# Electrochemical Carbon-Carbon Bond Formation using Carboxylic Acids and Redox Active Esters

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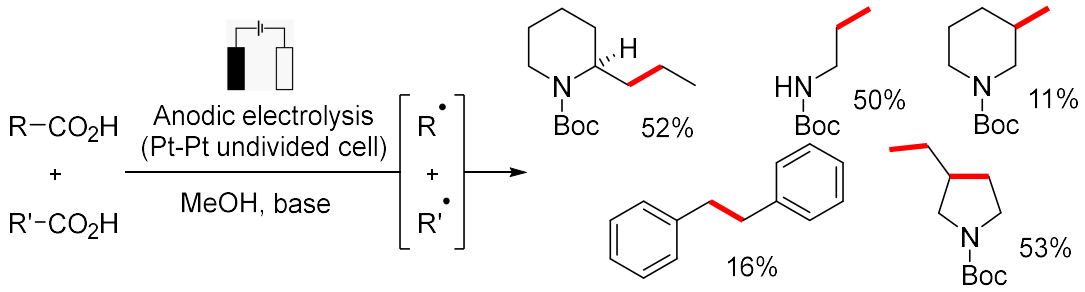
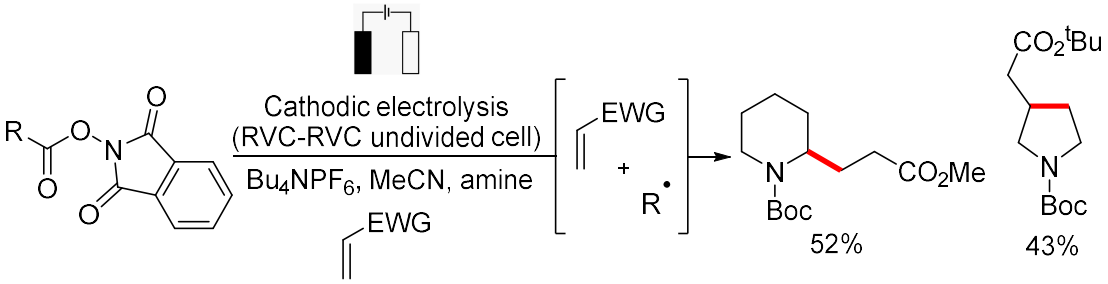
# Abstract

Synthetic organic electrochemistry is a versatile tool for carbon-carbon bond formation. In this thesis, an electrochemical approach to generate carbon-centred radicals and subsequent reactions is described. In Chapter 1, a brief literature overview of oxidative and reductive synthetic electrochemical reactions is presented.

Chapter 2 details the anodic oxidation of carboxylic acids using a Kolbe electrolysis approach and the heterocoupling of the so-generated carbon-centred radicals. After a detailed summary of the background literature, the development of a bespoke electrochemical cell, an investigation of the scope and limitations of heterocoupling on nitrogen-containing substrates and cyclisation-heterocoupling reactions are discussed. It was found that primary carboxylic acids worked best whereas secondary carboxylic acids were lower yielding due to over-oxidation of the secondary radical at the anode. Selected results are summarised below.




In Chapter 3, the cathodic reduction of redox active *N*-hydroxyphthalimide esters to form carbon-centred radicals and subsequent radical heterocoupling or addition to electron deficient alkenes is described. The heterocoupling approach was not very successful. In contrast, a procedure for electrochemical radical generation and addition to methyl acrylate was developed. In order to minimise a competitive electrochemical process, novel NHP esters with different aromatic groups attached were designed and explored with some success. Cyclic voltammetry and mechanistic studies were performed to understand this transformation in more detail. Selected results are summarised below.



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Finally, a special thanks to Liam, who has been by my side throughout. He has given me endless love and encouragement throughout the good times and the bad. I owe this achievement to him.

## Author's Declaration

I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as References.

Sophie Berrell

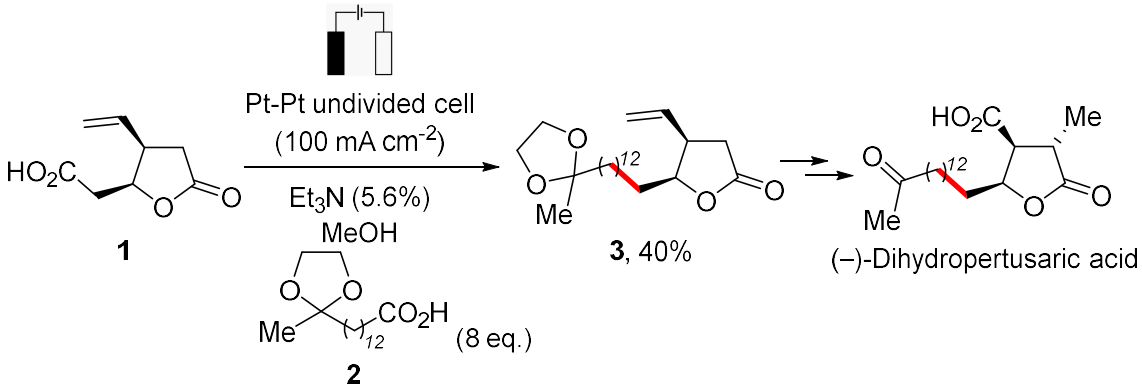
# Chapter 1: Introduction

It is now well established that electrochemistry is a valuable method for the synthesis of new carbon-carbon bonds. Since Faraday's pioneering work in the 1830s,[1] electrochemistry has proven to be a diverse and useful method for organic synthesis. In particular, in the last 5-10 years, there has been a so-called "renaissance" in electrochemical organic synthesis. Baran has been one of the key figures in this recent popularisation of synthetic electrochemistry and the developments since 2000 were reviewed by his group in late 2017,[2] an article that has already been cited over 600 times. In its basic form, electrochemistry involves the addition or removal of an electron to a substrate through an applied electrical potential. As a result, a wide range of oxidative and reductive methodology has been developed.

The results of the research described in this thesis are contained in two chapters, each focusing on methods for carbon-carbon bond formation on scaffolds of relevance to medicinal chemistry. In Chapter 2, our efforts on the development of an oxidative method, namely the anodic decarboxylation of carboxylic acids and heterocoupling of the generated radicals, is described. In contrast, in Chapter 3, the focus is on the reductive cathodic decarboxylation of redox active esters and addition of the generated radicals to electron deficient alkenes. Each chapter is accompanied by its own comprehensive literature review section. As a result, in Chapter 1, a brief overview of important and representative synthetic transformations mediated by anodic oxidation or cathodic reduction are presented in order to set the scene and context for the research described in this thesis.

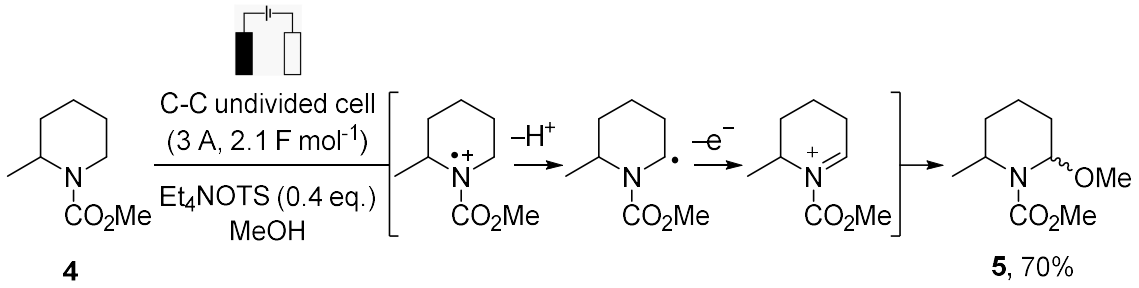
## 1.1 Selected Synthetic Transformations Using Anodic Oxidation

One of the most famous synthetic electrochemical transformations is the anodic oxidation of carboxylic acids to access alkyl radicals and subsequent radical homo- or heterocoupling. This process is known as Kolbe electrolysis.[3] One example of Kolbe electrolysis heterocoupling was performed by Renaud *et al.* during studies on the synthesis of (−)-dihydropertusaric acid.[4] Acids **1** and **2** were electrolysed in MeOH with platinum electrodes to give heterocoupled lactone **3** in 40% yield (Scheme 1.1). For this transformation, an undivided cell with platinum electrodes was used. A large current density was required for the reaction to complete, which is typical of Kolbe electrolysis.[5] Lactone **3** was then used to complete a synthesis of (−)-dihydropertusaric acid. Kolbe electrolysis and its mechanistic features are discussed in detail in Chapter 2.



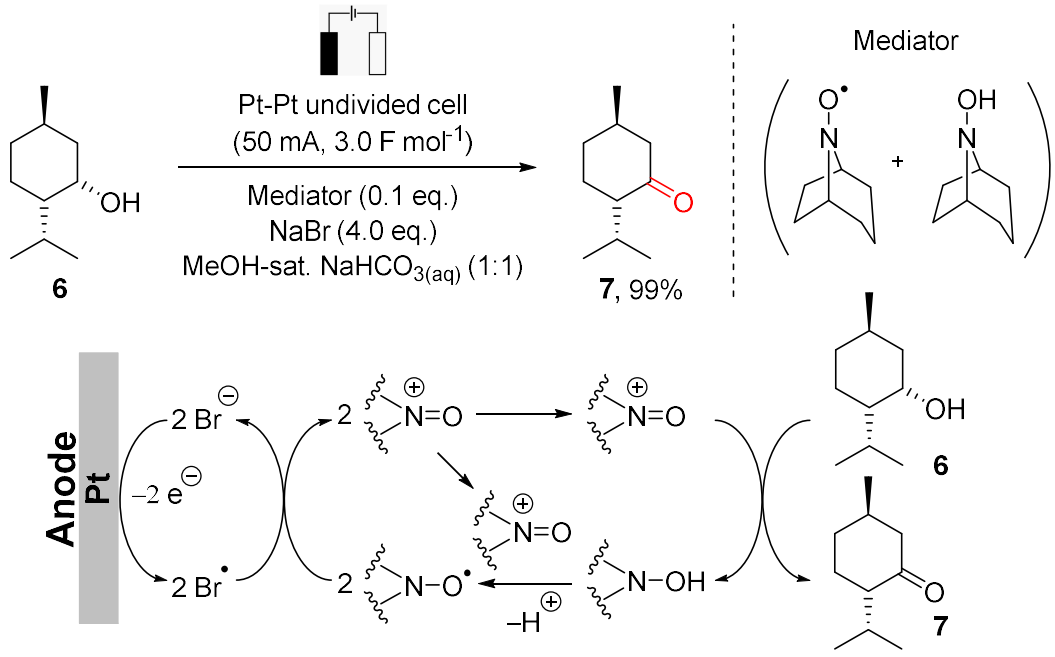

Scheme 1.1

Anodic oxidation has been used for α-methoxylation adjacent to a heteroatom, most commonly nitrogen and oxygen, *via* a method known as Shono oxidation.[6] As an example, Shono *et al*. reported the electrochemical oxidation of methyl carbamate **4** in the presence of MeOH to give α-methoxy piperidine **5** in 70% yield (Scheme 1.2). An undivided cell with carbon electrodes and $Et_4NOTs$ as electrolyte were used. Mechanistically, oxidation of carbamate **4** gives a radical cation which can be deprotonated to yield a radical intermediate. Further oxidation of the radical to an iminium ion, followed by nucleophilic attack by the MeOH solvent, gives α-methoxy piperidine **5**.



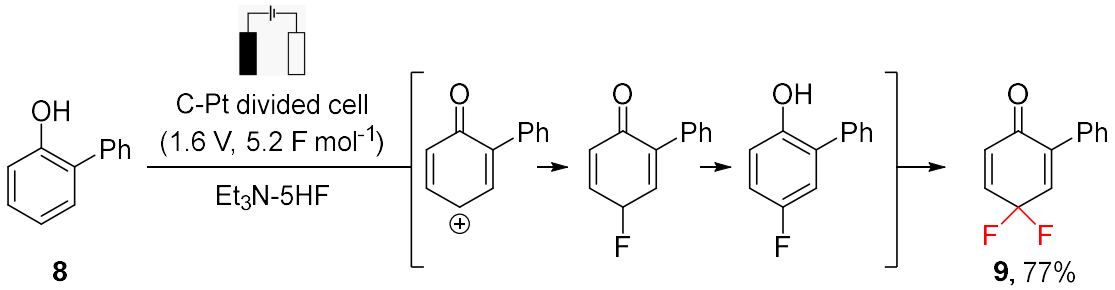

Scheme 1.2

There are many examples of the electrochemical oxidation of alcohols to ketones. Direct oxidation of alcohols require very high potentials.[7] A way to overcome this is to use an indirect electrolysis approach, by using mediators. Mediators are redox catalysts that transport electrons between the electrode and the substrate. One example, described by Onomura *et al.*,[8] is shown in Scheme 1.3. Nitroxyl-mediated electrochemical oxidation of alcohol **6** to ketone **7** was performed in 99% yield. An undivided cell with platinum electrodes and a double mediator system were used. The mechanism is shown in Scheme 1.3. The bromide is oxidised to give a bromide radical, which in turn oxidises the nitroxyl radical to an oxoammonium species which acts as the reactive oxidant for alcohol **6**. A biphasic solvent mixture was used as nitroxyl mediators can be sparingly soluble in polar solvents.[2] This then allows the bromide to be oxidised in the aqueous phase, and the nitroxyl oxidation occurs at the aqueous/organic phase interface.



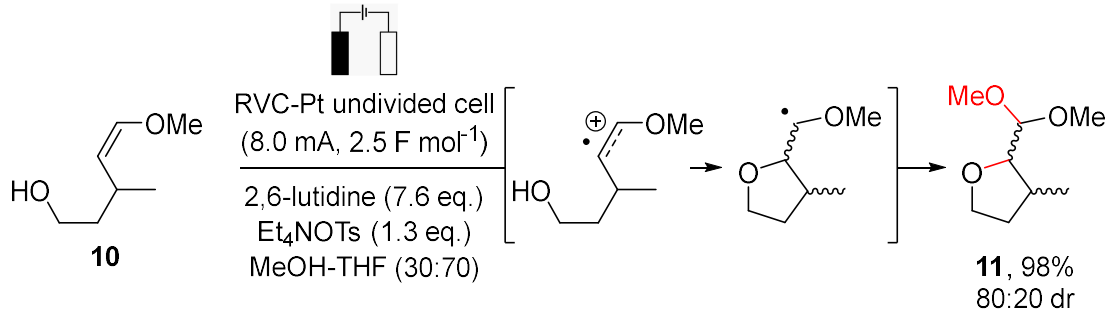

Scheme 1.3

Fluorination can be performed electrochemically. For example, Hara *et al*. fluorinated phenol **8** to form difluorocyclohexadienone **9** in 77% yield (Scheme 1.4).[9] For this transformation, a divided cell with a carbon anode and platinum cathode was used with $Et_3N$-HF as solvent and electrolyte. The authors also noted that slow addition of the phenol throughout the electrolysis was required in order to avoid polymerisation at the anode surface. In terms of the mechanism, phenol **8** can be oxidised twice to form a cation, which can then be attacked by a fluoride ion present in the solution. After rearomatisation, this process can be repeated to give difluorosubsituted cyclohexadienone **9**.



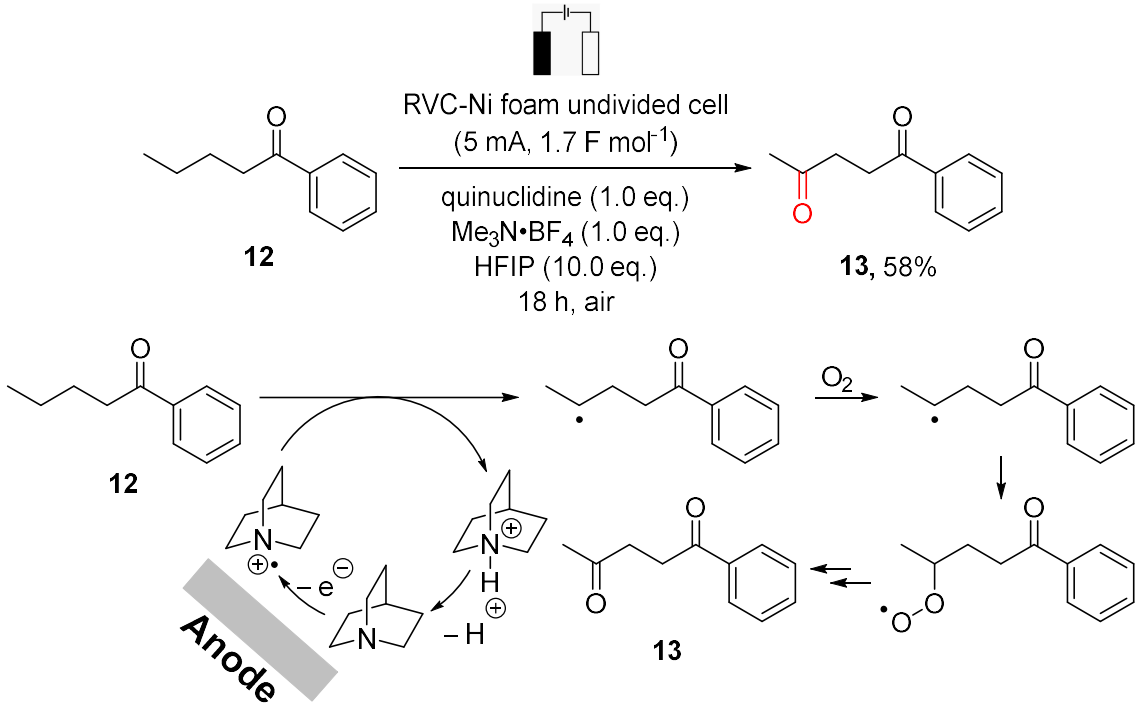

Scheme 1.4

Electron rich alkenes can be oxidised electrochemically to facilitate subsequent synthetic transformations. As an example of this strategy, Moeller *et al*. described the synthesis of tetrahydrofuran **11** from enol ether **10** in 98% yield (80:20 dr) (Scheme 1.5).[10] An undivided cell was used with a reticulated vitreous carbon (RVC) anode, a platinum cathode and $Et_4NOTs$ electrolyte. In the mechanism, the alkene was oxidised to a radical cation which was trapped by the alcohol to give a cyclised radical intermediate. Oxidation of the radical to a cation is facile as it is α to oxygen and subsequent quenching by the MeOH solvent gives tetrahydrofuran **11**.




Scheme 1.5

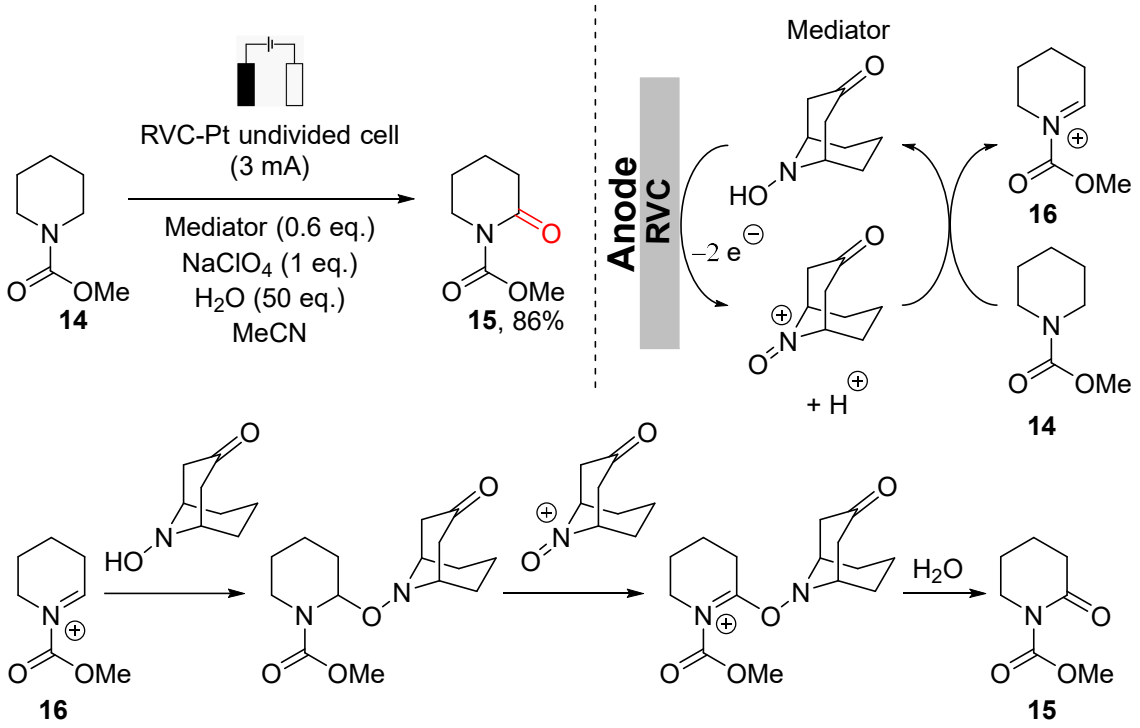
Unactivated carbon-hydrogen bonds can also be oxidised at the anode but this is challenging since they have a high redox potential (typically above 2.5 V).[11] At such high potentials, detrimental oxidation to other functional groups and solvents could occur instead. Baran *et al*. overcame this problem by using a mediator.[12] Using their procedure, alkane **12** was oxidised to diketone **13** in 58% yield when using quinuclidine as the mediator (Scheme 1.6). In this case, an undivided cell was used containing an RVC anode, a nickel foam cathode and $Me_3N.BF_3$ as electrolyte. The mechanism for the oxidation of alkane **12** to ketone **13** first involved the oxidation of quinuclidine at the anode to give a radical cation. This radical cation cleaves a carbon-hydrogen bond on the γ position relative to the carbonyl to generate protonated quinuclidine and an alkane radical. The alkane radical is then oxidised by molecular oxygen with further oxidation giving diketone **13**.




Scheme 1.6

Recently, Stahl *at al*. published an electrochemical approach to the oxidation of carbamates *via* a Shono-type oxidation.[13] Piperidine **14** was electrolysed in the presence of an aminoxyl mediator to give piperidinone **15** in 86% yield (Scheme 1.7). In this case, an aminoxyl mediator was used to lower the required potential required for the electrolysis. Piperidine **14** has an oxidation potential of 1.6 V (vs $Fc/Fc^+$) whereas that of

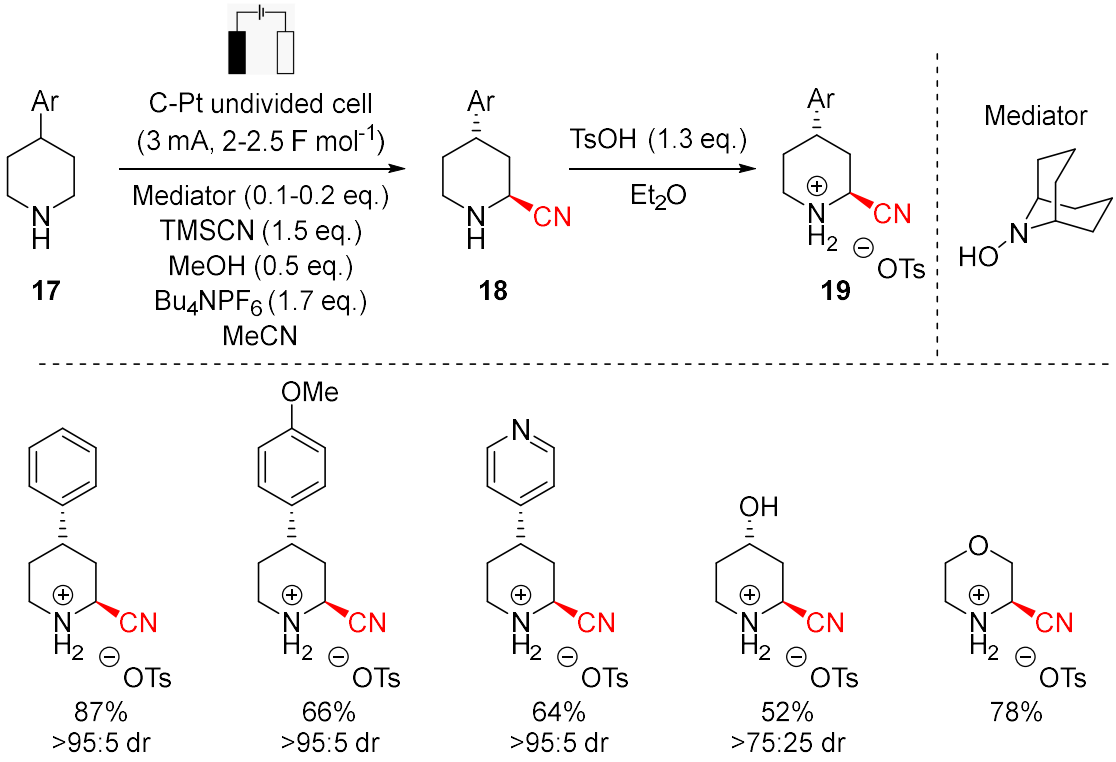
aminoxyl mediator is much lower at 0.45 V (vs $Fc/Fc^+$). This means that more functional groups will be tolerant to the electrolysis conditions. The set-up consisted of an undivided cell containing an RVC anode, platinum cathode and $NaClO_4$ as electrolyte. The mechanism for this oxidation is shown in Scheme 1.7. The aminoxyl mediator is oxidised at the anode to give an oxoammonium species that in turn, oxidises piperidine **14** to iminium ion **16**. Iminium ion **16** is attacked by the aminoxyl mediator, and subsequently oxidised a second time *via* another oxoammonium species to give a second iminium ion. Then, hydrolysis of the iminium ion gives piperidine **15**.




Scheme 1.7

Stahl *et al*. also reported the α-cyanation of secondary piperidines (Scheme 1.8).[14] Using an adapted method of their previous work shown in Scheme 1.7, piperidines **17** were oxidised in the presence of an aminoxyl mediator and TMSCN to give nitriles **18** which were isolated as tosylate salts **19**. A graphite anode and platinum cathode were used for this transformation in an undivided cell. The mechanism for this reaction involves the oxidation of the mediator to an oxoammonium species which oxidises piperidine **17** to an iminium ion (see Scheme 1.7 for a similar mechanism). Once the iminium ion is formed, it is trapped by cyanide to form nitriles **18**. The α-cyanation of various aromatic

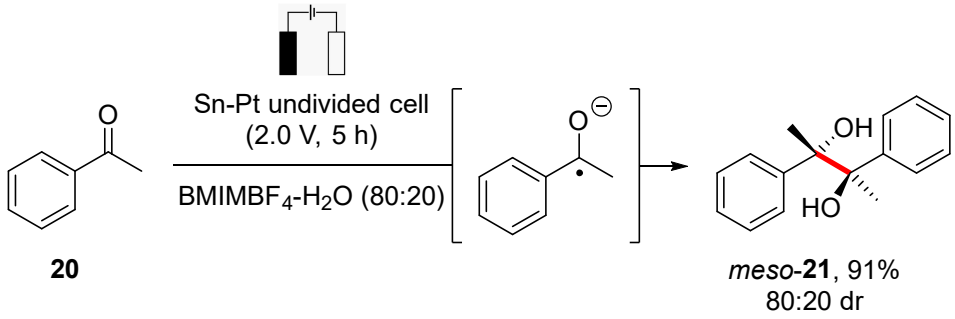
containing piperidines in excellent diastereomeric ratios was described, and it was found that the transformation even tolerated alcohols and ethers.




Scheme 1.8

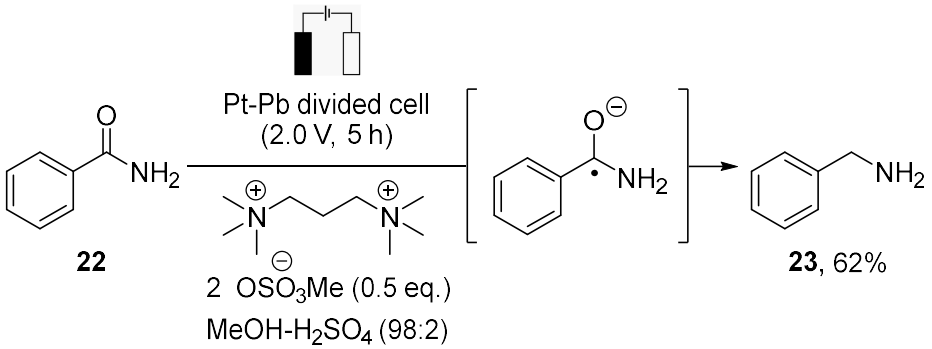
## 1.2 Selected Synthetic Transformations Using Cathodic Reduction

Electrochemical reduction of ketones is a useful technique to generate ketyl radical anions. Manchanayakage *et al*. performed the reduction of ketone **20** to give homocoupled diol *meso*-**21** in 91% yield (80:20 dr) (Scheme 1.9).[15] An undivided cell with a sacrificial tin anode and a platinum cathode was used. A sacrificial tin anode was used since the tin salts that are generated can be Lewis acidic and can coordinate to the carbonyls.[16] An ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate ($BMIMBF_4$), was employed to replace the use of volatile organic solvents and electrolyte. Mechanistically, ketone **20** is reduced to a ketyl radical anion, which homocouples to give diol *meso*-**21**.



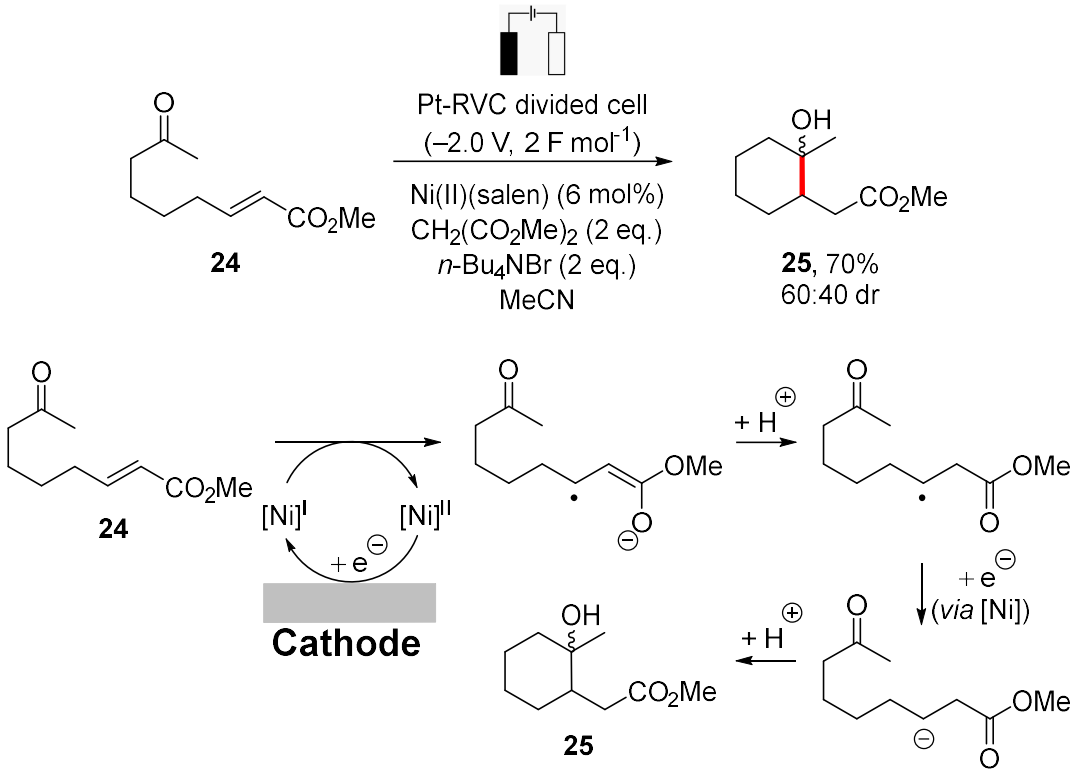

Scheme 1.9

The reduction of amides to amines can also be performed electrochemically. Waldvogel *et al*. electrochemically reduced amide **22** to amine **23** in 62% yield using a lead cathode, platinum anode and a diammonium salt as electrolyte (Scheme 1.10).[17] As amides have a high reduction potential, the reduction of hydrogen ions to hydrogen needed to be minimised. This was achieved by using a lead cathode, which has a very high overpotential for hydrogen evolution. A mechanism was not proposed by the authors but likely includes sequential one-electron reduction of the carbonyl group of amide **22** to give a radical anion.



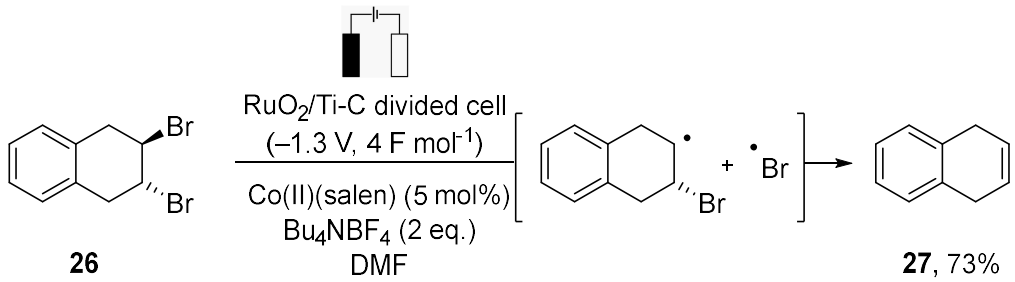

Scheme 1.10

Electron poor alkenes can undergo electrochemical reduction. For example, Little *et al*. reported the conversion of keto-alkene **24** into cyclohexanols **25** in 70% yield (60:40 dr) via a process which started with electrochemical alkene reduction (Scheme 1.11).[18] A divided cell was used with an RVC cathode, platinum anode and $Bu_4NBr$ as electrolyte. In this case, a nickel mediator, *N*,*N*'-bis(salicylidine)ethylenediaminonickel(II), (Ni(II)(salen)), was used. During the reaction, the Ni(II) is reduced to Ni(I) which in turn reduces alkene **24** to a radical anion. This radical anion is stabilised by the adjacent carbonyl group. After protonation and another reduction to a carbanion *via* Ni(I), cyclisation occurs to give cyclohexanols **25**.




Scheme 1.11

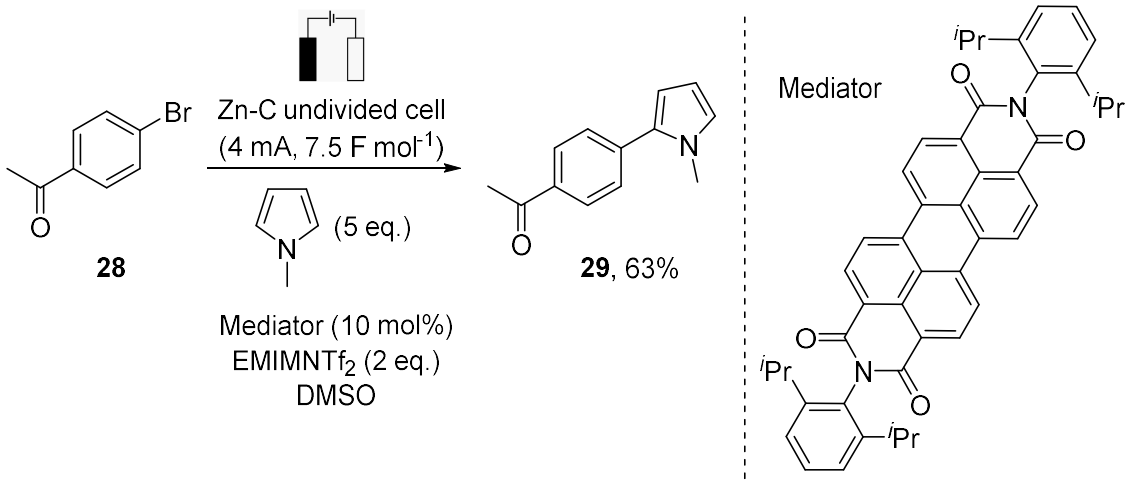
Alkyl halides can be reduced electrochemically. For example, Atobe *et al*. reduced alkyl bromide **26** with a cobalt mediator to give alkene **27** in 73% yield (Scheme 1.12).[19] The authors used a divided cell with a carbon cathode and a $RuO_2$/Ti anode. A mixed metal anode gave better results than a platinum anode in this case, although no explanation was proposed. For this reaction, Co(II) is reduced to Co(I) which reduces alkyl bromide **26** to a radical intermediate. Reduction of the radical intermediate to a carbanion and subsequent elimination of a bromide ion generates alkene **27**.




Scheme 1.12

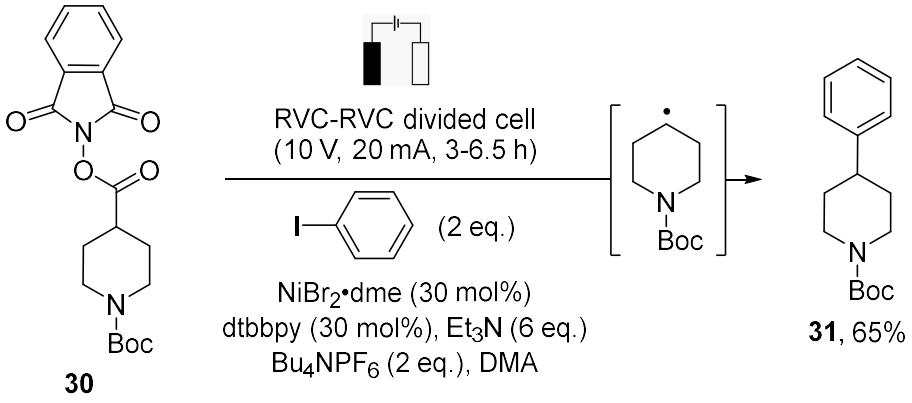
Aryl halides can be electrochemically reduced. Zhu *et al*. reduced aryl bromide **28** with a perylene mediator and reacted it with *N*-methyl pyrrole to give functionalised pyrrole **29**

in 63% yield (Scheme 1.13).[20] An undivided cell was used with a carbon cathode, a sacrificial zinc anode and 1-ethyl-3-methylimidazolium bis((trifluoromethyl)sulfonyl)-imide, $EMIMNTf_2$, as the electrolyte. Reduction of aryl bromide **28**, *via* initial reduction of the perylene mediator, gave an aryl radical which then attacks the pyrrole to ultimately generate functionalised pyrrole **29**.




Scheme 1.13

As a final example of cathodic reduction transformations, redox active esters have been reduced electrochemically. For example, Jamison *et al*. electrolysed a *N*-hydroxyphthalimide (NHP) ester **30** to give a carbon centred radical which then participated in a nickel-catalysed cross-coupling reaction with iodobenzene to give 4-phenyl *N*-Boc piperidine **31** in 65% yield (Scheme 1.14).[21] For this transformation, an undivided cell with RVC electrodes with $Bu_4NPF_6$ as electrolyte, $Et_3N$ as a sacrificial oxidant and a nickel catalyst and ligand were used. The use of redox active esters and this procedure are discussed in more detail in Chapter 3 as it formed the basis of the results described in that chapter.

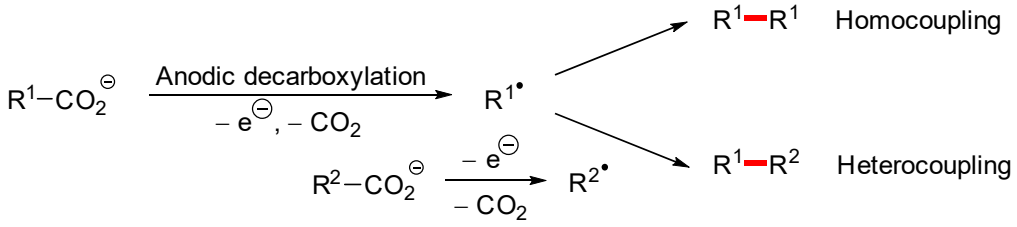



Scheme 1.14

As shown in the brief overview presented in the previous two sections, electrochemistry can be used as a way of carrying out a wide range of synthetic transformations. In addition, this overview showed how electrochemistry can be tailored in multiple ways to obtain the best results. Electrode material, voltage, use of mediators and type of electrochemical cell are just some of the conditions that can be changed to achieve a specific reaction. This thesis delves into more detail for both oxidative and reductive synthetic electrochemistry and our contribution to the field.

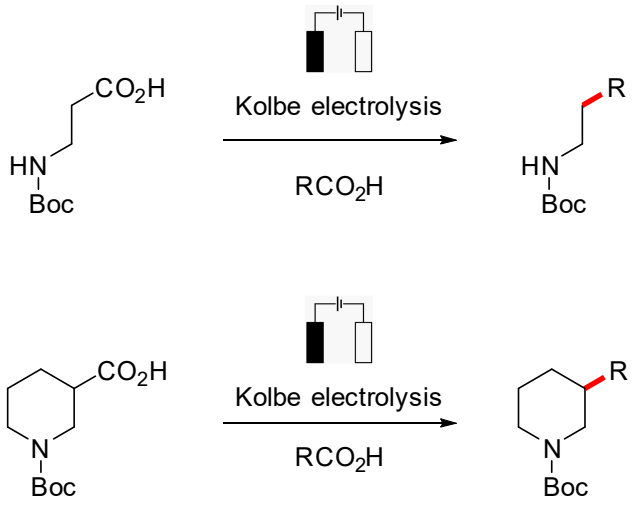
# Chapter 2: Anodic Decarboxylation of Carboxylic Acids for Carbon-Carbon Bond Formation

This Chapter is concerned with the anodic decarboxylation of carboxylic acids and subsequent radical coupling using a Kolbe electrolysis approach (Scheme 2.1). In the first part of this Chapter, an overview of the previous examples of radical generation using anodic decarboxylation and use in synthesis is presented. In particular, this overview focuses on the typical reaction conditions that are used for Kolbe homo- and heterocoupling reactions.




Scheme 2.1

In Section 2.2, generation of a bespoke electrochemical cell and the efforts on performing Kolbe homocoupling reactions are discussed. The next few sections detail the work performed on Kolbe heterocoupling reactions involving nitrogen containing substrates (Scheme 2.2). The scope and limitations of this transformation are then described.

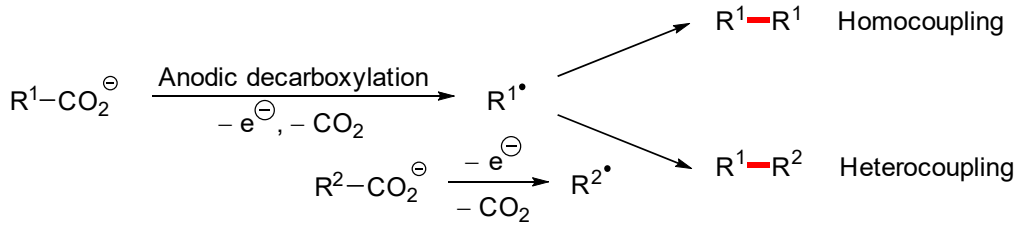



Scheme 2.2

## 2.1 Previous Use of Anodic Decarboxylation for Radical Generation

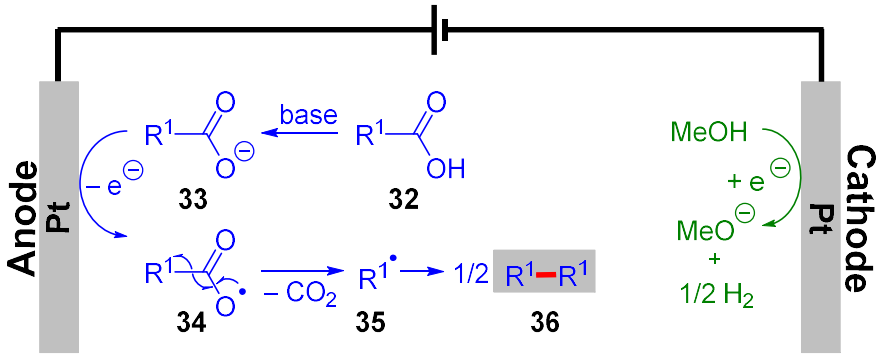
### 2.1.1 Anodic Decarboxylation for Radical Generation and Subsequent Homo- or Heterocoupling

The first anodic decarboxylation was performed by Faraday in 1834.[1] Faraday passed a current through a solution of acetate and observed the formation of $CO_2$ and a hydrocarbon at the anode. 15 years later, Kolbe investigated this reaction further and found that upon electrolysis of the potassium salt of pentanoic acid, $CO_2$ and *n*-octane were formed at the anode and $H_2$ gas was evolved at the cathode.[3] This transformation is now currently known as Kolbe electrolysis. Since Kolbe's initial discovery, a variety of work has been published using this approach for the generation and subsequent reactions of alkyl radicals as well as numerous reviews.[22–32] An overview of Kolbe electrolysis is shown in Scheme 2.3. A deprotonated carboxylic acid can undergo anodic decarboxylation to give a radical, which can then couple with a radical with the same substituent (homocoupling) or a different substituent (heterocoupling). This section summarises some of the synthetic applications of homo- and heterocoupling reactions using Kolbe electrolysis.




Scheme 2.3

Kolbe electrolysis reactions are typically carried out in an undivided cell with platinum electrodes and a high current density.[5] The solvent is usually an alcohol such as MeOH and a base is also required. The mechanism for anodic decarboxylation and homocoupling is shown in Scheme 2.4. Carboxylic acid **32** is deprotonated to form carboxylate anion **33** which is oxidised at the anode to give carboxylate radical **34** (blue route). Then, carboxylate radical **34** decarboxylates to give alkyl radical **35** which couples with another of the same radical to form homocoupled product **36**. Meanwhile, the solvent, MeOH, is reduced at the cathode to give methoxide and $H_2$ (green route).




Scheme 2.4

Solvent choice is an important consideration for electrodecarboxylation reactions. The solvent can affect the reactive intermediate (radical or carbocation) that is generated. Either protic, protic/water mixtures, or water are the preferred solvents as they favour radical formation and MeOH and aqueous MeOH are the two most commonly used solvents in Kolbe electrolysis.[29] Other solvents such as dipolar/water mixtures (*e.g.* pyridine/water) favour carbocation formation and can be useful for other electrodecarboxylative reactions such as alkene formation.[32]

For Kolbe electrolysis, neutral or slightly acidic media are recommended.[32] To keep the solution slightly acidic, the acid starting material is neutralised to usually 5-10% using an alkali metal hydroxide or alkoxide. The alkoxide that is formed during the counter process at the cathode is generated at the same rate as the consumption of carboxylate ions at the anode. Therefore, the concentration of carboxylate ions remains approximately constant throughout the electrolysis process.

Current density is another important factor for Kolbe electrolysis. A high current density, usually higher than 250 mA $cm^{-2}$, is recommended since the rate of radical coupling is proportional to the radical concentration per unit of electrode.[32] However, it can be assumed that the oxidation of the solvent, for example MeOH which occurs at 0.9 V (*vs* NHE),[33] would occur predominately over the carboxylic acid oxidation which is at 2.0-2.8 V (*vs* NHE). Figure 2.1 shows a plot of anode potential against the logarithm of the current density for an aqueous NaOAc (0.5 M) system.[34] At a certain value of current density, the anode potential 'jumps' and the discharge of carboxylate ions to radicals occurs, which releases $CO_2$. Before this value, $O_2$ gas is primarily produced, which indicates an undesirable process, such as $O_2$ evolution from the water solvent. This can

be explained by electrostatic forces. When the anode potential is high, the solvent is displaced from the surface of the anode and is replaced by the negatively charged carboxylate anions, forming a layer against the solvent. Thus, the competing oxidation of the solvent is suppressed.

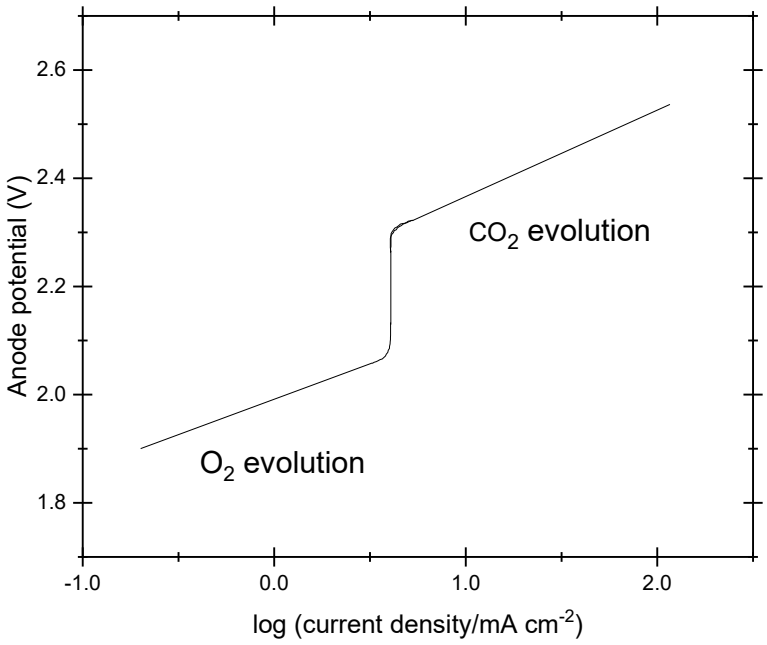



Figure 2.1 – Tafel plot showing the anode potential (*vs* NHE) as a function of log (current density) in a $H_2O$-NaOAc (0.5 M) system.[34]

Passivation on the electrodes can cause problems during Kolbe electrolysis reactions.[24] When sparingly soluble products form on the anode surface (such as inorganic salts, polymers and inorganic oxides), the current significantly drops as these products form a non-conducting layer on the anode. When this occurs, longer reaction times may be required. To overcome passivation, small amounts of organic solvents (THF, dioxane) can be added. Alternatively, polarity reversal of the electrodes can be performed, i.e. throughout the experiment the electrode that is the cathode is switched to the anode (and *vice versa*) every few minutes. In this way, passivation is suppressed as the layer should cathodically dissolve with each polarity reversal.[35]

Supporting electrolytes are often required for electrolysis experiments, as they increase the conductivity of the solution. However, since foreign anions can disturb the carboxylate layer that forms on the anode, electrolytes are generally avoided in Kolbe electrolysis.[27] The carboxylic anion and its counter ion effectively act as the supporting

electrolyte. As there is no electrolyte added, the concentration of the carboxylic acid needs to be relatively high, typically 0.5-0.8 M.[24]

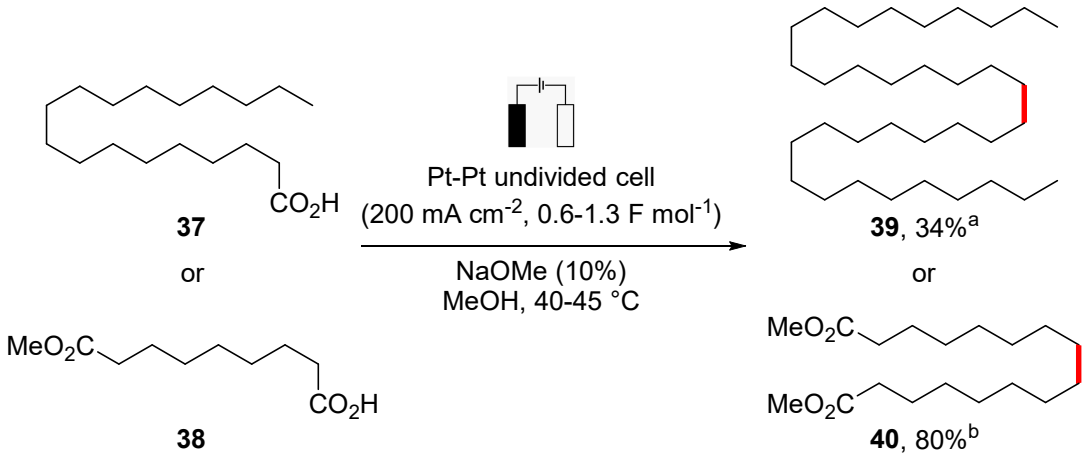
Temperature can affect Kolbe electrolysis reactions. At slightly elevated temperatures the viscosity and mass transport can be increased which increases the yield of the Kolbe coupled product. However, temperatures above 50 °C can cause problems since at these higher temperatures, the carboxylic acid can be converted into its methyl ester when MeOH is used as the solvent.[27] Degradation of the solvent and reagents can also occur.

The material that makes up the anode can also have an effect on the outcome of Kolbe electrolysis reactions. Platinum is the most universally applicable material.[27] Platinum favours one-electron oxidations, resulting in a radical. In contrast, other materials such as graphite or porous carbon, facilitate two-electron oxidations, resulting in carbocation intermediates that form so-called "non-Kolbe" products. One hypothesis for this observation is that a carbon electrode adsorbs the radical stronger than platinum, allowing the second oxidation to occur quicker. In addition, when a porous electrode is used, the surface area of the material drastically increases which decreases the relative concentration of radicals at the surface. Therefore, radical coupling is less likely.The cathodic material is less important as both the starting materials and products are not easily reduced at potentials that are less negative than that is required for $H_2$ evolution. However, when the polarity of the electrodes is reversed, the same material for both needs to be used.

When heterocoupling reactions are performed, an excess of the cheaper, more readily available acid is normally used in order to increase the yield of the heterocoupled product. Statistically, two major products should be observed, the homocoupled product of the acid that is in excess, and the heterocoupled product. Therefore, the most expensive, more valuable acid will have been incorporated into the desired product.[27]

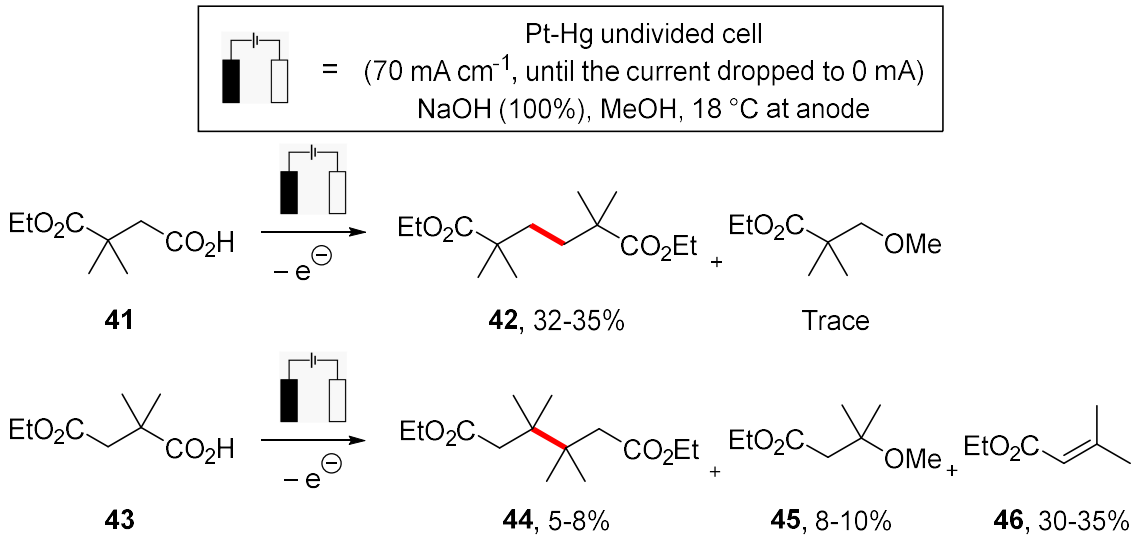
In terms of synthetic applications, Kolbe electrolysis has been widely used for the coupling of fatty acids as a method for generating long chain alkanes.[22] For example, Schäfer *et al*. performed homocoupling of stearic acid **37** and alkyl chain containing ester **38** (Scheme 2.5).[23] The homocoupling of these acids was carried out in an undivided cell with platinum electrodes. 200 mA $cm^{-2}$ of current density was passed through a solution of carboxylic acid in MeOH at 40-45 °C. 10% NaOMe was also added to this reaction,

where the percentage refers to 10% of the acid concentration to achieve 10% neutralisation. A 0.3 M solution of stearic acid **37** was electrolysed using these conditions to give alkane **39** in 34% yield. Due to the poor solubility of acid **37** in MeOH, the compound partially precipitated at the electrode, which caused passivation and it was only possible to pass 0.6 F $mol^{-1}$ through the cell. 0.6 F $mol^{-1}$ refers to the amount of charge being passed through the solution per mole of carboxylic acid. Ester **38** was electrolysed at a higher concentration (0.9 M) due to its increased solubility and this gave di-ester **40** in 80% yield.



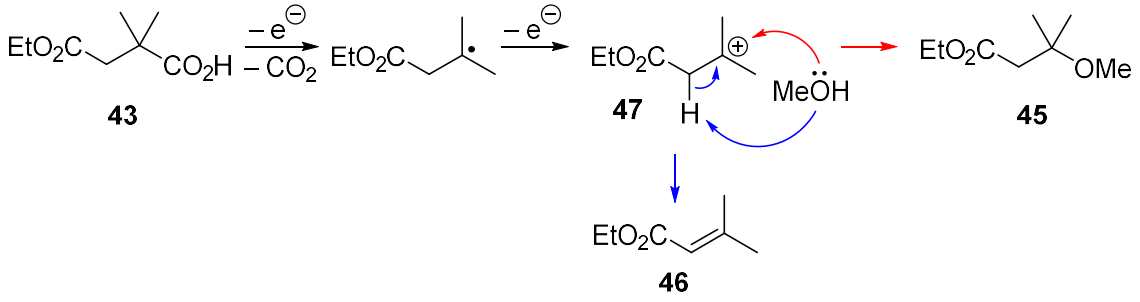

Scheme 2.5 – [a] Performed with 0.3 M solution of **37**. [b] Performed with 0.9 M solution of **38**

Kolbe electrolysis and subsequent homo- or heterocoupling is generally more succesful with primary carboxylic acids compared to tertiary carboxylic acids. Farmer *et al.*[36] reported a significant difference in the homocoupling product yield when using primary acid **41** and tertiary acid **43** (Scheme 2.6). A platinum anode and mercury cathode were used with 100% of NaOH in MeOH. The mercury cathode produces sodium amalgam whereas a platinum cathode produces NaOMe. Mercury can be used as the cathode when using a high percentage of base to stop the solution becoming basic as anodic decarboxylation is preferred in acidic solutions.[37] By using a current density of 70 mA $cm^{-2}$, homocoupling of primary acid **41** gave di-ester **42** in 32-35% yield (Scheme 2.6). However, when tertiary acid **43** was subjected to the same conditions, homocoupled product **44** was obtained in only 5-8% yield. Other "non-Kolbe" products, such as methoxy amine **45** and alkene **46**, were isolated from these reactions.




Scheme 2.6

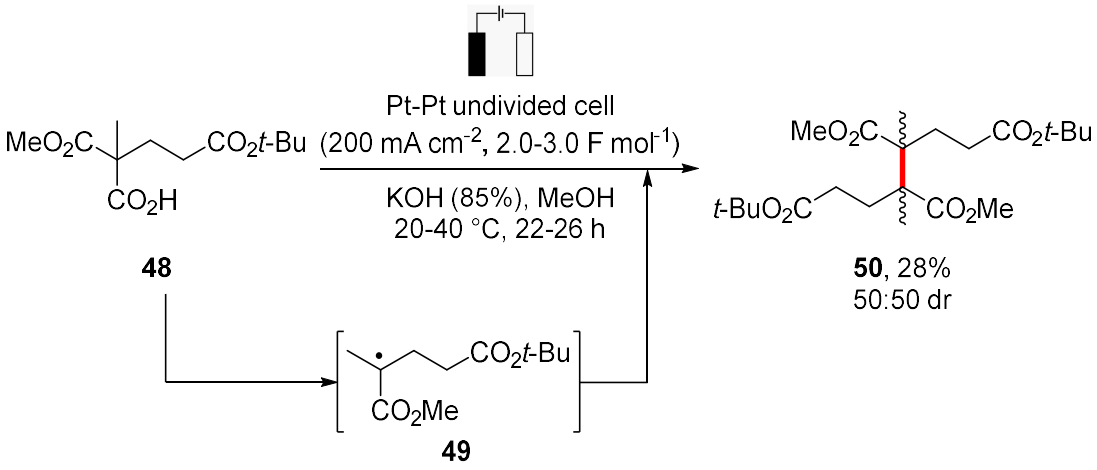
Farmer *et al*. suggested that the low yield with tertiary carboxylic acid **43** was due to the "greater probability of degradation" to ether **45** and alkene **46**, although this was not further commented on in the paper.[36] A suggestion for the formation of ether **45** and alkene **46** is shown in Scheme 2.7. Presumably, the radical intermediate can be oxidised a second time to give carbocation **47**. This carbocation can then be quenched with the nucleophilic solvent to give ether **45** (red route) or it can undergo elimination to give alkene **46** (blue route). The over-oxidation of the radical intermediate is more prominent with tertiary radicals compared to primary ones due to the increased stability of the carbocation generated.




Scheme 2.7

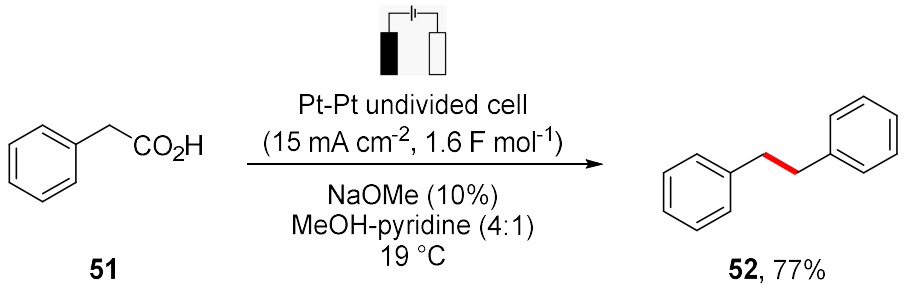
The homocoupling of tertiary carboxylic acids can be achieved in adequate yields by introducing an electron withdrawing group adjacent to the carboxylic acid. Quast *et al.* were able to homocouple tertiary acid **48** to obtain the homocoupled product **50** in 28% yield, with no diasteroselectivity (Scheme 2.8).[38] In this case, 85% of KOH in MeOH was

used and 200 mA $cm^{-2}$ of current density was passed for 2.0-3.0 F $mol^{-1}$. The radical intermediate **49** is less susceptible to over-oxidation to the carbocation due to the adjacent electron withdrawing ester.




Scheme 2.8

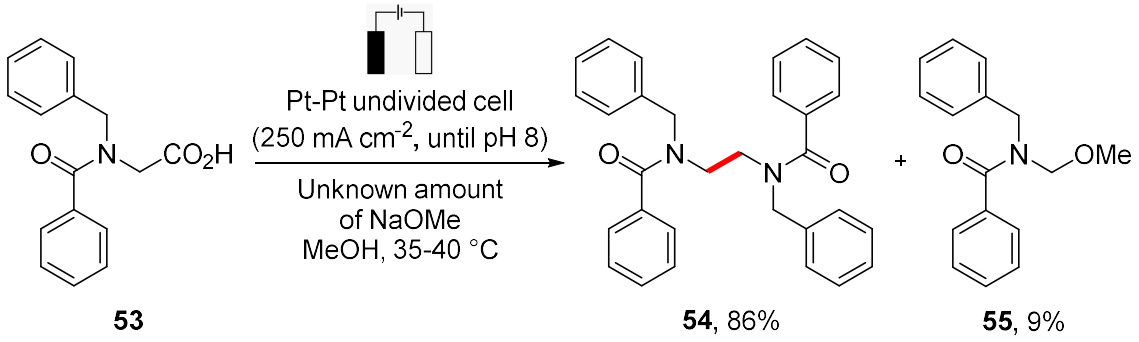
The homocoupling of phenylacetic acid **51** has been well explored.[39–41] One example was reported by Mendonça *et al*. where diphenylethane **52** was synthesised in 77% yield (Scheme 2.9).[42] This study used a 0.8 M solution of phenylacetic acid **51** and 10% NaOMe in a mixture of MeOH-pyridine (4:1) at 19 °C. Platinum electrodes with a low current density of 15 mA $cm^{-2}$ and 1.6 F $mol^{-1}$ of charge were used. Each electrode had a surface area of 12.5 $cm^2$ and therefore required 188 mA of current to achieve the current density. Pyridine was used as a co-solvent as it is reported to minimise passivation on the electrodes. This example used an unusually low current density.




Scheme 2.9

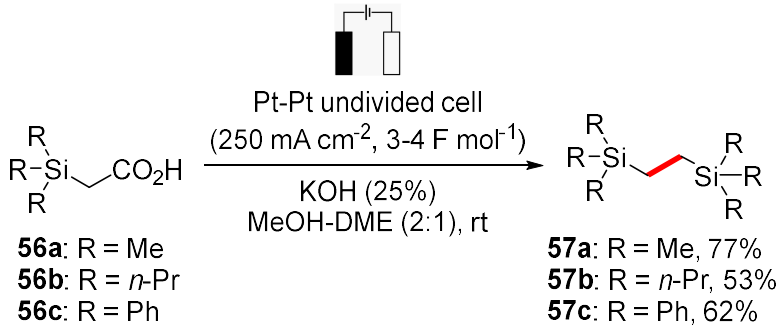
The homocoupling of nitrogen-containing carboxylic acids has also been studied. Lateef *et al*. reported that the homocoupling of α-amido acetic acid **53** gave di-amide **54** in a surprisingly high 86% yield (Scheme 2.10).[43] A 0.13 M solution of α-amido acetic acid

**53** in MeOH at 35-40 °C was used together with an unreported amount of NaOMe. A current density of 250 mA $cm^{-2}$ was passed until the pH showed that the solution had turned slightly basic. The pH of the solution is a common way to determine when the carboxylic acid starting material has been consumed as base is continuously being formed at the cathode. Methoxy amine **55** was also obtained in 9% yield. Methoxy amine **55** was presumably formed by the over-oxidation of the radical to the carbocation, which was then quenched by MeOH.




Scheme 2.10

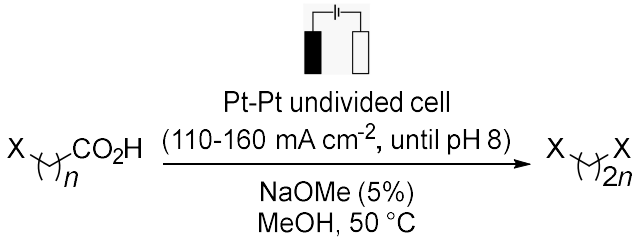
Silyl-containing carboxylic acids have also been explored in homocoupling reactions. Becker *et al*. performed anodic decarboxylation on α-silyl carboxylic acids **56a-c**.[44] Using a 0.13 M solution of the acid in a MeOH/DME (2:1) mixture with 25% of KOH, 250 mA $cm^{-2}$ of current density was passed through the cell for 3-4 F $mol^{-1}$ to give di-silyl ethanes **57a-c** in 53-77% yields (Scheme 2.11).




Scheme 2.11

Carboxylic acids containing halogens have been used with variable sucesses in Kolbe electrolysis. In 1955, Woolford *et al*. explored the homocoupling of ω-halocarboxylic acids (Table 2.1).[45] An undivided cell with platinum electrodes was used for the electrolysis of ω-halocarboxylic acids in 5% NaOMe methanolic solution at 50 °C. For

shorter chain carboxylic acids ($n$ < 4), no homocoupled product was found with the exception of 3-chloropopanoic acid (entry 2, X = Cl). It was stated that no other recognisable products were observed except for HF for entries 2 and 3 (X = F). For longer chain carboxylic acids containing fluorine and chlorine (entries 4-10, X = F, Cl), the homocoupled products were isolated in 45-82% yield. When the halogen was bromine, only the carboxylic acids with a chain length greater than 11 produced homocoupled product (entries 10 and 11, X = Br). The shorter chain lengths yielded no coupled product and liberated bromine. Finally, none of the iodocarboxylic acids gave coupled products and, in all cases, iodine was liberated (entries 1-11, X = I).



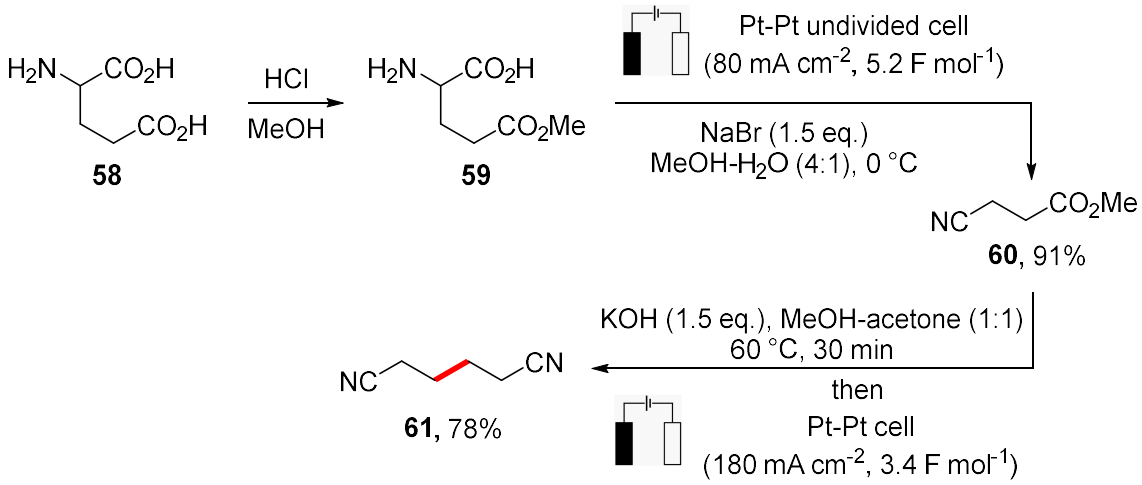

| Entry | $n$ | Product Yield (%) | | | |
|---|---|---|---|---|---|
| | | X = F | X = Cl | X = Br | X = I |
| 1 | 1 | 0 | 0 | 0 | 0 |
| 2 | 2 | 0 | 39 | 0 | 0 |
| 3 | 3 | 0 | 0 | 0 | 0 |
| 4 | 4 | 45 | 52 | 0 | 0 |
| 5 | 5 | 45 | 55 | 0 | 0 |
| 6 | 6 | 58 | - | - | - |
| 7 | 7 | 64 | - | 0 | - |
| 8 | 8 | 65 | - | - | - |
| 9 | 9 | 69 | 82 | 0 | 0 |
| 10 | 10 | 61 | - | 54 | 0 |
| 11 | 15 | - | - | 31 | - |

Table 2.1 – Kolbe electrolysis of halogen-containing carboxylic acids.[45]

Woolford reasoned that ω-halo *n*-butryic acids are inherently unstable. No other explanation for the other unsuccessful reactions were given. It is presumed that nucleophilic substitutiuon of the halide with methoxide could occur. Another possibility

is the reduction of the halogens at the cathode, forming a halogen radical anion which could eliminate to form carbon-centered radicals.

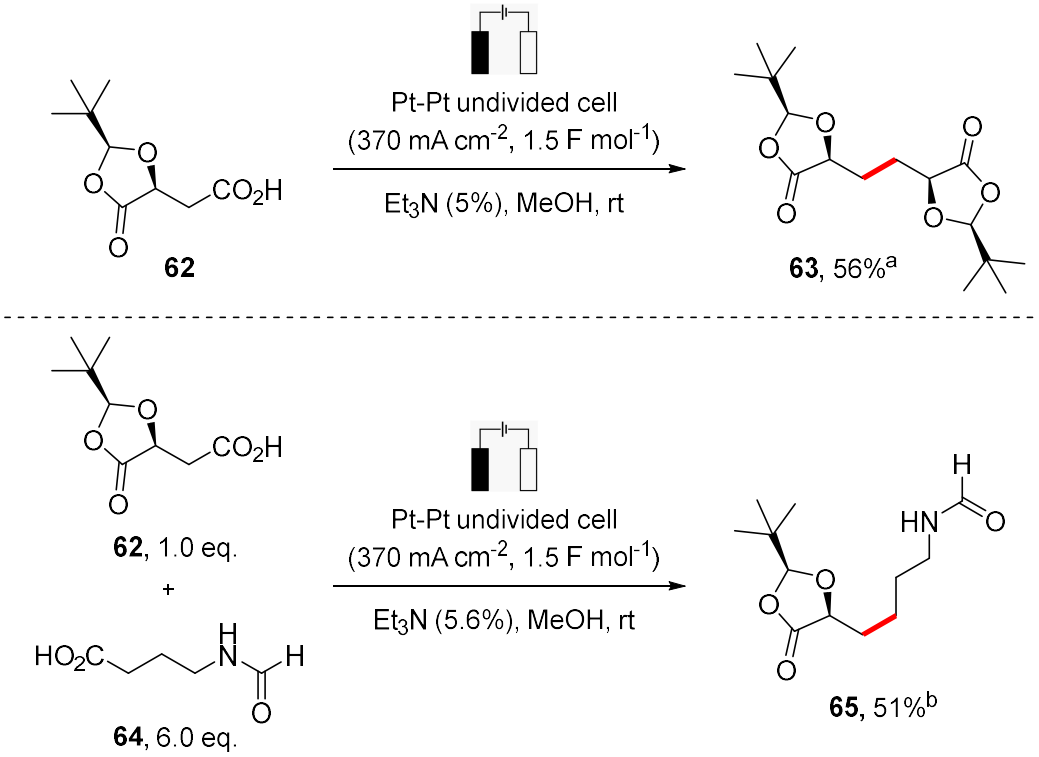
Kolbe electrolysis has also been used to synthesise adiponitrile **61**, a precursor to nylon 66, starting from glutamic acid **57** (Scheme 2.12).[46] The first step was the esterification of glutamic acid **58** to methyl ester **59**. Next, in the presence of a mediator (NaBr), methyl ester **59** can be electrodecarboxylated and subsequently reduced to give nitrile **60**. The ester present in nitrile **60** was hydrolysed *in situ* by heating the ester in the presence of KOH. Then, Kolbe electrolysis was performed to give homocoupled nitrile **61** in 78% yield. An undivided cell with platinum electrodes was used for this procedure. 1.5 eq. of KOH was added to a solution in order to form the carboxylate anion of nitrile **60** in a MeOH-acetone (1:1) mixture and heated at 60 °C for 30 min before the electrolysis was performed. Then, a current density of 180 mA $cm^{-2}$ was passed through the solution for 3.4 F $mol^{-1}$ of charge to give homocoupled nitrile **61**.




Scheme 2.12

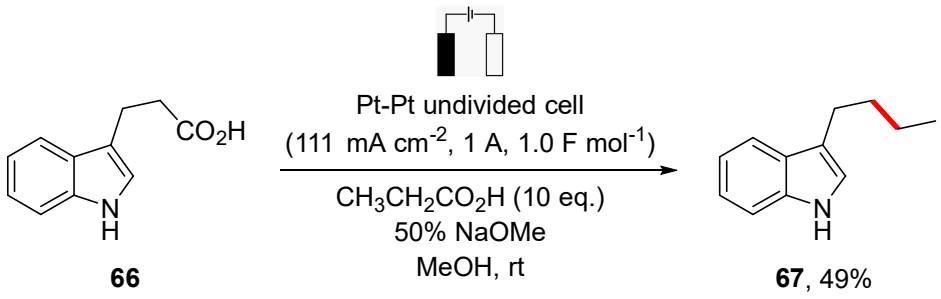
An example of Kolbe electrolysis on a functionalised acid **62** was reported by Seebach *et al*.[47] The homocoupling of acid **62** was performed in an undivided cell with platinum electrodes. 370 mA $cm^{-2}$ of current density was passed through a solution of acid **61** and $Et_3N$ (5%) in MeOH. This gave homocoupled product **63** in 56% yield (Scheme 2.13). The heterocoupling reaction between acid **62** and formamide **64** was also reported. A percentage of 5.6% $Et_3N$ was used in this reaction, where the percentage refers to 5.6% of the total of both acids to achieve 5.6% neutralisation of the solution. An excess of formamide **64** was used to give heterocoupled product **65** in 51% yield. 1.5 F $mol^{-1}$ of

charge was used in the heterocoupling reaction and it refers to the amount of charge passed through the solution per mole of total acid (both **62** and **64**).




Scheme 2.13 – [a] Performed with 0.25 M solution of acid **61**, [b] Performed with 0.7 M solution of total acid

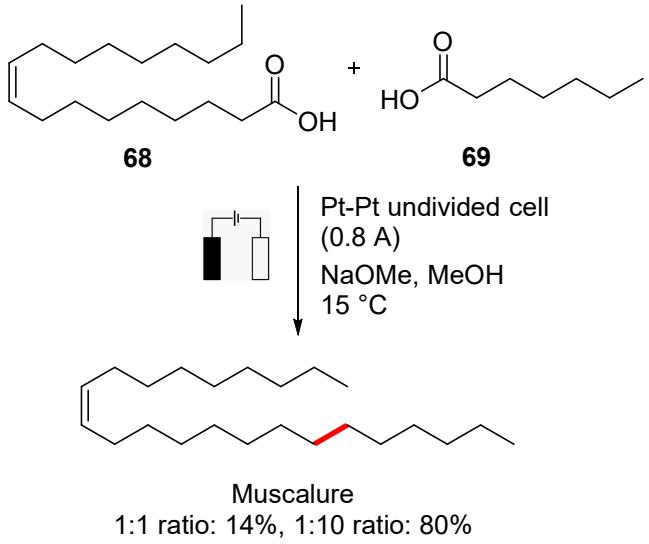
Yadav *et al*. generated 3-alkyl indole **67** by heterocoupling indole-3-propanoic acid **66** and propanoic acid.[48] 111 mA cm$^{-2}$ of current density was passed through a solution of indole **66**, 10 eq. of propanoic acid and 50% NaOMe in MeOH for 1.0 F mol$^{-1}$ of charge. In this way, 3-alkyl indole **67** was obtained in 49% yield (Scheme 2.14).




Scheme 2.14

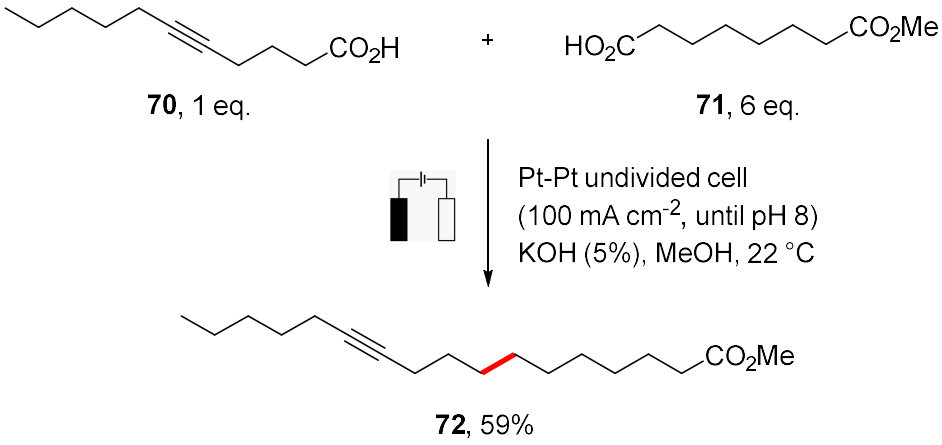
Kolbe electrolysis has also been used in natural product synthesis. For example, muscalure, a pheromone of the housefly, was synthesised from two fatty acids. Heterocoupling of oleic acid **68** and heptanoic acid **69** was performed to give muscalure.

The acids were electrolysed in a 1:1 ratio in MeOH and neutralised using an unknown amount of NaOMe. A current of 0.8 A was passed through the cell for an unkown time, which gave muscalure in only 14% yield.[49] However, when 10 eq. of the cheaper heptanoic acid **69** was used, the yield of muscalure increased significantly to 80% yield (Scheme 2.15).[31]



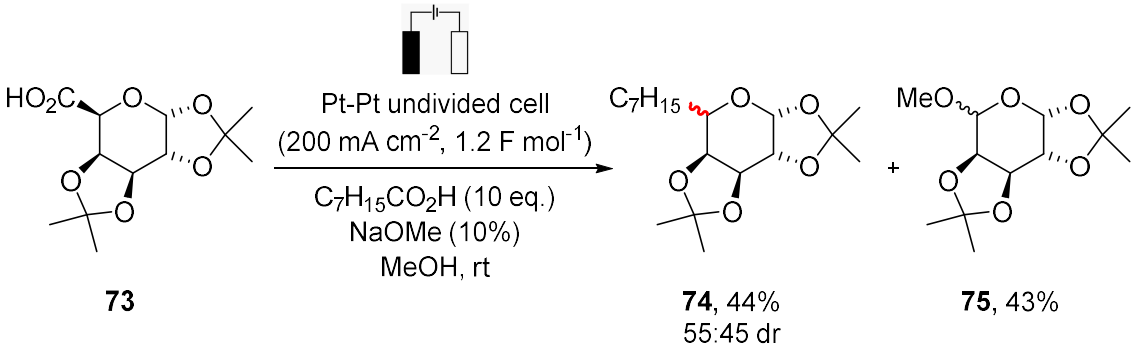

Scheme 2.15

Alkynes are compatible with Kolbe electrolysis. Schäfer *et al*. published a synthetic route towards a moth pheromone precursor by performing Kolbe electrolysis on alkyne acid **70**. A solution of alkyne acid **70** and ester **71** was electrolysed in a platinum undivided cell with a current density of 100 mA $cm^{-2}$. This gave alkyne **72** in 59% yield (Scheme 2.16).



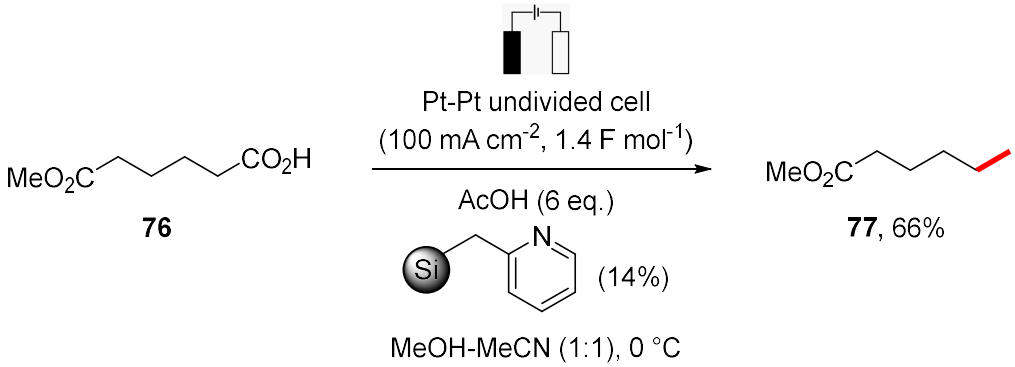

Scheme 2.16

Schäfer *et al*. have performed Kolbe heterocoupling on carbohydrate-containing carboxylic acids.[50] A current density of 200 mA $cm^{-2}$ was passed through a solution of carbohydrate-containing carboxylic acid **73** and octanoic acid, with 10% NaOMe in MeOH. Using these conditions, alkylated carbohydrate **74** was obtained in 44% yield with little diastereoselectivity (Scheme 2.17). Ether **75** was also obtained in 43% yield, presumably from the over-oxidation of the radical intermediate to the oxygen-stabilised carbocation and reaction with MeOH.




