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Developments in C-H Oxidation Methodologies

A thesis submitted to The University of Nottingham for the degree of Doctor of Philosophy by

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Abstract

Chapter One of this thesis describes classical oxidation methodologies and the importance of the development of sustainable methodologies. The overall thesis aims are also outlined in relation to this.

In Chapter Two, cross-dehydrogenative coupling reactions to form benzylic C-C bonds are investigated with photo-activated 1,4-hydroquinone (BQH_2). A review of the relevant literature describes catalytic DDQ oxidations and known CDC reactions. This is followed by our research findings with photo-activated BQH_2 in Chapter Three.

The use of visible light and BQH_2 is extended to the synthesis of benzylic esters in Chapter Four. The protocol employs sub-stoichiometric quantities of BQH_2 and copper chloride dihydrate in dimethyl carbonate (DMC) and displays how the natural product arbutin, derived from bearberry (*uva-ursi)* leaves, may also be used as a sustainable pre-oxidant.

The oxidation of unactivated alkanes is discussed in Chapter Five. Discussed are Nature's approaches, both metal and non-metal mediated to oxidise alkanes. The most common modern synthetic procedures for such transformations are also reviewed as well as previous work by the Moody Group.

Chapter Six reports the research findings which focus on the further exploration of the work published by the Moody group, focusing on the use of commercial hydrogen peroxide solutions commonly used in cleaning as an oxidant in the presence of acid. Work has been conducted to optimise existing conditions and further investigate the scope of the reaction. Potential future work in this area is also reported.

Chapter Seven contains full experimental details for the described research.

Declaration

I hereby declare that, except for where specific reference is made to other sources, the work contained within this thesis is the original work of my own research and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification. I confirm that the work submitted is my own, except work which has formed part of jointly-authored publications. The contributions of myself and other authors to this work have been specifically indicated where relevant. I confirm that appropriate credit has been given within this thesis where references have been made to the work of others. Part of this work contains results reported in the following publication:

1. Visible light mediated oxidation of benzylic sp3 C–H bonds using catalytic 1,4-hydroquinone, or its biorenewable glucoside, arbutin, as a pre-oxidant; Laura C. Finney, Lorna J. Mitchell and Christopher J. Moody, *Green Chem*., 2018, **20**, 2242-2249.

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Contents

Abbreviations

ACT – 4-acetamido-TEMPO

BQ – *p*-benzoquinone

BQH_2 – 1,4-hydroquinone

CDC – cross-dehydrogenative coupling

CI – chemical ionisation

Cu_{NP} – copper nanoparticles

$DBADH_2$ – di-*tert*-butyl hydrazine-1,2-dicarboxylate

DCE – 1,2-dichloroethane

DDQ – 2,3-dichloro-4,5-dicyano-1,4-benzoquinone

$DDQH_2$ – 2,3-dichloro-4,5-dicyano-1,4-hydroquinone

DFT – density functional theory

DIBAL-H –di*iso*butylaluminium hydride

DMC – dimethyl carbonate

DMDO – dimethyldioxirane

DMF – *N.N*-dimethyl formamide

DMP – Dess-Martin periodinate

DMS – dimethylsulfide

DMSO – dimethylsulfoxide

EI – electron ionisation

ESI – electrospray ionisation

ETM – electron transfer mediator

GC – gas chromatography

GCMS – gas chromatography mass spectrometry

HPLC – high performance liquid chromatography

HQI - hydrargyrum quartz iodide

HRMS – high resolution mass spectrometry

IBX – 2-iodoxybenzoic acid

IR – infrared

J – coupling constant

LD_{50} – lethal dose, 50%

LED – light-emitting diode

mp – melting point

NCS – *N*-chlorosuccinimide

ND – not detected

NMR – nuclear magnetic spectroscopy

NR – no reaction

Nu – nucleophile

PCC – pyridinium chlorochromate

PDC – pyridinium dichromate

perTFA – trifluoroperacetic acid

PMB – *para*-methoxybenzyl

SET – single electron transfer

SHE – standard hydrogen electrode

TBN – *tert*-butyl nitrite

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

TFA – trifluoroacetic acid

TFAA – trifluoroacetic anhydride

TFDO – trifluoromethyldioxirane

TFT – trifluorotoluene

THF – tetrahydrofuran

TLC – thin layer chromatography

UHP – urea-hydrogen peroxide complex

Unless someone like you cares an awful lot,

nothing is going to get better.

It's not.

The Lorax

(written by Dr. Suess in The Lorax, 1971)

1. Introduction to Oxidation reactions and Sustainability

Oxidation reactions are amongst the most important reactions known to man. As well as being reactions in which atoms lose electrons, they are also defined as reactions in which a atoms, ions or molecule gains an atom/s of oxygen. In fact, oxygen is the third most abundant element in the universe, and the most abundant on Earth. It makes up nearly 2°% of the Earth's atmosphere, 66% of the mass of the human body, 47% of the Earth's crust and 90% of the oceans. Therefore, it is easy to see why oxygen and its oxidative reactions are fundamental to life on Earth. It has even been described as 'the molecule that made the World'.[1]

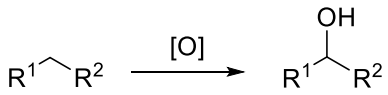
Many biological processes are reliant on oxidation reactions. For example, cellular respiration is the oxidation of glucose to CO_2 which is accompanied by the reduction of oxygen to water (**Scheme 1**).

$$C_6H_{12}O_6 + 6O_2 \longrightarrow 6CO_2 + 6H_2O$$

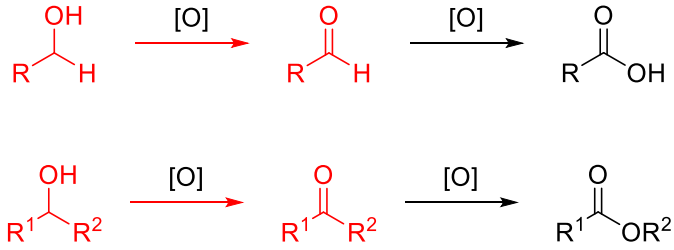
Scheme 1 The oxidation of glucose and reduction of oxygen, as seen in respiration processes.

This means that the manipulation of functional groups by oxidation has been of great importance to biology and chemistry. A range of chemical oxidation methodologies have been developed that have allowed access to many different synthetic handles at various oxidation states. It has been used to increase oxidation levels in order to synthesise alcohols, ketones, carboxylic acids, epoxides and sulfoxides to name but a few (**Scheme 2**).[2]

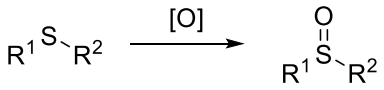
C-H oxidation



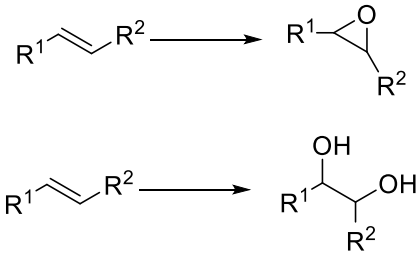
C-OH oxidation



C-X oxidation



C=C oxidation



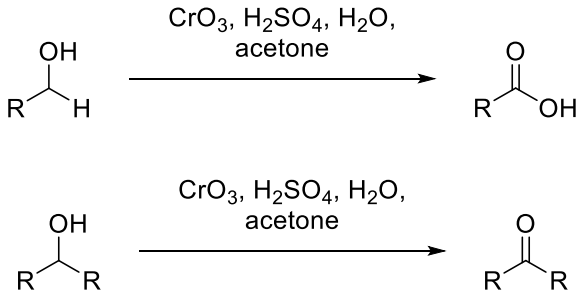
Scheme 2 General scheme displaying commonly encountered oxidation reactions in the laboratory.

This list of oxidation reactions is by no means comprehensive, but nevertheless gives an indication of their importance to chemistry to access a diverse range of functional groups. It is important to note however that many of the reactions shown have commonly been conducted in a largely unsustainable manner. The oxidation of alcohols will be focussed on as an example (**Scheme 2**, highlighted in red), since this is one of the most commonly encountered transformations in the organic synthesis and the chemical laboratory.

1.1 Classic Synthetic Laboratory Oxidation Strategies

Numerous strategies for oxidation, and more specifically alcohol oxidation, are available to the synthetic chemist. However, the most commonly employed laboratory protocols have often used stoichiometric quantities of high valent metal salts that pose problems with their cost, toxicity, atom economy and waste stream production.

One of the best-known examples of reagents capable of oxidising an alcohol are chromium (VI) reagents, such as the Jones' reagent. This allowed the oxidation of secondary alcohols to the corresponding ketones. However primary alcohols could not be selectively oxidised to the aldehydes as these were oxidised further, to the carboxylic acid (**Scheme 3**).[3]



Scheme 3 Jones' oxidation of both primary and secondary alcohols.

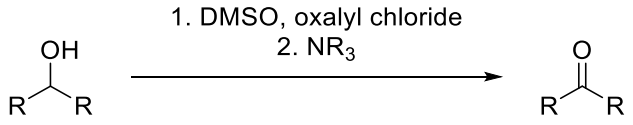
The Sarett reagent[4] (CrO_3•2py) was developed to circumvent some of the selectivity issues with the Jones' reagent and pleasingly, it allowed the oxidation of primary alcohols to the aldehydes. However, preparation of the Sarett reagent is risky since the improper addition of chromium trioxide to pyridine is potentially explosive. Additionally, the reagent needs to be used immediately due to its hygroscopic nature.

Furthermore, pyridine was used as the solvent and so base sensitive groups could not be present in the substrate. The alternative Collins reagent, which is the Sarett reagent diluted in dichloromethane, is easier to prepare and allowed for the reagent to be used more widely.

The Corey-Suggs[5] (pyridinium chlorochromate or PCC) and Corey-Schmidt[6] (pyridinium dichromate or PDC) reagents were both developed in attempts to improve upon the aforementioned chromium reagents. Both reagents could convert primary and secondary alcohols into aldehydes and ketones respectively in dichloromethane at room temperature. Although, both came with their own associated problems regarding hygroscopicity, acidity, difficult work-up and isolation procedures, as well as over-oxidation in some cases. It also remained that these all employ stoichiometric quantities of the metal reagent to conduct the reactions.

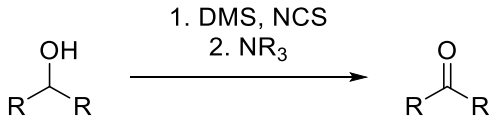
While these reagents are synthetically useful, they all utilise chromium. Chromium(VI) is notorious for its high toxicity (LD_{50} 13-28 chromium(VI)/kg) and carcinogenic nature and therefore is avoided where possible in modern chemistry.[7] Alternatives to chromium such as manganese dioxide (MnO_2)[8] and potassium permanganate ($KMnO_4$)[9] have also been employed in stoichiometric quantities to replace chromium in oxidation reactions.

However, we live in an age where sustainability in science continues to grow in importance. As a result, metal-mediated oxidation reactions have become increasingly unattractive due to their expense and often their lack of abundance.[10] As a solution to this, various organo-oxidation protocols have been developed. Probably the most famous of these is the Swern oxidation (**Scheme 4**).[11]



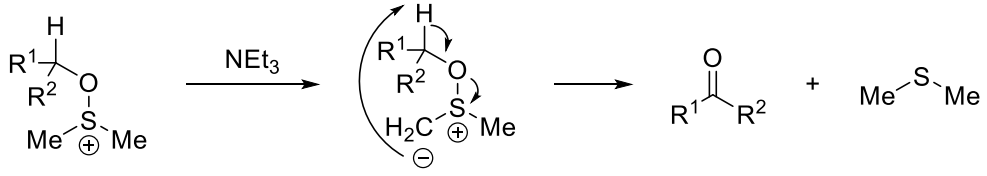
Scheme 4 General scheme for the Swern oxidation.

This protocol allows the oxidation of primary and secondary alcohols under mild conditions without the need for a metal, although it produces the malodorous dimethyl sulphide (DMS) in stoichiometric quantities. The Corey-Kim oxidation was developed as an improvement to the Swern methodology.[12] It employed DMS as a stoichiometric reagent (**Scheme 5**). However, this may also contaminate the products and the reactions must be performed at cryogenic temperatures which are energy intensive to reach and maintain.



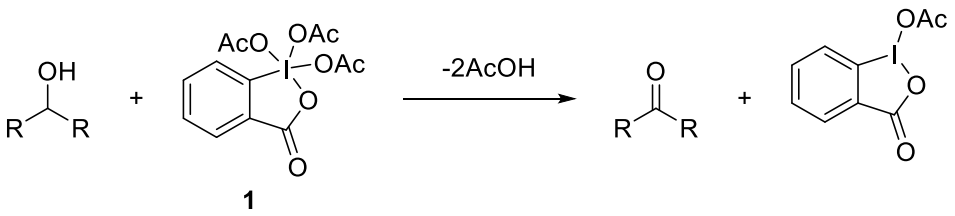
Scheme 5 The Corey-Kim oxidation.

Mechanistically, these two reactions are similar. They both proceed to generate the chlorodimethylsulfonium ion, which upon reaction with an alcohol generates an alkoxysulfonium ion. Deprotonation leads to the elimination of DMS and generation of the oxidised species (**Scheme 6**).



Scheme 6 Mechanism of the Corey-Kim oxidation from the dimethylsulfonium ion.

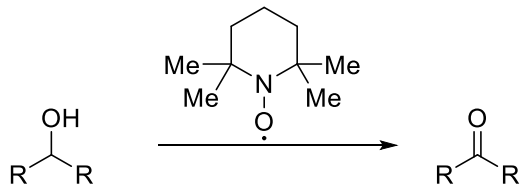
Hypervalent iodine reagents such as 2-iodoxybenzoic acid (IBX) or Dess-Martin periodinate (DMP)[13] **1** have also offered selective and mild oxidation of alcohols at room temperature and in short time frames. The products are easily separated from the reaction mixture. However, these reagents have disadvantages, with harmful and potentially explosive by-products (**Scheme 7**).



Scheme 7 DMP oxidation of alcohols.

Chlorinated solvents are also required which are known to be poor choices for the environment since they are toxic and carcinogenic to both land and aquatic life, as well as being environmentally persistent. They are predicted to be restricted by legislation in the future. In line with this, they are repeatedly listed as undesirable solvents in all of the popular solvent selection guides. [14]

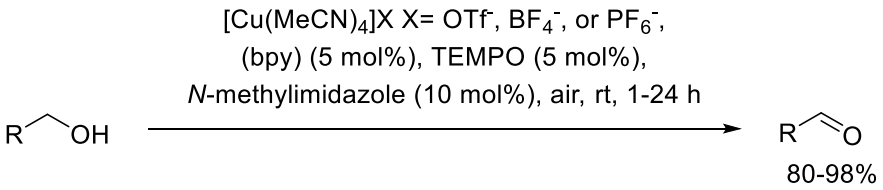
2,2,6,6-Tetramethylpiperidinyloxy (TEMPO) is a stable nitroxyl radical that has been used as a catalyst for alcohol oxidations and has provided a relatively environmentally benign route to oxidation products otherwise accessed using chromium reagents (**Scheme 8**).



Scheme 8 TEMPO-mediated oxidation of an alcohol.

TEMPO is very selective for alcohols and allows the oxidation to occur under mild conditions and short reaction times. The oxidations can also occur under both acidic and alkaline conditions. However, NaOCl is often used as the terminal oxidant for the reactions and they also require some form of bromide present to act as a co-catalyst, as well as chlorinated solvents.[15] Ideally, oxygen from air would be used as the terminal oxidant since it is abundant and cheap.

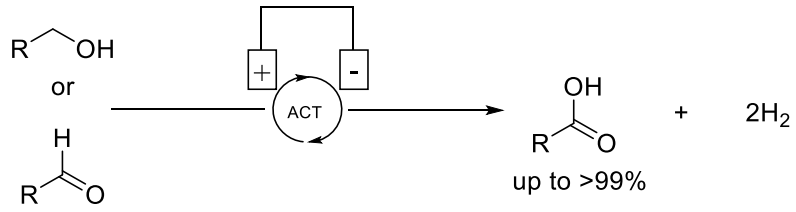
Pleasingly, in 2011 Stahl and co-workers achieved this aim using a copper(I)/TEMPO catalyst system for the aerobic oxidation of primary alcohols (**Scheme 9**).[16]



Scheme 9 General scheme for alcohol oxidation using copper/TEMPO catalysis with air as the terminal oxidant.

It was noted by Stahl that chemistry of this nature to date had been limited since it could not tolerate heteroatoms due to competing oxidation reactions. However, this methodology displayed impressive scope with examples of heteroatom-containing alcohols being oxidised, as well as those in the presence of alkenes and alkynes.

Stahl and co-workers also developed an electrochemical 4-acetamido-TEMPO (ACT) regeneration method to perform the oxidation of primary alcohols and aldehydes to carboxylic acids in excellent yields (**Scheme 10**).[17]

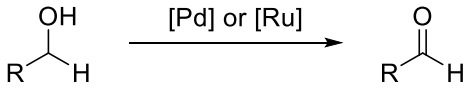


Scheme 10 General scheme for the oxidation of alcohols and aldehydes to carboxylic acids by electrochemical recycling of TEMPO.

A range of aromatic aldehydes and primary alcohols were oxidised in excellent yield, as well as cyclic alkyl alcohols. The yields of the reactions were consistently above 90%.

This methodology is an excellent example of green and sustainable catalysis since it uses aqueous reaction media, proceeds at room temperature, uses a cheap catalyst and carbonate/bicarbonate base as the electrolyte, and can be scaled up. However, the methodology was not extended to secondary alcohols and it is unfortunate that the oxidation cannot be stopped at the aldehyde during the oxidation of the primary alcohols.

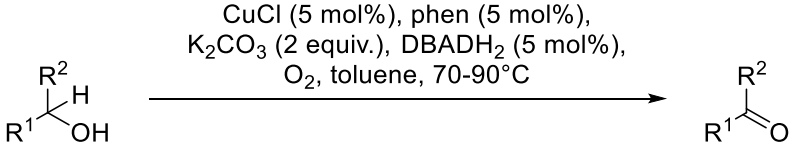
Catalysis has been a significant move in the right direction in terms of 'green and sustainable' alcohol oxidations, since it significantly reduced quantities of the oxidant employed. Metals have been the focus of such strategies in conjunction with an oxidant and palladium and ruthenium have been particularly popular (**Scheme 11**).



Scheme 11 Oxidation of alcohols using a Pd catalyst in which the conditions vary with the substrate.

Despite the success of palladium and other transition metal reagents to oxidise alcohols with high selectivity and yields, many of these metals are known to be expensive and non-abundant. Therefore, transition metal catalysts are far from the ideal in terms of reagent choice. Furthermore, on many occasions they have been used together with large and bulky ligands which add synthetic steps to the synthesis of the catalyst as well as impacting the atom economy and general sustainability of the processes.

Cheaper and more abundant metals have been used for alcohol oxidations, such as copper for example, in conjunction with a TEMPO co-catalyst as previously mentioned. Copper and di-*tert*-butyl hydrazine-1,2-dicarboxylate ($DBADH_2$) has also been used to oxidise secondary alcohols using air as the terminal oxidant and producing only water as a side-product, which is generally considered to be benign (**Scheme 12**).[18]



Scheme 12 General scheme for the oxidation of both primary and secondary alcohols by copper.

Despite the high product yields in both the oxidation of primary and secondary alcohols, the requirement of a large ligand (phenanthroline, phen) and hydrazine is not ideal. Furthermore,

the methodology uses an unsustainable solvent and high temperatures to achieve these results.[14]

It is the failure of these classic strategies to provide the chemistry community with truly green and sustainable methodologies for the oxidation of substrates that has led to a wealth of modern research in this area.

Nature has evolved many efficient oxidation procedures since oxygen appeared in significant quantities in the atmosphere almost 2.5 billion years ago. Nature possesses the means to stringently control the conditions under which its reactions occur, but moreover, Nature can perform efficient reactions designed for specific substrates. However, this means the scope of substrates on which it performs specific transformations is very small. Therefore, it is much more difficult for synthetic laboratory chemistry to achieve its goals in terms of high yields, short time frames, high selectivity, wide substrate scope and mild reaction conditions which all pertain to a 'green' and sustainable process. Regardless, chemists have sought inspiration from Nature to provide more environmentally friendly and sustainable, metal-free approaches to meet the oxidative needs of both industry and academia.

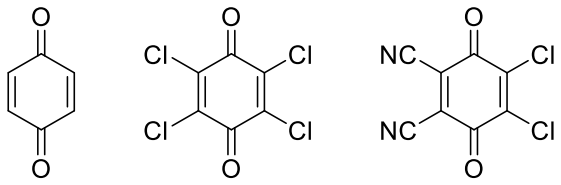
1.2 Thesis aims

Oxidation reactions are fundamental to organic chemistry in order to access everyday materials that have become essential to modern life. Pharmaceuticals, agrochemicals and plastics are but a few examples of materials that contain oxygen in a variety of oxidation levels.

Classical synthetic strategies aimed at facilitating oxidation reactions have typically employed harsh, toxic or expensive and rare reagents, and many times under forcing conditions. However, in an age where resources are dwindling, and focus is increasingly on the environmental effects of processes on the Earth, it is imperative that the chemistry community seeks to increase its sustainability. Hence, the aims of this thesis were to develop oxidation methodologies which were as environmentally benign, friendly and mild as possible. Specifically, this research focusses on the reduction of metal use in oxidation. Efforts were made to reduce or eliminate metals wherever possible, and where metals were used, those which are cheap and abundant were implemented.

2. Introduction to Quinone Mediated Oxidation Reactions as a Potential Solution

Nature is known to exploit low potential quinones for electron transport and redox reactions, with oxygen as the terminal oxidant. A number of quinones are commercially available such as *p*-benzoquinone **2** (BQ), *p*-chloranil **3** and 2,3-dichloro-4,5-dicyano-1,4-benzoquinone **4** (DDQ). Depending on the function groups attached to these quinone cores, the redox potentials can vary significantly.[19] Whilst BQ **2** itself possesses moderate oxidising ability (E_0 = 711 mV), this is further enhanced by the presence of electron withdrawing groups, such as those found in *p*-chloranil **3** (E_0 = 742 mV), or DDQ **4** (E_0 = 1000 mV).[20] Conversely, electron donating groups reduce this oxidising ability (**Figure 1**).



2 **3** **4**

Figure 1 Structures of benzoquinone **2**, *o*-chloranil **3** and DDQ **4** respectively.

Therefore, with sustainability in mind, chemists are inspired by the efficiency of Nature, and thus commercially available quinones have attracted attention for oxidation reactions in the laboratory.

2.1 DDQ-Mediated Oxidation Reactions

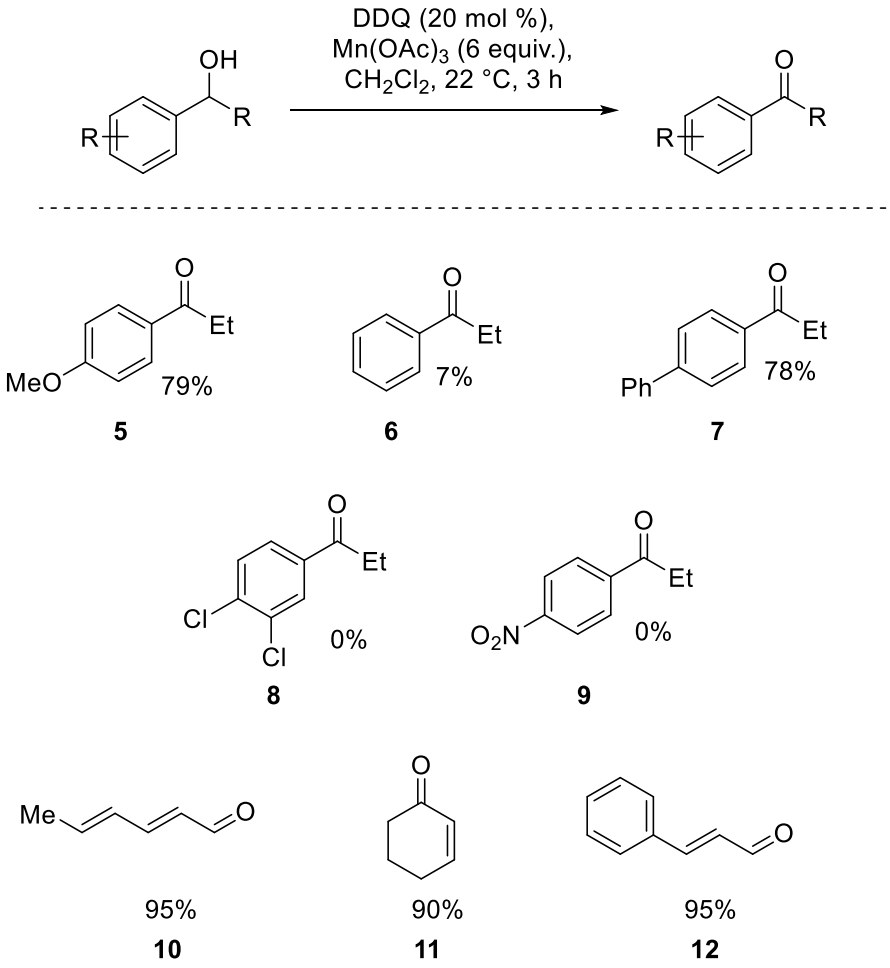
The most commonly used quinone is DDQ **4**; due to its high redox potential.[21] This makes DDQ **4** a good oxidant for a range of reactions including alcohol oxidations, PMB ether deprotection and dehydrogenation reactions. However, rather than present a comprehensive overview of DDQ **4** chemistry, the following sections focus on more recent developments, particularly those involving the use of catalytic amounts of DDQ **4** together with a co-oxidant, and on cross-dehydrogenative coupling (CDC) reactions.

2.1.1 Catalytic DDQ Alcohol Oxidation Reactions by DDQ

DDQ **4** and other high potential quinones have long been used for the oxidation of alcohols to the corresponding carbonyl compounds. However, the relatively high cost, toxicity (LD_{50} 82 mg/kg) and potential for HCN release on water exposure has limited the practical use of DDQ **4** at large scale.[22] Additionally, the by-product of these oxidations is $DDQH_2$ **13** which is formed in stoichiometric quantities and can cause problems during purification.[23] This, combined with an increased focus on sustainability and attempts to prevent resource scarcity in the modern era, has meant that these properties have driven the research focus towards utilising DDQ **4** in catalytic quantities in the presence of a terminal oxidant.

Manganese (II) salts have been shown to oxidise $DDQH_2$ **13** back to DDQ **4**. Inspired by the work of Sharma in 2010 on DDQ-mediated PMB ether removal.[24] Helquist *et. al.* reported the oxidation of alcohols by DDQ **4** where $Mn(OAc)_3$ was also used as a terminal oxidant (**Scheme 13**).[25] Reported was a chemoselective oxidation of benzylic alcohols, using substoichiometric

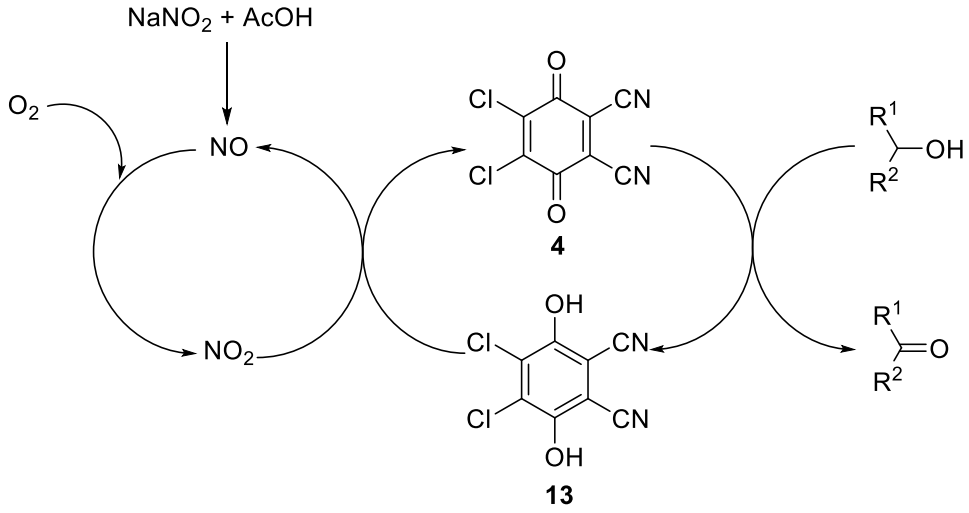
quantities of DDQ **4.** Unfortunately, this transformation required 6 equivalents of $Mn(OAc)_3$ as the co-oxidant, although it did give the products in good yield.



Scheme 13 General scheme for the selective oxidation of benzylic and allylic alcohols in the presence of catalytic DDQ **4**/$Mn(OAc)_3$ reported by Helquist.[25]

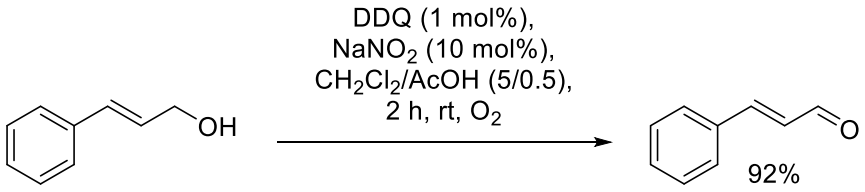
It was observed clearly that electron donating substituents (**5** and **7**) facilitated the reaction, however unactivated systems with electron withdrawing groups (**8** and **9**) produced significantly lower yields or the reaction failed. When the system was applied to allylic alcohols, all the oxidised products were obtained in excellent yield. Although such large quantities of terminal oxidant were somewhat disadvantageous, Helquist and co-workers noted that by loading $Mn(OAc)_3$ at 6 equiv., the catalytic loading of DDQ **4** could be reduced to 20 mol%.

Although these reported conditions were mild and reaction times relatively short (1-6 h), the use of such a large excess of co-oxidant was undesirable. An ideal oxidation strategy would use an inexpensive oxidant such as oxygen/air to recycle $DDQH_2$ **13** to DDQ 4. This would produce water as a benign by-product. In 2012, Wang *et. al.* developed an oxidation methodology which employed sodium nitrite as a co-catalyst which reacted with acetic acid to generate nitric oxide. This is then oxidised to nitric dioxide by oxygen which in turn can facilitate the oxidation of $DDQH_2$ **13** to DDQ **4** (**Scheme 14**). [26]



Scheme 14 Oxidation of alcohols to carbonyl species, implementing catalytic DDQ **4** and oxygen as the terminal oxidant.[26]

Preliminary studies demonstrated that acetic acid was crucial to the reaction. In the oxidation of cinnamyl alcohol **14**, increased quantities of acetic acid increased the cinnamaldehyde **12** yield from 24% to 95%. The optimal conditions were found to be 1 mol% DDQ **4** and 10 mol% $NaNO_2$. Poor reactivity was observed when performed in absence of either reagent (**Scheme 15**).



14 **12**

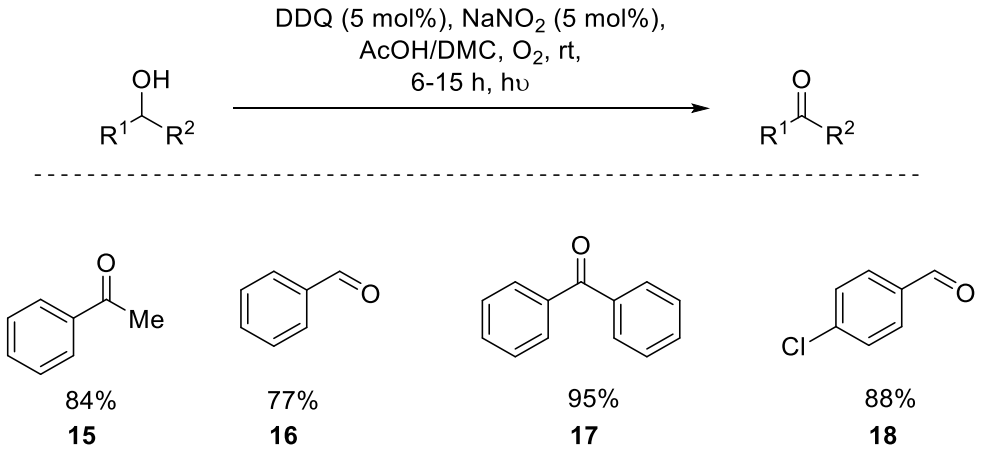
Scheme 15 Oxidation of cinnamyl alcohol **14** to cinnamaldehyde **12** with DDQ/$NaNO_2$/AcOH as reported by Wang.[26]

In terms of scope, good reactivity was seen with allylic alcohols, propargylic alcohols and electron rich benzyl alcohols. Conversely, poor yields were observed with electron poor benzylic alcohols and saturated aliphatic alcohols. Selection studies saw preference for allylic and propargylic alcohols over benzylic alcohols. The process was also shown to be scalable up to 10 g and was applied to lignin models which have potential for use as sustainable chemical feedstocks. Such models contain a primary aliphatic alcohol and secondary benzylic alcohol which make up 50% of the linkages in lignin. Therefore, selective oxidation of these functional groups is of significance to allow access to high-value aromatic materials through the facile cleavage of C-C bonds upon C-OH activation. Overall, Wang and co-workers reported a mild, practical and metal-free oxidation process.

Wang's alcohol oxidation methodology using DDQ **4** and sodium nitrite was later improved by Moody and co-workers .[27]

In the presence of visible light, the oxidising ability of DDQ **4** is much enhanced (from E_{red} = 0.51 V vs SCE to E_{red} = 3.18 V vs SCE).[28] Therefore, this property has been exploited and photo-activated DDQ **4** has been used oxidise the lignin model 3,4-dimethoxybenzyl alcohol[26] and other lignin models.[10] Moody reported that Wang's chemistry gave poor yields when alcohols with electron withdrawing groups were used but that the use of visible light can circumvent this

issue. This is due to the much higher oxidizing ability of DDQ **4** in the triplet-excited state and hence can oxidise previously unreactive substrates.[28] This allowed the oxidation of the aforementioned substrates as well as β-O-4 lignin models under mild conditions (**Scheme 16**).



Scheme 16 DDQ-mediated oxidation of alcohols as reported by Moody *et. al.*[29]

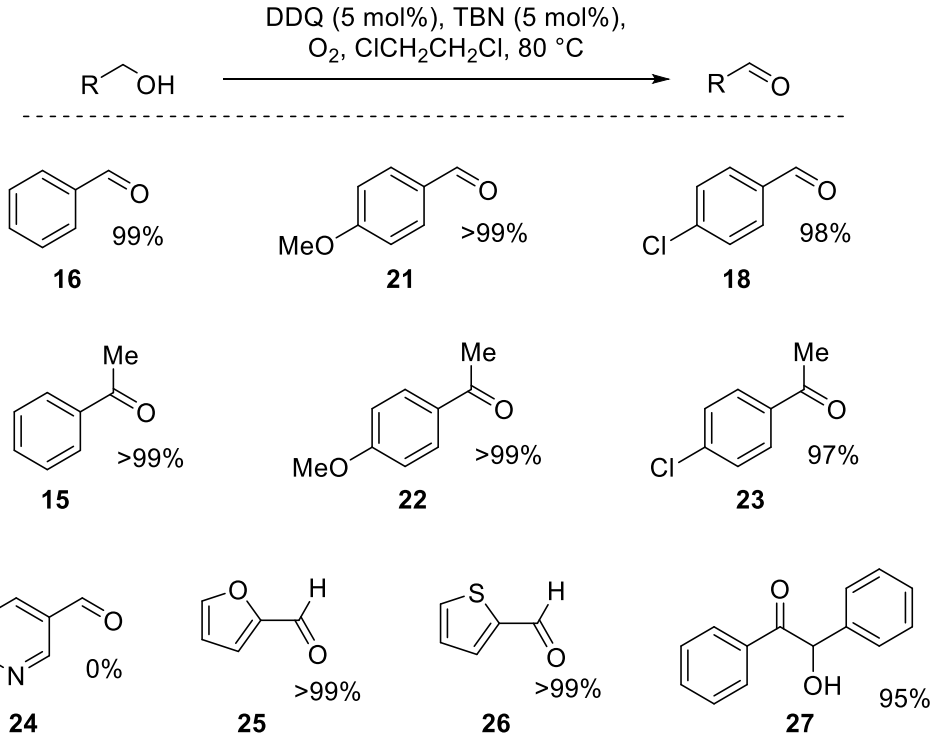
Moody reported the use of a 'sunlight-mimicking' lamp, which is a cheap and readily available light source which is commonly used in greenhouses. The reactions gave significantly lower yields in the dark which demonstrated the increased oxidising ability of DDQ under visible light irradiation. It was noted that unactivated substrates saw a significant drop in the yield without sunlight irradiation. To improve the results of unactivated, less electron rich systems, sodium nitrite and acetic acid were replaced with *t*-butyl nitrite, which led to a significant increase in the yields.

Moody also demonstrated that the oxidation of β-O-4 lignin models was possible under the reported conditions with high success (**Scheme 17**).

19 **20**

Scheme 17 DDQ-mediated oxidation of lignin model **20** as reported by Moody *et. al*.[29]

Hu had also previously reported a metal-free approach to alcohol oxidation - a TEMPO-catalysed, metal-free oxidation reaction that showed that nitric oxide (NO), created *in situ* from *tert*-butylnitrite (TBN), was converted into the oxidant NO_2.[30,31] Hu extended this work in 2011, replacing TEMPO with DDQ **4**, using the NO_2 generated from TBN and oxygen to regenerate DDQ **4**.[32]

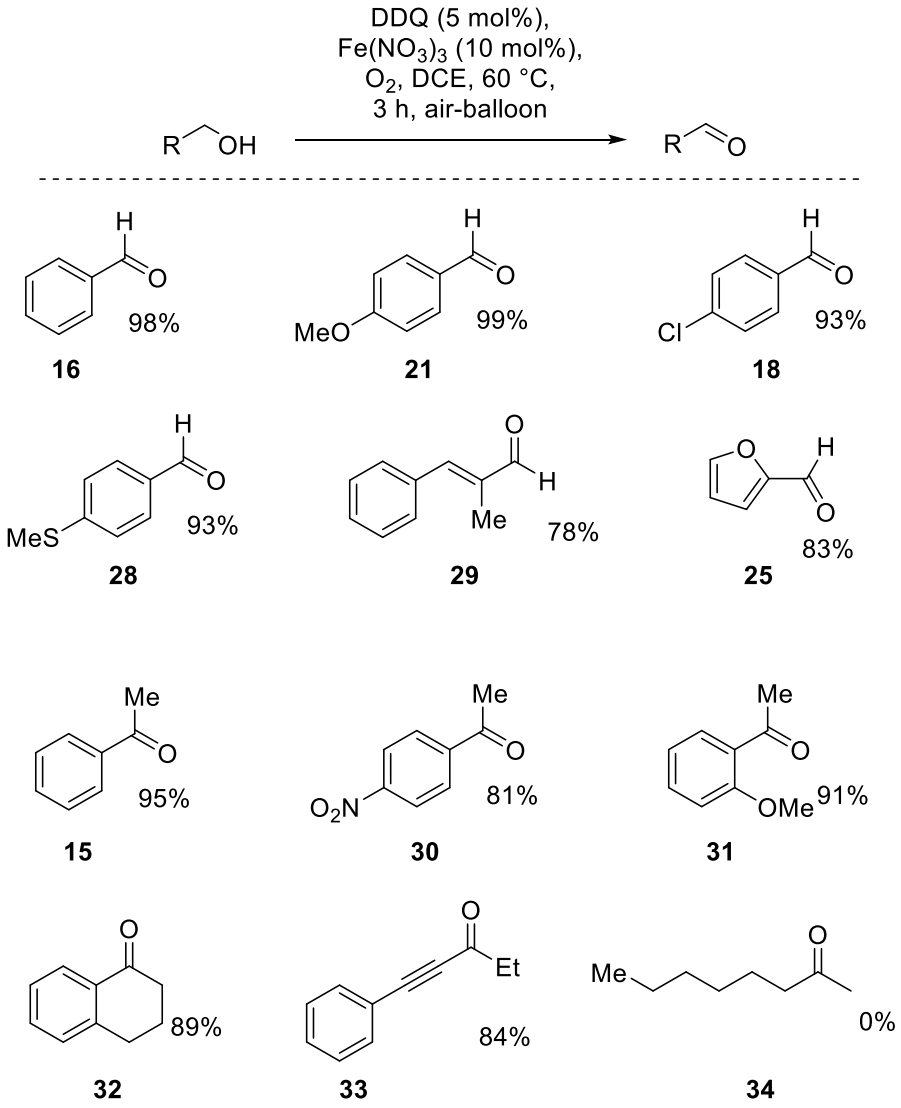


Note: All yields were determined by GC with area normalisation.

Scheme 18 The model substrate for the TEMPO-mediated oxidation, 3-pyridinemethanol **24**, could not be oxidised *via* the DDQ **4**/TBN system.

The reaction proceeded using 5 mol% of both DDQ **4** and TBN in dichloroethane (DCE). It was successful with a range of primary and secondary benzylic alcohols, with a variety of electron donating and withdrawing substituents. Additionally, heterocyclic alcohols of furan **25** and thiophene **26** were oxidised under these conditions.

Most recently in 2018, Li reported the oxidation of a similar set of alcohols to those reported by Hu, using a system catalytic in both DDQ **4** and $Fe(NO_3)_3$ (**Scheme 19**).[33] This is the first report where the metal oxidant for DDQ **4** has also been present in substoichiometric quantities. Additionally, iron is a particularly desirable as a metal for catalysis since it is abundant, cheap and non-toxic.

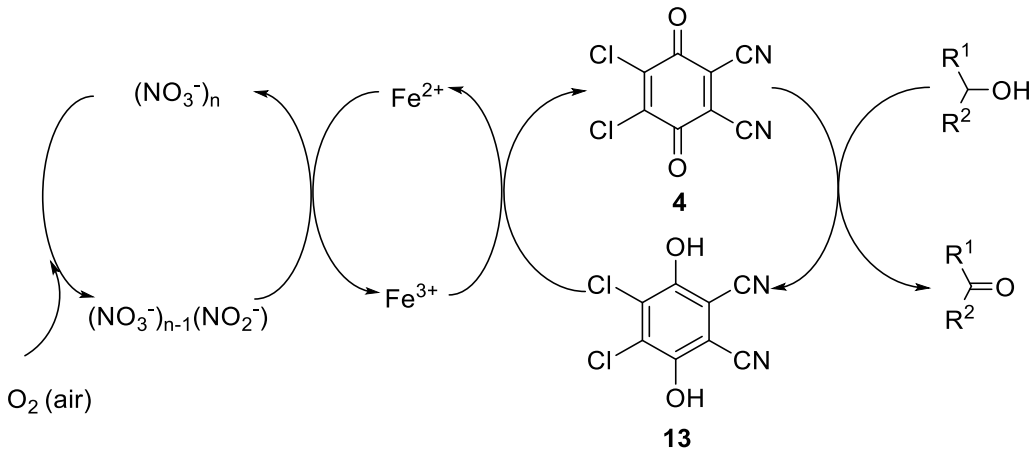


Scheme 19 Iron and DDQ **4** catalysed oxidation of alcohols.

This system was able to oxidise a range of primary benzylic alcohols in excellent yields under an air atmosphere and in a short amount of time. Both electron withdrawing **30** and electron donating **31** substituents on the aromatic ring were tolerated. The authors also displayed that 2-furanemethanol **25** could be oxidised in excellent yield. Alkyl alcohols were unreactive under these conditions.

The authors were careful to note that this chemistry is also amenable to scale up. They performed the large-scale oxidation (1 mol) of benzyl alcohol and isolated benzaldehyde **16** in 93% yield.

The ligand on the iron catalyst was found to be crucial for the success of the reaction. The report details control reactions conducted to prove this assumption. When the reaction was conducted in the presence of $FeCl_3 \bullet 6H_2O$ or $NaNO_3$, 10% and 29% of benzaldehyde **16** was isolated respectively. Additionally, when $NaNO_3$ (30 mol%) and $FeCl_3$ (10 mol%) were employed together, 76% of the benzaldehyde product **16** was isolated. Therefore, it was shown that both Fe^{3+} and NO_3^- were required and the authors proposed the mechanism displayed below (**Scheme 20**).



Scheme 20 The mechanism proposed by Li for the $Fe(NO_3)_3$ and DDQ **4** catalysed reaction.

DDQ **4** oxidised the alcohol, and in turn was reduced to $DDQH_2$ **13**, which reduces Fe^{3+} to Fe^{2+}. The present NO_3^- then plays a role in the oxidation of Fe^{2+} back to Fe^{3+} with air as the terminal oxidant.

Despite the obvious improvements to the DDQ **4** system in terms of sustainability, the solvent choice for the reaction was disappointing. DCE is a solvent of concern according to the popular solvent guides.[34] Although, the reaction was shown to proceed using methanol albeit in lower yield - benzaldehyde **16** was isolated in 69% yield (vs 98% in DCE) under the same conditions.

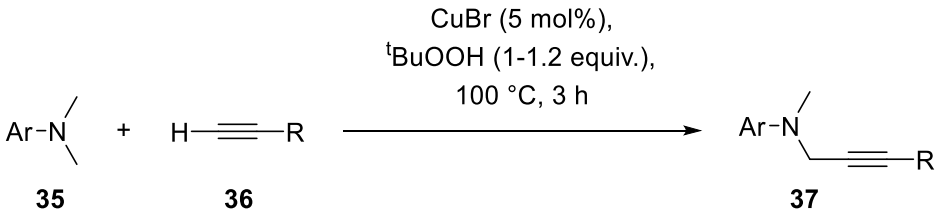
Despite these developments in this area towards catalytic and metal-free DDQ **4** oxidation protocols, the ideal system which utilises oxygen as the sole terminal oxidant without a co-catalyst has not been realised for alcohol oxidations. Thus, there remains further scope for improvement in this area with regards to sustainability.

2.1.2 Cross Dehydrogenative Coupling Reactions

A further class of fundamental transformations in organic synthesis are C-C bond forming reactions. C-C bonds are important since they are one of the most common bonds in organic chemistry, are found throughout Nature and in a plethora of man-made chemicals.

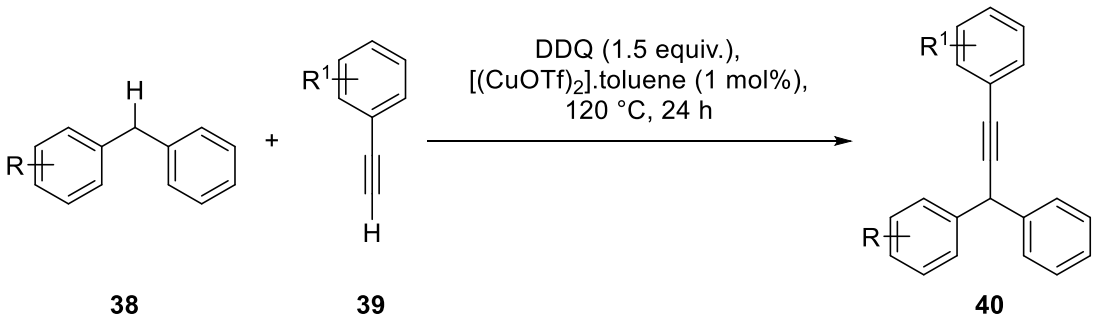
Modern advances in chemistry, and the increased focus on improving the 'greenness' and sustainability of reactions, means that it is desirable to be able to utilise a C-H bond without prior functionalisation; improving the atom economy and waste production of the process. Thus much research has been conducted in the area of transition metal-catalysed C-H activation (some of which is discussed in Section 1.1).[35,36] However, metal catalysts have often been exploited in such protocols which are short in supply and are high in cost. Therefore, the development of an efficient, metal-free approach would be preferable.[37]

One solution could be the cross-dehydrogenative cross-coupling (CDC) reactions, which have received recent attention. These are reactions that can create C-C bonds from C-H bonds, without their prior functionalisation. The concept of CDC reactions was first introduced by Li in 2004 with a report on construction of propargylic amines **35** by the catalytic coupling of C(sp^3)-H, adjacent to nitrogen, with a terminal alkyne **36** to give the product **37** (**Scheme 21**). [38,39]



Scheme 21 The first CDC reaction reported by Li in 2004.[39]

Developments by Li eventually led to reactions with benzylic C-H bonds that were not adjacent to a heteroatom as reported in 2004.[40] In addition, Li published the coupling of alkynes **39** and diphenylmethane derivatives **38**, which utilised DDQ **4** and catalytic $CuOTf_2$. (**Scheme 22**).

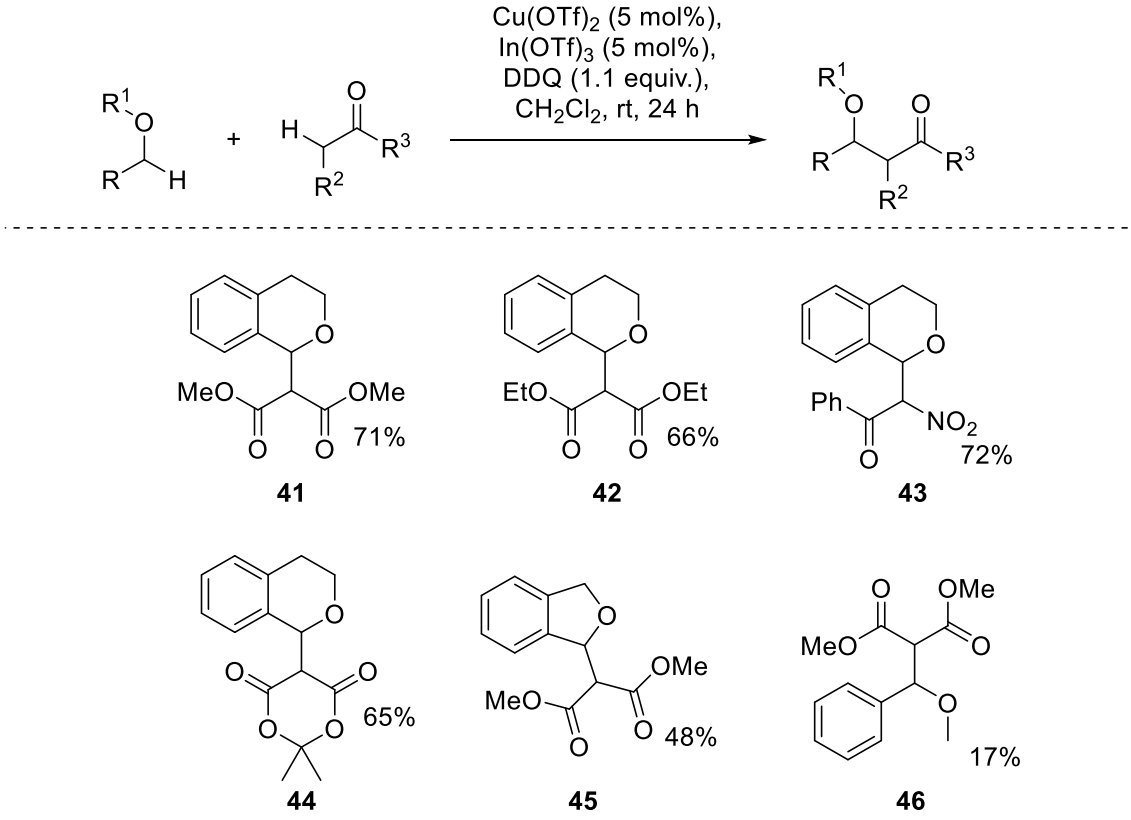


Scheme 22 CDC reaction of alkynes and diphenylmethane derivatives, giving C-C bond formation.

The reaction proceeded with ease and electron-rich derivatives gave slightly improved yields although unfortunately, aliphatic alkynes could not be converted using this reaction.

Additionally, this appeared to be the first report where neither of the starting materials had a reacting centre adjacent to a heteroatom which is helpful for the scope.

Later, in 2006, Li developed a further CDC reaction of isochromans, pthalans and benzyl methyl ethers with carbonyl compounds. Li's initial attempts employed a mixture of $Cu(OTf)_2$/$In(OTf)_3$ in dichloromethane. The In/Cu catalyst mixture in this reaction was thought to have two roles - to activate DDQ **4** by increasing the oxidative potential and activate the malonate starting materials (**Scheme 23**).



