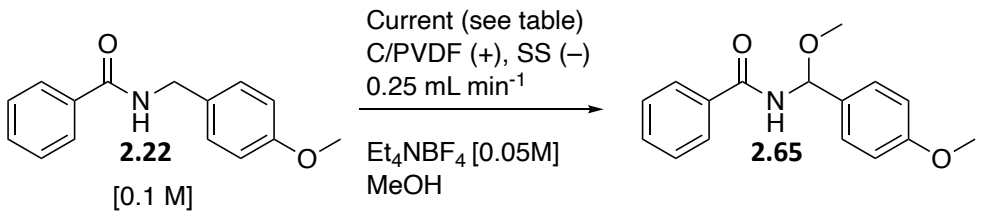
Substrates prepared using these methods are reported in the experimental section. The chlorination procedure was shown to be effective as subsequent amide and sulfonamide coupling reactions from the respective acid and sulfonyl chlorides proceeded in high yield.

2.3 Optimisation of electrochemical PMB deprotection in *N*-(4-Methoxybenzyl)benzamide

Following on from the group's work on the electrochemical deprotection of PMB ethers, [198] the ammonite 8 was reactor was utilised for the proposed deprotection of PMB amides and other nitrogen containing compounds, starting with the same conditions utilised for the deprotection of the PMB group in ethers,[198] with the exception of reverting to stoichiometric current (as an excess was required previously in the PMB ether deprotection). The electrolysis was conducted under constant current and was calculated using the equations given in section 1.2.2. *N*-(4-Methoxybenzyl)benzamide was the first substrate selected for optimisation, having characteristics such as simple functionality, a good chromophore (for HPLC and detection by UV after TLC), non-volatile but sufficiently low boiling point that GC could be used to probe the deprotection step, with a cheap and commercial starting material.

2.3.1 Optimisation of applied current

Initial studies of the method included the trialling of applied current, in order to establish the minimum that would enable complete conversion, and/or lead to the highest product yield. Optimisation for the applied current is summarised in Table 2.5.



Entry	Current/ mA	Current/ F mol^{-1}	Yield[a] /%	Current efficiency/%
1	80	2.0	75	82
2	90	2.3	85	76
3	100	2.5	81	65
4	**95**	**2.2**	**87**	**73**

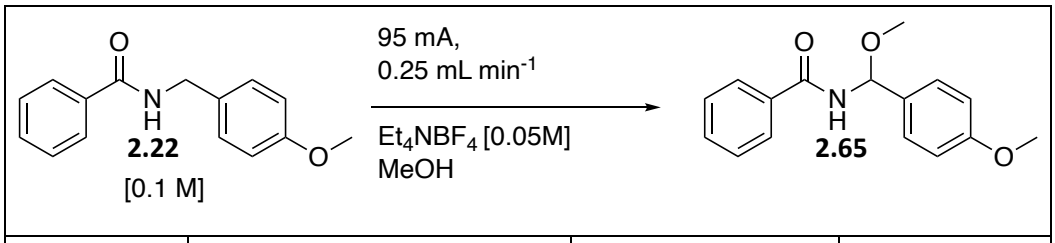
a. Yield by calibrated GC

Table 2.5: Optimisation of applied current for the methoxylation of *N*-(4-Methoxybenzyl)benzamide

The deprotection of benzamide did not lead directly to cleavage of the PMB protecting group. Oxidation at the benzyl position occurred as expected, followed by methoxide insertion to yield the hemiaminal ether **2.65**. Using the theoretical current for full conversion (80 mA, entry 1), hemiaminal ether **2.65** was isolated in 75% yield, with starting material (15%) remaining. When an increased current of 100 mA was applied (entry 3) some by-products were seen, seemingly due to the degradation of the methoxylated product **2.65** seeing as the % consumption did not appear to change (monitored by GC). Through careful modulation of the current (using a more sensitive power pack that would accurately deliver current to the nearest 1 mA), the optimum current applied was found to be 95 mA (entry 4), giving 94% conversion and good selectivity. Recovery of starting material from this reaction suggests that the reaction either has a sub-optimal mass transfer coefficient or competing side reactions are taking place.

2.3.2 Trialling different anode materials

Next different anode materials were explored to identify the most efficacious material to carry out the electrolysis. The results of these experiments are illustrated in Table 2.6.



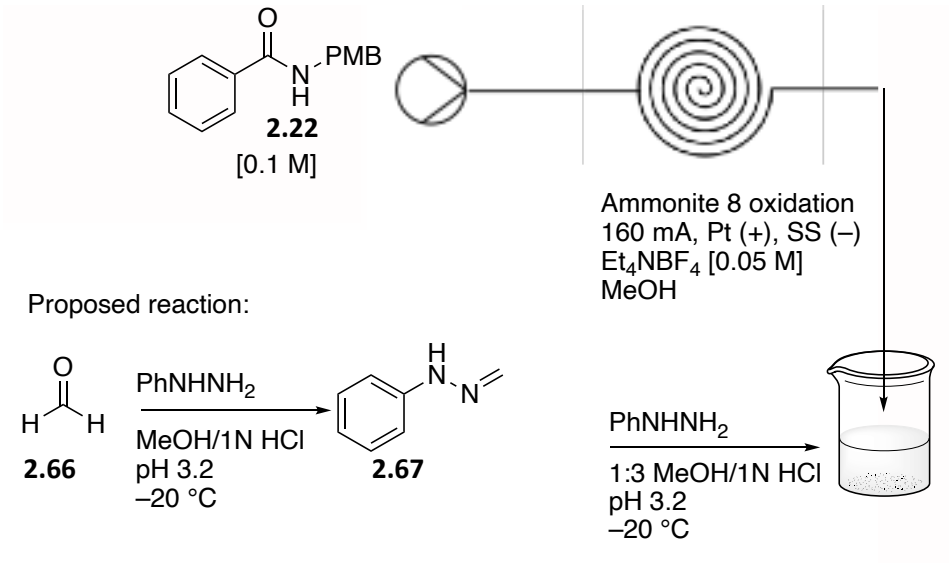
Entry	Anode	Cell Voltage /V	Yield[a]/%
1	**C/PVDF**	**3.2**	**87**
2	C/PVDF	3.2	87[b]
3	Graphite Y459 (fine grain)	3.1	78
4	Graphite Y597 (fine grain)	3.1	77
5	Graphite MCCA (medium grain)	3.1	77
6	Glassy carbon	3.3	72
7	Platinum	3.6	0[c]

a. Yield by quant. NMR, dimethyl terephthalate (DMT) as internal standard.
b. Reaction run in the absence of air: argon purged
c. SM recovered quantitatively

Table 2.6: Screening different anode materials for electrochemical PMB deprotection

Anode material C/PVDF was found to produce the highest yield for the oxidation, giving an 87% yield of methoxylated product **2.65** when the optimised current of 95 mA was applied (entry 1). Similar but slightly inferior yields (77-78%) was observed for the other carbon-based electrodes (entries 3-5). A marginally lower steady state voltage was also observed with the graphite anodes, proposed to be due to be a disintegration of the anode surface, evidenced by small black flecks in the effluent reaction solution. Glassy carbon (entry 6) was inferior still, with a 72% yield observed. The lower yield for other carbon-based electrodes might be the result of a lower overpotential for oxidation of the substrate. Platinum proved inefficient for the oxidation of the PMB protected substrate (entry 7), with starting material recovered quantitatively. This could be due to the high overpotential for oxidation of alcohols on platinum electrodes, and with a methanol solvent this could be the preferred reaction under the conditions implemented. The optimised electrochemical reaction was conducted in the absence of oxygen (entry 2), by passing argon through the reactor, then argon-purged solvent (MeOH), and finally argon-purged reaction solution. The yield of **2.65** was the same with or without oxygen in the reactor, which shows that oxygen does not negatively impact the reaction.

It is proposed that the solvent was being oxidised on the platinum anode, since current passed through the solution without substrate conversion. Alcohol oxidation is known to have a low overpotential on platinum and so it is of little surprise that MeOH is oxidised under these conditions. To confirm this, the reaction solution was passed into an aqueous solution of Phenylhydrazine at –20 °C in an attempt to trap formaldehyde that would otherwise escape as a gas.

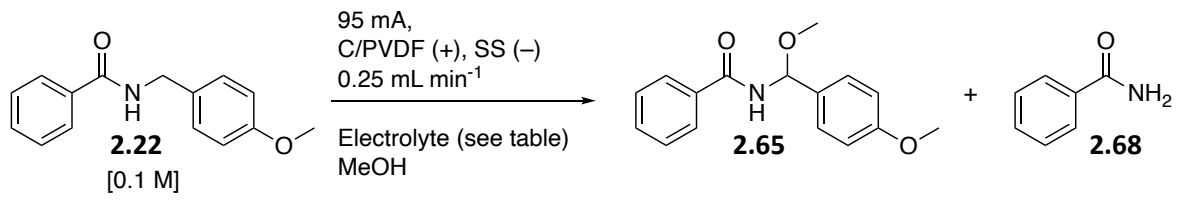


Scheme 2.10: Unsuccessful trapping of formaldehyde from Ammonite 8 reaction solution (allegedly formed by oxidation of MeOH on Pt anode)

The attempt to isolate the formylated hydrazine **2.67**, the procedure of which has been reported by Akhmetova *et al.*[209] was unsuccessful, and so it was presumed that the oxidised product of the reaction was formic acid, or CO_2 instead of formaldehyde. The PMB substrate **2.22** was recovered quantitatively.

2.3.3 Electrolyte screen

A study of different electrolytes was conducted to identify which is the most effective with respect to product yield and recovery of electrolyte from the crude (Table 2.3). Other considerations include safety and cost.



Entry	Electrolyte (equiv.)	Electrolyte	Yield[a]/%

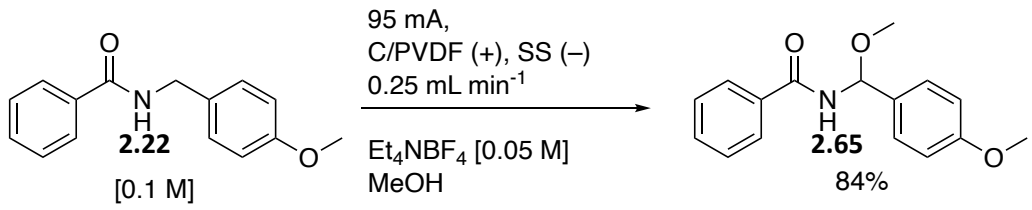
		recovery/ %	2.65	2.68	SM
1	**Et_4NBF_4 (0.5)**	**95**	**85**	**2**	**13**
2	Bu_4NHSO_4 (1)	85	60	20	19
3	Bu_4NHSO_4 (2)	85	51	32	17
4	Bu_4NClO_4 (0.5)	0	84	2	10
5	$NaClO_4$ (0.5)	92	73	6	10
6	NH_4Br (0.5)	95[b]	2	4	92

a. Yield estimated using calibrated GC
b. Composition of electrolyte likely to be altered in the reaction

Table 2.7: Electrolyte screening for PMB oxidation/deprotection of PMB protected benzamide 2.22

Et_4NBF_4 and Bu_4NClO_4 (entries 1, & 4 respectively) gave the best yields (85% and 84% respectively) of methoxylated product **2.65**. $NaClO_4$ (entry 5) gave a slightly lower yield of the oxidised products **2.65** and **2.68**. NH_4Br showed very poor conversion and 92% recovery of starting material **2.22** was observed. This could be due to oxidation of the bromide ion, presumably to bromine. The hydrogen sulfate electrolytes (entries 2 and 3) gave good overall conversion to oxidised products, but with the formation of a mixture of methoxylated and deprotected products and so not seen as efficient. Recovery of electrolyte was efficient in all cases except Bu_4NClO_4 where the electrolyte failed to precipitate from the crude solution in EtOAc. This is an obvious drawback to this electrolyte as it is fairly costly, unless recovery of the electrolyte can be carried out in a different solvent (which would require additional development). Of additional concern is the potential explosive nature of perchlorate salts[210] (despite being widely used in electrosynthesis[211]), so perchlorates were not explored further here. The cost of the process is in part dependant on the electrolyte recovery, since it was reused as part of this work. Based on this, any of the electrolytes with the exception of Bu_4NClO_4 would be cost-efficient. Although Et_4NBF_4 is relatively expensive, it can be recovered from the reaction mixture and combines good reaction yield and safety. With hindsight, NaOMe would have been a good electrolyte to trial, although this is strongly basic and might disrupt the electrochemistry.

Following optimisation of applied current, electrode material and electrolyte, the electrochemical reaction was be considered optimised. The conditions for electrochemical oxidation were then applied to PMB protected amide **2.22** (Scheme 2.11).

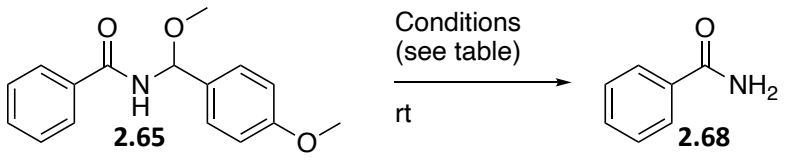


Scheme 2.11: Optimised electrochemical oxidation of PMB-protected amides

From 1 mmol of PMB protected amide **2.22,** hemiaminal ether **2.65** was isolated in 84% yield with a current efficiency of 71% and a productivity of 1.26 mol hr^{-1}.

2.3.4 Optimisation of acid-induced hydrolysis of electrochemical product

Following oxidation of the PMB group to the hemiaminal ether, it was anticipated that the PMB group could be easily cleaved in mild acid conditions, and a selection of various acids and solvent combinations were tested (Table 2.4).



Entry	Acid	Solvent	Time/mins	Yield[a]/%
1	HCl aq.	EtOAc	60	68
2	HCl aq.	MeOH	60	82
3	MsOH	Toluene, 5 equiv. H_2O	30	98
4	TFA	DCM, 5 equiv. H_2O	5	Quant.
5	TFA	EtOAc, 5 equiv. H_2O	180	Quant.
6	TFA	Me–THF, 5 equiv. H_2O	5	Quant.
7	**HCl aq.**	**Acetone**	**30**	**Quant.**

a. Yield by calibrated GC

Table 2.8: Optimisation of conditions for the acid hydrolysis of the PMB-oxidation product

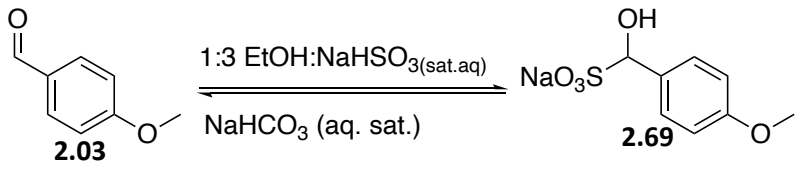
Treatment of the purified hemiaminal ether **2.65** in EtOAc with 2N aqueous HCl gave incomplete (68%) conversion to benzamide in 60 min at RT. It was proposed that the poor yield was the result of inefficient mixing of the organic and the aqueous solutions. Subsequent optimisation found that homogeneous solutions of organic acids such as TFA were efficient at cleaving the PMB group (as expected; TFA in DCM are common conditions for deprotecting the PMB group).[200] However, the use of these acids is undesirable, as the PMB group can itself be

cleaved under acidic conditions without oxidation, albeit using more forcing conditions (higher temperature and larger excess of acid). Ultimately, hydrolysis under mild conditions was achieved using 2N aqueous HCl with acetone as co-solvent. This proved efficient, and was employed as a convenient, safe and low-cost method to carry out the acid step in future substrates.

2.3.5 Purification of deprotected amide/sulfonamide substrates, recovery and purification of electrolyte

The electrolyte was recovered by removal of the reaction solvent (MeOH), followed by the addition of EtOAc to precipitate the electrolyte, which could be recovered by filtration. A recovery of 95–100% by crude mass of Et_4NBF_4 was typical. When sufficient electrolyte had been collected from reactions, it was purified using a literature method[212] by recrystallisation from MeOH/Et_2O. This was then filtered and dried under vacuum at 80 °C. The purified recovered Et_4NBF_4 was of high purity and suitable for use in subsequent electrolyses.[213] Characterisation of the electrolyte was achieved through CHN elemental analysis, cyclic voltammetry, melting point and ^{19}F NMR.

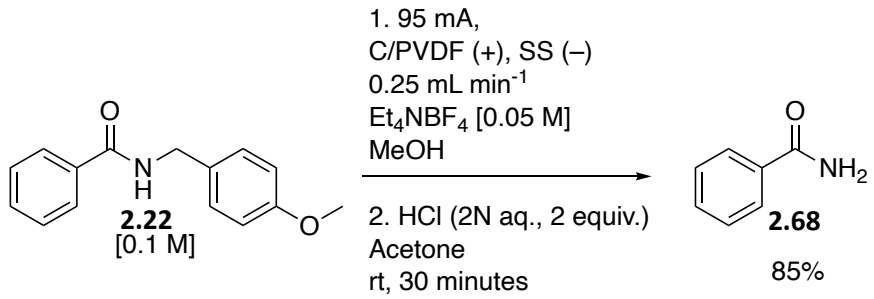
In line with the key characteristic of protecting groups, detailed in section 2.1.1, it is important that the cleavage co-product of the reaction can be easily separated from the target product. Happily this is the case with the PMB group, as 4-methoxybenzaldehyde can be removed in a workup procedure[214], utilising sodium bisulfite as a nucleophile to form a water soluble adduct (Scheme 2.12).



2.03 **2.69**

Scheme 2.12: Removal of 4-methoxybenzaldehyde by formation of a bisulfite adduct

The bisulfite adduct can be removed in the aqueous phase of a workup. The process was utilised following the acid treatment of hemiaminal ether **2.65**. The resulting crude material was almost exclusively deprotected amide **2.68**, which could be purified by recrystallisation from EtOAc. The deprotection of **2.22**, performed as a two-step process, gave benzamide **2.68** in 85% yield with a current efficiency of 71% and a productivity of 154 mg hr^{-1} (not accounting for the acid hydrolysis step).

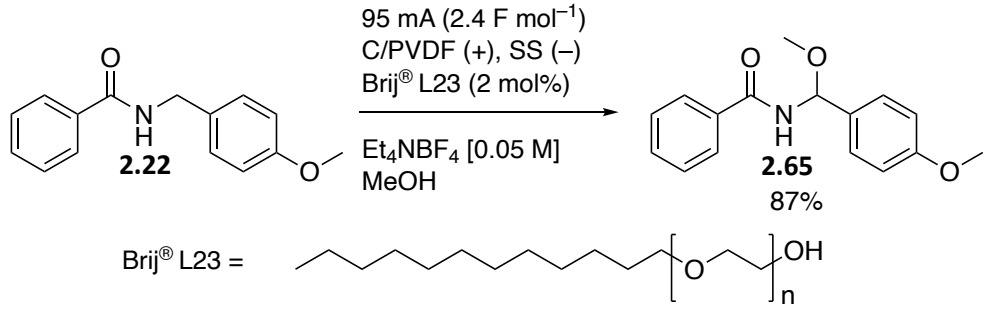


Scheme 2.13: Electrochemical deprotection of PMB-protected amides

2.3.6 Miscellaneous experiments

2.3.6.1 Effect of surfactant on the electrochemical reaction

Since the electrolysis of **2.22** did not reach full conversion, even with a modest excess of current applied (2.4 F mol^{-1}, 1.2 equiv.) , the influence of a surfactant was tested. We had previously found that addition of surfactant could improve mass transfer in some electrolyses, which can improve conversion.[215] Surfactants act by lowering the surface tension of the solution, thereby inhibiting the accumulation of solution and gas bubbles (which occurs during slug flow, illustrated in Figure 2.4). The dispersion of small bubbles in the solution promotes turbulent flow, thereby improving mass transfer in the reactor. The same reaction conditions as those optimised were used, except for the addition of Brij® L23, a non-ionic surfactant (Scheme 2.14). The choice of surfactant was carefully considered; anionic surfactants such as CTAB (cetrimonium bromide) are susceptible to oxidation (specifically, the bromide counter-ion), and similarly Triton X-100 (a non-ionic surfactant) can be oxidised owing to the presence of electron-rich aromatic functionality in its structure. Clearly, reaction of the surfactant itself leads to side-products and will reduce the current available to the substrate.

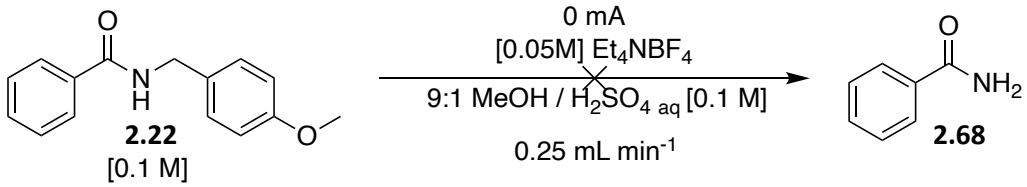


Scheme 2.14: Use of surfactant (Brij® L23) in electrochemical PMB deprotection

The electrolysis in the presence of 2 mol % of the surfactant afforded the methoxylated product **2.65** in 87% isolated yield, with 6% starting material remaining, which is comparable to the reaction without surfactant. Increasing the path length or trialling alternative solvents (where the surfactant could have a greater impact), might lead to improved product yield.

2.3.6.2 Acid treatment of 2.22 in the absence of electricity

To confirm that the deprotection of the PMB group requires the application of electricity, and cannot proceed under mild acidic conditions alone, the reaction was conducted in the presence of acid but with no current passing through the reactor (Scheme 2.15).

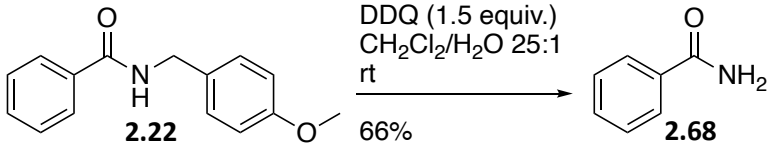


Scheme 2.15: Acid treatment of *N*-(4-Methoxybenzyl)benzamide

As expected, no reaction occurred and quantitative recovery of PMB benzamide was obtained. This confirms that the deprotection of the PMB functional group, from this substrate at least, requires an oxidative step followed by mild acid treatment.

2.3.6.3 Chemical PMB deprotection of 2.22 by DDQ

To compare the efficacy of the electrochemical process compared to a more traditional deprotection using a chemical oxidant, the model substrate **2.22** was subjected to DDQ in CH_2Cl_2/H_2O (Scheme 2.16). The chemical oxidant gave the deprotected benzamide in an unoptimised 66% yield, which is lower than the yield obtained for the electrolysis approach.

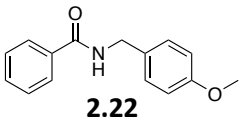
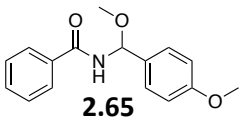
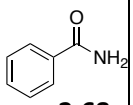


Scheme 2.16: PMB deprotection of *N*-(4–Methoxybenzyl)benzamide using DDQ

2.3.6.4 Investigating the effect of solvent mixing in the reactor

The electrochemical reaction is typically run using a peristaltic pump, in which there is nothing to separate the plug of reaction solution from the solvent passed through the reactor at the beginning and end of the reaction volume. As such, it is possible for mixing to occur at both ends of the electrolysis cell, which may change the substrate and electrolyte concentration at these points and expose them to an overcurrent (since the amount of current applied across the reactor is calculated based on a fixed concentration of substrate). In order to investigate this, a reaction was setup whereby 0.25 mL (approximate) aliquots of reaction solution were analysed using a calibrated HPLC. It should be noted that gas (H_2) formation in the reactor will accelerate the flow of the reaction solution as it passes through the reactor compared to the rate set on the

pump, and as such time is not a reliable method to determine the volume of effluent solution. Hence the aliquots were measured by volume instead, although an indeterminable degree of evaporation of the reaction solution is expected and so the quantitative data cannot be considered to be truly accurate. Key results are illustrated in Table 2.9.

Entry	Time in reactor/ minutes	Volume of reaction solution passed[a]/ mL	Yield[b] /%		
			 **2.22**	 **2.65**	 **2.68**
1	3	0.75	0.2	4.7	5.8
2	4	1.00	4.9	56.6	18.4
3	5	1.25	6.7	67.7	10.7
4	6	1.50	8.9	74.6	7.9
5	7	1.75	9.4	78.2	3.4
6	8	2.00	9.9	82.9	2.8
7	9	2.25	9.1	85.0	2.7
8	24	6.00	9.0	76.1	3.1
9	25	6.25	5.7	48.6	3.9
10	26	6.50	3.5	16.9	4.8
11	27	6.75	2.4	6.5	3.7
12	28	7.00	1.6	5.5	1.9
13	29	7.25	0.9	4.9	1.2
14	30	7.50	0.3	2.5	0.6

a. Volume from when the reaction solution enters the Ammonite 8 reactor.
b. Yield by calibrated HPLC

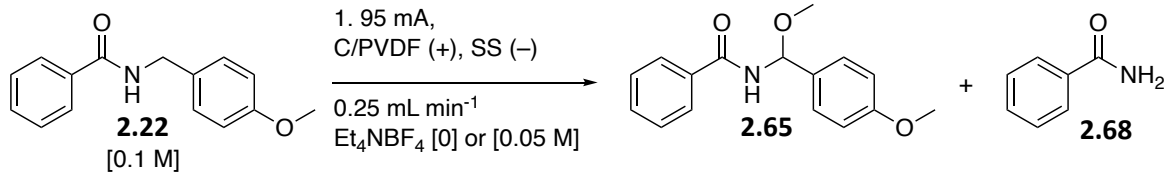
Table 2.9 Investigating the effect of reaction solution dilution on the electrochemical oxidation of *N*-(4-Methoxybenzyl) benzamide by taking aliquots of reaction solution

The time was recorded from when the reaction solution entered the reactor. The results showed that, for a 5 mL reaction solution, there was significant mixing of the reaction solution with solvent either side of the reaction plug, leading to a reduced concentration of all

components. Interestingly, the results show that a greater proportion of the deprotected benzamide **2.68** is produced in comparison to the methoxylated product at both ends of the run. HPLC analysis of the 0.25 mL aliquots indicated steady state was reached only after 2.25 mL of reaction solution (also indicated by a stabilisation in voltage), equating to roughly 9 minutes of passing solution through the reactor. Significant dilution occurred at the start and end of the run, and it took even longer than expected for the reagents and products to leave the reactor. The investigation showed that mixing of the reaction solution with the bulk solvent led to a decrease in conversion to either oxidation product **2.65** or **2.68**, possibly due to poorer conductivity. Increasing the volume of reaction solution would minimise the influence of mixing effects on total yield, conversion and selectivity, ensuring that a greater proportion of the electrolysis solution is subjected to steady state conditions. Alternatively, increasing the flow rate would also reduce mixing effects. In view of the results reported above, it is good practice to perform an extended run in the reactor once "optimised" conditions have been achieved.

2.3.7 Direct PMB deprotection

In the electrolyses of PMB benzamide **2.22** discussed so far, the methoxylated product is the major product, requiring an additional hydrolysis step to achieve deprotection. It was proposed that the deprotection process could be carried out in one step either by introducing water as a co-solvent to the reaction in the electrochemical flow reactor or acidifying the reaction solution.



Entry	Solvent	Acid (equiv.)	Electrolyte (Et_4NBF_4)	Yield[a] /%		Current efficiency /%
				2.65	**2.68**	
1	MeCN/H_2O 9:1	n/a	Y	0	66	56
2	MeOH	H_2SO_4 (0.5)	N	0	70	59
3	MeOH	H_2SO_4 (1.0)	N	1	84	71
4	MeOH/H_2O 9:1	Bu_4NHSO_4 (2.0)	N	56	32	n/a
5	MeOH/H_2O 9:1	AcOH (2.0)	Y	70	3[c]	n/a
6	MeOH	AcOH (2.0)	Y	84	3[c]	n/a

7	MeOH	2N aq. HCl (2.0)	N	n/a	87[b]	73
8	**MeOH**	**2N aq. HCl (1.0)**	**N**	**n/a**	**86[b]**	**72**

a. GC yield
b. Isolated yield

Table 2.10: Conditions trialled in direct PMB deprotection of 2.22

Poor solubility of substrate **2.22** in MeOH/H_2O co-solvent with a high percentage of water (which was necessary for deprotection instead of methoxide insertion) led to precipitation. Swapping to a MeCN/H_2O co-solvent led to poor selectivity with multiple trace by-products forming. Bu_4NHSO_4 as a combined electrolyte and acid source was found to be inefficient at deprotection, with significant formation of methoxylated product **2.65**. Addition of HCl to the reaction mixture, whilst efficient at direct deprotection, corrodes the SS cathode, and so this cannot be considered a reliable method for deprotection. Furthermore, the Cl^- anion is susceptible to oxidation as a competing reaction as suggested by the following half–equation potentials (as quoted vs. SHE):[216]

$$Cl^-_{(aq)} + 2OH^-_{(aq)} \xrightarrow[0.90\ V]{} ClO^-_{(aq)} + H_2O_{(l)} + 2e^-$$

$$ClO^-_{(aq)} + 2OH^-_{(aq)} \xrightarrow[0.59\ V]{} ClO_2^-{}_{(aq)} + H_2O_{(l)} + 2e^-$$

Scheme 2.17: Oxidation potentials of the chloride and hypochlorite anions

Electrolyses using oxidatively stable acids including H_2SO_4, TFA and acetic acid were also conducted.[48] Sulfuric acid and TFA, whilst effective in the reactor at directly converting the PMB protected compound **2.22** to the deprotected benzamide **2.68** (in 84% yield) also led to corrosion of the SS electrode during the electrolysis. In addition, acetic acid was found to be inefficient at inducing deprotection in the reactor. As a result of these tests, further investigation of direct deprotection was suspended.

2.4 Deprotection of *N*-PMB β-lactam substrates

2.4.1 Relevance to pharmaceutical industry

β-Lactams form a class of broad-spectrum antibiotics, developed following the initial discovery of Penicillin by Alexander Fleming in 1928.[217] They typically inhibit cell-wall biosynthesis, and recent generations of the drugs have shown to be effective against gram positive and gram negative bacteria. β-Lactams can be categorised by structure into fused and unfused variants (

Figure 2.1).

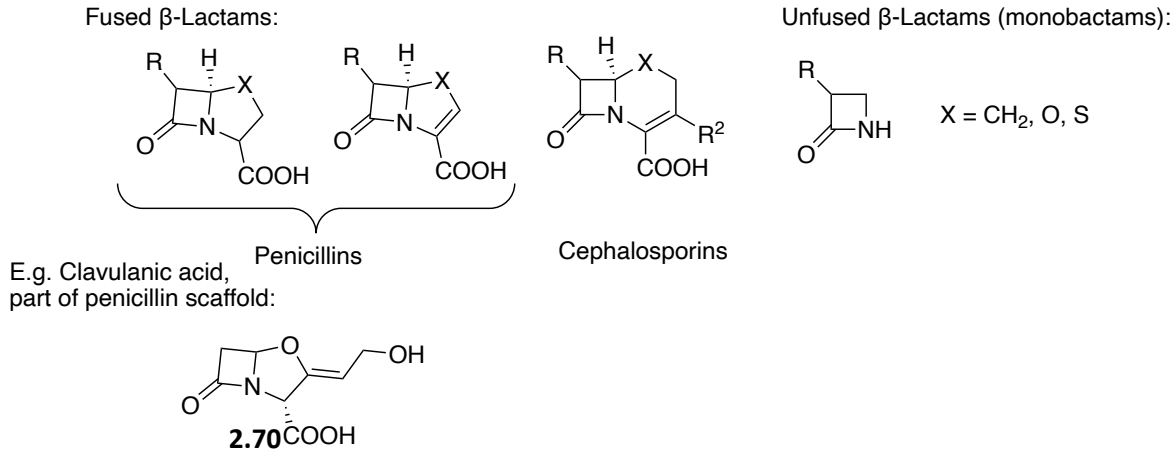


Figure 2.1: β-Lactam core structures

Resistance to β-lactams readily occurs in bacterial strains through attack on the strained lactam ring by β-lactamases. Therefore treatment of bacterial infections typically is a combination therapy with a β-lactamase inhibitor such as Clavulanic acid. Clavulanic acid acts as a competitive

antagonist of β-lactamase, which preferentially binds and prevents deactivation of the β-lactam antibiotic.[218]

Synthesised β-lactams in this work feature the monobactam motif: drug candidates of this type are effective on aerobic, gram negative bacteria, and the monobactam structure also features as a key intermediate in syntheses of many complex drug molecules.[218] The specific substrates investigated in this work are **2.71** and **2.72** (Figure 2.2).

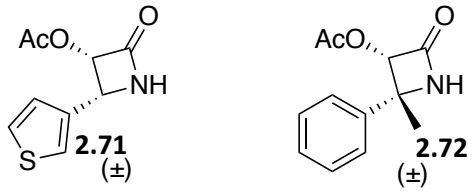
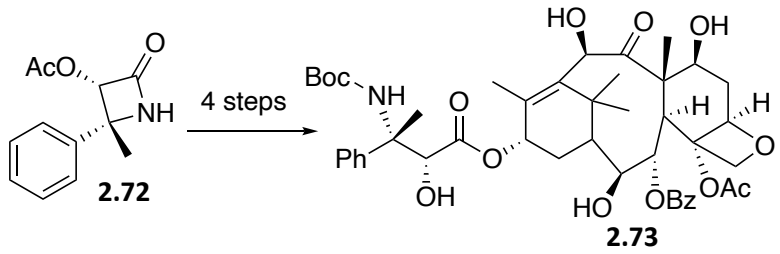


Figure 2.2: Structures of β-Lactams used in this work

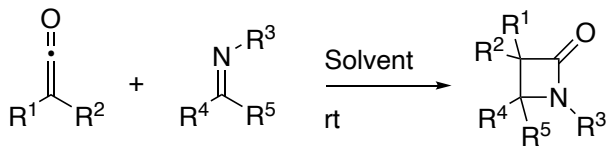
β-Lactams have shown to be important synthetic intermediates in many pharmaceutical agents, including synthetic taxanes, and in the case of **2.72**, the semi-synthetic pharmaceutical Taxotere (Scheme 2.19). Taxotere is a broad-spectrum cancer chemotherapeutic agent that stabilises microtubules, thus inhibiting mitosis:[219] **2.71** has also been found to display bioactivity in bacterial assays.[220, 221]



Scheme 2.18: β-Lactam intermediate used in the synthesis of Taxotere

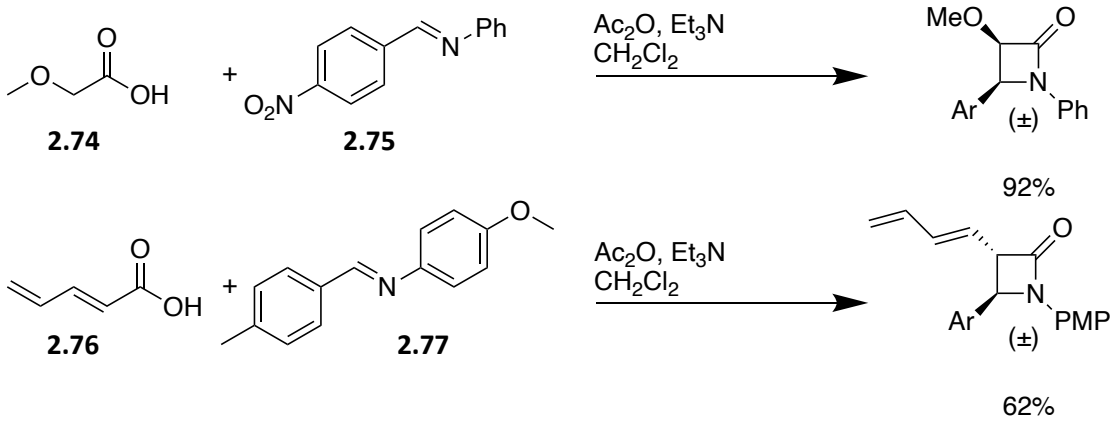
2.4.2 Synthesis of β-Lactam substrates

β-Lactams are most commonly made using the Staudinger synthesis, which is illustrated in Scheme 2.19.



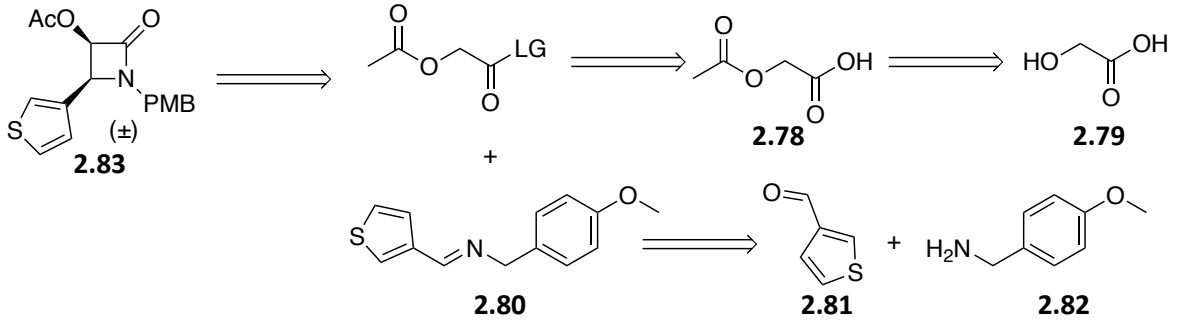
Scheme 2.19: Staudinger synthesis

The stereochemistry of the Staudinger synthesis can be controlled by several conditions, including electronic effects in the substrate. Literature examples of stereoselectivity are illustrated in Scheme 2.20:[222]



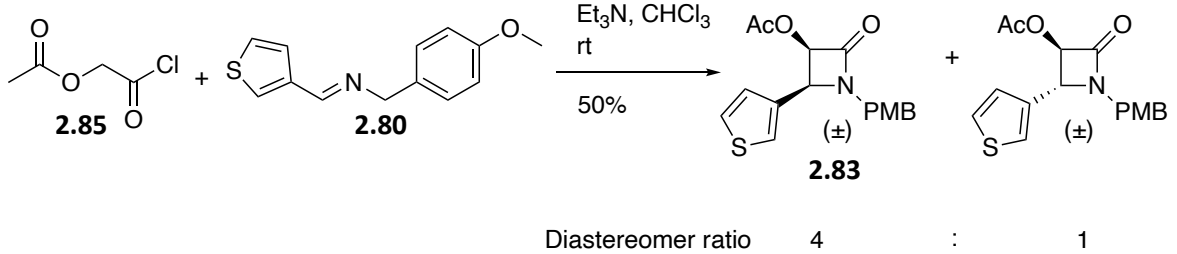
Scheme 2.20:Effect of substituents on *syn*/*anti* stereoselectivity in Staudinger synthesis

A retrosynthesis for β-Lactam substrate **2.71,** offering selectivity towards the *syn* isomer is outlined (Scheme 2.21).



Scheme 2.21: Retrosynthesis for the preparation of 2.83

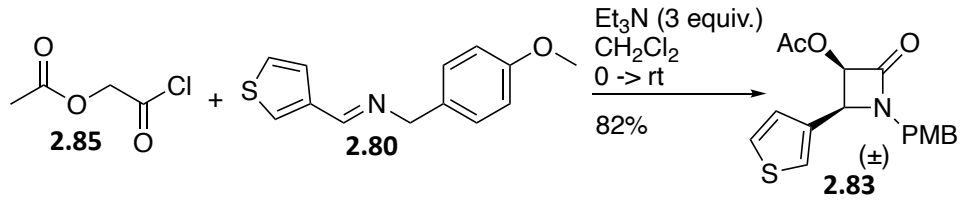
A literature reaction which offered stereoselectivity to the *syn* product was employed.[221] Conditions for this are illustrated in Scheme 2.22.



Scheme 2.22: β–lactam 2.83 preparation by Staudinger synthesis

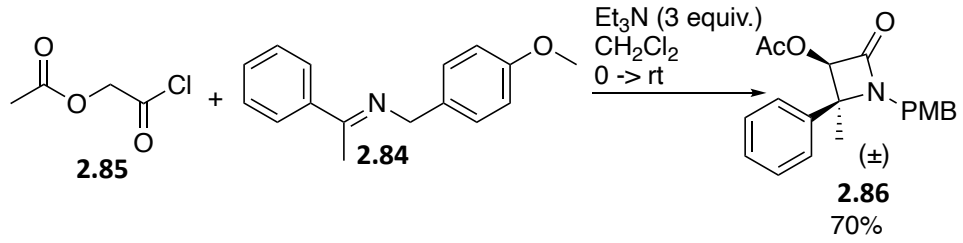
Whilst selectivity towards the *syn* product **2.83** was achieved, the yield was modest (50% w.r.t. the two diastereomers), and a mixture of diastereomers was still obtained. A search of the literature led to the findings that the best reaction yield would be achieved through the use of

CH_2Cl_2 as a solvent, and addition of the acid chloride to the pre-mixed solution of imine and base at 0 °C instead of rt.[223, 224] Under these conditions, the yield and selectivity dramatically increased, with complete selectivity to the *syn* product in 82% yield. The conditions are illustrated in Scheme 2.23.



Scheme 2.23: Optimised conditions for Staudinger synthesis of β–lactam 2.71

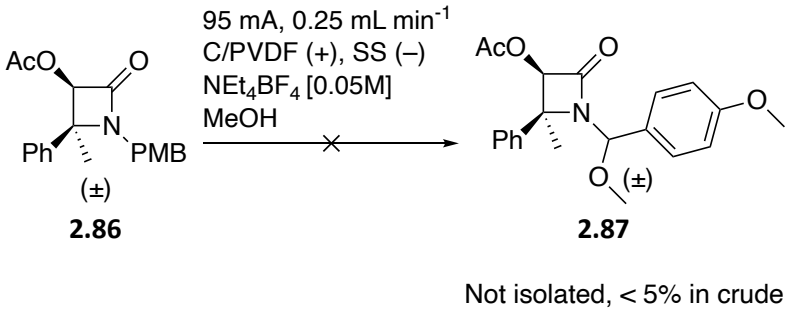
The optimised conditions for Staudinger synthesis were applied in the synthesis of substrate 2.72, obtaining the syn product in 70% yield.



Scheme 2.24: Application of optimised Staudinger synthesis to form β– lactam 2.86

2.4.3 Chemical deprotection of β–lactam substrates by CAN

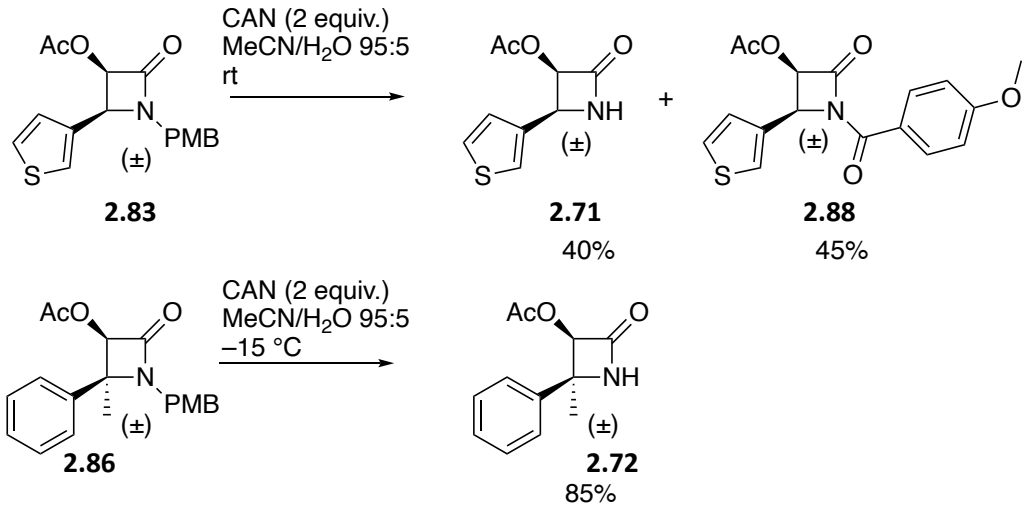
The optimised conditions for PMB deprotection were applied to the β-lactam substrates (Scheme 2.25)



Scheme 2.25: PMB deprotection of β-lactam substrates by optimised conditions

The conditions optimised for PMB-deprotection of aryl amides proved to be less suitable for β-lactam deprotection. When **2.86** was subjected to the electrolysis conditions, less than 5% of the desired hemiaminal ether **2.87** was observed despite complete conversion. To confirm that

the failure of the electrochemical deprotection method was not substrate–specific, substrates **2.83** and **2.86** were subjected to conventional PMB deprotection conditions (Scheme 2.26).

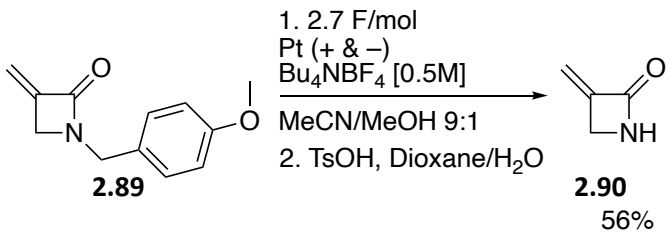


Scheme 2.26: Chemical deprotection of PMB protected β-lactams using CAN

PMB deprotection of substrate thiophene derivative **2.83** proceed with some further oxidation of the product, forming N-acyl β-lactam **2.88** in 45% yield. Careful control of temperature in the deprotection of **2.86** afforded the deprotected β-lactam **2.72** in good yield (85%) and without over oxidation. This gave a sample of the deprotected product for which to compare TLC and NMR spectra and provided reassurance that the PMB deprotection could proceed under oxidative conditions.

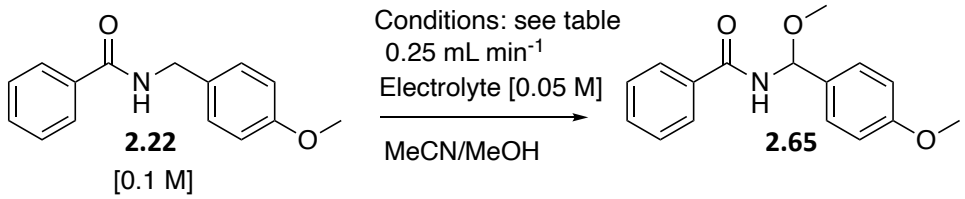
2.4.4 Optimisation of electrochemical deprotection of complex β-lactams

Initial conditions took inspiration from a literature report of electrochemical deprotection of simple β-Lactams in a batch cell by Mori and co-workers (Scheme 2.27).[225]



Scheme 2.27: Electrochemical PMB deprotection of β-lactams reported by Mori *et al.*[225]

The interesting co-solvent was likely implemented following method development, where they found those conditions to be optimal. In preparation for the application of electrochemical PMB deprotection on β-Lactam substrates **2.83** and **2.86**, conditions were first investigated using the PMB benzamide **2.22** due to its availability in large quantities (Table 2.11).



Entry	Electrode	MeCN/MeOH ratio	Electrolyte	Current/ mA (Fmol^{-1})	Yield[a]
1	C/PVDF	0:100	Et_4NBF_4	95 (2.4)	87[b]
2	Pt	90:10	Bu_4NBF_4	110 (2.7)	20[c]
3	C/PVDF	90:10	Bu_4NBF_4	110 (2.7)	50
4	Pt	50:50	Bu_4NBF_4	110 (2.7)	42[c]
5	Pt	90:10	Et_4NBF_4	110 (2.7)	22[c]
6	C/PVDF	90:10	Et_4NBF_4	95 (2.4)	82
7	Pt	25:75	Et_4NBF_4	135 (3.4)	43[c]
8	Pt	50:50	Et_4NBF_4	135 (3.4)	58[c]
9	Pt	75:25	Et_4NBF_4	135 (3.4)	69[c]
10	**Pt**	**75:25**	**Et_4NBF_4**	**190 (4.8)**	**81[c]**
11	**C/PVDF**	**75:25**	**Et_4NBF_4**	**95 (2.4)**	**85**

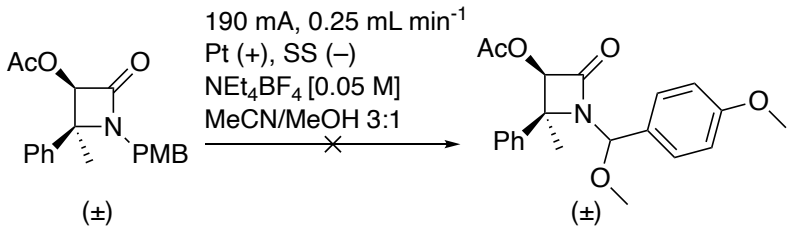
a. Yield by quant. NMR, DMT as internal standard
b. PMB deprotection conditions optimised in this work
c. Starting material remained

Table 2.11: Optimisation of alternative reaction conditions for PMB deprotection

Trialling the Mori conditions on this substrate under flow reactions (Table 2.6, entry 2) led to very low conversion. This was not entirely unexpected, since they closely resemble conditions trialled using a Pt anode previously (see Table 2.6, entry 7), which produced no conversion. Following this, a systematic optimisation of each variable was performed. Entry 3 shows that, all conditions the same except the anode led to consumption of starting material but an inferior yield to those of optimised conditions on the C/PVDF anode. Altering the ratio of MeCN to MeOH (entry 4) on Pt anode was beneficial: a 42% yield of hemiaminal ether **2.65** was observed with starting material remaining. Entry 5 showed that the electrolyte has little if any significance in the reaction, and because Et_4NBF_4 could be recovered from the crude this was used going forward.

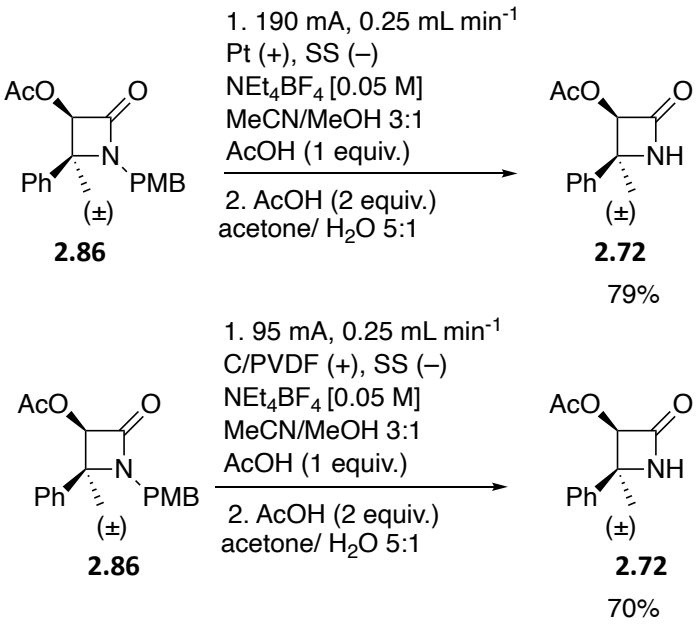
Entry 6 shows that in the 9:1 cosolvent the substrate is still sensitive to current, as returning to 95 mA from the current Mori applied led to an improved yield.

Now that it was discovered that the solvent ratio was significant on the Pt anode, different ratios of MeCN and MeOH were trialled (entries 7-9). It was also clear that MeOH oxidation competed with that of oxidation of the benzylic position, and so an increased current was applied across these. Of the conditions tested, 3:1 MeCN/MeOH was found to be optimum: the ratio affected the redox potential of the substrate and so too high or low and MeOH would oxidise preferentially instead. Hence entry 9 was repeated with higher current (entry 10), which afforded **2.65** in 81% yield. These conditions were found to be replicable on the C/PVDF anode (entry 11), but solvent effect had less significance. The conditions from entry 10 were trialled on the β-Lactam substrate:



Scheme 2.28: Unsuccessful transfer of reoptimised PMB conditions on β-Lactam substrate

The product was found to deacetylate under these conditions. Pleasingly this could be overcome through the addition of 1 equiv. of AcOH to the reaction solution. However, deacetylation also occurred during the HCl acid hydrolysis step. Utilising AcOH (2 equiv.) in acetone/water 5:1 was effective in cleaving the methoxylated PMB substrate **2.87** (which was unsuccessful in substrate **2.65**), without deacetylating, albeit with a longer reaction time (2 hours instead of 30 minutes). It is thought that the relative instability of **2.87** (which could not be isolated) compared to **2.65**, which was isolated in 85% yield, is the underlying reason that a milder acid could perform the hydrolysis. Finally, trialling the two-step process on the two anode materials, with the new conditions, the successful PMB deprotection of β-Lactam **2.86** was achieved. These are illustrated in Scheme 2.29.

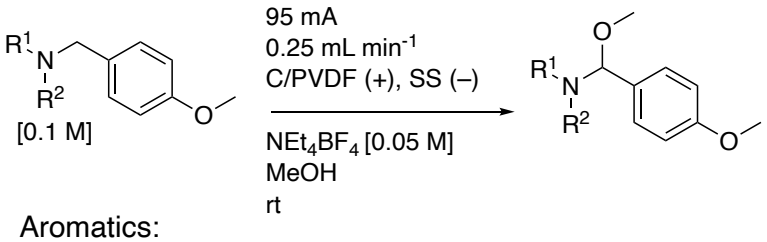


Scheme 2.29: Successful two-step PMB deprotection of β-lactam 2.86 on Pt and C/PVDF anode materials

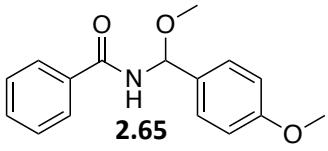
2.5 Substrate scope for electrochemical oxidation and deprotection of nitrogen containing compounds

2.5.1 Isolation and utilisation of methoxylated secondary PMB amides

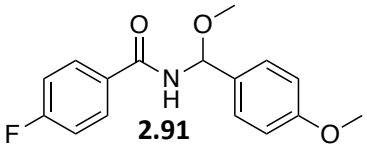
Table 2.12 illustrates a number of methoxylated secondary PMB amides isolated as part of this methodology.



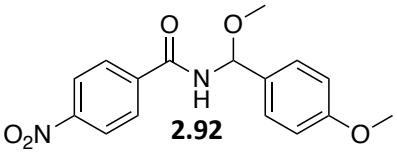
Aromatics:


2.65

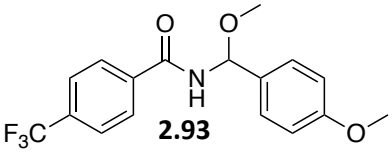
84%, 342 mg hr^{-1}


2.91

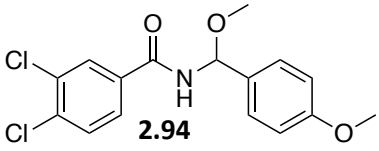
85%, 370 mg hr^{-1}


2.92

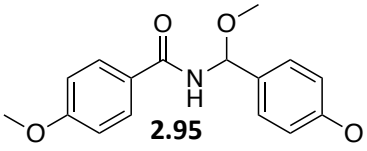
75%[a], 178 mg hr^{-1}


2.93

92%, 465 mg hr^{-1}

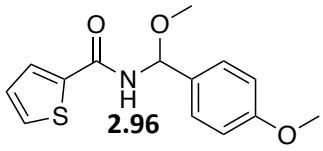

2.94

80%[a,c], 204 mg hr^{-1}

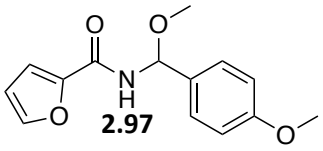

2.95

88%, 398 mg hr^{-1}

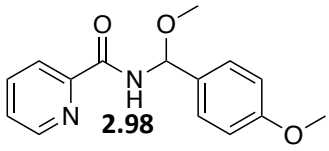
Heterocycles:


2.96

92%, 383 mg hr^{-1}

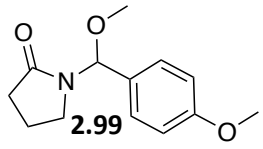

2.97

91%, 358 mg hr^{-1}


2.98

91%[a], 258 mg hr^{-1}

Lactams:


2.99

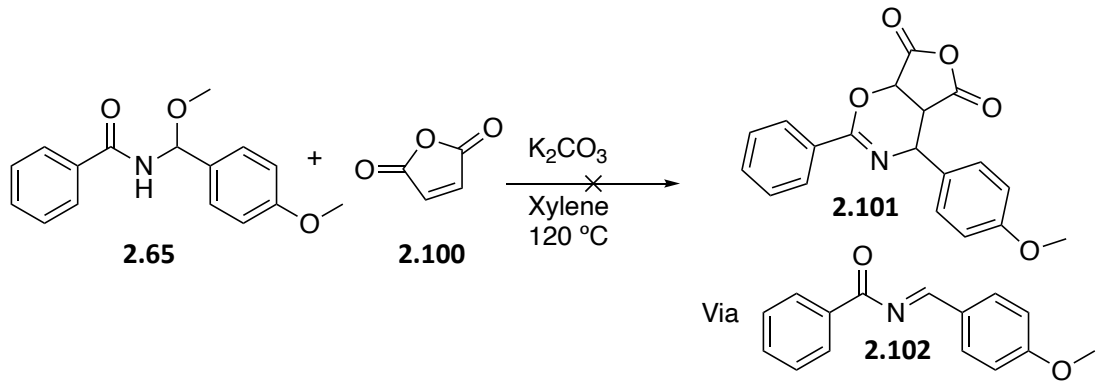
60%[b], 212 mg hr^{-1}

a. Two passes of the reactor (95 mA, 50 mA)
b. Yield by calibrated GC
c. 0.5 mmol scale

Table 2.12: Substrate scope for electrochemical methoxylation of PMB-protected amides and lactams

Yields were good to excellent in each case, with some substrates requiring two passes of the Ammonite 8 reactor to reach completion. Purification was by flash chromatography in most instances.

The Diels-Alder coupling of methoxylated amides to electron-rich dienophiles has been reported by Gizecki *et al.*[226] An attempt to utilise this methodology (without the use of $SnCl_4$ as a Lewis acid, and on a cheaper, commercial dienophile) on the substrates prepared in this work was trialled.

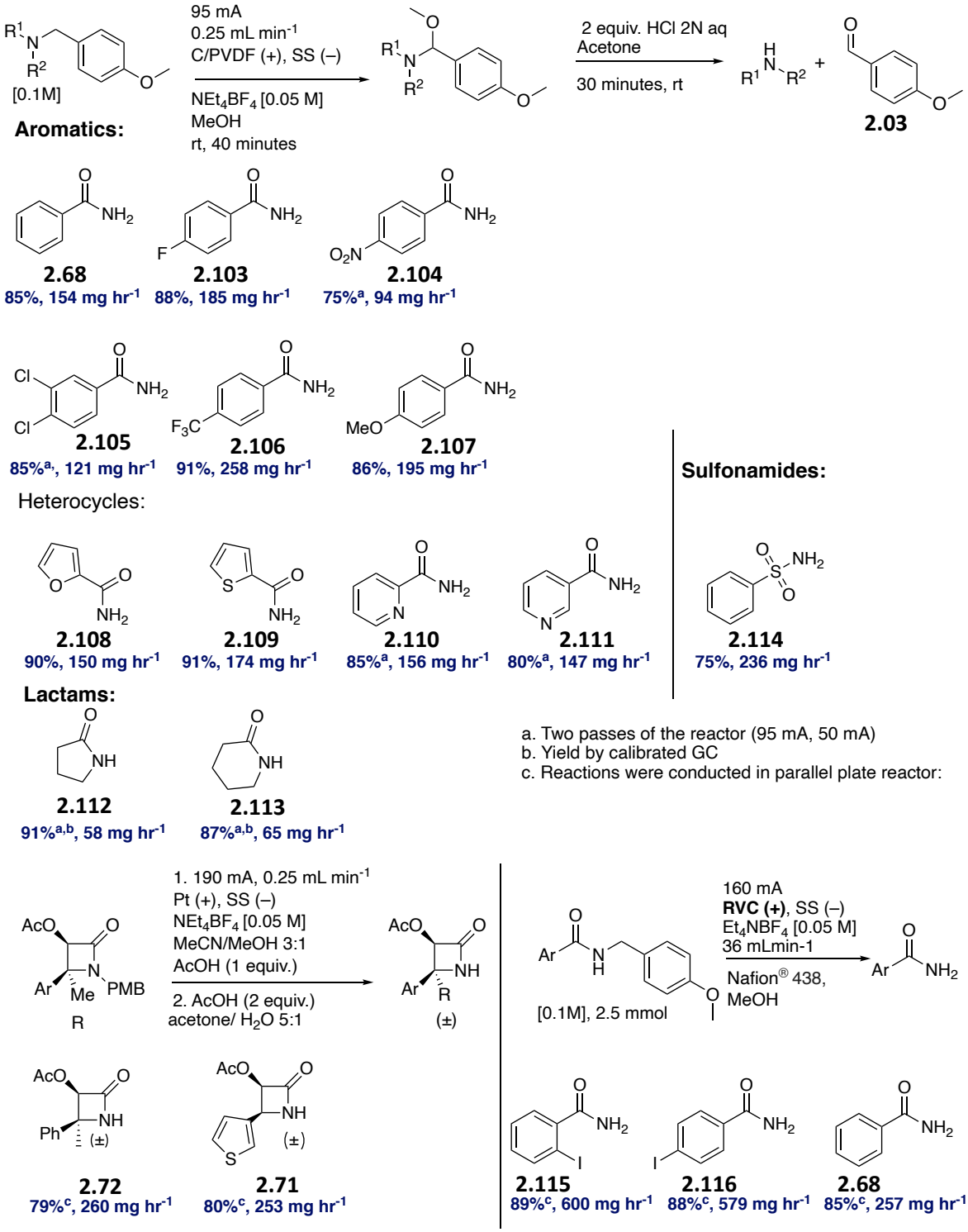


Scheme 2.30: Unsuccessful Diels-Alder reaction with hemiaminal ether 2.65

Under these conditions the methoxylated PMB group was cleaved, with none of the Diels-Alder product formed. This could be because the diene is unsuitable as a substrate for the reaction, or that the Lewis Acid is integral to the cyclisation. Further experiments on this will be the basis of future work.

2.5.2 Electrochemical deprotection of secondary PMB amides

Scheme 2.31 illustrates substrates that have been successfully deprotected:



Scheme 2.31 Substrate scope of the electrochemical PMB deprotection

All reactions, unless stated otherwise, were performed in the Ammonite 8 electrochemical flow reactor equipped with a C/PVDF anode and SS cathode. Reactions were conducted on 1.0 mmol or 0.5 mmol scale (40/20 min run time for 10.0/5.0 mL reaction volume, respectively). The reported yields represent isolated purified products except where stated otherwise. Substrates **2.115** and **2.116** were synthesised in the parallel plate divided reactor, which is discussed in 2.13.2.1. Complex beta lactams **2.71** and **2.72** were prepared under different conditions in the

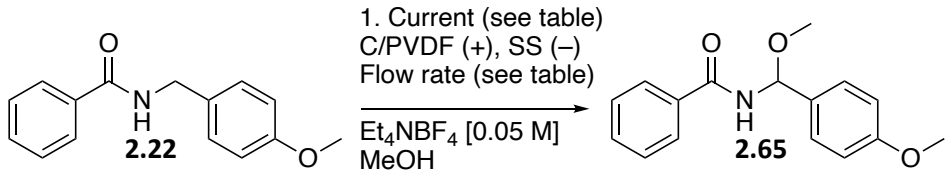
Ammonite 8 (see Scheme 2.29). Seventeen substrates, including benzamides, heterocyclic amides, sulfonamides, and β-, γ- and δ-lactams were found to deprotect efficiently, with good to excellent yields. PMB protected benzamides including electron-poor (e.g. CF_3, NO_2) and electron-rich (e.g. OMe) substitution afforded primary amides in yields ranging from 75% to 96%. Heterocyclic amides including pyridyl, thiophenyl and furyl substitution were tolerated. Some substrates, namely simple lactams and electron poor aromatics required two passes of the reactor in order to react all the starting material. The electrolyte could be recovered and reused for each reaction following recrystallisation, the cleaved PMB product **2.03** could be isolated by bisulfite wash. High current efficiencies (up to 77%) were displayed, and whilst productivities are modest (1.4 mmol hr^{-1}), later work would demonstrate that this parameter can be greatly increased. The substrate scope was found to be quite limited, with several competing processes possible.

2.6 Scale-up of PMB deprotection in Ammonite 15 reactor

The PMB deprotection process was explored in the larger Ammonite 15 reactor to demonstrate the potential to increase productivity. The higher currents required to convert larger amounts of material cause heating of the reactor due to faradaic losses, resulting in a need for cooling. The Ammonite 15 was designed to allow cooling using a Polar Bear Cub™ cooling device. Additional safety precautions included ventilation of the fume cupboard was maximised, and a stream of inert gas was passed over the outlet tube in order to disperse the increased quantity of hydrogen gas produced in the counter electrode reaction, which if allowed to build up would pose an explosion hazard. A high-voltage power pack was also necessary, which could provide the high current and potential applied.

Two ways to increase productivity in flow electrosynthesis are by increasing the substrate concentration, and by increasing the flow rate. An proportional increase in current also needs to be applied. There can be problems in increasing productivity: many reactions in electrochemistry are sensitive to the current density of the electrode surface, which increases as the current is raised for a given electrode surface area. Side reactions may occur reducing reaction yield, and passivation of the electrode surface can be accelerated, which ultimately prevents electrolysis and requires disassembly and cleaning of the electrodes. Furthermore, in order to synthesise large amounts of material, the reactor needs to be able to run for a sustained length of time, which is not typically considered when developing new electrosynthetic methodology.[22] Indeed, testing the scope for a reaction is commonly only conducted on 1 mmol or less of material for each substrate. As such, factors such as progressive heating of the reactor, and the corrosion resistance of the electrodes need to be considered.[37]

Another important factor related to the productivity of a reaction is reactor performance, which is intrinsically related to its design. The Ammonite 15 reactor is designed to enable high productivity with high conversion, with a long spiral channel length (2 m), a narrow interelectrode gap. The channel design, combined with gas production is believed to give good mixing in the reactor. These factors combine to give what is expected to be a high mass transfer coefficient (crucial for high productivity), which is evidenced by high conversion in a single pass of the reactor when stoichiometric current is applied. In order to increase productivity, experiments were setup whereby the concentration, flow rate and current were adjusted to identify conditions which produced both a high productivity and yield. The results of this are presented in Table 2.14.



Entry	Conc./ mol dm^{-3}	Flow rate/ mL min^{-1}	Current/ A (F/mol)	Yield[a] %	
				2.65	**SM**
1	0.1	0.25	0.08 (2.2)	85	6
2	0.2	5.0	4.80 (3)	59	20
3	0.2	5.0	6.40 (4)	52	19
4	0.1	5.0	2.40 (3)	61	20
5	0.2	2.5	2.40 (3)	68	15
6	0.2	2.5	2.80 (3.5)	70	14
7	0.2	2.0	1.93 (3)	61	25
8	0.5	2.5	6.00 (3)	54	27
9	**0.4**	**2.5**	**5.63 (3.5)**	**67**	**15**

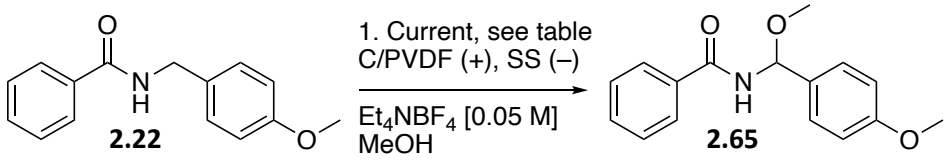
a. Yield estimated using 1H NMR, DMT as internal standard

Table 2.13: Optimisation of conditions for PMB oxidation (single pass) in Ammonite 15 reactor

Scaling-up of the electrochemical PMB oxidation was found to be sensitive to higher flow rates: a reduction in reaction yield of **2.65** from 85% (entry 1) to 61% (entry 4) was observed when increasing flow rate from 0.25 mL min^{-1} to 5 mL min^{-1} for a 0.1 M substrate solution. The optimum flow rate of 2.5 mL min^{-1} led to a 70% yield of **2.65** at 0.2M (entry 6). Pleasingly, the concentration could be increased up to 0.4 M with minimal reduction in yield. The reaction solution became saturated beyond 0.4 M leading to precipitation of product in the reactor and

consequently a lower than expected yield of 54% (entry 8). Under the optimum conditions (entry 9 of Table 2.13), an NMR yield of 67% was observed in a short run, with a current efficiency of 38% and a productivity of 40.2 mmol hr^{-1}.

Conditions were trialled (Table 2.14) utilising two passes of the reactor to investigate whether the reaction could be pushed to completion.



2.22 **2.65**

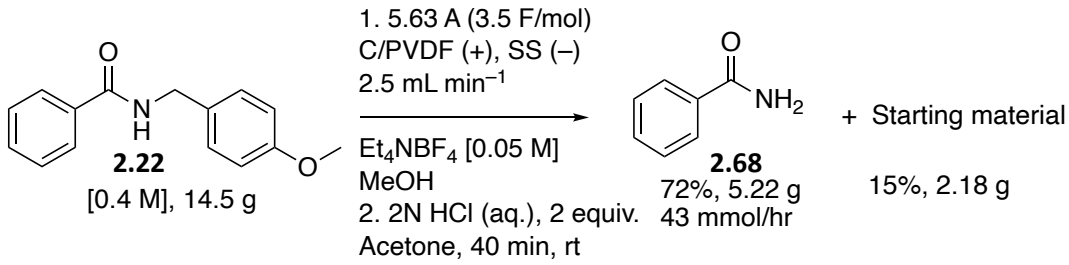
Entry	Conc./ mol dm^{-3}	Flow rate/ mL min^{-1}	Current/ A (F/mol)		Yield[a] %	
			1st pass	2nd pass	2.65	SM
1	0.4	2.5	5.63 (3.5)	1.35 (0.8)	65	10
2	0.4	2.5	5.63 (3.5)	2.80 (1.8)	55	10
3	0.4	2.5	5.63 (3.5)	2.08 (1.3)	54	11
4	0.4	2.5	3.20 (2)	2.40 (1.5)	70	12

a. Yield estimated using quantitative ^1H NMR, DMT as internal standard

Table 2.14: Optimisation of conditions for PMB oxidation (two passes) in Ammonite 15 reactor

The highest yield of **2.65** observed (70%, entry 4) for two passes of the reactor was no improvement compared to a single pass, with less starting material present in the reaction solution. As such there was no benefit to carrying out the reaction in two-passes (since a reduction in productivity follows from the extra time in the reactor). The modest improvement in yield is not justified by the reduced productivity.

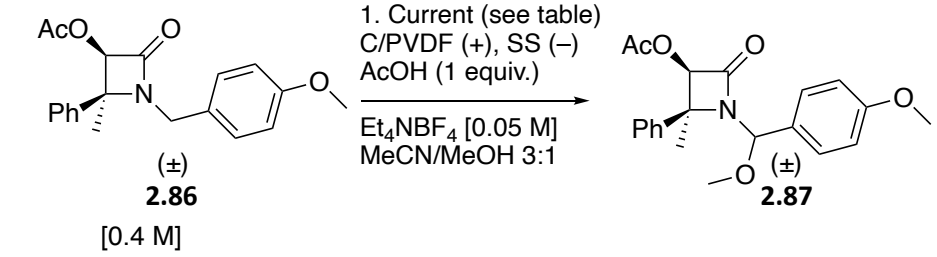
The two step PMB deprotection of **2.22** over a 45 minute run, under conditions illustrated in entry 9 of Table 2.9 (0.4 M substrate, 2.5 mL min^{-1}, 5.63 A (3.5 F mol^{-1}), followed by treatment with 2N aq. HCl in acetone was implemented (Scheme 2.32).



Scheme 2.32: Extended run of PMB deprotection of 2.22 in Ammonite 15 reactor

5.22 g of benzamide, **2.68** was produced in the reaction, in 72% yield (with 15% starting material remaining), with a current efficiency of 41% and a productivity of 43.2 mmol hr^{-1}.

Anodic oxidation of the PMB protected β-lactam **2.86** was also investigated in the Ammonite 15 reactor (Table 2.15). As observed from the Ammonite 8 deprotection of this substrate it was clear that alternative conditions (relative to those illustrated in Scheme 2.31 for amides **2.68** and **2.103** to **2.113**) would be required in the Ammonite 15 reactor as well.



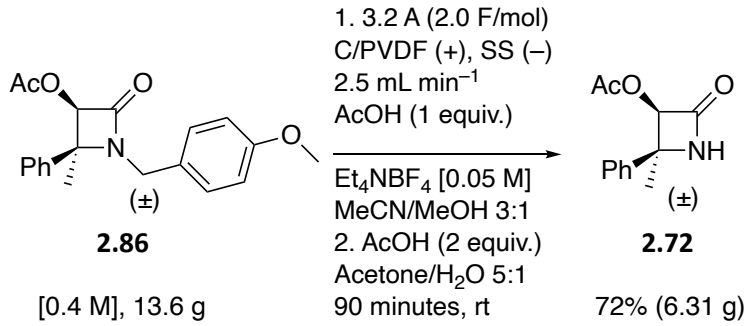
Entry	Conc./ mol dm^{-3}	Flow rate/ mL min^{-1}	Current/ A (F/mol)	Yield[a] %	
				2.87	**2.86**
1	0.4	2.5	4.8 (3.0)	59	25
2	0.4	5.0	8.0 (2.5)	51	14
3	0.4	2.5	4.0 (2.5)	65	12
4	**0.4**	**2.5**	**3.2 (2.0)**	**67**	**15**

a. Yield by quantitative NMR, DMT as internal standard

Table 2.15: Optimisation of anodic methoxylation of β-Lactam in the Ammonite 15 reactor

At a substrate concentration of 0.4 M, with a flow rate of 2.5 mL min^{-1} the methoxylated intermediate **2.86** was obtained in 59-67% yield (entries 1, 3 and 4, Table 2.9). Pleasingly, when the total charge was reduced to the theoretical amount required for a two-electron oxidation, the highest yield of 67% was obtained (entry 4). Increasing the flow rate, with commensurate increase in current, gave a reduced yield of 51% (entry 2), with SM and side-products (such as deacetylated

material) constituting the remaining material. A 40 minute run was conducted using the optimised electrolysis conditions, followed by acid treatment and purification by recrystallisation affording 6.31 g of deprotected lactam **2.72** in 72% yield (Scheme 2.33). A high productivity of 43.2 mmol hr^{-1} was demonstrated on a multi-gram scale and with a high current efficiency (72%).

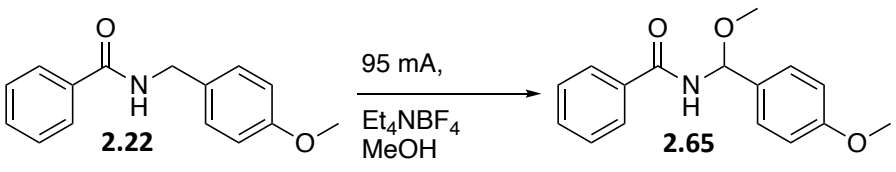


Scheme 2.33: PMB deprotection of 2.86 on a multi-gram scale in the Ammonite 15 reactor

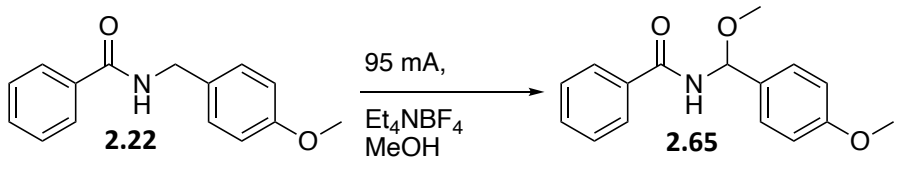
2.7 Development of two-step PMB deprotection in continuous flow

Since an efficient one-step PMB deprotection was not achieved (see section 2.3.7), a method to carry out the electrolysis as a two-step process under continuous flow was investigated. One of the merits of electrosynthesis in flow, unlike a batch electrolysis, is that productivity can be increased easily (as demonstrated in section 2.6) and with little modification of the equipment. However, with a batch acid step following the electrochemical step, some of the benefit of carrying out the process in flow is lost. Performing the acid step as part of the process is clearly desirable.

Initial studies of a continuous two-step deprotection included minimising the electrolyte concentration, without compromising yield or conversion (Table 2.16). This was to mitigate the downside that the electrolyte cannot be recovered in the two-step deprotection, as ion exchange would occur with the acid introduced in the hemiaminal hydrolysis.



Entry	[Et_4NBF_4] / M	Yield of 2.65[a] /%
1	0.05	85
2	0.025	86
3	0.01	84



4	**0.005**	**82**
5	0.001	73

a. Yield determined using quantitative ^{1}H NMR with DMT as internal standard

Table 2.16: Optimisation of electrolyte concentration for continuous flow process

The electrolysis of PMB benzamide **2.22** was investigated with Et_4NBF_4 concentrations in the range 0.05 – 0.001 M (Table 2.10). It was found that only modest decrease in yield (82%) was observed with a ten-fold reduction in supporting electrolyte (0.005 M, entry 4). This concentration could have been utilised in the previous work, but at low concentrations it was difficult to recover the material. Using this result, a flow setup was setup (Figure 2.3).

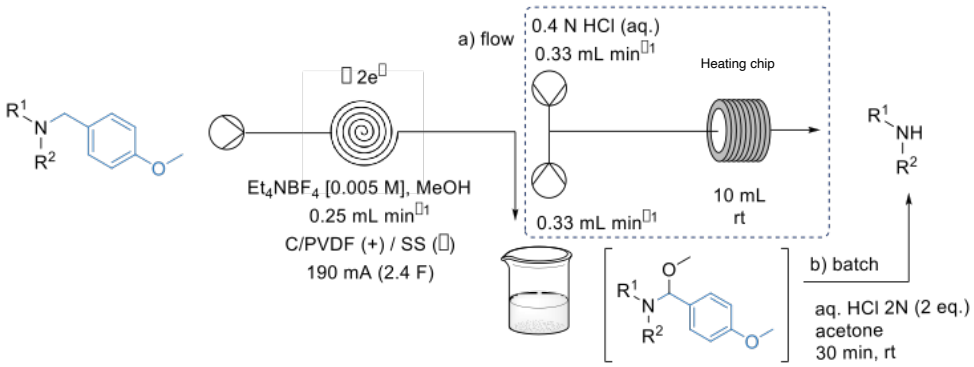
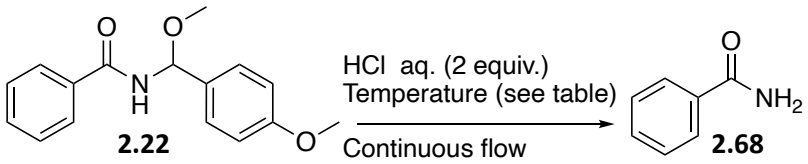


Figure 2.3: Illustration of continuous flow process for PMB deprotection

There were some initial issues with the continuous setup (Scheme 2.32). For example, the effluent solution needed to be first collected in a reservoir before being drawn into the heating chip/tube reactor with an acid stream being added. This enabled hydrogen gas dissipation; if the gas was not allowed to escape, a backpressure developed which prevented the reaction solution from the Ammonite 8 from being drawn up. An alternative solution could involve the use of tube-in-tube technology,[227] whereby the tube is gas permeable and enables dissipation prior to the acid hydrolysis. Another problem was inefficient mixing of the acid solution and the electrolysis product, which led to incomplete reaction initially. It was found that the simple T-piece was inefficient in effecting efficient mixing, however the use of a specialist T-piece, with glass beads to improve mixing in the initial phase was an effective solution to this. Inconsistencies with respect to the flow rates of the two inlets meant that large volumes of electrolysis solution were not exposed to the acid solution. Utilising the same pump with two channels, thereby matching the flow rate of the two streams overcame this.