Scheme 2.17

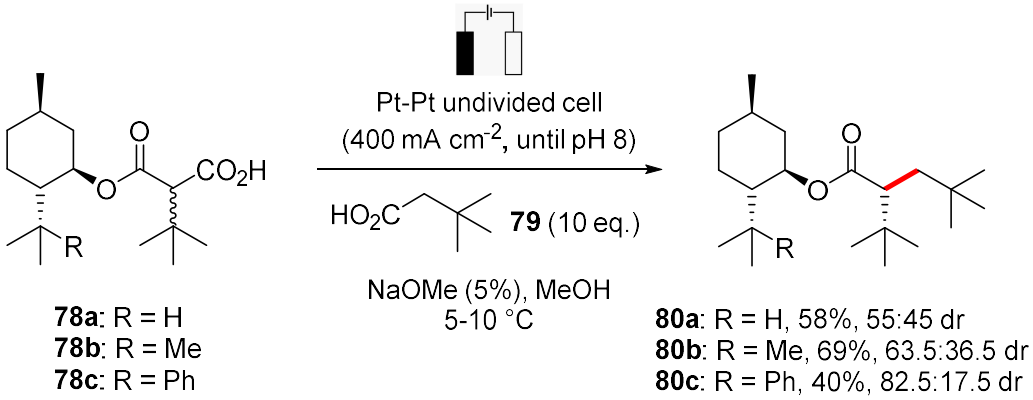
The use of solid-supported amine bases for Kolbe electrolysis was studied by Fuchigami *et al*.[51] The advantages of using a solid-supported base are that it is stable enough to withstand high currents and it can be recycled. A 0.1 M solution of acid **76** in a MeOH-MeCN (1:1) mixture with 6 eq. acetic acid and 14% of a solid-supported pyridine base was used. After passing 100 mA $cm^{-2}$ current density for 1.4 F $mol^{-1}$ of current, alkyl ester **77** was obtained in 66% yield (Scheme 2.18).




Scheme 2.18

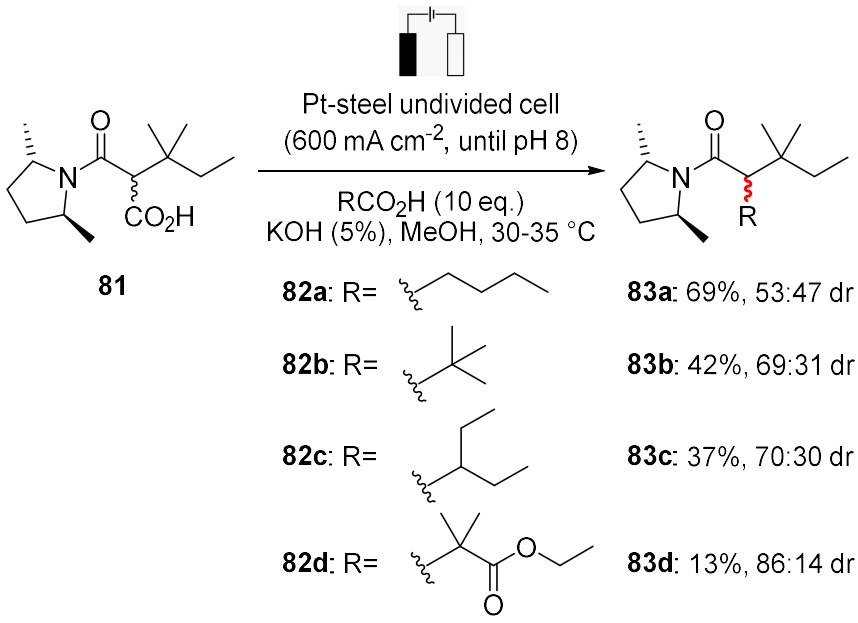
Schäfer *et al*. have investigated the use of chiral auxiliaries to control the stereochemistry of the radical coupling.[52] A solution of acid **78a-c** with 10 eq. of acid **79** and 5% NaOMe

was electrolysed until the pH of the solution was 8. Using these conditions, heterocoupled esters **80a-c** were formed in 40-69% yields and up to 82.5:17.5 dr (Scheme 2.19). It was found that increasing the size of the R group on the chiral auxiliary from R = H to R = Ph led to higher diastereoselectivity.




Scheme 2.19

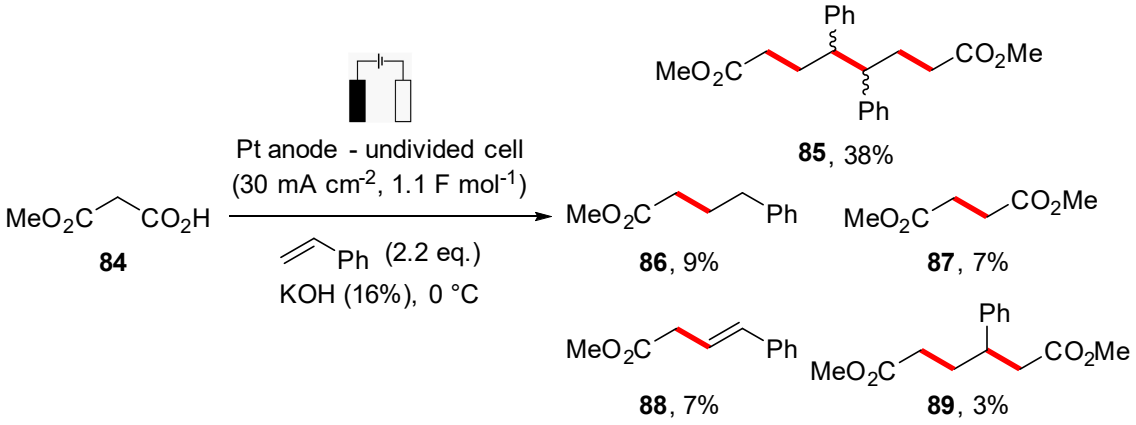
Schäfer *et al*. also performed experiments with an amide chiral auxiliary.[53] Acid **81** was heterocoupled with acids **82a-d** using 600 mA cm$^{-2}$ of current density and 5% KOH in MeOH. This gave heterocoupled products **83a-d** in 13-69% yields (Scheme 2.20). It was found that increasing the size of the R group in the co-acid increased the diasteroselectivity from 53:47 dr to 86:14 dr. However, there was a noticeable drop in yield from 69% to 13% on increasing the size of the R group.




Scheme 2.20

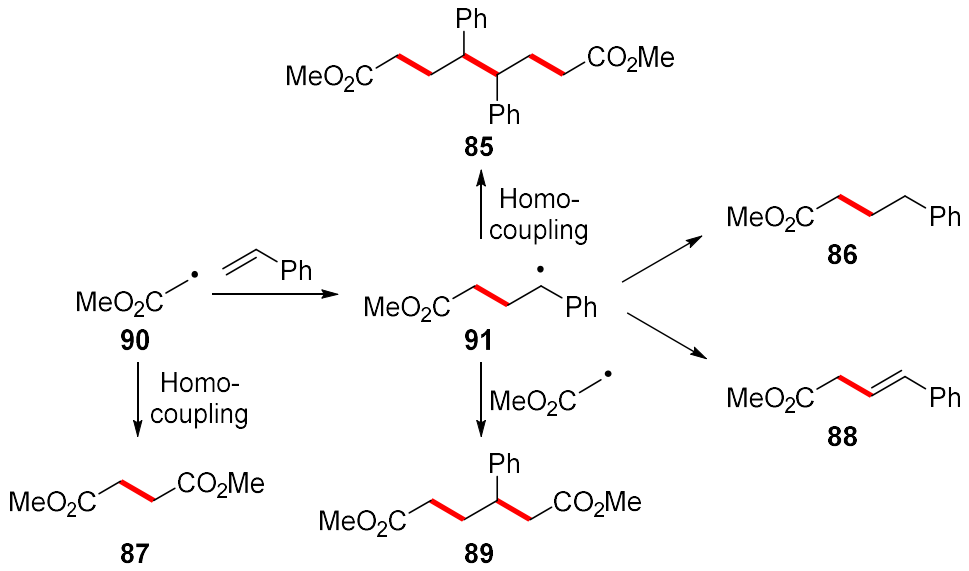
### 2.1.2 Anodic Decarboxylation for Radical Generation and Subsequent Addition to Alkenes

Kolbe electrolysis can also be combined with the functionalisation of alkenes. For example, the radical intermediate that is generated can add onto an alkene which can then undergo radical-radical coupling. However, multiple products can be formed. Schäfer *et al*. electrolysed mono-methyl malonate **84** in the presence of styrene (Scheme 2.21).[54] A platinum anode electrode cell containing mono-methyl malonate **84**, styrene (2.2 eq.) and KOH (16%) was electrolysed with 30 mA $cm^{-2}$ current density for 1.1 F $mol^{-1}$ of charge. No solvent was used and the cathode material was not specified. The main product obtained from this reaction was di-ester **85** in 38% yield. Various other products were obtained in 3-9% yield.



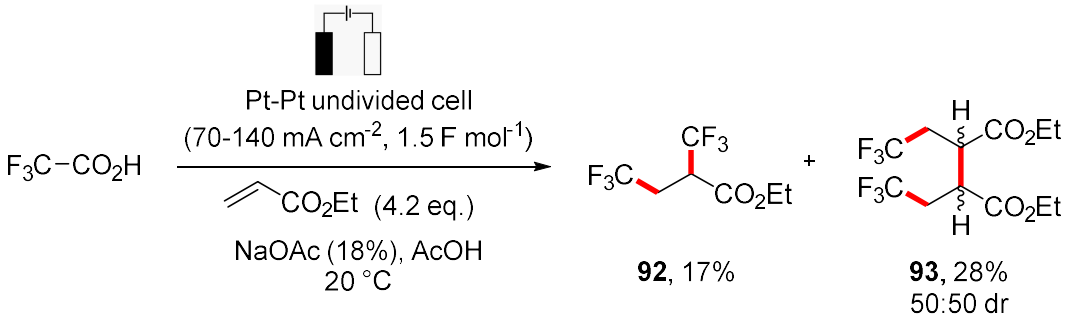

Scheme 2.21

The mechanisms for formation of products **85**-**89** are presented in Scheme 2.22. Mono-methyl malonate **84** can be electrolysed and decarboxylated to give radical intermediate **90**. Radical **90** could then homocouple to give di-ester **87** or add to styrene to give radical **91**. Radical **91** would then undergo homo- and heterocoupling to give **85** and **89** respectively, or it could form alkane **86** (*via* hydrogen abstraction) or alkene **88** (probably *via* over-oxidation to the carbocation and elimination).




Scheme 2.22

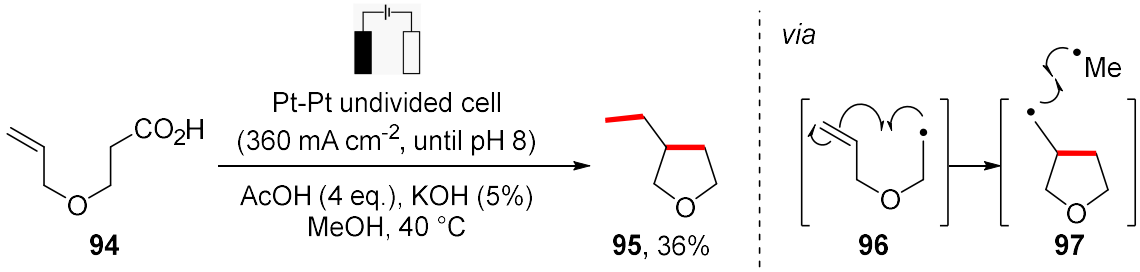
Renaud *et al*. reported the functionalisation of alkenes with trifluoromethyl groups using Kolbe electrolysis.[55] Trifluoroacetic acid was electrolysed in the presence of ethyl acrylate and NaOAc (18%) in acetic acid. A current density between 70-140 mA $cm^{-2}$ was passed for 1.5 F $mol^{-1}$ of charge. This gave ester **92** in 17% yield and di-ester **93** in 28% yield with no diastereoselectivity (Scheme 2.23). Acetic acid was used as the solvent to keep the solution acidic, as a basic solution favours fluoride ion formation. As the p*K*a value for acetic acid is higher than trifluoroacetic acid, only a small amount of acetate ions are formed in the reaction, allowing mainly trifluoroacetic acid to be deprotonated and subsequently undergo electrolysis.




Scheme 2.23

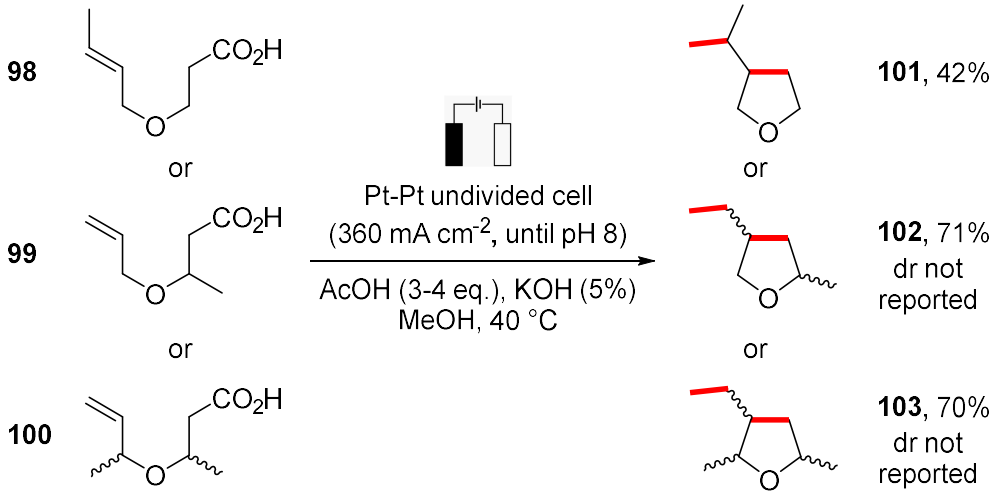
Kolbe electrochemistry has also been used for the synthesis of oxygen and nitrogen heterocycles by cyclisation of the initially generated radical onto an internal alkene and subsequent heterocoupling. In 1984, Schäfer *et al*. used this technique to perform

cyclisation reactions followed by heterocoupling as a route to substituted tetrahydrofurans.[56] The conditions used a solution of 0.13 M of 3-allyloxycarboxylic acid **94** and 5% KOH in MeOH with 4 eq. of acetic acid at 40 °C. Platinum electrodes that had a surface area of 3 $cm^2$ each were used and a current density of 360 mA $cm^{-2}$ was passed until pH 8 was reached. Under these conditions, tetrahydrofuran **95** was formed in 36% yield (Scheme 2.24). Mechanistically, 3-alloxycarboxylic acid **94** forms radical **96** after anodic decarboxylation, which adds onto the alkene in a 5-*exo-trig* fashion to give cyclised radical **97**. Heterocoupling of radical **97** and a methyl radical, which is generated from acetic acid, then gives tetrahydrofuran **95**.



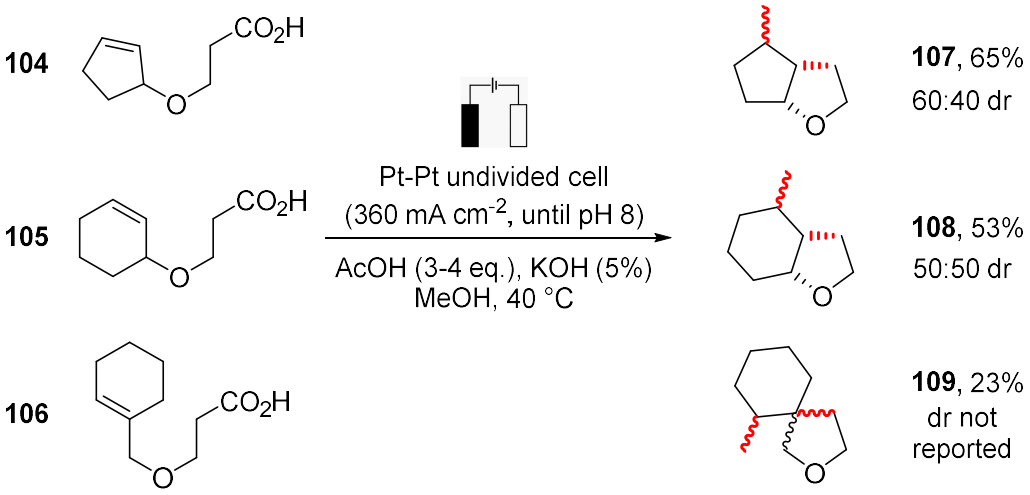

Scheme 2.24

The effect of methyl substituents at various positions in the starting alkene acid was explored by Schäfer in order to generate different tetrahydrofurans (Scheme 2.25).[56] Ether **98**, with a methyl substituent on the alkene, gave tetrahydrofuran **101** in 42% yield. In contrast, with methyl substituents at the α-positions to the oxygen, namely ethers **99** and **100**, tetrahydrofurans **102** and **103** respectively were obtained in 70-71% yield.



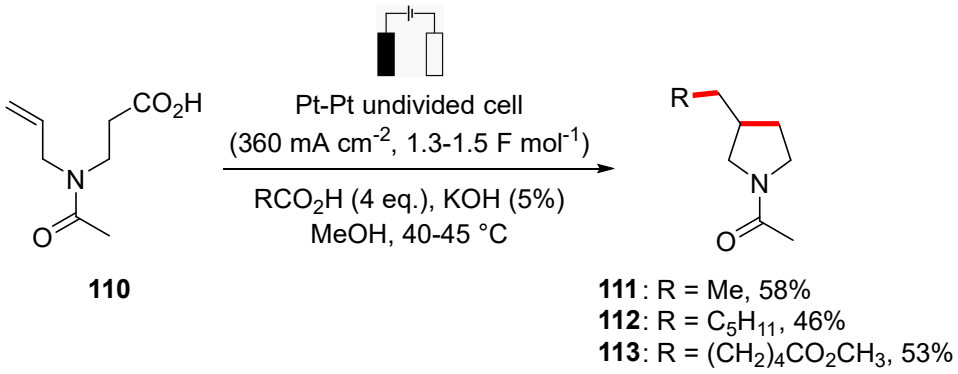

Scheme 2.25

In a further extension of this type of reaction, Schäfer *et al*. also used cyclic alkenes as substrates (Scheme 2.26).[56] A 5- and 6-membered ring, ether **104** and **105** respectively, produced bicyclic compounds **107** and **108** in good yields of 53-65% with 60:40 dr and 50:50 dr respectively. The geometry of the transition state forces the ring to be *cis*-annulated. Spirocyclic tetrahydrofuran **106** was also synthesised from ether **109** in 23% yield.



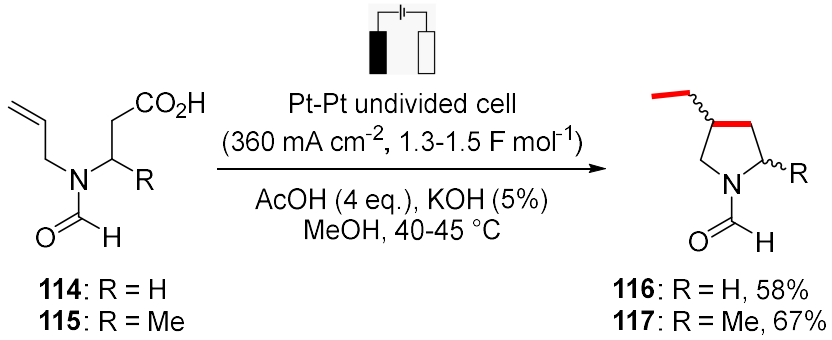

Scheme 2.26

A few years later, Schäfer *et al*. extended the method to the synthesis of substituted pyrrolidines.[57] Although not clearly stated, the conditions described are presumed to be the same as those used in the tetrahydrofuran synthesis described above. A 0.13 M solution of alkene acid **110**, 5% KOH and 4 eq. co-acid in MeOH was electrolysed using a current density of 360 mA $cm^{-2}$ for 1.3-1.5 F $mol^{-1}$ of charge. Using acetyl protected amine **110** and acetic acid, pyrrolidine **111** was isolated in 58% yield (Scheme 2.27). The amine group was protected in order to avoid oxidation of the amine's lone pair under the relatively harsh conditions of Kolbe electrolysis. Use of hexanoic acid mono-methyl adipic acid gave pyrrolidines **112** and **113** in 46% and 53% yields respectively.



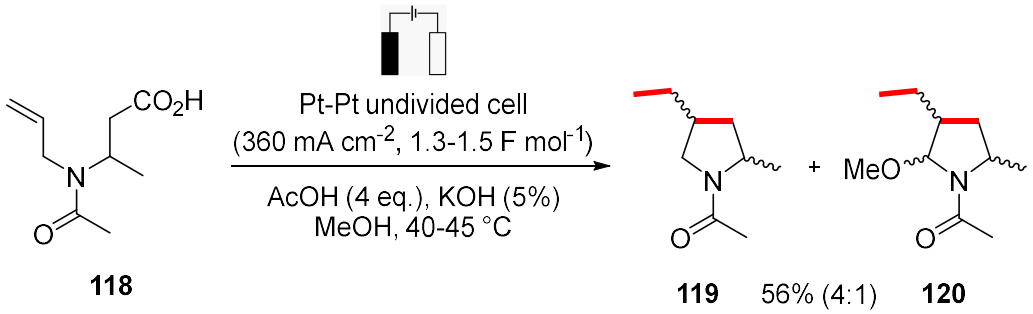

Scheme 2.27

A formyl amine protecting group was also explored.[57] Using *N*-formyl alkene acid **114**, pyrrolidine **116** was formed in 58% yield. With a methyl substituent at the α-position to the nitrogen, amide **115**, pyrrolidine **117** was obtained in 67% yield (Scheme 2.28). The addition of a methyl substituent adjacent to the heteroatom appears to give the best yields, as shown by this example and those in Scheme 2.25 for the tetrahydrofuran synthesis.



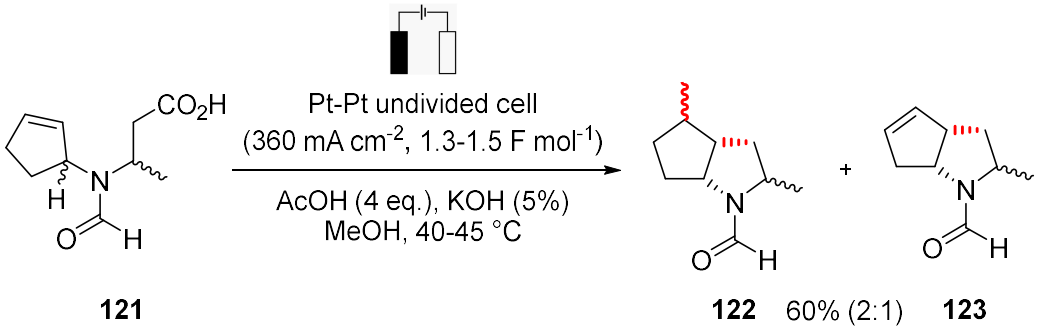

Scheme 2.28

However, when the methyl substituent was included in the acetyl protected compound, amide **118**, two products were formed (Scheme 2.29).[57] The desired pyrrolidine **119** was formed along with methoxy amine **120** in a 4:1 ratio. Methoxy amine **120** could be formed from a Shono oxidation,[6] which is the α-methoxylation adjacent to a heteroatom. The nitrogen present in amine **119** could oxidise at the anode to form a radical cation. Hydrogen abstraction from the carbon at the α-position could then occur to form an iminium ion which would be attached by MeOH to form methoxy amine **120**.



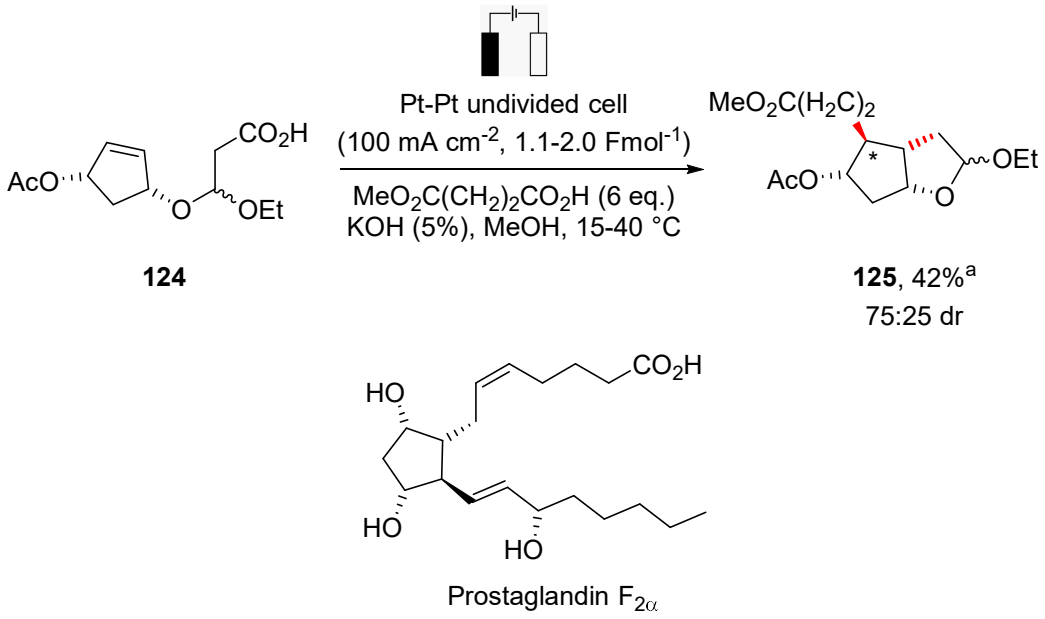

Scheme 2.29

A cyclic alkene, amide **121**, was also used as a possible substrate (Scheme 2.30).[57] In this case, a 2:1 mixture of desired pyrrolidine **122** and alkene **123** was isolated. Alkene **123** is formed from the over-oxidation of the cyclised radical intermediate to form a carbocation and subsequent elimination. The stereochemistry of the bicyclic structures is due to the same reasoning as the previous tetrahydrofuran synthesis in Scheme 2.26, but the diastereomeric ratio of the products **122** and **123** was unfortunately not reported.



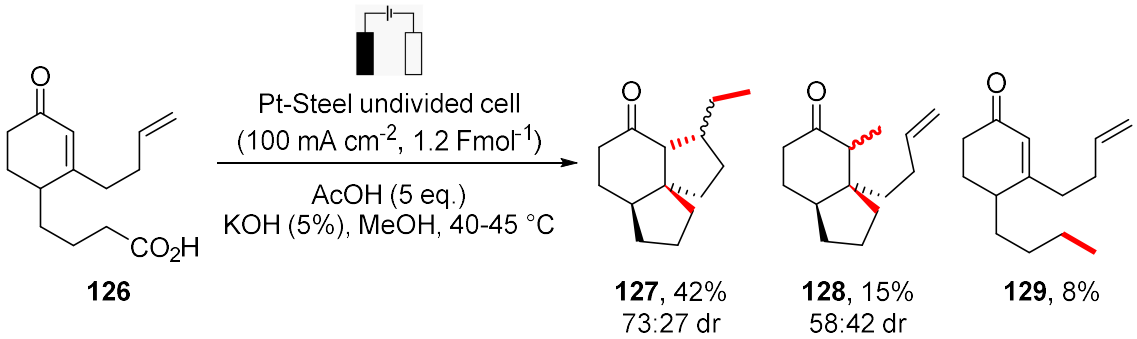

Scheme 2.30

The Schäfer group used this electrochemical cyclisation-heterocoupling approach in a route to prostaglandin precursors.[58] The conditions used for the electrolysis of alkene acid **124** were a 0.13 M solution of alkene acid **124** and 5% KOH in MeOH with 6 eq. of monomethyl succinate at 15-40 °C. A current density of 100 mA $cm^{-2}$ was used until 1.1-2.0 F $mol^{-1}$ of charge was passed. In this way, prostaglandin precursor **125** was obtained in 42% yield (Scheme 2.30). This precursor can be used in the synthesis of prostaglandin $F_{2\alpha}$. The relative stereochemistry of the bicyclic compound is established in the cyclisation step as the radical can only attack the alkene from the same face it is on. During the radical heterocoupling reaction, a 75:25 mixture of diastereomers were formed at the highlighted carbon. These diastereomers were were seperated by chromatography to give the desired diastereomer in 42% yield.




Scheme 2.31 – [a] Isolated yield after separation of diastereomers at C* by chromatography.

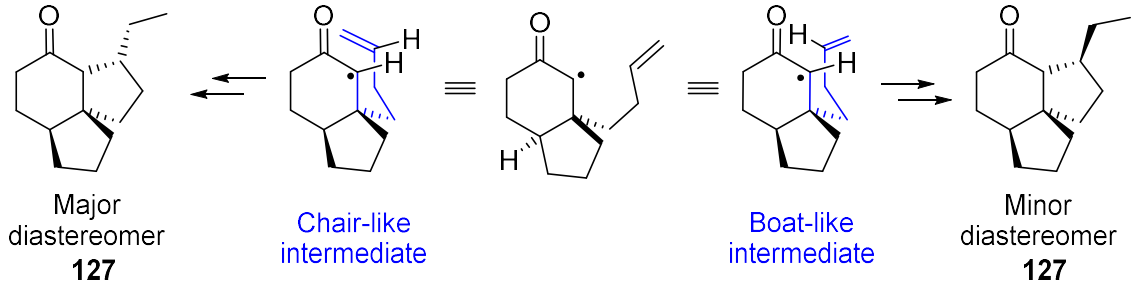
Multi-functional carboxylic acid **126** was also used in Kolbe electrolysis and, through a tandem radical cyclisation reaction, led to the formation of tricyclic ketone **127**.[59] A platinum anode and steel cathode were used in an undivided cell. A solution of alkene acid **126**, 5 eq. of AcOH and 5% KOH in MeOH was electrolysed with a current density of 100 mA $cm^{-2}$ for 1.2 F $mol^{-1}$ of charge. These conditions gave tricyclic ketone **127** in 42% yield, with bicyclic ketone **128** and cyclohexene **129** also being formed in 15% and 8% yields respectively (Scheme 2.32). Bicyclic ketone **128** and cyclohexenone **129** are formed when heterocoupling of the radicals occur before one or both cyclisations.




Scheme 2.32

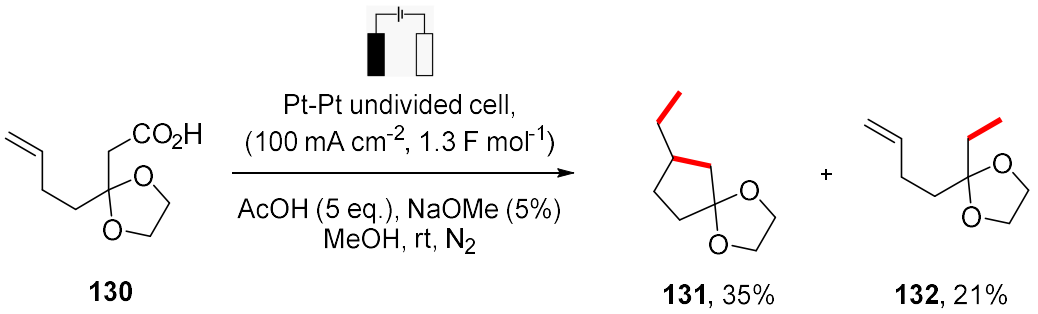
The initially formed 5-membered rings in tricyclic ketone **127** and bicyclic ketone **128** are *cis*-annelated as the radical can only attack the alkene at the *cis* face. Similarly, the second 5-membered ring formed in tricyclic ketone **127** is *cis*-annulated. The final

cyclisation of the radical intermediate to give tricyclic ketone **127** showed some diastereoselectivity (73:27 dr). This step proceeds in accordance with the Beckwith-Houk model.[60,61] The major pathway is *via* a chair-like intermediate which is less sterically hindered than the boat-like intermediate (Scheme 2.33).



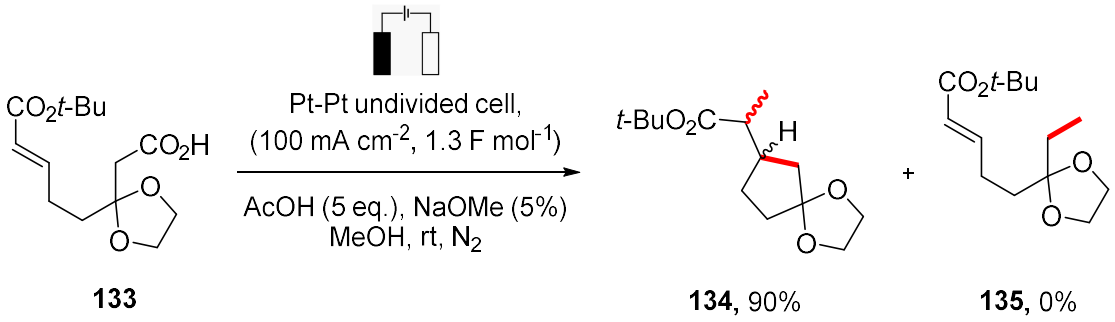

Scheme 2.33

Markó *et al*. have reported several high yielding examples of Kolbe electrolysis decarboxylation followed by cyclisation and heterocoupling with a co-acid.[62] An example is shown in Scheme 2.34. Alkene acid **130** was subjected to electrolysis using acetic acid as the co-acid, with 5% NaOMe in MeOH. 100 mA $cm^{-2}$ of current density was passed for 1.3 F $mol^{-1}$ of charge. This gave cyclopentane **131** in 35% yield together with heterocoupled product **132** in 21% yield. Clearly, the rate of cyclisation of the alkyl radical intermediate onto the alkene is slow enough to allow some direct heterocoupling.




Scheme 2.34

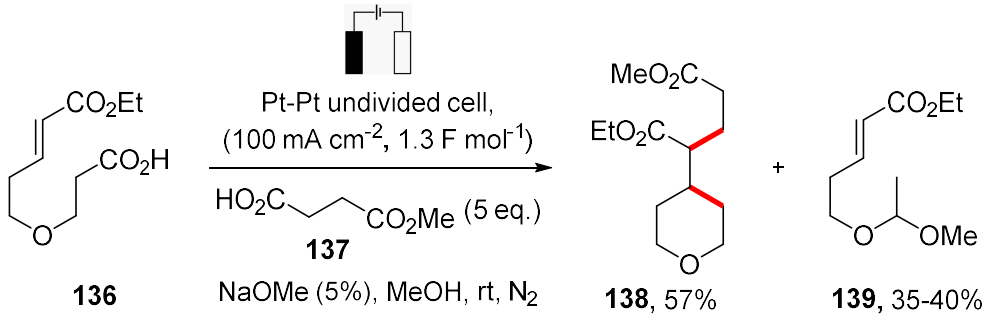
Markó *et al*. proposed that the rate of cyclisation could be increased by matching the electron rich alkyl radical with an electron deficient alkene. Thus, the reaction of alkene ester **133**, with an electron withdrawing group (*t*-butyl ester) on the alkene, was studied. This gave cyclopentane **134** in 90% yield with no evidence for the formation of the heterocoupled product **135** (Scheme 2.35).




**133** **134**, 90% **135**, 0%

Scheme 2.35

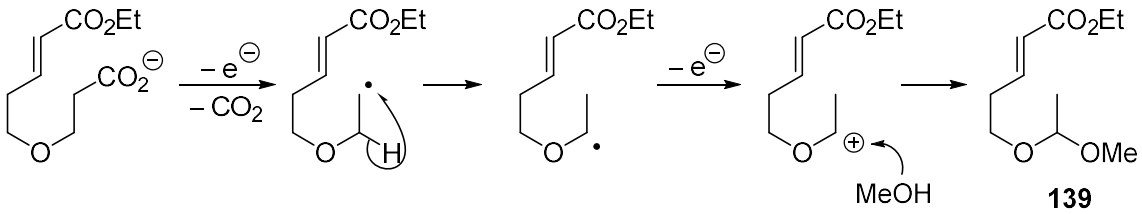
Markó *et al*. also synthesised a 6-membered ring from the electrolysis of alkene acid **136**.[62] Acid **136** was electrolysed with ester **137** to give tetrahydropyran **138** in 57% yield after a 6-*exo*-*trig* cyclisation. Ether **139** was also obtained in 35-40% yield (Scheme 2.36).




**136** **138**, 57% **139**, 35-40%

Scheme 2.36

The mechanism for the formation of ether **139** was not described in the paper. One suggestion is that ether **139** is formed from a hydride shift to form a more stabilised radical. Over-oxidation could then occur, which can be quenched by MeOH to form ether **139** (Scheme 2.37).

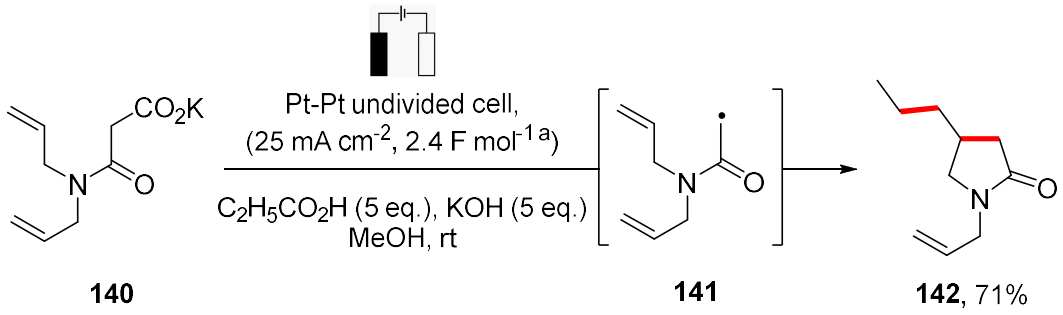



**139**

Scheme 2.37

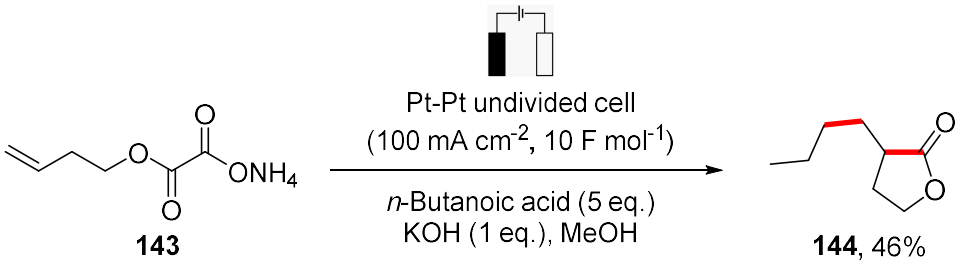
Earlier this year, Lam *et al*. published a new way to generate substituted pyrrolidinones *via* Kolbe electrolysis.[63] One example of this is shown in Scheme 2.38 where potassium salt **140** was oxidised and decarboxylated to give radical **141**, which cyclised and

subsequently heterocoupled with the radical generated from the co-acid decarboxylation to give pyrrolidinone **142**. The potassium salt was used instead of the carboxylic acid in this case due to the inherent instability of the malonic acids. The co-acid was also deprotonated fully in order to increase the likelihood of heterocoupling rather than homocoupling of potassium salt **140**. Therefore, a large amount of KOH (5 eq.) was used to deprotonate all of the co-acid. An electrolysis cell containing smooth platinum electrodes (4 $cm^2$), potassium salt **140** (0.066 M), propanoic acid (5 eq.) and KOH (5 eq.) in MeOH was electrolysed with 25 mA $cm^{-2}$ until the reaction was completed. Pyrrolidinone **142** was produced in 71% yield. The reaction proceeded with 30% faradaic yield which equates to 2.4 F $mol^{-1}$ of charge being passed through the reaction.



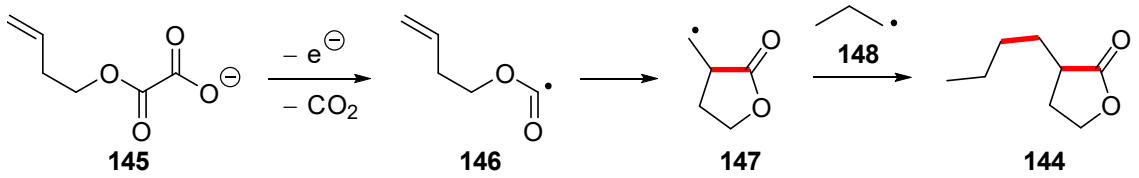

Scheme 2.38 [a] Calculated from faradaic efficiency

In recent work, Lam *et al*. reported the synthesis of lactones from the electrochemical decarboxylation of oxalates, cyclisation onto an internal alkene and subsequent radical heterocoupling.[64] The ElectraSyn 2.0 apparatus with platinum electrodes and a 0.1 M solution of oxalate salt **143**, 5 eq. of *n*-butanoic acid and 1 eq. of KOH in MeOH were used. The solution was electrolysed at a current density of 100 mA $cm^{-2}$ for 10 F $mol^{-1}$ of charge. Using these conditions, lactone **144** was observed in 83% yield by $^1$H NMR spectroscopy but was isolated in only 46% yield due to the volatility of the product (Scheme 2.39).




Scheme 2.39

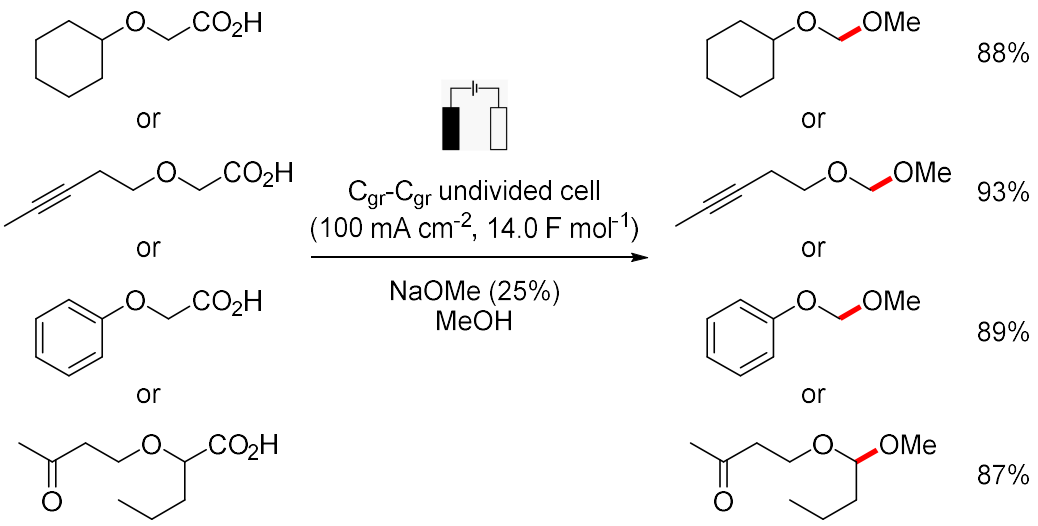
The proposed mechanism for the formation of lactone **144** is shown in Scheme 2.40. Anodic oxidation and decarboxylation of oxalate salt **145** would form acyl radical **146**. Acyl radical **146** can then add to the alkene in a 5-*exo*-*trig* cyclisation to form lactone radical **147** which can homocouple with propyl radical **148** (generated from *n*-butanoic acid) to form lactone **144**.




Scheme 2.40

## 2.1.3 Recent Developments on the Electrochemical Synthesis of non-Kolbe-Type Products

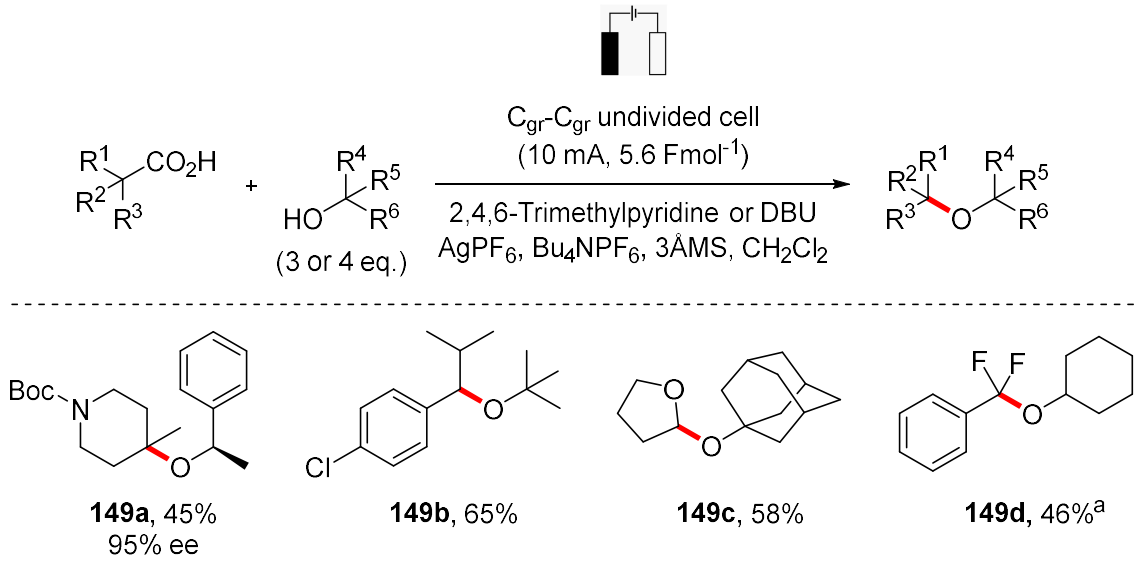
The anodic electrochemical methods discussed thus far have been limited to decarboxylation of carboxylic acids and subsequent radical coupling (with or without cyclisation onto an alkene). However, carboxylic acids have been used extensively in anodic electrochemistry to generate "non-Kolbe" coupled products.[24,65] Here, a few recent examples are presented. One example is the anodic decarboxylation of α-alkoxy carboxylic acids to form methoxymethyl ethers reported by Lam *et al*. in 2018.[66] α-Alkoxy carboxylic acids were formed from the corresponding alcohols by deprotonation with NaH and reaction with a bromoacetic acid derivative. This meant that, upon electrolysis of the α-alkoxy carboxylic acids, the methoxymethyl ethers can be formed in an efficient approach from the corresponding alcohols without the need for using toxic methoxymethyl halides (Scheme 2.41).




Scheme 2.41

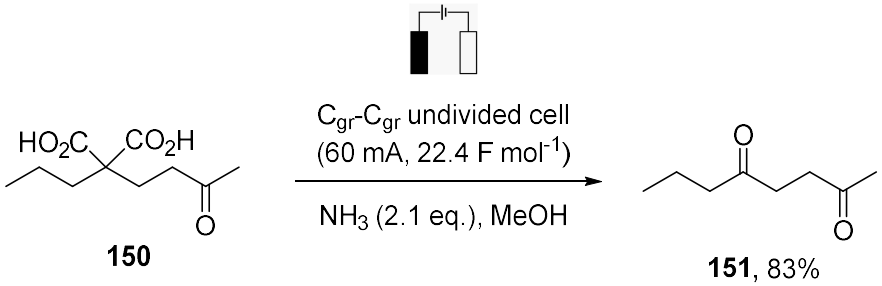
Electrolysis of the α-alkoxy carboxylic acids was carried out in an undivided cell with carbon graphite electrodes. A current density of 10 mA $cm^{-2}$ was passed through a solution containing an α-alkoxy carboxylic acid and 25% NaOMe in MeOH for 14.0 F $mol^{-1}$ of charge. By using these conditions, methoxymethyl ethers were isolated in 87-93% yield (Scheme 2.41). Mechanistically, oxidation and decarboxylation of the α-alkoxy carboxylate ion would generate the radical in the usual way and, due to the use of graphite electrodes, a second oxidation to the oxonium ion will occur readily which is quenched by MeOH to give the products.

In 2019, Baran *et al*. published an approach to generate sterically hindered ethers using anodic decarboxylation of a carboxylic acid, oxidation to a carbocation and subsequent attack with alcohols.[67] In these reactions, the alcohol is usually used as the solvent as it also acts as a sacrificial oxidant. However, it was possible to reduce the amount of alcohol to 3 or 4 equivalents by using a more readily reduced oxidant, $AgPF_6$, in $CH_2Cl_2$ solvent. Molecular sieves were also used to remove the water from the solvent as water would be a competing nucleophile. For the electrolysis, graphite electrodes in an undivided cell, with a solution containing the carboxylic acid, alcohol (3 or 4 eq.), a sterically hindered base, $AgPF_6$, molecular sieves and $Bu_4NPF_6$ (electrolyte) in $CH_2Cl_2$ were used. A current of 10 mA was passed through the solution for 5.6 F $mol^{-1}$ of charge to give the hindered ethers **149a-d** in 45-65% yield (Scheme 2.42).



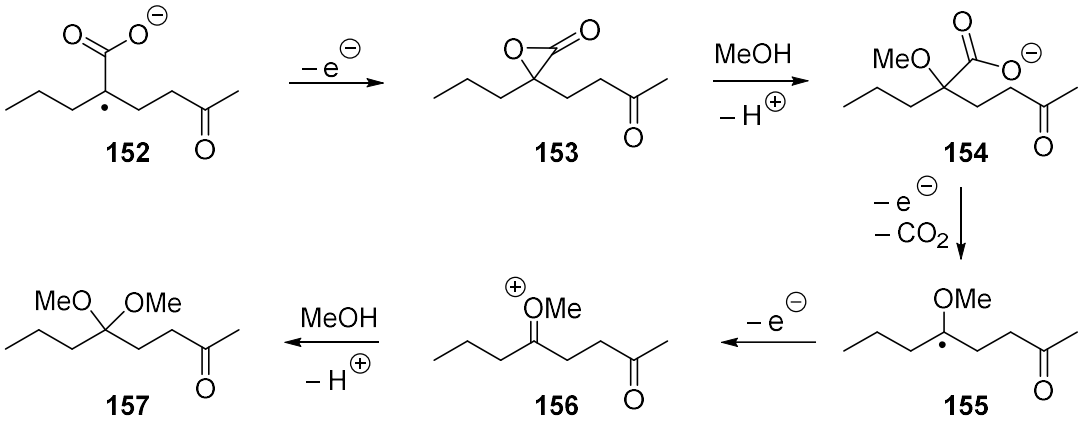

Scheme 2.42 – [a] $AgClO_4$ and $BuNClO_4$ was used instead of $AgPF_6$ and $BuNPF_6$

Markò *et al*. have reported that anodic decarboxylation of malonic acids can be used to generate ketones.[68,69] One example of this transformation is shown in Scheme 2.43. The conditions used included graphite electrodes in an undivided cell with a solution of malonic acid **150** and a large amount of ammonia (210% - equal to 2.1 eq.) in MeOH. A current of 60 mA was passed through the solution for a large excess of charge (22.4 F $mol^{-1}$). After aqueous acidic work-up, di-ketone **151** was obtained in 83% yield.



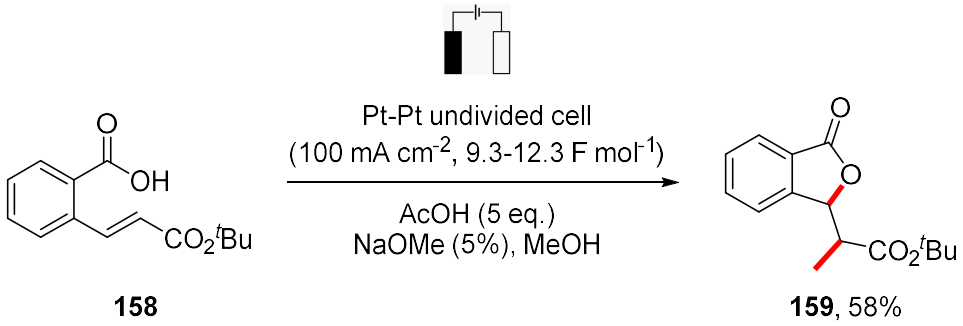

Scheme 2.43

Key steps in the mechanism for the formation of di-ketone **151** are shown in Scheme 2.44. Anodic decarboxylation would generate carboxylate **152** which can be further oxidised to a carbocation which is captured by the carboxylate to give lactone **153** Attack by MeOH would give ether **154** which can then undergo another anodic decarboxylation-oxidation to give oxonium ion **155**. Nucleophilic attack of MeOH onto oxonium ion **156** would form ketal **157** which can be hydrolysed to di-ketone **151**.




Scheme 2.44

Lam *et al*. have reported that anodic oxidation of aromatic carboxylic acids such as **158** does not lead to decarboxylation. Instead, cyclisation onto the electron deficient alkene and subsequent heterocoupling with the radical derived from AcOH to give phthalide **159** takes place.[70] This occurs because the rate of decarboxylation of aryl carboxyl radicals is much slower than that of its aliphatic analogues. An undivided cell with platinum electrodes, a 0.04 M solution of aromatic carboxylic acid **158**, 5 eq. of AcOH and 5% NaOMe in MeOH were used. The solution was electrolysed at a current density of 100 mA $cm^{-2}$ for 9.3-12.3 F $mol^{-1}$ of charge. Using these conditions, phthalide **159** was isolated in 58% yield (Scheme 2.45).

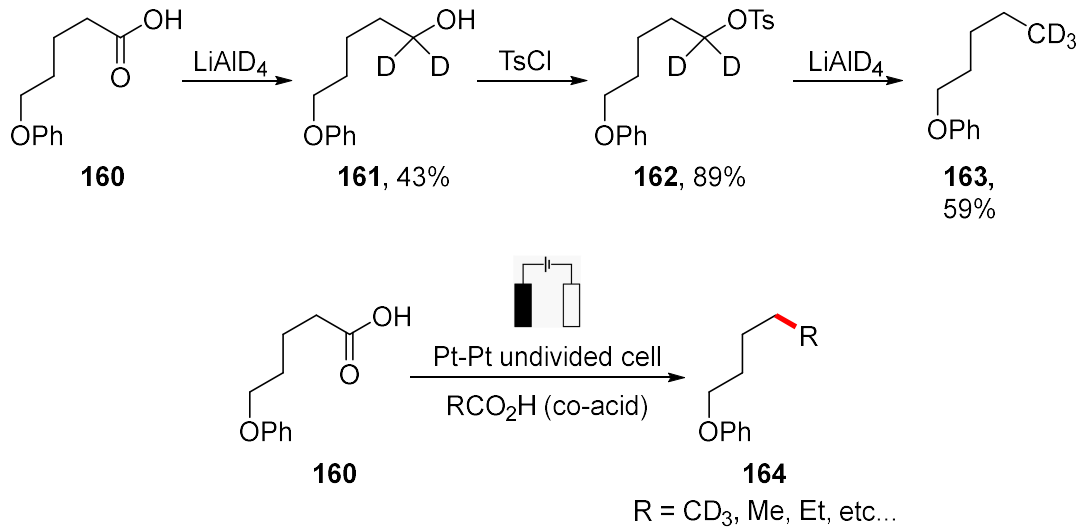



Scheme 2.45

In summary, Kolbe electrolysis is a useful tool for carbon-carbon bond formation and was originally used for fatty acid coupling reactions. However, as shown throughout this section, Kolbe electrolysis can be used with more complicated acids and alkenes to generate more diverse molecules. The conditions required for Kolbe electrolysis have been extensively studied and modifications of Kolbe electrolysis have been performed to generate "non-Kolbe" products as well.

## 2.2 Project Outline

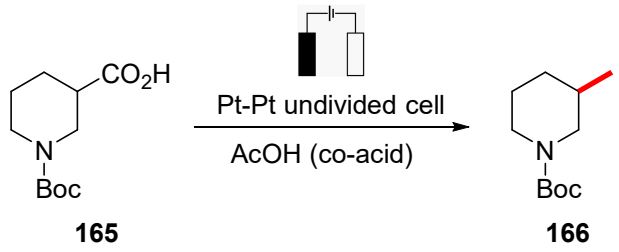
Kolbe-style anodic decarboxylation and heterocoupling of two radicals is a potentially very powerful synthetic transformation. In particular, it can enable transformations to be achieved in a much shorter number of steps compared to non-electrochemical approaches. An example of this would be the conversion of a carboxylic acid or ester derivative into a methyl group. During work carried out for mass spectrometry studies, Schwarz *et al.* reported the three-step conversion of ether acid **160** into deuterated ether **163** in which the acid was transformed into a deuterated methyl group (Scheme 2.46).[71] This was achieved by reduction of acid **160** to alcohol **161** using $LiAlD_4$, tosylation of the alcohol and then a second reduction with $LiAlD_4$ to give deuterated ether **163**. In contrast, using a Kolbe electrolysis approach, this transformation could be achieved in just one step using trideuterated acetic acid (**160** to **164**, R = $CD_3$) (Scheme 2.46). If a different substituent was desired, then a different co-acid could simply be used. For the reduction-tosylation approach, introduction of different substituents could be achieved by reaction of the tosylates with organocuprates.[71]




Scheme 2.46 - General route to transforming carboxylic acids using classical methods[71] and Kolbe electrolysis

The main aim of this part of the project is to explore the scope and limitations of the anodic decarboxylation-heterocoupling approach for the conversion of carboxylic acids into alkyl groups. In particular, the plan was to focus on carboxylic acids (acid and co-acid) that would be of structural relevance to medicinal chemistry. Thus, a range of heterocycles of interest within medicinal chemistry would be explored. An example of

the type of transformation that could be explored is shown in Scheme 2.47. Heterocoupling of *N*-Boc protected piperidine acid **165** with acetic acid under Kolbe electrolysis-type conditions should give methyl piperidine **166**. If such a transformation could be optimised, then it would represent cross-coupling methodology that is complementary to existing methods.




**165** **166**

Scheme 2.47 - Kolbe electrolysis on medicinally relevant heterocycles.

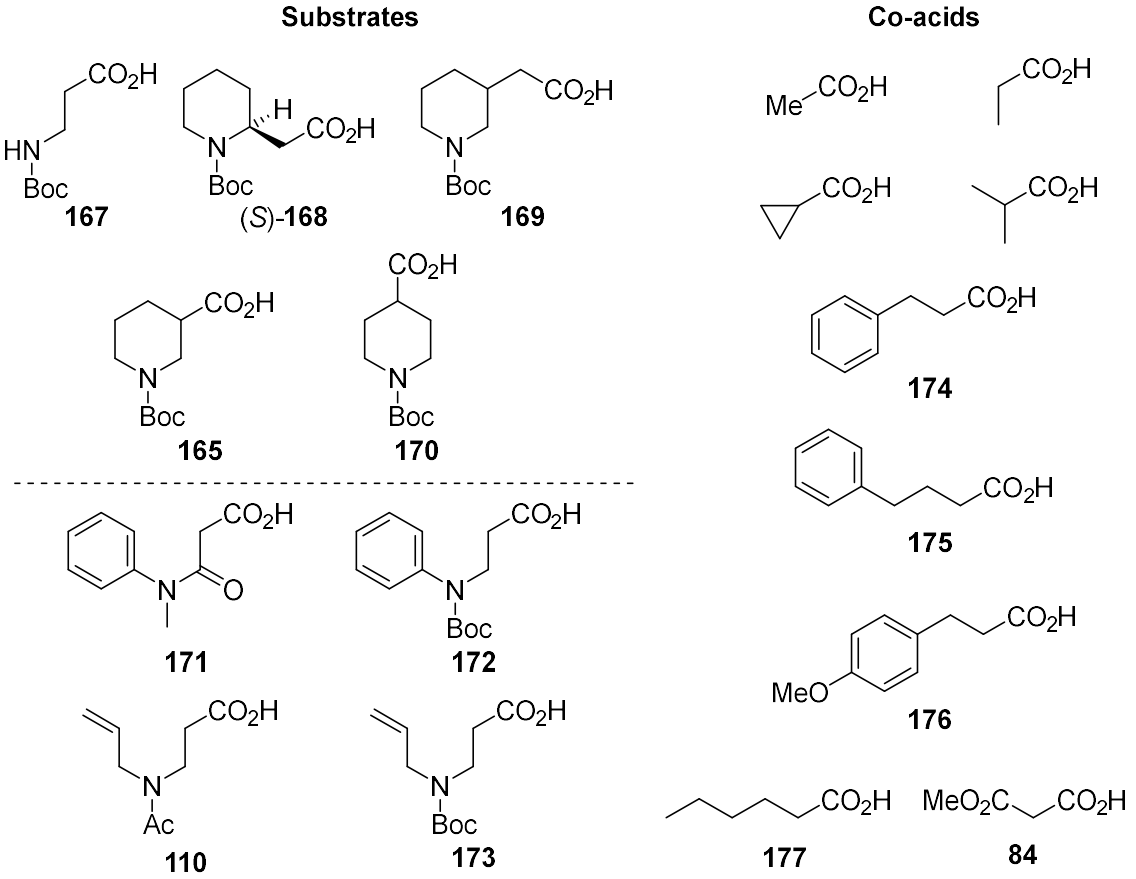



Figure 2.2 – Substrates scope for Chapter 2

This Chapter describes Kolbe heterocoupling of nitrogen-containing acids with a range of co-acids. The acids explored are shown in Figure 2.2 and include an acyclic example, *N*-Boc β-alanine **167**, and four *N*-Boc piperidines (*S*)-**168**, **169**, **165**, and **170**. These were

chosen to explore the heterocoupling of primary, secondary, electron rich, electron deficient, aromatic-containing and cyclopropyl radicals. Four other carboxylic acids, **171**, **172**, **110** and **173**, were included as they contained unsaturated groups that would potentially allow cyclisation to form a pyrrolidine under the reaction conditions. The scope and limitations of the methodology are discussed in this Chapter.

## 2.3 Electrochemical Equipment Design and Phenylacetic Acid Decarboxylation and Homocoupling

A homocoupling reaction that had been reported in the literature was chosen for the initial set of experiments in order to establish that the electrochemical equipment and set-up was suitable. Homocoupling was chosen due to the simplicity of the reaction compared to heterocoupling. The first electrolysis cell was designed using glass flanges and ground glass joints (Figure 2.3). The cell could hold a minimum of 20 mL of solvent and includes five ports for inserting the anode and cathode working electrodes, reference electrode, thermocouple and reagent/gas inlet. For the anode and cathode electrodes, two parallel glass rod supports with platinum wire coiled around them were used. The wires are approximately 7 mm apart and each has a surface area of 2.4 $cm^2$. Platinum was used for both electrodes so that polarity inversion could be used to limit passivation.

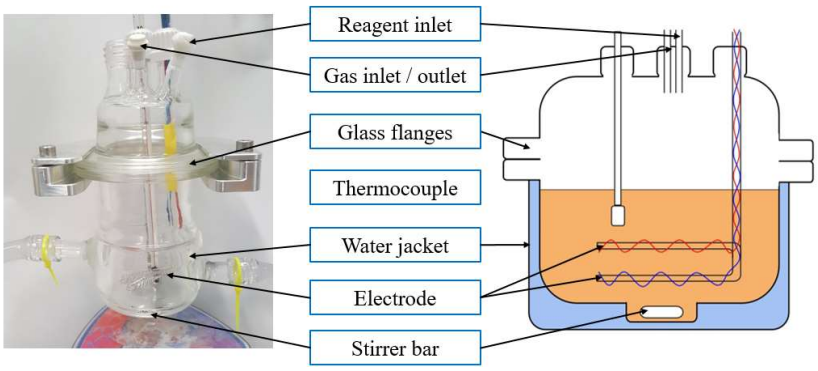



Figure 2.3 – Picture and schematic of the first electrolysis cell

A power pack (HQ-Power, PS1503SB) was used to apply the voltage between the anode and cathode that is necessary to achieve the desired current flow. To monitor the individual voltages of the anode and cathode, a LabJack© was used. A LabJack© is a device that converts analogue into digital outputs. Figure 2.4 shows a schematic of the circuit designed. The voltage drop that occurs across the 10 Ω resistor is converted into to a current measurement by applying Ohm's law (V = IR, where V is the voltage, I is the current and R is the resistance). There is also a polarity inverter, that switches which electrode is the anode and cathode. Due to the layout of the circuit, only constant voltage experiments can be performed. Two power packs were included in order to reach a maximum of 30 V as each power pack can achieve 15 V.

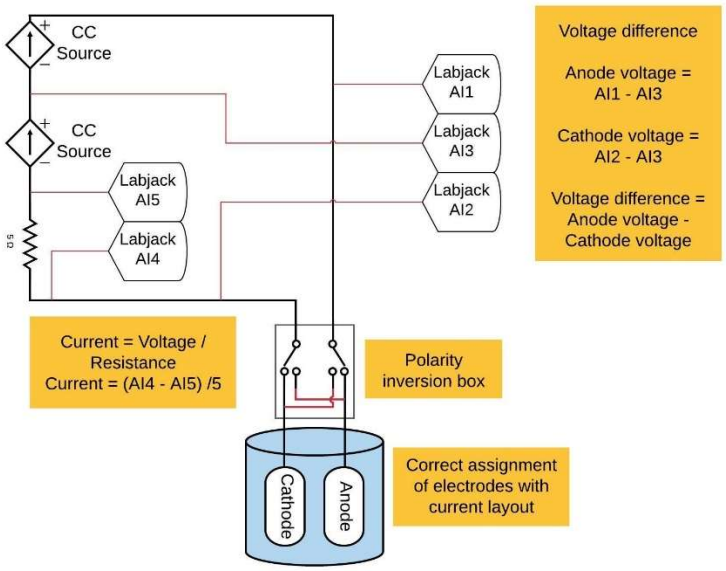
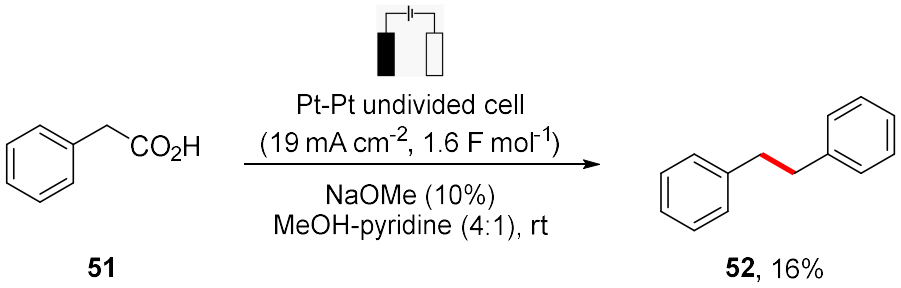



Figure 2.4 – Circuit diagram of the LabJack©

Once the initial cell and the LabJack© circuit were constructed, Kolbe electrolysis could be performed. The homocoupling of phenylacetic acid **51** was investigated as it had been reported by Mendonça *et al*. (see Scheme 2.9). It was decided to try and replicate this procedure for the initial experiment. Thus, a 0.8 M solution of phenylacetic acid **51** with 10% NaOMe in a MeOH-pyridine (4:1) mixture was prepared. A voltage of 8 V was applied to give an average of 41 mA of current and 17 mA $cm^{-2}$ of current density. The current was passed for 1.6 F $mol^{-1}$ of charge. This gave bibenzyl **52** in only 16% yield after purification by chromatography (Scheme 2.48). The low yield compared to Mendonça's work (77% yield) is likely due to the significantly smaller electrode size (2.2 $cm^2$ compared to 12.5 $cm^2$) which significantly changes the amount of current required to obtain the same current density. Attempts to increase the current to improve the yield failed because, in this electrochemical cell, the voltage required to drive a higher current is very high, indicating a very high solution resistance. Minimising the distance between the electrodes would reduce the resistance. However, this was not possible in this cell as the platinum wires were too flexible so it would not be safe to bring them closer together.




Scheme 2.48

The desire to lower the resistance inspired the design of a new cell and electrodes with a shorter anode-cathode separation distance. Furthermore, it was beneficial to have a cell that had a smaller solvent volume so that smaller scale reactions could be carried out. This was important as the plan was to use more valuable substrates in the future. New electrodes were designed that were more rigid so that the distance between the electrodes could be reduced from 7 mm. Platinised titanium mesh was therefore selected and an electrode separation of 2 mm was possible. A schematic of the electrodes and new electrochemical cell is shown in Figure 2.5. PTFE was used as the electrode mount as it is sturdy and resistant to the MeOH solvent usually used in Kolbe electrolysis. Platinum wires were used to electrochemically connect the mesh to the circuit. A new cell design was constructed in order to accommodate these electrodes and to simultaneously reduce the solvent volume required which would reduce the amount of starting material needed per reaction. A rubber stopper with needles was used to secure the electrodes and the thermocouple in the cell. The platinised titanium mesh electrodes also have a slightly larger surface area (3.3 $cm^2$) compared to the platinum wire electrodes (2.2 $cm^2$).

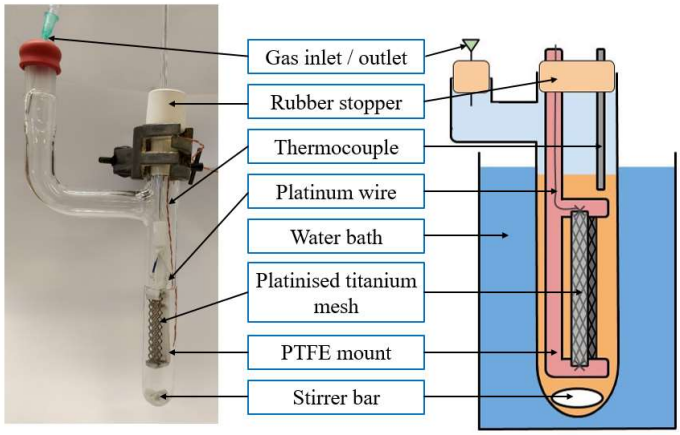
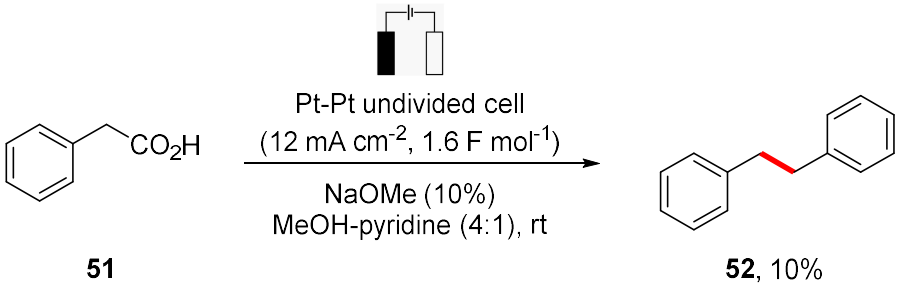



Figure 2.5 – Picture and schematic of the second electrolysis cell

With the new cell in hand, the homocoupling of phenylacetic acid **51** was performed. The reaction used a 0.8 M solution of phenylacetic acid **51** with 10% NaOMe in a 4:1 mixture of MeOH-pyridine at rt (Scheme 2.49). A voltage of 5 V was passed through the cell to achieve an average current of 39 mA and an average current density of 12 mA $cm^{-2}$. Under these conditions, bibenzyl **52** was isolated in only 10% yield after chromatography, even lower than that from the equivalent experiment in the first cell. It is not clear why this reaction was so low yielding.



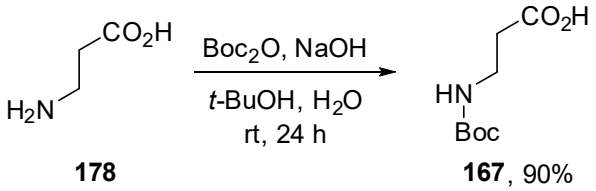

Scheme 2.49

Initial efforts on Kolbe electrolysis for the homocoupling of phenylacetic acid **51** were disappointing as the result obtained from Mendonça *et al.*'s work could not be reproduced. However, an electrochemical cell had been developed that uses rigid platinised titanium mesh which ultimately lowered the solution resistance of the cell. Rather than spending time optimising a homocoupling reaction that was of no synthetic interest, work moved onto investigating the heterocoupling of nitrogen-containing carboxylic acids.

## 2.4 Anodic Decarboxylation of Primary Carboxylic Acids

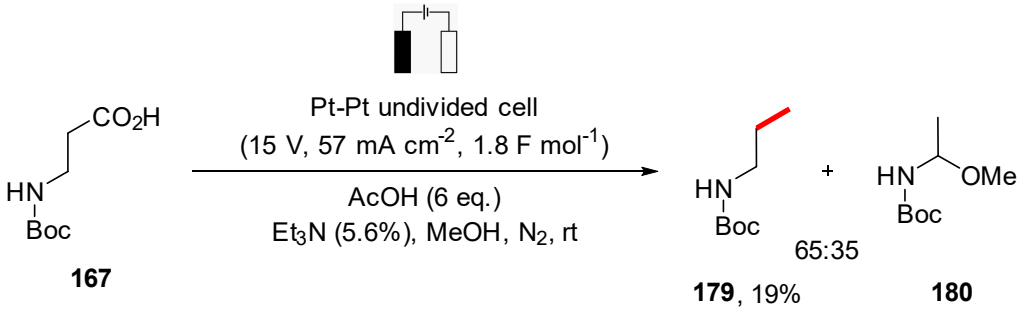
### 2.4.1 Heterocoupling of Acyclic *N*-Boc Amino Acids and Acetic Acid

The heterocoupling of *N*-Boc β-alanine **167** was chosen as the next reaction to explore. The synthesis of *N*-Boc β-alanine **167** was carried out using a literature procedure.[72] Boc protection of β-alanine **178** with $Boc_2O$ was performed to give *N*-Boc β-alanine **167** in 90% yield on a 56 mmol scale (Scheme 2.50).




Scheme 2.50

With *N*-Boc β-alanine **167** in hand, Kolbe electrolysis was performed with acetic acid in an attempt to synthesise *N*-Boc propyl amine **179** (Scheme 2.51). The initial set of conditions were based on Seebach *et al.*'s work on the electrochemical heterocoupling of acid **61** and acid **63** (see Scheme 2.13).[47] Therefore, a 0.09 M solution of *N*-Boc β-alanine **167** in MeOH with 6 eq. of acetic acid and 5.6% $Et_3N$ at rt under $N_2$ was used. The 5.6% $Et_3N$ refers to the percentage of $Et_3N$ compared to the total concentration of acids (substrate and acetic acid) required to give 5.6% neutralisation. A voltage of 15 V was passed through the solution to achieve 57 mA $cm^{-2}$ for 1.8 F $mol^{-1}$ of charge.




Scheme 2.51

There are three key differences to Seebach's original conditions. First, the high current density (370 mA $cm^{-2}$) used in Seebach's work could not be replicated since 15 V was the maximum that this circuit could achieve as only one power pack was used at this point (see later for use of two power packs). Second, in this set-up, the reaction was carried out

under constant voltage rather than constant current. Third, in this experiment, 1.8 F $mol^{-1}$ was passed whereas 1.5 F $mol^{-1}$ was used by Seebach. During the experiment, the voltage and current density were measured using the LabJack©. Figure 2.6 shows the voltage (black line) and current density (red line) throughout the experiment that is shown in Scheme 2.51. The voltage stayed fairly constant at around 15 V with regular fluctuations. The fluctuations are due to the polarity inversion of the electrodes which is used to minimise passivation. The current density increased slightly from 56 to 59 mA $cm^{-2}$ before dropping to 50 mA $cm^{-2}$ after 1 hour. This could be due to passivation of the electrodes, which would increase the resistance through the cell. Alternatively, the decrease in current density could indicate that there was no starting material left after 1 hour, as this would also increase the resistance since the starting material acts as the electrolyte. The reaction was stopped after 1.5 h and, at this point, 1.8 F $mol^{-1}$ of charge had been passed.

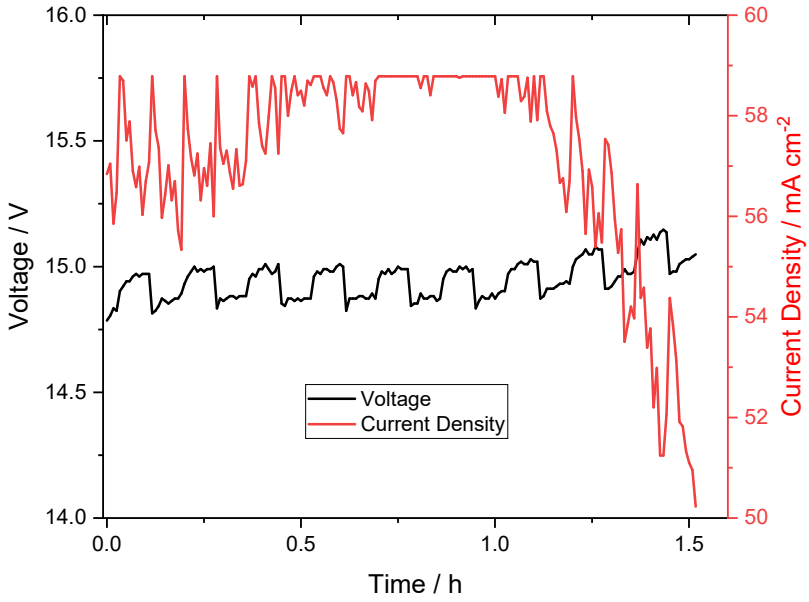
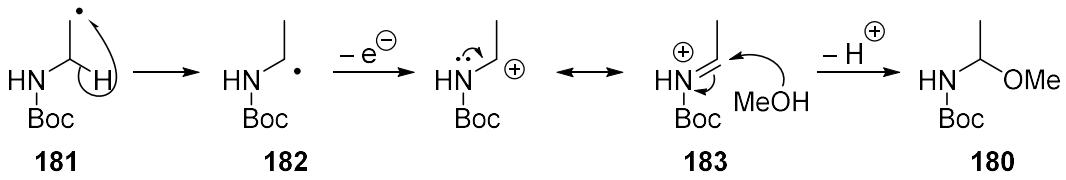



Figure 2.6 – Cell voltage and current density throughout the electrolysis of *N*-Boc β-alanine **167** and acetic acid (Scheme 2.51).

In the crude product obtained after work-up, a 65:35 mixture of the desired heterocoupled product *N*-Boc propyl amine **179** and *N*-Boc methoxy amine **180** was observed by $^{1}H$ NMR spectroscopy. Upon purification by chromatography, *N*-Boc propyl amine **179** was isolated in 19% yield. In this particular experiment, *N*-Boc methoxy amine **180** was not isolated, but it has been isolated and characterised in other experiments, as discussed later.

A proposed mechanism for the formation of *N*-Boc methoxy amine **180** is shown in Scheme 2.52. Radical **181** would be formed in the standard way for Kolbe electrolysis. Then, a hydride shift to form the more stabilised radical **182**. This radical could then over oxidised to give iminium ion **183** which will be attacked by MeOH to give *N*-Boc methoxy amine **180**.

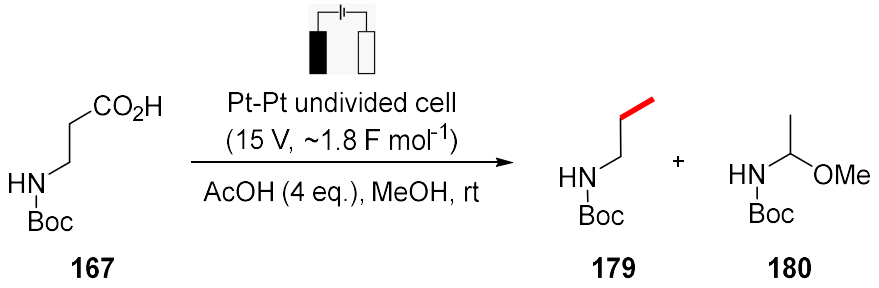



Scheme 2.52

Alternative conditions were then sought in order to improve the yield of the heterocoupled product, *N*-Boc propyl amine **179**. The use of KOH instead of $Et_3N$ was explored, and the conditions were based on those used by Schäfer *et al*. for the cyclisation and heterocoupling of alkene acid **110** to form pyrrolidine **111** (see Scheme 2.27).[57] Based on Schäfer's conditions, only 4 eq. of acetic acid was used, although a total concentration of acid was maintained at ~0.65 M. The KOH conditions were run under an air atmosphere instead of a $N_2$ atmosphere.

Thus, *N*-Boc β-alanine **167** was heterocoupled with acetic acid using a 0.13 M solution of *N*-Boc β-alanine **167**, 4 eq. of acetic acid and 5% KOH in MeOH in air at rt. 15 V were passed though the solution to achieve a current density of 49 mA $cm^{-2}$ for 1.8 F $mol^{-1}$ of charge. In this case, *N*-Boc propyl amine **179** was formed in a more encouraging 38% yield and *N*-Boc methoxy amine **180** was isolated in 17% yield (Table 2.2, entry 1). The ratio of *N*-Boc propyl amine **179** and *N*-Boc methoxy amine **180** in the crude product was 63:35, which is the same as that using $Et_3N$ (see Scheme 2.51). As the current density for this experiment (49 mA $cm^{-2}$) was lower than that used by Schäfer (360 mA $cm^{-2}$), higher current density was explored. The percentage of base was raised from 5% to 10% and 12%. This increased the current density from 49 to 84 and 93 mA $cm^{-2}$ due to the increased concentration of ions in the solution. At these higher current densities, the yield of *N*-Boc propyl amine **179** decreased (26-31%, Table 2.2, entries 2 and 3). Therefore, for subsequent reactions, 5% of base was used. Similar amounts of *N*-Boc methoxy amine

**180** were also observed in both experiments (65:35 mixture of **179** and **180** in the crude products).



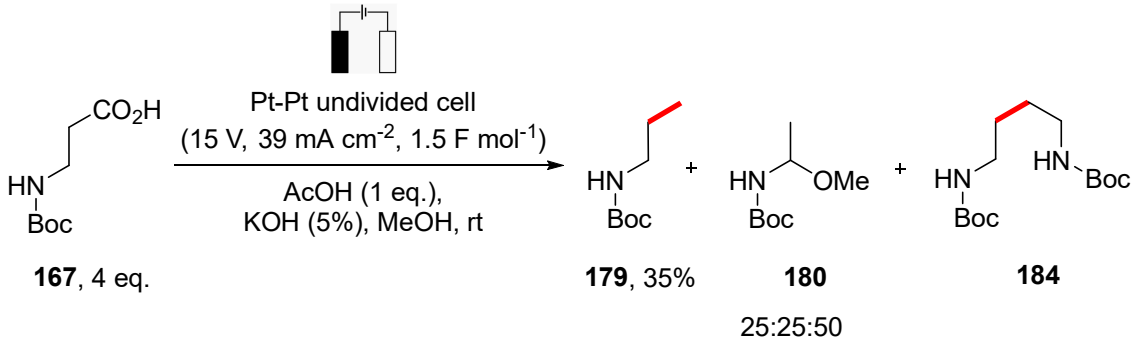

**167** **179** **180**

| Entry | Time (h:m) | Current Density ($mAcm^{-2}$) | KOH (%) | Yield of **179** (%)[a] | Yield of **180** (%)[a] | **179**:**180** |
|---|---|---|---|---|---|---|
| 1 | 1:48 | 49 | 5 | 38 | 17 | 65:35 |
| 2 | 1:03 | 84 | 10 | 31 | 13 | 65:35 |
| 3 | 0:52 | 93 | 12 | 26 | -[c] | 65:35 |

Table 2.2 – Kolbe electrolysis of *N*-Boc β-alanine with varying concentrations of base.

[a] Yield after chromatography, [b] Ratio of **179**:**180** determined from the $^1$H NMR spectrum of the crude product, [c] Not isolated.

Due to the nature of Kolbe electrolysis, it should not matter which acid is in excess. Therefore, the equivalents of the acids were switched. The KOH conditions from entry 1 of Table 2.2 were used, but with 1 eq. of acetic acid and 4 eq. of *N*-Boc β-alanine **167**. The heterocoupled *N*-Boc propyl amine **179** was obtained in 35% yield (Scheme 2.53), which compares well with the 38% yield of the standard reaction.




**167**, 4 eq. **179**, 35% **180** **184**

25:25:50

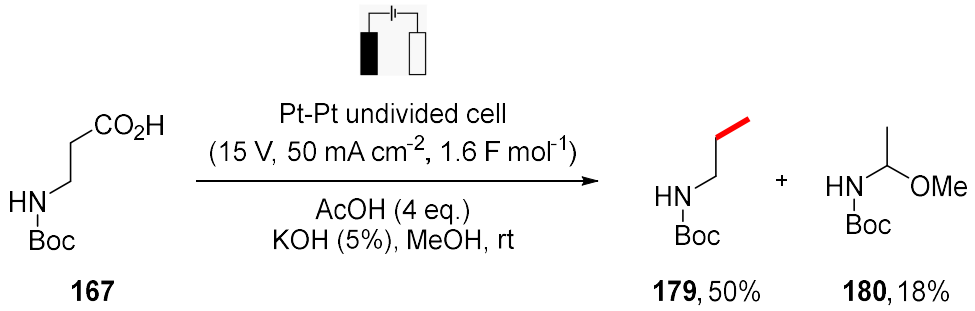
Scheme 2.53

The ratio of *N*-Boc propyl amine **179**, *N*-Boc methoxy amine **180** and di-*N*-Boc amine **185** in the crude product was 25:25:50 (by $^1$H NMR spectroscopy). In this experiment,

the total Kolbe coupling products includes both *N*-Boc propyl amine **179** and di-*N*-Boc amine **184**, as homocoupling was also observed. The ratio of Kolbe coupled products and *N*-Boc methoxy amine **179** was 75:25 (which is similar to the 65:35 ratio observed in the reactions presented in Table 2.2). The large amount of di-*N*-Boc amine **184** observed was unsurprising as, in this experiment, *N*-Boc β-alanine **167** was in excess (4 eq.). Therefore, the likelihood of two *N*-Boc ethyl radicals coupling was much more likely.

