4-π Photocyclisation:

A New Route to Functionalised

Four-Membered Rings

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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.

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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-dihydropyrdazines 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.

Acknowledgements

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.

The most important thanks must go to my partner, Izzy, who has been unbelievably supportive, understanding, motivating and patient over the last 3.5 years. You took a leap of faith moving here, much like me, but you have been truly fantastic and now we can move forward into an exciting future. Thank you to my family (Sally, Russell, Nan, Emily, Jamie, Jack, Archie, James, Catherine, Edison, Brenda, Louise) for your unwavering support, not only throughout my PhD but throughout my entire academic career thus far. Thank you to my fantastic pets (Peanut, Cashew, Duchess and Poppy) for helping to take my mind off my PhD and providing a rare cuddle, though I am not thankful for all the rabbit fur that has gotten everywhere! Thank you to my boys from university (Dipen, Rob, Josh, Jack, Kam, Ross, Baines, Pete) for helping me to get through my PhD and I apologise that I have not seen some of you all that much.

Finally, I would like to thank everybody here in the Chemistry Department at Lancaster University for helping to create a great working environment and I will miss you all. I would like to personally thank Henry, Mark, Josh, Charlie, James, Bette, Abbie, Patch, Callum, Miles, Gillian, Eleanor, Vassilis, Dhruv, Ross, Ben, Olivia, Izaak, Stuart, Weronika, Bara, Chloe, Pip, Jack, Craig and Sapphire for making my PhD enjoyable and providing some fantastic memories.

Contents

List of Abbreviations and Acronyms

A	absorbance
Ac	acetyl
ADMET	absorption, distribution, metabolism, excretion and toxicity
AIBN	2,2'-azobis(2-methylpropionitrile)
Aq	aqueous
Ar	unspecified aryl group
APCI	atmospheric pressure chemical ionization
ATR	attenuated total reflection
BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bp	boiling point
br	broad
Bu	butyl
Bz	benzoyl
c	concentration
C	centigrade
CAN	cerium ammonium nitrate
COSY	correlation spectroscopy
Cy	cyclohexane
d	doublet
D	dimensional
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBAD	di-*tert*-butyl azodicarboxylate
DBB	di-*tert*-butylbiphenyl
DBU	1,8-diazabicycloundec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DMAD	dimethyl azodicarboxylate
DMAP	4-dimethylaminopyridine

DME	1,2-dimethoxyethane
DMEDA	1,2-dimethylethylenediamine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DPAD	diphenyl azodicarboxylate
dppp	1,3-bis(diphenylphosphino)propane
DSC	differential scanning calorimetry
EDG	electron donating group
ee	enantiomeric excess
Eq	equivalents
ESI	electrospray ionization
Et	ethyl
FTIR	fourier transform infrared
h	Planck's constant (6.626×10^{-34} Js)
HMBC	heteronuclear multiple-bond coherence
HMDS	bis(trimethylsilyl)amine
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
hr(s)	hour(s)
HSQC	heteronuclear single quantum coherence
Hz	hertz
i	iso
IBDA	iodobenzene diacetate
IBX	2-iodoxybenzoic acid
IR	infrared
ISC	intersystem crossing
IT	ion trap
J	coupling constant
l	path length
LED	light-emitting diode
LLAMA	lead-likeness and molecular analysis
logP	octanol-water partition coefficient
LUMO	lowest unoccupied molecular orbital
m	multiplet

M	molar
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeTAD	4-methyl-1,2,4-triazoline-3,5-dione
Mes	mesitylene
MIDA	methyliminodiacetic acid
mins	minutes
mL	millilitre
mm	millimetre
mmol	millimole
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	mass spectrometry
MTBE	methyl *tert*-butyl ether
m/*z*	mass/charge (mass spectrometry)
NBD	norbornadiene
NBS	*N*-bromosuccinimide
n.d	not determined
nm	nanometer
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
nOesy	nuclear overhauser effect spectroscopy
n.r	not reported
Ns	*p*-nitrobenzenesulfonyl
PCC	pyridinium chlorochromate
PG	unspecified protecting group
Ph	phenyl
PIBDA	polymer supported iodobenzene diacetate
Piv	pivaloyl
PMB	*para*-methoxybenzyl
ppm	parts per million
Pr	propyl
PTAD or PhTAD	4-phenyl-1,2,4-triazoline-3,5-dione
Py	pyridine

q	quartet
R	unspecified group
R_f	retention factor
rt	room temperature
s	singlet
SAR	structure-activity relationship
t	triplet
tert (^{t})	tertiary
^{t}Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
TCE	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
λ_{max}	absorption maximum
ε	molar absorption coefficient
°	degrees
ν	frequency
Δ	heat
ΔG	Gibbs free energy
δ	chemical shift
‡	transition state

Chapter 1: Introduction

1.1 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.[1] 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.[2,3] 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.[4,5] 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.[6] 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.[7] 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.[8] 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.[9] 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).[9] 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.[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.[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^2 systems, and the exploration of saturated systems (sp^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^3 carbon atoms.[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.[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.[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.[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.[13] Two literature studies on the reactions used within medicinal chemistry have shown that a lot of the same reactions are used.[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.[15]

The seminal analysis by Lovering and co-workers discovered the link between the presence of sp^3 character and/or chirality and the improved success of drug candidates going from discovery through to market.[16] A few years later, Lovering also reported that an increase in sp^3 character can improve the selectivity of drug candidates, thus reducing the amount of off-target interactions.[17] Through computational analysis, Hann and co-workers have shown that increasing molecular complexity (e.g. greater sp^3 character), resulted in fewer interactions of

compounds with off-target biological receptors.[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.[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^3 character resulted in improved selectivity.[20] In addition to selectivity, the use of saturated systems provides three-dimensional shapes, unlike flat sp^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.[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.[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.[6] 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^3 compounds over the time period, and many compounds violated one or more of Lipinski's rules of five.[22] An interesting example of the power of sp^3-hybridised compounds has been the use of cubane as a bioisostere for an aromatic ring (Figure 1.1).[23] In 1992, Eaton proposed the pharmaceutical potential of cubanes,[24] however it was over twenty years until Tsanaktsidis, Savage, Williams and various co-workers proved this.[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^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.[25]

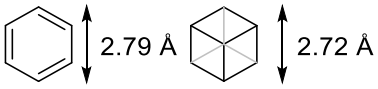


Figure 1.1

New open-access computational tools have recently been developed that can help guide synthetic methodology and provide more relevant scaffolds.[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).[27] The molecules generated are ranked according to a lead-likeness penalty based on guidelines proposed by Churcher and co-workers ($-1 \leq \log P \leq 3$, $14 \leq$heavy atoms≤ 26

e.g. molecular weight 200-350, remove reactive functional groups, decrease the amount sp^2 character e.g. 1 or 2 aromatic rings),[28] 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 sp^3 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]

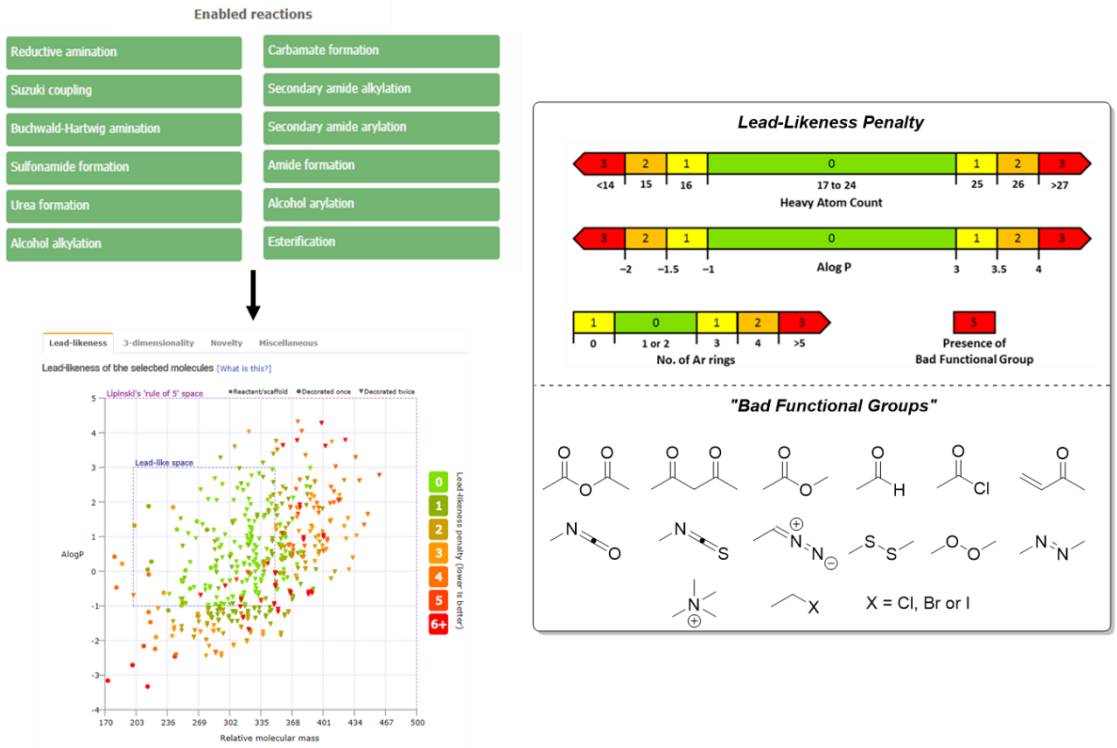


Figure 1.2 The lead-likeness penalty predicts whether a substrate will fall within lead-like space. Guidelines for good substrates: 14≤heavy atoms≤26 (count of all atoms apart from hydrogen), -1≤ logP≤3 (lipophilicity), number of aromatic rings = 1 or 2 (limit sp^2 character), presence of bad (reactive) 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 sp^3 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.

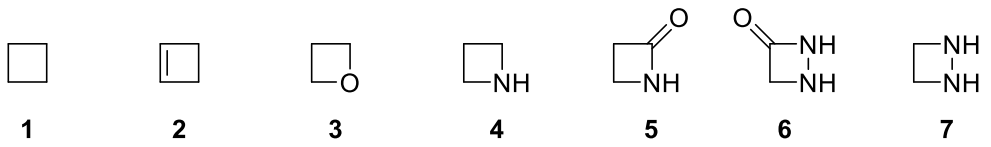
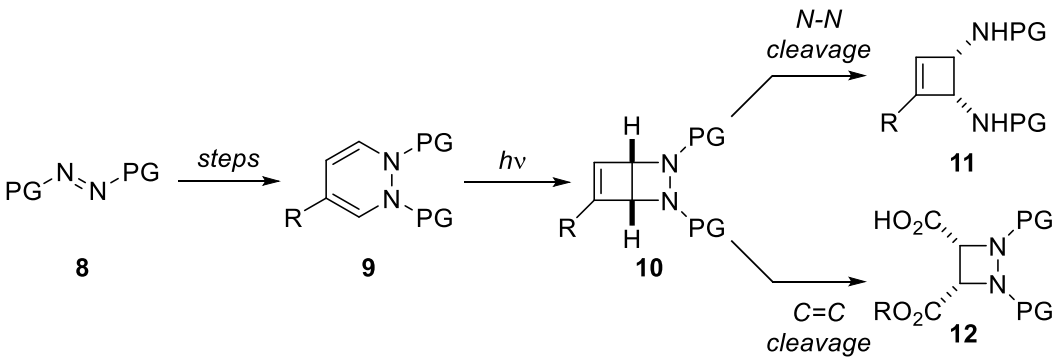


Figure 1.3

1.2 Project Aims and Objectives

The project aimed to develop new methodology for the photochemical 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,[33–36] 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.



Scheme 1.1 PG = protecting group

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.[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.[39,40]

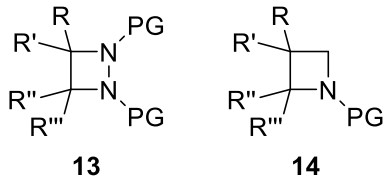
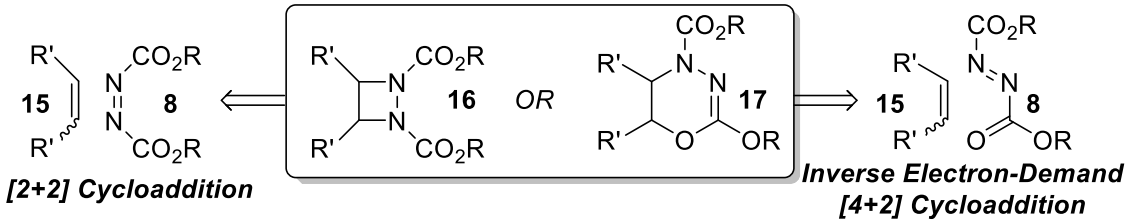


Figure 1.4

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

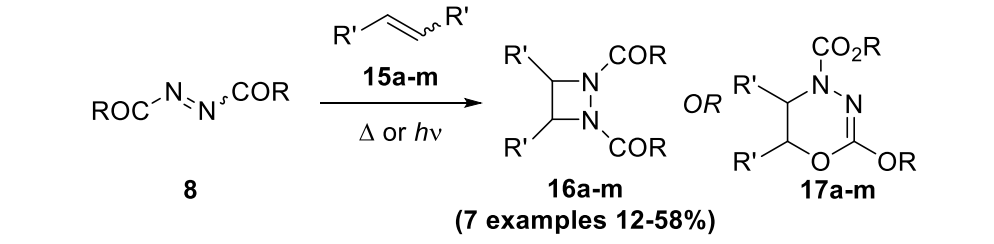
One of the most common ways to synthesise 1,2-diazetidines has been to utilise [2+2] cycloadditions of alkenes and azo compounds in which one of the two reactants must be activated with either electron donating or withdrawing groups. The most common examples have used azo compounds **8** bearing electron withdrawing groups (azodicarboxylates), whilst the alkene **15** possesses electron donating groups,[40] though there are limited examples using halogenated alkenes (Scheme 1.2).[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.[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.



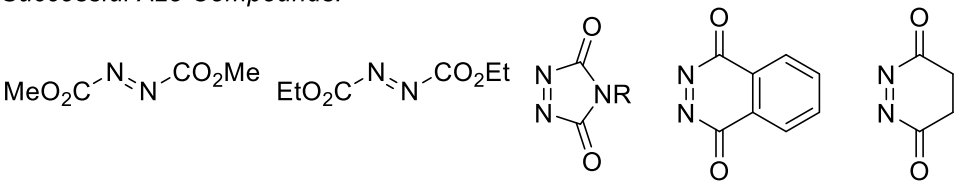
Scheme 1.2

The [2+2] cycloaddition of acyclic and cyclic azo compounds with a variety of different alkenes has given varied results (Scheme 1.3).[47–56] In 1926, Diels and Alder first reported the reaction of indene **15a** with an acyclic azo compound **8b**,[48] however it was originally proposed these two compounds underwent an ene reaction, not a [2+2] cycloaddition.[49] Huebner and co-workers

suggested that the 1,2-diazetidine had formed through analysis by infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy,[50] although a few years later a couple of different research groups concluded that the oxadiazine **17a** had formed.[51,53] 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.[51,54,55] 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.[57] 1,2-Diazetidines **16d-h** have also been successfully formed with azo compounds **8b,h** when diadamantyl-substituted alkene **15d**,[58,59] tetracyclopropylethene **15e**,[60] fluorinated diene **15f**, cyclopropyl alkene **15g** and various fluorinated alkenes **15h** were employed.[39,41,42,56,61] The use of cyclohexene **15i**, hex-1-ene **15j** or (*E/Z*)-but-2-ene **15k** resulted in an ene reaction taking place,[47,62] 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**.[56,63]

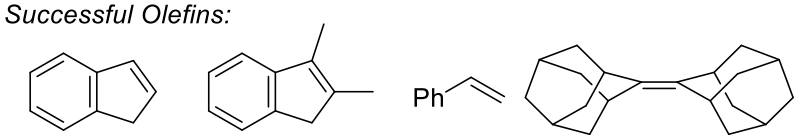


Successful Azo Compounds:

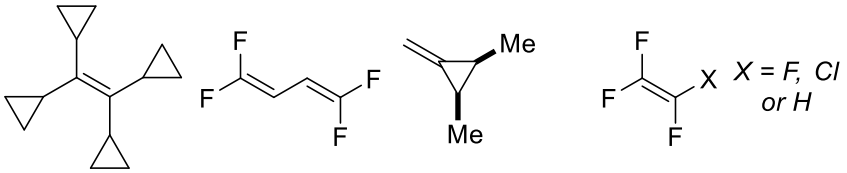


8a **8b** **8h,n** **8o** **8p**

Successful Olefins:

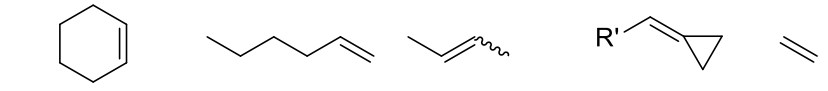


15a **15b** **15c** **15d**



15e **15f** **15g** **15h**

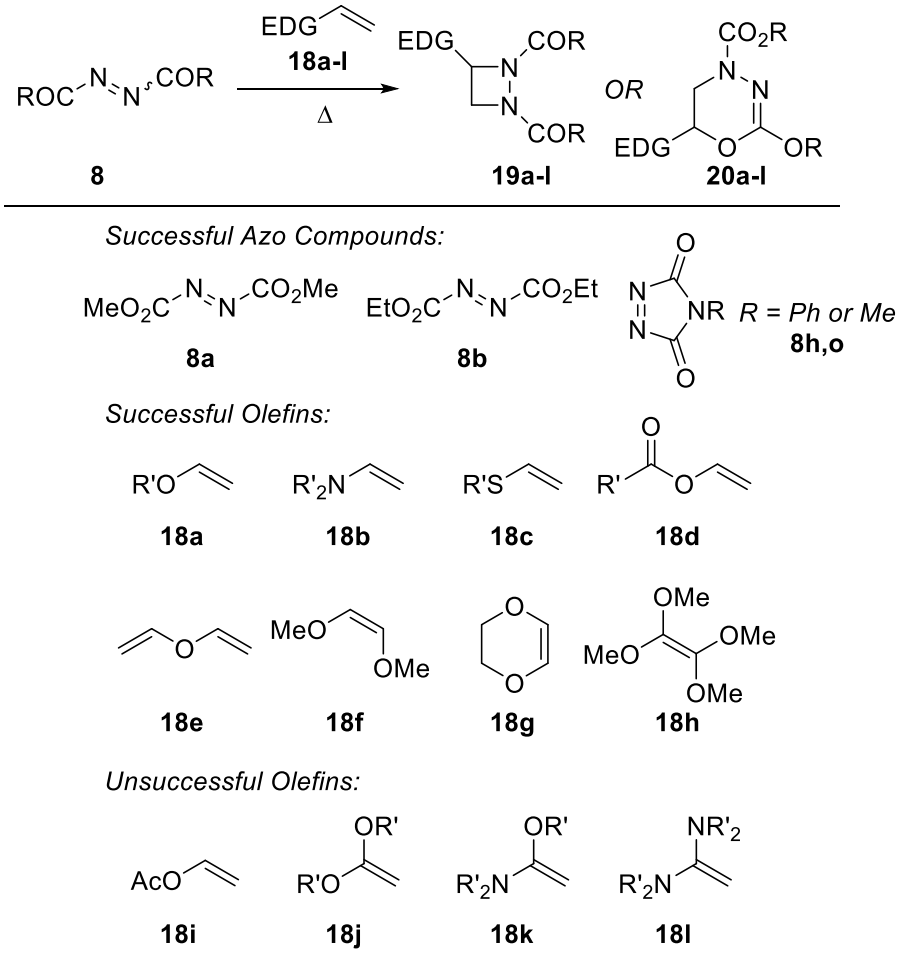
Unsuccessful Olefins:



