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Photochemical Approaches to Azetidines

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Declaration

All work presented in this Thesis is the original work of the author, with the exception of results referenced to other sources. It has not been submitted as part of another degree or professional qualification.

Signed: 

Date: 27/03/2022

Kipp Baldwin

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Abstract

This thesis concerns the application of continuous flow photochemistry to the 4π electrocyclisation of nitrogen-containing heterocycles, in particular 2-pyridinones and 1,2-dihydropyridines, for the synthesis of so-called Dewar heterocycles, which were envisaged as convenient starting materials for the synthesis of sp^3-rich, highly substituted small molecules.

The introduction chapter covers a brief history of photochemistry in organic synthesis, as well as the basic principles of organic photochemistry. The synthesis and subsequent uses of various Dewar heterocycles is then discussed, with a focus on Dewar heterocycles derived from 2-pyrones, 2-pyridones and 1,2-dihydropyridines, the latter of which includes discussion on the chemical properties of 1,2-dihydropyridines and synthesis of derivatives by various methods.

The results and discussion chapter first describes construction of a continuous flow photochemical reactor based on the design developed by the Booker-Milburn group and its application to the synthetic goals.[1]

Initially, commercially available 2-pyridones were transformed into azetidinone-bearing Dewar structures. Following optimisation of productivity, a novel route to a cyclobutane-containing β-amino acid was achieved in 3 steps from the Dewar azetidinone, requiring no chromatographic purification in an overall 60% yield.

Subsequently, photosynthesis of azetidine bearing Dewar heterocycles from 1,2-dihydropyridines was investigated. A selection of 1,2-dihydropyridines were synthesised by addition of various nucleophiles to acyl pyridinium salts, and subsequently transformed by photoirradiation. Productivities of up to 1622 mg h^{-1} were achieved, which compared favourably with a batch method with maximum productivity of 67 mg h^{-1}.

Next, a synthesis of dihydropyridines with quaternary substitution at the 2-position by heating propargyl vinyl ethers with primary amines was employed. Subsequent irradiation gave the corresponding Dewar azetidines

with good productivity. This route was an interesting way to make novel spirocyclic azetidines.

Further transformations of the Dewar photoproducts were investigated with the aim of accessing highly substituted, sp^3-rich small molecules. Of the methods investigated, a route involving epoxidation and further Lewis acid promoted substitution was the most productive.

Abbreviations

Common abbreviations used are listed in the Journal or Organic Chemistry abbreviations web page.*

BINAP	(2,2’-bis(diphenylphosphino)-1,1’-binaphthyl)
CM	cross metathesis
CSI	chlorosulfonylisocyanate
DHP	dihydropyridine
DMAD	dimethyl acetylenedicarboxylate
EDA	ethyl diazoacetate
FEP	fluoroethylene propylene
LED	light-emitting diode
PTFE	polytetrafluoroethylene
RCD	residual-current device
ROM	ring-opening metathesis
TPP	tetraphenylporphyrin

*Common abbreviations can be accessed on the JOC website:

http://pubs.acs.org/userimages/ContentEditor/1218717864819/joceah_abbreviations.pdf

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Table of Contents

1 Introduction 1
1.1 Photochemistry for the synthesis of small molecules 1
1.1.1 The Importance of sp^3-rich molecules 1
1.2 History of Photochemistry 2
1.3 Photochemical Principles 3
1.4 Practical Photochemistry 4
1.4.1 Modes of Illumination 4
1.4.2 Batch versus Flow Photochemistry 5
1.4.3 Applications of Flow Photochemistry 7
1.5 Dewar Heterocycles 11
1.5.1 Dewar 2-pyrone 17
1.5.2 Dewar 2-pyridone 21
1.6 Dewar 1,2-dihydropyridines 29
1.6.1 Synthesis 29
1.6.2 Uses 41
2 Aims and Objectives 56
3 Results and Discussion 58
3.1 Reactor Construction 58
3.2 Dewar 2-Pyridone Synthesis 63
3.3 Dewar 2-Pyridone Reactivity 69
3.3.1 β-Amino Acid Synthesis 69
3.3.2 Azocinone Derivative Synthesis 71
3.3.3 Dewar 2-Pyridone *N*-H Insertion 74
3.4 Synthesis of Dewar 1,2-Dihydropyridines 76
3.4.1 Batch Synthesis 78
3.4.2 Continuous Flow Synthesis 80
3.4.3 Summary 89
3.5 Synthesis of Substituted Dewar Dihydropyridines 90
3.6 Route to Quaternary Dewar Dihydropyridines 95
3.7 Investigations into Dewar 1,2-dihydropyridine reactivity 97
3.7.1 Rearrangement to Bridged Pyrrolidines 97
3.7.2 Investigation into alkene oxidations 102
3.8 Comparison Between Dewar Heterocycle Reactivity 111

4 Summary and Future Work.....115
4.1 Reactor Construction.....115
4.2 Dewar 2-pyridones 115
4.3 Dewar 1,2-Dihydropyridines.....117
4.4 Future Work 120
5 Experimental.....122
6 References.....163

1 Introduction

1.1 Photochemistry for the synthesis of small molecules

1.1.1 The Importance of sp^3-rich molecules

Analysis of drug molecules found that the chemical space they occupy was relatively small, compared to the theoretical chemical space available, with the majority of drug molecules possessing extended sp^2 scaffolds.[2] This was attributed partly to the limited variety of chemical reactions typically performed, with amine alkylation, amide bond formations and palladium coupling reactions being the most popular.[3,4] A comparison between drug molecules and natural products revealed that the latter occupy a much wider area of chemical space, and in general possess more stereocentres, increased scaffold diversity, more bridged carbocycles and more spirocyclic centres.[3] The need to explore more areas of chemical space therefore requires molecules which are more 'natural product-like' and as such, molecules rich in sp^3 hybridised centres are highly desirable in this regard.[5–7]

Analysis of the GVK BIO database by Lovering and co-workers showed that molecules with high Fsp^3 (fraction of sp^3 centres i.e., the ratio of sp^3 carbon centres to the total number of carbon atoms) were more likely to proceed through clinical trials. In a later study, they also showed that molecules with high Fsp^3 and chiral carbon count values are less likely to induce off-target effects through non-specific binding, which often cause toxicity.[5,6,8,9] In this analysis Lovering *et al*. found that inhibitor promiscuity decreased with increasing Fsp^3 and chiral carbon count. This analysis was fortified by Hann who showed that more structurally complex molecules made for more efficient binding partners to proteins.[10] Experimental demonstration of this analysis was achieved by screening ~15,000 molecules against 100 different proteins and showed that increased shape complexity and intermediate stereogenic complexity increased binding frequency and selectivity when compared to commercially available compounds and

natural products. Where shape complexity is the ratio of sp^3 carbon atoms to the total sp^3 and sp^2 hybridised carbon atom, and stereogenic complexity is the ratio of stereogenic carbon atoms to total number of carbon atoms.[11]

It is clear from these analyses that there is a need to diversify the structures of drug molecules and move towards developing robust syntheses of structurally complex molecules, with high sp^3 character to improve the number of successful drug candidates, by reducing toxicity and improving pharmacokinetic properties.

Utilising photochemically accessible reaction pathways can give rise to complex scaffold structures amenable to further modification, and thus generation of small molecule compound arrays with distinctive backbone structures. Photochemistry is particularly useful in the synthesis of saturated polycyclic and bridged cyclic structures, either carbocyclic or heterocyclic in nature.[12,13] For example, this chemistry has been exploited to great effect in the synthesis of bioactive natural products which possess unusual and complex scaffold structures and as such can be applied to the synthesis of small molecules.[13,14]

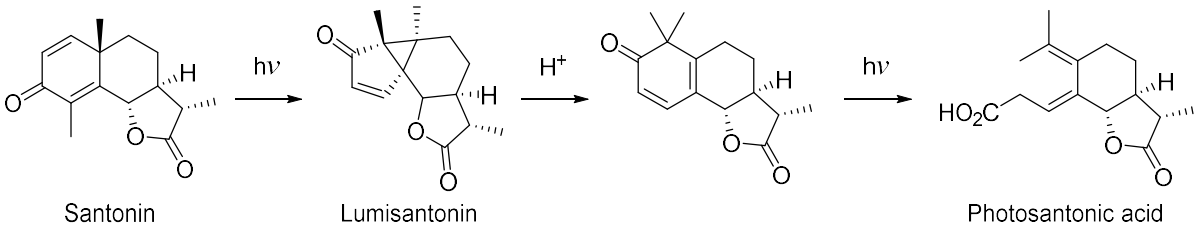
1.2 History of Photochemistry

The use of light in a chemical process has fascinated chemists for the last 300 years and many of the early experiments were undertaken by some of the founding fathers of modern chemistry. Although most of these early reactions were actually thermal processes brought about through the heat generated by focussing sunlight, Joseph Priestly did investigate some genuine photochemical processes, specifically the generation of nitrogen dioxide by the irradiation of nitric acid vapours with sunlight.[15]

The first photochemical reaction of an isolated organic compound in the laboratory was observed in 1834, where Trommsdorff noted that crystals of santonin began to yellow in colour, and occasionally burst open. He also noted, upon experiments utilising a prism to separate the wavelengths of

the incident light, that only blue-violet light promoted the reaction; the first example of an experiment investigating the wavelength dependence of an organic photoreaction.[15]

Trommsdorff's observations were further developed by Italian chemists Fausto Sestini and Stanislao Cannizzaro, who were able to isolate two different photoproducts, photosantonic acid and isophotosantonic acid (Scheme 1). The structures of these photoproducts eluded them, however, and would not be elucidated until 1958, with intermediates discovered later, in 1963.[16–19] The early-mid 20th century saw a vast increase in the activity in the field. However, towards the later decades of the 20th century, photochemistry fell out of favour, and the number of papers covering the subject reduced significantly. After its hiatus from the spotlight, the 2000's and 2010's saw a renaissance in photochemistry, with many chemists now rediscovering the benefits of photochemical processes and furthering the field once more.



Scheme 1: Synthesis of photosantonic acid by irradiation of santonin. The structure of the intermediate Lumisantonin was only elucidated in the 1960's.

1.3 Photochemical Principles

There are two laws that govern photochemistry:

- The Grotthuss-Draper law states that in order for a photochemical reaction to occur, light must be absorbed.
- The Stark-Einstein law states that no more than one molecule can be excited per photon absorbed.

- For a molecule to absorb light and enter an excited state, the wavelength of the incident light must correspond to the energy of an allowed electron transition of the molecule in question. When the molecule is in an excited state, additional reaction pathways become accessible, and the scope of available products increases (Figure 1). This is the key to why photochemistry is such a powerful tool in organic chemistry, as it allows access to structures that are either impossible or very difficult to access through 'conventional' means.

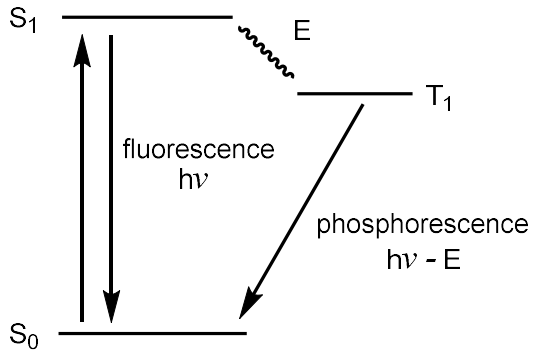


Figure 1: Jablonski diagram showing absorption of light and promotion to the first excited state. Energy is lost either by fluorescence, or by intersystem crossing to the triplet state, followed by phosphorescence.

1.4 Practical Photochemistry

1.4.1 Modes of Illumination

Traditionally mercury vapour lamps have been used for UV photochemistry, as they provide a broad spectrum of UV radiation, allowing the user to perform a wide range of reactions using the same light source. They are available with varying vapour pressures, which allows for a degree of control of the range of wavelengths output. In addition to selecting the required pressure, UV filters can be used to block radiation below certain wavelengths, for instance, quartz glass blocks radiation below ~250 nm, Pyrex® below ~300 nm and uranium glass below ~350 nm. Despite this, the broad band emission is still a drawback, as irradiation at different wavelengths may cause competing reactions to occur as other electron

transitions are accessed. These lamps also have high operating temperatures and require active cooling.

A more modern light source, which is becoming increasingly available, are LEDs, with both visible light and UV LEDs seeing use in photochemistry.[20,21] UV LEDs seem like an attractive alternative to mercury vapour lamps: they are energy efficient, meaning that passive cooling is sufficient, and they can provide near-monochromatic light, allowing for a greater degree of control of the reaction taking place. However, UV LEDs are still expensive compared to mercury vapour lamps, and tend to only be suitable for small-scale microreactors, due to their low power. These two factors mean that in many cases the use of mercury vapour lamps is favourable, for the time being, until UV LED technology has advanced to a point where high-powered LEDs become available.

1.4.2 Batch versus Flow Photochemistry

1.4.2.1 Batch Photochemistry

Traditionally a researcher would perform photochemical transformations using a batch methodology, for example, by using an immersion well photoreactor. For this, the substrate solution must first be degassed, usually by sonication or freeze-pump-thaw techniques, to eliminate oxygen, and prevent the formation of singlet oxygen during irradiation. The double-jacketed, water-cooled immersion well, which houses the lamp, is then placed in the flask containing the substrate solution for irradiation. The equipment is relatively inexpensive and a convenient scale for use in the laboratory for small batches of product, however, it, and batch photochemistry in general, does have some drawbacks.

Typically, with this kind of batch photoirradiation there is difficulty in scaling up the reactions. While this method offers scales of a few grammes of material, anything beyond this will lead to long reaction times and the need for higher concentration solutions, both of which may lead to the formation

of unwanted side-products. This issue is exacerbated by the exponential reduction in transmission through the reaction solution, as given by the Beer-Lambert equation (equation 1), causing the outer few millimetres of solution to experience greater irradiation than the solution at greater penetration depth.

$$A = \varepsilon cl = -\log_{10}\frac{I}{I_0} \quad (1)$$

Batch methods that aim to minimise the effect of the reduction in transmission have been developed, such as Rayonet Reactor© systems, which position a batch of solution in the middle of an array of lamps, aiming to irradiate the sample with maximum intensity. However, they still only allow for relatively small batches, and reaction times are often still long.

1.4.2.2 Flow Photochemistry

A developing field over the last 20 years, flow photochemistry has been applied to a range of small molecule syntheses and has often been found to negate the downfalls found in batch photochemistry. Generally, flow photochemical reactors fall into one of two categories. Microflow reactors are precision engineered reactors generally consisting of a UV transparent block with a set of etched channels with a path length of <1 mm thickness. These can accommodate flow rates of a few microlitres per minute.[22] The main drawback of microflow reactors is their poor productivity, and since the surface of the reactor is planar, the reactor has limited exposure to the incident light.[23]

Macroflow reactors can vary in design, however the most common general design involves the flow of reactant solution through tubing of >0.5 mm diameter around the light source, to capture the maximum light possible, with flow rates of >1 mL min^{-1}. Both designs have benefits over batch photochemistry.[23]

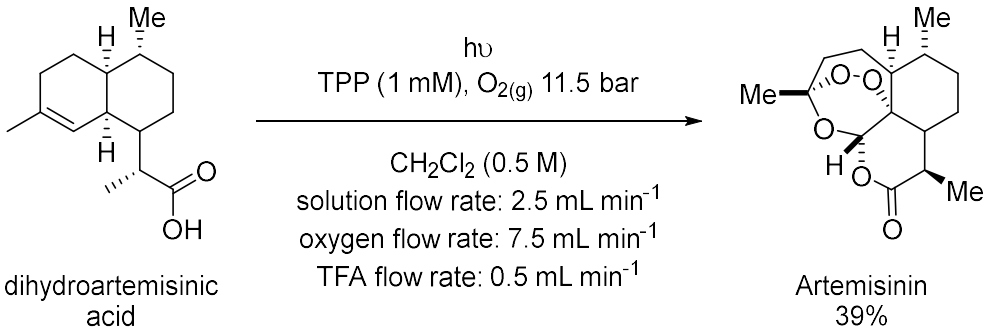
In a photochemical flow reactor, the path length is dependent on the diameter of the channel or tube the solution is pumped through, a small diameter reduces the effects of light attenuation by the reaction solution. This gives a more uniform irradiation in comparison to batch photochemistry. The short path length allows solutions of higher concentration to be used without increasing reaction times, as would be the case in a batch photoreactor. The exposure time, or reaction time can be controlled by altering the flow rate of the reaction solution, preventing over-irradiation. Further to this, Booker-Milburn and co-workers found that the optimum flow rate for a photoreaction under continuous flow could be calculated using the optimum reaction time under batch conditions, thus reducing the need to repeated experiments at varying flow rates to determine the optimum.[24] Perhaps one of the most attractive benefits of flow photochemistry over conventional batch photochemistry is that reaction scale is based solely on the amount of time the photoreactor is allowed to run.

1.4.3 Applications of Flow Photochemistry

An important application of photochemical flow technology was in the synthesis of artemisinin, an important anti-malarial drug, by Seeberger and co-workers.[25,26] Their investigation into the application of flow chemistry to the semi-synthesis of artemisinin was an important step towards finding an easily scalable synthesis of artemisinin, which previously had been extracted directly from the leaves of the artemisia herb, and previously reported synthetic routes were too synthetically complex for large-scale production.[27,28]

In their setup Seeberger and co-workers used flow chemistry to control the addition of reagents during the reaction (Scheme 2). Oxygen was pumped into the flowing dihydroartemisinic acid/tetraphenylporphyrin solution such that a so-called ‘slug-flow’ was achieved, where bubbles of oxygen move along with the flow of solvent, separating portions of solution inside the

reactor tubing. The irradiation of the flowing gas/liquid mixture allowed the reaction between the dihydroartemisinic acid and the singlet oxygen generated by the excitation of oxygen. Their setup was such that the outflow from the photoreactor was then mixed with trifluoroacetic acid before entering a temperature-controlled PTFE reactor where the acid promoted Hock cleavage took place, before being dropped into a solution of $NaHCO_3$ for subsequent work-up. They determined that the increase in productivity over batch methods used could produce up to 200 g of artemisinin in a single day.[25]

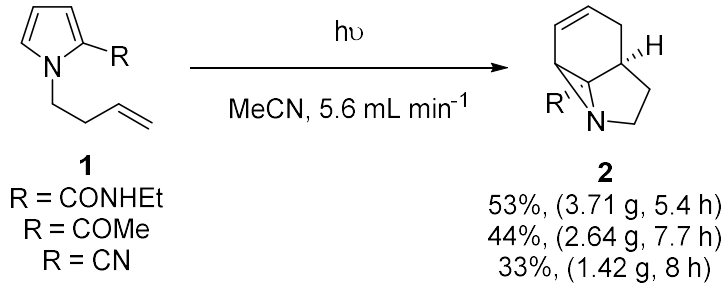


Scheme 2: Seeberger, Lévesque and co-worker's continuous flow synthesis of artemisinin from dihydroartemisinic acid.

The adaptation of photochemistry to flow conditions has also made improvements in the production of small molecules by improving productivity, and therefore economic viability. Booker-Milburn and co-workers have demonstrated the use of flow photochemistry in the production of several small molecules at multi-gram scales.

In one paper Booker-Milburn *et al*. utilised an FEP photochemical reactor, consisting of a coil of UV transparent FEP tubing wrapped around a quartz tube, housing a low-pressure UV lamp, to synthesise a highly strained aziridine **2** (Scheme 3).[29] Pyrrole **1** was irradiated using three single layer FEP reactors connected in series, each fitted with 36 W low-pressure lamps, affording the strained aziridine species **2**.[29] The use of a continuous flow photoreactor was necessary to facilitate the production of the aziridine at

high productivity, as due to the high extinction coefficient and low quantum yield, the batch reaction needed to be run at high dilution, therefore giving a low productivity.[30] When performing the reaction in the continuous flow photoreactor, the reaction gave high productivity, generating up to 4 g in 5-8 hours in a single pass through the reactor.

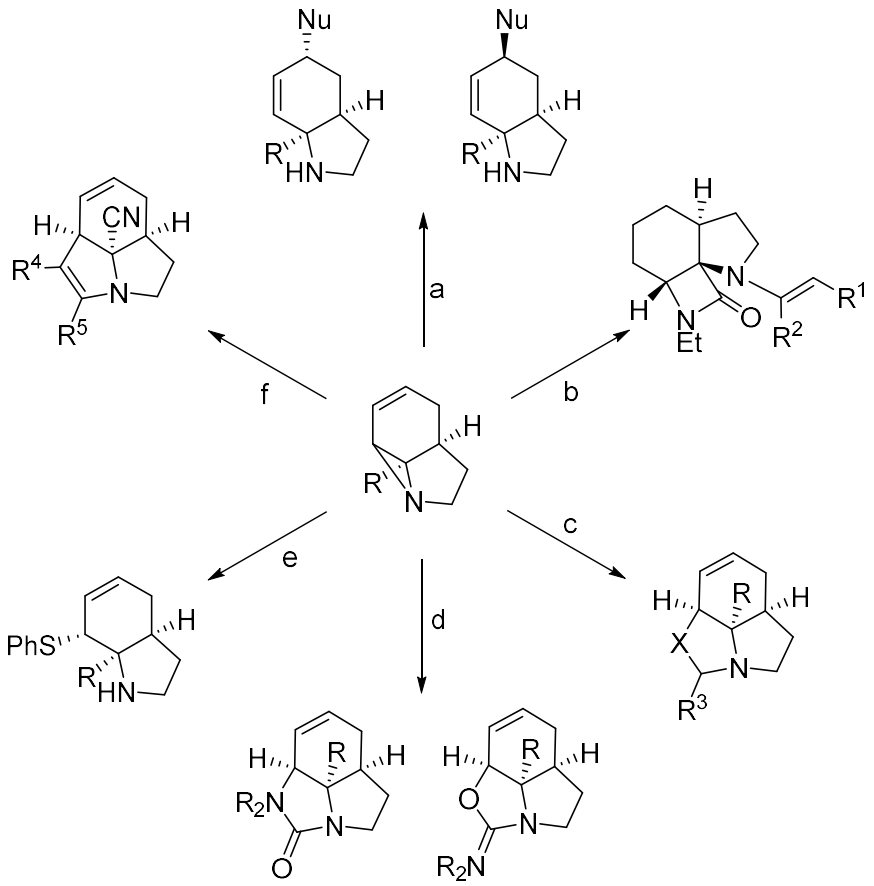


1
R = CONHEt
R = COMe
R = CN

2
53%, (3.71 g, 5.4 h)
44%, (2.64 g, 7.7 h)
33%, (1.42 g, 8 h)

*Scheme 3: Continuous flow synthesis of the aziridine **2**, a synthetically useful precursor to a range of structurally diverse small molecules.*

The highly strained aziridine **2** was then subjected to a series of palladium-catalysed reactions with an array of coupling partners to afford bicyclic and tricyclic compounds with a high proportion of sp^3 centres, and good scope for further functionalisation (Scheme 4). Examples include the generation of the tricyclic lactam containing a vinyl amine (Scheme 4, b) and strained tricyclic dienes (Scheme 4, f).



Scheme 4: a) NuH (e.g. PhOH $CH(CN)_2$, $CH(COCH_3)_2$), 5 mol% $Pd(PPh_3)_4$, dioxane or MeCN, rt-80 °C; b) $Pd_2(dba)_3$ (3 mol%), $P(OPh)_3$ (0.25 eq), TBAI (0.1 eq), CH_2Cl_2, 36 °C, or alkyne, MeCN, rt; c) alkene/aldehyde/imine (X = CR_2, NTs or O), $Pd_2(dba)_3$ (3 mol%), $P(OPh)_3$ (0.25 eq), TBAI (0.1 eq), CH_2Cl_2, 36 °C, 16 h; d) R^2NCO, $Pd(PPh_3)_4$ (5 mol%), dioxane, rt; e) PhSH, Et_3N, THF, rt, or PhSH, MeCN, rt; f) alkyne, $Pd_2(dba)_3$ (3 mol%), $P(OPh)_3$ (0.25 eq), TBAI (0.1 eq), CH_2Cl_2, 36 °C, or alkyne, MeCN, rt. (R = CONHEt, CO_2Me, R^1 = CO_2Me, CO_2Et, $CONH_2$, CHO, R^2 = H, TMS, CO_2Me, R^3 = H, Me, CO_2Et, Ph, 4-$NO_2C_6H_4$, R^4 = COMe, CHO, CO_2Me, CN, R^5 = H, TMS, CO_2Me).

This exemplified the utility of highly strained molecules that are generated through photochemical techniques, and coupled it with the high productivity and throughput offered by flow photochemistry. Highly strained heterocycles are therefore a valuable feedstock and routes to their synthesis require more investigation. We identified Dewar heterocycles as

a class of heterocycle that may be subject to improved photochemical synthesis using flow photochemistry, and their strained structure may be amenable to further processing to a range of small molecules.

1.5 Dewar Heterocycles

Dewar heterocycles are defined as the valence-bond isomers of heteroaromatic compounds that contain a cyclobutene ring, as such these heterocycles are highly strained species that offer high reactivity and scope for further modification to low molecular-weight, lead-like molecules (Figure 2). Many Dewar heterocycles have been proposed as intermediates in other reactions, however few have been isolated due to many of them being unstable.

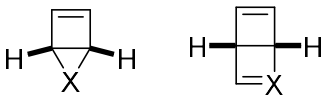


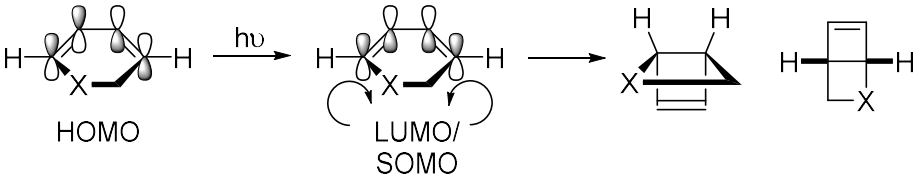
Figure 2: Example Dewar heteocycle structures.

The photoirradiation of a heterocyclic diene allows access to these uniquely strained bicycles, with hinge-shaped structures, by a $4\pi_s$ electrocyclisation. Excitation of the molecule from the ground state to the first excited state permits this reaction pathway. The heterocyclic diene, in this situation, is analogous to 1,3-butadiene. The directionality of the electrocyclisation, that is, whether the bond formation occurs in a conrotatory antarafacial or disrotatory suprafacial fashion under thermal or photochemical conditions is governed by the Woodward-Hoffmann rules.[31] These rules state:

- For a system containing 4n π electrons, in the ground state, the terminal lobes of the HOMO possess opposite symmetry, and for constructive overlap to take place they must rotate in a conrotatory fashion.
- For systems containing 4n + 2 π electrons, to necessitate constructive overlap of the terminal bonds of the HOMO in the ground state, a disrotatory displacement must take place.

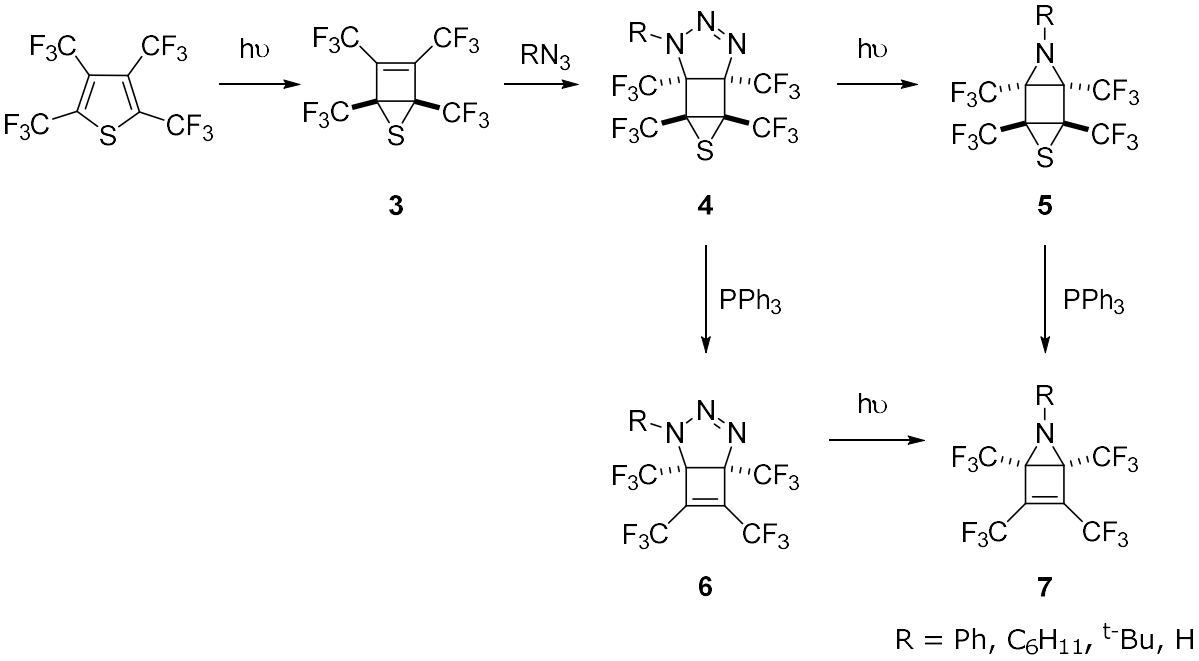
- For electrocyclisations under photochemical control, the relationship between the terminal bond symmetry and displacement mechanism is reversed.

As such, for the case of 1,3-butadiene, and by extension the cyclic heterocycles of interest, the π system contains 4n π electrons, meaning the photochemical process occurs in a disrotatory fashion (Scheme 5). Since the new σ bond is forming between orbital lobes which possess the same symmetry, the new bond is formed suprafacially, hence $4\pi_s$.



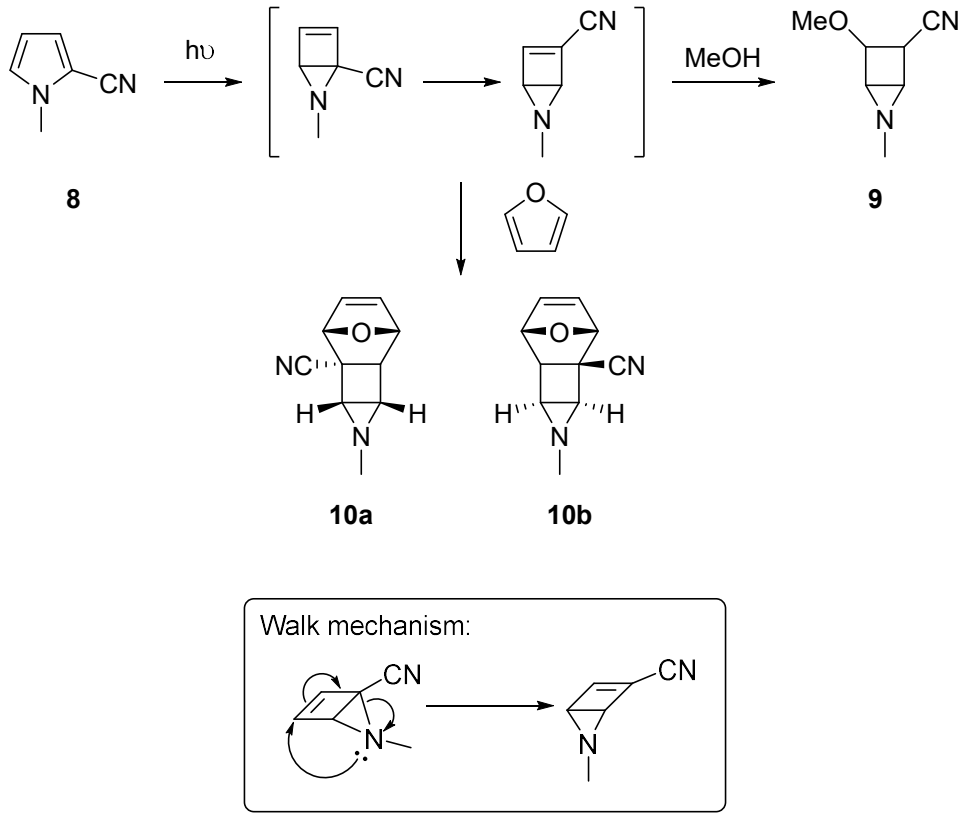
Scheme 5: Excitation of an electron from the HOMO to the LUMO/SOMO permits orbital overlap of the terminal diene orbitals by a disrotatory mechanism, giving rise to a cis-fused bicycle.

Many of the Dewar heterocycles deriving from 5-membered rings are unstable, reverting to their starting isomer, however, highly electron withdrawing substituents appear to have a stabilising effect. The first Dewar heterocycle that was isolated was tetrakis(trifluoromethyl)thiophene **3** (Scheme 6). The structure was in dispute for several years until the Dewar structure was confirmed by ^{19}F and ^{13}C NMR and evaluation of its reactivity in 1972.[32,33] The Dewar thiophene **3** was subsequently used in the synthesis of the Dewar pyrrole **7**, by addition of an azide across the Dewar thiophene alkene, to form the triazole **4**. This was followed by photoirradiation to eliminate N_2, forming the sulphur-containing aziridine **5**, which was then subjected to desulfurisation with triphenylphosphine to yield the Dewar pyrrole **7**. Alternatively desulfurisation could be performed first, furnishing the unsaturated triazole **6**, which was then irradiated to give the desired Dewar pyrrole **7**.[34]



Scheme 6: Generation of Dewar pyrroles from Dewar thiophene.[32]

Dewar pyrrole has not been directly isolated from the photoirradiation of pyrroles, however, its formation has been suggested by intermolecular trapping with methanol or furan, giving **9, 10a** and **10b** respectively (Scheme 7).[35] Interestingly, 2-CN substituted Dewar pyrrole isomerises through a 'walk-mechanism', where nitrogen lone pair participation enables the CN group to seemingly change position on the ring (Scheme 7). This walk-mechanism appears to be common to both nitrogen and sulphur containing Dewar heterocycles derived from 5-membered rings.[32]



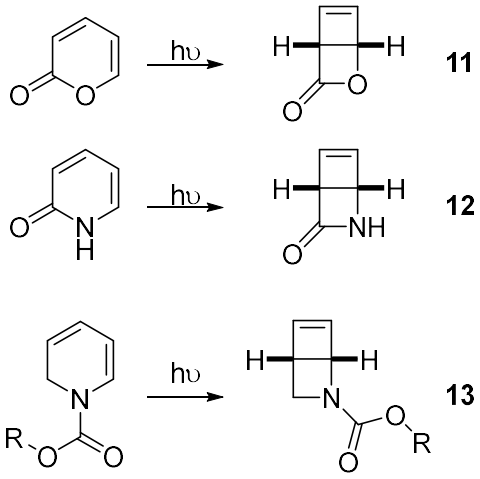
*Scheme 7: Generation of heterocycles by intermolecular trapping of Dewar pyrrole **8** with furan and methanol.*

The Dewar heterocycles deriving from five-membered rings, while interesting, are of little use for the synthesis of lead-like molecules, due to the instability of the unsubstituted forms, requiring highly electron withdrawing trifluoromethyl or nitrile substituents to allow isolation of a stable product.

Dewar structures obtained from six-membered rings, however, are relatively more stable in most cases.

Of particular interest are the Dewar products of 2-pyrones, 2-pyridones and 1,2-dihydropyridines (**11**, **12**, and **13** respectively, Scheme 8), which have been shown in the literature to be amenable to further functionalisation and modification, highlighting the synthetic utility brought about by the ring-strain present in their structures. Recently there has been an increase in

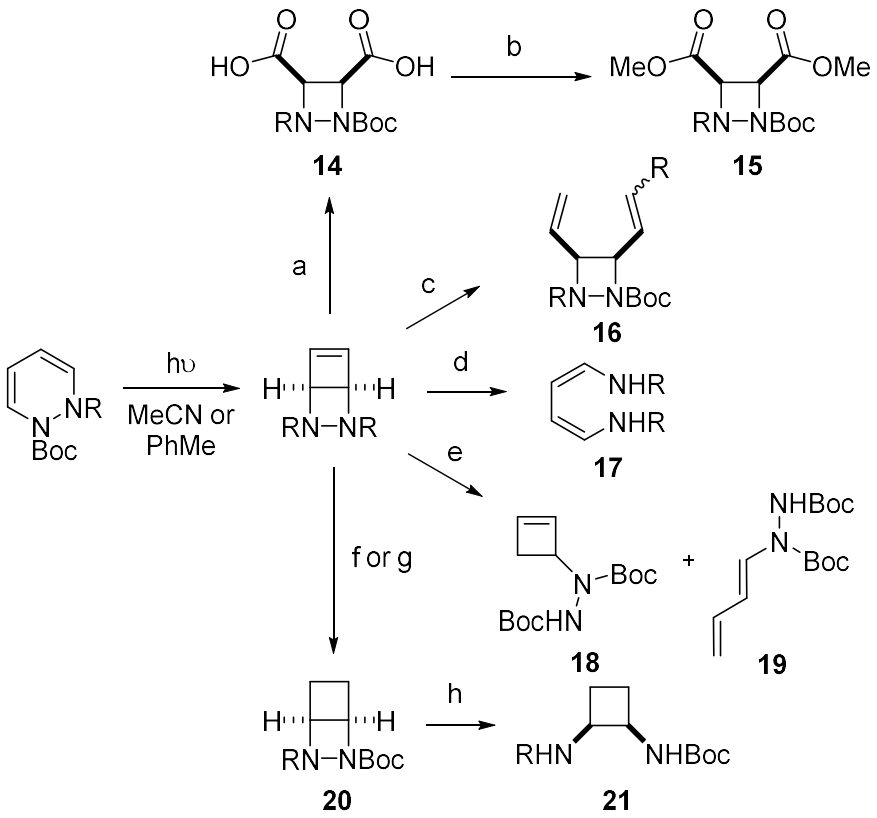
the number of papers investigating the synthesis or biological activity of 4-membered heterocycles.[36]



*Scheme 8: Photochemical products (**11**-**13**) derived from photoirradiation of l pyrone, 2-pyridone and 1,2-dihydropyridines respectively.*

The utility of these types of molecules was exemplified in a recent paper by Coote and co-workers, who, in an analogous photochemical process, generated bicyclic 1,2-diazetidines from 1,2-dihydropyridazines (Scheme 9).[37] The diazetidine was then modified to form a range of structurally diverse products. Oxidative cleavage of the alkene moiety by RuO_4 under oxidising conditions gave the *cis* diacid **14**, or the *cis* diester **15** after treatment with trimethylsilyldiazomethane. This occurs with retention of stereochemistry of the bridging carbon centres, since protons 1 and 4 are *cis* to one another, the *cis* geometry is retained. Grubbs' ring-opening metathesis/cross-metathesis gave the divinyl product **16**. Treatment with samarium iodide led to *N*-*N* cleavage, subsequent thermal 4π electrocyclic ring-opening and isomerisation gave the *Z,Z* diene **17**, since the *cis* geometry is retained in the thermal ring-opening. Birch reduction lead to the formation of a mixture of cyclobutene **18** and *E* diene **19**. Since the Birch reduction is a single electron process, the radical intermediate will be able to rotate into its lowest energy configuration, giving rise to the *E* diene. If the alkene moiety is reduced prior to Birch reduction however, the *cis*

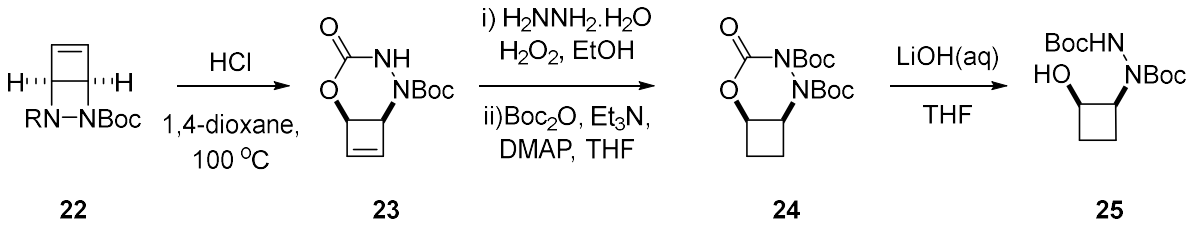
cyclobutane **21** forms, since the alkene is not present to accept an electron and undergo ring-opening of the cyclobutene moiety.



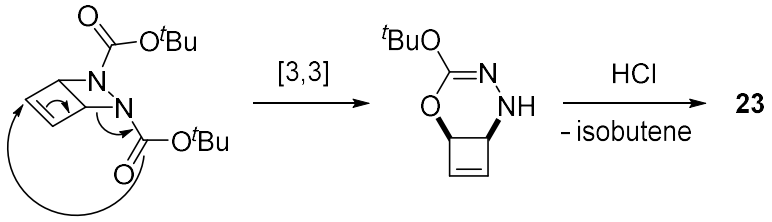
Scheme 9: Generation of a range of sp^3 rich small molecules from Dewar diazetidine, displaying the synthetic utility Dewar heterocycles as small molecule precursors. a) $RuO_2 \cdot xH_2O$, $NaIO_4$, EtOAc/H_2O, 0 °C to rt; b) $TMSCHN_2$, MeOH, 1 h; c) Hoveyda-Grubbs II, ethylene (1 atm), CH_2Cl_2, 1 h; d) SmI_2, THF, 0 °C; e) Na, $NH_3(l)$, -78 – 0 °C; f) $NH_2NH_2 \cdot H_2O$, H_2O_2, EtOH, 0 °C; g) $KO_2CN{=}NCO_2K$, AcOH, CH_2Cl_2, 0 °C to rt; h) Na, $NH_3(l)$, THF, -78 °C.

An interesting thermal rearrangement was also found (Scheme 10). Under acidic conditions after heating at 100 °C, it was found that one of the *N* protecting groups participated in a ring-expansion, which was postulated to proceed *via* [3,3] sigmatropic rearrangement between one of the Boc groups and the alkene. This is presumably due to the hinge-shaped geometry of the Dewar diazetidine, bringing the Boc carbonyl in close proximity to the alkene carbon centres (Scheme 10). Subsequent

elimination of isobutene then gave the carbamate **23**. The alkene in the resulting cyclic carbamate was then reduced and the Boc protecting group added to the hydrazine nitrogen to give cyclobutane **24**, and subsequent basic hydrolysis revealed the cyclobutanol **25**. This paper highlights the potential to obtain various small-molecule building blocks from a common strained Dewar heterocycle precursor.



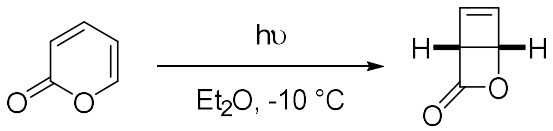
Mechanism of [3,3] sigmatropic rearrangement:



Scheme 10: Route to novel cyclobutanol via [3,3] sigmatropic rearrangement.

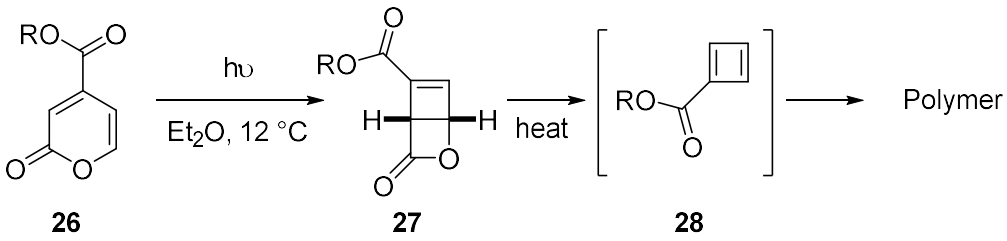
1.5.1 Dewar 2-pyrone

The Dewar heterocycles derived from 2-pyrones has proven to be highly useful in the synthesis of small lead-like molecules with a high Fsp^3. The route to Dewar 2-pyrone was first reported by Corey in the 1960's, with the photoproduct thought to be a useful precursor to cyclobutadiene (Scheme 11).[38,39] The synthesis of Dewar 2-pyrone is non-trivial, however. Photoirradiation of the unsubstituted 2-pyrone yields a highly unstable Dewar isomer, so reactive that it is pyrophoric in air at room temperature.



Scheme 11: Synthesis of Dewar 2-pyrone as described by Maulide and co-workers.

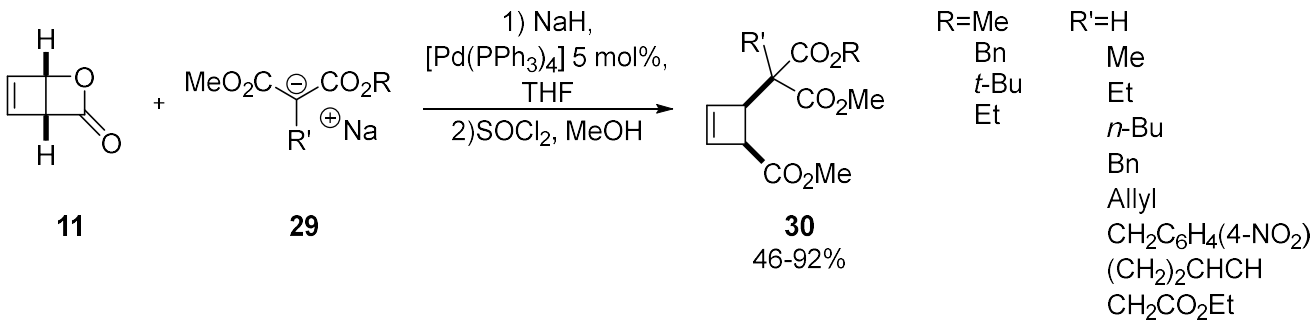
The 4-carboxylic acid and 4-methylcarboxylate ester derivatives of Dewar 2-pyrone can also be synthesised from coumalic acid or coumalate esters **26**, described by Neckers and Javaheripour (Scheme 12).[40] These substituted Dewar 2-pyrones were found to be more stable compared to the unsubstituted version, however handling at low temperatures was still required. They found that upon heating, the Dewar coumalic acid or its methyl ester derivatives underwent decarboxylation, proposing that the lactone ring was most likely to do so, leading to the formation of the cyclobutadiene carboxylic acid derivative **28**. Cyclobutadiene is highly reactive, as it is antiaromatic, and is known to explosively polymerise upon gentle heating.[40,41]



*Scheme 12: Formation of Dewar 2-pyrones from coumalic acid and coumalate esters. Upon heating, **5** decarboxylates and polymerises.*

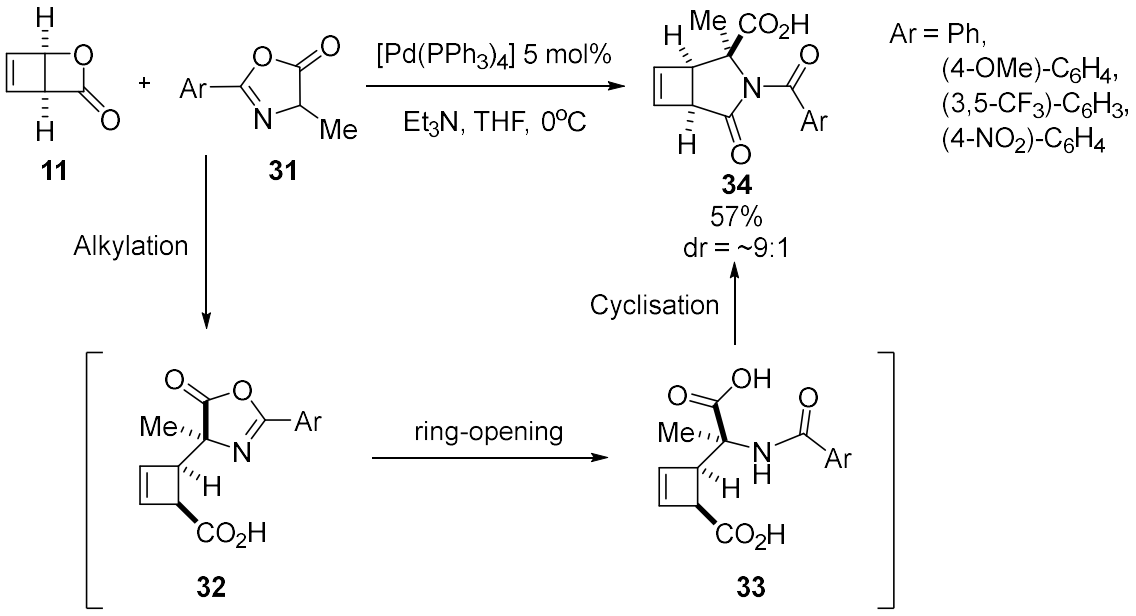
More recently, Maulide and co-workers have used 2-pyrone as a precursor to novel, substituted cyclobutenes. Dilute solutions and palladium catalysis were required to control the reactive nature of the compound. Under Tsuji-Trost conditions with a chiral ligand they found the lactone **11** to undergo stereoselective ring-opening of the lactone in the presence of malonate nucleophiles, leading to a *syn* substituted cyclobutenes **30**. With this

reaction they produced a range of products by variation of the functionality α to the malonate carbonyl groups (Scheme 13).[42]



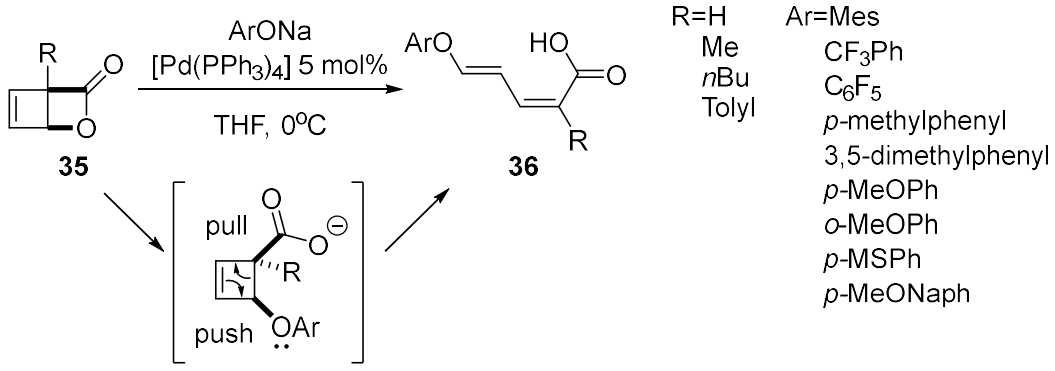
*Scheme 13: Tsuji-Trost alkylation of **11** in the presence of malonate nucleophiles to form alkylated cyclobutenes.*[42]

Maulide and co-workers also investigated the use of an azlactone nucleophile **31** in the same reaction, and found that instead of the alkylation product, the azabicycle **34** formed, which they postulated was *via* the rearrangement of the alkylated intermediate **32**, which underwent ring-opening to the amide **33**, followed by intramolecular cyclisation to **34** (Scheme 14).[42] They were intrigued to find that despite the absence of external chiral ligands, the reaction with azlactones proceeded with high double diastereoselectivity. Higher yields were also obtained when more electron withdrawing substituents were included on the aryl group.