The outlet from the acid hydrolysis was passed into an aqueous solution of $NaHCO_3$ to quench the reaction, with workup and purification following. One of the advantages of the continuous flow process is that the acid step is more efficient in flow than in batch, with a reaction time of 15 min instead of 30 min in the batch process (both conducted at rt). This is quite typical for such a process; more efficient mixing often leads to a reduction in reaction time and/or a reduction in the required energy input e.g. temperature. In contrast, the reaction had not reacted completion after 1 hour in a 50:50 MeOH/HCl aq. mixture in batch.

Following the success of the continuous flow PMB deprotection, attempts were made to increase the productivity of the process (Table 2.17.), with the aim that the acid hydrolysis step could match the productivity of the electrolysis in the Ammonite 15.



2.22 **2.68**

Entry	Concentration /M	Flow rate /mL min^{-1}	Heating chip temperature/ °C	Yield[a]/ %
1	0.1	0.5	rt	87
2	0.1	0.66	rt	85
3	0.1	5.0	70	86
4	0.1	5.0	50	30
5	0.1	0.66	50	87
6	**0.2**	**0.66**	**50**	**85**
7	0.1	0.66	rt	85

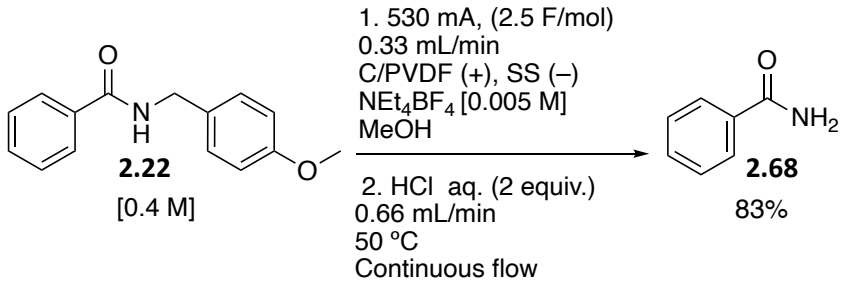
a. Yield estimated using quantitative NMR, DMT as internal standard
b. Isolated yield, 0.5 mmol substrate per experiment.

Table 2.17: Optimisation of continuous two-step PMB deprotection

Conducting the hydrolysis at 70 °C led to boiling of the MeOH/HCl aq. co-solvent (most likely due to an azeotrope of the two solvents), and consequently the solution was passed though the reactor much faster than the rate set on the pump. This was solved by lowering the temperature to 50 °C. Unfortunately, the productivity of the acid hydrolysis could not match that which was possible for oxidation in the Ammonite 15 (43.2 mmol hr^{-1}, corresponding to a flow rate of 5 mL min^{-1} and a substrate concentration of 0.4 M); incomplete reaction was observed

under these conditions. The highest productivity for the process arose under the conditions illustrated in entry 6,

Potential methods of overcoming the inadequate flow rate for the acid hydrolysis would be to increase the path length of the heating chip reactor, and/or introducing a Back Pressure Regulator (BPR) such that the temperature for the reaction could be increased without causing the solvent to boil. Both of these will be the subject of future work. The best conditions for the process are illustrated in Scheme 2.34.



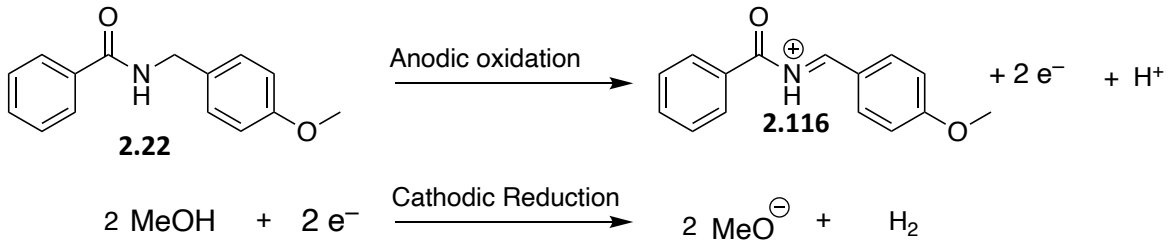
Scheme 2.34: Continuous two-step PMB deprotection of 2.22

The two-step PMB deprotection of **2.22** was carried out, utilising hydrolysis conditions illustrated in entry 6 of Table 2.17. At a substrate concentration of 0.4 M, with a flow rate of 0.66 mL min^{-1} the deprotected benzamide **2.68** was obtained in 83% yield, with a current efficiency of 66% and a productivity of 13.1 $mmol^{-1}$.

2.8 Mechanistic studies, and cyclic voltammetry

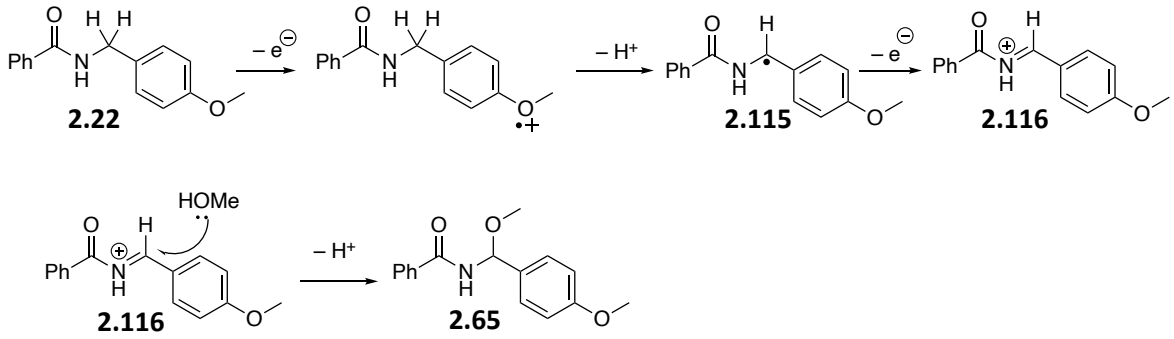
2.8.1 Mechanistic studies

Scheme 2.35 outlines the electrochemical processes occurring in the reactor:



Scheme 2.35: Anode and cathode reactions for the electrolysis of PMB benzamide (2.22)

It is proposed that the anodic reaction follows a similar mechanistic pathway to deprotection of PMB ethers by chemical oxidants, such as CAN or DDQ (see Scheme 2.2). A proposed mechanism for electrochemical PMB deprotection follows (Scheme 2.36).



Scheme 2.36: Proposed mechanism for chemical processes in electrochemical methoxylation of 2.22

It is proposed that an electron is removed from PMB benzamide **2.22** (either from nitrogen lone pair, or from the aryl ring) to form a radical cation (Scheme 2.36), after which loss of a proton forms radical species **2.115**. Loss of a second electron forms benzylic cationic species**, 2.116** which is susceptible to nucleophilic attack by the solvent MeOH, which following deprotonation forms the hemiaminal ether **2.65.** The counter electrode reaction is the electro-formation of methoxide, and molecular hydrogen which is observed as bubbles leaving the Ammonite reactor (see Figure 2.4).

Figure 2.4: Pictures illustrating slug flow from the Ammonite 8 reactor

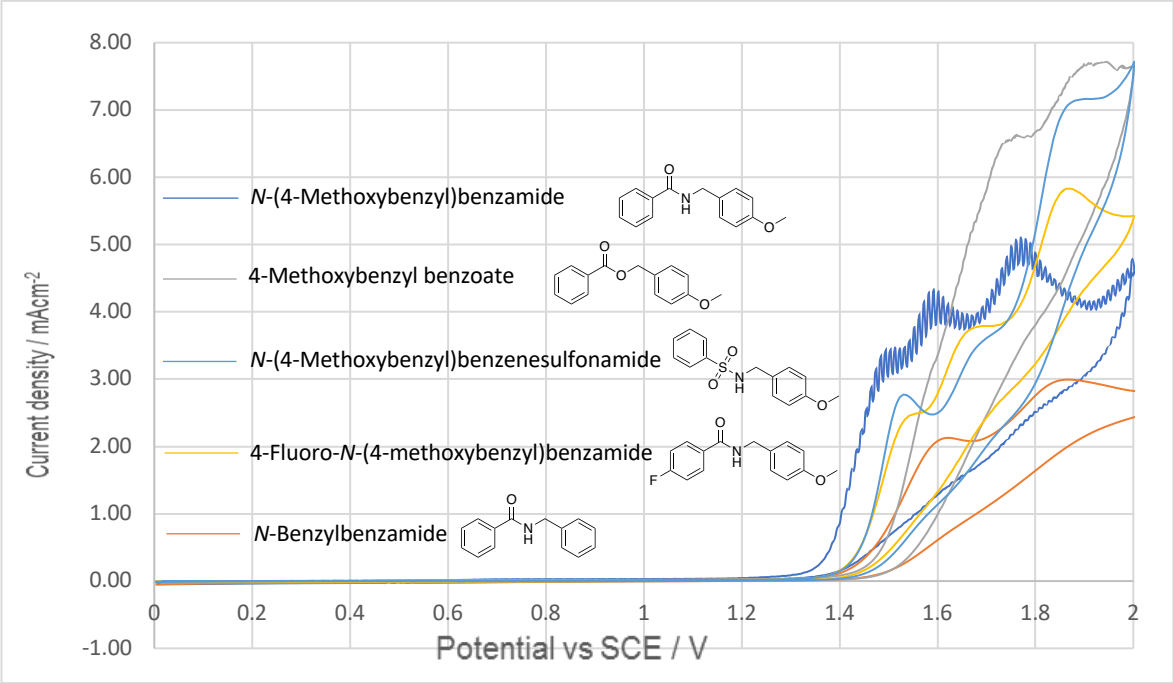
Formation of base at the cathode compensates for anodic acid and means that the overall pH of the reaction solution should remain neutral, thus negating the need for buffering as is often used in electrosynthetic processes where H^+ is formed during oxidation. Furthermore, it is proposed that the gas formation (as H_2) within the reactor can improve cell performance. This is because it can create better mixing in the reactor, which combined with the design of the Ammonite flow reactor means that the mass transfer is maximised which can allow improved current efficiency at higher currents.[37]

2.8.2 Cyclic Voltammetry experiments on PMB protected secondary amides, sulfonamide and esters

Cyclic Voltammetry was conducted on *N*-(4-Methoxybenzyl)benzamide (**2.22**), 4-Methoxybenzyl benzoate (**2.62**), *N*-(4-Methoxybenzyl)benzenesulfonamide (**2.42**), 4-Fluoro-*N*-(4-methoxybenzyl)benzamide (**2.25**) and *N*-Benzylbenzamide (**2.48**) in order to probe the electrochemical behaviours of these substrates, elucidate the reaction mechanism for electrochemical PMB deprotection (by identifying what part of the molecule oxidises first).

It should be noted that CV is a batch process, and so even in the same solvent system and using the same electrode materials, care should be taken when drawing comparisons to reactions that occur in the Ammonite reactor, which is of course a flow cell.

Figure 2.5: Cyclic voltammetry for selection of secondary amides, sulfonamides and esters



Setup for the cyclic voltammetry is illustrated in Chapter 1. Conditions are as follows: substrate [0.01 M], Et_4NBF_4 [0.1 M], MeOH (25 mL), rt, range 0 to 2.0 V, other experiments conducted), scan rate 25 mV s^{-1}, 100 mV s^{-1} also conducted). The scans were conducted over different voltage ranges (0.0–2.0 V and 0.0–2.5 V) in order to highlight the substrate and solvent oxidation peaks. It was found that, within the timescale of the CV study (controlled by the scan rate), all the oxidation processes seen in the CV are irreversible. This was deduced by controlling the voltage range such that the reverse sweep was conducted immediately after each oxidation had taken place, thereby observing whether a reverse peak was seen. Furthermore, the electrochemistry for the substrates investigated in Figure 2.5 are under mass transfer control. This means that the rate of the electrochemical reaction is dependent on processes such as diffusion

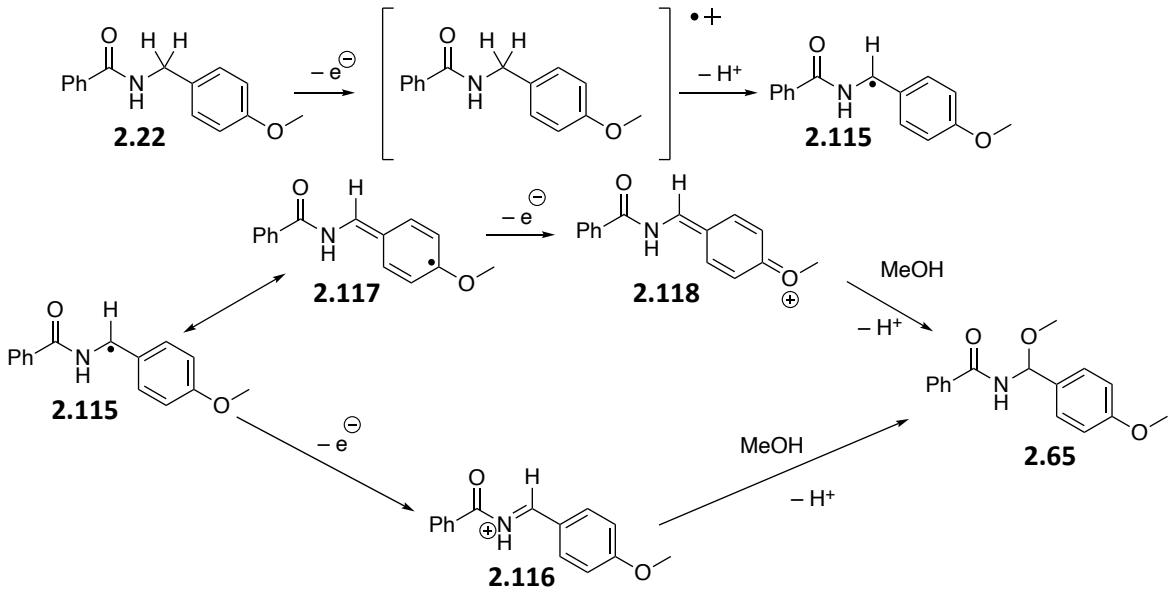
(i.e. transport of the substrate to the electrode surface), as opposed to the electron transfer itself. It can be determined that the processes are under mass transfer control if a relationship exists between the current density and the scan rate.[23] If the reaction is mass transfer controlled, the cell current is given by:

$$J = \frac{I}{A} = 2.69 \times 10^5 \, n^{\frac{3}{2}} \, D^{\frac{1}{2}} \, C \, v^{\frac{1}{2}}$$

Figure 2.6: Equation linking mass transfer coefficient to scan rate in CV

Where J is current density, I is maximum current, A is electrode area, n is the number of electrons transferred in the redox event, D is the mass transfer coefficient, C is substrate concentration and v is scan rate. The relationship between scan rate and current density is such that multiplying the scan rate by 4 will double the current density (if mass transfer control applies). By maintaining the same parameters in–between CV runs and observing if the current density doubles when the scan rate is increased from 0.025 A s^{-1} to 0.1 A s^{-1}, we can determine if the mass transfer coefficient remains constant and thereby whether the reaction is under mass transfer control. This was the case for the experiments conducted, as is very common in CV studies.

The PMB deprotection is formally a two-electron oxidation process, and yet there are three defined oxidation events occurring in the CV. Of note is that the second and third peaks produce the same net current density as the first, which might suggest that the second oxidation is split across two parts of the molecule (but which lead to the same product). An illustration follows (Scheme 2.37).



Scheme 2.37: Proposed mechanism for second electron transfer in PMB deprotection

From radical species **2.115**, it is proposed that the second electron transfer can occur on the aromatic ring (stabilised by the methoxy substituent, forming intermediate **2.118**), or from the nitrogen lone pair, forming intermediate **2.116**. Both cationic species **2.118** and **2.116** are electrophilic, and attack by methanol lead to the hemiaminal ether, **2.65**. Evidence of this mechanism is substantiated by the CV spectrum for the benzyl protected amide **2.48**, where only two oxidation peaks occur. It is proposed that the first oxidation in **2.48** is that of the benzyl aromatic (as it occurs at a higher potential than the PMB group as displayed in substrates **2.22** and **2.25**), and the second oxidation occurs on the nitrogen lone pair, as this appears largely independent of the protecting aryl group (evidenced that the final oxidation peak in the substrates tested in Figure 2.5 occurs consistently at 1.9 V). The two secondary PMB protected aryl amides **2.22** and **2.25** both display three oxidation peaks, and CV of other secondary PMB aryl amides in the literature follow the same trend of three oxidations.[228]

The solvent (MeOH) was found to oxidise at 2.1 V, and it is unknown whether substrates oxidise further after this voltage. Methanol is a suitable solvent for the reaction because the substrates illustrated in Figure 2.5 oxidise at a lower potential than it.

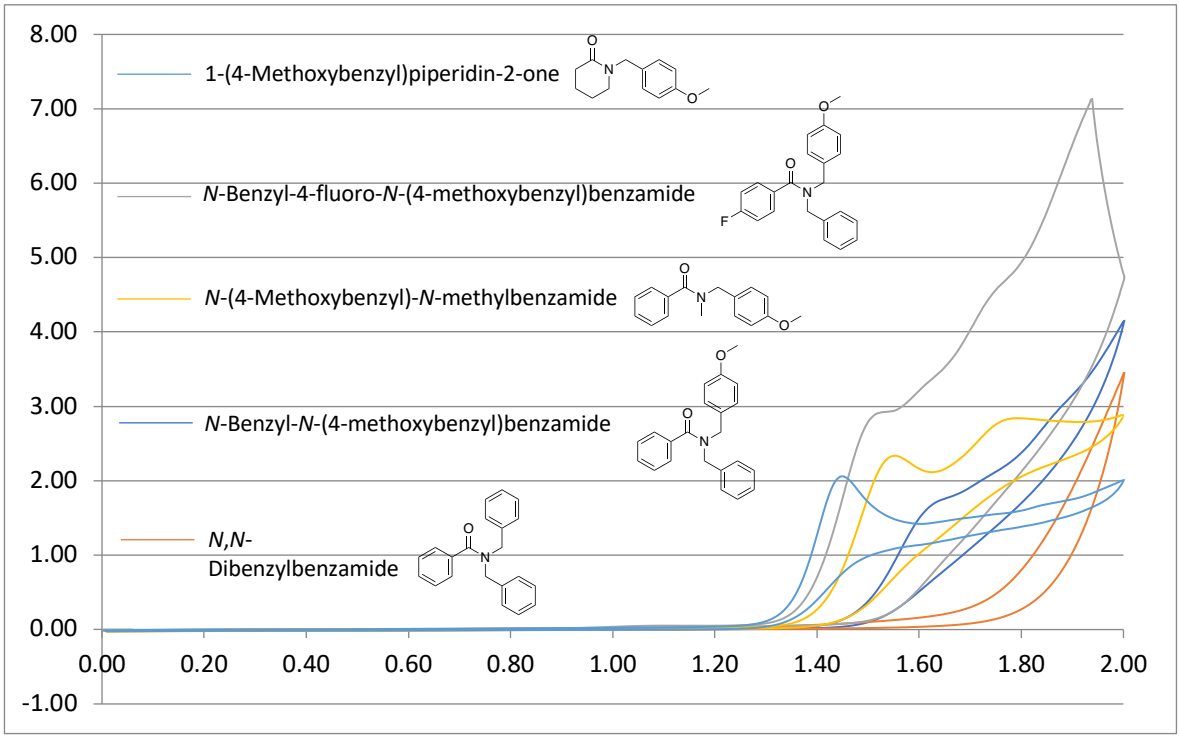
The absence of the 4-methoxy substituent on the benzyl protecting group modifies the oxidation potential of the protected amide by 0.12 V (by comparing **2.22** and **2.48**). Oxidation of **2.48** occurs at only a slightly lower potential than the solvent and so it is plausible that the substrate competes with solvent molecules for the available electrons (although this could not be proven as solvent oxidation products could not be isolated). The result of the Ammonite 8 reaction on the benzyl protected amide **2.48** (where only a 15% conversion was observed), combined with the CV data where substrate oxidation competes with the solvent (MeOH) effectively illustrates why oxidative deprotection of benzylic groups is rare in the literature.

Oxidation of the PMB ester **2.62** occurs at higher potential than the corresponding secondary amide **2.22** (1.7 V vs 1.5 V), which is consistent with the greater electron-withdrawing influence of the ester group. The CV data for the PMB protected sulfonamide (**2.42**) displays similar characteristics to the amide analogue **2.22**.

2.8.3 CV experiments on tertiary amide and lactam series

Cyclic Voltammetry was conducted on a series of tertiary aromatic PMB-protected amides in the same way as with the secondary substrates in an attempt to elucidate why the unexpected ester products form in these sub–group of substrates.

Figure 2.7: Cyclic voltammetry on selection of tertiary amides



Conditions are as follows: substrate [0.01 M], Et_4NBF_4 [0.1 M], MeOH (25 mL), rt, range 0 to 2.0 V (illustrated in

Figure 2.7, other experiments conducted), scan rate 25 mV s^{-1} (illustrated in

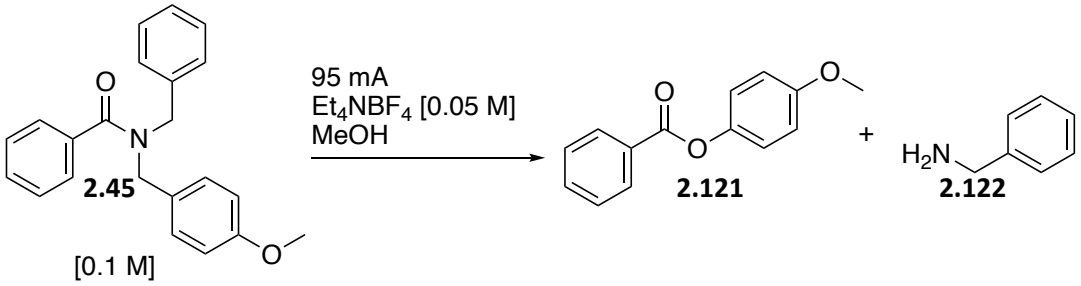
Figure 2.7, 100 mV s^{-1} also conducted). Oxidation of all substrates occurred under mass transfer control, and each oxidation was electrochemically irreversible as expected.

Oxidation of the dibenzylbenzamide **2.49** occurs at higher potential (1.8 V) compared to the PMB protected tertiary amide **2.45** (1.6 V), and close to the potential for solvent oxidation. This is expected for the less electron-rich *N*-Benzyl groups and is also consistent with lower observed conversion to **2.121** (see entry 2 of Table 2.18).

Of note is that tertiary PMB protected amide substrates **2.44**, **2.45**, **2.46** and **2.24** display two oxidations within the scan range as opposed to three frequently seen in the secondary protected PMB amides (see Figure 2.5). The different electrochemical behaviour suggests at an alternative oxidation mechanism, and indeed experimentally these substrates have shown to lead to unusual oxidation products (see section 2.9). The higher current density for the CV of fluoroamide **2.46** is likely an experimental anomaly, possible due to a higher concentration of substrate compared to the other substrates.

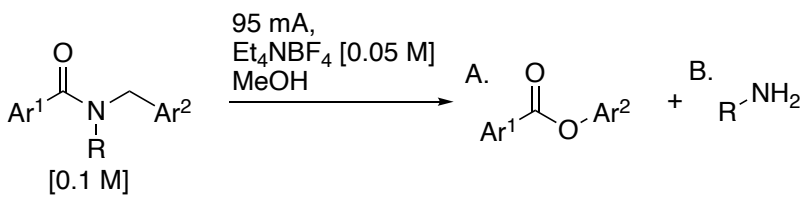
2.9 Electrolysis of tertiary benzamide derivatives: unexpected conversion to aryl esters

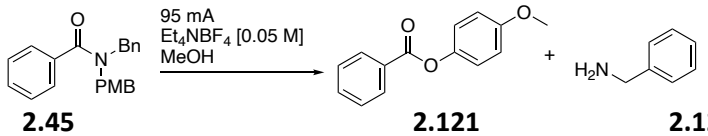
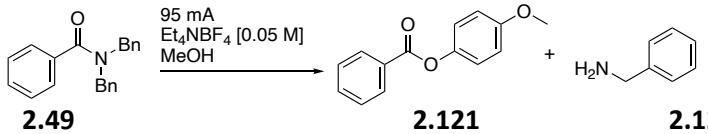
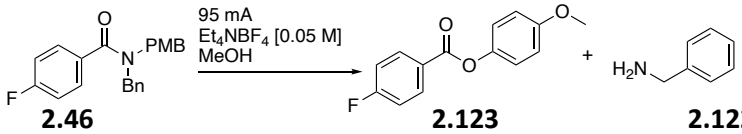
Electrolysis of the tertiary benzamide **2.45** did not lead to the expected methoxylated or deprotected products. Instead, 4-Methoxyphenyl benzoate **2.121** was obtained as the major product in 60% yield (Scheme 2.38). Benzylamine **2.122** was obtained as a co-product from the reaction in 45% yield.

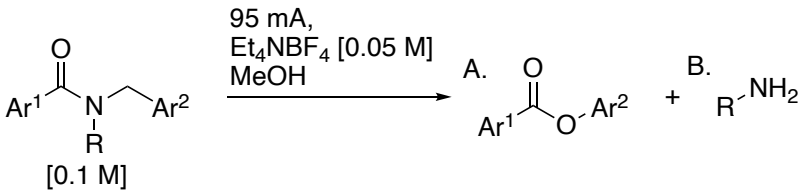


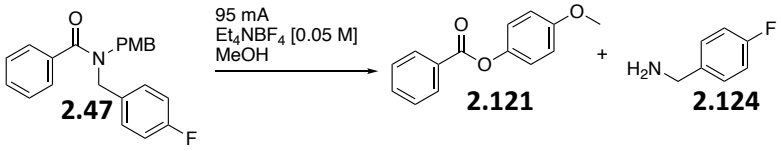
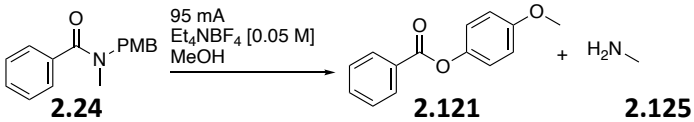
Scheme 2.38: Anodic oxidation of tertiary PMB amide 2.45

To further investigate the unexpected result, four other tertiary benzamides **2.46, 2.47, 2.49** and **2.24** were subjected to the same electrolysis conditions, and in all cases the corresponding aryl esters **2.121** and **2.123**, and amine **2.122** were obtained in low to modest yields (20-60%, amines **2.124** and **2.125** were not isolated). A lower yield (30%) of the ester **2.121** was obtained when the PMB group was replaced with Bn, which can be explained by the lower conversion of the less electron-rich *N*-benzyl benzamide **2.48** compared to PMB-protected benzamide **2.22**.



Entry	Reaction scheme	Yield[a] A/%	Yield[a] B/%
1	 **2.45** **2.121** **2.122**	60	45
2	 **2.49** **2.121** **2.122**	30	27
3	 **2.46** **2.123** **2.122**	60	40

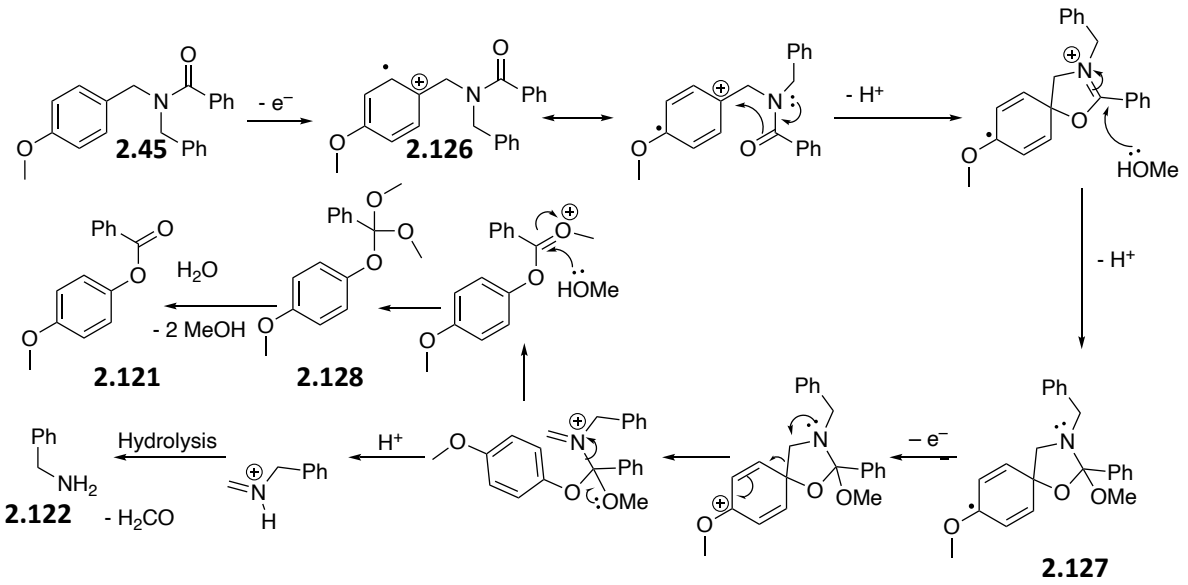


Entry	Reaction scheme	Yield[a] A/%	Yield[a] B/%
4	 **2.47** **2.121** **2.124**	55	–
5	 **2.24** **2.121** **2.125**	20	-

a. Isolated yield

Table 2.18 Substrate scope for oxidative deamidation reaction

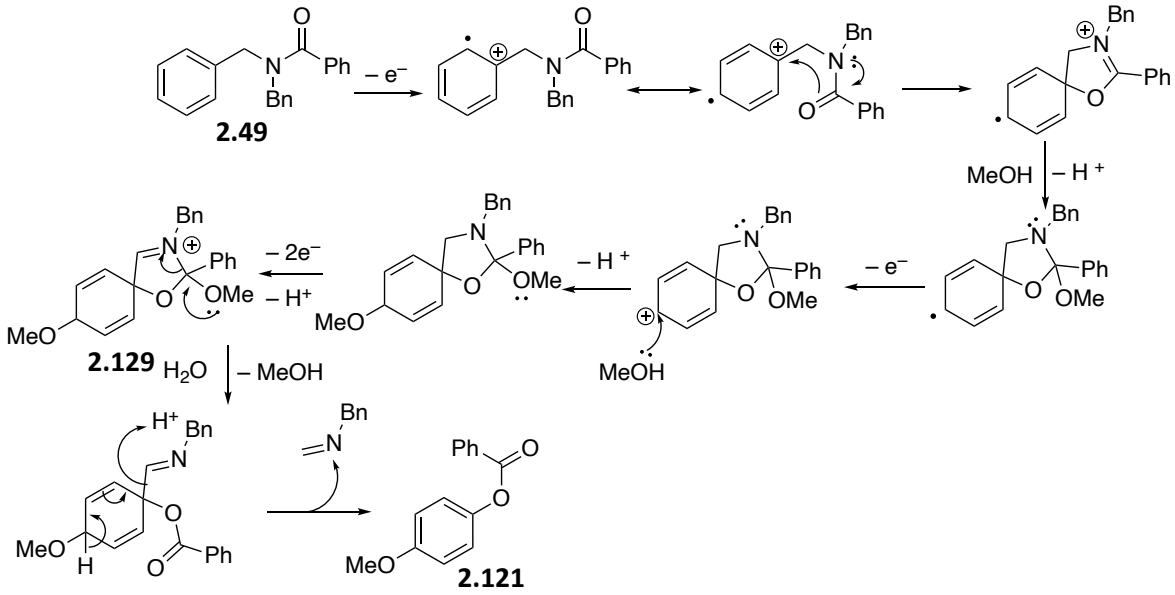
N-Benzyl-*N*-(4-methoxybenzyl)benzamide **2.45** was originally trialled to investigate whether the PMB group could be selectively deprotected with another oxidatively active benzyl group present in the substrate; formation of the PMB ester was not anticipated. Subsequent reactions were conducted to probe which ring system was being cleaved in the reaction, replacing one phenyl group in the substrate with a fluorinated aromatic marker. Interestingly, reaction of **2.49** (entry 2) also led to the PMP ester **2.121**, despite the notable absence of the PMB ring system in the starting material. This implies functionalisation of the aromatic ring occurred in the electrolysis. A mechanism for the electrolysis of **2.45** is proposed (Scheme 2.39), which is consistent with the results obtained.



Scheme 2.39: Proposed mechanism for electrochemical oxidative deamidation

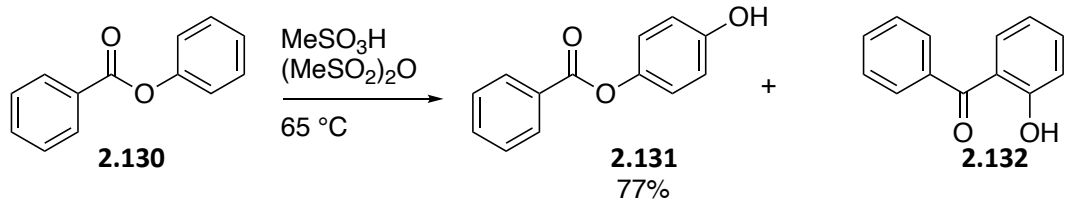
Oxidation of the electron-rich ring occurs initially (on the electron-rich aromatic owing to the lower oxidation potential) but contrary to the electrolysis of secondary PMB amide **2.22** (illustrated in Scheme 2.37) of losing a proton from the benzylic position to stabilise the radical cation (**2.126**), cyclisation of the amide carbonyl occurs onto the *ipso*-carbon centre of the activated aryl ring. The resulting oxazoline cation radical is charged and therefore unstable, undergoing further oxidation and solvolytic trapping to give **2.127**. From this point, the proposed pathway is a bit more speculative, including a Grob-like fragmentation driven by aromatisation and, finally, hydrolysis of the acyliminium affording the observed PMP ester **2.121**. It is believed that adventitious water present in the solvent was responsible for the formation of the ester instead of the orthoester **2.128**, as the MeOH was not dried prior to use.

Electrolysis of N,N-Dibenzyl benzamide **2.49** afforded the PMP ester **2.121** in 30% yield at about 35% conversion (crude ^{1}H NMR), which was surprising on first inspection (entry 2, Table 2.18). However, formation of the PMP ester may be explained by the mechanism proposed in Scheme 2.40.



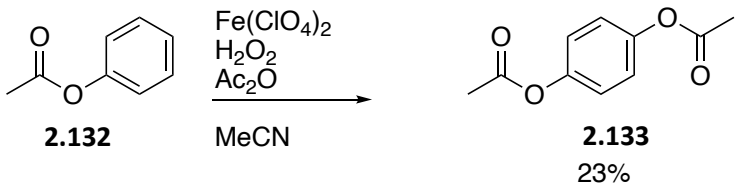
Scheme 2.40: Proposed mechanism for electrolysis of *N,N*-dibenzylbenzamide to give PMP benzoate (2.121).

It is proposed that *N,N*-Dibenzyl benzamide undergoes a four electron oxidation, commencing with conversion to the aryl ester **2.129** following the mechanism proposed above (see Scheme 2.39). The theoretical current required for full conversion is 160 mA, however only 95 mA was passed because the second oxidation was unexpected. The higher oxidation potential of dibenzyl benzamide **2.49**, which occurs close to the solvent oxidation potential, was consistent with the low conversion observed. Thus the formation of the methoxylated aryl ester and the lower conversion of the benzamide **2.49** can be accounted for. Jeon *et al.* observed that oxidative functionalisation (hydroxylation) of aryl esters is possible by Fries rearrangement (Scheme 2.41).[229]



Scheme 2.41: Oxidative oxidation of aryl esters by Fries rearrangement

Substitution was observed exclusively at the *para* position in the work of Jeon *et al.*, and the same was true in the electrolysis of **2.49**, with no evidence of *ortho* or *meta* methoxylation. Indeed, there is further literature precedence (from the work of Kotani *et al.*) that oxidative substitution occurs at the *para* position in aromatic esters (e.g. **2.132**) closely resembling the aryl ester **2.129** (Scheme 2.42).[230]

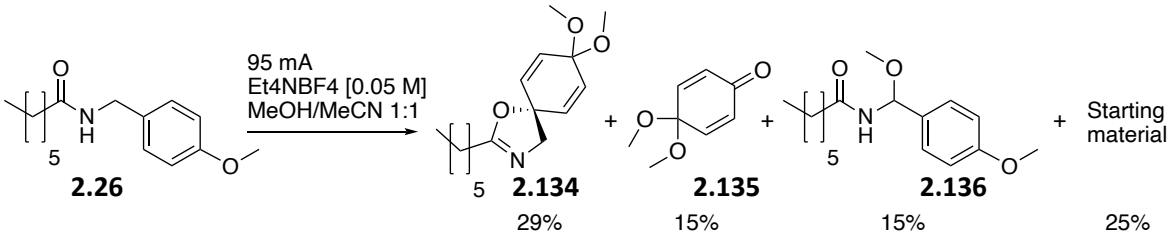


2.132 **2.133**
23%

Scheme 2.42: Oxidative *para* functionalisation of electron-rich aromatics by Kotani *et al.*

2.10 Electrolysis of secondary PMB aliphatic amides: unexpected conversion to spiro-oxazolines

As part of the investigation into substrate scope for electrolysis of PMB amides, secondary aliphatic amide **2.26** was subjected to the optimised PMB oxidation conditions (Scheme 2.43). In this substrate an unusual oxidative cyclisation occurred to form the spirocyclic oxazoline **2.134** in 29% yield, with accompanying dearomatisation of the aryl ring. Quinone mono-acetal **2.135** was obtained (15% yield), methoxylated hemiaminal ether **2.136** (15%, not isolated pure) and starting material (25%) were also recovered, accounting for the majority of the mass balance. The relatively low yield reflects in the loss of material during purification (**2.134** degraded during each column purification), with around 45% yield possible.

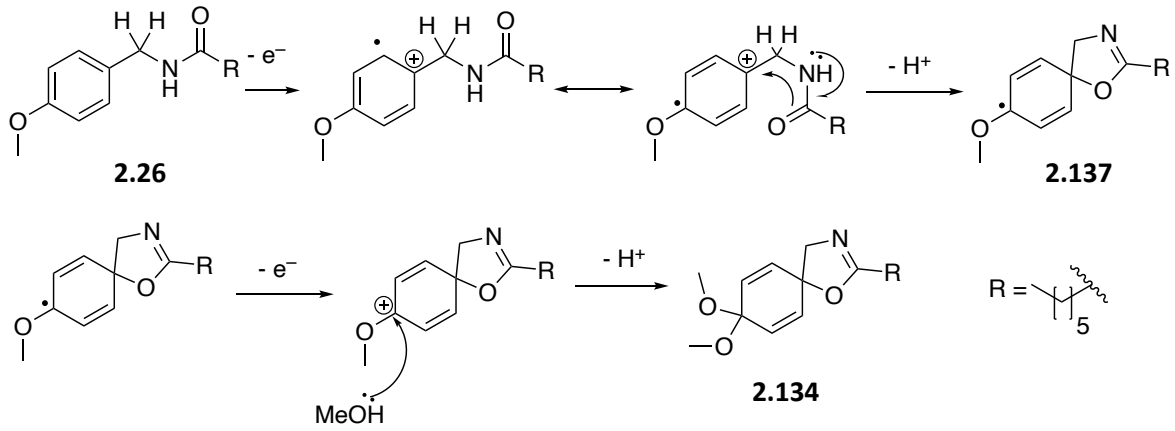


2.26 **2.134** **2.135** **2.136**
29% 15% 15% 25%

Scheme 2.43: Oxidative cyclisation of *N*-(4-Methoxybenzyl)heptanamide, 2.26

Poor solubility of the product in methanol led to precipitation within the reactor, leading to reactor fouling. Consequently a 1:1 co-solvent mixture of acetonitrile and methanol was used, which circumvented the problem. The acetal **2.134** was unstable and some material decomposed during flash chromatography.

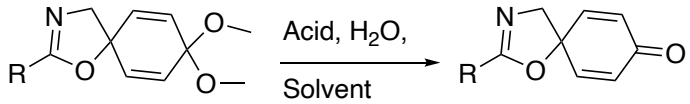
A proposed mechanism is illustrated in Scheme 2.44



Scheme 2.44: Proposed mechanism for electrochemical dearomatisation of aliphatic PMB-amides

The mechanism proposes that the molecule reacts in the same way initially described as for tertiary amide **2.45**, through a radical cation intermediate, followed by intramolecular attack by the amide moiety, then loss of a proton to form radicalised spirocentre **2.137**. Following the loss of a second electron the carbocation is trapped by methanol to afford the spirocyclic acetal.

The hydrolysis of acetals **2.134 and 2.135** was explored in an effort to isolate the corresponding dienones. Conditions (Table 2.19) mimicked those of the acetal hydrolysis to dienone transformation implemented on similar substrates as reported in literature.[231-233]



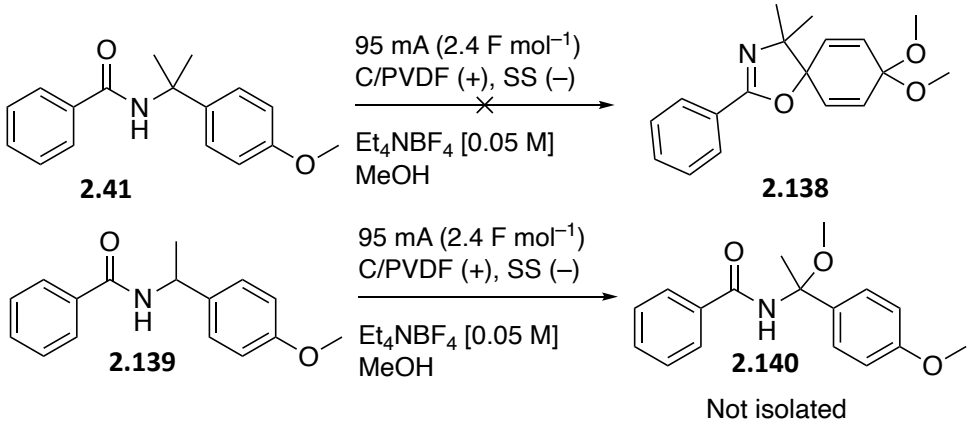
Entry	R	Compound no.		Acid	Solvent	Reaction outcome
		SM	Product			
1	Me	**2.135**	**2.136**	NH_4Cl	EtOAc	No reaction
2	Me	**2.135**	**2.136**	SiO_2	$CHCl_3$	SM and by-products, no **2.136**
3	n(C_6H_{13})	**2.134**	**2.137**	AcOH	Acetone	SM and side-products, no **2.136**
4	n(C_6H_{13})	**2.134**	**2.137**	HCl	Acetone	Decomposition to side-products, no SM

Table 2.19: Acid conditions tested for acetal deprotection

Unfortunately, it was not possible to achieve clean conversion to the corresponding dienones **2.136** or **2.137**, with either no reaction, incomplete reaction with no product formed, or decomposition to a range of unidentified products.

Two benzamide substrates **2.41** and **2.139** were proposed in an attempt to increase the scope of the spirocyclisation reaction (Scheme 2.45), introducing methyl groups to block oxidation

of the benzylic position and to favour cyclisation. Unfortunately, no reaction was observed for the dimethyl PMB derivative **2.41**, and methoxylation of the benzylic position the main reaction occurring in the mono-methyl compound **2.139**. This might be explained by the different electronic character of these substrates compared to aliphatic amides.

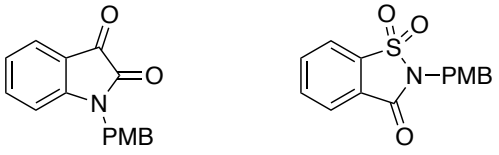


Scheme 2.45: Unsuccessful spirocyclisation substrates

2.10.1 Unsuccessful substrates

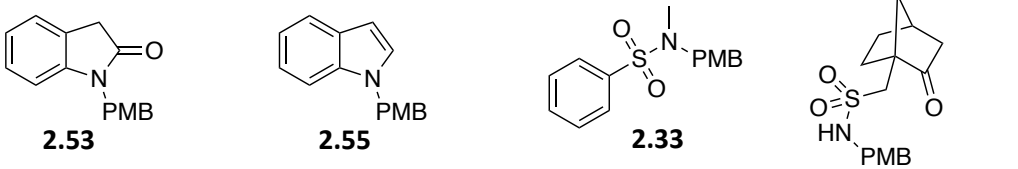
There are limitations in terms of substrate scope for PMB deprotection in nitrogen-containing compounds, examples of which feature in this work (Figure 2.8). We have already seen in sections 2.9 and 2.10 some examples of other reaction pathways for substrates containing the PMB group under electrolysis on MeOH (Figure 2.8).

Poor solubility:

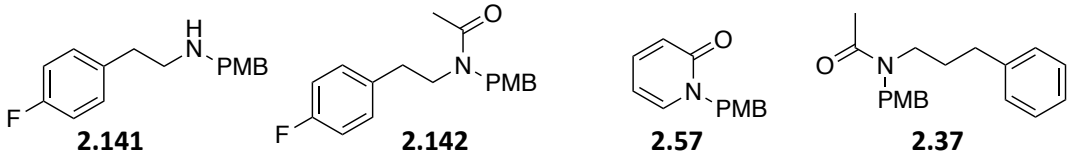


2.52 **2.59**

Poor selectivity:

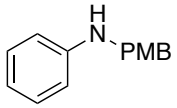


2.53 **2.55** **2.33** **2.34**



2.141 **2.142** **2.57** **2.37**

Electrode passivation:



2.143

Figure 2.8: Substrates that failed to undergo anodic PMB deprotection in this work

PMB-protected isatin **2.52** and saccharin **2.59** were insoluble in solvent mixtures such as MeOH, MeCN/MeOH (1:1–9:1), MeCN/H_2O (9:1), THF/MeOH (1:1), even at low concentration (0.05 M). The issue could be solved by utilising an ether solvent for electrolysis, although these are electroactive themselves.

Substrates **2.53, 2.55, 2.33, 2.34, 2.141, 2.142, 2.57** and **2.37** displayed poor selectivity: oxidation occurred at multiple positions on the compound, evidenced by ^{1}H NMR and LCMS (multiple compounds present in the crude mixture). Electrolysis of indoles **2.53** and **2.55** led to oxidation of the electron-rich heterocyclic systems. In tertiary sulfonamide **2.33**, oxidation occurred at the methyl group as well as the PMB group. In secondary sulfonamide **2.34** the products could not be discerned but there were multiple, as well as significant starting material remaining. In 2.141 and 2.142 oxidation occurred at the benzylic position of the fluorobenzene as well as the PMB group. In pyridone **2.57**, no reaction was observed with quantitative recovery of starting material. In all cases at least some starting material remained, which is to be expected as where multiple oxidations occur on the same compound there will be insufficient electrons available to convert all the initial material. It was later proposed that for the amine substrates 2.141 and 2.143, addition of an acid in order to protonate the molecule might lead to a better reaction outcome, as protonation of the basic centre means it is not liable to oxidation at this position, and could thereby circumvent formation of byproducts that arise through this intermediate.

When aniline **2.143** was exposed to the reaction conditions, passivation of the anode occurred. This is likely due to facile oxidation of aniline and its substituted derivatives.

2.11 TMS-methylene as electroauxiliary: addressing selectivity issues in PMB-protected compounds

2.11.1 Introduction

The utilisation of the TMS-methylene moiety in conjunction with this was proposed in order to lower the oxidation potential in substrates of interest. In this respect, the TMS- methylene moiety would act as an electroauxilliary, giving regioselectivity and facilitating anodic deprotection.

Electroauxiliaries have been discussed in section 1.1.3.2: as well as the use of the TMS-methylene group in amides (Scheme 1.7). The PMB group has a relatively low oxidation potential

(around 1.6V vs SCE for the amides discussed in this work, see Figure 2.5). In this respect, the 4-methoxyphenyl (PMP) group is an electroauxiliary of sorts to the alpha position of the amide in a PMB-protected amide (Figure 2.9). By incorporating the TMS group to this position would lower the oxidation potential further and would offer additional selectivity to oxidation.

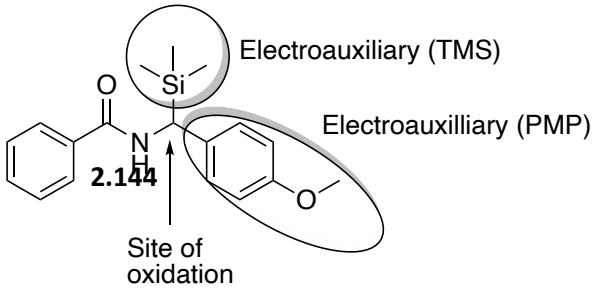
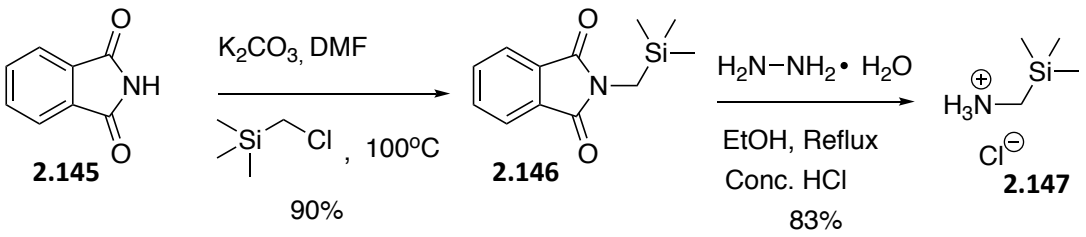


Figure 2.9: Proposed substrate incorporating PMP and TMS electroauxilliaries

The incorporation of the TMS electroauxiliary might offer improved selectivity in substrates where PMB deprotection was unsuccessful (see substrates in Figure 2.8). It is expected that introducing a TMS group at the alpha position would lead to the same electrochemical product as with the PMB group but the oxidation of the alpha position would be less than that where only the TMS or PMB electroauxiliaries were present. In order to trial this, a synthetic strategy for TMS-CH_2 protected amides was developed.

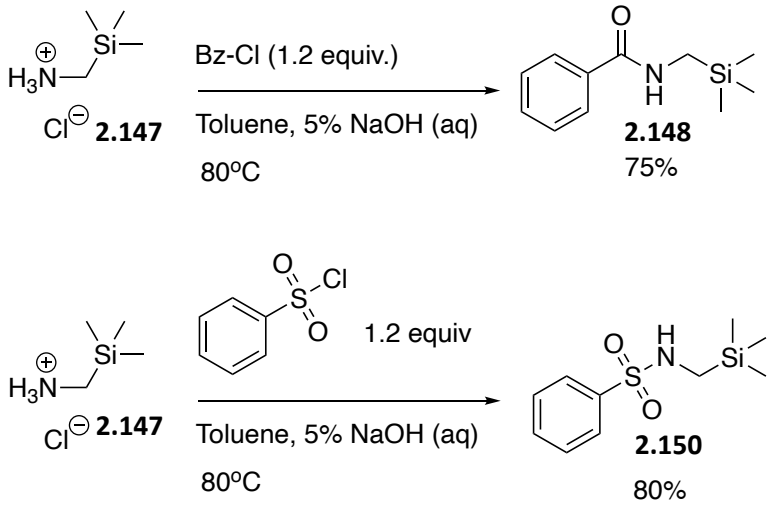
2.11.2 Synthesis of *N*-Trimethylsilylmethyl amides

N-Trimethylsilymethyl amides may be synthesised from the corresponding acid chlorides under Schotten–Baumann conditions. However, *N*-trimethylsilymethylamine (or its HCl salt, **2.147**) are not commercially available and so required synthesis following a literature Gabriel synthesis (Scheme 2.46).[234]



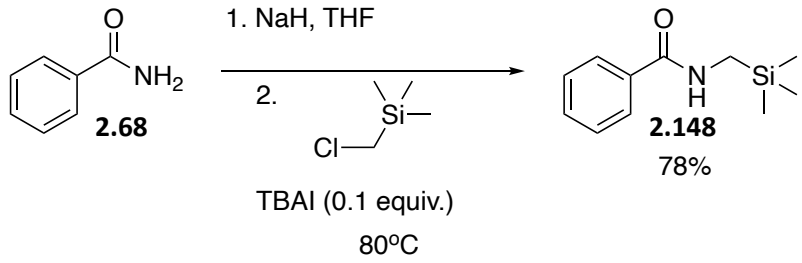
Scheme 2.46: Preparation of (trimethylsilyl)methanamine hydrochloride

Alkylation to the tertiary isoindolinone **2.146** and subsequent unmasking to the primary ammonium salt **2.147** occurred in good to excellent yields (90 and 83% respectively), and a 5 g supply of the latter was made using this procedure. Subsequent amide and sulfonamide coupling reactions were conducted under Schotten-Baumann conditions, giving the *N*-silylmethyl derivatives **2.148** and **2.149** in 75% and 80% yields, respectively (Scheme 2.47).



Scheme 2.47: Synthesis of *N*-((Trimethylsilyl)methyl)benzamide and *N*-((Trimethylsilyl)methyl)benzenesulfonamide under Schotten-Baumann conditions

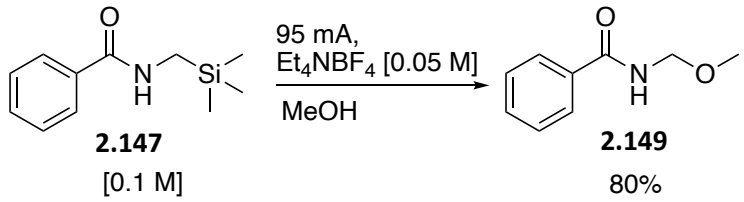
As an alternative procedure (where Schotten-Baumann conditions might be unsuitable), the *N*-TMS methyl benzamide **2.148** could also be synthesised by alkylation benzamide **2.68** in 78% yield (Scheme 2.48).



Scheme 2.48: Synthesis of *N*-((Trimethylsilyl)methyl)benzamide by alkylation of benzamide

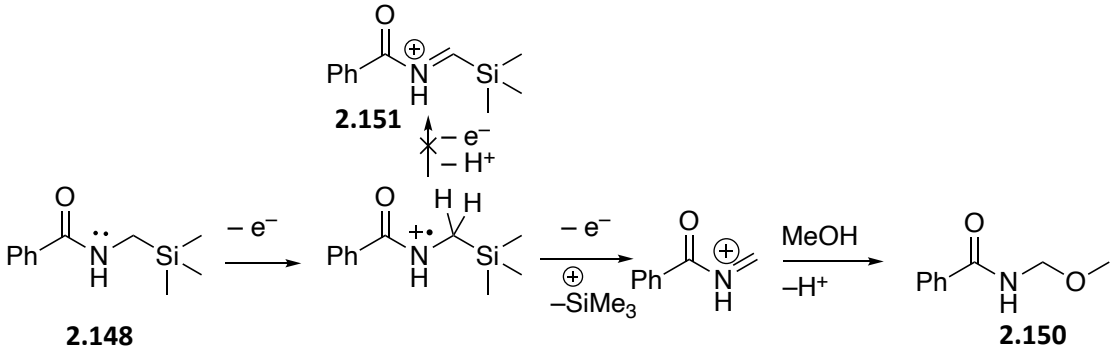
2.11.3 Anodic oxidation of *N*-((Trimethylsilyl)methyl)benzamide

Oxidative methoxylation of the *N*-TMS-CH_2 protected amide **2.148** (Scheme 2.49) proceeded under the optimised conditions for anodic PMB oxidation of amides (found in Scheme 2.11).



Scheme 2.49: Oxidative methoxylation of N-((Trimethylsilyl)methyl)benzamide

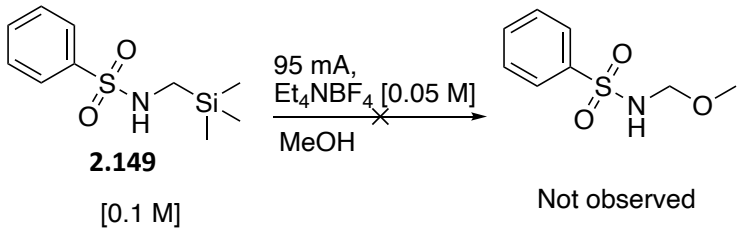
Anodic oxidation of the *N*-TMS-CH_2 protected amide **2.148** afforded the MOM ether **2.150** in 80% yield after removal of electrolyte by solvent swap. A mechanism for the reaction is proposed (Scheme 2.50).



Scheme 2.50: Proposed mechanism for methoxylation of *N*-((Trimethylsilyl)methyl)benzamide

Because of the reaction outcome, it can be deduced that the reaction does not proceed via a methoxylated TMS intermediate **2.151**, i.e. the TMS group is cleaved instead of loss of a proton as per the Shono oxidation.[51] This is because a second oxidation would need to occur, making the overall oxidation a 4-electron process. This does not correlate with the full conversion observed, as a maximum of 60% conversion would be possible based on 95 mA (2.4 F mol^{-1}) of applied current.

The reaction of the TMS-CH_2 protected sulfonamide **2.149** did not lead to the expected MOM ether (Scheme 2.51). This could be due to multiple chemical pathways occurring after the electrochemical oxidation.



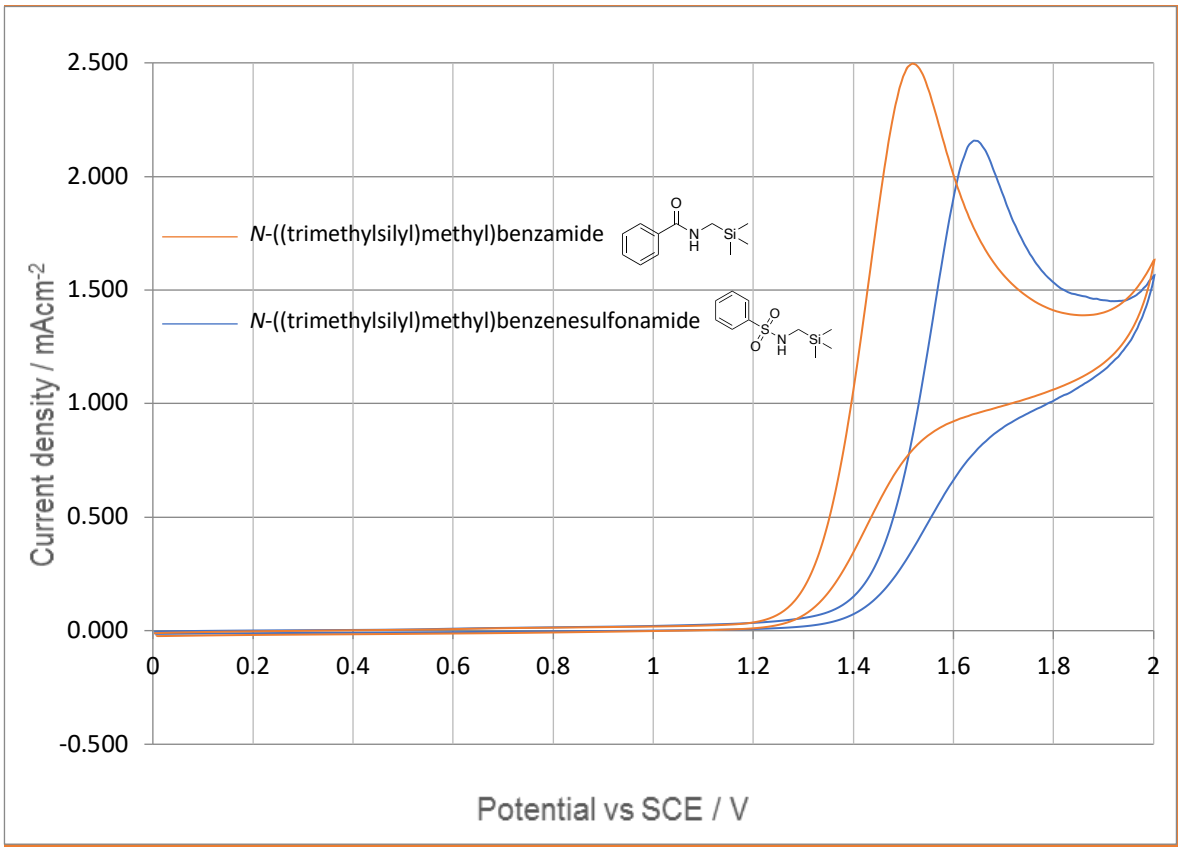
Scheme 2.51: Unsuccessful oxidation of TMS-CH_2 protected sulfonamide 2.149

Subjecting sulfonamide **2.149** to the reaction conditions illustrated led to the formation of several methoxylated compounds and so was not pursued further. Selectivity for the CH_2 position appeared poor.

2.11.4 Cyclic voltammetry of TMS-CH_2 substrates

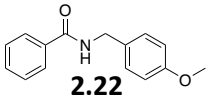
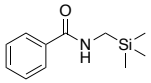
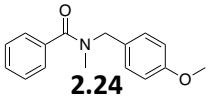
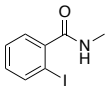
CV of two TMS-CH_2 substrates (**2.148** and **2.149**) synthesised in this work were conducted, to assist in understanding the electrochemical oxidation process in these compounds and therefore the reaction outcome in the Ammonite 8 reactor.

Figure 2.10: Cyclic voltammetry of TMS-CH_2 protected amide 2.148 and sulfonamide 2.149 (10 mM), Et_4NBF_4 (100 mM) in MeOH (25 mL), 25 mV/s, RT



Setup for the CV is illustrated in Chapter 1. Conditions are as follows: substrate [0.01 M], Et_4NBF_4 [0.1 M], MeOH (25 mL), rt, range 0 to 2.0 V, other experiments conducted), scan rate 25 mV s^{-1}, 100 mV s^{-1} also conducted). By the methods discussed in 2.8.2 it was deduced that within the timescale of the CV study (controlled by the scan rate), the oxidation processes seen in the spectra are irreversible, and that the electron transfer occurs under mass transfer conditions. The product of the electrochemical processes appears to be stable, at least oxidatively owing to an absence of further oxidative processes (prior to solvent oxidation at 2.0 V).

The oxidation potential for *N*-((Trimethylsilyl)methyl)benzamide (**2.149**), at 1.5 V, is lower than many other amide systems as recorded in this work and reported in literature. Some of these are illustrated in Table 2.20.

Entry no.	Structure	Oxidation potential/s[a] (V)	Reference
1	 **2.22**	1.6	n/a (this work)
2	 **2.148**	1.4	n/a (this work)
3	 **2.24**	1.6, 1. 8	n/a (this work)
4	 **2.152**	1.89	[215]
5	 **2.153**	2.2[b]	[235]

a. Vs SCE
b. Vs Ag/AgCl, about 1.9 V vs SCE

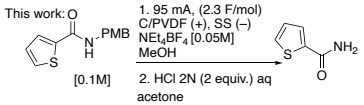
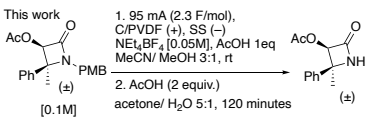
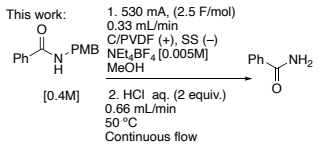
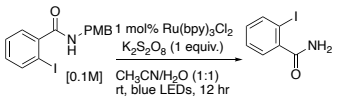
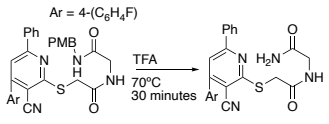
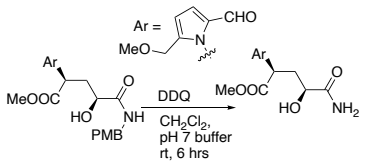
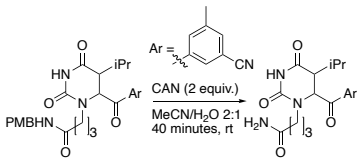
Table 2.20: Oxidation potentials for amides in this work and reported in literature

Observing entries 4 and 5 (amides **2.152** and **2.153**), we have examples of amides where there is little to alter the oxidation potential of the alpha-position carbon i.e. they are not stabilised by an electroauxiliary. As such, their oxidation potentials are relatively high (1.89 vs SCE for **2.152** and 2.2 V vs Ag/AgCl for **2.153**, which would be roughly 1.9 V on SCE). In contrast, PMB-protected amide 2.22 has a potential significantly lower at 1.6 V, and the TMS-CH_2 protected compound lower still at 1.4 V. entry 3 (amide 2**.24**) exhibits two oxidation potentials at 1.6 and 1.8 V, and it would be logical to propose that these correspond to oxidation of the benzylic PMB carbon and the methyl group (1.6 and 1.8 V respectively).

It is clear that the two protecting groups (PMB and TMS-CH_2) act as electroauxiliaries, reducing the oxidation potential in the compounds they feature in compared to other functionality e.g. alkyl chains. It is this reason that combining these electroauxiliaries would likely reduce the oxidation potential in **2.144** (illustrated in Figure 2.9) to less than that of amides **2.22** and **2.148,** i.e. would have a more pronounced effect on the alpha position than one electroauxiliary alone.

2.12 Green metrics of PMB-deprotection process

Electrosynthesis in flow is viewed as a sustainable methodology, although little evidence is typically provided to support this claim. To this end criteria to assess the environmental impact, safety and sustainability of chemical processes was applied to the electrochemical deprotection method reported in this thesis.[163] Full tables of these metrics can be found in Appendix A, with an abbreviated version in Table 2.21 for discussion.

Reaction and conditions	Yield (%)	RME[a] (%)	PMI[b]	PMI[c]	Hazardous/ precious chemicals	Solvent	Ref.
	91●	36.3	3.7	144	-●	MeOH, acetone●	n/a (this work)
	70●	29.7	4.1	109	-●	AcOH, MeCN●	n/a (this work)
	83●	36.1	2.8	44.6	-●	MeOH, H_2O●	n/a (this work)
	90●	34.5	3.2	40.2	Ru● 5-50 years of known reserves[d]	MeCN, H_2O●	199
	52●	2.9	34.8	243	TFA● H412: environmental concerns	TFA●	200
	86●	20.5	4.9	567	DDQ● H301: acute toxicity	CH_2Cl_2●	201
	75 ●	18.5	46.7	41.2	CAN● Ce: 50-500 years of known reserves[d] H410: environmental concerns	MeCN, H_2O●	202

a. RME is Reaction Mass Efficiency (no. moles product/no. moles reagents),
b. PMI is Process Mass Intensity (mass of product/mass of materials). With respect to reactant, reagents, catalysts used
c. PMI with respect to solvents used
d. Based on current rate of extraction[163]

Table 2.21: Comparison of green metrics for amide PMB deprotections

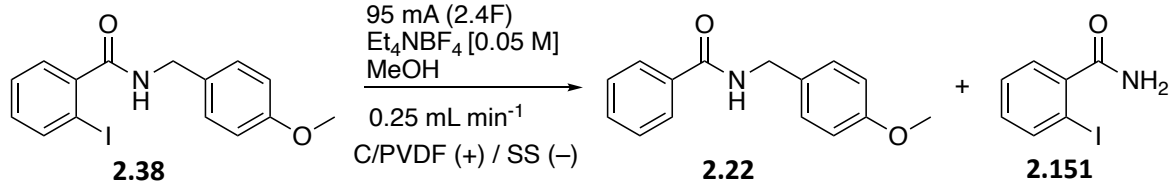
For a process to score highly on green metrics, it should be high-yielding, with a high reaction mass efficiency (RME), low process mass intensity (PMI), ideally use no materials deemed to be hazardous or precious, and use solvents that are considered preferable. The atom economy for any deprotection is inherently low because a group is being removed, and so this is not considered an important metric for the PMB deprotection process.

The RME for entries 1-3 (the processes carried out in this work) compares favourably to those of entries 4-7, owing to their reagentless nature. Electrosynthesis enables "reagentless" redox transformations, whereas traditional chemical reactions using reagents inherently reduces the RME because the reagents do not contribute to the mass of the product. Supporting electrolyte is recovered, and it is not considered here as a reagent and hence does not contribute to the RME. Similarly the PMI for the reaction is favourable in anodic PMB deprotection, although the two-step oxidation-hydrolysis using two different solvents, and an extractive workup, leads to a high solvent PMI. It does still compare well to many other processes, and in fact can be improved by increasing the concentration of substrate in the reaction solution, although a small decrease in yield was seen. The two-step electrolysis under continuous flow (entry 3) has a lower PMI, even with the low mw of the product, and this is because of removing the need for additional solvent for the acid step. A significant benefit for the electrochemical processes in this work is that no hazardous reagents are used, along with highly–rated solvents for entries 1 (the method used for the majority of substrates in this work) and 3, and acceptable solvents for entry 2 (used for the deprotection of complex β-lactams). Although the electrodes are not consumed in the electrosynthetic procedures, being able to conduct the electrolysis process using C/PVDF electrodes rather than more costly Pt for example is a significant benefit.

2.13 Anodic PMB deprotection in a divided flow cell

2.13.1 Initial studies on 2-Iodo-*N*-(4-methoxybenzyl)benzamide

Whilst investigating substrate scope for the anodic PMB deprotection of amides (see Scheme 2.31), the following reaction occurred in the Ammonite 8 reactor with 2-Iodo-*N*-(4-methoxybenzyl)benzamide, **2.38** (Scheme 2.52).

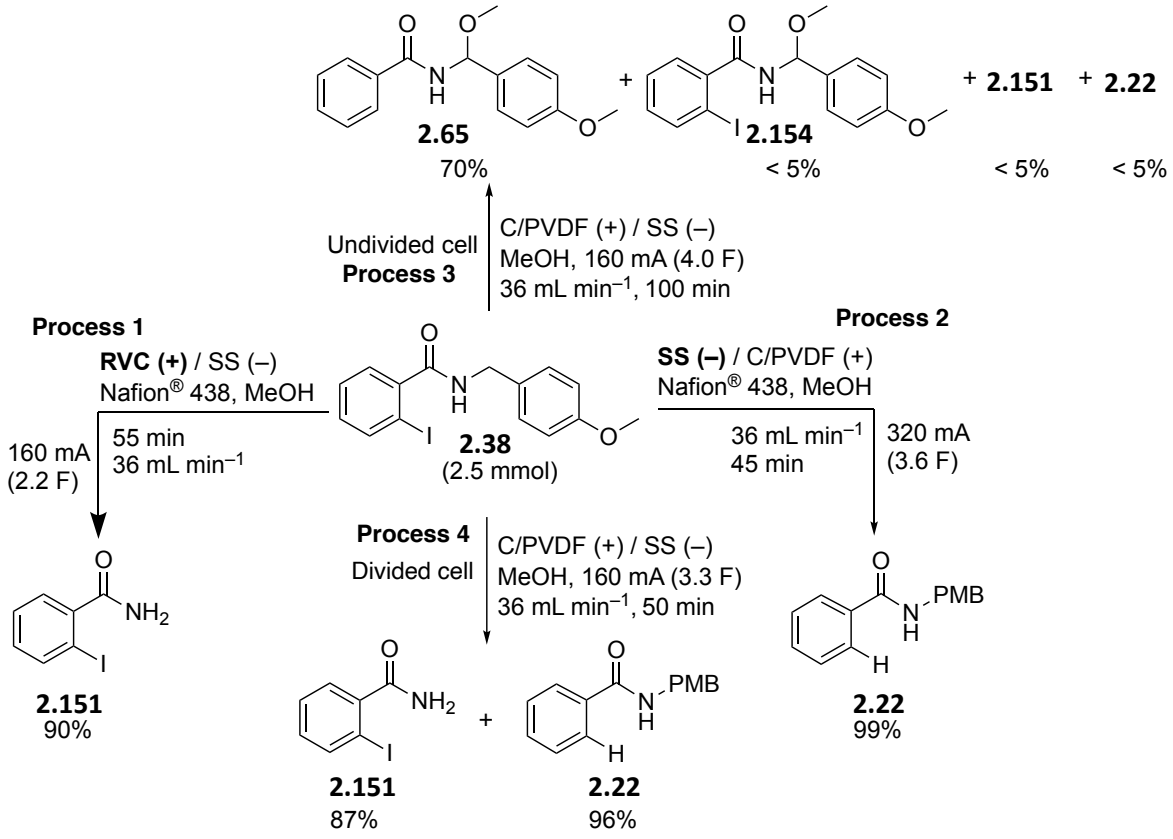


2.38 [0.1 M] **2.22** 44% + **2.151** 45%

Scheme 2.52: Electrolysis of 2.38 in the Ammonite 8 reactor

Instead of oxidation of the benzylic position of the PMB amide accompanied by reduction of solvent at the anode, the iodobenzamide underwent reactions at both electrodes, whereby the PMB group was oxidatively removed and the carbon-iodine bond was reductively cleaved. The latter process meant that the usual counter-electrode reaction for PMB oxidation in MeOH (formation of H_2 and methoxide) did not occur. The cathodic reduction of MeOH provides electrogenerated base (methoxide), which mops up protons formed at the anode. Clearly, iodide anion is a far weaker base than methoxide, and therefore the reaction solution became acidic (pH 2) during the electrosynthesis, accounting for hydrolysis of the hemiaminal ether intermediate leading directly to the deprotected benzamide **2.151**.

A series of follow-up experiments were outlined, including identifying the mechanism and harnessing the reductive reaction to carry out more useful transformations. Initially, a series of experiments were conducted on the iodinated PMB-protected amide **2.38** in the parallel late recycle cell (Scheme 2.53), in divided and undivided mode. These included anodic PMB deprotection (process 1), cathodic proto-dehalogenation (process 2), a convergent paired electrosynthesis featuring PMB oxidation and dehalogenation (process 3), and a divergent paired electrosynthesis (process 4).



Scheme 2.53: Electrosynthesis reactions conducted on 2-Iodo-*N*-(4-methoxybenzyl)benzamide in parallel plate recycle cell

The transformations illustrated are possible because amide **2.38** is electroactive at the anode and cathode. The convergent electrosynthesis in undivided setup (process 3, Scheme 2.53) afforded methoxylated dehalogenated product **2.65** in 70% yield, with traces of the iodinated methoxylated intermediate **2.154**, iodobenzamide **2.151** and dehalogenated PMB amide **2.22** also present. The major product **2.65** results from cathodic C—I bond cleavage and anodic methoxylation α to the nitrogen. This is in distinct contrast to the reaction illustrated in Scheme 2.52, whereby two different products formed in the Ammonite 8, an undivided reactor. In undivided setup one might expect the two reactors to produce the same product, and so this is an interesting example that demonstrates that not all electrochemical reactors are the same; they can be used to make different products under similar reaction conditions, owing to their design and the method by which the substrate is passed through the reactor. Subsequent cleavage of the hemiaminal ether **2.65** to give the deprotected benzamide **2.68** required an acid treatment step (conditions illustrated following the electrolysis as is consistent with this work (entry 7, Table 2.8), as without a separator cathodic processes maintain neutrality of the reaction solution).

Selective oxidative cleavage of the N-PMB group was achieved by introducing a Nafion® 438 membrane between anolyte and catholyte chambers. The deprotected 2-Iodobenzamide **2.151** was obtained with a fractional conversion of 66% after 90 min (2.5 mmol scale) using a flat C/PVDF electrode at 160 mA, with full consumption of **2.151** after 165 min, with 90% isolated yield and 27% current efficiency. In this divided mode the anolyte becomes acidic so that the hemiaminal ether cleavage occurs in situ within the cell giving **2.151** directly. Figure 2.11 illustrates the reaction progress over time as monitored by ^{1}H NMR spectroscopy.

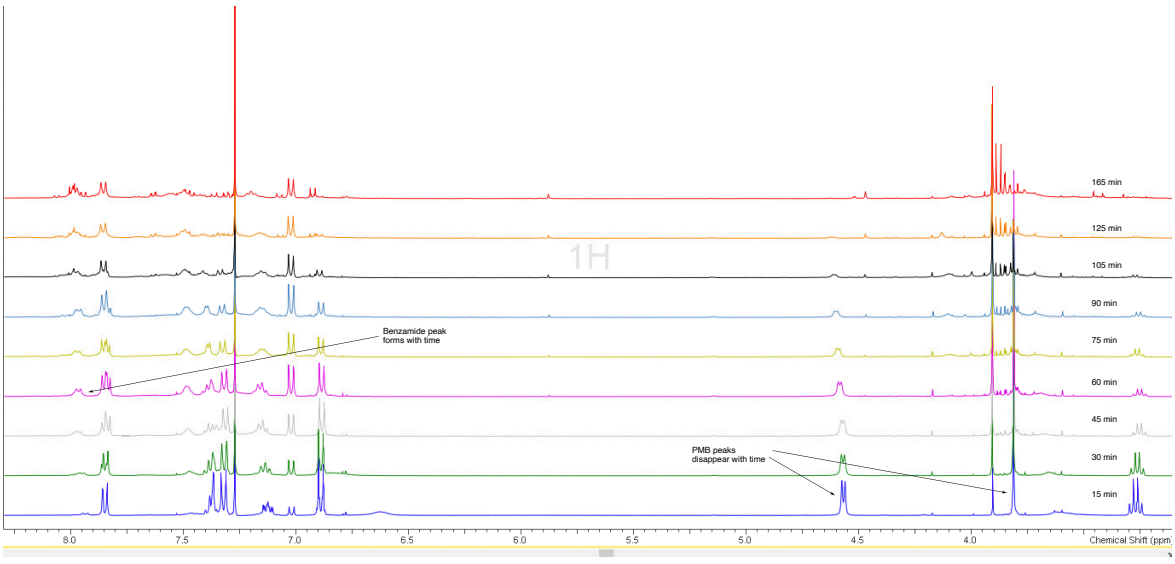


Figure 2.11: PMB deprotection of 2.38 analysed over time

A substantial improvement in the efficiency of the anodic process was obtained using a three dimensional RVC electrode (process 1, Scheme 2.53), delivering full conversion in 55 min, with 90% isolated yield and an 82% current efficiency, a vast improvement to the flat plate electrode. Figure 2.12 illustrates the difference in conversion over time for the C/PVDF and the RVC anodes.

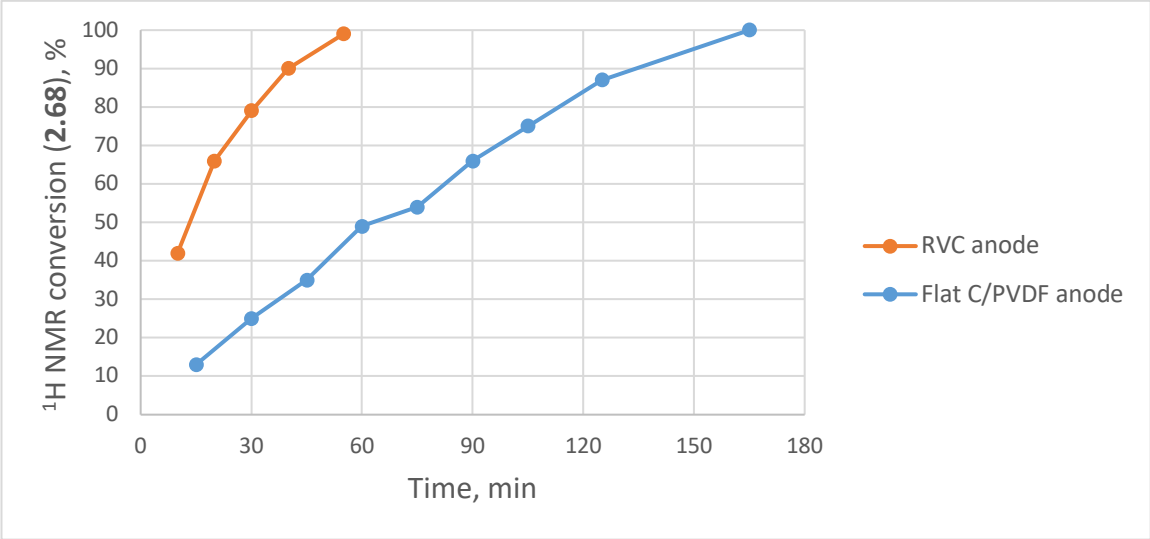


Figure 2.12: Difference in conversion over time for the PMB deprotection of 2.38 on C/PVDF vs. RVC anode

It was also possible to reduce the aryl iodide **2.38** selectively in the divided cell (process 2, Scheme 2.53). The dehalogenated product **2.22** was obtained in 99% yield in 45 min by carrying out the electrolysis on a stainless steel cathode at 320 mA. In the cathodic reaction, full conversion was achieved at a faster rate, but using more current than the anodic deprotection (55% current efficiency). Reduction of the substrate competes with that of methanol. The electrolyte could be efficiently recovered from both compartments in this reaction, but not from the anodic deprotection, as the generation of acid in the anolyte resulted in ion exchange. The reaction displayed remarkable selectivity, which was evident from the isolation of pure **2.22** without purification (except a solvent swap to recover the electrolyte).Figure 2.13 illustrates conversion of the dehalogenated compound **2.22** over time, with Figure 2.14 showing the reaction profile by ^{1}H NMR.