15i **15j** **15k** **15l** **15m**

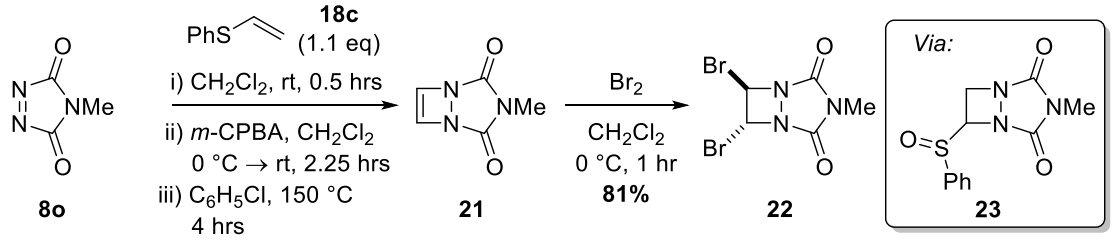
Scheme 1.3

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%).[51,64–66] 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.[53] 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.[64,67–69] 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%).[70] 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,[71] in contrast vinyl acetate **18i** resulted in the [4+2] reaction to give oxadiazines **20i** as the major pathway.[53] 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.[72] Similar observations were found with methanol for [2+2] cycloadditions using either but-2-ene or isobutylene.[62,73] 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.[51] Hoffmann and Häuser have studied the [2+2] cycloaddition using tetramethoxyethene **18h**.[74,75] 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.[76–78]



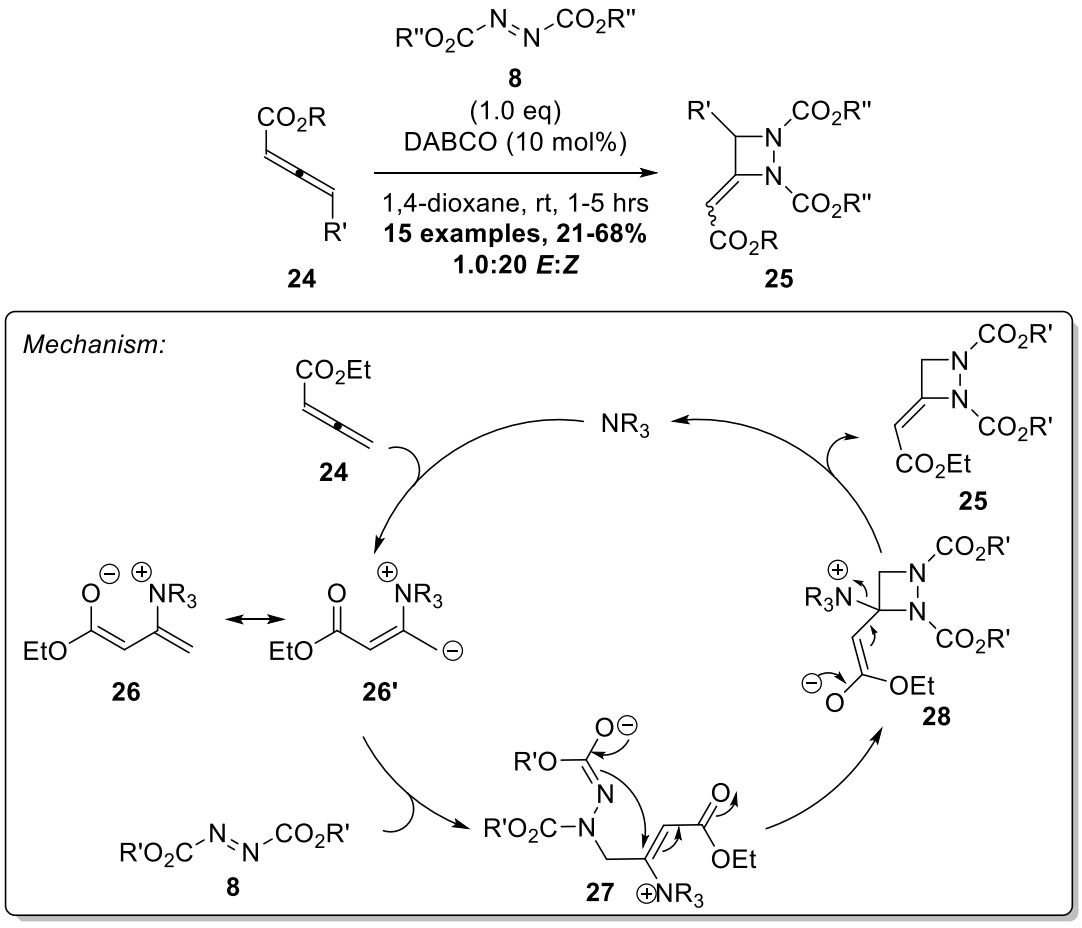
Scheme 1.4 EDG = electron donating group

More recently, Breton and co-workers have utilised a [2+2]-cycloaddition to synthesise 1,2-diazetine **21** (Scheme 1.5).[79] 4-Methyl-1,2,4-triazoline-3,5-dione (MeTAD) **8o** was reacted with phenyl vinyl sulfide **18c** to form an unstable 1,2-diazetidine intermediate that was immediately further reacted to give the more stable sulfoxide **23** in low yields (15%), followed by pyrolysis to give 1,2-diazete **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.[35,80] 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.[81]



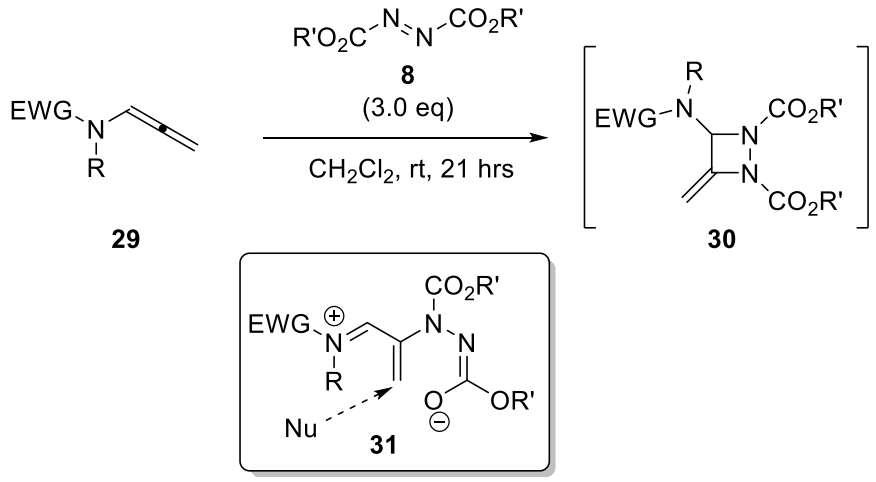
Scheme 1.5

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).[82] 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, ^{i}Pr or ^{t}Bu

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).[83] 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).

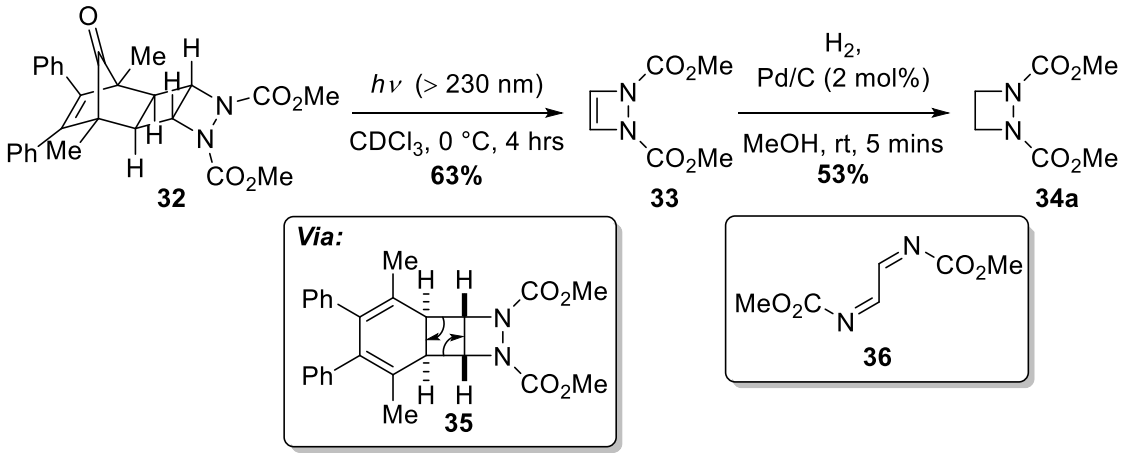


Scheme 1.7 R' = Me, Et, ^{i}Pr and CH_2CCl_3

1.3.2 Other Methods to Synthesise 1,2-Diazetidines

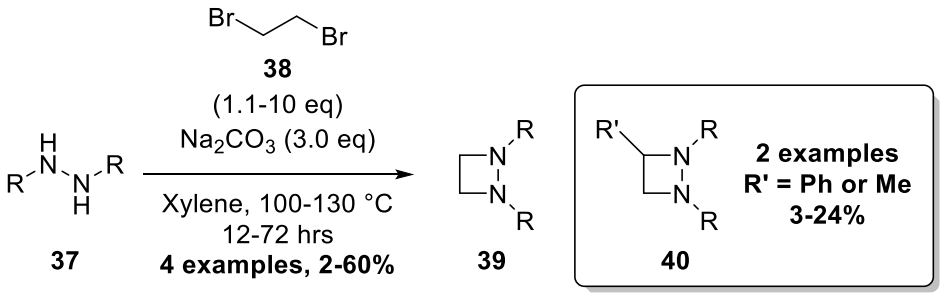
1.3.2.1 Synthesis of 1,2-Diazetidines

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



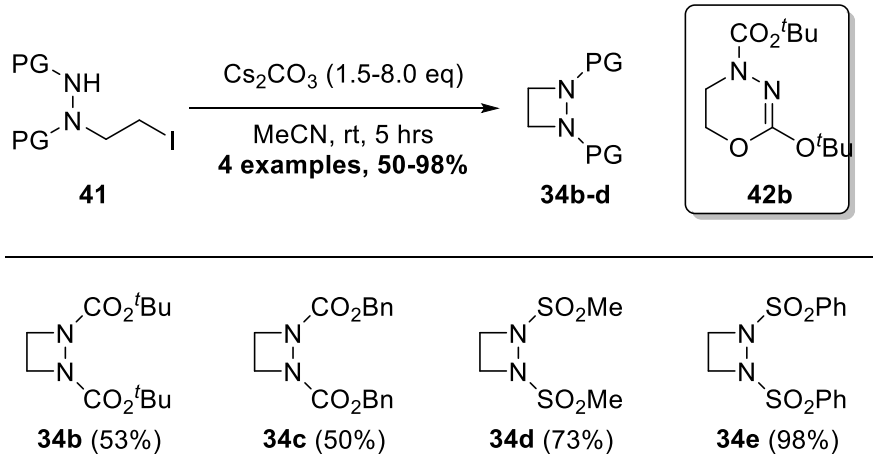
Scheme 1.8

In the mid-1960's, Horvitz of the FMC Corporation patented a new route to access 1,2-diazetidines starting from alkyl hydrazines **37** and dihalides **38**.[84] Hall *et al*. and Nelsen *et al.* have utilised this methodology on multigram scales to access some alkyl-1,2-diazetidines **39** in moderate to low yields (Scheme 1.9).[85,86] The authors reported that slow addition of 1,2-dibromoethane **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 **40** in low yields.



Scheme 1.9

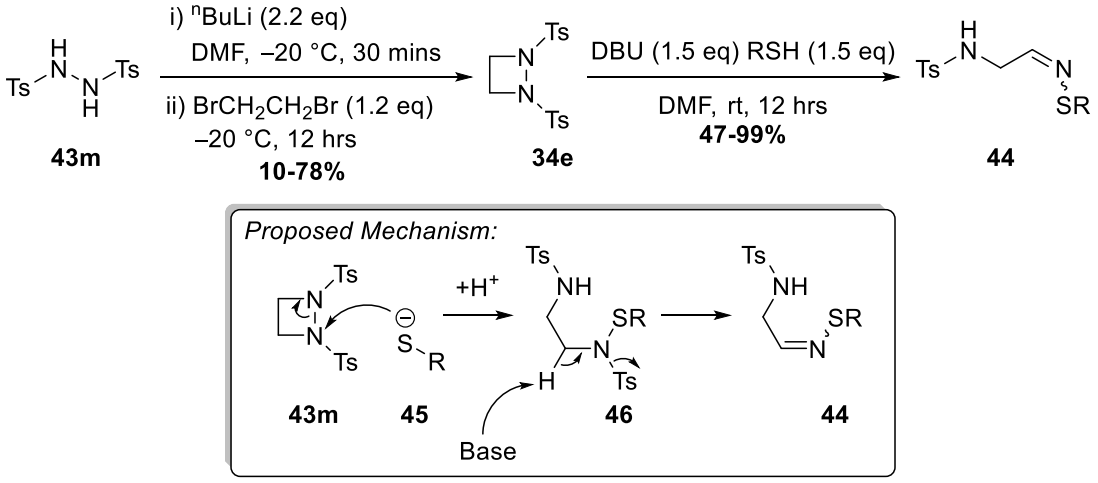
Shipman and co-workers have developed a synthesis to a series of 1,2-diazetidines **34b-d** from tri-substituted hydrazines **41** equipped with a iodide leaving group (Scheme 1.10).[87] The presence of iodide was found to be crucial and for hydrazines with carbamate protecting groups, leaving groups 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.



Scheme 1.10

Cui *et al.* have developed a multigram synthesis for unsubstituted 1,2-diazetidines **34** bearing sulfonyl protecting groups (Scheme 1.11).[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_N2) N-N

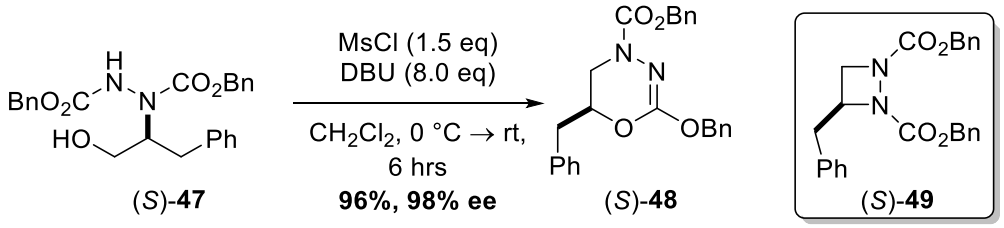
cleavage to give amine **46** after protonation of the nitrogen anion, followed by elimination of the tosyl group to give the observed product **44**.



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

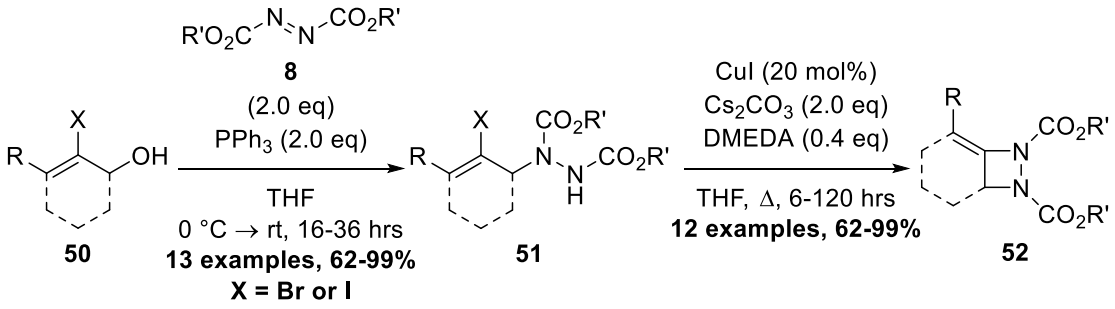
1.3.2.2 Synthesis of 3-Substituted-1,2-Diazetidines

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).[89] 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**.[87]



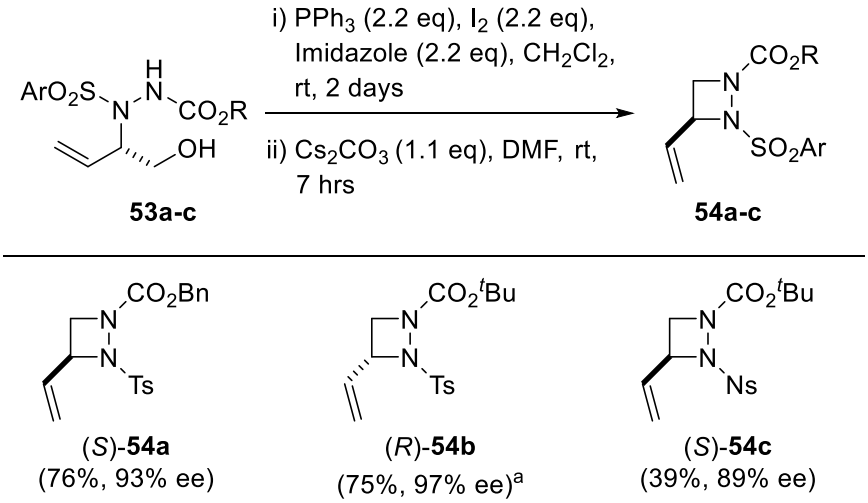
Scheme 1.12

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).[90,91] 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).



Scheme 1.13 X = Br or I; DMEDA = 1,2-dimethylethylenediamine

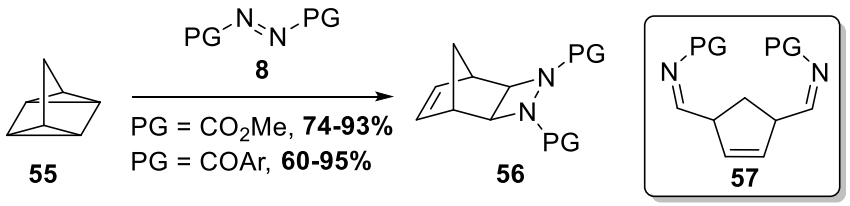
More recently, Shipman and co-workers have exploited enantioenriched hydrazines **53a-c** to synthesise 1,2-diazetidines equipped with an alkene functional handle (Scheme 1.14).[92] The primary alcohol in hydrazine **53a-c** had to be first converted into the required iodide leaving group, then cyclisation 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 [a] *R*-enantiomer synthesised; Ts = toluenesulfonyl; Ns = *p*-nitrobenzenesulfonyl

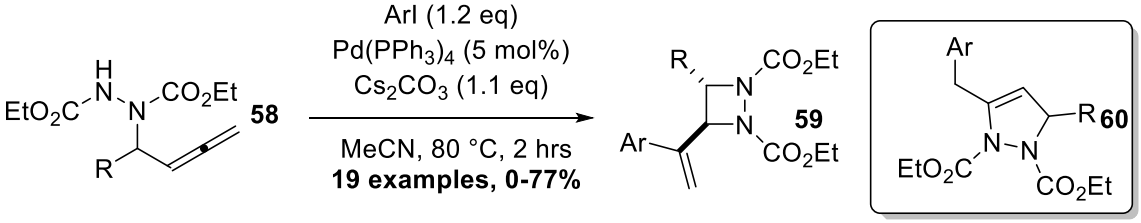
1.3.2.3 Synthesis of Other Substituted-1,2-Diazetidines

The $2_\pi + 2_\sigma + 2_\sigma$ cycloaddition reaction between quadricyclane **55** and azo compounds **8** has been widely studied (Scheme 1.15).[86,93–98] The reaction has been successful with azo compounds equipped with methyl and ethyl carbamates or benzoyl groups with electron donating and withdrawing groups,[86,93,94] which can be reduced using lithium aluminium hydride to give alkyl and benzyl 1,2-diazetidines.[86,96,98] 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**.[95] 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).[97] Zare and co-workers found the reaction rate could be sped up even further using microdroplets generated through electrospray ionisation.[99]



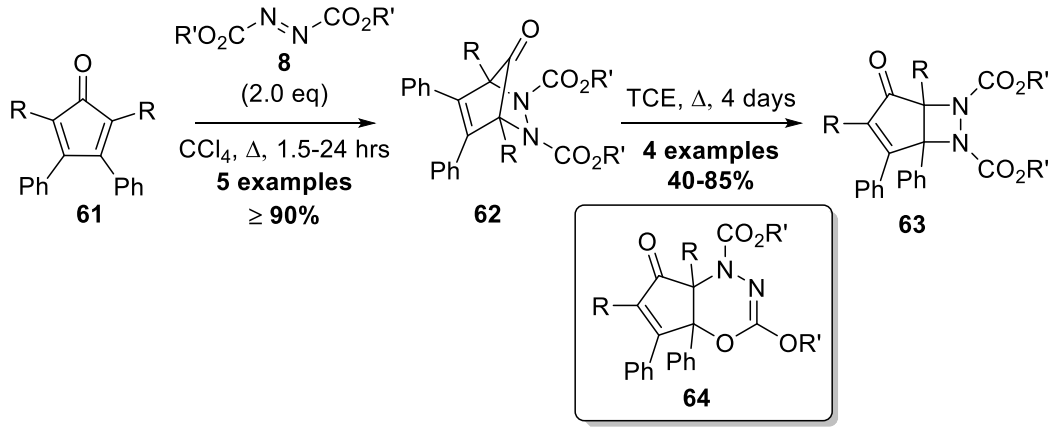
Scheme 1.15 Conditions: neat or organic solvent, Δ

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).[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.



