4-$\pi$ Photocyclisation:
A New Route to Functionalised
Four-Membered Rings

Thomas Britten

This dissertation is submitted for the degree of Doctor of Philosophy

April 2019

School of Chemistry
Dedicated to Elsie Daisy Alice Moore (1916-2018)

and Karin Dixon Wilkins (1962-2015)
Declaration

This thesis has not been submitted in support of an application for another degree at this or any other university. It is the result of my own work and includes nothing that is the outcome of work done in collaboration except where specifically indicated. Many of the ideas in this thesis were the product of discussion with my supervisor Dr Susannah Coote.

Thomas K. Britten MChem

Lancaster University, UK
Abstract
The work disclosed within this thesis describes the use of photochemistry to develop efficient and scalable methodology to access functionalised four-membered rings.

Chapter 2 examines the synthesis and synthetic potential of 1,2-dihydropyridazines. The feasibility of the current literature syntheses of 1,2-dihydropyridazines on multigram scales has been investigated, which has resulted in the development of a novel, scalable route to unsubstituted 1,2-dihydropyridazines. Currently, the synthesis is not amenable to the synthesis of substituted 1,2-dihydropyridazines. 1,2-Dihydropyridazines are precursors to interesting molecular scaffolds through double bond transformations, however in some cases the isolated product was not the expected product.

Chapter 3 investigates the optimisation and scale up of the 4-π photocyclisation of 1,2-dihydropyridazines using commercially available batch and flow photoreactors. The use of a batch photoreactor gave better yields, purity and productivity for the synthesis of bicyclic 1,2-diazetidines compared to the flow photoreactor. The photophysical properties of 1,2-dihydropyridazines have been studied and the data has provided guidance for optimisation and rationale for the observed results.

Chapter 4 explores the stability and synthetic potential of bicyclic 1,2-diazetidines to access functionalised 1,2-diazetidines, cyclobutenes and other products that were not expected at the outset of the project. Attempts to access cyclobutenes (through N-N cleavage) were unsuccessful due to a facile 4-π electrocyclic ring opening, whereas it was possible to synthesis a range of novel monocyclic functionalised 1,2-diazetidines.

Chapter 5 provides overall conclusions, as well as a comparison of the synthesised compounds to Lipinski’s “rule of five” and lead-like space using open access software and ideas for future work.

Chapters 6 and 7 will provide the experimental details and characterisation of novel compounds that have been reported in this thesis. The appendix gives details on the X-ray crystal structures and differential scanning calorimetry traces for a select few examples.
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Firstly, I would like to thank my supervisor Dr Susannah Coote for all her help, support and guidance throughout my PhD. In the same manner, I would like to thank my industry supervisor Dr Paul Kemmitt for your support, input into the project and making me feel welcome when I completed my placement at AstraZeneca. A special thank you my second supervisor Dr Mike Coogan, Dr Nicholas Evans, as well as my appraisal panel members Dr Vilius Franckevicius and Dr Verena Görtz. In addition, I would like to thank Lancaster University and AstraZeneca for funding my PhD project, as well as the Society of Chemical Industry (SCI) for a scholarship to support my studies.

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>absorbance</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>ADMET</td>
<td>absorption, distribution, metabolism, excretion and toxicity</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2'-azobis(2-methylpropionitrile)</td>
</tr>
<tr>
<td>Aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>unspecified aryl group</td>
</tr>
<tr>
<td>APCI</td>
<td>atmospheric pressure chemical ionization</td>
</tr>
<tr>
<td>ATR</td>
<td>attenuated total reflection</td>
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<tr>
<td>BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butylloxy carbonyl</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>c</td>
<td>concentration</td>
</tr>
<tr>
<td>C</td>
<td>centigrade</td>
</tr>
<tr>
<td>CAN</td>
<td>cerium ammonium nitrate</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexane</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>D</td>
<td>dimensional</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DBAD</td>
<td>di-tert-butyl azodicarboxylate</td>
</tr>
<tr>
<td>DBB</td>
<td>di-tert-butylbiphenyl</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicycloundec-7-ene</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DMAD</td>
<td>dimethyl azodicarboxylate</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Name</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMEDA</td>
<td>1,2-dimethylethylenediamine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>DPAD</td>
<td>diphenyl azodicarboxylate</td>
</tr>
<tr>
<td>dppp</td>
<td>1,3-bis(diphenylphosphino)propane</td>
</tr>
<tr>
<td>DSC</td>
<td>differential scanning calorimetry</td>
</tr>
<tr>
<td>EDG</td>
<td>electron donating group</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>Eq</td>
<td>equivalents</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>FTIR</td>
<td>fourier transform infrared</td>
</tr>
<tr>
<td>h</td>
<td>Planck's constant (6.626 x 10^{-34} Js)</td>
</tr>
<tr>
<td>HMBC</td>
<td>heteronuclear multiple-bond coherence</td>
</tr>
<tr>
<td>HMDS</td>
<td>bis(trimethylsilyl)amine</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>hr(s)</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HSQC</td>
<td>heteronuclear single quantum coherence</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>i</td>
<td>iso</td>
</tr>
<tr>
<td>IBDA</td>
<td>iodobenzene diacetate</td>
</tr>
<tr>
<td>IBX</td>
<td>2-iodoxybenzoic acid</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>ISC</td>
<td>intersystem crossing</td>
</tr>
<tr>
<td>IT</td>
<td>ion trap</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>I</td>
<td>path length</td>
</tr>
<tr>
<td>LED</td>
<td>light-emitting diode</td>
</tr>
<tr>
<td>LLAMA</td>
<td>lead-likeness and molecular analysis</td>
</tr>
<tr>
<td>logP</td>
<td>octanol-water partition coefficient</td>
</tr>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chloroperxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeTAD</td>
<td>4-methyl-1,2,4-triazoline-3,5-dione</td>
</tr>
<tr>
<td>Mes</td>
<td>mesitylene</td>
</tr>
<tr>
<td>MIDA</td>
<td>methyliminodiacetic acid</td>
</tr>
<tr>
<td>mins</td>
<td>minutes</td>
</tr>
<tr>
<td>mL</td>
<td>millilitre</td>
</tr>
<tr>
<td>mm</td>
<td>millimetre</td>
</tr>
<tr>
<td>mmol</td>
<td>millimole</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl (mesyl)</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>MTBE</td>
<td>methyl tert-butyl ether</td>
</tr>
<tr>
<td>m/z</td>
<td>mass/charge (mass spectrometry)</td>
</tr>
<tr>
<td>NBD</td>
<td>norbornadiene</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>n.d</td>
<td>not determined</td>
</tr>
<tr>
<td>nm</td>
<td>nanometer</td>
</tr>
<tr>
<td>NMO</td>
<td>N-methylmorpholine N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>nOesy</td>
<td>nuclear overhauser effect spectroscopy</td>
</tr>
<tr>
<td>n.r</td>
<td>not reported</td>
</tr>
<tr>
<td>Ns</td>
<td>p-nitrobenzenesulfonyl</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>PG</td>
<td>unspecified protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PIBDA</td>
<td>polymer supported iodobenzene diacetate</td>
</tr>
<tr>
<td>Piv</td>
<td>pivaloyl</td>
</tr>
<tr>
<td>PMB</td>
<td>para-methoxybenzyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>PTAD or PhTAD</td>
<td>4-phenyl-1,2,4-triazoline-3,5-dione</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
</tbody>
</table>
q  quartet
R  unspecified group
$R_f$ retention factor
rt room temperature
s  singlet
SAR structure-activity relationship
t  triplet
tert $^{(t)}$ tertiary
'tBu tert-butyl
TBS tert-butyldimethylsilyl
t C E tetrachloroethylene
Tf trifluoromethanesulfonate
TFA trifluoroacetic acid
TFAA trifluoroacetic anhydride
THF tetrahydrofuran
TIPS triisopropylsilyl
TLC thin-layer chromatography
TMEDA $N,N,N',N'$ tetramethylethylene diamine
TMS trimethylsilyl
TOF time-of-flight
Troc 2,2,2-trichloroethoxycarbonyl
Ts 4-toluenesulfonyl (tosyl)
UV-Vis ultraviolet-visible
VT variable-temperature
w/v weight/volume
$\lambda_{\text{max}}$ absorption maximum
$\varepsilon$ molar absorption coefficient
$\degree$ degrees
$\nu$ frequency
$\Delta$ heat
$\Delta G$ Gibbs free energy
$\delta$ chemical shift
$\dagger$ transition state
Chapter 1: Introduction
11 The Growing Interest In sp$^3$-Rich Compounds

A recent study exemplified the huge investment required for drug discovery and showed that the estimated cost for each new marketable drug was around 2.6 billion dollars. As a result, significant effort has focused on making the process more efficient and determining at the earliest possible stage whether the drug candidate will fail. A key addition has been the development of computational techniques and these have become a vital tool in improving efficiency and reducing costs of the drug discovery process. More commonly, there are some key structural factors that can help medicinal chemists to validate potential drug candidates. The pioneering work by Lipinski, termed Lipinski’s rule of five, has helped to provide some guidelines for the development of drug molecules. Lipinski’s rule of five is made up of four elements: ≤ 5 hydrogen bond donors; ≤ 10 hydrogen bond donors; molecular weight ≤ 500; logP ≤ 5. Firstly, hydrogen bond donors are hydrogen atoms attached to electronegative heteroatoms such as oxygen and nitrogen, whereas the hydrogen bond acceptors are the heteroatoms themselves. Molecular weight is the total weight of the compound and the octanol-water partition coefficient, logP, provides information on whether a substance will be absorbed by a plant, animals, humans or other tissue and whether it will be easily removed and distributed by water. A positive value implies the compound is lipophilic (non-polar), whereas a negative value implies the compound is hydrophilic (polar). For drug candidates to have good solubility in aqueous media requires more polar molecules and as such a lower logP. Lipophilic compounds have been shown to have poor aqueous solubility and can lead to an increase in toxicity. Subsequently, factors such as the number of rotatable bonds (≤ 10 – making the compound more rigid) and the polar surface area (≤ 12 hydrogen bond donors and acceptors), the ability of a compound to get into cells, have been found to be important for orally active drugs. In addition, drug candidates must have good absorption, distribution, metabolism, excretion and toxicity (ADMET) properties, as well as having good stability under a variety of conditions.

Over the last decade there has been a movement within the pharmaceutical industry to introduce more structural diversity into drug discovery programmes. The development of robust methodologies that tolerate a variety of functional groups and the broad range of commercially available substrates has resulted in aromatic systems (sp$^2$ hybridisation) being widely used. These compounds play a crucial role in drug discovery and can provide π-π stacking/π-cation interactions to increase binding efficiency with biological targets, whilst stereochemistry is not a concern as found with saturated compounds. Macdonald and co-workers at GlaxoSmithKline have reported that any synthetic methodology needs to be robust, have the functionality to carry out parallel synthesis to easily access a library of compounds, be tolerant of a variety of functional groups and potentially amendable to late stage functionalisation. The authors went on to report that medicinal chemists used a lot of the same reactions because reactions such as alkylations, palladium-catalysed cross couplings, condensation reactions and protecting group manipulations are amenable to a lot of substrates (63% of nearly 4900 reactions at GSK). Cross-coupling reactions exemplify these desired characteristics and can tolerate a
variety of different functional groups attached to aromatic, heteroaromatic and aliphatic substrates, which are invaluable when trying to determine the structure-activity-relationship (SAR). More recently, a perspective written by leaders from the pharmaceutical industry has highlighted some key points for the field of organic chemistry in relation to drug discovery.\textsuperscript{10} One of the key messages was that organic synthesis is often the thing that slows down the discovery process, however through collaboration with academia, the growing potential in areas such as C-H functionalisation and photoredox catalysis, as well as the constant improvement of enantioselective catalysis and C-C/C-X bond formation, reactions are providing new methodologies that can be rapidly used and speed up the process. Other emerging areas such as machine-assisted synthesis, artificial intelligence and computational retrosynthesis software have the potential to have a huge effect on the discovery of new drugs.\textsuperscript{10} The authors again stressed that a major hindrance with the uptake of methodology into industry is that often the substrate scope does not exemplify functional group tolerance and/or negative results are not published. Drug candidates are required fast and medicinal chemists do not have the time to develop and optimise novel methodologies, which can lead to a lot of the same types of compounds being used in their library screenings. As a consequence, a vast number of current drugs are rich in sp\textsuperscript{2} systems, and the exploration of saturated systems (sp\textsuperscript{3} hybridisation) is often overlooked due to ineffective or under-developed methodologies. A study in 2014 by Taylor and co-workers found that 40\% of current drugs on the market did not have any rings that contained any sp\textsuperscript{3} carbon atoms.\textsuperscript{8} As a result, there has been a skew towards the compounds that organic chemists are likely to include in their target molecules, which has led to certain fragments being extensively used.\textsuperscript{11-13} From the analysis of the types of rings used in compounds listed on the CAS registry, Lipkus and co-workers found that chemists are more likely to use a specific ring system if they have seen it used before.\textsuperscript{11} Brown and co-workers reported from analysis of a variety of databases and current drugs that para-substituted aromatic rings, in particular para-chloro and fluoro-aromatic rings, have been widely used compared to ortho- and meta- derivatives.\textsuperscript{12} At the start of 2016, Foley, Nelson and Marsden found similar results from the analysis of recent synthetic methodology papers in two high impact journals and also found that aromatic rings were used more often than heteroaromatic rings.\textsuperscript{13} Two literature studies on the reactions used within medicinal chemistry have shown that a lot of the same reactions are used.\textsuperscript{14,15} Brown and Boström have found that through comparison of the reactions used in 250 papers from 1984 and 2014, that a lot of similar reactions were still being used and some of the most commonly used reactions in 2014 had not been discovered in the last twenty years.\textsuperscript{15}

The seminal analysis by Lovering and co-workers discovered the link between the presence of sp\textsuperscript{3} character and/or chirality and the improved success of drug candidates going from discovery through to market.\textsuperscript{16} A few years later, Lovering also reported that an increase in sp\textsuperscript{3} character can improve the selectivity of drug candidates, thus reducing the amount of off-target interactions.\textsuperscript{17} Through computational analysis, Hann and co-workers have shown that increasing molecular complexity (e.g. greater sp\textsuperscript{3} character), resulted in fewer interactions of
compounds with off-target biological receptors.\textsuperscript{18} Selzer and co-workers found that from a selection of drugs in the World Drug Index that on average, highly active molecules were structurally more complex, however stressed that complexity had to be balanced with other properties, e.g. lipophilicity.\textsuperscript{19} Clemons and co-workers have put the theories proposed by Lovering and Hann into practice by screening around 15,000 compounds either from commercial or academic sources against 100 different proteins, and demonstrated that greater sp\textsuperscript{3} character resulted in improved selectivity.\textsuperscript{20} In addition to selectivity, the use of saturated systems provides three-dimensional shapes, unlike flat sp\textsuperscript{2} systems, which enable a greater area of chemical space to be explored, and has the potential to provide compounds with more desirable “drug-like” properties, such as improved solubility and lower melting points.\textsuperscript{6,16} Ishikawa and Hashimoto have found that replacing an aromatic ring on lead compounds with poor aqueous solubility with a saturated ring can give improved aqueous solubilities and lower melting points.\textsuperscript{21} The authors reasoned that the improved properties stemmed from the disruption of molecular planarity and symmetry through decreasing the efficiency of crystal packing through a reduction in aromatic character. Ritchie and Macdonald’s study on compounds in the GlaxoSmithKline collection showed that for substrates where the number of aromatic rings were low, there was a greater chance of progression, whereas three or more aromatic rings correlated with a higher attrition rate.\textsuperscript{5} Walters and co-workers analysed over 400,000 compounds published in the Journal of Medicinal Chemistry over a fifty year period (1959-2009) and found a steady decline in the proportion of sp\textsuperscript{3} compounds over the time period, and many compounds violated one or more of Lipinski’s rules of five.\textsuperscript{22} An interesting example of the power of sp\textsuperscript{3}-hybridised compounds has been the use of cubane as a bioisostere for an aromatic ring (Figure 1.1).\textsuperscript{23} In 1992, Eaton proposed the pharmaceutical potential of cubanes,\textsuperscript{24} however it was over twenty years until Tsanaktsidis, Savage, Williams and various co-workers proved this.\textsuperscript{23} The biological activity of five known drugs and five cubane derivatives in which cubane replaced the aromatic ring, showed the same or marginally increased biological activity for four out of five of the cubane-containing compounds. These results exemplify the potential sp\textsuperscript{3} systems have in drug discovery. More recently, Faul, Walker and co-workers have discussed how the increase in molecular complexity in drug candidates has helped to drive innovation in process development.\textsuperscript{25}

![Figure 1.1](image)

New open-access computational tools have recently been developed that can help guide synthetic methodology and provide more relevant scaffolds.\textsuperscript{26,27} One such example has been the development of the lead-likeness and molecular analysis (LLAMA) software by Marsden, Nelson and co-workers, which enables the generation of virtual libraries through common transformations on a single scaffold to give a variety of different compounds and a lead-likeness score (Figure 1.2).\textsuperscript{27} The molecules generated are ranked according to a lead-likeness penalty based on guidelines proposed by Churcher and co-workers (\(-1\leq\log\text{P}\leq3, 14\leq\text{heavy atoms}\leq26\))

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Chapter 1: Introduction

e.g. molecular weight 200-350, remove reactive functional groups, decrease the amount sp² character e.g. 1 or 2 aromatic rings), which is set within the guidelines set out by Lipinski’s rule of five. Using both rules enables chemists to get an idea of what types of medicinally relevant compounds could be made when investigating a substrate scope. Other information such as three-dimensionality (whether the compounds is rod, disc or spherical in shape), novelty, mass distribution, AlogP distribution and fraction of sp³ distribution data can also be acquired for the library. Foley, Nelson and Marsden have used this software to study a variety of literature reactions and propose some future targets.¹³

Guidelines for good substrates: 14≤heavy atoms≤26 (count of all atoms apart from hydrogen), -1≤logP≤3 (lipophilicity), number of aromatic rings = 1 or 2 (limit sp² character), presence of bad (reactive) functional groups. From https://llama.leeds.ac.uk/help.php#lead-likeness-penalty

It is clear that there is a growing need for the development of efficient and robust methodologies to access sp³ hybridised systems. One class of compounds that has gained attention recently has been four-membered rings.²⁹,³⁰ The development of more robust synthetic methodologies, driven by a move to introduce more structural diversity into drug candidates, has resulted in the use of more carbocyclic four-membered rings such as cyclobutanes ¹ and cyclobutenes ²,²⁹,³¹ and heterocyclic four-membered rings such as oxetanes ³, azetidines ⁴, β-lactams ⁵ and 1,2-diazetidinones ⁶ (Figure 1.3).²⁹,³² Currently there are no examples of 1,2-diazetidines ⁷ as drug candidates, however the synthesis of these compounds has been a lot less studied in comparison to other four-membered ring systems (vide infra). The development of new synthetic methodology to generate these systems can provide access to new areas of chemical space, which can be used in screening libraries with the potential of having therapeutic value.

Figure 1.2 The lead-likeness penalty predicts whether a substrate will fall within lead-like space. Guidelines for good substrates: 14≤heavy atoms≤26 (count of all atoms apart from hydrogen), -1≤logP≤3 (lipophilicity), number of aromatic rings = 1 or 2 (limit sp² character), presence of bad (reactive) functional groups. From https://llama.leeds.ac.uk/help.php#lead-likeness-penalty
1.2 Project Aims and Objectives

The project aimed to develop new methodology for the photocatalytic 4-π electrocyclisation of 1,2-dihydropyridazines 9 to access key bicyclic 1,2-diazetidines 10, which could be further transformed through cleavage of the N-N bond to yield highly functionalised cyclobutene derivatives 11, as well as through oxidative cleavage of the C=C to generate 1,2-diazetidines 12 (Scheme 1.1). The successful development of this synthetic approach would allow the conversion of simple starting materials into complex small ring systems in very few steps, in contrast with the long synthetic sequences that would be required to access these building blocks using traditional approaches (i.e. non-photochemical routes). The key photochemical step would be optimised using commercially available batch and flow photoreactors. Initial investigations were to be done with batch photoreactor before being transferred to the flow photoreactor for optimisation and scale-up work. The use of flow chemistry would hopefully reduce scale-up concerns associated with batch photochemistry by reducing reaction times, which can lead to over irradiation (degradation), and ensure good light penetration into the reaction mixture. A good understanding of the stability of bicyclic 1,2-diazetidines 10 was not already known, therefore it was essential to gain a good understanding of the properties of 10 and whether safety precautions were required. It was desirable that this new methodology provided 1,2-dihydropyridazines 9 and bicyclic 1,2-diazetidines 10 in multigram quantities, which meant that the synthesis and photochemistry of 1,2-dihydropyridazines 2 had to be efficient. The synthesis of 1,2-dihydropyridazines 9 starting from azo compounds 8 is known, however if this proved unsuccessful a new route would have to be developed. In any case, the synthesis of 1,2-dihydropyridazines 9 should enable the synthesis of derivatives to ascertain the effect that this would have on the 4-π photocyclisation. The synthetic potential of 1,2-dihydropyridazines 9 has not been exploited in the literature and they are interesting synthetic intermediates that should undergo typical double bond transformations to give novel structures.
1.3 The Synthesis of 1,2-Diazetidines

1,2-Diazetidines 13 are four-membered rings that contain two nitrogen atoms adjacent to one another, and aside from the nitrogen atoms there are up to two positions where substituents can be added (Figure 1.4). Nevertheless, the reported syntheses of 1,2-diazetidines remain limited, especially compared with the renewed interest in azetidines 14 over the last decade.\textsuperscript{37,38} The attempted synthesis of 1,2-diazetidines has been reported over the last 150 years, however many of these early reports were found to be incorrect and it was not until the late 1940’s that the first legitimate examples were published.\textsuperscript{39,40}

![Figure 1.4](image)

**Figure 1.4**

**1.3.1 Synthesis of 1,2-Diazetidines via [2+2] Cycloaddition**

One of the most common ways to synthesise 1,2-diazetidines has been to utilise [2+2] cycloadditions of alkenes and azo compounds in which one of the two reactants must be activated with either electron donating or withdrawing groups. The most common examples have used azo compounds 8 bearing electron withdrawing groups (azodicarboxylates), whilst the alkene 15 possesses electron donating groups,\textsuperscript{40} though there are limited examples using halogenated alkenes (Scheme 1.2).\textsuperscript{39–42} A concerted thermal [2+2] cycloaddition is forbidden by Woodward-Hoffmann rules on orbital symmetry grounds and as such these reactions must go via a stepwise mechanism through diradical or dipolar intermediates.\textsuperscript{43–46} A possible side reaction is the inverse electron-demand [4+2] cycloaddition, in which the highest occupied molecular orbital (HOMO) of an alkene 15 with electron donating groups reacts with the lowest unoccupied molecular orbital (LUMO) of an electron deficient heterodiene 8 to form oxadiazines 17. For reactions with electron rich alkenes, the electron deficient nitrogen of the heterodiene was attached to β-carbon of the olefin.

![Scheme 1.2](image)

**Scheme 1.2**

The [2+2] cycloaddition of acyclic and cyclic azo compounds with a variety of different alkenes has given varied results (Scheme 1.3).\textsuperscript{47–56} In 1926, Diels and Alder first reported the reaction of indene 15a with an acyclic azo compound 8b,\textsuperscript{48} however it was originally proposed these two compounds underwent an ene reaction, not a [2+2] cycloaddition.\textsuperscript{49} Huebner and co-workers
suggested that the 1,2-diazetidine had formed through analysis by infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy, although a few years later a couple of different research groups concluded that the oxadiazine 17a had formed. A similar observation was made when indene 15a was changed to styrene 15c, although when cyclic cis-locked azo compounds 8h,o,p were used both indene 15a and styrene 15c formed 1,2-diazetidine 16a,b products in 34-58% yield. Subsequent work has shown that the [2+2] cycloaddition at low temperatures also worked with indene derivative 15b, although above room temperature an ene reaction is favoured. 1,2-Diazetidines 16d-h have also been successfully formed with azo compounds 8b,h when diadamantyl-substituted alkene 15d, tetracyclopropylenes 15e, fluorinated diene 15f, cyclopropyl alkene 15g and various fluorinated alkenes 15h were employed. The use of cyclohexene 15i, hex-1-ene 15j or (E/Z)-but-2-ene 15k resulted in an ene reaction taking place, whereas none of the desired 1,2-diazetidines 16l,m were obtained when azo compounds 8a,h were reacted with substituted alkenes 15l and ethylene 15m.

\[
\text{Scheme 1.}
\]

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**Successful Azo Compounds:**

- MeO₂C=N=N⁻CO₂Me
- EtO₂C=N=N⁻CO₂Et
- N=N⁻NR
- N=N⁻CO₂Et
- N=N⁻O

**Successful Olefins:**

- 15a
- 15b
- 15c
- 15d
- 15e
- 15f
- 15g
- 15h

**Unsuccessful Olefins:**

- 15i
- 15j
- 15k
- 15l
- 15m

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Thomas Britten – April 2019
The [2+2] cycloaddition of azo compounds 8a,b,h,o with substituted alkenes bearing stronger electron donating groups has been more extensively studied (Scheme 1.4). Various research groups have used enol-ethers 18a with alkyl chains (R' = alkyl) to synthesise O-substituted 1,2-diazetidines 19a in low-good yields (28-86%). For enol ethers that possessed an aromatic group (R' = Ar), there was competition between 1,2-diazetidine 19a and oxadiazine 20a formation dependent on what groups were attached to the aromatic ring. The highest yields of 1,2-diazetidines 19a were achieved with no substitution, a methyl, methoxy or chloro group attached to the aromatic ring (67-87%), whereas when a strong electron withdrawing group, such as a nitro group, was present the yield sharply dropped (5%). The opposite was true for the formation of oxadiazines 20a and the highest yields were achieved when a nitro group was present on the aromatic ring (>95%). In addition, oxadiazines 20a are the major product if the nitrogen atoms are protected with benzoyl groups (>95%). The use of monocyclic and acyclic enamines 18b tended to give N-substituted 1,2-diazetidines 19b, however little to no isolated yields have been reported and the products were easily ring-opened through hydrolysis. The [2+2] cycloaddition reaction with vinyl sulfides 18c (R' = alkyl) gave small amounts of 1,2-diazetidine 19c formation (28-35%) and the major products were oxadiazines 20c (65-72%). Vinyl esters 18d with isopropyl, tert-butyl and phenyl groups produced 1,2-diazetidines 19d in low yields but provided evidence for a stepwise mechanism, in contrast vinyl acetate 18i resulted in the [4+2] reaction to give oxadiazines 20i as the major pathway. For vinyl ethers 18e, low yields of 1,2-diazetidines 20e were obtained (22%), however the use of acetone as the solvent trapped any dipolar intermediates preventing 1,2-diazetidine formation. Similar observations were found with methanol for [2+2] cycloadditions using either but-2-ene or isobutylene. The use of (Z)-1,2-methoxyethene 18f with acyclic azo compounds 8a resulted in the formation of a 1:4 mixture of 1,2-diazetidine 19f and oxadiazine 20f, however when 1,4-dioxene 18g was reacted with cyclic azo compounds 8h only 1,2-diazetidine 19g formation was observed. Hoffmann and Häuser have studied the [2+2] cycloaddition using tetramethoxymethene 18h. The authors reported that 1,2-diazetidine 19h was isolated in high yields (95%) and no sign of the oxadiazine product 20h was observed under these reaction conditions. Finally, the [2+2] cycloaddition of ketene acetals 18j, keten-\(N,N\)-acetals 18k and aminals 18l formed unstable 1,2-diazetidines that could not be isolated and immediately reacted further to give non-cyclic products.
More recently, Breton and co-workers have utilised a \([2+2]\)-cycloaddition to synthesise 1,2-diazetine 21 (Scheme 1.5). 4-Methyl-1,2,4-triazoline-3,5-dione (MeTAD) 8o was reacted with phenyl vinyl sulfide 18c to form an unstable 1,2-diazetidin-1-one intermediate that was immediately further reacted to give the more stable sulfoxide 23 in low yields (15%), followed by pyrolysis to give 1,2-diazette 21 in around 70% yield. 1,2-Diazete 21 was stable and did not undergo thermal ring opening as found when acyclic protecting groups were attached to the nitrogen atoms. The authors went on to form a variety of bicyclic 1,2-diazetidines through Diels-Alder reactions with various dienes, whilst Breton and Martin carried out a bromination reaction to access dibromide 22 in good yields.

Scheme 1.4 EDG = electron donating group

Scheme 1.5
Xu and co-workers have detailed a tertiary amine-catalysed [2+2] cycloaddition reaction between allenoates 24 and azo compounds 8 to give a series substituted 1,2-diazetidines 25 (Scheme 1.6). The functionalised 1,2-diazetidines 25 were synthesised in moderate-good yields and all gave a cis-double bond in the product. Unsubstituted and γ-alkyl-substituted allenoates 24 with either ethyl or benzyl esters were tolerated under the reaction conditions, whereas α-allenoates did not react. The authors suggested the formation of 1,2-diazetidines 25 began with the addition of the tertiary amine to allenoate 24 to give a stabilised zwitterion 26/26', which underwent a Michael-type reaction with the azo compound to give intermediate 27. Cyclisation of zwitterion 27 produces the 1,2-diazetidine ring 28, followed by elimination of the tertiary amine catalyst to form the double bond and product 25.

Scheme 1.6 DABCO = 1,4-diazabicyclo[2.2.2]octane; R' = alkyl or benzyl; R'' = Et, iPr or tBu

Okitsu and co-workers have reported the thermal [2+2] cycloaddition reaction of allenamides 29 with a series of azo compounds 8 (Scheme 1.7). These reactions formed unstable 1,2-diazetidines 30, which could not be isolated as they underwent a ring opening reaction to give zwitterion 31. The authors were able to trap intermediate 31 with a variety of silyl enol ethers, allyl- and allenylsilanes in the presence of a Lewis acid, trimethylsilyl trifluoromethanesulfonate (TMSOTf).
1.3.2 Other Methods to Synthesise 1,2-Diazetidines

1.3.2.1 Synthesis of 1,2-Diazetidines

Warrener and co-workers have demonstrated the synthesis of 1,2-diazetidine \( \text{34} \) from 1,2-diaze \( \text{33} \) (Scheme 1.8 and see also Section 4.1.1, Scheme 4.4).\(^{35,80}\) 1,2-Diaze \( \text{33} \) was synthesised from tricycle \( \text{32} \) in a good yield, though it was found to be thermally unstable and started to form diimine \( \text{36} \) in solution (\textit{vide infra}). Nevertheless, 1,2-diazetidine \( \text{34} \) was formed in moderate yield when 1,2-diaze \( \text{33} \) was reduced through hydrogenation.

In the mid-1960’s, Horvitz of the FMC Corporation patented a new route to access 1,2-diazetidines starting from alkyl hydrazines \( \text{37} \) and dihalides \( \text{38} \).\(^{84}\) Hall \textit{et al}. and Nels \textit{et al}. have utilised this methodology on multigram scales to access some alkyl-1,2-diazetidines \( \text{39} \) in moderate to low yields (Scheme 1.9).\(^{85,86}\) The authors reported that slow addition of 1,2-dibromoethane \( \text{38} \) was essential to ensure good reactivity and a large excess of the dihalide was required, as it was susceptible to an elimination reaction. These conditions were used to synthesise two 3-substituted-1,2-diazetidines \( \text{40} \) in low yields.
Chapter 1: Introduction

Shipman and co-workers have developed a synthesis to a series of 1,2-diazetidines 34b-d from tri-substituted hydrazines 41 equipped with a iodide leaving group (Scheme 1.10).\(^\text{87}\) The presence of iodide was found to be crucial and for hydrazines with carbamate protecting groups, leaving groups such as bromide, chloride, mesylate or under Mitsunobu conditions, gave oxadiazine 42b as the major product. The authors reason that the use of the softer iodide leaving group promoted cyclisation through the nitrogen, whereas for harder leaving groups cyclisation was favoured through the carbamate oxygen.

Cui et al. have developed a multigram synthesis for unsubstituted 1,2-diazetidines 34 bearing sulfonyl protecting groups (Scheme 1.11).\(^\text{88}\) Hydrazine 43m was first doubly deprotonated and the dianion reacted with 1,2-dibromoethane to give 1,2-diazetidine 34e in a good yield (78%) and has been successfully performed on a fifty gram scale. The methodology has been expanded to give 1,2-diazetidines with aryl-sulfonyl groups that contained aromatic rings with electron donating (OMe) and withdrawing groups (CF\(_3\) and CN), as well as 2-naphthalene sulfonamide. Introduction of nitro groups or a mesitylene ring caused a sharp decrease in yields and the procedure was not successful with hydrazines that contained carbonyl groups. 1,2-Diazetidine 34e was successfully ring-opened to give sulfonyl imines 44 in mostly high yields using a variety of alkyl and aromatic thiols bearing bulky, electron donating or withdrawing groups and alkyl thiols. The authors suggested that, after deprotonation of the thiols with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the thiolate 45 would facilitate a nucleophilic (S\(_\text{N}2\)) N-N
cleavage to give amine 46 after protonation of the nitrogen anion, followed by elimination of the tosyl group to give the observed product 44.

**Scheme 1.11** DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene; DMF = dimethylformamide

### 1.3.2.2 Synthesis of 3-Substituted-1,2-Diazetidines

Ma and co-workers reported the first enantioselective synthesis of 3-substituted 1,2-diazetidine 49 from an enantioenriched hydrazine 47 acquired from a (R)-proline-catalysed Michael addition from the corresponding aldehyde and dibenzyl azodicarboxylate (Scheme 1.12).

Seven other examples were shown, however the legitimacy of this route has been disputed by Shipman and co-workers, who proved that with the hard mesylate leaving group the major product should be oxadiazine 48 and not the 1,2-diazetidine 49.

**Scheme 1.12**

Shipman and co-workers were the first to report the synthesis of 1,2-diazetidines 52 bearing an alkene directly attached to the ring (Scheme 1.13). Allylic alcohols 50 were converted into trisubstituted hydrazines 51 in good yields under Mitsunobu conditions, without an external nucleophile present. Hydrazines 51 were then converted into 1,2-diazetidines 52 in excellent yields through a copper-catalysed cyclisation reaction with an alkenyl bromide or iodide group (X in Scheme 1.13). The reaction tolerated a variety carbamate protecting groups, including an orthogonally protected system and was successful for alkenes substituted with a phenyl, chloro, acyclic and cyclic alkyl groups. The reaction does not give the desired product when an additional iodo group was present on the alkene (R = I in Scheme 1.13).
More recently, Shipman and co-workers have exploited enantioenriched hydrazines 53a-c to synthesise 1,2-diazetidines equipped with an alkene functional handle (Scheme 1.14). The primary alcohol in hydrazine 53a-c had to be first converted into the required iodide leaving group, then cyclisation under basic conditions gave the desired 1,2-diazetidines 54a-c in good yields with a tosyl group and lower yields with a nosyl group. In all cases, the enantiomeric excess (ee) was retained from the enriched hydrazines 53a-c.

**Scheme 1.14** *(R)-enantiomer synthesised; Ts = toluenesulfonyl; Ns = p-nitrobenzenesulfonyl*

1.3.2.3 Synthesis of Other Substituted-1,2-Diazetidines

The $2\pi + 2\sigma + 2\sigma$ cycloaddition reaction between quadricyclane 55 and azo compounds 8 has been widely studied (Scheme 1.15). The reaction has been successful with azo compounds equipped with methyl and ethyl carbamates or benzoyl groups with electron donating and withdrawing groups, which can be reduced using lithium aluminium hydride to give alkyl and benzyl 1,2-diazetidines. Thermolysis experiments have shown that at high temperatures cleavage of the N-N bond took place, followed by a ring opening to give imine 57. Sharpless and co-workers have shown that reactions with dimethyl azodicarboxylate (DMAD) 8a can be speeded up when an aqueous suspension is used (on water conditions). Zare and co-workers found the reaction rate could be sped up even further using microdroplets generated through electrospray ionisation.

**Scheme 1.15**
Cheng and Ma have evaluated the palladium-catalysed cyclisation reaction of allene-substituted hydrazines 58 with aryl iodides to access substituted 1,2-diazetidines 59 (Scheme 1.16).\textsuperscript{100,101} The use of alkyl and benzyl substituted allenes 58 and methyl, methoxy or unsubstituted aryl iodides resulted in the formation of 1,2-diazetidines 59 in 63-77% yield. When aryl iodides with electron withdrawing groups were used, the yields of 1,2-diazetidines 59 decreased and the formation of dihydropyrazoles 60 began to dominate. In the cases where 1,2-diazetidine 59 was formed, the authors found that the alkene and the R were trans to each other, probably to reduce steric clashes.

Mackay and co-workers have described the synthesis of bicyclic 1,2-diazetidines 63 formed through a Diels-Alder reaction, followed by a thermal rearrangement (Scheme 1.17).\textsuperscript{102,103} The Diels-Alder reaction of 2,5-dimethyl-3,4-diphenyl-cyclopentadienone 61 and a variety of azodicarboxylates 8 gave cycloadducts 62 in good yields, which isomerised to give oxadiazines 64 when heated to 80°C. When the cycloadducts 62 were heated at higher temperatures (120°C), 1,2-diazetidines 63 were formed in good yields apart from when tert-butyl carbamate protecting groups were used. The isomerisation reactions are reversible, however prolonged reaction times resulted in degradation of cycloadduct 62.
1.3.2.4 Peripheral Functionalisation of 1,2-Diazetidines

Shipman and co-workers have utilised alkylidene 1,2-diazetidine 52a for derivatisation (Scheme 1.18). A palladium-catalysed Heck reaction with iodobenzene installed a phenyl group to give 1,2-diazetidine 52b in a moderate yield and selectively gave the trans-double bond, which was proposed to minimise any steric clashes between the phenyl group and the carbamate protecting groups. Shipman and co-workers have also carried out an asymmetric hydrogenation of the double bond in 52a to access an enantiomeric alkyl hydrazine 65 in good yields and enantiomeric excess.

![Scheme 1.18](image)

Shipman and co-workers have employed the double bond attached to the ring to synthesise some spirocyclic 1,2-diazetidines (Scheme 1.19). Under typical conditions to form dichloro- and difluoro-carbene, alkylidene-1,2-diazetidines 52 were converted into a variety of spirocyclic 1,2-diazetidines 67 in moderate-excellent yields. The reaction was successful with 1,2-diazetidines with symmetrical and orthogonal protecting groups on the nitrogen atoms, however only unsubstituted or methyl substituted alkenes were successful and alkenes bearing an electron withdrawing group did not give the desired products. The yields for the difluoro-carbene derived products were higher than those found with dichloro-carbene, as the latter tended to insert into the N-N bond to form a ring expanded urea 68, after hydrolysis of 68’. 1,2-Diazetidine 52 also underwent a [2+2] cycloaddition with the electron poor alkene tetracyanoethylene 69 to give spirocycles 70 in good yields. The highest yields were achieved when there was less steric bulk on the carbamate protecting groups and with little substitution on the double bond.
Shipman and co-workers have employed some common double bond transformations with vinyl-1,2-diazetidines 54a,b to access novel 1,2-diazetidine scaffolds (Scheme 1.20 and 1.21). Ozonolysis, followed by reductive work up with either triphenylphosphine or sodium borohydride formed an aldehyde and alcohol, respectively. In the case of the former, the aldehyde was immediately further reacted through a reductive amination reaction to give amine 71 in moderate yields and when sodium borohydride was used, alcohol 72 was isolated in excellent yields. The alkene could be reduced using in situ formed diimide to give ethyl-1,2-diazetidine 73 in high yields. Using 73, it was possible to selectively deprotect each of the carbamate and sulfonamide protecting groups in good yields under acidic conditions or with magnesium-methanol.

The same authors went on to demonstrate the use of olefin cross metathesis on 1,2-diazetidine 54a,b bearing a vinyl group (Scheme 1.21). Using either Grubbs 2nd generation 75 or
Hoveyda-Grubbs 2nd generation 76 catalysts and external alkenes that contained either alkyl chains, esters, halogens or phenyl rings, 1,2-diazetidines 54a,b was selectively transformed into (E)-vinyl-1,2-diazetidines 74 in good yields.

Scheme 1.21 \( R = t\text{Bu or Bn} \)

1.4 The Thermal Stability of Substituted Cyclobutenes

Cyclobutenes are strained four-membered rings, which can be derivatised through the double bond to give cyclobutanes or used to make dienes through a thermal electrocyclic ring opening (Scheme 1.22). The synthesis of dienes from cyclobutenes is often stereoselective and is governed by Woodward-Hoffmann rules and the properties of the substituents are also a key factor.43–45 Moreover, there are rare examples of cyclobutenes in natural products (e.g. 79),31 however the ring opening of cyclobutenes has been utilised more in the synthesis of various natural products.105–111

In relation to this project, there are currently no examples in the literature for the synthesis of protected cis- or trans-diaminocyclobutenes 11 (Figure 1.5). These cyclobutenes are not expected to be thermally stable, and have been predicted to undergo a 4-π electrocyclic ring opening to the corresponding dienes (vide infra).112 Herein, the 4-π electrocyclic ring opening of cyclobutenes and any substituent effects shall be discussed.
1.4.1 Torquoselectivity - Theory

The thermal 4-π electrocyclic ring opening of cis- and trans-3,4-disubstituted cyclobutenes can technically give four potential diene products (Scheme 1.23). The advent of Woodward-Hoffmann rules described, based on orbital symmetry, that 4-π electrocyclic reactions are conrotary and disrotary for thermal and photochemical reactions, respectively. As a result, the thermal formation of dienes derived from the disrotary process are forbidden. For both isomers, the conrotatory ring opening process can form two products, however the favoured formation of one diene can be predicted using theories developed by Houk and various co-workers.[71-83] They termed the preferential formation of one diene as torquoselectivity and this is the stereoselective twisting of the breaking C-C σ orbital in the transition state with the substituents rotating inwards or outwards dependent on their electronic properties. In general, electron donors (e.g. R = OH or NH$_2$) and mild electron acceptors (e.g. CO$_2$H) favour outward rotation, whereas strong electron acceptors (e.g. CHO) tend to favour inward rotation (vide infra).[112,115,116] Houk and Dolbier have written a short review on this area and outline how experimental results have provided further support to the theory.[126]

Electron donor substituents, upon inward rotation in the transition state, undergo a destabilising four electron interaction between the filled orbital of the donor and the HOMO of the breaking C-C σ bond (85), which results in a large increase in the activation energy (Figure 1.6). Outward
rotation of the donor minimises this interaction (80 and 84) and enables the stabilisation of the C-C σ* LUMO by the filled orbital on the donor, which in turn lowers the activation energy for this process (80). Stabilisation of the LUMO is minimal when the donor rotates inward (81). The opposite is observed when a strong electron acceptor is used that contains a low energy LUMO. When the acceptor rotates inwards, a stabilising interaction is possible between the empty orbital located on the acceptor and the HOMO of the breaking C-C σ bond (87). The interaction lowers the activation energy for the process, more so than if the acceptor rotates outwards where it can only interact with one of the orbitals (86).

Houk and co-workers, as well as other research groups, have carried out computational calculations on 3-substituted cyclobutenes to predict whether substituents prefer to rotate inwards or outwards (Table 1.1). In simple terms, the activation energies of the inward and outward rotations were first calculated and the values were subtracted from one another to give positive values if outward rotation is favoured and negative values for inward rotation. In almost all cases, the activation energies were lower for 3-substituted cyclobutenes in comparison to cyclobutene itself. Examples of functional groups that strongly favoured outward rotation include alkoxides (entry 2), alcohols (entry 3), amines (entries 4 and 5), thiols (entry 6), fluorine (entry 7), chlorine (entry 8), alkanes (entries 10 and 11), alkenes (entry 12), alkynes (entry 13), carboxylates (entry 18), nitriles (entry 23), nitro (entry 24) and phosphines (entry 34). Nitriles and nitro groups were described as a relatively poor acceptors and in the case of the former the filled orbitals on the nitrile can help to stabilise the LUMO of the breaking C-C bond. Trifluoromethyl groups (entry 9), ketones (entry 14), acids (entry 16), esters (entry 19), cis-imines (entry 21) and sulfoxides (entry 26) showed only a partial preference for outward rotation. Cyclobutenes substituted with aldehydes (entry 15), imines (entries 20 and 22), nitroso (entry 25), sulfonic acid groups (entry 27), sulfonyl groups (entry 28), boron (entries 29 and 30), silyl groups (entries 31-33) and organostannanes (entry 35) all showed a strong preference for inward rotation. Aldehydes, protonated imines and boron containing compounds gave the lowest activation energies for inward rotation. Houk and co-workers calculated that protonation
of acids and imines, which in the process makes them more electron withdrawing, switched the rotation preference from outwards to inwards (entries 17 and 22). In contrast to these findings, when the donor or acceptor substituent is directly attached to the double bond the activation energy for ring opening is similar to that of cyclobutene.

<table>
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<td>112,115</td>
</tr>
<tr>
<td>8</td>
<td>Cl</td>
<td>13.6</td>
<td>115</td>
</tr>
<tr>
<td>9</td>
<td>CF$_3$</td>
<td>2.3-2.6</td>
<td>115</td>
</tr>
<tr>
<td>10</td>
<td>Me</td>
<td>5.9-7.4</td>
<td>112,115,116</td>
</tr>
<tr>
<td>11</td>
<td>tBu</td>
<td>7.1</td>
<td>128</td>
</tr>
<tr>
<td>12</td>
<td>HC=CH</td>
<td>4.9</td>
<td>115</td>
</tr>
<tr>
<td>13</td>
<td>C≡CH</td>
<td>7.6</td>
<td>115</td>
</tr>
<tr>
<td>14</td>
<td>C(O)Me</td>
<td>1.2-2.1</td>
<td>112,115</td>
</tr>
<tr>
<td>15</td>
<td>CHO</td>
<td>-3.9-4.6</td>
<td>115</td>
</tr>
<tr>
<td>16</td>
<td>CO$_2$H</td>
<td>2.3</td>
<td>115</td>
</tr>
<tr>
<td>17</td>
<td>CO$_2$H$_2^+$</td>
<td>-4.8</td>
<td>115,119</td>
</tr>
<tr>
<td>18</td>
<td>CO$_2^-$</td>
<td>7.3</td>
<td>115</td>
</tr>
<tr>
<td>19</td>
<td>CO$_2$Me</td>
<td>1.2</td>
<td>115</td>
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<tr>
<td>20</td>
<td>HC=NH$_{\text{trans}}$</td>
<td>-3.0</td>
<td>115</td>
</tr>
<tr>
<td>21</td>
<td>HC=NH$_{\text{cis}}$</td>
<td>3.0</td>
<td>115</td>
</tr>
<tr>
<td>22</td>
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<td>-10.1</td>
<td>115</td>
</tr>
<tr>
<td>23</td>
<td>CN</td>
<td>4.3-4.7</td>
<td>112,115</td>
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<tr>
<td>24</td>
<td>NO$_2$</td>
<td>6.4-7.3</td>
<td>112,115</td>
</tr>
<tr>
<td>25</td>
<td>NO</td>
<td>-2.6</td>
<td>115</td>
</tr>
<tr>
<td>26</td>
<td>S(O)H</td>
<td>0.1</td>
<td>115</td>
</tr>
<tr>
<td>27</td>
<td>SO(OH)</td>
<td>-1.4</td>
<td>115</td>
</tr>
<tr>
<td>28</td>
<td>SO$_2$H</td>
<td>-0.3</td>
<td>115</td>
</tr>
<tr>
<td>29</td>
<td>B(Me)$_2$</td>
<td>-11.5</td>
<td>115</td>
</tr>
<tr>
<td>30</td>
<td>BH$_2$</td>
<td>-15.9-18.2</td>
<td>115</td>
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<tr>
<td>31</td>
<td>SiH$_3$</td>
<td>-1.5-1.7</td>
<td>116,127</td>
</tr>
<tr>
<td>32</td>
<td>SiMe$_3$</td>
<td>-1.0-1.3</td>
<td>116</td>
</tr>
<tr>
<td>33</td>
<td>SiF$_3$</td>
<td>-3.8-4.1</td>
<td>116</td>
</tr>
<tr>
<td>34</td>
<td>PH$_2$</td>
<td>4.1-4.2</td>
<td>116</td>
</tr>
<tr>
<td>35</td>
<td>SnMe$_3$</td>
<td>-0.6</td>
<td>128</td>
</tr>
</tbody>
</table>

*Table 1.1* Calculated activation energies for outward and inward 4-π electrocyclic ring opening of 3-substituted cyclobutenes; *a* positive value = outward rotation favoured, negative value = inward rotation favoured
For 3,3 and cis-3,4 disubstituted cyclobutenes one group must rotate inwards, which can lead to an increase in the activation energy. Houk and Rondan have shown this increase in energy for cis-dimethyl- and dichloro-3,4-cyclobutenes.\textsuperscript{114} Sheikh has carried out a computational study on the activation energies of 4-π electrocyclic ring opening of 1,2-, 1,3-, 1,4- and trans-3,4-disubstituted cyclobutenes in comparison to unsubstituted cyclobutene (Figure 1.7).\textsuperscript{112} In most cases, the addition of two substituents on the double bond 2b resulted in an increase in the activation energy, which was highest with one electron donating and one withdrawing group to give an extended π system (e.g. NH\textsubscript{2} and NO\textsubscript{2}). 1,3-, 1,4- and trans-3,4 disubstitution 2c-e all gave lower activation energies than cyclobutene, with the trans-3,4 systems giving the lowest values especially when both an electron donating and withdrawing group were present. The author termed the effect of having electron donating and withdrawing substituents on the rate of electrocyclic ring opening as captodative substitution.

Maryasin and Maulide have computationally studied the stability of cis- and trans-cyclobutene derivatives 88a-f towards 4-π electrocyclic ring opening at room temperature (Scheme 1.24).\textsuperscript{129} The activation energy for the malonate derived cyclobutene 88a was too high for the reaction to take place at room temperature, in line with the groups experimental findings.\textsuperscript{130} For cyclobutenes 88b-f, the activation energies were considerably lower, with the energy barrier decreasing from alkyne 88b through to ether 88f and were expected to undergo ring opening spontaneously. In agreement with the theories proposed by Houk (vide supra), the authors found that the group adjacent the acid component showed preference for outward rotation to give dienes 89a.

\begin{center}
\begin{tabular}{ccc}
\includegraphics[width=0.15\textwidth]{88a.png} & \includegraphics[width=0.15\textwidth]{88b.png} & \includegraphics[width=0.15\textwidth]{88c.png} \\
88a & 88b & 88c \\
\includegraphics[width=0.15\textwidth]{88d.png} & \includegraphics[width=0.15\textwidth]{88e.png} & \includegraphics[width=0.15\textwidth]{88f.png} \\
88d & 88e & 88f \\
\end{tabular}
\end{center}

\textbf{Scheme 1.24}

1.4.2 Torquoselectivity – Experimental Evidence

The pioneering work between 1950-1970 provided experimental evidence for the conrotatory nature of the thermal 4-π electrocyclic ring opening of 3,3 and 3,4 disubstituted cyclobutenes 2e,f, however the effect of substituents was not fully understood and the products from these reactions were often rationalised on steric grounds (Figure 1.7).\textsuperscript{131-139} Since the development of the concept of torquoselectivity, these results could all be described using the theories proposed by Houk and co-workers and research has since focused on obtaining experimental
evidence to support the theoretical calculations. For many of the early examples the formation of the diene was highly selective to give a preferred isomer. Vogel was the first to report that the addition of electronegative atoms to the allylic positions of cyclobutene resulted in a sharp decrease in stability, whilst Brauman and Archie noted similar observations with cis-3,4-diphenylcyclobutenes. On the other hand, Frey and various co-workers noticed that the addition of alkyl groups to give 3,3- or 3,4-disubstituted cyclobutenes resulted in an increase in the activation energy for ring opening. Criegee and co-workers found that when heated, trans-3,4-dimethylcyclobutene selectively formed the E/E-diene and none of the Z/Z-diene was observed. In addition, various research groups have reported that bicyclic cyclobutenes have activation energies that are considerably higher than unsubstituted and alkyl substituted cyclobutenes, likely caused by the unfavourable strain that the formed dienes would possess.

Jefford, Boschung and Rimbault showed that 3-cyclobutenes bearing oxygen atoms selectively formed E-dienes.

![Figure 1.7](image)

The early steric explanation for the preferential formation of certain dienes began to be called into question when unexpected results began to arise. Curry and Stevens noticed that the ring opening of some 3,3-disubstituted cyclobutenes bearing a methyl group and an alkyl chain did not agree with this theory (Table 1.2). Systems that contained ethyl, propyl or isopropyl groups favoured inward rotation to form diene in slight excess (entries 1-3). For the larger tert-butyl and phenyl groups outward rotation was preferred to form diene (entries 4 and 5). Houk and co-workers reasoned that outward rotation of the methyl group minimised destabilising interactions in the transition state.

![Table 1.2](image)
Dolbier, Burton and various co-workers cast further doubt on the steric explanation from the ring opening of cyclobutenes bearing fluoroalkyl groups (Scheme 1.25).\textsuperscript{144-146} The authors discovered through the formation of dienes 95, 97, 99, 101 that fluorine preferred to rotate outwards, meaning that the fluoroalkyl groups had to rotate inwards. These observations were opposite to what was observed with alkyl substituents, and could be explained using the theory proposed by Houk and co-workers, in which fluorine acts as a donor to stabilise the LUMO $\sigma^*$ of the breaking C-C bond. Dolbier and co-workers have also evaluated the ring opening of 3-substituted cyclobutenes with fluorine or trifluoromethyl groups.\textsuperscript{147} Fluorine exclusively gave E-diene 103, whilst a trifluoromethyl group 104 was found to be more stable than cyclobutene itself. Upon heating at high temperatures, a mixture of dienes 105a,b was formed, and this was the first example where more than one product was observed for the ring opening of 3-substituted cyclobutenes. For 3,3-difluorocyclobutene 106 there was large increase in the activation energy shown by the high temperatures that required due to a fluorine atom having to rotate inwards.

\begin{align*}
\text{F} & \quad \text{CF}_3 & \quad \text{F} & \quad \text{CF}_3 & \quad \text{F} & \quad \text{CF}_3 \\
94 & & 95 & & 96 & & 97 & & 98 & & 99 & & 100 & & 101 \\
\text{F} & \quad \text{CF}_3 & \quad \text{F} & \quad \text{CF}_3 & \quad \text{F} & \quad \text{CF}_3 & \quad \text{F} & \quad \text{CF}_3 & \quad \text{F} & \quad \text{CF}_3 & \quad \text{F} & \quad \text{CF}_2\text{CF}_3 & \quad \text{F} & \quad \text{CF}_2\text{CF}_3
\end{align*}

\[\text{Scheme 1.25} \ n.r = \text{not reported}\]

Houk, Rudolf and Spellmeyer have proven experimentally that aldehyde 108 favoured inward rotation to give Z-diene 109 after heating, which rearranged to the more stable E-isomer under acidic or basic conditions (Scheme 1.26).\textsuperscript{118} In a similar fashion, Murakami and co-workers have shown that the ring opening of boronic ester 110 gave solely Z-diene 111, which is in agreement with the theoretical predictions.\textsuperscript{148} Niwayama and Houk have shown the slight preference for outward rotation for the electrocyclic ring opening of 3-acetylcylobutene 112 to give dienes 113a,b.\textsuperscript{123} The calculated values above suggested that ketones were less powerful $\pi$ acceptors
compared to aldehydes and favoured outward rotation (Table 1.1, entry 14), however the addition of a Lewis acid, specifically zinc iodide, reversed the torquoselectivity from outward to inward rotation to give diene 113b as the major product.\textsuperscript{123,125} Sodium carbonate had to be present to prevent the Lewis acid from isomerising Z-diene 113b to E-diene 113a. Murakami and co-workers have gone on to show that the 3-cyclobutenes that contained silyl and tin groups \textsuperscript{114,116} gave considerably more inward rotation than found with 3-\textit{tert}-butylcyclobutene \textsuperscript{118,127,128} The silyl and tin compounds contain a low energy $\sigma^*$ (Si-C or Sn-C) orbital that is able to accept electron density from the HOMO of the cleaving C-C bond, thus lowering the activation energy for inward rotation. Cyclobutene 118 does not have a low energy C-C $\sigma^*$ orbital preventing the \textit{tert}-butyl group from accepting electron density and resulting in outward rotation of this group only.