Scheme 14: Unexpected azalactone formation by rearrangement of the alkylated Dewar 2-pyrone.[42]

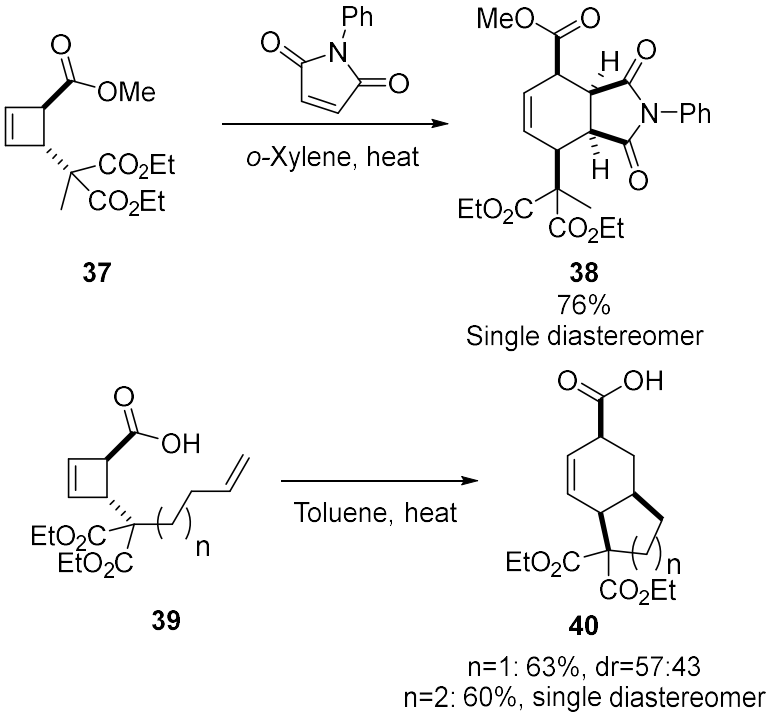
Separately Maulide *et al*. investigated Tsuji-Trost reactions with sodium phenoxide salts as the nucleophile and found that the (*Z*,*E*)-diene **36** formed cleanly. They reasoned that the reaction proceeds *via* the cyclobutene intermediate, which undergoes spontaneous ring-opening stimulated by the 'push-pull' effect of having the aryloxy group β to the carboxylate group on the ring (Scheme 15).[43]



Scheme 15: Formation of (Z,E) dienes by Tsuji-Trost reaction.[43]

Further to this, they showed that the cyclobutene products were amenable to *in situ* thermal ring-opening, revealing the 1,3-diene which then

undergoes Diels-Alder cycloaddition when presented with a dienophile (Scheme 16). Simply heating the cyclobutene **37** in the presence of *N*-phenylmaleimide gave the Diels-Alder product **38**, arising from the butadiene ring opening, in good yield. They were also able to perform domino-style cycloadditions by using cyclobutenes with pendant alkene groups. On heating, the cyclobutene ring opened, revealing the diene, which underwent an intramolecular Diels-Alder reaction forming the bicyclic products **38** and **40** (Scheme 16).[43]



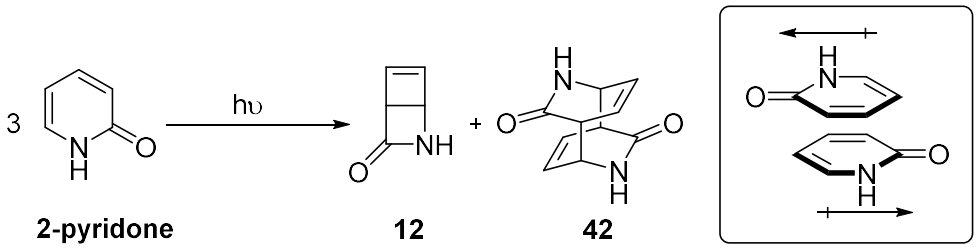
Scheme 16: Domino cycloadditions of cyclobutenes. Reaction proceeds via the diene resulting from cyclobutene ring-opening.

1.5.2 Dewar 2-pyridone

1.5.2.1 Synthesis

The photochemistry of 2-pyridones has been explored somewhat more extensively than that of pyrone, due to a combination of reduced cost compared to pyrones, and product stability; Dewar 2-pyridones are stable and pose no explosion risk. Studies into the photoreactions of 2-pyridones with different substitution patterns, as well as variations in concentrations,

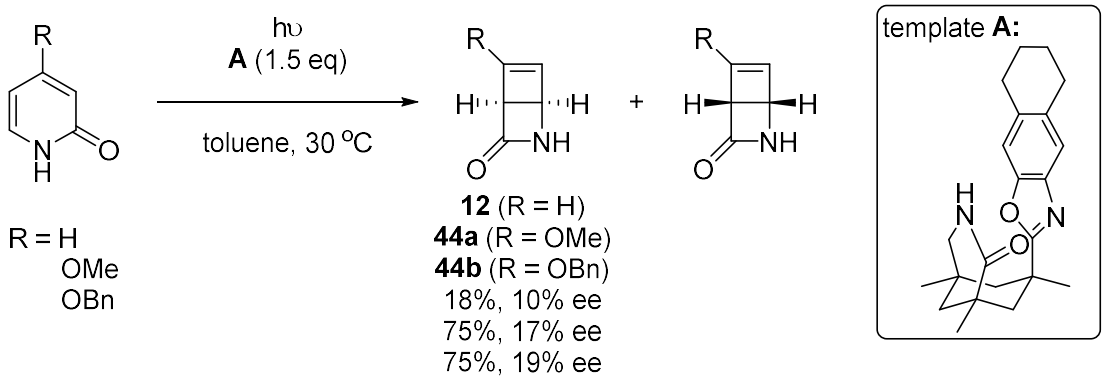
temperature and solvents were undertaken by Matsushima and Terada in 1985.[44] They found that as well as the intramolecular electrocyclisation to the Dewar 2-pyridone photoisomer, a competing, intermolecular [4+4] photodimerisation was also taking place, to give the dimer **42**, (Scheme 17). This dimerisation was found to occur more frequently at high concentrations. They postulated that the 2-pyridone molecules associated to each other in solution due to dipole-dipole interactions. The contribution of hydrogen bonding to this dimerisation was ruled out since irradiation of *N*-alkylated pyridones also gave the dimer in similar quantities to non-*N*-alkylated pyridones. The dipole-dipole interaction leads to exclusively the *trans-anti* photodimer forming at lower concentrations, however at high concentrations other diastereomers also form, with the *trans-anti* configuration (**42**) dominating in most cases.[45]



Scheme 17: Photoreaction of 2-pyridones to the Dewar form and the photodimer. Also shown is the dipole-dipole interaction leading to the trans-anti dimer.

Bach and co-workers developed the photochemical synthesis of Dewar 2-pyridones further, by employing a templated photochemistry technique (Scheme 18). They had previously used the same technique in [2+2] cycloaddition of quinolones, leading to high enantioselectivity.[46–48] In this case, however, poor enantioselectivity was achieved. The lactam additive was designed to bind to the substrate by two hydrogen bonds, with the extended ring-system providing a steric blockage of one face of the pyridone, preventing rotation in that direction to provide torquoselectivity. In a series of experiments it was found that Dewar 2-pyridone and some

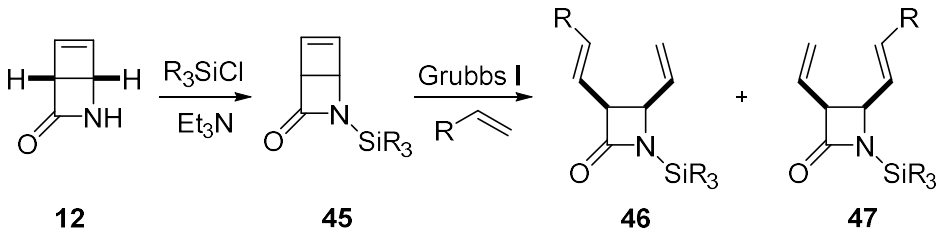
4-substituted derivatives, in the templated photoreaction, gave modest enantioselectivity (ee 10-23%).[48]



Scheme 18: Mild torquoselectivity achieved by irradiation of 2-pyridones in the presence of a hydrogen-bonding template.

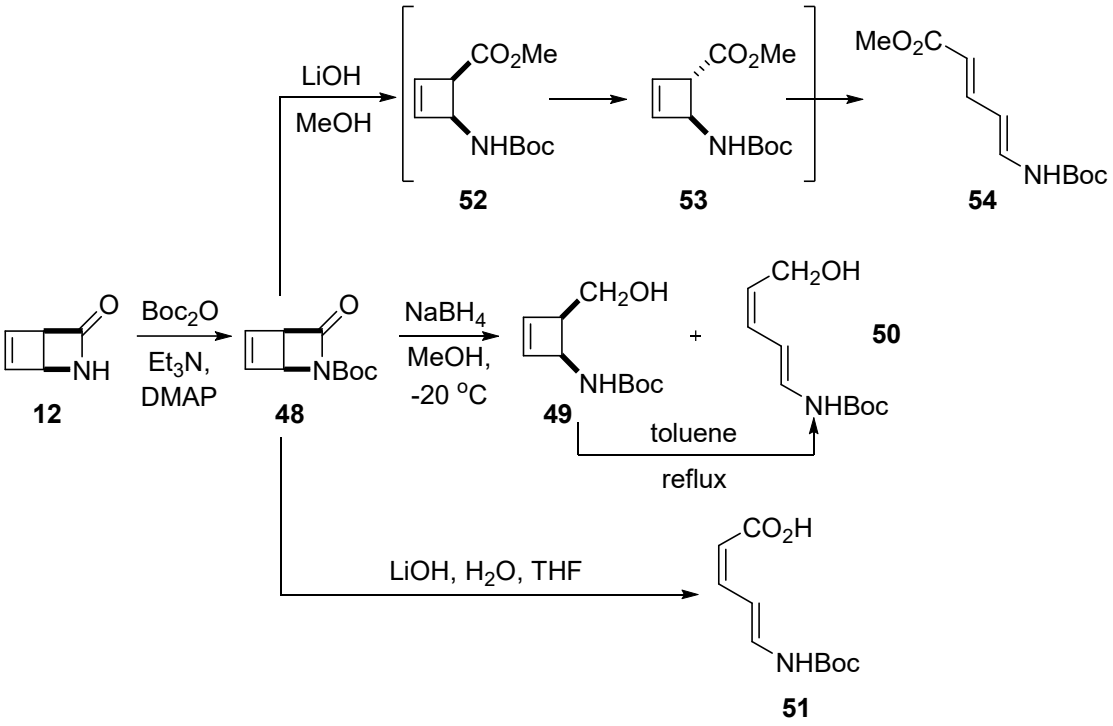
1.5.2.2 Uses

The Dewar 2-pyridones themselves have previously been utilised in the formation of monobactams by Piras and co-workers. Here, silyl protected **45** was subjected to a Grubbs' ring-opening metathesis to form a range of unsaturated β-lactam structures, with R-group variation based on the structure of the alkene present in the reaction (Scheme 19), the most successful example being the ring-opening metathesis/cross-metathesis with ethylene under pressure (300psi), yielding the divinylic monobactam.[49]



Scheme 19: Monobactam formation by Grubbs' ring-opening metathesis of the silyl prodected Dewar 2-pyridone. R=H, Ph, C_4H_9.

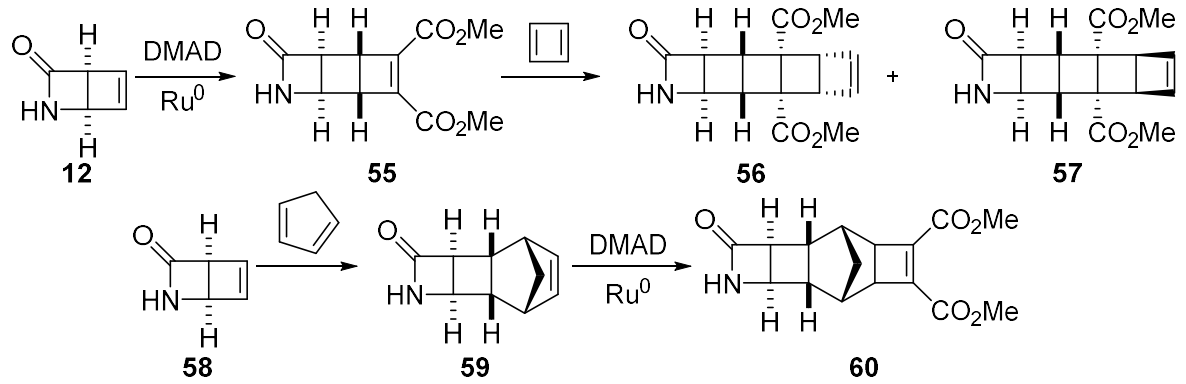
Similar to the Dewar 2-pyrones, Dewar 2-pyridones can form dienes by successive ring-opening reactions (Scheme 20). Huet and Gauvry found that treating the Boc-protected Dewar 2-pyridone **48** with sodium borohydride in methanol at -20 °C gave a 1:1 mixture of the cyclobutene **49** and the diene **50**. Upon heating, the cyclobutene decomposes to diene **50**. They reported that the diene **51** can be synthesised by the hydrolysis of the β-lactam by aqueous LiOH, forming the cyclobutene as an unstable intermediate, which decomposes by spontaneous push-pull ring-opening reaction to Z,E diene **51**. The *E,E* diene **54** can be formed by the β-lactam hydrolysis being performed in methanol with LiOH. They then utilised the diene **54** in a series of Diels-Alder cycloadditions to furnish cyclohexenes.[50]



Scheme 20: Formation of various dienes from the Boc protected Dewar 2-pyridone.

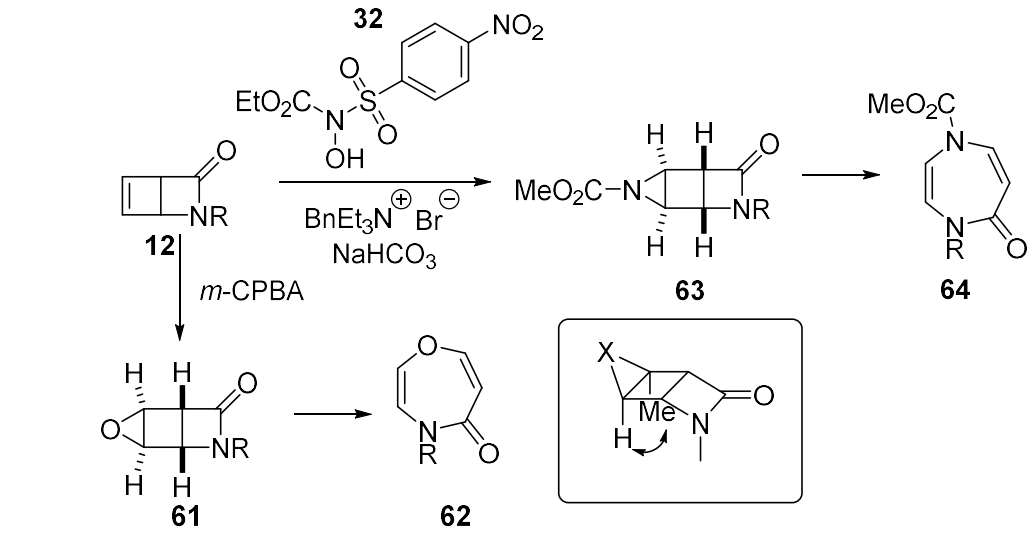
Margetic *et al*. developed a novel route to aza[n]ladderanes and azahomo[n]ladderanes, with the terminal ring being the β-lactam, utilising Dewar 2-pyridone as the starting material (Scheme 21). **12** was treated with dimethylacetylene dicarboxylate (DMAD) with a Ru^0 catalyst to form

the tricycle **55**, which can undergo cycloaddition with cyclobutadiene, forming polycycles **56** and **57** in a 3:2 mixture. Also synthesised was the azahomo[n]ladderane **58** by an analogous process of cycloadditon of **12** to cyclopentadiene followed by reaction with DMAD with Ru^0 catalyst, forming **60**.[51]



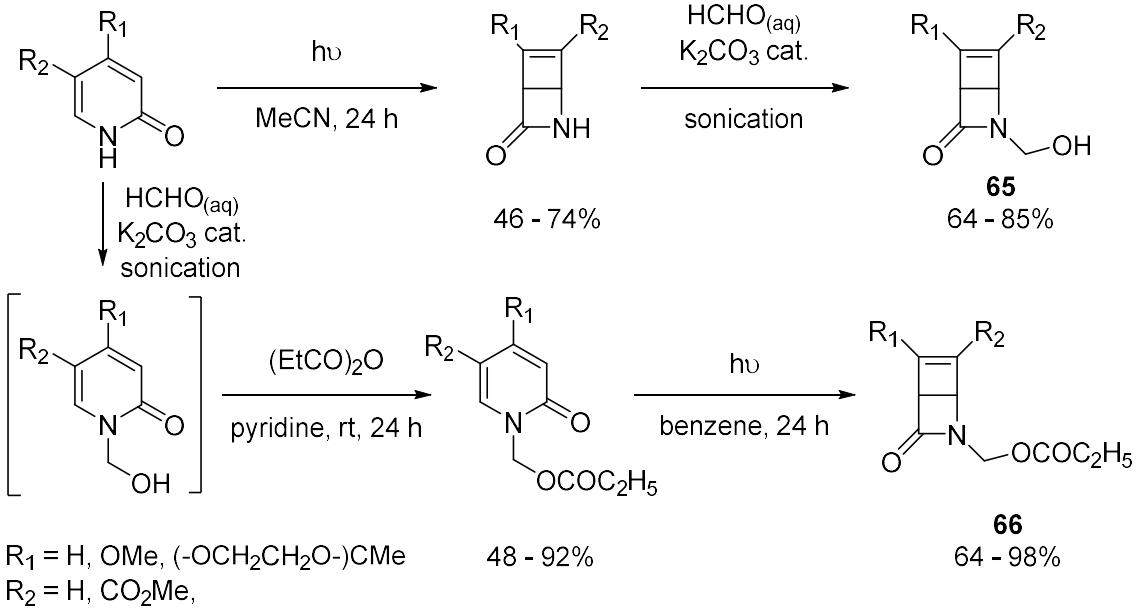
Scheme 21: Formation of aza[n]ladderanes and azahomo[n]ladderanes developed by Margetic et al.

Tsuchiya and co-workers have extensively researched strain-release mechanisms of tricyclic derivates of Dewar 2-pyridone **12** to form oxazepines and diazepines (Scheme 22). Treatment of **12** with either m-CPBA or a nitrene generated *in situ* from *N*-ethoxycarbonyl-*p*-nitrobenzenesulfonylhydroxylamine (**32**) gave the epoxide **61** and the aziridine **63** respectively. Simply heating these compounds then formed the 1,4-oxazepin-5-one **62** and 1H-1,4-diazepin-5-ones **64** by ring expansion, driven by the release of strain of the tricyclic system.[52–54] It was determined by nOe spectroscopy that the epoxide possessed *anti-endo* stereochemistry, due to an nOe signal between 1-H and 6-Me (Scheme 22). This shows that addition to the C=C double bond present in these Dewar heterocycles occurs stereoselectively to the, less hindered face.



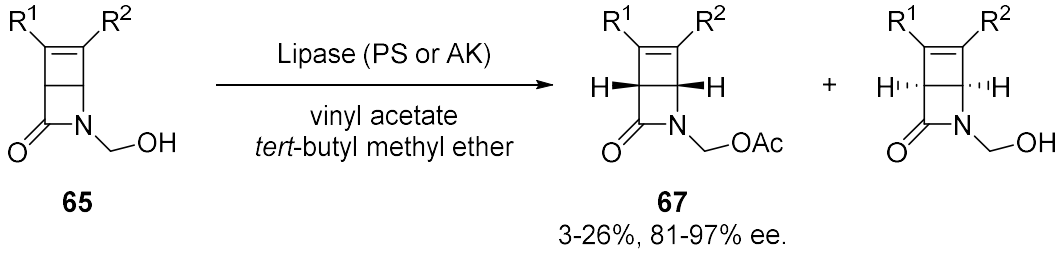
*Scheme 22: Formation of seven-membered heterocycles by ring expansion of tricycles **61** and **64**.*

Hongo and co-workers developed an effective enzymatic kinetic resolution of Dewar 2-pyridone derivatives. To enable lipase-catalysed transesterification the Dewar 2-pyridone nitrogen must first be subjected to alkylation to provide a pendant hydroxyl group, forming **65** and **66** as racemic mixtures (Scheme 23).



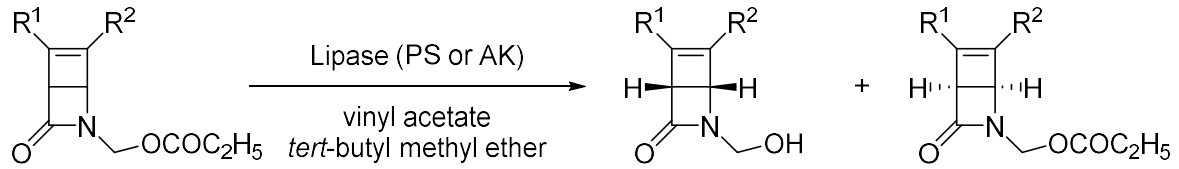
Scheme 23: Alkylation of the Dewar 2-pyridone nitrogen to enable kinetic resolution by acetylation, or ester hydrolysis with Lipase enzymes.

Lipase enzymes from two different Pseudomonas species were found to catalyse the transesterification specifically of the 1*S,* 4*R* enantiomer forming **67** with high enantiomeric excess (Scheme 24). Separately the enzymatic kinetic resolution of the hydrolysis of Dewar 2-pyridone **66** with ethyl esters at the *N* position was investigated. This selectively hydrolysed the 1*S*, 4*R* enantiomer in low-moderate yield and high enantiomeric excess (Scheme 25).[55]



65 **67**
3-26%, 81-97% ee.

Scheme 24: Kinetic resolution of alkylated Dewar 2-pyridone. The lipase enzyme selectively acetylates the pendant hydroxyl group on the 1S,4R enantiomer, leaving the 1R,4S enantiomer deacetylated. (R^1 = H, OMe, R^2 = H, CO_2Me).

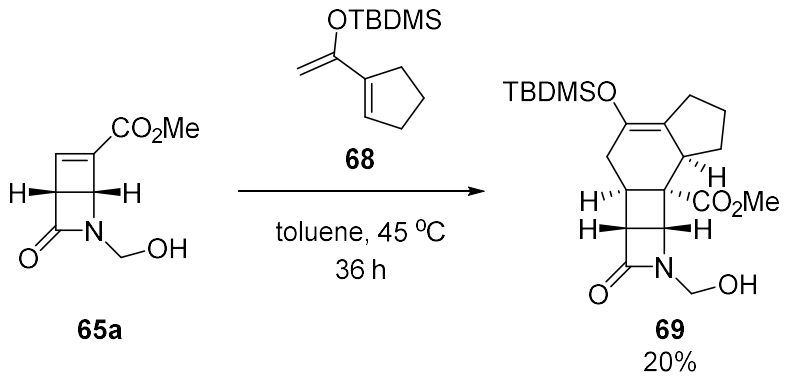


66 **65a**
12-28%, 92->98% ee.

Scheme 25: Kinetic resolution of alkylated Dewar 2-pyridone with pendant ester by hydroxylation by Lipase. The 1S,4R enantiomer is selectively hydrolysed, leaving the 1R,4S enantiomer unreacted. (R^1 = H, OMe, R^2 = H, CO_2Me).

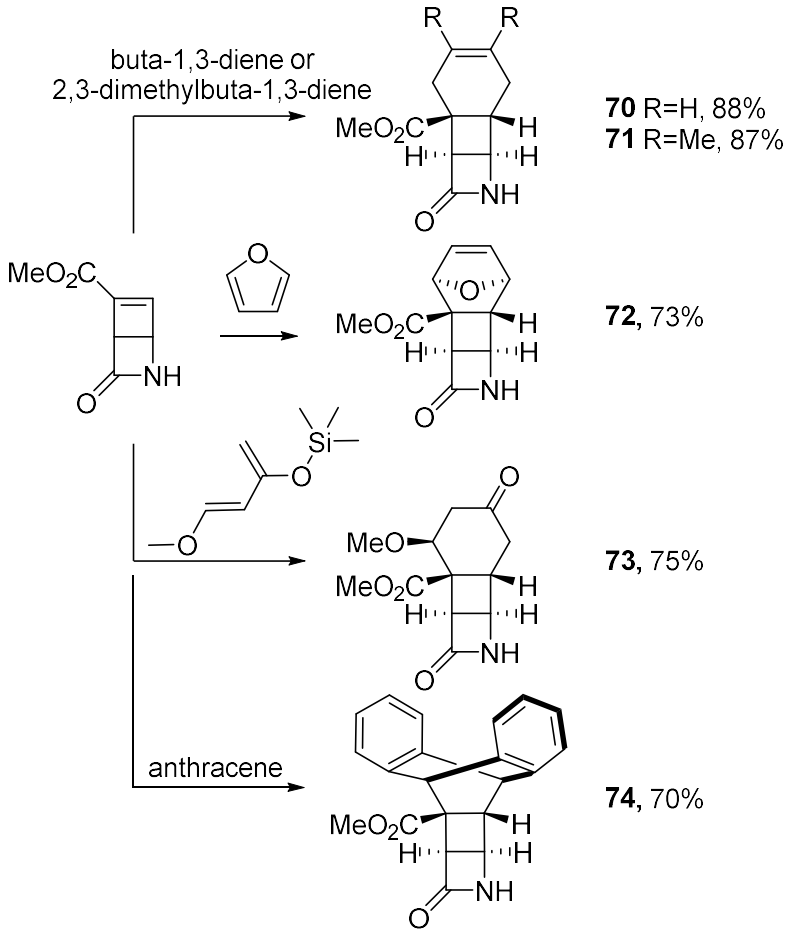
In the same paper, they utilised the now enantiomerically enriched Dewar 2-pyridone **65a** in a Diels-Alder cycloaddition with cyclopentene **68** to form the tetracyclic lactam **69** (Scheme 26). Cycloaddition occurred at the top

face of the cyclobutene moiety, which was postulated to be due to the steric influence of the β-lactam moiety.[55]



*Scheme 26: Stereoselective Diels-Alder cycloaddition, yielding tetracyclic heterocycle **69**.*

Separately, Hongo and co-workers have also investigated the high-pressure Diels-Alder reaction of Dewar 2-pyridone derivatives with a small variety of dienes, to form a number of cycloadduct products (**70-74**, Scheme 27).[56]



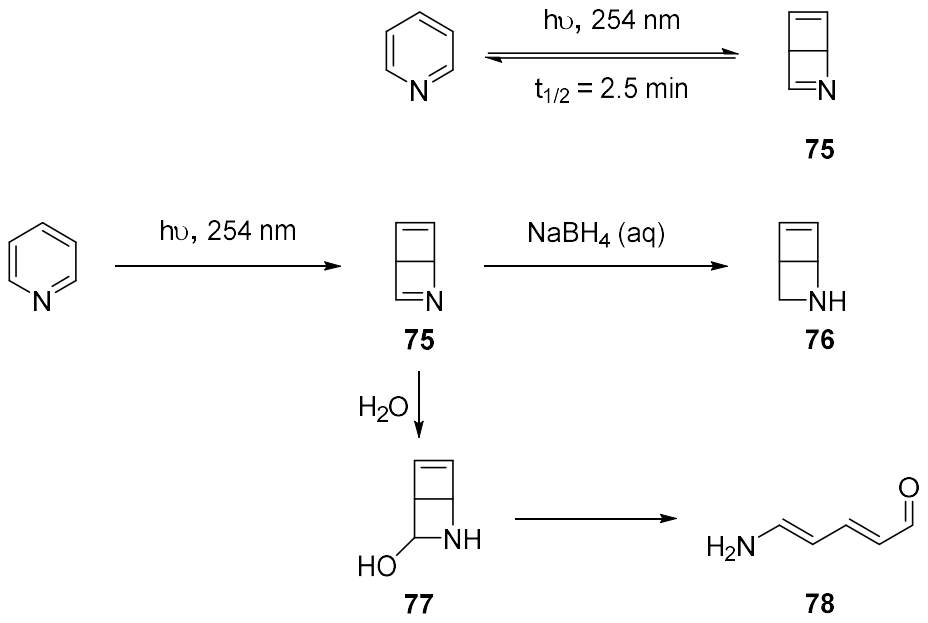
Scheme 27: Diels-Alder cycloadditions of Dewar 2-pyridone with a range of dienes, forming a variety of multi-cyclic products high in sp^3 carbon centres.

1.6 Dewar 1,2-dihydropyridines

1.6.1 Synthesis

1.6.1.1 Pyridine Irradiation

Dewar pyridine was identified by Wilzbach and Rausch in 1973, where they reported that upon UV irradiation, pyridine converts to its Dewar form **75**, which reverts to pyridine at room temperature with a half-life of 2.5 minutes (Scheme 28).[57] They found that performing the irradiation in aqueous sodium borohydride gives the reduced form of Dewar pyridine **76**. They also found that a competing hydrolysis of the imine moiety takes place, which gave the unsaturated aldehyde **78** *via* the alkanolamine **77**.



*Scheme 28: Irradiation of pyridine gives Dewar pyridine. If the reaction takes place in aqueous sodium borohydride, the product **76** was observed. No yields reported.*[57]

1.6.1.2 1,2-Dihydropyridine Irradiation

1.6.1.2.1 1,2-Dihydropyridine Synthesis

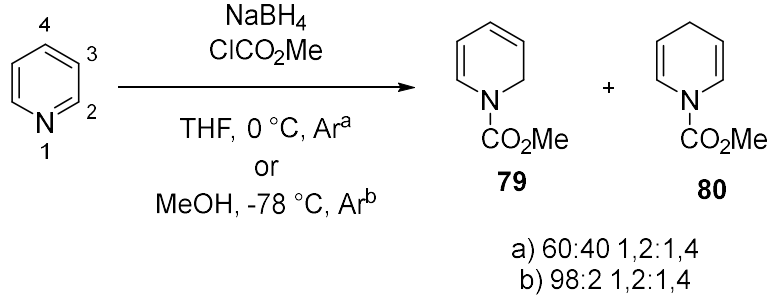
The main method of synthesising Dewar dihydropyridines is through the irradiation of 1,2-dihydropyridines. These represent an important structural motif in organic chemistry in their own right, finding use in a wide variety of synthetic applications, including in a number of syntheses of medicinally relevant compounds.[58] In order to understand the chemistry of Dewar dihydropyridines it is important to examine the synthesis and chemical properties of 1,2-dihydropyridines in general.

While not as extensively examined in experimental work compared to 1,4-dihydropyridines, 1,2-dihydropyridines have been examined extensively using computational methods. In the 1960's several groups found that π electron distributions in free base 1,2-dihydropyridine were consistent with a pair of localised π bonds, with the nitrogen possessing strong enamine character.[59] These same calculations showed that the energy of the HOMO

was high, indicating that 1,2-dihydropyridines are strong electron donors, which is empirically proven by their ready oxidation and their propensity to form stable π complexes with chromium.[59–61]

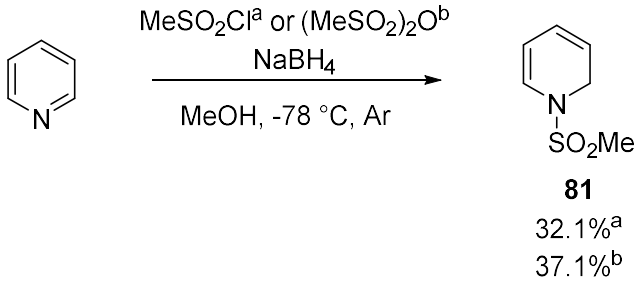
The synthesis of 1,2-dihydropyridines is generally more challenging than the synthesis of the 1,4- regioisomer, especially given its propensity to oxidise to the relevant pyridine. However, there are several synthetic methods which have been employed in the literature with perhaps the most convenient and general method being by reduction of pyridines.

The reduction of pyridine proceeds by sodium borohydride reduction of a pyridinium carbamate salt, which is generated *in situ* by addition of a chloroformate (Scheme 29). In THF at 0 °C this gave a mixture of the 1,2- and 1,4- dihydropyridines **79** and **80** respectively, with the reaction favouring the 1,2-dihydropyridine (60:40 1,2:1,4).[62] This was later modified to use methanol as solvent and the temperature reduced to -78 °C, which increased the relative quantity of 1,2-dihydropyridines to >9:1. This regioselectivity has since been found to be due to a combination of steric effects as well as the hard or soft nature of the nucleophile. Hard nucleophiles generally add to the 2-position, and soft nucleophiles generally add to the 4-position. The presence of the carbamate protecting group helps to stabilise the dihydropyridine ring by occupying the nitrogen lone pair, reducing the enamine character of the π bond α to the nitrogen almost completely.[62] This improves their stability and allows much greater ease of handling and performing subsequent reactions.

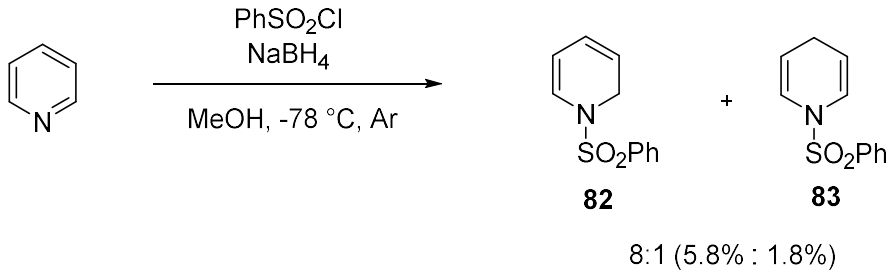


Scheme 29: Fowler reduction of pyridine.

An analogous process was used by Knaus and Redda whereby the chloroformate species used in the above examples was exchanged for phenylsulfonyl chloride or methanesulfonic anhydride in methanol under cryogenic conditions to furnish the *N*-methanesulfonyl-1,2-dihydropyridine **81** as the sole product (Scheme 30).[63] When benzenesulfonyl chloride was used, regioselectivity was reduced, giving an 8:1 mixture of the 1,2- and 1,4- dihydropyridines **82** and **83** being isolated (Scheme 31).[63]



Scheme 30: Synthesis of methylsulfonate protected 1,2-dihydropyridine.

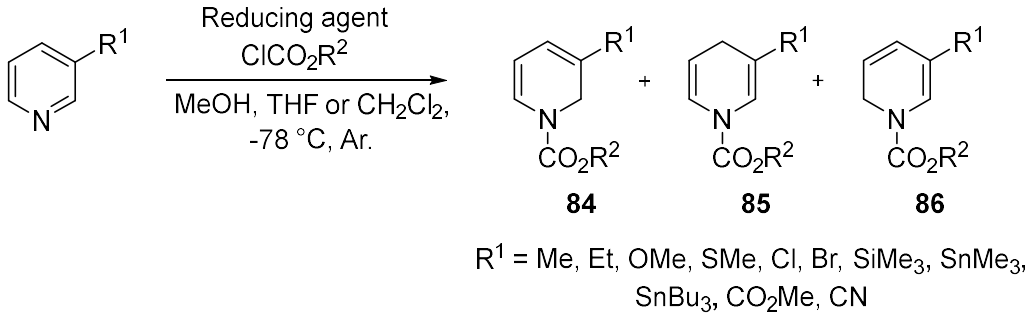


Scheme 31: Synthesis of benzenesulfonyl protected 1,2- and 1,4-dihydropyridines.

Challenges arise when introducing a substituent to the 3-position on the pyridine ring. This allows for 3 possible products of the Fowler reduction, the 1,2- dihydropyridine, 1,4- dihydropyridine and 1,6- dihydropyridine.

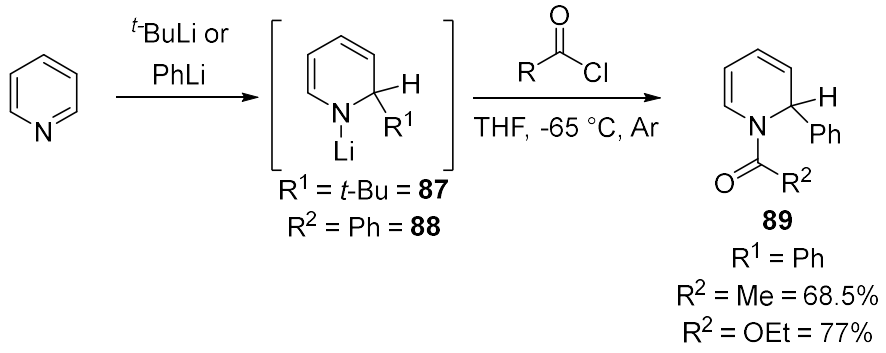
Sundberg *et al.* performed extensive studies on various 3-substituted pyridines, with a range of reducing agents (Scheme 32). They found that reduction with sodium borohydride occurred with regioselectively at the 2-position when electron-donating substituents were present in the 3-position (inductive - methyl, ethyl, and mesomeric - methoxy, methylthio, bromo,

chloro) with the reaction favouring the 1,2-dihydropyridines **84**, with the 1,4-dihydropyridine **85** as a minor product and no 1,6-dihydropyridines being observed. With electron-withdrawing substituents (CO_2Me and CN) the reaction became less regioselective, leading to 1,6-dihydropyridines being present in the product mixture at ~30%. They also established that with sterically non-demanding substituents in the 3-position, reduction with bulky reducing agents did not affect the regioselectivity and reduction at the 2-position still dominated. Only when larger groups were present in the 3-position (trimethylsilyl, trimethylstannyl) did the regioselectivity switch to the 6-position.



Scheme 32: Investigation into regioselectivity $NaBH_4$ reduction, with varying 3-substituents on pyridine.

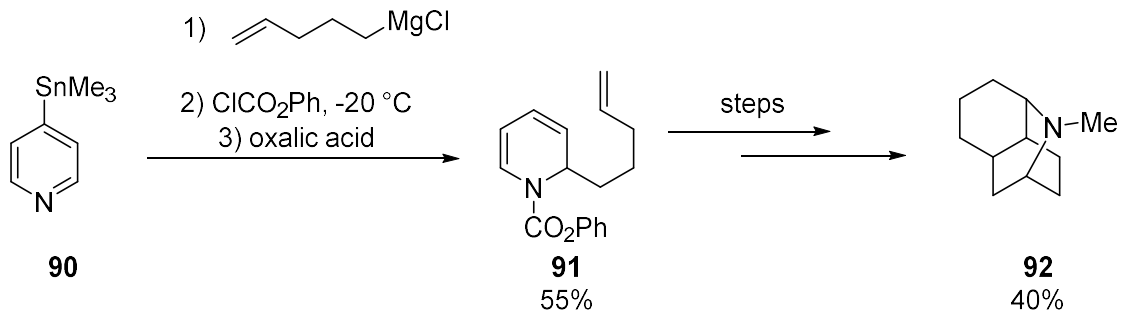
The nucleophilic addition to activated pyridines can be expanded to carbon nucleophiles, for example organolithium and Grignard reagents. For organolithium reagents, typically addition occurs at the 2- position. As demonstrated by the formation of the *N*-lithiated species **87** and **88** by reaction of pyridine with *tert*-butyllithium and phenyllithium respectively (Scheme 33).[64,65] *N*-lithium-2-phenyl-1,2-dihydropyridine **88** was then taken forward to *N*-acyl-1,2-dihydropyridine **89** by treatment with an excess of acyl chlorides or acetic anhydrides in THF at -65 °C (Scheme 33).[64]



*Scheme 33: Preparation of N-lithiated dihydropyridines **87** and **88** with subsequent N acylation to the dihydropyridine **89**.*

For Grignard reagents, those derived from sp and sp^2 hybridised organohalides, e.g. alkynyl, aryl and vinyl Grignard reagents, addition to activated pyridine occurs regioselectively to the 2- position. Addition of alkyl Grignard reagents proves to be less controlled when it comes to regioselectivity. While addition to the 2- position usually predominates slightly, it is strongly influenced by the sterics of both the incoming nucleophile, and the activating species on the nitrogen.

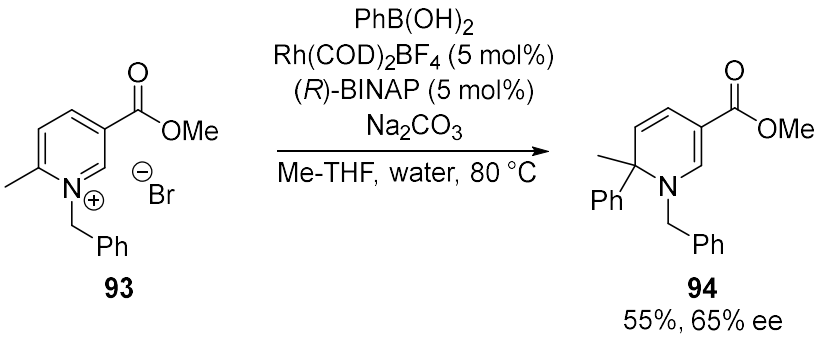
The only guaranteed method of forcing regioselectivity is to employ a substituent or a blocking group in the 4- position.[66,67] This tactic has been used to great effect by Comins *et al*. in various syntheses, in particular the use of a cleavable trimethylstannyl blocking group in the 4- position allowed for regioselective addition of an unsaturated alkyl Grignard reagent, to install a pendant alkene (**91**, Scheme 34). This trimethylstannyl blocking group was then cleaved with oxalic acid, allowing for intramolecular Diels-Alder cycloaddition to eventually form the bridged tricylic dihydrocannivonine **92**.



Scheme 34: Dihydrocannivonine synthesis from 4-trimethylstannylpyridine.

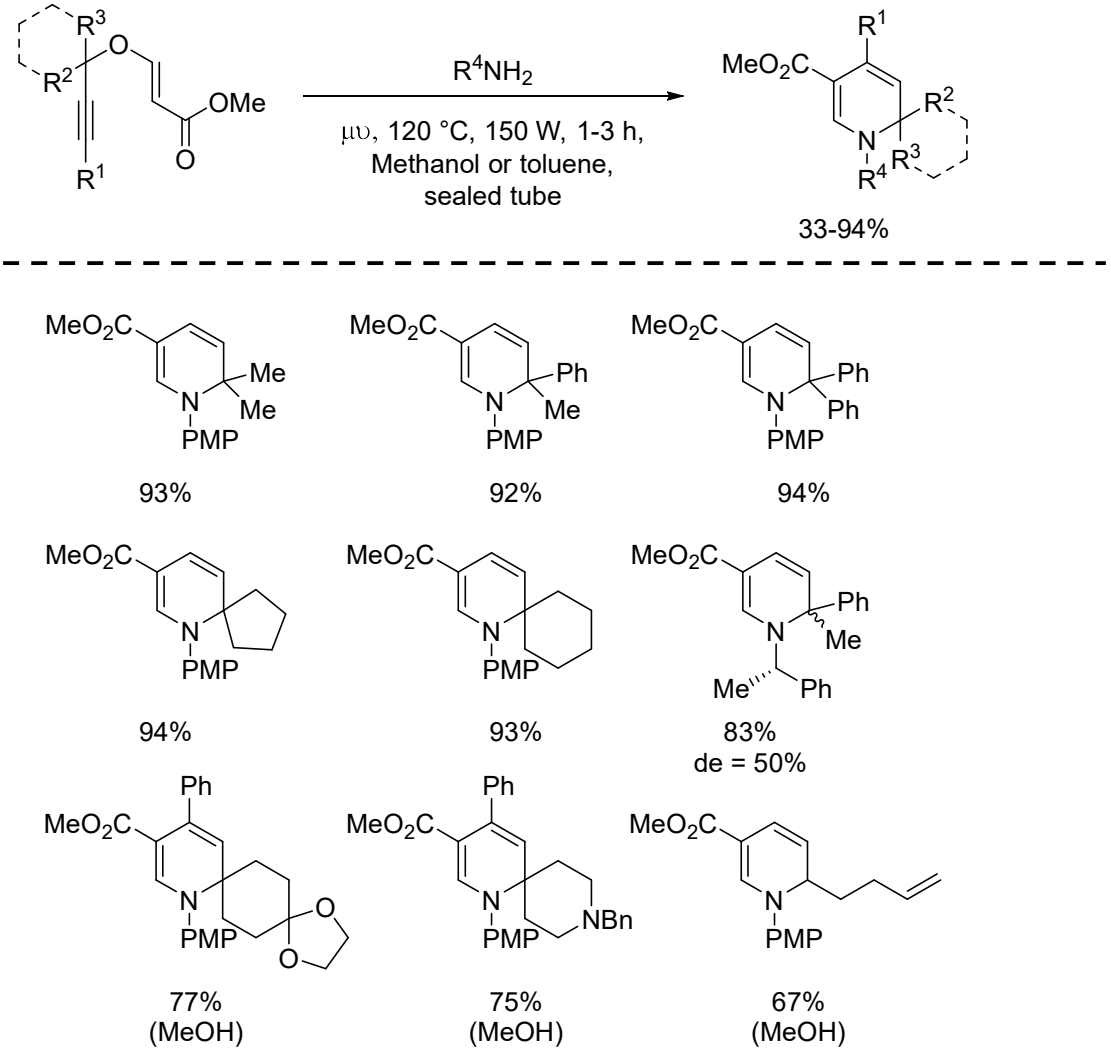
Finally, perhaps the dihydropyridines which are least well explored are quaternary 1,2-dihydropyridines, with geminal or spiro substituents in the 2- position. There are currently only two literature methods for accessing these structures, and both have limitations and drawbacks.

The first method was mentioned in a paper by Nadeau *et al*. Principally the paper describes the application of a rhodium-based enantioselective addition of aryl and vinyl boronic acids with *N*-benzyl methylnicotinate **93** (Scheme 35).[68] They found that the same catalytic system with an (R)-BINAP ligand could add phenylboronic acid to the *N*-benzyl salt of 6-methyl methylnicotinate in moderate yield and enantiomeric excess (**94** Scheme 35). Fundamentally this route is limited by the need for vinyl and aryl boronic acids, and the need for a substituent already present in the 6-position of the pyridinium salt.



Scheme 35: Phenylboronic acid addition to N-benzyl-6-methyl methylnicotinate with catalytic Rh.

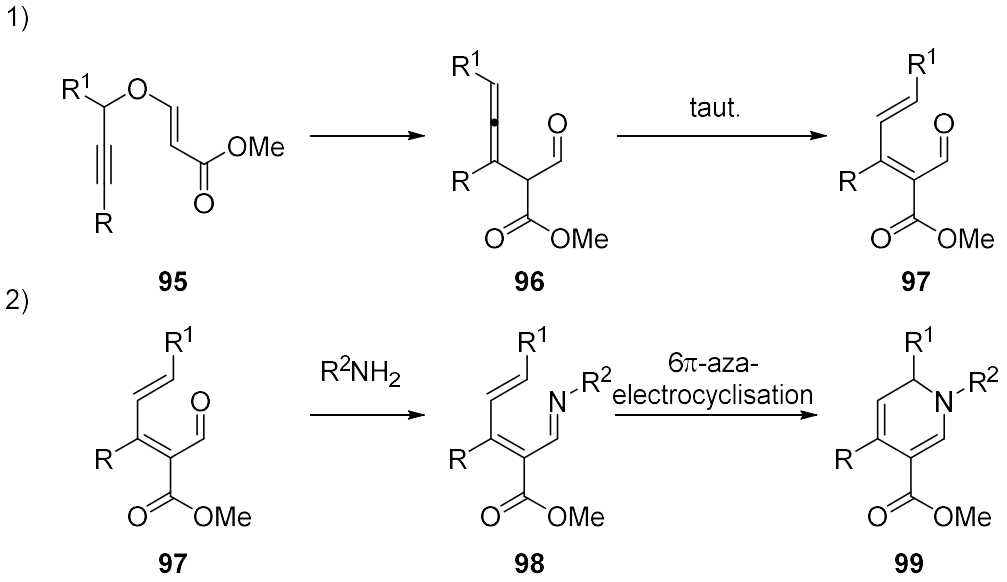
Tejedor's work on propargyl vinyl ethers led to the development of a convenient microwave route to 2- quaternary dihydropyridines (Scheme 36).[69,70] In the presence of a primary amine in either methanol or toluene heated at 120 °C by microwave irradiation, propargyl vinyl ethers were converted into the corresponding dihydropyridines in moderate to excellent yields depending on the substituents. This strategy was employed to synthesise mono-, geminal, and spiro-substituted 1,2-dihydropyridines.



Scheme 36: Tertiary and quarternary 1,2-dihydropyridine synthesis by microwave assisted domino reaction of propargyl vinyl ethers with amines.

The reaction occurs in two stages, firstly, the propargyl vinyl ether undergoes a propargyl Claisen rearrangement to the 3,4-allene **96**, which

can then tautomerise to the 2,4-dienal **97**. Secondly, in the presence of a primary amine, **97** can undergo a condensation reaction to the 2,4-unsaturated imine **98**, which is then poised for 6π-aza-electrocyclisation to form the desired 1,2-dihydropyridine **99**. One important structural limitation of this route is the presence of the ester in the 5-position of the dihydropyridine, as an electron-withdrawing group is required to be present in this position of the propargyl vinyl ether to facilitate the propargyl Claisen rearrangement (Scheme 37).

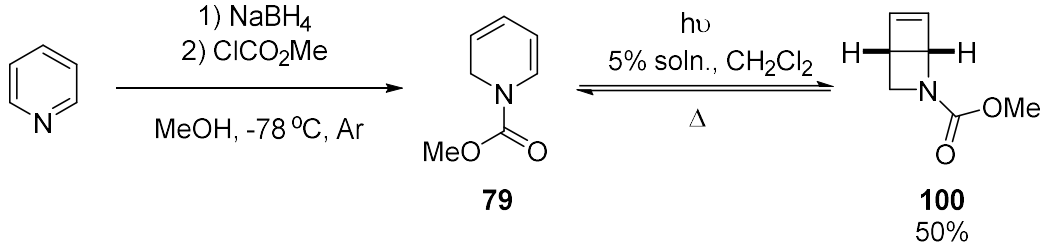


Scheme 37: 1,2-dihydropyridine synthesis from propargyl vinyl ethers via two-stage process with primary amines.

They were also able to influence the stereochemistry of the substituents in the 2-position by using enantioenriched α-methylbenzylamine as the amine, giving a diasteromeric excess of 50% when R^2 is H and R^3 is Ph.[70] Using propargyl vinyl ethers as starting materials for dihydropyridine synthesis has been used in the literature previously, generally utilising transition metal catalysts, however none of the other methods have been used to generate quaternary dihydropyridines.[71–73]

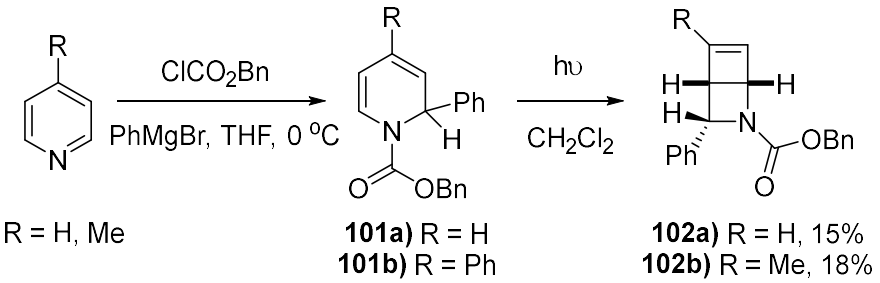
1.6.1.2.2 Dewar 1,2-dihydropyridine Synthesis

Fowler *et al*. were the first to utilise isolated 1,2-dihydropyridines in the synthesis of Dewar dihydropyridines.[62,74] First, pyridine was converted into the *N*-methoxycarbonyl-1,2-dihydropyridine **79**. Subsequent irradiation of this formed the Dewar heterocycle **100** (Scheme 38). They found that the Dewar form was significantly more stable with regards to oxidation, compared to the parent compound and could withstand temperatures of >100 °C for multiple hours before decomposition.[62,74] Fowler envisioned the Dewar dihydropyridine as a 'masked' 1,2-dihydropyridine. Since thermal reversion of the Dewar dihydropyridine is possible, he envisioned being able to convert 1,2-dihydropyridines into their Dewar isomer to take advantage of this increased stability, utilise them in further synthesis, then revert the moiety back to the 1,2-dihydropyridine when desired.



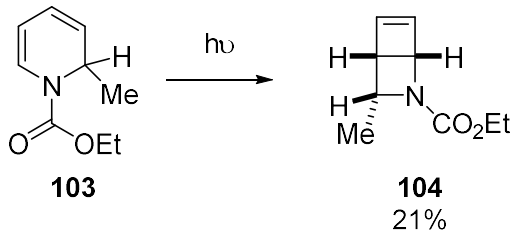
Scheme 38: Fowler and co-worker's photochemical route to azabicyclohexenes, via a 1,2-dihydropyridine.[62,74]

This methodology was then expanded to include other carbamate protecting groups and substituents (Scheme 39).[54] Treatment of pyridine or 4-picoline with phenylmagnesium bromide with subsequent addition of a benzyl chloroformate, allowed the substituted dihydropyridines **101a** and **101b** to be accessed. Irradiation using the same conditions as Fowler allowed isolation of the 3-*endo*-phenyl-2-azabicyclohexenes **102a** and **102b**.



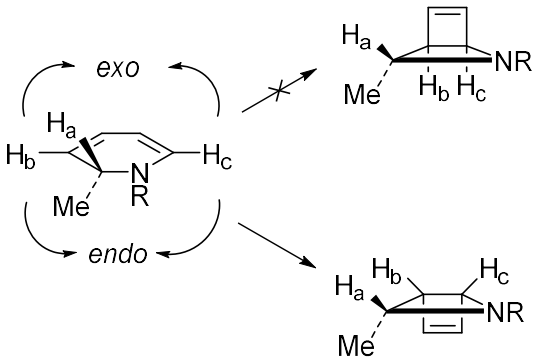
Scheme 39: Preparation of 3-Ph substituted Dewar dihydropyridines.[54]

Introduction of a substituent in the 2-position has the potential to produce a mixture of *exo* and *endo* products, by the disrotatory cyclisation occurring in either direction. This was examined by Krow and co-workers (Scheme 40).[75] Irradiation of 2-methyl-*N*-ethoxycarbonyl-1,2-dihydropyridine **103** (synthesised by an analogous treatment with methylmagnesium bromide, in the presence of ethyl chloroformate), gave only the *endo* Dewar-product **104**.