Scheme 1.16

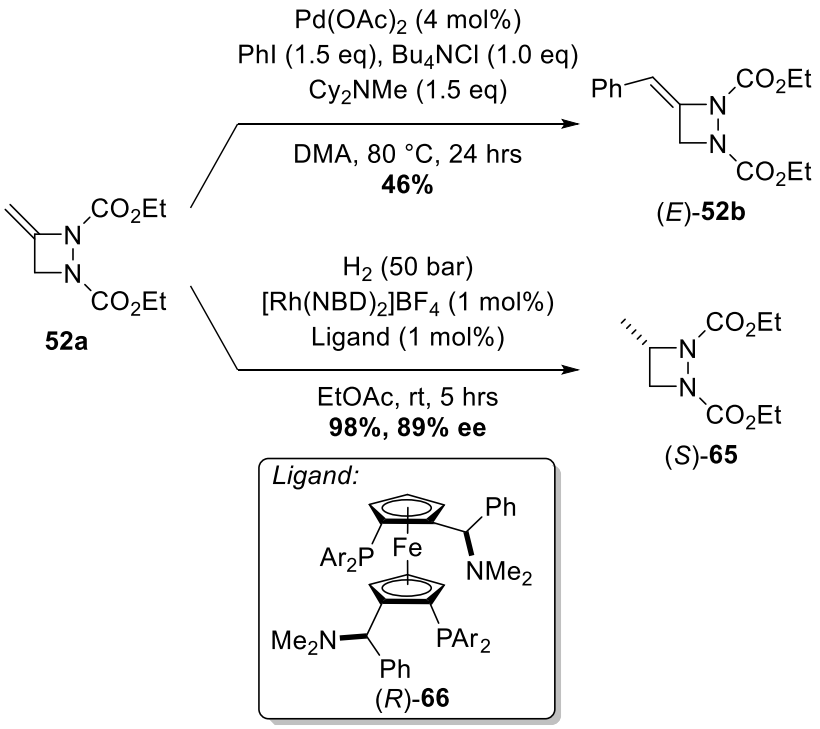
Mackay and co-workers have described the synthesis of bicyclic 1,2-diazetidines **63** formed through a Diels-Alder reaction, followed by a thermal rearrangement (Scheme 1.17).[102,103] The Diels-Alder reaction of 2,5-dimethyl-3,4-diphenyl-cyclopentadienone **61** and a variety of azodicarboxylates **8** 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**.



Scheme 1.17 R = Me or Et; R' = Me, Et, ^{t}Bu, Ph or CH_2CCl_3; TCE = tetrachloroethylene

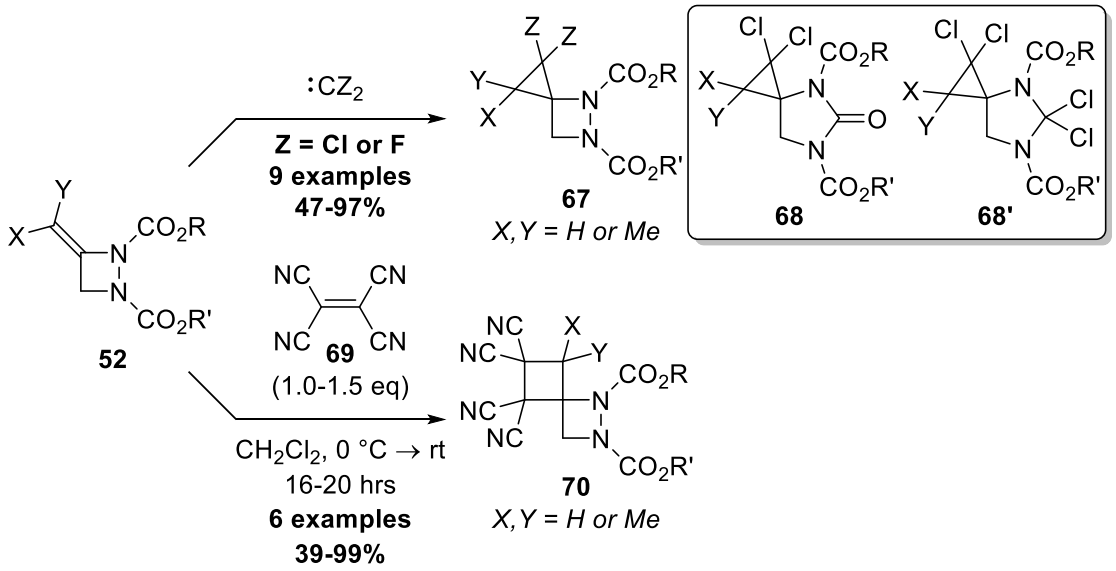
1.3.2.4 Peripheral Functionalisation of 1,2-Diazetidines

Shipman and co-workers have utilised alkylidene 1,2-diazetidine **52a** for derivatisation (Scheme 1.18).[90,104] 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.[90] Shipman and co-workers have also carried out an asymmetric hydrogenation of the double bond in **52a** to access an enantioenriched alkyl hydrazine **65** in good yields and enantiomeric excess.[104]



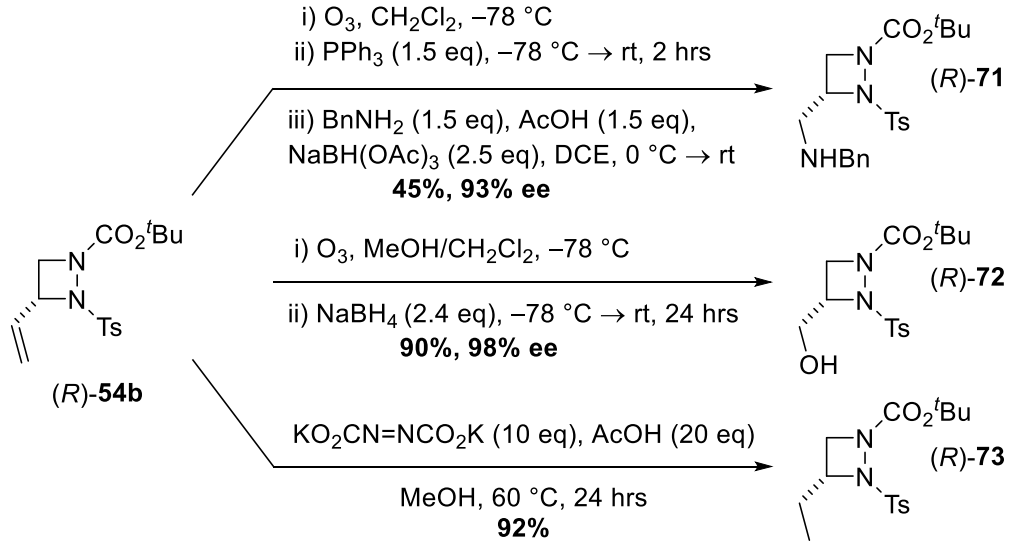
Scheme 1.18 NBD = norbornadiene

Shipman and co-workers have employed the double bond attached to the ring to synthesise some spirocyclic 1,2-diazetidines (Scheme 1.19).[91] 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.



Scheme 1.19 Dichlorocarbene conditions: $Et_3N(Bn)Cl$ (10 mol%), $CHCl_3$, NaOH (50 wt. %), rt, 0.25-6 hrs; difluorocarbene conditions: $TMSCF_3$ (2.5 eq), NaI (0.2 eq), THF, 65 °C, 5-6 hrs; TMS = trimethylsilyl

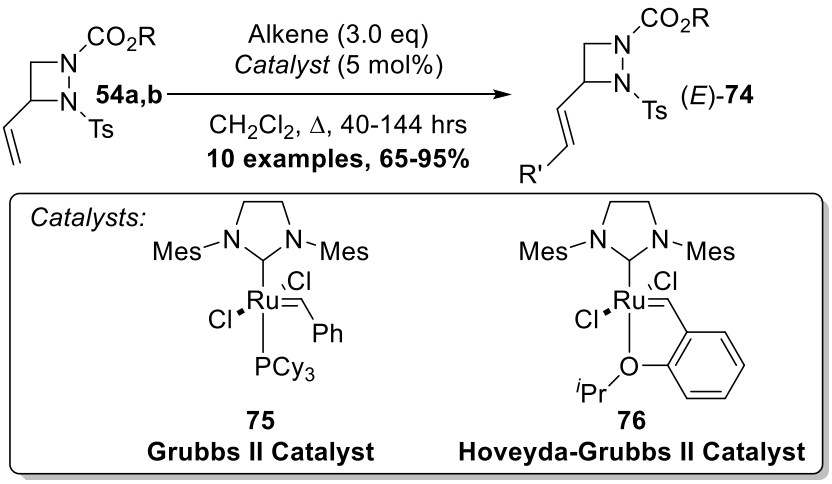
Shipman and co-workers have employed some common double bond transformations with vinyl-1,2-diazetidines **54a,b** to access novel 1,2-diazetidine scaffolds (Scheme 1.20 and 1.21).[92] Ozonolysis, followed by reductive work up with either triphenylphosphine or sodium borohydride formed an aldehyde and 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.



Scheme 1.20

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).[92] Using either Grubbs 2nd generation **75** or

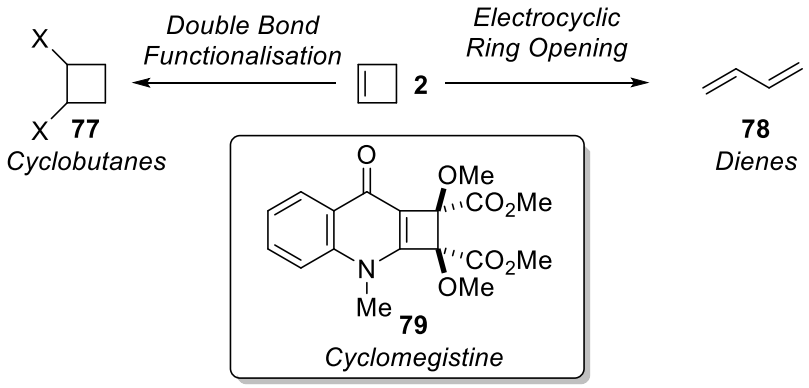
Hoveyda-Grubbs 2nd generation **76** catalysts and external alkenes that contained either alkyl chains, esters, halogens or phenyl rings, 1,2-diazetidines **54a,b** was selectively transformed into (*E*)-vinyl-1,2-diazetidines **74** in good yields.



Scheme 1.21 R = ^{t}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]



Scheme 1.22

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.

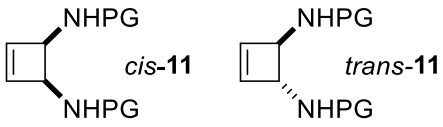
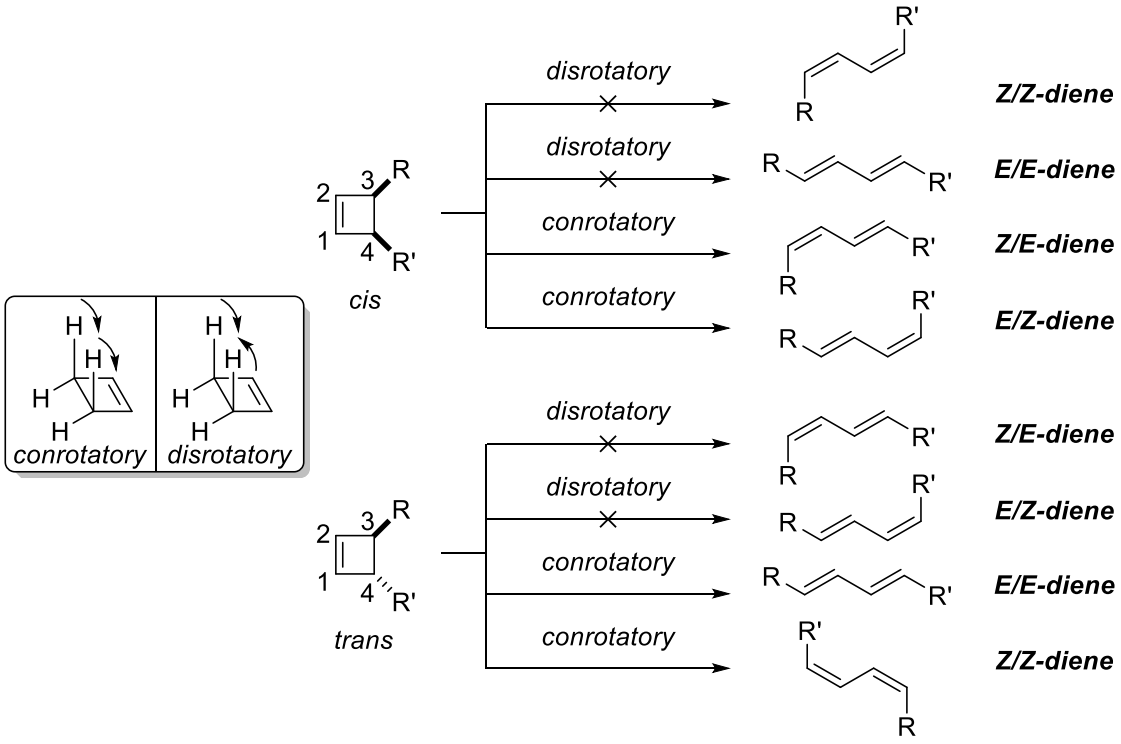


Figure 1.5 PG = protecting group

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.[43–45] 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_2H) 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]



Scheme 1.23

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**).

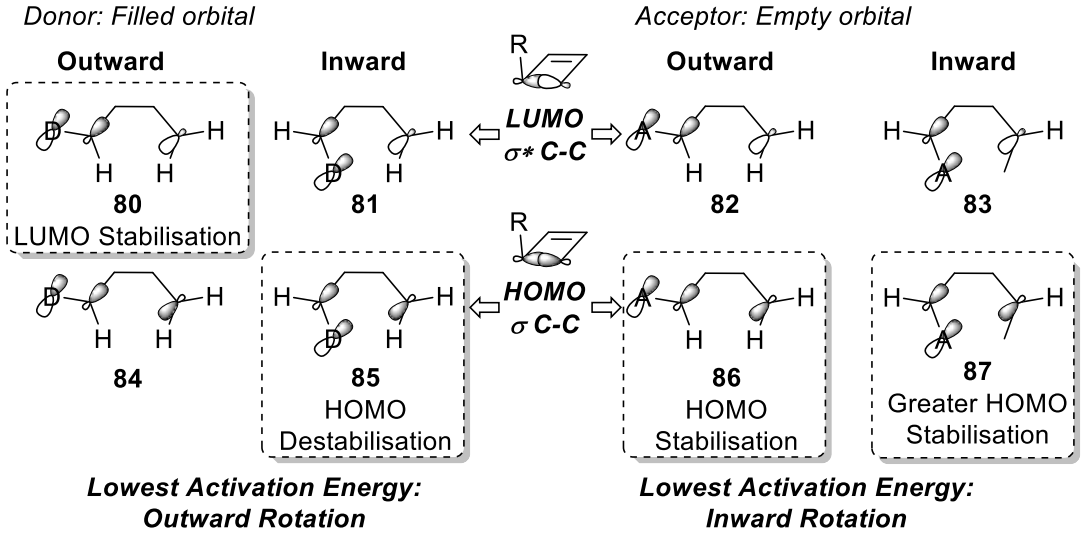


Figure 1.6

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).[112,113,115,116,127,128] 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), sulfinic 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).[115,119] 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.[112,115]

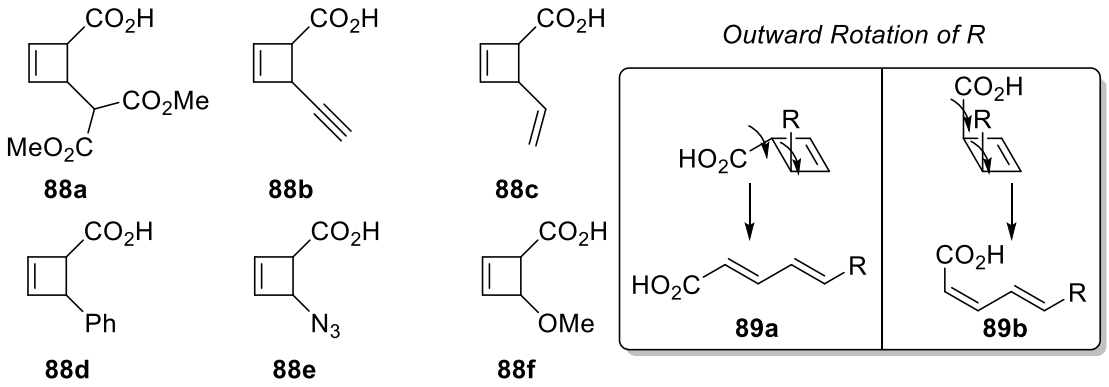
2a

Entry	-R	$E_{inwards} - E_{outwards}$[a]	Reference
1	H	0	115
2	OLi	24.4	115
3	OH	16.4-17.2	112,115
4	NH_2	14.7-19.6	112,115,116
5	NH_3^+	6.2-7.9	115
6	SH	13.7	115
7	F	14.4-16.9	112,115
8	Cl	13.6	115
9	CF_3	2.3-2.6	115
10	Me	5.9-7.4	112,115,116
11	^{t}Bu	7.1	128
12	$HC=CH_2$	4.9	115
13	C≡CH	7.6	115
14	C(O)Me	1.2-2.1	112,115
15	CHO	−3.9-−4.6	115
16	CO_2H	2.3	115
17	$CO_2H_2^+$	−4.8	115,119
18	CO_2^-	7.3	115
19	CO_2Me	1.2	115
20	$HC=NH_{trans}$	−3.0	115
21	$HC=NH_{cis}$	3.0	115
22	$HC=NH_2^+$	−10.1	115
23	CN	4.3-4.7	112,115
24	NO_2	6.4-7.3	112,115
25	NO	−2.6	115
26	S(O)H	0.1	115
27	SO(OH)	−1.4	115
28	SO_2H	−0.3	115
29	$B(Me)_2$	−11.5	115
30	BH_2	−15.9-−18.2	115
31	SiH_3	−1.5-−1.7	116,127
32	$SiMe_3$	−1.0-−1.3	116
33	SiF_3	−3.8-−4.1	116
34	PH_2	4.1-4.2	116
35	$SnMe_3$	−0.6	128

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.[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).[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_2 and NO_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).[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.[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**.