![Scheme 1](image)

Houk and Niwayama have further evaluated the inward rotation of aldehydes with cyclobutene \textsuperscript{120}, which selectively formed diene 121 where the aldehyde group rotated inwards and the ester group rotated outwards (Scheme 1.27).\textsuperscript{122} Diene 121 was unstable and readily cyclised to

\begin{align*}
\text{CHO} & \xrightarrow{\text{C}_6\text{D}_6, 50-70 \ ^\circ\text{C}} \text{CHO} \\
\text{Bpin} & \xrightarrow{\text{PhMe-}d_6, 90 \ ^\circ\text{C}, 4 \text{ hrs}} \text{Bpin} \\
\text{O} & \xrightarrow{\text{C}_6\text{D}_6, 80 \ ^\circ\text{C}} \text{CHO} \\
\text{SiMe}_2\text{Ph} & \xrightarrow{\text{m-xylene}, 140 \ ^\circ\text{C}, 9 \text{ hrs}} \text{SiMe}_2\text{Ph} \\
\text{SnMe}_3 & \xrightarrow{\text{m-xylene}, 140 \ ^\circ\text{C}, 9 \text{ hrs}} \text{SnMe}_3 \\
\text{Bu} & \xrightarrow{\text{m-xylene}, 140 \ ^\circ\text{C}, 12 \text{ hrs}} \text{Bu}
\end{align*}

\begin{align*}
\text{108} & \rightarrow 109 \\
\text{110} & \rightarrow 111 \\
\text{112} & \rightarrow 113a + 113b \\
\text{114} & \rightarrow 115a:b \\
\text{116} & \rightarrow 117a:b \\
\text{118} & \rightarrow 119
\end{align*}

\textbf{Scheme 1.26} Yields not reported; pin = pinacol; R = \text{PhMe}_2\text{C}
Chapter 1: Introduction
give pyran 122. From the calculated values above (Table 1.1), acids and esters only show a minor preference for outward rotation and aldehyde a strong preference for inward rotation, therefore this result was not unexpected. If an acid was used instead of an aldehyde the selectivity of the reaction was lost and equal quantities of dienes 124a,b were formed for the ring opening of cyclobutene 123.\textsuperscript{149} The ring opening 3,3-disubstituted cyclobutenes 125 bearing a methyl group with either an acid, ester or a carboxylate formed only dienes 126 where the methyl group preferentially rotated outwards.\textsuperscript{150} The authors reasoned that the energy barrier for outward rotation of the methyl group should be slightly lower than for the carboxylate. Changing the methyl group to a primary alcohol formed diene 128, in which the primary alcohol group rotated outwards and it was shown that this functional group showed similar rotation properties to a methyl group.\textsuperscript{150} Replacement of the carbonyl group with a nitrile group resulted in the formation of a mixture of dienes 130a,b, as nitriles also favour outward rotation.\textsuperscript{118,150}

![Scheme 1.27](image)

Curry and Stevens found that the ring opening of 3-tert-butyl-3-methylcyclobutene gave a larger proportion of a diene where the larger tert-butyl group rotated outwards (Scheme 1.28).\textsuperscript{143} Houk and co-workers noticed that when the methyl group was replaced with a silyl ether or a methoxy group, the ring opening of this cyclobutene 131 only formed diene 132, where the methoxy group rotated outwards and the tert-butyl group rotated inwards.\textsuperscript{151} These findings suggested that oxygen was a strong donor and can force even bulky groups to rotate inwards.
For cyclobutene 133, Murakami and co-workers established that when a strong and a weak electron acceptor were present a larger proportion of diene 134a where the strong electron acceptor group rotated inwards was formed. The authors reasoned that the vacant p orbital on the boron atoms accepted electron density more efficiently than the Si-C σ*.

\[
\text{133} \quad \xrightarrow{\text{C}_6\text{D}_6, 90^\circ \text{C}} \quad \text{132}
\]

**Scheme 1.28** Yields not reported

Murakami and co-workers have demonstrated the selective formation of dienes from 3,3-disubstituted cyclobutenes (Scheme 1.29). For cyclobutene 135 (which contains both donor and acceptor substituents), diene 136 was formed through preferential inward and outward rotation of each group, respectively, however when the silyl group was changed to a butyl group a mixture of dienes 138a,b was again formed. 1,2-Addition of an organolithium to a cyclobutenone formed cyclobutene 139 in situ, which at 0 °C ring opened spontaneously to give diene 140, and the enolate was trapped with acetyl chloride. The strong preference of alkoxides for outward rotation was observed in this reaction.

\[
\text{135} \quad \xrightarrow{\text{C}_6\text{H}_6, 80^\circ \text{C}, 2 \text{ hrs}} \quad \text{136}
\]

**Scheme 1.29**

Trost and McDougal have shown the minor preference for the outward rotation of esters compared to acids from cis-3,4-cyclobutene 141 (Table 1.3). The authors noticed an increase in E-selectivity as the solvent was changed from dimethyl sulfoxide (DMSO) to 1,2-
dichloroethane (DCE). The authors rationalised that in DMSO hydrogen bonding of the solvent to the acid moiety would increase the steric bulk of the acid and helps to increase the amount of outward rotation (entries 1-6). In chlorinated solvents such as DCE, this hydrogen bond interaction is not present and resulted in the ester group preferably rotating outwards (entries 3 and 6).

### Table 1.3

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>E:Z 142a:142b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-Bu</td>
<td>DMSO</td>
<td>110</td>
<td>50:50</td>
</tr>
<tr>
<td>2</td>
<td>n-Bu</td>
<td>DME</td>
<td>85</td>
<td>55:45</td>
</tr>
<tr>
<td>3</td>
<td>n-Bu</td>
<td>DCE</td>
<td>83</td>
<td>75:25</td>
</tr>
<tr>
<td>4</td>
<td>CH₂CH₂TMS</td>
<td>DMSO</td>
<td>85</td>
<td>55:45</td>
</tr>
<tr>
<td>5</td>
<td>CH₂CH₂TMS</td>
<td>DME</td>
<td>83</td>
<td>75:25</td>
</tr>
<tr>
<td>6</td>
<td>CH₂CH₂TMS</td>
<td>CCl₄</td>
<td>76</td>
<td>75:25</td>
</tr>
</tbody>
</table>

**Table 1.3** DMSO = dimethyl sulfoxide; DME = 1,2-dimethoxyethane; DCE = 1,2-dichloroethane; TMS = trimethylsilyl

As described above, the steric argument to answer the observed selectivity is often unreliable and Wallace and co-workers have found esters to have a stronger preference for outward rotation in comparison acids and acid chlorides (144a,b), thus meaning esters are slightly better donors than these groups (Scheme 1.30). Piers and Lu have also found experimentally that esters preferred outward rotation. Wallace and co-workers have also shown the selective formation of diene 146 from cis-3,4-cyclobutene 145 using groups which favoured inward and outward rotation.153–155

In accordance with the results seen with 3,3-disubstituted cyclobutenes, Huet and co-workers have shown that cis-3,4-disubstituted cyclobutene 147 that contained an amide and a primary alcohol gave a mixture of dienes 148a,b, where the major product (148a) was a result of the outward rotation of the primary alcohol group (Scheme 1.31). Huet and co-workers were the
4-π Photocyclisation: A New Route to Functionalised Four-Membered Rings

first to demonstrate the strong outward rotation preference for nitrogen substituents on 3,4-disubstituted cyclobutenes 149 in the presence of other groups that favour the same rotation.\textsuperscript{157–159}

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme1.png}
\caption{Scheme 1.31}
\end{figure}
\end{center}

There have been a couple of examples of the thermal ring opening of highly substituted cyclobutenes 151-153, which have resulted in the outward rotation of the oxygen substituents (Figure 1.8).\textsuperscript{160,161}

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Figure 1.8}
\end{figure}
\end{center}

\textbf{1.5 Conclusions}

From analysis of the literature, for synthetic methodology to be adopted and used in drug development programmes there needs to be robust methodology in place that can access a wide variety of scaffolds. In addition, these new methodologies need to be tolerant towards other functionality in the molecules, as well as giving properties that adhere to Lipinski’s rule of five, amongst other guidelines. To this end, the synthesis of unsubstituted and substituted 1,2-diazetidines has been achieved in moderate to high yields under a variety of conditions. There are currently no general routes to efficiently access a broad scope of highly substituted 1,2-diazetidines and most of the cutting-edge research has focused on the synthesis of the 3-substituted systems. To have any chance of 1,2-diazetidines being adopted by industry, new methodologies are required that are scalable and able to access a large variety of scaffolds bearing a variety of functional handles or groups.

For cyclobutenes, in order to synthesise compounds that are stable at room temperature, careful consideration must be given to which functional groups will be attached to the ring, otherwise there is a high chance that only diene products can be isolated. Groups bearing alkyl groups have been shown to increase the activation energy of the 4-π electrocyclic ring opening,
whereas heteroatoms and electron donating groups seemed to decrease the activation energy and make diene formation a lot easier. The development of torquoselectivity has provided valuable prediction and rationalisation tools on the preferential rotation of certain functional groups in the ring opening of cyclobutenes. In combination with these rules, cyclobutenes have fantastic potential for selectively giving defined dienes and through further exploration, can provide access to novel diene building blocks.
Chapter 2: Synthesis and Reactions of 1,2-Dihydropyridazines
Chapter 2: Synthesis and Reactions of 1,2-Dihydropyridazines

2.1 Introduction

2.1.1 Synthetic Approaches to 1,2-Dihydropyridazines

1,2-Dihydropyridazines 9 are heterocycles that possess two nitrogen atoms adjacent to one another and can be viewed as precursors to pyridazines 155 (Figure 2.1). There are only limited examples of the synthesis and use of 1,2-dihydropyridazines in the literature and they have most commonly been synthesised from 1,2,3,6-tetrahydropyridazines 154 (herein referred to as tetrahydropyridazines) through a range of reactions: allylic bromination-elimination,\textsuperscript{33-36,162,163} bromination-elimination,\textsuperscript{164-166} under basic conditions,\textsuperscript{167} using selenium dioxide.\textsuperscript{168} Nevertheless, other routes to synthesise 1,2-dihydropyridazines 9 have been developed from: substituted dienes,\textsuperscript{167,169} 1,4-diketones,\textsuperscript{170} cyclopentadienones,\textsuperscript{102,103} metallacycles,\textsuperscript{171,172} and pyrones.\textsuperscript{173,174}

![Figure 2.1](image)

Figure 2.1 PG = protecting group

Tetrahydropyridazines 154 are related heterocycles with two adjacent nitrogen atoms, and have often been synthesised through Diels-Alder reactions between dienes and azo compounds (Scheme 2.1). Successful reactions have been reported using a range of dienes: butadiene,\textsuperscript{35,36,168,175-189} butadiene derivatives,\textsuperscript{162,168,180,182,190-197} bicycloheptadiene,\textsuperscript{185} cycloheptatriene,\textsuperscript{185,198} cyclopentadiene\textsuperscript{177,183,185,198} and furans,\textsuperscript{168,199-207} though more recently alternative methods using organo- and transition metal catalysis have been developed.\textsuperscript{208-211}

![Scheme 2.1](image)

Scheme 2.1

The first reported synthesis of 1,2-dihydropyridazines was in the mid-1950’s by Alder and Niklas.\textsuperscript{168} The authors described the oxidation of the diphenyl-cycloadduct 156 with selenium dioxide (SeO\textsubscript{2}) to give 1,2-dihydropyridazine 157a (Scheme 2.2). Treatment of 156 with selenium dioxide would form intermediate 158, which under the reaction conditions should facilitate the formation of iminium ion 159 to form the desired product 157a after deprotonation. Rigaudy and Brelière also utilised this reaction in their synthesis of a similar 1,2-dihydropyridazine 157b that possessed ethyl carbamate protecting groups.\textsuperscript{212} Fisher and co-workers found that diphenyl-1,2-dihydropyridazine 157b did not react with 4-phenyl-1,2,4-
Triazoline-3,5-dione 8h (PTAD or PhTAD) even when heated at 120 °C.\textsuperscript{213} The authors reasoned that in order for a Diels-Alder reaction to occur a high energy planar transition state would have to form, in which unfavourable steric interactions between the carbamate protecting groups and the adjacent phenyl groups would occur.

\[
\begin{array}{c}
\begin{array}{c}
\text{Ph} \\
\text{N} \text{CO}_2\text{Me} \\
\text{Ph} \\
\text{N} \text{CO}_2\text{Me}
\end{array}
\end{array}
\xrightarrow{\text{SeO}_2, \text{AcOH}}
\begin{array}{c}
\begin{array}{c}
\text{Ph} \\
\text{N} \text{CO}_2\text{Me} \\
\text{Ph} \\
\text{N} \text{CO}_2\text{Me}
\end{array}
\end{array}
\]

\text{Δ, 3.5 hrs Yield: n.d.}

\text{Scheme 2.2}

A few years later, Rink and co-workers exploited a two-step bromination-dehydrobromination reaction in the synthesis of 1,2-dihydropyridazine 9b on decagram scales (Scheme 2.3).\textsuperscript{164} Bromination of tetrahydropyridazine 154b gave dibromide 160, which was then treated with potassium hydroxide to form 1,2-dihydropyridazine 9b in good yield. When more potassium hydroxide was used, hydrolysis of the carbamate protecting group was observed and gave the mono-protected 1,2-dihydropyridazines 161 in low yield. More recently, Sheradsky and Moshenberg have synthesised gram quantities of bicyclic 1,2-dihydropyridazines through a bromination-elimination reaction.\textsuperscript{165,166} Bicycles 162h,o derived from PTAD 8h and phthalazine-1,4-dione 8o were converted into their respective dibromides 163h,o, then subjected to basic conditions to access 1,2-dihydropyridazines 9h,o in moderate yields. The reaction with dibromide 163h was temperature sensitive, and above −55 °C the ring opened 1,2-dihydropyridazine 9q was formed in a moderate yield. No such issues were described with bromide 163o under the basic conditions. Sheradsky and Moshenberg have also studied the reactivity of the bicyclic 1,2-dihydropyridazines 9h,o. 9h,o reacted rapidly with PTAD 8h in a Diels-Alder reactions to give tricycles 164 and 165 in moderate-good yields, however 9h,o did not react with carbon dienophiles.
**Scheme 2.3** Yield over two steps

Altman *et al.* first reported the conversion of tetrahydropyridazines 154 into 1,2-dihydropyridazines 9 using a two-step allylic bromination-elimination reaction (Scheme 2.4)\(^{33, 34}\). Oxidation of tetrahydropyridazine 154a through an allylic bromination reaction with N-bromosuccinimide (NBS) in carbon tetrachloride (CCl\(_4\)) formed bromide 166, which underwent
an elimination reaction when heated in the presence of base to give 1,2-dihydropyridazine 9a in 66-81% yield. Moreover, this method was successfully applied for the synthesis of another two 1,2-dihydropyridazines 9b,c, although no experimental details were disclosed. More recently, Warrener et al. have further evaluated this methodology. Under nearly identical conditions, except for the addition of benzoyl peroxide in the allylic bromination reaction, cycloadduct 154a was converted into 1,2-dihydropyridazine 9a in 74% yield. Whitman and Carpenter have subsequently used this route to access a partially deuterated version of 1,2-dihydropyridazine 9a. Stearns and Ortiz de Montellano have demonstrated the synthesis of 1,2-dihydropyridazine 9b in moderate yields from cycloadduct 154b through an analogous allylic bromination-elimination reaction. In all cases, the authors completed these reactions on gram scales and did not attempt to isolate bromide 166, but instead immediately took the crude reaction mixture into the elimination reaction.

\[
\text{Scheme 2.4}^a \text{ Yield over two steps}
\]

Sheradsky and Moshenberg employed a similar two-step methodology to access tricyclic 1,2-dihydropyridazine 157o (Scheme 2.5). Tricycle 156o did not react with selenium dioxide under the conditions developed by Alder and Niklas for monocyclic systems. Instead, an allylic bromination reaction in the presence benzoyl peroxide was carried out to give bromide 167 in 68% yield. Bromide 167 readily underwent Sn1 reactions but attempts to convert bromide 167 into the desired product 157o under basic conditions resulted in the removal of the protecting group to give pyridazine 155o. Instead, the bromide 167 was heated at high temperatures, under a vacuum (1 mm Hg) to form the product 157o in a 40% yield. No mechanistic details were provided for the formation of 157o, but the first step is likely to be the cleavage of the C-Br bond to give stabilised cation 168, followed by deprotonation to give the
The same authors have synthesised diphenyl substituted 1,2-dihydropyridazine 157h in low yields through an initial allylic bromination reaction, followed by treatment under basic conditions at low temperatures, which was tolerated with these protecting groups.\textsuperscript{163}

\begin{equation}
\text{Chapte} \text{r 2: Synthesis and Reactions of 1,2-Dihydropyridazines}
\end{equation}

Ried and Reiher have exploited enones derived from substituted dienes 169 in their synthesis of substituted 1,2-dihydropyridazines (Scheme 2.6).\textsuperscript{169} Enone 170 was accessed in moderate-good yields through a Diels-Alder reaction between silyl-diene 169 and either diethyl azodicarboxylate (DEAD) 8b or PTAD 8h, followed by removal of the silyl groups with hydrofluoric acid. The $\alpha,\beta$-unsaturated ketones 170 were then converted into substituted 1,2-dihydropyridazines 171b,h in high yields through the formation of an enolate, which was trapped with tert-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf).

\begin{equation}
\text{Scheme 2.5} \text{a Yield over two steps}
\end{equation}

\begin{equation}
\text{Scheme 2.6} \text{a Yield over three steps}
\end{equation}
Avery and co-workers have also used substituted dienes in their attempts to synthesise bicyclic 1,2-dihydropyridazine 173 (Scheme 2.7).\textsuperscript{167} When the pyrazolin-5-one derivative adduct mixture 172 was treated under basic conditions, 1,2-dihydropyridazine 174 was isolated in 16\% yield alongside the addition products 174\textsubscript{a,b} in 42\% yield. The authors attempted to improve the yield under different conditions: 1,8-diazabicycloundec-7-ene (DBU)/dichloromethane, pyridine/dichloromethane, potassium carbonate/dichloromethane, boron trifluoride ethyl etherate/dichloromethane, however these resulted in either decomposition or no reaction at all (no specific details were disclosed for which reactions failed or decomposed).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {172};
\node (b) at (1,0) {173 (16\%)};
\node (c) at (2,0) {174\textsubscript{a,b} (42\%, 78:22)};
\node (d) at (0,1) {or};
\node (e) at (1.5,1) {K\textsubscript{2}CO\textsubscript{3}};
\node (f) at (2.5,1) {MeOH, Å, 3 hrs};
\end{tikzpicture}
\end{center}

An alternative route to access 1,2-dihydropyridazines directly would be to use 2-pyrones 175. These reactions proceed via an initial Diels-Alder reaction with azo compounds 8 to give the intermediate 176, followed by a retro-Diels-Alder reaction to eliminate carbon dioxide to form 1,2-dihydropyridazines 9 (Scheme 2.8).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {175};
\node (b) at (1.5,0) {176};
\node (c) at (3,0) {9};
\node (d) at (0,1) {PG\textsuperscript{+}N\textsuperscript{-}N\textsuperscript{-}PG};
\node (e) at (1.5,1) {PG\textsuperscript{+}N\textsuperscript{-}N\textsuperscript{-}PG};
\node (f) at (3,1) {PG\textsuperscript{+}N\textsuperscript{-}N\textsuperscript{-}PG};
\node (g) at (1.5,1.5) {-CO\textsubscript{2}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 2.8} PG = protecting group

Arora and Mackay demonstrated the first example of this reaction in 1969 with acyclic azo compounds (Table 2.1).\textsuperscript{173} When equimolar amounts of 2-pyrone 175 and azo compounds 8 were heated in benzene only minor amounts of 1,2-dihydropyridazines 9 were formed (entries 1-3). The major product from these reactions were the bis-adducts 175 in 22-60\% yield, which were formed from the reaction of the azo compounds 8 with 1,2-dihydropyridazines 9. The low yields observed for azo compounds with small alkyl groups could be attributed to the degradation of azo compounds at higher temperatures. Altman \textit{et al.} have shown that 1,2-dihydropyridazine 9\textsubscript{i} can be accessed through the reaction with 2-pyrone 175 and bis(2,2,2-trichloroethyl) azodicarboxylate 8\textsubscript{i}, but no further details were reported (entry 4).\textsuperscript{34}
Chapter 2: Synthesis and Reactions of 1,2-Dihydropyridazines

\[
\begin{align*}
\text{RO}_2\text{C}^\cdot \text{N}^\cdot \text{N}^\cdot \text{CO}_2\text{R} \\
\text{C}_8\text{H}_6, \Delta, 3-10 \text{ days} \\
\text{175} \\
\text{8} \\
\text{176} \\
\text{177} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time (days)</th>
<th>Yield 9 (%)</th>
<th>Yield 177 (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>10</td>
<td>n.d</td>
<td>26</td>
<td>173</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>7</td>
<td>16</td>
<td>22</td>
<td>173</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>3</td>
<td>0</td>
<td>60</td>
<td>173</td>
</tr>
<tr>
<td>4</td>
<td>CH\text{2CCI3}</td>
<td>n.r</td>
<td>n.r</td>
<td>n.r</td>
<td>34</td>
</tr>
</tbody>
</table>

Table 2.1 n.r = not reported

Sheradsky and Moshenberg further evaluated the use of pyrones in their synthesis of the substituted bicyclic 1,2-dihydropyridazine 179h (Scheme 2.9). Here, the reaction between an ester substituted 2-pyrene 178 and PTAD 8h afforded 1,2-dihydropyridazine 179h in 42% yield, though the bis-adduct 180 was still formed in 20% yield. When 1,2-dihydropyridazine 179h was directly reacted with PTAD 8h, the bis-adduct 180 was formed in quantitative yields. The authors used 2-pyrones after failure to convert bicycle 181h into 1,2-dihydropyridazine 179h with selenium dioxide or the two-step allylic bromination-elimination reactions.

\[
\begin{align*}
\text{CO}_2\text{Me} \\
\text{N}^\cdot \text{N}^\cdot \text{O}^\cdot \text{Ph} \\
\text{8h} \\
\text{(1.0 eq)} \\
\text{acetone} \\
0 ^\circ \text{C} \rightarrow \text{r.t}, \text{ 1 hr} \\
\text{178} \\
\text{179} \text{h (42\%)} \\
\text{180} \text{ (20\%)} \\
\text{181} \text{h} \\
\text{182} \\
\end{align*}
\]

Scheme 2.9

Mackay and co-workers found that cyclopentadienone derived cycloadducts 62 decomposed at high temperatures to give small quantities of 1,2-dihydropyridazines 182, as well as other major products (Scheme 2.10). At temperatures above 80 °C, a select few cycloadducts 62 underwent decarbonylation to give 1,2-dihydropyridazines 182, but most only underwent rearrangement reactions (Section 1.3.2, Scheme 1.17). In all cases, irradiation of cycloadducts 62 resulted in decarbonylation to give the tetrasubstituted 1,2-dihydropyridazines 182, though no yields were reported.
Takahashi and co-workers have demonstrated the only example where zirconacyclopentadienes 183 were used to form tetra-substituted 1,2-dihydropyridazines 184a-e, through a reaction with a variety of azo compounds (Scheme 2.11).\textsuperscript{171,172} The reaction was successful with methyl, ethyl, isopropyl and benzyl azo compounds and tetra-alkyl-substituted zirconacyclopentadienes to give a series of 1,2-dihydropyridazines 184a-e in moderate to good yields.

Scheme 2.10 a) R' = Me; b) R' = Et; c) R' = CH$_2$CCl$_3$; d) R' = Ph; e) R' = ‘Bu
Zelenin and Dumpis have described the condensation reaction of a 1,4-diketone 185 with alkyl hydrazines 37 to access methyl substituted 1,2-dihydropyridazines 186 (Table 2.2). The condensation reaction of acetonylaceton 185 with methyl and ethyl hydrazine 37, in the presence of a Lewis acid, gave 1,2-dihydropyridazine 186 in moderate yields, as well as the formation of the side product 187.

\[
\begin{array}{c|cc|c|c}
\text{Entry} & \text{R} & \text{Yield 186} & \text{Yield 187} \\
1 & \text{Me} & 36 & 10 \\
2 & \text{Et} & 39 & 8 \\
\end{array}
\]

Table 2.2

In 2007, Lautens and co-workers proposed a Lewis acid catalysed synthesis of monoprotected 1,2-dihydropyridazine 191 from methylenecyclopropyl hydrazones 188 (Scheme 2.12). When hydrazone 188 was treated with magnesium chloride (MgCl\(_2\)) and N,N,N,N-tetramethylethylenediamine (TMEDA) it was initially thought that 1,2-dihydropyridazine 191 was formed in 86% yield, with >20:1 selectivity over the 1,6-dihydropyridazine 190. It has since been determined that the product was pyrrole 189 and not 1,2-dihydropyridazine 191. The authors proposed that after initial coordination of the Lewis acid to the hydrazone to give intermediate 192 that formation of the five membered ring could take place through two pathways. Firstly, through a direct rearrangement reaction or secondly, through an initial ring opening of the cyclopropyl ring to give allylic cation 193, which could then undergo cyclisation to form 194. The precursor 194 could then undergo a hydrogen atom transfer to give the product 189.

\[
\text{Scheme 2.12}
\]
There are limited examples in which hydrazines and azo compounds have been reacted with aromatic compounds to form fused 1,2-dihydropyridazines 195-198 using vinlnaphthalene,216 perylenes,217 pyrroles,218 and other aromatic derivatives (Figure 2.2).219,220 In addition, the oxidation of alkylated hydrazines with mercuric oxide (HgO) produced small quantities of 1,2-dihydropyridazines 199.221

![Chemical structures](image)

**Figure 2.2**

2.1.2 Conformational Studies

Previous studies have shown that the use of nuclear magnetic resonance (NMR) spectroscopy to analyse and characterise tetrahydropyridazines and, to a lesser extent, 1,2-dihydropyridazines is not trivial due to complex NMR spectra.187,213,222-231 Three major factors are thought to be the cause of these problems: restricted rotation about the N-CO₂R bond, nitrogen inversion of the carbamate and ring inversion. It has been proposed that in solution the slow equilibration of two half-chair (tetrahydropyridazines) or twist boat (1,2-dihydropyridazine) conformations is the major cause of the complicated NMR spectra at room temperature. The use of variable-temperature (VT) NMR showed that as the temperature was increased, so did the rate of interconversion, to give an average molecule that is rendered symmetrical on the NMR timescale.187,213,222-224,226-228,230,231 From ¹H NMR analysis, Anderson and Lehn proposed that the diphenyl 1,2-dihydropyridazine 157b had a non-planar and non-symmetrical structure (Figure 2.3).222 The authors observed non-equivalent peaks for the ethyl carbamate CH₂ hydrogens at temperatures where rotation about the carbamate bond was thought to be fast. Instead, it was thought that 1,2-dihydropyridazine 157b underwent a slow equilibration between two “twisted” conformations, which is the known conformation of 1,3-cyclohexadiene.232 From ¹³C NMR analysis of the same 1,2-dihydropyridazine 157b, Fisher and co-workers suggested a symmetrical structure due the presence of only one set of peaks for the ethyl carbamate protecting groups.213 Kaftory and co-workers provided further evidence to support Anderson and Lehn’s theory through determination that 1,2-dihydropyridazine 157b adopted a twist-boat conformation in the solid state.223
2.1.3 Conclusions

Currently, there is no general methodology to access a variety of unsubstituted and substituted 1,2-dihydropyridazines. Most 1,2-dihydropyridazine syntheses have utilised tetrahydropyridazines, which can be easily accessed through Diels-Alder reactions and provide easily accessible building blocks. The most efficient method for the synthesis of 1,2-dihydropyridazines is through allylic bromination-elimination or bromination-elimination reactions from the corresponding tetrahydropyridazine (Scheme 2.13). A limitation to these methodologies is the atom efficiency of the reactions (addition, followed by removal, of one or two bromines) and for the allylic bromination reactions, the environmental and health impact associated with the use of carbon tetrachloride. Other routes are possible, however they use reagents which are not commercially available or lead only to a specific substitution pattern (cyclopentadienones and zirconium diene complexes). 1,2-Dihydropyridazines can be accessed directly with 2-pyrones in moderate yields when reacted with cyclic dienophiles, whereas when acyclic dienophiles are used, very poor yields are obtained. A major characteristic of 1,2-dihydropyridazines is the complicated rate processes in solution that lead to complicated NMR spectra and structure determination can be aided through VT-NMR and X-ray crystallography.

![Crystal structure of 157b](image)

Scheme 2.13

2.2 Aims

The main goal was to access 1,2-dihydropyridazines in meaningful quantities from commercially available building blocks through existing or newly developed methodologies (Figure 2.4). Multigram quantities of 1,2-dihydropyridazines were required for the optimisation of the 4-π photocyclisation (Chapter 3), as well as the exploration of other transformations of 1,2-dihydropyridazines to validate their synthetic potential (Section 2.3.4). Treatment of 1,2-dihydropyridazines under typical conditions for double bond functionalisation should enable
novel and potentially synthetically valuable building blocks to be accessed. The synthesis of 1,2-dihydropyridazines through literature procedures needed to be evaluated, to determine whether these procedures were suitable for this application on multi-gram scale. For example, the use of the two-step allylic bromination-elimination reactions developed by Altman and co-workers was dependent on finding an alternative solvent to replace carbon tetrachloride in the allylic bromination reaction. If not, this route would have to be discarded as the use of carbon tetrachloride would not be possible on any reasonable scale, due to detrimental environmental and health impacts. If none of the literature procedures were successful, a novel synthesis would have to be developed, which would require significant route planning and optimisation. Ideally, any new methodology would be applicable to the synthesis of substituted 1,2-dihydropyridazine to enable more substrates to be studied in downstream applications.

Figure 2.4

2.3 Results and Discussion

2.3.1 Synthesis of 1,2-Dihydropyridazines Through Literature Procedures

2.3.1.1 Synthesis of 1,2,3,6-Tetrahydropyridazines

Stearns and Montellano de Ortiz have reported the synthesis of tetrahydropyridazine 154b from butadiene sulfone 200 and DEAD 8b in high yields (Scheme 2.14). An unspecified amount of butadiene sulfone 200 was heated to form butadiene 78, which was then bubbled into a solution of DEAD 8b in benzene for two hours and left for two days.

Applying these conditions, the reaction of DEAD 8b and butadiene 78 (from butadiene sulfone) provided the cycloadduct 154b in 61% yield (Scheme 2.15). The use of di-tert-butyl azodicarboxylate (DBAD) 8d resulted in the formation of a complex mixture, however cycloadduct 154d was isolated in 11% yield. When a "one-pot" procedure was attempted, in which butadiene sulfone 200 and DBAD 8d were heated in high boiling point solvents (toluene...
or xylene), a complex mixture was formed. None of the isolated samples were ever pure enough to consider pursuing this method any further (determined by $^1$H NMR). At these temperatures, degradation of azo compound 8d was likely to occur, which would lead to the formation of complex mixtures. In addition, the inconvenience of heating butadiene sulfone further detracted from this synthetic approach.

![Scheme 2.15](image)

A commercially available 15% (w/v) butadiene solution in hexane was also investigated, and it was expected to provide a more convenient source of butadiene 78 (Table 2.3). The use of equimolar amounts of butadiene 78 and DBAD 8d in dichloromethane or methanol at room temperature proceeded slowly, though the reactions were cleaner than the reactions with butadiene sulfone 200 (entries 1 and 2). When the reaction was run in dichloromethane cycloadduct 154d was isolated in 17% yield, however a significant amount of DBAD 8d remained (entry 1). In methanol, the yield increased but the reaction was accompanied by the formation of unidentified side-products (entry 2). When three equivalents of butadiene were used, the product 154d was isolated in 76% yield after stirring for a week at room temperature (entry 3). Changing the solvent to hexane was detrimental due to solubility issues with DBAD 8d and the cycloadduct 154d was isolated in only 7% yield (entry 4). Further modifications were to use a sealed flask and to increase the temperature to reflux. After four days, this method gave the desired product 154d in a 93% yield, which increased to 97% on gram scale (entry 5). When the azo compound was changed to DEAD 8b or diisopropyl azodicarboxylate (DIAD) 8c, the reaction proceeded in excellent yields in under 24 hours at room temperature (entry 6) or at reflux (entry 7). Cycloadduct 154b was obtained in high yields and of sufficient purity that no purification was required.
4-π Photocyclisation: A New Route to Functionalised Four-Membered Rings

\[
\text{RO}_2\text{C}^-\text{N}^-\text{N}^-\text{CO}_2\text{R} \xrightarrow{\text{78}} \text{N}^-\text{N}^-\text{CO}_2\text{R}
\]

15% (w/v) solution in hexane (eq)

solvent, temperature, time

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Equivalents of 78</th>
<th>Temperature</th>
<th>Solvent</th>
<th>Time (days)</th>
<th>Yield 154b-d (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>tBu</td>
<td>1.0</td>
<td>rt</td>
<td>CH₂Cl₂</td>
<td>1</td>
<td>17 (154d)</td>
</tr>
<tr>
<td>2</td>
<td>tBu</td>
<td>1.0</td>
<td>rt</td>
<td>MeOH</td>
<td>4</td>
<td>22 (154d)</td>
</tr>
<tr>
<td>3</td>
<td>tBu</td>
<td>3.0</td>
<td>rt</td>
<td>CH₂Cl₂</td>
<td>7</td>
<td>76 (154d)</td>
</tr>
<tr>
<td>4</td>
<td>tBu</td>
<td>3.0</td>
<td>rt</td>
<td>hexane</td>
<td>2</td>
<td>7 (154d)</td>
</tr>
<tr>
<td>5</td>
<td>tBu</td>
<td>3.0</td>
<td>40 °C\textsuperscript{a}</td>
<td>CH₂Cl₂</td>
<td>4</td>
<td>93-97 (154d)</td>
</tr>
<tr>
<td>6</td>
<td>Et</td>
<td>3.0</td>
<td>rt</td>
<td>CH₂Cl₂</td>
<td>1</td>
<td>96 (154b)</td>
</tr>
<tr>
<td>7</td>
<td>iPr</td>
<td>3.0</td>
<td>40 °C\textsuperscript{a}</td>
<td>CH₂Cl₂</td>
<td>1</td>
<td>97 (154c)</td>
</tr>
</tbody>
</table>

Table 2.3 \textsuperscript{a} Reaction carried out in a sealed vessel

2.3.1.2 Synthesis of 1,2-Dihydropyridazines from Tetrahydropyridazines

Altman and Ortiz de Montellano’s allylic bromination reactions were successful without an initiator and were run in carbon tetrachloride, a solvent well-known for its detrimental environmental impact, toxicity and hazards (Scheme 2.16).\textsuperscript{33,34,36} It was necessary to investigate the use of an alternative solvent that would not undergo radical reactions itself under the reaction conditions and would be more environmentally acceptable. Allylic bromination reactions have been completed without carbon tetrachloride on aromatic systems utilising ionic liquids or solvent free conditions and on lipids in cyclohexane.\textsuperscript{233-235}

Inspired by these reaction conditions, the allylic bromination-elimination reaction was attempted on tetrahydropyridazine 154b using different solvents for the allylic bromination reaction (Table 2.4). When cyclohexane was used, tetrahydropyridazine 154b was converted into 1,2-dihydropyridazine 9b in 25% yield, however this was lower than the 50% yield reported in the literature in carbon tetrachloride (entry 1). When the solvent was changed to acetonitrile, no product formation was observed (entry 2). The use of cyclohexane for both the allylic bromination and the elimination steps did not give any promising results and showed only trace formation of the desired product (entry 3). The addition of a catalytic or stoichiometric amount of azobisisobutyronitrile (AIBN), a radical initiator, also did not significantly improve the yield (entries 4 and 5). In all cases, a complex mixture was formed and apart from when
stoichiometric quantities of AIBN were used, poor conversions of tetrahydropyridazine 154b was observed in the allylic bromination reaction. The 1,2-dihydropyridazine 9b samples isolated by this method were of poor purity and degraded upon storage.

![Chemical structure of 154b and 9b](image)

Table 2.4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent for i)</th>
<th>Solvent for ii)</th>
<th>Initiator</th>
<th>Yield 9b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cy</td>
<td>PhMe</td>
<td>-</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>MeCN</td>
<td>PhMe</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Cy</td>
<td>Cy</td>
<td>-</td>
<td>traces</td>
</tr>
<tr>
<td>4</td>
<td>Cy</td>
<td>PhMe</td>
<td>AIBN (1 mol%)</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>Cy</td>
<td>PhMe</td>
<td>AIBN (1.0 eq)</td>
<td>21</td>
</tr>
</tbody>
</table>

Alternatively, the conversion of tetrahydropyridazine 154b into 1,2-dihydropyridazine 9b was attempted using selenium dioxide or bromination-elimination reactions, which have been successful on related systems (Scheme 2.3). When tetrahydropyridazine 154b was treated with selenium dioxide in acetic acid (AcOH), 1,2-dihydropyridazine 9b was not formed and only degradation was observed by 1H NMR spectroscopy (Scheme 2.17). The literature example used the diphenyl substituted system 156a as opposed to cycloadduct 154b, which could easily undergo an E1 reaction to eliminate the organoselenium intermediate and form 1,2-dihydropyridazine 157a, whereas the organoselenium intermediate that would form from 154b might be less likely to undergo an E1 elimination reaction. An attempted bromination of tetrahydropyridazine 154b resulted in a loss of material after work-up. The 1H NMR spectrum of the crude product was clearly different to the starting material, as the double bond signal had disappeared, however the peaks observed in the 1H NMR spectrum were not in a similar range to those reported. The bromination reaction was not pursued any further due to scale-up and atom efficiency concerns.

![Scheme 2.17](image)
2.3.1.3 Synthesis of 1,2-Dihydropyridazines from 2-Pyrones

2-Pyrones 175 were an attractive option to directly access 1,2-dihydropyridazines 9. The Diels-Alder reaction of 2-pyrones 175 and azo compounds 8 forms intermediate 176, which can then undergo a retro-Diels-Alder reaction to eliminate carbon dioxide and form 1,2-dihydropyridazine 9 (Scheme 2.18). A major limitation of these reactions previously was the low yields using acyclic azo compounds and the formation of bis-adducts 177 through the reaction of 1,2-dihydropyridazines 9 with the starting azo compound 8 present in the reaction mixture (Scheme 2.9).165,174,213

![Scheme 2.18](image)

Using 2-pyrones (175) and DEAD (8b), the feasibility of using 2-pyrones to access 1,2-dihydropyridazines 9 was investigated (Table 2.5). Under conditions that were successful with PTAD 8h and a 2-pyrone derivative 178,174 the reaction showed no change when stirred at room temperature for prolonged reaction times (entry 1). PTAD 8h is a highly reactive dienophile and more reactive than DEAD 8b, which likely enabled the reaction to proceed at lower temperatures. When the Diels-Alder reaction was heated at 100 °C for two days, only trace amounts of 1,2-dihydropyridazine 9b was observed by 1H NMR spectroscopy and no product was observed when the temperature was increased to 120 °C (entries 2 and 3). At these temperatures, degradation of the azo compound was likely to be a significant limiting factor to the success of these reactions. Attempts to synthesise and use a 2-pyrone derivative 201 with silyl protecting groups proved to be difficult, as these compounds were unstable. The use of 2-pyrones was therefore not continued as a potential route to 1,2-dihydropyridazines, as no promising results had been obtained.

![Reaction Conditions](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield 9b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetone, 0 °C → rt, 7 days</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>PhMe, 100 °C, 2 days</td>
<td>traces</td>
</tr>
<tr>
<td>3</td>
<td>PhMe, 120 °C, 1 day</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2.5
2.3.2 Novel Synthesis of 1,2-Dihydropyridazines from O-Substituted Dienes

With other routes failing to provide an efficient method to produce simple, unsubstituted 1,2-dihydropyridazines of sufficient purity and in useful quantities, the development of a novel synthetic route starting from O-substituted dienes was investigated. A suitable leaving group was incorporated into the structure of diene 202, which after a Diels-Alder reaction would give an intermediate 203 that could potentially be treated under acidic, basic or catalytic conditions to generate 1,2-dihydropyridazines 9 (Scheme 2.19). The idea was to start from the commercially available crotonaldehyde 204, which could be converted into various types of O-substituted dienes 202. Initially, it would be necessary to isolate cycloadducts to find the optimum conditions for the second step. Once these conditions have been determined, it was hoped that a one-pot method could be developed.

Scheme 2.19 LG = leaving group; Ac = acetyl; Bz = benzoyl; Piv = pivaloyl; TBS = tert-butyldimethylsilyl; Ts = tosyl; Ms = mesyl.

2.3.2.1 Diene Synthesis

Initial attempts focused on the conversion of crotonaldehyde 204 into 1-acetoxybutadiene 202a, which was known in the literature.236–238 The synthesis of diene 202a was first attempted under conditions that used a large excess of acetic anhydride at room temperature (Table 2.6).238 Under these conditions, diene 202a was isolated in moderate yield, however it was imperative to quench any residual acetic anhydride, otherwise the product was contaminated with acetic anhydride after purification (entry 1). Attempts to reduce the amount of acetic anhydride resulted in a slower conversion of crotonaldehyde 204, but through longer reaction times diene 202a was formed in an improved yield, albeit with a slightly reduced E/Z ratio (entry 2). In contrast, when a slight excess of acetic anhydride was used diene 202a was formed in a 58% yield after two days, albeit with a reduced E/Z selectivity of 5.5:1 (entry 3). In all cases, the yield was lower than found in the literature and it was likely influenced by the volatility of the product. The synthesis of diene 202a has been successfully scaled-up on a decagram scale using three equivalents of acetic anhydride and gave a comparable yield to that obtained on a small scale.
An alternative method for the synthesis of diene 202a was to run at low temperatures in the presence of potassium tert-butoxide and acetyl chloride (Table 2.7).\textsuperscript{237} Under these conditions, diene 202a was formed in 38% yield and with a 50:1 $E/Z$ selectivity (entry 1). There were two main issues with this reaction. Firstly, isolation of the diene 202a in high purity was difficult due to presence of high boiling point solvents after aqueous work up (tetrahydrofuran and tert-butanol), which were hard to remove without the loss of product due to its volatility. The second issue was the low yield, which stemmed from the loss of product during isolation and a large proportion of a degradation products being formed. When 2-methyltetrahydrofuran (2-MeTHF) was used, it was harder to isolate pure samples due to the solvent’s higher boiling point, even though its water immiscibility made the procedure easier to carry out (entry 2). When alternative bases and solvents were investigated, the main difficulty was the deprotonation of crotonaldehyde 204 prior to acetylation. The use of lower boiling point solvents, such as diethyl ether were successful, however the reaction was not as clean as when carried out in tetrahydrofuran (entry 3). Changing the base to sodium ethoxide, triethylamine or sodium hydride (entries 4-6), gave no reaction and only starting material was recovered, whereas the use of lithium bis(trimethylsilyl)amine (LiHMDS) showed the formation of an unidentified diene compound (entry 7).

![Diagram of photocyclisation reaction]

Table 2.6 \textsuperscript{a} $E/Z$ ratio calculated by $^1$H NMR through comparison of diene peaks. No internal standard used; \textsuperscript{b} It was not possible to determine the major product; Ac$_2$O = acetic anhydride.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ac$_2$O (eq)</th>
<th>Time (days)</th>
<th>Yield 202a (%)</th>
<th>$E/Z$ or $Z:E$\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.0</td>
<td>1</td>
<td>50</td>
<td>10:1.0</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>4</td>
<td>62</td>
<td>8.0:1.0</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>2</td>
<td>58</td>
<td>5.5:1.0</td>
</tr>
</tbody>
</table>

Table 2.7 \textsuperscript{a} $E/Z$ ratio calculated by $^1$H NMR through comparison of diene peaks. No internal standard used; \textsuperscript{b} It was not possible to determine the major product; \textsuperscript{c} 202a was formed but not isolated; MTBE = methyl tert-butyl ether; THF = tetrahydrofuran; LiHMDS = lithium bis(trimethylsilyl)amine.
Under similar or modified conditions, the synthesis of other O-substituted dienes 202b-g was attempted (Table 2.8). Benzoyl-diene 202b would likely be less volatile than acetoxy-diene 202a and reduce the likelihood of losing material during isolation. Adaptation of the procedure used for the synthesis of acetoxy diene 202a, but using benzoyl chloride instead of acetic anhydride, formed a suspension that was difficult to stir. Purification proved to be difficult as the diene was unstable on silica gel, but diene 202b was isolated in 22% yield with 3:1 E/Z selectivity (entry 1). When the synthesis of diene 202b was completed at lower temperatures, the yield was improved to 53% with 20:1 E/Z selectivity (entry 2). The low temperature synthesis has since been expanded to access the pivalate diene 202c in 54% yield with 50:1 E/Z selectivity and the carbonate diene 202d in 34% yield with 30:1 E/Z selectivity (entries 3 and 4). The lower yield for the carbonate reaction could be rationalised due to the volatility of the product. Attempts to form the tosyl-diene 202e at low temperatures failed, however using the other conditions where acetic anhydride was replaced with tosyl chloride showed more promise. The $^1$H NMR spectrum showed signs that the tosyl-diene 202e could have formed, however the reaction showed poor conversion of crotonaldehyde and any attempt to isolate the diene resulted in degradation (entry 5). Formation of dienes equipped with either a trifluoroacetate (202f) or mesyl (202g) group gave no reaction and only starting material was observed by $^1$H NMR spectroscopy (entries 6 and 7).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Conditions</th>
<th>Yield 202b-g (%)</th>
<th>E:Z or Z:E$^{ab}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bz</td>
<td>BzCl (1.1 eq), NEt$_3$ (2.1 eq), DMAP (0.2 eq), neat, rt, 24 hrs</td>
<td>22 (202b)</td>
<td>3.0:1.0</td>
</tr>
<tr>
<td>2</td>
<td>Bz</td>
<td>BzCl (1.2 eq), KO'Bu (1.1 eq), THF, −78 °C, 30 mins</td>
<td>53 (202b)</td>
<td>20:1.0</td>
</tr>
<tr>
<td>3</td>
<td>Piv</td>
<td>PivCl (1.2 eq), KO'Bu (1.1 eq), THF, −78 °C, 30 mins</td>
<td>54 (202c)</td>
<td>50:1.0</td>
</tr>
<tr>
<td>4</td>
<td>CO$_2$Et</td>
<td>EtOC(O)Cl (1.2 eq), KO'Bu (1.1 eq), THF, −78 °C, 30 mins</td>
<td>34 (202d)</td>
<td>30:1.0</td>
</tr>
<tr>
<td>5</td>
<td>Ts</td>
<td>TsCl (5.0 eq), NEt$_3$ (2.1 eq), DMAP (0.2 eq), neat, rt, 3 days</td>
<td>0 (202e)</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>C(O)CF$_3$</td>
<td>TFAA (5.0 eq), NEt$_3$ (2.1 eq), DMAP (0.2 eq), neat, rt, 24 hrs</td>
<td>0 (202f)</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Ms</td>
<td>MsCl (1.2 eq), NEt$_3$ (2.5 eq), CH$_2$Cl$_2$, −78 °C → rt, 21 hrs</td>
<td>0 (202g)</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2.8 $^a$ E/Z calculated by $^1$H NMR through comparison of diene peaks. No internal standard used; $^b$ It was not possible to determine major product; TFAA = trifluoroacetic anhydride

2.3.2.2 Diels-Alder Optimisation

Optimisation of the Diels-Alder reaction was carried out using DIAD 8c and dienes 202a-d (Scheme 2.20). In most cases, the reaction gave cycloadducts 203,205-207 in excellent yields.
except with benzoyl-diene 202b. The synthesis of cycloadduct 207 led to the formation of a complex mixture of products and cycloadduct 207 was found to be unstable to purification and isolation. These initial reactions were completed in methyl tert-butyl ether, however dichloromethane could also be used to give identical yields (99% for cycloadduct 203). It should be noted that these cycloadducts 203 formed small quantities of the alcohol 208 when purified on silica gel, neutral alumina and neutralised silica gel. It had to be accepted that if column chromatography was necessary, then it was likely that some material would be lost. All the dienes were soluble in hexane, which meant that if the cycloadduct was a solid it could be purified by the addition of hexane and filtration. Alternatively, the removal of any excess diene by vacuum distillation gave suitably pure material, apart from pivalate 205, which still contained minor impurities.

Scheme 2.20

2.3.2.3 Synthesis of 1,2-Dihydropyridazines
Elimination of the acetate group of the cycloadduct 203c to give 1,2-dihydropyridazine 9c was attempted under acidic or basic conditions and with Lewis acids (Table 2.9). With p-toluenesulfonic acid or a Lewis acid, 1,2-dihydropyridazine 9c was not formed and produced materials very difficult to characterise due to complicated NMR spectra (entries 1-3). The use of sodium hydride resulted in degradation of cycloadduct 203c (entry 4), whereas with weaker bases no reaction was observed at room temperature and at higher temperatures (entries 5-9)
An alternative strategy was to use palladium chemistry, as cycloadduct 203 is an allylic acetate. Palladium catalysis has been utilised in the conversion of allylic compounds with a suitable leaving group into 1,3-dienes via an η³ π-allyl complex, and it was hoped that similar conditions could be developed to access heterocyclic 1,3-dienes (Scheme 2.21). These reactions were expected to give competition between elimination to form 1,2-dihydropyridazines and formation of the isomerised starting material. 209 may arise from the nucleophilic attack of an acetate anion in solution or the reductive elimination of an acetate group back onto the palladium η³ π-allyl complex on the opposite side to that of the starting material.

Pleasingly, it was possible to convert cycloadduct 203c into 1,2-dihydropyridazine 9c (Table 2.10). When cycloadduct 203c was treated with the commercially available tetrakis(triphenylphosphine)palladium(0) (Pd(PPh₃)₄) catalyst - with some base – 1,2-dihydropyridazine 9c was formed in 58% (entry 1). Small quantities of 2-aminopyrrole 211c were also formed, which are usually formed in the 4-π photocyclisation of 1,2-dihydropyridazines and there have been no reports of this being formed under thermal
4-π Photocyclisation: A New Route to Functionalised Four-Membered Rings

conditions (*vide infra*). If the base was switched to potassium tert-butoxide, 1,2-dihydropyridazine 9c was not formed and degradation of cycloadduct 203c was observed (entry 2). Comparable yields were observed when other bases were used (entries 3-5), with potassium acetate and potassium carbonate giving the highest yields (67% and 72% respectively). Surprisingly, when no base was used, 1,2-dihydropyridazine 9c was formed in moderate to good yields, but a significant amount of another product was formed too (entry 6 and 7). This side product resulted from the competing side reaction to give the rearranged starting material 209c in varied amounts (entry 6, 40%). When the rearranged starting material 209c was treated under the developed palladium conditions, 1,2-dihydropyridazine 9c did form but the rate of reaction sharply decreased. Both the allylic pivalate 205 and carbonate 206 reacted to give 1,2-dihydropyridazine 9c, but it was not possible to separate the product from impurities that were not observed in the allylic acetate reactions (entries 8 and 9). In terms of atom economy, the use of an acetate group is more favourable than the heavier pivalate and carbonate groups. Thus, coupled with the better performance in the palladium-catalysed reactions, allylic acetate 203c was selected for further studies. Due to the relative cost and sensitivity of tetrakis(triphenylphosphine)palladium(0), a palladium(0) precursor was required that would improve the practicality of the reaction once scaled up. Three alternative palladium sources were investigated in the presence of triphenylphosphine (entries 10-12). Issues during purification with another palladium(0) source (tris(dibenzylideneacetone)palladium(0)), caused by a difficult separation of 1,2-dihydropyridazine 9c from dibenzylideneacetone, resulted in 1,2-dihydropyridazine 9c being isolated in 48% yield (entry 10). Starting from a palladium(II) source (palladium(II) acetate or trifluoroacetate) gave 1,2-dihydropyridazine 9c in 72% and 67% yield and gave yields comparable to when the tetrakis(triphenylphosphine) catalyst was used (entries 11 and 12). Palladium(II) acetate was selected over palladium(II) trifluoroacetate, which gave small amounts of impurities in the isolated product 9c. Next, whether the use of bidentate phosphine ligands would help to inhibit the formation of the rearranged starting material 209c was selected for further studies. The best ligand was found to be Xantphos, which showed no formation of the isomerised side product 209c, giving 1,2-dihydropyridazine 9c in 75% yield (entry 14). The reaction with dppp and SPANphos were slower and resulted in large amounts of the by-product 209c being isolated (entries 13 and 15). The best ligand for this reaction was Xantphos, but triphenylphosphine could be used if necessary. The use of different solvents gave varied results (entries 16-21). At lower temperatures the formation of rearranged starting material 209c dominated, but no 2-aminopyrrole 211c formation was observed. Aside from toluene, 2-methyltetrahydrofuran gave similar yields, and would be used as an alternative solvent if necessary. The deacetylated product 208, formed from degradation during column chromatography, only gave a minor amount of 1,2-dihydropyridazine 9c (2% yield) when treated under the developed palladium-catalysed elimination conditions (entry 22), though the structure of the major product was not determined.
### Table 2.10

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Base</th>
<th>Time (hrs)</th>
<th>Yield 9c (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield 209c (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield 211c (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ac</td>
<td>PhMe</td>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>-</td>
<td>NEt&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1</td>
<td>58 (n.d)</td>
<td>&lt;5 (n.d)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ac</td>
<td>PhMe</td>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>-</td>
<td>KO/But</td>
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<td>- (n.d)</td>
<td></td>
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<td>PhMe</td>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>-</td>
<td>KOAc</td>
<td>1</td>
<td>67 (14 traces)</td>
<td>14 (6 traces)</td>
<td></td>
</tr>
<tr>
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<td>PhMe</td>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>-</td>
<td>DBU</td>
<td>4</td>
<td>52 (15 traces)</td>
<td>15 (traces)</td>
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<td>PhMe</td>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>-</td>
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<td>1.5</td>
<td>72 (6 traces)</td>
<td>14 (traces)</td>
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<td>PhMe</td>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>54 (15 traces)</td>
<td>40 (n.d)</td>
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</tr>
<tr>
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<td>-</td>
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<td>73 (n.d traces)</td>
<td>- (traces)</td>
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<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>-</td>
<td>-</td>
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<td>- (n.d)</td>
<td>- (n.d)</td>
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</tr>
<tr>
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<td>PhMe</td>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>-</td>
<td>-</td>
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<td>- (n.d)</td>
<td>- (n.d)</td>
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</tr>
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<td>PhMe</td>
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<td>48 (n.d traces)</td>
<td>- (n.d traces)</td>
<td></td>
</tr>
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<td>PhMe</td>
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<td>5 (n.d)</td>
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<td>dppp&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>1</td>
<td>42 (39 traces)</td>
<td>- (5 traces)</td>
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</tr>
<tr>
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<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Xantphos&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
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<td>- (n.d)</td>
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<tr>
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<td>PhMe</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>SPANphos&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>55 (11 traces)</td>
<td>- (11 traces)</td>
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<td>20</td>
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<td>48</td>
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<td>66 (n.d)</td>
<td>- (n.d)</td>
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<td>PhMe</td>
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<td>-</td>
<td>16</td>
<td>2 (2 traces)</td>
<td>- (2 traces)</td>
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</tr>
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</table>

<sup>a</sup> Isolated yields
<sup>b</sup> 40 mol% ligand; 20 mol% ligand; 3 Reaction run at room temperature; n.d = not determined; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; Piv = pivalate; Pd<sub>2</sub>(dba)<sub>3</sub> = tris(dibenzylideneacetone)dipalladium(0); Pd(OAc)<sub>2</sub> = palladium(II) acetate; Pd(TFA)<sub>2</sub> = palladium trifluoroacetate; dppp = 1,3-bis(diphenylphosphino)propane.
The next step was to see whether the amount of catalyst could be decreased (Table 2.11). It was already known that with 10 mol% palladium(II) acetate and triphenylphosphine or Xantphos, 1,2-dihydropyridazine 9c was formed in 72% and 75% yield, respectively. It was found that as the catalyst and ligand loading was decreased, the yield of 1,2-dihydropyridazine 9c decreased, and the yield of the rearranged starting material 209c increased (entries 1-7).