At this point, it was possible that *N*-Boc propyl amine **179** could be volatile, which could be affecting its isolated yields. The boiling point of *N*-Boc propyl amine **179** reported in the literature was variable. According to Yoshifuji *et al*., *N*-Boc propyl amine **179** boils at 68 °C at 11 mbar[73] whereas Kim *et al*. reports it as boiling at 65-70 °C at 51 mbar.[74] Therefore, the volatility of *N*-Boc propyl amine **179** was investigated on the high vacuum in the laboratory (approximately 1 mbar) and it was found that 6 mg of material (from 52 mg) was lost over 2 h 30 min. Since some of *N*-Boc propyl amine **179** was lost during the high vacuum drying, the yields reported so far may not give a good indication of the success of the reaction. Hence, to minimise loss of product, the experimental procedure for the synthesis of *N*-Boc propyl amine **179** was modified. This included changing to more volatile solvents for the chromatography, and not drying the crude and purified product under high vacuum.

The reaction shown in Table 2.2 entry 1 with *N*-Boc β-alanine **179** and acetic acid was repeated with the knowledge of its volatility. The rotary evaporator was not set at full vacuum when removing the solvents in the work-up and chromatography. In addition, the chromatography solvents were changed from hexane-EtOAc to hexane-$Et_2O$ and the product was not dried under high vacuum. With these changes, the heterocoupled product, *N*-Boc propyl amine **179**, was isolated in an improved 50% yield along with an 18% yield of *N*-Boc methoxy amine **180** (Scheme 2.54). Further work completed by another member of the O'Brien group showed that the heterocoupling of *N*-Boc β-alanine and acetic acid gave *N*-Boc propyl amine **179** and *N*-Boc methoxy amine **180** in 53% and 25% yield respectively,[75] indicating the reproducibility of the reaction. Reactions carried out from here onwards using *N*-Boc β-alanine **167** used this procedure for the work-up and purification.




**167** **179**, 50% **180**, 18%

Scheme 2.54

The current density and voltage trace throughout the Kolbe electrolysis of *N*-Boc β-alanine **167** and acetic acid is show in Figure 2.7. The voltage remains at 15.2 V for the duration of the experiment and the current density increases slightly from 48 to 55 mA $cm^{-2}$. The reaction was stopped after 1.6 F $mol^{-1}$ of charge was passed.

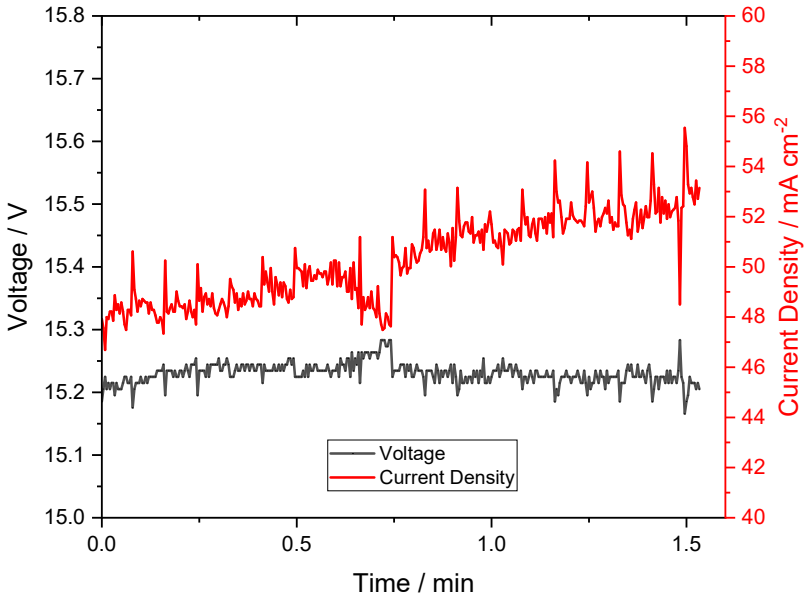
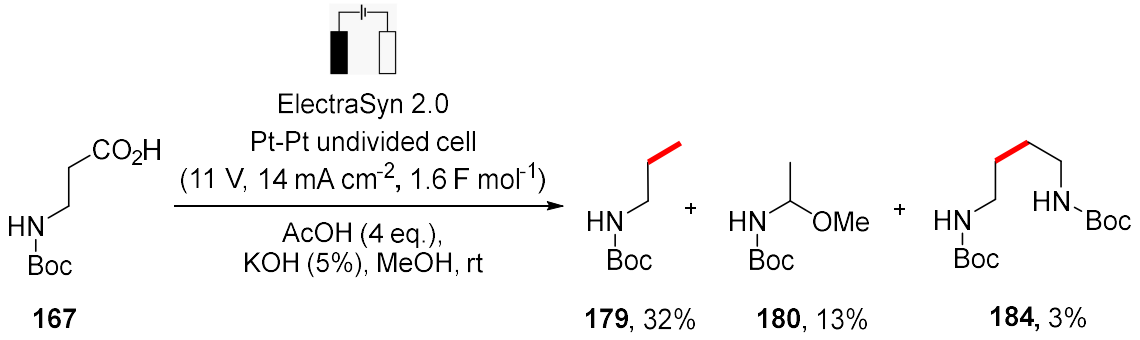



Figure 2.7 – Cell voltage and current density for electrolysis of *N*-Boc β-alanine **167** and acetic acid (Scheme 2.54)

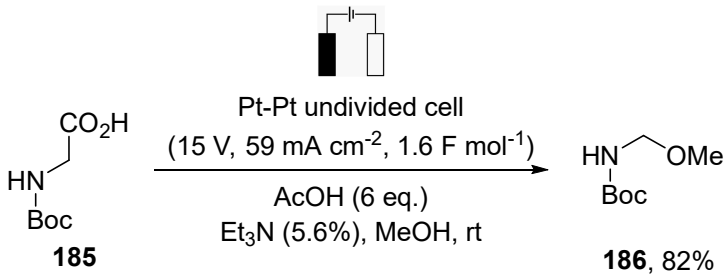
One of the main issues with organic electrochemistry is the need for bespoke electrochemical cells.[76] To address this, Baran collaborated with the company IKA® to design and build a standardised set-up (ElectraSyn 2.0) that organic chemists could use. The Kolbe electrolysis coupling of *N*-Boc β-alanine **167** and acetic acid was therefore performed in an IKA® ElectraSyn 2.0 set-up. The undivided electrochemical set-up contained two platinised copper electrodes, each with a surface area of 7.1 $cm^2$. The standard KOH conditions were used and an average current density of 14 mA $cm^{-2}$ was applied until 1.6 F $mol^{-1}$ of current was passed, by using an average voltage of 11 V. Upon

purification by chromatography, *N*-Boc propyl amine **179** and *N*-Boc methoxy amine **180** were isolated in 32% and 13% yields respectively (Scheme 2.55). The homocoupling of *N*-Boc β-alanine **167**, forming di-*N*-Boc amine **184** (3% yield), was also observed. This was the first experiment in the ElectraSyn 2.0 cell and it was pleasing that it worked. However, the yield of *N*-Boc propyl amine **179** (32%) was lower than the best result in the bespoke set-up (see Scheme 2.54, 50% yield). This is likely due to the lower current density employed in the ElectraSyn 2.0 experiment.



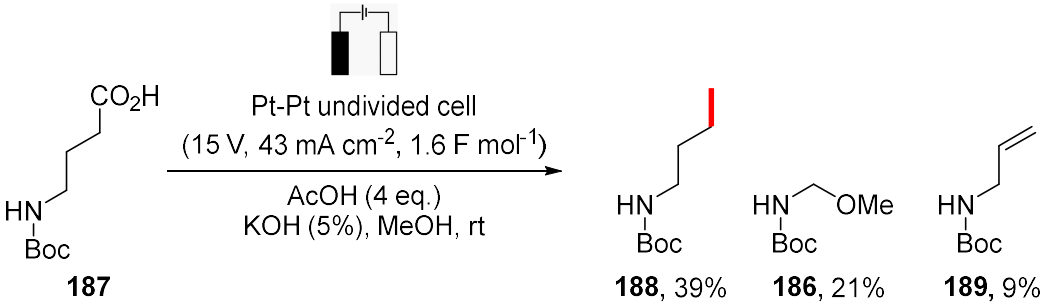

Scheme 2.55

Further work completed by a co-worker, J. Churchill, investigated the formation of methoxy amine and alkene products using *N*-Boc carboxylic acids with varying chain lengths.[75] Subjection of *N*-Boc glycine **185** and acetic acid to Kolbe electrolysis conditions gave no observable heterocoupled product. However, *N*-Boc methoxy amine **186** was isolated in 82% yield after chromatography (Scheme 2.56). It is likely that the radical intermediate readily underwent over-oxidation to the more stable carbocation. Attack of MeOH onto the carbocation would then give *N*-Boc methoxy amine **186**. *N*-Boc glycine **185** is more prone to over-oxidation due to the formed carbocation being α to nitrogen.



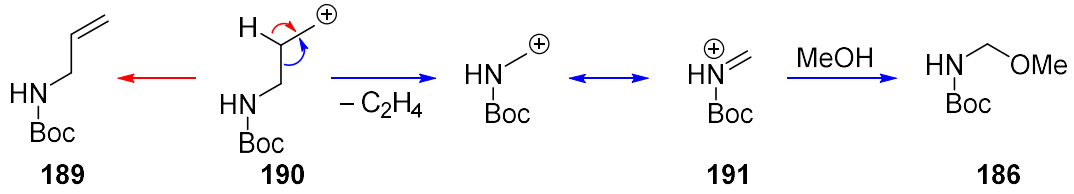

Scheme 2.56

J. Churchill also subjected *N*-Boc butanoic acid **187** to Kolbe electrolysis with acetic acid. In this case, with a longer separation between the amine and the formed radical, the heterocoupled product, *N*-Boc butyl amine **188**, was isolated in a good 39% yield. In addition, *N*-Boc methoxy amine **186** (21%) and *N*-Boc alkene **189** (9% yield) were also obtained (Scheme 2.57).



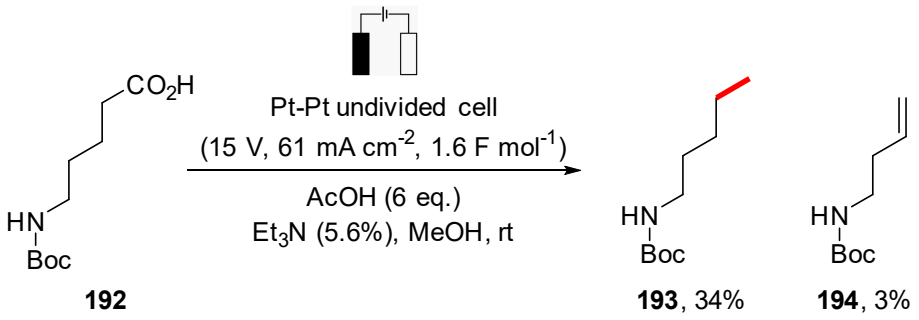

Scheme 2.57

Both isolated side-products, *N*-Boc methoxy amine **186** and *N*-Boc alkene **189**, would be formed from carbocation **190** itself formed by over-oxidation of the radical intermediate after decarboxylation. Carbocation **190** could undergo elimination to form *N*-Boc alkene **189** (Scheme 2.58, red route). Alternatively, carbocation **190** could fragment to an akene and a more stable carbocation (α to nitrogen), iminium ion **191**. Subsequent reaction of iminium ion **191** with MeOH would give *N*-Boc methoxy amine **186 (**Scheme 2.58, blue route).




Scheme 2.58

Finally, the heterocoupling of *N*-Boc pentanoic acid **192** and acetic acid was also investigated by the other group member. The heterocoupled product, *N*-Boc pentyl amine **193**, was formed in 34% yield along with a small amount of *N*-Boc alkene **194** (3%) (Scheme 2.59). Overall, it is shown that over-oxidation of the radical intermediate is a common problem, regardless of the distance of the radical to the nitrogen.




Scheme 2.59

Overall, all of the results in the group with primary radicals derived from acyclic *N*-Boc amino acids have shown that over-oxidation of the radical intermediate to a carbocation is a significant competing process. It is thus a common problem, regardless of the distance between the radical and the amino group. This competing process leads to a range of different products, depending on the *N*-Boc amino acid structure. Nonetheless, yields of heterocoupled product from 34-53% were obtained.

## 2.4.2 Heterocoupling of *N*-Boc Piperidines and Acetic Acid

Piperidine is a very common motif in pharmaceuticals[77] and, therefore, to expand the scope of Kolbe electrochemical heterocoupling, two primary carboxylic acids, *N*-Boc piperidine carboxylic acids, (*S*)-**168** and *rac*-**169** were selected (Figure 2.8). *N*-Boc 2-acetic acid piperidine (*S*)-**168** of high er (98:2 er) was available from within the group[78] and *N*-Boc 3-acetic acid piperidine **169** is commercially available.

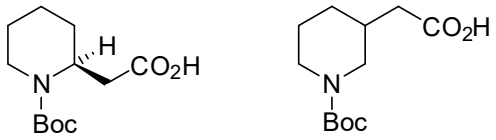
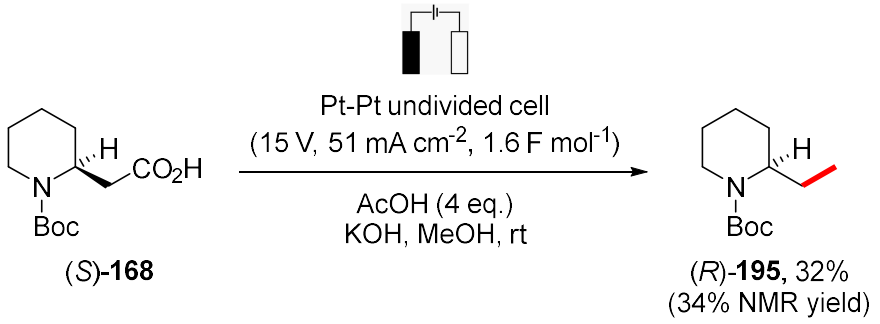



Figure 2.8 – Two *N*-Boc piperidine carboxylic acids

The heterocoupling of *N*-Boc 2-acetic acid piperidine (*S*)-**168** with acetic acid was investigated first. The standard KOH conditions established in the previous section (Table 2.2, entry 1) were used. A 0.13 M solution of *N*-Boc 2-acetic acid piperidine (*S*)-**168**, 4 eq. of acetic acid and 5% KOH in MeOH at rt was used. An average current density of 51 mA $cm^{-2}$ was used until 1.6 F $mol^{-1}$ of charge was passed, by using an average voltage

of 15 V. Upon purification, *N*-Boc 2-ethyl piperidine (*R*)**-195** was isolated in 32% yield (Scheme 2.60).



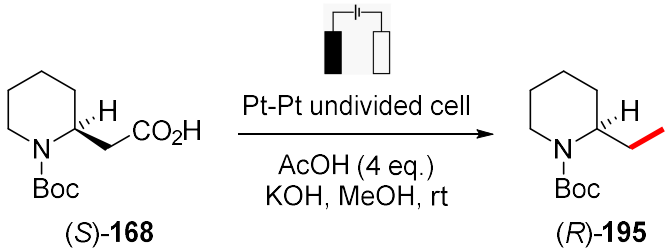

Scheme 2.60

In order to establish a quick method for analysing the amount of product without the need for purification, it was decided to develop an analytical method to determine the NMR yield of *N*-Boc 2-ethyl piperidine (*R*)**-195**. This was achieved by taking a known percentage of the crude product and performing $^{1}$H NMR spectroscopy along with a known amount of an internal standard. Mesitylene was used as the internal standard and the integrals of its aromatic protons were compared with the $CH_3$ protons on *N*-Boc 2-ethyl piperidine (*R*)**-195**, which allowed calculation of an NMR yield. For this reaction (Scheme 2.60), the NMR yield was 34%, which matched well with the isolated yield (32%).

In an attempt to increase the yield of the heterocoupled product (*R*)**-195**, reactions under different conditions were investigated and the results are presented in Table 2.3. It was thought that the excess current could potentially oxidise the product further when all of the starting material had been used up. Therefore, the reaction was repeated using 1.2 F mol$^{-1}$ of current instead of 1.6 F mol$^{-1}$. *N*-Boc 2-ethyl piperidine (*R*)**-195** was obtained in an NMR yield of 43% with an isolated yield of 29% (Table 2.3, entry 2).

The maximum voltage was then raised to 30 V by adjusting the set-up to use two power packs instead of one. The heterocoupling of *N*-Boc 2-acetic acid piperidine (*S*)**-168** with acetic acid was performed using 30 V. This more than doubled the current density achieved from 51 to 112 mA cm$^{-2}$ and halved the reaction time from 1 h 30 min to 43 min. Nevertheless, *N*-Boc 2-ethyl piperidine (*R*)**-195** was observed in 28% NMR yield and an isolated yield of 25% (Table 2.3, entry 3). Finally, in an attempt to increase the current density even further, the percentage of base was raised from 5% to 10% and using

30 V. This raised the current density to 186 mA $cm^{-2}$ and the NMR yield for *N*-Boc 2-ethyl piperidine (*R*)**-195** was 32% (Table 2.3, entry 4). An isolated yield was not obtained for this reaction. Disappointingly, the changes made to the electrochemical conditions seemed to have little effect on the outcome.



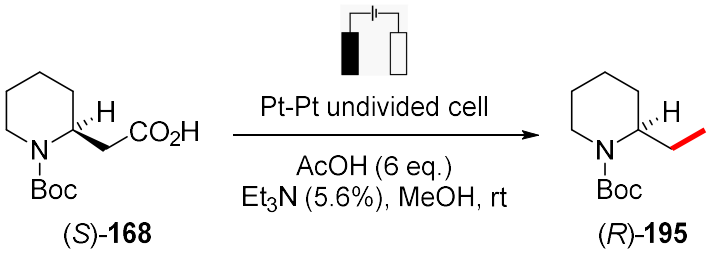

(*S*)-**168** (*R*)-**195**

| Entry | % KOH (%) | Eq. of current (F $mol^{-1}$) | Current Density (mA $cm^{-2}$) | Voltage (V) | Yield (%)[a] | NMR Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | 5 | 1.6 | 51 | 15 | 32 | 34 |
| 2 | 5 | 1.2 | 50 | 15 | 29 | 43 |
| 3 | 5 | 1.7 | 112 | 30 | 25 | 28 |
| 4 | 10 | 1.6 | 186 | 30 | - | 32 |

Table 2.3 – Kolbe electrolysis of *N*-Boc 2-acetic acid piperidine (*S*)-**168** with varying concentrations of base. [a] Yield after chromatography, [b] NMR yield determined by comparing the integrals of the product and internal standard in the $^1$H NMR spectrum of the crude product.

Next, the preparation of *N*-Boc 2-ethyl piperidine (*R*)**-195** was studied using the standard $Et_3N$ conditions. A 0.09 M solution of *N*-Boc 2-acetic acid piperidine (*S*)-**168**, 6 eq. of acetic acid and 5.6% of $Et_3N$ in MeOH at rt and under $N_2$ was used. A voltage of 15 V was passed through a solution to achieve an average current density of 59 mA $cm^{-2}$ for 1.5 F $mol^{-1}$ of charge. *N*-Boc 2-ethyl piperidine (*R*)**-195** was isolated in 28% yield (Table 2.4, entry 1).

Three more optimisation attempts were made by increasing the voltage up to 30 V, not using an inert atmosphere, and lowering the equivalents of current to 1.2 F $mol^{-1}$. The NMR yields for *N*-Boc 2-ethyl piperidine (*R*)**-195** were 20%, 25% and 27% respectively, with the latter also having an isolated yield of 24% (Table 2.4, entries 2-4). As with the KOH conditions, these changes to the electrochemical conditions had little effect on the yield of *N*-Boc 2-ethyl piperidine (*R*)**-195**.



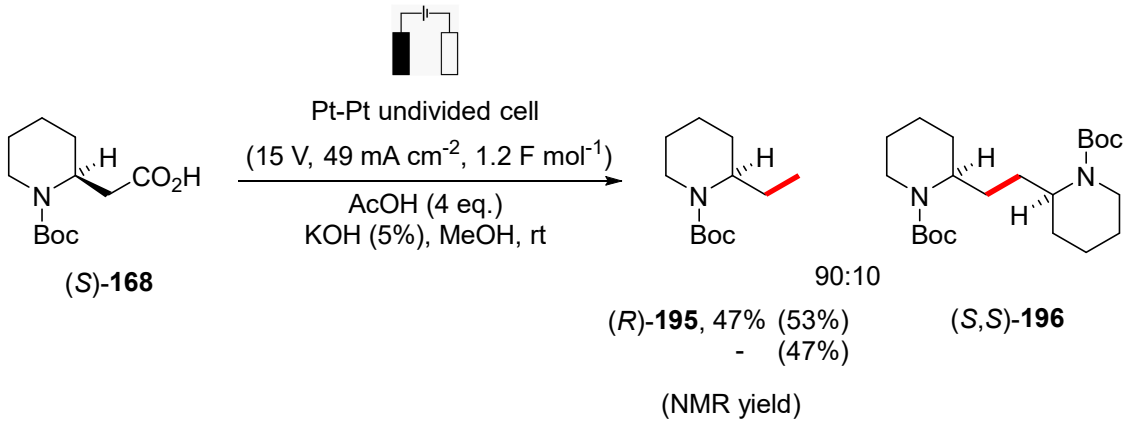

(*S*)-**168** (*R*)-**195**

| Entry | Eq. of current (F mol$^{-1}$) | Atmosphere | Current Density (mA cm$^{-2}$) | Voltage (V) | Yield (%)[a] | NMR Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | 1.5 | $N_2$ | 59 | 15 | 28 | - |
| 2 | 1.5 | $N_2$ | 138 | 30 | - | 20 |
| 3 | 1.5 | Air | 140 | 30 | - | 25 |
| 4 | 1.2 | Air | 143 | 30 | 24 | 27 |

Table 2.4 – Kolbe elecytrolysis of *N*-Boc 2-acetic acid piperidine (*S*)-**168** with varying conditions.
[a] Yield after chromatography, [b] NMR yield determined by comparing the integrals of the product and internal standard in the $^1$H NMR spectrum of the crude product.

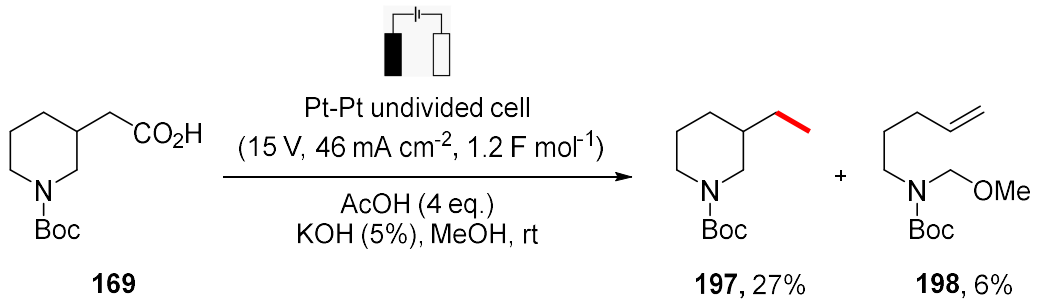
At this stage, it was thought that *N*-Boc 2-ethyl piperidine (*R*)-**195** may also be volatile and that some of the product could be lost during high vacuum drying. The boiling point of (*R*)-**195** has not been reported in the literature. Therefore, the compound was tested in the same way previously used on *N*-Boc propyl amine **179**, by subjecting it to low pressure (approximately 1 mbar) on the high vacuum in the laboratory. After 3 h 30 min on the high vacuum, 15 mg of *N*-Boc 2-ethyl piperidine (*R*)-**195** was lost (from 36 mg).

Therefore, a repeat of the reaction shown in Table 2.4 (entry 2) was performed whilst adjusting the purification method by using more volatile solvents and no use of the high vacuum. Encouragingly, *N*-Boc 2-ethyl piperidine (*R*)-**195** obtained in a 53% NMR yield and was isolated in 47% yield (Scheme 2.61). This reaction was then repeated and a 47% NMR yield was obtained, showing that the reaction is reproducible. The crude product from both experiments contained a 90:10 mixture of heterocoupled (*R*)-**195** and homocoupled (*S*,*S*)-**196**. On re-analysis of the previous reactions shown in Table 2.4, homocoupled (*S*,*S*)-**196** was observed in the $^1$H NMR of the crude products but the amount of it could not be quantified accurately due to overlapping signals.



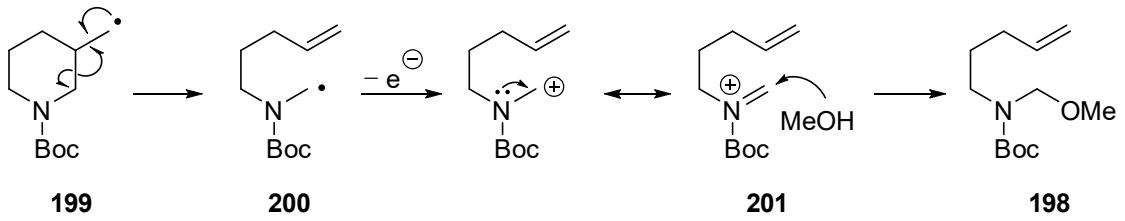

Scheme 2.61

Next, racemic *N*-Boc 3-acetic acid piperidine **169** was explored in order to determine the effect of the location of the carboxylic acid group around the ring. Using the standard KOH conditions with 1.2 F $mol^{-1}$ of current, *N*-Boc 3-acetic acid piperidine **169** was coupled with acetic acid to give *N*-Boc 3-ethyl piperidine **197** in 27% yield (Scheme 2.62). In this experiment, an unexpected side-product, *N*-Boc alkene methoxy amine **198**, was also isolated in 6% yield.




Scheme 2.62

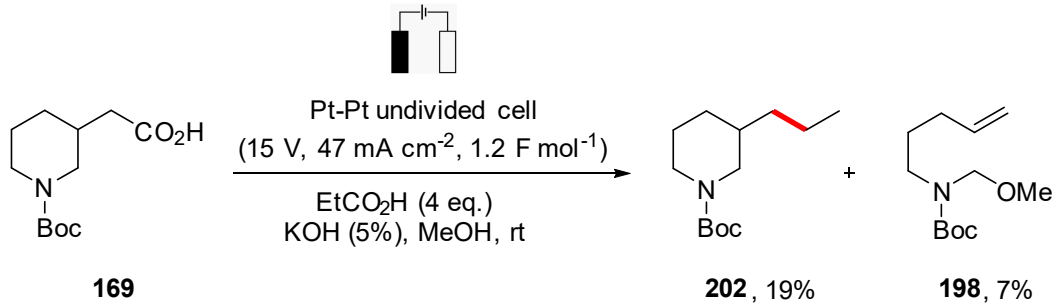
The proposed mechanism for the formation of *N*-Boc alkene methoxy amine **198** is shown in Scheme 2.63. The radical intermediate **199** generated from the oxidation and decarboxylation could undergo a ring opening to form the more stable radical **200**. Over oxidation of the radical could give iminium ion **201**. The iminium ion can then be attacked by MeOH to form the observed *N*-Boc alkene methoxy amine **198**. This fragmentation process matches well with the acyclic substrate **187** shown in Scheme 2.58.




Scheme 2.63

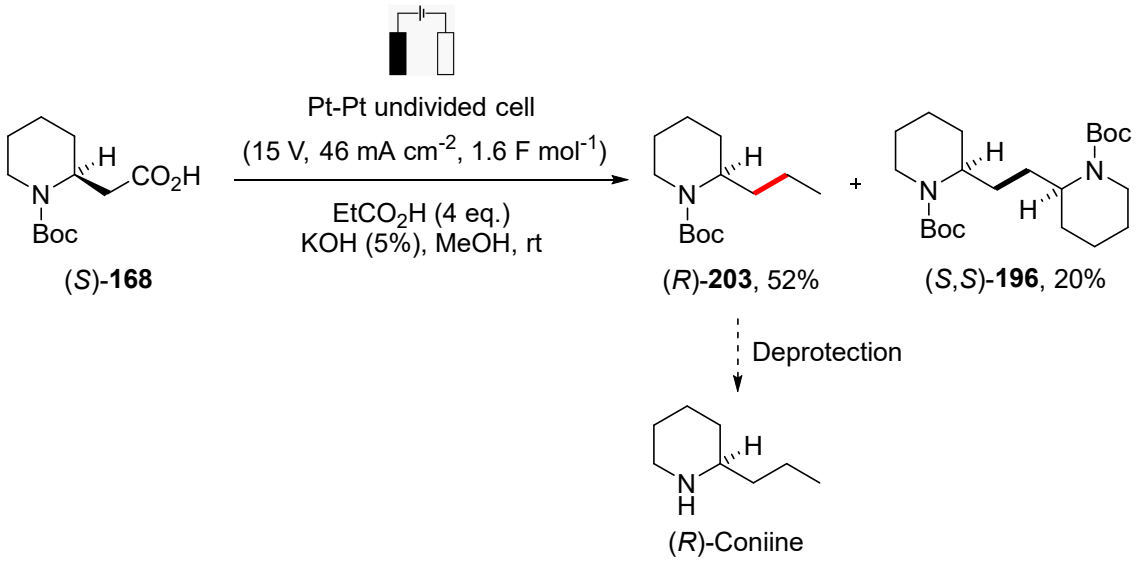
## 2.4.3 Heterocoupling with a Range of Co-Acids

In order to explore the scope of the reaction, the use of different co-acids to introduce a group other than a methyl substituent was investigated. To start, the heterocoupling of *N*-Boc 3-acetic acid **169** with propanoic acid was explored. A solution of *N*-Boc 3-acetic acid piperidine **169**, 4 eq. of propanoic acid and 5% KOH in MeOH was used. 15 V were passed through the solution for 1.2 F $mol^{-1}$ of charge which gave a current density of 47 mA $cm^{-2}$. Using these conditions, *N*-Boc propyl piperidine **202** was isolated in 19% yield with *N*-Boc alkene methoxy amine **198** in 7% yield (Scheme 2.64). It is unclear as to why using propanoic acid as the co-acid gave a slightly reduced heterocoupling yield compared to acetic acid (27%).



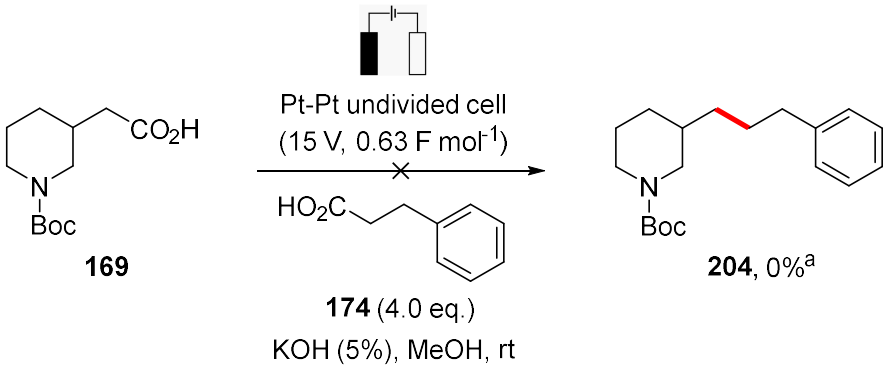

Scheme 2.64

In contrast, the heterocoupling of *N*-Boc 2-acetic acid piperidine (*S*)-**168** with propanoic acid was more successful and, pleasingly, *N*-Boc propyl piperidine (*R*)-**203** was isolated in 52% yield. The homocoupled product, di-*N*-Boc piperidine (*S*,*S*)-**196**, was also isolated in 20% yield (Scheme 2.65). A natural product from the hemlock plant, (*R*)-coniine, could be synthesised from *N*-Boc 2-propyl piperidine (*R*)-**203**. The synthesis of (*R*)-coniine would involve the deprotection of *N*-Boc 2-propyl piperidine (*R*)-**203**. However, the removal of the Boc group was not carried out due to the toxicity of (*R*)-coniine ($LD_{50}$ = 7.0 mg/kg).[79]




Scheme 2.65

It was then decided to look at aromatic-containing substrates for use in Kolbe electrolysis to see if they were compatible co-acids. The higher molecular weight would also help with the volatility issues as it should remove any loss of product due to volatility. In an attempt to couple *N*-Boc 3-acetic acid piperidine **169** with hydrocinnamic acid **174**, 15 V and KOH was used as the base (Scheme 2.66). Unexpectedly, the current density, shown in Figure 2.9 (red line), dropped significantly at the start of the reaction from 33 mA $cm^{-2}$ to 9 mA $cm^{-2}$ after only 30 minutes. Therefore, only 0.6 F $mol^{-1}$ of current was passed during this reaction as the current density decreased to 3 mA $cm^{-2}$ and the reaction would have taken too long to complete the full 1.6 F $mol^{-1}$. The electrodes could have passivated during the reaction, even with polarity inversion, which greatly increases the resistance of the cell. In addition, by using an aromatic-containing substrate, the aromatic group could be oxidised instead, and could passivate the electrodes by binding to it. Purification was not performed on the crude product as only the starting materials **169** and **174** were observed in the $^{1}$H NMR spectrum of the crude product.




Scheme 2.66 – [a] No product by mass spectrometry. Starting materials observed in $^1$H NMR spectroscopy of the crude mixture.

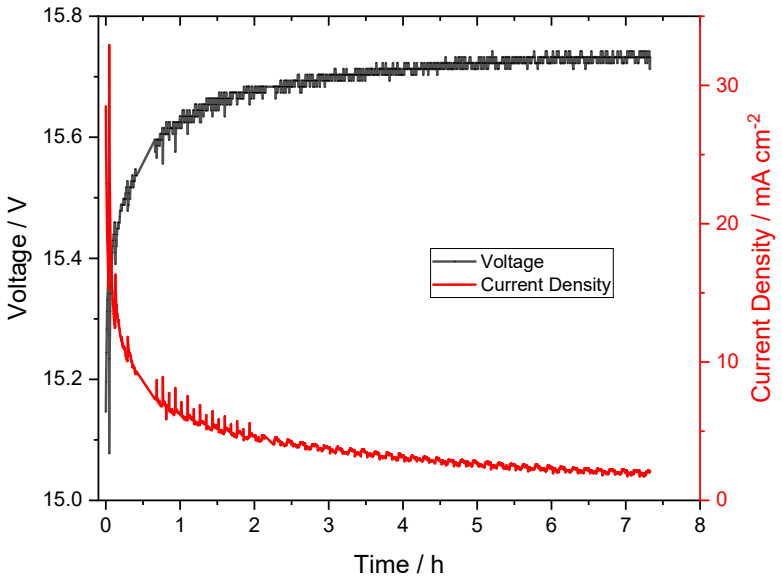
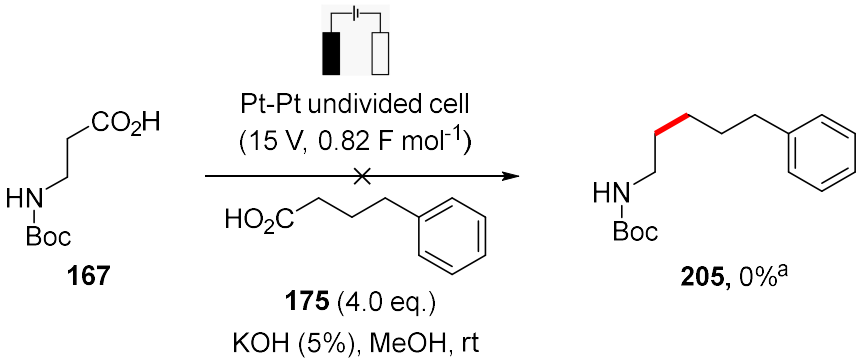


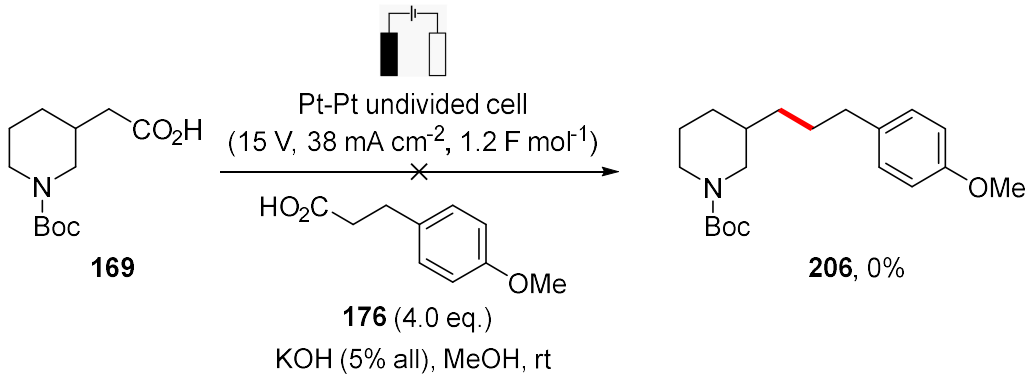

Figure 2.9 – Cell potential throughout the electrolysis of *N*-Boc 3-acetic acid **169** and hydrocinnamic acid **174**

Next, 4-phenylbutryic acid **175** was investigated. A different *N*-Boc acid, *N*-Boc β-alanine **167**, was also chosen in order to determine if the issues still occurred with a different substrate. Unfortunately, the current density decreased in a similar fashion to the previous reaction and only 0.8 F mol$^{-1}$ of current was passed (Scheme 2.67). Purification was not performed on the crude product as only the starting materials **167** and **175** were observed in the $^1$H NMR spectrum of the crude product.



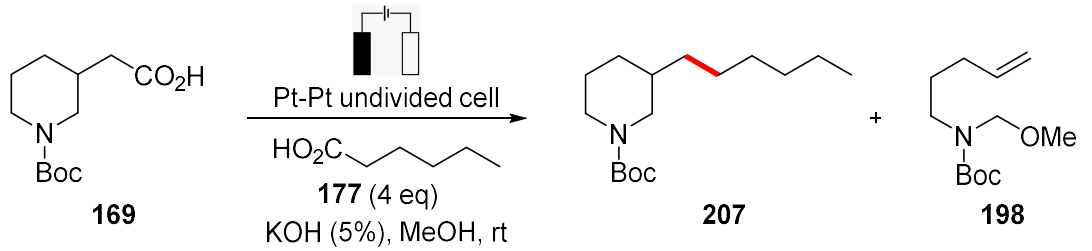

Scheme 2.67 – [a] No product by mass spectrometry. Starting materials observed in $^1$H NMR spectroscopy of the crude mixture.

An aromatic co-acid that contained an electron donating group was then explored. *N*-Boc 3-acetic acid piperidine **169** and 3-(4-methoxyphenyl)propanoic acid **176** were subjected to Kolbe electrolysis with 1.2 F mol$^{-1}$ of current. In this case, the current density stayed relatively stable at 38 mA cm$^{-2}$. However, upon purification by chromatography, only 3-(4-methoxyphenyl)propanoic acid **176** was observed (Scheme 2.68).




Scheme 2.68

Finally, an aliphatic, higher molecular weight co-acid was then considered as the aromatic co-acids were unsuccessful. *N*-Boc 3-acetic acid piperidine **169** was coupled with hexanoic acid **177** with 1.2 F mol$^{-1}$ of charge and *N*-Boc 3-hexyl piperidine **207** was isolated in 27% yield (Table 2.5, entry 1). However, both starting materials were isolated, *N*-Boc 3-acetic acid piperidine **169** in 41% yield, and hexanoic acid **177** in 20% yield (relative to 4 eq. of hexanoic acid **177**). *N*-Boc methoxy amine **198** was also observed in the $^1$H NMR spectrum of the crude product but was not isolated.



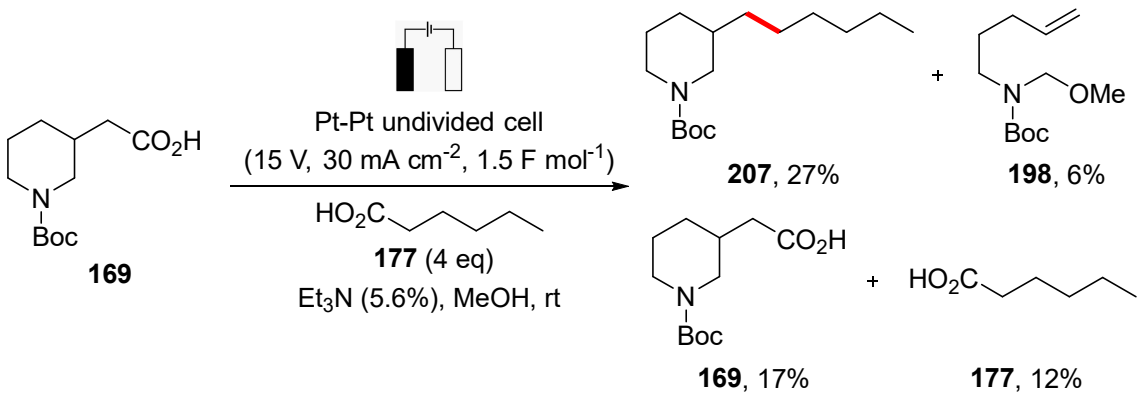

| Entry | Charge (F mol$^{-1}$) | Current Density (mA cm$^{-2}$) | Voltage (V) | Yield (%)[a] | | | |
|---|---|---|---|---|---|---|---|
| | | | | **207** | **198** | **169** | **177**[b] |
| 1 | 1.24 | 31 | 15 | 27 | -[c] | 41 | 20 |
| 2 | 1.58 | 30 | 15 | 38 | 7 | 25 | 12 |
| 3 | 1.59 | 60 | 31 | 28 | 5 | -[c] | 16 |
| 4 | 2.48 | 24 | 15 | 38 | 7 | 0 | 0 |

Table 2.5 – Kolbe electrolysis of *N*-Boc 3-acetic acid piperidine **169** with hexanoic acid **177**.

[a] Yield after chromatography, [b] Relative to 4 eq. of hexanoic acid **177**, [c] Not isolated but observed in the $^1$H NMR spectrum of the crude product.

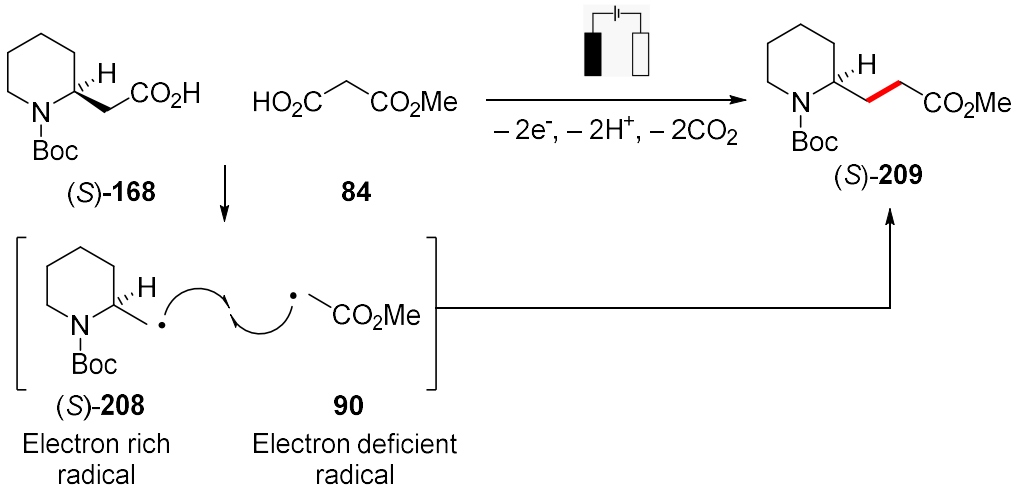
In an attempt to consume all of the starting material and increase the yield of the heterocoupled product, 1.6 F mol$^{-1}$ of charge was used instead of 1.2 F mol$^{-1}$. *N*-Boc 3-hexyl piperidine **207** was isolated in 38% yield with 7% *N*-Boc methoxy amine **198** (Table 2.5, entry 2). Unfortunately, *N*-Boc 3-acetic acid piperidine **169** and hexanoic acid **177** were still present in 25% and 12% yield respectively. The voltage was then increased to 31 V to see if the yield of the heterocoupled *N*-Boc 3-hexyl piperidine **207** increased. However, the yield was only 28% and both starting materials were still observed (Table 2.5, entry 3). Finally, the electrolysis was run until no starting material was observed by thin layer chromatography, which required 2.5 F mol$^{-1}$ of charge. In this case, *N*-Boc 3-hexyl piperidine **207** was isolated in 38% yield with 7% *N*-Boc methoxy amine **198** (Table 2.5, entry 4). It was unclear as to why such a large amount of current (2.5 F mol$^{-1}$) was required.

The use of $Et_3N$ in place of KOH was then studied. Using $Et_3N$, *N*-Boc 3-hexyl piperidine **207** was isolated in 27% yield, along with *N*-Boc methoxy amine **198** (6% yield), *N*-Boc 3-acetic acid piperidine **169** (17% yield) and hexanoic acid **177** (12% yield) (Scheme 2.69).




Scheme 2.69

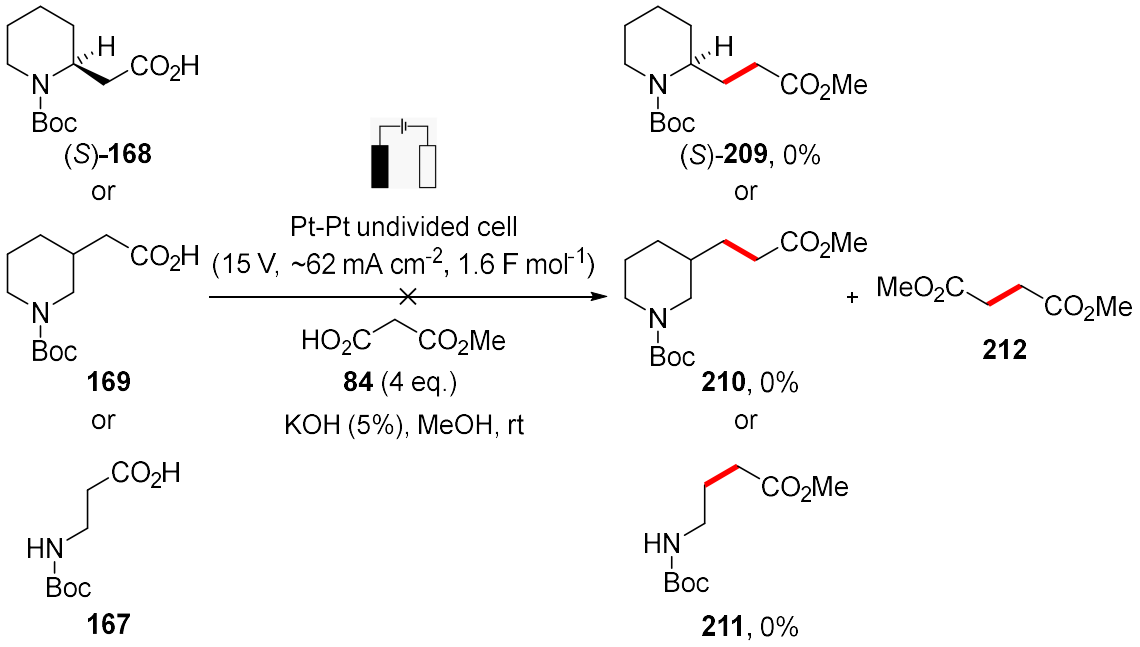
Next, radical polarity was briefly explored to see if it could have an influence on the heterocoupling reaction. Thus, a heterocoupling between an electron rich alkyl radical and an electron deficient alkyl radical was considered. For example, with monomethyl malonate **84**, an electron deficient radical **90** would be produced. This radical could couple efficiently with an electron rich alkyl radical such as *N*-Boc piperidine radical (*S*)-**168**. In addition, the electron deficient radical will be less likely to be over-oxidised to a carbocation (Scheme 2.70).




Scheme 2.70

In order to test this, three different *N*-Boc acids ((*S*)-**168**, **169** and **167**) were chosen to couple with monomethyl malonate **84**, using the standard KOH conditions. Unfortunately, no heterocoupled products were observed for all three reactions (Scheme 2.71). The major components in the crude products were monomethyl malonate **84** and di-ester **212** as shown by the $^{1}$H NMR spectra. In the reaction with *N*-Boc 2-acetic

acid piperidine (*S*)-**168**, a 37% yield of di-ester **212** was isolated (based on 4 eq. of **84**). It is possible that the difference in p$K_a$ of the acids could explain the lack of success in the heterocoupling reactions with monomethyl malonate **84**. The p$K_a$ of monomethyl malonate **84** is ~3 (malonic acid p$K_a$ is 2.83)[80], whereas alkyl acids typically have a p$K_a$ of ~5 (acetic acid p$K_a$ is 4.76[81]). Therefore, with only 5% base present, monomethyl malonate **84** will be preferentially deprotonated and could undergo oxidation to the radical and homocouple before any of the radicals from the *N*-Boc acids were generated.

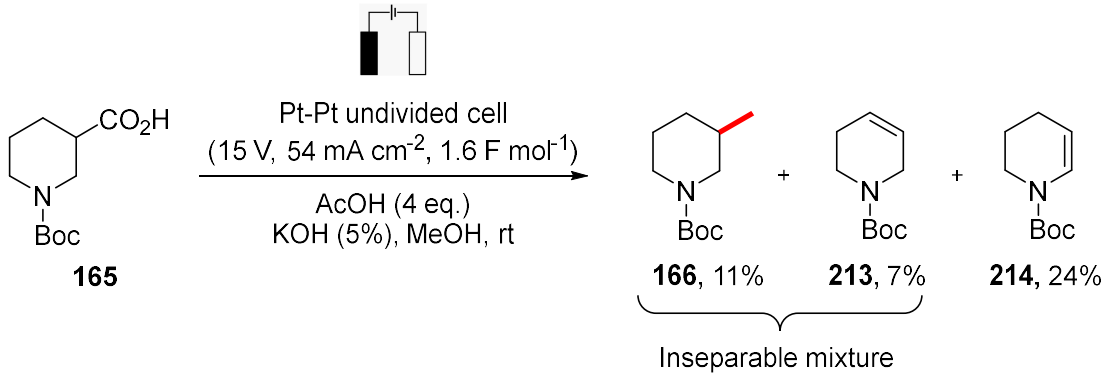



Scheme 2.71

Overall, an electrochemical set-up has been developed and the heterocoupling of primary carboxylic acids using Kolbe electrolysis has been shown to be successful. However, use of hydrocinnamic acid **174** and monomethyl malonate **84** as co-acids did not generate any products.

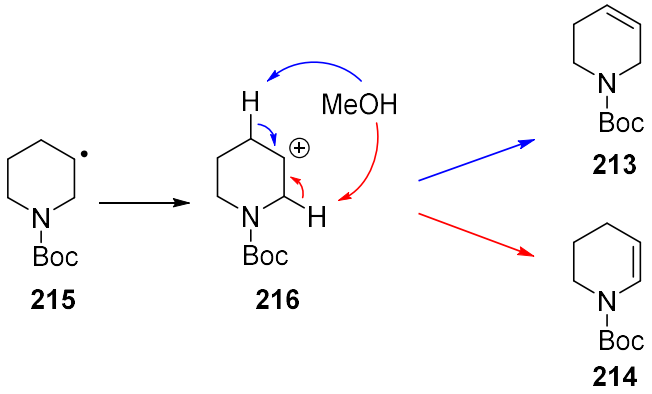
## 2.5 Anodic Decarboxylation of Secondary Carboxylic Acids

The heterocoupling of secondary radicals was investigated next in order to assess the scope and limitations of the methodology, as well as opening up the generation of more diverse compounds. To start, *N*-Boc 2-carboxylic acid piperidine **165** was electrolysed in the presence of acetic acid. A 0.13 M solution of *N*-Boc 2-carboxylic acid piperidine **165**, 4 eq. acetic acid and 5% KOH in MeOH was used. A voltage of 15 V was passed through the solution to achieve a current density of 54 mA $cm^{-2}$ for 1.6 F $mol^{-1}$. Upon purification, *N*-Boc methyl piperidine **166** and *N*-Boc alkene piperidine **213** were formed in 11% and 7% yield respectively as an inseparable mixture (Scheme 2.72). *N*-Boc alkene piperidine **214** was also isolated in 24% yield.



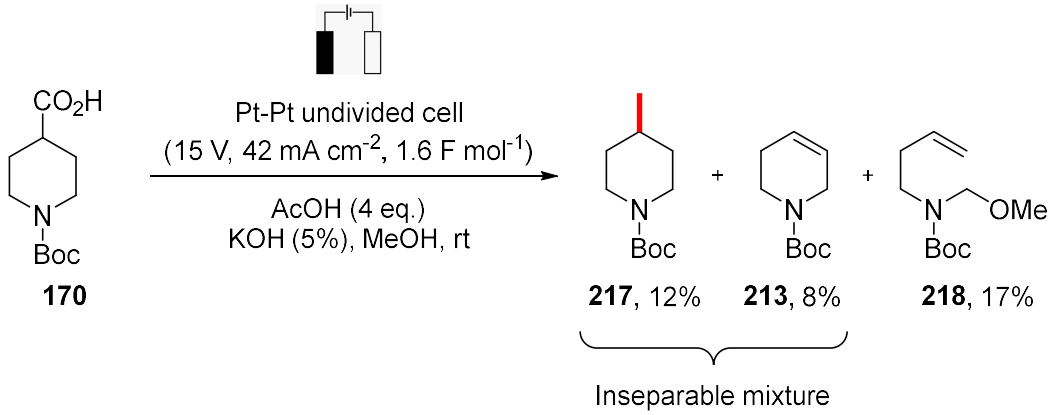

Scheme 2.72

A proposed mechanism for the formation of *N*-Boc alkene piperidines **213** and **214** is shown in Scheme 2.73. Radical intermediate **215** would undergo over-oxidation to form carbocation **216** which can eliminate in two different ways to form *N*-Boc alkene piperidines **213** and **214**.

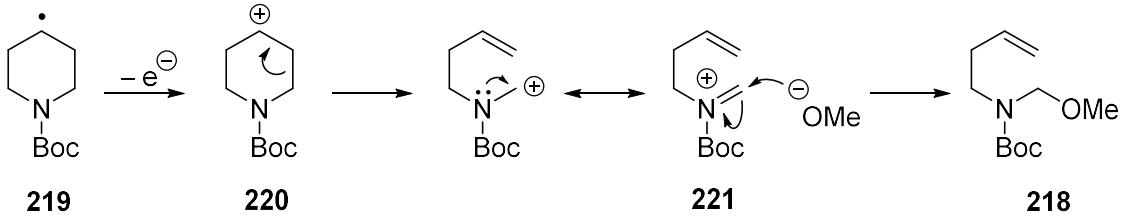



Scheme 2.73

A similarly unsuccessful heterocoupling was obtained with a different secondary *N*-Boc piperidine acid. *N*-Boc 4-carboxylic acid piperidine **170** was heterocoupled with acetic acid to give *N*-Boc 4-methyl piperidine **217** (12%) and *N*-Boc alkene piperidine **213** (8%) as an inseparable mixture. *N*-Boc methoxy amine alkene **198** was also isolated in 17% yield (Scheme 2.74). *N*-Boc methoxy amine alkene **218** is formed in a ring fragmentation process, similar to the formation of *N*-Boc methoxy amine alkene **198** (see Scheme 2.62) Radical intermediate **219** would undergo over-oxidation to form carbocation **220** which would ring open to form a more stable iminium ion **221**. A subsequent reaction with MeOH would yield *N*-Boc methoxy amine alkene **218** (Scheme 2.75).

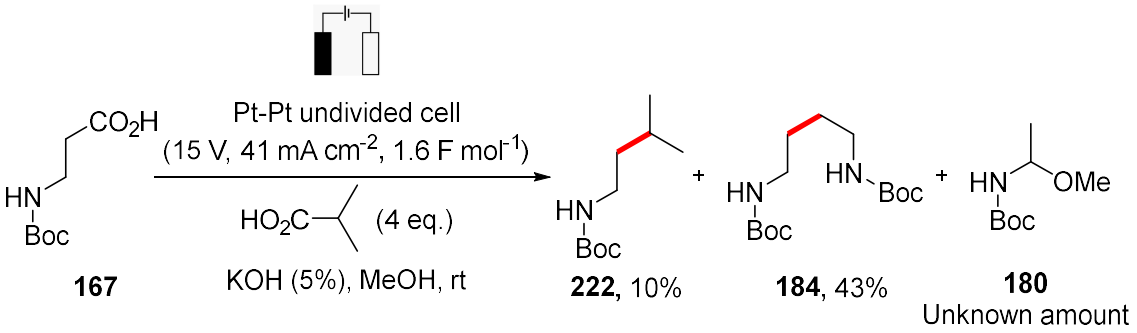



Scheme 2.74



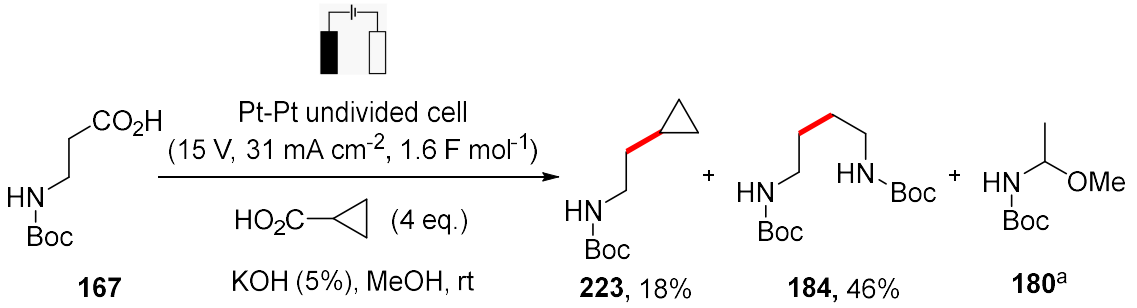

Scheme 2.75

Two secondary co-acids, *iso*-butyric acid and cyclopropanoic acid were explored next. *N*-Boc β-alanine **167** and *iso*-butyric acid were subjected to Kolbe electrolysis conditions. Upon purification, *N*-Boc 3-methylbutyl amine **222** was isolated in only 10% yield (Scheme 2.76). Surprisingly, a 43% yield of the homocoupled product, di-*N*-Boc amine **184**, was also isolated. *N*-Boc methoxy amine **180** was also observed in the $^{1}$H NMR spectrum of the crude product but was not isolated.




Scheme 2.76

A slightly better result was obtained with cyclopropanoic acid. *N*-Boc β-alanine **167** was electrolysed with cyclopropanoic acid to give *N*-Boc alkyl amine **223** in 18% yield. A significant amount of homocoupling to give di-*N*-Boc amine **184** (46% yield) was also observed. *N*-Boc methoxy amine **180** was identified in the $^{1}$H NMR spectrum of the crude product but was not isolated (Scheme 2.77).



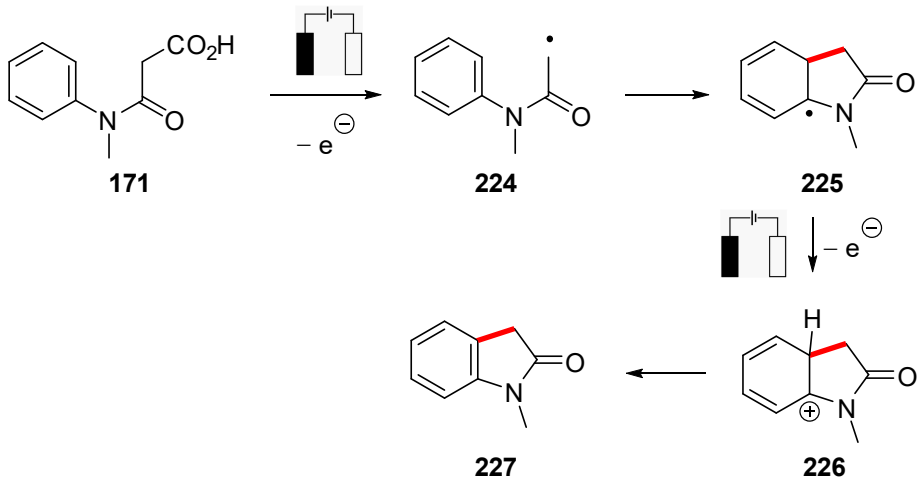

Scheme 2.77 - [a] Not isolated but observed in the $^{1}$H NMR spectrum of the crude product.

Overall, secondary carboxylic acids appear to give reduced yields of heterocoupled products when compared to primary carboxylic acids. It is presumed that, due to the increased stability of the secondary carbocation compared to a primary carbocation, the likelihood of over-oxidation of the secondary radical intermediate increased. As a result, "non-Kolbe" products such as alkenes and ethers and others formed due to carbocation rearrangement processes are prevalent.

## 2.6 Anodic Decarboxylation and Subsequent Radical Cyclisation

### 2.6.1 Radical Cyclisation onto an Aromatic Ring

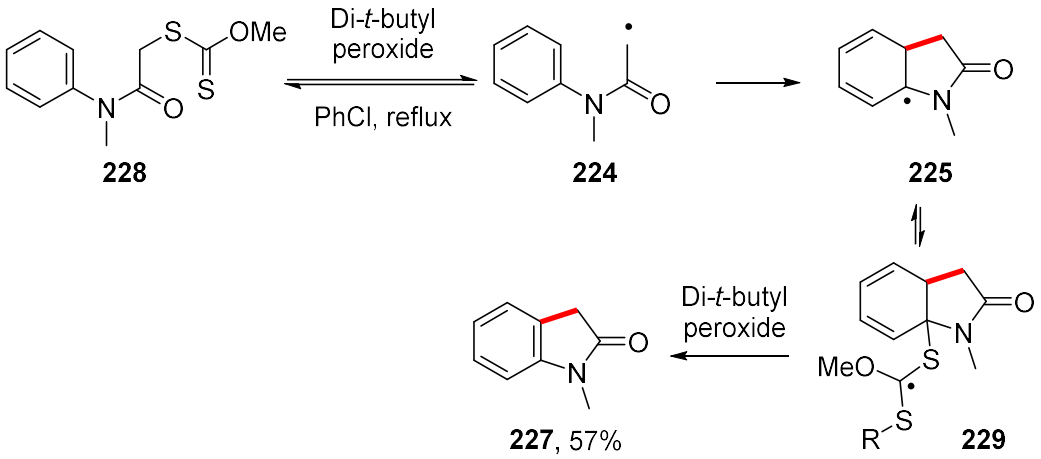
In the results to date, the most common problem associated with Kolbe electrolysis was the over-oxidation of the radical intermediate to produce a carbocation. Thus, a new idea was formed which could potentially utilise the over-oxidation to a carbocation. The plan was to explore the cyclisation of acid **171** to ultimately give oxindole **227** *via* the mechanism shown in Scheme 2.78. Electrochemical oxidation of the carboxylate derived from carboxylic acid **171** would form radical **224** which should be resistant to further oxidation to the carbocation as it is α to a carbonyl group. Instead, radical **224** could cyclise onto the aromatic ring, forming cyclised radical intermediate **225**. It should be possible for cyclised radical intermediate **225** to be readily oxidised further to give carbocation **226** which could then be deprotonated in order to rearomatise to give oxindole **227**.




Scheme 2.78

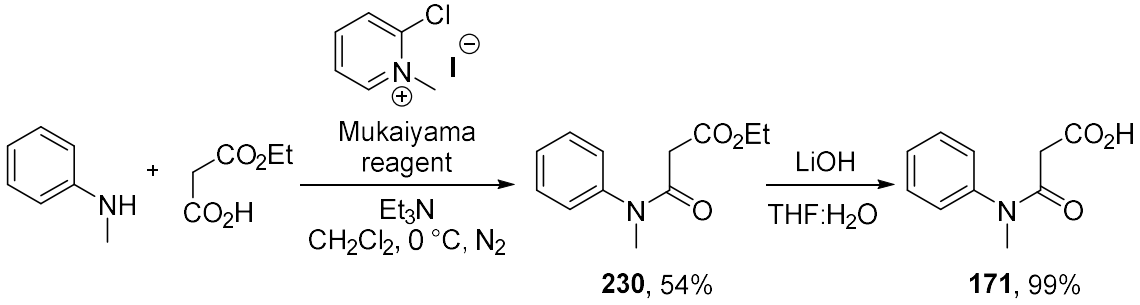
To date, there have been no electrochemical reports of oxidising a carboxylic acid and subsequent cyclisation onto an aromatic ring in this way. However, non-electrochemical radical generation and subsequent cyclisation onto an aromatic ring does have precedent. Zard *et al*. described similar radical cyclisations using xanthate esters to generate the key radical intermediates.[82,83] For example, reaction of xanthate ester **228** with an unknown amount of di-*t*-butyl peroxide at reflux in chlorobenzene gave a 57% yield of oxindole **227** (Scheme 2.79). It was reported that the reaction was sluggish and required several

additions of initiator to go to completion. In Zard's proposed mechanism, cyclised radical intermediate **225** is not oxidised to a carbocation but instead reacts with the starting xanthate **228** to give stabilised radical **229** in a radical chain mechanism. Nevertheless, it was hoped that oxidation of cyclised radical intermediate **225** to the carbocation would be straightforward under oxidative electrochemical conditions.



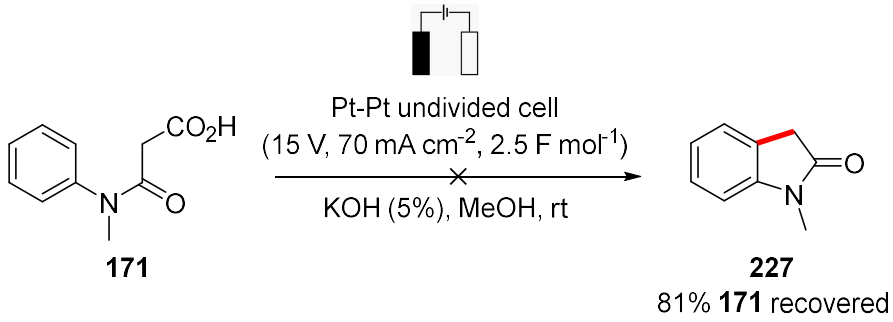

Scheme 2.79

With Zard's precedent, development of the oxindole synthesis outlined in Scheme 2.78 was attempted. The synthesis of carboxylic acid **171** was carried out using a method adapted from Taylor *et al.*[84] and involved an amide coupling reaction of aniline and mono-ethyl malonate followed by the hydrolysis of the ethyl ester (Scheme 2.80). Thus, *N*-methyl aniline was reacted with mono-ethyl malonate in the presence of Mukaiyama's reagent, 2-chloro-1-methylpyridinium iodide, and $Et_3N$ in $CH_2Cl_2$ at 0 °C. After chromatography, ester **230** was isolated in 54% yield. Subsequent hydrolysis of the ester using LiOH in a THF-$H_2O$ mixture resulted in the desired acid **171** in 99% yield.



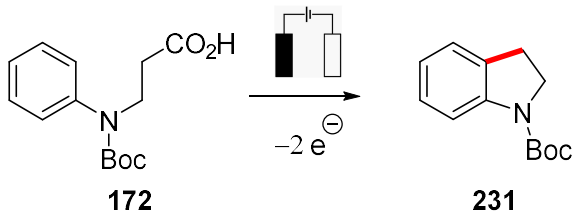

Scheme 2.80

With the starting material at hand, Kolbe electrolysis was performed on acid **171**. A 0.3 M solution of acid **171** with 5% KOH in MeOH was used. A voltage of 15 V was passed through the solution to achieve 70 mA $cm^{-2}$ of current density for 2.5 F $mol^{-1}$ of charge. In this reaction, more charge was passed through the cell (2.5 F $mol^{-1}$) compared to the heterocoupling reactions (e.g. 1.6 F $mol^{-1}$ in Scheme 2.54) as two oxidations would be required to generate oxindole **227**. Unfortunately, under these conditions, the formation of oxindole **227** was not observed. Acid **171** was recovered in 81% yield indicating that little starting material had participated in the electrolysis (Scheme 2.81). It is assumed that the MeOH solvent was oxidised instead.




Scheme 2.81

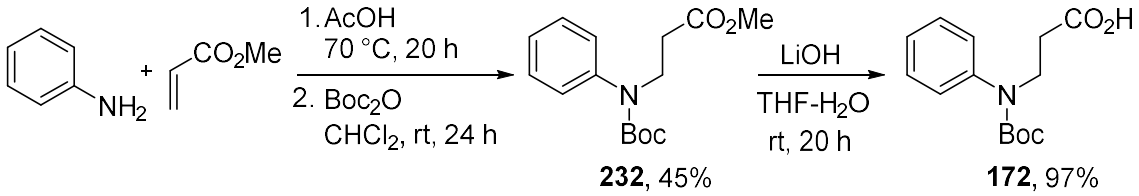
A different substrate, *N*-phenyl-*N*-Boc β-alanine **172**, that lacked an amide group and had similar functionality to some of the substrates studied in the previous sections, was then explored. The hope was that after radical generation, the radical should cyclise onto the aromatic ring and be oxidised before elimination to give *N*-Boc dihydro-indole **231** (Scheme 2.82).




Scheme 2.82

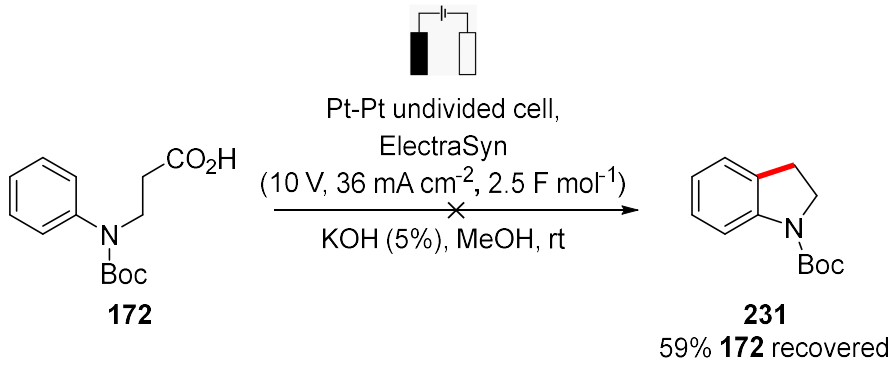
*N*-Phenyl-*N*-Boc β-alanine **172** was synthesised from a conjugate addition reaction of aniline to methyl acrylate, followed by Boc protection and, finally, hydrolysis of the ester (Scheme 2.83). Following a procedure by Youn *et al*., aniline was reacted with methyl acrylate in AcOH at 70 °C for 20 h.[85] Without purification, the crude substituted aniline

was protected with $Boc_2O$ to give ester **232** in 45% yield after purification. Subsequent hydrolysis of the ester using LiOH in a THF-$H_2O$ mixture resulted in the desired acid **172** in 97% yield.



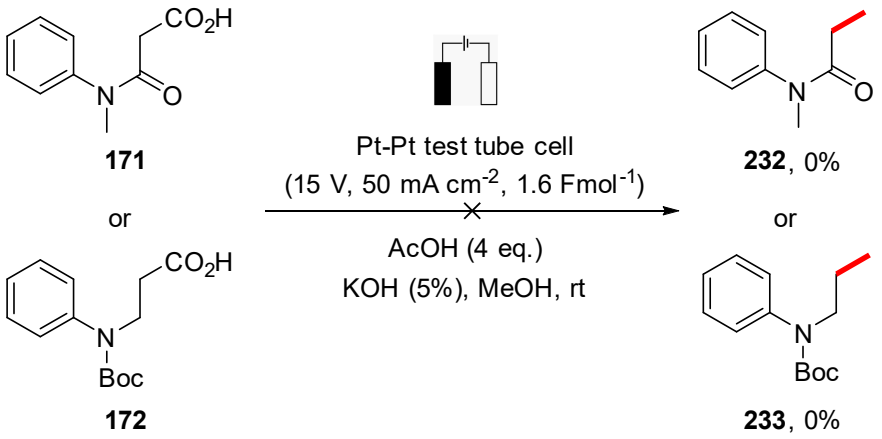

Scheme 2.83

Next, a solution of *N*-phenyl-*N*-Boc β-alanine **172** and 5% KOH was electrolysed in the ElectraSyn 2.0 set-up. A voltage of 10 V was passed through the solution to achieve a current density of 36 mA $cm^{-2}$ for 2.5 F $mol^{-1}$ of charge. Unfortunately, *N*-Boc dihydroindole **231** was not observed and 59% of *N*-phenyl-*N*-Boc β-alanine **172** was recovered after chromatography.




Scheme 2.84

At this point, it was unclear whether some of the starting material was undergoing oxidation and subsequent decarboxylation but without cyclisation onto the aromatic ring from the two reactions in Schemes Scheme 2.81 and Scheme 2.84. In an attempt to prove that the initial radical had been generated, AcOH was added in the hope that it would perform a heterocoupling reaction that could be isolated and characterised. Therefore, a solution of acid **171**, 4 eq. of AcOH and 5% KOH in MeOH was used. A voltage of 15 V was passed through the solution to achieve a current density of 50 mA $cm^{-2}$ for 1.6 F $mol^{-1}$ of charge. However, no heterocoupled product **232** or starting material was observed at the end of the reaction (Scheme 2.85). Acid **172** was also subjected to the same conditions but the reaction was similarly unsuccessful.




Scheme 2.85

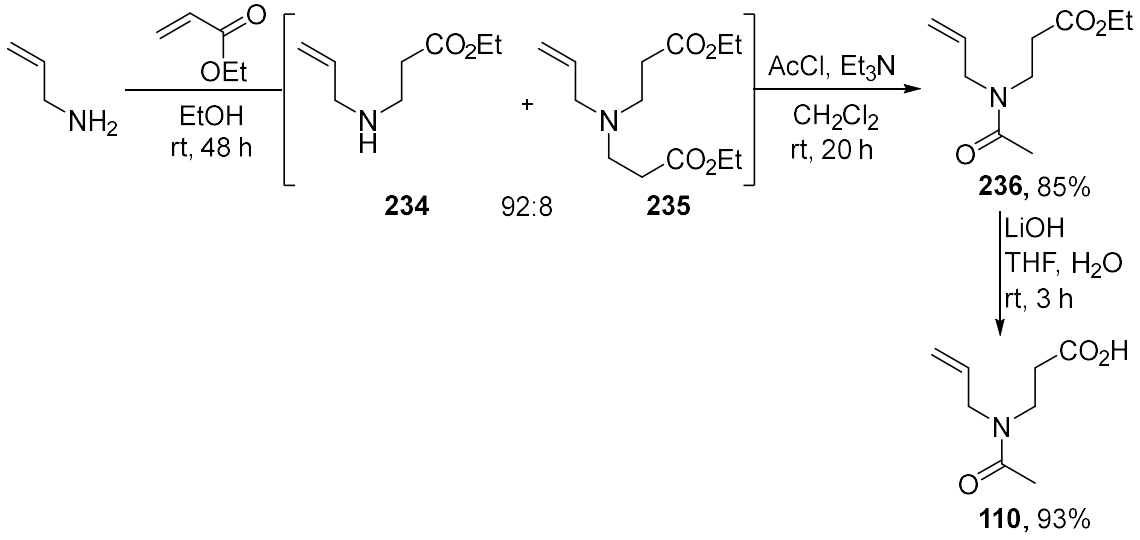
Unfortunately, attempts at cyclising the radical onto an aromatic ring were unsuccessful. The attempted heterocoupling experiments using AcOH suggest that the initial radical was not generated. Once again, anodic oxidations of aromatic-containing substrates were not successful.

### 2.6.2 Radical Cyclisation onto an Alkene and Subsequent Heterocoupling

Finally, attention turned to a different class of radical cyclisation reaction. Radical cyclisation onto internal alkenes *via* Kolbe electrolysis and subsequent heterocoupling have previously been reported (see Section 2.1.2). Therefore, the synthesis of pyrrolidines *via* radical cyclisation onto alkenes was explored. The initial objective was to replicate a cyclisation and heterocoupling reaction performed by Schäfer *et al*.[57] Kolbe electrolysis of *N*-Ac alkene acid **110** and acetic acid was reported to give pyrrolidine **111** in 58% yield (see Scheme 2.27).

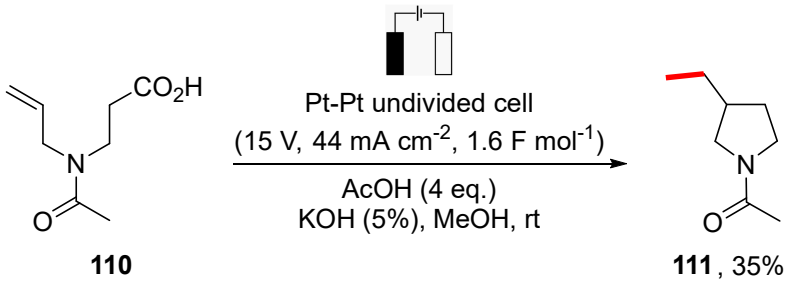
The synthesis of *N*-Ac alkene acid **110** was carried out *via* a three-step approach (Scheme 2.86). The first step was the conjugate addition reaction of allyl amine with ethyl acrylate, previously reported by Nagarapu *et al*.[86] Following their method, allyl amine was reacted with ethyl acrylate at rt for 48 h. The work-up involved rotary evaporation and the volatile unreacted starting materials were easily removed. This gave the crude product which contained a 92:8 mixture of desired amine **234** and disubstituted amine **235** (by $^1$H NMR spectroscopy). The $^1$H NMR spectra of amines **234** and **235** matched those in the literature.[86,87] The crude mixture of amines **234** and **235** was used in the next step without

purification as it was found that disubstituted amine **235** could be removed during the purification of this next step. Acetyl protection of the crude mixture gave *N*-Ac alkene ester **236** in 85% yield over the two steps after chromatography. *N*-Ac alkene ester **236** was then hydrolysed under basic conditions using LiOH. This gave *N*-Ac alkene acid **110** in 93% yield with no purification required.




Scheme 2.86

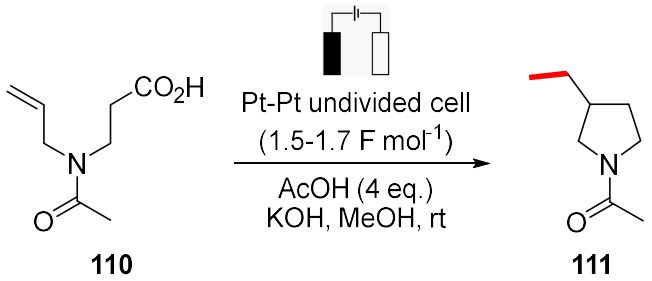
With the starting material in hand, Kolbe electrolysis heterocoupling was performed with *N*-Ac alkene acid **110** and acetic acid. The standard KOH conditions were used. A 0.13 M solution of *N*-Ac alkene acid **110**, 4 eq. of acetic acid and 5% (of the total acid) of KOH in MeOH at rt were used. A voltage of 15 V was passed through the solution to achieve a current density of 44 mA $cm^{-2}$ for 1.6 F $mol^{-1}$ of charge. Using these conditions, pyrrolidine **111** was isolated in 35% yield after chromatography (Scheme 2.87).




Scheme 2.87

Various optimisation attempts were then performed (Table 2.6). This included the use of lower voltage which lowered the current density to 25 mA $cm^{-2}$ and gave pyrrolidine **111**

in 36% yield (entry 1). An inert atmosphere was next investigated with 15, 10 and 6 V which gave 41, 24 and 12 mA $cm^{-2}$ of current density respectively and yields of pyrrolidine **111** of 23-44% (entries 2-4). Finally, the base was decreased to 1% which also lowered the current density to 12 mA $cm^{-2}$ and gave pyrrolidine **111** in 33% yield (entry 5). Overall, the yield of pyrrolidine **111** did not change significantly with each change in conditions.



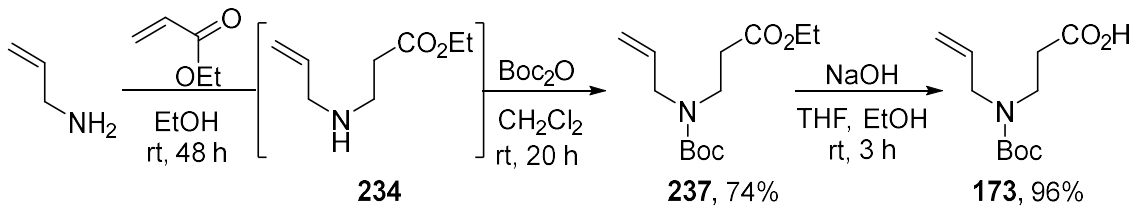

**110** **111**

| Entry | KOH (%) | Time (h:m) | Current Density (mA $cm^{-2}$) | Voltage (V) | Atmosphere | Yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 | 5 | 3:12 | 25 | 10 | Air | 36 |
| 2 | 5 | 2:00 | 41 | 15 | $N_2$ | 37 |
| 3 | 5 | 3:16 | 24 | 10 | $N_2$ | 44 |
| 4 | 5 | 6:10 | 12 | 6 | $N_2$ | 23 |
| 5 | 1 | 5:45 | 12 | 15 | $N_2$ | 33 |

Table 2.6 – Kolbe electrolysis of *N*-Ac alkene acid **110** with acetic acid.

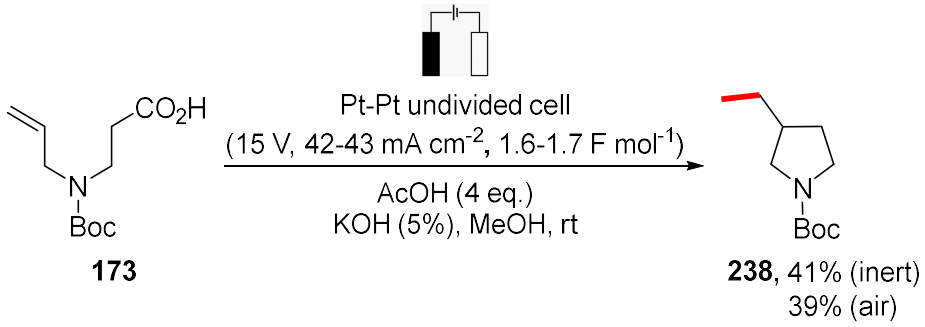
[a] Yield after chromatography.

Since a Boc group is easier to remove from an amine that an acetyl group, the same type of reaction with *N*-Boc alkene acid **173** was also explored. The synthesis of *N*-Boc alkene acid **173** using the same approach as that for *N*-Ac alkene acid **110**. Reaction of allyl amine with ethyl acrylate followed by amine protection using $Boc_2O$ gave *N*-Boc alkene ester **237** in 74% yield after chromatography. Next, *N*-Boc alkene ester **237** was hydrolysed under basic conditions using NaOH to give *N*-Boc alkene acid **173** in 96% yield with no purification needed (Scheme 2.88).



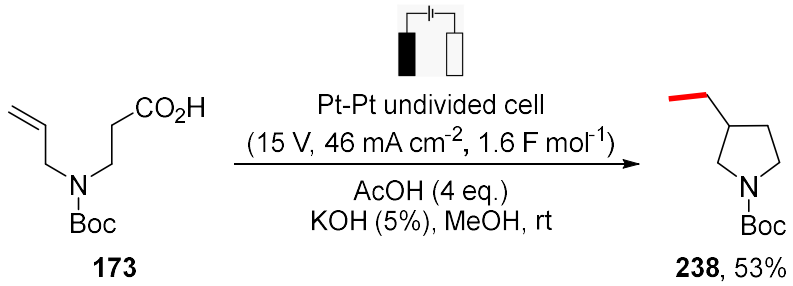

Scheme 2.88

*N*-Boc alkene acid **173** was then subjected to the standard Kolbe electrolysis conditions: a solution of *N*-Boc alkene acid **173**, 4 eq. of acetic acid with 5% KOH in MeOH under an inert atmosphere. A voltage of 15 V was passed through the solution to give 42 mA $cm^{-2}$ current density for 1.6 F $mol^{-1}$ of charge. This gave pyrrolidine **238** in 41% yield after chromatography. The reaction was also performed under air which gave pyrrolidine **238** in 39% yield (Scheme 2.89). Performing the reaction under air entails a much easier set-up and was not detrimental to the yield of the product.