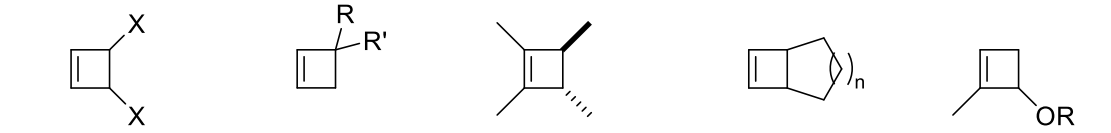


Scheme 1.24

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).[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,[131] whilst Brauman and Archie noted similar observations with *cis*-3,4-diphenylcyclobutenes.[139] 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.[135–137] Criegee and co-workers found that when heated, *trans*-3,4-dimethylcyclobutene **90** selectively formed the *E*/*E*-diene and none of the *Z*/*Z*-diene was observed.[132] In addition, various research groups have reported that bicyclic cyclobutenes **91** 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.[131,140,141] Jefford, Boschung and Rimbault showed that 3-cyclobutenes **92** bearing oxygen atoms selectively formed *E*-dienes.[142]



2e *X = CO_2Me, Cl, Br, OAc, Ph, alkyl*

2f *R, R' = alkyl*

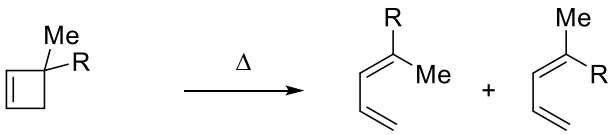
90

91 *n = 1 or 2*

92 *R = H, D, TMS*

Figure 1.7

The early steric explanation for the preferential formation of certain dienes began to be called into question when unexpected results began to arise.[143–146] Curry and Stevens noticed that the ring opening of some 3,3-disubstituted cyclobutenes **2e** bearing a methyl group and an alkyl chain did not agree with this theory (Table 1.2).[143] Systems that contained ethyl, propyl or isopropyl groups favoured inward rotation to form diene **93b** in slight excess (entries 1-3). For the larger *tert*-butyl and phenyl groups outward rotation was preferred to form diene **93a** (entries 4 and 5). Houk and co-workers reasoned that outward rotation of the methyl group minimised destabilising interactions in the transition state.[120]



2e *R = alkyl or Ph*

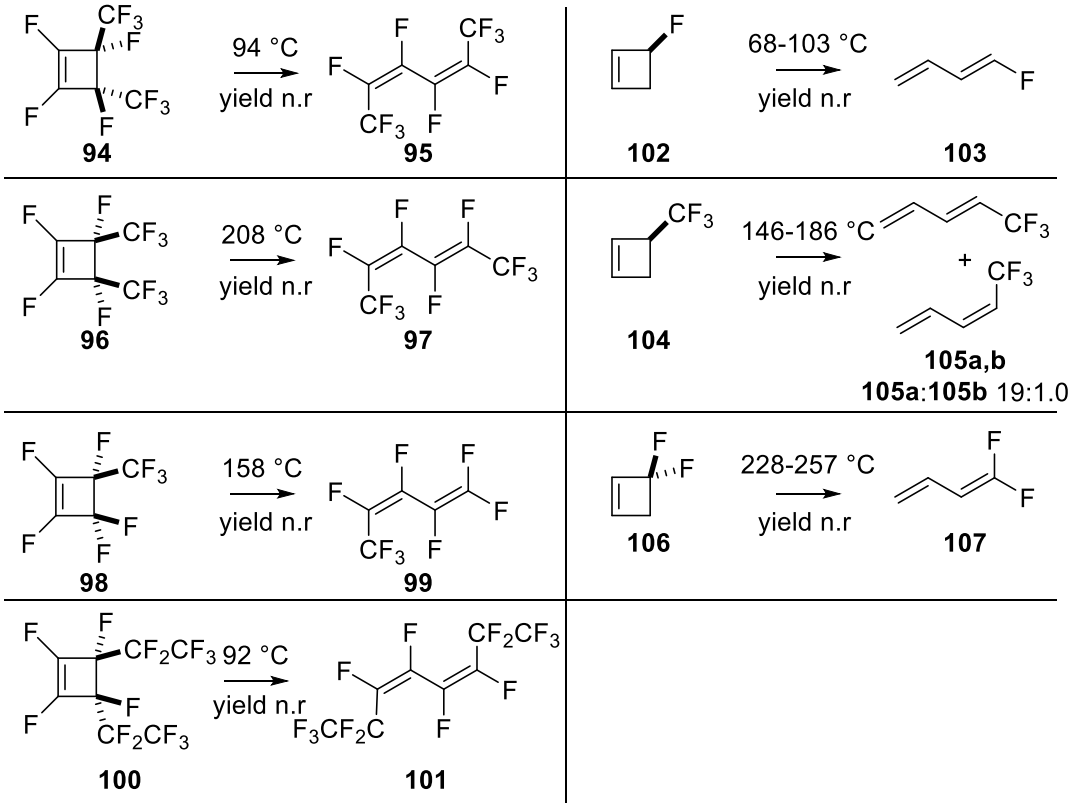
93a

93b

Entry	R	93a:93b
1	Et	32:68
2	n-Pr	38:62
3	^{i}Pr	34:66
4	^{t}Bu	68:32
5	Ph	70:30

Table 1.2

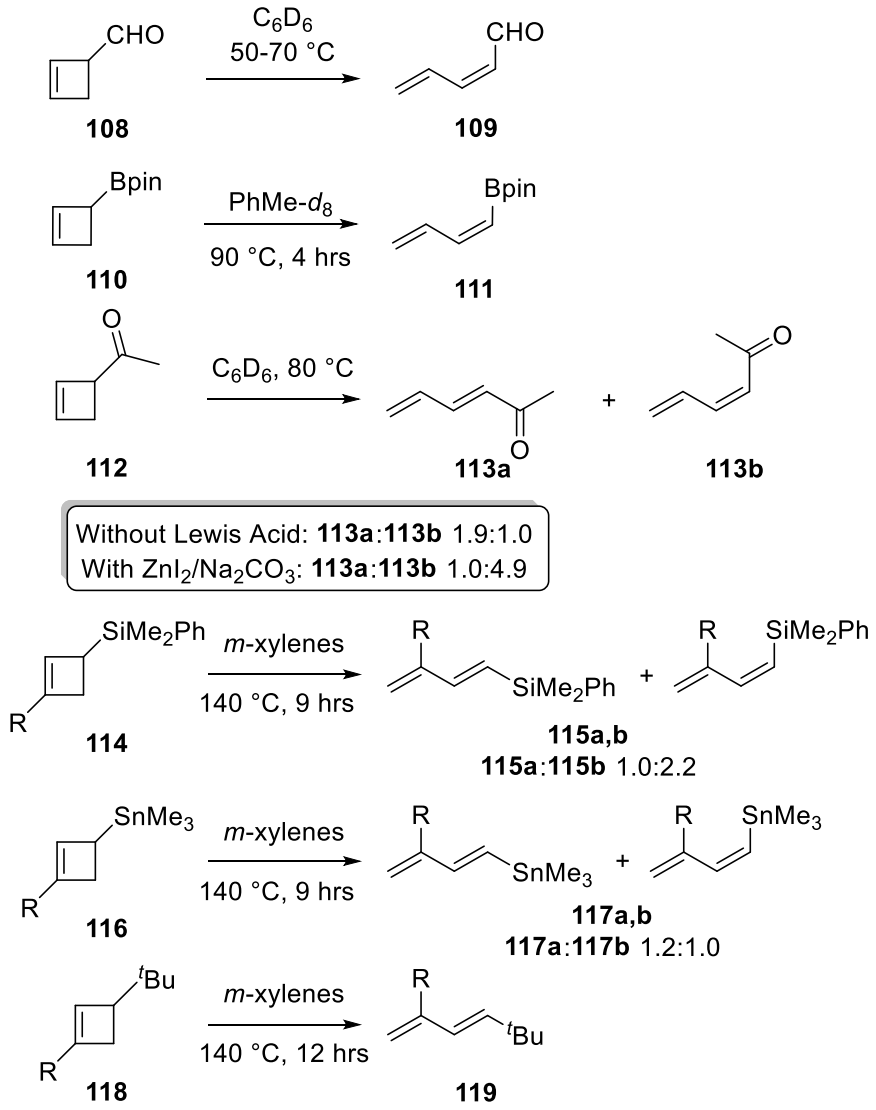
Dolbier, Burton and various co-workers cast further doubt on the steric explanation from the ring opening of cyclobutenes bearing fluoroalkyl groups (Scheme 1.25).[144–146] The authors discovered through the formation of dienes **95, 97, 99, 101** that fluorine preferred to rotate outwards, meaning that 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 σ* 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.[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.



Scheme 1.25 n.r = 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).[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.[148] Niwayama and Houk have shown the slight preference for outward rotation for the electrocyclic ring opening of 3-acetylcyclobutene **112** to give dienes **113a,b**.[123] The calculated values above suggested that ketones were less powerful π acceptors

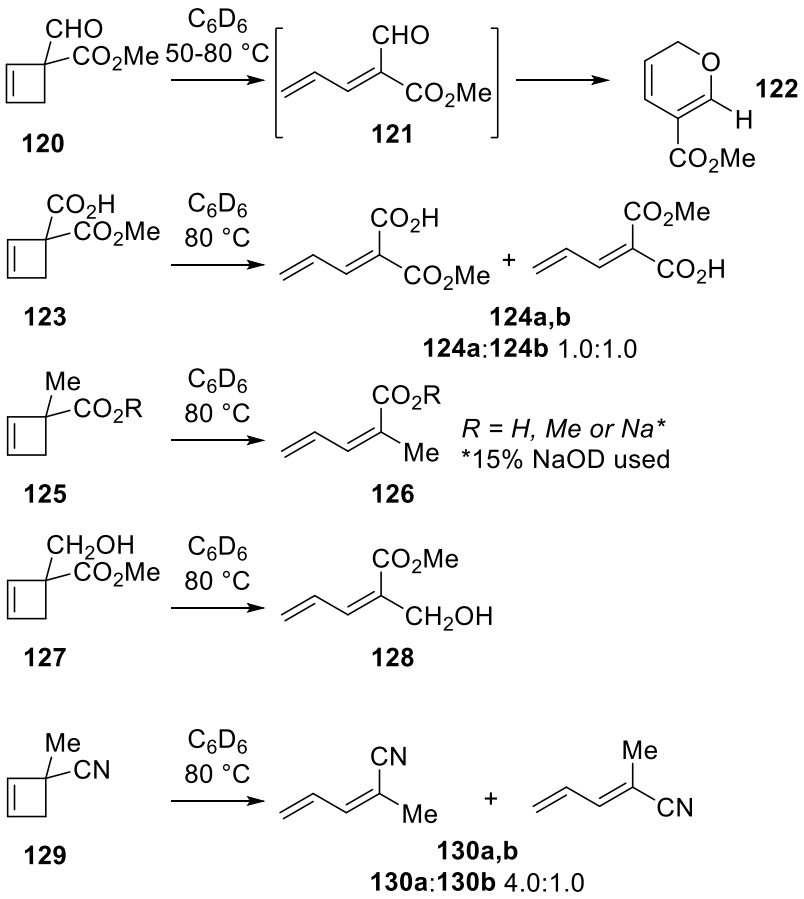
compared to aldehydes and favoured outward rotation (Table 1.1, entry 14), however the addition of a Lewis acid, specifically zinc iodide, reversed the torquoselectivity from outward to inward rotation to give diene **113b** as the major product.[123,125] Sodium carbonate had to be present to prevent 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 **114,116** gave considerably more inward rotation than found with 3-*tert*-butylcyclobutene **118**.[127,128] The silyl and tin compounds contain a low energy σ* (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 σ* orbital preventing the *tert*-butyl group from accepting electron density and resulting in outward rotation of this group only.



Scheme 1.26 Yields not reported; pin = pinacol; R = $PhMe_2C$

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

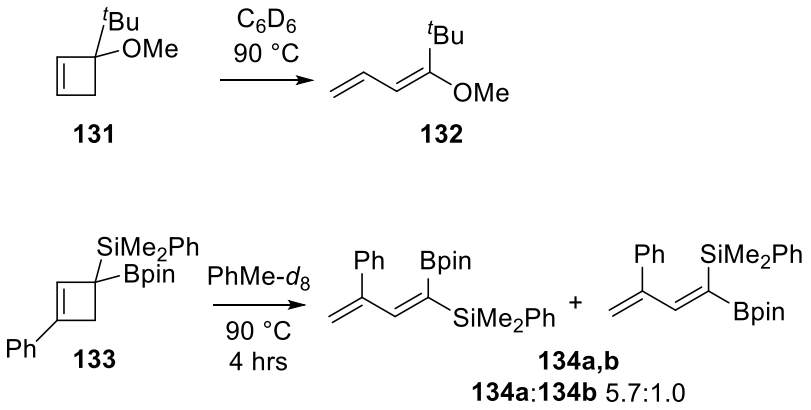
give pyran **122**. From the calculated values above (Table 1.1), acids and esters only show a minor preference for outward rotation and aldehyde a strong preference for inward rotation, therefore this result was not unexpected. If an acid was used instead of an aldehyde the selectivity of the reaction was lost and equal quantities of dienes **124a,b** were formed for the ring opening of cyclobutene **123**.[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.[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.[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.[118,150]



Scheme 1.27 Yields not reported

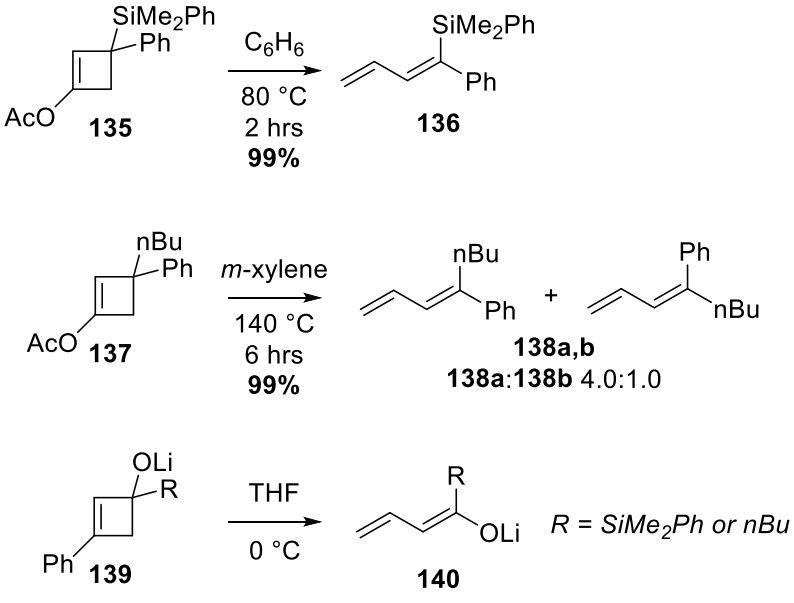
Curry and Stevens found that the ring opening of 3-*tert*-butyl-3-methylcyclcobutene gave a larger proportion of a diene where the larger *tert*-butyl group rotated outwards (Scheme 1.28).[143] Houk and co-workers noticed that when the methyl group was replaced with a silyl ether or a methoxy group, the ring opening of this cyclobutene **131** only formed diene **132**, where the methoxy group rotated outwards and the *tert*-butyl group rotated inwards.[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*.[148]



Scheme 1.28 Yields not reported

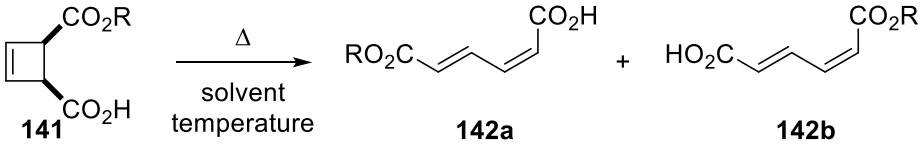
Murakami and co-workers have demonstrated the selective formation of dienes from 3,3-disubstituted cyclobutenes (Scheme 1.29).[152] For cyclobutene **135** (which contains both donor and acceptor substituents), diene **136** was formed through preferential inward and outward rotation of each group, respectively, 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.



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).[105] The authors noticed an increase in *E*-selectivity as the solvent was changed from dimethyl sulfoxide (DMSO) to 1,2-

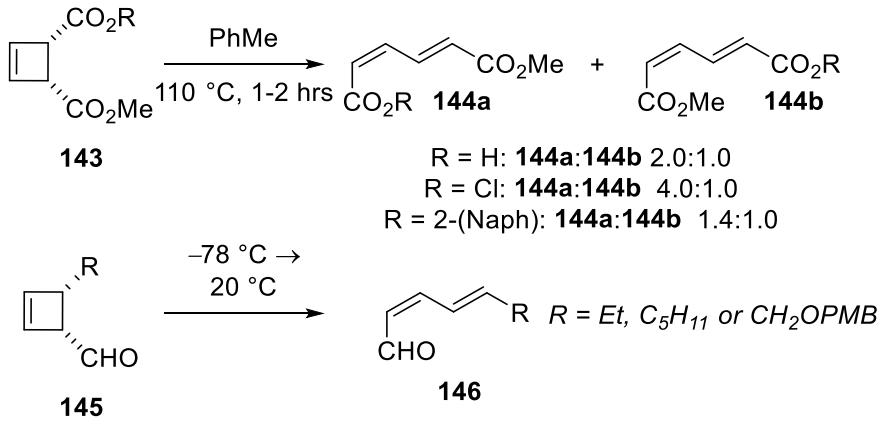
dichloroethane (DCE). The authors rationalised that in DMSO hydrogen bonding of the solvent to the acid moiety would increase the steric bulk of the acid and helps to increase the amount of outward rotation (entries 1-6). In chlorinated solvents such as DCE, this hydrogen bond interaction is not present and resulted in the ester group preferably rotating outwards (entries 3 and 6).



