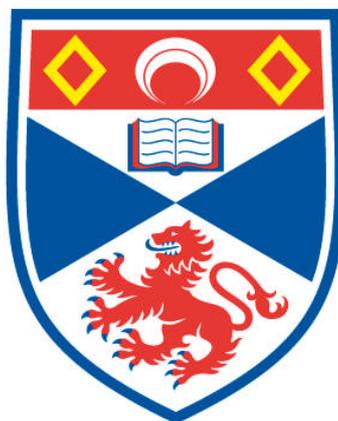


**EXPLORING THE SCOPE OF ORGANIC SYNTHESSES WITH  
SEMICONDUCTOR PHOTOREDOX CATALYSIS**

**David Manley**

**A Thesis Submitted for the Degree of PhD  
at the  
University of St Andrews**



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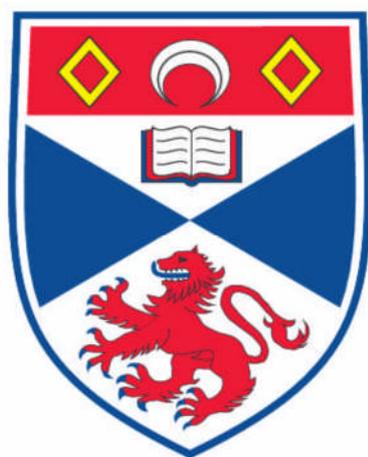
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# Exploring the Scope of Organic Syntheses with Semiconductor Photoredox Catalysis

David Manley



A thesis submitted in application for the degree of  
Doctor of Philosophy at the University of St Andrews

April 2014

*"If you're not failing every now and again, it's a sign you're not doing anything very innovative."*

- Woody Allen

*"I may not have gone where I wanted to go, but I think I have ended up where I needed to be."*

- Douglas Adams

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I was admitted as a research student in September, 2010 and as a candidate for the degree of PhD in September, 2011; the higher study for which this is a record was carried out in the University of St Andrews between 2010 and 2014.

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## List of Non-Standard Abbreviations

bpy	bipyridine
Hfs	Hyperfine splitting
<i>i</i> Pr	<i>iso</i> -propyl
ISC	Inter-system crossing
MAP	4-Methoxyacetophenone
MLCT	Metal to ligand charge transfer
MO	Molecular orbital
NHC	<i>N</i> -heterocyclic carbene
P25	Degussas titania catalyst comprised of a 3:1 mixture of anatase and rutile (full details pg. 30)
ppy	Phenylpyridine
SCPC	Semiconductor photoredox catalysis
SED	Super electron donor
SET	Single electron transfer
SOMO	Singularly occupied molecular orbital
TTF	Tetrathiafulvalene

## Abstract

Under dry, anaerobic conditions TiO<sub>2</sub> photoredox catalysis has been directed away from oxidative/degradative chemistry. Instead, carboxylic acid photoredox reactions resulted in carbon-carbon bond forming processes. High yields of radical homodimers were obtained from TiO<sub>2</sub> treatment of carboxylic acids alone. "Benzyl-type" radicals in particular performed very well in this system. Attempts at carrying out hetero-dimerisations were unsuccessful as it is thought that the differing rates of formation of radicals at the titania surface precludes the formation of cross-coupled products. A straightforward reaction mechanism involving hole-capture by the carboxylate at the catalyst surface has been put forward and is supported by literature precedent. Intramolecular dimerisations of di-carboxylic acids have been applied to the preparation of macrocycles but with disappointing yields being recorded.

Photoredox reactions employing TiO<sub>2</sub> and carboxylic acids, under dry anaerobic conditions, led to several types of C-C bond forming processes with electron deficient alkenes. The efficiency of alkylation varied appreciably with substituents in the carboxylic acids. The reactions of aryloxyacetic acids with maleimides resulted in a cascade process in which a pyrrolo-chromene derivative accompanied the alkylated succinimide. Selectivity for one or other of these products could be tuned to some extent by employing the photoredox catalyst in different conditions. An array of different catalyst forms was trialed for efficiency and ease of use. The proposed mechanism, involving hole capture at the TiO<sub>2</sub> surface by the carboxylates followed by CO<sub>2</sub> loss, was supported by EPR spectroscopic evidence of the intermediates. Deuterium labelling indicated the titania likely donates protons from surface hydroxyl groups as well as supplying electrons and holes thus acting as both a catalyst and a reaction partner.

Suitably functionalised carboxylic acids undergo a previously unknown photoredox reaction when irradiated with UVA in the presence of maleimide. Maleimide was found to synergistically act as a radical generating photooxidant and as a radical acceptor, negating the need for a photoredox catalyst. Modest to excellent yields of the product chromenopyrroledione, thiochromenopyrroledione and pyrroloquinolinedione derivatives were obtained in thirteen preparative photolyses. *In-situ* NMR spectroscopy was used to study each reaction. Reactant decay and product build-up were monitored, enabling reaction profiles to be plotted. A plausible mechanism, whereby photo-excited maleimide acts as an oxidant to generate a radical ion pair, has been postulated and is supported by UV-vis.

spectroscopy and DFT computations. The radical-cation reactive intermediates were also characterised in solution by EPR spectroscopy.

# **Chapter 1:**

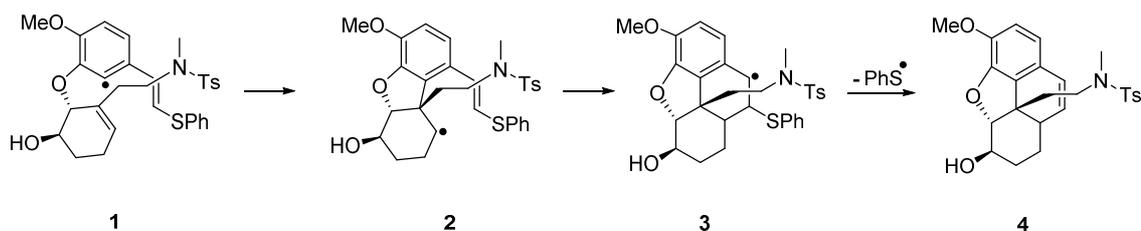
## **General Introduction**

## 1.0 Radical Chemistry

### 1.1 Free Radicals & Organic Synthesis

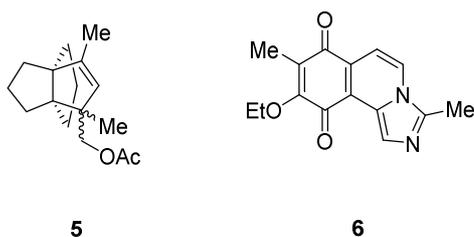
Free radicals are reactive intermediates which possess an unpaired electron. They are commonly formed by homolysis of weak bonds - by photolysis or thermolysis - and by electron transfer processes. As they contain an uneven number of electrons they are extremely reactive. In French the term "*electron célibataire*" is given to these species, likening their reactive nature to a bachelor earnestly seeking a partner. Typical radical reactions include dimerisation, abstraction, addition to unsaturated bonds, fragmentations and disproportionation. Radical chemistry dates back to the early 1900's when Moses Gomberg reported the formation of the triphenylmethyl radical upon treatment of triphenylchloromethane with zinc and other metals.<sup>[1]</sup> The first reference to the use of free radicals in organic synthesis was not until 1937 however when the homolytic phenylation of aromatic substrates was reported.<sup>[2]</sup> For many years radical intermediates were generally considered too reactive to be employed synthetically and were viewed mostly as curiosities.

Since the 1980's radical reactions have become an important tool in synthetic organic chemistry due to the fact that they boast several synthetic advantages over traditional, ionic methodologies.<sup>[3]</sup> Carbon-centered radicals are extremely reactive but the conditions required for their generation are generally mild and neutral. Additions of carbon-centered radicals to C=C bonds are usually irreversible, with an early transition state. Thus under kinetic control, radical reactions can produce products which would be unavailable using traditional, ionic methods. Carbon-centered radicals are generally unreactive towards N-H and O-H bonds, thus making it unnecessary to protect groups such as amines and alcohols, potentially removing two steps from a synthesis. Due to negligible barriers to inversion, carbon-centered radicals don't normally retain their stereochemistry. Whilst on one hand this is a major drawback, it does greatly simplify the synthesis of radical precursors. Furthermore, radicals very readily partake in tandem reaction processes, facilitating the preparation of complex polycyclic products from relatively simple precursors which makes them highly appealing from a total-synthesis viewpoint.



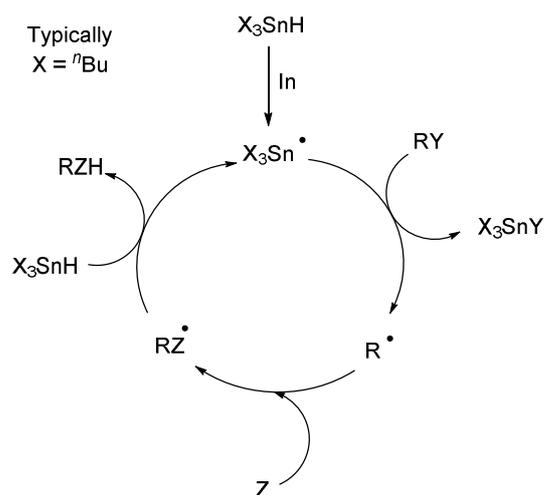
**Scheme 1.**

A practical illustration of these benefits can be seen in the synthesis of ( $\pm$ ) morphine reported by Parker and co-workers (Sch. 1).<sup>[4]</sup> The key step of this synthesis involved a radical tandem cyclisation-elimination to yield tetracyclic intermediate **3** and subsequent  $\beta$ -scission with loss of the PhS group furnishing the key styrene intermediate **4** which was taken on to ( $\pm$ ) morphine in two further steps. More recently a number of natural products have been prepared using this approach; the first reported stereoselective synthesis of two acetoxymodhephenes<sup>[5]</sup> **5** and the total synthesis of criboastatin **6**<sup>[6]</sup> **6** being two recent examples.



**Figure 1.**

The generation of carbon-centered radicals has traditionally been dominated by reductive chain processes mediated by group 14 metal hydrides, tin in particular.<sup>[7]</sup> In fact since their discovery organotin-hydride reagents have dominated the field of free radical mediated synthesis to the extent that the two have become virtually synonymous.<sup>[8]</sup> Many bond forming, ring closure, ring expansion and cascade reactions have been developed utilising this methodology. Radical reactions with tin hydride are frequently chain processes, as illustrated in Sch. 2.



**Scheme 2.**

The popularity of these reagents is down to the many virtues they possess. They are extremely mild and selective whilst also being robust and easy to use. Importantly, the well understood kinetic behaviour of tin hydride is such that the carbon-centered radical (R•) generated from a suitable precursor (RY) in the presence of a low concentration of tin hydride has a reasonably long lifetime within which to react (with species “Z” in Sch. 2) before being reduced by another molecule of tin hydride. Unfortunately, the reagents themselves are notoriously toxic<sup>[9]</sup> and difficult to remove<sup>[10]</sup> thus precluding their use in the synthesis of pharmaceuticals, foodstuffs or any other formulation intended for human consumption. Because of this there has been considerable research into alternative methods of radical generation.<sup>[11]</sup>

## 1.2 Cleaner Methods for Radical Generation

Much endeavour has been put into the development of cleaner methods of radical generation in the past few decades. As this area has been extensively and excellently reviewed<sup>[12]</sup> only a brief overview will be provided here, illustrated with selected recent examples. A variety of protocols have been developed whereby the noxious tin-hydride reagents can be used catalytically<sup>[13]</sup> or their residues can be removed more effectively.<sup>[14]</sup> Other group 14 hydrides, silanes and germanes, have been shown to be a viable alternative. Of these, it is tris(trimethylsilyl)silane<sup>[15]</sup> which has proved the most successful tin replacement. Germanium hydrides can also be used in place of tin hydrides in radical chain processes but generally are not employed synthetically due to their cost.<sup>[16]</sup> A plethora of protocols employing sulfur compounds, thiols<sup>[17]</sup>, thiocarbonyls<sup>[18]</sup> and xanthates<sup>[19]</sup> for instance, pro-aromatic cyclohexadienes<sup>[20]</sup> and phosphorus-based reagents such as phosphites<sup>[21]</sup> and hypophosphorous acid derivatives<sup>[22]</sup> have also achieved noteworthy successes as clean radical sources.

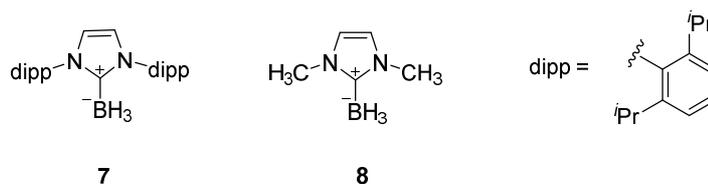
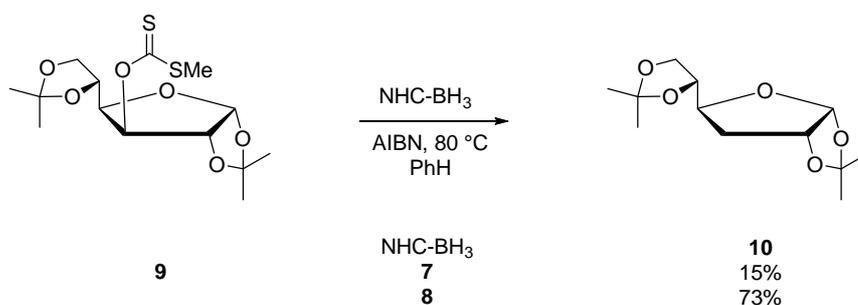


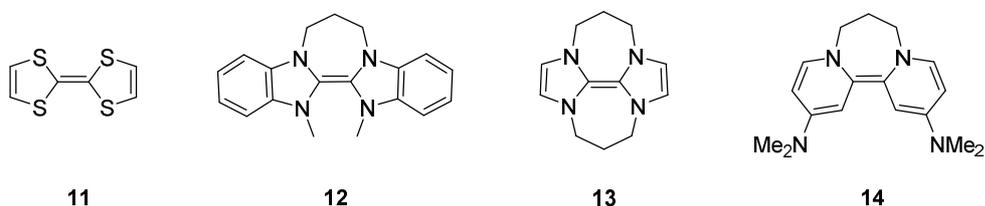
Figure 2.

Lewis acid-base pairings of boranes with *N*-heterocyclic carbenes (NHC-boranes) have recently emerged as a new class of hydrogen atom donor, capable of replacing tin hydride in certain radical chain processes. NHC-boranes, such as **7**, were shown to be worthy replacements for tin in the Barton-McCombie deoxygenation.<sup>[23]</sup> A range of secondary xanthates was successfully reduced upon exposure to **7** (typically 50-100%) with a large amount of initiator (typically 2 equiv.) in good yields. Second-generation, “minimalist” NHC-boranes (**8** for instance) were subsequently developed<sup>[24]</sup> and found to be better hydrogen atom donors and thus more efficient reagents (Sch. 3).<sup>[25]</sup> These NHC-boranes were found to be capable of reducing alkyl halides, albeit only those bearing electron withdrawing substituents in proximity to the reaction center.<sup>[26]</sup> Polarity reversal catalysis with thiols improved the scope and efficacy of this process.<sup>[27]</sup>



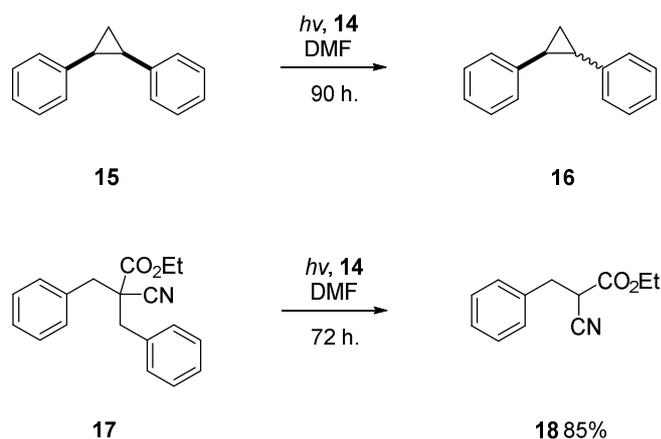
**Scheme 3.**

The intermediacy of radicals in these reduction reactions was supported by the EPR experiments and by the observation of signature radical reactions such as  $\beta$ -scission and cyclopropyl ring opening. Rate constant measurements revealed that NHC-boranes are less efficient hydrogen atom donors than tin hydrides and tris(trimethylsilyl)silane.<sup>[24]</sup> They are slightly slower than germanium hydrides and more effective than silicon hydrides, meaning that they are still above the threshold for conducting radical chain reactions. EPR spectroscopy complimented by DFT computations on NHC-boryl radicals and revealed them to be planar,  $\pi$ -type radicals with the unpaired spin being delocalised from boron across the NHC moiety, thus explaining the superior ability of NHC-boranes to act as hydrogen donors when compared with their un-complexed analogues.<sup>[28]</sup>



**Figure 3.**

The formation of aryl radicals by the de-diazotisation of aryldiazonium salts upon treatment with Cu<sup>I</sup> has long been known. A key discovery was made in the late 90's in that the copper in this process could be replaced by the entirely organic electron donor tetrathiafulvalene (TTF) **11**.<sup>[29]</sup> This paved the way for the development of neutral organic super-electron donors (SED's) as a new class of clean, radical generating reagents.<sup>[30]</sup> More powerful SED's have since been developed deriving from the benzimidazole<sup>[31]</sup> **12**, imidazole<sup>[32]</sup> **13**, and DMAP<sup>[33]</sup> **14** core structures. The reaction scope of these SED's was expanded to include the reduction of aryl iodides and bromides and the cleavage of phenylalkylsulfones in excellent yields.



**Scheme 4.**

More recently, a number of impressive reactions have been achieved by photoactivation of SED **14**. Reduction of a previously unreactive chlorobenzene was achieved in this fashion while the epimerisation of the diphenylcyclopropane **15** illustrated that electron transfer to unactivated arenes from photo-excited **14** takes place readily (Sch. 4, top).<sup>[34]</sup> The scope of the photoactivated process<sup>[34]</sup> was further extended to a number of bond-breaking reactions. Benzylic esters and ethers were deprotected to carboxylic acids and alcohols respectively, both in excellent yields.<sup>[35]</sup> When this approach was extended to *C*-benzyl malonates and cyanoacetates reductive cleavage of one of the benzyl groups occurred selectively in each instance (Sch. 4, bottom).<sup>[36]</sup> This was in direct contrast to the outcome of metal based reductions of similar substrates. C-N and S-N bonds also proved susceptible to cleavage under these conditions.<sup>[37]</sup>

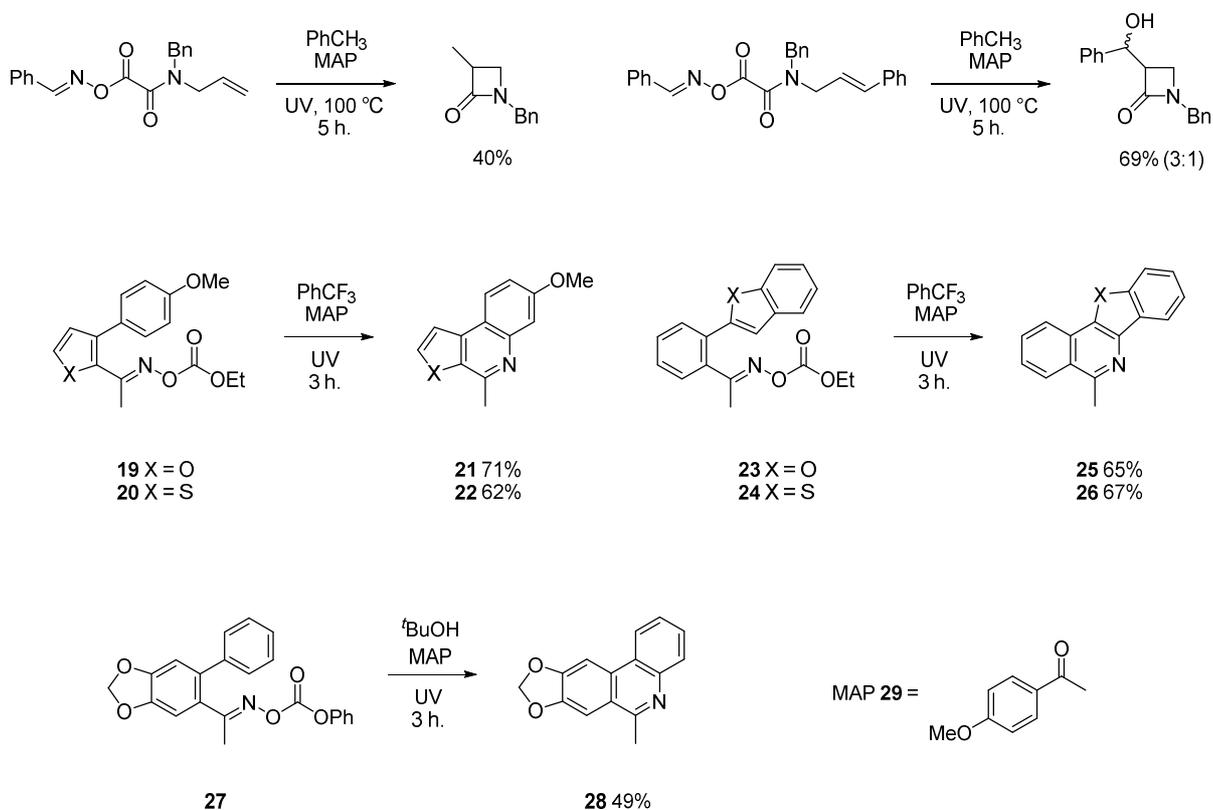
### 1.3 Photochemistry & Radical Generation by Photochemical Means

Perhaps the best known example of light-mediated process is photosynthesis, the process whereby most green plants and algae reduce carbon dioxide to carbohydrates such as glucose. They do so using only solar energy, water and co-enzymes. The products of photosynthesis, such as starch and cellulose, are essential to plant life and consequently to mankind while the oxygen produced as a byproduct is essential to all aerobic life on earth. The notion of using light rather than heat or chemical pressure to promote chemical reactions dates back to the work of Giacomo Ciamician at the turn of the 20<sup>th</sup> century. He reported the photoreduction of benzophenone, *via* H-abstraction in its excited state followed by dimerisation of the resultant ketyl radicals, to benzopinacol. Solutions of benzophenone were exposed to sunlight for several months.<sup>[38]</sup> Ciamician is widely regarded as the forefather of modern organic photochemistry. In his address, entitled 'The Photochemistry of the Future', he put forward his belief that a new, more environmentally benign chemical industry could replace high-energy synthetic processes with clean, cost-efficient photochemical transformations, with dramatic ecological benefits.<sup>[39]</sup>

*"On the arid lands there will spring up industrial colonies without smoke and without smokestacks; forests of glass tubes will extend over the plains and glass buildings will rise everywhere; inside of these will take place the photochemical processes that hitherto have been the guarded secret of the plants, but that will have been mastered by human industry which will know how to make them bear even more abundant fruit than nature, for nature is not in a hurry and mankind is. And if in a distant future the supply of coal becomes completely exhausted, civilization will not be checked by that, for life and civilisation will continue as long as the sun shines!"*

In the following century photocatalysis has gone on to become a major branch of synthetic organic chemistry with many C-C bond forming reactions having been reported. As these reactions exploit the energy of photons rather than relying on high pressures/temperatures or the use of toxic/undesirable reagents they are generally carried out under very mild, benign conditions. The photon itself leaves no traces or byproducts which need to be removed while allowing access to high energy intermediates that react with high selectivities and yields.<sup>[40]</sup> The generation of radicals and radical ions go hand in hand with photochemical processes and this represents an appealing alternative to undesirable organotin hydride based methods. The preparation of heterocycles by exploiting the

photochemical homolysis of the weak N-O bond of carefully designed oxime precursors has been the focus of recent research in the Walton research group.<sup>[41]</sup>

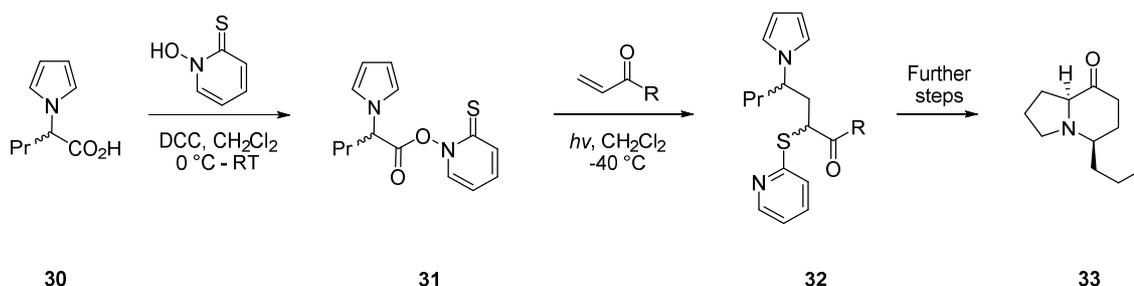


**Scheme 5.**

UV photolyses of dioxime oxalates in the presence of 4-methoxyacetophenone **29** (MAP) led to the clean formation of dihydropyrroles and phenanthridines in moderate to good yields with CO<sub>2</sub> as the only by-product.<sup>[42]</sup> Treatment of oxime oxalate amides in the same way generated carbamoyl radicals which underwent an unusual cyclisation to yield azetidin-2-ones similar to 4-membered rings found the  $\beta$ -lactam family of antibiotics (Sch. 5, top).<sup>[43]</sup> Oxime carbonates proved to be a highly effective route to heterocycles such as phenanthridines, quinolones and isoquinolines as well as the natural product Trispheridine **28**.<sup>[44]</sup> The closely related oxime carbamates were also found to provide a viable synthetic route to phenanthridines.<sup>[45]</sup>

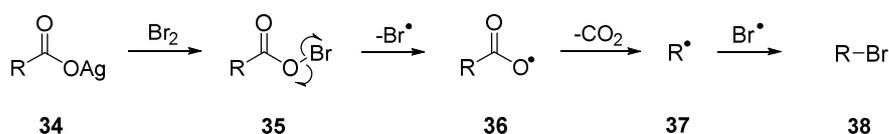
## 1.4 Carboxylic Acids as Radical Precursors

Carboxylic acids are found widely in nature, as well as being produced industrially on a large scale, marking them as an attractive source of free radicals. Furthermore the carboxylate moiety is easily introduced synthetically and many protocols exist for its protection/deprotection. Homolytic decarboxylations have tended to rely on the derivatisation of the acid precursors in order to facilitate radical generation. The Barton-McCombie reaction sequence, first described in the early 80's, is perhaps the most well-known example of this approach.<sup>[46]</sup> The carboxylate group is converted to a thiohydroxamate ester (known as Barton esters) before being subjected to homolytic cleavage. The radicals produced in this way can be employed for the formation of C-C bonds, C-X (X = O, S, Se, halogen) bonds or to abstract hydrogen in a reductive decarboxylation.<sup>[47]</sup> This flexibility coupled with the effectiveness of the process made it one of the first radical reactions to gain prominence within the field of organic synthesis.



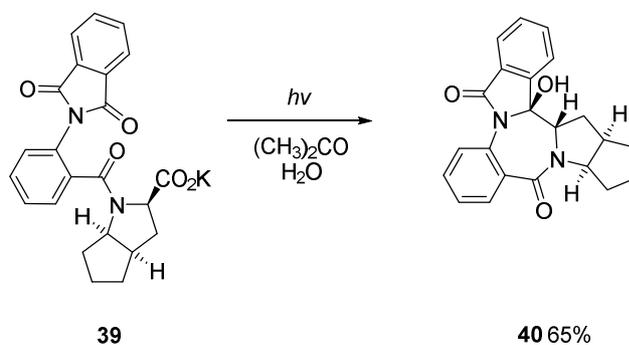
**Scheme 6.**

Tadano and co-workers are just one of many groups to employ the Barton-McCombie reaction for the purpose of deoxygenation in a total synthesis (Sch. 6). The carboxylic acid **30** was converted to its Barton ester **31** before being irradiated in  $\text{CH}_2\text{Cl}_2$  at  $-40\text{ }^\circ\text{C}$  in the presence of a range of chiral acrylates and acrylamides and forming products in yields ranging from 12-58%.<sup>[48]</sup> Similar radical decarboxylative alkylations rely on derivatisation of the carboxylic acid to unappealing precursors such as Hunsdieker<sup>[49]</sup> salts and diacylperoxides or peresters.<sup>[50]</sup> In the former case the carboxylic acid is converted to its silver salt **34** which then reacts with halogens to give an unstable intermediate **35** which readily decarboxylates homolytically to yield an alkyl halide **38** (Sch. 7).



**Scheme 7.**

Carboxylic acids are well known to homolytically decarboxylate upon photolysis, generating carbon centred radicals in many cases, and this area has been reviewed in depth.<sup>[51]</sup> The carboxylate moiety however generally needs to be irradiated with short wavelength ( $\lambda \leq 250$  nm) UV light<sup>[52]</sup> which is undesirable due to its adverse effects on human health and its propensity to degrade organic molecules.<sup>[53]</sup> A plethora of photosensitisers have been developed which facilitate photodecarboxylation at longer wavelengths. Organic molecules such as aromatic ketones,<sup>[54]</sup> quinones<sup>[55]</sup> and nitro aromatics,<sup>[56]</sup> catalytic iodine,<sup>[53]</sup> metal complexes<sup>[57]</sup> and heavy metals<sup>[58]</sup> have all been used for this purpose. Several elegant syntheses<sup>[59]</sup> employing phthalimide as the photoactive species to promote photodecarboxylation have been reported by the research group of Griesbeck, the diastereo- and enantioselective synthesis of pyrrolo[1,4]benzodiazepines such as **40** (Sch. 8) being one example.<sup>[60]</sup>



**Scheme 8.**

## 2.0 Photoredox Catalysis

### 2.1 Homogeneous Photoredox Catalysis

Photoredox catalysis harnesses the energy of light to facilitate chemical reactions by electron transfer, producing oxidised and/or reduced species. Typically these processes employ a small quantity of a light-absorbing species that, when photo-excited, can mediate this electron transfer between chemical compounds that otherwise would not react.<sup>[61]</sup> This has proved to be an effective, clean method for the generation of radicals and radical ions. Whilst organic dyes can be used effectively for this purpose<sup>[62]</sup> transition metal complexes based on the Ru(II)polypyridine scaffold are currently the focus of intense research in this field.<sup>[63]</sup> This is due to their ease of synthesis, stability at room temperature and under photo-irradiation as well as their excellent photoredox properties. Furthermore, they can be activated by visible light – precluding the requirement for specialised irradiation setups – and their reactivity can be readily tuned by altering the substitution pattern on the ligands and by changing the metal. The fundamentals of photoredox catalysis are outlined in Fig. 4, illustrated using the prototypical catalyst  $\text{Ru}(\text{bpy})_3^{2+}$  (bpy = 2,2'-bipyridyl).

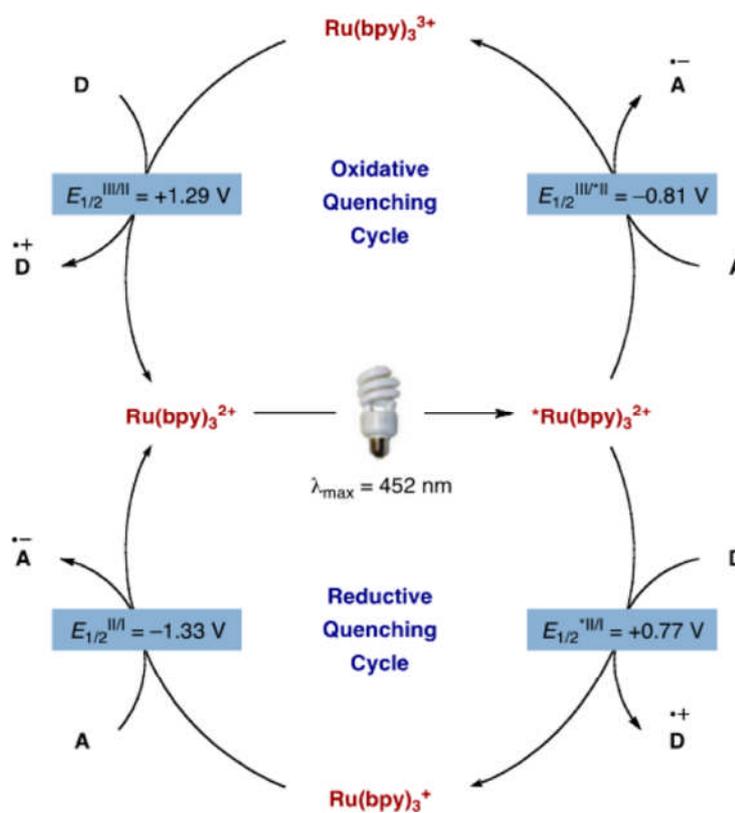
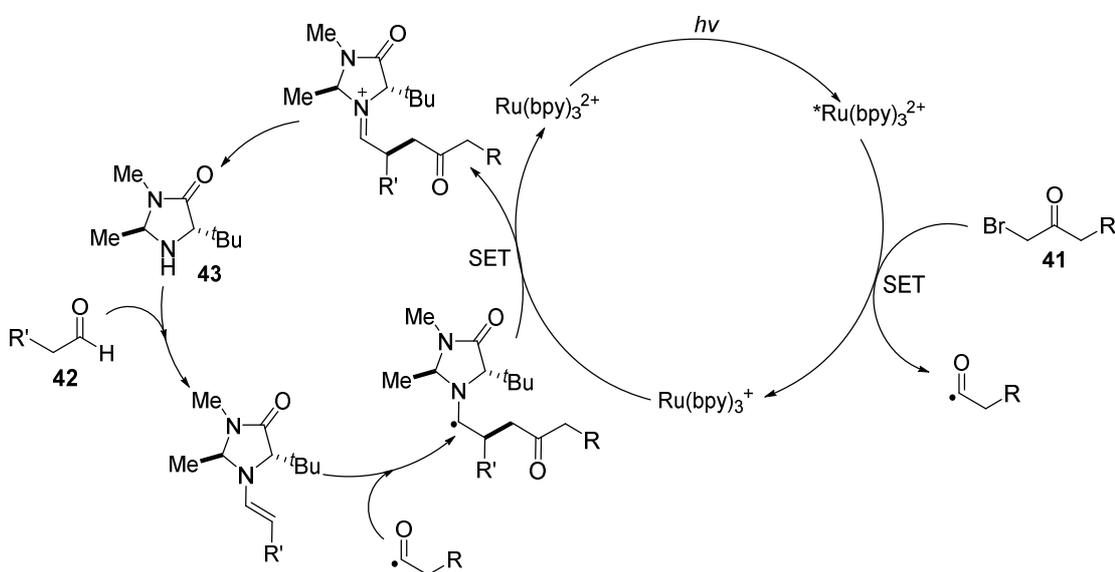
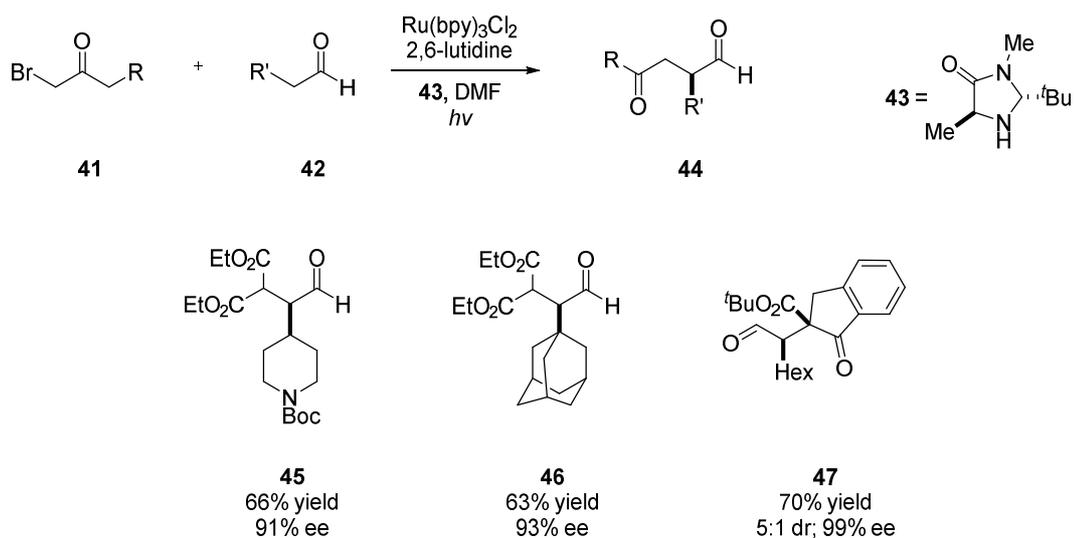


Figure 4.<sup>[63]</sup>

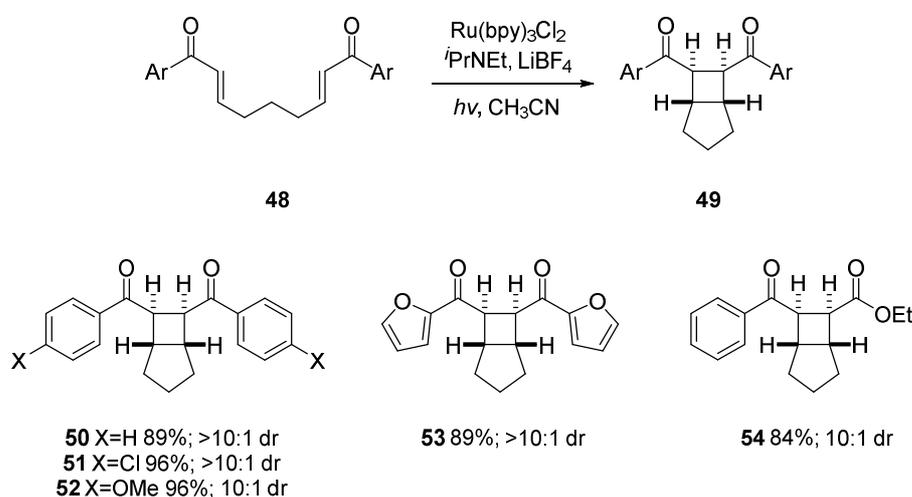
Absorption of a photon by  $\text{Ru}(\text{bpy})_3^{2+}$  promotes metal to ligand charge transfer (MLCT) which is followed by inter-system crossing (ISC) to the long-lived triplet species  $^*\text{Ru}(\text{bpy})_3^{2+}$ . This species can act both as a reductant and an oxidant, thus redox transformations may proceed by either reductive or oxidative quenching cycles. In the oxidative quenching cycle  $^*\text{Ru}(\text{bpy})_3^{2+}$  acts as a reductant, reducing an electron accepting molecule **A** (known as an oxidative quencher) generating the radical anion  $\text{A}^{\bullet-}$ . Conversely, in the reductive quenching cycle  $^*\text{Ru}(\text{bpy})_3^{2+}$  acts as an oxidant, accepting an electron from a donor species **D** (reductive quencher) to furnish the radical cation  $\text{D}^{\bullet+}$ . Whilst sporadic reports<sup>[64]</sup> of chemical transformations mediated by photoredox catalysis appeared in the past few decades it was in 2008 that interest in the field took off, sparked by a number of seminal papers published in that year.



**Scheme 9.**

MacMillan and Nicewicz reported the marriage of photoredox catalysis with organo-SOMO catalysis for the successful enantioselective  $\alpha$ -alkylation of aldehydes.<sup>[65]</sup> Irradiation of racemic aldehydes **42** and  $\alpha$ -bromocarbonyls **41** in the presence of chiral amine catalyst **43**  $\text{Ru(bpy)}_3\text{Cl}_2$ , and 2,6-lutidine in DMF with visible light for 6 hours provided the  $\alpha$ -alkylated products **44** in excellent yields and enantioselectivities. The reaction showed broad applicability, performed well with sterically demanding substrates (to yield **45** and **46** for instance) and could be employed for the formation of quaternary centers in high ee (**47**). Mechanistically it was postulated that the reaction comprised of two cooperative catalytic cycles. Firstly the excitation of  $\text{Ru(bpy)}_3^{2+}$  and subsequent sacrificial reductive quenching by the enamine product of condensation between the aldehyde **41** and **43** generated  $\text{Ru(bpy)}_3^{3+}$ .

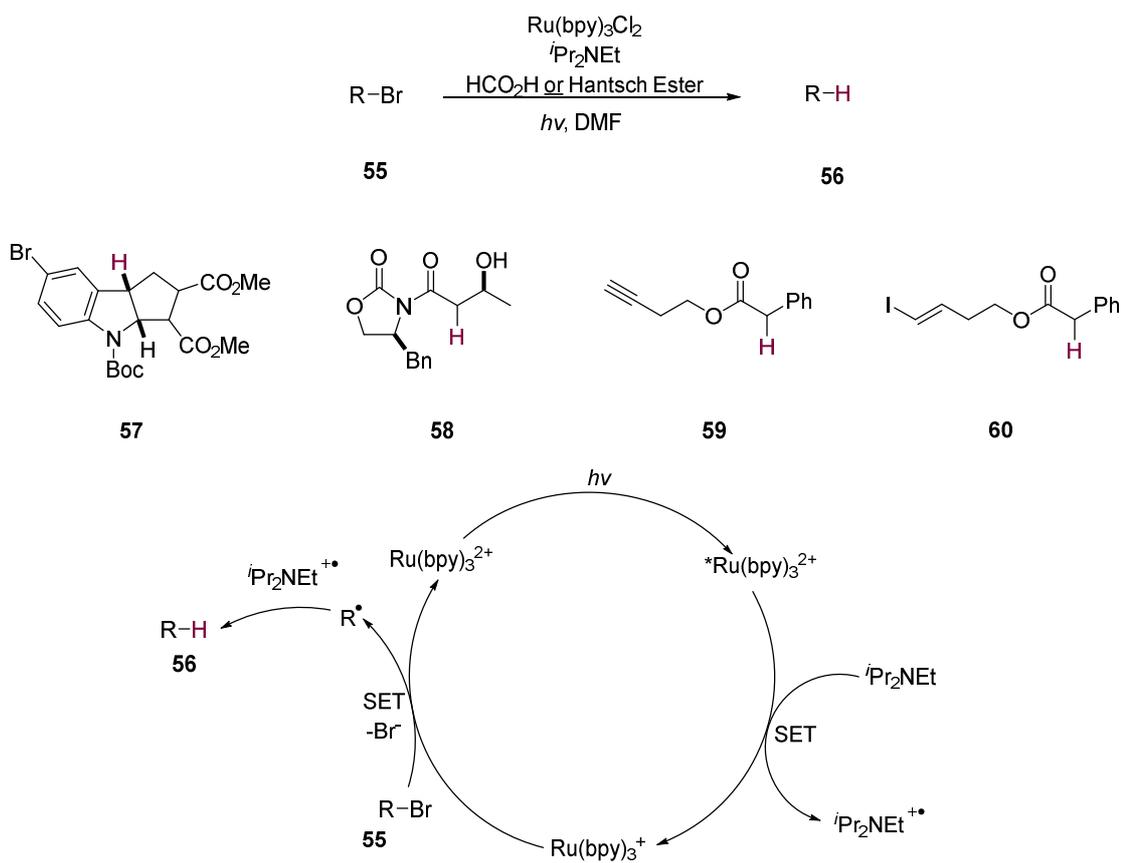
Single electron transfer (SET) from  $\text{Ru}(\text{bpy})_3^+$  to the  $\alpha$ -bromocarbonyl component **42** furnished the corresponding electron-deficient radical while regenerating  $\text{Ru}(\text{bpy})_3^{2+}$  to complete the first catalytic cycle. The second catalytic cycle began with the coupling of the electron-deficient radical with the electron rich enamine to form the key C–C bond, generating an  $\alpha$ -amino radical which was then oxidised by  $^*\text{Ru}(\text{bpy})_3^{2+}$  to generate an iminium cation and the reductant  $\text{Ru}(\text{bpy})_3^+$ , which re-enters the first catalytic cycle. Hydrolysis regenerates the amine catalyst **43** while releasing the enantioenriched  $\alpha$ -alkylated product **44**. In an extension of this work they used a similar approach to achieve the asymmetric trifluoromethylation of aldehydes.<sup>[66]</sup> Recent reports from the group of MacMillan have focused on the enantioselective  $\beta$ -arylation of ketones and aldehydes,<sup>[67]</sup> the  $\beta$ -functionalisation of cyclic ketones with aryl ketones<sup>[68]</sup> and decarboxylative arylation of  $\alpha$ -amino acids.<sup>[69]</sup>



**Scheme 10.**

Concurrently with MacMillan's initial foray into the field of photoredox catalysis, Yoon and co-workers reported the photoredox-mediated highly diastereoselective [2+2] cycloaddition of enones (Sch. 10).<sup>[70]</sup> Irradiation of an aryl dienones **48** with visible light in the presence of  $\text{Ru}(\text{bpy})_3^{2+}$ ,  $i\text{Pr}_2\text{NEt}$ , and  $\text{LiBF}_4$  in  $\text{CH}_3\text{CN}$  gave rise to the formation of the intramolecular formal [2+2] cycloaddition products **49** in excellent yields with very pleasing diastereomeric control. Precursors bearing both electron-withdrawing and electron-releasing functionality (products **51** and **52**) heterocycles (**53**) and  $\alpha,\beta$ -unsaturated carbonyl compounds (**54**) were shown to be suitable partners for this reaction. The *cis*-cyclobutanes were obtained preferentially in each of these intramolecular cycloadditions reported. In contrast, intermolecular reactions carried out in this manner furnished all *trans*-cyclobutanes. Mechanistically this process is thought to begin with photoexcitation of  $\text{Ru}(\text{bpy})_3^{2+}$  in the usual

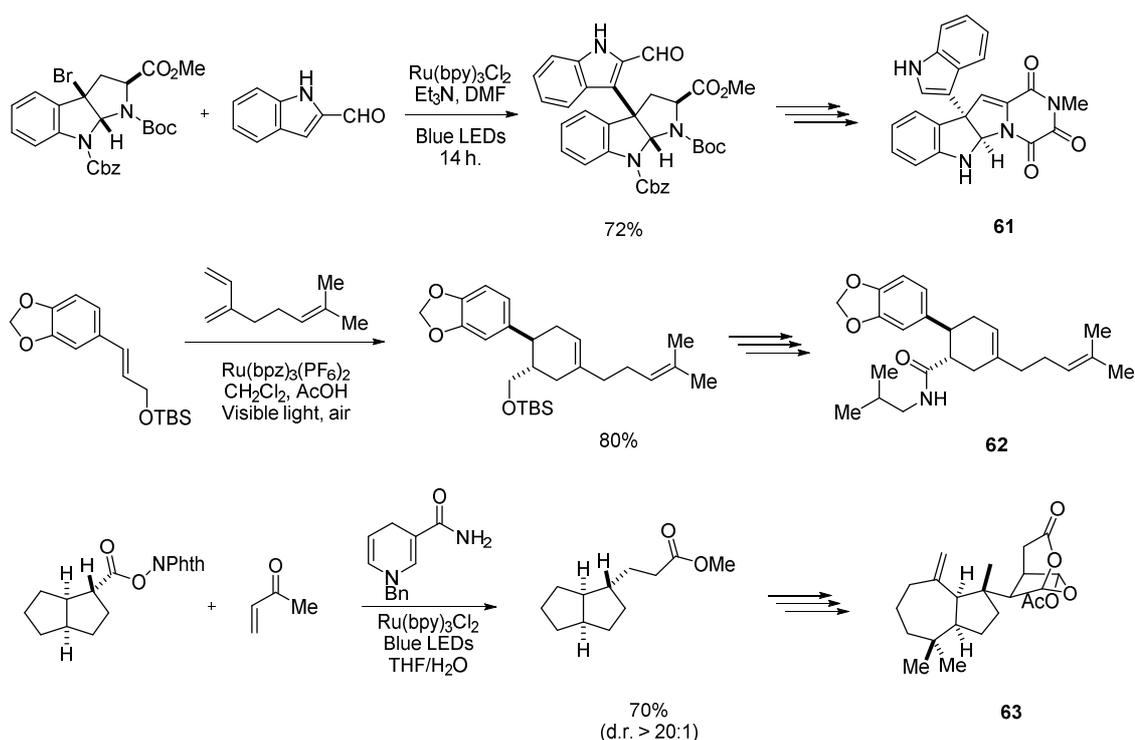
fashion followed by a reductive quench with  $i\text{Pr}_2\text{NEt}$  to generate the strongly reducing  $\text{Ru}(\text{bpy})_3^+$  species. Reduction of the lithium coordinated enone **48** ensued, bringing about a 1,4-radical addition followed by radical cyclisation to yield the cyclobutane product **49**. Expanding on the scope of this initial report, crossed intramolecular versions of the process have been successfully carried out.<sup>[71]</sup> Furthermore, it has been demonstrated that these reactions can be carried out on multi-gram scale and using sunlight as the irradiation source.



**Scheme 11.**

Following on from these two high-impact reports, the group of Stephenson developed a photoredox protocol for reductive dehalogenation (Sch. 11).<sup>[72]</sup> Again,  $\text{Ru}(\text{bpy})_3^{2+}$  is utilised as the photoredox catalyst and  $i\text{Pr}_2\text{NEt}$  along with a Hantzsch ester or formic acid as the sacrificial electron donor. SET from the amine to  $^*\text{Ru}(\text{bpy})_3^{2+}$  generates an aminium radical cation and  $\text{Ru}(\text{bpy})_3^+$ , which can reduce  $\alpha$ -haloesters to  $\alpha$ -carbonyl radicals. The aminium radical cation exhibits significantly lower bond dissociation energy in its  $\alpha$ -C-H bonds compared to its unoxidised analogue, facilitating hydrogen abstraction by the  $\alpha$ -carbonyl radicals to yield the desired reduced product. Generally excellent yields were recorded and tolerance of free hydroxyl, (**58**) olefin (**59**) and acetylene (**60**) functionalities was noted. The protocol could be applied to the reduction of both alkyl bromides and chlorides and is selective for the

dehalogenation of benzylic and  $\alpha$ -carbonyl halides over aryl and vinyl halides. A significant limitation of this work was the requirement for activated (benzylic or  $\alpha$ -carbonyl) halides. Subsequent to this initial report, the same research group described the reductive dehalogenation of unactivated alkyl, alkenyl, and aryl iodides using the more reductive iridium catalyst *fac*-Ir(ppy)<sub>3</sub> (ppy = 2-phenylpyridine).<sup>[73]</sup> The *fac*-Ir(ppy)<sub>3</sub> catalyst was found to be a sufficiently strong electron donor to reduce these substrates directly from its photoexcited state. Using a reductant system comprising tributylamine with a Hantzsch ester or formic acid, a range of unactivated iodides undergoes reductive dehalogenation in high yields. As in the Ru(bpy)<sub>3</sub><sup>2+</sup> mediated reactions, the stoichiometric reductants serve to both turn over the photocatalytic cycle and act as a source of hydrogen. Remarkably, these conditions allowed for the selective dehalogenation of aryl iodides in the presence of aryl bromides and chlorides.<sup>[74]</sup> The same group have also reported the functionalization of indoles and pyrroles by intramolecular radical cyclisation.<sup>[75]</sup>



**Figure 5**

Photoredox catalysis has proven to be a valuable tool for the construction of complex molecules, as demonstrated by its application in a number of total syntheses. Stephenson applied an intermolecular version of the aforementioned photoredox indole alkylation reaction to the total synthesis of (+)-gliocladin C **61**, a natural product having a C3–C3' linked indole/pyrroloindoline core. A bromopyrroloindoline was coupled successfully with a

protected indole by treatment with photoactivated  $\text{Ru}(\text{bpy})_3^{2+}$  to create the key C3–C3' link.<sup>[76]</sup> Yoon and co-workers employed a photoredox radical cation Diels–Alder cycloaddition in their total synthesis of the natural product heitziamide A **62**. Exposure of a styrene derivative and myrcene to photoredox conditions afforded a cyclohexene intermediate in 80% yield which was then carried on to the target compound in three further steps in a very concise synthesis.<sup>[77]</sup> The group of Overman have reported the conjugate addition of a tertiary carbon-centered radical, formed by the reaction of  $\text{Ru}(\text{bpy})_3^+$  with an *N*-(acyloxy)phthalimide, in their synthesis of (–)-aplyviolene **63**.<sup>[78]</sup>

## 2.2 Photoredox Catalysis with Semiconductors

### 2.2.1 Basic Principles & Overview

In solid state physics band theory is used to describe the ranges of energy that an electron within a solid may have. The bands which are close in energy to the ground state are full, up to a band known as the valence band. The band immediately above the valence band is known as the conduction band. These are separated by the band gap. Materials can be categorised as insulators, conductors and semiconductors by their ability to conduct electricity. Insulators do not conduct electricity as the bands up to and including the valence band are all filled. Higher energy levels do exist but promotion is impractical due to the energy requirement – *i.e.* the band gap is too large, typically far greater than the thermal energy of an electron. Metals on the other hand conduct electricity with ease as the movement of electrons between energy levels occurs readily – *i.e.* there is no band gap. Semiconducting materials fall in between these two categories and typically have a band gap in the region of 1 eV. Upon photoexcitation of a semiconductor particle by light of energy greater or equal to that of the band gap, an electron is promoted from the valence band to the conduction band, leaving behind it an electron hole ( $h^+$ ). Holes are unoccupied states in the valence band but behave as if they are positively charged particles. Holes don't actually move, but neighboring electrons can move to fill the hole so it appears as if they do.<sup>[79]</sup>

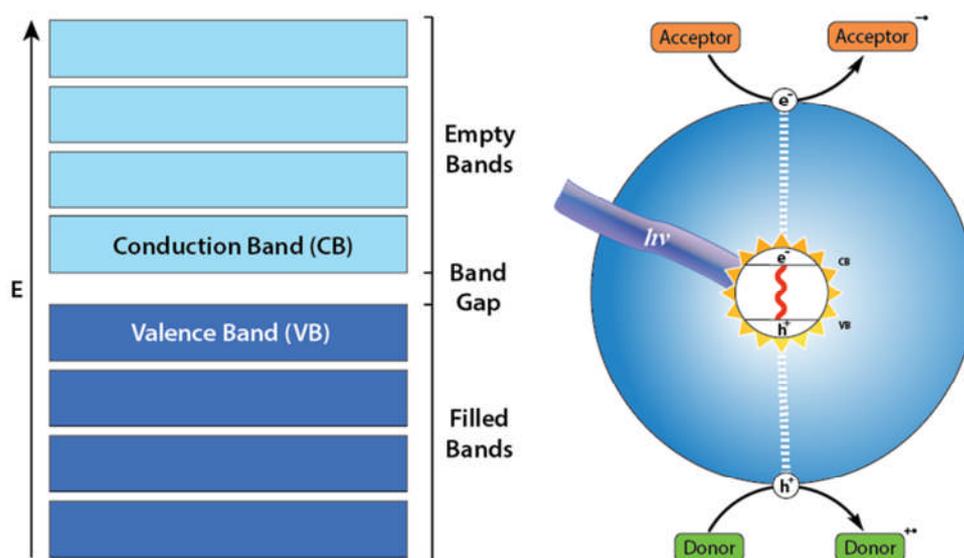
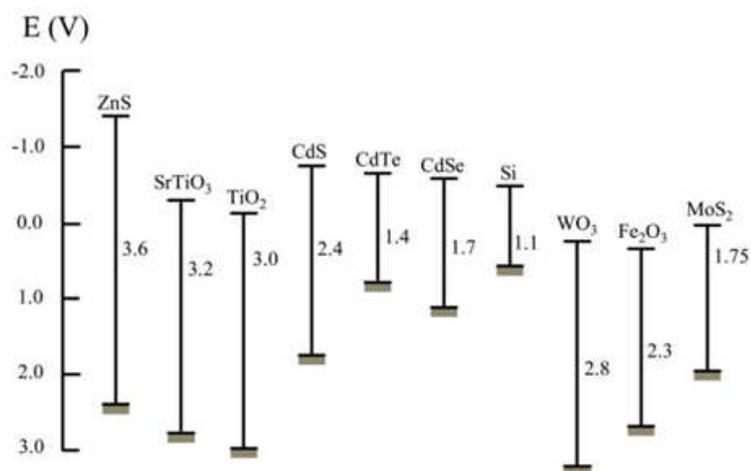


Figure 6.

Semiconductors are capable of mediating photoredox processes. Upon separation of the electron-hole pair, a number of fates are possible. Under the right circumstances they can migrate to the surface of the semiconductor particle where the electron can reduce an

electron acceptor and/or the hole can oxidise an electron donor. In competition with this is recombination, whereby the electron drops back down to the valence band. This can occur in the bulk of the semiconductor particle or at the surface. Also possible is the back transfer of an electron from the acceptor/donor species to the semiconductor.

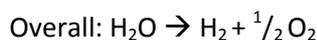
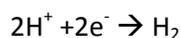
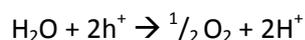


**Figure 7.** Band gaps and redox potentials (vs. NHE, pH = 1) of several semiconductor photocatalysts.<sup>[80]</sup>

Many semiconductors are employed as photoredox catalysts; ZnS, CdS, WO<sub>3</sub> and NiO to name but a few. Several semiconductors commonly employed for this purpose are shown in Fig. 7 along with their corresponding bandgaps. It is widely accepted that titanium dioxide (TiO<sub>2</sub>) and its related compounds are by far the most effective and reliable. This is down to its low cost, high activity and stability under irradiation. TiO<sub>2</sub> has a large band gap which corresponds to the UV region (anatase excitation wavelength 385 nm) of the spectrum. Whilst this is less convenient than the visible light activated ruthenium based catalysts, the band edge positions are consequently more powerful redox agents. Two naturally occurring crystal structures of TiO<sub>2</sub>, rutile and anatase, exhibit photocatalytic activity with anatase proving superior.<sup>[79]</sup> A third naturally occurring form, brookite, shows no photoactivity.

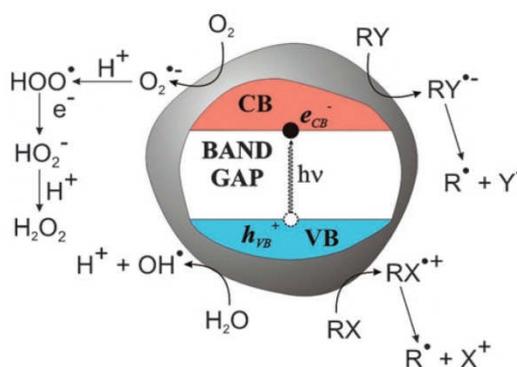
An abundance of commercial TiO<sub>2</sub> photoredox catalysts is available, either as single polymorphs of anatase or rutile or as mixtures of the two. Of these, Degussa P25 is the most widely employed and is considered the “gold standard” for semiconductor photocatalysed reactions. It has a relatively large surface area (49 m<sup>2</sup> g<sup>-1</sup>) and consists of roughly 75% anatase and 25% rutile.<sup>[81]</sup> This combination exhibits a synergistic effect and has been shown to be much more active than anatase or rutile alone. It is thought that contact between the two phases facilitates charge separation by allowing electron transfer from anatase to rutile. The

rutile acts as an electron sink, preventing recombination and increasing the photo-activity of the holes in the anatase. Other groups have proposed the formation of catalytic “hot spots” at the interface between the phases as the reason for this synergy.<sup>[82]</sup>



**Scheme 12.**

The oil crisis of the 1970's gave new impetus to research in the field of alternative energy sources. One area of interest was in imitating nature by converting solar energy to a more easily utilised form of chemical energy (Sch. 12).<sup>[83]</sup> It was hoped that sunlight could be used to convert water to hydrogen. Hydrogen has the potential to be an excellent fuel due to its high energy capacity and the fact that it doesn't produce CO<sub>2</sub> or other pollutants when burned. However water splitting, under normal conditions would require temperatures in excess of 2,000°C.<sup>[84]</sup> Photoexcited TiO<sub>2</sub> is capable of splitting water as its band gap is sufficiently large to encompass the redox potentials of water.<sup>[83]</sup> As previously mentioned though, this band gap corresponds to high energy UV photons which only make up a small proportion of sunlight. Fujishima and Honda first demonstrated the photocatalytic splitting of water in 1972 using a photoelectrochemical cell.<sup>[85]</sup> This consisted of a rutile TiO<sub>2</sub> photo-anode and a Pt counter-electrode. Since then many efforts have been made to alter the TiO<sub>2</sub> photocatalytic system in order to achieve visible light driven water splitting, but as of yet this “Holy Grail” of chemistry remains out of reach.



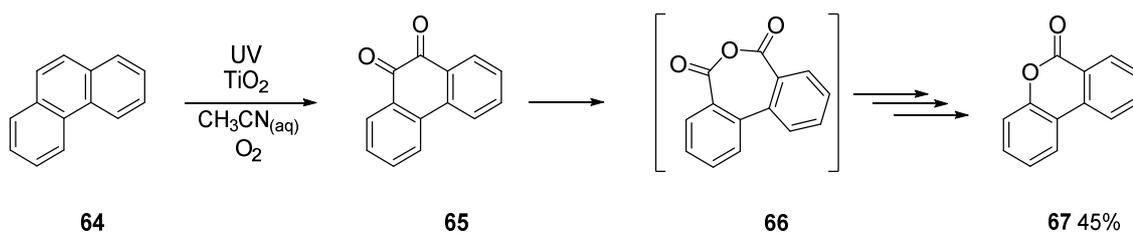
**Figure 8.**<sup>[83]</sup>

The most common application of semiconductor photoredox catalysis (also semiconductor photocatalysis; SCPC) has been the degradation of organic molecules for the

purpose of environmental remediation. Pollutants present in water, soil, and the atmosphere can be removed either by complete photomineralisation or by their photomediated transformation into non-toxic products. When irradiated in the presence of oxygen, water and a photocatalyst, organic material can be completely degraded to CO<sub>2</sub> water and mineral acids (Fig. 8).<sup>[79]</sup> The main processes involved are summarised in Figure 8. Photogenerated holes produce hydroxyl radicals - the most active species involved in this process due to their high reactivity with organic molecules. Photoexcited electrons give rise to superoxide anions, which can be transformed to hydroperoxyl radicals and ions as well as hydrogen peroxide. The holes and electrons can also directly oxidise/reduce any adsorbed pollutants themselves.<sup>[83]</sup> Ollis *et al.* first made reference to this application in 1983 when they reported the mineralisation of several halogenated hydrocarbons, such as chloroform and carbon tetrachloride, in irradiated, aqueous suspensions of TiO<sub>2</sub>.<sup>[86]</sup> Since then research in this area has been extensive and as a result many different classes of organic (and inorganic) pollutants have been shown to undergo photodegradation. This area has been reviewed in depth.<sup>[87]</sup>

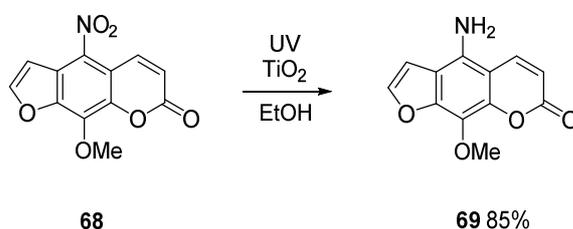
### 2.2.2 Application to Oxidative and Reductive Transformations

Constructive synthetic transformations of organic molecules using SCPC have attracted significantly less attention than these two destructive endeavors. None-the-less several reports have been published in the past few decades, with photo-oxidation processes accounting for the majority of the reactions studied.<sup>[88]</sup> The superoxide and hydroxyl radical species produced can be utilised as powerful oxidizing agents, taking the place of noxious metals (such as chromium or manganese), making this an attractive approach from both an economic and environmental viewpoint. Many SCPC oxidations of aromatics have been reported, but of these it is perhaps the oxidation of benzene to form phenol which is the most significant.<sup>[89]</sup> Due to its extensive use as a disinfectant, as well as in the pharmaceutical industry, global production of phenol is in the region of  $5 \times 10^6$  tonnes per annum. The industrial preparation of phenol is routinely carried out using the multistep cumene process.<sup>[90]</sup> This requires high temperatures and pressures and thus has high energy requirements. It also suffers from poor selectivity and as such, produces large quantities of byproducts. There have been numerous reports of phenol production by the SCPC oxidation of benzene.<sup>[91]</sup> Addition of photogenerated hydroxyl radicals to the benzene, *via* homolytic substitution, results in phenol formation. Poor selectivity is displayed however due to the phenol formed reacting further with hydroxyl radicals and/or being completely decomposed. Recent modifications to the TiO<sub>2</sub> system have improved on this front but still report only 11% selectivity.<sup>[92]</sup>



**Scheme 13.**

Similar approaches have also been applied to the oxidation of aliphatic hydrocarbons - such as cyclohexane to cyclohexanone,<sup>[93]</sup> the oxidation of benzylic and allylic alcohols to carbonyl compounds,<sup>[94]</sup> alkene epoxidation<sup>[95]</sup> and the benzylic fluorination of toluene.<sup>[96]</sup> An interesting application of the SCPC system is the oxidation of phenanthrene **64** to a coumarin derivative **67**, using oxygen and a dispersion of TiO<sub>2</sub> in aqueous CH<sub>3</sub>CN as the oxidant (Sch. 13).<sup>[97]</sup> Coumarins are widely employed in the synthesis of pharmaceuticals and fluorescent dyestuffs and many steps are involved in their synthesis from commercially available reagents by conventional methods. Thus this one-pot process is very appealing from a green chemistry point of view. The authors propose that the reaction proceeds *via* anhydride intermediate **66** which would readily decarboxylate to form **67**.



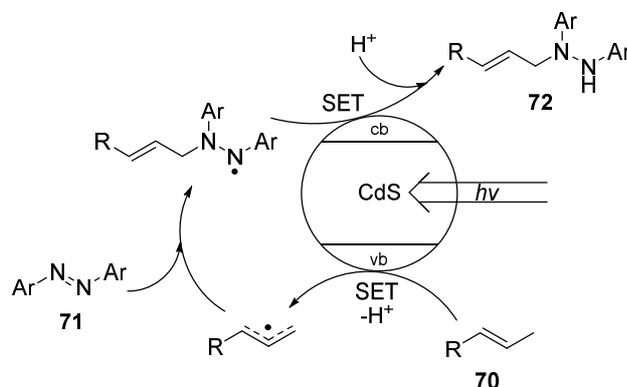
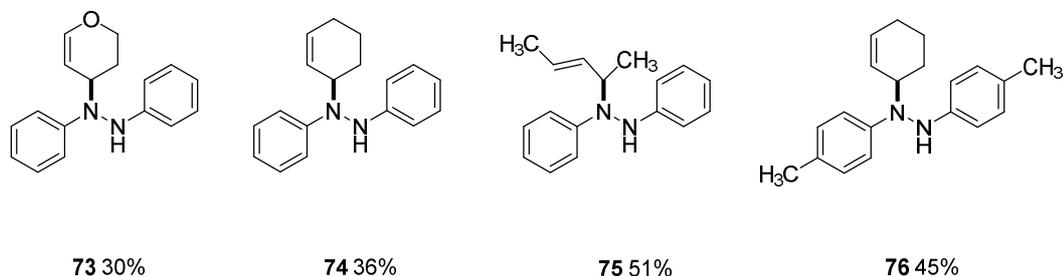
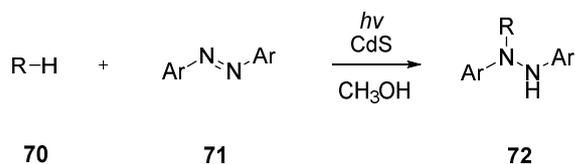
**Scheme 14.**

Much less attention has been paid to the reductive photochemistry of photoexcited TiO<sub>2</sub>, *i.e.* utilising the conduction band electrons. This is partly down to the fact that, whilst strongly oxidising at 3.2 eV it is only weakly reducing (-0.3 eV). In order to carry out reductive transformations a large excess of an electron donor (reductive quencher) is needed to scavenge the valence band holes and prevent recombination. Alcohols are commonly employed in this role. One example of such a process is the photocatalytic reduction of nitroaromatics in aqueous TiO<sub>2</sub> slurries, with methanol, ethanol or isopropanol playing the role of hole scavenger. First reported in the late 90s<sup>[98]</sup> this approach has successfully been applied in the reduction of 5-nitro-8-methoxypsoralen **68** to 5-amino-8-methoxypsoralen **69** in an ethanolic dispersion of TiO<sub>2</sub> (Sch. 14).<sup>[99]</sup> Mechanistically, it is thought that the reaction

proceeds *via* a series of two electron reductions. The reduction of CO<sub>2</sub> by SCPC has received extensive attention, albeit mostly using the more strongly reducing CdS and ZnS semiconductors as catalysts.

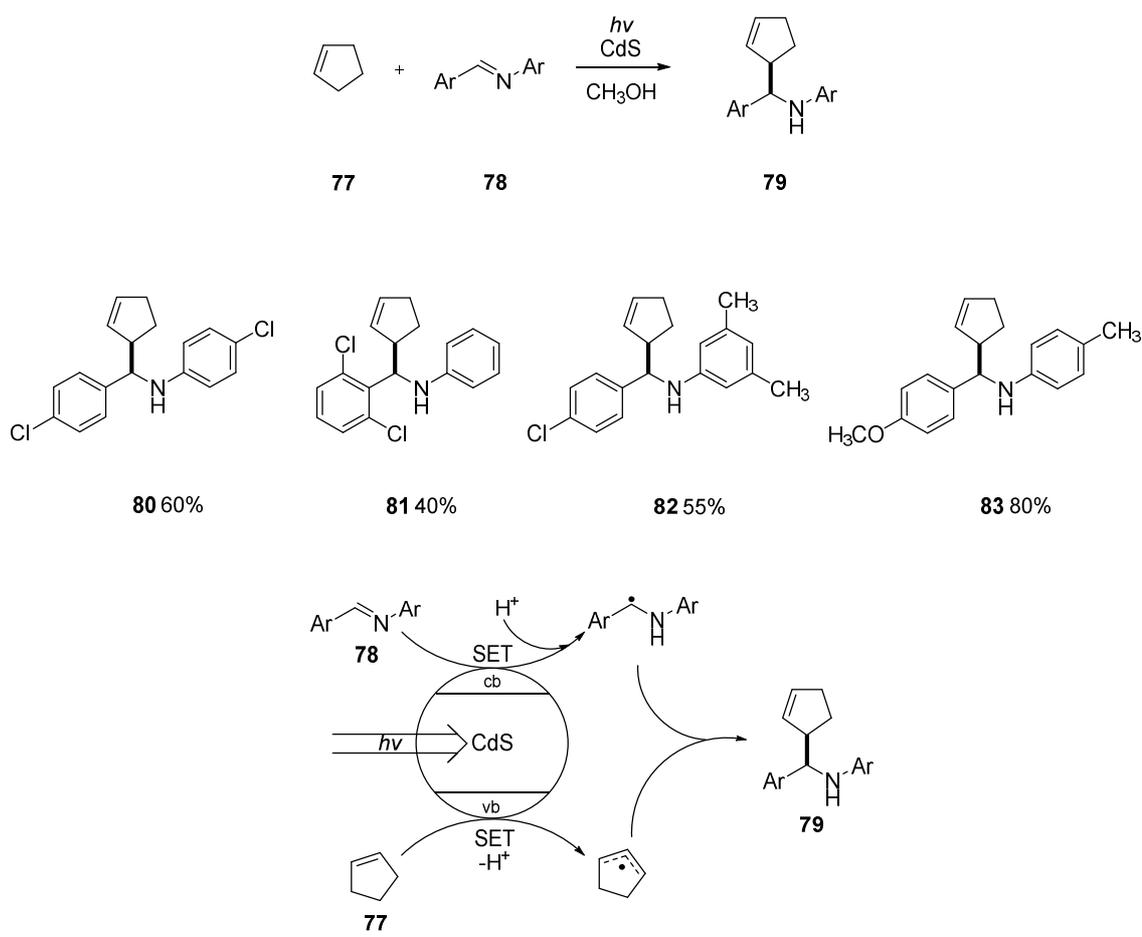
### 2.2.3 Application to Bond-Forming Processes

As illustrated by the aforementioned examples, most synthetic transformations employing SCPC involve oxidations with molecular oxygen or functional group reductions. A number of investigations into semiconductor-mediated bond forming processes and ring closures were also carried out in the mid 80's and early 90's.<sup>[96, 100]</sup> However these were mostly spectroscopic studies on the formation of well-known compounds where the products were not isolated. The work of the research group of Kisch represented the first successful example of SCPC being applied to the formation of novel organic compounds which could be isolated on a gram scale.<sup>[101]</sup>



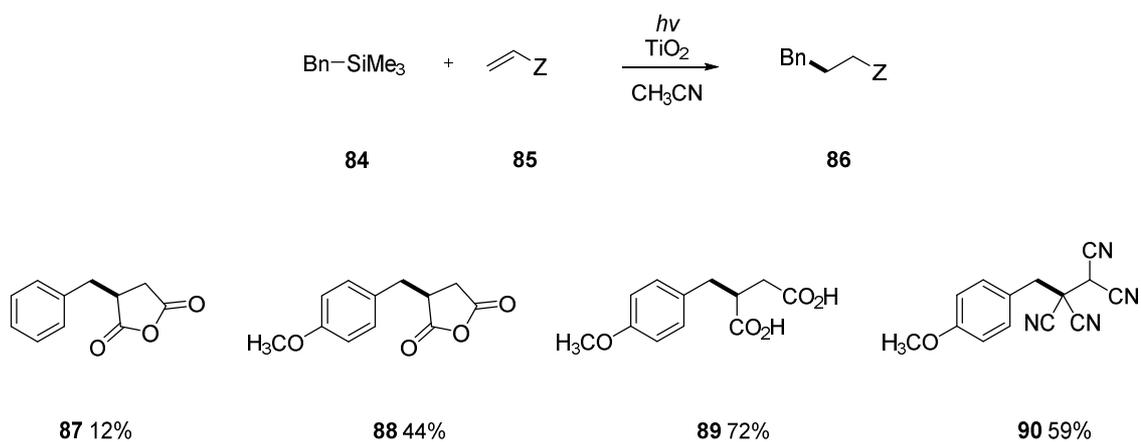
Scheme 15.

These researchers also investigated the use of methanolic suspensions of CdS to promote the insertion of various substrates into allylic C-H bonds. The addition of alkenes and enol ethers to 1,2-diazines resulted in the formation of allylhydrazines **72** (Sch. 15).<sup>[102]</sup> Oxidation of the alkene/enol ether component **70** by the valence band of CdS furnished a radical cation. Deprotonation to an allylic radical was followed by addition to the N=N bond of the diazine **71**. A two electron reduction/protonation side reaction resulting in the formation of diphenylhydrazine was also observed. While the recorded yields were modest, the products **72** formed were novel entities and could be isolated after photolysis. The same research group also reported the creation of  $\gamma,\delta$ -unsaturated tertiary amines **79** from imines **78** and cyclopentene **77** (Sch. 16).<sup>[103]</sup> The reaction proceeded *via* a proton-coupled electron transfer from the conduction band of the semiconductor to the imine **78** to furnish an  $\alpha$ -aminobenzyl radical. Hole oxidation of **77** generated cyclopentyl radicals and heterodimerisation between these species with subsequent deprotonation furnished the desired products **79**. Subsequent work was carried out using *N*-phenylbenzophenone imine and a series of alkenes, enol ethers and allyl ethers.<sup>[104]</sup> The imine was reduced, forming  $\alpha$ -aminodiphenylmethyl radical as in the previous example. This underwent heterocoupling with allyl radicals, generated from the allylic C-H containing substrates as in the first example, to yield a homoallylamine. Cyclohexanes, dihydrofurans, cyclopentenes and  $\alpha$ -pinene were all compatible with this protocol, with yields ranging from 55-80% being recorded. The simultaneous activation of both reactants by reductive and oxidative interactions with the photoexcited semiconductor marked these processes as both elegant and highly efficient.



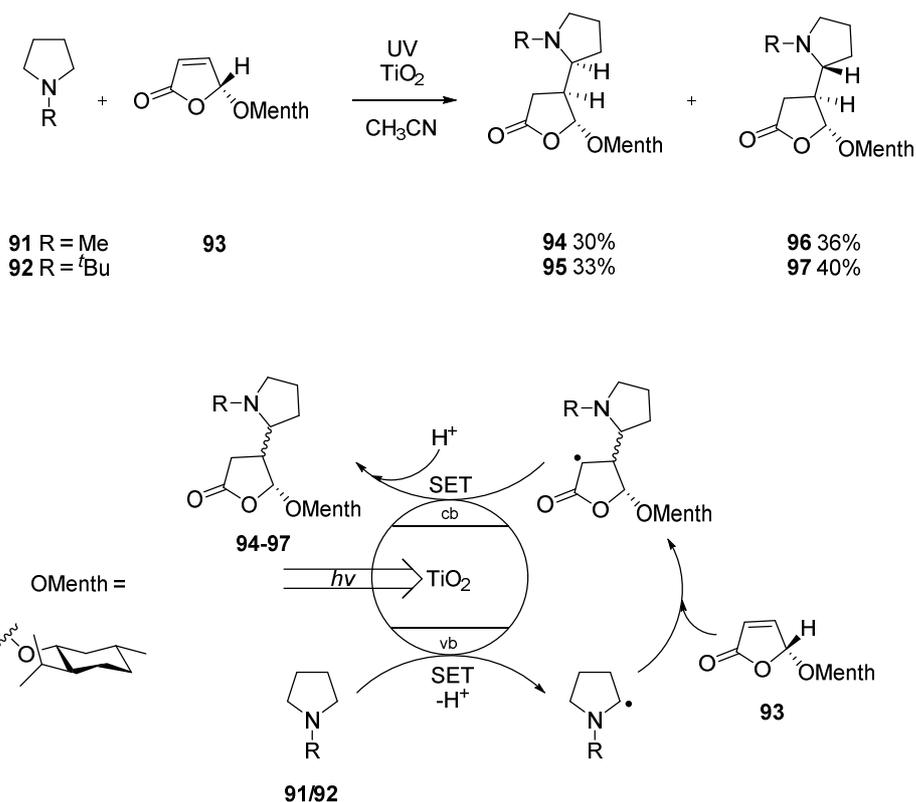
**Scheme 16.**

Albini and coworkers reported the use of photoexcited dispersions of TiO<sub>2</sub> to mediate the benzylation of a series of electron-deficient alkenes (Sch. 17).<sup>[105]</sup> Electron donor molecules were typically activated by hole-oxidation, giving rise to a radical cation which subsequently underwent fragmentation to furnish benzyl radicals. The resultant benzyl radical was then trapped by the electron deficient alkene **85**. Excess alkene was required to act as a trap for the conduction band electrons, preventing recombination and electron back transfer of the radical cation. Toluenes and phenylacetic acids were found to be suitable donor molecules but most of their work focused on the use of trimethylsilanes **84** as these proved the most efficient. Maleic anhydride, maleic acid and related nitriles were benzylation in good yields in this manner. The formation of small quantities of bis-adducts and homodimers were also reported. In one instance a multigram reaction was successfully carried out with sunlight as the irradiation source.