![Chemical structure](image)

Table 2.11

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Catalyst loading (mol%)</th>
<th>Ligand (mol%)</th>
<th>Time (hours)</th>
<th>Yield 9c (%)</th>
<th>Yield 209c (%)</th>
<th>Yield 211c (%)</th>
</tr>
</thead>
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<td>Pd(OAc)₂</td>
<td>PPh₃</td>
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<td>20</td>
<td>1</td>
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<td>n.d</td>
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<td>PPh₃</td>
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<td>n.d</td>
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<td>Xantphos</td>
<td>5</td>
<td>10</td>
<td>1</td>
<td>65</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)₂</td>
<td>Xantphos</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>44</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)₂</td>
<td>Xantphos</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>17</td>
<td>47</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)₂</td>
<td>Xantphos</td>
<td>10</td>
<td>10</td>
<td>1</td>
<td>23</td>
<td>54</td>
<td>n.d</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)₂</td>
<td>Xantphos</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>69</td>
<td>n.d</td>
</tr>
</tbody>
</table>

At this point, the optimal conditions were to use palladium(II) acetate (10 mol%), without any base and either triphenylphosphine or Xantphos as the ligand, with the latter giving less formation of the rearranged starting material 209c. Under these conditions, if the reaction was to be completed on any sort of scale a large amount of palladium catalyst and ligand would be required, which would have a financial and environmental impact. Further issues arose when four grams of cycloadduct 203c was subjected to these conditions. Using palladium(II) acetate and triphenylphosphine, the yield considerably dropped to give 1,2-dihydropyridazine 9c in 32% yield, less than half of what was achieved on a small scale. After considerable experimentation, the discrepancy between the two was put down to excess water present in the starting material, which was found to cause the reaction to lose all selectivity and give poor conversions of cycloadduct 9c. Thus, the reactions using palladium(II) acetate needed to be repeated with thoroughly dried starting materials (Table 2.12). It was necessary for the starting materials to be dried in a desiccator (calcium chloride was the optimal desiccant) for a minimum of two weeks to ensure the highest yields possible for 1,2-dihydropyridazine 9c. Initial experiments took inspiration from a test reaction in which, in the presence of base, the reaction gave a moderate yield (56%) at low catalyst loadings (1 mol%). It seemed plausible that the use of a base should enable lower catalyst loadings to be employed. Early results with triphenylphosphine as the ligand showed that the bases potassium carbonate and triethylamine gave 1,2-dihydropyridazine 9c in good yields (entries 1 and 2), with triethylamine giving the
highest yield seen for this reaction so far. Pleasingly, when the catalyst loading was lowered the reaction efficiency remained high, even at 1 mol% (entries 3-5). The reaction could now be carried out in a variety of solvents and tolerated different temperatures without a noticeable decrease in yields (entries 6-10). 1,4-Dioxane was selected as the optimal solvent, giving the most reproducible yields, ease of purification and minimal side products.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst Loading (mol%)</th>
<th>Base</th>
<th>Ligand (mol%)</th>
<th>Solvent</th>
<th>Time (hrs)</th>
<th>Yield 9c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>K₂CO₃</td>
<td>PPh₃ (40 mol%)</td>
<td>PhMe</td>
<td>1</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>NEt₃</td>
<td>PPh₃ (40 mol%)</td>
<td>PhMe</td>
<td>1</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>NEt₃</td>
<td>PPh₃ (20 mol%)</td>
<td>PhMe</td>
<td>1</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>NEt₃</td>
<td>PPh₃ (8 mol%)</td>
<td>PhMe</td>
<td>1</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>NEt₃</td>
<td>PPh₃ (4 mol%)</td>
<td>PhMe</td>
<td>1</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>NEt₃</td>
<td>PPh₃ (4 mol%)</td>
<td>THF</td>
<td>2</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>NEt₃</td>
<td>PPh₃ (4 mol%)</td>
<td>EtOAc</td>
<td>2</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>NEt₃</td>
<td>PPh₃ (4 mol%)</td>
<td>2-MeTHF</td>
<td>3</td>
<td>87ᵇ</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>NEt₃</td>
<td>PPh₃ (4 mol%)</td>
<td>MeCN</td>
<td>4</td>
<td>81</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>NEt₃</td>
<td>PPh₃ (4 mol%)</td>
<td>1,4-dioxane</td>
<td>1</td>
<td>84</td>
</tr>
</tbody>
</table>

Table 2.12 *Highest yields achieved when starting material thoroughly dried (in a desiccator for a minimum of two weeks); presence of water in the reaction mixture led to a sharp decrease in efficiency;ᵇ Difficulties in purification

2.3.2.4 Scope

With a working methodology in hand, the aim was to expand the substrate scope of the cycloaddition-palladium-catalysed elimination reaction and to scale up the reaction. Herein, the attempted synthesis of some other 1,2-dihydropyridazines 9a-m with different protecting groups attached to the nitrogen atoms is reported and was completed starting from a minimum of one gram of azo compound of the corresponding hydrazine (Figure 2.5). The scope will be broken down into four sections:

2.3.2.4.1 Synthesis of Hydrazines

2.3.2.4.2 Synthesis of Azo Compounds

2.3.2.4.3 Diels-Alder Reactions

2.3.2.4.4 Palladium-Catalysed Elimination Reactions
2.3.2.4.1 Synthesis of Hydrazines

Due to the commercial availability of DEAD 8b, DIAD 8c and DBAD 8d, it was not necessary to synthesise them. Bis(trichloroethyl)azodicarboxylate and dibenzyl azodicarboxylate are also commercially available, though due to cost the decision was made to synthesise them. The synthesis of these hydrazines has been reported in the literature from the reaction of chloroformates with hydrazine 211 in the presence of a base. Hydrazines 43e,i were synthesised in 95% and 82% yields respectively and without the need for further purification (Scheme 2.22).

Starting from commercially available hydrazides, a series of symmetrical and unsymmetrical hydrazines 43 have been synthesised (Table 2.13). Attempts to synthesise the dimethyl carbamate hydrazine 43a from hydrazine 211 resulted in the loss of the product into the aqueous layer during the work-up and any material that was recovered was not of a high purity. Starting from methyl carbazate 212a instead proved to be more successful and the desired hydrazine 43a was isolated in 58% yield (entry 1), though some material was still lost into the aqueous layer. The product 43a is a polar molecule with six hydrogen bond acceptors, two
hydrogen bond donors and relatively small protecting groups attached to the nitrogen atoms, therefore it was unsurprising that it is water soluble. There are examples in the literature for the synthesis of unsymmetrical hydrazines possessing tert-butyl or benzyl carbamates on one side of the molecule and tosyl groups attached to the other side.\textsuperscript{92,248-250} More specifically, the methodology reported by Shipman and co-workers would enable the synthesis of other unsymmetrical hydrazines starting from tert-butyl carbazate \textit{212b} and \textit{p}-toluenesulfonyl hydrazide \textit{212c}.\textsuperscript{92} Through a modified procedure, tert-butyl carbazate \textit{212b} was transformed into the methyl, benzyl- and trichloroethyl-carbamate hydrazines \textit{43f},\textit{g},\textit{i} in 83\%, 83\% and 94\% yield respectively (entries 2-4). For hydrazine \textit{43i}, the reaction had to be run at low concentration (0.1 M) to reduce by-product formation, however the synthesis of hydrazines \textit{43f},\textit{g} could be run at higher concentrations (1 M). A tosyl group could also be installed to form hydrazine \textit{43k} in 68\% yield (entry 5).\textsuperscript{92} The synthesis of a hydrazine equipped with a sulfonamide and a benzyl carbamate proved to be more challenging. \textit{p}-Toluenesulfonyl hydrazide \textit{212c} was reacted with benzyl chloroformate to give hydrazine \textit{43l} in 52\% yield (entry 6).\textsuperscript{92} A moderate yield was proposed to have been due to the insolubility of the starting hydrazide in water. Starting from the same hydrazide \textit{212c}, ditosyl hydrazine \textit{43m} was synthesised in 64\% yield through a known procedure (entry 7).\textsuperscript{251}

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Conditions</th>
<th>Yield 43 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CO\textsubscript{2}Me (212a)</td>
<td>CO\textsubscript{2}Me</td>
<td>MeCO\textsubscript{2}Cl (1.1 eq), pyridine (3.0 eq), 2-MeTHF, 0 °C → rt, 1.5 hrs</td>
<td>58 (43a)</td>
</tr>
<tr>
<td>2</td>
<td>CO\textsubscript{2}Bu (212b)</td>
<td>CO\textsubscript{2}Me</td>
<td>MeCO\textsubscript{2}Cl (1.1 eq), pyridine (6.0 eq), 2-MeTHF, 0 °C → rt, 1.5 hrs</td>
<td>83 (43f)</td>
</tr>
<tr>
<td>3</td>
<td>CO\textsubscript{2}Bu (212b)</td>
<td>CO\textsubscript{2}Bn</td>
<td>BNCO\textsubscript{2}Cl (1.1 eq), pyridine (6.0 eq), 2-MeTHF, 0 °C → rt, 1.5 hrs</td>
<td>83 (43g)</td>
</tr>
<tr>
<td>4</td>
<td>CO\textsubscript{2}Bu (212b)</td>
<td>Troc</td>
<td>TroCl (1.1 eq), pyridine (6.0 eq), 2-MeTHF, 0 °C → rt, 1.5 hrs</td>
<td>94 (43j)</td>
</tr>
<tr>
<td>5</td>
<td>CO\textsubscript{2}Bu (212b)</td>
<td>Ts</td>
<td>TsCl (1.1 eq), pyridine (6.0 eq), THF, 0 °C → rt, 4 hrs</td>
<td>68 (43k)</td>
</tr>
<tr>
<td>6</td>
<td>Ts (212c)</td>
<td>CO\textsubscript{2}Bn</td>
<td>BNCO\textsubscript{2}Cl (1.2 eq), NaHCO\textsubscript{3} (1.2 eq), H\textsubscript{2}O, 0 °C → 60 °C, 2.5 hrs</td>
<td>52 (43l)</td>
</tr>
<tr>
<td>7</td>
<td>Ts (212c)</td>
<td>Ts</td>
<td>TsCl (1.5 eq), pyridine (1.5 eq), CH\textsubscript{2}Cl\textsubscript{2}, rt, 2.5 hrs</td>
<td>64 (43m)</td>
</tr>
</tbody>
</table>

Table 2.13

2.3.2.4.2 Synthesis of Azo Compounds

With a range of hydrazine intermediates in hand, oxidation of hydrazines \textit{43e},\textit{h},\textit{i} to the corresponding azo compounds was investigated (Scheme 2.23). The use of the hypervalent
iodine reagent iodobenzene diacetate (IBDA) has been successful for the oxidation of diethyl hydrazine-1,2-dicarboxylate and 4-phenyl urazole. According to this procedure, PTAD 8h was synthesised from 4-phénylurazole 43h in 91% yield. Dibenzyl- and bis(trichloroethyl)-carbamate hydrazines 43e,i were successfully oxidised using IBDA to give the azo compounds 8e,i in 78% and 78% yield respectively. A higher yield would have been achieved but both azo compounds were partially soluble in hexane, which was used to separate the product from the iodobenzene by-product. Purification on silica gel gave the dibenzyl azo 43e in 46% yield, however bis(trichloroethyl)-azo 43i degraded on silica gel. Due to the instability and potential safety hazard of isolating dimethyl azodicarboxylate, it was reacted straight away in a Diels-Alder reaction. For ease, all the unsymmetrical dicarbamate azo compounds 8f,g,j were not isolated, although the azo compounds do form efficiently.

Scheme 2.23

For hydrazines 43k-m the introduction of a sulfonamide group seemed to completely change the efficiency of the oxidation reaction to the corresponding azo compound (Scheme 2.24). For the tert-butyl substrate 43k, no azo formation was observed, and a complex mixture formed when the reaction was carried out at room temperature and at 0 °C. The benzyl substrate 43l showed more promise when shorter reaction times were used at room temperature and at 0 °C, however over prolonged periods of time the azo compound became less prominent when analysed by thin layer chromatography (TLC). No attempt was made to isolate the azo compound (8l) and instead it was further reacted with acetoxy-diene 202a (vide infra). For hydrazine 43m with two sulfonamide groups, the reaction mixture quickly turned from a suspension to a solution, however it was not possible to isolate the suspected azo compound 8m without degradation. The addition of a diene to the reaction mixture resulted in complete degradation, which was backed up by a discovery in the literature that described an unsuccessful attempt to oxidise hydrazine 43m and trap the corresponding azo compound with cyclopentadiene.

Scheme 2.24

Thomas Britten – April 2019
The investigation of other oxidation conditions was carried out using *tert*-butyl-hydrazine-1,2-carboxylate 43d, due to DBAD 8d being a known and stable compound (Table 2.14).\(^{247}\) A logical alternative to IBDA was the use of polymer supported iodobenzene diacetate (PIBDA), which would simplify purification and has been reported in the literature for the oxidation of alcohols, phenol, sulfides, thioamides, thiophenols and triphenylphosphine.\(^{255}\) When hydrazine 43d was treated with PIBDA, the reactivity was considerably slower in comparison to IBDA and the reaction did not go to completion even after six days (entry 1). The use of another hypervalent iodine reagent, 2-iodoxybenzoic acid (IBX), gave only traces of the azo compound 8d (entry 2). Using conditions developed for the copper-catalysed oxidation of nitroso compounds,\(^{257}\) the azo compound 8d was formed in 79% yield (entry 3). Fétizon's reagent was prepared from silver nitrate and Celite,\(^{258}\) and when a large excess of the reagent was used, the desired product 8d was formed in 34% yield (entry 4). Wary of azo compound degradation at high temperatures, the reaction was repeated at room temperature and 50 °C (entries 5 and 6). No reaction was observed at room temperature, but at 50 °C the product 8d was formed in 88% yield. When the copper-catalysed oxidation reaction was applied to the dimethylcarbamate hydrazine 43a, no reaction took place and only starting material was recovered. Some recent literature has shown that for the synthesis of DEAD 8b, DIAD 8c and DBAD 8d the use of copper salts as an additive did not provide a general procedure to access all three of the substrates, which could be a reason as to why no reaction was observed for hydrazine 43a.\(^{259}\) When unsymmetrical hydrazines 43j,k were combined with Fétizon's reagent, only starting material was recovered for hydrazine 43j. For hydrazine 43k, no starting material remained and \(^1\)H NMR spectroscopy suggested a new compound had formed, though no reaction was observed when this compound was combined with acetoxy-diene 202a. It became apparent that none of these alternative oxidation conditions were perfect for all substrates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield 8d (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PIBDA (0.8 mmol/g, 1.1 eq), CH(_2)Cl(_2), rt, 6 days</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>IBX (1.4 eq), DMSO, rt, 17 hours</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>CuCl (20 mol%), pyridine (5 mol%), 2-MeTHF, rt, 19 hours</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>Ag(_2)CO(_3)/Celite (4 eq), PhMe, 75 °C, 15 minutes</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>Ag(_2)CO(_3)/Celite (1.5 eq), PhMe, 1 hour</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Ag(_2)CO(_3)/Celite (1.5 eq), PhMe, 50 °C, 25 minutes</td>
<td>88</td>
</tr>
</tbody>
</table>

Table 2.14 PIBDA = polymer supported iodobenzene diacetate

Finally, the use of NBS and pyridine was tested (Scheme 2.25).\(^{260,261}\) For hydrazine 43a, the reaction went to completion and then started to degrade back to the starting material, which was not observed for any of the reactions with IBDA. A similar observation was found with hydrazine 43g, and it was possible to isolate the impure azo compound 8g. It should be noted that for the trichloroethyl system 43j, the reaction did not go to completion and with prolonged
reaction times, the starting material began to reform again. Finally, no reaction was observed for the hydrazine 43l.

\[
\begin{align*}
\text{RO}_2\text{C}^\circ & N^\circ \text{R}^\circ & & \times & & \text{NBS (1.2 eq)} & & \text{Pyridine (1 eq)} & & \text{CH}_2\text{Cl}_2, \text{rt, 30 mins} & & \text{RO}_2\text{C}^\circ & N^\circ \text{R}^\circ & 8a, g, j, l
\end{align*}
\]

Scheme 2.25

From these results, it was clear that the only reagent that provided a general way of accessing these azo compounds was IBDA. Though not all the azo compounds have been isolated, it can be said with confidence that they have formed and were taken on into the next step (Diels-Alder reaction, Section 2.3.2.4.3). The only issue with the use of IBDA is that the azo compound must be separated from the by-product, iodobenzene, which is not always straightforward. In a later section a negative effect that the presence of iodobenzene caused will be described (Section 2.3.2.4.4).

2.3.2.4.3 Diels-Alder Reactions

Subsequently, the Diels-Alder reaction of commercially available azo compounds 8b-e (diethyl-disopropyl- di-tert-butyl- and dibenzyl azodicarboxylate) or in situ generated azo compounds 8a,f-l with 1-acetoxy-1,3-butadiene 202a was completed to give cycloadducts 203a-j in mostly high yields (Scheme 2.26). The Diels-Alder reactions were completed in dichloromethane and were run either at room temperature or at reflux (dependent on the azo compound) to give the desired allylic acetates 203a-j. The cycloadducts were then purified to remove any excess diene through a short plug of silica gel or washed with hexane (for 203d,h). An excess of acetoxy-diene 202a (1.5 eq) was essential to ensure good reactivity and more equivalents can be used to increase the rate of the reaction, however larger quantities of the diene would be needed on a larger scale and would not be cost-effective. As described in the previous section (Section 2.3.2.4.3), no attempt was made to isolate dimethyl azodicarboxylate 8a and instead the azo compound was trapped with the acetoxy-diene 202a to give the cycloadduct 203a in near quantitative yields. The symmetrical azo compounds DEAD 8b, DIAD 8c, DBAD 8d, dibenzyl 8e and bis(trichloroethyl) azodicarboxylates 8i were smoothly converted into their respective cycloadducts 203b-e,i in high yields. To obtain the highest yields possible of cycloadduct 203d, the Diels-Alder reaction had to be heated at reflux to ensure full conversion of azo compound 8d. With cycloadduct 203f, which was a solid, the removal of diene 202a was achieved through addition of hexane and without distillation or chromatography, however when purified on silica gel the yield decreased to 63%. Similar results were obtained with the method that started from their respective hydrazines 43f-h,j, and cycloadducts 203f-h,j were synthesised in good yields. For hydrazine 43h, upon addition of acetoxy-diene 202a to the reaction mixture the cycloadduct 203h formed instantly, which was unsurprising given the high reactivity of PTAD 8h.\textsuperscript{185,198} A different outcome was observed for the carbamate-sulfonamide substrate 43k, where issues with azo formation and stability have meant that it has not been possible to synthesise the cycloadduct 203k starting from hydrazine 43k. For the benzyl substrate 43l, it was possible to
isolate the deacetylated product \textit{208l} in 59\% yield, but not the acetylated cycloadduct \textit{203l}. \textit{1}H NMR analysis has confirmed that the cycloadduct \textit{203l} does form, though on standing in deuterated chloroform it degraded to form the deacetylated product \textit{208l}. The structure of \textit{208l} was tentatively proposed through 2-dimensional (2-D) \textit{1}H-\textit{1}H NMR experiment, Nuclear Overhauser Effect Spectroscopy (nOesy), that suggested the tosyl group was near to the NCH$_2$ group and not the acetate group.

Interestingly, under typical conditions an attempted deacetylation with cycloadduct \textit{203d} did not give any of the expected alcohol \textit{208d} (Scheme 2.27). The product that formed was ether \textit{212d} in moderate yields, which is proposed to have formed through an initial elimination of the acetate group to give iminium ion \textit{213}, followed by trapping with methanol. It seemed likely that the formation of alcohol \textit{208}, the degradation product observed from column chromatography, was not actually formed through deacetylation but through elimination of the acetate group and addition of water.
2.3.2.4 Palladium-Catalysed Elimination Reactions

With the cycloadducts $203a$-$j$ in hand, all the material from the Diels-Alder reactions was taken on into the palladium-catalysed elimination reactions to make a two-step reaction and access 1,2-dihydropyridazines $9a$-$h$ (Scheme 2.28). The allylic acetates $203$ directly derived from azo compounds (not from hydrazines) could be used in the palladium-catalysed elimination reaction without purification, but significant degradation of the diene $202a$ took place at high temperatures, which made separation of the desired products difficult. It was not possible to couple the processes when starting from the hydrazine precursors, because the cycloadducts $203$ had to be separated from iodobenzene, a by-product of oxidation reaction with iodobenzene diacetate. If not, issues arose in the palladium step, presumably caused by the oxidative addition of iodobenzene to the palladium(0) catalyst. In most cases, conversion of allylic acetates $203$ into 1,2-dihydropyridazines $9$ proceeded without any problems. No reactions took place for cycloadducts $203i,j$ that contained trichloroethyl-carbamate protecting groups and the starting material was recovered unchanged, though it is not currently understood why these compounds did not react. Under the optimised conditions, 1,2-dihydropyridazines $9f,g$ were obtained in low yields due to the formation of the isomerised starting material $209f,g$. When the catalyst loading was increased, 1,2-dihydropyridazines $9f,g$ were accessed in higher yields. In all cases, the two-step reaction sequence was completed starting from one gram of the azo compound or hydrazine. 1,2-Dihydropyridazine $9d$ has been synthesised on five- and ten-gram scales to give the desired product in 72% and 75% yield, respectively. The yields remained comparable from one up to ten grams, thus multigram quantities of 1,2-dihydropyridazines $9$ can be accessed efficiently.

Scheme 2.28  

Over three steps from hydrazine with iodobenzene diacetate (1.0 eq); Over two steps; $2$ mol% Pd(OAc)$_2$ used; $34\%$ isomerised starting material $209f$; $22\%$ isomerised starting material $209g$
To expand the substrate scope, the synthesis of a methyl-substituted 1,2-dihydropyridazine was attempted (Scheme 29). 1-Acetoxy-3-methyl-1,3-butadiene 214 was synthesised in 49% yield according to a literature procedure starting from commercially available starting materials. The Diels-Alder reaction of the substituted diene 214 and azo compound 8d formed allylic acetate 215 in moderate yield, but it was found to be highly unstable on silica gel. When the material was used in the palladium-catalysed elimination reaction without purification, the product isolated was not the desired 1,2-dihydropyridazine but diene 216. No other identifiable products were isolated from the reaction and potentially allylic acetate 215 was unstable at high temperatures. The reaction preferentially formed the exocyclic double bond to give a diene that would not undergo the desired 4-π photocyclisation.

Scheme 2.29

Another potential route to access 1,2-dihydropyridazine derivatives would be to utilise Danishefsky’s diene 217 (Scheme 2.30). Treatment of azo compound 8d with diene 217, without a work-up, gave an inseparable mixture of enone 218 and cycloadduct 219. The addition of acid to the reaction mixture was enough to facilitate elimination of the methoxy group to give enone 218 in 89% yield, after work-up and purification. The synthesis of enone 218 was a preliminary result and the reaction remains unoptimised, but showed that it is possible to access these cycloadducts in very high yields. Further work needs to be completed to see if enone 218 can be converted into O-substituted 1,2-dihydropyridazines.

Scheme 2.30
2.3.3 Variable Temperature NMR of 1,2-Dihydropyridazines

As mentioned in the introduction, it has been well documented that the NMR spectra for tetrahydropyridazines and 1,2-dihydropyridazines are non-trivial.\textsuperscript{187,213,222–228,231} As a result, at ambient temperature the $^1$H and $^{13}$C NMR spectra for these systems can appear complex due to line broadening and extra peaks present due to the slow interconversion of two conformations on the NMR timescale.\textsuperscript{229} These literature examples have shown that variable-temperature (VT) NMR can aid characterisation and simplify the spectrum. In this work, all the tetrahydropyridazines and 1,2-dihydropyridazines were affected by these factors and in most cases, it was only desirable to run the NMR characterisation at higher temperatures to try simplify the spectra and to allow full characterisation. VT-NMR analysis for cycloadduct 203 and 1,2-dihydropyridazine 9 was completed in $d_6$-DMSO (Figures XX). For these systems, $d_6$-DMSO provided a combination of a high boiling point solvent and simplified NMR spectra in comparison to deuterated chloroform, benzene and acetone.

![Figure 2.6](image)

Cycloadducts 203b could be characterised without VT-NMR, as the $^1$H and $^{13}$C NMR spectra at room temperature were not too complicated (Figure 2.7 and 2.8). In both cases, as the temperature was increased the peaks began to sharpen up and multiple peaks began to coalesce to give single peaks. The peaks for the CH$_2$ group on the protecting groups are not equivalent due to one of the protecting groups being on the same face as the acetate group and one not. Fisher and co-workers reported a similar phenomenon for the diphenyl substituted system 157b.\textsuperscript{213} The $^1$H-VT NMR analysis of 1,2-dihydropyridazine 9b showed very broad peaks at room temperature, which all began to resolve as the temperature was increased (Figure 2.9 and 2.10). The CH$_3$ groups of the protecting group became a triplet at temperatures above 25 °C (298 K), whilst the CH$_2$ groups on the carbamates and hydrogens attached to the ring became clearer but did not fully resolve at 75 °C (348 K). The $^{13}$C NMR spectrum of 1,2-dihydropyridazine at room temperature showed broad peaks for the ring carbon atoms and a very weak carbonyl peak around 150–160 ppm, though the carbonyl stretch was observed in the IR spectra (Figure 2.10). The protecting group carbons remained single peaks throughout the VT-NMR study of 1,2-dihydropyridazine 9b. As the temperature increased, the peaks for the ring carbons and carbonyl resolved and became sharp peaks. Higher temperatures could be used, however 1,2-dihydropyridazines 9 start to form 2-aminopyrroles 210 at temperatures above 100 °C. Our data for 1,2-dihydropyridazine 9b supported Anderson and Lehn’s proposal that there are two-twisted conformations and interconversion is slow on the NMR timescale at room temperature.
Figure 2.7 $^1$H VT-NMR in d$_6$-DMSO of cycloadduct 203b
4-π Photocyclisation: A New Route to Functionalised Four-Membered Rings

Figure 2.8 $^{13}$C VT-NMR in $d_6$-DMSO of cycloadduct 203b
Figure 2.9 $^1$H VT-NMR in $d_6$-DMSO of 1,2-dihydropyridazine 9b
Figure 2.10 $^{13}$C VT-NMR in $d_6$-DMSO of 1,2-dihydropyridazine 9b
2.3.4 Reactions of 1,2-Dihydropyridazines

It was envisaged that the 1,2-dihydropyridazines 9 could be interesting intermediates themselves (i.e. not only as substrates for the 4-π photocyclisation) and could be used to access other useful building blocks.

Pyrrole 210c, the side product from the palladium-catalysed elimination reactions, was selected as the initial target building block (Table 2.15). Through control experiments, it was found that conversion of 1,2-dihydropyridazine 9c into pyrrole 210c was not a palladium-catalysed reaction, but a thermal rearrangement reaction (entry 1). Lautens and co-workers have proposed from computational calculations that the 6-π electrocyclic ring opening of 1,2-dihydropyridazines 9c should be facile at 120 °C.215 The reaction in toluene was slow but the use of higher boiling point solvents such as dimethylformamide (DMF) and ortho-xylene gave better conversions and yields. From preliminary reactions, DMF and o-xylene gave identical yields, but the latter was chosen to pursue further due to an easier method of solvent removal (entries 2 and 3). The pyrrole 210c was not stable to silica gel, but if it was quickly passed through a short silica gel column it could be isolated in 90% yield (entry 4). The reaction mixture could be purified without the removal of the solvent and purified by column chromatography directly without a decrease in yields. The reaction has been used to synthesise three other pyroles 210a-c in moderate to excellent yields. Substrates bearing methyl and ethyl carbamate protecting groups were tolerated, but for the tert-butyl carbamate substrate 210d a lot of degradation was observed (entries 5-7). Pyrrole 210d was isolated in a moderate yield and another pyrrole 220d that contained only one tert-butyl carbamate group was also isolated in 11% yield. Obviously at these temperatures the tert-butyl carbamate protecting groups are labile and, combined with the instability of the pyroles 210a-d anyway, it is likely that this is the cause of degradation and lower yields for this substrate.

![Reactions of 1,2-Dihydropyridazines](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Solvent</th>
<th>Yield 210a-d (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>iPr</td>
<td>PhMe</td>
<td>46 (210c)(^a)</td>
</tr>
<tr>
<td>2</td>
<td>iPr</td>
<td>DMF</td>
<td>52 (210c)(^b)</td>
</tr>
<tr>
<td>3</td>
<td>iPr</td>
<td>o-xylene</td>
<td>52 (210c)(^b)</td>
</tr>
<tr>
<td>4</td>
<td>iPr</td>
<td>o-xylene</td>
<td>90 (210c)</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>o-xylene</td>
<td>62 (210a)</td>
</tr>
<tr>
<td>6</td>
<td>Et</td>
<td>o-xylene</td>
<td>86 (210b)</td>
</tr>
<tr>
<td>7</td>
<td>tBu</td>
<td>o-xylene</td>
<td>28 (210d), 11 (220d)(^c)</td>
</tr>
</tbody>
</table>

Table 2.15 \(^a\) Reaction run for 19 hours; \(^b\) Reaction run for 2 hours; \(^c\) Product bearing one carbamate protecting group

From the crystal structure of 9c, the 1,2-dihydropyridazine ring is puckered and potentially the p-orbitals are not able to overlap as extensively as found for other 1,3-dienes, such as 1,3-butadiene, which could prevent any Diels-Alder reactions from happening (Scheme 2.31).
the solid state, the protecting groups are trans to one another, which should mean that in solution the thermal 6-π electrocyclic ring opening would give E/Z triene 221. Triene 221 could then undergo a 5-exo-trig cyclisation to give zwitterion 222, followed by aromatisation to give 2-aminopyrrole 210c. The photochemical synthesis of 2-aminopyrroles 210 has been suggested to go via a photochemical π4 + π2 s cycloaddition based on the extensive study on the conversion 1,3,5-hexatrienes into bicyclo[3.1.0]hexane.263–269 Such a transformation is not possible under thermal conditions and even the π4s + π2s reaction would not be possible based on orbital overlap. As a result, potentially the thermal process is going via a step-wise mechanism as proposed here.

Scheme 2.31 X-ray crystal structure for 1,2-dihydropyridazine 9c (top); mechanism (bottom)

With 1,2-dihydropyridazines 9a-h being dienes, one might expect that they take part in Diels-Alder reactions, however they were found to be inert to such reactions. When 1,2-dihydropyridazine 9c and a dienophile were heated at reflux in toluene, it was instead observed that the pyrrole 210c took part in Diels-Alder reactions. Thus, when pyrrole 210c was reacted with dimethyl acetylenedicarboxylate 223, the expected cycloadduct 225 was not isolated but instead the para-phenylenediamine derivative 224 was isolated in 65% yield (Scheme 2.32). It is proposed that after the formation of the initial cycloadduct 225, it then undergoes ring opening, followed by aromatisation to give the observed product 224. Mackay and Arora obtained a similar product to 224 when 1,2-dihydropyridazine 9b was heated at reflux in toluene with alkyne 223. The authors suggested that 224 had formed through a direct Diels-Alder reaction between 1,2-dihydropyridazine 9 and alkyne 223, which underwent aromatisation to give the product, although a mechanism for this aromatisation was not discussed. Instead, what was likely happening was 1,2-dihydropyridazine 9 rearranged to form 2-aminopyrrole 210, which then underwent the Diels-Alder reaction.
The Diels-Alder reaction of 2-aminopyrrole 210c with two other alkynes has been investigated (Scheme 2.33). In the presence of the weakly electron withdrawing and methyliminodiacetic acid (MIDA)-boronate alkynes 28 and 30, no reaction was observed and 2-aminopyrrole 210c was recovered unchanged. A combination of solubility issues and the lack of electron withdrawing groups were likely a caused for the reaction to fail with the boronate alkyne 30. 2-Aminopyrrole 210c also reacted with maleic anhydride 231 to give an unknown aromatic compound that could not be separated from 1,2-dihydropyridazine 9c. The reaction was a lot slower and a significant amount of starting material remained after the reaction was heated at reflux in toluene for 24 hours. Padwa and co-workers have reported the Diels-Alder reactions of 2-aminofurans with alkenes to give substituted aromatic compounds and this should provide some direction for future work.270

Scheme 2.33 MIDA = methyliminodiacetic acid
Preliminary results with commercially available aryne precursors 233a-c have shown that it was possible to access some interesting aromatic fragments (Scheme 2.34). When 2-(trimethylsilyl)phenyl trifluoromethanesulfonate 233a was treated with caesium fluoride and an excess of 2-aminopyrrole 210c, the naphthalene derivative 234a was formed in good yield. Efforts to form quinoline and isoquinoline derivatives 234b,c were less successful and were obtained in low yields. With optimisation it is hoped that these yields can be improved.

When 2-aminopyrrole 210c was reacted with azo compounds, a completely different outcome was observed (Scheme 2.35). Once again, none of the cycloadduct 236 was isolated and instead it has been tentatively proposed that pyrrole 235 was the product formed. After the initial formation of cycloadduct 236, it is hypothesised that cleavage of the newly formed C-N bond from the Diels-Alder reaction occurred to give zwitterion 237 and not through the C-N cleavage that was observed with alkynes. Zwitterion 237 can then undergo aromatisation and protonation to give the pyrrole 235. Further evidence for pyrrole 235 was obtained from $^1$H-$^{15}$N heteronuclear single quantum coherence (HSQC) NMR analysis, which suggested that there were two different NH groups. It has not been possible to confirm the structure of 235 through X-ray crystallography, due to pyrrole 235 not being a crystalline solid and any deprotection attempts under acidic conditions have only resulted in degradation. In addition, pyrrole 235 did not react with dimethyl acetylenedicarboxylate 223 when heated at reflux in toluene and $^1$H NMR analysis showed only the starting materials.
An attempted monoepoxidation of 1,2-dihydropyridazine 9c using m-CPBA (meta-chloroperoxybenzoic acid) showed no sign of epoxide formation and poor conversions. The major product was the trans-diol 238 isolated in 56% yield, and the structure was confirmed by X-ray crystallography (Scheme 2.36). Diol 238 is thought to have potentially arisen from an initial epoxidation (239), followed by intramolecular ring opening to give an iminium ion (240), which could be trapped by water present in the reaction mixture. Aitken and co-workers have shown in a similar system the direct involvement of the nitrogen lone pair in a rearrangement reaction. The remaining mass balance was mostly starting material and an unidentified compound. From the crystal structure, all the groups in 238 are positioned away from each other, which could mean that the trans-diol 238 is the thermodynamic product.

It was hoped that it should be possible to carry out a cyclopropanation of the double bonds in 9c (Scheme 2.37). When treated under conditions that formed dichlorocarbene in situ, tricycle 241 was isolated in good yield and possessed two cyclopropane rings that were positioned anti with respect to one another. To selectively only react one double bond, it should be possible to carry out a Simmons-Smith reaction to leave the other double bond to be further functionalised. Here, a limited amount of carbene precursor could be used, in contrast to the formation of the...
dichlorocarbene where an excess of the reagents is required and therefore, selective monocyclopropanation is not feasible. Tricycle 241 showed surprising thermal stability and remained unchanged after heating at reflux in xylene for six hours.

From the outset, it was not known whether dihydroxylation of 1,2-dihydropyridazine 9c would result in the reaction of one or both double bonds. Preliminary results have shown that only one of the double bonds reacted to give diols 242 and 243 in a combined good yield and one was formed in a slight excess (Scheme 2.38). Two compounds were isolated, both of which are thought to be diols and 1-dimensional (1-D) and 2-D NMR analysis of these compounds was complex. One such 2-D 1H-1H NMR experiment, nOesy, suggested that the major product was trans-diol 243. A key difference between the two nOesy spectra was that cis-diol 242 did not show any through space interactions between the OH adjacent to the nitrogen and the hydrogen on the adjacent carbon (see experimental for details). Even VT-NMR did not fully resolve the spectra, though cis-diol 242 started to rearrange to the trans-diol 243 (but not vice versa) after heating. Derivatisation attempts (for example, using 4-bromobenzoyl chloride) have not given more crystalline compounds to submit for X-ray crystallography. Diols 242 and 243 are thought to have been formed through initial formation of osmate ester 244, which could then be ring-opened either by the adjacent lone pair on the nitrogen atom (Path A) or the lone pair on the other nitrogen atom (Path B). Path A would give an iminium ion 245 that could be attacked by water on either face of the molecule to eventually give the observed diols. Path B would give zwitterion 246 in which water could attack either at the double bond ortho to the osmate ester or the iminium ion to give diols 243 and 238 (formed from the epoxidation reaction of 9c). Diol 238 was not observed in the NMR spectra of the crude products.
A series of other reactions have been attempted (iodination, halohydration, hydroboration, Heck reactions and treatment with acid), but have either led to the formation of complex mixtures or unidentifiable major products. The NMR spectra of all these compounds was very complicated and it was essential to obtain crystal structures to confirm the identities of the products obtained.

**2.4 Conclusion**

Attempts to replicate and modify the existing literature procedures for the synthesis of 1,2-dihydropyridazines did not give promising results. When carbon tetrachloride was changed to cyclohexane in the allylic bromination reaction developed by Altman and co-workers, the reaction efficiency significantly dropped and the formation of complex mixtures with very poor conversions of tetrahydropyridazines 154 was observed. A second approach involved the use of 2-pyrones, however this route did not provide a direct route to access 1,2-dihydropyridazines and the temperatures that were required resulted in degradation of the azo compounds.

As a result, a novel route to 1,2-dihydropyridazines 9 has been successfully developed through a two-step novel synthesis starting from O-substituted dienes and azo compounds in good overall yields. The methodology has been applied to the synthesis of eight other 1,2-dihydropyridazines from the corresponding azo compounds, each bearing symmetrical or non-symmetrical carbamate protecting groups. With 1,2-dihydropyridazine 9d, the reaction was successfully completed on a ten gram scale without a noticeable decrease in the reaction efficiency. It should be noted that it was vital that the cycloadducts 203 were thoroughly dried prior to the palladium-catalysed elimination reaction to minimise the formation of side products. Attempts to expand the substrate scope to enable the synthesis of substituted 1,2-dihydropyridazines has led to problems. When a methyl group was added to the starting diene 214, the cycloadduct 215 formed from the Diels-Alder reaction was not that stable and the major product formed in palladium-catalysed elimination was diene 216, with the newly formed double bond outside the ring. The successful formation of enone 218, derived from Danishefsky’s diene, has potential for accessing a wider range of substrates, though this will require further work.

The reactions of 1,2-dihydropyridazines have shown interesting results. When 1,2-dihydropyridazines are heated at high temperatures, a clean rearrangement reaction to 2-aminopyrroles 210 took place in high yields. From the attempted Diels-Alder reactions of 1,2-dihydropyridazines 9, it was found that 2-aminopyrroles 210 and not 1,2-dihydropyridazines reacted with carbon dienophiles. The Diels-Alder reactions of 2-aminopyrrole 210 is currently limited to reactive alkynes (such as dimethyl acetylenedicarboxylate and arynes) but has shown the potential to access useful aromatic building blocks. Under typical conditions for dihydroxylation, cyclopropanation and epoxidation, 1,2-dihydropyridazine 9c has given interesting products that were not always expected. The double bonds underwent cyclopropanation, with dichlorocarbene, to form a tricycle 241 with two cyclopropane rings that
were \textit{trans} to each another. With the dihydroxylation and epoxidation reactions, some unexpected products were formed, which must have stemmed from the involvement of the nitrogen lone pairs. Some other unidentified products were formed when 1,2-dihydropyridazines were subjected to other double bond reactions, however this requires further study and the acquisition of crystal structures to confirm the structures. In all cases, VT-NMR was essential for structure determination but, even at high temperatures, the 1-D and 2-D NMR spectra did not always resolve, and characterisation was still difficult. Specifically, compounds that contained only one double bond and other groups around the ring gave the most complicated NMR spectra.
Chapter 3: Photochemistry of 1,2-Dihydropyridazines
3.1 Introduction

To date, there are limited literature examples for the synthesis of bicyclic 1,2-diazetidines 10 (Scheme 3.1). The current ways to synthesise bicyclic 1,2-diazetidines can be divided into: the 4-π photocyclisation of 1,2-dihydropyridazines (Method 1), reaction of metal complexes with azo compounds (Method 2) and trapping cyclobutadiene with azo compounds (Method 3). Herein, each method shall be discussed in more detail.

Scheme 3.1

3.1.1 4-π Photocyclisation of 1,2-Dihydropyridazines

Altman et al. published the first 4-π photocyclisation of 1,2-dihydropyridazines in 1968. Irradiation of 1,2-dihydropyridazine 9a in diethyl ether afforded the bicyclic 1,2-diazetidine 10a and 2-aminopyrrole 210a in 61% and 14% yield, respectively (Scheme 3.2). It was proposed that 2-aminopyrrole 210a is formed through the 6-π electrocyclic ring opening of 1,2-dihydropyridazine 2d to give triene 221, which underwent a second photoreaction to give the aziridine intermediate 247, followed by aromatization to give 2-aminopyrrole 210a. No mechanistic details were described for conversion of triene 221 into aziridine 247, however one suggested mechanism is summarised in Scheme 3.2: triene 221 should undergo a radical 5-exo-trig cyclisation to form pyrroline 248, which could then undergo another cyclisation reaction to give aziridine 247. However, a photochemical π + π cycloaddition has been proposed and extensively studied for the photo-transformation of 1,3,5-hexatrienes into bicyclo[3.1.0]hexane, the carbocyclic equivalent of aziridine 247.

Scheme 3.2
Since this pioneering work, the synthesis of the bicyclic 1,2-diazetidine 10a has been repeated and further experimental details have been reported.\textsuperscript{35} Warrener et al. ran the 4-π photocyclisation at 0 °C for nine hours to give bicyclic 1,2-diazetidine 10a in a 20% yield (Scheme 3.3). The authors attempted to improve the yield through the removal of oxygen but were unable to reproduce the yields that Altman et al. found.

![Scheme 3.3](image1)

More recently, Stearns and Ortiz de Montellano developed a multigram synthesis to access bicyclic 1,2-diazetidine 10b for biological testing.\textsuperscript{36} Low temperatures were employed for the 4-π photocyclisation and bicyclic 1,2-diazetidine 10b was isolated in 61% yield and again 2-aminopyrrole 210b was formed, though no yields were reported (Scheme 3.4). Bicyclic 1,2-diazetidine 10b is biologically active and inhibited a cytochrome P-450 enzyme in rats and the double bond and bicyclic structures were crucial to the biological activity.\textsuperscript{36}

![Scheme 3.4](image2)

3.1.2 Organometallic Complexes with Azo Compounds

Feng employed an alternative synthesis to access substituted bicyclic 1,2-diazetidines using metal complexes (Scheme 3.5).\textsuperscript{272} Titanium complexes 249 were treated with a Lewis acid, followed by the addition of azo compounds 8a,b in the presence of a nickel catalyst to give tetra-substituted bicyclic 1,2-diazetidines 250a,b. The exact conditions and reaction pathway were not clear (this research was reported in a patent without full details), but this methodology has only been applied to two examples.

![Scheme 3.5](image3)
3.1.3 Cyclobutadiene and Azo Compounds

Alternatively, bicyclic 1,2-diazetidines have been synthesised through a Diels-Alder reaction between azo compounds and cyclobutadiene. Masamune and co-workers first reported the use of cyclobutadieneiron tricarbonyl complex 251 to access bicyclic 1,2-diazetidines 10. Cyclobutadiene was generated through oxidation of the cyclobutadieneiron tricarbonyl complex 251 with lead(IV) tetraacetate, which could then undergo a Diels-Alder reaction with the azo compounds 8b and 8s to give the bicyclic 1,2-diazetidines 10b,s in moderate yields (Scheme 3.6).

![Scheme 3.6](image)

Inspired by these results, Warrener et al. demonstrated a similar reaction between dimethyl azodicarboxylate (DMAD) 8a and cyclobutadieneiron tricarbonyl complex 251 in the presence of the oxidant cerium ammonium nitrate (CAN) to give the bicyclic 1,2-diazetidine 10a in 31% yield (Scheme 3.7).

![Scheme 3.7](image)

Kobayashi and co-workers have exploited hexa-substituted fluorinated benzvalene 252 as another route to make a substituted cyclobutadiene and form substituted bicyclic 1,2-diazetidines (Scheme 3.8). Benzvalene 252 can be accessed through irradiation of hexa(trifluoromethyl)benzene in reasonable yields, and was found to be stable in comparison to other benzvalenes. Through ozonolysis, benzvalene 252 was converted into ozonide 253, which was also found to be stable at room temperature. Irradiation of ozonide 253 resulted in the loss of trifluoroacetic anhydride to form diradical 255, which ring-opened to form cyclobutadiene 256 and was trapped with DEAD 8b to give the bicyclic 1,2-diazetidine 254 in moderate yield.
Eisenbarth and Regitz have explored the photolysis of diazo compound 257 to access cyclobutadiene 258, which bares large substituents (Scheme 3.9). Cyclobutadiene 258a (but not the methyl ester derivative 258b) was isolable and both cyclobutadienes 258 underwent Diels-Alder reactions with DEAD 8b and PTAD 8h to give bicyclic 1,2-diazetidines 259a-c in good yields (Scheme 3.9a). The authors observed that PTAD 8h reacted with the more electron rich double bond to give 259b,c, whereas DEAD 8b reacted with the more electron deficient double bond to give 259a (Scheme 3.9b). Interestingly, when PTAD 8h was directly reacted with diazo 257 the product isolated was bicyclic 1,2-diazetidine 259d,e and not 259b,c. It was proposed that elimination of nitrogen gas formed carbene 260, which could then attack PTAD 8h and undergo a 1,2-shift to form allylic cation 262, followed by ring closing to form the product 259d,e.

![Scheme 3.8](image-url)
To summarise this section, these literature examples have shown that it is possible to synthesis bicyclic 1,2-diazetidines. The 4-π photocyclisation of 1,2-dihydropyridazines 9 is the simplest route to access bicyclic 1,2-diazetidines 10 and even though there are very few examples the yields are moderate to good, whilst the reaction has been performed on a reasonable scale without any issues. The only alternative routes to access bicyclic 1,2-diazetidines employ cyclobutadiene or metal complexes but these methodologies have serious practical limitations. The patent methodology uses non-commercially available organotitanium dienes and has only described two examples for the synthesis of bicyclic 1,2-diazetidines. It is not known whether simpler dienes can be used, which leads to uncertainty on whether this route would be suitable as a general synthesis for bicyclic 1,2-diazetidines. The use of cyclobutadiene also requires non-commercially available starting materials: cyclobutadieneiron tricarbonyl complex 251, benzvalene 252 and diazo 257, which must first be synthesised using expensive, hazardous or toxic reagents (Scheme 3.10). The cyclobutadieneiron tricarbonyl complex 251 can be synthesised in moderate-low yields through treatment of either dichlorocyclobutene 263 or bicyclic lactone 265 with diiron nonacarbonyl 264. 280,281 Cyclobutene 263 is commercially available, although it is very expensive and the synthesis of 263 is not trivial and requires
chlorine gas. Bicyclic lactone 265 must be first synthesised from 2-pyrene 175 through a 4-π photocyclisation, though bicycle 265 is not that stable and has been found to be pyrophoric in air. Benzvalene 252 was synthesised through irradiation of hexa(trifluoromethyl)benzene 266, which in the process formed two other products 267 and 268. Therefore, the 4-π photocyclisation of 1,2-dihydropyridazines 9 is the most viable route to access bicyclic 1,2-diazetidines and while they are currently not commercially available can provide a methodology that has less of an environmental impact.

3.1.4 Photochemistry of Other 1,2-Dihydropyridazines

As has already been discussed, various research groups have shown that the photochemistry of 1,2-dihydropyridazines can go via two pathways, a 4-π photocyclisation to give 10 and an initial 6-π electrocyclic ring opening, which eventually forms 2-aminopyrrole 210 (Scheme 3.11). In this next section the photochemistry of 1,2-dihydropyridazines that do not give any products from the 4-π photocyclisation shall be discussed.

The photochemistry of substituted and bicyclic 1,2-dihydropyridazines has given varied results. Rigaudy and Brelière have explored the photochemistry of the diphenyl substituted 1,2-dihydropyridazine 157b, which exclusively formed triene 271 after irradiation in diethyl ether (Scheme 3.12). The bicyclic 1,2-diazetidine 272 was not formed, and potentially the 4-π photocyclisation pathway is disfavoured due to the formation of additional steric strain caused by two adjacent phenyl groups on the same face of the molecule.
Ried and Reiher have investigated the photochemistry of a similar system 171b and also found that the 6-π electrocyclic ring opening pathway was favoured (Scheme 3.13). Irradiation of 1,2-dihydropyridazine 171b in diethyl ether gave heterocycle 274 after purification on silica gel. The authors proposed a similar mechanism to Altman et al. for the formation of the 2-aminopyrrole ring (Scheme 3.2), however in their case purification on silica gel converted the silyl enol ether 277 to the observed product 274. As with the examples described by Altman et al., it cannot be ruled out that this reaction proceeded through a photochemical [4+2] cycloaddition.

The photochemistry of unsubstituted and substituted bicyclic 1,2-dihydropyridazines with urazole-derived (9h, 157h and 179h) and phthalazine-1,4-dione (9o and 157o) have been studied (Figure 3.1). In all cases, tricyclic 1,2-diazetidines with the general structure 10h,o were not formed, and the use of these protecting groups resulted in either preferential 6-π electrocyclic ring opening and/or other reactions (vide infra). The synthesis of the diphenyl substituted 1,2-dihydropyridazine 157h has been reported, however it was found to be light sensitive and no details on the photochemistry have been described.

![Scheme 3.12](image)

**Scheme 3.12**

![Scheme 3.13](image)

**Scheme 3.13**

**Figure 3.1**

![Figure 3.1](image)
When the unsubstituted bicyclic 1,2-dihydropyridazine 9h was irradiated in three different solvents (methanol, dichloromethane and diethyl ether), there was no sign of the 4-π photocyclisation product (Scheme 3.14). The use of dichloromethane or diethyl ether gave bicyclic pyrrole 210h and the dimers 278a,b in poor yields. These reactions did not go to completion and small quantities of starting material 9h were recovered. When the reaction solvent was changed to methanol, the addition products 279 were isolated in 60–80% yield, and again, small quantities of dimers 278a,b were formed. Here, only bicyclic pyrrole 210h was thought to have formed from an initial 6-π electrocyclic ring opening.

Scheme 3.14 * Major product not determined

In comparison, the photochemistry of the phthalazine-1,4-dione-1,2-dihydropyridazines 9o gave completely different results (Scheme 3.15). Irradiation of 1,2-dihydropyridazine 9o in methanol and dichloromethane gave the unexpected cycloadduct 280 in good yields, where the hydrogen atoms (highlighted in red) are trans to each other in the new bicycle ring. 280 was suggested to have formed through an initial $E/Z$ isomerisation to give a highly strained alkene, which undergoes an intermolecular thermally allowed $\pi_4+\pi_2$ Diels-Alder reaction with another molecule of 1,2-dihydropyridazine 9o. Alternatively, a direct photochemical $\pi_4+\pi_2$ Diels-Alder reaction between two 1,2-dihydropyridazine compounds would also lead to the expected product.

Scheme 3.15
Sheradsky and Moshenberg have also studied the photochemistry of the ester substituted 1,2-dihydropyridazine 179h, which gave products derived from a triene intermediate 285 (Scheme 3.16).\textsuperscript{174} Irradiation of 1,2-dihydropyridazine 179h in alcohols (methanol and tert-butanol) gave bicycles 281 and 283 in poor-moderate yields and it was proposed that these products were formed by the addition of an alcohol to the acyl imines of triene 285. Bicyclic pyrrole 284 was formed in trace amounts and in moderate yield in dichloromethane. The authors proposed that pyrrole 284 had formed through an alternative photochemical reaction in which triene 284 was converted into aziridine 286, which after aromatisation gave the observed product 284. No further mechanistic details were provided for this transformation, but the authors suggested that the reaction may go via a photochemical $\pi_{4s} + \pi_{2a}$ cycloaddition.

\[ \text{Scheme 3.16} \]

The modification of 9o through the addition of two phenyl groups had another unexpected effect on the photochemistry (Scheme 3.17).\textsuperscript{166} Thus, irradiation of 1,2-dihydropyridazine 157o quickly formed tetracycle 287 in a good yield. The proposed mechanism began with an electrocyclic ring opening to give $E/Z$-triene 288 with the carbonyl positioned to undergo a further photochemical reaction, whereas this was not possible if $E/E$-triene 291 had formed, due to its configuration. Irradiation of the conjugated ketone 288 gave the triplet excited state, illustrated as diradical 289, which reacted to first form a C-N bond (290) and secondly to form a C-O bond to give the product 287. An alternative mechanism would see the C-O bond formed first (to give
and then the C-N bond. The authors suggested that the first mechanism should prevail, likely caused by the added stability from the formation of an allylic and benzylic radical.

Scheme 3.17 ISC = intersystem crossing

3.1.5 Conclusions
In summary, it is possible to synthesise bicyclic 1,2-diazetidines 10 but currently there is no general route to access them. As mentioned above, the 4-π photocyclisation of 1,2-dihydropyridazines 9 is currently the most practical route to access bicyclic 1,2-diazetidines 10 and for the limited examples the yields are useable. Alternative methodology uses cyclobutadiene precursors or organotitanium diene complexes, which are not commercially available, and the synthesis of these compounds can be costly, requires multiple steps and the use of toxic building blocks. 1,2-Dihydropyridazines 9 are also not commercially available but, with optimisation, could provide a more effective and sustainable methodology. The reaction course for the 4-π photocyclisation of 1,2-dihydropyridazines is highly dependent on structure and literature examples have shown that significant care must be taken on the choice of the protecting groups on the nitrogen atoms and the substituents that are attached to the 1,2-dihydropyridazine ring. Multiple examples have shown that the use of cyclic protecting groups and the presence of phenyl groups adjacent the nitrogen atoms favoured the 6-π electrocyclic ring opening pathway and stopped the 4-π photocyclisation from taking place. The effect that other substituents, such as alkyl groups and other functional groups, will have on the 4-π
Photocyclisation of 1,2-dihydropyridazines is not known and it is vital that future endeavours seek to answer this question.