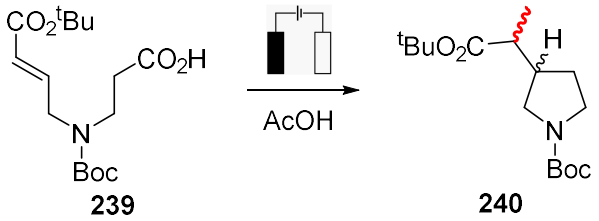

Scheme 2.89

As *N*-Boc pyrrolidine **173** has a similar molecular weight to *N*-Boc products **179** and (*R*)-**195** which were previously shown to be volatile, a reaction of *N*-Boc alkene acid **173** with a modified work-up and chromatography was performed. Using more volatile solvents for column chromatography and restricting the use of the high vacuum, *N*-Boc pyrrolidine **238** was isolated in 53% yield (Scheme 2.90). Thus, the high yield obtained by Schäfer was essentially replicated. Additionally, this example uses a more readily removed Boc protecting group on the amine.



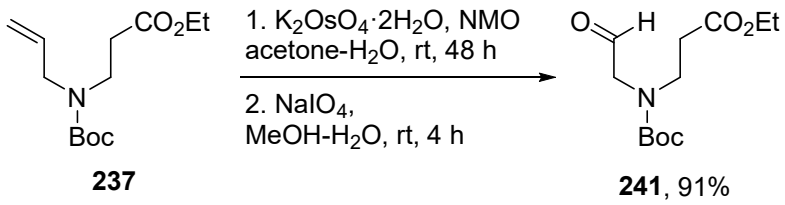

Scheme 2.90

When Markó *et al*. studied the cyclisation of radicals onto internal alkenes in the closely related oxygen series of compounds (to make a cyclopentane and other rings), the best results were obtained when the alkene contained an electron withdrawing group (see Scheme 2.34 and Scheme 2.35). The explanation proposed was that polarity matching of the electron rich alkyl radical with an electron deficient alkene led to an efficient cyclisation. Therefore, it was hoped that a similar effect could lead to a higher yielding pyrrolidine synthesis. Thus, the study of the cyclisation and heterocoupling of *N*-Boc acid **239** (with a *t*-butyl ester group on the alkene) to give pyrrolidine **240** was explored (Scheme 2.91).



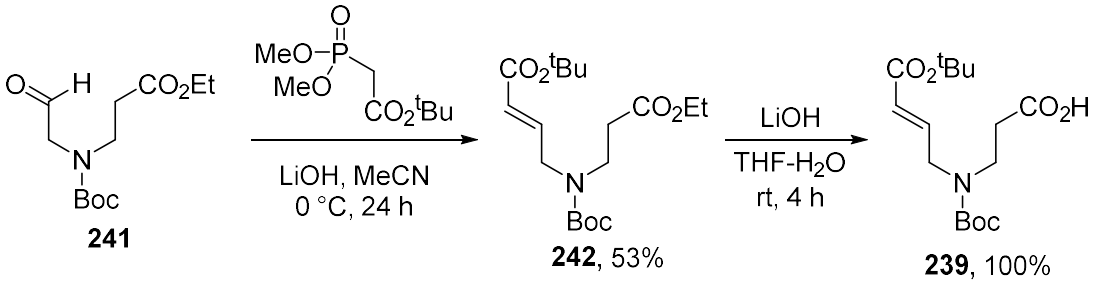

Scheme 2.91

The first step of the synthesis of *N*-Boc acid **239** involves the oxidation of *N*-Boc alkene ester **237** to a diol using potassium osmate and subsequent oxidative cleavage using $NaIO_4$ to give aldehyde **241**, using a procedure reported by Marsden *et al*.[88] The reaction was carried out by another member of the O'Brien group, J. Ashton, under my supervision and gave aldehyde **241** in 91% yield with no purification.[89]



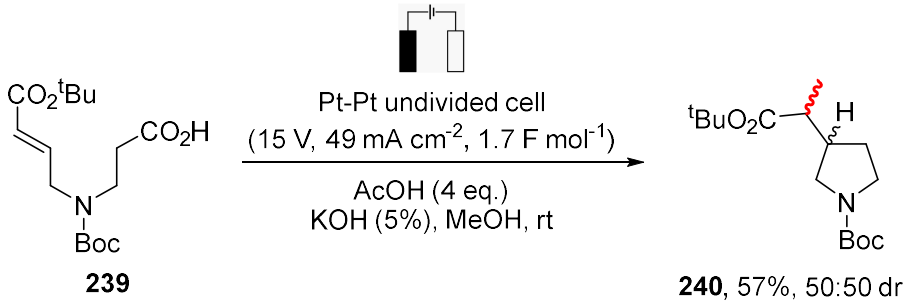

Scheme 2.92

Following a procedure performed by Darses *et al*., [90] aldehyde **241** was then subjected to a Horner-Wadsworth-Emmons reaction to give *N*-Boc alkene ester (*E*)**-242**. Aldehyde **241** was reacted with *tert*-butyl diethylphosphonoacetate and dry LiOH in MeCN to give *N*-Boc alkene ester **242** in 53% yield after chromatography. Finally, *N*-Boc alkene ester **242** was hydrolysed under basic conditions using LiOH to give *N*-Boc alkene acid **239** in 100% yield (Scheme 2.93).




Scheme 2.93

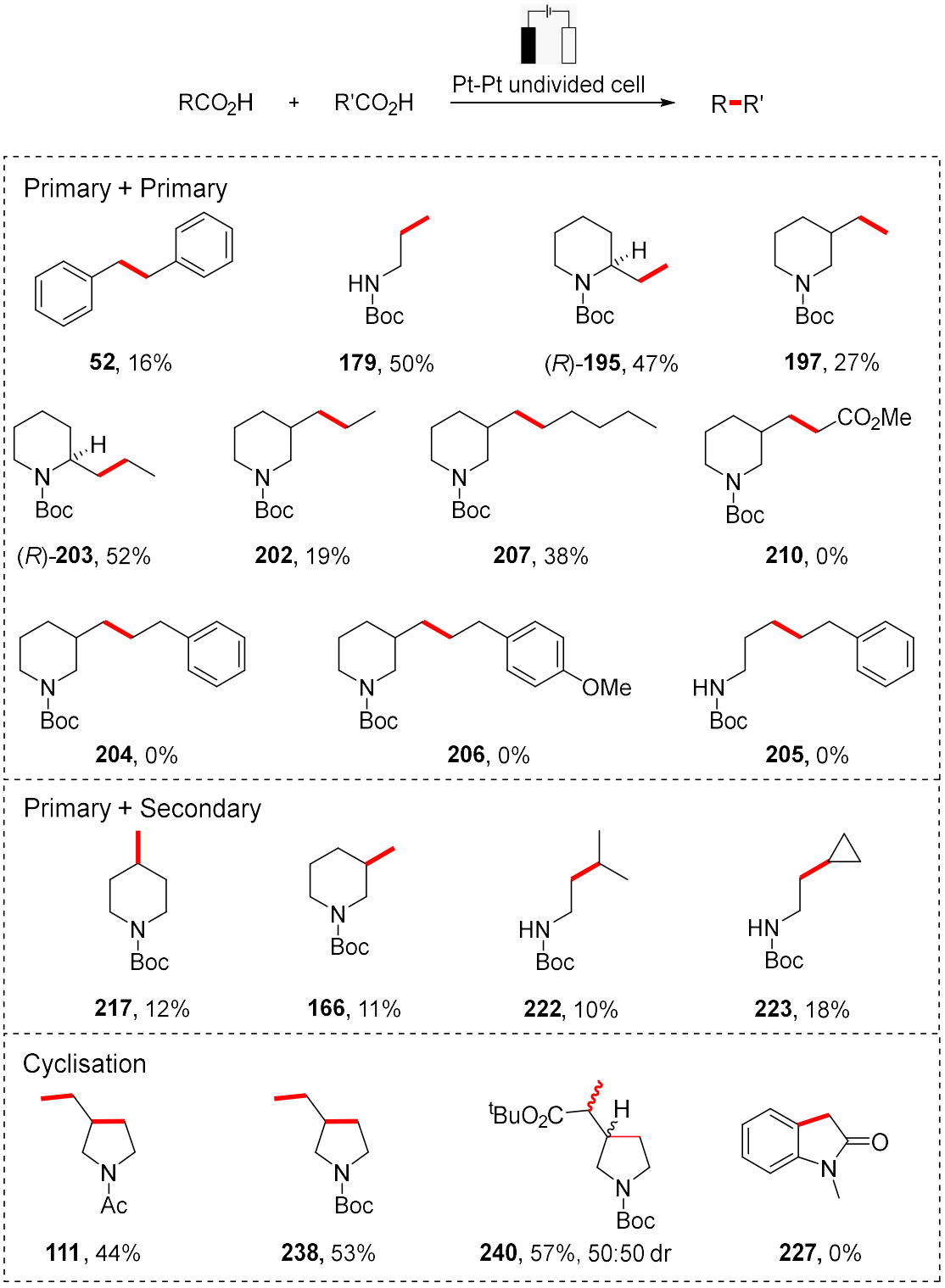
With *N*-Boc alkene acid **239** in hand, Kolbe electrolysis was performed using the standard KOH conditions to give pyrrolidine **240** in 57% yield (50:50 dr) after chromatography (Scheme 2.94). Encouragingly, addition of an electron withdrawing group to the alkene did indeed increase the yield of the cyclised product, although the improvement was not as dramatic as initially hoped.




Scheme 2.94

## 2.7 Conclusions and Future Work

In summary, heterocoupling reactions *via* Kolbe electrolysis on a range of substrates has successfully been performed and the results are summarised in Scheme 2.95.




Scheme 2.95

It was found that primary carboxylic acids gave the best yields. For example, *N*-Boc 2-acetic acid (*S*)-**168** heterocoupled with either acetic acid or propanoic acid to form piperidine (*R*)-**195** (47% yield) and (*R*)-**202** (52% yield) respectively. Pyrrolidines can also be synthesised using a primary carboxylic acid and an internal alkene followed by heterocoupling: *N*-Boc alkene acid **173** cyclised and heterocoupled with acetic acid to give pyrrolidine **238** in 53% yield. When using secondary carboxylic acids as substrates, it was found that the generated secondary radicals were prone to over-oxidation and their heterocoupled products were formed in a lower yield compared to their primary analogues. For comparison, the reaction with *N*-Boc β-alanine **167** with either acetic acid or *iso*-butyric acid gave the coupled products **179** and **222** in 50% and 10% yield respectively. On top of this, carboxylic acids containing aromatic groups, also failed to give the desired heterocoupled product, as shown by piperidine **227**.

In future, over-oxidation of radicals derived from secondary carboxylic acids could be reduced by incorporating an electron-withdrawing carbonyl group next to the acid functional group. This could help due to the instability of a cation being formed adjacent to an electron-withdrawing group. Lam *et al*. have recently performed similar reactions with primary carboxylic acids to generate pyrrolidinones in high yields (see Scheme 2.38). With this in mind, a selection of substrates bearing this moiety for future work is shown in Figure 2.10. Examples include piperidinones, lactones and dihydroquinolones. It is hoped that, since the radical derived from these substrates would be less likely to over-oxidise to a carbocation, fewer undesired side-products should be generated.

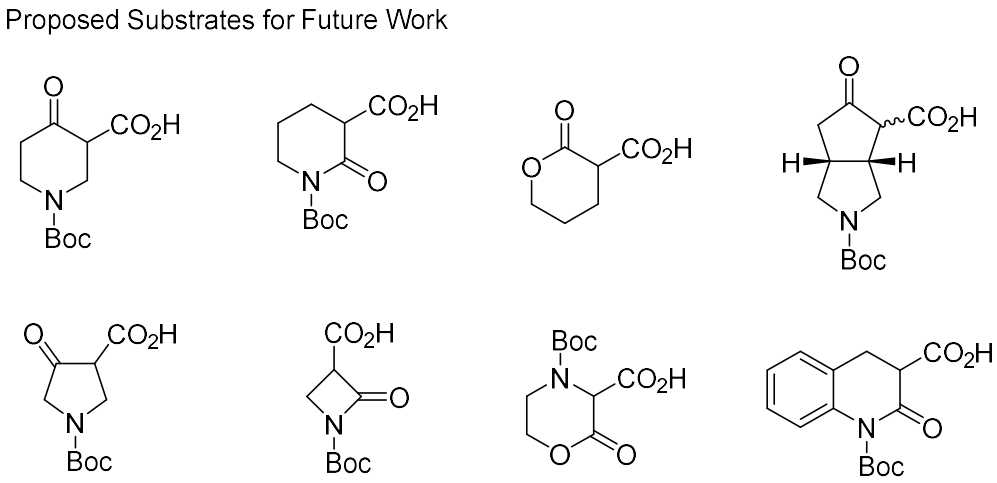
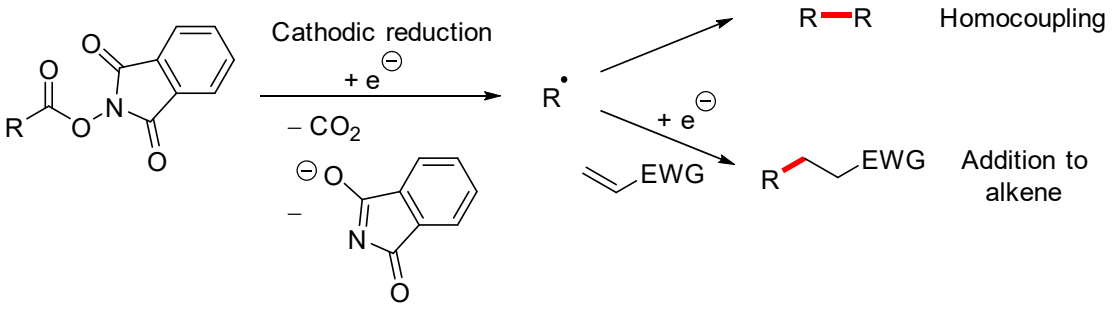



Figure 2.10 – Proposed substrates for future work

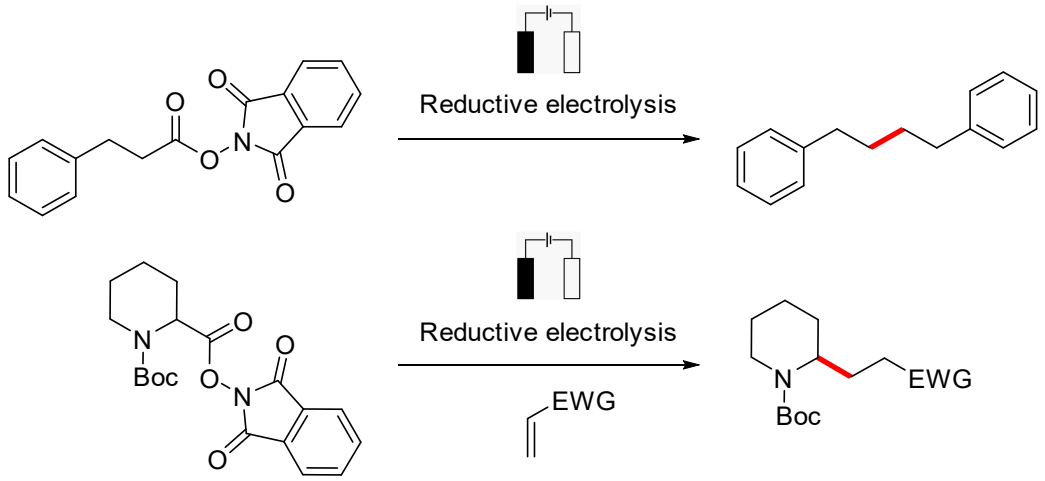
# Chapter 3: Cathodic Decarboxylation of Redox Active Esters for Carbon-Carbon Bond Formation

This Chapter is concerned with the electrochemical cathodic reduction of redox active esters to give radicals which are either homocoupled, heterocoupled or added to electron deficient alkenes (Scheme 3.1). Section 3.1 provides a brief overview of the previous use of redox active esters, particularly *N*-hydroxyphthalimide esters, in synthesis.




Scheme 3.1

The subsequent sections describe efforts towards developing transformations for carbon-carbon bond formation by using *N*-hydroxyphthalimides and reductive electrochemistry. In particular, radical homocoupling and heterocoupling (Section 3.3) and addition to alkenes (Sections 3.4-3.6) are described (Scheme 3.2). These sections also describe mechanistic studies using cyclic voltammetry and a small family of novel electron rich and electron deficient *N*-hydroxyphthalimide analogues.

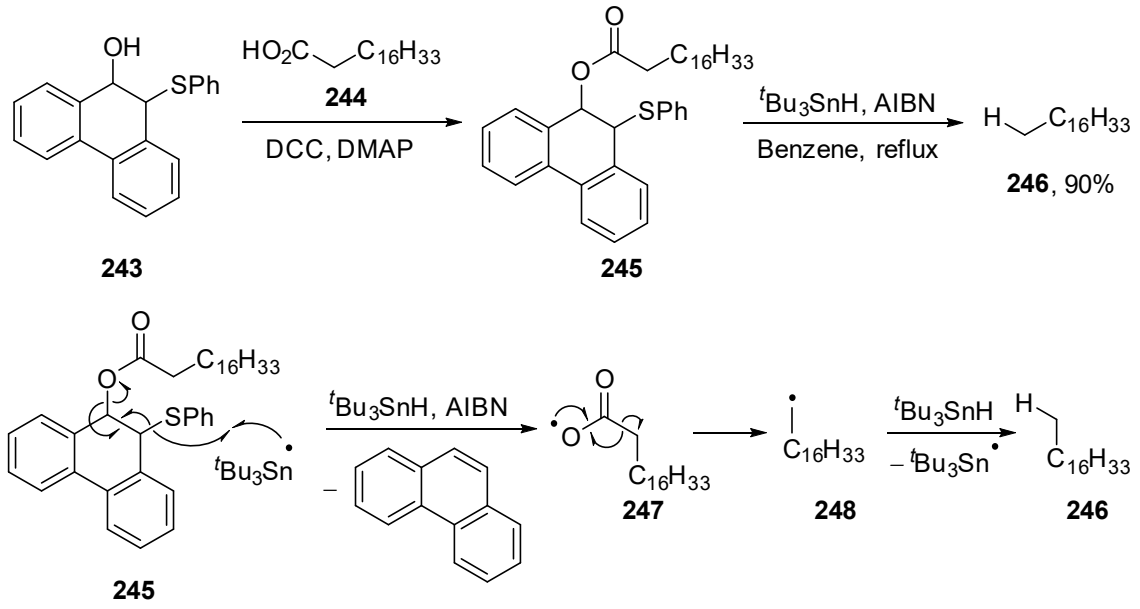



Scheme 3.2

## 3.1 Previous Use of Redox Active Esters for Radical Generation

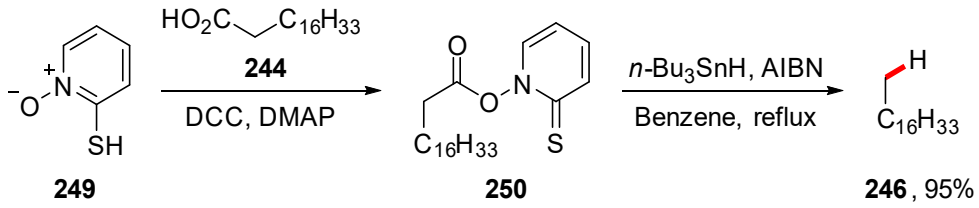
### 3.1.1 Introduction to Barton's Esters

In 1980, Barton *et al*. reported that esters could be reduced to give the corresponding hydrocarbon.[91] Ester **245** was synthesised from alcohol **243** by esterification with stearic acid **244** (yield not provided). Upon treatment of ester **245** with *n*-$Bu_3SnH$ and AIBN, hexadecane **246** was generated in 90% yield (Scheme 3.3). Mechanistically, the *n*-$Bu_3Sn^{\bullet}$ attacks the sulfide in ester **245** and the resulting radical fragments to give carboxylate radical **247** and phenanthrene. Carboxylate radical **247** then decarboxylates to give carbon-centred radical **248** which subsequently abstracts a hydrogen atom from *n*-$Bu_3SnH$ to give hydrocarbon **246**.




Scheme 3.3

A few years later, Barton *et al*. reported that the esterification reaction shown in Scheme 3.3 gave variable yields.[92] In order to overcome this problem, a new ester was developed, now referred to as the Barton ester. Ester **250** was synthesised from the esterification of stearic acid **244** with thione **249** (yield not reported). Then, ester **250** was reduced using *n*-$Bu_3SnH$ and AIBN in refluxing benzene to give hexadecane **246** in 95% yield (Scheme 3.4). After the initial attack of *n*-$Bu_3Sn^{\bullet}$ on the sulfur, the reduction is thought to proceed *via* a similar type of fragmentation mechanism to that shown in Scheme 3.3.




**249** **250** **246**, 95%

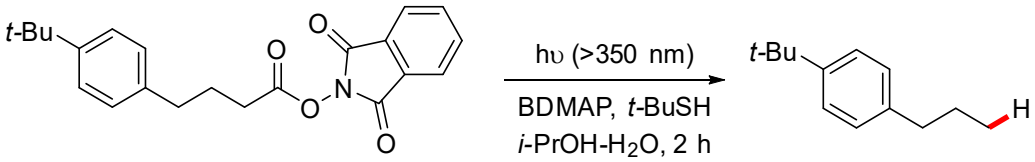
Scheme 3.4

## 3.1.2 Reductive Reactions using *N*-Hydroxyphthalimide Esters

Since the development of the Barton ester, redox active esters have also proved to be useful precursors for the reductive generation of a carbon-centred radical, which can then undergo various reactions. However, Barton esters tend to be difficult to handle and store due to light sensitivity.[93] One common, more stable alternative redox active ester is the *N*-hydroxyphthalimide (NHP) ester and it has been used in photochemical, transition metal and electrochemical reactions. This section outlines a number of transformations that utilise NHP redox active esters.

### 3.1.2.1 Light-Mediated Reduction of NHP esters

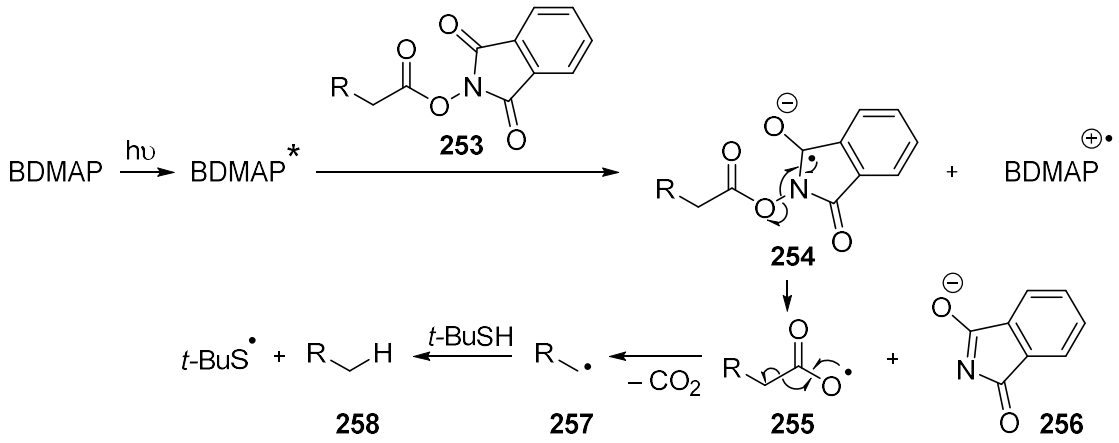
NHP esters were first used as redox active esters by Okado *et al*. in 1988. It was possible to reduce NHP ester **251** with a 100 Hg lamp in the presence of a photoinitiator, BDMAP (1,6-bis(dimethylamino)pyrene), and *t*-BuSH to give the corresponding hydrocarbon **252** in 88% yield by GC.[94]




**251** **252**, 88%

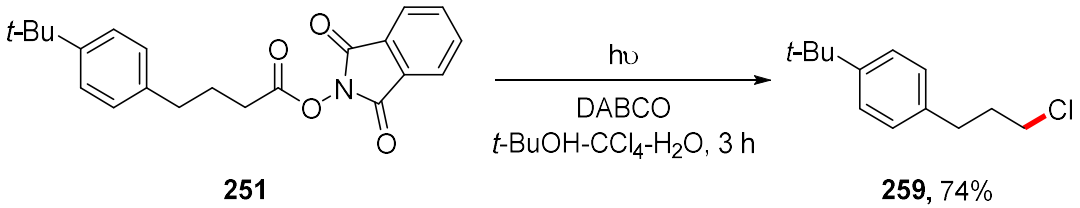
Scheme 3.5

The proposed mechanism for the reduction of NHP ester **253** is shown in Scheme 3.6. Irradiation of the photoinitiator BDMAP gives the excited singlet state of BDMAP, which then reduces *N*-hydroxyphthalimide ester **253** to give radical anion **254**. Fragmentation then leads to carboxylate radical **255** and phthalimide anion **256**. Then, decarboxylation of carboxylate radical **255** yields carbon-centred radical **257** which subsequently abstracts a hydrogen atom from *t*-BuSH to afford hydrocarbon **258** and a sulfur-centred radical.



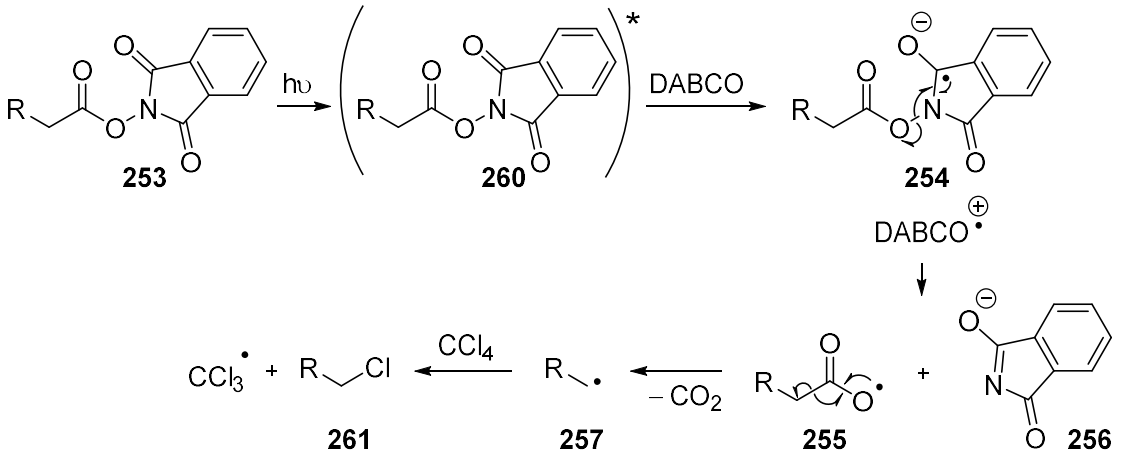

Scheme 3.6

NHP esters are poor oxidants ($E_{1/2}$ = −1.37 V vs SCE) when in the ground state.[95] However, when exposed to light, the ester is excited to the triplet state which is a much better oxidant ($E_{1/2}^*$ = +1.60 V vs SCE).[95] Therefore, a photoinitiator such as BDMAP is not essential for light-activation of the reaction to proceed. Okada *et al*. demonstrated this by irradiating NHP esters using a high pressure Hg lamp and a Pyrex filter, in the presence of a mild electron donor (DABCO, $E_{1/2}$ = +0.69 V vs SCE)[96] in order to carry out decarboxylation and form radical intermediates.[97] The radical intermediates were then intercepted with carbon tetrachloride to give chlorinated products. For example, irradiation of NHP ester **251** in the presence of DABCO in a solvent mixture of *t*-BuOH-$CCl_4$-$H_2O$ for 3 h gave chloride **259** in 74% yield (Scheme 3.7).[97]



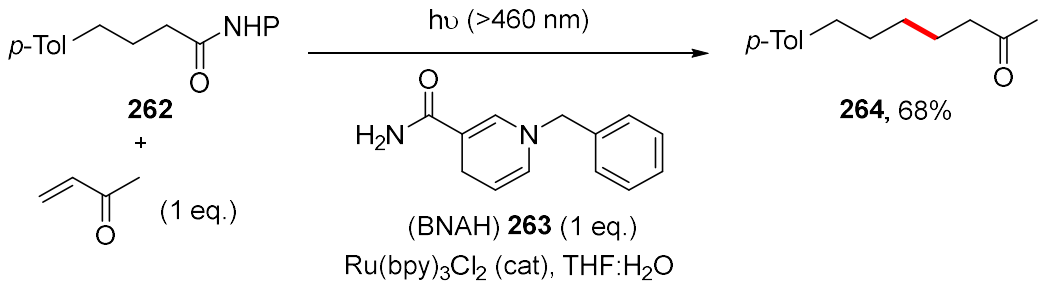

Scheme 3.7

The mechanism proposed for the chlorodecarboxylation of NHP ester **253** is shown in Scheme 3.8. Irradiation of NHP ester **253** to its excited state followed by an electron transfer from DABCO gives radical anion **254**. Fragmentation, decarboxylation and chlorine atom abstraction from the solvent then occurs to give chloride **261**.




Scheme 3.8

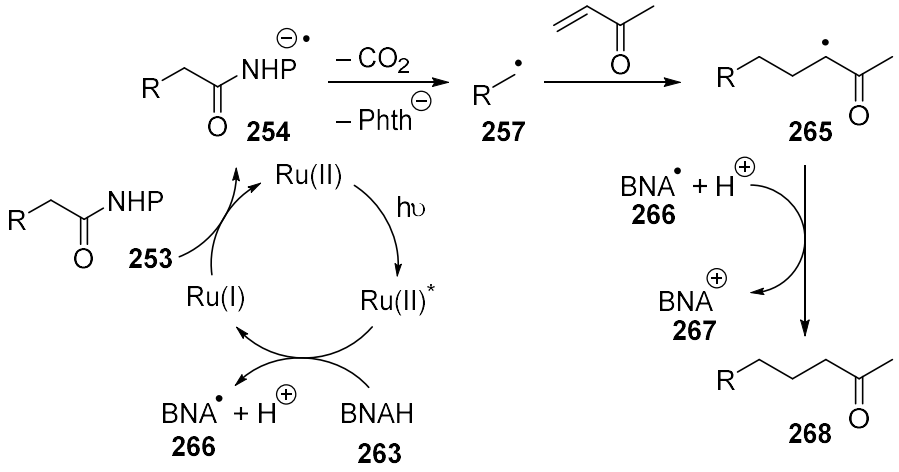
In 1991, Okada *et al*. utilised a ruthenium photocatalyst for the reduction of NHP ester **262** and subsequent addition of the radical that is generated to an electron deficient alkene.[98] The use of a ruthenium photocatalyst enabled a photocatalytic cycle to occur. As a representative example, NHP ester **262** was irradiated in the presence of $Ru(bpy)_3Cl_2$, 1-benzyl-1,4-dihydronicotinamide (BNAH) **263** and methyl vinyl ketone which gave ketone **264** in 68% yield (Scheme 3.9).




Scheme 3.9

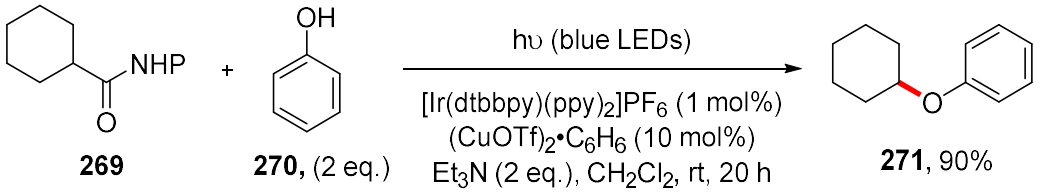
The mechanism proposed by the authors for the reaction is shown in Scheme 3.10. Irradiation of the $Ru(bpy)_3Cl_2$ photocatalyst, indicated by Ru(II), gives the excited photocatalyst Ru(II)* which oxidises BNAH **263** to give BNA radical **266**. The NHP ester **253** can then be reduced by the reduced form of the photocatalyst (Ru(I)) to complete the catalytic cycle and give radical anion **254**. Decarboxylation of the radical anion **254** gives the carbon-centred radical **257** which adds to the electron deficient alkene to give radical

**265**. Radical **265** can then be reduced by BNA radical **266** to give an enolate. Subsequent protonation will give product **268** and BNA cation **267**.



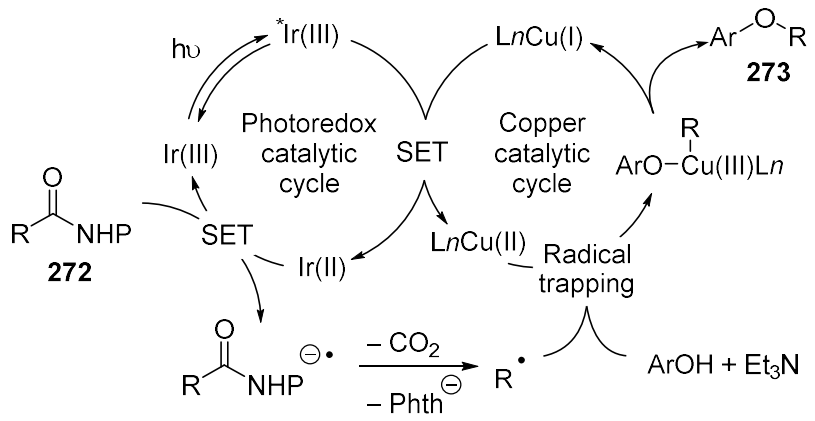

Scheme 3.10

After these initial reports, photoredox catalysis using NHP redox active esters has surged in popularity.[99] A common method of trapping the carbon-centred radical intermediate is with a transition metal catalyst which allows new transformations to be developed. Hu *et al.* were able to utilise a copper catalyst with NHP esters and a photoredox iridium catalyst to perform $C_{sp3}$-O cross-couplings.[100] Irradiation of an iridium complex ligated by, 4,4′-di-*tert*-butyl-2,2′-dipyridyl (dtbbpy) and 2-phenylpyridine (ppy), in the presence of NHP ester **269**, phenol **270** and a copper catalyst gave ether **271** in 90% yield (Scheme 3.11).




Scheme 3.11

The mechanism for an iridium and copper catalysed carbon-oxygen coupling is shown in Scheme 3.12. The Ir(III) photocatalyst is irradiated to give the excited photocatalyst which reacts with the Cu(I) complex to give Ir(II) and Cu(II) species. The Ir(II) species reduces NHP ester **272** which regenerates the photocatalyst and, upon decarboxylation, gives an alkyl radical. The alkyl radical is then trapped by the Cu(II) species, which is likely to be coordinated to phenol, to give the Cu(III) complex. Reductive elimination of this complex then yields the coupled product **273** and regenerates the Cu(I) catalyst.

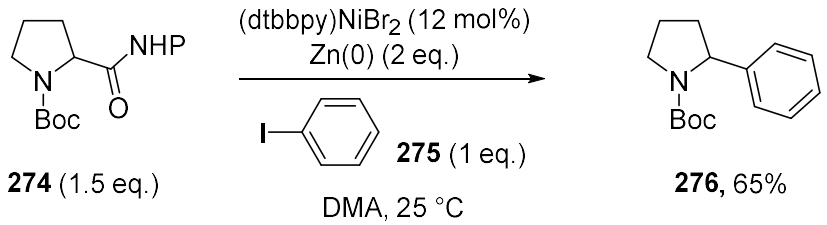



Scheme 3.12

Photoredox catalysis with NHP esters can be used for a multitude of coupling reactions including $C_{sp3}$ to $C_{sp3}$,[101–103] $C_{sp2}$[104–106] or $C_{sp}$[107,108] bond formation. This methodology can also be used for carbon to heteroatom cross-coupling as well, including nitrogen,[109] boron,[93,110] sulfur[111] and selenium[112] coupling.

### 3.1.2.2 Transition Metal Catalysed Reduction of NHP esters

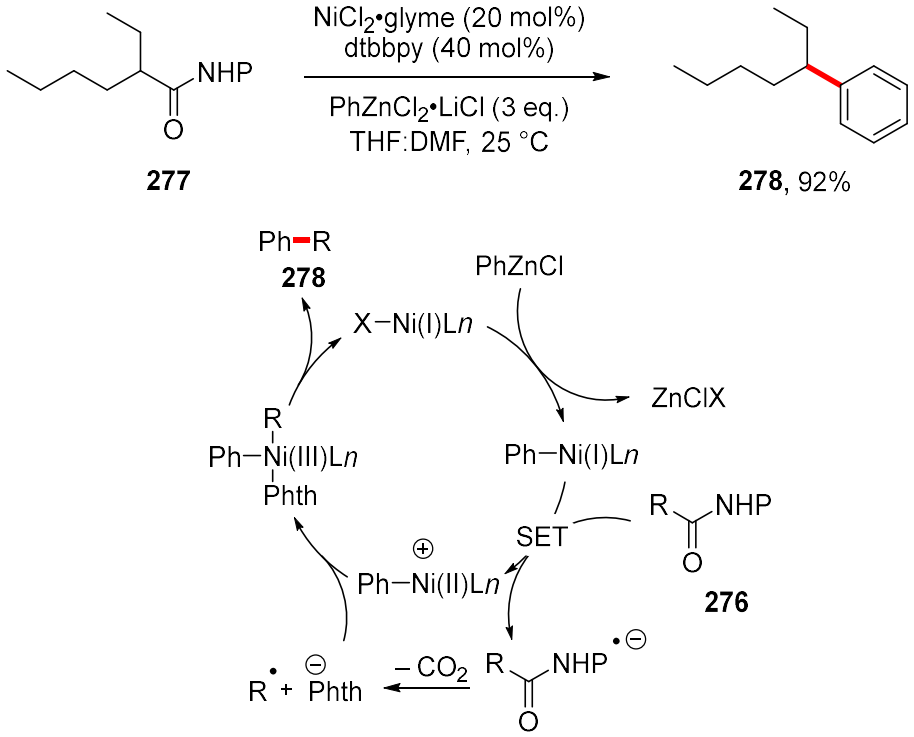
A transition metal catalyst can be used instead of photoredox catalysis for the reduction of NHP esters. Recently, NHP esters have been shown to readily accept an electron from a low-valent nickel catalyst in order to be reduced without the need for photochemistry. Weix *et al*. showed that *N*-Boc pyrrolidinyl NHP ester **274** could be reduced and cross-coupled in the presence of (dtbbpy)$NiBr_2$, zinc and aryl iodide **275** to give 2-phenyl *N*-Boc pyrrolidine **276** in 65% yield (Scheme 3.13).[113] The mechanism for this reaction was not detailed.




Scheme 3.13

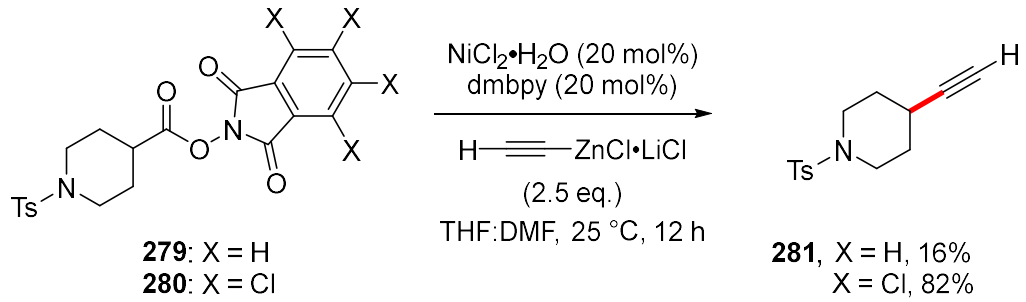
In a similar method, Baran *et al*. reported the reduction and cross-coupling of NHP ester **277** in the presence of $NiCl_2$.glyme catalyst, dtbbpy and an aryl zinc species to give cross-coupled product **278** in 92% yield (Scheme 3.14).[114] Mechanistically, the Ni(I) catalyst transmetalates with an aryl zinc reagent to give an aryl Ni(I) species. This nickel species

then reduces the NHP ester **277** to give Ni(II) and the reduced NHP ester. Upon fragmentation and decarboxylation, the alkyl radical and phthalimide anion generated then oxidatively add into the Ni(II) species to give Ni(III) complex. Reductive elimination then affords the desired coupled product **278** and the nickel catalyst is regenerated.




Scheme 3.14

This methodology has also been adapted to be used with different transition metals (*e.g.* iron,[115] cobalt[116] and copper[117]) as well as generating a variety of coupled products (*e.g.* via reactions such as alkylation,[118] alkynylation[119] and borylation[120]). For example, Baran *et al*. found that in reaction of NHP ester **279** in the presence of a nickel catalyst, 4,4′-dimethoxy-2,2′-bipyridine (dmbpy) and an alkynyl zinc reagent gave the coupled product **281** in only 16% yield (Scheme 3.15).[121] In contrast, when using the much more electron deficient tetrachloro-NHP ester **280**, a much higher (82%) yield of cross-coupled product **281** was obtained. However, the authors did not specify why one ester gave better results than the other.

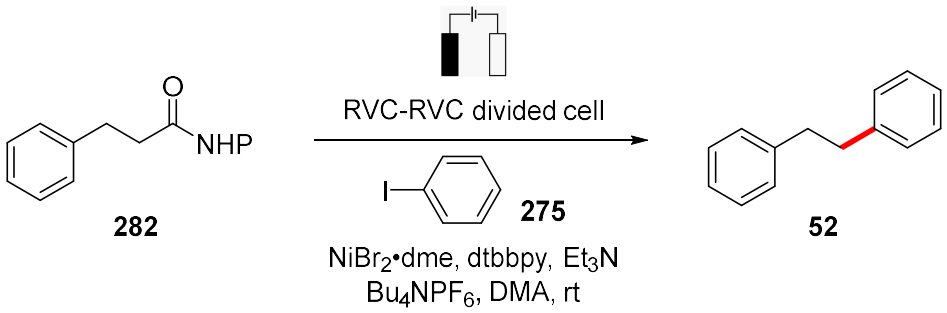



Scheme 3.15

### 3.1.2.3 Electrochemical Reduction of NHP esters

As an alternative to photo-activation to enable mild reduction of the triplet state, direct reduction of unactivated NHP esters can be achieved electrochemically as long as sufficiently reducing potentials are used. As discussed before, NHP esters have a reduction potential of $E_{1/2} = -1.37$ V vs SCE when in the ground state.[95]

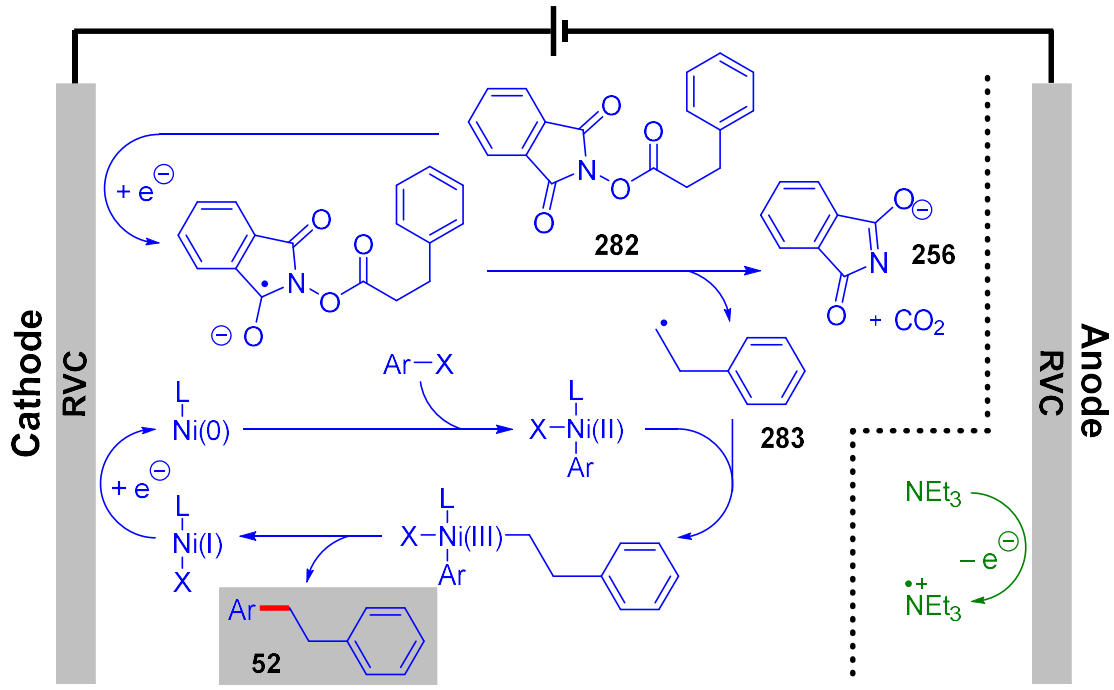
Prior to the work described in this Chapter, to the best of our knowledge, there were only a few reports on electrochemical transformations using NHP esters. In 2018, Jamison *et al*. reported a nickel catalysed electrochemical decarboxylative coupling of *N*-hydroxyphthalimide esters with aryl halides.[21] A divided cell was used with RVC (reticulated vitreous carbon) electrodes and $Bu_4NPF_6$ as the electrolyte. A nickel catalyst with a dtbbpy ligand was used to perform the cross-coupling of the NHP ester and aryl iodide **275**. $Et_3N$ was the sacrificial oxidant in this process. Scheme 3.16 shows one example in which 3-phenyl propanoic *N*-hydroxyphthalimide ester **282** and iodobenzene gave cross-coupled product **52**.




Scheme 3.16

The mechanism for the reductive electrolysis of NHP ester **282** and an aryl iodide is shown in Scheme 3.17. NHP ester **282** is first reduced at the cathode after which it

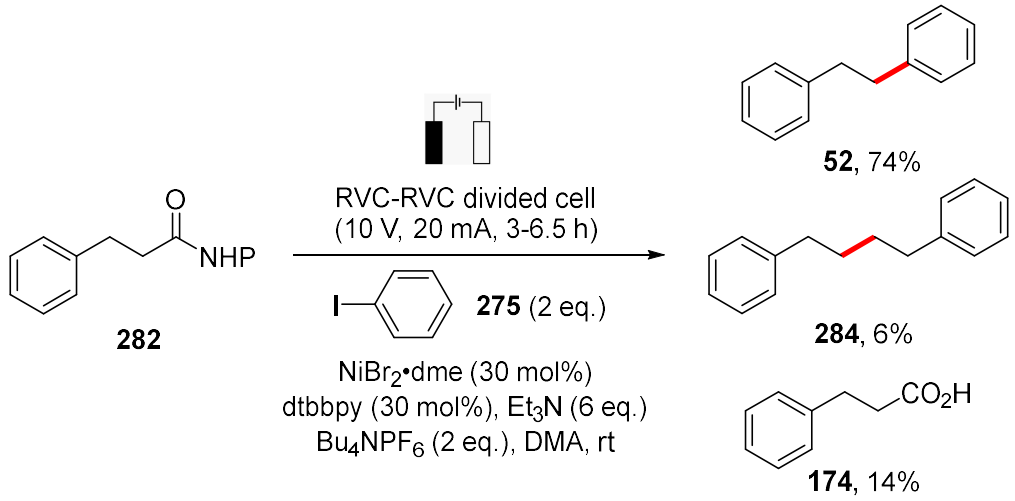
fragments to give the carbon-centred radical **283**, $CO_2$ and phthalimide anion **256**. Radical **283** is then intercepted by a Ni(II) catalyst that is generated from the oxidative addition of iodobenzene to Ni(0). Reductive elimination forms the cross-coupled product **52** and the resulting Ni(I) species is reduced at the cathode to Ni(0), thus completing the catalytic cycle (blue route). Meanwhile, $Et_3N$ is oxidised at the anode in a separate chamber (green route).




Scheme 3.17

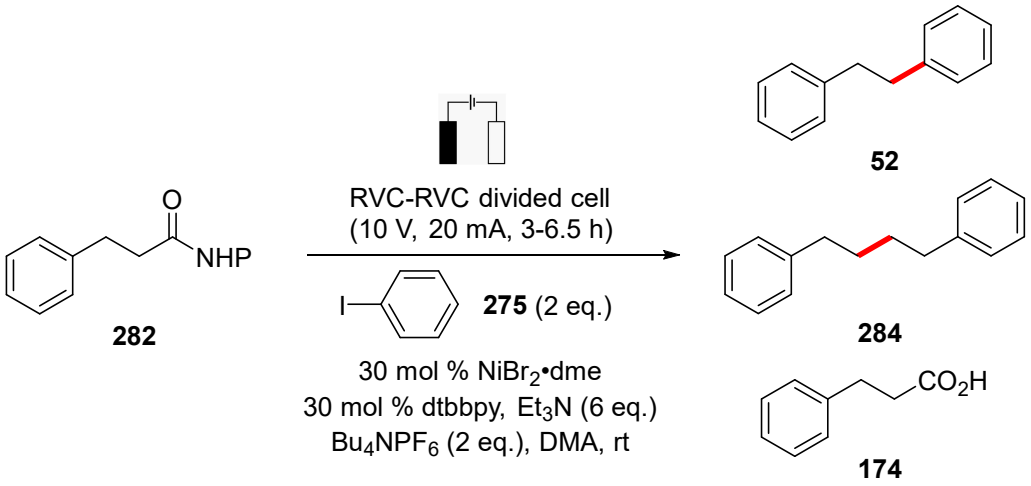
Jamison's optimised procedure is shown in Scheme 3.18. A divided cell was used that contained an RVC anode and cathode. The cathodic chamber contained a 0.1 M solution of NHP ester **282**, iodobenzene (2 eq.), $Bu_4NPF_6$ (0.2 M), $NiBr_2$·dme (30 mol %) and dtbbpy (30 mol %) in DMA. The anodic chamber contained a solution of $Et_3N$ (0.6 M) and $Bu_4NPF_6$ (0.2 M) in DMA. The reaction mixtures were then electrolysed at 10 V / 20 mA until full consumption of the NHP ester **282** was observed *via* HPLC analysis (typically 3-6.5 h). Cross-coupled product **52** was isolated in 74% yield. The authors did not specify the amount of charged passed or if the experiment was run at constant current or constant voltage. In addition, 1,4-diphenyl butane **284** was formed in 6% yield which was generated from a Kolbe-type dimerisation of radical **283** to give the homocoupled product. Propanoic acid **174** was also generated in 14% yield. Jamison proposed that propanoic acid **174** was not formed from the hydrolysis of NHP ester **282** as the water

content of the reaction mixture was too low to account for the 14% yield of acid **174**. It was therefore concluded that acid **174** was formed from a competitive electrochemically-mediated process but did not give further details.




Scheme 3.18

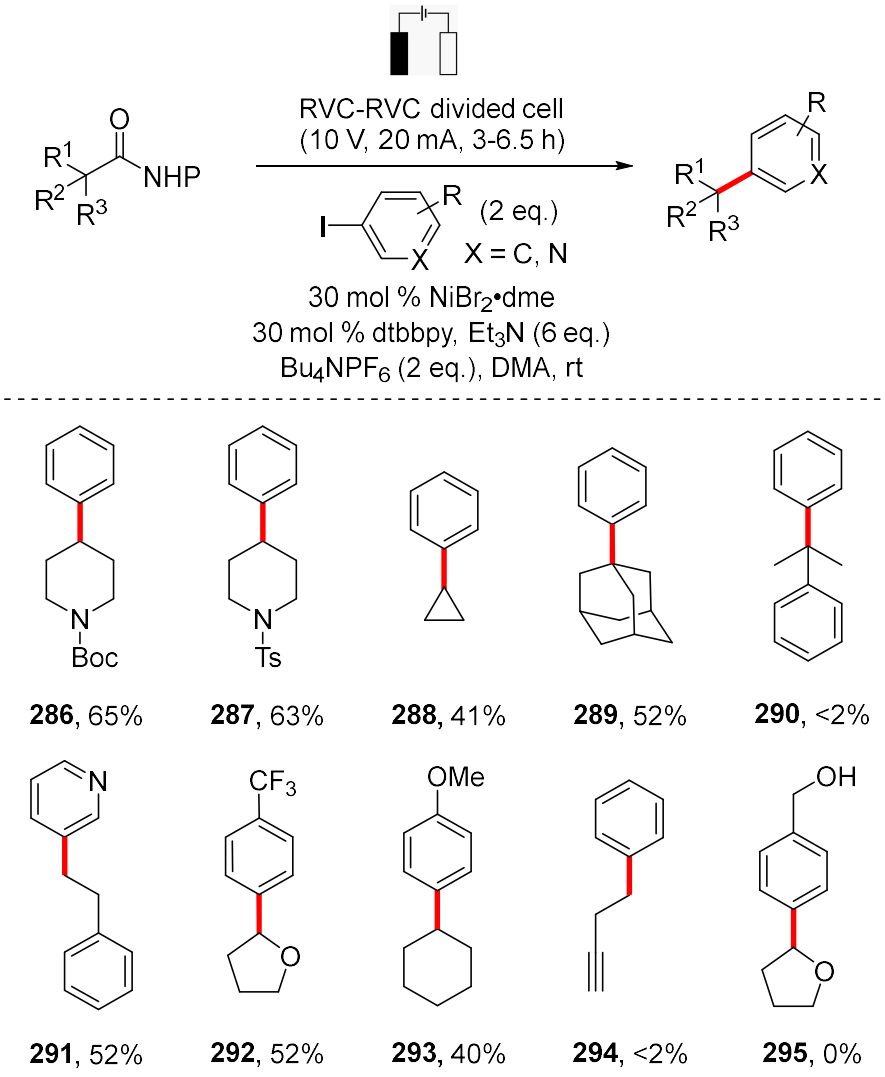
Table 3.1 summarises a selection of the optimisation experiments. When an undivided cell was used, homocoupled product **284** was formed in 39% yield (entry 2). It was proposed that a competitive oxidation of the nickel catalyst is taking place which reduces the yield of the cross-coupling product **52**. When no nickel catalyst was used, cross-coupling was not observed and homocoupled product **284** was formed in 44% yield together with acid **174** in 38% yield (entry 3). With no current, product **52** was not formed (entry 4). However, acid **174** was also not formed which supported the theory that acid **174** was formed by an electrochemical process and not by hydrolysis. In MeCN, less cross-coupled product **52** and more homocoupled product **284** were obtained (entry 5). The reaction was also performed under flow conditions which gave cross-coupled product **52** in 81% yield and homocoupled **284** and acid **174** in 6% and 8% yield respectively (entry 6). It was suggested that using flow conditions, the mixing of the reaction was improved throughout the electrolysis.




| Entry | Deviation from above | Yield of 52 (%) | Yield of **284** (%) | Yield of **174** (%) |
|---|---|---|---|---|
| 1 | None | 74 | 6 | 14 |
| 2 | Undivided cell | 6 | 39 | 18 |
| 3 | No $NiBr_2$·dme | 0 | 44 | 38 |
| 4 | No current | 0 | 0 | 0 |
| 5 | MeCN instead of DMA | 48 | 26 | 19 |
| 6 | Flow cell | 81 | 6 | 8 |

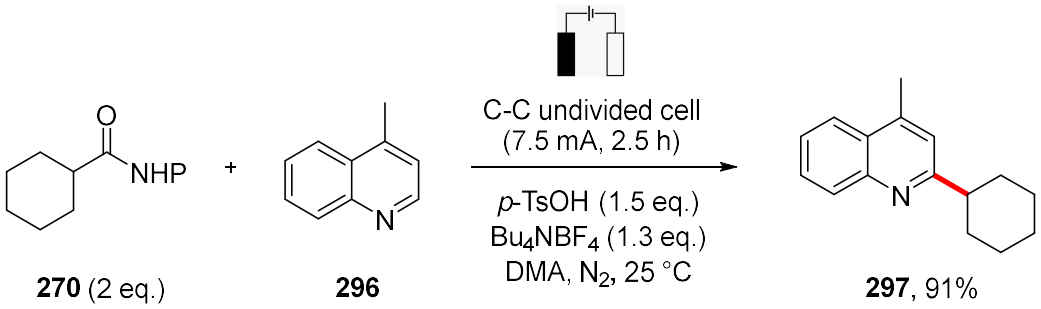
Table 3.1 – Nickel catalysed electrochemical decarboxylation arylation reaction.[21]

The scope of this decarboxylative cross-coupling reaction is summarised in Scheme 3.19. Secondary NHP esters including protected piperidines (**286** and **287**) and a cyclopropyl group (**288**) worked well (41-65% yield). Adamantyl NHP esters can be incorporated in 52% yield (**289**). However, non-constrained benzylic quaternary $sp^3$ centres do not couple in good yields (**290**). Electron deficient and electron rich aryl halides coupled in good yields (40-52% yield) (**291**, **292** and **293**) but terminal alkynes (**294)** and benzylic alcohols (**295**) were not compatible.



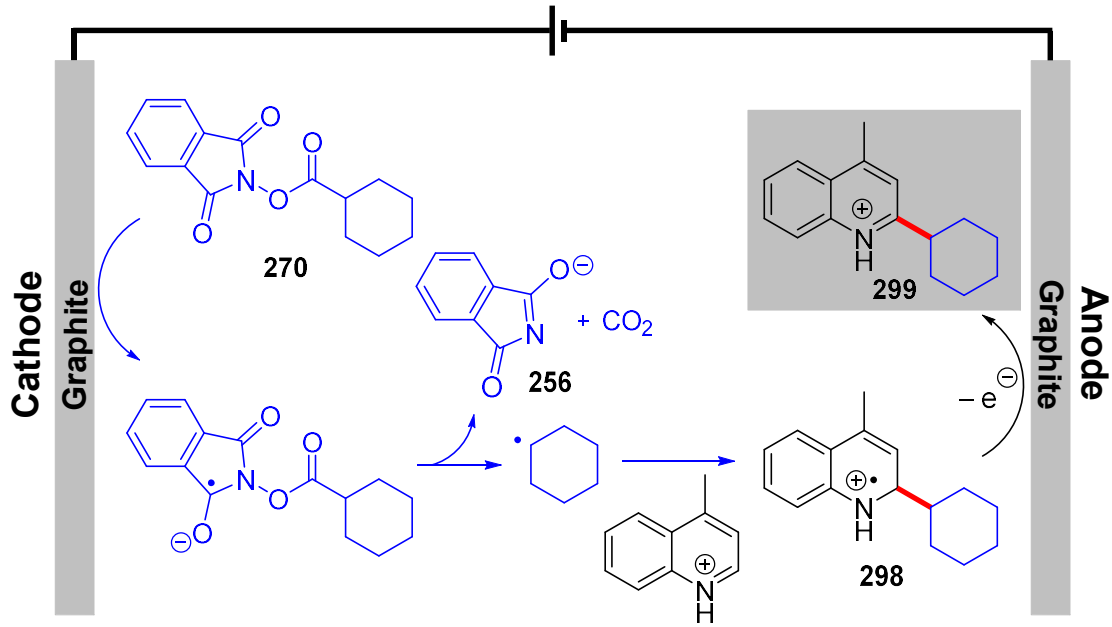

Scheme 3.19

More recently, and after work on this stage of the PhD project had commenced, Lei *et al.* described the electrochemical reduction of NHP esters and subsequent addition of the so-generated radicals to *N*-heteroarenes (Scheme 3.20).[122] An undivided cell with a graphite anode and cathode was used with $Bu_4NBF_4$ as the electrolyte. For example, NHP ester **270** was electrochemically reduced in the presence of quinoline **296** and coupled product **297** was isolated in 91% yield.




Scheme 3.20

The proposed mechanism for this reaction is shown in Scheme 3.21. NHP ester **270** is reduced at the cathode, fragments and decarboxylates to give the cyclohexyl radical. This radical then adds to quinoline which is protonated by the sulfonic acid present to give radical cation **298**. Then, radical cation **298** is oxidised at the anode to give the protonated coupled product **299** which can undergo deprotonation to give the desired product **297**. This work is particularly useful as no catalyst is required but there are a limited range of *N*-heteroarenes that can be used in these types of Minisci reactions. At this point, there was no electrochemical methodology for $C_{sp3}$-$C_{sp3}$ coupling.

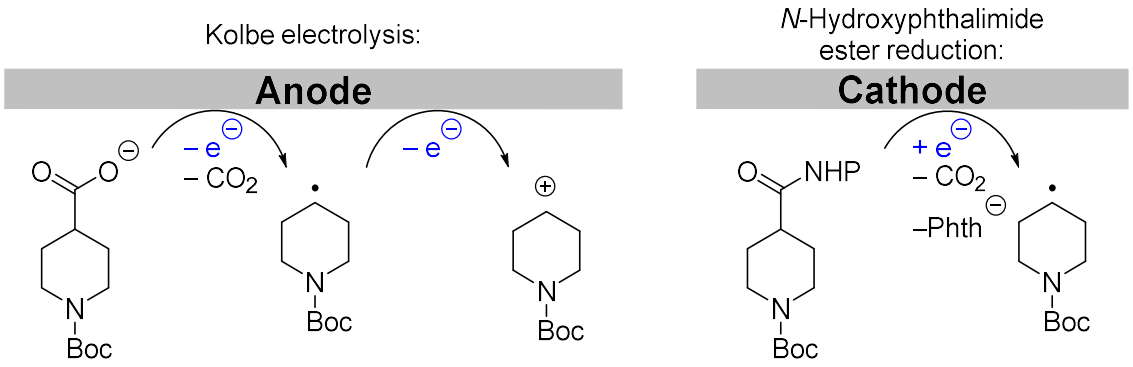



Scheme 3.21

Overall, the reduction of NHP esters is a useful tool for carbon-carbon bond formation with numerous photochemical and transition metal methodologies. However, there are very few electrochemical methodologies involving the reduction of these esters.

## 3.2 Project Outline

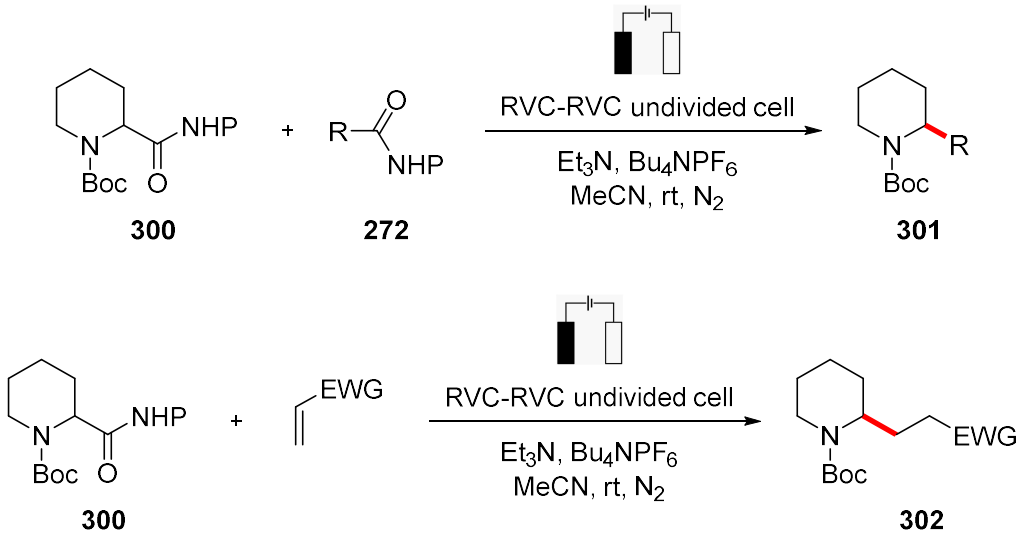
Previous work in this thesis shows that Kolbe electrolysis of deprotonated carboxylic acids uses oxidative decarboxylation to produce carbon radicals for participation in subsequent coupling reactions. However, the scope of this reaction is severely limited by the tendency of the radicals to over-oxidise at the anode and therefore generate unwanted carbocation-derived side products (see Chapter 2). As shown in the Introduction to this Chapter, an alternative electrochemical route to similar carbon-centred radicals is the reductive decarboxylation of *N*-hydroxyphthalimide esters. Therefore, experiments have been designed to explore the scope of achieving radical coupling reactions *via* reductive decarboxylation of *N*-hydroxyphthalimide esters rather than oxidative Kolbe electrolysis. Since the radical intermediate will be generated at the cathode, over-oxidation of the radical intermediate is far less likely. Thus, it was proposed that substrates which were unsuited to Kolbe electrolysis should now be amenable to electrochemical radical generation, most notably secondary carboxylic acid starting materials (Scheme 3.22).




Scheme 3.22

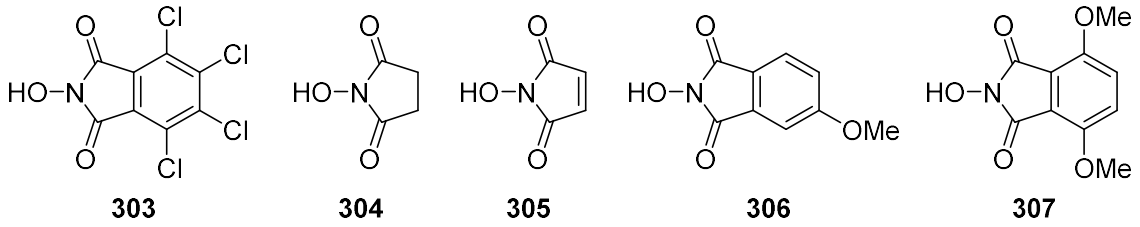
As shown in Section 3.1.2, there are few electrochemical methods for the reduction of NHP esters, one of which was the $C_{sp3}$-$C_{sp2}$ formation performed by Jamison *et al*. (see Scheme 3.16).[21] However, when this project was started, there was no electrochemical method for the reduction of NHP esters and subsequent $C_{sp3}$-$C_{sp3}$ coupling. The initial aims of this project took inspiration from Jamison's work, with the aim being to develop an electrochemical procedure to fill in this gap. Scheme 3.23 shows the procedure involving both radical coupling and radical addition into electron deficient alkenes. The proposed reaction conditions were taken and adapted from Jamison's work[21] and include RVC electrodes, $Et_3N$ (sacrificial oxidant) and $Bu_4NPF_6$ (electrolyte) in MeCN. A

divided cell would not be necessary, so an undivided cell was chosen due to the simplicity of the set-up. In Jamison's work, a divided cell was used to separate the nickel catalyst from the anode.




Scheme 3.23

As part of this project, it was decided to explore NHP analogues in order to investigate how different functional groups affect the electrochemical properties of the redox active ester. The NHP analogues that were studied are shown in Scheme 3.24 and include the addition of chlorine groups and methoxy groups onto the aromatic moiety or even removing the aryl ring altogether.




Scheme 3.24

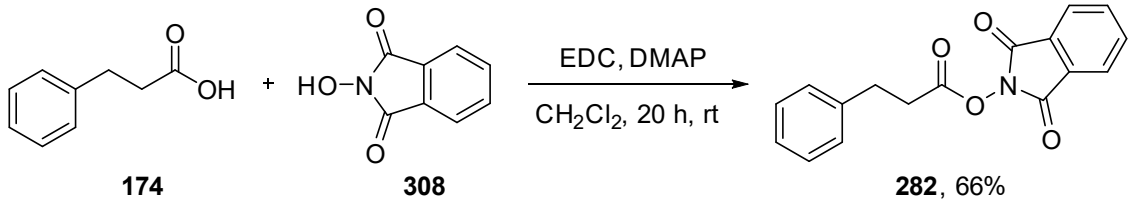
Since commencing the work described in this Chapter, an electrochemical method for the reduction of a *N*-hydroxyphthalimide ester and subsequent $C_{sp3}$-$C_{sp3}$ coupling was reported by Wang *et al*. and is discussed in more detail in Section 3.7.[123]

## 3.3 Reductive Decarboxylation of *N*-Hydroxyphthalimide Esters and Subsequent Homo- and Heterocoupling Reactions.

### 3.3.1 Homocoupling of 3-Phenylpropanoic *N*-Hydroxyphthalimide Ester

As a starting point, the homocoupling of the radical derived from the electrochemical reduction of NHP ester **282** was explored. This was an unwanted side-reaction in Jamison's work on nickel catalysed electrochemical decarboxylative arylations (see Section 3.1.2 and Table 3.1) and under certain conditions, yields of homocoupled product **284** of 26-44% were obtained. Before moving on to the planned heterocoupling reactions, it was hoped that it would at least be possible to reproduce these yields of homocoupled product **284**.

First, the synthesis of NHP ester **282** was carried out using a literature procedure.[21] Acid **174** was coupled with *N*-hydroxyphthalimide **308** in the presence of EDC and DMAP to give NHP ester **282** in 66% yield (Scheme 3.25).

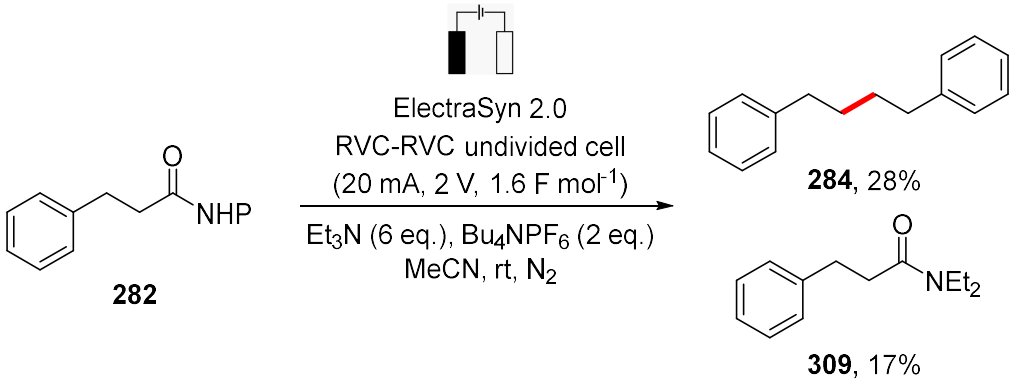



**174** **308** **282**, 66%

Scheme 3.25

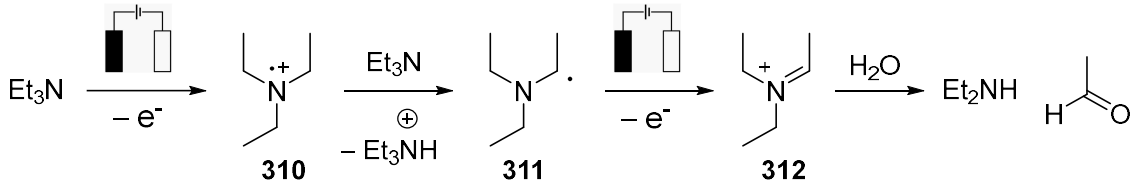
With the starting material in hand, the reductive decarboxylation and subsequent homocoupling of NHP ester **282** was performed using an IKA ElectraSyn 2.0 set-up with a 10 mL electrochemical cell. The undivided cell contained two commercial RVC IKA electrodes that each were 50 × 8 × 2 mm in dimension. RVC is a porous carbon material and the surface area of the electrode is difficult to measure or estimate. Therefore, the current densities for the electrolysis reactions discussed in this Chapter are not presented. A 0.11 M solution of NHP ester **282** with $Et_3N$ (6 eq.) and $Bu_4NPF_6$ (2 eq.) in MeCN was prepared. A current of 20 mA was applied to give an average cell voltage of 2 V. The current was applied for a sufficient time to ensure a total of 1.6 F $mol^{-1}$ of charge had passed. This gave 1,4-diphenyl butane **284** and amide **309** in 28% and 17% yield respectively after purification by chromatography. In this experiment, the work-up

involved the addition of ethyl acetate and the resulting organic layer was washed with brine and concentrated before purification.



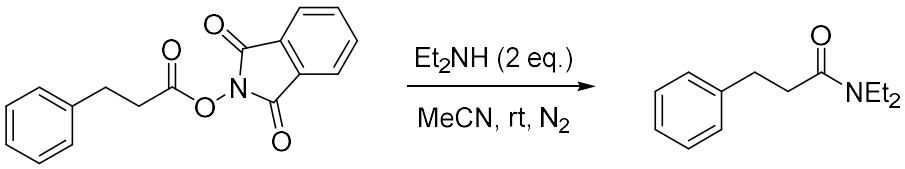

Scheme 3.26

The formation of amide **309** was unexpected. Amide **309** could not be formed in Jamison's reactions since a divided cell was used and the $Et_3N$ was separated from the starting material **282** by a membrane (see Scheme 3.18). To explain the formation of amide **309**, it is presumed that the $Et_3N$ is converted into $Et_2NH$ which undergoes amide formation with the activated NHP ester **282**. A proposed mechanism for the formation of $Et_2NH$ is shown in Scheme 3.27. The $Et_3N$ could be oxidised to give radical cation **310** and, after deprotonation, radical **311** would form.[124] Radical **311** could undergo another oxidation to iminium ion **312** and subsequent hydrolysis would form $Et_2NH$. At this point, it was presumed that the water came from the solvent as no effort was made to dry the solvent.




Scheme 3.27

In order to see if $Et_2NH$ could displace the ester in NHP ester **282**, an experiment was performed using similar conditions to the reductive decarboxylation reaction. A solution of NHP ester **282** and $Et_2NH$ in MeCN was stirred at rt for 4 h and amide **309** was isolated in 71% yield (Scheme 3.28).




**282** **309**, 71%

Scheme 3.28

In an attempt to increase the yield of 1,4-diphenyl butane **284**, four more electrolysis reactions were carried out with various changes including using a different solvent and current (results not shown). However, the yield of 1,4-diphenyl butane **284** decreased with each experiment. A repeat of the exact experiment performed in Scheme 3.26 was then run in order to test the reproducibility of the reaction but 1,4-diphenyl butane **284** was isolated in only 6% yield. At this point, it was noticed that the electrode material had become discoloured which indicated that passivation of the electrodes was occurring. Re-use of these electrodes presumably led to the lower yields. Fortunately, since RVC is a cheap material, new electrodes could be used for each reaction. The experiment was therefore repeated with new electrodes and, gratifyingly, coupled product **284** was isolated in 26% yield. The yield of amide **309** remained relatively unchanged (15-20%) throughout these reactions. From this point onward, new electrodes were used for each experiment.

The ElectraSyn 2.0 should record the current and voltage throughout the reaction. However, in my hands, this information was not reliably recorded by the equipment. Therefore, a modified version of the bespoke cell and circuit from Chapter 2 (see Figure 2.5) was used. The modified electrolysis cell is shown in Figure 3.1. The construction of the home-built RVC (36 × 6 × 5 mm) electrodes was inspired by literature from the Baran group[12] and these electrodes were connected to the circuit by tinned copper wire. New RVC electrodes were used for each reaction. Plastic inserts were used to hold the electrodes at a distance of 2 mm. During the electrolysis reactions, care was taken to avoid oxidation of the tinned copper wire by keeping the level of solution below the wire. All subsequent reactions in this Chapter were performed in the modified cell.

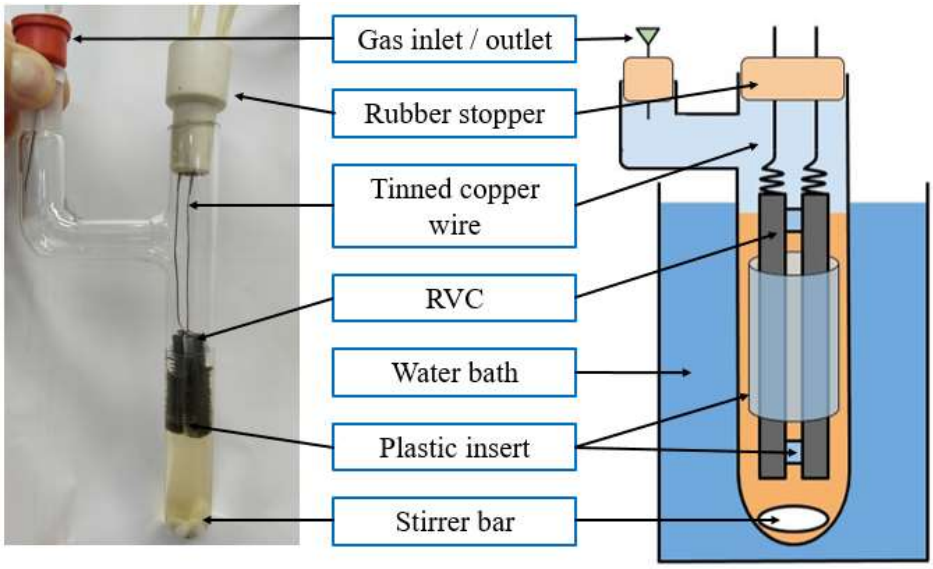
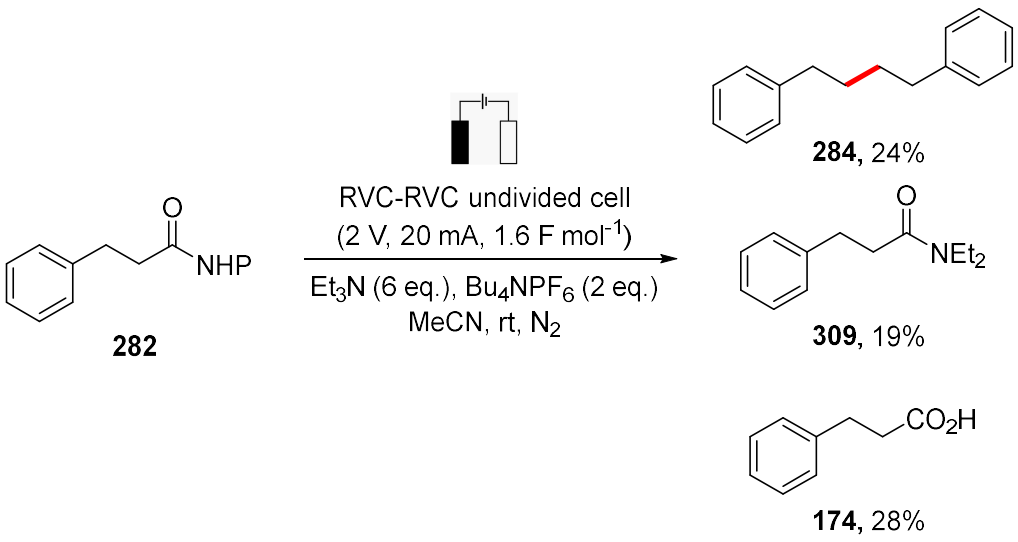



Figure 3.1 – Picture and schematic of the electrolysis cell

With the new cell in hand, reductive decarboxylation and homocoupling of NHP ester **282** was performed (Scheme 3.29). A 0.11 M solution of NHP ester **282** with $Et_3N$ (6 eq.) and $Bu_4NPF_6$ (2 eq.) in MeCN was used. A voltage of 2 V was applied to the cell to give an initial current of 20 mA. The voltage was applied until a total charge of 1.6 F $mol^{-1}$ had passed. As detailed in Figure 3.2, the current dropped to reach a final level of 9 mA but only the initial current is indicated in the scheme; this approach is followed throughout the rest of this Chapter. After purification, 1,4-diphenyl butane **284** and amide **309** were isolated in 24% and 19% yield respectively.




Scheme 3.29

At this point, the low mass recovery of 1,4-diphenyl butane **284** and amide **309** (43% in total) for this reaction was a concern. Therefore, it was considered that carboxylic acid **174** could have formed but was removed during the work-up (as noted by Jamison, see Scheme 3.18). The standard work-up involved washing the organic layer with brine and concentrating the organic layer before purification. The brine washings would be basic due to the excess $Et_3N$ present and could contain deprotonated carboxylic acid. Therefore, the brine washings of the reaction shown in Scheme 3.29 were acidified with 1 M $HCl_{(aq)}$, extracted with $CH_2Cl_2$ and concentrated to obtain a second crude product. $^1H$ NMR spectroscopic analysis showed it to contain acid **174** and the electrolyte ($Bu_4NPF_6$). The yield of acid **174** in this sample was calculated to be 28%. Acid **174** could be formed from the hydrolysis of the *N*-hydroxyphthalimide ester as no specific precautions were taken to remove water from the solvent and electrolyte, although Jamison proposed that an undefined electrochemical pathway was responsible for the formation of acid **174**.

During the experiment, the voltage and current were measured using a LabJack©, as described in Section 2.3 (see Figure 2.4). Figure 3.2 shows the voltage (black line) and current (red line) throughout the experiment that is summarised in Scheme 3.29. The voltage stayed fairly constant at around 2 V. The current decreased from 20 to 10 mA during the first 1.5 h and then remained steady at ~10 mA for the remainder of the experiment. After 1.5 h, 0.9 F $mol^{-1}$ of charged had passed through the reaction. It is assumed that the current began to plateau at 1.5 h because the majority of NHP ester **282** was depleted.

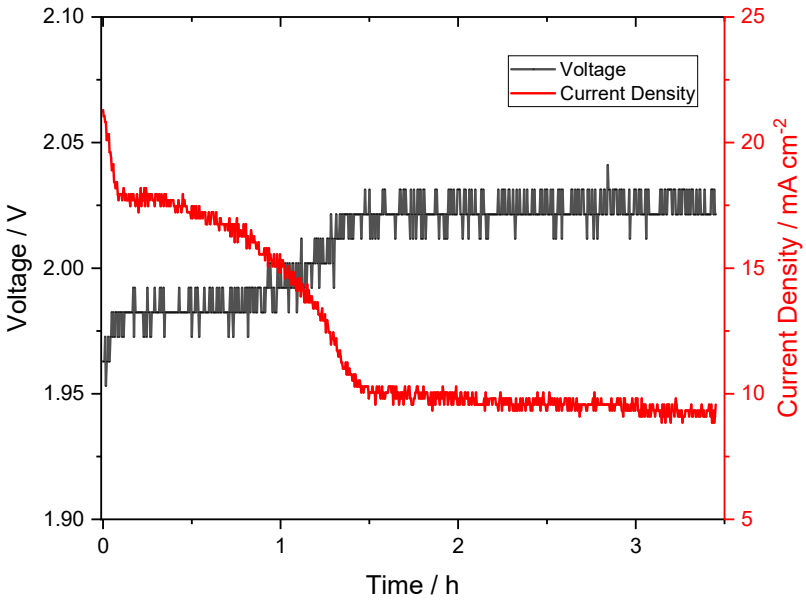
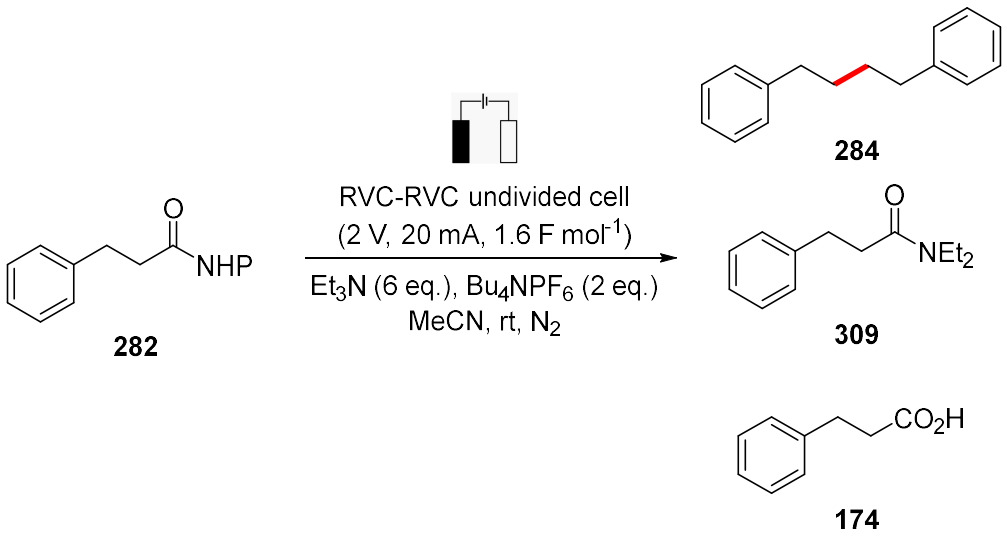



Figure 3.2 – Cell voltage and current throughout the electrolysis of NHP ester **282** (Scheme 3.29)

In order to try to improve the yield of 1,4-diphenyl butane **284**, various adjustments were made to the reaction and the results are summarised in Table 3.2. First, dry solvent and fresh $Bu_4NPF_6$ were used to try and minimise any water present in the system. However, the yield of 1,4-diphenyl butane **284** remained largely unchanged (entries 2 and 3). Using DMA in place of MeCN, 1,4-diphenyl butane **284** was obtained in only 8% yield and a large amount of acid **174** was formed (71%) (entry 4). In an attempt to limit the production of amide **309**, it was envisaged that 1,4-diazabicyclo[2.2.2]octane (DABCO) could be used as the sacrificial oxidant due to its inability to form an iminium ion because of the bridgehead position of the nitrogen. Thus, DABCO was utilised in the electrochemical reaction and 1,4-diphenyl butane **284** was obtained in a similar yield (18%) with no amide being observed (entry 5). Reactions at either 40 °C or at two different currents did not increase the yield of 1,4-diphenyl butane **284** (entries 6-8). Finally, the experiment was carried out until the current plateaued and **284**, **309** and **174** were formed in 24%, 19% and 31% yield respectively (entry 9). This is essentially the same result as in entry 1, suggesting that there is no further formation of 1,4-diphenyl butane **284** after the current plateaus. Thus, it is not detrimental to leave the current on for the standard length of time (1.6 F $mol^{-1}$). Disappointingly, none of the changes led to any improvement regarding the formation of 1,4-diphenyl butane **284**.