Entry	R	Solvent	Temperature (°C)	*E*:*Z* 142a:142b
1	n-Bu	DMSO	110	50:50
2	n-Bu	DME	85	55:45
3	n-Bu	DCE	83	75:25
4	CH_2CH_2TMS	DMSO	85	55:45
5	CH_2CH_2TMS	DME	83	75:25
6	CH_2CH_2TMS	CCl_4	76	75:25

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

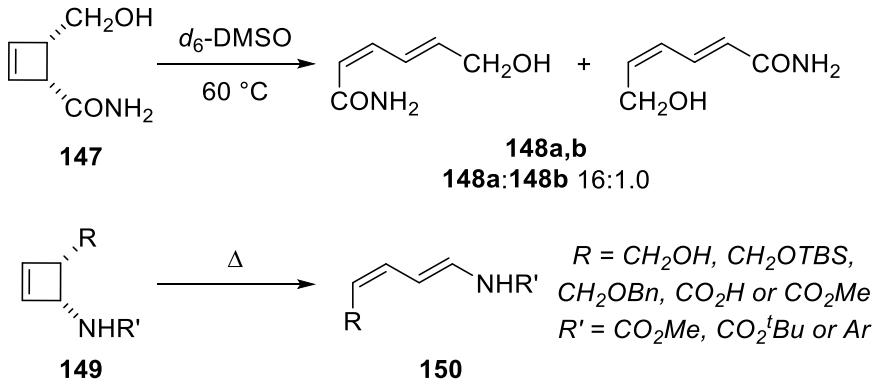
As described above, the steric argument to answer the observed selectivity is often unreliable and Wallace and co-workers have found esters to have a stronger preference for outward rotation in comparison acids and acid chlorides (**144a,b**), thus meaning esters are slightly better donors than these groups (Scheme 1.30).[153–155] Piers and Lu have also found experimentally that esters preferred outward rotation.[156] 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]



Scheme 1.30 PMB = *para*-methoxybenzyl

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).[157] Huet and co-workers were the

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.[157–159]



Scheme 1.31

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).[160,161]

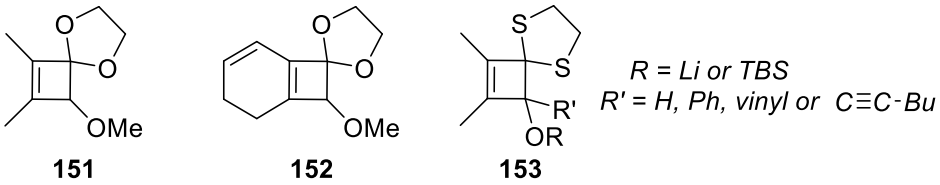


Figure 1.8

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,

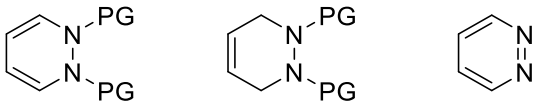
whereas heteroatoms and electron donating groups seemed to decrease the activation energy and make diene formation a lot easier. The development of torquoselectivity has provided valuable prediction and rationalisation tools on the preferential rotation of certain functional groups in the ring opening 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

2.1 Introduction

2.1.1 Synthetic Approaches to 1,2-Dihydropyridazines

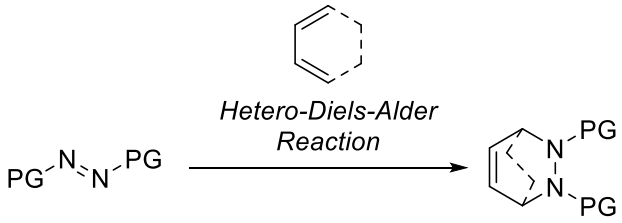
1,2-Dihydropyridazines **9** are heterocycles that possess two nitrogen atoms adjacent to one another and can be viewed as precursors to pyridazines **155** (Figure 2.1). There are only limited examples of the synthesis and use of 1,2-dihydropyridazines in the literature and they have most commonly been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



9 **154** **155**

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,[35,36,168,175–189] butadiene derivatives,[162,168,180,182,190–197] bicycloheptadiene,[185] cyclcoheptatriene,[185,198] cyclopentadiene[177,183,185,198] and furans,[168,199–207] though more recently alternative methods using organo- and transition metal catalysis have been developed.[208–211]

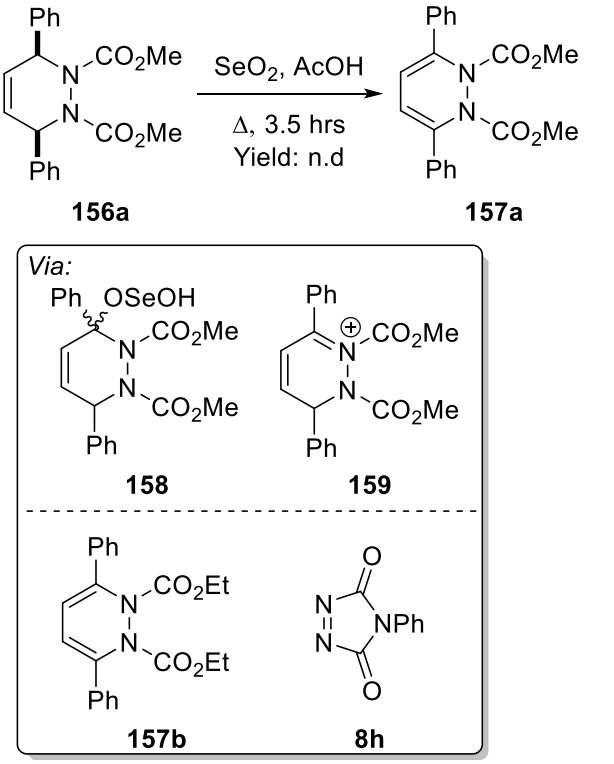


8 **154**

Scheme 2.1

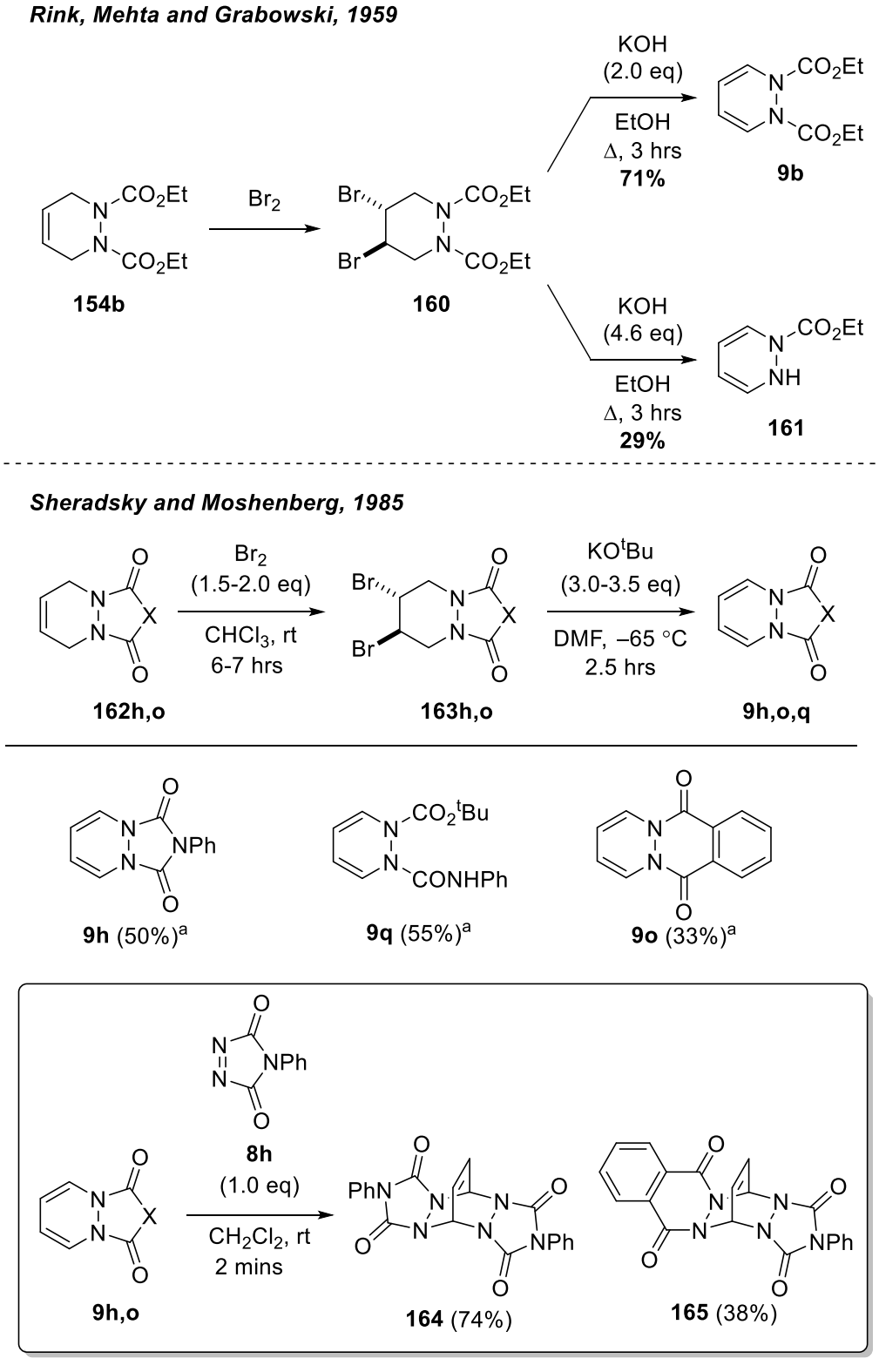
The first reported synthesis of 1,2-dihydropyridazines was in the mid-1950's by Alder and Niklas.[168] The authors described the oxidation of the diphenyl-cycloadduct **156** with selenium dioxide (SeO_2) to give 1,2-dihydropyridazine **157a** (Scheme 2.2). Treatment of **156** with selenium dioxide 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.[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.[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.



Scheme 2.2

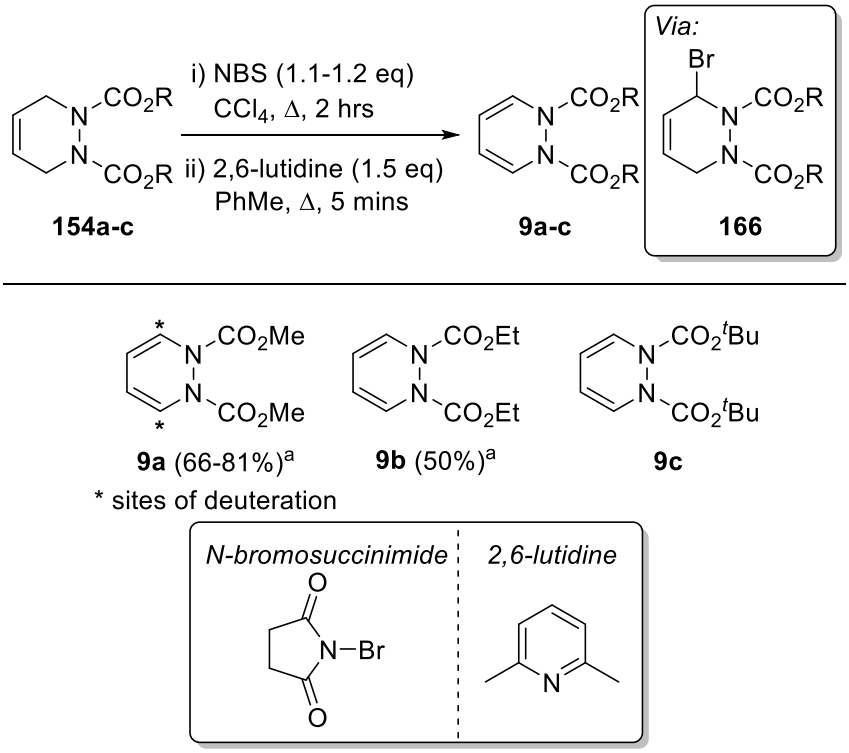
A few years later, Rink and co-workers exploited a two-step bromination-dehydrobromination reaction in the synthesis of 1,2-dihydropyridazine **9b** on decagram scales (Scheme 2.3).[164] Bromination of tetrahydropyridazine **154b** gave dibromide **160**, which was then treated with potassium hydroxide 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.[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 [a] 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

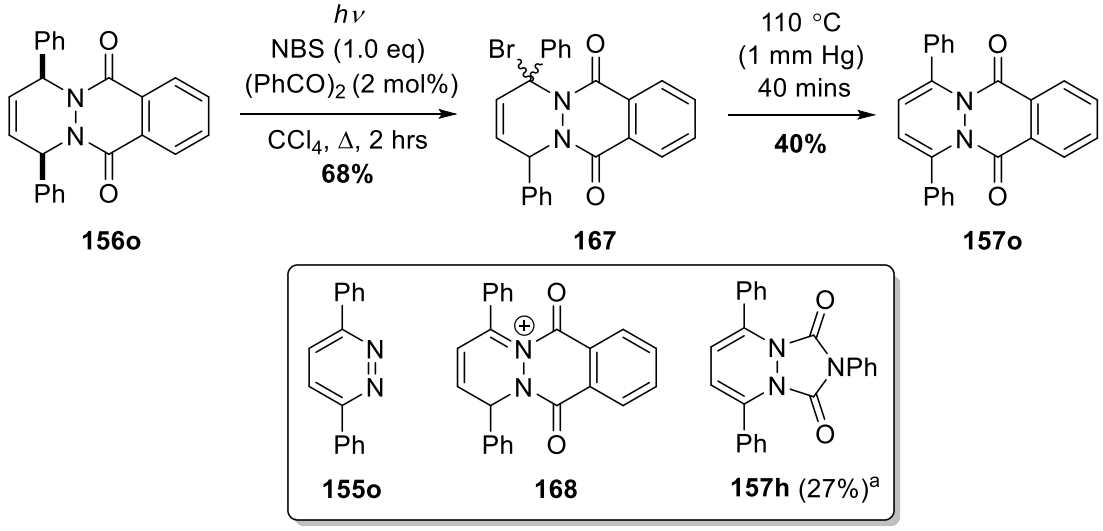
an elimination reaction when heated in the presence of base to give 1,2-dihydropyridazine **9a** in 66-81% yield. Moreover, this method was successfully applied for the synthesis of another two 1,2-dihydropyridazines **9b,c**, although no experimental details were disclosed. More recently, Warrener *et al.* have further evaluated this methodology.[35] 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**.[162] 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.[36] 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.



Scheme 2.4 [a] Yield over two steps

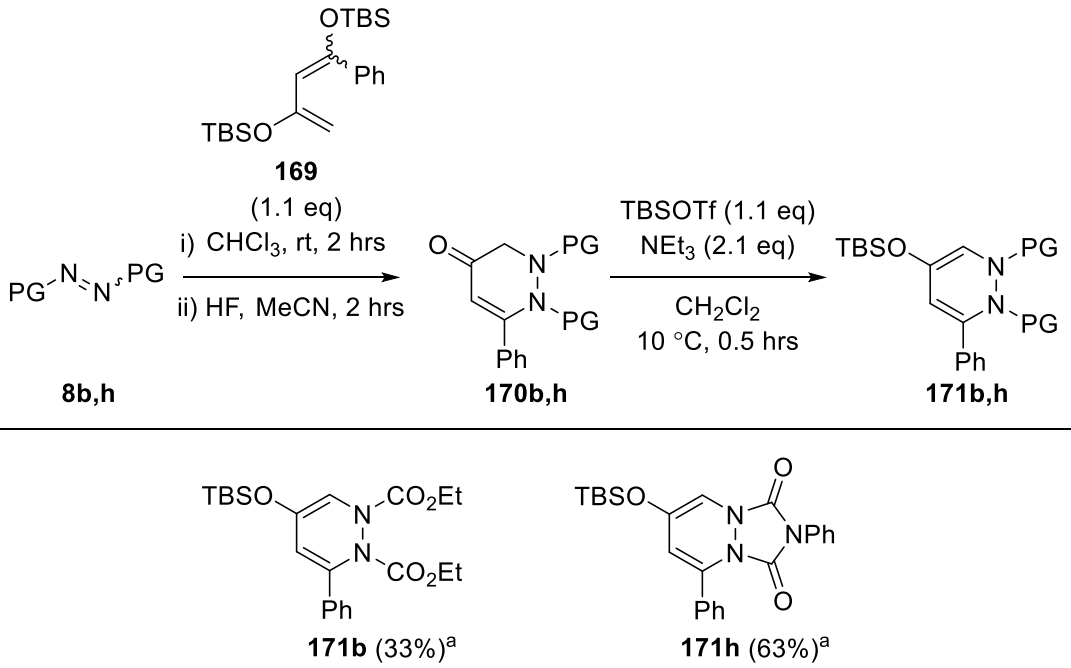
Sheradsky and Moshenberg employed a similar two-step methodology to access tricyclic 1,2-dihydropyridazine **157o** (Scheme 2.5).[166] Tricycle **156o** did not react with selenium dioxide under the conditions developed by Alder and Niklas for monocyclic systems.[168] Instead, an allylic bromination reaction in the presence benzoyl peroxide was carried out to give bromide **167** in 68% yield. Bromide **167** readily underwent S_N1 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

product **157o**. 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.[163]



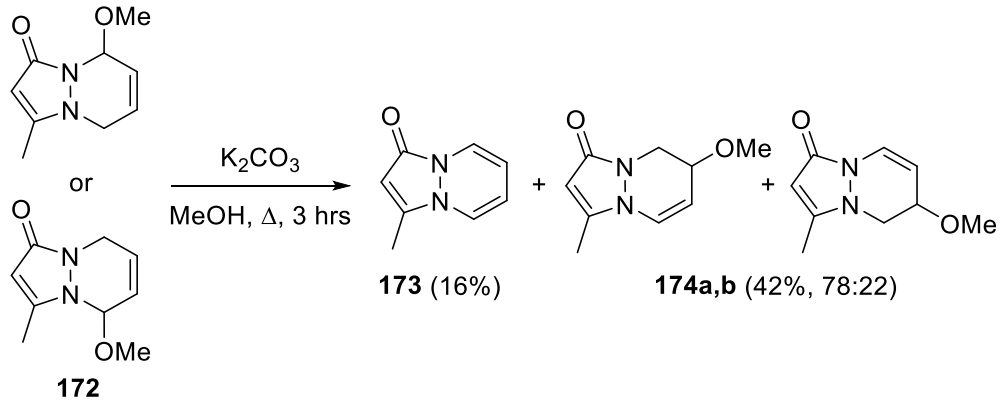
Scheme 2.5 [a] Yield over two steps

Ried and Reiher have exploited enones derived from substituted dienes **169** in their synthesis of substituted 1,2-dihydropyridazines (Scheme 2.6).[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 α,β-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).



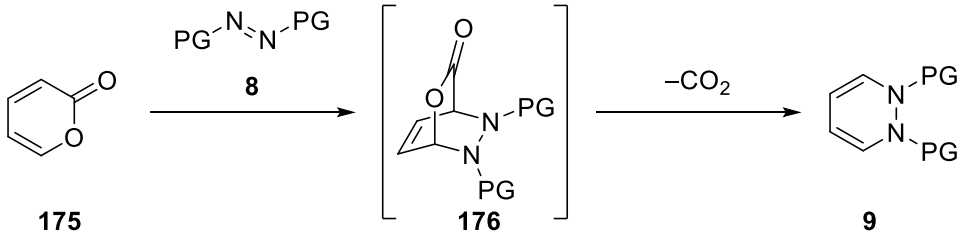
Scheme 2.6 [a] Yield over three steps

Avery and co-workers have also used substituted dienes in their attempts to synthesise bicyclic 1,2-dihydropyridazine **173** (Scheme 2.7).[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 **174a,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).



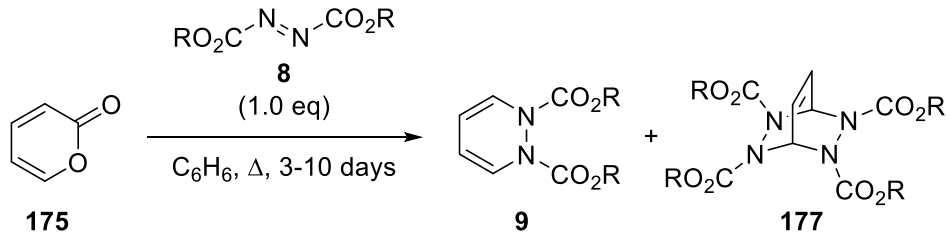
Scheme 2.7

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).