Scheme 40: Irradiation of 1-ethoxycarbonyl-2-methyl-1,2-dihydropyridine to give 3-methyl-2-azabicyclo[2.2.0]hex-5-ene.[75]

They rationalised that this torquoselectivity was caused by a 'least-motion' ring closure pathway during the electrocyclisation (Scheme 41). They found that in the dihydropyridine, H_a and H_b are at an angle of 30° to each other. By examining the *exo* and *endo* pathways it was revealed that the protons would need to move over 100° away from each other in the *exo* pathway, whereas they would only need to move by ~20° in the *endo* pathway.[75]



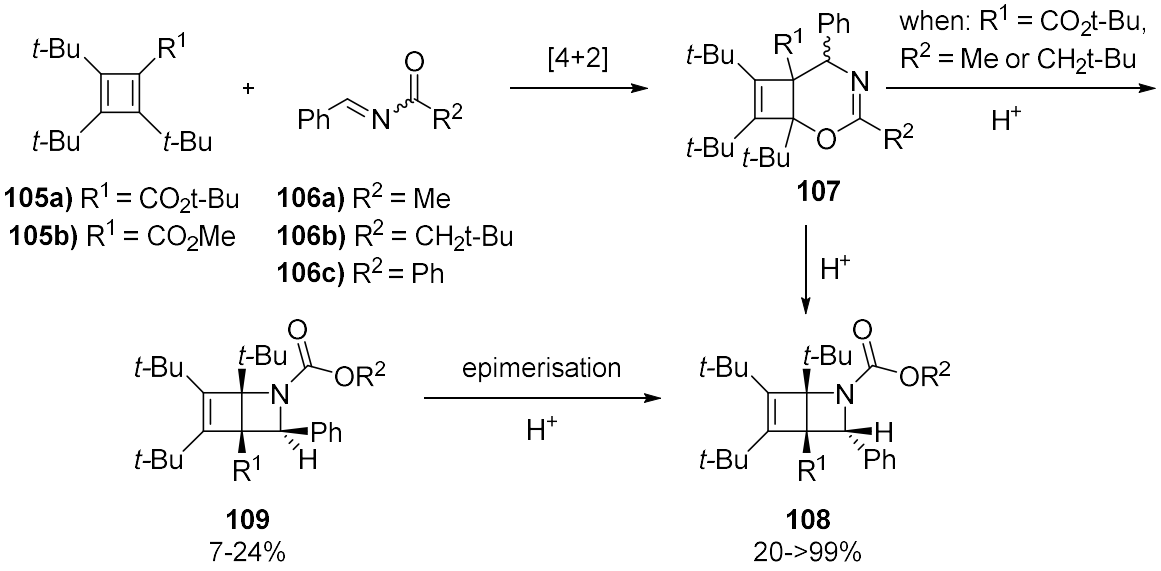
Scheme 41: exo vs. endo pathways for electrocyclic ring-closure of 2-substituted 1,2-dihydropyridines.

While a more convenient preparation than Wilzbach and Rausch's photoirradiation of pyridine, Fowler's method is still limited by the inherent restrictions imposed by batch photochemistry. These limitations are namely the long reaction times required for full conversion, typically in the range of 20 to 40 hours, due to absorption of incident light effectively blocking light from reaching solution further away from the light source, and the need for multiple separate reactions to process large volumes of starting material – scale up by increasing the volume of reaction solution in batch can make it difficult to reach satisfactory conversion and may therefore cause over-irradiation. In the literature, typical batch sizes range from 10s of mL, to ~1 L.

1.6.1.2.3 Other methods

Thermal [4+2] cycloaddition of *N*-acylimines and cyclobutadienes to form the Dewar dihydropyridine **108** was reported by Michels and co-workers in the 1980's (Scheme 42).[76] The *N*-acylimine **106a-c** acts as the diene, with the cyclobutadiene **105a-b** as dienophile, forming the bicyclic oxazine **107**. They then performed an acid-mediated isomerisation to give the *endo*-2-substituted azabicyclo[2.2.0]hex-5-enes **108**. In some cases, the *exo*-isomer **109** was isolated as a side-product in 7-24% yield, conveniently, they found the *endo*- isomer **5** could be formed by epimerisation of **109** under acidic conditions. This [4+2] cycloaddition strategy relies on the

bulky t-butyl substituents on the cyclobutadiene stabilising the structure, as without these, cyclobutadiene has a propensity to polymerise, and thus is highly restrictive in its potential for including more synthetically useful substituents.



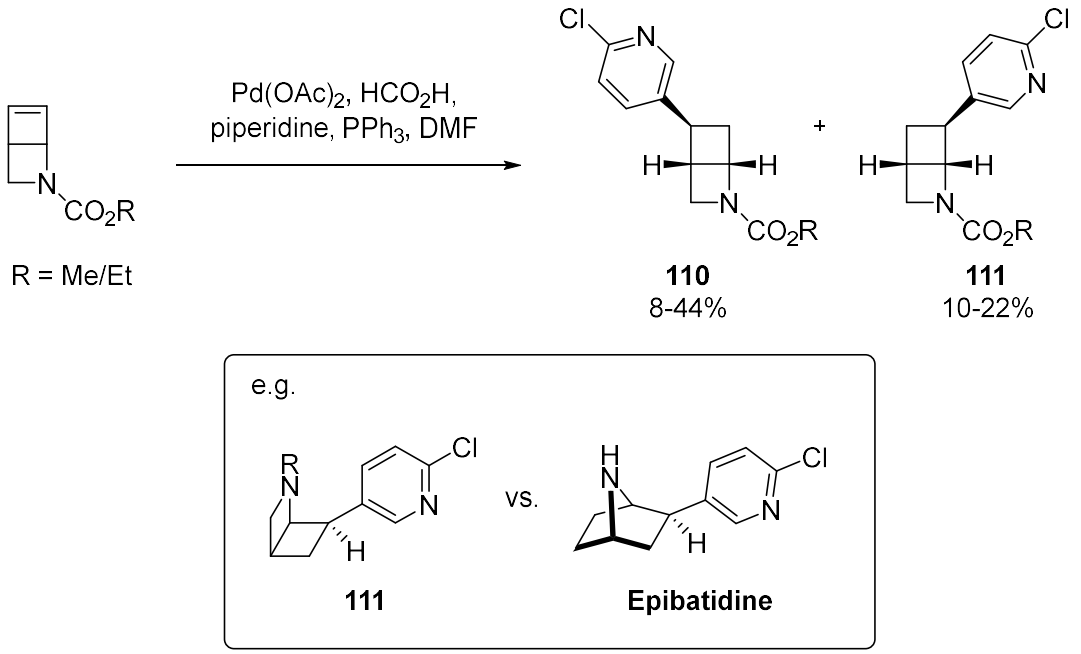
*Scheme 42: [4+2] cycloaddition followed by treatment with acid under reflux gave the substituted azabicyclohex-5-ene **5**.*[76]

1.6.2 Uses

Dewar dihydropyridines have been shown in the literature to be amenable to a variety of chemical transformations. The high level of geometric strain in the alkene present in 2-aza-bicyclo[2.2.0]hex-5-enes means that it is more reactive when compared to a non-geometrically strained alkene. Many transformations in the literature therefore revolve around modification of this functionality, with fewer examples of transformations at other positions.

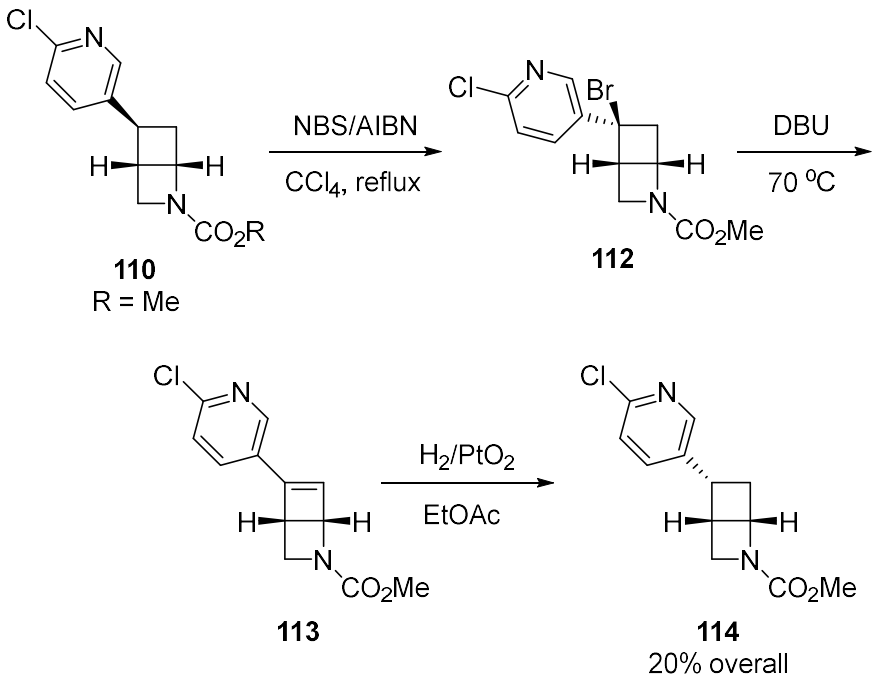
Krow and co-workers showed that the alkene can undergo a reductive Heck reaction with 3-iodo-6-chloropyridine, catalysed by $Pd(OAc)_2$ in the presence of formic acid, piperidine, triphenylphosphine and DMF (Scheme 43).[77] This afforded *exo* regioisomers **110** and **111**, with relative quantities

dependent on reaction temperature. The goal of this work was to generate analogues to the alkaloid epibatidine.



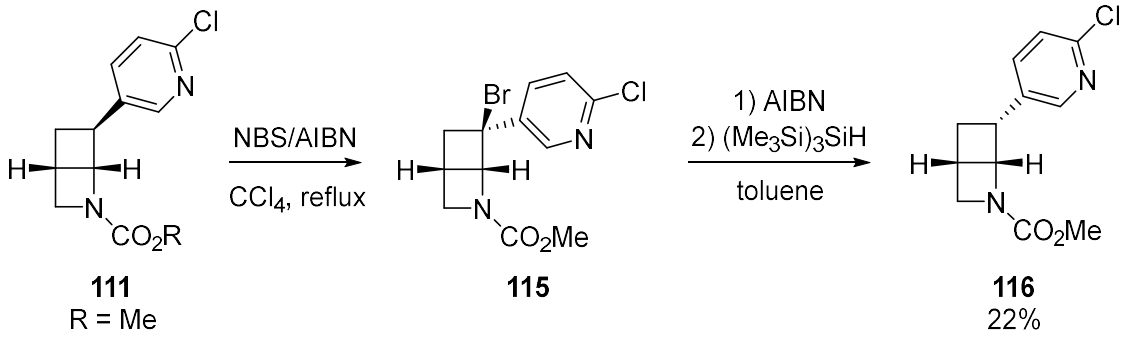
*Scheme 43: Reductive Heck reaction to aryl-azabicyclohexanes and a comparison of compound **111** with Epibatidine.*[77]

110 (when R = Me) could then be epimerised to the corresponding *endo*-form **114** by treatment with *N*-bromosuccinimide to brominate the more hindered position, followed by elimination of HBr by DBU, with subsequent *exo*-selective hydrogenation with H_2 and PtO_2. This afforded them the 5-*endo* product **114** in 20% overall yield (Scheme 44).[77]



Scheme 44: Epimerisation of aryl-azabicyclohexanes by treatment with NBS, DBU then exo-selective hydrogenation.

111 could also be epimerised, however, an alternative methodology was required, as they reported decomposition during the bromide elimination step when using the conditions they had used previously. As before, *N*-bromosuccinimide was used to brominate the more hindered position, however, to achieve the desired epimerisation they employed AIBN to initiate a radical cleavage of the C-Br bond (Scheme 45). The resulting heterocyclic radical is then quenched by tris(trimethylsilyl)silane, giving the desired *endo*-6-substituted heterocycle.[77]



111
R = Me

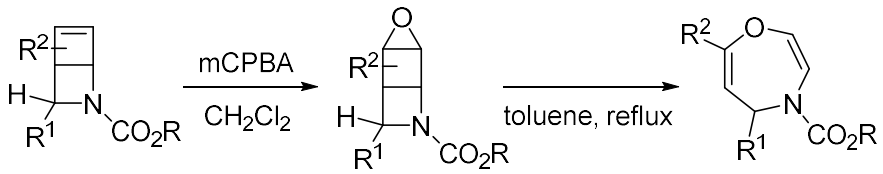
115

116
22%

Scheme 45: Alternative epimerisation protocol by treatment with NBS followed by radical formation by AIBN, then radical quenching with tris(trimethylsilyl)silane.

Tsuchiya *et al*. have extensively investigated 2+1 cycloadditions to the alkene moiety, with subsequent thermal ring opening to give a range of unsaturated, 7-memebered heterocycles.[53,54]

4,5-dihydro-1,4-oxazepines were synthesised by initial oxirane formation by mCPBA at room temperature, which gave the epoxide **117**. This was followed by thermal ring-opening in refluxing toluene, affording the 1,4-oxazepine **118** (Scheme 46).



R = Me/Bn
R^1 = H/Ph
R^2 = H/5-Me/5-Ph/
5,6-diMe

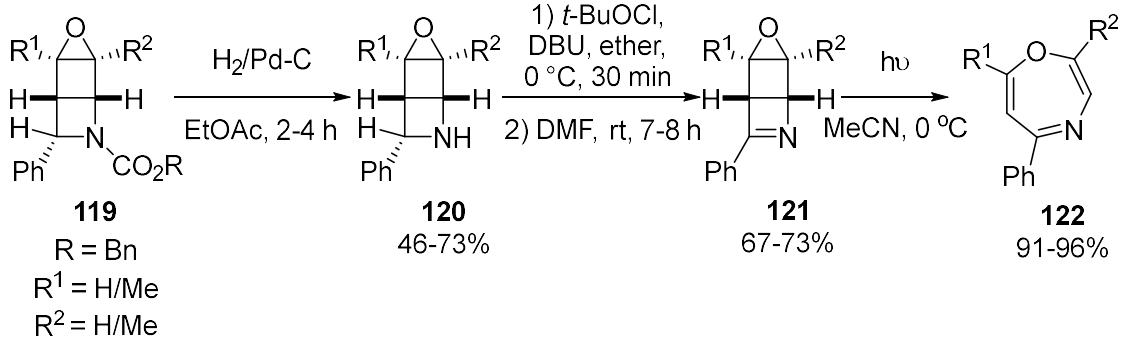
117

118
67-89%

Scheme 46: Epoxidation by mCPBA, followed by thermal ring-opening afforded Tsuchiya and co-workers with the oxazepines.[54]

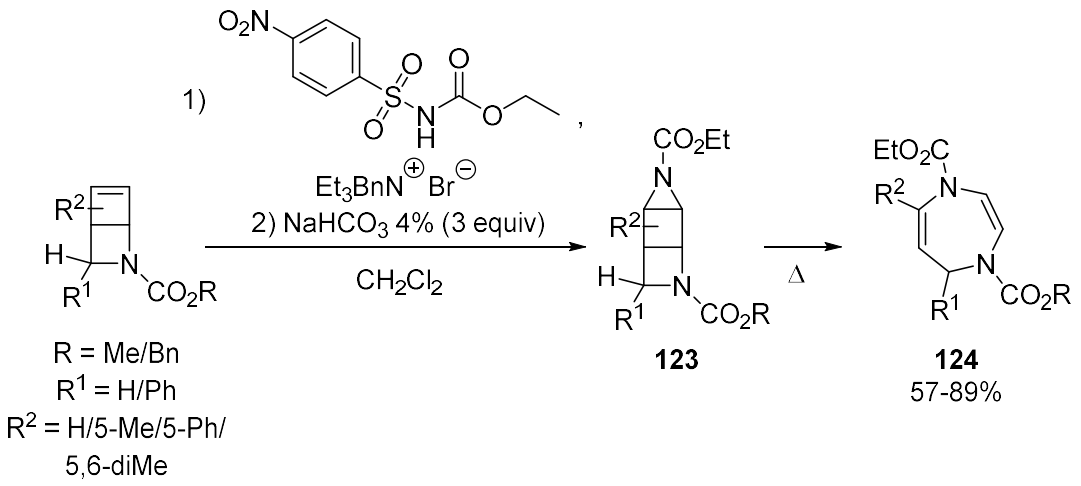
Alternatively, the fully unsaturated 1,4-oxazepine **122** was synthesised by CBz deprotection by palladium-catalysed hydrogenation of the epoxide **119**, followed by amine oxidation to the cyclic imine **121** with t-butyl

hypochlorite and DBU in DMF (Scheme 47). Photochemical ring-opening then gave the unsaturated 1,4-oxazepines **122**.[78]



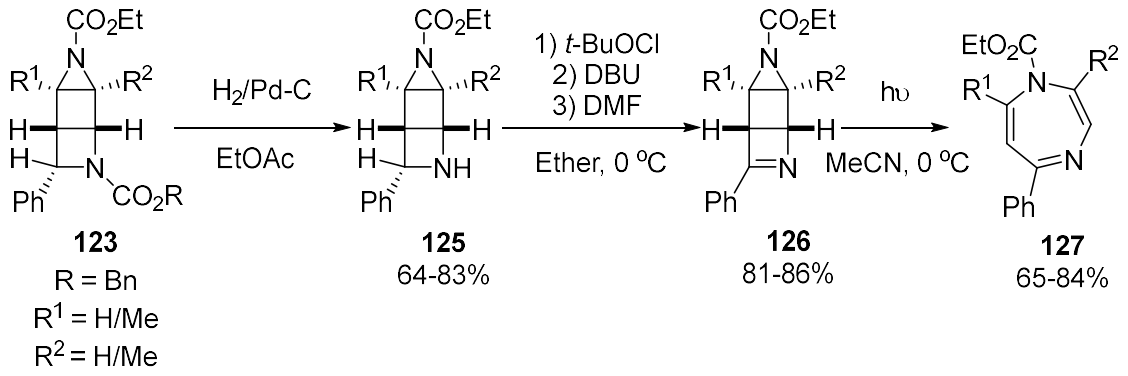
*Scheme 47: Deprotection of **119** followed by amine oxidation to the imine **121** with subsequent photochemical ring-opening gave unsaturated oxazepines **122**.*[79]

In an analogous transformation, 4,5-dihydro-1,4-diazepines **124** were synthesised by addition of ethoxycarbonylnitrene, generated from *N*-ethoxycarbonyl-4-nitrobenzenesulfonamide, to the alkene, which gave the aziridines **123** (Scheme 48). These were then transformed to the diazepines **124** by thermal ring-opening, as above.



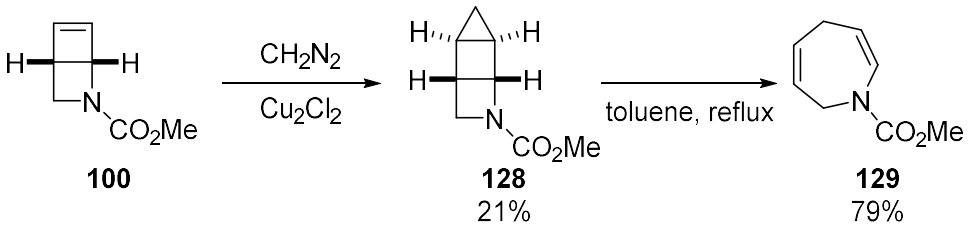
*Scheme 48: Nitrene addition to the alkene gave the aziridines **27**, which were subjected to thermal ring-opening to the diazepines **28**.*[54]

They also used the same protocol as for the formation of **122** to form fully unsaturated 1,4-diazepines **127** (Scheme 49).[79]



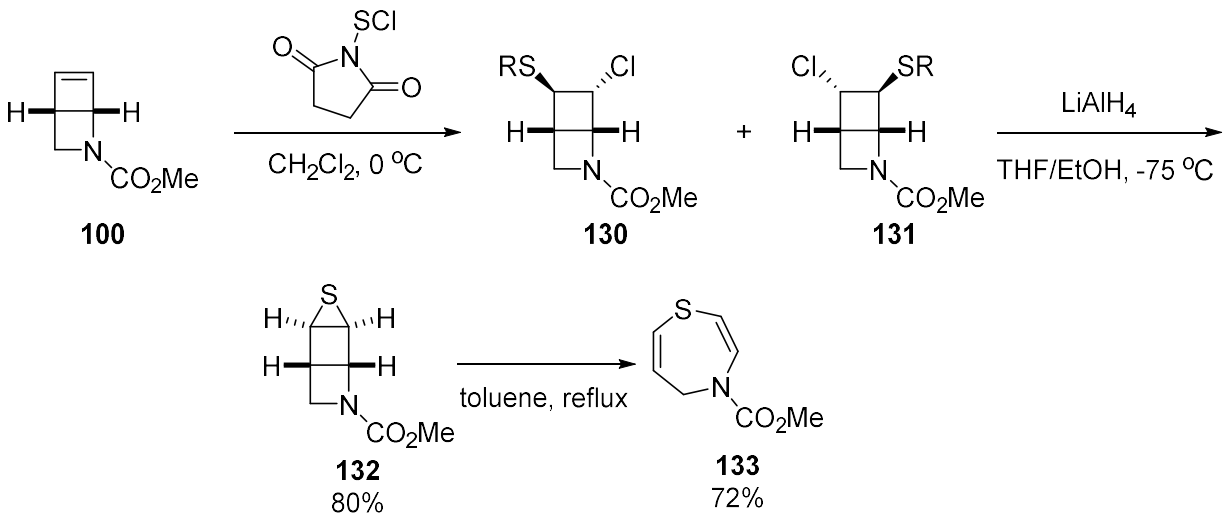
*Scheme 49: **127** was synthesised by deprotection, followed by amine oxidation then photochemical ring-opening.*[79]

Separately, treatment of the alkene **100** with diazomethane in the presence of copper(I) chloride gave the tricyclic heterocycle **128**, which was then converted to the 2,5-dihydroazepine **129** (Scheme 50).[80]



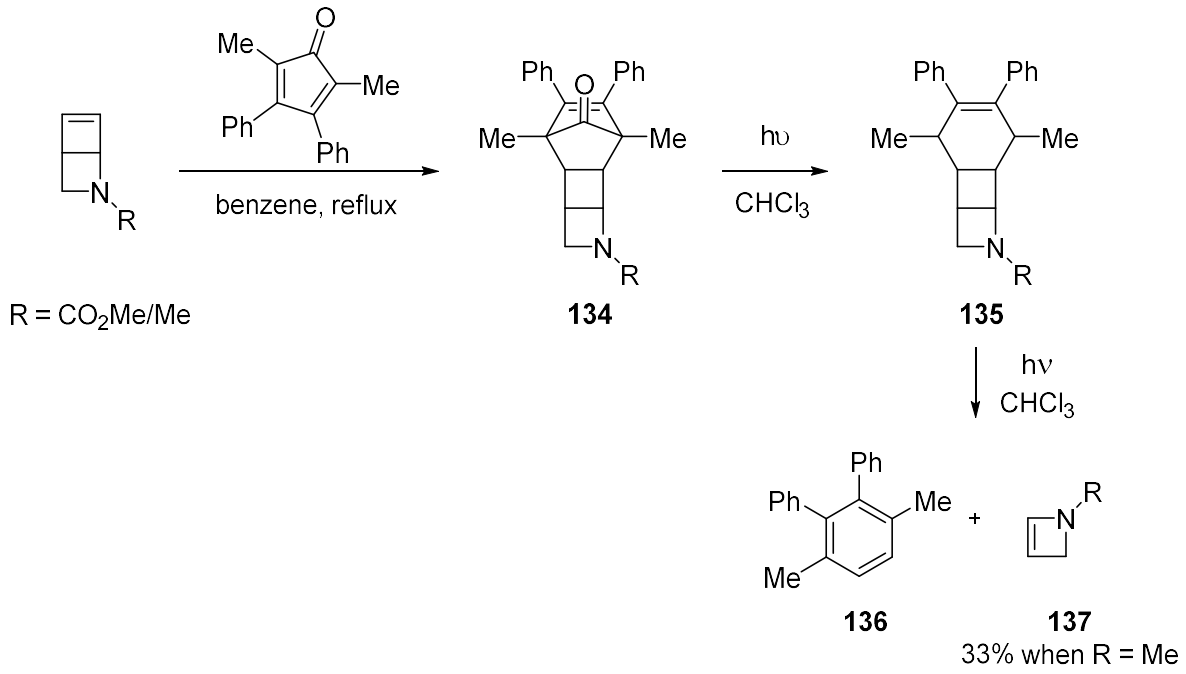
*Scheme 50: Carbene addition with diazomethane forms the cyclopropane **128**, which can undergo thermal ring-opening to the azepine **129**.*[54]

The 4,5-dihydro-1,4-thiazepines were synthesised from **100** by treatment with succinimide-*N*-sulfenyl chloride in dichloromethane (Scheme 51). This initially forms the addition products **130** and **131**. Thiirane **132** was then formed by reaction with $LiAlH_4$. Episulfide **132** was then heated at reflux in toluene, as previous examples, to form the thiazepine **133**.[79]



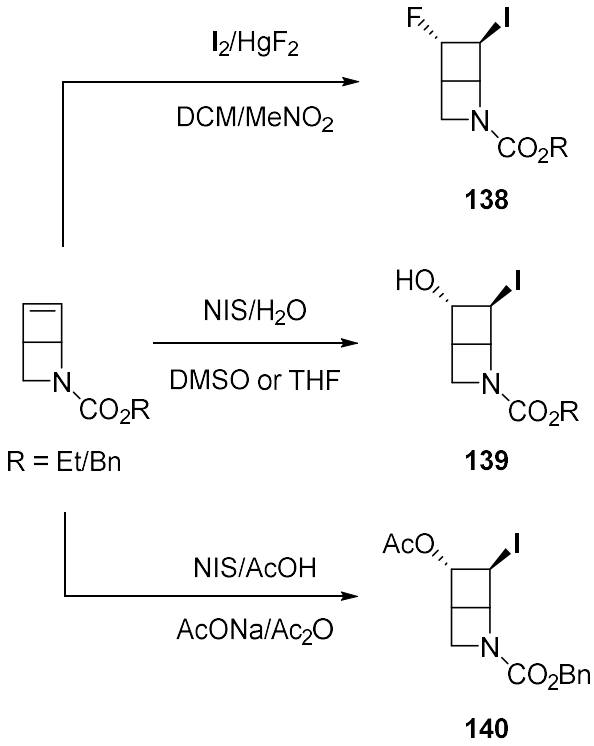
*Scheme 51: Thiazepine **133** was also synthesised, first by treatment with succinimide-N-sulfenyl chloride, $LiAlH_4$ reduction then thermal ring-opening.*[54]

Azabicyclo[2.2.0]hex-5-enes have also been shown to be amenable to other cycloadditions, with Warrener and co-workers reporting the [4+2] cycloaddition of Dewar 1,2-dihydropyridines with 2,5-dimethyl-3,4-diphenylcyclopenta-2,4-dienone in refluxing benzene to give cycloaddition products **134** (Scheme 52).[81] UV irradiation of these products allowed decarbonylation to form unsaturated tricycle **135**, which decomposed to 1,4-dimethyl-2,3-diphenylbenzene **136** and the 2-azetine **137**.



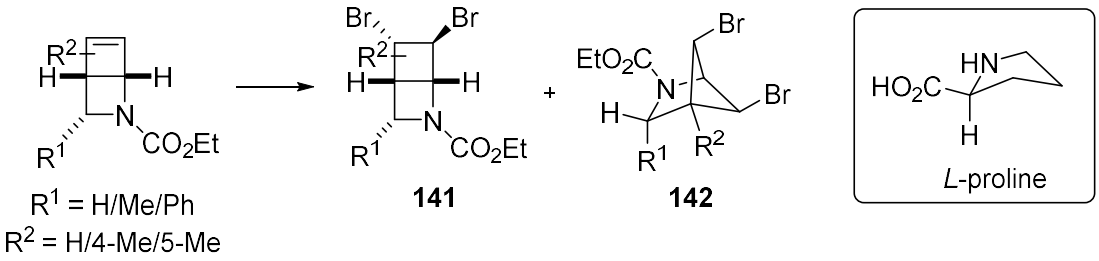
*Scheme 52: [4+2] cycloaddition of 2,5-dimethyl-3,4-diphenylcyclopenta-2,4-dienone afforded cycloadduct **134**, which could be decarbonylated under photochemical conditions. The resulting product then decomposes to benzene derivative **136** and the 2-azetine **137**.*[81]

Halogenation of the alkene moiety in Dewar dihydropyridines has been thoroughly researched by Krow and co-workers (Scheme 53).[82] Treatment of the Dewar heterocycle in a polar aprotic solvent mixture, with iodine and mercury fluoride gave the 6-iodo-5-*endo*-fluoro product **138**. Similarly, iodination was achieved by treatment with *N*-iodosuccinimide in DMSO, aqueous THF or buffered acetic acid, to give **139** and **140** respectively.



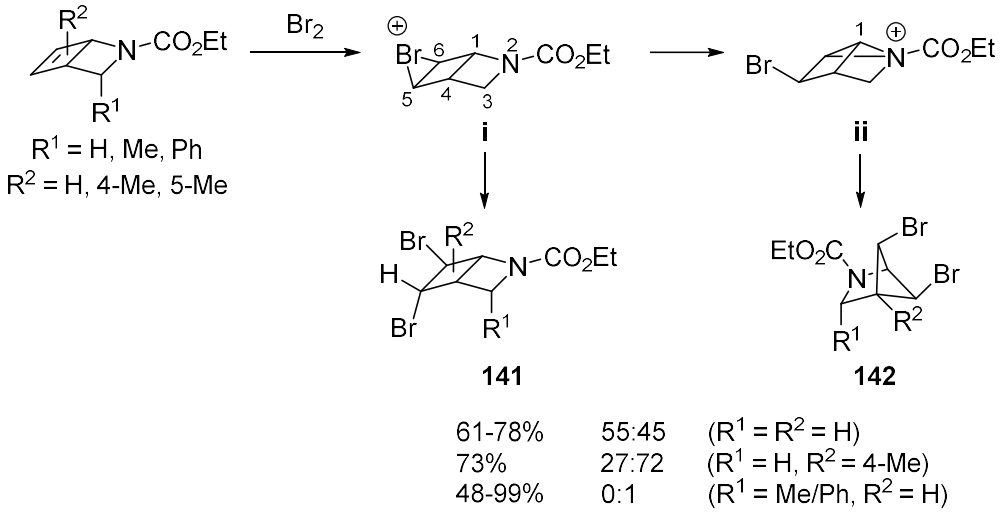
*Scheme 53: Three routes to iodinated Dewar dihydropyridines by treatments with iodine and mercury fluoride, giving **138**, N-iodosuccinimide in a polar protic solvent mixture to give **139** and N-iodosuccinimide in buffered acetic acid to give **140**.*[82]

Addition of bromine has been the most researched halogenation reaction of the Dewar heterocycle, however, as Krow *et al*. found that the reaction generated products with the 2-azabicyclo[2.1.1]hexane scaffold, which they saw as an interesting structural mimic of proline (Scheme 54).[75,83] Reaction of bromine with Dewar 1,2-dihydropyridines in dichloromethane gave a mixture of the unrearranged dibromide **141** and the rearranged dibromide **142**, with ratios varying depending on the substitution pattern. Interestingly they found that *endo*- methyl- or phenyl- substituents in the 3-position gave exclusively the rearranged products **142**. They also observed that an increase in solvent polarity gave an increase in the ratio of rearranged product compared to unrearranged product.



*Scheme 54: Bromination of Dewar 1,2-dihydropyridines gave a mixture of the dibromide **141** and the rearranged dibromide **142**, a structural analogue of proline.*[75,83]

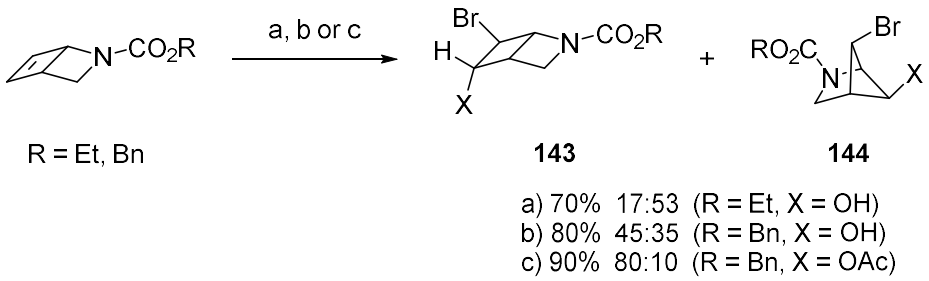
Their proposed reaction pathway starts with *exo*-selective bromination to form the bromonium ion **i**, which can then be attacked by the generated bromide ion at the 5-position, to give **141** (Scheme 55). Alternatively, they suggest that neighbouring-group participation by the nitrogen forms the strained aziridinium species **ii**, which can be regioselectively attacked by bromide at C-1, to give the rearranged product **142**.



*Scheme 55: Route to brominated Dewar heterocycle **141** and bridged pyrrolidine **142** via cyclic bromonium **i**. Ratios refer to proportions of **141**:**142** respectively.*

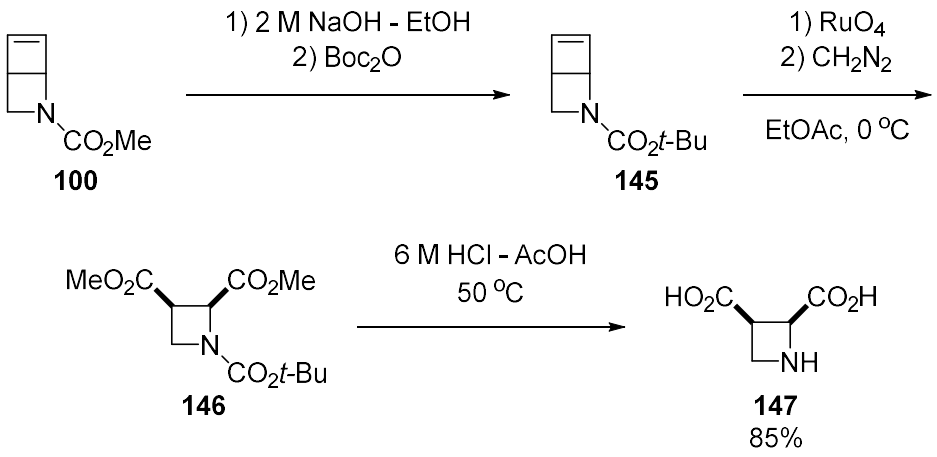
Using other sources of electrophilic bromine gave them products with different substituents. Using *N*-bromosuccinimide in either a DMSO/water or THF/water mixture gave the bromo-alcohols **143** and **144** (X = OH, ratio

(**143**:**144**) of 23:17 or 35:45), whereas in buffered acetic acid the reaction gave the bromo-acetates **143** and **144** (X = OAc, ratio of 1:8 respectively, Scheme 56).[83–85]



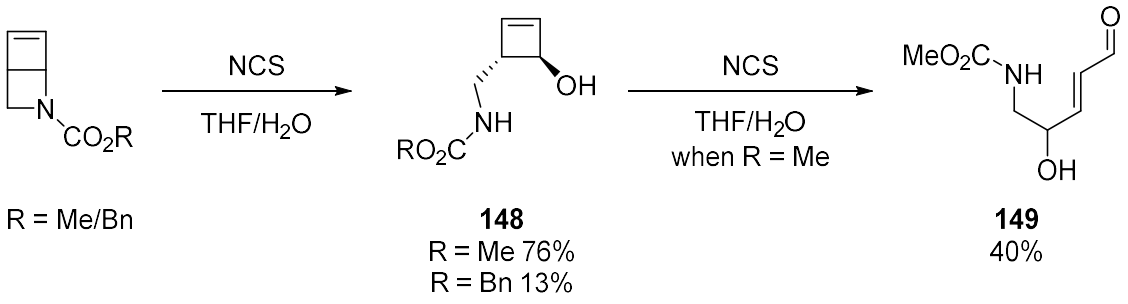
Scheme 56: a) NBS in DMSO/water (2:1); b) NBS in THF/water (2:1); c) NBS in AcOH/NaOAc/Ac_2O.[75,83]

Arakawa and co-workers researched the use of oxidative cleavage of the alkene bond, allowing access to functionalised azetidines from the Dewar dihydropyridine **100** (Scheme 57).[86] They found that the carbamate protecting group of **100** required exchange with the less reactive t-butyloxycarbonyl protecting group, as their attempts to form **147** from **100** directly failed. Protecting group exchange of **100** to **145** was performed by treatment with a 2 M NaOH solution in ethanol, followed by addition of Boc_2O. Following this, oxidation of the alkene moiety by ruthenium tetroxide, with *in situ* ester formation by diazomethane then formed the methyl diester species **146**. Hydrolysis of the diesters then afforded the azetidine-derived amino acid **147**.



*Scheme 57: Protecting group exchange with 2 M NaOH in ethanol gave Boc-protected Dewar dihydropyridine **145**, which Arakawa and co-workers successfully converted to the amino acid **147** by RuO_4 catalysed oxidation with in situ ester formation with diazomethane, followed by ester hydrolysis and protecting group removal.*[86]

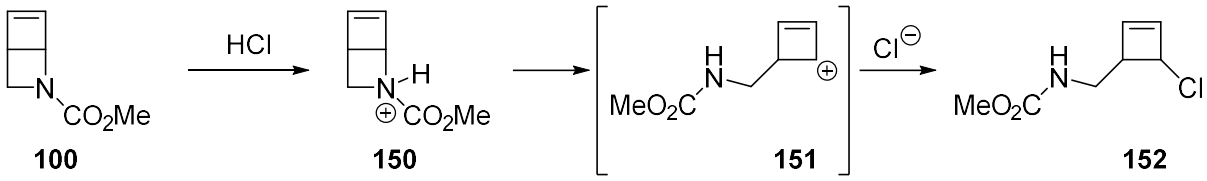
The Dewar heterocycle behaves remarkably differently when treated with *N*-chlorosuccinimide compared to *N*-bromosuccinimide. *N*-chlorosuccinimide in a THF/water mixture leads to C-N bond cleavage, to give the hydroxy-cyclobutene **148**, which reacts further to form hydroxy-aldehyde **149** (Scheme 58).[83]



*Scheme 58: NCS-mediated ring opening ultimately leads to the unsaturated hydroxy-aldehyde **149**.*[83]

Fowler and co-workers also described the *C-N* bond cleavage, using HCl in benzene, which gave the chlorinated cyclobutene **152** (Scheme 59).[74] They speculate that protonation of the nitrogen leads to heterolytic bond

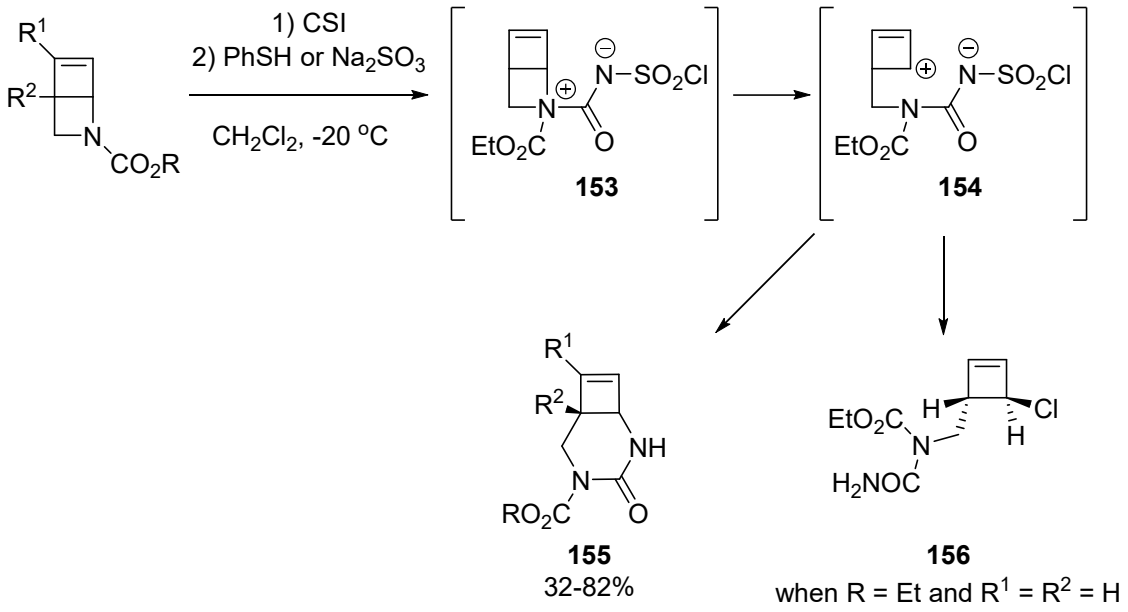
cleavage, leading to the cyclobutene carbocation **151**, which is then quenched by a chloride ion, forming **152**.



*Scheme 59: Protonation by HCl leads to C-N bond cleavage, with subsequent chlorination of the cyclobutene ring, to form **152**. No yields given by the authors.*[74]

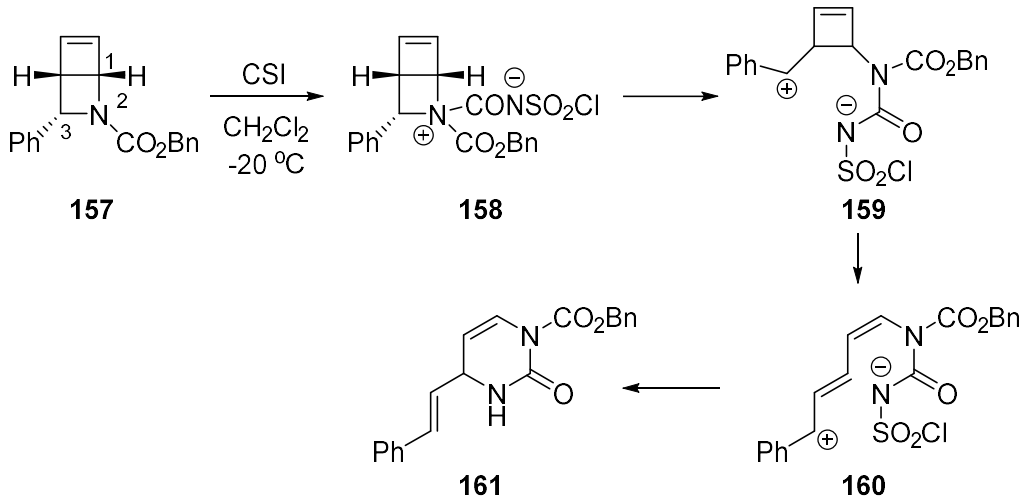
An interesting cleavage/insertion reaction was described by Krow *et al*. Treatment of substituted Dewar dihydropyridines with chlorosulfonyl isocyanate (CSI), followed by chlorosulfonyl- removal by thiophenol or sodium sulfite gave the bicyclic urea **155** and cyclobutene **156** when the ethoxycarbonyl protecting group was employed and without any substituents on the ring (Scheme 60).[87]

They suggest that initial addition of CSI to the nitrogen atom on the ring leads to the zwitterionic species **153**, which can undergo bond cleavage to form the cyclobutenyl carbocation **154**. Intramolecular ring closure onto the nitrogen anion then gives the bicyclic urea **156** after reductive work up with either thiophenol or sodium sulfite, whereas, if chloride ions are present, the chloro-cyclobutene **156** may be isolated after reductive work up.



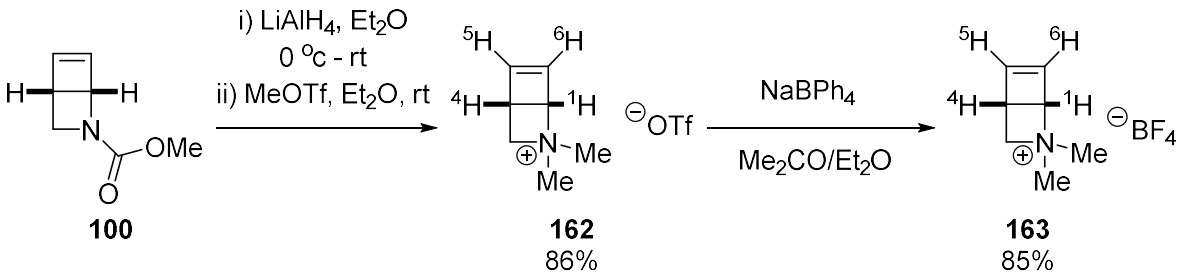
*Scheme 60: Treatment of carbamate protected Dewar dihydropyridines with chlorosulfonyl isocyanate leads to the 2-atom insertion product **155**. In the case that R = Et, R^1 = R^2 = H, product **156** was also reported (ratio (**155**:**156**) = 45:55).*[87]

Interestingly, when the 3-phenyl substituted **157** was used in the same reaction, an alternative product **161** was formed (Scheme 61). It was postulated that the presence of the phenyl substituent could stabilise a carbocation at the 3-position, leading to cleavage of the *N*-C3 bond, to form the carbocation **159**. Spontaneous cyclobutene ring-opening could then give the unsaturated species **160**, which could feasibly undergo intramolecular conjugate addition, when the vinylic nitrogen is in the *cis* configuration, to form the unsaturated, cyclic urea **161**.



Scheme 61: An alternative reaction pathway was reported for 3-phenyl substituted Dewar dihydropyridines, rationalised by stabilisation of a carbocation in the 3-position by the presence of the phenyl group. No yield reported.[87]

Opatz and co-workers were interested in the unusual NMR spectra obtained from the 2-azabicyclo[2.2.0]hexenium salts **162** and **163** (Scheme 62). Conversion of **100** to the free base Dewar dihydropyridine by lithium aluminium hydride was a known process, which was combined with addition of methyl triflate to afford the dimethylammonium salt **162**.[74,88] They observed no ^3J coupling between protons 1 and 6, nor protons 4 and 5, however there was strong ^4J coupling between 1 and 5 and 4 and 6. Comparing these results with DFT calculations for the system showed strong correlation to the experimentally derived results. Anion exchange to a tetrafluoroborate counterion allowed crystallisation, to confirm the structure by X-ray crystallography.



Scheme 62: 2-azabicyclo[2.2.0]hexenium salt preparation.

The strain present in these types of heterocycles therefore allows for a multitude of chemical transformations to structurally diverse products, as described. They therefore represent a promising starting point into the development of highly sp^3-rich, lead-like molecules.

Typically, Dewar heterocycles have been synthesised in batch processes by the photoirradiation of their respective 6-membered starting materials, meaning their synthesis has so far been restricted by the limitations imposed by traditional photochemistry methodology, discussed above. By applying a flow photochemistry method to their synthesis, it may be possible to remove these limitations and scale up these reactions in order to facilitate further research into processing the Dewar heterocycles into a range of structurally diverse small molecules, which may be of utility in drug discovery.

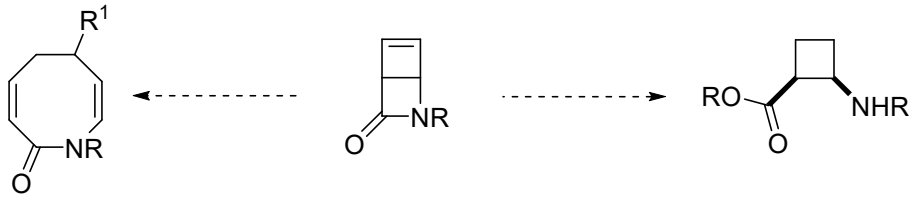
2 Aims and Objectives

We were attracted to Dewar products arising from photoirradiation of 1,2-dihydropyridines and 2-pyridinones and their potential to deliver new building blocks for exploration of novel pharmaceuticals. These compact photoproducts are low-molecular weight and sp^3-rich, yet offer reactive functionality that allow their further elaboration. This generated two main aims for our investigations:

First, it was envisaged that the productivity of the production of the Dewar heterocycles could be increased, compared to batch production, by

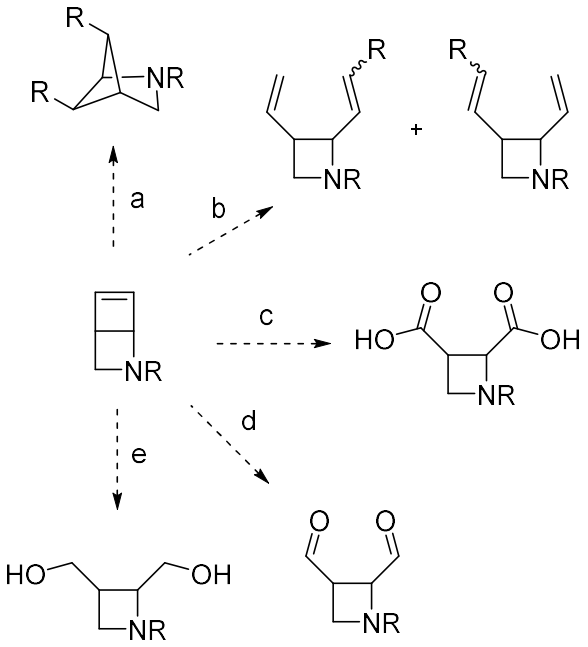
developing continuous flow technology for the UV irradiation step. To that end, construction of a continuous flow photochemical reactor was sought. A simple and relatively inexpensive reactor design first described by Booker-Milburn was identified for our investigations.[1] We therefore set out to evaluate and optimise the productivity of Dewar heterocycle synthesis using this setup, for which comparing the batch and continuous methods was planned.

Second, we sought to explore the range of possible Dewar heterocycles that could be obtained by photoirradiation of a variety of starting materials. Subsequent elaboration of these photoproducts by further development of their reactive functional groups was envisaged. For example, development of a novel route to a cyclobutane-containing β-amino acid derived from the photoproduct of 2-pyridinone was envisaged. Separately, investigation of Grubbs' catalysis to elaborate the strained cyclobutene functionality within the Dewar photoproducts and subsequent transformation to novel azocinones was planned (Scheme 63).



Scheme 63: Proposed products potentially available from Dewar 2-pyridone.

Using Dewar dihydropyridines as a starting material, it was envisaged that a range of sp^3-rich small molecules could be synthesised. Based on the literature it was desirable to investigate a novel route to bridged pyrrolidines first identified by Krow and co-workers, as well as various routes to highly substituted azetidines, such as through Grubbs' ROM/CM and oxidative cleavage of the alkene (Scheme 64).[75,83,85,89]



Scheme 64: a) Alkene activation with neighbouring group participation leading to bridged pyrrolidines b) Grubbs' ROM/CM, c) Ozonolysis with oxidative work-up, d) Ozonolysis with mild reducing work up, e) Ozonolysis with reductive work-up.

3 Results and Discussion

3.1 Reactor Construction

It was hypothesised that the productivity of the photoreaction to produce Dewar heterocycles could be increased by moving from a batch method, to production using continuous flow technology.[23] To this end, a continuous flow photochemical reactor was constructed.[1] The main factors that went into deciding on a reactor design were cost, ease of use, and scalability. For this reason, the fluoroethylene propylene (FEP) reactor design from the Booker-Millburn group was used, as this fulfils those criteria: the individual components are relatively inexpensive compared to more high-end equipment (such as Vapourtec modular systems), the setup is easy to use, and most importantly scalable as the reactor is a microflow reactor (as opposed to microflow), allowing for a high throughput of reaction mixture.[1]

The main body of the photochemical reactor is simply a large quartz glass immersion well, housing a 400 W medium pressure mercury lamp; a broad-

band emitter, which provides radiation at several UV wavelengths simultaneously (predominantly 365-366 nm but the lamp also emits a small portion of its light at 254, 265, 270, 289, 297, 302, 313 and 334 nm) as well as wavelengths in the visible region, spectrum published by Photochemical reactors Ltd. (Figure 3). The immersion well allows the insertion of a Pyrex® glass filter sleeve, which can be used to block the transmission of wavelengths below ~280 nm, to allow for a certain degree of control with respect to the wavelength transmitted.

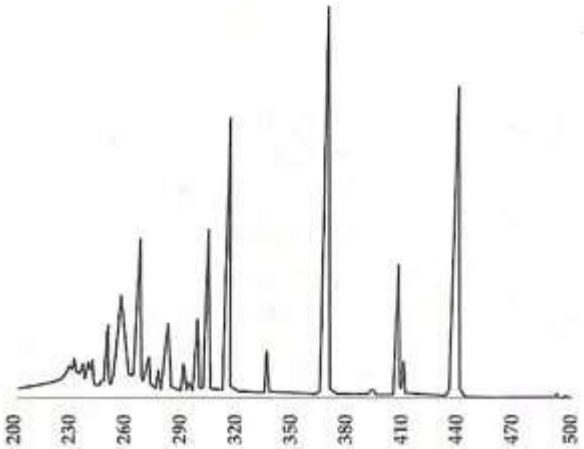


Figure 3: An example of the emission spectrum of the medium pressure 400 W Hg arc lamp from Photochemical Reactors ltd. Image reproduced with permission from Photochemical Reactors ltd.