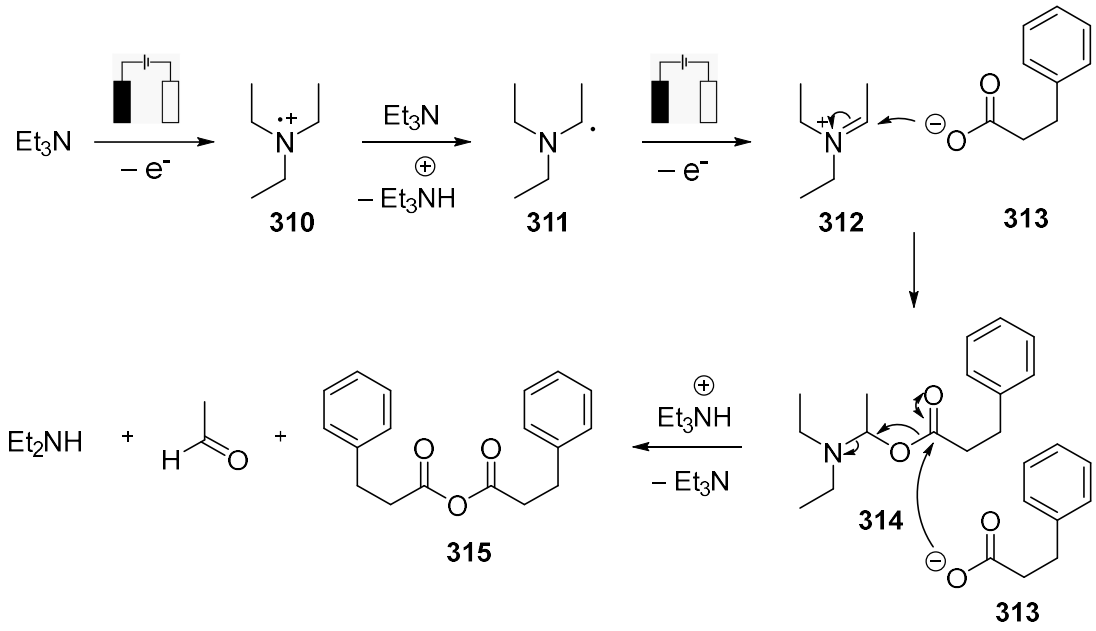

| Entry | Deviation from above | Yield of **284** (%)[a] | Yield of **309** (%)[a] | Yield of **174** (%)[b] |
|---|---|---|---|---|
| 1 | None | 24 | 19 | 28 |
| 2 | Dry MeCN | 24 | 15 | 27 |
| 3 | Fresh $Bu_4NPF_6$ | 23 | 20 | 29 |
| 4 | DMA | 8 | 9 | 71 |
| 5 | DABCO | 18 | n/a | 37 |
| 6 | 40 °C | 20 | 28 | 36 |
| 7 | 10 mA | 17 | 24 | 38 |
| 8 | 40 mA | 15 | 12 | 33 |
| 9 | 0.76 F $mol^{-1}$ [c] | 24 | 19 | 31 |

Table 3.2 – Reductive decarboxylation of 3-phenylpropanoic *N*-hydroxyphthalimide ester **282**.

[a] Yield after chromatography. [b] Calculated from the $^1H$ NMR spectrum of the acidified crude sample. [c] The experiment was run until the current plateaued.

As outlined in Scheme 3.27, it was initially thought that $Et_2NH$ forms *via* hydrolysis of iminium ion **312** during the reaction in order to react with NHP ester **282** and form amide **309**. However, with dry MeCN and dry $Bu_4NPF_6$, there was no change in the amount of amide **309** formed (compare entries 1-3). An alternative approach for generating $Et_2NH$ could involve carboxylate **313** (derived from acid **174**). For example, carboxylate **313** could add to iminium ion **312** to form hemiaminal **314** (Scheme 3.30). Another carboxylate **313** could then attack hemiaminal **314** to form $Et_2NH$ (upon protonation) and

anhydride **315**. Anhydride **315** would then form acid **174** during the aqueous work-up and would therefore not be isolated.



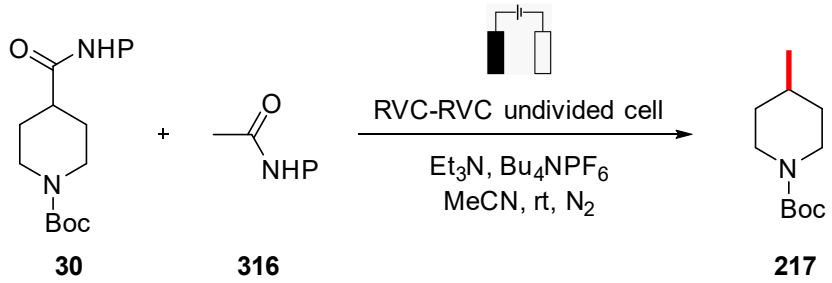

Scheme 3.30

In addition, since acid **174** was still generated using dry MeCN, it seemed likely that formation of acid **174** would occur *via* an electrochemical process rather than *via* hydrolysis. As previously mentioned, Jamison *et al*. also came to the same conclusion without providing any details. To explore this, an experiment was performed using the conditions described in Scheme 3.29 but without connection of the electrodes to any external circuitry. No carboxylic acid **174** was observed and the starting NHP ester **282** was recovered in high yield, indicating that the formation of acid **174** occurs electrochemically and not by hydrolysis of the ester. Suggestions for the electrochemical formation of acid **174** are discussed in Section 3.6.

The initial efforts on the reductive decarboxylation and subsequent homocoupling of NHP ester **282** proved to be successful and although the homocoupled product **284** was only obtained in a maximum of 24% yield. However, it was decided that, at this stage, further optimisation of this reaction was futile and instead, the feasibility of a heterocoupling reaction was investigated next.

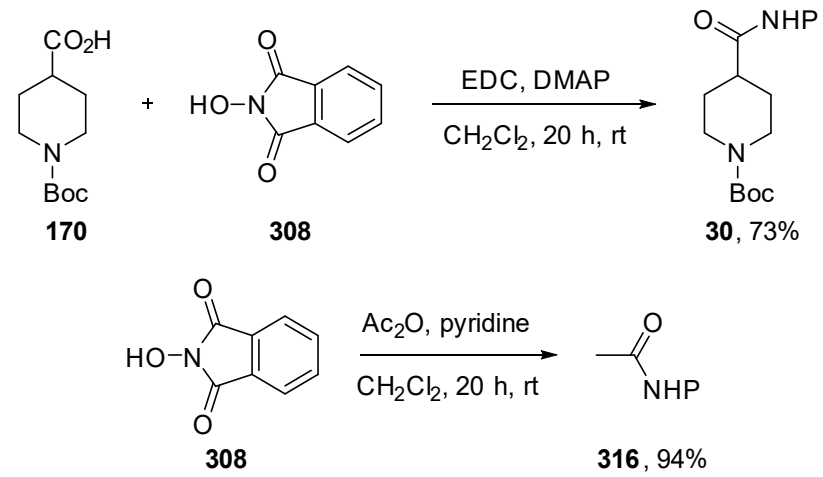
### 3.3.2 Heterocoupling of *N*-Boc Piperidine and Acetate *N*-Hydroxyphthalimide Esters

The reductive decarboxylation and subsequent heterocoupling of NHP ester **30** and NHP acetate **316** was attempted (Scheme 3.31). These NHP esters give a direct comparison between the new reductive methodology being developed and the oxidative Kolbe electrolysis experiments in Section 2.5 (see Scheme 2.74) which generate the same product, 4-methyl *N*-Boc piperidine **217**.



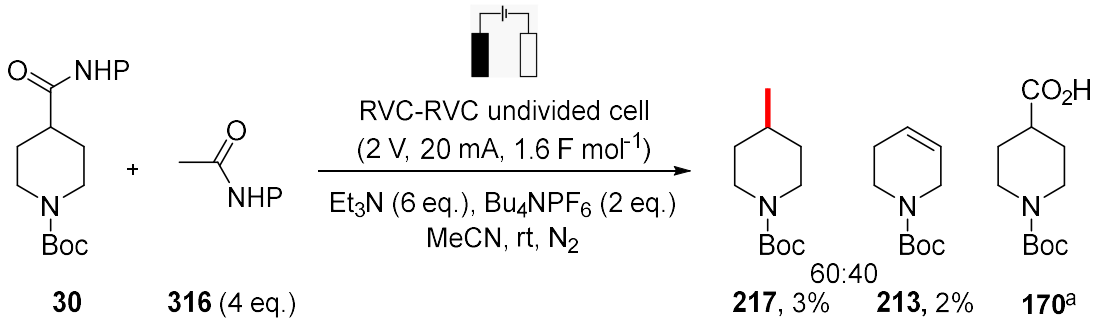

Scheme 3.31

The synthesis of NHP ester **30** was carried out using a modified literature procedure.[21] *N*-Boc piperidine 4-carboxylic acid **170** was coupled with *N*-hydroxyphthalimide **308** in the presence of EDC and DMAP to give NHP ester **30** in 72% yield after purification by chromatography (Scheme 3.32). The synthesis of *N*-hydroxyphthalimide acetate **316** was carried out using a literature procedure.[125] *N*-hydroxyphthalimide **308** was reacted with acetic anhydride in the presence of pyridine to give NHP acetate **316** in 94% yield (Scheme 3.32).




Scheme 3.32

Next, reductive decarboxylation and heterocoupling was attempted. The conditions used for this experiment were based on the oxidative work described in Scheme 2.74. An excess of one of the NHP esters was used in order to increase the likelihood of the two radicals heterocoupling. The NHP ester used in excess will homocouple but the other NHP ester will be incorporated into the heterocoupled product. In this case, NHP acetate **316** was used in excess as the homocoupled product, ethane, will be easily removed. Thus, a 0.2 M solution of NHP ester **30** with NHP acetate **316** (4 eq.), $Et_3N$ (6 eq.) and $Bu_4NPF_6$ (2 eq.) in MeCN was prepared. A voltage of 2 V was applied through the solution and an initial current of 20 mA was obtained. The voltage was applied until a total of 1.6 F (total mol of NHP ester)$^{-1}$ was passed. This reaction was not very successful as piperidine **217** and alkene piperidine **213** were formed as an inseparable mixture in yields of only 3% and 2% respectively (Scheme 3.33). Acid **170** was also observed in the $^1$H NMR spectrum of the acidified crude sample but the amount was unquantified.




Scheme 3.33 – [a] Observed in the $^1$H NMR spectrum of the acidified crude sample but in an unknown amount.

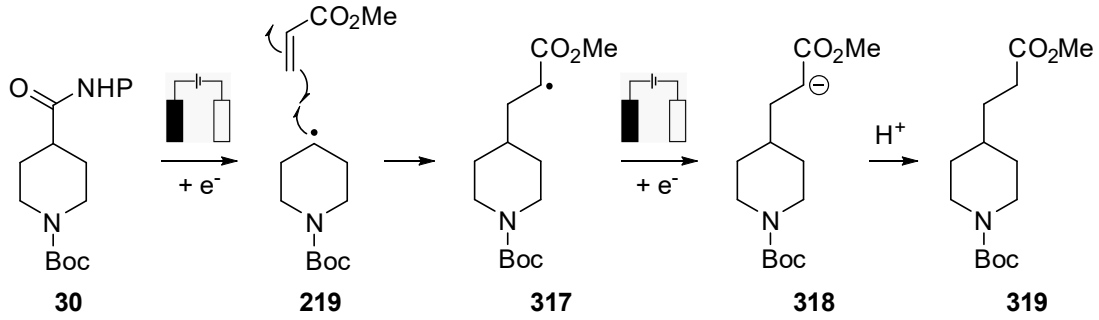
The formation of alkene **213** was assumed to come from the oxidation of the radical intermediate to form a cation. Subsequent removal of a proton adjacent to the cation would result in alkene **213**. This process was typically observed in Kolbe electrolysis. It is proposed that only a small amount of alkene **213** was formed as the radical is generated at the cathode, and therefore must travel to the anode for oxidation. It is probable that the reductive decarboxylation-heterocoupling reaction is very low yielding due to the current density being significantly lower (20 mA applied to an RVC cathode of geometric area ~4 cm$^2$) compared to the oxidative equivalent reaction (140 mA applied to a Pt anode of geometric area 3.3 cm$^2$, see Section 2.5, Scheme 2.74).[29] Given the extensive porous nature of RVC, the concentration of radicals at the cathode would be orders of magnitude lower than in the Kolbe method, very significantly decreasing the likelihood of

heterocoupling. This could also explain the moderate yield of the decarboxylation and homocoupling of NHP ester **282**. The decarboxylation and hetero-homocoupling reaction was not performed at a higher current, as this would require higher voltage. The solvent and electrolyte have a voltage window (approximately between + 3 V and −3 V vs SCE) at which no oxidation or reduction of the solvent or electrolyte is taking place.[126] By increasing the voltage, the solvent and electrolyte could be degraded in a competing electrochemical reaction. With this in mind, a new reaction was proposed that did not require the coupling of two radicals and instead involved radical addition to an alkene.

## 3.4 Reductive Decarboxylation of *N*-Hydroxyphthalimide Esters and Subsequent Addition to Alkenes

### 3.4.1 *N*-Hydroxyphthalimide Ester Reduction and Addition to Methyl Acrylate

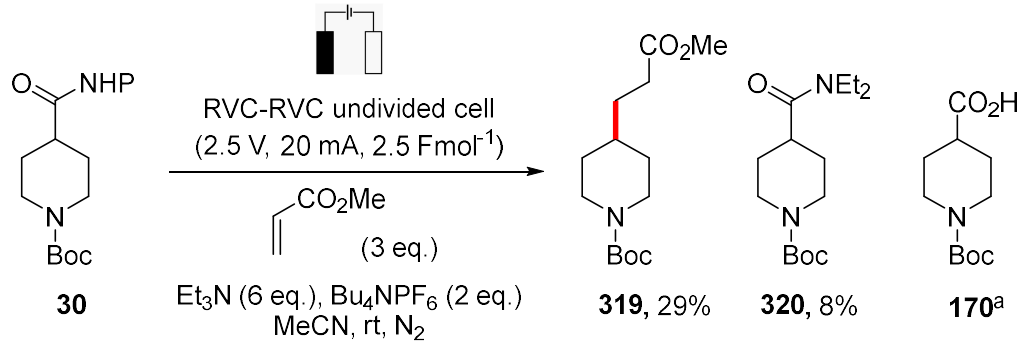
Investigation of reductive decarboxylation followed by radical addition to an alkene was explored next. This is analogous to the Kolbe reactions reported in Section 2.6.2 of Chapter Two. NHP ester **30** and methyl acrylate were initially chosen and the mechanism for the proposed reaction is shown in Scheme 3.34. Reductive decarboxylation of NHP ester **30** should give radical **219** which would subsequently add to an electron deficient alkene, methyl acrylate, to give radical **317**. The radical in **317** is α to a methyl ester and should therefore be easily reduced to give anion **318**. Subsequent protonation during the work-up would produce the desired $C_{sp3}$-$C_{sp3}$ coupled piperidine ester **319**. During the course of writing up the work described in the rest of this Chapter, a closely related reaction was reported by Wang and co-workers.[123] The work in that paper is discussed in detail in Section 3.7 and compared with the results in this thesis.




Scheme 3.34

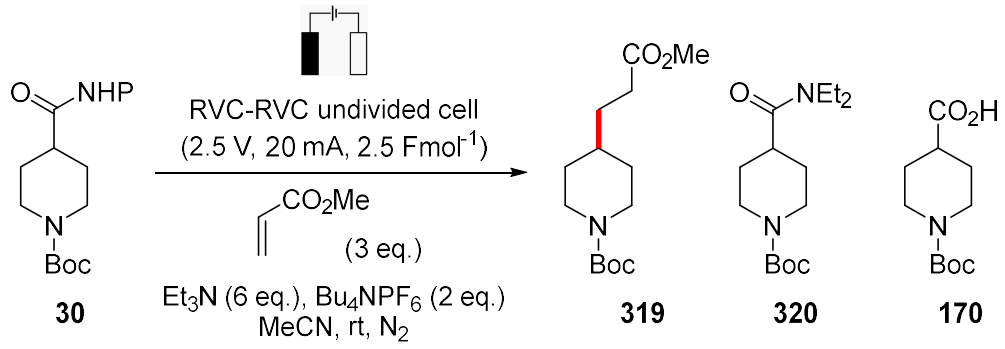
To start, reductive decarboxylation was performed on NHP ester **30** in the presence of methyl acrylate (Scheme 3.35). A 0.1 M solution of NHP ester **30** with methyl acrylate (3 eq.), $Et_3N$ (6 eq.) and $Bu_4NPF_6$ (2 eq.) in MeCN under an inert atmosphere was prepared. A voltage of 2.5 V (initial current of 20 mA) was applied across the cell until a total of 2.5 F (mol NHP ester)$^{-1}$ of charge had passed. It was necessary to pass more charge than in the previous electro-reduction experiments (1.6 F mol$^{-1}$ was used) since in this alkene addition methodology a total of two one-electron reductions are required per substrate, whereas in radical-radical coupling only one-electron is required per NHP ester.

A voltage of 2.5 V was used as this was required to achieve an initial current of 20 mA. From this reaction, piperidine ester **319** and amide **320** were isolated in 29% and 8% yield respectively after purification by chromatography. Acid **170** was also observed by $^{1}$H NMR spectroscopy in the acidified crude sample but the amount was not quantified.




Scheme 3.35 – [a] Observed in the $^{1}$H NMR spectrum of the acidified crude sample but in an unknown amount.

In an attempt to increase the yield of piperidine ester **319**, reactions under different conditions were investigated and the results are presented in Table 3.3. The equivalents of methyl acrylate were increased to 6 eq. but there was little change to the yield of piperidine ester **319** (26%) (entry 2). In this case, amide **320** was isolated in 15% yield and acid **170** was formed in 28% yield. As shown in Table 3.2 when DABCO was trialled as an alternative sacrificial electron donor, use of a sterically hindered base should limit the formation of amide **320** (or equivalent amide). With this in mind, di-*iso*-propylethylamine (DIPEA) was used to ensure that any secondary amine that was formed was less nucleophilic; this gave piperidine ester **319** in a satisfying 41% yield after purification by chromatography (entry 3). No amide was observed during this reaction and acid **170** was generated in 20% yield. However, when another sterically hindered base, tetramethyl piperidine (TMP), was used, the yield of piperidine ester **319** decreased to 18% (entry 4). As TMP is very sterically hindered and a secondary amine, it is speculated that oxidation of this species is not as efficient as DIPEA, and so gave lower yields.[127] When polarity inversion was employed with DIPEA, piperidine ester **319** was isolated in 31% yield (entry 5). Overall, the use of DIPEA as the sacrificial oxidant proved to be successful and therefore the conditions shown in Table 3.3, entry 3 were used as the standard conditions for subsequent reactions described in this Chapter. To check reproducibility, the experiment in entry 3 was repeated and piperidine ester **319** and acid **170** were obtained in similar yields (37% and 22% respectively).

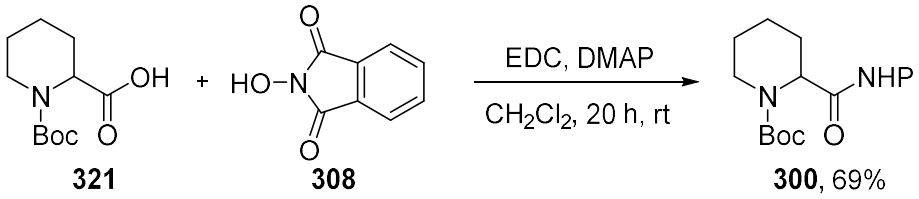



| Entry | Deviation from above | Yield of **319** (%)[a] | Yield of **320** (%)[a] | Yield of **170** (%)[b] |
|---|---|---|---|---|
| 1 | None | 29 | 8 | -[c] |
| 2 | Methyl acrylate (6 eq.) | 26 | 15 | 28 |
| 3 | DIPEA | 41 | - | 20 |
| 4 | TMP | 18 | - | 13 |
| 5 | Polarity inversion and DIPEA | 31 | - | 25 |

Table 3.3 – Reductive decarboxylation NHP ester **30** with methyl acrylate.

[a] Yield after chromatography. [b] Calculated from the $^1$H NMR spectrum of the acidified crude sample. [c] Observed in the $^1$H NMR spectrum but in an unknown amount.

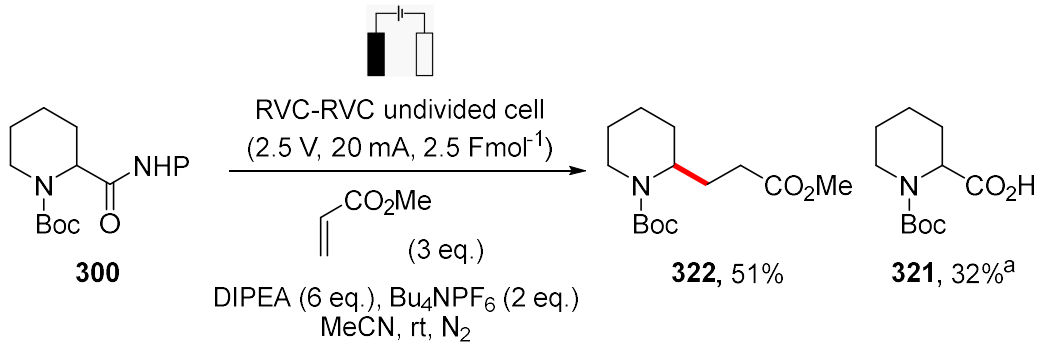
Next, the plan was to explore the use of piperidine NHP ester **300** which is a substrate that was not suitable for oxidative Kolbe methodology due to the simple oxidation of the α-amino carbon-centred radical to a stabilised iminium ion. In contrast, it was anticipated that, under reductive conditions, it should be a viable substrate. Thus, the reductive decarboxylation of NHP ester **300** and subsequent addition to methyl acrylate was investigated. NHP ester **300** was synthesised from a coupling reaction of acid **321** and *N*-hydroxyphthalimide **308** using EDC. NHP ester **300** was isolated in 69% yield after purification (Scheme 3.36).




Scheme 3.36

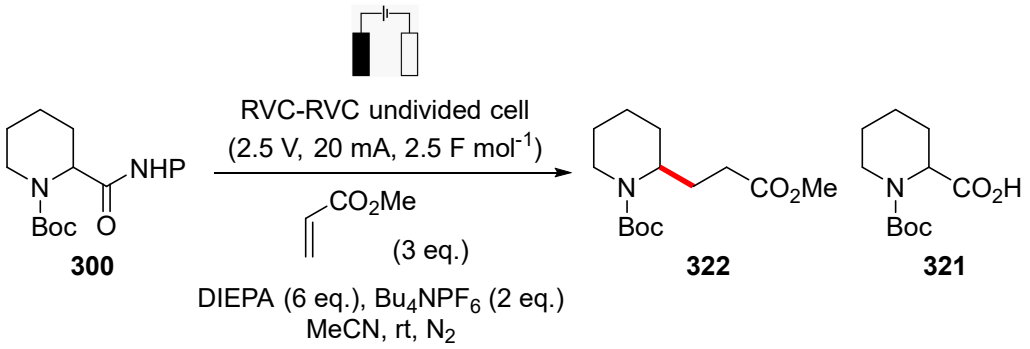
NHP ester **300** was subjected to the standard conditions (Table 3.3, entry 3). Pleasingly, piperidine ester **322** was isolated in 51% yield after purification by chromatography. Acid

**321** (32% yield) was observed in the $^{1}$H NMR spectrum of the acidified crude sample. The experiment was repeated in order to test the reproducibility and piperidine ester **322** and acid **321** were formed in 48% and 20% yield respectively. It is unclear as to why a smaller amount of acid **321** was obtained in the repeat reaction, even though the yield of piperidine ester **322** was similar in both cases.




Scheme 3.37 – [a] Calculated from the $^{1}$H NMR spectrum of the acidified crude sample

In an attempt to increase the yield of piperidine ester **300**, some reaction parameters were varied, including electrolyte, voltage and concentration (Table 3.4). When using $Bu_4NBr$ as the electrolyte, piperidine ester **322** was isolated in 44% yield and acid **321** was observed in 9% yield (Table 3.4, entry 2). It is unclear to why the amount of acid **321** decreased when using a different electrolyte. Next, different voltages were applied to the system, including 2 V, 3 V and 4 V. However, the yield of piperidine ester **322** dropped slightly (Table 3.4, entries 3-5). Finally, the reaction was performed at half concentration as using less substrate for each reaction would mean that the substrate would last longer before more needed to be synthesised. In this case, piperidine ester **322** was isolated in 52% yield.

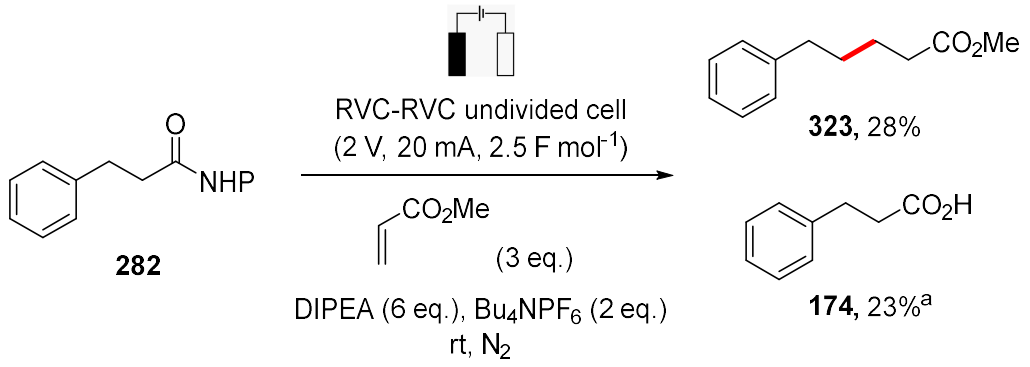



| Entry | Deviation from above (initial current achieved) | Yield of **322** (%)[a] | Yield of **321** (%)[b] |
|---|---|---|---|
| 1 | None | 51 | 32 |
| 2 | $Bu_4NBr$ | 44 | 9 |
| 3 | 2 V (15 mA) | 42 | 17 |
| 4 | 3 V (37 mA) | 48 | 16 |
| 5 | 4 V (60 mA) | 42 | 20 |
| 6 | Half concentration (0.05 M of **300**) | 52 | 20 |

Table 3.4 – Reductive decarboxylation NHP ester **300** with methyl acrylate.

[a] Yield after chromatography. [b] Calculated from the $^1$H NMR spectrum of the acidified crude sample

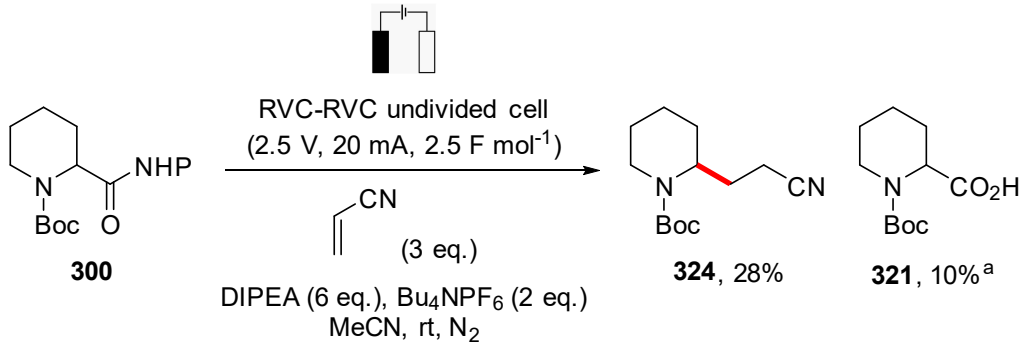
Finally, for comparison, acyclic NHP ester **282** was also reacted with methyl acrylate using the standard conditions. Ester **323** was isolated in 28% yield and acid **174** (23% yield) was observed in the acidified crude sample (Scheme 3.38). Given that this was one of Jamison's successful substrates,[21] it was disappointing that ester **392** was formed in only 28% yield and it is not clear why the yield is lower than those obtained with the piperidine NHP esters **30** and **300**.




Scheme 3.38 – [a] Calculated from the $^1$H NMR spectrum of the acidified crude sample

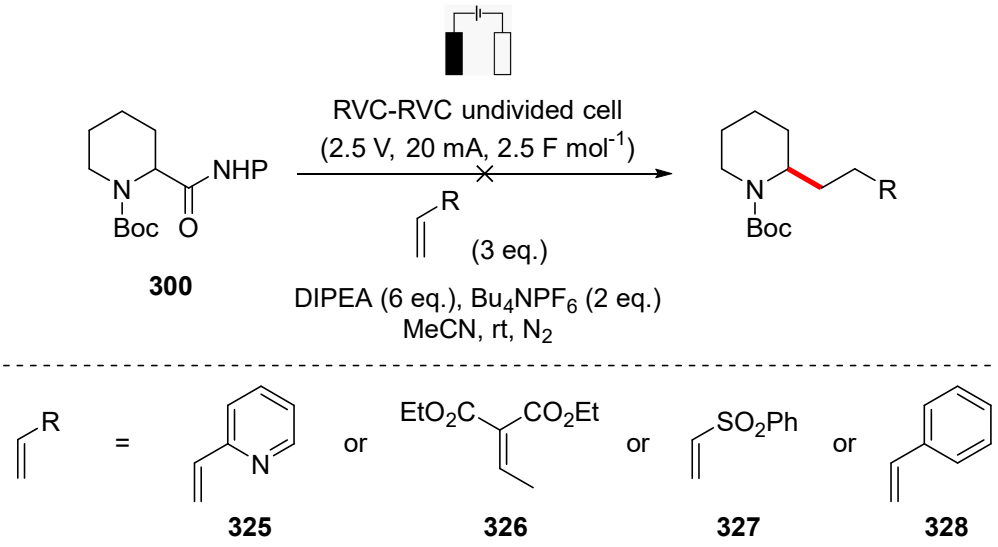
### 3.4.2 *N*-Hydroxyphthalimide Ester Reduction and Addition to other Electron Deficient Alkenes

Given that the reaction between three NHP esters and methyl acrylate had been successfully developed, other electron deficient alkenes were investigated in the reductive decarboxylation and subsequent addition reaction. Since the highest yield with methyl acrylate was obtained using NHP ester **300**, this substrate was used for the scope study. Thus, NHP ester **300** was reacted with acrylonitrile using the standard conditions. Piperidine nitrile **324** was isolated in 28% yield and carboxylic acid **321** was observed in 10% yield from the $^{1}$H NMR spectrum of the acidified crude sample (Scheme 3.39).



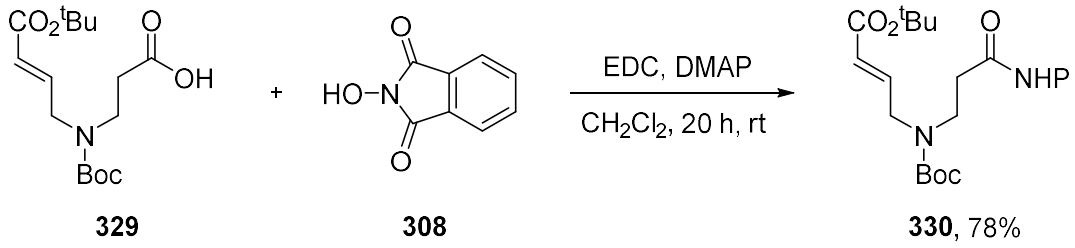

Scheme 3.39

In order to expand the scope further, vinyl pyridine **325**, di-ester alkene **326**, vinyl sulfone **327** and styrene **328** were also explored in the reductive decarboxylation of NHP ester **300**. Unfortunately, in these cases, none of the hoped-for addition products were observed (Scheme 3.40).




Scheme 3.40

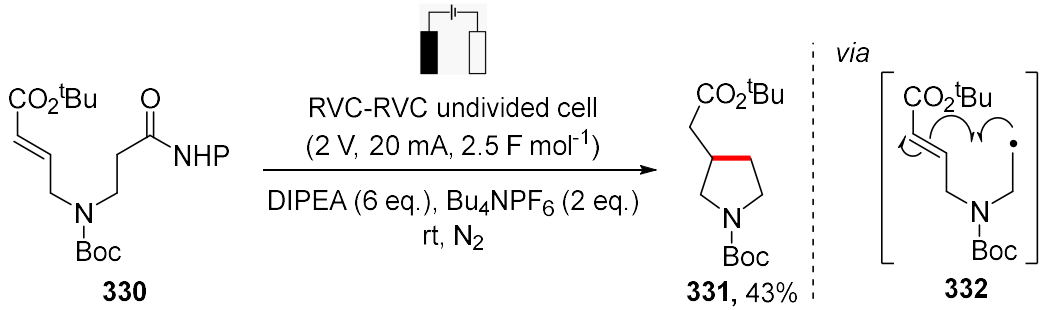
Finally, an intramolecular addition to an acrylate was explored. For this, NHP ester **330** was chosen to perform reductive decarboxylation and subsequent cyclisation as the analogous reaction under Kolbe oxidation conditions had been successful (see Section 2.6.2, Scheme 2.93). The synthesis of NHP ester **330** was performed using acid **329** (see Section 2.6.2, Schemes 2.85, 2.91 and 2.92 for its synthesis). A coupling reaction using acid **329** and *N*-hydroxyphthalimide **308** in the presence of EDC and DMAP gave NHP ester **330** in 78% yield (Scheme 3.41).




Scheme 3.41

Upon reductive decarboxylation of NHP ester **330**, radical **332** should be generated and this should then perform a 5-*exo-trig* cyclisation to generate a pyrrolidine ring (Scheme 3.42). To explore this, a 0.1 M solution of NHP ester **330** with $Et_3N$ (6 eq.) and $Bu_4NPF_6$ (2 eq.) was subjected to electrolysis. A voltage of 2 V was applied to the cell to give an initial current of 20 mA. The voltage was applied until a total charge of 2.5 F (mol NHP ester)$^{-1}$ was passed and pyrrolidine **331** was isolated in 43% yield. This compares well with a similar Kolbe electrolysis example shown in Chapter 2, Scheme 2.94, where

radical cyclisation onto an electron deficient alkene and subsequent heterocoupling gave pyrrolidine **240** in 57% yield.

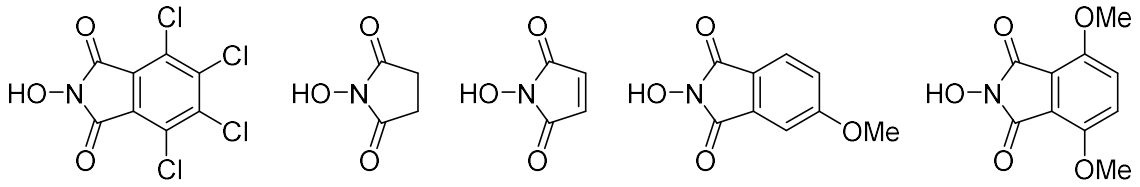



Scheme 3.42

Ultimately, extending the reductive methodology of NHP esters to other electron deficient alkenes were not very successful. The reactions with methyl acrylate gave the best results. Further optimisation of other electron deficient alkenes could be explored in the future.

## 3.5 Reductive Decarboxylation of *N*-Hydroxyphthalimide Ester Analogues

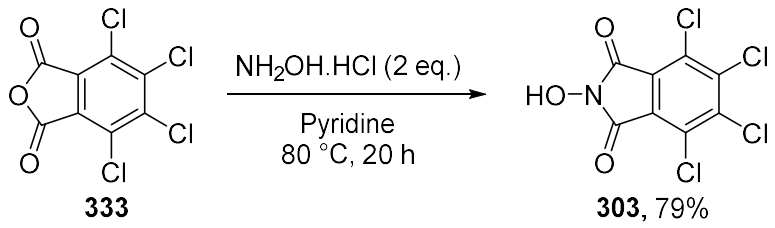
Efforts then turned to trying to increase the yield of the product obtained from the reductive decarboxylation of NHP esters and subsequent addition to methyl acrylate. To do this, it was thought that more product could be obtained if a way to reduce the amount of carboxylic acid that was formed could be found. So far, it is established that the carboxylic acid is likely formed from a competitive electrochemical pathway. By altering the electronics of the *N*-hydroxyphthalimide ester, it was hoped that the selectivity of the two electrochemical pathways could be controlled in order to favour product formation over carboxylic acid formation. Therefore, five different *N*-hydroxyphthalimide analogues (Figure 3.3) were chosen in order to prepare the corresponding redox active esters. An electron deficient NHP (NHPCl) **303** was selected as it has been previously explored in nickel-catalysed cross-coupling of alkynylzinc reagents (see Scheme 3.15).[121] *N*-Hydroxysuccinimide (NHS) **304** and its conjugated analogue, *N*-hydroxymaleimide (NHM) **305** were also chosen to see whether the aromatic group was important. Finally, electron rich NHPs were selected that contained methoxy groups on the aromatic ring. NHPOMe **306** and NHP(OMe)$_2$ **307** were investigated since there were established routes for the synthesis of key intermediates.




**303** **304** **305** **306** **307**

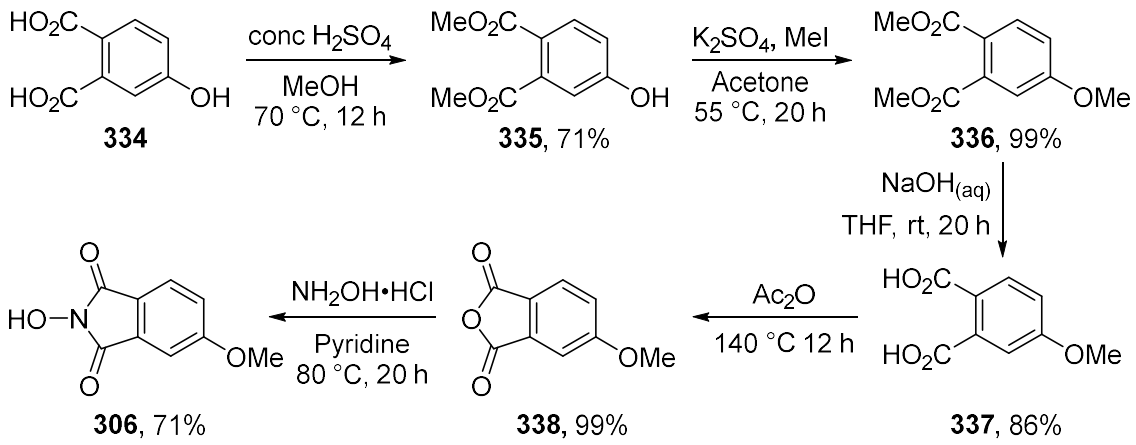
Figure 3.3 – Five analouges of *N*-hydroxyphthalimide

While NHS **304** and NHM **305** are commercially available, it was necessary to develop methods for the synthesis of the other NHP esters. The synthesis of NHPCl **303** was carried out using a literature procedure and is shown in Scheme 3.43.[128] A substitution reaction between anhydride **333** and $NH_2OH{\cdot}HCl$ was used to form NHPCl **303**. Thus, a solution of anhydride **333** and $NH_2OH{\cdot}HCl$ (2 eq.) in pyridine were heated at 80 °C for 20 h. After acidification, the solid formed was collected to give NHPCl **303** in 79% yield without the need for chromatography.




Scheme 3.43

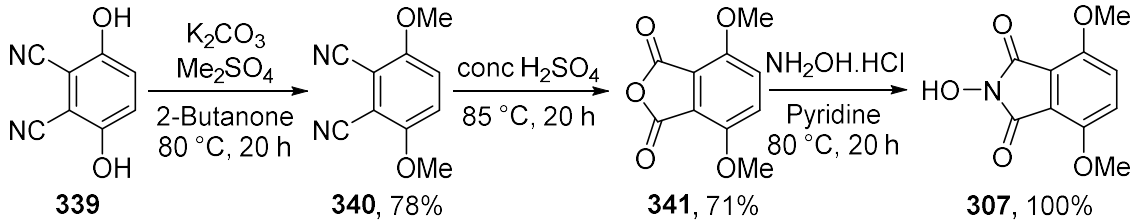
The synthesis of NHPOMe **306** is shown in Scheme 3.44. The synthesis of anhydride **338** was reported by Waser and co-workers[129] and the procedure for the conversion of anhydride **338** to NHPOMe **306** was adapted from the work completed by Chen and co-workers.[128] An esterification reaction on alcohol **334** in the presence of sulfuric acid and MeOH gave methyl ester **335** in 71% yield after chromatography. Then, methylation of the alcohol was performed using MeI to give methoxy diester **336** in 99% yield after isolation by filtration. Next, hydrolysis of the methyl esters using $NaOH_{(aq)}$ gave diacid **337** in 86% yield with no purification required. By heating diacid **337** in the presence of acetic anhydride, anhydride **338** was formed in 99% yield. Finally, a substitution reaction between anhydride **338** and $NH_2OH{\cdot}HCl$ was performed to give the desired NHPOMe **306** in 71% yield with no purification needed. Using this sequence, a 10 g batch of NHPOMe **306** was prepared.




Scheme 3.44

Next, the synthesis of *N*-hydroxy-3,6-dimethoxyphthalimide **307** was performed (Scheme 3.45). The synthesis of anhydride **341** was prepared using the procedure developed by Hacker and co-workers[130] and the conversion of anhydride **341** into $NHP(OMe)_2$ **307** was performed using the same procedure as above. First, the two

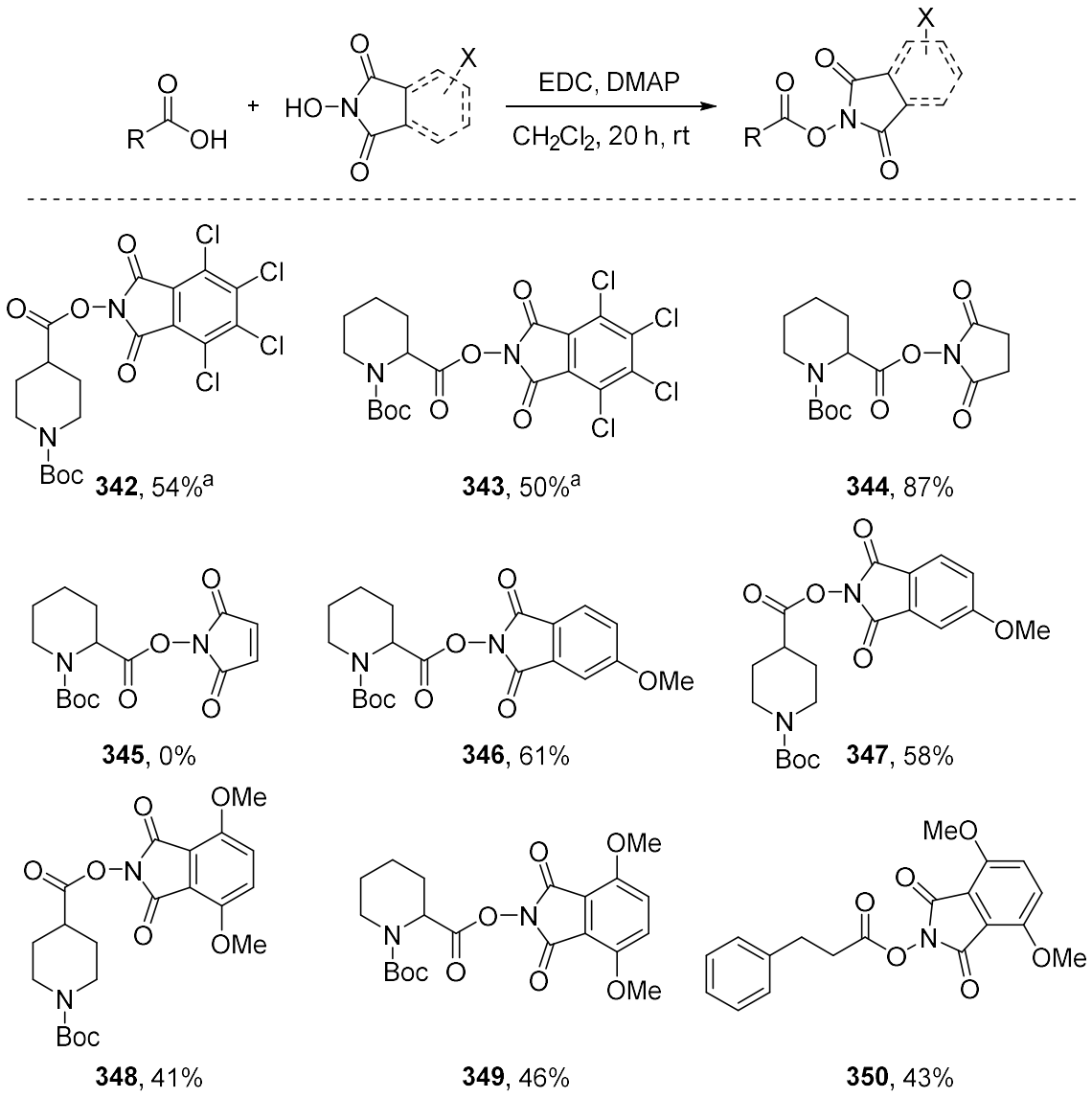
phenols in nitrile **339** were methylated using dimethyl sulfate and $K_2CO_3$. This gave dimethoxy nitrile **340** in 78% yield. Reaction of dimethoxy nitrile **340** with concentrated $H_2SO_{4(aq)}$ at 85 °C gave anhydride **341** in 71% yield. In this reaction, the two nitriles were hydrolysed to give a diacid that cyclised with loss of water under the acidic conditions. Lastly, anhydride **341** was substituted with $NH_2OH{\cdot}HCl$ to give the desired $NHP(OMe)_2$ **307** in quantitative yield with no purification required.




**339** **340**, 78% **341**, 71% **307**, 100%

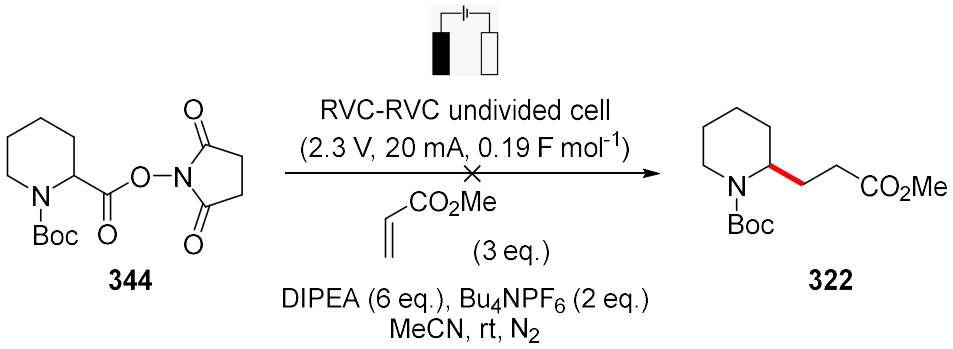
Scheme 3.45

With the *N*-hydroxyphthalimide analogues in hand, the syntheses of the *N*-hydroxy esters were performed (Scheme 3.46). The *N*-hydroxy compounds were coupled with two piperidine carboxylic acids and one acyclic carboxylic acid using EDC and DMAP to give the NHP esters in 41-87% yield after purification by chromatography. DIC was used as the coupling agent for both NHCl esters **342** and **343**, since attempts with EDC were unsuccessful. Unfortunately, the coupling of *N*-hydroxymaleimide **305** and piperidine acid **321** to form NHM ester **345** was unsuccessful.



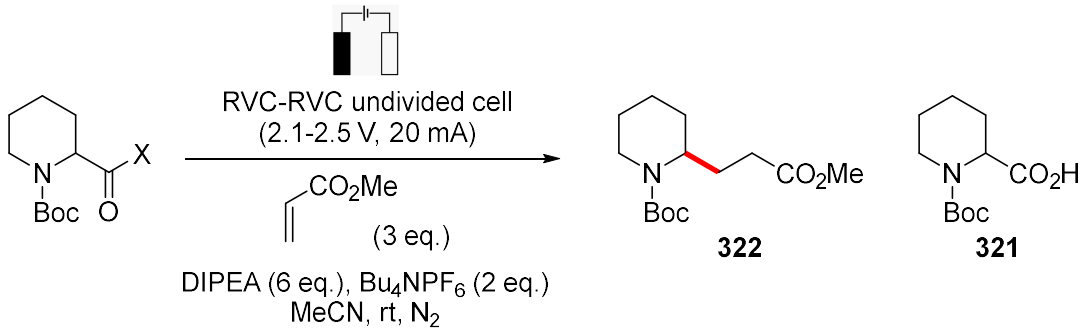

Scheme 3.46 – [a] DIC was used as the coupling agent.

The reductive decarboxylation and subsequent addition to methyl acrylate for NHS ester **344** was initially studied (Scheme 3.47). A 0.1 M solution of NHS ester **344** with methyl acrylate (3 eq.), DIPEA (6 eq.) and $Bu_4NPF_6$ (2 eq.) in MeCN was used. A voltage of 2.3 V was applied to the cell to give an initial current of 20 mA. However, within a few minutes the current dropped significantly to 1 mA and only 0.19 F $mol^{-1}$ was therefore passed. The reaction was discarded. It is unclear as to why the reaction did not go to completion, but it is theorised that conjugation is needed between the carbonyls of the succinimide to lower the reduction potential to an appropriate level.[131] Unfortunately, as NHM ester **345** was not synthesised, this theory could not be tested further.




Scheme 3.47

The electron deficient (**343**) and electron rich (**346** and **349**) NHP analogues were then tested under the standard electrochemical conditions. The results of these experiments, along with the original NHP ester **300**, are shown in Table 3.5. NHPCl ester **343** and NHP(OMe)$_2$ **349** were partially insoluble in MeCN but the electrolysis experiments were carried out regardless. For NHPCl **343**, piperidine ester **322** and acid **321** were formed in 14% and 37% yield respectively (entry 2). When NHPOMe **346** was used, piperidine ester **322** and acid **321** were obtained in 45% and 11% yield respectively (entry 3) whereas NHP(OMe)$_2$ **349** gave piperidine ester **322** in 50% yield with very little acid formation (**321**, 2% yield) (entry 4). Unfortunately, the current dropped significantly during the reaction and only 1.69 F mol$^{-1}$ of charge was passed. This could be due to the low solubility of the starting material.



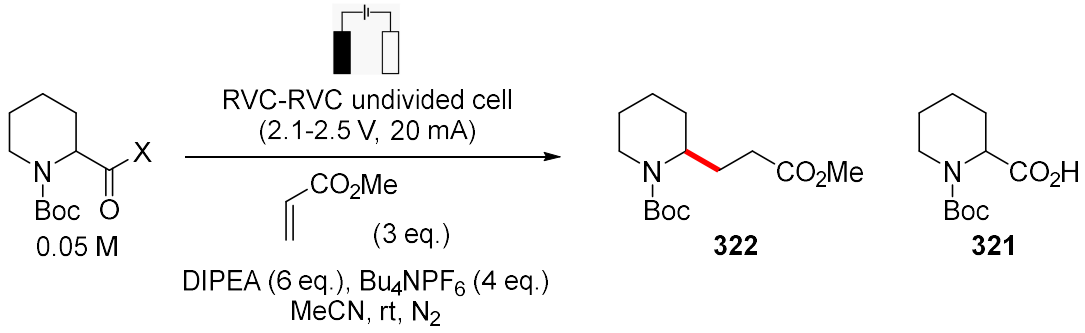

| Entry | X | NHP ester | Charge (F mol$^{-1}$) | Yield of **322** (%)[a] | Yield of **321** (%)[b] |
|---|---|---|---|---|---|
| 1 | NHP | **300** | 2.67 | 51 | 32 |
| 2 | NHPCl | **343** | 2.50 | 14 | 37 |
| 3 | NHPOMe | **346** | 2.57 | 45 | 11 |
| 4 | NHP(OMe)$_2$ | **349** | 1.69 | 50 | 2 |

Table 3.5 – Reductive decarboxylation of NHP ester analogues.

[a] Yield after chromatography. [b] Calculated from the $^1$H NMR spectrum of the acidified crude sample.

Due to the partial solubility of NHPCl ester **343** and NHP(OMe)$_2$ **349** at 0.1 M in MeCN, the reactions were also carried out at 0.05 M concentration with respect to the NHP ester analogues (Table 3.6). The amount of DIPEA and methyl acrylate were also reduced in order to keep the reagents in the same ratios, but there was no change made to the electrolyte concentration to avoid excess solution resistance, therefore 4 eq. of $Bu_4NPF_6$ was used. Under these conditions, NHP(OMe)$_2$ ester **349** was fully soluble at this concentration but NHPCl ester **343** still had limited solubility. When NHP ester **300**, NHPOMe ester **346** and NHP(OMe)$_2$ ester **349** were used, piperidine ester **322** was isolated in 49-52% yield, with acid **321** in 20%, 7% and 5% yield respectively (entries 1, 3 and 4). Relative to the reaction at the standard concentration (entry 2), NHPCl ester **343** gave a higher yield of piperidine ester **322** (26% yield) and the same amount of acid **321** (32% yield). However, the yield of piperidine ester **322** when using NHPCl was still low compared to the other NHP analogues, which may be due to the solubility of the starting material. However, the larger amount of acid **321** generated with the electron deficient NHPCl **343** indicates that the selectivity between the two electrochemical pathways has been shifted to favour acid formation over alkene addition product. With the electron rich NHP analogues, the amount of acid formed was much lower than with the original NHP ester **300**, indicating that the competitive electrochemical pathway that generates acid has

become less favourable. Unfortunately, however, this change in selectivity did not lead to an associated increase in the yield of piperidine ester **322** in the process.

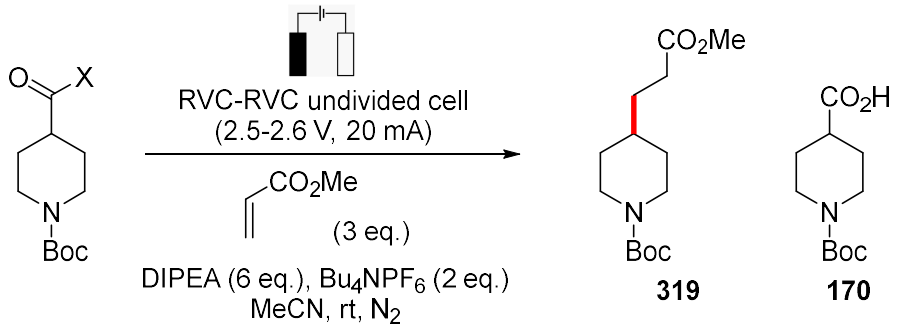



| Entry | X | NHP ester[a] | Charge (F mol$^{-1}$) | Yield of **322** (%)[b] | Yield of **321** (%)[c] |
|---|---|---|---|---|---|
| 1 | NHP | **300** | 2.53 | 52 | 20 |
| 2 | NHPCl | **343** | 2.58 | 26 | 32 |
| 3 | NHPOMe | **346** | 2.55 | 49 | 7 |
| 4 | NHP(OMe)$_2$ | **349** | 2.49 | 50 | 5 |

Table 3.6 – Reductive decarboxylation of NHP ester analogues at half concentration.

[a] (0.05 M of NHP ester analogue and 4 eq. of $Bu_4NPF_6$ was used). [b] Yield after chromatography. [c] Calculated from the $^1$H NMR spectrum of the acidified crude sample.

For comparison, the NHP analogues were then tested at the 4-position of the piperidine and the results are shown in Table 3.7 along with the standard reaction with NHP ester **30**. The reaction with NHPCl **342** ester was performed at the standard concentration (0.1 M) and gave piperidine ester **319** and acid **170** in 8% and 58% yield respectively (entry 2). Since such a large amount of acid **170** was observed, the reaction was not attempted at 0.05 M concentration. Fortunately, when NHPOMe ester **347** and NHP(OMe)$_2$ ester **348** were used (entries 3 and 4), the same trend was observed compared to the 2-position of the piperidine, NHP esters **346** and **349** (see Table 3.6, entries 3 and 4). However, when NHP(OMe)$_2$ ester **348** was used, the yield of piperidine ester **319** was only 29% yield, which is lower than that with the 4-substituted NHP ester **30** (41%) (entry 1).

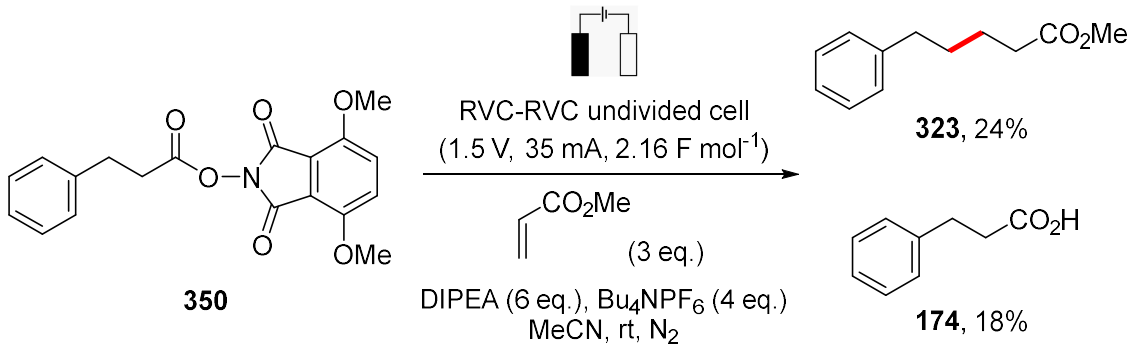



| Entry | X | NHP ester | Charge (F mol$^{-1}$) | Yield of **319** (%)[a] | Yield of **170** (%)[b] |
|---|---|---|---|---|---|
| 1 | NHP | **30**[c] | 2.41 | 41 | 20 |
| 2 | NHPCl | **342**[c] | 2.45 | 8 | 58 |
| 3 | NHPOMe | **347**[d] | 2.50 | 39 | 14 |
| 4 | NHP(OMe)$_2$ | **348**[d] | 1.99 | 29 | 3 |

Table 3.7 – Reductive decarboxylation NHP ester analogues.

[a] Yield after chromatography. [b] Calculated from the $^1$H NMR spectrum of the acidified crude sample. [c] 0.1 M concentration of NHP ester. [d] 0.05 M concentration of NHP ester and 4 eq. of $Bu_4NPF_6$ was used.

As shown so far, electron rich, novel NHP esters, NHP(OMe)$_2$ ester **349** and NHPOMe ester **346**, lead to much less acid being generated compared to the original NHP ester **300**. The best NHP analogue is NHP(OMe)$_2$ **349** as it gave the lowest amount of acid in the reactions. Therefore, the reaction of NHP(OMe)$_2$ ester **350** with methyl acrylate was attempted. Using these standard conditions at half concentration, NHP(OMe)$_2$ ester **350** gave ester **323** in 24% yield with acid **174** in 18% yield (Scheme 3.48). Disappointingly, the yields of ester **323** and acid **174** were similar to the reaction performed with the initial NHP ester **282** (see Scheme 3.39).




Scheme 3.48

## 3.6 Analysis of *N*-Hydroxyphthalimide Analogues by Cyclic Voltammetry and Mechanistic Analysis

At the same time as carrying out the synthetic work described in the previous sections, various mechanisms were considered to account for the electrochemical pathway that would lead to the formation of the different carboxylic acids. It was previously proven that NHP ester **282** does not undergo hydrolysis to the carboxylic acid in the absence of an applied cell voltage. The same experiment was performed with NHPCl **343**, NHPOMe **346**, and $NHP(OMe)_2$ **349** and, in each case, there was no sign of any hydrolysis. In order to help to determine the electrochemical pathway that gives rise to the carboxylic acids, cyclic voltammetry was used alongside the synthetic studies. In particular, it was of interest to investigate whether any differences between the cyclic voltammograms of the NHP ester analogues containing electron donating and withdrawing groups could help to determine how the carboxylic acid is formed. The cyclic voltammogram of NHP ester **300** was initially investigated (Figure 3.4). All cyclic voltammograms in this Chapter were obtained using a glassy carbon working electrode, platinum wire counter electrode and a Ag/AgCl reference electrode. All solutions were prepared in MeCN with $Bu_4NPF_6$ as the supporting electrolyte (0.22 M). A blank cyclic voltammogram was recorded to measure any background processes (black line). Based on comparison with the literature,[132] the reversible redox process centred at about approximately –0.8 V is attributed to the reversible reduction of oxygen to superoxide. The oxygen is present because the experiment was run with the solution open to air.[132] Next, the cyclic voltammogram of NHP ester **300** was measured (Figure 3.4). The oxygen reduction process observed in the blank experiment becomes irreversible in the presence of NHP ester, presumably due to consumption of the superoxide *via* reaction with the NHP ester. A new irreversible reduction peak solely attributable to the presence of **300** is observed with $E_p^{red1} = -1.61$ V. This is assigned to the initial one-electron reduction of the carbonyl group in NHP ester **300** to a radical anion, as is consistent with the first step in the consensus mechanism for reduction of a redox active ester.[94] A second reversible peak, $E_p^{red2}$, also solely attributable to **300** was also observed at –1.78 V and the electrochemical processes that could account for this will be discussed later in this section.

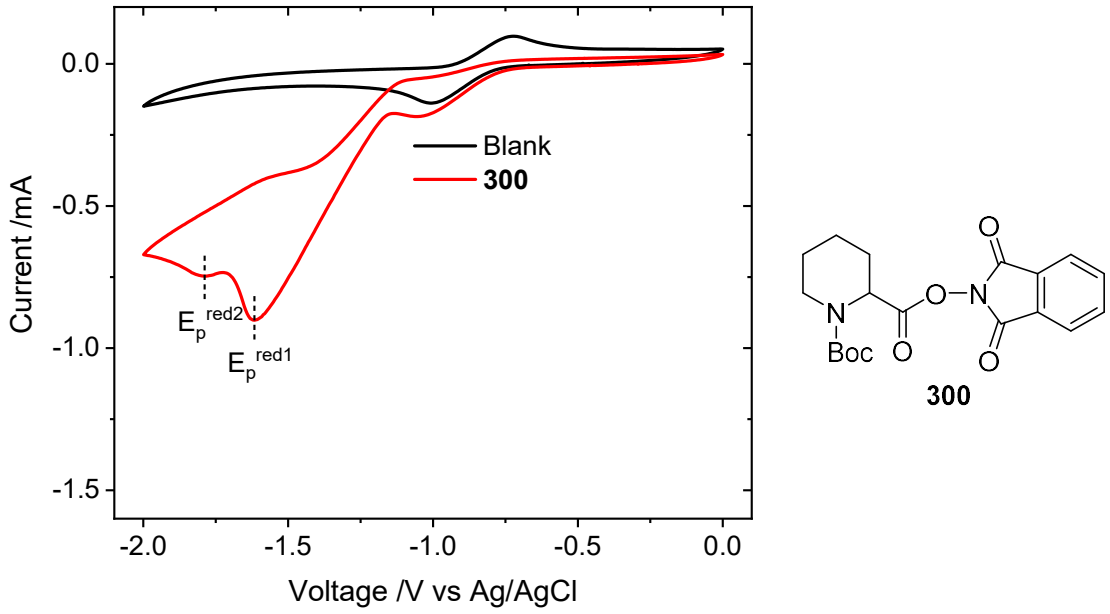



Figure 3.4 – Cyclic voltammograms containing $Bu_4NPF_6$ (0.20 M) in MeCN with; no additives (black line), NHP ester **300** (0.05 M red line). Scan rate of 200 mv/s.

In order to see if the electrodes were passivating throughout the cyclic voltammetry experiment, the scan was repeated for 40 consecutive scans. Satisfyingly, the scans were consistent, indicating that the electrodes were slow to passivate and therefore the experimental conditions do not change substantially as the scans proceed. Next, it was important to demonstrate that the NHP esters were the main substrate being reduced in the electrolysis reaction and not any other of the reaction starting materials. Therefore, as shown in Figure 3.5, cyclic voltammograms were obtained for each of (i) methyl acrylate; (ii) a mixture of methyl acrylate and DIPEA; (iii) a mixture of NHP ester **300** and methyl acrylate; (iv) and a mixture of NHP ester **300**, methyl acrylate and DIPEA (i.e. all reagents in the reaction). The cyclic voltammogram of methyl acrylate (dashed blue line) and a mixture of methyl acrylate and DIPEA (dashed grey line) were essentially the same as the blank solution (black line). The cyclic voltammograms of NHP ester **300** (red line), NHP ester **300** and methyl acrylate (blue line) and NHP ester **300**, methyl acrylate and DIPEA (grey line) all show a reduction process with a very similar onset potential of approximately −1.1 V and a corresponding peak potential $E_p^{red1}$ between −1.61 V and −1.82 V. indicating that the same one-electron NHP ester reduction process occurs in each sample. With methyl acrylate present, the peak current associated with $E_p^{red1}$ increases, and the voltage correspondingly shifts in a negative direction. This is consistent with the methyl acrylate reacting with the product of the reduction process.

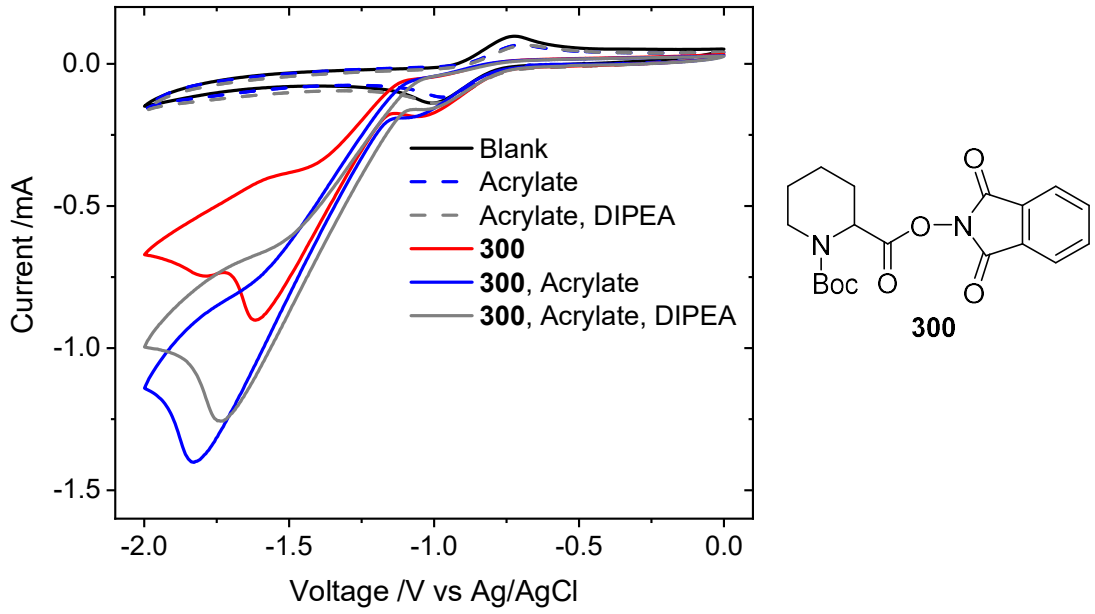



Figure 3.5 – Cyclic voltammograms containing $Bu_4NPF_6$ (0.20 M) in MeCN with; no additives (black line); methyl acrylate (0.16M) (dashed blue line); methyl acrylate (0.16 M) and DIPEA (0.30 M) (dashed grey line); NHP ester **300** (0.05 M) (red line); NHP ester **300** (0.05 M) and methyl acrylate (0.16 M) (blue line); NHP ester **300** (0.05 M), methyl acrylate (0.16 M) and DIPEA (0.30 M) (grey line). Scan rate of 200 mv/s.

The oxidation process was then explored in order to show that only the sacrificial amine, DIPEA, is oxidised in the mixture of reagents. Cyclic voltammograms were again obtained for each of (i) methyl acrylate; (ii) a mixture of methyl acrylate and DIPEA; (iii) a mixture of NHP ester **300** and methyl acrylate; and (iv) a mixture of NHP ester **300**, methyl acrylate and DIPEA (all reagents in the reaction) (Figure 3.6). As expected, the blank solution (black line), methyl acrylate (dashed blue line), NHP ester **300** (red line) and a mixture of NHP ester **300** and methyl acrylate (blue line) all showed essentially no oxidation peaks. The solutions containing a mixture of methyl acrylate and DIPEA (dashed grey line) and a mixture of NHP ester **300**, methyl acrylate and DIPEA (grey line) all showed oxidation above 0.5 V which is expected due to the oxidation of the nitrogen lone pair in DIPEA to a radical cation.[124] The oxidation of DIPEA is shown as a continuous increase rather than a peak because the high concentration of DIPEA in the solution ensures that the oxidation is not diffusion-limited.[133]

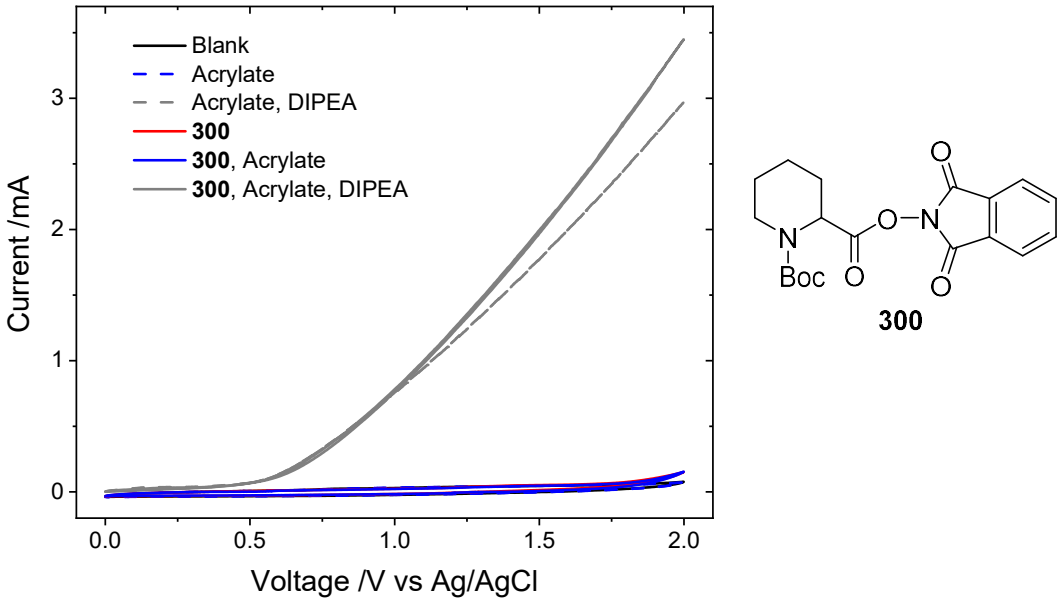



Figure 3.6 – Cyclic voltammograms containing $Bu_4NPF_6$ (0.20 M) in MeCN with; no additives (black line); methyl acrylate (0.16M) (dashed blue line); methyl acrylate (0.16 M) and DIPEA (0.30 M) (dashed grey line); NHP ester **300** (0.05 M) (red line); NHP ester **300** (0.05 M) and methyl acrylate (0.16 M) (blue line); NHP ester **300** (0.05 M), methyl acrylate (0.16 M) and DIPEA (0.30 M) (grey line). Scan rate of 200 mv/s.

Comparable cyclic voltammograms were then obtained for NHP esters **300**, **30** and **282**. Values for $E_p^{red1}$ for 2-piperidine **300** (red line), 4-piperidine **30** (blue line) and acyclic **282** (green line) were very similar at −1.46 V, −1.46 V and −1.49 V, respectively (Figure 3.7). This strongly supports the conclusion that the first reduction process is the same for each substrate, and further supports the proposal that this is the one-electron reduction of the carbonyl group in the *N*-hydroxyphthalimide ester group. Since an identical NHP ester moiety is contained within each of the molecules, the addition of an electron to this group would be expected to have similar electrochemical properties in each case.

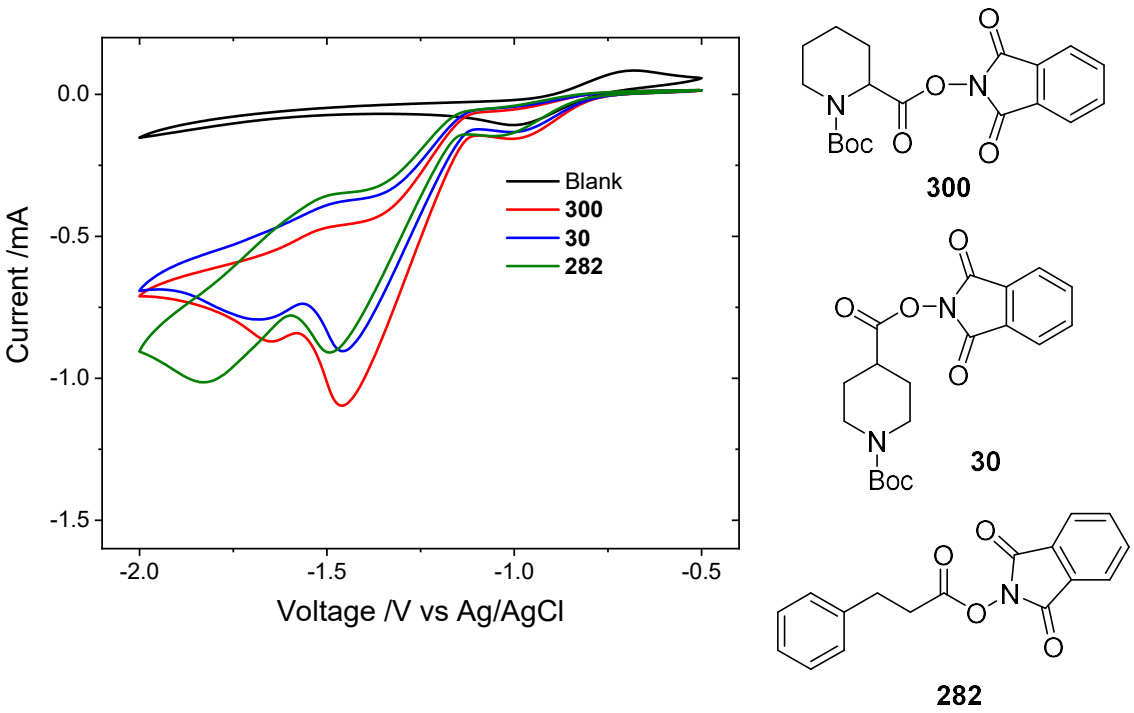
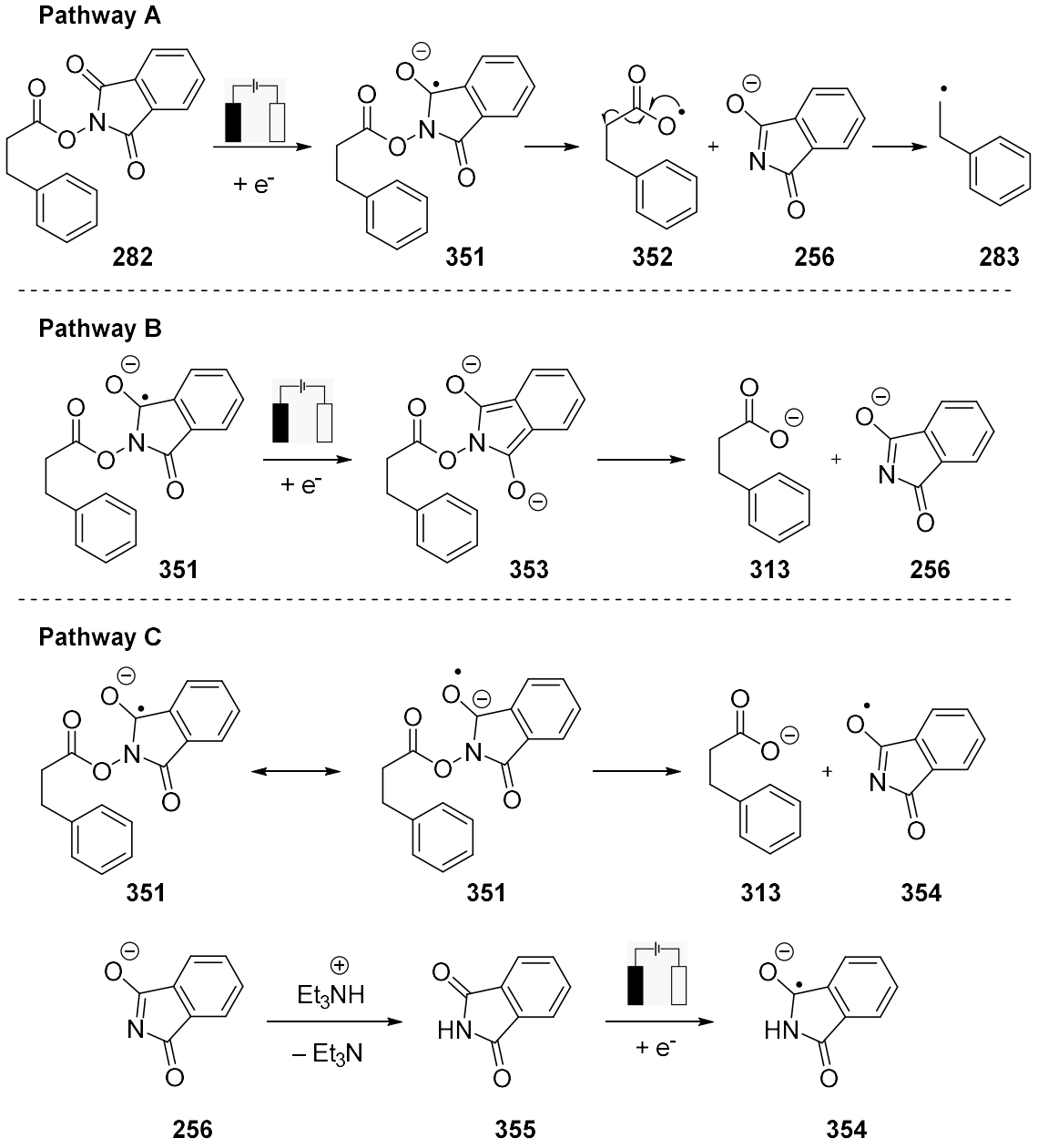



Figure 3.7 – Cyclic voltammograms containing $Bu_4NPF_6$ (0.20 M) in MeCN with; no additives (black line); NHP ester **300** (0.05 M) (red line); NHP ester **30** (0.05 M) (blue line); NHP ester **282** (0.05 M) (green line). Scan rate of 200 mv/s.

Notably, unlike the first reduction process, the second reduction process in Figure 3.7 does not remain unchanged for each substrate. This is highlighted by comparing the $E_p^{red2}$ values of **300** for **282**. This indicates that the second reductive process observed in the cyclic voltammetry is a reaction which involves a different molecule. One hypothesis is that this second reduction process could be responsible for the formation of the carboxylic acid. Using NHP ester **282** as a representative example, Scheme 3.49 shows three different possible reduction pathways. In pathway A, a single one-electron reduction (as is attributed to the process giving rise to $E_p^{red1}$) gives rise to radical anion **351** and this fragments and decarboxylates to ultimately form radical **283**, as desired for addition to the alkene. However, both pathways B and C can be envisaged to give rise to the formation of the carboxylic acid. In pathway B, electrochemical reduction of radical anion **351** gives dianion **353** which fragments to give carboxylate **313** and anion **256**. This pathway could therefore account for the second reduction peak, $E_p^{red2}$, in the cyclic voltammogram. Alternatively, radical anion **351** could fragment to give carboxylate **313** and radical **354** (pathway C). However, this pathway does not involve a second reduction. If this were the major route to the carboxylic acid, it is suggested that the second reduction

peak could correspond to the reduction of phthalimide **256** (formed from anion **351** generated from the first reduction and fragmentation in pathway A) to radical anion **354**.




Scheme 3.49

However, if pathway C was occurring, the second reduction peak should be the same for each substrate that are compared in Figure 3.7 because this process corresponds to the reduction of phthalimide **256** to give radical anion **354**. Conversely, if pathway B was occurring, the reduction potential would be expected to alter between each substrate. Since the $E_p^{red2}$ of NHP ester **300** varies in voltage compared to NHP esters **30** and **282**

(see Figure 3.7), these experiments suggest that the second reduction process could be attributed to pathway B.

The cyclic voltammograms of NHP esters **300**, **30** and **282** in the presence of methyl acrylate were then compared (Figure 3.8). In the cyclic voltammograms of NHP ester **300** (red line) and NHP ester **30** (blue line), there is little evidence of the second reduction peak, $E_p^{red2}$, whereas that of NHP ester **282** shows $E_p^{red2}$ (green line) with little change compared to that without acrylate (Figure 3.7, green line). These results also rule out pathway C as giving rise to the second reduction process because the reactivity changes despite the NHP ester portion of the molecule remaining unchanged.