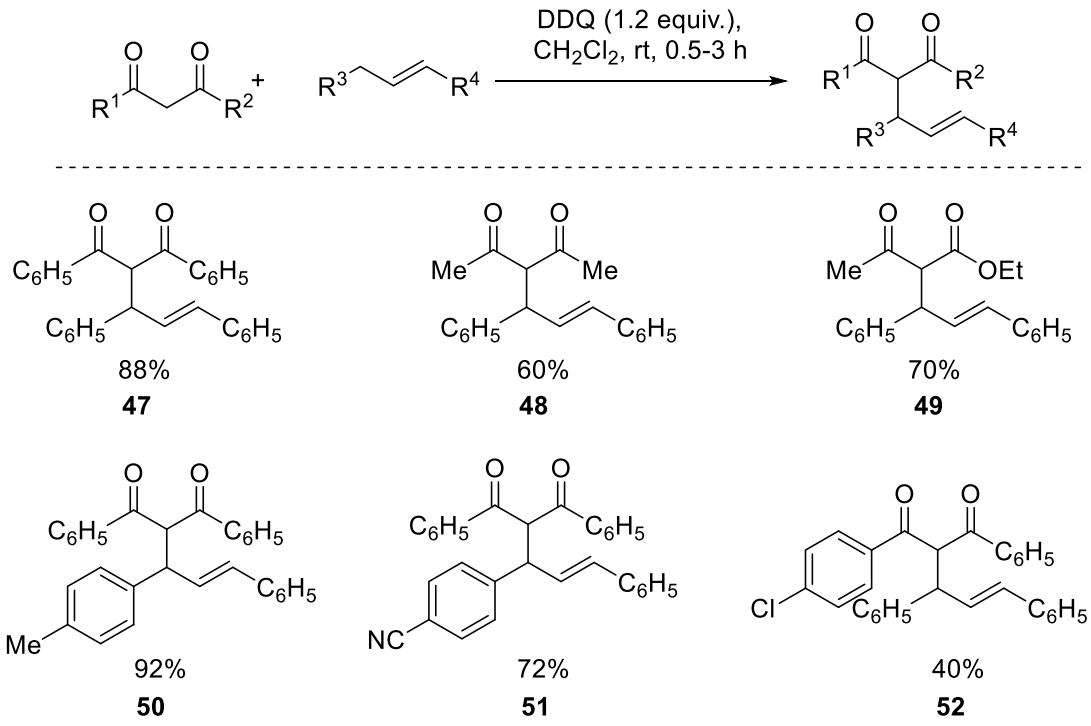
Scheme 23 CDC reaction using In/Cu catalysts as reported by Li.

Isochroman **76** was shown to be a good reaction partner for the CDC reaction with malonates to give adducts **41** and **42** as well as other carbonyl compounds with various functionality. Phthalan could also be employed albeit in lower yields with dimethyl malonate to give **45**. However, it was noted that open chain ethers such as benzyl methyl ether were less successful

in their reaction with dimethyl malonate and only gave the CDC adduct **46** in 17 % yield (see Section 2.1.2).

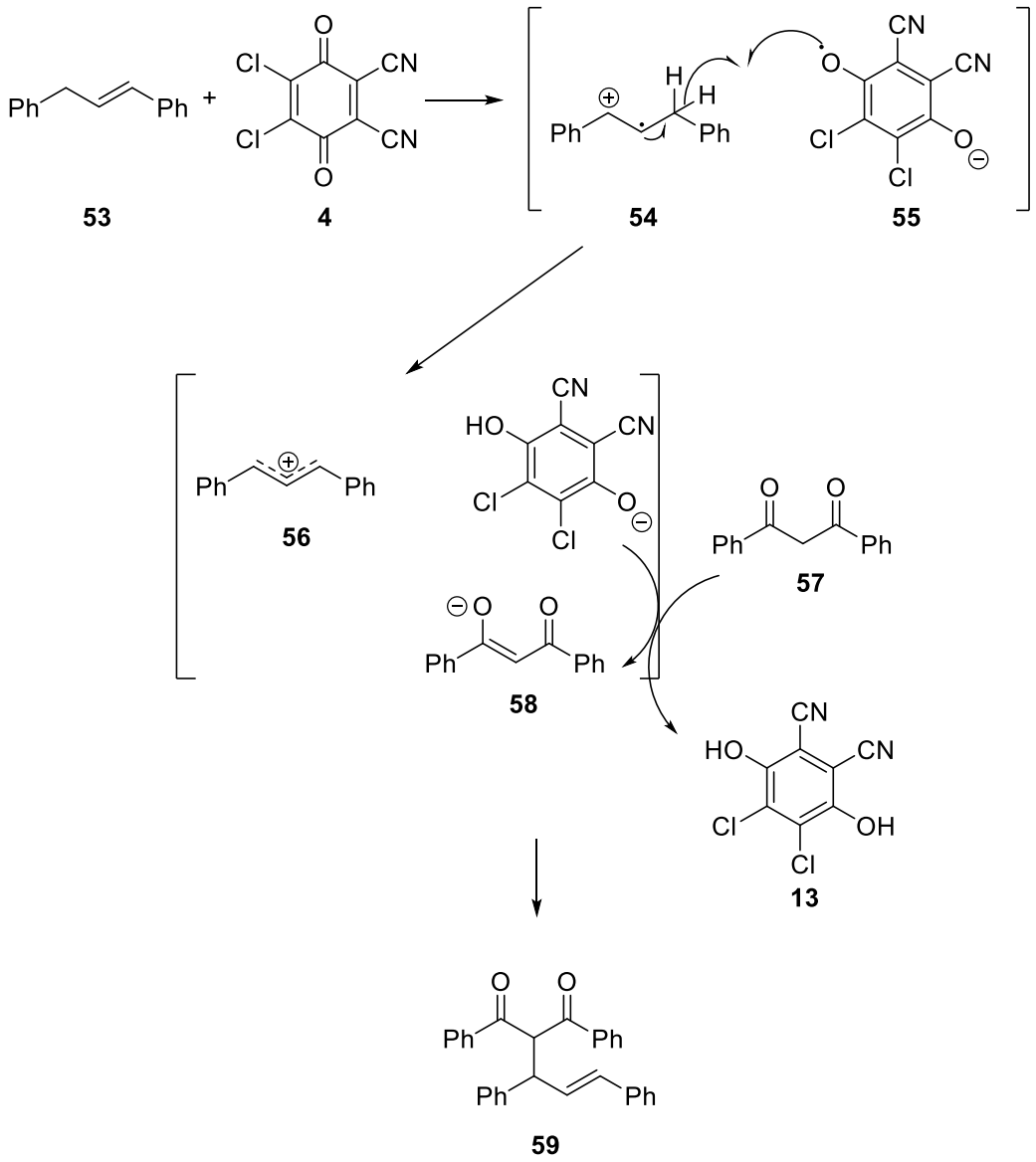
Unfortunately, this system was limited to CDC reactions between benzyl ethers and relatively reactive malonates – less reactive species gave low yields or no reaction.[38] Furthermore, the methodology utilised dichloromethane as solvent, which is unsustainable and predicted future legislation on this solvent means it should be avoided wherever possible.[14,34,41]

Bao reported that DDQ **4** could mediate a concise oxidative coupling between diaryl allylic C(sp^3)-H and active methylene C(sp^3)-H bonds without using any metal catalyst. The reaction occurred in good yields with electron donating substituents on the aromatic rings, as well as with heteroaryl derivatives. However, when a *p*-chloro-substituent was installed **52**, the reaction became slow and only moderate yields were obtained. Similar results were seen with acyclic and cyclic β-keto esters. Notably, the reaction also proceeded in the absence of solvent with comparable results (**Scheme 24**).[42]



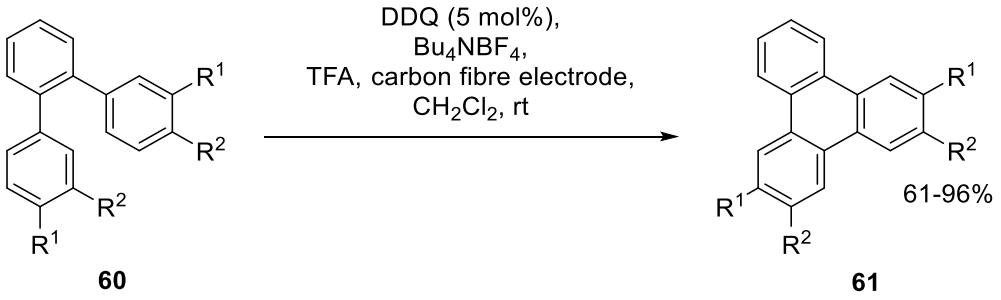
Scheme 24 Metal-free CDC reaction as reported by Bao.[42]

The mechanism of DDQ **4** mediated reactions is not well understood, and those proposed are tentative. Nevertheless, Bao proposed that there was evidence to suggest a radical mechanism occurred where a single electron transfer (SET) occurred between DDQ **4** and diphenylpropene **53** to give a radical cation **54**. The radical cation **54** then participates in a hydride abstraction and the resulting secondary carbocation **56** reacts with the enol form of the diketone **58** to yield the coupled product **59** (**Scheme 25**).



Scheme 25 CDC reaction mechanism as proposed by Bao.[42]

Recent reports from Röse *et. al.* detailed a DDQ-mediated, electrochemical CDC reaction of two arenes.[43] The methodology claims to be the first example on *in situ* recycling of DDQ **4**, which until this report, had only been recyclable after isolation.[44,45] The authors recognise that CDC reactions that are catalytic in DDQ **4** have been reported, but that electrolysis could provide a 'promising environmentally benign method for the *in situ* oxidation of $DDQH_2$ **13** (**Scheme 26**).



Scheme 26 Electrochemical C-C bond forming reaction using catalytic DDQ **4** with a carbon fibre electrode.

Terphenyl substrate **60** was intramolecularly coupled using DDQ **4**, trifluoroacetic acid (TFA) and dichloromethane in 69% yield. Pleasingly, other terphenyl substrates underwent the reaction in good yield regardless of substituents and represents an atom economical methodology that could be used to replace some Suzuki couplings or Scholl reactions. However, the reaction had to be stopped immediately once starting material had been consumed or side-products were produced.

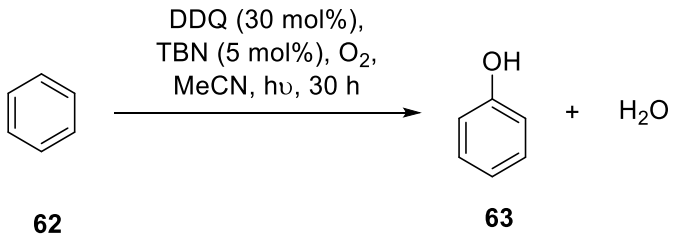
Overall, the system avoids the use of stoichiometric oxidants, although the use of a platinum electrode is less than ideal. Electrodes are generally regarded as consumables and thus are destroyed over time. Therefore, since platinum is a rare and expensive metal, an electrode which is made of less precious material would be preferable. The highly acidic nature of the system could also be problematic if the scope of the reaction underwent further investigations.

Despite the obvious progress made in the field of DDQ-catalysed chemistry, its toxicity and expense remain a problem. It is already known that Nature exploits low potential quinones and light for oxidation reactions, hence research has also been directed towards uncovering the capability of light-irradiated quinones in synthetic laboratory chemistry for various transformations (for alcohol oxidation examples see Section 2.1.1).

2.1.3 Miscellaneous Reactions of Photo-Activated DDQ

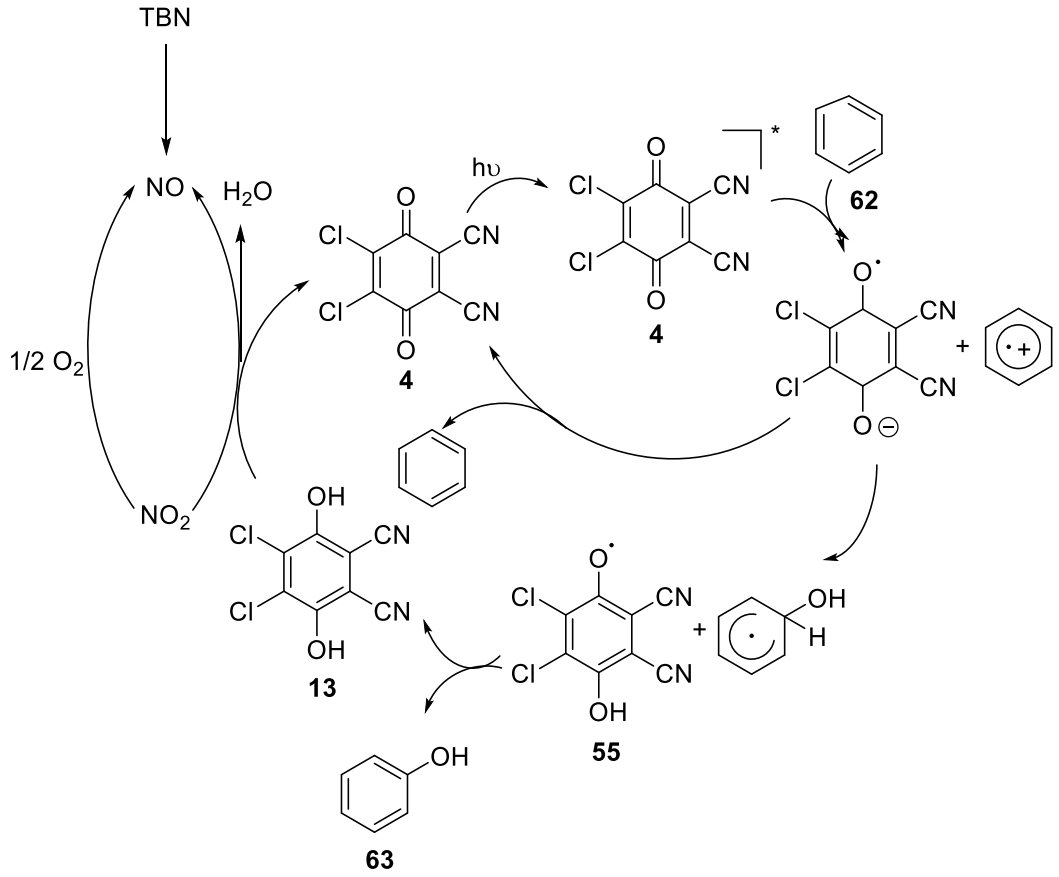
According to the literature and as previously mentioned, the redox potential of quinones is increased by photoexcitation to their triplet-excited state; making them more able oxidising agents (see Section 2.1.1). Differing reactivity has also been observed between the ground and excited-state reactivities of the quinones, meaning that although a quinone may not participate in a reaction in the ground-state, it may do so when excited.[46]

Fukuzumi and co-workers envisaged that this property could be used to improve the oxidising ability of DDQ **4**, and thus change its reactivity. They demonstrated the oxidising ability of photo-excited DDQ **4** in the remarkable photooxidation of benzene **62** to phenol **63** (**Scheme 27**).



Scheme 27 Photo-induced catalytic DDQ **4** oxidation of benzene **62** to phenol **63**, as reported by Fukuzumi, 2013.

In this reaction, TBN is used as the catalytic terminal oxidant to re-oxidise $DDQH_2$ **13** to DDQ **4** as previously seen in the literature, giving phenol **63** in excellent yield with water as a waste product (**Scheme 28**).[28,32]



Scheme 28 Mechanism for the oxidation of benzene **62** to phenol **63** as proposed by Fukuzumi.[28]

The one-step functionalization of benzene **62** to phenol **63** one of the "dream reactions" in chemistry. This chemistry is impressive since it is usually very challenging as it is difficult to achieve without further oxidation or oxygenation of phenol **63** to the BQH_2 **67**.

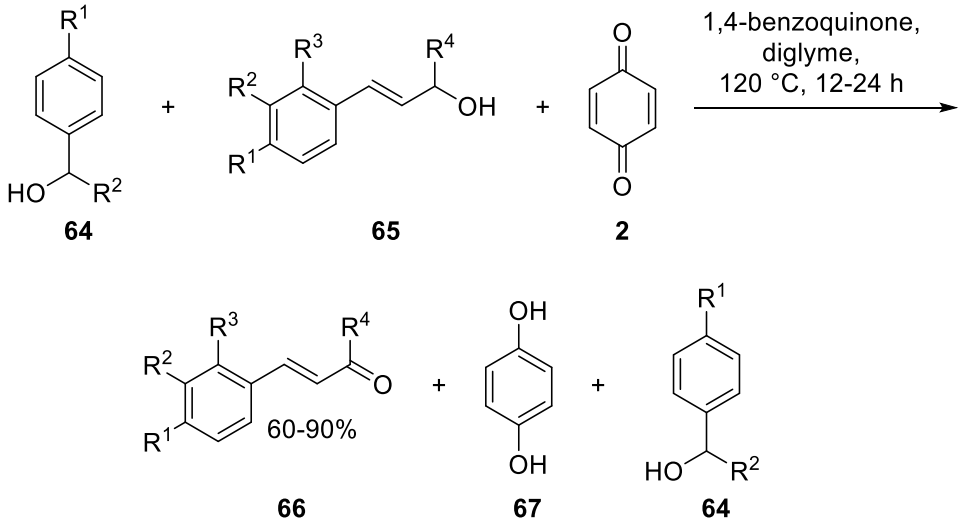
2.1.4 Summary

On balance, DDQ **4** has displayed an impressive ability to perform numerous oxidation reactions, including the oxidation of benzene, although its issues with toxicity, expense and purification remain. Throughout the literature it has been reported that it is difficult to remove from the reaction products and is well known for its toxic properties. This has meant that other quinones have been sought as sustainable alternatives to DDQ **4**. Many reactions with alternative quinones require light as most commercially available quinones, such as BQ **2**, possess oxidising abilities below that of DDQ **4** and so are unreactive in the ground state.

2.2 Benzoquinone as an Organo-oxidant

Few research groups have focussed on the use of BQ **2** as an organo-oxidant for the oxidation of organic molecules to date, mainly due to its modest redox potential in the ground state. The low reduction potential means BQ **2** does not perform many organic oxidation reactions, *cf.* DDQ **4** in its ground state. However, BQ **2** mediated methodologies would represent a marked improvement compared to DDQ **4** which suffers due to its high cost, toxicity and release of HCN upon contact with water.

The first example of where BQ **2** was utilised for an alcohol oxidation was reported in 1990, by Kulkarni.[47] A range of cinnamyl alcohols **65** were oxidised selectively in moderate yields, in the presence of benzylic alcohols **64** which was rather impressive. However, the protocol suffered from forcing reaction conditions, since high temperatures and prolonged reaction times were required (**Scheme 29**).

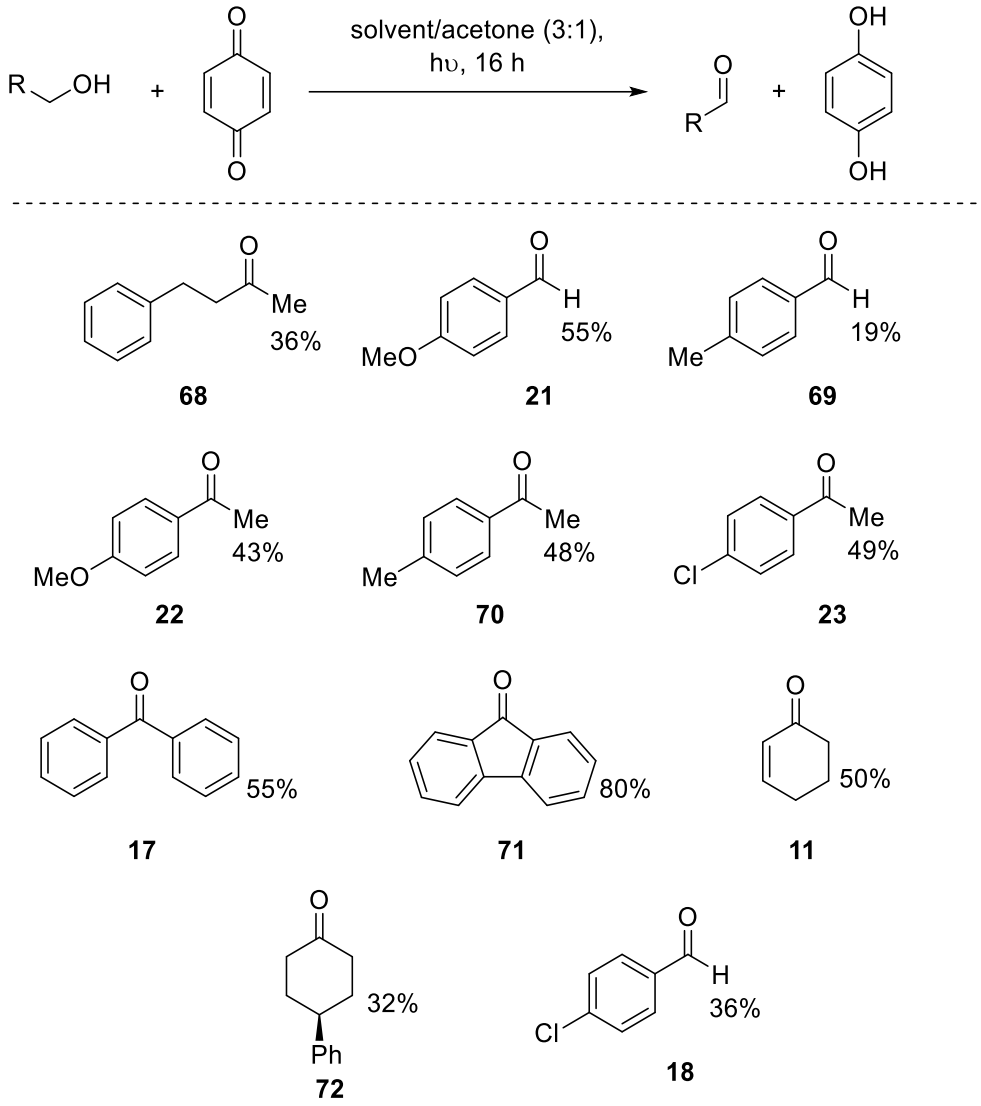


Scheme 29 Selective oxidation of cinnamyl alcohols **65** in the presence of benzyl alcohols **64**.

As well as selective oxidation of cinnamyl alcohols **65** in the presence of benzylic alcohols **64**, interestingly merely changing the solvent to xylene meant primary cinnamyl alcohols could also be selectively oxidised in the presence of secondary cinnamyl alcohols (**Scheme 29**). Furthermore, where aryl conjugated primary alcohols and benzylic/aryl conjugated secondary primary alcohols were present, the primary alcohol was always selectively oxidised which meant that the oxidation could be predicted. Such selectivity is useful for complex molecules with multiple positions for potential oxidation. Unfortunately, benzylic alcohols were unreactive under these conditions.

In a similar manner to DDQ **4**, it was found that the oxidising ability of BQ **2** is also enhanced upon photochemical irradiation to the triplet excited state (E_{red} 2.40 V vs. SCE).[48] In fact, once irradiated with light, the oxidation potential of BQ **2** is increased to that beyond ground state DDQ **4**, thus it was assumed that it may conduct similar chemistry. Hence, this property was exploited for the oxidation of alcohols.

In 2014, Moody and co-workers reported a method for oxidation of alcohols using stoichiometric amounts of BQ **2.** It is known to be cheaper and less toxic than DDQ **4** and was utilised in the presence of visible light and acetone as a green and sustainable solvent. This methodology was applied to a range of benzylic, allylic and aliphatic alcohols which had seen success with DDQ **4** and the products were isolated in moderate yields (**Scheme 30**).[30]

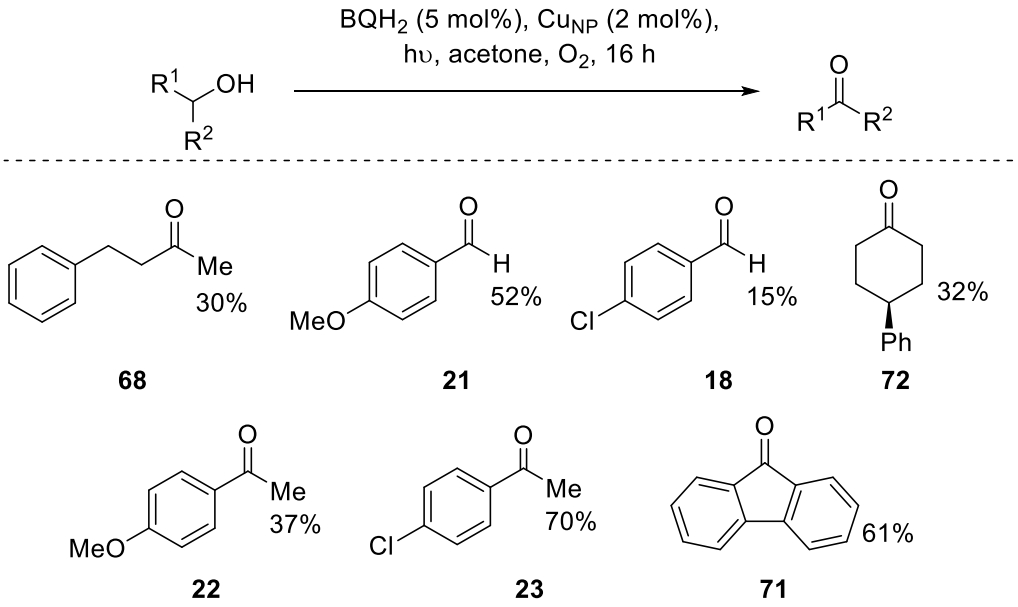


Scheme 30 Oxidation of primary and secondary alcohols using BQ **2** under visible light irradiation as reported by Moody.[29]

The protocol was applied to primary alcohols with varying success. 4-Methoxybenzyl alcohol was oxidised to 4-methoxybenzaldehyde **21** in good yield, whereas 4-methylbenzaldehyde **69** and 4-chlorobenzaldehyde **18** were accessed in low yields. This demonstrated that the benzylic position needed to be activated by an electron donating group in these cases. In contrast, secondary alcohols did not seem to be affected by the presence of *para* substituents. 4-Methoxyacetophenone **22**, 4-methylacetophenone **70** and 4-chloroacetophenone **23** were all accessed in 40-50% yield. Diphenyl substrates **17** and **21** saw more success, presumably due to the higher level of activation provided by two aromatic groups and cyclic alkyl alcohols **11** and **72** could also be oxidised.

Concerns with regards to the toxicity of BQ **2** are similar to that of DDQ **4** and therefore its use in stoichiometric quantities was undesirable. A system that was catalytic in BQ **2** would be preferred which was recognised by Moody and co-workers. It was noted that BQ **2** could be prepared by *in situ* oxidation of the less toxic 1,4-hydroquinone (BQH_2) **67** which could provide benefits in terms of the sustainability of the system. BQH_2 **67** is less toxic than both BQ **2** and DDQ **4** and the authors also detailed that it could potentially be sourced biorenewably.

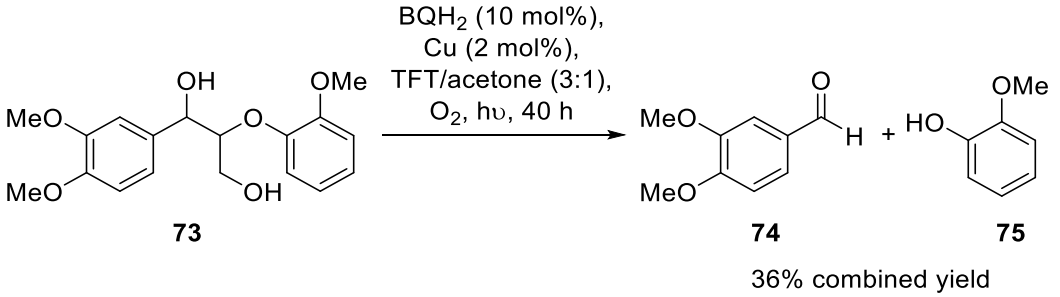
An electron transfer mediator (ETM) was required to achieve the oxidation of BQH_2 **67** to BQ **2**. Therefore, several copper salts were tested as potential ETMs. The best results were obtained with copper nanoparticles (Cu_{NP}) at 2 mol% and the reaction even proceeded in air rather than an oxygen atmosphere (albeit in slightly lower yields). Again, promising results were obtained with primary and secondary benzylic alcohols, although success was seen with **23** which has a *para*- electron withdrawing group (**Scheme 31**).



Scheme 31 The catalytic application of BQ **2** as reported by Moody and co-workers.[10]

These conditions were also applied to benzylic alcohols within lignin models including 1,2-diols and β-O-4 linked aryl-ethers **73**. Interestingly, not only was oxidation observed but oxidative

cleavage of C-C bonds, leading to a range of relatively low molecular weight, high value aromatic compounds. Although only modest conversion was observed, alternative methods of C-C bond cleavage require separate oxidation and cleavage steps, so it is promising that this has been achieved in a single step (**Scheme 32**).



Scheme 32 Oxidation of lignin models **73** leading to C-C bond cleavage as demonstrated by Moody *et. al.*

As previously discussed in this report (see Section 2.1.1), lignin models could help the chemical community to gain access to many important platform chemicals from renewable sources of lignin. Furthermore, the strategy is catalytic with respect to all reagents and is proven to work in the presence of sunlight, even in areas of high latitude

The aim of quinone oxidations was to avoid metals as the oxidant as reported classically, but somewhat unfortunately, thus far a metal has always been required as the electron transfer mediator, although catalytic. Even though the copper used by Moody and co-workers is a more abundant metal, it would still be preferable to design a process which avoids the use of metals completely.

“Happiness can be found even in the darkest of times, if only one remembers to turn on the light.”

Professor Albus Dumbledore

(Harry Potter and The Prisoner of Azkaban, J. K. Rowling)

3. Cross-Dehydrogenative Coupling (CDC) Reactions using Photoactivated BQ

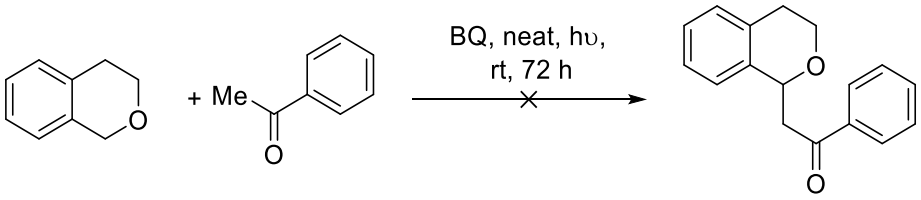
CDC reactions have received recent attention as methods to create new C-C bonds from C-H bonds, without prior functionalisation of starting materials and under metal-free conditions. Literature reactions of CDC reactions performed by ground state DDQ **4** (see Section 2.), led to the hypothesis that photochemically excited BQ **2** may also be able to participate in CDC type reactions.

3.0.1 Project Aims

The CDC reaction is well established with DDQ **4**, but no reports existed to our knowledge that used photo-activated BQ **2**. Since photo-excited BQ **2** is known to have a higher oxidation potential than that of ground state DDQ **4**, it seemed reasonable that, in the presence of a nucleophile, a CDC reaction of this type could occur if the reaction proceeds *via* the same or similar mechanism. BQ **2** would also represent a less toxic, cheaper and safer alternative to DDQ **4** in these CDC reactions. Therefore, the aims of this project were to develop a CDC reaction methodology using catalytic BQ **2** as a more sustainable alternative to DDQ **4**. However, it was also known that BQ **2** could be accessed *via* BQH_2 **67**, which is itself a lot less toxic and more economically viable than BQ **2**.

2.0.2 Results and Discussion

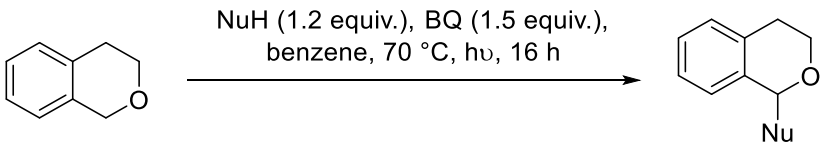
Initial attempts towards BQ-mediated CDC reactions were based on successful CDC reactions using ground state DDQ **4**, as reported by Li.[38,49] Disappointingly, and unlike those reaction reported by Li, irradiation of BQ **2** with visible light in the presence of isochroman **76** and acetophenone **15** for 72 h did not convert the starting materials to the product **77** (**Scheme 33**).[49]



76 **15** **77**

Scheme 33 Unsuccessful CDC reaction between isochroman **76** and acetophenone **15**, attempted as reported by Li where BQ **2** replaced DDQ **4**.[49]

The failure of this reaction meant that investigations into a range of alternative nucleophiles began, in order to identify more suitable coupling partners for the reaction. Nucleophiles were selected due to their precedence for successfully participating in such CDC reactions with DDQ **4**.[50] Benzene has been demonstrated to facilitate photochemical reactions in the past and was selected as a suitable solvent due to its lack of abstractable hydrogen atoms which could participate in the reaction (**Table 1**).[38]



76

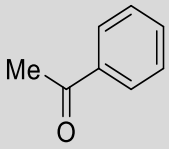
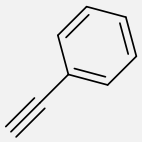
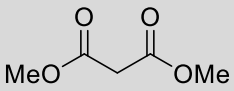
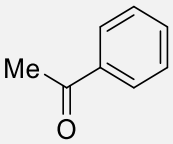
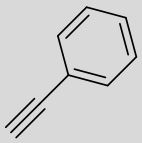
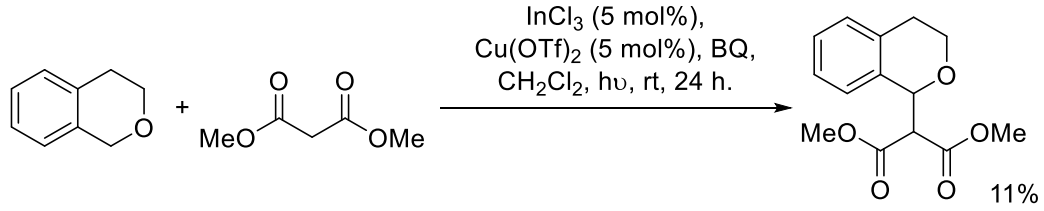
Entry	Nucleophile	Isochroman:NuH ratio	Product Yield/%
1		1:1.2	No reaction
2		1:1.2	No reaction
3		5:1.2	No reaction
4		5:1.2	No reaction
5		5:1.2	No reaction

Table 1 Table of results for each nucleophile used in an attempted CDC reaction.

Initially, for acetophenone (**Table 1; Entry 1**) and phenylacetylene (**Table 1; Entry 2**), a slight excess of nucleophile (1.2 equiv.) was used compared to isochroman **76**, to increase the likelihood that it would be incorporated into the starting material. Unfortunately, in all cases no starting material was converted to any products during the reaction. When Li performed these reactions with DDQ **4**, he employed 5 equivalents of isochroman **76**.[40] Therefore, this was also

attempted with the aforementioned nucleophiles as well as dimethyl malonate (**Table 1; Entry 3**) but was unsuccessful.

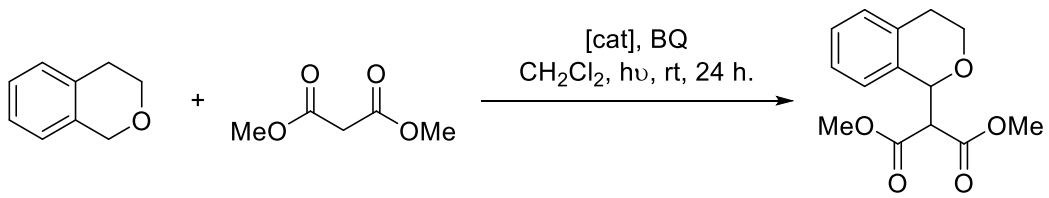
Li and co-workers had also previously reported a successful CDC reaction between isochroman **76** and dimethyl malonate **77** in the presence of DDQ **4**, $Cu(OTf)_2$ and $InCl_3$.[51] This methodology had the potential to provide a catalytic approach to the CDC reaction. Since all previously attempted nucleophiles had been unsuccessful, it was decided to turn attention towards this methodology and use it to test the hypothesis that DDQ **4** could be directly replaced with visible light irradiated BQ **2**. When DDQ **4** was substituted with BQ **2** and visible light, pleasingly, a CDC reaction was observed between isochroman **76** and dimethyl malonate **77**. Although the yield was low under these conditions (11%) it represented a promising start for the protocol (**Scheme 34**).



76 **78** **41**

Scheme 34 CDC reaction between isochroman **76** and dimethyl malonate **78** in the presence of light-irradiated BQ **2**.

Given the success of this reaction, control reactions were immediately performed to establish the reaction requirements and ensure that all components were essential (**Table 2**).



76 **78** **41**

Entry	Quinone /equiv.	$Cu(OTf)_2$ /mol%	$InCl_3$/mol%	Light	Conv/%
1	1.2	5	5	✓	36 (11%[a], 8.5%[b])
2	1.2	5	0	✓	29
3	0	5	5	✓	8
4	1.2	0	5	✓	38
5	1.2	5	5	×	0
6	1.2	0	0	✓	7

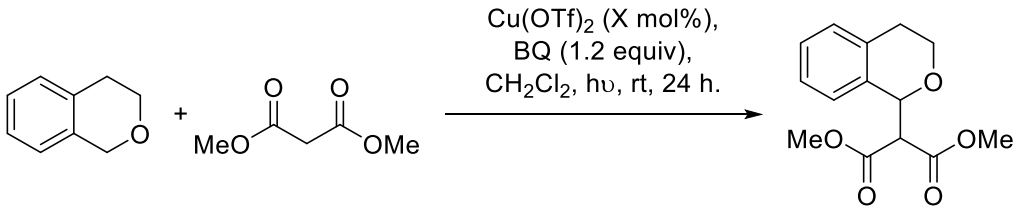
Note: [a]Isolated yield; [b]NMR yield of the lactone side product as calculated using 1,1,2,2-tetrachloroethane as an internal standard.

Table 2 Table of control reaction results from the CDC reaction between isochroman **76** and dimethylmalonate **78**.

The reaction conversions were drastically reduced in the absence of quinone and in the absence of both metals (**Table 2, Entries 3 and 6**). However, similar conversions were seen when both copper and indium were both used, as well as when either the copper or indium catalysts were used independently (**Table 2, Entries 2 and 4**). This strongly suggested that the presence of both metals was unnecessary and that the reaction would proceed with Cu or In alone. This result was consistent with that reported by Li and suggested that the role of the copper is two-fold; to turn over the hydroquinone formed in the reaction, and to activate the malonate in a coordination process.[51] Light was clearly required for the reaction since no conversion was observed in the dark (**Table 2, Entry 5**).

Li had also reported uncertainty with regards to the role of $InCl_3$ in the reaction, since the DDQ **4** reactions also proceeded well in its absence. It is notable that in Li's report there appears to be little benefit to the presence of $InCl_3$ alongside copper with respect to the yield of the reaction. Hence, due to the relatively low abundance of indium compared to copper, the use of $InCl_3$ was abandoned and it was decided that future reactions would be conducted with copper as the single metal ETM.[52]

With the control reactions complete and the decision taken to abandon $InCl_3$ use, optimisation of the reaction conditions was essential to increase the yield of the product. Firstly, the effects of the copper catalyst loading were investigated (**Table 3**).



76 **78** **41**

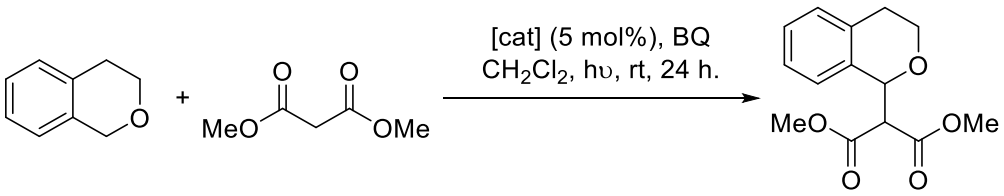
Entry	Cu(OTf)$_2$/mol%	Conversion[a]/ %
1	10	35
2	5	36(11)[b]
3	3	21
4	1	19

Notes: [a]Conversions were calculated using ^{1}H NMR by comparison between the starting material and product peaks; [b]Isolated yield.

Table 3 Table displaying the effects of varying concentration of $Cu(OTf)_2$ in the reaction.

Since the reduction of the copper loading below 5 mol% had a negative effect on the conversion and increase to 10 mol% gave only a minor benefit in conversion (**Table 3, Entries 2 and 1 respectively**), it was decided to maintain the copper loading at 5 mol%.

The ^{1}H-NMR spectra of the reactions also displayed characteristic peaks which corresponded to the formation of the lactone by-product in the ratio 8.5:11 (lactone **81**:CDC product). The oxidation of isochroman **76** to the lactone was later reported in the Moody group under similar conditions (see Section 4.). An atmosphere of argon was required to reduce the quantity of this by-product.[53] The reaction yields, and conversions remained low at this stage and so further optimisation was attempted through a screen of alternative metal salts (**Table 4**).



76 **78** **41**

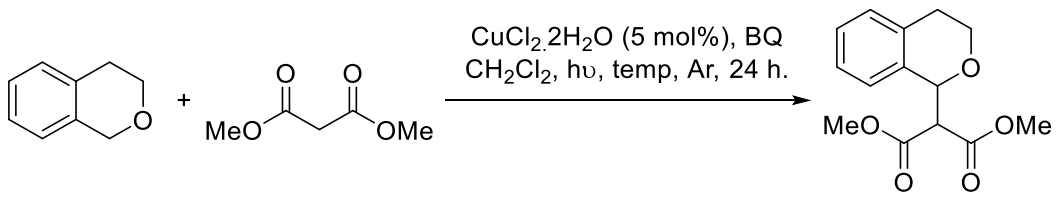
Entry	Catalyst	Atmosphere	Yield by NMR/%	Lactone yield/%
1	$CuCl_2.2H_2O$	Ar	15	-
2	$Cu(OTf)_2$	air	11	9
3	$Cu(OTf)_2$	Ar	8	0
4	CuBr	air	2	-
5	CuI	air	2	-
6	CuCl	Ar	2	-
7	$CuCl_2$	air	1	-
8	$CuBr_2$	air	2	-
9	$CuCl_2$	Ar	0	-
10	$Cu(OAc)_2$	Ar	0	-
11	$InCl_3/Cu(OTf)_2$	air	11	-
12	$InCl_3$	Ar	13	3
13	$InCl_3$	Ar	10	4
14	$FeCl_3$	Ar	6	1
15	$FeBr_3$	Ar	4	-
16	$FeCl_2$	Ar	10	0
17	CoF_3	Ar	0	-

Note: All yields obtained using ^1H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.

Table 4 Table of results from the metal electron transfer mediator.

A number of metal catalysts were screened but somewhat disappointingly, the yield never rose above 15%. Copper was the most successful ETM overall which was satisfying since it is both abundant and cheap. The best results were usually achieved with Cu(II) salts and the reaction clearly proceeded the best in the presence of $Cu(OTf)_2$ (**Table 4, Entry 2**).

The results of these reactions were notably reliant on the position of the lamp. When it was placed further away, significantly lower yields of the product were observed. It was unclear whether this was due to light penetration differences at different distances or thermal effects (the lamp radiates a large quantity of heat). In order to investigate thermal effects a bath was required to heat the reactions which would not shield them from light. It is known that light does not penetrate oil well (the light penetration distance in oil is approximately 1 mm)[54] so a water bath was the only available and suitable alternative. However, this limited the temperature to approximately 50 °C with a large water bath (>1 L) due to significant quantities of evaporation, which eventually led to the reaction being suspended above, and not in, the water and therefore it was not efficiently heated. Nevertheless, the reaction was attempted at various temperatures with the lamp situated at a suitable distance so as to have a negligible influence on the reaction temperature (**Table 5**).



76 **78** **41**

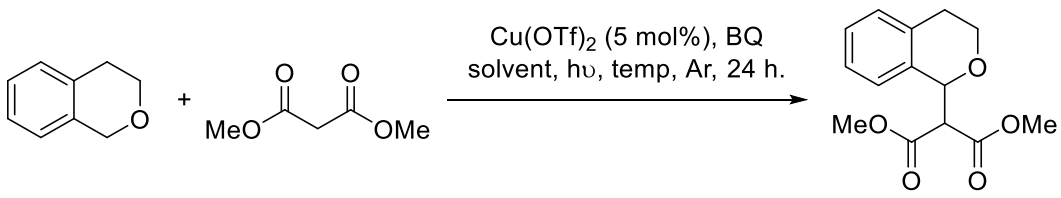
Entry	Temp/°C	Yield[a]/%
1	rt	0
2	30	0
3	50	11

Note: [a]Yields calculated by NMR using 1,1,2,2-tetrachloroethane as an internal standard.

Table 5 Reaction results at varying temperatures.

As suspected, the reaction clearly required heat to proceed. Unfortunately, the use of a water bath and dichloromethane as a solvent meant that bath temperatures above 50 °C could not be explored over the course of the reaction (16 h). Nevertheless, with these results in hand a solvent screen was also performed at different temperatures.

Li and co-workers had reported that the reactions with DDQ **4** were most successful in dichloromethane and 1,2-dichloroethane (DCE) but failed in the presence of water and THF.[51] This is in contrast to the results observed in our reaction with which dichloromethane, dimethyl carbonate (DMC) or acetone were the best solvents (**Table 6**, **Entries 2, 3 and 7** respectively). However, despite their success, this did not translate into yields above 15% (**Table 6**).



76 **78** **41**

Entry	Solvent	Temp	Yield[a]/%
1	dichloromethane	30	9
2	dichloromethane	50	11
3	DMC	50	9
4	TFT	50	5
5	MeCN	50	3
6	DCE	50	4
7	acetone	30	11
8	chloroform	30	8
9	acetone	45	14

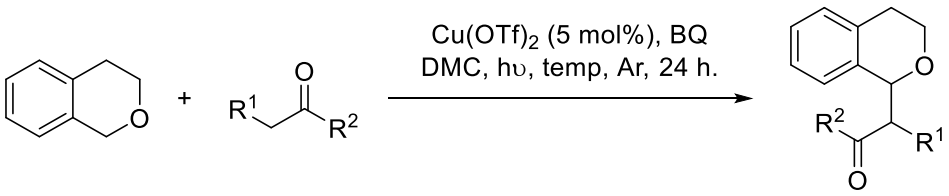
Note: [a]Yields obtained using ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.

Table 6 Solvent screen for the CDC reaction at various temperatures.

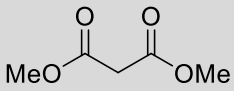
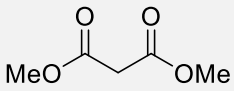
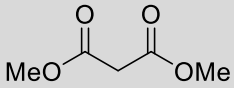
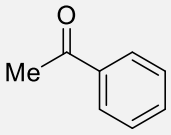
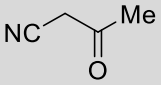
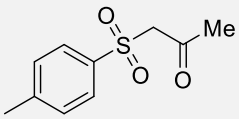
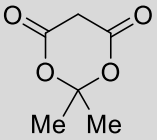
DMC has a good sustainability profile according to the popular reaction solvent guides and had been the solvent of choice in the past for similar reactions, therefore it was chosen for future studies.[14,34]

Final attempts to optimise the reaction led to considerations regarding the stoichiometry of the nucleophile (**Table 7**)**.** Unfortunately, increasing the number of equivalents of the nucleophile so that more was available to react with isochroman **76** appeared to have no effect and it was

clear that malonate-based nucleophiles continued to be poor reaction partners for this process (**Table 7, Entries 1-3**). Therefore, other nucleophiles which had been reported to undergo successful CDC reactions with DDQ **4** in the literature were selected and used under the reaction conditions reported above (**Table 7**).[51]



76

Entry	Nucleophile	Equiv. of Nucleophile	Product Yield[a]/%
1		2	9
2		5	13
3		1.2	3
4		1.2	5
5		1.2	NR
6		1.2	NR
7		1.2	2

Note: [a]Yields obtained using ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.

Table 7 Range of nucleophiles attempted in the CDC reaction with isochroman.

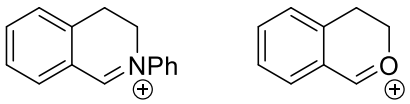
Unfortunately, all nucleophiles used in the reaction gave the product in poor yield or no reaction (NR).

Amongst those previously mentioned, an issue with the DDQ **4** based CDC reactions was that DDQ **4** can be difficult to remove from the product. BQ **2** was seen as a good alternative due to its reduced toxicity, cost and biorenewability.[29] It was also found to be easier to remove from the reaction mixtures. Work in the Moody group at this time had displayed that light irradiated BQH_2 **67** can form BQ **2** *in situ* and which could then perform other reactions.[55] Therefore, at this stage focus naturally moved towards this new research in this area.

3.1 Project Conclusions & Future Work

Despite significant efforts to optimise this reaction, the yield never improved beyond 15%. This was disappointing and indicated that CDC reactions did not appear to be viable with visible light irradiated BQ **2** under the investigated conditions.

It is possible that the failure so far to develop a C-C bond forming CDC reaction using light-irradiated BQ **2** as a cheaper and more sustainable alternative to DDQ **4** had been due to the differences in the reaction mechanism of the reaction. The inability of the isochroman intermediate to trap nucleophiles similar to those used with DDQ **4** suggests that the reaction may not proceed *via* proposed oxonium intermediate **80** proposed by Klussman (**Figure 2**).[56] However, this supports the hypothesis that the reaction proceeds *via* a radical reaction mechanism.



79 **80**

Figure 2 Iminium-type intermediate proposed by Klussman and proposed intermediate for isochroman where DDQ **4** is used in the CDC reactions respectivaly.[56]

A radical mechanism would not necessarily allow the coupling of the standard nucleophilic substrates investigated thus far in this report. Therefore, future work may focus on further work to establish and confirm a radical mechanism, and then more appropriate coupling partners could be selected for the reaction.

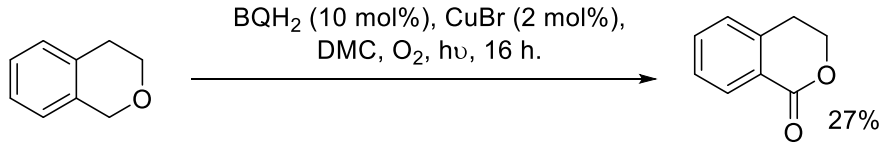
It had been noted however that light-irradiated BQ **2** appeared to be capable of creating a lactone **81** from isochroman **76** which had not yet been reported in the literature. [55]

Biorenewability is also advantageous from a sustainability perspective as it means that the chemical can be accessed from a renewable feedstock. We had previously reported that, in principle, the active BQ **2** can be created *in situ* by the oxidation of BQH_2 **67** and used without purification, so it would be advantageous to be able to perform oxidation reactions directly from the natural product from which it is accessed, and this was therefore of interest to the Moody group.

4. BQ as an alternative to DDQ in benzylic oxidation reactions

4.0.1 Project Aims

Whilst investigations in the Moody group were underway into the potential for visible light mediated BQH_2 **67** to remove PMB protecting groups, it was also discovered that under those conditions employed, BQH_2 **67** could oxidise benzylic ethers to ester groups (**Scheme** 35).[55]



76 **81**

Scheme 35 Oxidation of isochroman to isochromanone **81** discovered by Moody and co-workers.

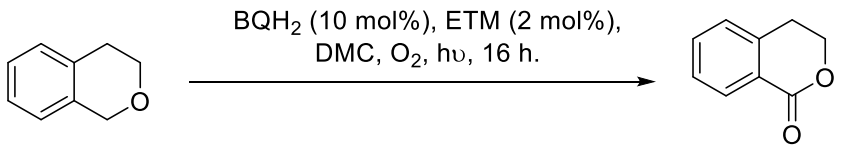
This reaction had also been observed while investigations were underway in the Moody group, by Lorna Mitchell, into BQ-mediated CDC reactions.[55] The ability of BQH_2 **67** to install such functionality in one step was interesting since few methodologies exist which can achieve this. It could provide a way to improve the sustainability of the current methodology available for benzylic oxidation reactions. Modern strategies usually still require the ether to be converted into another functional group e.g. an acid, which may then be converted into an ester group. However, a reaction discovered in the Moody group showed that BQ **2** could be used to create an ester from an ether directly, thus reducing the step count and resource use whilst increasing the efficiency of the reaction; and therefore, could improve the sustainability of the process.

The findings were also considered interesting since isochroman **76** had coupled with oxygen, and this suggested that the substrate may indeed move through a radical-based intermediate - since dioxygen is a radical. Therefore, investigations into this reaction were pursued and initially investigated by Lorna Mitchell.