A coil of UV transparent tubing, made from fluoroethylene propylene (FEP) polymer was wrapped directly onto the exterior of the immersion well, to be exposed to the maximum light intensity possible (Figure 4). The photoreaction takes place within this tubing, with the reaction mixture being pumped in at the bottom of the reactor coil. FEP was chosen as the coil material due to its versatile physical properties, required to coil the tubing tightly around the immersion well, and its excellent UV transmittance.[1]

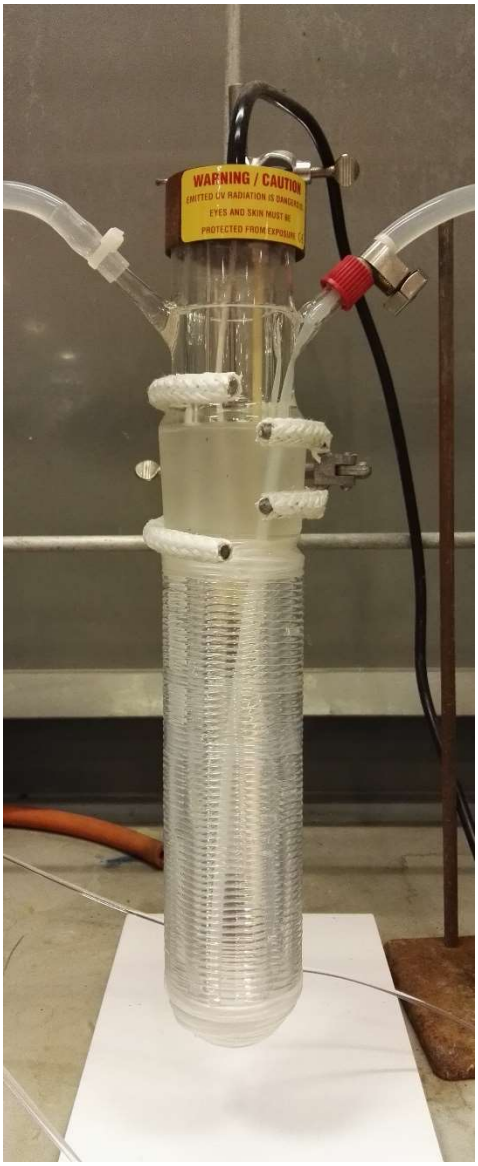


Figure 4: Close-up of reactor, showing the immersion well wrapped with coils of FEP tubing.

The reactor coil was joined to a variable speed peristaltic pump, used to pump the reaction mixture through the coil (Figure 5 a). This pump displays revolutions per minute of the bearing race, thus it was necessary to measure flow rates at varying rpm e.g. an rpm of 20 provided a flow rate of 1.25 mL min^{-1}. At the minimum rpm the pump provided a flow rate of 0.6 mL min^{-1}, calculated by measuring the volume of solvent (isopropanol)

pumped through the coil over a period of 10 minutes. The actual flow rate will vary slightly, depending on the viscosity of the reaction mixture.

The immersion well itself is attached to a mains water feed, to supply the immersion well jacket with water to cool the equipment during operation (Figure 5 e). A flow monitor is installed along the input tubing, which is connected in turn to a power cut-off controller. The monitor detects the rate of water flow and cuts power to the lamp if the water flow drops below a certain threshold (Figure 5 h). This prevents damage to the lamp if water flow is ceased during operation. The 400 W power supply is plugged into the cut-off controller *via* a conventional 3-pin plug fitted with an RCD unit, which also cuts the power if the power supply itself becomes damaged.

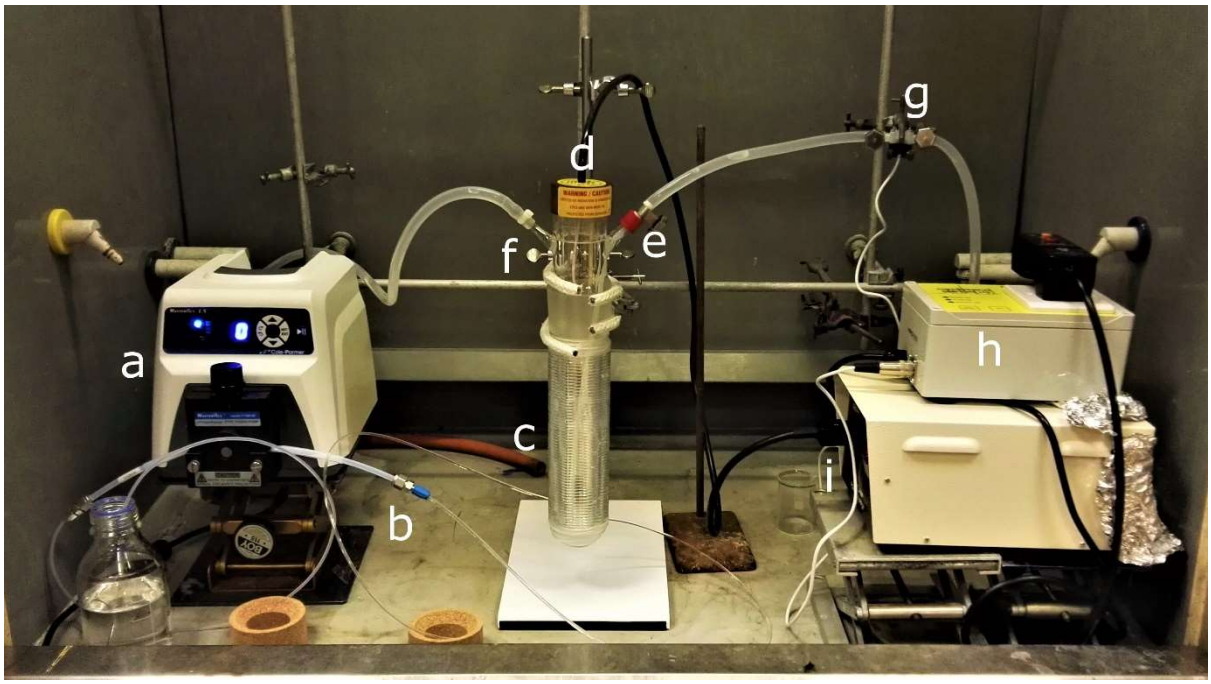


Figure 5: Reactor set up. a) peristaltic pump, b) PTFE to FEP union (contains O-Rings), c) Reactor coil, d) 400 W Hg lamp, e) water coolant input, f) water coolant output, g) coolant water flow monitor, h) power cut-off control, i) 400 W power supply.

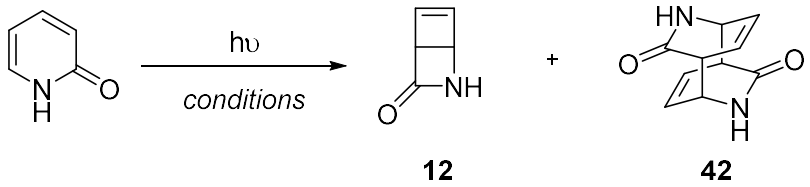
The initial reactor was constructed with 1 layer of FEP tubing, providing an internal volume of ~50 mL (referred to as "50 mL reactor"). Later iterations of the reactor increased the number of layers of tubing, increasing the

internal volume from ~50 mL to ~220 mL (referred to as "220 mL reactor") by winding further layers of tubing around the reactor (3 layers). Finally, two of the 220 mL reactors were connected in series such that the total internal volume reached ~440 mL (referred to as "440 mL reactor").

The coil was attached to the peristaltic pump by unions sealed by FKM O-rings (fluoroelastomer). With this initial set up, problems were encountered with the original O-rings, as they proved incompatible with several reaction solvents. The original O-rings were therefore exchanged for more chemically resistant FFKM O-rings (perfluoroelastomer), which alleviated these issues and allowed for a wider range of solvents to be used.

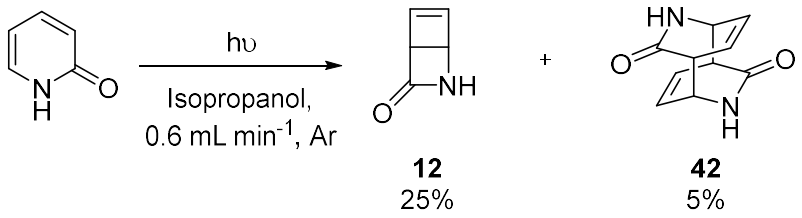
3.2 Dewar 2-Pyridone Synthesis

To gain an understanding of the equipment, the irradiation of 2-pyridone was initially undertaken as a relatively simple starting point as it uses a cheap, commercially available precursor. The Dewar 2-pyridone **12** photoproduct was identified as a potentially versatile starting material for which exploration of a number of reaction pathways were envisioned, so it was desirable to investigate further.



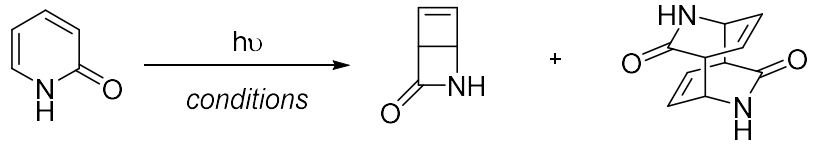
*Scheme 65: Photoirradiation of 2-pyridone to form the desired photoisomer **12** and the [4+4] photodimer **42**. Yields are based on conversion of starting material.*

Earlier investigations of this transformation using flow photochemistry were carried out in the George group, which suggested a starting concentration of 0.02 M would be productive.[90] Isopropanol was chosen as the initial solvent, as it was readily available and able to dissolve the 2-pyridone. A 0.02 M solution of 2-pyridone, pumped through the 220 mL reactor at a rate of 0.6 mL min^{-1}, gave a 25% yield of photoisomer **12** after chromatography. As previously reported, photodimer **42** was also obtained from this reaction mixture, isolated as a solid in 5% yield. The photodimer can simply be filtered from the reaction mixture after concentrating *in vacuo*, leaving a solution of unreacted starting material and azetidinone, which can then be purified by flash column chromatography. The remaining mass balance was unreacted starting material.



Scheme 66: Initial conditions for the continuous flow irradiation of 2-pyridone.

Reaction conditions were varied from the initial conditions above (Scheme 66) to ascertain a set of optimum conditions, which balanced conversion and productivity. Initially, reaction concentrations were varied from 0.02 M to 0.1 M at a set flow rate of 0.6 mL min^{-1} (Table 2). Conversion to Dewar 2-pyridone was calculated based on the relative integration of ^{1}H NMR peaks corresponding to the starting material and the Dewar product (2-pyridone peak: 7.23 ppm; Dewar product peak: 6.64 ppm).



12 42

Conc. (M)	Flow Rate (mL min^{-1})	Ratio (12:42)	Dewar Yield (%)	Dimer Yield (%)	Productivity (mg h^{-1})
0.02	0.6	-	25[a]	5[a]	23
0.04	0.6	84:16	15[b]	11[a]	34
0.06	0.6	86:14	11[b]	23[a]	38
0.10	0.6	93:7	4[b]	15[a]	23
0.02	0.6	1:1	25[a]	5[a]	23
0.02	1.25	71:29	10[b]	n/a	48
0.02	1.90	85:15	10[b]	n/a	47

Table 2: Productivity as a function of reaction concentration and flow rate. All experiments were performed on the 220 mL photoreactor [a] Isolated yield. [b] Calculated yield by relative integration of the ^{1}H NMR spectrum (6.28 ppm vs. 4.44 ppm) from total yield.

It was found that by increasing the concentration of the reaction solution, the amounts of dimeric products isolated increased, starting at 5% at 0.02 M and increasing to a maximum of 23% at 0.06 M (Table 2). It was therefore concluded that the optimum concentration for the reaction was 0.02 M, as this gave the highest yield of the desired Dewar product compared to dimeric by-products. Productivity was low at concentrations of less than 0.02M.

The flow rate was next investigated using 2-pyridone solution at 0.02 M, which was pumped through the reactor at various flow rates, starting from 0.6 mL min^{-1} and increasing to 1.9 mL min^{-1}. The reaction mixture expelled from the reactor was collected for a 1-hour period for each specified flow rate, then concentrated *in vacuo*. The dimer precipitate was removed by filtration and the resulting filtrate analysed by ^{1}H NMR to obtain a ratio of

starting material and the Dewar product (SM:DP) by relative integration. Since the material was collected over a 1-hour period, productivity in mg h^{-1} could be calculated.

At a 0.6 mL min^{-1} flow rate a 1:1 mixture of starting material and Dewar product was obtained (based on relative integration of the corresponding starting material and Dewar 2-pyridone peaks in ^{1}H NMR), however productivity was low at only 23 mg $hour^{-1}$ due to the low flow rate (Table 2).

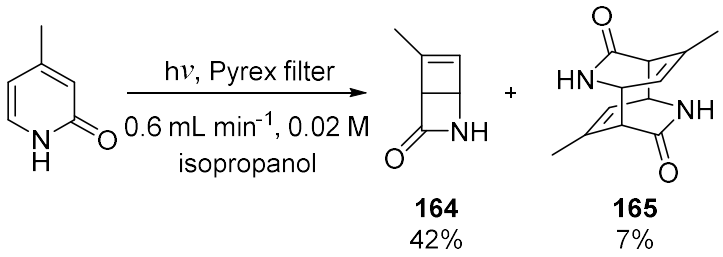
Doubling the flow rate to 1.25 mL min^{-1} more than doubled the productivity to 48 mg $hour^{-1}$, despite the fact that proportionately less Dewar heterocycle was formed with the ratio of starting material: Dewar product decreasing to 7:3 (Table 2).

Increasing the flow rate further to 1.9 mL min^{-1} saw almost no change in productivity (47 mg h^{-1}) compared the 1.25 mL min^{-1} (48 mg h^{-1}), but overall conversion was reduced as the ratio of starting material to product decreased to 85:15. At this point, the decrease in residence time gives low conversion and negatively affects productivity, thus, higher flow rates were not investigated further (Table 2).

Lower flow rates than 0.6 mL min^{-1} were also not investigated, both due to the greatly diminished productivity at lower flow rates, and the equipment itself being unable to pump lower than ~0.5 mL min^{-1}.

It was proposed that the optimum concentration and flow rate for single-pass continuous flow of 2-pyridones on the 220 mL photoreactor was 0.02 M and 1.25 mL min^{-1} respectively, as this provides the best compromise between dimer formation, conversion, and productivity. It may be possible to increase the conversion to further boost productivity by performing the reaction on several reactors connected in series (e.g. 440 mL reactor), or recirculating the reaction mixture, to increase residence time, however these experiments have not yet been attempted.

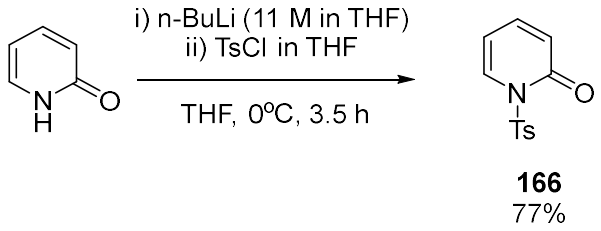
The photoisomerisation of 4-methyl-2-pyridone was performed similarly to that of the unsubstituted 2-pyridone. A 0.02 M solution was pumped through the 220 mL reactor at a rate of ~0.6 mL min^{-1} to give the photodimer **165** in 7% yield, and the desired Dewar product **164** in 42% yield after column chromatography. The remaining 51% was unreacted starting material.



*Scheme 67: Photoirradiation of 4-methyl-2-pyridone to give the desired photoisomer **164** and the [4+4] photodimer **165**. Yields are based on conversion of starting material.*

To improve productivity of the photochemical step, the obvious choice would be to increase reaction concentration. However, as demonstrated, increasing the concentration in this case only increases the relative quantity of photodimer produced. It was proposed that a sterically demanding *N*-protecting group may disrupt the dimerisation and improve the relative production of the Dewar photoproduct and possibly allow for increased reaction concentrations.

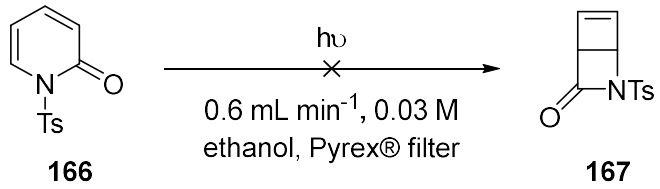
To that end, *N*-tosyl-2-pyridone was synthesised, as tosyl protection is simple and reliable. Deprotonation of 2-pyridone, using *n*-butyllithium and subsequent reaction with *p*-toluene sulfonyl chloride gave *N*-tosyl-2-pyridinone **166** in good yield (Scheme 68).[91] Only the *N*-tosylated compound was isolated, since in polar solvent the 2-pyridone tautomer is favoured, as such, no *O*-tosylated product was observed.



166
77%

Scheme 68: Synthesis of N-tosyl-2-pyridone.

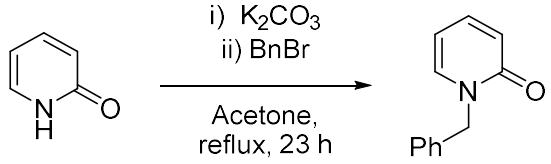
A 0.03 M solution of *N*-tosyl-2-pyridone (1.246 g) in ethanol (150 mL) was then irradiated, with a flow rate of ~0.6 mL min^{-1} (50 mL reactor). This gave a complex mixture of products. ^{1}H NMR spectroscopy of the crude mixture did not show any of the peaks indicative of the Dewar heterocycle.



166 **167**

*Scheme 69: Photoirradiation of N-tosyl-2-pyridone **166** did not form the desired photoisomer **167**.*

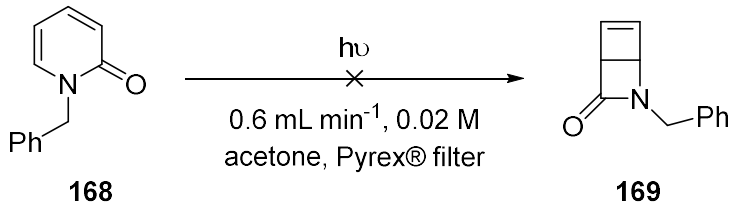
Since irradiation of *N*-tosyl-2-pyridone failed to produce the desired photoisomer, *N*-benzyl-2-pyridone **168** was synthesised as an alternative. This was synthesised using a simple literature procedure by the dropwise addition of benzyl bromide to a stirring suspension of 2-pyridone and potassium carbonate in acetone, which was then heated at reflux for 23 hours.[92] After an aqueous work up and purification by washing with cyclohexane, *N*-benzyl-2-pyridone was obtained in good yield (78%) and high purity (Scheme 70).



168
78%

*Scheme 70: N-benzyl-2-pyridone **168** synthesis.*

This material was then irradiated, using a 0.02 M solution in acetone (0.92 g of *N*-benzyl-2-pyridone), at a flow rate of ~0.6 mL min^{-1} (50 mL reactor). This gave a complex mixture of products (Scheme 71). Acetone was used here due to low solubility in isopropanol.



*Scheme 71: Photoirradiation of N-benzyl-2-pyridone **169** gave a complex mixture of products.*

It could be that in both these cases the presence of a UV-absorbing phenyl/tolyl based protecting group contributed to the formation of complex mixtures of products, since these groups could potentially enter their excited states and react in other reaction pathways than desired. Given photoirradiation of *N*-protected 2-pyridones had so far failed to give the desired outcome, attentions were then turned to further processing the Dewar heterocycle, with the aim to furnish sp^3-rich azetidinones.

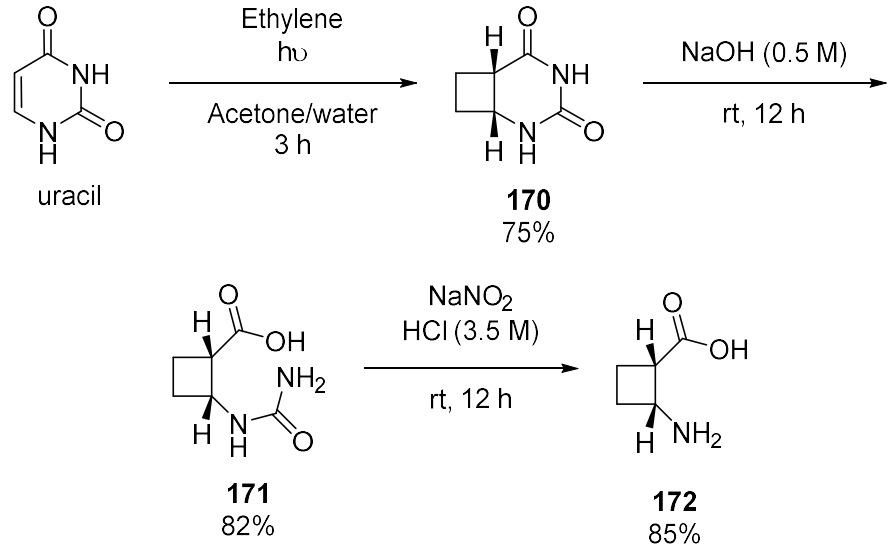
3.3 Dewar 2-Pyridone Reactivity

3.3.1 β-Amino Acid Synthesis

A novel route to an unnatural β-amino acid derivative was envisioned which took advantage of the inherent reactivity and propensity to ring opening of the lactam moiety in Dewar 2-pyridone. β-Amino acids offer promise as building blocks for unnatural β-peptides that could mirror the activity of natural α-peptides but provide a reduced rate of degradation by proteolytic enzymes.[93]

Previously, synthesis of a cyclobutane-containing β-amino acid was reported in the literature, most recently by Aitken *et al*.[94] Starting from uracil they performed a photochemical [2+2] cycloaddition to install the cyclobutane ring. Two hydrolysis steps followed, cleaving the amide bond with dilute sodium hydroxide, followed by removal of the urea with sodium

nitrite and hydrochloric acid. This gave the β-amino acid **172** in 52% overall yield (Scheme 72). They also noted that the amino acid was relatively unstable and could undergo spontaneous ring-opening.[95]



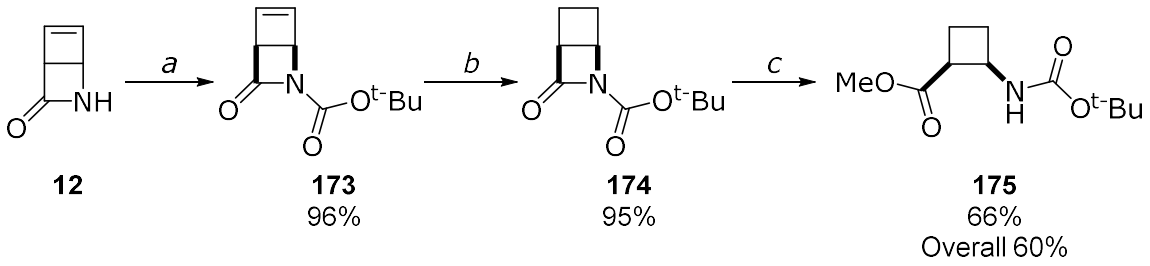
*Scheme 72: Aitken et al. method to unnatural amino acid **172**.*

It was therefore decided to install a nitrogen protecting group to avoid product degradation by ring opening and to aid in purification. Protection of the azetidinone photoproduct **12** was achieved by reaction with di-*tert*-butyl dicarbonate, DMAP and triethylamine in CH_2Cl_2. This gave excellent yields of *tert*-butyl 3-oxo-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate, **173** (96%), following an acidic work up, with no need for chromatography (Scheme 73, a).[50]

Subsequent hydrogenation was investigated. Performing the reaction in methanol with hydrogen and using Pd/C (10 wt%) as catalyst gave a complex mixture of products, and NMR analysis did not indicate any of the desired product was present. Performing the same reaction in ethyl acetate proved successful, giving the desired cyclobutane **174** in good yield and high purity (Scheme 73, b).

To aid in the final purification steps it was also decided to perform the azetidinone ring opening with sodium methoxide instead of lithium hydroxide, forming the methyl ester as opposed to the free carboxylic

acid.[96] Ring opening of the azetidinone **174** using sub-stoichiometric sodium methoxide (20 mol%) in methanol was performed, which cleanly gave the desired cyclobutane β-amino acid derivative **175** in good yield (Scheme 73, c, 66%), giving an overall yield of 60% over 3 steps.



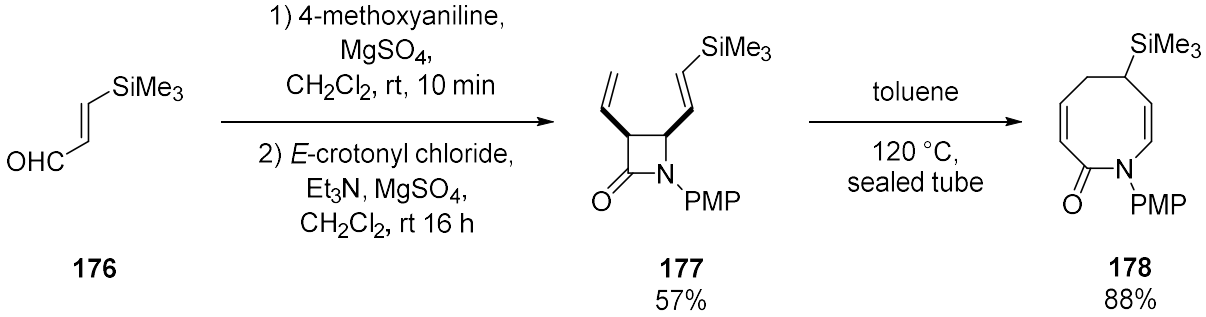
Scheme 73: a) DMAP, Et_3N, $(Boc)_2O$, CH_2Cl_2, 0-20 °C, 2.5 h; b) H_2, Pd/C 10 wt%, EtOAc, RT, 16 h; c) NaOMe, methanol, 16 h RT.

The Aitken method and the route presented here are comparable in terms of number of steps, reaction times and overall yield (starting at the Dewar pyridone in this work), furthermore the price of uracil and 2-pyridone starting materials seem to be comparable. The main issue with this novel route compared to that reported by Aitken is the yield of the photochemical step, the latter proceeding more efficiently.

3.3.2 Azocinone Derivative Synthesis

Previous work in the group established a route to the trimethylsilyl azocinone **178** *via* thermal Cope rearrangement from the divinyl β-lactam **177** obtained from Staudinger synthesis (Scheme 74).[97] It was envisioned that a route to divinyl β-lactams from Dewar 2-pyridones established by Piras and co-workers (see Scheme 19 Introduction) could be used to access further azocinone analogues, which were identified as a potentially interesting compounds for investigation due to their dense functionality and previous use as β-peptide turn mimics.[49,98,99] This novel route offers an

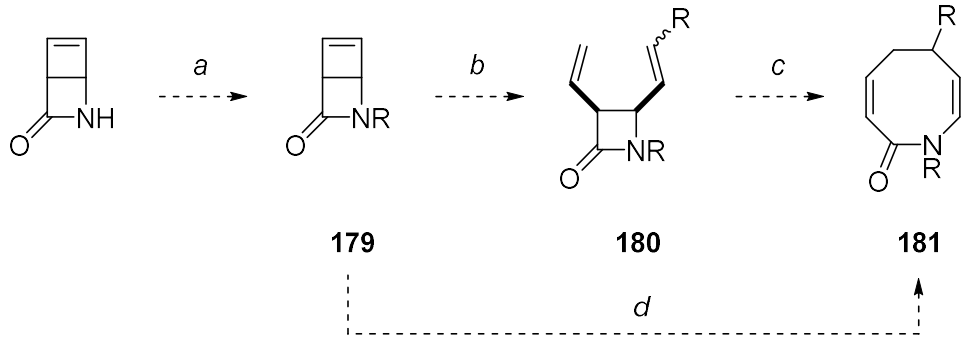
economic alternative to potentially expensive reagents, such as the silyl aldehyde **176** used in the previous route.



176 **177** 57% **178** 88%

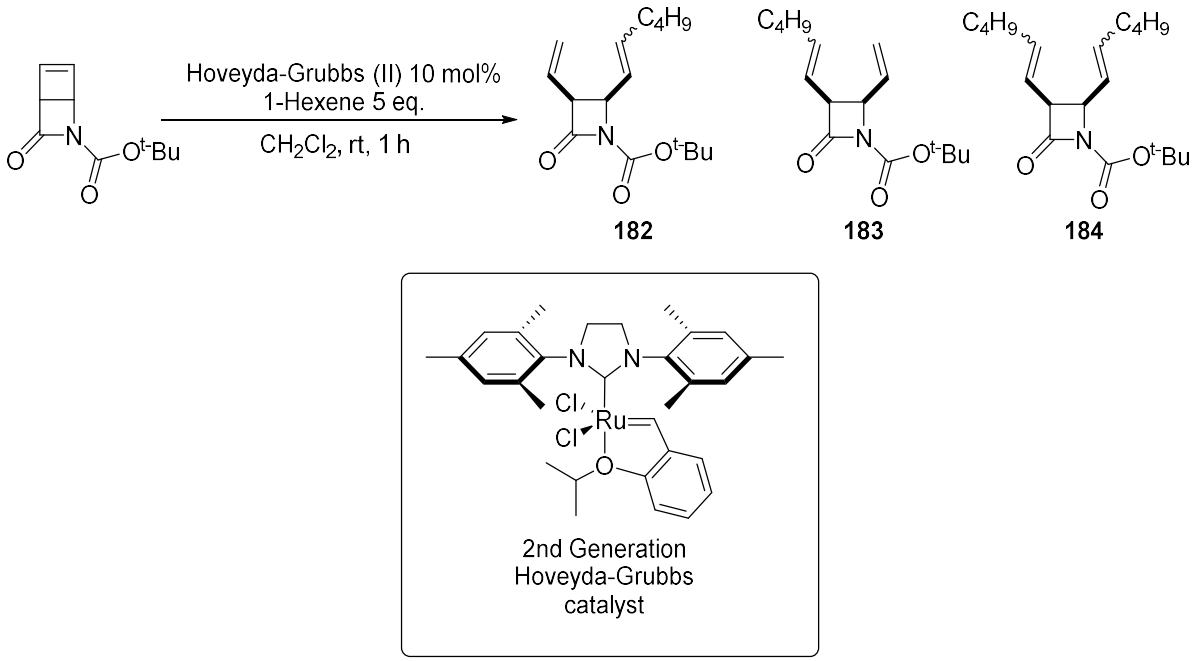
*Scheme 74: Azocinone synthesis by thermal Cope rearrangement from divinyl b-lactam **178**.*

The proposed strategy would involve the ring-opening metathesis/cross metathesis (ROM/CM) of the protected Dewar 2-pyridone **179**. In principle, varied cross metathesis partners could provide for variation of functionality. Subsequently, the divinyl species **180** would be subjected to thermal Cope rearrangement to furnish the azocinones **181**. Isolation of the ROM/CM product could also potentially be bypassed, by performing the ROM/CM *in situ* under thermal Cope conditions, allowing one-pot synthesis of the azocinones directly from the *N*-protected Dewar pyridone **179** (Scheme 75, d).



*Scheme 75: Envisioned synthetic strategy to azocinone **181**. a) Dewar 2-pyridone N protection, b) Ring-opening metathesis/cross metathesis, c) Cope rearrangement, d) in situ ROM/CM + Cope rearrangement.*

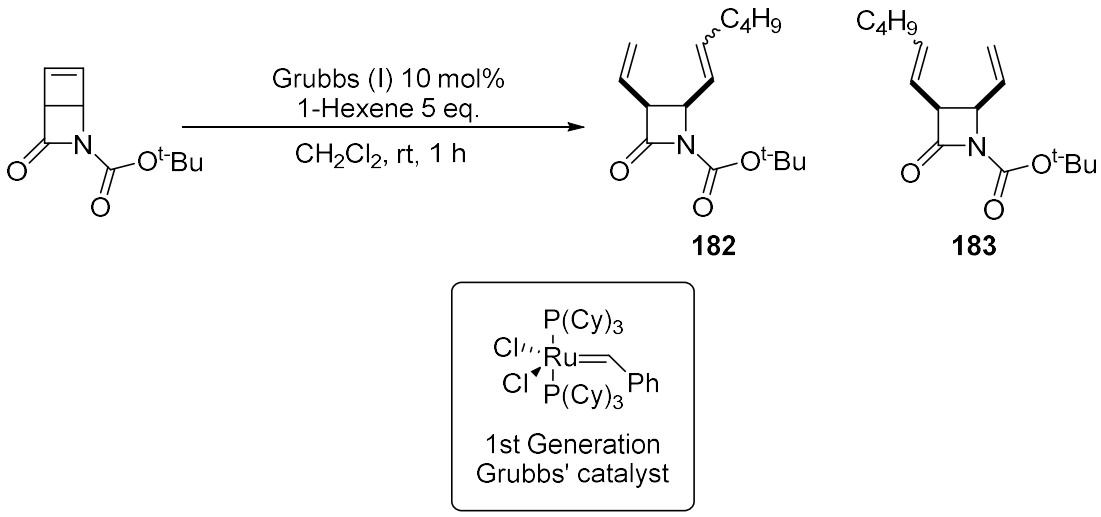
Initial experimentation used the Boc-protected Dewar 2-pyridone as this was straightforward to synthesise. Methathesis using Hoveyda-Grubbs (2nd generation) catalyst and five equivalents of 1-hexene as the coupling partner in dichloromethane at room temperature was investigated.[49] Mass spectrometry data of the crude material suggested the presence of the ring opened derivatives **182**, **183**, and **184**, but these could not be isolated from a complex mixture of products (Scheme 76). Increasing the amount of 1-hexene (to 10 equivalents) did not alter the complex nature of the resulting reaction mixture.



Scheme 76: Formation of a mixture of metathesis products.

The reaction was repeated using Grubbs 1st generation catalyst and 5 eq. of 1-hexene. This time, mass spectrometry data suggested that the reaction favours formation of the compounds **182** and **183**, which have

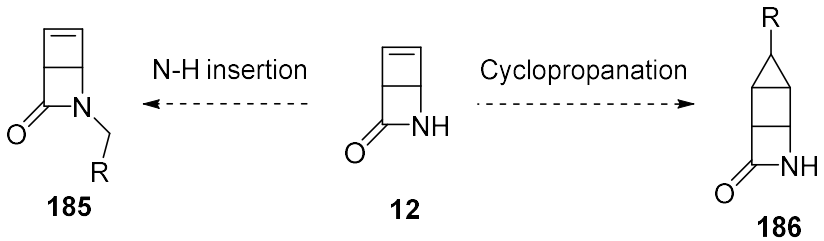
undergone a single cross-metathesis but again products could not be isolated from the reaction mixture upon work up (Scheme 77).



*Scheme 77: Alternative route to **182** and **183** using Grubbs (I), giving none of the doubly-metathesised material.*

3.3.3 Dewar 2-Pyridone *N*-H Insertion

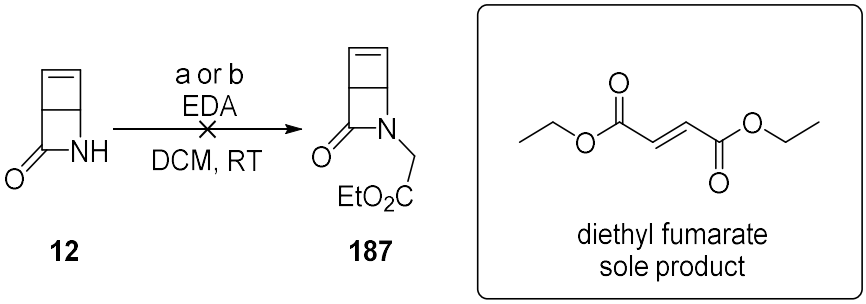
Metal carbenoid chemistry has previously been employed within the group in the synthesis of various indolizine derivatives, in particular the use of iron-porphyrin (FeTPP) derived metal carbenoids have been used to great effect.[97,100,101] It was envisaged NH insertion of the Dewar 2-pyridone could lead to an ammonium ylide which may undergo further reaction or at least allow a facile method to install functionality at nitrogen. Alternatively, the metal carbenoid could add to the alkene, producing the cyclopropane **186** (Scheme 78).



*Scheme 78: Potential reaction pathways for a metal carbenoid with Dewar pyridone **12**.*

As a proof-of-concept ethyl diazoacetate (EDA) was used as the reaction partner. The Dewar pyridone and iron catalyst were dissolved in dichloromethane and a dilute solution of EDA added *via* syringe pump over a period of 2 hours (slow addition sought to minimise EDA dimerisation). Despite this, no reaction with the Dewar pyridone was observed and only Dewar starting material and diethyl fumarate were observed in the reaction mixture (Scheme 79, a).

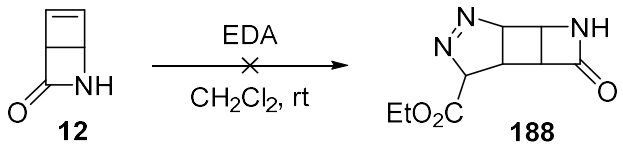
An alternative method that replaced the FeTPPCl catalyst with the more widely used rhodium acetate dimer catalyst ($Rh_2(OAc)_4$) was then attempted, however this gave the same results as above (Scheme 79, b). No addition to the alkene was observed during either of these reactions.[102]



Scheme 79: Unsuccessful N-H insertion reaction. a) $Fe^{(III)}$TPPCl, b) $Rh_2(OAc)_4$.

The fact that diethyl fumarate is formed in both reactions suggests that the metal carbenoid is indeed formed but undergoes dimerisation rather than react with the Dewar azetidinone. It may be possible to influence this by further decreasing the concentration of the EDA solution and increasing the concentration of the Dewar pyridone solution, to increase the likelihood of favourable interactions between the two different species.

The same reaction was performed in the absence of catalyst to determine whether the Dewar azetidinone might undergo 1,3-dipolar cycloaddition with the EDA to give the dihydropyrazole **188**, but no such reaction was observed.[102]



*Scheme 80: No cycloaddition between ethyl diazoacetate and **12** was observed.*

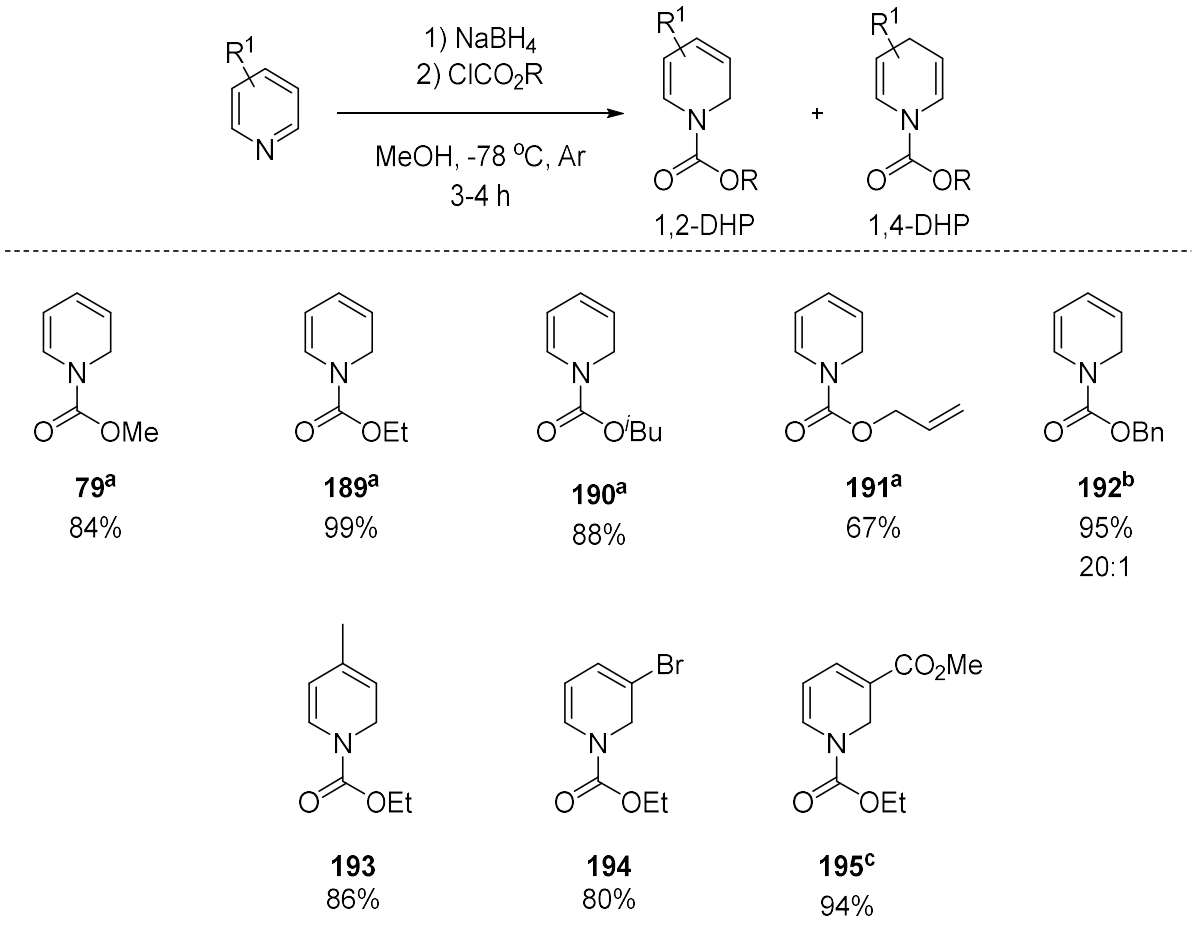
3.4 Synthesis of Dewar 1,2-Dihydropyridines

Building on previous work undertaken on the synthesis of Dewar 2-pyridones, attention was then turned to the synthesis of Dewar 1,2-dihydropyridines. It was envisaged that this would be a convenient method of synthesising azetidines, and that application of continuous flow technology may improve the scale and productivity of synthesis when compared to batch production.[54,62,83]

Following the method first reported by Fowler, several 1,2-dihydropyridines possessing different carbamate groups were synthesised (Scheme 81).[62] In each case this gave a mixture of 1,2- and 1,4- dihydropyridines generally in 9:1 ratios in favour of the desired regioisomer when using ethyl chloroformate. The alternative benzyl chloroformate resulted in Cbz-protected dihydropyridines with much greater selectivity of 20:1 in favour of the 1,2-dihydropyridine (Scheme 81). These were used in subsequent transformations as a crude mixture, and generally made as required, as the 1,2-dihydropyridines are unstable in air and on silica, making storage and purification challenging.

The 4-picoline derived 1,2-dihydropyridine **193** (Scheme 81) was also synthesised so that the photoirradiation could be compared to that of the unsubstituted 1,2-dihydropyridine, as well as to provide some differential reactivity at the alkene of the later Dewar products. Since the 4-position is blocked by the methyl group in this case, the 1,2-dihydropyridine **193** was isolated as the sole product in excellent yield, without the need for further purification.

Using 3-bromopyridine furnished the dihydropyridine **194** as the sole product in good yield (80%), and the reaction using methylnicotinate to synthesise dihydropyridine **195** proceeded as expected, with 1:1 formation of both the 1,2 and 1,6 dihydropyridines. Unfortunately, the product was isolated as a 1:1:1 mixture containing equal amounts of the dihydropyridines and starting material, which could not be separated however, this mixture was used in the photochemical step regardless.



Scheme 81: Carbamate protected dihydropyridines were synthesised. All yields reported are crude. a) Product isolated as a mixture of 1,2 and 1,4 DHPs, 9:1 ratio obtained by relative integration in the ^{1}H NMR spectrum, b) 20:1 ratio of 1,2- to 1,4- dihydropyridines, c) 1:1:1 mixture of starting material, 1,2-dihydropyridine and 1,6-dihydropyridine obtained.

3.4.1 Batch Synthesis

Literature synthesis of Dewar 1,2-dihydropyridines have so far all been performed using a batch methodology,[54,62,83] typically using Rayonet© batch reactors. These reactors consist of a ring of UV lamps positioned around a central reaction flask such that the flask experiences the maximum light intensity. The light source for these reactors are specific to a certain wavelength, in the case of Dewar dihydropyridine synthesis, the chosen wavelength is typically 300 nm, presumably as this corresponds with the absorption maximum of these species (Figure 6).[62,75] Tsuchiya and co-workers opted for a 400 W high pressure lamp, similar to the one used in this work, presumably as this is more readily available, and less expensive than a Rayonet Reactor©.[54]

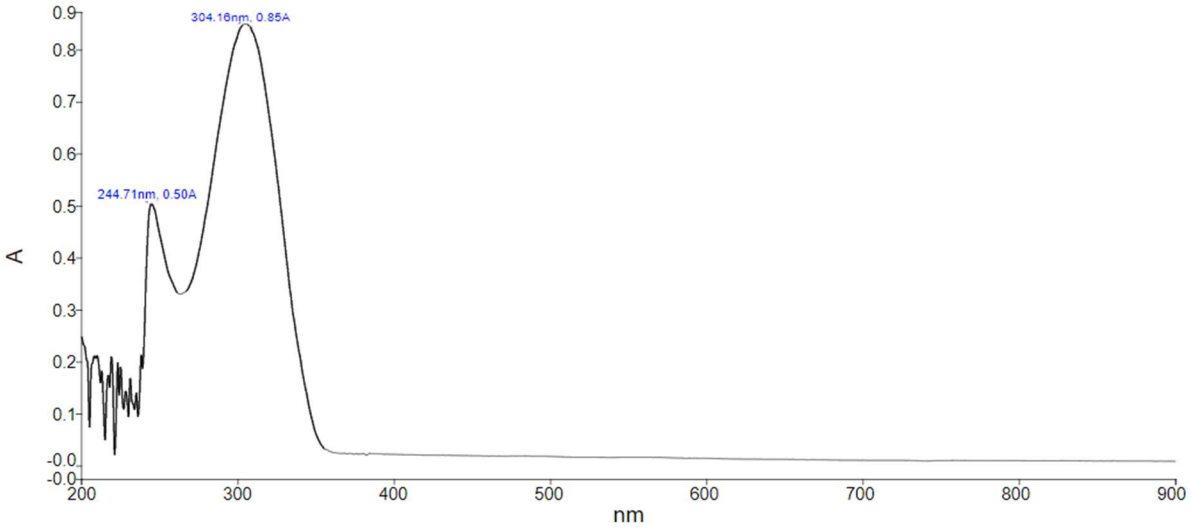
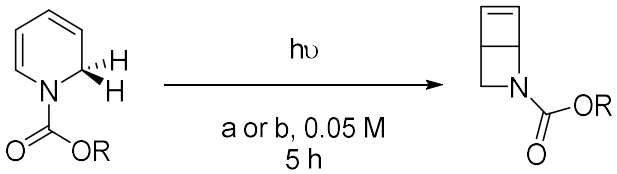


Figure 6: UV spectrum of ethoxycarbamate-1,2-dihydropyridine showing two distinct absorption peaks. These peaks are typical to carbamate-protected 1,2-dihydropyridines. Spectrum taken at ~6 mM in chloroform.

The UV spectrum of ethoxycarbonyl protected 1,2-dihydropyridine shows two distinct peaks at 244 nm and 304 nm (Figure 6). Presumably these absorptions correspond to the n-π^* transition of the carbamate carbonyl and the π–π^* transition of the diene, respectively. In order to produce the Dewar dihydropyridine the π–π^* transition must be accessed, hence irradiation at 300 nm.

To evaluate the equipment on this new system and to use as a comparison to the flow methodology, batch reactions with solutions of the ethoxycarbonyl and benzyloxycarbonyl 1,2-dihydropyridines (**189** and **192** respectively) were undertaken. Using the same 400W medium pressure mercury arc lamp, 200 mL of a 0.05 M solution of **189** and **192** in dichloromethane were irradiated under typical immersion well batch conditions (Table 2). Monitoring of the reaction by ^{1}H NMR spectroscopy was used to find the point at which the reaction was completed, and the reactions were ceased upon full consumption of starting material.



R = Et (**189**) or Bn (**192**)

Dihydropyridine	Conc. (M)	Solvent	Yield (%)	Productivity (mg h^{-1})
189	0.05	dichloromethane	16	52
192	0.05	dichloromethane	12	52
192	0.05	isopropanol	15	67

Table 2: 200 mL of 0.05 M solution batch yields and productivities. Productivity calculated by: productivity (mg h^{-1}) = mass (mg) ÷ reaction time (h).

Under these conditions, the starting material was fully consumed after ~5 hours in each case, the ^{1}H NMR data showed generation of the desired product (characteristic peaks at ~6.5 ppm, corresponding to the alkene protons in the Dewar dihydropyridine were monitored), however they also showed generation of a significant quantity of by-products which could not be identified or isolated.

Isolation of the desired products gave yields of 12% and 15% for **192** in dichloromethane and isopropanol respectively. These equate to productivities of 52 mg h^{-1} and 67 mg h^{-1}. Using the dihydropyridine **189**

afforded the Dewar dihydropyridine in a 16% yield, which corresponds to a productivity of 52 mg h^{-1}.

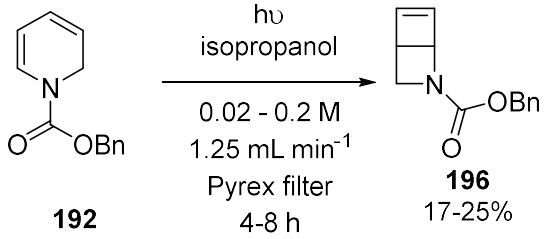
Comparing this method to that used by Krow in the synthesis of the ethoxycarbonyl Dewar dihydropyridine shows that the only real difference is the light source used – a single wavelength Rayonet Reactor© vs. a broad-band Hg arc lamp, which emits light according to the graph shown (3.1 Figure 3).[83] Krow reports an isolated yield of 50% after 24 h of irradiation, compared to 16% after 5 h in this work. A more apt comparison, therefore, is between this work and that of Tsuchiya and co-workers, specifically the irradiation of the benzyloxycarbonyl-1,2-dihydropyridine **189**. Under analogous conditions they obtained a yield of 23% after 10-18 h vs. 12% after 5 h in the results obtained here.

With these results in hand, the development of this reaction in continuous flow was investigated.

3.4.2 Continuous Flow Synthesis

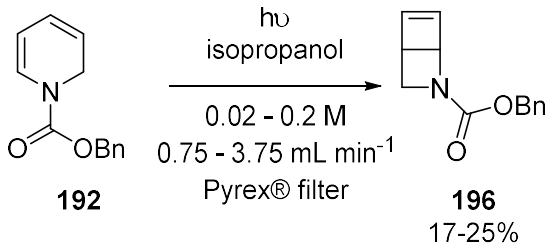
In order to address some of the problems associated with batch photochemistry, i.e. the long reaction times, and scalability issues, it was desirable to develop a protocol for the continuous flow synthesis of Dewar dihydropyridines using the knowledge and equipment already developed during this work. In principle this would allow ready access to large quantities of the Dewar dihydropyridines required for further processing. Literature examples of this reaction in batch use a range of solvents,

however they all use 5% solutions of the 1,2-dihydropyridine, which corresponds to roughly 0.05 M, so this was used as a starting point.



Scheme 82: Irradiation of the 1,2-dihydropyridine under continuous flow conditions gave the Dewar dihydropyridine.