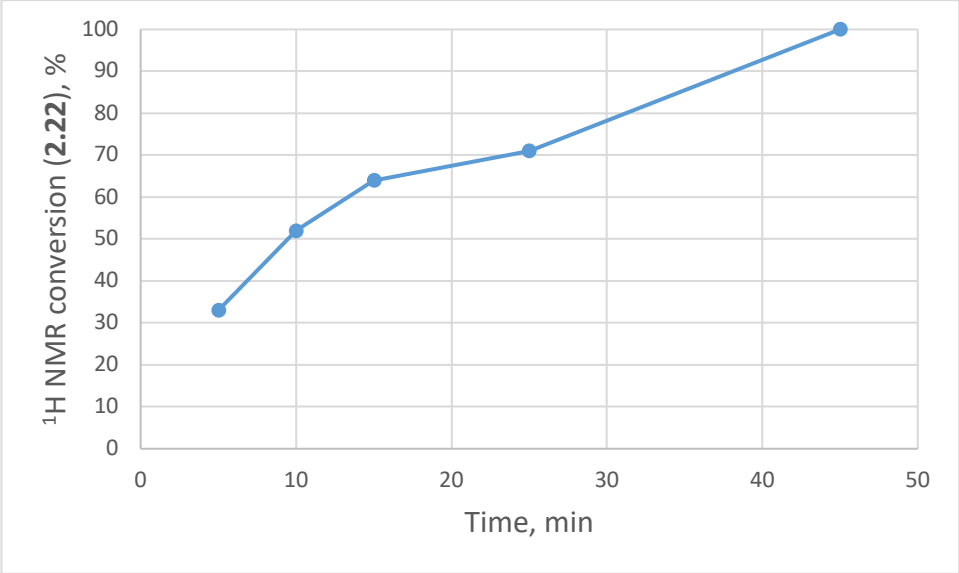


Figure 2.13: Conversion over time for the dehalogenation of 2-Iodo-N-(4-methoxybenzyl)benzamide 2.38 on flat SS cathode

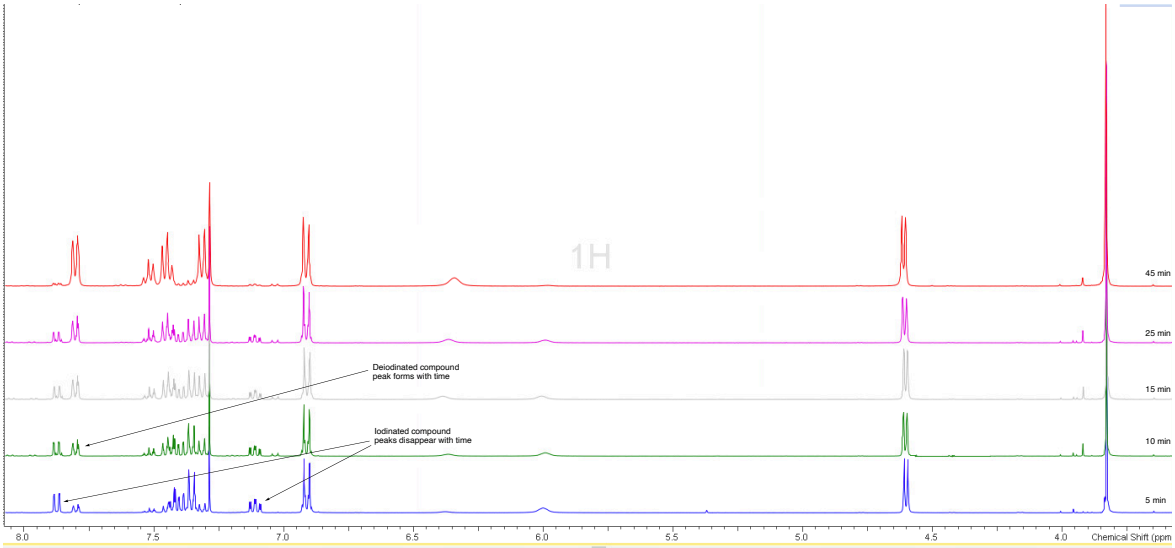
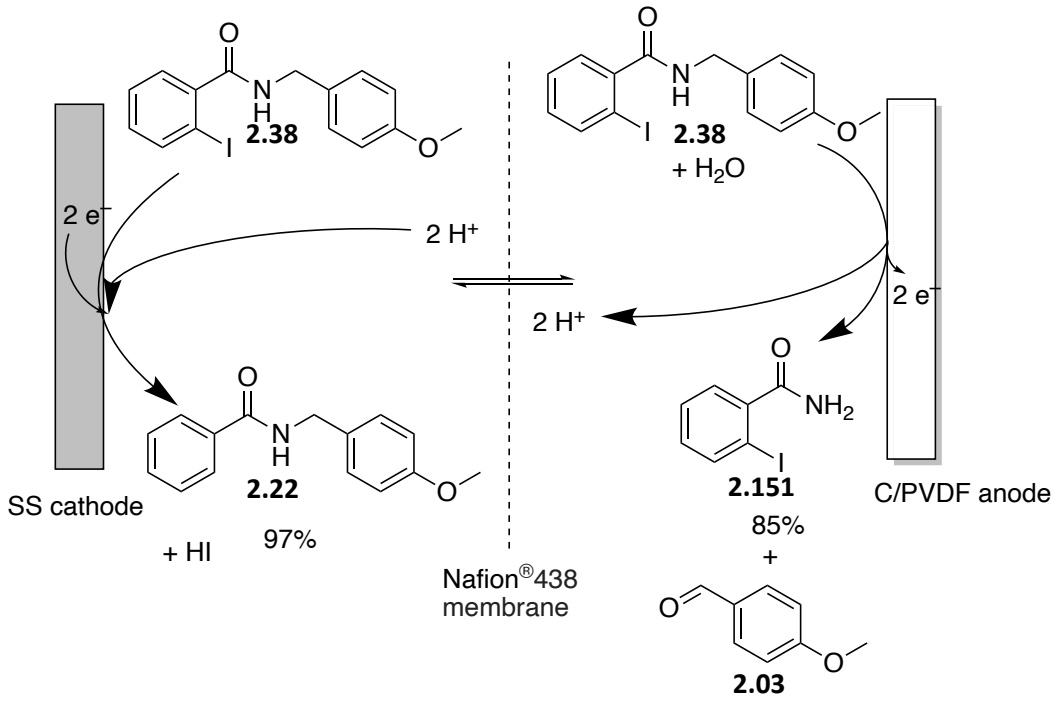


Figure 2.14: Dehalogenation of 2.38 at SS cathode displayed over time

For the divergent paired electrosynthesis of **2.38** (process 4, Scheme 2.53), the products **2.22** and **2.68** were isolated in 87% and 96% yield respectively after 50 minutes. There was no evidence of substrate mixing from the separate reaction chambers, which facilitated the

purification procedure. A scheme for the paired electrosynthesis follows (Scheme 2.54).



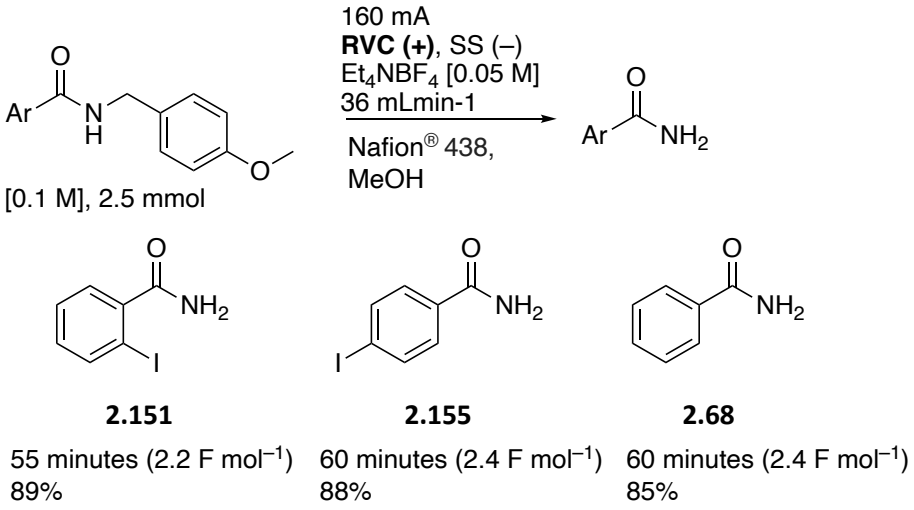
Scheme 2.54: Scheme for paired PMB deprotection/reductive dehalogenation of 2-Iodo-N-(4-methoxybenzyl)benzamide in parallel plate recycle cell

The same concentrations of substrate and electrolyte (0.1 M and 0.05 M respectively) flow rate (36 mL min^{-1}) and current (160 mA) were used as for the undivided electrolysis, with a reaction time of 50 minutes. This corresponded to a transfer of 3.3 F mol^{-1} of charge, or 1.7 equivalents. Protons are formed at the anode and consumed at the cathode, and are allowed to pass between the two chambers due to the permeability of Nafion® 438 to H^+. H_2O is present in the "wet" MeOH solvent, which allows the formation of aldehyde **2.03** instead of an acetal. This facilitates the purification since it can be removed by bisulfite wash as described in Scheme 2.12.

2.13.2 Substrate scope

2.13.2.1 Oxidative PMB deprotection

With a successful, robust process in place the conditions for PMB deprotection in the divided cell was applied to other substrates (Scheme 2.55).

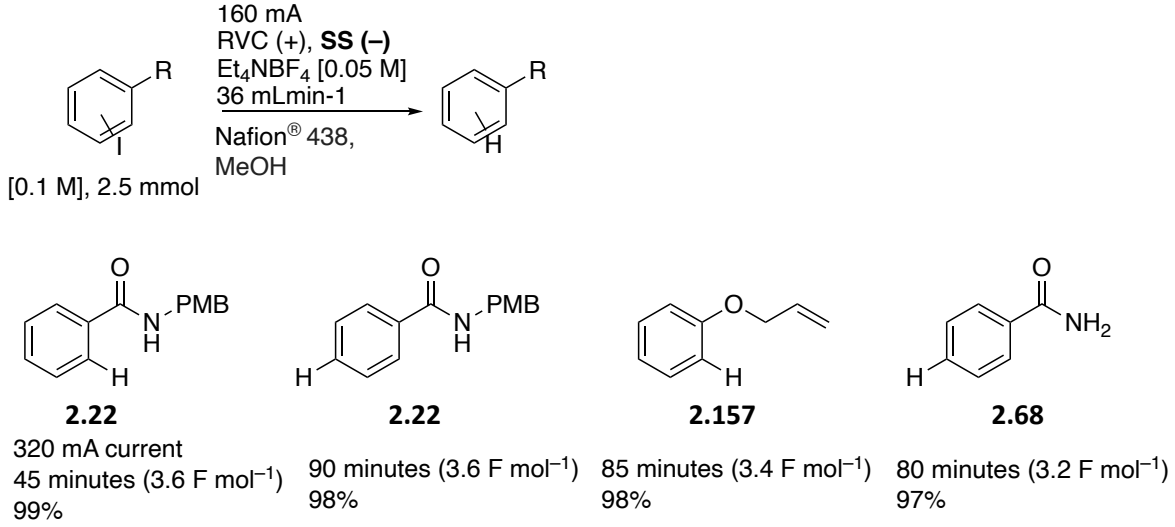


Scheme 2.55: Successful substrates in divided cell PMB deprotection

Using the conditions illustrated in Scheme 2.55, the deprotected amides **2.68**, **2.151** and **2.155** were afforded from their corresponding protected amides (**2.22**, **2.38** and **2.39** respectively) in good yields (85 to 89%) at productivities of up to 2.43 mmol hr^{-1} and current efficiencies of up to 81%.

2.13.2.2 Reductive dehalogenation

The conditions for cathodic proto-dehalogenation of **2.38** (process 2, Scheme 2.53) were applied to further iodinated substrates **2.39**, **2.156** and **2.68** (Scheme 2.56).

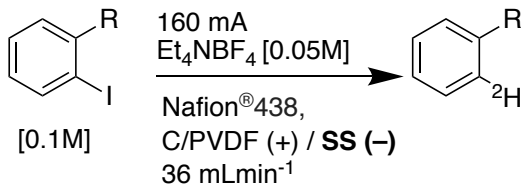


Scheme 2.56: Successful substrates in divided-cell reductive dehalogenation

Using the conditions illustrated in Scheme 2.56, the dehalogenated compounds **2.22** (twice), **2.157** and **2.68** were afforded from their corresponding iodoarenes (**2.38**, **2.39**, **2.156** and **2.68** respectively) in excellent yields (97 to 99%) at productivities of up to 1.82 mmol hr^{-1} and current efficiencies of up to 61%.

2.13.2.3 Deuterium labelling

In specific scenarios, it is necessary to proto-dehalogenate an aryl ring, for example where the halogen is providing a specific electronic effect on the molecule that is improving the yield of another synthetic transformation. However, such examples are relatively uncommon and so in order to increase the synthetic utility of the reductive dehalogenation reaction, a method deuterium label at the previously halogenated position was investigated (Table 2.22).



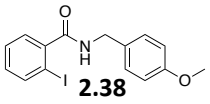
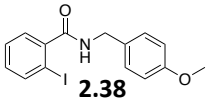
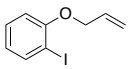
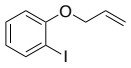
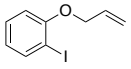
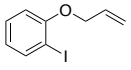
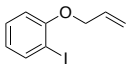
Entry	SM	Solvent	Conversion /%	^{2}H to ^{1}H product ratio
1	 **2.38**	MeCN/MeOH–d_4 95:5	95	10:90
2	 **2.38**	MeCN/D_2O 90:10	90	40:60
3	 **2.156**	MeCN/MeOH–d_4 95:5	100	22:71
4	 **2.156**	MeCN/D_2O 95:5	95	40:60
5	 **2.156**	MeCN/D_2O 90:10	60	50:50
6	 **2.156**	MeCN (anhydrous) /D_2O 90:10	20	60:40
7	 **2.156**	**CH_3OD**	**70**	**90:10**

Table 2.22: Deuterium labelling experiments in parallel plate reactor

Initial experiments in the pursuit of cathodic deuterio-dehalogenation were unsatisfactory as the degree of enrichment were deemed insufficient. The deuterium labelled compound could not be separated from the proto-dehalogenated product or the starting material in either case owing to their similar polarities. The substrate for dehalogenation was changed from **2.38** (entries 1 and 2) to **2.156** (entries 3-7)**,** based on the concern that the exchangeable proton on the amide nitrogen in **2.38** might interfere with the desired reaction. It is inconclusive as to whether the

substrate change had a significant improvement on deuterium enrichment, as only a modest increase in ^{2}H enrichment was observed for subsequent experiments on this substrate. Entry 7 gave promising ^{2}H enrichment (90:10) in 70% yield, however the use of CH_3OD as a solvent is relatively expensive, albeit significantly cheaper than d_4-MeOH. Attempting to find a more successful method to deuterium label will be the basis of future work.

It is proposed that substitution of the aryl halide with ^{1}H or ^{2}D occurs through a carbanion species following a two-electron reduction, rather than through a radical mechanism. The carbanion can abstract a proton from the deuterated solvent, or MeCN. This is substantiated by comparing entries 1 to 6 with entry 7 in Table 2.22, where the first 6 entries all display relatively low ^{2}D incorporation in the product and all feature MeCN in the reaction solvent. Swapping to a solvent other than MeCN led to vastly improved ^{2}D enrichment (entry 7). Cyclisation was not observed in any of the reactions, also disproving a radical mechanism.

2.14 Conclusions and future work

2.14.1 Conclusions

The anodic deprotection of nitrogen containing compounds has successfully been carried out. The deprotection of the 4-methoxybenzyl group has been extensively studied and can be applied to a range of aromatic and heterocyclic amides, aliphatic lactams and sulfonamides through a two-step process (Scheme 2.31), with recovery and reuse of Et_4NBF_4 electrolyte and simple removal of the aldehyde coproduct through a bisulfite wash. Seventeen substrates have been successfully tested, with yields of up to 91%, current efficiencies of up to 77% and productivities of up to 1.37 mmol hr^{-1} in the Ammonite 8 reactor. The process could be applied on a multigram scale, with the deprotection of two substrates: a secondary amide (**2.22**) and a β-lactam (**2.86**) tested in the Ammonite 15 reactor (Scheme 2.32 and Scheme 2.33). For both of these substrates, yields of 72% and productivities of 43.2 mmol hr^{-1} were achieved. Furthermore the PMB deprotection of **2.22** could be carried out in a continuous flow process (Scheme 2.34) in 83% yield, with a current efficiency of 66% and a productivity of 13.1 mmol hr^{-1}.

The parallel plate reactor was utilised as a divided and undivided cell in order to selectively remove the PMB group in the presence of other electroactive groups (aryl iodide), and carry out convergent electrosynthesis (Scheme 2.53). Using this reactor three substrates were successfully unmasked of their PMB protecting groups (Scheme 2.55), with yields of up to 89%, current efficiencies of up to 81% and productivities of up to 2.43 mmol hr^{-1}, and four substrates were reductively dehalogenated in excellent yields (97 to 99%) at productivities of up to 1.82 mmol hr^{-1} and current efficiencies of up to 61%.

Secondary aliphatic amides protected by the 4-methoxybenzyl group also displayed some interesting electrochemical behaviour, undergoing cyclisation to form spirocyclic oxazolines (section 2.10). Furthermore, tertiary aromatic amides underwent fragmentation to form secondary esters with concomitant loss of the corresponding amine (2.9).

The TMS-CH_2 was briefly explored for use as a protecting group and a method to oxidatively methoxylate in the Ammonite 8 was discovered (Scheme 2.49).

2.14.2 Future work

2.14.2.1 Improving productivity and reliability of continuous flow PMB deprotection

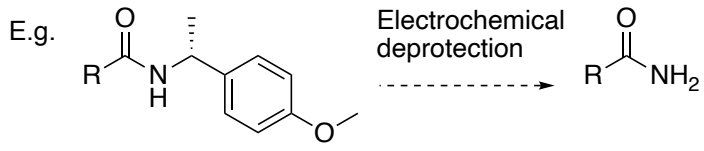
The continuous flow process for the PMB deprotection of nitrogen containing compounds requires further development, in order to improve reliability and also productivity. It is hoped that the productivity of the acid-hydrolysis step can be made as productive as the electrochemical step, which achieved full conversion at a flow rate of 2.5 mL min^{-1} and a substrate concentration of 0.4 M. When these conditions were applied to the acid step, incomplete conversion was observed. In order to improve productivity, a number of suggestions are proposed:

- The use of a back-pressure regulator to increase the enable a higher temperature for the hydrolysis to be possible. Beyond 50 °C, boiling of the co-solvent occurred, propelling the reaction solution through the heating coil, hence significantly lowering the residence time and leading to incomplete reaction. A higher temperature will likely increase reaction rate.
- Modification of the co-solvent and ratio in order to favour acid hydrolysis (being careful to retain efficient electrochemical oxidation in the previous step).
- Increasing the path length of the heating coil, either with larger volume or by numbering up.
- Increasing the concentration of acid, using an alternative acid (e.g. H2SO4) or passing the solution through a solid–supported acidic resin.

2.14.2.2 Chiral PMB protecting group

The use of the m-PMB group has not featured as part of this work, but the electrochemical deprotection method described should be applicable to molecules with this group attached. The facile removal of the m-PMB electrochemically would undoubtedly increase the impact of this work and allow the application of this method in chiral synthesis, which is often essential in

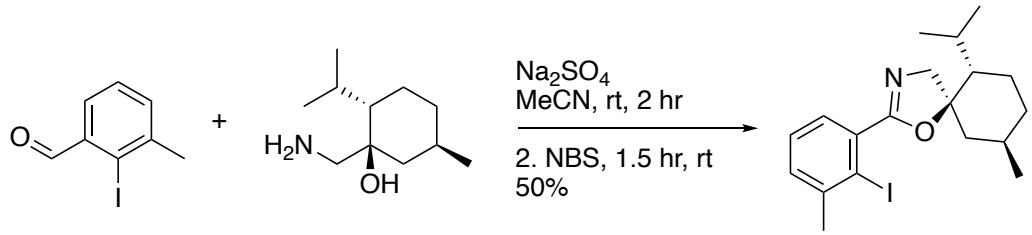
making natural products and pharmaceuticals. As such the electrochemical removal of the m-PMB work would be a logical extension to this work (Scheme 2.57):



Scheme 2.57: Proposed electrochemical removal of the chiral m-PMB group from amides

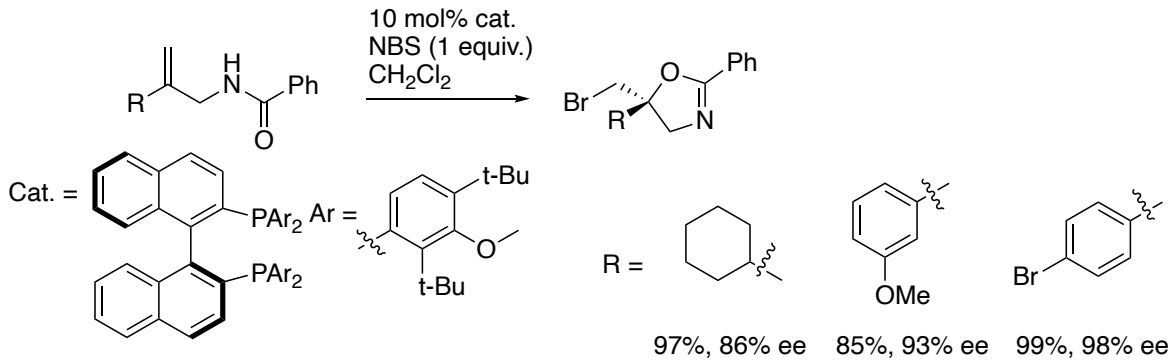
2.14.2.3 Spirocyclisation

The spirocyclisation of aliphatic PMB protected secondary amides shows promise as it enables the facile synthesis of interesting scaffolds (spiro-oxazolines). Indeed, such structures are rare in the literature and their synthesis usually features cyclisation with the spirocentre already in place (Scheme 2.58).



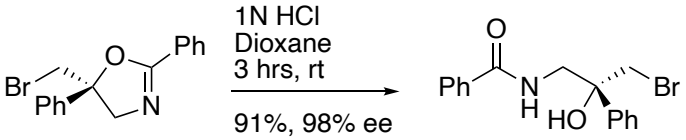
Scheme 2.58: Spirocyclisation reaction carried out by Therién *et al.* [236]

An alternative synthesis method that more closely resembles the method employed in this work was proposed by Hamashima *et al.*[237] (Scheme 2.59):



Scheme 2.59: Spirocyclisation synthesis by Hamashima *et al.*

Part of the methodology carried out by Hamashima included the functionalisation of the oxazoline compounds produced, including acid hydrolysis to the tertiary alcohol (Scheme 2.60). The mild conditions for acid hydrolysis indicate the reactivity of these compounds, which gives insight into why the isolation of the spirooxazoline compounds formed in this work was so difficult.



Scheme 2.60: Acid hydrolysis of spirooxazoline

Considering the ease of acid hydrolysis, a different protecting group may be required in order to carry out this methodology, since it appears the electron-rich character of the PMB group makes it too susceptible to hydrolysis. However, a compromise will be required that enables oxidation of the aromatic part such that cyclisation can occur (see higher oxidation potential of *N*-benzylbenzamide, **2.48** compared to PMB protected amide **2.22** in Figure 2.5). The methodology could also be extended to alkenyl moieties, and similarly the nucleophile could be modified to create alternative heterocycles. Some suggested modifications are illustrated in Figure 2.15:

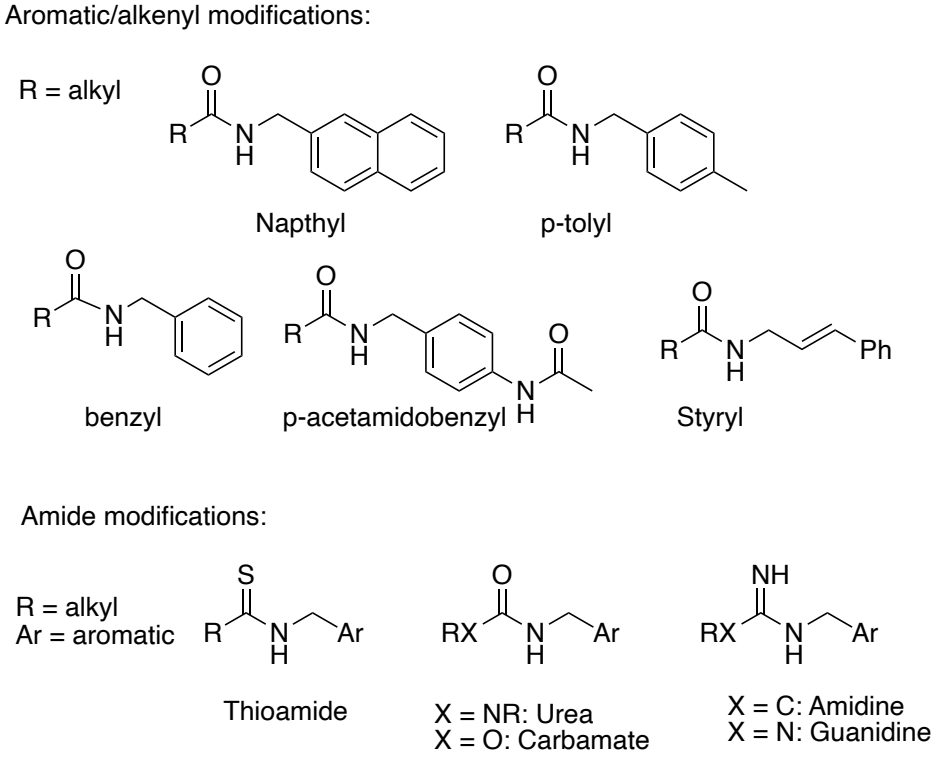


Figure 2.15: Substrate modifications to spirocyclisation by electrosynthesis

2.14.2.4 Deuterium labelling by electrolysis

Whilst some promise had been demonstrated that a robust method for deuterium labelling on aromatic rings by electrosynthesis could be achieved, more development is required. This is in order to improve the substrate scope as well as increase the degree of deuterium enrichment in the product, as previous results indicated that hydrogen abstraction was a competing process in the reaction (Table 2.22). The use of CH_3OD clearly improved the process significantly, however to require the use of the deuterated solvent CH_3OD is inefficient. The low pka of the CH_3 in MeCN

means that this is not a suitable solvent for the electrolysis, and so other solvents should be explored.

2.14.2.5 N-Acyl imine Diels-Alder process

Attempts to functionalise the electrochemical product formed by PMB oxidation in the Ammonite 8 reactor (**2.65**) were unsuccessful. Despite the relative stability of the hemiaminal ether intermediates formed (indicated by their isolation in some examples, see Scheme 2.31), conditions for a subsequent Diels-Alder cyclisation (via the N-Acyl imine formed by elimination of the methoxy group, see Scheme 2.36) could not be found. Modification of the aromatic part of the molecule (Figure 2.16) to allow oxidation of the benzylic position, without subsequent fragmentation would open the possibility of a subsequent hetero Diels-Alder reaction.

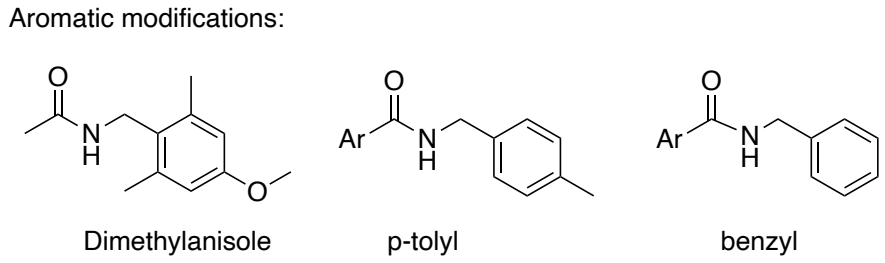
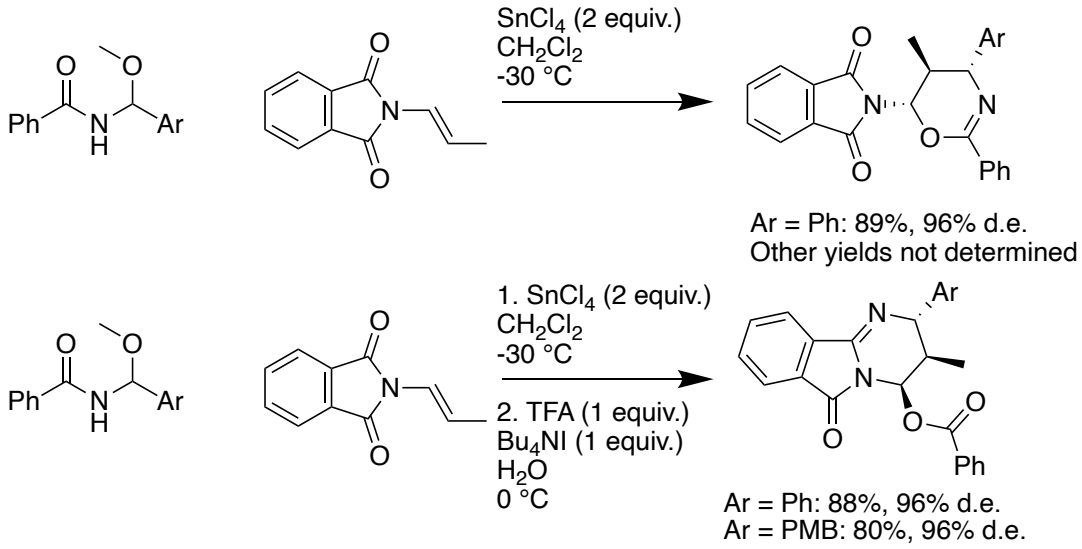


Figure 2.16 : Substrate (aromatic) modifications for the Diels-Alder cyclisation from methoxylated amide substrates

Following unsuccessful efforts in this area as part of this work, a later publication by Kramer *et al.* [238] demonstrated the successful application of this methodology, using α-methoxylated N-acyl substrates to furnish the desired dihydro 1,3-oxazine scaffold (Scheme 2.61), which was transformed into the dihydro-pyrimido[2,1-a]isoindole-6(2H)-one moiety by acid treatment:



Scheme 2.61: Hetero Diels-Alder synthesis of dihydro 1,3-oxazines and acid rearrangement to dihydro-pyrimido[2,1-a]isoindole-6(2H)-one scaffolds by Kramer *et al.*

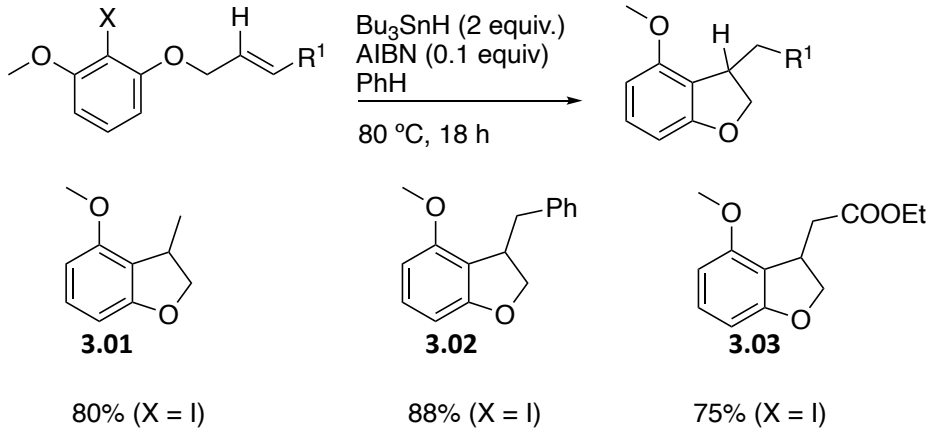
This impressive transformation would dovetail very well with the methodology in this work, since many of the methoxylated starting materials can easily be synthesised electrochemically. The substrate scope in Kramer's work is extensive, although the hetero Diels-Alder step is very sensitive to the dienophile structure. The conditions employed for the hetero Diels-Alder could be applied to the substrates made in this work to create bespoke, highly functionalised scaffolds, with even the potential of a daisy-chained process to generate these under continuous flow (with suitable cooling methods in place to account for the conditions used in the Diels-Alder reaction). Combining with potential modifications for the electrochemical step illustrated in Figure 2.16 might increase the substrate scope, and improve the stability of these scaffolds, facilitating isolation.

Chapter 3 Cathodic cyclisation of aryl halides

3.1 Introduction

Reductive radical–initiated cyclisation is an important process in organic synthesis. Cyclic compounds are a major class of molecules involved in the structure and function of living organisms and constitute a large proportion of synthetic molecules prepared in the pharmaceutical, agrochemical and materials industries.

Historically, the most widely used process for radical cyclisations used organotin reagents for example, Bu_3SnH, and a radical initiator such as AIBN. One method was reported by Snieckus *et al.*[239], and is illustrated in Scheme 3.1.

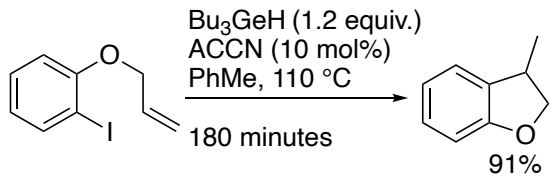


Scheme 3.1: Tin–mediated cyclisation used by Snieckus *et al.*

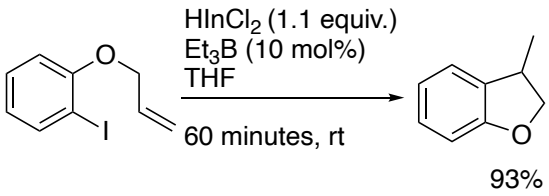
Whilst this and other similar methods are suitably robust to induce cyclisation in a range of substrates in excellent yields[239-241], the use of this procedure is limited by the toxicity of both the organotin reagents and the solvent, benzene and the difficulty of purifying cyclised products from tin halide species. This process performs poorly in many of the green metric criteria utilised in industry and hence very few, if any, compounds are synthesised via this methodology in commercial processes now.

Alternative procedures have been developed in recent years, using reagents such as:

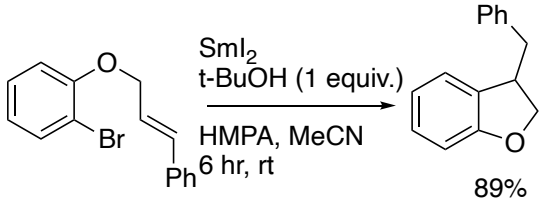
- organogermanium reagents[242]



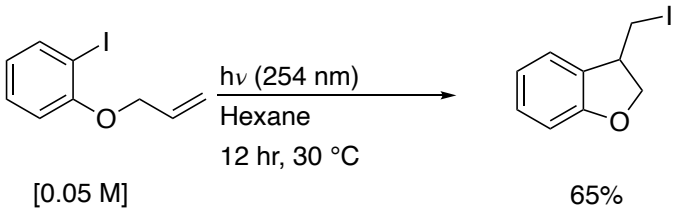
- Gallium and indium hydrides[243]



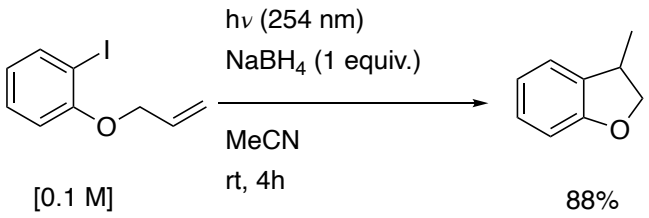
- Samarium diodide[244, 245]



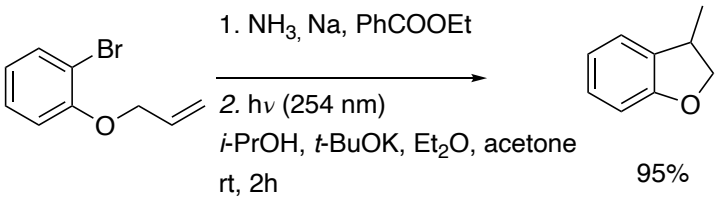
- Photochemical methods:
  - Reagentless[246]



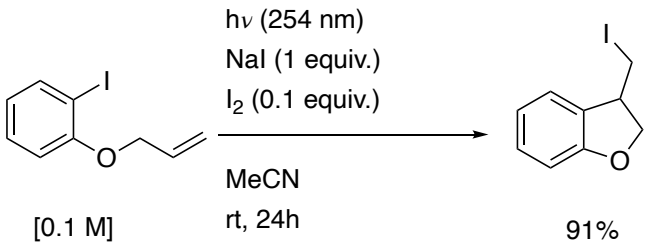
  - $NaBH_4$ additive[247]



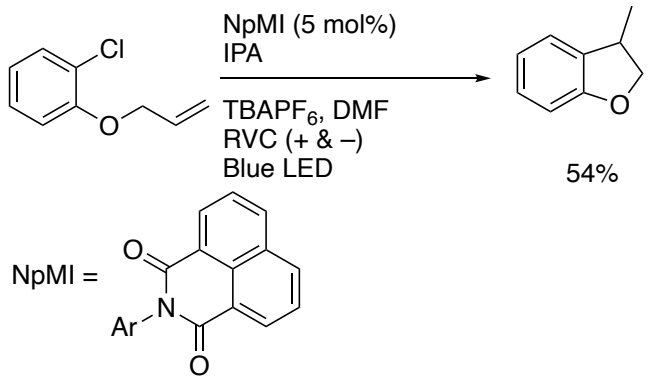
  - Ethyl benzoate anion[248]



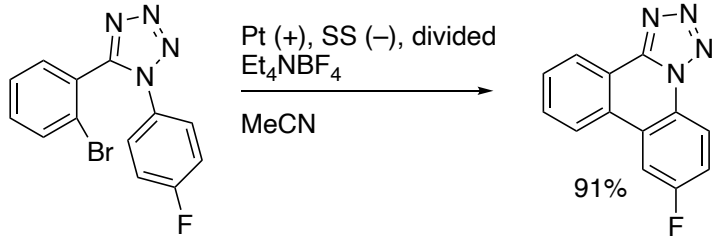
  - Iodine/NaI additives[249]



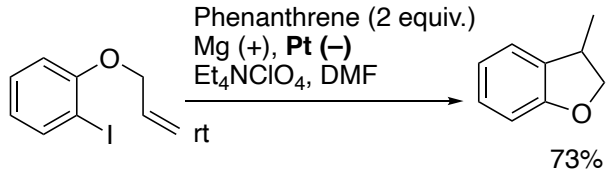
- Electrochemical methods
  - Photoredox[250]



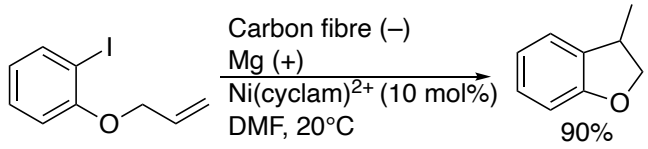
- Steel and platinum electrodes in a divided setup[251]



- Sacrificial anodes (Zn/Mg) with:
  - Phenanthrene/fluorene mediator[252, 253]



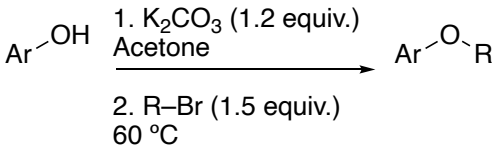
  - Ni^{II} mediator[254]

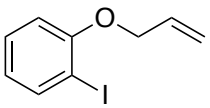


In nearly all of the above methods a reagent is consumed and so cannot be considered to be reagentless techniques. Furthermore, the aforementioned electrochemical processes use expensive and/or hazardous elements as electrode materials, which largely limits their synthetic use. The method proposed in this work represents the first undivided electrochemical reductive cyclisation process that does not feature a sacrificial anode, thereby circumventing many of the associated inherent complications. Recent reviews by Baran *et al.*[255] and Kärkäs *et al.*[256] highlighted that reductive electrosynthesis rarely occurs on non-sacrificial anodic materials. This work not only allows the synthesis of highly privileged structures (i.e. those uncommon in nature) on a scale that would not be possible through existing methods, but achieves this in a sustainable, environmentally friendly manner without the need for hazardous or precious metals.

3.2 Synthesis of substrates

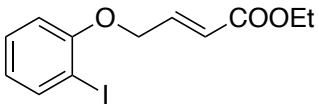
The majority of substrates were made by Williamson ether synthesis, a method originally proposed by Alexander Williamson in 1850.[257] The method followed was a mild procedure reported many times for phenol substrates,[242] the conditions of which are illustrated in Scheme 3.2.





2.156

quant.



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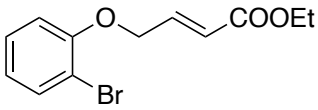

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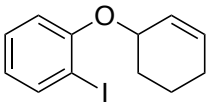

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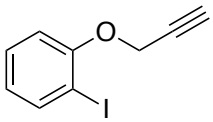

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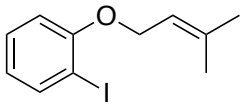

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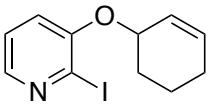

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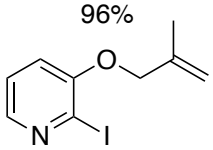

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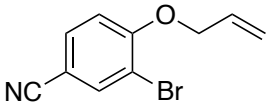

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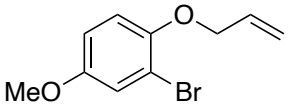

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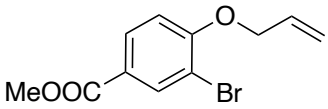

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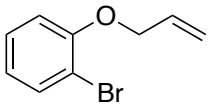

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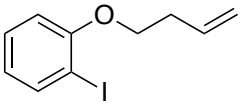

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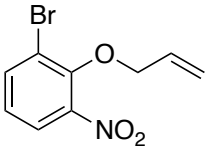

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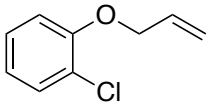

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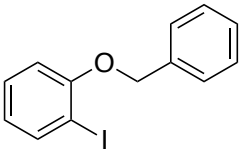

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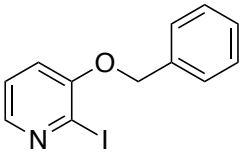

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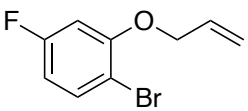

3.20

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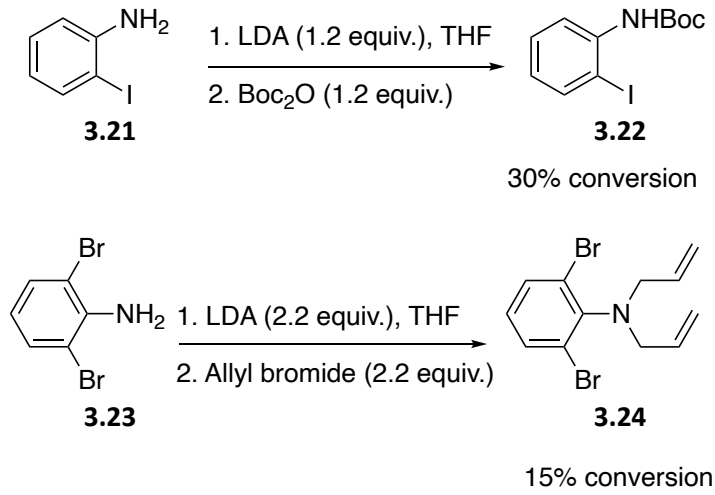
Scheme 3.2: Preparation of alkylated halophenols by Williamson ether synthesis

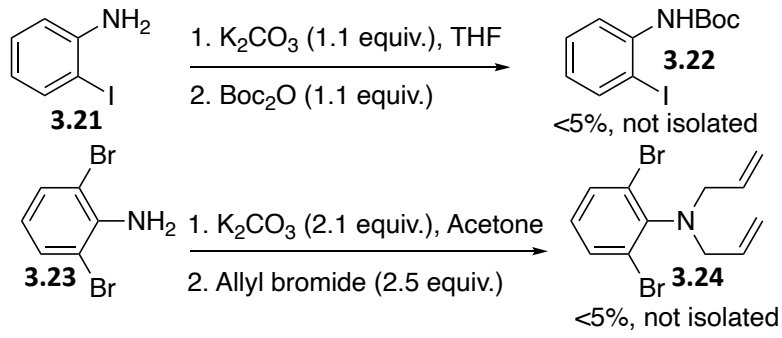
Yields were excellent to quantitative in each case, with in many cases only a simple filtration required to obtain the pure product. For other substrates, purification by silica plug or flash chromatography was required to yield the pure material. The use of acetone as a solvent is favourable from a green chemistry perspective, since it is safe, convenient and not energy–intensive to produce.

Aniline substrates were prepared by alkylation. Due to the significantly lower acidity of aniline derivatives compared to phenols, a stronger base was required. When LDA was used as a base, incomplete reaction was observed (Scheme 3.3). The product was not isolated in either example.



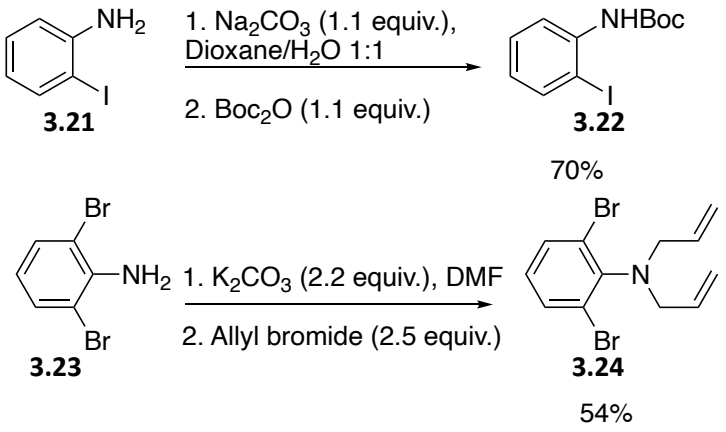
Scheme 3.3: Aniline substrate preparations with LDA

Satisfactory conversions were not achieved with LDA, even when it was freshly prepared and used *in–situ*. A lithium-halogen exchange might be responsible for the poor yield. Attempted synthesis of these substrates with potassium carbonate as base also proved unsuccessful, with only traces of product forming in each case (Scheme 3.4).



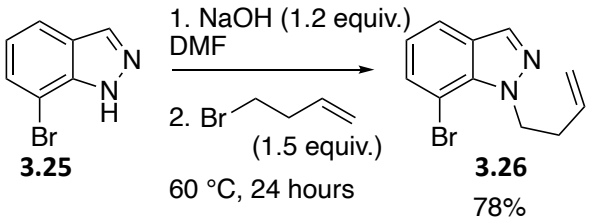
Scheme 3.4: Aniline substrate preparations with K_2CO_3

It was proposed that the limitation of this method was the solubility of potassium carbonate in the reaction media, rather than it's basicity (pkb). As such, alternative solvent systems were investigated (Scheme 3.5).



Scheme 3.5: Improved aniline substrate preparations with potassium carbonate

This proposal was proven right, as in alternative solvent systems the alkylated anilines **3.22** and **3.24** were furnished from their respective amines in 70 and 54% yields respectively. The synthesis of **3.26** was attempted following an alkylation procedure for indoles (Scheme 3.6).[258]

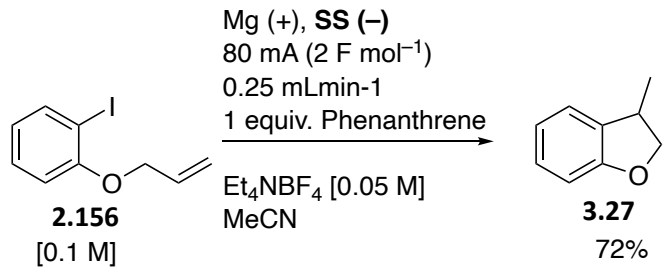


Scheme 3.6: *N*-alkylation of 7-Bromo-1*H*-indazole 3.25

Under these conditions the reaction proceeded smoothly, with the alkylated indazole **3.26** synthesised in 78% yield.

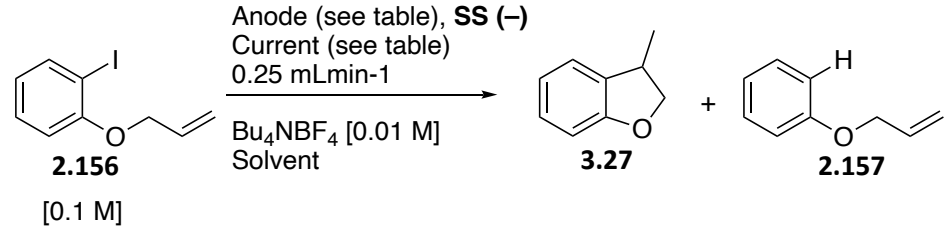
3.3 Initial studies of reductive cyclisation in Ammonite 8 reactor

Initial studies of the reaction were conducted on 1-(Allyloxy)-2-iodobenzene **2.156** as substrate using conditions closely resembling literature procedures (Scheme 3.7)[252] This preliminary trial was undertaken to establish if the process would proceed in the Ammonite 8 reactor before further optimisation.



Scheme 3.7: Reductive cyclisation on Mg anode in Ammonite 8 reactor.

The reaction proceeded to furnish dihydrobenzofuran **3.27** in 72% isolated yield, which ignoring inefficiencies with purification was comparable to that observed by Olivero *et al.* for the same substrate by electrolysis (90%).[254] It was also found that the concentration of the electrolyte (Et_4NBF_4) could be reduced to 0.01 M without loss in yield, a significant advance considering that it is unrecoverable under the current conditions, since it is contaminated by the Mg^{2+} salts produced in the reaction by anodic Mg metal oxidation. Further investigations were conducted, including: the use of the cheaper and less reactive zinc metal as anode material; changing the reaction solvent; and attempting to conduct the reaction in the absence of phenanthrene. The use of phenanthrene, a stoichiometric mediator, is seen as undesirable in the process; in theory the cyclisation could occur without it, or at least it could be used catalytically. The results of these experiments are illustrated in Table 3.1.



Entry	Anode	Solvent	Current / mA (F mol^{-1})	Yield[a] / %		
				3.27	**2.156**	**2.157**
1	Mg	THF	80 (2)	30	4	60
2	Mg	MeCN	80 (2)	30	30	30
3	Mg	DMF	80 (2)	15	60	13
4	Zn	THF	80 (2)	15	34	34
5	Zn	THF	120 (3)	23	10	53
6	Zn	MeCN	120 (3)	0	21	70

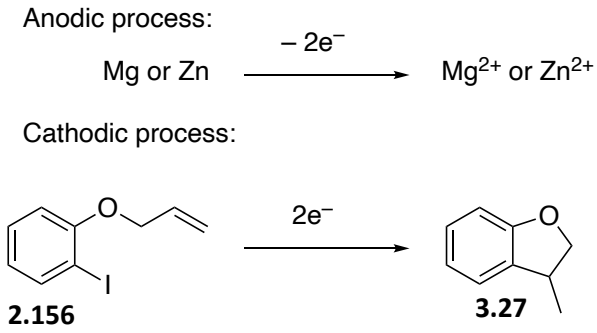
a. Yield by quant. NMR, Bu_4NBF_4 electrolyte as internal standard

Table 3.1: Optimisation of reductive cyclisation

A change of electrolyte to Bu_4NBF_4 was necessary to improve solubility in THF. In the absence of the stoichiometric mediator, cyclisation of the radical intermediate competes with significant reductive deiodination to arene **2.157**. However, the results were sufficiently encouraging to suggest that the amount of mediator could at least be reduced, even if not removed altogether. Zinc appeared to be a reasonable alternative to magnesium as anode under these conditions, although an excess of current was required for near–full consumption of starting material. Solvent plays a role in the reaction, as the ratio of products and yields differ widely over the range of reactions illustrated. It came as a surprise that no cyclised product was observed for entry 6; MeCN was expected to be a promising solvent for the conditions it was trialled in. However, later results show that the solvent is effective provided that other parameters are favourable. Overall, none of the illustrated conditions was suitably attractive and so developing a method to reduce the quantity of phenanthrene in the reaction solution was temporarily paused. The next significant step would be to improve the process such that the counter-electrode process is sufficiently robust and suitable for the Ammonite reactors, or other flow electrolysis reactors, which poorly tolerate precipitation of materials from solution.

3.4 Examining the counter-electrode process

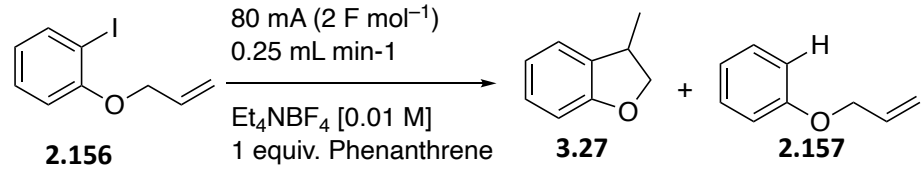
In the cathodic cyclisation reaction, the reduction of the organic substrate is the useful reaction, and oxidation of a sacrificial metal anode is the counter-electrode reaction. This is illustrated in Scheme 3.8.



Scheme 3.8: Electrode processes in reductive cyclisation

The use of magnesium and zinc as anode materials (which as well as being easily corroded in air, are also consumed in the reaction) and the precipitation of metal salts from the reaction solution (that led to reactor fouling and blockages). The main use of sacrificial anodes is to establish a robust counter-electrode process without the need for a protic solvent, which would likely interfere with the useful reaction (in this case due to the high hydrogen affinity of the

radical intermediate). A protic solvent, such as methanol, can also be used as the counter-electrode reaction in electrochemistry, producing compounds such as formaldehyde, formic acid or CO_2. The use of a protic solvent (as a minor component of the co–solvent) for the process was initially trialled in the Ammonite 8 reactor and several conditions illustrated in Table 3.2 were investigated.



2.156 [0.1 M] **3.27** **2.157**

Entry	Anode	Cathode	Solvent	Yield[a] / %		
				3.27	**2.156**	**2.157**
1	C/PVDF	Graphite	MeCN, MeOH (2 equiv.)	<5%	25	59
2	Pt	Graphite	MeCN, 2 equiv. MeOH	<5%	18	70
3	C/PVDF	SS	MeCN, 2 equiv. MeOH	<5%	22	68
4	Pt	SS	MeCN, 2 equiv. MeOH	<5%	10	79
5	C/PVDF	Graphite	MeCN, 2 equiv. HFIP	<5%	34	55
6	Pt	Graphite	MeCN, 2 equiv. HFIP	<5%	36	55
7	C/PVDF	SS	MeCN, 2 equiv. HFIP	<5%	31	59
8	Pt	SS	MeCN, 2 equiv. HFIP	<5%	20	70

a. Yield by quant. NMR, DMT as IS

Table 3.2: Trialled conditions for reductive cyclisation with protic solvents in Ammonite 8 reactor

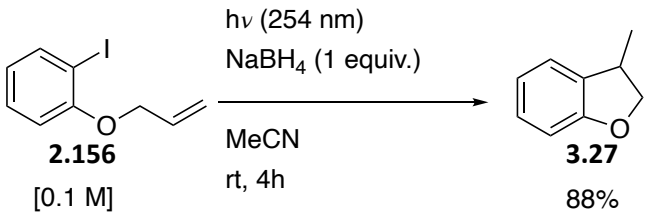
All of the conditions led to only trace amounts of the cyclised product being formed, with the dehalogenated arene **2.157** the main product. It was reasoned that the protic solvent was interfering with the radical process, even with HFIP as a protic solvent (which is known to have an especially low hydrogen affinity). To circumvent this problem, two different routes to the cyclised product were proposed. First that the cyclisation be executed photochemically (following literature methods), either to furnish the cyclised dehalogenated product **2.156** directly, or by dehalogenation of the cyclised iodinated compound. Second was for the electrolysis to be carried out in divided mode, such that the protic solvent is separated from the cathodic chamber.

3.5 Combined photochemical/electrochemical cyclisation process

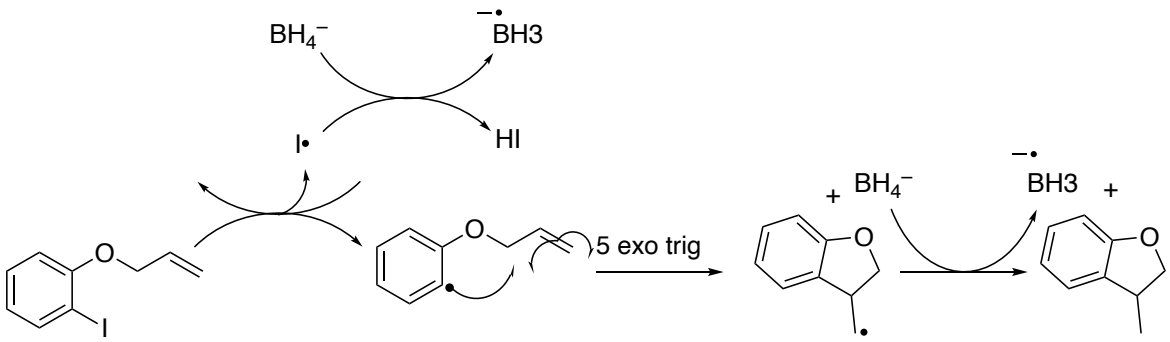
3.5.1 Photochemical cyclisation

Photochemical cyclisations of aryl iodides to dihydrobenzofurans are widely reported in the literature.[248, 249, 259] Photochemical cyclisations of this type are inherently similar to their electrochemical counterpart (which is being explored in this work), since the cyclisation is driven through radical intermediates. If satisfactory reaction conditions could be established for photochemical cyclisation leading to good yields of the desired product, it was envisaged that parts of these conditions (e.g. solvent, additives, flow rate etc) may translate to an effective electrochemical method of cyclisation.

Three photochemical methods for the cyclisation of iodinated alkylated phenol **2.156** are described in the literature. Conditions developed by Yu *et al.* in 2005 (Scheme 3.9), along with mechanism (Scheme 3.10) are illustrated.[247]

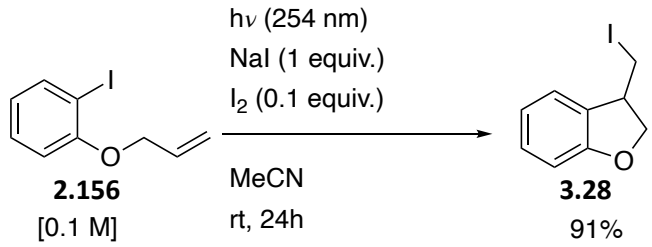


Scheme 3.9: Photochemical cyclisation of 1-(Allyloxy)-2-iodobenzene by Yu *et al.*



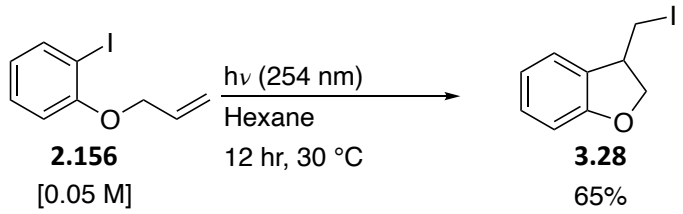
Scheme 3.10: Mechanism for photo-induced radical cyclization with sodium borohydride

The borohydride in the reaction mixture serves to induce hydrogen abstraction of the alkyl radical species, instead of iodine. A later method by Li *et al.*, uses stoichiometric NaI and catalytic I_2 to produce the iodinated cyclised product **3.28** (Scheme 3.11).[249]



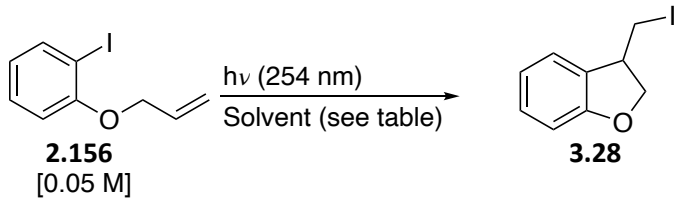
Scheme 3.11: Photochemical cyclisation of 1-(Allyloxy)-2-iodobenzene by Li *et al.*

Finally, a reagentless method developed by Beckwith *et al.* is illustrated (Scheme 3.12).[246]



Scheme 3.12: Photochemical cyclisation of 1-(Allyloxy)-2-iodobenzene by Beckwith *et al.*

The use of additives such as NaI, I_2 or $NaBH_4$ in the cyclisation is a limitation because of the material requirement and the hazards associated with the specific additives involved. Furthermore, the PMI for the reaction increases (see green metrics in chapter 2 for description of PMI). It is for this reason that the conditions used in the work of Beckwith *et al.* (Scheme 3.12) were used for further studies, albeit the conditions modified such that the reaction was conducted in flow. The results of these studies, trialling various solvents and flow rates, is illustrated in Table 3.3.



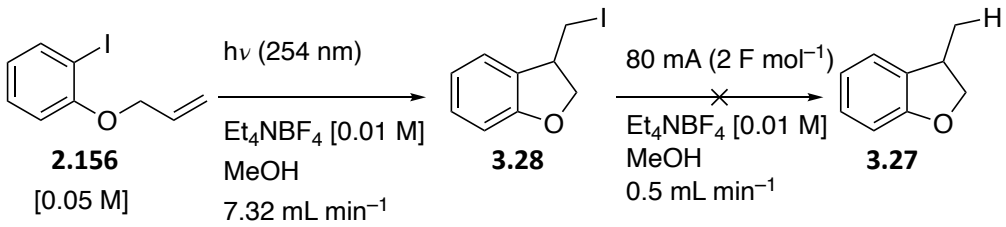
Entry	Solvent	Flow rate/ mL min^{-1} (residence time / min)	Yield[a] /%
1	THF	1.83 (60)	<5
2.	MeCN	1.83 (60)	70
3	MeCN	3.66 (30)	87[b]
4	MeCN	3.66 (30)	38[d]
5	MeOH	3.66 (30)	89[b]

6	MeOH[c]	3.66 (30)	89
7	MeCN/ HFIP (5 equiv.)	3.66 (30)	85

a. Yield by quant. NMR, dimethyl terephthalate as Internal standard
b. Isolated yield
c. Et_4NBF_4 [0.01M] added to reaction solution
d. UV lamp stopped after 5 minutes

Table 3.3: Photochemical cyclisation in flow reactor

The reaction performed in THF (entry 1, table 3.3) led to decomposition of the SM, with only trace amounts of product formed. Pleasingly when the reaction was conducted in MeCN or MeOH (entries 2–6), cyclisation to **3.28** occurred in good yield None of the solvents tested were able to induce H abstraction from the cyclised species to afford the dehalogenated benzofuran **3.27** (which was the reason for the solvent study). A distinct advantage of conducting the reaction in flow was the increase in yield of **3.28** compared to the work by Beckwith *et al.*, from 65% to 90%. The reaction was shown to reach completion in 30 minutes. For entry 4 (table 3.3), UV illumination was stopped after 5 minutes, to investigate if the reaction could proceed with only a catalytic quantity of UV photons. However, the reaction was not complete, presumably due to the requirement for a stoichiometric quantity of UV photons to enable the reaction to reach completion. The reaction tolerated the addition of an electrolyte (entry 6), which is significant because the next proposed step involved breaking the C–I bond by electrolysis (requiring electrolyte in the reaction solution). These results demonstrated that, in principle, a daisy–chained continuous two–step process of a photochemical cyclisation followed by electrochemical reduction (Scheme 3.13) could be performed. This process is outlined in Scheme 3.13:



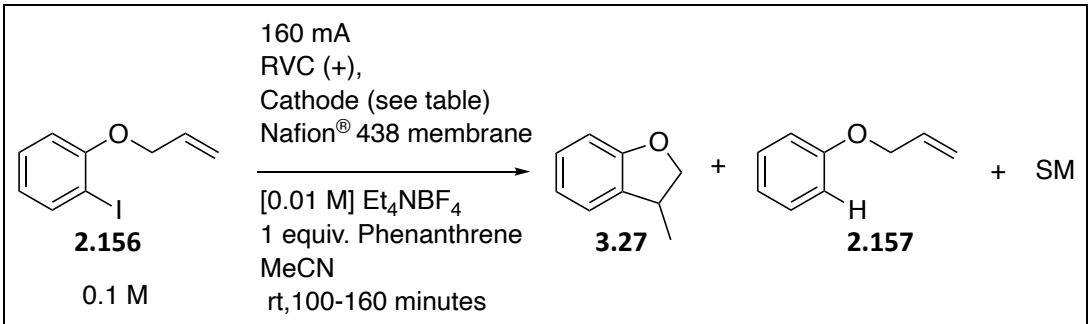
Scheme 3.13: Attempted two–step cyclisation process in flow

Unfortunately, all attempts to achieve the two-step process proved unsuccessful. The photochemical product could not be reduced in the Ammonite 8 reactor, perhaps owing to the increased strength of the C–I bond in the iodinated dihydrobenzofuran **3.38** than in the aryl iodide **2.156**. It was proposed that the reduction of methanol occurred in the reactor, since a current was allowed to pass. For this process to be viable a different solvent would be required. Since

further development was required, and because a direct route to the cyclised product 3.27 was to be preferable (over a daisy-chained, two-step process), work on this route was paused.

3.6 Reductive cyclisation in parallel plate reactor

The cathodic cyclisation reaction was carried out on substrate **2.156** in the divided cell, trialling different cathode materials. The counter-electrode reaction was the oxidation of MeOH on an RVC anode, in a similar process to that of the dehalogenation reaction described in section 2.13. The shift for the cyclisation reaction to the divided cell was so that the counter-electrode reaction (oxidation of a protic solvent) could be segregated from the working electrode reaction (reductive cyclisation), thereby minimising the risk of the protic solvent interfering with the useful reaction. The results of these experiments are illustrated in Table 3.4.



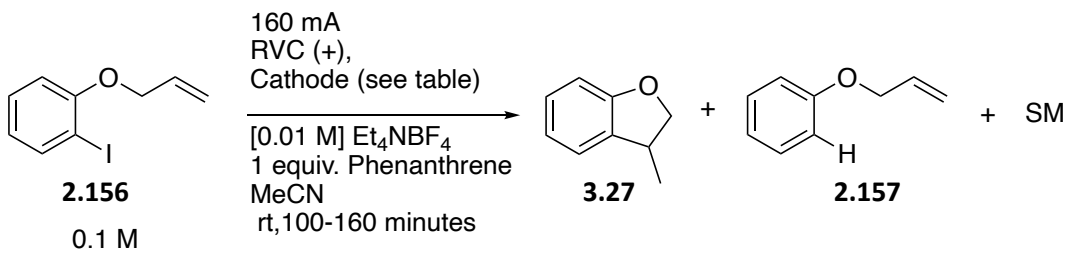
Entry	Cathode	Yield[a] / %		
		3.27	**2.156**	**2.157**
1	Ag	62	25	5
2	Ni	46	30	10
3	Stainless Steel	60	20	5
4	Leaded bronze	30	20	35

a. Yield by quant. NMR, phenanthrene as IS

Table 3.4: Cathode study on reductive cyclisation in parallel plate reactor (divided mode)

The cathodic chamber contained a 0.1 M solution of substrate and phenanthrene, and 0.01 M electrolyte (Et_4NBF_4) in MeCN. The anodic chamber contained 0.01 M Et_4NBF_4 in MeCN with 5 equiv. MeOH. The MeOH was provided as a protic solvent by which oxidation would provide the counter-electrode reaction. Complete consumption of SM could not be achieved under these conditions, as the cell failed to pass current after specific periods of time, owing to passivation of the cathode. However, the results showed significant promise, with silver (entry 1) and stainless

steel (entry 3) displaying good conversion to the desired cyclised product. Pleasingly, the removal of the membrane did little to harm the yield, as illustrated in Table 3.5.



Entry	Cathode	Yield[a] / %		
		3.27	2.156	2.157
1	Ag	60	26	9
2	Stainless Steel	59	19	10

a. Yield by quant. NMR, phenanthrene as IS

Table 3.5: Cathode study on reductive cyclisation in parallel plate reactor (undivided mode)

When Ag cathode was utilised (entry 1), both in divided and undivided modes, passivation of the electrode was seen after a short time in the reactor, causing a cessation of current. On disassembly of the reactor, a yellow coating layer had formed on the surface of the cathode, which was proposed to be silver iodide. Indeed, it is known that iodide forms a strong bond with silver (and to a lesser extent Ni[112], glassy carbon[114], Pt[109] and even stainless steel[111]) and studies have reported that iodide readily corrodes electrode materials in electrochemistry.[260] In these materials, a surface coating of AgI can prevent further reaction which can only be rectified with extensive cleaning.

Since the cyclisation had worked well in undivided mode in the parallel plate, it was proposed that the most significant parameter in the method was the flow rate, since this was the only significantly different parameter between the conditions used in the parallel plate and the Ammonite 8 reactor.

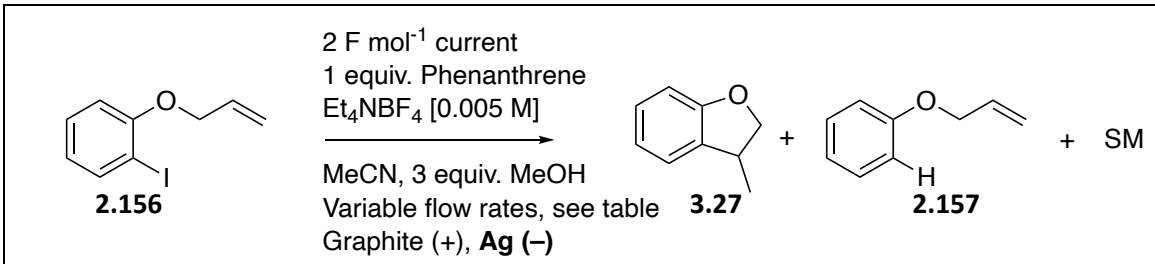
3.7 Development and optimisation of reductive cyclisation in Ammonite 8 reactor

Following the successful radical cyclisation carried out in the parallel plate reactor (Table 3.5), conditions mimicking those from that process (reverting to a protic solvent for the counterelectrode process) in the Ammonite 8 reactor were investigated, including the effect of electrode materials, flow rates, electrolytes, mediators (at varying concentrations), quantity of

MeOH in the reaction mixture, temperature, concentration, current and number of reactor passes.

3.7.1 Flow rate and reaction concentration studies

Conditions with varying flow rate (Table 3.6) on silver cathode in the Ammonite 8 reactor were investigated.

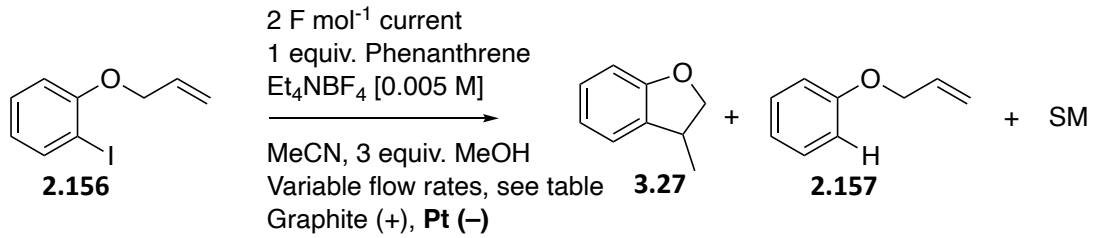


Entry	Flow rate/ mL min^{-1}	Concentration / mol dm^{-3}	Yield[a]/ %		
			3.27	**2.156**	**2.157**
1	0.25	0.1	2	39	57
2	1.0	0.1	6	19	74
3	2.0	0.1	25	25	41
4	4.0	0.05	25	35	37
5	8.0	0.25	40	42	7
6	16.0	0.0125	40	57	1

a. Yield by quantitative NMR, DMT as internal standard

Table 3.6: Effect of concentration on yield of reductive cyclisation of (1-Allyloxy)-2-iodobenzene on silver cathode/graphite anode

The concentration was lowered at high flow rates in order to maintain the stoichiometric current within a considered safe limit, as heating occurs at high current. For reference, a current of 640 mA across the Ammonite 8 reactor corresponds to a current density of 32 mA cm^{-2}. As a comparison, the same set of experiments were trialled using a platinum cathode (Table 3.7).



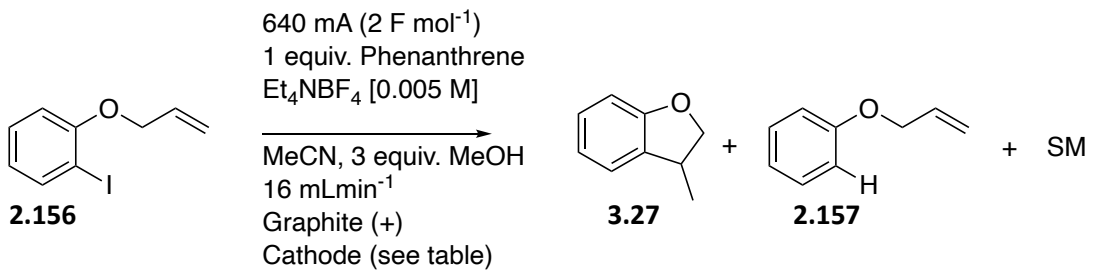
Entry	Flow rate/ mL min^{-1}	Concentration / mol dm^{-3}	Yield[a]/ %		
			3.27	**2.156**	**2.157**
1	0.25	0.1	3	34	60
2	0.5	0.1	10	40	47
3	1.0	0.1	15	32	48
4	2.0	0.1	17	27	50
5	4.0	0.05	16	39	43
6	8.0	0.25	21	48	28
7	16.0	0.0125	25	50	22

a. Yield by quantitative NMR, DMT as internal standard

Table 3.7: Effect of concentration on yield of reductive cyclisation of (1-Allyloxy)-2-iodobenzene on platinum cathode/graphite anode

It was observed that at higher flow rates (lower concentrations) through the Ammonite 8 reactor there was better conversion to the desired product. Very little, cyclised product **3.27** was observed at low flow rates under these conditions.

A high flow rate is usually employed in order to improve the mass transfer coefficient in the parallel plate reactor, and so it proved that this was crucial to the success of the method, at least with respect to the initial studies with MeOH doped into the reaction solution (see Table 3.6 and Table 3.7).With this information in hand, a range of electrode materials were trialled at 16 mL min^{-1}.

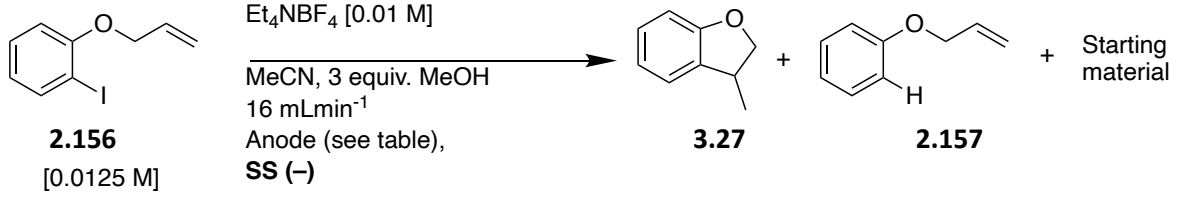


Entry	Cathode	Yield[a]/%		
		3.27	**2.156**	**2.157**
1	Pt	10	59	27
2	Ag	40	57	1
3	Leaded bronze	10	59	25
4	Ni	23	60	10
5	Glassy carbon	14	80	2
6	C:PVDF	44	47	6
7	SS	35	53	4

a. Yield by quantitative NMR, DMT as internal standard

Table 3.8: investigating cathode materials in reductive cyclisation in Ammonite 8 reactor

Silver and stainless steel were the most selective cathode materials for conversion of aryl iodide **2.156** to the desired dihydrobenzofuran **3.27**, in 40 and 35% yields respectively (entries 2 and 7) The use of silver was limited by corrosion; the surface quickly fouled due to a silver iodide layer (see discussion in section 1.6) that substantially lowered the yield. Such problems were not observed with stainless steel. Moreover, stainless steel is readily available and an inexpensive electrode material. Hence stainless steel was chosen as the cathode material for future optimisation experiments. Attempts to improve conversion in one pass of the reactor proved unsuccessful and highlighted a problem with using graphite as an anode material: that fragmentation of the electrode occurred at high current. To establish the optimum anode material another study, this time on anode material was conducted (Table 3.9).



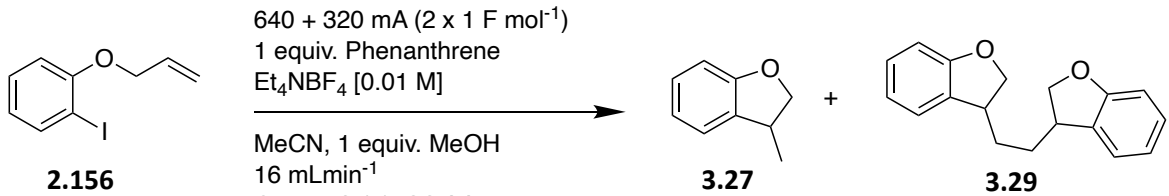
2.156 [0.0125 M] **3.27** **2.157**

Entry	Anode	Yield[a] / %		
		3.27	**2.156**	**2.157**
1	Graphite	61	31	2
2	Pt	36	68	2
3	C:PVDF	56	36	1
4	Graphene	56	38	2
5	Glassy Carbon	57	36	2

a. Yield by quantitative NMR, DMT as internal standard

Table 3.9: Investigating anode materials for counterelectrode reaction in reductive cyclisation electrosynthesis

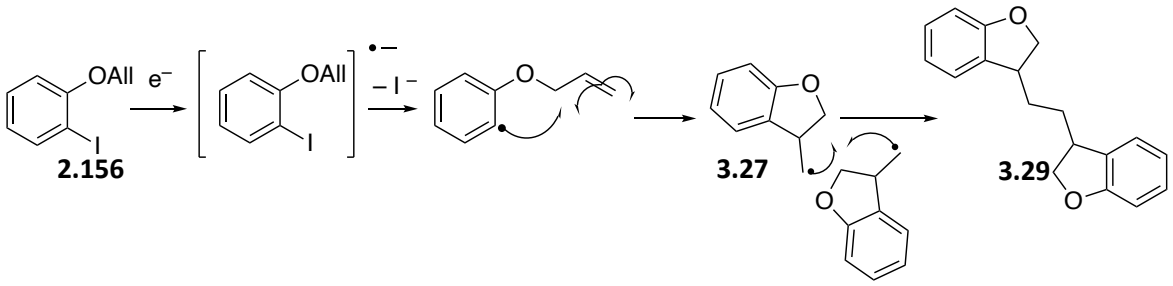
The survey of anode materials showed that glassy carbon (entry 5) would make an excellent candidate. It gave a similar yield of cyclised product to graphite (entry 1), and it is also not susceptible to the degradation observed in graphite, graphene or carbon polymer. Pt was shown to be inefficient, yielding only 36% of the desired cyclised material. Final optimisation reactions were performed to investigate the effect of temperature, which did not appear significant. Experiments examining MeOH concentration demonstrated that 1 equiv. was the optimal amount, and further experiments on the use of non–anhydrous, HPLC grade MeCN showed it to be equally efficient as anhydrous. Pleasingly, a second pass of the reactor, utilising 1 equivalents of current on the first pass and 0.5 equiv. on the second was found to induce full conversion of SM, with a GC yield of 76%. When repeated this produced an isolated yield of 73%. The optimised conditions are shown in Scheme 3.14.