Scheme 2.8 PG = protecting group

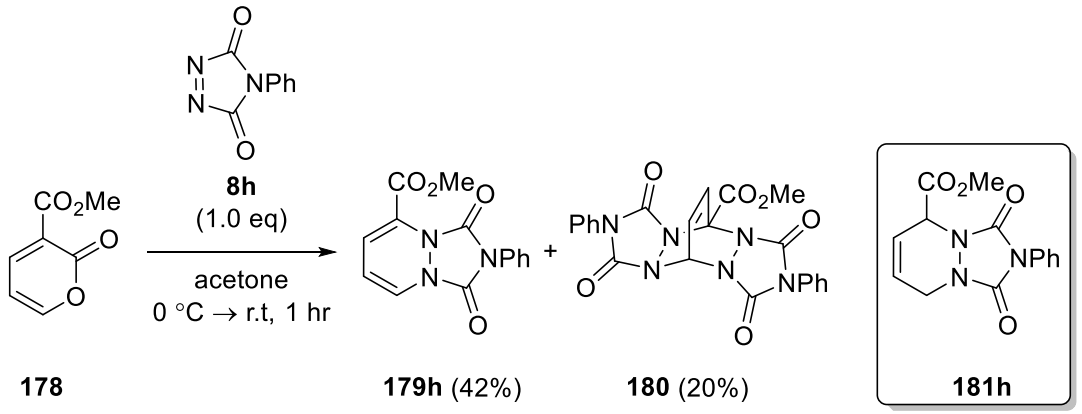
Arora and Mackay demonstrated the first example of this reaction in 1969 with acyclic azo compounds (Table 2.1).[173] When equimolar amounts of 2-pyrone **175** and azo compounds **8** were heated in benzene only minor amounts of 1,2-dihydropyridazines **9** were formed (entries 1-3). The major product 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 *et al.* have shown that 1,2-dihydropyridazine **9i** can be accessed through the reaction with 2-pyrone **175** and bis(2,2,2-trichloroethyl) azodicarboxylate **8i**, but no further details were reported (entry 4).[34]



Entry	R	Time (days)	Yield 9 (%)	Yield 177 (%)	Reference
1	Me	10	n.d	26	[173]
2	Et	7	16	22	[173]
3	Ph	3	0	60	[173]
4	CH2CCl3	n.r	n.r	n.r	[34]

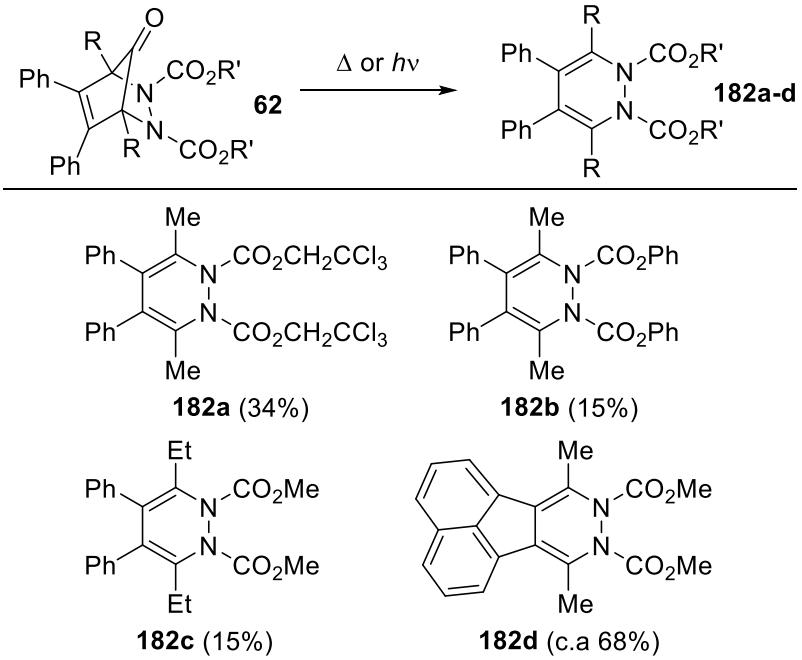
Table 2.1 n.r = not reported

Sheradsky and Moshenberg further evaluated the use of pyrones in their synthesis of the substituted bicyclic 1,2-dihydropyridazine **179h** (Scheme 2.9).[174] Here, the reaction between an ester substituted 2-pyrone **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.



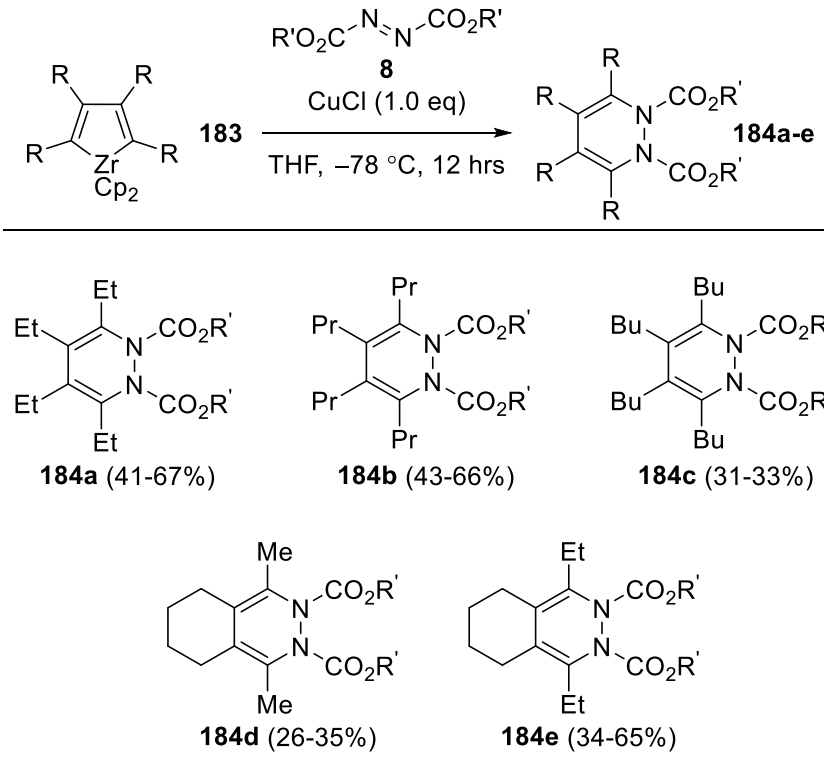
Scheme 2.9

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).[102,103] 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.



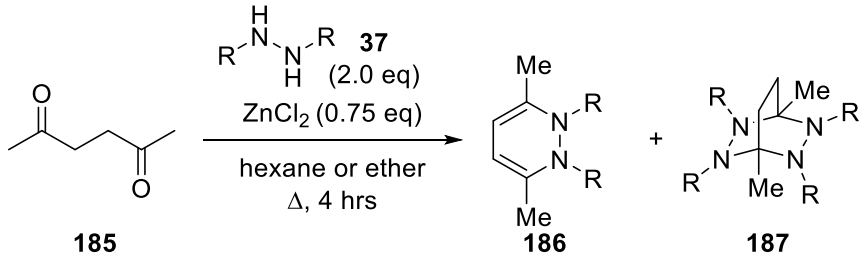
Scheme 2.10 a) R' = Me; b) R' = Et; c) R' = CH_2CCl_3; d) R' = Ph; e) R' = ^{t}Bu

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).[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 2.11 R' = Me, Et, ^{i}Pr or Bn

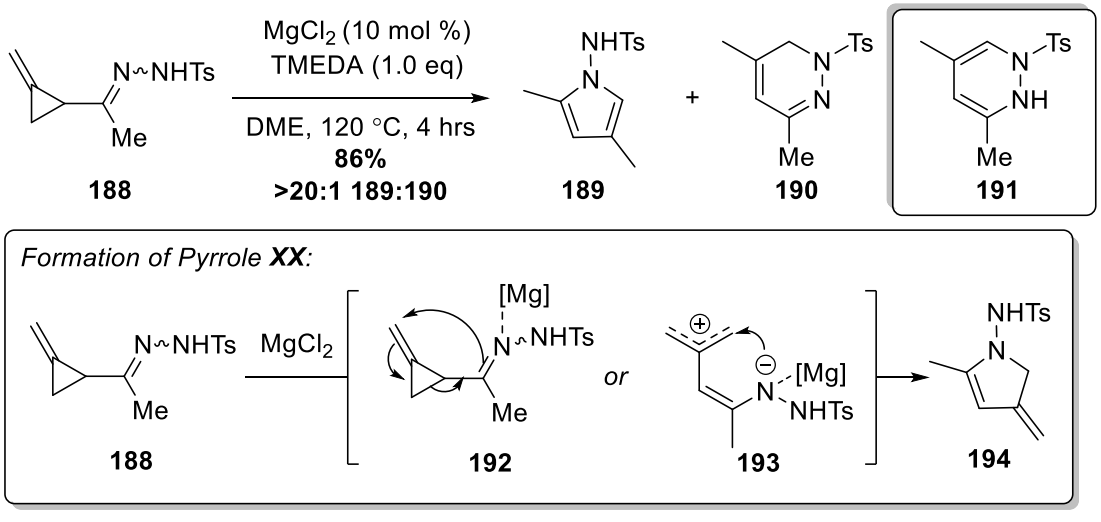
Zelenin and Dumpis have described the condensation reaction of a 1,4-diketone **185** with alkyl hydrazines **37** to access methyl substituted 1,2-dihydropyridazines **186** (Table 2.2).[170] The condensation reaction of acetonylacetone **185** with methyl and ethyl hydrazine **37**, in the presence of a Lewis acid, gave 1,2-dihydropyridazine **186** in moderate yields, as well as the formation of the side product **187**.



Entry	R	Yield 186 (%)	Yield 187 (%)
1	Me	36	10
2	Et	39	8

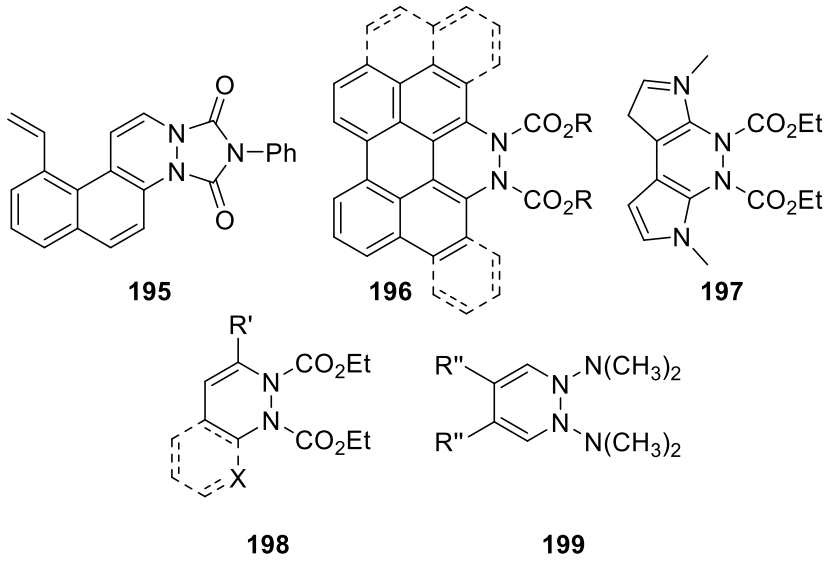
Table 2.2

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).[214] 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**.[215] The authors proposed that after initial coordination of the Lewis acid to the hydrazine 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**.



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 vinylnaphthalene,[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]



195 **196** **197**

198 **199**

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-CO_2R 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 ^{1}H 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 CH_2 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 ^{13}C 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]

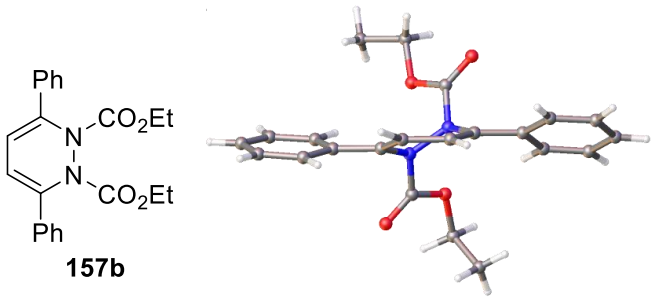
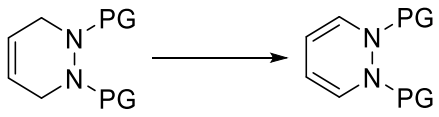


Figure 2.3 Crystal structure of **157b** from Cambridge Crystallographic Data Centre (database ID: JAYHIA)[223]

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 **154**, 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 **9** is through allylic bromination-elimination or bromination-elimination reactions from the corresponding tetrahydropyridazine **154** (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.



154 **9**

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.

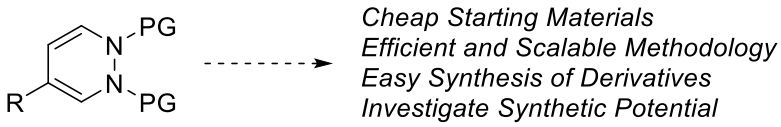


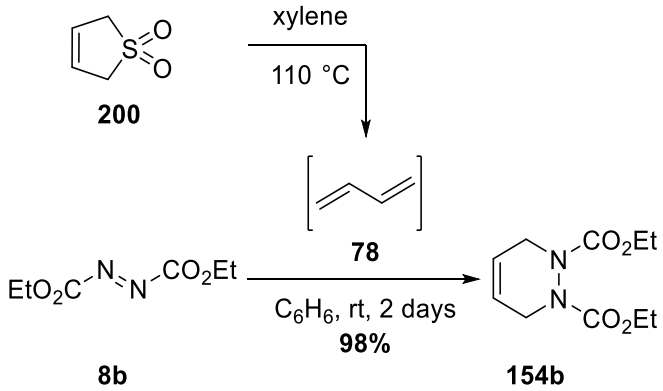
Figure 2.4

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

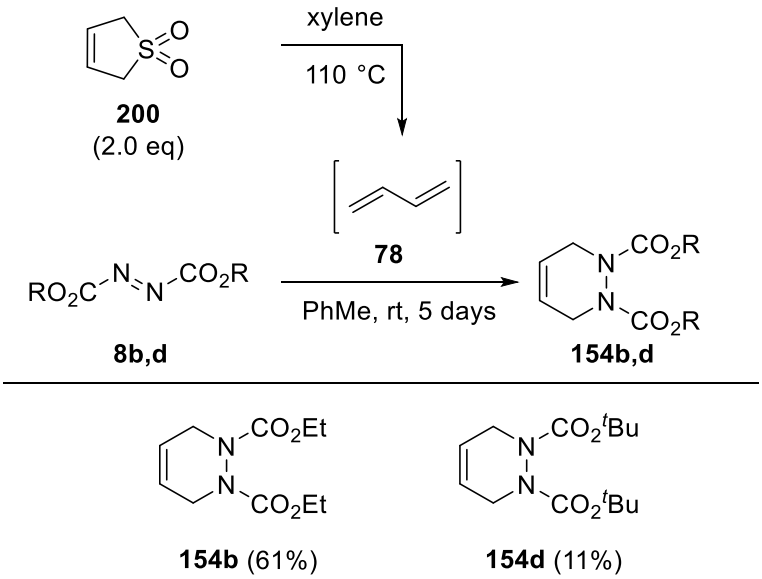
Stearns and Montellano de Ortiz have reported the synthesis of tetrahydropyridazine **154b** from butadiene sulfone **200** and DEAD **8b** in high yields (Scheme 2.14).[36] An unspecified amount of butadiene sulfone **200** was heated to form butadiene **78**, which was then bubbled into a solution of DEAD **8b** in benzene for two hours and left for two days.



Scheme 2.14

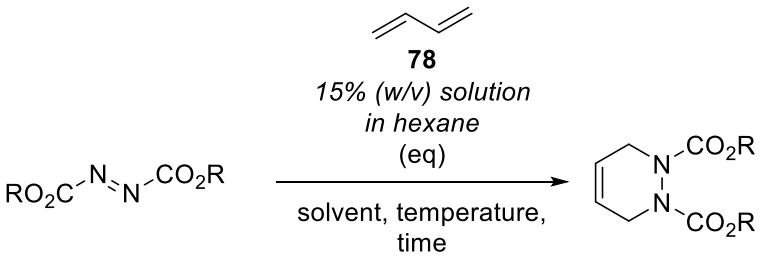
Applying these conditions, the reaction of DEAD **8b** and butadiene **78** (from butadiene sulfone) provided the cycloadduct **154b** in 61% yield (Scheme 2.15). The use of di-*tert*-butyl azodicarboxylate (DBAD) **8d** resulted in the formation of a complex mixture, however cycloadduct **154d** was 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

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.



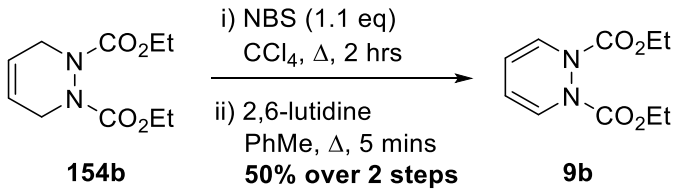
8b-d **154b-d**

Entry	R	Equivalents of 78	Temperature	Solvent	Time (days)	Yield 154b-d (%)
1	^{t}Bu	1.0	rt	CH_2Cl_2	1	17 (**154d**)
2	^{t}Bu	1.0	rt	MeOH	4	22 (**154d**)
3	^{t}Bu	3.0	rt	CH_2Cl_2	7	76 (**154d**)
4	^{t}Bu	3.0	rt	hexane	2	7 (**154d**)
5	^{t}Bu	3.0	40 °C[a]	CH_2Cl_2	4	93-97 (**154d**)
6	Et	3.0	rt	CH_2Cl_2	1	96 (**154b**)
7	^{i}Pr	3.0	40 °C[a]	CH_2Cl_2	1	97 (**154c**)

Table 2.3 [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).[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.[233–235]

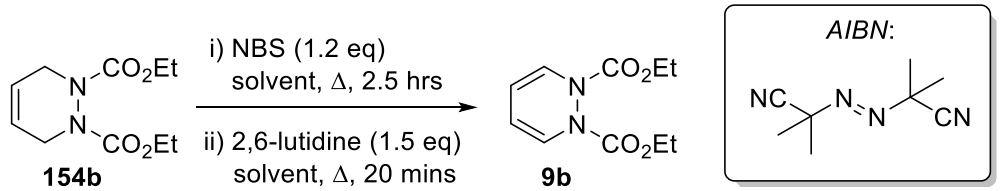


154b **9b**

Scheme 2.16

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

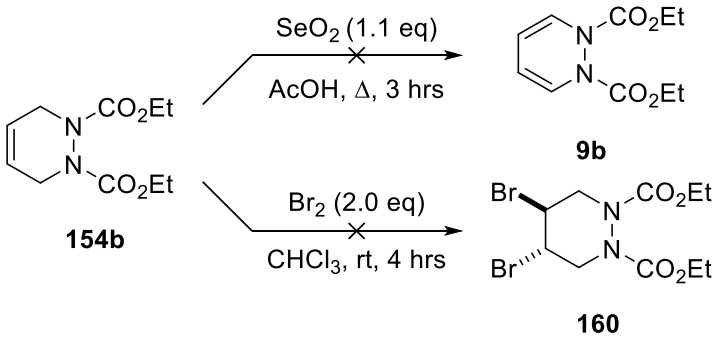
stoichiometric quantities of AIBN were used, poor conversions of tetrahydropyridazine **154b** was observed in the allylic bromination reaction. The 1,2-dihydropyridazine **9b** samples isolated by this method were of poor purity and degraded upon storage.