A 0.05 M solution was pumped at 1.25 mL min^{-1} on the 220 mL photoreactor (3 layers of tubing, total path length = ~94 m, ~220 mL internal volume, irradiated through a Pyrex® filter using a 400W medium-pressure Hg arc lamp, Scheme 82). The desired Dewar heterocycle **196** was obtained in 17% yield, along with a complex mixture of side products which could not be purified or characterised. This was comparable to the yield obtained by Tsuchiya and co-workers from the batch photo-irradiation of **196** in dichloromethane (23%).[53]



Concentration (M)	Flow Rate (mL min^{-1})	Yield (%)	Productivity (mg h^{-1})
0.05	0.75	9	46.3
0.05[a]	1.25	17	102
0.05	2.50	15	272
0.05	3.75	17	462
0.02	1.25	20	67.5
0.05[a]	1.25	17	102[b]
0.10	1.25	24	390[b]
0.20	1.25	25	844[b]
0.20	3.75	17	1622[b]

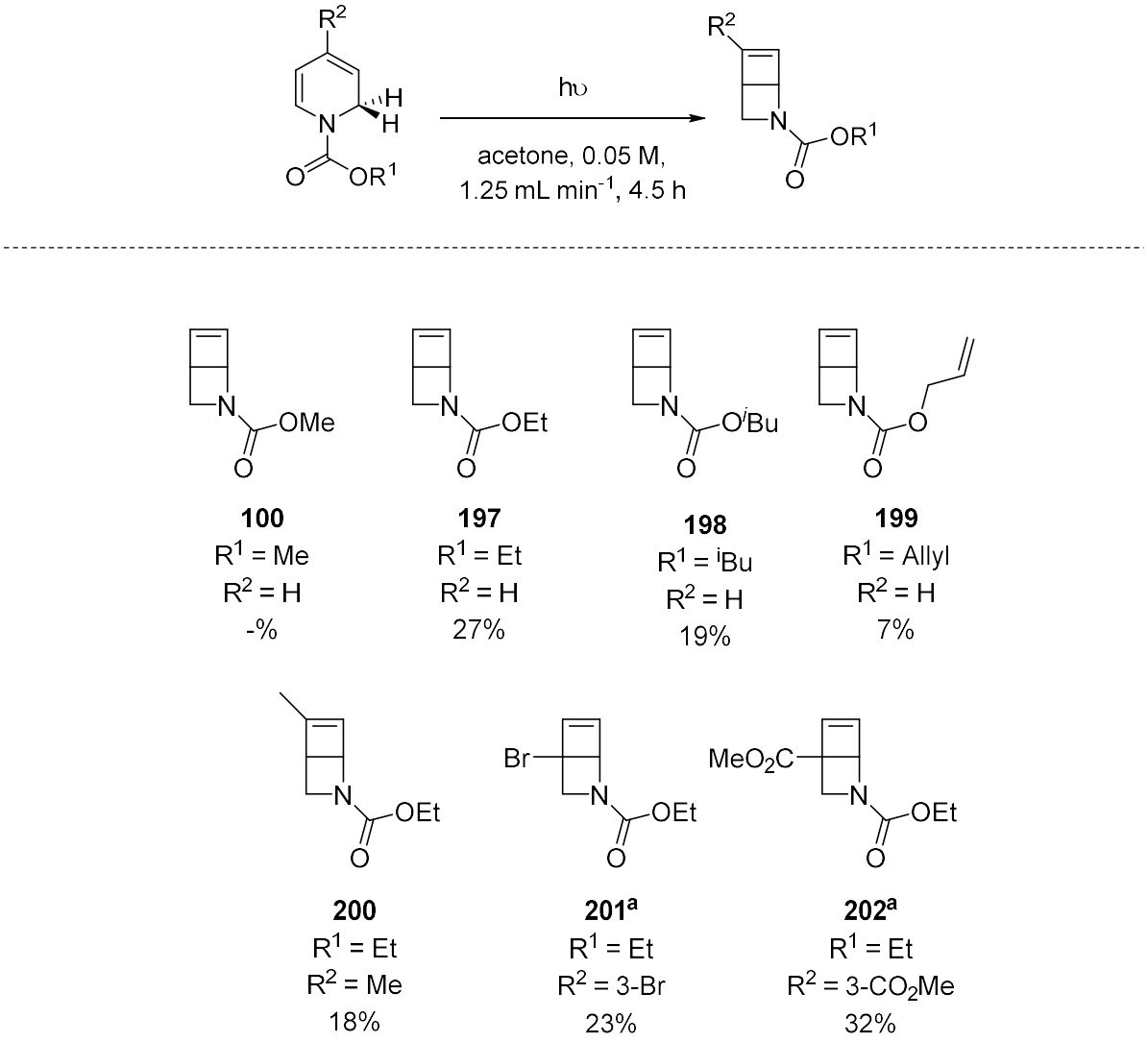
Table 3: Productivity calculated by:

p (mg h^{-1}) = concentration (mg mL^{-1}) × flow rate (mL h^{-1}) × yield. a) Same experiment/result. b) Product co-eluted with unidentified impurities.

The reaction concentration and flow rates were then varied. No significant decrease in yields were observed when the reaction was performed at increased flow rate or concentration, however purity of the isolated product was highly dependent on both variables (Table 3). The flow rates were tested in the range between 0.75 mL min^{-1} and 3.75 mL min^{-1}, and concentrations between 0.02 and 0.2 M. The reaction yield does not appear to depend on concentration or flow rate within the ranges tested. Difficulties were encountered on purification, and in general, the product co-eluted with impurities and could not be isolated in pure form. Therefore, despite the high productivity at high concentration and flow rate (0.2 M, 3.75 mL min^{-1}), difficulty in purification from these conditions prevented further application. Analysis of the ^{1}H NMR spectrum showed the impurity as

possessing aromatic and benzylic protons, so it was postulated that the benzyl carbamate protecting group was the cause of this, and alternatives were investigated (Scheme 83). In all cases, starting material was present in the reaction mixture post-irradiation, as demonstrated by TLC analysis, however measuring conversion was impossible as the 1,2-dihydropyridine could not be isolated by chromatography due to its instability, and measuring by relative integration could not be achieved due to the significant quantities of by-products.

The yields obtained for the photoirradiation of substituted 1,2-dihydropyridines are shown in Scheme 83. For R = Me a complex mixture of products was obtained and as such purification proved impossible, however, for the other 3 examples, isolated yields of the desired products were obtained. The highest yield obtained was that of the ethyl carbamate product **197** at 27% and the *iso*-butyl carbamate product **198** behaved similarly, giving a 19% yield. The allyl carbamate product **199** however gave a significantly diminished yield, at 7%, compared to the other two successful examples. There is a potential here for the pendant alkene to participate in unwanted side reactions, such as [2+2] photocycloadditions, during photoirradiation, e.g. [2+2] cycloaddition, however no evidence of this was observed.



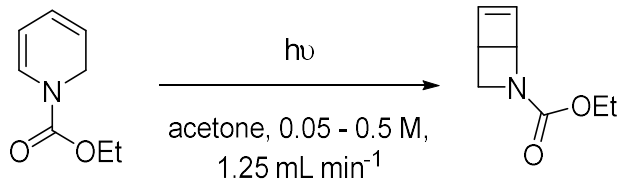
Scheme 83: Yields obtained from the photoirradiation of corresponding dihydropyridines. When R = Me only a complex mixture was formed. a) dichloromethane used as the reaction solvent.

The 4-methyl substituted dihydropyridine behaved in a similar manner to the unsubstituted variant, as did the 3-bromo variant, with comparable yields being obtained in both cases. The 4-bromo Dewar dihydropyridine (derived from the 3-bromodihydropyridine **194**) was identified as a potentially useful synthetic building block, as the presence of the allylic bromine might allow for additional reaction pathways to be explored in the future.

Overall yields obtained in the reactions shown in Scheme 83 did not provide significant increase when compared to those obtained previously for the

Cbz-protected product (Scheme 82), however product purification was greatly improved.

Ethyl chloroformate was chosen as the protecting group of choice for further reactions, as this gave the highest yield of desired product overall and it is the protecting group most well established in the literature. Acetone was also used as the solvent as this was the one used by Krow for this particular substrate.[83] Variations in concentration from 0.05 M to 0.5 M showed that yield diminished significantly, from 27% to 6% although productivity almost doubled at the increased concentration (Table 4). This can be attributed to the increased throughput of material due to the increased concentration. Swapping the solvent for dichloromethane made no appreciable difference in yield or productivity.



189 197

Entry	Concentration (M)	Flow Rate (mL min^{-1})	Yield (%)	Productivity (mg h^{-1})
1[a]	0.05	1.25	27	155
2[b]	0.05	1.25	20	113
3[a]	0.20	1.25	14	328
4[a]	0.50	1.25	6	349
5[c]	0.05	1.25	9	51
6[b]	0.05	1.25	20	113
7[d]	0.05	1.25	16	92
8[e]	0.05	1.25	6	35
9[f]	0.05	1.25	9	52

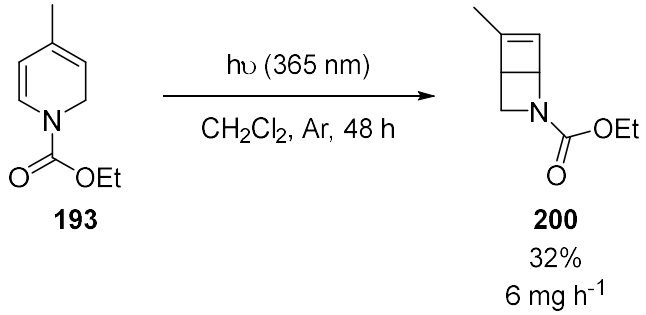
Table 4: Variation from stated conditions for ethoxycarbonyl-1,2-dihydropyridine irradiation. a) Pyrex® filter; b) Pyrex® filter,

dichloromethane solvent; c) no filter; d) Pyrex filter + Backström filter; e) Pyrex® filter + $NiSO_4$ (aq 50% w/v); f) $KCr(SO_4)_2$.

The fact that the light source emits light of varying wavelengths, could be contributing to the diminished yields obtained, and possibly leading to the generation of side-products by alternative reaction pathways. The effect of using different UV filters was therefore investigated. Typically, a Pyrex® glass filter is used to absorb wavelengths below ~280 nm. It was shown that without this filter, yield was significantly reduced to 9%. A filter solution of aqueous $NiSO_4$ and $CoSO_4$ was used in conjunction with the Pyrex® filter, as literature reports that it only allows transmission of wavelengths of ~300 nm, which corresponds to the absorption maximum of the dihydropyridine.[103,104] It was found that use of these filters did not affect the yield significantly. Using 50% w/v $NiSO_4$ or $KCr(SO_4)_2/H_2SO_4$ (0.5 M) separately as solution filters, as these reportedly allow transmission at ~300 nm, decreased the yield significantly to 6% and 9% respectively (Table 4). This is likely due to the fact that the filters were largely opaque unless very high intensity light was used. This reduced light intensity transmitted through the filters could have contributed to the low yields, as large quantities of starting material were present in the reaction mixture, as evident by TLC analysis.

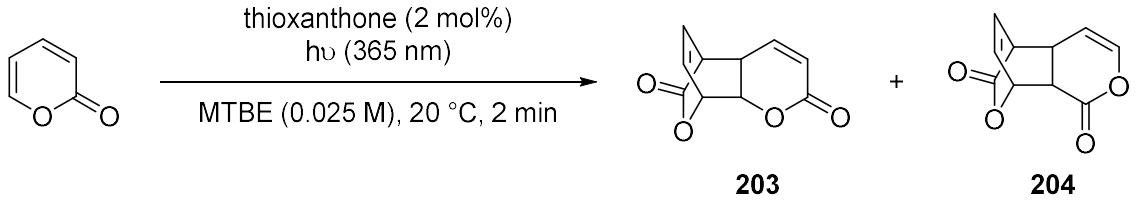
Irradiation at 365 nm was investigated next, as 365 nm light sources are common and relatively inexpensive. Unfortunately, the light source could not be adapted for use in continuous flow, so batch irradiation had to be performed instead. Irradiation of the 4-methyl dihydropyridine **193** at 365 nm for 48 h, using a UV curing lamp fitted with 365 nm fluorescent bulbs returned a yield of 32% - within the range of yields obtained from the

continuous flow reaction, however with a much lower productivity of 6 mg h^{-1}, due to the long reaction times (Scheme 84).



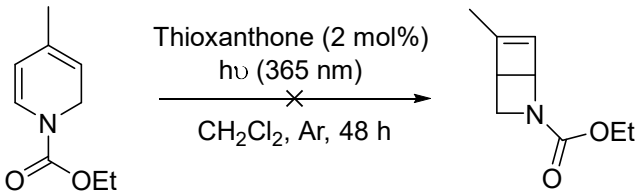
*Scheme 84: Irradiation of the 4-methyl dihydropyridine **193** at 365 nm.*

This study at 365 nm was extended to irradiation at 365 nm in the presence of a triplet photosensitiser, in this case thioxanthone. It was suggested in a recent paper by Maulide *et al*. that irradiation of 2-pyrones at 365 nm in the presence of a thioxanthone-derived triplet photosensitiser allowed access to alternative reaction pathways, in their case the [4+2] photodimerisation of 2-pyrone to products **203** and **204**, which also demonstrated that 4π electrocyclisation to the desired Dewar 2-pyrone required singlet excitation (Scheme 85).[105]



*Scheme 85: Triplet sensitised formation of 2-pyrone photodimers **203** and **204**.*

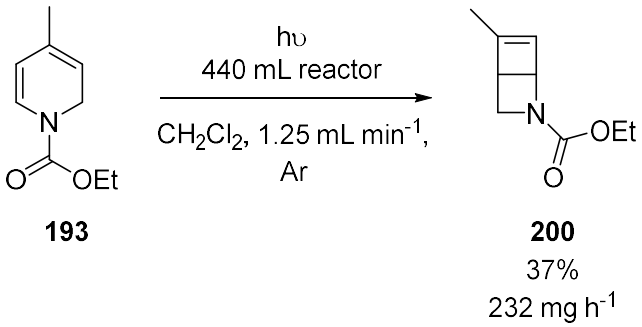
To investigate whether inclusion of a photosensitiser affected the products obtained from the photoirradiation of 1,2-dihydropyridines, a reaction was performed on the 4-methyl dihydropyridine substrate using a 0.05 M solution of **193** in dichloromethane with 2 mol% thioxanthone (Scheme 86). In this case, none of the Dewar dihydropyridine was observed, unfortunately despite consumption of starting material, the reaction yielded only a complex mixture of products, which could not be purified.



*Scheme 86: Triplet photosensitised irradiation of **193** did not give any of the Dewar product **200**.*

Since irradiation at 365 nm (without photosensitiser) yielded the Dewar product, and the results where solution filters were employed were lacklustre, further investigation as to why the yields were low when compared to literature was required. Since starting material was still present in the reaction mixture, clearly the reactions were not going to completion, however running the reaction at lower flow rates decreased the yield and productivity significantly (Table 3). The presence of starting material in the reaction solution collected post-irradiation might have also been contributing to difficulties in purification, as degradation of the 1,2-dihydropyridine occurs while in solution at room temperature.

With this in mind it was thought that doubling the reactor volume by utilising two identical lamps connected in series could increase the conversion and would hence increase the yield and productivity. 4-methyl dihydropyridine **193** was pumped through the new reactor (440 mL reactor) in a 0.05 M solution in dichloromethane, at 1.25 mL min^{-1}. This saw an increase in yield to 37% - roughly twice the yield of the previous attempts using only 1 lamp (Scheme 87).



Scheme 87: Improvement in yield and productivity when using the 2-lamp 440 mL flow reactor.

3.4.3 Summary

Comparing the results obtained between the batch and continuous flow methodologies shows that at almost every concentration and flow rate tested, the continuous flow methodology provides greater productivity at comparable yield (Tables 2, 3 and 4). Purification of the Dewar dihydropyridines was hampered when using the Cbz protecting group but using ethoxycarbonyl as an alternative alleviated this issue. Further development of the continuous flow technology saw the use of two reactor coils in series. This was found to increase the yield and productivity of the formation of 4-methyl substituted Dewar dihydropyridine **200** by roughly double, providing ~230 mg h^{-1}. Future development of this methodology should expand on this to use three reactor coils connected in series to further increase productivity.

An investigation into irradiation at specific wavelengths was also undertaken, which showed that when using a 1 cm thick filter composed of aqueous $NiSO_4$ and $CoSO_4$, yield and productivity were comparable. This dropped off to 6% yield when using a 1 cm thick filter of aqueous $NiSO_4$ (50% w/v) alone, and 9% yield when using a $KCr(SO_4)_2/H_2SO_4$ (0.5 M) filter (Table 4).

This investigation was expanded to cover irradiation at 365 nm in a batch method, which found that a comparable yield of Dewar heterocycle was

accessed, however the reaction time was long (48 h) and hence the productivity was low (6 mg h^{-1}).

In an attempt to prove that singlet excitation was required for Dewar dihydropyridine synthesis, the 4-methyl dihydropyridine **193** was irradiated at 365 nm in the presence of a triplet photosensitiser, thioxanthone. Indeed, the reaction saw no production of Dewar dihydropyridine **200**, although unfortunately no product could be identified from the complex mixture obtained.

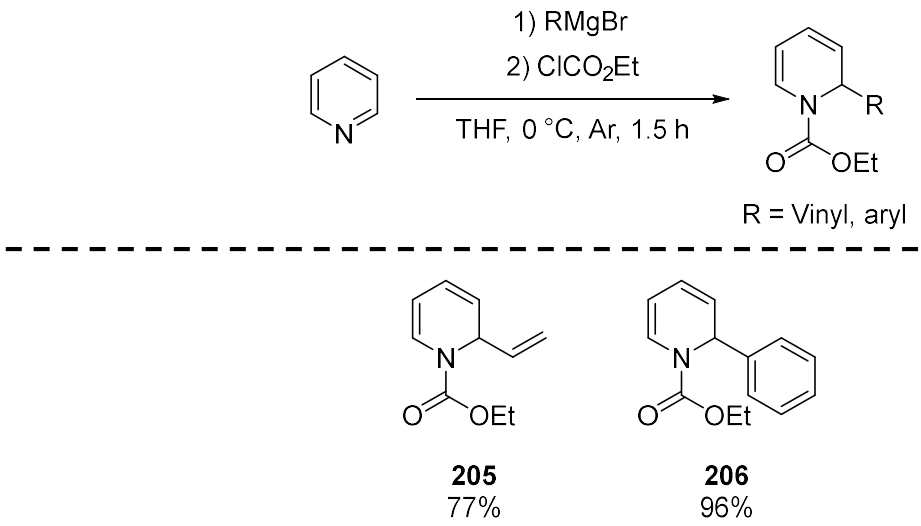
The continuous flow methodology for the synthesis of Dewar 1,2-dihydropyridines in general seems like an attractive alternative to traditional batch methods due to the increase in productivity, however there are some obvious improvements that need to be made in terms of addressing the poor yields by increasing conversion.

3.5 Synthesis of Substituted Dewar Dihydropyridines

Attention then turned to the synthesis of substituted dihydropyridines, with the goal of subjecting these to the photoirradiation conditions. It was envisaged as a convenient route to installing substituents onto the Dewar heterocycle to add them prior to photoirradiation, as the addition of nucleophiles to activated pyridines is established in the literature.[58,106–109]

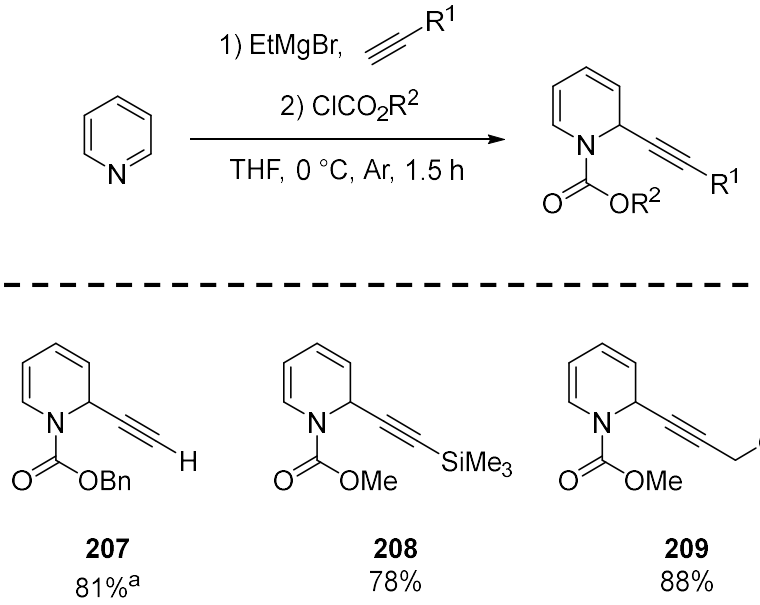
Since the addition of sp and sp^2 hybridised nucleophiles, i.e. alkynyl, vinyl and aryl derived nucleophiles occurs regioselectively to the 2-position, leading to the 1,2-dihydropyridines as the sole products, this was investigated first.

Phenyl magnesium bromide and vinyl magnesium bromide were used to synthesise the 2-vinyl- and 2-phenyl- substituted dihydropyridines **205** and **206** in good to excellent yield (Scheme 88). These reactions, as expected, cleanly gave the 2-substituted dihydropyridines.[110]



*Scheme 88: Regioselective addition of vinyl and phenylmagnesium bromide to activated pyridine to yield the 1,2-dihydropyridine **205** and **206**.*

Grignard reagents were also employed in the synthesis of alkynyl substituted 1,2-dihydropyridines. Ethynyl magnesium bromide was used to synthesise compound **207** directly, however for the other two examples ethyl magnesium bromide was needed for *in situ* generation of new Grignard reagents derived from the alkynes. Here, ethyl magnesium bromide acts as a strong base, deprotonating the terminal alkyne. The magnesium bromide present in solution (from the ethyl magnesium bromide) presumably coordinates and stabilises the new carbanion, which can then attack the 2-position of the pyridinium salt, which is forming *in situ* from the addition of chloroformate. Using a solution of pyridine and ethyl magnesium bromide with either ethynyl trimethylsilane or phenyl propargyl ether with slow addition methyl chloroformate, at 0 °C gave the desired 2-substituted dihydropyridines **208** and **209** in high yield (78% and 88% respectively).[111] Dihydropyridine **207** was obtained in high yield by the addition of benzyl chloroformate to a mixture of pyridine and ethynyl magnesium bromide, at 0 °C in THF.



207
81%[a]

208
78%

209
88%

Scheme 89: Synthesis of alkynyl substituted 1,2-dihydropyridines. a) Ethynyl magnesium bromide used.

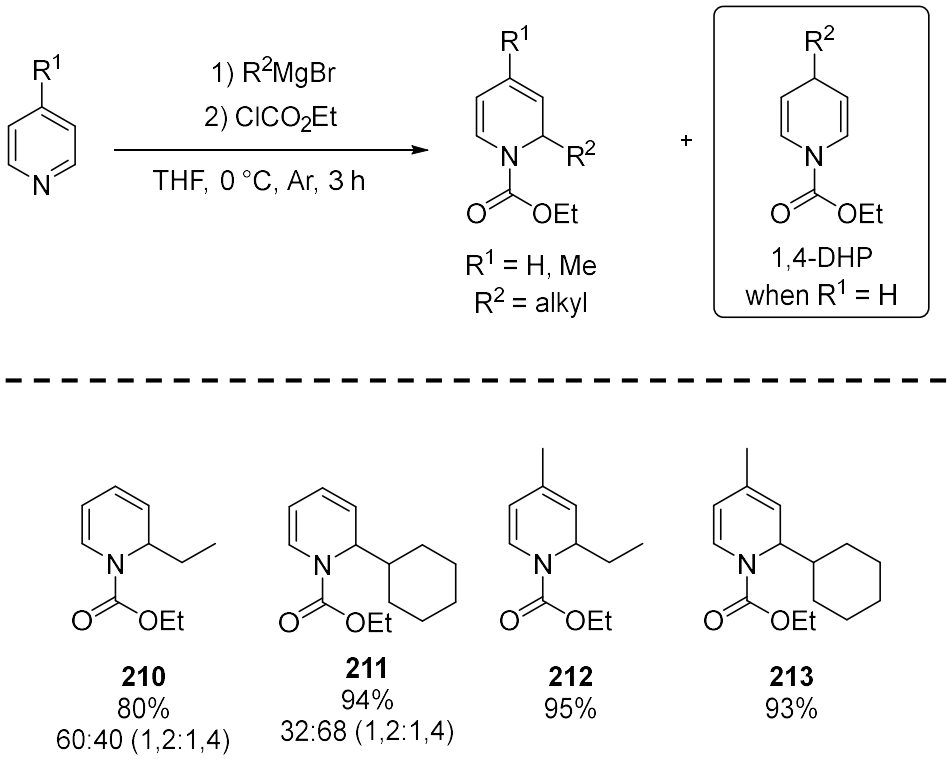
Addition of alkyl Grignard reagents to pyridines (in the presence of alkyl chloroformates) brings about the issue of regioselectivity, as addition can occur at either the 2- position or the 4-position and steric demand of both the carbamate substituent and the incoming nucleophile.[112]

Using ethylmagnesium bromide in the reaction with pyridine and ethyl chloroformate gave a total yield of 80% with the product containing a mixture of the 1,2- and 1,4- dihydropyridines. ^{1}H NMR analysis of the mixture, and relative integration of peaks corresponding to the individual components (5.90 ppm for the 1,2-DHP and 2.90 ppm for the 1,4-DHP) revealed the product contained 60% 1,2-dihydropyridine and 40% 1,4-dihydropyridine (**210**, Scheme 90). This mixture was used in the photochemical reaction without further purification due to the relative instability of the dihydropyridines to chromatographic purification, as mentioned previously.

Cyclohexyl magnesium chloride gave a mixture of 2- and 4-substituted dihydropyridines, in a higher overall yield of 94%, but a lower proportion of the desired product with ^{1}H NMR analysis and relative integration

indicating a mix of the 1,2-dihydropyridine (32%) and 1,4-dihydropyridine (68%). This is likely due to steric demand of the incoming cyclohexyl Grignard reagent and the ethyl carbamate group (**211**, Scheme 90).

Utilising 4-picoline instead of pyridine allowed for regioselective addition to the 2- position, as the 4-position was blocked by the methyl substituent, giving the 1,2-dihydropyridine as the sole product. Both ethyl magnesium bromide and cyclohexyl magnesium bromide performed similarly in this reaction achieving 95% and 93% yields respectively (**212** and **213** Scheme 90).

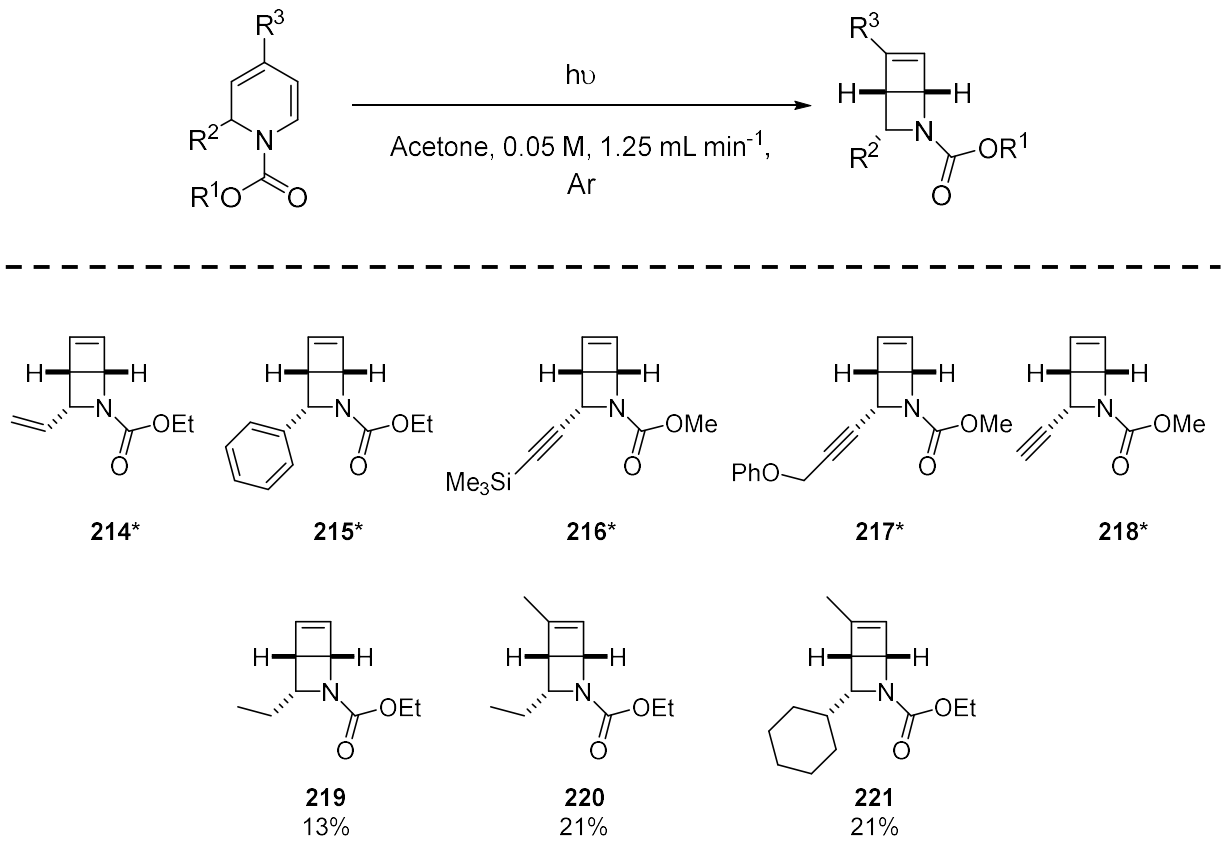


Scheme 90: Synthesis of 2-substituted 1,2-dihydropyridines from pyridine and 4-picoline by addition of Grignard reagents. Ratios of 1,2-:1,4- DHPs determined by relative integration of peaks in the 1H NMR (5.90 ppm vs. 2.90 ppm).

The substituted dihydropyridines were subsequently irradiated using the 220 mL FEP reactor as 0.05 M solutions in acetone, at 1.25 mL min^{-1}. Vinyl, phenyl and the alkynyl substituted dihydropyridines behaved similarly, with an inseparable mixture of products being generated in each case. A

potential hypothesis as to why this might be the case was the due to the broad-band light source used, as Krow and others have previously reported the synthesis of 2-phenyl substituted Dewar dihydropyridine **215**, albeit in relatively low yield, when using a Rayonet® reactor fitted with 300 nm lamps.[54,113]

The irradiation of alkyl-substituted dihydropyridines, in contrast, performed as expected, giving yields in the range of those obtained previously for the unsubstituted Dewar dihydropyridines, and also of substituted Dewar dihydropyridines reported in the literature.[54,83,113,114] Here the Dewar dihydropyridines **219**, **220** and **221** were obtained in yields of 13%, 21% and 21% respectively (Scheme 91). Presumably this occurs with diastereoselectivity, based on that reported by Krow and co-workers, due to the cyclisation occurring through a least-motion ring-closure pathway.[83]



*Scheme 91: Synthesis of substituted Dewar dihydropyridines from the corresponding dihydropyridines. *Complex mixture.*

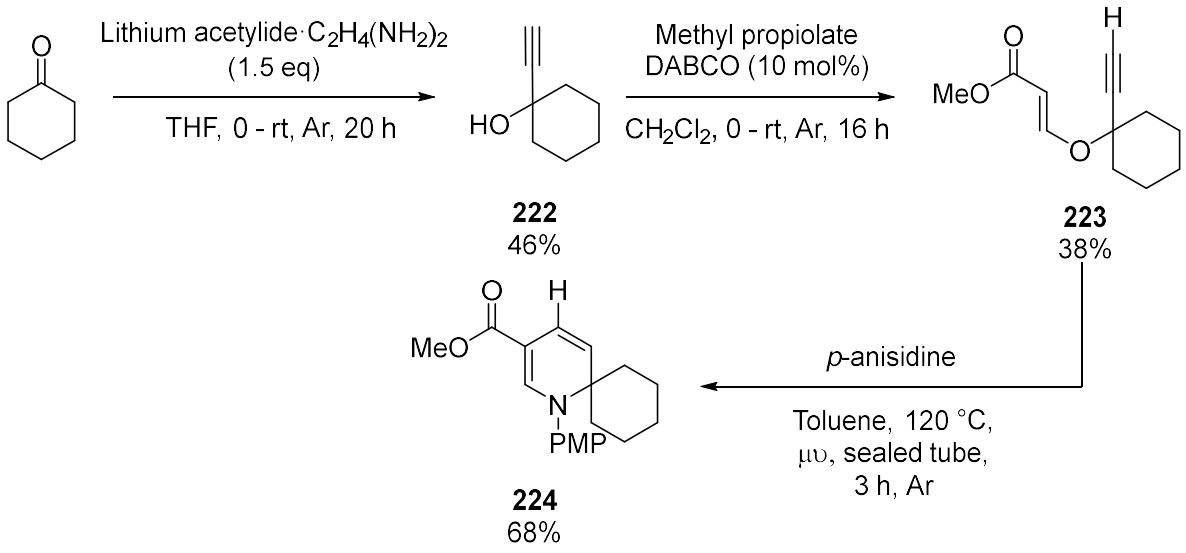
3.6 Route to Quaternary Dewar Dihydropyridines

The dihydropyridines used up to this point were all either secondary or tertiary at the 2-position, which caused them to be unstable with respect to oxidation. A logical next step was to attempt the photochemical reaction with dihydropyridines that are quaternary at the 2- position. These have the added benefit of increased stability over their secondary and tertiary counterparts, because the 2- position cannot be oxidised.

There are two main pathways for the synthesis of quaternary dihydropyridines which have been described in the literature, either by addition of substituents to an amenable pyridine derivative, or assembling the ring from scratch.[68,69]

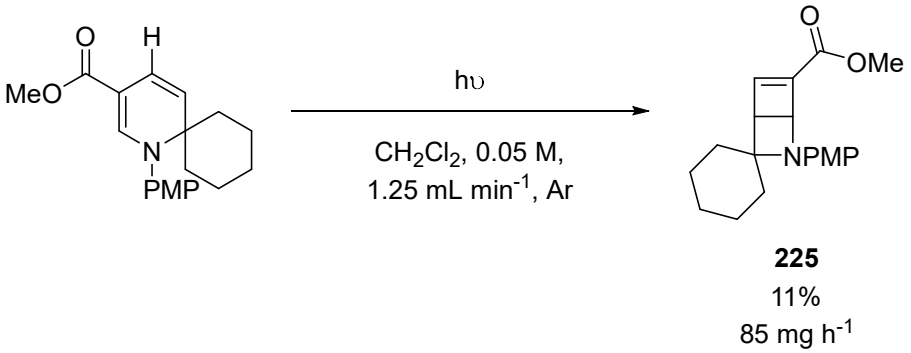
Tejedor *et al*.'s method of dihydropyridine synthesis was chosen as the desired method, as the alternative palladium catalysed addition to 2-methylpyridinium salts was limited to aryl substituents (Introduction section 1.6.1.2.1, Scheme 35). Acetone was initially used due to its low cost and wide availability, however problems were encountered due to volatility of the products, so cyclohexanone was chosen as a less volatile alternative.

The first step of this route involved the treatment of cyclohexanone with lithium acetylide ethylenediamine complex, which formed the corresponding propargyl alcohol **222** in moderate yield (Scheme 92). The alcohol was then transformed into the propargyl vinyl ether **223** (PVEs) through addition of methyl propiolate with catalytic 1,4-diazabicyclo[2.2.2]octane (DABCO), which occurred in moderate yield (Scheme 92). Following the literature method, the final step was the microwave-assisted dihydropyridine synthesis with *p*-anisidine at 120 °C, which gave the desired quaternary dihydropyridine **223** in good yield (Scheme 92). Due to scale limitations of the microwave reactor, a conventional hotplate with sealed tube was also used, which gave the desired compound in comparable yield (69%).



*Scheme 92: Synthetic route to quaternary dihydropyridine **224** from cyclohexanone.*

The final step was the photoreaction with the quaternary dihydropyridine. Using the already established conditions used for the secondary and tertiary dihydropyridines (0.05 M concentration, 1.25 mL min^{-1}, dichloromethane solvent, under argon *via* balloon), the quaternary dihydropyridine **224** was irradiated on the 220 mL FEP reactor. This successfully gave the novel quaternary Dewar dihydropyridine **225** in relatively low yield (Scheme 93, 11%, 85 mg h^{-1}). Some starting material (41%) was also isolated from the reaction mixture, however, on attempting to increase conversion by using the 440 mL reactor, only a complex mixture of inseparable products was obtained, suggesting that the product may degrade under photochemical conditions. Nevertheless, the novel quaternary Dewar dihydropyridine **225** was obtained, and investigations into expanding the scope of this transformation with additional quaternary dihydropyridines should be investigated in the future.



225
11%
85 mg h^{-1}

*Scheme 93: Synthesis of novel quaternary Dewar dihydroypridine **225**.*

3.7 Investigations into Dewar 1,2-dihydropyridine reactivity

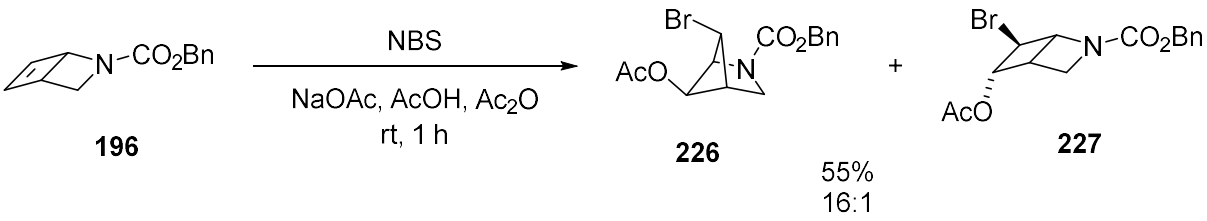
At this point it was desirable to investigate some potential uses for these Dewar dihydropyridines, as their dense functionalisation and unique geometry offered scope to synthesise a range of sp^3-rich small molecules.

3.7.1 Rearrangement to Bridged Pyrrolidines

The most intriguing reaction pathway from the literature was Krow's synthesis of bridged pyrrolidines from Dewar 1,2-dihydropyridines as it provided a convenient route, under relatively mild conditions, to some sp^3-rich building blocks (Introduction Section 1.6.2, Scheme 56).[75,83,84] While this route showed promise, the range of nucleophiles used was limited, and it was desirable to attempt to develop a methodology which might expand this scope.

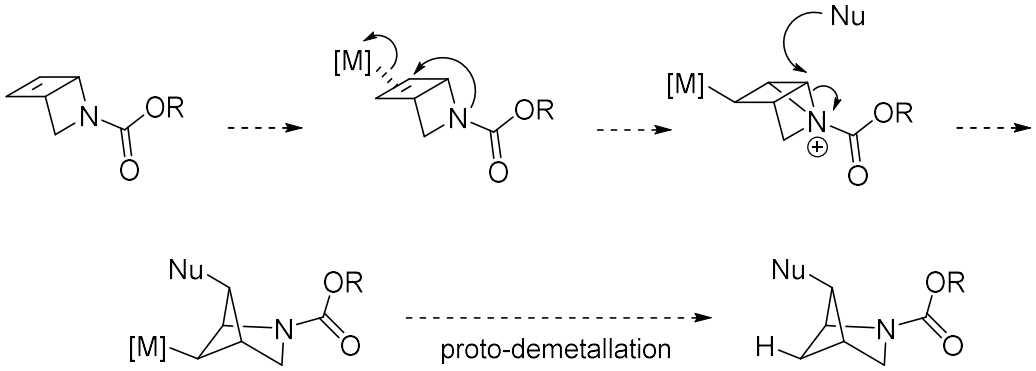
Krow and co-workers have previously utilised palladium catalysis in a reductive Heck reaction to access an analogue of epibatidine (Introduction section 1.6.2, Scheme 45), which proved that the alkene is amenable to activation by transition metal catalysis. It was therefore hypothesised that similar use of a π Lewis acid could be used in the rearrangement reaction.[77] In the original route, the alkene is activated through formation of the bromonium – by replacing this with a π Lewis acid it was envisaged that this could generalise the reaction and allow a wider range of nucleophiles to be used. It was first desirable to follow the literature procedure for the *N*-bromosuccinimide-mediated rearrangement to form these bridged pyrrolidines to better understand the process and act as a model reaction.[89]

The literature procedure for the synthesis of the acetate-substituted azabicyclo[2.1.1]hexane was chosen as the model reaction, as this gave the highest reported yield and was most productive for the rearranged pyrrolidine **226** over the addition product **227**. It was found that the purity of the *N*-bromosuccinimide impacted the reaction and required recrystallisation prior to use. Purification of products was also made difficult by co-elution of products on silica gel chromatography. Overall, the desired products were obtained as a mixture of the rearranged and unrearranged products **226** and **227** (16:1) in 55% overall yield (Scheme 94).



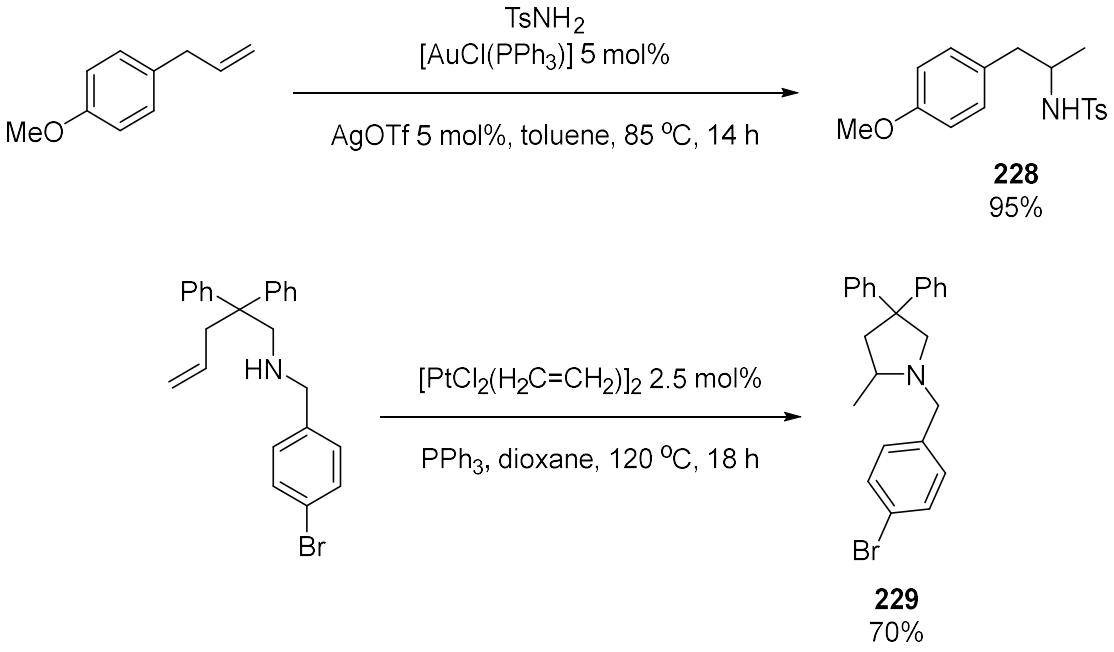
Scheme 94: Ratio of products obtained from relative integration of appropriate peaks in the ^{1}H NMR spectrum.

As stated previously, it was envisioned that this process might be amenable to π Lewis acid catalysis. In principle, this type of π Lewis acid catalysis could be used to install structurally diverse nucleophiles to the bridgehead position (Scheme 95). The mechanistic rationale is shown in Scheme 95, where the Lewis acid coordinates to the alkene, followed by neighbouring-group participation by the nitrogen lone pair, resulting in an aziridinium intermediate, subsequent intermolecular attack by a nucleophile at the apical carbon centre, followed by catalyst turnover and liberation of the product (Scheme 95). In this case, a β-hydride elimination may be challenged, given that both β hydrogen atoms are bonded to bridgehead carbon atoms. There is, however, literature precedent for proto-demetallation as a mechanism for catalytic turnover in similar systems.[115,116]



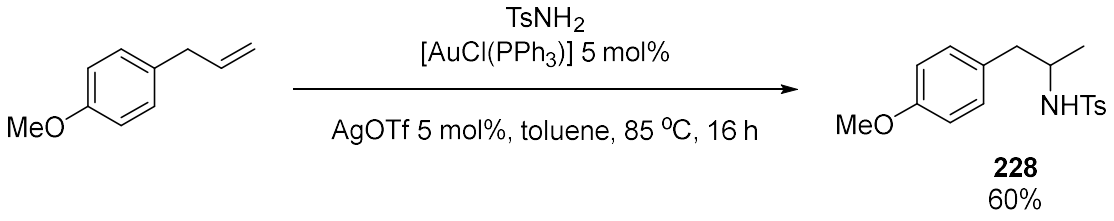
Scheme 95: Proposed mechanism for π-Lewis acid catalysed rearrangement.

An initial literature search gave some promising examples of using $Au^{(I)}$ or $Pt^{(II)}$ catalysts to activate an alkene by coordination, followed by nucleophilic attack and catalyst turnover to generate a variety of different molecules, most relevant examples of which are shown in (Scheme 96).[117–120] The first reaction shows the $Au^{(I)}$ catalysed addition of *p*-toluenesulfonamide to allylanisole, which demonstrates that electron-deficient amides are able to react with π activated alkenes. The second reaction shows intramolecular nucleophilic attack by a secondary amine to the alkene, catalysed by Zeise's dimer, a $Pt^{(II)}$ species. It was hoped that one, or both of these examples may be applicable to the Dewar dihydropyridine substrate.



Scheme 96: Literature examples of the use of π Lewis acids for alkene activation, with subsequent nucleophilic attack.[118]

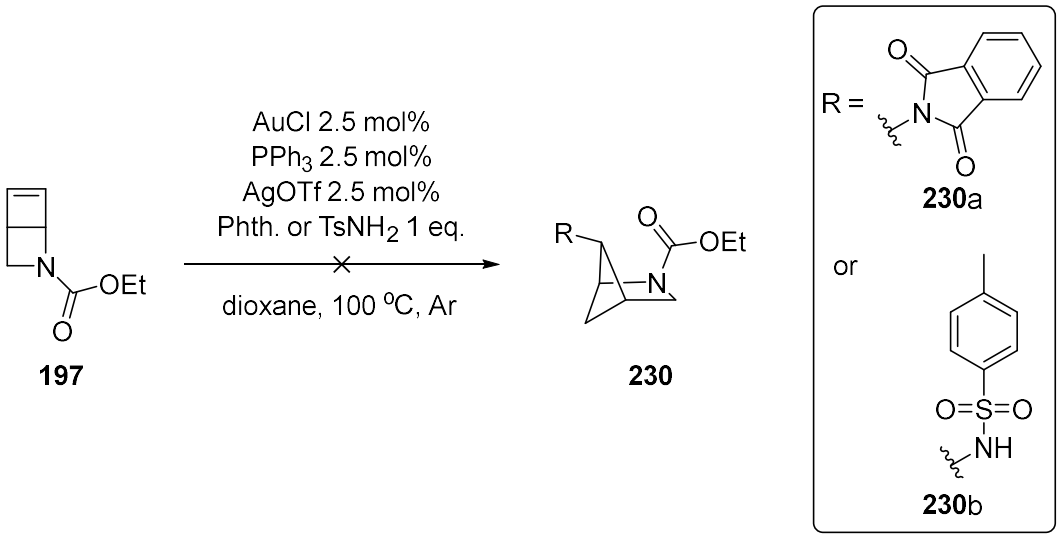
A repeat of the literature experiment with 4-allylanisole under the same conditions with *p*-toluene sulfonamide was used as a positive control to verify the reaction conditions. This was successful and gave the desired product in acceptable yield (Scheme 97).



Scheme 97: Recreation of gold catalysed addition of p-toluenesolfonamide to allylanisole.

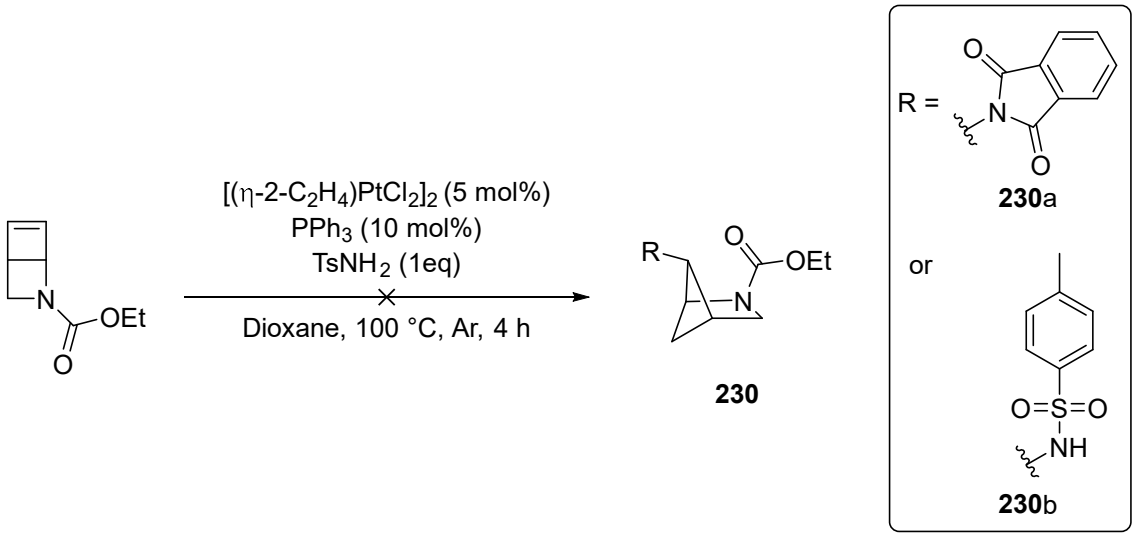
Attempts at this reaction using $Au^{(I)}$ catalysis were then performed with conditions adapted from the literature.[119] In principle, the AuCl is acting as a pre-catalyst, coordinating to the triphenylphosphine *in situ* to form Ph_3PAuCl, which can then undergo substitution with AgOTf to form $Ph_3PAuOTf$. The labile Au-O bond then dissociates in the presence of alkene to allow the Au centre to coordinate. When this reaction was performed

with phthalimide as the nucleophile none of the desired product was observed when the reaction mixture was analysed by mass spectrometry. Replacing phthalimide with *p*-toluene sulfonamide gave only a complex mixture of products, with none of the desired mass present in the mass spectrometry data (Scheme 98). Replacing the dioxane with toluene at 85 °C also gave only a complex mixture of products which could not be isolated.



Scheme 98: Attempted Au(I) catalysis lead only to a complex mixture of products.

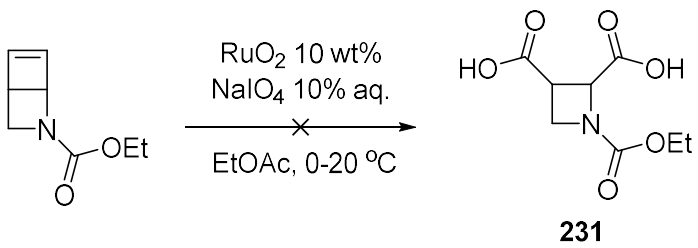
Reactions utilising $Pt^{(II)}$, in the form of Zeise's dimer as a catalyst in conjunction with triphenyl phosphine, with varying solvent and nucleophilic species showed no reaction had taken place, showing only starting material present on analysis (Scheme 99).



Scheme 99: Attempt at $Pt^{(II)}$ catalysed rearrangement with phthalimide or p-toluenesulfonamide nucleophiles.

3.7.2 Investigation into alkene oxidations

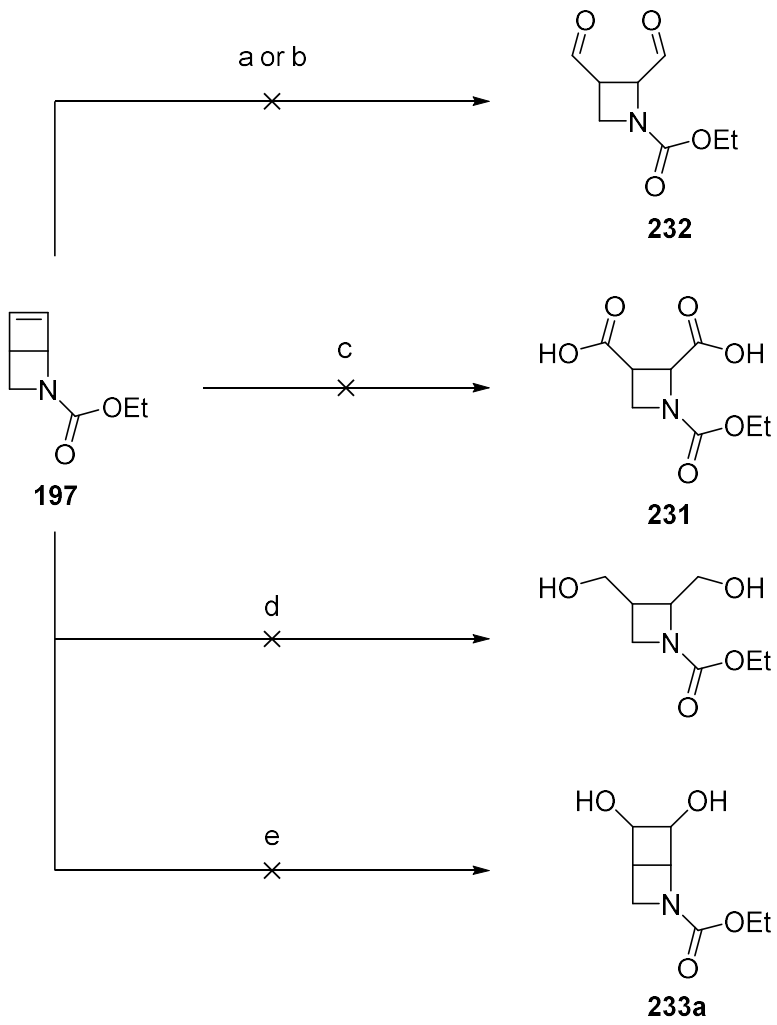
It was envisaged that oxidative cleavage of the C=C bond, driven by a release of ring-strain, in the Dewar dihydropyridine might be a convenient route to highly functionalised azetidines, which in principle could possess substituents on all 4 positions on the ring. This would provide a wide scope for further functionalisation, and increased utility as a small molecule building block. There is one example of alkene cleavage by oxidation in the literature, using RuO_4 followed by diazomethane to form the dimethyldiester (Section 1.6.2, Scheme 57).[86] The literature transformation was attempted, with the intent to form the diacid by aqueous work up of the material without treatment with diazomethane, due to concerns over its toxicity and explosivity. Initial attempts to reproduce this reaction have so far failed to deliver the desired results, with the reaction forming only a complex mixture of products.