2.156 [0.0125 M] **3.27** 73% **3.29** 21%

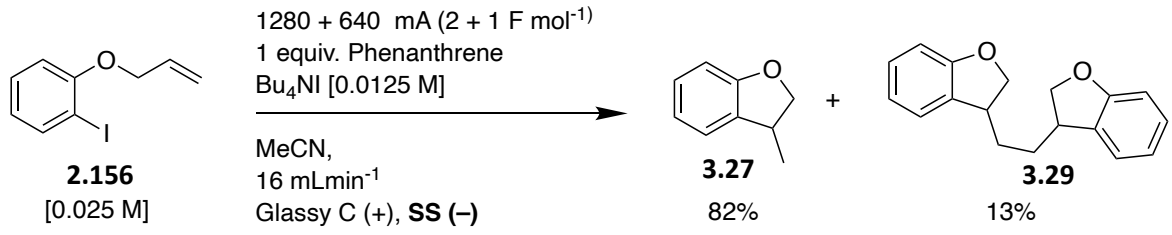
Scheme 3.14: 1st optimised conditions for reductive cyclisation in Ammonite 8

The dimerised compound, **3.29** has been synthesised in similar radical cyclisations[254, 261], but in lower quantities. Its formation arises from the coupling of two cyclised alkyl radicals in a radical termination sequence (Scheme 3.15).



Scheme 3.15: Radical cyclisation followed by dimerisation of 1-Allyloxy-2-iodobenzene

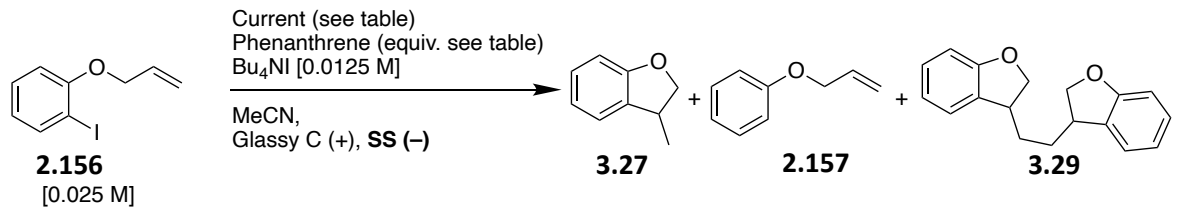
The formation of the dimer indicates that the reduction of the cyclised alkyl radical species **3.30** competes with two of these species coupling to each other. This could be due to mass transfer (if the reduction occurs at the electrode surface), or an effect of substrate concentration (since high substrate concentration should promote dimerisation as large alkyl radical molecules will be in close proximity to each other in solution). The solvent could also be influential if it inhibits the second electron transfer. Such hypotheses led to a series of further experiments to investigate if the yield for the synthesis of dimer **3.29** could be increased or decreased. Switching the electrolyte to a sacrificial salt, Bu_4NI, meant that MeOH was no longer required for the counterelectrode reaction (oxidation to formaldehyde, formic acid or CO_2). In addition, a higher concentration of substrate was trialled, since the glassy carbon anode could tolerate the high currents passed in the Ammonite 8 (Scheme 3.16).



Scheme 3.16: 2nd optimised conditions for reductive cyclisation in Ammonite 8

Surprisingly, under these conditions, in contradiction to the hypothesis, a higher yield of the cyclised monomer **3.27** was observed (82%) with lower yield of the dimer **3.29** (13%). These conditions were found to be more favourable for synthesis of cyclised dihydrobenzofurans and so were employed in the synthesis of the majority of the substrates in this work (it was later discovered that the conditions illustrated in Scheme 3.15 led to higher yields than those in Scheme 3.16 in a small subset of substrates).

The new electrolyte improved the efficiency of the reaction at lower flow rates, offering the same excellent conversion to the cyclised product **3.27** with little formation of the dehalogenated compound **2.157**. Further optimisation of the process (i.e., reducing the mediator concentration) conducted by Dr Ana Folgueiras in the Brown group led to improvements in the process (Table 3.10).



Entry	Phenanthrene equiv.	Conditions	Yield %[a]			
			2.156	**3.27**	**2.157**	**3.29**
1	0	16 mL min^{-1}, 1.286 A (2.0 F)	35	18	15	2
2	0.5	16 mL min^{-1}, 1.286 A (2.0 F)	15	52	<1	4
3	1	0.5 mL min^{-1}, 0.04 A (2.0 F)	34	55	5	2
4	1	2 mL min^{-1}, 1.286 A (2.0 F)	14	85	<1	5
5	0.5	2 mL min^{-1}, 1.286 A (2.0 F)	15	84	1	6
6	0.25	2 mL min^{-1}, 1.286 A (2.0 F)	15	84	4	5
7	0.1	2 mL min^{-1}, 1.286 A (2.0 F)	17	81	3	6
8	**0.05**	**2 mL min^{-1}, 1.286 A (2.0 F)**	**16**	**81**	**4**	**6**
9	0.01	2 mL min^{-1}, 1.286 A (2.0 F)	18	64	15	4
10	0	2 mL min^{-1}, 1.286 A (2.0 F)	20	27	48	<1
11	0.05	2 mL min^{-1}, 0.2 A (2.5 F)	10	86	2	5

a. Yield by calibrated GC

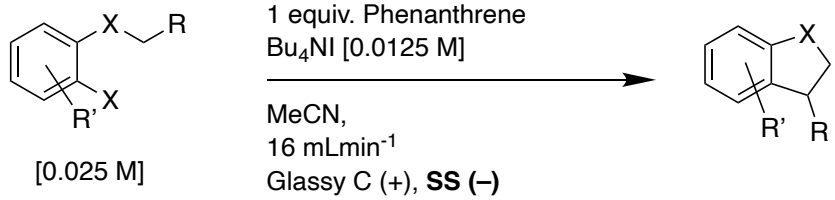
Table 3.10: Further development of reductive cyclisation by Dr Ana Folgueiras

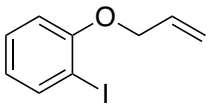
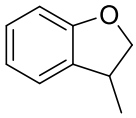
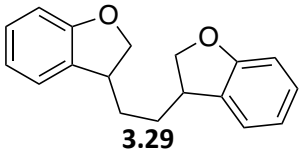
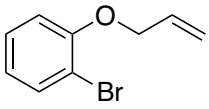
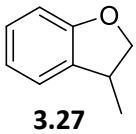
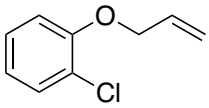
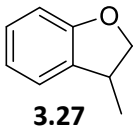
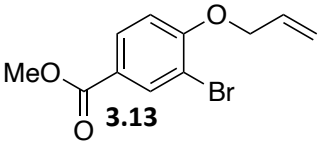
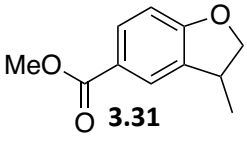
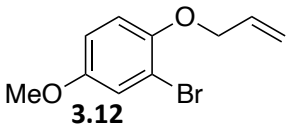
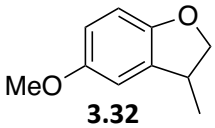
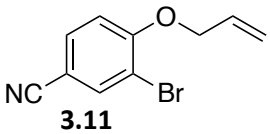
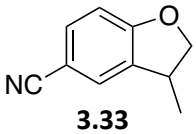
The introduction of the new electrolyte (Bu_4NI) addressed many of the shortcomings of the previous method. There was now no need to use a high flow rate through the reactor (which involved a concomitantly high amount of current being passed and was only performed at them because the process was otherwise yield inefficient). The requirement for two passes through the reactor was now unnecessary: high conversion was possible in a single pass of the reactor. Furthermore, and most significantly, no loss of efficacy was observed when using a catalytic

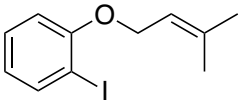
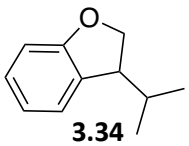
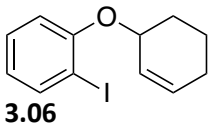
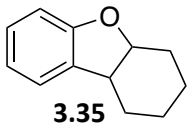
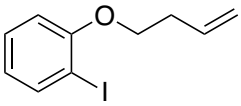
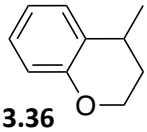
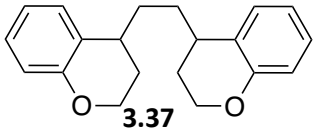
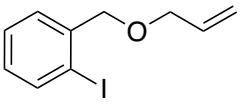
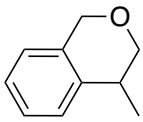
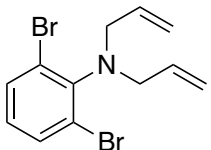
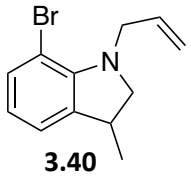
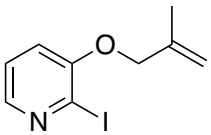
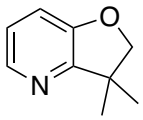
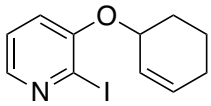
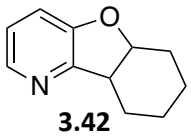
quantity of the phenanthrene mediator. An explanation of how the reaction proceeded efficiently with only catalytic quantities of the mediator is given in 3.10.1. The conditions illustrated in entry 8 of Table 3.10 will be used in future work on this project.

3.8 Substrate scope

The conditions illustrated in Scheme 3.16 were applied to a range of aryl halide substrates (Table 3.11).



Entry	SM	Product		Yield	
		Monomer	Dimer	Monomer	Dimer
1	 **2.156**	 **3.27**	 **3.29**	83	13
2	 **3.14**	 **3.27**	n/a	59[a]	n/a
3	 **3.17**	 **3.27**	n/a	51[a]	n/a
4	 **3.13**	 **3.31**	n/a	73	n/a
5	 **3.12**	 **3.32**	n/a	91	n/a
6	 **3.11**	 **3.33**	n/a	83	n/a

7	 **3.08**	 **3.34**	n/a	60	n/a
8	 **3.06**	 **3.35**	n/a	84	n/a
9	 **3.15**	 **3.36**	 **3.37**	83	6
10	 **3.38**	 **3.39**	n/a	85	n/a
11	 **3.24**	 **3.40**	n/a	55	n/a
12	 **3.10**	 **3.41**	n/a	75[b]	n/a
13	 **3.09**	 **3.42**	n/a	92[b]	n/a

a. Yield by calibrated GC, single pass of Ammonite 8 reactor.
b. Substrates prepared by Mateo Salam–Perez of Prof. Richard Brown's research group

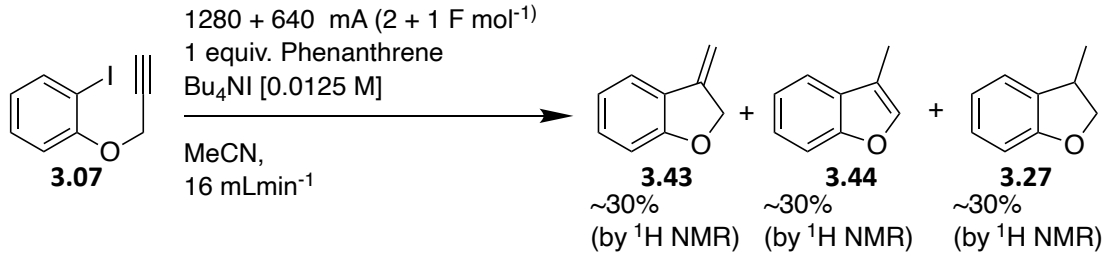
Table 3.11: Substrate scope for reductive cyclisation

Using conditions illustrated in Scheme 3.16, Eleven substrates were successfully cyclised to their corresponding heterocycles in 60–92% yield It was found that the method was applicable for alkylated anilines (entry 10), phenols (entries 1–9, 10–12) and pyridines (entries 11 & 12), and functionalisation was tolerated both on the aromatic ring (entries 4–6) and on the alkene chain (entries 7–9, 11). Furthermore, a variety of aryl halides could be used in the reaction, including iodides, bromides and chlorides. In some cases (entries 1 & 9), the dimerised compound was isolated from the reaction. Further testing of substrates will be the basis of the future work on this project, along with repeating those tested in Table 3.11 using the refined conditions illustrated in entry 8 of Table 3.10 (developed by Dr Ana Folgueiras).

3.9 Limitations in substrate scope

Using the conditions illustrated in Scheme 3.16, the cyclisation of a number of substrates were investigated. However, the anticipated reaction outcomes were not always observed as detailed below.

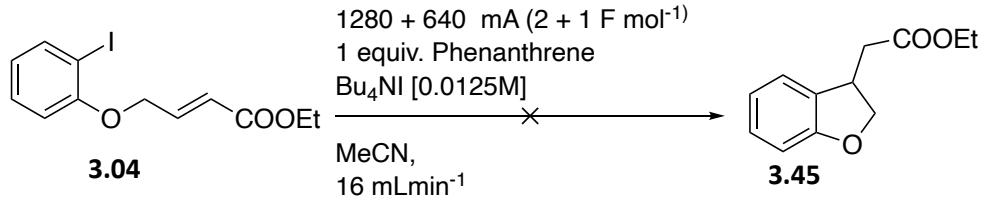
3.9.1 1-Iodo-2-(prop-2-yn-1-yloxy)benzene



Scheme 3.17: Reductive cyclisation of 1-iodo-2-(prop-2-yn-1-yloxy)benzene

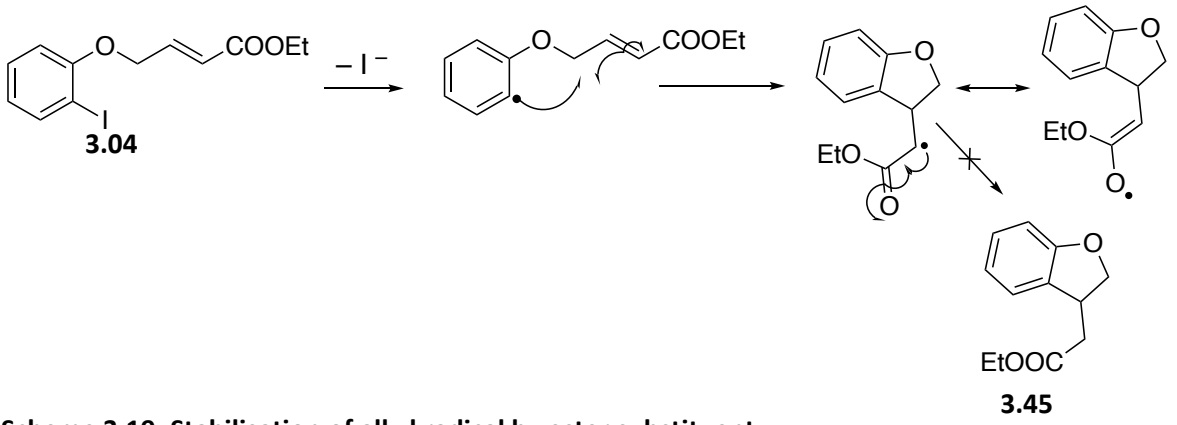
The cyclisation of 1-iodo-2-(prop-2-yn-1-yloxy)benzene **3.07** led to a mixture of products, including the exo and endo alkene products **3.42** and **3.44** respectively, and the over-reduced dihydrobenzofuran **3.27**. The products could not be separated from each other by column chromatography as their polarities are very similar.

3.9.2 Ethyl (*E*)-4-(2-iodophenoxy)but-2-enoate



Scheme 3.18: Reductive cyclisation of Ethyl (*E*)-4-(2-iodophenoxy)but-2-enoate

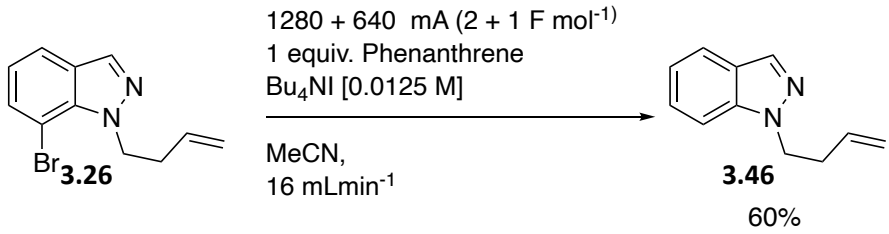
With this substrate, a poor mass recovery was observed from the reaction, with only a very small amount of the cyclised product **3.45** observed by ^{1}H NMR. It is proposed that the cyclised radical is very stable, since it is conjugated to the ester motif. This might slow the polar crossover step, thereby inhibiting monomer formation and promoting formation of polymers, which would be insoluble in the workup solvent. Scheme 3.19 Illustrates this process.



Scheme 3.19: Stabilisation of alkyl radical by ester substituent

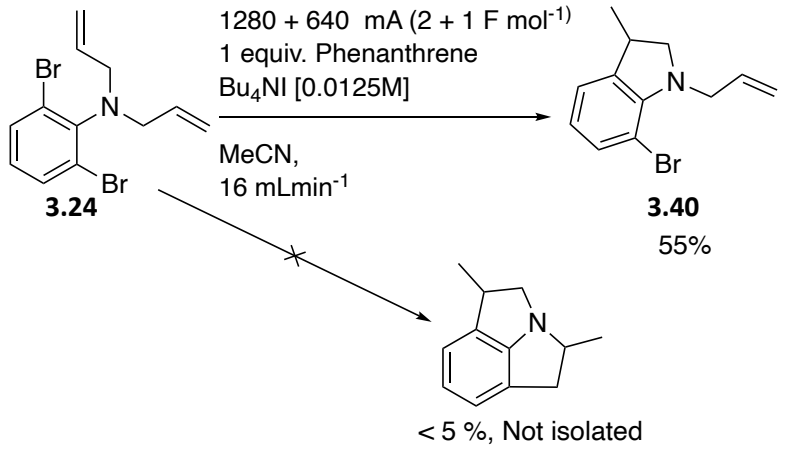
The addition of a proton donor might serve to improve the reaction outcome by promoting the protonation of the reduced substrate.

3.9.3 7-Bromo-1-(but-3-en-1-yl)-1*H*-indazole



Scheme 3.20: Reductive cyclisation of 7-bromo-1-(but-3-en-1-yl)-1*H*-indazole

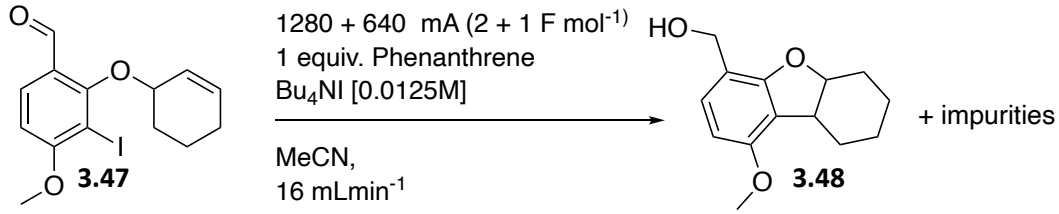
The desired cyclisation of this substrate was not successful with a 60% isolated yield of the debrominated product **3.46**. It is supposed that as the nitrogen of the rigid indazole ring reduces the degrees of freedom of the allyl chain, thereby reducing the likelihood of the alkene tether coming into sufficient proximity to the aryl radical for cyclisation to occur. The experimental result is supported by Dobbs *et al.*[258], who reported that proto-dehalogenation of 7-bromoindoles outpaced cyclisation. The indazole in this work bears a very close resemblance to a substrate tested by Dobbs. The same effect was observed for aniline substrate **3.24**, where only one cyclisation occurred instead of the intended two (Scheme 3.21).



Scheme 3.21: Reductive cyclisation of *N,N*-diallyl-2,6-dibromoaniline 3.24

The proposed rationale for cyclisation of one allyl group instead of two is that the indoline intermediate has a rigid structure and, in order to limit steric interactions, the second allyl substituent is projected away from the aromatic ring. This inhibits the second cyclisation. Cyclisation of anilines **3.24** and **3.26** might be promoted by heating the reaction solution as the reaction is seemingly hindered by kinetics.

3.9.4 2-(Cyclohex-2-en-1-yloxy)-3-iodo-4-methoxybenzaldehyde



Scheme 3.22: Reductive cyclisation of 2-(cyclohex-2-en-1-yloxy)-3-iodo-4-methoxybenzaldehyde

The electrochemical cyclisation of this substrate led to several side-products forming, the majority (50% by ^{1}H NMR) including the benzylic alcohol **3.46** that was not isolated owing to the small scale implemented. This confirms that the aldehyde is not tolerated in this process as is susceptible to reduction. Protection of the aldehyde as an acetal may alleviate this problem.

3.10 Mechanistic studies, cyclic voltammetry (CV) and mediator role

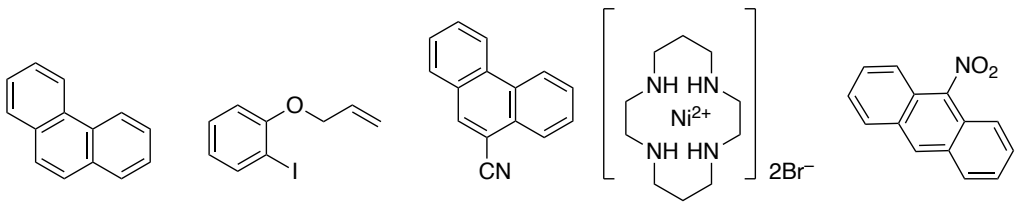
The mechanism for the cathodic cyclisation (and the counterelectrode process) will be discussed in this section. Initially the role of the mediator will be discussed, and therefore the three possible modes of action it can take in the reaction. Following these discussions, various studies (including cyclic voltammetry and other experiments) will be described that attempt to prove or disprove the *modus operandi* of the mediator. Finally, a summary will be carried out that

offers the most likely mechanism for the reaction and mediator (as there is insufficient evidence to definitively prove this).

3.10.1 Mediator studies and potential modes of action

The use of a mediator is deemed essential in the cyclisation process, at least to establish acceptable selectivity for cyclisation over dehalogenation. However, the use of a mediator in stoichiometric quantities (despite the mediator being recovered after the reaction) is undesirable. Ideally the reaction would be run in the absence of a mediator, or the mediator used catalytically (i.e., recycled using stoichiometric current, which was discovered to be possible after the completion of my work, see Table 3.10). Whether the mediator can be used catalytically is inherently conditional on the mechanism, with the redox potential of the mediator playing a key role in this (see section 1.3.4 for a description of this).

Various molecules have been shown to mediate cyclisations of aryl halides in the literature.[252, 254, 262] Work by Tokuda *et al.* described phenanthrene as the most efficient mediator for cyclisations in similar systems to those reported in this work[263], and phenanthrene also has the advantage of being cheap and commercially available. However, phenanthrene was found to be efficacious for conditions where there was no competing reaction (i.e., dehalogenation of aryl iodide **2.156** to phenol **2.157**), since use of an aprotic solvent and sacrificial magnesium anode significantly inhibits the capacity for the reaction to produce the noncyclised compound **2.157**. For reaction conditions where the dehalogenation reaction can more readily occur (e.g., when using a protic solvent in an undivided setup), a different mediator might have proved to be superior to phenanthrene. For this reason, several mediators were purchased or synthesised, and their reduction potentials and electrochemical characteristics measured by CV to investigate which is the most effective for the electrochemical conditions utilised in this work. The reduction potentials for a selection of mediators commonly used in electrochemical cyclisations, as well as that of the aryl iodide **2.156**, are depicted in Figure 3.1.

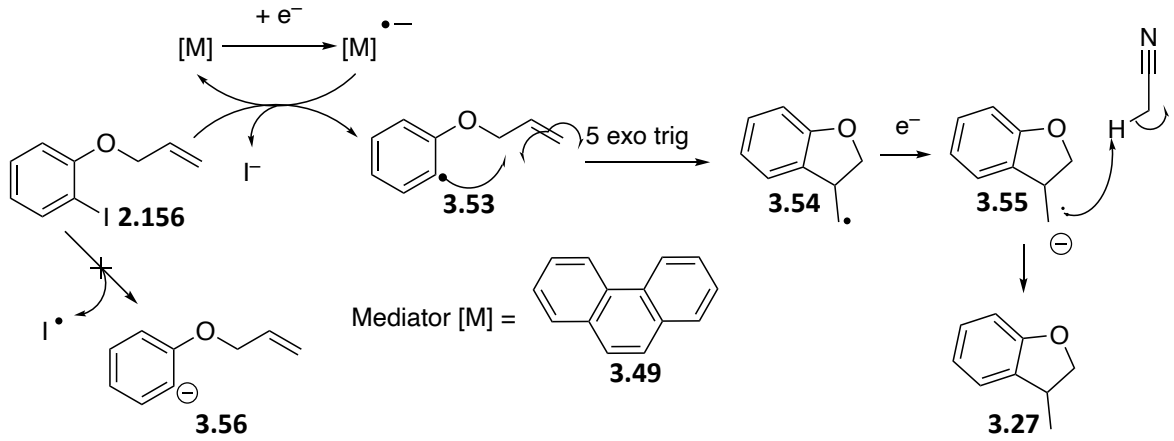


	3.49	**2.156**	**3.50**	**3.51**	**3.52**
V_r vs SCE / V	-2.6	-2.2	-1.9	-1.2	-1.1

Figure 3.1: Structure and reduction potentials for several known mediators in reductive cyclisation reaction, in comparison to that of 1-(Allyloxy)-2-iodobenzene 2.156

Experimentally, phenanthrene (**3.49)** was highly efficacious in this work (where dehalogenation is a competing process), however there is merit in comparing other mediators available, in order to potentially elucidate a reaction mechanism and as troubleshoot if certain substrates fail (where introduction of a different mediator might remedy).

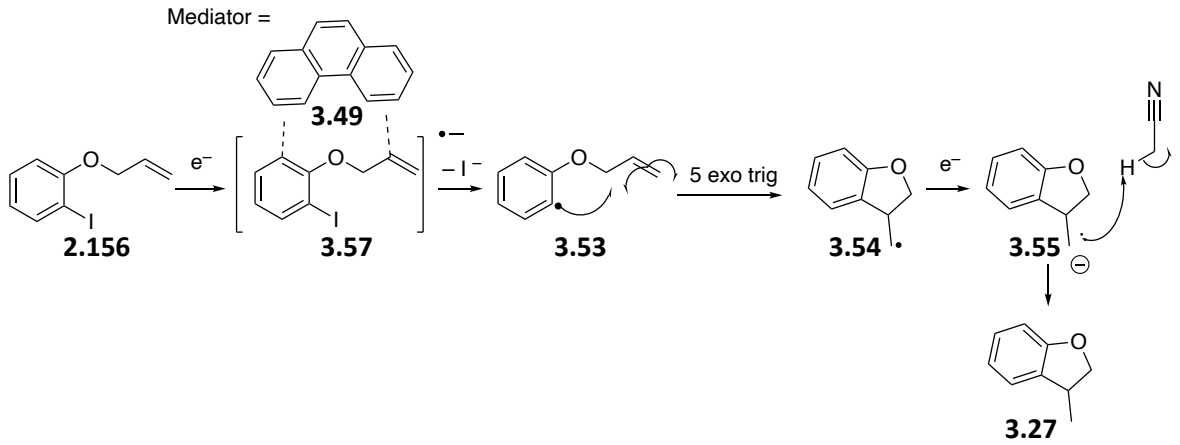
These selected mediators have reduction potentials both smaller and greater in magnitude than that of the aryl iodide **2.156**, on which the electrochemical method was tested on. This could be of significance in how they participate in the reaction. There are three proposed mechanisms for the cyclisation, with the mediator playing a different role in each. The first is illustrated (Scheme 3.23).



Scheme 3.23: Mechanism for reductive cyclisation with a mediator of a less-negative reduction potential than substrate

For this mechanism to be feasible, the mediator should have a less negative reduction potential than that of the substrate (such that mediator reduction occurs first), allowing the mediator to transfer its electron to the substrate to form radical species **3.53** that goes on to cyclise. In this context, the regenerated mediator can then return to the cathode to be re-reduced, allowing it to act catalytically. Observing the reduction potentials for the mediators in Figure 3.1, it appears that **3.50** to **3.52** can all operate via this mechanism (as they are reduced at significantly lower potentials than that of the substrate **2.156**), but not phenanthrene **3.49**. This point will be further discussed in section 3.10.3.

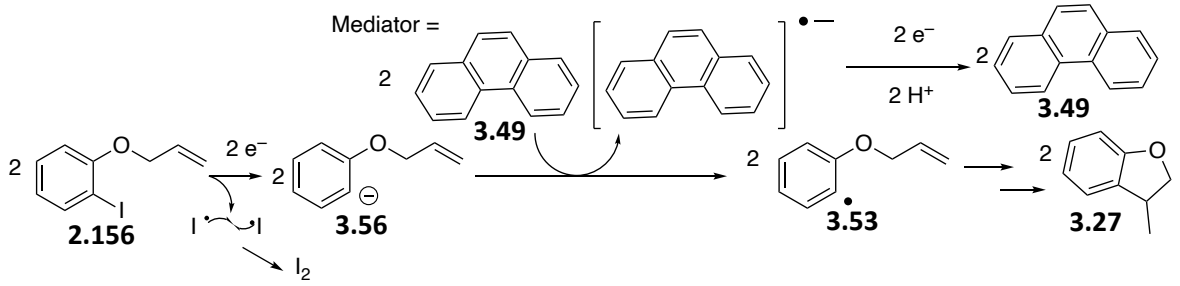
The second suggested mechanism proposes a molecular stabilisation of the intermediate that doesn't involve a redox process (Scheme 3.24).



Scheme 3.24: Mechanism for reductive cyclisation with a redox inactive mediator

For a mediator to partake in the reaction in the manner proposed in Scheme 3.24, it should not display any significant redox behaviour, either reductive or oxidative, since it is unchanged by the reaction conditions. In this context, the mediator does not play a role in electron transfer; that occurs purely between the substrate **2.156** and the cathode. The mediator stabilises the radical intermediate **3.57** through intermolecular interactions. A mediator with a more negative reduction potential could act through this mechanism, since the substrate would preferentially be reduced leaving the mediator unchanged. On this basis, phenanthrene **3.49** is the only mediator from the selection in Figure 3.1 that could participate in this way.

The third suggested mechanism proposes a reoxidation of the deprotonated substrate by the mediator (Scheme 3.25).



Scheme 3.25: Mechanism for reductive cyclisation with a mediator of a more-negative reduction potential than substrate

In order for the mediator to oxidise the anionic species **3.56** to the radical intermediate **3.53** the mediator should have a more negative reduction potential than the substrate **2.156**, but also be capable of accepting electrons. From 3.51, the cyclisation should occur in the same way as that illustrated in Scheme 3.24. Such a mediator cannot operate catalytically, since a stoichiometric quantity of the mediator is required to accept one equivalent of electrons from the

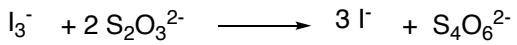
substrate. On the basis of reduction potentials, only phenanthrene (**3.49**) could act through this mode.

One of the key differences in the possible mechanisms (illustrated in Scheme 3.23, Scheme 3.24 and Scheme 3.25) is the initial reduction of substrate **2.156**. Scheme 3.23 and Scheme 3.24 portray the formation of radical species **3.53**, with loss of I^- i.e., the charge is localised on the iodide. This is contrary to Scheme 3.25 where the charge localises on the substrate, forming anion **3.56** and an iodine radical, which can couple with another to form I_2. The next section will describe experiments designed to validate or repudiate the possible mechanisms put forward in this section.

3.10.2 Mechanism elucidation studies (including Cyclic Voltammetry)

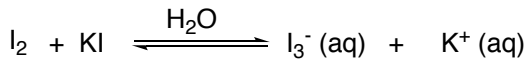
3.10.2.1 Further experiments

The amount of I_2 in the reaction solution of aryl iodide **2.156** after electrolysis (conditions illustrated in Scheme 3.16) was determined by titration (Scheme 3.26). The amount of I_2 in the reaction solution after electrolysis will indicate whether the first SET localises the negative charge on the substrate or on iodine.



Scheme 3.26: Thiosulfate/Iodine titration on electrolysis solution

I_2 has a very low solubility in water and so KI was added in excess to the reaction solution, which reversibly reacts to form the water-soluble I_3^- anion (Scheme 3.27):

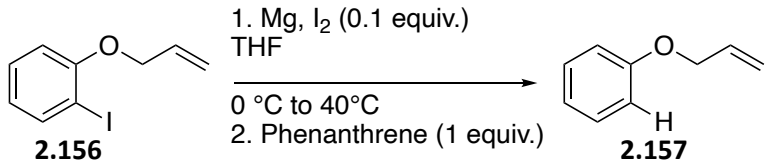


Scheme 3.27: Triiodide formation from iodine in aqueous media

The amount of I_2 produced in the titration, following the reaction conditions illustrated in Scheme 3.16, was determined as 1 mol% relative to SM **2.156**. This gives evidence that the initial $1e^-$ reduction of the substrate localises the charge on the iodide instead of the aromatic. This suggests that the mechanism follows that illustrated in either Scheme 3.23 or Scheme 3.24, although it should not be ruled out that the I_2 could, once formed, react in the cell prior to the solution leaving the reactor. Literature studies of the mechanism support the hypothesis whereby the radical species **3.53** forms initially.[252, 263]

As another test to investigate the mechanism, the substrate **2.156** was allowed to react with magnesium, forming a Grignard reagent in the presence of phenanthrene to observe if

cyclisation occurs. If the reaction follows the mechanism proposed in Scheme 3.25, then the formation of the carbanion **3.56** (or equivalent whereby magnesium iodide stabilises the carbanion) followed by addition of phenanthrene should allow reoxidation to the radical species **3.53** and then cyclisation. The conditions are illustrated in Scheme 3.28:



Scheme 3.28: Grignard reaction with (1-Allyloxy)2-iodobenzene

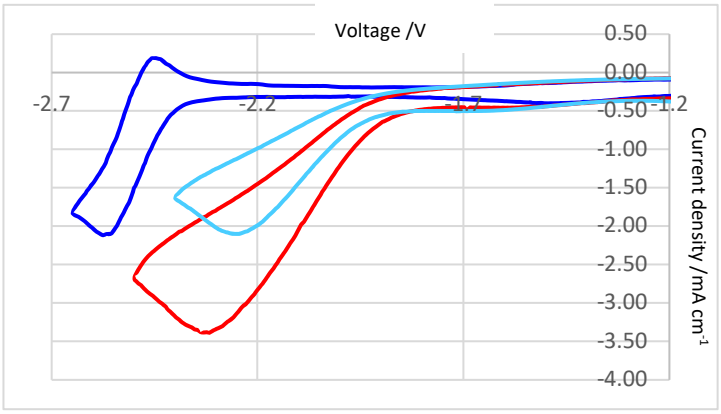
In the presence of magnesium and catalytic iodine, the Grignard reagent was formed. However, upon addition of phenanthrene, cyclisation was not observed and on quenching the dehalogenated compound **2.157** was formed. It should not be ruled out though that magnesium could inhibit cyclisation by complexing with the carbanion, and so perhaps the reaction should be repeated using a lithiated base before refuting the mechanism outlined in Scheme 3.25.

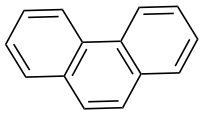
The deuterium labelling experiment conducted in CH_3OD described in section 2.12.3 suggests that the mechanism could follow that illustrated in Scheme 3.25, although it would be unwise to draw conclusions as to the mechanism in the absence of a mediator (since its presence in the reaction solution, even if only catalytically seems to be integral to the cyclisation occurring). Using CH_3OD as solvent offers two routes for quenching; either via the radical species which favours the weaker CH bond, or via the anion which favours D abstraction (due to lower pKa). Since primarily D abstraction was observed (90:10 ^2H to ^1H incorporation, entry 7), it might suggest that reduction to the carbanion **3.56** occurs initially. However, it is also plausible that in the reaction the radical species **3.53** is rapidly reduced again (instead of H abstraction with CH_3OD). As such this experiment neither proves nor disproves the possible mechanisms illustrated.

3.10.2.2 Cyclic Voltammetry of mediators and aryl iodide 2.156

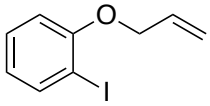
The cyclic voltammetry traces for key substrates and mediators are illustrated and their behaviour analysed in this section.

Figure 3.2: Cyclic voltammetry of phenanthrene and (1-Allyloxy)-2-iodobenzene





3.49



2.156

[0.005 M] phenanthrene, -1.2 to -2.65 V, 25 mV s^{-1}, VC/Pt, MeCN, 5 equiv. MeOH

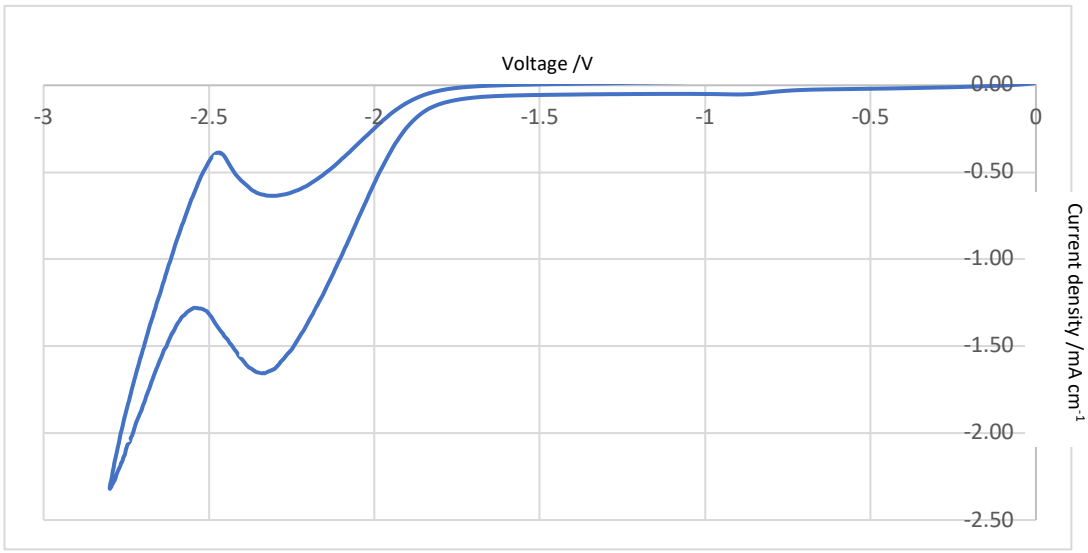
[0.005 M] phenanthrene, [0.005 M] aryl iodide, -1.2 to -2.3 V, 25 mV s^{-1}, VC/Pt, MeCN, 5 equiv. MeOH

[0.005 M] aryl iodide, -1.2 to -2.5 V, 25 mV s^{-1}, VC/Pt, MeCN, 5 equiv. MeOH

Observing each spectrum of Figure 3.1 in turn, the phenanthrene mediator **3.51** (dark blue spectrum in Figure 3.2) displays reversible electrochemical behaviour within the timeframe of the CV, with a reduction potential of –2.5 V. The aryl iodide substrate **2.156** (turquoise spectrum in Figure 3.2) displays irreversible redox behaviour with a reduction potential of –2.2 V. There appears to only be one reduction event in substrate **2.156** in the experiment; one might expect two peaks corresponding to formation of radical **3.53** and then reduction to cyclised anion **3.55**. However, the CV conditions differ from those in the Ammonite and so care should be taken to suggest a mechanism based on this information, especially in absence of mediator. CV conducted on a mixture of these two compounds (red spectrum in Figure 3.1) suggests that the aryl iodide reduction potential has not changed since the fractional current density is the same as that of the compound alone. However, by observing the increased current density for the red spectrum (aryl iodide and mediator), it is apparent that phenanthrene is reduced at –2.2 V, the same potential as the substrate and therefore at a less negative potential in the presence of the aryl iodide **2.156**. This, along with the phenanthrene/substrate mixture displaying irreversible redox behaviour, indicates that an interaction is occurring between substrate and mediator, confirming that the mediator plays a role in the reductive cyclisation. The implications of the mediator reducing at a more negative potential than the substrate will be discussed in 3.10.1.

A subsequent CV study where the scan range was extended to between 0 and –3 V was carried out (Figure 3.3).

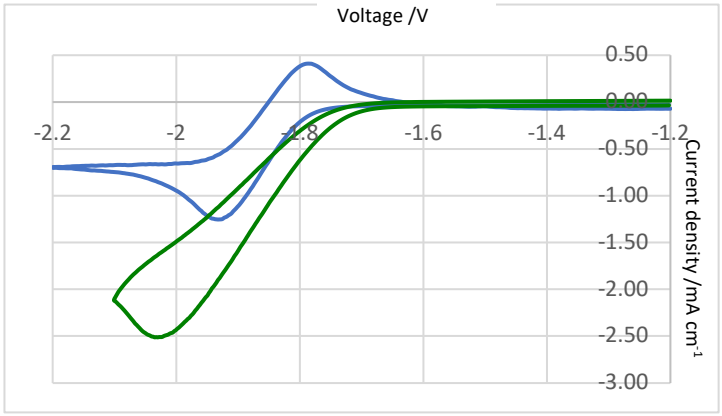
Figure 3.3: Cyclic voltammetry of phenanthrene and (1-Allyloxy)-2-iodobenzene with extended scan range

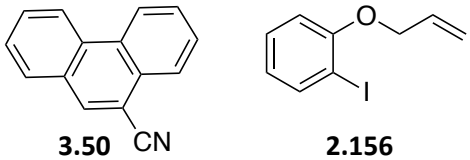


From Figure 3.3 it can be deduced that one of the substrates in the experiment is being reoxidised on the reverse sweep, most likely the phenanthrene radical. This demonstrates that it displays reversible redox behaviour and can transfer electrons to or from the substrate.

It should be noted that the conditions for CV experiments are different to those of the Ammonite reactor, not least because the working electrodes are made of different materials (glassy carbon for CV, SS for the reactor) and therefore the redox potentials may differ.

Figure 3.4: Cyclic voltammetry of 9–Cyanophenanthrene 3.50 and (1-Allyloxy)-2-iodobenzene 2.156





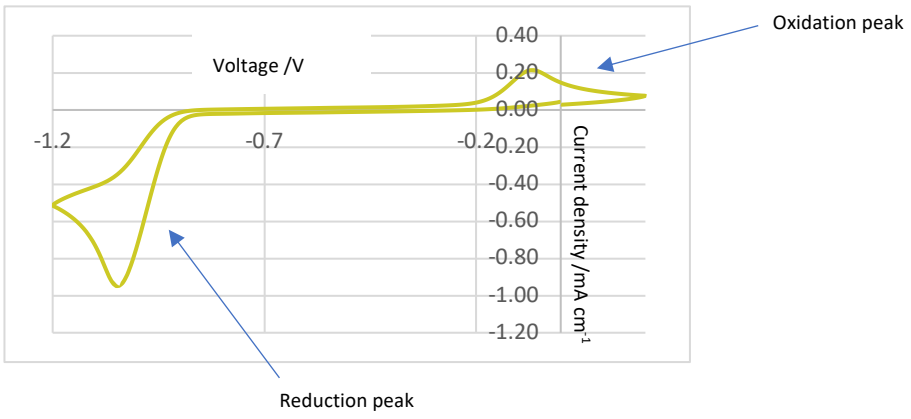
3.50 **2.156**

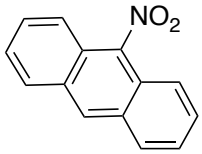
[0.005 M] 9–cyanophenanthrene, -1.2 to -2.2V, 25 mV s^{-1}, VC/Pt, MeCN, 5 equiv. MeOH

[0.005 M] 9–Cyanophenanthrene, 0.005 M aryl iodide, -1.2 to -2.1 V, 25 mV s^{-1}, VC/Pt, MeCN, 5 equiv.

In comparison to phenanthrene (**3.49**), 9-cyanophenanthrene (**3.50**) as mediator displays a significantly less negative reduction potential, with reversible redox behaviour in the experiment. It is noteworthy that the mediator in this experiment has a slightly higher (i.e., less negative) reduction potential than that of the substrate **2.156**, meaning that the mechanism by which it acts (and even for the process entirely) could be different to that of phenanthrene (**3.49)**. This is discussed in section 3.10.1. There appears to be little difference between the CV behaviour of this mediator–substrate mixture (**3.50** and **2.156**) to that in Figure 3.2 (**3.49** and **2.156**). 9–cyanophenanthrene was not pursued as a mediator because experimentally it was found to be no more efficacious than phenanthrene at promoting cyclisation but is significantly more laborious to synthesise.

Figure 3.5: Cyclic voltammetry of 9-Nitroanthracene





3.51

——[0.005 M] 9-Nitroanthracene, 0.2 to -1.2 V, 25 mV s^{-1}, VC/Pt, MeCN, 5 equiv. MeOH

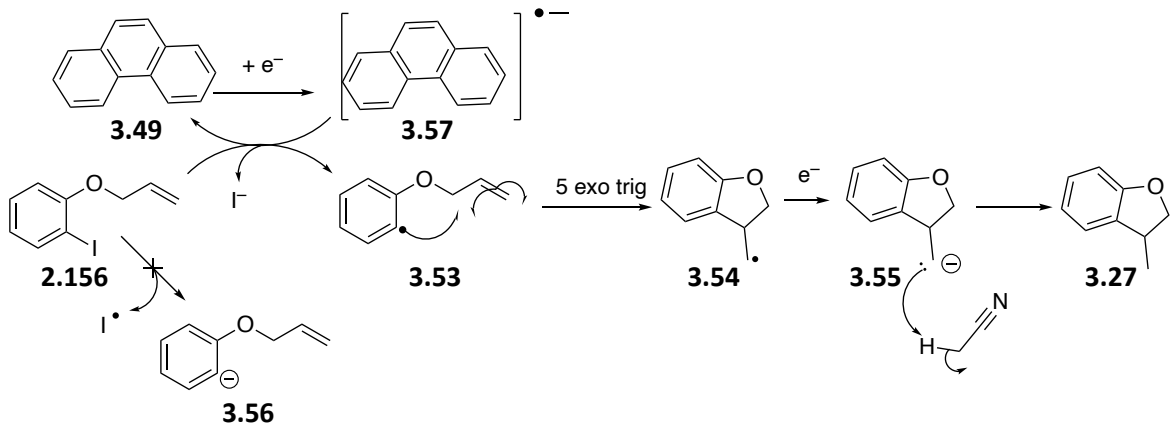
9-Nitroanthracene has a reduction potential of -1.0 V but does not display reversible behaviour since the reverse oxidation peak has a lower peak area than the reduction peak. This suggests that some of the mediator is being consumed in the reverse sweep of the CV, which is perhaps unsurprising since the nitro group has been found to be reductively active (as confirmed by the Haber reduction in section 1.5.2.1). The proposed products are the nitroso and/or amine derivates. Due to this result, this mediator was not utilised in this work as it would not be recovered, and its reactivity would likely lead to problems in the synthesis.

3.10.3 Proposed mechanism

Summarising the previous two sections, it is clear that of the three possible cathodic mechanisms illustrated in 3.10.2, only Scheme 3.23 and Scheme 3.24 are plausible, as it has been proven beyond reasonable doubt that the substrate is reduced to the radical species **3.53** rather than the non–cyclised anionic form **3.56**, thereby producing I^- instead of I_2 (which contradicts Scheme 3.24).

In establishing which of Scheme 3.23 or Scheme 3.24 is the most likely mechanism, it is worth considering whether the mediator is redox active in the reaction. CV studies of phenanthrene, **3.49** (Figure 3.2) demonstrate that the mediator has a reduction potential (–2.6 V), which is greater in magnitude than the substrate **2.156** (–2.2 V). On first impressions then it would suggest the substrate can be reduced with 1 equiv. of current without the mediator ever experiencing a redox process. However, it is also noteworthy that the reduction event that occurs in the mixture of **2.156** and **3.49** is less negative than that of phenanthrene alone. This not only suggests the mediator has a redox role in the reaction, but it also demonstrates that in the presence of the substrate, the reduction potential of phenanthrene **3.49** is shifted to a less negative value. It is not possible from the CV trace to determine what this is, as the reduction peak for the two molecules coalesces, however it is very plausible that phenanthrene, in the presence of the substrate, reduces at a lower potential than the substrate. Even if not, it is possible that fractional conversion of the mediator might be sufficient to catalyse the cyclisation process (**3.53** to **3.54**). If this is indeed the case (or if the mediator reduces at a less negative potential than the substrate in the reaction solution), the mechanism follows that of Scheme 3.23

whereby the mediator transfers electrons to the substrate and not the cathode. To further validate this theory, the mechanism outlined in Scheme 3.23 strongly suggests that the mediator can operate catalytically, and indeed conditions by Dr Ana Folgueiras confirmed that phenanthrene **3.49** operates catalytically (as low as 5 mol%) in the reaction (Entry 7, Table 3.10). It is possible that a mediator could act catalytically in the mechanism outlined in Scheme 3.24, but it would be unlikely since the intermolecular interaction between mediator and substrate would need to accelerate the cyclisation step (from **3.53** to **3.54**), otherwise the uncoordinated radical species will quickly reduce to the non-cyclised anion **3.56**, leading to dehalogenated product **2.157**. With all this in mind, the proposed cathodic mechanism is illustrated (Scheme 3.29).

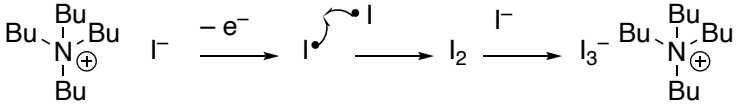


Scheme 3.29: Proposed cathodic cyclisation mechanism, acknowledging experimental data

The proposed mechanism is a two-electron reduction, whereby the first SET produces the aryl radical **3.53** with concomitant loss of I^-. Next a 5–exo–trig cyclisation occurs to form cyclised radical **3.54**. Then, following a second SET and hydrogen abstraction (proposed to be from MeCN as the pKa of this is far lower than that of the carbanion) the dihydrobenzofuran **3.27** is furnished. The mediator **3.49** is initially reduced at the cathode to the radical cation **3.57**, which then donates its free electron to substrate **2.156** and in the process reoxidises to **3.49**.

The counterelectrode reaction is proposed to be the oxidation of I^- to I_2 (Scheme 3.30). The I^- anion can be sourced from the tetrabutylammonium salt, or from the cathodic process.

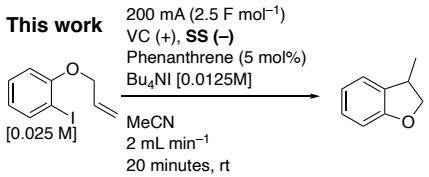
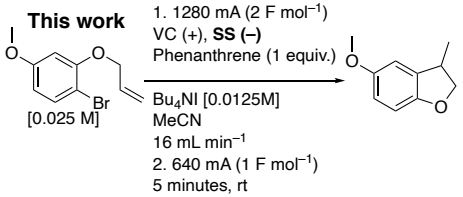
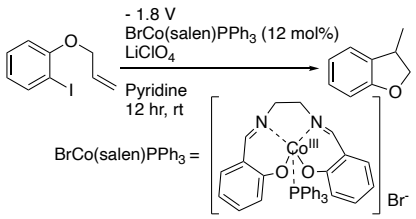
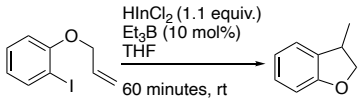
Anodic process:

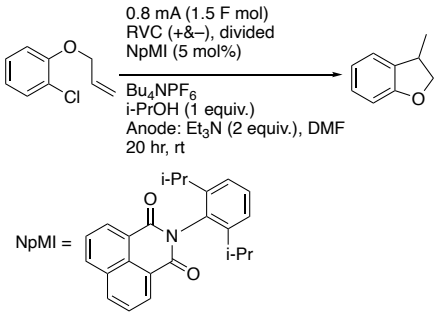
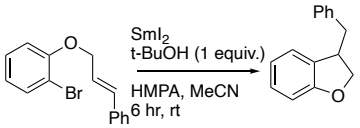
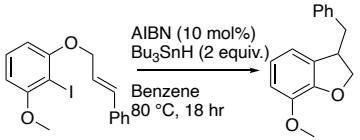


Scheme 3.30: Mechanism for the counterelectrode reaction in reductive cyclisation electrosynthesis

3.11 Green metrics of cathodic cyclisation process

The environmental impacts of the reductive cyclisation reaction were compared to literature methods.

Reaction and conditions	Yield (%)	RME[a]	PMI[b] reagents	PMI[b] solvents	Hazardous/ precious chemicals	Solvent	Ref
This work 	86●	25.8	3.9	273	Phenanthrene● H410[d]	MeCN●	n/a
This work 	91●	34.9	4.1	210	Phenanthrene● H410[d]	MeCN●	n/a
	45●	13.0	5.9	8.2	Co●, Hg● Co: 50-500 years of reserves[c] Hg: H330[f], 360[e], 372[e], 410[d]	Pyridine●	262
	93●	26.3	3.8	71.1	$HInCl_2$● In: 5–50 years of reserves[c]	THF●	243

Reaction and conditions	Yield (%)	RME[a]	PMI[b] reagents	PMI[b] solvents	Hazardous/ precious chemicals	Solvent	Ref
	54●	4.3	23.3	331.2	–●	DMF, Et_3N●	250
	89●	5.2	19.3	362.6	SmI_2● Sm: 50–500 years of reserves[c]	HMPA●, MeCN●	244
	88●	21.9	4.6	208	$SnBu_3H$●, AIBN● Sn: 5–50 years of reserves[c] H372[c], 360FD[e], 410[b]	Benzene●	239

a. RME is Reaction Mass Efficiency (no. moles product/no. moles reagents),
b. PMI is Process Mass Intensity (mass of product/mass of materials)
c. Based on current rate of extraction[163]
d. Environmental concerns
e. Long–term toxicity
f. Acute toxicity

Table 3.12: Comparison of green metrics for reductive cyclisations

The processes developed in this work compare favourably to other methods in many respects, for example, in avoiding the use of hazardous reagents or solvents. However, unfortunately, acetonitrile is not considered a 'green' solvent and phenanthrene exhibits moderate toxicity. To improve the environmental impact of the process, it would be advantageous to replace acetonitrile with a less hazardous solvent such as acetone, ethyl acetate or a green polar aprotic solvent. In this process, phenanthrene is used catalytically, and therefore only in small quantities, which is beneficial from an environmental perspective. It is possible that an alternative, less hazardous, mediator could be utilised in the reaction: literature reports describe the use of other mediators which offer improved environmental impact.[253] The RME and PMI values for the two processes in this work are similar to or better than those of other methods. Increasing the concentration of substrate would improve the PMI: this is feasible as under conditions in Table 3.1 the reaction can proceed efficiently at flow rates in the Ammonite 8 reactor, allowing a higher concentration of substrate to be passed without an unsafe current passing.

3.12 Applications in synthesis of pharmaceuticals

The objective of developing a method for reductive cyclisation on multigram scale, without utilising toxic or expensive metals is of great importance in the fields of pharmaceuticals and fine chemicals. Electrochemistry has been identified as a sustainable methodology that should be utilised in the synthesis of compounds where possible, owing to favourable green metrics and improved safety ratings for many processes. As such it is desirable that the electrochemical reductive cyclisation process described in this work can be applied in a wide range of applications.

3.12.1 Bioactivity of cyclised compounds

Many natural products, approved drugs and drug development candidates contain a cyclised core. The cyclised scaffolds synthesised in this work are illustrated below (Figure 3.6).

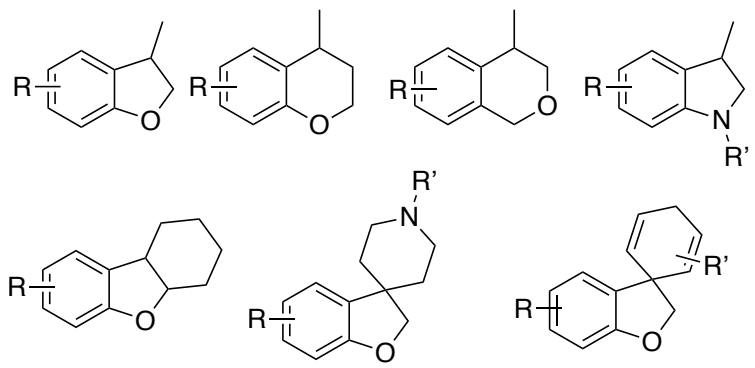
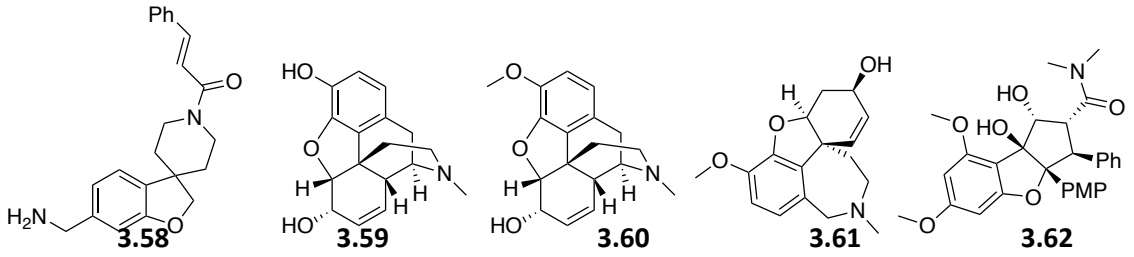


Figure 3.6: Cyclised scaffolds synthesised in this work

These scaffolds cannot be readily synthesised by many other methods, therefore, new methods for their preparation are highly advantageous. The methods described herein may also offer the opportunity to create scaffolds previously unexplored and thereby Increase chemical space. Utilising the methods described in this work could provide a range of novel chemical entities available for assay against known biological targets. For example, high binding affinities of such scaffolds has been reported for the tryptase enzymes, which are a family of enzymes involved in mast–cell degranulation, a key process in inflammation. Tryptase inhibitors have been shown to be effective in treating asthma symptoms and arthritis.[264] Compounds featuring the benzofuran–spiropiperidine scaffold have been shown to be potent inhibitors of this tryptase enzyme family[265]. In addition, the dihydrobenzofuran motif features in a wide range of opioid analgesics such as morphine and codeine, other alkaloids such as galantamine and flavaglines such as rocaglamide (Figure 3.7). The application of this work to the synthesis of such motifs would significantly increase its impact.



(*E*)-1-(6-(aminomethyl)-2*H*-spiro[benzofuran-3,4'-piperidin]-1'-yl)-3-phenylprop-2-

Morphine

Codeine

Galantamine

Rocaglamide

Figure 3.7: Experimental and approved drug candidates featuring the dihydrobenzofuran motif

3.13 Conclusions and future work

3.13.1 Conclusions

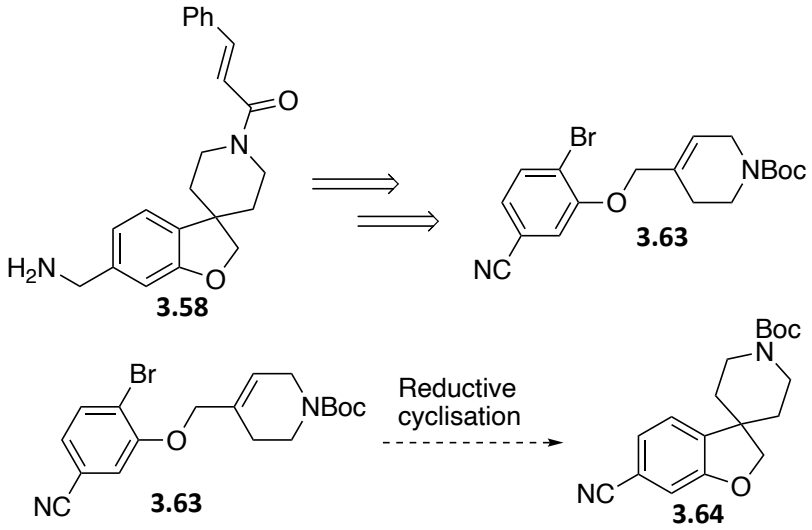
The cathodic cyclisation of aryl halides to afford benzofurans, benzopyrans and indolines has been successfully carried out using the Ammonite 8 flow electrolysis cell. The reaction proceeds smoothly with a 5 mol% loading of mediator and a cheap electrolyte (Bu_4NI), which serves as a substrate for the counterelectrode oxidation. Several substrates have been tested with an existing method (prior to improved conditions being discovered), with excellent yields (up to 92%), high current efficiencies (up to 63%) and high productivities (up to 16.8 mmol hr^{-1}). Thus,

this process provides a highly desirable method for industrial scale-up and future research projects, owing to its favourable green metrics and sustainable methodology, replacing methods that utilise harmful reagents (e.g., $SnBu_3H$ and AIBN). Furthermore, this is the first example of an electrochemical radical-mediated synthesis that avoids the use of a sacrificial anode material which offers great scope for applying this methodology to flow electrosynthesis.

3.13.2 Future work

3.13.2.1 Reductive cyclisation

The improved conditions for reductive cyclisation (developed by me and later Dr Ana Folgueiras) will be tested on all previous substrates. The methods described will also be applied to the synthesis of compounds of medicinal interest, for example the spiropiperidine scaffold, providing a library of tryptase inhibitors (as discussed in section 3.12.1), with the key cyclisation as illustrated (Scheme 3.31).



Scheme 3.31: Reductive cyclisation in the synthesis of experimental drug candidate dihydrobenzofuran–spiropiperidine 3.56

Since indolines, functionalised dihydrobenzofurans, tetrahydrobenzopyrans have already been furnished by this method (Table 3.11), one could imagine that the scope of this cyclisation reaction could be expanded to other heterocycles. It could also be extended to alkenyl iodides in order to furnish carbocycles (Figure 3.8). A radical cascade pathway might also be possible, although stereoselectivity may prove difficult to control.

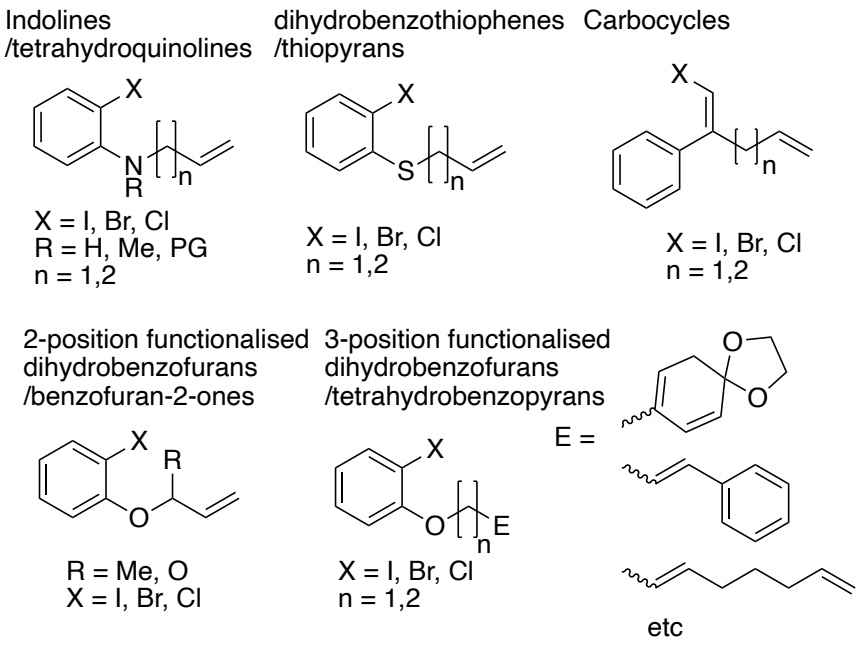
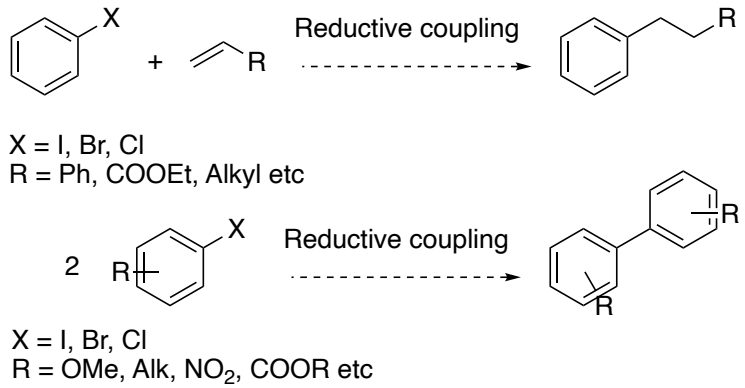


Figure 3.8: Proposed substrates for intramolecular reductive cyclisation

3.13.2.2 Intermolecular coupling

Since the reaction proceeds through a radical species, the methodology could be extended to induce intermolecular coupling reactions by employing a range of electrophiles. The coupling of two radical species (as in the case of biaryl coupling) is also feasible. Such powerful transformations are widely used in organic synthesis; as such, a metal–free reductive electrochemical method would be of great significance. Potential substrates are illustrated in Scheme 3.32.



Scheme 3.32: Proposed intermolecular reductive coupling reactions

Chapter 4 Experimental

4.1 Equipment specifications

4.1.1 Ammonite 8 specification[91]

The anode is a disc of carbon-filled polyvinylidenefluoride (C/PVDF), and the cathode is a circular 316 L stainless steel plate of diameter 85 mm and thickness 5.0 mm. A 0.5 mm depth spiral groove is machined into the steel electrode, which accepts a 1.0 mm thick gasket/spacer to create an interelectrode gap of approximately 0.5 mm, channel length of 100 cm and reactor volume of 1 mL. A copper disc backing plate improves the current distribution across the C/PVDF electrode. The cell is compressed between an aluminium base plate and a Perspex top via a central bolt and 6 bolts around the perimeter. The solution enters and exits the cell through steel tubing (1/8th inch diameter), typically pumped using a peristaltic pump. Flow rates between 0.1 – 16.0 cm^3 min^{-1} could be achieved without leaking. Electrolysis is controlled with a Rapid Electronics switching mode power supply, with currents starting at 30 mA, with an upper limit for the reactor set at 2500 mA to avoid damage by heating caused by faradaic losses. A maximum cut-off voltage of 14 V was set. Electrosynthesis was carried out in the reactor using constant current mode, owing to the absence of a reference electrode and to optimise reactions for high productivity.

4.1.2 Parallel-plate reactor specification[98]

Syntheses were carried out in the cell described in section 1.1.8.3.6, equipped with a C/PVDF or RVC anode and a 316 stainless steel cathode. When a divided cell was needed, a Nafion® 438 membrane was placed between the anodic and the cathodic compartments. The cell current was controlled with a Rapid Electronics switching mode power supply (85-1903). A peristaltic pump (Ismatec Reglo Digital Model ISM831C) was used to flow the solutions through the electrochemical cell, using a two-channel six-roller cassette. The flow rate of the pump was calibrated periodically by measuring the volume of solvent collected over a given time. Two-stop Tygon® MHLL tubing (3.9 mm OD, 2.06 mm ID) was connected to peristaltic tubing connectors (PEEK), at each end. PTFE tubing of appropriate diameter was inserted into the connectors. The polymer mesh used as turbulence promoter is polyester (1000 micron aperture) purchased from Plastok Associates (www.plastok.co.uk; product reference: 07-1000/58). The mesh was cut to size using a sharp blade so that it could be inserted into the electrolysis compartment in stacks (7 per 3 mm).

4.1.3 Supply of chemicals

Chemicals and solvents were purchased from Sigma–Aldrich, Fisher Scientific, Alfa Aesar or Fluorochem. NaH was used as a 60% dispersion in oil. All air/moisture sensitive reactions were carried out under an inert atmosphere, in oven-dried or flame-dried glassware. The solvents CH_2Cl_2 (from CaH_2) were distilled before use, and where appropriate, other reagents and solvents were purified by standard techniques. TLC was performed on aluminium-precoated plates coated with silica gel 60 with an F_{254} indicator; visualised under UV light (254 nm) and/or by staining with potassium permanganate or DNPH. Flash column chromatography was performed using high purity silica gel, pore size 60 Å, 230-400 mesh particle size, purchased from Merck, or using a Biotage™ with pre-packed silica cartridges.

4.1.4 Characterisation equipment and methods

^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, d_4-MeOH, d_6-DMSO or D_2O (purchased from Cambridge Isotope Laboratories), or D_2O or d_6-DMSO from Sigma-Aldrich at 298 K using Bruker DPX400 (400 and 101 MHz respectively) spectrometers. Variable temperature ^1H NMR and ^{13}C NMR spectra was recorded using Bruker DPX500 (500 and 126 MHz respectively) spectrometers in D_6-DMSO. Chemical shifts are reported on the δ scale in ppm and were referenced to residual solvent ($CDCl_3$: 7.27 ppm for ^1H spectra and 77.0 ppm for ^{13}C spectra. d_4-MeOH: 3.50 ppm for ^1H and 49.0 for ^{13}C. d6-DMSO: 2.50 for ^1H and 39.5 for ^{13}C. D_2O: 4.79 for ^1H NMRs). All spectra were reprocessed using ACD/Labs software version 2015 or ACD/Spectrus. Coupling constants (*J*) were recorded in Hz and matched where possible. DEPT and 2D spectra (COSY, HSQC, HMBC and NOESY) were used to assign signals. The following abbreviations for the multiplicity of the peaks are s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), br. (broad), and m (multiplet). Dimethyl Terephthalate (DMT) was used as an internal standard within the crude material where NMR yields were determined.

Electrospray (ESI) low resolution mass spectra were recorded on a Waters TQD quadrupole spectrometer coupled to a waters UPLC. Electronimpact (EI) low resolution mass spectra were recorded on a Trace 2000 Series GC-MS coupled to a HP5890 GC. High resolution mass spectra were recorded on a Bruker APEX III FT-ICR mass spectrometer. Fourier-transform infrared (FT–IR) spectra are reported in wavenumbers (cm^{-1}) and were collected as solids or neat liquids on a Nicolet 380 using OMNIC software package. The abbreviations s (strong), m (medium), w (weak) and br. (broad) are used when reporting the spectra. Melting points were obtained using a Gallenkamp Electrothermal apparatus.

4.1.5 GC method

GC chromatograms were recorded on a Shimadzu GC using an Agilent HP-5 column 30 m, 0.32 mm diameter, 0.25 μm film. GC Method: (HP-5, 30 m, 0.32 mm diameter, 0.25 μm film, 60-325 °C. Method file: 80 °C injection, 60-240 °C, ramp 10 °C min^{-1}).

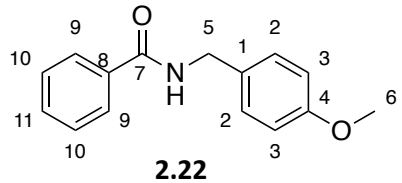
4.2 Synthesis of compounds in Chapter 2: Anodic deprotection of nitrogen-containing compounds

4.2.1 Amides and sulfonamides

4.2.1.1 General method A: Schotten–Baumann biphasic conditions

Preparation of amides was achieved using a literature procedure for amide coupling under Schotten–Baumann conditions:[207] To an ice–cooled solution of 4-methoxybenzylamine (1.31 mL, 10.0 mmol) in EtOAc (11 mL) and 15% aqueous Na_2CO_3 solution (25.0 mmol Na_2CO_3, 20 mL) was added the corresponding acid chloride (12.0 mmol). The reaction was stirred at RT for 16 hours and then the organic phase was separated. The aqueous phase was washed with EtOAc (2 x 10 mL). The combined organic phase was treated sequentially with 1M HCl (10 mL), sat. aq. $NaHCO_3$ (10 mL) and then brine (10 mL). The organic phase was dried ($MgSO_4$), and solvents were removed under reduced pressure. The crude product was recrystallised in EtOAc to afford the pure compound.

***N*-(4-Methoxybenzyl)benzamide**



2.22

Chemical Formula: $C_{15}H_{15}NO_2$

Molecular Weight: 241.29

N-(4-Methoxybenzyl)benzamide (**2.22**) was prepared using general method A: from Benzoyl chloride (3.711 g, 26.4 mmol), *N*-(4-Methoxybenzyl)benzamide (5.12 g, 21.2 mmol, 96%) was prepared as a white solid. The data are consistent with reported values.[266]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.80 (d, *J* = 7.6 Hz, 2H, **H**$_9$), 7.53 – 7.48 (m, 1H, **H**$_{11}$), 7.45 – 7.41 (m, 2H, **H**$_{10}$), 7.30 (d, *J* = 8.7 Hz, 2H, **H**$_2$), 6.90 (d, *J* = 8.7 Hz, 2H, **H**$_3$), 6.36 (br. s, 1H, N**H**), 4.59 (d, *J* = 5.6 Hz, 2H, **H**$_5$), 3.82 (s, 3H, **H**$_6$).

^{1}H NMR (VT): (DMSO-d_6, 500 MHz, 343 K) δ ppm = 8.74 (t, *J* = 6.0 Hz, 1H, N**H**), 7.88 (d, *J* = 7.3 Hz, 2H, **H**$_9$), 7.54 – 7.51 (m, 1H, **H**$_{11}$), 7.48 – 7.44 (m, 2H, **H**$_{10}$), 7.26 (d,

J = 8.4 Hz, 2H, **H**$_2$), 6.89 (d, *J* = 8.4 Hz, 2H, **H**$_3$), 4.43 (d, *J* = 6.0 Hz, 2H, **H**$_5$), 3.74 (s, 3H, **H**$_6$).

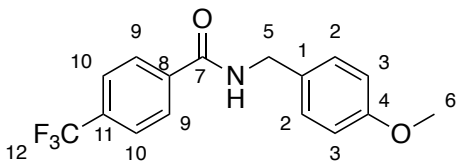
^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 167.2 (C, **C**$_7$), 159.1 (C, **C**$_4$), 134.43 (C, **C**$_8$), 131.5 (CH, **C**$_4$), 130.2 (C, **C**$_1$), 129.3 (2CH, **C**$_2$), 128.6 (2CH, **C**$_9$), 126.9 (2CH, **C**$_{10}$), 114.1 (2CH, **C**$_3$), 55.3 (CH_3, **C**$_6$), 43.6 (CH_2, **C**$_5$).

^{13}C NMR (VT): (DMSO-d_6, 126 MHz, 343 K): δ ppm = 165.9 (C, **C**$_7$), 158.0 (C, **C**$_4$), 134.4 (C, **C**$_8$), 131.4 (CH, **C**$_{11}$), 130.6 (C, **C**$_1$), 128.3 (2CH, **C**$_2$), 127.8 (2CH, **C**$_9$), 126.8 (2CH, **C**$_{10}$), 113.5 (2CH, **C**$_3$), 54.8 (CH_3, **C**$_6$), 41.9 (CH_2, **C**$_5$).

LRMS: (ESI+) m/z = 242 $[M+H]^+$.

MP: 96.9 – 98.2 °C (Lit:[267] 97 – 98 °C)

***N*-(4-Methoxybenzyl)-4-(trifluoromethyl)benzamide**



2.35

Chemical Formula: $C_{16}H_{14}F_3NO_2$

Molecular Weight: 309.29

N-(4-Methoxybenzyl)-4-(trifluoromethyl)benzamide (**2.35**) was prepared using general method A: from 4-(trifluoromethyl)benzoyl chloride (1.04 g, 5.0 mmol), *N*-(4-Methoxybenzyl)-4-(trifluoromethyl)benzamide (1.46 g, 3.8 mmol, 94%) was synthesised as a white solid. The data are consistent with reported values.[267, 268]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.89 (d, *J* = 8.6 Hz, 2H, **H**$_9$), 7.69 (d, *J* = 8.6 Hz, 2H, **H**$_{10}$), 7.29 (d, *J* = 8.7 Hz, 2H, **H**$_2$), 6.90 (d, *J* = 8.7 Hz, 2H, **H**$_3$) 6.42 (br. s, 1H, N**H**), 4.60 (d, *J* = 5.5 Hz, 2H, **H**$_5$), 3.81 (s, 3H, **H**$_6$).

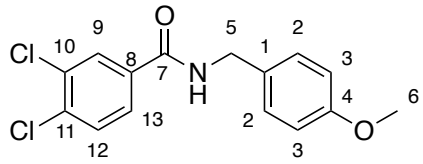
^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 166.0 (C, **C**$_7$), 159.3 (C, **C**$_4$), 137.7 (C, **C**$_8$), 133.23 (q, *J* = 32.5 Hz, C, **C**$_{11}$), 129.8 (C, **C**$_1$), 129.3 (2CH, **C**$_2$), 127.4 (2CH, **C**$_9$), 125.6 (q, *J* = 3.6 Hz, 2CH, **C**$_{10}$), 123.6 (q, *J* = 273.7 Hz, C, **C**$_{12}$), 114.2 (2CH, **C**$_3$), 55.3 (CH_3, **C**$_6$), 43.8 (CH_2, **C**$_5$).

^{19}F NMR: ($CDCl_3$, 376 MHz) δ ppm = –63.1.

LRMS: (ESI+) m/z = 310 $[M+H]^+$.

MP: 136.0 – 136.5 °C (Lit:[267] 132 – 133 °C)

3,4-Dichloro-*N*-(4-methoxybenzyl)benzamide



2.36

Chemical Formula: $C_{15}H_{13}Cl_2NO_2$

Molecular Weight: 310.17

3,4-Dichloro-*N*-(4-methoxybenzyl)benzamide (**2.36**) was prepared using general method A: from 3,4-dichlorobenzoyl chloride (1.05 g, 5.0 mmol), 3,4-Dichloro-*N*-(4-methoxybenzyl)benzamide (1.41 g, 3.6 mmol, 91%) was synthesised as a white solid. The data are consistent with (incomplete) reported values.[268]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.86 (d, *J* = 2.1 Hz, 1H, **H**$_9$), 7.58 (dd, *J* = 8.3, 2.1 Hz, 1H, **H**$_{13}$), 7.44 (d, *J* = 8.3 Hz, 1H, **H**$_{12}$), 7.23 (d, *J* = 8.6 Hz, 2H, **H**$_2$), 6.85 (d, *J* = 8.6 Hz, 2H, **H**$_3$) 6.78 (br. t, *J* = 5.6 Hz, 1H, N**H**), 4.51 (d, *J* = 5.6 Hz, 2H, **H**$_5$), 3.79 (s, 3H, **H**$_6$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 165.1 (C, **C**$_7$), 159.1 (C, **C**$_4$), 135.79 (C, **C**$_{11}$), 134.2 (C, **C**$_8$), 132.9 (C, **C**$_{10}$), 130.5 (CH, **C**$_{12}$), 129.7 (C, **C**$_1$), 129.2 (2CH, **C**$_2$), 126.2 (CH, **C**$_{13}$), 114.1 (2CH, **C**$_3$), 55.2 (CH_3, **C**$_6$), 43.7 (CH_2, **C**$_5$).

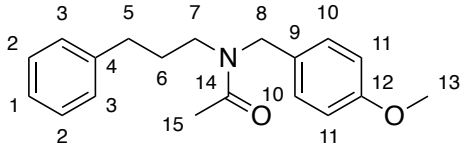
LRMS: (ESI+) m/z = 310 $[M+H]^+$, Cl^{35}.