Therefore, the aims of this project were to develop a photo-activated strategy that employed BQ **2** as a cheap oxidant to convert benzylic ethers into esters and to optimise the process so that it may be as sustainable as possible. Investigations into whether the reaction could be applied to other substrates would also be conducted, and finally deductions regarding the mechanism of the light-driven reaction would be made.

4.1 Preliminary Work

To establish the utility of BQ **2** to oxidise benzylic ethers, isochroman **76** was chosen as the initial substrate of study, since it has been widely used in the literature for various oxidation reactions with DDQ **4** and BQ **2** chemistry (see Introduction, Section 2.). Previous studies in the Moody group had already established that BQ **2** could be accessed *via* the *in situ* oxidation of BQH_2 **67** using a metal based ETM. Since BQH_2 **67** is cheaper and less toxic than BQ **2**, it was also the obvious and more sustainable reagent choice for this work.[29] Copper was chosen as an abundant and cheap metal and so the benzylic oxidation reaction was screened for an appropriate copper salt ETM in the presence of BQH_2 **67** (**Table 8**).



76 **81**

Entry	ETM	Yield/%
1	CuBr	27
2	$CuBr \bullet CH_3SCH_3$	51
3	CuCl	25
4	CuI	16
5	CuOAc	27
6	$CuBr_2$	55
7	$CuCl_2 \bullet 2H_2O$	66
8	$Cu(OAc)_2$	42
9	$Cu(OTf)_2$	76
10	$CuSO_4$	11
11	$Cu(acac)_2$	43
12	$Cu(hfaa)_2 \bullet xH_2O$	34
13	$Cu(TFA)_2 \bullet xH_2O$	3
14	Cu powder	6
15	1p coin	0

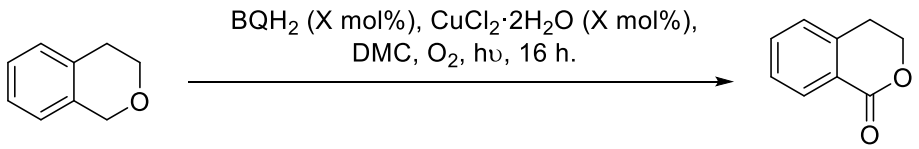
Note: All of the above experiments conducted by Lorna Mitchell.[55]

Table 8 Catalyst screen conducted by Lorna Mitchell.[55]

A catalyst screen quickly established that the reaction proceeded in the presence of most copper sources, but the best results were obtained when a Cu (II) catalyst was used. Copper (I) sources gave the product in low yield, whereas every copper (II) source tested gave yields above 40%. Pleasingly, the screen found that $CuCl_2 \bullet 2H_2O$ or $CuOTf_2$ could be used as the ETM with good results (**Table 8, Entries 7 and 9 respectively**), although the significant difference in price

($3009/mol – September 2018, Millipore Sigma for $CuOTf_2$ vs $74.67/mol – September 2018, Millipore Sigma for $CuCl_2•2H_2O$) meant that $CuCl_2•2H_2O$ was chosen as the preferred copper salt.[57]

Furthermore to our satisfaction, when optimisation reactions were conducted to establish the ideal catalyst loading for the reaction, it was found that only 5 mol% of BQH_2 **67** in the presence of 2 mol% of $CuCl_2•2H_2O$ was needed (**Table 9**). Attempts to lower the copper quantities were met with reduced yields, and increased loadings had little bearing on the reaction yield.



76 **81**

Entry	BQH_2 /mol%	$CuCl_2•2H_2O$ /mol%	Yield /%
1	10	2	64
2	5	4	60
3	5	2	70
4	5	1	39
5	2.5	4	51
6	2.5	2	51
7	2.5	1	40

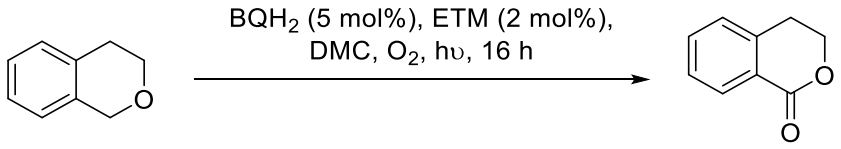
Note*:* All of the above experiments conducted by Lorna Mitchell.[55]

Table 9 Optimisation of the Catalytic Loadings performed by Lorna Mitchell.[55]

Since the aims of this work were to produce a benzylic oxidation methodology in the presence of BQH_2 **67** and light in the most sustainable way possible, DMC was used as the solvent due to its sustainable credentials and history of success with in similar reactions studied by the Moody group.[14]

4.2 Results and Discussion

It had now been established that isochroman **76** could be oxidised to isochromanone **81** when stirred at rt in the presence of visible light irradiated BQH_2 **67** and an ETM, under an atmosphere of oxygen. Control reactions also established that no reaction was observed in the absence of BQH_2 **67**, $CuCl_2 \bullet 2H_2O$, oxygen or in darkness (**Table 10**).[58]



76 **81**

Entry	Isochroman	BQH_2	$CuCl_2 \bullet 2H_2O$	Light	Yield/%
1	✓	✓	✓	✓	70
2	✓	×	✓	✓	15
3	✓	✓	×	✓	16
4[a]	✓	✓	✓	×	NR
5	×	✓	✓	✓	(BQ detected)

Note: [a]Reaction heated to 30 °C to ensure temperature is the same as when in light; NR = no reaction.

Table 10 Table of control reactions.

Despite the confirmation of the requirement of light, established through the control reactions, the effect of the lamp type had not yet been investigated. The mercury halide lamp used in the reactions thus far had produced a significant quantity of heat over the course of the reaction time and so it had been impossible to investigate the role of the light in the absence of heat which was important to establish their combined effects. Additionally, the mercury halide lamp

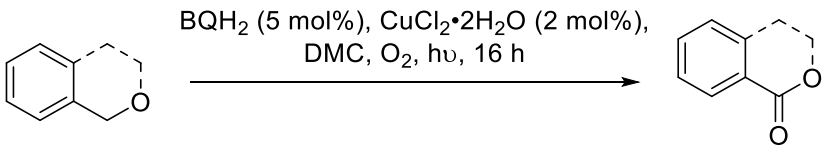
emitted a very broad range of wavelengths (see Appendix) and so lights which emitted in a shorter range with higher efficiency were desirable in some respects. The reaction had however been performed in the dark whilst being heated to 30 °C (the approximate temperature the reaction reaches in the presence of the heat from the lamp), and no reaction occurred.

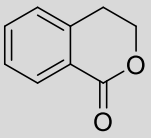
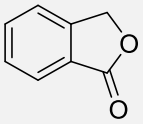
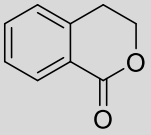
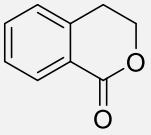
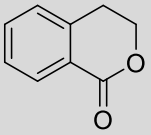
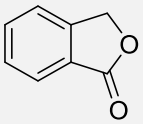
It was also wondered what the effects of a more efficient LED lamp would be. Such lamps target the visible light region of the electromagnetic spectrum at which BQ **2** absorbed light (see Appendix for the lamp output spectra) more efficiently than the mercury halide lamp. This meant it was plausible that an LED lamp accelerate the reaction or improve the yield over the full 16 h reaction time.

A minisun LED flood lamp was sourced (see Appendix for the lamp output spectrum) which, when used in the reaction, gave both isochromanone **81** and phthalide **82** in comparable yields (77% and 67% respectively) (**Table 11, Entries 5 and 6**) to those produced when the mercury-halide lamp was used. This lamp also produced a similar quantity of heat over the course of the reaction and so it was deduced that targeting a shorter wavelength range actually made no difference to the reaction outcome.

Instead, a bespoke-made LED fan-cooled system was provided by the George group at the University of Nottingham that consequently did not heat the reaction to such temperatures (see Appendix for the lamp output spectrum). With this fan-cooled lamp, the oxidation of isochroman **76** proceeded and gave isochromanone **81** (**Table 11, Entry 4**) in comparable yield to reactions with the mercury-halide lamp (73% vs 70%) when the reaction was both performed at rt or heated to 30 °C. This lamp was far smaller and more portable than those previously described in this report, and work reported by the George and Poliakoff groups suggested that

thin-film reaction mixtures, created by spinning the reaction flask on a rotary evaporator, enhance the light absorption efficiency of the photocatalytic system.[59] Thus, the portable fan-cooled lamp was suspended above a rotary evaporator, and the reaction performed whilst spinning and heating to 40 °C were combined. However, despite achieving a thin film dispersion of the flask contents and possible increase in light penetration to the reaction, no notable increase in the yield of the reaction was observed (**Table 11, Entry 6**).



Entry	Product	Compound No	Lamp	Temp/°C	Isolated Yield/%
1		**81**	LED flood lamp	30	72
2		**82**	LED flood lamp	30	42
3		**81**	LED block	40[a]	67
4		**81**	LED block	30[a]	73
5		**81**	LED block	50[a]	77
6		**81**	LED block	40[b]	67

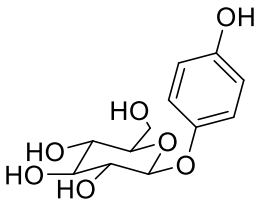
Notes: [a]Heated using a sand bath; [b]heated in a thermostatically controlled water bath as part of a rotary evaporator set up.

Table 11 Comparison of the isolated yield of isochromanone **81** and pthalide **82** under visible light irradiation using two different LED light sources.

Since the reaction had seemingly been optimised as much as possible with respect to isochroman **76**, the means to increase the reaction sustainability credentials further was sought, and it was postulated that a biorenewable source of BQH_2 **67** could be used.

4.2.2 Arbutin as a pre-oxidant

Although the concept of biorenewable platform chemicals has been explored extensively by the scientific community,[58] the use of biorenewable reagents appears to be largely unexplored. We had previously reported that BQH_2 **67** had the potential to be a biorenewable reagent, since its β-D-glucopyranoside, known as arbutin **83** (**Figure 3**) could be used as a source.[29] This is found in the leaves of the bearberry (*Arctostaphylos uva-ursi*) and the commonly known 'elephant ears' or bergenia plant (*Bergenia crassiflora*).[60] Therefore, it seemed possible that we may be able to use arbutin **83** as a biorenewable source of BQH_2 **67**.

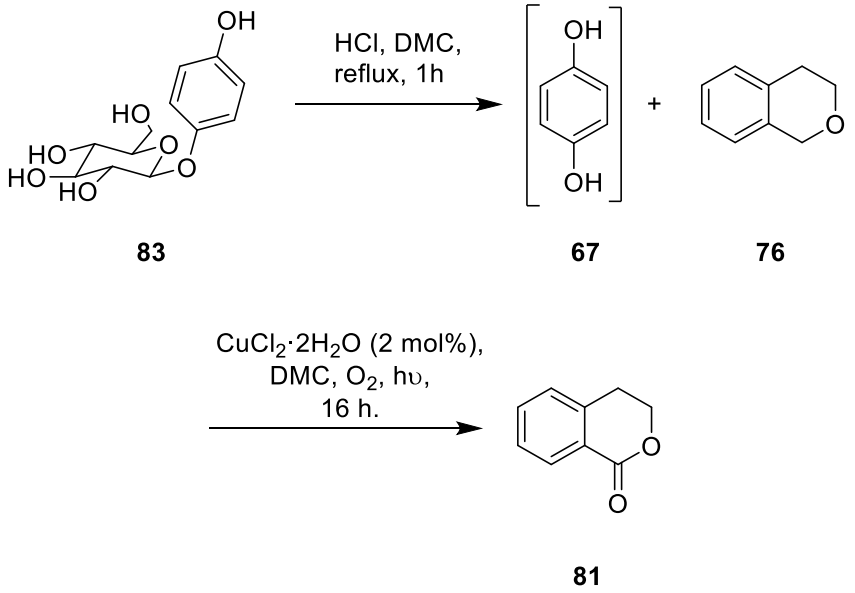


83

Figure 3 Structure of arbutin **83**.

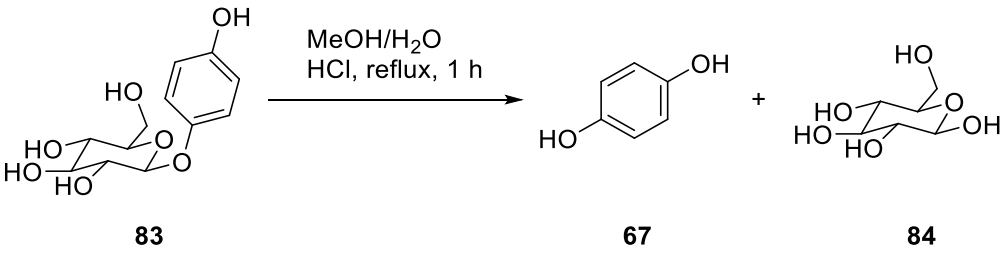
Fortunately, arbutin **83** is commercially available (it can be found in many skin lightening creams), so it was envisaged that arbutin **83** could be used as a 'pre-oxidant' to BQH_2 **67**. Unfortunately, a simple replacement of BQH_2 **67** in the reaction with arbutin **83** did not give the desired product – in fact no conversion of starting material was observed in the reaction at all. It was likely that the BQH_2 **67** would have to be cleaved from its glycone in order to make it available for the reaction, and the oxidation reaction conditions were unable to achieve this

alone. Hence, it was suggested that the deglycosylation reaction and oxidation reaction may have the potential to be telescoped (**Scheme 36**).



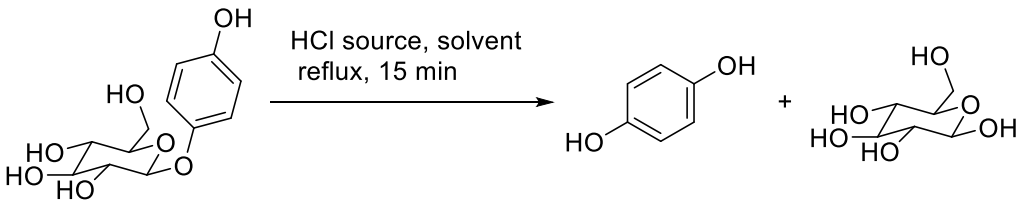
Scheme 36 Proposed scheme for the telescoping of both the deglycosylation of arbutin **83** and the subsequent oxidation of isochroman **81**.

Initial experiments focussed on the deglycosylation of arbutin **83** under standard acidic conditions using methanol, water and hydrochloric acid at reflux (**Scheme 37**). BQH_2 **67** formation was confirmed by both the presence of the characteristic peak at 6.8 ppm in the ^{1}H-NMR spectrum and presence in the HPLC trace (see Appendix), by comparison with commercially sourced sample of BQH_2 **67**.



Scheme 37 Initial arbutin **83** deglycosylation attempted.

In order to establish whether the deglycosylation was solvent dependent, and whether any of those solvents could also be used for the oxidation reaction, a screen was conducted of hydrolysis solvents and three HCl sources – aqueous and anhydrous sources of hydrogen chloride in methanol and dioxane. Arbutin **83** was successfully hydrolysed to BQH_2 **67** and glucose **84** in moderate to excellent yields (calculated by ^1H NMR spectroscopic analysis using an internal standard) in all solvents, in fewer than 45 min. However, when concentrated HCl was used, dark reaction mixtures formed that indicated degradation and the yields were lower than those where anhydrous HCl source, methanolic HCl, was used (**Table 12**).



83 **67** **84**

Entry	Solvent	HCl source	Hydroquinone yield[a] / %		
			15 min	30 min	45 min
1	TFT	HCl in MeOH	46	-	100
2	TFT	Conc. HCl	22	-	31
3	MeOH	HCl in dioxane	70	100	93
4	MeOH	Conc. HCl	59	100	100
5	DMC	HCl in MeOH	19	37	85
6	DMC	Conc. HCl	37	96	100
7[b]	Acetone	Conc.HCl	0	0	0
8[b]	Acetone	HCl in MeOH	0	0	0

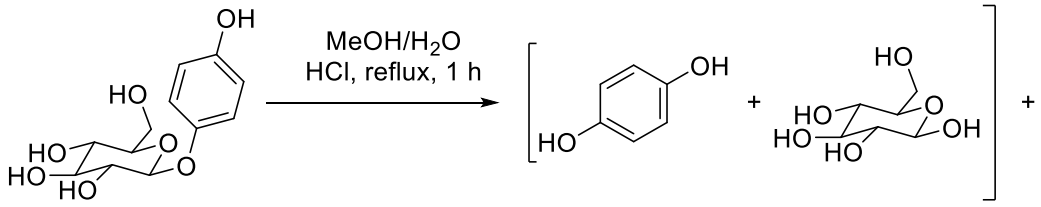
Notes: [a]Yields were deduced by ^{1}H-NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard. [b]Hydroquinone was not detected in the NMR.

Table 12 Table of results for the deglycosylation of arbutin **83** under various conditions.

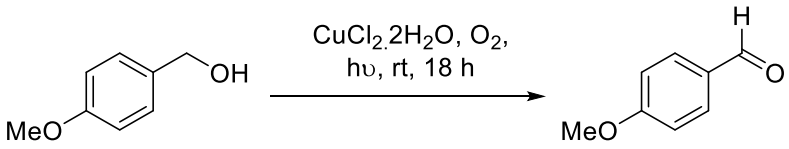
In most cases, the deglycosylation was complete in under an hour. The low yield in TFT with concentrated HCl (**Table 12, Entry 2**) is attributed to the immiscibility of water and TFT. Since the hydrolysis occurred quickly and effectively, attempts to telescope the hydrolysis and oxidation could now be made. Previous work in the group had focussed on the oxidation of alcohols under extremely similar conditions, and therefore it was envisaged that the alcohol

oxidation may be easier to achieve under the acidic conditions.[29] Therefore, once the hydrolysis was complete, 4-methoxybenzyl alcohol **85** and $CuCl_2 \bullet 2H_2O$ were added to each of the acidic mixtures and the reactions were cooled. They were each then purged with oxygen and stirred at room temperature under visible light irradiation for 18 h.

Unfortunately, the oxidation gave poor yields or failed in each attempt in the acidic media. The use of anhydrous methanolic HCl in TFT for the hydrolysis, followed by addition of the final components, gave the aldehyde **21** (**Table 13, Entry 10**) in higher, but still unacceptably low, yield (15%).



83 **67** **84**



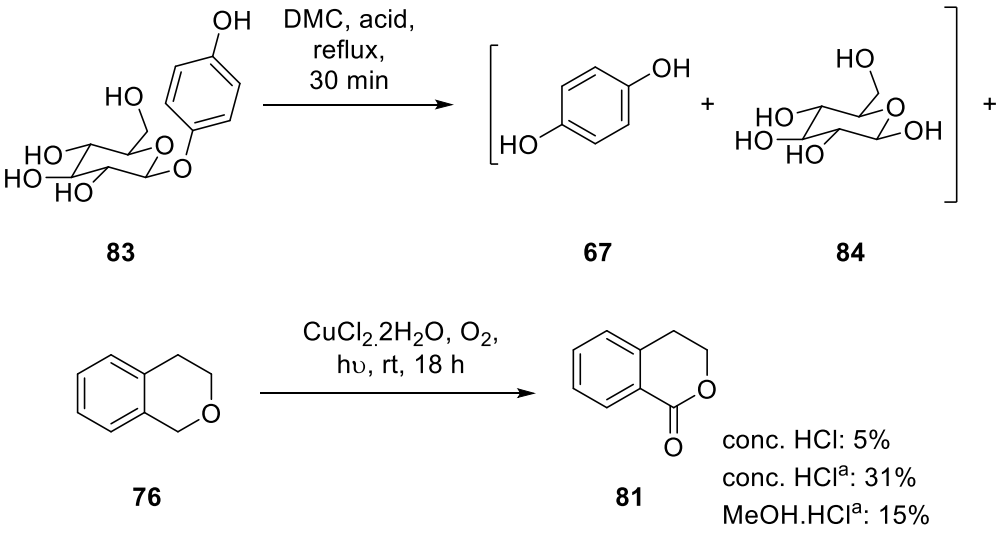
85 **21**

Entry	Solvent	Hydrolysis time/h	Copper/equiv.	Oxidation time	Yield[a] /%
1	Acetone	1	0.2	24	0
2	DMC	1	0.2	24	0
3	MeOH/H_2O	1	1	18	2
4[b]	Acetone	-	1	18	3
5	Acetone	1	1	24	0
6	THF	1	1	24	0
7[c]	MeOH/dioxane	0.25	1	18	15
8[d]	Acetone	0.25	1	18	5
9	TFT	0.25	1	18	2
10[d]	TFT	0.25	1	18	15

Notes: Reactions were performed with conc. HCl unless otherwise stated. The hydrolysis products were used without work up or purification. [a]Yields were deduced by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard. [b]Reaction attempted without an initial hydrolysis step. Deglycosylation and oxidation attempted together with $CuCl_2 2H_2O$ (1 equiv.), acetone, hυ, O_2, rt, 18 h. [c]Anhydrous HCl in dioxane used. [d]Methanolic HCl used.

Table 13 Attempts at a one-pot hydrolysis of arbutin **83** and oxidation reaction of 4-methoxybenzyl alcohol **85**.

Evidently, the success of the oxidation reaction relied heavily on the conditions used in the hydrolysis reaction. Concentrated HCl and/or the presence of water appeared to be detrimental to the oxidation reaction. The oxidation of isochroman **76** was attempted under the same conditions and only gave the product **81** in low yield (5% yield by NMR). It did not seem possible to telescope the deglycosylation and oxidation reactions and so it was decided to remove the solvent and acid prior to the oxidation reaction. When the solvent and acid were removed *in vacuo* and then the reagents, substrate and solvent for the oxidation added, a vast improvement in the yield of the product was seen immediately (5% vs 31% yield). Isochromanone **81** was isolated in 31% yield when the hydrolysis reaction was performed with concentrated aqueous HCl which had previously been deemed detrimental to the reaction. This is presumably due to a higher proportion of arbutin **83** being converted to BQH_2 **67**, and conveniently aqueous HCl is the most available and economical of the two HCl sources (**Scheme 38**).



83 **67** **84**

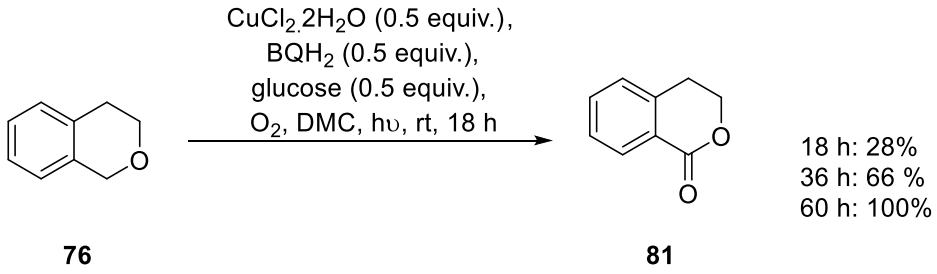
76 **81**

Note: [a]Solvent and acid removed *in vacuo* before the oxidation reaction was performed.

Scheme 38 One-pot deglycosylation of arbutin **83** and oxidation of isochroman **76**.

Despite the reaction success in this case, the yield remained significantly lower than that seen with commercially available BQH_2 **67** (70%). It was suggested that, since glucose is a reducing sugar, it may have a detrimental effect on the oxidation reaction. A simple control reaction

confirmed this hypothesis. Isochroman **76** was placed under oxidation conditions in the presence of equimolar quantities of BQH_2 **67** and an equimolar quantity of commercially sourced glucose **84**. Its presence was found to reduce the reaction yield significantly (28%) compared to reactions performed under the optimised conditions with BQH_2 **67** over 18 h. Significantly longer reaction times were required to achieve comparable yields to those seen previously without glucose **84** and demonstrated that it clearly hindered the oxidation reaction (**Scheme 39**).



76 **81**

Scheme 39 Oxidation of isochroman **76**, in the presence of glucose **84**.

Longer reaction times are not only inconvenient, but also costly in terms of energy consumption thus it was desirable to overcome this issue. Initially, quantities of both BQH_2 **67** and arbutin **83** were reduced in order to reduce the probability that a glucose molecule **84** would encounter the active BQ **2** in the reaction mixture. Thereby, hopefully increasing the yield of the oxidation reaction. This was somewhat successful, although even a small quantity of glucose **84** had a negative consequence for the reaction yield. Therefore, its removal from the reaction was essential.

Fortunately, a simple solubility test found that DMC was the only solvent that would dissolve BQH_2 **67** only which was identified after solvent was removed by ^{1}H-NMR spectroscopic analysis (**Table 14**).

Solvent	Water	Dichloromethane	Chloroform	Toluene	DMC
Glucose	✓	×	×	×	×
BQH_2	✓	×	×	×	✓

Table 14 Table displaying the solubility differences observed between glucose **84** and BQH_2 **67** in various solvents.

Therefore, once the hydrolysis was complete and the solvent and HCl were removed *in vacuo*, the residue was triturated with DMC in order to extract the BQH_2 **67**. It was imperative that the residue was completely free of water before trituration with DMC or the BQH_2 **67** would preferentially remain in the water. Dryness could be ensured by azeotroping the mixture with a small amount of toluene in the final stages of solvent removal. DMC was then removed *in vacuo* from the extracts to give a colourless solid which was confirmed as BQH_2 **67** on ^{1}H NMR analysis.

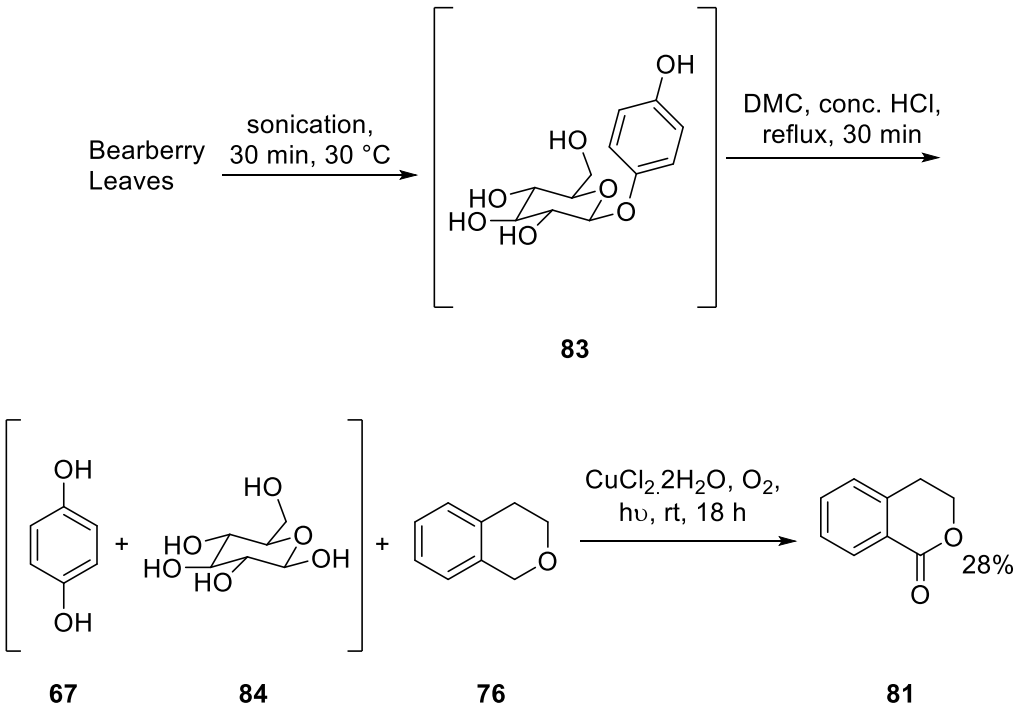
Isolation of BQH_2 **67** in this way provides a sustainable and potentially biorenewable alternative route to the reagent if arbutin **83** was isolated from plant material, without any cumbersome or complicated synthetic methods and avoiding column chromatography. Traditionally, BQH_2 **67** is synthesised by one of three methods; hydroperoxidation of *p*-diisopropylbenzene, hydroxylation of phenol, or the oxidation of aniline.[61] These processes are harsh, high in energy and are largely inconvenient processes that rely on petrochemical starting materials. Therefore, it is important to note that the preparation of BQH_2 **67** from plant material represents a more sustainable alternative to the current state of the art in industrial production of BQH_2 **67**.

The isolated BQH_2 **67** was used in the isochroman **76** oxidation with success and gave isochromanone **81** in 72% yield which was comparable to the attempts with commercially

sourced BQH_2 **67**. With these conditions in hand, focus was turned to how arbutin **84** may be obtained from the leaves of either the bearberry or bergenia plants.

Dried bearberry leaves were purchased from Serbia and bergenia leaves were harvested and dried by ourselves in Nottingham, UK. Initially, both the bearberry and bergenia leaves were powdered and extracted using a literature procedure described by Codina and co-workers.[62] The ground leaves were suspended in a water:methanol mixture (95:5) and sonicated at 30 °C for 30 min before the mixture was centrifuged and a known quantity of supernatant was removed for analysis. Quantitative HPLC showed that the bearberry leaves contained 1 mg of arbutin **83** per mL of supernatant, a small quantity of BQH_2 **67** (less than 1 mg) and other unidentifiable plant material. Analysis of the bergenia leaves (grown and harvested in Nottingham) unfortunately found only 0.3 mg of arbutin **83** per mL of supernatant (see Appendix for HPLC traces). Therefore, the bearberry leaves were selected to continue our research.

Since the arbutin **83** concentration was known, solvent was removed from an appropriate quantity of supernatant *in vacuo*. The residue was then subjected to the established hydrolysis conditions and DMC trituration as previously described. The solvent was removed from the extract and presence of BQH_2 **67** in the residue was again confirmed by its characteristic peak in the ^{1}H-NMR spectrum. Isochroman **76**, $CuCl_2 \bullet 2H_2O$ and DMC were then added to the residue and the photochemical benzylic oxidation reaction was attempted (**Scheme 40**).



Scheme 40 Leaf extraction, arbutin hydrolysis and subsequent oxidation of isochroman **76**.

Isochromanone **81** was isolated from the final reaction in 28% yield after 18 h. The reduction in yield, compared to previous attempts with BQH_2 **67**, was ascribed to the presence of unidentifiable plant material in the mixture which could inhibit in the reaction in a plethora of unpredictable ways since the composition of this material was unknown. Thus, lower yields and the possibility of longer reaction times being required had been anticipated. Although this yield is lower than that observed with both commercial BQH_2 **67** and arbutin-derived BQH_2 **67**, it was satisfying to demonstrate that the BQH_2 **67** used in these reactions could truly be sourced biorenewably and facilitate a successful oxidation reaction.

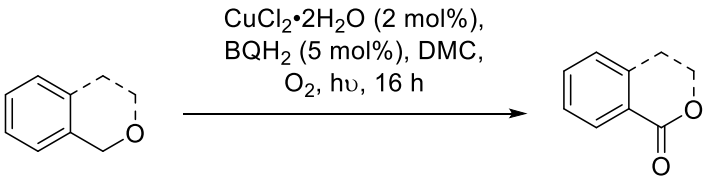
Although it could be possible to separate the BQH_2 **67** from the complex mixture of plant material, this would require complicated column chromatography procedures. Since, the aims of this project were to be as sustainable as possible and chromatography is known to use large quantities of solvent and silica gel, it was not appropriate to spend lengthy amounts of time in the development of a purification procedure for this methodology. The work performed thus

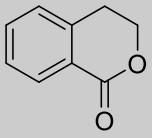
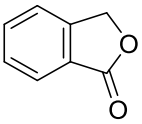
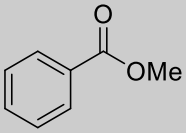
far demonstrated the potential and promise that biorenewable reagents may have in future reactions.

4.3 Substrate Scope

4.3.1 Cyclic and acyclic ethers

Since the oxidation of isochroman **76** had been successful in the presence of both commercial arbutin-derived BQH_2 **67** and plant-derived BQH_2 **67**, we set out to demonstrate the scope of the oxidation reaction. This began with the chemoselective oxidation of both cyclic and acyclic ethers to the corresponding cyclic and acyclic esters (**Table 15**). Isochroman, phthalan and benzylmethyl ether were all commercially available.



Entry	Compound No	Product	Yield/%
1	**81**		70(72[a])
2	**82**		67(62[a])
3	**15**		38[b](43)

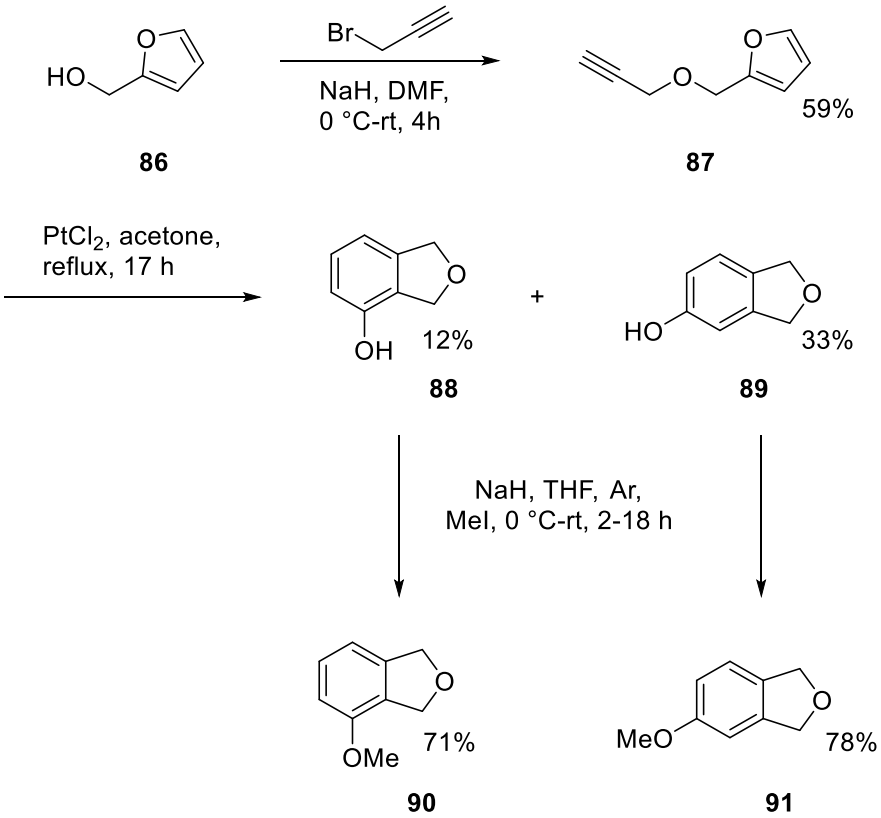
Notes: [a]In the presence of BQH_2 derived from arbutin; [c]Combined yield of ester (43%) and acid (21%); [b]Reaction performed by Lorna Mitchell.[55]

Table 15 Oxidation of phthalan and benzylmethyl ether in comparison with isochroman **76**.

When these optimized conditions were applied to phthalan, it was oxidised in good yield to phthalide **82** in the presence of both commercial BQH_2 **67** (67%) (**Table 15, Entry 2**) and that

derived from arbutin (62%). The α-oxidation of open chain benzylic ether to the corresponding benzoate esters was achieved in moderate yield (38%) which could also be reproduced with arbutin (43%) (**Table 15, Entry 3**).

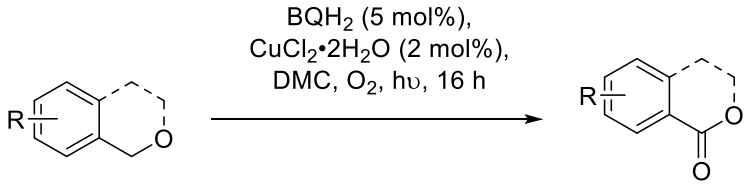
In order to investigate the effect of substituents, a range of substituted isochromans and phthalans were synthesised. Both electron withdrawing and donating groups were installed in the 6-position of isochroman. Fluorinated isochroman was synthesised *via* a literature procedure,[63] as was the methoxy derivative and thiophene.[55] The 5-methoxy and 6-methoxy phthalans and were synthesised by a route described in the literature.[64] Briefly, the intramolecular Diels-Alder reaction of furfuryl alcohol **86** derived furan **87** produced the 4-hydroxy **88** and 5-hydroxy phthalans **89** and which could then be methylated under standard conditions to give the desired substrates **90** and **91** (**Scheme 41**).[65]

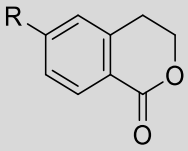
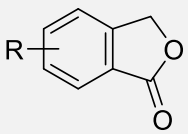
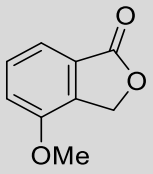


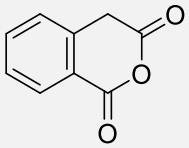
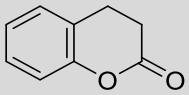
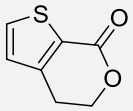
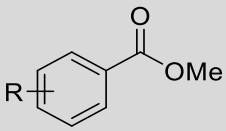
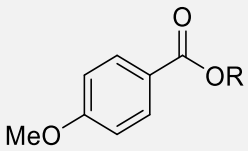
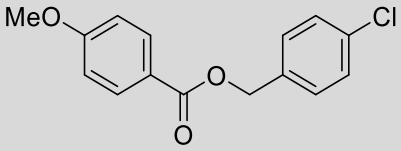
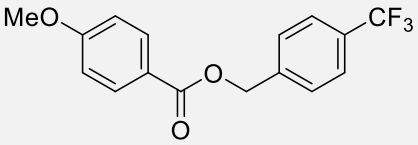
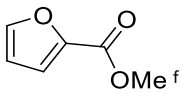
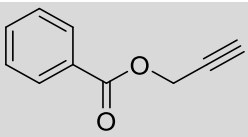
Scheme 41 Synthesis of 4- and 5-methoxy phthalan substrates **90** and **91** for oxidation.

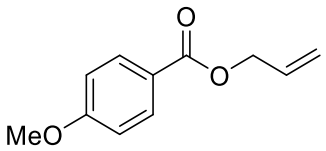
Pleasingly the benzylic positions of both isochroman derivatives **92** and **93** were oxidised in good yields (**Table 16, Entries 2 and 3**). Since they are unsymmetrical, substituted phthalans have two benzylic positions for oxidation, and in the case of 5-methoxyphthalan (**Table 16, Entries 5 and 6**), the *para* oxidation product **95** was produced in slightly higher yield than its isomer **94** during the same reaction, presumably due to the *para* position being favoured electronically, as a result of the methoxy group.

In the oxidation of 4-methoxyphthalan (**Table 16, Entry 7**), 4-methoxyphthalide **96** only was observed, even though it is the least favoured through electronic factors. Presumably, in this instance the steric hindrance caused by the methoxy group in the 4-position overrides any electronic effects, and so the *meta* product is favoured. In all cases the structures of the phthalide products were confirmed by comparison with literature data.



Entry	Compound No.	Product	R	Yield/%
1	**81**		H	70(72[b])
2	**92**		OMe	53[e]
3	**93**		F	51
4	**82**		H	67(62[b])
5	**94**		5-MeO	21[a,g]
6	**95**		6-MeO	30[a,g]
7	**96**			21

8	**97**			0
9	**98**			0
10	**99**			0
11	**15**		H	38[e](43)
12	**100**		4-OMe	64[e]
13	**101**		4-Cl	57[e](60)
14	**102**		4-CF_3	22[e](6)
15	**103**		2-Br	38[e](42)
16	**104**		3-F	0
17	**5**		Et	40[e]
18	**105**		^{i}Pr	40[e]
19	**106**		^{n}Bu	0[e]
20	**107**			28[e]
21	**108**			20[e]
22	**109**			0
23	**110**			0[e]

24	**111**		0[e]

Notes: All reactions were carried out on 1 mmol scale at a 0.08 M concentration in sealed 25 mL Pyrex tubes, using a 400 W HQI-T metal halide lamp. [a]BQH_2 (5 mol%), ETM (4 mol%), DMC, O_2, hυ, rt 16 h; [b]In the presence of BQH_2 derived from arbutin; [c]Combined yield of ester (43%) and acid (21%); [d]Yield by ^{1}H NMR integration against 1,1,2,2-tetrachloroethane as an internal standard; [e]Reaction performed and starting materials synthesised by Lorna Mitchell.[55]; [f]Substrate synthesis only was performed by Lorna Mitchell[55]; [g]Both of these products are produced in the same reaction.

Table 16 Oxidation of cyclic and acyclic ethers to the corresponding cyclic and acyclic esters.

As well as cyclic ethers, substituted benzylmethyl ethers were investigated. These substrates were synthesised by methylation of the corresponding commercially available alcohol (see Experimental Section). Both 4-methoxybenzyl methyl ether (**Table 16, Entry 12**) and 4-chlorobenzyl methyl ether (**Table 16, Entry 13**) were oxidised in good yield, but the more electron deficient 4-trifluoromethyl derivative (**Table 16, Entry 14**) was oxidised to ester **102** in only moderate yield. Additionally, 3-fluoromethyl benzyl ethyl ether (**Table 16, Entry 16**) and 2-bromobenzyl methyl ether (**Table 16, Entry 15**) also showed a modest reduction in yield and suggested that electron withdrawing groups are less desirable for this reaction, since they deactivate the benzylic position.

Substrates with two benzylic positions, and therefore two possible positions for oxidation were synthesised by Lorna Mitchell the known Williamson Ether synthesis.[55] Lorna also performed the subsequent oxidation reaction (**Table 16, Entries 20 and 21**). Despite the low yields of the products, it was notable that the oxidation only occurred on the most electron rich benzylic position. No other products were reported. Unfortunately, ethers (**Table 16, Entries 23 and 24**), which were also synthesised by Lorna Mitchell, did not react under the oxidation conditions.

Having successfully explored the oxidation of cyclic and acyclic ethers in a single step, it was envisaged that this methodology could also be applied to both cyclic and acyclic tertiary amine

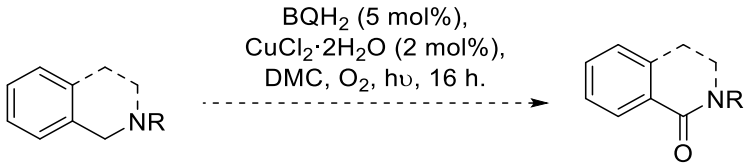
substrates.

4.3.2 Amine Oxidation

One of the most important and most common bonds in organic chemistry is the amide bond since it is found throughout Nature and allows the amino acid building blocks that are fundamental to life - to bond to each other to create proteins. They are also found throughout chemistry in agrochemicals, polymers, biologically active chemicals and pharmaceuticals. In fact, they are found in 25% of all commercially available drug molecules.[66]

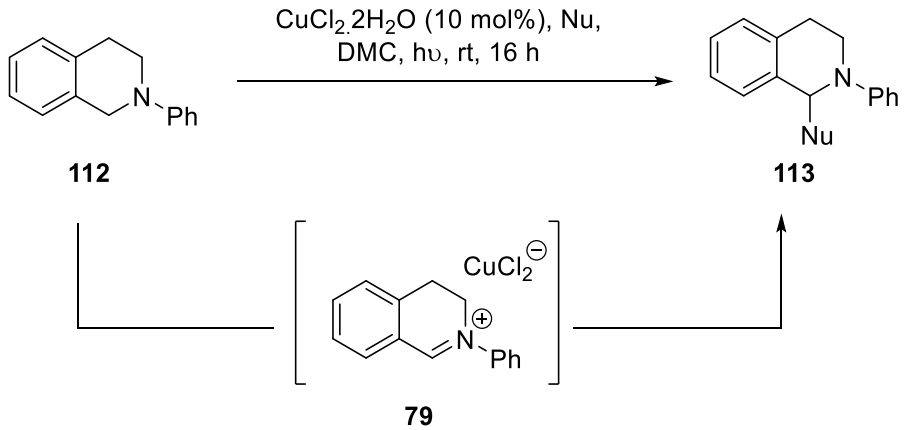
This prevalence of amide bonds, and the fact that amide forming reactions make up quite a significant proportion (16%) of all reactions performed in the pharmaceutical industry,[67] often means that they are mistakenly regarded as non-problematic with regards to their synthesis - that they do not present any challenges.[68] However, the sustainable and effective formation of amide groups is actually a common problem in organic synthesis. They are usually formed by the coupling of a carboxylic acid and an amine, but this requires the activation of the carboxylic acid, to make the hydroxy group a better leaving group, prior to reacting with the amine portion. This activation is usually achieved through the conversion of the carboxylic acids into the corresponding acid chlorides, (mixed) anhydrides, carbonic anhydrides or active esters. This consequently adds additional steps to the synthesis of an amide bond or requires the use of a coupling reagent. However, the choice of coupling reagent can depend heavily on the nature of the coupling partners - many small amides can require both expensive and large coupling reagents, which have large negative implications on the sustainability of the reactions. These reagents are not incorporated into the final product, and so have consequences on the atom economy and E-factor.

All of this means that the oxidation methodology described in this report was particularly attractive for the synthesis of amide bonds, since it had the potential to create amides *via* the simple and direct α-oxidation of an amine. An expensive or large coupling partner is not necessary, the atom economy of the oxidation of isochroman had been shown to be high (89%) and the E-factor is similar to that seen in the pharmaceutical industry (25-100). Hence, it was decided to investigate whether this methodology could be applied to the formation of amide bonds (**Scheme 42**).



Scheme 42 Envisaged amine oxidation under the optimised conditions using visible light irradiated BQH_2 **67**.

Amine substrates were approached with caution since Klussman had already reported that copper salts alone could facilitate the oxidation of *N*-phenyl-1,2,3,4-tetrahydroisoquinoline **112** to the corresponding isoquinoline and this was confirmed in control reactions performed under our conditions (**Scheme 43**).[56,69–74]



Scheme 43 Reaction of 1,2,3,4-tetrahydroquinonline **112** as reported by Klussman, in the absence of quinone.[70]

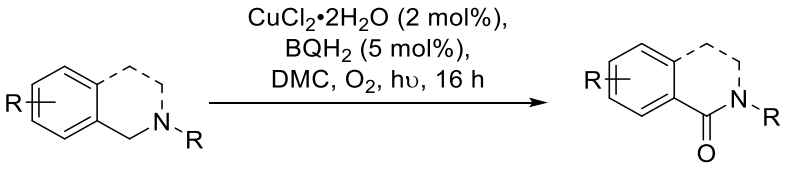
It was noted that such reports focussed entirely on *N*-phenyl-1,2,3,4-tetrahydroisoquinoline **112** alone, and seem to be limited to this substrate. It was plausible that N-phenyl-1,2,3,4-tetrahydroisoquinoline **112** was unique in its reactivity in the presence of copper since the α-position to the amine group was particularly activated by the presence of both a phenyl and a benzyl group. Therefore, it was postulated that simple derivatives of this substrate may differ in their reactivity and variations on this substrate were investigated for this report. However, in order to selectively direct the oxidation to the α-position of these secondary amines, protection of the NH functionality was first required. *N*-Acetyl-1,2,3,4-tetrahydroisoquinoline was selected as a suitable substrate to test this hypothesis, since an acetyl group is substantially more electron withdrawing than the phenyl protecting group used by Klussman and would make the benzyl position less susceptible to oxidation by copper alone. Therefore, *N*-Acetyl-1,2,3,4-tetrahydroisoquinoline was synthesised by the acetylation of 1,2,3,4-tetrahydroisoquinoline as described in the literature.[75]

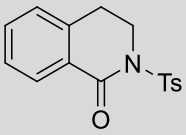
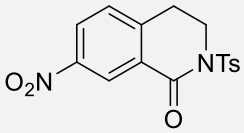
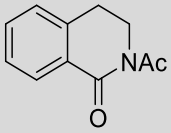
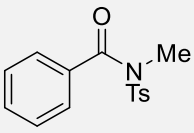
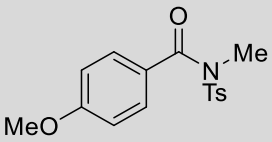
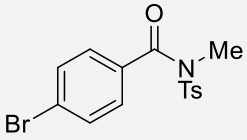
Disappointingly, when this substrate was subjected to the optimised oxidation conditions no reaction was observed (**Table 17, Entry 3**), but this did confirm the theory that the protecting group has a great influence on the success of the reaction. Therefore, both *N*-tosyl-1,2,3,4-tetrahydroisoquinoline and its 7-nitro derivative were synthesised by tosylation of 1,2,3,4-tetrahydroisoquinoline and 7-nitro-1,2,3,4-tetrahydroisoquinolines.[76,77] Pleasingly, both of these substrates (**Table 17, Entries 1 and 2**) were oxidised smoothly to the corresponding isoquinolones **114** and **115** in 51 and 63% yield respectively (**Table 17**).

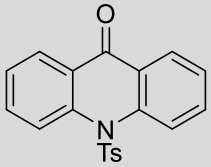
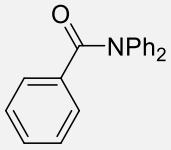
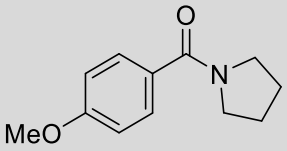
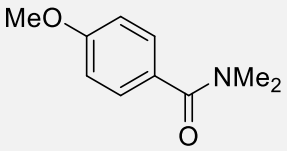
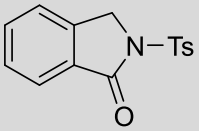
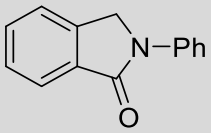
To further establish the scope of the methodology, tosyl and phenyl protected isoindolines, as well as 10-tosyl-9,10-dihydroacridine were synthesised by literature procedures.[78,79] Non-cyclic *N*-tosylbenzylamines were accessed *via* tosylation of the corresponding benzylamine.[80] Substrates for **Entries 7, 8,** and **9** were synthesised *via* nucleophilic substitution reactions

between the benzyl chloride and corresponding amine by the use of an appropriate base (see Experimental, Section 7.).

The oxidation of both protected isoindoline derivatives and non-cyclic *N*-tosylbenzylamines however were less successful (**Table 17, Entries 4,5,6 and 11,12**) with the amides either being formed in poor yield or not at all. It seemed reasonable to assume that a subtle electronic change in the substrate when acyclic leads to a drop in the yield for the oxidation reaction.



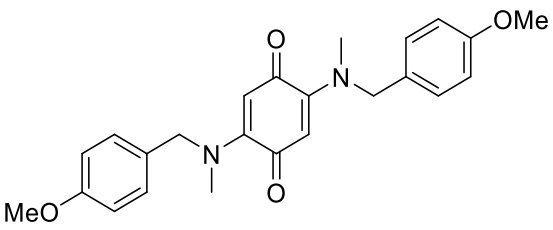
Entry	Compound No	Product	Yield/%
1	**114**		51[a](54[b])
2	**115**		63
3	**116**		0
4	**117**		9
5	**118**		16
6	**119**		0

7	**120**		0
8	**121**		0
9	**122**		0
10	**123**		35 (30%[C])
11	**124**		0
12	**125**		0

Notes: [a]BQH_2 (5 mol%), $CuCl_2$•$2H_2O$ (4 mol%), DMC, O_2, hυ, rt 16 h; [b]In the presence of BQH_2 derived from arbutin; [c]BQH_2-amine adduct **124** isolated when this reaction was attempted with stoichiometric quantities of BQH_2.

Table 17 Attempts towards the oxidation of cyclic and acyclic amine substrates to give the corresponding amide products in a single step.

It is important to note that the 4-methoxybenzylamine oxidation (**Table 17, Entry** 5) was also attempted in the presence of stoichiometric quantities of BQH_2 **67**, in attempts to optimise the reaction with respect to these substrates, and interestingly the formation of a BQ-amine adduct **126** was observed in 30% yield (**Figure 4**). Unfortunately, this could not be repeated with the other amines and no other adducts were formed, therefore this reaction was not pursued any further.