231

*Scheme 100: Attempted oxidative cleavage using RuO_4 catalysis failed to afford the desired diacid **231**.*

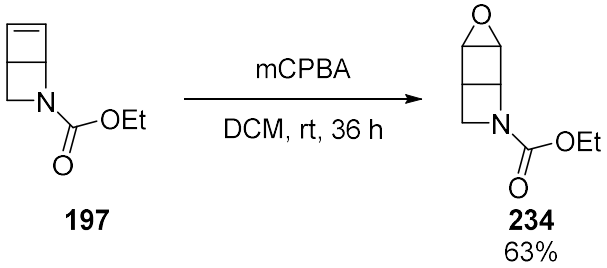
Ozonolysis was identified as a potentially powerful tool for synthesising several different azetidine derivatives, possessing substituents with various oxidation states. Several different work-up conditions were attempted, with the intent to produce the dialdehyde using either triphenylphosphine or dimethylsulfide, the diacid by using hydrogen peroxide solution and the diol using sodium borohydride. However, in each case the reactions failed to deliver the desired products (Scheme 101). Also attempted was the osmium tetroxide catalysed oxidation to the diol **233a**, however the reaction failed to give the desired product, and only returned starting material.



*Scheme 101: Attempted ozonolysis of Dewar dihydropyridine **197**. a) 1) O_3 2) triphenylphosphine, dichloromethane, -78 °C; b) 1) O_3 2) dimethylsulfide, dichloromethane, -78 °C; c) 1) O_3 2) H_2O_2 (30% aq.), dichloromethane, -78 °C; d) 1) O_3 2) $NaBH_4$, dichloromethane, -78 °C; e) 1) N-methylmorpholine-N-oxide (1.1 eq) 2) OsO_4 (4 wt%), acetone, 16 h.*

With oxidative cleavage not giving the desired outcomes, attention was turned to epoxidation, as this has been previously reported in the literature.[78] The epoxide presented interesting scope for further transformations, either by simple epoxide opening to give substituted bicycles or, more interestingly, it was also hypothesised that acid activation of the epoxide could stimulate neighbouring group participation of the nitrogen, as an alternative route to the bridged pyrrolidines previously discussed (Section 3.7.1).

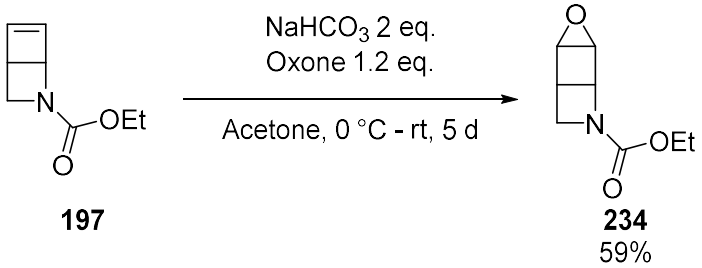
Literature reports that using *m*CPBA as the epoxidizing agent gives the desired epoxide **234** in acceptable yield, however the reaction times were long (36 h). Repeating this reaction confirmed the long reaction times were necessary to obtain sufficient yields (Scheme 102). Heating the reaction mixture to 60 °C in 1,2-dichloroethane to accommodate the increased temperature, did not increase the rate of reaction by any significant amount.



197 **234** 63%

Scheme 102: Epoxidation with mCPBA yielded the desired product, in relatively long reaction times.

Alternative methodologies were then attempted, in an effort to yield the same epoxide. Oxone® (potassium peroxymonosulfate) oxidation in acetone gave the desired epoxide in good yield (59%), comparable to those obtained with *m*CPBA, however the reaction took 5 days (Scheme 103). The reaction proceeds by oxidation of the acetone solvent to generate dimethyldioxirane *in situ*, which can then oxidise the alkene.[121]

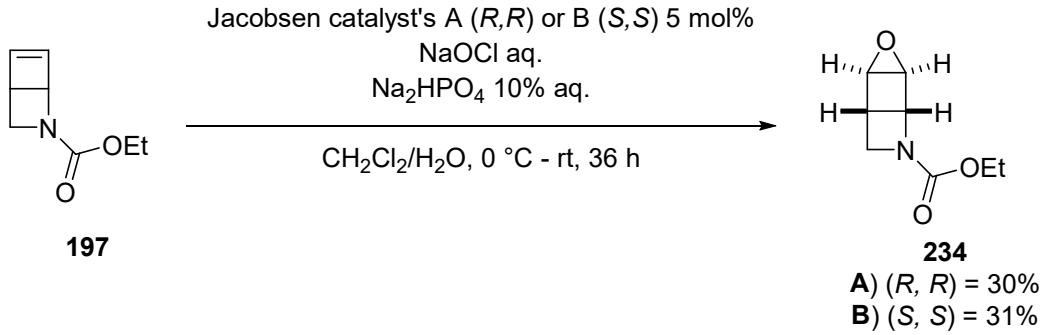


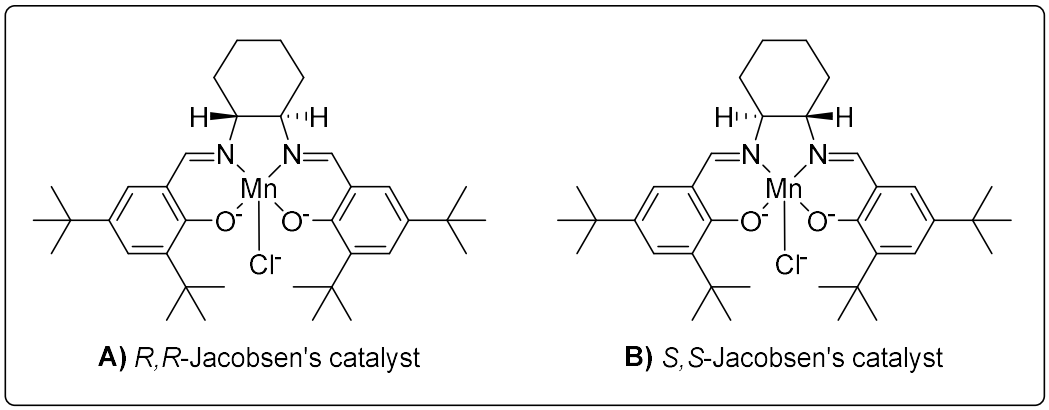
197 **234** 59%

Scheme 103: Epoxidation with Oxone® under basic conditions gave good yields but in very slow reaction times.

Another method that was investigated was Jacobsen epoxidation. Utilising both (*R,R*) and (*S,S*) Jacobsen catalyst yielded the desired epoxide **234** in

low yield (Scheme 104, 30-31%), Reaction times, however, remained relatively long and yields were roughly half that obtained by *m*CPBA oxidation (Scheme 104). Given the starting materials are racemic, this reaction may proceed with kinetic resolution, so the products would be expected to possess high enantiomeric excess. Unfortunately, this was not measured here, however it should be investigated in the future.

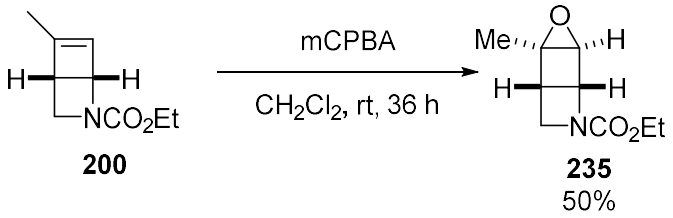




*Scheme 104: Jacobsen epoxidation of the Dewar dihydropyridine with accompanying structures of R,R and S,S-Jacobsen's catalyst **A** and **B** respectively.*

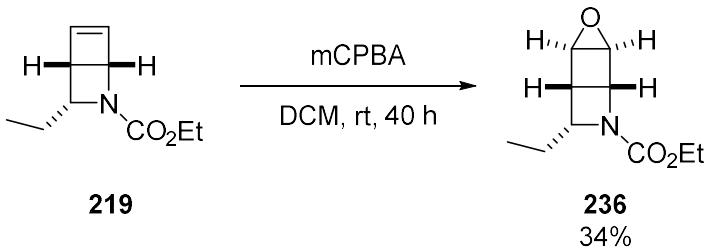
For the epoxidation it was therefore concluded that *m*CPBA was the optimal choice out of those methods tested, despite the relatively long reaction times. As such, this method was used to epoxidise some substituted Dewar dihydropyridines synthesised previously.

Epoxidation of the 5-methyl substituted Dewar dihydropyridine proceeded in similar rate and yield (36 h, 50%), despite what should be a more reactive alkene due to hyperconjugation from the methyl substituent (Scheme 105).



Scheme 105: Epoxidation of the 5-Methyl substituted Dewar dihydropyridine.

Epoxidation of 3-ethyl Dewar dihydropyridine **219** proceeded as expected, however the yield of epoxide **236** was roughly half that of the equivalent unsubstituted alkene **234** (Scheme 106, 34%). According to the work by Krow and co-workers on the 3-methyl Dewar dihydropyridine, the epoxide group adds across the alkene on the top face of the molecule due to the steric hindrance of the bottom face, caused by the folded geometry of the molecule. This would position the protons in positions 1 and 4 *trans* to the protons in positions 5 and 6. Molecular modelling reveals that this configuration leads to these protons being almost 90° to each other, leading to greatly diminished coupling than what might be expected.[114] Unfortunately in the ^{1}H NMR, the peaks of the indicative protons were poorly resolved in chloroform at 400 MHz and as such the coupling constants between the two sets of protons could not be determined. Alternative solvents were used to try and elucidate this, as well as utilising the NMR spectrometer fitted with a cryoprobe, however the spectrum remained broad.



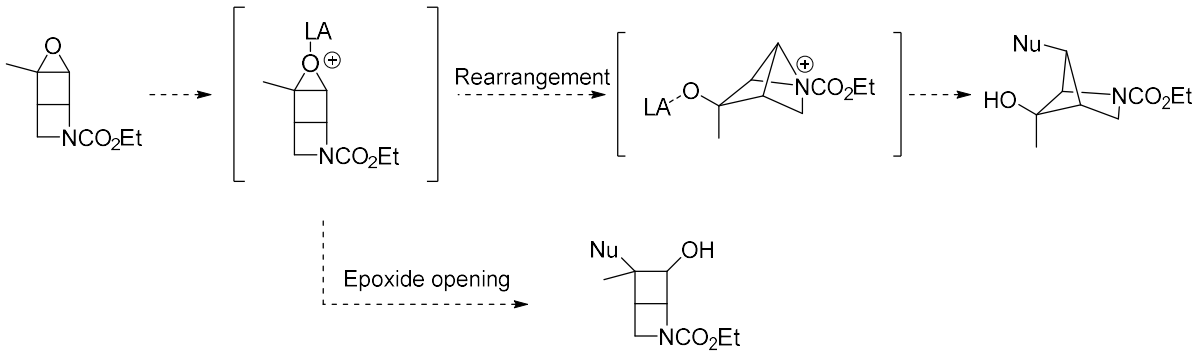
Scheme 106: Epoxidation of 3-ethyl substituted Dewar dihydropyridine.

With the slow reaction times of epoxidation, it was hypothesised that the alkene of Dewar 1,2-dihydropyridines may be less reactive than expected.

For this reason, a direct comparison between Dewar 1,2-dihydropyridines and other Dewar heterocycles, Dewar 2-pyridones and Dewar 1,2-dihydropyridazines was made to compare their relative reactivity.

The epoxide was identified as a synthetically useful starting material, which had the potential to undergo a number of transformations to sp^3 rich molecules. The epoxides of Dewar dihydropyridines have been reported previously, and have been used by a number of groups to access molecules with vastly different structures, from unsaturated oxazepines to bridged pyrrolidine alcohols (Introduction Section 1.6.2) so it was envisaged that similar reactivity could be exploited here.[79,114]

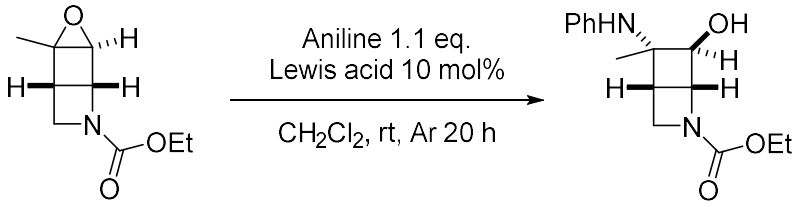
It was envisioned that treatment of the 5-methyl epoxide **235** with a Lewis acid and a nucleophile could lead to bridged pyrrolidines (Scheme 107), the rationale being that Lewis acid activation of the epoxide could allow the neighbouring nitrogen to participate in epoxide opening in a similar mechanism to that detailed previously for this type of compound (Section 3.7.1). The 5-methyl substituted epoxide was chosen for this as the methyl group would provide some differential reactivity between the two epoxide carbon centres and would also aid in structural elucidation.



Scheme 107: Proposed reaction pathways for Dewar DHP epoxide + Lewis acid and nucleophile.

Aniline was chosen as the nucleophile as there has been previous literature covering Lewis acid catalysed epoxide opening with anilines.[122,123] Evaluation of various Lewis acids and solvents revealed that $Cu(OTf)_2$ and

CuOTf·toluene complex in dichloromethane gave the best yields of product, with CuOTf·toluene complex giving slightly higher yields (Table 5).



235 237

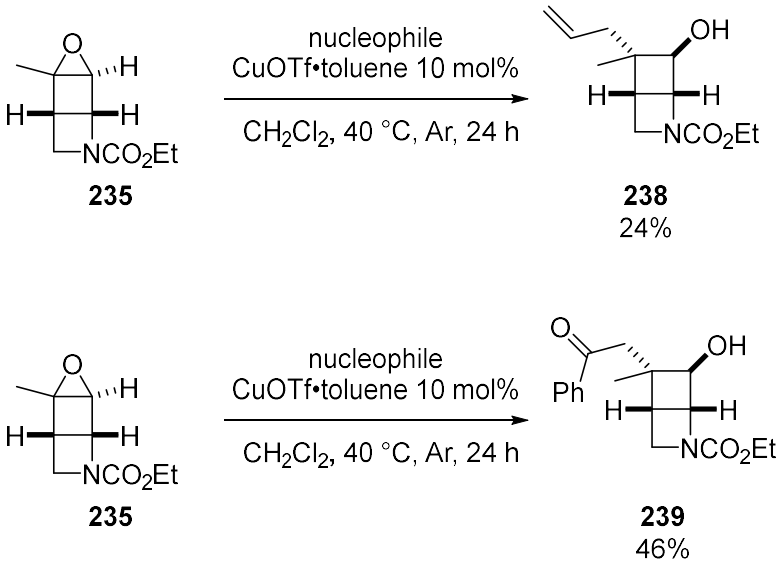
Lewis acid	Solvent	Yield (%)
$FeNO_3$	CH_2Cl_2	No reaction
$Ti(O^{i}Pr)$	CH_2Cl_2	No reaction
MgI_2	CH_2Cl_2	No reaction
$Pd(OAc)_2$	CH_2Cl_2	No reaction
CuCl	CH_2Cl_2	No reaction
AgOTf	CH_2Cl_2	21
	MeCN	Trace
	$MeNO_2$	Trace
	THF	9
$Cu(OTf)_2$	CH_2Cl_2	42
CuOTf·toluene	CH_2Cl_2	68
	MeCN	No reaction
	$MeNO_2$	37
	THF	21

Table 5: Lewis acid and solvent screen for Lewis acid catalysed epoxide opening with aniline.

The reaction between the epoxide **235** and aniline, with catalytic CuOTf·toluene gave the addition product **237** in 68% yield, which, on analysis proved to be the epoxide ring-opened product (**Error! Reference source not found.**). This reaction produced a densely functionalised, novel compound, with the reaction providing good scope for inclusion of alternative nucleophiles. Since epoxide opening occurs *via* an S_N2-like process, the resulting alcohol will be *trans* to the amine, leading to formation of a single diastereomer.

A screen of various nucleophiles was then undertaken. The reaction conditions had to be altered slightly, insomuch as the temperature was raised from room temperature to 40 °C to provide an increased rate of reaction. Unfortunately, reactions using boronic acids and phenols returned only starting material in each case. However, the reactions with allyltrimethylsilane and trimethyl((1-phenylvinyl)oxy)silane were successful in low to moderate yield as single diastereomers, providing novel alcohols (**238** and **239**, Scheme 108). There was no evidence of the rearrangement product in any example tested, however the epoxide opening products are interesting enough in their own right.

The ring-opening with allyltrimethylsilane, was interesting as it introduces a quaternary centre and an allyl group that could be exploited for further reactivity. Given only moderate yields were isolated it would be desirable to optimise these reactions further; it may be necessary to tailor the Lewis acid to each individual nucleophile, for example.



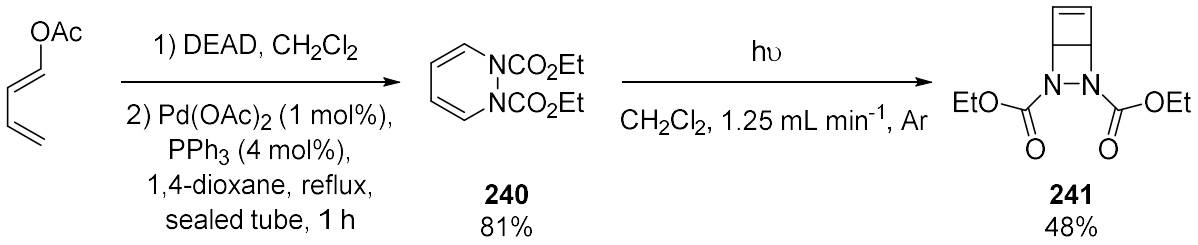
Scheme 108: Epoxide ring-opening reactions with allyltrimethylsilane and catalytic CuOTf·toluene.

3.8 Comparison Between Dewar Heterocycle Reactivity

Given the slow reaction times observed for the epoxidation of the Dewar dihydropyridines, it was hypothesised that despite the high ring-strain

present, the reactivity of the Dewar dihydropyridine alkene may be lower than expected.

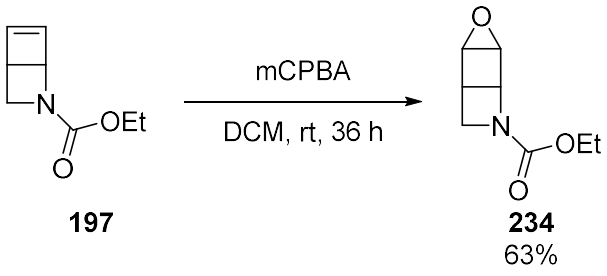
For the purposes of comparison, the 1,2-dihydropyridiazine was synthesised, following the method of Coote and co-workers.[37,124] 1-acetoxy-1,3-butadiene was reacted with diethylazodicarboxylate in a [4+2] cycloaddition to yield the tetrahydropyridazine, which was purified by short column chromatography before being submitted to the palladium-catalysed elimination to yield the desired 1,2-dihydropyridazine starting material **240**. This was then submitted to batch photoirradiation, to access the Dewar isomer **241** with a yield of 48% (Scheme 109).[124]



*Scheme 109: Synthesis of diazetidine **240** via dihydropyridzaine **241**.*[37,124]

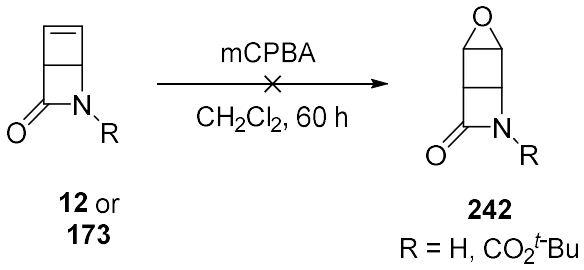
As a comparison between the different Dewar heterocycles, the rate of epoxidation with *m*CPBA was investigated. Here, solutions of Dewar 1,2-dihydropyridine, 2-pyridone and 1,2-dihydropyridazine in dichloromethane were prepared and to each was added a suspension of *m*CPBA and the reactions monitored.

After 36 hours the Dewar 1,2-dihydropyridine was consumed, as expected, and furnished the desired epoxide (Scheme 110).



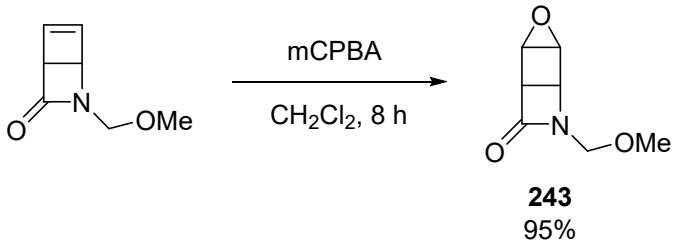
*Scheme 110: Epoxidation of Dewar dihydropyridine **234**.*

The Dewar 2-pyridone **12**, unexpectedly, showed no reaction, even when left for a further 24 hours. This prompted the use of the Boc-protected Dewar 2-pyridone in the same reaction. A carbamate protection seemed appropriate given the other two molecules in the comparison test had their nitrogen centres protected by carbamate protecting groups, this would give a more direct comparison of reactivities, however no reaction was observed in this case either when using compound **173** (Scheme 111).



Scheme 111: Attempted epoxidation of unprotected and Boc protected Dewar 2-pyridone.

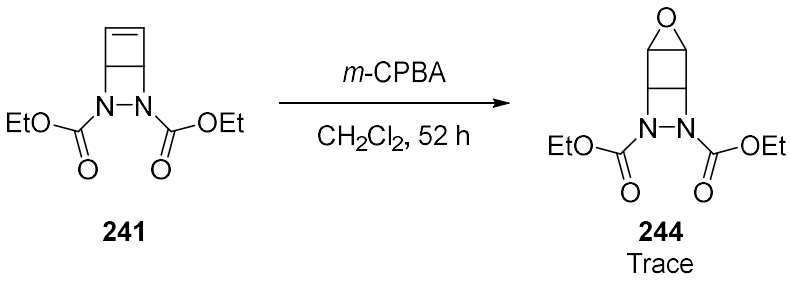
In the literature the methoxymethyl ether protected Dewar 2-pyridone was successfully epoxidized in excellent yield, in 8 h – a significantly shorter reaction time compared to the Dewar 1,2-dihydropyridine, both in this work and reported in the literature (Scheme 112).[114]



*Scheme 112: Epoxidation of methoxymethyl ether protected Dewar azetidinone **243**.*

The diazetidine **241** showed no reaction by TLC analysis, however mass spectrometry showed the generation of trace amounts of the epoxide after 36 h. After a further 16 h there was no change in the TLC or the mass spectrometry data. The epoxide **244** has not been previously reported in

the literature, so comparisons between the results obtained here is not possible.



241 **244** Trace

*Scheme 113: Attempted epoxidation of diazetidine **241**, achieving only trace quantities of the desired product.*

While a more rigorous study should be undertaken in the future, it appears that the alkene in these Dewar heterocycles is less reactive than other cyclic alkenes.

4 Summary and Future Work

4.1 Reactor Construction

In summary, the construction of a continuous flow photochemical reactor, based on the design from the Booker-Milburn group, was achieved.[1] The reactor consists of a quartz glass immersion well, with a coil of FEP tubing wrapped directly onto the glass as per Figure 7. A 400 W medium pressure Hg vapour lamp as well as a Pyrex® filter sleeve are housed inside the immersion well. The internal volume of this reactor could be varied by wrapping additional layers of FEP tubing, as well as connecting two reactor coils in series. Three permutations were used in this work 50 mL, 220 mL and 440 mL.

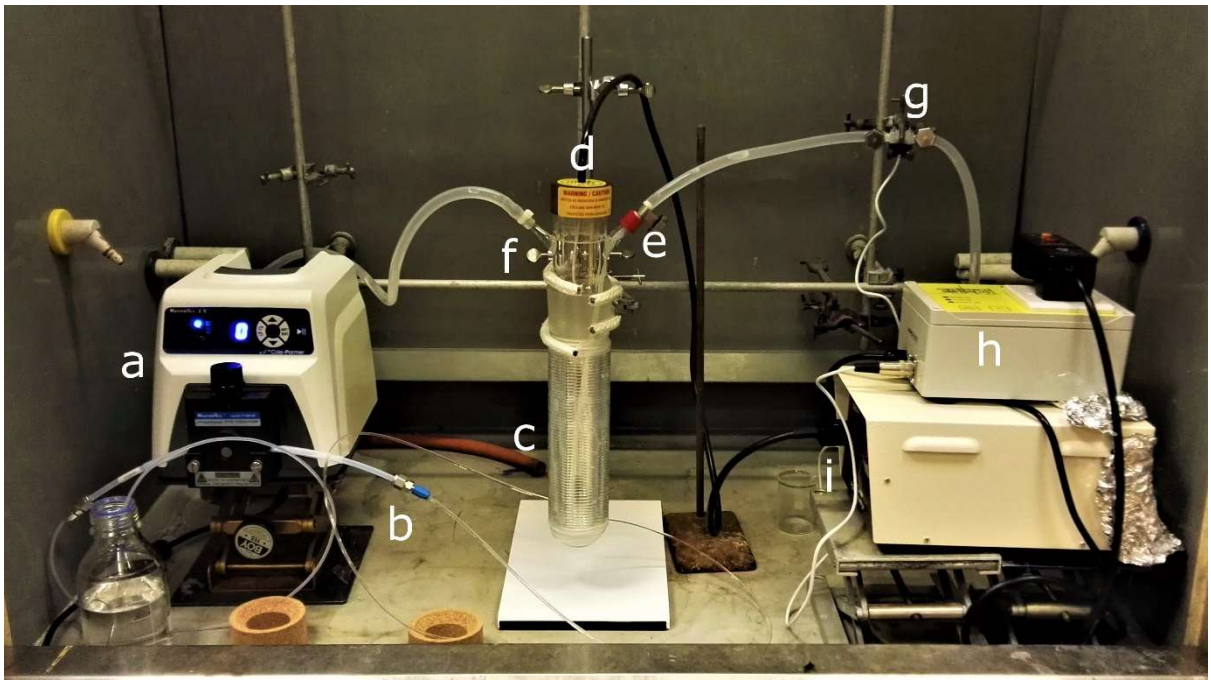
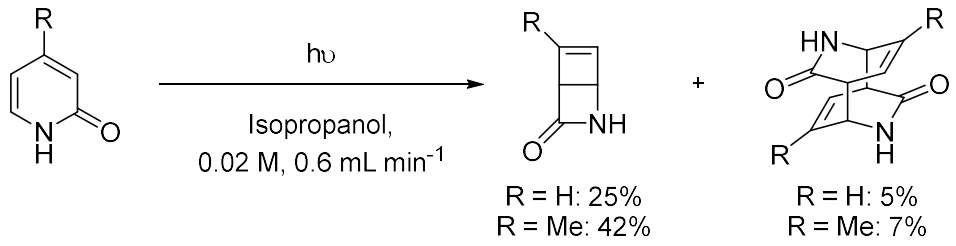


Figure 7: Reactor set up. a) peristaltic pump, b) PTFE to FEP union (contains O-Rings), c) Reactor coil, d) 400 W Hg lamp, e) water coolant input, f) water coolant output, g) coolant water flow monitor, h) power cut-off control, i) 400 W power supply.

4.2 Dewar 2-pyridones

Attention was then turned to developing the synthesis of Dewar 2-pyridones in continuous flow, as it was thought this would enable the production with greater productivity over using batch photochemistry. To

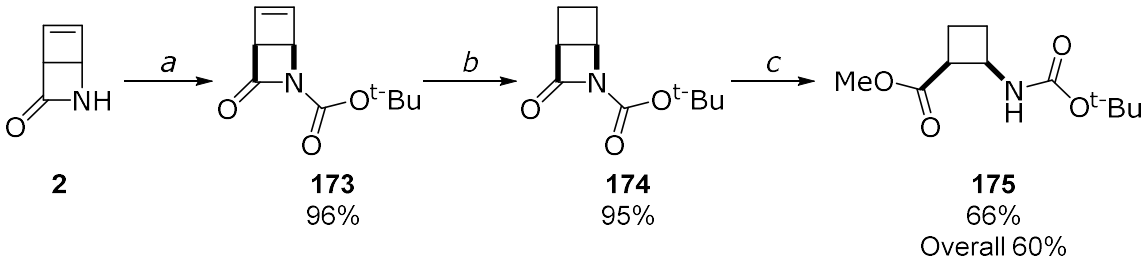
determine optimum conditions for yield of Dewar 2-pyridone and reaction productivity the reaction was performed at varying concentrations and flow rates. The maximum yield obtained was 25% at a concentration of 0.02 M and 0.6 mL min^{-1} flow rate, with a productivity of 23 mg h^{-1}. Productivity could be increased by performing this reaction at increased flow rate, at the cost of yield, with the maximum productivity of 48 mg h^{-1} was achieved at 0.02 M at 1.25 mL min^{-1}, with a yield of 10% (NMR yield). Using the conditions which gave maximum yield (0.02 M, 0.6 mL min^{-1}) the 4-methyl Dewar 2-pyridone was also successfully synthesised in 42% yield.



Scheme 114: Photochemical synthesis of Dewar 1-pyridones.

The yield (and therefore productivity) of the desired Dewar isomer was limited by a competing dimerisation, which was exacerbated at increased concentrations. It was therefore thought that inclusion of a sterically demanding group on the nitrogen might disrupt dimer formation, which would allow the reaction to be performed at increased concentrations. Unfortunately, photoirradiation of tosyl and benzyl protected 2-pyridones were unsuccessful.

Having synthesised the Dewar 2-pyridone it was then desirable to explore its reactivity and attempt to develop routes to some sp^3-rich small molecules. Based on previous work done in the group, a novel route to the cyclobutane-containing β-amino acid was achieved with an overall yield of 60%, requiring no chromatographic purification at any step. The product obtained contained only one diastereomer due to the nature of the Dewar 2-pyridone starting material.



*Scheme 115: β-amino acid **175** via Boc protection, hydrogenation, and β-lactam hydrolysis.*

Based on previous literature it was also thought that the Dewar 2-pyridones may be amenable to Grubbs' ring-opening metathesis, the product of which was envisioned could undergo a Cope rearrangement, driven by release of ring strain. However, the ROM/CM reaction failed to deliver the desired product.

Metal carbenoids had also been used within the group, and it was thought that the Dewar 2-pyridone could be amenable to reactions with them. Two products were envisaged from reactions between the Dewar 2-pyridone and a metal carbenoid derived from ethyl diazoacetate: an *N*-functionalised Dewar 2-pyridone derivative, *via* N-H insertion, and a cyclopropane *via* carbenoid addition to the C=C bond. In each case however the metal carbenoid failed to react with the Dewar heterocycle, leaving only unreacted starting material and diethyl fumarate.

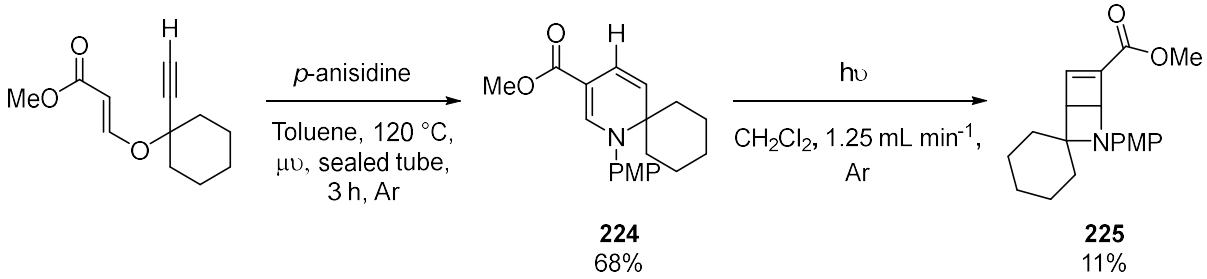
4.3 Dewar 1,2-Dihydropyridines

A range of 1,2-dihydropyridines were synthesised and subjected to the photochemical reaction to produce a range of Dewar 1,2-dihydropyridines. Optimisation of the flow photochemical reaction was first attempted on the CBz-protected 1,2-dihydropyridine however this proved problematic due to the generation of inseparable contaminants in the product. Optimisation of concentration and use of UV filters was then performed on the ethoxycarbonyl as an alternative protecting group. This did not generate the previously observed impurities. Here it was found that by increasing concentration the productivity increased from ~150 mg h^{-1} at 0.05 M to

~350 mg h^{-1} at 0.2 M, simply due to the increased quantity of starting material. Yield, however, dropped significantly over the values tested, from 27% to 6%. The conditions which gave the highest yield were used for subsequent reactions (0.05 M, 1.25 mL min^{-1}) to minimise wastage, despite the lower productivity.

The scope of the photochemistry was expanded to include 2-substituted Dewar dihydropyridines from the irradiation of 2-substituted 1,2-dihydropyridines. These were synthesised by Grignard addition to activated pyridine and 4-picoline. Yields for the photochemical reactions were comparable to those for 2-unsubstituted dihydropyridines for alkyl substituents, however vinyl, aryl and alkynyl substituents gave only complex mixtures of products.

A route to Dewar dihydropyridines which are quaternary at the 2-position was also developed, using a route to quaternary 1,2-dihydropyridines from propargyl vinyl ethers. The spirocyclohexyl Dewar dihydropyridine **225** was obtained in 11% yield (Scheme 116). This is an important development, as it represents the first Dewar dihydropyridine which is quaternary at the 2-position. This chemistry should be expanded in the future to include a wider array of substituents, as well as a deeper investigation into the photochemistry of this compound, to improve yield.



224
68%

225
11%

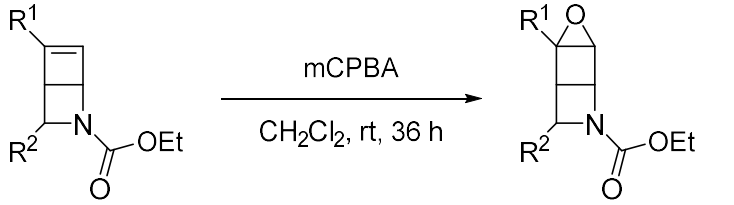
Scheme 116: Route to quaternary Dewar dihydropyridines from propargyl vinyl ethers.

The reactivity of Dewar 1,2-dihydropyridines was also investigated, as it was envisaged that they may provide a good starting material for the synthesis of highly substituted azetidines – a structural motif important in

medicinal chemistry, and one that is under-represented in the literature – or bridged pyrrolidines, which have been reported previously.[75] The rearrangement was investigated first, where it was thought that π-Lewis acid catalysis could be developed to generate a wide range of substituted bridged pyrrolidines. Unfortunately, this was not the case for the conditions attempted in this work. This should be revisited in the future to more thoroughly test conditions, as literature suggests the alkene present in the Dewar dihydropyridine is amenable to transition metal catalysis.[77]

Cleavage of the alkene bond present in the Dewar dihydropyridines was investigated through both Grubbs' ring-opening metathesis/cross metathesis, and by oxidative cleavage by ozonolysis and RuO_4 oxidation, however the desired products could not be obtained in any case attempted.

Epoxidation of the Dewar dihydropyridines was successful and gave decent yields for those attempted, however the reaction times were relatively long, at 36 hours (Scheme 117). Alternative methods were attempted, such as dimethyl dioxirane oxidation and Jacobsen oxidation, however reaction times for these were longer and yields were lower.



Scheme 117: Epoxidation of Dewar dihydropyridines.

Given the long reaction times observed from the epoxidation it was observed that the alkene present in Dewar dihydropyridine is less reactive than initially assumed. It was therefore desirable to compare the reactivity of the Dewar dihydropyridine with other Dewar heterocycles. The Dewar dihydropyridazine was synthesised following the literature procedure and submitted to the epoxidation.[37,124] After ~48 hours, the desired epoxide

had only formed in trace quantities (trace on mass spec. data). The epoxidation of Dewar 2-pyridone and Boc protected Dewar 2-pyridone were also attempted, however these failed to give the desired products. At this point it is difficult to verify whether the C=C bonds present in the Dewar dihydropyridines are less reactive that anticipated. In the future a more rigorous study should be undertaken which would include other cyclic alkenes as a comparison.

Overall, despite the increased productivity over batch methods for synthesising Dewar dihydropyridines, the method presented here is perhaps less productive than hoped, although the improved yield and productivity observed when using the 440 mL reactor does present a promising improvement over the results obtained from the 220 mL reactor.

4.4 Future Work

Further improvement of the photoirradiation of 1,2-dihydropyridines is desirable. Given the relative success of using 2 lamps in series, this could be expanded to include additional lamps, which should subsequently be tested on the various dihydropyridines.

Despite the use of filter solutions proving disappointing so far, there is scope for using light sources of specific wavelengths, such as excimer lamps or UV LEDs, to potentially increase yields and productivity, however the equipment may require modification to accommodate these. LEDs in particular are an attractive alternative to Hg arc lamps, due to their low operating temperature and energy efficiency, and as UV LEDs of the required wavelengths and power become more widely available they should be investigated as a potential alternative light source. To that end, alternative reactor designs could also be considered, such as the so-called 'PhotoVap' system.[125]

This work has generated some promising leads which should be expanded on in the future. In particular, the prospect of further developing the route to quaternary and spirocyclic azetidines by photoirradiation is desirable as

these are structures which are difficult to synthesise by other methods. Expanding the substrate scope of this process should be the first step as there are a multitude of different, readily available ketones from which to synthesise the propargyl vinyl ether starting materials. The paper detailing the synthesis of quaternary 1,2-dihydropyridines presents a large array of substrates which may be amenable to the photochemical process, and as such would be a sensible place to start.

One area which should also be explored is the reactivity at the nitrogen position of the Dewar dihydropyridines. Deprotection of the Dewar dihydropyridine nitrogen would expose a reactive secondary amine, which could be amenable to a range of further functionalisation to potentially desirable azetidines.

The 4-bromo Dewar dihydropyridine **201** should also be investigated further, as the presence of an allylic bromine could allow for some interesting transformations, such as radical debromination with subsequent C-C bond formation.

5 Experimental

General Experimental

All reagents and solvents were from commercial suppliers and used as supplied. 4-Picoline was dried by distillation over potassium hydroxide onto activated molecular sieves (4 Å). Room temperature reflects ambient laboratory conditions ranging from 18-22 °C. Analytical thin layer chromatography was carried out on aluminium backed plates coated with Merck Kieselgel 60 GF254 and visualized under UV light at 254 and/or 360 nm, or by $KMnO_4$. Flash chromatography was carried out using Davisil silica 60Å. Infrared spectra were recorded using a Bruker Alpha IR spectrometer fitted with an ATR attachment over the range 4000-500 cm^{-1}. NMR spectra were recorded at 298 K using a Bruker AV(III)400, AV400, DPX400 (400 MHz ^{1}H frequency, 100 MHz ^{13}C frequency). Chemical shifts are quoted in parts per million (ppm), referenced to residual solvent peak (1H NMR: CDCl3 = 7.26 ppm, $(CD_3)_2SO$ = 2.05 ppm; ^{13}C NMR: $CDCl_3$ = 77.16 ppm, $(CD_3)_2SO$ = 39.52 ppm). 2D NMR experiments (COSY, HSQC-ME) were utilised where necessary to aid in structural elucidation. High resolution mass spectrometry experiments were recorded on a Bruker MicroTOF (ESI^+) mass spectrometer.

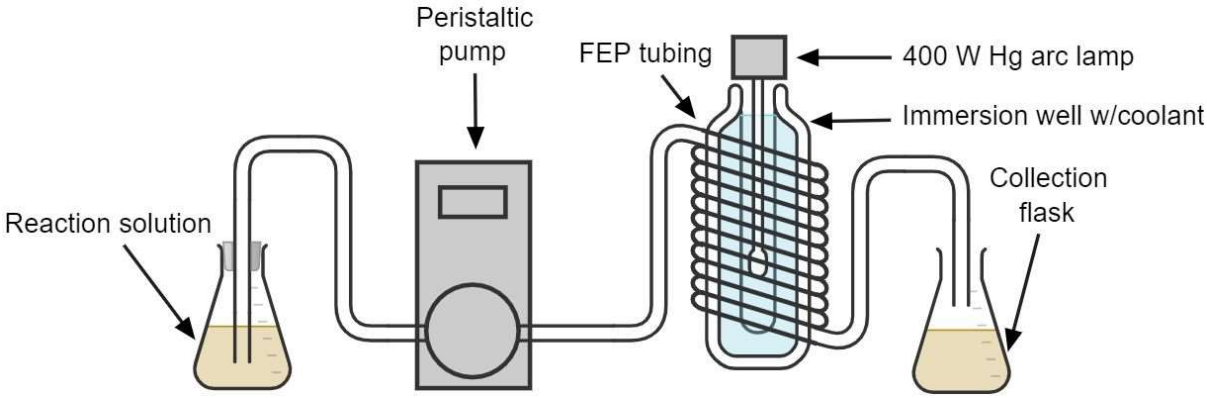
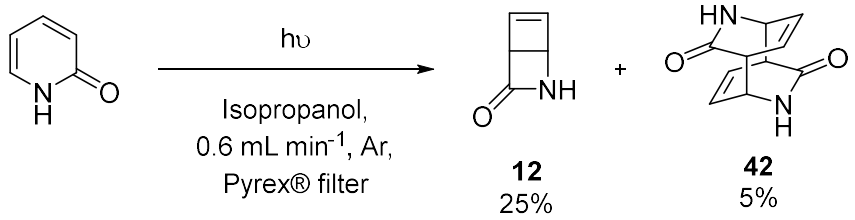


Figure 8: Diagram of FEP reactor setup.

Irradiation was performed on an FEP reactor consisting of an immersion well wound with FEP tubing (2.7 mm ID, 3.1 mm OD) with varying layer numbers (1 layer = 50 mL reactor, 3 layers = 200 mL reactor).[1] For some experiments (as indicated) 2 of these reactor coils were connected in series

(internal volume = 400 mL reactor). Pumping of reaction mixture was performed by a peristaltic pump with variable speed. The lamp was a 400 W, medium pressure mercury arc lamp purchased from Photochemical Reactors ltd. connected to a 400 W power supply. As a safety precaution, the power supply is connected to a flow monitor which shuts off the reactor when the flow of coolant (water) drops below a certain threshold.

2-azabicyclo[2.2.0]hex-5-en-3-one (12):



2-pyridone (476 mg, 5.01 mmol) was dissolved in isopropanol (250 mL) to give a 0.02 M solution, which was degassed by sonication for 5 minutes under argon. This was pumped through the 220 mL photoreactor, fitted with a Pyrex® filter, at a rate of 2 mL/min, irradiated with a 400 W medium pressure mercury arc lamp. Once the reaction mixture was fully depleted the reactor was flushed with clean isopropanol with lamp still operational. The solvent was then removed from the resulting solution in vacuo to yield a yellow oil with suspended crystals. This was dissolved in ethyl acetate which formed a white precipitate, which was filtered off under reduced pressure and washed with ethyl acetate to yield the photodimer **42** as a white powder (24.0 mg, 5%, 10% based on recovered starting material). The filtrate solvent was then removed in vacuo and the residue was purified by column chromatography (eluent: 100% ethyl acetate then 5% methanol in ethyl acetate) to yield the title compound **12** (121 mg, 25%, 50% based on recovered starting material) and recovered starting material (232 mg, 51% conversion).

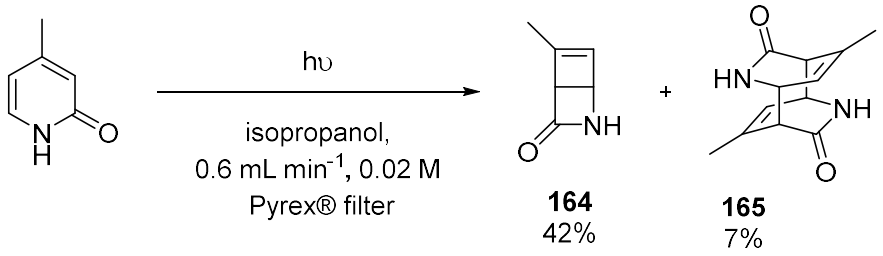
2-azabicyclo[2.2.0]hex-5-en-3-one (12): m.p.: 58-59 °C, c.f. lit.: 65.5-66.5 °C[126]; IR (ATR neat, ν_{max}): 3216, 3011, 1696, 1540 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.64 (1H, dd, *J* = 2.5, 0.9 Hz, CH=CH), 6.52 (dd, 1H, *J* = 2.5, 1.2 Hz, CH=CH), 6.05 (br. s, 1H, NH), 4.43 (app. t, 1H, *J* = 2.5 Hz, O=CCH), 4.17 – 4.14 (m, 1H, NCH); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.4 (C), 142.6 (CH=CH), 140.6 (CH=CH), 59.6 (CH), 50.9 (CH); HRMS m/z (ESI+): $[M+H]^+$ calcd. for $C_5H_6NO^+$: 96.0449, found: 96.0448.

(1R,2R)-3,7-diazatricyclo[4.2.2.2^{2,5}]dodeca-9,11-diene-4,8-dione (42): IR (ATR neat, ν_{max}): 3206, 3073, 2924, 2865, 1661 cm^{-1}; ^1H NMR

(400 MHz, d_6-DMSO): δ 7.63 (d, 2H, *J* = 4.1 Hz, NH), 6.60 - 6.55 (m, 2H, OCCHCH=CH), 6.07 – 6.02 (m, 2H, NHCHCH=CH), 4.07 – 4.00 (m, 2H, NH-CH), 3.30 – 3.24 (m, 2H, CO-CH); ^{13}C NMR (101 MHz, $CDCl_3$): δ 177.5 (C), 135.8 (CH), 131.5 (CH), 52.7 (CH), 50.3 (CH); HRMS m/z (ESI+): calcd. for: $C_{10}H_{10}N_2O_2Na^+$: 213.0640, found: 213.0635.

Data match that reported in literature.[44]

5-methyl-2-azabicyclo[2.2.0]hex-5-en-3-one (164):



164 42%

165 7%

A 0.02 M solution of 4-methyl-2-pyridone (546 mg, 5.00 mmol) in isopropanol (250 mL) was prepared and subsequently degassed by sonication for 5 minutes under argon. This was pumped through FEP Reactor 2 with 2 layers of tubing, fitted with a Pyrex® filter, at a rate of 2 mL/min, irradiated with a 400 W medium pressure mercury arc lamp. Once the reaction mixture was fully depleted the reactor was flushed with isopropanol. The solvent was then removed from the resulting solution in vacuo to yield a yellow oil with suspended crystals. This was dissolved in ethyl acetate which precipitated a white powder, which was filtered off under reduced pressure and washed with ethyl acetate to yield the photodimer **165** (36.0 mg, 7%). The filtrate solvent was removed in vacuo and the residue was purified by column chromatography (eluent: 100% ethyl acetate then 5% methanol in ethyl acetate) to yield the title compound **164** (231 mg, 42%) and recovered starting material (191 mg, 51%).

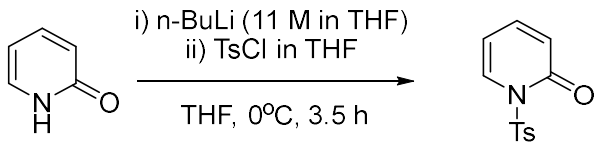
5-methyl-2-azabicyclo[2.2.0]hex-5-en-3-one (164): m.p.: 49-50 °C; IR (ATR neat, ν_{max}): 3251, 2998 2948, 1716, 1618 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.32 (br. s, 1H, NH), 6.18 - 6.15 (m, 1H, C=CH), 4.33 – 4.17

(m, 1H, O=CCH), 4.04 – 4.01 (m, 1H, NCH), 1.92 – 1.84 (m, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.0 (C), 151.5 (C), 134.6 (CH), 61.1 (CH), 47.3 (CH), 16.8 (CH_3); HRMS m/z (ESI+): $[M+H]^+$ calcd. for $C_6H_8NO^+$: 110.0606, found: 110.0613; $[M+Na]^+$ calcd. for $C_6H_7NONa^+$: 132.0425, found: 132.0416.

(1R*,2R*)-9,11-dimethyl-3,7-diazatricyclo[4.2.2.2^{2,5}]dodeca-9,11-diene-4,8-dione (165): IR (ATR neat, ν_{max}): 3242, 2965, 1631, 1606 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.29 (br. s, 2H, 2xNH), 7.22 (d, 2H, *J* = 6.6 Hz, 2xC=CH), 6.15 – 6.06 (m, 2H, 2xNH-CH), 6.00 (dd, 2H, *J* = 6.6, 1.7 Hz, 2xCO-CH), 2.10 (d, 6H, *J* = 1.1 Hz, 2xCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.9 (C), 152.4 (C), 134.8 CH), 118.8 (CH), 107.7 (CH), 21.5 (CH_3); HRMS m/z (ESI+): $[M+Na]^+$ calcd. for $C_{12}H_{14}N_2O_2Na^+$: 241.0953, found: 241.0909.

Data match that reported in literature.[44]

***N*-tosyl-2-pyridone (166):**



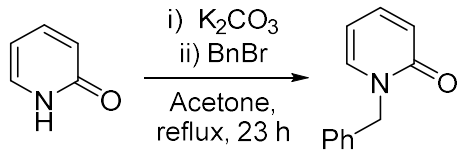
166
77%

$^{n-}$Butyl lithium (11 M in THF, 3.5 mL, 38.5 mmol),) was added to a stirring solution of 2-pyridone (2.49 g, 68.4 mmol) in dry tetrahydrofuran (40 mL) at 0 °C, under argon. The resulting solution was then left to stir for 40 min at 0 °C before addition of a solution of tosyl chloride (5.00 g, 26.2 mmol) in dry tetrahydrofuran and further stirring at 0 °C for 3.5 h. Water (50 mL) was then added, and the organics extracted with ethyl acetate (4 x 15 mL). The organics were combined, washed with brine (15 mL) and subsequently dried over magnesium sulphate, filtered and the solvent removed in vacuo. This yielded the desired product as an orange solid (5.00 g, 77%, 20.1 mmol). m.p.: 119-120 °C; IR (ATR neat, ν_{max}): 3373, 3232, 3157, 2871, 1672, 1594 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 8.10 (ddd, 1H, *J* = 7.5, 1.9,

0.8 Hz, PyrH), 7.98-8.02 (m, 2H, ArH), 7.36 – 7.31 (m, 2H, ArH) 7.29 (ddd, 1H, *J* = 9.3, 6.4, 1.9 Hz, PyrH), 6.42 (ddd, 1H, *J* = 9.3, 1.3, 0.8 Hz, PyrH), 6.23 (ddd, 1H, *J* = 7.5, 6.4, 1.3 Hz, PyrH), 2.45 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): 160.1 (C), 146.3 (C), 141.2 (CH), 133.3 (C), 131.7 (CH), 129.9 (CH), 129.5 (CH), 123.4 (CH), 106.3 (CH), 21.8 (CH_3); HRMS m/z (ESI+): [M+Na^+] calcd for $C_{12}H_{11}NO_3SNa$: 272.0357, found: 272.0358, [2M+Na^+] calcd for $C_{24}H_{22}N_2O_6S_2Na$: 521.0817, found: 521.0823.