Entry	Solvent for i)	Solvent for ii)	Initiator	Yield 9b (%)[a]
1	Cy	PhMe	-	25
2	MeCN	PhMe	-	-
3	Cy	Cy	-	traces
4	Cy	PhMe	AIBN (1 mol%)	7
5	Cy	PhMe	AIBN (1.0 eq)	21

Table 2.4 [a] Yield over two steps; Cy = cyclohexane

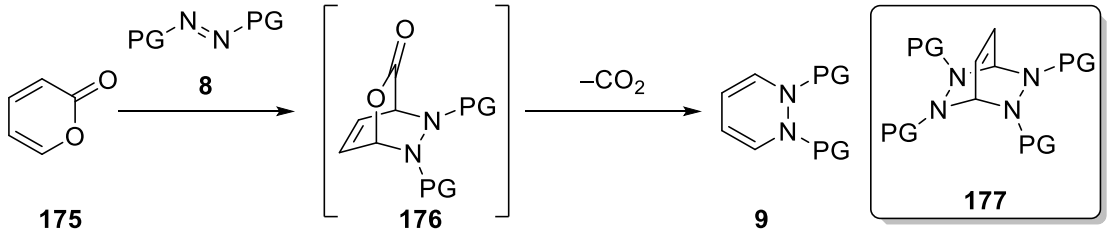
Alternatively, the conversion of tetrahydropyridazine **154b** into 1,2-dihydropyridazine **9b** was attempted using selenium dioxide or bromination-elimination reactions, which have been successful on related systems (Scheme 2.3).[164,165,168] When tetrahydropyridazine **154b** was treated with selenium dioxide in acetic acid (AcOH), 1,2-dihydropyridazine **9b** was not formed and only degradation was observed by ^{1}H 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 ^{1}H 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 ^{1}H NMR spectrum were not in a similar range to those reported.[165] The bromination reaction was not pursued any further due to scale-up and atom efficiency concerns.



Scheme 2.17

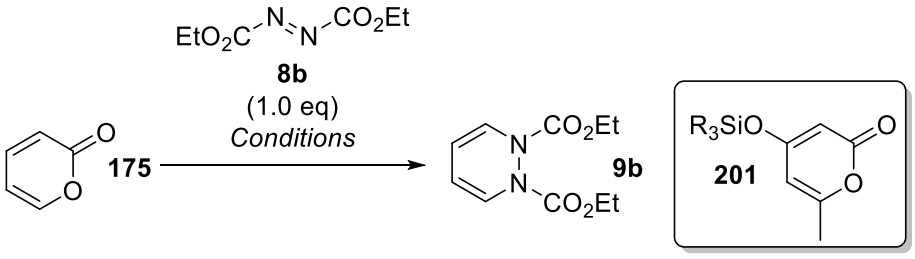
2.3.1.3 Synthesis of 1,2-Dihydropyridazines from 2-Pyrones

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

Using 2-pyrone (**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 ^{1}H 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.

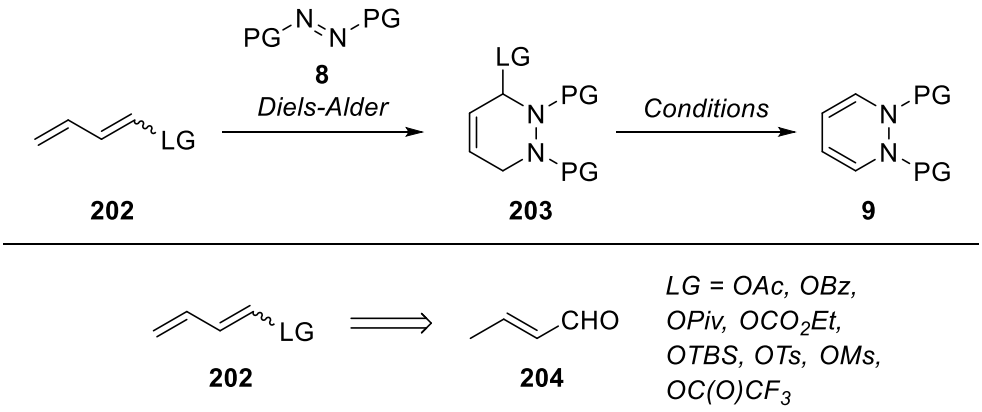


Entry	Conditions	Yield 9b (%)
1	Acetone, 0 °C → rt, 7 days	0
2	PhMe, 100 °C, 2 days	traces
3	PhMe, 120 °C, 1 day	0

Table 2.5

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

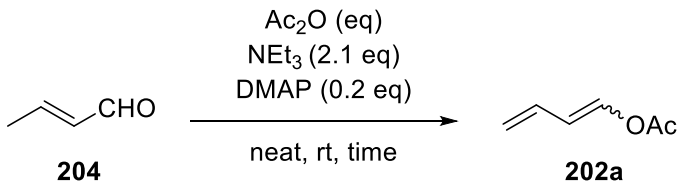
With other routes failing to provide an efficient method to produce simple, unsubstituted 1,2-dihydropyridazines of sufficient purity and in useful quantities, the development of a novel synthetic route starting from *O*-substituted dienes was investigated. A suitable leaving group was incorporated into 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.

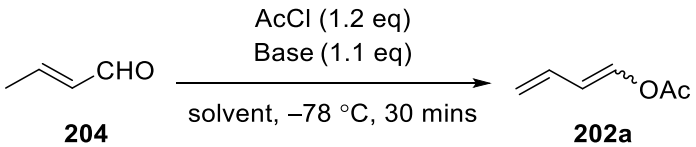


204 **202a**

Entry	Ac_2O (eq)	Time (days)	Yield 202a (%)	*E*:*Z* or *Z*:*E*[a,b]
1	5.0	1	50	10:1.0
2	3.0	4	62	8.0:1.0
3	1.5	2	58	5.5:1.0

Table 2.6 [a] *E*/*Z* ratio calculated by ^{1}H NMR through comparison of diene peaks. No internal standard used; [b] It was not possible to determine the major product; Ac_2O = acetic anhydride.

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).[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).

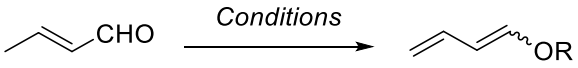


204 **202a**

Entry	Base	Solvent	Yield 202a (%)	*E*:*Z* or *Z*:*E*[a,b]
1	KO^{t}Bu	THF	38	50:1.0
2	KO^{t}Bu	2-MeTHF	0	-
3	KO^{t}Bu	Et_2O	0[c]	-
4	NaOEt	Et_2O	0	-
5	NEt_3	MTBE	0	-
6	NaH	THF	0	-
7	LiHMDS	THF	0	-

Table 2.7 [a] *E*/*Z* ratio calculated by ^{1}H NMR through comparison of diene peaks. No internal standard used; [b] It was not possible to determine the major product; [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. Adaption 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 not stable 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).



204 **202b-g**

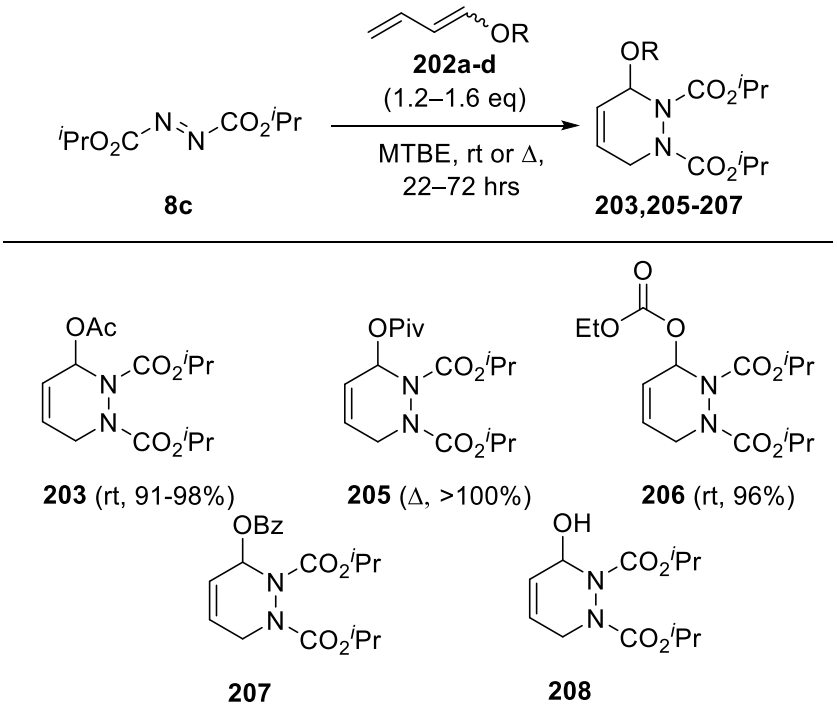
Entry	R	Conditions	Yield 202b-g (%)	*E*:*Z* or *Z*:*E*[a,b]
1	Bz	BzCl (1.1 eq), NEt_3 (2.1 eq), DMAP (0.2 eq), neat, rt, 24 hrs	22 (**202b**)	3.0:1.0
2	Bz	BzCl (1.2 eq), KO^{t}Bu (1.1 eq), THF, −78 °C, 30 mins	53 (**202b**)	20:1.0
3	Piv	PivCl (1.2 eq), KO^{t}Bu (1.1 eq), THF, −78 °C, 30 mins	54 (**202c**)	50:1.0
4	CO_2Et	EtOC(O)Cl (1.2 eq), KO^{t}Bu (1.1 eq), THF, −78 °C, 30 mins	34 (**202d**)	30:1.0
5	Ts	TsCl (5.0 eq), NEt_3 (2.1 eq), DMAP (0.2 eq), neat, rt, 3 days	0 (**202e**)	-
6	$C(O)CF_3$	TFAA (5.0 eq), NEt_3 (2.1 eq), DMAP (0.2 eq), neat, rt, 24 hrs	0 (**202f**)	-
7	Ms	MsCl (1.2 eq), NEt_3 (2.5 eq), CH_2Cl_2, −78 °C → rt, 21 hrs	0 (**202g**)	-

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

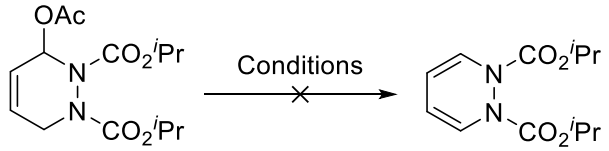
except with benzoyl-diene **202b**. The synthesis of cycloadduct **207** led to the formation of a complex mixture of products and cycloadduct **207** was found to be unstable to purification and isolation. These initial reactions were completed in methyl *tert*-butyl ether, however dichloromethane could 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)

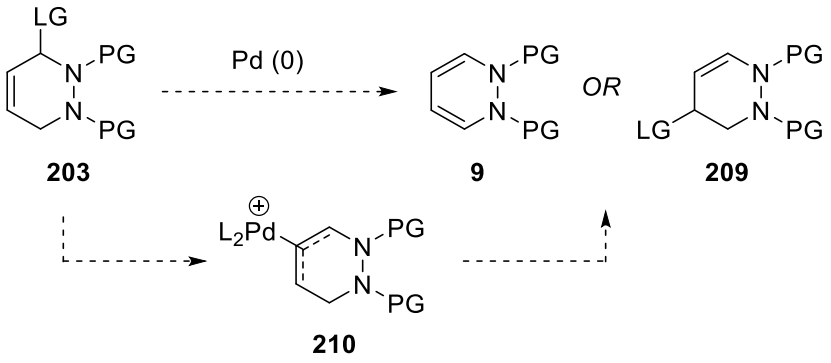


203c **9c**

Entry	Conditions	Yield 9c (%)
1	TsOH.H_2O (10 mol%), CH_2Cl_2, rt, 24 hrs	0
2	$Sc(OTf)_3$ (20 mol%), CH_2Cl_2, rt, 72 hrs	0
3	$FeCl_3$ (20 mol%), CH_2Cl_2, rt, 72 hrs	0
4	NaH (1.2 eq), THF, 0 °C → rt, 1 hr	0
5	2,6-lutidine (3.0 eq), PhMe, rt or Δ, 24 hrs	0
6	NEt_3 (2.0 eq), PhMe, Δ, 24 hrs	0
7	NaOAc (3.0 eq), PhMe, Δ, 24 hrs	0
8	K_2CO_3 (6.0 eq), PhMe, Δ, 5 hrs	0
9	$CsCO_3$ (2.0 eq), MeCN, Δ, 6 hrs	0

Table 2.9

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 η^3 π-allyl complex,[239–245] 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 **9** and formation of the isomerised starting material **209**. **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 η^3 π-allyl complex on the opposite side to that of the starting material

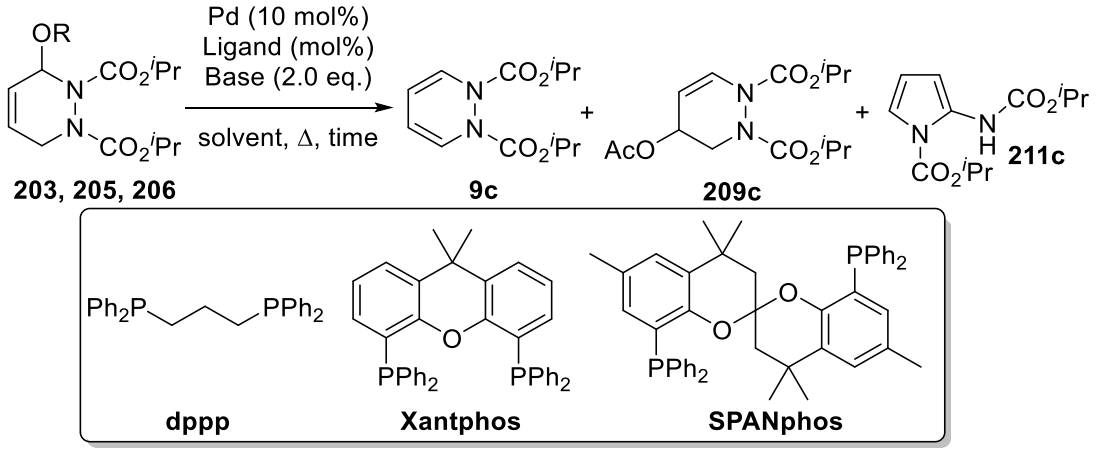


203 **9** **209** **210**

Scheme 2.21

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) ($Pd(PPh_3)_4$) 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

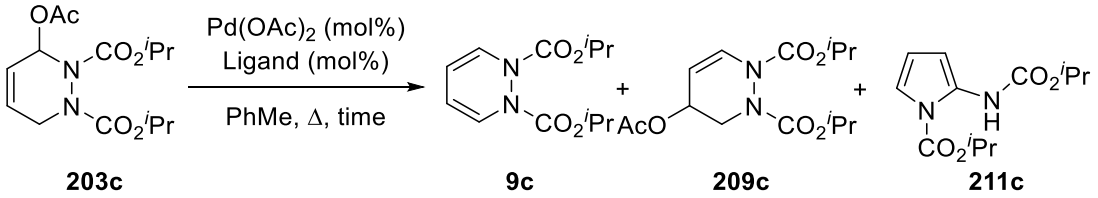
conditions (*vide infra*).[33,35,36] If the base was switched to potassium *tert*-butoxide, 1,2-dihydropyridazine **9c** was not formed and degradation of cycloadduct **203c** was observed (entry 2). Comparable yields were observed when other bases were used (entries 3-5), with potassium acetate and 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 investigated (entries 13-15). 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.



Entry	R	Solvent	Catalyst	Ligand	Base	Time (hrs)	Yield 9c (%)[a]	Yield 209c (%)[a]	Yield 211c (%)[a]
1	Ac	PhMe	$Pd(PPh_3)_4$	-	NEt_3	1	58	n.d	<5
2	Ac	PhMe	$Pd(PPh_3)_4$	-	KO^{t}Bu	1	-	-	-
3	Ac	PhMe	$Pd(PPh_3)_4$	-	KOAc	1	67	14	traces
4	Ac	PhMe	$Pd(PPh_3)_4$	-	DBU	4	52	15	traces
5	Ac	PhMe	$Pd(PPh_3)_4$	-	K_2CO_3	1.5	72	6	traces
6	Ac	PhMe	$Pd(PPh_3)_4$	-	-	1	54	40	traces
7	Ac	PhMe	$Pd(PPh_3)_4$	-	-	1	73	n.d	traces
8	Piv	PhMe	$Pd(PPh_3)_4$	-	-	2	-	-	-
9	CO_2Et	PhMe	$Pd(PPh_3)_4$	-	-	4	-	-	-
10	Ac	PhMe	$Pd_2(dba)_3$	PPh_3[b]	-	1	48	n.d	traces
11	Ac	PhMe	$Pd(OAc)_2$	PPh_3[b]	-	2	72	n.d	5
12	Ac	PhMe	$Pd(TFA)_2$	PPh_3[b]	-	1	67	n.d	7
13	Ac	PhMe	$Pd(OAc)_2$	dppp[c]	-	1	42	39	traces
14	Ac	PhMe	$Pd(OAc)_2$	Xantphos[c]	-	1	75	-	4
15	Ac	PhMe	$Pd(OAc)_2$	SPANphos[c]	-	1	38	35	7
16	Ac	THF	$Pd(OAc)_2$	Xantphos[c]	-	4	56	4	-
17	Ac	MeCN	$Pd(OAc)_2$	Xantphos[c]	-	1	21	28	-
18	Ac	EtOAc	$Pd(OAc)_2$	Xantphos[c]	-	1	55	11	-
19	Ac	2-MeTHF	$Pd(OAc)_2$	Xantphos[c]	-	1	72	-	-
20	Ac	2-MeTHF[d]	$Pd(OAc)_2$	Xantphos[c]	-	48	12	52	-
21	Ac	1,4-dioxane	$Pd(OAc)_2$	Xantphos[c]	-	1	66	n.d	-
22	H	PhMe	$Pd(OAc)_2$	Xantphos[c]	-	16	2	-	-

Table 2.10 [a] Isolated yields [b] 40 mol% ligand; [c] 20 mol% ligand; [d] Reaction run at room temperature; n.d = not determined; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; Piv = pivalate; $Pd_2(dba)_3$ = tris(dibenzylideneacetone)dipalladium(0); $Pd(OAc)_2$ = palladium(II) acetate; $Pd(TFA)_2$ = 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).



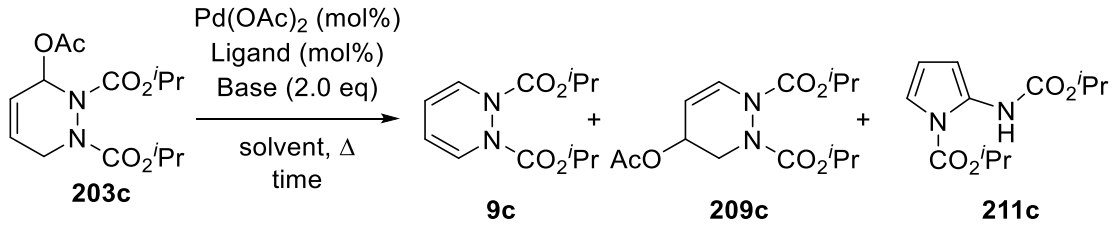
203c **9c** **209c** **211c**

Entry	Catalyst	Ligand	Catalyst loading (mol%)	Ligand (mol%)	Time (hours)	Yield 9c (%)	Yield 209c (%)	Yield 211c (%)
1	$Pd(OAc)_2$	PPh_3	5	20	1	61	n.d	n.d
2	$Pd(OAc)_2$	PPh_3	2	10	1	38	n.d	n.d
3	$Pd(OAc)_2$	Xantphos	5	10	1	65	-	6
4	$Pd(OAc)_2$	Xantphos	2	4	2	44	21	11
5	$Pd(OAc)_2$	Xantphos	1	2	4	17	47	9
6	$Pd(OAc)_2$	Xantphos	10	10	1	23	54	n.d
7	$Pd(OAc)_2$	Xantphos	10	5	1	4	69	n.d

Table 2.11

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.