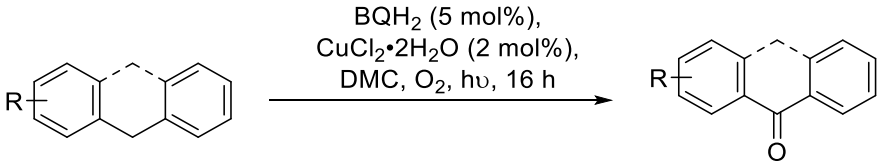
126

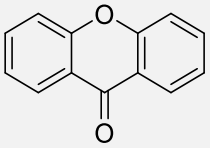
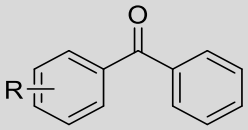
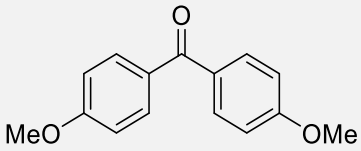
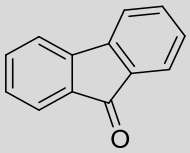
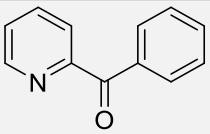
Figure 4 BQH_2-amine adduct **126** formed in the presence of stoichiometric BQH_2 **67** and 4-methoxybenzylamine.

Disappointingly, many of the amine substrates failed to participate in any reaction at all (**Table 17, Entries 6-10**) and only starting materials were observed by ^{1}H NMR spectroscopic analysis of the reaction mixture after 16 h. Hence, since the amines were less successful than the ether derivatives, a new class of substrates was investigated which we believed would be activated enough in the benzylic position for the reaction to proceed.

4.3.3 Hydrocarbon Oxidation

Until now all oxidations had been performed adjacent to a heteroatom, therefore it was thought that an additional aromatic group, rather than a heteroatom, may activate the benzylic position sufficiently for the oxidation reaction. Therefore, the class of substrates explored next were the diarylmethanes which may be oxidised to the corresponding diarylketones. Xanthane, diphenyl methane, fluorene and 2-benzylpyridine were all commercially available compounds. Whereas, diphenylmethanes and were synthesised by the reduction of the benzhydrol as described in the literature.[81] All substrates were then subjected to the optimised oxidation conditions (**Table 18**).



Entry	Compound No	Product	R	Yield/%
1	127			93[a] (87[b])
2	17		H	38
3	128		4-MeO	35
4	129		3-CF_3	Trace
5	130		4-Cl	Trace
6	131		2-Me	NR
7	132		4-Me	Trace
8	133			16
9	71			19
10	134			0

Notes: [a]BQH_2 (5 mol%), ETM (4 mol%), DMC, O_2, hυ, rt 16 h; [b]In the presence of BQH_2 derived from arbutin.

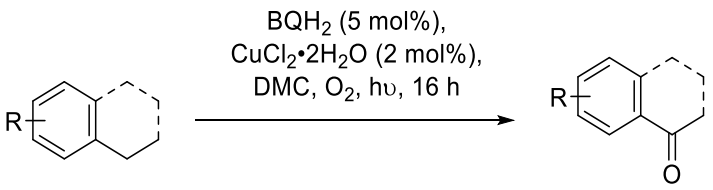
Table 18 Oxidation of diphenylmethane substrates and mono-phenyl substrates to the corresponding carbonyl compounds.

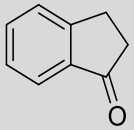
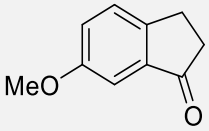
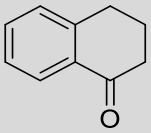
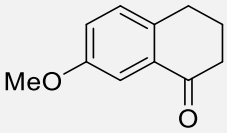
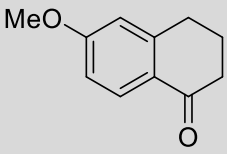
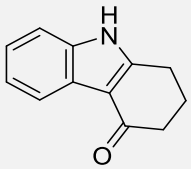
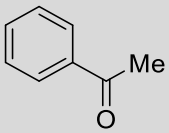
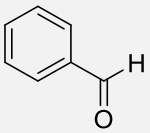
9H-Xanthene (**Table 18, Entry 1**) was successfully oxidised to 9H-xanthen-9-one **127** in excellent yield in both the presence of commercial BQH_2 **67** as well as arbutin-derived BQH_2. Diphenylmethane (**Table 18, Entry 2**) and 4-methoxydiphenylmethane (**Table 18, Entry 3**) gave

the corresponding ketones **17** and **128** in moderate yield, suggesting that an electron donating group was desirable to activate the benzylic position. However, disappointingly electron withdrawing groups (**Table 18, Entries 4 and 5**) were detrimental to the reaction and no product was isolated. The reaction appeared to be sensitive to the presence of methyl groups however, and unfortunately only traces of product were observed in the crude 1H-NMR spectra. Fluorene and 4,4-dimethoxydiphenylmethane (**Table 18, Entries 8 and 9**) were oxidised in low yield – presumably due to the sensitivity of the reaction to changes in the electronics of the substrates.

4.3.4 Less Activated Benzylic Species Oxidation

It had been established that sufficiently activated benzylic positions could be oxidised under the optimised conditions. However, less activated benzylic species had not yet been explored. All the selected substrates for oxidation were commercially available (**Table 19**).



Entry	Compound No	Product	Yield[a]/%
1	**135**		16[a]
2	**136**		7
3	**32**		30
4	**137**		4
5	**138**		44
6	**139**		0
7	**15**		8
8	**16**		4

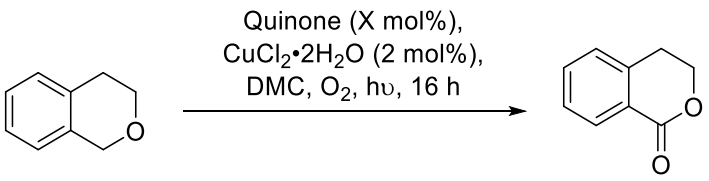
Notes: [a]NMR yields were calculated using 1,1,2,2-tetrachloroethane as an internal standard.

Table 19 Table of less-activated benzylic hydrocarbon substrates attempted.

Indan was oxidised to the ketone product (**Table 19, Entry 1**) in poor yield, as well as those reactions performed with ethyl benzene (8%, **Table 19, Entry 7**) and toluene (4%, **Table 19, Entry 8**). Interestingly, when indan was substituted with a methoxy group (**Table 19, Entry 2**), a notable reduction in the yield was observed, which suggests that these reactions are quite sensitive to the effects of substituents on the aromatic ring. Tetralin was oxidised in 30% yield (**Table 19, Entry** 3) and 6-methoxytetralin was oxidised to both 7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**Table 19, Entry 4**) and 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**Table 19, Entry 5**) in 4% and 44% yield respectively; presumably due to the fact that the methoxy group is *para* directing and so 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one **138** is preferred.

4.3.5 Mechanistic Studies

These results further confirmed that the reaction required substrates that had sufficient activation at the benzylic position through the presence of a heteroatom with an available lone pair of electrons or a second aromatic ring. Such reaction requirements led to mechanistic investigations, to establish why the reaction needs such specific substrates and establish whether it indeed proceeded *via* the proposed radical mediated mechanism. The role of the copper catalyst needed to be confirmed, since it had been suggested that it is only present to turn over the BQH_2 **67** to the photo-active form BQ **2**, and therefore additional control experiments were carried out (**Table 20**).



76 **81**

Entry	Quinone	mol%	$CuCl_2•2H_2O$/mol%	Conversion to product[a]/%
1	BQH_2	5	2	89
2	BQ	5	2	83
3	BQ	5	-	3
4	BQ	10	-	10

Note: [a]Conversation calculated by comparison of starting material and product peaks in the ^{1}H NMR spectrum.

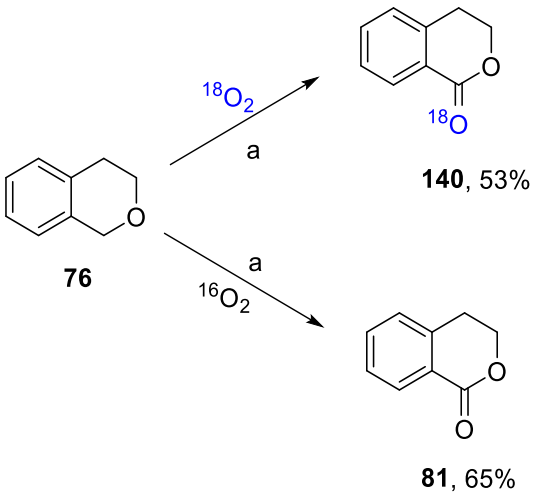
Table 20 Table which demonstrates the role of the copper catalyst as the ETM to turn over the hydroquinone.

The reaction conversion was calculated by ^{1}H-NMR spectroscopic analysis of ratio between the starting material and desired product, which was found to be high (89%) under the optimised reaction conditions (**Table 20, Entry 1**). As expected, when BQ **2** was used directly instead of BQH_2 **67** the reaction conversion was similar. This is because BQH_2 **67** is continuously turned over to BQ **2**, and so it does not matter which starting material is used, although BQH_2 **2** is preferable as it is less toxic. The previously described control reactions had already established that the reaction did not proceed well in the absence of BQH_2 **67** or the copper ETM since this prevented the BQH_2 **67** from being turned over to the photo-active BQ **2** - the copper could not perform the oxidation reaction alone.

Further evidence for the role of copper was obtained when BQ **2** was used in the reaction in only 5 mol% and in the absence of copper. It was predicted that the conversion could not be

higher than 5%, since only 5 mol% of the active BQ **2** was present and would then be rendered inactive when it is reduced as part of a redox reaction since it can only proceed through one reaction cycle. In fact, only 3% conversion to product was observed (**Table 20, Entry 3**) and indeed, when 10 mol% of BQ **2** was used in the absence of copper, only 10% conversion to product was observed (**Table 20, Entry 4**). The maximum conversion of starting material to product that can be observed is the same as the quantity (in mol%) of BQ **2** in the reaction at the start. This combined with the results from the control reactions provided further evidence that the copper is merely present to turn over the BQH_2 **67** catalyst and does not perform any additional role during the reaction.

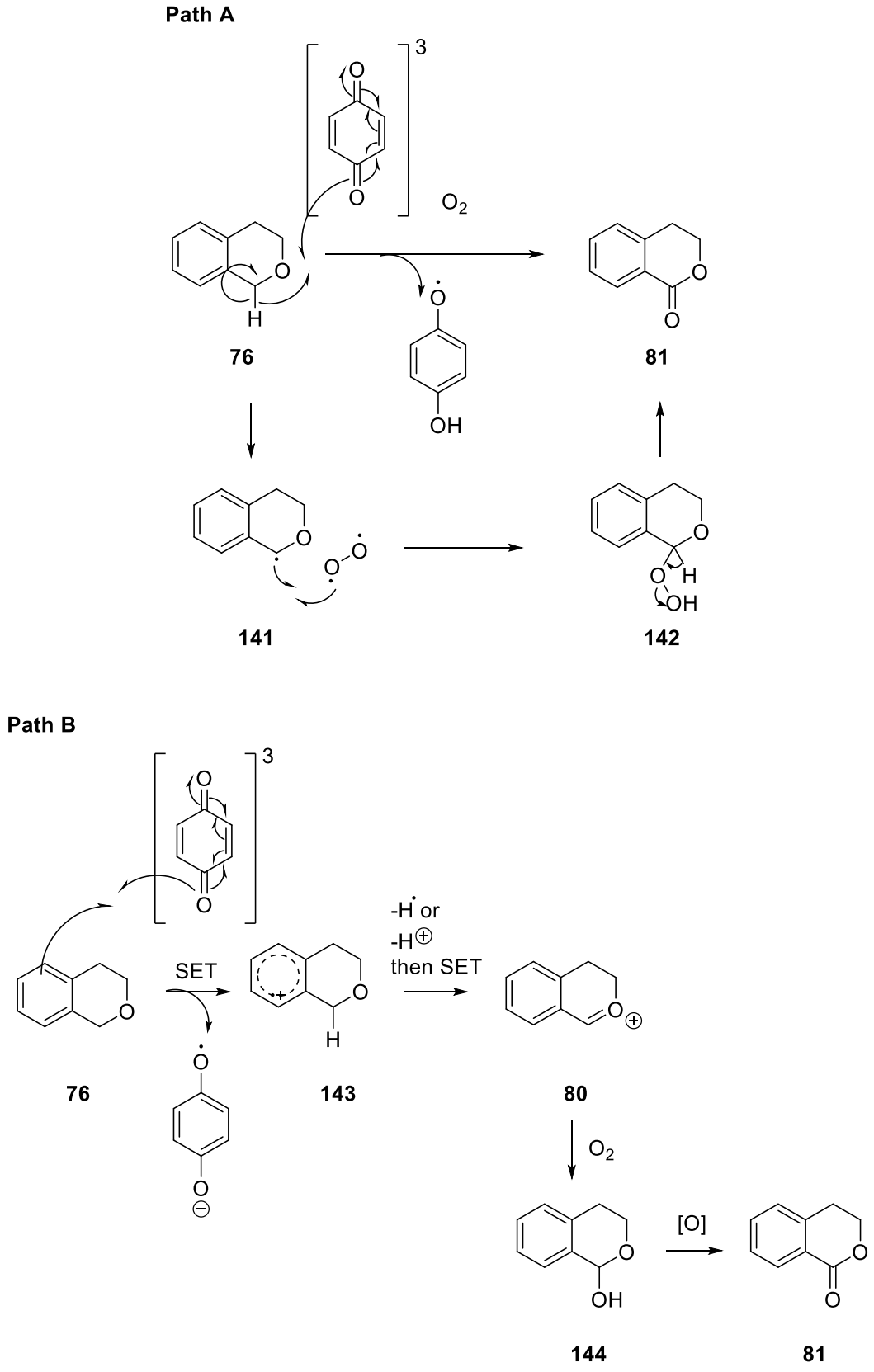
With sustainability in mind, none of the reactions were performed under completely dry conditions since this requires stringent reaction conditions and is far less convenient to the chemist in terms of time and energy use. Hence, it was also required to provide evidence for the source of the oxygen in the reaction - to prove that this was indeed from oxygen provided to the reaction *via* an oxygen atmosphere and was not obtained from residual water in the reactions. In order to achieve this, Lorna Mitchell conducted the oxidation of isochroman **76** using dried reagents under an atmosphere of $^{18}O_2$ (**Scheme 44**).



Conditions: a) BQH_2 (5 mol%), $CuCl_2$ (2 mol%, dried at 100 °C for 5 days under vacuum prior to use), DMC (dried over powdered 4 A° molecular sieves and then fractionally distilled), *hv*.

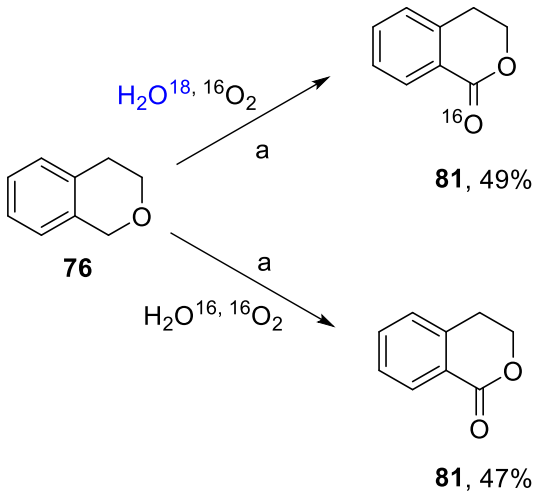
Scheme 44 Oxygen-18 label experiments conducted by Lorna Mitchell.[55]

Incorporation of the $^{18}O_2$ (98.1%) was observed and unambiguously determined by a characteristic peak in the IR spectroscopic analysis which showed shift in the carbonyl peak from 1714 cm^{-1} in the ^{16}O labelled product to 1691 cm^{-1} in the ^{18}O product. HRMS also confirmed the incorporation of $^{18}O_2$ with the presence of a mass ion at 149.0609 (100%) for the ^{16}O isochromanone **81**, and 151.0653 (100%) for the corresponding ^{18}O product. This suggested that oxygen acts as the coupling partner for the reaction, rather than water. It was plausible that the oxygen may react with the benzylic radical **141** formed by hydrogen abstraction from the benzylic position by the photochemically excited BQ **2**. The hydroperoxide intermediate **142** could then undergo another hydrogen abstraction and elimination of the hydroxyl radical to give the oxidised product **81** (**Path A, Scheme 45**).



Scheme 45 Two proposed mechanistic pathways for the photo-activated oxidation reaction.

Despite the fact that this reaction is performed under completely anhydrous conditions, small quantities of water are produced as part of the copper catalyst cycle, and so at this stage it could not be proven without a doubt that the oxygen isotope is not, in part, incorporated into this water which then may react with the reactive isochroman intermediate **80**. It was possible that water reacted with such species to form a lactol intermediate **144** which could then be oxidised to the lactone **81**. Regardless of this, the control reactions had already shown that oxygen was required for the reaction to occur but in order to collate further evidence for mechanistic pathway A, the reaction was performed under dry conditions in the presence of single drop of H_2O^{18}, alongside a control reaction in the presence of a single drop of H_2O^{16} (**Scheme 46**).

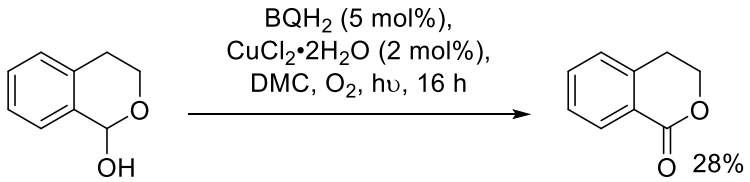


Conditions: a) BQH_2 (5 mol%), $CuCl_2$ (2 mol%, dried at 100 °C for 5 days prior to use), DMC (distilled), O_2, H_2O, hv, 16 h.

Scheme 46 Oxidation of isochroman performed in the presence of H_2O^{18}.

In the presence of H_2O^{18} and $^{16}O_2$, no incorporation of ^{18}O was observed in the final product. As previously described, the HRMS for both the ^{18}O labelled **140** and unlabelled **81** products are obvious and characteristic, and no such peak was observed at 151.06 Da was observed for the labelled product **140**. This led to increased confidence that oxygen is indeed the coupling partner for this reaction and that mechanistic Path A is the most probable route for the reaction. In both the labelled and control reactions a yield reduction was observed which suggested that the presence of water had a negative impact on the reaction.

Additionally, if the reaction proceeded *via* the proposed Path B, then lactol **144** would be oxidised under the optimised reaction conditions into the lactone **81**. Hence, lactol **144** was synthesised by the reduction of isochromanone **81** with DIBAL-H (see Experimental, Section 7.3.6). This was then subjected to the optimised oxidation reaction conditions with BQH_2 **67**, to investigate whether this reaction was possible in comparable yield (**Scheme 47**).



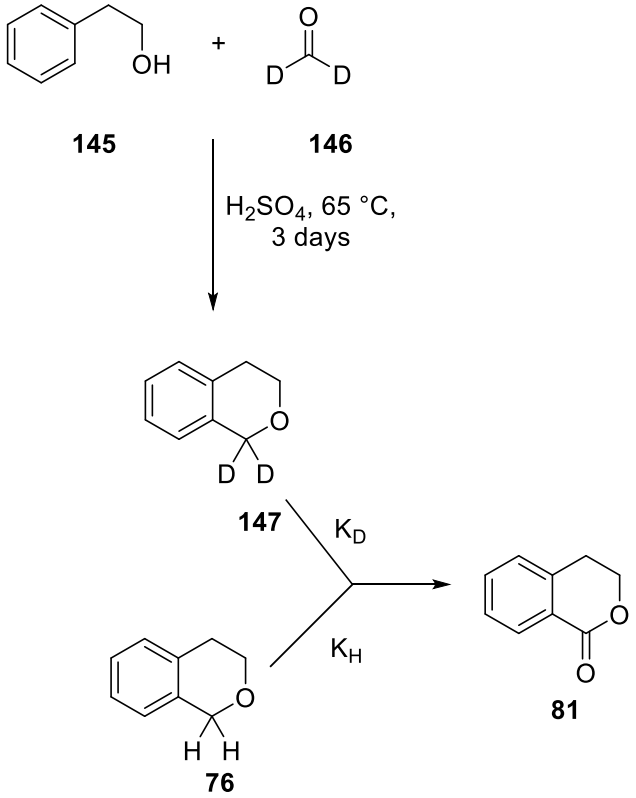
144 **81**

Scheme 47 The oxidation of lactol **144** into lactone **81** by the optimised conditions.

Lactone **81** was only obtained in 28% yield after 16 h which suggested that the reaction probably does not proceed *via* Path B. If Path B was likely then it would be expected that lactone **81** would be isolated in approximately 70% yield, since this is what was observed in the oxidation of isochroman **81**. It was evident that the production and oxidation of lactol **144** was unlikely.

Since it was hypothesised that the reaction proceeded *via* a radical mechanism, Lorna Mitchell attempted to quench the radical intermediate with a radical scavenger (butylated hydroxytoluene, BHT). No oxidation reaction was observed and so supported the proposition of a radical pathway. It was suggested that this could be evidenced further by trapping of the radical using TEMPO or an electron deficient alkene such as benzyl 3-butenyl ether. Unfortunately, all attempts to do this failed.

To further prove that the reaction proceeded *via* a radical mechanism, Lorna Mitchell synthesised deuterated isochroman **147** by the reaction of phenethyl alcohol **145** with *d*-formaldehyde **146** in the presence of acid.[53] The deuterium isotope effect for the reaction was then measured (K_H/K_D = 1.4) (**Scheme 48**).[53,55]



Scheme 48 Investigation into the kinetic isotope effect of the oxidation of isochroman **81** as conducted by Lorna Mitchell.

When Lorna Mitchell compared this value to the deuterium isotope effects for similar benzylic C-H oxidation reactions (K_H/K_D = 4-8) it was found to be small.[82–84] Although, values as small as 1-2 have previously been reported and so a hydrogen abstraction mechanism cannot be discounted, despite the fact that it does suggest that the hydrogen abstraction step is not rate determining.[85]

4.4 Project Conclusions

It has been shown that benzylic oxidation reactions can be achieved in the presence of visible light irradiated and catalytic BQH_2 **67**, in the presence of a copper salt as an electron transfer mediator, and an oxygen atmosphere. The reaction can be applied to the oxidation of isochroman **76** in good yield. This substrate can even be oxidised using BQH_2 **67** that is derived from the deglycosylation of the commercially available glucoside, arbutin **83**, which in turn may be extracted from plants grown in both Serbia and the UK. Arbutin **83** can also be used as a pre-oxidant to facilitate the oxidation of isochroman **76**. This adds to the sustainable credentials of the methodology and demonstrates that BQH_2 **67** can truly be sourced biorenewably, providing an alternative and more sustainable route to BQH_2 **67** than the current industrial route.

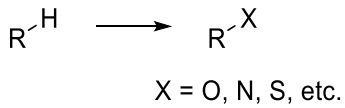
The methodology has been expanded to include both cyclic and acyclic benzylic ether substrates as well as cyclic amines and activated hydrocarbons in moderate to good yield and high atom economy. Arbutin-derived BQH_2 **67** has also been shown to facilitate these reactions in comparable yields in substrates of all these categories.

Unfortunately, the reactions are somewhat limited in substrate scope, since the oxidation is limited to benzylic substrates which are sufficiently activated in the α-position for the reaction to proceed. However, a balance is required as over-activation of the benzylic position leads to oxidation in the presence of copper alone. Subtle changes in the electronic properties of the substrates can lead to diminished yields.

The mechanism of the reaction has been proposed to proceed *via* the trapping of the benzylic radical formed with oxygen, to create a hydroperoxide intermediate which can then collapse to form a carbonyl group. Experimental evidence supports the proposal that oxygen, rather than water, acts as the coupling partner for the reaction.

5. Introduction to Unactivated Alkane Hydroxylation Methodologies

Methods for the functionalisation of unactivated hydrocarbons have long been regarded as the 'Holy Grail' of organic chemistry (**Scheme 49**).



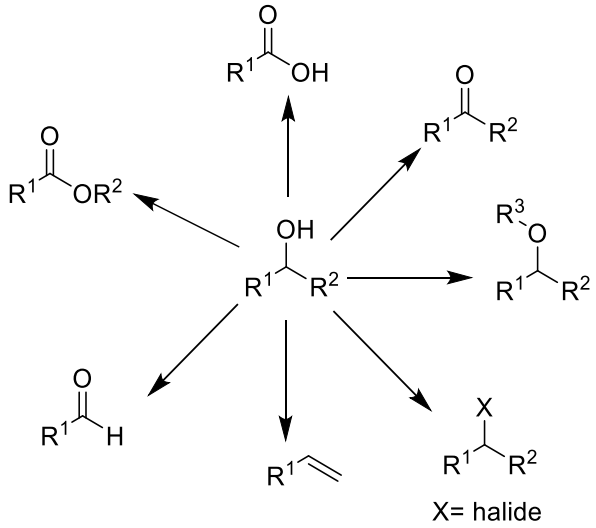
Scheme 49 General scheme for the functionalisation of unactivated C-H bonds.

An appropriate and successful strategy for such chemistry would allow quick access to value added and complex molecules *via* synthesis from unreactive, unfunctionalised starting materials. Such methodologies which are efficient and selective have been sought for over 100 years. The main challenge lies in finding a way to efficiently functionalise an unactivated C(sp^3)-H bond in a predictable and selective manner with respect to both site- and stereo-selectivity. This is particularly difficult in complex molecules where there are few/no functional groups to direct a reaction to a specific site, and so ways to overcome this must be an inherent part of any alkane functionalisation chemistry.

A successful strategy of this kind would allow the late-stage functionalisation of complex substrates and quickly install synthetic handles in only one step, thus reducing the need for complicated and resource intensive reaction sequences to access various functional groups. Most current methods require the presence of a directing group - a pre-installed functionality which has an influence on the position of functionalisation *via* steric and/or electronic means.

5.1 Alkane Hydroxylation Strategies

One of the most attractive functional groups to install into such unreactive substrates is the hydroxyl group. The hydroxyl group can be used as a precursor to install a range of more complex structures such as ethers, esters, carboxylic acids etc. Hydroxyl groups alone are also valuable since they are found in many valuable molecules across pharmaceuticals, agrochemicals and polymer chemistry but to name a few (**Scheme 50**).



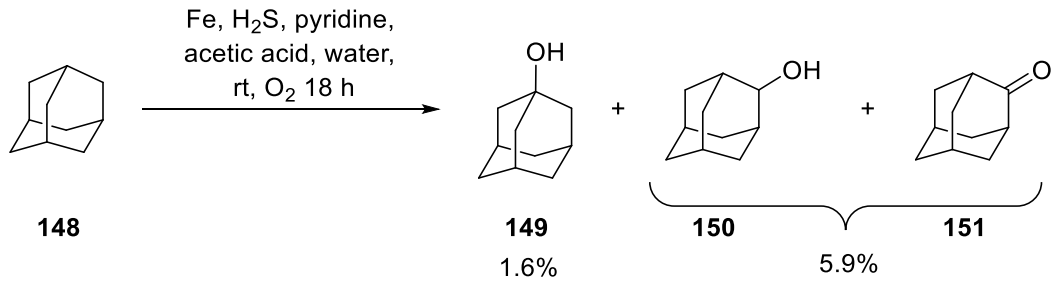
Scheme 50 Transformations possible with a hydroxyl group.

Such challenges are naturally attractive to scientists and so there is already a plethora of research dedicated to solving this complex chemical problem *via* both metal and non-metal means. A selection of these have been discussed in the following sections of this thesis.

5.1.1 Metal-Mediated Approaches

Oxidation chemistry has been conducted in Nature and has contributed to keeping the atmospheric oxygen levels low - *via* its removal from the air to conduct biological chemistry. In the early stages of life, the most abundant metal on earth was iron, and it is known that early prebiotic chemistry utilised iron to facilitate chemical reactions.[86] Chemists have thus been inspired by Nature's ability to conduct such reactions and sought to mimic some of the earliest reactions that are thought to have been fundamental to the creation of life. For example, Gif systems for oxidation using iron were developed.

The systems developed by Barton at Gif-sur-Yvette implement iron and a mimic of the early Earth's atmosphere to conduct the oxidation of unactivated alkanes. Barton was the first to propose a system which could oxidise such species and used elemental iron as a catalyst in the presence of hydrogen sulfide, pyridine and acetic acid under an oxygen atmosphere (also known as Gif^{III}).[87] When Barton applied this to adamantane **148** an unusually high selectivity for secondary C-H bonds was observed with a mixture of adamantan-1-ol **149**, adamantan-2-ol **150** and adamantan-2-one **151** being formed (**Scheme 51**).

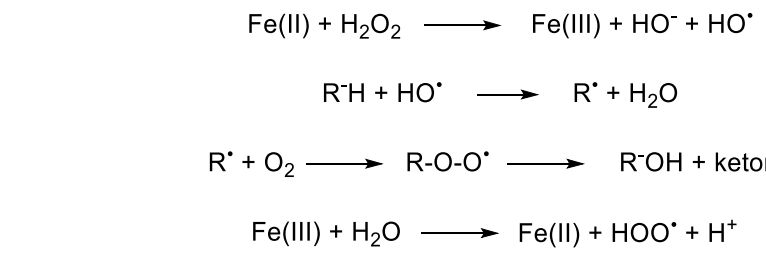


Scheme 51 The first oxidation of adamantane **148** by Gif chemistry.

The yield of this reaction is considerably lower than that desired for preparative chemistry, although, it is a good indicator to how Nature was able to create functionalised molecules with limited resources. Since this work was reported many variations on this system have been developed. Attempts to make the process catalytic in iron have seen success with the use of zinc (Gif^{IV}) and it was later discovered that both the Gif^{III} and Gif^{IV} systems would operate in the absence of hydrogen sulfide if the temperature was raised to 30-40 °C. This led to vastly improved yields of 20-30%.[88] Later variations even included electrochemical regeneration of the iron catalyst, replacing the zinc, which became known as the Gif-Orsay system.[89,90] In fact, there is a large body of research that has been conducted into what is now known as the 'Gif family', since many systems and variations have been invented.[91]

The reaction of iron(II) with hydrogen peroxide is widely known as the Fenton reaction, famously as part of the Haber-Weis process. However, it is well known to be highly toxic generating intermediates that are capable of oxidising a wide range of substrates, causing biological damage.[92] Hence, the Gif and Fenton chemistry is plagued by issues including low yields, the high toxicity of the systems.

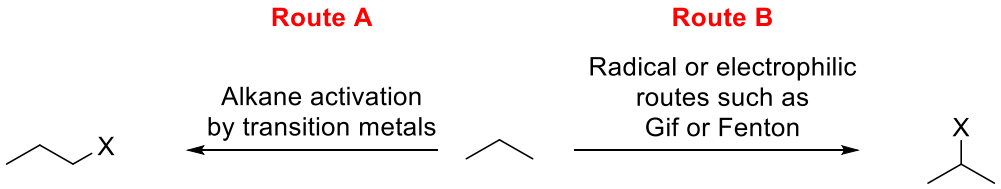
Disagreements with regards to the mechanism of Gif chemistry has now become popularly known as 'The Gif Paradox'.[91] However, it is most widely believed that reactions of the Gif or Fenton type typically operate by the formation of a hydroxyl radical which can then abstract a hydrogen atom from an alkane, RH, to give the alkyl radical which is then ready to react with oxygen (**Scheme 52**).



Scheme 52 Typical general mechanism of Gif and Fenton type systems.

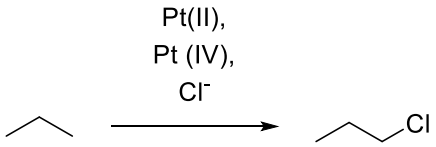
The primitive nature of prebiotic chemistry means that, although it can reveal a huge deal regarding the formation of the Earth and atmosphere we know today, challenges remain in terms of the development of catalysts capable of the oxidation of complex systems. Furthermore, those which can do this in an enantioselective manner would be invaluable.[93]

In contrast to Gif and Fenton systems that operate under radical mechanisms (Route B), low valent transition metals are regarded as undergoing C-H activation processes (**Scheme 53**). This means that they are thought to perform oxidation reactions *via* insertion into an alkane C-H bond (Route A), giving differing selectivity, and have been shown to have significance in the area of alkane oxidation (**Scheme 53**).[94]



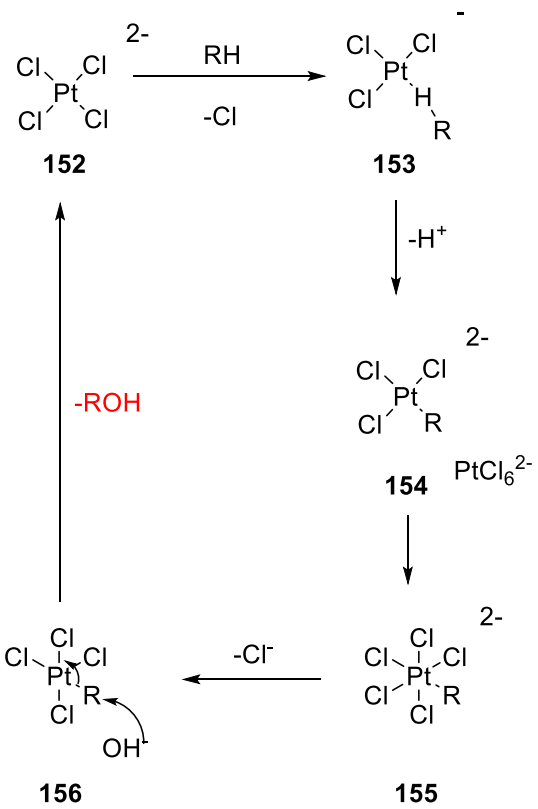
Scheme 53 Difference between radical and C-H activation processes.

One important example of such C-H activation processes was reported by Shilov and co-workers in the 1970s.[95] They found that the activation of the terminal position, even in a long chain alkane, was preferred, which is in direct contrast to Gif and Fenton systems. Shilov could access both the hydroxy or chloro-substituted product by way of subtle changes to the catalyst (**Scheme 54**).



Scheme 54 Shilov oxidation of propane.

The mechanistic insights into this observation were elucidated in the 1990s by Bercaw and Labinger.[36] It is believed that an alkane complex must undergo an oxidative addition to platinum followed by loss of a proton, or the alkane complex must lose a proton directly. Oxidation of this Pt(II) alkyl **154** by Pt(IV) gives the Pt(IV) alkyl **155** and now Pt(IV) is a good leaving group. This means that a hydroxyl ion can attack the species **156** with departure of Pt(II) and the catalyst is regenerated with the production of ROH (**Scheme 55**).

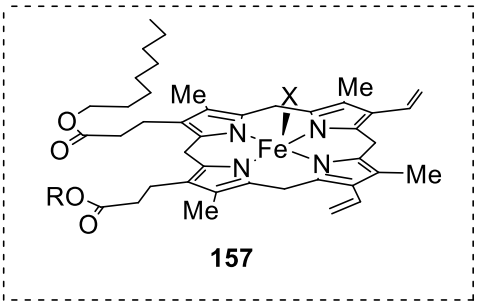


Scheme 55 Mechanism of CH activation performed by the Shilov process as proposed by Bercaw and Labinger.

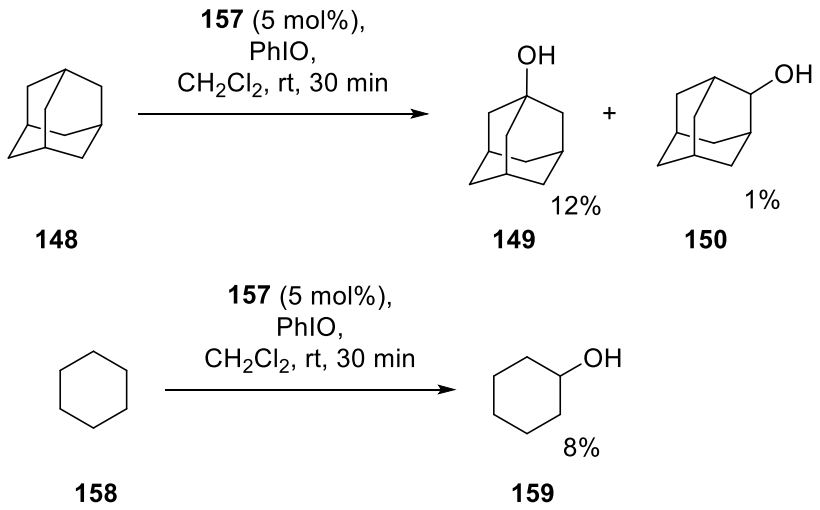
5.1.1.1 Biomimetic Metal-Mediated Hydroxylations

Chemists have again taken further inspiration from Nature's ability to use iron in living systems. It is well known that iron is found in many enzymes and biological systems capable of oxidation and thus many groups, while Gif chemistry was being developed, were also researching iron-haem based P450 enzymes and the non-haem metalloenzymes.

Research groups have sought to mimic nature using iron metal surrounded by non-haem type metal-ligands. Early examples sought to create relatively simple ligands for iron, based on porphyrin-type structures. In 1979, Groves and co-workers showed that alkenes could be epoxidised using iron catalyst **157**. However, this report focussed on the hydroxylation of adamantane **148** and cyclohexane **158** to adamantanols **149, 150** and cyclohexanol **159** respectively (**Scheme 56**).[96]



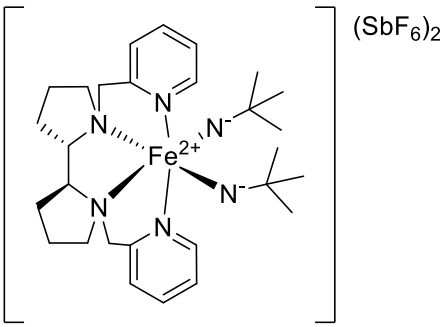
157



Scheme 56 Iron-porphyrin catalysed oxidation of cyclohexane and adamantane.

The yields of the products in both cases are very low, which the authors attributed to destruction of the catalyst. Such non-haem oxidation chemistry has been hypothesised to proceed *via* a Fenton-type mechanism upon catalyst degradation, leading to less selectivity and mixtures of products. Therefore, strategies to create more stable ligand structures have been investigated by the chemistry community.[97]

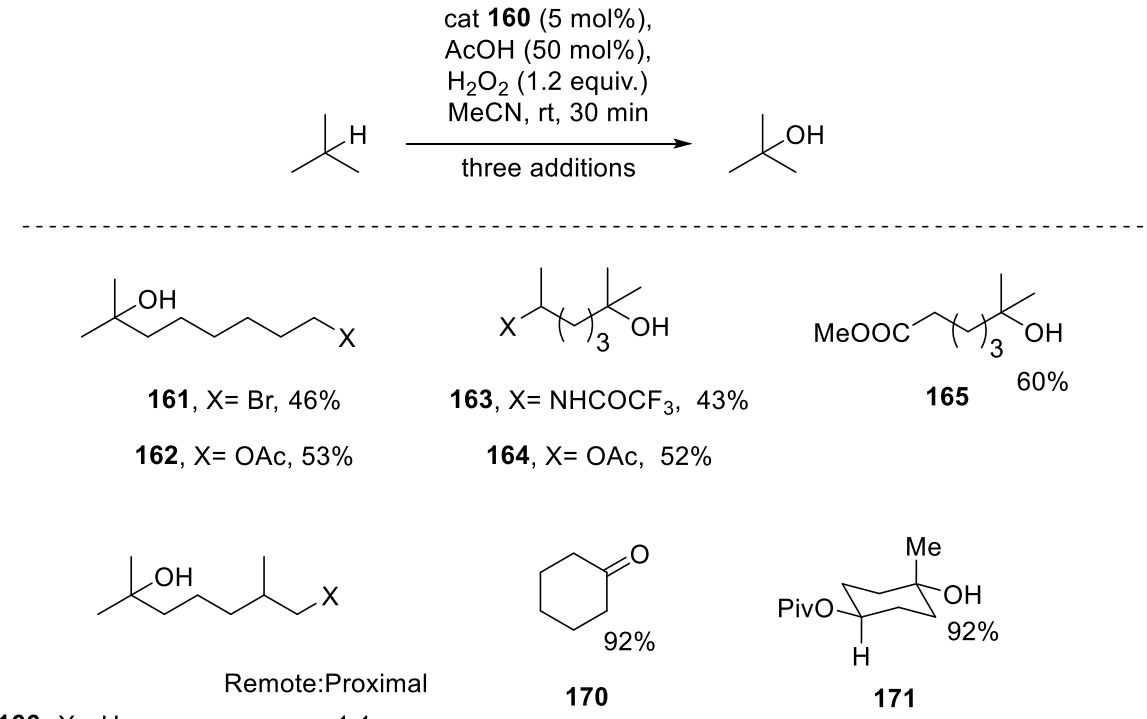
In a major advance, White and co-workers reported the oxidation of hydrocarbon substrates using what is now known as the Chen-White catalyst or Fe(PDP) **160** (**Figure 5**).[97]



160

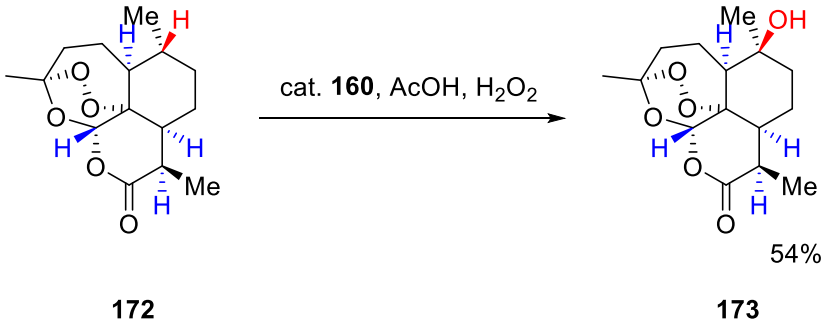
Figure 5 The Chen-White catalyst.

It was noted that when a tertiary bond was present in an alkyl substrate, this was oxidised preferentially over the secondary carbons, despite many more of these being present and statistically favoured. Moreover, when two tertiary positions were available, the oxidation occured at the tertiary C-H bond which is the furthest from the electron withdrawing group with high levels of selectivity, i.e. in the remote position rather than the proximal position. Where no such electron withdrawing group is present a 1:1 mixture of both oxidation isomers **166** was seen. Cyclohexane **158** underwent oxidation to cyclohexanone **170** in good yield, but most interestingly, when cis-4-methylcyclohexyl pivalate **171** was subjected to the conditions, stereo-retention of both the methyl and hydroxy was observed (**Scheme 57**).



Scheme 57 Oxidation of substrates using the Chen-White catalyst **160**.

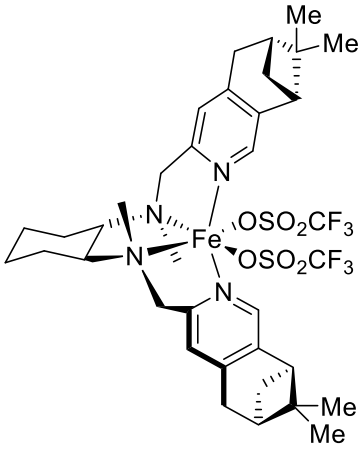
Despite the unarguable success of this work, there remain a few issues; the reaction required three additions of reagents over the course of the reaction and the ligand for the catalyst was bulky and has a high molecular weight. Both of these factors impact the sustainability and efficiency of this reaction and thus improvements could still be made to this excellent C-H oxidation methodology. However, impressively Chen and White managed to apply this methodology to the oxidation of the natural product artemisinin **172**. The reaction proceeded in a predictable nature and selectively oxidised the 6- position tertiary carbon above the four others (**Scheme 58**).



172 **173**

Scheme 58 Oxidation of artemisinin **172** as reported by Chen and White.

This clearly demonstrates the excellent utility that this reaction could have for late stage functionalisation in the future. Further advancements by Costas *et al*., using non-haem catalyst **174** provided site and stereoselectivity (**Figure 6**).[98]



174

Figure 6 Iron catalyst **174** reported by Costas and co-workers.

The low catalyst loading, high product yields and predictable selectivity of this reaction make it attractive as a C(sp^3)-H oxidation strategy, although the scope reported in the paper is limited and questions remain regarding its limitations. Furthermore, the catalyst ligand size and synthesis have a negative contribution to the sustainability of the reaction, and this continues to be a problematic theme in oxidation strategies that employ haem or non-haem iron catalysts.

Beyond the use of iron, there are examples of porphyrin and non-porphyrin oxidations using manganese based on its role as an oxidant in metalloenzymes and photosynthesis, and other non-biomimetic metals such as rhenium and cobalt.[99–101]

Despite the success thus far of metal based non-haem/porphyrin catalysts to conduct efficient and selective oxidations of hydrocarbons, the bulky ligands leave more to be desired around sustainability. Furthermore, the substrates investigated thus far have somewhat lacked numerous and diverse functionality, as well as aromatic substrates. Therefore, there remains scope to investigate and develop these strategies further.

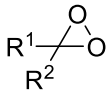
5.1.2 Non-Metal Mediated Alkane Hydroxylation

Although metals have shown potential for the oxidation of unactivated alkanes, many of the metals used are rare, expensive or toxic. Additionally, regardless of their prevalence in Nature, metals are not unlimited in supply and therefore it remains that the scientific community should limit their use and reliance wherever it is possible.

Much research has been conducted into the use of non-metal methodologies for numerous chemical transformations including alkane oxidation, and a review of the most important areas is reported below.

5.1.2.1 Dioxiranes

Dioxiranes are a class of compounds made up of a three membered ring, constructed from a carbon atom and two oxygen atoms that form a strained peroxide. The most popular of the dioxiranes used in synthesis is dimethyldioxirane (DMDO) **175** and (methyl)trifluoromethyldioxirane (TFDO) **176**, primarily due to their ease of access and improved stability compared to many other dioxiranes (**Figure 7**).[102]



DMDO 175, R^1, $R^2 = CH_3$
TFDO 176, $R^1 = CH_3$, $R^2 = CF_3$

Figure 7 Dioxiranes DMDO **175** and TFDO **176**.

The first dioxirane was synthesised by Montgomery and co-workers in 1974, by the reaction of acetone with caroate (potassium peroxymonosulfate). It was first shown to facilitate the oxidation of chloride ions.[103] Dioxiranes were then shown to conduct other oxidation reactions

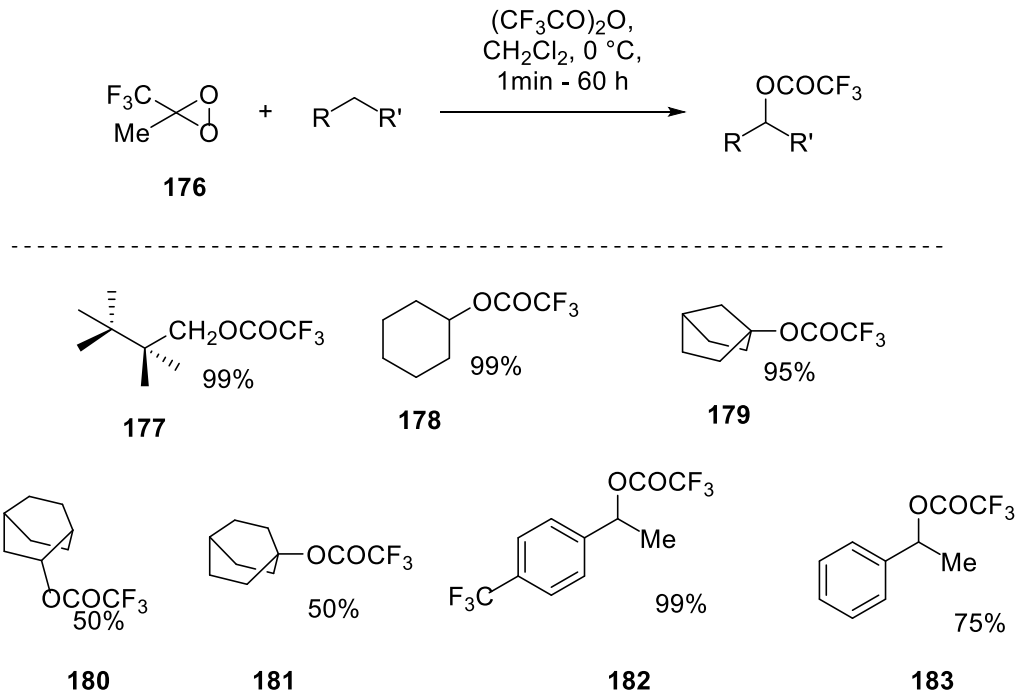
such as alkene epoxidations[104] and Baeyer-Villiger oxidation reactions.[105] Disappointingly, the necessity of using aqueous media, strong acids and the production of stoichiometric sulfate waste means that they were not the most sustainable reagent choice.[106]

Dioxiranes can carry out oxidation of unactivated C(sp^3) atoms via a method of oxygen insertion. One of the first reports of an *O*-insertion of this type using a dioxirane was reported by Murray and co-workers in 1986, when they reported the isolation of DMDO **175** in solution.[107] The dioxirane was distilled at low temperature and then condensed as it formed - as a yellow liquid in acetone, which could be dried over magnesium sulfate and stored in the freezer for future use. This therefore meant that it could be used unencumbered by the presence of acid, base, or the use of high-boiling solvents in the reactions. It also represented the first time that a dioxirane was isolated from the reaction mixture in which it was made and provided the final evidence required to prove the dioxirane existence beyond doubt. Murray displayed that this solution could be used by simple addition to the substrate at room temperature.

Mello *et. al.* later reported the synthesis and application of TFDO **176**.[108] They claimed it was more stable than DMDO **175**, and could react in a shorter amount of time – minutes rather than the hours reported with DMDO **175** previously.[107] They reported that the synthesis of TFDO **176** was straight forward and could be obtained by following the simple procedure previously described by Murray and co-workers[107] for DMDO **175** with buffered (pH 7, $NaHCO_3$) aqueous potassium peroxomonosulfate and 1,1,1-trifluoro-2-propanone, and could be done on scale. The authors also updated this preparation many years later to allow the preparation of the reagent and oxidation of substrates on a preparative scale,[109] using 1,1,1-trifluoroacetone hydrate (a non-volatile and water-soluble alternative). The protocol is simple, avoids the use of specialist equipment and complicated separation steps. TFDO **176** is produced as required and

there is no need for dioxirane storage and handling – thereby vastly improving the safety of any protocol which uses TFDO **176** – and pleasingly the authors claim that it can be performed in any solvent. TFDO **176** reacts successfully with various hydrocarbons although there is little selectivity and over-oxidation often occurs.

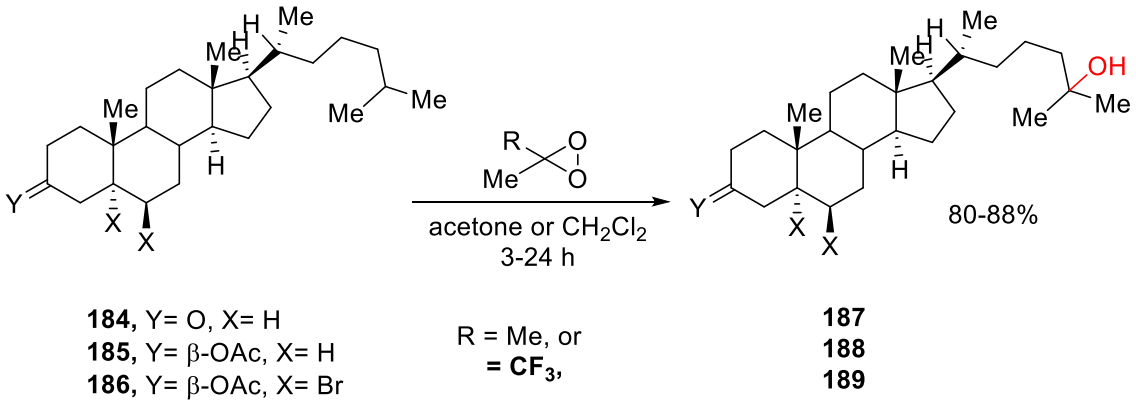
This strategy saw further developments in 1996, when Mello *et. al.* published an approach which overcame some of the over-oxidation issues previously encountered.[110] The authors discovered that acylated hydroxy groups appeared to be protected from the oxidation reaction, presumably due to electronic effects, and thus developed a protocol which combined the oxidation-acylation procedure to circumvent the problems associated with alcohol oxidation. This was applied to substrates which had previously been studied under the original methodology and with similar reaction times (**Scheme 59**).



Scheme 59 Oxidation of various hydrocarbons using TFDO **176** to give the acylated product, thus preventing over-oxidation.[110]

In the cases of cyclohexane **158**, trifluoroacetycyclohexane **178** was isolated in 99% yield, which is almost identical to the yield reported for cyclohexanone **170** in the earlier report (see above). Pleasingly, this protocol allowed the trifluoroacetates of other substrates to be accessed in higher yields than the alcohols previously reported since it was no longer reduced by formation of ketones. *exo*-2-Norborneol **179** was accessed almost exclusively in excellent yield (95%), similar selectivity was observed for **180** and **181**, and the yields of the benzylic substrates **182** and **183** were similar to those seen for the corresponding ketones.