HRMS: (ESI+) for $C_{15}H_{13}Cl_2NO_2Na^+$ requires 332.0216 found 332.0214 Da.

FT–IR (cm^{-1}) neat: 3260 (br., m, N-H), 2832 (w, C-H), 1630 (s, C=O).

MP: 128.0 – 129.0 °C (Lit:[268] 125 – 126 °C)

***N*-(4-Methoxybenzyl)-*N*-(3-phenylpropyl)acetamide**



2.37

Chemical Formula: $C_{19}H_{23}NO_2$

Molecular Weight: 297.40

N-(4-Methoxybenzyl)-*N*-(3-phenylpropyl)acetamide (**2.37**) was prepared using general method A: from Acetyl chloride (0.43 mL, 6.0 mmol) and *N*-(4-Methoxybenzyl)-3-phenylpropan-1-amine (1.28 g, 5.0 mmol), *N*-(4-Methoxybenzyl)-*N*-(3-phenylpropyl)acetamide (1.41 g, 4.9 mmol, 95%) was synthesised as a white solid. Novel compound.

^{1}H NMR (VT)*: (d_6-DMSO, 400 MHz) δ ppm = 7.28-7.25 (m, 2H, $\mathbf{H}_{10}$), 7.18-7.12 (m, 5H, $\mathbf{H}_{1-3}$), 6.88 (br. s, 2H, $\mathbf{H}_{11}$), 4.45 (s, 2H, $\mathbf{H}_8$), 3.75 (s, 3H, $\mathbf{H}_{13}$), 3.25 (s, 2H, $\mathbf{H}_7$), 2.55 (t, *J* = 7.7 Hz, 2H, $\mathbf{H}_5$) 2.02 (s, 3H, $\mathbf{H}_{15}$), 1.79 (br. s, 2H, $\mathbf{H}_6$).

*Exists as pair of rotamers, 42:58 ratio

^{13}C NMR: (d_6-DMSO, 101 MHz) δ ppm = 169.1 (C, $\mathbf{C}_{14}$) 158.2 (C, $\mathbf{C}_{12}$), 140.8 (C, $\mathbf{C}_4$), 128.6 (2CH, $\mathbf{C}_{10}$), 127.8 (2CH, $\mathbf{C}_{2/3}$) 127.7 (2CH, $\mathbf{C}_{2/3}$), 127.5 (C, $\mathbf{C}_9$) 125.3 (CH, $\mathbf{C}_1$), 113.6 (2CH, $\mathbf{C}_{11}$), 54.8 (CH_3, $\mathbf{C}_{13}$), 50.5 (CH_2. $\mathbf{C}_8$), 46.6 (CH_2. $\mathbf{C}_7$), 31.9 (CH_2. $\mathbf{C}_5$), 29.8 (CH_2, $\mathbf{C}_6$), 21.0 (CH_3, $\mathbf{C}_{15}$).

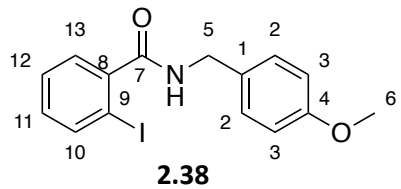
LRMS: (ESI+) m/z = 298 $[M+H]^+$

HRMS: (ESI+) for $C_{19}H_{23}NO_2Na^+$ requires 320.1621 found 320.1622 Da. (ESI+) for $C_{19}H_{23}NO_2H^+$ requires 298.1802 found 298.1801 Da.

FT–IR (cm^{-1}) neat: 3025 (w, C-H), 1637 (s, C=O).

MP: 112.0 – 113.5 °C

2-Iodo-*N*-(4-methoxybenzyl)benzamide



2.38

Chemical Formula: $C_{15}H_{14}INO_2$

Molecular Weight: 367.19

2-Iodo-*N*-(4-methoxybenzyl)benzamide (**2.38**) was prepared using general method A: from 2-Iodobenzoyl chloride (2.66 g, 10.0 mmol), 2-Iodo-*N*-(4-methoxybenzyl)benzamide (3.07 g, 8.3 mmol, quantitative) was afforded as a white solid. The data are consistent with (incomplete) reported values.[199]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.86 (d, *J* = 7.8, 1.4 Hz, 1H, $\mathbf{H}_{10}$), 7.43-7.37 (m, 2H, $\mathbf{H}_{11,13}$), 7.34 (d, *J* = 8.6 Hz, 2H, $\mathbf{H}_2$), 7.10 (td, *J* = 7.8, 1.4 Hz, 1H, $\mathbf{H}_{12}$), 6.90 (d, *J* = 8.6 Hz, 2H, $\mathbf{H}_3$), 5.96 (br. s, 1H, N**H**), 4.59 (d, *J* = 5.6 Hz, 2H, $\mathbf{H}_5$), 3.81 (s, 3H, $\mathbf{H}_6$).

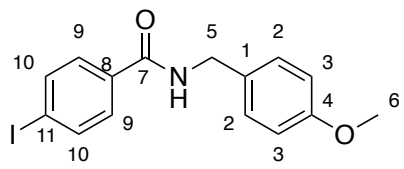
^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 169.1 (C, $\mathbf{C}_7$), 159.2 (C, $\mathbf{C}_4$), 142.1 (C, $\mathbf{C}_8$), 139.9 (CH, $\mathbf{C}_{10}$), 131.1 (C, $\mathbf{C}_{11}$), 129.6 (2CH, $\mathbf{C}_2$), 128.3 (CH, $\mathbf{C}_{12}$), 128.2 (CH, $\mathbf{C}_{13}$), 114.1 (2CH, $\mathbf{C}_3$), 92.4 (C, $\mathbf{C}_9$), 55.3 (CH_3, $\mathbf{C}_6$), 43.7 (CH_2, $\mathbf{C}_5$).

LRMS: (ESI+) m/z = 389 $[M+Na]^+$.

HRMS: (ESI+) for $C_{15}H_{14}INO_2Na^+$ requires 389.9961 found 389.9962 Da.

MP: 113.5 – 115.0 °C (Lit not reported)

4-Iodo-*N*-(4-methoxybenzyl)benzamide



2.39

Chemical Formula: $C_{15}H_{14}INO_2$

Molecular Weight: 367.19

4-Iodo-*N*-(4-methoxybenzyl)benzamide (**2.39**) was prepared using general method A: from 4-Iodobenzoyl chloride (5.33 g, 20.0 mmol), 4-Iodo-*N*-(4-methoxybenzyl)benzamide (7.39 g, 18.0 mmol, quantitative) was isolated as a white solid. The data are consistent with (incomplete) reported values.[269]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.78 (d, *J* = 8.6 Hz, 2H, $\mathbf{H}_{10}$), 7.50 (d, *J* = 8.6 Hz, 2H, $\mathbf{H}_9$), 7.28 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_2$), 6.89 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_3$), 6.33 (br. s, 1H, N**H**), 4.56 (d, *J* = 5.6 Hz, 2H, $\mathbf{H}_5$), 3.81 (s, 3H, $\mathbf{H}_6$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 166.4 (C, $\mathbf{C}_7$), 159.2 (C, $\mathbf{C}_4$), 137.8 (2CH, $\mathbf{C}_{10}$), 133.8 (C, $\mathbf{C}_8$), 129.9 (C, $\mathbf{C}_1$), 129.3 (2CH, $\mathbf{C}_2$), 128.5 (2CH, $\mathbf{C}_9$), 114.2 (2CH, $\mathbf{C}_3$), 98.4 (C, $\mathbf{C}_{11}$), 55.3 (CH_3, $\mathbf{C}_6$), 43.7 (CH_2, $\mathbf{C}_5$).

LRMS: (ESI+) m/z = 389 $[M+Na]^+$.

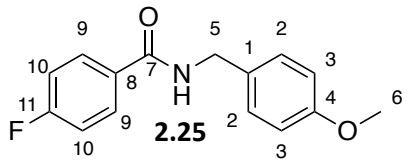
HRMS: (ESI+) for $C_{15}H_{14}INO_2Na^+$ requires 389.9961 found 389.9962 Da.

MP: 159.5 – 160.5 °C (Lit:[269] 158 – 159 °C)

4.2.1.2 General method B: Schotten–Baumann biphasic conditions

Another method of amide coupling (prior to safety and green metric analysis), also under Schotten–Baumann conditions was utilised:[206] To an ice–cooled solution of 4-methoxybenzylamine (1.31 mL, 10.0 mmol) in Me-THF or Et_2O (75 mL) and 5% aq. NaOH solution (25.0 mmol NaOH, 20 mL) was added the corresponding acid chloride (12.0 mmol). The reaction was stirred at RT for 16 hours and then the organic phase was separated. The aqueous phase was made up to 50 mL with water and washed with Et_2O (2 x 50 mL). The combined organic phase was treated sequentially with 1M HCl (40 mL), sat. aq. $NaHCO_3$ (30 mL) and then Brine (30 mL). The organic phase was dried ($MgSO_4$), and solvents were removed under reduced pressure. The crude product was recrystallised in EtOAc or triturated with ice–cold Et_2O to afford the pure compound.

4-Fluoro-*N*-(4-methoxybenzyl)benzamide



2.25

Chemical Formula: $C_{15}H_{14}FNO_2$

Molecular Weight: 259.28

4-Fluoro-*N*-(4-methoxybenzyl)benzamide (**2.25**) was prepared using general method B: from 4-Fluorobenzoyl chloride (2.54 g, 16.0 mmol), in Et_2O, 4-Fluoro-N-(4-methoxybenzyl)benzamide (3.11 g, 12.0 mmol, 80%) was synthesised as a white solid. The data are consistent with reported values.[270]

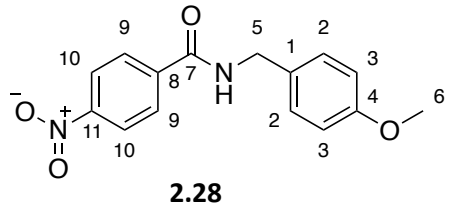
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.80 (dd, $J_{H\text{-}F}$ = 5.4, J = 9.1 Hz, 2H, $\mathbf{H}_9$), 7.28 (d, J = 8.6 Hz, 2H, $\mathbf{H}_2$), 7.09 (dd, $J_{H\text{-}F}$ = 8.6 Hz, J = 9.1 Hz 2H, $\mathbf{H}_{10}$), 6.89 (d, J = 8.6 Hz, 2H, $\mathbf{H}_3$), 6.38 (br. s, 1H, N**H**), 4.56 (d, J = 5.5 Hz, 2H, $\mathbf{H}_5$), 3.81 (s, 3H, $\mathbf{H}_6$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 166.2 (C, $\mathbf{C}_7$), 164.7 (d, $J_{C\text{-}F}$ = 252.5 Hz, C, $\mathbf{C}_{11}$), 159.1 (C, $\mathbf{C}_4$), 130.6 (d, $J_{C\text{-}F}$ = 3.0 Hz, C, $\mathbf{C}_8$), 130.1 (CH, $\mathbf{C}_1$), 129.3 (2CH, $\mathbf{C}_2$), 129.3 (d, $J_{C\text{-}F}$ = 9.1 Hz, 2CH, $\mathbf{C}_9$), 115.6 (d, $J_{C\text{-}F}$ = 22.2 Hz, 2CH, $\mathbf{C}_{10}$), 114.2 (2CH, $\mathbf{C}_3$), 55.3 (CH_3, $\mathbf{C}_6$), 43.7 (CH_2, $\mathbf{C}_5$).

LRMS: (ESI+) m/z = 260 $[M+H]^+$.

MP: 113.7 – 114.9 °C (Lit:[267] 114 –115 °C)

***N*-(4-Methoxybenzyl)-4-nitrobenzamide**



2.28

Chemical Formula: $C_{15}H_{14}N_2O_4$

Molecular Weight: 286.29

N-(4-Methoxybenzyl)-4-nitrobenzamide (**2.28**) was prepared using general method B: from 4-Nitrobenzoyl chloride (1.43 g, 7.7 mmol), in Et_2O, *N*-(4-Methoxybenzyl)4-nitrobenzamide (2.18 g, 7.6 mmol, 98%) was synthesised as a yellow solid. The data are consistent with reported values.[271, 272]

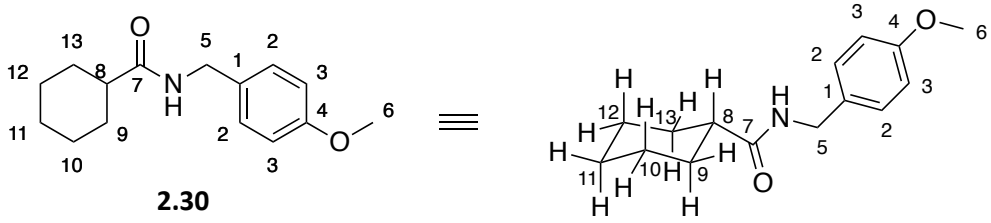
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 8.29 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_{10}$), 7.95 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_9$), 7.30 (d, *J* = 8.8 Hz, 2H, $\mathbf{H}_2$), 6.91 (d, *J* = 8.8 Hz, 2H, $\mathbf{H}_3$), 6.41 (br. s, 1H, N**H**), 4.61 (d, *J* = 5.5 Hz, 2H, $\mathbf{H}_5$), 3.82 (s, 3H, $\mathbf{H}_6$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 165.1 (C, $\mathbf{C}_7$), 159.4 (C, $\mathbf{C}_4$), 149.6 (C, $\mathbf{C}_{11}$), 140.0 (C, $\mathbf{C}_8$), 129.5 (2CH, $\mathbf{C}_2$), 129.4 (C, $\mathbf{C}_1$), 128.1 (2CH, $\mathbf{C}_9$), 123.8 (2CH, $\mathbf{C}_{10}$), 114.3 (2CH, $\mathbf{C}_3$), 55.3 (CH_3, $\mathbf{C}_6$), 44.0 (CH_2, $\mathbf{C}_5$).

LRMS: (ESI+) m/z = 287 $[M+H]^+$.

MP: 136.2 – 137.2 °C (Lit:[272] 136 – 138 °C)

***N*-(4-Methoxybenzyl)cyclohexane carboxamide**



2.30

Chemical Formula: $C_{15}H_{21}NO_2$

Molecular Weight: 247.34

N-(4-Methoxybenzyl)cyclohexane carboxamide (**2.30**) was prepared using general method B: from Cyclohexanecarbonyl chloride (0.77 g, 5.3 mmol) in Et_2O, *N*-(4-Methoxybenzyl)cyclohexane carboxamide (0.980 g, 4.0 mmol, 89%) was synthesised as a white solid. The data are consistent with reported values.[267]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.20 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_2$), 6.87 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_3$), 5.65 (br. s, 1H, N**H**), 4.38 (d, *J* = 5.5 Hz, 2H, $\mathbf{H}_5$), 3.81 (s, 3H, $\mathbf{H}_6$), 2.09 (tt, *J* = 11.8, 3.5 Hz, 1H, $\mathbf{H}_{8ax}$), 1.89 (d*, *J* = 13.2 Hz, 2H, $\mathbf{H}_{9eq}$ & $\mathbf{H}_{13eq}$), 1.82 – 1.78 (m, 2H, $\mathbf{H}_{10eq}$ & $\mathbf{H}_{12eq}$), 1.68 – 1.64 (m, 1H, $\mathbf{H}_{11eq}$), 1.46 (qd, *J* = 12.2, 2.9 Hz, 2H, $\mathbf{H}_{9ax}$ & $\mathbf{H}_{13ax}$), 1.28 – 1.23 (m, 3H, $\mathbf{H}_{11ax}$, $\mathbf{H}_{10ax}$ & $\mathbf{H}_{12ax}$).

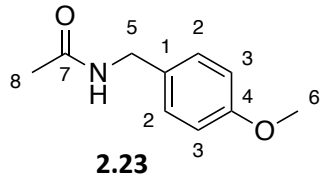
*With unresolved splitting

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 175.8 (C, **C**$_7$), 159.0 (C, **C**$_4$), 130.6 (C, **C**$_1$), 129.1 (2CH, **C**$_2$), 114.1 (2CH, **C**$_3$), 55.3 (CH_3, **C**$_6$), 45.6 (CH_2, **C**$_5$), 42.9 (CH, **C**$_8$), 29.7 ($2CH_2$, **C**$_9$ & **C**$_{13}$), 25.7 ($3CH_2$, **C**$_{10,11,12}$).

LRMS: (ESI+) m/z = 248 $[M+H]^+$.

MP: 118.2 – 119.4 °C (Lit:[267] 136 – 138 °C)

***N*-(4-Methoxybenzyl)acetamide**



2.23

Chemical Formula: $C_{10}H_{13}NO_2$

Molecular Weight: 179.22

N-(4-Methoxybenzyl)acetamide (**2.23**) was prepared using general method B: from Acetyl chloride (0.79 g, 10 mmol), in Me-THF, *N*-(4-Methoxybenzyl)acetamide (1.33 g, 7.4 mmol, 74%) was synthesised as a white solid. The data are consistent with reported values.[273, 274]

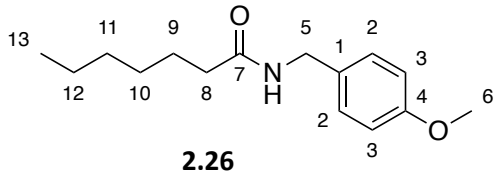
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.21 (d, *J* = 8.8 Hz, 2H, **H**$_2$), 6.87 (d, *J* = 8.8 Hz, 2H, **H**$_3$), 5.74 (br. s, 1H, N**H**), 4.37 (d, *J* = 5.6 Hz, 2H, **H**$_5$), 3.80 (s, 3H, **H**$_6$), 2.01 (s, 3H, **H$_8$**).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 169.8 (C, **C**$_7$), 159.1 (C, **C**$_4$), 130.4 (C, **C**$_1$), 129.2 (2CH, **C**$_2$), 114.1 (2CH, **C**$_3$), 55.3 (CH_3, **C**$_6$), 43.2 (CH_2, **C**$_5$), 23.3 (CH_2, **C$_8$**).

LRMS: (ESI+) m/z = 180 $[M+H]^+$.

MP: 94.6 – 95.4 °C (Lit:[274] 94 – 95 °C)

***N*-(4-Methoxybenzyl)heptanamide**



2.26

Chemical Formula: $C_{15}H_{23}NO_2$

Molecular Weight: 249.35

N-(4-Methoxybenzyl)heptanamide (**2.26**) was prepared using general method B: from Heptanoyl chloride (0.74 g, 5.0 mmol), in Et_2O, *N*-(4-Methoxybenzyl)heptanamide (1.21 g, 4.9 mmol, 97%) was synthesised as a white solid. The data are consistent with (incomplete) reported values.[275]

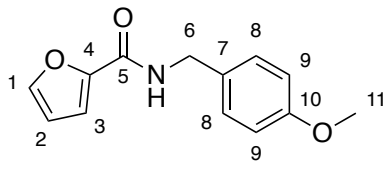
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.21 (d, *J* = 8.8 Hz, 2H, **H**$_2$), 6.87 (d, *J* = 8.8 Hz, 2H, **H**$_3$), 5.63 (br. s, 1H, N**H**), 4.38 (d, *J* = 5.6 Hz, 2H, **H**$_5$), 3.81 (s, 3H, **H**$_6$), 2.20 (t, *J* = 7.6 Hz, 2H, **H$_8$**), 1.65 (quin, *J* = 7.6 Hz, 2H, **H**$_9$), 1.36 – 1.27 (m, 6H, **H**$_{10\text{-}12}$) 0.89 (t, *J* = 7.0 Hz, 3H, **H**$_{13}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 172.8 (C, **C**$_7$), 159.0 (C, **C**$_4$), 130.5 (C, **C**$_1$), 129.2 (2CH, **C**$_2$), 114.1 (2CH, **C**$_3$), 55.3 (CH_3, **C**$_6$), 43.1 (CH_2, **C**$_5$), 36.9 (CH_2, **C$_8$**), 31.5 (CH_2, **C$_9$**), 29.0 (CH_2, **C$_{10}$**), 25.7 (CH_2, **C$_{11}$**), 22.5 (CH_2, **C$_{12}$**), 14.0 (CH_3, **C$_{13}$**).

LRMS: (ESI+) m/z = 250 $[M+H]^+$.

MP: 94.4 – 95.4 °C (Lit not reported)

***N*-(4-Methoxybenzyl)furan-2-carboxamide**



2.29

Chemical Formula: $C_{13}H_{13}NO_3$

Molecular Weight: 231.25

N-(4-Methoxybenzyl)furan-2-carboxamide (**2.29**) was prepared using general method B. From Furan-2-carbonyl chloride (1.31 g, 10.0 mmol) in Et_2O, *N*-(4-Methoxybenzyl)furan-2-carboxamide (2.11 g, 9.1 mmol, 91%) was synthesised as a white solid. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.41 (dd, *J* = 1.7, 0.7 Hz, 1H, **H**$_1$), 7.30 (d, *J* = 8.7 Hz, 2H, **H**$_8$), 7.15 (dd, *J* = 3.5, 0.7 Hz, 1H, **H**$_3$), 6.89 (d, *J* = 8.7 Hz, 2H, **H**$_9$), 6.60 (br. s, 1H, N**H**), 6.50 (dd, *J* = 3.5, 1.7 Hz, 1H, **H**$_2$), 4.56 (d, *J* = 5.9 Hz, 2H, **H**$_6$), 3.81 (s, 3H, **H$_{11}$**).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 159.1 (C, **C**$_7$), 158.1 (C, **C**$_5$), 150.0 (C, **C**$_4$), 143.8 (CH, **C**$_1$), 130.1 (C, **C**$_7$), 129.3 (2CH, **C**$_8$), 114.3 (CH, **C**$_{2/3}$), 114.1 (2CH, **C**$_9$) 112.1 (CH, **C**$_{2/3}$) 55.3 (CH_3, **C**$_{11}$), 42.6 (CH_2, **C**$_6$).

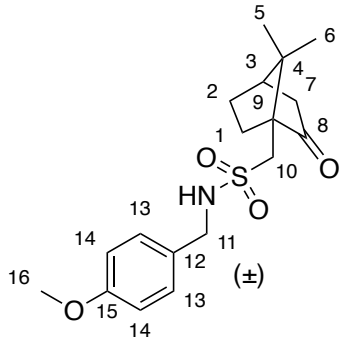
LRMS: (ESI+) m/z = 232 $[M+H]^+$

FT–IR (cm^{-1}) neat: 3271 (br., m, N-H), 3122 (w, C-H), 1639 (s, C=O).

HRMS: (ESI+) for $C_{13}H_{13}NO_3H^+$ requires 232.0968 found 232.0969 Da.

MP: 94.6 – 95.6 °C

***N*-(4-Methoxybenzyl)10-camphorsulfonamide**



2.34

Chemical Formula: $C_{18}H_{25}NO_4S$

Molecular Weight: 351.46

N-(4-Methoxybenzyl)10-camphorsulfonamide (**2.34**) was prepared using general method B: from (1S)-10-Camphorsulfonyl chloride (3.01 g, 12.0 mmol in Me-THF, *N*-(4-Methoxybenzyl)camphorsulfonamide (0.982 g, 2.8 mmol, 28% was afforded as a yellow oil. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm =7.31 (d, *J* = 8.7 Hz, 2H, **H**$_{13}$), 6.88 (d, *J* = 8.7 Hz, 2H, **H**$_{14}$), 5.67-5.63 (br. m, 1H, N**H**), 4.30 (m, 2H, H$_{11}$), 3.80 (s, 3H, **H**$_{16}$), 3.15 (m, 1H, **H**$_{10a}$), 2.86 (m, 1H, **H**$_{10b}$) 2.41-2.34 (m, 1H, **H**$_3$), 2.20-1.89 (m, 6H, **H**$_{1,2,7}$), 0.96 (s, 3H, **H**$_{5/6}$), 0.76 (s, 3H, **H**$_{5/6}$).

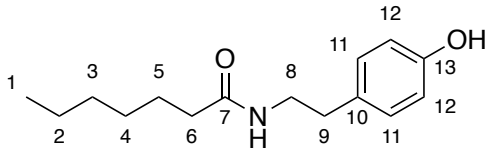
^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 217.0 (C, **C**$_8$), 159.3 (C, **C**$_{15}$), 129.8 (2CH, **C**$_{13}$) 128.9 (C, **C**$_{12}$), 114.1 (2CH, **C**$_{14}$), 59.3 (C, **C**$_9$), 55.3 (CH_3, **C**$_{16}$), 50.7 (CH_2, **C**$_{10}$), 48.8 (C, **C**$_4$), 47.4 (CH_2, **C**$_{11}$), 43.0 (CH, **C**$_3$), 42.8 (CH_2, **C**$_7$), 27.0 ($2CH_2$, **C**$_{1,2}$), 19.8 (CH_3, **C**$_{5/6}$), 19.4 (CH_3, **C**$_{5/6}$).

LRMS: (ESI+) m/z = 374 $[M+Na]^+$.

HRMS: (ESI+) for $C_{18}H_{25}NO_4SNa^+$ requires 374.1397 found 374.1389 Da.

FT–IR (cm^{-1}) neat: 3290 (br., m, N-H), 2958 (w, C-H), 1738 (s, C=O).

***N*-(4-Hydroxyphenethyl)heptanamide**



2.31

Chemical Formula: $C_{15}H_{23}NO_2$

Molecular Weight: 249.35

N-(4-Hydroxyphenethyl)heptanamide (**2.31**) was prepared using general method B: From Tyramine (1.50 g, 10.9 mmol), and Heptanoyl chloride (1.61 mL, 10.4 mmol) in Me-THF, *N*-(4-Hydroxyphenethyl)heptanamide (2.42 g, 10.1 mmol, 93%) was prepared as a white solid. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.04 (d, *J* = 8.6 Hz, 2H, **H**$_{11}$), 6.87 (d, *J* = 8.6 Hz, 2H, **H**$_{12}$), 6.10 (br. s, 1H, O**H**), 5.48 (br. t, *J* = 6.6 Hz, 1H, N**H**), 3.50 (q, *J* = 6.6 Hz, 2H, **H**$_8$), 2.74 (t, *J* = 6.6 Hz, 2H, **H**$_9$), 2.14 (t, *J* = 7.6 Hz, 2H, **H**$_6$) 1.59 (quin, *J* = 7.2 Hz, 2H, **H**$_5$), 1.32 – 1.23 (m, 6H, **H**$_{2\text{-}4}$) 0.88 (t, *J* = 6.8 Hz, 3H, H$_1$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 173.6 (C, **C**$_7$), 154.9 (C, **C**$_{13}$), 130.2 (C, **C**$_{10}$), 129.7 (2CH, **C**$_{11}$), 115.6 (2CH, **C**$_{12}$), 40.8 (CH_2, **C**$_8$), 36.9 (CH_2, **C**$_6$), 34.8 (C, **C**$_9$), 31.5 (CH_2, **C**$_3$), 28.9 (CH_2, **C**$_4$), 25.7 (CH_2, **C**$_5$), 22.5 (CH_2, **C**$_2$), 14.0 (CH_3, **C**$_1$).

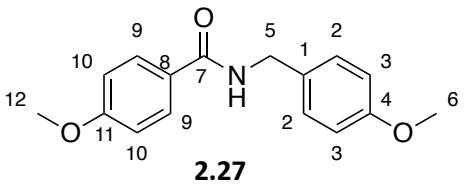
LRMS: (ESI+) m/z = 250 $[M+H]^+$.

HRMS: (ESI+) for $C_{15}H_{23}NO_2H^+$ requires 250.1802 found 250.1805 Da.

FT–IR (cm^{-1}) neat: 3373 (br., m, O-H), 2926 (w, C-H), 1633 (s, C=O).

MP: 94.4 – 95.4 °C

4-Methoxy-*N*-(4-methoxybenzyl)benzamide



2.27

Chemical Formula: $C_{16}H_{17}NO_3$

Molecular Weight: 271.32

4-Methoxy-*N*-(4-methoxybenzyl)benzamide (**2.27**) was prepared using general method B: from 4-Methoxybenzoyl chloride (1.62 mL, 12.0 mmol) in Me-THF, 4-Methoxy-*N*-(4-methoxybenzyl)benzamide (2.69 g, 9.9 mmol, 99%) was synthesised as a white solid. The data are consistent with reported values.[272, 276]

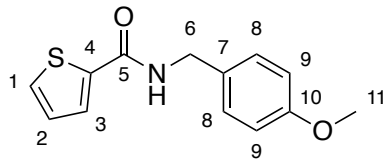
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.75 (d, *J* = 8.9 Hz, 2H, **H**$_9$), 7.29 (d, *J* = 8.7 Hz, 2H, **H**$_2$) 6.92 (d, *J* = 8.9 Hz, 2H, **H**$_{10}$), 6.89 (d, *J* = 8.7 Hz, 2H, **H**$_3$) 6.25 (br. s, 1H, N**H**), 4.58 (d, *J* = 5.6 Hz, 2H, **H**$_5$), 3.85 (s, 3H, **H**$_{12}$), 3.81 (s, 3H, **H**$_6$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 166.7 (C, **C**$_7$), 162.2 (C, **C**$_{11}$), 159.1 (C, **C**$_4$), 130.5 (C, **C**$_1$), 129.3 (2CH, **C**$_9$), 128.7 (2CH, **C**$_2$), 126.7 (C, **C**$_8$), 114.1 (2CH, **C**$_{10}$), 113.7 (2CH, **C**$_3$), 55.4 (CH_3, **C**$_{12}$), 55.3 (CH_3, **C**$_6$), 43.6 (CH_2, **C**$_5$)

LRMS: (ESI+) m/z = 272 $[M+H]^+$.

MP: 132.0 – 133.0 °C

***N*-(4-Methoxybenzyl)thiophene-2-carboxamide**



2.32

Chemical Formula: $C_{13}H_{13}NO_2S$

Molecular Weight: 247.31

N-(4-Methoxybenzyl)thiophene-2-carboxamide (**2.32**) was prepared using general method B: from Thiophene-2-carbonyl chloride (1.28 mL, 12.0 mmol) in Me-THF, *N*-(4-Methoxybenzyl)thiophene-2-carboxamide (2.48 g, 10.0 mmol, quantitative) was synthesised as a white solid. The data are consistent with (incomplete) reported values.[277]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.51 (d, *J* = 3.4 Hz, 1H, $\mathbf{H}_3$), 7.47 (d, *J* = 4.8 Hz, 2H, $\mathbf{H}_1$), 7.28 (d, *J* = 8.6 Hz, 2H, $\mathbf{H}_8$) 7.06 (dd, *J* = 4.8, 3.4 Hz, 1H, $\mathbf{H}_2$), 6.88 (d, *J* = 8.6 Hz, 2H, $\mathbf{H}_9$), 6.30 (br. s, 1H, N**H**), 4.55 (d, *J* = 5.5 Hz, 2H, $\mathbf{H}_6$), 3.81 (s, 3H, $\mathbf{H}_{11}$).

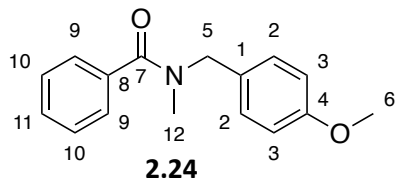
^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 161.7 (C, $\mathbf{C}_5$), 159.1 (C, $\mathbf{C}_{10}$), 138.8 (C, $\mathbf{C}_4$), 130.1 (C, $\mathbf{C}_7$), 129.9 (CH, $\mathbf{C}_3$), 129.3 (2CH, $\mathbf{C}_8$), 128.0 (CH, $\mathbf{C}_1$), 127.6 (CH, $\mathbf{C}_2$), 114.1 (2CH, $\mathbf{C}_9$), 55.3 (CH_3, $\mathbf{C}_{11}$), 43.5 (CH_2, $\mathbf{C}_6$).

LRMS: (ESI+) m/z = 270 $[M+Na]^+$

FT–IR (cm^{-1}) neat: 3260 (br., m, N-H), 3100 (w, C-H), 1615 (s, C=O).

HRMS: (ESI+) for $C_{13}H_{13}NO_2Na^+$ requires 270.0559 found 270.0555 Da.

***N*-(4-Methoxybenzyl)-*N*-methylbenzamide**



2.24

Chemical Formula: $C_{16}H_{17}NO_2$

Molecular Weight: 255.32

N-(4-Methoxybenzyl)-*N*-methylbenzamide (**2.24**) was prepared using general method B: from Benzoyl chloride (0.813 mL, 7.0 mmol), and 1-(4-Methoxyphenyl)-N-methylmethanamine (1.07 g, 7.0 mmol) in Et_2O, *N*-(4-Methoxybenzyl)-*N*-methylbenzamide (1.31 g, 5.1 mmol, 73%) was synthesised as a white solid following purification by flash chromatography (20% EtOAc in hexane). The data are consistent with reported values.[278, 279]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm* = 7.48 -7.37 (m, 5H, $\mathbf{H}_{9\text{-}11}$), 7.30 & 7.09 (br. s, 2H, $\mathbf{H}_2$), 6.70 (d, *J* = 8.4 Hz, 2H, $\mathbf{H}_3$), 4.70 & 4.45 (s, 2H, $\mathbf{H}_5$) 3.82 (s, 3H, $\mathbf{H}_6$), 3.01 & 2.85 (s, 3H, $\mathbf{H}_{12}$).

*Exists as 1:1 ratio of rotamers

^{1}H NMR (VT): (DMSO-d_6, 500 MHz, 343 K) δ ppm* = 7.44 -7.40 (m, 5H, $\mathbf{H}_{9\text{-}11}$), 7.20 (br. s, 2H, $\mathbf{H}_2$), 6.93 (d, *J* = 8.8 Hz, 2H, $\mathbf{H}_3$), 4.52 (s, 2H, $\mathbf{H}_5$), 3.76 (s, 3H, $\mathbf{H}_6$), 2.84 (s, 3H, $\mathbf{H}_{12}$).

*Room temperature **^{1}H** NMR in DMSO-d_6 gave a 57:43 ratio of rotamers

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm* = 171.5 (C, $\mathbf{C}_7$), 159.1 (C, $\mathbf{C}_4$), 136.4 (C, $\mathbf{C}_8$), 129.5 (CH, $\mathbf{C}_{11}$), 128.4 (C, $\mathbf{C}_1$), 128.1 (2CH, $\mathbf{C}_2$), 126.9 (2CH, $\mathbf{C}_{9/10}$), 126.8 (2CH, $\mathbf{C}_{9/10}$) 114.1 (2CH, $\mathbf{C}_3$), 55.3 (CH_3, $\mathbf{C}_6$), 54.6 & 50.2 (CH_2, $\mathbf{C}_5$), 36.8 & 32.9 (CH_3, $\mathbf{C}_{12}$).

*Exists as 1:1 ratio of rotamers

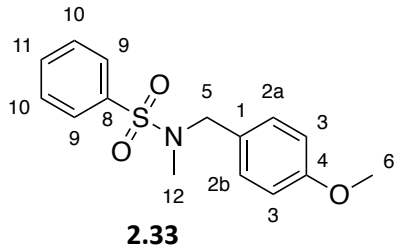
^{13}C NMR (VT): (DMSO-d_6, 126 MHz, 343 K): δ ppm = 170.2 (C, $\mathbf{C}_7$), 158.4 (C, $\mathbf{C}_4$), 136.3 (C, $\mathbf{C}_8$), 128.9 (C, $\mathbf{C}_{11}$), 128.3 (C, $\mathbf{C}_1$) 128.0 (2CH, $\mathbf{C}_2$), 126.3 (4CH, $\mathbf{C}_{9\text{-}10}$), 113.9 (2CH, $\mathbf{C}_3$), 54.8 (CH_3, $\mathbf{C}_6$), 44.7 (CH_2, $\mathbf{C}_5$), 37.6 (CH_3, $\mathbf{C}_{12}$).

LRMS: (ESI+) m/z = 256 $[M+H]^+$

HRMS: (ESI+) for $C_{16}H_{17}NO_2H^+$ requires 256.1332 found 256.1334 Da.

MP: 57.1 – 58.9 °C (Lit:[278] 58 °C)

***N*-(4-Methoxybenzyl)-*N*-methylbenzenesulfonamide**



2.33

Chemical Formula: $C_{15}H_{17}NO_3S$

Molecular Weight: 291.37

N-(4-Methoxybenzyl)-*N*-methylbenzenesulfonamide (**2.33**) was prepared using general method B: from 1-(4-Methoxyphenyl)-*N*-methylmethanamine (1.06 g, 7.0 mmol) and Benzenesulfonyl chloride (1.36 g, 7.1 mmol) in Et_2O, *N*-(4-Methoxybenzyl)-*N*-methylbenzenesulfonamide (1.51 g, 5.1 mmol, 73%) was synthesised as an off–white solid. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm* = 7.45 (br. s, 2H, $\mathbf{H}_9$), 7.40 (m, 3H, $\mathbf{H}_{10,11}$), 7.32 – 7.30 (m, 1H, $\mathbf{H}_{2a}$), 7.08 (m, 1H, $\mathbf{H}_{2b}$), 6.90 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_3$), 4.70 (s, 1H, $\mathbf{H}_5$), 4.45 (s, 2H, $\mathbf{H}_5$), 3.82 (s, 3H, $\mathbf{H}_6$) 3.01 & 2.75 (s, 3H, $\mathbf{H}_{12}$)

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm* = 159.1 (C, $\mathbf{C}_4$), 136.3 (C, $\mathbf{C}_8$), 129.9 (CH, $\mathbf{C}_{11}$), 129.5 (CH, $\mathbf{C}_{2a/b}$), 129.1 (CH, $\mathbf{C}_{2a/b}$), 128.4 (C, $\mathbf{C}_1$), 128.0 (2CH, $\mathbf{C}_{10}$), 126.9 (2CH, $\mathbf{C}_9$), 114.1 (2CH, $\mathbf{C}_3$), 55.3 (CH_3, $\mathbf{C}_{10}$), 54.6 & 50.2 (CH_2, $\mathbf{C}_5$) 36.8 & 32.9 (CH_3, $\mathbf{C}_{12}$).

*Exists as 54:46 ratio of rotamers

LRMS: (ESI+) m/z = 300 $[M+Na]^+$.

FT–IR (cm^{-1}) neat: 2962 (w, C-H), 1511 (m, S=O).

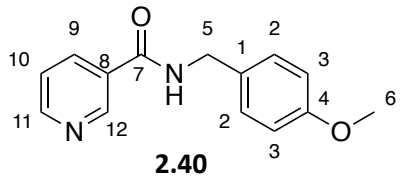
HMRS: (ESI+) for $C_{15}H_{17}NO_3SNa^+$ requires 314.0821 found 314.0828 Da.

MP: 75.8 – 76.4 °C (Lit:[279] 64 – 66 °C)

4.2.1.3 General method C: Amide coupling

A third method for amide coupling using literature conditions[280] is described: A solution of the corresponding acid chloride (10 mmol) in THF or CH_2Cl_2 (20 mL) was cooled on ice. A solution of 4-methoxybenzylamine (1.29 mL, 10.5 mmol) and Et_3N (1.39 mL, 10.0 mmol) in THF or CH_2Cl_2 (20 mL) was added dropwise over 30 minutes. The solution was stirred at 0 °C for 1 hour and then rt for 16 hours. Concentration under reduced pressure followed by recrystallisation afforded the pure product.

***N*-(4-Methoxybenzyl)nicotinamide**



2.40

Chemical Formula: $C_{14}H_{14}N_2O_2$

Molecular Weight: 242.28

N-(4-Methoxybenzyl)nicotinamide (**2.40**) was prepared using general method C: from Nicotinoyl chloride hydrochloride (1.78 g, 10.0 mmol) in THF (20 mL), *N*-(4-Methoxybenzyl)nicotinamide (1.32 g, 5.5 mmol, 55%) was synthesised as a white solid. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 8.96 (d, *J* = 1.7 Hz, 1H, **H**$_{12}$), 8.71 (dd, *J* = 4.9, 1.5 Hz, 1H, **H**$_{11}$), 8.13 (dt, *J* = 7.9, 1.7 Hz, 1H, **H**$_9$), 7.38 (dd, *J* = 7.9, 4.9 Hz, 1H, **H**$_{10}$) 7.29 (d, *J* = 8.7 Hz, 2H, **H**$_2$) 6.89 (d, *J* = 8.7 Hz, 2H, **H**$_3$), 6.55 (br. s, 1H, N**H**), 4.59 (d, *J* = 5.7 Hz, 2H, **H**$_5$), 3.81 (s, 3H, **H**$_6$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 165.3 (C, **C**$_7$), 159.2 (C, **C**$_4$), 152.3 (CH, **C**$_{12}$), 147.8 (CH, **C**$_{11}$), 135.1 (CH, **C**$_9$), 130.1 (C, **C**$_8$), 129.7 (C, **C**$_1$), 129.4 (2CH, **C**$_2$), 123.5 (CH, **C**$_{10}$), 114.2 (2CH, **C**$_3$), 55.3 (CH_3, **C**$_6$), 43.7 (CH_2, **C**$_5$).

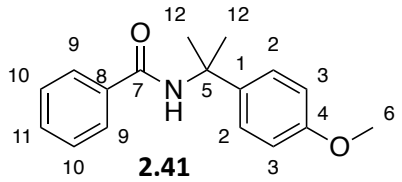
LRMS: (ESI+) m/z = 243 $[M+H]^+$

FT–IR (cm^{-1}) neat: 3303 (br., m, N-H), 3047 (w, C-H), 1630 (s, C=O).

HMRS: (ESI+) for $C_{14}H_{14}N_2O_2Na^+$ requires 265.0947 found 265.0945 Da.

MP: 117.5 – 118.5 °C

***N*-(2-(4-Methoxyphenyl)propan-2-yl)benzamide**



2.41

Chemical Formula: $C_{17}H_{19}NO_2$

Molecular Weight: 269.34

N-(2-(4-Methoxyphenyl)propan-2-yl)benzamide (**2.41**) was prepared using general method C: from Benzoyl chloride (0.39 mL, 3.3 mmol), and 2-(4-Methoxyphenyl)propan-2-amine (0.50 g, 3.0 mmol), in CH_2Cl_2, *N*-(2-(4-Methoxyphenyl)propan-2-yl)benzamide (0.29 g, 1.1 mmol, 59%) was synthesised as a white solid. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.76 (d, *J* = 7.6 Hz, 2H, **H**$_9$), 7.52 – 7.48 (m, 1H, **H**$_{11}$), 7.45 – 7.39 (m, 4H, **H**$_{2,10}$), 6.89 (d, *J* = 8.7 Hz, 2H, **H**$_3$), 6.36 (br. s, 1H, N**H**), 3.81 (s, 3H, **H**$_6$), 1.83 (s, 6H, **H**$_{12}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 166.4 (C, **C**$_7$), 158.3 (C, **C**$_4$), 139.1 (C, **C**$_8$), 135.5 (C, **C**$_1$), 131.3 (CH, **C**$_{11}$), 128.5 (2CH, **C**$_{10}$), 126.8 (2CH, **C**$_2$), 126.0 (2CH, **C**$_9$), 113.8 (2CH, **C**$_3$), 55.9 (C, **C**$_5$), 55.24 (CH_3, **C**$_6$), 29.1 ($2CH_3$, **C**$_{12}$).

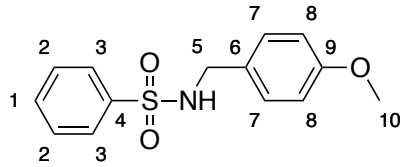
LRMS: (ESI+) m/z = 292 $[M+Na]^+$.

FT–IR (cm^{-1}) neat: 3313 (br., m, N-H), 2973 (w, C-H), 1644 (s, C=O).

HMRS: (ESI+) for $C_{10}H_{19}NO_2Na^+$ requires 292.1315 found 292.1314 Da.

MP: 141.5 – 143.0 °C

***N*-(4-Methoxybenzyl)benzenesulfonamide**



2.42

Chemical Formula: $C_{14}H_{15}NO_3S$

Molecular Weight: 277.34

N-(4-Methoxybenzyl)benzenesulfonamide (**2.42**) was prepared using general method C: from Benzenesulfonyl chloride (1.325 g, 7.5 mmol), in CH_2Cl_2, *N*-(4-Methoxybenzyl)benzenesulfonamide (1.781 g, 6.5 mmol, 86%) was synthesised as an off-white solid. The data are consistent with reported values.[281-283]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.90 – 7.87 (m, 2H, $\mathbf{H}_3$), 7.62 – 7.59 (m, 1H, $\mathbf{H}_1$), 7.55 – 7.51 (m, 2H, $\mathbf{H}_2$), 7.11 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_7$), 6.81 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_8$), 4.58 (br. s, 1H, N**H**), 4.10 (d, *J* = 6.1 Hz, 2H, $\mathbf{H}_5$), 3.79 (s, 3H, $\mathbf{H}_{10}$).

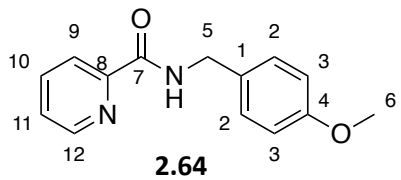
^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 159.4 (C, $\mathbf{C}_9$), 140.0 (C, $\mathbf{C}_4$), 132.7 (CH, $\mathbf{C}_1$), 129.3 (2CH, $\mathbf{C}_3$), 129.1 (2CH, $\mathbf{C}_7$), 128.1 (C, $\mathbf{C}_6$), 127.1 (2CH, $\mathbf{C}_2$), 114.1 (2CH, $\mathbf{C}_8$), 55.3 (CH_3, $\mathbf{C}_{10}$), 46.8 (CH_2, $\mathbf{C}_5$).

LRMS: (ESI+) m/z = 300 $[M+Na]^+$.

MP: 76.0 – 76.5 °C (Lit:[284] 72 – 75 °C)

4.2.1.4 Amide coupling

***N*-(4-Methoxybenzyl)picolinamide**



2.64

Chemical Formula: $C_{14}H_{14}N_2O_2$

Molecular Weight: 242.28

N-(4-Methoxybenzyl)picolinamide (**2.64**) was prepared using literature procedure for amide synthesis:[285] A solution of 4-Methoxybenzylamine (1.44 mL, 11.0 mmol), 2-Picolinic acid (**2.63**) (1.23 g, 10.0 mmol), DCC (2.27 g, 11.0 mmol), HOBt hydrate (1.49 g, 11.0 mmol) and Et_3N (2.79 mL, 20.0 mmol) in DMF (15 mL) was stirred at rt for 24 hours when all SM was consumed. Water (20 mL) was added, and the product was extracted with EtOAc (3 x 20 mL), separating the organic phase each time. The combined organic phase was washed with water (5 x 15 mL), and brine (20 mL), dried ($MgSO_4$), filtered and solvents were removed under reduced pressure. The yellow oil was purified by flash chromatography (5 to 25% EtOAc in petroleum ether) to afford *N*-(4-Methoxybenzyl)picolinamide (2.29 g, 9.5 mmol, 95%) as a yellow oil. The data are not consistent with reported values (melting points differ).[286, 287]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 8.52 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H, $\mathbf{H}_{12}$), 8.32 (br. s, 1H, N**H**), 8.25 (dt, *J* = 7.9, 1.1 Hz, 1H, $\mathbf{H}_{10}$), 7.85 (td, *J* = 7.9, 1.8 Hz, 1H, $\mathbf{H}_{11}$), 7.43 (ddd, *J* = 7.9, 4.9, 1.1 Hz, 1H, $\mathbf{H}_9$) 7.32 (d, *J* = 8.8 Hz, 2H, $\mathbf{H}_2$) 6.89 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_3$), 4.62 (d, *J* = 6.0 Hz, 2H, $\mathbf{H}_5$), 3.81 (s, 3H, $\mathbf{H_6}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 164.1 (C, $\mathbf{C}_7$), 159.0 (C, $\mathbf{C}_4$), 149.9 (C, $\mathbf{C}_8$), 148.0 (CH, $\mathbf{C}_{12}$), 137.3 (CH, $\mathbf{C}_{10}$), 130.3 (C, $\mathbf{C}_1$), 129.2 (2CH, $\mathbf{C}_2$), 126.1 (CH, $\mathbf{C}_{11}$), 122.3 (CH, $\mathbf{C}_9$), 114.0 (2CH, $\mathbf{C}_3$), 55.3 (CH_3, $\mathbf{C}_6$), 42.9 (CH_2, $\mathbf{C}_5$).

LRMS: (ESI+) m/z = 243 $[M+H]^+$

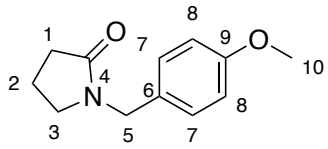
MP: 117.5 – 118.5 °C (Lit:[287] 52 – 53 °C)

4.2.2 Miscellaneous amides, sulfonamides and lactams

4.2.2.1 General method D: Amide/lactam synthesis by alkylation:

Preparation of amides and lactams was achieved using a literature procedure for amide alkylation:[288] To an ice–cooled suspension of amide (8.3 mmol) in THF (30 mL) was added NaH (0.363 g of 60% in mineral oil, 9.1 mmol) (CAUTION: Evolution of H2 gas). The grey suspension was allowed to warm to rt and stirred for 30 min before Bu4NI (0.305 g, 0.8 mmol) was added in one portion under a stream of argon. 1-(Chloromethyl)-4-methoxybenzene (1.12 mL, 8.4 mmol) was added dropwise by syringe over 10 min. The suspension was heated to reflux and stirred for 16 h. On completion, the reaction was quenched by dropwise addition of water, and the product was extracted with EtOAc (3 x 30 mL). The combined organic phase was washed with water (2 x 20 mL) followed by brine (30 mL), and then dried (MgSO4). Removal of solvents under reduced pressure gave the crude product. Purification by flash column chromatography (SiO2), eluting with EtOAc/ hexane afforded the title compound.

1-(4-Methoxybenzyl)pyrrolidin-2-one



2.43

Chemical Formula: $C_{12}H_{15}NO_2$

Molecular Weight: 205.26

1-(4-Methoxybenzyl)pyrrolidin-2-one (2.43) was prepared using general method D: From Pyrrolidin-2-one (1.50 g, 17.6 mmol), 1-(4-Methoxybenzyl)pyrrolidin-2-one was isolated as a colourless oil (2.50 g, 12.0 mmol, 69%). The data are consistent with reported values.[289, 290]

1H NMR: (CDCl3, 400 MHz) δ ppm = 7.17 (d, J = 8.7 Hz, 2H, H7), 6.85 (d, J = 8.7 Hz, 2H, H8), 4.38 (s, 2H, H5), 3.79 (s, 3H, H10), 3.24 (t, J = 7.1 Hz, 2H, H1), 2.42 (t, J = 8.1 Hz, 2H, H3), 1.97 (quin, J = 7.6 Hz, 2H, H2).

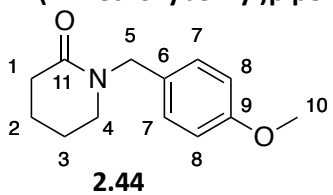
1H NMR (VT): (DMSO-d6, 500 MHz, 343 K), 7.15 (d, J = 8.7 Hz, 2H, H7), 6.90 (d, J = 8.7 Hz, 2H, H8), 4.29 (s, 2H, H5), 3.74 (s, 3H, H10), 3.19 (t, J = 7.2 Hz, 2H, H1), 2.27 (t, J = 8.1 Hz, 2H, H3), 1.89 (quin, J = 7.6 Hz, 2H, H2).

13C NMR: (CDCl3 101 MHz) δ ppm = 174.8 (C, C4), 160.0 (C, C9), 129.4 (2CH, C7), 128.6 (C, C6), 113.9 (2CH, C8), 55.2 (CH3, C10), 46.4 (CH2, C5), 45.9 (CH2, C3,5), 31.0 (CH2, C1), 17.6 (CH2, C2).

13C NMR (VT): (DMSO-d6, 126 MHz, 343 K): δ ppm = 173.4 (C, C4), 158.3 (C, C9), 128.8 (C, C6) 128.6 (2CH, C7), 113.7 (2CH, C8), 54.8 (CH3, C6), 45.7 (CH2, C5), 44.7 (CH2, C3), 30.0 (CH2, C1), 17.0 (CH2, C2).

LRMS: (ESI+) m/z = 206 [M+H]+.

1-(4-Methoxybenzyl)piperidin-2-one



2.44

Chemical Formula: $C_{13}H_{17}NO_2$

Molecular Weight: 219.28

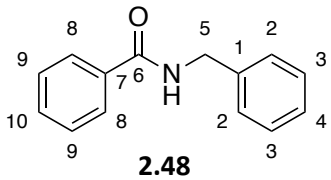
1-(4-Methoxybenzyl)piperidin-2-one (2.44) was prepared using general method D: from Piperidin-2-one (0.466 mL, 5.0 mmol), 1-(4-Methoxybenzyl)piperidin-2-one was afforded as a colourless oil (0.764 g, 3.5 mmol, 69%) The data are consistent with reported values.[291]

1H NMR: (CDCl3, 400 MHz) δ ppm = 7.17 (d, J = 8.7 Hz, 2H, H7), 6.85 (d, J = 8.7 Hz, 2H, H8), 4.38 (s, 2H, H5), 3.79 (s, 3H, H10), 3.24 (t, J = 7.1 Hz, 2H, H1), 2.42 (t, J = 8.1 Hz, 2H, H4), 1.99 – 1.95 (m, 4H, H2-3).

13C NMR: (CDCl3 101 MHz) δ ppm = 169.7 (C, C11), 158.8 (C, C9), 129.4 (2CH, C7), 129.3 (C, C6), 113.8 (2CH, C8), 55.2 (CH3, C10), 49.4 (CH2, C5), 46.9 (CH2, C1), 32.3 (CH2, C4), 23.1 (CH2, C2), 21.3 (CH2, C3).

LRMS: (ESI+) m/z = 220 [M+H]+.

***N*-Benzylbenzamide**



2.48

Chemical Formula: C14H13NO

Molecular Weight: 211.26

N-Benzylbenzamide (2.48) was prepared using general method D: from Benzamide (2.68) (2.42 g, 20.0 mmol), *N*-Benzylbenzamide was isolated as a white solid (2.32 g, 11.0 mmol, 55%). The data are consistent with reported values.[292]

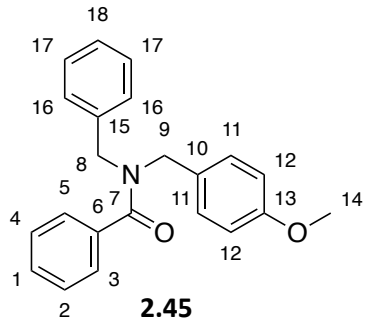
1H NMR: (CDCl3, 400 MHz) δ ppm = 7.81 (d, J = 7.6 Hz, 2H, H9), 7.53 – 7.50 (m, 1H, H9), 7.46 – 7.42 (m, 2H, H9), 7.38 – 7.37 (m, 4H, H2,3), 7.33 -7.31 (m, 1H, H4) 6.42 (br. s, 1H, NH), 4.66 (d, J = 5.7 Hz, 2H, H5).

13C NMR: (CDCl3, 101 MHz) δ ppm = 166.6 (C, C6), 140.2 (C, C7), 134.8 (C, C1), 131.7 (2CH, C8), 128.8 (CH, C4), 128.8 (2CH, C2), 127.7 (2CH, C9), 127.6 (CH, C10), 127.2 (2CH, C3), 43.0 (CH2, C5).

LRMS: (ESI+) m/z = 212 [M+H]+

MP: 113.4 – 115.1 °C (Lit:[267] 103 – 104 °C)

***N*-Benzyl-*N*-(4-methoxybenzyl)benzamide**



2.45

Chemical Formula: $C_{22}H_{21}NO_2$

Molecular Weight: 331.42

N-Benzyl-*N*-(4-methoxybenzyl)benzamide (2.45) was prepared using general method D: From *N*-(4-Methoxybenzyl)benzamide (1.21 g, 5.0 mmol), *N*-Benzyl-*N*-(4-methoxybenzyl)benzamide (1.194 g, 3.6 mmol, 72%) was isolated as a white solid. The data are consistent with (incomplete) reported values.[293]

1H NMR (VT): (DMSO-d6, 500 MHz, 373 K) δ ppm = 7.45 – 7.41 (m, 5H, H1-5), 7.36 – 7.33 (m, 2H, H17), 7.29 – 7.26 (m, 1H, H18), 7.21 (br. d, J = 8.6 Hz, 2H, H11), 7.13 (br. d, J = 8.0 Hz, 2H, H16) 6.91 (d, J = 8.6 Hz, 2H, H12), 4.51 (s, 2H, H8), 4.46 (s, 2H, H9), 3.77 (s, 3H, H14).

^{13}C NMR (VT): (DMSO-d_6, 126 MHz, 373 K): δ ppm = 170.6 (C, **C**$_7$) 158.3 (C, **C**$_{13}$), 136.6 (C, **C**$_6$), 136.1 (C, **C**$_{15}$), 128.7 (CH, **C**$_{18}$), 128.4 (C, **C**$_{10}$), 128.2 (2CH, **C**$_{16}$) 128.0 (2CH, **C**$_{3,5}$), 127.8 (2CH, **C**$_{11}$), 126.8 (2CH, **C**$_{2,4}$), 126.6 (CH, **C**$_1$), 125.9 (2CH, **C**$_{17}$), 113.8 (2CH, **C**$_{12}$**)** 54.7 (CH_3, **C**$_{14}$), 48.6 ($2CH_2$, **C**$_{8,9}$).

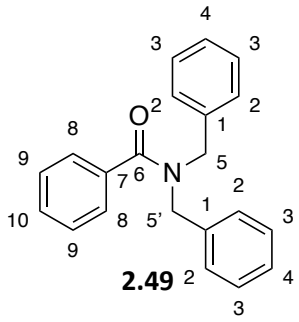
LRMS: (ESI+) m/z = 332 $[M+H]^+$

FT–IR (cm^{-1}) neat: 2928 (w, C-H), 1630 (s, C=O), 1244 (s, C-O).

HRMS: (ESI+) for $C_{22}H_{21}NO_2H^+$ requires 332.1645 found 332.1646 Da.

MP: 66.0 – 67.2 °C (Lit:[293] 65 °C)

***N*,*N*-Dibenzylbenzamide**



2.49

Chemical Formula: $C_{21}H_{19}NO$

Molecular Weight: 301.39

N,*N*-Dibenzylbenzamide (**2.49**) was prepared using general method D: From Benzamide (**2.68**) (2.42 g, 20.0 mmol), *N*,*N*-Dibenzylbenzamide (1.808 g, 6.0 mmol, 30%) was isolated as a white solid. The data are consistent with reported values.[294]

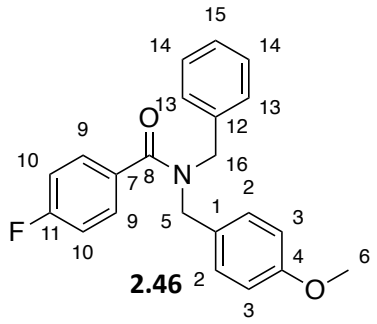
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.51 – 7.48 (m, 2H, $\mathbf{H}_8$), 7.40 – 7.24 (m, 11H, $\mathbf{H}_{2\text{-}4,\,10}$), 7.16 – 7.13 (m, 2H, $\mathbf{H}_9$), 4.71 (s, 2H, $\mathbf{H}_{5/5'}$) 4.40 (s, 2H, $\mathbf{H}_{5/5'}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 172.2, 136.2, 129.6, 128.7, 128.5, 128.4, 127.5, 127.1, 126.7, 51.4, 46.8.

LRMS: (ESI+) m/z = 302 $[M+H]^+$

MP: 113.4 – 115.1 °C (Lit:[294] 113 – 115 °C)

***N*-Benzyl-4-fluoro-*N*-(4-methoxybenzyl)benzamide**



Chemical Formula: $C_{22}H_{20}FNO_2$

Molecular Weight: 349.41

N-Benzyl-4-fluoro-*N*-(4-methoxybenzyl)benzamide (**2.46**) was prepared using general method D: from 4-Fluoro-*N*-(4-methoxybenzyl)benzamide (0.358 g, 1.4 mmol), *N*-Benzyl-4-fluoro-*N*-(4-methoxybenzyl)benzamide (0.286 g, 0.8 mmol, 59%) was isolated as a yellow oil. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm* = 7.48 (br. t, *J* = 5.8 Hz, 2H, $\mathbf{H}_{10}$), 7.40 – 7.31 (m, 4H, $\mathbf{H}_{13\text{-}14}$), 7.23 – 7.14 (m, 2H, $\mathbf{H_2}$), 7.07 (m, 3H, $\mathbf{H}_{9,15,}$) 6.90 (d, *J* = 8.6 Hz, 2H, $\mathbf{H}_3$), 4.67 (m, 2H, $\mathbf{H}_{16}$), 4.37 (m, 2H, $\mathbf{H}_5$), 3.83 (s, 3H, $\mathbf{H}_6$).

^{13}C NMR: ($CDCl_3$, 101 MHz): δ ppm* = 171.2 (C, $\mathbf{C}_8$) 163.3 (d, $J_{C\text{-}F}$ = 250.5 Hz, $\mathbf{C_{11}}$), 159.1 (C, $\mathbf{C}_4$), 132.2 (d, $J_{C\text{-}F}$ = 3.3 Hz, C, $\mathbf{C_7}$), 129.9 (C, $\mathbf{C_{12}}$), 129.0 (d, $J_{C\text{-}F}$ = 9.1 Hz, 2CH, $\mathbf{C_9}$), 128.5 (CH, $\mathbf{C_{15}}$), 128.4 (2CH, $\mathbf{C_{14}}$), 128.2 (C, $\mathbf{C_1}$), 127.6 (2CH, $\mathbf{C_{13}}$), 126.8 (2CH, $\mathbf{C_2}$), 115.6 (d, $J_{C\text{-}F}$ = 20.2 Hz, 2CH, $\mathbf{C_{10}}$), 114.2 (2CH, $\mathbf{C_3}$) 55.3 (CH_3, $\mathbf{C_6}$), 51.0 (CH_2, $\mathbf{C}_{16}$) 46.5 (CH_2, $\mathbf{C_5}$).

*Exists as 1:1 ratio of rotamers

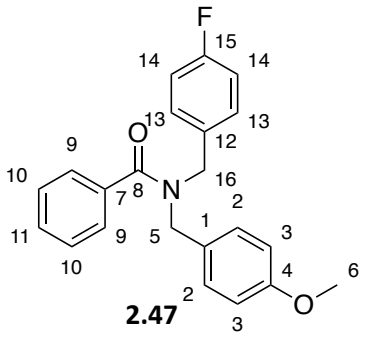
^{19}F NMR: ($CDCl_3$, 376 MHz) δ ppm = -110.4.

LRMS: (ESI+) m/z = 350 $[M+H]^+$

FT–IR (cm^{-1}) neat: 2928 (w, C-H), 1630 (s, C=O), 1244 (s, C-O).

HRMS: (ESI+) for $C_{22}H_{20}FNO_2H^+$ requires 350.1551 found 350.1559 Da.

_N_-(4-Fluorobenzyl)-_N_-(4-methoxybenzyl)benzamide



Chemical Formula: $C_{22}H_{20}FNO_2$

Molecular Weight: 349.41

_N_-(4-Fluorobenzyl)-_N_-(4-methoxybenzyl)benzamide (**2.47**) was prepared general method D: from _N_-(4-Methoxybenzyl)benzamide (1.21 g, 5.0 mmol), _N_-(4-Fluorobenzyl)-_N_-(4-methoxybenzyl)benzamide was isolated as a colourless oil that solidified on standing. (1.379 g, 3.9 mmol, 79%). Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm** = 7.48 (br. s, 2H, $\mathbf{H}_9$), 7.42 – 7.38 (m, 3H, $\mathbf{H}_{10}$ & $\mathbf{H}_{11}$), 7.29 -7.21 (m, 2H, $\mathbf{H}_2$), 7.10 – 7.02 (m, 4H, $\mathbf{H}_{13\text{-}14,}$) 6.90 (d, J = 8.6 Hz, 2H, $\mathbf{H}_3$), 4.64 (s, 2H, $\mathbf{H}_{16}$), 4.34 (s, 2H, $\mathbf{H}_5$), 3.83 (s, 3H, $\mathbf{H}_6$).

^{13}C NMR: ($CDCl_3$, 101 MHz): δ ppm** = 172.1 (C, $\mathbf{C}_8$) 162.2 (d, $J_{C\text{-}F}$ = 247.5 Hz, $\mathbf{C}_{15}$), 159.2 (C, $\mathbf{C}_4$), 136.2 (C, $\mathbf{C}_7$), 130.1 (C, $\mathbf{C}_{14}$), 129.8 (d, $J_{C\text{-}F}$ = 3.3 Hz, C, $\mathbf{C}_{12}$), 129.7* (2CH, $\mathbf{C}_{13}$), 128.6 (2CH, $\mathbf{C}_9$), 128.3 (2CH, $\mathbf{C}_2$), 126.7 (2CH, $\mathbf{C}_{10}$), 115.5 (d, $J_{C\text{-}F}$ = 20.9 Hz, 2CH, $\mathbf{C}_{14}$), 114.2 (2CH, $\mathbf{C}_3$**)** 55.3 (CH_3, $\mathbf{C}_6$), 51.0 (CH_2, $\mathbf{C}_{16}$) 48.6 (CH_2, $\mathbf{C}_5$).

^{19}F NMR: ($CDCl_3$, 376 MHz)** δ ppm = –114.7, –115.1.

*Unresolved coupling

**Exists as 45:55 ratio of rotamers

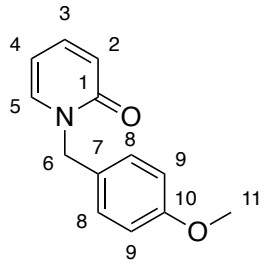
LRMS: (ESI+) m/z = 350 $[M+H]^+$

FT–IR (cm^{-1}) neat: 2932 (w, C-H), 1630 (s, C=O), 1219 (s, C-F).

HRMS: (ESI+) for $C_{22}H_{20}FNO_2H^+$ requires 350.1551 found 350.1547 Da.

MP: 79.3 – 80.6 °C

1-(4-Methoxybenzyl)pyridin-2(1*H*)-one



2.57

Chemical Formula: $C_{13}H_{13}NO_2$

Molecular Weight: 215.25

1-(4-Methoxybenzyl)pyridin-2(1*H*)-one (**2.57**) was prepared by literature alkylation: a solution of 4-Methoxybenzyl chloride (2.24 mL, 15.0 mmol) in acetone (5 mL) was added dropwise to a suspension of pyridine-2(1H)-one (**2.56**) (0.952 g, 10.0 mmol) and K_2CO_3 (4.15 g, 30.0 mmol) in acetone (25 mL) at rt. The suspension was heated to reflux and stirred for 36 hours and then filtered, washing with acetone (2 x 5 mL). Removal of solvents under reduced pressure afforded a yellow slurry that was purified by flash chromatography (1% Et_3N, 40% EtOAc in petrol) to afford 1-(4-Methoxybenzyl)pyridin-2(1*H*)-one (1.79 g, 8.3 mmol, 83%) as a white solid. The data are consistent with reported values.[295]

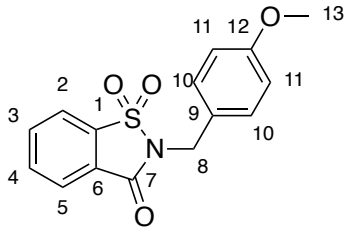
1H NMR (CDCl3, 400 MHz) δ ppm = 7.32 -7.24 (m, 4H, $\mathbf{H}_{3,5,8}$), 6.88 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_9$), 6.60 (d, *J* = 9.2 Hz, 1H, $\mathbf{H}_2$), 6.13 (td, *J* = 6.7, 1.3 Hz, 1H, $\mathbf{H}_4$), 5.08 (s, 2H, $\mathbf{H}_6$), 3.80 (s, 3H, $\mathbf{H}_{11}$).

^{13}C NMR: ($CDCl_3$, 101 MHz): δ ppm = 162.7 (C, $\mathbf{C}_1$), 159.4 (C, $\mathbf{C}_{10}$), 139.2 (CH, $\mathbf{C}_3$), 137.0 (CH, $\mathbf{C}_5$), 129.8 (2CH, $\mathbf{C}_8$), 128.4 (C, $\mathbf{C}_7$), 121.2 (CH,$\mathbf{C}_2$), 114.3 (2CH, $\mathbf{C}_9$), 106.1 (CH, $\mathbf{C}_4$), 55.3 (CH_3, $\mathbf{C}_{11}$), 51.4 (CH_2, $\mathbf{C}_6$).

LRMS: (ESI+) m/z = 216 $[M+H]^+$

MP: 93.0 – 94.5 °C (Lit:[295] 106 – 107 °C)

2-(4-Methoxybenzyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide



2.59

Chemical Formula: $C_{15}H_{13}NO_4S$

Molecular Weight: 303.33

2-(4-Methoxybenzyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (**2.59**) was prepared using the alkylation procedure described for the synthesis of 1-(4-Methoxybenzyl)pyridin-2(1*H*)-one: from Saccharin (**2.58**) (2.75 g, 15.0 mmol), 2-(4-Methoxybenzyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (3.64 g, 12.0 mmol, 80%) was afforded as a white solid. The data are consistent with reported values.[296, 297]

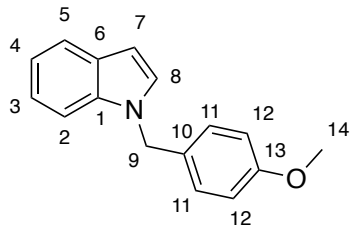
1H NMR (CDCl3, 400 MHz) δ ppm = 8.05 (d, *J* = 7.4 Hz, 1H, $\mathbf{H}_5$), 7.94 – 7.91 (m, 1H, $\mathbf{H}_2$), 7.88 – 7.80 (m, 2H, $\mathbf{H}_{3,4}$), 7.46 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_{10}$), 6.89 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_{11}$), 4.86 (s, 2H, $\mathbf{H}_8$), 3.80 (s, 3H, $\mathbf{H}_{13}$).

^{13}C NMR: ($CDCl_3$, 101 MHz): δ ppm = 159.6 (C, $\mathbf{C}_7$), 158.8 (C, $\mathbf{C}_{12}$), 137.8 (C, $\mathbf{C}_1$), 134.7 (CH, $\mathbf{C}_3$), 134.3 (CH, $\mathbf{C}_4$), 130.4 (2CH, $\mathbf{C}_{10}$), 127.4 (C, $\mathbf{C}_9$), 126.6 (C, $\mathbf{C}_6$), 125.2 (CH, $\mathbf{C}_2$), 121.0 (CH, $\mathbf{C}_5$), 114.3 (2CH, $\mathbf{C}_{11}$), 55.2 (CH_3, $\mathbf{C}_{13}$), 42.3 (CH_2, $\mathbf{C}_8$).

LRMS: (ESI+) m/z = 304 $[M+H]^+$

MP: 152.5 – 153.5 °C (Lit:[296] 153.1 – 154 °C)

1-(4-Methoxybenzyl)-1*H*-indole



2.55

Chemical Formula: $C_{16}H_{15}NO$

Molecular Weight: 237.30

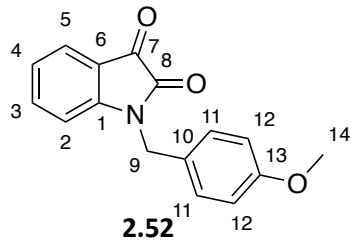
1-(4-Methoxybenzyl)-1H-indole (**2.55**) was prepared by indole alkylation: To a 0.4 M solution of Indole (**2.54**) (1.17 g, 10.0 mmol), in DMSO (25 mL) was added KOH (0.842 g, 15.0 mmol). The yellow solution was stirred at rt for 30 min. DMSO (10 mL) was added to fully dissolve solids. Solution was then cooled to 5°C over ice and 4-Methoxybenzyl chloride (2.04 mL, 15.0 mmol) was added dropwise by syringe over 10 min. Reaction was allowed to warm to rt and stirred for 24 h. The reaction was quenched by dropwise addition of water (30 mL) over ice. EtOAc (30 mL) was added, and the organic phase was extracted. Aqueous phase was washed with EtOAc (3 x 30 mL). The combined organic phase was washed with water (3 x 30 mL) and then dried ($MgSO_4$). Removal of solvents under reduced pressure gave the crude product as a yellow oil. Purification by flash chromatography (5 to 30% EtOAc in petroleum ether) gave 1-(4-Methoxybenzyl)-1*H*-indole (1.69 g, 7.1 mmol, 71%) as a red oil. The data are consistent with reported values.[298, 299]

1H NMR (CDCl3, 400 MHz) δ ppm = 7.66 (d, *J* = 7.8 Hz, 1H, $\mathbf{H}_1$), 7.32 (d, *J* = 8.2 Hz, 1H, $\mathbf{H}_4$), 7.19 (td, *J* = 7.8, 0.8 Hz, 1H, $\mathbf{H}_3$), 7.13-7.07 (m, 4H, $\mathbf{H}_{2,8,11}$), 6.84 (d, *J* = 8.6 Hz, 2H, $\mathbf{H}_{12}$), 6.55 (d, *J* = 3.0 Hz, 1H, $\mathbf{H}_7$), 5.27 (s, 2H, $\mathbf{H}_9$), 3.78 (s, 3H, $\mathbf{H}_{14}$).

13C NMR (CDCl3 101 MHz) δ = 159.1 (C, $\mathbf{C}_{13}$), 136.2 (C, $\mathbf{C}_5$), 129.5 (C, $\mathbf{C}_{10}$), 128.2 (C, $\mathbf{C}_6$), 128.2 (2CH, $\mathbf{C}_{11}$), 128.1 (CH, $\mathbf{C}_8$), 121.6 (CH, $\mathbf{C}_3$), 120.9 (CH, $\mathbf{C}_1$), 119.4 (CH, $\mathbf{C}_2$), 114.1 (2CH, $\mathbf{C}_{12}$), 109.7 (CH, $\mathbf{C}_4$), 101.5 (CH, $\mathbf{C}_7$), 55.3 (CH_3, $\mathbf{C}_{14}$), 49.6 (CH_2, $\mathbf{C}_9$).

LRMS: (ESI+) m/z = 238 $[M+H]^+$

1-(4-Methoxybenzyl)indoline-2,3-dione



2.52

Chemical Formula: $C_{16}H_{13}NO_3$

Molecular Weight: 267.28

1-(4-Methoxybenzyl)indoline-2,3-dione (**2.52**) was prepared using literature procedure for alkylation of isatin (**2.51**):[300] To a solution of K_2CO_3 (1.04 g, 7.5 mmol) in DMF (25 mL) was added isatin (0.736 g, 5.0 mmol). The black suspension was stirred at rt for 30 min. 4-Methoxybenzyl chloride (0.749 mL, 5.5 mmol) was added dropwise by syringe over 10 min followed by Bu_4NI (0.185 g, 0.500 mmol, 0.1) in one portion. The black suspension was stirred at rt for 20 h. The reaction was quenched with water (40 mL) and EtOAc (25 mL) was added. The organic phase was extracted, and aqueous phase was washed with EtOAc (2 x 40 mL). The combined organic phase was washed with water (4 x 40 mL) and then dried ($MgSO_4$). Removal of solvents under reduced pressure gave the crude product as an orange solid that was recrystallised in EtOAc to give 1-(4-Methoxybenzyl)indoline-2,3-dione (1.15 g, 4.3 mmol, 85%) as orange needles. The data are consistent with reported values.[301]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.61 (dd, *J* = 7.5, 0.8 Hz, 1H, **H**$_2$), 7.49 (td, *J* = 7.8, 1.4 Hz, 1H, **H**$_3$), 7.28 (d, *J* = 8.7 Hz, 2H, **H**$_{11}$) 7.09 (td, *J* = 7.6, 0.8 Hz, 1H, **H**$_4$) 6.83 (d, *J* = 8.7 Hz, 2H, **H**$_{12}$), 6.81 (d, *J* = 8.0 Hz, 1H, **H**$_5$) 4.88 (s, 2H, **H**$_9$) 3.79 (s, 3H, **H**$_{14}$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 183.4 (C, **C**$_7$), 159.5 (C, **C**$_{13}$), 158.2 (C, **C**$_8$), 150.8 (C, **C**$_1$), 138.2 (CH, **C**$_3$), 128.9 (2CH, **C**$_{11}$), 126.5 (C, **C**$_{10}$), 125.4 (CH, **C**$_4$), 123.8 (C, **C**$_5$), 117.7 (C, **C**$_6$), 114.4 (2CH, **C**$_{12}$), 111.0 (CH, **C**$_2$), 55.3 (CH_3, **C**$_{14}$), 43.5 (CH_2, **C**$_9$).

LRMS: (ESI+) m/z = 290 $[M+Na]^+$.

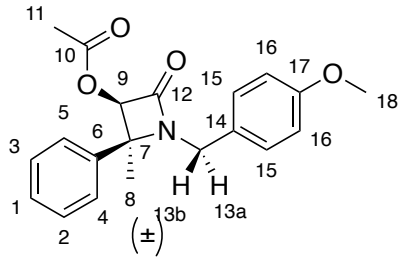
MP: 172.1 – 172.9 °C (Lit:[301] 161 –162 °C)

4.2.3 β-lactams

4.2.3.1 General method E: Staudinger synthesis

Preparation of β-lactams was achieved using a literature procedure for Staudinger synthesis:[219] To an ice–cooled solution of corresponding imine (7.18 g, 30.0 mmol) and Et_3N (10.5 mL, 75.0 mmol) in dry CH_2Cl_2 (200 mL) was added a solution of 2-Acetoxyacetyl chloride (7.68 g, 45.0 mmol) in dry CH_2Cl_2 (40 mL) dropwise over 60 minutes at 0 °C. The yellow solution turned brown, then black. The reaction was maintained at 0 °C for 2 hours and then allowed to warm to rt and stirred for 16 hours. On completion, water (100 mL) was added, and the organic phase was separated. This was sequentially washed with $NaHCO_3$ (2 x 100 mL), and brine (100 mL), and then dried ($MgSO_4$), and filtered. Removal of solvents under reduced pressure followed by purification by flash chromatography afforded the pure compound.

1-(4-Methoxybenzyl)-2-methyl-4-oxo-2-phenylazetidin-3-yl acetate



2.86

Chemical Formula: $C_{20}H_{21}NO_4$

Molecular Weight: 339.39

1-(4-Methoxybenzyl)-2-methyl-4-oxo-2-phenylazetidin-3-yl acetate (**2.86**) was prepared by general method E: from (E)-*N*-(4-Methoxybenzyl)-1-phenylethan-1-imine (**2.84**) (7.18 g, 30.0 mmol) 1-(4-Methoxybenzyl)-2-methyl-4-oxo-2-phenylazetidin-3-yl acetate (7.12 g, mmol, 70%) was afforded as an off–white solid. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.37-7.32 (m, 3H, $\mathbf{H}_{1\text{-}3}$), 7.25-7.23 (m, 2H, $\mathbf{H}_{4\text{-}5}$), 7.17 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_{15}$), 6.82 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_{16}$), 5.36 (s, 1H, $\mathbf{H}_9$), 4.75 (d, *J* = 14.8 Hz, 1H, $\mathbf{H}_{13a}$), 3.97 (d, *J* = 14.8 Hz, 1H, $\mathbf{H}_{13b}$) 3.80 (s, 3H, $\mathbf{H}_{18}$), 1.67 (s, 3H, H_{11}), 1.60 (s, 3H, H_8).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 169.4 (C, $\mathbf{C}_{10}$), 164.3 (C, $\mathbf{C}_{12}$), 159.3 (C, $\mathbf{C}_{17}$), 136.5 (C, $\mathbf{C}_6$), 130.1 (2CH, $\mathbf{C}_{15}$) 128.1 (2CH, $\mathbf{C}_{2,3}$), 128.0 (CH, $\mathbf{C}_1$), 128.0 (C, $\mathbf{C}_{14}$), 127.5 (2CH, $\mathbf{C}_{4,5}$), 114.0 (2CH, $\mathbf{C}_{16}$), 83.5 (CH, $\mathbf{C}_9$), 67.6 (C, $\mathbf{C}_7$), 55.3 (CH_3, $\mathbf{C}_{18}$), 43.6 (CH_2, $\mathbf{C}_{13}$), 22.3 (CH_3, $\mathbf{C}_8$), 19.7 (CH_3, $\mathbf{C}_1$).