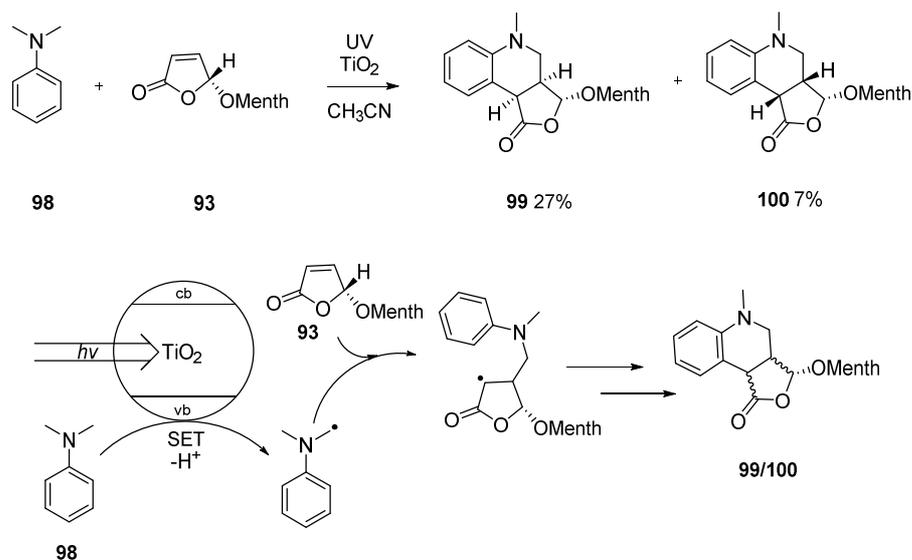
**Scheme 17.**

Hoffmann and co-workers have used various semiconductors, notably  $\text{TiO}_2$ , CdS and ZnS, to sensitise the addition of tertiary amines to electron deficient alkenes via a radical chain process.<sup>[106]</sup> This work was based upon established chemistry by the same author using aromatic ketones as photosensitisers.<sup>[107]</sup> SET from the nitrogen lone pair of a tertiary amine to the valence band of the photoexcited semiconductor generated a radical cation which then deprotonated to furnish an  $\alpha$ -aminoalkyl radical. Addition of these species to various electron-deficient alkenes facilitated several C-C bond forming and ring closing reactions. *N*-methylpyrrolidine **91** and *N-tert*-butylpyrrolidine **92** were both reported to undergo addition to the  $\alpha,\beta$ -unsaturated lactone **93** in good yields.<sup>[106a]</sup> Due to the incorporation of a menthylchiral auxiliary in the lactone **93**, addition of the amine took place exclusively from the less hindered face but, due to poor selectivity at the chiral center formed *alpha* to the nitrogen, very poor diastereomeric excess was achieved (Sch. 18).



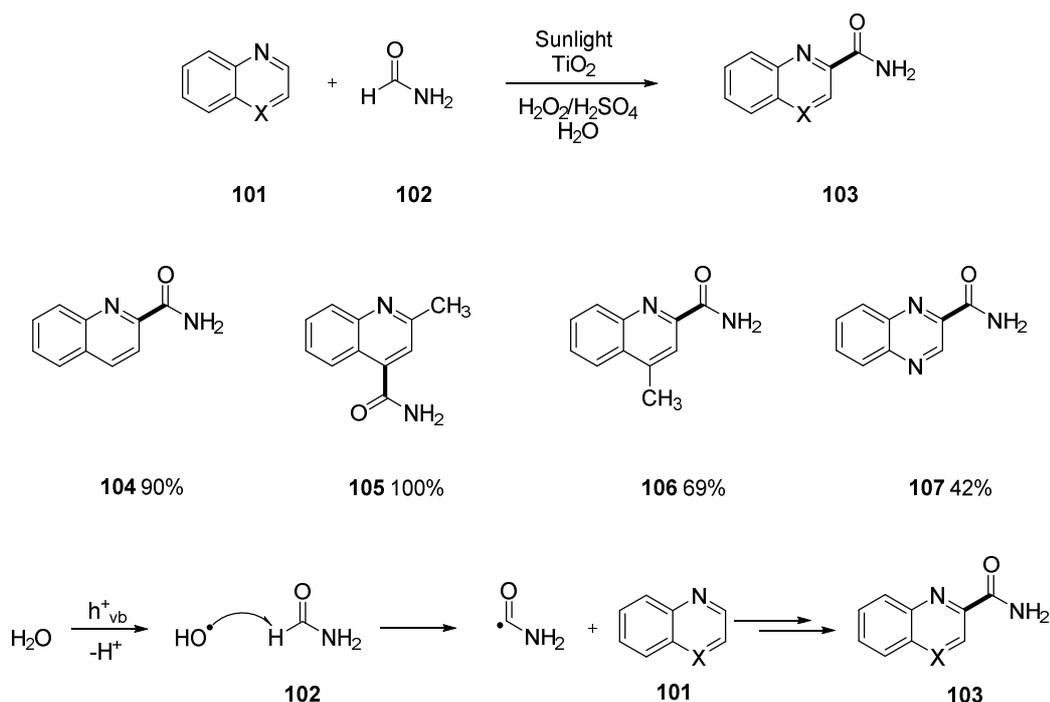
**Scheme 18.**

Use of *N*-methylpiperidine as the amine component resulted in the C-N coupled product being obtained in 53% yield. The low reactivity of the piperidine-derived  $\alpha$ -aminoalkyl radicals is thought to result in their being oxidised to cations, bringing about demethylation to piperidine. This then undergoes Michael addition to **93**. When *N,N*-dimethylaniline **98** was irradiated in the presence of lactone **93** and various inorganic semiconductors, such as  $\text{TiO}_2$  and  $\text{ZnS}$ , a tandem radical addition-cyclisation was observed (Sch. 19).<sup>[106c]</sup> The two diastereomeric tetrahydroquinoline derivatives **99** and **100** were formed as a result. In the proposed mechanism, the photoexcited semiconductor oxidised **98** to a radical cation, which subsequently deprotonated to give nucleophilic  $\alpha$ -aminoalkyl radicals which then added to the double bond of **93**. The major product **99** was formed by attack of this species *anti* to the menthyloxy substituent of **93**. The intermediate radical thus formed was highly electrophilic and added readily to the electron-rich aromatic ring in an intramolecular cyclisation, furnishing **99** and **100** by oxidative rearomatisation.



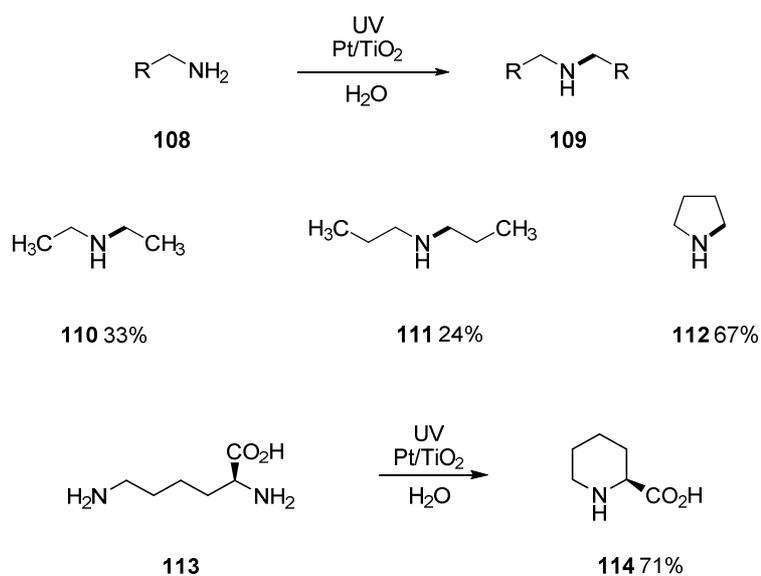
**Scheme 19.**

The functionalisation of heterocyclic bases with amides or ethers using photoexcited dispersions of titania in water or water/acetonitrile mixtures has been reported. Irradiation with sunlight of aqueous solutions containing heterocyclic bases **101** such as quinoline, quinaldine, lepidine, or quinoxaline and amides like formamide **102** and acetamide with titania furnished the corresponding amide-functionalised heterocycles **103** in good to near-quantitative yields (Sch. 20).<sup>[108]</sup> Inclusion of H<sub>2</sub>SO<sub>4</sub> and H<sub>2</sub>O<sub>2</sub> in the reaction mixture was necessary for reaction to take place. It was postulated by the authors that amide radicals are formed *via* hydrogen abstraction by <sup>•</sup>OH radicals from the amide **102**. The amide radical then attacks the heterocyclic base and yields the functionalised product after oxidative rearomatisation. Similarly, sunlight irradiation of ethers such as tetrahydropyran, dioxane, dioxolane, diethyl ether, and trioxane with a similar array of heterocyclic bases afforded the alkylated products, again in good yields.<sup>[109]</sup> In this case,  $\alpha$ -oxyalkyl radicals were generated by hydrogen abstraction from the  $\alpha$ -carbon of the ethers.



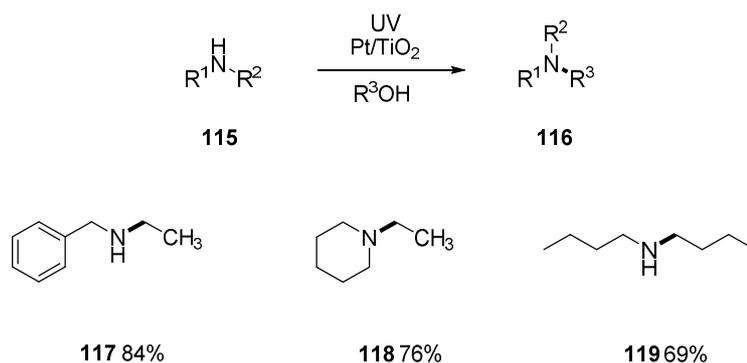
**Scheme 20.**

Ohtani and co-workers have carried out a number of SCPC C-N bond forming reactions. Photoirradiation of an aqueous dispersion of a Pt/TiO<sub>2</sub> catalyst with primary amines **108** yielded the corresponding secondary amines **109** *via* C-N coupling (Sch. 21, top).<sup>[110]</sup> The reaction is thought to proceed in two successive oxidation/deprotonation steps, converting the amine **108** to a primary imine. This imine reacts with another molecule of the starting amine to form a secondary imine which is reduced to the secondary amine product **109** at the surface of the platinised catalyst. Only trace amounts of the products were observed in the absence of platinum. Simple aliphatic amines afforded the corresponding secondary amines in rather modest yields (**110** & **111**) while terminal diamines cyclised in more pleasing yields (**112**). This cyclisation reaction was applied for one-pot synthesis of L-pipecolic acid **114**, a biologically active heterocyclic compound, from L-lysine **113** (Sch. 21, bottom).<sup>[111]</sup> Reactions were carried out in deaerated aqueous dispersions of the platinised TiO<sub>2</sub> and other semiconductors. Mechanistically, the reaction is thought to have proceeded firstly *via* hole oxidation of the ε-amino group of **113** to yield an imine, its subsequent hydrolysis to an aldehyde and intramolecular imine condensation to yield **114** following two electron reduction. **114** was formed with the (*S*) configuration from L-lysine **113** still intact.

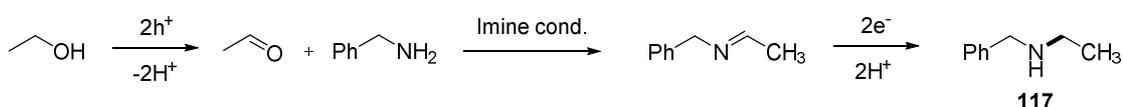


**Scheme 21.**

In a modified version of this protocol, photolysis of alcoholic solutions of primary or secondary amines **115** with Pt/TiO<sub>2</sub> led to the formation of the corresponding secondary or tertiary amines **116** respectively (Sch. 22).<sup>[112]</sup> Two successive SET's from the alcohol to the valence band of the photoexcited titania catalyst and subsequent proton loss brought about conversion to the corresponding aldehyde/ketone. Imine condensation with the amine **115** ensued with reduction-protonation by conduction band of the titania yielding the desired products **116**. Reaction occurred readily in case of benzylic amines and piperidine (**117** & **118**), but aliphatic amines and aniline exhibited poor reactivity.



For example **117**:



**Scheme 22.**

Several reviews on the progress of SCPC as a synthetic tool in organic chemistry are available and only selected examples have been presented here.<sup>[89, 101, 113]</sup>

### 3.0 Aims & Objectives

The main aim of this work is to answer the question if titania SCPC can provide a viable route to carry out selective, high-yielding, commercially significant reactions in a controllable manner which can be stopped instantly with the flick of a switch. There is a strong need for novel radical methods in organic synthesis; preferably those that are more environmentally friendly and less wasteful of time and energy and chemicals. SCPC has potential to be such a method but has not, to date, been explored in a systematic way with regard to the production of chemicals of industrial significance.

A major goal is to exploit the known ability of  $\text{TiO}_2$ , as well as other heterogeneous photoredox catalysts, to generate free radicals under UV irradiation. This approach is to be employed for the development of new methodologies in organic synthesis which are environmentally attractive, and which have the potential to achieve higher selectivity than conventional routes. The use of SCPC for promoting a number of radical reactions will be investigated. Addition reactions to alkenes and other acceptors, annulations, dimerisations, reductions and oxidations will all be targeted.

Not enough is currently known about the reaction mechanism(s) that operate in SCPC reactions – apart from the fact that they are almost certainly radical based - and this information is needed for effective reaction design and encouraging a wider application. This project will aim use established techniques to elucidate the underlying reaction mechanisms and so aid greatly the promotion of SCPC in organic synthesis.

## 4.0 References

- [1] M. Gomberg, *J. Am. Chem. Soc.* **1900**, *22*, 757-771.
- [2] D. H. Hey, W. A. Waters, *Chem. Rev.* **1937**, *21*, 169-208.
- [3] a) D. P. Curran, *Synthesis* **1988**, *1988*, 417-439; b) C. P. Jasperse, D. P. Curran, T. L. Fevig, *Chem. Rev.* **1991**, *91*, 1237-1286.
- [4] K. A. Parker, D. Fokas, *J. Am. Chem. Soc.* **1992**, *114*, 9688-9689.
- [5] H.-Y. Lee, R. N. Murugan, D. K. Moon, *Eur. J. Org. Chem.* **2009**, *2009*, 5028-5037.
- [6] D. Knueppel, S. F. Martin, *Angew. Chem. Int. Ed.* **2009**, *48*, 2569-2571.
- [7] a) P. Renaud, M. P. Sibi, Eds., *Radicals in Organic Synthesis*, Wiley-VCH, Weinheim, **2001**; b) A. Gansäuer, Ed., *Radicals in Synthesis*, Vol. 263 264, Springer-Verlag, Berlin, **2006**.
- [8] W. P. Neumann, *Synthesis* **1987**, *1987*, 665,683.
- [9] a) B. Buck, A. Mascioni, L. Que, G. Veglia, *J. Am. Chem. Soc.* **2003**, *125*, 13316-13317; b) J. Gui-bin, Z. Qun-fang, H. Bin, *Bull. Environ. Contam. Toxicol.* **2000**, *65*, 277-284.
- [10] A. Studer, S. Amrein, *Synthesis* **2002**, *14*, 835-849.
- [11] P. A. Baguley, J. C. Walton, *Angew. Chem. Int. Ed.* **1998**, *37*, 3072-3082.
- [12] a) P. A. Baguley, J. C. Walton, *Angew. Chem. Int. Ed.* **1998**, *37*, 3072-3082; b) A. Studer, S. Amrein, *Synthesis* **2002**, *2002*, 835-849; c) J. C. Walton, A. Studer, *Acc. Chem. Res.* **2005**, *38*, 794-802; d) V. Darmency, P. Renaud, in *Radicals in Synthesis I*, Vol. 263 (Ed.: A. Gansäuer), Springer Berlin Heidelberg, **2006**, pp. 71-106; e) S. Z. Zard, *Chem. Soc. Rev.* **2008**, *37*, 1603-1618.
- [13] a) H. G. Kuivila, L. W. Menapace, *J. Org. Chem.* **1963**, *28*, 2165-2167; b) E. J. Corey, J. W. Suggs, *J. Org. Chem.* **1975**, *40*, 2554-2555; c) G. Stork, P. M. Sher, *J. Am. Chem. Soc.* **1986**, *108*, 303-304; d) D. S. Hays, G. C. Fu, *J. Org. Chem.* **1996**, *61*, 4-5; e) R. M. Lopez, D. S. Hays, G. C. Fu, *J. Am. Chem. Soc.* **1997**, *119*, 6949-6950; f) J. Tormo, D. S. Hays, G. C. Fu, *J. Org. Chem.* **1998**, *63*, 5296-5297.
- [14] a) J. M. Berge, S. M. Roberts, *Synthesis* **1979**, *1979*, 471-472; b) D. P. Curran, C. T. Chang, *J. Org. Chem.* **1989**, *54*, 3140-3157; c) D. Crich, S. Sun, *J. Org. Chem.* **1996**, *61*, 7200-7201; d) D. P. Curran, S. Hadida, *J. Am. Chem. Soc.* **1996**, *118*, 2531-2532; e) S. Hadida, M. S. Super, E. J. Beckman, D. P. Curran, *J. Am. Chem. Soc.* **1997**, *119*, 7406-7407.
- [15] a) M. L. Bannasar, C. Juan, J. Bosch, *Chem. Commun.* **2000**, 2459-2460; b) E. Bandini, G. Favi, G. Martelli, M. Panunzio, G. Piersanti, *Org. Lett.* **2000**, *2*, 1077-1079; c) C. Mathe, J. L. Imbach, G. Gosselin, *Carbohydr. Res.* **2000**, *323*, 226-229; d) C. Chatgililoglu, J. Lalevee, *Molecules (Basel, Switzerland)* **2012**, *17*, 527-555.
- [16] C. Chatgililoglu, M. Ballestri, *Organomet.* **1995**, *14*, 5017-5018.
- [17] a) S. J. Cole, J. N. Kirwan, B. P. Roberts, C. R. Willis, *J. Chem. Soc., Perkin Trans. 1* **1991**, 103-112; b) H.-S. Dang, M. R. J. Elsegood, K.-M. Kim, B. P. Roberts, *J. Chem. Soc., Perkin Trans. 1* **1999**, 2061-2068.
- [18] a) D. Crich, L. Quintero, *Chem. Rev.* **1989**, *89*, 1413-1432; b) S. Z. Zard, *Angew. Chem. Int. Ed.* **1997**, *36*, 672-685.
- [19] a) P. Delduc, C. Tailhan, S. Z. Zard, *J. Chem. Soc., Chem. Commun.* **1988**, 308-310; b) J. E. Forbes, S. Z. Zard, *J. Am. Chem. Soc.* **1990**, *112*, 2034-2036; c) J. Axon, L. Boiteau, J. Boivin, J. E. Forbes, S. Z. Zard, *Tetrahedron Lett.* **1994**, *25*, 1719-1722.
- [20] a) G. Binmore, J. C. Walton, L. Cardellini, *J. Chem. Soc., Chem. Commun.* **1995**, 27-28; b) G. Binmore, L. Cardellini, J. C. Walton, *J. Chem. Soc., Perkin Trans. 2* **1997**, 757-762; c) P. A. Baguley, J. C. Walton, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2073-2082.
- [21] a) D. H. R. Barton, D. O. Jang, J. C. Jaszberenyi, *Tetrahedron Lett.* **1992**, *33*, 2311-2314; b) D. H. R. Barton, D. O. Jang, J. C. Jaszberenyi, *J. Org. Chem.* **1993**, *58*, 6838-6842.

- [22] a) S. R. Graham, J. A. Murphy, A. R. Kennedy, *J. Chem. Soc., Perkin Trans. 1* **1999**, 3071-3073; b) A. E. Graham, A. V. Thomas, R. Yang, *J. Org. Chem.* **2000**, *65*, 2583-2585.
- [23] S.-H. Ueng, M. Makhlof Brahmī, É. Derat, L. Fensterbank, E. Lacôte, M. Malacria, D. P. Curran, *J. Am. Chem. Soc.* **2008**, *130*, 10082-10083.
- [24] A. Solov'yev, S.-H. Ueng, J. Monot, L. Fensterbank, M. Malacria, E. Lacôte, D. P. Curran, *Org. Lett.* **2010**, *12*, 2998-3001.
- [25] S.-H. Ueng, L. Fensterbank, E. Lacôte, M. Malacria, D. P. Curran, *Org. Lett.* **2010**, *12*, 3002-3005.
- [26] S.-H. Ueng, L. Fensterbank, E. Lacote, M. Malacria, D. P. Curran, *Org. Biomol. Chem.* **2011**, *9*, 3415-3420.
- [27] X. Pan, E. Lacôte, J. Lalevée, D. P. Curran, *J. Am. Chem. Soc.* **2012**, *134*, 5669-5674.
- [28] a) J. C. Walton, *Angew. Chem. Int. Ed.* **2009**, *48*, 1726-1728; b) J. C. Walton, M. M. Brahmī, L. Fensterbank, E. Lacôte, M. Malacria, Q. Chu, S.-H. Ueng, A. Solov'yev, D. P. Curran, *J. Am. Chem. Soc.* **2010**, *132*, 2350-2358; c) J. C. Walton, M. M. Brahmī, J. Monot, L. Fensterbank, M. Malacria, D. P. Curran, E. Lacôte, *J. Am. Chem. Soc.* **2011**, *133*, 10312-10321.
- [29] a) J. A. Murphy, F. Rasheed, S. J. Roome, N. Lewis, *Chem. Commun.* **1996**, 737-738; b) J. A. Murphy, F. Rasheed, S. Gastaldi, T. Ravishanker, N. Lewis, *J. Chem. Soc., Perkin Trans. 1* **1997**, 1549-1558.
- [30] J. A. Murphy, *J. Org. Chem.* **2014**, Article ASAP.
- [31] J. A. Murphy, T. A. Khan, S.-z. Zhou, D. W. Thomson, M. Mahesh, *Angew. Chem. Int. Ed.* **2005**, *44*, 1356-1360.
- [32] J. A. Murphy, S.-z. Zhou, D. W. Thomson, F. Schoenebeck, M. Mahesh, S. R. Park, T. Tuttle, L. E. A. Berlouis, *Angew. Chem. Int. Ed.* **2007**, *46*, 5178-5183.
- [33] J. A. Murphy, J. Garnier, S. R. Park, F. Schoenebeck, S. Zhou, A. T. Turner, *Org. Lett.* **2008**, *10*, 1227-1230.
- [34] E. Cahard, F. Schoenebeck, J. Garnier, S. P. Y. Cutulic, S. Zhou, J. A. Murphy, *Angew. Chem. Int. Ed.* **2012**, *51*, 3673-3676.
- [35] E. Doni, S. O'Sullivan, J. A. Murphy, *Angew. Chem. Int. Ed.* **2013**, *52*, 2239-2242.
- [36] E. Doni, B. Mondal, S. O'Sullivan, T. Tuttle, J. A. Murphy, *J. Am. Chem. Soc.* **2013**, *135*, 10934-10937.
- [37] S. O'Sullivan, E. Doni, T. Tuttle, J. A. Murphy, *Angew. Chem. Int. Ed.* **2014**, *53*, 474-478.
- [38] G. Ciamician, P. Silber, *Ber. Dtsch. Chem. Ges* **1900**, *33*, 2911-2913.
- [39] G. Ciamician, *Science* **1912**, *36*, 385-394.
- [40] M. Fagnoni, D. Dondi, D. Ravelli, A. Albinì, *Chem. Rev.* **2007**, *107*, 2725-2756.
- [41] J. C. Walton, *Acc. Chem. Res.* **2014**, *47*, 1406-1416.
- [42] a) F. Portela-Cubillo, J. Lymer, E. M. Scanlan, J. S. Scott, J. C. Walton, *Tetrahedron* **2008**, *64*, 11908-11916; b) F. Portela-Cubillo, E. M. Scanlan, J. S. Scott, J. C. Walton, *Chem. Commun.* **2008**, 4189-4191.
- [43] a) E. M. Scanlan, A. M. Z. Slawin, J. C. Walton, *Org. Biomol. Chem.* **2004**, *2*, 716-724; b) E. M. Scanlan, J. C. Walton, *Chem. Commun.* **2002**, 2086-2087.
- [44] a) R. T. McBurney, A. D. Harper, A. M. Z. Slawin, J. C. Walton, *Chem. Sci.* **2012**, *3*, 3436-3444; b) R. T. McBurney, A. M. Z. Slawin, L. A. Smart, Y. Yu, J. C. Walton, *Chem. Commun.* **2011**, *47*, 7974-7976.
- [45] R. T. McBurney, J. C. Walton, *J. Am. Chem. Soc.* **2013**, *135*, 7349-7354.
- [46] a) D. H. R. Barton, D. Crich, W. B. Motherwell, *J. Chem. Soc., Chem. Commun.* **1983**, 939-941; b) D. H. R. Barton, D. Crich, W. B. Motherwell, *Tetrahedron Lett.* **1983**, *24*, 4979-4982; c) D. H. R. Barton, D. Crich, W. B. Motherwell, *Tetrahedron Lett.* **1983**, *24*, 4979-4982.
- [47] M. F. Saraiva, M. R. C. Couri, M. Le Hyaric, M. V. de Almeida, *Tetrahedron* **2009**, *65*, 3563-3572.

- [48] M. C. Corvo, M. M. A. Pereira, *Tetrahedron Lett.* **2002**, *43*, 455-458.
- [49] a) R. G. Johnson, R. K. Ingham, *Chem. Rev.* **1956**, *56*, 219-269; b) Z. Wang, L. Zhu, F. Yin, Z. Su, Z. Li, C. Li, *J. Am. Chem. Soc.* **2012**, *134*, 4258-4263; c) F. Yin, Z. Wang, Z. Li, C. Li, *J. Am. Chem. Soc.* **2012**, *134*, 10401-10404.
- [50] D. C. Nonhebel, J. C. Walton, *Free Radical Chemistry*, Cambridge University Press, Cambridge, UK, **1974**, pp. 99-127.
- [51] a) D. Budac, P. Wan, *J. Photochem. Photobiol. A: Chem.* **1992**, *67*, 135-166; b) M. Consuelo Jimenez, M. A. Miranda, in *Photochemistry: Volume 38, Vol. 38*, RSC, **2010**, pp. 143-167.
- [52] J. G. Calvert, J. N. Pitts, Wiley, **1966**.
- [53] H. Nakayama, A. Itoh, *Tetrahedron Lett.* **2008**, *49*, 2792-2794.
- [54] R. S. Davidson, K. Harrison, P. R. Steiner, *J. Chem. Soc. C* **1971**, 3480-3482.
- [55] R. S. Davidson, P. R. Steiner, *J. Chem. Soc. C* **1971**, 1682-1689.
- [56] R. S. Davidson, S. Korkut, P. R. Steiner, *J. Chem. Soc. D* **1971**, 1052-1052.
- [57] A. Sugimori, K. t. Takada, T. Kimura, J. Kamimura, *Bul. Chem. Soc. Jpn.* **1981**, *54*, 2068-2071.
- [58] S. Farhadi, P. Zaringhadam, R. Z. Sahamieh, *Tetrahedron Lett.* **2006**, *47*, 1965-1968.
- [59] a) A. G. Griesbeck, K.-D. Warzecha, J. M. Neudörfl, H. Görner, *Synlett* **2004**, 2347-2350; b) A. Soldevilla, R. Perez-Ruiz, Y. D. Miara, A. Griesbeck, *Chem. Commun.* **2010**, *46*, 3747-3749; c) A. G. Griesbeck, N. Nazarov, J. M. Neudorfl, M. Heffen, *Green Chem.* **2012**, *14*, 3004-3006; d) M. Horvat, K. Mlinaric-Majerski, A. G. Griesbeck, N. Basaric, *Photochem. Photobiol. Sci.* **2011**, *10*, 610-617.
- [60] A. G. Griesbeck, W. Kramer, J. Lex, *Angew. Chem. Int. Ed.* **2001**, *40*, 577-579.
- [61] M. Reckenthäler, A. G. Griesbeck, *Adv. Synth. Catal.* **2013**, *355*, 2727-2744.
- [62] D. A. Nicewicz, T. M. Nguyen, *ACS Catal.* **2013**, *4*, 355-360.
- [63] a) K. Zeitler, *Angew. Chem. Int. Ed.* **2009**, *48*, 9785-9789; b) T. P. Yoon, M. A. Ischay, J. Du, *Nat. Chem.* **2010**, *2*, 527-532; c) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102-113; d) J. Xuan, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 6828-6838; e) J. W. Tucker, C. R. J. Stephenson, *J. Org. Chem.* **2012**, *77*, 1617-1622; f) Y.-Q. Zou, J.-R. Chen, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2013**, *52*, 11701-11703; g) J. Xuan, L.-Q. Lu, J.-R. Chen, W.-J. Xiao, *Eur. J. Org. Chem.* **2013**, *2013*, 6755-6770; h) Y. Xi, H. Yi, A. Lei, *Org. Biomol. Chem.* **2013**, *11*, 2387-2403; i) T. Koike, M. Akita, *Synlett* **2013**, *24*, 2492-2505; j) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322-5363.
- [64] a) H. Cano-Yelo, A. Deronzier, *J. Chem. Soc., Perkin Trans. 2* **1984**, 1093-1098; b) H. Cano-Yelo, A. Deronzier, *J. Chem. Soc., Faraday Trans. 1* **1984**, *80*, 3011-3019; c) J.-M. Zen, S.-L. Liou, A. S. Kumar, M.-S. Hsia, *Angew. Chem. Int. Ed.* **2003**, *42*, 577-579; d) S. Fukuzumi, S. Mochizuki, T. Tanaka, *J. Phys. Chem.* **1990**, *94*, 722-726; e) K. Okada, K. Okamoto, N. Morita, K. Okubo, M. Oda, *J. Am. Chem. Soc.* **1991**, *113*, 9401-9402.
- [65] D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77-80.
- [66] Y. Yoshimi, M. Masuda, T. Mizunashi, K. Nishikawa, K. Maeda, N. Koshida, T. Itou, T. Morita, M. Hatanaka, *Org. Lett.* **2009**, *11*, 4652-4655.
- [67] M. T. Pirnot, D. A. Rankic, D. B. C. Martin, D. W. C. MacMillan, *Science* **2013**, *339*, 1593-1596.
- [68] F. R. Petronijević, M. Nappi, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2013**, *135*, 18323-18326.
- [69] Z. Zuo, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 5257-5260.
- [70] M. A. Ischay, M. E. Anzovino, J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **2008**, *130*, 12886-12887.
- [71] J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **2009**, *131*, 14604-14605.

- [72] J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2009**, *131*, 8756-8757.
- [73] J. D. Nguyen, E. M. D'Amato, J. M. R. Narayanam, C. R. J. Stephenson, *Nature Chem.* **2012**, *4*, 854-859.
- [74] J. D. Nguyen, Rei, C. Dai, C. R. J. Stephenson, *Chem. Commun.* **2013**, *49*, 4352-4354.
- [75] J. W. Tucker, J. M. R. Narayanam, S. W. Krabbe, C. R. J. Stephenson, *Org. Lett.* **2010**, *12*, 368-371.
- [76] L. Furst, J. M. R. Narayanam, C. R. J. Stephenson, *Angew. Chem. Int. Ed.* **2011**, *50*, 9655-9659.
- [77] S. Lin, M. A. Ischay, C. G. Fry, T. P. Yoon, *J. Am. Chem. Soc.* **2011**, *133*, 19350-19353.
- [78] M. J. Schnermann, L. E. Overman, *Angew. Chem. Int. Ed.* **2012**, *51*, 9576-9580.
- [79] A. L. Linsebigler, G. Lu, J. T. Yates, *Chem. Rev.* **1995**, *95*, 735-758.
- [80] G. Palmisano, V. Augugliaro, M. Pagliaro, L. Palmisano, *Chem. Commun.* **2007**, 3425-3437.
- [81] T. Ohno, K. Sarukawa, K. Tokieda, M. Matsumura, *J. Catal.* **2001**, *203*, 82-86.
- [82] D. C. Hurum, A. G. Agrios, K. A. Gray, T. Rajh, M. C. Thurnauer, *J. Phys. Chem. B* **2003**, *107*, 4545-4549.
- [83] D. Ravelli, D. Dondi, M. Fagnoni, A. Albini, *Chem. Soc. Rev.* **2009**, *38*, 1999-2011.
- [84] J. A. Turner, *Science* **2004**, *305*, 972-974.
- [85] A. Fujishima, K. Honda, *Nature* **1972**, *238*, 37-38.
- [86] C.-Y. Hsiao, C.-L. Lee, D. F. Ollis, *J. Catal.* **1983**, *82*, 418-423.
- [87] U. I. Gaya, A. H. Abdullah, *J. Photochem. & Photobiol. C* **2008**, *9*, 1-12.
- [88] a) M. A. Fox, M. T. Dulay, *Chem. Rev.* **1993**, *93*, 341-357; b) M. A. Fox, *Acc. Chem. Res.* **1983**, *16*, 314-321; c) X. Lang, W. Ma, C. Chen, H. Ji, J. Zhao, *Acc. Chem. Res.* **2013**, *47*, 355-363.
- [89] Y. Shiraishi, T. Hirai, *J. Photochem. Photobiol. C* **2008**, *9*, 157-170.
- [90] V. M. Zakoshansky, *Petrol. Chem.* **2007**, *47*, 273-284.
- [91] Y. Shiraishi, T. Hirai, *J. Photochem. & Photobiol. C* **2008**, *9*, 157-170.
- [92] Y. Shiraishi, N. Saito, T. Hirai, *J. Am. Chem. Soc.* **2005**, *127*, 12820-12822.
- [93] C. B. Almquist, P. Biswas, *Appl. Catal. A - Gen.* **2001**, *214*, 259-271.
- [94] O. S. Mohamed, A. E.-A. M. Gaber, A. A. Abdel-Wahab, *J. Photochem. Photobiol. A: Chem.* **2002**, *148*, 205-210.
- [95] H. Yoshida, C. Murata, T. Hattori, *Chem. Commun.* **1999**, 1551-1552.
- [96] C. M. Wang, T. E. Mallouk, *J. Am. Chem. Soc.* **1990**, *112*, 2016-2018.
- [97] A. H. S. Higashida, R. Kawakatsu, N. Fujiwara, M. Matsumura, *Chem. Commun.* **2006**, 2804-2806.
- [98] a) J. L. Ferry, W. H. Glaze, *Langmuir* **1998**, *14*, 3551-3555; b) J. L. Ferry, W. H. Glaze, *J. Phys. Chem. B* **1998**, *102*, 2239-2244.
- [99] F. Mahdavi, T. C. Bruton, Y. Li, *J. Org. Chem.* **1993**, *58*, 744-746.
- [100] a) H. Al-Ekabi, P. De Mayo, *Tetrahedron* **1986**, *42*, 6277-6284; b) A. M. Draper, M. Ilyas, P. De Mayo, V. Ramamurthy, *J. Am. Chem. Soc.* **1984**, *106*, 6222-6230; c) A. Maldotti, R. Amadelli, C. Bartocci, V. Carassiti, *J. Photochem. Photobiol. A: Chem.* **1990**, *53*, 263-271; d) M. Ilyas, P. De Mayo, *J. Am. Chem. Soc.* **1985**, *107*, 5093-5099.
- [101] H. Kisch, *Angew. Chem. Int. Ed.* **2013**, *52*, 812-847.
- [102] R. Künne, C. Feldmer, F. Knoch, H. Kisch, *Chem. Eur. J.* **1995**, *1*, 441-448.
- [103] W. Schindler, F. Knoch, H. Kisch, *Chem. Ber.* **1996**, *129*, 925-932.
- [104] H. Keck, W. Schindler, F. Knoch, H. Kisch, *Chem. Eur. J.* **1997**, *3*, 1638-1645.
- [105] L. Cermenati, M. Mella, A. Albini, *Tetrahedron* **1998**, *54*, 2575-2582.
- [106] a) N. H. S. Marinković, *Chem. Commun.* **2001**, 1576-1578; b) N. H. S. Marinković, *Int. J. Photoenergy* **2003**, *5*, 175-182; c) S. Marinković, N. Hoffmann, *Eur. J. Org. Chem.* **2004**, *2004*, 3102-3107.

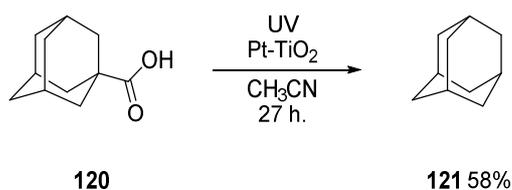
- [107] S. Bertrand, C. Glapski, N. Hoffmann, J.-P. Pete, *Tet. Lett.* **1999**, *40*, 3169-3172.
- [108] T. Caronna, C. Gambarotti, L. Palmisano, C. Punta, F. Recupero, *Chem. Commun.* **2003**, 2350-2351.
- [109] T. Caronna, C. Gambarotti, L. Palmisano, C. Punta, F. Recupero, *J. Photochem. Photobiol. A: Chem.* **2005**, *171*, 237-242.
- [110] S. Nishimoto, B. Ohtani, T. Yoshikawa, T. Kagiya, *J. Am. Chem. Soc.* **1983**, *105*, 7180-7182.
- [111] B. Pal, S. Ikeda, H. Kominami, Y. Kera, B. Ohtani, *J. Catal.* **2003**, *217*, 152-159.
- [112] B. Ohtani, H. Osaki, S. Nishimoto, T. Kagiya, *J. Am. Chem. Soc.* **1986**, *108*, 308-310.
- [113] a) D. Ravelli, D. Dondi, M. Fagnoni, A. Albinì, *Chem. Soc. Rev.* **2009**, *38*, 1999-2011; b) J.-M. Herrmann, *Appl. Catal. B - Environ.* **2010**, *99*, 461-468.

## **Chapter 2:**

# **Radical Dimerisations of Carboxylic Acids by Homolytic Decarboxylation**

## 1.0 Introduction

First studied in the late 70's by Bard and co-workers, the photo-Kolb  reaction involves the homolytic decarboxylation of carboxylic acids using photoexcited TiO<sub>2</sub>.<sup>[1]</sup> Oxidation of the carboxylate moiety by the titania valence band furnishes a radical cation which loses a proton and eliminates CO<sub>2</sub> by  $\beta$ -scission to generate the corresponding alkyl radical. Contrary to the classical Kolb  reaction, where the major product is the radical homo-dimer, the authors reported saturated alkanes as the major products, purportedly formed by a proton-coupled electron transfer at the titania surface. A range of simple, aliphatic carboxylic acids – acetic acid, propionic acid, *n*-butyric acid, *n*-valeric acid and pivalic acid – were demonstrated to react in this way with the volatile hydrocarbon products characterised by GC-analysis of the headspace gas following photolysis. Only one isolated yield was achieved; the decarboxylation of adamantane-1-carboxylic acid **120** to furnish adamantane **121** (Sch. 1). The intermediacy of radicals was supported by EPR studies.



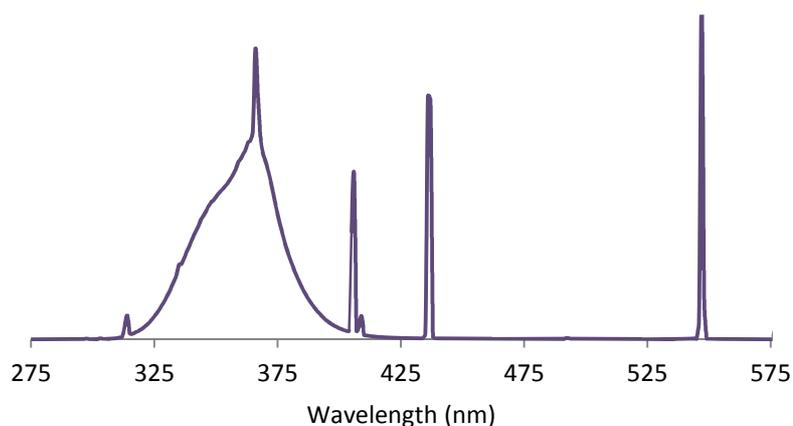
**Scheme 1.**

The aim of this work is to investigate the synthetic utility of the photo-Kolb  reaction as a means of generating free radicals. A diverse range of carboxylic acids is to be examined under differing conditions with the goal of finding out the strengths and limitations of this approach and determining its viability as a synthetic tool.

## 2.0 Results & Discussion

### 2.1 Experimental Setup

As previously discussed, titania photoredox catalysis has been studied in depth in the fields of water splitting and environmental depollution. As such there are a great many forms of the titania catalyst which are either available to purchase or can be conveniently prepared. Degussa's P25 (now supplied by Evonik) was chosen for this work as it has been demonstrated to be the catalyst *par excellence* in several studies.<sup>[2]</sup> Consisting of a 3:1 mixture of the anatase and rutile polymorphs it has a surface area of  $49 \text{ m}^2 \text{ g}^{-1}$  and a band gap of 3.2 eV. This approximates to an excitation wavelength of *ca.* 365 nm (in anatase) which lies in the UVA region of the spectrum. Conveniently, this means that fluorescent tubes designed for use in facial tanning lamps can be used to provide photons with sufficient energy to excite the  $\text{TiO}_2$  band gap. Two hemispherical banks of six Phillips Cleo 29 cm 15 W tubes (output profile shown in Fig. 1) were fabricated for a fraction of the cost of a specialised photoreactor setup. As UVA photons are not cut out by Pyrex there was no need to employ expensive quartz reaction vessels.



**Figure 1.** Lamp output profile of Phillips Cleo 29 cm 15 W tubes used in reaction setup.

To preclude the destructive, reactive oxygen species-mediated processes, for which titania photoredox catalysis has become well known, it was necessary to carry out photolyses in the absence of oxygen and water. To achieve this, Pyrex Schlenk tubes were placed in an oven at  $130 \text{ }^\circ\text{C}$  for a minimum of 1 hour prior to use, evacuated and then back filled with argon three times before being allowed to cool to ambient temperature under a positive argon atmosphere. The  $\text{TiO}_2$  and desired reagents were then added with a fast stream of

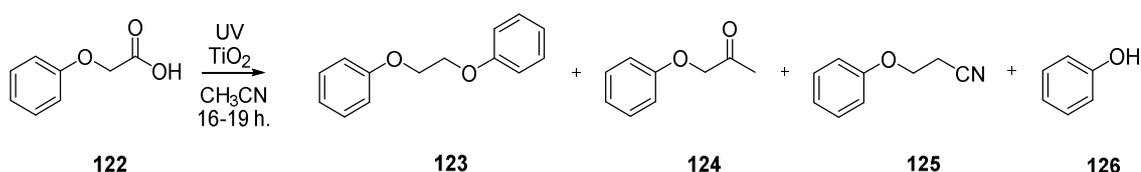
argon flowing. Solvents were distilled immediately prior to use and were introduced to the reaction vessel *via* an oven-dried syringe. CH<sub>3</sub>CN was the solvent of choice for the vast majority of reactions carried out and was distilled over CaH<sub>2</sub>. The reaction mixture was then degassed, typically by bubbling with argon for 20 minutes, before the light source was switched on. A positive argon atmosphere was maintained for the duration of the photolysis. The P25 nanoparticles have a particle size of *ca.* 21 nm, meaning that they could conveniently be removed by filtration through a Celite plug upon completion of the reaction. A photograph illustrating a typical reaction setup is shown in in Fig. 2 below.



**Figure 2.**

## 2.2 Reaction Optimisation

By analogy with the work carried out by Bard and co-workers, investigations were initiated by photolysing carboxylic acids alone in a dispersion of titania in CH<sub>3</sub>CN. Phenoxyacetic acid **122** was chosen as the reagent with which to optimise this process as it had been demonstrated to successfully decarboxylate and release phenoxyethyl radicals under similar conditions.<sup>[3]</sup> Furthermore, unlike the simple acids employed by Bard, the photolysis products were expected to be non-volatile making them much easier to handle. For the purpose of the optimisation work it was decided to use NMR yields, determined from the <sup>1</sup>H spectra after work up by integration relative to a known amount of a CH<sub>2</sub>Br<sub>2</sub> standard.



Scheme 2.

Overnight irradiation of **122** using the reaction setup described in the previous section led to the observation of four products. The major product was determined to be 1,2-diphenoxyethane **123**, formed *via* the homo-dimerisation of two phenoxyethyl radicals generated upon reaction of **122** with the photoexcited titania. Phenoxyacetone **124** was also observed in each case. This is thought to form from the addition of phenoxyethyl radicals to the C≡N bond of the solvent to furnish an iminyl radical which in turn abstracts a hydrogen atom from another CH<sub>3</sub>CN molecule to give a primary imine and an α-cyanomethyl radical. Upon exposure to atmospheric moisture this imine is thought to rapidly hydrolyse to **124**. Heterodimerisation between α-cyanomethyl radicals and phenoxyethyl radicals gives rise to nitrile **125**. Phenol **126** was also detected in each case.

Entry	Equiv. TiO <sub>2</sub> Wrt <b>122</b>	Dispersion mg mL <sup>-1</sup>	Catalyst	Time h.	Yield <b>123</b>	Combined Yield
1	4	1	P25	16	21%	40%
2	4	2	"	"	7%	23%
3	8	2	"	18	16%	21%
4	8	5	"	16	28%	41%

Table 1. Yields determined from the <sup>1</sup>H spectra after work up by integration relative to a known amount of a CH<sub>2</sub>Br<sub>2</sub> standard.

Using the unaltered P25 catalyst yields were low and selectivities modest (Table 1). Bard and co-workers employed platinumised titania powders in their early work on the photo-Kolb  reaction, although details of the Pt-loading and method of preparation were vague.

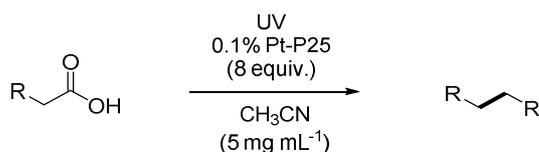
Platinised P25 with a loading of 0.1% (w/w) was prepared by destabilisation of a Pt-citrate colloid as this method has been shown to be facile, robust and efficient.<sup>[4]</sup> This catalyst proved much more effective and the optimum conditions were found to be eight equivalents of 0.1% Pt-P25 in a 5 mg mL<sup>-1</sup> dispersion in CH<sub>3</sub>CN (Table 2; entry 2). The high surface area (*ca.* 300 m<sup>2</sup> g<sup>-1</sup>) pure anatase catalyst PC500 performed poorly as did an immobilized titania catalyst which had been coated on the inside of a Pyrex tube by a sol-gel method<sup>[5]</sup> (Table 2; entries 3 & 4).

Entry	Equiv. TiO <sub>2</sub> Wrt <b>122</b>	Dispersion mg mL <sup>-1</sup>	Catalyst	Time h.	% Yield <b>123</b>	Combined Yield
1	8	2	Pt-P25 <sup>a</sup>	18	26%	52%
2	8	5	"	"	52%	73%
3	8	5	PC500	19	13%	32%
4	-	-	Coated Tube	18	12%	14%

**Table 2.** Yields determined from the <sup>1</sup>H spectra after work up by integration relative to a known amount of a CH<sub>2</sub>Br<sub>2</sub> standard. <sup>a</sup> 0.1% loading (w/w).

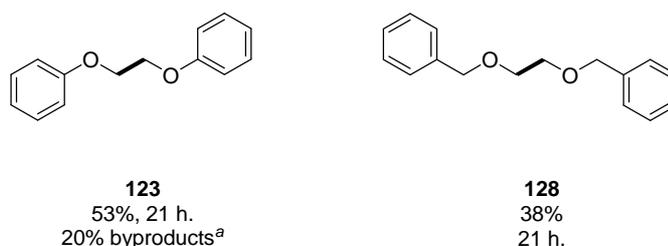
As two of the byproducts being formed are solvent derived (**124** & **125**), alternative reaction media were investigated in hope of improving the selectivity and yield. When photolyses were carried out in PhCF<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub> and DMF formation of these two byproducts was indeed eliminated. Conversion of **122** and yields of **123** were poor however. Thus CH<sub>3</sub>CN was still deemed the optimum reaction medium. Curiously, no anisole was detected in any photolyses under this setup. In an attempt to promote hydrogen abstraction over dimerisation, known H-donor solvents were introduced to the reaction vessel. Photolyses with toluene, THF and 1,4-cyclohexadiene present as a 10% (v/v) mixture in CH<sub>3</sub>CN each showed no evidence for the formation of anisole.

### 2.3 Substrate Scope of the Homo-Dimerisation Process



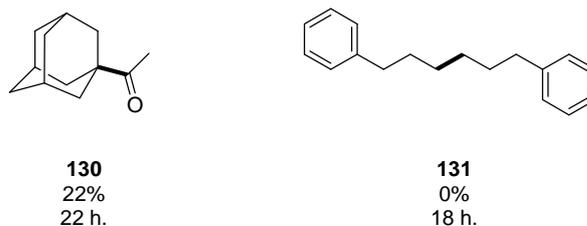
**Scheme 3.**

Scaling up of the reaction of **122** using the optimum conditions (Sch. 3) led to the isolation of **123** in a yield of 53% (Fig. 3). A combined yield of 20% for the aforementioned by-products was also determined. Benzyloxyacetic acid **127**, the benzyl analogue of **122**, was reacted under identical conditions but returned dimer **128** in a more modest yield of 38%. While no significant by-products were identified it is thought that the presence of readily abstractable benzylic hydrogens in **128** as well as the starting material **127** led to a number of degradative side reactions taking place.



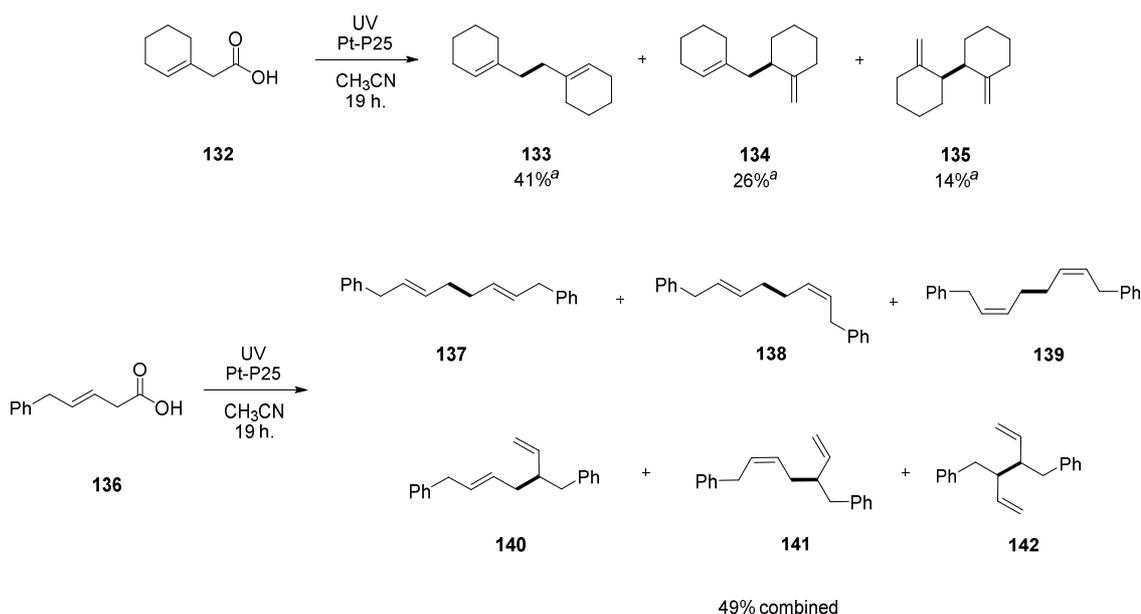
**Figure 3.** <sup>a</sup> 11% phenoxyacetone **124**, 6% phenol **126** & 3% 3-phenoxypropanenitrile **125**.

As previously discussed, the research group of Bard<sup>[1]</sup> reported the conversion of adamantane-1-carboxylic acid **120** to adamantane **121** in an isolated yield of 58%. When **120** was reacted under the conditions outlined above the only product detected was 1-adamantyl methyl ketone **129** in a yield of 22%. This presumably is formed by reaction with the solvent as outlined for **124**. When phenylbutyric acid **130** was photolysed under the optimised conditions no evidence for reaction taking place could be discerned. This suggested that some stabilising group must be present in the R moiety of the starting acid for reaction to take place.



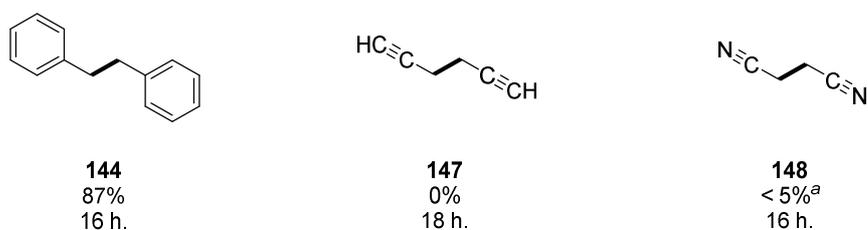
**Figure 4.**

Allyl and benzyl radicals are amongst the most highly stabilised to have been studied, hence it was decided to examine if they could be generated under these conditions. When cyclohex-1-enylacetic acid **132** was photolysed it did indeed lead to the formation of the desired allyl radicals. These dimerised rather unselectively however due to the existence of two reactive sites within the radical (Sch. 4, top). Due to the low boiling point of these dimers (*ca.* 80 °C) yields were calculated by running the reaction in CD<sub>3</sub>CN and taking an aliquot which was filtered directly into an NMR tube. Yields were then determined by integration relative to a CH<sub>2</sub>Br<sub>2</sub> standard. (*E*)-5-Phenylpent-3-enoic acid **136** was prepared in hope that any dimers formed would be sufficiently non-volatile to isolate. Photolysis followed by chromatography yielded a fraction containing six compounds. These have tentatively been assigned as six isomeric forms of the desired allyl dimers **137-142** (Sch. 4, bottom) based on their retention times, molecular mass and fragmentation patterns determined by GC-MS analysis. The additional isomers are thought to have arisen from *E/Z* isomerisation of the allyl radicals prior to dimerisation. The <sup>1</sup>H NMR spectrum of the mixture was too crowded to be interpreted in a useful manner. Gratifyingly, phenylacetic acid **143** dimerised cleanly and selectively giving rise to the desired product bibenzyl **144** in an excellent yield of 87% (Fig. 5).



**Scheme 4.** <sup>a</sup> Yields determined from the <sup>1</sup>H spectra after work up by integration relative to a known amount of a CH<sub>2</sub>Br<sub>2</sub> standard.

Disappointingly, propargyl radicals and  $\alpha$ -cyanomethyl radicals proved to be a great deal less successful. Photolyses of ethynylacetic acid **145** and cyanoacetic acid **146** resulted in the observation of unreacted starting material in both cases with only very insignificant amounts of the desired product **148** being observed in the latter case (Fig. 5). For the photolysis of **145**, analysis was carried out in a similar manner to the reaction of **132** due to the expected volatility of any products that may have been formed.



**Figure 5.** <sup>a</sup> Yields determined from the <sup>1</sup>H spectra after work up by integration relative to a known amount of a CH<sub>2</sub>Br<sub>2</sub> standard.

At this stage it was decided to examine a range of “benzyl type” radicals to further investigate the scope and limitation of this dimerisation reaction. This decision was made based on the poor selectivity observed with allyl radicals, the limited availability of  $\alpha$ -oxyalkyl radical generating precursors as well as their side reactions and the poor yields of the other radicals trialed to date.

## 2.4 Dimerisation of “Benzyl-Type” Radicals

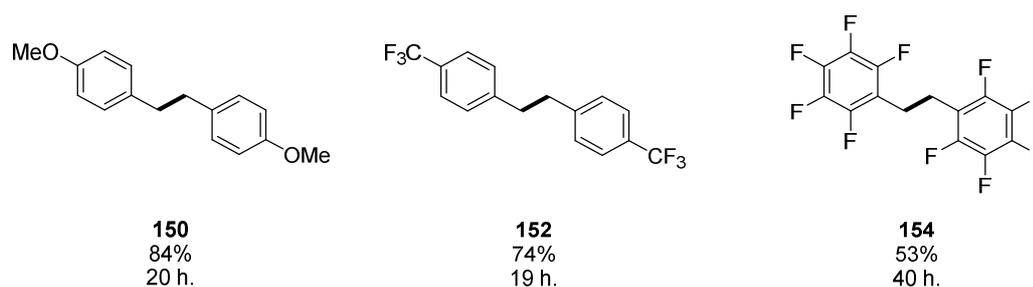


Figure 5.

Incorporation of substituents on the phenyl ring proved a success, with dimers bearing both electron withdrawing and electron releasing groups being formed *via* photolysis with the respective phenylacetic acids. 4-Methoxyphenylacetic acid **149** yielded the corresponding dimer **150** in a near identical yield to its unsubstituted analogue while 4-trifluoromethylphenylacetic acid **151** returned a slightly lower yield (Fig. 5). The heavily substituted, highly electron poor perfluorophenylacetic acid **153** did prove somewhat less reactive however. After an extended reaction time of 40 hours a still pleasing yield of 53% was obtained for the corresponding dimer **154**.

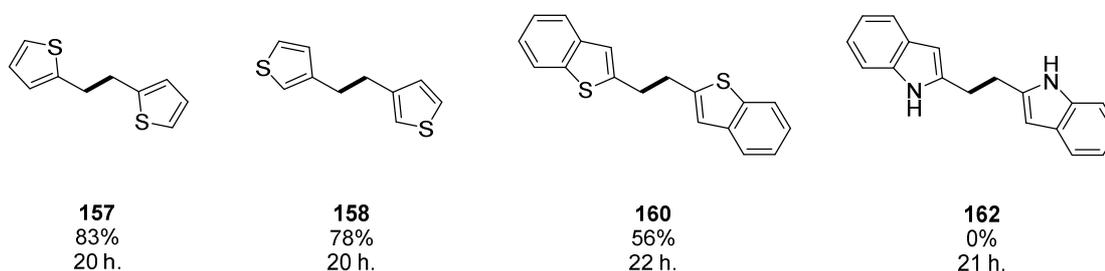
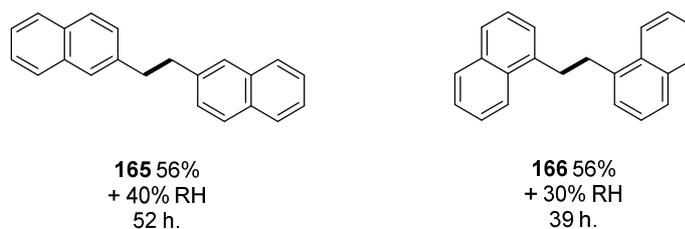


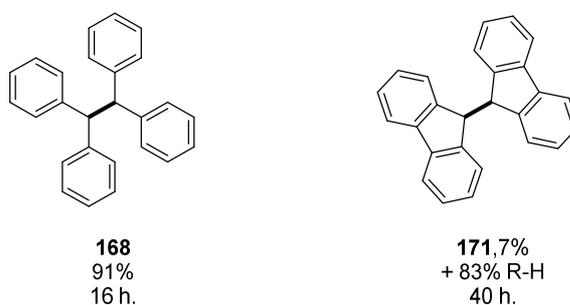
Figure 6.

Heterocyclic arylacetic acids also furnished the corresponding dimers. Photolysis of thiophenylacetic acids returned the expected dimers (**157** & **158**) in yields slightly lower than phenylacetic acid **143**. Benzo[*b*]thiophen-3-ylacetic acid **159** furnished the desired dimer **160** in a more modest yield of 56% upon photo-irradiation. Surprisingly, indole-3-acetic acid **161** proved to be entirely unreactive.  $^1\text{H}$  NMR and GC-MS analysis revealed only starting material present and repeat experiments confirmed this outcome.



**Figure 7.** Yields determined from the  $^1\text{H}$  spectra after work up by integration relative to a known amount of a  $\text{CH}_2\text{Br}_2$  standard.

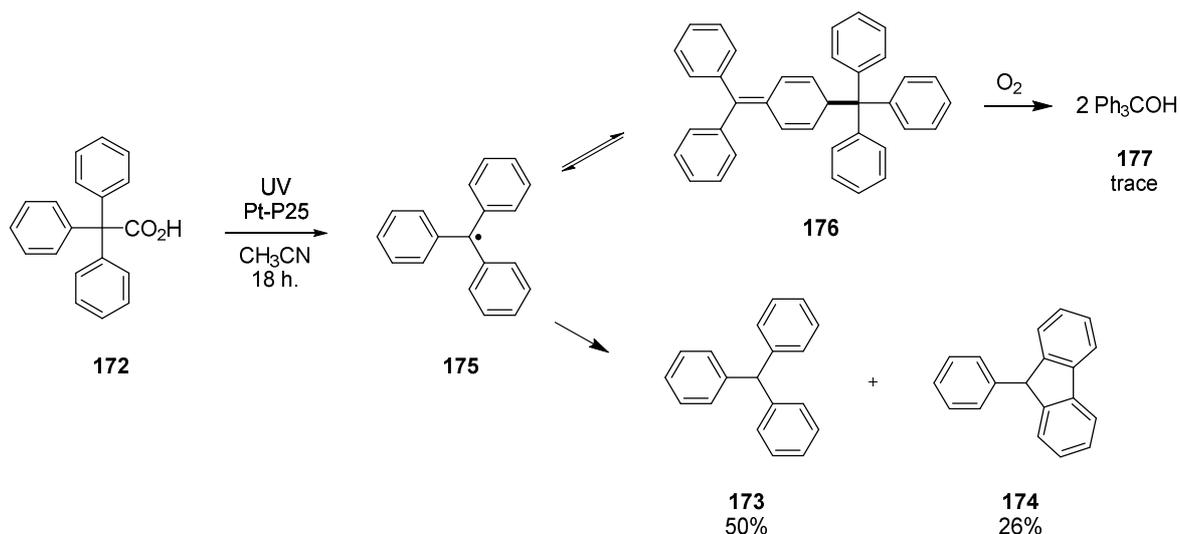
Increasing the size of the aryl group led to the saturated alkane, the major product reported by Bard for all photolyses, being obtained for the first time. Naphthalenylacetic acids **163** and **164** both generated a mixture of the homodimers **165** and **166** with the respective methylnaphthalenes (Fig. 7). The combined yields, although excellent, had to be determined by NMR as the mixtures proved inseparable by chromatographic means. Diphenylacetic acid **167** was converted to tetraphenylethane **168** in a near-quantitative yield of 91% upon reaction with the photoexcited titania (Fig. 8). The major product of the photolysis of 9*H*-fluorene-9-carboxylic acid **169** was the saturated alkane, 9*H*-fluorene **170**. Only 7% of the expected homodimer **171** was formed. Given the degree of similarity between acids **167** and **169** this was quite a surprising outcome.



**Figure 8.**

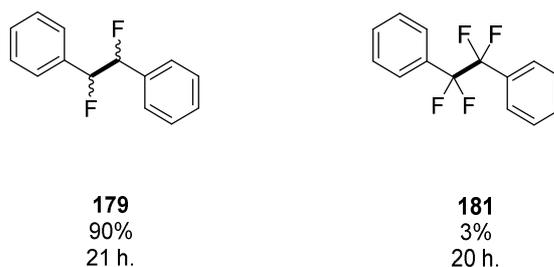
While Bard and co-workers reported the observation of trityl radicals when triphenylacetic acid **172** was photolysed with  $\text{TiO}_2$  in the resonant cavity of an EPR spectrometer, no corresponding preparative experiment was carried out. When **172** was reacted in the same manner as previous acids, triphenylmethane **173** and fluorene derivative **174** were obtained as an inseparable mixture (Sch. 6). **174** is thought to form either by hole-oxidation of the triphenylmethyl radical **175** to a cation which then undergoes electrophilic aromatic substitution with a neighbouring phenyl ring or *via* homolytic aromatic substitution followed by oxidative rearomatisation. No dimeric products were isolated, but given the now well understood behaviour of the trityl radical this was not unexpected. Gomberg's radical

exists as an equilibrium between the open shell system **175** and the quinoid dimer **176**.<sup>[6]</sup> It is probable that **176** is indeed formed during photolysis but that it converts back to **175** which is then transformed to **173** and **174** by the electrons and/or holes of the photoexcited titania. In accordance with Le Chatelier's principle this would take place until virtually no **176** remained. Traces of triphenylmethanol **177** (the expected product from the reaction of **176** with atmospheric oxygen) were detected by GC-MS prior to chromatography adding credence to this notion.



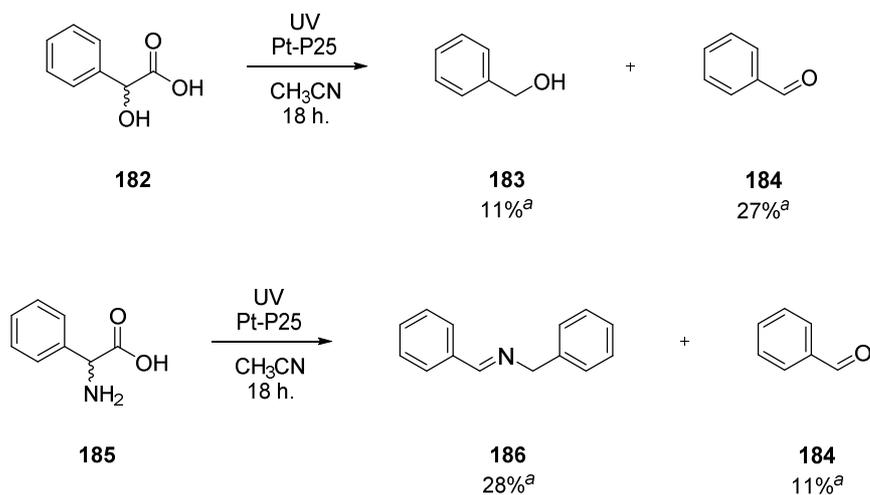
**Scheme 6.**

Following on from the success of introducing a second phenyl ring at the *alpha* position it was decided to explore the effects of the introduction of a variety of different substituents at this position. Racemic *alpha*-fluorophenylacetic acid **178** was converted to two stereoisomeric dimers **179** in an excellent combined yield of 90%. Inspection of the integral ratios in the <sup>1</sup>H {<sup>19</sup>F} NMR spectrum revealed that, as expected, the D/L and *meso* isomers were present in a 1:1 ratio. Chemical shifts were assigned with the assistance of literature values as well as a <sup>1</sup>H, <sup>19</sup>F HMBC experiment. Incorporation of a second fluorine substituent at the same position in *alpha, alpha*-difluorophenylacetic acid **180** essentially shut down the reaction however. Following overnight irradiation a mere 3% of the product **181** was isolated. It is well known that the pyramidal character of C-centered radicals increases as more fluorine substituents are introduced.<sup>[7]</sup> It is thought that this alters the geometry of the acid-derived radical, hindering conjugation of the unpaired spin with the phenyl ring, to the extent that decarboxylation at the TiO<sub>2</sub> surface becomes energetically unfavourable.



**Figure 9.**

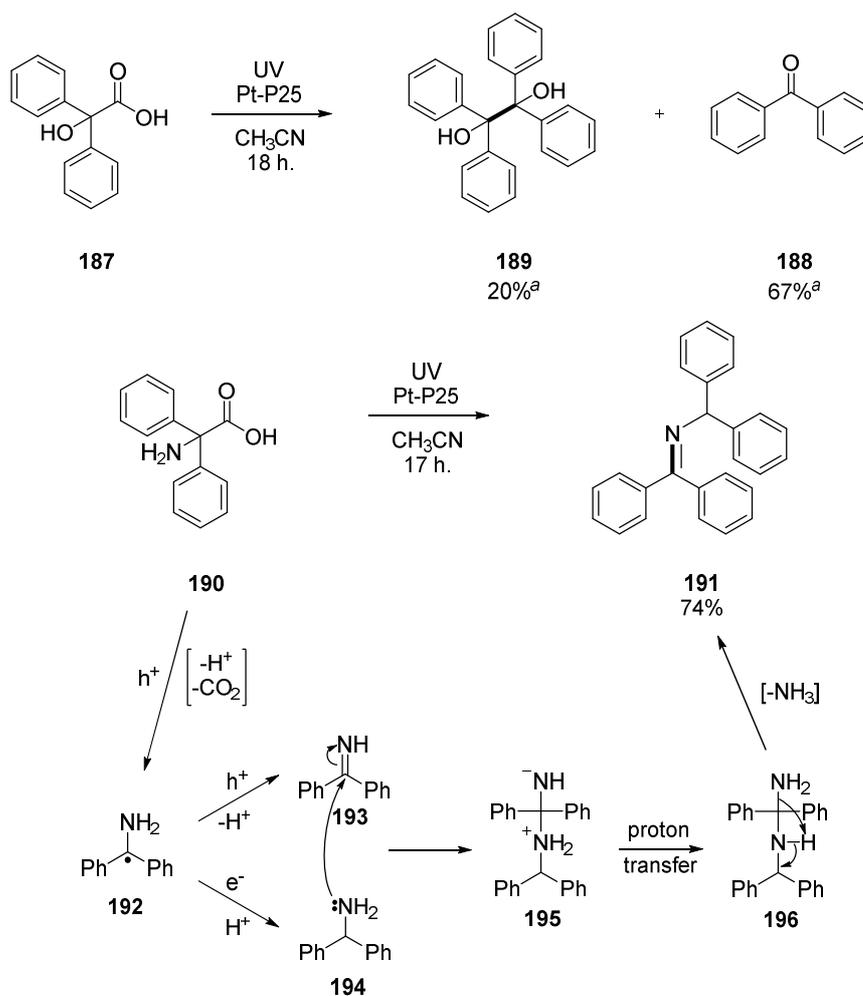
When alcohol and amine functional groups were introduced at the *alpha* position of the phenylacetic acid scaffold the chemistry was diverted away from homo-dimerisation. Racemic mandelic acid **182** was converted to benzyl alcohol **183** and benzaldehyde **184** (Sch. 7 top). It is believed that the *alpha*-hydroxybenzyl generated from **182** radical is reduced by the conduction band of the excited TiO<sub>2</sub> to form an anion which is then protonated to furnish **183** while oxidation to a cation and subsequent proton loss accounts for the formation of **184**. The reaction of *alpha*-phenylglycine **185** is thought to proceed in a similar fashion (Sch. 7 bottom). In this instance it appears that a condensation takes place between the products benzylamine (formed in a manner analogous to **183**) and benzaldimine (formed in a manner analogous to **184**) to form the secondary imine **186** with loss of ammonia. Any benzaldimine not consumed in this process was hydrolysed to benzaldehyde **184** upon exposure to atmospheric moisture during work up.



**Scheme 7.** <sup>a</sup> Yields determined from the <sup>1</sup>H spectra after work up by integration relative to a known amount of a CH<sub>2</sub>Br<sub>2</sub> standard.

Substitution of the diphenylacetic acid scaffold in a similar manner also yielded interesting results. Benzilic acid **187** returned benzophenone **188** as the major product after

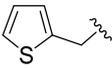
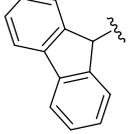
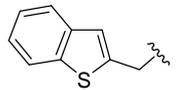
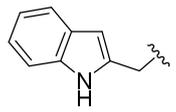
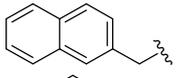
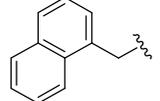
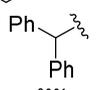
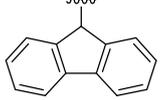
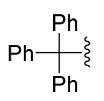
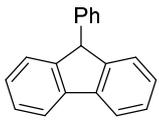
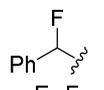
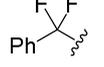
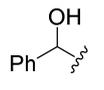
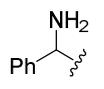
photolysis (Sch. 8 top), presumably *via* hole oxidation and subsequent proton loss. In this case however it was accompanied by the homodimer **189** in a modest yield of 20%. The photolysis of  $\alpha,\alpha$ -diphenylglycine **190** yielded only one product. The secondary ketimine **191** was isolated in a pleasing yield of 74% (Sch. 8 middle). It is believed that this was formed in a similar condensation to **186** between benzhydrylamine **194** and benzophenone imine **193** (Sch. 8 lower). Neither of these products was detected however, nor was the homodimer.

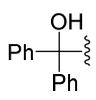
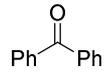
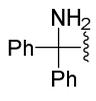
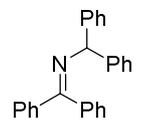


**Scheme 8.** <sup>a</sup> Yields determined from the <sup>1</sup>H spectra after work up by integration relative to a known amount of a CH<sub>2</sub>Br<sub>2</sub> standard.

The yields obtained during this work are summarised below in Table 3.



Entry	R	R-R (% Yield)	R-H (% Yield)	Other Product(s)
1	PhCH <sub>2</sub>	87%	-	-
2	4-MeO-PhCH <sub>2</sub>	84%	-	-
3	4-CF <sub>3</sub> -PhCH <sub>2</sub>	74%	-	-
4	C <sub>6</sub> F <sub>5</sub> CH <sub>2</sub>	53%	-	-
5		83%	-	-
6		78%	-	-
7		56%	-	-
8		-	-	-
9		56%	40%	-
10		56%	30%	-
11		91%	-	-
12		7%	83%	-
13		-	50%	 26%
14		90%	-	-
15		3%	-	-
16		-	11%	Ph-CHO 26%
17		-	-	Ph-CH=N-Ph 28% Ph-CHO 11%

Entry	R	Dimer (% Yield)	Reduced Alkane (% Yield)	Other Product(s)
18		20%	-	 67%
19		-	-	 74%

**Table 3.** Summary of results obtained during photolyses leading to the formation of “benzyl-type” radicals.

## 2.5 Attempted Hetero-Dimerisations

In order to improve the synthetic utility of the C-C bond forming process taking place it was decided to investigate the feasibility of carrying out hetero-dimerisations between acids with differing R groups. The persistent radical effect (PRE) is a phenomenon which leads to a highly selective cross coupling between two radicals when one is persistent, the other transient and both are formed at equal rates.<sup>[8]</sup> It exploits the reluctance of persistent radicals to terminate *via* homo-dimerisation reactions meaning that they can only be consumed by reaction with the transient species. Several elegant syntheses have made use of the PRE in recent years, the majority of these employing nitroxides.<sup>[9]</sup> In hope of making use of this effect in a titania-mediated dimerisation process, phenylacetic acid **143** and triphenylacetic acid **172** were reacted under a variety of conditions (Table 3).

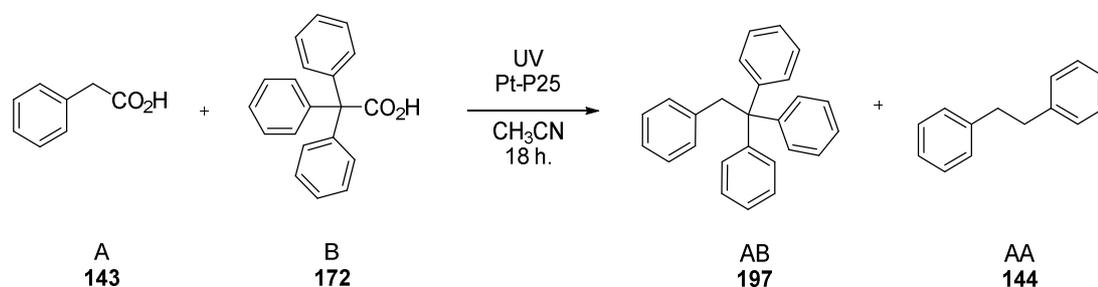


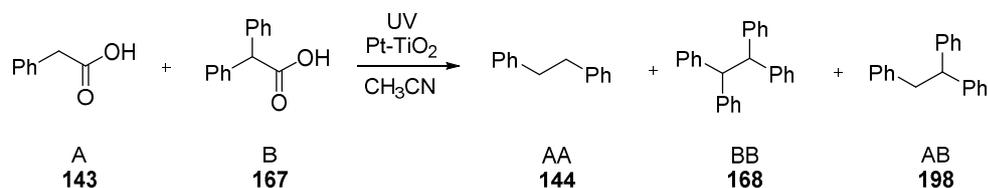
Figure 10.

Entry	Eqiuv. <b>143</b>	Eqiuv. <b>172</b>	Eqiuv. <b>TiO<sub>2</sub></b>	Yield <b>AB 197</b>	Yield <b>AA 144</b>	Ratio <b>AB:AA</b>
1	1.0	1.0	3.75	-	trace	nd
2	1.0	1.0	7.5	nd	nd	0.10 : 1.0
3	1.0	1.5	7.5	nd	nd	0.14 : 1.0
4	1.5	1.0	7.5	5%	44%	0.11 : 1.0
5	1.0	1.0	15	13%	48%	0.27 : 1.0
6	1.5	1.0	15	6%	48%	0.13 : 1.0

**Table 4.** Yields determined from the <sup>1</sup>H spectra after work up by integration relative to a known amount of a CH<sub>2</sub>Br<sub>2</sub> standard.

Disappointingly the PRE appeared unable to influence the reaction outcome in the desired fashion. Overnight photolyses with **143** and **172** led to the observation of bibenzyl **144** as the major product with insignificant amounts of the AB dimer 1,2,2,2-tetraphenylethane **197**. Trace amounts of triphenylmethane **173** were also detected in each case. The reaction with **172** and phenoxyacetic acid **122** was similarly unproductive. A 54% yield of the AA homodimer 1,2-diphenoxyethane **123** was determined with minimal amounts of **173** and no trace of the expected heterodimer. Moving away from reactions with the persistent trityl

radical it was decided to investigate the reactions of a range of other carboxylic acids to find out if anything better than a statistical product distribution could be achieved.



**Figure 11.**

Entry	Equiv. 143	Equiv. 167	Equiv. TiO <sub>2</sub>	Yield 144	Yield 168	Yield 198
1	1.0	1.0	7.5	40%	5%	8%
2	1.0	2.0	7.5	40%	2%	10%
3	1.0	5.0	7.5	26%	2%	13%
4	2.0	1.0	7.5	22%	12%	5%
5	5.0	1.0	7.5	1%	18%	-
6	1.0	1.0	15.0	11%	-	3%
7	5.0	1.0	15.0	11%	-	5%
8	1.0	5.0	15.0	65%	6%	30%

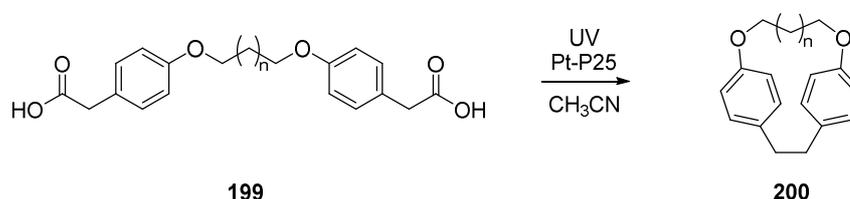
**Table 5.** Yields determined from the <sup>1</sup>H spectra after work up by integration relative to a known amount of a CH<sub>2</sub>Br<sub>2</sub> standard.

Using a variety of stoichiometric variations for the photolysis between **143** and diphenylacetic acid **167** a selective hetero-coupling still could not be achieved (Table 4). The best result was achieved using one equivalent of **143** with a five-fold excess of **167** and fifteen equivalents of the platinised titania catalyst, affording the 1,2,2-triphenylethane **198** in a 30% yield. Retaining these conditions whilst replacing the **167** component with a range of differing arylacetic acids returned dissatisfying results. When phenoxyacetic acid **122**, 2-thiopheneacetic acid **155** and 4-methoxyphenylacetic acid **149** were reacted with **143** the heterodimers were detected in yields ranging from 6-10% with poor conversion of starting materials also noted.