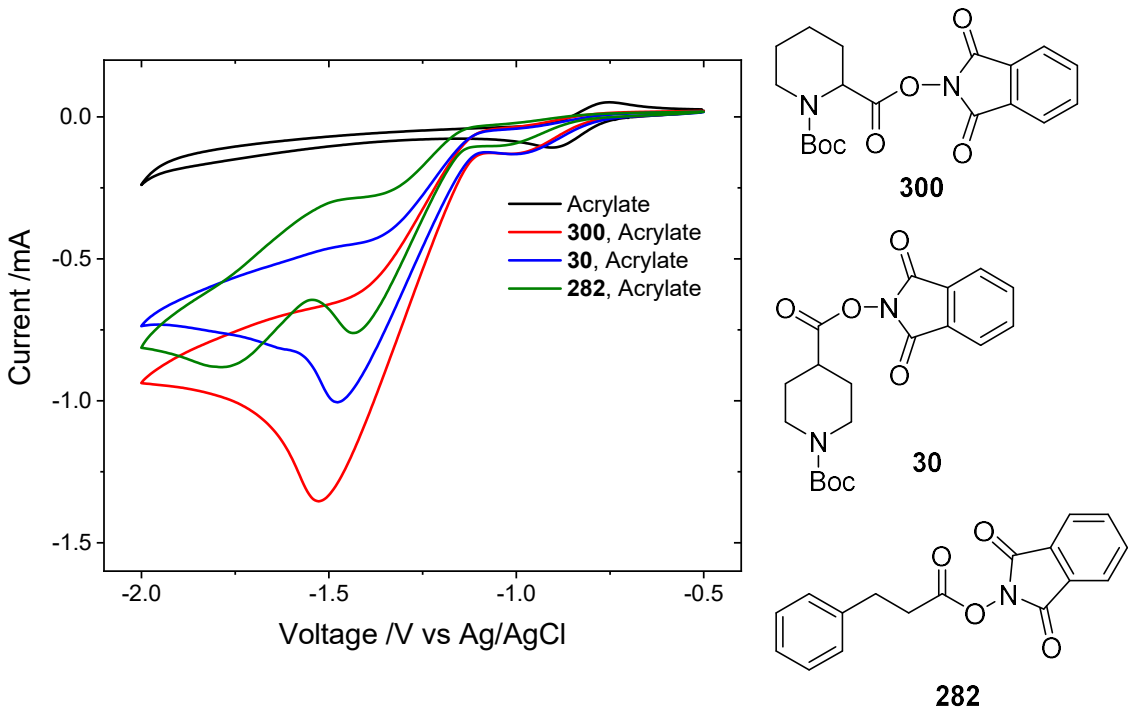



Figure 3.8 – Cyclic voltammograms containing $Bu_4NPF_6$ (0.20 M) in MeCN with; methyl acrylate (0.16M) (black line); NHP ester **300** (0.05 M) and methyl acrylate (0.16 M) (red line); NHP ester **30** (0.05 M) and methyl acrylate (0.16 M) (blue line); NHP ester **282** (0.05 M) and methyl acrylate (0.16 M) (green line). Scan rate of 200 mv/s.

Next, the cyclic voltammograms of the NHP ester analogues were investigated. It was expected that relative to the original NHP ester, the electron deficient 2-piperidine NHPCl ester **343** would have a more positive reduction potential for $E_p^{red1}$ due to the stabilisation of the radical anion formed in the first step of pathway A. In contrast, for the electron rich NHPOMe ester **346** and $NHP(OMe)_2$ ester **349**, the reduction potential for $E_p^{red1}$ should be more negative. The cyclic voltammograms of the 2-piperidine NHP ester analogues

are shown in Figure 3.9. The electron deficient NHPCl ester **343** (blue line) was partially insoluble in MeCN and so did not produce a meaningful cyclic voltammogram although some low intensity reduction peaks can still be identified. The first peak at −0.81 V is not reversible and does not match with the reversible reduction of oxygen which is present in the blank sample with methyl acrylate (black line). It is likely that this reduction peak corresponds to the reduction of NHPCl ester **343** to the radical anion as it has a higher reduction potential than the standard NHP ester **300** ($E_p^{red1}$, red line). The electron rich esters, NHPOMe **346** (purple line) and NHP(OMe)$_2$ **349** (green line), showed reduction potentials of −1.63 V and −1.58 V respectively, which are slightly more negative than NHP ester **300** at –1.52 V (red line). This further confirms the assignment of for $E_p^{red1}$ to the one-electron reduction shown in pathway A.

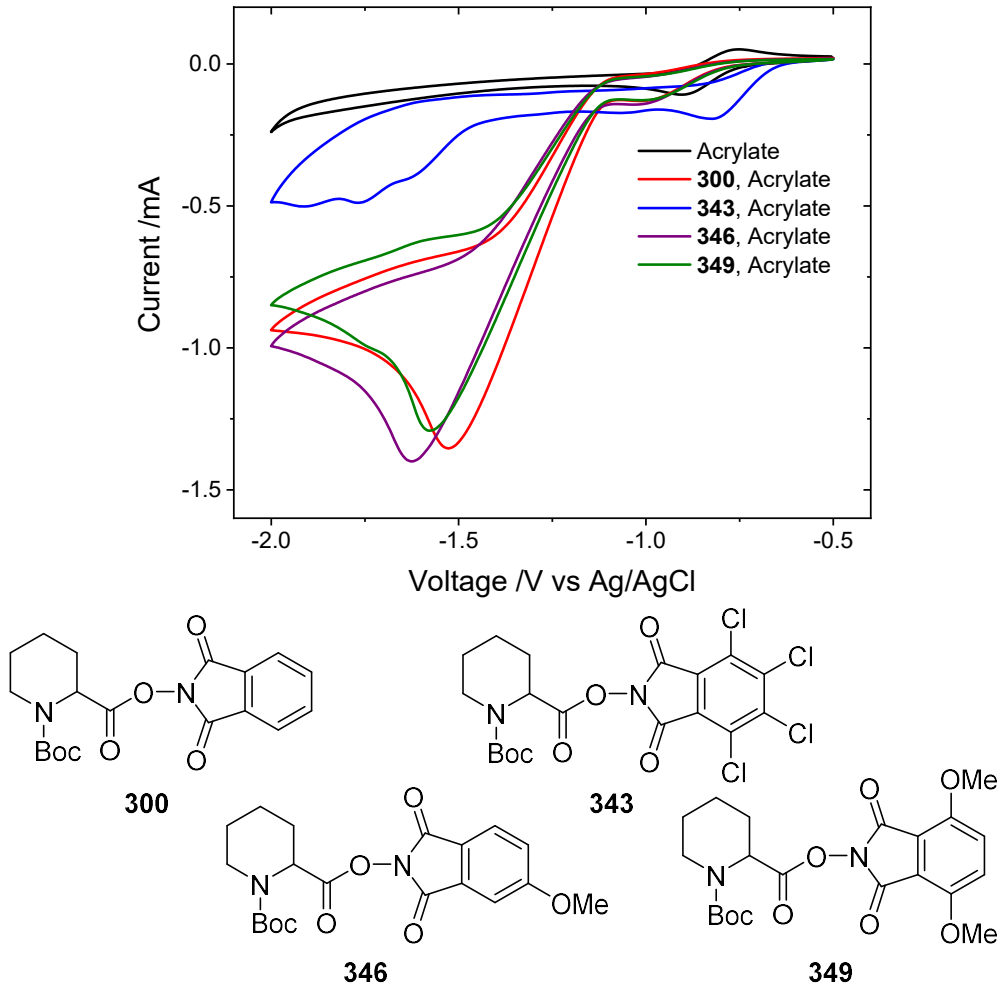
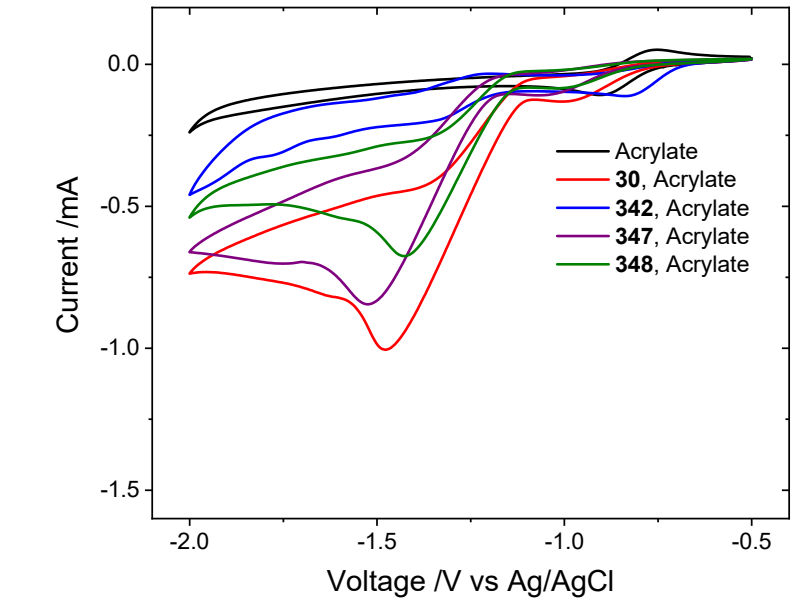



Figure 3.9 – Cyclic voltammograms containing $Bu_4NPF_6$ (0.20 M) in MeCN with; methyl acrylate (0.16M) (black line); NHP ester **300** (0.05 M) and methyl acrylate (0.16 M) (red line); NHP ester **343** (0.05 M) and methyl acrylate (0.16 M) (blue line); NHP ester **346** (0.05 M) andmethyl acrylate (0.16 M) (purple line); NHP ester **349** (0.05 M) and methyl acrylate (0.16 M) (green line). Scan rate of 200 mv/s.

The cyclic voltammograms of the *N*-Boc 4-piperidine NHP ester analogues **30**, **342**, **347** and **348** showed a similar pattern as the *N*-Boc 2-piperidine NHP analogues (Figure 3.10).



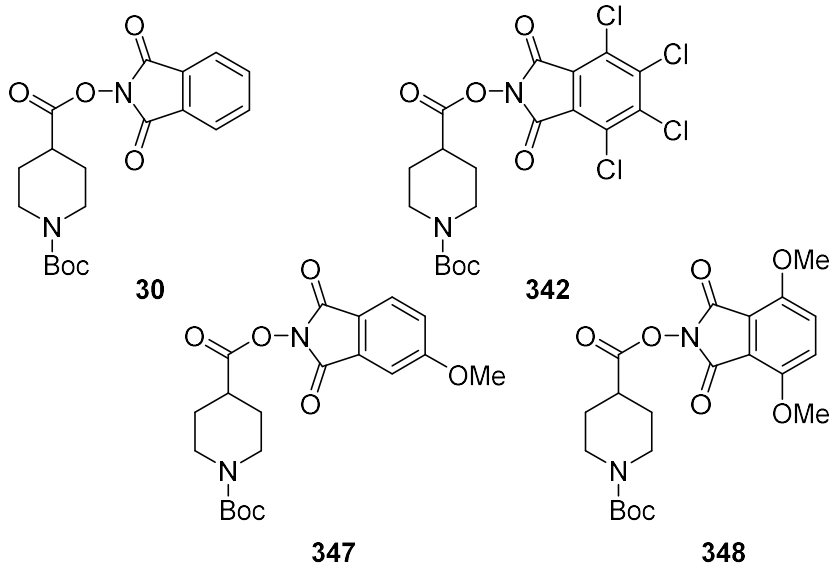



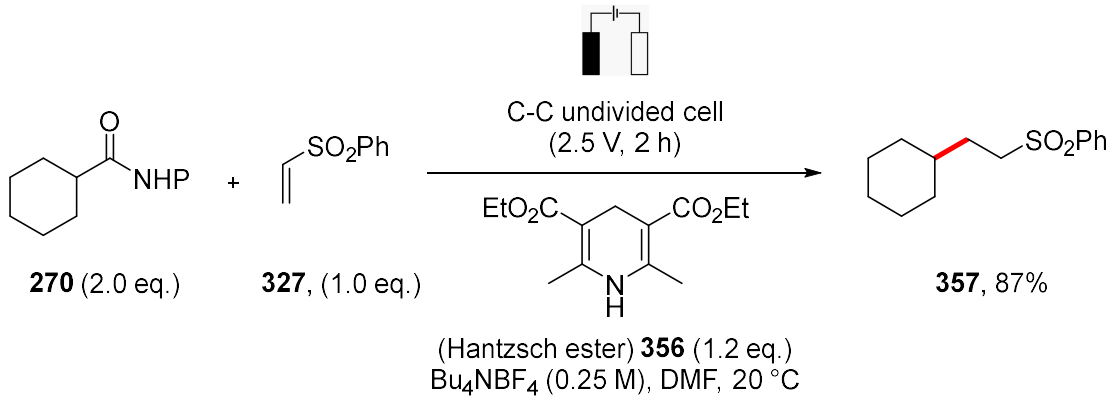

Figure 3.10 – Cyclic voltammograms containing $Bu_4NPF_6$ (0.20 M) in MeCN with; methyl acrylate (0.16M) (black line); NHP ester **30** (0.05 M) and methyl acrylate (0.16 M) (red line); NHP ester **342** (0.05 M) and methyl acrylate (0.16 M) (blue line); NHP ester **347** (0.05 M) and methyl acrylate (0.16 M) (purple line); NHP ester **348** (0.05 M) and methyl acrylate (0.16 M) (green line). Scan rate of 200 mv/s.

Taken together, all of the cyclic voltammetry data indicates that the NHP ester substrates are susceptible to two reduction processes. The first reduction can be confidently assigned to the one-electron reduction of the NHP ester to a radical anion (e.g. **282** to **351**, see Scheme 3.49, pathway A). The second reduction is tentatively assigned as the reduction

of the radical anion to dianion (e.g. **351** to **353**, pathway B), a process which accounts for both the second reduction and the formation of carboxylic acid. In summary, a novel electron rich redox-active ester has been discovered that can be electrochemically reduced to give carbon-centred radicals that can then add into electron deficient alkenes with minimal generation of a carboxylic acid by-product.

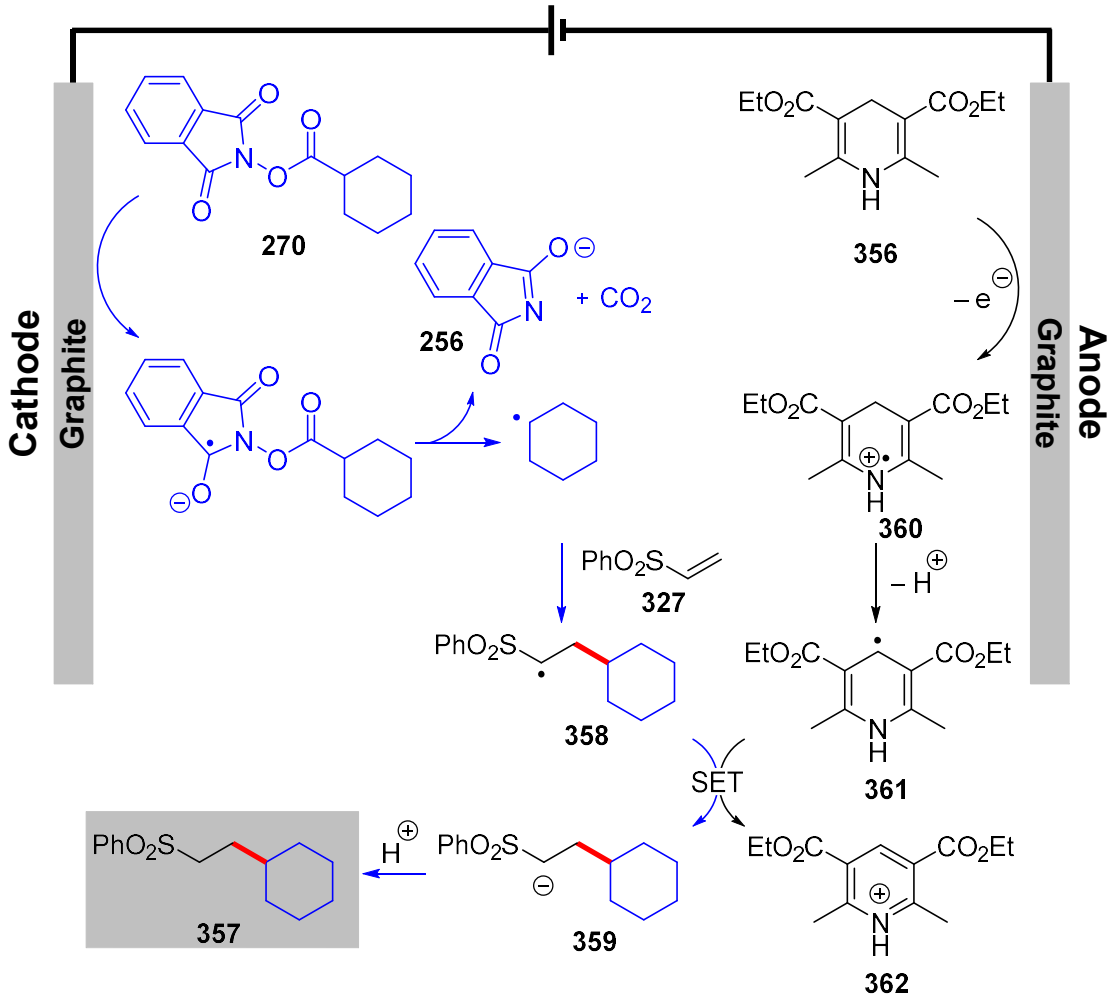
## 3.7 Electrochemical *N*-Hydroxyphthalimide Ester Reduction and Addition to Electron Deficient Alkenes – a Recently Published Paper

Whilst writing this thesis, Wang *et al*. published the electrochemical reduction of NHP esters followed by fragmentation/decarboxylation and subsequent addition into electron deficient alkenes.[123] The authors used graphite electrodes in an undivided cell with $Bu_4NBF_4$ as electrolyte in DMF. Using these conditions, NHP ester **270** underwent reaction with vinyl sulfone **327** in the presence of Hantzsch ester **356** to give functionalised sulfone **357** in 87% yield (Scheme 3.50).




Scheme 3.50

The proposed mechanism for the reaction performed by Wang *et al.* is shown in Scheme 3.51. As in the other examples throughout this thesis, NHP ester **270** is reduced at the cathode, fragments and decarboxylates to give cyclohexyl radical. This radical then adds to vinyl sulfone **327** (Giese reaction)[134] to give sulfone-stabilised radical **358**. Meanwhile, Hantzsch ester **356** is oxidised at the anode to give radical cation **360**. Deprotonation results in radical **361** which can donate an electron to radical **358** *via* single electron transfer to give anion **359** and **362**. After protonation of anion **359**, functionalised sulfone **357** is formed.




Scheme 3.51

Wang's methodology is related to the work described in Section 3.4 since both involve the electrochemical reduction of NHP esters to give carbon-centred radicals which then add to electron deficient alkenes. In the highest yielding example in this thesis (see Scheme 3.37), $Bu_4NPF_6$, MeCN and RVC were used in the presence of DIPEA as a sacrificial oxidant. In contrast, Wang *et al.* reported the use of a similar electrolyte ($Bu_4NBF_4$), a different solvent (DMF), Hantzsch ester **356** and graphite electrodes. In addition, whereas for the reactions in this thesis, the NHP ester was the limiting reagent (with 3 eq. of the alkene), in Wang's work, the alkene was the limiting reagent and 2.0 eq. of the NHP ester were used in the majority of examples. The scope of Wang's reaction was also explored and an impressive set of results were obtained. For example, successful reactions were described using NHP esters derived from primary, secondary and tertiary

carboxylic acids together with acrylates, acrylonitrile and vinyl sulfone **327**. Selected examples (54-95% yields) are shown in Figure 3.11.

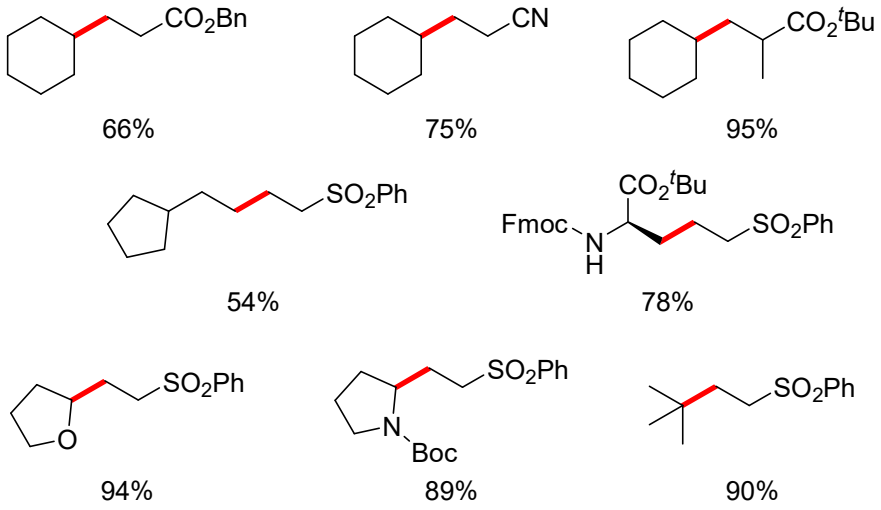


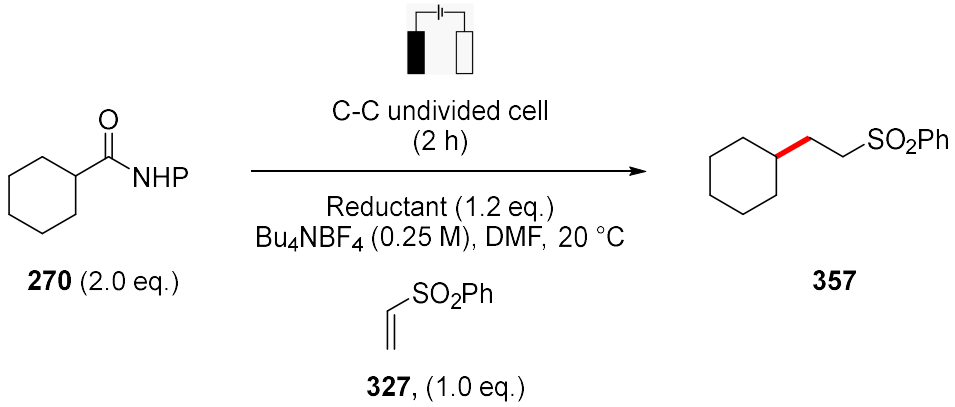

Figure 3.11 – Wang *et al*.'s scope for their reductive electrochemical methodology[123]

Wang *et al*. obtained cyclic voltammograms of NHP ester **270** and vinyl sulfone **327** in DMF with $Bu_4NBF_6$ as electrolyte. They found that NHP ester **270** had a reduction potential at −1.15 V and a second one at approximately −1.5 V. This cyclic voltammogram matches well with the cyclic voltammograms obtained in this thesis (e.g. NHP ester **300** in Figure 3.4) and the difference in reduction potential could be due to the use of a different solvent, electrolyte and NHP ester.

Considering the proposed mechanism shown in Scheme 3.50, Wang proposes that sulfone-stabilised radical **358** formed from the addition of the cyclohexyl radical to the alkene is reduced by Hantzsch ester derived radical **361** *via* single electron transfer to give anion **359**. However, comparing with the work presented in this thesis, it seems more likely that, in their reaction, radical **358** is reduced to anion **359** at the cathode and that Hantzsch ester derived radical **361** is oxidised at the anode. To support this conjecture, radical **361** has $E_{1/2}$ = −1.1 V vs SCE[135] and would therefore be easily oxidised at the anode where it will have been formed by deprotonation of radical cation **360**.

Wang also obtained some interesting results when the reaction was carried out in the absence of Hantzsch ester **356** (Table 3.8). It was found that most of NHP ester **270** and vinyl sulfone **327** were recovered when 2.5 V was used and only traces of functionalised sulfone **357** were formed. However, when the voltage was raised to 5.0 V, sulfone **357**

was produced in 69% yield. For this reaction, Wang proposed that the reductive process to generate the cyclohexyl radical was the same and that radical **358** would then be reduced at the cathode to form anion **359**. For the oxidation counter-process, it was suggested that oxidation of water occurs to form hydrogen ions and oxygen. It is debatable whether this would occur, however, since there should only be a small amount of water present in the solution. Instead, a more plausible proposal would be that oxidation of the solvent, DMF, is the oxidative counter-process that is occurring in their reaction. The cyclic voltammograms presented by Wang show a large oxidation peak at around +1.8 V in their "blank" (DMF and electrolyte) which presumably indicates the oxidation of DMF. Therefore, in order to form product in the reaction without any Hantzsch ester **356**, a larger voltage is needed to oxidise DMF rather than if Hantzsch ester **356** was present ($E_{1/2}$ = +0.9 V).



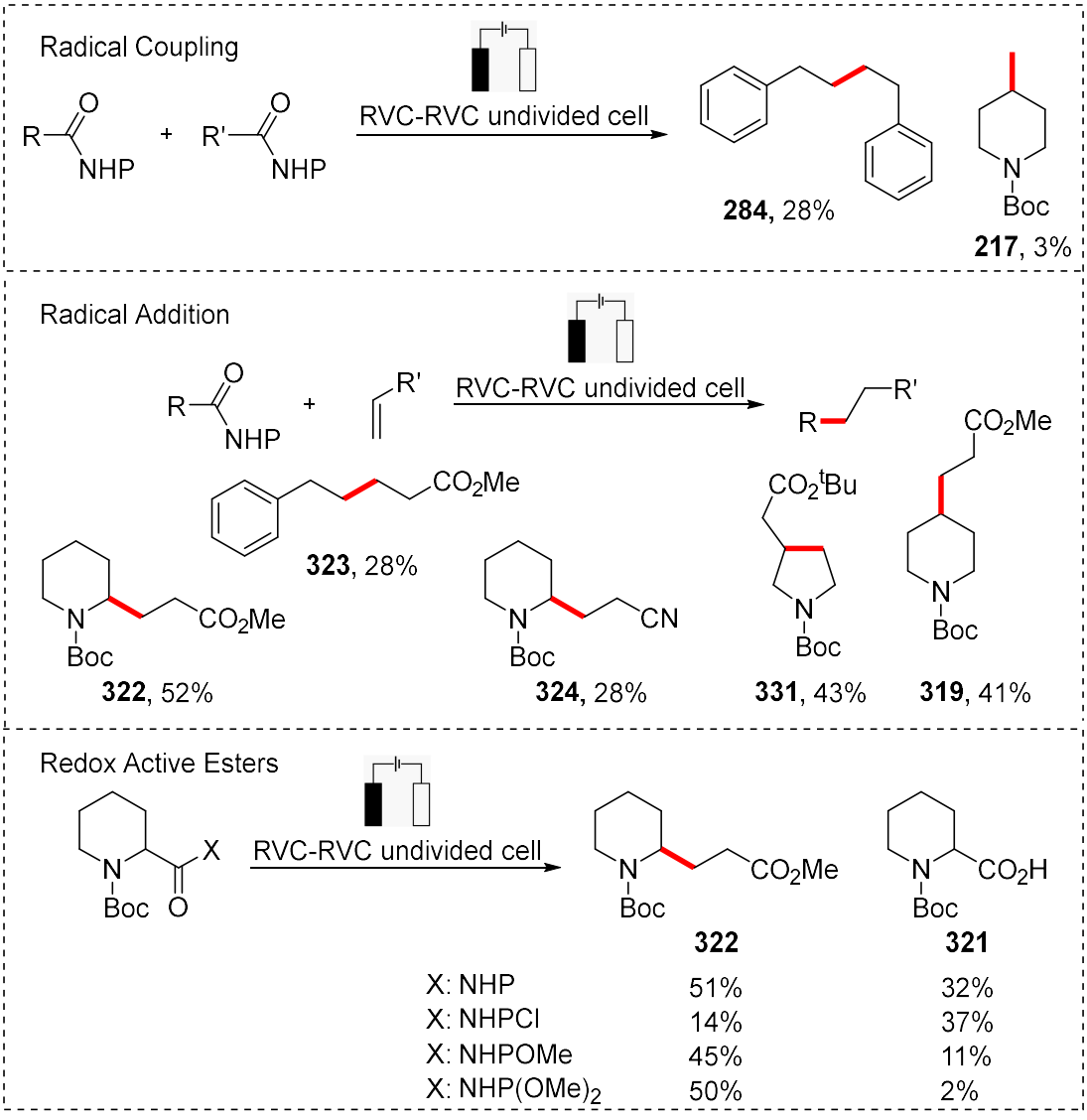

| Entry | Hantzsch ester **356** | Voltage (V) | Yield of **357** (%) |
|---|---|---|---|
| 1 | Yes | 2.5 | 87% |
| 2 | No | 2.5 | Trace |
| 3 | No | 5.0 | 69% |

Table 3.8 – Wang *et al.*'s optimisation for their reductive electrochemical methodology.[123]

In summary, Wang *et al.* present some very good and high yielding examples of reactions that are very similar to those described in the latter parts of this Chapter. It is difficult to pinpoint for certain the main reason for the difference in yield between the reaction that was discussed and developed in section 3.4 and Wang's reaction; Wang's reactions are clearly higher yielding. The use of Hantzsch ester **356** instead of DIPEA, together with using the alkene as the limiting reagent, are probably the key differences.

## 3.8 Conclusions and Future Work

In summary, reductive electrolysis on *N*-hydroxyphthalimide esters to form a carbon-centred radical and subsequent radical coupling or addition to electron deficient alkenes has been developed (Scheme 3.52). It was found that coupling the radicals with other/the same radical gave moderate to poor yields (*e.g.* **284** and **217**, radical coupling). In contrast, performing an addition reaction of these radicals to electron deficient alkenes gave superior yields (radical addition). For example, NHP ester **300** was reduced in the presence of methyl acrylate to give ester **322** in 52% yield.




Scheme 3.52

It was found that a large amount of carboxylic acid was being formed in the reduction of NHP esters. After synthetic and cyclic voltammetry analysis, it was deduced that the carboxylic acid was formed from a competitive electrochemical reaction. With this in mind, alternative NHP esters were explored and the amount of carboxylic acid obtained was reduced significantly from 32% to 2% (see Scheme 3.52, where X = NHP and X = $NHP(OMe)_2$ respectively).

Future work for this project could focus on exploring some of the failed reactions, notably the small range of electron deficient alkenes that was studied (see Scheme 3.40). Since Wang *et al*. reported a high yielding methodology on electrochemical NHP ester reduction and subsequent addition reactions (see Section 3.7),[123] it would be useful to identify the key differences between Wang's work and the work described in this Chapter. For example, the use of the same solvent, electrolyte and sacrificial oxidant as in Wang's work could lead to improvements with different alkenes. Furthermore, the scope and limitations of this work could be expanded, and a selection of redox active esters and electron deficient alkenes that could be studied is shown in Figure 3.12.

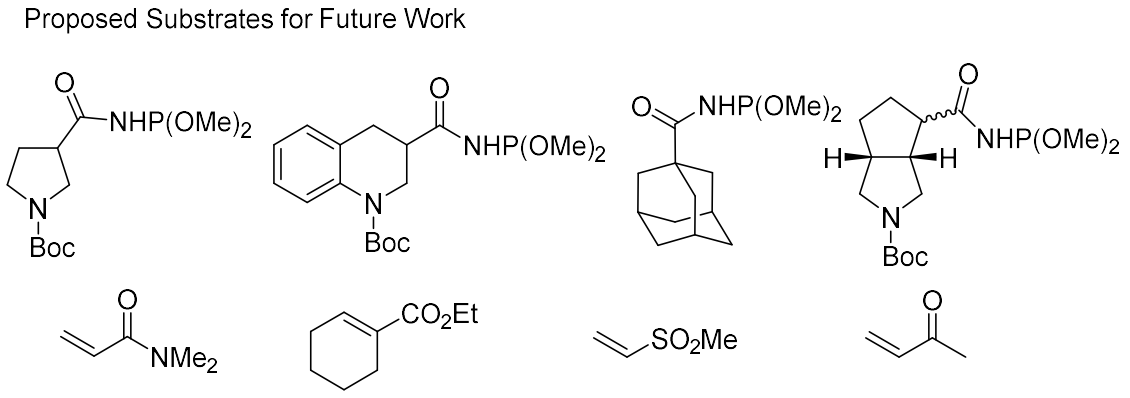



Figure 3.12 – Proposed substrates for future work

# Chapter 4: Experimental

## 4.1 General Methods

Brine refers to saturated aqueous sodium chloride solution and water is deionised water. Flash column chromatography was out carried according to standard techniques using silica gel [(60 Å, 220-440 mesh particle size 40–63 μm) purchased from Sigma-Aldrich or Fluka silica gel, 35–70 μm, 60 Å and the solvent system as stated. Thin layer chromatography was carried out using Merck TLC Silica gel 60G $F_{254}$ aluminium backed plates (100390 Supelco). Spots were visualised by UV and appropriate stains ($KMnO_4$, Vanillin, Ninhydrin). Melting points were carried out on a Gallenkamp melting point apparatus and were uncorrected

Proton (400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 or a JEOL ECS400 instrument using an internal deuterium lock. Chemical shifts ($\delta$) are recorded in parts per million (ppm) and referenced to the residual solvent peak of the stated solvent, with tetramethylsilane defined as 0 ppm. NMR spectra were analysed, assigned and reported using recommended methods and DEPT as well as 2D NMR techniques such as HH-COSY, HMQC, HMBC and NOESY where required. Coupling constants ($J$) are quoted in Hertz. For samples recorded in $CDCl_3$, chemical shifts are quoted in parts per million relative to $CHCl_3$ ($\delta_H$ 7.26 ppm) and $CDCl_3$ ($\delta_C$ 77.16 ppm, central line of triplet). For samples recorded in $CD_3OD$, chemical shifts are quoted in parts per million relative to $CD_3OD$ ($\delta_H$ 3.31 ppm, central line of quintet) and $CD_3OD$ ($\delta_C$ 49.0 ppm, central line of heptet). For samples recorded in $d^6$-DMSO, chemical shifts are quoted in parts per million relative to $d^6$-DMSO ($\delta_H$ 2.50 ppm, central line of quintet) and $d^6$-DMSO ($\delta_C$ 39.5 ppm, central line of quintet).

Infrared spectra were recorded on a PerkinElmer UATR 2 FT-IR spectrometer. Electrospray and Atmospheric Pressure Chemical ionisation techniques (ESI and APCI) have been applied and mass spectra were recorded at room temperature on a Bruker Daltronics microOTOF spectrometer. Optical rotations were recorded at room temperature on a Perkin Elmer Model 341 or Jasco DIP-370 polarimeter using a Na/Hal lamp (sodium D line, 589 nm) and $[\alpha]_D$ values are given in units of $10^{-1}$ deg $cm^3$ $g^{-1}$.

## 4.2 Electrochemical Information

Platinised titanium mesh supplied by CM Scientific Ltd. A DC power supply (HQ-Power, PS1503SB) was used to apply the voltage between the electrodes that is required to achieve the desired current flow. A LabJack© (U12) was used to record the voltages of the anode and cathode electrodes relative to a reference electrode and to measure a current flow. During the reaction, every 10 min, polarity inversion was performed to avoid electrode passivation. A Traceable® Total-Range Thermometer (FB50281) was used to record the temperature, supplied by Fisher Scientific.

## 4.3 Electrochemical Cell

### 4.3.1 Bespoke Electrochemical Cell 1

An undivided cell was used. The cell was designed using glass flanges and ground glass joints (Figure 4.1). The cell could hold a minimum of 20 mL of solvent and included five ports for inserting the anode and cathode working electrodes, reference electrode, thermocouple and reagent/gas inlet. The electrodes were platinum wire that were coiled around two parallel glass rods. The wires are approximately 7 mm apart and each had a surface area of 2.4 $cm^2$.

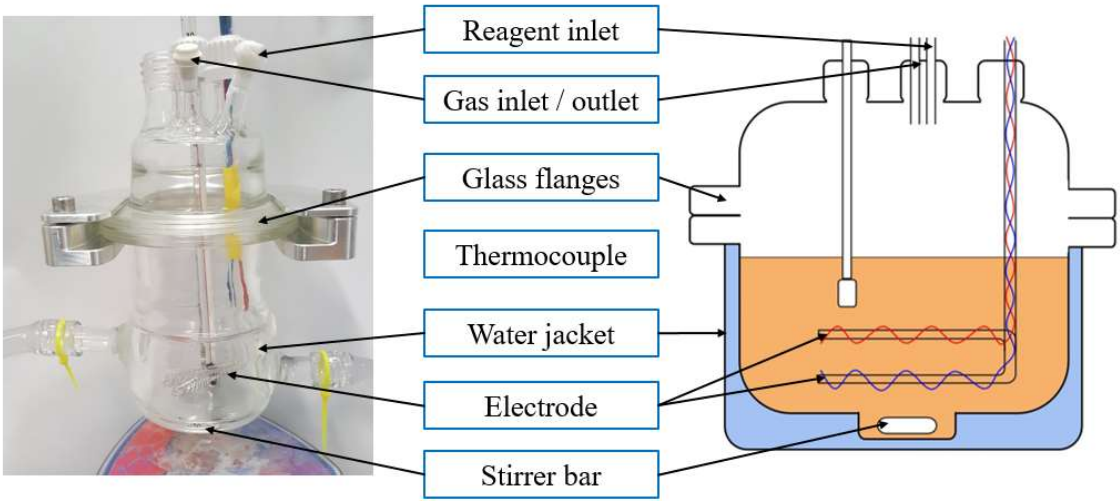



Figure 4.1 – Picture and schematic of bespoke electrochemical cell 1

### 4.3.1 Bespoke Electrochemical Cell 2

An undivided cell was used. The cell was designed using a test tube shaped glass container with a rubber seal at the top (Figure 4.2). The electrodes were two platinised titanium meshes with a separation of 2 mm and a surface area of 3.3 $cm^2$ each. Polytetrafluoroethylene (PTFE) was used as an electrode mount and platinum wire was used to electrochemically connect the mesh to the circuit. The electrodes were inserted into the rubber seal, along with the thermocouple and needles for reagent/gas inlet/outlet. There was also a glass joint at the side of the cell that can fit a water condenser when needed.

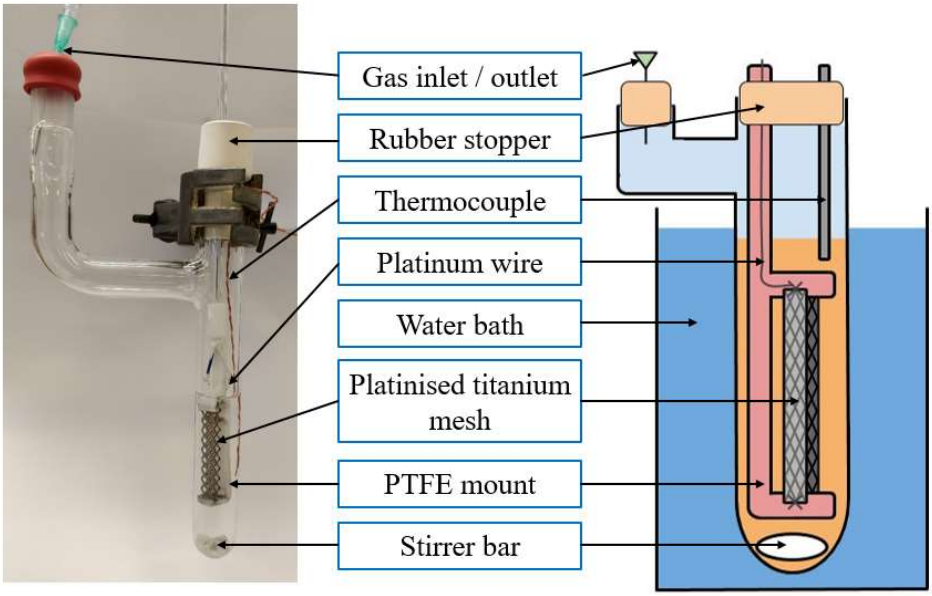



Figure 4.2 – Picture and schematic of bespoke electrochemical cell 2

### 4.3.1 Bespoke Electrochemical Cell 3

An undivided cell was used. The cell was designed using a test tube shaped glass container with a rubber seal at the top (Figure 4.3). The electrodes were reticulated vitreous carbon (RVC) with a separation of 2 mm and 50 × 8 × 2 mm in dimension. Coiled tinned copper wire was used as an electrode mount. The tinned copper wire was inserted into the rubber seal *via* a 20 gauge needle. The RVC electrodes were kept from touching by plastic inserts.

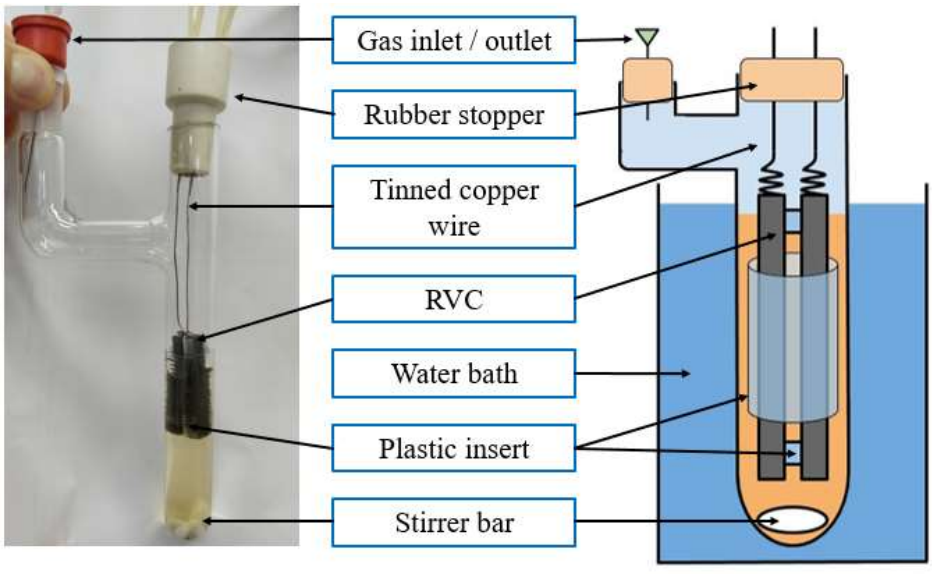



Figure 4.3 – Picture and schematic of bespoke electrochemical cell 3

### 4.3.2 ElectraSyn 2.0

ElectraSyn 2.0 was supplied by IKA®. ElectraSyn 2.0 contains a potentiostat, an analytical device and a stirrer plate. Platinised copper electrodes (7.1 $cm^2$) and RVC electrodes (50 × 8 × 2 mm) and an electrochemical cell (10 mL) were also supplied by IKA®.


Figure 4.4 – Picture of ElectraSyn 2.0

## 4.4 General Procedures

**General procedure A: Acid decarboxylation and heterocoupling using $Et_3N$ conditions (no precautions taken relating to the volatility of the product)**

Acid (0.86 mmol, 1.0 eq.), co-acid (6.0 eq.), $Et_3N$ (0.39 eq.) and MeOH (9 mL) were added to cell 2. The rubber stopper containing the platinum electrodes and thermocouple was inserted into the cell and the cell was either flushed with $N_2$ or kept without an inert atmosphere. The electrodes were connected to the electrolysis circuit *via* crocodile clips. The power pack was turned on (voltage at 0 V) simultaneously with the data acquisition software (LabJack©). The voltage was quickly raised to the desired setting. The solution was stirred at rt until 1.5-1.6 F $mol^{-1}$ of current had been passed through the cell. Then, the power pack and data acquisition software were turned off. $CH_2Cl_2$ (10 mL) was added and the reaction mixture was washed with brine (10 mL). The aqueous washings were extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. No precautions were taken relating to the volatility of the product.

**General procedure B: Acid decarboxylation and heterocoupling using KOH conditions (no precautions taken relating to the volatility of the product)**

Acid (1.17 mmol, 1.0 eq.), co-acid (4.0 eq.), KOH (0.25 eq.) and MeOH (9 mL) were added to cell 2. The rubber stopper containing the electrodes and thermocouple was inserted into the cell and the cell was either flushed with $N_2$ or kept without an inert atmosphere. The electrodes were connected to the electrolysis circuit *via* crocodile clips. The power pack was turned on (voltage at 0 V) simultaneously with the data acquisition software (LabJack©). The voltage was quickly raised to the desired setting. The solution was stirred at rt until 1.2-2.5 F $mol^{-1}$ of current had been passed through the cell. Then, the power pack and data acquisition software were turned off. $CH_2Cl_2$ (10 mL) was then added and the reaction mixture was washed with brine (10 mL). The aqueous washings were extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. No precautions were taken relating to the volatility of the product.

**General procedure C: Acid decarboxylation and heterocoupling using KOH conditions (precautions taken relating to the volatility of the product)**

Acid (1.17 mmol, 1.0 eq.), co-acid (4.0 eq.), KOH (0.25 eq.) and MeOH (9 mL) were added to cell 2. The rubber stopper containing the electrodes and thermocouple was inserted into the cell. No inert atmosphere was used. The electrodes were connected to the electrolysis circuit *via* crocodile clips. The power pack was turned on (voltage at 0 V) simultaneously with the data acquisition software (LabJack©). The voltage was quickly raised to the desired setting. The solution was stirred at rt until 1.2-2.5 F $mol^{-1}$ of current had been passed through the cell. Then, the power pack and data acquisition software were turned off. $CH_2Cl_2$ (10 mL) was then added and the reaction mixture was washed with brine (10 mL). The aqueous washings were extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The crude product and purified product were not put on the high vacuum and rotary evaporation was not carried out under full vacuum.

**General procedure D: Determination of NMR yield using mesitylene**

In order to determine the NMR yield for a reaction using (*R*)-*N*-Boc 2-ethyl piperidine (*R*)-**195** (1.17 mmol scale), the crude sample after the work-up was transferred to a 2 mL volumetric flask with $CH_2Cl_2$. The volumetric flask was made up to volume with $CH_2Cl_2$ and an aliquot (0.25 mL) was taken and transferred to a glass vial. Compressed air was used to dry the aliquot as much as possible. High vacuum should not be used to dry the aliquot as the product is volatile and any residual $CH_2Cl_2$ should not affect the NMR yield. 0.6 mL of a stock solution of mesitylene in $CDCl_3$ (28.8 mM) was added to the glass vial. The total contents of the glass vial was then transferred to an NMR tube and a $^1H$ NMR spectrum was recorded. The integral of the aromatic C-H of mesitylene ($\delta$ 6.79, s, 3H) was compared to the Me signal of (*R*)-*N*-Boc 2-ethyl piperidine (*R*)-**195** ($\delta$ 0.83, t, $J$ = 7.5 Hz, 3H) and a ratio was determined. The number of moles of product (*R*)-**195** contained in the aliquot was then calculated from the number of moles of mesitylene in the NMR sample. The total number of moles of (*R*)-**195** in the crude product can then be calculated along with the NMR yield.

**General procedure E: NHP ester decarboxylation and homocoupling using cell 3**

NHP ester (0.99 mmol, 1.0 eq.), base (5.94 mmol, 6.0 eq.), electrolyte (1.98 mmol, 2.0 eq.) and solvent (9 mL) were added to cell 3. The RVC electrodes were newly-made for each experiment. The rubber stopper containing the RVC electrodes and thermocouple was inserted into the cell and the cell was flushed with $N_2$. The electrodes were connected to the electrolysis circuit *via* crocodile clips. The power pack was turned on (voltage at 0 V) simultaneously with the data acquisition software (LabJack©). The voltage was quickly raised to the desired setting. The solution was stirred at rt or 40 ºC until 0.7 or 1.6 F $mol^{-1}$ of current had been passed through the cell. Then, the power pack and data acquisition software were turned off. EtOAc (10 mL) was added and the reaction mixture washed with brine/$H_2O$ (1:1) (3 × 20 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

**General procedure F: NHP ester decarboxylation and reaction with an alkene**

NHP ester (0.99 or 0.50 mmol, 1.0 eq.), alkene (2.97 or 1.50 mmol, 3.0 eq.), base (5.94 or 3.00 mmol, 6.0 eq.), electrolyte (1.98 mmol, 2.0 or 4.0 eq.) and MeCN (9 mL) were added to cell 3. The rubber stopper containing the RVC electrodes and thermocouple was inserted into the cell and the cell was flushed with $N_2$. The electrodes were connected to the electrolysis circuit *via* crocodile clips. The power pack was turned on (voltage at 0 V) simultaneously with the data acquisition software (LabJack©). The voltage was quickly raised to the desired setting. The solution was stirred at rt until 2.5 F $mol^{-1}$ of current had been passed through the cell. Then, the power pack and data acquisition software were turned off. EtOAc (10 mL) was added and the reaction mixture washed with brine/$H_2O$ (1:1) (3 × 20 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

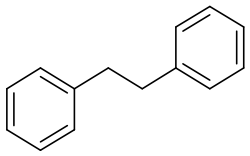
**General procedure G: Determination of carboxylic acid yield *via* acidification of the aqueous layer from the work-up**

The brine washings obtained from the work-up were acidified to pH 1-2 with 1 M $HCl_{(aq)}$ (20 mL). The mixture was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressed to give the acidified crude sample which contained carboxylic acid and $Bu_4NPF_6$ by $^1H$ NMR spectroscopy. The integral of the Me signal of $Bu_4NPF_6$ ($\delta$ 1.01, t, $J$ = 7.5 Hz, 12H) was compared to a

distinctive signal in the carboxylic acid and a ratio was determined. The number of moles of carboxylic acid was then calculated from the mass of the acidified crude sample along with the NMR yield.

## 4.5 Experimental for Chapter Two

**Bibenzyl 52**



**52**

Phenylacetic acid **51** (2.18 g, 16.0 mmol, 1.0 eq.), NaOMe (85.0 mg, 1.60 mmol, 0.1 eq.) and MeOH-pyridine (4:1, 20 mL) were added to nitrogen-flushed cell 1. The platinum electrodes were connected to the electrolysis circuit *via* crocodile clips. The power pack was turned on (voltage at 0 V) simultaneously with the data acquisition software (LabJack©). The voltage was quickly raised to the desired setting. The solution was stirred at rt under $N_2$ until a current of 1.6 eq. (2754 C of charge) of 7 V had been passed (17 h) with an average current density of 19 mA $cm^{-2}$. Then, the power pack and data acquisition software were turned off and the solvent was evaporated under reduced pressure to give a residue. The residue was dissolved in 3 M $HCl_{(aq)}$ (20 mL) and the mixture was extracted with $Et_2O$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 50:2 hexane-EtOAc as eluent gave bibenzyl **52** (453 mg, 16%) as a white solid, mp 50-51 °C (lit.,[42] 50-51 °C), $R_F$ (50:2 hexane-EtOAc) 0.56; IR (ATR) 3057, 3026, 2854, 1946, 1490, 1450, 748 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.30-7.24 (m, 4H, Ph), 7.21-7.15 (m, 6H, Ph), 2.91 (s, 4H, $CH_2$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 141.9 (*ipso*-Ph), 128.6 (Ph), 128.5 (Ph), 126.1 (Ph), 38.1 ($CH_2$); MS (EI) *m/z* 182 [$M^+$, 100]; HRMS (EI) *m/z* calcd for $C_{14}H_{14}$ $M^+$ 182.1101, found 182.1096 (+2.7 ppm error). Spectroscopic data are consistent with those reported in the literature.[42]

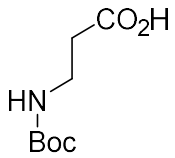
Lab Book Reference: SLB E-1-10-2

Phenylacetic acid **51** (980 mg, 7.20 mmol, 1.0 eq.), NaOMe (39.0 mg, 0.72 mmol, 0.1 eq.) and MeOH-pyridine (4:1, 9 mL) were added to nitrogen-flushed cell 2. The platinum electrodes were connected to the electrolysis circuit *via* crocodile clips. The power pack was turned on (voltage at 0 V) simultaneously with the data acquisition software

(LabJack©). The voltage was quickly raised to the desired setting. The solution was stirred at rt under $N_2$ until a current of 1.6 eq. (1081 C of charge) of 5 V had been passed (7 h 42 min) with an average current density of 12 mA $cm^{-2}$. Then, the power pack and data acquisition software were turned off. $CH_2Cl_2$ (10 mL) was added and the reaction mixture was washed with brine (10 mL). The aqueous washings were extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 50:2 hexane-EtOAc as eluent gave bibenzyl **52** (131 mg, 10%) as a white solid.

Lab Book Reference: SLB E-1-12-1

**3-{[(*tert*-Butoxy)carbonyl]amino}propanoic acid 167**



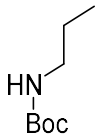

**167**

Di-*t*-butyl dicarbonate (13.5 g, 61.8 mmol, 1.1 eq.) was added to a stirred solution of β-alanine (5.0 g, 56.1 mmol, 1.0 eq.) and NaOH (2.45 g, 61.5 mmol, 1.1 eq.) in *t*-BuOH (60 mL) and $H_2O$ (30 mL) at rt under Ar. The resulting solution was stirred at rt for 24 h. $H_2O$ (50 mL) was then added and the mixture was washed with hexane (3 × 80 mL). The mixture was then acidified to pH 1 using 3 M $HCl_{(aq)}$ (25 mL) and a white precipitate formed. The mixture was extracted with EtOAc (3 × 80 mL) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an oil. Hexane (50 mL) was added slowly, with stirring to aid crystallisation, and a white solid was formed. The resulting slurry was stirred at rt for 2 h and the solid was collected by filtration, washed with hexane (3 × 20 mL) and dried under reduced pressure to give *N*-Boc β-alanine **167** (9.57 g, 90%) as a white solid, mp 79-80 °C (lit.,[136] 78-79 °C); IR (ATR) 3438 (N-H), 2966, 2952, 1700 (C=O), 1509, 1439, 1235, 1159, 1151, 978 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) $\delta$ 9.48 (br s, 1H, $CO_2H$), 6.30 (br s, 0.3H, NH), 5.10 (br s, 0.7H, NH), 3.44-3.30 (m, 2H, $NCH_2$), 2.61-2.47 (m, 2H,

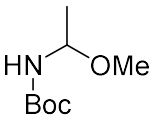
$NCH_2CH_2$), 1.46 (s, 2.7H, $CMe_3$), 1.43 (s, 6.3H, $CMe_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 177.7 (C=O, $CO_2H$), 176.4 (C=O, $CO_2H$), 157.7 (C=O, Boc), 156.1 (C=O, Boc), 81.2 ($OCMe_3$), 79.8 ($OCMe_3$), 37.3 ($NCH_2$), 36.0 ($NCH_2$), 34.6 ($NCH_2CH_2$), 28.5 ($CMe_3$); MS (ESI) *m/z* 212 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_8H_{15}NO_4$ $(M + Na)^+$ 212.0893, found 212.0899 (−2.8 ppm error). Spectroscopic data are consistent with those reported in the literature.[137]

Lab Book Reference: SLB 1-68

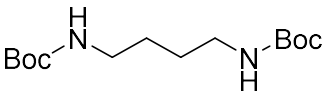
### *tert*-Butyl *N*-propylcarbamate 179, *tert*-butyl *N*-(1-methoxyethyl)carbamate 180 and *tert*-butyl *N*-(4-{[(*tert*-butoxy)carbonyl]amino}butyl)carbamate 184




**179**




**180**




**184**

Using general procedure A under $N_2$, *N*-Boc β-alanine **167** (162 mg, 0.86 mmol, 1.0 eq.), AcOH (0.29 mL, 5.13 mmol, 6.0 eq.) and $Et_3N$ (47.0 µL, 0.34 mmol, 0.39 eq.) in MeOH (9 mL) were used. A current of 1.79 F $mol^{-1}$ (1032 C of charge) of 14.9 V was passed for 1 h 30 min with an average current density of 57.3 mA $cm^{-2}$. This gave the crude product which contained a 65:35 mixture (by $^1H$ NMR spectroscopy) of *N*-Boc propyl amine **179** and *N*-Boc methoxy amine **180**. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-Boc propyl amine **179** (26 mg, 19%) as a colourless oil, $R_F$ (80:20 hexane-$Et_2O$) 0.30; IR (ATR) 3347 (N-H), 2966, 2938, 1686 (C=O), 1518, 1364, 1271, 1244, 1168, 1140 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.53 (br s, 1H, NH), 3.12-3.02 (m, 2H, $NCH_2$), 1.55-1.44 (m, 2H, $NCH_2CH_2$), 1.43 (s, 9H, $CMe_3$), 0.90 (t, $J$ = 7.5 Hz, 3H, Me); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 156.2 (C=O), 79.1 ($OCMe_3$), 42.4 ($NCH_2$), 28.6 ($CMe_3$), 23.4 ($NCH_2CH_2$), 11.4 (Me); MS (ESI) *m/z* 182 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_8H_{17}NO_2$ $(M + Na)^+$ 182.1551, found 182.1158 (+3.8 ppm error). *N*-Boc methoxy amine **180** was not isolated. Spectroscopic data are consistent with those reported in the literature.[138]

Lab Book Reference: SLB-E-035

Using general procedure B under air, *N*-Boc β-alanine **167** (221 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.84 F $mol^{-1}$ (1042 C of charge) of 15.1 V was passed for 1 h 48 min with an average current density of 49 mA $cm^{-2}$. This gave the crude product which contained a 65:35 mixture (by $^{1}H$ NMR spectroscopy) of *N*-Boc propyl amine **179** and *N*-Boc methoxy amine **180**. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-Boc propyl amine **179** (70 mg, 38%) as a colourless oil and *N*-Boc methoxy amine **180** (37 mg, 17%) as a white solid, mp 72-74 °C, $R_F$ (80:20 hexane-EtOAc) 0.26; IR (ATR) 3322 (N-H), 2978, 2937, 1685 (C=O), 1523, 1364, 1250, 1132, 1088, 1067, 1044, 1027 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.02-4.93 (m, 1H, NCH), 4.80 (br s, 1H, NH), 3.33 (s, 3H, OMe), 1.45 (s, 9H, $CMe_3$), 1.31 (d, $J$ = 6.0 Hz, 3H, NCH*Me*); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 155.4 (C=O), 79.9 (O*C*$Me_3$), 79.5 (NCH), 55.3 (OMe), 28.4 (C*Me*$_3$), 21.8 (NCH*Me*); MS (ESI) *m/z* 198 [(M + Na)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_8H_{17}NO_3$ (M + Na)$^+$ 198.1106, found 198.1105 (+0.5 ppm error). Spectroscopic data are consistent with those reported in the literature.[139]

Lab Book Reference: SLB-E-034

Using general procedure B under air, *N*-Boc β-alanine **167** (221 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mL, 4.68 mmol, 4.0 eq.) and KOH (33 mg, 0.59 mmol, 0.50 eq.) in MeOH (9 mL) were used. A current of 1.88 F $mol^{-1}$ (1061 C of charge) of 14.5 V was passed for 1 h 03 min with an average current density of 84 mA $cm^{-2}$. This gave the crude product which contained a 65:35 mixture (by $^{1}H$ NMR spectroscopy) of *N*-Boc propyl amine **179** and *N*-Boc methoxy amine **180**. Purification by flash column chromatography on silica with 93:7 hexane-EtOAc as eluent gave *N*-Boc propyl amine **179** (57 mg, 31%) as a colourless oil and *N*-Boc methoxy amine **180** (26 mg, 13%) as a white solid.

Lab Book Reference: SLB-E-045

Using general procedure B under air, *N*-Boc β-alanine **167** (221 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mL, 4.68 mmol, 4.0 eq.) and KOH (39 mg, 0.70 mmol, 0.60 eq.) in MeOH (9 mL) were used. A current of 1.71 F $mol^{-1}$ (965 C of charge) of 14.5 V was passed for

52 min with an average current density of 93 mA $cm^{-2}$. This gave the crude product which contained a 65:35 mixture (by $^{1}H$ NMR spectroscopy) of *N*-Boc propyl amine **179** and *N*-Boc methoxy amine **180**. Purification by flash column chromatography on silica with 93:7 hexane-EtOAc as eluent gave *N*-Boc propyl amine **179** (49 mg, 26%) as a colourless oil. *N*-Boc methoxy amine **180** was not isolated.

Lab Book Reference: SLB-E-047

Using general procedure B under air, *N*-Boc β-alanine **167** (886 mg, 4.68 mmol, 4.0 eq.), AcOH (67 μL, 1.17 mmol, 1.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.63 F $mol^{-1}$ (917 C of charge) of 15.3 V was passed for 1 h 58 min with an average current density of 39 mA $cm^{-2}$. This gave the crude product which contained a 25:25:50 mixture (by $^{1}H$ NMR spectroscopy) of *N*-Boc propyl amine **179**, *N*-Boc methoxy amine **180** and di-*N*-Boc amine **184**. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave *N*-Boc propyl amine **179** (64 mg, 35%) as a colourless oil. *N*-Boc methoxy amine **180** and di-*N*-Boc amine **184** were not isolated.

Lab Book Reference: SLB-E-040

Using general procedure C, *N*-Boc β-alanine **167** (221 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.62 F $mol^{-1}$ (916 C of charge) of 15.2 V was passed for 1 h 32 min with an average current density of 50 mA $cm^{-2}$. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave *N*-Boc propyl amine **179** (93 mg, 50%) as a colourless oil and *N*-Boc methoxy amine **180** (37 mg, 18%) as a white solid.

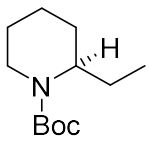
Lab Book Reference: SLB-E-092

*N*-Boc β-alanine **167** (246 mg, 1.30 mmol, 1.0 eq.), AcOH (0.30 mL, 5.20 mmol, 4.0 eq.), KOH (18 mg, 0.33 mmol, 0.25 eq.) and MeOH (10 mL) were added to an ElectraSyn 2.0

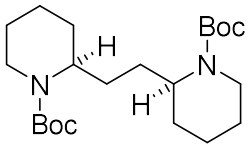
10 mL glass cell with platinum electrodes and the cell was flushed with $N_2$. The cell was connected to the main ElectraSyn 2.0 set-up and a constant current experiment was selected. The solution was stirred at rt until a current of 1.60 F $mol^{-1}$ of 14 mA $cm^{-2}$ current density was passed with an average voltage of 11.0 V. $CH_2Cl_2$ (10 mL) was then added and the reaction mixture was washed with brine (10 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave *N*-Boc propyl amine **179** (66 mg, 32%) as a colourless oil, *N*-Boc methoxy amine **180** (30 mg, 13%) as a white solid and di-*N*-Boc amine **184** (7 mg, 3%) as a white solid, mp 130-132 °C (lit.,[140] 139-140 °C), $R_F$ (80:20 hexane-$Et_2O$) 0.09; IR (ATR) 3367 (N-H), 3346 (N-H), 2977, 2932, 1683 (C=O), 1525, 1363, 1251, 1162, 1136 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.56 (br s, 2H, NH), 3.17-3.07 (m, 4H, $NCH_2$), 1.52-1.45 (m, 4H, $NCH_2CH_2$), 1.44 (s, 18H, $CMe_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 156.1 (C=O), 78.4 ($OCMe_3$), 40.4 ($NCH_2$), 28.6 ($CMe_3$), 27.6 ($NCH_2CH_2$); MS (ESI) *m/z* 311 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{14}H_{28}N_2O_4$ $(M + Na)^+$ 311.1941 , found 311.1945 (−1.2 ppm error). Spectroscopic data are consistent with those reported in the literature.[140]

Lab Book Reference: SLB-E-105

**(*R*)-*tert*-Butyl 2-ethylpiperidine-1-carbamate (*R*)-195 and (*S*,*S*)-di-*tert*-butyl 2,2'-(ethane-1,2-diyl)bis(piperidine-1-carboxylate) (*S*,*S*)-196**




(*R*)-**195**




(*S*,*S*)-**196**

Using general procedure B under air, *N*-Boc 2-carboxylic acid piperidine (*S*)-**168** (98:2 er, 285 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.59 F $mol^{-1}$ (902 C of charge) of 15.0 V was passed for 1 h 30 min with an average current density of 51 mA $cm^{-2}$. This gave the crude product which contained an unknown ratio of *N*-Boc 2-ethyl piperidine (*R*)-**195** and di-*N*-Boc piperidine (*S*,*S*)-**196**. Using general procedure D, *N*-Boc

2-ethyl piperidine (*R*)-**195** was formed in 34% NMR yield. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave *N*-Boc 2-ethyl piperidine (*R*)-**195** (79 mg, 32%) as a colourless oil, $R_F$ (80:20 hexane-$Et_2O$) 0.35; $[\alpha]_D$ – 19.4 (*c* 1.0 in $CHCl_3$); IR (ATR) 2965, 2931, 1685 (C=O), 1412, 1363, 1264, 1144, 1069, 1021 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.10 (br s, 1H, NCH), 4.03-3.91 (m, 1H, NCH), 2.79-2.66 (m, 1H, NCH), 1.75-1.47 (m, 6H, CH), 1.45 (s, 9H, $CMe_3$), 1.42-1.32 (m, 2H, CH), 0.84 (t, *J* = 7.5 Hz, 3H, $CH_2$*Me*); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 155.5 (C=O), 79.1 (O*C*$Me_3$), 52.1 (NCH), 38.8 ($NCH_2$), 28.7 (C*Me*$_3$), 28.5 ($CH_2$), 25.8 ($CH_2$), 22.7 ($CH_2$), 19.2 ($CH_2$), 11.0 ($CH_2$*Me*); MS (ESI) *m/z* 236 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{12}H_{23}NO_2$ $(M + Na)^+$ 236.1621, found 236.1627 (−2.5 ppm error). Di-*N*-Boc piperidine (*S*,*S*)-**196** was not isolated. Spectroscopic data are consistent with those reported in the literature.[141]

Lab Book Reference: SLB-E-049

Using general procedure B under air, *N*-Boc 2-carboxylic acid piperidine (*S*)-**168** (285 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.20 F $mol^{-1}$ (680 C of charge) of 15.1 V was passed for 1 h 08 min with an average current density of 50 mA $cm^{-2}$. This gave the crude product which contained an unknown ratio of *N*-Boc 2-ethyl piperidine (*R*)-**195** and di-*N*-Boc piperidine (*S*,*S*)-**196**. Using general procedure D, *N*-Boc 2-ethyl piperidine (*R*)-**195** was formed in 43% NMR yield. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave *N*-Boc 2-ethyl piperidine (*R*)-**195** (73 mg, 29%) as a colourless oil. Di-*N*-Boc piperidine (*S*,*S*)-**196** was not isolated.

Lab Book Reference: SLB-E-061

Using general procedure B under air, *N*-Boc 2-carboxylic acid piperidine (*S*)-**168** (285 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.72 F $mol^{-1}$ (972 C of charge) of 30.3 V was passed for 43 min with an average current density of 112 mA $cm^{-2}$. This

gave the crude product which contained an unknown ratio of *N*-Boc 2-ethyl piperidine (*R*)-**195** and di-*N*-Boc piperidine (*S*,*S*)-**196**. Using general procedure D, *N*-Boc 2-ethyl piperidine (*R*)-**195** was formed in 28% NMR yield. Purification by flash column chromatography on silica with 96:4 hexane-EtOAc as eluent gave *N*-Boc 2-ethyl piperidine (*R*)-**195** (62 mg, 25%) as a colourless oil. Di-*N*-Boc piperidine (*S*,*S*)-**196** was not isolated.

Lab Book Reference: SLB-E-048

Using general procedure B under air, *N*-Boc 2-carboxylic acid piperidine (*S*)-**168** (285 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mL, 4.68 mmol, 4.0 eq.) and KOH (33 mg, 0.59 mmol, 0.5 eq.) in MeOH (9 mL) were used. A current of 1.61 F $mol^{-1}$ (908 C of charge) of 30.3 V was passed for 43 min with an average current density of 186 mA $cm^{-2}$. This gave the crude product which contained an unknown ratio of *N*-Boc 2-ethyl piperidine (*R*)-**195** and di-*N*-Boc piperidine (*S*,*S*)-**196**. Using general procedure D, *N*-Boc 2-ethyl piperidine (*R*)-**195** was formed in 32% NMR yield.

Lab Book Reference: SLB-E-051

Using general procedure A under $N_2$, *N*-Boc 2-carboxylic acid piperidine (*S*)-**168** (208 mg, 0.86 mmol, 1.0 eq.), AcOH (0.29 mL, 5.13 mmol, 6.0 eq.) and $Et_3N$ (47 µL, 0.34 mmol, 0.39 eq.) in MeOH (9 mL) were used. A current of 1.48 F $mol^{-1}$ (855 C of charge) of 14.9 V was passed for 1 h 14 min with an average current density of 59 mA $cm^{-2}$. This gave the crude product which contained an unknown ratio of *N*-Boc 2-ethyl piperidine (*R*)-**195** and di-*N*-Boc piperidine (*S*,*S*)-**196**. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave *N*-Boc 2-ethyl piperidine (*R*)-**195** (71 mg, 28%) as a colourless oil. Di-*N*-Boc piperidine (*S*,*S*)-**196** was not isolated.

Lab Book Reference: SLB-E-044

Using general procedure A under $N_2$, *N*-Boc 2-carboxylic acid piperidine (*S*)-**168** (208 mg, 0.86 mmol, 1.0 eq.), AcOH (0.29 mL, 5.13 mmol, 6.0 eq.) and $Et_3N$ (47 µL, 0.34

mmol, 0.39 eq.) in MeOH (9 mL) were used. A current of 1.48 F $mol^{-1}$ (854 C of charge) of 29.7 V was passed for 31 min with an average current density of 138 mA $cm^{-2}$. This gave the crude product which contained an unknown ratio of *N*-Boc 2-ethyl piperidine (*R*)-**195** and di-*N*-Boc piperidine (*S*,*S*)-**196**. Using general procedure D, *N*-Boc 2-ethyl piperidine (*R*)-**195** was formed in 20% NMR yield.

Lab Book Reference: SLB-E-057

Using general procedure A under air, *N*-Boc 2-carboxylic acid piperidine (*S*)-**168** (208 mg, 0.86 mmol, 1.0 eq.), AcOH (0.29 mL, 5.13 mmol, 6.0 eq.) and $Et_3N$ (47 µL, 0.34 mmol, 0.39 eq.) in MeOH (9 mL) were used. A current of 1.50 F $mol^{-1}$ (867 C of charge) of 29.8 V was passed for 31 min with an average current density of 140 mA $cm^{-2}$. This gave the crude product which contained an unknown ratio of *N*-Boc 2-ethyl piperidine (*R*)-**195** and di-*N*-Boc piperidine (*S*,*S*)-**196**. Using general procedure D, *N*-Boc 2-ethyl piperidine (*R*)-**195** was formed in 25% NMR yield.

Lab Book Reference: SLB-E-058

Using general procedure A under air, *N*-Boc 2-carboxylic acid piperidine (*S*)-**168** (208 mg, 0.86 mmol, 1.0 eq.), AcOH (0.29 mL, 5.13 mmol, 6.0 eq.) and $Et_3N$ (47 µL, 0.34 mmol, 0.39 eq.) in MeOH (9 mL) were used. A current of 1.22 F $mol^{-1}$ (705 C of charge) of 29.7 V was passed for 25 min with an average current density of 143 mA $cm^{-2}$. This gave the crude product which contained an unknown ratio of *N*-Boc 2-ethyl piperidine (*R*)-**195** and di-*N*-Boc piperidine (*S*,*S*)-**196**. Using general procedure D, *N*-Boc 2-ethyl piperidine (*R*)-**195** was formed in 27% NMR yield. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave *N*-Boc 2-ethyl piperidine (*R*)-**195** (44 mg, 24%) as a colourless oil. Di-*N*-Boc piperidine (*S*,*S*)-**196** was not isolated.

Lab Book Reference: SLB-E-059

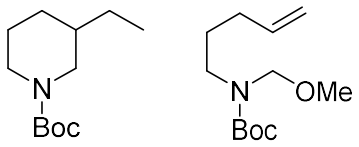
Using general procedure C, *N*-Boc 2-carboxylic acid piperidine (*S*)-**168** (285 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.20 F $mol^{-1}$ (678 C of charge) of 15.1 V was passed for 1 h 10 min with an average current density of 49 mA $cm^{-2}$. This gave the crude product which contained a 90:10 mixture of *N*-Boc 2-ethyl piperidine (*R*)-**195** and di-*N*-Boc piperidine (*S*,*S*)-**196**. Using general procedure D, *N*-Boc 2-ethyl piperidine (*R*)-**195** was formed in 53% NMR yield. Purification by flash column chromatography on silica with 95:5 hexane-$Et_2O$ as eluent gave *N*-Boc 2-ethyl piperidine (*R*)-**195** (129 mg, 47%) as a colourless oil. Di-*N*-Boc piperidine (*S*,*S*)-**196** was not isolated.

Lab Book Reference: SLB-E-070

Using general procedure C, *N*-Boc 2-carboxylic acid piperidine (*S*)-**168** (285 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.24 F $mol^{-1}$ (699 C of charge) of 15.2 V was passed for 1 h 10 min with an average current density of 50 mA $cm^{-2}$. This gave the crude product which contained a 90:10 mixture of *N*-Boc 2-ethyl piperidine (*R*)-**195** and di-*N*-Boc piperidine (*S*,*S*)-**196**. Using general procedure D, *N*-Boc 2-ethyl piperidine (*R*)-**195** was formed in 47% NMR yield.

Lab Book Reference: SLB-E-071

***tert*-Butyl 3-ethylpiperidine-1-carbamate 197 and *tert*-butyl *N*-(methoxymethyl)-*N*-(pent-4-en-1-yl)carbamate 198**



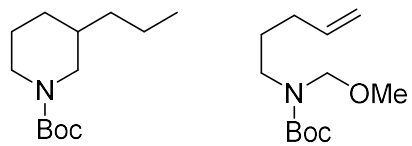

**197** **198**

Using general procedure C, *N*-Boc 3-acetic acid piperidine **169** (285 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.20 F $mol^{-1}$ (676 C of charge) of 15.2 V was passed for 1 h 13 min with an average current density of 46 mA $cm^{-2}$. This gave the crude

product. Purification by flash column chromatography on silica with 98:2 hexane-$Et_2O$ as eluent gave *N*-Boc 3-ethyl piperidine **197** (67 mg, 27%) as a colourless oil, $R_F$ (80:20 hexane-$Et_2O$) 0.35; IR (ATR) 2964, 2930, 2854, 1690 (C=O), 1418, 1364, 1265, 1176, 1148, 1109 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.13-3.78 (m, 2H, NCH), 2.82-2.65 (m, 1H, NCH), 2.59-2.25 (m, 1H, NCH), 1.86-1.77 (m, 1H, CH), 1.68-1.55 (m, 1H, CH), 1.45 (s, 9H, $CMe_3$), 1.37-1.11 (m, 4H, CH), 1.10-0.95 (m, 1H, CH), 0.90 (t, $J$ = 7.0 Hz, 3H, $CH_2Me$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 155.0 (C=O), 79.3 ($OCMe_3$), 49.9 ($NCH_2$), 44.9 ($NCH_2$), 37.7 (CH), 30.9 ($CH_2$), 28.6 ($CMe_3$), 26.6 ($CH_2$), 25.3 ($CH_2$), 11.4 ($CH_2Me$); MS (ESI) *m/z* 236 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{12}H_{23}NO_2$ $(M + Na)^+$ 236.1621, found 236.1619 (+0.8 ppm error) and *N*-Boc methoxy alkene **198** (17 mg, 6%) as a colourless oil, $R_F$ (80:20 hexane-$Et_2O$) 0.17; IR (ATR) 2976, 2931, 1698 (C=O), 1415, 1366, 1295, 1150, 1080, 909 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.80 (ddt, $J$ = 17.0, 10.0, 7.0 Hz, 1H, $CH=CH_2$), 5.02 (dd, $J$ = 17.0, 1.0 Hz, 1H, CH=C*H*H), 4.96 (br d, $J$ = 10.0 Hz, 1H, CH=CH*H*), 4.72-4.63 (br s, 2H, $NCH_2OMe$), 3.27 (s, 3H, OMe), 3.32-3.16 (m, 2H, $NCH_2$), 2.04 (dt, $J$ = 7.0, 7.0 Hz , 2H, $CH_2CH=CH_2$), 1.72-1.56 (m, 2H, $NCH_2CH_2$), 1.46 (s, 9H, $CMe_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 155.2 (C=O), 138.2 ($CH=CH_2$), 115.0 ($CH=CH_2$), 80.2 ($NCH_2OMe$), 79.0 ($OCMe_3$), 78.8 ($OCMe_3$), 55.5 (OMe), 55.4 (OMe), 46.0 ($NCH_2$), 45.8 ($NCH_2$), 31.3 ($CH_2CH=CH_2$), 28.5 ($CMe_3$), 28.3 ($NCH_2CH_2$), 27.8 ($NCH_2CH_2$); MS (ESI) *m/z* 252 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{12}H_{23}NO_3$ $(M + Na)^+$ 252.1570, found 252.1569 (+0.3 ppm error).

Lab Book Reference: SLB-E-076

**_tert_-Butyl 3-propylpiperidine-1-carbamate 202 and _tert_-butyl _N_-(methoxymethyl)-_N_-(pent-4-en-1-yl)carbamate 198**



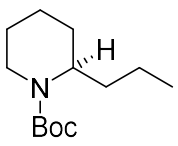

**202** **198**

Using general procedure C, *N*-Boc 3-acetic acid piperidine **169** (285 mg, 1.17 mmol, 1.0 eq.), propanoic acid (0.35 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25

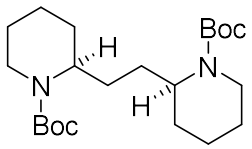
eq.) in MeOH (9 mL) were used. A current of 1.22 F $mol^{-1}$ (689 C of charge) of 15.2 V was passed for 1 h 14 min with an average current density of 47 mA $cm^{-2}$. This gave the crude product. Purification by flash column chromatography on silica with 96:4 hexane-$Et_2O$ as eluent gave *N*-Boc 3-propyl piperidine **202** (51 mg, 19%) as a colourless oil, $R_F$ (80:20 hexane-$Et_2O$) 0.38; IR (ATR) 2958, 2929, 2850, 1690 (C=O), 1418, 1364, 1264, 1148, 1109 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.12-3.74 (m, 2H, NCH), 2.81-2.64 (m, 1H, NCH), 2.59-2.22 (m, 1H, NCH), 1.86-1.75 (m, 1H, CH), 1.67-1.56 (m, 1H, CH), 1.45 (s, 9H, $CMe_3$), 1.47-0.95 (m, 7H, CH), 0.87 (t, $J$ = 6.5 Hz, 3H, $CH_2$*Me*); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 155.1 (C=O), 79.2 (O*C*$Me_3$), 50.1 ($NCH_2$), 44.5 ($NCH_2$), 36.1 ($CH_2$), 35.7 (CH), 31.2 ($CH_2$), 28.6 (C*Me*$_3$), 25.0 ($CH_2$), 19.9 ($CH_2$), 14.4 ($CH_2$*Me*); MS (ESI) *m/z* 250 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{13}H_{25}NO_2$ $(M + Na)^+$ 250.1777, found 250.1783 (−2.1 ppm error) and *N*-Boc methoxy alkene **198** (17 mg, 7%) as a colourless oil.

Lab Book Reference: SLB-E-077

**(*R*)-*tert*-Butyl 2-propylpiperidine-1-carbamate (*R*)-203 and (*S*,*S*)-di-*tert*-butyl 2,2'-(ethane-1,2-diyl)bis(piperidine-1-carboxylate) (*S*,*S*)-196**




(*R*)-**203**



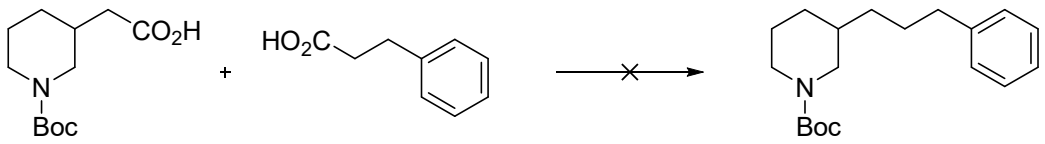

(*S*,*S*)-**196**

Using general procedure C, *N*-Boc 2-acetic acid piperidine (*S*)- **168** (285 mg, 1.17 mmol, 1.0 eq.), $EtCO_2H$ (0.35 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.62 F $mol^{-1}$ (912 C of charge) of 15.4 V was passed for 1 h 40 min with an average current density of 46 mA $cm^{-2}$. This gave the crude product. Purification by flash column chromatography on silica with 96:4 hexane-$Et_2O$ as eluent gave *N*-Boc 2-propyl piperidine (*R*)-**203** (139 mg, 52%) as a colourless oil, $R_F$ (80:20 hexane-$Et_2O$) 0.38; $[\alpha]_D$ –33.3 (*c* 1.0 in $CHCl_3$) (lit.,[142] –32.5 (*c* 1.34, $CHCl_3$)); IR (ATR) 2931, 2864, 1686 (C=O), 1414, 1363, 1169, 1143, 1073 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.20 (br s, 1H, NCH), 4.01-3.89 (m, 1H, NCH), 2.81-2.66 (m, 1H, NCH), 1.71-1.47 (m, 6H, CH), 1.44 (s, 9H, $CMe_3$), 1.41-1.18 (m, 4 H, CH), 0.91 (t, $J$ = 7.0 Hz, 3H,

$CH_2$*Me*); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 155.3 (C=O), 79.0 (O*C*Me$_3$), 50.2 (NCH), 38.8 ($NCH_2$), 32.0 ($CH_2$), 28.6 (C*Me*$_3$), 25.8 ($CH_2$), 19.6 ($CH_2$), 19.1 ($CH_2$), 14.2 ($CH_2$*Me*) (one $CH_2$ resonance not resolved); MS (ESI) *m/z* 250 [(M + Na)$^+$, 100], 228 [(M + H)$^+$, 10]; HRMS (ESI) *m/z* calcd for $C_{13}H_{25}NO_2$ (M + H)$^+$ 228.1958, found 228.1963 (−2.3 ppm error) and di-*N*-Boc piperidine (*S*,*S*)- **196** (45 mg, 20%) as a white solid, mp 96-100 °C, $R_F$ (80:20 hexane-$Et_2O$) 0.12; $[\alpha]_D$ –52.6 (*c* 1.0 in $CHCl_3$); IR (ATR) 2931, 2859, 1683 (C=O), 1412, 1363, 1271, 1160, 1142 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.29-4.17 (br s, 2H, NCH), 4.06-3.90 (br s, 2H, NCH), 2.76-2.64 (m, 2H, NCH), 1.73-1.21 (m, 16H, CH), 1.45 (s, 18H, CMe$_3$); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 155.3 (C=O), 79.2 (O*C*Me$_3$), 50.2 (NCH), 38.6 ($NCH_2$), 29.2 ($CH_2$), 28.7 (C*Me*$_3$), 26.3 ($CH_2$), 25.8 ($CH_2$), 19.2 ($CH_2$); MS (ESI) *m/z* 419 [(M + Na)$^+$, 100], 397 [(M + H)$^+$, 29]; HRMS (ESI) *m/z* calcd for $C_{22}H_{40}N_2O_4$ (M + H)$^+$ 397.3061, found 397.3066 (−1.4 ppm error). Spectroscopic data for *N*-Boc 2-propyl piperidine (*R*)-**203** are consistent with those reported in the literature.[143]

Lab Book Reference: SLB-E-099

**Attempted synthesis of *tert*-butyl 3-(3-phenylpropyl)piperidine-1-carbamate 204**

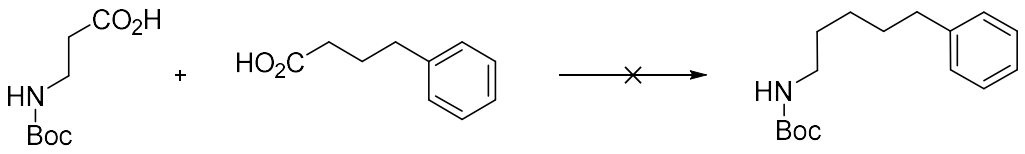



**169** **174** **204**

Using general procedure C, *N*-Boc 3-acetic acid piperidine **169** (285 mg, 1.17 mmol, 1.0 eq.), 3-phenylpropanoic acid **174** (703 mg, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. An initial current density of 30 mA cm$^{-2}$ was passed using 15.7 V but the current density immediately decreased exponentially to 3 mA cm$^{-2}$. A current of 0.63 F mol$^{-1}$ (354 C of charge) was passed for 7 h 19 min. This gave the crude product which did not contain *N*-Boc 3-(phenylpropyl) piperidine **204** by $^1$H NMR spectroscopy and mass spectrometry. Recovered starting materials, **169** and 3-phenylpropanoic acid **174**, were observed in the $^1$H NMR spectrum of the crude product but they were not isolated.