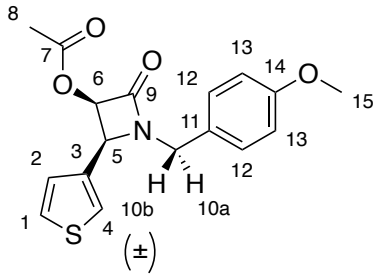
LRMS: (ESI+) m/z = 340 $[M+H]^+$

FT–IR (cm^{-1}) neat: 2909 (w, C-H), 1757 (s, C=O), 1742 (s, C=O).

MP: 96.0 – 97.0 °C

HRMS: (ESI+) for $C_{20}H_{21}NO_4Na^+$ requires 362.1363 found 362.1367 Da.

1-(4-Methoxybenzyl)-2-oxo-4-(thiophen-3-yl)azetidin-3-yl acetate



2.83

Chemical Formula: $C_{17}H_{17}NO_4S$

Molecular Weight: 331.39

1-(4-Methoxybenzyl)-2-oxo-4-(thiophen-3-yl)azetidin-3-yl acetate (**2.83**) was prepared using general method E: from (*E*)-*N*-(4-Methoxybenzyl)-1-(thiophen-3-yl)methanimine (**2.80**) (2.31 g, 10.0 mmol) and 2-Acetoxyacetyl chloride (1.64 g, 12.0 mmol), 1-(4-Methoxybenzyl)-2-oxo-4-(thiophen-3-yl)azetidin-3-yl acetate (2.65 g, 8.0 mmol, 80%) was afforded as a clear oil. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.29 (dd, *J* = 5.0, 3.0 Hz, 1H, $\mathbf{H}_1$), 7.16 (dd, *J* = 3.0, 1.2 Hz, 1H, $\mathbf{H}_4$), 7.06 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_{12}$), 6.94 (dd, *J* = 5.0, 1.2 Hz, 1H, H_2) 6.82 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_{13}$), 5.72 (d, *J* = 4.5 Hz, 1H, $\mathbf{H}_6$), 4.83 (d, *J* = 4.5 Hz), 1H, $\mathbf{H}_5$) 4.73 (d, *J* = 14.7 Hz, 1H, $\mathbf{H}_{13a}$), 3.89 (d, *J* = 14.7 Hz, 1H, $\mathbf{H}_{13b}$) 3.78 (s, 3H, $\mathbf{H}_{15}$), 1.76 (s, 3H, H_8).

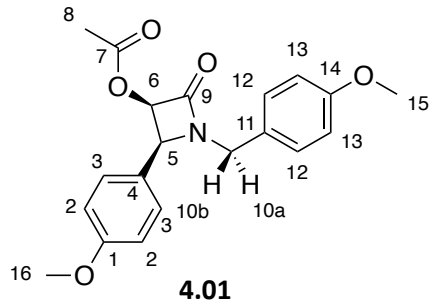
^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 169.1 (C, $\mathbf{C}_7$), 164.3 (C, $\mathbf{C}_9$), 159.2 (C, $\mathbf{C}_{14}$), 134.2 (C, $\mathbf{C}_3$), 129.8 (2CH, $\mathbf{C}_{12}$) 127.0 (CH, $\mathbf{C}_2$), 126.4 (C, $\mathbf{C}_{11}$), 125.9 (CH, $\mathbf{C}_1$), 124.9 (CH, $\mathbf{C}_4$), 114.1 (2CH, $\mathbf{C}_{13}$), 56.5 (CH, $\mathbf{C}_6$), 55.2 (CH_3, $\mathbf{C}_{15}$), 43.9 (**(**CH_2, $\mathbf{C}_{10}$), 19.8 (CH_3, $\mathbf{C}_8$).

LRMS: (ESI+) m/z = 354 $[M+Na]^+$

FT–IR (cm^{-1}) neat: 3102 (w, C-H), 1746 (s, C=O).

HRMS: (ESI+) for $C_{17}H_{17}NO_4SNa^+$ requires 354.0774 found 354.0771 Da.

1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl acetate



4.01

Chemical Formula: $C_{20}H_{21}NO_5$

Molecular Weight: 355.39

1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl acetate (**4.01**) was prepared as a side-product from general method E: from (*E*)-*N*-(4-Methoxybenzyl)-1-(thiophen-3-yl)methanimine (2.31 g, 10.0 mmol) and 2-Acetoxyacetyl chloride (1.64 g, 12.0 mmol), 1-(4-methoxybenzyl)-2-(4-Methoxyphenyl)-4-oxoazetidin-3-yl acetate (0.32 g, 0.9 mmol, 9%) was afforded as a white solid. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.14 (d, *J* = 8.8 Hz, 2H, **H**$_3$), 7.06 (d, *J* = 8.8 Hz, 2H, **H**$_{12}$), 6.88 (d, *J* = 8.7 Hz, 2H, **H**$_{13}$), 6.83 (d, *J* = 8.8 Hz, 1H, H_2), 5.71 (d, *J* = 4.5 Hz, 1H, **H**$_6$), 4.80 (d, *J* = 14.7 Hz, 1H, **H**$_{13a}$), 4.69 (d, *J* = 4.5 Hz, 1H, **H**$_5$) 3.83 (d, *J* = 14.7 Hz, 1H, **H**$_{13b}$) 3.83 (s, 3H, **H**$_{15}$), 3.80 (s, 3H, **H**$_{16}$)1.72 (s, 3H, H_8).

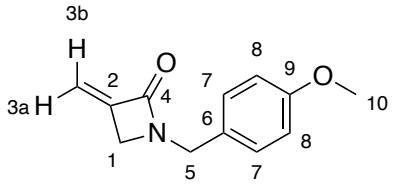
^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 169.2 (C, **C**$_7$), 164.60 (C, **C**$_9$), 159.9 (C, **C**$_{1/14}$), 159.3 (C, **C**$_{1/14}$), 129.9 (2CH, **C**$_3$), 129.7 (2CH, **C**$_{12}$) 126.5 (C, **C**$_{11}$), 124.2 (C, **C**$_4$), 114.2 (2CH, **C**$_2$), 113.8 (2CH, **C**$_{13}$), 60.2 (CH, **C**$_6$), 55.3 (2CH_3, **C**$_{15,16}$), 43.8 (**C**H_2, **C**$_{10}$), 19.9 (CH_3, **C**$_8$).

LRMS: (ESI+) m/z = 356 $[M+H]^+$

FT–IR (cm^{-1}) neat: 3106 (w, C-H), 1744 (s, C=O).

MP: 98.0 – 99.0 °C

1-(4-Methoxybenzyl)-3-methyleneazetidin-2-one



4.02

Chemical Formula: $C_{12}H_{13}NO_2$

Molecular Weight: 203.24

1-(4-Methoxybenzyl)-3-methyleneazetidin-2-one (**4.02**) was prepared by literature procedure for β lactam cyclisation:[302] KOH (0.185 g, 3.3 mmol) was added in portions to a solution of 3-Bromo-2-(bromomethyl)-*N*-(4-methoxybenzyl)propenamide (0.400 g, 1.1 mmol) and TBAB (0.036 g, 0.1 mmol) in CH_2Cl_2 (7.1 mL) at rt. The solution was stirred for 16 hours at rt and then water (10 mL) was added. The organic phase was separated, and the aqueous phase was washed with CH_2Cl_2 (2 x 5 mL). The combined organic phase was dried ($MgSO_4$), filtered and solvent was evaporated under reduced pressure. Purification by flash chromatography (30% EtOAc in hexane) afforded 1-(4-Methoxybenzyl)-3-methyleneazetidin-2-one (0.109 g, 58%) as a white solid. The data are consistent with (incomplete) reported values.[302]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.19 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_7$), 6.88 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_8$), 5.72 (q, *J* = 1.4 Hz, 1H, $\mathbf{H}_{3b}$), 5.15 (q, *J* = 1.4 Hz), 1H, $\mathbf{H}_{3a}$) 4.46 (s, 2H, $\mathbf{H}_5$), 3.81 (s, 3H, $\mathbf{H}_{10}$), 1.76 (t, *J* = 1.4 Hz, 2H, $\mathbf{H}_1$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 163.4 (C, $\mathbf{C}_4$), 159.2 (C, $\mathbf{C}_9$), 145.1 (C, $\mathbf{C}_2$), 129.5 (2CH, $\mathbf{C}_7$) 127.4 (C, $\mathbf{C}_6$), 114.2 (2CH, $\mathbf{C}_8$), 109.5 (CH_2, $\mathbf{C}_3$), 55.3 (CH_3, $\mathbf{C}_{10}$), 47.6 (CH_2, $\mathbf{C}_1$), 45.4 (CH_2, $\mathbf{C}_5$).

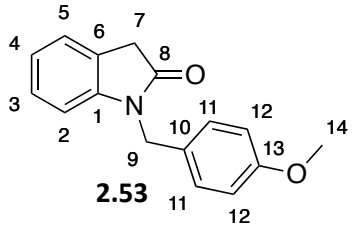
LRMS: (ESI+) m/z = 204 $[M+H]^+$

HRMS: (ESI+) for $C_{12}H_{13}NO_2Na^+$ requires 226.0838 found 226.0839 Da.

MP: 72.0 – 73.0 °C (Lit:[302] 71.0 –71.5 °C)

4.2.3.2 Miscellaneous substrates for electrosynthesis

1-(4-Methoxybenzyl)indolin-2-one



Chemical Formula: $C_{16}H_{15}NO_2$

Molecular Weight: 253.30

1-(4-Methoxybenzyl)indolin-2-one (**2.53**) was prepared by a literature procedure for a Wolff-Kishner reduction:[303] 1-(4-Methoxybenzyl)indoline-2,3-dione (**2.52**) (0.600 g, 2.2 mmol) was suspended in hydrazine hydrate (1 mL). The mixture was stirred vigorously under reflux for 72 hours, then allowed to cool to RT. The reaction mixture was taken into EtOAc (20 mL), and water (20 mL) was added. The organic phase was separated, and the aqueous phase was washed with EtOAc (2 x 10 mL). The combined organic phase was dried ($MgSO_4$). Removal of solvents under reduced pressure afforded an orange solid that was purified by flash chromatography (10% to 40% EtOAc in petroleum ether) to afford 1-(4-Methoxybenzyl)indolin-2-one (0.492 g, 1.9 mmol, 88%) as an off–white solid. The data are consistent with reported values.[301]

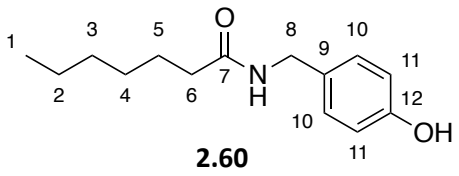
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.27 – 7.24 (m, 3H, $\mathbf{H}_{11}$ & $\mathbf{H}_5$), 7.18 (t, *J* = 7.8 Hz, 1H, $\mathbf{H}_3$), 7.01 (t, *J* = 7.6 Hz 1H, $\mathbf{H}_4$), 6.76 (d, *J* = 7.8 Hz, 1H, $\mathbf{H}_2$), 4.86 (s, 2H, $\mathbf{H}_9$), 3.78 (s, 3H, $\mathbf{H}_{14}$), 3.61 (s, 2H, $\mathbf{H}_7$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 175.1 (C, $\mathbf{C}_8$), 159.1 (C, $\mathbf{C}_{13}$), 144.4 (C, $\mathbf{C}_1$), 128.8 (CH, $\mathbf{C}_3$), 128.0 (2CH, $\mathbf{C}_{11}$), 127.8 (C, $\mathbf{C}_{10}$), 124.5 (CH, $\mathbf{C}_4$), 124.4 (C, $\mathbf{C}_5$), 122.3 (CH, $\mathbf{C}_6$), 114.1 (2CH, $\mathbf{C}_{12}$), 109.1 (CH, $\mathbf{C}_2$), 55.2 (CH_3, $\mathbf{C}_{14}$), 43.2 (CH_2, $\mathbf{C}_9$), 35.8 (CH_2, $\mathbf{C}_7$).

LRMS: (ESI+) m/z = 254 $[M+H]^+$

MP: 105.2 – 106.4 °C (Lit:[301] 105 –106 °C)

***N*-(4-Hydroxybenzyl)heptanamide**



2.60

Chemical Formula: $C_{14}H_{21}NO_2$

Molecular Weight: 235.33

N-(4-Hydroxybenzyl)heptanamide (**2.60**) was prepared by literature procedure for demethylation:[304] A solution of BBr_3 (0.68 M in CH_2Cl_2, 8.80 mL, 6.0 mmol) was added dropwise to a solution of *N*-(4-Methoxybenzyl)heptanamide (**2.26**) (0.748 g, 3.0 mmol) in CH_2Cl_2 (7 mL) at 0 °C. The solution was allowed to warm to rt, stirred for 4 hours and then quenched by cautious addition of ice–water (10 mL) The organic phase was separated, dried ($MgSO_4$), and filtered. Removal of solvents under reduced pressure afforded a yellow oil. Purification by flash chromatography (50% EtOAc in hexane) afforded *N*-(4-Hydroxybenzyl)heptanamide (0.459 g, 55%) as a white solid. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.11 (d, *J* = 8.5 Hz, 2H, $\mathbf{H}_{10}$), 6.87 (d, *J* = 8.5 Hz, 2H, $\mathbf{H}_{11}$), 5.82 (br. s, 1H, N**H**), 4.36 (d, *J* = 5.6 Hz, 2H, $\mathbf{H}_8$), 2.22 (t, *J* = 7.6 Hz, 2H, $\mathbf{H}_6$), 1.76 (br. s, 1H, O**H**), 1.65 (quin, *J* = 7.6 Hz, 2H, $\mathbf{H}_5$), 1.35 – 1.27 (m, 6H, $\mathbf{H}_{2\text{-}4}$) 0.87 (t, *J* = 7.0 Hz, 3H, H_1).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 173.5 (C, $\mathbf{C}_7$), 155.8 (C, $\mathbf{C}_{12}$), 129.6 (C, $\mathbf{C}_9$), 129.2 (2CH, $\mathbf{C}_{10}$), 115.7 (2CH, $\mathbf{C}_{11}$), 43.3 (CH_2, $\mathbf{C}_8$), 36.8 (CH_2, $\mathbf{C}_6$), 31.5 (CH_2, $\mathbf{C}_3$), 28.9 (CH_2, $\mathbf{C}_4$), 25.7 (CH_2, $\mathbf{C}_5$), 22.5 (CH_2, $\mathbf{C}_2$), 14.0 (CH_3, $\mathbf{C}_1$).

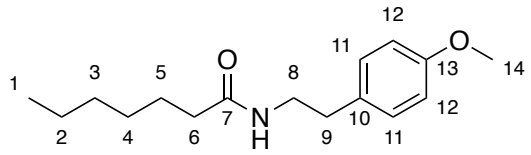
LRMS: (ESI+) m/z = 258 $[M+Na]^+$.

HRMS: (ESI+) for $C_{14}H_{21}NO_2Na^+$ requires 258.1465 found 258.1458 Da.

FT–IR (cm^{-1}) neat: 3413 (br., w, O-H), 3289 (br., w, N-H), 2951 (w, C-H), 1629 (s, C=O).

MP: 74.0 – 75.0 °C

***N*-(4-Methoxyphenethyl)heptanamide**



2.50

Chemical Formula: $C_{16}H_{25}NO_2$

Molecular Weight: 263.38

N-(4-Methoxyphenethyl)heptanamide (**2.50**) was prepared by literature procedure for alkylation: a suspension of *N*-(4-Hydroxyphenethyl)heptanamide (**2.31**) (0.748 g, 3.0 mmol) and K_2CO_3 (0.498 g, 3.6 mmol) in acetone (15 mL) was stirred at rt for 30 minutes and then MeI (0.053 mL, 3.15 mmol) was added dropwise. The reaction was stirred at rt for 16 hours and then quenched with water (10 mL). EtOAc (10 mL) was added, and the organic phase was separated. The aqueous phase was washed with EtOAc (2 x 10 mL). The combined organic phase was washed with NaOH (1N, 2 x 10 mL) and brine (10 mL) and then dried ($MgSO_4$) and filtered. Removal of solvents under reduced pressure afforded *N*-(4-Methoxyphenethyl)heptanamide (0.579 g, 2.2 mmol, 73%) as a yellow solid. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.11 (d, *J* = 8.6 Hz, 2H, **H**$_{11}$), 6.86 (d, *J* = 8.6 Hz, 2H, **H**$_{12}$), 5.42 (br. s, 1H, N**H**), 3.80 (s, 3H, **H**$_{14}$) 3.49 (q, *J* = 6.6 Hz, 2H, **H**$_8$), 2.76 (t, *J* = 6.6 Hz, 2H, **H**$_9$), 2.14 (t, *J* = 7.6 Hz, 2H, **H**$_6$) 1.59 (quin, *J* = 7.2 Hz, 2H, **H**$_5$), 1.32 – 1.25 (m, 6H, **H**$_{2\text{-}4}$) 0.88 (t, *J* = 6.7 Hz, 3H, **H**$_1$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 173.1 (C, **C**$_7$), 158.3 (C, **C**$_{13}$), 130.9 (C, **C**$_{10}$), 129.7 (2CH, **C**$_{11}$), 114.0 (2CH, **C**$_{12}$), 55.2 (CH_3, **C**$_{14}$), 40.6 (CH_2, **C**$_8$), 36.9 (CH_2, **C**$_6$), 34.8 (C, **C**$_9$), 31.5 (CH_2, **C**$_3$), 28.9 (CH_2, **C**$_4$), 25.7 (CH_2, **C**$_5$), 22.5 (CH_2, **C**$_2$), 14.0 (CH_3, **C**$_1$).

LRMS: (ESI+) m/z = 286 $[M+Na]^+$.

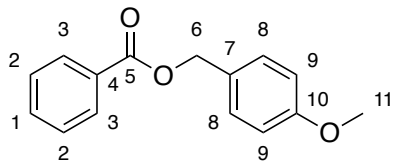
HRMS: (ESI+) for $C_{16}H_{25}NO_2Na^+$ requires 286.1778 found 286.1776.

FT–IR (cm^{-1}) neat: 3306 (br., m, N-H), 2928 (w, C-H), 1636 (s, C=O).

MP: 85.5 – 86.5 °C

4.2.4 Miscellaneous compounds

***N*-(4-Methoxybenzyl)benzoate**



2.62

Chemical Formula: $C_{15}H_{14}O_3$

Molecular Weight: 242.27

N-(4-Methoxybenzyl)benzoate (**2.62**) was prepared by a literature procedure for carboxylic acid alkylation:[305] To a solution of Benzoic acid (**2.61**) (0.610 g, 5.0 mmol) in DMF (6.1 mL) was added K_2CO_3 (1.04 g, 7.5 mmol). The white suspension was stirred for 30 minutes. 4-methoxybenzyl chloride (0.817 mL, 6.0 mmol) was added dropwise by syringe over 10 min and suspension stirred for 24 h. The reaction was quenched with water (10 mL) and EtOAc (10 mL) was added. The organic phase was extracted, and the aqueous phase was washed with EtOAc (2 x 10 mL). The combined organic phase was washed with water (4 x 20 mL) and dried ($MgSO_4$). Removal of solvents under reduced pressure gave the crude product as a colourless oil. Purification by flash chromatography (5 to 30% EtOAc in petroleum ether) gave *N*-(4-Methoxybenzyl)benzoate (1.18 g, 4.9 mmol, 97%) as a colourless oil. The data are consistent with reported values.[306,307]

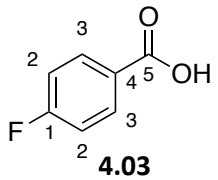
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.80 (d, *J* = 7.6 Hz, 2H, **H**$_9$), 7.53 – 7.48 (m, 1H, **H**$_{11}$), 7.45 – 7.41 (m, 2H, **H**$_{10}$), 7.30 (d, *J* = 8.7 Hz, 2H, **H**$_2$), 6.90 (d, *J* = 8.7 Hz, 2H, **H**$_3$), 6.36 (br. s, 1H, N**H**), 4.59 (d, *J* = 5.6 Hz, 2H, **H**$_5$), 3.82 (s, 3H, **H**$_6$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 167.2 (C, **C**$_7$), 159.1 (C, **C**$_4$), 134.4 (C, **C**$_8$), 131.5 (CH, **C**$_{11}$), 130.2 (C, **C**$_1$), 129.3 (2CH, **C**$_2$), 128.6 (2CH, **C**$_9$), 126.9 (2CH, **C**$_{10}$), 114.1 (2CH, **C**$_3$), 55.3 (CH_3, **C**$_6$), 43.6 (CH_2, **C**$_5$).

LRMS: (EI) m/z = 242

MP: 29.8 – 30.7 °C (Lit:[307] 29 – 30 °C)

4-Fluorobenzoic acid



4.03

Chemical Formula: $C_7H_5FO_2$

Molecular Weight: 140.11

4-Fluorobenzoic acid (**4.03**) was prepared by literature procedure for Pinnick oxidation:[308] a solution of 4-Fluorobenzaldehyde (2.48 g, 20.0 mmol), $NaClO_2$ (3.62 g, 40.0 mmol) and $NaHPO_4$ (3.60 g, 30.0 mmol) in 1:1 THF/water cosolvent (100 mL) was stirred at rt for 72 hours and then 2-methylbutene (6.36 mL, 60.0 mmol) was added to quench the reaction. The solution was reduced to ½ volume and basified with 1M aq. NaOH solution (50 mL). EtOAc (3 x 50 mL) was used to extract impurities. The aqueous phase was re-acidified by dropwise addition of conc. HCl (20 mL) until pH1 was reached. White solids precipitated and were collected by filtration, washing with 1N aq. HCl to give 4-Fluorobenzoic acid (2.46 g, 17.6 mmol, 88%) as a white solid. The data are consistent with reported values.[309, 310, 311]

^{1}H NMR: (d_4-MeOH, 400 MHz) δ ppm = 8.07 (dd, *J* = 8.9, 5.5 Hz, 2H, **H**$_3$), 7.19 (t, *J* = 8.9 Hz, 2H, **H**$_2$), 3.35 (s, 1H, **OH**).

^{13}C NMR: (d_4-MeOH, 101 MHz) δ ppm = 168.9 (C, **C**$_5$), 167.3 (d, *J* = 250 Hz, C, **C**$_1$), 133.6 (d, *J* = 10.1 Hz, 2CH, **C**$_3$), 128.6 (d, *J* = 2.5 Hz C, **C**$_4$), 116.5 (d, *J* = 22.2 Hz, 2CH, **C**$_2$).

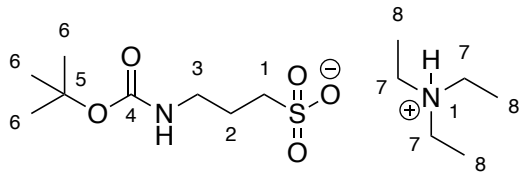
^{19}F NMR: (d_4-MeOH, 376 MHz) δ ppm = -108.7.

LRMS: (ESI-) m/z = 139 $[M-H]^-$

MP: 177.0 – 179.0 °C (Lit:[311] 184 – 186 °C)

FT–IR (cm^{-1}) neat: 2827 (w, C-H), 1670 (s, C=O), 1225 (s, C-F).

Triethylammonium 3-((*tert*-butoxycarbonyl)amino)propane-1-sulfonate



4.04

Chemical Formula: $C_{14}H_{32}N_2O_5S$

Molecular Weight: 340.48

Triethylammonium 3-((*tert*-butoxycarbonyl)amino)propane-1-sulfonate (**4.04**) was prepared by literature procedure for BOC protection: BOC_2O (2.53 mL, 11.0 mmol) was added to a solution of 3-Aminopropane-1-sulfonic acid (1.39 g, 10.0 mmol) and Et_3N (1.53 mL, 11 mmol) in dioxane (12.5 mL) and water (12.5 mL) at rt. The solution was stirred for 48 hours. Removal of solvents under reduced pressure afforded Triethylammonium 3-((*tert*-butoxycarbonyl)amino)propane-1-sulfonate (3.40 g, 10.0 mmol, quantitative) as a clear oil. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 10.25 (br. s, 1H, $\mathbf{H}_9$), 5.02 (br. s, 1H, $\mathbf{H}_{11}$), 3.25 (q, *J* = 2H, $\mathbf{H}_{10}$), 3.13 (q, *J* = Hz, 6H, $\mathbf{H}_2$), 2.87 (t, *J* = Hz, 2H, $\mathbf{H}_3$), 2.34 (br. s, 1H, N**H**), 1.97 (quin, *J* = 5.6 Hz, 2H, $\mathbf{H}_5$), 1.39 (s, 9H, **H**), 1.34 (t, *J* = Hz, 9H, $\mathbf{H}_6$).

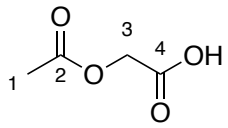
^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 156.0 (C, $\mathbf{C}_4$), 78.8 (C, $\mathbf{C}_5$), 48.8 (CH_2, $\mathbf{C}_1$), 46.0 ($3CH_2$, $\mathbf{C}_7$), 39.3 (CH_2, $\mathbf{C}_3$), 30.9 (C, $\mathbf{C}_1$), 28.3 ($3CH_3$, $\mathbf{C}_6$), 25.4 (CH_2, $\mathbf{C}_2$), 8.5 ($3CH_3$, $\mathbf{C}_8$).

LRMS: (EI) m/z = 363 $[M+Na]^+$

FT–IR (cm^{-1}) neat: 3369 (br., m, N-H), 2979 (w, C-H), 1688 (s, C=O), 1225 (s, C-F).

HRMS: (ESI+) for $C_{14}H_{32}N_2O_5SNa^+$ requires 363.1924 found 363.1929 Da.

2-Acetoxyacetic acid



2.78

Chemical Formula: $C_4H_6O_4$

Molecular Weight: 118.09

2-Acetoxyacetic acid (**2.78**) was prepared by literature esterification:[53] Acetyl chloride (1.69 mL, 23.7 mmol) was added to 2-Hydroxyacetic acid (1.00 g, 13.0 mmol) in a neat reaction at 0 °C. After 15 minutes a white solid formed. After 30 minutes, excess Acetyl chloride was removed under reduced pressure to give 2-Acetoxyacetic acid (1.54 g, 13.0 mmol, quantitative) as a white solid. The data are consistent with reported values.[312, 313]

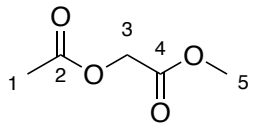
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 10.97 (br. s, 1H, OH), 4.67 (s, 2H, $\mathbf{H}_3$), 2.18 (s, 3H, $\mathbf{H}_1$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 173.5 (C, $\mathbf{C}_4$), 170.3 (C, $\mathbf{C}_2$), 60.1 (CH_2, $\mathbf{C}_3$), 20.4 (CH_3, $\mathbf{C}_1$).

LRMS: (ESI-) m/z = 117 $[M-H]^-$

MP: 68.0 – 68.5 °C

Methyl 2-acetoxyacetate



4.05

Chemical Formula: $C_5H_8O_4$

Molecular Weight: 132.12

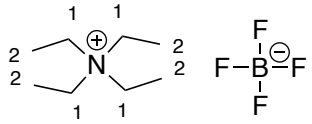
Methyl 2-acetoxyacetate (**4.05**) was prepared by literature procedure for ester coupling:[314] Acetyl chloride (2.85 mL, 40.0 mmol) was added dropwise to Methyl 2-hydroxyacetate (1.55 mL, 20.0 mmol) in a neat reaction. The mixture was stirred for 48 hours at rt and then dried under vacuum to afford methyl 2-acetoxyacetate (2.510 g, 95%) as a clear oil. The data are consistent with reported values.[315]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 4.62 (s, 2H, **H**$_3$), 3.78 (s, 3H, **H**$_5$), 2.17 (s, 3H, **H**$_1$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 170.3 (C, **C**$_4$), 168.3 (C, **C**$_2$), 60.6 (CH_2, **C**$_3$), 52.2 (CH_3, **C**$_5$), 20.4 (CH_3, **C**$_1$).

LRMS: (EI) m/z = 132 $[M]^{\bullet+}$

Tetraethylammonium tetrafluoroborate



4.06

Chemical Formula: $C_8H_{20}NBF_4$

Molecular Weight: 217.06

Tetraethylammonium tetrafluoroborate (**4.06**) was purified by literature procedure for recrystallisation:[212] A brown suspension of impure Et_4NBF_4 (168. 40 g, 776.0 mmol) in MeOH (1700 mL) at 60 °C was filtered, and the filtrate was allowed to cool to rt and then cooled over ice. Solids precipitated and were filtered, washing with ice-cold Et_2O (2 x 25 mL). The mother liquor was concentrated to ¾ volume and solids re-dissolved in the minimum quantity of hot MeOH. Cooling to 0 °C afforded more crystals. The crystallisation process was repeated once more, with addition of Et_2O (5 mL) to the cold solution to induce precipitation. The crystals from each stage were combined and dried under vacuum at 80 °C to afford pure Tetraethylammonium tetrafluoroborate (145.21 g, 86%) as clear crystals. The data are consistent with reported values.[212, 213]

^{1}H NMR: (D_2O, 400 MHz) δ ppm 3.35 (q, *J* = 7.3 Hz, 8H, **H**$_1$), 1.35 (t, *J* = 7.3 Hz 12H, **H**$_2$).

^{13}C NMR: (D_2O, 101 MHz) δ ppm = 53.4 ($4CH_2$, **C**$_1$), 7.7 ($4CH_3$, **C**$_2$).

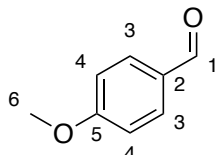
^{19}F NMR: (D_2O, 376 MHz) δ ppm = -154.5.

Elemental analysis: CHN for $C_8H_{20}NBF_4$ requires 44.27% C, 9.29% H, 6.45 N found 44.32% C, 9.13% H, 6.38% N.

MP: 365.0 – 366.0 °C

4.2.5 Aldehydes

4-Methoxybenzaldehyde



2.03

Chemical Formula: C8H8O2

Molecular Weight: 136.15

4-Methoxybenzaldehyde (**2.03**) was isolated as the cleavage product of general method J: from *N*-(4-Methoxybenzyl)benzamide (0.120 g, 0.5 mmol), the filtered solid from the bisulfite wash was treated with sat. aq. $NaHCO_3$. Following cessation of bubbling the product was extracted with EtOAc (3x10 mL), and then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give 4-Methoxybenzaldehyde (0.055 g, 0.4 mmol, 80%) as a yellow oil. The data are consistent with reported values.[316, 317]

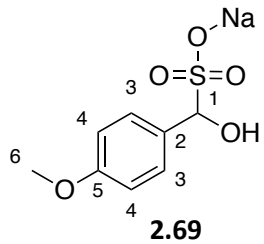
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm 9.81 (s, 1H, H_1), 7.76 (d, *J* = 7.5 Hz, 2H, **H**$_3$), 7.93 (d, *J* = 7.5 Hz 2H, **H**$_4$), 3.81 (s, 3H, **H**$_6$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 190.6 (C, **C**$_1$), 164.4 (C, **C**$_5$), 131.7 (2CH, **C**$_3$), 129.7 (C, **C**$_2$), 114.1 (2CH, **C**$_4$), 55.3 (CH_3, **C**$_6$).

FT–IR (cm^{-1}) neat: 2937 (w, C-H), 1509 (s, C=O).

LRMS: (EI) m/z = 136 $[M]^{\bullet+}$

Sodium hydroxy(4-methoxyphenyl)methanesulfonate



2.69

Chemical Formula: $C_8H_9NaO_5S$

Molecular Weight: 240.20

Sodium hydroxy(4-methoxyphenyl)methanesulfonate (**2.69**) was prepared by treatment of 4-Methoxybenzaldehyde with sodium bisulfite solution as part of purification in the deprotection of PMB-amides: The crude product from the two–step deprotection of (4-Methoxybenzyl) benzamide was treated with sat. aq. $NaHSO_3$ solution (10 mL), and then EtOH (2.5 mL) was added. The solid precipitate was collected by filtration and washed with EtOH (2 x 5 mL) and then EtOAc (2 x 5 mL) to give Sodium hydroxy(4-methoxyphenyl)methanesulfonate as a white solid (yield not obtained). The data are consistent with reported values.[318]

^{1}H NMR: (D_2O, 400 MHz) δ ppm 7.44 (d, *J* = 7.6 Hz, 2H, **H**$_3$), 6.96 (d, *J* = 7.6 Hz 2H, **H**$_4$), 5.40 (s, 1H, H 3.81 (s, 3H, **H**$_1$) 3.86 (s, 1H, OH), 3.78 (s, 3H, **H**$_6$).

^{13}C NMR: (D_2O, 101 MHz) δ ppm = 159.4 (C, **C**$_5$), 129.0 (2CH, **C$_3$**), 127.9 (C, **C$_2$**) 113.8 (2CH, **C**$_3$), 113.8 (2CH, **C**$_4$), 85.2 (CH, C_1) 55.3 (CH_3, **C**$_6$).

LRMS: (ESI-) m/z = 217 $[M-Na]^-$

MP: 155.6 – 157.0 °C

4.2.6 Acid/sulfonyl/alkyl chlorides

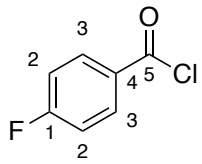
4.2.6.1 General method F: Chlorination with thionyl chloride

Preparation of acid/sulfonyl chlorides was carried out using a literature chlorination procedure:[319] $SOCl_2$ (1.74 mL, 24.0 mmol) was added dropwise to a stirred solution of carboxylic acid or sulfonic acid (12.0 mmol) in Et_2O (35 mL) at 0 °C. DMF (1-2 drops) were added and the mixture was allowed to warm to room temperature and stirred for an additional 2 h or until cessation of bubbling occurred (gas scrubbers fitted). Removal of solvents under reduced pressure afforded the acid chloride as an oil that was used without further purification.

4.2.6.2 General method G: Chlorination with oxalyl chloride

A chlorination procedure for more volatile alkyl and acid chlorides (using oxalyl chloride) was also employed in some substrates:[320] Carboxylic acid (12.0 mmol) was dissolved in dry CH_2Cl_2 (5 mL) Oxalyl chloride (1.31 mL, 15.0 mmol) was dropwise added to the stirred solution at rt, and then DMF (1-2 drops) was added. The solution was stirred until cessation of bubbling occurred (gas scrubbers fitted, aq. NaOH quench). Removal of solvents under reduced pressure afforded acid chloride as an oil that was used without further purification.

4-Fluorobenzoyl chloride



4.07

Chemical Formula: C_7H_4ClFO

Molecular Weight: 158.56

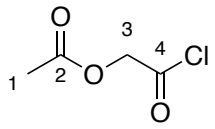
4-Fluorobenzoyl chloride (**4.07**) was prepared by general method F: from 4-Fluorobenzoic acid (1.58 g, 12.0 mmol), 4-Fluorobenzoyl chloride was afforded as a clear oil. The data are consistent with reported values.[321, 322]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 8.15 (t, *J* = 8.6 Hz, 2H, **H**$_3$), 7.16 (t, *J* = 8.6 Hz, 2H, **H**$_2$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 171.1 (C, **C**$_5$), 166.4 (d, *J* = 257 Hz, C, **C**$_1$), 132.9 (d, *J* = 10.1 Hz, 2CH, **C**$_3$), 125.5 (d, *J* = 3.0 Hz C, **C**$_4$), 115.7 (d, *J* = 22.2 Hz, 2CH, **C**$_2$).

^{19}F NMR: ($CDCl_3$ 376 MHz) δ ppm = -104.2.

2-Acetoxyacetyl chloride



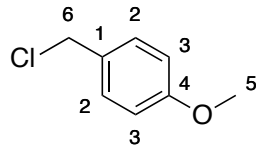
2.85

Chemical Formula: $C_4H_6ClO_3$

Molecular Weight: 136.53

2-Acetoxyacetyl chloride (**2.85**) was prepared by general method G: from 2-Acetoxyacetic acid (1.42 g, 12.0 mmol), 2-Acetoxyacetyl chloride was produced as a yellow oil that was used without further purification. No data recorded.

1-(Chloromethyl)-4-methoxybenzene



4.08

Chemical Formula: C_8H_9ClO

Molecular Weight: 156.61

1-(Chloromethyl)-4-methoxybenzene (**4.08**) was prepared general method F: from (4-Methoxyphenyl)methanol (26.0 g, 18.8 mmol) 1-(Chloromethyl)-4-methoxybenzene (30.12 g, 18.8 mmol, quant.) was afforded as a yellow oil. The data are consistent with reported values.[323]

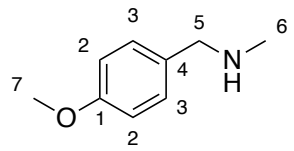
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.33 (d, *J* = 8.6 Hz, 2H, $\mathbf{H}_2$), 6.90 (d, *J* = 8.6 Hz, 2H, $\mathbf{H}_8$), 4.58 (s, 2H, $\mathbf{H}_6$), 3.82 (s, 3H, $\mathbf{H}_5$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 159.7 (C, $\mathbf{C}_4$), 130.0 (2CH, $\mathbf{C}_2$), 129.7 (C, $\mathbf{C}_1$), 114.1 (2CH, $\mathbf{C}_3$), 55.3 (CH_3, $\mathbf{C}_5$), 46.3 (CH_2, $\mathbf{C}_6$).

LRMS: (EI) m/z = 156 $[M]^{\bullet+}$

4.2.7 Amines and imines

1-(4-Methoxyphenyl)-*N*-methylmethanamine



4.09

Chemical Formula: $C_9H_{13}NO$

Molecular Weight: 151.21

1-(4-Methoxyphenyl)-*N*-methylmethanamine (**4.09**) was prepared by literature procedure for reductive amination:[324] A mixture of 4-Methoxybenzaldehyde (4.08 g, 30.0 mmol), Titanium (IV) isopropoxide (8.53 mL, 30.0 mmol), methylamine hydrochloride (4.05 g, 60.0 mmol) and triethylamine (8.36 mL, 60.0 mmol) in absolute ethanol (45 mL) was stirred at rt for 4 hrs. Sodium borohydride (1.70 g, 45.0 mmol) was then added and the resulting mixture was stirred for an additional 3 hrs at rt. The reaction was then quenched by pouring into 2M aq. ammonium

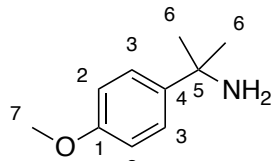
hydroxide (30 mL). The resulting inorganic precipitate was filtered and washed with EtOAc (2x10 mL). The organic layer was separated, and the remaining aqueous layer was extracted with EtOAc (2x25 mL). The combined organic phase was acidified with 2N HCl (30 mL), the aqueous phase was separated and then washed with EtOAc (2 x 20 mL). The aqueous phase was basified with 5M aq. NaOH to pH 12 and the product was extracted with EtOAc (4 x 30 mL). The combined basified organic phases were dried (Na_2SO_4), and solvents were removed under reduced pressure to afford 1-(4-Methoxyphenyl)-*N*-methylmethanamine (3.91 g, 25.8 mmol, 86%) as a yellow oil. The data are consistent with reported values.[324]

1H NMR: (CDCl3, 400 MHz) δ ppm = 7.24 (d, *J* = 8.6 Hz, 2H, H_2), 6.87 (d, *J* = 8.6 Hz, 2H, H_3), 3.81 (s, 3H, **H**$_7$), 3.69 (s, 2H, **H**$_5$), 2.45 (s, 3H, H_6), 1.30 (br. s, 1H, N**H**).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 158.6 (C, **C**$_1$), 132.4 (C, **C**$_4$), 129.3 (2CH, **C**$_3$), 113.7 (2CH, **C**$_2$), 55.5 (C, **C**$_5$), 55.3 (CH_3, **C**$_7$) 36.0 (CH_3, **C**$_6$)

LRMS: (ESI+) m/z = 152 $[M+H]^+$

2-(4-Methoxyphenyl)propan-2-amine



4.10

Chemical Formula: $C_{10}H_{15}NO$

Molecular Weight: 165.24

2-(4-Methoxyphenyl)propan-2-amine (**4.10**) was prepared by a literature procedure for Grignard alkylation under microwave conditions:[325] A 10 mL microwave tube was charged with 4-Methoxybenzonitrile (0.13 g, 1.0 mmol) and THF (3 mL) to which was added 3 M methylmagnesium bromide in Et_2O (1 mL, 3.0 mmol). The resulting mixture was heated under microwave conditions at 100°C for 10 min after which time Titanium (IV) isopropoxide (0.29 mL, 1.0 mmol) was carefully added. After heating under microwave irradiation at 50°C for 1 h, brine (10 mL) was added. The product was extracted with CH_2Cl_2 (3x10 mL), and the combined organic phase was washed with brine (2 x 20 mL), separated, dried over Na_2SO_4 and filtered. Concentration under reduced pressure afforded a yellow oil that was treated with 2 N HCl in MeOAc (1 mL). Solids precipitated and were filtered, washing with Et_2O to give 2-(4-

Methoxyphenyl)propan-2-amine (0.160 g, 79%) as an off–white solid. Novel compound (free base known[326]).

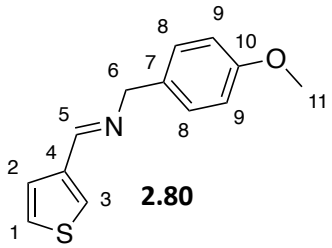
^{1}H NMR: (D_2O, 400 MHz) δ ppm = 7.48 (d, *J* = 8.6 Hz, 2H, **H**$_2$), 7.06 (d, *J* = 8.6 Hz, 2H, **H**$_3$), 3.84 (s, 3H, **H**$_7$), 1.72 (s, 6H, **H**$_6$)

^{13}C NMR: (D_2O, 101 MHz) δ ppm = 158.7 (C, **C**$_1$), 133.8 (C, **C**$_4$), 126.3 (2CH, **C**$_3$), 114.3 (2CH, **C**$_2$), 55.7 (C, **C**$_5$), 55.4 (CH_3, **C**$_7$), 26.8 ($2CH_3$, **C**$_6$)

LRMS: (ESI+) m/z = 149 $[M\text{-}NH_3]^+$

FT–IR (cm^{-1}) neat: 3657 (br., w, N-H), 2981 (s, C-H), 1382 (m, C-N).

(E)-*N*-(4-Methoxybenzyl)-1-(thiophen-3-yl)methanimine



2.80

Chemical Formula: $C_{13}H_{13}NOS$

Molecular Weight: 231.31

(E)-*N*-(4-Methoxybenzyl)-1-(thiophen-3-yl)methanimine (**2.80**) was prepared by literature imine synthesis:[327] A suspension of Thiophene-3-carbaldehyde (0.876 mL, 10.0 mmol), 4-Methoxybenzylamine (1.31 mL, 10.0 mmol) and $MgSO_4$ (5.0 g) in dry CH_2Cl_2 (20 mL) was stirred at rt for 16 hours, filtered and solvents removed under reduced pressure to afford (E)-*N*-(4-Methoxybenzyl)-1-(thiophen-3-yl)methanimine (2.33 g, 10.0 mmol, quantitative) as a brown oil that solidified on standing, and was used without further purification. The data are consistent with (incomplete) reported values.[327]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 8.38 (s, 1H, **H**$_5$) 7.63 (dd, *J* = 2.9, 1.1 Hz, 1H, **H**$_1$), 7.57 (dd, *J* = 5.0, 1.1 Hz, 1H, **H**$_3$), 7.32 (dd, *J* =5.0, 2.9 Hz, 1H, **H**$_2$), 7.25 (d, *J* = 8.7 Hz, 2H, **H**$_8$), 6.89 (d, *J* = 8.7 Hz, 2H, **H**$_9$), 4.73 (s, 2H, **H**$_6$), 3.81 (s, 3H, **H**$_{11}$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 158.7 (CH, **C**$_{10}$) 155.9 (C, **C**$_5$), 140.5 (C, **C**$_7$), 131.3 (2CH, **C**$_4$), 129.2 (CH, **C**$_8$) 128.5 (C, **C**$_1$), 126.3 (CH, **C**$_2$), 125.9 (CH, **C**$_3$), 113.9 (2CH, **C**$_9$), 64.4 (CH_2, **C**$_6$), 55.3 (CH_3, **C**$_{11}$).

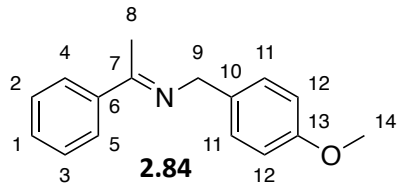
LRMS: (EI) m/z = 231 $[M]^{\cdot+}$

FT–IR (cm^{-1}) neat: 3050 (m, N=CH), 2862 (w, C-H), 1636 (s, C=N).

HRMS: (ESI+) for $C_{13}H_{13}NOSH^+$ requires 232.0791 found 232.0791 Da.

MP: 55.0 – 56.0 °C (lit not reported)

(E)-*N*-(4-Methoxybenzyl)-1-phenylethan-1-imine



2.84

Chemical Formula: $C_{16}H_{17}NO$

Molecular Weight: 239.32

(E)-*N*-(4-Methoxybenzyl)-1-phenylethan-1-imine (**2.84**) was prepared by literature procedure for imine condensation:[328] $Ti(O^iPr)_4$ (5.92 mL, 20.0 mmol) was added dropwise to a solution of 4-Methoxybenzylamine (2.74 g, 20.0 mmol) and Acetophenone (2.40 g, 20.0 mmol) in dry CH_2Cl_2 (30 mL) at rt. The yellow solution was stirred at rt for 16 hours and then the reaction was quenched with 15% aq. KOH solution (15 mL). A white suspension formed, which was stirred for 5 minutes and then filtered through Na_2SO_4, washing with CH_2Cl_2 (2 x mL). Solvents were removed under reduced pressure to give a brown slurry that was recrystallised in Et_2O to afford (E)-*N*-(4-Methoxybenzyl)-1-phenylethan-1-imine (3.76 g, 16.2 mmol, 81 %) as a brown solid. The data are consistent with reported values.[329, 330]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.88 (dd, *J* = 6.5, 3.1 Hz, 2H, **H**$_{4\text{-}5}$), 7.38-7.42 (m, 3H, **H**$_{1\text{-}3)}$, 7.36 (d, *J* = 8.7 Hz, 2H, **H**$_{11}$), 6.92 (d, *J* = 8.7 Hz, 2H, **H**$_{12}$), 4.70 (s, 2H, **H**$_9$), 3.82 (s, 3H, **H**$_{14}$) 2.35 (s, 3H, **H**$_8$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 165.6 (C, **C_7**), 158.3 (C, **C_{13}**), 141.1 (C, **C_6**), 132.7 (C, **C_{10}**), 129.5 (CH, **C_1**) 128.7 (2CH, **C_{11}**), 128.1 (2CH, **$C_{4\text{-}5}$**), 128.7 (2CH, **$C_{2\text{-}3}$**), 113.8 (2CH, **C_{12}**), 55.2 (CH_3, **C_{14}**), 55.1 (CH_2. **C_9**), 15.7 (CH_3, **C_8**).

LRMS: (EI) m/z = 239 $[M]^{\cdot+}$

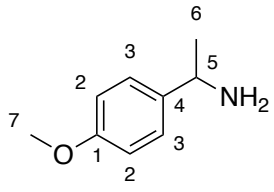
FT–IR (cm^{-1}) neat: 2999 (s, C-H), 1684 (m, C=N).

MP: 48.0 – 50.0 °C (lit not reported)

4.2.7.1 General method H: reductive amination

Preparation of amines was carried out using a procedure for reductive amination:[331] A slurry of the corresponding aldehyde or ketone (10.0 mmol), titanium(IV) isopropoxide (5.92 mL, 20.0 mmol), in the corresponding amine (50.0 mmol) and MeOH (20 mL) was stirred at rt for 16 h. Sodium borohydride (15.0 mmol) was then added and the resulting mixture was stirred at rt for an additional 3 h. The reaction was quenched by pouring into 2M aq. ammonium hydroxide (30 mL). the resulting inorganic precipitate was filtered and washed with EtOAc (2x10 mL). The organic layer was separated, and the remaining aqueous layer was extracted with EtOAc (2x25 mL). The combined organic phase was acidified with 2N HCl (30 mL), the aqueous phase was separated and then washed with EtOAc (2 x 20 mL). The aqueous phase was basified with 5M aq. NaOH to pH 12 and the product was extracted with EtOAc (4 x 30 mL). The combined basified organic phases were dried (Na_2SO_4), and solvents were removed under reduced pressure to afford the pure compound.

1-(4-Methoxyphenyl)ethan-1-amine



4.11

Chemical Formula: $C_9H_{13}NO$

Molecular Weight: 151.21

Preparation of 1-(4-Methoxyphenyl)ethan-1-amine (**4.11**) was carried out using general method H: from 4-Methoxyacetophenone (1.50 g, 10.0 mmol) and ammonia (7N in MeOH, 7.14

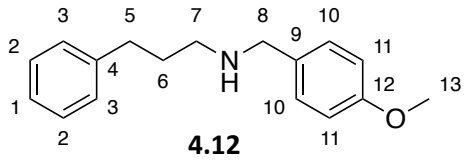
mL), 1-(4-Methoxyphenyl)ethan-1-amine (1.30 g, 8.6 mmol, 86%) was afforded as a yellow oil. The data are consistent with reported values.[332, 333]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.28 (d, *J* = 8.7 Hz, 2H, **H**$_2$), 6.87 (d, *J* = 8.7 Hz, 2H, **H**$_3$), 4.10 (q, *J* = 6.6 Hz, 1H, **H**$_5$) 3.81 (s, 3H, **H**$_7$), 1.95 (s, 2H, N**H**$_2$), 1.39 (d, *J* = 6.6 Hz, 3H, **H**$_6$)

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 158.5 (C, **C**$_1$), 139.5 (C, **C**$_4$), 126.8 (2CH, **C**$_3$), 113.8 (2CH, **C**$_2$), 55.3 (C, **C**$_7$), 50.7 (CH_3, **C**$_5$) 25.5 (CH_3, **C**$_6$)

LRMS: (ESI+) m/z = 152 $[M+H]^+$

***N*-(4-Methoxybenzyl)-3-phenylpropan-1-amine**



4.12

Chemical Formula: $C_{17}H_{21}NO$

Molecular Weight: 255.36

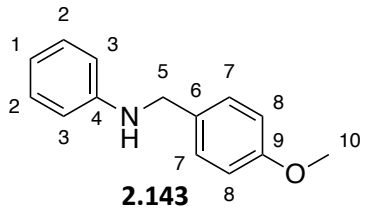
N-(4-Methoxybenzyl)-3-phenylpropan-1-amine (**4.12**) was prepared by general method H: from 3-Phenylpropanal (2.01 g, 15.0 mmol) and 4-Methoxybenzylamine (2.35 mL, 18.0 mmol) in MeOH, *N*-(4-Methoxybenzyl)-3-phenylpropan-1-amine was afforded as a brown oil. The data are consistent with reported values.[326]

^{1}H NMR: (d_4-MeOH, 400 MHz) δ ppm = 7.26-7.12 (m, 7H, **H**$_{1\text{-}3,\ 10}$), 6.87 (d, *J* = 8.7 Hz, 2H, **H**$_{11}$), 3.77 (s, 3H, **H**$_{13}$), 3.66 (s, 2H, **H**$_8$), 2.64-2.57 (m, 4H, **H**$_{5\&7}$), 1.83 (quin, *J* = 7.6 Hz, 2H, **H**$_6$).

^{13}C NMR: (d_4-MeOH, 101 MHz) δ ppm = 160.6 (C, **C**$_{12}$), 143.3 (C, **C**$_4$), 132.5 (C, **C**$_9$), 131.0 (CH, **C**$_1$) 129.5 (2CH, **C**$_{10}$), 127.0 (4CH, **C**$_{2\text{-}3}$), 115.0 (2CH, **C**$_{11}$), 55.8 (CH_3, **C**$_{13}$), 53.8 (CH_2. **C**$_8$), 49.4 (CH_2. **C**$_7$), 34.7 (CH_2. **C**$_5$), 32.1 (CH_2, **C**$_6$).

LRMS: (ESI+) m/z = 256 $[M+H]^+$

***N*-(4-Methoxybenzyl)aniline**



2.143

Chemical Formula: $C_{14}H_{15}NO$

Molecular Weight: 213.28

N-(4-Methoxybenzyl)aniline (**2.143**) was prepared by general method H: from 3-Phenylpropanal (2.01 g, 15.0 mmol) and 4-Methoxybenzylamine (2.35 mL, 18.0 mmol) in MeOH, *N*-(4-Methoxybenzyl)-3-phenylpropan-1-amine was afforded as a yellow solid. The data are consistent with reported values.[334]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.31 (d, *J* = 8.5 Hz, 2H, **H**$_7$), 7.20 (dd, *J* = 8.5, 7.3 Hz, 2H, **H**$_2$), 6.90 (d, *J* = 8.5 Hz, 2H, **H**$_8$), 6.73 (tt, *J* = 7.3, 1.0 Hz, 1H, **H**$_1$), 6.66 (dd, *J* = 8.5, 1.0 Hz, 2H, **H**$_3$), 4.27 (s, 2H, **H**$_5$), 3.95 (br. s, 1H, N**H**), 3.82 (s, 3H, **H**$_{10}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 158.9 (C, **C**$_9$), 148.2 (C, **C**$_4$), 131.4 (C, **C**$_6$), 129.2 (CH, **C**$_7$) 128.8 (2CH, **C**$_2$), 117.5 (CH, **C**$_1$), 114.0 (2CH, **C**$_8$), 112.8 (2CH, **C**$_3$), 55.3 (CH_3, **C**$_{10}$), 47.8 (CH_2. **C**$_5$).

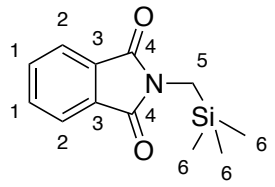
LRMS: (ESI+) m/z = 214 $[M+H]^+$

FT–IR (cm^{-1}) neat: 3416 (br., m, N-H), 2932 (w, C-H), 1602 (s, N-H (bend)).

MP: 61.0 – 62.0 °C (lit:[334] 61 – 62 °C)

4.2.8 TMS-CH_2 substrates and compounds

2-((Trimethylsilyl)methyl)isoindoline-1,3-dione



2.146

Chemical Formula: $C_{12}H_{15}NO_2Si$

Molecular Weight: 233.34

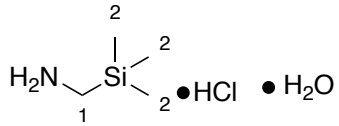
2-((Trimethylsilyl)methyl)isoindoline-1,3-dione (**2.146**) was prepared by literature Gabriel synthesis:[78] To a suspension of K_2CO_3 (3.455 g, 25.0 mmol) in DMF (30 mL) was added Phthalimide (7.356 g, 50.0 mmol) and (Chloromethyl)trimethylsilane (6.977 mL, 50.0 mmol) Gas scrubbers were fitted (5% NaOH aq. quench) and the yellow mixture was heated to 110 °C and stirred for 20 hours. The reaction was allowed to cool to RT and quenched by addition of water (30 mL) and the product was extracted with CH_2Cl_2 (50 mL). The organic phase was separated, and the aqueous phase was washed with more CH_2Cl_2 (3 x 30 mL). The combined organic phase was treated with 1N HCl aq. (50 mL) and separated, followed by sat. aq. $NaHCO_3$ (50 mL) and finally brine (50 mL). The organic phase was dried ($MgSO_4$), and removal of solvents under reduced pressure (care, product volatile!) afforded 2-((Trimethylsilyl)methyl)isoindoline-1,3-dione (10.50 g, 45.0 mmol, 90%) as a pale yellow oil. The data are consistent with reported values.[234, 335]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.81 (dd, *J* = 5.4, 3.1 Hz, 2H, **H**$_2$), 7.69 (dd, *J* = 5.4, 3.1 2H, **H**$_1$), 3.20 (S, 2H, **H**$_5$), 0.12 (s, 9H, **H**$_6$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 168.5 (2C, **C**$_4$), 133.6 (2CH, **C**$_2$), 132.3 (2C, **C**$_3$), 122.9 (2CH, **C**$_1$), 29.2 (CH_2, **C**$_5$), -1.9 ($3CH_3$, **C**$_6$).

LRMS: (ESI+) m/z = 234 $[M+H]^+$

(Trimethylsilyl)methanamine hydrochloride monohydrate



2.147

Chemical Formula: $C_4H_{13}NSi$

Molecular Weight: 103.24

(Trimethylsilyl)methanamine hydrochloride monohydrate (**2.147**) was prepared by literature Gabriel deprotection:[78] Hydrazine hydrate (2.21 mL, 45.0 mmol) was added to a solution of 2-((Trimethylsilyl)methyl)isoindoline-1,3-dione (10.50 g, 45.0 mmol) in EtOH (25 mL). The solution was heated under reflux for 3 hours after which solids had precipitated. Conc. HCl (5 mL, 54.0 mmol) was added dropwise, and the mixture was stirred for 2 hours, allowing to cool to RT. The precipitate was filtered, and the solids were washed with 6N HCl aq. The residual liquid was treated with 6N HCl (10 mL), heated to reflux and stirred for 5 minutes, after which more solids precipitated. The combined solids were dried under vacuum at 80 °C for 16 hours. The filtrate solution was concentrated to dryness by azeotroping with toluene (3 x 10 mL), and the solid was triturated with Et_2O (2 x 10 mL). Solids were combined to give (Trimethylsilyl)methanamine hydrochloride (5.209 g, 37.0 mmol, 83%) as a fluffy yellow solid (hydrated species). Novel compound.

^{1}H NMR: (d_4-MeOH, 400 MHz) δ ppm* = 2.65 (s, 1H, N**H**) 2.31 (br. s, 2H, $\mathbf{H}_1$), 0.14 (s, 9H, $\mathbf{H}_2$).

^{13}C NMR: (d_4-MeOH, 101 MHz) δ ppm* = 29.7 (CH_2, $\mathbf{C}_1$), 2.7 ($3CH_3$, $\mathbf{C}_2$),

LRMS: (ESI+) m/z = 104 $[M+H]^+$

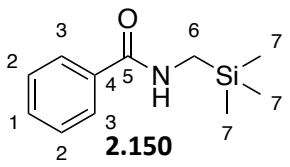
FT–IR (cm^{-1}) neat: 2951 (br., m, N-H), 1245 (s, C-Si).

HRMS: (ESI+) for $C_4H_{13}NSiH^+$ requires 104.0890 found 104.0893 Da.

MP: 204.2 – 205.3 °C

***Compound exists as hydrated species

***N*-((Trimethylsilyl)methyl)benzamide**



2.150

Chemical Formula: $C_{11}H_{17}NOSi$

Molecular Weight: 207.35

N-((Trimethylsilyl)methyl)benzamide (**2.150**) was prepared using general method B (toluene/water co-solvent, 80 °C): from (Trimethylsilyl)methanamine hydrochloride monohydrate (0.838 g, 6.0 mmol), *N*-((Trimethylsilyl)methyl)benzamide (0.995 g, 4.8 mmol, 80%) was yielded as a white solid. The data are consistent with reported values.[275]

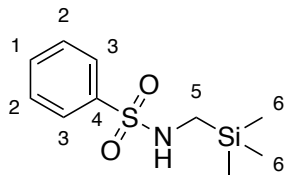
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm 7.75 – 7.73 (m, 2H, $\mathbf{H}_3$), 7.51 – 7.38 (m, 3H, $\mathbf{H}_{1\text{-}2}$), 5.97 (br. s, 1H, N**H**), 2.97 (d, *J* = 5.8 Hz, 2H, $\mathbf{H}_6$), 0.14 (s, 9H, $\mathbf{H_7}$)

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 167.8 (C, $\mathbf{C}_5$), 135.2 (C, $\mathbf{C}_4$), 131.1 (CH, $\mathbf{C}_1$), 128.6 (2CH, $\mathbf{C}_3$), 126.7 (2CH, $\mathbf{C}_2$), 30.3 (CH_2, $\mathbf{C}_6$), -2.6 ($3CH_3$, $\mathbf{C}_7$)

LRMS: (ESI+) m/z = 208 $[M+H]^+$

MP: 112.6 – 113.4 °C

***N*-((Trimethylsilyl)methyl)benzenesulfonamide**



2.148

Chemical Formula: $C_{10}H_{17}NO_2SSi$

Molecular Weight: 243.40

N-((Trimethylsilyl)methyl)benzenesulfonamide (**2.148**) was prepared using general method B (toluene/water co-solvent, 80 °C): from (Trimethylsilyl)methanamine hydrochloride monohydrate (0.838 g, 6.0 mmol) in (toluene (20 mL), *N*-((Trimethylsilyl)methyl)benzenesulfonamide (1.090 g, 4.5 mmol, 75%) was yielded as an off–white solid. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm 7.89 – 7.87 (m, 2H, $\mathbf{H}_3$), 7.61 – 7.52 (m, 3H, $\mathbf{H}_{1\text{-}2}$), 4.34 (br. s, 1H, N**H**), 2.32 (br. s, 2H, $\mathbf{H}_5$), 0.14 (s, 9H, $\mathbf{H_6}$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 136.5 (C, $\mathbf{C}_4$), 132.6 (C, $\mathbf{C}_1$), 129.0 (2CH, $\mathbf{C}_3$), 127.4 (2CH, $\mathbf{C}_2$), 32.3 (CH_2, $\mathbf{C}_5$), -3.1 ($3CH_3$, $\mathbf{C}_6$).

LRMS: (ESI+) m/z = 244 $[M+H]^+$

FT–IR (cm^{-1}) neat: 3269 (br., m, N-H), 1314 (s, S=O).

HRMS: (ESI+) for $C_{10}H_{17}NO_2SSiH^+$ requires 244.0822 found 244.0819 Da.

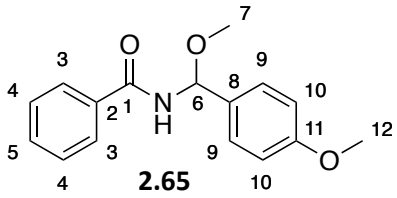
MP: 71.8 – 72.6 °C

4.2.9 Electrochemical oxidation products (general method I)

4.2.9.1 General method I: Electrochemical methoxylation procedure

PMB-protected amides and nitrogen-containing compounds were oxidised in the Ammonite 8/15 reactor, using optimised conditions developed in this work: A solution of PMB-amide (0.5 mmol) and Et_4NBF_4 (0.054 g, 0.3 mmol) in MeOH (5 mL) was passed through the Ammonite 8 flow reactor (0.25 mL min^{-1}) with constant current (95 mA, 2.4 F) applied. A steady state voltage was reached between 2.3 and 2.7 V. Effluent solution was concentrated *in vacuo* and crude product was taken into EtOAc (10 mL). Boron salts precipitated and were filtered, and the resulting solution was concentrated under reduced pressure. The crude product was purified by recrystallisation in EtOAc and hexane, or by flash chromatography using mixtures of EtOAc and petroleum ether if non-crystalline.

***N*-(Methoxy(4-methoxyphenyl)methyl)benzamide**



2.65

Chemical Formula: $C_{16}H_{17}NO_3$

Molecular Weight: 271.32

N-(Methoxy(4-methoxyphenyl)methyl)benzamide (**2.65**) was prepared using general method I: from *N*-(4-Methoxybenzyl)benzamide (**2.22**) (0.121 g, 0.5 mmol), *N*-(Methoxy(4-methoxyphenyl)methyl)benzamide (0.114 g, 0.4 mmol, 84%) was isolated as a yellow solid. The data are consistent with (incomplete) reported values.[281-283]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.81 (d, *J* = 7.6 Hz, 2H, **H**$_4$), 7.56 – 7.52 (m, 1H, **H**$_5$), 7.49 – 7.42 (m, 4H, **H**$_3$ & **H**$_9$), 6.93 (d, *J* = 8.7 Hz, 2H, **H**$_{10}$), 6.54 (br. d, *J* = 9.0 Hz, 1H, N**H**), 6.33 (d, *J* = 9.0 Hz, 1H, **H**$_6$), 3.83 (s, 3H, **H**$_7$), 3.54 (s, 3H, **H**$_{12}$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 167.2 (C, **C**$_1$), 159.8 (C, **C**$_8$), 133.8 (C, **C**$_2$), 132.0 (CH, **C**$_5$), 131.5 (C, **C**$_8$), 128.7 (2CH, **C**$_3$), 127.1 (2CH, **C**$_9$), 127.1 (2CH, **C**$_4$), 114.0 (2CH, **C**$_{10}$), 81.7 (CH, **C**$_6$), 56.2 (CH_3, **C**$_7$), 55.3 (CH_3, **C**$_{12}$).

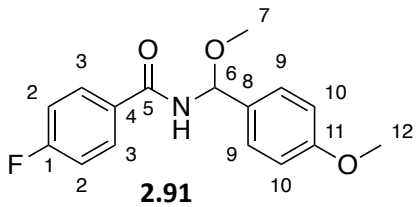
LRMS: (ESI+) m/z = 294 $[M+Na]^+$.

FT IR (cm^{-1}) neat: 3305 (br., w, N-H), 2932 (w, CH3), 1644 (s, C=O), 1247 (s, C-O).

HRMS: (ESI+) for $C_{16}H_{17}NO_3Na^+$ requires 294.1101 found 294.1095 Da.

MP: 103.0- 104.0 °C

4-Fluoro-*N*-(methoxy(4-methoxyphenyl)methyl)benzamide



2.91

Chemical Formula: $C_{16}H_{16}FNO_3$

Molecular Weight: 289.31

4-Fluoro-*N*-(methoxy(4-methoxyphenyl)methyl)benzamide (**2.91**) was prepared using general method I: from 4-Fluoro-*N*-(4-methoxybenzyl)benzamide (**2.25**) (0.259 g, 1.0 mmol), 4-Fluoro-*N*-(methoxy(4-methoxyphenyl)methyl)benzamide (0.245 g, 0.3 mmol, 85%, 92% based on recovered SM) was isolated as an off–white solid. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.83 (dd, *J* = 8.8 Hz, 5.2 Hz, 2H, **H**$_3$), 7.42 (d, *J* = 8.9 Hz, 2H, **H$_9$**) 7.13 (t, *J* = 8.8 Hz, 2H, **H$_2$**) 6.93 (d, *J* = 8.9 Hz, 2H, **H**$_{10}$), 6.49 (d, *J* = 9.0 Hz, 1H, N**H**), 6.30 (d, *J* = 9.0 Hz, 1H, **H**$_6$), 3.83 (s, 3H, **H**$_{12}$) 3.53 (s, 3H, **H**$_7$)

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 166.3 (C, **C**$_5$), 163.0 (d, $J_{C\text{-}F}$ = 320.2 Hz, C, **C**$_1$) 131.3 (C, **C**$_{11}$), 129.9 (d, $J_{C\text{-}F}$ = 4.0 Hz, C, **C**$_4$), 129.5 (d, $J_{C\text{-}F}$ = 9.8 Hz, 2CH, **C**$_3$), 127.1 (2CH, **C**$_9$), 115.8 (d, $J_{C\text{-}F}$ = 22.3 Hz, 2CH, **C**$_2$), 114.0 (2CH, **C**$_{10}$), 81.7 (CH, **C**$_6$) 56.2 (CH_3, **C**$_7$), 55.3 (CH_3, **C**$_{12}$).

^{19}F NMR: ($CDCl_3$, 376 MHz) δ ppm = -107.4.

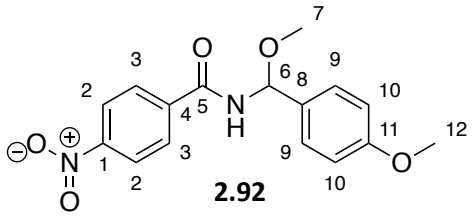
LRMS: (ESI+) m/z = 312 $[M+Na]^+$.

HRMS: (ESI+) for $C_{15}H_{16}FNO_3Na^+$ requires 312.1006 found 258.1009 Da.

FT–IR (cm^{-1}) neat: 3303 (br., m, N-H), 2957 (w, C-H), 1645 (s, C=O).

MP: 131.6 – 132.7 °C

***N*-(Methoxy(4-methoxyphenyl)methyl)-4-nitrobenzamide**



2.92

Chemical Formula: $C_{16}H_{16}N_2O_5$

Molecular Weight: 316.31

N-(Methoxy(4-methoxyphenyl)methyl)-4-nitrobenzamide (**2.92**) was prepared using general method I: from *N*-(4-Methoxybenzyl)-4-nitrobenzamide (**2.28**) (0.286 g, 1.0 mmol), *N*-(Methoxy(4-methoxyphenyl)methyl)-4-nitrobenzamide (0.221 g, 0.3 mmol, 75%, 80% based on recovered SM) was isolated as a pale pink solid. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 8.30 (dd, *J* = 8.7 Hz, 2H, $\mathbf{H}_2$), 7.97 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_3$) 7.42 (d, *J* = 8.6 Hz, 2H, $\mathbf{H}_9$) 6.93 (d, *J* = 8.9 Hz, 2H, $\mathbf{H}_{10}$), 6.62 (br. d, *J* = 8.9 Hz, 1H, N**H**), 6.29 (d, *J* = 8.9 Hz, 1H, $\mathbf{H}_6$), 3.83 (s, 3H, $\mathbf{H}_{12}$) 3.54 (s, 3H, $\mathbf{H}_7$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 165.2 (C, $\mathbf{C}_5$), 160.0 (C, $\mathbf{C}_{11}$), 149.9 (C, $\mathbf{C}_1$), 139.3 (C, $\mathbf{C}_4$), 130.8 (C, $\mathbf{C}_8$), 128.3 (2CH, $\mathbf{C}_3$), 127.1 (2CH, $\mathbf{C}_{10}$), 123.9 (2CH, $\mathbf{C}_2$), 114.2 (2CH, $\mathbf{C}_9$), 82.1 (CH, $\mathbf{C}_6$) 56.4 (CH_3, $\mathbf{C}_7$) 55.2 (CH_3, $\mathbf{C}_{12}$).

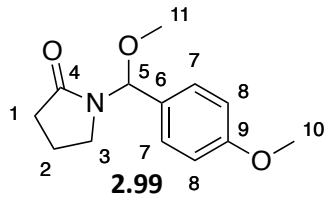
LRMS: (ESI+) m/z = 339 $[M+Na]^+$.

HRMS: (ESI+) for $C_{16}H_{16}N_2O_5Na^+$ requires 339.0951 found 339.0951 Da.

FT–IR (cm^{-1}) neat: 3309 (br., m, N-H), 2935 (w, C-H), 1670 (s, C=O).

MP: 139.9 – 141.4 °C

1-(Methoxy(4-methoxyphenyl)methyl)pyrrolidin-2-one



2.99

Chemical Formula: $C_{13}H_{17}NO_3$

Molecular Weight: 235.28

1-(Methoxy(4-methoxyphenyl)methyl)pyrrolidin-2-one (**2.99**) was prepared using general method I: from *N*-(4-Methoxybenzyl)pyrrolidinone (**2.43**) (0.103 g, 0.5 mmol,), 1-(Methoxy(4-methoxyphenyl)methyl)pyrrolidin-2-one (0.071 g, 0.3 mmol, 60%) was isolated as a yellow liquid. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.29 (d, *J* = 8.6 Hz, 2H, $\mathbf{H}_7$), 6.88 (d, *J* = 8.6 Hz, 2H, $\mathbf{H}_8$), 6.22 (s, 1H, $\mathbf{H}_5$), 3.80 (s, 3H, $\mathbf{H}_{10}$), 3.41 (s, 3H, $\mathbf{H}_{11}$), 3.24 (t, *J* = 7.1Hz, 2H, $\mathbf{H}_1$), 2.42 (t, *J* = 8.1Hz, 2H, $\mathbf{H}_3$), 1.97 (tt, *J* = 7.6Hz, 2H, $\mathbf{H}_2$).

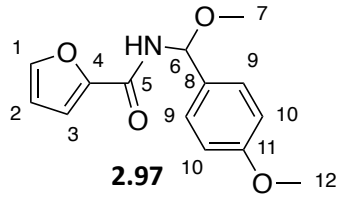
^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 174.8 (C, $\mathbf{C}_4$), 160.0 (C, $\mathbf{C}_9$), 129.4 (2CH, $\mathbf{C}_7$), 128.6 (C, $\mathbf{C}_6$), 113.9 (2CH, $\mathbf{C}_8$), 55.2 (CH_3, $\mathbf{C}_{10}$), 46.4 (CH_2, $\mathbf{C}_5$), 45.9 (CH_2, $\mathbf{C}_1$), 31.0 (CH_2, $\mathbf{C}_3$), 17.6 (CH_2, $\mathbf{C}_2$).

LRMS: (ESI+) m/z = 258 $[M+Na]^+$.

HRMS: (ESI+) for $C_{13}H_{17}NO_3Na^+$ requires 258.1101 found 258.1099 Da.

FT–IR (cm^{-1}) neat: 2936 (w, C-H), 1684 (s, C=O), 1245 (s, C-O).

***N*-(Methoxy(4-methoxyphenyl)methyl)furan-2-carboxamide**



2.97

Chemical Formula: $C_{14}H_{15}NO_4$

Molecular Weight: 261.28

N-(Methoxy(4-methoxyphenyl)methyl)furan-2-carboxamide (**2.97**) was prepared using general method I: from *N*-(4-Methoxybenzyl)furan-2-carboxamide (**2.29**) (0.231 g, 1.0 mmol), *N*-(Methoxy(4-methoxyphenyl)methyl)furan-2-carboxamide (0.237 g, 0.9 mmol, 91%) was isolated as a white solid. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.45 (dd, *J* = 1.8, 0.8 Hz, 2H, $\mathbf{H}_1$), 7.42 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_9$), 7.20 (dd, *J* = 3.5, 0.8 Hz, 1H, $\mathbf{H}_3$), 6.92 (d, *J* = 8.7 Hz, 2H, $\mathbf{H}_{10}$), 6.76 (br. d, *J* = 9.4 Hz, 1H, N**H**), 6.53 (dd, *J* = 3.5, 1.8 Hz, 1H, $\mathbf{H}_2$), 6.27 (d *J* = 9.4 Hz, 1H, $\mathbf{H}_6$), 3.82 (s, 3H, $\mathbf{H}_{12}$), 3.52 (s, 3H, $\mathbf{H}_7$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 159.8 (C, $\mathbf{C}_5$), 158.1 (C, $\mathbf{C}_{11}$), 147.3 (C, $\mathbf{C}_4$), 144.3 (CH, $\mathbf{C}_1$), 131.4 (C, $\mathbf{C}_8$), 127.1 (2CH, $\mathbf{C}_9$), 115.3 (CH, $\mathbf{C}_3$), 114.0 (2CH, $\mathbf{C}_{10}$), 112.3 (CH, $\mathbf{C}_2$), 80.9 (CH, $\mathbf{C}_6$), 56.1 (CH_3, $\mathbf{C}_7$), 55.3 (CH_3, $\mathbf{C}_{12}$).

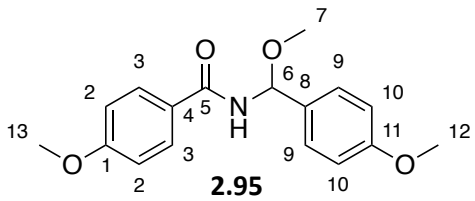
LRMS: (ESI+) m/z = 284 $[M+Na]^+$.

HRMS: (ESI+) for $C_{14}H_{15}NO_4Na^+$ requires 284.0893 found 284.0897 Da.

FT–IR (cm^{-1}) neat: 3307 (br., m, N-H), 2957 (w, C-H), 1649 (s, C=O).

MP: 92.6 – 93.7 °C

4-Methoxy-*N*-(methoxy(4-methoxyphenyl)methyl)benzamide



2.95

Chemical Formula: $C_{17}H_{19}NO_4$

Molecular Weight: 301.34

4-Methoxy-*N*-(methoxy(4-methoxyphenyl)methyl)benzamide (**2.95**) was prepared using general method I: from 4-Methoxy-*N*-(4-methoxybenzyl)benzamide (**2.27**) (0.271 g, 1.0 mmol), 4-Nethoxy-*N*-(methoxy(4-methoxyphenyl)methyl)benzamide (0.265 g, 0.9 mmol, 88%) was afforded as a white solid. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.78 (d, *J* = 8.1 Hz, 2H, **H**$_3$), 7.43 (d, *J* = 8.6 Hz, 2H, **H**$_9$) 7.95-6.91 (m, 4H, **H**$_{4,10}$), 6.45 (br. d, *J* = 9.1 Hz, 1H, N**H**), 6.32 (d, *J* = 9.1 Hz, 1H, **H**$_6$), 3.86 (s, 3H, **H**$_{13}$), 3.83 (s, 3H, **H**$_{12}$) 3.54 (s, 3H, **H**$_7$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 162.6 (C, **C**$_5$), 159.8 (C, **C**$_{1/11}$), 159.7 (C, **C**$_{1/11}$), 131.7 (C, **C**$_8$), 129.0 (2CH, **C**$_3$), 127.1 (2CH, **C**$_9$), 126.0 (C, **C**$_4$), 114.0 (2CH, **C**$_{2/10}$), 113.9 (2CH, **C**$_{2/10}$), 81.6 (CH, **C**$_6$) 56.1 (CH_3, **C**$_7$) 55.4 (CH_3, **C**$_{13}$), 55.3 (CH_3, **C**$_{12}$).

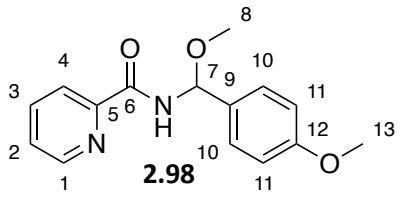
LRMS: (ESI+) m/z = 302 $[M+H]^+$.

HRMS: (ESI+) for $C_{17}H_{19}NO_4Na^+$ requires 324.1206 found 324.1209 Da.

FT–IR (cm^{-1}) neat: 3305 (br., m, N-H), 2839 (w, C-H), 1637 (s, C=O).

MP: 138.5 – 140.0 °C

***N*-(Methoxy(4-methoxyphenyl)methyl)picolinamide**



2.98

Chemical Formula: $C_{15}H_{16}N_2O_3$

Molecular Weight: 272.30

N-(Methoxy(4-methoxyphenyl)methyl)picolinamide (**2.98**) was prepared using general method I: from *N*-(4-Methoxybenzyl)picolinamide (**2.64**) (0.242 g, 1.0 mmol), *N*-(Methoxy(4-methoxyphenyl)methyl)picolinamide (0.196 g, 0.7 mmol, 72%) was isolated as a white solid. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 8.55 (d, *J* = 4.8 Hz, 1H, **H**$_{1,3}$), 8.51 (br. s, 1H, N**H**), 8.26 (dt, *J* = 7.8, 0.9 Hz, 1H, **H**), 7.88 (td, *J* = 7.8, 1.7 Hz, 1H, **H**$_2$),7.45 (d, *J* = 8.8 Hz, 2H, **H**$_{10}$), 6.92 (d, *J* = 8.8 Hz, 2H, **H**$_{10}$), 6.29 (d *J* = 9.8 Hz, 1H, **H**$_7$), 3.82 (s, 3H, **H**$_{13}$), 3.52 (s, 3H, **H**$_8$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 164.4 (C, **C**$_6$), 159.7 (C, **C**$_9$), 149.3 (C, **C**$_5$), 148.2 (CH, **C**$_1$) 137.4 (CH, **C**$_3$), 131.6 (C, **C**$_8$), 127.2 (2CH, **C**$_9$), 126.5 (CH, **C**$_2$), 122.6 (CH, **C**$_4$), 113.9 (2CH, **C**$_{10}$), 81.4 (CH, **C**$_6$), 55.9 (CH_3, **C**$_8$), 55.3 (CH_3, **C**$_{13}$).