Dioxiranes have also been applied to the late-stage functionalisation of important biologically relevant molecules, and natural products. For example, cholestane was selectively oxidised in the C-25 position utilising DMDO **175** as the oxidant, and vitamin D_3 derivatives **184**, **185**, and **186** were selectively oxidised to access 25-hydroxy-vitamin D_3 derivatives **187**, **188**, and **189**. This latter oxidation had previously been difficult to achieve and allows rapid access to a molecule of biological significance (**Scheme 60**).



Scheme 60 Oxidation of steroidal compounds using dioxiranes.[111]

Despite the obvious success thus far of TFDO **176** and its advantages over DMDO **175**, it remains a volatile and highly reactive dioxirane (bp 22 °C) and therefore its reactions must be conducted at low temperature which is an energy intensive to reach and maintain. This combined with

issues around storage and over-oxidation have seen chemists seek alternative methods to install hydroxy functionalities into unactivated alkanes.

5.1.2.2 Oxaziridines

Alternative yet similar reagents in structure to dioxiranes are the oxaziridines. Both are strained three-membered ring structures, although unlike dioxiranes, an oxaziridine is made from a carbon, oxygen and nitrogen atom (**Figure 8**).

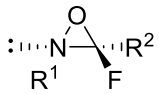
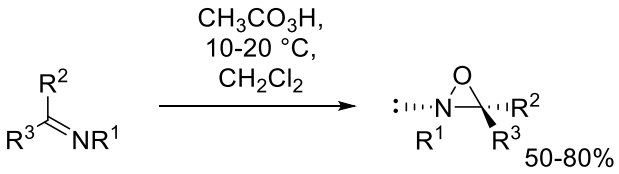


Figure 8 General structure of an oxaziridine.

Oxaziridines have many advantages over dioxiranes since they can be synthesised easily, isolated and then stored almost indefinitely – they do not need to be synthesised every time they are required.[112] The first preparation of an oxaziridines was reported by Emmons in 1957 by the reaction of an imine with peracetic acid (**Scheme 61**).[113]

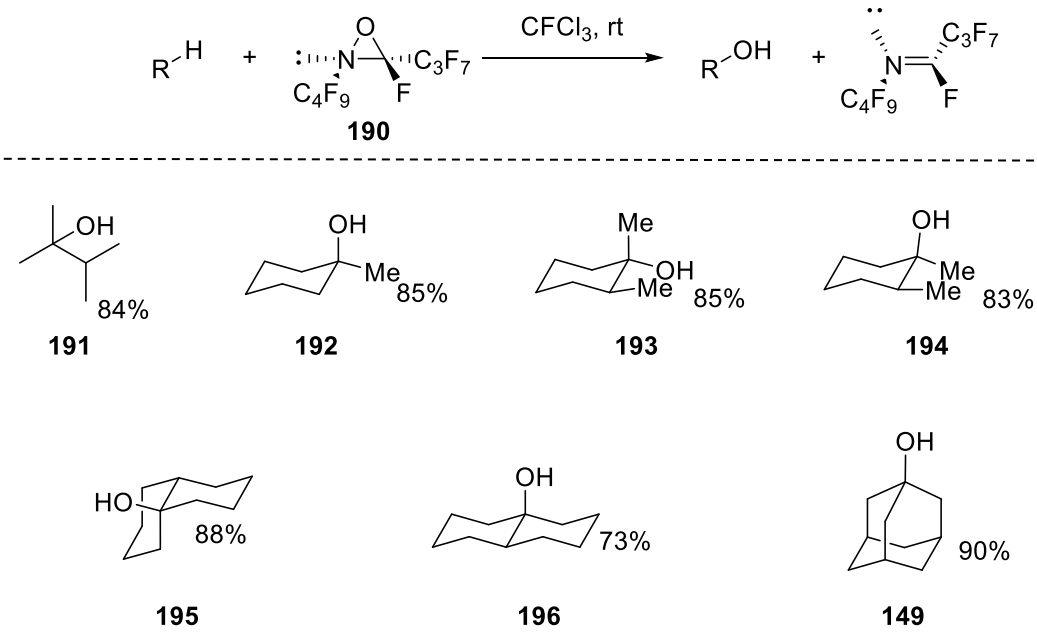


Scheme 61 First reported synthesis of an oxaziridine as reported by Emmons.

Early research into oxaziridines focussed on both the preparation and use of the hydrocarbon substituted oxaziridines, although their chemistry was found to be limited.[114,115] Therefore, as well as alkyl oxaziridines, *N*-sulfonyloxaziridines (the optically active of which are now known as Davis oxaziridines)[116–120] and perfluorinated oxaziridines were developed as reagents with a higher oxidising potential.[116,121] It wasn't until the first perfluorinated derivative was reported in

the 1970s that oxaziridines truly displayed their potential for C-H oxidation reactions. Perfluorinated oxaziridines are much closer to dioxiranes than to hydrocarbon oxaziridines or *N*-sulfonyloxaziridines. To our knowledge, these are the only type of oxaziridines reported to be able to perform such oxidations. However, the most important difference between dioxiranes and oxaziridines lies in the stability of oxaziridines and their ability to be stored indefinitely. There is no need for anhydrous or oxygen free conditions which is in direct contrast to the unstable nature of dioxiranes. It is these properties make them attractive as economical and general oxidants.

In 1993, DesMarteau *et al.* first described their ability to oxidise unactivated hydrocarbons at room temperature (**Scheme 62**).[122]



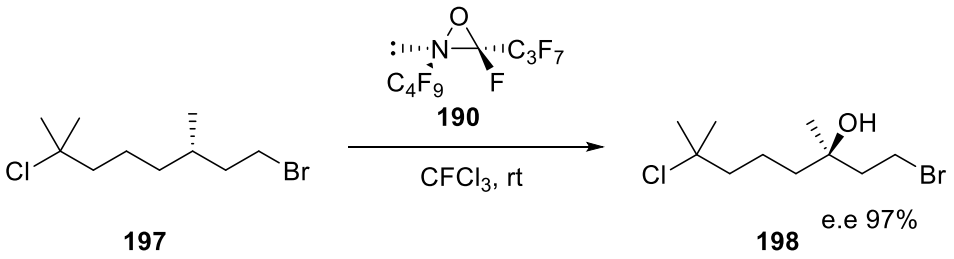
190 **191** **192** **193** **194** **195** **196** **149**

Scheme 62 Oxaziridine-mediated oxidation of unactivated hydrocarbons.

Oxaziridine **190** was able to oxidise 1,1,2,2-dimethylethane to **191**, methyl substituted cyclohexanes to **191, 193, 194** and bicyclic alkanes to **195** and **196** in good to excellent yields. Selectivity for tertiary C-H bonds was found immediately and was displayed in all substrates, similarly to dioxirane chemistry (see Section 5.1.2.1). In all cases the yields were good or

excellent and only minor quantities of the over-oxidation product of the alcohols (the ketone) was observed with some reactions complete in only minutes. Retention of stereochemistry was also observed in the case of decalins**,** as with 1,2-dimethylcyclohexane substrates.

Resnati and co-workers later sought to expand the study of such compounds to demonstrate the highly enantiospecific oxyfunctionalisations of non-activated hydrocarbons by polyfluorinated oxaziridine reagents (**Scheme 63**).[123]



Scheme 63 Enantiospecific hydroxylation of alkanes

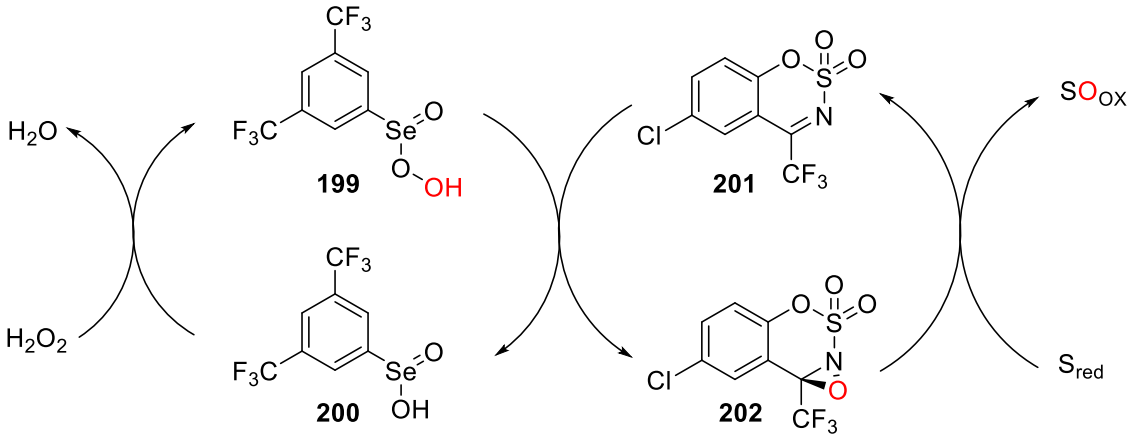
Alkane **195** was oxidised at the tertiary position remote from the electron withdrawing chlorine atom in excellent enantio-excess. The yield of this reaction was not reported.

Unfortunately, the sustainability of both of the oxidation strategies comes into question when the solvent system is considered. The oxaziridines are sparsely soluble in solvents other than those that are chlorinated. $CFCl_3$ is of particularly concern since it is an ozone depleting molecule which has since been banned under the Montreal Protocol.[124] Attempts to change the solvent caused the yield of the reaction to be reduced. Furthermore, the reactions can take hours to go to completion with particular substrates and are in the presence of stoichiometric quantities of oxidant. Hence, a more sustainable alternative was necessary.

Despite a wealth of work having been conducted in oxaziridine chemistry, little had been seen yet which gives promise to making the oxidation catalytic in nature. It was well known that once consumed the oxaziridine is converted back into an imine which is a known starting material

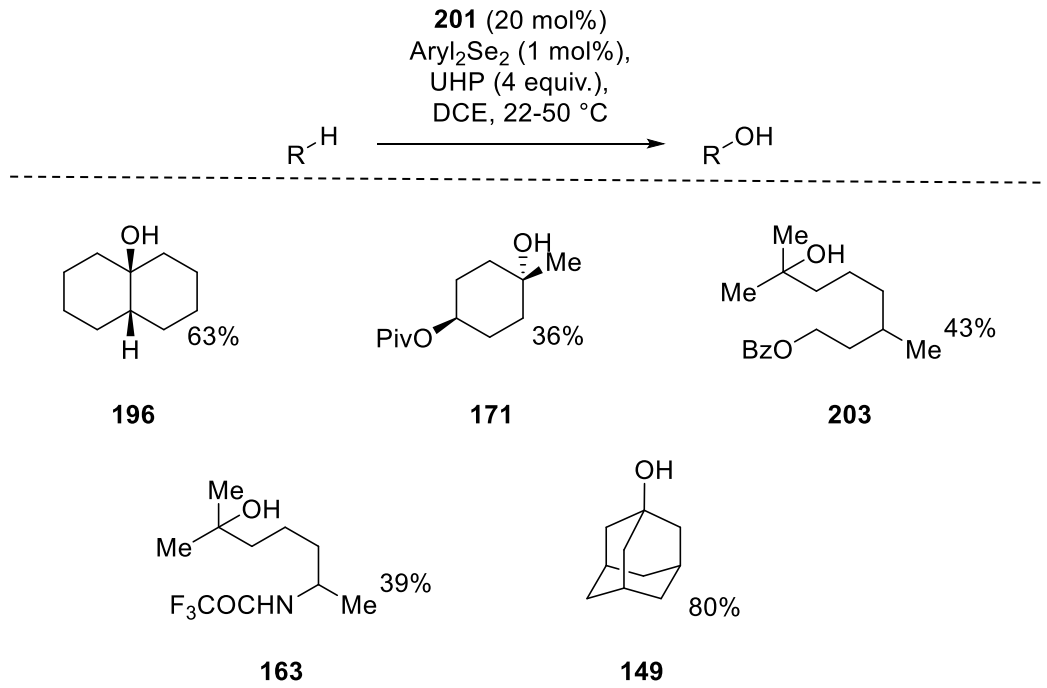
used to access the reactive reagents. Therefore, in principle it was believed that it should be possible to oxidise this imine back to the oxaziridine.

In 2005, Brodsky and DuBois reported the first examples of catalytic hydroxylation of unactivated tertiary C-H bonds using a benzoxathiazine catalyst employing hydrogen peroxide as the terminal oxidant, in the presence of a selenium catalyst. Such a system allows the oxidation of the substrate to occur, alongside the re-oxidation of the benzoxathiazine **201** to the oxaziridine **202** by a perselenic acid **199**, formed from the oxidation of **200** by hydrogen peroxide (**Scheme 64**).



Scheme 64 Catalytic cycle demonstrating how oxaziridine **202** is regenerated *in situ*.

The ability to make oxaziridine chemistry catalytic represents a clear advantage over dioxirane chemistry, for which there does not appear to be a single catalytic example. Pleasingly however, and much the same as reported previously with both dioxiranes (see Section 5.1.2.1) and previously mentioned oxaziridines, the selectivity for tertiary C-H bonds remained the same. This was demonstrated when the developed protocol was applied to various hydrocarbon substrates (**Scheme 65**).

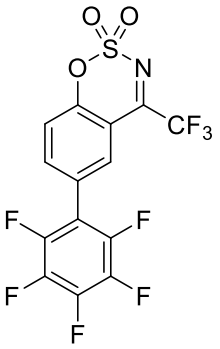


Scheme 65 The first catalytic strategy for the oxidation of hydrocarbons using oxaziridines.[125]

With respect to the unactivated hydrocarbon oxidation examples only, decalin and adamantane **148** were oxidised again in good yield, to **196** and **149** respectively, which was similar to previous reports. Selectivity was clear for the tertiary C-H despite the prevalence of secondary C-H bonds, and in the cases of **203** and **163** these were the single products observed. The only issue with this approach appeared to be that the reaction times were increased.

The catalyst was improved by the replacement of chlorine with a stronger electron withdrawing group. DFT calculations indicated that this position was critical for influencing the activation barrier for oxygenation, and that electron withdrawing groups would lower the energy barrier.

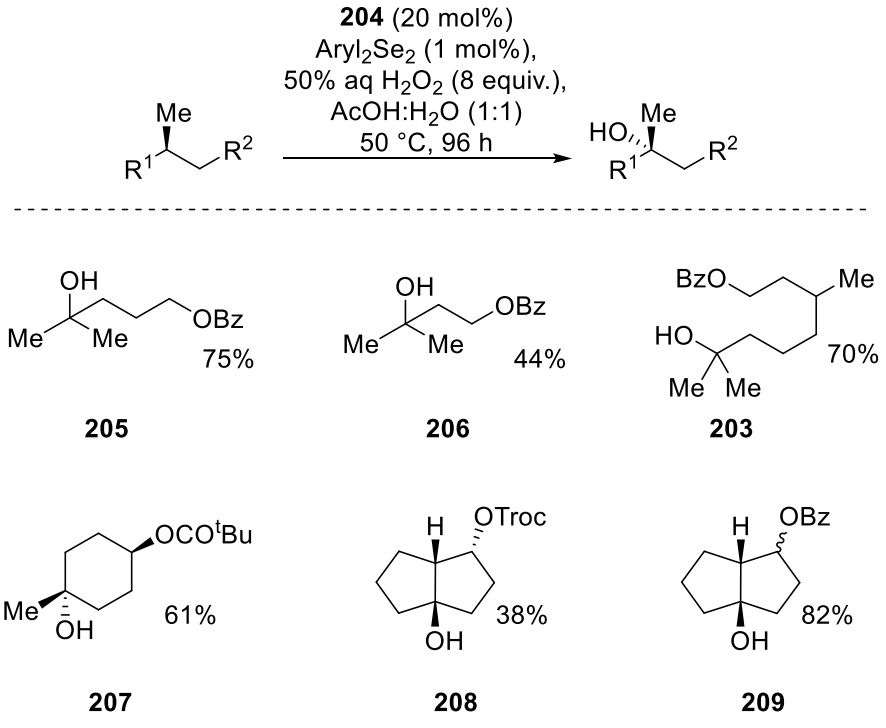
Perfluorophenyl catalyst **204** was found to oxidise numerous hydrocarbon substrates with as much or more success than its predecessor (**Figure 9**).



204

Figure 9 Optimal oxaziridine catalyst **204** found by DuBois and co-workers.

Additionally, switching to a solvent mixture of acetic acid and water provides a more desirable and sustainable solvent system cf. DCE. Disappointingly, this methodology suffers even more so from extended reaction times compared to the previous report and would be prohibitive to scale up (**Scheme 66**).[126]

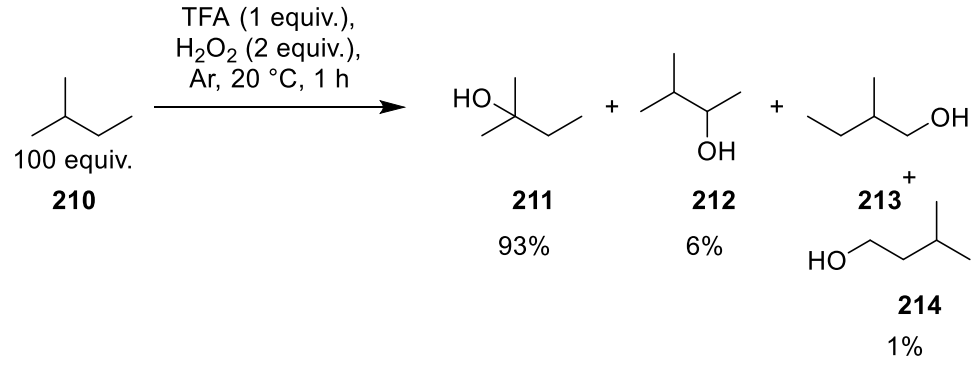


Scheme 66 Substrates oxidised by catalyst **204** as designed by DuBois and co-workers.

5.1.2.3 Peracids

Peracids have also been shown to conduct some interesting chemistry, with abilities to perform Baeyer-Villiger oxidations, epoxidations and many more reactions which include the synthesis of both dioxiranes and oxaziridines previously discussed. However, they have also been found to perform oxidations of unactivated hydrocarbons.

Frommer and Ullrich were interested in how monooxygenase enzymes are able to add a single oxygen into an organic compound in an oxygen-transfer process, and their earlier work showed that they could hydroxylate alkanes in the microsomal fraction of liver.[127] Much like previous work discussed in this report, they saw that the hydroxylation occurred selectively at the tertiary C-H position of such alkanes and suggested that this was occurring with virtually no steric influence from the enzyme. They later provided evidence for this when they found three chemical systems that would selectively oxidise the tertiary C-H bond of an alkane, in the presence of multiple secondary or primary C-H bonds. One of these chemical systems used trifluoroperacetic acid (perTFA) (**Scheme 67**).[128]

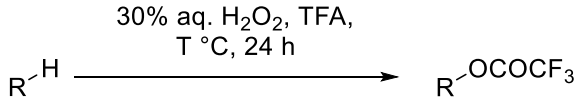


Scheme 67 First reported 3° C-H selective oxidation of alkanes using perTFA formed *in situ.*

The oxidation required a huge excess of starting material to minimise over oxidation and so presumably the yield was calculated with respect to the TFA. It is not typically desirable for the

starting material to be present in 'solvent' quantities and has a large impact on the sustainability of the reaction since such an excess will have detrimental effects on metrics such as the E-factor.

However, perTFA in particular, has since attracted more attention in the literature for the oxidation of hydrocarbons. Deno and Messer sought to extend the known oxidations performed by peroxide and TFA, but also to reduce the vast quantities of reactant that were used in the prior report.[129] The oxidation of the alkanes is performed using 30% aqueous hydrogen peroxide in the presence of TFA and dichloromethane. The mixture is stirred for 24 h at 25 °C and gives the trifluoroacetate product with only a trace of the alcohol (**Table 21**).



Entry	Alkane	T/°C	Relative yield of alcohols/%				
			1-	2-	3-	4-	5-
1	*n*-hexane	25	0.2	53	48	-	-
2	*n*-heptane	83	ND	41	40	19	-
3	*n*-decane	83	ND	30	26	21	21

Notes: ND – could not be determined.

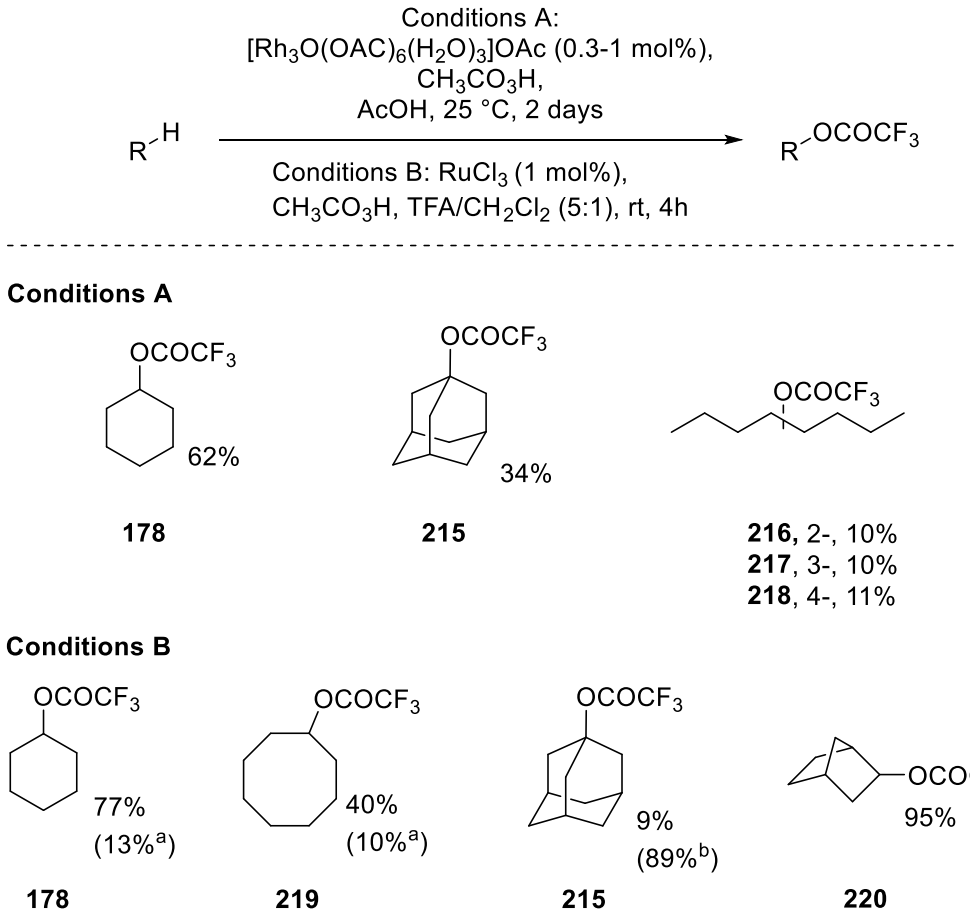
Table 21 Relative yields of alcohols obtained *via* the oxidation of unactivated alkanes as reported by Deno and co-workers.

It was clear that the oxidation preferentially occurred on the secondary C-H positions, although there appeared to be little distinction between them. The oxidation of cyclohexane **156** was also conducted which produced the trifluoroacetate in 78% yield with only a trace of the cyclohexanol **159**. Where larger alkanes were used such as decanes (**Table 21, Entry 3**), bis-hydroxylation was observed, both of which were remote from each other. The addition of a

metal catalyst has also been shown to facilitate the reaction, with reports from Nomura *et al*. and Murahashi utilising rhodium and ruthenium respectively. Nomura *et. al.* also reported the oxidation of alkanes using a peracid created by the presence of 30% aqueous hydrogen peroxide and TFA, although now with the addition of $[Rh_3O(OAC)_6(H_2O)_3]OAc$ (**Scheme 68, Conditions A**).[130]

Cyclohexane **156** was oxidised in good yield as well as adamantane **148** which displayed complete selectivity for the tertiary C-H bond to give trifluoroacetate **215**. Unfortunately, no selectivity was seen using *n*-octane and an almost equal ratio of 2-,3- and 4-octanol, **216, 217** and **218** respectively, was seen.

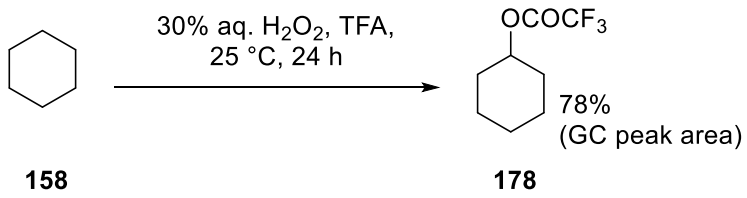
In the same year, Murahashi reported that the oxidation of hydrocarbons could also be facilitated using hydrogen peroxide and peracetic acid, in the presence of a ruthenium catalyst (**Scheme 68, Conditions B**).[131] The oxidations of cyclohexane, cyclooctane and norbornane were successful and gave the trifluoroacetates **178, 219** and **220** in good yields, with minor quantities of the ketone isolated. In the case of adamantane **148**, the tertiary alcohol was the major product with trifluoroacetyloxyadamantane **215** being isolated in only 9% yield.



Notes: [a]isolated yield of the ketone; [b]isolated yield of the alcohol.

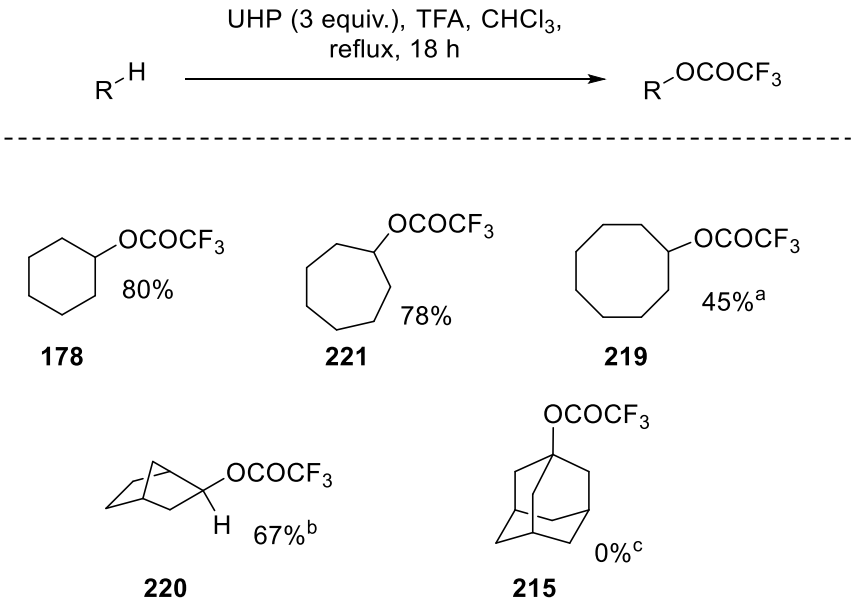
Scheme 68 Oxidation of alkanes reported by Nomura *et. al.,* using a peracid and metal catalyst (Conditions A) and the ruthenium and peracetic acid mediated oxidation reported by Murahashi (Conditions B).

Although both Nomura and Murahashi reported that the metal catalysts were necessary, Moody and co-workers commented that they found such reports surprising since no control reaction was reported.[132] To further add to the dispute, it was pointed out that Deno *et. al.*, had previously reported the oxidation of cyclohexane **158** under almost identical conditions but in the absence of any metal (**Scheme 69**).[129,133]



Scheme 69 Oxidation of cyclohexane **158** reported by Deno *et. al.,* in peracid media which does not require a metal catalyst.

Such reports were noted by Moody and co-workers in 2000 and thus, this methodology was 're-investigated' to establish whether this reaction was truly metal-dependent.[132] It was quickly established that in the presence of both aqueous hydrogen peroxide (30%) or urea-hydrogen peroxide (UHP) and TFA in chloroform, no metal was required for the oxidation reaction to occur. A number of trifluoroacetate products were accessed from the unactivated alkanes (**Scheme 70**).



Notes: [a] GC yield; [b] *exo*-product only observed; [c] degradation observed.

Scheme 70 Oxidation of hydrocarbons using peracids formed using peroxide and acid.

The strategy can be employed with cyclic hydrocarbons such as cyclohexane **158**, cycloheptane and norbornane to **178**, **221**, and **219** with good results. Interestingly, in this metal-free approach, the trifluoroacetate of adamantanol **215** was isolated but this was in contrast to the

previously discussed metal-mediated approach which produced the alcohol as the major product. However, the scope explored in this report is severely limited. There are no examples of substituted alkanes which allow investigations into the effects of groups with varying electronic natures. The use of UHP rather than aqueous hydrogen peroxide is preferable, since it is a solid source of hydrogen peroxide and therefore is more convenient and safer to use.

Such claims were later rebutted by Murahashi, who claimed that the conditions reported by themselves in an earlier report were sufficiently different to that described by Moody, such that a metal is required. They reported that this was because of the difference in reactivity and behaviour between peracetic acid and the perTFA, produced in the Moody report, and that these investigations had not been sufficiently representative. Therefore, Murahashi conducted further experiments to prove the reliance of the peracetic acid methodology on the presence of the ruthenium salt.[131] Such a claim is reasonable since it is well known that peracetic acid is not as strong as perTFA due to the electron withdrawing nature of the fluorine atoms in perTFA and so they would indeed be expected to react differently. They claimed that further rate experiments demonstrated this, since the rate constant obtained in the absence of the metal was significantly smaller than when it was present. As well this, they report the production of the ketone by-products as further evidence since they are not observed with a peroxide-TFA system in the absence of a metal.

Nevertheless, the sustainability profile of all oxidations conducted under metal free conditions using peracids, regardless of the source, is poor and the scope of such reactions has not been investigated extensively. Therefore, there is room in this research area for further investigations as well as many improvements to be made with regards to the sustainability of the processes whilst maintaining a metal-free approach.

6. Oxidation of unactivated hydrocarbon substrates using peroxides and acid

6.0.1 Project Aims

Despite a wealth of effort and research in the area, the ideals of having a range of selective and efficient methodologies available to convert low value, unfunctionalised starting materials, such as alkanes, into value added chemical commodities has not yet been realised. This leads us to identify this as a desired transformation in sustainable chemistry. Considering the methodology described in this thesis (see Section 5.1.2.3, **Scheme 70**) by the Moody group, the published methodology had been limited to only five reaction substrates and used chloroform as a co-solvent.

Therefore, the aim of this project was to improve the conditions described by Moody and co-workers, with a focus on sustainability. Immediately identified were the reduction of the quantities of acid and peroxide required, as well as substituting the chloroform co-solvent for a one which is deemed as 'green' and sustainable. The scope and selectivity of the reaction was also to be investigated further to include more complex substrates than the simple cyclic hydrocarbons used thus far.

Nobody said it was easy
No one ever said it would be this hard

Coldplay – The Scientist

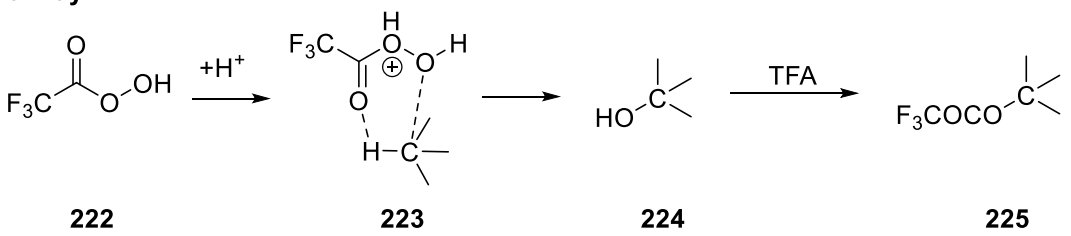
(A Rush Of Blood To The Head, 2002)

6.0.2 Results and Discussion

6.0.3 Optimisation reactions

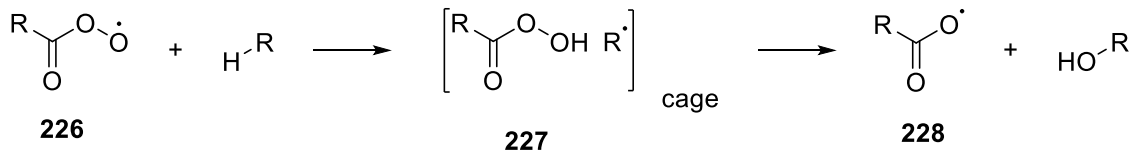
The mechanism for the C-H oxidation reaction of peracids has been debated in the literature for some time. An "oxenoid" type mechanism which would proceed *via* a cyclic transition state **223**, was originally reported by Bartlett in 1950 and was also proposed by Deno and co-workers in 1977 for oxidations using TFA and peroxide (**Scheme 71, Pathway A**).[1,2]

Pathway A



222 **223** **224** **225**

Pathway B



226 **227** **228**

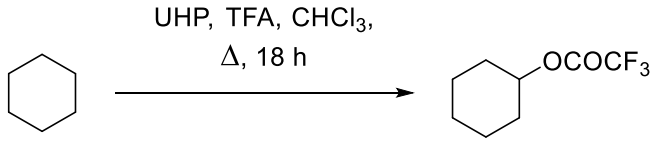
Scheme 71 Two mechanistic suggestions for the alkane hydroxylation reaction, concerted "oxenoid" mechanism (Pathway A) and a radical based mechanism (Pathway B).

An alternative mechanism was suggested by Tokumaru and Simamura in 1962.[3] They proposed that a radical chain mechanism was in operation, which involved the "homolytic rupture of the oxygen-oxygen bond of peroxybenzoic acid as the initiation process and an induced decomposition of this bond by solvent radicals derived from hydrocarbon molecules".[3] However, Bravo *et. al.* did not believe that this mechanism accounted for the high regio- and chemo- selectivity observed during their oxidation of alkanes with aromatic peracids. [4,5] The high degree of stereo-retention observed in these reactions had previously led others to conclude that a radical mechanism did not occur, and hence the concerted "oxenoid"

mechanism (**Pathway A**) had gained support. Instead, Bravo *et. al.* used this rationale to discount the possibility of the radical mechanism proposed by Tokumaru and Simamura, since it also could not account for the selectivity observed, and led them to propose a new radical-based mechanism for the process (**Scheme 71, Pathway B**).[4,5] They suggested that a radical chain mechanism *via* the formation of a peroxyl radical **223**, which can abstract a hydrogen from the alkane, followed by the rapid reaction of this radical in a "cage" **227** with the peracid which led to hydroxyl transfer and the alcohol product. They claimed that this could explain the selectivity previously seen in these reactions.[5]

However, LFER studies with both dioxiranes and peracids, performed by Murray and Gu in 1995, indicated that these hydroxylations occurred in a concerted electrophilic process, much like that proposed by Deno.[6] Furthermore, Kinetic isotope studies by Moody and O'Connell in 2000 also supported with the hypothesis of a concerted "oxenoid" mechanism (**Pathway A**). However, ambiguity remained in this case since the KIE value was low (2.3), therefore despite supporting the possibility of a concerted "oxenoid" mechanism, it did not discount the possibility of a radical based mechanism, since the KIE values of these types of reactions have also been known to be as low as 1.[7,8]

The mechanism for this type of reaction remains unclear. Nonetheless, obvious improvements could be made to the methodology previously reported work by Moody and co-workers (see Section 5.1.2.3). The authors used 3 molar equivalents of UHP in the reaction whereas, in this reaction, regardless of the mechanism, only a single equivalent of both the acid and peroxide source should be required to form the peracid **222**. Therefore, with sustainability in mind, initial attempts were made to reduce the quantities of UHP required for the reaction. UHP is a solid alternative to aqueous hydrogen peroxide. An investigation into the stoichiometry of UHP required is reported below (**Table 22**).



158 **178**

Entry	UHP/Equiv.	TFA/Equiv.	n[d]	GC Yield (%)
1	3	53	5	54[a]
2	1	53	2	33[a]
3	2	53	2	52[a]
4	10	53	1	33
5	3	53	1	53[b]
6	3	53[c]	1	7
7	3	30	1	42
8	3	10	1	8
9	3	5	1	2

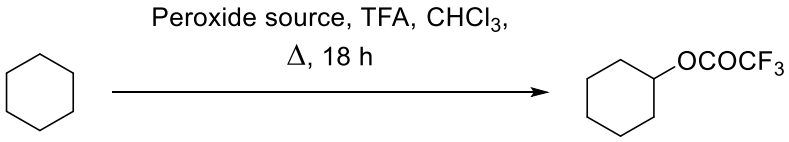
Notes: Yields calculated by quantitative GC with methylcyclohexane as an internal standard; [a]Average yield over all attempts; [b]Distilled TFA; [c]TFAA attempted in place of TFA; [d]number of experimental repeats.

Table 22 Investigations into the stoichiometric effects of TFA and UHP.

Initial tests using 3 equivalents of UHP gave the desired product **178** in good yield as reported previously by Moody and co-workers.[132] Unfortunately, any attempts made to reduce the quantities of UHP in the reaction led to a reduction in the yield of the final product **178** and somewhat counterintuitively, when the quantities of peroxide were increased to 10 equivalents, a drop in the yield was also observed (**Table 22, Entry 4**). This was presumably due to over oxidation or destruction of the final compound since a very dark reaction mixture was observed. The yields of the reactions for both 3 and 2 equivalents of UHP were minor, therefore it was decided to proceed with 2 equivalents of UHP for the remainder of the reactions.

The quantities of TFA were also reduced in attempts to increase the sustainability profile of this reaction, but unfortunately could not be achieved without having a detrimental effect on the reaction yield (**Table 22, Entries 2 and 3**). Prior distillation of the TFA also had no effect on the reaction and substitution with trifluoroacetic anhydride (TFAA) unfortunately led to a drastic drop in the yield of the desired product **178** (**Table 22, Entry 6**). This result with TFAA suggested that the peracid formation did not occur in the presence of the relatively weak 35% aqueous hydrogen peroxide found in UHP – according to the literature a more concentrated solution of aqueous peroxide is required.[140]

An alternative to UHP is aqueous hydrogen peroxide which is deemed a more hazardous reagent compared to UHP, however it is used throughout research and industrial laboratories across the world and is only regarded as a real concern where the peroxide concentrations are high. Therefore, 30% aqueous hydrogen peroxide is viewed as less of an issue and was investigated as an alternative and more available source of hydrogen peroxide than the complex-bound peroxide in UHP. Furthermore, 30% aqueous hydrogen peroxide is slightly cheaper than UHP per mol of reagent ($26/mol vs $32/mol respectively – Millipore Sigma, September 2018).[57] Sodium percarbonate was also explored as an option for a safe and solid peroxide source (**Table 23**).



158 **178**

Entry	Peroxide Source	Equiv. of peroxide	TFA/equiv.	GC Yield/%
1	H_2O_2 (30% aq.)	3	53	64
2	H_2O_2 (30% aq.)	10	53	47
3	H_2O_2 (30% aq.)	2	53	52
4	H_2O_2 (30% aq.)	1	53	29
5	H_2O_2 (30% aq.)	3	25	63
6	H_2O_2 (30% aq.)	3	10	24
7	H_2O_2 (30% aq.)	5	25	55
8	H_2O_2 (30% aq.)	3	53	62[a]
9	H_2O_2 (30% aq.)	2	25	41[b]
10	H_2O_2 (30% aq.)	3	53	24[c]
11	H_2O_2 (30% aq.)	3	53	44[d]
12	$2Na_2CO_3 \bullet 3H_2O_2$	3	53	Failed[c]
13	$2Na_2CO_3 \bullet 3H_2O_2$	3	53	Failed

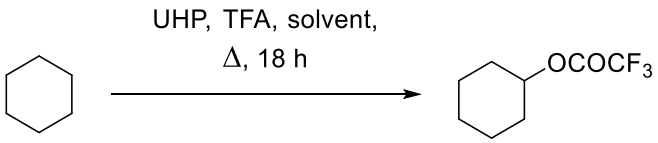
Notes: Yields calculated by quantitative GC with methylcyclohexane as an internal standard; [a]H_2O_2 (30% aq.) and TFA stirred for 30 min first; [b]No chloroform; [c] rt; [d]reflux for 8 h.

Table 23 Exploration of alternative sources of peroxide.

Pleasingly, 30% aqueous hydrogen peroxide gave the trifluoroacetate product **178** in good yield (**Table 23, Entry 1**), but similarly to UHP, attempts to reduce the quantities of hydrogen peroxide gave a reduction in yield (**Table 23, Entries 3 and 4**). The same was seen when the quantity was increased to 10 equivalents (**Table 23, Entry 2**). Sodium percarbonate (**Table 23, Entries 12 and 13**) was a poor substitute for both aqueous hydrogen peroxide and UHP - it failed to convert

any starting material **158** to product **178**. It was clear at this stage that aqueous peroxide was the best reagent for the reaction, and it was unfortunate that it could not be replaced by a solid alternative. However, there remained scope to improve the sustainability profile of this reaction *via* other means.

One of the most obviously unsustainable components of the reaction was the chloroform that was used as a solvent. Chloroform is well known for its poor sustainability profile.[34] Since the optimisations so far had been unsuccessful, alternative solvents to chloroform were investigated. Solvents had to be carefully selected due to the nature of the reaction conditions which are strongly acidic and actively generate peroxides which are then heated at reflux (approx. 90 °C). Based on this, ether-based solvents were excluded due to safety concerns. The combination of ethers and peroxides/peracids is explosive.[141] Furthermore, any solvent which itself may be oxidised under these conditions, for example hydrocarbon-based solvents, also had to be avoided. A summary of these results is shown below (**Table 24**).



158 **178**

Entry	Solvent	GC Yield/%
1	$CHCl_3$	63
2	DMC	40
3	EtOAc	32
4	acetic acid	18
5	dichloromethane	49
6	DCE	45
7	water	14
8	$CHCl_3$/Water (1:1)	21
9	DMF	21
10	Dioxane	25
11	-	18

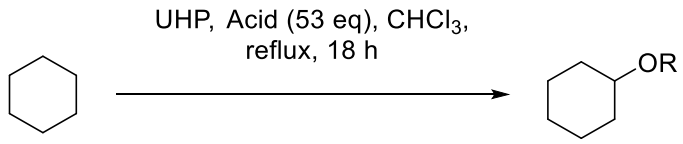
Note: Yields calculated by quantitative GC with methylcyclohexane as an internal standard.

Table 24 Solvent screen for the oxidation reaction.

Unfortunately, solvents with good sustainability profiles compared to chloroform, such as ethyl acetate (**Table 24, Entry 1**), water (**Table 24, Entry 7**) and DMC (**Table 24, Entry 2**) did not give an improved yield. Dichloromethane (**Table 24, Entry 5**) was the most successful, but this too is well known for its poor sustainability and carcinogenicity.[14] The success of dichloromethane (**Table 24, Entry 5**) and DCE (**Table 24, Entry 6**), combined with the low yield when no solvent was present, did suggest however that solvents, and more specifically chlorinated solvents are preferable in this reaction, the poor yield in the absence of solvent suggests that they may even

play an important mechanistic role, but unfortunately, this is not currently well understood and warrants further investigation in the future.

Since the acid has a role in the formation of the peracid, it was also suggested that it may be possible to form peracids of weaker and more user-friendly acids. Peracids of various other acid sources are known in the literature and so further screening attempts were made (**Table 25**).[142]



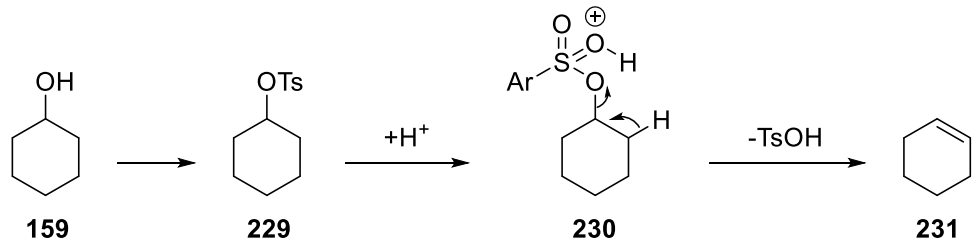
158

Entry	Acid	Equiv. of acid	GC Yield/%
1	TFAA	53	7
2	acetic acid	53	8
3	acetic acid[a]	53	33
4	methanesulfonic acid	53	Failed
5	trifluoromethanesulfonic acid	53	Trace
6	difluoroacetic acid	53	failed
7	trichloroacetic acid	53	19[c]
8	Conc. HCl	53	Trace[b]
9	TFA/Acetic acid	53	7

Notes: R = corresponding ester/sulfonate of acid used; Yields calculated by quantitative GC with methylcyclohexane as an internal standard; [a]10 equiv. of UHP; [b]Cyclohexanol detected in trace amounts; [c]yield of the alcohol detected.

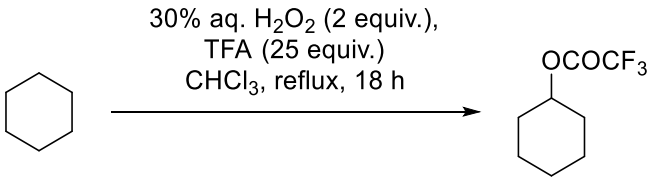
Table 25 Screen to find a suitable acid alternative for the reaction.

The weaker, non-fluorinated acetic acid (**Table 25, Entry 2**) failed to produce such successful results – only 8% of the acetylcyclohexanol was observed by GC and GCMS analysis. Although this could be increased to 33% with 10 equivalents of UHP (**Table 25, Entry 3**). The stronger difluoroacetic acid (**Table 25, Entry 6**) and the trichloro counterpart (**Table 25, Entry 7**) also gave no reaction and a poor yield respectively. Despite the low pK_a, methanesulfonic acid (**Table 25, Entry 4**) failed to produce any product while both concentrated HCl (**Table 25, Entry 8**) and trifluoromethanesulfonic acid (**Table 25, Entry 5**) merely produced a trace. It is possible in some instances, particularly with methanesulfonic acid and trifluoromethanesulfonic acid, that once an alcohol is formed it would be immediately protected by a mesyl or tosyl group **229** and can then undergo a subsequent elimination reaction to give cyclohexene **231** (**Scheme 72**). This product would be difficult to identify by GCMS due to its low boiling point – it would be eluted along with the solvent front.



Scheme 72 Proposed elimination of *p*-toluenesulfonic acid to give cyclohexene **231**.

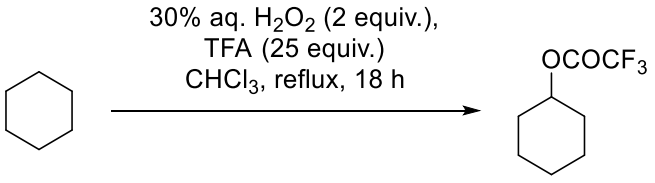
Finally, since the acid source could not be changed under these conditions, the temperature of the reaction was investigated. When performed at room temperature, the reaction yield was low (40%, cf. 63% under reflux) at 50 °C, a modest amount of product was formed. Therefore, based on these optimisation studies, it was concluded that the optimum conditions found so far were H_2O_2 (30% aqueous, 2 equiv.), TFA (25 equiv.), $CHCl_3$, under reflux for 18 h (**Scheme 73**).



158 **178**

Scheme 73 Optimal conditions found for the oxidation of cyclohexane.

Control reactions also established the requirement for the presence of both the acid and hydrogen peroxide since no reaction was observed in their absence (**Table 26**).



158 **178**

Entry	Acid	Hydrogen Peroxide	Chloroform	Temp/°C	Yield[a]/%
1	✓	✓	✓	reflux	63
2	×	✓	✓	✓	0
3	✓	×	✓	✓	0
4	✓	✓	×	✓	18
5	✓	✓	✓	rt	trace
6	✓	✓	✓	50	40

Notes: [a]Yields calculated by quantitative GC with methylcyclohexane as an internal standard.

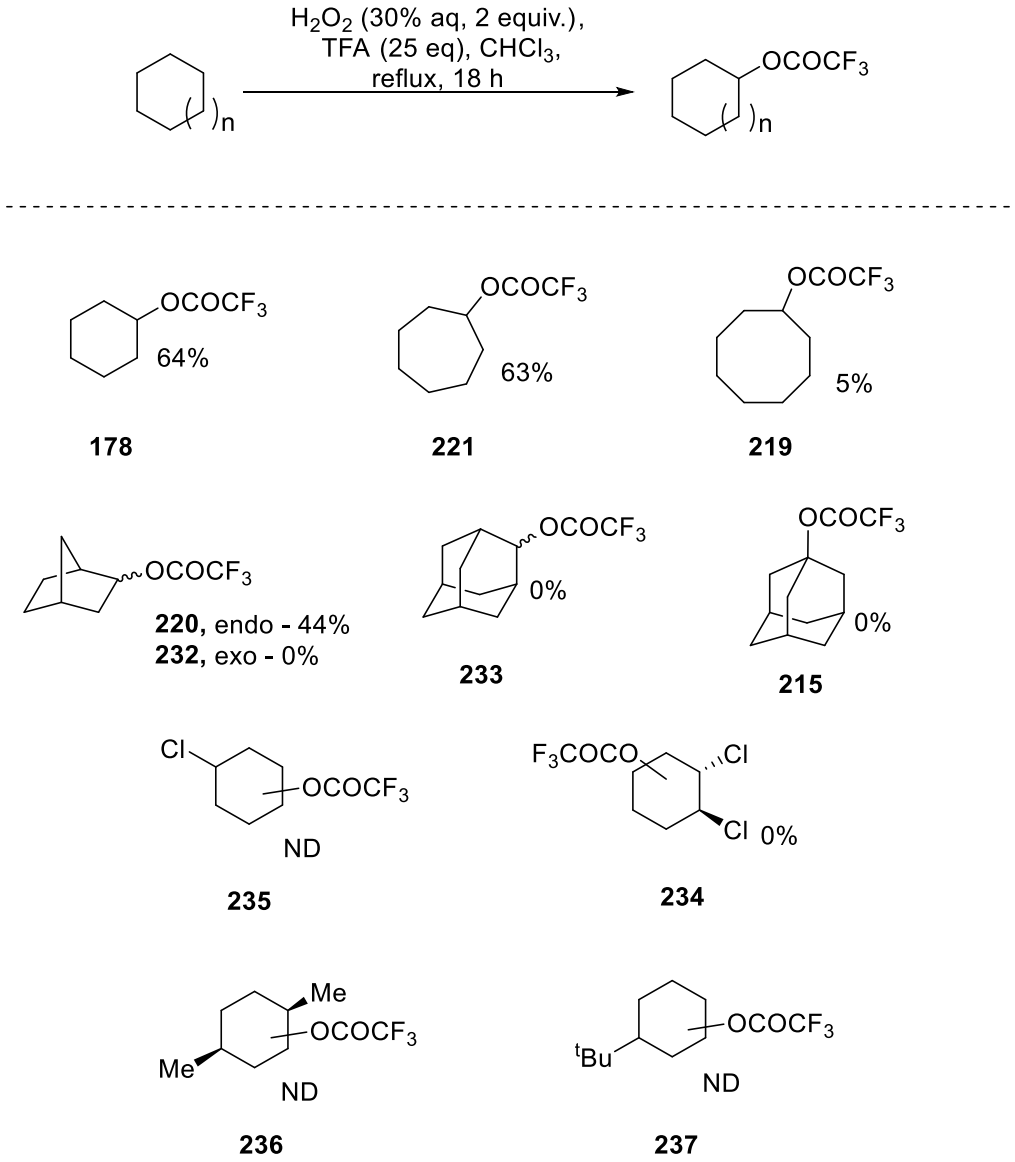
Table 26 Table of control reactions.

Despite the limitations of the optimisations having been realised, it cannot be ignored that improvements have been made since the quantities of both the peroxide source and acid had

been reduced. Additionally, since H_2O_2 (30% aq.) is used widely throughout industry and academia, rather than its more concentrated form, it was deemed as an acceptable and safe form of hydrogen peroxide for these reactions.

6.0.4 Substrate screen

Following optimisation of the reaction, it was important to investigate the substrate scope in order to establish what kind of substrates could be oxidised and what the reaction limitations were. A range of commercially available cyclic alkanes were subjected to the optimised conditions (**Scheme 74**).



Note: Yields calculated by quantitative GC with methylcyclohexane as an internal standard.