3.2 Aims

As described above, the 4-π photocyclisation of 1,2-dihydropyridazines 9 has not been widely studied, which meant that there were a variety of objectives that needed to be completed (Figure 3.2). Firstly, the photophysical properties of 1,2-dihydropyridazines 9 have not been reported, therefore ultraviolet-visible (UV-Vis) spectroscopy will be used to study the absorption profile in a variety of organic solvents to guide the 4-π photocyclisation optimisation. Optimisation was to be carried out using commercially available batch and flow photoreactors: Rayonet RPR-100 Batch Photochemical Reactor and a Vapourtec E-series Flow System equipped with the UV-150 Photochemical Reactor. Once optimised, the aim was to complete the 4-π photocyclisation on 1,2-dihydropyridazines 9 and to scale-up the reaction to access multigram quantities of bicyclic 1,2-diazetidines 10 for downstream applications.

4-π Photocyclisation of 1,2-Dihydropyridazines:

- UV/Vis spectroscopy in different solvents
- Optimisation in batch and flow photoreactor
- Investigation of various substrates
- Scale-up to multigram quantities

Figure 3.2

3.3 Results and Discussion

With multigram quantities of 1,2-dihydropyridazines 9 now available, it was now possible to move on to the investigation of the 4-π photocyclisation. It was already known from the literature that irradiation of simple 1,2-dihydropyridazines 9 formed bicyclic 1,2-diazetidines 10 and 2-aminopyrroles 210, with the 10 being the major product (Scheme 3.18).\textsuperscript{33,35,36} It was hoped that the yield of and selectivity for the bicycle 10 could be improved with optimisation.

\textit{Scheme 3.18}

3.3.1 Ultraviolet-Visible (UV-Vis) of 1,2-Dihydropyridazine 9b

The ultraviolet-visible (UV-Vis) spectra of 1,2-dihydropyridazines 9b should show two transitions: π→π* and a weak n→π*. 1,2-Dihydropyridazine 9b showed a single absorption band with an absorption maximum (λ_{max}) around 300 nm in a variety of solvents except for acetone, which was closer to 330 nm (Table 3.1). Potentially, a large π→π* band and a smaller n→π* band are both present, but they overlap to give a single absorption peak. A slight
bathochromic shift (a shift to a longer wavelength) was observed when more non-polar solvents were used, with methyl tert-butyl ether (MTBE) and toluene giving an $\lambda_{\text{max}}$ at longer wavelengths. The cut-off wavelength (when the solvent would start to absorb light) for each solvent is included for comparison (Table 3.1). Acetone has a cut-off wavelength at longer wavelengths (330 nm) compared to the other solvents and it is likely that any experimental work below this wavelength would result in the excitation of the solvent and side reactions could occur. The same case can be made for toluene, when looking at wavelengths below 300 nm (cut-off wavelength: 285 nm).

![1,2-Dihydropyridazine 9b in different solvents (0.2 mM)](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Cut-off Wavelength (nm)</th>
<th>$\lambda_{\text{max}}$ (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>190</td>
<td>298</td>
</tr>
<tr>
<td>2</td>
<td>MTBE</td>
<td>210</td>
<td>302</td>
</tr>
<tr>
<td>3</td>
<td>EtOAc</td>
<td>255</td>
<td>300</td>
</tr>
<tr>
<td>4</td>
<td>PhMe</td>
<td>285</td>
<td>303</td>
</tr>
<tr>
<td>5</td>
<td>Acetone</td>
<td>330</td>
<td>327</td>
</tr>
</tbody>
</table>

**Table 3.1**

UV-Vis analysis of 1,2-dihydropyridazine 9b at different concentrations was completed to investigate whether the peak around 300 nm remained a single peak or split into two peaks (Figure 3.3). As the concentration was decreased from 0.2-0.001 mM, the absorption spectrum remained a single peak. At concentrations below 0.002 mM, a noticeable increase in signal to noise was observed and even though two peaks were observed at 0.0005 mM it could not be said with any confidence that this was real, rather than being due to contaminants.
The $\lambda_{\text{max}}$ values for the other 1,2-dihydropyridazines 9 in acetonitrile are listed in Table 3.2. For systems that possess acyclic protecting groups 9a–g an $\lambda_{\text{max}}$ around 300 nm was observed (entries 1-6). For bicyclic 1,2-dihydropyridazine 9h, which has a cyclic protecting group, a broad absorption between 200-300 nm that potentially contained three peaks and a weak absorption around 377 nm was observed (entry 7). The addition of substituents around the 1,2-dihydropyridazine ring is likely to affect the absorption characteristics, but the effect on $\lambda_{\text{max}}$ is currently unknown as previous studies did not report UV-Vis data.
1,2-Dihydropyridazine 9a-c-g in MeCN (0.2 mM)

Table 3.2

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>1,2-Dihydropyridazine 9</th>
<th>λ_{max} (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OMe</td>
<td>OMe</td>
<td>9a</td>
<td>296</td>
</tr>
<tr>
<td>2</td>
<td>O'Pr</td>
<td>O'Pr</td>
<td>9c</td>
<td>298</td>
</tr>
<tr>
<td>3</td>
<td>O'Bu</td>
<td>O'Bu</td>
<td>9d</td>
<td>303</td>
</tr>
<tr>
<td>4</td>
<td>OBn</td>
<td>OBn</td>
<td>9e</td>
<td>296</td>
</tr>
<tr>
<td>5</td>
<td>O'Bu</td>
<td>OMe</td>
<td>9f</td>
<td>299</td>
</tr>
<tr>
<td>6</td>
<td>O'Bu</td>
<td>OBn</td>
<td>9g</td>
<td>298</td>
</tr>
<tr>
<td>7</td>
<td>-N(Ph)-</td>
<td></td>
<td>9h</td>
<td>377</td>
</tr>
</tbody>
</table>

3.3.2 Optimisation in a Batch Photoreactor

Initially, the 4-π photocyclisation was studied in a commercially available batch photoreactor (Rayonet RPR-100) and 1,2-dihydropyridazine 9b was chosen for optimisation (Figure 3.4). The
batch photoreactor has a chamber in which a mirrored surface has lamps arranged in a circle and has a central area to accommodate a carousel, which can house test tubes made from either Pyrex (absorbs below 300 nm) or Quartz (for wavelengths below 300 nm). The carousel can fit up to 18 x 20 mL tubes or 12 x 60 mL tubes, therefore this reactor is ideal for both small and larger scale applications. The lamps are cooled by a fan and the standard operating temperature is around 40 °C.

In the literature, the irradiation of 1,2-dihydropyridazinone 9b was carried out at low temperatures and at wavelengths above 285 nm to obtain a 1.5:1.0 mixture of the bicyclic 1,2-diazetidine 10b and the 2-aminopyrrole 210b. From UV-Vis studies, it was found that 1,2-dihydropyridazinone 9b has an absorption around 300 nm in a variety of solvents, therefore irradiation of 1,2-dihydropyridazinone 9b at 300 nm was studied in a variety of solvents (Table 3.3). From the solvents studied, it was found that acetonitrile gave the best selectivity for and yield of 10b (entry 1). It should be noted that 2-aminopyrrole 210b was not stable on silica gel, which explains the difference between the crude and isolated ratios. As the absorption maximum of 1,2-dihydropyridazinone 9b increased (as the solvent became less polar), the yield and selectivity of the 4-π photocyclisation decreased (entries 1-5) and when acetone was used only trace amounts of product 10b was observed, most likely caused by the expected absorption of the solvent and side reactions. Preliminary results were also obtained for 1,2-dihydropyridazines 9c and 9d (entries 6 and 7). In both cases, bicyclic 1,2-diazetidines 10c,d were obtained in moderate yields, however the product selectivity observed for the ethyl system in acetonitrile had been significantly reduced for these systems. These preliminary results showed that as the λmax increased, using different solvents and protecting groups, the overall yield of and selectivity

Figure 3.4 Rayonet RPR-100
Chapter 3: Photochemistry of 1,2-Dihydropyridazines

for bicyclic 1,2-diazetidine 10 decreased. In these examples (entries 3, 4 and 7), irradiation at 300 nm targeted a slightly shorter wavelength than the $\lambda_{\text{max}}$ (left hand side of absorption peak) and promoted more of the 6-π electrocyclic ring opening, whereas when acetonitrile was used a slightly longer wavelength was targeted (right hand side of absorption peak) and less of the 6-π electrocyclic ring opening was observed.

\[
\begin{align*}
\text{hv (300 nm)} & \quad \text{solvent (10 mM), r.t., time} \\
9 & \quad 10:210 \\
& \quad \text{Entry} \quad \text{R} \quad \text{Solvent} \quad \lambda_{\text{max}} \quad \text{Time (hours)} \quad 10:210^a \quad \text{Bicycle 10 (%)$^b$} \quad \text{Pyrrole 210 (%)$^b$}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Solvent</th>
<th>$\lambda_{\text{max}}$</th>
<th>Time (hours)</th>
<th>10:210$^a$</th>
<th>Bicycle 10 (%)$^b$</th>
<th>Pyrrole 210 (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>MeCN</td>
<td>298</td>
<td>1.75</td>
<td>2.8:1.0</td>
<td>56</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>EtOAc</td>
<td>300</td>
<td>1</td>
<td>1.1:1.0</td>
<td>42</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>MTBE</td>
<td>302</td>
<td>2</td>
<td>1.3:1.0</td>
<td>45</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>PhMe</td>
<td>303</td>
<td>1</td>
<td>1.2:1.0</td>
<td>39</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>Acetone</td>
<td>327</td>
<td>1</td>
<td>-</td>
<td>traces</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>iPr</td>
<td>MeCN</td>
<td>298</td>
<td>1</td>
<td>1.2:1.0</td>
<td>42</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>tBu</td>
<td>MeCN</td>
<td>303</td>
<td>1</td>
<td>1.2:1.0</td>
<td>42</td>
<td>30</td>
</tr>
</tbody>
</table>

Table 3.3$^a$ Calculated from $^1$H NMR spectra of the crude product through comparison of bicycle 10 and pyrrole 210 peaks. No internal standard used; $^b$ Isolated yields

Whilst the formation of bicyclic 1,2-diazetidine 10 was assumed to result from 4-π photocyclisation and 2-aminopyrrole 210 from 6-π electrocyclic ring opening, the potential interconversion of 2-aminopyrrole 210 and bicycle 10 upon extended irradiation had not been ruled out. UV-Vis analysis on the 4-π photocyclisation of 1,2-dihydropyridazine 9b showed the gradual disappearance of the starting material and 2-aminopyrrole 210b over the course of the study and at the end there was only the absorption peak for bicyclic 1,2-diazetidine 10b (Figure 3.5). Next, both 10b and 210b were subjected to prolonged irradiation at 300 nm and monitored by $^1$H NMR over a twenty-four hour period (Figure 3.6 and 3.7). Bicyclic 1,2-diazetidine 10b showed no signs of degradation, whilst 2-aminopyrrole 210b showed gradual degradation over the time period. Importantly, no interconversion of the two products was observed. Bicyclic 1,2-diazetidine 10b absorbs at shorter wavelengths (broad absorption from 200-250 nm) in comparison to 1,2-dihydropyridazines 9b (298 nm) and 2-aminopyrrole 210 (271 nm), thus 10b does not absorb any light at 300 nm and remained unchained upon prolonged irradiation. On the other hand, 2-aminopyrrole 210b absorbs between 240-320 nm, therefore it is likely to undergo further reactions at this wavelength. Another theory that needed to be investigated was the potential 2-aminopyrrole 210b catalysed retro-4-π photocyclisation of 10b to re-form 1,2-dihydropyridazine 9b. To test this hypothesis, bicyclic 1,2-diazetidine 10b was irradiated in the presence of a catalytic amount of 2-aminopyrrole 210b (10 mol%) and monitored by $^1$H NMR and UV-Vis (Figure 3.8 and 3.9). 1,2-Dihydropyridazine 9b did not reform and only the degradation of 2-aminopyrrole 210b was observed.
Photocyclisation: A New Route to Functionalised Four-Membered Rings

**Figure 3.5**

1,2-Dihydropyridazine 9b 4-π photocyclisation (300 nm)

9b, 10b and 210b in MeCN (0.2 mM)
Figure 3.6 $^1$H NMR in CDCl$_3$ of bicyclic 1,2-diazetidine 10b, irradiated at 300 nm over a 24 hour period
Figure 3.7 $^1$H NMR in CDCls of 2-aminopyrrole 210b, irradiated at 300 nm over a 24 hour period.
Figure 3.8 $^1$H NMR in CDCl$_3$ of bicyclic 1,2-diazetidine 10b with 10 mol% 2-aminopyrrole 210b, irradiated at 300 nm over a 6 hour period.
Figure 3.9

The batch photoreactor can be used with a variety of lamps with different wavelengths (254, 300, 350, 419, 575 nm), which has enabled a range of wavelengths to be investigated for the 4-π photocyclisation (Table 3.4). The 4-π photocyclisation of 1,2-dihydropyridazine 9b at 300 nm had been already completed (entry 1), but moving to 254 nm (right on the edge of the absorption peak in Table 3.1) resulted in a sharp decrease in rate of reaction, yield and selectivity for bicyclic 1,2-diazetidine 10b (entry 2). A lot of degradation was observed, and it was thought that a combination of moving to the shorter, higher energy wavelength and that bicyclic 1,2-diazetidine 10b and 2-aminopyrrole 210b both absorbed light around 254 nm was causing the destruction of the starting material and products.

Irradiation at 350 nm (on the opposite edge of the absorption peak) completely changed the bicycle:pyrrole selectivity (entry 3). The reaction was slower compared to 300 nm (20 hours compared to 1 hour), but now only trace amounts of pyrrole 210b were formed, and the desired bicycle 10b was isolated in a good yield. The drop in the rate of reaction between 350 and 300 nm was rationalised through calculation of the molar absorption coefficient (ε) (how well light is absorbed at a certain wavelength) from the Beer-Lambert Law (A = εcl; A = absorbance, c = concentration, l = path length). When this was applied to the UV-Vis data for 1,2-dihydropyridazine 9b in acetonitrile (Table 3.1, path length = 1.0 cm, concentration = 0.2 mM), a twentyfold decrease in ε was observed when the wavelength was changed from 300 and 350 nm.
nm (300 nm, \( \varepsilon = 2975 \); 350 nm, \( \varepsilon = 146 \)) and showed that at 350 nm the photoreaction was less efficient (since 1,2-dihydropyridazine 9b does not absorb strongly at this wavelength), which in turn led to an increase in the reaction times. The increase in selectivity was proposed to arise from irradiation of a smaller \( n \rightarrow \pi^* \) absorption band at the edge of the main \( \pi - \pi^* \) absorption peak, which leads to the promotion of the \( 4 - \pi \) photocyclisation pathway. In addition, this explanation further supports the suggestion that irradiation on the longer wavelength side of the \( \Lambda_{\text{max}} \) resulted in less of the \( 6 - \pi \) electrocyclic ring opening. From UV-Vis studies, it has not been possible to prove the presence of this smaller absorption band, but currently this rationale provides the most plausible explanation for the observed selectivity.

At 419 nm, no reaction was expected to happen due to the lack of an absorption peak in this area for starting material 9bb (entry 4). Experimentally, this was what was observed and only starting material 9bb was seen by \(^1\)H NMR analysis. The addition of triplet sensitiser 294, a ketone that aids the generation of hard to access triplet states through energy transfer (the triplet state of the sensitiser converts the substrate from the ground to the excited state and concurrently the sensitiser is converted back down to the ground state), showed no sign of the bicycle 10b and only degradation of the starting material 9b (entry 5). As a result, 350 nm was selected as the chosen wavelength to take forward into future experiments.

![Chemical structure diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Wavelength (nm)</th>
<th>Time (hours)</th>
<th>10b (%)</th>
<th>210b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>300</td>
<td>1</td>
<td>56</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>254</td>
<td>2.5</td>
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<td>20</td>
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</tr>
<tr>
<td>4</td>
<td>419</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>419</td>
<td>1</td>
<td>- (^a)</td>
<td>-</td>
</tr>
</tbody>
</table>

\( ^a \) Isopropylthioxanthone 294 used as a photosensitiser

\(^1\)H NMR analysis of the crude reaction mixtures from each wavelength showed very different spectra (Figure 3.10). The reaction at 350 nm gave the cleanest formation of product 10b formation and the amount of pyrrole 210b present decreased moving from 254 up to 350 nm. The degradation peaks seen for the reaction in the presence of the photosensitiser (419 nm) were similar to the ones at 254 nm, but it has not been possible to identify these products. The broad nature of these peaks suggested that may be due to polymeric degradation products, which could not be isolated from the reaction mixtures.
4-π Photocyclisation: A New Route to Functionalised Four-Membered Rings

Figure 3.10 $^1$H NMR for irradiation of 1,2-dihydropyridazine 9b at different wavelengths; a
Isopropylthioxanthone 294 used as a photosensitiser
With the optimal wavelength settled upon, another solvent screen was judged worthwhile (Table 3.5). In all cases only trace amounts of the pyrrole were observed and good yields for the bicycle 10b were obtained (entries 1-5). The change in wavelength meant that it was now possible to use acetone as the reaction solvent because it should no longer absorb at the chosen wavelength. Acetonitrile and MTBE were found to be the optimum solvents and toluene could be used as a further back-up if necessary.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Bicycle 10b (%)</th>
<th>Pyrrole 210b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>77</td>
<td>traces</td>
</tr>
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<td>2</td>
<td>MTBE</td>
<td>77</td>
<td>traces</td>
</tr>
<tr>
<td>3</td>
<td>EtOAc</td>
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<td>PhMe</td>
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</tr>
<tr>
<td>5</td>
<td>Acetone</td>
<td>62</td>
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</tr>
</tbody>
</table>

Table 3.5

To carry this photoreaction out on a meaningful scale the 4-π photocyclisation of 9b was investigated at different concentrations (Table 3.6). At 20 mM, the reaction gave higher yields of bicycle 10b than at 10 mM (entry 1) with a slight increase in the reaction times. At 50 mM the reaction time doubled, and the yield decreased slightly (entry 2). When the solvent was switched to toluene, the reactions at 20 and 50 mM were complete in 24 hours and the yields were comparable to those observed at lower concentrations (entries 2 and 3). The use of MTBE at higher concentrations showed poor conversions and starting material was still present after 48 hours. Even though the yield dropped, running the reactions at 50 mM in either acetonitrile or toluene was chosen due to the larger amounts of material that could be processed.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Concentration (mM)</th>
<th>Time (hrs)</th>
<th>Bicycle 10b (%)</th>
<th>Pyrrole 210b (%)</th>
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<tr>
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<tr>
<td>2</td>
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</tr>
<tr>
<td>3</td>
<td>PhMe</td>
<td>20</td>
<td>24</td>
<td>71</td>
<td>traces</td>
</tr>
<tr>
<td>4</td>
<td>PhMe</td>
<td>50</td>
<td>24</td>
<td>71</td>
<td>traces</td>
</tr>
</tbody>
</table>

Table 3.6

The 4-π photocyclisation has now been applied to the other 1,2-dihydropyridazines 9a-g in either acetonitrile or toluene to give the bicycles 10a-g in good yields (Scheme 3.19). In most cases, the bicycle yields in acetonitrile and toluene were similar and only the best yields are shown. The reason for this observed improvement is thought to have been from a slight
bathochromic shift in the $\lambda_{\text{max}}$ (as seen for 1,2-dihydropyridazine 9b) when the solvent was switched from acetonitrile to toluene, which reduced reaction times and degradation. 1,2-Dihydropyridazine 9a was not soluble in toluene, whereas the dibenzyl carbamate system 9e was not soluble in acetonitrile. The reaction can also be carried out at 100 mM, as exemplified with diene 9d, without a decrease in yield, however the reaction time doubled even on a small scale in both acetonitrile and toluene. Irradiation of 1,2-dihydropyridazine 9h gave no sign of tricyclic diazetidine 10h and $^1$H NMR analysis only showed the presence of 2-aminopyrrole 210h, which supported previously reported observations.165

**Scheme 3.19**

In MeCN; $^b$ Irradiated for 44 hours; $^c$ In PhMe; $^d$ 100 mM scale for 44 hours

Attention then turned to the scale-up of this reaction with diene 9d, due to its ease of synthesis on a large scale (Scheme 3.20). Starting with nearly one gram of diene 9d, the reaction times doubled to that on a smaller scale, though the yield of bicycle 10d was comparable (82% compared to 81% in Scheme 3.19). On ten times the scale the yield dropped by 10%, but the product 10d was still isolated in a good yield. These results are unusual for most UV photoreactions, which on larger scales often require longer reaction times and show a drop off in yield caused by inefficient irradiation and product degradation.

**Scheme 3.20**
3.3.2 Optimisation in a Flow Photoreactor

To aid scale-up, the aim was to optimise and run the 4-π photocyclisation on the commercially available E-series Vapourtec flow system equipped with a photoreactor (Figure 3.11). The scale-up of photochemistry has long been seen as a major limitation to the field, however the development of new flow technologies has helped to circumvent these problems.\textsuperscript{288-291} The penetration of light into a solution is governed by the Beer-Lambert Law ($A = \varepsilon cl$; $A$ = absorbance, $c$ = concentration, $l$ = path length) and as the distance from the light source increases (path length) the absorption efficiency sharply decreases. The scale-up of batch photoreactions often requires a larger reactor, which in turn decreases the ability of light to get into the reaction mixture, thus leading to longer reaction times and over-irradiation of the products. Photoreactions are also concentration dependent and as the concentration of the reaction mixture increases, the molecules closest to the light source absorb a greater proportion of the light, thus preventing light from penetrating the whole solution and increasing reaction times. Therefore, more dilute concentrations often lead to faster reactions. Flow photochemistry can solve these issues by exposing smaller volumes of the reaction mixture to the light source through microchannels or tubing. As a result, the photoreactions are more efficient due to the reaction mixture being in close proximity to the light source (decreasing the path length) and often enables higher concentrations to be used. The residence time (time the reaction mixture spends in the flow cell) can be optimised using different flow rates to control the exposure time and can help to reduce the formation of by-products. In a flow photoreactor, a smaller volume of flammable organic solvent is in the reactor at any given time in comparison to a batch photoreactor, which helps to drastically improve the safety and fire-risk. For example, the photoreactor size is 10 mL for the E-series Vapourtec flow system, which is considerably lower than exposing 18 x 20 mL or 12 x 60 mL tubes in the Rayonet batch photoreactor used above. It should be noted that even though flow photochemistry provides an easier platform for scale-up, comparison of the yields and productivity between batch and flow photoreactors have been shown to give nearly equal performance.\textsuperscript{292}

![Figure 3.11 E-series Vapourtec flow system equipped with a photoreactor (UV-150)](image_url)
The medium pressure mercury lamp can be used in conjunction with various filters to enable the use of narrower wavelength bands (Figure 3.12). For this work the type 2 and 4 filters were used, as well as a 365 nm LED light source (instead of the mercury lamp). The type 2 filter passes wavelengths from 240-400 nm, whereas the type 4 filter passes wavelengths from 310-390 nm. A 350 nm lamp is not currently available for the Vapourtec flow system, which prevents a direct comparison between the batch and flow photoreactors.

Figure 3.12 Images supplied and used with permission from Vapourtec Ltd

The results from optimisation with 1,2-dihydropyridazine 9b with type 2 and 4 filters is summarised below (Table 3.7). In all cases, poor conversions were observed at fast flow rates (entries 1, 5, 9 and 17), but at slower flow rates no starting material remained and the selectivity for the bicycle 10b increased (entries 2-4, 6-8, 10-12 and 14-16). Given the instability of 2-aminopyrrole 210b upon prolonged irradiation at 300 nm in the batch photoreactor, there is a high possibility that at slower flow rates (in which longer residence (reaction) times were required) 2-aminopyrrole 210b reacted further and/or degraded. If so, the observed increase in selectivity was influenced by this factor and not from the 4-π photocyclisation pathway being somehow favoured. Whilst the conversions and bicycle selectivity looked promising, the major limitation from these reactions were the purity of the crude products (Figure 3.13). When compared to the results from the batch photoreactor, the crude mixtures from the flow photoreactor showed significantly more degradation, which was likely to have an impact on the yields. The likely cause of this is that even though a narrower wavelength band was used, the type 2 filter still passed wavelengths between 240-300 nm and significant degradation was observed in the batch photoreactor at 254 nm. In attempt to minimise this issue, the type 4 filter was used that did not pass wavelengths below 300 nm (entries 21-24). At high dilutions (10 mM) only low conversions were observed, with around 50% conversion at a flow rate of 0.5 mL/min and there were still signs of degradation. Lower concentrations were not attempted, as even if this approach proved successful the concentration would have been ten times lower than what could be used in the batch photoreactor, thus the productivity of the reaction would be much lower. Finally, the use of a 365 nm LED lamp led to very poor conversions (entries 25-28), probably caused by the very low absorption of the starting material 9b at this wavelength.
Chapter 3: Photochemistry of 1,2-Dihydropyridazines

\[
\begin{array}{c}
\text{9b} \quad \text{CO}_2\text{Et} \\
\text{h} (\text{Flow}) \\
\text{MeCN, 20-25 °C} \\
\end{array}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Flow rate (mL/min)</th>
<th>Concentration (mM)</th>
<th>Conversion 9b (%)(^a)</th>
<th>Product ratio (10b:210b)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>20</td>
<td>25</td>
<td>1.7:1.0</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>20</td>
<td>100</td>
<td>3.0:1.0</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>20</td>
<td>100</td>
<td>5.5:1.0</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>20</td>
<td>100</td>
<td>19:1.0</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>10</td>
<td>57</td>
<td>2.3:1.0</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>10</td>
<td>100</td>
<td>5.4:1.0</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>10</td>
<td>100</td>
<td>18:1.0</td>
</tr>
<tr>
<td>8</td>
<td>0.5</td>
<td>10</td>
<td>100</td>
<td>No pyrrole</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>5</td>
<td>18</td>
<td>3.4:1.0</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>5</td>
<td>57</td>
<td>15:1.0</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>5</td>
<td>100</td>
<td>No pyrrole</td>
</tr>
<tr>
<td>12</td>
<td>0.5</td>
<td>5</td>
<td>100</td>
<td>14:1.0</td>
</tr>
<tr>
<td>13(^b)</td>
<td>5</td>
<td>10</td>
<td>48</td>
<td>4.0:1.0</td>
</tr>
<tr>
<td>14(^b)</td>
<td>2</td>
<td>10</td>
<td>100</td>
<td>6.9:1.0</td>
</tr>
<tr>
<td>15(^b)</td>
<td>1</td>
<td>10</td>
<td>100</td>
<td>13:1.0</td>
</tr>
<tr>
<td>16(^b)</td>
<td>0.5</td>
<td>10</td>
<td>100</td>
<td>No pyrrole</td>
</tr>
<tr>
<td>17(^c)</td>
<td>5</td>
<td>10</td>
<td>18</td>
<td>1.9:1.0</td>
</tr>
<tr>
<td>18(^c)</td>
<td>2</td>
<td>10</td>
<td>57</td>
<td>2.4:1.0</td>
</tr>
<tr>
<td>19(^c)</td>
<td>1</td>
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</tr>
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<td>100</td>
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</tr>
<tr>
<td>21(^d)</td>
<td>5</td>
<td>10</td>
<td>4</td>
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</tr>
<tr>
<td>22(^d)</td>
<td>2</td>
<td>10</td>
<td>9</td>
<td>-(^e)</td>
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<td>10</td>
<td>22</td>
<td>-(^e)</td>
</tr>
<tr>
<td>24(^d)</td>
<td>0.5</td>
<td>10</td>
<td>48</td>
<td>-(^e)</td>
</tr>
<tr>
<td>25(^f)</td>
<td>5</td>
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<td>5</td>
<td>4</td>
<td>-(^e)</td>
</tr>
<tr>
<td>28(^f)</td>
<td>0.5</td>
<td>5</td>
<td>7</td>
<td>-(^e)</td>
</tr>
</tbody>
</table>

Table 3.7: Calculated by \(^1\)H NMR through comparison of starting material 9b, bicycle 10b and pyrrole 210b peaks. No internal standard used, so does not capture degradation; \(^a\) Completed at lower temperature (ranged between: -4 and 0 °C); \(^b\) Completed at 50% lamp power; \(^c\) Type 4 filter used instead of Type 2; \(^d\) Not possible to calculate ratio due to presence of starting material; \(^e\) 365 nm LED used instead of medium pressure mercury lamp.
Figure 3.13 Batch vs Flow comparison for 4-\pi photocyclisation of 1,2-dihydropyridazine 9b
3.4 Conclusions

An extensive investigation has been carried out on the properties and 4-π photocyclisation of 1,2-dihydropyridazines 9. Through UV-Vis analysis, it was possible to gain an understanding of the photophysical properties of 1,2-dihydropyridazine 9 in a variety of solvents and the data was used to help guide and quantify the results observed experimentally. As a result, the 4-π photocyclisation of 1,2-dihydropyridazines 9 has been successfully optimised in a batch photoreactor to give good yields of bicyclic 1,2-diazetidines 10 and implemented to synthesise seven bicycles, five of which were novel. Subsequently, the 4-π photocyclisation has been scaled-up using 1,2-dihydropyridazine 9d and was successfully completed on multigram scales without a significant drop in yield. Currently, it is possible to process more material for the 4-π photocyclisation of 1,2-dihydropyridazines in the batch photoreactor and not the flow photoreactor. The major limitation with the flow photoreactor is the amount of degradation that is caused by shorter wavelengths (type 2 filter), the poor conversions (type 4 filter and 365 nm LED) and the need for dilute concentrations (both filters). In addition, it has not been possible to investigate the 4-π photocyclisation in flow at 350 nm due to the light source not being available from Vapourtec. If the highest yields of bicyclic 1,2-diazetidines 10 in the batch photoreactor had been achieved at 300 nm, where 1,2-dihydropyridazines 9 have the highest ε values, the flow photoreactor optimisation may have been better. The slow conversion of 1,2-dihydropyridazines 10 at 350 nm can be solved in the batch photoreactor through longer reaction times, but in the flow photoreactor slower flow rates (longer residence times) have given poor conversions and more degradation products in comparison to the batch photoreactor. If these issues can be addressed, then this could be a viable alternative for scale-up in the future. In combination with the new synthesis for 1,2-dihydropyridazines 10, bicyclic 1,2-diazetidines 9 can now be easily accessed in meaningful quantities in two or three steps from simple building blocks.
Chapter 4: Reactions of Bicyclic 1,2-Diazetidines
4.1 Introduction

4.1.1 Derivatisation of Bicyclic 1,2-Diazetidines

The synthetic potential of bicyclic 1,2-diazetidines 10 has not been extensively explored but have the potential to be transformed into a variety of synthetically valuable building blocks (Figure 4.1). Cleavage of the N-N bond would give cis-1,2-diamino-cyclobutenes, which could be further derivatised to access cyclobutane scaffolds. On the other hand, the double bond should undergo classical reactions to enable functionalised monocyclic 1,2-diazetidines to be accessed.

![Double bond functionalisation](Figure 4.1)

Most of the current literature has focused on the deprotection of the carbamate protecting groups attached to the nitrogen atoms under basic conditions and oxidation of the diamine to access cyclobutadiene.\(^{162,273}\) The successful removal of the ethyl carbamate protecting groups from bicyclic 1,2-diazetidine 10b and similar bicyclic systems has been reported, albeit under forcing conditions (potassium hydroxide in ethylene glycol at 130 °C).\(^{36,273,293}\) Masamune and co-workers reported the seminal example, in which milder deprotection conditions were employed to deprotect bicyclic 1,2-diazetidines 10b and 10r, which after neutralisation with trifluoroacetic acid gave the air-sensitive diamine 295 (Scheme 4.1).\(^{273}\)

![Scheme 4.1](image)

Oxidation of diamine 295 with a range of benzoquinones (benzoquinone, 2,6-dimethylbenzoquinone and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone/DDQ) or aqueous sodium hypochlorite was assumed to form azo compound 300, which spontaneously underwent a retro-[2+2] reaction to eliminate nitrogen gas and to form cyclobutadiene 301 (Scheme 4.2). Benzoquinones served not only as an oxidant but also as trapping agents for cyclobutadiene 301, to give bicycles 296 (the relative configuration was not described). Oxidation of diamine 295 with sodium hypochlorite resulted in dimerization of cyclobutadiene 301 to give dimer 298 but a 1.0:1.0 mixture of dimer 298 and bicycle 299 was formed when cyclopentadiene 297 was present. Currently, other synthetic routes to access cyclobutadiene 301 are not trivial and often require expensive and toxic reagents (see Scheme 3.10 in Section 3.1.3).\(^{280,281}\) The further development of this methodology could establish bicyclic diazetidines 10 as simple precursors to cyclobutadiene.
These findings formed the basis of another publication by Whitman and Carpenter, in which a different set of reaction conditions were employed for the basic hydrolysis and oxidation of a deuterated bicyclic 1,2-diazetidine 302 to access deuterated cyclobutadienes 304 and 305 (Scheme 4.3). Here, potassium tert-butoxide successfully removed the methyl carbamate protecting groups of 302 and the resulting amine was oxidised in the presence of lead(IV) tetraacetate to form azo compound 303, which immediately formed cyclobutadiene 304. The authors found similar Gibbs free energy ($\Delta G^\ddagger$) values for the interconversion between cyclobutadienes 304 and 305 and for trapping with a dienophile. When a reactive dienophile such as 3-cyanoacrylate 306 was used, cycloaducts possessed an isotope distribution that matched cyclobutadiene 304, which suggested no interconversion had taken place. Whereas, for less reactive dienophiles (e.g. 307) a mixture of isotope distributions 304 and 305 were observed.

It has been previously reported that the double bond in bicyclic 1,2-diazetidines 10b can be reduced through hydrogenation to give saturated bicycle 308b (Scheme 4.4). Removal of the ethyl carbamate protecting groups from saturated bicycle 308b was then achieved under modified conditions developed for the deprotection of amides. Diamine 309 was oxidised with copper(II) salts to give azo compound 310, which could be isolated as the copper complex 311.
Chapter 4: Reactions of Bicyclic 1,2-Diazetidines

To date, there has been only one example where the double bond in bicyclic 1,2-diazetidine 10a has been the focus for derivatisation (Scheme 4.5). Bicyclic 1,2-diazetidine 10a underwent a Diels-Alder reaction with cyclopentadienone 61 to give the cycloadduct 32 (structure confirmed by X-ray crystallography). Interestingly, it appeared that bicyclic 1,2-diazetidine 10a was stable enough to be heated in benzene, but the moderate yield could be a sign that some degradation had taken place. Irradiation of cycloadduct 32 resulted in extrusion of carbon monoxide to give intermediate 35, which immediately further reacted to give the unstable 1,2-diazete 33 in a good yield.

The authors confirmed the structure of 1,2-diazete 33 through hydrogenation of the double bond to give 1,2-diazetidine 34a (Scheme 4.6). 1,2-Diazete 33 was thermally unstable and over time started to ring open to give imine 36. The authors reported that it was not possible to isolate imine 36 because the compound readily polymerised and attempts to trap 1,2-diazete 33 with electron-rich olefin 18a, electron-deficient tetrazine 313 or cyclopentadiene 297 all gave no reaction.

Thomas Britten – April 2019
4.1.2 Conclusions
In summary, a variety of mild conditions are available for the deprotection of the carbamate protecting groups in bicyclic 1,2-diazetidines 10 and it is possible to access cyclobutadiene 301 through oxidation of diamine 295. The double bond in 10 can either be reduced, or it can undergo a Diels-Alder reaction with a reactive electron deficient diene, but no other transformations on the double bond have been reported.

4.2 Aims
The main objective was to carry out a full investigation on the synthetic potential of bicyclic 1,2-diazetidines 10 (Scheme 4.7). Based on the current literature, there is a significant amount of transformations that have not yet been reported that should give novel scaffolds, which meant that any discoveries would be new intellectual property and enable new areas of chemical space to be accessed. At the outset of these studies, the stability of bicyclic 1,2-diazetidines 10 had not been determined and it was vital to gain an understanding of any potential hazards to ensure that they were safe to handle. Bicyclic 1,2-diazetidines 10 possess an N-N bond that should be reduced with single electron donors (e.g. Na/NH₃ or SmI₂) and a double bond that should undergo “classical” double bond reactions, such as halogenation, hydroboration, epoxidation, etc. For any new reactions, the conditions needed to be developed and optimised or modified from existing literature procedures to enable potential scaffolds to be accessed in the highest yields possible. From the literature focusing on similar bicycles, there is precedent for the conversion of bicyclic lactones 265 into functionalised cyclobutenes through palladium catalysis and the conversion of bicyclic azetidines 314 (through double bond transformations) into functionalised azetidines and other interesting scaffolds.²⁹⁶–³⁰⁴
4.3 Results and Discussion

4.3.1 Thermal Stability of Bicyclic 1,2-Diazetidines

From the knowledge of the thermal rearrangement reactions of 1,2-dihydropyridazine 9 combined with the newly formed strained rings in the bicyclic-1,2-diazetidines 10, the first step was to investigate their thermal stabilities. It should be not possible under thermal conditions for bicyclic-1,2-diazetidines 10 to ring open to give 1,2-dihydropyridazines 9 because thermal 4-π electrocyclic reactions are conrotatory, which would form the highly strained 1,2-dihydropyridazine 315 containing a trans-alkene (Scheme 4.8). Only through a photochemical 4-π electrocyclic reaction, which are disrotatory, would 1,2-dihydropyridazines 9 form.

It was found that bicyclic 1,2-diazetidine 10d was stable when stored at room temperature under ambient conditions, but when heated at temperatures above 60 °C bicyclic 1,2-diazetidines 10 started to undergo a ring expansion reaction to give the rearranged bicycles 316 in good to excellent yields (Scheme 4.9). The N-N linkage to the cyclobutene has been replaced by an N-O linkage and was confirmed by 13C and 2-D NMR spectroscopy. The carbons adjacent to nitrogen in 10 appear as a single peak at 66.7 ppm in the 13C NMR, whereas for the rearranged bicycle 316 there are two peaks with a difference in chemical shift of around 20 ppm (carbon adjacent heteroatom in 316: 79.0 and 55.4 ppm). In addition, when bicyclic 1,2-diazetidines 10 were heated above 100 °C small amounts of another bicycle 317 were formed. The structures of 316 and 317 were confirmed by X-ray crystallography and proved that the N-N linkage to the cyclobutene ring had been replaced with the N-O linkage. In collaboration with AstraZeneca, all three bicycles 10d, 316d, 317d were submitted for differential scanning calorimetry (DSC) analysis to gain a better understanding of their stabilities (see Appendix). The DSC trace of 10d showed an initial endotherm (associated with the sample melting), then a complex non-stop exotherm that was associated with rearrangement reaction to 316d, followed by decomposition of the tert-butyloxycarbonyl (Boc) groups at higher temperatures. Similar DSC traces were obtained for the rearranged bicycles 316d and 317d. In all cases, the analysis showed that none of the bicycles possessed explosive properties and any changes were caused by the rearrangement of the compounds or the loss of Boc groups. These findings are very different to the bicyclic lactone system 265, which has been reported to have flammable and explosive properties at room temperature and when heated.283 The tendency for bicyclic-1,2-diazetidines 10 to thermally rearrange provides an in-built safety measure that prevents the potential formation of cyclobutadiene and an azo compound.
Attempts to drive the conversion of 316d into 317d at high temperatures and prolonged reaction times only resulted in degradation. Instead, inspiration was taken from the acidic conditions required to access enone 218 (from the Diels-Alder reaction with Danishefsky’s diene). It was postulated whether similar conditions could be employed to remove the thermally labile tert-butyl group under milder conditions (Scheme 4.10). Thus, in a one-pot procedure bicycle 10d was heated at reflux for six hours to give a mixture of the bicycle 316d and trace amounts of the bicycle 317d and starting material 10b. The reaction mixture was then stirred with aqueous acid and showed complete conversion to bicycle 317d only, which after work-up and purification gave the product 317d in good yield.

It was noticed above that the trace amount of starting bicycle 10d was also converted to the new bicycle 317d under acidic conditions (Scheme 4.10), which suggested that treatment of the bicycle 10d with an acid could form 317d exclusively and negate the need for the heating step (Table 4.1). The reaction proceeded in moderate yields with a variety of acids (entries 1-8), with 1M aqueous hydrochloric acid and p-toluenesulfonic acid giving the highest yields (entries 1 and 7). In all these cases, several side products were formed and after purification the product 317d was isolated in poor purity in comparison to the previous reaction (Scheme 4.9).
successful reaction with trifluoroacetic acid to form 317d meant that it is not possible remove the protecting groups on bicycle 10d under acidic conditions without inducing rearrangement. The reaction did not go to completion in the presence of a catalytic amount of acid (entry 9) and no sign of 317d was observed when the bicycle 10d was stirred in silica gel for three days (entry 10). Surprisingly, an attempted iodination of the double bond in bicycle 10d only gave bicycle 317d in moderate yield and no sign of the iodinated product (entry 11). Under mild basic conditions, the bicycle 10d seemed to be stable and only starting material was recovered (entry 12). The discovery of bicycle 317d has provided another interesting building block that could be used to access further functionalised cyclobutenes (vide infra).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Time (hours)</th>
<th>Yield 317d (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1M aqueous HCl, 1,4-dioxane:HCl (1:1)</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>0.1M aqueous HCl, MeOH:HCl (1:1)</td>
<td>2</td>
<td>47</td>
</tr>
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<td>2</td>
<td>53</td>
</tr>
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<td>4</td>
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<td>51</td>
</tr>
<tr>
<td>5</td>
<td>0.1M aqueous HCl, MeOH:HCl (8:1)</td>
<td>2</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>Dowex H⁺ resin, MeOH</td>
<td>2</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>p-TsOH (1.1 eq), CH₂Cl₂</td>
<td>0.2</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
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<td>n.i²</td>
</tr>
<tr>
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<td>0.2</td>
<td>38</td>
</tr>
<tr>
<td>12</td>
<td>1,4-dioxane:1M aqueous NaOH (1:1)</td>
<td>7</td>
<td>0</td>
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</table>

Table 4.1 *Not isolated

The major side product from the reaction of bicyclic-1,2-diazetidine 10d with p-toluenesulfonic acid was diene 320, which was obtained in 35% yield (Scheme 4.11). From ¹H NMR analysis, a trans-configuration was determined for the double bond attached to the hydrazine from the coupling constant of the hydrogen attached to the same carbon as the hydrazine fragment (13.6 Hz, H¹ in Scheme 4.10). It was not possible to determine the double bond configuration for the other end of the molecule because the coupling constant did not give a clear indication as to whether the hydrogen was cis or trans (11.7 Hz, H² in Scheme 4.10). A similar product was thought to have formed in the reactions with aqueous hydrochloric acid, though this has not been fully characterised. A tentative mechanism for the formation of diene 320 is described below under the assumption that the rearranged bicycle 316d was formed first (Scheme 4.10). The first pathway begins with an Sn2' reaction in which a molecule of p-toluenesulfonic acid or a tosylate anion attacks the carbon diagonally opposite the C-O bond in rearranged bicycle 316d to give cyclobutene 319, which can undergo a thermal 4-π electrocyclic ring opening
reaction to form the diene (Scheme 4.11, path A). Alternatively, protonation of the oxygen atom attached to the cyclobutene, followed by an S$_{N}1$ cleavage of the C-O bond, to give an allyl cation 318, that could then be trapped by p-toluenesulfonic acid or a tosylate anion (Scheme 4.11, path B). Based on the findings reported by various research groups that heteroatom substituents lower the activation energy of the 4-\(\pi\) electrocyclic ring opening (see Section 1.4),$^{112,115,118,151}$ it was no surprise that cyclobutene 319 could not be isolated and only diene 320 was observed. As the geometry of the diene could not be fully determined and the proposed product may be sensitive to E-Z isomerisation, it is not possible to reach any further conclusions about the mechanism. Attempts grow a crystal for X-ray crystallography resulted in degradation of the diene 320, but if 320 was trapped with a dienophile it should be possible to get a better understanding of the stereochemistry. It cannot be ruled out that the formation of diene 320 could also stem from bicyclic 1,2-diazetidine 10d, through protonation of the nitrogen atom and an S$_{N}2'$ reaction.

![Scheme 4.11](image)

Derivatisation of bicycle 317d was attempted under basic conditions to try and access cyclobutene 321 (Scheme 4.12). Initial experiments with sodium hydroxide in methanol had shown the formation of a new product, but this was not reproducible and only starting material was recovered when repeated. When sodium methoxide was used, 317d was recovered unchanged.

![Scheme 4.12](image)

Attention then turned to the use of a reducing agent to access cyclobutene 322 (Scheme 4.13). Disappointingly, when bicycle 317d was treated with lithium aluminium hydride no reaction took place and only the starting material was observed in the $^1$H NMR spectrum of the crude product.
Attempts to carry out a palladium(0)-catalysed decarboxylation - via a palladium π-allyl intermediate - and subsequent trapping with a nucleophile to give cyclobutene 323 did not show any promise and once again only the starting material was recovered (Scheme 4.14).

Treatment of bicycle 317d with freshly prepared and titrated samarium(II) iodide, which was prepared according to a previously published procedure, resulted in a large loss in material and the isolation of the starting material in 14% yield (Scheme 4.15).

The outcome from these reactions suggested that the bicycle 317d was more stable than first imagined and that more forcing conditions are required. Bicycle 317d was already found to be stable in acid at room temperature (Table 4.1 from above), but it is not known how stable it would be if heat was applied under acidic conditions.

Given the computational results reported by Sheikh, the cis-3,4-disubstituted cyclobutenes described above all contain an oxygen and a nitrogen connected to a cyclobutene ring, which should have a low activation energy for 4-π electrocyclic ring opening (Scheme 4.16). As a result, cyclobutenes 322/323 should not be isolable and immediately form either aldehyde 325 or diene 326 (in the case where an alcohol is attached to the ring). From the torquoselectivity theories developed by Houk and various co-workers, it is not known whether the oxygen or the nitrogen substituent will preferentially favour outward rotation.
Taking inspiration from successful palladium-catalysed π-allyl reactions reported for the bicyclic lactones 265,296–299 some preliminary investigations on the treatment of bicycle 10d with a palladium(0) catalyst have been completed (Table 4.2). The reaction took place at room temperature to give the rearranged bicycle 316d exclusively in good yields (entries 1 and 2). It was hoped that if the reaction went via π-allyl intermediate 327 that an external nucleophile could compete with the ring closing reaction. However, when the reaction was run in methanol no sign of trapping was observed (entry 2).

![Scheme 4.16](image)

Taking inspiration from successful palladium-catalysed π-allyl reactions reported for the bicyclic lactones 265,296–299 some preliminary investigations on the treatment of bicycle 10d with a palladium(0) catalyst have been completed (Table 4.2). The reaction took place at room temperature to give the rearranged bicycle 316d exclusively in good yields (entries 1 and 2). It was hoped that if the reaction went via π-allyl intermediate 327 that an external nucleophile could compete with the ring closing reaction. However, when the reaction was run in methanol no sign of trapping was observed (entry 2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (hours)</th>
<th>Yield 316d (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>29</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>MeOH</td>
<td>2</td>
<td>60</td>
</tr>
</tbody>
</table>

Table 4.2

When bicyclic 1,2-diazetidine 10d was treated with a Lewis acid, an unexpected diamine 330 was formed (Scheme 4.17). This reaction was only observed with zinc chloride and no reaction was observed when magnesium chloride was used. It was not possible to isolate any pure samples of the diamine 330, but full characterisation was nevertheless possible. Diamine 330 was postulated to be a precursor to cyclobutadiene, through oxidation to azo compound 331, followed by elimination of carbon dioxide and nitrogen to give cyclobutadiene. To this end, very preliminary experiments with iodobenzene diacetate and DIAD 8c have shown complete conversion of diamine 330 to a new compound. This new compound was not the bicyclic 1,2-diazetidine 10c or the cyclobutadiene dimer 298, but it did have similar 1H NMR peaks to those
found for bicyclic 1,2-diazetidine 10. Due to the very small scale and time constraints, it was unfortunately not possible to identify this new product.

Scheme 4.17

4.3.2 Synthesis of Functionalised 1,2-Diazetidines

Oxidative cleavage of the double bond in bicyclic 1,2-diazetidine 10d was expected to enable functionalised 1,2-diazetidines scaffolds to be accessed (Table 4.3). Under a variety of oxidative conditions, one major product was isolated that gave no further reaction when reacted with sodium periodate (entries 1-3). The structure was determined through X-ray crystallography and was found to be bicycle 333. The desired diacid 332 could be isolated in good yield with longer reaction times, which ensured that bicycle 332 was converted into the desired product (entry 4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield 332 (%)</th>
<th>Yield 333 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RuO2·xH2O (5 mol%), 10% aqueous NaIO4, EtOAc, rt, 20 mins</td>
<td>0</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>OsO4 (5 mol%), NaIO4 (4.0 eq), 2,6-lutidine (2.0 eq) 1,4-dioxane:H2O (3:1), rt, 24 hrs</td>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>OsO4 (5 mol%), NMO (3.0 eq), acetone:H2O (8:1), rt, 50 hrs</td>
<td>0</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>RuO2·xH2O (5 mol%), 10% aqueous NaIO4, EtOAc, rt, 41 hrs</td>
<td>76</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4.3 NMO: N-methylmorpholine N-oxide

Formation of bicycle 333 was thought to have started with formation of dialdehyde 334, which in the presence of water (from the reaction mixture) resulted in the hydration of one of the aldehydes 335, followed by cyclisation to give bicycle 333 (Scheme 4.18). The bicyclic 1,2-diazetidine 10d was quickly converted into bicycle 333, which then slowly underwent oxidation to diacid 332. It is proposed that this takes place through oxidation of bicycle 333 to an anhydride 336 and ring opening with water or ring opening of bicycle 333 to hydrate 335,
followed by oxidation to diacid 332. An attempted oxidation reaction to convert the bicycle 333 into an anhydride 336 with pyridinium chlorochromate (PCC) showed no signs of the anhydride or diacid 332. Currently, it has not been possible to convert diacid 332 into anhydride 336 through heating or the use of a coupling agent.

Scheme 4.18

Derivatisation of diacid 332 was expected to give an easier to handle product for further reactions. Esterification was chosen as an easy way to access another 1,2-diazetidine scaffold, however it was not known how stable diacid 332 would be when heated and under acidic conditions. Thus, a milder esterification method was chosen: treatment with an excess (trimethylsilyl)diazomethane (a safer alternative to diazomethane) converted diacid 332 into diester 337 in a good yield (Scheme 4.19). It was not possible to carry out a monodeprotection on diester 337 to access 1,2-diazetidine 338, and only diacid 332 was recovered under these conditions.

Scheme 4.19

It was thought that 1,2-diazetidines 332 and 337 would be ideal precursors to the alcohol 339 (Table 4.4). The attempted reduction of diacid 332 led to the formation of complex mixtures (entries 1 and 2), likely caused by competition reactions between the reduction of the acid and the carbamate protecting groups. To try and overcome this issue, lithium borohydride was employed instead of lithium aluminium hydride for the reduction of diester 337 to (entry 3). Under these conditions, a less complicated mixture was formed, and one product could be isolated, though purification was difficult. The $^1$H NMR spectrum of this product was complex, and did not provide comprehensive evidence that alcohol 339 had been formed, however mass spectrometry provided the target mass for the product.
Chapter 4: Reactions of Bicyclic 1,2-Diazetidines

The double bond in bicyclic 1,2-diazetidines 10d was expected to undergo a ring opening cross metathesis sequence in the presence of a suitable alkene (Table 4.5). Styrene 15c was chosen as the alkene for optimisation and both catalysts 75 and 76 were investigated (See Scheme 1.21 for structures of 75 and 76). With both catalysts, preliminary experiments showed that when the reaction was heated at low concentrations the ring-opened 1,2-diazetidine 340 was formed in moderate yield, with some E/Z selectivity (entries 1 and 5). The other products formed in the reaction were polystyrene and some oligomeric derivatives of the 340. From 2-D NMR analysis, it was possible to determine that the major product had a Z-configuration around the disubstituted double bond, in which the phenyl group was cis to the 1,2-diazetidine ring. For both catalysts, the highest yields of the ring-opened 1,2-diazetidine 340 and similar E/Z ratios were achieved when the concentration of the reaction mixture was increased, with the Hoveyda-Grubbs 2nd generation catalyst giving the best yield (entries 2 and 6). In all cases, when the amount of styrene 15c was decreased or the reaction was run at room temperature, similar E/Z ratios and a drop in the yield of the product 340 were observed (entries 3, 4, 7 and 8). Importantly, no reaction took place when no catalyst was present (entry 9).

Table 4.4

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Yield 339 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>LiAlH₄ (3.0 eq), THF, 0 °C → rt, 30 mins</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>BH₃•THF (3.0 eq), THF, 0 °C → rt, 24 hrs</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>LiBH₄ (2.5 eq), THF, 0 °C → rt, 4 hrs</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.5

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Styrene (eq)</th>
<th>Concentration (M)</th>
<th>Temperature (°C)</th>
<th>Time (hrs)</th>
<th>Yield 340a,b (%)</th>
<th>E/Z ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>5.0</td>
<td>0.05</td>
<td>40</td>
<td>1.0</td>
<td>63</td>
<td>1.0:1.6</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>5.0</td>
<td>0.1</td>
<td>40</td>
<td>1.0</td>
<td>66</td>
<td>1.0:1.6</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>3.0</td>
<td>0.1</td>
<td>40</td>
<td>1.0</td>
<td>51</td>
<td>1.0:1.7</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>5.0</td>
<td>0.1</td>
<td>rt</td>
<td>6.0</td>
<td>63</td>
<td>1.0:1.7</td>
</tr>
<tr>
<td>5</td>
<td>76</td>
<td>5.0</td>
<td>0.05</td>
<td>40</td>
<td>1.5</td>
<td>61</td>
<td>1.0:1.5</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
<td>5.0</td>
<td>0.1</td>
<td>40</td>
<td>0.5</td>
<td>73</td>
<td>1.0:1.5</td>
</tr>
<tr>
<td>7</td>
<td>76</td>
<td>3.0</td>
<td>0.1</td>
<td>40</td>
<td>1.0</td>
<td>49</td>
<td>1.0:1.7</td>
</tr>
<tr>
<td>8</td>
<td>76</td>
<td>5.0</td>
<td>0.1</td>
<td>rt</td>
<td>3.0</td>
<td>63</td>
<td>1.0:1.6</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>5.0</td>
<td>0.1</td>
<td>40</td>
<td>1.0</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 4.5 *Calculated from ¹H NMR spectra in d₆-DMSO through comparison of Z-isomer 340a and E-isomer 340b peaks. No internal standard used
With optimisation complete, the alkene was changed from styrene 15c to tert-butyl acrylate 341 and treated with both Grubbs catalysts 75 and 76 (Scheme 4.20). Interestingly, no reaction took place in both cases, and only the starting materials were observed from $^1$H NMR spectroscopic analysis of the crude product.