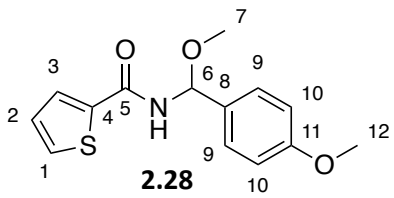
LRMS: (ESI+) m/z = 295 $[M+Na]^+$.

HRMS: (ESI+) for $C_{15}H_{16}N_2O_3Na^+$ requires 295.1053 found 295.1052 Da.

FT–IR (cm^{-1}) neat: 3375 (br., m, N-H), 2934 (w, C-H), 1682 (s, C=O).

MP: 54.5 – 59.0 °C

***N*-(Methoxy(4-methoxyphenyl)methyl)thiophene-2-carboxamide**



2.28

Chemical Formula: $C_{14}H_{15}NO_3S$

Molecular Weight: 277.34

N-(Methoxy(4-methoxyphenyl)methyl)thiophene-2-carboxamide (**2.96**) was prepared using general method I: from *N*-(4-Methoxybenzyl)picolinamide (**2.32**) (0.277 g, 1.0 mmol), *N*-(Methoxy(4-methoxyphenyl)methyl)picolinamide (0.280 g, 0.9 mmol, 91%) was isolated as a white solid. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.53-7.52 (m, 2H, **H**$_{1,3}$), 7.42 (d, *J* = 8.7 Hz, 2H, **H**$_9$), 7.09 (t, *J* = 4.4 Hz, 1H, **H**$_2$), 6.92 (d, *J* = 8.7 Hz, 2H, **H**$_{10}$), 6.42 (br. d, *J* = 9.3 Hz, 1H, N**H**), 6.28 (d *J* = 9.3 Hz, 1H, **H**$_6$), 3.82 (s, 3H, **H**$_{12}$), 3.53 (s, 3H, **H**$_7$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 161.7 (C, **C**$_5$), 159.8 (C, **C**$_{11}$), 138.3 (C, **C**$_4$), 131.3 (C, **C**$_8$), 130.8 (CH, **C**$_3$), 128.5 (CH, **C**$_1$), 127.7 (CH, **C**$_2$), 127.1 (2CH, **C**$_9$), 114.0 (2CH, **C**$_{10}$), 81.6 (CH, **C**$_6$), 56.2 (CH_3, **C**$_7$), 55.3 (CH_3, **C**$_{12}$).

LRMS: (ESI+) m/z = 300 $[M+Na]^+$.

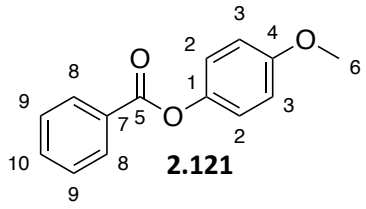
HRMS: (ESI+) for $C_{14}H_{15}NO_3SNa^+$ requires 300.0665 found 300.0662 Da.

FT–IR (cm^{-1}) neat: 3305 (br., m, N-H), 2932 (w, C-H), 1630 (s, C=O).

MP: 94.0 – 95.0 °C

4.2.10 Miscellaneous products from protected amide electrolyses

4-Methoxyphenyl benzoate



2.121

Chemical Formula: $C_{14}H_{12}O_3$

Molecular Weight: 228.25

4-Methoxyphenyl benzoate (**2.121**) was prepared using general method I: from *N*-Benzyl-*N*-(4-methoxybenzyl)benzamide (**2.45**) (0.331 g, 1.0 mmol), 1-(Methoxy(4-4-methoxyphenyl benzoate (0.138 g, 0.6 mmol, 60%) was isolated as a white solid. The data are consistent with reported values.[336]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 8.22 (dd, *J* = 8.4, 1.4 Hz, 2H, **H**$_9$), 7.67 – 7.62 (m, 1H, **H**$_{10}$), 7.54 – 7.50 (m, 2H, **H**$_8$), 7.15 (d, *J* = 9.1 Hz, 2H, **H**$_2$), 6.96 (d, *J* = 9.1 Hz, 2H, **H**$_3$), 3.84 (s, 3H, **H**$_6$).

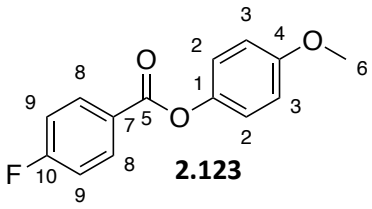
^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 166.5 (C, **C**$_5$), 157.3 (C, **C**$_4$), 144.4 (C, **C**$_1$), 133.5 (CH, **C**$_{10}$), 130.1 (2CH, **C**$_8$), 129.7 (C, **C**$_7$), 128.5 (2CH, **C**$_9$), 122.4 (2CH, **C**$_2$), 114.5 (2CH, **C**$_3$), 55.6 (CH_3, **C**$_6$)

LRMS: (ESI+) m/z = 229 $[M+H]^+$

FT–IR (cm^{-1}) neat: 2927 (w, C-H), 1724 (s, C=O), 1194 (s, C-O).

MP: 86.6 – 87.8 °C

4-Methoxyphenyl 4-fluorobenzoate



2.123

Chemical Formula: $C_{14}H_{11}FO_3$

Molecular Weight: 228.25

4-Methoxyphenyl 4-fluorobenzoate (**2.123**) was prepared using general method I: from *N*-Benzyl-4-fluoro-*N*-(4-methoxybenzyl)benzamide (**2.46**) (0.350 g, 1.0 mmol), 4-Methoxyphenyl 4-fluorobenzoate (0.228 g, 0.6 mmol, 60%) was isolated as a white solid. The data are consistent with (incomplete) reported values.[337]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 8.23 (dd, *J* = 8.7, 5.4 Hz, 2H, $\mathbf{H}_8$), 7.19 (t, *J* = 8.7 Hz, 2H, $\mathbf{H}_9$), 7.13 (d, *J* = 9.1 Hz, 2H, $\mathbf{H}_2$), 6.95 (d, *J* = 9.1 Hz, 2H, $\mathbf{H}_3$), 3.84 (s, 3H, $\mathbf{H}_6$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 166.1 (d, *J* = 256.5 Hz, C, $\mathbf{C}_{10}$), 164.6 (C, $\mathbf{C_5}$) 157.4 (C, $\mathbf{C}_4$), 144.3 (C, $\mathbf{C}_1$), 132.8 (d, *J* = 9.1 Hz, 2CH, $\mathbf{C}_8$), 125.9 (d, *J* = 4.0 Hz, C, $\mathbf{C}_7$), 122.4 (2CH, $\mathbf{C}_2$), 115.8 (d, *J* = 22.1 Hz, 2CH, $\mathbf{C}_9$), 114.5 (2CH, $\mathbf{C}_3$), 55.6 (CH_3, $\mathbf{C}_6$).

^{19}F NMR: ($CDCl_3$, 376 MHz) δ ppm = -104.7.

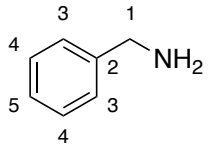
LRMS: (ESI+) m/z = 247 $[M+H]^+$

HMRS: (ESI+) for $C_{14}H_{11}FO_3Na^+$ requires 269.0584 found 269.0582 Da.

FT–IR (cm^{-1}) neat: 2927 (w, C-H), 1735 (s, C=O), 1193 (s, C-O).

MP: 87.7 – 88.8 °C

Benzylamine



2.122

Chemical Formula: C_7H_9N

Molecular Weight: 107.16

Benzylamine (**2.122**) was isolated as a cleavage product when *N*-Benzyl-*N*-(4-methoxybenzyl)benzamide (**2.45**) was subjected to general method I: From *N*-Benzyl-*N*-(4-methoxybenzyl)benzamide (0.331 g, 1.0 mmol), benzylamine (0.138 g, 0.6 mmol, 60%) was isolated as a yellow oil following acid workup and extraction from the basified aqueous phase. The data are consistent with reported values.[338, 339]

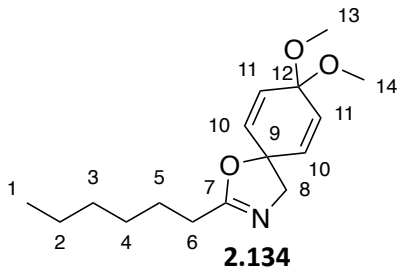
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.32 – 7.19 (m, 5H, **H**$_{2\text{-}5}$), 1,45 (s, 2H, N**H$_2$**).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 143.1 (C, **C**$_2$), 128.2 (C, **C**$_4$), 126.8 (C, **C**$_3$), 126.5 (CH, **C**$_5$), 46.2 (CH_2, **C**$_1$)

LRMS: (ESI+) m/z = 108 $[M+H]^+$

LRMS: (EI) m/z = 107

2-Hexyl-8,8-dimethoxy-1-oxa-3-azaspiro[4.5]deca-2,6,9-triene



2.134

Chemical Formula: $C_{16}H_{25}NO_3$

Molecular Weight: 279.38

2-Hexyl-8,8-dimethoxy-1-oxa-3-azaspiro[4.5]deca-2,6,9-triene (**2.134**) was prepared by general method I: from *N*-(4-Methoxybenzyl)heptanamide (**2.26**) (0.249 g, 1.0 mmol) in MeCN (5 mL) and MeOH (5 mL), 2-Hexyl-8,8-dimethoxy-1-oxa-3-azaspiro[4.5]deca-2,6,9-triene (0.081 g, 0.3

mmol, 29%) was isolated as a yellow oil, after purification by flash chromatography (Al_2O_3 stationary phase, eluent 10 to 80% EtOAc in petroleum ether). Novel compound.

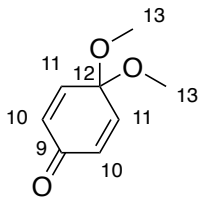
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 6.08 (d, *J* = 10.3 Hz, 2H, **H**$_{11}$), 5.96 (d, *J* = 10.3 Hz, 2H, **H**$_{10}$), 3.71 (s, 2H, H_8) 3.28 (s, 3H, **H**$_{13/14}$), 3.25 (s, 3H, **H**$_{13/14}$) 2.27 (t, *J* = 7.6 Hz, 2H, **H$_6$**), 1.63 (quin, *J* = 7.6 Hz, 2H, **H$_5$**), 1.36 – 1.24 (m, 6H, **H**$_{2\text{-}4}$), 0.87 (t, *J* = 7.0 Hz, 3H, **H$_1$**).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 167.6 (C, **C**$_7$) 132.8 (2CH, **C**$_{11}$) 127.5 (2CH, **C**$_{10}$), 93.0 (C, **C**$_{12}$), 78.4 (C, **C**$_9$), 64.9 (C, **C**$_8$), 50.1 (CH_3, **C**$_{13/14}$), 49.6 (CH_3, **C**$_{13/14}$), 31.3 (CH_2, **C**$_6$), 28.8 (CH_2, **C**$_{2/3/4/5}$), 28.1 (CH_2, **C**$_{2/3/4/5}$), 25.8 (CH_2, **C**$_{2/3/4/5}$), 22.4 (CH_2, **C**$_{2/3/4/5}$), 14.0 (CH_3, **C**$_1$)

FT–IR (cm^{-1}) neat: 2931 (m, C-H), 1669 (s, C=N), 1460 (w, C=C).

LRMS: (ESI+) m/z = 280 $[M+H]^+$

4,4-Dimethoxycyclohexa-2,5-dien-1-one



2.135

Chemical Formula: $C_8H_{10}O_3$

Molecular Weight: 154.17

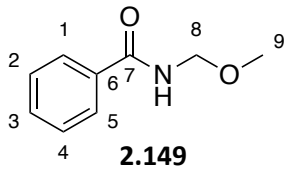
4,4-Dimethoxycyclohexa-2,5-dien-1-one (**2.135**) was formed as a minor product from the electrochemical spirocyclisation reaction of *N*-(4-Methoxybenzyl)heptanamide (**2.26**) : from *N*-(4-Methoxybenzyl)heptanamide (0.249 g, 1.0 mmol), 4,4-Dimethoxycyclohexa-2,5-dien-1-one (0.023 g, 0.2 mmol, 15%) was formed as a yellow oil. The data are consistent with reported values.[340]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 6.84 (d, *J* = 10.3 Hz, 2H, **H**$_{10}$), 6.29 (d, *J* = 10.3 Hz, 2H, **H**$_{11}$), 3.39 (s, 6H, **H**$_{13}$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 185.1 (C, **C**$_9$) 143.3 (2CH, **C**$_{11}$) 130.0 (2CH, **C**$_{10}$), 92.5 (C, **C**$_{12}$), 50.1 ($2CH_3$, **C**$_{13}$).

LRMS: (ESI+) m/z = 123 $[M\text{-}OMe]^+$

***N*-(Methoxymethyl)benzamide**



2.149

Chemical Formula: $C_9H_{11}NO_2$

Molecular Weight: 165.19

N-(Methoxymethyl)benzamide (**2.149**) was prepared by general method I: from *N*-((Trimethylsilyl)methyl)benzamide (**2.147**) (0.104 g, 0.5 mmol), *N*-(Methoxymethyl)benzamide (0.066 g, 80%) was afforded as a yellow oil that did not require further purification. The data are consistent with reported values.[341]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.67 (d, *J* = 8.0 Hz, 2H, $\mathbf{H}_{1,5}$), 7.38-7.34 (m, 1H, $\mathbf{H}_3$), 7.29-7.25 (m, 2H, $\mathbf{H}_{2,4}$), 7.09 (br. s, 1H, N**H**), 4.73 (d, *J* = 6.7 Hz, 2H, $\mathbf{H}_8$), 3.23 (s, 3H, $\mathbf{H}_9$)

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 168.1 (C, $\mathbf{C}_7$) 133.8 (C, $\mathbf{C}_6$) 131.8 (CH, $\mathbf{C}_3$), 128.5 (2CH, $\mathbf{C}_{2,4}$), 127.1 (2CH, $\mathbf{C}_{1,5}$), 71.8 (CH_2, $\mathbf{C}_8$), 56.0 (CH_3, $\mathbf{C}_9$).

LRMS: (ESI+) m/z = 188 $[M+Na]^+$

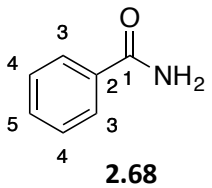
4.2.11 Two–step deprotection of PMB amides, sulfonamides and lactams

4.2.11.1 General method J: two–step PMB deprotection

PMB-protected amides and nitrogen-containing compounds were deprotected in a two–step process, starting in the Ammonite 8/15 reactor, using optimised conditions developed in this work: A solution of PMB-amide or sulfonamide (1.0 mmol) and Et_4NBF_4 (0.108 g, 0.5 mmol) in MeOH (10 mL) was prepared and passed through the Ammonite 8 flow reactor (C/PVDF anode, SS cathode, 0.25 mL min^{-1}, 95 mA (2.4 F/mol). Steady state voltage was reached at 2.7 V. Effluent solution was concentrated under reduced pressure and crude product was taken into Me-THF (10 mL). Electrolyte was recovered by filtration. The resulting solution was treated with TFA (0.015 mL, 2.0 mmol) and stirred at RT for 10 minutes. Solution was concentrated and crude treated with sat. aq. $NaHSO_3$ (7.5 mL). EtOH (2.5 mL) was added, salts precipitated and were filtered, washing filtrate with EtOH. Resulting solution was concentrated to 50% volume and EtOAc was added. Organic phase was extracted and aqueous further washed with EtOAc. Organic phases were combined, washed with sat. aq. $NaHCO_3$ (5 mL), water (5 mL), then brine (5 mL). Organic phase

was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give solid or oil. Purification by recrystallisation or flash chromatography afforded the pure product.

Benzamide



2.68

Chemical Formula: C_7H_7NO

Molecular Weight: 121.14

Benzamide (**2.68**) was prepared using general method J: from *N*-(4-Methoxybenzyl)benzamide (**2.22**) (0.242 g, 1.0 mmol) benzamide (0.080 g) was isolated by recrystallisation as a crystalline white solid. The mother liquor was purified by flash chromatography (Eluent 25% to 60% EtOAc in petroleum ether) to give benzamide (0.020 g) and *N*-(4-methoxybenzyl)benzamide (0.012 g, 0.1 mmol, 5%) as crystalline white solids. Benzamide solids were combined to give crystalline white solid (0.100 g, 0.8 mmol, 83%, 87% based on recovered SM). The data are consistent with reported values.[266, 342, 343]

The title compound was also prepared through a continuous-flow electrolysis: a solution of *N*-(4-Methoxybenzyl)benzamide (0.54 g, 2.0 mmol) and Et_4NBF_4 (0.0068 g, 0.03 mmol) in MeOH (5 mL) was passed through the Ammonite 8 flow reactor (0.33 mL min^{-1}, 530 mA). The outlet solution was mixed with 2N aq. HCl solution (5 mL) in continuous flow, connected with a T-piece. The combined solution was allowed to react in a heated coil, passed at 0.66 mL min^{-1} at 50 °C. The effluent solution was quenched by passing into a solution of sat. aq. $NaHCO_3$ (10 mL). EtOAc (10 mL) was added, and the organic phase was separated. The organic phase was washed with $NaHSO_3$ (3 x 10 mL), and brine (10 mL) and then dried ($MgSO_4$) and filtered. Removal of solvents under reduced pressure afforded a brown solid that was recrystallised in EtOAc to afford benzamide (0.20 g, 1.7 mmol, 83%) as a white solid.

The title compound was also prepared by oxidative DDQ deprotection:[344] DDQ (0.17 g, 1.5 mmol) was added in portions to a solution of *N*-(4-Methoxybenzyl)benzamide (0.270 g, 1.0 mmol) in CH_2Cl_2 (25 mL) and water (1 mL) at rt. The orange solution was stirred at rt for 16 hours and then quenched with sat. aq. $NaHCO_3$ solution (10 mL). The organic phase was separated and washed with water (10 mL) and brine (10 mL), then dried ($MgSO_4$), and filtered. Removal of

solvent under reduced pressure afforded a brown slurry. Purification by flash chromatography (50% EtOAc in petroleum ether) afforded benzamide (0.080 g, 0.7 mmol, 66%) as a white solid.

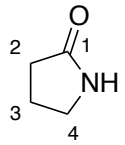
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm 7.83 (d, *J* = 8.5 Hz, 2H, **H**$_4$), 7.57 – 7.53 (m, 1H, **H**$_5$), 7.49 – 7.45 (m, 2H, **H**$_3$), 6.05 (br. s, 1H, N**H**), 5.66 (br. s, 1H, N**H**).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 167.2 (C, **C**$_1$), 134.4 (C, **C**$_2$), 131.5 (CH, **C**$_5$), 128.6 (2CH, **C**$_3$), 126.9 (2CH, **C**$_4$).

LRMS: (ESI+) m/z = 122 $[M+H]^+$

MP: 127.4 – 128.6 °C

Pyrrolidin-2-one



2.112

Chemical Formula: C_4H_7NO

Molecular Weight: 85.11

Pyrrolidin-2-one (**2.112**) was prepared using general method J: from 1-(4-Methoxybenzyl)pyrrolidin-2-one (**2.43**) (0.205 g, 1.0 mmol), following flash chromatography (eluent: 20% to 50% EtOAc in hexane) Pyrrolidin-2-one (0.050 g, 0.6 mmol, 59%) was isolated as a clear oil. Due to volatility of the product, the yield was also determined by calibrated GC (91%, 97% based on unreacted SM). The data are consistent with reported values.[345, 346]

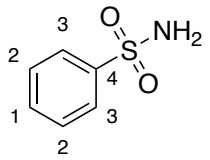
Pyrrolidin-2-one was also prepared by acid deprotection: 1-(Methoxy(4-methoxyphenyl)methyl)pyrrolidin-2-one (0.100 g, 0.4 mmol) was dissolved in Me-THF (10 mL) and TFA (0.096 g, 0.8 mmol) was added. The solution was stirred for 1 hour and then solvents were removed under reduced pressure. GC yield determined a quantitative yield of the title compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm 7.49 (br. s, 1H, N**H**), 3.25 (t, *J* = 7.2 Hz, 2H, **H**$_4$), 2.15 (t *J* = 7.2 Hz, 2H, **H**$_2$) 1.96 (quin, *J* = 7.2 Hz, 2H, **H**$_3$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 179.3 (C, **C**$_1$), 42.1 (CH_2, **C**$_4$), 29.9 (CH_2, **C**$_2$), 20.3 (CH_2, **C**$_3$).

LRMS: (EI) m/z = 85 $[M]^{\bullet+}$.

Benzenesulfonamide



2.114

Chemical Formula: $C_6H_7NO_2S$

Molecular Weight: 157.19

Benzenesulfonamide (**2.114**) was prepared using general method J: from (4-*N*-(4-methoxybenzyl)benzenesulfonamide (**2.42**) (0.139 g, 0.5 mmol), Benzenesulfonamide (0.046 g) was isolated by recrystallisation as a crystalline white solid. The mother liquor was purified by flash chromatography (Eluent 25% to 60% EtOAc in petroleum ether) to give Benzenesulfonamide (0.012 g) as a crystalline white solid. Benzenesulfonamide solids were combined to give crystalline white solid (0.058 g, 0.4 mmol, 75%,). The data are consistent with reported values.[347]

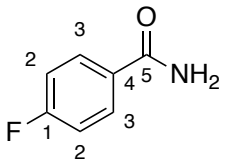
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm 7.95 (d, *J* = 7.5 Hz, 2H, $\mathbf{H}_3$), 7.63 – 7.59 (m, 1H, $\mathbf{H}_1$), 7.56 – 7.52 (m, 2H, $\mathbf{H}_2$), 4.83 (br. s, 2H, N$\mathbf{H}_2$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 141.9 (C, $\mathbf{C}_4$), 132.8 (CH, $\mathbf{C}_1$), 129.2 (2CH, $\mathbf{C}_2$), 126.4 (2CH, $\mathbf{C}_3$).

LRMS: (ESI+) m/z = 158 $[M+H]^+$

MP: 127.9 – 128.6 °C

4-Fluorobenzamide



2.28

Chemical Formula: C_7H_6FNO

Molecular Weight: 139.13

4-Fluorobenzamide (**2.103**) was prepared using general method J: from 4-Fluoro-*N*-(4-methoxybenzyl)benzamide (**2.25**) (0.260 g, 1.0 mmol), following purification by recrystallisation from EtOAc, 4-Fluorobenzamide (0.122 g, 0.9 mmol, 88%) was isolated as a crystalline white solid. The data are consistent with reported values.[348, 349]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm 7.85 (dd, *J* = 8.7, 5.2 Hz, 2H, **H**$_3$), 7.14 (t, *J* = 8.7 Hz, 2H, **H**$_2$), 5.93 (br. s, 2H, N**H$_2$**).

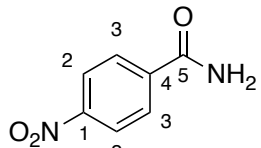
^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 168.2 (C, **C**$_5$), 165.1 (d, *J* = 253.5 Hz, C, **C**$_1$), 129.8 (d, *J* = 10.1 Hz, 2CH, **C**$_3$), 129.5 (d, *J* = 3.3 Hz, C, **C**$_4$), 115.7 (d, *J* = 22.2 Hz, 2CH, **C**$_2$).

^{19}F NMR: ($CDCl_3$, 376 MHz) δ ppm = -107.4.

LRMS: (ESI+) m/z = 140 $[M+H]^+$

MP: 153.5 – 154.5 °C

4-Nitrobenzamide



2.104

Chemical Formula: $C_7H_6N_2O_3$

Molecular Weight: 166.14

4-Nitrobenzamide (**2.104**) was prepared using general method J: from *N*-(4-Methoxybenzyl)-4-nitrobenzamide (**2.28**) (0.286 g, 1.0 mmol), following purification by recrystallisation from EtOAc, 4-Nitrobenzamide (0.125 g, 0.8 mmol, 75%) was isolated as a crystalline white solid. The data are consistent with reported values.[348, 350]

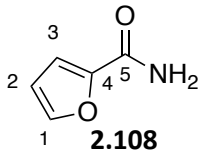
^{1}H NMR: (d4-MeOH, 400 MHz) δ ppm 8.32 (d, *J* = 9.0 Hz, 2H, **H**$_2$), 8.08 (d, *J* = 9.0 Hz, 2H, **H**$_3$).

^{13}C NMR: (d4-MeOH, 101 MHz) δ ppm = 170.3 (C, **C**$_5$), 151.4 (C, **C**$_1$), 141.1 (C, **C**$_4$), 130.1 (2CH, **C**$_3$), 124.7 (2CH, **C**$_2$).

LRMS: (ESI+) m/z = 167 $[M+H]^+$

MP: 200.0 – 201.0 °C

Furan-2-carboxamide



2.108

Chemical Formula: $C_5H_5NO_2$

Molecular Weight: 111.10

Furan-2-carboxamide (**2.108**) was prepared using general method J: from *N*-(4-Methoxybenzyl)-furan-2-carboxamide (**2.29**) (0.231 g, 1.0 mmol), following purification by recrystallisation from EtOAc, Furan-2-carboxamide (0.100 g, 0.9 mmol, 90%) was isolated as a crystalline white solid. The data are consistent with reported values.[351, 352]

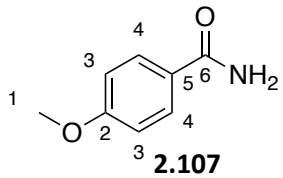
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm 7.48 (dd, *J* = 1.8, 0.8 Hz, 1H, $\mathbf{H}_1$), 7.18 (dd, *J* = 3.5, 0.8 Hz, 1H, $\mathbf{H}_3$), 6.53 (dd, *J* = 3.5, 1.8 Hz, 1H, $\mathbf{H}_2$), 6.26 (br. s, 1H, N**H**), 5.80 (br. s, 1H, N**H**).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 160.0 (C, $\mathbf{C}_5$), 147.4 (C, $\mathbf{C}_4$), 144.4 (CH, $\mathbf{C}_1$), 115.2 (CH, $\mathbf{C}_3$), 112.3 (2CH, $\mathbf{C}_2$).

LRMS: (ESI+) m/z = 112 $[M+H]^+$

MP: 138.5 – 139.5 °C

4-Methoxybenzamide



2.107

Chemical Formula: $C_8H_9NO_2$

Molecular Weight: 151.17

4-Methoxybenzamide (**2.107**) was prepared using general method J: from 4-Methoxy-*N*-(4-methoxybenzyl)benzamide (**2.27**) (0.271 g, 1.0 mmol), following purification by recrystallisation

from EtOAc, 4-Methoxybenzamide (0.130 g, 0.9 mmol, 86%) was isolated as a crystalline white solid. The data are consistent with reported values. [348, 353, 354]

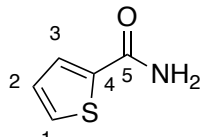
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm 7.79 (d, *J* = 8.8 Hz, 2H, **H**$_4$), 6.94 (d, *J* = 8.8 Hz, 2H, **H**$_3$), 5.89 (br. s, 2H, N**H**$_2$), 3.86 (s, 3H, **H**$_1$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 168.8 (C, **C**$_6$), 162.6 (C, **C**$_2$), 129.3 (2CH, **C**$_4$), 125.6 (C, **C**$_5$), 113.8 (2CH, **C**$_3$), 55.4 (CH_3, **C**$_1$)).

LRMS: (ESI+) m/z = 152 $[M+H]^+$

MP: 163.5 – 165.0 °C

Thiophene-2-carboxamide



2.109

Chemical Formula: C_5H_5NOS

Molecular Weight: 127.16

Thiophene-2-carboxamide (**2.109**) was prepared using general method J: from *N*-(4-Methoxybenzyl)thiophene-2-carboxamide (**2.32**) (0.247 g, 1.0 mmol), following purification by recrystallisation from EtOAc, Thiophene-2-carboxamide (0.116 g, 0.9 mmol, 91%) was isolated as a crystalline white solid. The data are consistent with reported values.[352, 355]

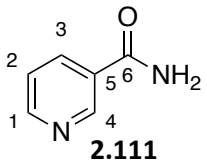
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm 7.54 (m, 2H, **H**$_{1,3}$), 7.18 (t, *J* = 3.5, 0.8 Hz, 1H, **H**$_2$), 5.79 (br. s, 2H, N**H**$_2$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 163.5 (C, **C**$_5$), 137.8 (C, **C**$_4$), 130.9 (CH, **C**$_3$), 129.3 (CH, **C**$_1$), 127.8 (2CH, **C**$_2$).

LRMS: (ESI+) m/z = 128 $[M+H]^+$

MP: 107.5 – 108.5 °C

Nicotinamide



2.111

Chemical Formula: $C_6H_6N_2O$

Molecular Weight: 122.13

Nicotinamide (**2.111**) was prepared using general method J with the exception of passing the reaction solution through the Ammonite 8 reactor twice, 95 and 50 mA current passed respectively. From *N*-(4-Methoxybenzyl)nicotinamide (**2.40**) (0.242 g, 1.0 mmol), following purification by recrystallisation from EtOAc, Nicotinamide (0.098 g, 0.8 mmol, 80%) was isolated as a crystalline white solid. The data are consistent with reported values.[356]

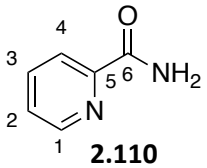
^{1}H NMR: (d6-DMSO, 400 MHz) δ ppm 9.00 (dd, *J* = 2.0, 0.8 Hz, 1H, $\mathbf{H}_4$), 8.52 (dd, *J* = 4.8, 2.0 Hz, 1H, $\mathbf{H}_1$), 8.15 (dt, *J* = 7.8, 2.0 Hz, 1H, $\mathbf{H}_3$), 7.33 (ddd, *J* = 7.8, 4.8, 0.8 Hz, 1H, $\mathbf{H}_2$).

^{13}C NMR: (d6-DMSO, 101 MHz) δ ppm = 167.9 (C, $\mathbf{C}_6$), 150.5 (C, $\mathbf{C}_4$), 149.3 (CH, $\mathbf{C}_1$), 136.3 (CH, $\mathbf{C}_3$), 133.8 (C, $\mathbf{C}_5$), 122.7 (CH, $\mathbf{C}_2$).

LRMS: (ESI+) m/z = 123 $[M+H]^+$

MP: 129.5 – 130.0 °C

Picolinamide



2.110

Chemical Formula: $C_6H_6N_2O$

Molecular Weight: 122.13

Picolinamide (**2.110**) was prepared using general method J with the exception of passing the reaction solution through the Ammonite 8 reactor twice, 95 and 50 mA current passed

respectively. From *N*-(4-Methoxybenzyl)picolinamide (**2.64**) (0.242 g, 1.0 mmol), following purification by recrystallisation from EtOAc, Picolinamide (0.104 g, 0.9 mmol, 85%) was isolated as a crystalline white solid. The data are consistent with reported values.[352]

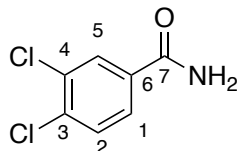
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm 8.59 (d, *J* = 4.8 Hz, 1H, **H**$_1$), 8.22 (d, *J* = 7.7 Hz, 1H, **H**$_4$), 7.89 (br. s, 1H, N**H**), 7.87 (td, *J* = 7.7, 1.3 Hz, 1H, **H**$_3$), 7.46 (ddd, *J* = 7.7, 4.8, 1.3 Hz, 1H, **H**$_2$), 5.78 (br. s, 2H, N**H**).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 166.7 (C, **C**$_6$), 149.5 (C, **C**$_5$), 148.3 (CH, **C**$_1$), 137.3 (CH, **C**$_3$), 126.5 (CH, **C**$_2$), 122.4 (CH, **C**$_4$).

LRMS: (ESI+) m/z = 123 $[M+H]^+$

MP: 107.5 – 108.5 °C

3,4-Dichlorobenzamide



2.105

Chemical Formula: $C_7H_5Cl_2NO_2$

Molecular Weight: 190.02

3,4-Dichlorobenzamide (**2.105**) was prepared using general method J with the exception of passing the reaction solution through the Ammonite 8 reactor twice, 95 and 50 mA current passed respectively. From 3,4-Dichloro-*N*-(4-methoxybenzyl)benzamide (**2.36**) (0.310 g, 1.0 mmol), following purification by recrystallisation from EtOAc, 3,4-Dichlorobenzamide (0.152 g, 0.8 mmol, 80%) was isolated as a white solid. The data are consistent with reported values.[357]

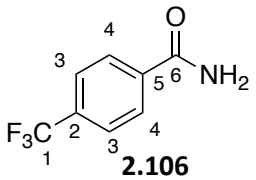
^{1}H NMR: (d4-MeOH, 400 MHz) δ ppm 8.03 (d, *J* = 2.1 Hz, 1H, **H**$_5$), 7.78 (dd, *J* = 8.3, 2.1 Hz, 1H, **H**$_1$), 7.61 (d, *J* = 8.3 Hz, 1H, **H**$_2$).

^{13}C NMR: (d4-MeOH, 101 MHz) δ ppm = 169.8 (C, **C**$_7$), 137.0 (C, **C**$_3$), 135.5 (C, **C**$_4$), 133.8 (C, **C**$_6$), 131.9 (CH, **C**$_2$), 131.0 (CH, **C**$_5$), 128.5 (CH, **C**$_1$).

LRMS: (ESI+) m/z = 191 $[M+H]^+$

MP: 139.0 – 140.5 °C

4-(Trifluoromethyl)benzamide



2.106

Chemical Formula: $C_8H_6F_3NO$

Molecular Weight: 189.14

4-(Trifluoromethyl)benzamide (**2.106**) was prepared using general method J: from *N*-(4-Methoxybenzyl)-4-(trifluoromethyl)benzamide (**2.35**) (0.309 g, 1.0 mmol), following purification by recrystallisation from EtOAc, 4-(Trifluoromethyl)benzamide (0.172 g, 0.9 mmol, 91%) was isolated as a crystalline white solid. The data are consistent with reported values.[358]

^{1}H NMR: (d4-MeOH, 400 MHz) δ ppm 8.05 (d, *J* = 8.2 Hz, 2H, $\mathbf{H}_4$), 7.77 (d, *J* = 8.2 Hz, 2H, $\mathbf{H}_3$).

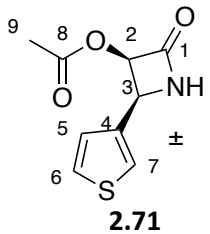
^{13}C NMR: (d4-MeOH, 101 MHz) δ ppm = 169.4 (C, $\mathbf{C}_6$), 137.4 (C, $\mathbf{C}_5$), 132.9 (q, *J* = 24.3 Hz, C, $\mathbf{C}_2$) 128.0 (2CH, $\mathbf{C}_4$), 125.1 (q, *J* = 3.1 Hz, 2CH, $\mathbf{C}_3$), 123.0 (q, *J* = 272.7 Hz, C, $\mathbf{C}_1$).

^{19}F NMR: (d4-MeOH, 376 MHz) δ ppm = -64.6.

LRMS: (ESI+) m/z = 190 $[M+H]^+$

MP: 184.0 – 185.0 °C

2-Oxo-4-(thiophen-3-yl)azetidin-3-yl acetate



2.71

Chemical Formula: $C_9H_9NO_3S$

Molecular Weight: 211.24

2-Oxo-4-(thiophen-3-yl)azetidin-3-yl acetate (**2.71**) was prepared using general method J, but with modified conditions: from a solution of 1-(4-Methoxybenzyl)-2-oxo-4-(thiophen-3-yl)azetidin-3-yl acetate (**2.83**) (0. 331 g, 1.0 mmol), AcOH (0.057 mL, 1.0 mmol) and Et_4NBF_4 (0.054 g, 0.3 mmol) in MeCN (7.5 mL) and MeOH (2.5 mL), following purification by flash chromatography (20 to 40% EtOAc in hexane), 2-Oxo-4-(thiophen-3-yl)azetidin-3-yl acetate (0.169 g, 0.8 mmol, 80%) was isolated as a yellow oil. The data are consistent with (incomplete) reported values.[221, 359]

The title compound was also prepared by literature procedure for CAN oxidation:[103] A solution of CAN (1.10 g, 2.0 mmol) in water (0.55 mL) was added dropwise over 20 minutes to a solution of 1-(4-Methoxybenzyl)-2-oxo-4-(thiophen-3-yl)azetidin-3-yl acetate (0. 331 g, 1.0 mmol) in MeCN (8.2 mL) at -15 °C. The solution was allowed to warm to rt and stirred for 60 minutes. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL). A precipitate formed and was filtered, washing with EtOAc (10 mL). The filtrate was washed with $NaHCO_3$ (2 x 10 mL) and then dried ($MgSO_4$) and filtered. Removal of solvents under reduced pressure afforded a yellow solid. Purification by flash chromatography (0.5% MeOH in CH_2Cl_2) afforded 2-Oxo-4-(thiophen-3-yl)azetidin-3-yl acetate (0.084 g, 0.4 mmol, 40%) as a white solid (previously characterised, data matches). The data are consistent with reported values.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.34 (dd, *J* = 5.0, 3.0 Hz, 1H, **H**$_6$), 7.28 – 7.26 (m, 1H, **H**$_7$), 7.04 (dd, *J* = 5.0, 1.2 Hz, 1H, **H**$_5$), 6.41 (br. s, 1H, N**H**), 5.84 (dd, *J* = 4.5, 2.6 Hz, 1H, **H**$_3$), 5.13 (d, *J* = 4.5 Hz, 1H, **H**$_2$), 1.80 (s, 3H, **H**$_9$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 169.3 (C, **C**$_8$), 165.3 (C, **C**$_1$), 136.3 (C, **C**$_4$), 126.7 (CH, **C**$_5$), 126.2 (CH, **C**$_7$), 124.0 (CH, **C**$_6$), 78.2 (CH, **C**$_2$), 54.1 (CH, **C**$_3$), 19.9 (CH_3, **C**$_8$).

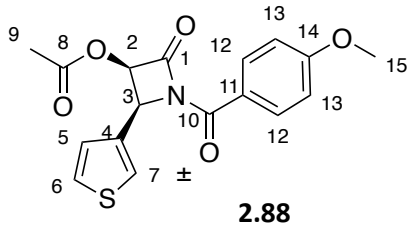
LRMS: (ESI+) m/z = 234 $[M+Na]^+$

FT–IR (cm^{-1}) neat: 3204 (br., m, N-H), 3100 (w, C-H), 1749 (s, C=O), 1720 (s, C=O).

HRMS: (ESI+) for $C_9H_9NO_3SNa^+$ requires 234.0195 found 234.0197 Da.

MP: 145.0 – 146.5 °C

1-(4-Methoxybenzoyl)-2-oxo-4-(thiophen-3-yl)azetidin-3-yl acetate



2.88

Chemical Formula: $C_{17}H_{15}NO_5S$

Molecular Weight: 345.37

1-(4-Methoxybenzoyl)-2-oxo-4-(thiophen-3-yl)azetidin-3-yl acetate (**2.88**) was prepared by literature procedure for oxidation by CAN:[103] from 1-(4-Methoxybenzyl)-2-oxo-4-(thiophen-3-yl)azetidin-3-yl acetate (**2.83**) (0. 331 g, 1.0 mmol), 1-(4-Methoxybenzoyl)-2-oxo-4-(thiophen-3-yl)azetidin-3-yl acetate (0.132 g, 0.4 mmol, 38%) was isolated as a white solid. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 8.01 (d, *J* = 9.0 Hz, 2H, **H**$_{12}$), 7.26-7.22 (m, 2H, **H**$_{6,7}$), 6.98 (dd, *J* = 5.0, 1.4 Hz, 1H, **H**$_5$), 6.91 (d, *J* = 9.0 Hz, 2H, **H**$_{13}$), 5.85 (d, *J* = 5.9 Hz, 1H, **H**$_2$), 5.63 (d, *J* = 5.9 Hz, 1H, **H**$_3$) 3.82 (s, 3H, **H**$_{15}$), 1.80 (s, 3H, **H**$_9$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 170.0 (C, **C**$_1$), 164.9 (C, **C**$_{10}$), 164.2 (C, **C**$_8$), 161.5 (C, **C**$_{14}$), 133.9 (C, **C**$_4$), 132.5 (2CH, **C**$_{12}$) 126.5 (CH, **C**$_{5/7}$), 126.2 (CH, **C**$_{5/7}$), 124.3 (CH, **C**$_7$), 123.5 (C, **C**$_{11}$), 113.7 (2CH, **C**$_{13}$), 83.5 (CH, **C**$_9$), 74.6 (CH, **C**$_2$), 55.5 (CH_3, **C**$_{15}$), 19.9 (CH_3, **C**$_9$).

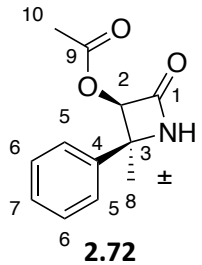
LRMS: (ESI+) m/z = 368 $[M+Na]^+$

FT–IR (cm^{-1}) neat: 2932 (w, C-H), 1800 (s, C=O), 1745 (s, C=O), 1666 (s, C=O).

MP: 120.5 – 121.5 °C

HRMS: (ESI+) for $C_{17}H_{15}NO_5SNa^+$ requires 368.0563 found 368.0566 Da.

2-Methyl-4-oxo-2-phenylazetidin-3-yl acetate



2.72

Chemical Formula: $C_{12}H_{13}NO_3$

Molecular Weight: 219.24

2-Methyl-4-oxo-2-phenylazetidin-3-yl acetate (**2.72**) was prepared using general method J, but with modified conditions: from a solution of 1-(4-Methoxybenzyl)-2-methyl-4-oxo-2-phenylazetidin-3-yl acetate (**2.86**) (0.339 g, 1.0 mmol), AcOH (0.057 mL, 1.0 mmol) and Et_4NBF_4 (0.054 g, 0.3 mmol) in MeCN (7.5 mL) and MeOH (2.5 mL), following purification by recrystallisation from EtOAc, 2-Methyl-4-oxo-2-phenylazetidin-3-yl acetate (0.153 g, 0.7 mmol, 70%) was isolated as a yellow solid. The data are consistent with (incomplete) reported values.[219]

With the same reaction solution, using a Pt anode and SS cathode and 190 mA current applied, following purification by recrystallisation from EtOAc, 2-Methyl-4-oxo-2-phenylazetidin-3-yl acetate (0.173 g, 0.8 mmol, 79%) was isolated as a yellow solid.

The process was also conducted on a large scale in the Ammonite 15 reactor: a solution of 1-(4-Methoxybenzyl)-2-methyl-4-oxo-2-phenylazetidin-3-yl acetate (13.6 g, 40.0 mmol), AcOH (2.29 mL, 40.0 mmol) and Et_4NBF_4 (1.09 g, 5.0 mmol) in MeCN (75 mL) and MeOH (25 mL) was passed through the Ammonite 15 (C/PVDF anode, SS cathode, 2.5 mL min^{-1}, 3.2 A (2.0 F mol^{-1} passed). Steady state voltage was reacted at 5.5 V. Recovery of electrolyte and workup procedure conducted as before. Purification by recrystallisation from EtOAc afforded 2-Methyl-4-oxo-2-phenylazetidin-3-yl acetate (6.31 g, 28.8 mmol, 72%) as a white solid.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.52 (br. s, 1H, N**H**), 7.31-7.24 (m, 5H, $\mathbf{H}_{5\text{-}7}$), 5.45 (d, *J* = 2.6 Hz, 1H, $\mathbf{H}_2$), 1.83 (s, 3H, $\mathbf{H}_{10}$), 1.62 (s, 3H, $\mathbf{H}_8$).

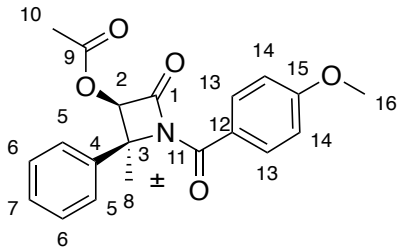
^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 169.6 (C, $\mathbf{C}_9$), 164.6 (C, $\mathbf{C}_1$), 138.6 (C, $\mathbf{C}_4$), 128.2 (2CH, $\mathbf{C}_6$) 127.9 (CH, $\mathbf{C}_7$), 126.4 (2CH, $\mathbf{C}_5$), 83.0 (CH, $\mathbf{C}_2$), 63.8 (CH_3, $\mathbf{C}_3$), 25.3 (CH_3, $\mathbf{C}_8$), 19.9 (CH_3, $\mathbf{C}_{10}$).

LRMS: (ESI+) m/z = 242 $[M+Na]^+$

FT–IR (cm^{-1}) neat: 3202 (br., w, N-H), 2932 (w, C-H), 1736 (s, C=O).

MP: 90.5 – 92.0 °C

1-(4-Methoxybenzoyl)-2-methyl-4-oxo-2-phenylazetidin-3-yl acetate



4.13

Chemical Formula: $C_{20}H_{19}NO_5$

Molecular Weight: 353.37

1-(4-Methoxybenzoyl)-2-methyl-4-oxo-2-phenylazetidin-3-yl acetate (**4.13**) was afforded as a by-product from the oxidative deprotection of 1-(4-Methoxybenzyl)-2-methyl-4-oxo-2-phenylazetidin-3-yl acetate (**2.86**) by CAN:[103] from 1-(4-Methoxybenzyl)-2-methyl-4-oxo-2-phenylazetidin-3-yl acetate (0.339 g, 1 mmol), 1-(4-Methoxybenzoyl)-2-methyl-4-oxo-2-phenylazetidin-3-yl acetate (0.159 g, 0.5 mmol, 45%) as a white solid. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 8.06 (d, *J* = 8.9 Hz, 2H, $\mathbf{H}_{13}$), 7.39-7.27 (m, 5H, $\mathbf{H}_{5\text{-}7}$), 6.99 (d, *J* = 8.9 Hz, 2H, $\mathbf{H}_{14}$), 5.56 (s, 1H, $\mathbf{H}_2$), 3.90 (s, 3H, $\mathbf{H}_1$) 2.25 (s, 3H, $\mathbf{H}_{10}$), 1.70 (s, 3H, H_8).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 170.3 (C, $\mathbf{C}_{11}$), 164.9 (C, $\mathbf{C}_9$), 164.4 (C, $\mathbf{C}_1$), 159.2 (C, $\mathbf{C}_{15}$), 134.2 (C, $\mathbf{C}_4$), 129.8 (2CH, $\mathbf{C}_{13}$) 127.0 (CH, $\mathbf{C}_7$), 126.4 (2CH, $\mathbf{C}_6$), 125.9 (2CH, $\mathbf{C}_5$), 114.3 (2CH, $\mathbf{C}_{14}$), 81.7 (CH, $\mathbf{C}_2$), 72.5 (C, $\mathbf{C}_3$), 56.5 (CH, $\mathbf{C}_{16}$), 25.4 (CH_3, $\mathbf{C}_8$), 19.8 (CH_3, $\mathbf{C}_{10}$).

LRMS: (ESI+) m/z = 376 $[M+Na]^+$

FT–IR (cm^{-1}) neat: 2937 (w, C-H), 1679 (s, C=O).

HRMS: (ESI+) for $C_{20}H_{19}NO_5Na^+$ requires 376.1155 found 376.1158 Da.

4.2.12 Compounds synthesised in the parallel–plate recycle cell

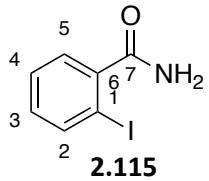
4.2.12.1 General method K: anodic deprotection of PMB protected amides (parallel–plate reactor)

PMB protected amides were deprotected in the parallel–plate, using conditions developed in this work:

Anolyte chamber: The electrolysis was carried out using a solution of PMB amide (2.5 mmol) and Et_4NBF_4 (0.272 g, 1.3 mmol) in MeOH (25 mL). The anolyte reservoir was connected to the pump for the anodic compartment, and the outlet of the reactor was inserted into the same reservoir to allow the continuous recycling of the reaction solution. On completion, sat. aq. $NaHCO_3$ (10 mL) was added, and the monophasic solution was evaporated under reduced pressure to ½ volume. The product was extracted with EtOAc (3 x 10 mL), and the combined organic phase was washed with sat. aq. $NaHSO_3$ (10 mL) to remove the PMB aldehyde co-product. The organic solution was dried ($MgSO_4$), filtered and solvent was removed under reduced pressure. Recrystallisation from EtOAc afforded the pure compound.

Catholyte chamber: The electrolysis was carried out using a solution of Et_4NBF_4 (0.272 g, 1.3 mmol) in MeOH (25 mL). The catholyte reservoir was connected to the pump for the cathodic compartment, and the outlet of the reactor was inserted into the same reservoir to allow the continuous recycling of the solution. On completion of the electrolysis, the solvent was removed under reduced pressure to recover electrolyte as an off–white solid. The recovered electrolyte is reused following recrystallisation from MeOH.

2-Iodobenzamide



2.115

Chemical Formula: C_7H_6INO

Molecular Weight: 247.04

2-Iodobenzamide (**2.115**) was prepared by anodic deprotection in the parallel plate divided cell from 2-Iodo-*N*-(4-methoxybenzyl)benzamide (**2.38**). With a flat C/PVDF anode, after 165 minutes of electrolysis (6.6 F), full conversion was observed. With an RVC anode, after 55 minutes of electrolysis (2.2 F), full conversion was observed. 2-Iodobenzamide was

isolated as a white solid (C/PVDF anode: 0.555 g, 2.3 mmol, 90%. RVC anode: 0.550 g, 2.2 mmol, 89%). The data are consistent with reported values.[360]

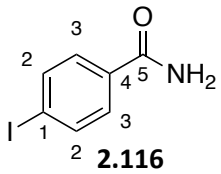
^{1}H NMR (d6-DMSO, 400 MHz) δ ppm = 7.88 (dd, *J* = 7.9, 0.8 Hz, 1H, **H**$_2$), 7.80 (br. s, 1H, N**H**), 7.49 (br. s, 1H, N**H**), 7.44-7.40 (m, 1H, H$_3$), 7.35-7.32 (m, 1H, H$_5$), 7.14 (td, *J* = 7.6, 1.8 Hz, 1H, H$_4$).

^{13}C NMR (101 MHz, d6-DMSO) δ ppm = 170.65 (C, **C**$_7$), 143.11 (C, **C**$_6$), 139.13 (CH, **C**$_2$), 130.53 (CH, **C**$_4$), 127.89 (CH, **C**$_3$), 127.74 (CH, **C**$_5$), 93.06 (C, **C**$_1$).

LCMS: (ESI+) 248 $[M+H]^+$.

MP: 186-187 °C; (lit: 183-184 °C)[360]

4-Iodobenzamide



2.116

Chemical Formula: C_7H_6INO

Molecular Weight: 247.04

4-Iodobenzamide (**2.116**) was synthesised using general method K: from 4-Iodo-*N*-(4-methoxybenzyl)benzamide (**2.39**) (0.918 g 2.5 mmol), 4-Iodobenzamide (0.531 g, 2.2 mmol, 86%) was isolated as a white solid. The data are consistent with reported values.[361]

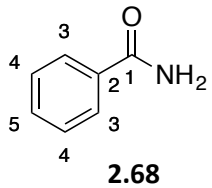
^{1}H NMR: (d_4-MeOH, 400 MHz) δ ppm = 7.84 (d, *J* = 7.6 Hz, 2H, **H**$_2$), 7.62 (d, *J* = 7.6 Hz, 2H, **H**$_3$).

^{13}C NMR: (d_4-MeOH, 101 MHz) δ ppm = 171.6 (C, **C**$_5$), 139.0 (2CH, **C**$_2$), 134.7 (C, **C**$_4$), 130.5 (2CH, **C**$_3$), 99.7 (C, **C**$_1$).

LCMS: (ESI+) m/z = 248 $[M+H]^+$.

MP: 214-216 °C; (lit: 215-217 °C)[360]

Benzamide



2.68

Chemical Formula: C_7H_7NO

Molecular Weight: 121.14

Benzamide (**2.68**) was synthesised using general method K: from *N*-(4-Methoxybenzyl)benzamide (**2.22**) (0.918 g 2.5 mmol), recrystalising from EtOAc, Benzamide (0.273 g, 2.3 mmol, 90%) was isolated as a white solid (previously characterised, data matches). The data are consistent with reported values.[360]

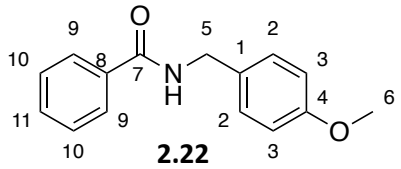
4.2.12.2 General method L: cathodic dehalogenation of aryl iodides (parallel–plate reactor)

Dehalogenated arenes were prepared by cathodic reduction in the parallel plate divided cell:

Catholyte chamber: The electrolysis was carried out using a solution of aryl halide (2.5 mmol) and Et_4NBF_4 (0.272 g, 1.3 mmol) in MeOH (25 mL). The catholyte reservoir was connected to the pump for the cathodic compartment, and the outlet of the reactor was inserted into the same reservoir to allow the continuous recycling of the reaction solution. On completion of the electrolysis, the solvent was removed under reduced pressure. The electrolyte (0.258 g, 95%) was recovered by precipitation from EtOAc (15 mL). Removal of solvent under reduced pressure afforded the pure compound.

Anolyte: The electrolysis was carried out using a solution of Et_4NBF_4 (0.272 g, 1.3 mmol) in MeOH (25 mL). The anolyte reservoir was connected to the pump for the anodic compartment, and the outlet of the reactor was inserted into the same reservoir to allow the continuous recycling of the reaction solution. On completion of the electrolysis, the solvent was removed under reduced pressure to recover electrolyte (0.270 g, 99%) as a pale yellow solid. The recovered electrolyte is reused following recrystallisation from MeOH.

***N*-(4-Methoxybenzyl)benzamide**



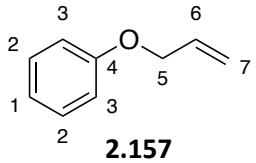
2.22

Chemical Formula: $C_{15}H_{15}NO_2$

Molecular Weight: 241.29

Cathodic chamber: *N*-(4-Methoxybenzyl)benzamide (**2.22**) was prepared by general method L from 2-Iodo-*N*-(4-methoxybenzyl)benzamide (**2.38**) (0.918 g, 2.5 mmol). After 45 min of electrolysis (320 mA, 3.6 F), full conversion was observed. *N*-(4-Methoxybenzyl)benzamide (0.597 g, 2.5 mmol, 99%) was isolated as a pale yellow solid that did not require further purification. The data are consistent with reported values.[362]

(Allyloxy)benzene



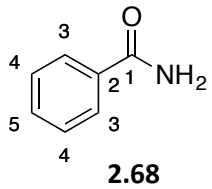
2.157

Chemical Formula: $C_9H_{10}O$

Molecular Weight: 134.18

(Allyloxy)benzene (**2.157**) was prepared by general method L from 1-(Allyloxy)-2-iodobenzene (0.650 g, 2.5 mmol), (Allyloxy)benzene (**2.156**) (0.329 g, 2.5 mmol, 98%) was afforded as a red oil that did not require further purification. The data are consistent with reported values.[363]

Benzamide



2.68

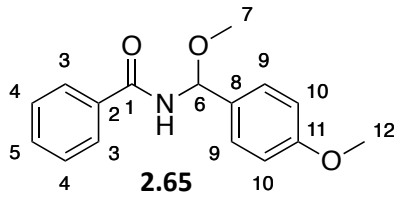
Chemical Formula: C_7H_7NO

Molecular Weight: 121.14

Benzamide (**2.68**) was prepared by general method L from 4-Iodobenzamide (**2.116**) (0.618 g, 2.5 mmol). Benzamide (0.294 g, 2.4 mmol, 97%) was afforded as a white solid (previously characterised, data matches). The data are consistent with reported values. [266, 342, 343]

4.2.12.3 Paired processes

***N*-(Methoxy(4-methoxyphenyl)methyl)benzamide**



2.65

Chemical Formula: $C_{16}H_{17}NO_3$

Molecular Weight: 271.32

N-(Methoxy(4-methoxyphenyl)methyl)benzamide (**2.65**) was prepared by paired electrolysis in the parallel plate divided cell: The electrolysis was carried out using a solution of 2-Iodo-*N*-(4-methoxybenzyl)benzamide (**2.38**) (0.918 g 2.5 mmol) and Et_4NBF_4 (0.272 g, 1.3 mmol) in MeOH (25 mL). The reactor inlet tube was inserted into the reservoir solution, and the outlet of the reactor was inserted into the same reservoir to allow the continuous recycling of the reaction solution. In order to study the formation of product with time, an aliquot (250 µL) was taken at intervals and analysed by ^{1}H NMR. Full conversion of 6 was observed after a reaction time of 100 minutes (4.0 F). On completion of the electrolysis, the solvent was removed under reduced pressure. The electrolyte (0.254 g, 93%) was recovered by precipitation from EtOAc (15 mL). Removal of solvent under reduced pressure afforded a yellow solid. Purification by flash chromatography (20% EtOAc in hexane) afforded *N*-(Methoxy(4-

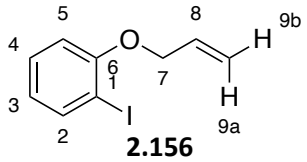
methoxyphenyl)methyl)benzamide (0.475 g, 1.8 mmol, 70%) as a white solid (previously characterised, data matches). The data are consistent with (incomplete) reported values.[281, 283]

4.3 Synthesis of compounds in Chapter 3: Cathodic cyclisation of aryl halides

4.3.1 Ethers

Alcohol alkylation was by literature procedure for Williamson ether synthesis:[242] halophenol (15.0 mmol) and K_2CO_3 (2.28 g, 16.5 mmol) were suspended in acetone (50 mL). The mixture was heated to 60 °C for 30 minutes and then allowed to cool to rt. Alkyl bromide (22.5 mmol) was added dropwise, following which the mixture was warmed to 60 °C and stirred for 16 hours. On completion of the reaction, the mixture was filtered. Removal of solvent under reduced pressure afforded the product, which was either used without further purification, or purified by silica plug or flash chromatography.

1-(Allyloxy)-2-iodobenzene



2.156

Chemical Formula: C_9H_9IO

Molecular Weight: 260.07

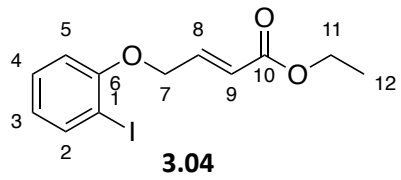
1-(Allyloxy)-2-iodobenzene (**2.156**) was prepared by Williamson ether synthesis: from 2-Iodophenol (3.30 g, 15.0 mmol) and Allyl bromide (1.95 mL, 22.5 mmol), 1-(Allyloxy)-2-iodobenzene (3.90 g, quantitative) was isolated as a pale red oil that was used without further purification. The data are consistent with reported values.[364]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.80 (dd, *J* = 7.8, 1.6 Hz, 1H, $\mathbf{H}_2$), 7.29 (ddd, *J* = 7.8, 7.3, 1.6 Hz, 1H, $\mathbf{H}_4$), 6.82 (dd, *J* = 8.3, 1.3 Hz, 1H, $\mathbf{H}_5$), 6.73 (td, *J* = 7.3, 1.3 Hz, 1H, $\mathbf{H}_3$), 6.08 (ddt, *J* = 17.2, 10.6, 4.7 Hz, 1H, $\mathbf{H}_8$), 5.54 (dq, *J* = 17.2, 1.6 Hz, 1H, $\mathbf{H}_{9b}$), 5.33 (dq, *J* = 10.6, 1.6 Hz, 1H, $\mathbf{H}_{9a}$), 4.61 (dt, *J* = 4.8, 1.6 Hz, 2H, $\mathbf{H}_7$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 157.1 (C, **C**$_6$), 139.5 (CH, **C**$_2$), 132.6 (CH, **C**$_8$), 129.3 (CH, **C**$_4$), 122.6 (CH, **C**$_3$), 117.6 (C, **C**$_9$), 112.5 (CH, **C**$_5$), 86.7 (C, **C**$_1$), 69.6 (CH_2, **C**$_7$).

LRMS: (EI) m/z = 260 $[M]^{\bullet+}$

Ethyl (*E*)-4-(2-iodophenoxy)but-2-enoate



3.04

Chemical Formula: $C_{12}H_{13}IO_3$

Molecular Weight: 332.14

Ethyl (*E*)-4-(2-iodophenoxy)but-2-enoate (**3.04**) was prepared by Williamson ether synthesis: from 2-Iodophenol (4.40 g, 20.0 mmol) and Ethyl-4-bromocrotonate (4.80 mL, 30.0 mmol), following flash chromatography (5% EtOAc/hexane), Ethyl (*E*)-4-(2-iodophenoxy)but-2-enoate (6.11 g, 92%) was isolated as a clear oil. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.80 (dd, *J* = 7.8, 1.6 Hz, 1H, **H**$_2$), 7.30 (ddd, *J* = 7.8, 7.2, 1.6 Hz, 1H, **H**$_4$), 7.08 (dt, *J* = 15.7, 3.8 Hz, 1H, **H**$_8$), 6.79 – 6.73 (m, 2H, **H**$_{3,5}$), 6.37 (dt, *J* = 15.7, 2.2 Hz, 1H, **H**$_9$), 4.75 (dd, *J* = 3.8, 2.2 Hz, 1H, **H**$_7$), 4.24 (q, *J* = 7.2 Hz, 2H, **H**$_{11}$), 1.32 (t, *J* = 7.2 Hz, 3H, **H**$_{12}$).

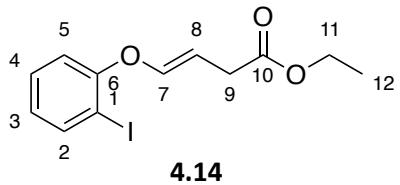
^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 166.1 (C, **C**$_{10}$), 156.5 (C, **C**$_6$), 141.4 (CH, **C**$_8$), 139.6 (CH, **C**$_2$), 129.4 (CH, **C**$_4$), 123.1 (CH, **C**$_3$), 122.4 (CH, **C**$_9$), 112.1 (CH, **C**$_5$), 86.4 (C, **C**$_1$), 67.4 (CH_2, **C**$_7$), 60.5 (CH_2, **C**$_{11}$), 14.2 (CH_3, **C**$_{12}$).

LRMS: (EI) m/z = 331 $[M]^{\bullet+}$

FT–IR (cm^{-1}) neat: 2980 (w, C-H), 1714 (s, C=O).

HRMS: (ESI+) for $C_{12}H_{13}IO_3Na^+$ requires 354.9802 found 354.9808 Da.

Ethyl (*E*)-4-(2-iodophenoxy)but-3-enoate



4.14

Chemical Formula: $C_{12}H_{13}IO_3$

Molecular Weight: 332.14

Ethyl (*E*)-4-(2-iodophenoxy)but-3-enoate (**4.14**) was formed as a by-product in the synthesis of Ethyl (*E*)-4-(2-iodophenoxy)but-2-enoate: from 2-Iodophenol (4.40 g, 20.0 mmol), Ethyl (*E*)-4-(2-iodophenoxy)but-3-enoate (0.252 g, 0.5 mmol, 5%) was afforded as a clear oil. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.80 (dd, *J* = 7.7, 1.3 Hz, 1H, **H**$_2$), 7.31 (td, *J* = 7.5, 1.6 Hz, 1H, **H**$_4$), 6.94 (dd, *J* = 8.3, 1.3 Hz, 1H, **H**), **H**$_5$), 6.82 (td, *J* = 7.7, 1.3 Hz, 1H, **H**$_3$), 6.49 (dt, *J* = 6.0, 1.3 Hz, 1H, **H**$_7$), 5.16 (q, *J* = 7.0 Hz, 1H, **H**$_9$), 4.18 (q, *J* = 7.2 Hz, 2H, **H**$_{11}$), 3.37 (dd, *J* = 7.0, 1.7 Hz, 2H, **H**$_9$), 1.28 (t, *J* = 7.2 Hz, 3H, **H**$_{12}$).

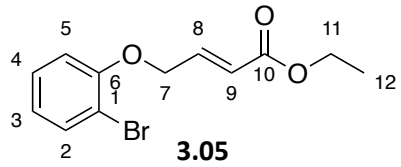
^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 171.6 C, **C**$_{10}$), 155.9 (C, **C**$_6$), 141.9 (CH, **C**$_7$), 139.6 (CH, **C**$_2$), 129.5 (CH, **C**$_4$), 124.6 (CH, **C**$_3$), 115.2 (CH, **C**$_5$), 105.3 (CH, **C**$_8$), 86.6 (C, **C**$_1$), 60.7 (CH_2, **C**$_{11}$), 30.0 (CH_2, **C**$_9$), 14.2 (CH_3, **C**$_{12}$).

LRMS: (EI) m/z = 331 $[M]^{\bullet+}$

FT–IR (cm^{-1}) neat: 2982 (w, C-H), 1715 (s, C=O).

HRMS: (ESI+) for $C_{12}H_{13}IO_3Na^+$ requires 354.9802 found 354.9809 Da.

Ethyl (*E*)-4-(2-bromophenoxy)but-2-enoate



3.05

Chemical Formula: $C_{12}H_{13}BrO_3$

Molecular Weight: 285.14

Ethyl (*E*)-4-(2-bromophenoxy)but-2-enoate (**3.05**) was prepared by Williamson ether synthesis: from 2-Bromophenol (1.74 mL, 15.0 mmol) and Ethyl-4-bromocrotonate (2.48 mL, 18.0 mmol), following flash chromatography (5% EtOAc/hexane), Ethyl (*E*)-4-(2-bromophenoxy)but-2-enoate (4.00 g, 93%) was isolated as a clear oil. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.57 (dd, *J* = 7.8, 1.6 Hz, 1H, $\mathbf{H}_2$), 7.27 (ddd, *J* = 7.8, 7.2, 1.6 Hz, 1H, $\mathbf{H}_4$), 7.10 (dt, *J* = 15.7, 3.9 Hz, 1H, $\mathbf{H}_8$), 6.90 – 6.86 (m, 2H, $\mathbf{H}_{3,5}$), 6.33 (dt, *J* = 15.7, 2.2 Hz, 1H, $\mathbf{H}_9$), 4.77 (dd, *J* = 3.9, 2.2 Hz, 1H, $\mathbf{H}_7$), 4.24 (q, *J* = 7.1 Hz, 2H, $\mathbf{H}_{11}$), 1.32 (t, *J* = 7.1 Hz, 3H, $\mathbf{H}_{12}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 166.0 (C, $\mathbf{C}_{10}$), 154.4 (C, $\mathbf{C}_6$), 141.5 (CH, $\mathbf{C}_8$), 133.5 (CH, $\mathbf{C}_2$), 128.4 (CH, $\mathbf{C}_4$), 122.5 (CH, $\mathbf{C}_3$), 122.3 (CH, $\mathbf{C}_9$), 113.3 (CH, $\mathbf{C}_5$), 112.3 (C, $\mathbf{C}_1$), 67.3 (CH_2, $\mathbf{C}_7$), 60.5 (CH_2, $\mathbf{C}_{11}$), 14.2 (CH_3, $\mathbf{C}_{12}$).

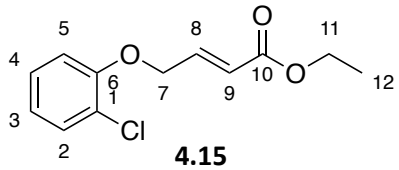
FT–IR (cm^{-1}) neat: 2981 (w, C-H), 1715 (s, C=O).

LRMS: (EI) m/z = 283 $[M]^{\bullet+}$ (^{79}Br)
(EI) m/z = 285 $[M]^{\bullet+}$ (^{81}Br)

HRMS: (ESI+) for $C_{12}H_{13}BrO_3Na^+$ requires 306.9940 found 306.9935 Da.

MP: 41.0 – 41.5 °C

Ethyl (*E*)-4-(2-chlorophenoxy)but-2-enoate



4.15

Chemical Formula: $C_{12}H_{13}ClO_3$

Molecular Weight: 240.68

Ethyl (*E*)-4-(2-chlorophenoxy)but-2-enoate (**4.15**) was prepared by Williamson ether synthesis: from 2-Chlorophenol (1.53 mL, 15.0 mmol) and Ethyl-4-bromocrotonate (2.48 mL, 18.0 mmol), following flash chromatography (5% EtOAc/hexane), Ethyl (*E*)-4-(2-bromophenoxy)but-2-enoate (3.29 g, 91%) was isolated as a clear oil. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.39 (dd, *J* = 7.8, 1.6 Hz, 1H, **H**$_2$), 7.21 (ddd, *J* = 7.8, 7.2, 1.6 Hz, 1H, **H**$_4$), 7.10 (dt, *J* = 15.7, 3.9 Hz, 1H, **H**$_8$), 6.90 – 6.86 (m, 2H, **H**$_{3,5}$), 6.29 (dt, *J* = 15.7, 2.2 Hz, 1H, **H**$_9$), 4.77 (dd, *J* = 3.9, 2.2 Hz, 1H, **H**$_7$), 4.23 (q, *J* = 7.1 Hz, 2H, **H**$_{11}$), 1.31 (t, *J* = 7.1 Hz, 3H, **H**$_{12}$).

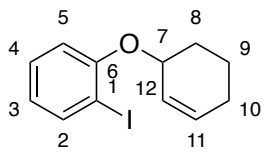
^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 166.0 (C, **C**$_{10}$), 154.5 (C, **C**$_6$), 141.6 (CH, **C**$_8$), 130.45 (CH, **C**$_2$), 127.7 (CH, **C**$_4$), 123.1 (C, **C**$_1$), 122.3 (CH, **C**$_3$), 122.0 (CH, **C**$_9$), 113.3 (CH, **C**$_5$), 67.3 (CH_2, **C**$_7$), 60.6 (CH_2, **C**$_{11}$), 14.2 (CH_3, **C**$_{12}$).

FT–IR (cm^{-1}) neat: 2981 (w, C-H), 1716 (s, C=O).

LRMS: (EI) m/z = 239 $[M]^{\bullet+}$ (^{35}Cl)

HRMS: (ESI+) for $C_{12}H_{13}ClO_3Na^+$ requires 263.0445 found 263.0447 Da.

1-(Cyclohex-2-en-1-yloxy)-2-iodobenzene



3.06

Chemical Formula: $C_{12}H_{13}IO$

Molecular Weight: 300.14

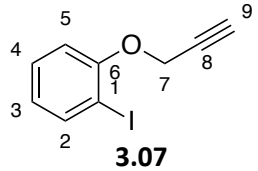
1-(Cyclohex-2-en-1-yloxy)-2-iodobenzene (**3.06**) was prepared by Williamson ether synthesis: from 2-Iodophenol (3.30 g, 15.0 mmol) and 3-Bromocyclohex-1-ene (2.30 mL, 18.0 mmol, 90%), following flash chromatography (5% EtOAc/hexane), 1-(Cyclohex-2-en-1-yloxy)-2-iodobenzene (4.19 g, 93%) was isolated as a clear oil. The data are consistent with reported values.[252, 365]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.76 (dd, *J* = 7.8, 1.6 Hz, 1H, $\mathbf{H}_2$), 7.27 (ddd, *J* = 7.8, 7.5, 1.6 Hz, 1H, $\mathbf{H}_4$), 6.86 (dd, *J* = 8.3, 1.3 Hz, 1H, $\mathbf{H}_{12}$), 6.70 (td, *J* = 7.5, 1.4 Hz, 1H, $\mathbf{H}_5$), 5.61 – 5.97 (m, 1H, $\mathbf{H}_{11}$), 5.93 – 5.87 (m, 1H, H_{12}), 4.83 – 4.76 (m, 1H, $\mathbf{H}_7$), 2.18 – 1.71 (m, 6H, $\mathbf{H}_{8\text{-}10}$)

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 157.0 (C, $\mathbf{C}_6$), 139.7 (CH, $\mathbf{C}_2$), 132.7 (CH, C_{11}), 129.3 (CH, $\mathbf{C}_4$), 125.9 (CH, $\mathbf{C}_{11}$), 122.6 (CH, $\mathbf{C}_3$), 114.6 (CH, $\mathbf{C}_{12}$), 88.7 (C, $\mathbf{C}_1$), 72.8 (CH, $\mathbf{C}_7$), 28.6 (CH_2, $\mathbf{C}_8$), 25.2 (CH_2, $\mathbf{C}_{10}$), 19.0 (CH_2, $\mathbf{C}_9$).

LRMS: (EI) m/z = 300 $[M]^{\bullet+}$

1-Iodo-2-(prop-2-yn-1-yloxy)benzene



3.07

Chemical Formula: C_9H_7IO

Molecular Weight: 258.06

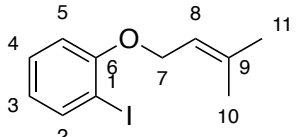
1-Iodo-2-(prop-2-yn-1-yloxy)benzene (**3.07**) was prepared by Williamson ether synthesis: from 2-Iodophenol (3.30 g, 15.0 mmol) and Propargyl bromide (2.50 mL, 22.5 mmol), following silica plug, 1-Iodo-2-(prop-2-yn-1-yloxy)benzene (3.71 g, 96%) was isolated as a pale yellow oil. The data are consistent with reported values.[242, 366]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.81 (dd, *J* = 7.8, 1.5 Hz, 1H, $\mathbf{H}_2$), 7.33 (ddd, *J* = 7.8, 7.4, 1.5 Hz, 1H, $\mathbf{H}_4$), 7.01 (dd, *J* = 8.3, 1.3 Hz, 1H, $\mathbf{H}_5$), 6.77 (td, *J* = 7.4, 1.5 Hz, 1H, $\mathbf{H}_3$), 4.77 (d, *J* = 2.5 Hz, 2H, $\mathbf{H}_7$), 2.55 (t, *J* = 2.5 Hz, 1H, $\mathbf{H}_9$)

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 156.3 (C, $\mathbf{C}_6$), 139.7 (CH, $\mathbf{C}_2$), 129.3 (CH, $\mathbf{C}_4$), 123.4 (CH, $\mathbf{C}_3$), 113.0 (CH, $\mathbf{C}_5$), 86.5 (C, $\mathbf{C}_1$), 78.0 (CH, $\mathbf{C}_8$), 76.1 (CH, $\mathbf{C}_9$), 56.9 (CH_2, $\mathbf{C}_7$).

LRMS: (EI) m/z = 258 $[M]^{\bullet+}$

1-Iodo-2-((3-methylbut-2-en-1-yl)oxy)benzene



3.08

Chemical Formula: $C_{11}H_{13}IO$

Molecular Weight: 288.13

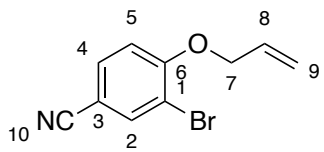
1-Iodo-2-((3-methylbut-2-en-1-yl)oxy)benzene (**3.08**) was prepared by Williamson ether synthesis: from 2-Iodophenol (3.30 g, 15.0 mmol) and 1-Bromo-3-methylbut-2-ene (3.00 mL, 22.5 mmol, 90%), following flash chromatography (5% EtOAc/hexane), 1-Iodo-2-((3-methylbut-2-en-1-yl)oxy)benzene (4.32 g, 92%) was isolated as a pale yellow oil. The data are consistent with reported values.[367]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.78 (dd, *J* = 7.8, 1.6 Hz, 1H, $\mathbf{H}_2$), 7.29 (ddd, *J* = 7.8=7, 7.3, 1.6 Hz, 1H, $\mathbf{H}_4$), 6.84 (dd, *J* = 8.3, 1.3 Hz, 1H, $\mathbf{H}_5$), 6.71 (td, *J* = 7.7, 1.3 Hz, 1H, $\mathbf{H}_3$), 5.52 (tsept, *J* = 6.5, 1.4 Hz, 1H, $\mathbf{H}_8$), 4.60 (d, *J* = 6.5 Hz, 2H, $\mathbf{H}_7$), 1.81 (d, *J* = 1.4 Hz, 3H, $\mathbf{H}_{11}$), 1.76 (s, 3H, $\mathbf{H}_{10}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 157.5 (C, $\mathbf{C}_6$), 139.5 (CH, $\mathbf{C}_2$), 137.9 (C, $\mathbf{C}_9$), 129.3 (CH, $\mathbf{C}_4$), 122.4 (CH, $\mathbf{C}_3$), 119.5 (CH, $\mathbf{C}_8$), 112.7 (CH, $\mathbf{C}_5$), 87.0 (C, $\mathbf{C}_1$), 69.3 (CH_2, $\mathbf{C}_7$), 25.8 (CH_3, $\mathbf{C}_{11}$), 18.4 (CH_3, $\mathbf{C}_{10}$).

LRMS: (EI) m/z = 288 $[M]^{\bullet+}$

4-(Allyloxy)-3-bromobenzonitrile



3.11

Chemical Formula: $C_{10}H_8BrNO$

Molecular Weight: 238.08

4-(Allyloxy)-3-bromobenzonitrile (**3.11**) was prepared by Williamson ether synthesis: from 4-Cyano-2-bromophenol (2.97 g, 15.0 mmol) and Allyl bromide (1.94 mL, 22.5 mmol), following silica plug, 4-(Allyloxy)-3-bromobenzonitrile (3.46 g, 97%) was isolated as a white solid. The data are consistent with reported values.[368]

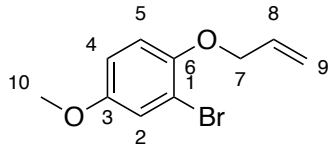
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.84 (d, *J* = 2.0 Hz, 1H, $\mathbf{H}_2$), 7.58 (dd, *J* = 8.6, 2.0 Hz, 1H, $\mathbf{H}_4$), 6.93 (d, *J* = 8.6 Hz, 1H, $\mathbf{H}_5$), 6.05 (ddt, *J* = 17.2, 10.6, 4.8 Hz, 1H, $\mathbf{H}_8$), 5.50 (dq, *J* = 17.2, 1.5 Hz, 1H, $\mathbf{H}_9$), 5.37 (dq, *J* = 10.6, 1.5 Hz, 1H, $\mathbf{H}_9$), 4.69 (dt, *J* = 4.8, 1.6 Hz, 2H, $\mathbf{H}_7$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 158.4 (C, $\mathbf{C}_6$), 136.8 (CH, $\mathbf{C}_2$), 132.9 (CH, $\mathbf{C}_8$), 131.3 (CH, $\mathbf{C}_4$), 118.6 (CH_2, $\mathbf{C}_9$), 117.7 (C, $\mathbf{C}_{10}$), 113.1 (CH, $\mathbf{C}_5$), 112.7 (C, $\mathbf{C}_1$), 105.3 (C, $\mathbf{C}_3$), 69.9 (CH_2, $\mathbf{C}_7$).