By definition the PRE is dependent on the radicals being formed at equal rates.<sup>[8a]</sup> As radical formation results from interaction with hole-trap sites on the titania, surface effects come into play making it highly unlikely that the different acids will react at the same rate. Furthermore, the PRE also depends on cross-dimerisation being the only termination process open to persistent species. Again, that is not the case with reactions with TiO<sub>2</sub> as further oxidation or reduction by the catalyst is possible. For the reactions not dependant on the PRE the ease/rate of hole oxidation and subsequent radical generation, is also thought to be responsible for the disappointing yields of heterodimers obtained.

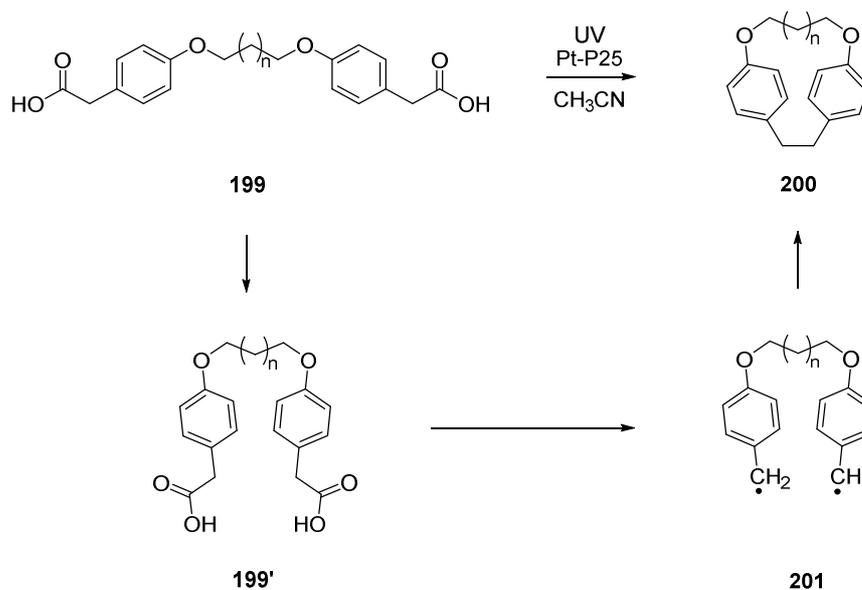
## 2.6 Intramolecular Dimerisations: Macrocyclisations

As per IUPAC a macrocycle is defined as "a cyclic macromolecule or a macromolecular cyclic portion of a molecule."<sup>[10]</sup> Generally, organic chemists consider any molecule containing a ring of nine or more atoms to be a macrocycle. Many drug molecules and total synthesis targets contain macrocyclic ring systems - the macrolide family of antibiotics being just one notable example.<sup>[11]</sup> Macrocyclisation reactions are mostly carried out under conditions of extreme dilution in order to minimise oligerimisation and tend to suffer from low yields in many cases.<sup>[12]</sup> This, coupled with the tendency for macrocycle ring-closures to be carried out late in a synthesis has driven the search for new, more efficient means of carrying out these reactions.



**Scheme 9.**

Based on the generally excellent yields and conversions obtained during the dimerisation of arylacetic acids in the previous section it was decided to attempt to extend this process towards intramolecular processes for the purpose of macrocycle syntheses (Sch. 9). Taking into account the various substituent effects which have already been discussed for the intermolecular dimerisation process, as well as the feasibility of preparation of the macrocycle precursors, di-alkoxyphenylacetic acids were the substrates of choice. These could conveniently be prepared from the corresponding phenols and alkyl bromides by treatment with base and, based upon the intermolecular photolysis of 4-methoxyphenylacetic acid **149** (pg 55), could reasonably be expected to react cleanly and efficiently.

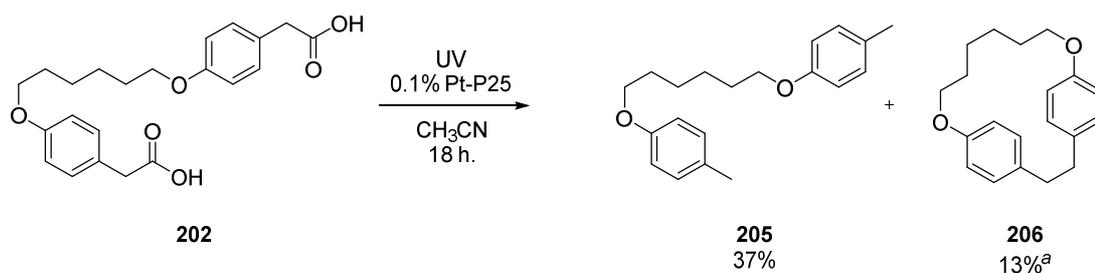


**Scheme 10.**

Entry	n	Ring Size	Strain Energy (kcal mol <sup>-1</sup> )	E <sub>199'-199</sub> (kcal mol <sup>-1</sup> )	E <sub>201-200</sub> (kcal mol <sup>-1</sup> )
1	4	18	22.7	19.1	-92.3
2	5	19	22.1	36.1	-113.0
3	6	20	23.9	38.8	-89.1

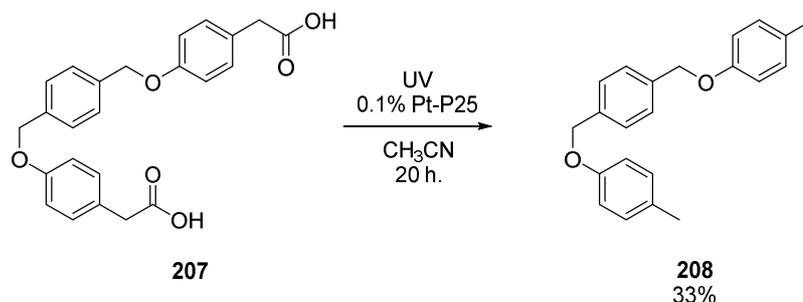
**Table 6**

Computational studies were carried out to help determine the ring size optimal for cyclisation prior to the undertaking of any synthetic work. Molecular modelling calculations at the MM2 level on a series of cyclophanes **199** (n = 1-10) revealed that 18-, 19- and 20-membered rings had the lowest strain energies. In addition, DFT computations at the B3LYP/6-31G(d,p) level were carried out. Geometries were optimised for the three diacids (**202**, **203** and **204**; n = 4,5,6) highlighted in the MM2 calculations. The energy of each diacid in a conformation (structure **199'**) whereby the two reaction centers were in sufficient proximity (3 Å) for dimerisation to take place was also computed. With these data in hand the energy cost of adopting such a conformation could be calculated. As expected it was found to be energetically unfavourable in all three cases. For diacids **203** and **204** however the energy requirement was in the region of double that of the energy required for **202**. Energies for the di-benzyl radical intermediates **201** were calculated in a similar conformation to **199'** and, using the energies computed for the optimised geometries of cyclophanes **200**, the energetics of the cyclisation of the **201** diradicals were calculated. Unsurprisingly these revealed the cyclisation process to be very thermodynamically downhill in all three instances.



**Scheme 11.** <sup>a</sup> Yield determined from the <sup>1</sup>H spectra after work up by integration relative to a known amount of a CH<sub>2</sub>Br<sub>2</sub> standard.

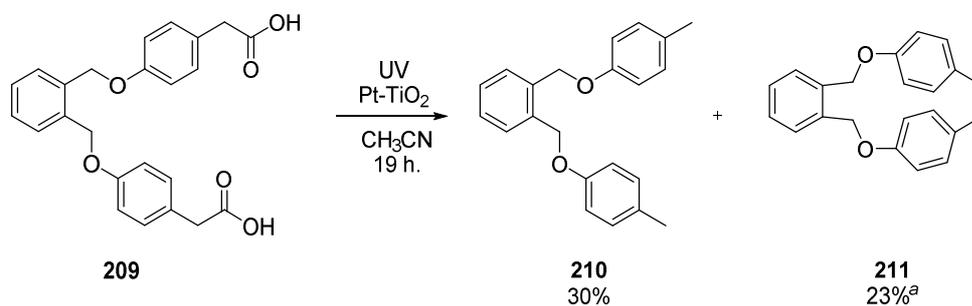
It was decided to prepare diacid **202** for photolysis as it was computed as having the lowest energy cost associated with adopting a conformation favourable for macrocyclisation while the other energies calculated were on a par with **203** and **204**. Heating of 1,6-dibromohexane and methyl 4-hydroxyphenylacetate with K<sub>2</sub>CO<sub>3</sub> in DMF for three days and subsequent basic hydrolysis with LiOH furnished **202** in a yield of 43% following recrystallisation from hot acetone. Photolysis of **202** did indeed lead to cyclisation *via* intramolecular dimerisation albeit in a disappointing yield of 13%. The major product of the reaction was the doubly reduced, saturated alkane **205** formed in a 37% yield. Due to the similarity between these two products, chromatography proved troublesome and **206** had to be characterised as a mixture with **205**. Sufficient **205** was isolated for it to be characterised pure.



**Scheme 12.**

It was hoped that inclusion of a rigid, planar phenyl ring in the linker between the two phenylacetic acid moieties would decrease the rotational freedom of the macrocyclisation precursors and result in higher yields of the desired cyclophane products. *Para*- and *ortho*-xylene based diacids **207** and **209** were prepared by a protocol analogous to that used for **202** and were obtained in yields of 77% and 18% respectively. Disappointingly, **207** returned only the di-alkane product **208** in a modest yield of 33% following photolysis. Evidently the two reaction centers are held too far apart by the rigid *p*-xylene linker. Photolysis of the *ortho*-

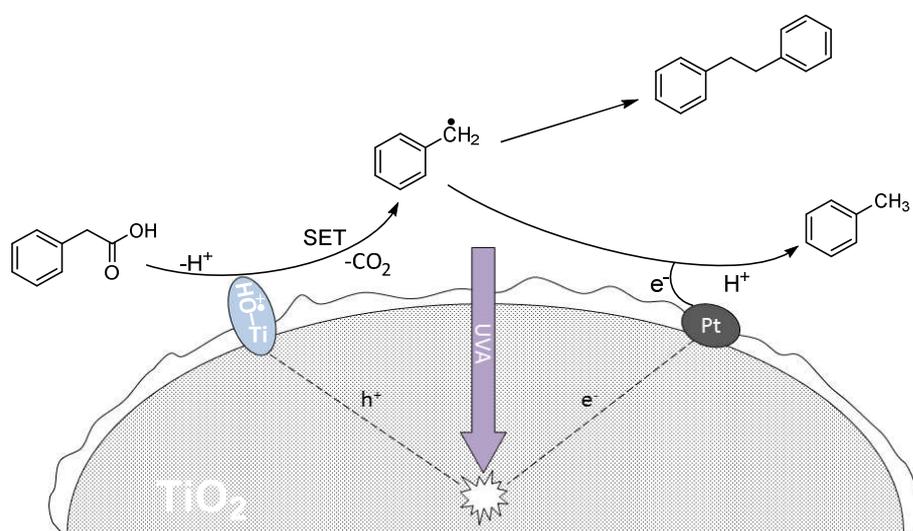
analogue **209** was more successful (Sch 13). As was the case with the reaction of **202**, **210** was isolated whilst **211** had to be characterised as a mixture.



**Scheme 13.** <sup>a</sup>Yield determined from the <sup>1</sup>H spectra after work up by integration relative to a known amount of a CH<sub>2</sub>Br<sub>2</sub> standard.

## 2.7 Mechanistic Considerations

Mechanistically the reaction is thought to be rather straightforward. Photoexcitation of the  $\text{TiO}_2$  by *ultra*-bandgap energy photons leads to the generation of an electron-hole pair which migrate through the bulk of the semiconductor to the surface where they react with trapping sites.<sup>[13]</sup> As per the earlier work by Bard,<sup>[1]</sup> interaction of the carboxylate of the acid with a hole-trap site leads to a single electron transfer (SET) which furnishes the surface bound carboxyl radical. Decarboxylation by  $\beta$ -scission in competition with back electron transfer gives rise to carbon centered radicals (typically “benzyl type” for this work). Subsequent EPR studies of similar radicals (pg 124-127) have shown that a significant portion of these radicals are freely tumbling in solution and not bound to the titania surface. Termination occurs by homo-dimerisation of two of these species in solution. Conversion of the benzyl-type radicals to the saturated alkane products is thought to be the result of a reduction/protonation cascade at the  $\text{TiO}_2$  surface and has some precedence.<sup>[14]</sup> A simplified representation of these events is presented in Sch. 14. Two significant questions remained to be answered however. Firstly - why does this reaction setup lead to dimerisation as the major chemical process whereas the previous work by Bard<sup>[1]</sup> selectively yielded the saturated alkanes? Secondly – what is the origin of the additional hydrogen atom in the saturated product?



Scheme 14.

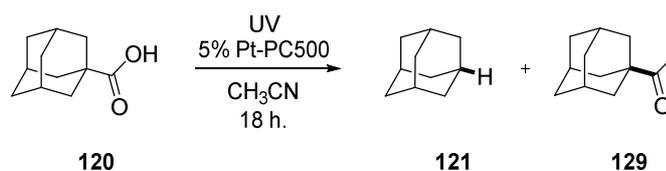
In an attempt to answer the first question it is necessary to scrutinise the details of the experimental conditions in both setups. Bard and co-workers employed 0.6 equivalents of a low surface area ( $1\text{-}10\text{ m}^2\text{ g}^{-1}$ ) pure anatase catalyst in  $6\text{ mg mL}^{-1}$  dispersion.<sup>[1]</sup> The platinum

loading of the catalyst was not quoted but from the general experimental section of the paper it is probable that it was in the range of 1-5%. The description of the reaction vessel was equally ambiguous but it seems likely that a Pyrex flat cell was employed. When compared with the setup described on pg 48 of this chapter it is clear that a number of variables exist which can be trialled (Table 6). The generation of adamantane **121** from adamantane-1-carboxylic **120** was the only isolated and fully characterised reaction reported so it was decided to use this as a test bed. When irradiated under the standard reaction conditions ketone **129** was the only product, isolated in a 22% yield.

Entry	Condition	This Work	Bard Work
1	Equiv. TiO <sub>2</sub>	8	0.6
2	TiO <sub>2</sub> polymorph	3:1 anatase/rutile	anatase
3	TiO <sub>2</sub> dispersion	5 mg mL <sup>-1</sup>	5 mg mL <sup>-1</sup>
4	Pt loading	0.1%	? <sup>a</sup>
5	Reaction vessel	Schlenk tube	Flat cell?
6	Light source	12 x 15W UVA tubes	2500 W Xe-Hg arc lamp

**Table 7**

PC500, a pure anatase catalyst with very large surface area (*ca.* 300 m<sup>2</sup> g<sup>-1</sup>), was loaded with 5% platinum in hope of mimicking the titania used by Bard.<sup>[1]</sup> When this was employed under the standard reaction conditions **129** was the only product observed (Table 7, entry 1). Inclusion of 10% heptane in the reaction mixture, as per the Bard work, saw little improvement as did a basic work up (entries 2 & 3). Using the stoichiometry reported by Bard saw only trace amounts of **129** formed with and without the heptane present. The reaction of naphthalene-2-ylacetic acid **163** to yield both the dimerised and reduced products was viewed as a more convenient comparison between the two catalysts. When the 5% Pt-PC500 was reacted under standard conditions the product distribution was essentially the same as with the 0.1% Pt-P25. In light of these results it is likely that the difference in selectivity and reactivity is arising from the difference in the power output of the light sources used and the efficiency with which the reaction vessels facilitate catalyst activation.



**Scheme 15.**

Entry	Conditions	Solvent	Yield 121	Yield 129
1	Standard	CH <sub>3</sub> CN	-	7%
2	Standard	10% Heptane/CH <sub>3</sub> CN	-	10%
3	Standard <sup>a</sup>	10% Heptane/CH <sub>3</sub> CN	-	9%
4	Bard	CH <sub>3</sub> CN	-	Trace
5	Bard	10% Heptane/CH <sub>3</sub> CN	-	Trace

**Table 8.** Yields determined from the <sup>1</sup>H spectra after work up by integration relative to a known amount of a CH<sub>2</sub>Br<sub>2</sub> standard. <sup>a</sup> with basic work up.

The source of the hydrogen atom in the reduced product is thought to be the titania catalyst. The intermediate radical is thought to pick up an electron and a proton from the surface of the catalyst. This proton is thought to originate from the surface species on the titania and this notion has been supported by later work with deuterium labelling (pg 127-128).

### 3.0 Conclusions

Irradiation with UVA of TiO<sub>2</sub>/CH<sub>3</sub>CN dispersions led to the generation of alkyl radicals from carboxylic acids. The major product of these reactions was the radical homo-dimer in most cases, not the saturated alkane.

Photolyses of phenylacetic acid derivatives provided a clean, efficient and generally selective route towards bibenzyl derivatives in good to excellent yields. Notable exceptions were acids with rigid, poly-cyclic aromatic groups such as naphthalene present which yielded significant quantities of the corresponding saturated alkane. Introduction of protic substituents such as alcohols and amines at the *alpha* position also resulted in nuisance side-reactions taking place.

The reactions of allyl and *alpha*-oxyalkyl radicals proved unselective even though the overall yields recorded were useful. Propargyl, *alpha*-cyanomethyl and saturated primary alkyl radical precursors proved unreactive.

Macrocyclisations to form cyclophanes were achieved by the photolysis of precursors containing two phenylacetic acid moieties. Yields were disappointing but this is a well-documented feature of macrocyclisations.

A simple mechanism has been proposed and is supported by experimental observations and literature precedent. The selectivity between dimerisation and reduction/protonation has been shown to be independent of the platinum loading and surface area of the catalyst used.

## 4.0 Experimental

### 4.1 General Experimental Details – Instrumentation and Techniques

**NMR Spectroscopy:** NMR spectra were recorded on Bruker AV III 500, Bruker AV II 400 and Bruker AV 300 instruments. Chemical shifts are reported in parts per million (ppm) from low to high frequency.  $^1\text{H}$  and  $^{13}\text{C}$  spectra are referenced to the residual solvent resonance while  $^{19}\text{F}$  spectra are references to  $\text{PhCF}_3$  ( $\delta = -63.72$ ). Coupling constants ( $J$ ) are reported in hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s = singlet, d = doublet, t = triplet, dd = double doublet, q = quartet, m = multiplet, b = broad.

**Mass Spectrometry:** Low and high resolution mass spectrometry was carried out at the EPSRC National Mass Spectrometry Service Centre, Swansea on a LTQ Orbitrap XL Spectrometer equipped with an ultra-high-field Orbitrap mass analyser with resolving power up to 450,000 FWHM and isotopic fidelity up to 240,000 FWHM at  $m/z$  200.

**GC-MS:** GC-MS analysis was performed using a Thermo Electron Corporation Trace GC Ultra combined with a Thermo Electron Corporation DSQ II. A Restex Rxi<sup>®</sup>-1ms column (30m x 0.25 mm x 0.1  $\mu\text{m}$ ) was used for compound separation and the ionisation mode was set to electron impact (EI). Injection volumes were between 1 and 10  $\mu\text{L}$ , depending on signal strength. Parameters: injector temperature 220  $^\circ\text{C}$ ; split ratio 20:1; constant column flow 3.0  $\text{mL min}^{-1}$ . Temperature profile: initial temperature 50  $^\circ\text{C}$ , heating to 300  $^\circ\text{C}$  at 10 $^\circ\text{C min}^{-1}$ ; 4 min hold time; total time 29 min.

**Melting Point Analysis:** Melting points (M.p.) were determined using a Sanyo Gallenkamp apparatus and are reported uncorrected.

**Chromatography:** Column chromatography was carried out using Silica 60A (particle size 40-63  $\mu\text{m}$ , Silicycle, Canada) as the stationary phase, and TLC was performed on precoated silica gel plates (0.20 mm thick, Sil G UV<sub>254</sub>, Macherey-Nagel, Germany) and observed under UV light.

**Anhydrous Solvents:** Tetrahydrofuran was distilled over sodium and acetonitrile was distilled over calcium hydride. Dimethylformamide was purchased anhydrous from Sigma Aldrich.

**Materials & Reagents:** All reagents and solvents were purchased from Sigma Aldrich, Alfa Aesar or TCI Europe and used without further purification unless stated.

**Computational Methods:** The ground-state geometries and energies of the precursor diacids were investigated using the Gaussian 09 program package. The standard B3LYP functional with the 6-31G(d,p) basis set was employed. Geometries were fully optimised without any symmetry constraints for all compounds.

Gaussian 09, Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

**Platinisation of titania powders:** Pt-TiO<sub>2</sub> was produced in accordance with the literature.<sup>[15]</sup>

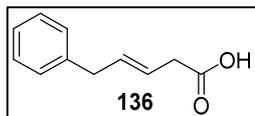
A platinum-citrate colloid was prepared by dissolving 30mg H<sub>2</sub>[PtCl<sub>6</sub>]·6H<sub>2</sub>O in 30mL of a 1% sodium citrate solution and 120 mL of deionised water. This mixture was refluxed at 150°C for four hours and the previously orange solution turned black. Pt-TiO<sub>2</sub> powders of various loadings were then prepared from this colloid as follows:

- 0.1% (w/w) Pt-P25 was prepared by adding 10 g of TiO<sub>2</sub> to 3.26 mL of the Pt-citrate colloid and 100 mL of deionised water followed by 14.4g of NaCl.
- 5.0% (w/w) Pt-PC500 was prepared by adding 1 g of TiO<sub>2</sub> to 132.5 mL of the Pt-citrate colloid followed by 10 g of NaCl.

Following de-stabilisation of the colloid the platinised TiO<sub>2</sub> powder was isolated by filtration, washed with copious amounts of deionised water and dried overnight at 130 °C.

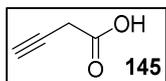
## 4.2 Preparation of Non-Commercially Available Reagents

### (E)-5-Phenylpent-3-enoic acid **136**



The title compound **136** was prepared in accordance with the previously reported method.<sup>[16]</sup> Hydrocinnamaldehyde (1.32 mL, 10 mmol), malonic acid (1.15 g, 11 mmol) and *N*-methylmorpholine (1.21 mL, 11 mmol) were heated at 95 °C for 7 hours. The reaction mixture was allowed to cool to room temperature before 11% H<sub>2</sub>SO<sub>4</sub> (5 mL) was added and the resultant mixture was allowed to stir for 30 minutes before being extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined extracts were washed with water (3 x 20 mL) before being dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Column chromatography on silica gel (eluent: 2% acetone in CH<sub>2</sub>Cl<sub>2</sub>) yielded **136** as a yellow solid (1.25 g, 71%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 295 K): δ = 3.13 (d, *J* = 6.9 Hz, 2H, CH<sub>2</sub>CO<sub>2</sub>H), 3.40 (d, *J* = 6.7 Hz, 2H, ArCH<sub>2</sub>), 5.61-5.67 (m, 1H, C=CH), 5.75-5.80 (m, 1H, C=CH'), 7.19-7.23 (m, 3H, ArH), 7.30-7.33 (m, 2H, ArH) 10.91 (bs, 1H, CO<sub>2</sub>H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 298 K): δ = 37.7, 38.9, 122.4, 126.2, 128.5, 128.6, 133.9, 140.0, 178.4. Data consistent with literature.<sup>[17]</sup>

### Ethynylacetic acid **145**



The title compound **145** was prepared in accordance with the previously reported method.<sup>[18]</sup> To a mixture of CrO<sub>3</sub> (3.0 g, 30 mmol) and H<sub>2</sub>SO<sub>4</sub> (20 mL) in water (75 mL) at 0 °C was added drop-wise a solution of but-3-yn-1-ol (1.14 mL, 15 mmol) in acetone (15 mL) over a period of two hours. The resultant mixture was allowed to warm to room temperature and stirred for a further six hours before being extracted with EtOAc (3 x 100 mL). The combined extracts were washed with H<sub>2</sub>O (2 x 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to give an off-white solid which was recrystallised from cyclohexane to yield **145** (0.59 g, 47%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 295 K): δ = 2.27 (t, *J* = 2.8 Hz, 2H, C≡CH), 3.40 (d, *J* = 2.8 Hz, 2H, CH<sub>2</sub>CO<sub>2</sub>H), 10.26 (bs, 1H, CO<sub>2</sub>H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 297 K): δ = 25.6, 72.4, 74.8, 174.0. Data consistent with literature.

## 4.3 General Procedures

### 4.3.1 General Procedure for SCPC Reactions

An oven-dried Pyrex Schlenk tube was evacuated while still hot and then back-filled with argon. This was repeated three times before the tube was allowed to cool to room temperature. Reagents and  $\text{TiO}_2$  were added with a fast stream of argon flowing before freshly distilled  $\text{CH}_3\text{CN}$  was added to generate the desired dispersion density (typically  $5 \text{ mg mL}^{-1}$  unless otherwise stated). The resulting mixture was typically degassed by bubbling with argon for 20 minutes. The mixture was then irradiated while still under a positive atmosphere of argon with two hemispherical banks of six 29 cm 15 W Philips Cleo tubes ( $\lambda = 350\text{nm}$ ) for the desired reaction time at ambient temperature. Following irradiation the  $\text{TiO}_2$  powder was removed by filtration through a Celite pad and the solvent removed under reduced pressure. Unless otherwise stated isolated yields are reported.

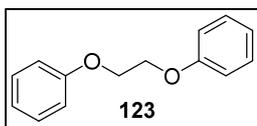
### 4.3.2 General Procedure for NMR Yields

In several instances yields were determined by  $^1\text{H}$  NMR spectroscopy. This was achieved by integration of peaks attributed to the product relative to a known amount (typically 1-5  $\mu\text{l}$ ) of a  $\text{CH}_2\text{Br}_2$  internal standard added directly to the tube prior to analysis. In most, but not all, instances spectra were recorded at 400-500 MHz from 32 scans at  $90^\circ$  pulse width using 30 second  $D_1$  relaxation time in order to obtain optimal signal to noise ratio and minimise the associated error.



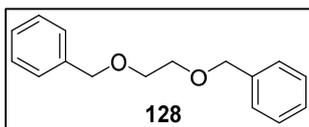
## 4.5 Preparative Photolyses

### 1,2-Diphenoxyethane **123**



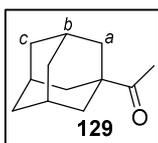
Phenoxyacetic acid (60 mg, 0.4 mmol), and Pt-TiO<sub>2</sub> (250 mg, 3.1 mmol) were reacted in accordance with the general procedure. Following irradiation for 21 h the crude reaction mixture was purified by column chromatography on silica gel (eluent: 50% CH<sub>2</sub>Cl<sub>2</sub> in petrol 40/60) to yield **123** as a colourless solid (22.5 mg, 53%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 297 K): δ = 4.34 (s, 4H, CH<sub>2</sub>), 6.95-7.00 (m, 6H, ArH), 7.28-7.34 (m, 4H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 298 K): δ = 66.5, 114.7, 121.1, 129.5, 158.7. Consistent with literature.<sup>[19]</sup> Analysis of the <sup>1</sup>H NMR prior to chromatography revealed phenoxyacetone (11% w.r.t. **123**), phenol (6% w.r.t. **123**) and 3-phenoxypropanenitrile (3% w.r.t. **123**). These data were consistent with literature.<sup>[20]</sup>

### 1,2-Bis(benzyloxy)ethane **128**



Benzyloxyacetic acid (66 mg, 0.4 mmol), and Pt-TiO<sub>2</sub> (250 mg, 3.1 mmol) were reacted in accordance with the general procedure. Following irradiation for 21 hours the crude reaction mixture was purified by column chromatography on silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>) to yield **128** as a colourless oil (18.6 mg, 53%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 295 K): δ = 3.67 (s, 4H, OCH<sub>2</sub>), 4.59 (s, 4H, ArCH<sub>2</sub>), 7.27-7.39 (m, 10H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 296 K): δ = 69.5, 73.3, 127.6, 127.8, 128.4, 138.3. Consistent with literature.<sup>[21]</sup>

### 1-Adamantyl methyl ketone **129**



Adamantane-1-carboxylic acid (115.3 mg, 0.64 mmol) and Pt-TiO<sub>2</sub> (410 mg, 5.12 mmol) were reacted in accordance with the general procedure. Following irradiation for 18 hours **129** was obtained as a yellow oil (24.8 mg, 22%) without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 296 K): δ = 1.67 (d, *J* = 11.5 Hz, 3H, H<sub>c</sub>), 1.74 (d, *J* = 11.5 Hz, 3H, H<sub>c</sub>'), 1.79 (d, *J* = 2.4 Hz, 6H, H<sub>a</sub>), 2.03 (bm, 3H, H<sub>b</sub>), 2.08 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 297 K): δ = 24.7, 28.3, 37.0, 38.7, 214.7. Data consistent with literature.<sup>[22]</sup>

### Photolysis reaction of phenylbutyric acid **130**

Phenylbutyric acid (14.8 mg, 0.09 mmol) and Pt-TiO<sub>2</sub> (60 mg, 0.75 mmol) were reacted in accordance with the general procedure. Following irradiation for 18 hours <sup>1</sup>H NMR and GC-MS analysis revealed only starting material present.

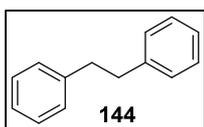
### Photolysis reaction of cyclohex-1-enylacetic acid **132**

Cyclohex-1-enylacetic acid (13 mg, 0.09 mmol) and Pt-TiO<sub>2</sub> (60 mg, 0.75 mmol) in CD<sub>3</sub>CN (12 mL) were reacted in accordance with the general procedure. Following irradiation for 19 hours <sup>1</sup>H NMR analysis wrt a CH<sub>2</sub>Br<sub>2</sub> standard revealed: 1,2-di(cyclohex-1-en-1-yl)ethane **133** (0.02 mmol, 41%), 2'-methylene-[1,1'-bi(cyclohexan)]-1-ene **134** (0.01 mmol, 26%) and 2,2'-dimethylene-1,1'-bi(cyclohexane) **135** (0.01 mmol, 14%). Data consistent with literature.<sup>[23]</sup>

### Photolysis reaction of (*E*)-5-phenylpent-3-enoic acid **136**

(*E*)-5-Phenylpent-3-enoic acid (112.8 mg, 0.64 mmol) and Pt-TiO<sub>2</sub> (410 mg, 5.12 mmol) were reacted in accordance with the general procedure for 19 hours. The reaction mixture was subjected to column chromatography on silica gel (eluent: 10% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) yielding a fraction containing five isomeric dimerised products (40.8 mg, 49 % combined). <sup>1</sup>H NMR analysis proved inconclusive but five compounds were observed by GC-MS (see pg 53-54 for full details). t<sub>R</sub> 14.59 & 14.90 min: *m/z* (%) 262 (2), 171 (23), 158 (29), 131 (85), 91 (100), 79 (6), 65 (7). t<sub>R</sub> 15.85 min: *m/z* (%) 262 (3), 171 (49), 131 (100), 115 (20), 91 (100), 77 (3), 67 (11). t<sub>R</sub> 16.73, 16.81 & 16.87 min: *m/z* (%) 262 (2), 171 (41), 158 (28), 143 (5), 131 (100), 115 (27), 91 (58), 77 (5), 65 (3).

### Bibenzyl **144**

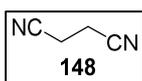


Phenylacetic acid (87 mg, 0.64 mmol), and Pt-TiO<sub>2</sub> (410 mg, 5.12 mmol) were reacted in accordance with the general procedure. Following irradiation for 16 hours **144** was obtained as a colourless solid (50.6 mg, 87%) without further purification. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 298 K): δ = 2.95 (s, 4H, CH<sub>2</sub>) 7.21-7.24 (m, 6H, ArH), 7.30-7.33 (m, 4H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 296 K): δ = 38.0, 126.0, 128.4, 128.5, 141.8. Consistent with literature.<sup>[24]</sup>

### Photolysis reaction of ethynylacetic acid **145**

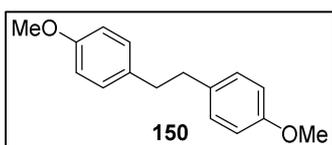
Ethynylacetic acid (7.9 mg, 0.09 mmol) and Pt-TiO<sub>2</sub> (60 mg, 0.75 mmol) were reacted in CD<sub>3</sub>CN (12 mL) in accordance with the general procedure. Following irradiation for 18 hours <sup>1</sup>H NMR and GC-MS analysis revealed only starting material present.

### Succinonitrile **148**



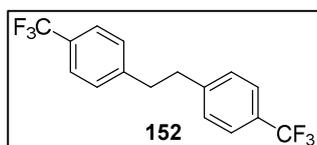
Cyanoacetic acid (54.5 mg, 0.64 mmol) and Pt-TiO<sub>2</sub> (410 mg, 5.12 mmol) were reacted in accordance with the general procedure. Following irradiation for 16 hours <sup>1</sup>H NMR analysis revealed **148** (< 0.03 mmol, < 5%) wrt a CH<sub>2</sub>Br<sub>2</sub> standard. Data consistent with literature.<sup>[25]</sup>

### 1,2-Bis(4-methoxyphenyl)ethane **150**



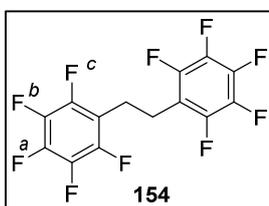
4-Methoxyphenylacetic acid (106.4 mg, 0.64 mmol) and 0.1% (w/w) Pt-TiO<sub>2</sub> (410mg, 5.12 mmol) were reacted in accordance with the general procedure. Following irradiation for 20 hours **150** was obtained as a colourless solid (65.3 mg, 84%) without further purification. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 295 K):  $\delta$  = 2.84 (s, 4H, CH<sub>2</sub>), 3.80 (s, 6H, OCH<sub>3</sub>), 6.83 (d, *J* = 8.6 Hz, 4H, ArH), 7.09 (d, *J* = 8.6 Hz, 4H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 298 K):  $\delta$  = 37.3, 55.3, 113.7, 129.4, 134.0, 157.8. Data consistent with literature.<sup>[26]</sup>

### 1,2-bis(4-(trifluoromethyl)phenyl)ethane **152**



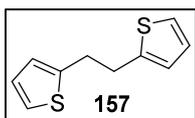
4-Trifluoromethylphenylacetic acid (204.2 mg, 0.64 mmol) and Pt-TiO<sub>2</sub> (410mg, 5.12 mmol) were reacted in accordance with the general procedure. Following irradiation for 19 hours **152** was obtained as a colourless solid (75.6 mg, 74%) without further purification. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 293 K):  $\delta$  = 3.00 (s, 4H, CH<sub>2</sub>), 7.27 (m, 4H, ArH), 7.55 (m, 4H, ArH); <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>, 293 K):  $\delta$  = -62.6. Data consistent with literature.<sup>[27]</sup>

### 1,2-Bis(perfluorophenyl)ethane **154**



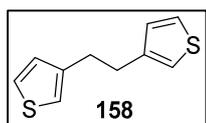
2,3,4,5,6-Pentafluorophenylacetic acid (144.7 mg, 0.64 mmol), and Pt-TiO<sub>2</sub> (410mg, 5.12 mmol) were reacted in accordance with the general procedure for 40 hours. The reaction mixture was subjected to column chromatography on silica gel (eluent: 20% CH<sub>2</sub>Cl<sub>2</sub> in pentanes) to yield **154** as a colourless crystalline solid (61 mg, 53%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 295 K):  $\delta$  = 3.02 (s, 4H, CH<sub>2</sub>); <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>, 295 K)  $\delta$  = -144.3 (dd, 4F, *J* = 8.2, 22.6 Hz, F<sub>c</sub>), -155.9 (t, 2F *J* = 21 Hz, F<sub>a</sub>), -162.1 (td, 4F, *J* = 9.1, 13.3 Hz, F<sub>b</sub>). 2,3,4,5,6-Pentafluoro toluene (3% wrt **154**) was also observed by NMR. Data consistent with literature.<sup>[28]</sup>

### 1,2-Di(thiophen-2-yl)ethane **157**



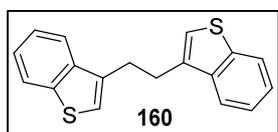
2-Thiopheneacetic acid (27 mg, 0.19 mmol), and Pt-TiO<sub>2</sub> (120 mg, 1.5 mmol) were reacted in accordance with the general procedure. Following irradiation for 20 hours **157** was obtained as a colourless solid (15.3 mg, 83%) without further purification. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 296 K):  $\delta$  = 3.20 (s, 4H, CH<sub>2</sub>), 6.80 (d, *J* = 3.4 Hz, 2H, ArH), 6.91-6.94 (m, 2H, ArH), 7.14 (d, *J* = 5.2 Hz, 2H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 296 K):  $\delta$  = 32.2, 123.4, 124.7, 126.8, 143.7. Consistent with literature.<sup>[29]</sup>

### 1,2-Di(thiophen-3-yl)ethane **158**



3-Thiopheneacetic acid (27 mg, 0.19 mmol), and Pt-TiO<sub>2</sub> (120 mg, 1.5 mmol) were reacted in accordance with the general procedure. Following irradiation for 20 hours **158** was obtained as a colourless solid (14.3 mg, 78%) without further purification. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 296 K):  $\delta$  = 2.96 (s, 4H, CH<sub>2</sub>), 6.93 (m, 4H, ArH), 7.24 (m, 2H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 296 K):  $\delta$  = 31.3, 120.4, 125.3, 128.2, 142.1. Consistent with literature.<sup>[30]</sup>

### 1,2-Bis(benzo[*b*]thiophen-3-yl)ethane **160**

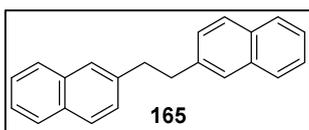


Benzo[*b*]thiophen-3-ylacetic acid (76.9 mg, 0.4 mmol) and 0.1% (w/w) Pt-TiO<sub>2</sub> (250 mg, 3.1 mmol) were reacted in accordance with the general procedure for 22 hours. The reaction mixture was subjected to column chromatography on silica gel (eluent: 20-40% CH<sub>2</sub>Cl<sub>2</sub> in pentanes) to yield **160** as a yellow oil (32.8 mg, 56%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 293 K):  $\delta$  = 3.31 (s, 4H, CH<sub>2</sub>), 7.12 (s, 2H, ArH), 7.35-7.44 (m, 4H, ArH), 7.76-7.82 (m, 2H, ArH), 7.87-7.93 (m, 2H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 295 K):  $\delta$  = 28.3, 121.6, 121.7, 123.0, 124.0, 124.3, 136.0, 138.9, 140.5; LR-ESIMS: *m/z* = 295 [MH]<sup>+</sup>; HR-ESIMS: *m/z* = 295.0610 (calcd. for C<sub>18</sub>H<sub>15</sub>S<sub>2</sub>, 295.0615). Benzo[*b*]thiophen-3-ylacetic acid (3% wrt **160**) was also observed by NMR.

### Photolysis reaction of Indole-3-acetic acid **161**

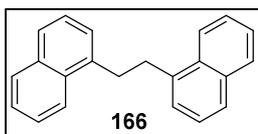
Indole-3-acetic acid (70.1 mg, 0.4 mmol) and Pt-TiO<sub>2</sub> (250 mg, 5.12 mmol) were reacted in accordance with the general procedure. Following irradiation for 21 hours <sup>1</sup>H NMR and GC-MS analysis revealed only starting material present.

### 1,2-Di(naphthalen-2-yl)ethane **165**



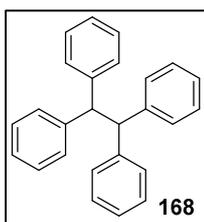
(Naphthalen-2-yl)acetic acid (58.3 mg, 0.31 mmol), and Pt-TiO<sub>2</sub> (200 mg, 2.5 mmol) were reacted in accordance with the general procedure. Following irradiation for 52 hours <sup>1</sup>H NMR analysis of the resultant mixture revealed **165** (0.087 mmol, 56%). 2-methylnaphthalene (0.125 mmol, 40%) was also observed. These data are consistent with literature.<sup>[31]</sup>

### 1,2-Di(naphthalen-1-yl)ethane **166**



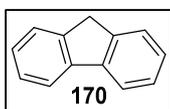
Naphthalen-1-ylacetic acid (119.2 mg, 0.64 mmol) and Pt-TiO<sub>2</sub> (410 mg, 5.12 mmol) were reacted in accordance with the general procedure. Following irradiation for 39 h, <sup>1</sup>H NMR analysis of the resultant mixture revealed **166** (0.18 mmol, 56%). 1-methylnaphthalene (0.19 mmol, 30%) was also observed. These data are consistent with literature.<sup>[32]</sup>

### 1,1,2,2-Tetraphenylethane **168**



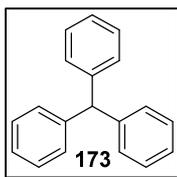
Diphenylacetic acid (84.9 mg, 0.4 mmol) and Pt-TiO<sub>2</sub> (250mg, 3.1 mmol) were reacted in accordance with the general procedure. Following irradiation for 22 hours the reaction mixture was purified by column chromatography on silica gel (eluent 30% CH<sub>2</sub>Cl<sub>2</sub> in petroleum 40/60) to yield **168** as a colourless solid (61 mg, 91%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 294 K):  $\delta$  = 4.79 (s, 2H, CH), 7.00-7.05 (m, 4H, ArH), 7.09-7.20 (m, 16H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 295 K):  $\delta$  = 56.4, 125.9, 128.2, 128.6, 143.5. Consistent with literature.<sup>[33]</sup>

### 9H-Fluorene **170**



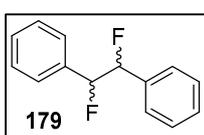
9H-fluorene-9-carboxylic acid (210.2 mg, 0.64 mmol) and Pt-TiO<sub>2</sub> (410 mg, 5.12 mmol) were reacted in accordance with the general procedure for 40 hours. The reaction mixture was subjected to column chromatography on silica gel (eluent: 10% CH<sub>2</sub>Cl<sub>2</sub> in pentanes) yielding a fraction containing two compounds. <sup>1</sup>H NMR analysis revealed the title compound **170** (0.53 mmol, 83%) along with 9,9'-bifluorene **171** (0.02 mmol, 7%) with respect to a CH<sub>2</sub>Br<sub>2</sub> standard. Data was consistent with literature.<sup>[34]</sup>

### Triphenylmethane **173**



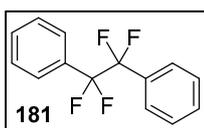
Triphenylacetic acid (184.5 mg, 0.64 mmol) and Pt-TiO<sub>2</sub> (410 mg, 5.12 mmol) were reacted in accordance with the general procedure. Following irradiation for 18 hours the reaction mixture was subjected to column chromatography on silica gel (eluent: 25% CH<sub>2</sub>Cl<sub>2</sub> in pentanes) yielding a fraction containing two compounds. <sup>1</sup>H NMR analysis revealed **173** (0.32 mmol, 50%) along with 9-phenyl-9H-fluorene **174** (0.17 mmol, 26%) with respect to a CH<sub>2</sub>Br<sub>2</sub> standard. Data was consistent with literature.<sup>[35]</sup>

### 1,2-Difluorobibenzyl **179**



$\alpha$ -Fluorophenylacetic acid (98.6 mg, 0.64 mmol) and Pt-TiO<sub>2</sub> (410 mg, 5.12 mmol) were reacted in accordance with the general procedure. Following irradiation for 21 hours a 1:1 mixture of the D/L and *meso* isomers of **179** was obtained as colourless oil (63.1 mg, 90% combined) without further purification. D/L isomer: <sup>1</sup>H {<sup>19</sup>F} NMR (500 MHz, CDCl<sub>3</sub>, 293 K):  $\delta$  = 5.61 (s, 2H, CHF), 7.11-7.13 (m, 4H, ArH), 7.26-7.28 (m, 6H, ArH); <sup>19</sup>F {<sup>1</sup>H} NMR (470 MHz, CDCl<sub>3</sub>, 293 K):  $\delta$  = -184.3. *Meso* isomer: <sup>1</sup>H {<sup>19</sup>F} NMR (500 MHz, CDCl<sub>3</sub>, 293 K):  $\delta$  = 5.68 (s, 2H, CHF), 7.17-7.19 (m, 4H, ArH), 7.33-7.34 (m, 6H, ArH); <sup>19</sup>F {<sup>1</sup>H} NMR (470 MHz, CDCl<sub>3</sub>, 293 K):  $\delta$  = -187.7. Data consistent with literature.<sup>[36]</sup>

### 1,1,2,2-Tetrafluorobibenzyl **181**



$\alpha,\alpha$ -Difluorophenylacetic acid (110.1 mg, 0.64 mmol) and Pt-TiO<sub>2</sub> (410 mg, 5.12 mmol) were reacted in accordance with the general procedure for 20 hours. The reaction mixture was subjected to column chromatography on silica gel (eluent: 20% CH<sub>2</sub>Cl<sub>2</sub> in pentanes) to yield **181** as a colourless solid (5 mg, 3%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 295 K):  $\delta$  = 7.39-7.51 (m, 10H, ArH); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>, 296 K):  $\delta$  = -112.4. Data consistent with literature.<sup>[37]</sup>

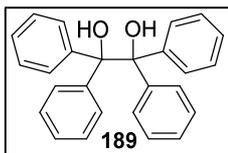
### Photolysis reaction of D/L Mandelic acid **182**

D/L Mandelic acid (97.4 mg, 0.64 mmol) and Pt-TiO<sub>2</sub> (410mg, 5.12 mmol) were reacted in accordance with the general procedure. Following irradiation for 18 hours <sup>1</sup>H NMR analysis of the resultant mixture revealed benzaldehyde **184** (0.17 mmol, 27%). Benzyl alcohol **183** (0.07 mmol, 11%) was also observed. Spectral data consistent with literature.<sup>[38]</sup>

### Photolysis reaction of 1-Phenylglycine **185**

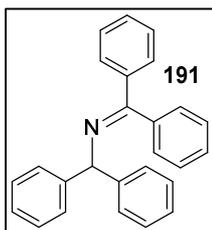
1-Phenylglycine (96.8 mg, 0.64 mmol) and Pt-TiO<sub>2</sub> (410 mg, 5.12 mmol) were reacted in accordance with the general procedure. Following irradiation for 18 hours <sup>1</sup>H NMR analysis of the resultant mixture revealed **191** (0.09 mmol, 14%). Benzaldehyde **184** (0.04 mmol, 11%) was also observed. Data consistent with literature.<sup>[38a, 39]</sup>

### 1,1,2-Tetraphenylethane-1,2-diol **189**



Benzilic acid (91.3 mg, 0.4 mmol) and Pt-TiO<sub>2</sub> (250 mg, 3.1 mmol) were reacted in accordance with the general procedure for 18 hours. The reaction mixture was subjected to column chromatography on silica gel (eluent: 25% CH<sub>2</sub>Cl<sub>2</sub> in pentanes) yielding a fraction containing two compounds. <sup>1</sup>H NMR analysis revealed **189** (0.04 mmol, 20%) along with benzophenone **188** (0.27 mmol, 67%) with respect to a CH<sub>2</sub>Br<sub>2</sub> standard. Data were consistent with literature.<sup>[37]</sup>

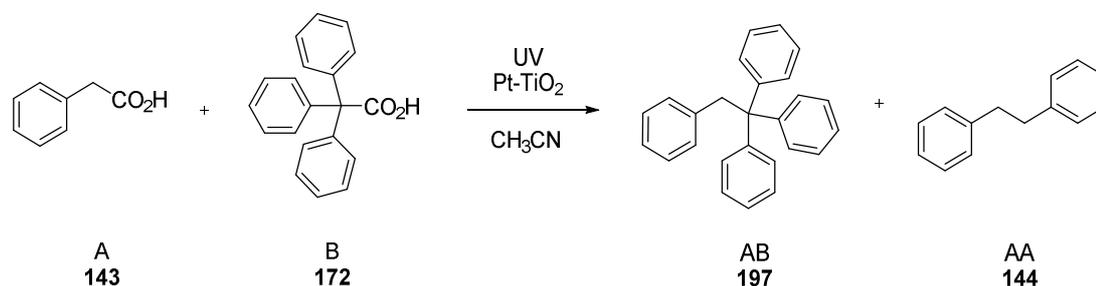
### *N*-Benzhydryl-1,1-diphenylmethanimine **191**



1,1-Diphenylglycine (145.5 mg, 0.64 mmol) and Pt-TiO<sub>2</sub> (410 mg, 5.12 mmol) were reacted in accordance with the general procedure for 17 hours. The reaction mixture was subjected to column chromatography on silica gel (eluent: 25% CH<sub>2</sub>Cl<sub>2</sub> in pentanes) to yield **191** as an off-white solid (83.5 mg, 74%) <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 295 K):  $\delta$  = 5.58 (s, 1H, NCH), 7.09-7.11 (m, 2H, ArH), 7.19-7.22 (m, 2H, ArH), 7.27-7.30 (m, 4H, ArH), 7.34-7.40 (m, 7H, ArH), 7.42-7.45 (m, 3H, ArH), 7.77-7.79 (m, 2H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 298 K):  $\delta$  = 70.0, 126.8, 127.7, 127.8, 128.1, 128.5, 128.6, 128.9, 130.2, 136.8, 139.9, 145.0, 167.0. Data consistent with literature.<sup>[40]</sup>

## 4.6 Heterodimerisations

### Reactions of Phenylacetic Acid with Triphenylacetic Acid

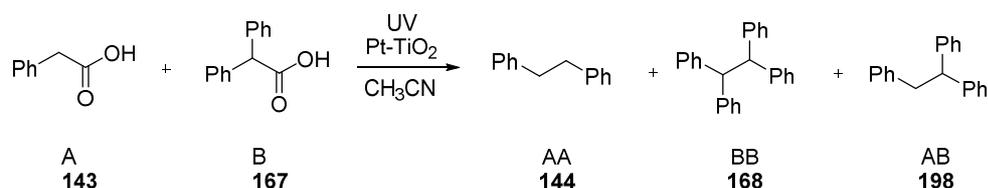


Phenylacetic acid (6.8-20.4 mg, 0.05-0.15 mmol), triphenylacetic acid (14.4 -43.3 mg, 0.05-0.15 mmol) and Pt-TiO<sub>2</sub> (60 mg, 0.75 mmol) in CH<sub>3</sub>CN (12 mL) were reacted in accordance with the general procedure for 18 hours. Yields were determined from <sup>1</sup>H NMR spectra using a CH<sub>2</sub>Br<sub>2</sub> internal standard with product peaks being assigned in accordance with previously reported chemical shifts.<sup>[24, 41]</sup> This data is summarised in Table 3 on pg 60.

### Reaction of Phenoxyacetic Acid with Triphenylacetic Acid

Phenoxyacetic acid (15.2 mg, 0.1 mmol), triphenylacetic acid (28.8 mg, 0.1 mmol) and Pt-TiO<sub>2</sub> (60 mg, 0.75 mmol) in CH<sub>3</sub>CN (12 mL) were reacted in accordance with the general procedure for 18 hours. <sup>1</sup>H NMR analysis revealed: 1,2-diphenoxyethane (0.05 mmol, 54%) and triphenylmethane (< 0.01 mmol, < 5%) wrt a CH<sub>2</sub>Br<sub>2</sub> internal standard. Chemical shifts were consistent with those previously reported.<sup>[19, 35a]</sup>

### Reactions of Phenylacetic Acid with Diphenylacetic Acid



Phenylacetic acid (6.8-34.1 mg, 0.05-0.25 mmol), diphenylacetic acid (10.6-106.2 mg, 0.05-0.5 mmol) and Pt-TiO<sub>2</sub> (60 mg, 0.75 mmol) in CH<sub>3</sub>CN (12 mL) were reacted in accordance with the general procedure for 18 hours. Yields were determined from <sup>1</sup>H NMR spectra using a CH<sub>2</sub>Br<sub>2</sub> internal standard with product peaks being assigned in accordance with previously reported chemical shifts.<sup>[24, 33, 42]</sup> This data is summarised in Table 4 on pg 61.

#### **Reaction of Phenylacetic Acid with Phenoxyacetic Acid**

Phenylacetic acid (6.8 mg, 0.05 mmol), phenoxyacetic acid (38.1 mg, 0.25 mmol) and Pt-TiO<sub>2</sub> (60 mg, 0.75 mmol) in CH<sub>3</sub>CN (12 mL) were reacted in accordance with the general procedure for 18 hours. <sup>1</sup>H NMR analysis revealed: phenethoxybenzene (< 0.01 mmol, 6%), 1,2-diphenoxyethane (0.06 mmol, 24%) and unreacted phenylacetic acid (0.08 mmol, 82% recovery) wrt a CH<sub>2</sub>Br<sub>2</sub> internal standard. Chemical shifts were consistent with those previously reported.<sup>[19, 43]</sup>

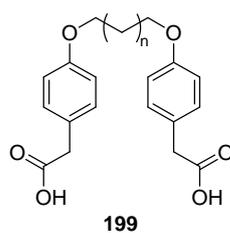
#### **Reaction of Phenylacetic Acid with 2-Thiopheneacetic Acid**

Phenylacetic acid (6.8 mg, 0.05 mmol), 2-thiopheneacetic acid (35.6 mg, 0.25 mmol) and Pt-TiO<sub>2</sub> (60 mg, 0.75 mmol) in CH<sub>3</sub>CN (12 mL) were reacted in accordance with the general procedure for 18 hours. <sup>1</sup>H NMR analysis revealed 1,2-di(thiophen-2-yl)ethane to be the major product formed with traces of 2-phenethylthiophene also formed. NMR yields could not be determined in this case due to peak overlap. Chemical shifts were consistent with those previously reported.<sup>[29, 44]</sup>

#### **Reaction of Phenylacetic Acid with 4-Methoxyphenylacetic Acid**

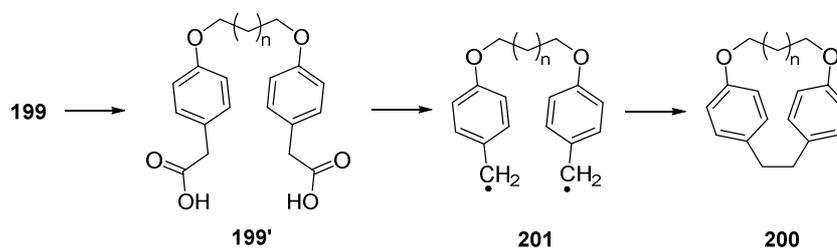
Phenylacetic acid (6.8 mg, 0.05 mmol), 4-methoxyphenylacetic acid (41.6 mg, 0.25 mmol) and Pt-TiO<sub>2</sub> (60 mg, 0.75 mmol) in CH<sub>3</sub>CN (12 mL) were reacted in accordance with the general procedure for 18 hours. <sup>1</sup>H NMR analysis revealed: 1,2-bis(4-methoxyphenyl)ethane (0.04 mmol, 30%), 1-methoxy-4-phenethylbenzene (< 0.01 mmol, 10%) and unreacted phenylacetic acid (0.02 mmol, 47% recovery) wrt a CH<sub>2</sub>Br<sub>2</sub> internal standard. Chemical shifts were consistent with those previously reported.<sup>[26, 45]</sup>

## 4.7 Macrocyclic Computations



Entry	n	Ring Size	Strain Energy kcal mol <sup>-1</sup>
1	1	16	27.1
2	2	17	23.1
3	3	18	26.1
4	4	19	22.7
5	5	20	22.1
6	6	21	23.9
7	7	22	29.3
8	8	23	27.4
9	9	24	124.6

**Table 10.** Calculated by the MM2 method using the Chem3D software suite.

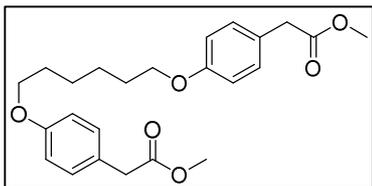


Entry	n	Ring Size	E <sub>199</sub>	E <sub>199'</sub>	E <sub>199'-199</sub>	E <sub>201</sub>	E <sub>200</sub>	E <sub>200-201</sub>
1	4	18	-819118	-819099	19	-581619	-581711	-92
2	5	19	-843788	-843752	36	-606269	-606382	-113
3	6	20	-868466	-868428	39	-630961	-631050	-89

**Table 11.** Calculated using the Gaussian 09 software suite at the B3LYP/6-31G(d,p) level of theory, all energies in kcal mol<sup>-1</sup>.

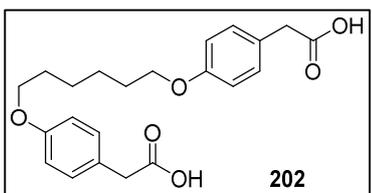
## 4.8 Preparation of Macrocyclisation Precursors

### 1,6-Di(4-oxyphenylacetic acid)hexane 202



1,6-Dibromohexane (1.53 mL, 10 mmol), methyl 4-hydroxyphenylacetate (22 mmol, 3.70 g) and  $K_2CO_3$  (50 mmol, 6.90 g) were dissolved in anhydrous DMF (60 mL) and heated at 60 °C for three days. The reaction mixture was

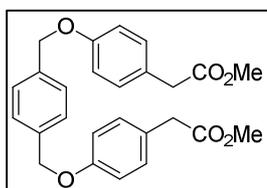
concentrated under reduced pressure, diluted with  $CH_2Cl_2$  (100 mL), washed with water (2 x 100 mL), dilute NaOH (100 mL) and saturated aqueous LiCl (100 mL) before being dried over  $MgSO_4$  and concentrated under reduced pressure to yield the desired diester as an off-white solid (3.56 g, 86%).  $^1H$  NMR (500 MHz,  $CDCl_3$ , 295 K)  $\delta$  = 1.51-1.54 (m, 4H,  $CH_2$ ), 1.79-1.82 (m, 4H,  $CH_2$ ), 3.56 (s, 4H,  $CH_2CO_2$ ), 3.68 (s, 6H,  $CO_2CH_3$ ), 3.95 (t,  $J$  = 6.3 Hz, 4H,  $OCH_2$ ), 6.85 (d,  $J$  = 8.6 Hz, 4H, ArH), 7.18 (d,  $J$  = 8.6 Hz, 4H, ArH);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ , 296 K)  $\delta$  = 26.3, 29.6, 40.7, 52.4, 68.2, 115.0, 126.3, 130.7, 158.7, 172.8. The diester (3.32 g, 8.0 mmol), was subjected to hydrolysis with LiOH (80 mmol, 7.42 g) in  $CH_3OH$  (120 mL) and  $H_2O$  (40 mL) for



two days at room temperature. The reaction mixture was concentrated under reduced pressure before being adjusted to pH 3 with conc.  $H_2SO_4$ . The resultant precipitate was isolated by filtration and washed with  $H_2O$  before being dried

*in vacuo* over silica desiccant. Dissolution of the resultant powder in hot acetone and subsequent cooling afforded **202** as off-white crystals (1.32 g, 43%). Mp 182-183 °C.  $^1H$  NMR (400 MHz, 4:1  $CDCl_3/CF_3CO_2H$ , 294 K):  $\delta$  = 1.49-1.57 (m, 4H,  $CH_2$ ), 1.81-1.85 (m, 4H,  $CH_2$ ), 3.69 (s, 4H,  $CH_2CO_2$ ), 4.07 (t,  $J$  = 6.6 Hz, 4H,  $OCH_2$ ), 6.92-6.94 (m, 4H, ArH), 7.21-7.23 (m, 4H, ArH);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ , 296 K)  $\delta$  = 26.6, 29.8, 40.4, 68.4, 115.2, 127.7, 131.2, 159.1, 173.0; LR-ESIMS:  $m/z$  = 385 [M-H] $^-$ ; HR-ESIMS:  $m/z$  = 385.1646 (calcd. for  $C_{22}H_{25}O_6$ , 385.1657).

### 1,4-Bis(4-oxyphenylacetic acid)-*p*-xylene 207



$\alpha,\alpha'$ -Dibromo-*p*-xylene (10 mmol, 2.64 g), methyl 4-hydroxyphenylacetate (22 mmol, 3.70 g) and  $K_2CO_3$  (50 mmol, 6.90 g) were dissolved in anhydrous DMF (60 mL) and heated at 60 °C for three days. After cooling to room temperature the reaction mixture

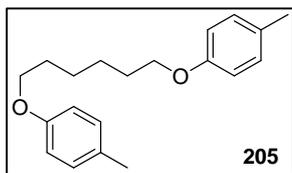
was poured in deionised water (2 L) and the resultant precipitate was collected by filtration, taken up in  $CH_2Cl_2$  (300 mL) and washed with  $H_2O$  (3 x 150 mL) and dilute NaOH (2 x 150 mL) before being dried with  $MgSO_4$ . The solvent was removed under reduced pressure to afford the desired di-ester as a colourless powder (3.90 g, 90%).  $^1H$  NMR (500 MHz,  $CDCl_3$ , 295 K)  $\delta$ :



6.88 (d,  $J = 8.0$  Hz, 4H, ArH), 7.15 (d,  $J = 8.0$  Hz, 4H, ArH), 7.36-7.38 (m, 2H, ArH), 7.50-7.51 (m, 2H, ArH);  $^{13}\text{C}$  NMR (75 MHz,  $d_6$ -acetone, 296 K)  $\delta$ : 40.8, 68.8, 116.0, 128.6, 129.3, 129.8, 131.7, 136.9, 159.0, 173.4.; LR-ESIMS:  $m/z = 405$  [M-H]; HR-ESIMS:  $m/z = 405.1334$  (calcd. for  $\text{C}_{24}\text{H}_{21}\text{O}_6$ , 405.1334).

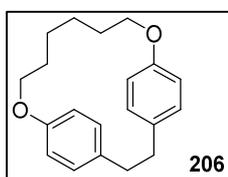
## 4.9 Macrocyclisation Photolyses

### 1,6-Bis(*p*-tolylloxy)hexane **205** & 5,12-dioxa-1,4(1,4)-dibenzenacyclododecaphane **206**



1,6-Di(4-oxyphenylacetic acid)hexane (96.6 mg, 0.25 mmol) and Pt-TiO<sub>2</sub> (400 mg, 5 mmol) in CH<sub>3</sub>CN (200 mL) were reacted in accordance with the general procedure for 18 hours. The reaction mixture was subjected to column chromatography on silica gel

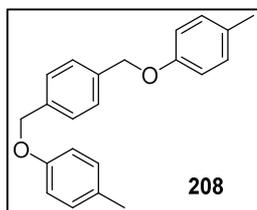
(eluent: 5% EtOAc in pentanes) yielding two distinct fractions. The first of these contained **205**, a colourless solid. Mp 68-70 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 297 K): δ = 1.49-1.55 (m, 4H, CH<sub>2</sub>), 1.77-1.84 (m, 4H, CH<sub>2</sub>), 2.28 (s, 6H, CH<sub>3</sub>), 3.94 (t, *J* = 6.5 Hz, 4H, OCH<sub>2</sub>), 6.78-6.81 (m, 4H, ArH), 7.06-7.08 (m, 4H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 297 K): δ = 20.9, 26.3, 29.7, 68.3, 114.8,



130.1, 130.3, 157.4.; LR-ESIMS: *m/z* = 316 [MNH<sub>4</sub>]<sup>+</sup>; HR-ESIMS: *m/z* = 316.2272 (calcd. for C<sub>20</sub>H<sub>30</sub>NO<sub>2</sub>, 316.2271). The second fraction contained a 2:1 mixture of **205** and the cyclophane **206** (13%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 295 K): δ = 1.50-1.56 (m, 4H, CH<sub>2</sub>), 1.77-1.84 (m, 4H, CH<sub>2</sub>), 2.81 (s,

4H, ArCH<sub>2</sub>), 3.94 (t, *J* = 6.4 Hz, 4H, OCH<sub>3</sub>), 6.78-6.81 (m, 4H, ArH), 7.06-7.08 (m, 4H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 297 K): δ = 29.3, 29.7, 44.4, 67.9, 114.4, 129.3, 129.9, 157.0, *m/z* = 297 [MH]<sup>+</sup>; HR-ESIMS: *m/z* = 297.1852 (calcd. for C<sub>20</sub>H<sub>25</sub>O<sub>2</sub>, 297.1849). Compound **205** was characterised pure and the yield reported is a combination of the portion isolated (8.1 mg, 11%) and the portion determined to be present in the mixed fraction by <sup>1</sup>H NMR (0.07 mmol, 26%). Compound **206** was characterised as a mixture with **205** with the assistance of 2D NMR experiments and aided by the knowledge of which peaks corresponded to **205**. The yield (0.03 mmol, 13 %) was calculated by <sup>1</sup>H NMR.

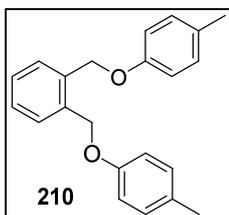
### 1,4-Bis(*p*-tolylloxy)-*p*-xylene **208**



1,4-Bis(*p*-oxyphenylacetic acid)-*p*-xylene (50 mg, 0.12 mmol) and Pt-TiO<sub>2</sub> (1.0 g, 12.5 mmol) in CH<sub>3</sub>CN (200 mL) were reacted in accordance with the general procedure for 17 hours. The reaction mixture was subjected to column chromatography on silica gel (eluent: 10% EtOAc

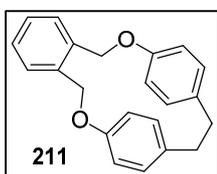
in pentanes) to yield **208** as a colourless solid (12.6 mg, 33%). Mp 137-139 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 295 K): δ = 2.29 (s, 6H, CH<sub>3</sub>), 5.05 (s, 4H, OCH<sub>2</sub>), 6.86-6.88 (m, 4H, ArH), 7.08-7.09 (m, 4H, ArH), 7.44 (s, 4H, ArH); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 296 K): δ = 20.6, 69.9, 114.8, 127.8, 130.1, 130.3, 137.1, 156.7; LR-ESIMS: *m/z* = 341 [MNa]<sup>+</sup>; HR-ESIMS: *m/z* = 341.1515 (calcd. for C<sub>22</sub>H<sub>22</sub>O<sub>2</sub>Na, 341.1512).

### 1,2-Bis(*p*-tolylxy)-*o*-xylene **210** & 2,6-dioxa-1,7(1,4),4(1,2)-tribenzenacyclononaphane **211**



1,2-Bis(*p*-oxyphenylacetic acid)-*o*-xylene (101.6 mg, 0.25 mmol) and Pt-TiO<sub>2</sub> (400 mg, 5 mmol) in CH<sub>3</sub>CN (200 mL) were reacted in accordance with the general procedure for 19 hours. The reaction mixture was subjected to column chromatography on silica gel (eluent: 40% CH<sub>2</sub>Cl<sub>2</sub> in pentanes) yielding two distinct fractions. The first of these contained **210**,

a colourless oil (30% overall yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 295 K): δ = 2.29 (s, 6H, ArCH<sub>3</sub>), 5.14 (s, 4H, OCH<sub>2</sub>), 6.87 (d, *J* = 9.0 Hz, 4H, ArH), 7.08 (d, *J* = 9.0 Hz, 4H, ArH), 7.35-7.37 (m, 2H, ArH), 7.51-7.53 (m, 2H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 296 K): δ = 20.6, 68.2, 114.9, 128.4, 129.0, 130.1, 130.5, 135.5, 156.7; LR-ESIMS: *m/z* = 336 [MNH<sub>4</sub>]<sup>+</sup>; HR-ESIMS: *m/z* = 336.1958



(calcd. for C<sub>22</sub>H<sub>26</sub>NO<sub>2</sub>, 336.1958). The second fraction contained a 1:1 mixture of **210** and the cyclophane **211** (23%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 295 K): δ = 2.83 (s, 4H, ArCH<sub>2</sub>), 5.14 (s, 4H, OCH<sub>2</sub>), 6.87-6.90 (m, 4H, ArH), 7.07-7.09 (m, 4H, ArH), 7.35-7.37 (m, 4H, ArH), 7.51-7.53 (m, 4H, ArH); <sup>13</sup>C

NMR (125 MHz, CDCl<sub>3</sub>, 295 K): δ = 37.4, 68.1, 114.8, 128.5, 129.0, 129.5, 134.5, 135.4, 157.0; LR-ESIMS: *m/z* = 317 [MH]<sup>+</sup>; HR-ESIMS: *m/z* = 317.1534 (calcd. for C<sub>22</sub>H<sub>21</sub>O<sub>2</sub>, 317.1536).

Compound **210** was characterised pure and the yield reported is a combination of the portion isolated (5.3 mg, 7%) and the portion determined to be present in the mixed fraction by <sup>1</sup>H NMR (0.06 mmol, 23%). Compound **211** was characterised as a mixture with **210** with the assistance of 2D NMR experiments and aided by the knowledge of which peaks corresponded to **210**. The yield (0.06 mmol, 23 %) was calculated by <sup>1</sup>H NMR.

## 4.10 Attempted Oxidative Decarboxylations

### Table 7; Entry 1

Adamantane-1-carboxylic acid (15.8 mg, 0.087 mmol) and 5% Pt-PC500 (60 mg, 0.75 mmol) in CH<sub>3</sub>CN (12 mL) were reacted in accordance with the general procedure for 18 hours. <sup>1</sup>H NMR analysis wrt a CH<sub>2</sub>Br<sub>2</sub> standard revealed: **129** (< 0.01 mmol, 7%).

### Table 7; Entry 2

Adamantane-1-carboxylic acid (15.8 mg, 0.087 mmol) and 5% Pt-PC500 (60 mg, 0.75 mmol) in CH<sub>3</sub>CN (10.8 mL) and heptane (1.2 mL) were reacted in accordance with the general procedure for 18 hours. <sup>1</sup>H NMR analysis wrt a CH<sub>2</sub>Br<sub>2</sub> standard revealed: **129** (< 0.01 mmol, 10%).

### Table 7; Entry 3

Adamantane-1-carboxylic acid (15.8 mg, 0.087 mmol) and 5% Pt-PC500 (60 mg, 0.75 mmol) in CH<sub>3</sub>CN (10.8 mL) and heptane (1.2 mL) were reacted in accordance with the general procedure for 18 hours. Following irradiation the reaction mixture was diluted with hexane (25 mL), washed with 1M NaOH (3 x 20 mL), dried over MgSO<sub>4</sub> and concentrated under reduced pressure. <sup>1</sup>H NMR analysis wrt a CH<sub>2</sub>Br<sub>2</sub> standard revealed: **129** (< 0.01 mmol, 9%).

### Table 7; Entry 4

Adamantane-1-carboxylic acid (288 mg, 1.6 mmol) and 5% Pt-PC500 (80 mg, 0.93 mmol) in CH<sub>3</sub>CN (12 mL) were reacted in accordance with the general procedure for 18 hours. <sup>1</sup>H NMR analysis wrt a CH<sub>2</sub>Br<sub>2</sub> standard revealed: **129** (0.02 mmol, < 1%) and unreacted starting material (0.82 mmol, 51% recovery).

### Table 7; Entry 5

Adamantane-1-carboxylic acid (288 mg, 1.6 mmol) and 5% Pt-PC500 (80 mg, 0.93 mmol) in CH<sub>3</sub>CN (10.8 mL) and heptane (1.2 mL) were reacted in accordance with the general procedure for 18 hours. <sup>1</sup>H NMR analysis wrt a CH<sub>2</sub>Br<sub>2</sub> standard revealed: **129** (trace) and unreacted starting material (1.02 mmol, 64% recovery).

### Reaction of (Naphthalen-2-yl)acetic acid

(Naphthalen-2-yl)acetic acid (16.4 mg, 0.09 mmol) and 5% Pt-PC500 (60 mg, 0.75 mmol) in CH<sub>3</sub>CN (12 mL) were reacted in accordance with the general procedure for 18 hours. <sup>1</sup>H NMR

analysis wrt a  $\text{CH}_2\text{Br}_2$  standard revealed: **165** (< 0.05 mmol, 54%) and 2-methylnaphthalene(0.02 mmol, 23%).

## 5.0 References

- [1] a) B. Kraeutler, A. J. Bard, *J. Am. Chem. Soc.* **1977**, *99*, 7729-7731; b) B. Kraeutler, A. J. Bard, *J. Am. Chem. Soc.* **1978**, *100*, 2239-2240; c) B. Kraeutler, C. D. Jaeger, A. J. Bard, *J. Am. Chem. Soc.* **1978**, *100*, 4903-4905; d) B. Kraeutler, A. J. Bard, *J. Am. Chem. Soc.* **1978**, *100*, 5985-5992.
- [2] a) T. Ohno, K. Sarukawa, K. Tokieda, M. Matsumura, *J. Catal.* **2001**, *203*, 82-86; b) D. C. Hurum, A. G. Agrios, K. A. Gray, T. Rajh, M. C. Thurnauer, *J. Phys. Chem. B* **2003**, *107*, 4545-4549.
- [3] N. Grant, PhD Thesis, University of Aberdeen **2010**.
- [4] A. Mills, *J. Chem. Soc., Chem. Commun.* **1982**, 367-368.
- [5] A. Mills, N. Elliott, G. Hill, D. Fallis, J. R. Durrant, R. L. Willis, *Photochem. Photobiol. Sci.* **2003**, *2*, 591-596.
- [6] J. Clayden, N. Greeves, S. Warren, *Organic Chemistry, Vol. 1*, Oxford University Press, Oxford, **2012**.
- [7] K. Uneyama, *Organofluorine Chemistry*, Wiley, **2006**.
- [8] a) A. Studer, *Chem. Eur. J.* **2001**, *7*, 1159-1164; b) H. Fischer, *Chem. Rev.* **2001**, *101*, 3581-3610.
- [9] A. Studer, *Chem. Soc. Rev.* **2004**, *33*, 267-273.
- [10] A. D. Jenkins, P. Kratochvíl, R. F. T. Stepto, U. W. Suter, *Pure. Appl. Chem.* **1996**, *68*, 2287-2311.
- [11] K.-S. Yeung, I. Paterson, *Angew. Chem. Int. Ed.* **2002**, *41*, 4632-4653.
- [12] J. Blankenstein, J. Zhu, *Eur. J. Org. Chem.* **2005**, *2005*, 1949-1964.
- [13] a) A. L. Linsebigler, G. Lu, J. T. Yates, *Chem. Rev.* **1995**, *95*, 735-758; b) C. Deiana, E. Fois, S. Coluccia, G. Martra, *J. Phys. Chem. C* **2010**, *114*, 21531-21538; c) C. Salazar, M. A. Nanny, *J. Catal.* **2010**, *269*, 404-410; d) M. A. Henderson, *Surf. Sci. Rep.* **2011**, *66*, 185-297.
- [14] a) S. Marinković, N. Hoffmann, *Chem. Commun.* **2001**, 1576-1578; b) S. Marinković, N. Hoffmann, *Eur. J. Org. Chem.* **2004**, *2004*, 3102-3107.
- [15] A. Mills, *Chem. Commun.* **1982**, 367-368.
- [16] S.-J. Zhang, W.-X. Hu, *Synth. Commun.* **2010**, *40*, 3093-3100.
- [17] N. S. Y. Loy, A. Singh, X. Xu, C.-M. Park, *Angew. Chem. Int. Ed.* **2013**, *52*, 2212-2216.
- [18] P. Wipf, P. D. G. Coish, *J. Org. Chem.* **1999**, *64*, 5053-5061.
- [19] S. Y. W. Lau, G. Hughes, P. D. O'Shea, I. W. Davies, *Org. Lett.* **2007**, *9*, 2239-2242.
- [20] a) Z. Qu, W. Shi, J. Wang, *J. Org. Chem.* **2004**, *69*, 217-219; b) S. A. Al-Awadi, M. R. Abdallah, M. A. Hasan, N. A. Al-Awadi, *Tetrahedron* **2004**, *60*, 3045-3049.
- [21] H. Hori, Y. Nishida, H. Ohru, H. Meguro, *J. Org. Chem.* **1989**, *54*, 1346-1353.
- [22] J. A. Wright, M. J. Gaunt, J. B. Spencer, *Chem. Eur. J.* **2006**, *12*, 949-955.
- [23] K. J. Shea, R. B. Phillips, *J. Am. Chem. Soc.* **1980**, *102*, 3156-3162.
- [24] F.-X. Felpin, J. Coste, C. Zakri, E. Fouquet, *Chem. Eur. J.* **2009**, *15*, 7238-7245.
- [25] X. Shu, S. Chen, J. Li, Z. Chen, L. Weng, X. Jia, C. Li, *Chem. Commun.* **2012**, *48*, 2967-2969.
- [26] K.-B. Oh, S.-H. Kim, J. Lee, W.-J. Cho, T. Lee, S. Kim, *J. Med. Chem.* **2004**, *47*, 2418-2421.
- [27] T. Chen, L. Yang, L. Li, K.-W. Huang, *Tetrahedron* **2012**, *68*, 6152-6157.
- [28] G. M. Brooke, J. A. K. J. Ferguson, *J. Fluor. Chem.* **1988**, *41*, 263-275.
- [29] P.-S. Chen, C.-H. Chou, *Tetrahedron* **1996**, *52*, 13615-13622.
- [30] B. D. Gupta, V. Singh, K. Qanungo, V. Vijai Kanth, R. S. Sengar, *J. Organomet. Chem.* **1999**, *582*, 279-281.
- [31] a) S. Inaba, H. Matsumoto, R. D. Rieke, *J. Org. Chem.* **1984**, *49*, 2093-2098; b) A. R. Jagdale, J. H. Park, S. W. Youn, *J. Org. Chem.* **2011**, *76*, 7204-7215.

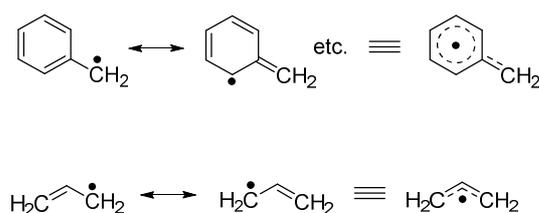
- [32] a) H. Koshima, K. Ding, Y. Chisaka, T. Matsuura, I. Miyahara, K. Hirotsu, *J. Am. Chem. Soc.* **1997**, *119*, 10317-10324; b) H.-C. Shen, S. Pal, J.-J. Lian, R.-S. Liu, *J. Am. Chem. Soc.* **2003**, *125*, 15762-15763.
- [33] J. J. Eisch, K. Yu, A. L. Rheingold, *Eur. J. Org. Chem.* **2012**, *2012*, 3165-3171.
- [34] a) K. Morimoto, M. Itoh, K. Hirano, T. Satoh, Y. Shibata, K. Tanaka, M. Miura, *Angew. Chem. Int. Ed.* **2012**, *51*, 5359-5362; b) J. J. Eisch, P. O. Fregene, *Eur. J. Org. Chem.* **2008**, *2008*, 4482-4492.
- [35] a) M. Horn, L. H. Schappele, G. Lang-Wittkowski, H. Mayr, A. R. Ofial, *Chem. Eur. J.* **2013**, *19*, 249-263; b) G. C. Vougioukalakis, M. M. Roubelakis, M. Orfanopoulos, *J. Org. Chem.* **2010**, *75*, 4124-4130.
- [36] D. H. R. Barton, R. H. Hesse, G. P. Jackman, L. Ogunkoya, M. M. Pechet, *J. Chem. Soc., Perkin Trans. 1* **1974**, 739-742.
- [37] a) C. Wang, Y. Pan, A. Wu, *Tetrahedron* **2007**, *63*, 429-434; b) B. Landers, C. Berini, C. Wang, O. Navarro, *J. Org. Chem.* **2011**, *76*, 1390-1397.
- [38] a) D. Bézier, S. Park, M. Brookhart, *Org. Lett.* **2013**, *15*, 496-499; b) F. Gao, Q.-H. Chen, F.-P. Wang, *Tet. Lett.* **2009**, *50*, 5270-5273.
- [39] Z. Hu, F. M. Kerton, *Org. Biomol. Chem.* **2012**, *10*, 1618-1624.
- [40] L. Liu, S. Zhang, X. Fu, C.-H. Yan, *Chem. Commun.* **2011**, *47*, 10148-10150.
- [41] C. Kleeberg, *Dalton Trans.* **2013**, *42*, 8276-8287.
- [42] S. Donck, A. Baroudi, L. Fensterbank, J.-P. Goddard, C. Ollivier, *Adv. Synth. Catal.* **2013**, *355*, 1477-1482.
- [43] E. Baciocchi, A. Piermattei, C. Rol, R. Ruzziconi, G. V. Sebastiani, *Tetrahedron* **1989**, *45*, 7049-7062.
- [44] X.-S. Ye, H. N. C. Wong, *J. Org. Chem.* **1997**, *62*, 1940-1954.
- [45] C.-S. Yan, Y. Peng, X.-B. Xu, Y.-W. Wang, *Chem. Eur. J.* **2012**, *18*, 6039-6048.