![Scheme 4.20](image

Aziridination, cyclopropanation or epoxidation of the double bond in bicyclic 1,2-diazetidine 10d was predicted to enable access to tricycles 343 (Table 4.6). However, disappointingly, it was not possible to form any of the desired tricycles 343 under typical reaction conditions for each reaction (entries 1-3). The starting material was recovered unchanged from the aziridination and epoxidation reactions, and when the aziridination reaction was heated at reflux, it was no surprise that only the rearranged bicycle 316d was observed in the $^1$H NMR of the crude product. On the other hand, the cyclopropanation reaction gave complete conversion of the starting material to give a product that was not tricycle 343.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>X</th>
<th>Yield 343 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe$_3$NBr$_3$ (0.1 eq), TsNCINa, 3H$_2$O (1.2 eq), MeCN, rt or 40 $^\circ$C, 24 hrs</td>
<td>NTs</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Bu$_4$NCl (10 mol%), aq. NaOH (50% w/v), CHCl$_3$, rt, 6 hrs</td>
<td>CCl$_2$</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>m-CPBA (1.2 eq), CH$_2$Cl$_2$, rt or 40 $^\circ$C, 24 hrs</td>
<td>O</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4.6

The major product from the cyclopropanation reaction contained no chlorine atoms (from mass spectrometry analysis) and relatively simple $^1$H and $^{13}$C NMR spectra, which suggested the presence of a symmetrical diene. From this information it has been tentatively suggested the product formed is diazepine 344, which is derived from insertion of dichlorocarbene into the N-N bond (Scheme 4.21). A recent publication from Shipman and co-workers showed that dichlorocarbene can insert into the N-N bond and is hydrolysed under the reaction conditions to give a urea.$^9$ The insertion of dichlorocarbene into the N-N bond in bicycle 1,2-diazetidine 10d would form bicycle 345, which could be hydrolysed to urea 345. A thermal 4-$\pi$ electrocyclic
ring opening would give a highly strained diene 347 that could undergo $E/Z$ isomerisation to give diazepine 344.

The hydroboration of 10d was also attempted, which was expected to form alcohol 348 (Scheme 4.22). Reactions with a borane tetrahydrofuran complex and 9-borabicyclo[3.3.1]nonane (9-BBN) gave a complex mixture in both cases and this reaction was not pursued any further due to time constraints.

The final reaction attempted on the double bond of bicyclic 1,2-diazetidine 10d was a Paternò–Büchi reaction with acetone, to try and form tricycle 349 (Scheme 4.23). Complete degradation of the starting material was observed with no identifiable products, a similar result to that seen for the 4-π photocyclisation of 1,2-dihydropyridazine 9b in acetone at 300 nm (Table 3.3, Section 3.3.2).
4.3.3 Synthesis of Functionalised Cyclobutenes

The efficient cleavage of the N-N bond in bicycle 10d would enable access to cis-diaminocyclobutenes 351, which were expected to undergo a spontaneous electrocyclic ring opening to give functionalised dienes (Scheme 4.24).

Samarium(II) iodide was freshly prepared, titrated and used according to a literature procedure. Under these conditions, cyclobutene 351 was not isolated, but two other compounds were formed and it was only possible to isolate one of the two compounds in meaningful quantities. $^{13}$C NMR analysis of this new compound suggested that cyclobutene was no longer present, due to the appearance of two new peaks at 122.3 and 100.2 ppm and no peak around 140 ppm as seen for bicyclic 1,2-diazetidine 10d. Cyclobutene 351 should readily undergo a 4-π electrocyclic ring opening to form $E/Z$-diene 352, given the small calculated energy barrier for the ring-opening of cis-3,4-diaminocyclobutenes reported by Sheikh. The structure was proven by X-ray crystallography to be $Z/Z$-diene 350 (see appendix), which was formed in 24% yield and not the expected $E/Z$-diene 352. The other compound formed in the reaction could not be isolated in meaningful quantities and it became less prominent in the crude samples over time. Mass spectrometry analysis has suggested it could be $E/Z$-diene 352, because it has the same molecular weight as $Z/Z$-diene 350. The formation of 350 was tentatively proposed to have started from the 4-π electrocyclic ring opening of cyclobutene 351 to form $E/Z$-diene 352, an enamine, which could undergo $E/Z$ isomerisation to give the observed $Z/Z$-diene 350, though it is not fully understood why this configuration would be favoured. It was difficult to separate the crude products from the large amount of inorganic salts that formed when the reaction mixture was exposed to air. Attempts to separate the mixture of products from the inorganic material by aqueous workup resulted in a loss of material into the aqueous phase and a significant amount of inorganic salts remained in the organic layer. The most straightforward method of purification was to solid load the crude product onto silica gel and purify by column chromatography, however this still resulted in loss of material. Another suggestion for the poor yield could be the presence of any Lewis acidic samarium salts that would lead to the loss of the Boc protecting groups and subsequent degradation of any of the products from this reaction.
There have been a variety of other methods described for the cleavage of N-N bonds published in the literature\textsuperscript{90,104} however when these conditions were applied to bicyclic 1,2-diazetidine 10d, an unexpected result was observed (Table 4.7). Instead of N-N bond cleavage the C-N bond was broken to form cyclobutene 353, which then underwent a thermal 4-π electrocyclic reaction to give diene 354 when heated or even stored at room temperature. Heat and prolonged storage at room temperature seemed to influence the ratio in which cyclobutene 353 and diene 354 were formed. Lithium 4,4'-di-tert-butylbiphenyl (LiDBB) was freshly prepared according to a previously published procedure.\textsuperscript{306} Using LiDBB, a complex mixture was formed, but a mixture of cyclobutene 353 and diene 354 was isolated in moderate yield (entry 1). The use of dissolving metal conditions (specifically, sodium in ammonia), formed 353 and 354 in excellent yield, with cyclobutene 353 as the major product (entry 2). At the end of the reaction, only the cyclobutene 353 was present in the reaction mixture and there is potential to further react the double bond before isolation to access functionalised cyclobutenes. Due to the bicycle’s instability under acid conditions, zinc powder in acetic acid could not be used for the reduction of the N-N bond, though the combination of zinc powder and ammonium salts has been used to reduce azo compounds to the corresponding amines (via the hydrazine).\textsuperscript{307} When bicyclic 1,2-diazetidine 10d was reacted with an excess of zinc powder in the presence of either ammonium acetate or ammonium chloride, a mixture of cyclobutene 353 and diene 354 was formed in good yield (entry 3 and 4). The reaction times were longer for these reactions and this probably influenced the amount of diene 354 formed.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield 353 and 354 (%)</th>
<th>Ratio 353:354&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiDBB (2.5 eq), THF, −78 °C, 10 mins</td>
<td>35</td>
<td>n.d</td>
</tr>
<tr>
<td>2</td>
<td>Na/NH\textsubscript{3}, THF, −78 °C → rt</td>
<td>87</td>
<td>2.4:1.0</td>
</tr>
<tr>
<td>3</td>
<td>Zn (10 eq), NH\textsubscript{4}OAc (1.1 eq), MeOH, rt, 22 hrs</td>
<td>69</td>
<td>1.3:1.0</td>
</tr>
<tr>
<td>4</td>
<td>Zn (10 eq), NH\textsubscript{4}Cl (1.1 eq), MeOH, rt, 22 hrs</td>
<td>79</td>
<td>1.0:1.4</td>
</tr>
</tbody>
</table>

Table 4.7<sup>a</sup> Calculated by \textsuperscript{1}H NMR in d\textsubscript{6}-DMSO through comparison of cyclobutene 353 and diene 354 peaks. No internal standard used

The formation of cyclobutene 353 is thought to have stemmed from the addition of an electron to the double bond in bicyclic 1,2-diazetidine 10d to give radical anion 355, which can be protonated (Scheme 4.25). The addition of another electron followed by protonation and tautomerization forms cyclobutene 353. It is tentatively proposed that the difference in selectivity between samarium iodide (N-N bond cleavage) and other single electron donors (C-N bond cleavage) can be described by samarium iodide being a “hard” electron donor, thus favouring attack of the nitrogen atom, whereas the other single electron donors are soft and favour addition at the double bond. Currently, it is not known what the active form of zinc is in this reduction, but potentially zinc is able to act as a single electron donor, which enables it to react
as observed with other single electron donors (e.g. sodium in ammonia). In addition, it is not known why samarium(II) iodide cleaved the N-N bond and other electron donors cleaved the C-N bond of bicyclic 1,2-diazetidines 10.

Variable temperature $^1$H NMR studies have shown the temperature sensitivity of cyclobutene 353 (Figure 4.2). When a 1.0:1.8 mixture of cyclobutene 353 and diene 354 was gradually heated from 298-348 K (25-75 °C), the intensity of the peaks for cyclobutene 353 started to decrease and the intensity of the peaks for diene 354 started to increase at temperatures above 308 K (35 °C). At 338 K (65 °C) only trace amounts of cyclobutene 353 was present, whilst when the temperature reached 348 K (75 °C) only diene 354 was observed.

Another potential method for cleaving the N-N bond was through hydrogenation, although the double bond would also be reduced in the process. It had been reported previously that it was not possible to cleave the N-N bond in 1,2-diazetidines for tert-butyl carbamate systems, but it was successful for the benzyl carbamate systems. To this end, hydrogenation was attempted on both these bicycles 10d,e (Scheme 4.26). As expected, no N-N bond cleavage was observed for bicycle 10d and the saturated bicycle 308d was isolated in very poor yields. The major product was the diazine 356, which was not expected to form, and was proposed to have formed from via reduction to form saturated bicycle 308d, followed by the addition of hydrogen across the C-C bond. $^1$H NMR analysis of the crude reaction mixture gave clear evidence for 356 due to the characteristic broad peaks seen for similar compounds. With shorter reaction times, it may be possible to isolate bicycle 308d in higher yields. The hydrogenation of the dibenzyl carbamate bicycle 10e furnished a complex mixture and no sign of the expected 1,2-diamino-cyclobutane.
Figure 4.2 Variable Temperature $^1$H NMR in d$_6$-DMSO of cyclobutene 353 and diene 354
Preliminary experiments on the use of diene 354 in Diels-Alder reactions have given some promising results (Scheme 4.27). The reaction of diene 354 and dimethyl acetylenedicarboxylate 223 gave cycloadduct 357 in good yield with no sign of the aromatised product. It was difficult to characterise cycloadduct 357 due to complex NMR spectra and even VT-NMR was of limited use due to signs of degradation of 357 upon heating. At temperatures above 75 °C, cycloadduct 357 started to form dimethyl benzene-1,2-dicarboxylate 358 and hydrazine 43d (Figure 4.3). Complete conversion of cycloadduct 357 to the degradation products 358 and 43d was observed by $^1$H NMR when heated at 130 °C for 4 hours.

Scheme 4.27
Figure 4.3: $^1$H NMR of cycloadduct 357 after heating at 130°C

$^1$H NMR in $d_6$-DMSO
4.4 Conclusions

In summary, bicyclic 1,2-diazetidine 10 has been successfully converted into a variety of different building blocks, which in some cases were unexpected. Initially, it had been hoped to convert bicyclic 1,2-diazetidines 10 into functionalised 1,2-diazetidines and cyclobutenes, however these results have shown that it is not possible to efficiently make cyclobutenes due to facile 4-π electrocyclic ring opening. Nevertheless, bicyclic 1,2-diazetidines 10 are a great way to access monocyclic functionalised 1,2-diazetidines (a conceptually new approach). A series of novel 1,2-diazetidine scaffolds equipped with acid, ester and alkene synthetic handles has been synthesised in good yields and further work needs to be completed on the use of these building blocks to access other new compounds. In addition, bicyclic 1,2-diazetidines 10 were found to readily undergo rearrangement reactions to form ring-expanded bicycles (316 and 317) under a variety of conditions (thermal, palladium-catalysed or acidic conditions), which was not anticipated at the outset of this work. It is thought that the tendency for 10 to rearrange complicated some double bond transformations (halogenation and hydroboration), whilst the double bond seemed remarkably unreactive towards other classical reactions (epoxidation, aziridination and cyclopropanation).

It should be noted that even though formation of cyclobutenes has proven difficult, it has been possible to access some interesting new diene moieties. Attempted N-N cleavage of bicyclic 1,2-diazetidines has given some surprising results, with samarium(II) iodide giving the desired reduction of the N-N bond and other single electron donors giving cleavage of the C-N bond. In all cases, ring opening of the cyclobutene ring took place to give N-functionalised dienes, albeit in differing quantities. The isolable product from the samarium(II) reaction was proven to be Z/Z-diene 350, which had the opposite configuration to that of the expected E/Z-diene 352 from the ring opening of cis-diamino cyclobutene 351. Cyclobutene 351 was not observed and the other product from the reaction needs to be isolated and characterised, but it is likely that this should be the expected E/Z-diene product 352 from the ring opening of cyclobutene 351. The yields of the diene(s) for the samarium(II) reaction were low, but this may have been caused by combination of purification issues caused by the presence of large quantities of inorganic material and potential degradation of any products formed by Lewis acidic inorganic salts. The cyclobutene product 353 from C-N cleavage was stable at low temperatures and showed no sign of diene 354 formation, however when cyclobutene 353 was heated or stored at room temperature for prolonged periods of time the amount of diene 354 present started to increase. It is hoped that through immediate functionalisation of the double bond, cyclobutene 353 could be converted into a cyclobutane derivative to prevent ring opening to the diene 354 happening (e.g. cyclopropanation or epoxidation). Nonetheless, diene 354 is useful compound, which can be formed at higher temperatures and has been shown to undergo a Diels-Alder reaction to give an interesting cycloadduct 357. Finally, bicyclic 1,2-diazetidine 10 and the rearrangements products 316 and 317 all showed high levels of stability and could be handled without the need for significant safety precautions.
Chapter 5: Conclusions and Future Work
5.1 Conclusions

The project set out to develop a scalable and efficient methodology for the 4-π photocyclisation of 1,2-dihydropyridazines 9 to access bicyclic 1,2-diazetidines 10, in which a variety of functionalised 1,2-diazetidines and cyclobutenes could be accessed.

5.1.1 Synthesis and Reactions of 1,2-Dihydropyridazines

The synthesis of 1,2-dihydropyridazines 9 proved to be non-trivial, and attempts to repeat or modify existing literature procedures (allylic bromination-elimination, bromination-elimination or allylic oxidation reactions of tetrahydropyridazines 154 and the reaction of azo compounds with pyrones 175) were unsuccessful. More specifically, the replacement of carbon tetrachloride in the allylic bromination reactions did not work well, and resulted in poor conversions of tetrahydropyridazines, low yields of 1,2-dihydropyridazines 9 (after the elimination step) and the formation of complex mixtures. As a result, a novel synthesis of 1,2-dihydropyridazines 9 was developed and executed on multigram scales through a two-step Diels-Alder and palladium-catalysed elimination reaction sequence in high yields (8 examples, up to 90%) starting from acetoxy-diene 202a and either the commercially available or in situ formed azo compounds 8.

The palladium-catalysed elimination reaction was completed using low catalyst loadings (1 mol%) of a palladium(0) precursor, which lowered the financial and environmental impacts of the process. It should be noted that the attempted synthesis of a methyl substituted-1,2-dihydropyridazines through the current palladium reaction exclusively formed an exocyclic double bond (216) and therefore, this method may not be suitable for the synthesis of substituted 1,2-dihydropyridazines. Instead, it is hoped that the use of enone 218 (derived from a Diels-Alder reaction between an azo compound and Danishefsky’s diene) could enable the synthesis of a range of substituted 1,2-dihydropyridazines (vide infra).

Attempts to validate 1,2-dihydropyridazines 9 as useful synthetic intermediates has proven more difficult that was initially expected. To this end, 1,2-dihydropyridazines undergo cyclopropanation reactions to form a tricycle 241 in which two cyclopropane rings were installed trans to one another. Treatment of 1,2-dihydropyridazines 9 under typical dihydroxylation (with osmium tetroxide) or epoxidation conditions (m-CPBA) has given unexpected diol products (238, 242 and 243), however these results have provided evidence that the lone pair of electrons on the nitrogen atoms can be involved in reactions and influence the products that are formed. Therefore, there is a high possibility that the involvement of the nitrogen lone pair of electrons can lead to degradation pathways and the formation of complex mixtures (as seen with hydroboration, halogenation and halohydrination reactions). The characterisation of 1,2-dihydropyridazines 9 and related products by NMR spectroscopy was not trivial, due to the slow interconversion (on the NMR timescale) of two main conformations, therefore it was crucial to utilise VT-NMR and obtain X-ray crystal structures. 1,2-Dihydropyridazines 9 have also been shown to undergo a thermal rearrangement reaction to give 2-aminopyrroles 210 in low-excellent yields (28-90%), though these pyrroles are relatively unstable, and must either be used immediately or stored under inert atmosphere in the freezer. The formation of 2-
aminopyrroles 210 is tentatively proposed to go via an initial 6-π electrocyclic ring opening of 1,2-dihydropyridazines 9, followed by a stepwise mechanism. Investigation into the use of 1,2-dihydropyridazines 9 in Diels-Alder reactions were unsuccessful, but resulted in the discovery that 2-aminopyrroles undergo Diels-Alder reactions with alkynes and benzyne derivatives to give a series of para-substituted phenylenediamine derivatives.

1,2-Dihydropyridazines 9 and related compounds (21 compounds) have been analysed using the lead-likeeness and molecular analysis (LLAMA) software developed by Marsden, Nelson and co-workers (Figure 5.1).27 All of the compounds fell within Lipinski’s “rule of five”, however systems that contained larger protecting groups (Boc or carboxybenzyl) or multiple aromatic rings were often more lipophilic (larger logP value) and did not fall within the smaller lead-like space guidelines outlined by the software (Figure 1.3). A couple of 1,2-dihydropyridazines 9a,c were borderline lead-like (systems with methyl or isopropyl carbamate groups), whereas three other 1,2-dihydropyrdazines 9b,f,h and the diols (from dihydroxylation and epoxidations reactions) fell nicely within lead-like space. Shape analysis of these compounds put a large proportion as either flat or in-between flat and rod-like. However, it is highly likely that the software did not factor in the twisted conformation of 1,2-dihydropyridazines 9, thus making it seem as if they resemble more disc-like structures. Interestingly, diol 238 (from the treatment of 1,2-dihydropyridazines 9c with m-CPBA) and pyrrole 235 (from the reaction of 2-aminopyrrole 210c with azo compound 8d) were judged to be the most spherical in this analysis.
5.1.2 Synthesis and Reactions of Bicyclic 1,2-Diazetidines

The key 4-π photocyclisation step was investigated using commercially available batch (Rayonet-RPR-100) and flow photoreactors (Vapourtec E-series flow system with UV-150 photoreactor). In the batch photoreactor, irradiation of 1,2-dihydropyridazines 9 near the absorption maximum, $\lambda_{\text{max}}$ (300 nm) formed bicyclic 1,2-diazetidines 10 in moderate yields (42-56%), however significant quantities of 2-aminopyrrole 210 were also formed (9-30%). Irradiation of 1,2-dihydropyridazines 9 at shorter wavelengths or in the presence of a photosensitiser (at 419 nm) resulted in low yields or significant degradation. Irradiation at 350 nm (near the longer wavelength edge of the 1,2-dihydropyridazine absorption peak) has resulted in a significantly improved yield of and selectivity for bicyclic 1,2-diazetidines 10 (seven examples, up to 83% yield). The selectivity increase is thought to have stemmed from the selective irradiation of a weak n-π* band amongst the larger π-π* band, which led to the greater preference for the 4-π photocyclisation pathway over the 6-π electrocyclic ring opening.

Currently, attempts to prove the presence of a weaker n-π* band through UV-Vis studies have not provided conclusive evidence. The 4-π photocyclisation was successfully scaled-up for one example starting from nearly nine grams of 1,2-dihydropyridazine 9 and gave only a marginal decrease in yield (72%) in comparison to small scale reactions. Investigation of the 4-π photocyclisation using the flow photoreactor has not provided the scale-up solutions that were anticipated. Significant degradation of both starting materials and products was observed, likely caused by the chosen filter letting through light below 300 nm. Attempts to use a filter with a narrower wavelength band (310-390 nm) still gave degradation and poor conversions of 1,2-dihydropyridazines 9 (4-48%), whilst the use of a 365 nm LED light source gave even poorer conversions (1-7%). At present, there is no commercially available 350 nm lamp for the Vapourtec flow system, therefore it was not possible to directly compare between the batch and flow photoreactors.

At the outset of the project, the aim was to convert bicyclic 1,2-diazetidines 10 into functionalised 1,2-diazetidines and cyclobutenes, however in the process some other interesting scaffolds have been accessed. To this end, bicyclic 1,2-diazetidines 10 have been successfully converted into monocyclic functionalised 1,2-diazetidines in good yields (up to 85%), which have functional handles such as acid, ester or alkene groups (through oxidative cleavage with ruthenium tetroxide or metathesis sequences). In addition, bicyclic 1,2-diazetidines 10 readily underwent rearrangement reactions under thermal, acidic or palladium-catalysed conditions to give two new bicycles in moderate to good yields (up to 92%), in which the N-N junction to the cyclobutene has been replaced with an N-O linkage. Degraded bicycle 317d turned out to be a lot more stable than was first expected, and did not react under basic, reductive conditions or in the presence of a palladium(0) catalyst. The rearrangement reactions of bicyclic 1,2-diazetidines 10 were an issue with some double bond transformations (halogenation), whereas the double bond was surprisingly inert under typical cyclopropanation, epoxidation or aziridination conditions. In the case of dichlorocarbene, insertion of dichlorocarbene into the N-N bond was exclusively observed instead of cyclopropanation. Bicyclic 1,2-diazetidines 10 are
good precursors to access \( N \)-functionalised dienes, but not cyclobutenes, due to the tendency to undergo a 4-\( \pi \) electrocyclic ring opening once the bicyclic array has been disrupted. Attempts to cleave the N-N bond with samarium iodide were successful, however the cyclobutene was not observed and only \( Z/Z \)-dienen 350 was isolated in low yields (24%), presumably from 4-\( \pi \) electrocyclic ring opening to give \( E/Z \)-dienen 352, followed by \( E/Z \) isomerisation. In contrast, other single electron donors unexpectedly gave cleavage of the C-N bond to give a hydrazine-cyclobutene 353 that could be isolated as a mixture with \( E \)-dienen 354 in good yields.

The bicyclic 1,2-diazetidines 10 and the products formed from the subsequent transformation reactions (20 compounds) have also been analysed using the LLAMA software (Figure 5.2). All apart from five scaffolds fell within lead-like space, which were either small, polar molecules (bicyclic 1,2-diazetidine with methyl carbamate groups and rearranged bicycle with no protecting groups) or larger lipophilic molecules (diester 337, 1,5-diene 340, cycloadduct 357). Disappointingly, the scaffolds were mostly situated closest to the disc (flat) area of the graph. The crystal structure of bicyclic 1,2-diazetidines suggests that they have a more 3-D shape, therefore it is not known whether the software has taken into account an accurate representation of the structure. Nevertheless, this data (in combination with Figure 1) gives a good idea of the properties of the synthesised compounds and can help to guide future endeavours.

Figure 5.2 Like-likeness (top left) and shape analysis (top right) of bicyclic 1,2-diazetidines and products from derivatisation reactions
5.2 Future Work

The investigation of the $4\pi$ photocyclisation of substituted 1,2-dihydropyridazines 359 is crucial in order to determine whether the improved yields of and selectivity for bicyclic 1,2-diazetidines is still observed (Figure 5.3). A variety of different substituents (electron donating, withdrawing, neutral, aromatic) need to be studied to build up a solid understanding of what effect each functional group has. Furthermore, it needs to be investigated whether the preference for $4\pi$ photocyclisation pathway can be applied to the substituted 1,2-dihydropyridazines that favoured the $6\pi$ electrocyclic ring opening pathway, through irradiation at a wavelength situated on the longer wavelength edge of the absorption peak of 1,2-dihydropyridazines (compounds in Figure 5.3).

Figure 5.3

Starting from enone 218, it should be possible to access a variety of substituted 1,2-dihydropyridazines (Scheme 5.1). Firstly, deprotonation of the acidic hydrogen in the $\alpha$-position and trapping of the enolate with an electrophile would provide access to O-substituted 1,2-dihydropyridazines 360. A similar strategy has been successful on a similar enone to 170 for the installation of a silyl group using triethylamine and tert-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf). Formation of a triflate would provide a handle for palladium-catalysed cross coupling reactions to install a variety of aromatic, heteroaromatic, alkene or alkyne groups. Under basic conditions and in the presence of a suitable electrophile, it should be possible to form a new C-C bond through addition of the electrophile to the carbon in-between the ketone and the nitrogen to form 361. Enone 218 should also react with Grignard reagents to form tertiary alcohol 362, which could then be dehydrated to form substituted 1,2-dihydropyridazines 359. Careful choice of Grignard reagent is essential to prevent competition between endo- and exocyclic double bond formation (e.g. if $R = \text{Me or Et}$). Formation of bromide
363 could be used in either of three reactions described above and provide another handle for palladium cross coupling reactions. Bovonsombat and co-workers have utilised N-bromosuccinimide and pyridine-N-oxide for the α-bromination of enones.\(^{310}\)

![Diagram](image)

**Scheme 5.1**

The successful synthesis of substituted 1,2-dihydropyridazines would make them suitable precursors to pyridazines with novel substitution patterns (Scheme 5.2). In addition, the diols 238 and 243 (from the reactions of 1,2-dihydropyridazines under dihydroxylation and epoxidation conditions) could also be used to access pyridazines bearing two alcohol groups.

![Diagram](image)

**Scheme 5.2**

With regards to the bicyclic 1,2-diazetidine transformation reactions, a simple next step would be to repeat the oxidative cleavage (to make diacid 332f,g) and ring opening cross metathesis (to make diene 364) on the orthogonally protected bicyclic 1,2-diazetidines 10f,g (Scheme 5.3). If successful, this would provide unsymmetrical fragments that could be selectively deprotected to give further building blocks. Moreover, the samarium iodide N-N cleavage of 10d needs to be repeated to isolate and characterise the second product. Also, it would be useful to repeat the samarium iodide N-N reduction reaction on a different substrate (without Boc groups) to determine whether any degradation is occurring from Lewis acidic by-products from the reaction.

![Diagram](image)

**Scheme 5.3**
If diacid 332 can be converted into anhydride 336, a wide range of novel 1,2-diazetidines fragments could be accessed (Scheme 5.4). Baran and co-workers have reported the synthesis of anhydrides under anhydrous conditions using trifluoroacetic anhydride (TFAA). Thus, treatment with methanol, an amine or organometallic reagents would form unsymmetrical 1,2-diazetidines (338, 365 and 366), which possess functional handles for further derivatisation. It should also be possible to carry out an esterification or reduction to access 1,2-diazetidines bearing ester and alcohol functional groups (337 and 339).

The treatment of bicyclic 1,2-diazetidines 10d with $p$-toluenesulfonic acid resulted in the formation of an unexpected diene product 320 in small quantities (Section 4.3, Scheme 4.10). Currently, it is not known whether bicyclic 1,2-diazetidines 10d or rearranged bicycles 316d are the precursor to diene 320 and it is hoped that through optimisation the selectivity for 320 could be improved. Inspired by the formation of this diene, treatment of rearranged bicycle 316d with hard and soft nucleophiles is essential to see which electrophilic site is attacked: the imine or the double bond (Scheme 5.5). If the use of a soft nucleophile results in the preferential attack at the double bond, it should enable the formation of hydrazine substituted cyclobutenes (and dienes) and allow the effect that different groups would have on the stability of the hydrazine cyclobutenes to be studied ($R =$ alkyl, aryl, vinyl or ethynyl).
Finally, the use bicyclic 1,2-diazetidines as precursors to cyclobutadiene needs to be fully investigated (Scheme 5.6). Literature examples have shown that it is possible to deprotect bicyclic 1,2-diazetidines 10a,b under mild basic conditions, followed by subsequent oxidation to form an azo compound that undergoes a retro-Diels Alder reaction to form cyclobutadiene 301.\textsuperscript{162,294} It would provide a powerful new route to form cyclobutadiene, which could be used to access other bicyclic systems 369 through trapping with dienophiles such as imines, nitroso or isocyanates. As a result, this would enable the synthesis of a wide variety of functionalised four membered rings.
Chapter 6: Experimental
6.1 General Information

Reagents were purchased in the highest purity available from Acros Organics, Alfa Aesar, Fluorochem, Sigma Aldrich and TCI. Anhydrous solvents used in reactions were purchased from Acros Organics equipped with AcroSeal™ and all other solvents used were of reagent grade. Triphenylphosphine was recrystallized from hexane prior to use. Brine refers to a saturated aqueous solution of sodium chloride, and water is distilled water. Reaction vessels were oven dried and cooled under an argon atmosphere prior to use and experiments were performed under argon gas. Palladium reactions were performed in Biotage 5 or 20 mL microwave vials and sealed with a cap. Reactions were monitored by thin-layer chromatography (TLC) and/or 1H NMR spectroscopic analysis. Photochemical reactions were performed using a Rayonet RPR-100 Photochemical batch reactor or a Vapourtec E-series flow system equipped with the UV-150 photochemical reactor. Analytical TLC was carried out using Merck pre-coated aluminum-backed TLC silica gel plates (silica gel 60 F_{254}) and the plates were visualised by UV light (254 nm) and by staining with either potassium permanganate or aqueous acidic ammonium molybdate(IV). Normal phase flash column chromatography on silica gel was carried out using silica gel from VWR (40-63 microns).

1H NMR spectroscopic data were obtained on either 300 or 400 MHz instruments and 13C{1H} NMR data were obtained at 100 MHz (Bruker Ultrashield 400 Plus) at 298 K unless otherwise specified. The chemical shifts are reported in parts per million (δ) relative to residual CHCl₃ (δ₇ = 7.26 ppm) and CDCl₃ (δC = 77.16 ppm, central line), residual d₅-DMSO (δH = 2.50ppm) and d₆-DMSO (δC = 39.52 ppm, central line). The assignment of the signals in the 1H and 13C NMR spectra was achieved through 2D-NMR techniques: COSY, HSQC and HMBC. Coupling constants (J) are quoted in Hertz. Infrared spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer. Melting points were performed on a Sanyo Gallenkamp capillary melting point apparatus and are uncorrected. High resolution mass spectrometry data were recorded using electron spray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on a Shimadzu LCMS-IT-TOF mass spectrometer. UV-Vis spectra were recorded using an Agilent Cary 60 UV-Vis spec spectrophotometer. For X-ray crystallography a suitable crystal was selected and mounted on a Mitegen loop using Paratone-N oil on a SuperNova, Dual, Cu at zero, AtlasS2 diffractometer. The crystal was kept at 100.2(5) K during data collection. Using Olex2, the structure was solved with the ShelXT structure solution program using direct methods and refined with the ShelXL refinement package using least squares minimisation. Figures and tables were prepared using Olex2 software.

Bicycles 10d, 316d and 317d were analysed by AstraZeneca (Macclesfield, UK) for thermal stability analysis using a Mettler differential scanning calorimeter (DSC). The sample crucible together with a reference crucible was heated to 500°C at 5K /minute. Any heat generation (exotherm) or heat absorption (endotherm) was observed as a deviation from the baseline. Any exothermic event(s) that exceeded 800 J/g indicated potential explosive properties.
6.2 General Procedures

General Procedure A: Synthesis of 1,2,3,6-tetrahydropyridazines from azo compounds and butadiene

A 15% (w/v) solution of butadiene in hexane (1.0-3.0 eq) was added in one portion to a stirred solution of the desired azo compound (1.0 eq) in CH$_2$Cl$_2$ (0.2-0.6 M) in a sealed flask at room temperature. The resulting mixture was stirred either at room temperature or 40 °C for a specific length of time depending on the azo compound, then evaporated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography using an appropriate solvent system, as described for each individual procedure.

General procedure B: Synthesis of O-substituted dienes at low temperature

Crotonaldehyde (1.0 eq) was added dropwise to a stirred solution of potassium tert-butoxide (1.1 eq) in THF (1.2-1.3 M) at −78 °C under argon and stirred for 10 minutes. Acid chloride (1.1 eq) was added dropwise over 10 minutes and stirred at −78 °C for 30 minutes. The reaction was quenched with a saturated aqueous solution of NaHCO$_3$ (25 mL) and extracted with Et$_2$O (4 x 30 mL). The combined organic layers were washed with a saturated aqueous solution of NaHCO$_3$ (3 x 50 mL), brine (3 x 10 mL), dried (MgSO$_4$) and evaporated under reduced pressure to give the crude product. The crude product was purified by vacuum distillation.

General Procedure C: Diels-Alder reaction of azo compounds with O-substituted dienes

The desired O-substituted diene (1.2-1.6 eq) was added in one portion to a stirred solution of the desired azo compound in methyl tert-butyl ether (1-3 M) at room temperature under argon. The resulting mixture was stirred either at room temperature or heated at reflux for a specific length of time depending on the azo compound, then evaporated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography using an appropriate solvent system or by vacuum distillation, as described for each individual procedure.
Chapter 6: Experimental

General procedure D: Synthesis of hydrazine-1,2-dicarboxylates from carbazates

Pyridine (3.0-6.0 eq) was added dropwise to a stirred solution of carbazate (1.0 eq) and the desired chloroformate (1.1-1.2 eq) in THF or 2-MeTHF (0.1-1M) at 0 °C under argon. The resulting suspension was stirred at 0 °C for 15 minutes and then at room temperature for 1.5 hours. A 10% (v/v) aqueous solution of HCl (10 mL) was added and the mixture was extracted with CH₂Cl₂ (5 x 20 mL). The combined organic layers were washed with brine (10 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. If purification was required, the crude product was purified by flash column chromatography using an appropriate solvent system, as described for each individual procedure.

General Procedure E: Preparation of Fétizon’s reagent [AgCO₃/Celite]

Celite (5.00 g) was washed with MeOH (50 mL), containing 10% concentrated HCl, water (100 mL) and dried under vacuum. Celite (1.50 g) was added to a stirred solution of AgNO₃ (1.70 g, 10 mmol, 1.0 eq), in water (10 mL) at room temperature. A solution of sodium carbonate (0.57 g, 5.38 mmol, 0.5 eq) in water (5.5 mL) was added dropwise, then stirred for 25 minutes. The suspension was filtered and dried under vacuum to give Fétizon’s reagent [AgCO₃/Celite] (2.82 g, the amount of Ag₂CO₃ per mass of Ag₂CO₃/Celite was not calculated, reported as 1 mmol per 0.57 g).

General procedure F: Synthesis of 1,2-dihydropyridazines starting from commercially available azo compounds

1-Acetoxyl-1,3-butadiene (1.5 eq) was added in one portion to a solution of the azo compound (1.0 eq) in CH₂Cl₂ (2.5-5 M) and stirred at either room temperature or 40 °C for a specific length of time depending on the azo compound. The reaction mixture was evaporated under reduced pressure and the crude product was passed through a short silica gel column using an appropriate solvent system, as described for each individual procedure, to give the cycloadducts that contained minor impurities. The cycloadducts were dried in a desiccator, dissolved in 1,4-dioxane (0.5 M) and added to an oven-dried vial under argon that contained Pd(OAc)₂ (1.0 mol%), PPh₃ (4.0 mol%) and triethylamine (2.0 eq) The vial was sealed, then heated at reflux for 1 hour. The reaction mixture was cooled to room temperature and evaporated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography using an appropriate solvent system, as described for each individual procedure.
4-π Photocyclisation: A New Route to Functionalised Four-Membered Rings

**General procedure G: Synthesis of 1,2-dihydropyridazines starting from hydrazine-1,2-dicarboxylates**

![Chemical structure](image)

1-Acetoxy-1,3-butadiene (1.5 eq) was added in one portion to a suspension of hydrazine-1,2-dicarboxylates (1.0 eq) and iodobenzene diacetate (1.0 eq) in CH$_2$Cl$_2$ (0.6, 1.0 or 2.5 M) and stirred at either room temperature or 40 °C for a specific length of time depending on the azo compound. The reaction mixture was evaporated under reduced pressure and the crude product was passed through a short silica gel column using an appropriate solvent system, as described for each individual procedure, to give the cycloadducts that contained minor impurities. The cycloadducts were dried in a desiccator, dissolved in 1,4-dioxane (0.5 M) and added to an oven-dried vial under argon that contained Pd(OAc)$_2$ (1.0 mol%), PPh$_3$ (4.0 mol%) and triethylamine (2.0 eq) The vial was sealed, then heated at reflux for 1 hour. The reaction mixture was cooled to room temperature and evaporated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography using an appropriate solvent system, as described for each individual procedure.

**General Procedure H: Diels-Alder reaction of azo compounds with Danishefsky’s diene**

![Reaction scheme]

Danishefsky's diene (2.4 eq) was added in one portion to a stirred solution of the desired azo compound (1.0 eq) in CH$_2$Cl$_2$ (0.4 M) and heated at reflux for 20 hours. The reaction was cooled to room temperature, then a 1M aqueous solution of HCl (1 mL) was added and the mixture stirred for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of NaHCO$_3$ (1 mL), the organic layer was separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (5 x 5 mL). The combined organic layers were dried (MgSO$_4$) and the solvent was evaporated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography using an appropriate solvent system, as described for each individual procedure.

**General Procedure I: Synthesis of 2-aminopyrrole from 1,2-dihydropyridazines**

![Chemical structure](image)

A solution of 1,2-dihydropyridazine (1.0 eq) in o-xylene (0.4-0.5 M) was heated at reflux for 5 hours. The reaction mixture was purified directly by flash column chromatography using an appropriate solvent system, as described for each individual procedure.
Note: 2-Aminopyrroles must be stored in the freezer under an inert atmosphere in order to prevent degradation.

**General Procedure J: Diels-Alder reaction of 2-aminopyrroles with aryne precursors**

![Chemical structure]

CsF (3.0 eq) was added in one portion to a stirred solution of 2-aminopyrrole (2.0 eq) and aryne precursor (1.0 eq) in MeCN (0.1 M) at room temperature under argon, then heated at 40 °C for 1.5-2.5 hours. The reaction mixture was cooled to room temperature, filtered through Celite and the solvent removed under reduced pressure to give the crude product. The crude product was purified by flash column chromatography using an appropriate solvent system, as described for each individual procedure.

**General Procedure K: 4π-Photocyclisation of 1,2-dihydropyridazines**

![Chemical structure]

A solution of 1,2-dihydropyridazine in either MeCN or PhMe (0.05 M/ 50 mM) was purged with argon for 15 minutes, then irradiated at room temperature (λ = 350 nm) until complete consumption of starting material (24-44 hours). The solvent was evaporated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography using an appropriate solvent system, as described for each individual procedure.

**General Procedure L: Thermal rearrangement of bicyclic 1,2-diazetidines**

![Chemical structure]

A solution of bicyclic 1,2-diazetidine in PhMe (0.1 M) was heated at reflux until complete consumption of starting material (4-24 hours). The solvent was evaporated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography using an appropriate solvent system, as described for each individual procedure.
6.3 Synthetic Procedures

**Diethyl-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate 154b**

![Structural formula](image)

Using general procedure A, a 15% (w/v) solution of butadiene in hexane (7 mL, 19.1 mmol, 3.0 eq) and diethyl azodicarboxylate 8b (1 mL, 6.35 mmol, 1.0 eq) in CH₂Cl₂ (10 mL) was heated at reflux for 19 hours. This gave the cycloadduct 154b (1.38 g, 6.08 mmol, 96%) as a colourless liquid, without further purification.

R₁ (petroleum ether-EtOAc, 2:1) = 0.33

^1^H NMR (400 MHz, CDCl₃): δ 5.83-5.74 (br m, 2H, H₂ and H₂'), 4.46-4.42 (br m, 2H, H₁ₐ and H₁ₐ'), 4.21-4.20 (br m, 4H, H₄ and H₄'), 3.80 (br s, 2H, H₁₉ and H₁₉'), 1.26 (t, J = 7.0 Hz, 6H, H₅ and H₅').

^1³^C NMR (100 MHz, CDCl₃); δ 155.6 (C₃), 123.7 (C₂), 62.4 (C₄), 43.7 (C₁), 14.6 (C₅).

FTIR (ATR) ν (cm⁻¹): 2982, 1705 (C=O).


**Diisopropyl-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate 154c**

![Structural formula](image)

Using general procedure A, a 15% (w/v) solution of butadiene in hexane (8 mL, 15.2 mmol, 3.0 eq) and diisopropyl azodicarboxylate 8c (1.0 mL, 5.08 mmol, 1.0 eq) in CH₂Cl₂ (2 mL) was heated at reflux for 24 hours. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 7:1→4:1) gave the cycloadduct 154c (1.26 g, 4.93 mmol, 97%) as a colourless oil.

R₁ (hexane-EtOAc, 4:1) = 0.25

^1^H NMR (400 MHz, CDCl₃); δ 5.79-5.72 (br m, 2H, H₂ and H₂'), 4.93 (sept, J = 6.2 Hz, 2H, H₄ and H₄'), 4.43-4.25 (br m, 2H, H₁ₐ and H₁ₐ'), 3.92-3.69 (br m, 2H, H₁₉ and H₁₉'), 1.22 (d, J = 6.2 Hz, 12H, H₅ and H₅').

^1³^C NMR (100 MHz, CDCl₃, additional peaks due to complex rate processes annotated by an asterisk); δ 155.3 (C₃), 123.8 (C₂), 69.9 (C₄), 44.6* (C₁), 43.7 (C₁), 22.2 (C₅), 22.1 (C₅).
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$^1$H NMR (400 MHz, CDCl$_3$); $\delta$ 5.79-5.72 (m, 2H, H$_2$ and H$_2'$, 4.94 (sept, $J = 6.2$ Hz, 2H, H$_4$ and H$_4'$). 4.47-4.26 (br m, 2H, H$_1A$ and H$_1'A$), 3.88-3.64 (br m, 2H, H$_1B$ and H$_1'B$), 1.24-1.22 (m, 12H, H$_5$ and H$_5'$).

$^{13}$C NMR (100 MHz, CDCl$_3$); $\delta$ 155.3 (C$_3$), 124.0 (C$_2$), 70.0 (C$_4$), 43.9 (C$_1$), 22.2 (C$_5$), 22.1 (C$_5'$).

FTIR (ATR) $\nu$ (cm$^{-1}$): 2980, 1703 (C=O).

HRMS (ESI): $m/z$ calculated for: C$_{12}$H$_{20}$N$_2$O$_4$ [M+H]$^+$ 257.1496 and [M+Na]$^+$ 279.1315, found 257.1495 and 279.1318 respectively.

Di-tert-butyl-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate 154d

Using general procedure A, a 15% (w/v) solution of butadiene in hexane (5 mL, 13.9 mmol, 3.0 eq) and di-tert-butyl azodicarboxylate 8d (1.07 g, 4.64 mmol, 1.0 eq) in CH$_2$Cl$_2$ (10 mL) was heated at reflux for three days. Purification by flash column chromatography on silica gel (eluent: petroleum ether-EtOAc, 20:1→10:1) gave the cycloadduct 154d (1.27 g, 4.48 mmol, 97%) as a white powder.

$R_f$ (petroleum ether-EtOAc, 5:1) = 0.33

mp = 66-68 °C

$^1$H NMR (400 MHz, CDCl$_3$); $\delta$ 5.81-5.71 (br m, 2H, H$_2$ and H$_2'$), 4.40-4.20 (m, 2H, H$_1A$ and H$_1'A$), 3.77-3.66 (m, 2H, H$_1B$ and H$_1'B$), 1.46 (s, 18H, H$_5$ and H$_5'$).

$^{13}$C NMR (100 MHz, CDCl$_3$, additional peaks due to complex rate processes denoted by an asterisk); $\delta$ 154.7 (C$_3$), 124.1 (C$_2$), 123.5* (C$_2$), 81.1 (C$_4$), 44.9* (C$_1$), 43.3 (C$_1'$), 28.4 (C$_5$).

FTIR (ATR) $\nu$ (cm$^{-1}$): 2981, 2894, 1693 (C=O).

HRMS (ESI): $m/z$ calculated for: C$_{14}$H$_{24}$N$_2$O$_4$ [M + K]$^+$ 323.1368 and [M + Na]$^+$ 307.1628, found 323.1349 and 307.1624 respectively.

(E/Z)-1-Acetoxy-1,3-butadiene 202a

Method A

Using general procedure B, crotonaldehyde 204 (5.0 mL, 60.4 mmol, 1.0 eq) was added to potassium tert-butoxide (7.54 g, 67.2 mmol, 1.1 eq) in THF (50 mL). Acetyl chloride (4.7 mL, 66.4 mmol, 1.1 eq) was added and stirred at –78 °C for 20 minutes. The crude product was purified by vacuum distillation (30 mbar, 80 °C) to give the diene 202a (2.58 g, 23.0 mmol, 38%, E/Z or Z/E 50:1.0) as a colourless liquid.
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Method B

4-Dimethylaminopyridine (4.43 g, 0.04 mol, 0.1 eq), triethylamine (106 mL, 0.76 mol, 2.1 eq) and acetic anhydride (103 mL, 1.09 mol, 3.0 eq) were added to crotonaldehyde 204 (30 mL, 0.36 mol, 1.0 eq) at room temperature under argon. The solution was stirred for 4 days at room temperature, then diluted with Et$_2$O (200 mL), poured onto ice water (1.0 L) and stirred for 2 hours. The organic layer was separated and washed with a saturated aqueous solution of NaHCO$_3$ (5 x 200 mL), dried (MgSO$_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: pentane-Et$_2$O, 98:2) gave the diene 202a (25.0 g, 0.22 mol, 62 %, E/Z or Z/E 8.0:1.0) as a colourless liquid.

The spectroscopic data are consistent with those reported previously.\textsuperscript{237,238}

Major Isomer:

$R_f$ (hexane-EtOA, 2:1) = 0.58

$^1$H NMR (400 MHz, CDCl$_3$); $\delta$ 7.39 (dd, $J = 12.4$, 0.6 Hz, 1H, H1), 6.31–6.22 (m, 1H, H3), 6.06–6.00 (m, 1H, H2), 5.23–5.18 (m, 1H, H4A), 5.10–5.07 (m, 1H, H4B), 2.14 (s, 3H, H6).

$^{13}$C NMR (100 MHz, CDCl$_3$); $\delta$ 167.9 (C5), 138.8 (C1), 131.8 (C3), 117.4 (C4), 116.2 (C2), 20.8 (C6).

\((E/Z)\)-Buta-1,3-dien-1-yl benzoate 202b\textsuperscript{315}

\[
\begin{array}{cccccccc}
8 & 7 & 6 & O & 1 & 3 & 2 & 4 \\
 & & & & & & & \\
9 & 8 & 7 & & & & & \\
\end{array}
\]

Method A

Using general procedure B, crotonaldehyde 204 (5.0 mL, 60.4 mmol, 1.0 eq) was added to potassium tert-butoxide (7.47 g, 66.5 mmol, 1.1 eq) in THF (40 mL). A solution of benzoyl chloride (8.4 mL, 72.4 mmol, 1.2 eq) in THF (10 mL) was added and stirred at –78 °C for 30 minutes. The crude product was purified by vacuum distillation (0.1 mbar, 90-110 °C) to give diene 202b (7.07 g, 40.6 mmol, 67%, E/Z or Z/E 20:1.0) as a colourless liquid.

Method B

4-Dimethylaminopyridine (600 mg, 4.91 mmol, 0.2 eq), triethylamine (7 mL, 50.2 mmol, 2.0 eq) and benzoyl chloride (3.1 mL, 26.5 mmol, 1.1 eq) were added to crotonaldehyde 204 (2.1 mL, 25.4 mmol, 1.0 eq) at room temperature under argon. The solution was stirred for 24 hours at room temperature, then diluted with Et$_2$O (100 mL) and washed with saturated aqueous solution of NaHCO$_3$ (3 x 30 mL), dried (MgSO$_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (elucent: petroleum ether-EtOAc, 60:1 → 40:1) gave diene 202b (992 mg, 5.69 mmol, 22%, E/Z or Z/E 3.0:1.0) as a colourless liquid.

$R_f$ (petroleum ether- EtOAc, 5:1) = 0.53
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\[^1\text{H}\text{ NMR}\ (400\text{ MHz, CDCl}_3); \ \delta\ 8.15–8.09\ (m, 2H, H7), 7.66\ (dd, J = 12.2, 0.5\ Hz, 1H, H1), 7.64–7.58\ (m, 1H, H9), 7.51–7.45\ (m, 2H, H8), 6.42–6.32\ (m, 1H, H3), 6.27–6.21\ (m, 1H, H2), 5.30–5.25\ (m, 1H, H4\_A), 5.15–5.12\ (m, 1H, H4\_B).\]

\[^{13}\text{C}\text{ NMR}\ (100\text{ MHz, CDCl}_3); \ \delta\ 163.6\ (C5), 139.1\ (C1), 133.8\ (C9), 131.9\ (C3), 130.1\ (C7), 128.9\ (C6), 128.7\ (C8), 117.5\ (C4), 116.8\ (C2).\]

\[^{\text{FTIR\ (ATR)}}\ \nu\ (\text{cm}^{-1}): 3087, 1731\ (\text{C}=\text{O}), 1656, 1601.\]

\[^{\text{HRMS\ (ESI):}}\ m/z\ \text{calculated for:}\ C_{11}H_{10}O_2\ [\text{M-H}]\ 173.0608,\ \text{found}\ 173.0606.\]

\((E/Z)\text{-Buta-1,3-dien-1-yl pivalate 202c}^{316}\)

![Buta-1,3-dien-1-yl pivalate 202c](image)

Using general procedure B, crotonaldehyde 204 (2.5 mL, 30.2 mmol, 1.0 eq) was added to potassium tert-butoxide (3.72 g, 33.2 mmol, 1.1 eq) in THF (18 mL). A solution of pivaloyl chloride (4.5 mL, 36.5 mmol, 1.2 eq) in THF (7 mL) was added and the resulting mixture was stirred at –78 °C for 30 minutes. The crude product was purified by vacuum distillation (0.1 mbar, 40 °C) to give the diene 202c (2.53 g, 16.4 mmol, 54%, E/Z or Z/E 50:1.0) as a colourless liquid.

\(R_f\) (hexane-EtOAc, 2:1) = 0.71

\[^1\text{H}\text{ NMR}\ (400\text{ MHz, CDCl}_3); \ \delta\ 7.39\ (d, J = 12.3\ Hz, 1H, H1), 6.33–6.24\ (m, 1H, H3), 6.09–6.03\ (m, 1H, H2), 5.22–5.18\ (m, 1H, H4\_A), 5.09–5.06\ (m, 1H, H4\_B), 1.24\ (s, 9H, H7).\]

\[^{13}\text{C}\text{ NMR}\ (100\text{ MHz, CDCl}_3); \ \delta\ 175.5\ (C5), 139.3\ (C1), 132.0\ (C3), 117.0\ (C4), 116.0\ (C2), 38.9\ (C6), 27.1\ (C7).\]

\[^{\text{FTIR\ (ATR)}}\ \nu\ (\text{cm}^{-1}): 2976, 1743\ (\text{C}=\text{O}).\]

\[^{\text{HRMS\ (ESI):}}\ \text{No mass peak found.}\]

\((E/Z)\text{-Buta-1,3-dien-1-yl ethyl carbonate 202d}^{317}\)

![Buta-1,3-dien-1-yl ethyl carbonate 202d](image)

Using general procedure B, crotonaldehyde 204 (5.2 mL, 62.8 mmol, 1.0 eq) was added to potassium tert-butoxide (7.75 g, 69.0 mmol, 1.1 eq) in THF (40 mL). A solution of ethyl chloroformate (7.2 mL, 75.0 mmol, 1.2 eq) in THF (10 mL) was added and the resulting mixture was stirred at –78 °C for 30 minutes. The crude product was purified by vacuum distillation (0.1 mbar, 40 °C) to give the diene 202d (3.05 g, 21.5 mmol, 34%, E/Z or Z/E 33:1.0) as a colourless liquid.

\(R_f\) (Hexane-EtOAc, 2:1) = 0.62

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¹H NMR (400 MHz, CDCl₃); δ 7.20 (d, J = 12.2 Hz, 1H, H1), 6.31-6.21 (m, 1H, H3), 6.08-6.02 (m, 1H, H2), 5.24-5.19 (m, 1H, H₄), 5.11-5.08 (m, 1H, H₄), 4.27 (q, J = 7.2 Hz, 2H, H6), 1.34 (t, J = 7.2 Hz, 3H, H7).

¹³C NMR (100 MHz, CDCl₃); δ 152.7 (C₅), 140.3 (C₁), 131.4 (C₃), 117.5 (C₄), 116.2 (C₂), 65.0 (C₆), 14.3 (C₇).

FTIR (ATR) ν (cm⁻¹): 2984, 1754 (C=O).

HRMS (ESI): No mass peak found.

1-Acetoxy-3-methyl-1,3-butadiene 214

![Diagram of 1-Acetoxy-3-methyl-1,3-butadiene 214]

4-Dimethylaminopyridine (0.64 g, 5.24 mmol, 0.2 eq), triethylamine (25 mL, 181 mmol, 2.1 eq) and acetic anhydride (12 mL, 130 mmol, 5.0 eq) were added to 3-methyl-2-butenal (2.5 mL, 25.9 mmol, 1.0 eq) at room temperature under argon. The solution was stirred for 5 days at room temperature, then diluted with Et₂O (50 mL), poured onto ice water (250 mL) and stirred for 2 hours. The organic layer was separated and washed with a saturated aqueous solution of NaHCO₃ (5 x 20 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: pentane-Et₂O, 100:0→96:4) gave the diene 214 (1.46 g, 11.6 mmol, 45%, E/Z or Z/E 5.9:1.0) as a colourless liquid.

The spectroscopic data are consistent with those reported previously.

¹H NMR (400 MHz, CDCl₃); δ 7.35 (d, J = 12.6 Hz, 1H, H), 6.13 (dd, J = 12.6, 0.3 Hz, 1H, H₂), 4.95-4.91 (m, 2H, H₄ and H₄), 2.14 (s, 3H, H₇), 1.85-1.84 (m, 3H, H₅).

¹³C NMR (100 MHz, CDCl₃); δ 168.2 (C₆), 138.6 (C₃), 136.5 (C₁), 118.3 (C₂), 116.6 (C₄), 20.8 (C₇), 18.8 (C₅).

Diisopropyl 3-(pivaloyloxy)-3,6-dihydropyridazine-1,2-dicarboxylate 205

![Diagram of Diisopropyl 3-(pivaloyloxy)-3,6-dihydropyridazine-1,2-dicarboxylate 205]

Using general procedure C, 1-pivaloyloxy-1,3-butadiene 202c (2.03 g, 13.2 mmol, 1.6 eq) and disopropyl azodicarboxylate 8c (1.6 mL, 8.23 mmol, 1.0 eq) in methyl tert-butyl ether (3 mL) were heated at reflux for 27 hours. The excess diene was removed by vacuum distillation (0.1 mbar, 60 °C) to give the impure cycloadduct 205 (3.02 g) as a pale-yellow oil.

Rᵣ (Hexane-EtOAc, 2:1) = 0.40.
H NMR (400 MHz, CDCl₃); δ 6.87-6.79 (br m, 1H, H1), 6.09-6.04 (br m, 1H, H3), 5.87-5.82 (br m, 1H, H2), 5.03-4.90 (br m, 2H, H6 and H9), 4.60-4.43 (br m, 1H, H4ₐ), 3.87-3.68 (br m, 1H, H4ₐ), 1.27-1.22 (br m, 12H, H7 and H10), 1.19 (br s, 9H, H13).

13C NMR (100 MHz, CDCl₃, additional peaks due to complex rate processes denoted by an asterisk); δ 177.2 (C11), 155.0 (C5 and C8), 128.2 (C3), 122.5 (C2), 74.6 (C1), 71.0 (C6 or C10), 70.4 (C6 or C10), 42.4 (C4), 38.9 (C12), 27.2 (C13), 22.3* (C7 or C10), 22.2* (C7 or C10), 22.1* (C7 or C10), 22.0 (C7 or C10).

FTIR (ATR) ν (cm⁻¹): 2980, 1709 (C=O), 1654 (C=O).

HRMS (APCI): m/z calculated for: C₁₇H₂₈N₂O₆ [M+Na]+ 379.1840, found 379.1837.