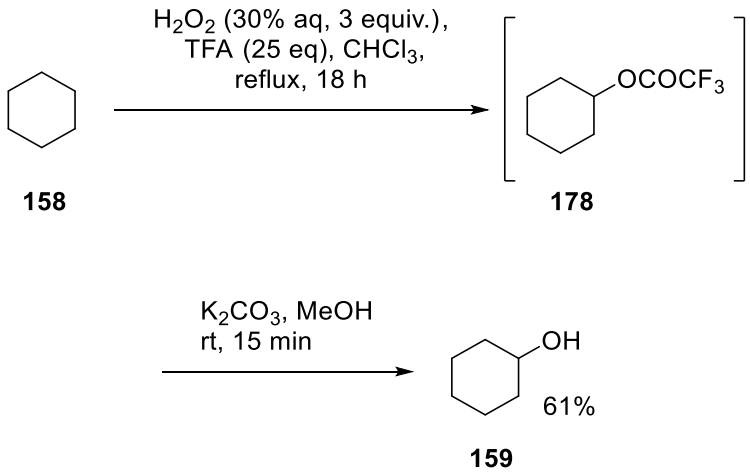
Scheme 74 Substrate screen performed with the optimised oxidation conditions.

In order to allow comparison with authentic material, the trifluoroacetates of cyclohexane **178**, cycloheptane **221**, cyclooctane **219**, norbornane **220** and **232** and adamantane **215** and **233** were synthesised by the trifluoroacetylation of the alcohols as reported in the literature (see Experimental Section 7).[143] Trifluoroacetate esters of chlorocyclohexane **234** and ^{t}butylcyclohexane **237** were also synthesised, although alcohols of every possible oxidisable position were not available, thus esters were only constructed of those that could be purchased.

Pleasingly, when subjected to the optimised oxidation conditions, cyclohexane **158**, cycloheptane, cyclooctane, norbornane and adamantane gave similar results to those reported by Moody previously.[132] Furthermore, the oxidation only occurred once, suggesting that the presence of the trifluoroacetate group altered the electronics of the substrate sufficiently such that the oxidation reaction cannot occur for a second time. To truly establish how robust these trifluoroacetate products were towards the oxidation reaction, cyclohexyltrifluoroacetate **178** was subjected to the oxidation conditions for a second time; no reaction was observed. This suggested that the reaction may be sensitive towards the presence of an electron withdrawing group, which was confirmed when *trans*-1,2-dichlorocyclohexane was subjected to the reaction conditions. Although a small quantity of starting material was converted into unknown material in this case, 80% of the starting material was recovered unreacted.

Unfortunately, more complex trifluoroacetate products **235**, **236**, and **237** were problematic with regards to analysis since they could not be identified with enough certainty by GCMS in either ESI/EI/CI mode. This meant it was difficult to gain a quantitative understanding of reactions where the products and starting materials were more volatile, could not be synthesised for an easy comparison and/or could not be isolated by conventional means without loss of material. Furthermore, ^{19}F NMR spectroscopy was not seen as a solution to the problems in analysis encountered during this project. Although a seemingly characteristic peak was observed at -75 ppm for a trifluoroacetate group, there was little to assist in the identification of each positional isomer. Furthermore, production of the trifluoroacetate made isolation difficult and it was desirable to pursue functionality which would later allow isolation of the products with ease – i.e. a product with a higher boiling point. A challenge also presented itself in the synthesis of every isomer in for comparison and subsequent identification.

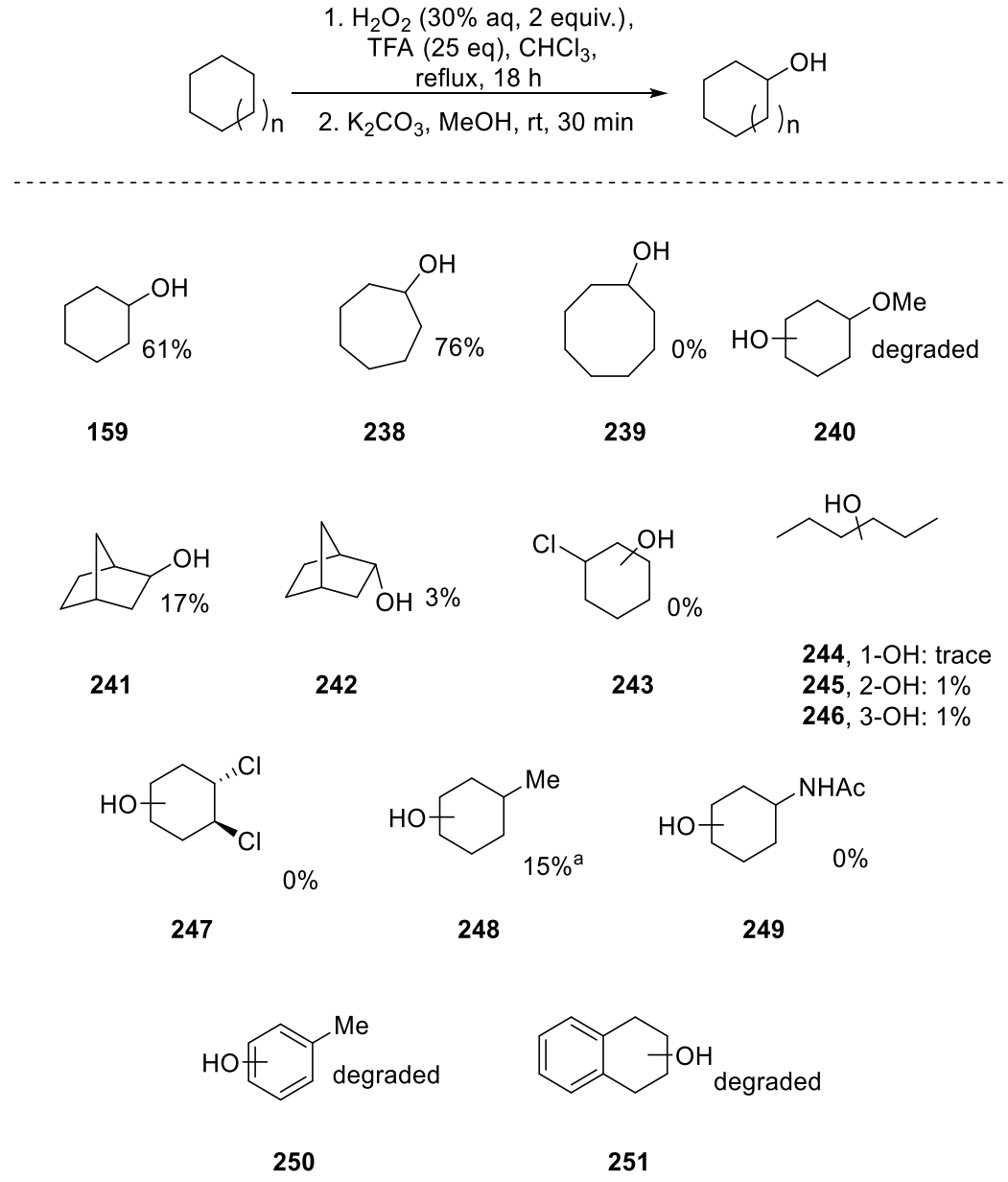
The analysis difficulties and desire for higher boiling products meant that hydrolysis of the trifluoroacetate group immediately following the oxidation reaction was attractive. Alcohols typically have higher boiling points than the corresponding trifluoroacetates, due to hydrogen bonding capabilities, and were products that were more easily identified with certainty *via* GCMS since they produce a molecular ion. Pleasingly, the simple addition of potassium carbonate and methanol to the reaction mixture quickly facilitated the hydrolysis of cyclohexyltrifluoroacetate **178** to cyclohexanol **159** in quantitative yield by GC and this product was easily identified by GCMS analysis (**Scheme 75**).



Note: Yields calculated by quantitative GC with methylcyclohexane as an internal standard.

Scheme 75 Oxidation of cyclohexane to trifluoroacetyloxycyclohexane **178** and then immediate hydrolysis to cyclohexanol **159**.

Since many alcohols are commercially available, this strategy also had the potential to make analysis easier, since many of the reaction products could be compared to the authentic material and were easier to identify by both GC and GCMS analysis. Therefore, various substrates were chosen and subjected to the optimised conditions (**Scheme 76**).



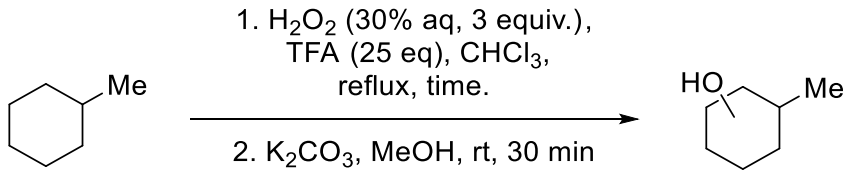
Note: Yields calculated by quantitative GC with methylcyclohexane as an internal standard. [a]Combined yield of a mixture of positional isomers.

Scheme 76 Substrate scope for the formation of hydroxy-substituted alkanes.

To our satisfaction, cycloheptane was oxidised to cycloheptanol **238** in good yield and the oxidation of norbornane, somewhat unsurprisingly, also displayed selectivity similar to that seen previously during the oxidation to the trifluoroacetate groups. In the case of more substituted substrates, the presence of a hydroxy group made the analysis by GCMS easier, since the molecular ions could now be observed using EI-MS. Additionally, authentic alcohols could also

be used for comparison of many of the potential positional isomers by GC, which allowed the correct peak to be selected for quantitative analysis, which had not previously been possible. Methylcyclohexane **252** was oxidised to methylcyclohexanol **248** in moderate yield, and as a mixture of the 2-,3-, and 4-hydroxy products, identified by comparison with the commercially available alcohols. Interestingly, only a trace of 1-methylcyclohexanol was observed. Unfortunately, *n*-hexane was not successfully oxidised under the optimised oxidation conditions and a mere trace of hexan-1-ol **244**, hexan-2-ol **245** and hexan-3-ol **246**. Any aromatic substrates attempted underwent rapid degradation giving a thick, black reaction mixture.

In the interest of investigating the reaction scope, simple substituted substrates were selected which had both electron donating and electron withdrawing character. Disappointingly, in the presence of any electron withdrawing group such as in chlorocyclohexane or 1,2-dichlorocyclohexane, the reaction failed to convert starting material into products **243** and **247**. In the case of an electron donating group such as that in methoxycyclohexane **252** however, some reaction was observed, although the resulting mixture of products could not be identified or separated. The drastically low yield of methylcyclohexanol **248** still could not be explained, since the presence of a methyl group was not expected to have such a negative consequence for the reaction yield. However, unlike most of the other reactions where the reaction mixtures mostly remained colourless, it was noted that the reaction mixture with methylcyclohexane **252** darkened significantly at approximately 7 h and hence it was suspected that long reaction times were resulting in loss of the desired product. Therefore, reaction times were investigated in this instance and as expected, they provided an improvement (**Table 27**).



252 **248**

Entry	Time/h	GC Yield/%[a]
1	2	12
2	4	34
3	8[b]	24
4	18	15

Notes: [a]Yields were calculated by quantitative GC, by comparison with authentic, commercially available products and cyclohexane as an internal standard; [b]The reaction mixture began to go brown at 7.5 h.

Table 27 Table displaying the difference in yield of methylcyclohexanol **248** isomers at different reaction times.

When the reaction was performed over 8 h and stopped shortly after the colour change was observed, an improvement to 24% was observed (**Table 27, Entry 3**) which was improved further when the reaction was stopped after 4 h (**Table 27, Entry 2**, 34% yield). This suggested that the reaction product may be being destroyed in the reaction after being formed and could account for the dark colour observed later during the reaction. Therefore, it is possible that milder reaction conditions may be required to prevent the degradation of the oxidation products but attempts towards this by the acid substitution previously described in this report had been unsuccessful thus far.

6.1 Project Conclusions & Future work

It had thus far been confirmed that a source of hydrogen peroxide, in the presence of TFA, was able to oxidise cyclohexane **158** and other hydrocarbons in varying yields, although attempts to optimise the reaction were met with limited success.

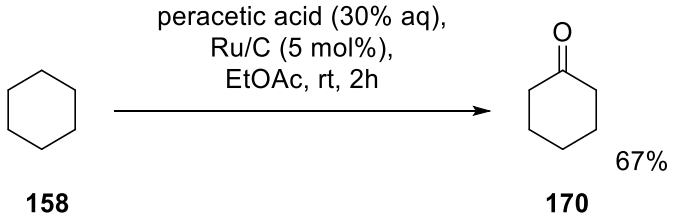
The trifluoroacetate functional group in the products made them difficult to handle. This functional group increases volatility compared to hydroxy groups, which made the reaction products difficult to isolate in their entirety. Analysis by quantitative GC was possible where the authentic trifluoroacetate could be synthesised from commercially available starting materials. However, attempts to analyse those trifluoroacetates, which could not be synthesised *via* other routes for comparison, was extremely difficult, since they could not be identified without doubt *via* ESI, EI nor CI mass spectrometry.

Fortunately, hydrolysis of the trifluoroacetates to a hydroxyl group could be facilitated easily, by the simple addition of methanol and potassium carbonate to the reaction mixture which was then stirred at rt for 30 min. This allowed for the identification of the alcohol peaks by GCMS (EI) for qualitative analysis, and the quantitative GC analysis of those alcohols which were commercially available, or able to be synthesised. The relevant peaks were identified by simple comparison with authentic products.

The scope of the reaction was briefly investigated but was quickly found to be limited. The presence of an electron withdrawing group prevented the reaction from occurring altogether, whereas the presence of an electron donating group gave a complex mixture of inseparable

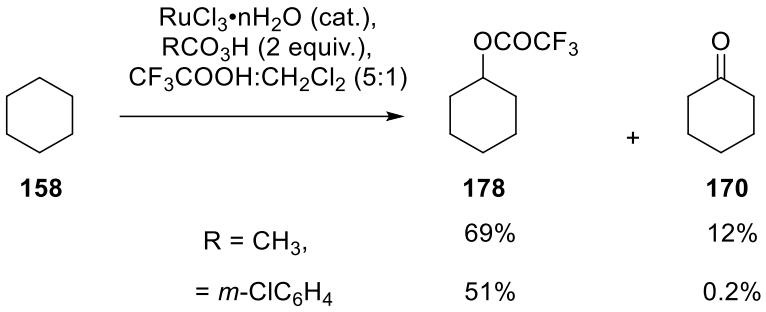
products. Much to our disappointment, it also appeared to show little regioselectivity in the case of methylcyclohexane **252** and caused the rapid degradation of aromatic substrates.

Future work could look at the introduction of a metal, since this could potentially assist in the production of the active species, thus reducing the severity of the reaction conditions required and allow the oxidation of more electron rich substrates, including aromatic species. Such reactions have been reported in the literature, for example the oxidation of various alkanes to the corresponding ketones in the presence of peracetic acid and a ruthenium catalyst at rt (**Scheme 77**).[83]



Scheme 77 Oxidation of cyclohexane **158** to cyclohexanone **170** in good yield as reported by Murahashi *et. al.*

In the same report, Murahashi and co-workers have also studied the oxidation of alkanes such as cyclohexane to the corresponding trifluoroacetates in good yield in the presence of a ruthenium catalyst, a peracid, trifluoroacetic acid and chloroform at rt (**Scheme 78**).



Scheme 78 Oxidation of cyclohexane **158** using peracids and a metal catalyst.

However, there remains scope develop such oxidation reactions which are selective, do not undergo over oxidation and use a more sustainable metal and mild reaction conditions.

7. Experimental

7.1 General Experimental Details

Commercially available reagents were used throughout without purification, unless otherwise stated. Reactions requiring anhydrous conditions were conducted under an inert atmosphere of dry argon in flame-dried apparatus. Tetrahydrofuran was distilled from sodium benzophenone ketyl radical according to standard procedures. All other solvents and reagents were used as supplied, without further purification. Light petroleum refers to the fraction with bp 40 – 60 °C. Ether refers to diethyl ether.

Thin Layer Chromatography (TLC) was performed using Merck aluminium foil backed plates, pre-coated with silica gel 60 F_{254}.Visualisation was carried out *via* U.V. fluorescence (λ_{max} = 254 nm and/or 360 nm) and/or staining with potassium permanganate and heating. Flash chromatography was carried out using Davisil silica 60 Å under medium pressure using the eluent specified.

For reactions that required visible light irradiation, a 400 W Trac metal halide floodlight containing a 400 W Ostram Powerstar HQI-T metal halide bulb (λ_{max} 590 nm), (illuminance: 80,000 lux) was used. All reactions that required irradiation were carried out in a sealed pyrex microwave tube and placed in front of the light source at a distance of 60 cm for the stated time period. Other light sources tested were a Minisun 20639 200W LED Pro2 Daylight Floodlight and LEDs comprised of 5 x Citizen CL-L233-C13N1-C LED chips (output: 1000 lumen) mounted on an in-house built aluminium block with fan cooling. Their emission spectra are shown in Figures S1-S3.

NMR experiments were performed on a Bruker DPX400 (^{1}H frequency 400 MHz, ^{13}C frequency 100 MHz), Bruker AV400 (^{1}H frequency 400 MHz, ^{13}C frequency 100 MHz), Bruker AV(III)400 (^{1}H frequency 400 MHz, ^{13}C frequency 100 MHz), Bruker AV(III)400HD (^{1}H frequency 400 MHz, ^{13}C frequency 100 MHz) or Bruker DPX300 (^{1}H frequency 300 MHz, ^{13}C 75 MHz) spectrometer at ambient temperature. Proton magnetic resonance shifts (δ_H) recorded in parts per million (ppm) are recorded to two decimal places and are referenced to residual H in the deuterated solvent as the internal standard. Coupling constants (*J*) are reported to the nearest 0.1 Hz. The multiplicity of each signal is designated a combination of the following abbreviations; s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Peaks were assigned using MestreNova software. Fluorine magnetic resonance chemical shifts (δ_F), recorded in ppm, are recorded to one decimal place. Carbon magnetic resonance chemical shifts (δ_C), recorded in ppm, are recorded to one decimal place and referenced to the carbon in the solvent as the internal standard. Multiplicity was determined by DEPT analysis.

Infrared spectra were obtained Nicolet Avatar 360 T instrument on the neat compound using attenuated total reflection technique. Absorption maxima (υ_{max}) of major peaks are reported in wavenumbers (cm^{-1}), quoted to the nearest integral wavenumber.

Mass spectra were recorded on a Bruker MicroTOF 61 (ESI) mass spectrometer which uses electrospray ionisation (ESI). All ESI mass spectrometry data are high resolution. GCMS data was obtained using EI with JEOL AccuTOF GCX MS alongside an Agilent 7890B gas chromatograph. The acquisition mass range was 40-500 Da and the mass calibration was conducted by PFTBA. Ionisation energy was set to 70eV with a temperature of 150°C. The GC column used was a J&W DB-5MS 30m x 0.25mm x 25um with a temperature programme of 40°C (2min) to 330°C at 10°C

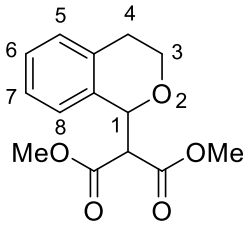
min^{-1}. Helium was used as the carrier gas with the inlet temperature of 200°C and a transfer line temperature of 180°C.

Melting points were measured on a Riechert-Kofter hot stage apparatus and are uncorrected.

7.2 CDC Reactions

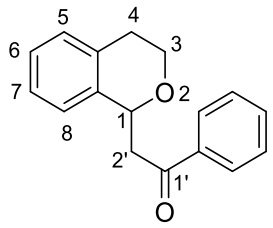
7.2.1 Experimental Data: CDC Adducts

Dimethyl 2-(isochroman-1-yl)malonate 41



To a solution of isochroman (0.13 mL, 1.0 mmol), $InCl_3$ (11 mg, 5.0 mol%), $Cu(OTf)_2$ (18 mg, 5.0 mol%) and DDQ (272 mg, 1.20 mmol) in dichloromethane (6 mL), was added dimethyl malonate (0.14 mL, 1.2 mmol) and the mixture was stirred at rt for 18 h. Ether (10 mL) was added and the mixture was filtered through a plug of silica. The solvent was removed *in vacuo*. Purification by column chromatography, eluting with light petrol and ethyl acetate (5%-10% step gradient) gave the product as a clear, colourless oil (47 mg, 18%); (Found: M+Na^+, 287.0897. $C_{14}H_{16}NaO_5^+$ requires 287.0890); (Found: 2M+Na^+, 581.1896. $C_{28}H_{32}NaO_{10}^+$ requires 581.1888); δ_H (400 MHz; $CDCl_3$); 7.22 – 7.10 (3 H, m, ArH), 7.03 (1 H, d, *J* 7.6, ArH), 5.49 (1 H, d, *J* 6.4, H-1), 4.18 (1 H, dt, *J* 11.3, 4.8, H-3), 4.01 (1H, d, *J* 6.4, COCHCO), 3.84 – 3.77 (1 H, m, H-3), 3.76 (3 H, s, OCH_3), 3.68 (3 H, s, OCH_3), 3.09 – 2.96 (1 H, m, H-4), 2.73 (1 H, dt, *J* 16.2, 4.2, H-4); δ_C (100 MHz; $CDCl_3$);168.0 (C), 167.1 (C), 134.7 (C), 134.4 (C), 129.1 (CH), 127.3 (CH), 126.3 (CH), 124.6 (CH), 74.1 (CH), 63.5 (CH_2), 58.0 (CH), 52.8 (CH_3), 52.5 (CH_3), 28.63 (CH_2). Data recorded matches those in the literature.[38,51]

2'-(Isochroman-1-yl)-1'-phenylethan-1'-one 77



To a solution of DDQ (2.7 g, 12 mmol) and acetophenone (2.3 mL, 20 mmol) under an atmosphere of argon, was added isochroman (1.3 mL, 10 mmol) dropwise over 5 min. The reaction mixture was heated and stirred at 100 °C for 3.5 h. Once cooled, ether (12 mL) was added and the mixture was filtered through a silica plug and concentrated *in vacuo*. Purification by column chromatography, eluting with 5-10% ethyl acetate in light petroleum gave the product as an orange oil (542 mg, 22%); (Found: $M+H^+$, 253.1125. $C_{17}H_{17}O_2^+$ requires 253.1123); (Found: $M+Na^+$, 275.1051. $C_{17}H_{16}NaO_2^+$ requires 275.1043); (Found: $2M+Na^+$, 527.2201. $C_{34}H_{32}NaO_4^+$ requires 527.2193)**;** δ_H (400 MHz; $CDCl_3$) 8.08 (2 H, d, *J* 8.2, Ar<u>H</u>), 7.69 – 7.58 (1 H, m, Ar<u>H</u>), 7.59 – 7.49 (2 H, m, Ar<u>H</u>), 7.34 – 7.13 (4 H, m, Ar<u>H</u>), 5.67 – 5.56 (1 H, m, <u>H</u>-1), 4.20 (1 H, ddd, *J* 3.8, 5.3, 12.3, <u>H</u>-3), 3.89 (1 H, ddd, *J* 3.8, 9.6, 12.3, <u>H</u>-3), 3.70 (1 H, dd, *J* 8.7, 16.2, <u>H</u>-2'), 3.41 (1 H, dd, *J* 3.5, 16.2, <u>H</u>-2'), 3.10 (1 H, ddd, *J* 5.6, 9.6, 15.6, <u>H</u>-4), 2.80 (1 H, m, <u>H</u>-4); δ_C (100 MHz; $CDCl_3$); 198.2 (C), 137.7 (C), 137.3 (C), 134.1 (C), 133.2 (CH), 129.1 (CH), 128.63 (CH), 128.1 (CH), 126.7 (CH), 126.4 (CH), 124.6 (CH), 72.8 (CH), 63.4 (CH_2), 45.6 (CH_2), 29.0 (CH_2). Data recorded matches those in the literature.[49]

7.3 Benzylic Oxidation

7.3.1 General Procedures: Benzylic Oxidation Starting Materials

General procedure A

To a suspension of sodium hydride (60% in mineral oil, 1.2 equiv.) in dry THF at 0 °C and under an atmosphere of Ar was added alcohol (1.0 equiv.) and the mixture was stirred for 15 min. Iodomethane (3.0 equiv.) was added and the mixture was allowed to warm to rt and stirred for a further 2-18 h. A saturated solution of sodium hydroxide was added and the mixture was extracted into ethyl acetate. The organic extracts were combined and washed with water and brine. The extracts were then dried over Na_2SO_4, filtered and solvent removed *in vacuo* to give the ether product. When necessary, purification was carried out by column chromatography.

General procedure B

To a solution of sodium methoxide (1.0 equiv.) in methanol, under an atmosphere of Ar was added benzyl halide (1 equiv.) and the mixture was stirred at reflux for 2 h. A saturated solution of sodium hydroxide was added and the mixture was extracted into ethyl acetate. The organic extracts were combined and washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the product.

General procedure C

To a solution of benzhydrol (1.0 equiv.) in ethyl acetate:acetic acid (9:1) was added Pd-C (0.1 equiv.) and the mixture was stirred under an atmosphere of H_2 at rt for 18 h. Water was added and the mixture extracted into ethyl acetate. The organic extracts were combined and washed with water, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*.

7.3.2 General Procedures: Arbutin Hydrolysis and Extraction

Arbutin Hydrolysis and BQH_2 Isolation

To a solution of arbutin (272 mg, 1.00 mmol) in DMC (12 mL) was added concentrated hydrochloric acid (2 mL) and the mixture stirred at reflux under an atmosphere of Ar for 2 h. The mixture was allowed to cool to rt and the solvent removed *in vacuo*. Any remaining solvent was azoetroped with toluene. The residue was triturated with DMC (5 x 5 mL), the extracts combined and the solvent removed *in vacuo* to give BQH_2 which was used without any further purification.

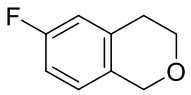
Arbutin Extraction from Leaves

To a mixture of powered leaves (5 g) in water (238 mL) was added methanol (12 mL). The mixture was sonicated at 30 °C for 30 min. The arbutin content was established using quantitative HPLC.

A suitable portion was removed from the extraction mixture and concentrated *in vacuo.* The residue was subjected to the above hydrolysis conditions and the product used in the oxidation reaction.

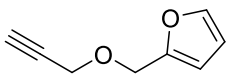
7.3.3 Experimental Data: Benzylic Oxidation Starting Materials

6-Fluoroisochromane



To TFA (0.6 mL) was added paraformaldehyde (90 mg, 30 mmol) and the mixture was stirred at 50 °C until the solid dissolved. The mixture was cooled to 0 °C and 3-fluorophenethyl alcohol (0.31 mL, 2.5 mmol) was added. The mixture was allowed to warm to rt and stir for 24 h. Water (10 mL)/ice was added to the solution and the organic products extracted into ethyl acetate (3 x 5 mL). The organic extracts were combined, washed with a saturated solution of $NaHCO_3$ (3 x 5 mL), brine (3 x 4 mL) and dried over Na_2SO_4, filtered and solvent removed *in vacuo*. Purification by column chromatography, eluting with ethyl acetate in light petroleum (0-2% step gradient) gave the product as a colourless oil (103 mg, 27%); δ_H (400 MHz; $CDCl_3$) 6.95 (1 H, dd, *J* 8.5, 5.6, Ar<u>H</u>), 6.91-6.80 (2 H, m, Ar<u>H</u>), 4.75 (2 H, s, C<u>H</u>$_2$O), 3.97 (2 H, t, *J* 5.8, $CH_2C\underline{H}_2O$), 2.87 (2 H, t, *J* 5.8, $C\underline{H}_2CH_2O$); δ_C (100 MHz; $CDCl_3$) 161.3 (C, d, *J* 243.9), 135.3 (C, d, *J* 7.3), 130.5 (C, d, *J* 3.0), 125.9 (CH, d, *J* 8.4), 115.2 (CH, d, *J* 20.7), 113.7 (CH, d, *J* 21.3), 67.8 (CH_2), 64.9 (CH_2), 28.4 (CH_2); δ_F (376 MHz; $CDCl_3$) -116.6. Data are consistent with those reported in the literature.[63]

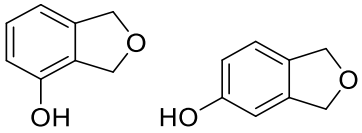
2-((Prop-2-yn-1-yloxy)methyl)furan 87



To a suspension of and sodium hydride (60% in mineral oil, 1.44 g, 35.8 mmol) in DMF (40 mL) at 0 °C was added furfuryl alcohol (2.80 mL, 32.6 mmol) dropwise over 5 min and stirred at 0 °C for 10 min. Propargyl bromide (6.60 mL, 35.8 mmol) was added and the mixture allowed to warm to rt over 4 h. Water (10 mL) was added and the mixture extracted into ethyl acetate (3 x 10 mL). The organic extracts were combined, washed with brine (3 x 5 mL), dried over Na_2SO_4,

filtered and solvent removed *in vacuo*. Purification by column chromatography, eluting with ethyl acetate in light petroleum (10%) gave the product as a clear, colourless oil (2.63 g, 59%); υ_{max} (ATR)/cm^{-1} 3291, 3119, 2907, 2856, 2116, 1607, 1502, 1442; δ_H (400 MHz; $CDCl_3$) 7.43 (1 H, dd, *J* 1.9, 0.9, Ar<u>H</u>), 6.40-6.31 (2 H, m, Ar<u>H</u>), 4.57 (2 H, s, CC<u>H_2</u>CO), 4.15 (2 H, d, *J* 2.5, COC<u>H_2</u>CCH), 2.49 (1 H, t, *J* 2.5, $COCH_2CC$<u>H</u>); δ_C (100 MHz; $CDCl_3$) 150.8 (C), 143.1 (CH), 110.3 (CH), 110.1 (CH), 79.4 (CH), 74.9 (C), 63.0 (CH_2), 56.7 (CH_2). Data are consistent with those reported in the literature.[64]

1,3-Dihydroisobenzofuran-4-ol 88 and 1,3-dihydroisobenzofuran-5-ol 89



To a solution of 2-((prop-2-yn-1-yloxy)methyl)furan **87** (2.5 g, 18 mmol) in acetone (150 mL) was added $PtCl_2$ (239 mg, 0.90 mmol) and the mixture was stirred at reflux for 17 h. Once cooled, the solvent was removed *in vacuo*. Purification by column chromatography, eluting with ethyl acetate in light petroleum (25%).

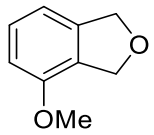
1,3-Dihydroisobenzofuran-4-ol 88 as a pale yellow solid (323 mg, 12%) followed by 1,3-dihydroisobenzofuran-5-ol **89** as a pale yellow solid (821 mg, 33%).

1,3-Dihydroisobenzofuran-4-ol 88 mp 125-127 °C (lit.,[144] mp 130-135 °C); (Found ($M-H^+$) 135.0444, $C_8H_7O_2^-$ requires 135.0452); δ_H (400 MHz; $CDCl_3$) 7.17 (1 H, app t, *J* 7.7, Ar<u>H</u>), 6.83 (1 H, d, *J* 7.5, 0.9, Ar<u>H</u>), 6.68 (1 H, dd, *J* 7.5, 0.9, Ar<u>H</u>), 5.96 (1 H, s, OH), 5.20 (2 H, d, *J* 2.3, C<u>H_2</u>O), 5.17 (2 H, d, *J* 2.3, C<u>H_2</u>O); δ_C (100 MHz; $CDCl_3$) 150.4 (C), 141.3 (C), 129.2 (CH), 125.1 (C), 113.8

(CH), 113.1 (CH), 74.1 (CH_2), 71.8 (CH_2). Data are consistent with those reported in the literature.[144]

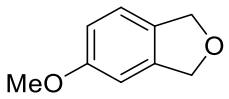
1,3-dihydroisobenzofuran-5-ol 89 mp 122-123 °C (lit.,[144] mp 120 °C); (Found ($M-H^+$) 135.0443, $C_8H_7O_2^-$ requires 135.0452**);** δ_H (400 MHz; $CDCl_3$) 7.10 (1 H, d, *J* 8.0, ArH), 6.80-6.68 (2 H, m, ArH), 5.08 (4 H, s, CH_2OCH_2), 5.06 (1 H, br s, OH); δ_C (100 MHz; $CDCl_3$) 155.3 (C), 141.0 (C), 131.1 (C), 121.8 (CH), 114.6 (CH), 107.9 (CH), 73.4 (CH_2) 73.2 (CH_2). Data are consistent with those reported in the literature.[144]

4-Methoxy-1,3-dihydroisobenzofuran 90



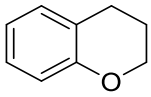
The *title compound* was synthesised according to General Procedure A using 1,3-dihydroisobenzofuran-4-ol (47 mg, 0.35 mmol), sodium hydride (60% in mineral oil, 17 mg, 0.42 mmol) and iodomethane (0.070 mL, 1.1 mmol) in THF (6 mL). The product was isolated as a pale yellow oil which did not require further purification (37 mg, 71%); υ_{max} (ATR)/cm^{-1} 3001, 2897, 2848, 2116, 1996, 1736, 1613, 1597, 1484; δ_H (400 MHz; CDCl3) 7.27 (1 H, d, *J* 7.9, ArH), 6.86 (1 H, dd, *J* 7.2 ArH), 6.77 (1 H, d, *J* 7.9, ArH), 5.10 (2 H, d, *J* 1.9, CH_2O), 5.08 (2 H, d, *J* 1.9, CH_2O), 3.86 (3 H, s, CH3); δ_C (100 MHz; $CDCl_3$) 154.2 (C), 141.1 (C), 129.2 (CH), 126.9 (C), 113.1 (CH), 108.8 (CH), 74.1 (CH_2), 72.2 (CH_2), 55.5 (CH_3). Data are consistent with those reported in the literature.[65]

5-Methoxy-1,3-dihydroisobenzofuran 91



The *title compound* was synthesised according to General Procedure A using 1,3-dihydroisobenzofuran-4-ol (77 mg, 0.60 mmol), sodium hydride (60% in mineral oil, 28 mg, 0.70 mmol) and iodomethane (0.12 mL, 1.8 mmol) in THF (6 mL). The product was isolated as a pale yellow oil which did not require further purification (70 mg, 78%); υ_{max} (ATR)/cm^{-1} 2998, 2904, 2847, 1613, 1590, 1491; δ_H (400 MHz; $CDCl_3$) 7.15 (1 H, d, *J* 8.2, Ar<u>H</u>), 6.84 (1 H, dd, *J* 8.2, 2.4, Ar<u>H</u>), 6.79 (1 H, d, *J* 2.4, Ar<u>H</u>), 5.10 (2 H, d, *J* 2.1, C<u>H</u>$_2$O), 5.08 (2 H, d, *J* 2.1, C<u>H</u>$_2$O), 3.83 (3 H, s, C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 159.5 (C), 140.8 (C), 131.0 (C), 121.6 (CH), 113.5 (CH), 106.3 (CH), 73.6 (CH_2), 73.2 (CH_2), 55.5 (CH_3). Data are consistent with those reported in the literature.[145]

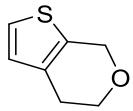
Chromane



To a suspension of zinc dust (11 g, 169 mmol) in glacial acetic acid (40 mL) was added a solution of 4-chromanone (1 g, 7 mmol) in glacial acetic acid (4 mL), and the mixture was stirred at 100 °C for 21 h. Once cooled to rt, the mixture was filtered over Celite and the Celite washed with ethyl acetate (3 x 20 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ solution (5 x 10 mL), water (3 x 10 mL) and brine (3 x 10 mL), dried over Na_2SO_4 and filtered. The solvent was removed in vacuo to give the product as a pale yellow oil which did not require further purification (655 mg, 72%); υ_{max} (ATR)/cm^{-1} 3069, 3041, 3022, 2934, 2861, 2744, 2307, 1487; δ_H (400 MHz; $CDCl_3$) 7.22-7.07 (2 H, m, Ar<u>H</u>), 6.98-6.84 (2 H, m, Ar<u>H</u>), 4.34-4.20 (2 H, m, OC<u>H</u>$_2$CH$_2$CH$_2$), 2.88 (2 H, t, *J* 6.6, OCH$_2$CH$_2$C<u>H</u>$_2$), 2.12-2.03 (2 H, m, OCH$_2$C<u>H</u>$_2$CH$_2$); δ_C (100 MHz;

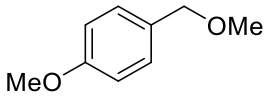
$CDCl_3$) 155.0 (C), 129.9 (CH), 127.3 (CH), 122.3 (C), 120.2 (CH), 116.8 (CH), 66.5 (CH_2), 25.0 (CH_2), 21.1 (CH_2). Data matched those reported in the literature.[146]

4,7-Dihydro-5H-thieno[2,3-c]pyran



To a solution of dimethoxymethane (0.13 mL, 1.5 mmol) in toluene (16 mL) was added thiophene-3-ethanol (0.14 mL, 1.5 mmol) followed by $Bi(OTf)_3$ (10 mg, 1 mol%) and stirred at 80 °C for 16 h. Once cooled, dichloromethane was added, and the organic solution washed with water (5 x 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography, eluting with dichloromethane (100%) gave the product as a clear, colourless oil (85 mg, 40%); (Found ($M+H^+$) 141.0380, $C_7H_9OS^+$ requires 141.0369); δ_H (400 MHz; $CDCl_3$) 7.17 (1 H, d, *J* 5.0, Ar<u>H</u>), 6.85 (1 H, d, *J* 5.0, Ar<u>H</u>), 4.86 (2 H, app t, *J* 1.7, C<u>H</u>$_2$O), 3.98 (2 H, t, *J* 5.6, $CH_2C\underline{H}_2O$), 2.78 (2 H, tt, *J* 5.6, 1.7, C<u>H</u>$_2CH_2O$); δ_C (100 MHz; $CDCl_3$) 132.8 (C), 132.7 (C), 127.1 (CH), 122.3 (CH), 65.6 (CH_2), 65.1 (CH_2), 26.2 (CH_2). Data matched those reported in the literature.[147]

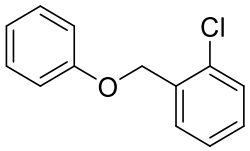
1-Methoxy-4-(methoxymethyl)benzene



The *title compound* was synthesised according to General Procedure A using 4-methoxybenzyl alcohol (2.1 g, 15 mmol), sodium hydride (60 % in mineral oil, 720 mg, 18.0 mmol) and iodomethane (2.8 mL, 45 mmol) in THF (150 mL). The title compound was isolated as a yellow oil (2.37 g, 100%) which did not require further purification; υ_{max} (ATR)/cm^{-1} 2924, 2851, 2835, 2820, 1611, 1585, 1510, 1462, 1379, 1364, 1300; δ_H (400 MHz; $CDCl_3$) 7.31-7.27 (2 H, m, Ar<u>H</u>),

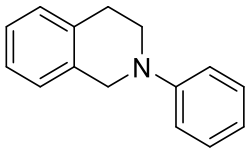
6.93-6.89 (2 H, m, Ar<u>H</u>), 4.41 (2 H, s, C<u>H</u>$_2$), 3.83 (3 H, s, C<u>H</u>$_3$), 3.39 (3 H, s, C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 159.3 (C), 130.3 (C), 129.4 (CH), 113.8 (CH), 74.3 (CH_2), 57.7 (CH_3), 55.2 (CH_3). Data recorded matches those in the literature.[148]

1-Chloro-2-(phenoxymethyl)benzene



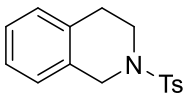
To a mixture of phenol (0.9 mL, 10 mmol), potassium carbonate (2.1 g, 15 mmol) and sodium iodide (75 mg, 0.5 mmol) was added acetone (10 mL).To the suspension was added 2-chlorobenzylchloride (0.63 mL, 5 mmol) and heated to 50 °C for 17 h. Once cooled, water (10 mL) was added and the organic products extracted with ethyl acetate (3 x 10 mL). The organic extracts were washed with brine (3 x 5 mL), dried over Na_2SO_4, filtered and solvent removed *in vacuo*. The residue purified by column chromatography, eluting with ethyl acetate and light petroleum (1:9) to give the product as a clear, colourless oil (525 mg, 48%); υ_{max} (ATR)/cm^{-1} 3179, 3064, 2916, 2849, 1597, 1586, 1572, 1541, 1493; δ_H (400 MHz; $CDCl_3$) 7.62 (1 H, dd, *J* 6.9, 2.2, Ar<u>H</u>), 7.45 (1 H, dd, *J* 7.3, 1.9, Ar<u>H</u>), 7.40-7.26 (2 H, m, Ar<u>H</u>), 7.09-7.00 (4 H, m, Ar<u>H</u>), 5.23 (2 H, s, C<u>H</u>$_2$); δ_C (100 MHz; $CDCl_3$) 158.6 (C), 134.9 (C), 132.6 (C), 129.63 (CH), 129.4 (CH), 129.0 (CH), 128.8 (CH), 127.0 (CH), 121.2 (CH), 114.9 (CH), 67.1 (CH_2). Data matched those reported in the literature.

_N_-Phenyl-1,2,3,4-tetrahydroisoquinoline 112



To a solution of $Pd_2(dba)_3$ (37.0 mg, 0.8 mmol) and (-)-BINAP (50 mg, 1.6 mmol) in THF (50 mL) was added sodium *tert*-butoxide (3.57 g, 37 mmol) followed by bromobenzene (2.14 mL, 20 mmol) and 1,2,3,4-tetrahydroisoquinoline (5.10 mL, 40 mmol). The mixture was heated under reflux for 18 h. Once cooled, the reaction mixture was filtered, and solvent was removed *in vacuo*. Purification by silica gel chromatography, eluting with ethyl acetate and light petrol (1 : 9) gave the product as a pale yellow oil which crystallised to a yellow solid (3.13 g, 74.8%); mp 39-40 °C; (Found: $M+H^+$, 210.1288. $C_{15}H_{16}N^+$ requires 210.1277); δ_H (400 MHz; $CDCl_3$) 7.35-7.28 (2 H, m, Ar<u>H</u>), 7.25-7.15 (4 H, m, Ar<u>H</u>), 7.03-6.99 (2 H, m, Ar<u>H</u>), 6.86 (1 H, tt, *J* 7.3, 7.0, 1.2, 0.9, Ar<u>H</u>) 4.44 (2 H, s, CC<u>H</u>$_2$N), 3.59 (2 H, t, *J* 5.9, CH$_2$C<u>H</u>$_2$N), 3.02 (2 H, t, *J* 5.9, C<u>H</u>$_2$CH$_2$N); δ_C (100 MHz; $CDCl_3$) 150.6 (C), 134.9 (C), 134.5 (C), 129.2 (CH), 128.5 (CH), 126.6 (CH), 126.4 (CH), 126.1 (CH), 118.7 (CH), 115.2 (CH), 50.8 (CH_2), 46.5 (CH_2), 29.2 (CH_2). Data recorded matches those in the literature.[149]

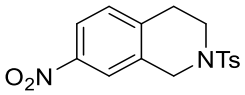
2-Tosyl-1,2,3,4-tetrahydroisoquinoline



To a solution of 1,2,3,4-tetrahydroisoquinoline (1 mL, 8 mmol) and pyridine (2 mL) in dry dichloromethane (20 mL) was added tosyl chloride (1.84 g, 9.6 mmol) in portions over 10 min. The mixture was stirred at rt for 1 h. HCl (1 N, 40 mL) was added and the mixture was extracted into ethyl acetate (4 x 10 mL). The organics extracts were combined and washed with brine (4 x 5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column

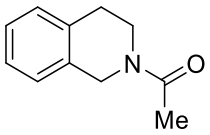
chromatography, eluting with ethyl acetate in light petroleum (10%) gave the product as a colourless solid (1.5 g, 66%); mp 142-143 °C (lit.,[76] mp 147 °C); (Found ($M+H^+$) 288.1056, $C_{16}H_{18}NO_2S^+$ requires 288.1053); δ_H (400 MHz; $CDCl_3$) 7.75 (2 H, d, *J* 8.3, ArH), 7.35 (2 H, d, *J* 8.3, ArH), 7.20-7.12 (2 H, m, ArH), 7.12-7.07 (1 H, m, ArH), 7.07-7.01 (1 H, m, ArH), 4.33 (2H, s, CCH_2N), 3.38 (2 H, t, *J* 5.9, CH_2CH_2N), 2.95 (2 H, t, *J* 5.9, CH_2CH_2N), 2.44 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 143.7 (C), 133.3 (C), 133.1 (C), 131.7 (C), 129.7 (CH), 128.8 (CH), 127.8 (CH), 126.7 (CH), 126.4 (CH), 126.3 (CH), 47.6 (CH_2), 43.8 (CH_2), 28.9 (CH_2), 21.5 (CH_3). Data recorded matched those in the literature.[76]

7-Nitro-2-tosyl-1,2,3,4-tetrahydroisoquinoline



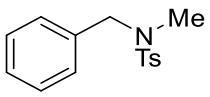
To a solution of 7-nitro-1,2,3,4-tetrahydroisoquinoline hydrochloride (132 mg, 1.00 mmol) and tosyl chloride (420 mg, 2.2 mmol) in dichloromethane (3 mL) under an atmosphere of argon, was added DIPEA (0.42 mL, 2.4 mmol) over 1 min. The mixture was stirred at rt for 2 h. Hydrochloric acid (1 N, 5 mL) was added and the solution was extracted using ethyl acetate (3 x 5 mL). The organic extracts were combined and washed with water (3 x 3 mL) and brine (3 x 3 mL) before it was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography, eluting with ethyl acetate in light petroleum (5%) gave the product as a pale yellow solid (120 mg, 36%); mp 170-173 °C; υ_{max} (ATR)/cm^{-1} 3071, 2922, 2823, 1735, 1612, 1595, 1520, 1491; (Found $M+H^+$ 333.0911, $C_{16}H_{17}N_2O_4S^+$ requires 333.0911); δ_H (400 MHz; $CDCl_3$) 8.03 (1 H, dd, *J* 8.4, 2.4, ArH), 7.97 (1 H, d, *J* 2.4, ArH), 7.76 (1 H, d, *J* 8.4, ArH), 7.37 (2 H, d, *J* 8.3, ArH), 7.28 (2 H, d, *J* 8.3, ArH), 4.34 (2 H, s, CCH_2NTs), 3.43 (2 H, t, *J* 5.9, CH_2CH_2NTs), 3.06 (2 H, t, *J* 5.9, CH_2CH_2NTs), 2.46 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 146.5 (C), 144.1 (C), 140.8 (C), 133.3 (C), 132.3 (C), 129.9 (CH), 127.7 (CH), 121.8 (CH), 121.7 (CH), 47.4 (CH_2), 43.1 (CH_2), 29.1 (CH_2), 21.6 (CH_3), One CH not observed.