## **Chapter 3:**

# **Titania-Promoted Carboxylic Acid Alkylations of Alkenes and Cascade Addition-Cyclisations**

## 1.0 Introduction

To follow on from the pleasing results obtained during the homodimerisation of carboxylic acids it was decided to attempt to carry out alkylations of unsaturated species using titania-generated radicals. As discovered during the dimerisation investigations, acids bearing a group capable of stabilising the resultant radical tended to react more readily than those that did not. The stability of species containing an unpaired electron is affected by the presence of functional groups adjacent to the radical center which can be classified as resonance effects, interaction with filled/vacant molecular orbitals, inductive effects and hyperconjugative effects.<sup>[1]</sup> Resonance stabilisation is the strongest and is responsible for several of the most stabilised carbon-centered radicals known. Conjugation of the radical center with unsaturated substituents leads to the unpaired spin being delocalised throughout the attached  $\pi$ -system. The benzyl and allyl radicals are the two most well-known examples in this class (Fig. 1).



**Figure 1.**

Interaction of singly occupied molecular orbitals (SOMO) with either an empty or filled molecular orbital (MO) can exert a stabilising effect. While less stabilising than resonance effects, these interactions can still impart notable levels of stabilisation. Electron-withdrawing groups (*e.g.*  $\text{C}\equiv\text{N}$ ,  $\text{C}=\text{O}$ ) possess low-lying vacant  $\pi^*$  orbitals. Overlap with the SOMO generates two new MOs (Fig. 2a). There is just one electron, from the old SOMO, available to fill the two new MOs. It enters the lower of these, rendering it the new SOMO, and thus the radical experiences stabilisation as a result of the fact that the electron is now lower in energy. This also imparts electrophilic nature to the radical as, energetically, it is more likely to accept another electron into this new low energy SOMO than to give one up.

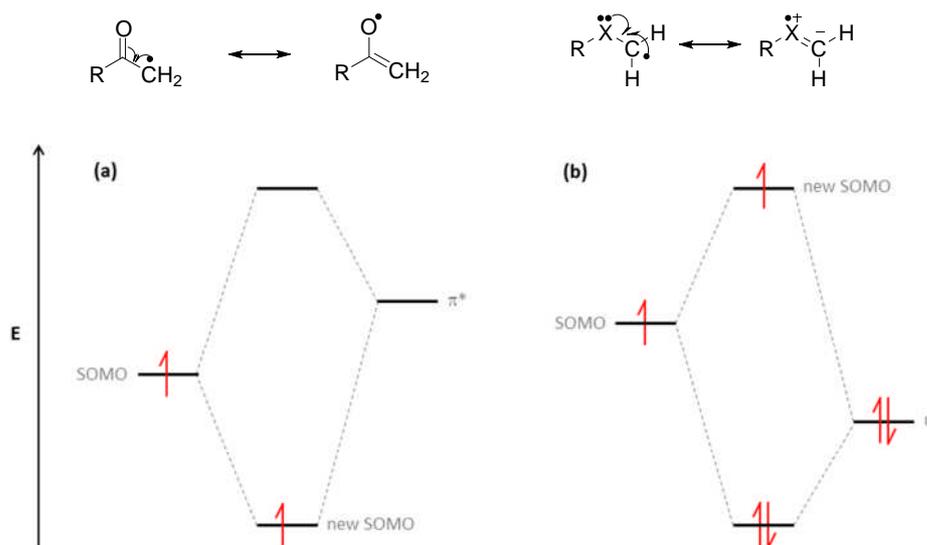


Figure 2.

Substitution of a radical with electron donating groups acts in a similar manner. Electron rich RX groups (*e.g.* ethers, thioethers or amines) possess relatively high-filled n-orbitals – their lone pairs. Again, overlap with the SOMO gives rise to two new MOs (Fig. 2b). With three electrons available to fill them the new SOMO is now higher in energy than it was to begin with. The lone pair however is lower in energy and thus, as two electrons have been lowered in energy while only one has been raised a net stabilising effect is exerted. This new high energy SOMO is much more willing to give up an electron than accept one, endowing a nucleophilic nature to radicals stabilised in this way.

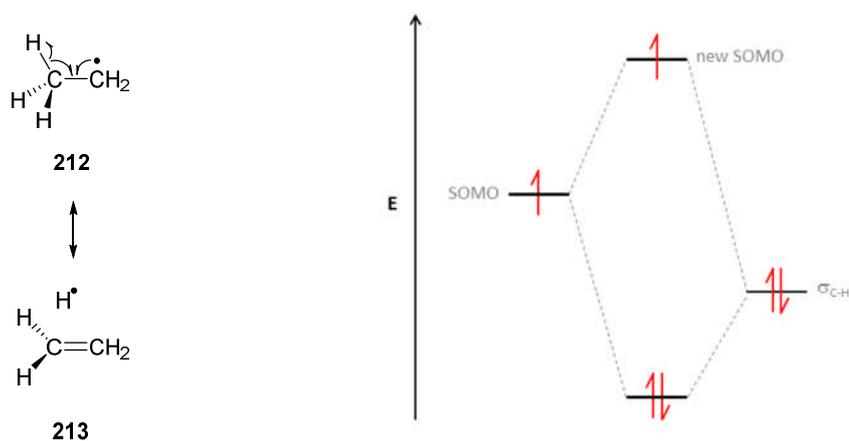
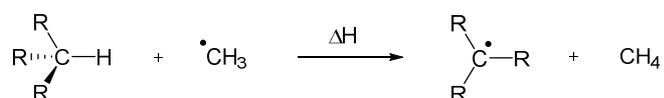


Figure 3.

Stabilisation by hyperconjugative interactions is the weakest of the three categories. In alkyl substituted radicals the unpaired electron can interact with the electrons in the C-H bonds of substituent(s) *beta* to the radical center. Much of this stabilisation is considered to

result from delocalisation of the spin density away from the carbon center and out onto the *beta* hydrogen atoms. This is conventionally visualised as shown in Fig. 3, using the ethyl radical as it is the simplest example, by a combination of the traditional resonance structure **212** with the “no-bond” structure **213**. This increases the stability of the system due to the interaction between the SOMO and the electrons of the C-H  $\sigma$ -bonding orbitals of the substituent(s). Again, a net stabilising effect is observed as two electrons are lowered in energy for one being raised. The higher the degree of alkyl substitution, the stronger the stabilisation will be as the number of *beta* hydrogen atoms increases. For this reason tertiary alkyl radicals are more stable than secondary which are more stable than primary.



$$\text{RSE}(\text{R}_3\text{C}^\bullet) = \Delta \text{H}(\text{R}_3\text{C}^\bullet) + \Delta \text{H}(\text{CH}_4) - \Delta \text{H}(\text{R}_3\text{CH}) - \Delta \text{H}(\cdot \text{CH}_3)$$

**Figure 4.**

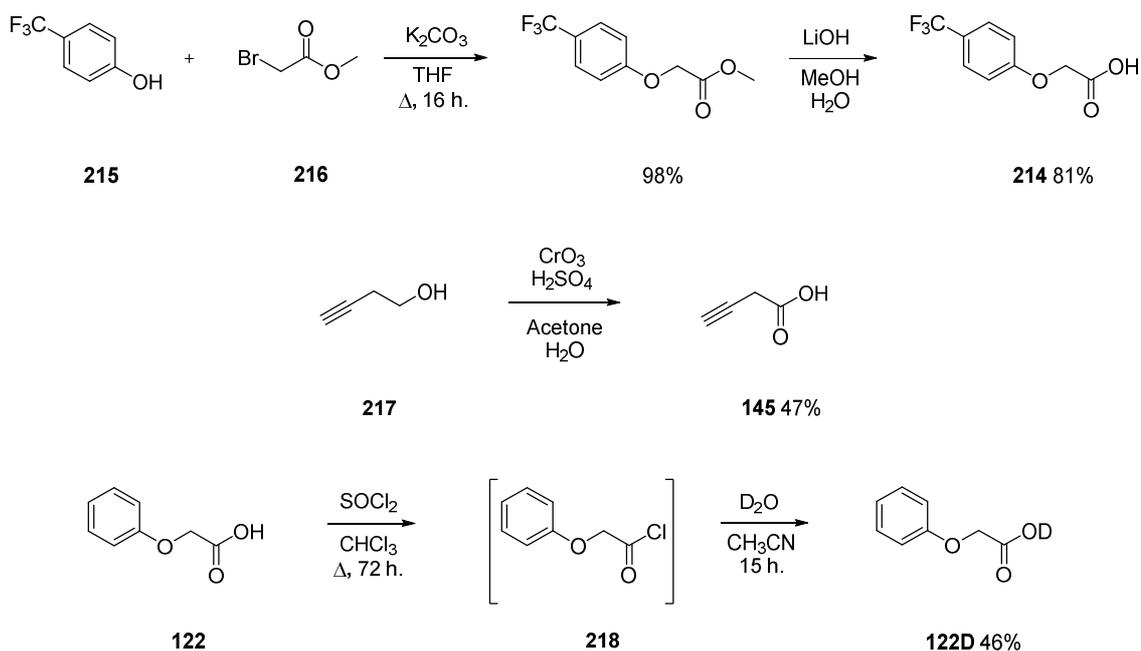
For a more quantitative approach towards comparing the radical stabilisation energies (RSE) of various species the hydrogen transfer reaction shown in Figure 4 is commonly employed. Using the experimentally determined heats of formation of the various chemical species the reaction energy can be calculated. This corresponds to the RSE of the radical  $\text{R}_3\text{C}^\bullet$  and is negative for species which are more stable than the methyl radical.

The objective of this work is to investigate the reactions of a range of carboxylic acids bearing radical stabilising groups with an array of acceptor compounds containing unsaturated bonds. For the most part the acceptors take the form of electron deficient alkenes as, due to the nature of the stabilising groups being employed, the radicals being studied are nucleophilic in character. These radicals are expected to react favourably with this type of acceptor in a radical Michael-type addition.<sup>[2]</sup>

## 2.0 Results and Discussion

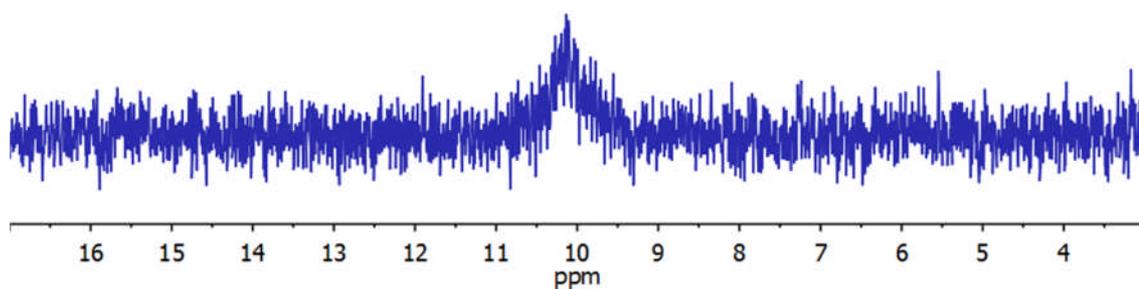
### 2.1 Preparation of commercially unavailable materials

4-Trifluoromethylphenoxyacetic **214** acid was prepared from 4-trifluoromethylphenol **215** and methyl bromoacetate **216** by treatment with potassium carbonate in refluxing THF and subsequent basic hydrolysis. This approach yielded **214** in a pleasing yield of 79% over the two steps (Sch. 1 top). Ethynylacetic acid **145** was prepared by treatment of 3-butyn-1-ol **217** with Jones' reagent in accordance with a previously reported method (Sch. 1 middle).<sup>[3]</sup>



Scheme 1.

For the preparation of  $d_1$ -phenoxyacetic acid **122D** (with the carboxylate proton replaced by a deuteron) initial preparation attempts were based on refluxing **122** in degassed  $D_2O$  overnight and subsequent drying in a desiccator. Using this approach did not lead to any observable peaks in the  $^2H$  NMR spectrum of the resultant product. A more reliable method was devised whereby **122** was converted to acid chloride **218** by reaction with  $SOCl_2$  and subsequently treated with 2.5 equivalents of  $D_2O$  in anhydrous  $CH_3CN$  overnight. Following recrystallisation from anhydrous  $Et_2O$  subsequent to drying in a desiccator the desired product **122D** was obtained in a yield of 46% (Sch 1 bottom).



**Figure 5.** <sup>2</sup>H NMR spectrum (76 MHz, CHCl<sub>3</sub>, 315 K) showing the broad peak attributed to the deuteriated carboxylate of **122D**.

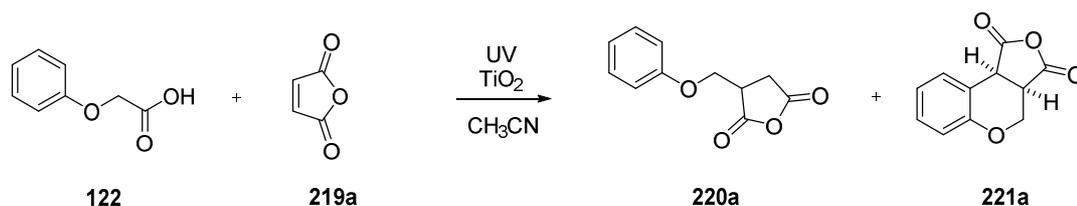
From the <sup>1</sup>H NMR spectra recorded for the various species involved in this synthesis it was observed that the broad peak for the carboxylic proton of **122** disappeared upon treatment with SOCl<sub>2</sub> along with an upfield shift in the CH<sub>2</sub> singlet. Treatment with D<sub>2</sub>O restored the CH<sub>2</sub> peak to its original chemical shift without the re-emergence of the carboxylate peak. Furthermore the <sup>2</sup>H NMR spectrum now showed a broad singlet consistent with what would be expected for a CO<sub>2</sub>D signal (Fig. 5).

## 2.2 Tandem Addition-Cyclisations

### 2.2.1 Reaction Optimisation

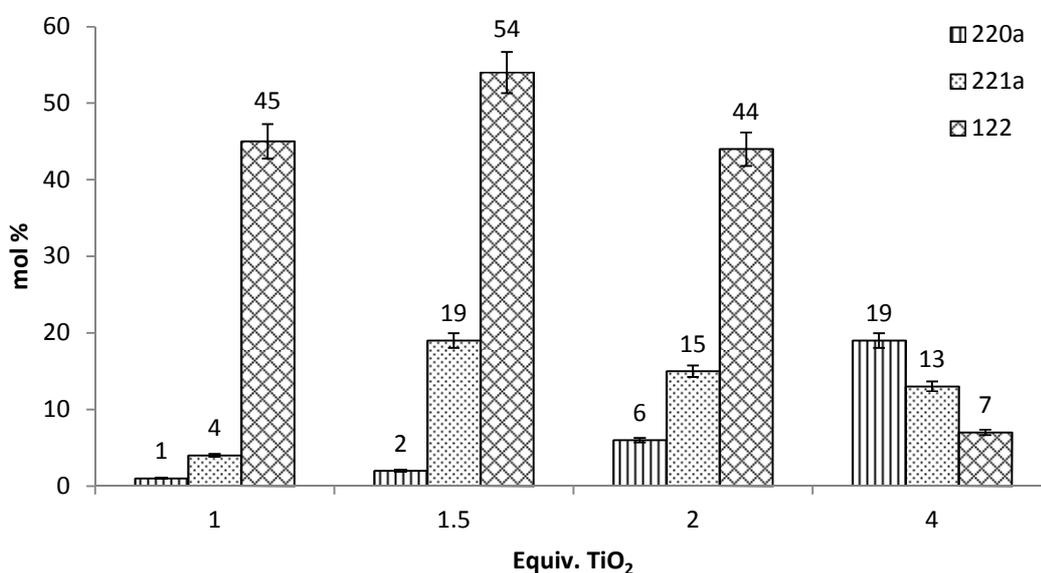
Investigations were initiated by attempting a relatively simple conjugate addition reaction whereby the acid-derived radicals would be intercepted by an electron-deficient alkene to furnish the corresponding adducts. The addition of phenoxyethyl radicals, generated by photoexcited TiO<sub>2</sub>, to maleic anhydride **219** in this manner had already been carried out at the University of Aberdeen so this was seen as a logical starting point.<sup>[4]</sup> In accordance with the reported protocol, 1 mmol of phenoxyacetic acid **122** and 4 mmol of **219** were added to a dispersion of 0.3 mmol (25 mg) of TiO<sub>2</sub> in 5 mL of anhydrous CH<sub>3</sub>CN. This mixture was degassed by bubbling with argon for 15 minutes before being photolysed for 16 hours (for a full description of the experimental apparatus used see the discussion on pg 48-49). In contrast with the 32% yield reported; analysis of the crude reaction mixture at this time revealed only starting materials present.

As previously outlined, this chemistry can be particularly sensitive to the presence of water and/or oxygen. To investigate if either of these were inhibiting the reaction various methods of drying and degassing were carried out. Multiple cycles of freeze-pump-thaw degassing of the reaction mixture prior to irradiation still did not deliver the expected outcome. Overnight drying of the TiO<sub>2</sub> at 150°C and azeotropic drying of the reagents prior to use was similarly unsuccessful. As a last resort, longer irradiation times were investigated. Following 55 hours photolysis of the same materials, the resultant mixture showed evidence for the presence of two products, **220a** and **221a**, albeit in small quantities (Sch. 2). **220a** was the expected addition adduct reported by Grant,<sup>[4]</sup> while **220b** was a tricyclic furochromenedione derivative, presumably formed in a cascade addition-cyclisation process. This identification was supported by the <sup>1</sup>H NMR spectrum of the product mixture as well as their retention times and fragmentation patterns observed by GC-MS. At this stage it became apparent that the optimum experimental parameters reported by Grant were not repeatable with the set-up being employed.



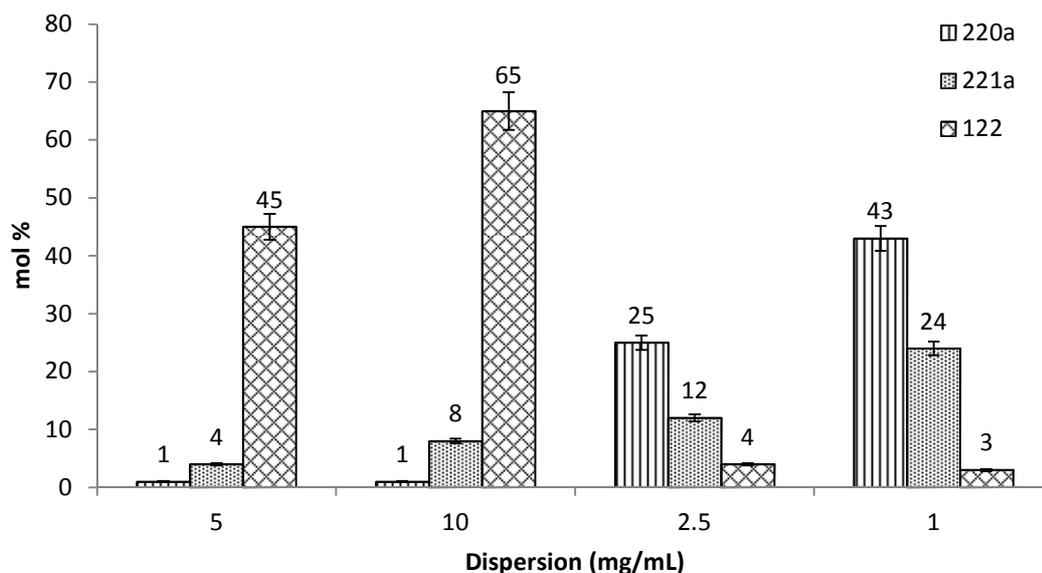
Scheme 2.

Due to the heterogeneous nature of this reaction a large number of variables was available to be scrutinized in search for the optimum reaction conditions. To expediate this process yields were calculated from  $^1\text{H}$  NMR spectra using a  $\text{CH}_2\text{Br}_2$  internal standard with a view to obtaining isolated yields once the optimised conditions were discovered. It was decided to retain the reaction of **122** with **219** for the purpose of this optimisation study. The first variable examined was the stoichiometry of the  $\text{TiO}_2$  catalyst. In all cases one equivalent (0.26 mmol) of phenoxyacetic acid **122** and two equivalents (0.52 mmol) of maleic anhydride **219** in dry  $\text{CH}_3\text{CN}$  were used. The results are summarised graphically in Fig 6. (The optimisation data is available in tabular form, along with full experimental details, on pages 136-137 of this chapter).



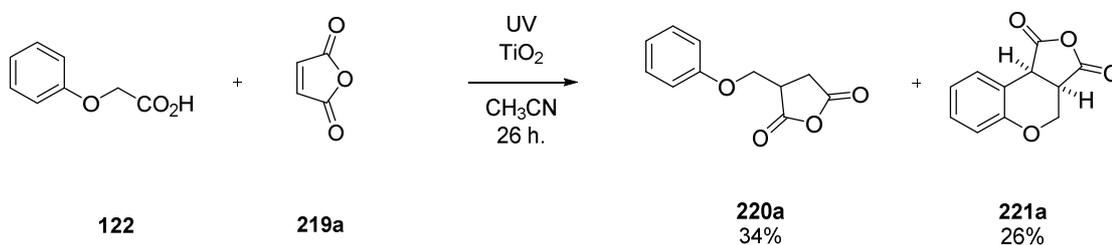
**Figure 6.** Graphical representation of the results obtained during optimisation of the reaction between **122** and **219**.

The data clearly indicates that increasing the amount of  $\text{TiO}_2$  enhances yields and conversions. This goes a long way towards explaining the earlier lack of results as previous work had been carried out using between 10 and 20 mol%  $\text{TiO}_2$ . While it is counterintuitive that a “catalyst” needs to be present in excess of the reagents it is worth bearing in mind that the great majority of the work carried out in the field of  $\text{TiO}_2$  photoredox catalysis has been on remediation of pollutants. Typically these pollutants are present in concentrations as low as parts per million and as such the excess of titania being employed is massive. The next factor that was examined was how the density of the titania dispersion in  $\text{CH}_3\text{CN}$  affected reactivity. These results are summarised graphically in Figure 7.



**Figure 7.** Graphical representation of the results obtained during optimisation of the reaction between **122** and **219**.

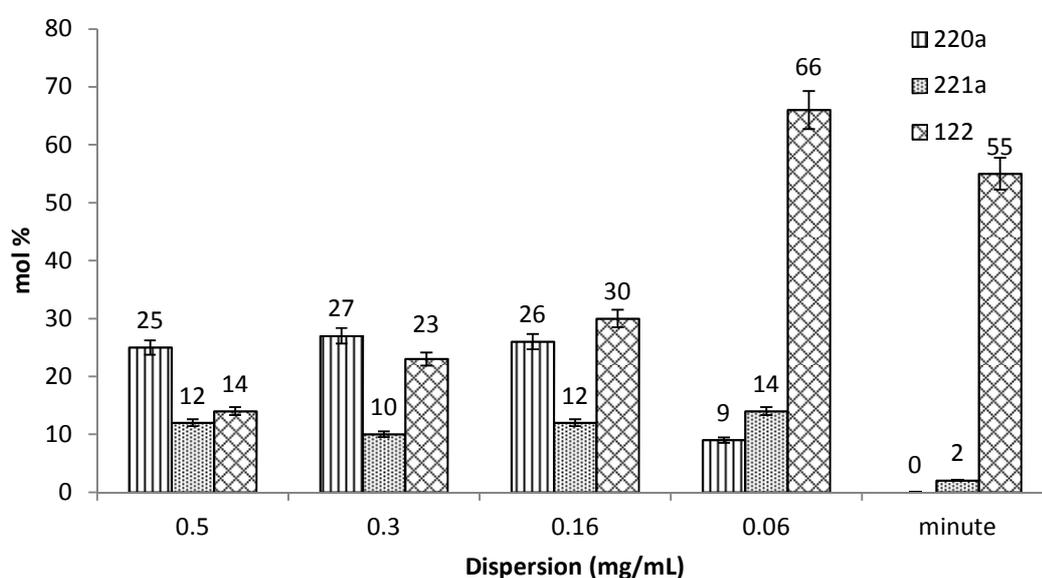
As per the findings of Grant,<sup>[4]</sup> previous photolyses were all carried out at a 5 mg mL<sup>-1</sup> dispersion. Reducing the amount of solvent by a factor of two whilst keeping everything else constant gave rise to a 10 mg mL<sup>-1</sup> dispersion. This showed little improvement in yield while conversion of starting materials was hindered. Increasing the volume of CH<sub>3</sub>CN to 12 mL and 30 mL gave rise to 2.5 and 1 mg mL<sup>-1</sup> dispersions respectively. Both of these runs demonstrated a marked improvement, with combined yields of 37% and 67% respectively being recorded. It is thought that at denser dispersions of titania the UVA photons necessary to excite the band gap have trouble penetrating the reaction dispersion and are instead scattered. This renders the semiconductor particles closer to the centre of the vessel unreactive, resulting in the poor yields and conversions obtained.



**Scheme 3.**

The conditions giving rise to the 67% yield were deemed suitable to scale up in order to isolate and fully characterise the products. Thus, **122** (0.65 mmol) and **219** (1.3 mmol) were

photolysed in a dispersion of 75 mg of titania (0.98 mmol) in 75 mL of anhydrous CH<sub>3</sub>CN for 26 hours. A small diameter (*ca.* 4.5 cm o.d.) Schlenk tube was used as the reaction vessel in preference to a round-bottomed flask in order to minimise the path-length while maximising the amount of TiO<sub>2</sub> being exposed to UVA. Isolation of both products followed by characterisation with the usual battery of spectroscopic techniques confirmed their identity. Whilst the combined yield of 60%, 34% **220a** and 26% **221a**, constitutes a great improvement on earlier efforts it was felt that there was still room for improvement. Thus it was decided to undertake further optimisation work in an attempt to further improve the yield and perhaps improve the selectivity of the reaction.

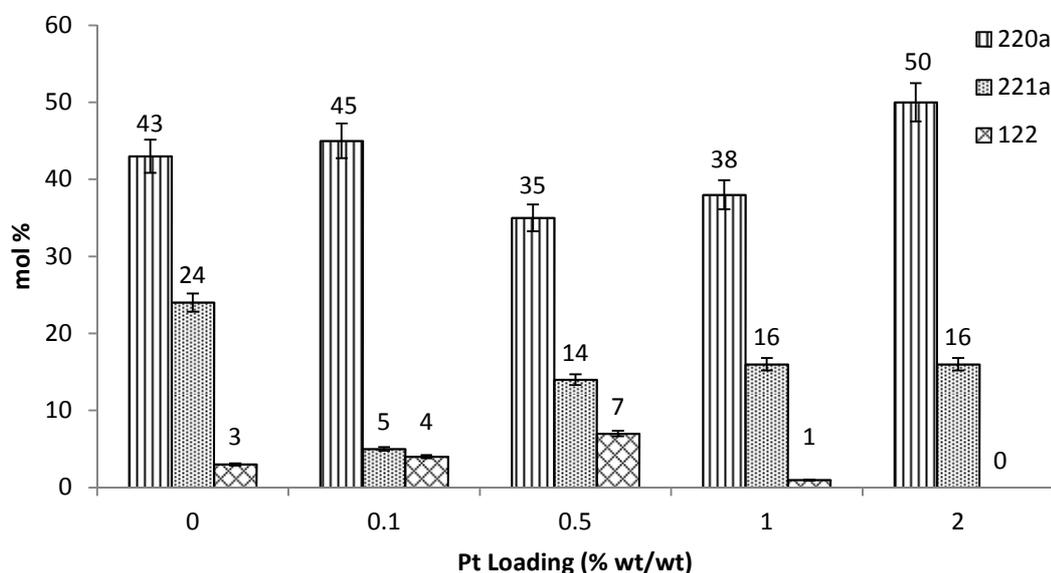


**Figure 8.**

The effects of further reducing the density of the dispersion were examined next. For practical reasons the amount of TiO<sub>2</sub> used was also decreased to facilitate this and the volume of solvent kept constant. The data obtained during these experiments is summarised in Fig. 8. As can clearly be seen the yields and conversions drop off as the concentration of titania and the density of the dispersion are lessened. Concentrations were again calculated by NMR. Varying the reaction medium also showed no improvement. When the reaction was run in DMF and CH<sub>2</sub>Cl<sub>2</sub> degradation of the starting materials was the only process observed to take place. Using THF, a known hydrogen donor solvent, as the reaction medium gave rise to anisole and the expected THF dimers. Yields and conversions were poor however. Thus, CH<sub>3</sub>CN was deemed the optimum reaction solvent. This is unsurprising given the well-established literature precedents.<sup>[5]</sup> Using a 1:1 ratio of **122** and **219a** favoured the selectivity towards the

addition adduct **220a** but saw a reduction in overall yield whilst employing a five-fold excess of acid **122** saw a further decrease in reactivity. Thus the stoichiometry employed for the scaled up reaction (1 equiv. **122**; 2equiv. **219a**; 1.5 equiv.  $\text{TiO}_2$  @  $1 \text{ mg mL}^{-1}$  in  $\text{CH}_3\text{CN}$ ) appears to be the optimum.

Referred to as “doping”, it is common practice to modify the  $\text{TiO}_2$  photocatalyst for the purpose of increasing photocatalytic activity. Noble metal particles are frequently deposited on  $\text{TiO}_2$  surfaces to assist in charge carrier separation and trapping. Of these the most extensively used is platinum. This is due to its ability to promote separation of electron-hole pairs by allowing the electrons to accumulate in the metal while leaving the holes in the  $\text{TiO}_2$ .<sup>[6]</sup> A platinum-citrate colloid was prepared and to this was added the  $\text{TiO}_2$  powder. The colloid was then destabilised by addition of NaCl resulting in the platinum being deposited on the semiconductor surface. This method was chosen as it has been shown to be a facile and effective way of preparing Pt- $\text{TiO}_2$  of high photocatalytic activity.<sup>[7]</sup>  $\text{TiO}_2$  powders with a range of platinum loadings were prepared and evaluated. The optimum conditions of 1 equivalent of **122**, 2 equivalents of **219a** and 1.5 equivalents of  $\text{TiO}_2$  were employed with  $\text{CH}_3\text{CN}$  used to generate a dispersion of  $1 \text{ mg mL}^{-1}$ . The results obtained are summarised in Fig. 9 and the previous run using undoped titania has been included for comparison purposes.

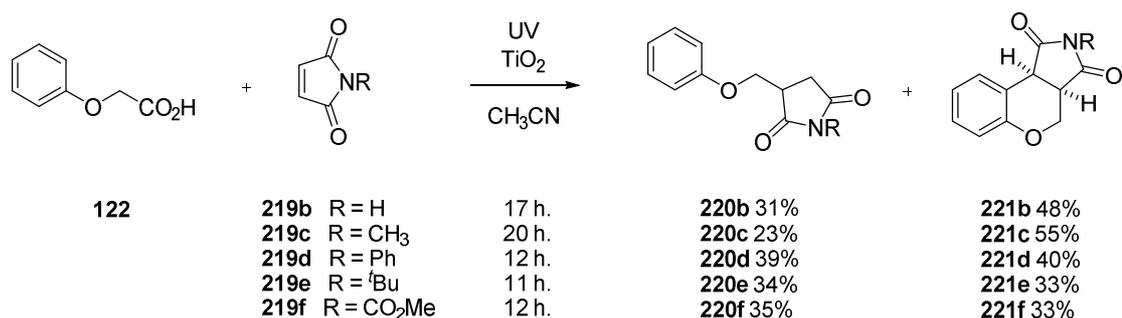


**Figure 9**

Platinisation at a variety of levels between 0.1% and 2.0% all had the effect of enhancing the selectivity for the formation of the addition adduct **220a** over the cyclised product **221a** with only the 2% loading offering a yield on par with the un-doped catalyst.

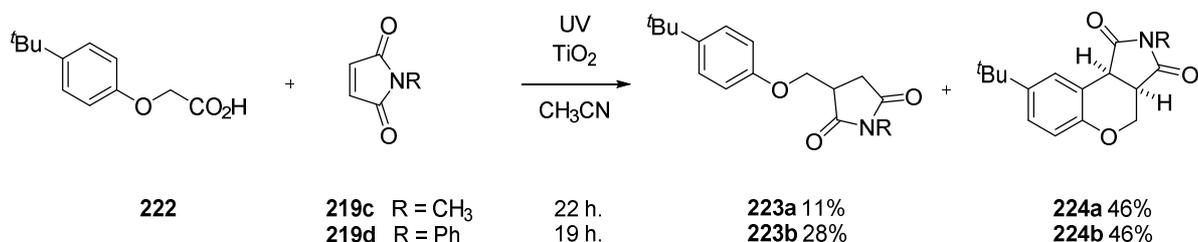
Hence it was decided at this point to carry forward the conditions previously used for scale up as the optimum and explore a variety of substrates. Before doing so however, two key control reactions were carried out. When the **112**, **219a** and  $\text{TiO}_2$  were stirred in the dark, no reaction was observed and starting materials were recovered virtually quantitatively. When the semiconductor powder was omitted and the same mixture was photolysed, no reaction was observed. However, only 78% of the phenoxyacetic acid **122** was recovered, indicating some photodegradation had taken place.

## 2.2.2 Examination of Reaction Scope



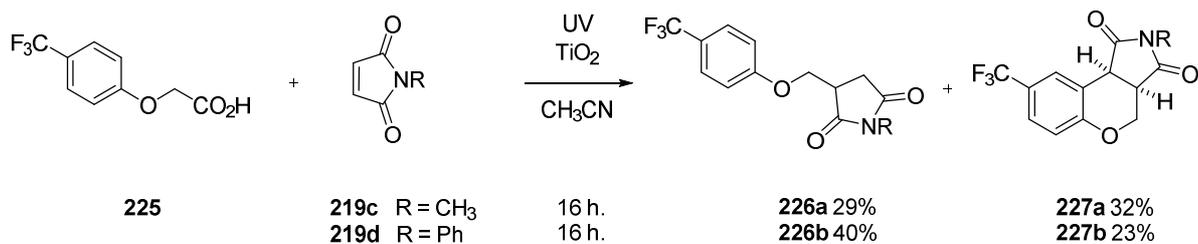
Scheme 4.

The chemistry of phenoxyacetic acids following their reaction with photoexcited  $\text{TiO}_2$  was next examined with a range of maleimides using the optimum conditions. Reactions were typically carried out overnight, unless otherwise stated, using P25 titania, in a  $1 \text{ mg mL}^{-1}$  dispersion in freshly distilled  $\text{CH}_3\text{CN}$  with the maleimide component present in a two-fold excess over the acid component. Interestingly, when unsubstituted maleimide **219b** or its *N*-methyl derivative **219c** were employed as the radical trap the chromenopyrroledione adducts (**220b** & **220c**) were observed to be the major products (Sch. 4). Incorporation of bulkier substituents at the maleimide nitrogen gave rise to a roughly 1:1 product distribution. Phenyl, *tert*-butyl and carboxymethyl substituted maleimides **219d**, **219e** and **219f** all behaved in this manner (Sch. 4). Good to excellent combined yields (67-78%) were obtained in each case.



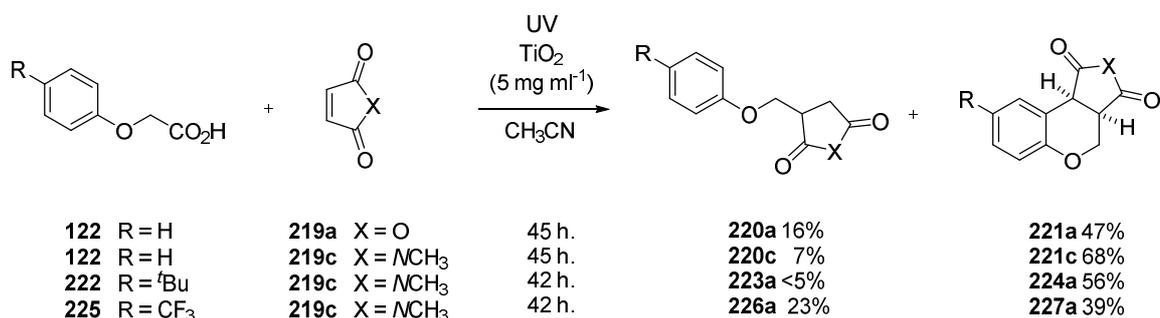
Scheme 5.

The process was seen to work well following the incorporation of electron-releasing *tert*-butyl and electron-withdrawing trifluoromethyl groups on the aromatic ring of the acid component. As expected, the acid **222** with increased electron density in the ring bearing the *tert*-butyl group cyclised more readily than its unsubstituted analogue. This was borne out by the increased quotient of chromenopyrrolediones **224a** and **224b** with respect to **223a** and **223b** isolated. The inverse was also seen to hold true as the decreased electron density in the aryl ring of **225** resulted in an increased quotient of addition adducts **226a** and **226b** being formed. Overall yields were slightly lower than those recorded with the unsubstituted acid **112** but were still very pleasing, ranging from 57-74%.



**Scheme 6.**

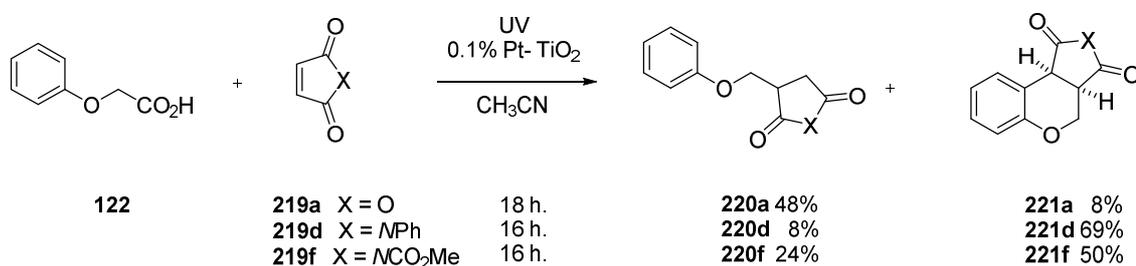
A major advantage of this heterogeneous photoredox methodology is the inherent opportunity for adjusting and adapting it. The synthetic value of the addition-cyclisation process described above is enhanced because the selectivity can be tuned in favour of either the tricyclic chromenedione derivatives or the addition adducts. In addition to the facility for modifying the substitution patterns in the reagents in order to achieve this, the heterogeneous catalyst can also be exploited to this end. During the earlier optimisation work it was observed that at denser dispersions of titania the cyclised product **221a** was favoured in the reaction between phenoxyacetic acid **122** and maleic anhydride **219a**. Yields and conversions were poor under these conditions however. In attempt to find a compromise between maintaining this selectivity whilst achieving decent reactivity the previously determined optimum reaction conditions were modified so as to generate a dispersion of 5 mg mL<sup>-1</sup>. This was achieved by reducing the volume of CH<sub>3</sub>CN by a factor of five while keeping all other conditions consistent. The results obtained using these conditions with a range of substrates in hope of maximising the selectivity of the cyclised products are shown in Sch. 7. Yields of the previously isolated products were calculated by NMR in the same manner as outlined earlier.



**Scheme 7.**

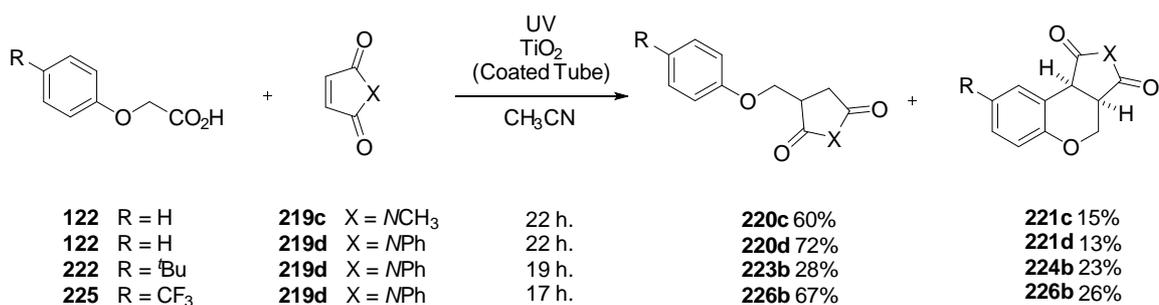
Conversion of reagents was less efficient under these conditions but with longer reaction times being employed the reaction achieved completion with the desired improvement in selectivity being observed. The cycloadduct **221a**, formed in the reaction between **122** and **219c**, was observed to be present in a much improved 2.9 fold excess over

the adduct **220c** when the denser dispersion was employed (*cf.* 0.8 : 1.0 @ 1mg mL<sup>-1</sup>). The reaction of **212** with **219c** followed a similar trend with the excess of **224c** improving from 2.4 : 1.0 to 9.7 : 1.0. None of the addition adduct **223c** was observed when the *tert*-butyl substituted acid **222** was reacted with the same acceptor (*cf.* 0.77 : 1) whilst the ratio of **227a** to **226a** from the reaction of CF<sub>3</sub> substituted acid **225** with **219c** was improved to 1.70 : 1 (*cf.* 1.1 : 1.0). It is postulated that the higher reactant concentrations under these conditions favour encounters between the ring-closed radicals and the titania catalyst, thus making it more likely to undergo oxidative rearomatisation in favour of potentially reverting to the adduct radical (for a detailed mechanistic discussion see pg 125-128). Less light can enter the system at this denser dispersion however, hence the longer photolysis times needed.



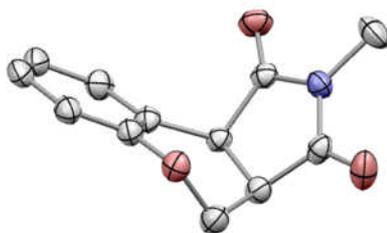
**Scheme 8.**

During the optimisation work it was also noted that use of platinumed TiO<sub>2</sub> powders favoured the formation of the adduct **220a**. At the time it was rationalised that as the platinum deposits prevent recombination by making the surface of the catalyst a more reductive environment. It was thought that the platinum nano-particles acted as reduction centers as they accumulated electrons, thus increasing the likelihood that the adduct radical would be converted to **220a** following protonation. However, when this approach was extended to other substrates in the hope of realising a means driving the selectivity towards the adduct product, the opposite was observed to happen. When **122** and **219d** were photolysed in a suspension of 0.1% Pt-P25 the cyclo-adduct **221d** was found to be present in an excess of 8.3 : 1.0 (*cf.* 1.0 : 1.0 using the un-doped catalyst). The reaction between **122** and **219f** behaved in a similar fashion. The reason for this inverted selectivity is unknown. However, the same results were obtained when the photolyses were repeated.



**Scheme 9.**

Pyrex tubes coated internally with fine layer of titania by a sol-gel method<sup>[8]</sup> were prepared by Christopher O'Rourke and Professor Andrew Mills at QUB and kindly provided for our use. When trialed in the addition cyclisation process this immobilised form of the photocatalyst proved to be highly efficient whilst showing good selectivity for the addition adducts. These were the predominant product in each case, even when the *tert*-butyl substituted acid **222** was employed which was previously shown to cyclise more favourably.

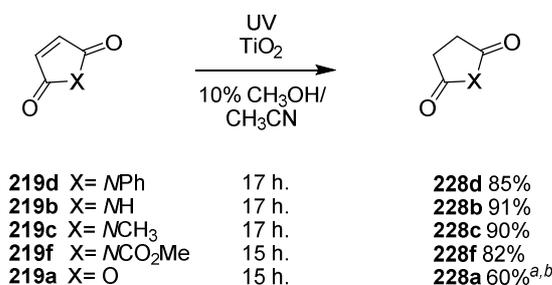


**Figure 10.** The X-ray crystal structures of chromenopyrroledione **221c**.

Cyclo-adduct **221c** yielded crystals of a quality suitable for X-ray analysis upon slow evaporation from a solution in CDCl<sub>3</sub>. The resultant crystal structure (Fig. 10) confirmed the structural assignment of **221c** and showed that the newly formed pryan ring and pyrrolidine ring adopted a *cis* geometry at their juncture. The <sup>1</sup>H NMR spectra of all isolated cycloadducts had <sup>3</sup>J<sub>H-H</sub> coupling constants between the two protons at this ring junction within the range of 9.2–9.3 Hz. This indicated a *cis* arrangement,<sup>[9]</sup> in agreement with the conclusion that the reaction selectively formed the *cis* isomer in every case.

## 2.3 Conduction-Band Reductions

These addition cyclisation reactions are relatively clean and efficient. It was anticipated that [2 + 2] dimerisation<sup>[10]</sup> of maleic anhydride **219a** and maleimides **219b-f** would be a nuisance side-reaction that would detract from the effectiveness of the process and make isolation of the desired products less convenient. In reality however this process was only observed when *N*-methylmaleimide **219c** was employed. The resultant cyclobutane dimer was formed in a small enough quantity so as not to impact seriously upon the yields and conversions of the addition-cyclisations. The only by-products consistently observed during this work were succinic anhydride **228a** and succinimides **228b-f**. It is thought that these form as a result of two sequential reduction protonations at the titania surface. They were formed in moderate yields (9-43%) from maleates **219** during each photolysis with included carboxylic acid.

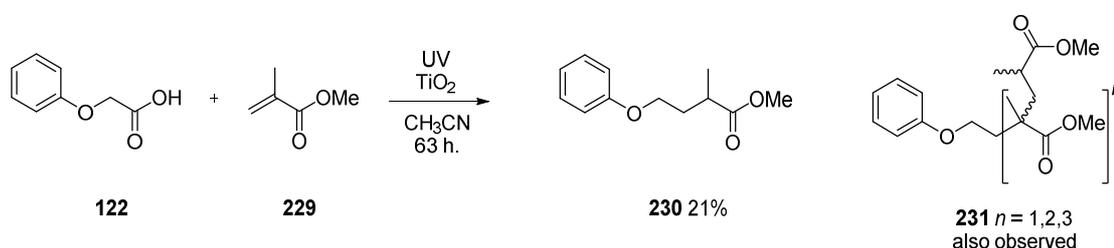


**Scheme 10.** <sup>a</sup> Yield determined from <sup>1</sup>H NMR by comparison to CH<sub>2</sub>Br<sub>2</sub> standard; <sup>b</sup> 17% ring opened product also observed.

When *N*-phenylmaleimide **219d** was photolysed alone in a dispersion of P25 titania in CH<sub>3</sub>CN poor conversion was observed. In the absence of a hole scavenger the system is inefficient as the catalyst becomes electron-deficient over time. When the reaction was repeated in methanol, a known hole-scavenger for TiO<sub>2</sub>, full conversion was achieved but nucleophilic ring-opening to the amide/ester was observed to take place in competition with the reduction. Thus, as a compromise, a 10% mixture of CH<sub>3</sub>OH in CH<sub>3</sub>CN was trialled. This proved to be effective with **219d** being converted to *N*-phenylsuccinimide **228d** in a pleasing yield of 85%. This approach was extended to a range of maleimides and good to excellent yields of 82-91% were obtained (Sch. 10). Only when the reduction was carried out using the highly electrophilic maleic anhydride **219a** was a significant quantity of the ring-opened product observed.

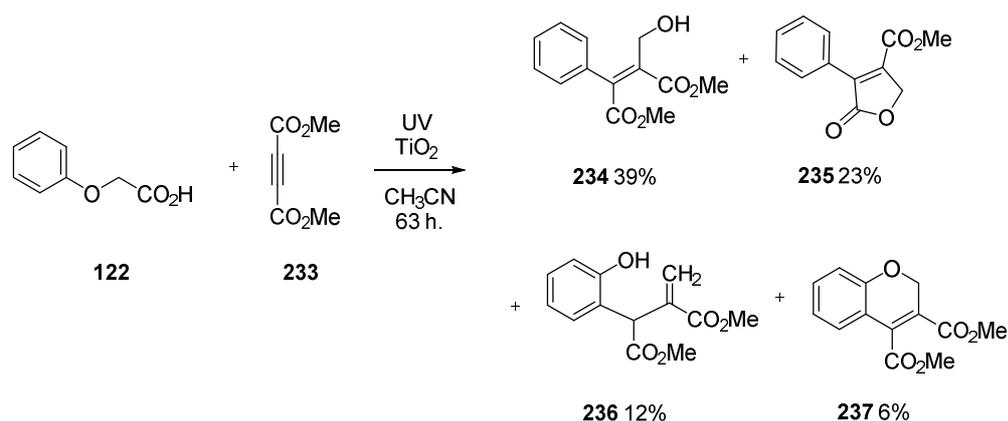
## 2.4 Variation of the Radical Trapping Component

At this point it was decided to examine the effects of replacing the maleate component with other types of radical traps. It was hoped that the scope of the reaction would be expanded by doing this and that improved selectivity would be established and/or that new reaction pathways would be discovered. By-and-large this endeavour proved unsuccessful. Acrylates<sup>[11]</sup> and styrenes<sup>[12]</sup> have found widespread use as radical accepting moieties. When methyl methacrylate **229** and *trans*- $\beta$ -nitrostyrene **232** were reacted under the optimum conditions determined in the previous addition-cyclisation work the major reaction outcomes were thought to be polymerisation in the former case and degradation in the latter.



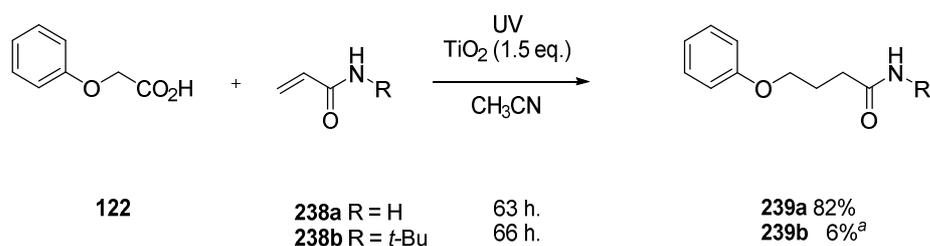
Scheme 11.

The photolysis of **122** and **229** required 63 hours in order to attain full consumption of the acid starting material. Following this prolonged reaction time the reaction mixture was subjected to column chromatography, leading to the isolation of the desired product **230** in a rather disappointing yield of 21%. A second fraction containing several compounds, many of which could not be identified, was also obtained following chromatography. GC-MS analysis of this mixture tentatively identified one component of this mixture was the di-oligomer **231**<sub>1</sub> ( $n=1$ ) suggesting that polymerisation was responsible for the poor yield recorded. Indeed, analysis of the total reaction mixture prior to purification, again by GC-MS, suggested that the tri- and quad-oligomers were also present. When **122** was irradiated with *trans*- $\beta$ -nitrostyrene no useful data could be obtained, neither by NMR nor GC-MS, after 18 hours. This, in combination with the fact that the reaction mixture following filtration and solvent evaporation had the appearance of a thick brown tar, suggested that the reagents had been degraded under the reaction conditions used.



**Scheme 12.**

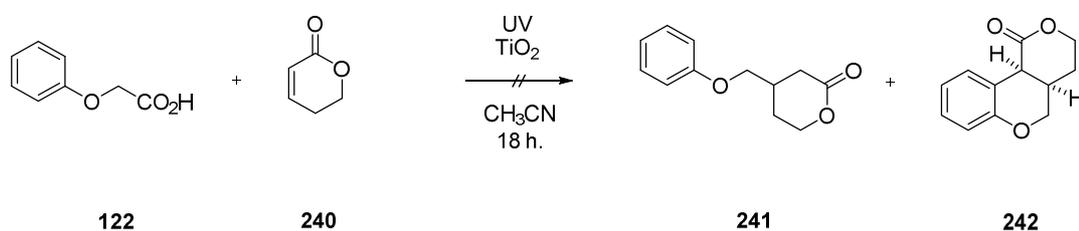
Dimethylacetylenedicarboxylate (DMAD) **233** proved much more reactive but a deal less selective than the maleate acceptors. Four significant products were isolated following the photolysis of phenoxyacetic acid **122** with **233**, all thought to stem from reactions of the vinyl radical formed upon addition of the phenoxyethyl radical to **233**. The first of these **234** is thought to form as a result of *ipso*-cyclisation to form a five-membered spiro intermediate which subsequently re-opens to form **234** following reduction-protonation or hydrogen abstraction. **235** is the result of thermal cyclisation of **234** with loss of methanol after *E/Z* isomerisation. **236** is formed in a manner akin to that of the addition adducts from the maleate addition cyclisations, however it undergoes a Claisen [3,3] sigmatropic rearrangement after reduction protonation. A cycloadduct **237** similar to those previously isolated was also found in this case. In spite of the pleasing overall yield, the complexity of the product distribution detracts significantly from the synthetic value of this process.



**Scheme 13.** <sup>a</sup> Yield determined from <sup>1</sup>H NMR by comparison to CH<sub>2</sub>Br<sub>2</sub> standard.

Acrylamide **238a** proved to be the radical acceptor most capable of delivering clean, efficient and selective results when irradiated with **122** in the presence of TiO<sub>2</sub>. Photolysis of **122** (5 equiv.) and **238a** (1 equiv.) for 62 hours with TiO<sub>2</sub> (1.5 equiv.) in CH<sub>3</sub>CN (1 mg mL<sup>-1</sup>) led to the formation of the desired adduct **239a** cleanly and selectively in a very pleasing yield of 82%. No by-products were detected, including propionamide, indicating that **238a** is not

reduced by the conduction band electrons. Inclusion of an alkyl substituent on the amidic nitrogen of **238b** had the effect of essentially shutting down the reaction. When **238b** was reacted with **122** under identical conditions only 6% of the desired product **239b** was observed in the NMR spectrum of the reaction mixture after 66 hours irradiation.

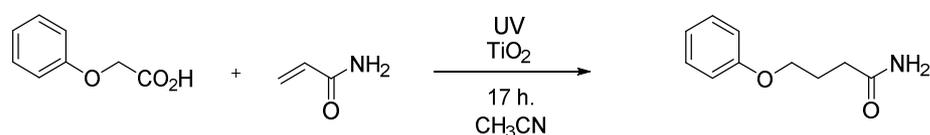


**Scheme 14.**

It was thought that the reaction of 5,6-dihydro-2*H*-pyran-2-one **240** could lead to the formation of two products in a similar manner to the addition-cyclisations discussed in section 2.2. However, no reaction was observed to take place when **122** and **240** were photolysed with the titania catalyst in the usual manner for 18 hours. Repetition confirmed this outcome, even when the lactone **240** had been purified by distillation immediately prior to photolysis.

## 2.5 Catalyst Comparison Study

Due to its widespread application as a means of detoxifying soil and water, as well as investigations into its potential for splitting water to form hydrogen fuel, a great deal of time and effort has been devoted to titania photoredox catalysis (see general introduction pg 30-31 for a full discussion of this). A plethora of different forms of the titania catalyst have been conceived, developed and marketed. Thus, with a clean and selective reaction now in hand it was decided to compare the efficiency of a selection of these catalysts. For each photolysis a sub-optimum 0.1 mmol of phenoxyacetic acid **122** and 0.2 mmol of acrylamide **238a** were irradiated for 17 hours in anhydrous CH<sub>3</sub>CN (12 mL). Where applicable 12 mg of the photocatalyst was employed in a 1 mg mL<sup>-1</sup> dispersion. These results are summarised in Table 1 below. Yields and conversions were determined by NMR spectroscopy.

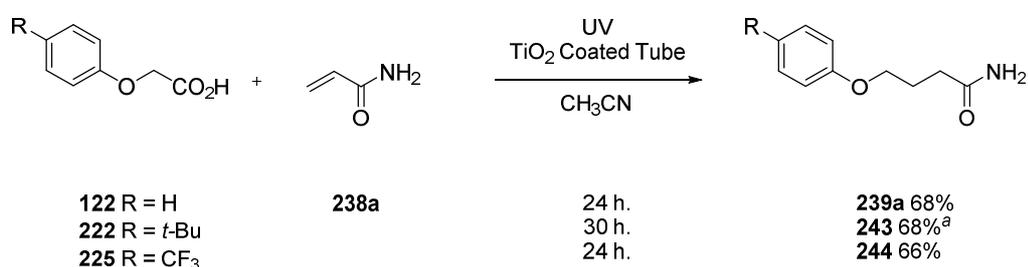


Entry	Catalyst	Conversion	Yield <b>239a</b>
1	P25	95%	47%
2	PC500	100%	39%
3	Sol-gel tube	100%	73%
4	Photospheres	41%	9%

**Table 1.**

P25 consists of roughly a 3:1 mixture of the anatase and rutile polymorphs of titania and has a particle size of ~21 nm and a surface area of ~50 m<sup>2</sup> g<sup>-1</sup>.<sup>[13]</sup> It has long been considered the “gold standard” catalyst in the field of TiO<sub>2</sub> SCPC. While there is a great deal of experimental evidence to back up this claim, explanations for its superiority vary. Synergistic cooperation between the anatase and rutile phases resulting in more efficient charge trapping, and thus preventing recombination,<sup>[14]</sup> is one theory whilst the generation of catalytic “hotspots”<sup>[15]</sup> at the interface between the two phases is another. When P25 was employed as the catalyst under the conditions outlined above a 47% yield of the 4-phenoxybutanamide adduct **239a** was recorded (entry 1). Millennium PC500 titania is a high surface area catalyst with particles in the region of four times smaller (*ca.* 5 nm) than P25, about six times (*ca.* 300 m<sup>2</sup> g<sup>-1</sup>) the surface area and is composed entirely of nanocrystalline anatase.<sup>[13]</sup> It is virtually identical to the photocatalyst employed by Bard and co-workers in their initial investigations of the photo-Kolb  reaction.<sup>[16]</sup> When PC500 was employed under our conditions the yield dropped slightly (entry 2) when compared with P25 although a higher

conversion was recorded. Reactions were also carried out in 5 mm diameter Pyrex tubes coated with a fine internal layer of TiO<sub>2</sub> by a sol-gel process.<sup>[8]</sup> These proved to be very efficient and led to the best yield (entry 3). TiO<sub>2</sub> Photospheres consist of hollow Pyrex beads (dia. 45 μm) coated externally with rutile titania and have been designed with a view to being an effective and reusable means of treating water contaminated with pollutants and/or microorganisms.<sup>[17]</sup> When trialled in our system however both conversion and adduct yields were low (entry 4). This is mainly attributed to difficulties in dispersing photospheres satisfactorily throughout the reaction flask. Due to their buoyancy they tended to accumulate at the top and this was compounded by the fact that the high rate of magnetic stirring used in attempts to overcome this tended to result in their becoming damaged.

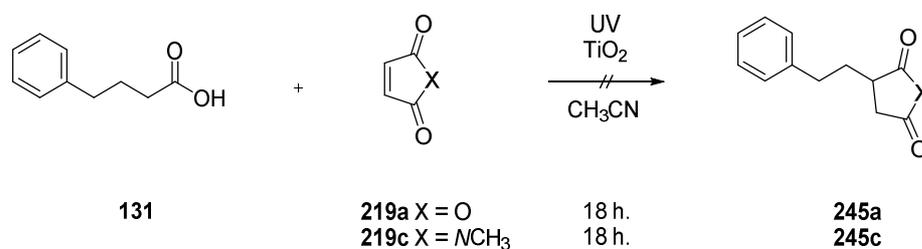


**Scheme 15.** <sup>a</sup> Isolated along with *ca.* 5% 4-*tert*-butylphenol.

An isolated yield of 68% was achieved upon scale up of the reaction in the coated tube (Sch. 15). Incorporation of 4-*tert*-butyl and 4-trifluoromethyl substituents in the aryl ring of the acid component furnished the corresponding adducts (**243** & **244**) in similarly attractive yields of 68% and 66% respectively. Although the sol-gel coated tubes gave the best yields and conversions the coatings tended to detach so they could only be used about three times. Furthermore, it has been shown that the activity of the immobilised titania catalyst drops off with each cycle of re-use; requiring that it be heat treated to restore it to optimum.<sup>[18]</sup> We concluded therefore that for ease of handling with conventional organic techniques, scale-up and efficient product formation, the orthodox P25 catalyst was the best compromise.

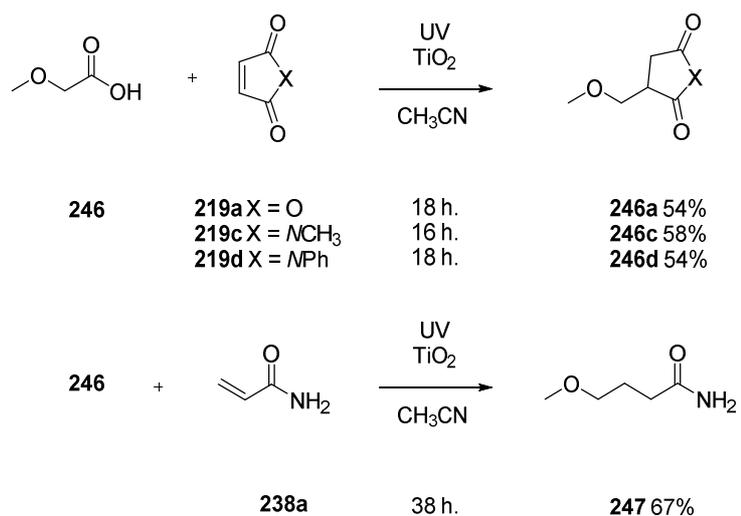
## 2.6 Variation of the Carboxylic Acid Component

Given the limited success obtained when varying the radical-accepting component up to this point it was decided to switch focus to the carboxylic acid component. Subsequent to the earlier work on the addition-cyclisations between phenoxyacetic acids **122** and maleates **219**, attempts were made to furnish the adducts **245** by irradiating 4-phenylbutyric acid **131** in the presence of maleic anhydride **219a** and *N*-methylmaleimide **219c**. The optimum conditions derived during the addition cyclisation work – 1 equiv. of **131**, 2 equiv. of **219a/c** with 1.5 equiv. of P25 TiO<sub>2</sub> at a 1 mg mL<sup>-1</sup> dispersion in anhydrous CH<sub>3</sub>CN – were employed for both of these reactions. However, in spite of this, not even a trace of the desired products could be discerned. In addition to the unreacted starting materials the only additional entity present was the reduced succinic anhydride **228a** or *N*-methylsuccinimide **228c**, albeit in small quantities.



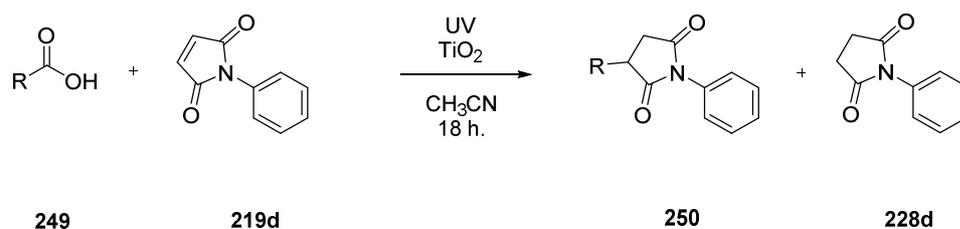
Scheme 16.

Methoxyacetic acid **246** was examined next. It was anticipated that it would be similarly reactive to its phenoxy analogue **122** whilst yielding only one product as it lacks the capacity to undergo the cyclisation process following addition of the photo-generated radical to the acceptor. Satisfyingly, this proved to be the case. Overnight reaction of **246** with maleates **219a**, **219c** and **219d** returned the corresponding radical addition products in yields of 54%, 58% and 54% respectively. As with previous reactions of maleates their corresponding reduction product was observed as a by-product. When **246** was reacted with acrylamide **238a**, using the same five-fold excess as with **122**, with P25 titania the butanamide product **248** was isolated in 67% yield after 38 hours photolysis. Again, no byproducts were detected.



**Scheme 17.**

The postulated reason for the opposing reactivities observed for alkoxyacetic acids **122** and **246** and phenylbutyric acid **131** the ability of the  $\alpha$ -O atom to exert a stabilising influence on the radical formed subsequent to homolytic photodecarboxylation (*vide infra* for a detailed discussion of the role of radical stability in the proposed reaction mechanism pg 125-128). Etheral oxygen atoms possess relatively high energy n orbitals – their lone pairs – which can interact with the SOMO as described in section 1.0 of this chapter. To further probe the role of radical stabilisation in this system, a simple study was undertaken. Six carboxylic acids **249** of known stabilisation energy<sup>[1d]</sup> were photolysed under standard, un-optimised conditions so that a clear comparison of behaviour from acid to acid could be obtained and to see what, if any, correlation could be drawn between radical stabilisation energy and yields/conversions.

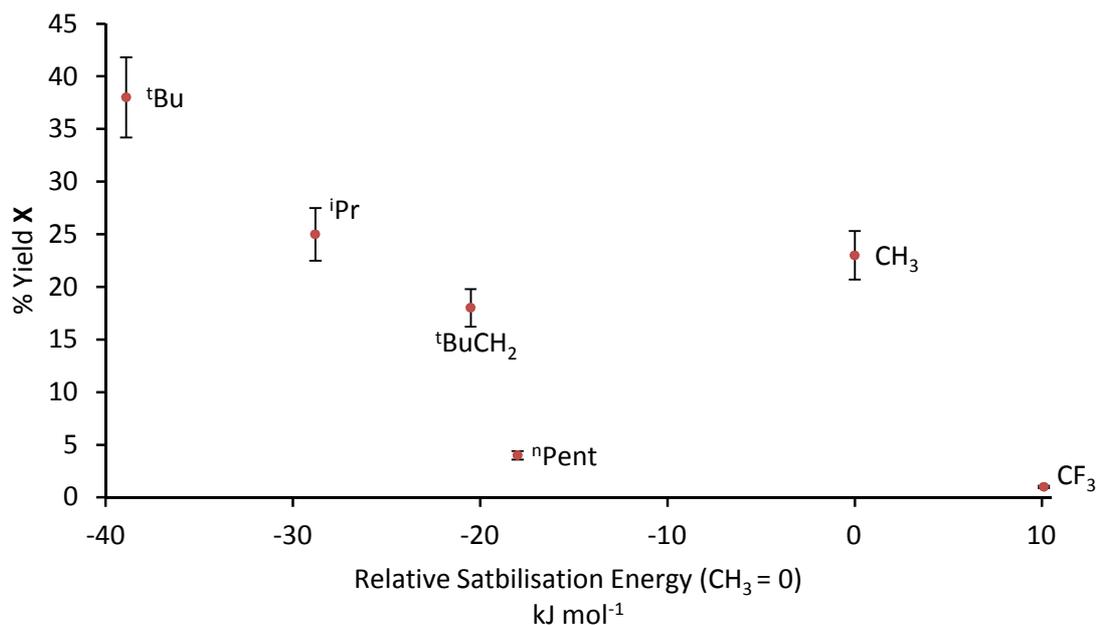


**Scheme 18.**

Entry	R	Radical	RSE <sup>[1d]</sup> kJ mol <sup>-1</sup>	% Yield		
				250	249	228d
1	CH <sub>3</sub>	methyl	0	23%	95%	41%
2	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub>	<i>n</i> -pentyl	-18.0	4%	65%	2%
3	<i>t</i> -BuCH <sub>2</sub>	neopentyl	-20.5	18%	77%	40%
4	<i>i</i> -Pr	isopropyl	-28.8	25%	74%	25%
5	<i>t</i> -Bu	<i>tert</i> -butyl	-38.9	38%	94%	31%
6	CF <sub>3</sub>	trifluoromethyl	+10.1	trace	nd	trace

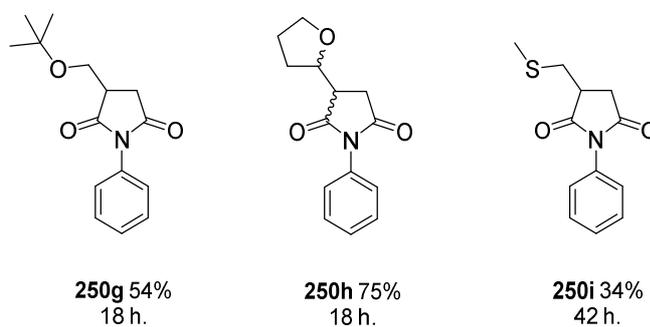
**Table 2.** Yields and conversions determined from <sup>1</sup>H NMR by comparison to CH<sub>2</sub>Br<sub>2</sub> standard.

In all instances 0.1 mmol of the acid **249** and 0.2 mmol of radical acceptor **219d** were photolysed in a suspension of 12 mg (0.15 mmol) of the P25 catalyst in 12 mL of CH<sub>3</sub>CN for 18 hours. In order to remove any inconsistencies associated with isolating each adduct, yields and conversions were measured by NMR. Initially acrylamide **238a** was used in these experiments but the yields obtained were so low that comparison was difficult as was identification of the actual products. Thus, *N*-phenylmaleimide **219d** was used in its place. The results obtained are summarised above in Table 2. These reactions did indeed lead to formation of adducts **250**, incorporating the carboxylic acid moiety R and an additional H-atom, together with significant amounts of succinimide **228d** (Sch. 18). For acids which decarboxylated to give methyl (entry 1) or primary alkyl radicals (entries 2, 3) yields were low. Increased yields were obtained with secondary and tertiary radicals (entries 4 and 5). Negligible adduct was detected for the de-stabilised,  $\sigma$ -type CF<sub>3</sub> radical (entry 6). Adducts from entries 1, 3, 4 and 5 were isolated and fully characterised under individually optimised, non-standard conditions by honours student Phillip Miller. Entry 6 is a known compound with its characterisation data previously published and entry 2 was identified based on characteristic peaks shared with its ethyl analogue, also a known compound.



**Figure 11.** Graph showing percent yields for adducts **250** under standard conditions vs. the stabilisation energy of the radical intermediates.

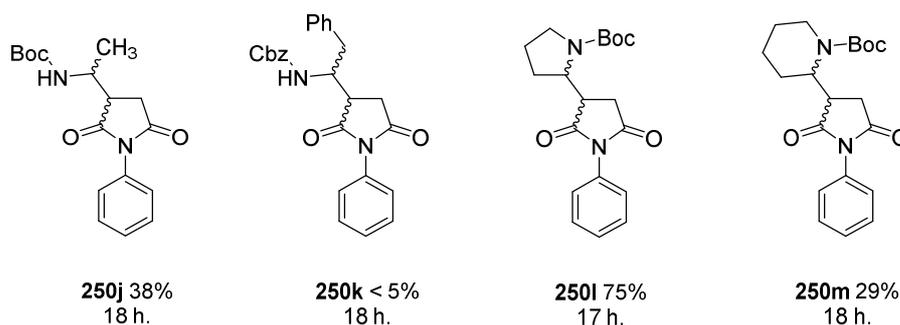
Figure 11 shows a plot the RSE values against the yields measured for **250** under the standardised conditions above. From this graph it is evident that the efficiency of the process increased as the stabilisation energy of the released radical increased. Interpolating from the CF<sub>3</sub> data point to the *tert*-butyl data point a clear increasing trend can be seen. The methyl and *n*-pentyl radicals perform better and worse respectively than would be expected based on the stabilisation energy. From this it can be deduced that radical stability is an important factor in this system but that other factors, as yet unknown, can supersede it in certain instances.



**Figure 12.**

Next, it was decided to examine a set of addition reactions with **219d** involving a diverse range of carboxylic acids containing a variety of different potential radical stabilising

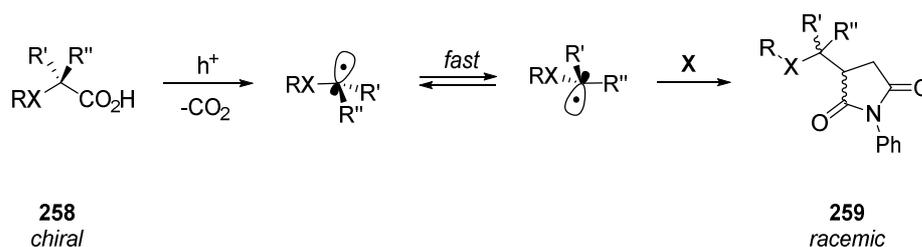
groups. These reactions were typically carried out using 0.66 mmol of the respective carboxylic acid, 4 equivalents of **219d** (2.67 mmol) and 1.5 equivalents (1 mmol) of P25 titania in a 1 mg mL<sup>-1</sup> dispersion in dried CH<sub>3</sub>CN. Reaction times were optimised for each individual run and are given below. Unless otherwise stated, isolated yields are quoted. Based on the success of employing  $\alpha$ -oxy acids **122** and **246** with **219d** it was decided to examine the outcome of photolysing an assortment of acids bearing heteroatoms *beta* to the carboxylate and thus *alpha* to unpaired electron in the acid derived radicals. *Tert*-butoxyacetic acid **251** returned an isolated yield of 57%, similar to that of its methoxy analogue **246**, following reaction for 18 hours. Photolysis of 2-tetrahydrofuroic acid **252** for the same reaction time gave rise to a highly pleasing yield of 75% for **250h**. **250h** was isolated as a 1:1 mixture of two diastereomers. 2D NMR and GC-MS experiments were used to characterise each individual isomer and their ratio was determined from the <sup>1</sup>H NMR spectrum. Methylthioacetic acid **253**, the thio analogue of **246**, proved to be a great deal less reactive. Requiring irradiation for 42 hours in order to achieve full conversion a disappointing yield of 34% was recorded for its adduct **250i**.



**Figure 13.**

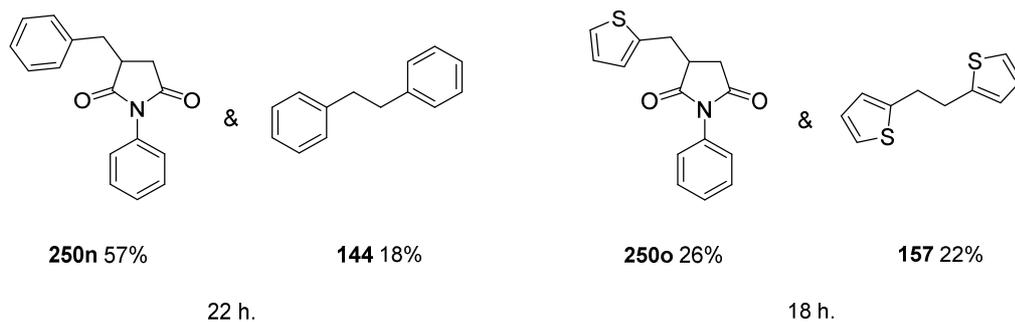
Amino acids are highly prevalent in nature and are widely available from commercial suppliers - natural, unnatural and derivatised – making them potentially a highly attractive feedstock for this reaction. Furthermore, the positioning of the amino nitrogen atom *alpha* to the radical center should provide a degree of radical stability. Indeed, reaction of Boc-L-alanine **254** with **219d** in the manner outlined above did indeed lead to the formation of two diastereomeric adducts **250j**. The second of the two diastereomers co-eluted with the *N*-phenylsuccinimide by-product **228d** and was characterised as a mixture. The chirality of the starting material was lost in the process, however, with 18% and 20% of each diastereoisomer being isolated. The radical intermediates exist with the unpaired electron at the chiral center and adopt a near planar configuration.<sup>[1c]</sup> At room temperature this undergoes rapid interconversion between *R* and *S* causing all stereochemical information to be lost (Sch. 19).

When Cbz protected phenylalanine **255** was subjected to photolysis under identical conditions analysis of the resultant reaction mixture suggested that a high degree of reagent degradation had taken place. Repeat photolysis confirmed this outcome. It is thought that the highly abstractable hydrogens of the Cbz group may be opening a plethora of alternative reaction pathways for this compound, making it unsuitable for use under these conditions. Boc-L-proline **256** was transformed to adducts **250i** in a fine yield of 75%. The two diastereomers proved inseparable after several rounds of chromatography. To compound this, both isomers exhibited conformational isomerism at room temperature on a time scale comparative to that of NMR. Hence the NMR spectrum of the reaction mixture was nearly impossible to interpret. Elevating the temperature at which the spectrum was measured overcame this and allowed the mixture to be characterised with the assistance of 2D NMR and GC-MS. The unnatural amino acid Boc-D/L-piperidinecarboxylic acid **257** returned a much more modest yield of 29% when photolysed for 18 hours under the same conditions. As before both of these products were formed as 1:1 mixtures of diastereoisomers regardless of the chirality of the starting materials.



**Scheme 19.**

The benzyl radical, with RSE = -61.0 kJ mol<sup>-1</sup>, is one typical example of this approach. Consequently phenylacetic acid **143** was deemed a highly attractive substrate for examination under the conditions being studied. Indeed, when **143** was subject to irradiation with **219d** in a manner identical to the previous photolyses the desired adduct **250n** was isolated in a pleasing yield of 57% after 22 hours. This was accompanied by 18% bibenzyl **144**, the radical dimerisation product. This highlights one of the drawbacks of attempted additions using highly stabilised radicals; radical dimerisation becomes energetically more favourable than the addition process to such an extent that it begins to outweigh the concentration effects and dimerisation competes with addition. 2-Thiopheneacetic acid **155** reacted in a similar fashion, delivering the desired adduct **250o** along with the radical dimer **157**, albeit in lower yields.



**Figure 19.**

The allyl radical,  $RSE = -72 \text{ kJ mol}^{-1}$ , was anticipated to be just as, if not more, reactive than the benzyl radical under the same conditions. Puzzlingly though, irradiation of vinylacetic acid **260** with **219d** led only to the recovery of starting materials. Repeat photolysis confirmed this surprising outcome. Cyclohex-1-enylacetic acid **132**, which successfully formed allyl radicals during the earlier dimerisation experiments, was reacted under the same conditions as **260**. Again, only starting materials were recovered. When acrylamide **238a** was substituted for **219d** and irradiated with **260** the outcome was as before. The propargyl radical also benefits from resonance stabilisation,  $RSE = -52.8 \text{ kJ mol}^{-1}$ , by delocalisation of the unpaired electron into the neighbouring acetylene moiety. However when ethynylacetic acid **145** was irradiated with **219d** the outcome was the same as for the allyl radical. The reason for these unexpected results is as yet unknown.