Diisopropyl 3-(ethoxycarbonyl)oxy)-3,6-dihydropyridazine-1,2-dicarboxylate 206

Using a general procedure C, 1-(ethoxycarbonyl)oxy-1,3-butadiene 202d (2.08 g, 14.6 mmol, 1.4 eq) and diisopropyl azodicarboxylate 8c (2.0 mL, 10.3 mmol, 1.0 eq) in methyl tert-butyl ether (3 mL) were stirred at room temperature 3 days. The excess diene was removed by vacuum distillation (0.1 mbar, 80 °C) to give the cycloadduct 206 (3.41 g, 9.90 mmol, 96%) as a pale yellow oil.

Rf – Not stable on silica gel (streaks).

¹H NMR (400 MHz, CDCl₃); δ 6.80-6.71 (br m, 1H, H1), 6.13-6.05 (br m, 1H, H3), 5.91-5.85 (br d, 1H, H2), 5.07-4.91 (m, 2H, H6 and H9), 4.64-4.39 (br m, 1H, H4ₐ), 4.27-4.14 (m, 2H, H12), 3.86-3.67 (br m, 1H, H4ₐ), 1.31-1.21 (m, 15H, H7, H10 and H13).

¹³C NMR (100 MHz, CDCl₃, additional peaks due to complex rate processes denoted by an asterisk); δ 177.2 (C11), 155.0 (C5 and C8), 128.2 (C3), 122.5 (C2), 74.6 (C1), 71.0 (C6 or C10), 70.4 (C6 or C10), 42.4 (C4), 39.9 (C12), 27.2 (C13), 22.3* (C7 or C10), 22.2* (C7 or C10), 22.1* (C7 or C10), 22.0 (C7 or C10).

FTIR (ATR) ν (cm⁻¹): 2984, 1737 (C=O), 1707 (C=O).

HRMS (ESI): m/z calculated for: C₁₂H₁₉N₂O₄ [M-O₂CO₂Et]+ 255.1339, found 255.1342.

Dimethyl hydrazine-1,2-dicarboxylate 43a

Using a general procedure D, pyridine (2.7 mL, 33.3 mmol, 3.0 eq), methyl carbazate (1.00 g, 11.1 mmol, 1.0 eq) and methyl chloroformate (1.0 mL, 12.9 mmol, 1.2 eq) in 2-MeTHF (22 mL) gave hydrazine 43e (0.95 g, 6.41 mmol, 58%) as a colourless solid, without further purification.
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Rt (CH₂Cl₂-EtOAc, 1:1) = 0.32
mp = 123-124 °C

¹H NMR (400 MHz, d₆-DMSO); δ 9.12-8.72 (br m, 2H, NH), 3.58 (s, 6H, H²).

¹³C NMR (100 MHz, d₆-DMSO); δ 157.1 (C₁), 51.9 (C₂).

FTIR (ATR) ν (cm⁻¹): 3278 (NH), 3047, 2958, 1743 (C=O), 1702 (C=O).

Dibenzyl hydrazine-1,2-dicarboxylate 43e

Benzyl chloroformate (2.9 mL, 20.3 mmol, 2.0 eq) and a solution of sodium carbonate (1.10 g, 10.4 mmol, 1.0 eq) in water (5 mL) were added dropwise to a stirred solution of hydrazine monohydrate (0.5 mL, 10.3 mmol, 1.0 eq) in ethanol (5 mL) at 0 °C, then stirred at room temperature for 30 minutes. The resulting solid was filtered, washed with water (8 mL) and dried to give hydrazine 43e (2.93 g, 9.74 mmol, 95%) as a colourless solid.

Rₜ (Hexane-EtOAc, 1:1) = 0.41
mp = 102-103 °C

¹H NMR (400 MHz, CDCl₃); δ 7.38-7.30 (br m, 10H, H⁴, H⁵, H⁶), 6.67 (br s, 2H, NH), 5.16 (s, 4H, H₂).

¹³C NMR (100 MHz, CDCl₃); δ 156.6 (C₁), 135.6 (C₃), 128.7 (C₄, C₅ or C₆), 128.6 (C₄, C₅ or C₆), 128.4 (C₄, C₅ or C₆), 127.9 (C₄, C₅ or C₆), 5.09 (s, 4H, H₂).

¹H NMR (400 MHz, d₆-DMSO); δ 9.33-8.88 (br m, 2H, NH), 7.40-7.33 (br m, 10H, H⁴, H⁵, H⁶), 5.09 (s, 4H, H₂).

¹³C NMR (100 MHz, d₆-DMSO); δ 156.5 (C₁), 136.6 (C₃), 128.4 (C₄, C₅ or C₆), 128.0 (C₄, C₅ or C₆), 66.0 (C₂).

FTIR (ATR) ν (cm⁻¹): 3379 (NH), 3308 (NH), 1763 (C=O), 1702 (C=O).

HRMS (APCI): m/z calculated for: C₁₆H₁₄N₂O₄ [M-H] 299.1037, found 299.1040.

1-tert-Butyl 2-methyl hydrazine-1,2-dicarboxylate 43f

Using general procedure D, pyridine (1.8 mL, 22.7 mmol, 3.0 eq), tert-butyl carbazate (1.00 g, 7.57 mmol, 1.0 eq) and methyl chloroformate (0.65 mL, 8.41 mmol, 1.1 eq) in 2-MeTHF (7.5 mL) gave hydrazine 43f (1.19 g, 6.26 mmol, 83%) as a colourless solid, without further purification.

Rₜ (Hexane-EtOAc, 1:1) = 0.25
mp = 103-105 °C
**1H NMR (400 MHz, CDCl₃):** δ 6.59 (br s, 1H, H₄ or H₅), 6.40 (br s, 1H, H₄ or H₅), 3.75 (s, 3H, H₇), 1.46 (s, 9H, H₁).

**13C NMR (100 MHz, CDCl₃):** δ 157.5 (C₃ or C₆), 155.9 (C₃ or C₆), 82.0 (C₂), 53.2 (C₇), 28.3 (C₁).

**FTIR (ATR) ν (cm⁻¹):** 3256 (NH), 3014, 2984, 1746 (C=O), 1690 (C=O).

**HRMS (APCI):** m/z calculated for: C₇H₁₄N₂O₄ [M-H]⁻ 189.0881, found 189.0885.

**1-Benzyl 2-tert-butyl hydrazine-1,2-dicarboxylate 43g**

Using general procedure D, pyridine (3.8 mL, 47.0 mmol, 6.0 eq), tert-butyl carbazate (502 mg, 3.80 mmol, 1.0 eq) and benzyl chloroformate (0.6 mL, 4.20 mmol, 1.1 eq) in 2-MeTHF (4 mL) gave the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1→2:1) gave the hydrazine 43g (835 mg, 3.14 mmol, 83%) as a colourless solid.

**Rₛ (Hexane-EtOAc, 2:1) = 0.27**

**mp = 75-76 °C**

**1H NMR (400 MHz, CDCl₃):** δ 7.37-7.29 (m, 5H, H₉, H₁₀, H₁₁), 6.64 (br s, 1H, H₄ or H₅), 6.39 (br s, 1H, H₄ or H₅), 5.16 (s, 2H, H₇), 1.46 (s, 9H, H₁).

**13C NMR (100 MHz, CDCl₃):** δ 156.8 (C₃ or C₆), 155.8 (C₃ or C₆), 135.8 (C₈), 128.7 (C₉, C₁₀, or C₁₁), 128.5 (C₉, C₁₀, or C₁₁), 128.4 (C₉, C₁₀, or C₁₁), 128.0 (C₉, C₁₀, or C₁₁), 127.9 (C₉, C₁₀, or C₁₁), 79.2 (C₂), 67.9 (C₇), 28.2 (C₁).

**1H NMR (400 MHz, d₆-DMSO):** δ 9.04 (br s, 1H, H₄ or H₅), 8.77 (br s, 1H, H₄ or H₅), 7.38-7.34 (m, 5H, H₉, H₁₀, H₁₁), 5.06 (br s, 2H, H₇), 1.40-1.33 (m, 9H, H₁).

**13C NMR (100 MHz, d₆-DMSO):** δ 156.5 (C₃ or C₆), 155.6 (C₃ or C₆), 136.3 (C₈), 128.4 (C₉, C₁₀, or C₁₁), 128.0 (C₉, C₁₀, or C₁₁), 127.9 (C₉, C₁₀, or C₁₁), 79.2 (C₂), 65.8 (C₇), 28.1 (C₁).

**FTIR (ATR) ν (cm⁻¹):** 3260 (NH), 2976, 1748 (C=O), 1687 (C=O).

**HRMS (ESI):** m/z calculated for: C₁₃H₁₈N₂O₄ [M+Na]⁺ 289.1159, found 289.1148.

**Bis(2,2,2-trichloroethyl) hydrazine-1,2-dicarboxylate 43**

2,2,2-Trichloroethyl chloroformate (3.0 mL, 21.8 mmol, 2.1 eq) and a solution of sodium carbonate (1.10 g, 10.4 mmol, 1.0 eq) in water (5 mL) were added dropwise to a stirred solution of hydrazine monohydrate (0.5 mL, 10.3 mmol, 1 eq) in ethanol (5 mL) at 0 °C, then stirred at room temperature for 30 minutes. The organic layer was separated and the aqueous layer was
extracted with Et$_2$O (2 x 5 mL). The combined organic layers were dried (MgSO$_4$) and evaporated under reduced pressure to give hydrazine 43i (3.04 g, 8.47 mmol, 82%) as a colourless solid.

$R_f$ (Hexane-EtOAc, 1:1) = 0.55

mp = 83-84 °C

$^1$H NMR (400 MHz, CDCl$_3$); $\delta$ 6.99-6.81 (br m, 2H, NH), 4.80 (s, 4H, H2).

$^{13}$C NMR (100 MHz, CDCl$_3$); $\delta$ 154.8 (C1), 94.7 (C3), 75.4 (C2).

FTIR (ATR) $\nu$ (cm$^{-1}$): 3261 (NH), 1765 (C=O), 1702 (C=O).

HRMS (APCI): $m/z$ calculated for: C$_6$H$_6$N$_2$O$_4$Cl$_6$ [M-H] - 378.8386, found 378.8376.

1-tert-Butyl 2-(2,2,2-trichloroethyl)-hydrazine-1,2-dicarboxylate 43j

Using general procedure D, pyridine (1.8 mL, 22.7 mmol, 3.0 eq), tert-butyl carbazate (1.00 g, 7.57 mmol, 1.0 eq) and 2,2,2-trichloroethyl chloroformate (1.1 mL, 8.33 mmol, 1.1 eq) in THF (75 mL) gave the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 7:1 → 4:1) gave the hydrazine 43j (2.20 g, 7.15 mmol, 94%) as a colourless solid.

$R_f$ (Hexane-EtOAc, 1:1) = 0.57

mp = 64-66 °C

$^1$H NMR (400 MHz, CDCl$_3$); $\delta$ 6.80 (br s, 1H, H4 or H5), 6.39 (br s, 1H, H4 or H5), 4.78 (s, 2H, H7), 1.48 (s, 9H, H1).

$^{13}$C NMR (100 MHz, CDCl$_3$); $\delta$ 155.4, (C3 or C6), 155.2 (C3 or C6), 95.0 (C8), 82.4 (C2), 75.4 (C7), 28.3 (C1).

$^1$H NMR (400 MHz, d$_6$-DMSO); $\delta$ 9.49 (br s, 1H, H4 or H5), 8.93 (br s, 1H, H4 or H5), 4.84-4.80 (br m, 2H, H7), 1.40 (br s, 9H, H1).

$^{13}$C NMR (100 MHz, d$_6$-DMSO); $\delta$ 155.4 (C3 or C6), 155.1 (C3 or C6), 95.8 (C8), 79.4 (C2), 73.7 (C7), 28.1 (C1).

FTIR (ATR) $\nu$ (cm$^{-1}$): 3293 (NH), 2980, 1741 (C=O), 1715 (C=O).

HRMS (ESI): $m/z$ calculated for: C$_6$H$_{13}$N$_2$O$_4$Cl$_3$ [M+Na]$^+$ 328.9833, found 328.9827.

1-tert-Butyl 2-tosyl hydrazine-1-carboxylate 43k

Using general procedure D, pyridine (3.8 mL, 47.0 mmol, 6.0 eq), tert-butyl carbazate (1.00 g, 7.57 mmol, 1.0 eq) and p-toluenesulfonyl chloride (1.58 g, 8.29 mmol, 1.1 eq) in THF (75 mL)
gave the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 9:1 → 4:1) gave the hydrazine 43k (1.47, 5.13 mmol, 68%) as a colourless solid.

\[ R_f (\text{Hexane-EtOAc}, 1:1) = 0.38 \]

mp = 99-101 °C

\(^1\)H NMR (400 MHz, CDCl\(_3\)); \( \delta \) 7.80 (d, \( J = 8.1 \) Hz, 2H, H\(_4\)), 7.29 (d, \( J = 8.1 \) Hz, 2H, H\(_3\)), 6.78 (br s, 2H, H\(_6\) and H\(_7\)), 2.40 (s, 3H, H\(_1\)), 1.22 (s, 9H, H\(_{10}\)).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)); \( \delta \) 154.3 (C\(_8\)), 144.7 (C\(_2\)), 133.7 (C\(_5\)), 129.6 (C\(_3\)), 128.9 (C\(_4\)), 82.4 (C\(_9\)), 27.9 (C\(_{10}\)), 21.7 (C\(_1\)).

FTIR (ATR) \( \nu \) (cm\(^{-1}\)): 3308 (NH), 3232 (NH), 2976, 1716 (C=O), 1331 (SO\(_2\)), 1150 (SO\(_2\)).


1-Benzyl 2-tosyl hydrazine-1-carboxylate 43l

Sodium bicarbonate (275 mg, 3.27 mmol, 1.2 eq) was added to a stirred suspension of \( p \)-toluenesulfonyl hydrazide (503 mg, 2.70 mmol, 1.0 eq) in water (27 mL) at room temperature under argon. Benzyl chloroformate (0.5 mL, 3.50 mmol, 1.3 eq) was added dropwise at 0 °C and the resulting mixture was stirred for a further 15 minutes, then heated at 60 °C for 2 hours. The reaction mixture was allowed to cool, then was extracted with CH\(_2\)Cl\(_2\) (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried (MgSO\(_4\)) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1 → 2:1) gave the hydrazine 43l (453 mg, 1.41 mmol, 52%) as a colourless solid.

\[ R_f (\text{Hexane-EtOAc}, 1:1) = 0.23 \]

mp = 141-142 °C

\(^1\)H NMR (400 MHz, \( d_6\)-DMSO)); \( \delta \) 9.69 (br s, 1H, H\(_6\) or H\(_7\)), 9.52 (br s, 1H, H\(_6\) or H\(_7\)), 7.66 (d, \( J = 8.1 \) Hz, 2H, H\(_4\)), 7.37-7.29 (br m, 5H, H\(_3\), H\(_{12}\), H\(_{13}\)), 7.22 (br d, \( J = 6.5 \) Hz, 2H, H\(_{11}\)), 4.93 (br s, 2H, H\(_9\)), 2.37 (s, 3H, H\(_1\)).

\(^{13}\)C NMR (100 MHz, \( d_6\)-DMSO)); \( \delta \) 155.7 (C\(_8\)), 143.2 (C\(_2\)), 136.4 (C\(_5\) or C\(_{10}\)), 136.1 (C\(_5\) or C\(_{10}\)), 129.4 (C\(_3\)), 128.3 (C\(_4\), C\(_{11}\), C\(_{12}\) or C\(_{13}\)), 127.9 (C\(_4\), C\(_{11}\), C\(_{12}\) or C\(_{13}\)), 127.6 (C\(_4\), C\(_{11}\), C\(_{12}\) or C\(_{13}\)), 65.9 (C\(_9\)), 21.1 (C\(_1\)).

FTIR (ATR) \( \nu \) (cm\(^{-1}\)): 3338 (NH), 3181 (NH), 1722 (C=O), 1340 (SO\(_2\)), 1163 (SO\(_2\)).

HRMS (APCI): \( m/z \) calculated for: C\(_{15}\)H\(_{16}\)N\(_2\)O\(_4\)S [M-H] 319.0758, found 319.0770.
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$N,N'$-Ditosylhydrazine 43m$^{251}$

Pyridine (1.2 mL, 14.8 mmol, 1.5 eq) was added dropwise over 1 minute to a stirred suspension of tosylhydrazide (1.87 g, 10.0 mmol, 1.0 eq) and tosyl chloride (2.95 g, 15.5 mmol, 1.5 eq) in CH$_2$Cl$_2$ (10 mL) at room temperature under argon. The resulting solution was stirred at room temperature for 2.5 hours, then Et$_2$O (40 mL) and water (20 mL) were added and the resulting mixture was stirred at 0 °C for 15 minutes. The solid was filtered and washed with cold Et$_2$O (20 mL) to give the crude product and then dissolved in hot MeOH (80 mL). Half of the solvent was evaporated under reduced pressure (c.a. 40 mL), followed by cooling to 0 °C. The resulting crystals were filtered, washed with cold MeOH (5 mL), Et$_2$O (20 mL) and dried to give the hydrazine 43m (2.17 g, 6.39 mmol, 64 %) as a colourless solid.

$R_f$ (petroleum ether- EtOAc, 1:1) = 0.44, slightly streaky.

$\text{mp} = 210-212$ °C (decomposition)

$^1$H NMR (400 MHz, d$_6$-DMSO); $\delta$ 9.58 (s, 2H, NH), 7.64 (d, $J = 8.0$ Hz, 4H, H$_2$), 7.38 (d, $J = 8.0$ Hz, 4H, H$_3$), 2.39 (s, 6H, H$_5$)

$^{13}$C NMR (100 MHz, d$_6$-DMSO); $\delta$ 143.6 (C$_4$), 135.5 (C$_1$), 129.6 (C$_3$), 127.9 (C$_2$), 21.1 (C$_5$).

FTIR (ATR) $\nu$ (cm$^{-1}$): 3230 (NH), 3204 (NH), 1331 (SO$_2$), 1164 (SO$_2$).

HRMS (ESI): No mass peak found.

Di-tert-butyl azodicarboxylate 8d

Fétonz’s Reagent Oxidation: Fétonz’s reagent (147 mg, 0.26 mmol, 1.5 eq, c.a 1 mmol per 0.57 g) was added in one portion to a stirred solution of hydrazine 43d (40 mg, 0.17 mmol, 1.0 eq) in PhMe (1.7 mL), then heated at 50 °C for 25 minutes. The reaction mixture was cooled, filtered and the filtrate evaporated under reduced pressure to give the azo compound 8d (35 mg, 0.15 mmol, 88%) as a yellow solid, with no further purification required.

Copper Oxidation: Copper(I) chloride (4 mg, 0.04 mmol, 0.2 eq) and pyridine (0.9 µl, 0.01 mmol, 0.05 eq) were added to a stirred solution of hydrazine 43d (49 mg, 0.21 mmol, 1.0 eq) in MeTHF (2.2 mL) at room temperature under aerobic conditions. The reaction mixture was stirred for 19 hours, then quenched with an aqueous EDTA solution (3 mL, 0.5 M, pH = 7), dried (MgSO$_4$)
and evaporated under reduced pressure to give azo compound 8d (39 mg, 0.17 mmol, 81%) as a yellow solid.

*The spectroscopic data was consistent with those reported previously.*

\[ R_f (\text{Hexane-ETOAc, 1:1}) = 0.67. \]

\[ ^1\text{H NMR (400 MHz, CDCl}_3\); \delta 1.61 (s, 18H, H3). \]

\[ ^{13}\text{C NMR (75 MHz, CDCl}_3\); \delta 159.4 (C1), 86.9 (C2), 27.8 (C3). \]

FTIR (ATR) \( \nu (\text{cm}^{-1}) \): 2986, 2943, 1761 (C=O).

**Dibenzy azodicarboxylate 8e**

\[
\begin{align*}
\text{O} & \quad \text{N} & \quad \text{O} \\
\text{N} & \quad \text{O} & \quad \text{N} \\
\text{O} & \quad \text{N} & \quad \text{O}
\end{align*}
\]

Iodobenzene diacetate (537 mg, 1.67 mmol, 1.0 eq) was added in one portion to a stirred suspension of hydrazine 43e (495 mg, 1.65 mmol, 1.0 eq) in CH\(_2\)Cl\(_2\) (5 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 50 minutes, then evaporated under reduced pressure. Addition of hexane (5 mL) to the residue and filtration gave the azo compound 8e (388 mg, 1.30 mmol, 78%) as a pale yellow solid.

\[ R_f (\text{Hexane-ETOAc, 1:1}) = 0.67. \]

mp = 43-45 °C

\[ ^1\text{H NMR (400 MHz, CDCl}_3\); \delta 7.44-7.37 (m, 10H, H4, H5, H6), 5.43 (s, 4H, H2). \]

\[ ^{13}\text{C NMR (100 MHz, CDCl}_3\); \delta 160.2 (C1), 133.7 (C3), 129.4 (C6), 129.0 (C4 or C5), 129.0 (C4 or C5), 71.0 (C2). \]

FTIR (ATR) \( \nu (\text{cm}^{-1}) \): 3060, 3029, 1757 (C=O).

HRMS (ESI): No mass peak found.

**4-Phenyl-1,2,4-triazoline-3,5-dione 8h**

\[
\begin{align*}
\text{N} & \quad \text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} & \quad \text{N}
\end{align*}
\]

Iodobenzene diacetate (2.82 g, 8.76 mmol, 1.3 eq) was added in one portion to a stirred suspension of 4-pheny lurazole 43h (1.15 g, 6.49 mmol, 1.0 eq) in CH\(_2\)Cl\(_2\) (20 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 15 minutes, then evaporated under reduced pressure. Addition of petroleum ether (20 mL) to the residue and filtration gave 8h (1.03 g, 5.88 mmol, 91%) as a brick red solid.

mp = 130-140 °C (decomposed)

\[ ^1\text{H NMR (400 MHz, CDCl}_3\); \delta 7.57-7.54 (m, 2H, H5 or H6), 7.51-7.45 (m, 3H, H5 or H6 and H7) \]
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\[ \text{C NMR (100 MHz, CDCl}_3, \text{C4 not visible); } \delta 157.9 (\text{C3}), 130.0 (\text{C5 or C6}), 129.6 (\text{C7}), 124.1 (\text{C5 or C6}). \]

FTIR (ATR) \( \nu (\text{cm}^{-1}) \): 1737 (C=O).

HRMS (ESI): \( m/z \) calculated for: C\(_8\)H\(_5\)N\(_3\)O\(_2\)M \(-175.0387\), found 175.0395.

Bis(2,2,2-trichloroethyl) azodicarboxylate 8i

Iodobenzene diacetate (432 mg, 1.34 mmol, 1.0 eq) was added in one portion to a stirred suspension of hydrazine 43i (511 mg, 1.34 mmol, 1.0 eq) in CH\(_2\)Cl\(_2\) (5 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 40 minutes, then evaporated under reduced pressure. Addition of hexane (5 mL) to the residue and filtration gave the azo compound 8i (398 mg, 1.05 mmol, 78%) as a pale yellow solid.

\( R_t \) - Not stable on silica gel

mp = 98-100 °C

\(^1\)H NMR (400 MHz, CDCl\(_3\)); \( \delta \) 5.06 (s, 4H, H2).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)); \( \delta \) 158.6 (C1), 93.3 (C3), 77.1 (C2).

FTIR (ATR) \( \nu (\text{cm}^{-1}) \): 3017, 2969, 1780 (C=O).

HRMS (ESI): No mass peak found.

Bis(trichloroethyl)-3-acetoxy-3,6-dihydropyridazine-1,2-dicarboxylate 203i

Using general procedure C, a mixture of 1-acetoxy-1,3-butadiene 202a (74 µL, 0.63 mmol, 1.2 eq) and bis(trichloroethyl) azodicarboxylate 8i (200 mg, 0.53 mmol, 1.0 eq) in methyl tert-butyl ether (0.5 mL) were stirred at room temperature for 10 hours. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1→2:1) gave the cycloadduct 203i (227 mg, 0.46 mmol, 87%) as a colourless oil.

\( R_t \) (Hexane-EtOAc, 2:1) = 0.29

\(^1\)H NMR (400 MHz, CDCl\(_3\)); \( \delta \) 6.96-6.91 (br m, 1H, H1), 6.16-6.09 (br m, 1H, H3), 5.98-5.89 (br m, 1H, H2), 4.99-4.57 (br m, 5H, H4\(_A\), H6 and H9), 4.08-3.88 (m, 1H, H4\(_A\)), 2.07-2.04 (br m, 3H, H12).
\(^{13}\)C NMR (100 MHz, CDCl\(_3\)), additional peaks due to complex rate processes denoted by an asterisk; \(\delta\) 169.5* (C11), 169.3 (C11), 153.3 (C5 or C8), 152.8* (C5 or C8), 152.0* (C5 or C8), 128.4 (C3), 128.2* (C3), 122.6* (C2), 122.3 (C2), 95.0* (C7 or C10), 94.9* (C7 or C10), 94.7 (C7 or C10) 75.7 (C6 or C9), 75.6* (C6 or C9), 73.7 (C1), 73.3* (C1), 44.4* (C4), 43.1 (C4), 21.1 (C9), 20.9* (C12).

FTIR (ATR) \(\nu\) (cm\(^{-1}\)): 2958, 1724 (C=O).

HRMS (ESI): \(m/z\) calculated for: C\(_{12}\)H\(_{13}\)N\(_2\)O\(_6\)Cl\(_6\) [M+Na]* 512.8719, found 512.8713.

1-tert-Butyl 2-(2,2,2-trichloroethyl)-3-acetoxy-3,6-dihydropyridazine-1,2-dicarboxylate/2-tert-butyl 1-(2,2,2-trichloroethyl)-3-acetoxy-3,6-dihydropyridazine-1,2-dicarboxylate 203j

Iodobenzene diacetate (487 mg, 1.51 mmol, 1.0 eq) and 1-acetoxy-1,3-butadiene 202a (215 \(\mu\)L, 1.81 mmol, 1.2 eq) were added to a stirred solution of hydrazine 43j (464 mg, 1.51 mmol, 1.0 eq) in CH\(_2\)Cl\(_2\) (4.5 mL) at room temperature under argon. The reaction mixture was stirred for 20 hours, then the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1—3:1) gave the cycloaduct 203j (607 mg, 1.45 mmol, 96%, unable to determine major regioisomer) as a colourless oil. 

\(R_s\) (Hexane-EtOAc, 2:1) = 0.38

\(^1\)H NMR (400 MHz, CDCl\(_3\)); \(\delta\) 6.92-6.85 (br m, 1H, H1), 6.14-6.07 (br m, 1H, H3), 5.94-5.84 (br m, 1H, H2), 4.92-4.44 (br m, 3H, H9 and H4\(_A\)), 3.93-3.88 (br m, 1H, H4\(_B\)), 2.09-2.04 (br m, 3H, H12), 1.50-1.43 (br m, 9H, H7).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)), additional peaks due to complex rate processes denoted by an asterisk; \(\delta\) 169.8* (C10), 169.5* (C10), 169.2 (C10), 154.1 (C5 or C8), 153.8 (C5 or C8), 153.0* (C5 or C8), 152.7* (C5 or C8), 151.6* (C5 or C8), 129.6 (C3), 129.0* (C3), 128.9* (C3), 128.4* (C3), 122.5 (C2), 121.9 (C2), 95.2* (C10), 94.9* (C10), 94.8 (C10), 83.4* (C6), 82.2* (C6), 81.9 (C6), 75.7 (C9), 75.6* (C9), 73.7 (C1), 73.3* (C1), 44.4* (C4), 43.9* (C4), 42.7* (C4), 42.4 (C4), 28.3 (C7), 28.2* (C7), 21.1* (C12), 21.0* (C12), 21.0 (C12).

FTIR (ATR) \(\nu\) (cm\(^{-1}\)): 2980, 1713 (C=O).

HRMS (ESI): \(m/z\) calculated for: C\(_{12}\)H\(_{13}\)N\(_2\)O\(_6\)Cl\(_6\) [M+Na]* 439.0201, found 439.0194.

1-Benzyl 2-(p-tolylsulfonyl)-3-hydroxy-3,6-dihydropyridazine-1-carboxylate/2-benzyl 1-(p-tolylsulfonyl)-3-hydroxy-3,6-dihydropyridazine-1-carboxylate 208l
Iodobenzene diacetate (52 mg, 0.16 mmol, 1.3 eq) was added in one portion to a stirred suspension of hydrazine 43I (42 mg, 0.13 mmol, 1.0 eq) in CH$_2$Cl$_2$ (0.4 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 10 minutes, then evaporated under reduced pressure. 1-Acetoxy-1,3-butadiene 202a (27 µL, 0.23 mmol, 1.8 eq) was then added in one portion to a stirred solution of the residue in methyl tert-butyl ether (0.4 mL) at room temperature under argon. The reaction was stirred for a further 21 hours, then the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1 → 2:1) gave the deacetylated product 208l (22 mg, 0.05 mmol, 39%, unable to determine major regioisomer) as a colourless oil.

$R_f$ (Hexane-EtOAc, 2:1) = 0.17

$^1$H NMR (400 MHz, CDCl$_3$); δ 7.80-7.73 (br m, 2H, H12), 7.39-7.33 (br m, 3H, H9, H10), 7.24-7.21 (br m, 2H, H8), 7.19-7.13 (br m, 2H, H13), 6.07-6.03 (br m, 1H, H3), 5.93-5.87 (br m, 1H, H2), 5.83-5.78 (br m, 1H, H1), 5.05-4.81 (br m, 2H, H6), 4.43-4.37 (m, 1H, H4A), 4.16-4.09 (m, 1H, OH), 3.73-3.66 (br m, 1H, H4B), 2.40-2.38 (br m, 3H, H15).

$^{13}$C NMR (100 MHz, CDCl$_3$), additional peaks due to complex rate processes denoted by an asterisk; δ 154.7 (C5), 145.0 (C14), 135.4 (C7), 133.4 (C11), 129.5 (C12 or C13), 129.5 (C12 or C13), 128.6 (C9), 128.5 (C10), 128.3 (C8), 126.2 (C2 or C3), 126.1 (C2 or C3), 73.4 (C1), 68.5 (C6), 43.4 (C4), 21.8 (C15), 21.8* (C15).

FTIR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3485 (OH), 3032, 1711 (C=O), 1340 (SO$_2$), 1157 (SO$_2$).

HRMS (ESI): $m/z$ calculated for: C$_{19}$H$_{20}$N$_2$O$_5$S [M+Na]$^+$ 411.0985, found 411.0977.

Di-tert-butyl 3-methoxy-3,6-dihydropyridazine-1,2-dicarboxylate 212d
K₂CO₃ (89 mg, 0.64 mmol, 1.1 eq) was added in one portion to a stirred solution of cycloadduct 203d (201 mg, 0.59 mmol, 1.0 eq) in MeOH (1.0 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 20 minutes, filtered through Celite and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1 → 1:1) gave the substituted product 212d (87 mg, 0.28 mmol, 47%) as a colourless oil.

Rf (Hexane-EtOAc, 2:1) = 0.40

¹H NMR (400 MHz, CDCl₃); δ 5.95-5.86 (br m, 1H, H3), 5.84-5.77 (br m, 1H, H2), 5.46-5.25 (br m, 1H, H1), 4.48-4.24 (br m, 1H, H4A), 3.73-3.56 (br m, 1H, H4B), 3.48-3.45 (br m, 3H, H8), 1.48-1.43 (br m, 18H, H7).

¹³C NMR (100 MHz, CDCl₃, additional peaks due to complex rate processes denoted by an asterisk); δ 154.5* (C5), 154.2 (C5), 127.8 (C3), 127.2* (C3), 124.4* (C2), 123.9 (C2), 81.7* (C6), 81.1* (C6), 80.9 (C6), 80.3 (C1), 56.3 (C8), 43.7* (C4), 41.7 (C4), 28.4 (C7), 28.3* (C7), 28.3 (C7).

FTIR (ATR) ν (cm⁻¹): 2976, 2932, 1702 (C=O).

HRMS (APCI): m/z calculated for: C₁₅H₂₆N₂O₅ [M+Na]+ 337.1734, found 337.1719.

**Dimethyl-1,2-dihydropyridazine-1,2-dicarboxylate 9a**

Using general procedure G, a mixture of hydrazine 43a (1.00 g, 6.74 mmol), iodobenzene diacetate (2.20 g, 6.75 mmol) and 1-acetoxy-1,3-butadiene 202a (1.2 mL, 10.1 mmol) in CH₂Cl₂ (2.7 mL) was stirred at room temperature for 17 hours. After being passed through a short silica gel column (eluent: hexane-EtOAc, 2:1→1:1), cycloadduct (1.72 g, 6.66 mmol), Pd(OAc)₂ (15 mg, 0.07 mmol), triphenylphosphine (70 mg, 0.27 mmol) and triethylamine (1.9 mL, 13.3 mmol) in 1,4-dioxane (13 mL) gave the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1) gave 1,2-dihydropyridazine 9a (923 mg, 4.66 mmol, 69%) as a yellow oil, which solidified to a colourless solid on standing.

**Cycloadduct 203a**

Rf (Hexane-EtOAc, 1:1) = 0.21
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1H NMR (400 MHz, CDCl₃); δ 6.88-6.76 (br m, 1H, H1), 6.08-6.05 (br m, 1H, H3), 5.90-5.79 (br m, 1H, H2), 4.61-4.41 (br m, 1H, H4), 3.89-3.71 (br m, 7H, H6, H8 and H4), 2.01 (br s, 3H, H10).

13C NMR (100 MHz, CDCl₃, additional peaks due to complex rate processes denoted by an asterisk); δ 169.5 (C9), 156.1 (C5 or C7), 154.8* (C5 or C7), 154.1 (C5 or C7) 129.1 (C3), 122.5* (C3), 122.0 (C2), 73.8 (C1), 54.0 (C6 or C8), 53.5 (C6 or C8), 43.8* (C4), 42.6 (C4), 21.0* (C10), 20.8 (C10).

FTIR (ATR) v (cm⁻¹): 2957, 1711 (C=O), 1655 (C=O).


1,2-Dihydropyridazine 9a

Diethyl 1,2-dihydropyridazine-1,2-dicarboxylate 9b

Using general procedure F, diethyl azodicarboxylate 8b (1.0 mL, 6.35 mmol) and 1-acetoxy-1,3-butadiene 202a (1.1 mL, 9.53 mmol) in CH₂Cl₂ (1.3 mL) was stirred at room temperature for 9 hours. After being passed through a short silica gel column (eluent: hexane-EtOAc, 5:1→2:1), cycloadduct (1.85 g, 6.44 mmol), Pd(OAc)₂ (14 mg, 0.06 mmol), triphenylphosphine (67 mg, 0.26 mmol) and triethylamine (1.8 mL, 12.7 mmol) in 1,4-dioxane (13 mL) gave the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 9:1→4:1) gave 1,2-dihydropyridazine 9b (1.29 g, 5.72 mmol, 90%) as a colourless solid.

Cycloadduct 203b
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\[ R_f (\text{hexane-EtOAc, 1:1}) = 0.24 \]

\(^1\)H NMR (400 MHz, CDCl\(_3\)); \( \delta 6.90-6.82 \) (br m, 1H, H1), 6.09 (br dd, \( J = 9.5, 3.8 \) Hz, 1H, H3) 5.92-5.83 (br m, 1H, H2), 4.64-4.44 (m, 1H, H4), 4.29-4.17 (m, 4H, H6 and H9), 3.89-3.73 (m, 1H, H4), 2.04 (br s, 3H, H12), 1.29-1.23 (m, 6H, H7 and H10).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\), additional peaks due to complex rate processes denoted by an asterisk); \( \delta 169.5 \) (C11), 155.6 (C5 or C8), 155.4 (C5 or C8), 129.2 (C3), 122.2 (C2), 73.9 (C1), 62.5 (C6 and C9), 42.6 (C4), 20.9 (C12), 14.5 (C7 and C10).

FTIR (ATR) \( \nu \) (cm\(^{-1}\)): 2984, 2937, 1733 (C=O), 1709 (C=O).

HRMS (ESI): \( m/z \) calculated for: C\(_{12}\)H\(_{18}\)N\(_2\)O\(_6\) [M+Na]\(^+\) 309.1057, found 309.1051.

1,2-Dihydropyridazine 9b

\[ R_f (\text{hexane-EtOAc, 1:1}) = 0.51 \]

mp = 56-58 °C

\(^1\)H NMR (400 MHz, 298 K, d\(_6\)-DMSO); \( \delta 6.89-6.65 \) (br m, 2H, H1), 5.89-5.72 (br m, 2H, H2), 4.24-4.09 (br m, 4H, H4), 1.21 (br t, \( J = 7.0 \) Hz, 6H, H5).

\(^1\)H NMR (400 MHz, 348 K, d\(_6\)-DMSO); \( \delta 6.75 \) (br dd, \( J = 5.2, 2.5 \) Hz, 2H, H1), 5.79 (br dd, \( J = 5.2, 2.5 \) Hz, 2H, H2), 4.26-4.14 (m, 4H, H4), 1.24 (t, \( J = 7.1 \) Hz, 6H, H5).

\(^{13}\)C NMR (100 MHz, 298 K, d\(_6\)-DMSO, additional peaks due to complex rate processes denoted by an asterisk); \( \delta 153.2 \) (C3), 127.3 (C1), 113.2 (C2), 111.9 (C2), 62.6 (C4), 14.2 (C5).

\(^{13}\)C NMR (100 MHz, 348 K, d\(_6\)-DMSO); \( \delta 152.6 \) (C3), 127.0 (C1), 112.0 (C2), 62.2 (C4), 13.8 (C5).

FTIR (ATR) \( \nu \) (cm\(^{-1}\)): 3088, 2989, 1754 (C=O), 1715 (C=O).

HRMS (ESI): \( m/z \) calculated for: C\(_{10}\)H\(_{14}\)N\(_2\)O\(_4\) [M+Na]\(^+\) 249.0846, found 249.0847.

Diisopropyl 1,2-dihydropyridazine-1,2-dicarboxylate 9c
Using general procedure F, diisopropyl azodicarboxylate 8c (1.0 mL, 5.08 mmol) and 1-acetoxy-1,3-butadiene 202a (0.9 mL, 7.62 mmol) in CH₂Cl₂ (1.0 mL) was stirred at room temperature for 18 hours. After being passed through a short silica gel column (eluent: hexane-EtOAc, 7:1→3:1), cycloadduct (1.59 g, 5.05 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol), triphenylphosphine (54 mg, 0.21 mmol) and triethylamine (1.4 mL, 10.1 mmol) in 1,4-dioxane (10 mL) gave the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 14:1→7:1) gave 1,2-dihydropyridazine 9c (1.06 g, 4.17 mmol, 82%) as a colourless solid.

**Cycloadduct 203c**

\[ R_f (\text{Hexane-EtOAc, 1:1}) = 0.40 \]

mp = 54-58 °C

\(^1\text{H} \text{NMR} (400 \text{ MHz, CDCl}_3); \delta 6.90-6.83 (br m, 1H, H₁), 6.09-6.05 (br m, 1H, H₃), 5.89-5.82 (br m, 1H, H₂), 4.99-4.94 (m, 2H, H₆ and H₉), 4.62-4.39 (br m, 1H, H₄A), 3.85-3.67 (br m, 1H, H₄B), 2.02 (br s, 3H, H₁₂), 1.25-1.21 (br m, 12H, H₇ and H₁₀).

\(^{13}\text{C} \text{NMR} (100 \text{ MHz, CDCl}_3, \text{additional peaks due to complex rate processes denoted by an asterisk}); \delta 169.5 (C₁₁), 155.1 (C₅ and C₈), 129.1 (C₃), 122.3 (C₂), 73.9 (C₁), 70.9 (C₆ or C₉), 70.0 (C₆ or C₉), 43.7* (C₄), 42.5 (C₄), 22.2* (C₇ or C₁₀), 22.1 (C₇ or C₁₀), 21.0 (C₁₂).

FTIR (ATR) \( \nu (\text{cm}^{-1}) \): 2984, 1731 (C=O), 1698 (C=O).

HRMS (APCI): \( m/z \) calculated for: \( \text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_6[M+Na]-337.1370, \text{found 337.1370}; \text{C}_{12}\text{H}_{19}\text{N}_2\text{O}_5[M-OAc]-255.1339, \text{found 255.1337}; \text{C}_{12}\text{H}_{19}\text{N}_2\text{O}_5[M-\text{CH}_3\text{CO}]-271.1299, \text{found 271.1295} \).

**Alcohol 208c**

\[ R_f (\text{Hexane-EtOAc, 1:1}) = 0.25. \]

mp = 73-76 °C

\(^1\text{H} \text{NMR} (400 \text{ MHz, d₆-DMSO}); \delta 6.31-6.26 (m, 1H, OH), 5.94-5.88 (br m, 1H, H₃), 5.84-5.79 (br m, 1H, H₂), 5.68-5.63 (br m, 1H, H₁), 4.88-4.76 (m, 2H, H₆ and H₉), 4.37-4.20 (br m, 1H, H₄A), 3.72-3.55 (br m, 1H, H₄B), 1.23-1.12 (br m, 12H, H₇ and H₁₀).

\(^{13}\text{C} \text{NMR} (100 \text{ MHz, d₆-DMSO, additional peaks due to complex rate processes denoted by an asterisk}); \delta 154.8 (C₅ or C₈), 153.6* (C₅ or C₈), 153.2* (C₅ or C₈), 126.2* (C₂), 126.1 (C₂),
125.8 (C3) 125.5* (C3), 72.8 (C1), 69.2* (C6 or C9), 68.9* (C6 or C9), 68.8 (C6 or C9), 42.1 (C4), 22.0* (C7 or C10). 21.8 (C7 or C10), 21.7 (C7 or C10), 21.6* (C7 or C10).

FTIR (ATR) ν (cm⁻¹): 3383 (OH), 2984, 2928, 1675 (C=O).


1,2-Dihydropyridazine 9c (see appendix for crystal structure)

\[ \text{Rf (Hexane-EtOAc, 2:1) = 0.45} \]

\[ \text{mp = 93-94 °C} \]

\[ \text{1H NMR (400 MHz, d₆-DMSO): } \delta 6.86-6.64 (br m, 2H, H1), 5.90-5.67 (br m, 2H, H2), 4.89 (br sept, J = 6.1 Hz, 2H, H4), 1.22 (br d, J = 6.1 Hz, 12H, H5). \]

\[ \text{1H NMR (400 MHz, 348 K, d₆-DMSO): } \delta 6.74 (br dd, J = 5.2, 2.4 Hz, 2H, H1), 5.77 (br dd, J = 5.2, 2.4 Hz, 2H, H2), 4.91 (sept, J = 6.2 Hz, 2H, H4), 1.25 (d, J = 6.2 Hz, 12H, H5). \]

\[ \text{13C NMR (100 MHz, d₆-DMSO, additional peaks due to complex rate processes denoted by an asterisk): } \delta 152.6* (C3), 151.9 (C3), 127.4 (C1), 113.0* (C2), 111.7 (C2), 70.5 (C4), 21.6 (C5). \]

\[ \text{13C NMR (100 MHz, 348 K, d₆-DMSO): } \delta 152.1 (C3), 127.0 (C1), 111.8 (C2), 70.1 (C4), 21.2 (C5). \]

FTIR (ATR) ν (cm⁻¹): 3090, 2986, 1748 (C=O), 1711 (C=O).

HRMS (APCI): m/z calculated for: C₁₂H₁₈N₂O₄ [M+H]⁺ 255.1339, found 255.1329.

Rearranged Allylic Acetate 209c

\[ \text{Rf (Hexane-EtOAc, 2:1) = 0.34} \]

\[ \text{1H NMR (400 MHz, d₆-DMSO): } \delta 7.23-7.19 (br m, 1H, H1), 5.22-5.15 (br m, 1H, H2), 5.02-4.99 (br m, 1H, H3), 4.93-4.78 (m, 2H, H6), 4.45-4.29 (br m, 1H, H4a), 3.47-3.26 (br m, 1H, H4a), 2.03-1.91 (m, 3H, H9), 1.24-1.17 (br m, 12H, H7). \]

\[ \text{13C NMR (100 MHz, d₆-DMSO, additional peaks due to complex rate processes denoted by an asterisk): } \delta 169.8* (C8), 169.7 (C8), 155.0 (C5), 154.4 (C5), 128.7 (C1), 102.7 (C2), 70.7 (C6), 70.5* (C6), 70.2 (C6), 70.1* (C6), 63.4 (C3), 48.5 (C4), 47.0* (C4), 21.6 (C7), 21.5* (C7), 21.4* (C7), 20.7 (C9), 20.6* (C9). \]

FTIR (ATR) ν (cm⁻¹): 2984, 1715 (C=O), 1646 (C=O).

HRMS (ESI): m/z calculated for: C₁₄H₂₂N₂O₆ [M+Na]⁺ 337.1357, found 337.1370.
Di-tert-butyl 1,2-dihydropyridazine-1,2-dicarboxylate 9d

Using general procedure F, di-tert-butyl azodicarboxylate 8d (1.00 g, 4.35 mmol) and 1-acetoxy-1,3-butadiene 202a (0.8 mL, 6.53 mmol) in CH₂Cl₂ (1.7 mL) was stirred at 40 °C for 2 days. After the addition of hexane (20 mL), filtration and drying, cycloadduct (1.45 g, 4.23 mmol), Pd(OAc)₂ (10 mg, 0.04 mmol), triphenylphosphine (44 mg, 0.17 mmol) and triethylamine (1.2 mL, 8.5 mmol) in 1,4-dioxane (8.5 mL) gave the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 19:1→9:1) gave 1,2-dihydropyridazine 9d (912 mg, 3.23 mmol, 74%) as a colourless solid.

5 gram scale: Using general procedure F, di-tert-butyl azodicarboxylate 8d (5.01 g, 21.7 mmol) and 1-acetoxy-1,3-butadiene 202a (3.9 mL, 32.6 mmol) in CH₂Cl₂ (4.4 mL) was stirred at 40 °C for 2 days. After the addition of hexane (40 mL), filtration and drying, cycloadduct (6.90 g, 20.2 mmol), Pd(OAc)₂ (44 mg, 0.20 mmol), triphenylphosphine (216 mg, 0.82 mmol) and triethylamine (5.6 mL, 40.2 mmol) in 1,4-dioxane (40 mL) gave the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 19:1→14:1→9:1) gave 1,2-dihydropyridazine 9d (4.40 g, 15.6 mmol, 72%) as a colourless solid.

10 gram scale: Using general procedure F, di-tert-butyl azodicarboxylate 8d (9.75 g, 42.3 mmol) and 1-acetoxy-1,3-butadiene 202a (7.5 mL, 63.5 mmol) in CH₂Cl₂ (8.5 mL) was stirred at 40 °C for 2 days. After the addition of hexane (80 mL), filtration and drying, cycloadduct (14.1 g, 41.2 mmol), Pd(OAc)₂ (93 mg, 0.41 mmol), triphenylphosphine (432 mg, 1.65 mmol) and triethylamine (11 mL, 82.4 mmol) in 1,4-dioxane (82 mL) gave the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 19:1→14:1→9:1) gave 1,2-dihydropyridazine 9d (8.97 g, 31.8 mmol, 75%) as a colourless solid.

Cycloadduct 203d

\[
R_f (\text{Hexane-EtOAc, } 2:1) = 0.36
\]
\[
\text{mp = 119-121 °C}
\]
\[
^1H \text{ NMR (400 MHz, CDCl}_3); \delta 6.87-6.72 \text{ (br m, 1H, H1), 6.08-6.00 (br m, 1H, H3), 5.89-5.75 (br m, 1H, H2), 4.57-4.34 (br m, 1H, H}_{4A}, 3.85-3.60 (br m, 1H, H}_{4B}, 2.04 (br s, 3H, H12), 1.46-1.43 (br m, 18H, H7 and H10).}
\]

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13C NMR (100 MHz, CDCl3, additional peaks due to complex rate processes denoted by an asterisk); δ 169.9* (C11), 169.4 (C11), 154.5 (C5 or C8), 152.5 (C5 or C8), 129.8* (C3), 129.3 (C3), 122.4 (C2), 82.1* (C6 or C9), 81.4 (C6 or C9), 81.0 (C6 or C9), 74.2* (C1), 73.5 (C1), 43.9* (C4), 42.1 (C4), 28.3 (C7 or C10), 28.2 (C7 or C10), 21.0 (C12).

FTIR (ATR) ν (cm⁻¹): 2980, 1733 (C=O), 1698 (C=O).


1,2-Dihydropyridazine 9d

Rf (Hexane-EtOAc, 1:1) = 0.64
mp = 94-95 °C

1H NMR (400 MHz, 298 K, d6-DMSO); δ 6.81-6.60 (br m, 2H, H1), 5.84-5.62 (br m, 2H, H2), 1.44 (s, 18H, H5).

1H NMR (400 MHz, 348 K, d6-DMSO); δ 6.69 (br dd, J = 5.3, 2.3 Hz, 2H, H1), 5.71 (br dd, J = 5.3, 2.3 Hz, 2H, H2), 1.46 (s, 18H, H5).

13C NMR (100 MHz, CDCl3, d6-DMSO); δ 151.8* (C3), 150.8 (C3), 127.6 (C1), 111.9* (C2), 111.6 (C2), 111.1* (C2), 81.9 (C4), 27.6 (C5).

13C NMR (100 MHz, CDCl3, d6-DMSO); δ 151.1 (C3), 127.2 (C1), 111.3 (C2), 81.5 (C4), 27.4 (C5).

FTIR (ATR) ν (cm⁻¹): 2974, 1733 (C=O), 1718 (C=O).

HRMS (ESI): m/z calculated for: C14H22N2O4[M+Na]⁺ 305.1472, found 305.1469.

Dibenzy1-1,2-dihydropyridazine-1,2-dicarboxylate 9e

Using general procedure F, dibenzyl azodicarboxylate 8e (1.24 g, 4.00 mmol) and 1-acetoxy-1,3-butadiene 202a (0.7 mL, 6.00 mmol) in CH2Cl2 (0.8 mL) was stirred at room temperature for 2 hours. After being passed through a short silica gel column (eluent: hexane-EtOAc, 7:1→3:1), cycloadduct (1.53 g, 3.72 mmol), Pd(OAc)2 (9 mg, 0.04 mmol), triphenylphosphine (42 mg, 0.16 mmol) and triethylamine (1.1 mL, 7.89 mmol) in 1,4-dioxane (8 mL) gave the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc,
9:1→6:1) gave 1,2-dihydropyridazine 9e (1.06 g, 3.02 mmol, 75%) as a highly viscous orange oil.

Cycloadduct 203e

\[
\begin{align*}
\text{O} & \quad \text{N} \\
2 & \quad 3 \\
4 & \quad 5 \\
6 & \quad 7 \\
8 & \quad 9 \\
10 & \quad 11 \\
12 & \quad 13 \\
14 & \quad 15 \\
16 & \quad 17 \\
18 & \quad 19
\end{align*}
\]

\( R_f (\text{Hexane-EtOAc, 2:1}) = 0.22 \)

\(^1\)H NMR (400 MHz, CDCl\(_3\)); \( \delta \) 7.34-7.29 (br m, 10H, H8, H9, H10, H14, H15 and H16), 6.94-6.87 (br m, 1H, H1), 6.10 (br dd, \( J = 9.9, 4.1 \) Hz, 1H, H3), 5.92-5.84 (br m, 1H, H2), 5.25-5.01 (br m, 4H, H6 and H12), 4.68-4.48 (m, 1H, H4\(_A\)), 3.98-3.69 (br m, 1H, H4\(_B\)), 2.06-1.76 (br m, 3H, H18).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\), additional peaks due to complex rate processes denoted by an asterisk); \( \delta \) 169.6 (C7), 155.4 (C5 or C11), 154.4 (C5 or C11), 153.6* (C5 or C11), 136.0 (C7 or C13), 135.6 (C7 or C13), 129.1 (C3), 128.7 (C8, C9, C10, C14, C15 or C16), 128.6 (C8, C9, C10, C14, C15 or C16), 128.5 (C8, C9, C10, C14, C15 or C16), 128.2 (C8, C9, C10, C14, C15 or C16), 127.7 (C8, C9, C10, C14, C15 or C16), 122.2 (C2), 73.8 (C1), 68.6* (C6 or C12), 68.4* (C6 or C12), 68.0 (C6 or C12), 44.1* (C4), 42.9 (C4), 21.0* (C18), 20.6 (C18).

FTIR (ATR) \( \nu \) (cm\(^{-1}\)): 3032, 1709 (C=O).

HRMS (ESI): \( m/z \) calculated for: C\(_{22}\)H\(_{22}\)N\(_2\)O\(_6\) [M+Na]\(^+\) 433.1370, found 433.1349.

1,2-Dihydropyridazine 9e

\[
\begin{align*}
\text{O} & \quad \text{N} \\
2 & \quad 3 \\
4 & \quad 5 \\
6 & \quad 7 \\
7 & \quad 8 \\
9 & \quad 10 \\
11 & \quad 12
\end{align*}
\]

\( R_f (\text{Hexane-EtOAc, 2:1}) = 0.37 \)

\(^1\)H NMR (400 MHz, 298 K, \( \text{d}_6\)-DMSO); \( \delta \) 7.43-7.29 (br m, 10H, H6, H7, H8), 6.90-6.75 (br m, 2H, H1), 5.92-5.74 (br m, 2H, H2), 5.31-5.16 (br m, 4H, H4).

\(^1\)H NMR (400 MHz, 348 K, \( \text{d}_6\)-DMSO); \( \delta \) 7.39-7.06 (br m, 10H, H6, H7, H8), 6.82 (dd, \( J = 5.2, 2.4 \) Hz, 2H, H1), 5.83 (dd, \( J = 5.2, 2.4 \) Hz, 2H, H2), 5.26-5.19 (br m, 4H, H4).

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\[^{13}\text{C} \text{NMR} \text{ (100 MHz, 298 K, d6-DMSO, additional peaks due to complex rate processes denoted by an asterisk)}; \delta 153.2 \text{ (C3)}, 152.4^* \text{ (C3)}, 135.6 \text{ (C5)}, 128.5 \text{ (C6, C7 or C8)}, 128.2 \text{ (C6, C7 or C8)}, 127.7 \text{ (C6,C7, C8 or C1)}, 127.2 \text{ (C6, C7, C8 or C1)}, 113.4^* \text{ (C2)}, 112.2 \text{ (C2)}, 67.8 \text{ (C4)}.\]

\[^{13}\text{C} \text{ NMR} \text{ (100 MHz, 348 K, d6-DMSO);} \delta 152.6 \text{ (C3)}, 135.3 \text{ (C5)}, 128.0 \text{ (C6, C7 or C8)}, 127.7 \text{ (C6,C7, C8 or C1)}, 127.2 \text{ (C6, C7, C8 or C1)}, 112.3 \text{ (C2)}, 67.4 \text{ (C4)}.\]

FTIR (ATR) \( \nu \)(cm\(^{-1}\)): 3032, 2954, 1716 (C=O).

HRMS (ESI): \( m/\text{z} \) calculated for: \( \text{C}_{20}\text{H}_{18}\text{N}_{2}\text{O}_{4} [\text{M+Na}]^+ \) 373.1159, found 373.1148.

1-tert-Butyl-2-methyl-1,2-dihydropyridazine-1,2-dicarboxylate 9f

Using general procedure G, a mixture of hydrazine 43f (1.02 g, 5.27 mmol), iodobenzene diacetate (1.78 g, 5.54 mmol) and 1-acetoxy-1,3-butadiene 202a (0.9 mL, 7.89 mmol) in \( \text{CH}_2\text{Cl}_2 \) (5.3 mL) was stirred at 40 °C for 24 hours. After being passed through a short silica gel column (eluent: hexane-\text{EtOAc}, 7:1→2:1), cycloadduct (1.47 g, 4.90 mmol), Pd(OAc)\(_2\) (24 mg, 0.11 mmol), triphenylphosphine (110 mg, 0.42 mmol) and triethylamine (1.5 mL, 10.5 mmol) in 1,4-dioxane (10.5 mL) gave the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-\text{EtOAc}, 7:1→5:1) gave 1,2-dihydropyridazine 9f (577 mg, 2.40 mmol, 46%) as an off-white solid.