1-(3,4-Dihydroisoquinolin-2(1H)-yl)ethan-1-one



To a solution of 1,2,3,4-tetrahydroisoquinoline (666 mg, 5.00 mmol) in dichloromethane (15 mL) was added triethylamine (0.84 mL, 6.0 mmol) and the mixture was cooled to 0 °C. Acetyl chloride (0.43 mL, 6.0 mmol) was added dropwise over 1 min and the reaction stirred at 0 °C for 10 min before it was stirred at rt for 2 h. The mixture was washed with water (3 x 10 mL) and dried over Na_2SO_4, filtered and solvent removed *in vacuo* to give the product as an orange oil which did not require further purification (921 mg, 100%); mp 47-49 °C (lit.,[150] mp 45-46 °C); (Found M+Na$^+$ 198.0886, $C_{11}H_{13}NNaO^+$ requires 198.0889); δ_H (400 MHz; $CDCl_3$) (two rotamers) 7.23-7.06 (8 H, m, Ar<u>H</u>), 4.70 (2 H, app. d, *J* 3.1, C<u>H</u>$_2$N), 4.69 (2 H, app. d, *J* 3.1, C<u>H</u>$_2$N), 3.82-3.77 (2 H, m, CH$_2$C<u>H</u>$_2$N), 3.68-3.62 (2 H, m, CH$_2$C<u>H</u>$_2$N), 2.88 (2 H, app. q, *J* 5.2, C<u>H</u>$_2$CH$_2$N), 2.82 (2 H, app. q, *J* 5.2, C<u>H</u>$_2$CH$_2$N), 2.16 (6 H, br s, 2 x C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) (two rotamers) 169.6 (C), 169.5 (C), 135.0 (C), 134.0 (C), 133.5 (C), 132.5 (C), 128.9 (CH), 128.3 (CH), 126.9 (CH), 126.6 (CH), 126.6 (CH), 126.5 (CH), 126.3 (CH), 126.0 (CH), 48.1 (CH_2), 44.1 (CH_2), 44.0 (CH_2), 39.5 (CH_2), 29.4 (CH_2), 28.5 (CH_2), 22.0 (CH_3), 21.7 (CH_3). Data are consistent with those reported in the literature.[75]

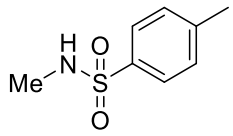
***N*-Benzyl-N,4-dimethylbenzenesulfonamide**



To a solution of *N*-benzylmethylamine (0.40 mL, 3.0 mmol) and pyridine (0.40 mL, 4.5 mmol) in THF (30 mL) at 0 °C under and atmosphere of Ar, was added tosyl chloride (858 mg, 4.50 mmol). The mixture was warmed to rt and stirred for 18 h. Saturated ammonium chloride solution (20 mL) was added and the mixture extracted into ethyl acetate (3 x 15 mL). The organic extracts

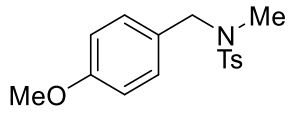
were combined and washed with water (3 x 10 mL) and brine (3 x 10 mL), dried over Na_2SO_4, filtered and solvent removed *in vacuo*. Purification by column chromatography, eluting with ethyl acetate in light petroleum (10%) gave the product as a colourless solid (340 mg, 41%); mp 92-93 °C (lit.,[80] mp 94-95 °C); δ_H (400 MHz; $CDCl_3$) 7.75 (2 H, d, *J* 8.2, Ar<u>H</u>), 7.38 (2 H, d, *J* 8.2, Ar<u>H</u>), 7.36-7.28 (5 H, m, Ar<u>H</u>), 4.15 (2 H, s, C<u>H</u>$_2$), 2.61 (3 H, s, NC<u>H</u>$_3$), 2.48 (3 H, s, C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 143.5 (C), 135.7 (C), 134.3 (C), 129.8 (CH), 128.7 (CH), 128.4 (CH), 127.9 (CH), 127.5 (CH), 54.2 (CH_2), 34.4 (CH_3), 21.6 (CH_3). Data recorded matched those in the literature.[80]

_N_,4-Dimethylbenzenesulfonamide



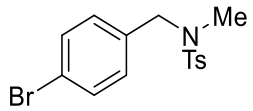
To a solution of methylamine hydrochloride (878 mg, 1.30 mmol) and tosyl chloride (953 mg, 5.00 mmol) in THF (50 mL) under an atmosphere of Ar at 0 °C, was added triethylamine (4.2 mL, 10 mmol). The mixture was allowed to warm to rt and stirred for 3 days. Water (30 mL) was added, and the mixture extracted into ethyl acetate (3 x 20 mL). The organic extracts were combined and washed with water (3 x 10 mL) and brine (3 x 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the product as a colourless solid which did not require further purification (821 mg, 87%); mp 74 °C (lit.,[151] 75-76 °C); δ_H (400 MHz; $CDCl_3$) 7.77 (2 H, app dt, *J* 8.2, 1.8, SO_2C<u>H</u>), 7.33 (2 H, d, *J* 8.2, C<u>H</u>CH_3), 2.64 (3 H, s, NC<u>H</u>$_3$), 2.44 (2 H, s, CC<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 143.5 (C), 135.8 (C), 129.7 (CH), 127.3 (CH), 29.3 (CH_3), 21.52 (CH_3). Data recorded matched those in the literature.[152]

***N*-(4-Methoxybenzyl)-N,4-dimethylbenzenesulfonamide**



To a solution of *N*,4-dimethylbenzenesulfonamide (400 mg, 1.10 mmol) and potassium carbonate (228 mg, 1.70 mmol) in acetonitrile (10 mL) was added 4-methoxybenzyl chloride (0.18 mL, 1.3 mmol) and stirred at reflux for 18 h. The mixture was cooled to rt before water (5 mL) was added and the mixture extracted with ethyl acetate (3 x 5 mL). The organic extracts were combined and washed concentrated *in vacuo* to give the product as a beige solid which did not require purification (331 mg, 99%); mp 71-73 °C ; δ_H (400 MHz; $CDCl_3$) 7.74 (2 H, ddd, *J* 8.3, 2.2, 1.7, Ar<u>H</u>), 7.37 (2 H, d, *J* 8.0, Ar<u>H</u>), 7.23 (2 H, ddd, *J* 8.8, 2.9, 2.2, Ar<u>H</u>), 6.88 (2 H, ddd, *J* 8.8, 2.9, 2.0, Ar<u>H</u>), 4.08 (2 H, s, C<u>H</u>$_2$), 3.82 (3 H, s, OC<u>H</u>$_3$), 2.58 (3 H, s, NC<u>H</u>$_3$), 2.47 (3 H, s, C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 159.3 (C), 143.4 (C), 134.4 (C), 129.7 (CH), 129.7 (CH), 127.6 (C), 127.5 (CH), 114.0 (CH), 55.3 (CH_3), 53.6 (CH_2), 34.1 (CH_3), 21.5 (CH_3). Data are consistent with those reported in the literature.[153]

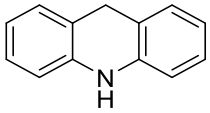
***N*-(4-Bromobenzyl)-N,4-dimethylbenzenesulfonamide**



To a solution of 4-bromo-N-benzylmethylamine (600 mg, 3.00 mmol), and pyridine (0.40 mL, 4.5 mmol) in THF (30 mL) at 0 °C under and atmosphere of Ar, was added tosyl chloride (858 mg, 4.50 mmol). The reaction was warmed to rt and stirred for 18 h. Saturated ammonium chloride solution (20 mL) was added and the mixture extracted into ethyl acetate (3 x 15 mL). The organic extracts were combined and washed with water (3 x 10 mL) and brine (3 x 10 mL) then dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography,

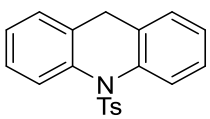
eluting with ethyl acetate in light petroleum (10%) gave the product as a colourless solid (440 mg, 41%); mp 93 °C; δ_H (400 MHz; $CDCl_3$) 7.74 (2 H, app dt, *J* 8.3, 1.9, Ar<u>H</u>), 7.48 (2 H, ddd, *J* 8.4, 2.6, 1.9, Ar<u>H</u>), 7.38 (2 H, d, *J* 8.3, Ar<u>H</u>), 7.21 (2 H, ddd, *J* 8.4, 2.6, 1.9), 4.10 (2 H, s, C<u>H</u>$_2$), 2.60 (3 H, s, NC<u>H</u>$_3$), 2.48 (3 H, s, C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 143.6 (C), 134.8 (C), 134.2 (C), 131.2 (CH), 130.0 (CH), 129.8 (CH), 127.5 (CH), 121.9 (C), 53.6 (CH_2), 34.4 (CH_3), 21.6 (CH_3). Data are consistent with those reported in the literature.[153]

9,10-Dihydroacridine



To a solution of acridone (976 mg, 5.00 mmol) in THF (10 mL) under an atmosphere of argon, was added BH_3•THF (7 mL, 7 mmol) and the mixture was stirred at reflux for 1 h. Once cooled, methanol (5 mL) was added dropwise over 5 min and the solvent was removed *in vacuo.* Purification by column chromatography, eluting with triethylamine in dichloromethane (2%) gave the product as a colourless solid (255 mg, 28%); mp 167-168 °C (lit.,[154] 169-170 °C); (Found M+H$^+$ 182.0961, $C_{13}H_{12}N^+$ requires 182.0964); δ_H (400 MHz; MeOD) 7.11-6.96 (4 H, m, Ar<u>H</u>), 6.80-6.71 (4 H, m, Ar<u>H</u>), 3.99 (2 H, s, C<u>H</u>$_2$); δ_C (100 MHz; MeOD) 140.9 (C), 127.8 (CH), 126.5 (CH), 119.5 (CH), 119.5 (C), 113.0 (CH), 30.9 (CH_2). Data matched those reported in the literature.[155]

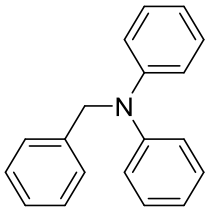
10-Tosyl-9,10-dihydroacridine



To a solution of 9,10-dihydroacridine (250 mg, 1.40 mmol) and pyridine (0.35 mL, 4.3 mmol) in dichloromethane (4 mL), under an atmosphere of argon was added tosyl chloride (324 mg, 1.70

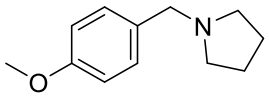
mmol) and the mixture was stirred at rt for 1 h. To the solution was added HCl (1 M, 10 mL) and the resultant solution was extracted with ether (4 x 4 mL), washed with water (3 x 3 mL) and brine (3 x 4 mL) before it was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography, eluting with ethyl acetate in light petroleum (5-10% step gradient) gave the product as a colourless solid (125 mg, 27%); mp 184-185 °C; (Found M+Na^+ 358.0872, $C_{20}H_{17}NNaO_2S^+$ requires 358.0872); δ_H (400 MHz; $CDCl_3$) 7.83 (dd, 2 H, *J* 7.9, 1.3, Ar<u>H</u>), 7.35 (2 H, td, *J* 7.9, 1.5, Ar<u>H</u>), 7.23 (2 H, td, *J* 7.6, 1.3, Ar<u>H</u>), 7.06 (4 H, s, Ar<u>H</u>), 7.04 (2 H, dd, *J* 7.6, 1.5, Ar<u>H</u>), 3.25 (1 H, d, *J* 17.9, C<u>H</u>$_a$H$_b$), 2.38 (3 H, s, CH_3), 2.31 (1 H, d, *J* 17.9, CH$_a$<u>H</u>$_b$); δ_C (100 MHz; $CDCl_3$) 144.8 (C), 144.0 (C), 137.0 (C), 134.6 (C), 129.3 (CH), 128.1 (CH), 127.4 (CH), 127.3 (CH), 127.0 (CH), 126.9 (CH), 32.1 (CH_2), 21.6 (CH_3).

***N,N*-Diphenylbenzylamine**



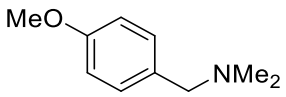
To a solution of diphenylamine (1.1 g, 5.9 mmol) in acetonitrile (20 mL), was added dropwise sodium *tert*-butoxide (680 mg, 7.00 mL) and stirred for 5 min at rt. To the mixture was added dropwise benzyl bromide (0.840 mL, 1.21 g, 7.10 mmol) and stirred at rt under an atmosphere of argon for 18 h. Solvent was removed *in vacuo.* Purification by column chromatography, eluting with ethyl acetate in light petroleum (5%) gave the product as a colourless solid (1 g, 65% yield); mp 72 °C (lit.,[156] mp 88 °C); (Found: M+H^+, 260.1431 $C_{19}H_{18}N^+$ requires 260.1434.); δ_H (400 MHz; $CDCl_3$) 7.46-7.23 (9 H, m, Ar<u>H</u>), 7.13-7.08 (4 H, m, Ar<u>H</u>), 7.00-6.95 (2 H, m, Ar<u>H</u>), 5.05 (2 H, s, C<u>H</u>$_2$); δ_C (100 MHz; $CDCl_3$) 148.1 (C), 139.2 (C), 129.4 (CH), 128.6 (CH), 126.8 (CH), 126.5 (CH), 121.4 (CH), 120.7 (CH), 56.3 (CH_2). Data recorded matches those in the literature.[156]

1-(4-Methoxybenzyl)pyrrolidine



To a solution of DIPEA (2.60 mL, 1.94 g, 15.0 mmol) and pyrrolidine (0.80 mL, 0.85 g, 10 mmol) in dichloromethane (25 mL) at 0 °C, was added dropwise 4-methoxybenzyl chloride (1.50 mL, 1.72 g, 11.0 mmol). The mixture was allowed to warm to rt and stirred for 18 h. The mixture was washed with water (3 x 10 mL) and brine (3 x 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the product as a pale yellow oil which did not require purification (775 mg, 41% yield)*;* (Found: M+H$^+$ 192.1395, $C_{12}H_{18}NO^+$ requires 192.1383, 100%); δ_H (400 MHz; $CDCl_3$); 7.30 – 7.25 (2 H, m, Ar<u>H</u>), 6.91 – 6.86 (2 H, m, Ar<u>H</u>), 3.81 (3 H, s, OC<u>H</u>$_3$), 3.59 (2 H, s, CC<u>H</u>$_2$N), 2.55 – 2.48 (4 H, m, NC<u>H</u>$_2$CH$_2$), 1.84 – 1.78 (4 H, m, NCH$_2$C<u>H</u>$_2$); δ_C (100 MHz; $CDCl_3$). 158.3 (C), 131.3 (C), 129.8 (CH), 113.3 (CH), 59.8 (CH_2), 54.9 (CH_3), 53.8 (CH_2), 23.2 (CH_2). Data recorded matches those in the literature.[157]

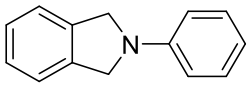
1-(4-Methoxyphenyl)-N,N-dimethylmethanamine



To a solution of 4-methoxybenzyl chloride (1.5 mL,11 mg) in dichloromethane (20 mL) and dimethylamine hydrochloride (4.4 g) in water (20 mL), was added slowly potassium hydroxide (12.3 g, 22.0 mmol) and stirred at rt for 3 h. The organic layer was separated and washed with NH_4Cl (3 x 15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the product as a colourless oil which did not require purification (869 mg, 35% yield). (Found: M+H$^+$, 166.1235. $C_{10}H_{16}NO^+$ requires 166.1226, 100%); δ_H (400 MHz; $CDCl_3$); 7.32 – 7.21 (2 H, m, Ar<u>H</u>), 6.97-6.83 (2 H, m Ar<u>H</u>), 3.83 (3 H, s, OC<u>H</u>$_3$), 3.40 (2 H, s, NC<u>H</u>$_2$), 2.27 (6 H, s, N(C<u>H</u>$_3$)$_2$); δ_C (100 MHz; $CDCl_3$)

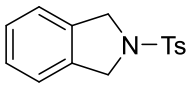
158.7 (C), 130.8 (C), 130.1 (CH), 113.5 (CH), 63.6 (CH_2), 55.05 (CH_3), 45.1 (CH_3). Data recorded matches those in the literature.[158]

_N_-Phenylisoindoline



To a solution of aniline (1.9 g, 20 mmol) and potassium carbonate (3.2 g, 23 mmol) in water (40 mL), was added 1,2-bis(bromomethyl)benzene (3.9 g, 22 mmol). The mixture was heated under reflux for 24 h. Ethyl acetate (50 mL) was added and the solid product was filtered and washed with water (3 x 15 mL) and ethyl acetate (4 x 15 mL). The colourless solid was dried under high vacuum to give the product as a colourless solid which did not require further purification (1.46 g, 37%), mp 166-168 °C (lit.,[79] 165 °C); δ_H (400 MHz; $CDCl_3$) 7.38-7.29 (6 H, m, ArH), 6.77 (1 H, m, ArH), 6.0 (2 H, dd, *J* 8.8, 1.0, ArH), 4.67 (4 H, s, CH_2NCH_2); δ_C (100 MHz; $CDCl_3$) 147.1 (C), 137.9 (C), 129.4 (CH), 127.2 (CH), 122.6 (CH), 116.3 (CH), 111.6 (CH), 53.8 (CH_2). Data matches those in the literature.[79]

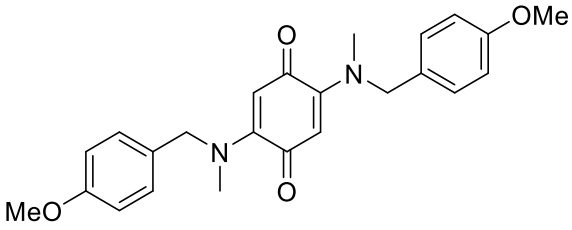
2-Tosylisoindoline



To a vigorously stirred suspension of NaH (60% in mineral oil, 585 mg, 14.5 mmol) in DMF (15 mL) under an atmosphere of Ar, was added dropwise at rt, a solution of *p*-toluenesulfonamide (2.50 g, 14.5 mmol) in DMF (9 mL). The mixture was stirred at rt for 1 h and a further 1 h at 65 °C. At 65 °C, was added a solution of α,α'-dibromo-*o*-xylene (1.5 g, 5.8 mmol) in DMF (21 mL) and continued to stir at 65 °C for 3 h. Once cooled to rt, ice and water (40 mL) was added and

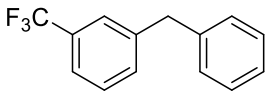
the mixture was allowed to stand for 3 days. The mixture was filtered and the solid was washed with water and dried under air to give the product which did not require further purification (1.57 g, 100%); mp 171-172 °C (lit.,[159] mp 176 °C); (Found ($M+H^+$) 274.0894, $C_{15}H_{16}NO_2S^+$ requires 274.0896); δ_H (400 MHz; $CDCl_3$) 7.77 (2 H, d, *J* 8.6, ArH), 7.31 (2 H, d, *J* 8.0, ArH), 7.25-7.20 (2 H, m, ArH), 7.20-7.14 (2 H, m, ArH), 4.68 (4 H, s, CH_2NCH_2), 2.40 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 143.7 (C), 136.1 (C), 133.8 (C), 129.8 (CH), 127.7 (CH), 127.6 (CH), 122.6 (CH), 53.7 (CH_2), 21.5 (CH_3). Data matched those in the literature.[78]

1,2-Benzoquinone adduct 126



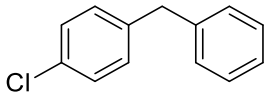
To a mixture of 1,4-benzoquinone (108 mg, 10.0 mol%) and copper(II) bromide (2.9 mg, 2.0 mol%) in DMC (12 mL) was added 4-methoxy-*N,N*-dimethylbenzylamine (165 mg, 1.00 mmol). The mixture was stirred at rt under an atmosphere of oxygen and visible light irradiation for 16 h. The solvent was removed *in vacuo*. Purification by column chromatography, eluting with ethyl acetate in light petroleum (50%) gave the product as an orange solid (12 mg, 30%); (Found: $M+H^+$, 407.1967 $C_{24}H_{27}N_2O_4^+$ requires 407.1965, 70.8%); (Found: $M+Na^+$, 429.1792 $C_{24}H_{26}N_2NaO_4^+$ requires 429.1785, 100%); υ_{maz} (ATR)/cm^{-1} 2926, 1622, 1581, 1549, 1508; δ_H (400 MHz; $CDCl_3$) 7.17 (4 H, d, *J* 7.2, ArH), 6.90–6.85 (4 H, m, ArH), 5.48 (2 H, s, CHCO), 4.90 (4 H, s, CCH_2N), 3.81 (6 H, s, OCH_3), 2.97 (6 H, s, NCH_3); δ_c (100 MHz; $CDCl_3$) 182.0 (C), 159.0 (C), 151.9 (C), 129.1 (C), 128.8 (CH), 114.1 (CH), 103.4 (CH), 56.7 (CH_2), 55.3 (CH_3), 40.0 (CH_3).

1-Benzyl-3-trifluoromethylbenzene



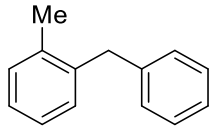
The *title compound* was synthesised according to General Procedure C using 3-trifluoromethylbenzhydrol (757 mg, 3.00 mmol), ethyl acetate:acetic acid (4.5 mL: 0.5 mL) and Pd-C (58 mg, 10 mol%). The *title compound* was isolated as a clear, colourless oil which did not require purification (71 mg, 3%); υ_{max} (ATR)/cm^{-1} 3063, 3028, 2927, 1597, 1494, 1447; δ_H (400 MHz; $CDCl_3$) 7.57-7.48 (2 H, m, Ar<u>H</u>), 7.48-7.34 (4 H, m, Ar<u>H</u>), 7.32-7.21 (3 H, m, Ar<u>H</u>), 4.09 (2 H, s, C<u>H</u>$_2$); δ_C (100 MHz; $CDCl_3$) 142.1 (C), 140.0 (C), 132.3 (CH), 130.8 (C, q, *J* 32.1), 128.9 (CH), 128.8 (CH), 128.7 (CH), 126.5 (CH), 125.6 (CH, q, *J* 3.9), 123.1 (CH, q, *J* 3.7), 120.2 (C, q, *J* 269.9), 41.7 (CH_2); δ_F (376 MHz; $CDCl_3$) -62.4. Data matches those reported in the literature.[160]

4-Chlorodiphenylmethane



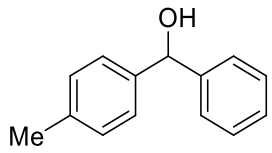
The *title compound* was synthesised according to General Procedure C using 4-chlorobenzhydrol (654 mg, 3.00 mmol) in a mixture of acetic acid:ethyl acetate (10 mL, 1:9) and Pd-C (125 mg, 10 mol%). The product was isolated as a colourless oil which did not require purification (379 mg, 62%); υ_{max} (ATR)/cm^{-1} 3083, 3061, 3025, 2913, 2842, 1661,1601, 1489, 1452, 1432; δ_H (400 MHz; $CDCl_3$) 7.41-7.16 (9 H, m, Ar<u>H</u>), 4.02 (2 H, s, C<u>H</u>$_2$); δ_C (100 MHz; $CDCl_3$) 140.7 (C), 139.7 (C), 132.0 (C), 130.4 (CH), 129.0 (CH), 128.7 (CH), 126.4 (CH), 41.4 (CH_2) one C not observed. Data matches those reported in the literature.[161]

1-Benzyl-2-methylbenzene



The *title compound* was synthesised according to a General Procedure C using 2-methylbenzhydrol (595 mg, 3.00 mmol) in a mixture of acetic acid:ethyl acetate (10 mL, 1:9) and Pd-C (125 mg, 10 mol%). The product was isolated as a colourless oil which did not require purification (300 mg, 55%); υ_{max} (ATR)/cm^{-1} 3060, 3023, 2914, 1600,1582, 1492, 1450; δ_H (400 MHz; $CDCl_3$) 7.34 (2 H, dd, *J* 8.1, 6.6, Ar<u>H</u>), 7.29-7.13 (7 H, m, Ar<u>H</u>), 4.06 (2 H, s, C<u>H</u>$_2$), 2.32 (3 H, s, C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 140.4 (C), 139.0 (C), 136.7 (C), 130.3 (CH), 130.0 (CH), 128.8 (CH), 128.4 (CH), 126.5 (CH), 126.0 (CH), 125.9 (CH), 41.4 (CH_2), 19.85 (CH_3). Data matches those reported in the literature.[162]

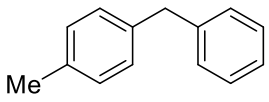
Phenyl(p-tolyl) methanol



To a solution of 4-methylbenzophenone (981 mg, 5.00 mmol) in isopropanol (14 mL) was added sodium borohydride (95 mg, 2.5 mmol) and stirred at rt for 5 days. Water (15 mL) was added and the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (10 mL) and this washed with water (3 x 5 mL) and brine (3 x 5 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the product as a colourless oil which did not require further purification (409 mg, 41%); (Found: M+Na^+, 221.0937. $C_{14}H_{14}NaO^+$ requires 221.0936); δ_H (400 MHz; $CDCl_3$) 7.43-7.33 (4 H, m, Ar<u>H</u>), 7.29 (3 H, app dt, *J* 7.0, 1.5, Ar<u>H</u>), 7.18 (2 H, d, *J* 7.9, Ar<u>H</u>), 5.84 (1 H, s, C<u>H</u>OH), 2.36 (3 H, s, C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 144.0 (C), 141.0 (C), 137.3 (C),

129.2 (CH), 128.5 (CH), 127.5 (CH), 126.5 (CH), 126.4 (CH), 76.1 (CH), 21.1 (CH_3). Data matches those reported in the literature.[163]

1-Benzyl-4-methylbenzene



The *title compound* was synthesised according to General Procedure C using phenyl(p-tolyl)methanol (396 mg, 2.00 mmol) in a mixture of acetic acid:ethyl acetate (6 mL, 1:9) and Pd-C (83 mg, 10 mol%).[164] The product was isolated as a colourless oil which did not require purification (123 mg, 34%); υ_{max} (ATR)/cm^{-1} 3060, 3023, 2914, 1600, 1582, 1492; δ_H (400 MHz; $CDCl_3$) 7.35-7.28 (2 H, m, Ar<u>H</u>), 7.26-7.20 (3 H, m, Ar<u>H</u>), 7.13 (4 H, br s, Ar<u>H</u>), 3.99 (2 H, s, C<u>H</u>$_2$), 2.36 (3 H, s, C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 141.4 (C), 138.1 (C), 135.6 (C), 129.2 (CH), 129.0 (CH), 128.8 (CH), 128.4 (CH), 126.0 (CH), 41.5 (CH_2), 21.0 (CH_3). Data matches those reported in the literature. [162]

7.3.4 Experimental Data: Benzylic Oxidation Products

7.3.5 General Procedures: Benzylic Oxidation

General procedure D

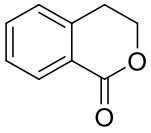
To a solution of substrate (1 mmol) and $CuCl_2 \bullet 2H_2O$ (3 mg, 2 mol%) in DMC (12 mL) was added BQH_2 (6 mg, 5 mol%). The mixture was stirred under an atmosphere of O_2 with light irradiation for 18 h. The solvent was removed *in vacuo* and the residue purified by column chromatography.

General procedure E

To a solution of arbutin-derived BQH_2 (6 mg, 5 mol%) and $CuCl_2 \bullet 2H_2O$ (3 mg, 5 mol%) in DMC (12 mL) was added the substrate (1 mmol). The mixture was stirred under an atmosphere of O_2 and visible light irradiation at rt for 18 h. The solvent was removed *in vacuo* and the residue purified by column chromatography.

7.3.6 Experimental Data: Benzylic Oxidation Products

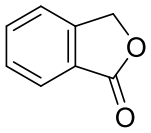
Isochromanone 76



The *title compound* was synthesised according to General Procedure D using isochroman **76** (0.13 mL, 1.0 mmol), $CuCl_2 \bullet 2H_2O$ (3 mg, 2 mol%) and BQH_2 (6 mg, 5 mol%) in DMC (12 mL). Purification by column chromatography, eluting with ethyl acetate in light petroleum (5%) gave the product as a clear, colourless oil (103 mg, 70%).

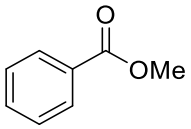
Also synthesised according to General Procedure E using isochroman **76** (0.13 mL, 1.0 mmol), $CuCl_2 \bullet 2H_2O$ (3 mg, 2 mol%) and arbutin-derived BQH_2 (6 mg, 5 mol%) in DMC (12 mL). Purification by column chromatography, eluting with ethyl acetate in light petroleum (5%) gave the product as a clear, colourless oil (107 mg, 72%); (Found: $M+Na^+$, 171.0420. $C_9H_8NaO_2^+$ requires 171.0417); (Found: $M+H^+$, 149.0597. $C_9H_9O_2^+$ requires 149.0597); δ_H (400 MHz; $CDCl_3$) 8.05 (1 H, d, *J* 7.8, Ar<u>H</u>), 7.52 (1 H, app. td, *J* 7.8, 1.4, Ar<u>H</u>), 7.39-7.34 (1, m, H, Ar<u>H</u>), 7.26 (1 H, d, *J* 7.7, Ar<u>H</u>), 4.51 (2 H, t, *J* 6.0, $CH_2C\underline{H_2}O$), 3.04 (2 H, t, *J* 6.0, $C\underline{H_2}CH_2O$); δ_C (100 MHz; $CDCl_3$) 165.0 (C), 139.4 (C), 133.5 (CH), 130.1 (CH), 127.5 (CH), 127.1 (CH), 125.1 (C), 67.2 (CH_2), 27.6 (CH_2). Data are consistent with those reported in the literature.[165]

Isobenzofuran-1(3H)-one 82



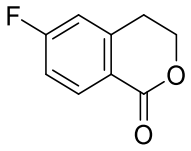
The *title compound* was synthesised according to General Procedure E using crude arbutin-derived BQH_2 (6 mg, 5 mol%), phthalan (0.10 mL, 1.0 mmol), $CuCl_2 \bullet 2H_2O$ (9.0 mg, 5.0 mol%) and DMC (12 mL). Purification by column chromatography, eluting with ethyl acetate in light petroleum (30%) gave the *title compound* as a clear, colourless oil (59 mg, 44%); υ_{max} (ATR)/cm^{-1} 2946, 1850, 1758, 1617, 1596, 1466, 1450, 1363, 1313; δ_H (400 MHz; $CDCl_3$) 7.95 (1 H, d, *J* 7.5, ArH), 7.70 (1 H, t, *J* 7.5, 1.1, ArH), 7.60-7.48 (2 H, m, ArH), 5.35 (2 H, s, CH_2O); δ_C (100 MHz; $CDCl_3$) 171.2 (C), 146.6 (C), 136.1 (C), 134.1 (CH), 129.1 (CH), 125.8 (CH), 122.1 (CH), 69.7 (CH_2); Data are consistent with those reported in the literature.[166]

Methyl benzoate 15



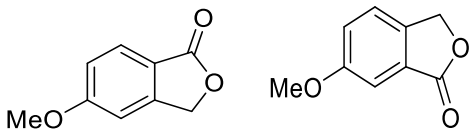
The *title compound* was synthesised according to General Procedure E using benzyl methyl ether (166 mg, 1.20 mmol), arbutin-derived BQH_2 (7 mg, 5 mol%), $CuCl_2 \bullet 2H_2O$ (4 mg, 2 mol%) in DMC (12 mL). The product was isolated as a colourless oil which did not require purification (63 mg, 38%); υ_{max} ($CHCl_3$)/cm^{-1} 3011, 2414, 2245, 1884, 1522, 1424, 1239; δ_H (400 MHz; $CDCl_3$) 8.07-8.03 (2 H, m, ArH), 7.57 (1 H, tt, *J* 7.4, 1.9, ArH), 7.47-7.40 (2 H, m, ArH), 3.93 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 167.1 (C), 132.9 (CH), 130.2 (C), 129.6 (CH), 128.3 (CH), 52.1 (CH_3). Data are consistent with those reported in the literature.[336]

6-Fluoroisochroman-1-one 93



The *title compound* was synthesised according to General Procedure D using 6-fluoroisochromane (76 mg, 0.5 mmol), BQH_2 (3 mg, 2.5 mol%) and $CuCl_2 \bullet 2H_2O$ (2 mg, 1 mol%) in DMC (6 mL). The product was purified *via* column chromatography eluting with ethyl acetate in light petroleum (10%) to give the product as a colourless oil (42 mg, 51%); υ_{max} (ATR)/cm^{-1} 3097, 3065, 2960, 2925, 1708, 1613, 1588, 1514, 1491, 1466, 1436, 1390, 1336, 1310, 1282; δ_H (300 MHz; $CDCl_3$) 8.14 (1 H, dd, *J* 8.6, 5.7, Ar<u>H</u>), 7.10 (1 H, app. td, *J* 8.6, 2.2, Ar<u>H</u>), 6.98 (1 H, dd, *J* 8.6, 2.2, Ar<u>H</u>), 4.56 (2 H, t, *J* 6.1, $CH_2C\underline{H}_2O$), 3.08 (2 H, t, *J* 6.1, $C\underline{H}_2CH_2O$); δ_C (125 MHz; $CDCl_3$) 166.8 (C), 164.5 (C, d, *J* 67.2), 142.5 (C, d, *J* 9.1), 133.5 (CH, d, *J* 10.0), 121.7 (C, d, *J* 2.7), 115.4 (CH, d, *J* 22.5), 114.1 (CH, d, *J* 22.4), 67.1 (CH_2), 28.0 (CH_2). Data are consistent with those reported in the literature.[63]

5-Methoxyisobenzofuran-1(3H)-one 94 and 6-methoxyisobenzofuran-1(3H)-one 95

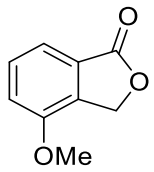


The *title compounds* were synthesised according to General Procedure D using 5-methoxy-1,3-dihydroisobenzofuran **91** (60 mg, 0.4 mmol), $CuCl_2 \bullet 2H_2O$ (1 mg, 2 mol%) and BQH_2 (2mg, 5 mol%) in DMC (5 mL). The residue was purified by column chromatography, eluting with ethyl acetate in light petroleum (25%) to give 5-methoxyisobenzofuran-1(3H)-one **94** as a colourless oil (20 mg, 30%) followed by 6-methoxyisobenzofuran-1(3H)-one **95** as a colourless oil (18 mg, 21%).

94 (Found M+Na$^+$ 187.0372, $C_9H_8NaO_3^+$ requires 187.0366); δ_H (400 MHz; $CDCl_3$) 7.82 (1H, d, *J* 8.5, Ar<u>H</u>), 7.04 (1 H, dd, *J* 8.5, 2.2, Ar<u>H</u>), 6.93 (1 H, d, *J* 2.2, Ar<u>H</u>), 5.26 (2 H, s, C<u>H</u>$_2$), 3.91 (3 H, s, C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 170.9 (C), 164.8 (C), 149.4 (C), 127.2 (CH), 118.0 (C), 116.5 (CH), 106.0 (CH), 69.1 (CH_2), 55.9 (CH_3). Data are consistent with those reported in the literature.[167]

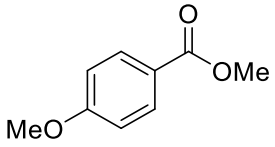
95 (Found M+Na$^+$ 187.0365, $C_9H_8NaO_3^+$ requires 187.0366); δ_H (400 MHz; $CDCl_3$) 7.40 (1 H, s, COCC<u>H</u>), 7.28 (1 H, d, *J* 5.9, Ar<u>H</u>), 7.27 (1 H, d, *J* 5.9, Ar<u>H</u>), 5.28 (2 H, s, C<u>H</u>$_2$), 3.89 (3 H, s, C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 171.2 (C), 160.3 (C), 138.9 (C), 127.1 (C), 123.1 (CH), 122.9 (CH), 107.5 (CH), 69.5 (CH_2), 55.8 (CH_3). Data are consistent with those reported in the literature.[168]

7-Methoxyisobenzofuran-1(3H)-one 96



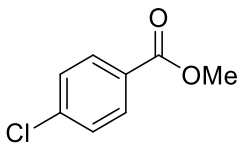
The *title compound* was synthesised according to General Procedure D using 4-Methoxy-1,3-dihydroisobenzofuran (150 mg, 1 mmol), $CuCl_2.2H_2O$ (3 mg, 2 mol%) and BQH_2 (6 mg, 5 mol%) in DMC (12 mL). Purification by column chromatography, eluting with ethyl acetate in light petroleum (25%) gave the product as a colourless solid (35 mg, 21%); mp 114-116 °C (lit.,[169] mp 117-120 °C); δ_H (400 MHz; $CDCl_3$) 7.52-7.50 (2 H, m, Ar<u>H</u>), 5.28 (2 H, s, C<u>H</u>$_2$), 3.94 (3 H, s, C<u>H</u>$_3$). δc (100 MHz; $CDCl_3$) 171.2 (C), 154.3 (C), 134.9 (C), 130.85 (CH), 127.4 (C), 117.3 (CH), 114.7 (CH), 68.1 (CH_2), 55.6 (CH_3). Data are consistent with those reported in the literature.[169]

Methyl 4-methoxybenzoate 100



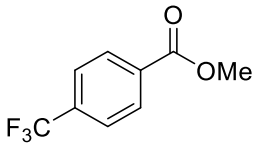
The *title compound* was synthesised according to General Procedure E using crude arbutin-derived BQH_2 (6 mg, 5 mol%), 1-methoxy-4-(methoxymethyl)benzene (152 mg, 1.00 mmol) and $CuCl_2 \bullet 2H_2O$ (9.0 mg, 5 mol%) in DMC (12 mL). Purification by column chromatography, eluting with ethyl acetate in light petroleum (5-10 % step gradient) gave the *title compound* as a clear, colourless oil (63 mg, 38%); υ_{max} (ATR)/cm^{-1} 2952, 2840, 1711, 1604, 1579, 1510, 1459, 1433, 1380, 1316; δ_H (400 MHz; $CDCl_3$) 8.03-7.99 (2 H, m, Ar<u>H</u>), 6.96-6.92 (2 H, m, Ar<u>H</u>), 3.90 (3 H, s, C<u>H</u>$_3$), 3.88 (3 H, s, C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 166.9 (C), 163.3 (C), 131.6 (CH), 122.6 (C), 114.0 (CH), 54.4 (CH_3), 51.9 (CH_3); Data are consistent with those reported in the literature.[170]

Methyl 4-chlorobenzoate 101



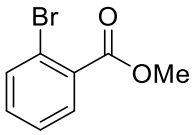
The *title compound* was synthesised according to General Procedure E using arbutin-derived BQH_2 (6 mg, 5 mol%), 1-chloro-4-(methoxymethyl) benzene (156 mg, 1.00 mmol) and $CuCl_2 \bullet 2H_2O$ (9 mg, 5 mol%) in DMC (12 mL). Purification by column chromatography, eluting with ethyl acetate in light petroleum (2-5 % step gradient) gave the product as a clear, colourless oil (65 mg, 38%); υ_{max} (ATR)/cm^{-1} 2997, 2952, 2843, 1720, 1595, 1488, 1433, 1400, 1272; δ_H (400 MHz; $CDCl_3$) 8.00-7.95 (2 H, m, Ar<u>H</u>), 7.43-7.39 (2 H, m, Ar<u>H</u>), 3.92 (3 H, s, C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 171.3 (C), 166.2 (C), 139.4 (C), 131.0 (CH), 128.7 (CH), 52.2 (CH_3). Data are consistent with those reported in the literature.[171]

Methyl 4-trifluoromethylbenzoate 102



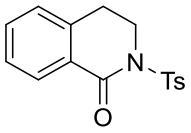
The *title compound* was synthesised according to General Procedure E using 1-(methoxymethyl)-4-(trifluoromethyl)benzene (190 mg, 1.00 mmol), arbutin-derived BQH_2 (6 mg, 5 mol%) and $CuCl_2 \bullet 2H_2O$ (3 mg, 2 mol%) in DMC (12 mL). Purification by column chromatography, eluting with ethyl acetate in light petroleum (1%) gave the product as a colourless oil (12 mg, 6%); υ_{max} (ATR)/cm^{-1} 2924, 2852, 1730, 1694, 1622, 1583, 1514, 1424, 1337; δ_H (400 MHz; $CDCl_3$); 8.01 (2 H, d, *J* 8.2, Ar<u>H</u>), 7.73 (2 H, d, *J* 8.2, Ar<u>H</u>), 3.98 (3 H, s, C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$); 165.9 (C), 134.2 (q, J 32.3, C), 133.1 (C), 129.9 (CH), 125.4 (q, *J* 3.7, CH), 123.6 (q, *J* 271.0, C), 52.5 (CH_3); Data are consistent with those reported in the literature.[172]

Methyl 2-bromobenzoate 103



The *title compound* was synthesised according to General Procedure E using 1-bromo-2-(methoxymethyl)benzene (213 mg, 1.00 mmol), arbutin-derived BQH_2 (6 mg, 5 mol%) and $CuCl_2 \bullet 2H_2O$ (3 mg, 2 mol%) in DMC (12 mL). Purification by column chromatography eluting with ethyl acetate in light petroleum (1%) gave product as a colourless oil (28 mg, 42%); υ_{max} (ATR)/cm^{-1} 3071, 2997, 2951, 2840, 1728, 1589, 1566, 1469, 1431; δ_H (400 MHz; $CDCl_3$); 7.81 (1 H, dd, *J* 7.5, 1.9, Ar<u>H</u>), 7.68 (1 H, dd, *J* 7.5,1.9, Ar<u>H</u>), 7.41-7.32 (2 H, m, Ar<u>H</u>), 3.96 (3 H, s, C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 166.6 (C), 134.3 (CH), 132.6 (CH), 132.1 (C), 131.3 (CH), 127.3 (CH), 121.6 (C), 52.2 (CH_3); Data are consistent with those reported in the literature.[173]

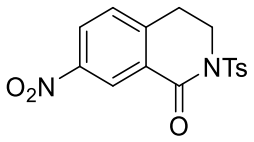
2-Tosyl-3,4-dihydroisoquinolin-1(2H)-one 114



The *title compound* was synthesised according General Procedure D using 2-tosyl-1,2,3,4-tetrahydroisoquinoline (287 mg, 1.00 mmol), BQH_2 (6 mg, 5 mol%) and $CuCl_2 \bullet 2H_2O$ (3 mg, 2 mol%) in DMC (12 mL). The residue was purified by column chromatography, eluting with ethyl acetate in light petroleum (5% – 10% step gradient) to give the products a colourless solid (71 mg, 23%).

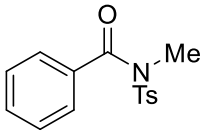
Also synthesised according to General Procedure E using arbutin-derived BQH_2 (6 mg, 5 mol%), 2-tosyl-1,2,3,4-tetrahydroisoquinoline (287 mg, 1.00 mmol) and $CuCl_2 \bullet 2H_2O$ (9.0 mg, 5.0 mol%) in DMC (12 mL). The residue was purified by column chromatography, eluting with ethyl acetate in light petroleum (5-10% step gradient) to give the product as a colourless solid (164 mg, 54%); mp 134-135 °C (lit.,[174] mp 132-133 °C); (Found ($M+H^+$) 302.0853, $C_{16}H_{16}NO_3S^+$ requires 302.0845); (Found ($M+Na^+$) 324.0663, $C_{16}H_{15}NNaO_3S^+$ requires 324.0665); δ_H (400 MHz; $CDCl_3$) 8.04-7.95 (3 H, m, Ar<u>H</u>), 7.49 (1 H, app. td, *J* 7.5, 1.4, Ar<u>H</u>), 7.35 (3 H, m, Ar<u>H</u>), 7.24 (1 H, d, *J* 7.5, Ar<u>H</u>), 4.26 (2 H, t, *J* 6.2, $CH_2C\underline{H}_2N$), 3.15 (2H, t, *J* 6.2, $C\underline{H}_2CH_2N$), 2.44 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 163.5 (C), 144.8 (C), 139.3 (C), 136.2 (C), 133.5 (CH), 129.4 (CH), 129.2 (CH), 128.6 (CH), 128.2 (C), 127.5 (CH), 127.4 (CH), 44.7 (CH_2), 29.0 (CH_2), 21.7 (CH_3). Data matched those in the literature.[174]

7-Nitro-2-tosyl-3,4-dihydroisoquinolin-1(2H)-one 115



The *title compound* was synthesised according to General Procedure D using 7-nitro-2-tosyl-1,2,3,4-tetrahydroisoquinoline (110 mg, 0.300 mmol) BQH_2 (2 mg, 5 mol%) and $CuCl_2 \bullet 2H_2O$ (1 mg, 2 mol%) in DMC (4 mL). Purification by column chromatography, eluting with ethyl acetate in light petroleum (30%) gave the product as a colourless solid (73 mg, 63%); mp 160 °C; (Found $M+Na^+$ 369.0513, $C_{16}H_{14}N_2NaO_5^+$ requires 369.0515); υ_{max} (ATR)/cm^{-1} 3116, 2924, 1693, 1614, 1593, 1520, 1473, 1431; δ_H (400 MHz; $CDCl_3$) 8.87 (1 H, d, *J* 2.4, $NO_2CC\underline{H}C$), 8.34 (1 H, dd, *J* 8.4, 2.4, $NO_2CC\underline{H}CH$), 8.02 (2 H, app. dt, *J* 8.4, 1.9, Ar$\underline{H}$), 7.46 (1 H, d, *J* 8.0, Ar$\underline{H}$), 7.38 (2 H, d, *J* 8.4, Ar$\underline{H}$), 4.30 (2 H, t, *J* 6.2, $CH_2C\underline{H}_2N$), 3.27 (2 H, t, *J* 6.2, $C\underline{H}_2CH_2N$), 2.47 (3 H, s, $C\underline{H}_3$); δ_C (00 MHz; $CDCl_3$) 161.4 (C), 147.6 (C), 145.6 (C), 145.4 (C), 135.4 (C), 129.7 (C), 129.6 (CH), 128.8 (CH), 128.7 (CH), 127.6 (CH), 124.6 (CH), 44.1 (CH_2), 29.1 (CH_2), 21.7 (CH_3).

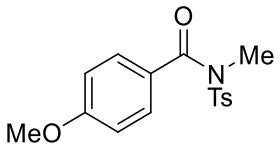
***N*-Methyl-*N*-tosylbenzamide 117**



The *title compound* was synthesised according to General Procedure D using N-benzyl-N,4-dimethylbenzenesulfonamide (275 mg, 1.00 mmol), BQH_2 (6 mg, 5 mol%) and $CuCl_2 \bullet 2H_2O$ (3 mg, 2 mol%) in DMC (4 mL). Purification by column chromatography, eluting with ethyl acetate in light petroleum (10%) gave the product as a colourless oil (46 mg, 16%); (Found ($M+H^+$) 290.0848, $C_{15}H_{16}NO_3S^+$ requires 290.0845); δ_H (400 MHz; $CDCl_3$) 7.86 (2 H, dt, *J* 8.2, 1.7, Ar$\underline{H}$), 7.58-7.49 (3 H, m, Ar$\underline{H}$), 7.43 (2 H, t, *J* 7.4, Ar$\underline{H}$), 7.35 (2 H, d, *J* 8.2, Ar$\underline{H}$), 3.30 (2 H, s, $C\underline{H}_2$), 2.46 (3 H, s, $NC\underline{H}_3$), 2.46 (3 H, s, $C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 171.5 (C), 144.9 (C), 135.2 (C), 134.5 (C),

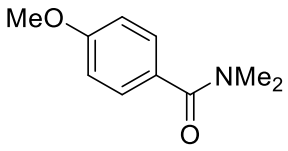
132.0 (CH), 129.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 35.6 (CH_3), 21.74 (CH_3). Data matched those in the literature.[175]

4-Methoxy-*N*-methyl-*N*-tosylbenzamide 118



The *title compound* was synthesised according to General Procedure D using N-(4-methoxybenzyl)-N,4-dimethylbenzenesulfonamide (305 mg, 1.00 mmol), BQH_2 (6 mg, 5 mol%) and $CuCl_2$•$2H_2O$ (2 mg, 2 mol%) in DMC (4 mL). Purification by column chromatography, eluting with ethyl acetate in light petroleum (20%) gave the product as a colourless solid (30 mg, 9%); mp 89-90 °C (lit.,[176] mp 39-41 °C); δ_H (400 MHz; $CDCl_3$) 7.82 (2 H, app dt, *J* 8.3, 1.8, Ar<u>H</u>), 7.62 (2 H, ddd, *J* 8.9, 2.9, 2.0, Ar<u>H</u>), 7.33 (2 H, d, *J* 8.3, Ar<u>H</u>), 6.91 (2 H, ddd, *J* 8.9, 2.9, 2.0, Ar<u>H</u>), 3.86 (3 H, s, C<u>H</u>$_3$O), 3.23 (3 H, s, NC<u>H</u>$_3$), 2.44 (3 H, s, C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 171.3 (C), 162.9 (C), 144.7 (C), 135.1 (C), 131.4 (CH), 129.6 (CH), 128.4 (CH), 126.4 (C), 113.6 (CH), 55.5 (CH_3), 35.8 (CH_3), 21.7 (CH_3). Data are consistent with those reported in the literature.[176]

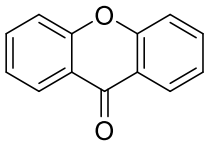
4-Methoxy-*N,N*-dimethyloxybenzamide 123



The *title compound* was synthesised according to General Procedure D using 1-(4-methoxyphenyl)-*N,N*-dimethyl methanamine (165 mg, 1 mmol), BQH_2 (6 mg, 5 mol%), $CuCl_2$•$2H_2O$ (3 mg, 2 mol%) and DMC (12 mL). Purification by column chromatography, eluting with ethyl acetate in light petroleum (20%) gave the product as a colourless pale yellow oil (35%,

63 mg); (Found: M+H$^+$, 180.1026, $C_{10}H_{14}NO_2^+$ requires 180.1019); (Found: M+Na$^+$, 202.0847 $C_{10}H_{13}NNaO_2^+$ requires 202.0838, 96.1%); δ_H (400 MHz; $CDCl_3$) 7.38-7.34 (2 H, m, ArH), 6.88-6.84 (2 H, m, ArH), 3.78 (3 H, s, OCH_3), 3.01 (6 H, s, $N(CH_3)_2$); δ_C (100 MHz; $CDCl_3$) 171.3 (C), 160.4 (C), 128.9 (CH), 128.2 (C), 113.3 (CH), 55.1 (CH_3), 36.5 (CH_3), 35.3 (CH_3). Data recorded matches those in the literature.[177]

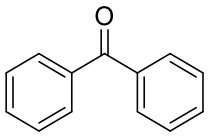
9H-Xanthen-9-one 127



The *title compound* was synthesised according to General Procedure D using xanthene (182 mg, 1.00 mmol), BQH_2 (6 mg, 5 mol%) and $CuCl_2 \bullet 2H_2O$ (6 mg, 4 mol%) in DMC (12 mL). The product was purified *via* column chromatography eluting with ethyl acetate in light petroleum (1%) to give the product as a colourless solid (65 mg, 33%).

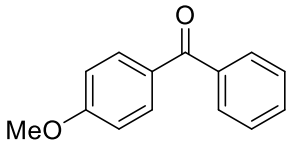
Also synthesised according to General Procedure E using arbutin derived BQH_2 (6 mg, 5 mol%), xanthene (182 mg, 1.00 mmol) and $CuCl_2 \bullet 2H_2O$ (9 mg, 5 mol%) in DMC (12 mL). Purification by column chromatography gave the product as a colourless solid (171 mg, 87%); mp 173-174 °C (lit.,[178] mp 174 °C); δ_H (300 MHz; $CDCl_3$) 8.37 (2 H, dd, *J* 8.0, 1.8, ArH), 7.76 (2 H, ddd, *J* 8.5, 7.1, 1.8, ArH), 7.53 (2 H, dd, *J* 8.5, 1.0, ArH), 7.41 (2 H, ddd, *J* 8.0, 7.1, 1.0, ArH); δ_C (75 MHz; $CDCl_3$) 177.5 (C), 156.1 (C), 134.0 (CH), 126.8 (CH), 123.9 (CH), 121.9 (C), 118.0 (CH). Data are consistent with those reported in the literature.[179]

Benzophenone 17



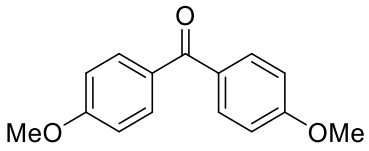
The *title compound* was synthesised according to General Procedure D using diphenylmethane (168 mg, 1.00 mmol), BQH_2 (6 mg, 5 mol%) and $CuCl_2 \bullet 2H_2O$ (3 mg, 2 mol%) in DMC (12 mL). The product was purified *via* column chromatography eluting with ethyl acetate in light petroleum (1%) to give the product as a colourless solid (60 mg, 33%); mp 47-48 °C (lit.,[180] mp 47-49 °C); δ_H (300 MHz; $CDCl_3$) 7.87-7.79 (4 H, m, Ar<u>H</u>), 7.65-7.57 (1 H, m, Ar<u>H</u>), 7.55-7.46 (4 H, m, Ar<u>H</u>); δ_C (75 MHz; $CDCl_3$) 196.7 (C), 137.6 (C), 132.4 (CH), 130.1 (CH), 128.3 (CH). Data are consistent with those reported in the literature.[181]

(4-Methoxyphenyl)(phenyl) methanone 128



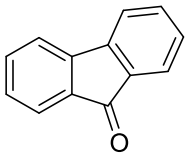
The *title compound* was synthesised according to General Procedure D using 4-methoxydiphenylmethane (198 mg, 1.00 mmol), BQH_2 (6 mg, 5 mol%) and $CuCl_2 \bullet 2H_2O$ (3 mg, 2 mol%) in DMC (12 mL). Purification by column chromatography, eluting with light petroleum (100%), gave the product as a colourless solid (74 mg, 35%); mp 60 °C (lit.,[182] mp 60-62 °C); (Found ($M+Na^+$) 235.0725, $C_{14}H_{12}NaO_2^+$ requires 235.0730); δ_H (300 MHz; $CDCl_3$) 7.85 (2 H, d, *J* 8.1, Ar<u>H</u>), 7.78 (2 H, d, *J* 8.1, Ar<u>H</u>), 7.63-7.54 (1 H, m, Ar<u>H</u>), 7.53-7.45 (2 H, m, Ar<u>H</u>), 6.99 (2 H, d, *J* 8.1, Ar<u>H</u>), 3.91 (3 H, s, OC<u>H_3</u>); δ_C (75 MHz; $CDCl_3$) 195.7 (C), 163.3 (C), 138.3 (C), 132.6 (CH), 131.9 (CH), 130.2 (C), 129.7 (CH), 128.2 (CH), 113.6 (CH), 55.5 (CH_3). Data are consistent with those reported in the literature.[183]

Bis(4-methoxyphenyl) methanone 133



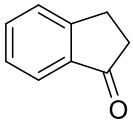
The *title compound* was synthesised according to General Procedure D using bis(4-methoxyphenyl) methane (228 mg, 1.00 mmol), BQH_2 (6 mg, 5 mol%) and $CuCl_2 \bullet 2H_2O$ (3 mg, 2 mol%) in DMC (12 mL). Purification by column chromatography, eluting with light petroleum (100%), gave the product as a colourless solid (38 mg, 16%); mp 139-140 °C (lit.,[184] mp 137-139 °C); (Found ($M+Na^+$) 265.0836, $C_{15}H_{14}NaO_3^+$ requires 265.0835); δ_H (400 MHz; $CDCl_3$) 7.81 (4 H, dt, *J* 8.9, 2.5, ArH), 6.99 (4 H, dt, *J* 8.9, 2.5, ArH), 3.90 (6 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 194.5 (C), 162.8 (C), 158.8 (CH), 132.3 (C), 130.7 (CH), 113.5 (CH_3), 55.3(CH_3). Data are consistent with those reported in the literature.[184]

9H-Fluoren-9-one 71



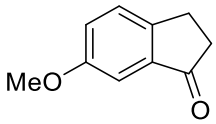
The *title compound* was synthesised according to General Procedure D using 9H-fluorene (166 mg, 1.00 mmol), BQH_2 (6 mg, 5 mol%) and $CuCl_2 \bullet 2H_2O$ (3 mg, 2 mol%) in DMC (12 mL). Purification by column chromatography, eluting with ethyl acetate in light petroleum (1%), gave the product as a yellow solid (33 mg, 19%); mp 80 °C (lit.,[185] mp 84 °C); δ_H (300 MHz; $CDCl_3$) 7.68 (2 H, app. dt, *J* 7.5, 0.9, ArH), 7.58-7.46 (4 H, m, ArH), 7.31 (2 H, app. td, *J* 7.5, 1.6, ArH); δ_C (75 MHz; $CDCl_3$) 194.0 (C), 144.3 (C), 134.6 (CH), 134.2 (C), 129.1 (CH), 124.3 (CH), 120.3 (CH). Data are consistent with those reported in the literature.[186]

2,3-Dihydro-1H-inden-1-one 135



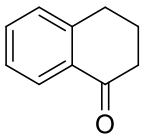
The *title compound* was synthesised according to General Procedure D using indane (118 mg, 1.0 mmol), $CuCl_2 \bullet 2H_2O$ (3 mg, 2 mol%) and BQH_2 (6 mg, 5 mol%) in DMC (12 mL). Solvent was removed *in vacuo* to give the impure product that could not be separated from impurities by column chromatography. (16% yield by ^1H NMR integration using 1,1,2,2-tetrachloroethane as an internal standard).

6-Methoxy-2,3-dihydro-1H-inden-1-one 136



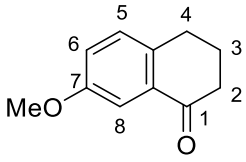
The *title compound* was synthesised according to General Procedure D using 5-methoxy-2,3-dihydro-1H-indane (148 mg, 1.0 mmol), $CuCl_2 \bullet 2H_2O$ (3 mg, 2 mol%) and BQH_2 (6 mg, 5 mol%) in DMC (12 mL). Solvent was removed *in vacuo* to give the impure product that could not be separated from impurities by column chromatography. (16% yield by ^1H NMR integration using 1,1,2,2-tetrachloroethane as an internal standard).