LRMS: (EI) m/z = 237 $[M]^{\bullet+}$ (^{79}Br)

MP: 51.5 – 52.5 °C (lit:[368] 51°C)

1-(Allyloxy)-2-bromo-4-methoxybenzene



3.12

Chemical Formula: $C_{10}H_{11}BrO_2$

Molecular Weight: 243.10

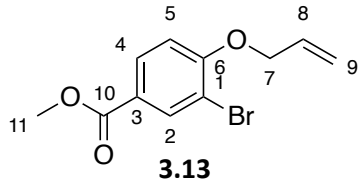
1-(Allyloxy)-2-bromo-4-methoxybenzene (**3.12**) was prepared by Williamson ether synthesis: from 4-Methoxy-2-bromophenol (3.65 g, 15.0 mmol) and Allyl bromide (1.94 mL, 22.5 mmol), 1-(Allyloxy)-2-bromo-4-methoxybenzene (3.65 g, quantitative) was isolated as an orange oil that was used without further purification. The data are consistent with reported values.[368, 369]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.13 (d, *J* = 2.9 Hz, 1H, $\mathbf{H}_2$), 6.85 (d, *J* = 9.0 Hz, 1H, $\mathbf{H}_5$), 6.79 (dd, *J* = 9.0, 2.9 Hz, 1H, $\mathbf{H}_4$), 6.05 (ddt, *J* = 17.3, 10.5, 5.1 Hz, 1H, $\mathbf{H}_8$), 5.50 (dq, *J* = 17.3, 1.6 Hz, 1H, $\mathbf{H}_9$), 5.37 (dq, *J* = 10.5, 1.6 Hz, 1H, $\mathbf{H}_9$), 4.69 (dt, *J* = 5.1, 1.6 Hz, 2H, $\mathbf{H}_7$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 154.2 (C, **C**$_3$), 149.3 (C, **C**$_6$), 133.0 (CH, **C**$_8$), 118.8 (CH_2, **C**$_2$), 117.6 (CH, **C**$_4$), 115.1 (CH, **C**$_9$), 113.6 (C, **C**$_5$), 112.9 (C, **C**$_1$), 70.7 (CH_2, **C**$_7$), 55.8 (CH, **C**$_{10}$).

LRMS: (EI) m/z = 242 $[M]^{\bullet+}$ (^{79}Br)

Methyl 4-(allyloxy)-3-bromobenzoate



3.13

Chemical Formula: $C_{11}H_{11}BrO_3$

Molecular Weight: 271.11

Methyl 4-(allyloxy)-3-bromobenzoate (**3.13**) was prepared by Williamson ether synthesis: from 2-Iodophenol (2.31 g, 10.0 mmol) and Allyl bromide (1.30 mL, 15.0 mmol), Methyl 4-(allyloxy)-3-bromobenzoate (2.71 g, quantitative) was isolated as a white solid that was used without further purification. The data are consistent with (incomplete) reported values.[370]

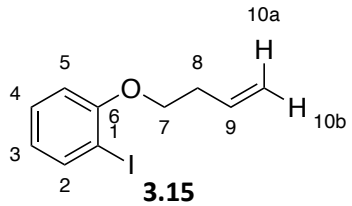
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 8.25 (d, *J* = 2.1 Hz, 1H, **H**$_2$), 7.58 (dd, *J* = 8.6, 2.1 Hz, 1H, **H**$_4$), 6.93 (d, *J* = 8.6 Hz, 1H, **H**$_5$), 6.05 (ddt, *J* = 17.2, 10.5, 5.0 Hz, 1H, **H**$_8$), 5.50 (dq, *J* = 17.2, 1.5 Hz, 1H, **H**$_9$), 5.37 (dq, *J* = 10.6, 1.5 Hz, 1H, **H**$_9$), 4.69 (dt, *J* = 5.0, 1.5 Hz, 2H, **H**$_7$), 3.90 (s, 3H, **H**$_{11}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 165.7 (C, **C**$_{10}$), 158.5 (C, **C**$_6$), 134.9 (CH, **C**$_2$), 131.8 (CH, **C**$_8$), 130.4 (CH, **C**$_4$), 123.8 (C, **C**$_3$), 118.3 (CH_2, **C**$_9$), 112.2 (CH, **C**$_5$), 111.9 (C, **C**$_1$), 69.7 (CH_2, **C**$_7$), 52.1 (CH_3, **C**$_{11}$).

LRMS: (EI) m/z = 270 $[M]^{\bullet+}$ (^{79}Br)

MP: 45 – 46 °C (Lit not reported)

1-(But-3-en-1-yloxy)-2-iodobenzene



3.15

Chemical Formula: $C_{10}H_{11}IO$

Molecular Weight: 274.10

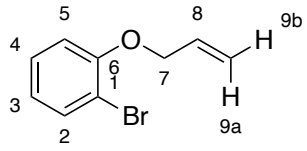
1-(But-3-en-1-yloxy)-2-iodobenzene (**3.15**) was prepared by Williamson ether synthesis: from 2-Iodophenol (2.20 g, 10.0 mmol) and 4-Bromobut-1-ene (1.522 mL, 15.0 mmol), following purification by flash chromatography (2% Et_2O/hexane), 1-(But-3-en-1-yloxy)-2-iodobenzene (2.28 g, 83%) was isolated as a clear oil. The data are consistent with reported values.[364]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.80 (dd, *J* = 7.7, 1.4 Hz, 1H, $\mathbf{H}_2$), 7.29 (ddd, *J* = 7.7, 7.3, 1.4 Hz, 1H, $\mathbf{H}_4$), 6.81 (dd, *J* = 8.2, 1.1 Hz, 1H, $\mathbf{H}_5$), 6.72 (td, *J* = 7.7, 1.1 Hz, 1H, $\mathbf{H}_3$), 5.99 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H, $\mathbf{H}_9$), 5.22 (dq, *J* = 17.1, 1.3 Hz, 1H, $\mathbf{H}_{10b}$), 5.15 (dq, *J* = 10.6, 1.3 Hz, 1H, $\mathbf{H}_{10a}$), 4.07 (t, *J* = 6.6 Hz, 2H, $\mathbf{H}_7$), 2.62 (q, *J* = 6.6 Hz, 2H, $\mathbf{H}_8$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 157.4 (C, $\mathbf{C}_6$), 139.4 (CH, $\mathbf{C}_2$), 134.3 (CH, $\mathbf{C}_9$), 129.4 (CH, $\mathbf{C}_4$), 122.5 (CH, $\mathbf{C}_3$), 117.3 (C, $\mathbf{C}_{10}$), 112.2 (CH, $\mathbf{C}_5$), 86.7 (C, $\mathbf{C}_1$), 68.6 (CH_2, $\mathbf{C}_7$), 33.6 (CH_2, $\mathbf{C}_8$).

LRMS: (EI) m/z = 274 $[M]^{\bullet+}$

1-(Allyloxy)-2-bromobenzene



3.14

Chemical Formula: $C_{10}H_{11}BrO$

Molecular Weight: 213.07

1-(Allyloxy)-2-bromobenzene (**3.14**) was prepared by Williamson ether synthesis: from 2-Bromophenol (1.73 g, 10.0 mmol) and Allyl bromide (1.30 mL, 15.0 mmol), following silica plug, 1-

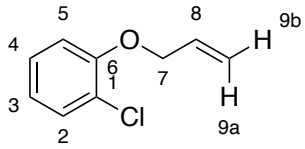
(Allyloxy)-2-bromobenzene (2.05 g, 9.6 mmol, 96%) was isolated as a clear oil. The data are consistent with reported values.[371, 372]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.52 (dd, *J* = 7.9, 1.4 Hz, 1H, **H**$_2$), 7.22 (ddd, *J* = 7.9, 7.3, 1.4 Hz, 1H, **H**$_4$), 6.91 (d, *J* = 7.9, 1.4 Hz, 1H, **H**$_5$), 6.83 (m, 1H, **H**$_3$), 6.05 (ddt, *J* = 17.2, 10.6, 5.0 Hz, 1H, **H**$_8$), 5.48 (dq, *J* = 17.2, 1.6 Hz, 1H, **H**$_{9b}$), 5.28 (dq, *J* = 10.6, 1.6 Hz, 1H, **H**$_{9a}$), 4.58 (dt, *J* = 5.0, 1.6 Hz, 2H, **H**$_7$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 155.1 (C, **C**$_6$), 133.6 (CH, **C**$_2$), 132.8 (CH, **C**$_8$), 128.5 (CH, **C**$_4$), 122.1 (CH, **C**$_3$), 117.9 (C, **C**$_9$), 113.8 (CH, **C**$_5$), 112.5 (C, **C**$_1$), 69.8 (CH_2, **C**$_7$).

LRMS: (EI) m/z = 212 $[M]^{\bullet+}$ (^{79}Br)

1-(Allyloxy)-2-chlorobenzene



3.17

Chemical Formula: $C_{10}H_{11}ClO$

Molecular Weight: 168.62

1-(Allyloxy)-2-chlorobenzene (**3.17**) was prepared by Williamson ether synthesis: from 2-Chlorophenol (1.29 g, 10.0 mmol) and Allyl bromide (1.30 mL, 15.0 mmol), following silica plug, 1-(Allyloxy)-2-chlorobenzene (1.59 g, 9.4 mmol, 94%) was isolated as a clear oil. The data are not consistent with reported values (differences noted).[373, 374]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.22 (dd, *J* = 7.8, 1.5 Hz, 1H, **H**$_2$), 7.03 (ddd, *J* = 8.1, 7.3, 1.6 Hz, 1H, **H**$_4$), 6.86 (d, *J* = 8.1, 1.5 Hz, 1H, **H**$_5$), 6.71 (m, 1H, **H**$_3$), 5.91 (ddt*, *J* = 17.2, 10.6, 5.0 Hz, 1H, **H**$_8$), 5.15 (dq**, *J* = 17.2, 1.6 Hz, 1H, **H**$_{9b}$), 5.28 (dq**, *J* = 10.6, 1.6 Hz, 1H, **H**$_{9a}$), 4.43 (dt, *J* = 5.0, 1.6 Hz, 2H, **H**$_7$).

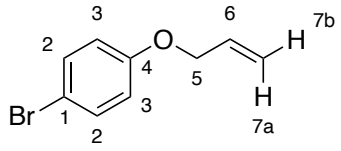
*assigned as ddd in literature[373]

** assigned as ddd in literature[374]

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 154.1 (C, **C_6**), 132.7 (CH, **C_8**), 130.3 (CH, **C_2**), 127.5 (CH, **C_4**), 122.9 (C, **C_1**), 121.4 (CH, **C_3**), 117.8 (CH, **C_9**), 113.7 (CH, **C_5**), 69.6 (CH_2, **C_7**).

LRMS: (EI) m/z = 167 $[M]^{\bullet+}$ (^{35}Cl)

1-(Allyloxy)-4-bromobenzene



4.16

Chemical Formula: C_9H_9BrO

Molecular Weight: 213.07

1-(Allyloxy)-4-bromobenzene (**4.16**) was prepared by Williamson ether synthesis: from 4-Bromophenol (1.73 g, 10.0 mmol) and Allyl bromide (1.30 mL, 15.0 mmol), following silica plug, 1-(Allyloxy)-2-chlorobenzene (3.07 g, 9.6 mmol, 96%) was isolated as a clear oil. The data are not consistent with reported values (differences noted).[374]

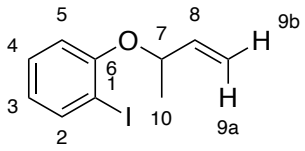
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.38* (d, *J* = 9.1 Hz, 2H, **H_2**), 6.81* (d, *J* = 7.9 Hz, 2H, **H_3**), 6.03 (ddt, *J* = 17.3, 10.5, 5.3 Hz, 1H, **H_6**), 5.42 (dq, *J* = 17.3, 1.5 Hz, 1H, **H_{7a}**), 5.28 (dq, *J* = 10.5, 1.5 Hz, 1H, **H_{7b}**), 4.52 (dt, *J* = 5.0, 1.6 Hz, 2H, **H_5**).

*Signals reported as 4H multiplet, clearly separate in NMR

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 157.7 (C, **C_4**), 132.8 (CH, **C_6**), 132.2 (2CH, **C_2**), 117.9 (CH_2, **C_7**), 116.5 (2CH, **C_3**), 113.0 (C, **C_1**), 69.0 (CH_2, **C_5**).

LRMS: (EI) m/z = 214 $[M]^{\bullet+}$ (^{81}Br)

1-(But-3-en-2-yloxy)-2-iodobenzene



4.17

Chemical Formula: $C_{10}H_{11}IO$

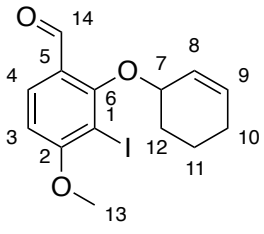
Molecular Weight: 274.10

1-(But-3-en-2-yloxy)-2-iodobenzene (**4.17**) was prepared by Williamson ether synthesis: from 4-Iodophenol (1.73 g, 10.0 mmol) and 3-Bromobut-1-ene (1.30 mL, 15.0 mmol), following silica plug, 1-(But-3-en-2-yloxy)-2-iodobenzene (3.07 g, 9.6 mmol, 96%) was isolated as a clear oil. No reported literature data.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.78 (dd, *J* = 7.8, 1.5 Hz, 1H, $\mathbf{H}_2$), 7.25 (td, *J* = 7.5, 1.5 Hz, 1H, $\mathbf{H}_4$), 6.84 (dd, *J* = 8.3, 1.3 Hz, 1H, $\mathbf{H}_5$), 6.70 (td, *J* = 7.5, 1.3 Hz, 1H, $\mathbf{H}_3$), 5.95 (ddd, *J* = 17.2, 10.6, 6.3 Hz, 1H, $\mathbf{H}_8$), 5.31 (d, *J* = 17.2 Hz, 1H, $\mathbf{H}_{9a}$), 5.20 (d, *J* = 10.6 Hz, 1H, $\mathbf{H}_{9b}$), 4.83 (quin, *J* = 6.3 Hz, 1H, $\mathbf{H}_7$), 1.52 (d, *J* = 6.3 Hz, 3H, $\mathbf{H}_{10}$)

LRMS: (EI) m/z = 274 $[M]^{\bullet+}$

2-(Cyclohex-2-en-1-yloxy)-3-iodo-4-methoxybenzaldehyde



3.47

Chemical Formula: $C_{14}H_{15}IO_3$

Molecular Weight: 358.18

2-(Cyclohex-2-en-1-yloxy)-3-iodo-4-methoxybenzaldehyde (**3.47**) was prepared by Williamson ether synthesis: from 2-Hydroxy-3-iodo-4-methoxybenzaldehyde (2.09 g, 7.5 mmol) and Cyclohexene bromide (1.29 mL, 11.3 mmol), following purification by flash chromatography (5% EtOAc in hexane), 2-(Cyclohex-2-en-1-yloxy)-3-iodo-4-methoxybenzaldehyde (1.41 g, 3.9

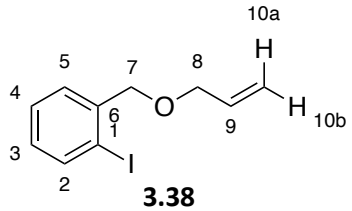
mmol, 52%) was isolated as a clear oil. Novel compound (single enantiomers known). The data are consistent with reported values.[375]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 10.00 (d, *J* = 0.7 Hz, 1H, **H**$_{14}$), 7.62 (d, *J* = 8.6 Hz, 1H, **H**$_4$), 6.93 (d, *J* = 8.6 Hz, 1H, **H**$_3$), 5.93-5.84 (m, 2H, **H**$_{8,9}$), 4.80-4.77 (m, 1H, **H**$_7$), 3.90 (s, 3H, **H**$_{13}$), 2.16-2.10 (m, 1H, **H**$_{10}$), 2.07-1.96 (m, 3H, **H**$_{11,12}$), 1.84-1.76 (m, 1H, **H**), 1.62-1.55 (m, 1H, **H**).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 195.3 (CH,**C**$_{14}$), 157.3 (C, **C**$_2$), 147.2, (C, **C**$_6$), 131.9 (CH, **C**$_6$), 129.0 (C, **C**$_2$), 126.7 (CH_2, **C**$_7$), 126.4 (2CH, **C**$_4$), 111.56(C, **C**$_1$), 101.4 (C, C), 76.6 (CH_2, **C**$_5$), 56.0 (CH_3, **C**$_{13}$), 29.1 (CH_2, **C**$_{12}$), 24.93 (CH_2, **C**$_{10}$), 18.91 (CH_2, **C**$_{11}$).

LRMS: (EI) m/z = 358 $[M]^{\bullet+}$

1-((Allyloxy)methyl)-2-iodobenzene



3.38

Chemical Formula: $C_{10}H_{11}IO$

Molecular Weight: 274.10

1-((Allyloxy)methyl)-2-iodobenzene (**3.38**) was prepared by literature procedure for alkylation: To an ice–cooled solution of 2-Iodobenzyl alcohol (3.00 g, 12.8 mmol) in THF (60 mL) was added NaH (60% in mineral oil, 0.768 g, 19.2 mmol) in portions. The grey suspension was allowed to warm to rt and then Allyl bromide (1.43 mL, 16.6 mmol) was dropwise added, followed by TBAI (0.48 g, 1.3 mmol) in one portion. The suspension was stirred for 16 hours at rt and then the reaction was quenched by slow addition of ice–water (60 mL). The mixture was concentrated to ½ volume and then the product was extracted with EtOAc (3 x 30 mL). The combined organic phase was washed with sat. aq. $NaHCO_3$ (50 mL), water (50 mL) and brine (50 mL), and then dried ($MgSO_4$) and filtered. Removal of solvents under reduced pressure afforded a yellow solid. Purification by flash chromatography (5% EtOAc in hexane) afforded 1-((Allyloxy)methyl)-2-iodobenzene (3.26 g, 11.9 mmol, 93%) as a clear oil. The data are consistent with reported values.[376-378]

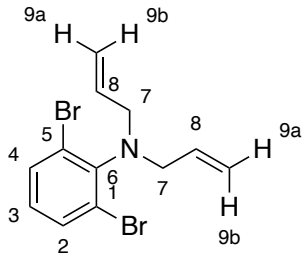
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.83 (dd, *J* = 7.7, 1.0 Hz, 1H, **H**$_2$), 7.47 (dd, *J* = 7.7, 1.7 Hz, 1H, **H**$_5$), 7.36 (td, J = 7.7, 1.0 Hz, 1H, **H**$_4$), 7.00 (td, *J* = 7.7, 1.7 Hz, 1H, **H**$_3$), 6.01 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H, **H**$_9$), 5.37 (dq, J = 17.2, 1.6 Hz, 1H, **H**$_{10a}$), 5.25 (dq, J = 10.4, 1.3 Hz, 1H, **H**$_{10b}$), 4.52 (s, 2H, **H**$_7$), 4.13 (dt, *J* = 5.6, 1.4 Hz, 2H, **H**$_8$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 140.6, (C, **C**$_6$), 139.1 (CH, **C**$_2$), 134.5 (CH, **C**$_9$), 129.1 (CH, **C**$_3$), 128.7 (CH, **C**$_5$), 128.2 (CH, **C**$_4$), 117.3 (CH_2, **C**$_{10}$), 97.7 (C, **C**$_1$), 75.9 (CH_2, **C**$_7$), 71.7 (CH_2, **C**$_8$).

LRMS: (EI) m/z = 274 $[M]^{\bullet+}$

4.3.2 Nitrogen-containing substrates and compounds

***N*,*N*-Diallyl-2,6-dibromoaniline**



3.24

Chemical Formula: $C_{12}H_{13}Br_2N$

Molecular Weight: 331.05

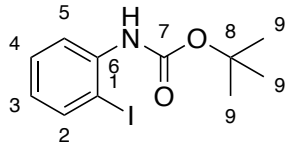
N,*N*-Diallyl-2,6-dibromoaniline (**3.24**) was prepared by literature procedure for alkylation: A suspension of 2,6-Dibromoaniline (1.25 g, 5.0 mmol) and K_2CO_3 (1.52 g, 11.0 mmol) and Allyl bromide (1.08 mL, 12.5 mmol) in DMF (14 mL) was stirred at 100 °C for 20 hours and then allowed to cool to rt. Water (20 mL) was added and the mixture was concentrated to ¾ volume. The product was extracted with EtOAc (3 x 10 mL), and the combined organic phase was washed with water (4 x 10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$) and filtered. Removal of solvents under reduced pressure afforded a brown oil. Purification by flash chromatography (0 to 5% Et_2O in hexane) afforded *N*,*N*-Diallyl-2,6-dibromoaniline (0.896 g, 2.7 mmol, 54%) as a clear oil. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.54 (d, *J* = 8.0 Hz, 2H, $\mathbf{H}_{2,4}$), 6.88 (t, *J* = 8.0 Hz, 1H, $\mathbf{H}_3$), 5.95 (ddt, *J* = 17.0, 10.1, 6.6 Hz, 2H, $\mathbf{H}_8$), 5.19 (d, J = 17.0 Hz, 2H, $\mathbf{H}_{9b}$), 5.06 (d, J = 10.4, 1.3 Hz, 2H, $\mathbf{H}_{9a}$), 3.79 (d, *J* = 6.6 Hz, 4H, $\mathbf{H}_7$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 147.0, (C, $\mathbf{C}_6$), 136.2 (2CH, $\mathbf{C}_8$), 132.8 (2CH, $\mathbf{C}_{2,4}$), 127.5 (CH, $\mathbf{C}_3$), 127.3 (2C, $\mathbf{C}_{1,5}$), 116.8 ($2CH_2$, $\mathbf{C}_9$), 55.3 ($2CH_2$, $\mathbf{C}_7$).

LRMS: (ESI+) m/z = 332 $[M+H]^+$

***tert*-Butyl (2-iodophenyl)carbamate**



3.22

Chemical Formula: $C_{11}H_{14}INO_2$

Molecular Weight: 319.14

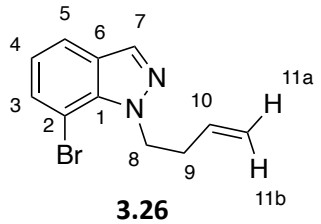
tert-Butyl (2-iodophenyl)carbamate (**3.22**) was prepared by literature procedure for BOC protection:[379] A solution of 2-Iodoaniline (**3.21**) (4.38 g, 20.0 mmol), Na_2CO_3 (3.18 g, 30.0 mmol) and Boc_2O (6.55 g, 30.0 mmol) in dioxane (8.6 mL) and water (8.6 mL) was stirred at 80 °C for 16 hours and then solvents were removed under reduced pressure. Purification by flash chromatography (0 to 2% Et_2O in hexane) afforded *tert*-Butyl (2-iodophenyl)carbamate (5.11 g, 16.0 mmol, 80%) as a white solid. The data are consistent with reported values.[379, 380]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 8.06 (d, *J* = 8.3, 1.4 Hz, 1H, $\mathbf{H}_5$), 7.76 (dd, *J* = 7.6, 1.5 Hz, 1H, $\mathbf{H}_2$), 7.32 (ddd, *J* = 8.3, 7.5, 1.5 Hz, 1H, $\mathbf{H}_4$), 5.19 (br. s, 1H, N**H**), 6.77 (ddd, J = 8.3, 7.6, 1.4 Hz, 1H, $\mathbf{H}_3$), 1.55 (s, 9H, $\mathbf{H}_9$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 152.6 (C, $\mathbf{C}_7$), 138.8 (CH+C, $\mathbf{C}_{2,6}$), 129.2 (CH, $\mathbf{C}_4$), 124.7 (CH, $\mathbf{C}_3$), 120.2 (2C, $\mathbf{C}_5$), 88.7 (C, $\mathbf{C}_1$), 81.1 (C, $\mathbf{C}_8$), 28.3 ($3CH_3$, $\mathbf{C}_9$).

LRMS: (EI) m/z = 319 $[M]^{\bullet+}$

7-Bromo-1-(but-3-en-1-yl)-1*H*-indazole



3.26

Chemical Formula: $C_{11}H_{11}BrN_2$

Molecular Weight: 251.13

7-Bromo-1-(but-3-en-1-yl)-1*H*-indazole (**3.26**) was prepared by literature procedure for alkylation:[258] A suspension of 7-Bromo-1H-indazole (**3.25**) (0.985 g, 5 mmol), KOH (0.337 g, 6 mmol) and 4-Bromobut-1-ene (0.609 mL, 6 mmol) in DMF (20 mL) was stirred at RT for 24 hours. Water (30 mL) was added, and the solution was concentrated to 1/2 volume. The product was extracted with EtOAc (3 x 30 mL), and the combined organic phase was washed with water (4 x 20 mL). The organic phase was dried ($MgSO_4$) and filtered. Removal of solvents under reduced pressure afforded a yellow paste. Purification by flash chromatography (20% EtOAc in hexane) afforded 7-Bromo-1-(but-3-en-1-yl)-1*H*-indazole (0.98 g, 3.9 mmol, 78%) as a white solid. Novel compound.

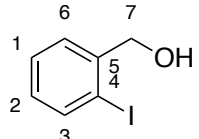
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 8.00 (s, 1H, $\mathbf{H}_7$), 7.67 (dd, *J* = 8.0, 0.9 Hz, 1H, $\mathbf{H}_3$), 7.56 (dd, *J* = 7.5, 0.9 Hz, 1H, $\mathbf{H}_3$), 6.99 (t, *J* = 7.7 Hz, 1H, $\mathbf{H}_3$), 5.86 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 2H, $\mathbf{H}_8$), 5.19 (d, J = 17.2, 1.6 Hz, 1H, $\mathbf{H}_{11b}$), 5.06 (d, J = 10.2, 1.6 Hz, 2H, $\mathbf{H}_{9a}$), 3.79 (d, *J* = 6.6 Hz, 4H, $\mathbf{H}_7$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 147.0, (C, $\mathbf{C}_6$), 136.2 (2CH, $\mathbf{C}_8$), 132.8 (2CH, $\mathbf{C}_{2,4}$), 127.5 (CH, $\mathbf{C}_3$), 127.3 (2C, $\mathbf{C}_{1,5}$), 116.8 ($2CH_2$, $\mathbf{C}_9$), 55.3 ($2CH_2$, $\mathbf{C}_7$).

LRMS: (ESI+) m/z = 332 $[M+H]^+$

4.3.3 Miscellaneous compounds

2-Iodobenzyl alcohol



4.18

Chemical Formula: C_7H_7IO

Molecular Weight: 234.04

2-Iodobenzyl alcohol (**4.18**) was prepared by literature procedure for ester reduction with DIBAL: a solution of DIBAL-H (1M in CH_2Cl_2, 15.0 mL) was added dropwise to a solution of Methyl-2-iodobenzoate (1.84 mL, 12.5 mmol) in CH_2Cl_2 (70 mL), maintained at -78 °C. The solution turned yellow and was stirred for 2 hours. A further 2.5 mL (2.5 mmol) DIBAL-H in CH_2Cl_2 was added after 1 hour. of MeOH (10 mL) was added, the solution was allowed to warm to rt and was stirred for 45 minutes. Rochelle salt (60 mL) was added, and a homogeneous mixture formed. The mixture was reduced to ½ volume under reduced pressure and the product was extracted with CH_2Cl_2 (4 x 30 ml). The combined organic phase was washed with NH_4Cl (50 mL), water (2 x 50 mL) and brine (50 mL), and then dried ($MgSO_4$) and filtered. Removal of solvents under reduced pressure afforded a yellow oil. Purification by flash chromatography (5% EtOAc in hexane) afforded 2-Iodobenzaldehyde (0.58 g, 2.5 mmol, 20%) as a white solid, 2-Iodobenzyl alcohol (1.70 g, 7.3 mmol, 58%) as a white solid and SM (0.66 g, 2.5 mmol, 20%) as a clear oil. The data are consistent with reported values.[381]

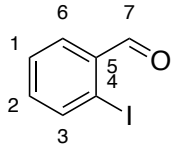
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.84 (dd, *J* = 7.8, 1.2 Hz, 1H, **H**$_3$), 7.47 (dd, *J* = 7.6, 1.8 Hz, 1H, **H**$_6$) 7.38 (td, *J* = 7.8, 1.2 Hz, 1H, **H**$_2$), 7.01 (td, *J* = 7.6, 1.8 Hz, 1H, **H**$_1$), 4.69 (d, *J* = 6.4 Hz, 2H, **H**$_7$), 2.01 (t, *J* = 6.4 Hz, 1H, O**H**).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 142.6 (C, **C**$_5$), 139.2 (CH, **C**$_3$), 129.3 (CH, **C**$_2$), 128.5 (C, **C**$_{1/6}$), 128.5 (CH, C$_{1/6}$), 97.5 (C, **C**$_4$), 69. 3 (CH_2, **C**$_7$).

LRMS: (ESI+) m/z = 216 $[M\text{-}OH]^+$

MP: 91.5 – 92.5°C

2-iodobenzaldehyde



4.19

Chemical Formula: C_7H_5IO

Molecular Weight: 232.02

2-Iodobenzaldehyde (**4.19**) was prepared by literature procedure for PCC oxidation:[382] PCC (3.23 g, 15.0 mmol) and celite (8.0 g) were vacuum dried for 1 hour and then suspended in CH_2Cl_2 (100 mL). The suspension was cooled on ice and then a solution of 2-Iodobenzyl alcohol (2.93 g, 12.5 mmol) in CH_2Cl_2 was added dropwise. The mixture was allowed to warm to rt and stirred for 5 hours, turning orange, red and finally black. The mixture was filtered through celite, washing with CH_2Cl_2 (2 x 10 mL). Removal of solvent under reduced pressure afforded a black solid. Purification by flash chromatography afforded 2-Iodobenzaldehyde (2.73 g, 11.8 mmol, 94%) as a white solid. The data are consistent with reported values.[381, 383]

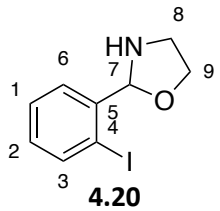
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 10.06 (d, *J* = 1.2 Hz, 1H, **H**$_7$), 7.94 (dd, *J* = 7.7, 1.2 Hz, 1H, **H**$_3$), 7.87 (dd, *J* = 7.7, 1.2 Hz, 1H, **H**$_6$), 7.46 (tt, *J* = 7.7, 1.2 Hz, 1H, **H**$_1$) 7.28 (td, *J* = 7.7, 1.2 Hz, 1H, **H**$_2$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 195.7 (CH, **C**$_7$), 140.6 (CH, **C**$_3$), 135.4 (CH, **C**$_2$), 135.0 (C, **C**$_5$) 130.2 (CH, **C**$_6$), 128.7 (CH, **C**$_1$), 100.7 (C, **C**$_4$)

LRMS: (EI) m/z = 232 $[M]^{\bullet+}$

MP: 37.0 – 38.0 °C

2-(2-Iodophenyl)oxazolidine



4.20

Chemical Formula: $C_9H_{10}INO$

Molecular Weight: 275.09

2-(2-Iodophenyl)oxazolidine (**4.20**) was prepared in-situ by literature procedure for oxidative conversion of aldehydes to 2-oxazolines:[384] Ethanolamine (0.363 mL, 6.0 mmol) was added dropwise to a suspension of 2-Iodobenzaldehyde (1.39 g, 6.0 mmol) and 4 Å molecular sieves in CH_2Cl_2 (36 mL) at rt. The mixture was stirred for 14 hours and then a 0.5 mL aliquot of reaction solution was filtered, concentrated and analysed. To the bulk solution was added NBS (1.07 g, 6.0 mmol) and the suspension was stirred at rt for 2 hours. The reaction mixture was filtered through celite, and the organic filtrate was washed with sat. aq. $NaHCO_3$ (30 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography (10 to 30% EtOAc in hexane) afforded 2-(2-Iodophenyl)oxazolidine (0.66 g, 2.4 mmol, 40%) as a clear oil, impure 2-bromo-2-(2-Iodophenyl)oxazolidine (0.63 g, 1.8 mmol, 30%), as a clear oil, 2-(2-Iodophenyl)-4,5-dihydrooxazole (0.06 g, 0.2 mmol, 4%) as a clear oil and SM (0.21 g, 0.9 mmol, 15%) as a white solid. The data are consistent with (incomplete) reported values.[385]

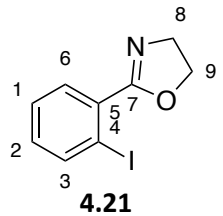
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 8.52 (s, 1H, $\mathbf{H}_7$), 7.96 (d, *J* = 6.9 Hz, 1H, $\mathbf{H}_3$), 7.87 (d, *J* = 7.7 Hz, 1H, $\mathbf{H}_6$), 7.38 (t, *J* = 7.7 Hz, 1H, $\mathbf{H}_2$) 7.13 (t, *J* = 6.9 Hz, 1H, $\mathbf{H}_1$), 3.94 (t, *J* = 4.1 Hz, 2H, $\mathbf{H}_9$), 3.83 (t, *J* = 4.1 Hz, 2H, $\mathbf{H}_8$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 166.3 (CH, $\mathbf{C}_7$), 139.7 (CH, $\mathbf{C}_3$), 136.7 (C, $\mathbf{C}_5$), 132.2 (C, $\mathbf{C}_1$) 128.7 (CH, $\mathbf{C}_6$), 128.4 (CH, $\mathbf{C}_2$), 100.1 (C, $\mathbf{C}_4$), 62.9 (CH_2, $\mathbf{C}_8$), 62.4 (CH_2, $\mathbf{C}_9$)

LRMS: (EI) m/z = 275 $[M]^{\bullet+}$

FT–IR (cm^{-1}) neat: 3356 (br., m, N-H), 2878 (w, C-H).

2-(2-Iodophenyl)-4,5-dihydrooxazole



4.21

Chemical Formula: C_9H_8INO

Molecular Weight: 273.07

2-(2-Iodophenyl)-4,5-dihydrooxazole (**4.21**) was synthesised by literature procedure outlined for 2-(2-Iodophenyl)oxazolidine: from 2-Iodobenzaldehyde (1.39 g, 6.0 mmol), 2-(2-

Iodophenyl)-4,5-dihydrooxazole (0.06 g, 0.2 mmol, 4%) was afforded as a clear oil. The data are consistent with (incomplete) reported values.[386]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.95 (dd, *J* = 7.8, 1.2 Hz, 1H, **H**$_3$), 7.65 (dd, *J* = 7.8, 1.7 Hz, 1H, **H**$_6$), 7.38 (td, *J* = 7.8, 1.2 Hz, 1H, **H**$_2$) 7.11 (td, *J* = 7.8, 1.7 Hz, 1H, **H**$_1$), 4.46 (t, *J* = 9.5 Hz, 2H, **H**$_9$), 4.12 (t, *J* = 9.5 Hz, 2H, **H**$_8$).

^{13}C NMR: ($CDCl_3$ 101 MHz) δ ppm = 164.8 (CH, **C**$_7$), 140.5 (CH, **C**$_3$), 133.5 (C, **C**$_5$), 131.6 (C, **C**$_1$) 130.7 (CH, **C**$_6$), 127.8 (CH, **C**$_2$), 94.6 (C, **C**$_4$), 67.7 (CH_2, **C**$_9$), 55.3 (CH_2, **C**$_8$)

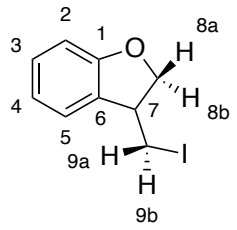
LRMS: (EI) m/z = 232 $[M]^{\bullet+}$

FT–IR (cm^{-1}) neat: 3344 (br., m, N-H), 2880 (w, C-H), 1635 (s, C=N).

MP: 37.0 – 38.0 °C

4.3.4 Photochemical cyclisation

3-(Iodomethyl)-2,3-dihydrobenzofuran



3.28

Chemical Formula: C_9H_9IO

Molecular Weight: 260.07

3-(Iodomethyl)-2,3-dihydrobenzofuran (**3.28**) was prepared by modified literature procedure for photochemical cyclisation:[387] A solution of 1-(Allyloxy)-2-iodobenzene (0.260 g, 1.0 mmol) in MeCN (20 mL) was degassed with argon and then passed through the photochemical reactor (254 nm, 3.66 mL min^{-1}, 30 minutes residence time). Removal of solvents under reduced pressure afforded a dark brown oil. Purification by flash chromatography (3 to 30% EtOAc in hexane) afforded 3-(Iodomethyl)-2,3-dihydrobenzofuran (0.226 g, 0.9 mmol, 87%) as a yellow oil. The data are consistent with reported values.[387]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.25 – 7.19 (m, 2H, $\mathbf{H}_{4,5}$), 6.91 (td, *J* = 7.7, 1.0 Hz, 1H, $\mathbf{H}_3$), 6.82 (d, *J* = 7.7 Hz, 1H, $\mathbf{H}_2$), 4.66 (t, *J* = 9.2 Hz, 1H, $H_{8a/8b}$), 4.36 (dd, *J* = 9.2, 5.5 Hz, 1H, $\mathbf{H}_{8a/8b}$), 3.86 (tt, *J* = 9.2, 4.9 Hz, 1H, $\mathbf{H}_7$), 3.48 (dd, *J* = 9.9, 4.4 Hz, 1H, $\mathbf{H}_{9a/9b}$), 3.23 (t, *J* = 9.9 Hz, 1H, $\mathbf{H}_{9a/9b}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 160.1 (C, $\mathbf{C}_1$), 129.3 (CH, $\mathbf{C}_5$), 128.7 (C, $\mathbf{C}_6$), 124.3 (CH, $\mathbf{C}_3$), 120.6 (CH, $\mathbf{C}_4$), 110.2 (CH,$\mathbf{C}_2$), 77.6 (CH_2, $\mathbf{C}_8$), 44.8 (CH, $\mathbf{C}_7$), 9.0 (CH_2, $\mathbf{C}_9$).

LRMS: (EI) m/z = 260 $[M]^{\bullet+}$

4.3.5 Reductive cyclisation substrates

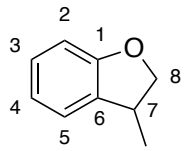
4.3.5.1 General method M: reductive cyclisation (MeOH/MeCN solvent)

Aryl halides were reductively cyclised to the respective dihydrobenzofurans, indolines and tetrahydrobenzopyrans in the Ammonite 8 reactor, using optimised conditions developed in this work: A solution of aryl halide (1.0 mmol), phenanthrene (0.178 g, 1.0 mmol) and Et_4NBF_4 (0.174 g, 0.8 mmol) in MeCN (80 mL) and MeOH (0.04 mL, 1.0 mmol) was prepared, degassed under argon for 20 minutes, and passed through the Ammonite 8 flow reactor twice (glassy carbon anode, SS cathode, 16 mL min^{-1}, 2 x 640 mA (2 x 2.0 F/mol). Steady state voltage was reached between 8.0 and 11.0 V. Effluent solution was concentrated under reduced pressure and the crude was taken into EtOAc (10 mL). Electrolyte was recovered by filtration.

Where the title compound possessed a basic centre, the solution was treated with 2N HCl (3 x 10 mL) and the organic phase set aside. The combined aqueous phase was basified to pH 12 with 5% aq. NaOH solution. Product was extracted with Et_2O (3 x 10 mL). The combined organic phase was washed with brine (20 mL), dried ($MgSO_4$) and filtered. Removal of solvent under reduced pressure afforded the pure compound.

For compounds lacking a basic centre, the crude product was purified by flash chromatography or Kügelrohr distillation.

3-Methyl-2,3-dihydrobenzofuran



3.27

Chemical Formula: $C_9H_{10}O$

Molecular Weight: 134.18

3-Methyl-2,3-dihydrobenzofuran (**3.27**) was prepared by general method M: from 1-(Allyloxy)-2-iodobenzene (**2.156**) (1.30 g, 5.0 mmol), following flash chromatography (0 to 5% Et_2O/hexane), 3-Methyl-2,3-dihydrobenzofuran (0.490 g, 3.7 mmol, 73%) was isolated as a clear oil. Phenanthrene (0.873 g, 98%) and 1,2-Bis(2,3-dihydrobenzofuran-3-yl)ethane (0.137 g, 0.5 mmol, 21%) were also isolated as white solids.

Using the same method, following purification by Kugelrohr distillation, 3-Methyl-2,3-dihydrobenzofuran (0.456 g, 3.4 mmol, 68%) was isolated as a clear oil.

3-Methyl-2,3-dihydrobenzofuran was also prepared by reductive cyclisation in the parallel-plate divided cell (cathodic chamber, RVC +, SS -): The electrolysis was carried out using a solution of 1-(Allyloxy)-2-iodobenzene (0.650 g, 2.5 mmol), Phenanthrene (0.446 g, 2.5 mmol) and Et_4NBF_4 (0.271 g, 1.3 mmol) in MeCN (25 mL) The catholyte reservoir was connected to the pump for the cathodic compartment, and the outlet of the reactor was inserted into the same reservoir to allow the continuous recycling of the reaction solution. After 55 minutes of electrolysis (160 mA, 2.2 F), current ceased to pass and so the solvent was removed under reduced pressure to afford a black slurry. Purification by flash chromatography (0:10:90 to 5:10:85 Et_2O/toluene/hexane) afforded 3-Methyl-2,3-dihydrobenzofuran (0.200 g, 1.5 mmol, 60%) as a clear oil. The data are consistent with reported values.[252, 329]

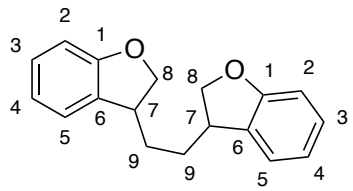
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.18 – 7.11 (m, 2H, $\mathbf{H}_{4,5}$), 6.87 (td, *J* = 7.4, 1.0 Hz, 1H, $\mathbf{H}_3$), 6.80 (dt, *J* = 8.1, 1.0 Hz, 1H, $\mathbf{H}_2$), 4.69 (t, *J* = 8.6 Hz, 1H, $\mathbf{H}_8$), 4.08 (dd, *J* = 8.6, 7.2 Hz, 1H, $\mathbf{H}_8$), 3.56 (sextet, *J* = 7.2 Hz, 1H, $\mathbf{H}_7$), 1.35 (d, *J* = 7.2 Hz, 3H, $\mathbf{H}_9$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 159.7 (C, $\mathbf{C}_1$), 132.2 (C, $\mathbf{C}_6$) 128.0 (CH, C_3), 123.8 (CH, C_5), 120.4 (CH, C_4), 109.4 (CH, C_2), 78.4 (CH_2, C_8), 36.5 (CH, C_7), 19.3 (CH_3, C_9).

LRMS: (EI) m/z = 134 $[M]^{\bullet+}$

BP: 40 °C @ 0.1 mbar (Lit:[252] 60 °C @ 5 mbar)

1,2-Bis(2,3-dihydrobenzofuran-3-yl)ethane



3.29

Chemical Formula: $C_{18}H_{18}O_2$

Molecular Weight: 266.34

1,2-Bis(2,3-dihydrobenzofuran-3-yl)ethane (**3.29**) was prepared by general method M: from 1-(Allyloxy)-2-iodobenzene (1.30 g, 5.0 mmol), following flash chromatography (0 to 5% Et_2O/hexane), 1,2-Bis(2,3-dihydrobenzofuran-3-yl)ethane (0.137 g, 0.5 mmol, 21%) was isolated as a white solid. The data are consistent with (incomplete) reported values.[261]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.18 – 7.12 (m, 4H, $\mathbf{H}_{4,5}$), 6.87 (tt, *J* = 7.4, 1.3 Hz, 2H, $\mathbf{H}_3$), 6.80 (dt, *J* = 8.1, 1.3 Hz, 2H, $\mathbf{H}_2$), 4.64 (t, *J* = 8.9 Hz, 2H, $\mathbf{H}_8$), 4.22 (ddd, *J* = 8.9, 6.2, 1.4 Hz, 2H, $\mathbf{H}_8$), 3.50 – 3.43 (m, 2H, $\mathbf{H}_7$), 1.97 – 1.57 (m, 4H, $\mathbf{H}_9$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 159.9 (2C, $\mathbf{C}_1$), 130.4 (C, $\mathbf{C}_6$), 130.3 (C, $\mathbf{C}_6$), 128.3 (2CH, $\mathbf{C}_3$), 124.3 (CH, $\mathbf{C}_5$), 124.3 (CH, $\mathbf{C}_5$) 120.4 (2CH, $\mathbf{C}_4$), 109.6 (2CH, $\mathbf{C}_2$), 76.6 (CH_2, $\mathbf{C}_8$), 76.6 (CH_2, $\mathbf{C}_8$), 41.9 (2CH, $\mathbf{C}_7$), 32.3 (CH_2, $\mathbf{C}_9$), 32.2 (CH_2, $\mathbf{C}_9$).

LRMS: (EI) m/z = 266 $[M]^{\bullet+}$

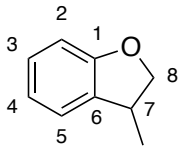
MP: 84 – 85 °C (Lit not reported)

4.3.5.2 General method N: reductive cyclisation (Bu_4NI electrolyte, MeCN solvent)

Aryl halides were reductively cyclised to the respective dihydrobenzofurans, indolines and tetrahydrobenzopyrans in the Ammonite 8 reactor, using optimised conditions developed in this work: A solution of aryl halide (1.0 mmol), phenanthrene (0.178 g, 1.0 mmol) and Bu_4NI (0.185 g, 0.5 mmol) in MeCN (40 mL) was prepared, degassed under argon for 20 minutes, and passed through the Ammonite 8 flow reactor twice (glassy carbon anode, SS cathode, 16 mL min^{-1}, 2 x

1280 mA (2.0 F/mol). Steady state voltage was reached between 9.0 and 14.5 V. Sat. aq. NaS_2O_3 solution (20 mL) and Et_2O (10 mL) was added to the effluent solution and the organic phase was separated. The organic phase was washed with sat. aq. $NaHCO_3$ (20 mL), dried ($MgSO_4$), and filtered. Removal of solvent under reduced pressure afforded the crude product that was purified by flash chromatography or Kügelrohr distillation.

3-Methyl-2,3-dihydrobenzofuran



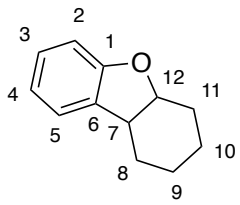
3.27

Chemical Formula: $C_9H_{10}O$

Molecular Weight: 134.18

3-Methyl-2,3-dihydrobenzofuran (**3.27**) was prepared by general method N: from 1-(Allyloxy)-2-iodobenzene (0.260 g, 1.0 mmol), following flash chromatography (0 to 5% Et_2O/hexane), 3-Methyl-2,3-dihydrobenzofuran (0.110 g, 0.8 mmol, 83%) was isolated as a clear oil. The data are consistent with reported values (previously characterised, data matches).[252]

1,2,3,4,4a,9b-Hexahydrodibenzo[*b*,*d*]furan



3.35

Chemical Formula: $C_{12}H_{14}O$

Molecular Weight: 174.24

1,2,3,4,4a,9b-Hexahydrodibenzo[*b*,*d*]furan (**3.35**) was prepared by general method N: from 1-(Cyclohex-2-en-1-yloxy)-2-iodobenzene (**3.06**) (0.300 g, 1.0 mmol), following purification by flash chromatography (0 to 0.5% Et_2O/hexane), 1,2,3,4,4a,9b-Hexahydrodibenzo[*b*,*d*]furan (0.145 g, 0.8 mmol, 84%) was isolated as a clear oil. The data are consistent with reported values.[252, 388]

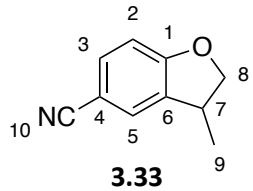
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.17 – 7.11 (m, 2H, $\mathbf{H}_{4,5}$), 6.89 – 6.82 (m, 2H, $\mathbf{H}_{2,3}$), 4.68 (dt, *J* = 6.9, 5.0 Hz, 1H, $\mathbf{H}_{12}$), 3.21 (q, *J* = 6.9 Hz, 1H, $\mathbf{H}_7$), 2.03 –

1.96 (m, 1H, $\mathbf{H}_{11eq}$), 1.92 – 1.79 (m, 2H, $H_{8ax,\ 11ax}$), 1.58 – 1.49 (m, 4H, $\mathbf{H}_{8ax,\ 9/10ax,\ 9,10\ eq}$), 1.45 – 1.35 (m, 1H, $H_{9/10ax}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 159.3 (C, $\mathbf{C}_1$), 134.5 (C, $\mathbf{C}_6$), 127.7 (CH, $\mathbf{C}_3$), 123.5 (CH, $\mathbf{C}_5$), 120.4 (CH, $\mathbf{C}_4$), 110.0 (CH, $\mathbf{C}_2$), 82.5 (CH, $\mathbf{C}_{12}$), 40.6 (CH_2, $\mathbf{C}_7$), 28.2 (CH_2, $\mathbf{C}_{11}$), 27.5 (CH_2, $\mathbf{C}_8$), 22.0 (CH_2, $\mathbf{C}_9$), 20.6 (CH_2, $\mathbf{C}_{10}$).

LRMS: (EI) m/z = 174 $[M]^{\bullet+}$

3-Methyl-2,3-dihydrobenzofuran-5-carbonitrile



3.33

Chemical Formula: $C_{10}H_{10}NO$

Molecular Weight: 159.19

3-Methyl-2,3-dihydrobenzofuran-5-carbonitrile (**3.33**) was prepared by general method N: from 4-(Allyloxy)-3-bromobenzonitrile (**3.11**) (0.238 g, 1.0 mmol), following purification by flash chromatography (0 to 5% Et_2O/hexane), 2,3-Dihydrobenzofuran-5-carbonitrile (0.115 g, 0.7 mmol, 72%) was isolated as a white solid. The data are consistent with reported values.[368]

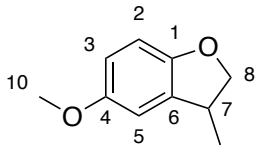
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.47 – 7.42 (m, 2H, $\mathbf{H}_{3,5}$), 6.83 (d, *J* = 8.2 Hz, 1H, $\mathbf{H}_2$), 4.78 (t, *J* = 9.0 Hz, 1H, $\mathbf{H}_8$), 4.19 (dd, J = 9.0, 7.4 Hz, 1H, $\mathbf{H}_8$), 3.59 (sextet, *J* = 7.7 Hz, 1H, $\mathbf{H}_7$), 1.36 (d, J = 7.0 Hz, 3H, $\mathbf{H}_9$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 163.4 (C, $\mathbf{C}_1$), 133.9 (C, $\mathbf{C}_6$), 133.6 (CH, $\mathbf{C}_3$), 128.0 (CH, $\mathbf{C}_5$), 119.6 (CH, $\mathbf{C}_{10}$), 110.4 (CH, $\mathbf{C}_2$), 103.7 (CH, $\mathbf{C}_4$), 79.4 (CH_2, $\mathbf{C}_8$), 35.9 (CH_2, $\mathbf{C}_7$), 19.3 (CH_3, $\mathbf{C}_9$).

LRMS: (EI) m/z = 174 $[M]^{\bullet+}$

MP: 58.0 – 60.0 °C (Lit:[368] 61 -63 °C)

5-Methoxy-3-methyl-2,3-dihydrobenzofuran



3.32

Chemical Formula: $C_{10}H_{12}O_2$

Molecular Weight: 164.20

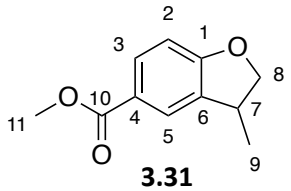
5-Methoxy-3-methyl-2,3-dihydrobenzofuran (**3.32**) was prepared by general method N: from 1-(Allyloxy)-2-bromo-4-methoxybenzene (**3.12**) (0.243 g, 1.0 mmol), following purification by flash chromatography (0:10:90 to 5:10:85 Et_2O/toluene/hexane), 2,3-Dihydrobenzofuran-5-carbonitrile (0.149 g, 0.9 mmol, 91%) was isolated as a clear oil. The data are consistent with (incomplete) reported values.[368]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.47 – 7.42 (m, 3H, $\mathbf{H}_{2,3,5}$), 4.67 (t, *J* = 8.7 Hz, 1H, $\mathbf{H}_8$), 4.06 (t, J = 8.0 Hz, 1H, $\mathbf{H}_8$), 3.78 (s, 3H, $\mathbf{H}_{10}$) 3.54 (sextet, *J* = 7.5 Hz, 1H, $\mathbf{H}_7$), 1.33 (d, J = 6.9 Hz, 3H, $\mathbf{H}_9$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 154.2 (C, $\mathbf{C}_4$), 153.8 (C, $\mathbf{C}_1$), 133.3 (C, $\mathbf{C}_6$), 112.6 (CH, $\mathbf{C}_2$), 110.2 (CH, $\mathbf{C}_3$), 109.3 (CH, $\mathbf{C}_5$), 78.7 (CH_2, $\mathbf{C}_8$), 56.0 (CH_3, $\mathbf{C}_{10}$), 37.0 (CH, $\mathbf{C}_7$), 19.0 (CH_3, $\mathbf{C}_9$).

LRMS: (EI) m/z = 164 $[M]^{\bullet+}$

Methyl 3-methyl-2,3-dihydrobenzofuran-5-carboxylate



3.31

Chemical Formula: $C_{11}H_{12}O_3$

Molecular Weight: 192.21

Methyl 3-methyl-2,3-dihydrobenzofuran-5-carboxylate (**3.31**) was prepared by general method N: from Methyl 4-(allyloxy)-3-bromobenzoate (**3.13**) (0.271 g, 1.0 mmol), following

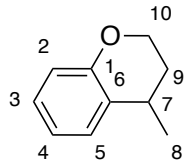
purification by flash chromatography (0:10:90 to 5:10:85 Et_2O/toluene/hexane), Methyl 3-methyl-2,3-dihydrobenzofuran-5-carboxylate (0.140 g, 0.7 mmol, 73%) was isolated as a clear oil. The data are consistent with reported values.[389]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.89 – 7.85 (m, 2H, $\mathbf{H}_{3,5}$), 6.79 (d, *J* = 8.3 Hz, 1H, $\mathbf{H}_2$), 4.77 (t, *J* = 9.0 Hz, 1H, $\mathbf{H}_8$), 4.16 (dd, J = 8.7, 7.5 Hz, 1H, $\mathbf{H}_8$), 3.88 (s, 3H, $\mathbf{H}_{10}$) 3.57 (sextet, *J* = 7.5 Hz, 1H, $\mathbf{H}_7$), 1.36 (d, *J* = 6.9 Hz, 3H, $\mathbf{H}_9$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 167.0 (C, $\mathbf{C}_{10}$), 163.9 (C, $\mathbf{C}_1$) 132.7 (C, $\mathbf{C}_6$), 131.1 (CH, $\mathbf{C}_3$), 125.7 (CH, $\mathbf{C}_5$), 122.7 (C, $\mathbf{C}_4$), 109.1 (CH, $\mathbf{C}_2$), 79.4 (CH_2, $\mathbf{C}_8$), 51.8 (CH_3, $\mathbf{C}_{11}$), 35.9 (CH, $\mathbf{C}_7$), 19.4 (CH_3, $\mathbf{C}_9$).

LRMS: (EI) m/z = 164 $[M]^{\bullet+}$

4-Methylchromane



3.36

Chemical Formula: $C_{10}H_{12}O$

Molecular Weight: 148.21

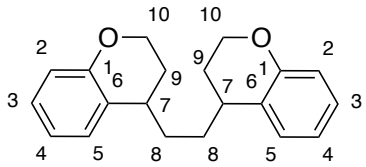
4-Methylchromane (**3.36**) was prepared by general method N: from Methyl 1-(but-3-en-1-yloxy)-2-iodobenzene (**3.15**) (0.274 g, 1.0 mmol), following purification by flash chromatography (0:10:90 to 5:10:85 Et_2O/toluene/hexane), 4-Methylchromane (0.123 g, 0.8 mmol, 83%) was isolated as a clear oil. The data are consistent with reported values.[390]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.17 (d, *J* = 7.9 Hz, 1H, $\mathbf{H}_5$), 7.10 (t, *J* = 7.9 Hz, 1H, $\mathbf{H}_4$), 6.88 (td, *J* = 7.9, 1.0 Hz, 1H, $\mathbf{H}_3$), 6.81 (dd, *J* = 7.9, 1.0 Hz, 1H, $\mathbf{H}_2$), 4.26 -4.16 (m, 2H, $\mathbf{H}_{10}$), 2.98 (sextet, *J* = 6.6 Hz, 1H, $\mathbf{H}_7$), 2.11 (ddd, J = 13.7, 7.7, 5.8 Hz, 1H, $\mathbf{H}_9$), 1.75 (dtd, *J* = 13.7, 6.7, 3.3 Hz, 1H, $\mathbf{H}_9$), 1.35 (d, *J* = 7.0 Hz, 3H, $\mathbf{H}_8$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 154.3 (C, $\mathbf{C}_1$), 128.6 (CH, $\mathbf{C}_5$), 127.6 (C, $\mathbf{C}_6$), 127.2 (CH, $\mathbf{C}_4$), 120.2 (CH, $\mathbf{C}_3$), 116.7 (CH, $\mathbf{C}_2$), 63.8 (CH_2, $\mathbf{C}_8$), 30.3 (CH_3, $\mathbf{C}_9$), 28.5 (CH, $\mathbf{C}_7$), 22.2 (CH_3, $\mathbf{C}_8$).

LRMS: (EI) m/z = 148 $[M]^{\bullet+}$

1,2-Di(chroman-4-yl)ethane



3.37

Chemical Formula: $C_{20}H_{22}O_2$

Molecular Weight: 294.39

1,2-Di(chroman-4-yl)ethane (**3.37**) was prepared by general method N: from Methyl 1-(but-3-en-1-yloxy)-2-iodobenzene (**3.15**) (0.274 g, 1.0 mmol), following purification by flash chromatography (0:10:90 to 5:10:85 Et_2O/toluene/hexane), 1,2-Di(chroman-4-yl)ethane (0.123 g, 0.1 mmol, 6%) was isolated as a clear oil. Novel compound.

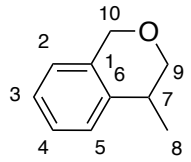
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.16 – 7.09 (m, 4H, $\mathbf{H}_{4,5}$), 6.90 – 6.85 (m, 2H, $\mathbf{H}_3$), 6.82 (d, *J* = 8.1, 1.1 Hz, 2H, $\mathbf{H}_2$), 4.25 – 4.17 (m, 4H, $\mathbf{H}_{10}$), 2.90 – 1.64 (m, 8H, $\mathbf{H}_{8,9}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 154.5 (C, $\mathbf{C}_1$), 154.5 (C, $\mathbf{C}_1$), 129.0 (CH, $\mathbf{C}_5$), 128.9 (CH, $\mathbf{C}_5$), 127.4 (CH, $\mathbf{C}_3$), 127.4 (CH, $\mathbf{C}_3$), 126.3 (C, $\mathbf{C}_6$), 126.2 (C, $\mathbf{C}_6$), 120.2 (CH, $\mathbf{C}_4$), 120.1 (CH, $\mathbf{C}_4$), 116.9 (CH, $\mathbf{C}_2$), 116.9 (CH, $\mathbf{C}_2$) , 63.5 (CH_2, $\mathbf{C}_{10}$), 63.5 (CH_2, $\mathbf{C}_{10}$) 34.0 (CH_2, $\mathbf{C}_9$), 33.8 (CH_2, $\mathbf{C}_9$), 33.6 (CH, $\mathbf{C}_7$), 33.4 (CH, $\mathbf{C}_7$), , 27.1 (CH_2, $\mathbf{C}_8$), 26.8 (CH_2, $\mathbf{C}_8$).

LRMS: (EI) m/z = 294 $[M]^{\bullet+}$

MP: 153.0 – 155.0 °C

4-Methylisochromane



3.39

Chemical Formula: $C_{10}H_{12}O$

Molecular Weight: 148.21

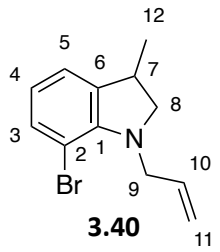
4-Methylisochromane (**3.39**) was prepared by general method N: from 1-((Allyloxy)methyl)-2-iodobenzene (**3.38**) (0.274 g, 1.0 mmol), following purification by flash chromatography (0:10:90 to 5:10:85 Et_2O/toluene/hexane), 4-Methylisochromane (0.126 g, 0.8 mmol, 85%) was isolated as a clear oil. The data are consistent with reported values.[391, 392]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.25 – 7.15 (m, 3H, $\mathbf{H}_{2,4,5}$), 6.99 (d, *J* = 7.5 Hz, 1H, $\mathbf{H}_2$), 4.80 (d, *J* = 5.7 Hz, 2H, $\mathbf{H}_{10}$), 4.98 (dd, *J* = 11.2, 4.5 Hz, 1H, $\mathbf{H}_9$), 3.69 (dd, *J* = 11.2, 5.4 Hz, 1H, $\mathbf{H}_9$), 2.95 (sextet, *J* = 6.6 Hz, 1H, $\mathbf{H}_7$), 1.32 (d, *J* = 7.1 Hz, 3H, $\mathbf{H}_8$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 138.7 (C, $\mathbf{C}_6$), 134.3 (C, $\mathbf{C}_1$), 127.7 (CH, $\mathbf{C}_2$), 126.5 (CH, $\mathbf{C}_4$), 125.9 (CH, $\mathbf{C}_3$), 124.2 (CH, $\mathbf{C}_5$), 71.4 (CH_2, $\mathbf{C}_9$), 68.4 (CH_2, $\mathbf{C}_{10}$), 31.9 (CH_3, $\mathbf{C}_7$), 19.3 (CH_3, $\mathbf{C}_8$).

LRMS: (EI) m/z = 148 $[M]^{\bullet+}$

1-Allyl-7-bromo-3-methylindoline



3.40

Chemical Formula: $C_{12}H_{14}BrN$

Molecular Weight: 252.16

1-Allyl-7-bromo-3-methylindoline (**3.40**) was prepared by general method N: from N,N-Diallyl-2,6-dibromoaniline (**3.24**) (0.331 g, 1.0 mmol), following purification by flash chromatography (0:10:90 to 5:10:85 Et_2O/toluene/hexane), 1-Allyl-7-bromo-3-methylindoline (0.139 g, 0.6 mmol, 55%) was isolated as a clear oil. Novel compound.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.16 – 7.12 (m, 2H, $\mathbf{H}_{4,5}$), 6.35 (d, *J* = 8.3 Hz, 1H, $\mathbf{H}_3$), 5.88 (ddt, *J* = 17.1, 10.2, 5.6 Hz, 1H, $\mathbf{H}_{10}$), 5.27 (dd, *J* = 17.1, 1.2 Hz, 1H, $\mathbf{H}_{11(E)}$), 5.21 (dd, *J* = 10.2, 1.2 Hz, 1H, $\mathbf{H}_{11(Z)}$), 3.77 – 3.71 (m, 1H, $\mathbf{H}_9$), 3.64 – 3.54 (m, 2H, $\mathbf{H}_{8,9}$), 3.29 (sextet, *J* = 7.5 Hz, 1H, $\mathbf{H}_7$), 2.89 (t, J = 8.6 Hz, 1H, $\mathbf{H}_8$), 1.30 (d, *J* = 7.1 Hz, 3H, $\mathbf{H}_{12}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 138.7 (C, $\mathbf{C}_6$), 134.3 (C, $\mathbf{C}_1$), 127.7 (CH, $\mathbf{C}_2$), 126.5 (CH, $\mathbf{C}_4$), 125.9 (CH, $\mathbf{C}_3$), 124.2 (CH, $\mathbf{C}_5$), 71.4 (CH_2, $\mathbf{C}_9$), 68.4 (CH_2, $\mathbf{C}_{10}$), 31.9 (CH_3, $\mathbf{C}_7$), 19.3 (CH_3, $\mathbf{C}_8$).

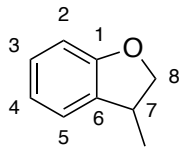
LRMS: (EI) m/z = 253 $[M]^{\bullet+}$ (Br^{81})

N.b. Other cyclised substrates prepared in Table 3.11 not included in this section were isolated and characterised by Mateo Salam–Perez of Prof. Richard Brown's research group, University of Southampton.

4.3.5.3 General method O: reductive cyclisation (catalytic phenanthrene, lower flow rate)

Aryl halides were reductively cyclised to the respective dihydrobenzofurans, indolines and tetrahydrobenzopyrans in the Ammonite 8 reactor, using optimised conditions developed by Dr Ana Folgueiras: A solution of aryl halide (1.0 mmol), phenanthrene (0.0089 g, 0.05 mmol) and Bu_4NI (0.185 g, 0.5 mmol) in MeCN (40 mL) was prepared, degassed under argon for 20 minutes, and passed through the Ammonite 8 flow reactor (glassy carbon anode, SS cathode, 2 mL min^{-1}, 160 mA (2.0 F/mol). Removal of solvent under reduced pressure afforded the crude product that was purified by flash chromatography or Kügelrohr distillation.

3-Methyl-2,3-dihydrobenzofuran



3.27

Chemical Formula: $C_9H_{10}O$

Molecular Weight: 134.18

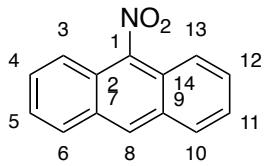
3-Methyl-2,3-dihydrobenzofuran (**3.27**) was prepared by general method O: from 1-(Allyloxy)-2-iodobenzene (**2.156**) (0.260 g, 1.0 mmol), 3-Methyl-2,3-dihydrobenzofuran was found to be present in the outlet solution (81% yield by calibrated GC).

Using the same method, from 1-(Allyloxy)-2-bromobenzene (**3.14**) (0.213 g, 1.0 mmol), 3-Methyl-2,3-dihydrobenzofuran was found to be present in the outlet solution (59% yield by calibrated GC).

Using the same method, from 1-(Allyloxy)-2-chlorobenzene (**3.17**) (0.169 g, 1.0 mmol), 3-Methyl-2,3-dihydrobenzofuran was found to be present in the outlet solution (51% yield by calibrated GC).

4.3.6 Mediator syntheses

9-Nitroanthracene



3.51

Chemical Formula: $C_{14}H_9NO_2$

Molecular Weight: 223.23

9-Nitroanthracene **3.51** was prepared by literature procedure, following the work of Hirano *et al.*[393] Conc. HNO_3 (69% w/v) (0.40 mL) was added dropwise to a suspension of Anthracene (0.89 g, 5 mmol) in glacial acetic acid (4 mL). The mixture was stirred at rt for 4 hours and then a mixture of conc. HCl (5 mL) and glacial acetic acid (5 mL) was added to the solution slowly to give yellow sticky precipitate. The precipitate was collected by filtration and washed with distilled

water (3 x 5 mL) until the filtrate became neutral. Recrystallisation of the yellow solid from glacial acetic acid gave the desired product as fine yellow needles (0.84 g, 3.8 mmol, 76%). The data are consistent with reported values.[393]

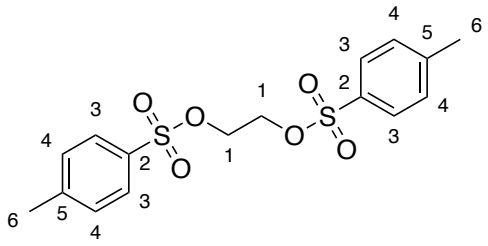
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 8.63 (s, 1H, $\mathbf{H}_8$), 8.08 (br. d, *J* = 8.6 Hz, 2H, $\mathbf{H}_{3,13}$), 7.96 (ddd, *J* = 8.9, 1.8, 1.0 Hz, 2H, $\mathbf{H}_{6,10}$), 7.66 (ddd, *J* = 8.9, 6.6, 1.0 Hz, 2H, $\mathbf{H}_{4,12}$), 7.58 (ddd, *J* = 7.6, 6.6, 1.0 Hz, 2H, $\mathbf{H}_{5,11}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 130.8 (2C, $\mathbf{C}_{7,9}$), 130.4 (C & CH, $\mathbf{C}_{1,8}$), 128.9 (CH, $\mathbf{C}_{6,10}$), 128.4 (CH, $C_{4,12}$), 126.2 (CH, $\mathbf{C}_{5,11}$), 122.7 (2C, $\mathbf{C}_{2,14}$), 121.4 (2CH, $\mathbf{C}_{3,13}$).

LRMS: (EI) m/z = 223 $[M]^{\bullet+}$

MP: 145 –146 °C (Lit:[394] 153 – 157 °C)

Ethane-1,2-diyl bis(4-methylbenzenesulfonate)



4.22

Chemical Formula: $C_{16}H_{18}O_6S_2$

Molecular Weight: 370.43

Ethane-1,2-diyl bis(4-methylbenzenesulfonate) (**4.22**) was prepared by literature procedure for sulfonate formation:[395] A solution of Tosyl chloride (6.7 g, 35.2 mmol) in CH_2Cl_2 (10 mL) was added to a solution of ethylene glycol (0.89 mL, 16 mmol) and Et_3N (6.6 mL) in CH_2Cl_2 (66 mL) at 0 °C. The reaction was allowed to warm to rt and stirred for 16 hours, then concentrated to ½ volume. Cooling on ice caused solids to precipitate. The solids were filtered, washing with Et_2O (2 x 10 mL). Recrystallisation from $CHCl_3$/ MeOH afforded the title compound (5.33 g, 90%) as a white solid. The data are consistent with reported values.[395, 396]

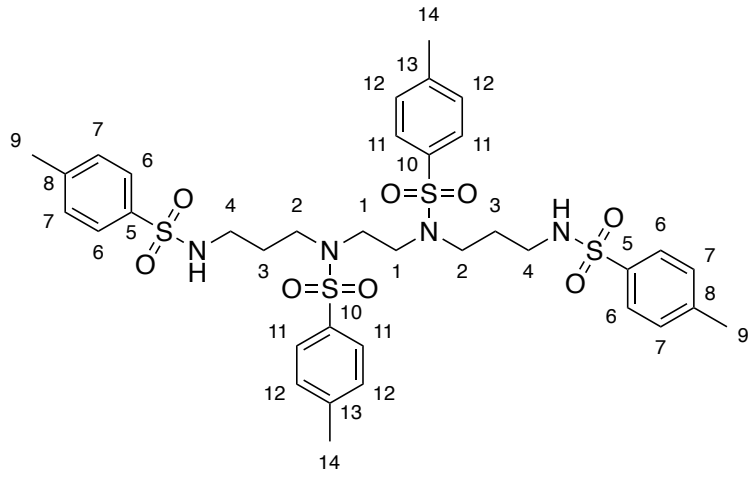
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.74 (d, *J* = 8.4 Hz, 4H, $\mathbf{H}_3$), 7.35 (d, *J* = 8.4 Hz, 4H, $\mathbf{H}_4$), 4.19 (s, 4H, $\mathbf{H}_1$), 2.47 (s, 6H, $\mathbf{H}_6$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 145.3 (2C, $\mathbf{C}_2$), 132.3 (2C, $\mathbf{C}_5$), 130.0 (2CH, $\mathbf{C}_4$), 128.0 (2CH, C_3), 66.7 (2CH_2, $\mathbf{C}_1$), 21.7 (2CH_3, $\mathbf{C}_6$).

LRMS: (ESI+) m/z = 393 $[M+Na]^+$

MP: 125 –126 °C (Lit:[396] 125 – 126 °C)

N,N'-(Ethane-1,2-diyl)bis(4-methyl-N-(3-((4-methylphenyl)sulfonamido)propyl)benzenesulfonamide)



4.23

Chemical Formula: $C_{36}H_{46}N_4O_8S_4$

Molecular Weight: 791.02

N,*N*'-(Ethane-1,2-diyl)bis(4-methyl-*N*-(3-((4-methylphenyl)sulfonamido)propyl)benzenesulfonamide) (**4.23**) was prepared by literature procedure for sulfonamide formation:[397] Tosyl chloride (12.4 g, 65 mmol) was added in portions to a biphasic mixture of *N*1,*N*1'-(Ethane-1,2-diyl)bis(propane-1,3-diamine) (2.78 g, 15 mmol) in Et_2O (50 mL) and 10% aq. NaOH (25 mL). The mixture was stirred at rt for 16 hours over which time solids precipitated. The mixture was filtered, washing with Et_2O furnished the title compound (11.2 g, 94%) as a white solid. The data are consistent with reported values.[397, 398]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.73 (d, *J* = 8.4 Hz, 4H, $\mathbf{H}_6$), 7.67 (d, *J* = 8.4 Hz, 4H, $\mathbf{H}_{11}$), 7.33 (d, *J* = 8.4 Hz, 4H, $\mathbf{H}_{12}$), 7.29 (d, *J* = 8.4 Hz, 4H, $\mathbf{H}_7$), 5.33 (br. t, *J* = 6.7 Hz, 2NH), 4.19 (s, 4H, $\mathbf{H}_1$), 3.23 (s, 4H, H_2), 3.15 (t, *J* = 6.7 Hz, 8H, H_2), 2.98 (q, *J* = 6.7 Hz, 8H, H_4), 2.44 (s, 6H, $\mathbf{H}_{9/14}$), 2.42 (s, 6H, $\mathbf{H}_{9/14}$), 1.80 (quin, *J* = 6.7 Hz, 8H, H_3).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 143.9 (2C, $\mathbf{C}_{10}$), 143.4 (2C, $\mathbf{C}_5$), 136.7 (2C, $\mathbf{C}_{8/13}$), 136.1 (2C, $\mathbf{C}_{8/13}$), 130.0 (2CH, $\mathbf{C}_{11}$), 129.7 (2CH, $\mathbf{C}_{12}$), 127.2 (2CH, C_{11}), 127.0 (2CH, C_6), 48.9 ($2CH_2$, $\mathbf{C}_1$), 47.1 ($2CH_2$, $\mathbf{C}_2$), 40.0 ($2CH_2$, $\mathbf{C}_4$), 29.0 ($2CH_2$, $\mathbf{C}_3$), 21.5 ($2CH_3$, $\mathbf{C}_{9/14}$), 21.5 ($2CH_3$, $\mathbf{C}_{9/14}$).

LRMS: (ESI+) m/z = 814 $[M+Na]^+$

MP: 146 – 147 °C (Lit:[398] 153 – 157 °C

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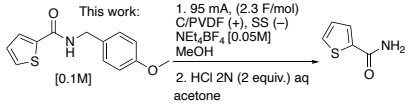
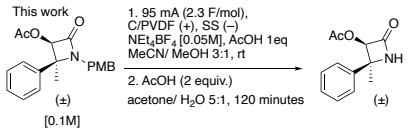
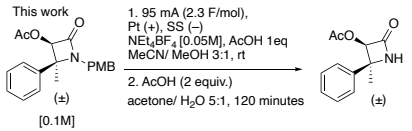
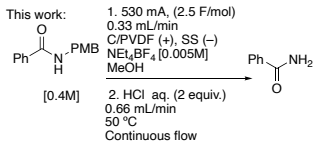
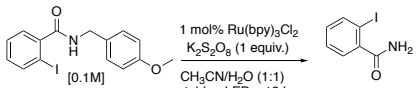
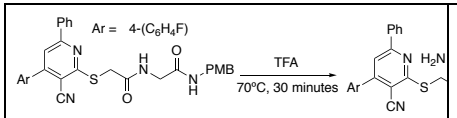
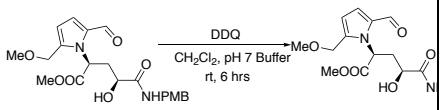
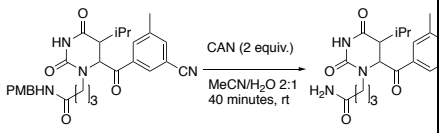
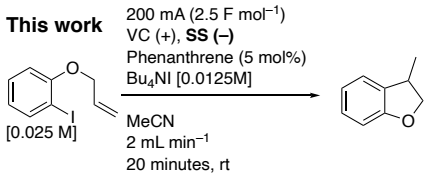
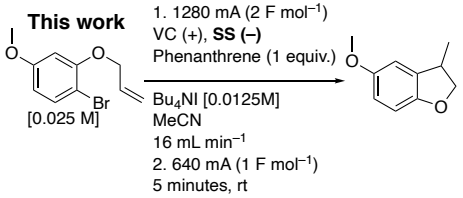
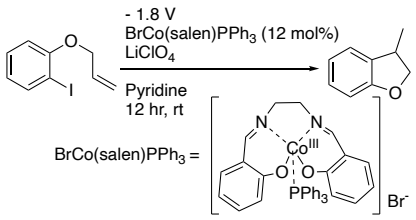
Appendix A Green metrics of PMB deprotection process in this work and literature

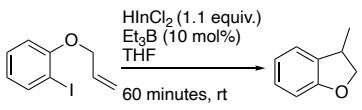
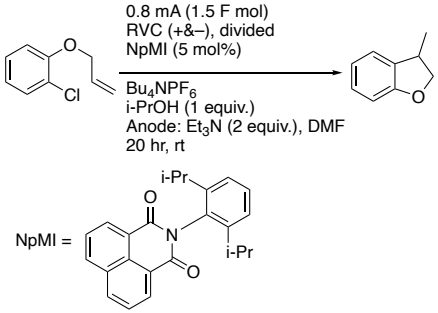
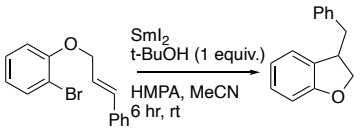
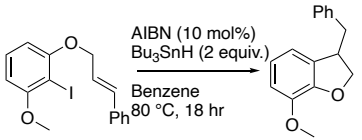
Reaction and conditions	Yield (%)	Scale (g)	Atom economy (%)	RME[a]	PMI[b]	PMI[c]	Hazardous/ precious chemicals	Solvent	Ref.
	91●	0.12	44.8 ●	36.3	3.7	144	-●	MeOH, acetone ●	n/a (this work)
	70●	0.15	54.9●	29.7	4.1	109	-●	AcOH, MeCN●	n/a (this work)
	79●	0.17	54.9	33.3	3.6	96.6	-●	AcOH, MeCN●	n/a (this work)
	83●	0.20	43.6●	36.1	2.8	44.6	-●	MeOH, H_2O●	n/a (this work)
	90●	0.22	38.8 ●	34.5	3.2	40.2	Ru● 5-50 years of known reserves[d]	MeCN, H_2O●	199

	52●	0.021	64.2 ●	2.9	34.8	243	TFA● H412: environmental concerns	TFA●	200
	86●	0.0009	46.2 ●	20.5	4.9	567	DDQ● H301: acute toxicity	CH_2Cl_2●	201
	75 ●	0.125	76.2 ●	18.5	46.7	41.2	CAN● Ce: 50-500 years of known reserves.[d] H410: environmental concerns	MeCN, H_2O●	202

a. RME is Reaction Mass Efficiency (no. moles product/no. moles reagents),
b. PMI is Process Mass Intensity (mass of product/mass of materials). With respect to reactant, reagents, catalysts used
c. PMI with respect to solvents used
d. Based on current rate of extraction[163]

Appendix B Green metrics of reductive cyclisation process in this work and literature

Reaction and conditions	Yield (%)	Scale (g)	Atom economy %	RME[a]	PMI[b] reagents	PMI[b] solvents	Hazardous/ precious chemicals	Solvent	Ref
This work 	86●	0.12	52●	25.8	3.9	273	Phenanthrene● H410[d]	MeCN●	n/a
This work 	91●	0.15	68●	34.9	4.1	210	Phenanthrene● H410[d]	MeCN●	n/a
	45●	0.06	52●	13.0	5.9	8.2	Co●, Hg● Co: 50-500 years of reserves[c] Hg: H330[f], 360[e], 372[e], 410[d]	Pyridine●	262

	93●	0.13	52●	26.3	3.8	71.1	$HInCl_2$● In: 5–50 years of reserves[c]	THF●	243
	54●	0.29	79●	4.3	23.3	331.2	–●	DMF, Et_3N●	250
	89●	0.028	73●	5.2	19.3	362.6	SmI_2● Sm: 50–500 years of reserves[c]	HMPA●, MeCN●	244
	88●	0.21	66●	21.9	4.6	208	$SnBu_3H$●, AIBN● Sn: 5–50 years of reserves[c] H372[c], 360FD[e], 410[b]	Benzene●	239

a. RME is Reaction Mass Efficiency (no. moles product/no. moles reagents),
b. PMI is Process Mass Intensity (mass of product/mass of materials)
c. Based on current rate of extraction[163]