Data matches that reported in literature.[91]

1-benzylpyridin-2(1H)-one (168):



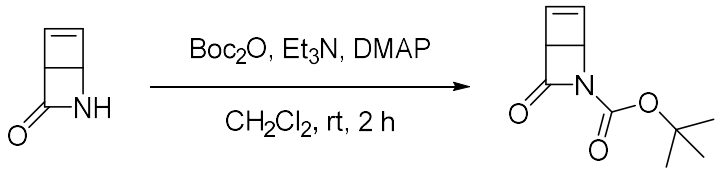
168
78%

2-pyridone (5.13 g, 53.9 mmol) and potassium carbonate (22.4 g, 162 mmol) were dissolved in acetone (150 mL) with heating (30 °C). Benzyl bromide (7.70 mL, 64.7 mmol) was added dropwise to the stirring solution and reaction mixture heated at reflux for 23 hours. The reaction mixture was cooled, and the solvent removed in vacuo. The mixture was dissolved in chloroform (10 mL) and washed with water (10 mL). The aqueous layer was washed with chloroform (3 x 10 mL), and the organic extracts combined, dried over magnesium sulphate, filtered, and the solvent removed in vacuo. The resulting pale-yellow crystals were washed with cyclohexane (3 x 10 mL) and dried under reduced pressure to yield the title compound as colourless crystals (7.83 g, 78%). m.p.: 64-65 °C lit.: 68-68.5 °C [92]; IR (ATR neat, ν_{max}): 3073, 3031, 1654, 1579, 1537 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.37– 7.23 (m, 7H, C_6H_5-CH_2 + Pyr), 6.61 (app. d, 1H, *J* = 9.2 Hz, Pyr), 6.13 (app. td, 1H, *J* = 6.6, 1.3 Hz, Pyr), 5.15 (s, 2H, $C_6H_5CH_2$); ^{13}C NMR (101 MHz, $CDCl_3$): 162.5 (C), 139.3 (CH), 137.2 (CH),

136.7 (C), 128.8 (CH), 128.2 (CH), 128.0 (CH), 121.3 (CH), 106.2 (CH), 51.9 (CH_2); HRMS m/z (ESI+): $[M+H]^+$ calcd. for $C_{12}H_{12}NO^+$: 186.0919, found: 186.0928; $[M+Na]^+$ calcd. for $C_{12}H_{11}NONa$: 208.0738, found: 208.0742.

Data match that reported in literature.[127]

***tert*-butyl 3-oxo-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (173):**

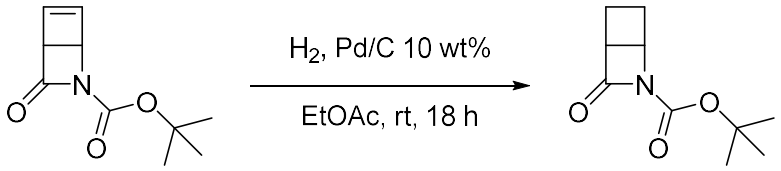


12 **173** 96%

2-azabicyclo[2.2.0]hex-5-en-3-one (0.049 g, 0.525 mmol) was dissolved in dichloromethane (4 mL) and the solution cooled to 0 °C. To the stirring solution was added triethylamine (0.04 mL, 0.287 mmol), Boc anhydride (0.129 g, 0.591 mmol) and N,N'-dimethylamino-pyridine (0.0.34 g, 0.278 mmol). The solution was allowed to stir at 0 °C for 10 min before warming to room temperature and stirring for a further 2 h. The reaction mixture was then diluted with dichloromethane (5 mL) and subsequently washed with hydrochloric acid solution (1 M, 5 mL) then water (5 mL) and further extracted with dichloromethane (3 x 3 mL). The combined organics were then dried over magnesium sulphate, filtered, and the solvent removed in vacuo, to yield the pure product as a yellow oil (96.0 mg, 94%, 0.492 mmol). IR (ATR neat, ν_{max}): 2979, 2936, 2606, 2498, 1796, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 6.61 (dd, 1H, *J* = 2.4, 1.1 Hz, C=CH), 6.54-6.56 (m, 1H, C=CH), 4.62 (dd, 1H, *J* = 2.8, 2.4 Hz, CH-CH), 4.12-4.14 (m, 1H, CH-CH), 1.52 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): 166.0 (C), 149.0 (C), 141.9 (CH), 140.4 (CH), 83.2 (C), 56.9 (CH), 52.8 (CH), 28.0 (CH_3); HRMS m/z (ESI+) $[M+H^+]$ calcd for: $C_{10}H_{14}NO_3^+$: 196.0974, found: 196.0968, $[M+NH_4^+]$ calcd for: $C_{10}H_{13}NO_3NH_4^+$: 213.1239, found: 213.1222, $[M+Na^+]$ calcd for $C_{10}H_{13}NO_3Na^+$: 218.0793, found: 218.0786,

Data match that reported in literature.[50]

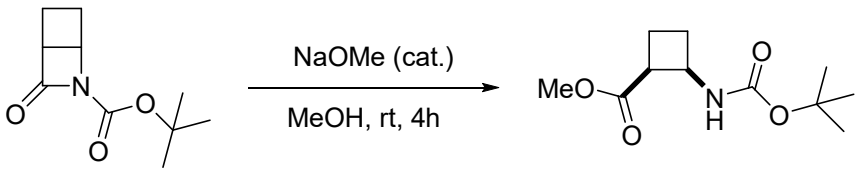
tert-butyl 3-oxo-2-azabicyclo[2.2.0]hexane-2-carboxylate (174):



173 **174** 95%

tert-butyl 3-oxo-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (127 mg, 0.651 mmol) was dissolved in anhydrous ethyl acetate. Palladium on carbon (14.0 mg, ~10 wt%) was then added, and the suspension subsequently purged with hydrogen. The suspension was then stirred under a hydrogen atmosphere for 18 h. The reaction mixture was then filtered through diatomaceous earth, and the solvent then removed in vacuo, yielding the desired product as a pale orange, crystalline solid, which required no further purification (122 mg, 95%, 0.619 mmol). mp.: 64-65 °C; IR (ATR neat, ν_{max}): 2978, 2952, 1775, 1707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 4.20-4.23 (m, 1H, CHCH), 3.51-3.56 (m, 1H, CHCH), 2.44-2.57 (m, 2H, CH_2), 2.12-2.28 (m, 2H, CH_2), 1.51 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): 167.8 (C), 147.8 (C), 83.3 (C), 51.3 (CH), 49.5 (CH), 28.1 (CH_3), 26.3 (CH_2), 20.0 (CH_2); HRMS m/z (ESI+) [M+H^+] calcd for: $C_{10}H_{16}NO_3^+$: 198.1130 found: 198.1125, [M+NH_4^+] calcd for: $C_{10}H_{15}NO_3NH_4^+$: 215.1396, found: 215.1392, [M+Na^+] calcd for $C_{10}H_{15}NO_3Na^+$: 220.0950, found: 220.0943.

Methyl 2-((*tert*-butoxycarbonyl)amino)cyclobutane-1-carboxylate (175):



174 **175**
66%

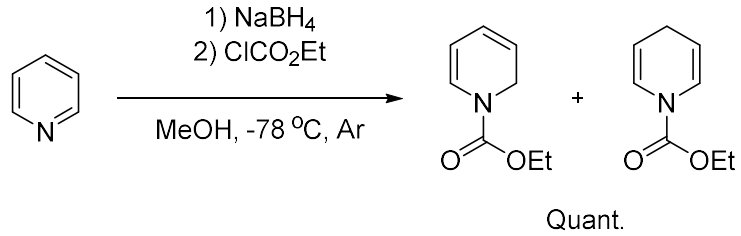
174 was dissolved in anhydrous methanol (2.00 mL) with stirring, at room temperature. To this was added a sodium methoxide solution (1.00 mL) taken from a stock solution made from sodium (13.0 mg) dissolved in anhydrous methanol (1.00 mL). This was then stirred at room temperature for 4 hours. The reaction mixture was then diluted with water (5 mL) and the organics then extracted with chloroform (2 x 10 mL). The combined organics were then combined, dried over magnesium sulphate, filtered, then the solvent removed in vacuo, to yield a colourless oil. (38.0 mg, 66%). IR (ATR neat, ν_{max}): 3338, 2958, 2477, 1727, 1678 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.33 (s, 1H, NH), 4.50-4.35 (m, 1H, CH), 3.69 (s, 3H, CH_3O), 3.42-3.32 (m, 1H, CH), 2.39-2.27 (m, 1H, CH_aH_b), 2.25 – 2.14 (m, 1H, CH_aH_b), 2.01-1.88 (m, 2H, CH_2), 1.40 (s, 9H, $(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.6 (C), 154.7 (C), 79.4 (C), 51.7 (CH_3), 45.7 (CH), 45.2 (CH), 29.5 (CH_2), 28.3 (CH_3), 18.5 (CH_2); HRMS m/z (ESI+): $[M+Na]^+$ calcd for $C_{11}H_{19}NO_4Na$ 252.1212, found: 252.1214, $[2M+Na]^+$ calcd for $C_{22}H_{38}N_2O_8Na^+$ 481.2526, found: 418.2527.

General procedure for synthesis of 1,2-dihydropyridine by reduction 1:

Dry pyridine or 4-picoline (1 equiv.) was diluted in dry methanol (~1 M) under an argon atmosphere and the solution cooled to -78 °C. Sodium borohydride (1 equiv.) was then added with stirring. The corresponding chloroformate (1.1 equiv.) was then added dropwise such that the reaction temperature did not exceed -60 °C. The reaction mixture was allowed to stir at -78 °C for a further 3-4 hours before being poured over ice water with stirring until gas evolution ceased. The mixture was then extracted with dichloromethane (3 x 25 mL), the organics combined, dried over magnesium sulphate, filtered and the solvent removed in vacuo. The resulting products were then used in the photoirradiation step without further purification.

NMR data for these mixtures lists the major component peaks, and the ratio of 1,2:1,4 dihydropyridines was determined based on relative integration of the appropriate peaks (1,2-dihydropyridine peak ~6.80 ppm, 1,4-dihydropyridine peak ~2.80 ppm).

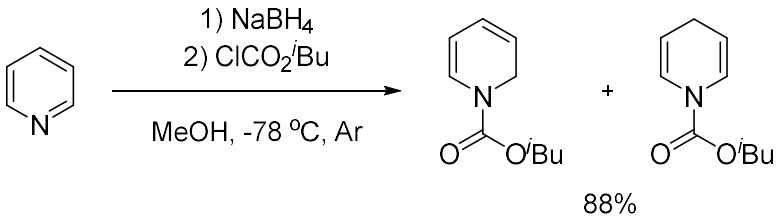
Ethyl pyridine-1(2H)-carboxylate (189):



65.8 mmol pyridine. Yellow oil, 99% yield; obtained as a mixture, relative integration = 9:1. This material was used without further purification in subsequent reactions; IR (ATR neat, v_{max}) 2982, 2829, 1705, 1650, 1586 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) d 6.81 – 6.56 (m, 1H, N-CH), 5.83 – 5.73 (m, 1H, NCH_2-CH), 5.53 – 5.35 (m, 1H, CH_2CH=CH), 5.16 – 5.00 (m, 1H, NCH=CH), 4.36 – 4.27 (m, 2H, NCH_2), 4.17 (q, *J* = 7.1, 2H, OCH_2), 1.25 (t, *J* = 7.1, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5 (C), 125.8 (CH), 122.0 (CH), 119.1 (CH), 104.6 (CH), 62.2 (CH_2), 43.4 (CH_2), 14.5 (CH_3). HRMS m/z (ESI+): $[M+H]^+$ calcd. for $C_8H_{12}NO_2^+$: 154.0868, found: 154.0873.

Data match that reported in literature.[75]

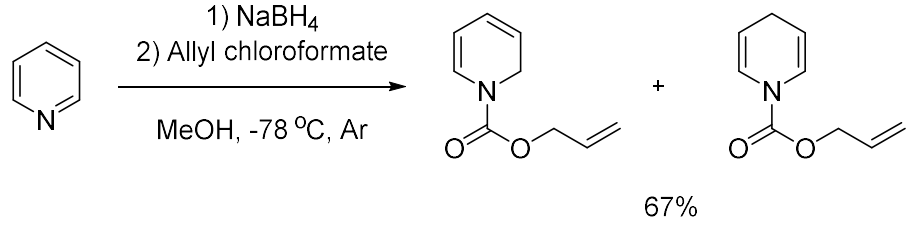
Isobutyl pyridine-1(2H)-carboxylate (190):



65.8 mmol pyridine. Colourless oil; 88%; obtained as a mixture, relative integration = 9:1. This material was used without further purification in subsequent reactions; IR (ATR neat, v_{max}) 2960, 2874, 1746, 1704, 1653, 1588 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 – 6.62 (m, 1H, N-CH), 5.87 – 5.75 (m, 1H, N-CH_2-CH), 5.55 – 5.33 (m, 1H, CH_2-CH=CH), 5.20 – 5.00 (m, 1H, N-CH=CH), 4.34 (s, 2H, N-CH_2), 3.94 – 3.88 (m, 2H, O-CH_2), 1.93 (hept, 1H, *J* = 6.8 Hz, $(CH_3)_2CH$), 0.92 (d, *J* = 6.8 Hz, 6H, $CH(CH_3)_2$); ^{13}C (101 MHz, $CDCl_3$) δ 162.7 (C), 126.4* + 125.7 (CH), 122.7* + 121.8 (CH),

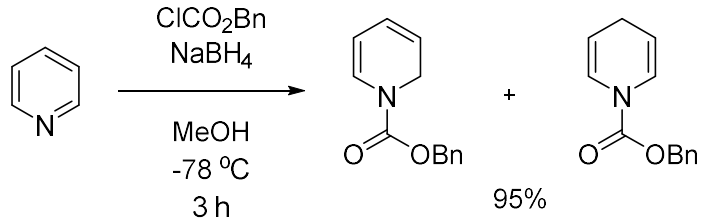
120.0 + 118.5* (CH), 104.6 (CH), 72.0 (CH_2), 43.6 (CH_2), 27.8 (CH), 18.9 (CH_3); HRMS m/z (ESI+): $[M+H+]^+$ calcd for $C_{10}H_{16}NO_2^+$: 182.1181, found: 182.1177; $[M+Na]^+$ calcd. for $C_{10}H_{15}NO_2Na^+$: 204.1000, found: 204.1001.

Allyl pyridine-1(2H)-carboxylate (191):



29.7 mmol pyridine. Yellow oil; 67%; obtained as a mixture, relative integration = 9:1. This material was used without further purification in subsequent reactions; IR (ATR neat, ν_{max}) 2939, 1748, 1702, 1649, 1589 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.80 – 6.63 (m, 1H, N-CH), 5.99 – 5.86 (m, 1H, Allyl CH), 5.86 – 5.79 (m, 1H, NCH_2-CH), 5.55 – 5.41 (m, 1H, CH_2CH=CH), 5.34 – 5.20 (m, 2H, Allyl CH_2), 5.19 – 5.06 (m, 1H, NCH=CH), 4.64 (dt, *J* = 5.6, 1.5 Hz, 2H, O-CH_2), 4.41 – 4.32 (m, 2H, N-CH_2); ^{13}C (101 MHz, $CDCl_3$) δ 158.0 (C), 122.1 (CH), 119.3 (CH), 118.6 (CH), 104.5 (CH), 72.2 (CH_2), 43.6 (CH_2), 28.0 (CH); HRMS m/z (ESI^+): $[M+H]^+$ calcd. for $C_9H_{12}NO_2^+$: 166.0868, found: 166.0861.

Benzyl pyridine-1(2H)-carboxylate (192):

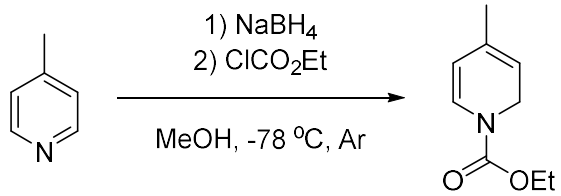


24.8 mmol pyridine. Pale yellow oil (5.10 g, 95%). Relative integration = 20:1. This material was used without further purification in subsequent reactions; IR (ATR neat, ν_{max}) 3033, 2955, 2830, 1704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41-7.31 (m, 5H, CH_2-C_6H_5), 6.82-6.68 (m, 1H, N-CH), 5.87-5.81 (m, 1H, CH_2-CH), 5.58-5.42 (m, 1H, CH_2=CH), 5.24-5.07 (m,

3H, NCH-CH + CH_2-C_6H_5), 4.40 (s, 1H, N-CH_2); HRMS m/z (ESI+): $[M+H]^+$ calcd. for $C_{13}H_{14}NO_2^+$: 216.1025, found: 216.1023; $[M+Na]^+$ calcd. for $C_{13}H_{13}NNaO_2^+$: 238.0844, found 238.0839.

Data match that reported in literature.[128]

Ethyl 4-methylpyridine-1(2H)-carboxylate (193):



86%

144 mmol pyridine. Colourless oil; 86%; IR (ATR neat, v_{max}): 2981, 2912, 1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.80 – 6.59 (m, 1H, N-CH), 5.24 – 5.07 (m, 1H, CH=CH), 5.07 – 4.87 (m, 1H, C=CH), 4.27 (s, 2H, N-CH_2), 4.19 (q, *J* = 7.1, 2H, O-CH_2), 1.68 (s, 3H, C-CH_3), 1.27 (t, 3H, *J* = 7.1, CH_2-CH_3); HRMS m/z (ESI+): $[M+H]^+$ calcd. for $C_9H_{14}NO_2^+$: 168.1025, found: 168.1032.

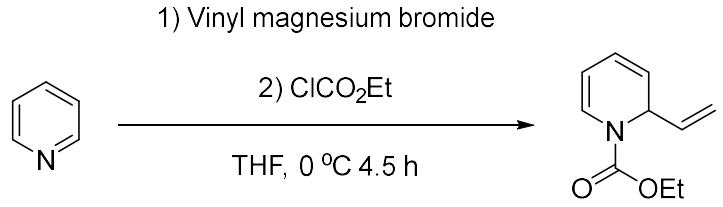
Data match that reported in literature.[83]

General procedure for Grignard addition 2:

Dry pyridine or 4-picoline (1 equiv.) was diluted in dry THF (~1 M) under argon and the solution cooled to 0 °C. The corresponding Grignard reagent (1.1 equiv.) was then added dropwise with stirring. The corresponding chloroformate (1.1 equiv.) was then added dropwise over a period of 30 minutes. The reaction mixture was then allowed to stir at 0 °C for a further 2.5-4 hours before an equal volume of water was added and the mixture allowed to reach room temperature. This was then extracted with three times with dichloromethane, the organics were combined, washed with brine, dried over magnesium sulphate, filtered and the solvent removed in vacuo. The resulting products were then used (where indicated) in the photoirradiation step without further purification.

NMR data for these mixtures lists the major component peaks (unless indicated), and the ratio of 1,2:1,4 dihydropyridines was determined based on relative integration of the appropriate peaks (indicated below).

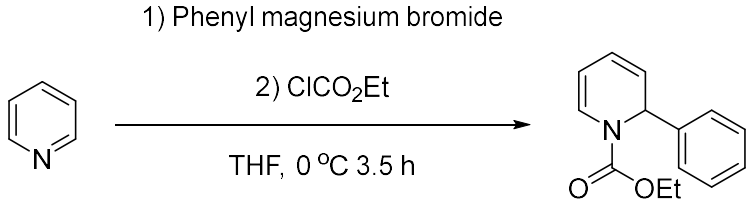
Ethyl 2-vinylpyridine-1(2H)-carboxylate (205):



205
77%

Following general procedure 2. Pyridine (2.2 mL), vinylmagnesium bromide (30.7 mL, 1 M), ethyl chloroformate (2.9 mL). Yielded 3.84 g, 77%. IR (ATR, neat) 2981, 1707, 1643 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 – 6.60 (m, 1H), 5.94 (dd, 1H, *J* = 9.5 Hz, 5.5 Hz), 5.85 – 5.69 (m, 1H), 5.58 – 5.43 (m, 1H), 5.31 – 5.01 (m, 4H), 4.26 – 4.17 (m, 2H, OC*H*$_2$), 1.28 (t, 3H, *J* = 7.0 Hz, C*H*$_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$, Rotamers denoted by *) δ 170.8 (C), 134.4 (CH), 125.5* (CH), 124.8 (CH), 122.1* (CH), 121.8 (CH), 120.5 (CH), 120.1* (CH), 115.2 (CH_2), 114.8* (CH_2), 105.1 (CH), 62.2 (CH_2), 54.2* (CH), 53.6 (CH), 14.5 (CH_3) ppm.

Ethyl 2-phenylpyridine-1(2H)-carboxylate (206):

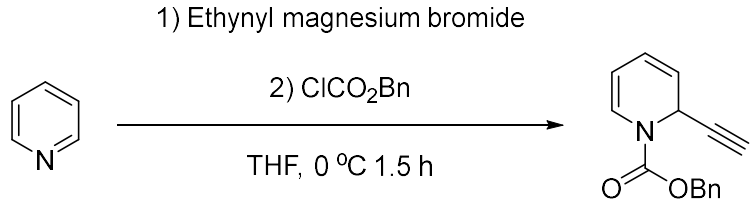


206
96%

Following general procedure 2: Pyridine (1.80 mL), phenylmagnesium bromide (8.00 mL, 3 M in diethyl ether), ethyl chloroformate (2.15 mL). Yielded 5.24 g, 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.25 (m, 5H, Ar*H*), 7.00 – 6.70 (m, 1H), 6.10 – 5.82 (m, 1H), 5.82 – 5.57 (m, 1H), 5.36 – 5.23 (m, 1H), 4.26 – 4.09 (m, 2H, OC*H*$_2$), 1.46 – 1.13 (m, 3H, C*H*$_3$) ppm; HRMS m/z (ESI^+): $[M+Na]^+$ calcd. for $C_{14}H_{15}NO_2Na^+$: 252.1000, found: 252.1082.

Data match that reported in literature.[110]

Methyl 2-ethynylpyridine-1(2H)-carboxylate (207):

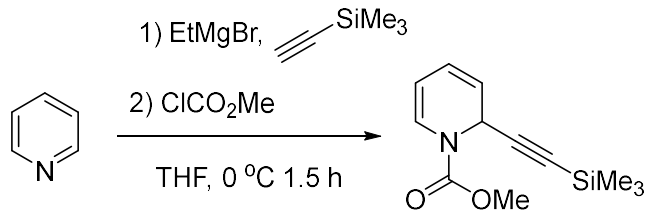


207
65%

Pyridine (1.40 mL, 17.4 mmol) was added to a solution of ethynylmagnesium bromide (0.5 M, 50 mL) in dry THF (50 mL) at 0 °C, under argon, with stirring. Benzyl chloroformate (3.40 mL, 23.9 mmol) was diluted in dry THF (10 mL) and the solution added dropwise to the pyridine solution over a period of 30 minutes. The reaction was allowed to stir for a further 1 hour before being poured over ice water (200 mL) and extracted into chloroform (3 x 50 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The resulting reside was purified by flash column chromatography (eluted with 10% ethyl acetate in pentane to yield the title compound (3.35 g, 65%). IR (ATR, neat) 3285, 1710, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.28 (m, 5H, Ar*H*), 6.91 – 6.70 (m, 1H), 6.04 – 5.96 (m, 1H), 5.71 – 5.48 (m, 2H), 5.46 – 5.19 (m, 3H), 2.37 (s, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$, Rotamers denoted by *) δ 152.8 (C), 135.7 (C), 128.6 (CH), 128.4* (CH), 128.3 (CH), 128.0 (CH), 125.4* (CH), 124.6 (CH), 122.8* (CH), 122.5 (CH), 118.5 (CH), 118.0* (CH), 105.4 (CH), 71.6 (CH), 68.4* (CH_2), 68.2 (CH_2), 43.7* (CH), 43.3 (CH) ppm; HRMS m/z (ESI^+): $[M+H]^+$ calcd. for $C_{15}H_{14}NO_2^+$ 240.1025, found: 240.1012; $[M+Na]^+$ calcd. for $C_{15}H_{13}NO_2Na^+$ 262.0844, found: 262.0838.

Data match that reported in literature.[129]

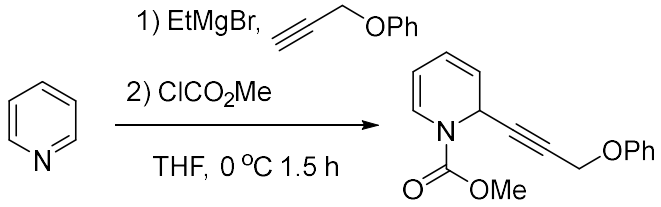
Ethyl 2-((trimethylsilyl)ethynyl)pyridine-1(2H)-carboxylate (208):



208
78%

Ethynyl trimethylsilane (2.90 mL, 20.9 mmol) was added to a stirring solution of ethyl magnesium bromide in THF (0.5 M, 50 mL) and the solution cooled to 0 °C. Pyridine (1.70 mL, 21.1 mmol) was added to this. Subsequently, a solution of methyl chloroformate (1.80 mL, 23.2 mmol) in THF (1.80 mL) was added dropwise over a period of 30 minutes, and stirring continued at 0 °C for a further 1 hour. The reaction mixture was then poured over ice water (300 mL) and the resulting mixture was extracted with ether (3 x 50 mL). The combined organic layers were dried over magnesium sulphate, filtered and the solvent removed in vacuo to give a crude product, which slowly crystallised. This was purified by flash chromatography on a short silica column, eluted with dichloromethane to yield the title compound as red/brown crystals (78%). m.p.: 38-39 °C; IR (ATR, neat) 3007, 2657, 2902, 2163, 1706, 1643 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 – 6.53 (m, 1H, NCH), 6.00 – 5.86 (m, 1H, NCH-C≡C), 5.69 – 5.38 (m, 2H, NCH-CH + NCHCH=CH), 5.38 – 5.24 (m, 1H, NCH=CH), 3.81 (s, 3H, O-CH_3), 0.11 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (Rotamers, 101 MHz, $CDCl_3$) δ 153.4 (C), 125.4 (CH), 124.7 (CH), 122.4 (CH), 122.0 (CH), 199.2 (CH), 118.5 (CH), 105.6 (CH), 102.5 (C), 87.8 (C), 53.5 (CH_3), 44.5 (CH), 44.0 (CH), -0.05 (CH_3); HRMS m/z (ESI+): $[M+H]^+$ calcd. for $C_{12}H_{18}NO_2Si^+$ 236.1101 found: 236.1099, $[M+Na]^+$ calcd. for $C_{12}H_{17}NNaO_2^+$ 258.0921, found: 258.0917.

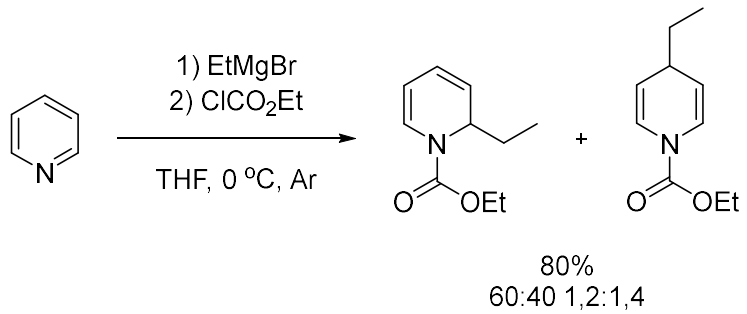
Ethyl 2-(3-phenoxyprop-1-yn-1-yl)pyridine-1(2H)-carboxylate (209):



209
88%

Ethyl magnesium bromide (7.40 mL, 3 M in diethyl ether) added at 0 °C to stirring THF (50 mL). To this was added phenyl propargyl ether (2.40 mL, 18.7 mmol) followed by pyridine (1.50 mL, 18.6 mmol). The addition funnel was charged with methyl chloroformate (1.60 mL, 20.7 mmol), which was then added dropwise to the stirring reaction mixture over a period of 30 minutes, followed by a further 1.5 hours of stirring upon addition completion. The reaction mixture was poured over ice water (200 mL) with stirring, and subsequently extracted with ether (3 x 50 mL), dried over magnesium sulphate, filtered and the solvent removed in vacuo to yield a yellow oil. This was purified by flash chromatography on silica, eluted with 10 % ethyl acetate in pentane, to yield the title compound as a viscous yellow oil (88%). IR (ATR, neat) 3040, 2954, 2856, 2087, 1715, 1646 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 2H, O-C_6H_5), 7.03 – 6.88 (m, 3H, O-C_6H_5), 6.86 – 6.59 (m, 1H, NCH), 5.96 (dd, 1H, *J* = 9.6, 5.4 Hz, NCH-C≡C), 5.72 – 5.44 (m, 2H, NCH-CH + NCHCH=CH), 5.45 – 5.22 (m, 1H, NCH=CH), 4.66 (s, 2H, $PhOCH_2$), 3.85 – 3.69 (m, 3H, O-CH_3); ^{13}C (Rotamers, 101 MHz, $CDCl_3$) δ 157.6 (C), 153.5 (C), 129.6 (CH), 125.4 (CH), 124.6 (CH), 122.7 (CH), 122.4 (CH), 121.4 (CH), 118.4 (CH), 117.8 (CH), 115.1 (CH), 105.4 (CH), 78.2 (C), 77.3 (C), 56.3 (CH_2), 53.5 (CH_3), 43.9 (CH), 43.5 (CH); HRMS m/z (ESI+): $[M+H]^+$ calcd. for $C_{16}H_{16}NO_3^+$ 270.1125, found: 270.1127, $[M+Na]^+$ calcd. for $C_{16}H_{15}NNaO_3^+$ 292.0924, found: 292.0951.

Ethyl 2-ethylpyridine-1(2H)-carboxylate (210):



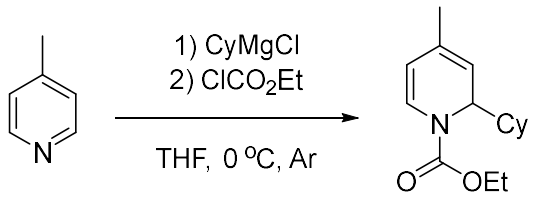
27.3 mmol pyridine. Orange oil; 80%; obtained as a mixture, relative integration = 6:4 (1,2:1,4; 5.90 vs. 2.90 ppm); IR (cm^{-1}) 2967, 2934, 2876, 1707, 1579; ^{1}H NMR (400 MHz, $CDCl_3$, contains both 1,2 and 1,4-dihydropyridines) δ 6.86 – 6.61 (m, 2H, 1,2- and 1,4- PyrH), 5.94 – 5.86 (m, 1H, 1,2- PyrH), 5.61 – 5.51 (m, 1H, 1,2- PyrH), 5.30 – 5.15 (m, 1H, 1,2- PyrH), 4.89 – 4.59 (m, 3H, 1x 1,2- PyrH and 2 x 1,4- PyrH), 4.28 – 4.15 (m, 4H, 1,2- and 1,4- O-CH_2CH_3), 2.90 (s, 1H, 1,4- PyrH), 1.71 – 1.57 (m, 1H, 1,2- $CH_3CH_aH_b$), 1.53 – 1.36 (m, 3H, 1,2- $CH_3CH_aH_b$ and 1,4- CH_3CH_2), 1.29 (t, 6H, *J* = 7.1 Hz, 1,2- and 1,4- OCH_2CH_3), 0.88 (t, 6H, *J* = 7.3 Hz, 1,2- and 1,4- CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$, Contains both 1,2 and 1,4-dihydropyridines, rotamers denoted by *, 1,4- denoted by †) δ 153.8 (C), 151.4† (C), 125.9* (CH), 125.1 (CH), 122.8† (CH), 122.6 (CH), 122.8 (CH), 121.7 (CH), 121.2* (CH), 110.2 (CH), 109.6† (CH), 105.8* (CH), 105.4 (CH), 62.2 (CH_2), 61.9† (CH_2), 53.4*† (CH), 53.1† (CH), 33.6† (CH), 30.5† (CH_2), 26.7 (CH_2), 14.5 (CH_3), 14.5 (CH_3), 14.4† (CH_3) 9.87 (CH_3), 8.70† (CH_3). HRMS m/z (ESI+): $[M+H]^+$ calcd. for $C_{10}H_{16}NO_2^+$: 182.1181, found: 182.1176; $[M+Na]^+$ calcd. for $C_{10}H_{15}NNaO_2^+$: 204.1000, found: 204.1003.

Ethyl 2-ethyl-4-methylpyridine-1(2H)-carboxylate (212):

95%

27.9 mmol 4-picoline. Yellow oil; 95%; IR (cm^{-1}) 2967, 2935, 1707, 1660, 1591; ^1H NMR (400 MHz, $CDCl_3$) δ 6.84 – 6.58 (m, 1H, NCH), 5.34 – 5.21 (m, 1H, CH=CH), 5.21 – 5.03 (m, 1H, C=CH), 4.69 – 4.51 (m, 1H, NCH-CH_2), 4.28 – 4.16 (m, 2H, O-CH_2), 1.75 (s, 3H, C-CH_3), 1.69 – 1.55 (m, 1H, CH_3-CH_aH_b), 1.55 – 1.38 (m, 1H, CH_3-CH_aH_b), 1.29 (t, 3H, *J* = 7.1, O-CH_2-CH_3), 0.87 (t, 3H, *J* = 7.7 Hz, CH_3CH_2-C); ^{13}C δ (101 MHz, $CDCl_3$), 153.7 (C), 149.6 (CH), 129.1 (C), 124.6 (CH), 117.6 (CH), 109.0 (CH), 62.0 (CH_2), 26.9 (CH_2), 20.5 (CH_3), 14.5 (CH_3), 8.8 (CH_3); HRMS m/z (ESI+): $[M+H]^+$ calcd. for $C_{11}H_{18}NO_2^+$: 196.1338, found: 196.1341; $[M+Na]^+$ calcd. for $C_{11}H_{17}NNaO_2^+$: 218.1157, found: 218.1154.

Ethyl 2-cyclohexyl-4-methylpyridine-1(2H)-carboxylate (213):



93%

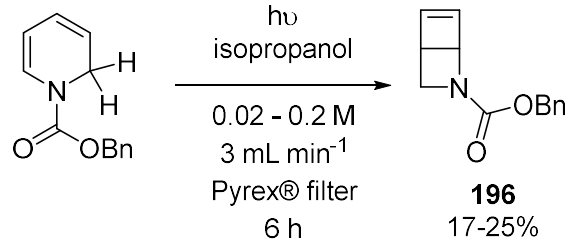
20.6 mmol 4-picoline. Orange oil; 93%; IR (ATR neat) 2934, 2852, 1710, 1688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.89 – 6.57 (m, 1H, NCH), 5.31 – 5.24 (m, 1H, CH=CH), 5.22 – 5.05 (m, 1H, C=CH), 4.73 – 4.35 (m, 1H, NCH-Cy), 4.26 – 4.14 (m, 2H, O-CH_2), 1.98 – 0.84 (m, 18H, CH-C_6H_{11} + CH_2-CH_3 + C-CH_3 + impurity); ^{13}C (101 MHz, $CDCl_3$) δ 151.6 (C), 149.6 (C), 125.1 (CH), 121.3 (CH), 116.7 (CH), 113.5 (CH), 109.9 (CH), 62.3 (CH_2), 48.9 (CH), 27.8 (CH_2), 26.8 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 26.1 (CH_2), 20.5 (CH_3), 14.5 (CH_3). HRMS m/z (ESI+): $[M+H]^+$ calcd. for

$C_{15}H_{24}NO_2^+$: 250.1807, found: 250.1797; $[M+Na]^+$ calcd. for $C_{15}H_{23}NNaO_2^+$: 272.1626, found: 272.1609.

Dihydropyridine photoirradiation, general procedure 3:

Crude dihydropyridine was diluted in degassed solvent under argon, such that the concentration of the resulting solution was 0.05 M. This was then degassed for a further 10-15 minutes before being pumped through FEP Reactor 3, fitted with a Pyrex® filter, at 20 rpm (~1.25 mL min^{-1}). Once this solution was depleted clean solvent was pumped through the reactor until clean solvent began to elute in the collection flask. The solvent was then removed in vacuo and the resulting residue purified on silica, eluted with diethyl ether or ethyl acetate and petroleum ether (as indicated below).

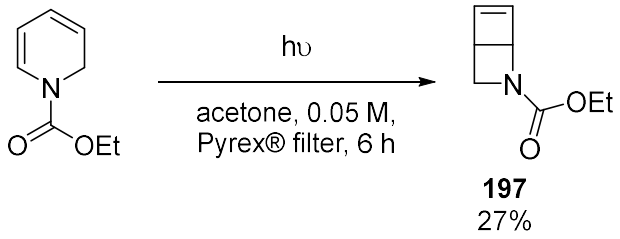
Benzyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (196):



Using general procedure 3: Gradient from 1:9 diethyl ether: petroleum ether to 1:1 diethyl ether: petroleum ether. Pale yellow oil, 25% yield. IR (ATR, neat) 2958, 2884, 1691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 5H, $CH_2C_6H_5$), 6.59 – 6.34 (m, 2H, CH=CH), 5.14 – 5.03 (m, 2H, $CH_2C_6H_5$), 4.90 – 4.76 (m, 1H, NCH), 4.01 – 3.89 (m, 1H, NCH_aH_b), 3.51 (ddd, 1H, *J* = 8.8, 2.7, 1.5 Hz, NCH_aH_b), 3.37 (m, 1H, NCH_2CH); ^{13}C (101 MHz, $CDCl_3$, Rotamers denoted by *) δ 156.8 (C), 143.1 (CH), 140.6 (CH), 140.2* (CH), 136.7 (C), 128.4 (CH), 127.9 (CH), 127.8* (CH), 66.4 (CH_2), 65.7 (CH), 65.1* (CH), 50.3 (CH_2), 49.3 (CH_2), 38.2 (CH); HRMS m/z (ESI+): $[M+H]^+$ calcd. for $C_{13}H_{14}NO_2^+$ 216.1025, found: 216.1026, $[M+Na]^+$: calcd. for $C_{13}H_{13}NNaO_2^+$: 238.0844, found: 238.0837.

Data match that reported in literature.[54]

Ethyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (197):

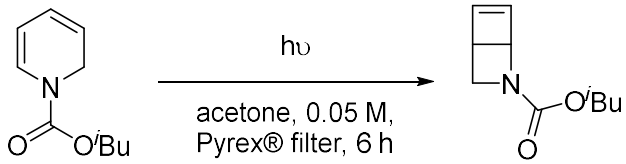


Using general procedure 3: 0.749 g, 4.89 mmol dihydropyridine. Eluent 1:1 diethyl ether : petroleum ether; Yellow oil; 27%; IR (ATR neat) 1975, 2886, 1698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 – 6.34 (m, 2H, CH=CH), 4.87 – 4.70 (m, 1H, NCH), 4.12 – 4.02 (m, 2H, O-CH_2), 3.91 (d, 1H, *J* = 8.0 Hz, NCH_aH_b), 3.49 – 3.41 (m, 1H, NCH_aH_b), 3.40 – 3.33 (m, 1H, CH_2-CH), 1.20 (t, 3H, *J* = 7.1 Hz, CH_3CH_2); ^{13}C (101 MHz, $CDCl_3$) δ 157.4 (C), 143.3 (CH), 140.3 (CH), 65.5 (CH), 60.7 (CH_2), 49.2 (CH_2), 38.2 (CH), 14.7 (CH_3);

HRMS m/z (ESI+): $[M+H]^+$ calcd. for $C_8H_{12}NO_2^+$ 154.0868, found: 154.0861, $[M+Na]^+$ calcd. for $C_8H_{11}NNaO_2^+$: 176.0687, found: 176.0687.

Data match that reported in literature.[62,74,85]

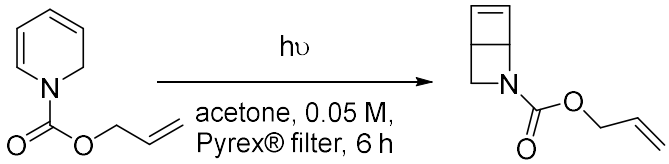
Isobutyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (198):



198
19%

Using general procedure 3: 0.899 g, 4.96 mmol dihydropyridine. Eluent 1:4 diethyl ether : petroleum ether; pale yellow oil; 19%; IR (ATR neat) 2960, 2876, 1702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.57 – 6.33 (m, 2H, CH=CH), 4.85 – 4.70 (m, 1H, NCH), 3.95 – 3.84 (m, 1H, NCH_aH_b), 3.44 (ddd, 1H, *J* = 8.7, 2.7, 1.5 Hz, NCH_aH_b), 3.38 – 3.33 (m, 1H, CH_2CH), 1.93 – 1.80 (m, 1H, $(CH_3)_2CH$), 0.87 (d, 6H, *J* = 6.8 Hz, $(CH_3)_2CH$); ^{13}C NMR (101MHz, $CDCl_3$) δ 157.7 (C), 143.3 (CH), 140.5 (CH), 71.0 (CH_2), 65.7 (CH), 49.3 (CH_2), 38.3 (CH), 27.9 (CH), 19.0 (CH_3); HRMS m/z (ESI+): $[M+H]^+$ calcd. for $C_{10}H_{16}NO_2^+$ 182.1181, found: 182.1177, $[M+Na]^+$ calcd. for $C_{10}H_{15}NNaO_2^+$ 204.1000, found: 204.0993.

Allyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (199):

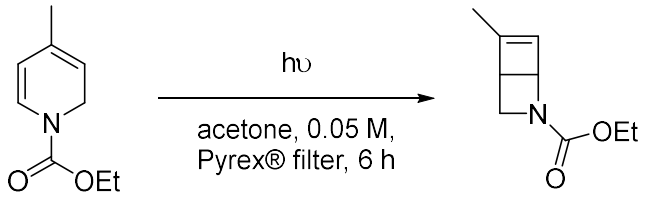


199
7%

Using general procedure 3: 0.820 g, 4.96 mmol dihydropyridine. Eluent 1:1 diethyl ether : petroleum ether; pale yellow oil; 0.057 g, 7%; ^1H NMR (400 MHz, $CDCl_3$) δ 6.61 – 6.37 (m, 2H, CH=CH), 5.98 – 5.82 (m, 1H, CH_2=CH), 5.37 – 5.10 (m, 2H, CH_2=CH), 4.89 – 4.76 (m, 1H, NCH_aH_b), 4.54 (d, 2H, *J* = 5.3 Hz, O-CH_2), 4.05 – 3.86 (m, 1H, NCH_aH_b), 3.54 – 3.43 (m, 1H, NCH), 3.45 – 3.34 (m, 1H, CH_2CH); ^{13}C (101 MHz, $CDCl_3$) δ 157.0 (C),

143.5 (CH), 140.5 (CH), 133.1 (CH), 117.5 (CH_2), 65.5 (CH_2), 49.4 (CH_2), 38.4 (CH), 30.0 (CH); HRMS m/z (ESI+): $[M+H]^+$ calcd for $C_9H_{12}NO_2^+$ 166.0868, found: 166.0859, $[M+Na]^+$ calcd for $C_9H_{11}NNaO_2^+$ 188.0687, found: 188.0685.

Ethyl 5-methyl-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (200):

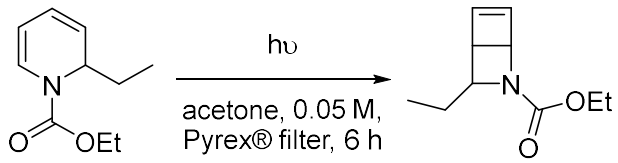


200
18%

Using general procedure 3: 0.873 g, 4.8 mmol dihydropyridine. Eluent 1:1 diethyl ether : petroleum ether; yellow oil; 0.157 g, 18%; IR (ATR neat) 2979, 2884, 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.27 – 6.06 (m, 1H, C=CH), 4.73 – 4.55 (m, 1H, NCH), 4.11 – 4.05 (m, 2H, OCH_2), 3.86 (app. t, 1H, *J* = 7.8 Hz, NCH_aH_b), 3.48 – 3.39 (m, 1H, NCH_aH_b), 3.30 – 3.18 (m, 1H, NCH_2CH), 1.79 (s, 3H, CH_3C), 1.21 (t, 3H, *J* = 7.1 Hz, OCH_2-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9 (C), 153.9 (C), 133.0 (CH), 62.1 (CH), 60.8 (CH_2), 48.6 (CH_2), 39.4 (CH), 15.4 (CH_3), 14.7 (CH_3); HRMS m/z (ESI+): $[M+H]^+$ calcd for $C_9H_{14}NO_2^+$ 168.1025, found: 168.1033, $[M+Na]^+$ calcd for $C_9H_{13}NNaO_2^+$ 190.0844, found: 190.0848, $[2M+Na]^+$ calcd for $C_{18}H_{26}N_2NaO_4^+$ 357.1790, found: 357.1791.

Data match that reported in literature.[83]

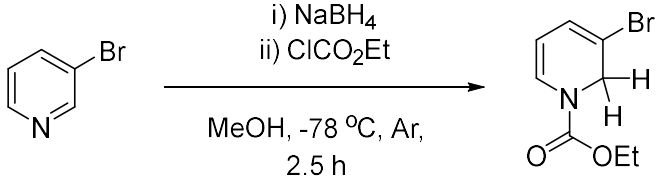
Ethyl 3-ethyl-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (219):



219
13%

Using general procedure 3: 1.08 g, 5.95 mmol dihydropyridine. Gradient elution 1:9 then 1:4 diethyl ether : petroleum ether; yellow oil; 0.140 g, 13%; IR (ATR neat) 2966, 2935, 1700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (app. s, 1H, NCHCH=CH), 6.32 (app. t, 1H, *J* = 3.0 Hz, NCHCH=CH), 4.77 – 4.64 (m, 1H, NCH), 4.15 – 3.93 (m, 3H, OCH_2-CH_3 + NCH-CH_2), 3.53 – 3.45 (m, 1H, NCH-CH), 2.13 – 1.75 (m, 1H, $NCHCH_aH_b$), 1.58 – 1.38 (m, 1H, $NCHCH_aH_b$), 1.19 (t, 3H, *J* = 7.1 Hz, O-CH_2CH_3), 0.80 (t, 3H, *J* = 7.5 Hz, CH_3CH_2CHN); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7 (C), 142.4 (CH), 140.5 (CH) 128.3 (CH), 127.7 (CH), 60.4 (OCH_2), 42.1 (CH_2), 23.6 (CH), 14.7 (CH_3), 9.06 (CH_3); HRMS m/z (ESI+): $[M+H]^+$ calcd for $C_{10}H_{16}NO_2^+$ 182.1181, found: 182.1178, $[M+Na]^+$ calcd for $C_{10}H_{15}NNaO_2^+$ 204.1000, found: 204.0993, $[2M+Na]^+$ calcd for $C_{20}H_{30}N_2NaO_4^+$ 385.2103, found: 385.2105.

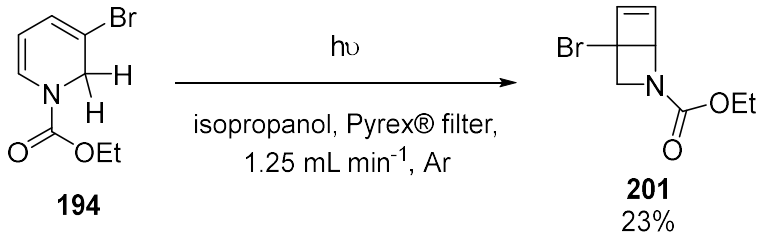
Ethyl 3-bromopyridine-1(2H)-carboxylate (194):



194
80%

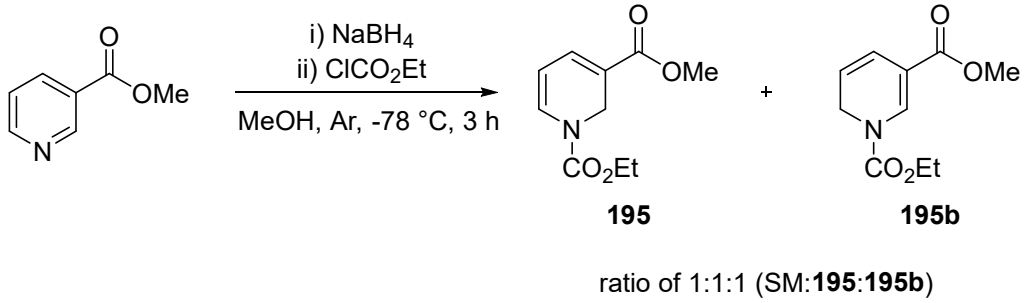
Following general procedure 1: 51.9 mmol 3-bromopyridine. Yellow oil; 9.89 g, 82%. This material was used in the photoirradiation step without purification. IR (ATR neat, v_{max}): 2981, 2934, 1711 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 – 6.63 (m, 1H, NCH), 6.15 (d, 1H, *J* = 6.1 Hz, BrC-CH), 5.08 – 4.94 (m, 1H, NCH-CH), 4.51 (s, 2H, NCH_2), 4.21 (q, 2H, *J* = 7.1 Hz, OCH_2), 1.31 – 1.25 (m, 3H, OCH_2-CH_3).

Ethyl 4-bromo-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (201):



Using general procedure 3: 1.18 g, 5.07 mmol dihydropyridine. Eluted with 20% ethyl acetate in petroleum ether. Colourless oil, 0.269 g, 23%. IR (ATR, neat) 2980, 2885, 1701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 – 6.43 (m, 2H, CH=CH), 4.96 (br s, 1H, CH_aH_b), 4.23 (d, 1H, *J* = 9.48 Hz, N-CH), 4.15 – 4.06 (m, 3H, OCH_2 + CH_aH_b), 1.23 (t, 3H, *J* = 7.10 Hz, OCH_2-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (C), 144.0 (CH), 137.9 (CH), 72.1 (CH), 68.0 (CH_2), 61.1 (CH_2), 49.3 (C), 14.4 (CH_3); HRMS m/z (ESI+): calcd for $C_8H_{11}{}^{79}BrNO_2{}^{+}$ 231.9973, found: 231.9951, calcd for $C_8H_{11}{}^{81}BrNO_2{}^{+}$ 233.9953, found: 233.9941, calcd. for $C_8H_{10}{}^{79}BrNO_2Na^{+}$ 253.9793, found: 253.9777, calcd for $C_8H_{10}{}^{81}BrNO_2Na^{+}$ 255.9772, found: 255.9768.

1-ethyl 3-methyl pyridine-1,3(2H)-dicarboxylate (195):

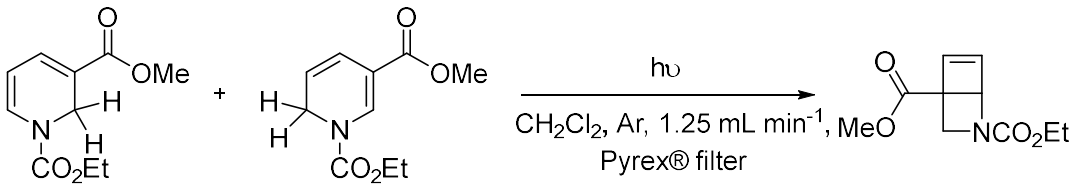


ratio of 1:1:1 (SM:**195**:**195b**)

Methyl nicotinate (13.0 g, 94.6 mmol) was dissolved in dry methanol under argon and cooled to -78 °C. Sodium borohydride (3.95 g, 104 mmol) was then added with stirring. Ethyl chloroformate (9.90 mL, 104 mmol) was added dropwise *via* addition funnel at a rate which prevented the reaction mixture exceeding -60 °C. Upon complete addition the reaction was stirred for a further 3 hours before being poured onto ice water. This was then stirred until bubbling had ceased and extracted into dichloromethane (3 x 20 mL). The organics were combined, dried over magnesium sulfate,

filtered and the solvent removed in vacuo. The resulting residue (18.8 g, 94% crude yield) contained a 1:1:1 mixture of the starting material, 1,2-dihyropyridine (**195**) and the 1,6-dihydropyridine (by relative integration of peaks at 8.74 ppm, 5.23 ppm and 2.98 ppm). This mixture was used in the photoirradiation step without purification.

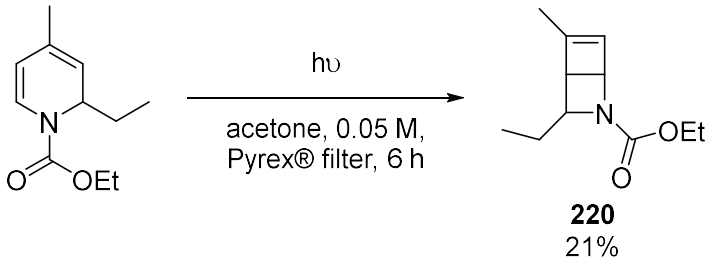
2-ethyl 4-methyl 2-azabicyclo[2.2.0]hex-5-ene-2,4-dicarboxylate (202):



202

195 (15.4 g) was diluted in dichloromethane. This was degassed by ultrasonic vibration with argon passed through the solution, before being pumped through the FEP reactor at 1.25 mL min^{-1}. The solvent was then removed in vacuo, and the residue purified by flash column chromatography (eluted with 30% ethyl acetate in pentane) to give the desired product (**202**, 4.65 g, 32%). IR (ATR neat): 2981, 2955, 1731, 1700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.66-6.42 (m, 2H, CH=CH), 4.84 (s, 1H, NCH), 4.34-4.15 (m, 1H, NCH_aH_b), 4.16-4.01 (m, 2H, OCH_2), 3.71 (s, 3H, OCH_3), 3.67-3.57 (m, 1H, NCH_aH_b), 1.21 (t, 3H, J=7.0 Hz, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4 (C), 156.7 (C), 141.2 (CH), 141.1 (CH), 67.3 (CH), 61.4 (CH_2), 52.3 (CH_3), 50.8 (CH_2), 49.5 (C), 14.7 (CH_3); HRMS m/z (ESI+): calcd for $C_{10}H_{13}NO_4Na^+$ 234.0742 found 234.0702 [$M+Na^+$].