Cycloadduct 203f

Note: Likely a mixture of both compounds in addition to the already complex NMR spectra for these compounds

\( R_f \) (Hexane-\text{EtOAc}, 2:1) = 0.24

\[^{1}\text{H} \text{ NMR} \text{ (400 MHz, CDCl}_3\text{);} \delta 6.88-6.75 \text{ (br m, 1H, H1)}, 6.11-6.02 \text{ (br m, 1H, H3)}, 5.92-5.81 \text{ (br m, 1H, H2)}, 4.61-4.38 \text{ (br m, 1H, H4A)}, 3.81-3.66 \text{ (m, 4H, H4B, H9)}, 2.08-2.00 \text{ (m, 3H, H11)}, 1.48-1.44 \text{ (br m, 9H, H7)}.\]

\[^{13}\text{C} \text{ NMR} \text{ (100 MHz, CDCl}_3\text{, additional peaks due to regioisomers and complex rate processes denoted by an asterisk)}; \delta 169.6^* \text{ (C10)}, 169.6 \text{ (C10)}, 154.3 \text{ (C5, C8)}, 129.4 \text{ (C3)}, 122.1 \text{ (C2)}, 81.9^* \text{ (C6)}, 81.4 \text{ (C6)}, 73.7 \text{ (C1)}, 53.8 \text{ (C8)}, 53.4^* \text{ (C8)}, 42.6^* \text{ (C4)}, 42.2 \text{ (C4)}, 28.3 \text{ (C7)}, 28.2^* \text{ (C7)}, 21.0 \text{ (C11)}, 21.0^* \text{ (C11)}, 20.6^* \text{ (C11)}.\]
FTIR (ATR) ν (cm⁻¹): 2980, 1709 (C=O).
HRMS (ESI): m/z calculated for: C₁₃H₂₀N₂O₆ [M+Na]⁺ 323.1214, found 323.1203.

1,2-Dihydropyridazine 9f

Rf (Hexane-EtOAc, 2:1) = 0.37
mp = 70-72 °C

¹H NMR (400 MHz, 298 K, d₆-DMSO); δ 6.84-6.60 (br m, 2H, H₁, H₄), 5.87-5.64 (br m, 2H, H₂, H₃), 3.73 (br s, 3H, H₉), 1.43 (br s, 9H, H₇).
¹H NMR (400 MHz, 348 K, d₆-DMSO); δ 6.74-6.70 (br m, 2H, H₁, H₄), 5.78-5.72 (br m, 2H, H), 3.75 (s, 3H, H₉), 1.45 (s, 9H, H₇).

¹³C NMR (100 MHz, 298 K, d₆-DMSO, additional peaks due to complex rate processes denoted by an asterisk); δ 153.7 (C₅ or C₈), 152.8* (C₅ or C₈), 151.8 (C₅ or C₈), 127.8 (C₁ or C₄), 127.0 (C₁ or C₄), 113.0* (C₂ or C₃), 112.1 (C₂ or C₃), 111.1 (C₂ or C₃), 82.3 (C₆), 53.5 (C₉), 27.6 (C₇).
¹³C NMR (100 MHz, 348 K, d₆-DMSO); δ 153.0 (C₈), 151.2 (C₅), 127.4 (C₁ or C₄), 126.8 (C₁ or C₄), 112.0 (C₂ or C₃), 111.4 (C₂ or C₃), 81.9 (C₆), 52.9 (C₉), 27.4 (C₇).

Rearranged Allylic Acetate 209f

Note: Likely a mixture of both compounds in addition to the already complex NMR spectra for these compounds

Rf (Hexane-EtOAc, 2:1) = 0.29
¹H NMR (400 MHz, 348 K, d₆-DMSO); δ 7.22-7.14 (br m, 1H, H₁), 5.21-5.12 (br m, 1H H₂), 5.06-5.00 (br m, 1H, H₃), 4.52-4.26 (br m, 1H, H₄a), 3.75-3.71 (br m, 3H, H₉), 3.47-3.22 (br m, 1H, H₄e), 2.04-1.90 (br m, 3H, H₁₁), 1.46-1.43 (br m, 9H, H₇).
¹³C NMR (100 MHz, 348 K, d₆-DMSO, additional peaks due to regioisomers and complex rate processes denoted by an asterisk); δ 169.3 (C₁₀), 155.4 (C₅ or C₈), 151.4 (C₅ or C₈), 128.8 (C₁), 128.3* (C₁), 102.8 (C₂), 101.9* (C₂), 82.0 (C₆), 81.0* (C₆), 63.2 (C₃), 63.1* (C₃), 53.1 (C₉), 52.9* (C₉), 48.5 (C₄, weak), 27.4 (C₇), 27.3* (C₇), 20.3* (C₁₁), 20.2 (C₁₁).
FTIR (ATR) \( \nu \) (cm\(^{-1}\)): 2958, 1718 (C=O), 1648 (C=O).

HRMS (ESI): \( m/z \) calculated for: \( \text{C}_{13}\text{H}_{20}\text{N}_{2}\text{O}_{6} [M+Na]^+ \) 323.1214, found 323.1205.

\textbf{1-Benzyl-2-tert-butyl-1,2-dihydropyridazine-1,2-dicarboxylate 9g}

Using general procedure X, a mixture of hydrazine \( 43g \) (1.01 g, 3.77 mmol), iodobenzene diacetate (1.27 g, 3.94 mmol) and 1-acetoxy-1,3-butadiene \( 202a \) (0.67 mL, 5.63 mmol) in \( \text{CH}_2\text{Cl}_2 \) (1.5 mL) was stirred at room temperature for 17 hours. After being passed through a short silica gel column (eluent: hexane-EtOAc, 7:1→3:1), cycloadduct (1.23 g, 3.27 mmol), \( \text{Pd(OAc)}_2 \) (15 mg, 0.07 mmol), triphenylphosphine (68 mg, 0.26 mmol) and triethylamine (0.9 mL, 6.54 mmol) in 1,4-dioxane (6.5 mL) gave the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 14:1→7:1) gave 1,2-dihydropyridazine \( 9g \) (658 mg, 2.08 mmol, 55%) as highly viscous orange oil.

\textbf{Cycloadduct 203g}

\( \delta \) 7.36-7.28 (br m, 10H, H\( _{11}, \text{H}_{12}, \text{H}_{13} \)), 6.92-6.80 (br m, 1H, H\( _1 \)), 6.09-6.02 (br m, 1H, H\( _3 \)), 5.93-5.79 (br m, 1H, H\( _2 \)), 5.28-5.11 (br m, 2H, H\( _9 \)), 4.63-4.38 (m, 1H, H\( _4A \)), 3.91-3.66 (br m, 1H, H\( _4B \)), 2.06-1.79 (br m, 3H, H\( _{15} \)), 1.47-1.34 (br m, 9H, H\( _7 \)).

\( ^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\), additional peaks due to regioisomers and complex rate processes denoted by an asterisk): \( \delta \) 169.6 (C\( _{14} \)), 169.4* (C\( _{14} \)), 155.4* (C\( _5 \) or C\( _8 \)), 154.4 (C\( _5 \) or C\( _8 \)), 136.1* (C\( _{10} \)), 135.7 (C\( _{10} \)), 129.4 (C\( _3 \)), 128.6 (C\( _{11}, \text{C}_{12} \) or C\( _{13} \)), 128.5 (C\( _{11}, \text{C}_{12} \) or C\( _{13} \)), 128.4* (C\( _{11}, \text{C}_{12} \) or C\( _{13} \)), 128.2* (C\( _{11}, \text{C}_{12} \) or C\( _{13} \)), 127.7 (C\( _{11}, \text{C}_{12} \) or C\( _{13} \)), 122.1 (C\( _2 \)), 81.4 (C\( _6 \)), 73.8 (C\( _1 \)), 68.3 (C\( _9 \)), 67.9* (C\( _9 \)), 42.7 (C\( _4 \)), 42.3* (C\( _4 \)), 28.1 (C\( _7 \)), 21.0 (C\( _{15} \)), 20.7* (C\( _{15} \)).
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FTIR (ATR) \( \nu \) (cm\(^{-1}\)): 2978, 1735 (C=O), 1707 (C=O).

HRMS (ESI): \( m/z \) calculated for: C\(_{19}\)H\(_{24}\)N\(_2\)O\(_6\) [M+Na]\(^+\) 399.1527, found 399.1516.

1,2-Dihydropyridazine 9g

\[ \text{Rf (Hexane-EtOAc, 2:1) = 0.45} \]

\(^1\)H NMR (400 MHz, 298 K, \( d_6 \)-DMSO); \( \delta \) 7.43-7.27 (br m, 5H, H\(_{11}\), H\(_{12}\), H\(_{13}\)), 6.86-6.68 (br m, 2H, H\(_1\), H\(_4\)), 5.89-5.67 (br m, 2H, H\(_2\), H\(_3\)), 5.37-5.04 (br m, 2H, H\(_9\)), 1.50-1.19 (br s, 9H, H\(_7\)).

\(^1\)C NMR (100 MHz, 298 K, \( d_6 \)-DMSO, additional peaks due to complex rate processes denoted by an asterisk); \( \delta \) 153.2 (C\(_5\) or C\(_8\)), 152.3 (C\(_5\) or C\(_8\)), 135.7 (C\(_10\)), 128.4 (C\(_{11}\), C\(_{12}\) or C\(_{13}\)), 128.2 (C\(_{11}\), C\(_{12}\) or C\(_{13}\)), 127.8 (C\(_{11}\), C\(_{12}\) or C\(_{13}\)), 127.4 (C\(_1\) or C\(_4\)), 126.9 (C\(_1\) or C\(_4\)), 113.1* (C\(_2\) or C\(_3\)), 112.3 (C\(_2\) or C\(_3\)), 111.2* (C\(_2\) or C\(_3\)), 82.4 (C\(_6\)), 67.5 (C\(_9\)), 27.6 (C\(_7\)).

\(^1\)C NMR (100 MHz, 348 K, \( d_6 \)-DMSO); \( \delta \) 152.5 (C\(_8\)), 151.3 (C\(_5\)), 135.4 (C\(_10\)), 128.0 (C\(_{11}\), C\(_{12}\) or C\(_{13}\)), 127.7 (C\(_{11}\), C\(_{12}\) or C\(_{13}\)), 127.5 (C\(_1\) or C\(_4\)), 127.3 (C\(_{11}\), C\(_{12}\) or C\(_{13}\)), 126.7 (C\(_1\) or C\(_4\)), 112.2 (C\(_2\) or C\(_3\)), 111.5 (C\(_2\) or C\(_3\)), 82.0 (C\(_6\)), 67.2 (C\(_9\)), 27.3 (C\(_7\)).

FTIR (ATR) \( \nu \) (cm\(^{-1}\)): 2978, 1713 (C=O).

HRMS (ESI): \( m/z \) calculated for: C\(_{17}\)H\(_{20}\)N\(_2\)O\(_4\) [M+Na]\(^+\) 339.1315, found 339.1316.

Rearranged Allylic Acetate 209g

\[ \text{Rf (Hexane-EtOAc, 2:1) = 0.34} \]

\(^1\)H NMR (400 MHz, 348 K, \( d_6 \)-DMSO); \( \delta \) 7.39-7.18 (br m, 6H, H\(_1\), H\(_{11}\), H\(_{12}\), H\(_{13}\)), 5.27-5.13 (br m, 3H, H\(_2\), H\(_9\)), 5.05-5.01 (br m, 1H, H\(_3\)), 4.53-4.33 (br m, 1H, H\(_4\)\(_A\)), 3.54-3.23 (br m, 1H, H\(_4\)\(_B\)), 2.04-1.84 (br m, 3H, H\(_{15}\)), 1.48-1.27 (br m, 9H, H\(_7\)).

Note: Likely a mixture of both compounds in addition to the already complex NMR spectra for these compounds

\[ \text{Rf (Hexane-EtOAc, 2:1) = 0.34} \]

\(^1\)H NMR (400 MHz, 348 K, \( d_6 \)-DMSO); \( \delta \) 7.39-7.18 (br m, 6H, H\(_1\), H\(_{11}\), H\(_{12}\), H\(_{13}\)), 5.27-5.13 (br m, 3H, H\(_2\), H\(_9\)), 5.05-5.01 (br m, 1H, H\(_3\)), 4.53-4.33 (br m, 1H, H\(_4\)\(_A\)), 3.54-3.23 (br m, 1H, H\(_4\)\(_B\)), 2.04-1.84 (br m, 3H, H\(_{15}\)), 1.48-1.27 (br m, 9H, H\(_7\)).
13C NMR (100 MHz, 348 K, d6-DMSO, additional peaks due to regioisomers and complex rate processes denoted by an asterisk, only one C5, C8 peaks and no C4 peak – spectrum still too broad); δ 169.2 (C14), 150.8 (C5 or C8), 135.6* (C10), 135.3 (C10), 128.8 (C1), 128.0 (C11, C12 or C13), 127.8 (C11, C12 or C13), 127.6 (C11, C12 or C13), 127.2 (C11, C12 or C13), 103.1 (C2), 82.1 (C6), 81.1* (C6), 67.4 (C9), 67.2* (C9), 63.1 (C3), 27.3 (C7), 20.3 (C15), 20.2* (C15).

FTIR (ATR) ν (cm⁻¹): 2976, 1716 (C=O), 1648 (C=O).


2-Phenyl-[1,2,4]triazolo[1,2-a]pyridazine-1,3-dione 9h

Using general procedure G, a mixture of 4-phenyl urazole 43h (1.03 g, 5.82 mmol), iodobenzene diacetate (1.88 g, 5.85 mmol) and 1-acetoxy-1,3-butadiene 202a (1.0 mL, 8.46 mmol) in CH₂Cl₂ (10 mL) was stirred at room temperature for 1 hour. After the addition of hexane (20 mL), filtration and drying, cycloadduct (1.64 g, 5.69 mmol), Pd(OAc)₂ (13 mg, 0.07 mmol), triphenylphosphine (60 mg, 0.23 mmol) and triethylamine (1.6 mL, 11.4 mmol) in 1,4-dioxane (11 mL) gave the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 1:1) gave 1,2-dihydropyridazine 9h (957 mg, 4.21 mmol, 72%) as a yellow solid. The spectroscopic data for 9h are consistent with those reported previously.⁴

Cycloadduct 203h

Rₜ (Hexane-EtOAc, 1:1) = 0.23
mp = 130-132 °C

1H NMR (400 MHz, CDCl₃); δ 7.55-7.45 (m, 4H, H7, H8), 7.41-7.37 (m, 1H, H9), 6.82-6.81 (m, 1H, H1), 6.26-6.22 (m, 1H, H3), 6.16-6.12 (m, 1H, H2), 4.52 (ddd, J = 17.2, 4.6, 1.7, 1H, H4A), 4.07-4.02 (m, 1H, H4B), 2.08 (s, 3H, H11).

13C NMR (100 MHz, CDCl₃); δ 169.7 (C10), 152.5 (C5 or C6), 150.8 (C5 or C6), 130.9 (C7), 129.3 (C9), 128.5 (C10), 126.4 (C3), 125.4 (C8), 121.1 (C2), 72.5 (C1), 43.7 (C4), 20.7 (C11).

FTIR (ATR) ν (cm⁻¹): 3014, 1785 (C=O), 1722 (C=O).

HRMS (ESI): m/z calculated for: C12H10N3O2 [M-OAc]+ 228.0768, found 228.0775.

1,2-Dihydropyridazine 9h

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\[
\begin{array}{c}
\text{H NMR (400 MHz, CDCl}_3\text{); } \delta 7.54-7.38 \text{ (br m, 5H, H5, H6, H7), 6.88 (br dd, } J = 6.1, 2.7 \text{ Hz, 2H, H1), 5.34 (br dd, } J = 6.1, 2.7 \text{ Hz, 2H, H2).}
\end{array}
\]

\[
\begin{array}{c}
\text{13C NMR (100 MHz, CDCl}_3\text{); } \delta 142.7 \text{ (C3), 131.0 (C4), 129.4 (C5), 128.7 (C7), 125.8 (C6), 120.9 (C1), 105.2 (C2).}
\end{array}
\]

Di-tert-butyl 4-methylidene-3,4-dihydropyridazine-1,2-dicarboxylate 216

Using general procedure F, di-tert-butyl azodicarboxylate 8d (1.00 g, 4.35 mmol) and 1-acetoxy-3-methyl-1,3-butadiene 202a (0.82 g, 6.51 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (0.9 mL) was stirred at 40 °C for 31 hours. After the addition of hexane (20 mL), filtration and drying, cycloadduct (1.01 g, 2.83 mmol), Pd(OAc\textsubscript{2}) (6 mg, 0.03 mmol), triphenylphosphine (29 mg, 0.11 mmol) and triethylamine (0.8 mL, 5.74 mmol) in 1,4-dioxane (5.7 mL) gave the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 14:1→9:1→7:1) gave diene 216 (506 mg, 1.71 mmol, 39%) as a colourless solid.

Cycloadduct 215

\[
\begin{array}{c}
R_f \text{(Hexane-EtOAc, 2:1) } = 0.35
\end{array}
\]

\[
\begin{array}{c}
\text{1H NMR (400 MHz, d}_6\text{-DMSO); } \delta 6.69-6.62 \text{ (m, 1H, H1), 5.62-5.54 (m, 1H, H2), 4.27-4.09 (m, 1H, H4A), 3.72-3.53 (m, 1H, H4B), 2.01 (br s, 3H, H13), 1.73 (br s, 3H, H5), 1.46-1.35 (m, 18H, H8 and H11).}
\end{array}
\]

\[
\begin{array}{c}
\text{13C NMR (100 MHz, d}_6\text{-DMSO, additional peaks due to complex rate processes denoted by an asterisk); } \delta 168.8 \text{ (C12), 153.5 (C6 or C9), 151.6 (C6 or C9), 138.1 (C3), 116.3 (C2), 81.3 (C7 or C10), 80.7^* (C7 or C10), 80.0 (C7 or C10), 73.3^* (C1), 72.8 (C1), 46.9^* (C4), 45.1 (C4), 28.0^* (C8 or C11), 28.0^* (C8 or C11), 27.7 (C8 or C11), 27.7 (C8 or C11), 20.7 (C13), 19.2 (C5).}
\end{array}
\]

FTIR (ATR) \nu \text{ (cm}^{-1}) \text{): 2978, 2933, 1733 (C=O), 1698 (C=O).}

HRMS (ESI): m/z calculated for: C\textsubscript{17}H\textsubscript{28}N\textsubscript{2}O\textsubscript{6} [M+Na]\textsuperscript{+} 379.1840, found 379.1825.

Diene 216
Chapter 6: Experimental

$R_f$ (Hexane-EtOAc, 7:1) = 0.32

$^1$H NMR (400 MHz, 348 K, $d_6$-DMSO); $\delta$ 6.98 (br d, $J = 8.0$ Hz, 1H, H1), 5.63 (br d, $J = 8.0$ Hz, 1H, H2), 4.91-4.88 (br m, 1H, H5A), 4.77-4.74 (br m, 1H, H5B), 4.57 (br d, $J = 15.3$ Hz, 1H, H4A), 3.74 (br d, $J = 15.3$ Hz, 1H, H4B), 1.47-1.39 (br m, 18H, H8 and H11).

$^{13}$C NMR (100 MHz, 348 K, $d_6$-DMSO); $\delta$ 154.3 (C9), 149.4 (C6), 134.1 (C3), 125.4 (C1), 108.8 (C5), 107.9 (C2), 81.4 (C7 or C10), 81.0 (C7 or C10), 49.3 (C4), 27.4 (C8 or C11), 27.3 (C8 or C11).

FTIR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2978, 2933, 1717 (C=O).

HRMS (APCI): m/z calculated for: C$_{15}$H$_{24}$N$_2$O$_4$ [M+Na]$^+$ 319.1628, found 319.1613.

Di-tert-butyl 4-oxo-3,4-dihydropyridazine-1,2-dicarboxylate 218

Using general procedure H, di-tert-butyl azodicarboxylate 8d (52 mg, 0.23 mmol, 1.0 eq) and Danishefsky’s diene 217 (106 µL, 0.54 mmol, 2.4 eq) in CH$_2$Cl$_2$ (0.5 mL) gave the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 9:1→7:1) gave enone 218 (60 mg, 0.20 mmol, 89%) as a colourless solid.

$R_f$ (Hexane-EtOAc, 2:1) = 0.33

mp = 84-86 ºC

$^1$H NMR (400 MHz, 348 K, $d_6$-DMSO); $\delta$ 8.11 (br d, $J = 8.6$ Hz, 1H, H1), 5.40 (br d, $J = 8.6$ Hz, 1H, H2), 4.41-3.95 (br m, 2H, H4A and H4B), 1.51 (s, 9H, H7 or H9), 1.42 (s, 9H, H7 or H9).

$^{13}$C NMR (100 MHz, 348 K, $d_6$-DMSO); $\delta$ 188.0 (C3), 154.1 (C5 or C8), 148.3 (C5 or C8), 141.8 (C1), 105.9 (C2), 83.6 (C6 or C9), 82.6 (C6 or C9), 53.2 (C4), 27.3 (C7 or C10), 27.2 (C7 or C10).

FTIR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3071, 2983, 2935, 1717 (C=O), 1670 (C=O).

HRMS (ESI and APCI): Target mass not found.
**Di-tert-butyl 3-methoxy-5-oxo-1,2-diazinane-1,2-dicarboxylate 219**

\[
\begin{align*}
\text{Rf (Hexane-EtOAc, 2:1) } &= 0.39 \\
^{1}H \text{ NMR (400 MHz, d6-DMSO); } &\delta 5.49-5.45 (\text{br m, H2}), 4.41-4.30 (\text{br m, H5A}), 3.68-3.59 (\text{br m, H5B}), 3.37 (\text{br s, H1}), 2.89 (\text{br dd, } J = 16.1, 6.4 \text{ Hz, H3A}), 2.56 (\text{br dd, } J = 16.1, 3.9 \text{ Hz, H3B}), 1.47-1.42 (\text{br m, H8 and H11}). \\
^{13}C \text{ NMR (100 MHz, } d_{6}-\text{DMSO); } &\delta 201.4 (C4), 153.2 (C6 or C9), 152.3 (C6 or C9), 83.3 (C2), 81.4 (C7 or C10), 80.4 (C7 or C10), 54.9 (C1), 53.8 (C5), 43.5 (C3), 27.5 (C8 or C11), 27.4 (C8 or C11). \\
\text{FTIR (ATR)} \nu (\text{cm}^{-1}); & 2978, 2933, 1730 (\text{C=O}), 1708 (\text{C=O}). \\
\text{HRMS (APCI)}: m/z \text{ calculated for: } C_{15}H_{26}N_{2}O_{6} [M+Na]^{+} 353.1683, \text{ found 353.1697.}
\end{align*}
\]

**Methyl 2-[(methoxycarbonyl)amino]-1H-pyrole-1-carboxylate 210a**

\[
\begin{align*}
\text{Using general procedure I, a solution of 1,2-dihydropyridazine 9a (520 mg, 2.62 mmol) in } &\text{ o-xylene (5 mL) was heated at reflux for 5 hours. Purification by flash column chromatography on } \\
\text{silica gel (eluent: hexane-EtOAc, 100% hexane→9:1) gave 2-aminopyrrole 210a (320 mg, 1.61 mmol, 62%) as a } &\text{colourless solid.} \\
\text{Rf (Hexane-EtOAc, 2:1) } &= 0.35 \\
\text{mp } &\text{46-47 °C} \\
^{1}H \text{ NMR (400 MHz, CDCl3); } &\delta 9.05 (\text{br s, NH}), 6.85 (\text{dd, } J = 3.6, 1.8 \text{ Hz, H1}), 6.42-6.32 (\text{br m, H3}), 6.13 (t, J = 3.6 \text{ Hz, H2}), 3.95 (s, 3H, H8), 3.77 (s, 3H, H6). \\
^{13}C \text{ NMR (100 MHz, CDCl3); } &\delta 153.1 (C5), 152.4 (C7), 130.5 (C4), 114.0 (C1), 111.6 (C2), 98.4 (C3), 54.2 (C8), 52.6 (C6). \\
\text{FTIR (ATR)} \nu (\text{cm}^{-1}); & 3349 (NH), 2950, 1724 (\text{C=O}). \\
\text{HRMS (APCI)}: m/z \text{ calculated for: } C_{8}H_{10}N_{2}O_{4} [M+H]^{+} 199.0713, \text{ found 199.0712.}
\end{align*}
\]

**Ethyl 2-[(ethoxycarbonyl)amino]-1H-pyrole-1-carboxylate 210b**
Using general procedure I, a solution of 1,2-dihydropyridazine 9b (562 mg, 2.48 mmol) in o-xylene (5 mL) was heated at reflux for 5 hours. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 100% hexane→14:1) gave 2-aminopyrrole 210b (481 mg, 2.13 mmol, 86%) as a pale yellow oil.

$R_f$ (Hexane-EtOAc, 1:1) = 0.57

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.08 (br s, 1H, NH), 6.87 (dd, $J = 3.6$, 1.8 Hz, 1H, H1), 6.42-6.31 (br m, 1H, H3), 6.13 (t, $J = 3.6$ Hz, 1H, H2), 4.40 (q, $J = 7.1$ Hz, 2H, H9), 4.22 (q, $J = 7.1$ Hz, 2H, H6), 1.41 (t, $J = 7.1$ Hz, 3H, H10), 1.30 (t, $J = 7.1$ Hz, 3H, H7).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 152.8 (C5), 152.0 (C8), 130.8 (C4), 113.9 (C1), 111.5 (C2), 98.2 (C3), 63.8 (C9), 61.6 (C6), 14.7 (C7), 14.3 (C10).

$^1$H NMR (400 MHz, d$_6$-DMSO) $\delta$ 8.92 (br s, 1H, NH), 7.07 (dd, $J = 3.6$, 1.9 Hz, 1H, H1), 6.15 (t, $J = 3.6$ Hz, 1H, H2), 6.10-6.06 (br m, 1H, H3), 4.32 (q, $J = 7.1$ Hz, 2H, H9), 4.08 (q, $J = 7.1$ Hz, 2H, H6), 1.30 (t, $J = 7.1$ Hz, 3H, H10), 1.20 (t, $J = 7.1$ Hz, 3H, H7).

$^{13}$C NMR (100 MHz, d$_6$-DMSO) $\delta$ 154.1 (C5), 150.0 (C8), 128.1 (C4), 117.3 (C1), 110.1 (C2), 105.3 (C3), 63.4 (C9), 60.6 (C6), 14.5 (C7), 13.9 (C10).

FTIR (ATR) $\nu$ (cm$^{-1}$): 3345 (NH), 3145 (NH), 2980, 1718 (C=O).

HRMS (ESI): $m/z$ calculated for: C$_{10}$H$_{14}$N$_2$O$_4$ [M+H]$^+$ 227.1026, found 227.1024.

Important NOE Contacts (d$_6$-DMSO)

Isopropyl 2-(isopropoxycarbonylamino)-1H-pyrrole-1-carboxylate 210c

Using general procedure I, a solution of 1,2-dihydropyridazine 9c (906 mg, 3.56 mmol) in o-xylene (10 mL) was heated at reflux for 5 hours. Purification by flash column chromatography...
on silica gel (eluent: hexane-EtOAc, 100% hexane→14:1) gave 2-aminopyrrole 210c (818 mg, 3.22 mmol, 90%) as yellow oil.

\[ R_f (\text{Hexane-EtOAc, 2:1}) = 0.58 \]

\(^1\)H NMR (400 MHz, CDCl\(_3\)); \(\delta \) 9.08 (br s, 1H, NH), 6.85 (dd, \(J = 3.6, 1.8 \text{ Hz, 1H, H1}\), 6.40-6.32 (br m, 1H, H3), 6.12 (t, \(J = 3.5 \text{ Hz, 1H, H2}\), 5.16 (sept, \(J = 6.2 \text{ Hz, 1H, H9}\), 5.00 (sept, \(J = 6.2 \text{ Hz, 1H, H6}\)), 1.39 (d, \(J = 6.2 \text{ Hz, 6H, H10}\)), 1.29 (d, \(J = 6.2 \text{ Hz, 6H, H7}\)).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)); \(\delta \) 152.4 (C5), 151.6 (C8), 131.0 (C4), 113.8 (C1), 111.3 (C2), 98.0 (C3), 72.3 (C9), 69.1 (C6), 22.2 (C7), 21.9 (C10).

FTIR (ATR) \(\nu \) (cm\(^{-1}\)): 3366 (NH), 2982, 1720 (C=O).

HRMS (APCI): \(m/z\) calculated for: \(\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_4\) [M+Na\(^+\)] 277.1159, found 277.1154.

**tert-Butyl 2-(tert-butoxycarbonylamino)pyrrole-1-carboxylate 210d**

![tert-Butyl 2-(tert-butoxycarbonylamino)pyrrole-1-carboxylate 210d](image)

Using general procedure X, a solution of 1,2-dihydropyridazine 9d (304 mg, 1.08 mmol) in o-xylene (3 mL) was heated at reflux for 5 hours. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 100% hexane→9:1) gave 2-aminopyrrole 210d (33 mg, 0.12 mmol, 11%) as a brown oil and 2-aminopyrrole 220d (56 mg, 0.31 mmol, 28%) as a brown film.

**2-Aminopyrrole 210d**

\[ R_f (\text{Hexane-EtOAc, 2:1}) = 0.58 \]

\(^1\)H NMR (400 MHz, CDCl\(_3\)); \(\delta \) 9.00 (br s, 1H, NH), 6.79 (dd, \(J = 3.5 \text{ Hz, 1H, H1}\), 6.35-6.29 (br m, 1H, H3), 6.08 (t, \(J = 3.5 \text{ Hz, 1H, H2}\), 1.59 (s, 9H, H7 or H10), 1.50 (s, 9H, H7 or H10).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)); \(\delta \) 151.8 (C5), 150.8 (C8), 131.2 (C4), 113.9 (C1), 110.8 (C2), 97.5 (C3), 84.8 (C6 or C9), 80.6 (C6 or C9), 28.5 (C7 or C10), 28.1 (C7 or C10).

FTIR (ATR) \(\nu \) (cm\(^{-1}\)): 3366 (NH), 2982, 1720 (C=O).

HRMS (APCI): \(m/z\) calculated for: \(\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_4\) [M+Na\(^+\)] 277.1159, found 277.1154.

**2-Aminopyrrole 220d**
Chapter 6: Experimental

\[ R_f (\text{Hexane-EtOAc, 2:1}) = 0.50 \]

\(^1\)H NMR (400 MHz, CDCl\(_3\)); \( \delta \) 9.60 (br s, 1H, NH\(_A\)), 7.26 (br s, 1H, NH\(_B\)), 6.50-6.45 (m, 1H, H1), 6.07 (m, 1H, H2), 5.61-5.51 (m, 1H, H3), 1.52 (s, 9H, H7).

\(^1^3\)C NMR (100 MHz, CDCl\(_3\)); \( \delta \) 153.4 (C5), 128.1 (C4), 112.1 (C1), 107.0 (C2), 92.5 (C3), 81.1 (C6), 28.4 (C).

FTIR (ATR) \( \nu \) (cm\(^{-1}\)): 3452 (NH), 3314 (NH), 2980, 1679 (C=O).

HRMS (ESI): \( m/z \) calculated for: C\(_9\)H\(_{14}\)N\(_2\)O\(_2\) [M+H]\(^+\) 183.1128, found 183.1127.

**Important NOE Contacts**

\[ \text{Dimethyl 3,6-bis(isopropoxycarbonylamino)benzene-1,2-dicarboxylate 224} \]

Dimethyl acetylenedicarboxylate 223 (31 µL, 0.25 mmol, 1.1 eq) was added in one portion to a stirred solution of 2-aminopyrrole 210c (58 mg, 0.23 mmol, 1.0 eq) in PhMe (3.0 mL). The reaction was heated at 60 °C for 18 hours, then cooled to room temperature and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1→2:1) gave \( p \)-phenylenediamine derivative 224 (59 mg, 0.15 mmol, 65%) as a yellow solid.

\( R_f (\text{Hexane-EtOAc, 2:1}) = 0.4 \)

Mp = 118-120 °C

\(^1\)H NMR (400 MHz, CDCl\(_3\)); \( \delta \) 8.42 (br s, 2H, NH), 8.31 (s, 2H, H2), 4.99 (sept, \( J = 6.3 \) Hz, 2H, H7), 3.87 (s, 6H, H5), 1.29 (d, \( J = 6.3 \) Hz, 12H, H8).

\(^1^3\)C NMR (100 MHz, CDCl\(_3\)); \( \delta \) 167.9 (C4), 153.4 (C6), 133.6 (C1), 124.7 (C2), 119.4 (C3), 69.3 (C7), 53.0 (C5), 22.2 (C8).

FTIR (ATR) \( \nu \) (cm\(^{-1}\)): 3343 (NH), 3308 (NH), 2984, 1720 (C=O ester), 1705 (C=O carbamate).

HRMS (APCI): \( m/z \) calculated for: C\(_{18}\)H\(_{26}\)N\(_2\)O\(_8\) [M+H]\(^-\) 395.1460, found 395.1454.
Diisopropyl naphthalene-1,4-diylbiscarbamate 234a

Using general procedure J, a solution of 2-aminopyrrole 210c (44 mg, 0.17 mmol, 2.1 eq) and aryne precursor 233a (20 µL, 0.08 mmol, 1.0 eq) in MeCN (0.8 mL) were heated at 40 °C for 2.5 hours. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1→2:1) gave diamine 234a (20 mg, 0.06 mmol, 74%) as a colourless solid.

Rf (Hexane-EtOAc, 2:1) = 0.26
mp = 187-189 °C (decomposition)

$^1$H NMR (400 MHz, $d_6$-DMSO); δ 9.37 (br s, 2H, NH), 8.02 (br dd, J = 6.5, 3.3 Hz, 2H, H4), 7.54 (br dd, J = 6.5, 3.3 Hz, 2H, H5) 7.51-7.49 (m, 2H, H2), 4.91 (sept, J = 6.2 Hz, 2H, H7), 1.28 (br d, J = 6.2 Hz, 12H, H8).

$^{13}$C NMR (100 MHz, $d_6$-DMSO); δ 154.7 (C6), 131.1 (C1), 128.7 (C3), 125.8 (C5), 123.1 (C4), 121.4 (C2), 67.6 (C7), 22.0 (C8).

FTIR (ATR) ν (cm⁻¹): 3263 (NH), 2974, 1737 (C=O), 1690 (C=O).


Diisopropyl quinoline-5,8-diylbiscarbamate 234b

Using general procedure J, a solution of 2-aminopyrrole 210c (44 mg, 0.17 mmol, 2.0 eq) and aryne precursor 233b (20 µL, 0.09 mmol, 1.0 eq) in MeCN (0.8 mL) were heated at 40 °C for 2.5 hours. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 7:1→2:1) gave diamine 234b (8 mg, 0.02 mmol, 28%) as an orange film.
$R_f$ (Hexane-EtOAc, 2:1) = 0.29

$^1$H NMR (400 MHz, $d_6$-DMSO): $\delta$ 9.44 (br s, 1H, NH$_A$), 9.05 (br s, 1H, NH$_B$), 8.89 (dd, $J$ = 4.2, 1.6 Hz, 1H, H$_6$), 8.44 (dd, $J$ = 8.6, 1.6 Hz, 1H, H$_8$), 8.21 (d, $J$ = 8.4 Hz, 1H, H$_3$), 7.65 (dd, $J$ = 8.6, 4.2 Hz, 1H, H$_7$), 7.40 (d, $J$ = 8.4 Hz, 1H, H$_2$), 5.01-4.86 (m, 2H, H$_{11}$ and H$_{14}$), 1.33-1.24 (m, 12H, H$_{12}$ and H$_{15}$).

$^{13}$C NMR (100 MHz, $d_6$-DMSO): $\delta$ 154.6 (C$_{10}$ or C$_{13}$), 152.5 (C$_{10}$ or C$_{13}$), 148.8 (C$_6$), 137.7 (C$_5$), 132.3 (C$_8$), 131.5 (C$_1$), 127.8 (C$_1$), 123.3 (C$_9$), 122.1 (C$_2$), 121.8 (C$_7$), 114.2 (C$_3$), 68.3 (C$_{11}$ or C$_{14}$), 67.8 (C$_{11}$ or C$_{14}$), 22.0 (C$_{12}$ or C$_{15}$), 21.9 (C$_{12}$ or C$_{15}$).

FTIR (ATR) $\nu$ (cm$^{-1}$): 3375 (NH), 3278 (NH), 2978, 1724 (C=O), 1689 (C=O).

HRMS (ESI): $m/z$ calculated for: C$_{17}$H$_{21}$N$_3$O$_4$ [M+H]$^+$ 332.1605, found 332.1598; [M+Na]$^+$ 354.1424, found 354.1423.

**Important NOE Contacts**

Diisopropyl isoquinoline-5,8-diylbiscarbamate 234c

Using general procedure J, a solution of 2-aminopyrrole 210c (44 mg, 0.17 mmol, 2.1 eq) and aryne precursor 233c (20 µL, 0.08 mmol, 1.0 eq) in MeCN (0.8 mL) were heated at 40 °C for 1.5 hours. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 1:1→100% EtOAc) gave diamine 234c (8 mg, 0.02 mmol, 29%) as a pink film.

$R_f$ (EtOAc, 100%) = 0.28

$^1$H NMR (400 MHz, $d_6$-DMSO): $\delta$ 9.73 (br s, 1H, NH$_B$), 9.52 (br s, 1H, NH$_A$), 9.39 (br s, 1H, H$_6$), 8.51 (d, $J$ = 5.8 Hz, 1H, H$_7$), 7.88 (dd, $J$ = 5.8, 0.6 Hz, 1H, H$_8$), 7.80 (d, $J$ = 8.3 Hz, 1H, H$_2$), 7.67 (d, $J$ = 8.3 Hz, 1H, H$_3$), 4.98-4.87 (m, 2H, H$_{11}$ and H$_{14}$), 1.31-1.25 (m, 12H, H$_{12}$ and H$_{15}$).
Photocyclisation: A New Route to Functionalised Four-Membered Rings

Thomas Britten – April 2019

$^{13}$C NMR (100 MHz, $d_6$-DMSO); δ 154.5 (C10 or C13), 154.4 (C10 or C13), 148.1 (C6), 142.6 (C7), 131.5 (C4), 130.7 (C9), 130.0 (C1), 124.9 (C2), 122.8 (C5), 121.8 (C3), 115.5 (C8), 68.0 (C11 or C14), 67.9 (C11 or C14), 22.0 (C12 and C15).

FTIR (ATR) ν (cm$^{-1}$): 3269 (NH), 2978, 1728 (C=O), 1694 (C=O).

HRMS (ESI): $m/z$ calculated for: C$_{17}$H$_{21}$N$_{3}$O$_{4}$ [M+H]$^+$ 332.1605, found 332.1591.

Important NOE Contacts

Di-tert-butyl-1-{1-(isopropoxy)carbonyl-5-[(isopropoxycarbonyl)amino]-pyrrol-2-yl}-hydrazine-1,2-dicarboxylate 235

Di-tert-butyl azodicarboxylate 8d (200 mg, 0.87 mmol, 1.1 eq) was added in one portion to a stirred solution of 2-aminopyrrole 210c (201 mg, 0.79 mmol, 1.0 eq) in PhMe (1.5 mL) at room temperature under argon. The reaction mixture was heated at 60 °C for 24 hours, cooled to room temperature and the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 7:1—5:1) gave pyrrole 235 (308 mg, 0.64 mmol, 81%) as a pale yellow solid.

$R_f$ (Hexane-EtOAc, 2:1) = 0.45

mp = 40-42 °C

$^1$H NMR (400 MHz, $d_6$-DMSO); δ 9.18-8.58 (br m, 2 H, NH$_A$ and NH$_B$), 6.10-6.05 (br m, 1 H, H2), 5.98-5.90 (br m, 1 H, H3), 5.01-4.95 (m, 1 H, H6 or H9), 4.83-4.77 (m, 1 H, H6 or H9), 1.47-1.17 (m, 30 H, H7, H10, H13 and H16).

$^{13}$C NMR (100 MHz, $d_6$-DMSO, additional peaks due to complex rate processes denoted by an asterisk); δ 154.8 (C11 or C14), 153.9 (C5 or C8), 153.7* (C5, C8, C11 or C14), 148.9 (C5 or C8), 128.0 (C1 or C4), 126.3 (C1 or C4), 107.7 (C2), 103.1 (C3), 82.4* (C12 or C15), 80.7 (C12 or C15), 79.7 (C12 or C15), 79.2* (C12 or C15), 71.8 (C6 or C9), 71.7* (C6 or C9), 68.0* (C6 or C9), 67.9 (C6 or C9), 28.0 (C13 or C16), 27.7 (C13 or C16), 21.9 (C7 or C10), 21.1 (C7 or C10), 21.1* (C7 or C10).
\(^1\)H NMR (400 MHz, 348 K, d<sub>6</sub>-DMSO); \(\delta \) 8.72 (s, 1H, NH<sub>A</sub>), 8.38 (br s, 1H, NH<sub>B</sub>), 6.11 (d, \(J = 3.7\) Hz, 1H, H2), 5.97 (br dd, \(J = 3.7, 0.4\) Hz, 1H, H3), 5.03 (sept, \(J = 6.3\) Hz, 1H, H6 or H9), 4.84 (sept, \(J = 6.3\) Hz, 1H, H6 or H9), 1.45-1.35 (m, 18H, H13 and H16), 1.33 (d, \(J = 6.3\) Hz, H7 or H10), 1.23 (d, \(J = 6.3\) Hz, H7 or H10).

\(^{13}\)C NMR (100 MHz, 348 K, d<sub>6</sub>-DMSO, additional peaks due to rotamers denoted by an asterisk); \(\delta \) 154.3 (C11 and C14), 153.2 (C5 or C8), 153.1 (C5, C8, C11 or C14), 148.9 (C5 or C8), 127.4 (C1 or C4), 126.5 (C1 or C4), 107.7 (C2), 102.2 (C3), 80.5 (C12 or C15), 79.5 (C12 or C15), 71.7 (C6 or C9), 67.7 (C6 or C9), 27.4 (C13 or C16), 21.4 (C7 or C10), 20.8 (C7 or C10).

FTIR (ATR) \(\nu\) (cm\(^{-1}\)): 3364 (NH), 2980, 1718 (C=O).

HRMS (ESI): \(m/z\) calculated for: C<sub>22</sub>H<sub>36</sub>N<sub>4</sub>O<sub>8</sub> [M+H]<sup>+</sup> 485.2606 and [M+Na]<sup>+</sup> 507.2425, found 485.2585 and 507.2401, respectively.

**Important NOE contacts**

\[ \text{Diisopropyl 3,6-dihydroxy-3,6-dihydropyridazine-1,2-dicarboxylate 238} \]

\(m\)-CPBA (76 mg, 0.44 mmol, 1.1 eq) was added in one portion to a stirred solution of 1,2-dihydropyridazine 9c (100 mg, 0.39 mmol, 1.0 eq) in MeCN (1 mL) at 0 °C under argon. The reaction mixture was stirred at room temperature for 44 hours, then the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 3:1→2:1→1:1) gave diol 238 (63 mg, 0.22 mmol, 56%) as a colourless oil which became an off-white solid upon standing.

\(R_f\) (Hexane-EtOAc, 1:1) = 0.11

mp = 108-110°C

\(^1\)H NMR (400 MHz, 328 K, CDCl<sub>3</sub>); \(\delta \) 6.03-5.98 (m, 2H, H2 and H3), 5.94-5.85 (br m, 2H, H1 and H4), 4.97 (sept, \(J = 6.3\) Hz, 2H, H6 and H9), 1.26 (br d, \(J = 6.3\) Hz, 12H, H7 and H10).

\(^{13}\)C NMR (100 MHz, 328 K, CDCl<sub>3</sub>); \(\delta \) 154.6 (C5 and C8), 127.6 (C2 and C3), 72.4 (C1 and C4), 70.9 (C6 and C9), 22.1 (C7 or C10), 22.0 (C7 or C10).

FTIR (ATR) \(\nu\) (cm\(^{-1}\)): 3416 (OH), 2982, 1679 (C=O).

HRMS (ESI): \(m/z\) calculated for: C<sub>12</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub> [M+Na]<sup>+</sup> 311.1214, found 311.1199.
Diisopropyl 3,3,8,8-tetrachloro-5,6-diazatricyclo[5.1.0.0\(^2,4\)]octane-5,6-dicarboxylate 241

An aqueous solution of NaOH (50% w/v, 5 mL) was added dropwise to a solution of 1,2-dihydropyridazine 9c (101 mg, 0.40 mmol, 1.0 eq) and tetrabutylammonium chloride (11 mg, 0.04 mmol, 0.1 eq) in CHCl\(_3\) (10 mL) at room temperature under argon, then stirred at room temperature for 3 hours. The reaction mixture was quenched with a saturated aqueous solution of NH\(_4\)Cl (10 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 10 mL), the combined organic layers were dried (MgSO\(_4\)) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 7:1→4:1) gave tricycle 241 (117 mg, 0.28 mmol, 71%) as an off-white sticky solid.

\(R_f\) (Hexane-EtOAc, 2:1) = 0.44

mp = 118-120 °C

\(^1\)H NMR (400 MHz, CDCl\(_3\)); \(\delta\) 5.04-4.94 (m, 2H, H\(_8\) and H\(_{11}\)), 3.63-3.54 (m, 2H, H\(_1\) and H\(_6\)), 2.15-2.11 (m, 2H, H\(_3\) and H\(_4\)), 1.35-1.23 (m, 12H, H\(_9\) and H\(_{12}\)).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)); \(\delta\) 153.2 (C\(_7\) and C\(_{10}\)), 71.5 (C\(_8\) and C\(_{11}\)), 63.0 (C\(_2\) and C\(_5\)), 42.2 (C\(_1\) and C\(_6\)), 25.8 (C\(_3\) and C\(_4\)), 22.3 (C\(_8\) or C\(_{11}\)), 21.8 (C\(_8\) or C\(_{11}\)).

FTIR (ATR) \(\nu\) (cm\(^{-1}\)): 2978, 2926, 1757 (C=O), 1724 (C=O).

HRMS (APCI): \(m/z\) calculated for: C\(_{14}\)H\(_{18}\)N\(_2\)O\(_4\)Cl\(_4\) [M+H]\(^+\) 419.0093, found 419.0079.

Diisopropyl 3,4-dihydroxy-3,4-dihydropyridazine-1,2-dicarboxylate 242 and 243

NMO (140 mg, 1.20 mmol, 3.0 eq) was added in one portion to a stirred solution of 1,2-dihydropyridazine 9c (102 mg, 0.40 mmol, 1.0 eq) and OsO\(_4\) (2.5% w/v in BuOH, 0.2 mL, 0.02 mmol, 0.05 eq) in acetone:H\(_2\)O (8:1, 4.5 mL) at room temperature under argon, then stirred at room temperature for 17 hours. The reaction mixture was diluted with a saturated aqueous solution of Na\(_2\)S\(_2\)O\(_3\) (5 mL) and extracted with CH\(_2\)Cl\(_2\) (5 x 5 mL). The combined organic layers were dried (MgSO\(_4\)) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc,
4:1→2:1→1:1) gave diol 242 (24 mg, 0.08 mmol, 21%) and diol 243 (66 mg, 0.23 mmol, 57%) as colourless solids.

cis-Diol 242

\[
\begin{align*}
\text{Rf (Hexane-EtOAc, 1:1) } &= 0.14 \\
\text{mp } &= 104-106^\circ C \\
^1\text{H NMR (400 MHz, } d_6\text{-DMSO): } &\delta 6.81-6.44 (\text{br m, 2H, H4} \text{ and OH}_A), 5.51-5.38 (\text{br m, 1H, H1}), 4.99-4.93 (\text{br m, 1H, OH}_B), 4.87-4.71 (\text{br m, 3H, H3, H6 and H9}), 4.10-4.04 (\text{br m, 1H, H2}), 1.24-1.19 (\text{m, 12H, H7 and H10}). \\
^{13}\text{C NMR (100 MHz, } d_6\text{-DMSO, C1 not visible, additional peaks due to complex rate processes denoted by an asterisk): } &\delta 152.6 (\text{C5 or C8}), 151.3 (\text{C5 or C8}), 123.7 (\text{C4}), 108.4 (\text{C3}), 70.1^* (\text{C6 or C9}), 69.9 (\text{C6 or C9}), 62.6^* (\text{C2}), 62.4 (\text{C2}), 21.7^* (\text{C7 or C10}), 21.6 (\text{C7 or C10}), 21.6 (\text{C7 or C10}). \\
\text{FTIR (ATR) } \nu (\text{cm}^{-1}): & 3424 (\text{OH}), 2980, 1687 (\text{C=O}). \\
\text{HRMS (APCI): } m/z \text{ calculated for: } C_{12}H_{20}N_2O_6 [M+Na]^+ 311.1214, \text{ found 311.1199.}
\end{align*}
\]

Important NOE Contacts

\[
\text{trans-Diol 243}
\]

\[
\begin{align*}
\text{Rf (Hexane-EtOAc, 1:1) } &= 0.08
\end{align*}
\]

\[
\begin{align*}
\text{H}^1 &\leftrightarrow \text{H}^2 \\
\text{H}^1 &\leftrightarrow \text{OH}_A \\
\text{H}^1 &\leftrightarrow \text{OH}_B \\
\text{H}^2 &\leftrightarrow \text{H}^3 \\
\text{H}^2 &\leftrightarrow \text{OH}_B \\
\text{No cross peak between } &\text{H}^2 \leftrightarrow \text{OH}_A
\end{align*}
\]
mp = 104-106 °C

\(^1\)H NMR (400 MHz, d6-DMSO); \(\delta \) 7.02-6.88 (br m, 1H, H4) 6.52-6.35 (br m, 1H OHa), 5.59-5.44 (br m, 1H, H1), 5.11-5.08 (br m, 1H, OHb), 5.06-4.95 (br m, 1H, H3), 4.86-4.77 (br m, 2H, H6 and H9), 3.71-3.66 (br m, 1H, H2), 1.26-1.14 (m, 12H, H7 and H10).

\(^13\)C NMR (100 MHz, d6-DMSO, additional peaks due to complex rate processes denoted by an asterisk); \(\delta \) 153.6 (C5 or C8), 153.4 (C5 or C8), 152.2 (C5 or C8), 150.9 (C5 or C8), 125.6* (C4), 125.3 (C4), 125.0* (C4), 105.4 (C3), 105.2* (C3), 80.4* (C1), 80.3 (C1), 79.3* (C1), 78.9* (C1), 70.1* (C6 or C9), 69.8 (C6 or C9), 69.4 (C6 or C9), 69.3* (C6 or C9), 69.1* (C6 or C9), 68.9* (C6 or C9), 63.7* (C2), 63.4 (C2), 21.9* (C7 or C10), 21.8* (C7 or C10), 21.7 (C7 or C10), 21.5 (C7 or C10).

\(^1\)H NMR (400 MHz, 348 K, d6-DMSO); \(\delta \) 6.95 (br d, \(J = 7.9 \text{ Hz}, 1H, H4\)), 6.18-6.12 (br m, 1H, OHa), 5.60-5.52 (br m, 1H, H1), 5.07-5.00 (br m, 1H, H3), 4.89-4.79 (br m, 3H, H6, H9 and OHb), 3.79-3.71 (br m, 1H, H2), 1.29-1.17 (m, 12H, H7 and H10).

\(^13\)C NMR (100 MHz, 348 K, d6-DMSO, additional peaks due to complex rate processes denoted by an asterisk); \(\delta \) 152.9 (C5 or C8), 125.0 (C4), 105.5 (C3), 79.8 (C1), 69.6 (C6 or C9), 68.8 (C6 or C9), 63.5 (C2), 21.4* (C7 or C10), 21.3 (C7 or C10), 21.2 (C7 or C10), 21.2* (C7 or C10).

FTIR (ATR) \(\nu\) (cm\(^{-1}\)) : 3422 (OH), 2984, 1702 (C=O), 1649 (C=O).

HRMS (APCI): \(m/z\) calculated for: C\(_{12}\)H\(_{20}\)N\(_{2}\)O\(_{6}\) \([\text{M+Na}^+]\) 311.1214, found 311.1199.

**Important NOE Contacts**

\[
\begin{array}{c}
\text{H}^1 \leftrightarrow \text{H}^2 \\
\text{H}^1 \leftrightarrow \text{OH}^A \\
\text{H}^2 \leftrightarrow \text{H}^3 \\
\text{H}^2 \leftrightarrow \text{OH}^A \\
\end{array}
\]

**Dimethyl 2,3-diazabicyclo[2.2.0]hex-5-ene-2,3-dicarboxylate 10a**

Using general procedure K, a solution of 1,2-dihydropyridazine 9a (140 mg, 0.71 mmol) in MeCN (14 mL) was irradiated for 44 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1→2:1) gave the bicycle 10a (61 mg, 0.31 mmol, 44%) as an off-white solid.

\(R_t\) (Hexane-EtOAc, 2:1) = 0.1

mp = 76-78 °C

\(^1\)H NMR (400 MHz, CDCl3); \(\delta \) 6.74-6.71 (m, 2H, H1), 5.21-5.18 (m, 2H, H2), 3.81 (s, 6H, H4).

\(^13\)C NMR (100 MHz, CDCl3); \(\delta \) 160.6 (C3), 143.7 (C1), 67.5 (C2), 53.7 (C4).

FTIR (ATR) \(\nu\) (cm\(^{-1}\)) : 2961, 1743 (C=O), 1720 (C=O).
Diethyl 2,3-diazabicyclo[2.2.0]hex-5-ene-2,3-dicarboxylate 10b

Using general procedure K, a solution of 1,2-dihydropyridazine 9b (170 mg, 0.75 mmol) in PhMe (15 mL) was irradiated for 24 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 7:1–4:1) gave the bicycle 10b (121 mg, 0.54 mmol, 71%) as a pale yellow oil.

\[ R_f \text{(Hexane-EtOAc, 1:1)} = 0.29 \]

\[^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta 6.76-6.68 \text{ (m, 2H, H1)}, 5.22-5.14 \text{ (m, 2H, H2), 4.31-4.17 \text{ (m, 4H, H4), 1.30 (t, } J = 7.1 \text{ Hz, 6H, H5).} \]

\[^{13}\text{C NMR (100 MHz, CDCl}_3\text{)} \delta 160.1 \text{ (C3), 143.6 (C1), 67.3 (C2), 62.8 (C4), 14.6 (C5).} \]

FTIR (ATR) \( \nu \text{ (cm}^{-1}\text{): 2984, 2935, 1746 (C=O), 1703 (C=O).} \]

HRMS (APCI): \( m/z \) calculated for: \( C_{10}H_{14}N_2O_4 \) [M+H]^+ 227.1026, found 227.1019.