## 2.7 EPR Spectroscopy

9 GHz EPR spectroscopy was employed with the aim of gaining some insight into the nature of the radical intermediates involved in the titania photocatalysed reactions in solution. Initial experiments were carried out using P25 titania in anhydrous CH<sub>3</sub>CN, as per the preparative photolyses. Samples were photolysed within the resonant cavity by unfiltered light from a 500 W super pressure mercury arc lamp. When pivalic acid **249e** was examined under these conditions no spectrum was observable. The use of CH<sub>3</sub>CN as solvent required that minimal volume be used due to the fact that it adsorbs microwave irradiation, hence these experiments were carried out in capillary tubes. It was thought that any radicals being formed were below the level of detection so larger volume tubes were employed. As a consequence apolar media had to be used. *Tert*-butylbenzene was the solvent of choice. The downside with this was the diminished solubility of the acid precursors. As a compromise 5mm diameter quartz tubes were filled with *ca.* 0.5 mL solutions of **249e** to maximise the quantity present in the resonant cavity of the spectrometer.

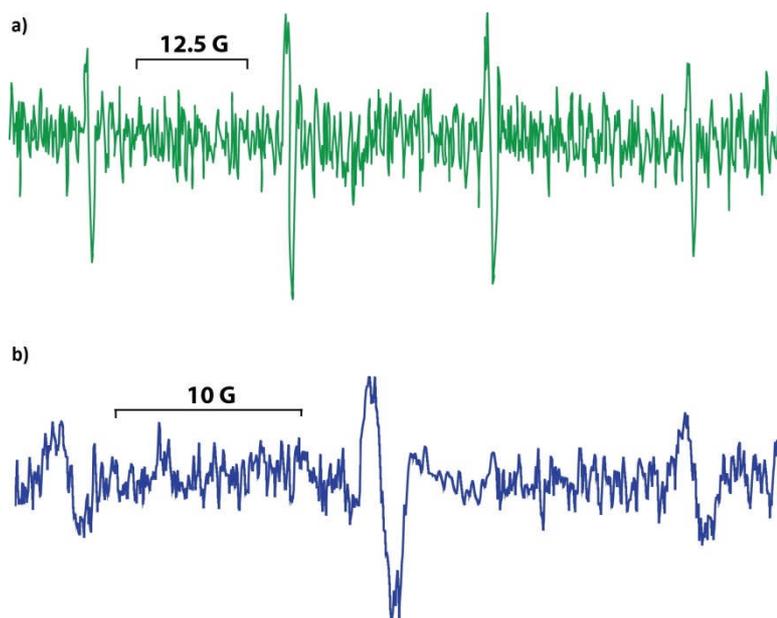


Figure 20.

Using this approach still resulted in no signal being obtained from **249e** with P25 TiO<sub>2</sub>. As magnetic stirring is not possible within the resonant cavity of the spectrometer the titania dispersion could not be maintained for a period of time long enough to collect sufficient scans. To combat this PC500 titania was used instead as its finer mesh would allow it to remain dispersed for longer. It was usually possible to accumulate 10-20 scans in this manner before the signal, if any, began to deteriorate. In most cases it was necessary to combine the spectra

obtained from several fresh samples. The spectrum shown in Fig. 20a, corresponding to the four central lines of the *tert*-butyl radical, was obtained in this manner. Recorded at 298 K, it is the result of overlaying the spectra from four separate runs. The hfs of  $a(9\text{H}) = 22.6$  G is consistent with the literature.<sup>[19]</sup> Attempts to improve the signal strength at lower temperatures resulted in no spectrum being observed.

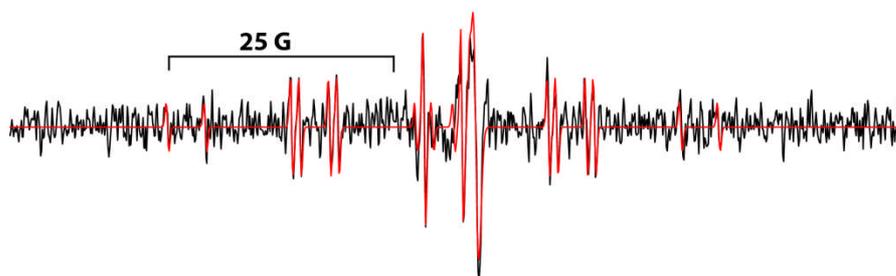


Figure 21.

Photolysis of **122** in a similar manner led to the observation of phenoxymethyl radical (Fig. 20b). The EPR parameters [ $g = 2.0024$ ;  $a(2\text{H}) = 17.4$  G] were in good agreement with the literature.<sup>[20]</sup> The very weak triplet shown is the result of overlaying the signals recorded from two separate runs. In similar EPR experiments with vinylacetic acid **260** and 2,2,2-triphenylacetic acid **172** allyl radicals and triphenylmethyl radicals respectively were detected and characterised. The spectrum for the allyl radical (Fig. 21), an accumulation of 100 scans, was satisfactorily simulated with hfs of  $a(2\text{H}) = 14.8$  G,  $a(2\text{H}) = 13.9$  G and  $a(1\text{H}) = 4.20$  G. These are essentially identical to the literature values for the allyl radical.<sup>[21]</sup> Also visible in both the spectrum and simulation is a singlet at  $g = 2.000$  thought to be due to the trapped electrons in the titania conduction band.

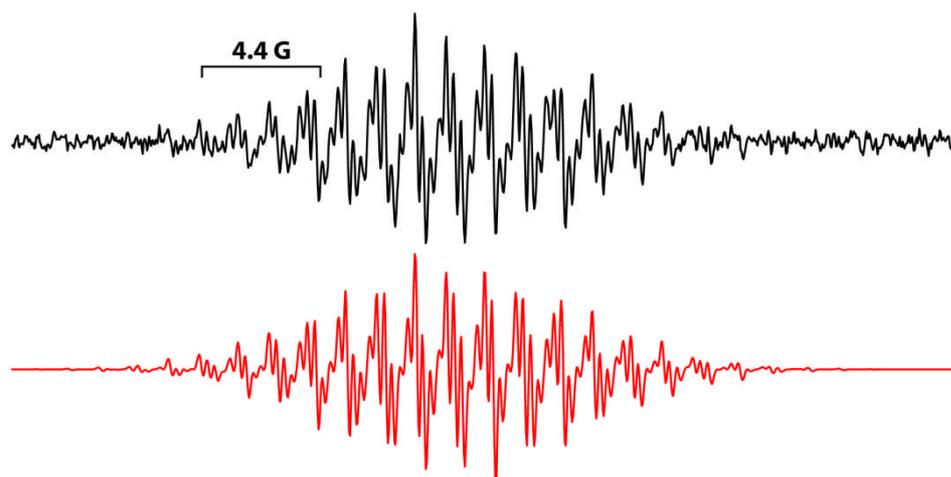
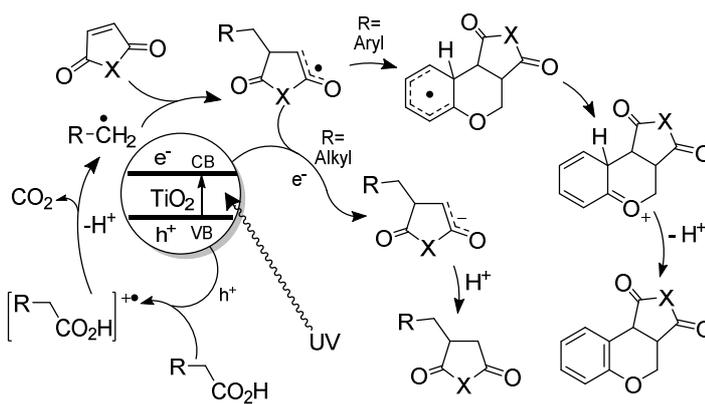


Figure 22.

The triphenylmethyl radical has previously been observed in a similar manner by Bard and co-workers in their initial investigations of the photo-Kolb  reaction.<sup>[16a]</sup> Fig. 22 (top) shows the signal recorded following the accumulation of 20 scans, indicating a highly satisfying reproduction of this result. Simulation with hfs of  $a(6H) = 2.58$  G,  $a(6H) = 1.14$  G and  $a(3H) = 2.80$  G gave an excellent fit of R = X. These parameters match very well with those previously reported for this radical.<sup>[22]</sup> A number of acids were examined which gave rise to no observable spectra. Acetic acid **249a**, *tert*-butylacetic acid **249b**, ethynylacetic acid **145** and phenylacetic acid **143** all fell into this category. The use of titania coated quartz tube also proved unsuccessful as the spectrometer could not be kept in tune while they were being photolysed in the spectrometer cavity.

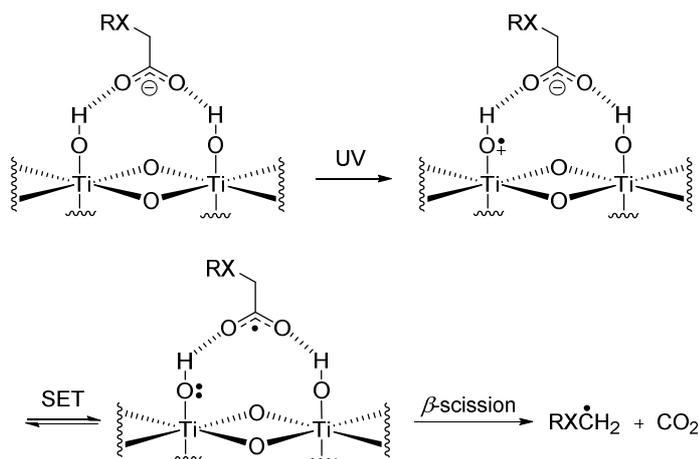
## 2.8 Postulated Mechanism

A plausible mechanism is outlined in Sch. 20. Hole capture at the TiO<sub>2</sub> surface by the carboxylate moiety will create the corresponding acyloxyl radical. Decarboxylation of this species furnishes the corresponding alkyl radicals. The isotropic character of the solution EPR spectra of these radicals established that in the main they were freely tumbling and not attached to the TiO<sub>2</sub> surface. Literature precedents imply that weakly nucleophilic RXCH<sub>2</sub>• radicals should add rapidly to the electron-deficient double bonds of maleimides (and similar acceptors).<sup>[2, 23]</sup> Most likely the resulting adduct radicals will be converted to enolates by electron transfer from the TiO<sub>2</sub> particles. Ready protonation<sup>[16b]</sup> will afford the radical addition adducts. For ArOCH<sub>2</sub>• radicals containing aromatic rings addition produces electrophilic β-carbonyl radicals for which a competition exists between reduction to the addition adducts or homolytic closure onto the aryl ring. As these radicals are weakly electrophilic in character this annulation should be favoured by increasing the electron density in the ring and, conversely, disfavoured by decreasing it.<sup>[24]</sup> In agreement with this, when an electron-releasing *tert*-butyl group was introduced to the ring then the proportion of cyclo-adduct increased whereas when an electron-withdrawing trifluoromethyl group was introduced it decreased. The resonance-stabilised cyclohexadienyl type radicals will re-aromatise to yield the functionalized chromenes. This aromatisation could result from hole capture from TiO<sub>2</sub> by the cyclohexadienyl radicals and subsequent proton loss as shown. Alternatively, electron transfer to more maleate might take place as suggested in related work by Hoffmann.<sup>[25]</sup> Protonation of the resulting radical anions, followed by further electron capture and protonation steps, would explain the significant yields of succinates obtained in our reactions. However, as greater amounts of these succinates than cyclised products were generally formed, it is thought that direct reduction of the maleimide acceptor by the conduction band of the TiO<sub>2</sub> also initiates this process. Control reactions confirmed the necessity of both UVA and TiO<sub>2</sub> in order for reaction to take place in all incidences bar one. When **222** was photolysed with **219c** in the absence of titania the cyclised product **224a** was observed in a 15% yield. It is believed that a catalyst-independent photoredox process is taking place between these two particular compounds. This process was explored in depth and the results are recorded in chapter 4 (pg. 170).



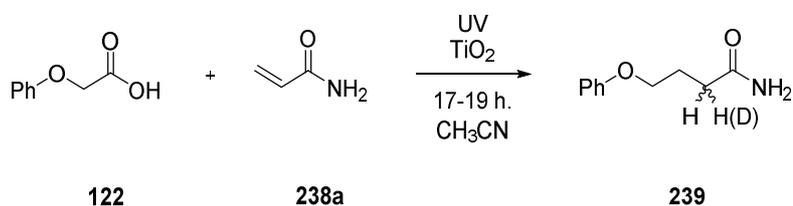
**Scheme 20.**

From the results described in this chapter it can be deduced that the stability of the titania-generated radicals is an important factor in this system. To understand this it is necessary to take a closer look at the SET photooxidation events taking place at the  $\text{TiO}_2$  surface in the initial two steps of the process (Sch. 21). Carboxylic acids thermally dissociate on the  $\text{TiO}_2$  surface to the corresponding surface bound carboxylate and proton.<sup>[26]</sup> Upon photolysis with UVA, and resultant photo-excitation, an electron-hole pair is generated which can migrate through the bulk of the semiconductor to the surface. The  $\text{TiO}_2$  surface is extensively hydroxylated<sup>[27]</sup> and it is thought that these species act as surface trapping sites for the valence band holes.<sup>[28]</sup> Electron transfer from the  $\pi$ -system of the carboxylate to a hole trap site furnishes the surface bound  $\text{RXCH}_2\text{-CO}_2^\bullet$  radical. It is proposed that a competition exists between  $\beta$ -scission of this surface bound species to yield the desired free  $\text{RXCH}_2^\bullet$  radical and back transfer of the electron, either from the trap site or from trapped conduction-band electrons, to the carboxylate. For acid precursors that will generate  $\text{RXCH}_2^\bullet$  radicals where the RX group exerts a stabilising influence, the decarboxylation step is more favorable, thus explaining the improved yields and conversions recorded. Conversely, for the simple aliphatic acids of Table 2 the radical stabilisation energy from the RX groups is minimal so back transfer of an electron to the  $\text{TiO}_2$  will take precedence over the loss of  $\text{CO}_2$ . This is illustrated in Sch. 21. It should be noted that while radical stability is believed to be a key aspect in this system, it is clear that there are other factors at play as well and that these take precedence in deciding the reaction outcome in a few instances. For example vinylacetic acid **260** would be expected to generate the allyl radical very readily in the presence of photo-excited  $\text{TiO}_2$ . Whilst the allyl radical was in fact observed during EPR experiments (*vide supra* pg 122-124, no products at all were observed in the preparative photolysis involving vinylacetic acid **260** and **219d**. In this case other, as yet unknown factors at the  $\text{TiO}_2$  surface, are evidently responsible for the lack of reactivity.



**Scheme 21.**

An intriguing feature of the process is that in forming the addition adducts a hydrogen atom is gained from some source within the dispersion. This is *not the proton lost from the aromatic ring* because reduced adducts were formed equally well from acids lacking aromatic rings. Several deuterium labeling experiments were carried out to try to identify the source. The reaction of phenoxyacetic acid **122** with acrylamide **238a** was again chosen as a test-bed process (Scheme 22; Table 3, entry 1). When this reaction was carried out in deuterated solvent ( $\text{CD}_3\text{CN}$ ) the isolated adduct **239** was screened for D-incorporation by  $^1\text{H}$  and  $^2\text{H}$  NMR and by GC-MS. However, no deuterium could be detected in the 4-phenoxybutanamide (**239**) (entry 2). Reaction with  $d_1$ -phenoxyacetic acid **122D** also yielded adduct with no detectable D-incorporation (entry 3). Thus, unless the acidic D-atom of **122D** rapidly and completely exchanges, the source of the additional H-atom is neither the acid nor the solvent. The most likely source therefore is the P25 semiconductor. Obviously it is counter-intuitive that a metal oxide would supply protons. However, it is well established that  $\text{H}_2\text{O}$  molecules and HO groups are attached to the surface of the  $\text{TiO}_2$  particles.<sup>[27a]</sup>



**Scheme 22.**

Entry	Conditions	Yield <b>239H</b> <sup>a</sup>	Yield <b>239D</b>
1	Control, 17 h.	47% <sup>c</sup>	-
2	CD <sub>3</sub> CN, 18 h.	55%	-
3	CO <sub>2</sub> D, 19 h.	49%	-
4	dry P25, <sup>b</sup> 18 h.	39%	-
5	TiO <sub>2</sub> -D, <sup>c</sup> 19 h.	58%	-
6	CO <sub>2</sub> D & TiO <sub>2</sub> -D, <sup>c</sup> 19 h.	nd	-

**Table 3.** <sup>a</sup> Calculated by NMR with respect to dibromomethane standard after 16 hours irradiation; <sup>b</sup> vacuum dried at 150 °C for 18 h.; <sup>c</sup> surface partly deuteriated.

Drying P25 in a vacuum at 150 °C removes a significant amount of the surface H<sub>2</sub>O, while leaving the chemically attached -OH groups.<sup>[28]</sup> When P25 dried in this way was used, the yield of **239** was scarcely reduced (entry 4). This suggested the -OH groups were likely the proton donors. Attempts were made by Shona Rhydderch and Prof. Russell Howe at the University of Aberdeen to deuteriate the H<sub>2</sub>O and -OH groups on the P25 surface by refluxing in degassed D<sub>2</sub>O in a glove box. However it was found that back exchange occurred immediately on exposure to air and rapidly with any moisture traces in solvents or on surfaces. Only partly deuteriated P25 (ca. 80% as judged by IR) could be obtained. Definitive experiments were difficult to achieve because of this. When the partly deuteriated titania was photolysed with the undeuteriated acid **122** the phenoxybutanamide product **239H** contained no deuterium (entry 5). It seemed possible, however, that P25 surface -OD groups could have rapidly exchanged with protons from the CO<sub>2</sub>H groups of **122H**. Experiments with partly deuteriated P25 and **122D** were also carried out but deuteriated **239D** was again not found. In view of the partially deuteriated nature of the titania and the ease with which it reverts to the protiated form, making handling difficult, the tentative conclusion remained that the surface of the TiO<sub>2</sub> catalyst is the source of the hydrogen atoms.

### 3.0 Conclusions

Optimised conditions have been derived whereby radicals generated at the surface of photo-excited titania particles are capable of forming new C-C bonds when paired with certain radical accepting unsaturated compounds. Aryloxy- radicals and maleates react to form the corresponding alkylated succinates in accompaniment with tricyclic functionalised hydrochromene derivatives. These are formed as a result of a cascade addition-cyclisation process. The process could be tuned to some degree to favour either product by altering the substitution patterns in the reagents and/or modifying the catalyst. Varying the radical accepting species proved unsuccessful on the whole with poor yields, low conversions and lack of selectivity being observed in many cases. Acrylamide however proved to be the exception to this trend, reacting cleanly and nearly quantitatively with phenoxyacetic acid to deliver the desired 4-phenoxybutanamide as the only product. This process would go on to be used as a test bed for several studies due to these attributes.

Simple aliphatic carboxylic acids alkylated *N*-phenylmaleimide albeit rather inefficiently. A relationship between yields/conversions and radical stabilisation energy was established in a simple study. Acids that yielded alkoxyalkyl, alkylthioalkyl and benzyl-type radicals alkylated electron-deficient alkenes in moderate to good yields. Boc-protected amino acids furnished aminoalkyl radicals that alkylated *N*-phenylmaleimide in useful yields. Vinyl and acetylenic acetic acids surprisingly failed to react under similar conditions in spite of the fact that they would be expected to form allyl and propargyl radicals very readily. A plausible mechanism has been put forward and is supported by deuterium labelling experiments, EPR spectroscopy and control reactions.

These photoredox reactions are cleanly, safely and cheaply carried out in the laboratory and the heterogeneous catalyst is simply filtered off during work-up. Thus with the correct choice of reaction partners they present a potentially useful synthetic protocol. At present however the synthetic utility is hampered by the lack of understanding of interactions between the reagents and the catalyst surface. Along with the stability of the acid derived radicals this is thought to be the most important factor in deciding the reaction outcome. The limited knowledge in this area precludes the ability to logically predict the outcome of a reaction.

## 4.0 Experimental

### 4.1 General Experimental Details – Instrumentation and Techniques

**NMR Spectroscopy:**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on Bruker AV III 500, Bruker AV II 400 and Bruker AV 300 instruments. Chemical shifts are reported in parts per million (ppm) from low to high frequency and referenced to the residual solvent resonance. Coupling constants ( $J$ ) are reported in hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s = singlet, d = doublet, t = triplet, dd = double doublet, q = quartet, m = multiplet, b = broad.

**Mass Spectrometry:** Low and high resolution mass spectrometry was carried out at the EPSRC National Mass Spectrometry Service Centre, Swansea on a LTQ Orbitrap XL Spectrometer equipped with an ultra-high-field Orbitrap mass analyser with resolving power up to 450,000 FWHM and isotopic fidelity up to 240,000 FWHM at  $m/z$  200.

**GC-MS:** GC-MS analysis was performed using a Thermo Electron Corporation Trace GC Ultra combined with a Thermo Electron Corporation DSQ II. A Restex Rxi<sup>®</sup>-1ms column (30m x 0.25 mm x 0.1  $\mu\text{m}$ ) was used for compound separation and the ionisation mode was set to electron impact (EI). Injection volumes were between 1 and 10  $\mu\text{L}$ , depending on signal strength. Parameters: injector temperature 220  $^{\circ}\text{C}$ ; split ratio 20:1; constant column flow 3.0  $\text{mL min}^{-1}$ . Temperature profile: initial temperature 50  $^{\circ}\text{C}$ , heating to 300  $^{\circ}\text{C}$  at 10 $^{\circ}\text{C min}^{-1}$ ; 4 min hold time; total time 29 min.

**Melting Point Analysis:** Melting points (M.p.) were determined using a Sanyo Gallenkamp apparatus and are reported uncorrected.

**Chromatography:** Column chromatography was carried out using Silica 60A (particle size 40-63  $\mu\text{m}$ , Silicycle, Canada) as the stationary phase, and TLC was performed on precoated silica gel plates (0.20 mm thick, Sil G UV<sub>254</sub>, Macherey-Nagel, Germany) and observed under UV light.

**EPR Spectroscopy:** EPR spectra were obtained at 9.5 GHz with 100 kHz modulation employing a Bruker EMX 10/12 spectrometer fitted with a rectangular ER4122 SP resonant cavity. Stock solutions of each acid (10 to 50 mg) in benzene or *tert*-butylbenzene (0.5 mL)

were prepared and sonicated if necessary. An aliquot (0.2 mL), to which any additional reactant had been added, was placed in a 5 mm o.d. quartz tube and de-aerated by bubbling nitrogen for 15 min. Photolysis in the resonant cavity was by unfiltered light from a 500 W super pressure mercury arc lamp. In all cases where spectra were obtained, hfs were assigned with the aid of computer simulations using the Bruker SimFonia and NIEHS Winsim2002 software packages. EPR signals were digitally filtered and double integrated using the Bruker WinEPR software and radical concentrations were calculated by reference to the double integral of the signal from a known concentration of the stable radical DPPH [ $1 \times 10^{-3}$  M in PhMe], run under identical conditions. The majority of EPR spectra were recorded with 2.0 mW power, 0.8 G<sub>pp</sub> modulation intensity and gain of *ca.*  $10^6$ .

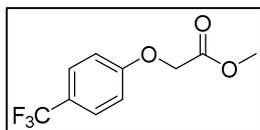
**X-Ray Crystallography:** Data was measured on Rigaku Mercury70 and Saturn70 diffractometers using Mo-K $\alpha$  radiation Cu-K $\alpha$  respectively. Data was collected and processed using CrystalClear (Rigaku). The structures are shown in the discussion.

**Anhydrous Solvents:** Tetrahydrofuran was distilled over sodium. Dichloromethane, methanol and acetonitrile were distilled over calcium hydride. Dimethylformamide was purchased anhydrous from Sigma Aldrich.

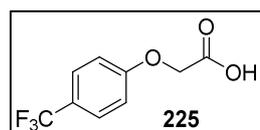
**Materials:** All reagents and solvents were purchased from Sigma Aldrich, Alfa Aesar or TCI Europe and used without further purification unless stated.

## 4.2 Preparation Of Non-Commercially Available Materials

### 4-Trifluoromethylphenoxyacetic acid **225**

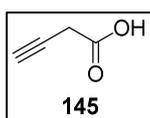


4-Trifluoromethylphenol (0.5 g, 3.1 mmol), methyl bromoacetate (0.708 g, 4.6 mmol) and anhydrous potassium carbonate (2.13 g, 15.38 mmol) were dissolved in anhydrous THF (90 mL) and refluxed under argon overnight. The reaction mixture was concentrated *in vacuo*, the resultant residue taken up in EtOAc (20 mL), washed with water (3 x 20 mL) and dried over anhydrous MgSO<sub>4</sub> before the solvent was removed *in vacuo*. Column chromatography on silica gel (eluent 50% CH<sub>2</sub>Cl<sub>2</sub> in petroleum 40/60) yielded methyl 4-trifluoromethylphenoxy acetate as a clear oil (0.71 g, 98%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 296 K): δ = 3.89 (s, 3H, OCH<sub>3</sub>), 4.66 (s, 2H, CH<sub>2</sub>), 6.95 (d, *J* = 7.5 Hz, 1H, ArH), 7.54 (d, *J* = 8.6 Hz, 1H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 296 K): δ = 52.3, 65.1, 114.6, 124.0 (q, <sup>2</sup>*J*<sub>C-F</sub> = 32.8 Hz, 1C), 124.3 (q, <sup>1</sup>*J*<sub>C-F</sub> = 271.2 Hz, 1C), 127.0 (q, <sup>3</sup>*J*<sub>C-F</sub> = 3.5 Hz, 2C), 160.2, 168.7; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>, 296 K): δ = -62.2; LR-EIMS: *m/z* = 234 [M]<sup>+</sup>; HR-ESIMS: *m/z* = 234.0498 (calcd. for C<sub>10</sub>H<sub>9</sub>F<sub>3</sub>O<sub>3</sub>, 234.0498). 4-Trifluoromethylphenoxy acetate (0.71 g, 3.2



mmol) was stirred overnight at room temperature with lithium hydroxide (0.38 g, 16 mmol) in methanol (30 mL) and water (10 mL). The reaction mixture was then reduced to ~10% its original volume *in vacuo* and 30 mL sat. (NH<sub>3</sub>)<sub>2</sub>SO<sub>4</sub> was added. The mixture was adjusted to pH 3 with concentrated H<sub>2</sub>SO<sub>4</sub> before being extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over anhydrous MgSO<sub>4</sub> and the solvent removed under reduced pressure to yield **225** as a white powder (0.60 g, 81%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 296 K): δ = 4.63 (s, 2H, CH<sub>2</sub>), 6.96 (d, *J* = 8.7 Hz, 2H, ArH), 7.53 (d, *J* = 8.7 Hz, 2H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 296 K): δ = 68.8, 118.5, 127.6 (q, <sup>2</sup>*J*<sub>C-F</sub> = 33.1 Hz, 1C), 128.2 (q, <sup>1</sup>*J*<sub>C-F</sub> = 271.1 Hz, 1C), 130.8 (q, <sup>3</sup>*J*<sub>C-F</sub> = 3.6 Hz, 2C), 164.1, 174.6; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>, 296 K): δ = -62.2; LR-ESIMS: *m/z* = 219 [M-H]<sup>+</sup>; HR-ESIMS: *m/z* = 219.0277 (calcd. for C<sub>9</sub>H<sub>6</sub>O<sub>3</sub>F<sub>3</sub>, 219.0275).

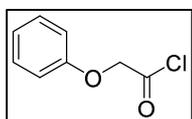
### Ethynylacetic acid **145**



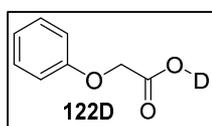
To a mixture of CrO<sub>3</sub> (3.0 g, 30 mmol) and H<sub>2</sub>SO<sub>4</sub> (20 mL) in water (75 mL) at 0 °C was added drop-wise a solution of but-3-yn-1-ol (1.14 mL, 15 mmol) in acetone (15 mL) over a period of two hours. The resultant mixture was allowed to warm to room temperature and stirred for a further six hours before being extracted with EtOAc (3 x 100 mL). The combined extracts were washed with H<sub>2</sub>O (2 x 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to give an off-white solid which was recrystallised from cyclohexane to yield the **145** (0.59 g, 47%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 295 K): δ = 2.27 (t, *J* = 2.8 Hz, 2H, C≡CH),

3.40 (d,  $J = 2.8$  Hz, 2H,  $\text{CH}_2\text{CO}_2\text{H}$ ), 10.26 (bs, 1H,  $\text{CO}_2\text{H}$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , 297 K):  $\delta = 25.6, 72.4, 74.8, 174.0$ . Data consistent with literature.<sup>[3]</sup>

#### **$d_1$ -Phenoxyacetic acid **122D****



Phenoxyacetic acid (304 mg, 2.0 mmol) and  $\text{SOCl}_2$  (0.74 mL, 10.0 mmol) were refluxed in  $\text{CHCl}_3$  for 72 hours. The volatiles were removed under reduced pressure to yield phenoxyacetyl chloride.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 296 K):  $\delta = 4.95$  (s, 2H,  $\text{CH}_2$ ), 6.93 (m, 2H, ArH), 7.09 (m, 1H, ArH), 7.35 (m, 2H, ArH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , 297 K):  $\delta = 64.9, 77.2, 114.8, 122.3, 129.9, 157.5, 174.2$ . This compound was immediately treated with  $\text{D}_2\text{O}$  (0.9 mL, 5.0 mmol) in anhydrous  $\text{CH}_3\text{CN}$  (10 mL) and allowed to stir overnight in an argon atmosphere. The solvent was removed under reduced pressure and



the resultant residue was recrystallised from anhydrous  $\text{Et}_2\text{O}$  to yield **122D** as a white crystalline solid (141 mg, 46%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 295 K):  $\delta = 4.70$  (s, 2H,  $\text{CH}_2$ ), 6.93 (m, 2H, ArH), 7.03 (m, 1H, ArH), 7.32 (m, 2H, ArH);  $^2\text{H}$  NMR (76 MHz,  $\text{CHCl}_3$ , 315 K):  $\delta = 10.13$  (bs, 1D,  $\text{CO}_2\text{D}$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , 297 K):  $\delta = 64.9, 114.8, 122.4, 129.9, 157.4, 172.8$ ; LR-ESIMS:  $m/z = 153[\text{M}]^+$ ; HR-ESIMS:  $m/z = 153.0543$  (calcd. for  $\text{C}_8\text{H}_8\text{O}_3\text{D}$ , 153.0513).

**Platinisation of titania powders:** Pt-TiO<sub>2</sub> was produced in accordance with the literature.<sup>[7]</sup> P25 was used and the various Pt loadings were prepared as described below:

A platinum-citrate colloid was prepared by dissolving 30mg H<sub>2</sub>[PtCl<sub>6</sub>]·6H<sub>2</sub>O in 30mL of a 1% sodium citrate solution and 120 mL of deionised water. This mixture was refluxed at 150°C for four hours and the previously orange solution turned black. Pt-TiO<sub>2</sub> powders of various loadings were then prepared from this colloid as follows:

- 0.1% (w/w) Pt-TiO<sub>2</sub> was prepared by adding 250mg of TiO<sub>2</sub> to 3.26 mL of the Pt-citrate colloid followed by 0.36 g of NaCl.
- 0.5% (w/w) Pt-TiO<sub>2</sub> was prepared by adding 250mg of TiO<sub>2</sub> to 16.3 mL of the Pt-citrate colloid followed by 1.8 g of NaCl.
- 1.0% (w/w) Pt-TiO<sub>2</sub> was prepared by adding 250mg of TiO<sub>2</sub> to 32.6 mL of the Pt-citrate colloid followed by 3.59 g of NaCl.
- 2.0% (w/w) Pt-TiO<sub>2</sub> was prepared by adding 250mg of TiO<sub>2</sub> to 65.2 mL of the Pt-citrate colloid followed by 7.17 g of NaCl

Following de-stabilisation of the colloid the platinised TiO<sub>2</sub> powder was isolated by filtration, washed with copious amounts of deionised water and dried overnight at 130 °C

## 4.3 General Procedures

### 4.3.1 General Procedure for Titania Mediated Photoredox Reactions

An oven dried Pyrex Schlenk tube was evacuated while still hot and then back-filled with argon. This was repeated three times before the tube was allowed to cool to room temperature. Reagents and  $\text{TiO}_2$  were added with a fast stream of argon flowing before freshly distilled  $\text{CH}_3\text{CN}$  was added to generate the desired dispersion density (typically  $1 \text{ mg mL}^{-1}$  unless otherwise stated). The resulting mixture was typically degassed by bubbling with argon for 20 minutes. The mixture was then irradiated while still under a positive atmosphere of argon with two hemispherical banks of six 29 cm 15 W Philips Cleo tubes ( $\lambda = 350\text{nm}$ ) for the desired reaction time at ambient temperature. Following irradiation the  $\text{TiO}_2$  powder was removed by filtration through a Celite pad and the solvent removed under reduced pressure. Unless otherwise stated isolated yields are reported.

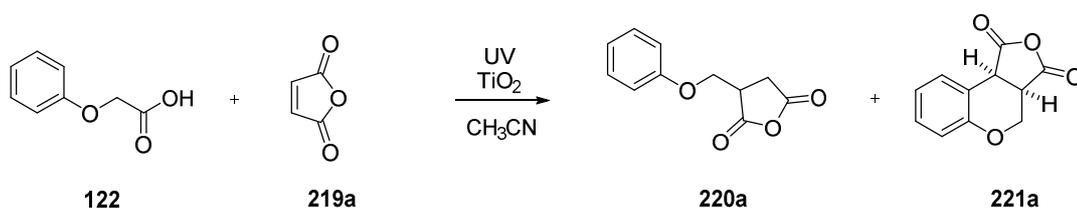
### 4.3.2 General Procedure for NMR Yields

In several instances yields were determined by  $^1\text{H}$  NMR spectroscopy. This was achieved by integration of peaks attributed to the product relative to a known amount (typically 1-5  $\mu\text{l}$ ) of a  $\text{CH}_2\text{Br}_2$  internal standard added directly to the tube prior to analysis. In most, but not all, instances spectra were recorded at 400-500 MHz from 32 scans at  $90^\circ$  pulse width using 30 second  $D_1$  relaxation time in order to obtain optimal signal to noise ratio and minimise the associated error.

## 4.4 Optimisation of Addition-Cyclisation Reaction Between 122 & 219a

### Photolysis Reaction of Phenoxyacetic Acid and Maleic Anhydride

Phenoxyacetic acid (304 mg, 1 mmol), maleic anhydride (392 mg, 4 mmol) and TiO<sub>2</sub> (25mg, 0.3 mmol) in CH<sub>3</sub>CN (5 mL) were reacted in accordance with the general procedure for 16 hours. NMR and GCMS analysis of the crude reaction mixture showed only starting materials present. Degassing by the freeze, pump and thaw technique resulted in the same outcome. When the reagents were azeotropically dried with toluene and the TiO<sub>2</sub> was dried overnight at 150°C under vacuum prior to reaction no evidence for product formation was observed either.



Optimisation reactions were carried out in accordance with the general procedure. Yields were determined by NMR. Full characterisation details for products **220a** and **221a** is available on pg 138.

**Optimisation of TiO<sub>2</sub> stoichiometry (Fig. 6):** phenoxyacetic acid (40 mg, 0.26 mmol), maleic anhydride (52 mg, 0.52 mmol) and TiO<sub>2</sub> (20-80 mg, 0.25-1.0 mmol) were dissolved in CH<sub>3</sub>CN and reacted in accordance with the general procedure for 16 hours. Concentrations of products were calculated as outlined above and are shown in Table 4.

Entry	TiO <sub>2</sub> (mol eq.)	% Yield 220a	% Yield 221a	% Unreacted 122
1	1	1	4	45
2	1.5	2	19	54
3	2	6	15	44
4	4	19	13	7

Table 4

**Optimisation of TiO<sub>2</sub> dispersion (Fig. 7):** phenoxyacetic acid (40 mg, 0.26 mmol), maleic anhydride (52 mg, 0.52 mmol) and TiO<sub>2</sub> (20-30 mg, 0.25-0.38 mmol) were dissolved in CH<sub>3</sub>CN (2-30 mL) and reacted in accordance with the general procedure for 16 hours. Concentrations of products were calculated as outlined above and are shown in Table 5.

Entry	Dispersion (mg mL <sup>-1</sup> )	% Yield 220a	% Yield 221a	% Unreacted 122
1	5	1	4	45
2	10	1	8	65
3	2.5	25	12	4
4	1	43	24	3

**Table 5.**

**Further optimisation of TiO<sub>2</sub> stoichiometry & dispersion (Fig. 8):** phenoxyacetic acid (10 mg, 0.07 mmol), maleic anhydride (52 mg, 0.14 mmol) and TiO<sub>2</sub> (7.5 mg, 0.1 mmol) were dissolved in CH<sub>3</sub>CN (16 mL) and reacted in accordance with the general procedure for 16 hours. Concentrations of products were calculated as outlined above and are shown in Table 6.

Entry	TiO <sub>2</sub> (mol eq.)	Dispersion (mg mL <sup>-1</sup> )	% Yield 220a	% Yield 221a	% Unreacted 122
1	0.75	0.5	25	12	14
2	0.5	0.3	27	10	23
3	0.25	0.16	26	12	30
4	0.1	0.6	9	14	66
5	traces	minute	0	2	55

**Table 6.**

**Investigation of Pt-TiO<sub>2</sub> (Fig. 9):** phenoxyacetic acid (20 mg, 0.13 mmol), maleic anhydride (26 mg, 0.26 mmol) and Pt-TiO<sub>2</sub> (0.2 mmol) were dissolved in CH<sub>3</sub>CN (16 mL) and reacted in accordance with the general procedure for 16 hours. Concentrations of products were calculated as outlined above and are shown in Table 7.

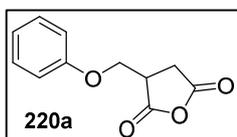
Entry	Pt-Loading (% wt/wt)	% Yield 220a	% Yield 221a	% Unreacted 122
1	0.1	45	5	4
2	0.5	35	14	7
3	1.0	38	16	1
4	2.0	50	16	0

**Table 7.**

## 4.5 Preparative Addition-Cyclisation Reactions

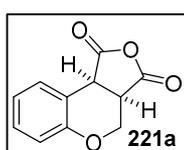
Reactions were carried out as described in the general procedure on page 135. Unless otherwise stated isolated yields are reported.

### (Phenoxymethyl)succinic anhydride **220a** & 3a,4-dihydro-1H-furo[3,4-c]chromene-1,3(9bH)-dione **221a**.



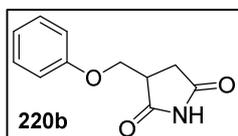
Phenoxyacetic acid (100 mg, 0.65 mmol), maleic anhydride (130 mg, 1.3 mmol) and TiO<sub>2</sub> (75 mg, 0.98 mmol) were reacted in accordance with the general procedure for 26 hours. The reaction mixture was purified

by column chromatography on silica gel (eluent: 5% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) to yield **220a** as a white crystalline solid (45.3 mg, 34%). Mp. 91-93°C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 297 K): δ = 3.15 (d, *J* = 7.9 Hz, 1H, C=OCH<sub>2</sub>), 3.46 – 3.52 (m, 1H, C=OCH), 4.17 (dd, *J* = 3.1, 9.2 Hz, 1H, OCH<sub>2</sub>), 4.44 (dd, *J* = 3.6, 9.3 Hz, 1H, OCH<sub>2</sub>'), 6.88 (d, *J* = 7.8 Hz, 2H, ArH), 7.01 (t, *J* = 7.4 Hz, 1H, ArH), 7.30 (t, *J* = 8.4 Hz, 1H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 298 K): δ = 31.4, 41.7, 65.6, 114.7, 122.1, 129.7, 157.7, 169.8, 171.9; LR-EIMS: *m/z* = 207 [MH]<sup>+</sup>; HR-ESIMS: *m/z* = 207.0646 (calcd. for C<sub>11</sub>H<sub>11</sub>O<sub>4</sub>,



207.0657). As above to yield **221a** as a yellow oil (34.5mg, 26%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 297 K): δ = 3.67-3.72 (m, 1H, CH<sub>2</sub>CH), 4.08 (dd, *J* = 4.1, 11.6 Hz, 1H, ArCH), 4.36 (d, *J* = 9.9 Hz, 1H, OCH<sub>2</sub>), 4.59 (dd, *J* = 3.5, 11.6 Hz, 1H, OCH<sub>2</sub>'), 6.95 (d, *J* = 8.3 Hz, 1H, ArH), 7.09 (t, *J* = 7.6 Hz, 1H, ArH), 7.27 (m, 1H, ArH), 7.53 (d, *J* = 7.7 Hz, 1H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 299 K): δ = 40.2, 42.6, 63.0, 114.5, 114.7, 118.3, 123.3, 129.7, 154.9, 169.9, 170.6; LR-EIMS: *m/z* = 204 [M]<sup>+</sup>; HR-ESIMS: *m/z* = 204.0415 (calcd. for C<sub>11</sub>H<sub>8</sub>O<sub>4</sub>, 204.0423). Succinic anhydride **228a** was also isolated as a colourless solid (43 mg, 33%).

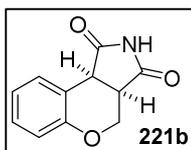
### 1-Methyl-3-(phenoxymethyl)pyrrolidine-2,5-dione **220b** & 3a,4-dihydrochromeno[3,4-c]pyrrole-1,3(2H,9bH)-dione **221b**



Phenoxyacetic acid (100 mg, 0.65 mmol), maleimide (127 mg, 1.3 mmol) and TiO<sub>2</sub> (75 mg, 0.98 mmol) were reacted in accordance with the general procedure for 17 hours. The reaction mixture was purified

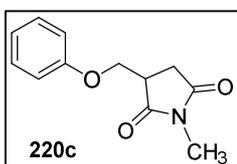
by column chromatography on silica gel (eluent: 20% EtOAc in petrol 40/60) to yield **220b** as a clear oil (41.7 mg, 31%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 296 K): δ = 2.88 (d, *J* = 7.6 Hz, 2H, C=OCH<sub>2</sub>), 3.18 – 3.24 (m, 1H, C=OCH), 4.18 (dd, *J* = 3.3, 9.2 Hz, 1H, OCH<sub>2</sub>), 4.37 (dd, *J* = 4.3, 9.2 Hz, 1H, OCH<sub>2</sub>'), 6.86 (d, *J* = 8.8 Hz, 2H, ArH), 6.96 (t, *J* = 8.3 Hz, 1H, ArH), 7.26 (t, *J* = 7.9 Hz, 2H, ArH), 9.55 (br-s, 1H, NH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 296 K): δ = 32.8, 42.0, 65.8, 114.6, 121.6, 129.6,

158.1, 177.2, 178.3; LR-ESIMS:  $m/z = 206 [MH]^+$ ; HR-ESIMS:  $m/z = 206.0809$  (calcd. for



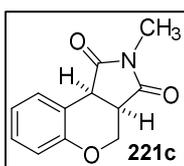
$C_{11}H_{12}NO_3$ , 206.0817). As above to yield **221b** as a colourless solid (63.1 mg, 48%). Mp: 158-160 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ , 296 K):  $\delta = 3.44$ -3.47 (m, 1H,  $CH_2CH$ ), 4.01 (dd,  $J = 4.2, 11.5$  Hz 1H,  $OCH_2$ ), 4.11 (d,  $J = 9.2$  Hz, 1H, ArCH), 4.59 (dd,  $J = 3.1, 11.4$  Hz 1H,  $OCH_2'$ ), 6.92 (d,  $J = 8.2$  Hz, 1H, ArH), 7.06 (t,  $J = 8.2$  Hz, 1H, ArH), 7.23 (t,  $J = 8.0$  Hz, 1H, ArH), 7.54 (d,  $J = 7.8$  Hz, 1H, ArH), 7.72 (br-s, 1H, NH);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ , 297 K):  $\delta = 40.9, 43.4, 63.7, 117.1, 117.9, 122.9, 129.2, 130.0, 155.3, 175.7, 176.3$ ; LR-ESIMS:  $m/z = 204 [MH]^+$ ; HR-ESIMS:  $m/z = 204.0649$  (calcd. for  $C_{11}H_{10}NO_3$ , 204.0661). Succinimide **228b** was also isolated as a white powder (52.1 mg, 41%).

***N*-Methyl-3-(phenoxyethyl)pyrrolidine-2,5-dione 220c & *N*-methyl-3a,4-dihydrochromeno[3,4-*c*]pyrrole-1,3(2*H*,9*bH*)-dione 221c**



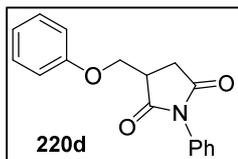
Phenoxyacetic acid (100 mg, 0.65 mmol), *N*-methylmaleimide (145 mg, 1.3 mmol) and  $TiO_2$  (75 mg, 0.98 mmol) were reacted in accordance with the general procedure for 20 hours. The reaction mixture was purified by column chromatography on silica gel (eluent: 20% EtOAc in petrol 40/60)

to yield **220c** as a colourless oil (32.6mg, 23%).  $^1H$  NMR (400 MHz,  $CDCl_3$ , 297 K):  $\delta = 2.88$ -2.90 (m, 2H,  $C=OCH_2$ ), 3.04 (s, 3H,  $CH_3$ ), 3.17-3.23 (m, 1H,  $C=OCH$ ), 4.17 (dd,  $J = 3.4, 9.2$  Hz, 1H,  $OCH_2$ ), 4.40 (dd,  $J = 4.4, 9.2$  Hz, 1H,  $OCH_2'$ ), 6.87 (d,  $J = 8.8$  Hz, 2H, ArH), 6.98 (t,  $J = 7.4$  Hz, 1H, ArH), 7.28 (t,  $J = 7.4$  Hz, 2H, ArH);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ , 297 K):  $\delta = 25.4, 32.1, 41.1, 66.4, 115.1, 122.0, 130.0, 158.5, 177.0, 178.0$ ; LR-MS:  $m/z = 219 [M]^+$ ; HR-MS:  $m/z = 219.0892$  (calcd.



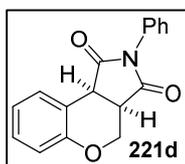
for  $C_{12}H_{13}NO_3$ , 219.0895). As above to yield **221c** as a white powder (77.8mg, 55%). Mp: 125-127 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ , 296 K):  $\delta = 3.00$  (s, 3H,  $CH_3$ ), 3.36 - 3.40 (m, 1H,  $CH_2CH$ ), 4.01 (dd,  $J = 4.2, 11.4$  Hz, 1H,  $OCH_2$ ), 4.07 (d,  $J = 9.2$  Hz, 1H, ArCH), 4.62 (dd,  $J = 2.9, 11.4$  Hz, 1H,  $OCH_2'$ ), 6.89 (d,  $J = 8.2$  Hz, 1H, ArH), 7.05 (t,  $J = 7.5$  Hz, 1H, ArH), 7.21 (t,  $J = 7.7$  Hz, 1H, ArH), 7.58 (d,  $J = 7.4$  Hz, 1H, ArH);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ , 297 K):  $\delta = 27.8, 40.1, 42.7, 64.3, 118.1, 118.3, 123.2, 129.4, 130.5, 155.7, 176.6, 177.2$ ; LR-MS:  $m/z = 217 [M]^+$ ; HR-MS:  $m/z = 217.0733$  (calcd. for  $C_{12}H_{11}NO_3$ , 217.0739). *N*-methylsuccinimide **228c** was also isolated as an off-white powder (57.2 mg, 39%).

**3-(Phenoxyethyl)-1-phenylpyrrolidine-2,5-dione 220d & N-phenyl-3a,4-dihydrochromeno[3,4-c]pyrrole-1,3(2H,9bH)-dione 221d**



Phenoxyacetic acid (100 mg, 0.65 mmol), *N*-phenyl maleimide (230 mg, 1.3 mmol) and TiO<sub>2</sub> (75 mg, 0.98 mmol) were reacted in accordance with the general procedure for 11 hours. The reaction mixture was purified by column chromatography on silica gel (eluent: 20% EtOAc in petrol 40/60)

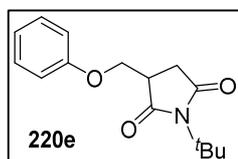
to yield **220d** as a yellow oil (71.5 mg, 39%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 297 K): δ = 3.01-3.07 (m, 2H, C=OCH<sub>2</sub>), 3.33-3.39 (m, 1H, C=OCH), 4.28 (dd, *J* = 3.2, 9.0 Hz, 1H, OCH<sub>2</sub>), 4.55 (dd, *J* = 4.1, 9.1 Hz, 1H, OCH<sub>2</sub>'), 6.91 (d, *J* = 8.8 Hz, 2H, ArH), 7.00 (t, *J* = 7.3 Hz, 1H, ArH), 7.28-7.33 (m, 2H, ArH), 7.41 (t, *J* = 7.4 Hz, 1H, ArH), 7.48 (d, *J* = 7.2, 2H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 297 K): δ = 32.4, 41.1, 66.9, 115.1, 122.1, 127.0, 129.2, 129.7, 130.0, 132.4, 158.5, 175.9, 177.1; LR-MS: *m/z* = 282 [MH]<sup>+</sup>; HR-MS: *m/z* = 282.1125 (calcd. for C<sub>17</sub>H<sub>16</sub>NO<sub>3</sub>, 282.1130). As above to



yield **221d** as a white powder (72.8mg, 40%). Mp: 143-145 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 297 K): δ = 3.54-3.58 (m, 1H, CH<sub>2</sub>CH), 4.11, (dd, *J* = 4.4, 11.4 Hz, 1H, OCH<sub>2</sub>), 4.23 (d, *J* = 9.3 Hz, 1H, CH<sub>2</sub>CH), 4.70 (dd, *J* = 3.3, 11.4 Hz, 1H, OCH<sub>2</sub>'), 6.94 (d, *J* = 8.2 Hz, 1H, ArH), 7.07 (t, *J* = 7.5 Hz, 1H, ArH), 7.22-7.27 (m,

2H, ArH), 7.37 (t, *J* = 7.4 Hz, 2H, ArH), 7.44 (t, *J* = 7.1 Hz, 1H, ArH), 7.63 (d, *J* = 7.4 Hz, 1H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 297 K): δ = 40.2, 42.6, 64.4, 77.1, 77.5, 77.9, 117.7, 118.3, 123.3, 126.7, 129.2, 129.5, 129.6, 130.7, 132.1, 155.7, 175.5, 176.1; LR-MS: *m/z* = 280 [MH]<sup>+</sup>; HR-MS: *m/z* = 280.0971 (calcd. for C<sub>17</sub>H<sub>14</sub>NO<sub>3</sub>, 280.0974). *N*-phenyl succinimide **228d** was also isolated (59.4 mg, 26%).

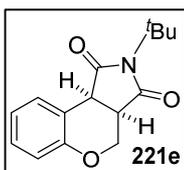
***N*-(tert-Butyl)-3-(phenoxyethyl)pyrrolidine-2,5-dione 220e & *N*-(tert-butyl)-3a,4-dihydrochromeno[3,4-c]pyrrole-1,3(2H,9bH)-dione 221e**



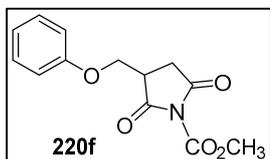
Phenoxyacetic acid (100 mg, 0.65 mmol), *N*-(*tert*-butyl)-maleimide (199 mg, 1.3 mmol) and TiO<sub>2</sub> (75 mg, 0.98 mmol) were reacted in accordance with the general procedure for 12 hours the reaction mixture was

purified by column chromatography on silica gel (eluent: 10% EtOAc in petrol 40/60) to yield **220e** as a clear oil (57mg, 34%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 297 K): δ = 1.58 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 2.70-2.81 (m, 2H, C=OCH<sub>2</sub>), 2.99-3.03 (m, 1H, C=OCH), 4.12 (dd, *J* = 3.2, 9.0 Hz, 1H, OCH<sub>2</sub>), 4.35 (dd, *J* = 4.8, 9.0 Hz 1H, OCH<sub>2</sub>'), 6.86 (d, *J* = 7.7 Hz, 2H, ArH), 6.97 (t, *J* = 7.3 Hz, 1H, ArH), 7.28 (t, *J* = 7.4 Hz, 1H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 297 K): δ = 28.4, 32.3, 40.4, 58.6, 66.7, 114.6, 121.5, 129.5, 158.2, 176.1, 178.3; LR-MS: *m/z* = 262 [MH]<sup>+</sup>; HR-MS: *m/z* = 262.1431 (calcd. for C<sub>15</sub>H<sub>20</sub>NO<sub>3</sub>, 262.1433). As above to yield **221e** as a white solid (55.7 mg, 33%). Mp = 80-81 °C

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 297 K):  $\delta$  = 1.54 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 3.20-3.25 (m, 1H, CH<sub>2</sub>CH), 3.89 (d,  $J$  = 9.4 Hz, 1H, ArCH), 3.99 (dd,  $J$  = 4.2, 11.3 Hz, 1H, OCH<sub>2</sub>), 3.49 (dd,  $J$  = 3.6, 11.3 Hz, 1H, OCH<sub>2</sub>'), 6.89 (d,  $J$  = 8.2 Hz, 1H, ArH), 7.03 (t,  $J$  = 7.6 Hz, 1H, ArH), 7.20 (t,  $J$  = 7.5 Hz, 1H, ArH), 7.54 (d,  $J$  = 7.7 Hz, 1H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 297 K):  $\delta$  = 28.3, 39.8, 41.9, 59.0, 64.2, 117.7, 117.9, 122.6, 128.8, 130.2, 155.1, 177.1; LR-MS:  $m/z$  = 260 [MH]<sup>+</sup>; HR-MS:  $m/z$  = 260.1277 (calcd. for C<sub>15</sub>H<sub>18</sub>NO<sub>3</sub>, 260.1287). Analysis of the crude reaction mixture revealed *N*-(tert-butyl)succinimide **228e** (11 % w.r.t. **220e** & **221e**).

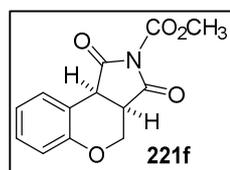


### Methyl 2,5-dioxo-3-(phenoxy)methylpyrrolidine-1-carboxylate **220f** & methyl 1,3-dioxo-1,3a,4,9b-tetrahydrochromeno[3,4-*c*]pyrrole-2(3*H*)-carboxylate **221f**



Phenoxyacetic acid (100 mg, 0.65 mmol), *N*-methoxycarbonylmaleimide (202 mg, 1.3 mmol) and TiO<sub>2</sub> (75 mg, 0.98 mmol) were in accordance with the general procedure for 12 hours.

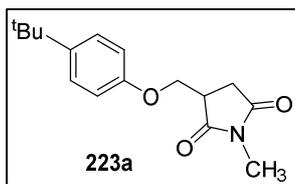
The reaction mixture was purified by column chromatography on silica gel (eluent: 20% EtOAc in petrol 40/60) to yield **220f** as a clear oil (59.7 mg, 35%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 297 K):  $\delta$  = 3.00 (m,  $J$  = 7.3 Hz, 2H, C=OCH<sub>2</sub>), 3.28 (m, 1H, C=OCH), 4.00 (s, 3H, CH<sub>3</sub>), 4.16 (dd,  $J$  = 3.3, 9.2 Hz, 1H, OCH<sub>2</sub>), 4.45 (d,  $J$  = 4.0, 9.2 Hz, 1H, OCH<sub>2</sub>'), 6.88 (d,  $J$  = 8.9 Hz, 2H, ArH), 6.99 (t,  $J$  = 7.4 Hz, 1H, ArH), 7.29 (t,  $J$  = 7.4 Hz, 2H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 298 K):  $\delta$  = 32.0, 41.0, 55.0, 65.8, 114.7, 121.9, 129.6, 148.6, 157.9, 171.7, 173.2; LR-MS:  $m/z$  = 281 [MNH<sub>4</sub>]<sup>+</sup>; HR-MS:  $m/z$  =



281.1131 (calcd. for C<sub>13</sub>H<sub>17</sub>N<sub>2</sub>O<sub>5</sub>, 281.1137). As above to yield **221f** as white solid (56.4 mg, 33%). Mp: 82-85 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 298 K):  $\delta$  = 3.45-3.49 (m, 1H, CH<sub>2</sub>CH), 3.95 (s, 3H, CH<sub>3</sub>), 4.03 (dd,  $J$  = 3.9, 11.4 Hz, 1H, OCH<sub>2</sub>), 4.16 (d,  $J$  = 9.6 Hz, 1H, ArCH), 4.63 (dd,  $J$  = 3.2, 11.4 Hz, 1H,

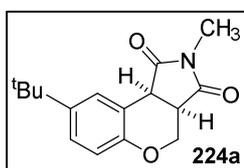
OCH<sub>2</sub>'), 6.91 (d,  $J$  = 8.2 Hz, 1H, OCH<sub>2</sub>), 7.05 (t,  $J$  = 7.5 Hz, 1H, OCH<sub>2</sub>), 7.23 (t,  $J$  = 8.1 Hz, 1H, OCH<sub>2</sub>), 7.56 (d,  $J$  = 7.8 Hz, 1H, OCH<sub>2</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 298 K):  $\delta$  = 40.0, 42.3, 55.1, 63.2, 115.9, 118.1, 123.0, 129.5, 130.0, 148.4, 155.1, 171.6, 172.1; LR-MS:  $m/z$  = 284 [MNa]<sup>+</sup>; HR-MS:  $m/z$  = 284.0531 (calcd. for C<sub>13</sub>H<sub>11</sub>NO<sub>5</sub>Na, 284.0535). Analysis of the crude reaction mixture revealed *N*-methoxycarbonylsuccinimide **228f** (19 % w.r.t. **220f** & **221f**).

### 3-((4-(*tert*-Butyl)phenoxy)methyl)-1-methylpyrrolidine-2,5-dione **223a** and 8-(*tert*-butyl)-2-methyl-3a,4-dihydrochromeno[3,4-*c*]pyrrole-1,3(2*H*,9*bH*)-dione **224a**



4-(*Tert*-butyl)phenoxyacetic acid (130.3 mg, 0.62 mmol), *N*-methylmaleimide (275.6 mg, 2.48 mmol) and TiO<sub>2</sub> (75mg, 0.98 mmol) were reacted in accordance with the general procedure. Following irradiation for 22 hours the reaction mixture was purified

by column chromatography on silica gel (eluent: 20% EtOAc in petrol 40/60) to yield **223a** as a clear oil (18.4 mg, 11%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 296 K): δ = 1.29 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 2.84-2.89 (m, 2H, C=OCH<sub>2</sub>), 3.03 (s, 3H, CH<sub>3</sub>), 3.21-3.16 (m, 1H, C=OCH), 4.16 (dd, *J* = 3.4, 9.2 Hz, 1H, OCH<sub>2</sub>), 4.39 (dd, *J* = 4.4, 9.2 Hz, 1H, OCH<sub>2</sub>'), 6.81 (d, *J* = 8.8 Hz, 2H, ArH), 7.29 (d, *J* = 8.8 Hz, 2H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 296 K): δ = 25.0, 29.7, 31.5, 34.1, 40.7, 66.1, 114.2, 126.4, 144.4, 155.8, 176.6, 177.60; LR-ESIMS: *m/z* = 276 [MH]<sup>+</sup>; HR-ESIMS: *m/z* = 276.1599 (calcd. for



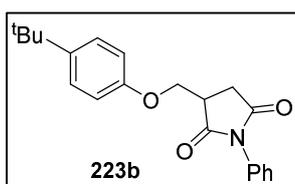
C<sub>16</sub>H<sub>22</sub>NO<sub>3</sub>, 276.1594). As above to yield **224a** as a white powder (77.2 mg, 46%). Mp 134-137 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 296 K): δ = 1.32 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 2.98 (s, 3H, CH<sub>3</sub>), 3.33-3.37 (m, 1H, CH<sub>2</sub>CH), 3.98 (dd, *J* = 4.1, 11.3 Hz, 1H, OCH<sub>2</sub>), 4.05 (d, *J* = 9.2 Hz, 1H, ArCH), 4.59 (dd, *J* = 3.0,

11.3 Hz, 1H, OCH<sub>2</sub>'), 6.82 (d, *J* = 8.6 Hz, 1H, ArH), 7.23 (dd, *J* = 2.4, 8.6 Hz, 1H, ArH), 7.58 (d, *J* = 2.4 Hz, 1H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 296 K): δ = 25.8, 31.9, 34.8, 40.3, 42.7, 64.3, 117.1, 117.6, 126.5, 127.3, 146.0, 153.3, 176.7, 177.3; LR-ESIMS: *m/z* = 274 [MH]<sup>+</sup>; HR-ESIMS: *m/z* = 274.1442 (calcd. for C<sub>16</sub>H<sub>20</sub>NO<sub>3</sub>, 274.1438).

#### Control reaction of 4-(*tert*-butyl)phenoxyacetic acid and *N*-methylmaleimide

4-(*tert*-Butyl)phenoxyacetic acid (20.8 mg, 0.1 mmol) and *N*-methylmaleimide (22.2 mg, 0.2 mmol) were photolysed in CH<sub>3</sub>CN (12 mL) for 18 hours. <sup>1</sup>H NMR analysis (w.r.t. CH<sub>2</sub>Br<sub>2</sub> standard) of the resultant mixture revealed: **224a** (0.015 mmol, 15%).

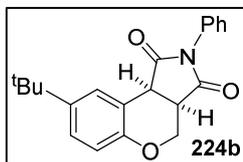
### 3-((4-(*tert*-butyl)phenoxy)methyl)-1-phenylpyrrolidine-2,5-dione **223b** and 8-(*tert*-butyl)-2-phenyl-3a,4-dihydrochromeno[3,4-*c*]pyrrole-1,3(2*H*,9*bH*)-dione **224b**



4-(*tert*-Butyl)phenoxyacetic acid (70 mg, 0.33 mmol), *N*-phenylmaleimide (117 mg, 0.66 mmol) and TiO<sub>2</sub> (40mg, 0.5 mmol) were reacted in accordance with the general procedure. Following irradiation for 19 hours the crude mixture was purified by column

chromatography on silica gel (eluent: 20% EtOAc in petrol 40/60) to yield **223b** as a clear oil (31.2 mg, 28%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 295 K): δ = 1.30 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 2.98-3.13 (m, 2H,

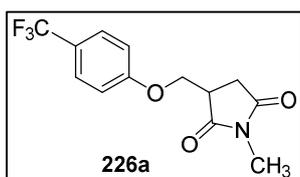
C=OCH<sub>2</sub>), 3.30-3.37 (m, 1H, C=OCH), 4.23 (dd, *J* = 3.2, 9.1 Hz, 1H, OCH<sub>2</sub>), 4.53 (dd, *J* = 3.9, 9.1 Hz, 1H, OCH<sub>2</sub>'), 6.85 (d, *J* = 8.9 Hz, 2H, ArH), 7.27-7.33 (m, 3H, ArH), 7.40-7.51 (m, 4H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 297 K): δ = 29.7, 31.5, 34.2, 40.8, 66.6, 114.2, 126.4, 126.6, 128.7, 129.2, 132.0, 144.6, 155.8, 175.6, 176.8; LR-ESIMS: *m/z* = 338 [MH]<sup>+</sup>; HR-ESIMS: *m/z* = 338.1755



(calcd. for C<sub>21</sub>H<sub>24</sub>NO<sub>3</sub>, 338.1751). As above to yield **224b** as a clear oil (50.3 mg, 46%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 296 K): δ = 1.32 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 3.51-3.56 (m, 1H, CH<sub>2</sub>CH), 4.10 (dd, *J* = 4.3, 11.4 Hz, 1H, OCH<sub>2</sub>), 4.23 (d, *J* = 7.3 Hz, 1H, ArCH), 4.66 (dd, *J* = 3.3, 11.5 Hz, 1H, OCH<sub>2</sub>'), 6.87

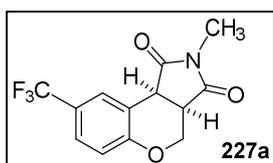
(d, *J* = 8.1 Hz, 1H, ArH), 7.24-7.29 (m, 2H, ArH), 7.33-7.48 (m, 4H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 297 K): δ = 31.5, 34.4, 40.0, 42.3, 64.1, 116.4, 117.3, 126.3, 127.0, 128.7, 129.1, 131.8, 134.2, 145.7, 153.0, 175.2, 175.7; LR-ESIMS: *m/z* = 336 [MH]<sup>+</sup>; HR-ESIMS: *m/z* = 336.1598 (calcd. for C<sub>22</sub>H<sub>21</sub>NO<sub>3</sub>, 336.1594).

### 1-Methyl-3-((4-(trifluoromethyl)phenoxy)methyl)pyrrolidine-2,5-dione **226a** and 2-methyl-8-(trifluoromethyl)-3a,4-dihydrochromeno[3,4-c]pyrrole-1,3(2H,9bH)-dione **227a**



4-(Trifluoromethyl)phenoxyacetic acid (143 mg, 0.65 mmol), *N*-methylmaleimide (145 mg, 1.3 mmol) and TiO<sub>2</sub> (75 mg, 0.98 mmol) were reacted in accordance with the general procedure. Following irradiation for 16 hours the reaction mixture was purified by two

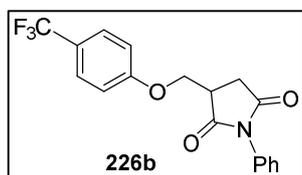
rounds of column chromatography on silica gel (eluent: 20% EtOAc in petrol 40/60 and subsequently 10% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) to yield **226a** as a clear oil (54.7 mg, 29%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 300 K): δ = 2.82-2.96 (m, 2H, C=OCH<sub>2</sub>), 3.05 (s, 3H, CH<sub>3</sub>), 3.20-3.26 (m, 1H, C=OCH), 4.22 (dd, *J* = 3.4, 9.2 Hz, 1H, OCH<sub>2</sub>), 4.46 (dd, *J* = 4.3, 9.2 Hz, 1H, OCH<sub>2</sub>'), 6.94 (d, *J* = 8.5 Hz, 2H, ArH), 7.54 (d, *J* = 8.5 Hz, 2H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 300 K): δ = 25.1, 31.6, 40.5, 66.1, 114.6, 123.9 (q, <sup>2</sup>*J*<sub>C-F</sub> = 32.9 Hz, 1C), 124.4 (q, <sup>3</sup>*J*<sub>C-F</sub> = 271.2 Hz, 2C), 127.0 (q, <sup>1</sup>*J*<sub>C-F</sub> = 3.7 Hz, 1C), 160.4, 176.2, 177.1; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>, 300 K): δ = -62.1; LR-EIMS: *m/z* = 288 [MH]<sup>+</sup>; HR-ESIMS: *m/z* = 288.0838 (calcd. for C<sub>13</sub>H<sub>13</sub>NO<sub>3</sub>F<sub>3</sub>, 288.0842).



As above to yield **227a** as a clear oil (60.1 mg, 32%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 298 K): δ = 3.01 (s, 3H, CH<sub>3</sub>), 3.40-3.44 (m, 1H, CH<sub>2</sub>CH), 4.04-4.10 (m-overlapped, 2H, ArCH, OCH<sub>2</sub>), 4.64 (dd, *J* = 3.2, 11.5 Hz, 1H, OCH<sub>2</sub>'), 6.98 (d, *J* = 8.6 Hz, 1H, ArH), 7.46 (d, *J* = 8.5 Hz, 1H, ArH), 7.87 (s, 1H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 298 K): δ = 25.5, 39.4, 41.8, 64.0, 117.9, 118.4, 123.9 (q, <sup>1</sup>*J*<sub>C-F</sub> = 271.7 Hz, 1C), 125.1 (q, <sup>2</sup>*J*<sub>C-F</sub> = 33.1 Hz, 1C), 127.2 (q, <sup>3</sup>*J*<sub>C-F</sub> = 3.5 Hz, 1C), 127.6 (q, <sup>3</sup>*J*<sub>C-F</sub> = 3.8 Hz, 1C), 157.7, 175.3,

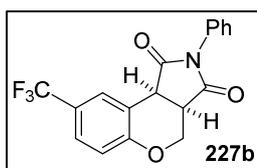
176.1;  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ , 298 K):  $\delta = -62.3$ ; LR-ESIMS:  $m/z = 286$   $[\text{MH}]^+$ ; HR-ESIMS:  $m/z = 286.0687$  (calcd. for  $\text{C}_{13}\text{H}_{11}\text{NO}_3\text{F}_3$ , 286.0686).

**1-Phenyl-3-((4-(trifluoromethyl)phenoxy)methyl)pyrrolidine-2,5-dione 226b and 8-(trifluoromethyl)-2-phenyl-3a,4-dihydrochromeno[3,4-c]pyrrole-1,3(2H,9bH)-dione 227b**



4-(Trifluoromethyl)phenoxyacetic acid (143 mg, 0.65 mmol), *N*-phenylmaleimide (230 mg, 1.3 mmol) and  $\text{TiO}_2$  (75 mg, 0.98 mmol) were reacted in accordance with the general procedure. Following irradiation for 16 hours the reaction mixture was purified by

column chromatography on silica gel (eluent: 25% EtOAc in Petrol 40/60) to yield **226b** as a colourless solid (52.9 mg, 40%). Mp: 121-124 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 297 K):  $\delta = 2.98$ -3.13 (m, 2H,  $\text{C}=\text{OCH}_2$ ), 3.35-3.40 (m, 1H,  $\text{C}=\text{OCH}$ ), 4.28 (dd,  $J = 3.1, 9.1$  Hz, 1H,  $\text{OCH}_2$ ), 4.57 (dd,  $J = 4.0, 9.1$  Hz, 1H,  $\text{OCH}_2'$ ), 6.97 (d,  $J = 8.5$  Hz, 2H, ArH), 7.29 (d,  $J = 7.2$  Hz, 2H, ArH), 7.41 (t,  $J = 7.3$  Hz, 1H, ArH), 7.49 (t,  $J = 7.2$  Hz, 2H, ArH), 7.56 (d,  $J = 8.6$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , 297 K):  $\delta = 31.9, 40.6, 66.6, 114.7, 124.0$  (q,  $^2J_{\text{C-F}} = 32.8$  Hz, 1C), 124.3 (q,  $^1J_{\text{C-F}} = 271.1$  Hz,



1C), 126.5, 127.1 (q,  $^3J_{\text{C-F}} = 3.7$  Hz, 2C), 128.8, 129.3, 131.9, 160.4, 175.2, 176.3;  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ , 297 K):  $\delta = -62.1$ ; LR-ESIMS:  $m/z = 367$   $[\text{M}+\text{NH}_4]^+$ ; HR-ESIMS:  $m/z = 367.1269$  (calcd. for  $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3\text{F}_3$ , 367.1275). As above to yield **227b** as a yellow oil (90 mg,

23%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 297 K):  $\delta = 3.57$ -3.61 (m, 1H,  $\text{CH}_2\text{CH}$ ), 4.15 (dd,  $J = 4.2, 11.4$  Hz, 1H, ArCH), 4.25 (d,  $J = 9.3$  Hz, 11.5, 1H, ArCH), 4.71 (dd,  $J = 3.4, 11.4$  Hz, 1H,  $\text{OCH}_2'$ ), 7.04 (d,  $J = 8.5$ , Hz, 1H, ArH), 7.24-7.27 (m, 2H, ArH), 7.36-7.51 (m, 4H, ArH), 7.93 (s, 1H, ArH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , 297 K):  $\delta = 39.5, 41.7, 64.1, 117.7, 118.5, 123.9$  (q,  $^1J_{\text{C-F}} = 271.8$  Hz, 1C), 125.2 (q,  $^2J_{\text{C-F}} = 33.0$  Hz, 1C), 126.2, 126.4 (q,  $^3J_{\text{C-F}} = 3.5$  Hz, 1C), 127.7 (q,  $^3J_{\text{C-F}} = 3.7$  Hz, 1C), 128.9, 129.2, 131.5, 157.8, 174.3, 175.0;  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ , 297 K):  $\delta = -62.3$ ; LR-ESIMS:  $m/z = 365$   $[\text{M}+\text{NH}_4]^+$ ; HR-ESIMS:  $m/z = 365.1114$  (calcd. for  $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3\text{F}_3$ , 365.1108).

**(Phenoxy)methylsuccinic anhydride 220a & 3a,4-dihydro-1H-furo[3,4-c]chromene-1,3(9bH)-dione 221a**

Phenoxyacetic acid (15.2 mg, 0.1 mmol), maleic anhydride (19.6 mg, 0.2 mmol) and  $\text{TiO}_2$  (P-25, 12 mg, 0.15 mmol) in MeCN (2.4 mL – 5 mg mL<sup>-1</sup> dispersion) were reacted in accordance with the general procedure for 45 h.  $^1\text{H}$  NMR analysis (w.r.t.  $\text{CH}_2\text{Br}_2$  standard) of the resultant mixture revealed: **220a** (0.02 mmol, 16%) and **221a** (0.05 mmol, 47%).

***N*-Methyl-3-(phenoxyethyl)pyrrolidine-2,5-dione 220c & *N*-methyl-3a,4-dihydrochromeno[3,4-*c*]pyrrole-1,3(2*H*,9*bH*)-dione 221c**

Phenoxyacetic acid (15.2 mg, 0.1 mmol), *N*-methylmaleimide (22.2 mg, 0.2 mmol) and TiO<sub>2</sub> (P-25, 12 mg, 0.15 mmol) in MeCN (2.4 mL – 5 mg mL<sup>-1</sup> dispersion) were reacted in accordance with the general procedure for 45 h. <sup>1</sup>H NMR analysis (w.r.t. CH<sub>2</sub>Br<sub>2</sub> standard) of the resultant mixture revealed: **220c** (0.01 mmol, 7%) and **221c** (0.07 mmol, 68%).

**8-(*tert*-Butyl)-2-methyl-3a,4-dihydrochromeno[3,4-*c*]pyrrole-1,3(2*H*,9*bH*)-dione 224a**

(4-(*tert*-Butyl)phenoxy)acetic acid (20.8 mg, 0.1 mmol), *N*-methylmaleimide (22.2 mg, 0.2 mmol) and TiO<sub>2</sub> (12 mg, 0.15 mmol) in MeCN (2.4 mL – 5 mg mL<sup>-1</sup> dispersion) were reacted in accordance with the general procedure for 42 h. <sup>1</sup>H NMR analysis (w.r.t. CH<sub>2</sub>Br<sub>2</sub> standard) of the resultant mixture revealed: **224a** (0.06 mmol, 56%).

**(Phenoxyethyl)succinic anhydride 220a & 3a,4-dihydro-1*H*-furo[3,4-*c*]chromene-1,3(9*bH*)-dione 221a**

Phenoxyacetic acid (20 mg, 0.13 mmol), maleic anhydride (26 mg, 0.26 mmol) and 0.1% Pt-TiO<sub>2</sub> (P-25, 16 mg, 0.2 mmol) were reacted in accordance with the general procedure for 17 h. <sup>1</sup>H NMR analysis (w.r.t. CH<sub>2</sub>Br<sub>2</sub> standard) of the resultant mixture revealed: **220a** (0.06 mmol, 48%) and **221a** (0.01 mmol, 8%).

**3-(Phenoxyethyl)-1-phenylpyrrolidine-2,5-dione 220d & *N*-phenyl-3a,4-dihydrochromeno[3,4-*c*]pyrrole-1,3(2*H*,9*bH*)-dione 221d**

Phenoxyacetic acid (20 mg, 0.13 mmol), *N*-phenylmaleimide (22.2 mg, 0.2 mmol) and 0.1% Pt-TiO<sub>2</sub> (P-25, 16 mg, 0.2 mmol) were reacted in accordance with the general procedure for 16 h. <sup>1</sup>H NMR analysis (w.r.t. a CH<sub>2</sub>Br<sub>2</sub> standard) of the resultant mixture revealed: **220d** (0.01 mmol, 8%) and **221d** (0.07 mmol, 69%).

**Methyl 2,5-dioxo-3-(phenoxyethyl)pyrrolidine-1-carboxylate 220f & methyl 1,3-dioxo-1,3a,4,9b-tetrahydrochromeno[3,4-*c*]pyrrole-2(3*H*)-carboxylate 221f**

Phenoxyacetic acid (20 mg, 0.13 mmol), *N*-carboxymethylmaleimide (31 mg, 0.2 mmol) and 0.1% Pt-TiO<sub>2</sub> (P-25, 16 mg, 0.2 mmol) were reacted in accordance with the general procedure A for 16 h. <sup>1</sup>H NMR analysis (w.r.t. a CH<sub>2</sub>Br<sub>2</sub> standard) of the resultant mixture revealed: **220f** (0.02 mmol, 24%) and **221f** (0.05 mmol, 50%).

***N*-Methyl-3-(phenoxy)methylpyrrolidine-2,5-dione 220c & *N*-methyl-3a,4-dihydrochromeno[3,4-*c*]pyrrole-1,3(2*H*,9*bH*)-dione 221c**

A solution of phenoxyacetic acid (15.2 mg, 0.1 mmol) and *N*-methylmaleimide (22.2 mg, 0.2 mmol) in MeCN (12 mL) were irradiated in a TiO<sub>2</sub> sol-gel coated tube in accordance with the general procedure for 22 h. <sup>1</sup>H NMR analysis (w.r.t. CH<sub>2</sub>Br<sub>2</sub> standard) of the resultant mixture revealed: **220c** (0.06 mmol, 60%) and **221c** (0.02 mmol, 15%).

**3-(Phenoxy)methyl-1-phenylpyrrolidine-2,5-dione 220d & *N*-phenyl-3a,4-dihydrochromeno[3,4-*c*]pyrrole-1,3(2*H*,9*bH*)-dione 221d**

A solution of phenoxyacetic acid (15.2 mg, 0.1 mmol) and *N*-phenylmaleimide (34.7 mg, 0.2 mmol) in MeCN (12 mL) were irradiated in a TiO<sub>2</sub> sol-gel coated tube in accordance with the general procedure for 22 h. <sup>1</sup>H NMR analysis (w.r.t. CH<sub>2</sub>Br<sub>2</sub> standard) of the resultant mixture revealed: **220d** (0.07 mmol, 72%) and **221d** (0.01 mmol, 13%).

**3-((4-(*tert*-butyl)phenoxy)methyl)-1-methylpyrrolidine-2,5-dione 223b and 8-(*tert*-butyl)-2-methyl-3a,4-dihydrochromeno[3,4-*c*]pyrrole-1,3(2*H*,9*bH*)-dione 224b**

A solution of 4-(*tert*-butyl)phenoxyacetic acid (20.8 mg, 0.1 mmol),) and *N*-phenylmaleimide (34.7 mg, 0.2 mmol) in MeCN (12 mL) were irradiated in a TiO<sub>2</sub> sol-gel coated tube in accordance with the general procedure for 19 h. <sup>1</sup>H NMR analysis (w.r.t. CH<sub>2</sub>Br<sub>2</sub> standard) of the resultant mixture revealed: **223b** (0.03 mmol, 28%) and **224b** (0.02 mmol, 23%).