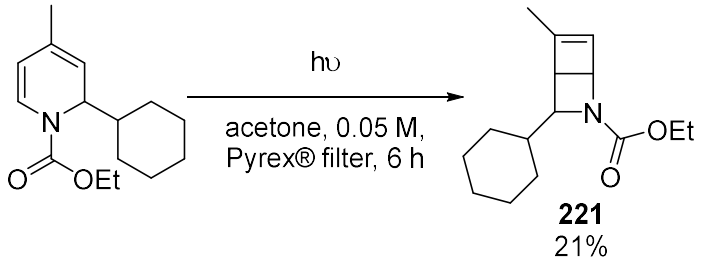
Ethyl 3-ethyl-5-methyl-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (220):



220
21%

Using general procedure 3: 0.959 g, 4.9 mmol dihydropyridine. Eluent 1:1 diethyl ether : petroleum ether; yellow oil; 0.201 g, 21%; IR (ATR, neat) 2972, 2938, 2880, 1699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (app. s, 1H, C=CH), 4.56 (app. s, 1H, NCH), 4.16 – 3.96 (m, 3H, O-CH_2CH_3 + NCH-CH_2), 3.43 – 3.34 (m, 1H, NCHCH), 2.30 – 1.86 (m, 1H, $NCHCH_aH_b$), 1.80 (s, 3H, C-CH_3), 1.53 – 1.38 (m, 1H, $NCHCH_aH_b$), 0.88 (t, 3H, *J* = 7.5 Hz, OCH_2-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8 (C), 134.5 (CH), 123.2 (CH), 122.1 (CH) 62.0 (CH), 60.4 (CH_2), 53.5 (C), 43.4 (CH_2), 16.9 (CH_3), 14.7 (CH_3), 9.92 (CH_3); HRMS m/z (ESI+): $[M+H]^+$ calcd for $C_{11}H_{18}NO_2^+$ 196.1338, found: 196.1327, $[M+Na]^+$ calcd for $C_{11}H_{17}NNaO_2^+$ 218.1157, found: 218.1153, $[2M+Na]^+$ calcd for $C_{22}H_{34}N_2NaO_4^+$ 413.2416, found: 413.2416.

Ethyl 3-cyclohexyl-5-methyl-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (221):

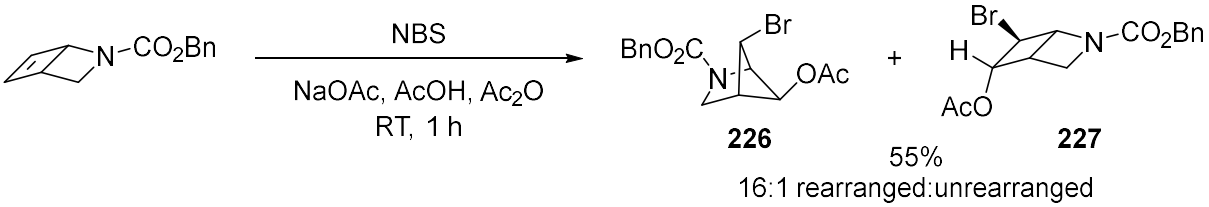


221
21%

Using general procedure 3: 1.27 g, 5.08 mmol dihydropyridine. Gradient elution 1:9 diethyl ether : petroleum ether then 1:1 diethyl ether : petroleum ether; pale yellow oil; 0.266 g, 21%; IR (ATR, neat) 2923, 2852, 1718, 1686 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 – 6.14 (m, 1H, C=CH), 4.68 – 4.56 (m, 1H, NCH), 4.15 – 3.99 (m, 2H, O-CH_2), 3.74 (dd, 1H, *J* =

10.3, 7.6 Hz, NCH-Cy), 3.45 – 3.33 (m, 1H, C-CH-CHN), 1.89 – 1.45 (m, 10H, CyH + CH_3-C=CH), 1.34 – 0.80 (m, 7H, CyH + OCH_2-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3 (C), 151.9 (C), 134.6 (CH), 65.6 (CH), 60.7 (CH_2), 60.6 (CH), 44.2 (CH), 41.2 (CH), 30.5 (CH_2), 29.1 (CH_2), 26.3 (CH_2), 25.8 (CH_2), 25.5 (CH_2), 17.0 (CH_3), 14.7 (CH_3); HRMS m/z (ESI+): $[M+H]^+$ calcd for $C_{15}H_{24}NO_2^+$ 250.1807, found: 250.1803, $[M+Na]^+$ calcd for $C_{15}H_{23}NNaO_2^+$ 272.1626, found: 272.1622, $[2M+Na]^+$ calcd for $C_{30}H_{46}N_2NaO_4^+$ 521.3355, found: 521.3367.

Benzyl (1R*,4S*,5S*,6R*)-5-acetoxy-6-bromo-2-azabicyclo[2.1.1]hexane-2-carboxylate (226):

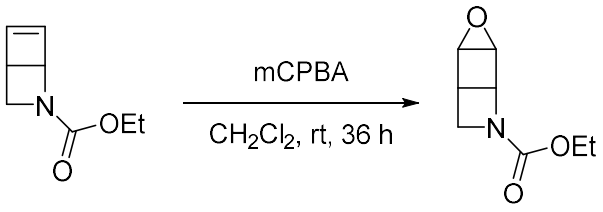


To acetic acid (8 mL) was added acetic anhydride (0.2 mL, 2.12 mmol), sodium acetate (0.210 g, 2.56 mmol) and benzyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (0.218 g, 1.01 mmol) with stirring. To this was added *N*-bromosuccinimide (0.452 g, 2.54 mmol) in portions over a period of 10 minutes. The reaction was allowed to stir at room temperature for a further 1 hour. It was subsequently diluted with water (25 mL) and extracted with ether (3 x 10 mL). The combined organics were then dried over magnesium sulphate, filtered and the solvent removed in vacuo. The resulting residue was purified by flash chromatography on silica, eluted with 50% diethyl ether in petroleum ether to give a 16:1 mixture of the rearranged and unrearranged products (0.195 g, 55%). IR (ATR, ν_{max}): 3033, 2962, 2901, 1740, 1704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 5H, $CH_2C_6H_5$), 5.15 (s, 2H, $C_6H_5CH_2$), 4.73 – 4.64 (d, 1H, *J* = 5.4 Hz, AcO-CH), 4.59 (d, 1H, *J* = 6.7 Hz, NCH), 4.02 (d, 1H, *J* = 7.1 Hz, BrCH), 3.65 – 3.52 (m, 2H, NCH_2), 3.21 – 3.08 (m, 1H, N-CH_2CH), 2.12 (s, 3H, OAc), ^{13}C NMR (101 MHz, $CDCl_3$, rotamers denoted by *) δ 175.9 (C), 170.6 (C), 136.1

(C), 128.6 (CH), 128.3* (CH), 128.1* (CH), 83.0 (CH_3), 67.5 (CH), 67.0 (CH_2), 64.7 (CH), 50.3 (CH), 48.9 (CH_2) 48.2* (CH), 21.2 (CH); HRMS m/z (ESI+): $[M+Na]^+$ calcd for $C_{15}H_{16}NNaO_4Br^+$ 376.0160 and 378.0140, found: 376.0166 and 378.0148.

Data match that reported in literature.[89]

Ethyl 3-oxa-6-azatricyclo[3.2.0.02,4]heptane-6-carboxylate (234):

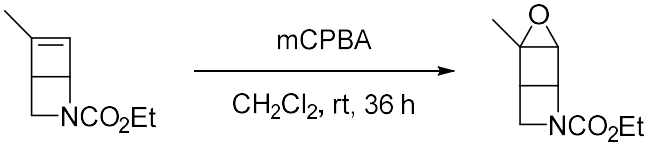


234
63%

Dewar dihydropyridine (**197**) (0.197 g, 1.29 mmol) was dissolved in dichloromethane (5 mL) with stirring. A suspension of mCPBA (0.448 g, 2.60 mmol) was then added dropwise. The reaction mixture was then allowed to stir for 36 hours then diluted with a further 15 mL dichloromethane. This was then washed with saturated $Na_2S_2O_3$ (aq.), then brine, then dried over $MgSO_4$, filtered and the solvent removed in vacuo. The residue (0.245 g) was purified by column chromatography (eluent: 10% - 20% ethyl acetate in petroleum ether) to yield the desired product **234** as a pale-yellow oil (0.141 g, 65%). IR (ATR neat): 2980, 2891, 1696 cm^{-1}; ^{1}NMR (400 MHz, $CDCl_3$): δ 4.51-4.40 (m, 1H, NCHCHO), 4.32-4.17 (m, 1H, NCHCHCHO), 4.17-4.10 (m, 2H, CH_3CH_2), 4.10-4.05 (m, 1H, NCH_aH_b), 4.06-4.04 (m, 1H, NCH_aH_b), 3.89 (d, 1H, *J* = 9.2 Hz, NCH), 2.98-2.93 (m, 1H, CH_2CH), 1.25 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl^3$): δ 156.2 (C), 67.7 (CH), 67.4* (CH), 61.2 (CH_2), 55.9 (CH), 55.7 (CH), 48.5 (CH_2), 47.7* (CH_2), 39.9 (CH), 14.7 (CH_3); HRMS m/z (ESI+): calcd for $C_8H_{12}NO_3$: 170.0817, found: 170.0802 $[M+H^+]$, calcd for $C_8H_{11}NO_3Na$: 192.0637, found 192.0632 $[M+Na^+]$.

Data match that reported in literature.[114]

Ethyl 2-methyl-3-oxa-6-azatricyclo[3.2.0.02,4]heptane-6-carboxylate (235):

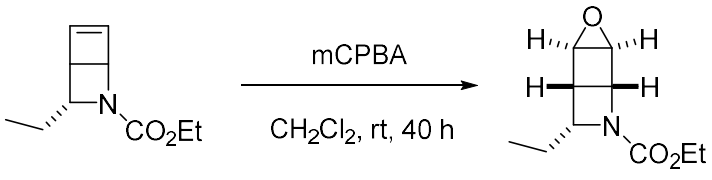


235
50%

Dewar dihydropyridine (**200**) (4.97 g, 29.7 mmol) was dissolved in dichloromethane (50 mL) with stirring. A suspension of mCPBA (10.2 g, 51.9 mmol) in dichloromethane (25 mL) was then added slowly. The reaction mixture was then allowed to stir for 36 hours then diluted with a further 25 mL dichloromethane. This was then washed with saturated $NaHCO_3$, then brine, then dried over $MgSO_4$, filtered and the solvent removed in vacuo. The residue was purified by trituration (petroleum ether) to yield the desired product **235** as a pale yellow oil (2.730 g, 50%). IR (ATR neat): 2980, 2930, 2891, 1702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.45-4.28 (m, 1H, NCH), 4.19-3.99 (m, 4H, OCH_2 + NCH_2), 3.83 (d, 1H, J=9.5 Hz, OCH), 2.94-2.85 (m, 1H, NCH_2CH), 1.57 (s, 3H, $OCCH_3$), 1.23 (t, 3H, J=7.1 Hz, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl^3$): δ 156.3 (C), 65.9 (CH), 64.1 (CH), 61.2 (CH_2), 53.5 (CH), 48.7+48.0* (CH), 41.7 (CH_2), 14.6 (CH_3), 12.1 (CH_3); HRMS m/z (ESI+): calcd for $C_9H_{13}NO_3Na$: 206.0793, found: 206.0796 [$M+Na^+$].

Data match that reported in literature.[114]

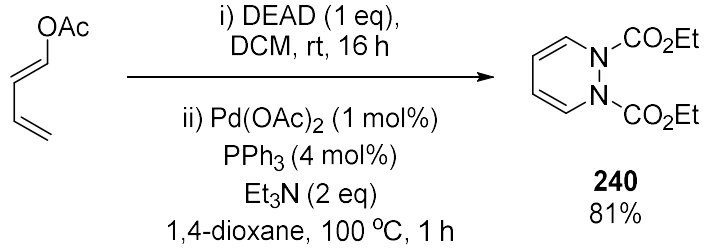
Ethyl 7-ethyl-3-oxa-6-azatricyclo[3.2.0.02,4]heptane-6-carboxylate (236):



219 **236** 34%

Dewar heterocycle (**219**) (0.203 g, 1.03 mmol) was dissolved in dichloromethane (5 mL) and a suspension of mCPBA (0.383 g, 2.22 mmol) in dichloromethane (1 mL) was added to the stirring solution in a dropwise fashion. The reaction mixture was allowed to stir for 40 hours before being diluted with dichloromethane (10 mL), washing with saturated $NaHCO_3$, dried over $MgSO_4$, filtered and the solvent removed in vacuo. The residue was then purified by column chromatography (eluent: 5% - 20% ethyl acetate/petroleum ether) to give the desired product (0.076 g, 34%). IR (ATR neat): 2967, 2936, 2880, 1698 cm^{-1}; ^{1}NMR (400 MHz, $CDCl_3$): 4.39 (s, 1H, OCH), 4.24-4.14 (m, 2H, CH_3CH_2CH + N-CH), 4.13-4.05 (m, 2H, OCH_2CH_3), 3.97 (dd, 1H, *J* = 4.4 Hz, 1.9 Hz, OCH), 2.98 (dt, 1H, *J* = 6.9 Hz, 3.3 Hz, CH_3CH_2CHCH), 2.10 (br s, 1H, $CH_3CH_aH_b$), 1.83-1.67 (m, 1H, $CH_3CH_aH_b$), 1.22 (t, 3H, *J* = 7.1 Hz, CH_3CH_2-O), 0.92 (t, 3H, *J* = 7.5 Hz, $CH_3CH_aH_b$); ^{13}C NMR (101 MHz, $CDCl^3$): 162.7 (C), 132.8 (CH), 130.0* (CH), 129.7 (CH), 128.1 (CH), 60.9 (CH_2), 56.8 (CH), 53.7 (CH), 24.8 (CH_2), 14.7 (CH_3), 9.6 (CH_3); HRMS m/z (ESI+): calcd for $C_{10}H_{16}NO_3$: 198.1130, found: 198.1129 [M+H^+]; calcd for $C_{10}H_{15}NO_3Na$ 220.0950, found: 220.0944 [M+Na^+].

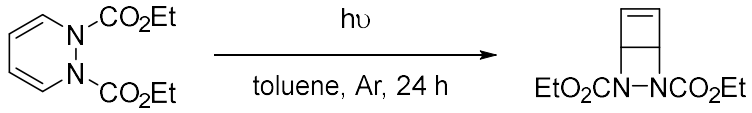
Diethyl pyridazine-1,2-dicarboxylate (240):



diethyl azodicarboxylate (500 μL, 3.19 mmol) was diluted in dichloromethane (1 mL) and 1-acetoxy-1,3-butadiene (0.5 mL, 4.28 mmol) added in one portion with stirring. The reaction mixture was stirred for 16 h before the solvent was removed in vacuo. The resulting colourless residue was purified by short column chromatography (eluent: ethyl acetate: petroleum ether 5:1 – 2:1) and the purified residue (0.95 g) stored in a desiccator overnight. The residue was then diluted in 1,4-dioxane (5 mL) and added to a mixture of $Pd(OAc)_2$ (7 mg, 0.031 mmol), PPh_3 (35 mg, 0.133 mmol) and triethylamine (0.9 mL, 6.41 mmol) under argon, in a sealed microwave vial. This was heated at 100 °C for 1 hour, after which time the reaction mixture was cooled to room temperature and the solvent removed in vacuo. The resulting residue was purified by column chromatography (eluent: 10% ethyl acetate/petroleum ether) to yield the desired product as an off-white solid (0.585 g, 81%). IR (ATR neat): 3088, 2991, 1755, 1717 cm^{-1}; ^{1}NMR (400 MHz, $CDCl_3$): δ 6.72 (2H, s, NCH), 5.66 (2H, s, NCHCH), 4.27 (4H, q, *J* = 7.3 Hz, CH_3CH_2), 1.31 (t, 6H, *J* = 7.3 Hz, CH_3CH_2); ^{13}C NMR (101 MHz, $CDCl_3$, rotamers denoted by *): 153.2 (C), 127.7 (CH), 113.4* (CH), 112.1 (CH), 63.0 (CH_2), 14.5 (CH_3) δ; HRMS m/z (ESI+): $[M+H^+]$ calcd for $C_{10}H_{15}N_2O_4^+$: 227.1032, found 227.1024; $[M+Na]^+$ calcd. for $C_{10}H_{14}N_2NaO_4^+$: 249.0851, found: 249.0844.

Data match that reported in literature.[124]

Diethyl 2,3-diazabicyclo[2.2.0]hex-5-ene-2,3-dicarboxylate (241):

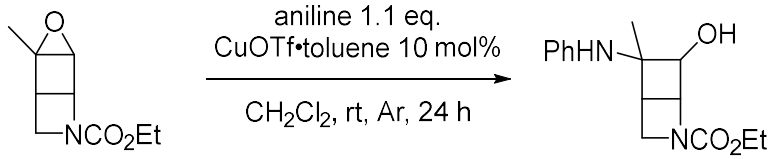


240 **241**
48%

240 (0.585 g, 2.59 mmol) dissolved in toluene (100 mL) and the solution degassed by sonication under argon. The solution was then irradiated for 24 hours with stirring using a 400 W medium-pressure mercury arc lamp. The solvent was then removed in vacuo and the residue purified by column chromatography (eluent: 40% ethyl acetate/petroleum ether) to give the desired product (0.280 g, 48%). IR (ATR neat): 2983, 2938, 1745, 1704 cm^{-1}; ^{1}NMR (400 MHz, $CDCl_3$): 6.71 (d, 2H, *J* = 3.6 Hz, CH=CH), 5.16 (d, 2H, *J* = 3.6 Hz, CH-CH), 4.27-4.18 (m, 4H, CH_3-CH_2), 1.28 (t, 6H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$: 159.9 (C), 143.4 (CH), 67.2 (CH), 62.7 (CH_2), 14.6 (CH_3); HRMS m/z (ESI+): $[M+H^+]$ calcd for $C_{10}H_{15}N_2O_4^+$: 227.1032, found 227.1037; $[M+Na]^+$ calcd. for $C_{10}H_{14}N_2NaO_4^+$: 249.0851, found: 249.0861.

Data match that reported in literature.[37]

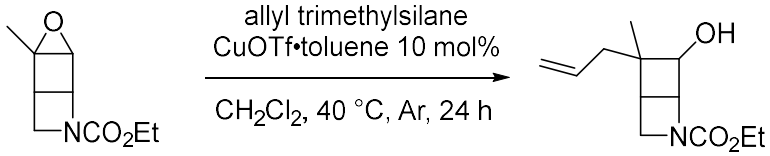
Ethyl 6-hydroxy-5-methyl-5-(phenylamino)-2-azabicyclo[2.2.0]hexane-2-carboxylate (237):



235 **237**
68%

Epoxide **235** (195 mg, 0.714 mmol) was diluted in dichloromethane (2 mL). Copper triflate toluene complex (57 mg, 10 mol%) was then added with stirring under argon. Aniline (0.12 mL, 1.31 mmol) was then added and the reaction allowed to stir at room temperature for 20 hours. The reaction mixture was concentrated, then purified by flash column chromatography (eluted with 30% ethyl acetate in pentane) to give the desired product (0.199 g, 68%). IR (ATR neat): 3361 (br), 2977, 2917, 1686, 1669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 7.27 – 7.15 (m, 2H, ArH), 6.86 – 6.70 (m, 3H, ArH), 6.04 – 5.84 (m, 1H, NCH), 5.75 – 5.58 (m, 1H, CHOH), 4.42 – 4.10 (m, 4H, OCH_2, NCH_aH_b, OH), 4.09 – 3.91 (m, 1H, NCH_2CH), 3.59 – 3.44 (m, 1H, NCH_aH_b), 1.94 (s, 3H, $NHCCH_3$), 1.33 – 1.20 (m, 4H, OCH_2CH_3, NH) δ; ^{13}C NMR (101 MHz, $CDCl_3$, rotamers denoted by *): δ 145.2 (C), 132.2 (C), 129.3 (CH), 122.5 (CH), 118.7 (CH), 114.3* (CH), 113.9 (CH), 70.4 (CH), 65.2 (CH), 64.1* (CH), 61.6 (CH_2), 60.2 (C), 39.4 (CH_2), 21.3 (CH_3), 14.2 (CH_3) ppm; HRMS m/z (ESI+): calcd for $C_{15}H_{20}N_2O_3Na$: 299.1372, found: 299.1358 [$M+Na^+$].

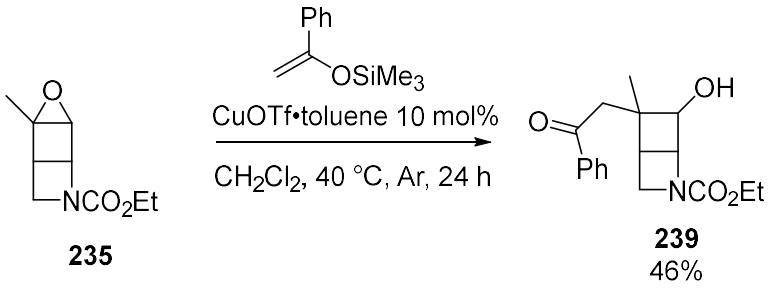
Ethyl 5-allyl-6-hydroxy-5-methyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (238):



235 **238** 24%

Epoxide (**235**) (0.103 g, 0.457 mmol) was diluted in dichloromethane (1 mL) and copper triflate toluene complex (0.028 g, 10 mol %) added with stirring under argon. Allyltrimethylsilane (0.02 mL, 0.126 mmol) was then added and the reaction mixture allowed to stir at 40 °C for 20 hours. The reaction mixture was concentrated and purified by flash column chromatography to give the desired product (**238** g, 24%). IR (ATR neat): 3410 (br.), 2979, 2917, 1693, 1675 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90-5.62 (m, 1H, CH_2=CH), 5.61-5.38 (m, 1H, OHCH), 5.11-4.94 (m, 2H, CH=CH_2), 4.55-3.97 (m, 4H, CH_aH_b + OCH_2CH_3 + NCH), 3.83-3.65 (m, 1H, NCH_2CH), 3.58-3.37 (m, 1H, NCH_aH_b), 2.70 (br. s, 1H, OH), 2.27-1.99 (m, 2H, CH_2=CH-CH_2), 1.83 (s, 3H, CCH_3), 1.33-1.18 (m, 3H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl^3$, rotamers denoted by *): δ 157.0 (C), 134.6 (CH), 134.4* (CH), 121.0 (CH) 120.5* (CH), 117.6 (CH_2), 77.3 (C), 70.0 (CH), 62.0* (CH_2), 61.5 (CH_2), 56.2 (CH), 55.9* (CH), 40.0 (CH_2), 34.3 (CH_2), 21.3 (CH_3), 14.4 (CH_3); HRMS m/z (ESI+): $[M+H]^+$ calcd for $C_{12}H_{20}NO_3^+$: 226.1443, found: 226.1442; $[M+Na]^+$ calcd. for $C_{12}H_{19}NNaO_3^+$: 248.1263, found: 248.1255.

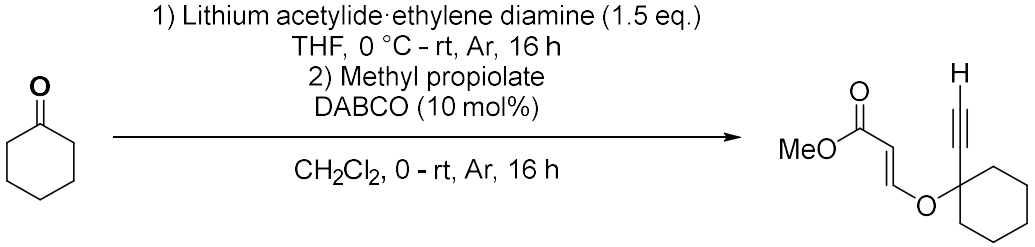
Ethyl 6-hydroxy-5-methyl-5-(2-oxo-2-phenylethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (239):



235 **239** 46%

Epoxide (**235**) (0.106 g, 0.579 mmol) was diluted in dichloromethane (1 mL) and copper triflate toluene complex added (0.027 g, 10 mol%). 1-phenyl-1-trimethylsiloxyethylene (0.12 mL, 0.579 mmol) was then added and the reaction mixture allowed to stir at 40 °C for 20 hours. The reaction mixture was then concentrated and purified by flash column chromatography (eluted with 30% ethyl acetate in pentane) to give the desired product (0.081 g, 46%). IR (ATR neat): 3417 (br.), 2980, 2916, 2849, 1673cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, 2H, J=7.8 Hz, ArH), 7.58-7.48 (m, 1H, ArH), 7.43 (t, 2H, J=7.8 Hz, ArH), 5.65-5.44 (m, 1H, OHCH), 5.04-4.84 (m, 1H, NCH), 4.40-4.20 (m, 1H, NCH_aH_b), 4.19-3.72 (m, 3H, OCH_2 + NCH_2CH), 3.66-3.49 (m, 1H, NCH_aH_b), 3.14-2.88 (m, 2H, CCH_2), 2.76 (br. s, 1H, OH), 1.81 (s, 3H, CCH_3), 1.26-0.99 (m, 3H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl^3$, rotamers denoted by *): δ 197.5 (C), 156.3 (C), 136.7 (C), 133.4 (CH), 128.7 (CH), 128.2 (CH), 121.1 (CH), 120.6* (CH), 70.0 (CH), 61.5 (CH_2), 60.3 (C), 53.8 (CH), 53.3* (CH), 40.4 (CH_2), 39.2 (CH_2), 21.3 (CH_3), 14.0 (CH_3); HRMS m/z (ESI+): $[M+H]^+$ calcd for $C_{17}H_{22}NO_4^+$: 304.1549, found: 304.1548; $[M+Na]^+$ calcd. for $C_{17}H_{21}NNaO_4^+$: 326.1368, found: 326.1372; $[2M+Na]^+$ calcd. for $C_{34}H_{42}N_2NaO_8$: 629.2839, found: 629.2871.

Methyl (E)-3-((1-ethynylcyclohexyl)oxy)acrylate (223):



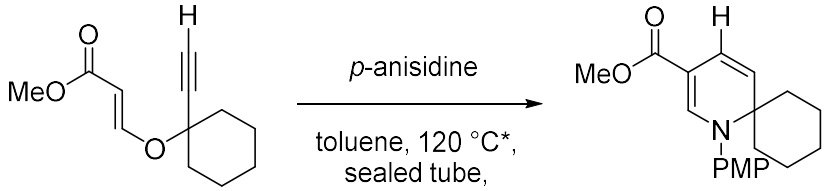
223
R = Cy, 38%

Cyclohexanone (10 mL, 9.48 g, 96.5 mmol) was diluted in tetrahydrofuran (500 mL) under argon, and the solution cooled to 0 °C with stirring. To this was added lithium acetylide ethylene diamine complex (15.0 g, 163 mmol) in portions with stirring. The resulting solution was allowed to stir for a further 16 hours without additional cooling before addition of saturated ammonium chloride solution (50 mL). This was then extracted into ethyl acetate (3 x 25 mL), the organics combined, dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting residue was then purified on a short silica gel column (eluted with 10% ethyl acetate in pentane). The resulting alcohol (5.5 g, 44.3 mmol) was diluted in dichloromethane (250 mL) in oven dried glassware under argon. DABCO (0.5 g, 10 mol%) was then added with stirring and the solution cooled to 0 °C. Methyl propiolate (5.9 mL, 66.3 mmol) was then added dropwise over 10 minutes and the resulting solution allowed to stir without additional cooling for a further 16 hours. The solution was concentrated in vacuo and the residue purified by flash column chromatography (eluted with 10% ethyl acetate in pentane) to yield the title compound as a colourless oil (3.48 g, 38%). IR (ν_{max}, cm^{-1}): 2939, 2863, 1707, 1638; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, 1H, *J* = 12.1 Hz, O=CCH), 5.37 (d, 1H, *J* = 12.1 Hz, CyOCH), 3.66 (s, 3H, OCH_3), 2.66 (s, 1H, C≡CH), 1.97-1.88 (m, 2H, Cy), 1.76-1.61 (m, 4H, Cy), 1.60-1.43 (m, 3H, Cy), 1.37-1.21 (m, 1H, Cy); ^{13}C NMR (101 MHz, $CDCl^3$): δ 168.0 (C), 158.0 (CH), 99.1 (CH), 76.5 (CH), 51.0 (CH_3), 37.5 (CH_2), 24.5 (CH_2), 22.1 (CH_2); HRMS m/z (ESI+): [M+Na^+] calcd for

$C_{12}H_{16}O_3Na^+$ 231.0997 found: 231.0999, [2M+Na^+] calcd for $C_{24}H_{32}O_6Na^+$ 439.2097 found 439.2102.

Data match that reported in literature.[130]

Methyl 1-(4-methoxyphenyl)-1-azaspiro[5.5]undeca-2,4-diene-3-carboxylate (224):

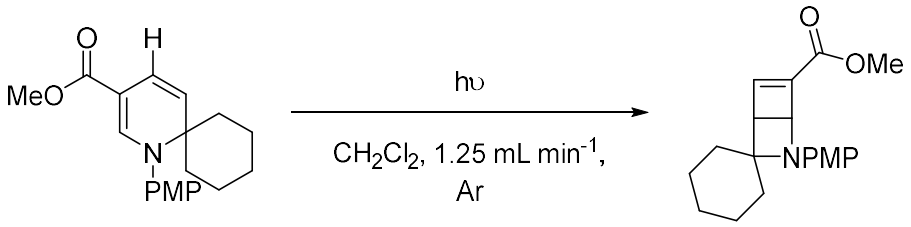


224
68%

Propargyl vinyl ether (**223**) (1 g, 4.80 mmol) was diluted in dry toluene (5 mL) in an oven dried microwave vial, under argon. *p*-anisidine (0.651 g, 5.20 mmol) was added and the microwave vial sealed. This was then irradiated on a Biotage microwave reactor at 120 °C for 3 hours with 20 minutes of pre-stirring. The solution was then concentrated in vacuo and the residue purified by flash column chromatography (eluted with 10% ethyl acetate in pentane) to yield the title compound (1.04 g, 69%). IR (ν_{max}, cm^{-1}): 2933, 2859, 1685; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, 1H, J=1.2 Hz, NCH), 7.12-7.08 (m, 2H, ArH), 6.87-6.82 (m, 2H, ArH), 6.47 (d, 1H, J=9.9Hz, CyCHCH), 5.34 (d, 1H, *J* = 9.9Hz, CyCH), 3.79 (s, 3H, CO_2CH_3), 3.66 (s, 3H, $ArOCH_3$), 2.06-1.96 (m, 2H, Cy), 1.61-1.47 (m, 5H, Cy), 1.38-1.28 (m, 2H, Cy), 1.03-0.85 (m, 1H, Cy); ^{13}C NMR (101 MHz, $CDCl^3$): δ 167.3 (C), 159.0 (C), 147.2 (CH), 130.9 (CH), 120.8 (CH), 115.6 (CH), 113.9 (CH), 98.8 (C), 60.3 (CH_2), 55.3 (CH_3), 50.7 (CH_3), 35.9 (CH_2), 25.3 (CH_2), 21.3 (CH_2) ppm; HRMS m/z (ESI+): $[M+H]^+$ calcd for $C_{19}H_{24}NO_3^+$: 314.1756, found: 314.1749; $[M+Na]^+$ calcd. for $C_{19}H_{23}NNaO_3^+$: 336.1576, found: 336.1570.

Data match that reported in literature.[69]

Methyl 3-(4-methoxyphenyl)-3-azaspiro[bicyclo[2.2.0]hexane-2,1'-cyclohexan]-5-ene-5-carboxylate (225):



225
11%

Dihydropyridine (**224**) (1.02 g, 3.25 mmol) was diluted in dichloromethane (100 mL) and degassed under argon by sonication for 15 minutes. The solution was then pumped through the FEP photochemical reactor (internal volume = ~200 mL) fitted with a Pyrex® filter sleeve, at a rate of 1.25 mL min^{-1}, and the eluted solution collected. The solvent was then removed in vacuo and the residue purified by flash column chromatography (eluted with 10% ethyl acetate in pentane) to yield the title compound (0.110 g, 11%). IR (v_{max}, cm^{-1}): 2929, 2857, 1683, 1626; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, 1H, J=3.2 Hz, C=CH), 6.80-6.75 (m, 2H, ArH), 6.73-6.68 (m, 2H, ArH), 4.85 (t, 1H, J=3.2 Hz, NCCH), 3.75 (s, 3H, CO_2CH_3), 3.73 (s, 3H, $ArOCH_3$), 3.28 (d, 1H, J=3.2 Hz, NCH), 2.19-2.03 (m, 1H, CyH), 1.91-1.61 (m, 6H, CyH), 1.32-1.13 (m, 3H, CyH); ^{13}C NMR (101 MHz, $CDCl^3$): δ 162.2 (C), 149.3 (CH), 114.7 (CH), 112.7 (CH), 58.7 (CH), 55.8 (CH_3), 51.4 (CH_3), 43.6 (CH), 36.4 (CH_2), 31.1 (CH_2), 25.3 (CH_2), 23.3 (CH_2), 22.1 (CH_2); HRMS m/z (ESI+): [$M+Na^+$] calcd for $C_{19}H_{23}NO_3Na^+$ 336.1576 found 336.1570.

6 References

1 K. I. Booker-Milburn, B. D. A. Hook, W. Dohle, P. R. Hirst, M. Pickworth and M. B. Berry, *J. Org. Chem.*, 2005, **70**, 7558–7564.

2 F. Mao, W. Ni, X. Xu, H. Wang, J. Wang, M. Ji and J. Li, *Molecules*, 2016, **21**, 1–18.

3 A. Barker, J. G. Kettle, T. Nowak and J. E. Pease, *Drug Discov. Today*, 2013, **18**, 298–304.

4 S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451–3479.

5 F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756.

6 F. Lovering, *MedChemComm*, 2013, **4**, 515–519.

7 M. D. Burke and S. L. Schreiber, *Angew. Chemie - Int. Ed.*, 2004, **43**, 46–58.

8 J. D. Hughes, J. Blagg, D. A. Price, S. Bailey, G. A. DeCrescenzo, R. V. Devraj, E. Ellsworth, Y. M. Fobian, M. E. Gibbs, R. W. Gilles, N. Greene, E. Huang, T. Krieger-Burke, J. Loesel, T. Wager, L. Whiteley and Y. Zhang, *Bioorganic Med. Chem. Lett.*, 2008, **18**, 4872–4875.

9 N. Greene and M. Song, *Future Med. Chem.*, 2011, **3**, 1503–1511.

10 M. M. Hann, A. R. Leach and G. Harper, *J. Chem. Inf. Comput. Sci.*, 2001, **41**, 856–864.

11 P. A. Clemons, N. E. Bodycombe, H. A. Carrinski, J. A. Wilson, A. F. Shamji, B. K. Wagner, A. N. Koehler and S. L. Schreiber, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 18787–18792.

12 N. Hoffmann, *Chem. Rev.*, 2008, **108**, 1052–1103.

13 T. Bach and J. P. Hehn, *Angew. Chemie - Int. Ed.*, 2011, **50**, 1000–1045.

14 M. D. Kärkäs, J. A. Porco and C. R. J. Stephenson, *Chem. Rev.*, 2016, **116**, 9683–9747.

15 H. D. Roth, *Angew. Chemie Int. Ed. English*, 1989, **28**, 1193–1207.

16 O. L. Chapman and L. F. Englert, *J. Am. Chem. Soc.*, 1963, **85**, 3028–3029.

17 M. H. Fisch and J. H. Richards, *J. Am. Chem. Soc.*, 1963, **85**, 3029–3030.

18 D. H. R. Barton, P. de Mayo and M. Shafiq, *J. Chem. Soc.*, 1958, 140–145.

19 E. E. van Tamelen, K. Kirk and G. Brieger, *Tetrahedron Lett.*, 1962, **21**, 939–943.

20 N. El Achi, F. Gelat, N. P. Cheval, A. Mazzah, Y. Bakkour, M. Penhoat, L. Chausette-Boissarie and C. Rolando, *React. Chem. Eng.*, 2019, **4**, 828–837.

21 L. Buglioni, F. Raymenants, A. Slattery, S. D. A. Zondag and T. Noël, *Chem. Rev.*, 2022, **122**, 2752–2906.

22 E. E. Coyle and M. Oelgemöller, *Photochem. Photobiol. Sci.*, 2008, **7**, 1313–1322.

23 K. I. Booker-milburn, J. P. Knowles and L. D. Elliott, *Beilstein J. Org. Chem.*, 2012, **8**, 2025–2052.

24 L. D. Elliott, J. P. Knowles, C. S. Stacey, D. J. Klauber and K. I. Booker-Milburn, *React. Chem. Eng.*, 2018, **3**, 86–93.

25 F. Lévesque and P. H. Seeberger, *Angew. Chemie - Int. Ed.*, 2012, **51**, 1706–1709.

26 M. B. Plutschack, B. Pieber, K. Gilmore and P. H. Seeberger, *Chem. Rev.*, 2017, **117**, 11796–11893.

27 M. G. Constantino, M. Beltrame Jr., G. Valdo José da Silva and J.

Zukerman-Schpector, *Synth. Commun.*, 1996, **26**, 321–329.

28 R. J. Roth and N. Acton, *J. Chem. Educ.*, 1991, **68**, 612–613.

29 E. E. Blackham, J. P. Knowles, J. Burgess and K. I. Booker-Milburn, *Chem. Sci.*, 2016, **7**, 2302–2307.

30 K. G. Maskill, J. P. Knowles, L. D. Elliott, R. W. Alder and K. I. Booker-Milburn, *Angew. Chemie - Int. Ed.*, 2013, **52**, 1499–1502.

31 R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, 1965, **87**, 395–397.

32 Y. Kobayashi and I. Kumadaki, in *Advances in Heterocyclic Chemistry*, 1st edn., 1982, vol. 31, pp. 169–206.

33 M. D'Auria, in *Advances in Heterocyclic Chemistry*, ed. A. R. Katritzky, Academic Press, London, 2001, vol. 79, pp. 41–88.

34 Y. Kobayashi, I. Kumadaki, A. Ohsawa and A. Ando, *J. Am. Chem. Soc.*, 1977, **99**, 7350–7351.

35 R. W. Ward, A. C. Day and J. A. Barltrop, *J. Chem. Soc. Chem. Commun.*, 1978, 131–133.

36 B. Melillo, J. Zoller, B. K. Hua, O. Verho, J. C. Borghs, S. D. Nelson, M. Maetani, M. J. Wawer, P. A. Clemons and S. L. Schreiber, *J. Am. Chem. Soc.*, 2018, **140**, 11784–11790.

37 T. K. Britten, P. D. Kemmitt, N. R. Halcovitch and S. C. Coote, *Org. Lett.*, 2019, **21**, 9232–9235.

38 E. J. Corey and J. Streith, *J. Am. Chem. Soc.*, 1964, **86**, 950–951.

39 W. H. Pirkle and L. H. McKendry, *J. Am. Chem. Soc.*, 1969, **91**, 1179–1186.

40 H. Javaheripour and D. C. Neckers, *J. Org. Chem.*, 1977, **42**, 1844–1850.

41 R. H. Wiley and N. R. Smith, *Org. Synth.*, 1951, **31**, 23.

42 N. Maulide, F. Frébault, M. Luparia, M. T. Oliveira and R. Goddard, *Angew. Chemie Int. Ed.*, 2010, **49**, 5672–5676.

43 N. Maulide, C. Souris, M. Luparia, F. Frébault, D. Audisio, C. Farès and R. Goddard, *Chem. - A Eur. J.*, 2013, **19**, 6566–6570.

44 R. Matsushima and K. Terada, *J. Chem. Soc. Perkin Trans. 2*, 1985, 1445.

45 V. Ramamurthy and J. Sivaguru, *Chem. Rev.*, 2016, **116**, 9914–9993.

46 J. K. Kershaw, N. J. Lennard, M. Jones, S. J. M. Jones, P. J. Solenberg, T. Bach, H. Bergmann and K. Harms, *Angew. Chemie - Int. Ed.*, 2000, **39**, 2302–2304.

47 T. Bach and H. Bergmann, *J. Am. Chem. Soc.*, 2000, **122**, 11525–11526.

48 T. Bach, H. Bergmann and K. Harms, *Org. Lett.*, 2001, **3**, 601–603.

49 M. F. A. Adamo, P. Disetti and L. Piras, *Tetrahedron Lett.*, 2009, **50**, 3580–3584.

50 N. Gauvry and F. Huet, *J. Org. Chem.*, 2001, **66**, 583–588.

51 D. Margetic, R. A. Russel and R. N. Warrener, *Synlett*, 1997, **1997**, 38–40.

52 T. Tsuchiya, N. Kakusawa, T. Yoneda and J. Kurita, *Heterocycles*, 1987, **26**, 3085–3088.

53 T. Tsuchiya, N. Kakusawa, T. Yoneda and J. Kurita, *Chem. Pharm. Bull.*, 1990, **38**, 2911–2918.

54 J. Kurita, K. Iwata, H. Sakai and T. Tsuchiya, *Chem. Pharm. Bull.*, 1985, **33**, 4572–4580.

55 H. Hongo, K. Iwasa, C. Kabuto, H. Matsuzaki and H. Nakano, *J. Chem. Soc. - Perkin Trans. 1*, 1997, 1747–1754.

56 H. Hongo and H. Nakano, *Chem. Pharm. Bull.*, 1993, **41**, 1885–1887.

57 K. E. Wilzbach and D. J. Rausch, *J. Am. Chem. Soc.*, 1970, **92(7)**, 2178–2179.

58 V. K. Sharma and S. K. Singh, *RSC Adv.*, 2017, **7**, 2682–2732.

59 U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1–42.

60 C. A. Bear, W. R. Cullen, V. E. Ridaura, J. Trotter, A. Zanarotti and J. P. Kutney, *Angew. Chem., Int. Ed. Engl*, 1973, **95**, 3058–3060.

61 S. G. Davies and M. R. Shipton, *J. Chem. Soc. Perkin Trans. 1*, 1991, 757–764.

62 F. W. Fowler, *J. Org. Chem.*, 1972, **37**, 1321–1323.

63 E. E. Knaus and K. Redda, *Can. J. Chem.*, 1977, **55**, 1788–1791.

64 C. S. Giam, E. E. Knaus and F. M. Pasutto, *J. Org. Chem.*, 1974, **39**, 3565–3568.

65 F. R. Francis, W. Davis and J. T. Wisener, *J. Org. Chem.*, 1974, **39**, 59–62.

66 D. L. Comins and N. B. Mantlo, *J. Org. Chem.*, 1985, **50**, 4410–4411.

67 D. L. Comins, A. H. Abdullah and N. B. Mantlo, *Tetrahedron Lett.*, 1984, **25**, 4867–4870.

68 C. Nadeau, S. Aly and K. Belyk, *J. Am. Chem. Soc*, 2011, **133**, 2878–2880.

69 D. Tejedor, L. Cotos, G. Méndez-Abt and F. García-Tellado, *J. Org. Chem.*, 2014, **79**, 10655–10661.

70 D. Tejedor, G. Méndez-Abt and F. García-Tellado, *Chem. - A Eur. J.*, 2010, **16**, 428–431.

71 T. Harschneck and S. F. Kirsch, *J. Org. Chem*, 2011, **76**, 2145–2156.

72 J. T. Binder and S. F. Kirsch, *Org. Lett.*, 2006, **8**, 2151–2153.

73 H. Wei, Y. Wang, B. Yue and P. F. Xu, *Adv. Synth. Catal.*, 2010, **352**, 2450–2454.

74 F. W. Fowler, P. Beeken, J. N. Bonfiglio, I. Hasan, J. J. Piwinski, B. Weinstein and K. A. Zollo, *J. Am. Chem. Soc.*, 1979, **101**, 6677–6682.

75 G. R. Krow, Y. B. Lee, W. S. Lester, N. Liu, J. Yuan, J. Duo, S. B. Herzon, Y. Nguyen and D. Zacharias, *J. Org. Chem.*, 2001, **66**, 1805–1810.

76 M. Regitz, G. Michels, J. Fink and G. Maas, *Tetrahedron Lett.*, 1985, **26**, 3315–3318.

77 G. R. Krow, J. Yuan, Q. Huang, M. D. Meyer, D. J. Anderson, J. E. Campbell and P. J. Carroll, *Tetrahedron*, 2000, **56**, 9233–9239.

78 J. Kurita, K. Iwata and T. Tsuchiya, *J. Chem. Soc., Chem. Comm.*, 1986, **574**, 1188–1189.

79 J. Kurita, K. Iwata and T. Tsuchiya, *Chem. Pharm. Bull.*, 1987, **35**, 3166–3174.

80 T. Tsuchiya, M. Hasebe, K. Iwata and J. Kurita, *J. Chem. Soc., Chem. Comm.*, 1983, **628**, 941–942.

81 R. K. Warrener and G. Kretschmer, *J. Chem. Soc., Chem. Comm.*, 1977, **0**, 806–807.

82 G. R. Krow, G. Lin, K. P. Moore, A. M. Thomas, C. DeBbrosse, C. W. Ross and H. G. Ramjit, *Org. Lett.*, 2004, **6**, 1669–1672.

83 G. R. Krow, Y. B. Lee, W. S. Lester, N. Liu, J. Yuan, J. Duo, S. B. Herzon, Y. Nguyen and D. Zacharias, *J. Org. Chem.*, 2001, **66**,

1805–1810.

84 G. R. Krow, G. Lin, D. Rapolu, Y. Fang, W. S. Lester, S. B. Herzon and P. E. Sonnet, *J. Org. Chem.*, 2003, **68**, 5292–5299.

85 C. L. Jenkins, G. Lin, J. Duo, D. Rapolu, I. A. Guzei, R. T. Raines and G. R. Krow, *J. Org. Chem.*, 2004, **69**, 8565–8573.

86 Y. A. Arakawa, T. M. Urakami, Y. A. Arakawa and S. Y. Oshifuji, *Chem. Pharm. Bull*, 2003, **51**, 96–97.

87 G. R. Krow, W. S. Lester, G. Lin, Y. Fang and P. J. Carroll, *J. Org. Chem.*, 2003, **68**, 1626–1629.

88 S. Pusch, D. Schollmeyer and T. Opatz, *European J. Org. Chem.*, 2018, **2018**, 1204–1207.

89 G. R. Krow, J. Yuan, G. Lin and P. E. Sonnet, *Org. Lett.*, 2002, **4**, 1259–1262.

90 T. Waldron-Clarke, *University of Nottingham, Unpublished works*, .

91 K. Hiroya, *Arkivoc*, 2003, **8**, 232–246.

92 M. Matsumoto, M. Yamada and N. Watanabe, *Chem. Commun.*, 2005, 483–5.

93 E. A. Porter, B. Weisblum and S. H. Gellman, *J. Am. Chem. Soc.*, 2002, **124**, 7324–7330.

94 D. J. Aitken, C. Gauzy and E. Pereira, *Tetrahedron Lett.*, 2002, **43**, 6177–6179.

95 D. J. Aitken, C. Gauzy and E. Pereira, *Tetrahedron Lett.*, 2004, **45**, 2359–2361.

96 Z. Szakonyi and F. Fülöp, *Arkivoc*, 2003, **14**, 225–232.

97 B. You Hamer, K., Lewis, W., Dowden, J., *Chem. Commun.*, 2013, **49**, 5–7.

98 P. Almendros, C. Aragoncillo, G. Cabrero, R. Callejo, R. Carrascosa, A. Luna, T. M. Del Campo, M. C. Pardo, M. T. Quirós, M. C. Redondo, C. Rodríguez-Ranera, A. Rodríguez-Vicente and M. P. Ruizb, *Arkivoc*, 2010, 74–92.

99 R. Kaul, S. Surprenant and W. D. Lubell, *J. Org. Chem.*, 2005, **70**, 3838–3844.

100 T. Douglas, A. Pordea and J. Dowden, *Org. Lett.*, 2017, acs.orglett.7b03252.

101 J. Day, B. McKeever-Abbas and J. Dowden, *Angew. Chemie - Int. Ed.*, 2016, **55**, 5809–5813.

102 K. Hassenrück, H. Höchstetter, H. Martin, A. Steigel and H. Wingen, *Chem. Ber.*, 1987, **120**, 203–212.

103 W. W. Wladimiroff, *Photochem. Photobiol.*, 1966, **5**, 243–250.

104 B. Muel and C. Malpiece, *Photochem. Photobiol.*, 1969, **10**, 283–291.

105 J. D. Williams, Y. Otake, G. Coussanes, I. Saridakis, N. Maulide and C. O. Kappe, *ChemPhotoChem*, 2019, **3**, 229–232.

106 D. L. Comins, K. Higuchi and D. W. Young, *Dihydropyridine preparation and application in the synthesis of pyridine derivatives*, Elsevier, 2013, vol. 110.

107 U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1–42.

108 A. Delgado, *Chem. Rev.*, 1982, 82, 223–243.

109 E. M. P. Silva, P. A. M. M. Varandas and A. M. S. Silva, *Developments in the synthesis of 1,2-dihydropyridines*, 2013, vol. 45.

110 D. L. Comins and A. H. Abdullah, *J. Org. Chem.*, 1982, **47**, 4315–4319.

111 R. Yamaguchi, M. Moriyasu, M. Yoshioka and M. Kawanisi, *J. Org. Chem.*, 1985, **50**, 287–288.

112 G. Bertuzzi, L. Bernardi and M. Fochi, *Catalysts*, 2018, **8**, 1–36.

113 G. R. Krow, G. Lin and F. Yu, *J. Org. Chem.*, 2005, **70**, 590–5.

114 G. R. Krow, W. S. Lester, N. Liu, J. Yuan, A. Hiller, J. Duo, S. B. Herzon, Y. Nguyen and K. Cannon, *J. Org. Chem.*, 2001, **66**, 1811–1817.

115 H. Nguyen and M. R. Gagné, *ACS Catal.*, 2014, **4**, 855–859.

116 C. A. Roselli and M. R. Gagné, *Org. Biomol. Chem.*, 2016, **14**, 11261–11265.

117 Y. Yamamoto, *J. Org. Chem.*, 2007, **72**, 7817–7831.

118 A. Fürstner and P. W. Davies, *Angew. Chemie Int. Ed.*, 2007, 46, 3410–3449.

119 J. Zhang, C. G. Yang and C. He, *J. Am. Chem. Soc.*, 2006, **128**, 1798–1799.

120 A. R. Chianese, S. J. Lee and M. R. Gagné, *Angew. Chemie Int. Ed.*, 2007, **46**, 4042–4059.

121 K. N. Houk, J. Liu, N. C. Demello and K. R. Condroski, *J. Am. Chem. Soc.*, 1997, **119**, 10147–10152.

122 X. L. Hou, J. Wu and L. X. Dai, *Chin. J. Chem.*, 1998, **16**, 557–560.

123 A. Dattagupta and V. K. Singh, *Tetrahedron Lett*, 1998, **63**, 34.

124 T. K. Britten, G. R. Akien, P. D. Kemmitt, N. R. Halcovitch and S. C. Coote, *Tetrahedron Lett.*, 2019, **60**, 1498–1500.

125 C. A. Clark, D. S. Lee, S. J. Pickering, M. Poliakoff and M. W. George, *Org. Process Res. Dev.*, 2016, **20**, 1792–1798.

126 R. C. De Selms and W. R. Schleigh, *Tetrahedron Lett.*, 1972, **34**,

68–70.

127 G. Hu, J. Xu and P. Li, *Org. Biomol. Chem.*, 2018, **16**, 4151.

128 P. A. Baguley and J. C. Walton, *J. Chem. Soc., Perkin Trans*.

129 C. Xie, M. T. C. Runnegar and B. B. Snider, *J. Am. Chem. Soc.*, 2000, **122**, 5017–5024.

130 D. Tejedor, S. J. Álvarez-Méndez, J. M. López-Soria, V. S. Martín and F. García-Tellado, *European J. Org. Chem.*, 2014, **2014**, 198–205.