Lab Book Reference: SLB-E-072

**Attempted synthesis of *tert*-butyl *N*-(5-phenylpentyl)carbamate 205**

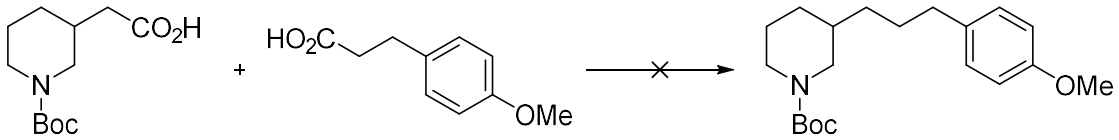


**167** **175** **205**

Using general procedure C, *N*-Boc β-alanine **167** (221 mg, 1.17 mmol, 1.0 eq.), 4-phenylbutanoic acid **175** (768 mg, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. An initial current density of 31 mA $cm^{-2}$ using 15.7 V was passed but the current density immediately decreased exponentially to 6 mA $cm^{-2}$. A current of 0.82 F $mol^{-1}$ (463 C of charge) was passed for 5 h 1 min. This gave the crude product which did not contain *N*-Boc 5-phenylpentyl **205** by $^{1}$H NMR spectroscopy and mass spectrometry. Recovered starting materials, **167** and 4-phenylbutanoic acid **175**, were observed in the $^{1}$H NMR spectrum of the crude product but they were not isolated.

Lab Book Reference: SLB-E-103

**Attempted synthesis of *tert*-butyl 3-(3-(4-methoxyphenyl)propyl)piperidine-1-carbamate 206**



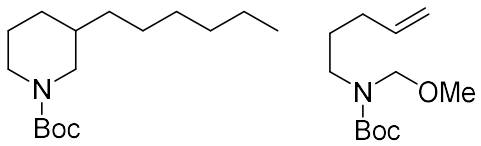
**169** **176** **206**

Using general procedure C, *N*-Boc 3-acetic acid piperidine **169** (285 mg, 1.17 mmol, 1.0 eq.), 3-(4-methoxyphenyl)propanoic acid **176** (843 mg, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.20 F $mol^{-1}$ (676 C of charge) of 15.2 V was passed for 1 h 30 min with an average current density of 38 mA $cm^{-2}$. This gave the crude product which did not contain *N*-Boc 3-(phenylpropyl) piperidine **206** by $^{1}$H NMR spectroscopy and mass spectrometry. Purification by flash

column chromatography on silica with 70:30 hexane-$Et_2O$ as eluent gave recovered 3-(4-methoxyphenyl)propanoic acid **176** (229 mg, 27%) as a pale yellow solid.

Lab Book Reference: SLB-E-074

### *tert*-Butyl 3-hexylpiperidine-1-carbamate 207 and *tert*-butyl *N*-(methoxymethyl)-*N*-(pent-4-en-1-yl)carbamate 198




**207** **198**

Using general procedure C, *N*-Boc 3-acetic acid piperidine **169** (285 mg, 1.17 mmol, 1.0 eq.), hexanoic acid **177** (0.59 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.24 F $mol^{-1}$ (702 C of charge) of 15.3 V was passed for 1h 56 min with an average current density of 31 mA $cm^{-2}$. This gave the crude product. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave *N*-Boc 3-hexyl piperidine **207** (86 mg, 27%) as a colourless oil, $R_F$ (80:20 hexane-$Et_2O$) 0.41; IR (ATR) 2924, 2853, 1692 (C=O), 1418, 1364, 1264, 1238, 1147, 1112 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.15-3.73 (m, 2H, NCH), 2.81-2.66 (m, 1H, NCH), 2.60-2.19 (m, 1H, NCH), 1.85-1.75 (m, 1H, CH), 1.67-1.56 (m, 1H, CH), 1.45 (s, 9H, $CMe_3$), 1.49-0.95 (m, 13H, CH), 0.87 (t, $J$ = 6.5 Hz, 3H, $CH_2\mathit{Me}$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 155.1 (C=O), 79.2 ($OCMe_3$), 49.8 ($NCH_2$), 44.7 ($NCH_2$), 36.0 (CH), 33.8 ($CH_2$), 32.0 ($CH_2$), 31.3 ($CH_2$), 29.7 ($CH_2$), 28.6 ($C\mathit{Me}_3$), 26.8 ($CH_2$), 25.4 ($CH_2$), 22.8 ($CH_2$), 14.2 ($CH_2\mathit{Me}$); MS (ESI) *m/z* 292 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{16}H_{31}NO_2$ $(M + Na)^+$ 292.2247, found 292.2249 (−0.5 ppm error), recovered hexanoic acid **177** (112 mg, 20%) as a colourless oil and recovered *N*-Boc 3-acetic acid piperidine **169** (117 mg, 41%) as a white solid. *N*-Boc methoxy alkene **198** was observed in the crude product (by $^1H$ NMR spectroscopy) but was not isolated.

Lab Book Reference: SLB-E-075

Using general procedure C, *N*-Boc 3-acetic acid piperidine **169** (285 mg, 1.17 mmol, 1.0 eq.), hexanoic acid **177** (0.59 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.58 F $mol^{-1}$ (893 C of charge) of 15.3 V was passed for 2 h 31 min with an average current density of 30 mA $cm^{-2}$. This gave the crude product. Purification by flash column chromatography on silica with 96:4 hexane-$Et_2O$ as eluent gave *N*-Boc 3-hexyl piperidine **207** (120 mg, 38%) as a colourless oil, *N*-Boc methoxy **198** (19 mg, 7%) as a colourless oil, recovered hexanoic acid **177** (63 mg, 12%) as a colourless oil and recovered *N*-Boc 3-acetic acid piperidine **169** (74 mg, 26%) as a white solid.

Lab Book Reference: SLB-E-078

Using general procedure C, *N*-Boc 3-acetic acid piperidine **169** (285 mg, 1.17 mmol, 1.0 eq.), hexanoic acid **177** (0.59 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.59 F $mol^{-1}$ (898 C of charge) of 31.1 V was passed for 1 h 15 min with an average current density of 60 mA $cm^{-2}$. This gave the crude product. Purification by flash column chromatography on silica with 96:4 hexane-$Et_2O$ as eluent gave *N*-Boc 3-hexyl piperidine **207** (88 mg, 28%) as a colourless oil, *N*-Boc methoxy alkene **198** (13 mg, 5%) as a colourless oil and recovered hexanoic acid **177** (87 mg, 16%) as a colourless oil. *N*-Boc 3-acetic acid piperidine **169** was observed in the crude product (by $^1H$ NMR spectroscopy) but was not isolated.

Lab Book Reference: SLB-E-079

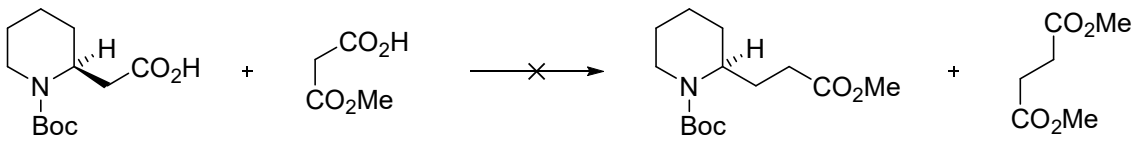
Using general procedure C, *N*-Boc 3-acetic acid piperidine **169** (285 mg, 1.17 mmol, 1.0 eq.), hexanoic acid **177** (0.59 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. The electrolysis was ran until no starting material was present by thin layer chromatography. A current of 2.48 F $mol^{-1}$ (1400 C of charge) of 15.4 V was passed for 4 h 10 min with an average current density of 24 mA $cm^{-2}$. This gave the crude product. Purification by flash column chromatography on silica with 96:4 hexane-$Et_2O$ as eluent gave *N*-Boc 3-hexyl piperidine **207** (122 mg, 38%) as a colourless oil and *N*-Boc methoxy alkene **198** (19 mg, 7%) as a colourless oil.

Lab Book Reference: SLB-E-081

*N*-Boc 3-acetic acid piperidine **169** (208 mg, 0.86 mmol, 1.0 eq.), hexanoic acid **177** (0.64 mL, 5.13 mmol, 6.0 eq.), $Et_3N$ (47.0 μL, 0.34 mmol, 0.39 eq.) and MeOH (9 mL) and added to cell 2. The rubber stopper containing the platinum electrodes and thermocouple was inserted into the cell and the cell was flushed with $N_2$. The electrodes were connected to the electrolysis circuit *via* crocodile clips. The power pack was turned on (voltage at 0 V) simultaneously with the data acquisition software (LabJack©). The voltage was quickly raised to the desired setting. The solution was stirred at rt until a current of 1.49 F $mol^{-1}$ (863 C of charge) of 15.4 V had been passed (2 h 23 min) with an average current density of 30 mA $cm^{-2}$. Then, the power pack and data acquisition software were turned off. $CH_2Cl_2$ (10 mL) was added and the reaction mixture was washed with brine (10 mL). The aqueous washings were extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 96:4 hexane-$Et_2O$ as eluent gave *N*-Boc 3-hexyl piperidine **207** (84 mg, 27%) as a colourless oil, *N*-Boc methoxy alkene **198** (12 mg, 6%) as a colourless oil, recovered hexanoic acid **177** (69 mg, 12%) as a colourless oil and recovered *N*-Boc 3-acetic acid piperidine **169** (35 mg, 17%) as a white solid. The crude product and purified product were not put on the high vacuum and rotary evaporation was not carried out under full vacuum.

Lab Book Reference: SLB-E-080

**Attempted synthesis of (*S*)-*tert*-butyl 2-(3-methoxy-3-oxopropyl)piperidine-1-carboxylate** (*S*)-**209**



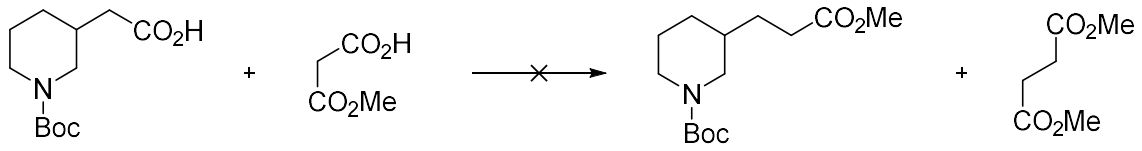

(*S*)-**168** **84** (*S*)-**209** **212**

Using general procedure C, *N*-Boc 2-acetic acid piperidine (*S*)-**168** (285 mg, 1.17 mmol, 1.0 eq.), monomethyl malonate **84** (0.49 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29

mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.59 F $mol^{-1}$ (896 C of charge) of 15.4 V was passed for 1 h 20 min with an average current density of 57 mA $cm^{-2}$. This gave the crude product which did not contain *N*-Boc 2-ester piperidine (*S*)- **209** by $^1$H NMR spectroscopy and mass spectrometry. Di-ester **212** ($^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.70 (s, 6H, OMe), 2.63 (s, 4H, $CH_2$)) and starting monomethyl malonate **84** were observed in the $^1$H NMR spectrum of the crude product but they were not isolated. Spectroscopic data are consistent with those reported in the literature.[144]

Lab Book Reference: SLB-E-086

**Attempted synthesis of *tert*-butyl 3-(3-methoxy-3-oxopropyl)piperidine-1-carboxylate 210**

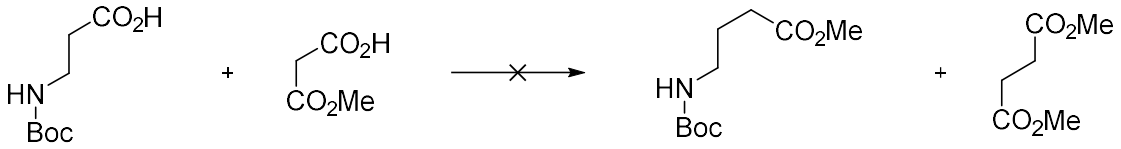



**169** **84** **210** **212**

Using general procedure C, *N*-Boc 3-acetic acid piperidine **169** (285 mg, 1.17 mmol, 1.0 eq.), monomethyl malonate **84** (0.49 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.59 F $mol^{-1}$ (895 C of charge) of 15.3 V was passed for 1 h 20 min with an average current density of 56 mA $cm^{-2}$. This gave the crude product which did not contain *N*-Boc 3-ester piperidine **210** by $^1$H NMR spectroscopy and mass spectrometry. Purification by flash column chromatography on silica with 85:15 hexane-$Et_2O$ as eluent gave di-ester **212** (127 mg, 37%) as a colourless oil and monomethyl malonate **84** (108 mg, 20%) as a colourless oil.

Lab Book Reference: SLB-E-089

**Attempted synthesis of ethyl 4-[(2-methylpropan-2-yl)oxycarbonylamino]butanoate 211**

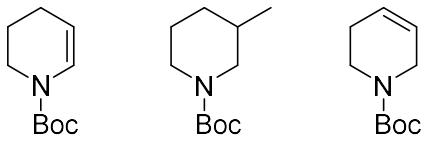


**167** **84** **211** **212**

Using general procedure C, *N*-Boc β-alanine **167** (221 mg, 1.17 mmol, 1.0 eq.), monomethyl malonate **84** (0.49 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.60 F $mol^{-1}$ (905 C of charge) of 15.3 V was passed for 1 h 19 min with an average current density of 57 mA $cm^{-2}$. This gave the crude product which did not contain *N*-Boc alkyl ester **211** by $^1$H NMR spectroscopy and mass spectrometry. Di-ester **212** and monomethyl malonate **84** were observed in the $^1$H NMR spectrum of the crude product but they were not isolated.

Lab Book Reference: SLB-E-090

***tert*-Butyl 1,2,3,6-tetrahydropyridine-1-carboxylate 213, *tert*-butyl 3-methylpiperidine-1-carbamate 166 and *tert*-butyl 1,2,3,4-tetrahydropyridine-1-carboxylate 214**



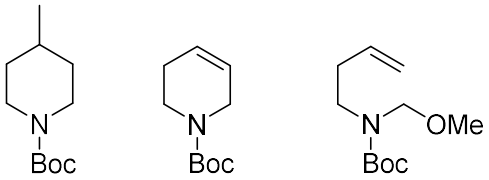
**213** **166** **214**

Using general procedure C, *N*-Boc 3-carboxylic acid piperidine **165** (268 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mg, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.65 F $mol^{-1}$ (928 C of charge) of 15.2 V was passed for 1 h 27 min with an average current density of 54 mA $cm^{-2}$. This gave the crude product. Purification by flash column chromatography on silica with 96:4 hexane-$Et_2O$ as eluent gave *N*-Boc alkene piperidine **214** (51 mg, 24%) as a colourless oil, $R_F$ (80:20 hexane-$Et_2O$) 0.41; IR (ATR) 2976, 2930, 1697 (C=O), 1650 (C=C), 1354, 1251, 1162, 1111, 1051 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) $\delta$ 6.84 (d, $J$ =

8.0 Hz, 0.4H, NCH), 6.71 (d, *J* = 8.0 Hz, 0.6H, NCH), 4.93-4.85 (m, 0.4H, NCH=C*H*), 4.79 (dt, *J* = 8.0, 4.0 Hz, 0.6H, NCH=C*H*), 3.59-3.49 (m, 2H, NCH), 2.06-1.98 (m, 2H, CH), 1.86-1.75 (m, 2H, CH), 1.48 (s, 9H, $CMe_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 152.5 (C=O), 125.8 (N*C*H=CH), 125.4 (N*C*H=CH), 105.8 (NCH=*C*H), 105.3 (NCH=*C*H), 80.6 (O*C*$Me_3$), 42.7 ($NCH_2$), 41.6 ($NCH_2$), 28.5 (C*Me*$_3$), 21.9 ($CH_2$), 21.6 ($CH_2$); MS (ESI) *m/z* 206 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{10}H_{17}NO_2$ $(M + Na)^+$ 206.1157, found 206.1157 (0 ppm error) and a 60:40 mixture of *N*-Boc 3-methyl piperidine **166** and *N*-Boc alkene piperidine **213** (42 mg, 25 mg, (11%) of **166** and 17 mg (7%) of **213**) as a colourless oil, $R_F$ (80:20 hexane-$Et_2O$) 0.29; IR (ATR) 2976, 2930, 1697 (C=O), 1650 (C=C), 1404, 1354, 1251, 1162, 1111 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) (60:40 mixture of **166** and **213**) $\delta$ 5.86-5.77 (m, 0.4H, $NCH_2C$*H*=CH), 5.70-5.60 (m, 0.4H, $NCH_2CH$=C*H*), 4.00-3.90 (m, 1.2H, NCH), 3.89-3.85 (m, 0.8H, NCH), 3.51-3.45 (m, 0.8H, NCH), 2.68 (ddd, *J* = 13.0, 12.0, 3.0 Hz, 0.6H, NCH), 2.33 (br s, 0.6H, NCH), 2.12 (br s, 0.8H, CH), 1.80-1.72 (m, 0.6H, CH), 1.68-1.48 (m, 1.2 H, CH), 1.46 (s, 3.6H, $CMe_3$) 1.45 (s, 5.4H, $CMe_3$), 1.42-1.35 (m, 0.6H, CH), 1.09-0.97 (m, 0.6H, CH), 0.86 (d, *J* = 6.5 Hz, 1.8H, CH*Me*); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ for *N*-Boc 3-methyl piperidine **166** 155.1 (C=O), 79.3 (O*C*$Me_3$), 51.1 ($NCH_2$), 44.6 ($NCH_2$), 33.2 (CH), 31.1 (CH), 28.6 (*C*$Me_3$), 25.2 (CH), 19.1 (Me); MS (ESI) *m/z* for **166** 222 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* for **166**, calcd for $C_{11}H_{21}NO_2$ $(M + Na)^+$ 222.1464, found 222.1467 (−1.2 ppm error). Spectroscopic data for *N*-Boc alkene piperidine **214**[145], *N*-Boc 3-methyl piperidine **166**[146] and *N*-Boc alkene piperidine **213**[147] are consistent with those reported in the literature.

Lab Book Reference: SLB-E-091

***tert*-Butyl 4-methylpiperidine-1-carbamate 217, *tert*-butyl 1,2,3,6-tetrahydropyridine-1-carboxylate 213 and *tert*-butyl *N*-(methoxymethyl)-*N*-(but-3-en-1-yl)carbamate 218**



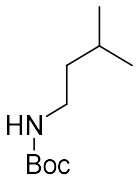

**217** **213** **218**

Using general procedure C, *N*-Boc 4-carboxylic acid piperidine **170** (268 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mg, 4.68 mmol, 4 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.60 F $mol^{-1}$ (901 C of charge) of 15.4 V was passed for 1 h 48 min with an average current density of 42 mA $cm^{-2}$. This gave the crude product. Purification by flash column chromatography on silica with 96:4 hexane-$Et_2O$ as eluent gave a 60:40 mixture of *N*-Boc 4-methyl piperidine **217** and *N*-Boc alkene piperidine **213** (44 mg, 25 mg (12%) of **217** and 19 mg (8%) of **213**) as a colourless oil, $R_F$ (80:20 hexane-$Et_2O$) 0.32; IR (ATR) 2925, 1692 (C=O), 1416, 1364, 1239, 1173, 1149 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.85-5.76 (m, 0.4H, $NCH_2CH$=C*H*), 5.70-5.61 (m, 0.4H, $NCH_2C$*H*=CH), 4.05 (br s, 1.2H, NCH), 3.90-3.85 (m, 0.8H, $NCH_2$) 3.48 (t, 0.8H, *J* = 5.5 Hz, $NCH_2$), 2.67 (br dd, *J* = 13.0, 12.5 Hz, 1.2H, NCH), 2.12 (br s, 0.8H, $NCH_2CH_2$), 1.64-1.54 (m, 1.2H, CH), 1.51-1.42 (m, 0.6H, CH), 1.46 (s, 3.6H, $CMe_3$) 1.45 (s, 5.4H, $CMe_3$), 1.07 (dddd, *J* = 12.5, 12.5, 12.0, 4.5 Hz, 1.2H CH), 0.93 (d, *J* = 7.0 Hz, 1.8H, CH*Me*); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 155.1 (C=O), 125.5 (=CH), 79.6 (O*C*$Me_3$), 79.3 (O*C*$Me_3$), 44.3 ($NCH_2$), 39.7 ($NCH_2$), 34.2 ($CH_2$), 31.1 (*C*HMe), 28.6 (C*Me*$_3$), 25.3 ($NCH_2CH_2$), 22.0 (CH*Me*) (some resonances not resolved); MS (ESI) *m/z* for **217** 222 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* for **217** calcd for $C_{11}H_{21}NO_2$ $(M + Na)^+$ 222.1464, found 222.1460 (+2.1 ppm error); MS (ESI) *m/z* for **213** 206 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* for **213** calcd for $C_{10}H_{17}NO_2$ $(M + Na)^+$ 206.1151, found 206.1145 (+3.0 ppm error) and *N*-Boc methoxy alkene **218** (44 mg, 17%) as a colourless oil, $R_F$ (80:20 hexane-$Et_2O$) 0.25; IR (ATR) 2972, 2933, 1698 (C=O), 1414, 1389, 1294, 1149, 1077, 1106 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.83-5.70 (m, 1H, C*H*=$CH_2$), 5.10-4.97 (m, 2H, CH=C*H*$_2$), 4.68 (s, 2H, NC*H*$_2$OMe), 3.36-3.25 (m, 2H, NC*H*$_2$$CH_2$), 3.27 (s, 3H, OMe), 2.37-2.36 (m, 2H, $NCH_2C$*H*$_2$), 1.47 (s, 9H, $CMe_3$); $^{13}$C NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 135.7 (*C*H=$CH_2$), 116.7 (CH=*C*$H_2$), 80.2 (O*C*$Me_3$), 79.2 (N*C*$H_2$OMe), 78.9

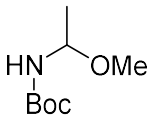
(N*C*H$_2$OMe), 55.6 (OMe), 55.4 (OMe), 46.0 (N*C*H$_2$CH$_2$), 45.6 (NCH$_2$*C*H$_2$), 33.8 (NCH$_2$*C*H$_2$), 33.1 (NCH$_2$*C*H$_2$), 28.5 (C*Me*$_3$); MS (ESI) *m/z* 238 [(M + Na)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{11}H_{21}NO_3$ (M + Na)$^+$ 238.1414, found 238.1411 (+1.1 ppm error). Spectroscopic data for **217**[148] and **218**[147] are consistent with those reported in the literature.

Lab Book Reference: SLB-E-102

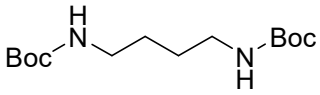
**_tert_-Butyl _N_-(3-methylbutyl)carbamate 222, _tert_-butyl _N_-(1-methoxyethyl)carbamate 180 and _tert_-butyl _N_-(4-{[(_tert_-butoxy)carbonyl]amino}butyl)carbamate 184**




**222**




**180**

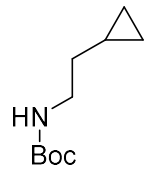



**184**

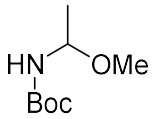
Using general procedure C, *N*-Boc β-alanine **167** (221 mg, 1.17 mmol, 1.0 eq.), *i*-PrCO$_2$H (0.43 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.58 F mol$^{-1}$ (893 C of charge) of 15.4 V was passed for 1 h 49 min with an average current density of 41 mA cm$^{-2}$. This gave the crude product which contained *N*-Boc 3-methylbutyl amine **222**, *N*-Boc methoxy amine **180** and di-*N*-Boc amine **184** in an unknown ratio. Purification by flash column chromatography on silica with 96:4 hexane-Et$_2$O as eluent gave *N*-Boc 3-methylbutyl amine **222** (21 mg, 10%) as a colourless oil, $R_F$ (80:20 hexane-Et$_2$O) 0.28; IR (ATR) 3354 (N-H), 2957, 2871, 1687 (C=O), 1518, 1365, 1249, 1167 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.46 (br s, 1H, NH), 3.17-3.05 (m, 2H, NCH$_2$), 1.65-1.53 (m, 1H, C*H*Me$_2$), 1.43 (s, 9H, CMe$_3$), 1.35 (dt, *J* = 7.0, 7.0 Hz, 2H, NCH$_2$C*H*$_2$), 0.89 (d, *J* = 7.0 Hz, 6H, CH*Me*$_2$); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 156.1 (C=O), 79.2 (O*C*Me$_3$), 39.0 (CH$_2$), 28.6 (C*Me*$_3$), 25.9 (*C*HMe$_2$), 22.6 (CH*Me*$_2$) (one CH$_2$ resonance not resolved); MS (ESI) *m/z* 210 [(M + Na)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{10}H_{21}NO_2$ (M + Na)$^+$ 210.1464, found 210.1466 (−0.7 ppm error) and di-*N*-Boc amine **184** (73 mg, 43%) as a white solid. *N*-Boc methoxy amine **180** was not isolated. Spectroscopic data are consistent with those reported in the literature.[149]

Lab Book Reference: SLB-E-100

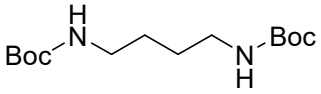
**_tert_-Butyl _N_-(2-cyclopropylethyl)carbamate 223, _tert_-butyl _N_-(1-methoxyethyl)carbamate 180 and _tert_-butyl _N_-(4-{[(_tert_-butoxy)carbonyl]amino}butyl)carbamate 184**




**223**




**180**

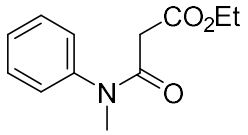



**184**

Using general procedure C, *N*-Boc β-alanine **167** (221 mg, 1.17 mmol, 1.0 eq.), cyclopropanoic acid (0.37 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.60 F $mol^{-1}$ (904 C of charge) of 15.4 V was passed for 1 h 29 min with an average current density of 31 mA $cm^{-2}$. This gave the crude product which contained *N*-Boc cyclopropyl amine **223**, *N*-Boc methoxy amine **180** and di-*N*-Boc amine **184** in an unknown ratio. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave *N*-Boc cyclopropyl amine **223** (40 mg, 18%) as a colourless oil, $R_F$ (90:10 hexane-$Et_2O$) 0.20; IR (ATR) 3354 (N-H), 2977, 2930, 1687 (C=O), 1514, 1364, 1249, 1166, 1014 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.61 (br s, 1H, NH), 3.26-3.08 (m, 2H, $NCH_2$), 1.43 (s, 9H, $CMe_3$), 1.37 (dt, $J$ = 7.0, 7.0 Hz, 2H, $NCH_2CH_2$), 0.71-0.59 (m, 1H, cyclopropyl-CH), 0.47-0.41 (m, 2H, cyclopropyl-CH), 0.08-0.02 (m, 2H, cyclopropyl-CH); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 156.1 (C=O), 79.2 ($OCMe_3$), 41.0 ($NCH_2$), 35.0 ($NCH_2CH_2$), 28.6 ($CMe_3$), 8.6 (cyclopropyl-CH), 4.2 (cyclopropyl-$CH_2$); MS (ESI) *m/z* 208 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{10}H_{19}NO_2$ $(M + Na)^+$ 208.1308, found 208.1313 (−2.2 ppm error) and di-*N*-Boc amine **184** (77 mg, 46%) as a white solid. *N*-Boc methoxy amine **180** was not isolated.

Lab Book Reference: SLB-E-093

**Ethyl 3-(methyl(phenyl)amino)-3-oxopropanoate 230**

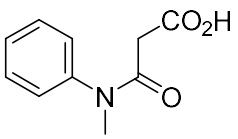


**230**

*N*-Methylaniline (1.50 mL, 13.8 mmol, 1.1 eq.), 2-chloro-1-methylpyridinium iodide (4.79 g, 18.8 mmol, 1.5 eq.) and $Et_3N$ (8.71 mL, 62.5 mmol, 5.0 eq.) were added to a stirred solution of ethyl malonate (1.48 mL, 12.5 mmol, 1.0 eq.) in $CH_2Cl_2$ (50 mL) at 0 °C under $N_2$. The resulting solution was stirred at 0 °C for 1 h. After being allowed to warm to rt, the solution was stirred at rt for 20 h. 3 M $HCl_{(aq)}$ (50 mL) was added and the two layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (2 × 50 mL). The combined organic extracts were washed with $H_2O$ (2 × 50 mL) and brine (2 × 50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 60:40 EtOAc-hexane as eluent gave ester **230** (1.50 g, 54%) as an orange oil, $R_F$ (60:40 EtOAc-hexane) 0.34; IR (ATR) 2982, 1735 (C=O, $CO_2Et$), 1657 (C=O, amide), 1595, 1495, 1381, 1154, 1118, 1028 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.43-7.36 (m, 2H, Ph), 7.37-7.31 (m, 1H, Ph), 7.24-7.19 (m, 2H, Ph), 4.10 (q, $J$ = 7.0 Hz, 2H, $OCH_2Me$), 3.28 (s, 3H, NMe), 3.18 (s, 2H, $CH_2C(O)$), 1.20 (t, $J$ = 7.0 Hz, 3H, $CH_2Me$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 167.8 (C=O), 166.1 (C=O), 143.6 (*ipso*-Ph), 130.0 (Ph), 128.4 (Ph), 127.3 (Ph), 61.3 ($OCH_2Me$), 41.6 ($CH_2C(O)$), 37.5 (NMe), 14.1 ($CH_2Me$); MS (ESI) *m/z* 244 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}NO_3$ $(M + Na)^+$ 244.0944, found 244.0949 (−2.0 ppm error). Spectroscopic data are consistent with those reported in the literature.[150]

Lab Book Reference: SLB 2-9

**3-(Methyl(phenyl)amino)-3-oxopropanoic acid 171**

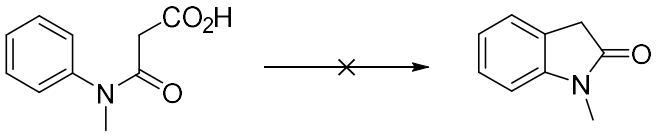


**171**

LiOH (891 mg, 37.2 mmol, 2.0 eq.) was added to a stirred solution of ester **230** (4.12 g, 18.6 mmol, 1.0 eq.) in THF (100 mL) and $H_2O$ (25 mL) at rt under Ar. The resulting solution was stirred at rt for 6 h and the solvent was evaporated under reduced pressure to give a residue. The residue was dissolved in water (100 mL) and acidified to pH 1-2 with 3 M $HCl_{(aq)}$ (7 mL). The mixture was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give acid **171** (3.44 g, 96%) as a white solid, mp 105-106 °C (lit.,[151] 120 °C, dec.); $R_F$ (99:1 EtOAc-AcOH) 0.25; IR (ATR) 3061 (OH), 2924, 1737 (C=O, $CO_2H$), 1620 (C=O, amide), 1590, 1495, 1395, 1123 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.52-7.41 (m, 3H, Ph), 7.21-7.16 (m, 2H, Ph), 3.35 (s, 3H, NMe), 3.12 (s, 2H, $CH_2C(O)$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 170.2 (C=O), 167.5 (C=O), 141.4 (*ipso*-Ph), 130.7 (Ph), 129.4 (Ph), 126.8 (Ph), 37.8 (NMe), 36.7 ($CH_2C(O)$); MS (ESI) *m/z* 216 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{10}H_{11}NO_3$ $(M + Na)^+$ 216.0631, found 216.0638 (−3.1 ppm error). Spectroscopic data are consistent with those reported in the literature.[152]

Lab Book Reference: SLB 2-13

**Attempted synthesis of 1-methylindolin-2-one 227**



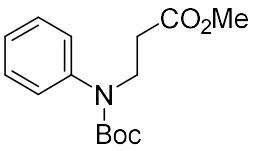

**171** **227**

Acid **171** (560 mg, 2.93 mmol, 1.0 eq.), KOH (8 mg, 0.15 mmol, 0.05 eq.) and MeOH (9 mL) were added to cell 2 and the cell was flushed with $N_2$. The rubber stopper containing the platinum electrodes and thermocouple was inserted into the cell. The electrodes were connected to the electrolysis circuit *via* crocodile clips. The power pack was turned on (voltage at 0 V) simultaneously with the data acquisition software (LabJack©). The voltage was quickly raised to the desired setting. The solution was stirred at rt until a current of 2.50 F $mol^{-1}$ (706 C) of 15.4 V had been passed (2 h 43 min) with an average current density of 72 mA $cm^{-2}$. Then, $CH_2Cl_2$ (10 mL) was added and the reaction mixture was washed with brine (10 mL). The aqueous washings were extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced

pressure to give the crude product which did not contain oxoindoline **227** by $^{1}$H NMR spectroscopy and mass spectrometry. Purification by flash column chromatography on silica with 60:40 EtOAc-hexane as eluent gave recovered starting acid **171** (457 mg, 81%) as a white solid.

Lab Book Reference: SLB-E-161

**Methyl 3-((*tert*-butoxycarbonyl)(phenyl)amino)propanoate 232**



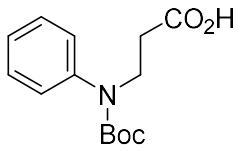

**232**

Methyl acrylate (1.98 mL, 21.9 mmol, 1.0 eq.) was added to a stirred solution of aniline (2.0 mL, 21.9 mmol, 1.0 eq.) in AcOH (6 mL) at rt under Ar. The resulting solution was stirred and heated at 70 °C for 20 h. After being allowed to cool to rt, $H_2O$ (50 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude amine as a brown oil. The crude amine was dissolved in MeOH (45 mL) at rt under Ar and $Et_3N$ (3.05 mL, 21.9 mmol, 1.0 eq.) was added. After cooling to 0 °C, di-*t*-butyl dicarbonate (5.26 g, 24.1 mmol, 1.1 eq.) was added slowly and the resulting solution was stirred at rt for 24 h. The solvent was then evaporated under reduced pressure to give a residue. The residue was dissolved in $CH_2Cl_2$ (100 mL) and washed with 1 M $HCl_{(aq)}$ (2 × 100 mL) and brine (2 × 100 mL). The organic layer was then dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 85:15 hexane-EtOAc as eluent gave carbamate **232** (2.75 g, 45%) as a red oil, $R_F$ (75:25 hexane-EtOAc) 0.41; IR (ATR) 2977, 1737 (C=O, ester), 1694 (C=O, Boc), 1496, 1391, 1366, 1157, 1106 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37-7.30 (m, 2H, Ph), 7.23-7.14 (m, 3H, Ph), 3.94 (t, $J$ = 7.5 Hz, 2H, $NCH_2$), 3.60 (s, 3H, OMe), 2.59 (t, $J$ = 7.5 Hz, 2H, $NCH_2CH_2$), 1.42 (s, 9H, $CMe_3$); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 172.1 (C=O, $CO_2Me$), 154.6 (C=O, Boc), 142.1 (*ipso*-Ph), 128.9 (Ph), 127.3 (Ph), 126.4 (Ph), 80.6 ($OCMe_3$), 51.7 (OMe), 46.2 ($NCH_2$), 33.5 ($NCH_2CH_2$), 28.4

(C*Me*$_3$); MS (ESI) *m/z* 302 [(M + Na)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{15}H_{21}NO_4$ (M + Na)$^+$ 302.1363, found 302.1359 (+1.1 ppm error).

Lab Book Reference: SLB 2-14

**3-((*tert*-Butoxycarbonyl)(phenyl)amino)propanoic acid 172**

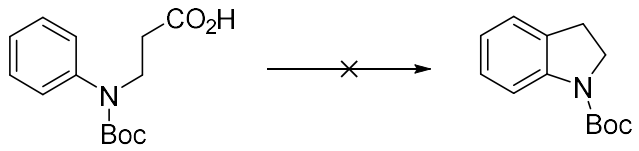



**172**

LiOH (833 mg, 34.8 mmol, 2.0 eq.) was added to a stirred solution of ester **232** (4.86 g, 17.4 mmol, 1.0 eq.) in THF (90 mL) and $H_2O$ (22 mL) at rt under Ar. The resulting solution was stirred at rt for 20 h and the solvent was evaporated under reduced pressure to give a residue. The residue was dissolved in water (150 mL) and acidified to pH 1-2 with 1 M $HCl_{(aq)}$ (20 mL). The mixture was extracted with $CH_2Cl_2$ (3 × 150 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give acid **172** (4.49 g, 97%) as a white solid, mp 53-55 °C; $R_F$ (99:1 EtOAc-AcOH) 0.25; IR (ATR) 3194 (OH), 2977, 1739 (C=O, $CO_2H$), 1700 (C=O, Boc), 1597, 1495, 1393, 1367, 1160 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37-7.31 (m, 2H, Ph), 7.24-7.15 (m, 3H, Ph), 3.94 (t, *J* = 7.5 Hz, 2H, $NCH_2$), 2.63 (t, *J* = 7.5 Hz, 2H, $NCH_2CH_2$), 1.42 (s, 9H, $CMe_3$); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 176.6 (C=O, $CO_2H$), 154.7 (C=O, Boc), 142.0 (*ipso*-Ph), 129.0 (Ph), 127.3 (Ph), 126.6 (Ph), 80.8 ($OCMe_3$), 45.9 ($NCH_2$), 33.3 ($NCH_2CH_2$), 28.3 (C*Me*$_3$); MS (ESI) *m/z* 288 [(M + Na)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{14}H_{19}NO_4$ (M + Na)$^+$ 288.1206, found 288.1209 (−1.1 ppm error). Spectroscopic data are consistent with those reported in the literature.[153]

Lab Book Reference: SLB 2-21

**Attempted synthesis of *tert*-butyl indoline-1-carboxylate 231**

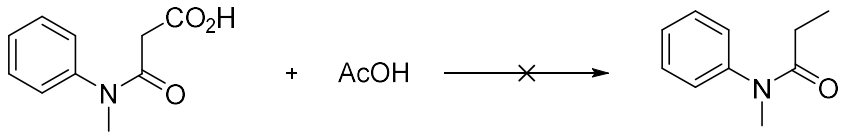



**172** **231**

Acid **172** (431 mg, 1.63 mmol, 1.0 eq.), KOH (5 mg, 0.08 mmol, 0.05 eq.) and MeOH (5 mL) were added to an ElectraSyn 2.0 10 mL glass cell with platinum electrodes and the cell was flushed with $N_2$. The cell was connected to the main ElectraSyn 2.0 set-up and a constant current experiment was selected. The solution was stirred at rt until a current of 2.50 F $mol^{-1}$ (706 C) of 11 V was passed with an average current density of 36 mA $cm^{-2}$. $CH_2Cl_2$ (10 mL) was then added and the reaction mixture was washed with brine (10 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which did not contain indoline **231** by $^1$H NMR spectroscopy and mass spectrometry. Purification by flash column chromatography on silica with 60:40 EtOAc-hexane as eluent gave recovered starting acid **172** (254 mg, 59%).

Lab Book Reference: SLB-E-164

**Attempted synthesis of *N*-methyl-*N*-phenylpropionamide 232**

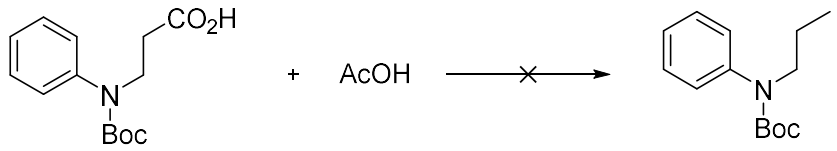



**171** **232**

Using general procedure C, acid **171** (226 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.60 F $mol^{-1}$ (904 C of charge) of 15.3 V was passed for 1 h 37 min with an average current density of 47 mA $cm^{-2}$. This gave the crude product which did not contain amide **232** by $^1$H NMR spectroscopy and mass spectrometry.

Lab Book Reference: SLB-E-163

**Attempted synthesis of *tert*-butyl phenyl(propyl)carbamate 233**

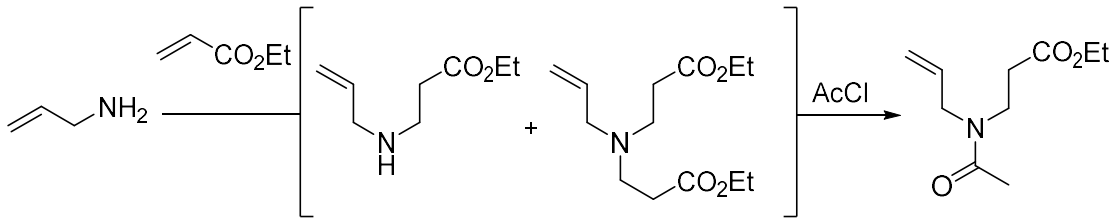



**172** **232**

Using general procedure C, acid **172** (310 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.60 F $mol^{-1}$ (905 C of charge) of 15.6 V was passed for 1 h 28 min with an average current density of 52 mA $cm^{-2}$. This gave the crude product which did not contain amide **232** by $^1$H NMR spectroscopy and mass spectrometry.

Lab Book Reference: SLB-E-168

**Ethyl 3-(*N*-allylacetamido)propanoate 236**



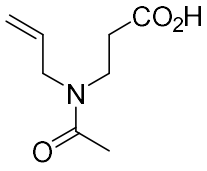

**234** **235** **236**

Allyl amine (1.87 mL, 25.0 mmol, 1.0 eq.) was added slowly to a stirred solution of ethyl acrylate (2.72 mL, 25.0 mmol, 1.0 eq.) in EtOH (50 mL) at rt. The resulting solution was stirred at rt for 72 h and the solvent was evaporated under reduced pressure to give a 92:8 mixture of amine **234** and amine **235** (3.99 g, 3.49 g (89%) of **234**) as a colourless oil, $^1$H NMR (400 MHz, $CDCl_3$) for **234** $\delta$ 5.94-5.82 (m, 1H, C*H*=$CH_2$), 5.21-5.06 (m, 2H, C$H_2$=CH), 4.14 (q, $J$ = 7.0 Hz, 2H, OC$H_2$Me), 3.26 (ddd, $J$ = 6.0, 1.5, 1.5 Hz, 2H, NC$H_2$CH), 2.87 (t, $J$ = 6.5 Hz, 2H, NC$H_2$$CH_2$), 2.51 (t, $J$ = 6.5 Hz, 2H, $NCH_2$C$H_2$), 1.26 (t, $J$ = 7.0 Hz, 3H, $CH_2$*Me*) and for **235** $\delta$ 5.83-5.73 (m, 1H, C*H*=$CH_2$), 5.21-5.06 (m, 2H, C$H_2$=CH), 4.12 (q, $J$ = 7.0 Hz, 4H, OC$H_2$Me), 3.11-3.07 (m, 2H, NC$H_2$CH), 2.78 (t, $J$ = 7.5 Hz, 4H, NC$H_2$$CH_2$), 2.44 (t, $J$ = 7.5 Hz, 4H, $NCH_2$C$H_2$), 1.25 (t, $J$ = 7.0 Hz, 6H,

$CH_2$*Me*). The crude amines were dissolved in $CH_2Cl_2$ (100 mL) at rt under Ar. After cooling to 0 °C, acetyl chloride (4.54 mL, 74.9 mmol, 3.0 eq.) and $Et_3N$ (10.6 mL, 74.9 mmol, 3.0 eq.) were added dropwise. The resulting solution was stirred at rt for 20 h. 1 M $HCl_{(aq)}$ (60 mL) was added and the two layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 60:40 hexane-EtOAc as eluent gave ester **236** (4.25 g, 85% over 2 steps) as a pale brown oil, $R_F$ (90:5:5 $CH_2Cl_2$-MeOH-AcOH) 0.61; IR (ATR) 2982, 2934, 1730 (C=O, $CO_2$Et), 1646 (C=O, amide), 1416, 1190, 1017 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) $\delta$ 5.90-5.64 (m, 1H, C*H*=$CH_2$), 5.26-5.08 (m, 2H, C$H_2$=CH), 4.15 (q, *J* = 7.0 Hz, 0.6H, OC$H_2$Me), 4.12 (q, *J* = 7.0 Hz, 1.4H, OC$H_2$Me), 3.98 (br d, *J* = 6.0 Hz, 0.6H, NC$H_2$CH), 3.96-3.93 (m, 1.4H, NC$H_2$CH), 3.59 (t, *J* = 7.0 Hz, 0.6H, NC$H_2CH_2$), 3.58 (t, *J* = 7.0 Hz, 1.4H, NC$H_2CH_2$), 2.60 (t, *J* = 7.0 Hz, 1.4H, $NCH_2CH_2$), 2.56 (t, *J* = 7.0 Hz, 0.6H, $NCH_2CH_2$), 2.16 (s, 0.9H, MeC(O)), 2.06 (s, 2.1H, MeC(O)), 1.26 (t, *J* = 7.0 Hz, 0.9H, $CH_2$*Me*), 1.25 (t, *J* = 7.0 Hz, 2.1H, $OCH_2$*Me*); $^{13}$C NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 172.2 (C=O), 171.0 (C=O), 133.2 (*C*H=$CH_2$), 132.8 (*C*H=$CH_2$), 117.3 (*C*$H_2$=CH), 116.6 (*C*$H_2$=CH), 60.9 (O*C*$H_2$Me), 60.6 (O*C*$H_2$Me), 52.0 (N*C*$H_2$CH), 43.7 (N*C*$H_2CH_2$), 42.6 (N*C*$H_2CH_2$), 33.6 ($NCH_2$*C*$H_2$), 33.0 ($NCH_2$*C*$H_2$), 21.5 (*Me*C(O)), 21.4 (*Me*C(O)), 14.2 ($OCH_2$*Me*); MS (ESI) *m/z* 200 [(M + H)$^+$, 100], 222 [(M + Na)$^+$, 77]; HRMS (ESI) *m/z* calcd for $C_{10}H_{17}NO_3$ (M + H)$^+$ 200.1281, found 200.1286 (−2.6 ppm error).

Lab Book Reference: SLB 1-36

**Ethyl 3-(*N*-allylacetamido)propanoic acid 110**



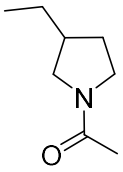

**110**

LiOH (1.02 g, 42.6 mmol, 2.0 eq.) was added to a stirred solution of ester **236** (4.24 g, 21.3 mmol, 1.0 eq.) in THF (100 mL) and $H_2O$ (27 mL) at rt under Ar. The resulting solution was stirred at rt for 2 h and the solvent was evaporated under reduced pressure

to give a residue. The residue was dissolved in brine (100 mL) and acidified to pH 1-2 using 3 M $HCl_{(aq)}$ (15 mL). The mixture was extracted with $CH_2Cl_2$ (3 × 80 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give acid **110** (3.37 g, 93%) as a dark brown solid, mp 61-62 °C, $R_F$ (90:5:5 $CH_2Cl_2$-MeOH-AcOH) 0.43; IR (ATR) 2926 (O-H), 1721 (C=O, $CO_2H$), 1596 (C=O, amide), 1367, 1195, 918 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers) $\delta$ 5.86-5.68 (m, 1H, C*H*=$CH_2$), 5.25-5.10 (m, 2H, C$H_2$=CH), 4.03-3.92 (m, 2H, NC$H_2$CH), 3.61 (t, $J$ = 7.0 Hz, 0.5H, NC$H_2$C$H_2$), 3.60 (t, $J$ = 7.0 Hz, 1.5H, NC$H_2$C$H_2$), 2.66 (t, $J$ = 7.0 Hz, 1.5H, NC$H_2$C$H_2$), 2.61 (t, $J$ = 7.0 Hz, 0.5H, NC$H_2$C$H_2$), 2.18 (s, 0.75H, Me), 2.08 (s, 2.25H, Me); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 175.7 (C=O), 174.6 (C=O), 172.1 (C=O), 171.1 (C=O), 132.9 (*C*H=$CH_2$), 132.3 (*C*H=$CH_2$), 117.6 (*C*$H_2$=CH), 117.0 (*C*$H_2$=CH), 52.1 (N*C*$H_2$CH), 47.8 (N*C*$H_2$CH), 43.6 (N*C*$H_2$C$H_2$), 42.7 (N*C*$H_2$C$H_2$), 33.3 (NC$H_2$*C*$H_2$), 32.9 (NC$H_2$*C*$H_2$), 21.2 (Me); MS (ESI) *m/z* 194 [$(M + Na)^+$, 100], 172 [$(M + H)^+$, 50]; HRMS (ESI) *m/z* calcd for $C_8H_{13}NO_3$ $(M + H)^+$ 172.0968, found 172.0972 (−2.1 ppm error).

Lab Book Reference: SLB 1-39-3

**1-(3-Ethylpyrrolidin-1-yl)ethan-1-one 111**




**111**

Using general procedure B under air, *N*-Ac alkene acid **110** (200 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mg, 4.68 mmol, 4 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.62 F $mol^{-1}$ (916 C of charge) of 15.1 V was passed for 1 h 46 min with an average current density of 44 mA $cm^{-2}$. This gave the crude product. Purification by flash column chromatography on silica with 95:5 $CH_2Cl_2$-acetone as eluent gave *N*-Ac pyrrolidine **111** (59 mg, 35%) as a brown oil, $R_F$ (90:10 $CH_2Cl_2$-acetone) 0.26; IR (ATR) 2932, 1623 (C=O), 1421, 1244, 1036 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) $\delta$ 3.75-3.47 (m, 2H, NCH), 3.42-3.26 (m, 1H, NCH),

3.01-2.90 (m, 1H, NCH), 2.21-1.94 (m, 2H, $NCH_2CH$), 2.02 (br s, 3H, MeC(O)), 1.63-1.36 (m, 3H, $CH_2Me$ and $NCH_2CH$), 0.94 (t, $J$ = 7.5 Hz, 1.5H, $CH_2Me$), 0.93 (t, $J$ = 7.5 Hz, 1.5 H, $CH_2Me$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 169.5 (C=O), 169.0 (C=O) 52.9 ($NCH_2$), 50.9 ($NCH_2$), 17.2 ($NCH_2$), 45.3 ($NCH_2$), 41.2 ($NCH_2CH$), 39.6 ($NCH_2CH$), 31.8 ($NCH_2CH_2$), 30.3 ($NCH_2CH_2$), 26.0 ($CH_2Me$), 25.9 ($CH_2Me$), 22.4 ($MeC(O)$), 22.1 ($MeC(O)$), 12.5 ($CH_2Me$); MS (ESI) *m/z* 164 [$(M + Na)^+$, 100], 142 [$(M + H)^+$, 45]; HRMS (ESI) *m/z* calcd for $C_8H_{15}NO$ $(M + H)^+$ 142.1226, found 142.1224 (+1.9 ppm error).

Lab Book Reference: SLB-E-028

Using general procedure B under air, *N*-Ac alkene acid **110** (200 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mg, 4.68 mmol, 4 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.66 F $mol^{-1}$ (939 C of charge) of 9.5 V was passed for 3 h 12 min with an average current density of 25 mA $cm^{-2}$. This gave the crude product. Purification by flash column chromatography on silica with 93:7 $CH_2Cl_2$-acetone as eluent gave *N*-Ac pyrrolidine **111** (60 mg, 36%) as a brown oil.

Lab Book Reference: SLB-E-023

Using general procedure B under $N_2$, *N*-Ac alkene acid **110** (200 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mg, 4.68 mmol, 4 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.72 F $mol^{-1}$ (972 C of charge) of 14.6 V was passed for 2 h 0 min with an average current density of 41 mA $cm^{-2}$. This gave the crude product. Purification by flash column chromatography on silica with 91:9 $CH_2Cl_2$-acetone as eluent gave *N*-Ac pyrrolidine **111** (61 mg, 37%) as a brown oil.

Lab Book Reference: SLB-E-022

Using general procedure B under $N_2$, *N*-Ac alkene acid **110** (200 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mg, 4.68 mmol, 4 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.68 F $mol^{-1}$ (951 C of charge) of 9.5 V was passed for 3 h

16 min with an average current density of 24 mA $cm^{-2}$. This gave the crude product. Purification by flash column chromatography on silica with 97:3 $CH_2Cl_2$-acetone as eluent gave *N*-Ac pyrrolidine **111** (72 mg, 44%) as a brown oil.

Lab Book Reference: SLB-E-020

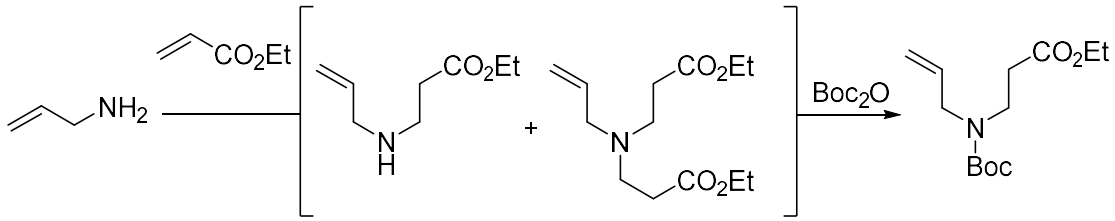
Using general procedure B under $N_2$, *N*-Ac alkene acid **110** (200 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mg, 4.68 mmol, 4 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.54 F $mol^{-1}$ (868 C of charge) of 6 V was passed for 6 h 10 min with an average current density of 12 mA $cm^{-2}$. This gave the crude product. Purification by flash column chromatography on silica with 93:7 $CH_2Cl_2$-acetone as eluent gave *N*-Ac pyrrolidine **111** (39 mg, 23%) as a brown oil.

Lab Book Reference: SLB-E-021

Using general procedure B under $N_2$, *N*-Ac alkene acid **110** (200 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mg, 4.68 mmol, 4 eq.) and KOH (3 mg, 0.06 mmol, 0.05 eq.) in MeOH (9 mL) were used. A current of 1.50 F $mol^{-1}$ (849 C of charge) of 15.4 V was passed for 5 h 45 min with an average current density of 12 mA $cm^{-2}$. This gave the crude product. Purification by flash column chromatography on silica with 95:5 $CH_2Cl_2$-acetone as eluent gave *N*-Ac pyrrolidine **111** (55 mg, 33%) as a brown oil.

Lab Book Reference: SLB-E-018

**Ethyl 3-(allyl(*t*-butoxycarbonyl)aminopropanoate 237**

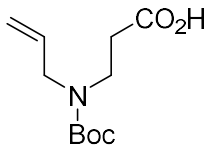



**224** **235** **237**

Allyl amine (0.37 mL, 4.99 mmol, 1.0 eq.) was added slowly to a stirred solution of ethyl acrylate (0.54 mL, 4.99 mmol, 1.0 eq.) in EtOH (10 mL) at rt. The resulting solution was stirred at rt for 72 h and the solvent was evaporated under reduced pressure to give a 93:7 mixture (by $^1$H NMR spectroscopy) of amine **234** and amine **235** (733 mg, 682 mg (87%) of **234**) as a colourless oil. The crude amines were dissolved in $CH_2Cl_2$ (15 mL) at rt under Ar. After cooling to 0 °C, a solution of di-*t*-butyl dicarbonate (1.198 g, 5.49 mmol, 1.1 eq.) in $CH_2Cl_2$ (15 mL) was added slowly and the resulting solution was stirred at rt for 24 h. 1 M $HCl_{(aq)}$ (20 mL) was added and the two layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 hexane-$Et_2O$ as eluent gave carbamate **237** (945 mg, 74% over 2 steps) as a colourless oil, $R_F$ (80:20 hexane-$Et_2O$) 0.38; IR (ATR) 2978, 1733 (C=O, $CO_2Et$), 1693 (C=O, Boc), 1464, 1366, 1161 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.83-5.67 (m, 1H, C*H*=$CH_2$), 5.17-5.08 (m, 2H, C*H*$_2$=CH), 4.12 (q, *J* = 7.0 Hz, 2H, OC*H*$_2$Me), 3.90-3.77 (br m, 2H, NC*H*$_2$CH), 3.46 (br s, 2H, NC*H*$_2$CH$_2$), 2.55 (br s, 2H, NCH$_2$C*H*$_2$), 1.45 (br s, 9H, $CMe_3$), 1.25 (t, *J* = 7.0 Hz, $CH_2$*Me*); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 155.0 (C=O, Boc), 134.2 (*C*H=$CH_2$), 116.3 (*C*H$_2$=CH), 80.0 (O*C*Me$_3$), 60.7 (O*C*H$_2$Me), 50.8 (N*C*H$_2$CH), 42.9 (N*C*H$_2$CH$_2$), 34.1 (NCH$_2$*C*H$_2$), 28.5 (C*Me*$_3$), 14.3 (OCH$_2$*Me*) (C=O, $CO_2Et$ resonance not resolved); MS (ESI) *m/z* 537 [(2M + Na)$^+$, 100], 280 [(M + Na)$^+$, 51], 258 [(M + H$^+$), 13]; HRMS (ESI) *m/z* calcd for $C_{13}H_{23}NO_4$ (M + H)$^+$ 258.1700 found 258.1702 (−1.0 ppm error). Spectroscopic data are consistent with those reported in the literature.[154]

Lab Book Reference: SLB 1-55-3

**3-(Allyl(*t*-butoxycarbonyl)amino)propanoic acid 173**



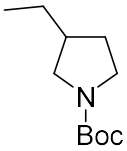

**173**

Ester **237** (1.14 g, 4.15 mmol, 1.0 eq.) was added to a stirred solution of NaOH (332 mg, 8.30 mmol, 2.0 eq.) in THF (12 mL) and EtOH (17 mL) at rt. The resulting solution was

stirred at rt for 20 h and the solvent was evaporated under reduced pressure to give a brown oil. $H_2O$ (20 mL) was then added to the oil and the mixture was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined aqueous extracts were acidified to pH 1 using 1 M $HCl_{(aq)}$ (12 mL) and a white precipitate formed. The mixture was extracted with $CH_2Cl_2$ (3 × 20 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give acid **173** (881 mg, 96%) as a brown oil, IR (ATR) 2977 (O-H), 1694 (C=O), 1658 (C=O), 1408, 1367, 1159 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.84-5.69 (m, 1H, C*H*=$CH_2$), 5.18-5.07 (m, 2H, C$H_2$=CH), 3.84 (br s, 2H, NC$H_2$CH), 3.47 (br t, $J$ = 6.0 Hz, 2H, NC$H_2$$CH_2$), 2.62 (br s, 2H, $NCH_2$C$H_2$), 1.45 (s, 9H, $CMe_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 177.3 (C=O, COOH), 155.4 (C=O, Boc), 133.9 (*C*H=$CH_2$), 116.6 (*C*$H_2$=CH), 80.2 (O*C*$Me_3$), 49.9 (N*C*$H_2$CH), 42.7 (N*C*$H_2$$CH_2$), 33.5 ($NCH_2$*C*$H_2$), 28.3 (C*Me*$_3$); MS (ESI) *m/z* 230 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{11}H_{19}NO_4$ $(M + H)^+$ 230.1387, found 230.1382 (+2.1 ppm error).

Lab Book Reference: SLB 1-4-2

***tert*-Butyl 3-ethylpyrrolidine-1-carboxylate 238**




**238**

Using general procedure B under $N_2$, *N*-Boc alkene acid **173** (268 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mg, 4.68 mmol, 4 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.69 F $mol^{-1}$ (956 C of charge) of 15.2 V was passed for 1 h 52 min with an average current density of 43 mA $cm^{-2}$. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-Boc pyrrolidine **238** (97 mg, 41%) as a colourless oil, $R_F$ (90:10 hexane-$Et_2O$) 0.10; IR (ATR) 2963, 1876, 1693 (C=O), 1398, 1364, 1168, 1140, 1105 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) $\delta$ 3.61-3.15 (m, 3H, NCH), 2.92-2.77 (m, 1H, NCH), 2.10-1.91 (m, 2H, CH), 1.49-1.33 (m, 3H, C$H_2$Me, CH), 1.46 (s, 9H, $CMe_3$), 0.92 (t, $J$ = 7.5 Hz, 3H, $CH_2$*Me*); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$

154.8 (C=O), 79.0 (O*C*Me$_3$), 52.6 (NCH$_2$), 52.2 (NCH$_2$), 46.0 (NCH$_2$), 45.6 (NCH$_2$), 41.0 (CH), 40.2 (CH), 31.7 (CH$_2$), 31.0 (CH$_2$), 28.7 (C*Me$_3$*), 26.3 (C*H$_2$*Me), 12.7 (CH$_2$*Me*); MS (ESI) *m/z* 222 [(M + Na)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{11}H_{21}NO_2$ (M + Na)$^+$ 222.1464, found 222.1467 (−1.3 ppm error).

Lab Book Reference: SLB-E-029

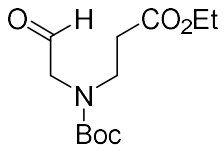
Using general procedure B under air, *N*-Boc alkene acid **173** (268 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mg, 4.68 mmol, 4 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.61 F mol$^{-1}$ (908 C of charge) of 15.2 V was passed for 1 h 49 min with an average current density of 42 mA cm$^{-2}$. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-Boc pyrrolidine **238** (92 mg, 39%) as a colourless oil,

Lab Book Reference: SLB-E-030

Using general procedure C, *N*-Boc alkene acid **173** (268 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mg, 4.68 mmol, 4 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.59 F mol$^{-1}$ (899 C of charge) of 15.2 V was passed for 1 h 17 min with an average current density of 46 mA cm$^{-2}$. This gave the crude product. Purification by flash column chromatography on silica with 93:7 hexane-EtOAc as eluent gave *N*-Boc pyrrolidine **238** (123 mg, 53%) as a colourless oil.

Lab Book Reference: SLB-E-084

**Ethyl 3-((*tert*-butoxycarbonyl)(2-oxoethyl)amino)propanoate 241**

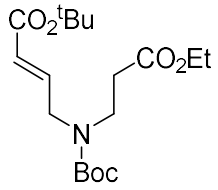



**241**

Potassium osmate (60 mg, 0.16 mmol, 0.01 eq.) was added to a stirred solution of alkene **237** (4.13 g, 16.4 mmol, 1.0 eq.) and *N*-methylmorpholine-*N*-oxide (2.50 g, 24.7 mmol, 1.5 eq.) in acetone (180 mL) and water (20 mL) at rt under Ar. The resulting solution was stirred at rt for 48 h. Sodium metabisulfite (0.5 g) was added and the mixture was stirred at rt for 1 h. The solids were removed by fitration through Celite® and washed with acetone (3 × 50 mL). The filtrate was evaporated under reduced pressure to give the crude diol as a white solid. The solid was dissolved in MeOH (100 mL) and $H_2O$ (10 mL) and $NaIO_4$ (5.27 g, 24.7 mmol, 1.5 eq.) was added. The resulting solution was stirred at rt for 4 h. Then, the solvent was evaporated under reduced pressure to give a residue. The residue was partitioned between brine (50 mL) and $CH_2Cl_2$ (50 mL) and the two layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (2 × 50 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give aldehyde **241** (3.86 g, 91%) as a colourless oil, IR (ATR) 3482, 2979 (CHO), 2934, 1733 (C=O), 1696 (C=O, Boc), 1465, 1368, 1164 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) $\delta$ 9.53 (s, 0.5H, CHO), 9.50 (s, 0.5H, CHO), 4.15-4.07 (m, 2H, OC$H_2$Me), 4.06 (s, 1H, NC$H_2$CHO), 3.98 (s, 1H, NC$H_2$CHO), 3.55 (t, $J$ = 6.5 Hz, 1H, NC$H_2$CH$_2$), 3.51 (t, $J$ = 6.5 Hz, 1H, NC$H_2$CH$_2$), 2.60 (t, $J$ = 6.5 Hz, 1H, NCH$_2$C$H_2$), 2.57 (t, $J$ = 6.5 Hz, 1H, NCH$_2$C$H_2$), 1.46 (s, 4.5H, CMe$_3$), 1.39 (s, 4.5H, CMe$_3$), 1.24 (t, $J$ = 7.0 Hz, 1.5H, CH$_2$*Me*), 1.23 (t, $J$ = 7.0 Hz, 1.5H, CH$_2$*Me*); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 198.8 (C=O, CHO), 198.6 (C=O, CHO), 172.5 (C=O, $CO_2$Et), 172.1 (C=O, $CO_2$Et), 155.6 (C=O, Boc), 155.0 (C=O, Boc), 81.1 (O*C*Me$_3$), 81.0 (O*C*Me$_3$), 60.9 (O*C*H$_2$Me), 60.8 (O*C*H$_2$Me), 59.3 (N*C*H$_2$CHO), 58.8 (N*C*H$_2$CHO), 45.3 (N*C*H$_2$CH$_2$), 45.1 (N*C*H$_2$CH$_2$), 34.4 (NCH$_2$*C*H$_2$), 34.0 (NCH$_2$*C*H$_2$), 28.4 (C*Me*$_3$), 28.3 (C*Me*$_3$), 14.3 (CH$_2$*Me*); MS (ESI) *m/z* 314 [(M + Na + MeOH)$^+$, 100], 282 [(M + Na)$^+$, 14]; HRMS (ESI) *m/z* calcd for $C_{12}H_{21}NO_5$ (M + Na)$^+$ 282.1312, found 282.1310 (+0.8 ppm error). This experiment was carried out by another member of the group under my supervision.[89]

Lab Book Reference: SLB 1-86

***tert*-Butyl (*E*)-4-((*tert*-butoxycarbonyl)(3-ethoxy-3-oxopropyl)amino)but-2-enoate 242**

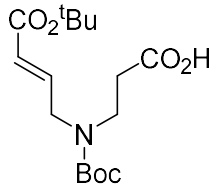



**242**

*t*-Butyl diethylphosphonoacetate (4.26 g, 19.0 mmol, 1.5 eq.) was added dropwise to a stirred solution of aldehyde **241** (3.29 g, 12.7 mmol, 1.0 eq.) and dry LiOH (780 mg, 19.0 mmol, 1.5 eq.) in MeCN (35 mL) at 0 °C under Ar. After being allowed to warm to rt, the resulting solution was stirred at rt for 24 h. The solvent was evaporated under reduced pressure to give a residue. The residue was dissolved in EtOAc (50 mL) and $H_2O$ (50 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (3 × 50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 hexane-$Et_2O$ as eluent gave ester **242** (2.38 g, 53%) as a colourless oil, $R_F$ (80:20 hexane-$Et_2O$) 0.18; IR (ATR) 2977, 2933, 1733 (C=O, $CO_2Et$), 1696 (br, C=O), 1408, 1366, 1148 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.72 (dt, $J$ = 15.5, 5.0 Hz, 1H, $NCH_2CH$=CH), 5.76 (dt, $J$ = 15.5, 2.0 Hz, 1H, $NCH_2CH$=C*H*), 4.12 (q, $J$ = 7.0 Hz, 2H, $OCH_2Me$), 4.05-3.78 (m, 2H, $NCH_2CH$=CH), 3.55-3.34 (m, 2H, $NCH_2CH_2$), 2.62-2.48 (m, 2H, $NCH_2CH_2$), 1.51-1.40 (m, 18H, $CMe_3$), 1.25 (t, $J$ = 7.0 Hz, 3H, $CH_2Me$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 172.2 (C=O, $CO_2Et$), 171.9 (C=O, $CO_2Et$), 165.5 (C=O, $CO_2CMe_3$), 155.2 (C=O, Boc), 142.9 ($NCH_2CH$=CH), 142.7 ($NCH_2CH$=CH), 123.9 ($NCH_2CH$=CH), 123.7 ($NCH_2CH$=CH), 80.7 ($OCMe_3$), 80.5 ($OCMe_3$), 80.4 ($OCMe_3$), 60.8 ($OCH_2Me$), 49.1 ($NCH_2CH$=CH), 48.2 ($NCH_2CH$=CH), 43.6 ($NCH_2CH_2$), 43.4 ($NCH_2CH_2$), 34.1 ($NCH_2CH_2$), 33.7 ($NCH_2CH_2$), 28.5 ($CMe_3$), 28.2 ($CMe_3$), 14.3 ($CH_2Me$); MS (ESI) *m/z* 380 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{18}H_{31}NO_6$ $(M + Na)^+$ 380.2044, found 380.2044 (0.0 ppm error).

Lab Book Reference: SLB 1-86

**(*E*)-3-((4-(*tert*-butoxy)-4-oxobut-2-en-1-yl)(*tert*-butoxycarbonyl)amino)propanoic acid 239**

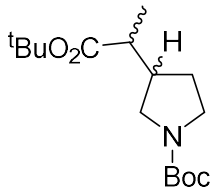



**239**

LiOH (130 mg, 5.43 mmol, 2.0 eq.) was added to a stirred solution of ester **242** (1.02 g, 2.72 mmol, 1.0 eq.) in THF (14 mL) and $H_2O$ (3.5 mL) at rt under Ar. The resulting solution was stirred at rt for 6 h and the solvent was evaporated under reduced pressure to give a residue. The residue was dissolved in water (100 mL) and acidified to pH 1-2 with 1 M $HCl_{(aq)}$ (6 mL). The mixture was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give acid **239** (893 mg, quant) as a pale yellow solid, mp 80-82 °C; IR (ATR) 3126 (O-H), 2977, 1700 (br, C=O), 1478, 1393, 1367, 1153 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.71 (dt, $J$ = 15.5, 5.0 Hz, 1H, $NCH_2CH$=CH), 5.75 (dt, $J$ = 15.5, 2.0 Hz, 1H, $NCH_2CH$=C*H*), 4.04-3.92 (m, 2H, $NCH_2CH$=CH), 3.46 (br s, 2H, $NCH_2CH_2$), 2.98-2.53 (m, 2H, $NCH_2CH_2$), 1.47-1.40 (m, 18H, $CMe_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 176.6 (C=O, $CO_2H$), 165.5 (C=O, $CO_2CMe_3$), 155.3 (C=O, Boc) 142.5 ($NCH_2CH$=CH), 124.0 ($NCH_2CH$=*C*H), 80.8 (O*C*$Me_3$), 48.3 ($NCH_2CH$=CH), 43.2 ($NCH_2CH_2$), 33.4 ($NCH_2CH_2$), 28.4 (C*Me*$_3$), 28.2 (C*Me*$_3$) (one O*C*$Me_3$ resonance not resolved); MS (ESI) *m/z* 352 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{16}H_{27}NO_6$ $(M + Na)^+$ 352.1731, found 352.1735 (−1.2 ppm error).

Lab Book Reference: SLB 1-95

***tert*-Butyl 3-(1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate 240**



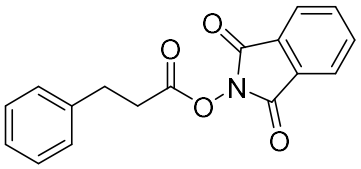

**240**

Using general procedure C, *N*-Boc acid **239** (385 mg, 1.17 mmol, 1.0 eq.), AcOH (0.27 mL, 4.68 mmol, 4.0 eq.) and KOH (16 mg, 0.29 mmol, 0.25 eq.) in MeOH (9 mL) were used. A current of 1.6 F $mol^{-1}$ (954 C of charge) of 15.2 V was passed for 1 h 38 min with an average current density of 49 mA $cm^{-2}$. This gave the crude product. Purification by flash column chromatography on silica with 70:30 hexane-EtOAc as eluent gave 50:50 mixture of diastereomeric *N*-Boc pyrrolidines **240** (198 mg, 57%) as a colourless oil, $R_F$ (70:30 hexane-$Et_2O$) 0.22; IR (ATR) 2975, 2933, 1725 (C=O, $CO_2CMe_3$), 1695 (C=O, Boc), 1401, 1365, 1149, 1125 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) $\delta$ 3.61-3.38 (m, 2H, NCH), 3.29-3.15 (m, 1H, NCH), 3.01-2.85 (m, 1H, NCH), 2.32-2.16 (m, 2H, C*H*Me and $NCH_2CH$), 2.04-1.91 (m, 1H, $NCH_2CH$), 1.61-1.40 (m, 1H, $NCH_2CH$), 1.45-1.41 (m, 18H, $CMe_3$), 1.14 (d, $J$ = 7.0 Hz, 1.5 H, CH*Me*), 1.12 (d, $J$ = 7.0 Hz, 1.5 H, CH*Me*); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 175.0 (C=O, $CO_2CMe_3$), 174.9 (C=O, $CO_2CMe_3$), 154.6 (C=O, Boc), 154.5 (C=O, Boc), 80.7 (O*C*$Me_3$), 80.6 (O*C*$Me_3$), 80.5 (O*C*$Me_3$), 79.2 (O*C*$Me_3$), 79.1 (O*C*$Me_3$), 50.3 ($NCH_2$), 49.8 ($NCH_2$), 49.6 ($NCH_2$), 49.4 ($NCH_2$), 46.0 ($NCH_2$), 45.9 ($NCH_2$), 45.6 ($NCH_2$), 45.3 ($NCH_2$), 44.3 (*C*HMe), 44.2 (*C*HMe), 44.1 (*C*HMe), 44.0 (*C*HMe), 42.4 (*C*HMe), 42.3 (*C*HMe), 41.6 (*C*HMe), 41.5 (*C*HMe), 30.5 ($NCH_2CH_2$), 30.4 ($NCH_2CH_2$), 29.9 ($NCH_2CH_2$), 29.7 ($NCH_2CH_2$), 29.2 ($NCH_2CH_2$), 28.6 (C*Me*$_3$), 28.5 (C*Me*$_3$), 28.3 ($NCH_2CH$), 28.2 ($NCH_2CH$), 28.1 (C*Me*$_3$), 16.4 (CH*Me*), 16.2 (CH*Me*), 15.9 (CH*Me*) (some resonances not resolved); MS (ESI) *m/z* 322 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{16}H_{29}NO_4$ $(M + Na)^+$ 322.1989, found 322.1988 (+0.2 ppm error).

Lab Book Reference: SLB-E-143

## 4.6 Experimental for Chapter Three

### 1,3-Dioxoisoindolin-2-yl 3-phenylpropanoate 282

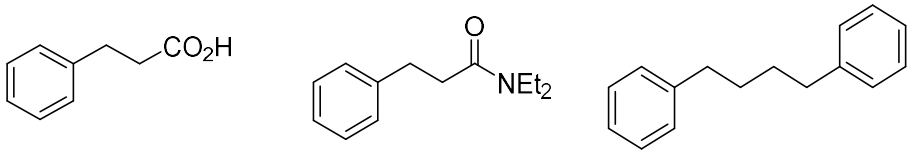


**282**

EDC (4.2 mL, 24 mmol, 1.2 eq.) was added dropwise to a stirred solution of hydrocinnamic acid (3.0 g, 20 mmol, 1.0 eq.), *N*-hydroxyphthalimide (3.26 g, 20 mmol, 1.0 eq,) and DMAP (3.18 g, 26 mmol, 1.3 eq.) in $CH_2Cl_2$ (70 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 20 h. The mixture was then washed with 1 M $HCl_{(aq)}$ (50 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with sat. $NaHCO_{3(aq)}$ (50 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 hexane-$Et_2O$ as eluent gave NHP ester **282** (3.89 g, 66%) as a white solid, mp 78-80 °C (lit.,[155] 84-85 °C); $R_F$ (70:30 hexane-EtOAc) 0.40; IR (ATR) 3144, 2929, 1815 (C=O), 1786 (C=O), 1734 (C=O,), 1710 (C=O), 1464, 1185, 961 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$ $\delta$ 7.92-7.87 (m, 2H, Ar), 7.82-7.77 (m, 2H, Ar), 7.37-7.31 (m, 2H, Ph), 7.29-7.23 (m, 3H, Ph), 3.14-3.07 (m, 2H, $CH_2$), 3.02-2.96 (m, 2H, $CH_2$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 169.0 (C=O), 162.1 (C=O), 139.3 (*ipso*-Ar), 134.9 (Ar), 129.0 (*ipso*-Ar), 128.9 (Ar), 128.5 (Ar), 126.9 (Ar), 124.2 (Ar), 32.9 ($CH_2$), 30.7 ($CH_2$); MS (ESI) *m/z* 350 [$(M + Na + MeOH)^+$, 100], 318 [$(M + Na)^+$, 24]; HRMS (ESI) *m/z* calcd for $C_{17}H_{13}NO_4$ $(M + Na)^+$ 318.0737, found 318.0739 (−0.6 ppm error). Spectroscopic data are consistent with those reported in the literature.[21]

Lab Book Reference: SLB 1-81

**3-Phenyl propanoic acid 174, *N*,*N*-Diethyl-3-phenylpropanamide 309 and 1,4-Diphenylbutane 284**




**174** **309** **284**

NHP **282** (325 mg, 1.1 mmol, 1.0 eq.), $Et_3N$ (0.92 mL, 6.6 mmol, 6.0 eq.), $Bu_4NPF_6$ (852 mg, 2.2 mmol, 2.0 eq.) and MeCN (10 mL) were added to an ElectraSyn 2.0 10 mL glass cell with RVC electrodes and the cell was flushed with $N_2$. The cell was connected to the main ElectraSyn 2.0 set-up and a constant current experiment was selected. The solution was stirred and a current of 1.6 F $mol^{-1}$ (167 C of charge) of 20 mA was passed for 2 h 21 min with an initial voltage of 1.8 V. This gave the crude product. Purification by flash column chromatography on silica with 70:30 hexane-EtOAc as eluent gave amide **309** (33 mg, 28%) as a yellow oil, $R_F$ (70:30 hexane-EtOAc) 0.20; IR (ATR) 2972, 2932, 1631 (C=O), 1452, 1430, 1265, 1138, 1074 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) $\delta$ 7.30-7.16 (m, 5H, Ph), 3.36 (q, $J$ = 7.0 Hz, 2H, $NCH_2$), 3.21 (q, $J$ = 7.0 Hz, 2H, $NCH_2$), 3.00-2.93 (m, 2H, $CH_2$), 2.61-2.55 (m, 2H, $CH_2$), 1.10 (t, $J$ = 7.0 Hz, 3H, $NCH_2$*Me*), 1.09 (t, $J$ = 7.0 Hz, 3H, $NCH_2$*Me*); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 171.4 (C=O), 141.7 (*ipso*-Ph), 128.6 (Ph), 128.5 (Ph), 126.2 (Ph), 42.0 ($NCH_2$), 40.3 ($NCH_2$), 35.2 ($CH_2$), 31.8 ($CH_2$), 14.4 (Me), 13.2 (Me); MS (ESI) *m/z* 228 [$(M + Na)^+$, 100], 206 [$(M + H)^+$, 40]; HRMS (ESI) *m/z* calcd for $C_{13}H_{19}NO$ $(M + Na)^+$ 206.1539, found 206.1541 (−1.0 ppm error) and 1,4-diphenyl butane **284** (38 mg, 17%) as a colourless oil, $R_F$ (70:30 hexane-EtOAc) 0.66; IR (ATR) 3061, 2930, 2855, 1602, 1495, 1452, 1029 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.33-7.27 (m, 4H, Ph), 7.24-7.17 (m, 6H, Ph), 2.72-2.63 (m, 4H, $CH_2$), 1.77-1.65 (m, 4H, $CH_2$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 142.7 (Ph-*ipso*), 128.5 (Ph), 128.4 (Ph), 125.8 (Ph), 35.9 ($CH_2$), 31.2 ($CH_2$); MS (TOF $EI^+$) *m/z* 210 [$(M + H)^+$, 100]; HRMS (TOF $EI^+$) *m/z* calcd for $C_{16}H_{18}$ $(M + H)^+$ 210.1409, found 210.1411 (−1.0 ppm error). Spectroscopic data for amide **309** and 1,4-diphenyl butane **284** are consistent with those reported in the literature.

Lab Book Reference: SLB E-106

The results shown in the Table below were obtained using different electrodes under very similar conditions:

| Name | Electrodes | Yield of **284** (%) | Yield of **309** (%) |
|---|---|---|---|
| SLB-E-106 | New – not been used | 28 | 17 |
| SLB-E-112 | Old – reused 5 time previously | 6 | 20 |
| SLB-E-114 | New – not been used | 26 | 15 |

Diethylamine (0.1 mL, 0.96 mmol, 2.5 eq.) was added to a stirred solution of NHP ester **282** (100 mg, 0.39 mmol, 1.0 eq.) in MeCN (3.5 mL) at rt under $N_2$. The resulting solution was stirred at rt for 4 h. Then, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 70:30 hexane-EtOAc as eluent gave amide **309** (56 mg, 71%) as a yellow oil.

Lab Book Reference: SLB-E-131

Using general procedure E, 3-phenyl propanoic NHP ester **282** (292 mg, 0.99 mmol, 1.0 eq.), $Et_3N$ (0.83 mL, 5.94 mmol, 6.0 eq.), $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) and MeCN (9 mL) were used at rt. A current of 1.62 F $mol^{-1}$ (154 C of charge) of 2.6 V was passed for 2 h 58 min with an initial current of 24 mA. This gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave amide **309** (39 mg, 19%) as a yellow oil and 1,4-diphenylbutane **284** (25 mg, 24%) as a colourless oil. Using general procedure G, the amount of acid **174** formed was 28%.

Lab Book Reference: SLB-E-119

Using general procedure E, 3-phenyl propanoic NHP ester **282** (292 mg, 0.99 mmol, 1.0 eq.), $Et_3N$ (0.83 mL, 5.94 mmol, 6.0 eq.), $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) and dry MeCN (9 mL) were used at rt. A current of 1.60 F $mol^{-1}$ (153 C of charge) of 2.5 V was passed for 4 h 55 min with an initial current of 20 mA. This gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave amide **309** (30 mg, 15%) as a yellow oil and 1,4-diphenylbutane **384** (25 mg, 24%) as a colourless oil. Using general procedure G, the amount of acid **174** formed was 27%.

Lab Book Reference: SLB-E-122

Using general procedure E, 3-phenyl propanoic NHP ester **282** (292 mg, 0.99 mmol, 1.0 eq.), $Et_3N$ (0.83 mL, 5.94 mmol, 6.0 eq.), $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) and DMA (9 mL) were used at rt. A current of 1.69 F $mol^{-1}$ (162 C of charge) of 3.1 V was passed for 2 h 50 min with an initial current of 22 mA. This gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave amide **309** (18 mg, 9%) as a yellow oil and 1,4-diphenylbutane **284** (8 mg, 8%) as a colourless oil. Using general procedure G, the amount of acid **174** formed was 71%.

Lab Book Reference: SLB-E-123

Using general procedure E, 3-phenyl propanoic NHP ester **282** (292 mg, 0.99 mmol, 1.0 eq.), $Et_3N$ (0.83 mL, 5.94 mmol, 6.0 eq.), freshly opened $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) and MeCN (9 mL) were used at rt. A current of 1.69 F $mol^{-1}$ (161 C of charge) of 2.2 V was passed for 4 h 1 min with an initial current of 20 mA. This gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave amide **309** (41 mg, 20%) as a yellow oil and 1,4-diphenylbutane **284** (24 mg, 23%) as a colourless oil. Using general procedure G, the amount of acid **174** formed was 29%.

Lab Book Reference: SLB-E-125

Using general procedure E, 3-phenyl propanoic NHP ester **282** (292 mg, 0.99 mmol, 1.0 eq.), $Et_3N$ (0.83 mL, 5.94 mmol, 6.0 eq.), $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) and MeCN (9 mL) were used at 40 °C. A current of 0.89 F $mol^{-1}$ (86 C of charge) of 2.4 V was passed for 5 h 8 min with an initial current of 20 mA. This gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave amide **309** (58 mg, 28%) as a yellow oil and 1,4-diphenylbutane **284** (21 mg, 20%) as a colourless oil. Using general procedure G, the amount of acid **174** formed was 36%.

Lab Book Reference: SLB-E-126

Using general procedure E, 3-phenyl propanoic NHP ester **282** (292 mg, 0.99 mmol, 1.0 eq.), $Et_3N$ (0.83 mL, 5.94 mmol, 6.0 eq.), $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) and MeCN (9 mL) were used at rt. A current of 1.09 F $mol^{-1}$ (104 C of charge) of 1.9 V was passed for 8 h 51 min with an initial current of 10 mA. This gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave amide **309** (48 mg, 24%) as a yellow oil and 1,4-diphenylbutane **284** (18 mg, 17%) as a colourless oil. Using general procedure G, the amount of acid **174** formed was 38%.

Lab Book Reference: SLB-E-127

Using general procedure E, 3-phenyl propanoic NHP ester **282** (292 mg, 0.99 mmol, 1.0 eq.), $Et_3N$ (0.83 mL, 5.94 mmol, 6.0 eq.), $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) and MeCN (9 mL) were used at rt. A current of 1.66 F $mol^{-1}$ (159 C of charge) of 3.2 V was passed for 2 h 18 min with an initial current of 40 mA. This gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave amide **309** (25 mg, 12%) as a yellow oil and 1,4-diphenylbutane **284** (16 mg, 15%) as a colourless oil. Using general procedure G, the amount of acid **174** formed was 33%.