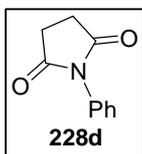
**1-Phenyl-3-((4-(trifluoromethyl)phenoxy)methyl)pyrrolidine-2,5-dione 226b and 8-(trifluoromethyl)-2-phenyl-3a,4-dihydrochromeno[3,4-*c*]pyrrole-1,3(2*H*,9*bH*)-dione 227b**

A solution of 4-(trifluoromethyl)phenoxyacetic acid (22.0 mg, 0.1 mmol) and *N*-phenylmaleimide (34.7 mg, 0.2 mmol) in MeCN (12 mL) were irradiated in a TiO<sub>2</sub> sol-gel coated tube in accordance with the general procedure for 17 h. <sup>1</sup>H NMR analysis (w.r.t. CH<sub>2</sub>Br<sub>2</sub> standard) of the resultant mixture revealed: **226b** (0.07 mmol, 67%) and **227b** (0.03 mmol, 26%).

## 4.6 Conduction Band Reductions

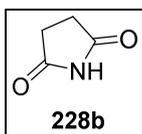
Reductions were carried out in the manner described on pg 135 with the addition of 10% (v/v) CH<sub>3</sub>OH to the reaction mixtures.

### *N*-phenylsuccinimide **228d**



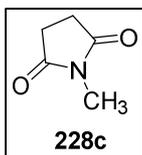
*N*-phenylmaleimide (17.3 mg, 0.1 mmol) and TiO<sub>2</sub> (12 mg, 0.15 mmol) in CH<sub>3</sub>OH (1.2 mL) and CH<sub>3</sub>CN (10.8 mL) were reacted in accordance with the general procedure. Following irradiation for 17 hours **228d** was obtained as an off-white powder (14.7 mg, 86%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 296 K):  $\delta$  = 2.90 (s, 4H, CH<sub>2</sub>), 7.24 (m, 2H, ArH), 7.37 (m, 1H, ArH), 7.44 (m, 2H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 297 K):  $\delta$  = 28.4, 126.5, 128.7, 129.2, 132.0, 176.3. Consistent with literature.<sup>[29]</sup>

### Succinimide **228b**



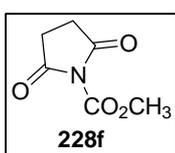
Maleimide (24.5 mg, 0.25 mmol) and TiO<sub>2</sub> (30 mg, 0.38 mmol) in CH<sub>3</sub>OH (3 mL) and CH<sub>3</sub>CN (27 mL) were reacted in accordance with the general procedure. Following irradiation for 17 hours **228b** was obtained as a white powder (22.8 mg, 91%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 296 K):  $\delta$  = 2.75 (s, 4H, CH<sub>2</sub>), 8.84 (br-s, 1H, NH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 299 K):  $\delta$  = 29.6, 177.9. Consistent with literature.<sup>[30]</sup>

### *N*-methylsuccinimide **228c**



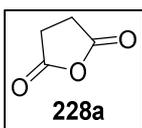
*N*-methylmaleimide (27.8 mg, 0.25 mmol) and TiO<sub>2</sub> (30 mg, 0.38 mmol) in CH<sub>3</sub>OH (3 mL) and CH<sub>3</sub>CN (27 mL) were reacted in accordance with the general procedure. Following irradiation for 17 hours **228c** was obtained as an off white powder (25.5 mg, 90%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 298 K):  $\delta$  = 2.69 (s, 4H, CH<sub>2</sub>), 2.97 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 299 K):  $\delta$  = 24.8, 28.2, 177.3. Consistent with literature.<sup>[31]</sup>

### *N*-carboxymethylsuccinimide **228f**



*N*-carboxymethylmaleimide (38.8 mg, 0.25 mmol) and TiO<sub>2</sub> (30 mg, 0.38 mmol) in CH<sub>3</sub>OH (3 mL) and CH<sub>3</sub>CN (27 mL) were reacted in accordance with the general procedure. Following irradiation for 15 hours **228f** was obtained as colourless oil (32.1 mg, 82%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 296 K):  $\delta$  = 2.81 (s, 4H, CH<sub>2</sub>), 3.96 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 299 K):  $\delta$  = 28.6, 172.6, 176.4.

### Succinic anhydride **228a** & 4-oxobutanoic acid

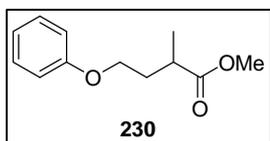


Maleic anhydride (24.5 mg, 0.25 mmol) and  $\text{TiO}_2$  (30 mg, 0.38 mmol) in  $\text{CH}_3\text{OH}$  (3 mL) and  $\text{CH}_3\text{CN}$  (27 mL) were reacted in accordance with the general procedure. Following irradiation for 15 hours **228a** was observed by  $^1\text{H}$  NMR (60% w.r.t. a  $\text{CH}_2\text{Br}_2$  standard).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 296 K):  $\delta$  = 3.00 (s, 4H,  $\text{CH}_2$ ). 4-Oxobutanoic acid was observed in the same manner (17%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 296 K):  $\delta$  = 2.59-2.70 (m, 4H, 2 x  $\text{CH}_2$ ), 3.69 (s, 3H,  $\text{CH}_3$ ), 9.86 (br-s, 1H,  $\text{CO}_2\text{H}$ ). Spectral data for both compounds consistent with literature.<sup>[32]</sup>

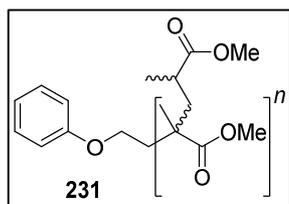
## 4.7 Variation of the Radical Trapping Component

Irradiations were carried out in accordance with the general procedure on pg 135. Unless otherwise stated, isolated yields are reported.

### Methyl 2-methyl-4-phenoxybutanoate **230**

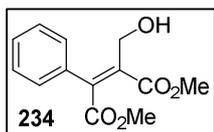


Phenoxyacetic acid (100 mg, 0.66 mmol), methyl methacrylate (132 mg, 1.32 mmol) and  $\text{TiO}_2$  (75 mg, 0.93 mmol) were reacted in accordance with the general procedure for 63 hours. The crude mixture was then purified by column chromatography on silica gel (eluent:  $\text{CH}_2\text{Cl}_2$ ) to yield **230** as a colourless oil (41.1 mg, 21%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 296 K):  $\delta$  = 1.24 (d,  $J$  = 7.1 Hz,  $\text{CHCH}_3$ ), 1.85-1.93 (m, 1H,  $\text{CHCH}_3$ ), 2.15-2.24 (m, 1H,  $\text{OCH}_2\text{CH}_2$ ), 2.72-2.80 (m, 1H,  $\text{OCH}_2\text{CH}_2'$ ), 3.69 (s, 3H,  $\text{OCH}_3$ ), 4.00 (td,  $J$  = 2.4, 6.2 Hz, 2H,  $\text{OCH}_2$ ), 6.87-6.89 (m, 2H,  $\text{ArH}$ ), 6.92-6.96 (m, 1H,  $\text{ArH}$ ), 7.26-7.30 (m, 2H,  $\text{ArH}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , 299 K):  $\delta$  = 17.3, 33.0, 36.3, 51.7, 65.4, 114.5, 120.7, 129.5, 158.8, 176.8; LR-ESIMS:  $m/z$  = 209  $[\text{MH}]^+$ ; HR-ESIMS:  $m/z$  = 209.1170



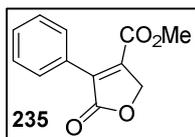
(calcd. for  $\text{C}_{12}\text{H}_{17}\text{O}_3$ , 209.1172). GC-MS analysis of the reaction mixture prior to chromatography suggested that of a number of oligomers **231** had been formed. **231**<sub>1</sub> ( $n=1$ ):  $t_R$  15.85 min;  $m/z$  (%) 307 (2), 245 (6), 216 (11), 215 (100), 183 (4), 155 (31), 123 (15), 95 (22), 77 (9). **231**<sub>2</sub> ( $n=2$ ):  $t_R$  20.26 min;  $m/z$  (%) 394 (1), 315 (100), 281 (13), 283 (7), 191 (15), 163 (32), 107 (25), 77 (10). **231**<sub>3</sub> ( $n=3$ ):  $t_R$  23.84 min;  $m/z$  (%) 480 (3), 415 (40), 281 (23), 207 (100), 190 (12), 147 (14), 96 (17), 73 (15).

### Dimethyl 2-(hydroxymethyl)-3-phenylmaleate **234**, methyl 5-oxo-4-phenyl-2,5-dihydrofuran-3-carboxylate **235**, dimethyl 2-(2-hydroxyphenyl)-3-methylenesuccinate **236** and dimethyl 2H-chromene-3,4-dicarboxylate **237**.



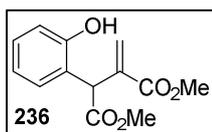
Phenoxyacetic acid (100 mg, 0.66 mmol), dimethylacetylenedicarboxylate (189 mg, 1.33 mmol) and  $\text{TiO}_2$  (80 mg, 1.0 mmol) were reacted in accordance with the general procedure for 65 hours. The crude mixture was then purified by column chromatography on silica gel (eluent: gradient of 10-40% EtOAc in petrol 40/60) to yield **234** as a yellow oil (64 mg, 39%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 298 K):  $\delta$  = 2.29 (br-s, 1H, OH), 3.79 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 3.85 (s, 3H,  $\text{CO}_2\text{CH}_3'$ ), 4.26 (s, 2H,  $\text{CH}_2\text{OH}$ ), 7.39 (m, 5H,  $\text{ArH}$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , 299 K):  $\delta$  = 52.66, 52.68, 59.5, 128.5, 128.7, 129.4, 132.4, 133.3, 144.3, 167.1, 168.4; LR-ESIMS:  $m/z$  = 251  $[\text{MH}]^+$ ; HR-ESIMS:  $m/z$  = 251.0913 (calcd. for

$C_{13}H_{15}O_5$ , 251.0914). As above to yield **235** (partially co-eluted with **236**) as a colourless oil (33.4 mg, 23%).  $^1H$  NMR (400 MHz,  $CDCl_3$ , 296 K):  $\delta$  = 3.82 (s, 3H,  $CO_2CH_3$ ), 5.07 (s, 2H,  $OCH_2$ ),



7.43-7.46 (m, 3H, ArH), 7.58 (m, 2H, ArH);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ , 298 K):  $\delta$  = 53.0, 69.9, 128.5, 129.0, 130.2, 130.6, 137.4, 144.7, 162.3, 172.3; LR-EIMS:  $m/z$  = 219  $[MH]^+$ ; HR-ESIMS:  $m/z$  = 219.0652 (calcd. for  $C_{12}H_{11}O_2$ , 219.0652).

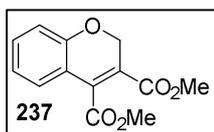
As above to yield **236** in 12% (co-eluted with **235**: yield determined from  $^1H$  NMR using a  $CH_2Br_2$  internal standard and characterised as a mixture).  $^1H$  NMR (400 MHz,  $CDCl_3$ , 296 K):  $\delta$  =



3.77 (s, 3H,  $CO_2CH_3$ ), 3.79 (s, 3H,  $CO_2CH_3'$ ), 4.90 (t,  $J$  = 1.5 Hz, 1H, ArCH), 5.58 (d,  $J$  = 1.6 Hz, 1H,  $C=CH_2$ ), 6.44 (d,  $J$  = 1.2 Hz, 1H,  $C=CH_2'$ ), 6.89-6.93 (m, 2H, ArH), 7.13 (d,  $J$  = 8.1 Hz, 1H, ArH);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ , 298 K):

$\delta$  = 50.6, 52.8, 53.4, 118.2, 121.4, 128.5, 129.0, 130.2, 131.4, 136.2, 155.2, 167.4, 174.6; LR-ESIMS:  $m/z$  = 251  $[MH]^+$ ; HR-ESIMS:  $m/z$  = 251.0917 (calcd. for  $C_{13}H_{15}O_5$ , 251.0914). As above

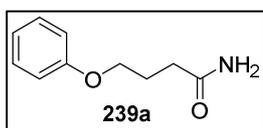
to yield **237** as a colourless oil (33.4 mg, 23%).  $^1H$  NMR (400 MHz,  $CDCl_3$ , 296 K):  $\delta$  = 3.81 (s,



3H,  $CO_2CH_3$ ), 3.95 (s, 3H,  $CO_2CH_3'$ ), 4.97 (s, 2H,  $OCH_2$ ), 6.89 (d,  $J$  = 8.1 Hz, 1H, ArH), 6.95 (t,  $J$  = 7.5 Hz, 1H, ArH), 7.09 (d,  $J$  = 7.7 Hz, 1H, ArH), 7.28 (d,  $J$  = 7.7 Hz, 1H, ArH);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ , 298 K):  $\delta$  = 52.60, 52.8, 69.6,

128.1, 129.5, 129.8, 130.2, 132.7, 133.3, 144.3, 151.8, 162.0, 166.3; LR-ESIMS:  $m/z$  = 247  $[M-2H+H]^+$ ; HR-ESIMS:  $m/z$  = 247.0605 (calcd. for  $C_{13}H_{11}O_5$ , 247.0601).

#### 4-Phenoxybutanamide **239a**



Phenoxyacetic acid (507 mg, 3.33 mmol), acrylamide (47 mg, 0.66 mmol) and  $TiO_2$  (80 mg, 1.0 mmol) were reacted in accordance with the general procedure. Following irradiation for 62 h the reaction

mixture was purified by column chromatography on silica gel (eluent: 2% MeOH in  $CH_2Cl_2$ ) to

yield **239a** as a colourless powder (97.3 mg, 82%). Mp: 110 °C.  $^1H$  NMR (300 MHz,  $CDCl_3$ , 294

K):  $\delta$  = 2.13 (m, 2H,  $C=OCH_2$ ), 2.45 (t,  $J$  = 7.2 Hz, 2H,  $CH_2CH_2$ ), 4.02 (t,  $J$  = 6.0 Hz, 2H,  $OCH_2$ ), 5.63

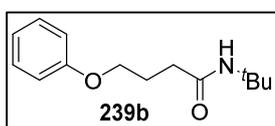
(br-s, 1H, NH), 5.82 (br-s, 1H, NH'), 6.90 (d,  $J$  = 8.8 Hz, 2H, ArH), 6.95 (t,  $J$  = 7.4 Hz, 1H, ArH),

7.29 (t,  $J$  = 7.4 Hz, 2H, ArH);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ , 295 K):  $\delta$  = 25.4, 32.6, 67.1, 114.9, 121.2,

129.9, 159.2, 175.4; LR-EIMS:  $m/z$  = 202  $[MNa]^+$ ; HR-ESIMS:  $m/z$  = 202.0838 (calcd. for

$C_{10}H_{13}NO_2Na$ , 202.0844).

#### *N*-(*tert*-butyl)-4-phenoxybutanamide **239b**



Phenoxyacetic acid (507 mg, 3.33 mmol), *N*-(*tert*-butyl)acrylamide (84 mg, 0.66 mmol) and  $TiO_2$  (80 mg, 1.0 mmol) were reacted in

accordance with the general procedure. Following irradiation for 66 hours  $^1\text{H}$  NMR analysis of the reaction mixture revealed **239b** (< 0.1 mmol, *ca.* 6%).  $^1\text{H}$  NMR (300 MHz,  $d_6$ -acetone, 295 K):  $\delta$  = 1.32 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.92-1.95 (m, 2H, C=OCH<sub>2</sub>), 2.29 (t,  $J$  = 7.5 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>), 3.91 (t,  $J$  = 5.8 Hz, 2H, OCH<sub>2</sub>), 6.85 (m, 2H, ArH), 6.95 (m, 1H, ArH), 7.23 (m 2H, ArH).

**Attempted synthesis of 4-(phenoxyethyl)tetrahydro-2H-pyran-2-one 241 and/or 3,4,4a,10b-tetrahydropyrano[4,3-c]chromen-1(5H)-one 242**

Phenoxyacetic acid (100 mg, 0.66 mmol), 5,6-dihydro-2H-pyran-2-one (0.17 mL, 1.32 mmol) and TiO<sub>2</sub> (75 mg, 0.93 mmol) in CH<sub>3</sub>CN (75 mL) were reacted in accordance with the general procedure. Following irradiation for 18 hours the reaction mixture was scrutinised by  $^1\text{H}$  NMR and GC-MS but no evidence for the formation of **241** or **242** was observed. Repetition of the above following distillation of 5,6-dihydro-2H-pyran-2-one yielded the same result.

## 4.8 Catalyst Comparison Study

Irradiations were carried out in accordance with the general procedure on pg 135 for a standard reaction time of 17 hours. 0.1 mmol of **122** and 0.2 mmol of **238** were used in all instances with 0.15 mmol (where applicable) of the titania catalyst. Yields and conversions were determined by NMR.

### Table 1; Entry 1 P25

Phenoxyacetic acid (15.2 mg, 0.1 mmol), acrylamide (14.2 mg, 0.2 mmol) and TiO<sub>2</sub> (P-25, 12 mg, 0.15 mmol) in CH<sub>3</sub>CN (12 mL) were reacted in accordance with the general procedure. <sup>1</sup>H NMR analysis (w.r.t. CH<sub>2</sub>Br<sub>2</sub> standard) of the resultant mixture revealed **239a** (0.05 mmol, 47%) as well as unreacted phenoxyacetic acid (0.01 mmol) indicating 95% conversion had been achieved.

### Table 1; Entry 2 PC500

Phenoxyacetic acid (15.2 mg, 0.1 mmol), acrylamide (14.2 mg, 0.2 mmol) and TiO<sub>2</sub> (PC500, 12 mg, 0.15 mmol) in CH<sub>3</sub>CN (12 mL) were reacted in accordance with the general procedure. <sup>1</sup>H NMR analysis (w.r.t. CH<sub>2</sub>Br<sub>2</sub> standard) of the resultant mixture revealed: **239a** (0.04 mmol, 39%).

### Table 1; Entry 3 Sol-gel coated tube

Phenoxyacetic acid (15.2 mg, 0.1 mmol) and acrylamide (14.2 mg, 0.2 mmol) in CH<sub>3</sub>CN (12 mL) were reacted in accordance with the general procedure in a TiO<sub>2</sub> sol-gel coated tube. <sup>1</sup>H NMR analysis (w.r.t. CH<sub>2</sub>Br<sub>2</sub> standard) of the resultant mixture revealed: **239a** (0.07 mmol, 73%).

### Table 1; Entry 4, Photospheres

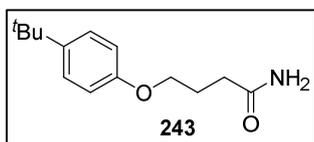
Phenoxyacetic acid (15.2 mg, 0.1 mmol), acrylamide (14.2 mg, 0.2 mmol) and TiO<sub>2</sub> (photospheres, 12 mg) in CH<sub>3</sub>CN (12 mL) were reacted in accordance with the general procedure. <sup>1</sup>H NMR analysis (w.r.t. CH<sub>2</sub>Br<sub>2</sub> standard) of the resultant mixture revealed: **239a** (0.01 mmol, 9%) as well as unreacted phenoxyacetic acid (0.06 mmol) indicating 41% conversion had been achieved.

### 4-Phenoxybutanamide **239a**

Phenoxyacetic acid (100 mg, 0.66 mmol) and acrylamide (93.9 mg, 1.32 mmol) in CH<sub>3</sub>CN (45 mL) were reacted in accordance with the general procedure in a TiO<sub>2</sub> sol-gel coated tube.

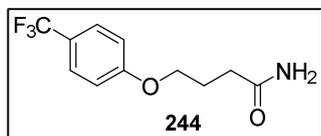
Following irradiation for 24 h the reaction mixture was purified by dry flash chromatography on silica gel (eluent: gradient of 2-10% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to yield **239a** as an off-white solid (79.8 mg, 68%).

#### 4-(*tert*-Butyl)phenoxybutanamide **243**



4-(*tert*-Butyl)phenoxyacetic acid (137.5 mg, 0.66 mmol) and acrylamide (93.9 mg, 1.32 mmol) in CH<sub>3</sub>CN (45 mL) were reacted in accordance with the general procedure in a TiO<sub>2</sub> sol-gel coated tube. Following irradiation for 30 h the reaction mixture was purified by dry flash chromatography on silica gel (eluent: gradient of 2-7.5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to yield **243** as an off-white solid (105.4 mg, 68%) containing ~5% 4-(*tert*-butyl)phenol. Mp 85-88°C. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, 297 K):  $\delta$  = 1.30 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 2.04-2.11 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>), 2.43 (t, *J* = 7.3 Hz, 2H, C=OCH<sub>2</sub>), 4.00 (t, *J* = 6.3 Hz, 2H, OCH<sub>2</sub>), 6.85 (d, *J* = 8.9 Hz, 2H, ArH), 7.30 (dd, *J* = 3.2, 11.5 Hz, 1H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 297 K):  $\delta$  = 27.0, 32.4, 33.4, 35.3, 68.5, 115.5, 127.6, 144.8, 158.5, 179.0; LR-ESIMS: *m/z* = 236 [MH]<sup>+</sup>; HR-ESIMS: *m/z* = 236.1647 (calcd. for C<sub>14</sub>H<sub>22</sub>NO<sub>2</sub>, 236.1645).

#### 4-(Trifluoromethyl)phenoxybutanamide **244**



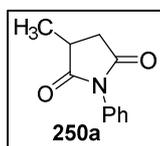
4-(Trifluoromethyl)phenoxyacetic acid (145.3 mg, 0.66 mmol) and acrylamide (93.9 mg, 1.32 mmol) in CH<sub>3</sub>CN (45 mL) were reacted in accordance with the general procedure in a TiO<sub>2</sub> sol-gel coated tube. Following irradiation for 24 h the reaction mixture was purified by dry flash chromatography on silica gel (eluent: 5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to yield **244** as an off-white solid (108.4 mg, 66%). Mp 93-94°C. <sup>1</sup>H NMR (500 MHz, *d*6-acetone, 295 K):  $\delta$  = 2.06-2.11 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>), 2.41 (t, *J* = 7.2 Hz, 2H, C=OCH<sub>2</sub>), 4.14 (t, *J* = 5.9 Hz, 2H, OCH<sub>2</sub>), 6.30 (bs, 1H, NH), 6.86 (bs, 1H, NH'), 7.14 (d, *J* = 8.7 Hz, 2H, ArH), 7.63 (d, *J* = 8.7 Hz, 2H, ArH); <sup>13</sup>C NMR (75 MHz, *d*6-acetone, 297 K):  $\delta$  = 29.9, 36.3, 72.7, 120.0, 127.2 (q, <sup>2</sup>*J*<sub>C-F</sub> = 33.1 Hz, 1C), 130.0 (q, <sup>1</sup>*J*<sub>C-F</sub> = 271.1 Hz, 1C), 132.0 (q, <sup>3</sup>*J*<sub>C-F</sub> = 3.6 Hz, 2C), 167.2, 178.9; <sup>19</sup>F NMR (470 MHz, *d*6-acetone, 295 K):  $\delta$  = -61.8; LR-ESIMS: *m/z* = 248 [MH]<sup>+</sup>; HR-ESIMS: *m/z* = 248.0896 (calcd. for C<sub>11</sub>H<sub>13</sub>NO<sub>2</sub>F<sub>3</sub>, 248.0896).

## 4.9 Variation of the Carboxylic Acid Component

Large scale irradiations were carried out in accordance with the general procedure on pg 135. Unless otherwise stated, isolated yields are reported. For the radical stability study standardised reaction conditions of 0.1 mmol of **249**, 0.2 mmol of **219d** and 0.15 mmol of P25 TiO<sub>2</sub> were adopted with a photolysis time of 18 hours. Yields were calculated by NMR but for the purpose of characterisation, novel compounds have been isolated under non-standard conditions and this data also provided.

### Radical Stability Study

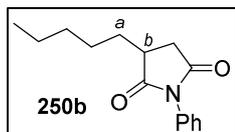
#### 3-Methyl-1-phenylpyrrolidine-2,5-dione **250a**



Acetic acid (6 mg, 0.1 mmol), *N*-phenylmaleimide (34.7 mg, 0.2 mmol) and TiO<sub>2</sub> (12 mg, 0.15 mmol) were reacted in accordance with the general procedure. Following irradiation a yield of 24% (0.024 mmol) was determined for **250a**.

Mp: 94-96 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 296 K): δ = 1.44 (d, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 2.47-2.54 (m, 1H, CHCH<sub>2</sub>), 2.97-3.14 (m-overlapped, 2H, CHCH<sub>2</sub>, CHCH<sub>2</sub>') 7.27-7.30 (m, 2H, ArH), 7.36-7.42 (m, 1H, ArH), 7.44-7.50 (m, 2H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 297 K): δ = 16.9, 34.9, 36.7, 126.4, 128.6, 129.2, 132.0, 175.5, 179.6; LR-ESIMS: *m/z* = 190[MH]<sup>+</sup>; HR-ESIMS: *m/z* = 190.0861 (calcd. for C<sub>11</sub>H<sub>12</sub>NO<sub>2</sub>, 190.0863). Also observed were: *N*-phenylsuccinimide **228d** (0.082 mmol, 41%) and unreacted acetic acid (0.005 mmol, 95% conversion).

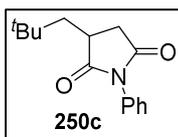
#### 3-Pentyl-1-phenylpyrrolidine-2,5-dione **250b**



*n*-Hexanoic acid (11.6 mg, 0.1 mmol), *N*-phenylmaleimide (34.7 mg, 0.2 mmol) and TiO<sub>2</sub> (12 mg, 0.15 mmol) were reacted in accordance with the general procedure. Following irradiation a yield of 4% (0.04 mmol) was

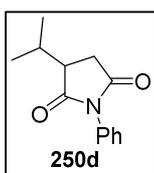
determined for **250b**. Yields were determined by assigning peaks "a" and "b" as follows, by analogy with the previously characterised 3-ethyl adduct.<sup>4</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 295 K): δ = 2.60 (dd, *J* = 3.3, 17.0 Hz, 1H, H<sub>a</sub>), 2.97-3.07 (m, 1H, H<sub>b</sub>). Also observed were: *N*-phenylsuccinimide **228d** (0.008 mmol, 4%) and unreacted *n*-hexanoic acid **249b** (0.035 mmol, 65% conversion).

### 3-Neopentyl-1-phenylpyrrolidine-2,5-dione **250c**



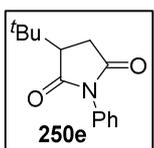
*tert*-Butylacetic acid (11.6 mg, 0.1 mmol), *N*-phenylmaleimide (34.7 mg, 0.2 mmol) and TiO<sub>2</sub> (12 mg, 0.15 mmol) were reacted in accordance with the general procedure. Following irradiation a yield of 18% (0.018 mmol) was determined for **250c**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 296 K):  $\delta$  = 0.94 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.36 (dd,  $J$  = 10.7, 14.0 Hz, 1H, *t*-BuCH<sub>2</sub>), 2.12 (dd,  $J$  = 2.0, 13.9 Hz, 1H, *t*-BuCH<sub>2</sub>'), 2.54 (dd,  $J$  = 5.3, 18.1 Hz, 1H, CHCH<sub>2</sub>), 3.03 (dd,  $J$  = 9.1, 18.1 Hz, 1H, CHCH<sub>2</sub>'), 2.84-2.92 (m, 1H, CHCH<sub>2</sub>), 7.19-7.22 (m, 2H, ArH), 7.29-7.34 (m, 1H, ArH), 7.37-7.42 (m, 2H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 297 K):  $\delta$  = 29.6, 29.7, 31.0, 37.6, 45.9, 126.4, 128.6, 129.2, 132.1, 175.8, 179.8; LR-ESIMS:  $m/z$  = 246 [MH]<sup>+</sup>; HR-ESIMS:  $m/z$  = 246.1486 (calcd. for C<sub>15</sub>H<sub>20</sub>NO<sub>2</sub>, 246.1489). Also observed were: *N*-phenylsuccinimide **228d** (0.080 mmol, 40%) and unreacted *tert*-butylacetic acid **249c** (0.023 mmol, 77% conversion).

### 3-*Iso*-propyl-1-phenylpyrrolidine-2,5-dione **250d**



Isobutyric acid (8.1 mg, 0.1 mmol), *N*-phenylmaleimide (34.7 mg, 0.2 mmol) and TiO<sub>2</sub> (12 mg, 0.15 mmol) were reacted in accordance with the general procedure. Following irradiation a yield of 25% (0.025 mmol) was determined for **250d**. Mp: 90-92°C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 297 K):  $\delta$  = 0.99 (d,  $J$  = 6.8 Hz, 3H, CH<sub>3</sub>), 1.07 (d,  $J$  = 6.9 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 2.32-2.40 (m, 1H, CH<sub>3</sub>'), 2.56 (dd,  $J$  = 4.4, 18.3 Hz, 1H, CHCH<sub>2</sub>), 2.79 (dd,  $J$  = 9.4, 18.3 Hz, 1H, CHCH<sub>2</sub>'), 2.87-2.92 (m, 1H, CHCH<sub>2</sub>), 7.18-7.21 (m, 2H, ArH), 7.29-7.34 (m, 1H, ArH), 7.37-7.43 (m, 2H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 300 K):  $\delta$  = 17.3, 20.0, 29.2, 30.6, 45.8, 126.5, 128.6, 129.2, 131.9, 175.9, 178.4; LR-ESIMS:  $m/z$  = 218 [MH]<sup>+</sup>; HR-ESIMS:  $m/z$  = 218.1178 (calcd. for C<sub>13</sub>H<sub>16</sub>NO<sub>2</sub>, 218.1176). Also observed were: *N*-phenylsuccinimide **228d** (0.005 mmol, 25%) and unreacted isobutyric acid **249d** (0.026 mmol, 74% conversion).

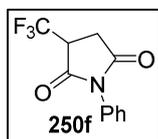
### 3-(*Tert*-butyl)-1-phenylpyrrolidine-2,5-dione **250e**



Pivalic acid (10.2 mg, 0.1 mmol), *N*-phenylmaleimide (34.7 mg, 0.2 mmol) and TiO<sub>2</sub> (12 mg, 0.15 mmol) were reacted in accordance with the general procedure. Following irradiation a yield of 38% (0.038 mmol) was determined for **250e**. Mp: 101-103 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 300 K):  $\delta$  = 1.12 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 2.67-2.80 (m-overlapped, 2H, CHCH<sub>2</sub>, CHCH<sub>2</sub>'), 2.89 (dd,  $J$  = 8.8, 17.6 Hz, 1H, CHCH<sub>2</sub>'), 7.24-7.26 (m, 2H, ArH), 7.36-7.41 (m, 1H, ArH), 7.45-7.49 (m, 2H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 300 K):  $\delta$  = 27.2, 32.0, 33.8, 49.9, 126.6, 128.6, 129.2, 132.0, 175.6, 177.4; LR-ESIMS:  $m/z$  = 232 [MH]<sup>+</sup>;

HR-ESIMS:  $m/z = 232.1326$  (calcd. for  $C_{14}H_{18}NO_2$ , 232.1332). Also observed were: *N*-phenylsuccinimide **228d** (0.062 mmol, 31%) and unreacted isobutyric acid **249e** (0.006 mmol, 94% conversion).

### 3-(Trifluoromethyl)-1-phenylpyrrolidine-2,5-dione **250f**

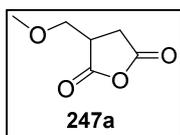


Trifluoroacetic acid (11.4 mg, 0.1 mmol), *N*-phenylmaleimide (34.7 mg, 0.2 mmol) and  $TiO_2$  (12 mg, 0.15 mmol) were reacted in accordance with the general procedure. Following irradiation a yield of  $\sim 1\%$  ( $<0.001$  mmol) was determined for **250f**.  $^1H$  NMR (400 MHz,  $CDCl_3$ , 295 K):  $\delta = 2.86$  (dd,  $J = 5.5, 18.6$  Hz, 1H,  $CHCH_2$ ), 2.99 (dd,  $J = 9.5, 18.6$  Hz, 1H,  $CHCH_2'$ ), 3.61 (m, 1H,  $H_a$ ), 7.10 (m, 2H, Ar-*H*), 7.39 (m, 3H, Ar-*H*);  $^{19}F$  NMR (375 MHz,  $CDCl_3$ , 296 K):  $\delta = -69.3$  (s, 3F,  $CF_3$ ). Data is consistent with literature.<sup>[33]</sup> Also observed was: *N*-phenylsuccinimide **228d** (trace).

### Large Scale Photolyses

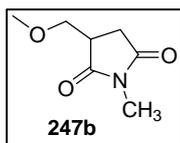
Large scale irradiations were carried out in accordance with the general procedure on pg 135. Unless otherwise stated, isolated yields are reported. For the radical stability study standardised reaction conditions of 0.1 mmol of **249**, 0.2 mmol of **219d** and 0.15 mmol of  $P25 TiO_2$  were adopted with a photolysis time of 18 hours. Yields were calculated by NMR but for the purpose of characterisation, novel compounds have been isolated under non-standard conditions and this data also provided.

### (Methoxymethyl)succinic anhydride **247a**



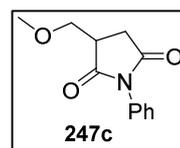
Methoxyacetic acid (60 mg, 0.66 mmol), maleic anhydride (259 mg, 2.64 mmol) and  $TiO_2$  (80 mg, 1.00 mmol) were reacted in accordance with the general procedure. Following irradiation for 18 hours the crude mixture was purified by column chromatography on silica gel (eluent: 5% EtOAc in  $CH_2Cl_2$ ) to yield **247a** as a clear oil (51.4mg, 54%).  $^1H$  NMR (400 MHz,  $CDCl_3$ , 296 K):  $\delta = 2.94$ -3.07 (m, 2H,  $CHCH_2$ ), 3.23-3.29 (m, 1H,  $CHCH_2$ ), 3.35 (s, 3H,  $OCH_3$ ), 3.55 (dd,  $J = 3.1, 9.2$  Hz, 1H,  $OCH_2$ ), 3.81 (dd,  $J = 3.3, 9.2$  Hz, 1H,  $OCH_2'$ );  $^{13}C$  NMR (75 MHz,  $CDCl_3$ , 298 K):  $\delta = 31.2, 42.1, 59.3, 70.0, 170.4, 172.8$ ; LR-ESIMS:  $m/z = 162$  [ $MNH_4$ ] $^+$ ; HR-ESIMS:  $m/z = 162.0761$  (calcd. for  $C_6H_{12}NO_3$ , 162.0766). Succinic anhydride **228a** was also isolated as a white powder (33.8 mg, 16%).

### 3-(Methoxymethyl)-1-methylpyrrolidine-2,5-dione **247b**



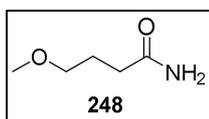
Methoxyacetic acid (60 mg, 0.66 mmol), *N*-methylmaleimide (296 mg, 2.64 mmol) and TiO<sub>2</sub> (80 mg, 1.0 mmol) were reacted in accordance with the general procedure for 16 hours. Following irradiation the reaction mixture was purified by column chromatography on silica gel (eluent: 50% EtOAc in petrol 40/60) to yield **247b** as a colourless oil (60.3 mg, 58%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 295 K): δ = 2.68-2.80 (m, 2H, CHCH<sub>2</sub>), 2.93-3.00 (m, 1H, CHCH<sub>2</sub>), 2.98 (s, 3H, NCH<sub>3</sub>), 3.32 (s, 3H, OCH<sub>3</sub>), 3.54 (dd, *J* = 3.4, 9.2 Hz, 1H, OCH<sub>2</sub>), 3.79 (dd, *J* = 4.2, 9.2 Hz, 1H, OCH<sub>2</sub>′); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 296 K): δ = 25.3, 32.1, 41.5, 59.6, 70.8, 177.3, 178.6; LR-ESIMS: *m/z* = 158 [MH]<sup>+</sup>; HR-ESIMS: *m/z* = 158.0811 (calcd. for C<sub>7</sub>H<sub>12</sub>NO<sub>3</sub>, 158.0817). *N*-methyl succinimide **228c** was also observed by <sup>1</sup>H NMR (10% w.r.t. **247b**).

### 3-(Methoxymethyl)-1-phenylpyrrolidine-2,5-dione **247c**



Methoxyacetic acid (54.4 mg, 0.63 mmol), *N*-phenylmaleimide (433.6 mg, 2.50 mmol) and TiO<sub>2</sub> (75 mg, 0.94 mmol) were reacted together in accordance with the general procedure. Following irradiation for 18 hours the reaction mixture was purified by column chromatography on silica gel (eluent: 30% EtOAc in petroleum ether 40-60) to yield **247c** as a white powder (74.4 mg, 54%). Mp: 109-111 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 299 K) δ = 2.86-2.99 (m, 2H, CHCH<sub>2</sub>), 3.08-3.15 (m, 1H, CHCH<sub>2</sub>), 3.38 (s, 3H, OCH<sub>3</sub>), 3.36 (dd, *J* = 3.3 Hz, 9.1 Hz, 1H, OCH<sub>2</sub>), 3.91 (dd, *J* = 3.9 Hz, 9.1 Hz, 1H, OCH<sub>2</sub>′), 7.26-7.30 (m, 2H, ArH), 7.36-7.41 (m, 1H, ArH), 7.44-7.49 (m, 2H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 298 K) δ = 31.9, 41.2, 59.3, 70.8, 126.6, 128.6, 129.1, 132.1, 175.8, 177.3; LR-ESIMS: *m/z* = 221 [MH]<sup>+</sup>; HR-EIMS: *m/z* = 220.0969 (calcd. for C<sub>12</sub>H<sub>14</sub>O<sub>3</sub>N<sub>1</sub>, 220.0974). *N*-phenyl succinimide **228d** was also isolated as an off-white solid (61.3 mg, 14 %).

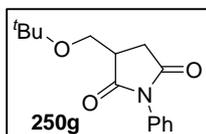
### 4-Methoxybutanamide **248**



Methoxyacetic acid (282 mg, 3.13 mmol), acrylamide (45 mg, 0.63 mmol) and TiO<sub>2</sub> (75 mg, 0.94 mmol) were reacted in accordance with the general procedure. Following irradiation for 38 hours the reaction mixture was purified by column chromatography on silica gel (eluent: gradient of 2-10% MeOH in CH<sub>2</sub>Cl<sub>2</sub>; visualised by staining with vanillin) to yield **248** as an off-white solid (48.9 mg, 67%). Mp: 39-40°C. <sup>1</sup>H NMR (500 MHz, *d*6-acetone, 295 K): δ = 1.76-1.82 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>), 2.21 (t, *J* = 7.5 Hz, 2H, C=OCH<sub>2</sub>), 3.24 (s, 3H, OCH<sub>3</sub>), 3.34 (t, *J* = 6.4 Hz, 2H, OCH<sub>2</sub>) 6.25 (br-s, 1H, NH) 6.76 (br-s, 1H,

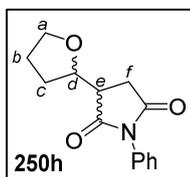
NH');  $^{13}\text{C}$  NMR (75 MHz, *d6*-acetone, 296 K):  $\delta$  = 26.2, 32.6, 58.4, 72.5, 175.0; LR-EIMS:  $m/z$  = 117  $[\text{M}]^+$ ; HR-ESIMS:  $m/z$  = 117.0782 (calcd. for  $\text{C}_5\text{H}_{11}\text{O}_2\text{N}_1$ , 117.0790).

### 3-(*tert*-Butoxymethyl)-1-phenylpyrrolidine-2,5-dione **250g**



*tert*-Butoxyacetic acid (87.3 mg, 0.66 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol) and  $\text{TiO}_2$  (80 mg, 1.0 mmol) were reacted together in accordance with the general procedure. Following irradiation for 17 hours.  $^1\text{H}$  NMR analysis revealed that *N*-phenylmaleimide had been consumed entirely while a significant quantity of *tert*-butoxyacetic acid remained. A further 462.3 mg of *N*-phenylmaleimide was hence added and the reaction photolysed for another 18 hours. before the reaction mixture was purified by column chromatography on silica gel (eluent: 25% EtOAc in pentanes) to yield **250g** as a yellow oil (97.8 mg, 57%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 295 K)  $\delta$  = 1.18 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 2.85-2.89 (m, 2H,  $\text{CHCH}_2$ ), 3.07-3.11 (m, 1H,  $\text{CHCH}_2$ ), 3.59 (dd,  $J$  = 2.9, 8.5 Hz, 1H,  $\text{OCH}_2$ ), 3.91 (dd,  $J$  = 3.5, 8.5 Hz, 1H,  $\text{OCH}_2'$ ), 7.27 (d,  $J$  = 7.4 Hz, 2H, ArH), 7.39 (t,  $J$  = 7.4 Hz, 1H, ArH), 7.48 (t,  $J$  = 7.4 Hz, 2H, ArH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , 297 K)  $\delta$  = 27.4, 32.3, 41.3, 60.7, 73.3, 126.6, 128.6, 129.2, 134.2, 176.3, 178.0; LR-ESIMS:  $m/z$  = 262  $[\text{MNa}]^+$ ; HR-ESIMS:  $m/z$  = 262.1440 (calcd. for  $\text{C}_{15}\text{H}_{20}\text{NO}_3$ , 262.1438).

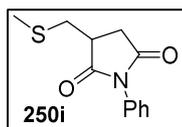
### 1-Phenyl-3-(tetrahydrofuran-2-yl)-pyrrolidine-2,5-dione **250h**



2-Tetrahydrofuroic acid (76.6 mg, 0.66 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol) and  $\text{TiO}_2$  (80 mg, 1.00 mmol) were reacted together in accordance with the general procedure. Following irradiation for 18 hours the reaction mixture was purified by column chromatography on silica gel (eluent:  $\text{Et}_2\text{O}$ ) to yield a 1:1 mixture of the two diastereoisomers of **250h** as a yellow oil (121.8 mg, 75%). This mixture was characterised with the assistance of the usual battery of 2D NMR experiments. *Diastereomer-1*:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 295 K):  $\delta$  = 1.92-2.02 (m-overlapped, 2H,  $\text{H}_b$ ), 2.02-2.12 (m-overlapped, 2H,  $\text{H}_c$ ), 2.79-2.84 (m-overlapped, 1H,  $\text{H}_f$ ), 2.99 (dd,  $J$  = 9.3, 18.3 Hz, 1H,  $\text{H}_g$ ), 3.26-3.30 (m, 1H,  $\text{H}_e$ ), 3.76-3.84 (m, 2H,  $\text{H}_a$ ), 4.23-4.27 (m, 1H,  $\text{H}_d$ ), 7.26-7.32 (m-overlapped, 2H, ArH), 7.37-7.42 (m-overlapped, 1H, ArH), 7.45-7.51 (m-overlapped, 2H, ArH);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , 297 K):  $\delta$  = 25.9, 27.9, 32.7, 43.4, 68.8, 79.1, 126.6, 128.6, 129.1, 132.0, 175.7, 175.9. *Diastereomer-2*:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 295 K):  $\delta$  = 1.63-1.71 (m, 1H,  $\text{H}_c$ ), 1.92-2.02 (m-overlapped, 2H,  $\text{H}_b$ ), 2.10-2.19 (m-overlapped, 1H,  $\text{H}_c$ ), 2.79-2.84 (m-overlapped, 2H,  $\text{H}_f$ ), 3.08-3.12 (m, 1H,  $\text{H}_e$ ), 3.86-3.94 (m- 2H,  $\text{H}_a$ ), 4.39-4.44 (m, 1H,  $\text{H}_d$ ), 7.26-7.32 (m-overlapped, 2H, ArH), 7.37-7.42 (m-overlapped, 1H, ArH), 7.45-7.51 (m-overlapped,

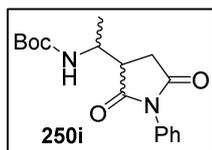
2H, ArH);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , 297 K):  $\delta$  = 25.9, 29.7, 29.8, 44.4, 68.8, 77.3, 126.6, 128.6, 129.1, 132.0, 176.5, 177.4. GC-MS:  $t_{\text{R}}$  15.75 min -  $m/z$  (%) 245 (38), 217 (10), 202 (58), 175 (100), 147 (10), 119 (28), 111 (11), 71 (98);  $t_{\text{R}}$  16.20 min -  $m/z$  (%) 245 (51), 217 (11), 202 (33), 175 (81), 147 (6), 119 (22), 111 (12), 71 (100); LR-ESIMS:  $m/z$  = 246  $[\text{MNa}]^+$ ; HR-ESIMS:  $m/z$  = 246.1127 (calcd. for  $\text{C}_{14}\text{H}_{16}\text{NO}_3$ , 246.1125).

### 3-(Methylthiomethyl)-1-phenylpyrrolidine-2,5-dione **250i**



Methylthioacetic acid (70.8 mg, 0.67 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol) and  $\text{TiO}_2$  (80 mg, 1.00 mmol) were reacted together in accordance with the general procedure. Following irradiation for 42 hours the reaction mixture was purified by column chromatography on silica gel (eluent: gradient of 20% - 40% EtOAc in petroleum ether 40-60) to yield **250i** as a white powder (53.6 mg, 34%) Mp: 90-94 °C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 299 K):  $\delta$  = 2.14 (s, 3H,  $\text{SCH}_3$ ), 2.84 (dd, 1H,  $J$  = 5.0, 18.4 Hz,  $\text{CHCH}_2$ ), 2.92 (dd, 1H,  $J$  = 7.4, 13.5 Hz,  $\text{SCH}_2$ ), 3.01 (dd, 1H,  $J$  = 9.2, 18.4 Hz,  $\text{CHCH}_2'$ ), 3.04 (dd, 1H,  $J$  = 4.1, 13.5 Hz,  $\text{SCH}_2'$ ), 3.21-3.28 (m, 1H,  $\text{CHCH}_2$ ), 7.22-7.27 (m, 2H, ArH), 7.35-7.39 (m, 1H, ArH), 7.42-7.47 (m, 2H, ArH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , 297 K):  $\delta$  = 16.5, 33.7, 35.5, 40.1, 126.5, 128.7, 129.2, 131.9, 175.2, 177.5; LR-ESIMS:  $m/z$  = 236  $[\text{MH}]^+$ ; HR-ESIMS:  $m/z$  = 236.0741 (calcd. for  $\text{C}_{12}\text{H}_{14}\text{NO}_2\text{S}$ , 236.0740).

### *tert*-Butyl (1-(2,5-dioxo-1-phenylpyrrolidin-3-yl)ethyl)carbamate **250i**



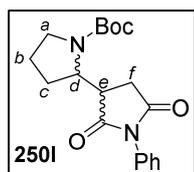
*N*-Boc-L-alanine (126.2 mg, 0.67 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol) and  $\text{TiO}_2$  (80 mg, 1.00 mmol) were reacted together in accordance with the general procedure. Following irradiation for 18 hours the crude mixture was purified by column chromatography on silica gel (eluent: gradient of 20% - 40% gradient EtOAc in petroleum ether 40-60) to yield two diastereomers of **250i**. *Diastereomer-1* was isolated as a white powder (36.7 mg, 18%). Mp 155-157 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 296 K):  $\delta$  = 1.29 (d,  $J$  = 6.9 Hz, 3H,  $\text{CH}_3$ ), 1.38 (s, 9H,  $(\text{CH}_3)_3$ ), 2.78 (dd,  $J$  = 4.8, 18.6 Hz, 1H,  $\text{CHCH}_2$ ) 2.89 (dd,  $J$  = 9.1, 18.5 Hz, 1H,  $\text{CHCH}_2'$ ), 3.15-3.20 (m, 1H,  $\text{CHCH}_2$ ), 4.08-4.18 (m, 1H, NCH), 4.53 (bs, 1H, NH), 7.18-7.22 (m, 2H, ArH), 7.30-7.35 (m, 1H, ArH), 7.38-7.43 (m, 2H, ArH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , 297 K):  $\delta$  = 18.7, 28.3, 32.2, 45.3, 47.7, 80.2, 126.5, 128.7, 129.2, 131.8, 155.5, 175.3, 176.6; LR-ESIMS:  $m/z$  = 341  $[\text{MNa}]^+$ ; HR-ESIMS:  $m/z$  = 341.1467 (calcd. for  $\text{C}_{17}\text{H}_{22}\text{O}_4\text{N}_2\text{Na}$ , 341.1472). *Diastereomer-2* (0.13 mmol, 20% wrt  $\text{CH}_2\text{Br}_2$  standard) was isolated as a 1:1 mixture with *N*-phenylsuccinimide.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 297 K):  $\delta$  = 1.25 (d,  $J$  = 6.8 Hz, 3H,  $\text{CH}_3$ ), 1.44 (s, 9H,  $(\text{CH}_3)_3$ ), 2.63 (dd,  $J$  = 4.5, 18.6 Hz, 1H,  $\text{CHCH}_2$ ) 3.00 (dd,

$J = 9.6, 18.5$  Hz, 1H, CHCH<sub>2</sub>'), 3.17-3.23 (m, 1H, CHCH<sub>2</sub>), 4.13-4.17 (m, 1H, NCH), 5.20 (bs, 1H, NH), 7.27-7.30 (m, 2H, ArH), 7.39-7.42 (m, 1H, ArH), 7.46-7.50 (m, 2H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 297 K):  $\delta = 17.1, 28.5, 31.9, 45.1, 47.1, 80.0, 126.6, 128.8, 129.3, 131.8, 155.2, 175.2, 177.5$ ; LR-ESIMS:  $m/z = 341$  [MNa]<sup>+</sup>; HR-ESIMS:  $m/z = 341.1475$  (calcd. for C<sub>17</sub>H<sub>22</sub>O<sub>4</sub>N<sub>2</sub>Na, 341.1472).

#### Attempted preparation of benzyl (1-(2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-phenylethyl)carbamate **250j**

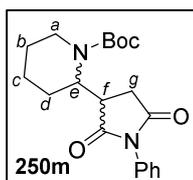
*N*-Cbz-D/L-phenylalanine (197.5 mg, 0.66 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol) and TiO<sub>2</sub> (80 mg, 1.00 mmol) were reacted together in accordance with the general procedure. Following irradiation for 18 hours the reaction mixture was scrutinised by <sup>1</sup>H NMR and GC-MS but no evidence for the formation of **250j** was observed.

#### *tert*-Butyl 2',5'-dioxo-1'-phenyl-[2,3'-bipyrrolidine]-1-carboxylate **250l**



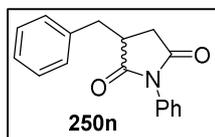
*N*-Boc-L-proline (144.3 mg, 0.67 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol) and TiO<sub>2</sub> (80 mg, 1.00 mmol) were reacted together in accordance with the general procedure. Following irradiation for 17 hours the crude mixture was purified by dry flash chromatography on silica gel (eluent: gradient of 20% - 60% EtOAc in petroleum ether 40-60) to yield an inseparable mixture of two diastereomers of **250l** (171 mg, 75%, 1:1 ratio) also containing 7% *N*-phenyl succinimide. This mixture was characterised with the assistance of the usual battery of 2D NMR experiments. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 326 K) *diastereomer 1*  $\delta = 1.44$  (s, 9H, (CH<sub>3</sub>)<sub>3</sub>), 1.94-1.99 (m, 2H, H<sub>c</sub>), 2.18-2.24 (m, 2H, H<sub>b</sub>), 2.73-2.75 (m, 1H, H<sub>e</sub>), 2.83 (dd,  $J = 3.8, 9.4$  Hz, 1H, H<sub>f</sub>), 3.53 (dd,  $J = 7.3, 11.1$  Hz, 1H, H<sub>f</sub>), 3.79-3.85 (m, 2H, H<sub>d</sub>), 4.34-4.39 (m-overlapped, 2H, H<sub>a</sub>), 7.27-7.47 (m-overlapped, 5H, ArH); *diastereomer 2*  $\delta = 1.49$  (s, 9H, (CH<sub>3</sub>)<sub>3</sub>), 2.14-2.17 (m, 2H, H<sub>c</sub>), 1.66-1.71 (m, 2H, H<sub>b</sub>), 2.69-2.71 (m, 1H, H<sub>e</sub>), 2.86 (dd,  $J = 4.3, 9.7$  Hz, 1H, H<sub>f</sub>), 3.30 (dd,  $J = 3.4, 7.8$  Hz, 1H, H<sub>f</sub>), 3.95-3.99 (m, 2H, H<sub>d</sub>), 4.31-4.35 (m-overlapped, 2H, H<sub>a</sub>), 7.27-7.47 (m-overlapped, 5H, ArH); <sup>13</sup>C NMR\* (75 MHz, CDCl<sub>3</sub>, 300 K):  $\delta = 23.3-24.0, 27.9, 28.4, 28.5, 29.7-30.1, 31.8, 43.7-44.1, 47.2-47.8, 57.1-57.8, 79.9-80.5, 126.5-126.8, 128.4-129.2, 131.2-132.0, 155.0-156.0, 174.1-177.3$ ; GC-MS:  $t_R$  19.81 min -  $m/z$  (%) 344 (2), 288 (19), 271 (17), 243 (48), 175 (16), 114 (50), 70 (100) 57 (41);  $t_R$  20.09 min -  $m/z$  (%) 344 (2), 288 (19), 271 (17), 243 (48), 175 (16), 114 (50), 70 (100) 57 (41); LR-ESIMS:  $m/z = 367$  [MNa]<sup>+</sup>; HR-ESIMS:  $m/z = 367.1632$  (calcd. for C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>Na, 367.1628).

### **tert-Butyl 2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)piperidine-1-carboxylate 250m**



*N*-Boc-D/L-2-piperidinecarboxylic acid (151.4 mg, 0.67 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol) and TiO<sub>2</sub> (80 mg, 1.00 mmol) were reacted together in accordance with the general procedure. Following irradiation for 18 hours the crude mixture was purified by column chromatography on silica gel (eluent: 30% EtOAc in pentanes) to yield two diastereomers of **250m**. Each diastereomer was characterised with the assistance of the usual battery of 2D NMR experiments. *Diastereomer-1* was isolated as an off-white solid (32.7 mg, 14%). Mp 107-110 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 295 K): δ = 1.39 (s, 9H, (CH<sub>3</sub>)<sub>3</sub>), 1.46-1.59 (bm, 2H, H<sub>c,d</sub>), 1.67-1.79 (bm, 4H, H<sub>b,c,d'</sub>), 2.52 (dd, *J* = 3.0, 18.2 Hz, 1H, H<sub>g</sub>), 2.98 (dd, *J* = 8.9, 18.2 Hz, 1H, H<sub>g'</sub>), 3.04 (t, *J* = 13.2 Hz, 1H, H<sub>a</sub>), 3.26-3.30 (m, 1H, H<sub>f</sub>), 4.06 (d, *J* = 13.2 Hz, 1H, H<sub>a'</sub>), 4.34-4.37 (m, 1H, H<sub>e</sub>), 7.32-7.36 (m, 3H, ArH), 7.41-7.45 (m, 2H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 297 K): δ = 18.9, 24.8, 27.0, 28.4, 34.2, 38.1, 40.2, 53.3, 79.9, 126.7, 128.4, 128.9, 132.1, 155.5, 174.9, 176.1; LR-ESIMS: *m/z* = 381 [MNa]<sup>+</sup>; HR-ESIMS: *m/z* = 381.1787 (calcd. for C<sub>20</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>Na, 381.1785). *Diastereomer-2* (0.10 mmol, 15% wrt CH<sub>2</sub>Br<sub>2</sub> standard) was isolated as a 1:2 mixture with *N*-phenylsuccinimide. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 295 K): δ = 1.42 (s, 9H, (CH<sub>3</sub>)<sub>3</sub>), 1.53 (m, 1H, H<sub>b</sub>), 1.68-1.72 (m, 1H, H<sub>d</sub>), 1.90-1.96 (m, 1H, H<sub>b'</sub>), 2.21-2.23 (m, 1H, H<sub>c</sub>), 2.40-2.45 (m, 1H, H<sub>c'</sub>), 2.54-2.58 (m, 1H, H<sub>a'</sub>), 2.95 (dd, *J* = 4.4, 19.0 Hz, 1H, H<sub>g</sub>), 3.05 (dd, *J* = 9.6, 17.6 Hz, 1H, H<sub>a</sub>), 3.26 (dd, *J* = 9.1, 19.0 Hz, 1H, H<sub>g'</sub>), 3.35 (dd, *J* = 6.3, 17.6 Hz, 1H, H<sub>a'</sub>), 3.37-3.42 (m, 1H, H<sub>f</sub>), 3.94-3.98 (m, 1H, H<sub>e</sub>), 7.38-7.42 (m, 3H, ArH), 7.44-7.49 (m, 2H, ArH); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 295 K): δ = 19.6, 24.4, 24.6, 28.3, 33.4, 37.8, 39.5, 46.1, 82.5, 126.4, 128.5, 129.1, 131.4, 152.6, 175.2, 175.5; LR-ESIMS: *m/z* = 381 [MNa]<sup>+</sup>; HR-ESIMS: *m/z* = 381.1787 (calcd. for C<sub>20</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>Na, 381.1785).

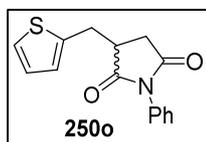
### **3-Benzyl-1-phenylpyrrolidine-2,5-dione 250n**



Phenylacetic acid (89.9 mg, 0.66 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol) and TiO<sub>2</sub> (80 mg, 1.00 mmol) were reacted together in accordance with the general procedure. Following irradiation for 22 hours the reaction mixture was purified by dry flash chromatography on silica gel (eluent: gradient of 10% - 20% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) to yield **250n** as a white powder (99.3 mg, 57%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 295 K): δ = 2.65 (dd, *J* = 4.7, 18.5 Hz, 1H, PhCH<sub>2</sub>), 2.88 (dd, *J* = 9.2, 18.5 Hz, 1H, PhCH<sub>2</sub>'), 3.08 (dd, *J* = 8.0, 13.8 Hz, 1H, CHCH<sub>2</sub>), 3.25 (dd, *J* = 4.4, 13.8 Hz, 1H, CHCH<sub>2</sub>'), 3.30-3.35 (m, 1H, CHCH<sub>2</sub>), 7.17 (m, 2H, ArH), 7.22 (m, 2H, ArH), 7.29 (m, 1H, ArH), 7.34 (m, 2H, ArH), 7.39 (m, 1H, ArH), 7.46 (m, 2H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 297 K): δ = 33.5, 36.7, 41.4, 77.2,

126.6, 127.4, 128.8, 129.0, 129.3, 129.4, 132.0, 136.8, 175.4, 178.4. Data consistent with literature.<sup>[34]</sup> Bibenzyl **144** (0.06 mmol, 18%) was observed by NMR prior to purification of the reaction mixture.

### 1-Phenyl-3-(thiophen-2-ylmethyl)pyrrolidine-2,5-dione **250o**



2-Thiopheneacetic acid (93.9 mg, 0.66 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol) and TiO<sub>2</sub> (80 mg, 1.00 mmol) were reacted together in accordance with the general procedure. Following irradiation for 17 hours the reaction mixture was purified by column chromatography on silica gel (eluent: 20% EtOAc in pentanes) to yield **250o** as a yellow oil (45.9 mg, 26%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 295 K): δ = 2.72 (dd, *J* = 4.8, 18.4 Hz, 1H, ArCH<sub>2</sub>), 2.98 (dd, *J* = 9.2, 18.4 Hz, 1H, ArCH<sub>2</sub>'), 3.30-3.35 (m, 1H, CHCH<sub>2</sub>), 3.37-3.45 (m, 2H, CHCH<sub>2</sub>), 6.89 (m, 1H, ArH), 6.98 (m, 1H, ArH), 7.20 (m, 2H, ArH), 7.39 (m, 1H, ArH), 7.46 (m, 2H, ArH); 30.7, 33.4, 41.3, 125.0, 126.5, 127.0, 127.3, 128.7, 129.2, 131.8, 138.2, 175.2, 177.8; 177.5; LR-ESIMS: *m/z* = 272 [MH]<sup>+</sup>; HR-ESIMS: *m/z* = 272.0743 (calcd. for C<sub>15</sub>H<sub>14</sub>NO<sub>2</sub>S, 272.0740). 1,2-Di(thiophen-2-yl)ethane **157** was also isolated as a clear oil (14.1 mg, 22%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 295 K): δ = 3.20 (s, 4H, CH<sub>2</sub>), 6.80 (d, *J* = 3.4 Hz, 2H, ArH), 6.91-6.94 (m, 2H, ArH), 7.14 (d, *J* = 5.2 Hz, 2H, ArH).

### Attempted preparation of 3-allyl-1-phenylpyrrolidine-2,5-dione

Freshly distilled vinylacetic acid (56.8 mg, 0.67 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol) and TiO<sub>2</sub> (80 mg, 1.00 mmol) were reacted together in accordance with the general procedure. Following irradiation for 17 hours the reaction mixture was scrutinised by <sup>1</sup>H NMR and GC-MS but no evidence for the formation of title compound was observed.

### Attempted preparation of 3-(cyclohex-1-en-1-ylmethyl)-1-phenylpyrrolidine-2,5-dione

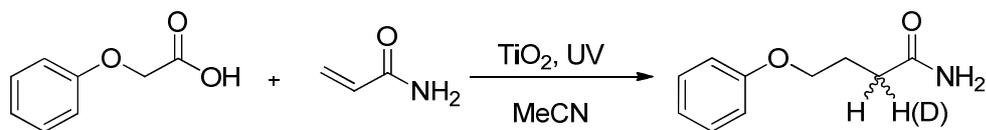
Cyclohex-1-enylacetic acid (95.5 mg, 0.66 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol) and TiO<sub>2</sub> (80 mg, 1.00 mmol) were reacted together in accordance with the general procedure. Following irradiation for 19 hours the reaction mixture was scrutinised by <sup>1</sup>H NMR and GC-MS but no evidence for title compound was observed.

### Attempted preparation of 1-phenyl-3-(prop-2-yn-1-yl)pyrrolidine-2,5-dione

But-3-ynoic acid (55.5 mg, 0.67 mmol), *N*-phenylmaleimide (462.3 mg, 2.67 mmol) and TiO<sub>2</sub> (80 mg, 1.00 mmol) were reacted together in accordance with the general procedure.

Following irradiation for 18 hours the reaction mixture was scrutinised by  $^1\text{H}$  NMR and GC-MS but no evidence for the formation of title compound was observed.

## 4.10 Deuterium Labelling Experiments



### P25 vacuum dried at 150 ° C.

TiO<sub>2</sub> (12 mg, 0.15 mmol) was dried overnight at 150 °C under a continuous vacuum in an oven-dried Schlenk tube. Phenoxyacetic acid (15.2 mg, 0.1 mmol) and acrylamide (14.2 mg, 0.2 mmol) in CH<sub>3</sub>CN (12 mL) were added via syringe and the resultant mixture was irradiated for 18 hours. <sup>1</sup>H NMR analysis of the resultant mixture revealed: **239H** (0.04 mmol, 39%).

### Deuteriated acetonitrile (CD<sub>3</sub>CN)

Phenoxyacetic acid (15.2 mg, 0.1 mmol), acrylamide (14.2 mg, 0.2 mmol) and TiO<sub>2</sub> (12 mg, 0.15 mmol) in CD<sub>3</sub>CN (12 mL) were irradiated for 18 hours. <sup>1</sup>H NMR analysis of the resultant mixture revealed: **239H** (0.06 mmol, 55%). Any deuterium incorporation was below the NMR and MS detection limits.

### Deuteriated phenoxyacetic acid 122D

*d*<sub>1</sub>-Phenoxyacetic acid (15.3 mg, 0.1 mmol), acrylamide (14.2 mg, 0.2 mmol) and TiO<sub>2</sub> (12 mg, 0.15 mmol) in CH<sub>3</sub>CN (12 mL) were irradiated for 19 hours. <sup>1</sup>H NMR analysis (w.r.t. CH<sub>2</sub>Br<sub>2</sub> standard) of the resultant mixture revealed: **239H** (0.049 mmol, 49%). Any deuterium incorporation was below the NMR and MS detection limits.

### Deuteriated P25

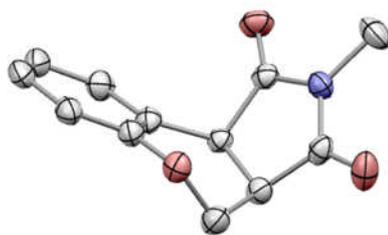
An oven dried Schlenk tube, complete with magnetic stirrer, was connected to a vacuum line and evacuated then back filled with argon while still hot from the oven. In a glovebox TiO<sub>2</sub> (P25, 0.15 mmol, 12 mg) was added and the tube was then heated at 150 °C for three hours under vacuum. In a separate oven dried vessel, 10 mL of D<sub>2</sub>O (freshly opened) was degassed by three cycles of freeze-pump-thaw before being transferred by cannula to the tube containing the TiO<sub>2</sub> once it had cooled to ambient temperature. The resultant mixture was allowed to stir overnight before the D<sub>2</sub>O was removed under reduced pressure. At this point the TiO<sub>2</sub> was again dried for three hours at 150 °C under vacuum. In a separate oven dried vessel phenoxyacetic acid (0.1 mmol, 15.2 mg) and acrylamide (0.2 mmol, 14.2 mg) were

dissolved in CH<sub>3</sub>CN (12 mL) that had been freshly collected having been distilled over calcium hydride. The resultant mixture was degassed for fifteen minutes by bubbling with argon and then transferred via cannula to the tube containing the TiO<sub>2</sub> once it had cooled to ambient temperature. The resultant mixture was then irradiated in accordance with the general procedure for 19 hours. <sup>1</sup>H NMR analysis of the resultant mixture revealed: **239H** (0.058 mmol, 58%). Any deuterium incorporation was below the NMR and MS detection limits.

**Deuteriated phenoxyacetic acid deuteriated P25**

As above, using *d*<sub>1</sub>-phenoxyacetic acid (15.3 mg, 0.1 mmol) for 19 hours. <sup>1</sup>H NMR analysis of the resultant mixture revealed: no clear signals indicating the formation of **239H** or **239D**.

## 4.11 X-Ray Crystallography



**Figure 22.** The X-ray crystal structures of chromenopyrroledione **221c**.

**Table 8.** Crystal data & structure refinement for **221g**.

Identification code	<b>221g</b>
Empirical Formula	C <sub>12</sub> H <sub>11</sub> NO <sub>3</sub>
Formula Weight	217.22
Crystal Colour, Habit	colourless prism
Crystal Dimensions	0.200 mm x 0.200 mm x 0.030 mm
Crystal System	orthorhombic
Lattice Type	Primitive
Lattice Parameters	a = 11.802(5) Å b = 6.0413(18) Å c = 14.845(6) Å
Volume	1058.4(6) Å <sup>3</sup>
Space Group	Pna2 <sub>1</sub> (#33)
Z value	4
Density (calculated)	1.363 g/mL
F(000)	456.00
μ(MoKα)	0.989 cm <sup>-1</sup>
Diffractometer	Mercury70
Radiation Voltage	MoKα (λ = 0.71075 Å)
Current Temperature	93 K
Detector Aperture	70 x 70 mm
Pixel Size	0.068 mm
2θmax	50.7°
No. of Reflections Measured	Total: 6166, Unique: 1637 (R <sub>int</sub> = 0.0324)

Corrections	Lorentz-polarization
Structure Solution	Direct Methods
Refinement	Full-matrix least-squares on $F^2$
Function Minimized	$\sum w (F_o^2 - F_c^2)^2$
Least Squares Weights	$w = 1/[\sigma^2(F_o^2) + (0.1051P)^2 + 2.9953P]$
	where $P = (\text{Max}(F_o^2, 0) + 2F_c^2)/3$
2 $\theta$ max cutoff	50.7°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations	(All reflections) 1637
No. Variables	146
Reflection/Parameter Ratio	11.21
Residuals: R1 ( $I > 2.00\sigma(I)$ )	0.0361
Residuals: R (All reflections)	0.0400
Residuals: wR2 (All reflections)	0.0808
Goodness of Fit	1.037
Indicator Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	0.14 e /Å <sup>3</sup>
Minimum peak in Final Diff. Map	-0.17 e /Å <sup>3</sup>

## 5.0 References

- [1] a) J. Clayden, *Organic Chemistry*, Oxford University Press, Oxford, **2001**, pp. 1019-1052; b) P. Renaud, M. Sibi, *Radicals in Organic Synthesis*, Wiley-VCH, New York, **2001**; c) S. Zard, *Radical Reactions in Organic Synthesis*, Oxford University Press, Oxford, **2003**; d) J. Hioe, H. Zipse, in *Encyclopedia of Radicals in Chemistry, Biology and Materials, Vol. 1* (Eds.: C. Chatgililoglu, A. Studer), Wiley & Sons, Chichester, **2012**, pp. 449-476.
- [2] H. Fischer, L. Radom, *Angew. Chem. Int. Ed.* **2001**, *40*, 1340-1371.
- [3] P. Wipf, P. D. G. Coish, *J. Org. Chem.* **1999**, *64*, 5053-5061.
- [4] N. Grant, PhD Thesis, University of Aberdeen **2010**.
- [5] M. A. Fox, M. T. Dulay, *Chem. Rev.* **1993**, *93*, 341-357.
- [6] A. L. Linsebigler, G. Lu, J. T. Yates, *Chem. Rev.* **1995**, *95*, 735-758.
- [7] A. Mills, *Chem. Commun.* **1982**, 367-368.
- [8] A. Mills, N. Elliott, G. Hill, D. Fallis, J. R. Durrant, R. L. Willis, *Photochem. Photobiol. Sci.* **2003**, *2*, 591-596.
- [9] R. B. Roy, G. A. Swan, *J. Chem. Soc. C* **1969**, 1886-1891.
- [10] P. Boule, J. Lemaire, *J. Chim. Phys. & Phys-Chim. Bio* **1980**, *77*, 161-165.
- [11] a) Y. Yoshimi, M. Masuda, T. Mizunashi, K. Nishikawa, K. Maeda, N. Koshida, T. Itou, T. Morita, M. Hatanaka, *Org. Lett.* **2009**, *11*, 4652-4655; b) M.-C. I. Lamas, A. Studer, *Org. Lett.* **2011**, *13*, 2236-2239; c) P. Fries, D. Halter, A. Kleinschek, J. Hartung, *J. Am. Chem. Soc.* **2011**, *133*, 3906-3912.
- [12] a) T. Taniguchi, Y. Sugiura, H. Zaimoku, H. Ishibashi, *Angew. Chem. Int. Ed.* **2010**, *49*, 10154-10157; b) C. J. Wallentin, J. D. Nguyen, P. Finkbeiner, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2012**, *134*, 8875-8884; c) M. Pirtsch, S. Paria, T. Matsuno, H. Isobe, O. Reiser, *Chem. Eur. J.* **2012**, *18*, 7336-7340.
- [13] M. Noorjahan, M. Pratap Reddy, V. Durga Kumari, B. Lavédrine, P. Boule, M. Subrahmanyam, *J. Photochem. Photobiol., A* **2003**, *156*, 179-187.
- [14] T. Ohno, K. Sarukawa, K. Tokieda, M. Matsumura, *J. Catal.* **2001**, *203*, 82-86.
- [15] D. C. Hurum, A. G. Agrios, K. A. Gray, T. Rajh, M. C. Thurnauer, *J. Phys. Chem. B* **2003**, *107*, 4545-4549.
- [16] a) B. Kraeutler, C. D. Jaeger, A. J. Bard, *J. Am. Chem. Soc.* **1978**, *100*, 4903-4905; b) B. Kraeutler, A. J. Bard, *J. Am. Chem. Soc.* **1978**, *100*, 5985-5992.
- [17] <http://microspheretechnology.com/wordpress/index.php/titanium-dioxide-coating-technology/>. Accessed 19 Nov. 2013.
- [18] A. Mills, C. O'Rourke, *Catal. Today* **2013**, Article ASAP.
- [19] M. Minozzi, D. Nanni, J. C. Walton, *J. Org. Chem.* **2004**, *69*, 2056-2069.
- [20] A. Hudson, K. D. J. Root, *J. Chem. Soc. B* **1970**, 656-660.
- [21] J. K. Kochi, P. J. Krusic, *J. Am. Chem. Soc.* **1968**, *90*, 7157-7159.
- [22] S. V. Kulkarni, C. Trapp, *J. Am. Chem. Soc.* **1970**, *92*, 4801-4808.
- [23] M. L. Poutsma, *J. Phys. Org. Chem.* **2008**, *21*, 758-782.
- [24] a) E.-A. I. Heiba, R. M. Dessau, W. J. Koehl, *J. Am. Chem. Soc.* **1968**, *90*, 1082-1084; b) E.-A. I. Heiba, R. M. Dessau, W. J. Koehl, *J. Am. Chem. Soc.* **1969**, *91*, 138-145; c) M. E. Kurz, V. Baru, P. N. Nguyen, *J. Org. Chem.* **1984**, *49*, 1603-1607; d) A. Citterio, R. Sebastiano, A. Maronati, R. Santi, F. Bergamini, *Chem. Commun.* **1994**, 1517-1518.
- [25] a) S. Marinković, N. Hoffmann, *Chem. Commun.* **2001**, 1576-1578; b) S. Marinković, N. Hoffmann, *Eur. J. Org. Chem.* **2004**, *2004*, 3102-3107.
- [26] M. A. Henderson, *Surf. Sci. Rep.* **2011**, *66*, 185-297.
- [27] a) C. Deiana, E. Fois, S. Coluccia, G. Martra, *J. Phys. Chem. C* **2010**, *114*, 21531-21538; b) C. Salazar, M. A. Nanny, *J. Catal.* **2010**, *269*, 404-410.

- [28] S. H. Szczepankiewicz, A. J. Colussi, M. R. Hoffmann, *J. Phys. Chem. B* **2000**, *104*, 9842-9850.
- [29] A. A. Poeylout-Palena, S. A. Testero, E. G. Mata, *Chem. Commun.* **2011**, *47*, 1565-1567.
- [30] C. Walling, G. M. El-Taliawi, C. Zhao, *J. Am. Chem. Soc.* **1983**, *105*, 5119-5124.
- [31] R. Ito, N. Umezawa, T. Higuchi, *J. Am. Chem. Soc.* **2004**, *127*, 834-835.
- [32] R. Kocz, J. Roestamadji, S. Mobashery, *J. Org. Chem.* **1994**, *59*, 2913-2914.
- [33] C. Brulé, J.-P. Bouillon, C. Portella, *Tetrahedron* **2004**, *60*, 9849-9855.
- [34] S. Montanaro, D. Ravelli, D. Merli, M. Fagnoni, A. Albini, *Org. Lett.* **2012**, *14*, 4218-4221.

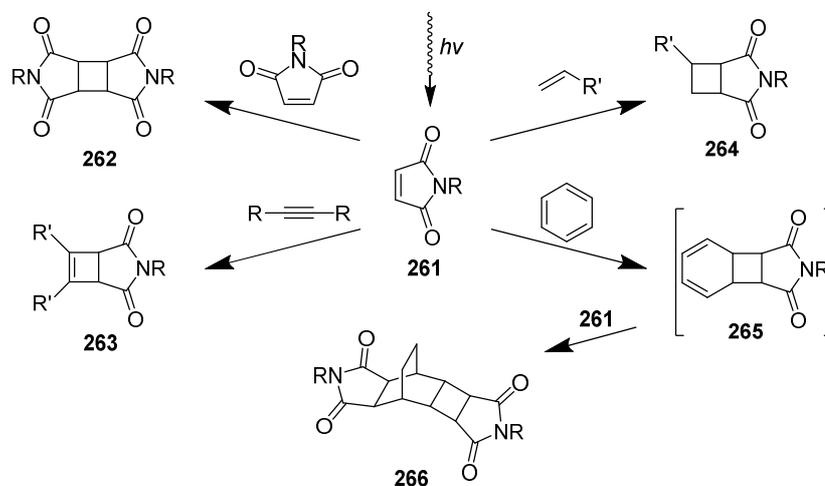
## **Chapter 4:**

# **Catalyst-Free Photoredox Addition– Cyclisations**

## 1.0 Introduction

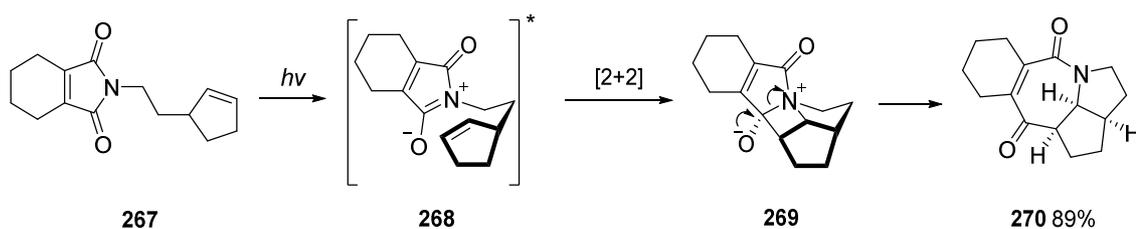
During investigations into the TiO<sub>2</sub> photo-mediated addition-cyclisations discussed in chapter 3 (pg 93-169) control photolyses uncovered that the titania photoredox catalyst was not required for reaction to take place with certain reaction partners. Because reactions that facilitate homolytic photodecarboxylation at benign wavelengths of light are highly desirable (see pg 23 for discussion) it was decided to attempt to develop this phenomenon into a synthetically useful protocol. Generally this was observed to take place when acids bearing electron rich aryl rings were partnered with certain maleimides.

Maleimides **261** possess a highly varied and interesting photochemistry. Their [2+2] photochemical dimerisation to form cyclobutane adducts **262** has long been established.<sup>[1]</sup> Furthermore, their [2+2] photocycloadditions with various olefinic,<sup>[2]</sup> acetylenic<sup>[3]</sup> and aromatic<sup>[4]</sup> moieties has also been well documented. In the latter case the initial cyclobutane product is the diene **265** which undergoes a [4+2] thermal cycloaddition with a second molecule of the highly dienophilic **261** to yield polycyclic final product **266** (Sch. 1).