Diisopropyl 2,3-diazabicyclo[2.2.0]hex-5-ene-2,3-dicarboxylate 10c

Using general procedure K, a solution of 1,2-dihydropyridazine 9c (191 mg, 0.75 mmol) in MeCN (15 mL) was irradiated for 24 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 9:1–4:1) gave the bicycle 10c (159 mg, 0.63 mmol, 83%) as an off-white solid.

\[ R_f \text{(Hexane-EtOAc, 1:1)} = 0.35 \]

mp = 48-50 °C

\[^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta 6.72-6.69 \text{ (m, 2H, H1)}, 5.17-5.14 \text{ (m, 2H, H2), 5.00 \text{ (sept, } J = 6.3 \text{ Hz, 2H, H4), 1.29-1.27 \text{ (m, 12H, H5).} \]

\[^{13}\text{C NMR (100 MHz, CDCl}_3\text{)} \delta 159.7 \text{ (C3), 143.5 (C1), 70.6 (C4), 67.1 (C2), 22.11 (C5), 22.09 (C5).} \]

FTIR (ATR) \( \nu \text{ (cm}^{-1}\text{): 2988, 2939, 1698 (C=O).} \]

HRMS (APCI): \( m/z \) calculated for: \( C_{12}H_{18}N_2O_4 \) [M+Na]^+ 277.1159, found 277.1147.
**Di-tert-butyl 2,3-diazabicyclo[2.2.0]hex-5-ene-2,3-dicarboxylate 10d**

Using general procedure K, a solution of 1,2-dihydropyridazine 9d (212 mg, 0.75 mmol) in MeCN (15 mL) was irradiated for 24 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 14:1→9:1) gave the bicycle 10d (171 mg, 0.61 mmol, 81%) as an off-white solid.

**Scale up procedures**

**0.85 grams:** Using general procedure K, a solution of 1,2-dihydropyridazine 9d (0.85 g, 3.00 mmol) in MeCN (60 mL, 1 x 60 mL tube) was irradiated for 48 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 14:1→9:1) gave the bicycle 10d (0.69 g, 2.45 mmol, 82%) as an off-white solid.

**8.5 grams:** Using general procedure K, a solution of 1,2-dihydropyridazine 9d (8.47 g, 30.0 mmol) in MeCN (600 mL) was split across 10 x 60 mL tubes, then irradiated for 48 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 14:1→9:1) gave the bicycle 10d (6.06 g, 21.5 mmol, 72%) as an off-white solid.

\[ R_f (\text{Hexane-EtOAc, 1:1}) = 0.46 \]

\[ \text{mp} = 81-83 \degree C \]

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\); \delta 6.71-6.70 (m, 2H, H1), 5.09-5.08 (m, 2H, H2), 1.49 (s, 18H, H5). \]

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3\); \delta 159.0 (C3), 143.5 (C1), 82.1 (C4), 66.7 (C2), 28.3 (C5). \]

\[ \text{FTIR (ATR) } \nu (\text{cm}^{-1}): 2982, 2937, 1694 (\text{C}=\text{O}). \]

\[ \text{HRMS (APCI): } m/z \text{ calculated for: } C_{14}H_{22}N_2O_4 [M+Na]^+ 305.1472, \text{ found } 305.1464. \]

**Dibenzyl 2,3-diazabicyclo[2.2.0]hex-5-ene-2,3-dicarboxylate 10e**

Using general procedure J, a solution of 1,2-dihydropyridazine 9e (263 mg, 0.75 mmol) in PhMe (15 mL) was irradiated for 24 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 9:1→4:1) gave the bicycle 10e (155 mg, 0.44 mmol, 59%) as a yellow oil.

\[ R_f (\text{Hexane-EtOAc, 2:1}) = 0.28 \]
1H NMR (400 MHz, CDCl₃): δ 7.36-7.31 (m, 10H, H₆, H₇, H₈), 6.66-6.63 (m, 2H, H₁), 5.26-5.18 (m, 4H, H₂, H₄).

13C NMR (100 MHz, CDCl₃): δ 159.9 (C₃), 143.6 (C₁), 135.7 (C₅), 128.6 (C₆ or C₇), 128.4 (C₆ or C₇), 68.2 (C₄), 67.4 (C₂).

FTIR (ATR) ν (cm⁻¹): 3032, 2954, 1703 (C=O).

HRMS (ESI): m/z calculated for: C₂₀H₁₈N₂O₄ [M+Na]⁺ 373.1159, found 373.1142.

**tert-Butyl methyl 2,3-diazabicyclo[2.2.0]hex-5-ene-2,3-dicarboxylate 10f**

![Image of compound 10f]

Using general procedure J, a solution of 1,2-dihydropyridazine 9f (180 mg, 0.75 mmol) in PhMe (15 mL) was irradiated for 24 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 7:1→4:1) gave the bicycle 10f (127 mg, 0.53 mmol, 70%) as an off-white solid.

Rᵣ (Hexane-EtOAc, 2:1) = 0.18

mp = 79-81 °C

1H NMR (400 MHz, CDCl₃): δ 6.74-6.72 (m, 1H, H₁ or H₂), 6.70-6.69 (m, 1H, H₁ or H₂), 5.17-5.16 (m, 1H, H₃ or H₄), 5.12-5.10 (m, 1H, H₃ or H₄), 3.79 (s, 3H, H₉), 1.49 (s, 9H, H₇).

13C NMR (100 MHz, CDCl₃): δ 160.6 (C₈), 158.9 (C₅), 143.6 (C₁ or C₂), 143.4 (C₁ or C₂), 82.4 (C₆), 67.2 (C₃ or C₄), 67.0 (C₃ or C₄), 53.6 (C₉), 28.3 (C₇).

FTIR (ATR) ν (cm⁻¹): 2978, 2932, 1735 (C=O), 1702 (C=O).

HRMS (ESI): m/z calculated for: C₁₁H₁₆N₂O₄ [M+Na]⁺ 263.1002, found 263.0991.

**Benzyl tert-butyl 2,3-diazabicyclo[2.2.0]hex-5-ene-2,3-dicarboxylate 10g**

![Image of compound 10g]

Using general procedure J, a solution of 1,2-dihydropyridazine 9g (237 mg, 0.75 mmol) in PhMe (15 mL) was irradiated for 24 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 14:1→9:1→7:1) gave the bicycle 10g (179 mg, 0.57 mmol, 75%) as a colourless oil.

Rᵣ (Hexane-EtOAc, 2:1) = 0.26
Ethyl 4-ethoxy-5-oxa-2,3-diazabicyclo[4.2.0]octa-3,7-diene-2-carboxylate 316b

Using general procedure L, a solution of bicyclic 1,2-diazetidine 10b (23 mg, 0.10 mmol) in PhMe (1 mL) was heated at reflux for 24 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane–EtOAc, 4:1→2:1) gave the rearranged bicycle 316b (17 mg, 0.08 mmol, 74%) as a pale yellow oil.

\[ R_f \text{ (Hexane–EtOAc, 1:1) } = 0.34 \]

\(^1^H\) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.36-7.29 (m, 5H, H11, H12, H13), 6.70-6.69 (m, 1H, H1 or H2), 6.67-6.65 (m, 1H, H1 or H2), 5.25-5.21 (m, 2H, H9), 5.18-5.16 (m, 1H, H3 or H4), 5.12-5.11 (m, 1H, H3 or H4), 1.46 (s, 9H, H7).

\(^1^C\) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 159.9 (C8), 158.9 (C5), 143.5 (C1 or C2), 143.5 (C1 or C2), 135.8 (C10), 128.6 (C11 or C12), 128.4 (C13), 128.2 (C11 or C12), 82.4 (C6), 68.0 (C9), 67.1, (C3 or C4), 67.1 (C3 or C4), 28.2 (C7).

FTIR (ATR) \( \nu \) (cm\(^{-1}\)): 2978, 2932, 1735 (C=O), 1666 (C=N).

HRMS (ESI): \( m/z \) calculated for: C\(_{17}\)H\(_{20}\)N\(_2\)O\(_4\) [M+H\(^+\)] \( = 339.1315 \), found 339.1310.

Isopropyl 4-isopropoxy-5-oxa-2,3-diazabicyclo[4.2.0]octa-3,7-diene-2-carboxylate 316c

Using general procedure L, a solution of bicyclic 1,2-diazetidine 10c (25 mg, 0.10 mmol) in PhMe (1 mL) was heated at reflux for 4 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane–EtOAc, 9:1→3:1) gave the rearranged bicycle 316c (23 mg, 0.09 mmol, 92%) as an off-white solid.

\[ R_f \text{ (Hexane–EtOAc, 2:1) } = 0.25 \]

mp = 48-50 °C
Chapter 6: Experimental

$^1$H NMR (400 MHz, CDCl$_3$); δ 6.46-6.44 (br m, 1H, H1), 6.30-6.29 (br m, 1H, H2), 5.43 (br dd, J = 4.3, 2.4 Hz, 1H, H3), 5.15-5.11 (br m, 1H, H4), 5.04-4.93 (br m, 2H, H6 and H9), 1.33-1.28 (br m, 6H, H7 or H10).

$^{13}$C NMR (100 MHz, CDCl$_3$); δ 153.6 (C8), 149.7 (C5), 142.0 (C1), 138.6 (C2), 79.4 (C3), 72.4 (C6 or C9), 69.7 (C6 or C9), 55.7 (C4), 22.3 (C7 or C10), 22.3 (C7 or C10), 21.9 (C7 or C10), 21.5 (C7 or C10).

FTIR (ATR) ν (cm$^{-1}$): 2976, 2933, 1731 (C=O), 1657 (C=N).

HRMS (ESI): m/z calculated for: C$_{12}$H$_{18}$N$_2$O$_4$ [M+Na]$^+$ 277.1159, found 277.1159.

**tert-Butyl 4-tert-butoxy-5-oxa-2,3-diazabicyclo[4.2.0]octa-3,7-diene-2-carboxylate 316d**

*Thermal Reaction:* Using general procedure L, a solution of bicyclic 1,2-diazetidine 10d (30 mg, 0.11 mmol) in PhMe (1 mL) was heated at reflux for 4 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 9:1→3:1) gave the rearranged bicycle 316d (21 mg, 0.07 mmol, 70%) as an off-white solid and trace amounts of the degraded bicycle 317d.

**Palladium(0) Reaction:** Bicyclic 1,2-diazetidine 10d (50 mg, 0.18 mmol, 1.0 eq), Pd(OAc)$_2$ (2 mg, 0.01 mmol, 0.05 eq) and PPh$_3$ (9 mg, 0.04 mmol, 0.02 eq) were added to a dried vial under argon. THF (0.9 mL) was added and the vial was sealed, then stirred at room temperature for 29 hours. The reaction mixture was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 14:1→9:1) gave the rearranged bicycle 316d (36 mg, 0.13 mmol, 72%) as an off-white solid.

$R_t$ (Hexane-EtOAc, 2:1) = 0.38

mp = 77-79 °C

$^1$H NMR (400 MHz, CDCl$_3$); δ 6.47-6.44 (br m, 1H, H1), 6.30-6.29 (br m, 1H, H2), 5.37 (br dd, J = 4.3, 2.3 Hz, 1H, H3), 5.09-5.04 (br m, 1H, H4), 1.52 (s, 9H, H7 or H10), 1.50 (s, 9H, H7 or H10).

$^{13}$C NMR (100 MHz, CDCl$_3$; C8 not observed); δ 148.1 (C5), 141.8 (C1), 138.7 (C2), 83.1 (C6 or C9), 80.8 (C6 or C9), 79.0 (C3), 55.4 (C4), 28.5 (C7 or C10), 28.1 (C7 or C10).

$^1$H NMR (400 MHz, d$_6$-DMSO); δ 6.57-6.38 (br m, 2H, H1 and H2), 5.47-5.44 (br m, 1H, H3), 5.02-4.94 (br m, 1H, H4), 1.53-1.43 (br m, 18H, H7 or H10).

$^{13}$C NMR (100 MHz, d$_6$-DMSO); δ 151.2 (C8), 148.1 (C5), 141.3 (C1), 139.2 (C2), 82.0 (C6 or C9), 79.7 (C6 or C9), 78.5 (C3), 55.1 (C4), 28.0 (C7 or C10), 27.5 (C7 or C10).

FTIR (ATR) ν (cm$^{-1}$): 2976, 2933, 1683 (C=O), 1646 (C=N).

HRMS (ESI): m/z calculated for: C$_{12}$H$_{18}$N$_2$O$_4$ [M+Na]$^+$ 305.1472, found 305.1469.
**t-t Butyl 4-oxo-5-oxa-2,3-diazabicyclo[4.2.0]oct-7-ene-2-carboxylate 317d**

**Two Step Reaction:** A solution of bicyclic 1,2-diazetidine 10d (512 mg, 1.81 mmol) in 1,4-dioxane (3.5 mL) was heated at reflux for 24 hours. The reaction mixture was cooled to room temperature, a 1M aqueous solution of HCl (1 mL) was added and the mixture stirred for at room temperature for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of NaHCO₃ (1 mL), the organic layer was separated and the aqueous phase was extracted with CH₂Cl₂ (5 x 5 mL). The combined organic layers were dried (MgSO₄) and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1→2:1) gave the degraded bicycle 317d (293 mg, 1.30 mmol, 72%) as a colourless solid.

**Acid Reaction:** p-Toluenesulfonic acid monohydrate (45 mg, 0.24 mmol, 1.1 eq) was added in one portion to a stirred solution of bicyclic 1,2-diazetidine 10d (58 mg, 0.21 mmol, 1.0 eq) in CH₂Cl₂ (1 mL) at room temperature under argon, then stirred at room temperature for 10 minutes. The reaction mixture was quenched with a saturated aqueous solution of NaHCO₃ (1 mL), the organic layer was separated and the aqueous phase was extracted with CH₂Cl₂ (5 x 5 mL). The combined organic layers were dried (MgSO₄) and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1→2:1) gave the degraded bicycle 317d (23 mg, 0.10 mmol, 50%) as a colourless solid and diene 320 (33 mg, 0.07 mmol, 35%) as a colourless solid.

**Bicycle 317d**

\[ R_f \text{ (Hexane-EtOAc, 2:1) = 0.07} \]

mp = 134-136 °C

\(^1\text{H NMR (400 MHz, CDCl}_3\); }\delta 7.21 \text{ (br s, 1H, NH), 6.42-6.41 (br m, 1H, H1 or H2), 6.34-6.33 (br m, 1H, H1 or H2), 5.44-5.42 (br m, 2H, H3 and H4), 1.50 (s, 9H, H8).} \]

\(^{13}\text{C NMR (100 MHz, CDCl}_3\); }\delta 153.6 \text{ (C5 or C6), 151.9 (C5 or C6), 141.5 (C1 or C2), 140.2 (C1 or C2), 83.6 (C7), 81.5 (C3), 60.2 (C4), 28.3 (C8).} \]

\(^1\text{H NMR (400 MHz, }d_6-\text{DMSO); }\delta 9.84 \text{ (br s, 1H, NH), 6.55-6.52 (br m, 1H, H1), 5.41-5.39 (br m, 1H, H2), 5.43-5.41 (br m, 1H, H3), 5.33-5.31 (br m, 1H, H4), 1.44 (br s, 18H, H8).} \]
Experimental

$^{13}$C NMR (100 MHz, $d_6$-DMSO); $\delta$ 154.1 (C6), 151.7 (C5), 142.2 (C1), 140.3 (C2), 81.8 (C7), 81.2 (C3), 60.6 (C4), 27.7 (C8).

FTIR (ATR) $\nu$ (cm$^{-1}$): 3293 (NH), 2982, 2933, 1728 (C=O), 1683 (C=O).

HRMS (ESI): $m/z$ calculated for: C$_{10}$H$_{14}$N$_2$O$_4$ [M+Na]$^+$ 249.0846, found 249.0839.

Diene 320

![Diene 320 structure](image)

Important NOE Contacts:

$H^1 \leftrightarrow H^{12}$

$H^3 \leftrightarrow H^N$

$H^4 \leftrightarrow H^2$

$R_f$ (Hexane-EtOAc, 2:1) = 0.29

mp = 48-50 °C

$^1$H NMR (400 MHz, $d_6$-DMSO); $\delta$ 9.19-8.69 (br m, 1H, NH), 7.79 (d, $J$ = 8.2 Hz, 2H, H12), 7.49 (d, $J$ = 8.2 Hz, 2H, H13), 7.05 (br d, $J$ = 13.6 Hz, 1H, H4), 6.72 (br d, $J$ = 11.7 Hz, 1H, H1), 6.16 (br t, $J$ = 11.4 Hz, 1H, H2), 5.55 (br t, $J$ = 12.5 Hz, 1H, H3), 2.43 (s, 3H, H15), 1.49-1.38 (br m, 18H, H7 and H10).

$^{13}$C NMR (100 MHz, $d_6$-DMSO, additional peaks due to complex rate processes denoted by an asterisk); $\delta$ 153.7 (C5 and C8), 145.0 (C14), 134.9 (C1), 131.8 (C11), 131.3 (C4), 129.8 (C13), 127.4 (C12), 119.5 (C2), 101.9 (C3), 81.6 (C5 or C9), 79.6 (C5 or C9), 76.8 (C5 or C9), 27.8* (C7 or C10), 27.7 (C7 or C10), 27.3 (C7 or C10), 20.7 (C15).

FTIR (ATR) $\nu$ (cm$^{-1}$): 3326 (NH), 2978, 1721 (C=O), 1709 (C=O), 1367 (SO$_2$), 1145 (SO$_2$).

HRMS (ESI): $m/z$ calculated for: C$_{21}$H$_{30}$N$_2$O$_7$S [M+Na]$^+$ 477.1666 and [M-H] - 453.1 477.1669 and 453.1714, respectively.

5-oxa-2,3-diazabicyclo[4.2.0]oct-7-en-4-one 330

![5-oxa-2,3-diazabicyclo[4.2.0]oct-7-en-4-one 330](image)

$\text{ZnCl}_2$ (40 mg, 0.29 mmol, 2.7 eq) was added in one portion to a stirred solution of bicyclic 1,2-diazetidine 10d (31 mg, 0.11 mmol, 1.0 eq) in MeOH (0.2 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 19 hours, then evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: CH$_2$Cl$_2$-MeOH, 100:0→99:1→98:1) gave the bicycle 330 as an orange oil with impurities.

$R_f$ (CH$_2$Cl$_2$-MeOH, 96:4) = 0.11

$^1$H NMR (400 MHz, $d_6$-DMSO); $\delta$ 8.45 (br s, 2H, NH$_B$), 6.41-6.38 (br m, 1H, H1), 6.31-6.28 (br m, 1H, H2), 5.48-5.45 (br m, H, NH$_A$), 5.20-5.16 (br m, H, H3), 4.22-4.18 (br m, 1H, H4).

$^{13}$C NMR (100 MHz, $d_6$-DMSO); $\delta$ 154.2 (C5), 142.3 (C1), 138.9 (C2), 80.3 (C3), 61.0 (C4).
Photocyclisation: A New Route to Functionalised Four-Membered Rings

FTIR (ATR) ν (cm⁻¹): 3319 (NH), 1655 (C=O).
HRMS (APCI): m/z calculated for: C₅H₆N₂O₂ [M+H]+ 127.0502, found 127.0509.

**Important NOE contacts:**

An aqueous 10% NaIO₄ solution (20 mL) was added dropwise to a stirred solution of bicyclic 1,2-diazetidine 10d (402 mg, 1.42 mmol, 1.0 eq) and RuO₂·xH₂O (2 mg, 0.01 mmol, 0.01 eq) in EtOAc (14 mL) at 0 °C, then stirred at room temperature for 41 hours. The organic layer was separated, the aqueous layer was saturated with NaCl and extracted with EtOAc (5 x 10 mL). Isopropanol (2 mL) was added to the combined organic layers and left to stand for 2 hours. The organic layer was dried (MgSO₄), filtered through Celite and evaporated under reduced pressure to give diacid 332 (374 mg, 1.08 mmol, 76%) as a grey solid.

Rf (CH₂Cl₂-MeOH, 9:1) = baseline
mp = 168-170 °C (decomposition)

¹H NMR (400 MHz, d₄-MeOD); δ 5.05 (s, 2H, H2), 1.48 (s, 18H, H5).

¹³C NMR (100 MHz, d₄-MeOD); δ 170.2 (C1), 159.9 (C3), 84.0 (C4), 63.2 (C2), 28.3 (C5).

An aqueous 10% NaIO₄ solution (2.1 mL) was added dropwise to a stirred solution of bicyclic 1,2-diazetidine 10d (50 mg, 0.18 mmol, 1.0 eq) and RuO₂·xH₂O (1 mg, 0.01 mmol, 0.05 eq) in EtOAc (1.8 mL) at 0 °C, then stirred at room temperature for 10 minutes. The organic layer was separated, the aqueous layer was saturated with NaCl and extracted with EtOAc (5 x 10 mL). Isopropanol (2 mL) was added to the combined organic layers and left to stand for 2 hours. The organic layer was dried (MgSO₄), filtered through Celite and evaporated under reduced pressure to give diacid 332 (374 mg, 1.08 mmol, 76%) as a grey solid.

Rf (CH₂Cl₂-MeOH, 9:1) = baseline
mp = 168-170 °C (decomposition)

¹H NMR (400 MHz, d₄-MeOD); δ 10.6 (br s, 2H, OH), 5.00 (br s, 2H, H2), 1.46 (s, 18H, H5).

¹³C NMR (100 MHz, CDCl₃); δ 170.8 (C1), 158.4 (C3), 84.2 (C4), 61.6 (C2), 28.0 (C5).

FTIR (ATR) ν (cm⁻¹): 3078 (OH), 2980, 2935, 1718 (C=O).

**Di-tert-butyl 2,4-dihydroxy-3-oxa-6,7-diazabicyclo[3.2.0]heptane-6,7-dicarboxylate 333**

An aqueous 10% NaIO₄ solution (2.1 mL) was added dropwise to a stirred solution of bicyclic 1,2-diazetidine 10d (50 mg, 0.18 mmol, 1.0 eq) and RuO₂·xH₂O (1 mg, 0.01 mmol, 0.05 eq) in EtOAc (1.8 mL) at 0 °C, then stirred at room temperature for 10 minutes. The organic layer was
separated, the aqueous layer was saturated with NaCl and extracted with EtOAc (5 x 5 mL). Isopropanol (1 mL) was added to the combined organic layers and left to stand for 2 hours. The organic layer was dried (MgSO₄), filtered through Celite and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 2:1→1:1) gave the bicycle 333 (50 mg, 0.15 mmol, 85%) as a colourless solid.

\[ R_f (\text{Hexane-EtOAc, 1:1}) = 0.11 \]

mp = 38-40 °C

\(^1\)H NMR (400 MHz, d₆-DMSO): \( \delta \) 6.63 (d, \( J = 5.5 \) Hz, 2H, OH), 5.50 (d, \( J = 5.5 \) Hz, 2H, H1), 4.60 (br s, 2H, H2), 1.41 (s, 18H, H5).

\(^{13}\)C NMR (100 MHz, d₆-DMSO): \( \delta \) 157.0 (C₃), 99.1 (C1), 81.4 (C4), 69.1 (C2), 27.7 (C5).

FTIR (ATR) \( \nu \) (cm\(^{-1}\)): 3407 (OH), 2980, 2935, 1702 (C=O)

HRMS (ESI): \( m/z \) calculated for: C₁₄H₂₄N₂O₇ [M+Na]⁺ 355.1476, found 355.1468.

\( \text{1,2-di-\textit{tert}-butyl 3,4-dimethyl 1,2-diazetidine-1,2,3,4-tetracarboxylate 337} \)

(Trimethylsilyl)diazomethane (2M solution in hexanes, 0.8 mL, 1.60 mmol, 10 eq) was added dropwise to a stirred solution of diacid 332 (54 mg, 0.156 mmol, 1.0 eq) in MeOH (1.4 mL) at room temperature, then stirred for 10 minutes. The solvent was removed under reduced pressure. The residue was dissolved in CHCl₃ (2 mL), washed with a saturated solution of sodium thiosulfate (5 mL), dried (Na₂SO₄) and the solvent removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 7:1→4:1) gave the diester 337 as a colourless film (41 mg, 0.11 mmol, 70%).

\[ R_f (\text{Hexane-EtOAc, 1:1}) = 0.48 \]

\(^1\)H NMR (400 MHz, CDCl₃): \( \delta \) 4.94 (s, 2H, H3), 3.76 (s, 6H, H1) 1.47 (s, 18H, H6).

\(^{13}\)C NMR (100 MHz, CDCl₃): \( \delta \) 167.7 (C2), 158.0 (C4), 83.2 (C5), 61.4 (C3), 52.9 (C1), 28.1 (C6).

FTIR (ATR) \( \nu \) (cm\(^{-1}\)): 2980, 1752 (C=O ester), 1709 (C=O carbamate).

HRMS (ESI): \( m/z \) calculated for: C₁₆H₂₈N₂O₈ [M+Na]⁺ 397.1581, found 397.1585; [2M+Na]⁺ 771.3271, found 771.3271.

\( \text{Di-\textit{tert}-butyl 3-ethenyl-4-[(E/Z)-2-phenylethenyl]-1,2-diazetidine-1,2-dicarboxylate 340a,b} \)
Photocyclisation: A New Route to Functionalised Four-Membered Rings

Styrene (61 µL, 0.53 mmol, 5.0 eq) was added in one portion to a stirred solution of bicyclic 1,2-diazetidine 10d (30 mg, 0.11 mmol, 1.0 eq) and Hoveyda-Grubbs 2nd generation catalyst (3 mg, 0.01, 0.05 eq) in CH₂Cl₂ at room temperature under argon, then heated at reflux for 1 hour. The reaction mixture was cooled to room temperature and the solvent removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (elucent: hexane-EtOAc, 11:1→7:1) gave the 1,2-diazetidine 340a,b (30 mg, 0.08 mmol, 73%, E:Z 1.0:1.5) as a light brown oil.

**Z-isomer 340a**

$R_f$ (Hexane-EtOAc, 2:1) = 0.48

$^1$H NMR (400 MHz, CDCl₃); δ 7.36-7.27 (m, 3H, H⁹ and H¹⁰), 7.21-7.18 (m, 2H, H⁸), 6.80 (d, J = 11.5 Hz, 1H, H⁶), 5.99-5.84 (m, 2H, H² and H⁵), 5.47-5.36 (m, 3H, H¹, H¹ and H⁴), 4.90-4.84 (m, 1H, H³), 1.47 (br s, 9H, H¹³), 1.44 (br s, 9H, H¹⁶).

$^{13}$C NMR (100 MHz, CDCl₃); δ 159.2 (C¹¹), 158.2 (C¹⁴), 135.8 (C⁷), 135.0 (C⁶), 132.3 (C²), 128.7 (C⁸), 128.5 (C⁹), 127.9 (C¹⁰), 126.1 (C⁵), 120.6 (C¹), 82.1 (C¹³ and C¹⁵), 66.8 (C³), 61.9 (C⁴), 28.3 (C¹³ or C¹⁶), 28.3 (C¹³ or C¹⁶).

FTIR (ATR) ν (cm⁻¹): 2978, 2932, 1702 (C=O).


**E-isomer 340b**

$R_f$ (Hexane-EtOAc, 2:1) = 0.44
An aqueous solution of NaOH (50% w/v, 1.6 mL) was added dropwise to a solution of bicyclic 1,2-diazetidine 10d (56 mg, 0.20 mmol, 1.0 eq) and tetrabutylammonium chloride (5 mg, 0.02 mmol, 0.1 eq) in CHCl₃ (3.5 mL) at room temperature under argon, then stirred at room temperature for 5 hours. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl (2 mL) and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (5 x 5 mL), the combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 9:1) gave diazepine 344 (13 mg, 0.04 mmol, 21%) as a colourless film.

\[ R_f \text{ (Hexane-EtOAc, 2:1) = 0.52} \]

\(^1\)H NMR (400 MHz, CDCl₃); \( \delta \) 6.50-6.47 (m, 2H, H1), 5.88-5.85 (m, 2H, H2), 1.52 (s, 18H, H6).

\(^{13}\)C NMR (100 MHz, CDCl₃); \( \delta \) 155.6 (C3), 151.5 (C4), 131.8 (C1), 128.0 (C2), 84.3 (C5), 28.1 (C6).

\(^1\)H NMR (400 MHz, \( d_6 \)-DMSO); \( \delta \) 6.51-6.48 (m, 2H, H1), 6.04-6.00 (m, 2H, H2), 1.45 (m, 2H, H6).

\(^{13}\)C NMR (100 MHz, \( d_6 \)-DMSO); \( \delta \) 154.3 (C3), 150.6 (C4), 127.5 (C1), 118.5 (C2), 83.7 (C5), 27.4 (C6).

FTIR (ATR) \( \nu \text{ (cm}^{-1}) \): 2980, 2933, 1718 (C=O).

HRMS (ESI): \( m/z \) calculated for: C₁₅H₂₂N₂O₅ \([\text{M+Na]}^+\) 333.1421, found 333.1404.
Di-tert-butyl (1Z,3Z)-buta-1,3-diene-1,4-diylbiscarbamate 350

Sml₂ prepared according to a previously reported procedure.\(^{305}\)

Note: It was essential for dry THF without stabilisers to be used for the preparation of Sml₂.

A solution of Sml₂ in THF (0.075 M, 21 mL, 1.57 mmol, 2.2 eq) was added in one portion to a stirred degassed solution of bicyclic 1,2-diazetidine 10d (202 mg, 0.72 mmol, 1.0 eq) in MeOH (7.2 mL) at room temperature under argon, then stirred at room temperature for 30 minutes. The reaction mixture was purged with air until the colour changed from blue to yellow and the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 14:1→9:1) gave diene 350 (48 mg, 0.17 mmol, 24%) as a colourless solid

\[ R_f (\text{Hexane-EtOAc}, 2:1) = 0.48 \]

\[ \text{mp} = 206-208 \degree \text{C (decomposition)} \]

\(^1\)H NMR (400 MHz, CDCl₃); \( \delta \) 6.47-6.26 (br m, 4H, NH, H₁), 5.17-4.99 (br m, 2H, H₂), 1.48 (br s, 18H, H₅).

\(^{13}\)C NMR (100 MHz, CDCl₃); \( \delta \) 152.6 (C₃), 122.3 (C₁), 100.2 (C₂), 81.3 (C₄), 28.4 (C₅).

\(^1\)H NMR (400 MHz, d₆-DMSO); \( \delta \) 9.07-8.77 (br m, 2H, NH), 6.14-6.04 (br m, 2H, H₁), 5.66-5.49 (br m, 2H, H₂), 1.43 (br s, 18H, H₅).

\(^{13}\)C NMR (100 MHz, d₆-DMSO); \( \delta \) 153.1 (C₃), 121.0 (C₁), 102.2 (C₂), 79.2 (C₄), 28.0 (C₅).

FTIR (ATR) \( \nu \) (cm⁻¹): 3325 (NH), 2980, 2935, 1690 (C=O), 1621 (C=O).


Di-tert-butyl 1-(cyclobut-2-en-1-yl)hydrazine-1,2-dicarboxylate 353

Na/NH₃(l) Reaction: A solution of bicyclic 1,2-diazetidine 10d (50 mg, 0.18 mmol, 1.0 eq) in THF (3 mL) was added to a stirred solution of distilled ammonia (3 mL) at -78 °C under argon.

Sodium metal (41 mg, 1.77 mmol, 10 eq) was added portion wise at -78 °C, then the reaction mixture was warmed to room temperature. The reaction mixture was left at room temperature overnight to remove the ammonia. The residue was dissolved in EtOAc (5 mL), dried (MgSO₄) and the solvent removed under reduced pressure to give the crude product. Purification by flash...
column chromatography on silica gel (eluent: hexane-EtOAc, 9:1→4:1) gave a mixture of cyclobutene 353 and diene 354 (44 mg, 0.16 mmol, 87%, 2.4:1.0 353:354) as a white cloudy oil.

**Zinc/Ammonium Chloride reaction:** NH₄Cl (15 mg, 0.20 mmol, 1.1 eq) was added in one portion to a stirred suspension of bicyclic 1,2-dizetidine 10d (53 mg, 0.19 mmol, 1.0 eq) and zinc powder (123 mg, 1.88 mmol, 10 eq) in MeOH (0.4 mL) at room temperature under argon, then stirred at room temperature for 22 hours. The reaction mixture was filtered through Celite and the filtrate evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 9:1→4:1) gave a mixture of cyclobutene 353 and diene 354 (42 mg, 0.15 mmol, 79%, 1.0:1.4 353:354) as a white cloudy oil.

*Note:* Diene 354 can be isolated as a colourless solid with careful purification. *The purification of cyclobutene 353 always resulted in the presence of diene 354.*

**Cyclobutene 353**

\[ R_f (\text{Hexane-EtOAc, 2:1}) = 0.46 \]

\(^1\)H NMR (400 MHz, \(d_6\)-DMSO); \(\delta\) 8.92-8.51 (br m, 1H, NH), 6.16-6.08 (br m, 1H, H1), 5.94-5.80 (br m, 1H, H2), 5.10-4.84 (br m, 1H, H4), 2.69-2.40 (br m, 2H, H3), 1.43-1.38 (br m, 18H, H7 and H10).

\(^13\)C NMR (100 MHz, \(d_6\)-DMSO, additional peaks due to rotamers annotated by an asterisk); \(\delta\) 155.6* (C5 or C8), 155.4 (C5 or C8), 154.0* (C5 or C8), 153.7 (C5 or C8), 137.2 (C1), 136.4* (C2), 136.2 (C2), 80.0* (C6 or C9), 79.6 (C6 or C9), 79.1 (C6 or C9), 56.3* (C4), 55.9 (C4), 55.6* (C4), 36.3 (C3), 28.0 (C7 or C10), 27.9 (C7 or C10).

FTIR (ATR) \(\nu\) (cm\(^{-1}\)): 3301 (NH), 2976, 2928, 1702 (C=O).

HRMS (ESI): \(m/z\) calculated for: \(C_{14}H_{24}N_2O_4\) [M+Na]\(^+\) 307.1628, found 307.1637.

**Important NOE contacts:**
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Diene 354

\[
\begin{align*}
\text{Rf (Hexane-EtOAc, 2:1)} & = 0.52 \\
\text{mp} & = 96-98 \text{ °C}
\end{align*}
\]

1H NMR (400 MHz, d6-DMSO); \( \delta \) 9.24-8.70 (br m, 1H, NH), 7.06 (br d, J = 13.6 Hz, 1H, H4), 6.42-6.32 (m, 1H, H2), 5.68-5.62 (m, 1H, H3), 5.06-5.01 (m, 1H, H1A), 4.89-4.86 (m, H, H1b), 1.47-1.41 (br m, 18H, H7 and H10).

13C NMR (100 MHz, d6-DMSO); \( \delta \) 153.7 (C5 and C8), 134.3 (C2), 130.2 (C4), 112.7 (C1), 109.6 (C3), 81.4 (C6 or C9), 79.5 (C6 or C9), 27.7 (C7 or C10), 27.4 (C7 or C10).

FTIR (ATR) \( \nu \) (cm\(^{-1}\)): 3289 (NH), 2978, 2932, 1715 (C=O), 1649 (C=O).

HRMS (ESI or APCI): target mass not found.

Di-tert-butyl 2,3-diazabicyclo[2.2.0]hexane-2,3-dicarboxylate 308d and di-tert-butyl 1,2-diazinane-1,2-dicarboxylate 356

Palladium on carbon (10 wt. %, 38 mg, 0.04 mmol, 0.05 eq) was added in one portion to a stirred solution of bicyclic 1,2-diazetidine 10d (201 mg, 0.71 mmol, 1.0 eq) in 7:1 THF:EtOH (8 mL) at room temperature under argon. The reaction flask was evacuated and refilled with hydrogen gas three times and then stirred at room temperature for 24 hours. The reaction mixture was filtered through Celite and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 9:1→4:1) gave the saturated bicycle 308d (13 mg, 0.05 mmol, 6%) as a colourless oil and diazinane 356 (174 mg, 0.61 mmol, 85%) as a colourless solid.

Saturated bicycle 308d

\[
\begin{align*}
\text{Rf (Hexane-EtOAc, 4:1)} & = 0.17 \\
\text{1H NMR (400 MHz, CDCl3)}; \delta \text{ 4.68-4.66 (br m, 2H, H2), 2.55-2.52 (br m, 4H, H1), 1.50 (br s, 18H, H5).}
\end{align*}
\]

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$^{13}$C NMR (100 MHz, CDCl$_3$); $\delta$ 158.7 (C3), 81.9 (C4), 64.1 (C2), 28.3 (C5), 27.4 (C1).

FTIR (ATR) $\nu$ (cm$^{-1}$): 2976, 2932, 1739 (C=O), 1700 (C=O).

HRMS (ESI and APCI): Target mass not found.

**Diazinane 356**

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{3} \\
\text{2} \\
\text{1} \\
\text{H} \\
\text{2} \\
\text{5} \\
\end{array}
\]

$R_{f}$ (Hexane-EtOAc, 4:1) = 0.24

mp = 56-58 °C

$^1$H NMR (400 MHz, CDCl$_3$); $\delta$ 4.16-3.97 (br m, 2H, H1$_A$), 3.05-2.82 (br m, 2H, H1$_B$), 1.66-1.57 (br m, 2H, H2), 1.46 (br s, 18H, H5).

$^{13}$C NMR (100 MHz, CDCl$_3$, additional peaks due to complex rate processes annotated by an asterisk, C3 not observed); $\delta$ 80.7 (C4), 46.5* (C1), 44.5 (C1), 28.4 (C5), 24.1* (C2), 23.7 (C2).

$^1$H NMR (400 MHz, $d_6$-DMSO); $\delta$ 4.01-3.83 (br m, 2H, H1$_A$), 2.94-2.70 (br m, 2H, H1$_B$), 1.62-1.37 (br m, 22H, H2 and H5).

$^{13}$C NMR (100 MHz, $d_6$-DMSO, additional peaks due to complex rate processes annotated by an asterisk); $\delta$ 153.9* (C3), 153.5 (C3), 153.1* (C3), 80.2* (C4), 79.8 (C4), 46.3* (C1), 46.0* (C1), 44.0 (C1), 43.5* (C1), 27.9 (C5), 23.4* (C2), 23.0 (C2).

$^1$H NMR (400 MHz, 348 K, $d_6$-DMSO); $\delta$ 4.01-3.89 (br m, 2H, H1$_A$), 2.88-2.79 (br m, 2H, H1$_B$), 1.63-1.42 (br m, 22H, H2 and H5).

$^{13}$C NMR (100 MHz, 348 K, $d_6$-DMSO); $\delta$ 153.1 (C3), 79.5 (C4), 44.4 (C1), 27.6 (C5), 22.8 (C2).

FTIR (ATR) $\nu$ (cm$^{-1}$): 2982, 2932, 1690 (C=O).

HRMS (APCI): $m/z$ calculated for: C$_{14}$H$_{26}$N$_2$O$_4$ [M+Na]$^+$ 309.1785, found 309.1794.

**Di-tert-butyl-1-[2,3-bis(methoxycarbonyl)cyclohexa-2,5-dien-1-yl]hydrazine-1,2-dicarboxylate 357**

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{N} \\
\text{O} \\
\text{O} \\
\end{array}
\]

Dimethyl acetylenedicarboxylate 223 (78 µL, 0.64 mmol, 5.0 eq) was added in one portion to a stirred solution of diene 354 (36 mg, 0.13 mmol, 1.0 eq) in MeCN (1.3 mL). The reaction was heated at 60 °C for 17 hours, then cooled to room temperature and evaporated under reduced
pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: CH₂Cl₂-MeOH, 100:0→99:1) gave cycloadduct 357 (42 mg, 0.10 mmol, 76%) as a colourless oil. 

\[ R_I (\text{Hexane-EtOAc, 1:1}) = 0.48 \]

¹H NMR (400 MHz, 378 K, d₆-DMSO); δ 7.84 (br s, 1H, NH), 5.99-5.94 (br m, 1H, H2), 5.77-5.72 (br m, 1H, H3), 5.50-5.46 (br m, 1H, H4), 3.71 (s, 3H, H8 or H10), 3.67 (s, 3H, H8 or H10), 3.04-2.80 (br m, 2H, H1A and H1B), 1.42 (s, 9H, H13 or H16), 1.40 (s, 9H, H13 or H16).

¹³C NMR (100 MHz, 378 K, d₆-DMSO, C₄ not visible, additional peaks due to complex rate processes annotated by an asterisk); δ 166.6 (C₈ or C10), 165.7 (C₈ or C10), 154.7 (C11 or C14), 153.3 (C11 or C14), 125.4 (C2), 122.4 (C3), 79.9 (C12 or C15), 79.0 (C12 or C15), 78.5* (C12 or C15), 51.3 (C8 or C10), 51.1 (C8 or C10), 27.6* (C13 or C16), 27.4 (C13 or C16), 27.4 (C13 or C16), 26.9 (C1).

FTIR (ATR) \( \nu (\text{cm}^{-1}) \): 3330 (NH), 2978, 1720 (C=O).

HRMS (ESI or APCI); \( m/z \) calculated for: C₂₀H₃₀N₂O₈ [M+Na]+ 449.1894, found 449.1890.

Note: When the NMR sample of 357 (in d₆-DMSO) was heated at temperatures above 130 °C, dimethyl benzene-1,2-dicarboxylate 358 and di-tert-butyl hydrazodicarboxylate 43d were formed.

**Dimethyl benzene-1,2-dicarboxylate 358**

\[
\text{H NMR (400 MHz, d₆-DMSO); } \delta 7.75-7.72 (m, 2H, H1), 7.69-7.66 (m, 2H, H2), 3.82 (s, 6H, H5).
\]

**Di-tert-butyl hydrazodicarboxylate 43d**

\[
\text{H NMR (400 MHz, d₆-DMSO); } \delta 8.61-8.14 (br m, 2H, NH), 1.38 (br s, 18H, H3).
\]

\[
\text{C NMR (100 MHz, d₆-DMSO, additional peaks due to rotamers denoted by an asterisk); } \delta 155.6 (C1), 79.0* (C2), 78.9 (C2), 28.2* (C3), 28.1 (C3), 27.9* (C3).
\]
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Express Reaction of Dimethyl Azodicarboxylate to Prepare Polycyclic Aza


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Chapter 8: Appendix
8.1 X-Ray Data

1. X-Ray Crystal Structure Data for 9c

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<th>Identification code</th>
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<td>2θ range for data collection/°</td>
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Index ranges
-23 \leq h \leq 17, -9 \leq k \leq 9, -23 \leq l \leq 24

Reflections collected
13406

Independent reflections
2731 [R_{int} = 0.0188, R_{sigma} = 0.0099]

Data/restraints/parameters
2731/0/167

Goodness-of-fit on F^2
1.057

Final R indexes [I=>2σ (I)]
R_1 = 0.0336, wR_2 = 0.0847

Final R indexes [all data]
R_1 = 0.0340, wR_2 = 0.0850

Largest diff. peak/hole / e Å^3
0.22/-0.28

2. X-Ray Crystal Structure Data for 218

Identification code
MC231-new

Empirical formula
C_{14}H_{22}N_{2}O_{5}

Formula weight
298.33

Temperature/K
293(2)

Crystal system
triclinic

Space group
P-1

a/Å
6.2354(2)

b/Å
11.0207(5)

c/Å
12.4263(6)

α/°
82.256(4)

β/°
79.645(4)

γ/°
83.269(4)
Volume/Å³  828.55(6)
Z  2
ρ_{calc}/g/cm³  1.196
μ/mm⁻¹  0.758
F(000)  320.0
Crystal size/mm³  0.472 × 0.082 × 0.025
Radiation  CuKα (λ = 1.54184)
2Θ range for data collection/°  7.282 to 152.928
Index ranges  -7 ≤ h ≤ 7, -13 ≤ k ≤ 13, -15 ≤ l ≤ 15
Reflections collected  17030
Independent reflections  3456 [R_{int} = 0.0373, R_{sigma} = 0.0226]
Data/restraints/parameters  3456/0/196
Goodness-of-fit on F²  1.048
Final R indexes [I>=2σ (I)]  R₁ = 0.0449, wR² = 0.1273
Final R indexes [all data]  R₁ = 0.0491, wR² = 0.1323
Largest diff. peak/hole / e Å⁻³  0.20/-0.20

3. X-Ray Crystal Structure Data for 238

Identification code  SC106
Empirical formula  C_{12}H_{20}N_{2}O_{6}
Formula weight  288.30
Temperature/K  100
Crystal system  monoclinic
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Space group P2₁/c

a/Å 10.0193(3)
b/Å 14.8599(4)
c/Å 9.9341(3)
α/° 90
β/° 110.451(3)
γ/° 90
Volume/Å³ 1385.83(7)
Z 4
ρ calc/g/cm³ 1.382
μ/mm⁻¹ 0.942
F(000) 616.0
Crystal size/mm³ 0.218 × 0.092 × 0.07
Radiation CuKα (λ = 1.54184)
2Θ range for data collection/° 9.42 to 153.318
Index ranges -12 ≤ h ≤ 12, -18 ≤ k ≤ 18, -10 ≤ l ≤ 12
Reflections collected 9374
Independent reflections 2863 [R int = 0.0287, R sigma = 0.0238]
Data/restraints/parameters 2863/0/187
Goodness-of-fit on F² 1.073
Final R indexes [I>=2σ (I)] R₁ = 0.0399, wR₂ = 0.1049
Final R indexes [all data] R₁ = 0.0420, wR₂ = 0.1065
Largest diff. peak/hole / e Å⁻³ 0.38/0.30
4. X-Ray Crystal Structure Data for 241

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</tr>
<tr>
<td>Volume/Å³</td>
<td>1897.44(7)</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>ρ_{calc}/g/cm³</td>
<td>1.471</td>
</tr>
<tr>
<td>μ/mm⁻¹</td>
<td>5.859</td>
</tr>
<tr>
<td>F(000)</td>
<td>864.0</td>
</tr>
<tr>
<td>Crystal size/mm³</td>
<td>0.433 × 0.247 × 0.18</td>
</tr>
</tbody>
</table>
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Radiation CuKα (λ = 1.54184)

2Θ range for data collection/° 7.6 to 152.966

Index ranges -11 ≤ h ≤ 12, -14 ≤ k ≤ 15, -19 ≤ l ≤ 20

Reflections collected 29243

Independent reflections 7879 [R_int = 0.0347, R_sigma = 0.0205]

Data/restraints/parameters 7879/0/441

Goodness-of-fit on F² 1.175

Final R indexes [I>=2σ (I)] R₁ = 0.0470, wR₂ = 0.1223

Final R indexes [all data] R₁ = 0.0473, wR₂ = 0.1224

Largest diff. peak/hole / e Å⁻³ 0.61/-0.38

5. X-Ray Crystal Structure Data for 224

Identification code pre_MC201

Empirical formula C₁₈H₂₄N₂O₈

Formula weight 396.39

Temperature/K 292.52(10)

Crystal system monoclinic

Space group P2₁/n

a/Å 9.8453(3)

b/Å 7.5243(2)

c/Å 26.0993(11)
\[\begin{align*}
\alpha/° & \quad 90 \\
\beta/° & \quad 98.958(3) \\
\gamma/° & \quad 90 \\
\text{Volume/Å}^3 & \quad 1909.82(11) \\
Z & \quad 4 \\
\rho_{\text{calc}}/\text{cm}^3 & \quad 1.379 \\
\mu/\text{mm}^{-1} & \quad 0.924 \\
F(000) & \quad 840.0 \\
\text{Crystal size/mm}^3 & \quad 0.203 \times 0.036 \times 0.024 \\
\text{Radiation} & \quad \text{CuK}\alpha (\lambda = 1.54184) \\
2\Theta \text{ range for data collection/°} & \quad 9.206 \text{ to } 147.368 \\
\text{Index ranges} & \quad -12 \leq h \leq 11, -9 \leq k \leq 6, -31 \leq l \leq 31 \\
\text{Reflections collected} & \quad 13128 \\
\text{Independent reflections} & \quad 3805 [R_{\text{int}} = 0.0411, R_{\sigma} = 0.0393] \\
\text{Data/restraints/parameters} & \quad 3805/0/259 \\
\text{Goodness-of-fit on } F^2 & \quad 1.045 \\
\text{Final R indexes [I>=2σ (I)]} & \quad R_1 = 0.0384, wR_2 = 0.0876 \\
\text{Final R indexes [all data]} & \quad R_1 = 0.0512, wR_2 = 0.0933 \\
\text{Largest diff. peak/hole} / \text{e Å}^{-3} & \quad 0.28/-0.26
\end{align*}\]
6. X-Ray Crystal Structure Data for 10d

Identification code  SC107
Empirical formula  C_{14}H_{22}N_{2}O_{4}
Formula weight  282.33
Temperature/K  99.99(10)
Crystal system  monoclinic
Space group  P2_{1}/c
a/Å  8.95843(13)
b/Å  19.3911(2)
c/Å  9.66742(12)
α/°  90
β/°  114.1195(17)
γ/°  90
Volume/Å\(^3\)  1532.75(4)
Z  4
ρ_{calc} g/cm\(^3\)  1.223
μ/mm\(^-1\)  0.740
F(000)  608.0
Crystal size/mm\(^3\)  0.433 \times 0.309 \times 0.26
Radiation  CuKα (λ = 1.54184)
2Θ range for data collection/°  9.122 to 153.564
Index ranges
-11 ≤ h ≤ 11, -23 ≤ k ≤ 24, -12 ≤ l ≤ 12

Reflections collected
17499

Independent reflections
3203 \[R_{int} = 0.0248, R_{sigma} = 0.0127\]

Data/restraints/parameters
3203/0/187

Goodness-of-fit on $F^2$
1.027

Final R indexes [I>=2σ(I)]
$R_1 = 0.0369, wR_2 = 0.0913$

Final R indexes [all data]
$R_1 = 0.0374, wR_2 = 0.0918$

Largest diff. peak/hole / e Å$^{-3}$
0.25/-0.24

7. X-Ray Crystal Structure Data for 316d

Identification code
SC112

Empirical formula
C$_{14}$H$_{22}$N$_2$O$_4$

Formula weight
282.33

Temperature/K
100.0(3)

Crystal system
monoclinic

Space group
P2$_1$/c

a/Å
9.5903(10)

b/Å
18.1507(15)

c/Å
9.6769(12)

α°
90

β°
117.983(15)

γ°
90
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Volume/Å³ 1487.5(3)
Z 4
ρcalc g/cm³ 1.261
μ/mm⁻¹ 0.762
F(000) 608.0
Crystal size/mm³ 0.325 × 0.246 × 0.236
Radiation CuKα (λ = 1.54184)
2Θ range for data collection/° 9.746 to 155.142
Index ranges -10 ≤ h ≤ 12, -21 ≤ k ≤ 22, -12 ≤ l ≤ 12
Reflections collected 12121
Independent reflections 3103 [Rint = 0.0489, Rsigma = 0.0302]
Data/restraints/parameters 3103/0/187
Goodness-of-fit on F² 1.156
Final R indexes [I>=2σ (I)] R₁ = 0.0871, wR₂ = 0.1955
Final R indexes [all data] R₁ = 0.0891, wR₂ = 0.1962
Largest diff. peak/hole / e Å⁻³ 0.57/-0.41

8. X-Ray Crystal Structure Data for 317d

Identification code SC108
Empirical formula C₁₀H₁₄N₂O₄
Formula weight 226.23
Temperature/K 100.2(4)
Crystal system: monoclinic

Space group: P2_1/c

a/Å: 10.3330(6)
b/Å: 9.5174(5)
c/Å: 11.5317(7)
α/°: 90
β/°: 102.715(7)
γ/°: 90

Volume/Å³: 1106.26(11)

Z: 4

ρ_{calc}/g/cm³: 1.358

μ/mm⁻¹: 0.893

F(000): 480.0

Crystal size/mm³: 0.171 × 0.142 × 0.07

Radiation: CuKα (λ = 1.54184)

2Θ range for data collection/°: 8.772 to 152.362

Index ranges: -12 ≤ h ≤ 12, -11 ≤ k ≤ 11, -14 ≤ l ≤ 8

Reflections collected: 6952

Independent reflections: 2281 [R_{int} = 0.0313, R_{sigma} = 0.0277]

Data/restraints/parameters: 2281/0/148

Goodness-of-fit on F²: 1.056

Final R indexes [I>=2σ (I)]: R₁ = 0.0545, wR₂ = 0.1455

Final R indexes [all data]: R₁ = 0.0604, wR₂ = 0.1504

Largest diff. peak/hole / e Å⁻³: 0.65/-0.28
X-Ray Crystal Structure Data for 333

- **Identification code**: SC111
- **Empirical formula**: C_{28}H_{48}N_{4}O_{14}
- **Formula weight**: 664.70
- **Temperature/K**: 99.8(6)
- **Crystal system**: monoclinic
- **Space group**: P2_{1}/n
- **a/Å**: 6.1413(2)
- **b/Å**: 17.9643(7)
- **c/Å**: 30.8961(13)
- **α/°**: 90
- **β/°**: 91.127(4)
- **γ/°**: 90
- **Volume/Å³**: 3407.9(2)
- **Z**: 4
- **ρ_{calc}/cm³**: 1.296
- **μ/mm⁻¹**: 0.880
- **F(000)**: 1424.0
- **Crystal size/mm³**: 0.435 × 0.064 × 0.022
- **Radiation**: CuKα (λ = 1.54184)
- **2Θ range for data collection/°**: 7.548 to 155.91
- **Index ranges**: -5 ≤ h ≤ 7, -21 ≤ k ≤ 22, -36 ≤ l ≤ 38
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Reflections collected 32146
Independent reflections 7047 \([R_{int} = 0.0749, R_{sigma} = 0.0534]\)
Data/restraints/parameters 7047/0/431
Goodness-of-fit on \(F^2\) 1.043
Final R indexes \([I>=2\sigma (I)]\) \(R_1 = 0.0532, wR_2 = 0.1323\)
Final R indexes [all data] \(R_1 = 0.0746, wR_2 = 0.1497\)
Largest diff. peak/hole / e \(\text{Å}^{-3}\) 0.36/-0.23

9. X-Ray Crystal Structure Data for 350

Identification code SC117
Empirical formula \(\text{C}_{14}\text{H}_{24}\text{N}_{2}\text{O}_{4}\)
Formula weight 284.35
Temperature/K 99.9(2)
Crystal system monoclinic
Space group \(P2_1/n\)
a/Å 5.23750(9)
b/Å 8.83307(15)
c/Å 16.5180(3)
\(\alpha^\circ\) 90
\(\beta^\circ\) 92.6082(17)
\(\gamma^\circ\) 90
Volume/Å\(^3\) 763.39(2)
Z 2
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\[4\pi \text{ Photocyclisation: A New Route to Functionalised Four-Membered Rings}\]

\[\rho_{\text{calc}}/\text{cm}^3 = 1.237\]
\[\mu/\text{mm}^{-1} = 0.743\]
\[F(000) = 308.0\]
\[\text{Crystal size/mm}^3 = 0.109 \times 0.098 \times 0.082\]
\[\text{Radiation} = \text{CuK}\alpha (\lambda = 1.54184)\]

2\(\Theta\) range for data collection/° 10.724 to 153

Index ranges 
-6 \(\leq h \leq 6\), -11 \(\leq k \leq 11\), -17 \(\leq l \leq 20\)

Reflections collected 9639

Independent reflections 1589 \([R_{\text{int}} = 0.0415, R_{\text{sigma}} = 0.0201]\)

Data/restraints/parameters 1589/0/94

Goodness-of-fit on \(F^2\) 1.058

Final R indexes \([l >= 2\sigma (l)]\) \(R_1 = 0.0369, wR_2 = 0.0961\)

Final R indexes [all data] \(R_1 = 0.0386, wR_2 = 0.0977\)

Largest diff. peak/hole / e \(\text{Å}^{-3}\) 0.21/-0.23

8.2 Differential Scanning Calorimetry (DSC) Traces

1. Bicyclic 1,2-Diazetidine 10d

\[\text{8.2 Differential Scanning Calorimetry (DSC) Traces}\]

\[1. \text{ Bicyclic 1,2-Diazetidine 10d}\]
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2. Rearranged Bicycle 316d

3. Degraded Bicycle 317d