Lab Book Reference: SLB-E-128

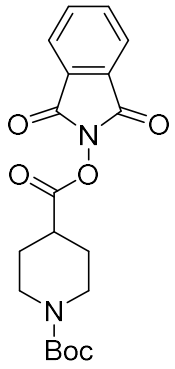
Using general procedure E, 3-phenyl propanoic NHP ester **282** (292 mg, 0.99 mmol, 1.0 eq.), DABCO (666 mg, 5.94 mmol, 6.0 eq.), $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) and MeCN (9 mL) were used at rt. A current of 1.59 F $mol^{-1}$ (152 C of charge) of 2.7 V was passed for 4 h 35 min with an initial current of 20 mA. This gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent 1,4-diphenylbutane **284** (18 mg, 18%) as a colourless oil. Using general procedure G, the amount of acid **174** formed was 37%.

Lab Book Reference: SLB-E-129

Using general procedure E, 3-phenyl propanoic NHP ester **282** (292 mg, 0.99 mmol, 1.0 eq.), $Et_3N$ (0.83 mL, 5.94 mmol, 6.0 eq.), $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) and MeCN (9 mL) were used at rt. A current of 0.76 F $mol^{-1}$ (73 C of charge) of 2.1 V was passed for 1 h 46 min with an initial current of 20 mA. This gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave amide **309** (39 mg, 19%) as a yellow oil and 1,4-diphenylbutane **284** (25 mg, 24%) as a colourless oil. Using general procedure G, the amount of acid **174** formed was 31%.

Lab Book Reference: SLB-E-134

**1-(*tert*-Butyl) 4-(1,3-dioxoisoindolin-2-yl) piperidine-1,4-dicarboxylate 30**



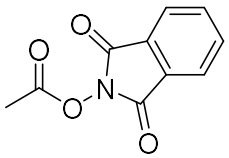

**30**

EDC (3.0 mL, 20 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc piperidine-4-carboxylic acid (3.90 g, 17 mmol, 1.0 eq.), *N*-hydroxyphthalimide (2.77 g, 17 mmol, 1.0 eq,) and DMAP (2.70 g, 22 mmol, 1.3 eq.) in $CH_2Cl_2$ (60 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 20 h. The mixture was then washed with 1 M $HCl_{(aq)}$ (50 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with sat. $NaHCO_{3(aq)}$ (50 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave NHP ester **30** (4.66 g, 73%) as a white solid, mp 104-106 °C (lit.,[114] 102-105 °C); $R_F$ (60:40 hexane-EtOAc) 0.27; IR (ATR) 2976, 2932, 1812 (C=O), 1783 (C=O), 1742 (C=O), 1691 (C=O, Boc), 1449, 1402, 1239, 1126 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.91-7.87 (m, 2H, Ar), 7.81-7.78 (m, 2H, Ar), 4.15-3.95 (m, 2H, NCH), 3.00 (dd, $J$ = 12.0, 12.0 Hz, 2H, NC*H*), 2.91 (tt, $J$ = 10.5, 4.0 Hz, 1H, CHC(O)), 2.12-2.02 (m, 2H, $NCH_2CH$), 1.91-1.79

(m, 2H, $NCH_2CH$), 1.46 (s, 9H, $CMe_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 170.8 (C=O), 162.1 (C=O), 154.7 (C=O, Boc), 135.0 (Ar), 129.0 (*ipso*-Ar), 124.2 (Ar), 80.0 ($OCMe_3$), 42.8 ($NCH_2$), 38.7 ($CHC(O)$), 28.5 ($CMe_3$), 27.9 ($NCH_2CH_2$); MS (ESI) *m/z* 397 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{19}H_{22}N_2O_6$ $(M + Na)^+$ 397.1370, found 397.1372 (−0.6 ppm error). Spectroscopic data are consistent with those reported in the literature.[114]

Lab Book Reference: SLB 1-78

**1,3-Dioxoisoindolin-2-yl acetate 316**

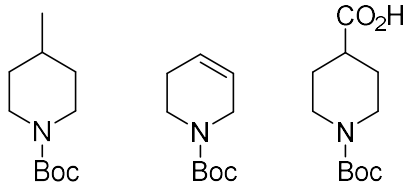


**316**

Acetic anhydride (15 mL, 156 mmol, 2.6 eq.) was added to a stirred solution of *N*-hydroxyphthalimide (10 g, 60 mmol, 1.0 eq.) and pyridine (5 mL, 60 mmol, 1.0 eq.) in $CH_2Cl_2$ (50 mL) at rt under Ar. The resulting mixture was stirred at rt for 20 h. The mixture was then poured into water (200 mL) and stirred vigorously for 30 min. The two layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (100 mL), sat. $NaHCO_{3(aq)}$ (100 mL), water (100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give NHP acetate **316** (11.6 g, 94%) as a white solid, mp 182-185 °C (lit.,[156] 184-185 °C); IR (ATR) 2397, 1807 (C=O), 1785 (C=O), 1735 (C=O), 1467, 1374, 1157, 1140 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.91-7.85 (m, 2H, Ar), 7.81-7.77 (m, 2H, Ar), 2.40 (s, 3H, Me); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 166.7 (C=O), 162.0 (C=O), 134.9 (Ar), 129.0 (*ipso*-Ar), 124.1 (Ar), 17.7 (Me); MS (ESI) *m/z* 260 [$(M + Na + MeOH)^+$, 100], 228 [$(M + Na)^+$, 27]; HRMS (ESI) *m/z* calcd for $C_{10}H_7NO_4$ $(M + Na)^+$ 228.0267, found 228.0264 (+1.5 ppm error). Spectroscopic data are consistent with those reported in the literature.[125]

Lab Book Reference: SLB 1-77

***tert*-Butyl 4-methylpiperidine-1-carbamate 217, *tert*-butyl 1,2,3,6-tetrahydropyridine-1-carboxylate 213 and 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid 170**

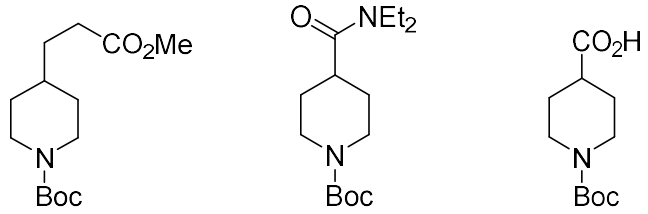



**217** **213** **170**

*N*-Boc piperidine 4-NHP ester **30** (75 mg, 0.2 mmol, 1.0 eq.), NHP acetate **316** (164 mg, 0.8 mmol, 4.0 eq.), $Et_3N$ (0.83 mL, 6.0 mmol, 30.0 eq.), $Bu_4NPF_6$ (767 mg, 2.0 mmol, 10.0 eq.) and MeCN (9 mL) were added to cell 3. The rubber stopper containing the RVC electrodes and thermocouple was inserted into the cell and the cell was flushed with $N_2$. The electrodes were connected to the electrolysis circuit *via* crocodile clips. The power pack was turned on (voltage at 0 V) simultaneously with the data acquisition software (LabJack©). The voltage was quickly raised to the desired setting. The solution was stirred at rt under $N_2$ until a current of 1.6 F $mol^{-1}$ (153 C of charge) of 2.1 V was passed for 3 h 10 min with an initial current of 20 mA. Then, the power pack and data acquisition software were turned off. EtOAc (10 mL) was added and the reaction mixture washed with brine/$H_2O$ (1:1) (3 × 20 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave a 60:40 mixture (by $^1H$ NMR spectroscopy) of *N*-Boc 4-methyl piperidine **217** and *N*-Boc alkene piperidine **213** (9 mg, 5 mg (3%) of **217** and 4 mg (2%) of **213**) as a colourless oil. Using general procedure G, acid **170** was observed but in an unknown amount.

Lab Book Reference: SLB-E-132

***tert*-Butyl 4-(3-methoxy-3-oxopropyl)piperidine-1-carboxylate 319, *tert*-butyl 4-(diethylcarbamoyl)piperidine-1-carboxylate 320 and 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid 170**




**319** **320** **170**

Using general procedure F, *N*-Boc piperidine 4-NHP ester **30** (371 mg, 0.99 mmol, 1.0 eq.), methyl acrylate (0.27 mL, 2.97 mmol, 3.0 eq.), $Et_3N$ (0.83 mL, 5.94 mmol, 6.0 eq.), $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) and MeCN (9 mL) were used. A current of 2.51 F $mol^{-1}$ (239 C) of 2.5 V was passed for 4 h 42 min with an initial current of 20 mA. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave piperidine 4-ester **319** (67 mg, 25%) as a colourless oil, $R_F$ (90:10 hexane-$Et_2O$) 0.13; IR (ATR) 2972, 1738 (C=O, $CO_2Me$), 1690 (C=O, Boc), 1422, 1365, 1277, 1160 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.06 (br s, 2H, NCH), 3.66 (s, 3H, OMe), 2.64 (dd, $J$ = 13.0, 13.0 Hz, NCH), 2.32 (t, $J$ = 8.0 Hz, 2H, C$H_2$C(O)), 1.67-1.61 (m, 2H, $NCH_2CH$), 1.57 (dt, $J$ = 7.5, 7.5 Hz, 2H, C$H_2CH_2$C(O)), 1.43 (s, 9H, $CMe_3$), 1.42-1.32 (m, 1H, CH), 1.07 (dddd, $J$ = 12.5, 12.0, 12.0, 4.5 Hz, 2H, $NCH_2CH$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 174.3 (C=O, $CO_2Me$), 156.0 (C=O, Boc), 79.4 (O*C*$Me_3$), 51.7 (OMe), 43.9 ($NCH_2$), 35.6 (CH), 31.9 ($CH_2$), 31.5 ($CH_2$), 31.4 ($CH_2$), 28.6 (C*Me*$_3$); MS (ESI) *m/z* 294 [(M + Na)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{14}H_{25}NO_4$ (M + Na)$^+$ 294.1676, found 294.1675 (+0.4 ppm error) and amide **320** (23 mg, 8%) as a colourless oil, $R_F$ (60:40 $Et_2O$-hexane) 0.07; IR (ATR) 2972, 1735 (C=O, amide), 1687 (C=O, Boc), 1633, 1422, 1364, 1228, 1165 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) $\delta$ 4.11 (s, 2H, NCH), 3.35 (q, $J$ = 7.0 Hz, 2H, N$CH_2$Me), 3.31 (q, $J$ = 7.0 Hz, 2H, N$CH_2$Me), 2.80-2.66 (m, 2H, NCH), 2.53 (tt, $J$ = 11.0, 4.0 Hz, CHC(O)), 1.81-1.54 (m, 4H, $NCH_2CH$), 1.44 (s, 9H, $CMe_3$), 1.18 (t, $J$ = 7.0 Hz, 3H, $NCH_2Me$), 1.08 (t, $J$ = 7.0 Hz, 3H, $NCH_2Me$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 173.9 (C=O, amide), 154.8 (C=O, Boc), 79.6 (O*C*$Me_3$), 43.8 (N*C*$H_2CH_2$), 41.8 (N*C*$H_2$Me), 40.3 (N*C*$H_2$Me), 38.9 (*C*HC(O)), 28.8 ($NCH_2CH_2$), 28.5 (C*Me*$_3$), 15.1 ($NCH_2Me$), 13.2 ($NCH_2Me$); MS (ESI) *m/z* 307 [(M + Na)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{15}H_{28}N_2O_3$ (M + Na)$^+$

307.2003, found 307.1993 (+3.3 ppm error). Using general procedure G, acid **170** was observed but in an unknown amount. Spectroscopic data for piperidine 4-ester **319**[157] and amide **320**[158] are consistent with those reported in the literature.

Lab Book Reference: SLB-E-135

Using general procedure F, *N*-Boc piperidine 4-NHP ester **30** (371 mg, 0.99 mmol, 1.0 eq.), methyl acrylate (0.54 mL, 5.94 mmol, 6.0 eq.), $Et_3N$ (0.83 mL, 5.94 mmol, 6.0 eq.), $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) and MeCN (9 mL) were used. A current of 2.51 F $mol^{-1}$ (240 C) of 2.2 V was passed for 5 h 51 min with an initial current of 20 mA. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave piperidine 4-ester **319** (70 mg, 26%) as a colourless oil and amide **320** (43 mg, 15%) as a colourless oil. Using general procedure G, the amount of acid **170** formed was 28%.

Lab Book Reference: SLB-E-139

Using general procedure F, *N*-Boc piperidine 4-NHP ester **30** (371 mg, 0.99 mmol, 1.0 eq.), methyl acrylate (0.27 mL, 2.97 mmol, 3.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.), $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) and MeCN (9 mL) were used. A current of 2.41 F $mol^{-1}$ (230 C) of 2.6 V was passed for 6 h 51 min with an initial current of 20 mA. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave piperidine 4-ester **319** (109 mg, 41%) as a colourless oil. Using general procedure G, the amount of acid **170** formed was 20%.

Lab Book Reference: SLB-E-139

Using general procedure F, *N*-Boc piperidine 4-NHP ester **30** (371 mg, 0.99 mmol, 1.0 eq.), methyl acrylate (0.27 mL, 2.97 mmol, 3.0 eq.), tetramethyl piperidine (1.0 mL, 5.94 mmol, 6.0 eq.), $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) and MeCN (9 mL) were used. A current of 1.96 F $mol^{-1}$ (187 C) of 2.5 V was passed for 6 h 50 min with an initial current of 20 mA. This gave the crude product. Purification by flash column chromatography on

silica with 90:10 hexane-$Et_2O$ as eluent gave piperidine 4-ester **319** (48 mg, 18%) as a colourless oil. Using general procedure G, the amount of acid **170** formed was 13%.

Lab Book Reference: SLB-E-140

Using general procedure F, *N*-Boc piperidine 4-NHP ester **30** (371 mg, 0.99 mmol, 1.0 eq.), methyl acrylate (0.27 mL, 2.97 mmol, 3.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.), $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) and MeCN (9 mL) were used. A current of 2.20 F $mol^{-1}$ (212 C) of 2.2 V was passed for 7 h 38 min with an initial current of 20 mA and the polarity of the electrodes were switched every 5 min. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave piperidine 4-ester **319** (83 mg, 31%) as a colourless oil. Using general procedure G, the amount of acid **170** formed was 25%.

Lab Book Reference: SLB-E-167

Using general procedure F, *N*-Boc piperidine 4-NHPCl ester **342** (507 mg, 0.99 mmol, 1.0 eq.), methyl acrylate (0.27 mL, 2.97 mmol, 3.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.), $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) and MeCN (9 mL) were used. A current of 2.45 F $mol^{-1}$ (234 C) of 2.0 V was passed for 7 h 47 min with an initial current of 20 mA. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave piperidine 4-ester **319** (22 mg, 8%) as a colourless oil. Using general procedure G, the amount of acid **170** formed was 58%.

Lab Book Reference: SLB-E-145

Using general procedure F, *N*-Boc piperidine 4-NHPOMe ester **347** (202 mg, 0.50 mmol, 1.0 eq.), methyl acrylate (0.13 mL, 1.50 mmol, 3.0 eq.), DIPEA (0.52 mL, 3.00 mmol, 6.0 eq.), $Bu_4NPF_6$ (767 mg, 2.00 mmol, 4.0 eq.) and MeCN (9 mL) were used. A current of 2.50 F $mol^{-1}$ (120 C) of 2.7 V was passed for 5 h 30 min with an initial current of 30 mA. This gave the crude product. Purification by flash column chromatography on silica

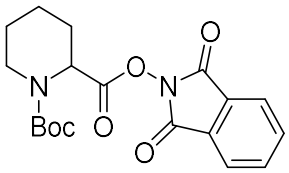
with 90:10 hexane-$Et_2O$ as eluent gave piperidine 4-ester **319** (52 mg, 39%) as a colourless oil. Using general procedure G, the amount of acid **170** formed was 14%.

Lab Book Reference: SLB-E-212

Using general procedure F, *N*-Boc piperidine 4-NHP$(OMe)_2$ ester **348** (217 mg, 0.50 mmol, 1.0 eq.), methyl acrylate (0.13 mL, 1.50 mmol, 3.0 eq.), DIPEA (0.52 mL, 3.00 mmol, 6.0 eq.), $Bu_4NPF_6$ (767 mg, 2.00 mmol, 4.0 eq.) and MeCN (9 mL) were used. A current of 1.99 F $mol^{-1}$ (96 C) of 2.7 V was passed for 6 h 28 min with an initial current of 36 mA. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave piperidine 4-ester **319** (40 mg, 29%) as a colourless oil. Using general procedure G, the amount of acid **170** formed was 3%.

Lab Book Reference: SLB-E-208

**1-(*tert*-Butyl) 2-(1,3-dioxoisoindolin-2-yl) piperidine-1,2-dicarboxylate 300**



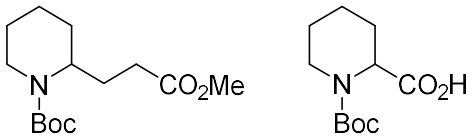

**300**

EDC (4.2 mL, 24 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc piperidine-2-carboxylic acid (4.59 g, 20 mmol, 1.0 eq.), *N*-hydroxyphthalimide (3.26 g, 20 mmol, 1.0 eq,) and DMAP (3.18 g, 26 mmol, 1.3 eq.) in $CH_2Cl_2$ (70 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 20 h. The mixture was then washed with 1 M $HCl_{(aq)}$ (50 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with sat. $NaHCO_{3(aq)}$ (50 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave NHP ester **300** (5.13 g, 69%) as a white amorphous solid, $R_F$ (70:30 hexane-EtOAc) 0.36; IR (ATR) 2937, 1786 (C=O), 1745 (C=O), 1702 (C=O, Boc), 1367, 1162, 991 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) $\delta$ 7.87-7.81 (m, 2H, Ar), 7.79-7.74 (m,

2H, Ar), 5.35 (br s, 0.3H, NCH), 5.10 (d, $J$ = 6.0 Hz, 0.7H, NCH), 4.03 (br d, $J$ = 12.5 Hz, 0.7H, NCH), 3.95 (br d, $J$ = 13.0 Hz, 0.3H, NCH), 3.14-2.91 (m, 1H, NCH), 2.39-2.28 (m, 1H, CH), 1.92-1.57 (m, 3H, CH), 1.57-1.41 (m, 2H, CH), 1.46 (s, 9H, $CMe_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 169.9 (C=O), 168.7 (C=O), 161.8 (C=O), 155.5 (C=O, Boc), 155.2 (C=O, Boc), 134.9 (Ar), 129.0 (*ipso*-Ar), 124.1 (Ar), 81.1 ($OCMe_3$), 80.6 ($OCMe_3$), 53.7 (NCH), 52.6 (NCH), 42.2 ($NCH_2$), 41.2 ($NCH_2$), 28.4 ($CMe_3$), 28.2 ($CMe_3$), 27.2 ($CH_2$), 24.8 ($CH_2$), 24.5 ($CH_2$), 20.7 ($CH_2$), 20.3 ($CH_2$); MS (ESI) *m/z* 397 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{19}H_{22}N_2O_6$ $(M + Na)^+$ 397.1370, found 397.1373 (−0.7 ppm error). Spectroscopic data are consistent with those reported in the literature.[159]

Lab Book Reference: SLB 1-91

**_tert_-Butyl 2-(3-methoxy-3-oxopropyl)piperidine-1-carboxylate 322 and 1-(_tert_-butoxycarbonyl)piperidine-2-carboxylic acid 321**




**322** **321**

Using general procedure F, *N*-Boc piperidine 2-NHP ester **300** (371 mg, 0.99 mmol, 1.0 eq.), methyl acrylate (0.27 mL, 2.97 mmol, 3.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) in MeCN (9 mL) were used. A current of 2.67 F $mol^{-1}$ (255 C) of 2.5 V was passed for 5 h 23 min with an initial current of 20 mA. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave piperidine 2-ester **322** (138 mg, 51%) as a colourless oil, $R_F$ (60:40 hexane-EtOAc) 0.51; IR (ATR) 2933, 2863, 1737 (C=O, $CO_2Me$), 1684 (C=O, Boc), 1413, 1364, 1247, 1156 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.22 (br s, 1H, NCH), 3.96 (br s, 1H, NCH), 3.64 (s, 3H, OMe), 2.71 (dd, $J$ = 13.0, 13.0 Hz, 1H, NCH), 2.34-2.18 (m, 2H, CH), 2.16-2.00 (m, 1H, CH), 1.70-1.46 (m, 6H, CH), 1.42 (s, 9H, $CMe_3$), 1.39-1.29 (m, 1H, CH); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 174.1 (C=O, $CO_2Me$), 155.1 (C=O, Boc), 79.4 ($OCMe_3$), 51.7 (OMe), 50.0 (NCH), 38.5 ($NCH_2$), 31.0 ($CH_2$), 29.0 ($CH_2$), 28.5 ($CMe_3$), 25.6 ($CH_2$), 25.1 ($CH_2$), 19.1 ($CH_2$); MS (ESI) *m/z* 294

[$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{14}H_{25}NO_4$ $(M + Na)^+$ 294.1676, found 294.1676 (0.0 ppm error). Using general procedure G, the amount of acid **321** formed was 31%. Spectroscopic data are consistent with those reported in the literature.[160]

Lab Book Reference: SLB-E-144

Using general procedure F, *N*-Boc piperidine 2-NHP ester **300** (371 mg, 0.99 mmol, 1.0 eq.), methyl acrylate (0.27 mL, 2.97 mmol, 3.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) in MeCN (9 mL) were used. A current of 2.68 F $mol^{-1}$ (256 C) of 2.5 V was passed for 4 h 15 min with an initial current of 21 mA. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave piperidine 2-ester **322** (130 mg, 48%) as a colourless oil. Using general procedure G, the amount of acid **321** formed was 20%.

Lab Book Reference: SLB-E-174

Using general procedure F, *N*-Boc piperidine 2-NHP ester **300** (371 mg, 0.99 mmol, 1.0 eq.), methyl acrylate (0.27 mL, 2.97 mmol, 3.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.) and $Bu_4NBr$ (638 mg, 1.98 mmol, 2.0 eq.) in MeCN (9 mL) were used. A current of 2.66 F $mol^{-1}$ (254 C) of 2.3 V was passed for 4 h 56 min with an initial current of 20 mA. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave piperidine 2-ester **322** (107 mg, 44%) as a colourless oil. Using general procedure G, the amount of acid **321** formed was 9%.

Lab Book Reference: SLB-E-177

Using general procedure F, *N*-Boc piperidine 2-NHP ester **300** (371 mg, 0.99 mmol, 1.0 eq.), methyl acrylate (0.27 mL, 2.97 mmol, 3.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) in MeCN (9 mL) were used. A current of 2.50 F $mol^{-1}$ (239 C) of 2.1 V was passed for 6 h 57 min with an initial current of 15 mA. This gave the crude product. Purification by flash column chromatography on silica

with 90:10 hexane-$Et_2O$ as eluent gave piperidine 2-ester **322** (112 mg, 42%) as a colourless oil. Using general procedure G, the amount of acid **321** formed was 17%.

Lab Book Reference: SLB-E-187

Using general procedure F, *N*-Boc piperidine 2-NHP ester **300** (371 mg, 0.99 mmol, 1.0 eq.), methyl acrylate (0.27 mL, 2.97 mmol, 3.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) in MeCN (9 mL) were used. A current of 2.61 F $mol^{-1}$ (249 C) of 3.2 V was passed for 2 h 51 min with an initial current of 37 mA. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave piperidine 2-ester **322** (129 mg, 48%) as a colourless oil. Using general procedure G, the amount of acid **321** formed was 16%.

Lab Book Reference: SLB-E-186

Using general procedure F, *N*-Boc piperidine 2-NHP ester **300** (371 mg, 0.99 mmol, 1.0 eq.), methyl acrylate (0.27 mL, 2.97 mmol, 3.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) in MeCN (9 mL) were used. A current of 2.50 F $mol^{-1}$ (238 C) of 4.0 V was passed for 1 h 27 min with an initial current of 61 mA. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave piperidine 2-ester **322** (114 mg, 42%) as a colourless oil. Using general procedure G, the amount of acid **321** formed was 20%.

Lab Book Reference: SLB-E-189

Using general procedure F, *N*-Boc piperidine 2-NHP ester **300** (187 mg, 0.50 mmol, 1.0 eq.), methyl acrylate (0.13 mL, 1.50 mmol, 3.0 eq.), DIPEA (0.52 mL, 3.00 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 2.00 mmol, 4.0 eq.) in MeCN (9 mL) were used. A current of 2.57 F $mol^{-1}$ (122 C) of 2.6 V was passed for 1 h 26 min with an initial current of 30 mA. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave piperidine 2-ester **322** (71 mg, 52%) as a colourless oil. Using general procedure G, the amount of acid **321** formed was 20%.

Lab Book Reference: SLB-E-204

Using general procedure F, *N*-Boc piperidine 2-NHS ester **344** (323 mg, 0.99 mmol, 1.0 eq.), methyl acrylate (0.27 mL, 2.97 mmol, 3.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) in MeCN (9 mL) were used. A current of 0.19 F $mol^{-1}$ (18 C) of 2.3 V was passed with an initial current of 20 mA and the current dropped to 1 mA within a few minutes. The reaction was turned off and discarded after 2 h 09 min had passed.

Lab Book Reference: SLB-E-157

Using general procedure F, *N*-Boc piperidine 2-NHPCl ester **343** (507 mg, 0.99 mmol, 1.0 eq.), methyl acrylate (0.27 mL, 2.97 mmol, 3.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) in MeCN (9 mL) were used. A current of 2.50 F $mol^{-1}$ (239 C) of 2.1 V was passed for 4 h 51 min with an initial current of 18 mA. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave piperidine 2-ester **322** (37 mg, 14%) as a colourless oil. Using general procedure G, the amount of acid **321** formed was 37%.

Lab Book Reference: SLB-E-146

Using general procedure F, *N*-Boc piperidine 2-NHPOMe ester **346** (400 mg, 0.99 mmol, 1.0 eq.), methyl acrylate (0.27 mL, 2.97 mmol, 3.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) in MeCN (9 mL) were used. A current of 2.61 F $mol^{-1}$ (245 C) of 2.6 V was passed for 4 h 43 min with an initial current of 22 mA. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave piperidine 2-ester **322** (121 mg, 45%) as a colourless oil. Using general procedure G, the amount of acid **321** formed was 11%.

Lab Book Reference: SLB-E-202

Using general procedure F, *N*-Boc piperidine 2-NHP(OMe)$_2$ ester **349** (430 mg, 0.99 mmol, 1.0 eq.), methyl acrylate (0.27 mL, 2.97 mmol, 3.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) in MeCN (9 mL) were used. A current of 1.69 F mol$^{-1}$ (162 C) of 265 V was passed for 6 h 39 min with an initial current of 20 mA. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave piperidine 2-ester **322** (132 mg, 50%) as a colourless oil. Using general procedure G, the amount of acid **321** formed was 2%.

Lab Book Reference: SLB-E-190

Using general procedure F, *N*-Boc piperidine 2-NHPCl ester **343** (256 mg, 0.50 mmol, 1.0 eq.), methyl acrylate (0.13 mL, 1.50 mmol, 3.0 eq.), DIPEA (0.52 mL, 3.00 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 2.00 mmol, 4.0 eq.) in MeCN (9 mL) were used. A current of 2.58 F mol$^{-1}$ (124 C) of 2.5 V was passed for 1 h 26 min with an initial current of 28 mA. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave piperidine 2-ester **322** (37 mg, 26%) as a colourless oil. Using general procedure G, the amount of acid **321** formed was 32%.

Lab Book Reference: SLB-E-205

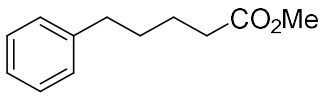
Using general procedure F, *N*-Boc piperidine 2-NHPOMe ester **346** (202 mg, 0.50 mmol, 1.0 eq.), methyl acrylate (0.13 mL, 1.50 mmol, 3.0 eq.), DIPEA (0.52 mL, 3.00 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 2.00 mmol, 4.0 eq.) in MeCN (9 mL) were used. A current of 2.55 F mol$^{-1}$ (123 C) of 2.6 V was passed for 1 h 54 min with an initial current of 29 mA. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave piperidine 2-ester **322** (67 mg, 49%) as a colourless oil. Using general procedure G, the amount of acid **321** formed was 7%.

Lab Book Reference: SLB-E-206

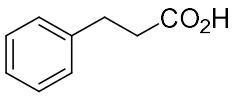
Using general procedure F, *N*-Boc piperidine 2-NHP(OMe)$_2$ ester **349** (217 mg, 0.50 mmol, 1.0 eq.), methyl acrylate (0.13 mL, 1.50 mmol, 3.0 eq.), DIPEA (0.52 mL, 3.00 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 2.00 mmol, 4.0 eq.) in MeCN (9 mL) were used. A current of 2.49 F mol$^{-1}$ (120 C) of 2.5 V was passed for 2 h 46 min with an initial current of 31 mA. This gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane-$Et_2O$ as eluent gave piperidine 2-ester **322** (69 mg, 50%) as a colourless oil. Using general procedure G, the amount of acid **321** formed was 5%.

Lab Book Reference: SLB-E-203

**Methyl 5-phenylpentanoate 323 and 3-phenyl propanoic acid 174**




**323**




**174**

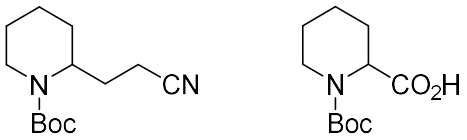
Using general procedure F, NHP ester **282** (292 mg, 0.99 mmol, 1.0 eq.), methyl acrylate (0.27 mL, 2.97 mmol, 3.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) in MeCN (9 mL) were used. A current of 2.18 F mol$^{-1}$ (208 C of charge) of 2.2 V was passed for 7 h 6 min with an initial current of 22 mA. This gave the crude product. Purification by flash column chromatography on silica 95:5 hexane-EtOAc as eluent gave ester **323** (53 mg, 28%) as a colourless oil, $R_F$ (60:40 hexane-EtOAc) 0.55; IR (ATR) 2946, 1735 (C=O), 1453, 1435, 1198, 1171 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.32-7.24 (m, 2H, Ph), 7.27-7.15 (m, 3H, Ph), 3.66 (s, 3H, OMe), 2.66-2.60 (m, 2H, $CH_2$), 2.37-2.27 (m, 2H, $CH_2$), 1.70-1.57 (m, 4H, $CH_2$); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 174.1 (C=O), 142.3 (*ipso*-Ph),128.5 (Ph), 128.4 (Ph), 125.9 (Ph), 51.7 (OMe), 35.7 ($CH_2$), 34.1 ($CH_2$), 31.0 ($CH_2$), 24.7 ($CH_2$); MS (ESI) *m/z* 193 [(M + H)$^+$, 100]; HRMS (APCI) *m/z* calcd for $C_{12}H_{16}O_2$ (M + H)$^+$ 193.1223, found 193.1218 (+2.4 ppm error). Using general procedure G, the amount of acid **174** formed was 23%. Spectroscopic data are consistent with those reported in the literature.[161]

Lab Book Reference: SLB-E-166

Using general procedure F, $NHP(OMe)_2$ ester **302** (178 mg, 0.05 mmol, 1.0 eq.), methyl acrylate (0.13 mL, 1.5 mmol, 3.0 eq.), DIPEA (0.52 mL, 3.0 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 2.0 mmol, 4.0 eq.) in MeCN (9 mL) were used. A current of 2.18 F $mol^{-1}$ (104 C of charge) of 1.4 V was passed for 7 h 6 min with an initial current of 35 mA. This gave the crude product. Purification by flash column chromatography on silica 95:5 hexane-EtOAc as eluent gave ester **323** (23 mg, 24%) as a colourless oil. Using general procedure G, the amount of acid **174** formed was 18%.

Lab Book Reference: SLB-E-210

**_tert_-Butyl 2-(2-cyanoethyl)piperidine-1-carboxylate 324 and 1-(_tert_-butoxycarbonyl)piperidine-2-carboxylic acid 321**

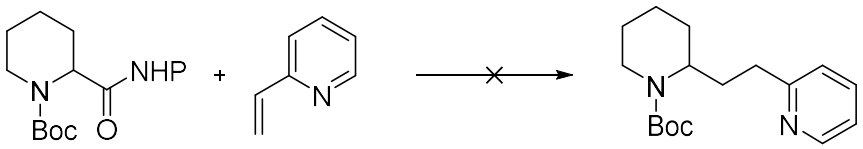



**324** **321**

Using general procedure F, NHP ester **300** (371 mg, 0.99 mmol, 1.0 eq.), acrylonitrile (0.20 mL, 2.97 mmol, 3.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) in MeCN (9 mL) were used. A current of 2.05 F $mol^{-1}$ (195.9 C of charge) of 2.3 V was passed for 5 h 59 min with an initial current of 20 mA. This gave the crude product. Purification by flash column chromatography on silica 90:10 hexane-EtOAc as eluent gave nitrile **324** (66 mg, 28%) as a light brown oil, $R_F$ (60:40 hexane-EtOAc) 0.28; IR (ATR) 2973, 2934, 2246 (C≡N), 1682 (C=O), 1413, 1364, 1160 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.36-4.28 (m, 1H, NCH), 4.08-3.96 (m, 1H, NCH), 2.76-2.64 (m, 1H, NCH), 2.30 (t, $J$ = 7.5 Hz, 2H, $CH_2CN$), 2.24-2.10 (m, 1H, CH), 1.79-1.27 (m, 7H, CH), 1.46 (s, 9H, $CMe_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 155.2 (C=O), 119.8 (C≡N), 80.1 (O*C*$Me_3$), 49.7 (NCH), 38.9 ($NCH_2$), 28.8 ($CH_2$), 28.5 (C*Me*$_3$), 26.3 ($CH_2$), 25.5 ($CH_2$), 19.2 ($CH_2$), 14.5 (*C*$H_2$CN); MS (ESI) *m/z* 261 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{13}H_{22}N_2O_2$ $(M + Na)^+$ 261.1573, found 261.1575 (−0.6 ppm error). Using general procedure G, the amount of acid **321** formed was 10%. Spectroscopic data are consistent with those reported in the literature.[160]

Lab Book Reference: SLB-E-171

**Attempted synthesis of *tert*-butyl 2-(2-(pyridin-2-yl)ethyl)piperidine-1-carboxylate 363**

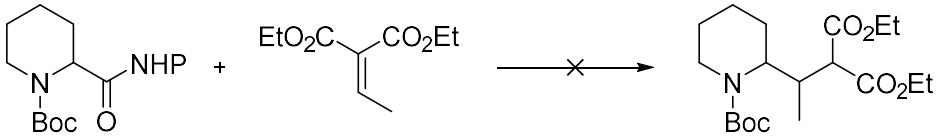



**300** **325** **363**

Using general procedure F, NHP ester **300** (371 mg, 0.99 mmol, 1.0 eq.), 2-vinylpyridine (0.32 mL, 2.97 mmol, 3.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) in MeCN (9 mL) were used. A current of 2.05 F $mol^{-1}$ (195.9 C of charge) of 2.3 V was passed for 5 h 59 min with an initial current of 20 mA. This gave the crude product which did not contain pyridine **363** by $^1H$ NMR spectroscopy and mass spectrometry.

Lab Book Reference: SLB-E-169

**Attempted synthesis of diethyl 2-(1-(1-(*tert*-butoxycarbonyl)piperidin-2-yl)ethyl)malonate 364**

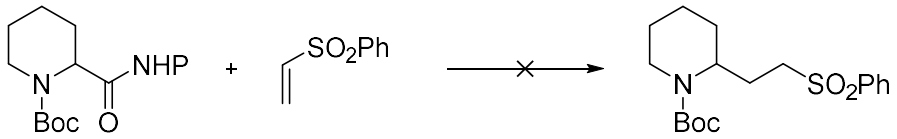



**300** **326** **364**

Using general procedure F, NHP ester **300** (371 mg, 0.99 mmol, 1.0 eq.), diethyl 2-ethylidenemalonate (0.54 mL, 2.97 mmol, 3.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) in MeCN (9 mL) were used. A current of 2.05 F $mol^{-1}$ (195.9 C of charge) of 2.3 V was passed for 5 h 59 min with an initial current of 20 mA. This gave the crude product which did not contain ester **364** by $^1H$ NMR spectroscopy and mass spectrometry.

Lab Book Reference: SLB-E-181

**Attempted synthesis of *tert*-butyl 2-(2-(phenylsulfonyl)ethyl)piperidine-1-carboxylate 365**

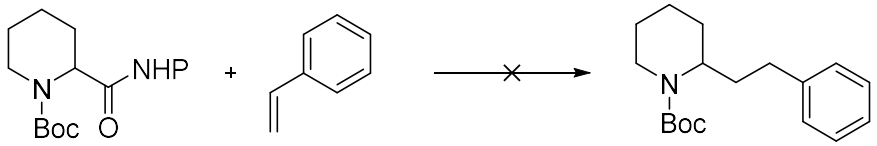



**300** **327** **365**

Using general procedure F, NHP ester **300** (371 mg, 0.99 mmol, 1.0 eq.), phenyl vinyl sulphone (0.27 mL, 2.97 mmol, 3.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) in MeCN (9 mL) were used. A current of 2.05 F $mol^{-1}$ (195.9 C of charge) of 2.3 V was passed for 5 h 59 min with an initial current of 20 mA. This gave the crude product which did not contain sulfonylbenzene **365** by $^1H$ NMR spectroscopy and mass spectrometry.

Lab Book Reference: SLB-E-175

**Attempted synthesis of *tert*-butyl 2-phenethylpiperidine-1-carboxylate 366**

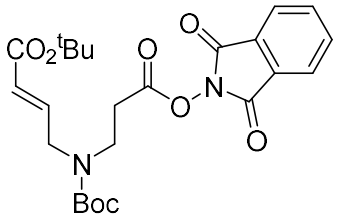



**300** **328** **366**

Using general procedure F, NHP ester **300** (371 mg, 0.99 mmol, 1.0 eq.), styrene (0.17 mL, 2.97 mmol, 3.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) in MeCN (9 mL) were used. A current of 2.05 F $mol^{-1}$ (195.9 C of charge) of 2.3 V was passed for 5 h 59 min with an initial current of 20 mA. This gave the crude product which did not contain phenyl piperidine **366** by $^1H$ NMR spectroscopy and mass spectrometry.

Lab Book Reference: SLB-E-211

***tert*-Butyl (*E*)-4-((*tert*-butoxycarbonyl)(3-((1,3-dioxoisoindolin-2-yl)oxy)-3-oxopropyl)amino)but-2-enoate 330**

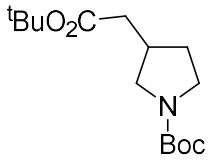



**330**

EDC (0.49 mL, 2.78 mmol, 1.2 eq.) was added dropwise to a stirred solution of alkene acid **329** (766 mg, 2.32 mmol, 1.0 eq.), *N*-hydroxyphthalimide (378 mg, 2.32 mmol, 1.0 eq,) and DMAP (368 mg, 3.02 mmol, 1.3 eq.) in $CH_2Cl_2$ (10 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 20 h. The mixture was then washed with 1 M $HCl_{(aq)}$ (20 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were washed with sat. $NaHCO_{3(aq)}$ (20 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 40:60 $Et_2O$-hexane as eluent gave NHP ester **330** (858 mg, 78%) as a white amorphous solid, $R_F$ (60:40 $Et_2O$-hexane) 0.32; IR (ATR) 2977, 2932, 1744 (C=O), 1697 (C=O, Boc), 1366, 1151 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.89-7.85 (m, 2H, Ar), 7.81-7.76 (m, 2H, Ar), 6.78-6.66 (m, 1H, $NCH_2CH$=CH), 5.76 (br d, $J$ = 16.0 Hz, 1H, $NCH_2CH$=C*H*), 4.10-3.97 (m, 2H, $NCH_2CH$=CH), 3.65-3.51 (m, 2H, $NCH_2CH_2$), 3.03-2.85 (m, 2H, $NCH_2CH_2$), 1.52-1.43 (m, 18H, $CMe_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 169.5 (C=O), 168.0 (C=O), 165.5 (C=O), 161.9 (C=O), 155.2 (C=O, Boc), 142.5 ($NCH_2CH$=CH), 142.3 ($NCH_2CH$=CH), 135.0 (Ar), 129.0 (*ipso*-Ar), 124.2 (Ar), 123.9 ($NCH_2CH$=*C*H), 81.1 ($OCMe_3$), 80.9 ($OCMe_3$), 80.7 ($OCMe_3$), 49.4 ($NCH_2CH$=CH), 48.4 ($NCH_2CH$=CH), 43.4 ($NCH_2CH_2$), 43.1 ($NCH_2CH_2$), 31.1 ($NCH_2CH_2$), 30.7 ($NCH_2CH_2$), 28.5 ($CMe_3$), 28.4 ($CMe_3$), 28.2 ($CMe_3$); MS (ESI) *m/z* 497 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{24}H_{30}N_2O_8$ $(M + Na)^+$ 497.1894, found 497.1904 (−1.8 ppm error).

Lab Book Reference: SLB 2-7

***tert*-Butyl 3-(2-(*tert*-butoxy)-2-oxoethyl)pyrrolidine-1-carboxylate 331**

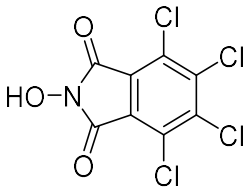



**331**

Using general procedure F, NHP ester **330** (470 mg, 0.99 mmol, 1.0 eq.), DIPEA (1.03 mL, 5.94 mmol, 6.0 eq.) and $Bu_4NPF_6$ (767 mg, 1.98 mmol, 2.0 eq.) in MeCN (9 mL) were used. A current of 2.50 F $mol^{-1}$ (238.6 C of charge) of 2.3 V was passed for 7 h 10 min with an initial current of 20 mA. This gave the crude product. Purification by flash column chromatography on silica 90:10 hexane-$Et_2O$ as eluent gave pyrrolidine **331** (122 mg, 43%) as a yellow solid, mp 46-48 °C (lit.,[162] 54-56 °C); $R_F$ (60:40 $Et_2O$-hexane) 0.32; IR (ATR) 2975, 2874, 1728 (C=O, $CO_2CMe_3$), 1693 (C=O, Boc), 1404, 1365, 1148, 1123 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.63-3.51 (m, 1H, NCH), 3.50-3.36 (m, 1H, NCH), 3.33-3.22 (m, 1H, NCH), 2.98-2.86 (m, 1H, NCH), 2.58-2.44 (m, 1H, $NCH_2CH$), 2.36-2.22 (m, 2H, CHC(O)), 2.10-1.98 (m, 1H, $NCH_2CH$), 1.62-1.50 (m, 1H, $NCH_2CH$), 1.44 (s, 18H, $CMe_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 171.6 (C=O, $CO_2CMe_3$), 154.7 (C=O, Boc), 80.8 ($OCMe_3$), 79.3 ($OCMe_3$), 51.3 ($NCH_2$), 50.9 ($NCH_2$), 45.6 ($NCH_2$), 45.2 ($NCH_2$), 39.2 ($CH_2C(O)$), 39.1 ($CH_2C(O)$), 35.7 ($NCH_2CH$), 34.9 ($NCH_2CH$), 31.6 ($NCH_2CH_2$), 30.9 ($NCH_2CH_2$), 28.7 ($CMe_3$), 28.2 ($CMe_3$); MS (ESI) *m/z* 308 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{15}H_{27}NO_4$ $(M + Na)^+$ 308.1832, found 308.1832 (0.0 ppm error). Spectroscopic data are consistent with those reported in the literature.[162]

Lab Book Reference: SLB-E-147

**4,5,6,7-Tetrachloro-2-hydroxyisoindoline-1,3-dione 303**



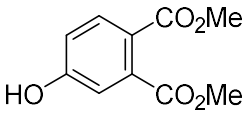

**303**

Hydroxyl amine hydrochloride (3.47 g, 50 mmol, 2.0 eq.) was added to a stirred solution of phthalic anhydride (7.15 g, 25 mmol, 1.0 eq.) in pyridine (32 mL) at rt. The resulting

red solution was stirred and heated at 80 °C for 20 h. After being allowed to cool to rt, the mixture was poured into $H_2O$ (100 mL) and acidified to pH 1 by the addition of 3 M $HCl_{(aq)}$ (100 mL). The solid was collected by filtration, washed with $H_2O$ (3 × 100 mL) and dried under reduced pressure to give tetrachloro-*N*-hydroxy phthalimide **303** (5.91 g, 79%) as an orange solid, mp 245-247 °C; IR (ATR) 3580 (O-H), 3495 (O-H), 2950, 2801, 1712 (C=O), 1619, 1359, 1303, 1158 $cm^{-1}$; $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 161.3 (C=O), 140.5 (*ipso*-Ar), 131.8 (*ipso*-Ar), 127.3 (*ipso*-Ar); MS (ESI) *m/z* 299 [$(M(^{35}Cl_3{}^{37}Cl) - H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_8H^{35}Cl_3{}^{37}ClNO_3$ $(M - H)^-$ 299.8608, found 299.8608 (0.0 ppm error).

Lab Book Reference: SLB 2-2

**Dimethyl 4-hydroxyphthalate 335**

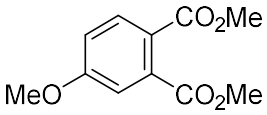



**335**

18 M sulphuric acid (0.3 mL, 5.6 mmol, 0.17 eq.) was added to a stirred solution of 4-hydroxyphthalic acid (6.0 g, 33 mmol, 1.0 eq.) in MeOH (60 mL) at rt. The resulting solution was stirred and heated at 70 °C for 12 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 50:50 hexane-EtOAc as eluent gave alcohol **335** (4.94 g, 71%) as a white solid, mp 103-105 °C (lit.,[163] 110-111 °C); $R_F$ (50:50 hexane-EtOAc) 0.35; IR (ATR) 3379 (O-H), 1730 (C=O), 1687, 1572, 1433, 1292, 1212, 1067 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.74 (d, $J$ = 8.5 Hz, Ar), 7.04 (br s, 1H, OH), 7.00 (d, $J$ = 2.5 Hz, 1H, Ar), 6.92 (dd, $J$ = 8.5, 2.5 Hz, 1H, Ar), 2.95 (s, 3H, OMe), 3.86 (s, 3H, OMe); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 169.7 (C=O), 167.3 (C=O), 159.4 (*ipso*-Ar), 135.7 (*ipso*-Ar), 132.0 (Ar), 121.7 (*ipso*-Ar), 117.4 (Ar), 115.4 (Ar), 53.1 (OMe), 52.6 (OMe); MS (ESI) *m/z* 233 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{10}H_{10}O_5$ $(M + Na)^+$ 233.0420, found 233.0415 (+2.3 ppm error). Spectroscopic data are consistent with those reported in the literature.[163]

Lab Book Reference: SLB 2-55

**Dimethyl 4-methoxyphthalate 336**

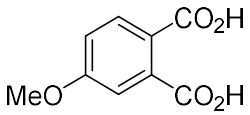



**336**

$K_2CO_3$ (16.2 g, 117 mmol, 5.0 eq.) was added to a stirred solution of alcohol **335** (4.94 g, 23.5 mmol, 1.0 eq.) in acetone (150 mL) at rt. The resulting solution was stirred and heated at 50 °C for 20 min. Then, MeI (3.2 mL, 52 mmol, 2.2 eq.) was added and the mixture was stirred and heated at reflux for 6 h. After being allowed to cool to rt, the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give ester **336** (5.23 g, 99%) as an orange oil, IR (ATR) 2953, 1721 (C=O), 1603, 1434, 1283, 1235, 1123 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.81 (d, $J$ = 9.0 Hz, 1H, Ar), 7.06 (d, $J$ = 2.5 Hz, 1H, Ar), 6.99 (dd, $J$ = 9.0, 2.5 Hz, 1H, Ar), 3.91 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.86 (s, 3H, OMe); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 169.1 (C=O), 166.9 (C=O), 162.2 (*ipso*-Ar), 135.9 (*ipso*-Ar), 131.8 (Ar), 122.3 (*ipso*-Ar), 115.9 (Ar), 113.6 (Ar), 55.8 (OMe), 52.9 (OMe), 52.5 (OMe); MS (ESI) *m/z* 247 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{11}H_{12}O_5$ $(M + Na)^+$ 247.0577, found 247.0577 (0.0 ppm error). Spectroscopic data are consistent with those reported in the literature.[164]

Lab Book Reference: SLB 2-47

**4-Methoxyphthalic acid 337**



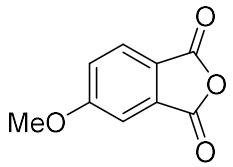

**337**

0.5 M $NaOH_{(aq)}$ (88 mL, 44 mmol, 3 eq.) was added to a stirred solution of ester **336** (12.3 g, 55 mmol, 1.0 eq.) and THF (90 mL) at rt. The resulting solution was stirred at rt for 20 h. The THF was evaporated under reduced pressure and the mixtures was acidified to pH 2 by the addition of 3 M $HCl_{(aq)}$ (15 mL). The mixture was extracted with EtOAc (3 × 150 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give acid **337** (9.34 g, 86%) as a pale yellow solid, mp 158-160 °C (lit.,[165] 160-165 °C); IR (ATR) 2984 (O-H), 2533 (O-H), 1672 (C=O), 1600, 1567, 1277, 1228, 1065 $cm^{-1}$; $^1H$ NMR (400 MHz, $d^6$-DMSO) $\delta$ 7.74 (d, $J$ = 8.5 Hz, 1H, Ar), 7.10 (d,

*J* = 3.0 Hz, 1H, Ar), 7.06 (dd, *J* = 8.5, 3.0 Hz, 1H, Ar), 3.84 (s, 3H, OMe); $^{13}$C NMR (100.6 MHz, d$^6$-DMSO) $\delta$ 169.2 (C=O), 167.4 (C=O), 161.4 (*ipso*- Ar), 137.1 (*ipso*- Ar), 131.3 (Ar), 122.7 (*ipso*- Ar), 115.1 (Ar), 113.0 (Ar), 55.7 (OMe); MS (ESI) *m/z* 219 [(M + Na)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_9H_8O_5$ (M + Na)$^+$ 219.0264, found 219.0266 (−1.1 ppm error). Spectroscopic data are consistent with those reported in the literature.[166]

Lab Book Reference: SLB 2-74

**5-Methoxyisobenzofuran-1,3-dione 338**

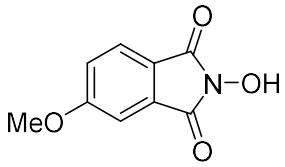



**338**

A solution of acid **337** (1.71 g, 8.7 mmol, 1.0 eq.) and $Ac_2O$ (24 mL) was stirred and heated at reflux for 12 h. The solution was evaporated under reduced pressure to give a solid residue. $CH_2Cl_2$ (50 mL) was added and the solids were removed by filtration through fritted glass. The filtrate was evaporated under reduced pressure to give anhydride **338** (1.53 g, 99%) as a pale brown solid, mp 87-92 °C (lit.,[167] 93-94 °C); IR (ATR) 3109, 1846, 1766 (C=O), 1611, 1491, 1291, 1264, 1086 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.90 (d, *J* = 8.5 Hz, 1H, Ar), 7.42 (d, *J* = 2.5 Hz, 1H, Ar), 7.35 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar), 3.98 (s, 3H, OMe); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 166.3 (C=O), 163.2 (C=O), 162.6 (*ipso*- Ar), 134.3 (*ipso*-Ar), 127.4 (Ar), 123.4 (Ar), 123.2 (*ipso*-Ar), 109.0 (Ar), 56.6 (OMe); MS (ESI) *m/z* 233 [(M + Na + MeOH)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_9H_6O_4$ (M + Na + MeOH)$^+$ 233.0431, found 233.0421 (+4.3 ppm error). Spectroscopic data are consistent with those reported in the literature.[168]

Lab Book Reference: SLB 2-63

**2-Hydroxy-5-methoxyisoindoline-1,3-dione 306**

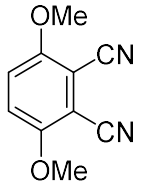



**306**

Hydroxyl amine hydrochloride (1.66 g, 24 mmol, 2.0 eq.) was added to a stirred solution of anhydride **338** (1.53 g, 12 mmol, 1.0 eq.) in pyridine (10 mL) at rt. The resulting red solution was stirred and heated at 80 °C for 20 h. After being allowed to cool to rt, the mixture was poured into $H_2O$ (100 mL) and acidified to pH 1 by the addition of 3 M $HCl_{(aq)}$ (100 mL). The solid was collected by filtration, washed with $H_2O$ (3 × 100 mL) and dried under reduced pressure to give *N*-hydroxy phthalimide **306** (1.64 g, 71%) as a pale yellow solid, mp 208-210 °C (dec.) (lit.,[167] 213 °C); IR (ATR) 3139 (O-H), 2955, 1706 (C=O), 1614, 1486, 1293, 1239, 1123 $cm^{-1}$; $^1H$ NMR (400 MHz, $d^6$-DMSO) $\delta$ 10.7 (OH), 7.73 (d, $J$ = 8.5 Hz, 1H, Ar), 7.32 (d, $J$ = 2.5 Hz, 1H, Ar), 7.26 (dd, $J$ = 8.5, 2.5 Hz, 1H, Ar), 3.87 (s, 3H, OMe); $^{13}C$ NMR (100.6 MHz, $d^6$-DMSO) $\delta$ 164.4 (C=O), 164.1 (C=O), 163.9 (*ipso*- Ar), 131.4 (*ipso*-Ar), 125.1 (Ar), 120.3 (*ipso*-Ar), 119.4 (Ar), 108.8 (Ar), 56.3 (OMe); MS (ESI) *m/z* 192 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_9H_7NO_4$ $(M - H)^-$ 192.0302, found 192.0301 (+0.7 ppm error). Spectroscopic data are consistent with those reported in the literature.[167]

Lab Book Reference: SLB 2-65

**3,6-Dimethoxyphthalonitrile 340**



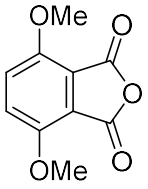

**340**

$K_2CO_3$ (12.4 g, 90 mmol, 9 eq.) and then dimethyl sulfate (8 mL, 85 mmol, 8.5 eq.) were added sequentially to a stirred solution of 1,4-dimethoxy-2,3-dicyanobenzene (1.60 g, 10 mmol, 1.0 eq.) in 2-butanone (50 mL) at rt. The resulting solution was stirred and heated at reflux for 20 h. After being allowed to cool to rt, the solid was collected by filtration to

give methoxy nitrile **340** (1.46 g, 78%) as a white solid, mp 270-272 °C (dec.) (lit.,[130] 273-274 °C) ; IR (ATR) 3094, 2227 (C≡N), 1483, 1284, 1198, 1058 $cm^{-1}$; $^1H$ NMR (400 MHz, $d^6$-DMSO) $\delta$ 7.64 (s, 2H, Ar), 3.93 (s, 6H, OMe); $^{13}C$ NMR (100.6 MHz, $d^6$-DMSO) $\delta$ 156.0 (*ipso*-Ar), 120.2 (Ar), 114.2 (*ipso*-Ar or C≡N), 103.0 (*ipso*-Ar or C≡N), 57.7 (OMe); MS (ESI) *m/z* 211 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{10}H_8N_2O_2$ $(M + Na)^+$ 211.0478, found 211.0477 (+0.2 ppm error). Spectroscopic data are consistent with those reported in the literature.[130]

Lab Book Reference: SLB 2-42

**4,7-Dimethoxyisobenzofuran-1,3-dione 341**

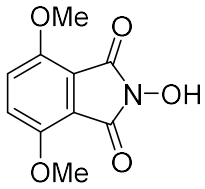



**341**

A solution of methoxy nitrile **340** (4.60 g, 24.4 mmol, 1.0 eq.) in 18 M $H_2SO_{4(aq)}$ (25 mL) was stirred and heated at 85 °C for 1 h. After being allowed to cool to rt, the mixture was stirred at rt for 20 h. The mixture was cooled to 0 °C and $H_2O$ (200 mL) was added slowly and the solid was collected by filtration. The solid was stirred in acetone (10 mL) at rt for 1 h. Then, the solid was collected by filtration to give anhydride **341** (3.56 g, 71%) as a pale yellow solid, mp 251-252 °C (dec.) (lit.,[169] 252-253 °C); IR (ATR) 2949, 1833 (C=O), 1766 (C=O), 1499, 1282, 1186, 1034 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 7.61 (s, 2H, Ar), 3.94 (s, 6H, OMe); $^{13}C$ NMR (100.6 MHz, $CD_3OD$) $\delta$ 161.1 (C=O), 151.7 (*ipso*- Ar), 123.1 (Ar), 117.3 (*ipso*-Ar), 57.2 (OMe) ; MS (ESI) *m/z* 263 [$(M + Na + MeOH)^+$, 100], 209 [{$(M + Na)^+$, 40]; HRMS (ESI) *m/z* calcd for $C_{10}H_8O_5$ $(M + Na + MeOH)^+$ 263.0537, found 263.0524 (+4.9 ppm error). Spectroscopic data are consistent with those reported in the literature.[169]

Lab Book Reference: SLB 2-43

**2-Hydroxy-4,7-dimethoxyisoindoline-1,3-dione 307**

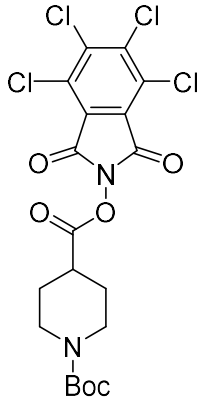



**307**

Hydroxyl amine hydrochloride (2.38 g, 34 mmol, 2.0 eq.) was added to a stirred solution of anhydride **341** (3.55 g, 17 mmol, 1.0 eq.) in pyridine (15 mL) at rt. The resulting red solution was stirred and heated at 80 °C for 20 h. After being allowed to cool to rt, the mixture was poured into $H_2O$ (100 mL) and acidified to pH 1 by the addition of 3 M $HCl_{(aq)}$ (100 mL). The solid was collected by filtration, washed with $H_2O$ (3 × 100 mL) and dried under reduced pressure to give *N*-hydroxy phthalimide **307** (3.81 g, 100%) as a pale yellow solid, mp 213-215 °C (dec.) (lit.,[170] 225-227 °C); IR (ATR) 3455 (O-H), 2717, 1693 (C=O), 1273, 1178, 1040 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 7.43 (s, 2H, Ar), 3.84 (s, 6H, OMe); $^{13}C$ NMR (100.6 MHz, $CD_3OD$) $\delta$ 162.6 (C=O), 150.5 (*ipso*- Ar), 122.1 (Ar), 114.6 (*ipso*-Ar), 56.9 (OMe); MS (ESI) *m/z* 268 [$(M + Na_2 - H)^+$, 100], 246 [$(M + Na)^+$, 90], 224 [$(M + H)^+$, 40] ; HRMS (ESI) *m/z* calcd for $C_{10}H_9NO_5$ $(M + H)^+$ 224.0553, found 224.0551 (+1.0 ppm error). Spectroscopic data are consistent with those reported in the literature.[170]

Lab Book Reference: SLB 2-45

**1-(*tert*-Butyl) 4-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl) piperidine-1,4-dicarboxylate 342**

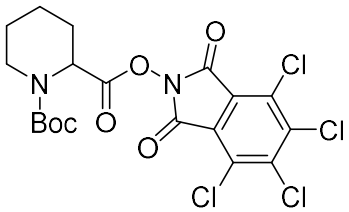


**342**

DIC (1.24 mL, 8.0 mmol, 1.1 eq.) was added dropwise to a stirred solution of *N*-Boc piperidine-4-carboxylic acid (1.68 g, 7.3 mmol, 1.0 eq.), tetrachloro-*N*-hydroxyphthalimide **303** (2.20 g, 7.3 mmol, 1.0 eq,) and DMAP (89 mg, 0.7 mmol, 0.1 eq.) in $CH_2Cl_2$ (50 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 20 h. The solution was evaporated under reduced pressure to ~10 mL and the solids were removed by filtration through a short pad of silica and washed with $CH_2Cl_2$ (50 mL). The filtrate was evaporated under reduced pressure to give NHPCl ester **342** (2.02 g, 54%) as a yellow solid, mp 192-195 °C (lit.,[114] 190-192 °C); IR (ATR) 973, 1742 (C=O), 1680 (C=O, Boc), 1380, 1364, 1161, 1038 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.01 (br s, 2H, NCH), 3.00 (dd, $J$ = 12.0, 12.0 Hz, 2H, NCH), 2.90 (tt, $J$ = 11.0, 4.0 Hz, 1H, CHC(O)), 2.03-1.97 (m, 2H, $NCH_2CH$), 1.89-1.76 (m, 2H, $NCH_2CH$), 1.45 (s, 9H, $CMe_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 170.3 (C=O), 157.7 (C=O), 154.6 (C=O), 141.2 (*ipso*-Ar), 130.6 (*ipso*-Ar), 124.8 (*ipso*-Ar), 80.0 ($OCMe_3$), 42.8 ($NCH_2$), 38.5 (CH), 28.5 ($CMe_3$), 27.8 ($NCH_2CH_2$); MS (ESI) *m/z* 534 [$(M(^{35}Cl_4{}^{37}Cl) + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}{}^{35}Cl_4{}^{37}ClN_2O_6$ $(M + Na)^+$ 534.9782, found 534.9775 (+1.2 ppm error). Spectroscopic data are consistent with those reported in the literature.[114]

Lab Book Reference: SLB 2-4

**1-(*tert*-Butyl) 2-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl) piperidine-1,2-dicarboxylate 343**

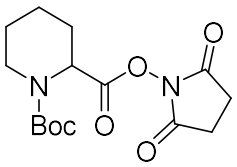



**343**

DIC (1.24 mL, 8.0 mmol, 1.1 eq.) was added dropwise to a stirred solution of *N*-Boc piperidine-2-carboxylic acid (1.68 g, 7.3 mmol, 1.0 eq.), tetrachloro-*N*-hydroxyphthalimide **303** (2.20 g, 7.3 mmol, 1.0 eq,) and DMAP (89 mg, 0.7 mmol, 0.1 eq.) in $CH_2Cl_2$ (50 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 20 h. The solution was evaporated under reduced pressure to ~10 mL and the solids were removed by filtration through a short pad of silica and washed with $CH_2Cl_2$ (50 mL). The filtrate was evaporated under reduced pressure to give NHPCl ester **343** (1.85 g, 50%) as a yellow solid, mp 170-172 °C (dec.) (lit.,[171] 180-183 °C); IR (ATR) 2981, 2942, 1748 (C=O), 1701 (C=O, Boc), 1367, 1161, 1033 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) $\delta$ 5.37 (br s, 0.3H, NCH), 5.12 (br d, $J$ = 6.0 Hz, 0.7H, NCH), 4.06 (br d, $J$ = 13.5 Hz, 0.7H, NCH), 3.96 (br d, $J$ = 14.0 Hz, 0.3H, NCH), 3.11-2.92 (m, 1H, NCH), 2.38-2328 (m, 1H, CH), 1.92-1.63 (m, 3H, CH), 1.54-1.36 (m, 2H, CH), 1.48 (s, 6.3H, $CMe_3$), 1.46 (s, 2.7H, $CMe_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 168.5 (C=O), 157.5 (C=O), 155.1 (C=O), 141.2 (*ipso*-Ar), 130.6 (*ipso*-Ar), 124.8 (*ipso*-Ar), 81.3 (O*C*$Me_3$), 80.8 (O*C*$Me_3$), 53.7 (NCH), 52.3 (NCH), 42.2 ($NCH_2$), 41.2 ($NCH_2$), 28.4 (C*Me*$_3$), 28.2 (C*Me*$_3$), 27.3 ($CH_2$), 24.8 ($CH_2$), 24.4 ($CH_2$), 20.6 ($CH_2$), 20.3 ($CH_2$); MS (ESI) *m/z* 567 [(M + Na + MeOH)$^+$, 100], 534 [(M + Na)$^+$, 30]; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}{}^{35}Cl_3{}^{37}ClN_2O_6$ (M + Na)$^+$ 534.9782, found 564.9777 (+0.9 ppm error). Spectroscopic data are consistent with those reported in the literature.[171]

Lab Book Reference: SLB 2-5

**1-(*tert*-Butyl) 2-(2,5-dioxopyrrolidin-1-yl) piperidine-1,2-dicarboxylate 344**

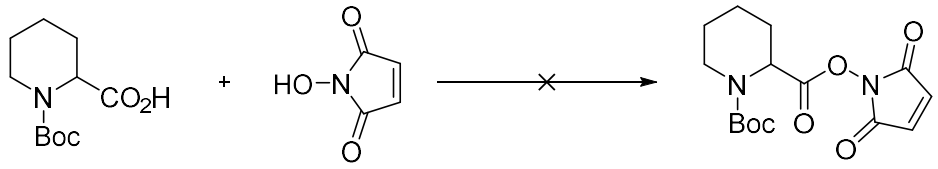



**344**

EDC (1.89 mL, 11 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc piperidine-2-carboxylic acid (2.06 g, 9 mmol, 1.0 eq.), *N*-hydroxysuccinimide (1.04 g, 9 mmol, 1.0 eq,) and DMAP (1.34 g, 12 mmol, 1.3 eq.) in $CH_2Cl_2$ (30 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 20 h. The mixture was then washed with 1 M $HCl_{(aq)}$ (50 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with sat. $NaHCO_{3(aq)}$ (50 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave NHS ester **344** (2.55 g, 87%) as a white solid, mp 118-120 °C; $R_F$ (60:40 hexane-EtOAc) 0.24; IR (ATR) 2944, 2866, 1738 (C=O), 1697 (C=O, Boc), 1392, 1366, 1202, 1136, 1067 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) $\delta$ 5.30 (br s, 0.3H, NCH), 5.06 (d, $J$ = 6.0 Hz, 0.7H, NCH), 4.03 (br d, $J$ = 13.5 Hz, 0.7H, NCH), 3.94 (br d, $J$ = 14.0 Hz, 0.3H, NCH), 3.09-2.90 (m, 1H, NCH), 2.83 (s, 4H, $NC(O)CH_2$), 2.29 (br d, $J$ = 14.0 Hz, 1H, CH), 1.86-1.69 (m, 3H, CH), 1.52-1.34 (m, 2H, CH), 1.45 (s, 9H, $CMe_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 168.8 (C=O), 167.9 (C=O), 155.2 (C=O, Boc), 81.1 ($OCMe_3$), 53.7 (NCH), 52.6 (NCH), 42.2 ($NCH_2$), 41.2 ($NCH_2$), 28.4 ($CMe_3$), 28.2 ($CMe_3$), 27.2 ($CH_2$), 25.7 ($NC(O)CH_2$), 24.4 ($CH_2$), 20.3 ($CH_2$); MS (ESI) *m/z* 349 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}N_2O_6$ $(M + Na)^+$ 349.1370, found 349.1364 (+1.7 ppm error).

Lab Book Reference: SLB 2-8

**Attempted synthesis of 1-(*tert*-butyl) 2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) piperidine-1,2-dicarboxylate 345**

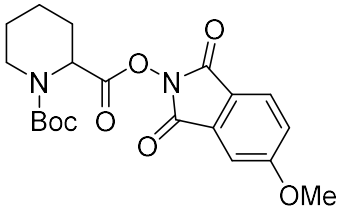


**300** **345**

EDC (0.1 mL, 0.5 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc piperidine-2-carboxylic acid (101 g, 0.4 mmol, 1.0 eq.), *N*-hydroxymaleimide (50 mg, 0.4 mmol, 1.0 eq,) and DMAP (70 mg, 0.6 mmol, 1.3 eq.) in $CH_2Cl_2$ (1.5 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 20 h. The mixture was then washed with 1 M $HCl_{(aq)}$ (10 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with sat. $NaHCO_{3(aq)}$ (10 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product that did not contain NHM **345** by $^1$H NMR spectroscopy and mass spectrometry.

Lab Book Reference: SLB 2-22

**1-(*tert*-Butyl) 2-(5-methoxy-1,3-dioxoisoindolin-2-yl) piperidine-1,2-dicarboxylate 346**



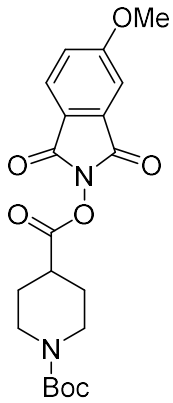
**346**

EDC (1.7 mL, 9.8 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc piperidine-2-carboxylic acid (1.87 g, 8.2 mmol, 1.0 eq.), NHP **306** (1.57 g, 8.2 mmol, 1.0 eq,) and DMAP (1.29 g, 10.7 mmol, 1.3 eq.) in $CH_2Cl_2$ (30 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 20 h. The mixture was then washed with 1 M $HCl_{(aq)}$ (50 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with sat. $NaHCO_{3(aq)}$ (50 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were dried ($MgSO_4$)

and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave NHP ester **346** (2.0 g, 61%) as a white solid, mp 100-102 °C; $R_F$ (80:20 hexane-EtOAc) 0.31; IR (ATR) 2943, 1740 (C=O), 1703 (C=O, Boc), 1489, 1289, 1250 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) $\delta$ 7.79 (d, $J$ = 8.5 Hz, 1H, Ar), 7.35 (d, $J$ = 2.5 Hz, 1H, Ar), 7.21 (dd, $J$ = 8.5, 2.5 Hz, 1H, Ar), 5.36 (br s, 0.3H, NCH), 5.12 (br d, $J$ = 6.0 Hz, 0.7H, NCH), 4.06 (br d, $J$ = 12.5 Hz, 0.7H, NCH), 4.02-3.90 (m, 0.3H, NCH), 3.94 (s, 3H, OMe), 3.09 (dd, $J$ = 12.5, 12.5 Hz, 0.3H, NCH), 3.03 (dd, $J$ = 12.5, 12.5 Hz, 0.7H, NCH), 2.36 (br d, $J$ = 13.5 Hz, 1H, CH), 1.91-1.64 (m, 3H, CH), 1.59-1.36 (m, 2H, CH), 1.50 (s, 6.3H, $CMe_3$), 1.48 (s, 2.7H, $CMe_3$) ; $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 165.3 (*ipso*-Ar), 162.1 (*ipso*-Ar), 161.9 (*ipso*-Ar), 155.3 (C=O, Boc), 131.6 (*ipso*-Ar), 126.1 (Ar), 120.8 (*ipso*-Ar), 120.5 (Ar), 109.1 (Ar), 81.2 (O*C*$Me_3$), 56.3 (OMe), 53.7 (NCH), 41.3 ($NCH_2$), 28.4 (C*Me*$_3$), 28.3 (C*Me*$_3$), 27.3 ($CH_2$), 24.5 ($CH_2$), 20.4 ($CH_2$); MS (ESI) *m/z* 427 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{20}H_{24}N_2O_7$ $(M + Na)^+$ 427.1476, found 427.1478 (−0.6 ppm error).

Lab Book Reference: SLB 2-67

**1-(*tert*-Butyl) 4-(5-methoxy-1,3-dioxoisoindolin-2-yl) piperidine-1,4-dicarboxylate 347**



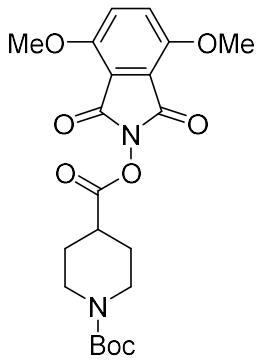

**347**

EDC (1.34 mL, 6.2 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc piperidine-2-carboxylic acid (1.2 g, 5.2 mmol, 1.0 eq.), NHP **306** (1.0 g, 5.2 mmol, 1.0 eq,) and DMAP (0.82 g, 6.7 mmol, 1.3 eq.) in $CH_2Cl_2$ (20 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 20 h. The mixture was then washed with 1 M $HCl_{(aq)}$

(50 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with sat. $NaHCO_{3(aq)}$ (50 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave NHP ester **347** (1.22 g, 58%) as a white solid, mp 85-87 °C; $R_F$ (60:40 hexane-EtOAc) 0.29; IR (ATR) 2974, 1740 (C=O), 1691 (C=O, Boc), 1489, 1364, 1289, 1169, 1017 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.79 (d, $J$ = 8.5 Hz, 1H, Ar), 7.35 (d, $J$ = 2.5 Hz, 1H, Ar), 7.21 (dd, $J$ = 8.5, 2.5 Hz, 1H, Ar), 4.03 (ddd, $J$ = 13.0, 4.0, 4.0 Hz, 2H, NCH), 3.94 (s, 3H, OMe), 3.00 (ddd, $J$ = 13.0, 10.5, 4.0 Hz, 2H, NCH), 2.89 (tt, $J$ = 10.5, 4.0 Hz, 1H, CHC(O)), 2.05 (dddd, $J$ = 14.0, 4.0, 4.0, 4.0 Hz, 2H, $NCH_2CH$), 1.84 (dddd, $J$ = 14.0, 10.5, 10.5, 4.0 Hz, 2H, $NCH_2CH$), 1.45 (s, 9H, $CMe_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 170.9 (C=O), 165.3 (*ipso*-Ar), 162.2 (*ipso*-Ar), 162.1 (*ipso*-Ar), 154.7 (C=O, Boc), 131.6 (*ipso*-Ar), 126.1 (Ar), 120.7 (*ipso*-Ar), 120.5 (Ar), 109.1 (Ar), 80.0 ($OCMe_3$), 56.3 (OMe), 42.7 ($NCH_2$), 38.7 ($CHC(O)$), 28.6 ($CMe_3$), 27.9 ($NCH_2CH_2$); MS (ESI) *m/z* 427 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{20}H_{24}N_2O_7$ $(M + Na)^+$ 427.1476, found 427.1469 (+1.6 ppm error).

Lab Book Reference: SLB 2-84

**1-(*tert*-Butyl) 4-(4,7-dimethoxy-1,3-dioxoisoindolin-2-yl) piperidine-1,4-dicarboxylate 348**



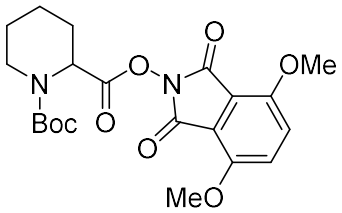

**348**

EDC (0.8 mL, 3.6 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc piperidine-4-carboxylic acid (688 mg, 3.0 mmol, 1.0 eq.), NHP **307** (669 mg, 3.0 mmol,

1.0 eq,) and DMAP (476 mg, 3.9 mmol, 1.3 eq.) in $CH_2Cl_2$ (10 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 20 h. The mixture was then washed with 1 M $HCl_{(aq)}$ (10 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with sat. $NaHCO_{3(aq)}$ (10 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 60:40 hexane-EtOAc as eluent gave NHP ester **348** (532 mg, 41%) as a yellow solid, mp 152-154 °C; $R_F$ (80:20 EtOAc-hexane) 0.33; IR (ATR) 2979, 1792 (C=O), 1691 (C=O, Boc), 1498, 11277, 1048 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.22 (s, 2H, Ar), 4.01-3.88 (m, 2H, NCH), 3.95 (s, 6H, OMe), 3.02 (ddd, $J$ = 14.0, 10.5, 3.0 Hz, 2H, NCH), 2.88 (tt, $J$ = 10.0, 4.0 Hz, 1H, CHC(O)), 2.05-1.97 (m, 2H, $NCH_2CH$), 1.88-1.77 (m, 2H, $NCH_2CH$), 1.44 (s, 9H, $CMe_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 170.9 (C=O), 160.5 (C=O), 154.7 (C=O, Boc), 141.1 (*ipso*-Ar), 121.1 (Ar), 114.9 (*ipso*-Ar), 79.8 ($OCMe_3$), 56.8 (OMe), 42.6 ($NCH_2$), 38.4 (*C*HC(O)), 28.5 ($CMe_3$), 27.8 ($NCH_2CH_2$); MS (ESI) *m/z* 457 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{21}H_{26}N_2O_8$ $(M + Na)^+$ 457.1581, found 457.1582 (−0.1 ppm error).

Lab Book Reference: SLB 2-80

**1-(*tert*-Butyl) 2-(4,7-dimethoxy-1,3-dioxoisoindolin-2-yl) piperidine-1,2-dicarboxylate 349**



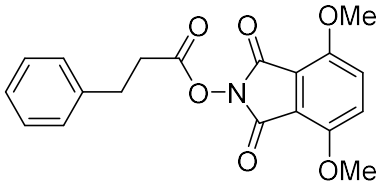

**349**

EDC (3.6 mL, 20.5 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc piperidine-2-carboxylic acid (3.92 g, 17.1 mmol, 1.0 eq.), NHP **307** (3.83 mg, 17.1 mmol, 1.0 eq,) and DMAP (2.72 mg, 22.2 mmol, 1.3 eq.) in $CH_2Cl_2$ (60 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 20 h. The mixture was then washed with 1 M $HCl_{(aq)}$ (100 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic layers were washed with sat. $NaHCO_{3(aq)}$ (10 mL) and the aqueous

layer was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 60:40 hexane-EtOAc as eluent gave NHP ester **349** (3.41 g, 46%) as a yellow solid, mp 168-170 °C; $R_F$ (60:40 EtOAc-hexane) 0.48; IR (ATR) 2934, 1736 (C=O), 1704 (C=O, Boc), 1500, 1280, 1162, 1050 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) $\delta$ 7.25 (s, 2H, Ar), 5.35 (br s, 0.3H, NCH), 5.10 (br d, $J$ = 6.0 Hz, 0.7H, NCH), 4.04 (br d, $J$ = 14.0 Hz, 0.7H, NCH), 4.00-3.90 (m, 0.3H, NCH), 3.97 (s, 6H, OMe), 3.09 (dd, $J$ = 13.5, 13.5 Hz, 0.3H, NCH), 3.03 (dd, $J$ = 12.5, 12.5 Hz, 0.7H, NCH), 2.36 (br d, $J$ = 12.0 Hz, 1H, CH), 1.89-1.70 (m, 3H, CH), 1.58-1.35 (m, 2H, CH), 1.48 (s, 6.3H, $CMe_3$), 1.46 (s, 2.7H, $CMe_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (rotamers) $\delta$ 169.0 (C=O), 160.4 (C=O), 155.3 (C=O, Boc), 151.2 (*ipso*-Ar), 121.0 (Ar), 115.1 (*ipso*-Ar), 81.1 (O*C*$Me_3$), 56.8 (OMe), 53.7 (NCH), 52.6 (NCH), 42.2 ($NCH_2$), 41.2 ($NCH_2$), 28.4 (C*Me*$_3$), 28.3 (C*Me*$_3$), 27.4 ($CH_2$), 24.7 ($CH_2$), 24.6 ($CH_2$), 20.6 ($CH_2$), 20.3 ($CH_2$); MS (ESI) *m/z* 457 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{21}H_{26}N_2O_8$ $(M + Na)^+$ 457.1581, found 457.1571 (+2.3 ppm error).

Lab Book Reference: SLB 2-54-1

**4,7-Dimethoxy-1,3-dioxoisoindolin-2-yl 3-phenylpropanoate 350**




**350**

EDC (0.8 mL, 3.6 mmol, 1.2 eq.) was added dropwise to a stirred solution of hydrocinnamic acid (451 mg, 3.0 mmol, 1.0 eq.), NHP **307** (669 mg, 3.0 mmol, 1.0 eq,) and DMAP (476 mg, 3.9 mmol, 1.3 eq.) in $CH_2Cl_2$ (10 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 20 h. The mixture was then washed with 1 M $HCl_{(aq)}$ (10 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with sat. $NaHCO_{3(aq)}$ (10 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 60:40 hexane-EtOAc as eluent gave NHP ester

**350** (457 mg, 43%) as a yellow solid, mp 126-127 °C; $R_F$ (60:40 EtOAc-hexane) 0.41; IR (ATR) 2941, 1728 (C=O), 1499, 1278, 1046 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.35-1.29 (m, 2H, Ph), 7.27-7.20 (m, 3H, Ph), 7.25 (s, 2H, Ar), 3.98 (s, 6H, OMe), 3.12-3.06 (m, 2H, $CH_2$), 2.99-2.65 (m, 2H, $CH_2$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 169.1 (C=O), 160.5 (C=O), 151.2 (*ipso*-Ar), 139.5 (*ipso*-Ar), 128.8 (Ar), 128.5 (Ar), 126.8 (Ar), 121.0 (Ar), 115.1 (*ipso*-Ar), 56.9 (OMe), 32.9 ($CH_2$), 30.8 ($CH_2$); MS (ESI) *m/z* 378 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{19}H_{17}NO_6$ $(M + Na)^+$ 378.0948, found 378.0954 (−1.5 ppm error).

Lab Book Reference: SLB 2-81

# Abbreviations

| | |
|---|---|
| A | Amps |
| Ac | Acetyl |
| acac | Acetylacetone |
| AIBN | Azobisisobutronitrile |
| app | apparent |
| aq. | Aqueous |
| Ar | Aryl |
| BDMAP | 1,6-bis(dimethylamino)pyrene |
| $BMIMBF_4$ | 1-Butyl-3-methylimidazolium tetrafluoroborate |
| Bn | Benzyl |
| BNAH | 1-Benzyl-1,4-dihydronicotinamide |
| Boc | *tert*-Butoxycarbonyl |
| bp | Boiling point |
| bpy | 2,2′-Bipyridine |
| br | Broad |
| Bu | Butyl |
| $cm^{-1}$ | Wave length |
| d | Doublet |
| DABCO | 1,4-Diazabicyclo(2,2,2)octane |
| DCC | *N*,*N*′-Dicyclohexylcarbodiimide |
| DIPEA | di-*iso*-propylethylamine |
| DMA | Dimethylacetamide |
| DMAP | Dimethylaminopyridine |
| dmbpy | 4-4′-Dimethoxy-2-2′-bipyridine |
| DME | Dimethyl ether |

| | |
|---|---|
| DMF | Dimethyl formamide |
| DMSO | Dimethylsulfoxide |
| dr | Diastereomeric ratio |
| dtbbpy | 4,4'-Di-*tert*-butyl-2,2'-dipyridyl |
| EDC | 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| $EMIMNTf_2$ | 1-Ethyl-3-methylimidazolium bis((trifluoromethyl)sulfonyl)imide |
| eq. | Equivalents |
| er | Enantiomeric ratio |
| ESI | Electrospray Ionisation |
| F $mol^{-1}$ | Charge equivalent |
| g | Gram(s) |
| GC | Gas chromatography |
| glyme | dimethoxyethane |
| h | Hour(s) |
| HFIP | Hexafluoro-2-propanol |
| HPLC | High-performance liquid chromatography |
| HRMS | High resolution mass |
| Hz | Hertz |
| *i*-Pr | *iso*-Propyl |
| IR | Infra-red |
| *J* | Coupling constant in Hertz |
| LED | Light Emitting Diode |
| M | molar |
| m | Multiplet |
| *m/z* | Mass to charge ratio |
| $M^+$ | Molecular ion |

| | |
|---|---|
| mA $cm^{-2}$ | Current density |
| Me | Methyl |
| mg | Milligrams |
| min | Minutes |
| mL | Millilitre |
| mmol | Millimole |
| mol | Mole |
| mp | Melting point |
| MS | Mass Spectrometry |
| NHE | Normal Hydrogen Electrode |
| NHM | *N*-hydroxymaleimide |
| NHP | *N*-Hydroxyphthalimide |
| NHS | *N*-hydroxysuccinimide |
| NMR | Nuclear Magnetic Resonance |
| Ph | Phenyl |
| phth | Phthalimide |
| ppm | Parts per million |
| ppy | 2-phenylpyridine |
| PTFE | Polytetrafluoroethylene |
| q | Quartet |
| R | Alkyl or aryl group |
| $R_F$ | Retention factor |
| rt | Room temperature |
| RVC | Reticulated vitreous carbon |
| s | Singlet |
| salen | *N*,*N*'-bis(salicylidine)ethylenediamino |

| | |
|---|---|
| SCE | Saturated calomel electrode |
| SET | Single Electron Transfer |
| t | Triplet |
| *t*-Bu | *tert*-Butyl |
| Tf | Trifluoromethylsulfonyl |
| THF | Tetrahydrofuran |
| TLC | Thin layer chromatography |
| TMP | tetramethyl piperidine |
| TMS | trimethylsilyl |
| Ts | *para*-Toluenesulfonyl |
| UV | Ultraviolet |
| V | Volts |
| δ | Chemical shift |

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