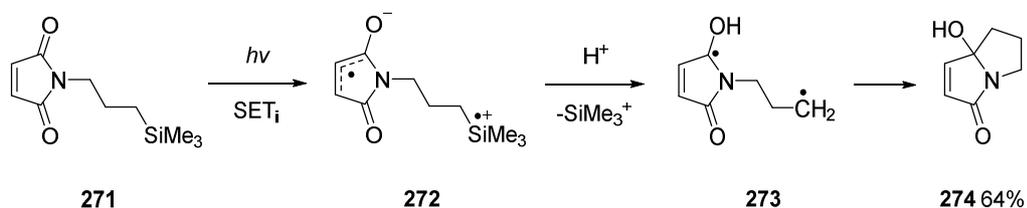
Scheme 1

More recently, the Booker-Milburn group reported the transformation of a series of *N*-substituted maleimides to perhydroazaazulenes, for instance **270**, upon UV irradiation.<sup>[5]</sup> It is postulated that the reaction proceeds *via* a [2+2] photocycloaddition between the amide resonance and the alkene moiety on the *N*-alkyl chain of excited intermediate **268** followed by spontaneous fragmentation to yield the final product (Sch. 2). The same research group also reported the photochemical synthesis of fused, polycyclic 1,3-diazepines in a similar process by replacing the alkene of the *N*-alkyl group with various imine functionalities.<sup>[6]</sup>



**Scheme 2**

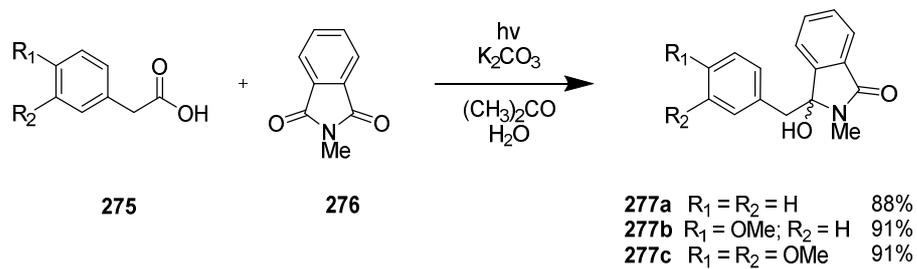
In each of these examples the maleimide is participating in a formal cycloaddition following photo-excitation. This is by far the most common mode in which they are employed in photochemical syntheses. There are however other, less well-known, reaction pathways in which excited maleimide species can be utilised synthetically. The radical chemistry of maleimides is widely thought to stem from their ability to act as hydrogen abstractors in their excited states.<sup>[7]</sup> For example, the photochemical additions of various alcohols to the maleimide C=C bond, furnishing the corresponding succinimides, exploits this ability.<sup>[8]</sup> Furthermore, in describing the preparation of a variety of functionalised nitrogen heterocycles (**274** for instance) from *N*-silylalkyl maleimides Mariano and co-workers proposed that singlet excited maleimide acts as a photo-oxidant (Sch. 3).<sup>[9]</sup>



**Scheme 3**

Although examples of this reaction pathway are relatively scarce for the maleimide chromophore, the propensity of the closely related phthalimide chromophore to carry out photo-electron-transfers of this nature has been extensively documented. In particular, Griesbeck and co-workers have published a great number of syntheses utilising phthalimide photo-oxidation of carboxylic acids with subsequent photodecarboxylation and radical addition.<sup>[10]</sup> The benzylation of a range of *N*-substituted phthalimides **276** in yields of 86-96% (as illustrated in Sch. 4) is just one example.<sup>[11]</sup> In this case the photo-excited *N*-methyl phthalimide oxidises the carboxylate of **275**, thus generating a benzyl radical upon decarboxylation. Recombination of this benzyl radical with the phthalimide radical anion

followed by protonation yields the desired adducts **277**.



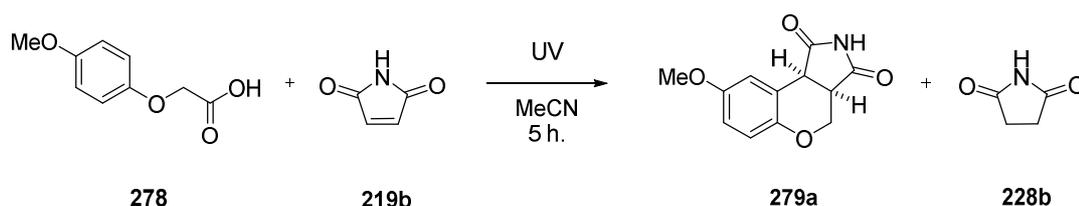
**Scheme 4**

The aim of this work is to explore this, thus far, unexploited reaction pathway for the maleimide chromophore as a means of carrying out photoredox chemistry with carboxylic acids without the need to employ catalyst or sensitising agent.

## 2.0 Results & Discussion

### 2.1 Reaction Optimisation

One such case was the reaction between 4-methoxyphenoxyacetic acid **278** and unsubstituted maleimide **219b** shown in Sch. 5. The reaction was relatively clean, with succinimide **228b** the only by-product identified, and it was decided to use it as a test-bed in attempts to optimise the process.



Scheme 5

Early work indicated that the reaction generally needed to be run overnight in order to achieve complete conversion. However, for the purposes of optimisation, a sub-optimum reaction time of 5 hours was adopted to better facilitate comparison of results. Degassed solutions of **278** and **219b** were irradiated with UVA through Pyrex for this sub-optimum reaction time in order to determine the stoichiometry and ideal reaction medium. These results are summarised in Tables 1 and 2 below.

<b>278</b> (mol eq.)	<b>219b</b> (mol eq.)	% Conversion <sup>a</sup>	% Yield <b>279a</b> <sup>a</sup>	% Yield <b>228b</b> <sup>a</sup>
1	1	28	22	13
1	2	51	33	9
1	4	66	41	5
1	10	nd <sup>b</sup>	nd	nd

**Table 1.** <sup>a</sup> determined from the NMR spectra of the reaction mixture by integration relative to a known amount of a CH<sub>2</sub>BR<sub>2</sub> standard; <sup>b</sup> could not be determined as the NMR sample repeatedly failed to shim.

A minimum five-fold excess of **219b** was found to be necessary for the reaction to run to completion. When less than five equivalents were used, they were entirely consumed before **278** could be fully converted to **279a**. Succinimide **228b** was the only by-product identified, but this accounted for <20% of **219b** used. Upon photolysis it is thought that **219b** polymerises in competition with the addition-cyclisation process and this accounts for the rest of the **219b** consumed. Maleimides photo-polymerise very readily as they exhibit the capability to act as both a photoinitiator and as a polymerisable monomer.<sup>[12]</sup> Under our

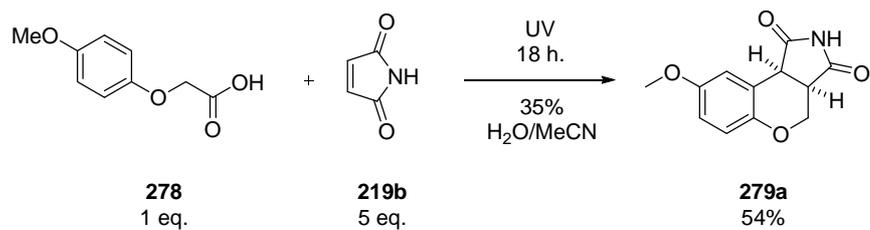
experimental conditions little to none of the [2+2] photodimer of maleimide was observed.

Solvent <sup>a</sup>	% Conversion <sup>b</sup>	%Yield <b>279a</b> <sup>b</sup>	% Yield <b>228b</b> <sup>b</sup>
CH <sub>3</sub> CN <sup>c</sup>	66%	41%	5%
CH <sub>3</sub> OH <sup>c</sup>	60%	40%	5%
t-BuOH	44%	37%	5%
Acetone	15%	12%	<5%
DMF <sup>d</sup>	nd	<5%	<5%
DCM <sup>c</sup>	nd	<5%	<5%
Benzene	nd	<5%	<5%
H <sub>2</sub> O	nd	<5%	<5%
35% H <sub>2</sub> O/MeCN	84%	61%	5%

**Table 2.** <sup>a</sup> solvents used as purchased unless stated; <sup>b</sup> determined from the NMR spectra of the reaction mixture by integration relative to a known amount of a CH<sub>2</sub>BR<sub>2</sub> standard; <sup>c</sup> anhydrous – distilled over CaH<sub>2</sub>; <sup>d</sup> purchased anhydrous.

Solvent screening revealed that the reaction generally proceeded well in polar media. Alcohols showed no improvement in yield and poorer conversions of acid starting material when compared with CH<sub>3</sub>CN, similarly acetone showed a significant decrease in both. Non-polar solvents CH<sub>2</sub>Cl<sub>2</sub> and benzene showed traces of products but mostly unreacted starting material. This was also the case for water. The polar nature of the reagents being used meant that they exhibited poor solubility when apolar reaction media were employed and this, in combination with the fact that electron transfer processes take place more readily in polar environments, is thought to be the reason for the trend observed. The optimum reaction medium was found to be 35% water in acetonitrile. Mariano and co-workers have demonstrated the beneficial effects of this solvent system during the aforementioned study on the intramolecular photochemistry of *N*-substituted maleimides.<sup>[9]</sup>

Based on these observations the optimum reaction conditions were determined to be as follows: 0.75 mmol of the acid component with 5 to 10 molar equivalents of maleimide **219b** in 20 mL 35% H<sub>2</sub>O/MeCN irradiated overnight with UVA using twelve Philips Cleo 15 W tubes after being degassed by bubbling with argon. When **279** and **219b** were subject to photolysis under these conditions (Sch. 6) the product **279a** was isolated in a pleasing yield of 54%.

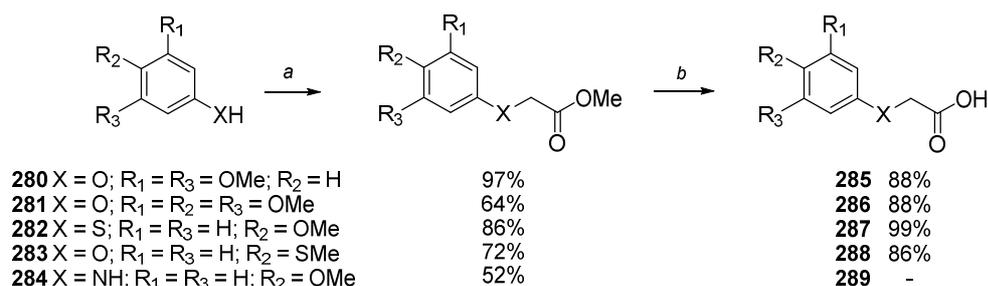


**Scheme 6**

When *N*-methylmaleimide **219c** was used in place of **219b**, its [2+2] dimerisation was the dominant process observed. Even when employing a ten-fold excess of **219c** over **278** a mere 30% conversion of the acid component **278** to chromenopyrroledione **279a** was observed by the time **219c** was entirely consumed. *N*-Phenylmaleimide **219d**, and the related maleic anhydride **219a** were found to be unreactive upon photolysis with our setup. Thus, it was decided to explore the photochemistry of unsubstituted maleimide **219b** with a range of aryloxy-, arylthio- and anilino-acetic acids.

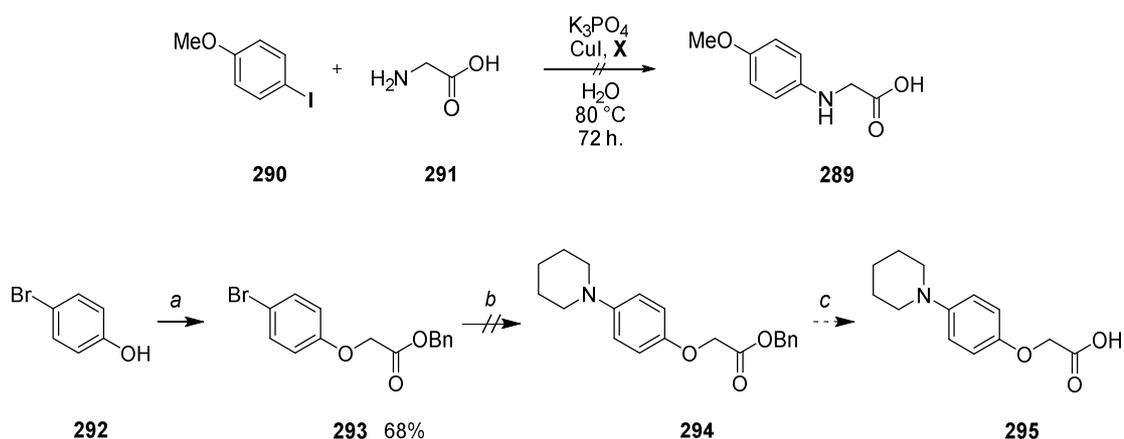
## 2.2 Preparative Addition-Cyclisations

Where possible commercially available carboxylic acids were used. For acids **285**, **286**, **287** and **288** the corresponding phenol or thiols was coupled to methyl bromoacetate in a straightforward S<sub>N</sub>2 reaction. Subsequent basic hydrolyses afforded the desired phenoxyacetic and phenylthioacetic acids in yields ranging from 56-85% (see Sch. 7). This approach was also employed in attempts to prepare the *N*-(4-methoxyphenyl)glycine precursor **289**. The initial alkylation was reasonably successful with the ester intermediate being isolated in a 52% yield from a tar-like crude reaction mixture following several recrystallisations. This ester was then subjected to hydrolysis with LiOH as before. The NMR spectrum of the total reaction mixture following work-up showed that the desired acid **289** had indeed been formed but attempts to isolate it by recrystallisation met with failure. Dissolution in hot EtOH and subsequent cooling resulted in the precipitation of a brown tar. NMR analysis of this, and the supernatant EtOH, revealed complex mixtures in which it was not clear if **289** was still present.



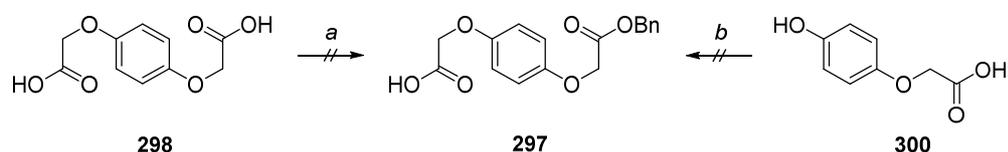
**Scheme 7.** Conditions - *a*: BrCH<sub>2</sub>CO<sub>2</sub>Me, K<sub>2</sub>CO<sub>3</sub>/NaOAc; *b*: LiOH, 3:1 MeOH/H<sub>2</sub>O.

An alternative preparation of **289** was thus required. Tweig and co-workers have reported a mild, copper catalysed amination of aryl halides employing water as solvent and 2-dimethylaminoethanol as ligand.<sup>[13]</sup> Using this approach *N*-phenylglycine was prepared in 87% yield from iodobenzene and glycine. Based on this success *para*-methoxyiodobenzene **290** was reacted with glycine **291** in the same fashion in attempt to prepare **289**. Analysis of the subsequent reaction mixture, again a brown/black tar, showed a multitude of peaks – none of which could be attributed to **289**. In an effort to see if amino substitution at the *para* position of the aromatic ring proved more feasible the preparation of 4-(piperidin-1-yl)phenoxyacetic acid **295** was investigated (Sch. 8, bottom). Alkylation of bromophenol **292** with benzyl bromoacetate proceeded in 68% yield. An adaptation of the Ullmann coupling reported by Buchwald, using the  $\beta$ -diketone 2-isobutyrylcyclohexan-1-one **296** as ligand, was employed to aminate the 4-position of **293**.<sup>[14]</sup> This approach was also unsuccessful.



**Scheme 8.** Attempted syntheses of arylacetic acids bearing amine substituents. Top: copper-catalysed alkylation of glycine. Bottom: alkylation of 4-bromophenol and subsequent Ullmann coupling. Conditions – *a*: BrCH<sub>2</sub>CO<sub>2</sub>Bn, K<sub>2</sub>CO<sub>3</sub>; *b*: piperidine, CuI, K<sub>3</sub>PO<sub>4</sub>, 296; *c*: H<sub>2</sub>, Pd/C.

It was undertaken to prepare **297**, the mono-benzyl ester of hydroquinone-*O,O'*-diacetic acid **298**, by two different approaches. Firstly the diacid **298** was reacted with a sub-stoichiometric amount of benzyl alcohol and the coupling reagent EDC. This, however, led to formation of exclusively the diester **299** in a diminished yield of 15% (Scheme 9, left). Secondly, attempts to alkylate 4-hydroxyphenoxyacetic acid **300** with benzyl bromoacetate were also unsuccessful (Scheme 9, right).

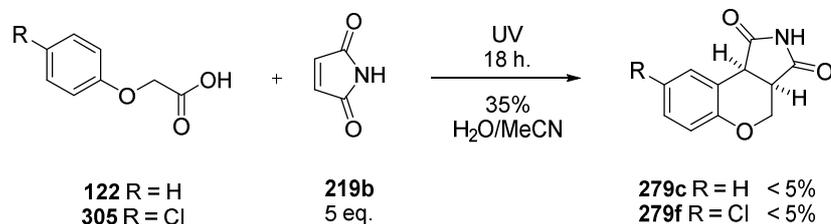


**Scheme 9.** Attempted syntheses of **297**. Conditions – *a*: EDC, BnOH, DMAP; *b*: BrCH<sub>2</sub>CO<sub>2</sub>Bn, K<sub>2</sub>CO<sub>3</sub>.

The preparative photolyses were typically carried out in the manner described above (pg. 175) using the optimised reaction conditions. Following the removal of solvent by rotary evaporation, reaction mixtures were analysed using NMR and GC-MS. Here the inherent advantage of not using a photoredox catalyst was seen in that purification of the reaction mixture was simplified without the necessity to remove it by potentially time consuming purification. Isolated yields for successful photolyses were obtained after column chromatography and are discussed below.

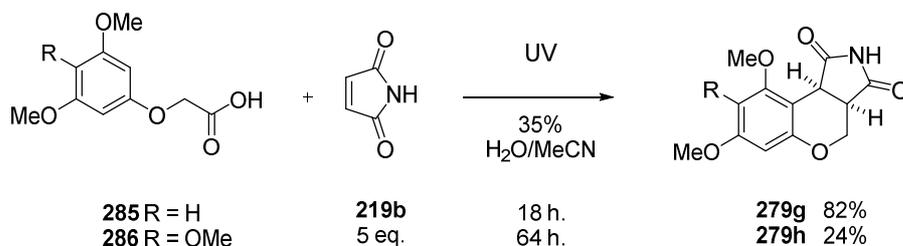


after an extended irradiation period of 25 hours. **304**, the *tert*-butyl analogue, performed more favourably and was converted to **279e** in a moderate yield of 54% after only 18 hours photolysis (Sch. 11).



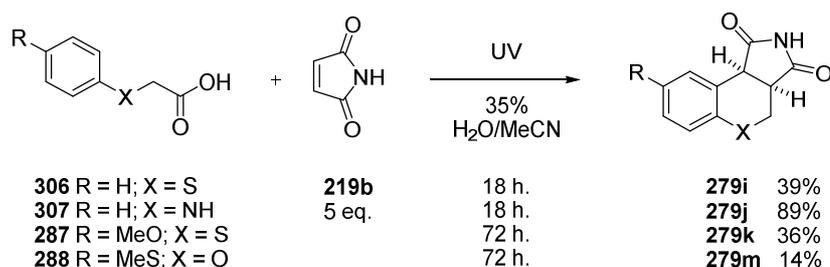
**Scheme 12**

Unsubstituted phenoxyacetic acid **122** proved unreactive under these preparative conditions. Subsequent to irradiation for 18 hours no evidence for product formation was observed following scrutiny of the reaction mixture by  $^1\text{H}$  NMR and GC-MS analyses. The expected product **279c** was however detected during *in-situ* NMR experiments (*vide infra* pg 184-187). It was next decided to probe the effects of the inclusion of electron withdrawing substituents in the aryl ring of the acid component. As was the case with the unsubstituted acid **305** this approach proved to be unsuccessful. Incorporation of a 4-chloro substituent in acid **305** resulted in <5% of the desired product **279f** being observed by NMR (Sch. 12).



**Scheme 13**

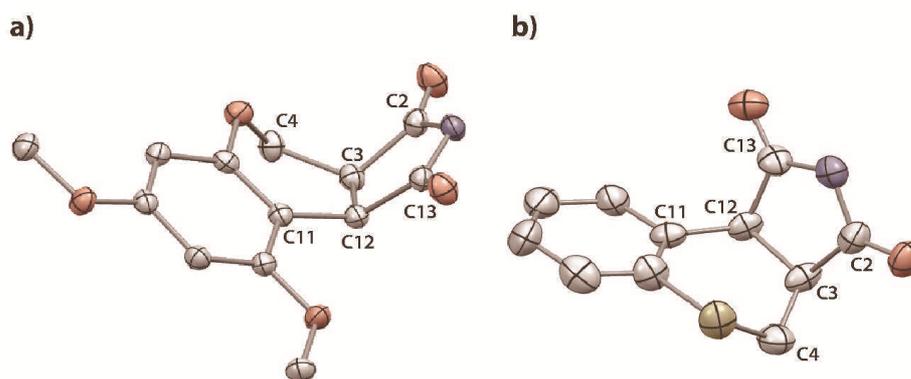
Inclusion of methoxy substituents at both of the *meta*-positions of **285** removed the possibility for the formation of regioisomers and gave the corresponding di-substituted product **279g** in an excellent yield of 82%. Rather surprisingly, **286**, the 3,4,5-trimethoxy analogue of **285**, did not exhibit the same behavior. Following 64 hours irradiation only 24% of **279h** was isolated and only 29% of **286** had been consumed. This reaction outcome was confirmed by repeat photolysis.



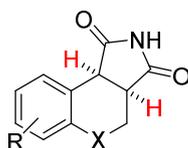
**Scheme 14**

Variation of the heteroatoms on the ring substituents and *beta* to the carboxylate moiety were next investigated. Unsubstituted phenylthioacetic acid **306** was more reactive than its oxy-analogue **122**, giving the corresponding thiochromenopyrroledione **279i** in a moderate yield of 39%. *N*-Phenylglycine **307** on the other hand was converted to the pyrroloquinolinedione derivative **279j** in an excellent yield of 89%, greatly outperforming its oxy- and thio- analogues in doing so. Unfortunately the preparation of acid starting materials containing nitrogen substituents proved unsuccessful (pg 177-178). It was anticipated that, as with the phenoxyacetic acids, introduction of a methoxy substituent to the phenyl ring in **306** would improve the yield and conversion. However it turned out that less **279k** than **279i** was actually isolated. Acid **288**, the methylthio-analogue of **287**, also performed comparatively poorly. Full conversion of the starting acids **287** and **288** was recorded in both instances.

Chromenopyrroledione **279g** and thiochromenopyrroledione **279i** formed crystals of suitable quality for X-ray crystallography upon dissolution in a hot mixture of cyclohexane/acetone and subsequent cooling in a sealed vessel. Analysis of the crystallographic structures obtained (Fig. 1) confirmed the tricyclic arrangement assigned to the products. Both **279g** and **279i** adopted a *cis*-geometry at the ring juncture between the newly formed six-membered heterocycle and the pyrroledione ring system. The lengths of the newly formed bonds were close to expectation, falling in the range of 1.50 Å to 1.53 Å. The bond angles between the five and six membered rings were also as expected, all being between 108° and 113°, indicating that the two carbon atoms at the bridge between the two ring systems were close to tetrahedral. Finally, the torsion angles between the two hydrogen atoms on the junction were observed to be 1.3° and 10.0° for **279g** and **279i** respectively. From the <sup>1</sup>H NMR spectra of the isolated products it was observed that the <sup>3</sup>J<sub>H-H</sub> coupling constants between these two protons all fell within the range of 9.2 - 9.7 Hz (Table 3), in agreement with the deduction that the reaction selectively forms the *cis*-isomer in each case.



**Figure 1.** The X-ray crystal structures of chromenopyrroledione **279g** (a) and thiochromenopyrroledione **279i** (b). Selected bond lengths, bond angles and torsion angles: **279g**: C3-C4 1.517(2) Å, C11-C12 1.508(2) Å, C2-C3-C4 112.5(1)°, C11-C12-C13, 110.2(1)°, H3-C3-C12-H12 1.3(2)°; **279i**: C3-C4 1.52(2) Å, C11-C12 1.53(1) Å, C2-C3-C4 111.2(9)°, C11-C12-C13, 108.2(9)°, H3-C3-C12-H12 10.0(1)°.

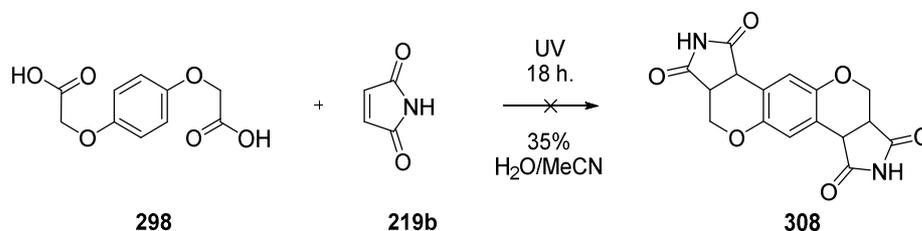


Entry	Product	R	X	$^3J_{\text{H-H}}$ (Hz)
1	<b>279a</b>	4-MeO	O	9.4
2	<b>279b</b>	3-MeO	O	9.2 ; 9.7 <sup>a</sup>
3	<b>279c</b>	H	O	9.2
4	<b>279d</b>	Me	O	9.2
5	<b>279e</b>	<sup>t</sup> Bu	O	9.2
6	<b>279g</b>	3,5-MeO	O	9.7
7	<b>279h</b>	3,4,5-MeO	O	9.7
8	<b>279i</b>	H	S	9.5
9	<b>279j</b>	H	NH	9.3
10	<b>279k</b>	4-MeO	S	9.4
11	<b>279m</b>	4-MeS	O	9.3

**Table 3.** Coupling constants between the protons at the ring junction in **X**. <sup>a</sup> 7-methoxy and 9-methoxy regioisomers respectively.

The fact that this process results in the formation of a complex, tricyclic product from relatively simple starting materials under benign conditions, allied to the synergistic cooperation between the acid and maleimide components, marks it as one with high synthetic potential. For example the various modes of ring opening of the pyrrole-dione ring system, aminolysis,<sup>[15]</sup> alcoholysis<sup>[16]</sup> or reaction with Grignard reagents,<sup>[17]</sup> to name a few, can be carried out to give diamides, amide/esters and  $\gamma$ -keto amides respectively. The imide *N*-H bond is a useful synthetic handle which could, for instance, be utilised as a nucleophile in the Mitsunobu reaction in order to obtain the *N*-alkylated derivatives.<sup>[17]</sup> Treatment with Red-Al

could reduce off the carbonyl groups to furnish the corresponding pyrrolidines,<sup>[18]</sup> opening up a variety of new reaction pathways in doing so. The cyclisation fixes the geometry at the ring junction as *cis* but, as there is no further stereo control involved, the products are formed as a mixture of the (*R,R*) and (*S,S*) diastereomers.

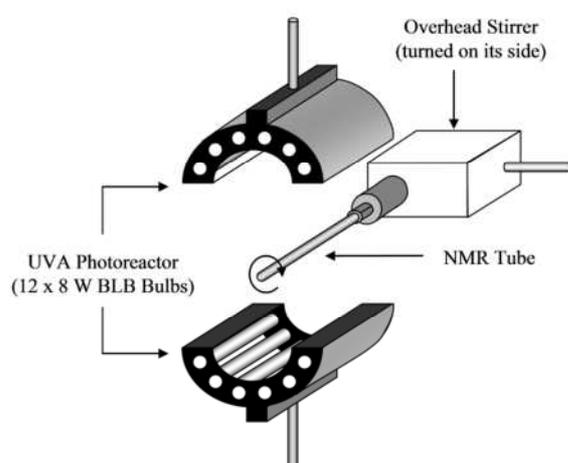


**Scheme 15**

It was envisaged that pentacyclic product **308** might be conveniently prepared from commercially available hydroquinone-*O,O'*-diacetic acid **298** and **219b** in two sequential addition-cyclisations (Scheme 13). **298** and **219b** were irradiated for 18 hours in 40 mL of 35% water/acetonitrile. <sup>1</sup>H NMR analysis revealed only a complex mixture that appeared to be dominated by polymeric material. No signals corresponding to either **308**, or the mono-cyclised intermediate, could be discerned. No signals corresponding to **298** were observed either, suggesting it had been entirely consumed. GC-MS analysis of the reaction mixture was unsuccessful as it was impossible to dissolve a sufficient quantity in a suitable solvent due to its polarity. Endeavors to prepare **297**, the mono-benzyl ester of **298**, to examine the possibility of performing a photolysis-deprotection-photolysis reaction sequence as a more successful route to **308**, failed.

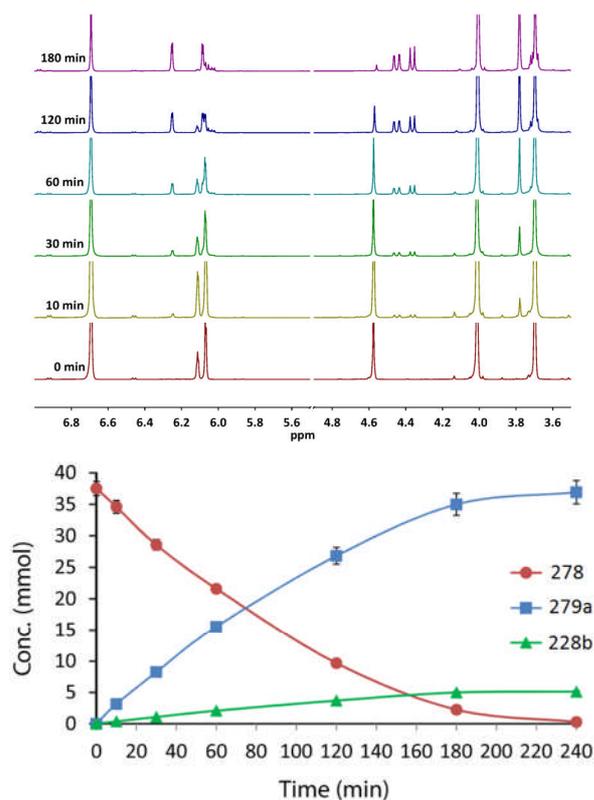
### 2.3 *In-situ* NMR monitoring

Supplementary to the preparative irradiations, a series of experiments to monitor reactant consumption and product formation were carried out by C. O'Rourke and Prof. A. Mills at Queens University Belfast using substrates supplied by us. *In-situ* NMR spectroscopy was the method of choice as it provided a simple, efficient and effective means of performing the desired measurements; analyses were relatively fast and sampling was not necessary. The high level of control associated with photochemical processes (*i.e.* the possibility to stop and start the reaction with the push of a button) made the addition-cyclisation process under study highly suitable for such an approach.



**Figure 2.** Irradiation setup for in-situ NMR monitoring.

The solutions used were identical in composition to those used in the corresponding preparative reaction, *i.e.* 37.5 mM of the acid and the corresponding amount of **219b**. Reactions were carried out on one twentieth the scale using 1 cm<sup>3</sup> of 35% deuterium oxide in *d*<sub>3</sub>-acetonitrile as the reaction medium. Typical reaction times were reduced from the region of 18 hours to 4 hours. Percentage conversions of maleimide **219b** and the acids as well as maximum yields and time taken to reach maximum yields for cyclic products **279** and succinimide **228b** were successfully measured.



**Figure 3.** The NMR spectra of the reaction mixture (top) taken at the marked intervals and the reaction profile (bottom) for photolysis of **278** and **219b**.

The  $^1\text{H}$  NMR spectra obtained at timed intervals during irradiation of acid **278** are shown in Fig. 3 (top). These spectra demonstrated how comparatively clean the reactions were. The growth in the signals at  $\delta$  4.36, 4.45 and aromatic signals at  $\delta$  6.25 with photolysis time showed the steady accumulation of the chromenopyrroledione product **279a**. The diminution of the signals from the acid **278** at  $\delta$  4.56 revealed its corresponding consumption. The resultant growth and decay curves are plotted in Figure 3 (top). This illustrates the practically mirror depletion of **278** and build-up of **279a** to a maximum in just 4 hours. The addition-cyclisation is accompanied by a steady formation of succinimide **228b** as disclosed by the growth of the signal at  $\delta$  2.61 (not shown in Fig. 3 top). Maleimide **219b** depletion has been omitted from the reaction profile for purposes of clarity. Similar profiles were obtained for all the acids.<sup>[19]</sup> The maximum yields of chromenopyrrolediones **279**, together with the corresponding photolysis times ( $t_{\text{max}}$ ), derived from the NMR studies are collected in Table 4.

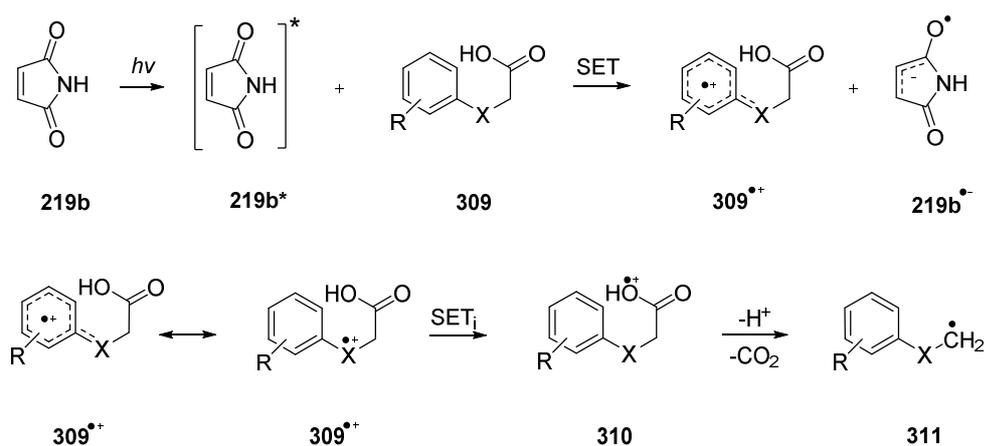
Entry	Acid	% Conv.	Max % yield 279	t <sub>max</sub> 279 (min.)	Max % yield 228b	t <sub>max</sub> 228b (min.)
1	<b>122</b>	88	7	420	>1	540
2	<b>278</b>	100	59	240	3	300
3	<b>285</b>	99	98	240	3	240
4	<b>286</b>	5	nd	240	nd	240
5	<b>287</b>	80	39	420	2	540
6	<b>288</b>	41	18	540	>1	540
7	<b>301</b>	100	94 <sup>a</sup>	180	3	240
8	<b>302</b>	98	54 <sup>b</sup>	240	1	240
9	<b>303</b>	100	47	180	3	240
10	<b>304</b>	100	46	540	3	540
11	<b>306</b>	98	41	180	4	240
12	<b>307</b>	97	96	90	3	120

**Table 4.** <sup>a</sup> Combined yield of 7-methoxy and 9-methoxy regioisomers (76% & 18% respectively); <sup>b</sup> Yield of **279c** (loss of MeO).

With a few minor exceptions, this data (Table 4) demonstrated generally good agreement of yields and conversions with those from the isolated components in the larger scale work.

## 2.4 Mechanistic Studies.

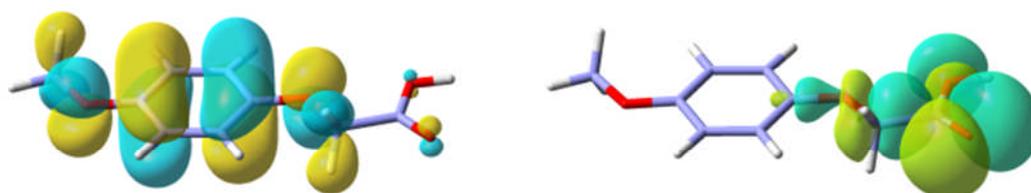
An intriguing mechanism is postulated, as outlined in Sch. 16 and 17. It is believed that **219b** is operating as a photo-oxidant, generating a radical ion pair (**219b<sup>•</sup>** and **309<sup>•+</sup>**) *via* SET from **309**. Upon photolysis, it is believed that **219b** transitions from the ground state to its excited state **219b<sup>\*</sup>** and accepts an electron from the electron rich aryl ring of **309** giving rise to the aryl radical cation **309<sup>•+</sup>** and the maleimide radical anion **219b<sup>•-</sup>**. This SET is thought to be favored by  $\pi$ - $\pi$  stacking interactions between **219b<sup>\*</sup>** and the aryl ring systems of **309**. The proximity of the carboxylate moiety of **309<sup>•+</sup>** to the aryl radical cation is such that an internal SET can easily take place, leading to the formation of unstable acyloxyl radical cation **310**. Precedent for such an internal SET exists; the research group of Young have reported that during the reaction of  $\text{SO}_4^{\bullet-}$  and a series of phenyl substituted carboxylic acids an electron transfer takes place from the carboxylate functional group to an aromatic radical cation or an intermediate species.<sup>[20]</sup>



Scheme 16

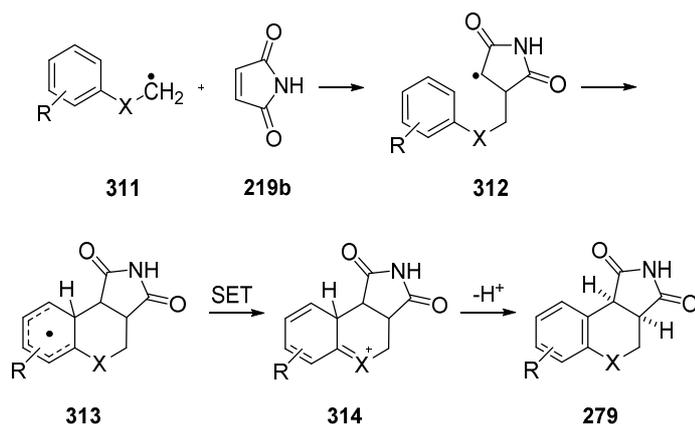
The maleimide radical anion **219b<sup>•-</sup>** is a known species and has previously been characterised by EPR<sup>[21]</sup> and UV-Vis<sup>[22]</sup> spectroscopy having been generated by treatment with reducing agents or photolysis under aqueous conditions. In our system the succinimide by-product of the reaction **228b** is thought to be formed from **219b<sup>•-</sup>**, likely via protonation and subsequent H-abstraction. To shed further light on the mechanism, DFT computations of the geometries and energies of the acids **309** and their radical cations **309<sup>•+</sup>** were carried out with the Gaussian 09 software suite.<sup>[23]</sup> The standard B3LYP functional<sup>[24]</sup> was employed together with 6-311+G(2d,p) and the triple-zeta quality aug-cc-pvtz basis sets. Geometries were fully optimised with the latter basis set. The CPCM polarisable conductor calculation model<sup>[25]</sup> was

then applied, with acetonitrile as the solvent, in an attempt to model the effect of solvent. For the radical cation of **278** the two computed frontier orbitals (HOMO-alpha and HOMO-beta, Fig. 4) corresponded quite closely to structures **278<sup>+•</sup>** and **278**. These demonstrate the ease with which internal electron migration from the carboxylate moiety into the aryl moiety could take place.



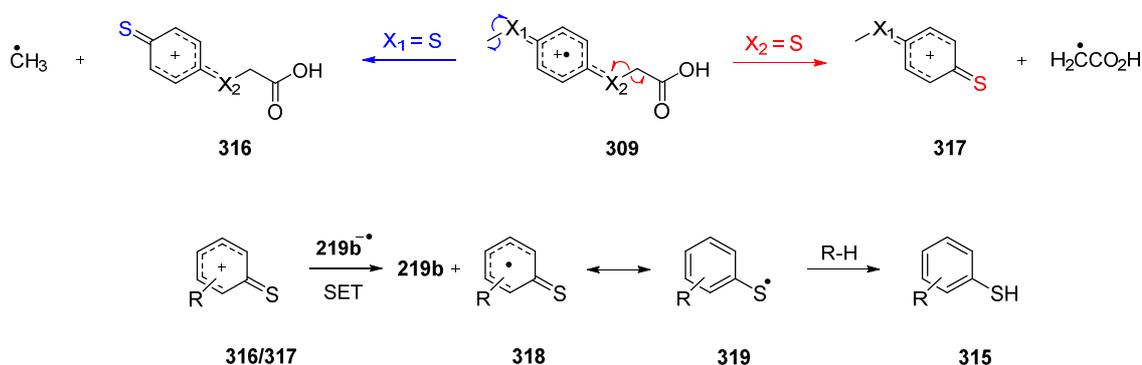
**Figure 4.** DFT optimised geometries of radical cations **278<sup>+•</sup>** and **278**. Computed at the UB3LYP/aug-cc-pvtz level: left; HOMO-alpha, right; HOMO-beta.

The ionisation energies (IE) of the acids obtained from the B3LYP/aug-cc-pvtz level computations in vacuum correlated well with the computed IEs including CPCM (solvent = acetonitrile). Both sets of IEs decreased as the electron releasing nature of the ring substituents increased (Table 5, pg 190). Interesting to note was that *cisoid*- and *transoid*-conformers of **278**, **286**, **287** and **288** were computed to have slightly different IE values. As expected, radical cation formation was easier as more electron-donating groups substituted the ring. However, the IE data did not correlate with the yields from the synthetic experiments. For instance, acids **286**, **287** and **288** have three of the lowest computed IE values of all the acids. However they also represent three of the poorest yields and conversions observed during the synthetic and NMR monitoring work. Therefore, it must be concluded that product formation is not entirely controlled by the ease of radical cation formation.



**Scheme 17**

In certain cases it is thought that the aryl radical cations are stabilised by the high degree of electron density that is present in the system, thus inhibiting the subsequent internal SET to **219b** and/or deprotonation with decarboxylation. Alternative reactions of **309<sup>•+</sup>** become competitive. In the case of **286** back electron transfer from **309<sup>•+</sup>** to **219b<sup>•-</sup>** is believed to be the competing pathway and this is borne out by the poor conversions of **286** and **219b** recorded for this photolysis. In some systems, particularly **287**, **288** and **306** low yields of **279** were recorded even though acid conversions were high. GC-MS analyses of reaction mixtures revealed only one additional product; the corresponding thiophenols **315**. We attribute this to a competing dissociation of radical cations **309<sup>•+</sup>** to  $\cdot\text{CH}_2\text{CO}_2\text{H}$  radicals (or  $\text{CH}_3\cdot$  radicals for **288<sup>•+</sup>**) and an aromatic cation which is reduced (possibly by **219b<sup>•-</sup>**) and converts to **315** after H-transfer (Sch. 18). This process is expected to compete particularly well due to the weak nature of the C-S bonds.



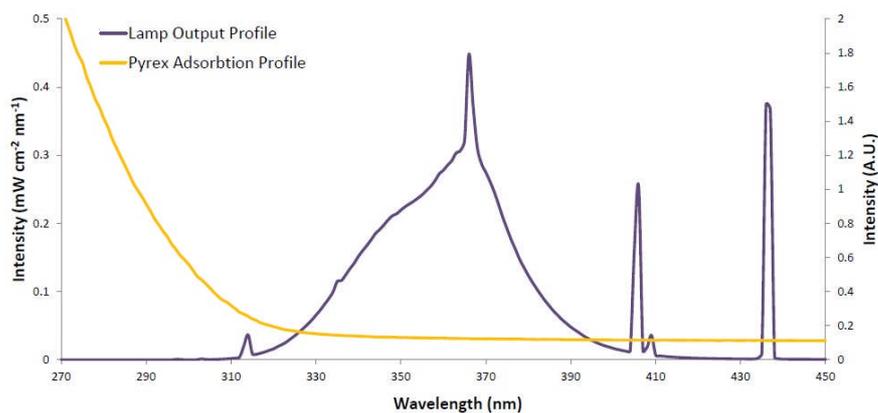
**Scheme 18**

It is the availability of the electron deficient C=C bond of **219b** that sets maleimides

aside from the related phthalimide chromophore, opening up a new avenue of chemical reactivity. This had been impossible to explore with phthalimide chromophore as it is flanked by an aromatic ring which precludes the type of molecular assembly occurring here. Proton loss from **310** followed by (or concerted with)  $\beta$ -scission and loss of CO<sub>2</sub> furnishes nucleophilic alkyl radical **311**. This species subsequently attacks another molecule of **219b** and the resultant adduct radical **312** ring closes onto the nearby aryl center. The cyclohexadienyl radical **313** formed then undergoes oxidative re-aromatisation to yield the final product **279**. Control reactions supported the postulated mechanism. The necessity of light was confirmed by stirring **278** and **219b** overnight in the dark; subsequent <sup>1</sup>H NMR and GC-MS analyses revealed only unreacted starting materials present. Acid **278** alone was similarly unreactive on photolysis through Pyrex; confirming the necessary presence of **219b** in order for photoredox chemistry to take place. As expected, photolysis of **320**, the benzyl ester of **278**, furnished **320<sup>•+</sup>** in the EPR experiments (*vide infra* pg 192-198) but proved unreactive when photolysed with **219b**, because the decarboxylation pathway was blocked. Furthermore the reaction proceeded much more favorably in polar reaction media and this is a hallmark of electron transfer processes.<sup>[26]</sup>

Entry	Compound	Ionisation energy (eV) <sup>a</sup>	$\lambda_{\max}$ (nm)	$\lambda_{\text{cutoff}}$ (nm) <sup>b</sup>	$\epsilon$ (L mol <sup>-1</sup> cm <sup>-1</sup> )
1	<b>219b</b>	-	269	351	652
2	<b>122</b>	6.28	269	309	971
3	<b>278</b>	5.69; 5.67 <sup>c</sup>	286	321	2529
4	<b>285</b>	6.01	246	286	482
5	<b>286</b>	5.17; 5.35 <sup>c</sup>	273	296	1099
6	<b>287</b>	5.53; 5.53 <sup>c</sup>	255	320	7307
7	<b>288</b>	5.53; 5.52 <sup>c</sup>	296	323	1295
8	<b>301</b>	6.01	278	291	1708
9	<b>302</b>	5.80	273	292	2119
10	<b>303</b>	6.00	281	294	1225
11	<b>304</b>	6.04	272	303	1229
12	<b>306</b>	5.99	246	302	6106
13	<b>307</b>	5.49	294	321	2120

**Table 5** <sup>a</sup> DFT method: UB3LYP/aug-cc-pvtz/CPCM-acetonitrile; IE values corrected to 298 K; <sup>b</sup> cut-off taken to be the point at which absorbance  $\leq 0.5$  A.U.; <sup>c</sup> *cisoid*- and *transoid*- conformers respectively see text.

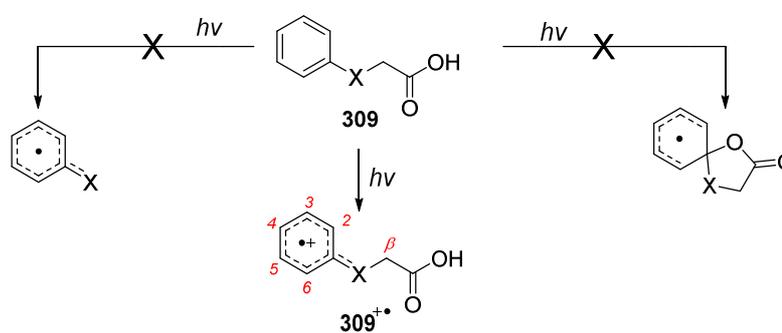


**Figure 5**

Molar absorbances of each of the acids and **219b** were determined using a range of concentrations from 10 mM down to 0.02 mM in acetonitrile, each measured using a 5 mm quartz cuvette. Absorption below 0.5 atomic units was deemed to be negligible and in this way absorption cut-offs ( $\lambda_{\text{cutoff}}$ ) were calculated (Table 5). Scrutiny of the lamp output profile of the photo-reactor and of the adsorption profile of Pyrex (Fig. 5) show that below approximately 325 nm no light can enter the reaction vessel. Examination of the UV-Vis data of all compounds used (Table 5) confirmed that **219b** was indeed the only compound capable of absorbing photons during the reactions and thus was the only photoactive species present. None of the acids was capable of adsorbing photons in the setup used and all were thus incapable of directly taking part in any photochemical processes.

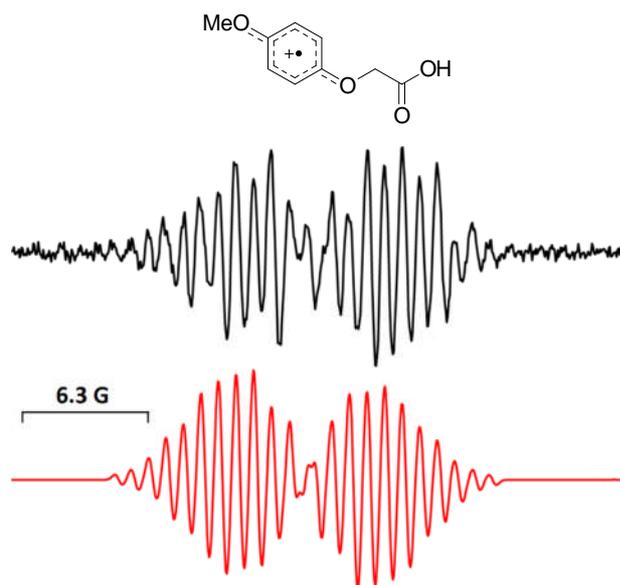
## 2.5 EPR Spectroscopy

Photolyses of acids, and their related esters, were studied by 9 GHz EPR spectroscopy to characterise radical intermediates generated in solution. Samples of each aryl-acetic acid or ester (ca. 10-20 mg) alone were dissolved or dispersed in solvent (0.5 cm<sup>3</sup>) de-aerated by bubbling N<sub>2</sub> for 15 min and then irradiated in quartz tubes directly in the spectrometer resonant cavity using a 500 W medium pressure mercury-arc lamp. In initial experiments, acetonitrile was used as solvent; but only very small samples in capillary tubes could be examined due to microwave absorption by the solvent. No well-defined spectra were obtained until much larger samples in benzene or *t*-butylbenzene solvent were employed.



**Scheme 19**

Figure 6 (top) shows the spectrum obtained from **278** after accumulating 20 scans at ambient temperature. This spectrum was simulated ( $R = 0.90$ ) with the EPR parameters listed in Table 6. The spectrum shown in Figure 6 is attributed to the radical cation of **278**. This is thought to form *via* direct photo-ionisation of the acid upon photolysis within the spectrometer cavity. Comparison of our hyperfine splittings (hfs) and  $g$ -factors (Table 6) with data available in the scientific literature enabled the possibility that we were observing spectra derived from phenoxy<sup>[27]</sup> or cyclohexadienyl radicals<sup>[28]</sup> to be discounted (Sch. 19).



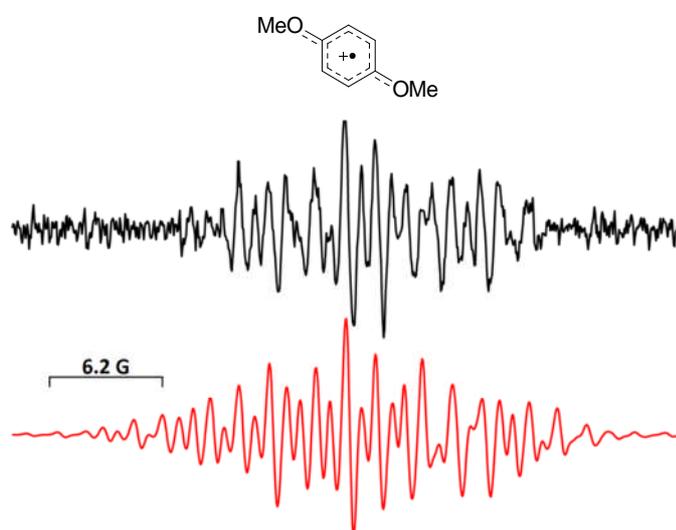
**Figure 6** EPR spectrum (top) obtained from the photolysis of 4-methoxyphenoxyacetic acid **278** at ambient temperature in PhH along with its computer simulation (bottom).

Radical Cation	Method	<i>g</i> -factor	<i>a</i> (2H <sup>β</sup> )	<i>a</i> (H <sup>2</sup> )	<i>a</i> (H <sup>3</sup> )	<i>a</i> (H <sup>4</sup> )	<i>a</i> (H <sup>5</sup> )	<i>a</i> (H <sup>6</sup> )
278 <sup>+•</sup>	Expt.	2.0039	2.6	1.9	0.8	1.7(3H)	4.8	0.8
278t <sup>+•</sup>	DFT	-	6.4	-2.7	-1.2	4.4(3H)	-3.1	-0.9
278c <sup>+•</sup>	DFT	-	6.1	-1.3	-1.3	4.2(3H)	-2.6	-2.6

**Table 6** Experimental and DFT computed EPR parameters for cation **278<sup>+•</sup>**. Spectra measured at 9.4 GHz in PhH solution at 300 K; HFS in Gauss; DFT computations at the UB3LYP/6-311+G(2d,p) level of theory; the signs of HFS cannot be obtained from CW EPR spectra.

When **278** was irradiated through a Pyrex filter, little to no signal was observed. This is attributed to the fact that the high energy light necessary to achieve the direct photo-ionisation of **278** could not penetrate the sample tube under these conditions. When maleimide **219b** was included in an otherwise identical sample of **278** in benzene and irradiated under the same conditions, again no signal was observed. It is believed that the SET process from **278** to **219b** is disfavored by the non-polar nature of the benzene solvent used. The species being observed are the same as those implicated in the postulated mechanism however, in spite of the fact that they are formed under slightly different conditions (pg 187, radical cation **309<sup>+•</sup>**). Direct photo-ionisation of the acid substrates can be discounted during the preparative work due to the fact that photolyses of acids **309** alone resulted in the detection of no products and only returned unreacted starting material. The key difference being that the preparative irradiation setup employs much less powerful lamps and relatively thick-walled Pyrex tubes; the combined effect of which precludes the involvement of the high-energy photons necessary to ionise **278** as occurs in the EPR experiments.

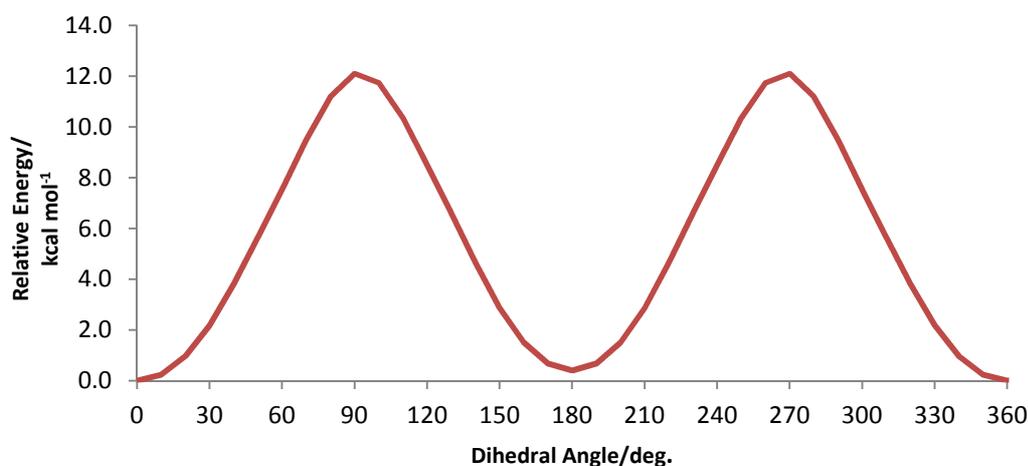
Irradiation of maleimide **219b** in the presence of TTF **11**, a known electron donor, inside the resonant cavity of the spectrometer led to the observation of a strong signal corresponding to the TTF radical cation.<sup>[29]</sup> No signal was observed when **219b** and **11** were examined in the dark, or when **11** was irradiated alone. This adds credence to the assertion that **219b** can act as a photo-oxidant under our conditions. Although the EPR spectrum of the maleimide radical anion **219b**<sup>•-</sup> was not observed, this should not be taken as evidence against its participation. The maleimide radical anion **219b**<sup>•-</sup> is transient<sup>[21a]</sup> so its concentration would be below the detection level under these conditions. On the other hand the **11**<sup>•+</sup> radical cations are comparatively persistent so their concentration builds to detectable levels.



**Figure 7** EPR spectrum (top) obtained from the photolysis of 1,4-dimethoxybenzene **321** at ambient temperature in PhH along with its computer simulation (bottom).

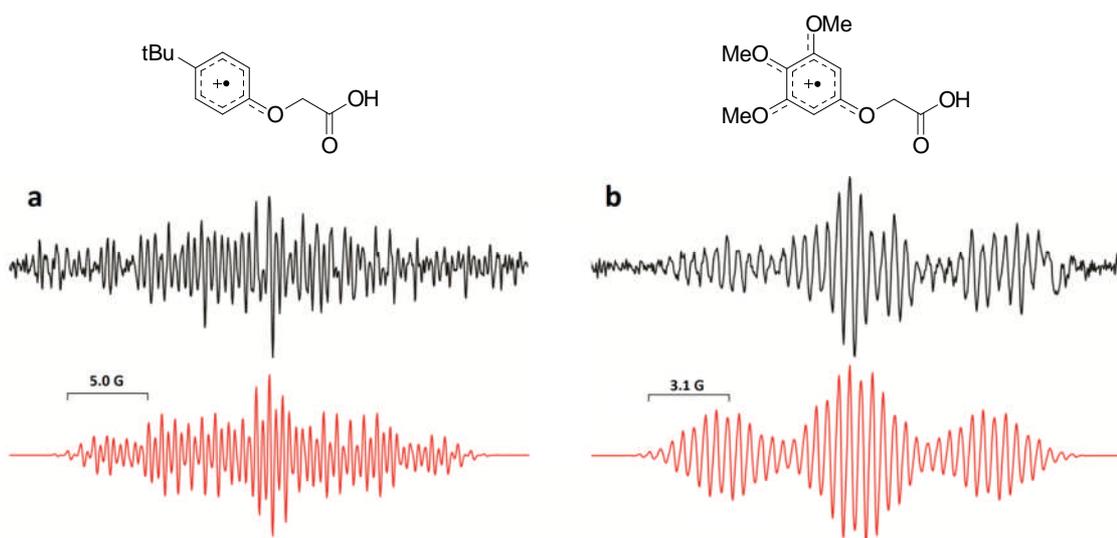
Radical cations of acids **309** had not previously been characterised by EPR spectroscopy but the *g*-factor and hfs were very similar to those reported for the radical cations of dimethoxybenzene **321**.<sup>[30]</sup> The aromatic core of this model compound is similar to that of 4-methoxyphenoxyacetic acid **278**. A pair of radical cations, with *transoid*- and *cisoid*-conformations of the two methoxy groups, having slightly different EPR spectra, were described for the oxidation of 1,4-dimethoxybenzene. However, very high resolution, not achieved in our spectra, was required to distinguish the two. DFT computations<sup>41</sup> of the structures and energies of the *transoid* and *cisoid* conformers of the radical cations **278t**<sup>•+</sup> and **278c**<sup>•+</sup> gave hfs in reasonable accord with experiment (Table 6, pg 193) and supported our identification. The difference in energy of the two conformers was computed to be < 0.5 kcal

$\text{mol}^{-1}$  with a sizable internal rotation barrier (twofold rotor with a  $12 \text{ kcal mol}^{-1}$  barrier, Figure 8). It is probable that all of the observed spectra are weighted averages of such conformers. When a sample of 1,4-dimethoxybenzene **321** in benzene was irradiated under our conditions an EPR spectrum very similar to those in the literature for the radical cation pair was observed (Figure 7 top). Simulation with two radical cations (*transoid* and *cisoid*) gave a fit of  $R = 0.79$  (bottom). One cation having 30% relative concentration, hfs of  $a(2\text{H}) = 1.8$ ,  $a(6\text{H}) = 3.0$ ,  $a(2\text{H}) = 3.8$  and a second 70% with  $a(2\text{H}) = 1.7$ ,  $a(6\text{H}) = 2.7$ ,  $a(2\text{H}) = 3.3 \text{ G}$ . This was further support that the spectra from acids **309** were due to radical cations.



**Figure 8.** Relative Energy vs. Dihedral Angle for Cation **278c\*\*** computed at UB3LYP/6-31G(d) level of theory.

Several acids and their ester derivatives yielded generally similar spectra upon irradiation within the resonant cavity of the spectrometer. All spectra were measured at ambient temperatures (typically *ca.* 300 K). Attempts to improve signal resolution by lowering the temperature resulted in much weaker and in most cases no signal being observed.



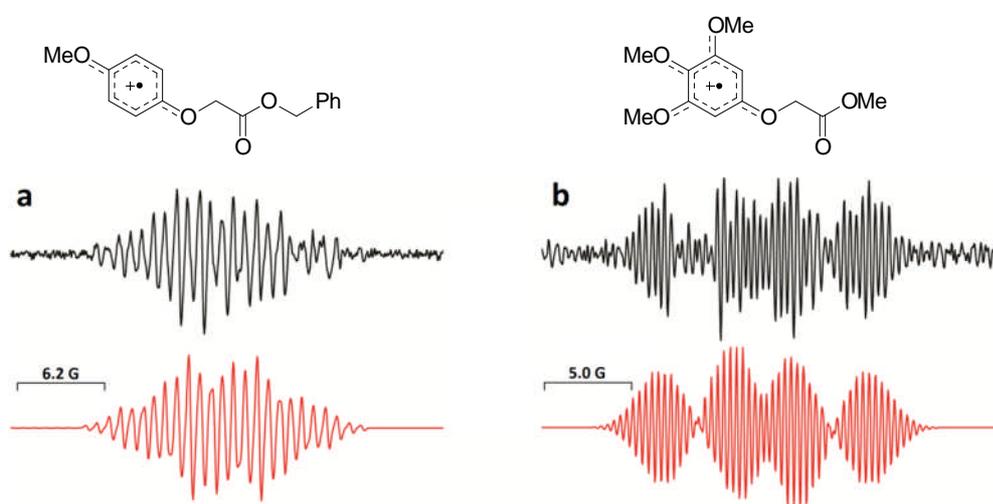
**Figure 9.** EPR spectra (black traces) obtained from the photolysis of 4-*tert*-butylphenoxyacetic acid **304** (a) and 3,4,5-trimethoxyphenoxyacetic acid **286** (b) at ambient temperature in PhH along with their computer simulations (red traces).

Radical Cation	Method	<i>g</i> -factor	<i>a</i> (2H <sup>β</sup> )	<i>a</i> (H <sup>2</sup> )	<i>a</i> (H <sup>3</sup> )	<i>a</i> (H <sup>4</sup> )	<i>a</i> (H <sup>5</sup> )	<i>a</i> (H <sup>6</sup> )
<b>304<sup>+•</sup></b>	Expt.	2.0036	6.3	3.6	1.0	13.3(3H)	1.0	2.6
	DFT	-	7.8	-4.2	0.6	16.7(3H)	-1.2	-2.5
<b>286c<sup>+•</sup></b>	Expt.	2.0030	6.7	3.4	0.7	0.8(9H)	1.2	2.1
	DFT	-	7.4	-4.2	0.4	0.9(9H)	-1.6	-2.0
<b>286t<sup>+•</sup></b>	Expt.	2.0040	5.2	1.3	0.4(3H)	0.9(3H)	0.4(3H)	0.9
	DFT	-	3.5	-1.5	1.6(3H)	5.7(3H)	2.1(3H)	-0.1

**Table 7.** Experimental and DFT computed EPR parameters for acid derived cations **304<sup>+•</sup>**, **286c<sup>+•</sup>** and **286t<sup>+•</sup>**. Spectra measured at 9.4 GHz in PhH solution at 300 K; hfs in Gauss; DFT computations at the UB3LYP/6-311+G(2d,p) level of theory; the signs of hfs cannot be obtained from CW EPR spectra.

The spectrum obtained after 100 scans during the photolysis of 4-*tert*-butylphenoxyacetic acid **304** in a PhH solution at ambient temperature is shown in Fig. 9a. The spectrum is somewhat difficult to discern from the noise due, in part, to the number of lines it is comprised of and to the weakness of the signal. None the less, the spectrum was simulated reasonably well ( $R = 0.70$ ) using the hfs listed in Table 7. To aid with the simulation DFT computations at the UB3LYP/6-311+G(2d,p) level of theory were employed. The hfs values computed in this way are also listed in Table 7. A much stronger spectrum (Fig. 9b) was observed upon photolysis of 3,4,5-trimethoxyphenoxyacetic acid **286** within the resonant cavity of the spectrometer in the same manner, although 100 scans were again required. This spectrum was simulated much more satisfactorily ( $R = 0.90$ ), again with the aid of DFT computed hfs. Generally good agreement was seen between the experimental and computed hfs. The exception to this was the hfs from *beta*-hydrogen atoms. These are very sensitive to the dihedral angle subtended about the C-X bond by the three bonds linking the H-atom to the

ring. The computed hfs are the values obtained for the single dihedral angle of the optimum geometry found by the DFT computation whilst the experimental EPR hfs are actually average values from all the dihedral angles the radicals access as they undergo internal motions in solution. This is the cause of the poor agreement. A very weak spectrum which could not satisfactorily be simulated ( $R = 0.35$ ; spectrum and simulation not shown) was obtained from the photolysis of 4-methylphenoxyacetic acid **303**. The experimental and computed parameters are listed in Table 7. No signals were discernible with samples of the unsubstituted phenoxyacetic acid **122**, the thio-analogue **306** or *N*-phenylglycine **307**. Broad spectra with  $g$ -factors of 2.0039, 2.0036 and 2.0034, appropriate for radical cations, were obtained from **285**, **301** and **302**. Possibly the poor resolution was due to broadening from exchange processes.



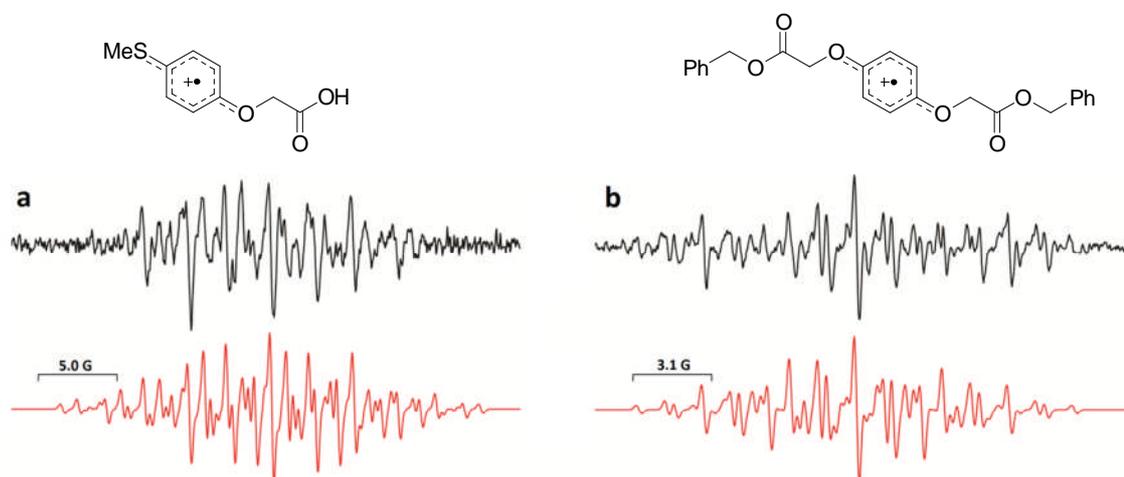
**Figure 10.** EPR spectra (black traces) obtained from the photolysis of benzyl 4-methoxyphenoxyacetate **320** (a) and methyl 3,4,5-trimethoxyphenoxyacetate **322** (b) at ambient temperature in PhH along with their computer simulations (red traces).

Radical Cation	$g$ -factor	$a(2H^{\beta})$	$a(H^2)$	$a(H^3)$	$a(H^4)$	$a(H^5)$	$a(H^6)$
<b>320<sup>+•</sup></b>	2.0041	3.2	1.7	0.8	1.7(3H)	4.9	0.8
<b>322<sup>+•</sup></b>	2.0037	4.1	3.2	0.4(3H)	1.1(3H)	0.7(3H)	1.1

**Table 8** Experimental and DFT computed EPR parameters for ester derived cations **320<sup>+•</sup>** and **322<sup>+•</sup>**. Spectra measured at 9.4 GHz in PhH solution at 300 K.

During the course of this investigation various esters of the acids were prepared. Interestingly, EPR spectra of the corresponding radical cations were also observed upon photolysis of benzene solutions of these compounds. **320**, the benzyl ester of 4-methoxyphenoxyacetic acid **278**, gave the spectrum shown in Fig. 10a upon photolysis. The

spectrum, which was recorded from only 12 scans, was simulated using the *hfs* listed in Table 8 and gave a fit in excess of 0.9. The radical cation of methyl 3,4,5-trimethoxyphenoxyacetate **322<sup>+•</sup>** was observed in a similar fashion (Fig. 10b). As with the related acid **286** the spectrum is the result of the accumulation of 100 scans. Simulation with parameters listed in Table 8 was satisfactory ( $R = 0.78$ ). Methyl 4-methylthiophenoxyacetate **323**, (Figure 11a) and **299**, the dibenzyl ester of hydroquinone-*O,O'*-diacetic acid **298** (Fig. 11b), both yielded interpretable spectra. The former was recorded after accumulating 50 scans and simulated with a fit of  $R = 0.75$  and the latter after 25 scans with  $R = 0.81$ . The parameters for these spectra are listed in Table 9. Obviously these ester radical cations cannot deprotonate, lose  $\text{CO}_2$  and generate the alkyl radicals **311**. This is thought to increase the persistence of cations **309<sup>+•</sup>** thus improving the quality of the spectra obtained. The much improved solubility of the esters in the PhH solvent when compared to the acids **309** is also believed to have been beneficial.



**Figure 11** EPR spectra (black traces) obtained from the photolysis of methyl 4-methylthiophenoxyacetate **323** (a) and dibenzyl 1,4-phenylenebis(oxy)diacetate **299** (b) at ambient temperature in PhH along with their computer simulations (red traces).

Radical Cation	<i>g</i> -factor	$a(2\text{H}^\beta)$	$a(\text{H}^2)$	$a(\text{H}^3)$	$a(\text{H}^4)$	$a(\text{H}^5)$	$a(\text{H}^6)$
<b>323<sup>+•</sup></b>	nd	2.8	1.0	1.4	5.2(3H)	1.8	1.0
<b>299<sup>+•</sup></b>	2.0039	3.4	1.5	1.1	2.6(2H)	1.1	1.5

**Table 9** Experimental and DFT computed EPR parameters for ester derived cations **323<sup>+•</sup>** and **299<sup>+•</sup>**. Spectra measured at 9.4 GHz in PhH solution at 300 K.

Our acid and ester derived radical cation spectra were much weaker than those described in the literature for alkoxybenzenes. The reason for this is that our species are believed to be formed as the result of direct photo-ionisation of acids **309** which is inefficient in the non-polar media used. In contrast, literature alkoxybenzene radical cations were all observed on treatment of the parent alkoxybenzene with an oxidising agent in a polar solvent.

### 3.0 Conclusions

A distinctive new reaction sequence for electron-rich aryloxy-, arylthio- and arylamino-acetic acids has been discovered whereby they decarboxylate, releasing alkyl radicals at a benign wavelength of light in the absence of a conventional photoredox catalyst. Maleimide synergistically acts as a radical generator and as a radical acceptor instigating a tandem addition-cyclisation process. Preparative scale irradiations enabled oxa-, thia- and azatricyclo pyroledione derivatives to be isolated. These products can therefore be prepared from relatively simple, readily available precursors and selectively form the *cis*-isomer in each case. The lack of necessity of a photoredox catalyst is highly pleasing from the viewpoint of subsequent purification as well as cost, availability and safety. Each reaction has been monitored by *in-situ* NMR spectroscopy, allowing reaction profiles to be obtained for each photolysis.

A plausible mechanism highlighting the key role of maleimide as the photoactive species has been postulated. SET from the acids to excited maleimide yielded radical cations which de-protonated and lost CO<sub>2</sub> thus supplying neutral C-centered radicals which took part in an addition-cyclisation cascade. Several of the novel acid-derived radical cations were characterised by EPR and the measured hfs showed good agreement with those computed by DFT. Maleimide was the essential UV-absorbing component as confirmed by UV-Vis spectroscopic investigations. Aryloxy-, arylthio- and arylamino-acetic acids were all suitable reaction partners which yielded the corresponding radical cations. Balance was required in the selection of substituents in the aromatic rings. Phenoxyacetic acid, with no ring substituent, and the 4-chloro-derivative with an electron-withdrawing substituent, delivered virtually none of the cascade product. Electron-releasing substituents in the aryl rings favored this step. However, over-substitution, as with the trimethoxyphenoxy-acid **286**, endowed the radical cations with inordinate stabilisation thus inhibiting dissociation and release the ArXCH<sub>2</sub>• radicals needed to set off the cascade.

## 4.0 Experimental

### 4.1 General Experimental Details – Instrumentation and Techniques

**NMR Spectroscopy:**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on Bruker AV III 500, Bruker AV II 400 and Bruker AV 300 instruments. Chemical shifts are reported in parts per million (ppm) from low to high frequency and referenced to the residual solvent resonance. Coupling constants ( $J$ ) are reported in hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s = singlet, d = doublet, t = triplet, dd = double doublet, q = quartet, m = multiplet, b = broad.

**Mass Spectrometry:** Low and high resolution mass spectrometry was carried out at the EPSRC National Mass Spectrometry Service Centre, Swansea on a LTQ Orbitrap XL Spectrometer equipped with an ultra-high-field Orbitrap mass analyser with resolving power up to 450,000 FWHM and isotopic fidelity up to 240,000 FWHM at  $m/z$  200.

**GC-MS:** GC-MS analysis was performed using a Thermo Electron Corporation Trace GC Ultra combined with a Thermo Electron Corporation DSQ II. A Restex Rxi<sup>®</sup>-1ms column (30m x 0.25 mm x 0.1  $\mu\text{m}$ ) was used for compound separation and the ionisation mode was set to electron impact (EI). Injection volumes were between 1 and 10  $\mu\text{L}$ , depending on signal strength. Parameters: injector temperature 220  $^\circ\text{C}$ ; split ratio 20:1; constant column flow 3.0  $\text{mL min}^{-1}$ . Temperature profile: initial temperature 50  $^\circ\text{C}$ , heating to 300  $^\circ\text{C}$  at 10 $^\circ\text{C min}^{-1}$ ; 4 min hold time; total time 29 min.

**Melting Point Analysis:** Melting points (M.p.) were determined using a Sanyo Gallenkamp apparatus and are reported uncorrected.

**Chromatography:** Column chromatography was carried out using Silica 60A (particle size 40-63  $\mu\text{m}$ , Silicycle, Canada) as the stationary phase, and TLC was performed on precoated silica gel plates (0.20 mm thick, Sil G UV<sub>254</sub>, Macherey-Nagel, Germany) and observed under UV light.

**Materials:** All reagents and solvents were purchased from Sigma Aldrich, Alfa Aesar or TCI Europe and used without further purification unless stated.

**Anhydrous Solvents:** Tetrahydrofuran was distilled over sodium. Dichloromethane, methanol and acetonitrile were distilled over calcium hydride. Dimethylformamide was purchased anhydrous from Sigma Aldrich.

**UV/Vis:** UV/Vis spectrometry was carried out using a Cary 50 spectrophotometer (Varian Inc.).

**EPR Spectroscopy:** EPR spectra were obtained at 9.5 GHz with 100 kHz modulation employing a Bruker EMX 10/12 spectrometer fitted with a rectangular ER4122 SP resonant cavity. Stock solutions of each acid (10 to 50 mg) in benzene or *tert*-butylbenzene (0.5 mL) were prepared and sonicated if necessary. An aliquot (0.2 mL), to which any additional reactant had been added, was placed in a 5 mm o.d. quartz tube and de-aerated by bubbling nitrogen for 15 min. Photolysis in the resonant cavity was by unfiltered light from a 500 W super pressure mercury arc lamp. In all cases where spectra were obtained, hfs were assigned with the aid of computer simulations using the Bruker SimFonia and NIEHS Winsim2002 software packages. EPR signals were digitally filtered and double integrated using the Bruker WinEPR software and radical concentrations were calculated by reference to the double integral of the signal from a known concentration of the stable radical DPPH [ $1 \times 10^{-3}$  M in PhMe], run under identical conditions. The majority of EPR spectra were recorded with 2.0 mW power, 0.8 G<sub>pp</sub> modulation intensity and gain of *ca.* 10<sup>6</sup>.

**X-Ray Crystallography:** Data was measured on Rigaku Mercury70 and Saturn70 diffractometers using Mo-K $\alpha$  radiation Cu-K $\alpha$  respectively. Data was collected and processed using CrystalClear (Rigaku). The structures are shown in the discussion.

**Computational Methods:** The ground-state geometries and energies of the precursor acids and their ions were investigated using the Gaussian 09 program package. The standard UB3LYP functional with the split-valence and with the aug-cc-pvtz basis sets was employed. Geometries were fully optimized with both basis sets without any symmetry constraints for all model compounds. Optimized structures were characterized as minima or saddle points by frequency calculations at the 6-311+G(2d,p) level. The experimental EPR data was all obtained in the non-polar hydrocarbon solvents *tert*-butylbenzene or benzene. Solvent effects, particularly differences in solvation between the neutral reactants and neutral transition

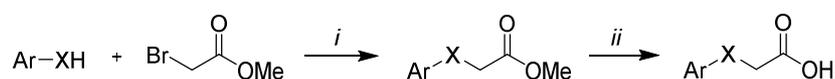
states, are therefore expected to be minimal for the EPR work. However, the addition/cyclisation reactions were carried out in acetonitrile/water. In an attempt to model the effect of solvent the CPCM polarizable conductor calculation model was then applied, with acetonitrile as the solvent, and with the aug-cc-pvtz basis set and geometry.

Gaussian 09, Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

***In-situ* NMR monitoring:** The reactions were carried out in NMR tubes with irradiations being in a similar manner to preparative work. In place of magnetic stirring, each NMR tube was clamped in a horizontally mounted stirrer and rotated at 250 rpm (Fig. 2, pg 184). The sample was irradiated and the tube removed periodically as needed to perform NMR analyses. Due to the fact that an internal standard could not be used in the NMR scale irradiations, concentrations of each of the products were determined using the acid as a reference. A series of accurately known standards of each acid was prepared and their NMR's were recorded. The areas of the singlet at 4.5 – 4.6 ppm (generated by the two protons *alpha* to the carboxylate moiety) were determined and plotted against concentration to obtain a straight line, *i.e.* similar to a Beer-Lambert calibration plot used to determine concentrations by UV/Vis spectrometry. This allowed the concentration of the acid to be determined during the progress of the subsequent reactions, which was then used effectively as an internal standard to determine the concentration of each of the other components.

## 4.2 Preparation of non-commercially available reagents

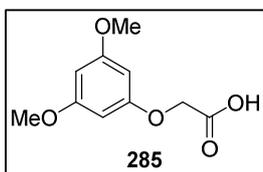
**General Procedure for the Preparation of Phenoxy- and Phenylthio-Acetic Acids 285, 286, 287 & 288:** To a solution of the phenol/thiol in was added methyl bromo acetate and potassium carbonate or sodium acetate at room temperature. The resultant mixture was refluxed at for 48-72 hours. The mixture was concentrated under reduced pressure, dissolved in 100 mL CH<sub>2</sub>Cl<sub>2</sub>, washed with H<sub>2</sub>O (3 x 100 mL), dried over MgSO<sub>4</sub> and the solvent removed under reduced pressure. To a solution of the resultant ester in MeOH/H<sub>2</sub>O (3:1 v/v) was added LiOH (5 equiv.) at room temperature and allowed to stir overnight. The reaction mixture was concentrated under reduced pressure, dissolved in 100 mL saturated (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, adjusted to ca. pH 3 and extracted with EtOAc (3 x 100 mL). The combined extracts were dried over MgSO<sub>4</sub> and the solvent removed under reduced pressure.



**Scheme 20.** Preparation of carboxylic acids. Reagents and conditions: (i)

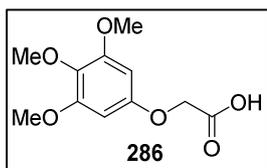
K<sub>2</sub>CO<sub>3</sub>, THF, reflux; (ii) LiOH, 3:1 MeOH/H<sub>2</sub>O, rt.