3,4-Dihydronaphthalen-1(2H)-one 32



The *title compound* was synthesised according to General Procedure D using tetralin (0.14 mL, 1 mmol), BQH_2 (6 mg, 5 mol%), $CuCl_2 \bullet 2H_2O$ (3 mg, 2 mol%) and DMC (12 mL). Purification by column chromatography, eluting with ethyl acetate in light petroleum (20%), gave the product as a colourless oil (30%, mg); υ_{max} (ATR)/cm^{-1} 3065, 3023, 2941, 2866, 1679, 1599, 1545, 1482; δ_H (300 MHz; $CDCl_3$) 8.06 (1 H, dd, *J* 7.8, 1.4, Ar<u>H</u>), 7.49 (1 H, td, *J* 7.4, 1.6, Ar<u>H</u>), 7.33 (1 H, tdt, *J* 7.4, 1.4, 0.7, Ar<u>H</u>), 7.29 (1 H, d, *J* 1.6, Ar<u>H</u>); δ_C (75 MHz; $CDCl_3$) 198.5 (C), 144.5 (C), 133.4 (CH), 132.6 (C), 128.8 (CH), 127.2 (CH), 126.6 (CH), 39.2 (CH_2), 29.7 (CH_2), 23.3 (CH_2). Data are consistent with those reported in the literature.[187]

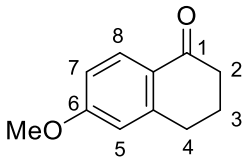
7-Methoxy-3,4-dihydronaphthalen-1(2H)-one 137



The *title compound* was synthesised according to General Procedure D using 6-methoxytetralin (0.16 mL, 1.0 mmol), $CuCl_2 \bullet 2H_2O$ (3 mg, 2 mol%) and BQH_2 (6 mg, 5 mol%) in DMC (12 mL). Purification by column chromatography, eluting with ethyl acetate in light petroleum (10%) gave the product as a pale yellow oil (7 mg, 4 %); (Found ($M+H^+$) 177.0904, $C_{11}H_{13}O_2^+$ requires 177.0910); δ_H (400 MHz; $CDCl_3$) 7.54 (1 H, d, *J* 2.8, <u>H</u>-8), 7.19 (1 H, d, *J* 8.1, <u>H</u>-5), 7.08 (1 H, dd, *J* 8.1, 2.8 <u>H</u>-6), 3.86 (3 H, s, C<u>H</u>$_3$), 2.93 (2 H, t, *J* 6.0, <u>H</u>-2), 2.66 (2 H, dd, *J* 7.1, 6.0, <u>H</u>-4), 2.14 (2 H, dd, *J* 12.5, 7.1, 6.0, <u>H</u>-3); δ_C (100 MHz; $CDCl_3$) 198.4 (C), 158.3 (C), 137.63 (C), 133.4 (C), 130.0

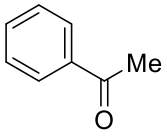
(CH), 121.8 (CH), 109.0 (CH), 55.5 (CH_3), 39.0 (CH_2), 28.9 (CH_2), 23.5 (CH_2). Data recorded matches those in the literature.[188]

6-Methoxy-3,4-dihydronaphthalen-1(2H)-one 138



The *title compound* was synthesised according to General Procedure D using 6-methoxytetralin (0.16 mL, 1.0 mmol), $CuCl_2 \bullet 2H_2O$ (3 mg, 2 mol%) and BQH_2 (6 mg, 5 mol%) in DMC (12 mL). Purification by column chromatography, eluting with ethyl acetate in light petroleum (10%) gave the product as a pale yellow solid (78 mg, 44 %); mp 70-72 °C (lit.,[189] mp 78 °C); δ_H (400 MHz; $CDCl_3$) 8.03 (1 H, d, *J* 8.7, H-5), 6.85 (1 H, dd, *J* 8.7, 2.6, H-7), 6.17 (1 H, d, *J* 2.6, H-8), 3.88 (3 H, s, CH_3), 2.95 (2 H, t, *J* 6.2, H-2), 2.63 (2 H, dd, *J* 7.2, 5.8, H-4), 2.14 (2 H, p, *J* 6.2, H-3); δ_C (100 MHz; $CDCl_3$) 197.2 (C), 163.5 (C), 147.0 (C), 129.7 (CH), 126.4 (C), 113.0 (CH), 112.6 (CH), 55.4 (CH_3), 38.9 (CH_2), 30.2 (CH_2), 23.4 (CH_2). Data recorded matches those in the literature.[189]

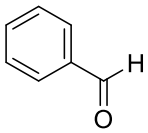
Acetophenone 15



The *title compound* was synthesised according to General Procedure D using ethylbenzene (0.11 mL, 1.0 mmol), $CuCl_2 \bullet 2H_2O$ (3 mg, 2 mol%) and BQH_2 (6 mg, 5 mol%) in DMC (12 mL). Purification by column chromatography, eluting with ethyl acetate in light petroleum (10%) gave the *title compound* as a cl ear, colourless oil (8 mg, 8%); υ_{max} (ATR)/cm^{-1} 3060.9, 3003.7, 2915.5, 1680.7, 1598.1, 1581.5, 1448.0; δ_H (400 MHz; $CDCl_3$) 8.01-7.96 (2 H, m, 2xCHCCO), 7.59 (1H, tt, *J* 7.4, 2.0,

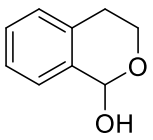
1.3, Ar<u>H</u>), 7.53-7.46 (2 H, m, Ar<u>H</u>), 2.64 (3 H, s, C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 198.2 (C), 137.1 (C), 133.1 (CH), 128.5 9CH), 18.3 (CH), 26.6 (CH_3). Data recorded matches those in the literature.[181]

Benzaldehyde 16



The *title compound* was synthesised according to General Procedure D using toluene (110 mg, 1.0 mmol), $CuCl_2 \bullet 2H_2O$ (3 mg, 2 mol%) and BQH_2 (6 mg, 5 mol%) in DMC (12 mL). Purification by column chromatography, eluting with ethyl acetate in light petroleum (8 mg, 4%); υ_{max} (ATR)/cm^{-1} 3062.6, 2817.2, 2735.5, 2694.9, 1696.9, 1652.8, 1596.0, 1583.0, 1454.6; δ_H (400 MHz; $CDCl_3$) 10.05 (1 H, s, COC<u>H</u>), 7.94-7.89 (2 H, m, Ar<u>H</u>), 7.67 (1 H, ddd, *J* 7.4, 2.1, 1.4, Ar<u>H</u>), 7.57 (2 H, app t, *J* 7.5, Ar<u>H</u>); δ_C (100 MHz; $CDCl_3$) 192.4 (C), 136.4 (C), 134.5 (CH), 129.7 (CH), 129.0 (CH). Data recorded matches those in the literature.[190]

Isochroman-1-ol 144



To a solution of isochromanone (741 mg, 5.00 mmol) in dichloromethane (10 mL) at -78 °C under an atmosphere of N_2 was added DIBAL-H (6 mL, 6 mmol) dropwise over 10 min. The mixture was stirred at -78 °C for 90 min before Rochelle's salt (1.25 M, 6 mL) was added and the mixture was allowed to warm to rt. The mixture was extracted into dichloromethane (3 x 5 mL). The organic extracts combined and washed with a saturated solution of ammonium chloride (3 x 10 mL) and brine (3 x 5 mL), dried over Na_2SO_4, filtered and solvent removed *in vacuo*. Purification by

column chromatography, eluting with methanol in dichloromethane (3-5% step gradient) gave the product as a colourless solid (208 mg, 28%); mp 76 °C (lit.,[191] 73-75 °C); δ_H (400 MHz; $CDCl_3$) 7.37-7.34 (1 H, m, Ar), 7.30-7.26 (3 H, m, Ar), 6.00 (1 H, s, C<u>H</u>OH), 4.25 (1 H, ddd, *J* 11.4, 3.5, 0.4, C<u>H</u>$_a$H$_b$CH$_2$O), 3.98 (1 H, ddd, *J* 11.4, 5.7, 2.6, CH$_2$C<u>H</u>$_a$CH$_b$O), 3.02 (1 H, ddd, *J* 16.6, 11.1, 5.7, CH$_a$<u>H</u>$_b$CH$_2$O), 2.71 (1 H, app dt, *J* 16.6, 3.1, CH$_2$CH$_a$C<u>H</u>$_b$O); δ_C (100 MHz; $CDCl_3$) 134.9 (C), 133.8 (C), 128.5 (CH), 128.3 (CH), 127.4 (CH), 126.4 (CH), 92.8 (CH), 58.4 (CH_2), 28.07 (CH_2). Data recorded matches those in the literature.[191]

7.4 Alkane Oxidation

Note: Trifluoroacetates could not be characterised by mass spectrometry by ESI/EI nor CI methods.

7.4.1 General Procedures

General Procedure F

To a solution of alcohol (1 equiv.) was added TFA and stirred at rt for 18 h. A saturated solution of sodium hydrogen carbonate was added and extracted into dichloromethane.

General Procedure G

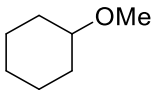
To a solution of alkane (1 mmol) in chloroform (1 mL) was added hydrogen peroxide (30% aqueous solution, 0.36 mL) and TFA (2 mL). The mixture was stirred at reflux for 18 h. Once cooled, the mixture was neutralised with a saturated solution of sodium hydrogen carbonate and extracted into dichloromethane.

General Procedure H

To a solution of alkane (1 mmol) in chloroform (1 mL) was added hydrogen peroxide (30% aqueous solution, 0.36 mL) and TFA (2 mL). The mixture was stirred at reflux for 18 h. Once cooled to rt, potassium carbonate (solid, 2 g) and methanol (5 mL) were added and the mixture was stirred at rt for 30 min. The mixture was extracted into dichloromethane. The organic extracts were combined, washed with water, brine and dried over Na_2SO_4, filtered and solvent removed *in vacuo* to give the product.

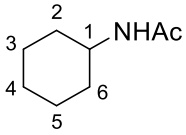
7.4.2 Experimental Data: Hydrocarbon Starting Materials

Cyclohexyl methyl ether



To a solution of NaH (60% in mineral oil, 710 mg) in THF (30 mL) was added cyclohexanol (1 mL, 10 mmol) and stirred at rt for 1 h. Iodomethane (1.3 mL, 20 mmol) was added and the mixture was left to stir for a further 16 h. A saturated solution of ammonium chloride (40 mL) was added and the mixture extracted into dichloromethane (3 x 15 mL). The organic extracts were combined and washed with water (3 x 10 mL) and brine (3 x 10 mL), and dried over Na_2SO_4, filtered and solvent removed *in vacuo* to give the product as a colourless oil (205 mg, 18 %); υ_{max} (ATR)/cm^{-1} 2928, 2855, 2819, 1450; δ_H (400 MHz; $CDCl_3$) 3.35 (3 H, s, C<u>H</u>$_3$), 3.15 (1 H, m, <u>H</u>-1), 3.20-3.09 (2 H, app m, <u>H</u>-2/6), 1.79-1.67 (2 H, m, <u>H</u>-3/5), 1.59- 1.49 (1 H, m, <u>H</u>-2), 1.33-1.17 (5 H, m, <u>H</u>-3/5/6 + <u>H</u>$_2$-4); δ_C (100 MHz; $CDCl_3$) . Data recorded matches those in the literature.[192]

***N*-cyclohexylacetamide**

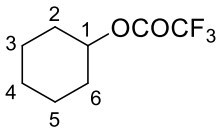


To a solution of cyclohexylamine (0.58 mL, 5.0 mmol) in dichloromethane (10 mL) was added acetic anhydride (0.52 mL, 5.5 mmol) and triethylamine (0.84 mL, 6.0 mmol) and stirred at rt for 24 h. A saturated solution of ammonium chloride (20 mL) was added and the mixture was extracted into dichloromethane (3 x 15 mL). The organic extracts were combined and washed with water (3 x 10 mL) and brine (3 x 10 mL) before being dried over Na_2SO_4, filtered and solvent removed *in vacuo* to give the product as a colourless solid which did not require purification (498 mg, 71%); mp 104 °C (lit.,[193] 103 °C); δ_H (500 MHz; $CDCl_3$) 5.31 (1 H, br s, N<u>H</u>), 3.78 (1 H, tdt,

J 10.8, 8.1, 4.0, H-1), 1.98 (3H, s, CH_3), 1.97-1.91 (2 H, m, H-2), 1.72 (2 H, dt, *J* 14.1, 3.9, H-3), 1.67-1.60 (1 H, m, H-4), 1.39 (2 H, dtt, *J* 13.3, 12.0, 3.6, H-5), 1.23-1.06 (3 H, m, H-4/6); δ_C (125 MHz; $CDCl_3$) 169.0 (C), 48.2 (CH), 33.3 (CH_2), 25.5 (CH_2), 24.8 (CH_2), 23.7 (CH_3). Data recorded matches those in the literature.[194]

7.4.3 Experimental Data: Hydrocarbon Oxidation Products

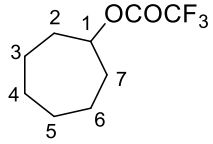
Cyclohexyl 2,2,2-trifluoroacetate 178



The title compound was synthesised according to General Procedure G using cyclohexane (84 mg, 1.0 mmol) in chloroform (1 mL) with hydrogen peroxide (30% aqueous solution, 0.36 mL) and TFA (2 mL). The yield of the product (64%) was obtained by quantitative GC using 1,1,2,2-tetrachloroethane as an internal standard.

An authentic sample of the *title compound* was synthesised according to General Procedure F using cyclohexanol (1.68 g, 20 mmol) and TFA (10 mL). The product was isolated as a colourless oil which did not require further purification (2.84 g, 79%); υ_{max} (ATR)/cm^{-1} 2942, 2865, 1775, 1453, 1390; δ_H (400 MHz; $CDCl_3$) 5.00 (1 H, tt, *J* 8.7, 3.9, H-1), 2.00-1.87 (2 H, m, 2 x H_{eq}-2/6), 1.85-1.72 (2 H, m, 2 x H_{eq}-3/5), 1.67-1.52 (3 H, m, 2 x H_{ax}-2/6 + H-4), 1.50-1.27 (3 H, m, 2 x H_{ax}-3/5 + H-4); δ_C (100 MHz; $CDCl_3$) 157.0 (C, q, *J* 41.7), 114.6 (C, q, *J* 286.3), 77.5 (CH), 31.0 (CH_2), 25.0 (CH_2), 23.3 (CH_2); δ_F (376 MHz; $CDCl_3$) -75.4. Data recorded matches those in the literature.[143]

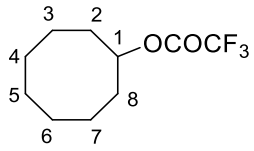
Cycloheptyl 2,2,2-trifluoroacetate 221



The title compound was synthesised according to General Procedure G using cycloheptane (98 mg, 1.0 mmol) in chloroform (1 mL) with hydrogen peroxide (30% aqueous solution, 0.36 mL) and TFA (2 mL). The yield of the product (63%) was obtained by quantitative GC using 1,1,2,2-tetrachloroethane as an internal standard.

An authentic sample of the *title compound* was synthesised according to General Procedure F using cycloheptanol (1.15 g, 10.0 mmol) and TFA (5 mL). The product was isolated as a colourless oil which did not require further purification (1.4 g, 67%); υ_{max} (ATR)/cm^{-1} 2931, 2863, 1776, 1461, 1391; δ_H (400 MHz; $CDCl_3$) 5.15 (1 H, tt, *J* 8.4, 4.5, H-1), 2.00 (2 H, dddd, *J* 13.2, 7.8, 4.4, 2.9, H_a-2/7), 1.81 (2 H, dddd, *J* 14.2, 9.4, 8.2, 2.9, H_b-2/7), 1.77-1.66 (2 H, m, H_a-3/6), 1.61 (4 H, dt, *J* 5.7, 3.1, H_2-4/5), 1.55-1.45 (2 H, m, H_b-3/6); δ_C (100 MHz; $CDCl_3$) 156.9 (C, q, *J* 41.7), 114.6 (C, q, *J* 285.4), 80.2 (CH), 33.2 (CH_2), 28.1 (CH_2), 22.5 (CH_2).

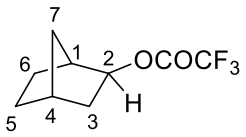
Cyclooctyl 2,2,2-trifluoroacetate 219



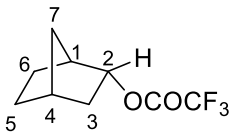
The title compound was synthesised according to General Procedure G using cyclooctane (112 mg, 1.00 mmol) in chloroform (1 mL) with hydrogen peroxide (30% aqueous solution, 0.36 mL) and TFA (2 mL). The yield of the product (5%) was obtained by quantitative GC using 1,1,2,2-tetrachloroethane as an internal standard.

An authentic sample of the *title compound* was synthesised according to General Procedure F using cyclooctanol (641 mg, 5.00 mmol) and TFA (2.5 mL). The product was furnished as a colourless oil which did not require further purification (697 mg, 64%); υ_{max} (ATR)/cm^{-1} 2629.5, 2860.4, 1776.5, 1472.0, 1449.8; δ_H (400 MHz; $CDCl_3$) 5.16 (1 H, app td, *J* 7.5, 3.9, H-1), 1.97-1.82 (4 H, m, H-2/8), 1.82-1.69 (2 H, m, CH_2), 1.69-1.45 (8 H, m, 4 x CH_2); δ_C (100 MHz; $CDCl_3$) 156.96 (C, q, *J* 41.9), 113.2 (C, q, *J* 287.0), 80.5 (CH), 30.9 (CH_2), 26.9 (CH_2), 25.2 (CH_2), 22.6 (CH_2); δ_F (376 MHz; $CDCl_3$) -75.5.

exo-Bicyclo[2.2.1]heptan-2-yl trifluoroacetate 220 and _endo_-Bicyclo[2.2.1]heptan-2-yl 2,2,2-trifluoroacetate 232



220



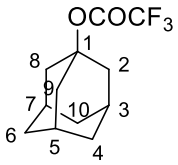
232

The title compound **220** synthesised according to General Procedure G using norbornane (96 mg, 1.0 mmol) in chloroform (1 mL) with hydrogen peroxide (30% aqueous solution, 0.36 mL) and TFA (2 mL). The yield of the *exo*-product **220** (44%) was obtained by quantitative GC using 1,1,2,2-tetrachloroethane as an internal standard. *endo*-Product **232** was not detected.

An authentic sample of the *title compound* **220** was synthesised according to General Procedure F using *exo*-norborneol (1.12 g, 10.0 mmol) and TFA (5 mL). The product was isolated as a colourless oil which did not require purification (787 mg, 38%); υ_{max} (ATR)/cm^{-1} 2966, 2879, 1776, 1456, 1441, 1389, 1347; δ_H (400 MHz; $CDCl_3$) 4.84 (1 H, app d, *J* 7.1, H-2) 2.44 (1 H, d, *J* 4.8, H-1), 2.38 (1 H, t, *J* 4.0, H-4), 1.83 (1 H, ddd, *J* 13.9, 7.1, 2.6, H-3), 1.67-1.45 (4 H, m, 4 x CHH), 1.26 (1 H, ddq, *J* 10.2, 2.9, 1.5, CHH), 1.22-1.10 (2 H, m, 2 x CHH) ; δ_C (100 MHz; $CDCl_3$) 157.0 (C, q, *J* 41.7), 114.5 (C, q, *J* 286.1), 82.0 (CH), 41.3 (CH), 39.0 (CH_2), 35.3 (CH_2), 35.1 (CH_2), 27.8 (CH_2), 23.8 (CH_2); δ_F (376 MHz; $CDCl_3$) -75.5.

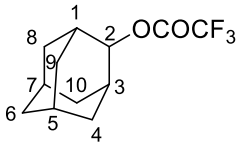
An authentic sample of the *title compound* ***232*** was synthesised according to General Procedure F and G using *endo*-norborneol (224 mg, 2.00 mmol) and TFA (1 mL). The product was isolated as a colourless oil which did not require purification (172 mg, 41%); υ_{max} (ATR)/cm^{-1} 2967, 2879, 1778, 1556, 1456, 1389; δ_H (400 MHz; $CDCl_3$) 5.22-5.13 (1 H, m, H-2), 2.62 (1 H, t, *J* 4.4, H-1), 2.31 (1 H, t, *J* 4.7, H-4), 2.15-2.04 (1 H, m, H-3), 1.82-1.72 (1 H, dddd, *J* 12.5, 8.7, 4.5, 2.2, CHH), 1.71-1.59 (1 H, m, CHH), 1.51-1.32 (4 H, m, 2 x CHH + CH_2), 1.15 (1 H, dt, *J* 13.6, 3.4, CHH); δ_C (100 MHz; $CDCl_3$) 157.5 (C, q, *J* 42.0), 114.6 (C, q, *J* 285.5), 80.2 (CH), 40.1 (CH), 37.3 (CH_2), 36.5 (CH_2), 36.3 (CH), 28.9 (CH_2), 20.6 (CH_2); δ_F (376 MHz; $CDCl_3$) -75.4.

(3s,5s,7s)-Adamantan-1-yl trifluoroacetate 215



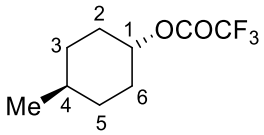
An authentic sample of the *title compound* was synthesised according to General Procedure F using 1-adamantanol (761 mg, 5.00 mmol) and TFA (2.5 mL). The product was isolated as a colourless oil which did not require purification (310 mg, 25%); υ_{max} (ATR)/cm^{-1} 2915, 2857, 1772, 1457, 1370; δ_H (400 MHz; $CDCl_3$) 2.26 (3 H, br s, H-7/3/5), 2.20 (6 H, d, *J* 3.1, H_2-2/8/9), 1.71 (6 H, t, *J* 3.1, CH_2-4/6/10); δ_c (100 MHz; $CDCl_3$) 155.8 (C, q, *J* 4.09), 114.3 (C, q, *J* 287.2), 86.8 (C), 40.8 (CH_2), 35.8 (CH_2), 31.0 (CH); δ_F (376 MHz; $CDCl_3$) -75.9. Data recorded matches those in the literature.[195]

(1r,3r,5r,7r)-Adamantan-2-yl trifluoroacetate 233



An authentic sample of the *title compound* was synthesised according to General Procedure F using 2-adamantanol (761 mg, 5.00 mmol) and TFA (2.5 mL). The product was isolated as a colourless oil which did not require purification (1.0 g, 83%); υ_{max} (ATR)/cm^{-1} 2910, 2859, 1776, 1453, 1394; δ_H (400 MHz; $CDCl_3$) 5.16 (1 H, s, H-2), 2.13 (2 H, br s, H-1/3), 2.05 (2 H, d, *J* 12.8, 2 x CHH), 1.98-1.87 (4 H, m, 2 x CHH + 2CH), 1.85-1.77 (4 H, m, CH_2 + 2CHH), 1.64 (2 H, d, *J* 12.8, 2 x CHH); δ_C (100 MHz; $CDCl_3$) 156.8 (C, q, *J* 41.5), 114.7 (C, q, *J* 286.2), 82.1 (CH), 37.0 (CH_2), 36.1 (CH_2), 31.5 (CH), 31.4 (CH_2), 26.9 (CH), 26.7 (CH); δ_F (376 MHz; $CDCl_3$) -75.5. Data recorded matches those in the literature.[196]

***trans*-4-Methylcyclohexyl trifluoroacetate 248**

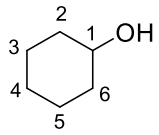


The title compound was synthesised according to General Procedure G using methylcyclohexane (98 mg, 1.0 mmol) in chloroform (1 mL) with hydrogen peroxide (30% aqueous solution, 0.36 mL) and TFA (2 mL). The yield of the *exo*-product **220** (44%) was obtained by quantitative GC using 1,1,2,2-tetrachloroethane as an internal standard. *endo*-Product **232** was not detected.

An authentic sample of the *title compound* was synthesised according to General Procedure F using *trans*-2-tertbutylcyclohexanol (1.56 g, 14 mmol) and TFA (5 mL). The product was isolated as a colourless oil which did not require further purification (1.55 g, 53%); υ_{max} (ATR)/cm^{-1} 2951,

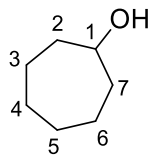
2871, 1776, 1455, 1390; δ_H (400 MHz; $CDCl_3$) 4.88 (1 H, tt, *J* 11.2, 4.4, 3.8, H-1), 2.12-2.00 (2 H, m, H_a-2/6), 1.86-1.75 (2 H, m, H_a-3/5), 1.51 (2 H, dddd, *J* 12.8, 12.0, 11.2, 3.8, H_b-2/6), 1.46-1.35 (1 H, m, H-4), 1.08 (2 H, tdd, *J* 13.6, 12.8, 3.3, H_b-3/5), 0.93 (3 H, d, *J* 6.6, CH_3); δ_C (100 MHz; $CDCl_3$) 157.0 (C, q, *J* 42.0), 114.6 (C, q, *J* 286.1), 78.4 (CH), 32.6 (CH_2), 31.3 (CH), 30.9 (CH_2), 21.5 (CH_3); δ_F (376 MHz; $CDCl_3$) -75.6.

Cyclohexanol 159



The *title compound* was synthesised according to General Procedure H using cyclohexane (0.11 mL, 1 mmol), H_2O_2 (30% aqueous, 0.36 mL, 3 mmol), TFA (2 mL) and $CHCl_3$ (1 mL). The product was isolated as a colourless oil which did not require further purification (61 mg, 61%); υ_{max} (ATR)/cm^{-1} 3314, 2927, 2853, 1449; δ_H (400 MHz; $CDCl_3$) 3.66-3.58 (1 H, m, H-1), 1.97-1.84 (3 H, m, H-2/OH), 1.82-1.63 (2 H, m, H-6), 1.60-1.49 (1 H, m, H-4), 1.36-1.23 (4 H, m, H-3/5), 1.23-1.11 (1 H, m, H-4); δ_C (100 MHz; $CDCl_3$) 70.3 (CH), 35.5(CH_2), 25.4 (CH_2), 24.2(CH_2). Data recorded matches those in the literature.[197]

Cycloheptanol 238



The *title compound* was synthesised according to General Procedure H using cycloheptane (0.12 mL, 1 mmol), H_2O_2 (30% aqueous, 0.36 mL, 3 mmol), TFA (2 mL) and $CHCl_3$ (1 mL). The product was isolated as a colourless oil which did not require further purification (86 mg, 76%); υ_{max} (ATR)/cm^{-1} 3331, 2921, 2854, 1458; δ_H (400 MHz; $CDCl_3$) 3.86 (1 H, tt, *J* 8.4, 4.3, H-1), 1.98-1.85

(2 H, m, H-2), 1.72-1.60 (3 H, m, H-4/OH), 1.60-1.51 (6 H, m, H-3/6/7), 1.47-1.36 (2 H, m, H-5); δ_C (100 MHz; $CDCl_3$) 72.8 (CH), 37.6 (CH_2), 28.1 (CH_2), 22.6(CH_2). Data recorded matches those in the literature.[198]

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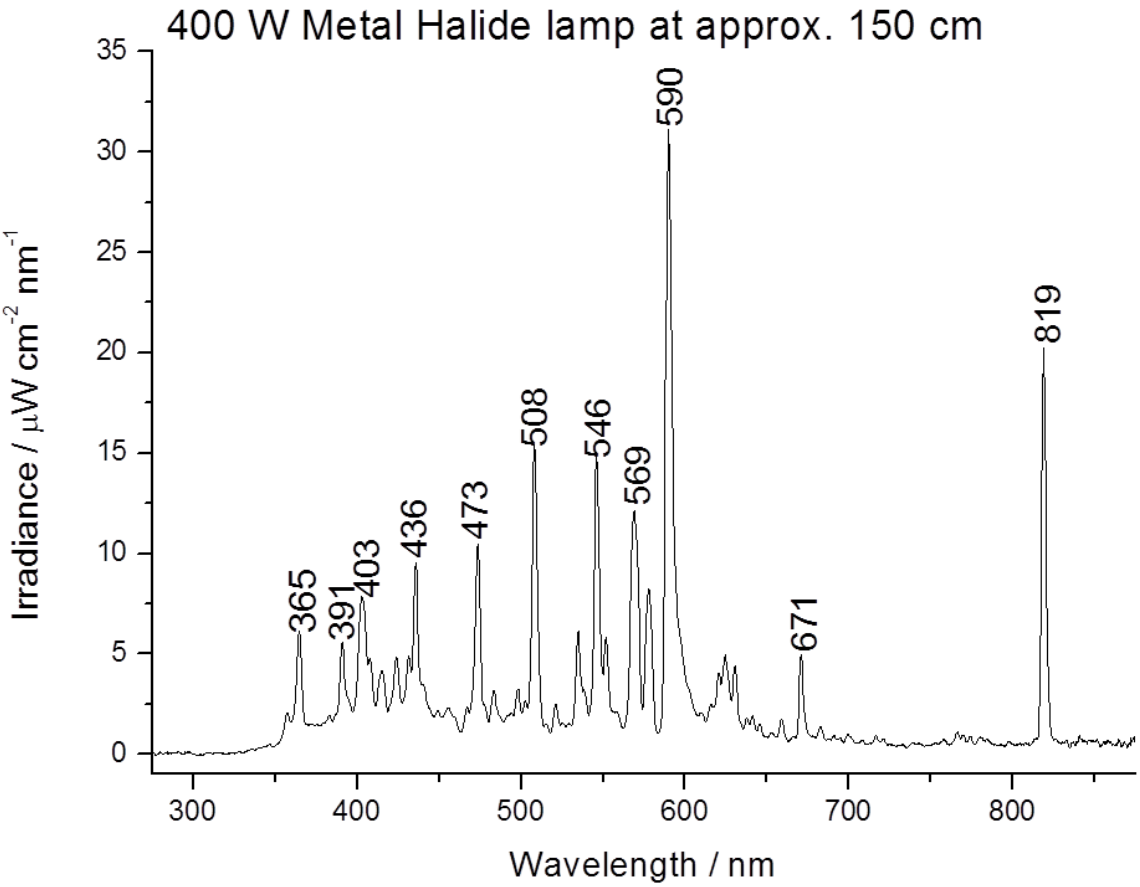
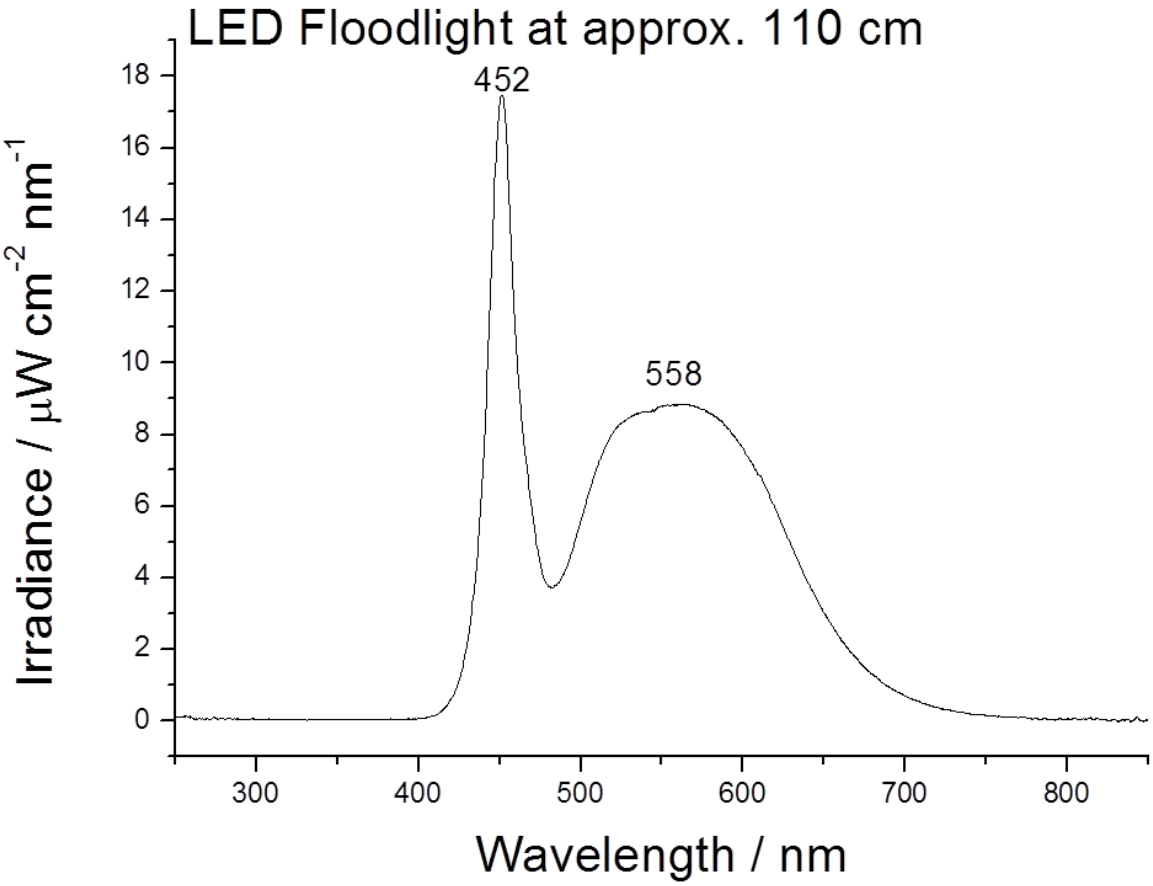
Appendix

Lamp Emission Spectra

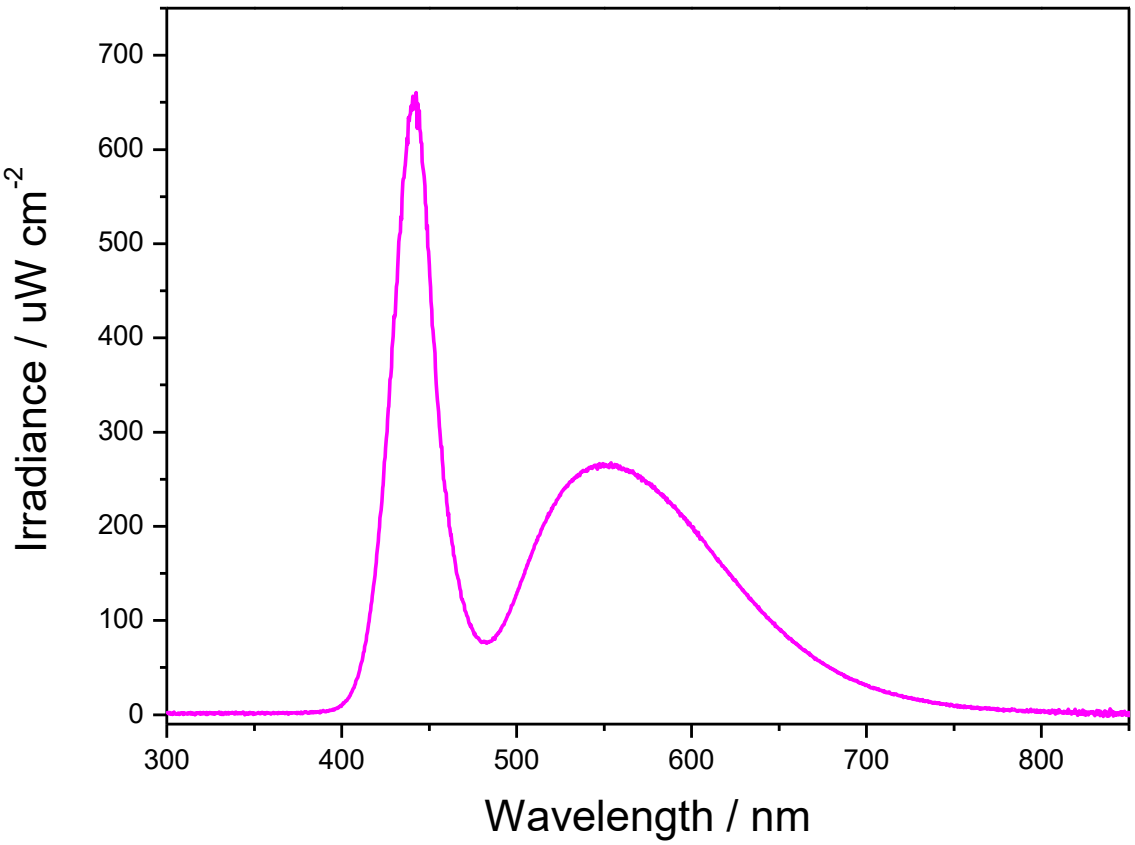
Emission spectrum of 400 W metal halide lamp.



Emission spectrum of Minisun 20639 200W LED Pro2 Daylight Floodlight



Emission spectrum of 5 x Citizen CL-L233-C13N1-C LED chips (output: 1000 lumen) mounted on an in-house built aluminium block.

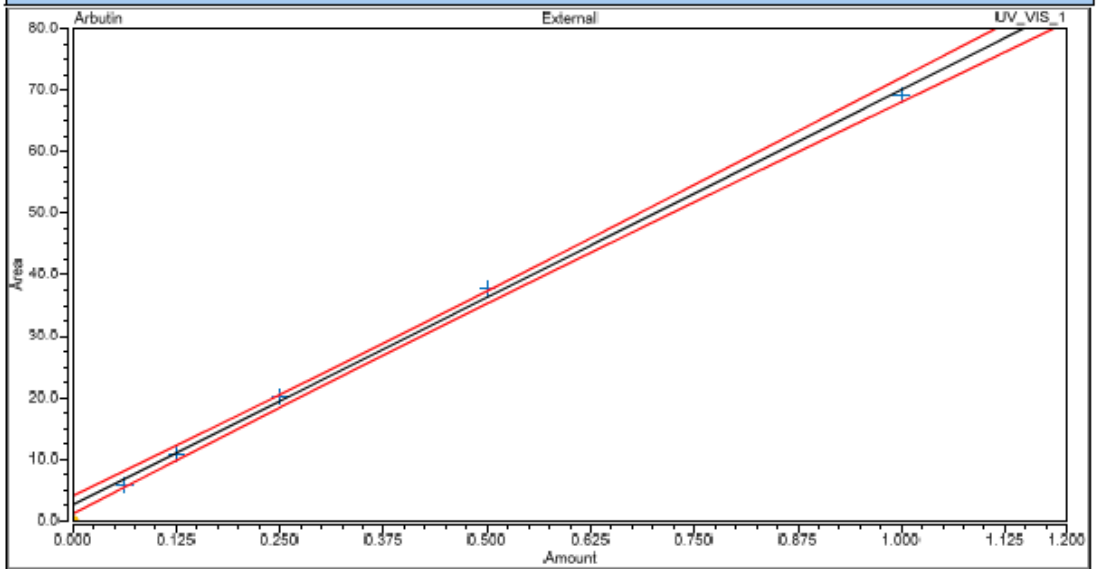


Arbutin LCMS Data

Arbutin calibration curve

Calibration			
Calibration Details	**n.a.**		
Calibration Type	Lin, WithOffset	*Offset (C0)*	n.a.
Evaluation Type	Area	*Slope (C1)*	n.a.
Number of Calibration Points	n.a.	*Curve (C2)*	n.a.
Number of disabled Calibration Points	n.a.	*R-Square*	n.a.

Calibration Plot **n.a.**

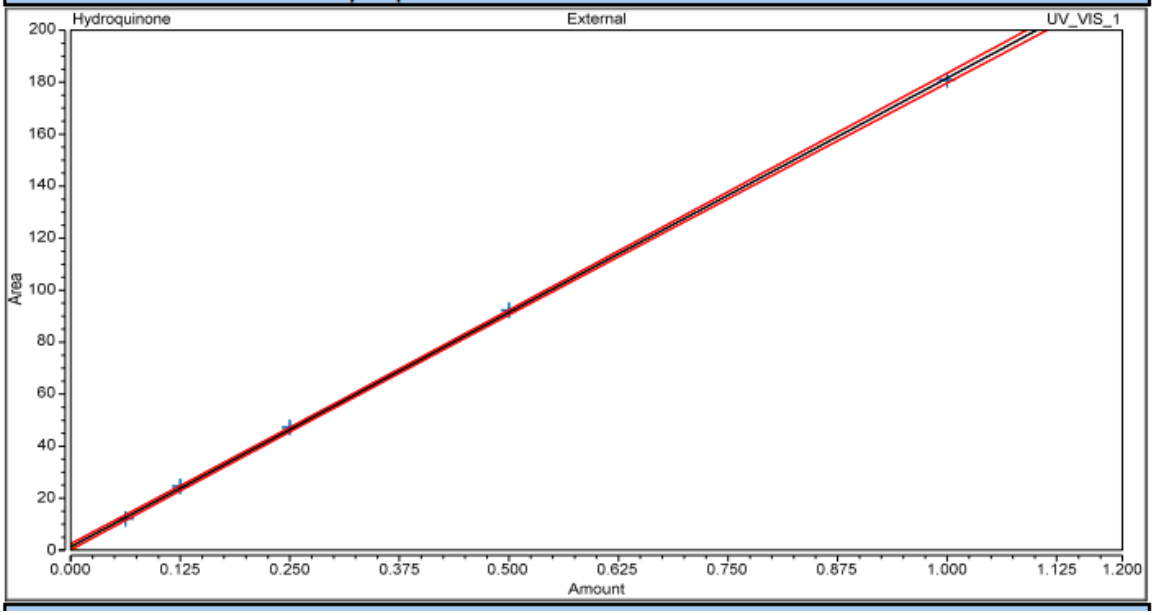


Hydroquinone Calibration Curve

Calibration

Calibration Details	Hydroquinone		
Calibration Type	Lin, WithOffset	*Offset (C0)*	1.2959
Evaluation Type	Area	*Slope (C1)*	180.2869
Number of Calibration Points	12	*Curve (C2)*	0.0000
Number of disabled Calibration Points	0	*R-Square*	0.9998

Calibration Plot **Hydroquinone**



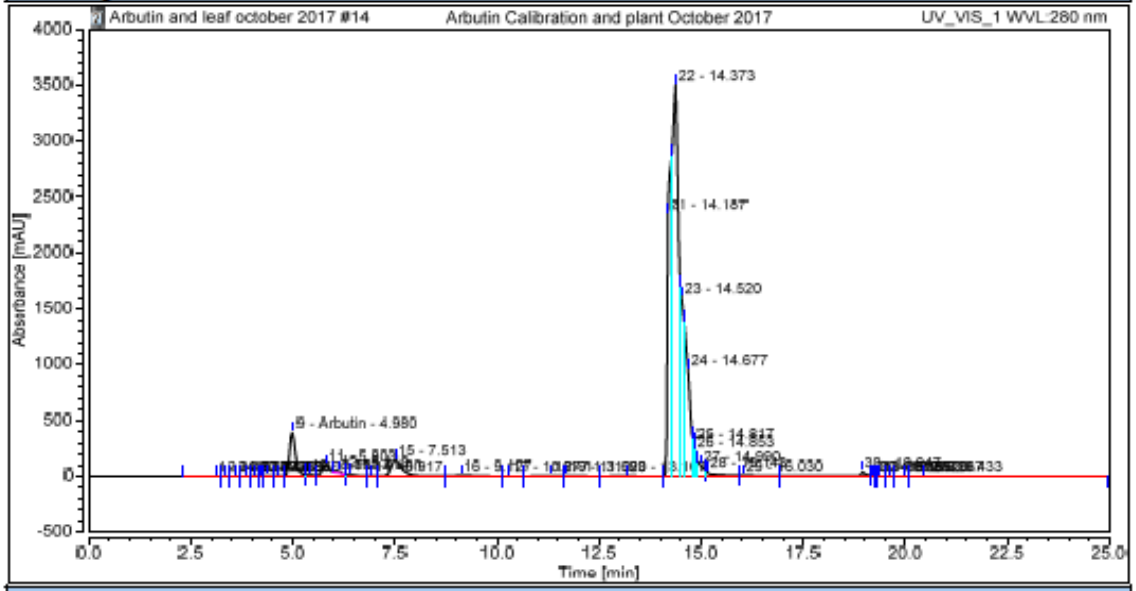
Quantitative HPLC of Arbutin in Bearberry leaves

Chromatogram and Results

Injection Details

Injection Name:	**Arbutin Calibration and plant October 2017**	*Run Time (min):*	**25.00**
Vial Number:	**RD7**	*Injection Volume:*	**10.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_1**
Calibration Level:		*Wavelength:*	**280**
Instrument Method:	**Sample Method**	*Bandwidth:*	**2**
Processing Method:	**Arbutin in leaves Octover 2017**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**17/Oct/17 19:06**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		3.107	0.297	0.900	0.02	0.01	n.a.
2		3.323	0.281	1.506	0.02	0.02	n.a.
3		3.577	0.439	1.792	0.03	0.02	n.a.
4		3.833	0.444	1.938	0.03	0.02	n.a.
5		4.087	0.572	3.624	0.04	0.04	n.a.
6		4.230	0.528	4.105	0.04	0.04	n.a.
7		4.380	0.949	4.963	0.06	0.05	n.a.
8		4.650	0.844	3.409	0.06	0.03	n.a.
9	Arbutin	4.980	68.058	392.953	4.60	3.99	0.9704
10		5.383	3.095	14.489	0.21	0.15	n.a.

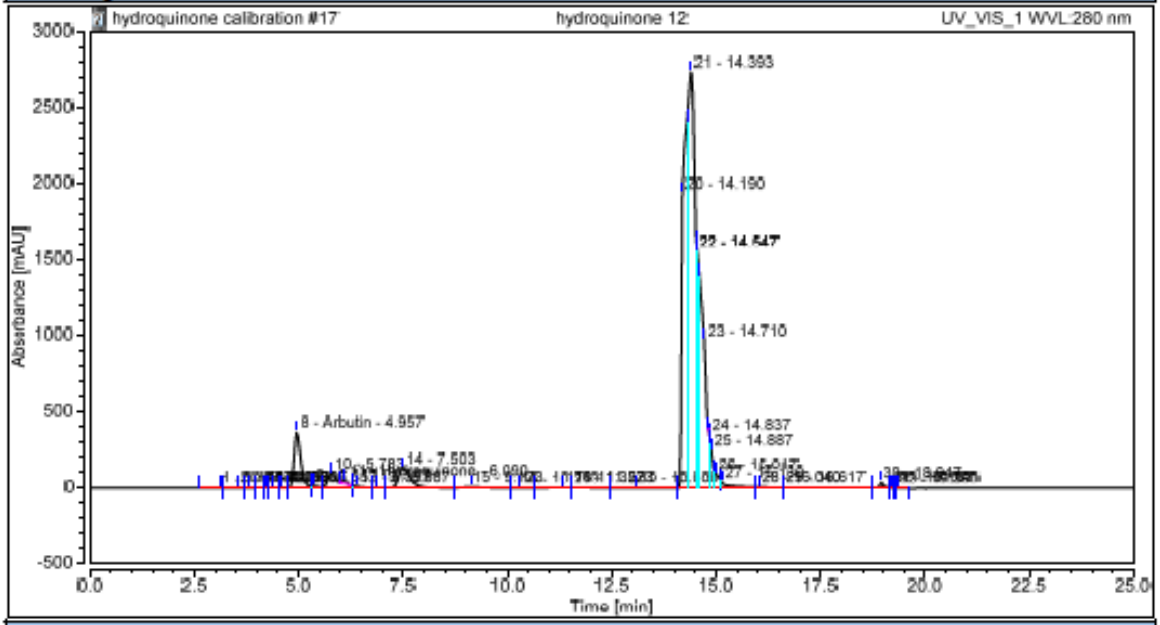
Quantitative HPLC of Hydroquinone in Bearberry leaves

Chromatogram and Results

Injection Details

Injection Name:	hydroquinone 12	*Run Time (min):*	25.00
Vial Number:	RD1	*Injection Volume:*	10.00
Injection Type:	Unknown	*Channel:*	UV_VIS_1
Calibration Level:		*Wavelength:*	280
Instrument Method:	Sample Method	*Bandwidth:*	2
Processing Method:	Hydroquinone processing method	*Dilution Factor:*	1.0000
Injection Date/Time:	17/Oct/17 15:28	*Sample Weight:*	1.0000

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		3.103	0.114	0.483	0.01	0.01	n.a.
2		3.563	0.603	1.504	0.04	0.02	n.a.
3		3.823	0.336	1.555	0.02	0.02	n.a.
4		4.150	0.496	3.075	0.04	0.04	n.a.
5		4.217	0.398	3.562	0.03	0.04	n.a.
6		4.360	0.878	4.256	0.06	0.05	n.a.
7		4.607	0.641	2.813	0.05	0.03	n.a.
8	Arbutin	4.957	67.827	365.368	4.86	4.40	n.a.
9		5.357	2.620	13.138	0.19	0.16	n.a.
10		5.783	29.807	90.482	2.14	1.09	n.a.
11	Hydroquinone	6.090	2.392	16.291	0.17	0.20	0.0061
12		6.397	3.595	12.183	0.26	0.15	n.a.
13		6.887	0.779	2.737	0.06	0.03	n.a.

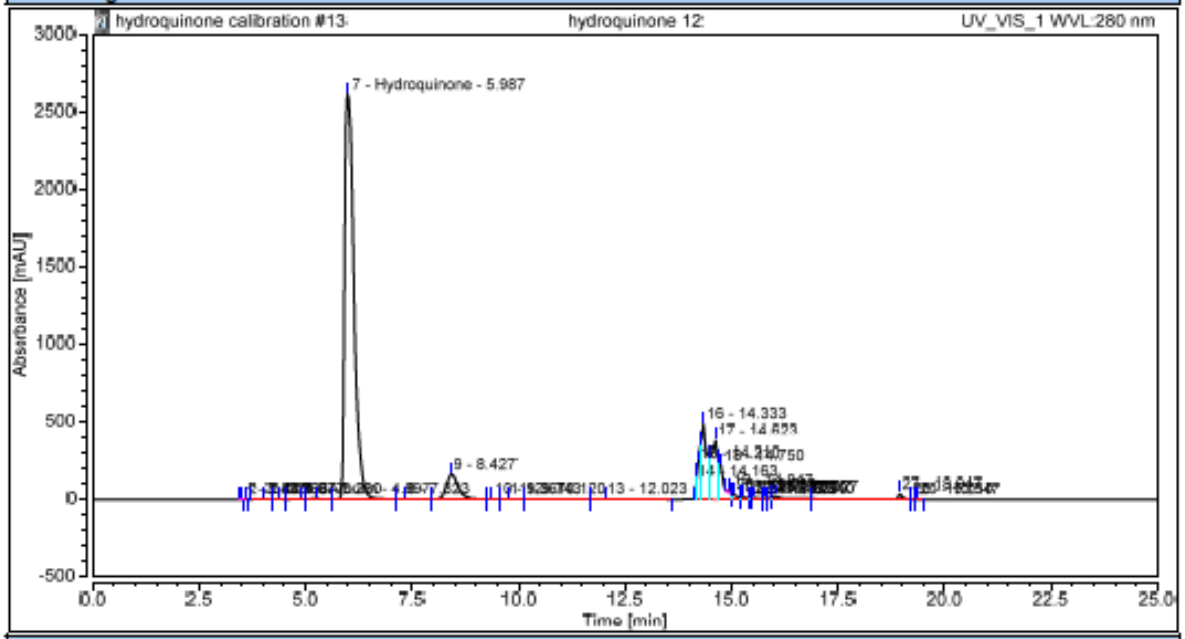
Quantity of Hydroquinone and Arbutin after 1 h hydrolysis

Chromatogram and Results

Injection Details

Injection Name:	**hydroquinone 12**	*Run Time (min):*	**25.00**
Vial Number:	**RB7**	*Injection Volume:*	**10.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_1**
Calibration Level:		*Wavelength:*	**280**
Instrument Method:	**Sample Method**	*Bandwidth:*	**2**
Processing Method:	**Hydroquinone processing method**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**17/Oct/17 13:34**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		3.503	0.002	0.032	0.00	0.00	n.a.
2		3.587	0.022	0.568	0.00	0.01	n.a.
3		3.983	0.511	2.007	0.05	0.05	n.a.
4		4.377	0.292	1.514	0.03	0.03	n.a.
5	Arbutin	4.897	0.451	1.620	0.05	0.04	n.a.
6		5.230	1.578	5.322	0.17	0.12	n.a.
7	Hydroquinone	5.987	659.318	2613.995	69.10	59.34	3.6499
8		7.323	1.473	3.054	0.15	0.07	n.a.