### 3,5-Dimethoxyphenoxyacetic acid 285



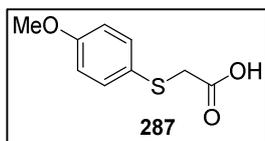
Prepared from 3,5-dimethoxyphenol (3.01 g, 20 mmol), methyl bromoacetate (6.12 g, 40 mmol) and potassium carbonate (13.82 g, 100 mmol) in 100 mL anhydrous THF. The resultant mixture was subjected to column chromatography on silica gel (eluent 50% CH<sub>2</sub>Cl<sub>2</sub> in pentanes) to yield methyl (3,5-dimethoxyphenoxy)acetate as an off white solid (4.43g, 97%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 294 K):  $\delta$  = 3.75 (s, 6H, ArO-CH<sub>3</sub>), 3.80 (s, 3H, OCH<sub>3</sub>), 4.59 (s, 2H, ArOCH<sub>2</sub>), 6.08 (m, 2H, ArH), 6.11 (m, 1H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 296 K):  $\delta$  = 52.7, 55.8, 65.6, 93.9, 94.3, 160.0, 162.0, 169.6. This ester (4.2 g, 18.6 mmol) was dissolved 135 mL CH<sub>3</sub>OH and 45 mL H<sub>2</sub>O in and subjected to hydrolysis by lithium hydroxide (9.48 g, 92.8 mmol) to yield **285** as an off-white solid (3.47 g, 88%). <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-acetone, 294 K):  $\delta$  = 3.75 (s, 6H, ArO-CH<sub>3</sub>), 4.13 (br-s, 1H, CO<sub>2</sub>H), 4.65 (s, 2H, ArOCH<sub>2</sub>), 6.11 (m, 3H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 295 K):  $\delta$  = 55.6, 65.5, 94.2, 94.3, 161.0, 162.6, 170.2. Data consistent with literature.<sup>[31]</sup>

### 3,4,5-Trimethoxyphenoxyacetic acid **286**



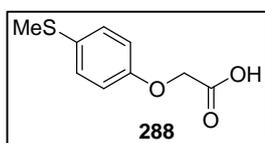
Prepared from 3,4,5-trimethoxy phenol (3.68 g, 20 mmol), methyl bromoacetate (6.12 g, 40 mmol) and potassium carbonate (13.82 g, 100 mmol) in 100 mL THF. The resultant mixture was subjected to column chromatography on silica gel (eluent  $\text{CH}_2\text{Cl}_2$ ) to yield methyl 3,4,5-trimethoxyphenoxyacetate as a colourless solid (3.27 g, 64%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 294 K):  $\delta$  = 3.70 (s, 3H,  $\text{OCH}_3$ ), 3.74 (s, 3H,  $\text{OCH}_3$ ), 3.75 (s, 6H,  $\text{ArOCH}_3$ ), 4.53 (s, 2H,  $\text{OCH}_2$ ), 6.10 (s, 2H,  $\text{ArH}$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , 295 K):  $\delta$  = 52.6, 56.5, 61.3, 66.1, 92.9, 133.4, 154.1, 154.7, 169.7. The ester (2.86 g, 11.1 mmol) was dissolved 90 mL  $\text{CH}_3\text{OH}$  and 30 mL  $\text{H}_2\text{O}$  in and subjected to hydrolysis by lithium hydroxide (5.67 g, 55.5 mmol) to yield **286** as an off-white solid which was recrystallized from (1:5) acetone/cyclohexane (2.36 g, 88%).  $^1\text{H}$  NMR (300 MHz, *d*6-acetone, 294 K):  $\delta$  = 3.64 (s, 3H,  $\text{ArOCH}_3$ ), 3.79 (s, 6H,  $\text{ArOCH}_3$ ), 4.52 (br-s, 1H,  $\text{CO}_2\text{H}$ ), 4.66 (s, 2H,  $\text{OCH}_2$ ), 6.27 (s, 2H,  $\text{ArH}$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , 295 K):  $\delta$  = 56.4, 60.6, 65.8, 93.7, 133.8, 154.8, 155.6, 170.4. Data consistent with literature.<sup>[31]</sup>

### 4-Methoxyphenylthioacetic acid **287**



Prepared from 4-methoxybenzenethiol (2.8 g, 20 mmol), methyl bromoacetate (6.12 g, 40 mmol) and potassium carbonate (13.8 g, 100 mmol) in 100 mL anhydrous THF. The resultant mixture was subjected to column chromatography on silica gel (eluent 50%  $\text{CH}_2\text{Cl}_2$  in pentanes) to yield methyl 4-methoxyphenylthioacetate as a colourless oil (3.64 g, 86%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 294 K):  $\delta$  = 3.51 (s, 2H,  $\text{SCH}_2$ ), 3.68 (s, 3H,  $\text{OCH}_3$ ), 3.78 (s, 3H,  $\text{ArOCH}_3$ ), 6.83 (d,  $J$  = 8.9 Hz, 2H,  $\text{ArH}$ ), 7.40 (d,  $J$  = 8.9 Hz, 2H,  $\text{ArH}$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , 296 K):  $\delta$  = 38.5, 52.4, 55.3, 114.7, 124.9, 134.2, 159.7, 170.4. This ester (3.0 g, 14.1 mmol) was dissolved 105 mL  $\text{CH}_3\text{OH}$  and 35 mL  $\text{H}_2\text{O}$  in and subjected to hydrolysis by lithium hydroxide (6.56 g, 71 mmol) to yield **287** as an off-white solid which was recrystallized from (1:10) acetone/cyclohexane (2.77 g, 99%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 296 K):  $\delta$  = 3.54 (s, 2H,  $\text{SCH}_2$ ), 3.79 (s, 3H,  $\text{ArOCH}_3$ ), 6.85 (d,  $J$  = 8.9 Hz, 2H,  $\text{ArH}$ ), 7.43 (d,  $J$  = 8.9 Hz, 2H,  $\text{ArH}$ ), 11.31 (br-s, 1H,  $\text{CO}_2\text{H}$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , 295 K):  $\delta$  = 38.6, 55.4, 114.8, 124.6, 134.3, 159.9, 176.3. Data consistent with literature.<sup>[32]</sup>

### 4-(Methylthio)phenoxyacetic acid **288**



Prepared from 4-(methylthio)phenol (2.80 g, 20 mmol), methyl bromoacetate (6.12 g, 40 mmol) and potassium carbonate (13.80 g, 100 mmol) in 100 mL THF. The resultant mixture was subjected to

column chromatography on silica gel (eluent 50% CH<sub>2</sub>Cl<sub>2</sub> in pentanes) to yield methyl 4-(methylthio)phenoxyacetate a colourless oil (3.07 g, 72%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 294 K): δ = 2.43 (s, 3H, ArS-CH<sub>3</sub>), 3.79 (s, 3H, CO<sub>2</sub>-CH<sub>3</sub>), 4.61 (s, 2H, ArO-CH<sub>2</sub>), 6.85 (m, 2H, ArH), 7.24 (m, 2H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 295 K): δ = 18.0, 52.7, 65.9, 155.8, 130.1, 130.8, 156.6, 169.7. This ester (2.50 g, 11.8 mmol) was dissolved 90 mL CH<sub>3</sub>OH and 30 mL H<sub>2</sub>O in and subjected to hydrolysis by lithium hydroxide (5.47 g, 59 mmol) to yield **288** as an off-white solid which was recrystallized from acetone/cyclohexane (1:10) to yield colorless needles (2.01 g, 86%). M.p. 108 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 296 K): δ = 2.45 (s, 3H, ArS-CH<sub>3</sub>), 4.67 (s, 2H, ArO-CH<sub>2</sub>), 6.86 (m, 2H, ArH), 7.26 (m, 2H, ArH), 9.54 (br-s, 1H, CO<sub>2</sub>H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 297 K): δ = 55.6, 65.5, 94.2, 94.3, 161.0, 162.6, 170.2; LR-ESIMS: *m/z* = 199 [MH]<sup>+</sup>; HR-ESIMS: *m/z* = 199.0424 (calcd. for C<sub>9</sub>H<sub>11</sub>O<sub>3</sub>S, 199.0429).

#### Attempted synthesis of 4-methoxyphenylglycine **289**

4-Methoxyaniline (2.47 g, 20 mmol), methyl bromoacetate (2.27 mL, 24 mmol) and sodium acetate (1.97 g, 24 mmol) were reacted in 200 mL EtOH in accordance with the general procedure. The resultant mixture was recrystallised from hot EtOH to yield methyl 4-methoxyphenylglycinate as off white crystals (1.71 g, 52%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 294 K): δ = 3.74 (s, 3H, OCH<sub>3</sub>), 3.77 (s, 3H, OCH<sub>3</sub>), 3.88 (s, 2H, NHCH<sub>2</sub>), 6.59 (d, *J* = 8.9 Hz, 2H, ArH), 6.79 (d, *J* = 8.9 Hz, 2H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 298 K): δ = 46.7, 52.2, 55.8, 114.5, 115.0, 141.2, 152.8, 171.9. This ester (1.0 g, 6.1 mmol) was dissolved 45 mL CH<sub>3</sub>OH and 15 mL H<sub>2</sub>O and subjected to hydrolysis by lithium hydroxide (2.8 g, 30.3 mmol). Attempted recrystallisation from hot EtOH was unsuccessful.

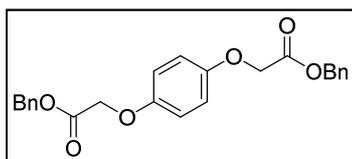
#### Attempted synthesis of 4-methoxyphenylglycine **289**

4-Iodoaniline (4.68 g, 20 mmol), glycine (3.0 g, 40 mmol), CuI (381 mg, 2 mmol), and K<sub>3</sub>PO<sub>4</sub> (14.86 g, 70 mmol) were dissolved in water (20 mL) and 2-dimethylaminoethanol (6 mL), degassed by bubbling with argon and stirred vigorously while heating at 80 °C for 72 hours. This mixture was allowed to cool, poured onto ice (100 g), Acidified to pH 4 with 1M HCl and extracted with EtOAc (3 x 300 mL). The combined extracts were washed with brine (200 mL), water (200 mL) and dried over anhydrous MgSO<sub>4</sub> before the solvent was removed under reduced pressure. NMR analysis revealed that the desired product **289** had not been formed.

### Attempted synthesis of 4-piperidin-1-ylphenoxyacetic acid **295**

4-Bromophenol (6.92 g, 40 mmol), benzyl bromoacetate (9.48 mL, 60 mmol) and  $K_2CO_3$  (27.6 g, 200 mmol), were dissolved in anhydrous THF (200 mL) and heated to 80 °C for 72 hours. This mixture was allowed to cool, concentrated under reduced pressure, dissolved in 200 mL  $Et_2O$ , washed with  $H_2O$  (3 x 200 mL) and dried over  $MgSO_4$  before the solvent removed under reduced pressure. Recrystallisation from hot cyclohexane yielded the desired product as colourless needles (8.78 g, 68%). 400 MHz,  $CDCl_3$ , 295 K):  $\delta$  = 4.64 (s, 2H,  $OCH_2$ ), 5.24 (s, 2H,  $ArCH_2$ ), 6.376-6.79 (m, 2H,  $ArH$ ), 7.32-7.39 (m, 8H,  $ArH$ );  $^{13}C$  NMR (75 MHz,  $CDCl_3$ , 297 K):  $\delta$  = 65.5, 67.2, 114.1, 116.6, 128.5, 128.7, 128.7, 132.4, 135.1, 156.9, 168.5. This ester (2.4 g, 7.5 mmol), piperidine (1.48 mL, 15 mmol),  $CuI$  (71.4 g, 0.375 mmol), 2-isobutyrylcyclohexan-1-one (0.25 mL, 1.5 mmol) and  $K_3PO_4$  (3.19 g, 15 mmol) were dissolved in anhydrous DMF (4 mL) in accordance with the procedure of Buchwald and co-workers.<sup>[14]</sup> No evidence for the formation of the desired product **295** was observed.

### Dibenzyl 2,2'-(1,4-phenylenebis(oxy))diacetate **299**



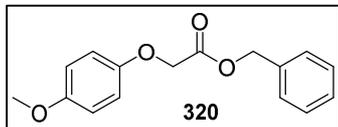
Hydroquinone-*O,O'*-diacetic acid (452.4 mg, 2.0 mmol) and benzyl alcohol (0.19 mL, 2.2 mmol) were dissolved in 20 mL anhydrous DMF. This mixture was cooled to 0°C and to it was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.39 mL, 2.2 mmol) and then DMAP (24.4 mg, 0.2 mmol). The mixture was then allowed to warm to room temperature and stirred overnight. The mixture was then concentrated, the resultant residue taken up in 50 mL  $EtOAc$ , washed with  $H_2O$  (3 x 100 mL) and dried over  $MgSO_4$ . The solvent was removed under reduced pressure to yield **299** as a clear oil (118.5 mg, 15%).  $^1H$  NMR (500 MHz, *d6*-acetone, 295 K):  $\delta$  = 4.73 (s, 4H,  $ArOCH_2$ ), 5.22 (s, 4H,  $CO_2CH_2Ph$ ), 6.88 (s, 4H,  $ArH$ ), 7.35-7.40 (m, 10H,  $ArH$ );  $^{13}C$  NMR (75 MHz, *d6*-acetone, 297 K):  $\delta$  = 66.5, 67.0, 116.5, 128.9, 129.0, 129.4, 137.0, 153.8, 169.6; LR-ESIMS:  $m/z$  = 424  $[MNH_4]^+$ ; HR-ESIMS:  $m/z$  = 424.1755 (calcd. for  $C_{24}H_{26}NO_6$ , 424.1760).

### Attempted synthesis of 4-(2-(benzyloxy)-2-oxoethoxy)phenoxyacetic acid **297**

4-Hydroxyphenoxyacetic acid (1.68 g, 10 mmol), benzyl bromoacetate (1.16 mL, 15 mmol) and  $K_2CO_3$  (6.91 g, 50 mmol) were dissolved in anhydrous THF (50 mL) and heated at 80 °C for 72 hours. The reaction mixture was allowed to cool, was concentrated under reduced pressure, dissolved in 50 mL saturated  $(NH_4)_2SO_4$ , adjusted to ca. pH 3 and extracted with  $EtOAc$  (3 x 100 mL). The combined extracts were dried over  $MgSO_4$  and the solvent removed under reduced

pressure. The resultant mixture was subject to column chromatography on silica gel (eluent: 2-5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) but none of the fractions obtained contained the desired product **297**.

#### Benzyl (4-methoxyphenoxy)acetate **320**



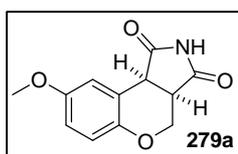
**320** was prepared by stirring (4-methoxyphenoxy)acetic acid (182.2 mg, 1 mmol), benzyl alcohol (119 mg, 1.1 mmol), *N,N'*-dicyclohexylcarbodiimide (413 mg, 1.1 mmol) and 4-dimethylaminopyridine (12 mg, 0.1 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (25 mL) overnight at room temperature in an argon atmosphere. The dicyclohexylurea biproduct was removed by filtration and the filtrate washed with water (3 x 30 mL) 5% acetic acid solution (3 x 30 mL), again with water (3 x 30 mL) and dried over anhydrous MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the crude reaction mixture purified by column chromatography on silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>) to yield **320** as a clear oil (160.7 mg, 59%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 297 K): δ = 3.77 (s, 3H, H<sub>a</sub>), 4.62 (s, 2H, OCH<sub>2</sub>), 5.24 (s, 2H, PhCH<sub>2</sub>), 6.80-6.87 (m, 4H, ArH), 7.33-7.37 (m, 5H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 297 K): δ = 55.7, 66.4, 67.0, 114.7, 116.0, 128.5, 128.5, 128.7, 135.2, 152.0, 154.6, 169.1; LR-ESIMS: *m/z* = 290 [MNH<sub>4</sub>]<sup>+</sup>; HR-ESIMS: *m/z* = 290.1390 (calcd. for C<sub>16</sub>H<sub>20</sub>NO<sub>4</sub>, 290.1387).

### 4.3 Optimisation

**Stoichiometry:** 4-Methoxyphenoxyacetic acid (47.4 mg, 0.26 mmol) and the corresponding amount of maleimide were dissolved in anhydrous MeCN (10 mL) and photolysed for 5 hours with twelve 29 cm 15 W Philips Cleo tubes ( $\lambda = 350$  nm) arranged in two hemispherical banks of six. Following removal of solvent under reduced pressure yields were determined by  $^1\text{H}$  NMR spectroscopy by integration relative to a known amount of a  $\text{CH}_2\text{Br}_2$  internal standard. Spectra were recorded at 400-500 MHz from 32 scans at  $90^\circ$  pulse width using 30 second  $\text{D}_1$  relaxation time in order to obtain optimal signal to noise ratio and minimise the associated error. This data is given in Table 1, pg 174.

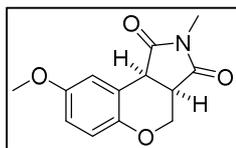
**Solvent Screening:** 4-Methoxyphenoxyacetic acid (47.4 mg, 0.26 mmol) and maleimide (101 mg, 1.04 mmol) were dissolved in the desired solvent (10 mL) and photolysed for 5 hours with twelve 29 cm 15 W Philips Cleo tubes ( $\lambda = 350$  nm) arranged in two hemispherical banks of six. Following removal of solvent under reduced pressure yields were determined by  $^1\text{H}$  NMR spectroscopy by integration relative to a known amount of a  $\text{CH}_2\text{Br}_2$  internal standard. Spectra were recorded at 400-500 MHz from 32 scans at  $90^\circ$  pulse width using 30 second  $\text{D}_1$  relaxation time in order to obtain optimal signal to noise ratio and minimise the associated error. This data is given in Table 2, pg 175.

#### 8-Methoxy-3a,4-dihydrochromeno[3,4-c]pyrrole-1,3(2H,9bH)-dione **279a**



Maleimide (366 mg, 3.75 mmol) and 4-methoxyphenoxyacetic acid (137 mg, 0.75 mmol) were dissolved in 13 mL  $\text{CH}_3\text{CN}$  and 7 mL  $\text{H}_2\text{O}$  and irradiated through Pyrex for 18 hours. Following irradiation the reaction mixture was concentrated under reduced pressure and the crude mixture was purified by column chromatography on silica gel (eluent: 10% EtOAc in  $\text{CH}_2\text{Cl}_2$ ) to yield **279a** as an off-white solid (93.9 mg, 54%). M.p.  $217^\circ\text{C}$ .  $^1\text{H}$  NMR (300 MHz,  $d_6$ -acetone, 295 K):  $\delta = 3.55$ - $3.60$  (m, 1H,  $\text{CH}_2\text{CH}$ ), 3.88 (s, 3H,  $\text{OCH}_3$ ), 3.91 (dd,  $J = 4.0, 11.2$  Hz, 1H,  $\text{OCH}_2$ ), 4.16 (d,  $J = 9.4$  Hz, 1H, ArCH), 4.50 (dd,  $J = 2.5, 11.2$  Hz, 1H,  $\text{OCH}_2'$ ), 6.79 (m, 2H, ArH), 7.06 (m, 1H, ArH), 10.18 (br-s, 1H, NH);  $^{13}\text{C}$  NMR (75 MHz,  $d_6$ -acetone, 295 K):  $\delta = 42.2, 44.3, 56.0, 65.0, 115.3, 115.4, 118.9, 120.4, 150.3, 155.6, 177.5, 178.6$ ; LR-EIMS:  $m/z = 233$  [ $\text{M}$ ] $^+$ ; HR-ESIMS:  $m/z = 233.0680$  (calcd. for  $\text{C}_{12}\text{H}_{11}\text{NO}_4$ , 233.0683).

### 8-Methoxy-2-methyl-3a,4-dihydrochromeno[3,4-c]pyrrole-1,3(2H,9bH)-dione.



*N*-Methylmaleimide (417 mg, 3.75 mmol) and 4-methoxyphenoxyacetic acid (137mg, 0.75 mmol) were dissolved in 13 mL CH<sub>3</sub>CN and 7 mL H<sub>2</sub>O and irradiated through Pyrex for 18 hours. Following irradiation a 0.5 mL aliquot was taken from the reaction mixture and the solvent was removed under reduced pressure. <sup>1</sup>H NMR analysis (w.r.t. CH<sub>2</sub>Br<sub>2</sub> standard) of the resultant mixture revealed: 8-methoxy-2-methyl-3a,4-dihydrochromeno[3,4-c]pyrrole-1,3(2H,9bH)-dione (0.19 mmol, 25%), and unreacted starting material (0.53 mmol, 70% recovery). Product characterisation data: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 297 K):  $\delta$  = 2.97 (s, 3H, CH<sub>3</sub>), 3.33 (m, 1H, CH<sub>2</sub>CH), 3.78 (s, 3H, OCH<sub>3</sub>), 3.93 (dd, *J* = 4.1 Hz, 11.4 Hz, 1H, OCH<sub>2</sub>), 4.01 (d, *J* = 9.2 Hz, 1H, ArCH), 4.56 (dd, *J* = 2.3, 11.4 Hz, 1H, OCH<sub>2</sub>'), 6.75 (dd, *J* = 2.6, 8.9 Hz, 1H, ArH), 6.80 (d, *J* = 8.9 Hz, 1H, ArH), 7.07 (d, *J* = 2.7 Hz, 1H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 297 K):  $\delta$  = 25.4, 40.1, 42.3, 55.8, 64.2, 114.0, 115.4, 118.1, 118.5, 149.2, 154.9, 176.0, 176.9; LR-ESIMS: *m/z* = 247 [M]<sup>+</sup>; HR-ESIMS: *m/z* = 247.0838 (calcd. for C<sub>13</sub>H<sub>13</sub>NO<sub>4</sub>, 247.0839).

### Attempted synthesis of 8-methoxy-2-phenyl-3a,4-dihydrochromeno[3,4-c]pyrrole-1,3(2H,9bH)-dione.

*N*-phenylmaleimide (1299 mg, 7.5 mmol) and 4-methoxyphenoxyacetic acid (137mg, 0.75 mmol) were dissolved in 13 mL CH<sub>3</sub>CN and 7 mL H<sub>2</sub>O and irradiated through Pyrex for 18 hours. Following irradiation a 0.5 mL aliquot was taken from the reaction mixture and the solvent was removed under reduced pressure. <sup>1</sup>H NMR analysis revealed only starting materials present.

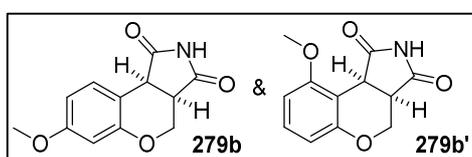
### Attempted synthesis of 8-methoxy-3a,4-dihydro-1H-furo[3,4-c]chromene-1,3(9bH)-dione

Maleic anhydride (736 mg, 7.5 mmol) and 4-methoxyphenoxyacetic acid (137mg, 0.75 mmol) were dissolved in 13 mL CH<sub>3</sub>CN and 7 mL H<sub>2</sub>O and irradiated through Pyrex for 18 hours. Following irradiation a 0.5 mL aliquot was taken from the reaction mixture and the solvent was removed under reduced pressure. <sup>1</sup>H NMR analysis revealed only starting materials present.

## 4.4 Preparative Photolyses

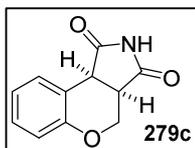
**General Procedure for Preparative Irradiations** Known amounts of desired reagents were dissolved in a mixture of 35 : 65 H<sub>2</sub>O in MeCN. The resulting mixture was degassed by bubbling with argon for 20 minutes. The mixture was then irradiated with twelve 29 cm 15 W Philips Cleo tubes ( $\lambda = 350$  nm) arranged in two hemispherical banks of six for the desired reaction time. Following irradiation the solvent was removed under reduced pressure and the crude reaction mixture was purified if necessary.

### 7-Methoxy-3a,4-dihydrochromeno[3,4-c]pyrrole-1,3(2*H*,9*bH*)-dione **279b** & 9-methoxy-3a,4-dihydrochromeno[3,4-c]pyrrole-1,3(2*H*,9*bH*)-dione **279a'**



Maleimide (366 mg, 3.75 mmol) and 3-methoxyphenoxyacetic acid (137 mg, 0.75 mmol) were dissolved in 13 mL CH<sub>3</sub>CN and 7 mL H<sub>2</sub>O and irradiated through Pyrex for 18 hours. Following irradiation the reaction mixture was concentrated under reduced pressure and the crude mixture was purified by column chromatography on silica gel (eluent: 5% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) to yield **279b** as an off-white solid (111 mg, 64%). M.p. 156 °C. <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-acetone, 295 K):  $\delta = 3.55$ -3.60 (m, 1H, CH<sub>2</sub>CH), 3.74 (s, 3H, OCH<sub>3</sub>), 3.95 (dd, *J* = 4.0, 11.4 Hz, 1H, OCH<sub>2</sub>), 4.08 (d, *J* = 9.2 Hz, 1H, ArCH), 4.53 (dd, *J* = 2.7, 11.3 Hz, 1H, OCH<sub>2</sub>'), 6.42 (d, *J* = 2.6 Hz, 1H, ArH), 6.61 (dd, *J* = 2.8, 8.7 Hz, 1H, ArH), 7.39 (d, *J* = 8.3 Hz, 1H, ArH), 10.14 (br-s, 1H, NH); <sup>13</sup>C NMR (75 MHz, *d*<sub>6</sub>-acetone, 296 K):  $\delta = 41.2, 44.1, 55.7, 64.7, 103.1, 109.9, 111.5, 131.7, 157.2, 161.0, 178.1, 178.6$ ; LR-ESIMS: *m/z* = 234 [MH]<sup>+</sup>; HR-ESIMS: *m/z* = 234.0765 (calcd. for C<sub>12</sub>H<sub>12</sub>NO<sub>4</sub>, 234.0766). As above to yield **279b'** as a yellow oil (28.2 mg, 16%). <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-acetone, 294 K):  $\delta = 3.52$ -3.57 (m, 1h, CH<sub>2</sub>CH), 3.79 (dd, *J* = 4.3, 11.2 Hz, 1H, OCH<sub>2</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 4.54 (dd, *J* = 1.8, 11.2 Hz, 1H, OCH<sub>2</sub>'), 4.60 (d, *J* = 9.7 Hz, 1H, ArCH), 6.50 (d, *J* = 8.2 Hz, 1H, ArH), 6.71 (d, *J* = 8.3 Hz, 1H, ArH), 7.15 (t, *J* = 8.2 Hz, 1H, ArH), 10.14 (br-s, 1H, NH); <sup>13</sup>C NMR (75 MHz, *d*<sub>6</sub>-acetone, 294 K):  $\delta = 37.5, 45.0, 56.4, 66.7, 106.3, 110.9, 139.4, 158.5, 160.1, 176.7, 179.0$ ; LR-EIMS: *m/z* = 234 [MH]<sup>+</sup>; HR-ESIMS *m/z* = 234.0763 (calcd. for C<sub>12</sub>H<sub>12</sub>NO<sub>4</sub>, 234.0766).

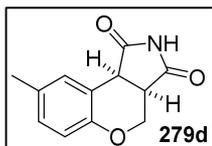
### 3a,4-Dihydrochromeno[3,4-c]pyrrole-1,3(2*H*,9*bH*)-dione **279c**



Maleimide (366 mg, 3.75 mmol) and 2-methoxyphenoxyacetic acid (137 mg, 0.75 mmol) were dissolved in 13 mL CH<sub>3</sub>CN and 7 mL H<sub>2</sub>O and irradiated through Pyrex for 18 hours. Following irradiation the reaction mixture was concentrated under reduced pressure and the crude mixture was purified by

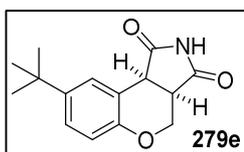
column chromatography on silica gel (eluent: 10% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) to yield **279c** as a colourless solid (81.5 mg, 54%). <sup>1</sup>H NMR (300 MHz, *d6*-acetone, 295 K):  $\delta$  = 3.61-3.67 (m, 1H, CH<sub>2</sub>CH), 4.00 (dd, *J* = 4.2, 11.5 Hz 1H, OCH<sub>2</sub>), 4.19 (d, *J* = 9.2 Hz, 1H, ArCH), 4.55 (dd, *J* = 3.1, 11.4 Hz 1H, OCH<sub>2</sub>'), 6.87 (d, *J* = 8.2 Hz, 1H, ArH), 7.03 (t, *J* = 8.2 Hz, 1H, ArH), 7.22 (t, *J* = 8.0 Hz, 1H, ArH), 7.51 (d, *J* = 7.8 Hz, 1H, ArH), 10.18 (br-s, 1H, NH). Data consistent with literature.<sup>[33]</sup>

#### 8-Methyl-3a,4-dihydrochromeno[3,4-*c*]pyrrole-1,3(2*H*,9*bH*)-dione **279d**



Maleimide (732 mg, 7.5 mmol) and 4-methylphenoxyacetic acid (124.7 mg, 0.75 mmol) were dissolved in 13 mL CH<sub>3</sub>CN and 7 mL H<sub>2</sub>O and irradiated through Pyrex for 25 hours. Following irradiation the reaction mixture was concentrated under reduced pressure and the crude mixture was purified by column chromatography on silica gel (eluent: 10% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) to yield **279d** as a colourless solid (46.6 mg, 29%). M.p. 172 °C. <sup>1</sup>H NMR (400 MHz, *d6*-acetone, 295 K):  $\delta$  = 2.27 (s, 3H, ArCH<sub>3</sub>), 3.59 (m, 1H, CH<sub>2</sub>CH), 3.93 (dd, *J* = 3.9, 11.3 Hz, 1H, OCH<sub>2</sub>), 4.12 (d, *J* = 9.2 Hz, 1H, ArCH), 4.51 (dd, *J* = 2.6, 11.2 Hz, 1H, OCH<sub>2</sub>'), 6.74 (d, *J* = 8.3 Hz, 1H, ArH), 7.00 (d, *J* = Hz, 1H, ArH), 7.30 (s, 1H, ArH), 10.15 (br-s, 1H, NH); <sup>13</sup>C NMR (75 MHz, *d6*-acetone, 295 K):  $\delta$  = 20.7, 41.9, 44.3, 64.8, 118.0, 119.4, 131.3, 132.1, 136.0, 154.2, 177.6, 178.5; LR-ESIMS: *m/z* = 218 [MH]<sup>+</sup>; HR-ESIMS: *m/z* = 218.0814 (calcd. for C<sub>12</sub>H<sub>12</sub>NO<sub>3</sub>, 218.0817).

#### 8-(*tert*-Butyl)-3a,4-dihydrochromeno[3,4-*c*]pyrrole-1,3(2*H*,9*bH*)-dione **279e**



Maleimide (732 mg, 7.5 mmol) and 4-*tert*-butylphenoxyacetic acid (156 mg, 0.75 mmol) were dissolved in 13 mL CH<sub>3</sub>CN and 7 mL H<sub>2</sub>O and irradiated through Pyrex for 18 hours. Following irradiation the reaction mixture was concentrated under reduced pressure and the crude mixture was purified by column chromatography on silica gel (eluent: 5-10% acetone in CH<sub>2</sub>Cl<sub>2</sub>) to yield **279e** as a colourless solid (104 mg, 54%). Mp 174 °C. <sup>1</sup>H NMR (400 MHz, *d6*-acetone, 295 K):  $\delta$  = 1.30 (s, 9H, CH<sub>3</sub>), 3.58-3.62 (m, 1H, OCH<sub>2</sub>), 3.95 (dd, *J* = 4.0, 11.3 Hz, 1H, OCH<sub>2</sub>), 4.16 (d, *J* = 9.2 Hz, 1H, ArCH), 4.51 (dd, *J* = 2.7, 11.3 Hz, 1H, OCH<sub>2</sub>'), 6.78 (d, *J* = 8.5 Hz, 1H, ArH), 7.25 (dd, *J* = 2.5, 8.6 Hz, 1H, ArH), 7.55 (d, *J* = 2.5 Hz, 1H, ArH), 10.15 (br-s, 1H, NH); <sup>13</sup>C NMR (75 MHz, *d6*-acetone, 297 K):  $\delta$  = 31.8, 34.8, 42.0, 44.3, 64.7, 117.7, 118.9, 126.4, 127.8, 145.6, 154.1, 177.7, 178.5 ; LR-ESIMS: *m/z* = 282 [MNa]<sup>+</sup>; HR-ESIMS: *m/z* = 282.1103 (calcd. for C<sub>15</sub>H<sub>17</sub>NO<sub>3</sub>Na, 282.1106).

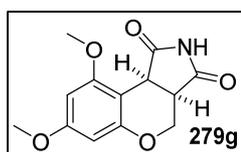
### 3a,4-Dihydrochromeno[3,4-c]pyrrole-1,3(2H,9bH)-dione 279c

Maleimide (366 mg, 3.75 mmol) and phenoxyacetic acid (114 mg, 0.75 mmol) were dissolved in 13 mL CH<sub>3</sub>CN and 7 mL H<sub>2</sub>O and irradiated through Pyrex for 18 hours. Following irradiation the reaction mixture was concentrated under reduced pressure. <sup>1</sup>H NMR analysis revealed that the desired product **279c** had not been formed.

### 8-Chloro-3a,4-dihydrochromeno[3,4-c]pyrrole-1,3(2H,9bH)-dione

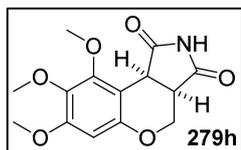
Maleimide (366 mg, 3.75 mmol) and 4-chlorophenoxyacetic acid (140 mg, 0.75 mmol) were dissolved in 13 mL CH<sub>3</sub>CN and 7 mL H<sub>2</sub>O and irradiated through Pyrex for 18 hours. Following irradiation the reaction mixture was concentrated under reduced pressure. <sup>1</sup>H NMR analysis revealed peaks that could be attributed to the desired product (0.025 mmol; 3%).

### 7,9-Dimethoxy-3a,4-dihydrochromeno[3,4-c]pyrrole-1,3(2H,9bH)-dione 279g



Maleimide (366 mg, 3.75 mmol) and 3,5-dimethoxyphenoxyacetic acid (159.2 mg, 0.75 mmol) were dissolved in 13 mL CH<sub>3</sub>CN and 7 mL H<sub>2</sub>O and irradiated through Pyrex for 18 hours. Following irradiation the reaction mixture was concentrated under reduced pressure and the crude mixture was purified by column chromatography on silica gel (eluent: 10-20% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) to yield **279g** as a colourless solid (161 mg, 82%). M.p. 236 °C. <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-acetone, 296 K):  $\delta$  = 3.52-3.58 (m, 1H, CH<sub>2</sub>CH), 3.79 (s, 3H, OCH<sub>3</sub>), 3.82 (dd, *J* = 4.3, 11.2 Hz, 1H, OCH<sub>2</sub>), 3.89 (s, 3H, OCH<sub>3</sub>), 4.50 (d, *J* = 9.7 Hz, 1H, ArCH), 4.55 (dd, *J* = 1.8, 11.2 Hz, 1H, OCH<sub>2</sub>'), 6.12 (d, *J* = 2.3 Hz, 1H, ArH), 6.32 (d, *J* = 2.3 Hz, 1H, ArH), 10.14 (br-s, 1H, NH); <sup>13</sup>C NMR (75 MHz, *d*<sub>6</sub>-DMSO, 297 K):  $\delta$  = 35.9, 43.5, 55.2, 55.8, 65.7, 93.6, 94.7, 101.6, 157.6, 159.2, 177.2, 179.2; LR-ESIMS: *m/z* = 264 [MH]<sup>+</sup>; HR-ESIMS: *m/z* = 246.0869 (calcd. for C<sub>13</sub>H<sub>14</sub>NO<sub>5</sub>, 264.0872).

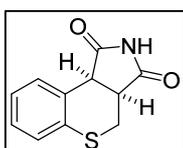
### 7,8,9-Trimethoxy-3a,4-dihydrochromeno[3,4-c]pyrrole-1,3(2H,9bH)-dione 279h



Maleimide (366 mg, 3.75 mmol) and 3,4,5-trimethoxyphenoxyacetic acid (181.7 mg, 0.75 mmol) were dissolved in 13 mL CH<sub>3</sub>CN and 7 mL H<sub>2</sub>O and irradiated through Pyrex for 64 hours. Following irradiation the reaction mixture was concentrated under reduced pressure, diluted with 100 mL CH<sub>2</sub>Cl<sub>2</sub>, washed with saturated aqueous NaHCO<sub>3</sub> (100 mL), deionised water (2 x 100 mL), dried over anhydrous MgSO<sub>4</sub> and the solvent evaporated to yield **279h** as a yellow solid (52.2 mg, 24%). Mp 165 °C. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-acetone, 295 K):  $\delta$  = 3.48-3.52 (m, 1H, CH<sub>2</sub>CH), 3.74 (dd-overlapped, *J* = 4.4, 11.2 Hz, 1H, OCH<sub>2</sub>), 3.75 (s-overlapped, 3H, OCH<sub>3</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 4.04 (s, 3H, OCH<sub>3</sub>),

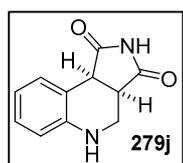
4.49 (d-overlapped,  $J = 9.7$  Hz, 1H, ArCH), 4.50 (dd-overlapped,  $J = 1.7, 11.2$  Hz, 1H, OCH<sub>2</sub>'), 6.31 (s, 1H, ArH), 10.21 (br-s, 1H, NH); <sup>13</sup>C NMR (75 MHz, d<sub>6</sub>-acetone, 297 K):  $\delta = 37.7, 44.9, 56.3, 60.7, 61.7, 67.0, 98.1, 107.1, 136.0, 138.6, 153.7, 154.6, 177.4, 179.2$ ; LR-ESIMS:  $m/z = 294$  [MH]<sup>+</sup>; HR-ESIMS:  $m/z = 294.0975$  (calcd. for C<sub>14</sub>H<sub>16</sub>NO<sub>6</sub>, 294.0978). Analysis of the reaction mixture by <sup>1</sup>H NMR prior to chromatography revealed 71% unreacted 3,4,5-trimethoxyphenoxyacetic (0.53 mmol w.r.t. **279h**) indicating that the reaction had achieved only 29% conversion.

### 3a,4-Dihydrothiochromeno[3,4-c]pyrrole-1,3(2H,9bH)-dione **279i**



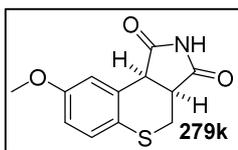
Maleimide (366 mg, 3.75 mmol) and phenylthioacetic acid (126 mg, 0.75 mmol) were dissolved in 13 mL CH<sub>3</sub>CN and 7 mL H<sub>2</sub>O and irradiated through Pyrex for 18 hours. Following irradiation the reaction mixture was concentrated under reduced pressure and the crude mixture was purified by column chromatography on silica gel (eluent: 7.5% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) to yield **279i** as a colourless solid (62.9 mg, 39%). Mp 157 °C. <sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-acetone, 295 K):  $\delta = 2.91$  (dd,  $J = 4.9, 13.3$  Hz, 1H, SCH<sub>2</sub>), 3.26 (dd,  $J = 2.4, 13.3$  Hz, 1H, SCH<sub>2</sub>'), 3.82-3.88 (m, 1H, CH<sub>2</sub>CH), 4.35 (d,  $J = 9.5$  Hz, 1H, ArCH), 7.20-7.30 (m, 3H, ArH), 7.43-7.49 (m, 1H, ArH), 10.37 (br-s, 1H, NH); <sup>13</sup>C NMR (75 MHz, d<sub>6</sub>-acetone, 295 K):  $\delta = 30.1, 46.4, 47.2, 127.3, 128.4, 129.9, 132.5, 133.1, 135.4, 177.3, 179.3$ ; LR-ESIMS:  $m/z = 237$  [MNH<sub>4</sub>]<sup>+</sup>; HR-ESIMS:  $m/z = 237.0696$  (calcd. for C<sub>11</sub>H<sub>13</sub>N<sub>2</sub>O<sub>2</sub>S, 237.0698).

### 3a,4,5,9b-Tetrahydro-1H-pyrrolo[3,4-c]quinoline-1,3(2H)-dione **279j**



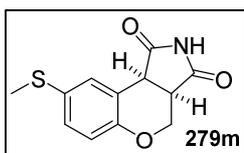
Maleimide (366 mg, 3.75 mmol) and *N*-phenylglycine (113.4 mg, 0.75 mmol) were dissolved in 13 mL CH<sub>3</sub>CN and 7 mL H<sub>2</sub>O and irradiated through Pyrex for 18 hours. Following irradiation the reaction mixture was concentrated under reduced pressure and the crude mixture was purified by column chromatography on silica gel (eluent: 20% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) to yield **279j** as an off-white solid (135 mg, 89%). M.p. 173-176 °C. <sup>1</sup>H NMR (500 MHz, d<sub>6</sub>-acetone, 293 K):  $\delta = 3.12$  (dd,  $J = 4.4, 11.3$  Hz, 1H, NCH<sub>2</sub>'), 3.47-3.51 (m, 1H, CH<sub>2</sub>CH), 3.54 (dt,  $J = 3.0, 11.3$  Hz, 1H, NCH<sub>2</sub>'), 4.04 (d,  $J = 9.3$  Hz, 1H, ArCH), 5.00 (br-s, 1H, ArNH), 6.68 (d,  $J = 7.9$  Hz, 1H, ArH), 6.72 (t,  $J = 7.5$  Hz, 1H, ArH), 7.01 (t,  $J = 7.4$  Hz, 1H, ArH), 7.36 (d,  $J = 7.6$  Hz, 1H, ArH), 10.04 (br-s, 1H, NH); <sup>13</sup>C NMR (75 MHz, d<sub>6</sub>-acetone, 298 K):  $\delta = 41.9, 43.5, 45.2, 116.2, 118.5, 119.5, 128.5, 131.1, 148.1, 178.2, 179.9$ ; LR-ESIMS:  $m/z = 203$  [MH]<sup>+</sup>; HR-ESIMS:  $m/z = 203.0815$  (calcd. for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>, 203.0821).

### 8-Methoxy-3a,4-dihydrothiochromeno[3,4-c]pyrrole-1,3(2H,9bH)-dione **279k**



Maleimide (366 mg, 3.75 mmol) and 4-methoxyphenylthioacetic acid (148.6 mg, 0.75 mmol) were dissolved in 13 mL CH<sub>3</sub>CN and 7 mL H<sub>2</sub>O and irradiated through Pyrex for 72 hours. Following irradiation the reaction mixture was concentrated under reduced pressure and the crude mixture was purified by column chromatography on silica gel (eluent: 10-20% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) to yield **279k** as a yellow oil (67.5 mg, 36%). <sup>1</sup>H NMR (300 MHz, *d6*-acetone, 296 K):  $\delta$  = 2.85 (dd, *J* = 4.9, 13.3 Hz, 1H, SCH<sub>2</sub>), 3.23 (dd, *J* = 2.3, 13.3 Hz, 1H, SCH<sub>2</sub>'), 3.77-3.83 (m, overlapped, 1H, CH<sub>2</sub>CH), 3.81 (s, overlapped, 3H, OCH<sub>3</sub>), 4.31 (d, *J* = 9.4 Hz, 1H, ArCH), 6.84 (dd, *J* = 2.8, 8.7 Hz, 1H, ArH), 7.05 (d, *J* = 2.7 Hz, 1H, ArH), 7.20 (d, *J* = 8.6 Hz, 1H, ArH), 10.37 (br-s, 1H, NH); <sup>13</sup>C NMR (75 MHz, *d6*-acetone, 297 K):  $\delta$  = 30.7, 46.2, 47.6, 55.8, 114.2, 118.8, 126.1, 130.9, 133.8, 159.4, 177.2, 179.4; LR-ESIMS: *m/z* = 250 [MH]<sup>+</sup>; HR-ESIMS: *m/z* = 250.0535 (calcd. for C<sub>12</sub>H<sub>12</sub>NO<sub>3</sub>S, 250.0538).

### 8-(Methylthio)-3a,4-dihydrochromeno[3,4-c]pyrrole-1,3(2H,9bH)-dione **279m**



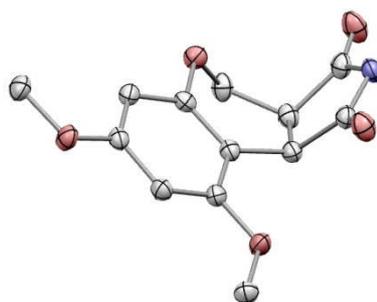
Maleimide (366 mg, 3.75 mmol) and 4-methylthiophenoxyacetic acid (148.6 mg, 0.75 mmol) were dissolved in 13 mL CH<sub>3</sub>CN and 7 mL H<sub>2</sub>O and irradiated through pyrex for 72 hours. Following irradiation the reaction mixture was concentrated under reduced pressure and the crude mixture was purified by column chromatography on silica gel (eluent: 10% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) to yield **279m** as a off-white solid (27.3 mg, 14%). M.p. 160 °C. <sup>1</sup>H NMR (400 MHz, *d6*-acetone, 300 K):  $\delta$  = 2.46 (s, 3H, SCH<sub>3</sub>), 3.61-3.64 (m, 1H, CH<sub>2</sub>CH), 3.98 (dd, *J* = 4.1, 11.3 Hz, 1H, OCH<sub>2</sub>), 4.18 (d, *J* = 9.2 Hz, 1H, ArCH), 4.53 (dd, *J* = 2.8, 11.3 Hz, 1H, OCH<sub>2</sub>'), 6.84 (d, *J* = 8.5 Hz, 1H, ArH), 7.16 (dd, *J* = 2.3, 8.5 Hz, 1H, ArH), 7.47 (d, *J* = 2.3 Hz, 1H, ArH), 10.16 (br-s, 1H, NH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 296 K):  $\delta$  = 17.2, 40.8, 43.2, 63.8, 117.7, 118.5, 128.9, 129.0, 131.9, 153.4, 175.7, 176.6; LR-ESIMS: *m/z* = 272 [MNa]<sup>+</sup>; HR-ESIMS: *m/z* = 272.0354 (calcd. for C<sub>12</sub>H<sub>11</sub>NO<sub>3</sub>SNa, 272.0357). Analysis of the reaction mixture by <sup>1</sup>H NMR prior to chromatography revealed 47% unreacted 4-methylthiophenoxyacetic acid (0.35 mmol w.r.t. **279m**) indicating that the reaction had achieved only 53% conversion.

### Attempted Synthesis of **308**

Maleimide (732 mg, 7.5 mmol) and hydroquinone-*O,O'*-diacetic acid (169.7 mg, 0.75 mmol) were dissolved in 26 mL CH<sub>3</sub>CN and 14 mL H<sub>2</sub>O and irradiated through pyrex for 18 hours.

Following irradiation the reaction mixture was concentrated under reduced pressure.  $^1\text{H}$  NMR and GC-MS analyses revealed that the desired product **308** had not been formed.

## 4.5 X-Ray Crystallography

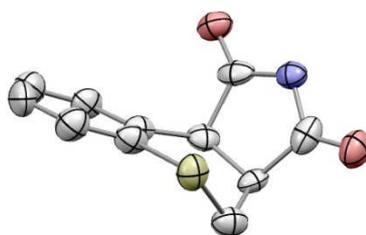


**Figure 12.** The X-ray crystal structure of **279g**.

**Table 10.** Crystal data & structure refinement for **279g**.

Identification code	<b>279g</b>
CCDC code	962517
Empirical Formula	$C_{13}H_{13}NO_5$
Formula Weight	263.25
Crystal Colour, Habit	colourless prism
Crystal Dimensions	0.200 mm x 0.100 mm x 0.030 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	$a = 7.925(4) \text{ \AA}$ $\beta = 92.336(8)^\circ$ $b = 8.466(3) \text{ \AA}$ $c = 17.187(6) \text{ \AA}$
Volume	$1152.2(8) \text{ \AA}^3$
Space Group	$P2_1/n(\#14)$
Z value	4
Density (calculated)	1.517 g/mL
F(000)	552.00
$\mu(\text{CuK}\alpha)$	$9.993 \text{ cm}^{-1}$
Diffractometer	Saturn70
Radiation Voltage	$\text{CuK}\alpha (\lambda = 1.54187 \text{ \AA})$
Current Temperature	173 K
Detector Aperture	70 x 70 mm
Pixel Size	0.034 nm
2 $\theta$ max	136.7°
No. of Reflections Measured	Total: 15,295, Unique: 2084 ( $R_{\text{int}} =$

	0.0431)
Corrections	Lorentz-polarization
Structure Solution	Direct Methods
Refinement	Full-matrix least-squares on $F^2$
Function Minimized	$\Sigma w (F_o^2 - F_c^2)^2$
Least Squares Weights	$w = 1/[\sigma^2(F_o^2) + (0.1051P)^2 + 2.9953P]$ where $P = (\text{Max}(F_o^2, 0) + 2F_c^2)/3$
2 $\theta$ max cutoff	136.7°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations	(All reflections) 2084
No. Variables	176
Reflection/Parameter Ratio	11.9
Residuals: R1 ( $I > 2.00\sigma(I)$ )	0.0361
Residuals: R (All reflections)	0.0389
Residuals: wR2 (All reflections)	0.1115
Goodness of Fit	0.956
Indicator Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	0.22 e / Å <sup>3</sup>
Minimum peak in Final Diff. Map	-0.20 e / Å <sup>3</sup>



**Figure 13.** The X-ray crystal structure of **279i**.

**Table 11.** Crystal data & structure refinement for **279i**.

Identification code	<b>279i</b>
CCDC code	962518
Empirical Formula	$C_{11}H_9NO_2S$
Formula Weight	219.26
Crystal Colour, Habit	colourless prism
Crystal Dimensions	0.100 mm x 0.060 mm x 0.030 mm
Crystal System	monoclinic

Lattice Type	C-centered
Lattice Parameters	$a = 12.590(7) \text{ \AA}$ $\beta = 96.690(12)^\circ$ $b = 11.384(5) \text{ \AA}$ $c = 27.890(13) \text{ \AA}$
Volume	3970(3) $\text{\AA}^3$
Space Group	Cc(#9)
Z value	16
Density (calculated)	1.467 g/mL
F(000)	1824.00
$\mu(\text{CuK}\alpha)$	3.016 $\text{cm}^{-1}$
Diffractometer	Mercury70
Radiation Voltage	MoK $\alpha$ ( $\lambda = 0.71075$ )
Current Temperature	93 K
Detector Aperture	70 x 70 mm
Pixel Size	0.068 mm
2 $\theta$ max	50.8°
No. of Reflections Measured	Total: 10656, Unique: 5199 ( $R_{\text{int}} = 0.0744$ )
Corrections	Lorentz-polarization
Structure Solution	Charge Flipping (Superflip)
Refinement	Full-matrix least-squares on $F^2$
Function Minimized	$\sum w (F_o^2 - F_c^2)^2$
Least Squares Weights	$w = 1/[\sigma^2(F_o^2) + (0.1051P)^2 + 2.9953P]$ where $P = (\text{Max}(F_o^2, 0) + 2F_c^2)/3$
2 $\theta$ max cutoff	50.8°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations	(All reflections) 5199
No. Variables	557
Reflection/Parameter Ratio	9.33
Residuals: R1 ( $I > 2.00\sigma(I)$ )	0.0738
Residuals: R (All reflections)	0.0979
Residuals: wR2 (All reflections)	0.1927
Goodness of Fit	1.073
Indicator Max Shift/Error in Final Cycle	0.000

Maximum peak in Final Diff. Map

0.52 e /Å<sup>3</sup>

Minimum peak in Final Diff. Map

-0.43 e /Å<sup>3</sup>

## 4.6 DFT Optimised Energies

### Acid PhOCH<sub>2</sub>CO<sub>2</sub>H (122).

UB3LYP/6-311+G(2d,p): E = -535.50894310 AU

UB3LYP/aug-cc-pvtz: E = -535.5474946

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -535.5577593

### Cation PhOCH<sub>2</sub>CO<sub>2</sub>H (122<sup>+</sup>).

UB3LYP/6-311+G(2d,p): E = -535.20722747 AU

UB3LYP/aug-cc-pvtz: E = -535.2455421

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -535.3267171

### Acid 4-MePhOCH<sub>2</sub>CO<sub>2</sub>H (303).

UB3LYP/6-311+G(2d,p): E = -574.83709304 AU

UB3LYP/aug-cc-pvtz: E = -574.878329

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -574.8885358

### Cation 4-MePhOCH<sub>2</sub>CO<sub>2</sub>H (303<sup>+</sup>).

UB3LYP/6-311+G(2d,p): E = -574.54764345 AU

UB3LYP/aug-cc-pvtz: E = -574.5888231

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -574.6669601

### Acid 4-*t*-BuPhOCH<sub>2</sub>CO<sub>2</sub>H (304).

UB3LYP/6-311+G(2d,p): E = -692.80775208 AU

UB3LYP/aug-cc-pvtz: E = -692.8575113

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -692.8678447

### Cation 4-*t*-BuPhOCH<sub>2</sub>CO<sub>2</sub>H (304<sup>+</sup>).

UB3LYP/6-311+G(2d,p): E = -692.52231987 AU

UB3LYP/aug-cc-pvtz: E = -692.5720663

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -692.646069

### Acid 4-MeOPhOCH<sub>2</sub>CO<sub>2</sub>H *cis* (278<sub>c</sub>).

UB3LYP/6-311+G(2d,p): E = -650.06645741 AU

UB3LYP/aug-cc-pvtz: E = -650.1132596

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -650.1251373

**Cation 4-MeOPhOCH<sub>2</sub>CO<sub>2</sub>H *cis* (278<sub>c</sub><sup>\*\*</sup>).**

UB3LYP/6-311+G(2d,p): E = -650.06645741 AU

UB3LYP/aug-cc-pvtz: E = -649.8396988

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -649.9169588

**Acid 4-MeOPhOCH<sub>2</sub>CO<sub>2</sub>H *trans* (278<sub>t</sub>).**

UB3LYP/6-311+G(2d,p): E = -650.06606387 AU

UB3LYP/aug-cc-pvtz: E = -650.1128708

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -649.8403027

**Cation 4-MeOPhOCH<sub>2</sub>CO<sub>2</sub>H *trans* (278<sub>t</sub><sup>\*\*</sup>).**

UB3LYP/6-311+G(2d,p): E = -650.06606387 AU

UB3LYP/aug-cc-pvtz: E = -650.1247972

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -649.9172627

**Acid 3-MeOPhOCH<sub>2</sub>CO<sub>2</sub>H (301).**

UB3LYP/6-311+G(2d,p): E = -650.06917168 AU

UB3LYP/aug-cc-pvtz: E = -650.1160242

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -650.1277081

**Cation 3-MeOPhOCH<sub>2</sub>CO<sub>2</sub>H (301<sup>\*\*</sup>).**

UB3LYP/6-311+G(2d,p): E = -649.78265669 AU

UB3LYP/aug-cc-pvtz: E = -649.8293864

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -649.9068673

**Acid 2-MeOPhOCH<sub>2</sub>CO<sub>2</sub>H (302).**

UB3LYP/6-311+G(2d,p): E = -650.05904354 AU

UB3LYP/aug-cc-pvtz: E = -650.1057583

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -650.116515

**Cation 2-MeOPhOCH<sub>2</sub>CO<sub>2</sub>H (302<sup>\*\*</sup>).**

UB3LYP/6-311+G(2d,p): E = -649.78110303 AU

UB3LYP/aug-cc-pvtz: E = -649.8277148

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -649.9046441

**Acid 3,5-DiMeOPhOCH<sub>2</sub>CO<sub>2</sub>H (285).**

UB3LYP/6-311+G(2d,p): E = -764.62806667 AU

UB3LYP/aug-cc-pvtz: E = -764.68494407 AU

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -764.6978636 AU

**Cation 3,5-DiMeOPhOCH<sub>2</sub>CO<sub>2</sub>H (285<sup>+</sup>).**

UB3LYP/6-311+G(2d,p): E = -764.35033790 AU

UB3LYP/aug-cc-pvtz: E = -764.4023231 AU

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -764.4771956

**Acid 3,4,5-TriMeOPhOCH<sub>2</sub>CO<sub>2</sub>H *cis* (286<sub>c</sub>).**

UB3LYP/6-311+G(2d,p): E = -878.907662

UB3LYP/aug-cc-pvtz: E = -879.2317218 AU

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -879.2469809

**Cation 3,4,5-TriMeO-PhOCH<sub>2</sub>CO<sub>2</sub>H *cis* (286<sub>c</sub><sup>+</sup>).**

UB3LYP/6-311+G(2d,p): E = -878.659239

UB3LYP/aug-cc-pvtz: E = -878.9853928 AU

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -879.0569931 AU

**Acid 3,4,5-TriMeOPhOCH<sub>2</sub>CO<sub>2</sub>H *trans* (286<sub>t</sub>).**

UB3LYP/6-311+G(2d,p): E = -879.16840878 AU

UB3LYP/aug-cc-pvtz: E = -879.2375054 AU

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -879.2536305 AU

**Cation 3,4,5-TriMeO-PhOCH<sub>2</sub>CO<sub>2</sub>H *trans* (286<sub>t</sub><sup>+</sup>).**

UB3LYP/6-311+G(2d,p): E = -878.92198901 AU

UB3LYP/aug-cc-pvtz: E = -878.9861185 AU

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -879.0571986 AU

**Acid PhSCH<sub>2</sub>CO<sub>2</sub>H (306).**

UB3LYP/6-311+G(2d,p): E = -858.48749778 AU

UB3LYP/aug-cc-pvtz: E = -858.5270246

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -858.537174

**Cation PhSCH<sub>2</sub>CO<sub>2</sub>H (306<sup>+</sup>).**

UB3LYP/6-311+G(2d,p): E = -858.19958129 AU

UB3LYP/aug-cc-pvtz: E = -858.2388601

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -858.3171062

**Acid 4-MeOPhSCH<sub>2</sub>CO<sub>2</sub>H *cis* (287<sub>c</sub>).**

UB3LYP/aug-cc-pvtz: E = -973.096988 AU

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -973.1093324 AU

**Cation 4-MeOPhSCH<sub>2</sub>CO<sub>2</sub>H *cis* (287<sub>c</sub><sup>+</sup>).**

UB3LYP/aug-cc-pvtz: E = -972.8298526 AU

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -972.9061419 AU

**Acid 4-MeOPhSCH<sub>2</sub>CO<sub>2</sub>H *trans* (287<sub>t</sub>).**

UB3LYP/6-311+G(2d,p): E = -973.04601836 AU

UB3LYP/aug-cc-pvtz: E = -973.09362539 AU

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -973.10554888 AU

**Cation 4-MeOPhSCH<sub>2</sub>CO<sub>2</sub>H *trans* (287<sub>t</sub><sup>+</sup>).**

UB3LYP/6-311+G(2d,p): E = -972.77988485 AU

UB3LYP/aug-cc-pvtz: E = -972.82811764 AU

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -972.90225631 AU

**Acid 4-MeSPhOCH<sub>2</sub>CO<sub>2</sub>H *cis* (288<sub>c</sub>).**

UB3LYP/6-311+G(2d,p): E = -973.04915177 AU

UB3LYP/aug-cc-pvtz: E = -973.096988 AU

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -973.1093324 AU

**Cation 4-MeSPhOCH<sub>2</sub>CO<sub>2</sub>H *cis* (288<sub>c</sub><sup>+</sup>).**

UB3LYP/6-311+G(2d,p): E = -972.78213124 AU

UB3LYP/aug-cc-pvtz: E = -972.8298535 AU

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -972.9061423 AU

**Acid 4-MeSPhOCH<sub>2</sub>CO<sub>2</sub>H *trans* (288<sub>t</sub>).**

UB3LYP/6-311+G(2d,p): E = -973.04890294 AU

UB3LYP/aug-cc-pvtz: E = -973.0967375 AU

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -973.1090995 AU

**Cation 4-MeSPhOCH<sub>2</sub>CO<sub>2</sub>H *trans* (288<sub>t</sub><sup>+</sup>).**

UB3LYP/6-311+G(2d,p): E = -972.78259053 AU

UB3LYP/aug-cc-pvtz: E = -972.8303133 AU

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -972.9061423 AU

**Acid PhNHCH<sub>2</sub>CO<sub>2</sub>H (307).**

UB3LYP/aug-cc-pvtz: E = -515.6816366 AU

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -515.6915143 AU

**Cation PhNHCH<sub>2</sub>CO<sub>2</sub>H (307<sup>+</sup>).**

UB3LYP/aug-cc-pvtz: E = -515.4099793 AU

UB3LYP/aug-cc-pvtz CPCM (solvent = acetonitrile): E = -515.4898162 AU

## 5.0 References

- [1] P. Boulle, J. Lemaire, *J. Chim. Phys. & Phys-Chim. Bio* **1980**, *77*, 161-165.
- [2] H.-D. Scharf, F. Korte, *Chem. Ber.* **1965**, *98*, 3672-3679.
- [3] H. D. Scharf, F. Korte, *Angew. Chem. Int. Ed.* **1965**, *77*, 452-452.
- [4] J. S. Bradshaw, *Tetrahedron Lett.* **1966**, *7*, 2039-2042.
- [5] K. I. Booker-Milburn, C. E. Anson, C. Clissold, N. J. Costin, R. F. Dainty, M. Murray, D. Patel, A. Sharpe, *Eur. J. Org. Chem.* **2001**, 1473-1482.
- [6] K. L. Cubbage, A. J. Orr-Ewing, K. I. Booker-Milburn, *Angew. Chem. Int. Ed.* **2009**, *48*, 2514-2517.
- [7] J. v. Sonntag, W. Knolle, *J. Photochem. Photobiol. A: Chem.* **2000**, *136*, 133-139.
- [8] M. A. S. Al-Amoudi, J. M. Vernon, *J. Chem. Soc., Perkin Trans. 2* **1999**, 2667-2670.
- [9] U. C. Yoon, S. W. Oh, S. M. Lee, S. J. Cho, J. Gamlin, P. S. Mariano, *J. Org. Chem.* **1999**, *64*, 4411-4418.
- [10] a) A. Soldevilla, R. Perez-Ruiz, Y. D. Miara, A. Griesbeck, *Chem. Commun.* **2010**, *46*, 3747-3749; b) M. Horvat, K. Mlinaric-Majerski, A. G. Griesbeck, N. Basaric, *Photoch. Photobiol. Sci.* **2011**, *10*, 610-617; c) A. G. Griesbeck, N. Nazarov, J. M. Neudorfl, M. Heffen, *Green Chem.* **2012**, *14*, 3004-3006.
- [11] A. G. Griesbeck, K.-D. Warzecha, J. M. Neudörfl, H. Görner, *Synlett* **2004**, 2347-2350.
- [12] S. Jonsson, K. Viswanathan, C. E. Hoyle, S. C. Clark, C. Miller, C. Nguyen, W. Zhao, L. Shao, F. Morel, C. Decker, *J. Photopolym. Sci. Technol.* **2000**, *13*, 125-143.
- [13] Z. Lu, R. J. Twieg, *Tetrahedron Lett.* **2005**, *46*, 2997-3001.
- [14] A. Shafir, S. L. Buchwald, *J. Am. Chem. Soc.* **2006**, *128*, 8742-8743.
- [15] V. B. Raandive, S. D. Samant, *Indian J. Chem., Sect. B* **1995**, *34B*, 102.
- [16] R. G. Pearson, J. Songstad, *J. Am. Chem. Soc.* **1967**, *89*, 1827-1836.
- [17] M. Sekiya, Y. Terao, *Chem. Pharm. Bull.* **1971**, *19*, 391-394.
- [18] M. Nishino, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2011**, *76*, 6447-6451.
- [19] D. W. Manley, A. Mills, C. O'Rourke, A. M. Z. Slawin, J. C. Walton, *Chem. Eur. J.* **2014**, Article ASAP.
- [20] B. C. Gilbert, C. J. Scarratt, C. B. Thomas, J. Young, *J. Chem. Soc., Perkin Trans. 2* **1987**, *0*, 371-380.
- [21] a) P. B. Ayscough, A. J. Elliot, *J. Chem. Soc., Faraday Trans. 1* **1976**, *72*, 791-798; b) J. von Sonntag, D. Beckert, W. Knolle, R. Mehnert, *Rad. Phys. Chem.* **1999**, *55*, 609-613.
- [22] J. von Sonntag, W. Knolle, S. Naumov, R. Mehnert, *Chem. Eur. J.* **2002**, *8*, 4199-4209.
- [23] Gaussian 09, Revision A.02, Frisch, M. J. et al. Gaussian, Inc., Wallingford CT, 2009 (see general experimental section for full citation).
- [24] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648-5652.
- [25] M. Cossi, N. Rega, G. Scalmani, V. Barone, *J. Comp. Chem.* **2003**, *24*, 669-681.
- [26] a) E. Vauthey, *J. Photochem. Photobiol. A: Chem.* **2006**, *179*, 1-12; b) S. R. Manjari, H. J. Kim, *J. Chem. Phys.* **2006**, *125*, 011101-011104; c) Y. Yoshimi, S. Hayashi, K. Nishikawa, Y. Haga, K. Maeda, T. Morita, T. Itou, Y. Okada, N. Ichinose, M. Hatanaka, *Molecules* **2010**, *15*, 2623-2630.
- [27] J. A. Pedersen, *CRC Handbook Of EPR Spectra From Quinones And Quinols*, CRC Press, **1985**.
- [28] *Landolt-Bornstein: Numerical Data and Functional Relationships in Science and Technology - New Series - Group II: Atomic and Molecular Physics., Vol. 9*, Springer-Verlag, Berlin, Heidelberg, New York, **1977**.
- [29] V. Khodorkovsky, L. Shapiro, P. Krief, A. Shames, G. Mabon, A. Gorgues, M. Giffard, *Chem. Commun.* **2001**, 2736-2737.
- [30] a) A. Zweig, W. G. Hodgson, W. H. Jura, *J. Am. Chem. Soc.* **1964**, *86*, 4124-4129; b) P. O'Neill, S. Steenken, D. Schulte-Frohlinde, *J. Phys. Chem.* **1975**, *79*, 2773-2779; c) C.

- Sieiro, P. Calle, N. Lorenzo, *Mol. Struct. (Theochem)* **1998**, 433, 329-338; d) J.-H. Dong, H.-Y. Dou, Y.-F. Gong, C.-X. Zhao, *Res. Chem. Intermed.* **2006**, 32, 137-144.
- [31] M. Morimoto, H. Fukumoto, T. Nozoe, A. Hagiwara, K. Komai, *J. Agric. Food Chem.* **2007**, 55, 700-705.
- [32] S. Cabiddu, C. Fattuoni, C. Floris, G. Gelli, S. Melis, *Tetrahedron* **1993**, 49, 4965-4974.
- [33] D. W. Manley, R. T. McBurney, P. Miller, R. F. Howe, S. Rhydderch, J. C. Walton, *J. Am. Chem. Soc.* **2012**, 134, 13580-13583.

## **Chapter 5:**

## **Outlook**

## 1.0 Conclusions

Titania SCPC has been successfully applied to a number of synthetically valuable reactions. Photolysis of carboxylic acids containing groups which resulted in the generation of resonance stabilised radicals, in CH<sub>3</sub>CN dispersions of platinised titania, led to the selective formation of the radical homodimers. These reactions were generally selective, with the reduced alkane only being formed in a few instances, high yielding and showed wide applicability. This approach has been extended to the preparation of cyclophanes with moderate success. Carboxylic acid precursors bearing a wide variety of radical stabilising groups were found to alkylate electron deficient alkenes in yields ranging from poor to moderate to excellent. When this approach was applied with aryloxyacetic acids and maleates a cascade annulation process occurred in conjunction with the Michael addition, leading to mixtures of tricyclic chromene derivatives and the addition adducts being obtained. The selectivity between these two products could be tuned to a reasonable degree by altering the form and deployment of the titania catalyst. Inclusion of methanol in the reaction medium as a sacrificial hole scavenger allowed the scope of the titania SCPC method to be extended to reductive processes. The reduction of a range of maleates to the corresponding succinates has been carried out cleanly and very effectively using this approach.

The major goal of this work was to answer the question of whether titania SCPC could be developed as a novel organic methodology to cleanly, selectively and efficiently carry out important transformations in an environmentally friendly manner. The examples discussed above illustrate that in several instances this goal has been realised with a number of oxidative and reductive functional group transformations and bond forming processes carried out successfully to date. Thus, titania SCPC reactions with carboxylic acids, and related species, have been developed as a noteworthy new entry in the field of carbon-centered radical generation. The protocols currently lack general applicability due to the necessity for radical stabilising groups in the precursors however.

Another goal of this investigation was to elucidate mechanisms at play in the SCPC reactions. EPR studies have suggested that at least some of the acid derived radicals are released from the surface and are tumbling freely in solution. Thus reactions of the titania-generated radicals are likely to take place, at least partially, in solution. The origin of the additional hydrogen atom in the reaction products has tentatively been assigned to the titania surface in a reduction/protonation sequence. Deuterium labelling experiments were inconclusive in proving this however. The role of the titania surface in the SCPC reaction

mechanisms is still unclear and makes logical reaction design based on previous results difficult. The dissimilar reactivity of benzyl and allyl radicals in chapter 3 is an example of this. More detailed studies on the mechanistic implications of the interactions between the solvated organic reactants and the inorganic heterogeneous catalyst are needed in order to overcome this.

A catalyst-independent process was serendipitously discovered during the course of the work on the SCPC mediated addition-cyclisation reactions. These reactions were generally more selective than their titania mediated counterparts as the reduction-protonation pathway was removed in the absence of the catalyst. Yields ranged from low to near-quantitative. A fascinating mechanism whereby maleimide acts in a little-documented role as a redox catalyst in its excited state has been put forward. This mechanism has been supported in great detail by high level DFT computations coupled with UV-Vis and EPR spectroscopy.

## 2.0 Future Work

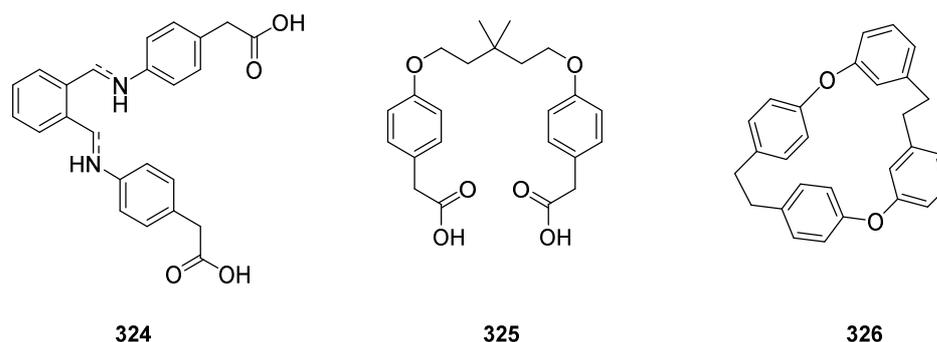
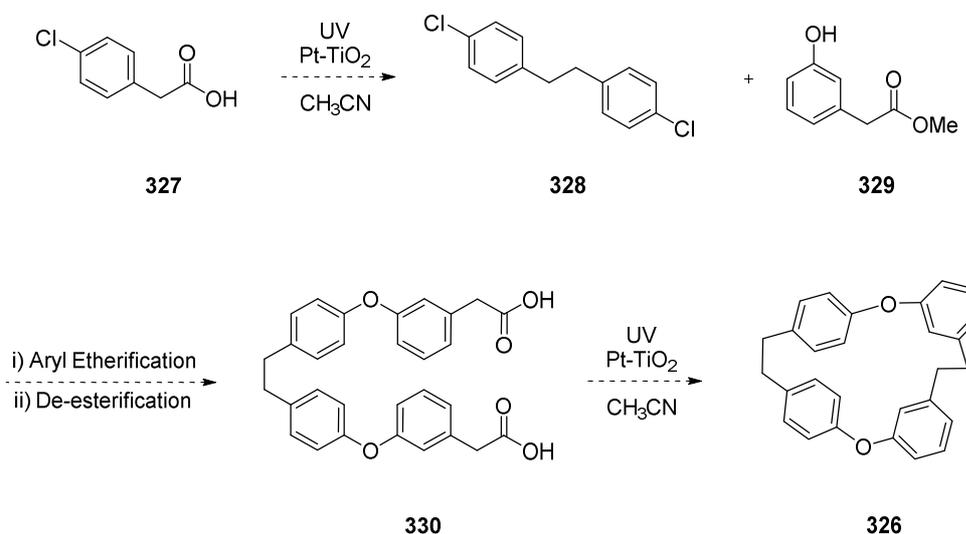


Figure 1.

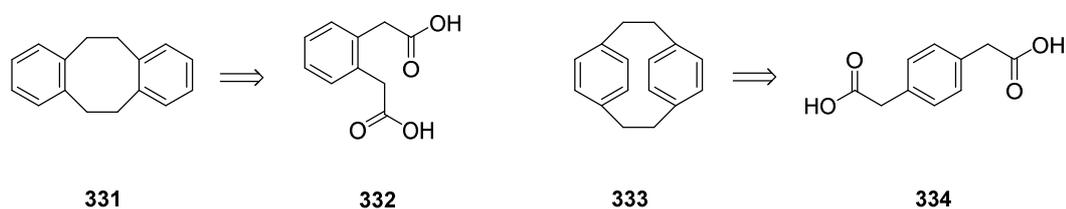
The preparation of cyclophane macrocycles is to be further explored using modified precursors based on the results obtained to date (**324** & **325** Fig. 1). Inclusion of certain functionalities known to favour cyclisations on the linker between the two phenylacetic acid moieties is also to be investigated. The gem-dimethyl group is well known to have this effect (Thorpe-Ingold effect).<sup>[1]</sup> The macrocyclic bis(bibenzyls) are a family of natural products commonly found in liverworts and other bryophytes. Each has a core comprising four aromatic rings and two ethano bridges. The cyclophane **326** is a core structure present in a number of these natural products, specifically the marchantins of which pakyonol is the only member to be prepared to date.<sup>[2]</sup>



Scheme 1.

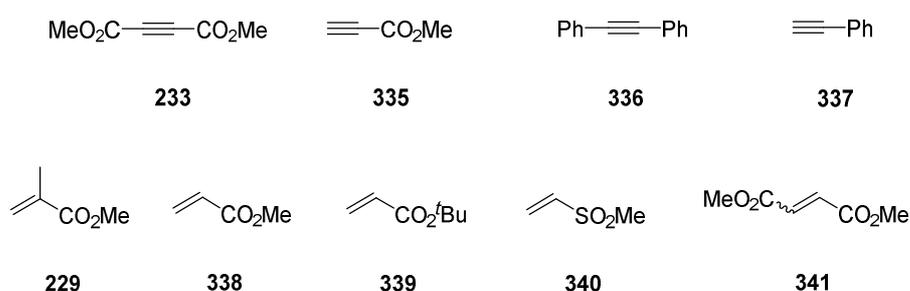
It can be easily envisaged how the two bibenzyl linkages of **326** could be constructed using the SCPC protocol developed in chapter 2. Intermolecular dimerisation of **327** can be

expected to proceed well based on results thus far. Aryl-etherification followed by deprotection would yield diacid **330** which would then be subjected to macrocyclisation (sch. 1).



**Scheme 2.**

Simple cyclophanes **331** and **333** could potentially be prepared very easily in one pot from diacids **332** and **334**. This is also to be investigated (sch. 2). The scope of the carboxylic acid component within the titania SCPC reactions has been studied extensively during the course of this work, both in the single acid irradiations for dimerisations and in the radical 1,4-additions. The number of radical acceptor used has been very limited however. The acceptor variation carried out was done exclusively with phenoxyacetic acid **122**. Since then, potentially more selective and higher yielding entities such as methoxyacetic acid **246** and tetrahydrofuroic acid **252** have been identified. The reactions of these acids could potentially provide a more suitable test-bed for identifying new radical acceptors compatible with this protocol.



**Figure 2.**

This approach could be particularly fruitful for the reaction of acetylene **233** with the acid derived radicals. Its reaction with **122** was high yielding (*ca.* 80%) but due to the number of reaction pathways opened up by the interaction of the vinyl radical formed upon addition to **233** with the neighbouring aryl moiety it was rather unselective. Reactions with **246** and **252** could potentially be much more selective. If successful this approach could be extended to a number of other acetylenes (**335**, **336** and **337** for instance). Similarly, these two acids

could be used to screen a range of acrylates, sulfones and other acceptors (Fig. 2) in hopes of achieving higher yields and less oligeramisation than in previous instances.

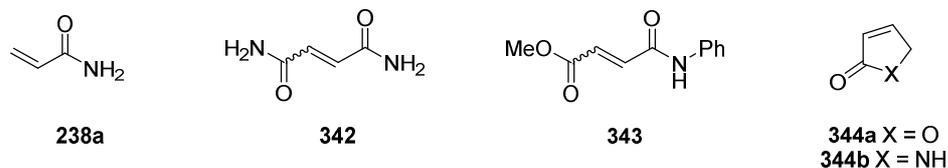


Figure 3.

The reduction of maleates **219** to succinates **228** by the conduction band of the photoexcited titania proceeded cleanly and selectively. The scope of this process could be expanded to test its limits. Non-cyclic electron deficient alkenes, based upon the maleates already trialled, can be examined to see if their reductions proceed as efficiently or at all (Fig. 3). The reactivity of other substrates such as acetylenes, phthalimides, aromatic ketones and aldehydes and activated alkyl halides could also be investigated. More reductive semiconductors such as CdS and ZnS may be useful for this.

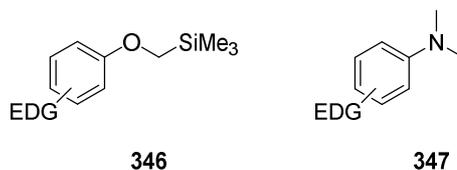


Figure 4.

The scope of the carboxylic acids compatible with the catalyst free reaction discussed in chapter 4 has been well examined. As the maleimide component was found to be essential the applicability of this process could be expanded by using different fragmentable electron donors in place of the carboxylic acid. Electron rich silanes **346** and tertiary amines **347** could potentially prove successful using this approach.

### 3.0 Bibliography

- [1] M. N. Levine, R. T. Raines, *Chem. Sci.* **2012**, *3*, 2412-2420.
- [2] D. C. Harrowven, S. L. Kostiuik, *Nat. Prod. Rep.* **2012**, *29*, 223-242.

## Appendices

### List of publications:

1. Unconventional Titania Photocatalysis: Direct Deployment of Carboxylic Acids in Alkylations and Annulations. D. W. Manley, R. T. McBurney, P. Miller, R. Howe, Shona Rhydderch, J. C. Walton. *J. Am. Chem. Soc.*, **2012**, *134* (33), 13580–13583.
2. Titania Promoted Carboxylic Acid Alkylations of Alkenes and Cascade Addition-Cyclizations. D. W. Manley, R. T. McBurney, P. Miller and J. C. Walton, *J. Org. Chem.*, **2014**, *79*(3), 1386–1398.
3. Catalyst-Free Photoredox Addition-Cyclisations: Exploitation of Natural Synergy between Aryl Acetic Acids and Maleimide. D. W. Manley, A. Mills, C. O'Rourke, A. M. Z. Slawin and J. C. Walton, *Chem. Eur. J.* **2014**, *20*, 5492 – 5500.

These publications are available in pdf form on the CD enclosed in the inside rear cover.