Entry	Catalyst Loading (mol%)	Base	Ligand (mol%)	Solvent	Time (hrs)	Yield 9c (%)[a]
1	10	K_2CO_3	PPh_3 (40 mol%)	PhMe	1	67
2	10	NEt_3	PPh_3 (40 mol%)	PhMe	1	77
3	5	NEt_3	PPh_3 (20 mol%)	PhMe	1	82
4	2	NEt_3	PPh_3 (8 mol%)	PhMe	1	79
5	1	NEt_3	PPh_3 (4 mol%)	PhMe	1	83
6	1	NEt_3	PPh_3 (4 mol%)	THF	2	87
7	1	NEt_3	PPh_3 (4 mol%)	EtOAc	2	86
8	1	NEt_3	PPh_3 (4 mol%)	2-MeTHF	3	87[b]
9	1	NEt_3	PPh_3 (4 mol%)	MeCN	4	81
10	1	NEt_3	PPh_3 (4 mol%)	1,4-dioxane	1	84

Table 2.12 [a] 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

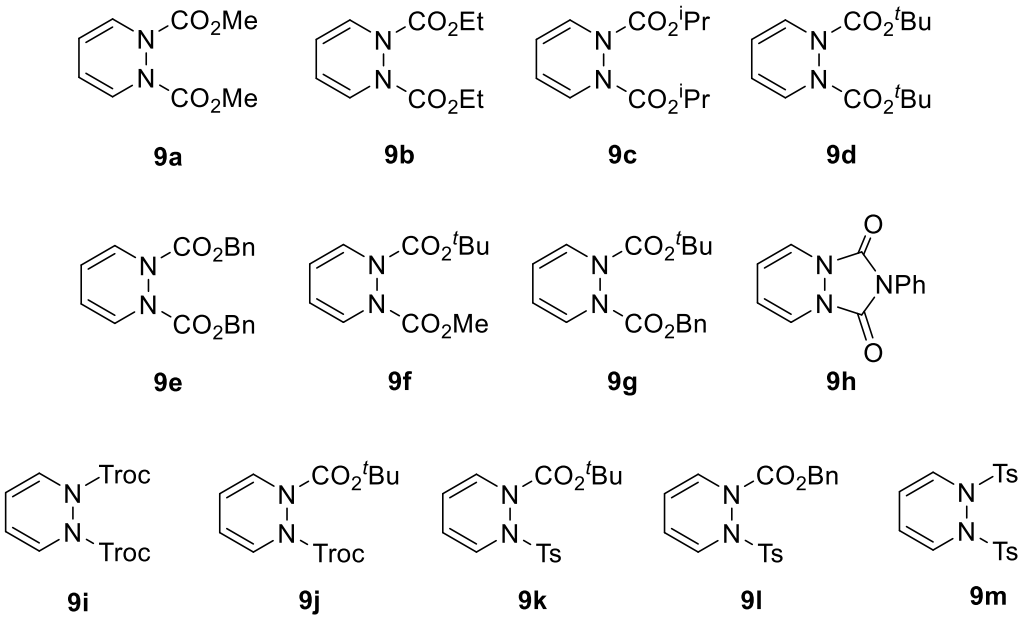
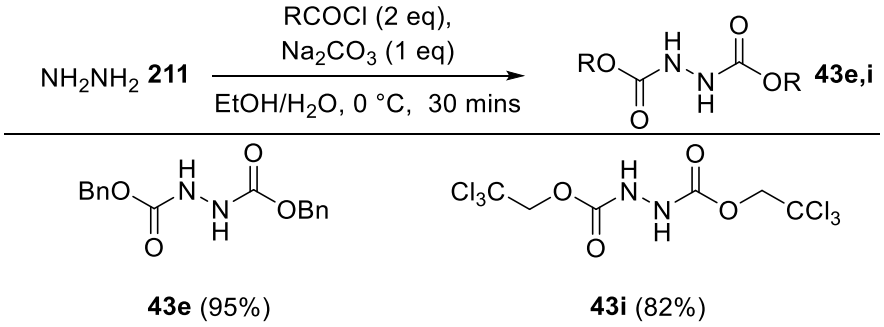


Figure 2.5

2.3.2.4.1 Synthesis of Hydrazines

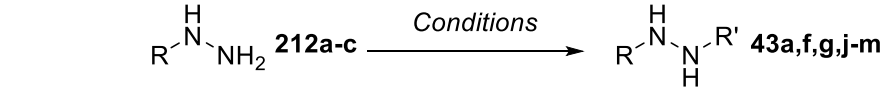
Due to the commercial availability of DEAD **8b**, DIAD **8c** and DBAD **8d**, it was not necessary to synthesise them. Bis(trichloroethyl)azodicarboxylate and dibenzyl azodicarboxylate are also commercially available, though due to cost the decision was made to synthesise them. The synthesis of these hydrazines has been reported in the literature from the reaction of chloroformates with hydrazine **211** in the presence of a base.[246,247] Hydrazines **43e,i** were synthesised in 95% and 82% yields respectively and without the need for further purification (Scheme 2.22).

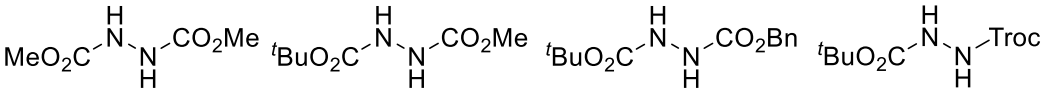


Scheme 2.22

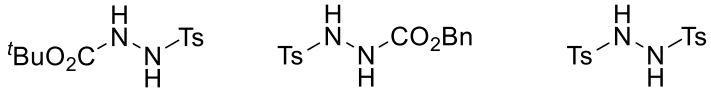
Starting from commercially available hydrazides, a series of symmetrical and unsymmetrical hydrazines **43** have been synthesised (Table 2.13). Attempts to synthesise the dimethyl carbamate hydrazine **43a** from hydrazine **211** resulted in the loss of the product into the aqueous layer during the 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.[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 **212b** and *p*-toluenesulfonyl hydrazide **212c**.[92] Through a modified procedure, *tert*-butyl carbazate **212b** was transformed into the methyl, benzyl- and trichloroethyl-carbamate hydrazines **43f,g,i** in 83%, 83% and 94% yield respectively (entries 2-4). For hydrazine **43i**, the reaction had to be run at low concentration (0.1 M) to reduce by-product formation, however the synthesis of hydrazines **43f,g** could be run at higher concentrations (1 M). A tosyl group could also be installed to form hydrazine **43k** in 68% yield (entry 5).[92] The synthesis of a hydrazine equipped with a sulfonamide and a benzyl carbamate proved to be more challenging. *p*-Toluenesulfonyl hydrazide **212c** was reacted with benzyl chloroformate to give hydrazine **43l** in 52% yield (entry 6).[92] A moderate yield was proposed to have been due to the insolubility of the starting hydrazide in water. Starting from the same hydrazide **212c**, ditosyl hydrazine **43m** was synthesised in 64% yield through a known procedure (entry 7).[251]





43a **43f** **43g** **43j**



43k **43l** **43m**

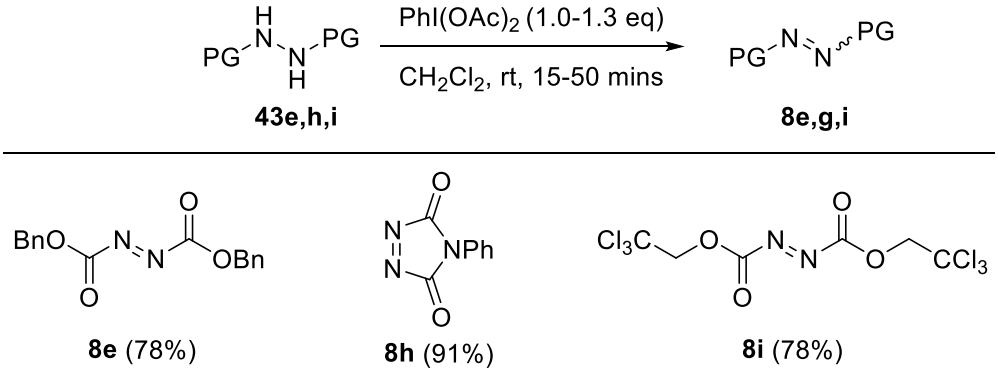
Entry	R	R'	Conditions	Yield 43 (%)
1	CO_2Me (**212a**)	CO_2Me	$MeCO_2Cl$ (1.1 eq), pyridine (3.0 eq), 2-MeTHF, 0 °C → rt, 1.5 hrs	58 (**43a**)
2	$CO_2{}^tBu$ (**212b**)	CO_2Me	$MeCO_2Cl$ (1.1 eq), pyridine (6.0 eq), 2-MeTHF, 0 °C → rt, 1.5 hrs	83 (**43f**)
3	$CO_2{}^tBu$ (**212b**)	CO_2Bn	$BnCO_2Cl$ (1.1 eq), pyridine (6.0 eq), 2-MeTHF, 0 °C → rt, 1.5 hrs	83 (**43g**)
4	$CO_2{}^tBu$ (**212b**)	Troc	TrocCl (1.1 eq), pyridine (6.0 eq), 2-MeTHF, 0 °C → rt, 1.5 hrs	94 (**43j**)
5	$CO_2{}^tBu$ (**212b**)	Ts	TsCl (1.1 eq), pyridine (6.0 eq), THF, 0 °C → rt, 4 hrs	68 (**43k**)
6	Ts (**212c**)	CO_2Bn	$BnCO_2Cl$ (1.2 eq), $NaHCO_3$ (1.2 eq), H_2O, 0 °C → 60 °C, 2.5 hrs	52 (**43l**)
7	Ts (**212c**)	Ts	TsCl (1.5 eq), pyridine (1.5 eq), CH_2Cl_2, rt, 2.5 hrs	64 (**43m**)

Table 2.13

2.3.2.4.2 Synthesis of Azo Compounds

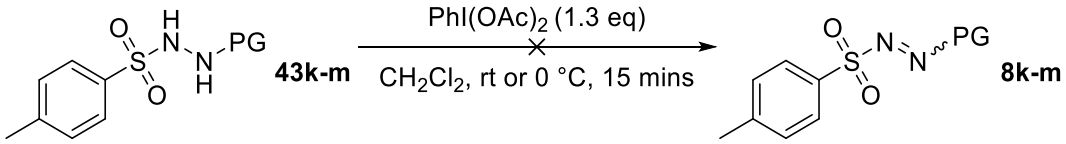
With a range of hydrazine intermediates in hand, oxidation of hydrazines **43e,h,i** to the corresponding azo compounds was investigated (Scheme 2.23). The use of the hypervalent

iodine reagent iodobenzene diacetate (IBDA) has been successful for the oxidation of diethyl hydrazine-1,2-dicarboxylate and 4-phenyl urazole.[252] According to this procedure, PTAD **8h** was synthesised from 4-phenylurazole **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.



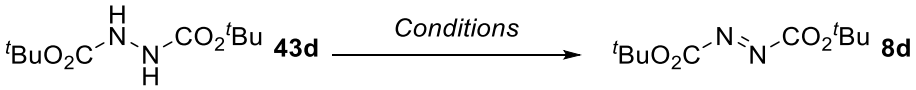
Scheme 2.23

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.[253]



Scheme 2.24

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,[254] hydrazones,[255] phenol, sulfides,[255] thioamides,[256] 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 dimethyl-carbamate 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.

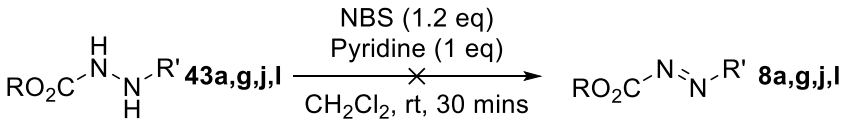


Entry	Conditions	Yield 8d (%)
1	PIBDA (0.8 mmol/g, 1.1 eq), CH_2Cl_2, rt, 6 days	<5
2	IBX (1.4 eq), DMSO, rt, 17 hours	<5
3	CuCl (20 mol%), pyridine (5 mol%), 2-MeTHF, rt, 19 hours	79
4	Ag_2CO_3/Celite (4 eq), PhMe, 75 ˚C, 15 minutes	34
5	Ag_2CO_3/Celite (1.5eq), PhMe, rt, 1 hour	0
6	Ag_2CO_3/Celite (1.5 eq), PhMe, 50 ˚C, 25 minutes	88

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**.



43a,g,j,l → **8a,g,j,l**

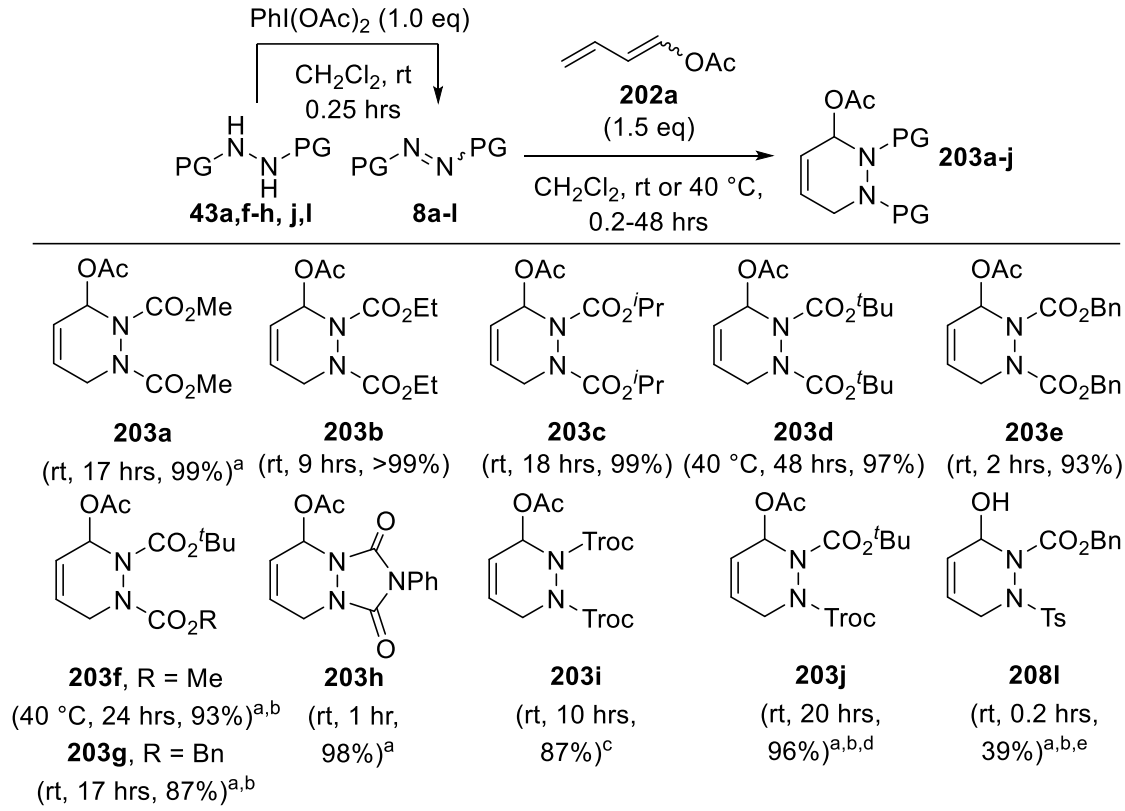
Scheme 2.25

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

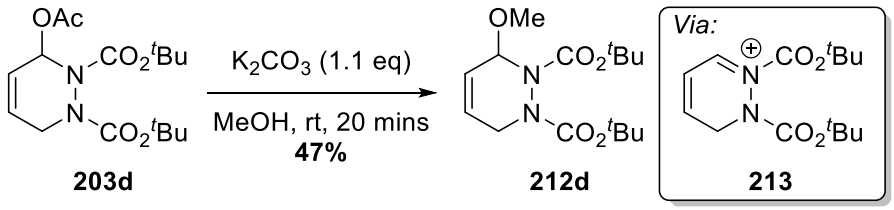
Subsequently, the Diels-Alder reaction of commercially available azo compounds **8b-e** (diethyl- diisopropyl- di-*tert*-butyl- and dibenzyl azodicarboxylate) or *in situ* generated azo compounds **8a,f-l** with 1-acetoxy-1,3-butadiene **202a** was completed to give cycloadducts **203a-j** in mostly 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**.[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 **208l** in 59% yield, but not the acetylated cycloadduct **203l**. ^{1}H NMR analysis has confirmed that the cycloadduct **203l** does form, though on standing in deuterated chloroform it degraded to form the deacetylated product **208l**. The structure of **208l** was tentatively proposed through 2-dimensional (2-D) ^{1}H-^{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.



Scheme 2.26 [a] Over two steps from hydrazine with iodobenzene diacetate (1.0 eq); [b] Only one of two possible regioisomers shown; [c] 1.2 eq acetoxy-diene **202a** used and reaction run in MTBE; [d] 1.2 eq acetoxy-diene **202a** used; [e] 1.3 eq of IBDA and 1.8 eq acetoxy-diene **202a** used.

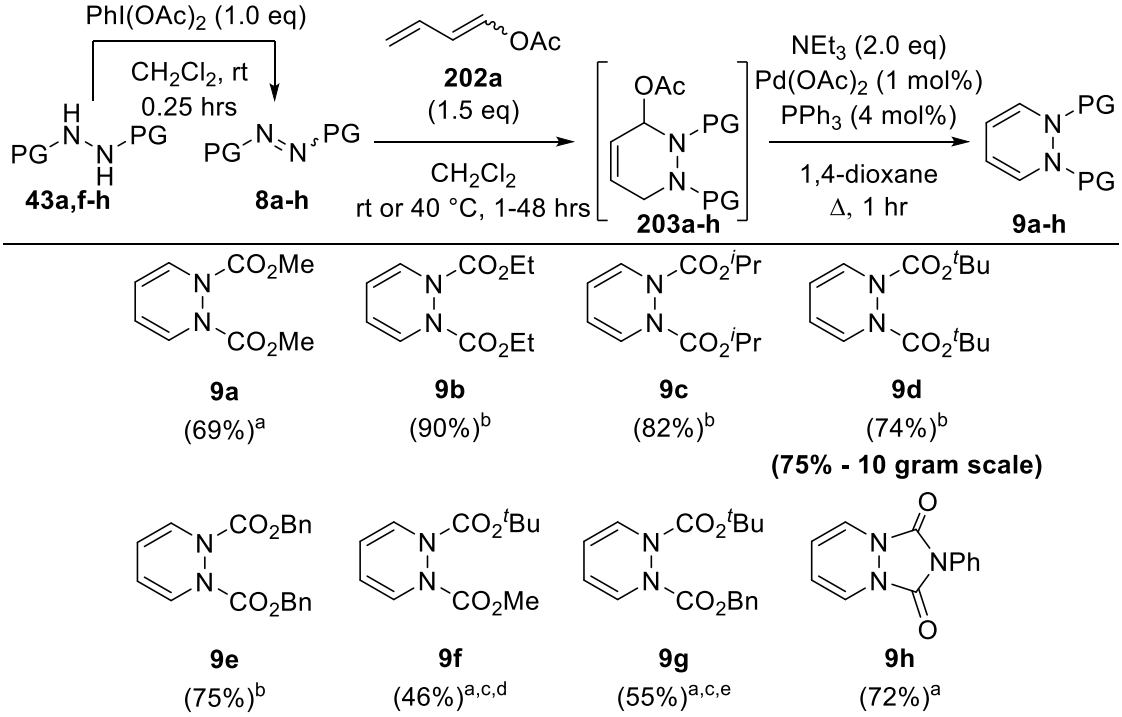
Interestingly, under typical conditions an attempted deacetylation with cycloadduct **203d** did not give any of the expected alcohol **208d** (Scheme 2.27). The product that formed was ether **212d** in moderate yields, which is proposed to have formed through an initial elimination of the acetate group to give iminium ion **213**, followed by trapping with methanol. It seemed likely that the formation of alcohol **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.



Scheme 2.27

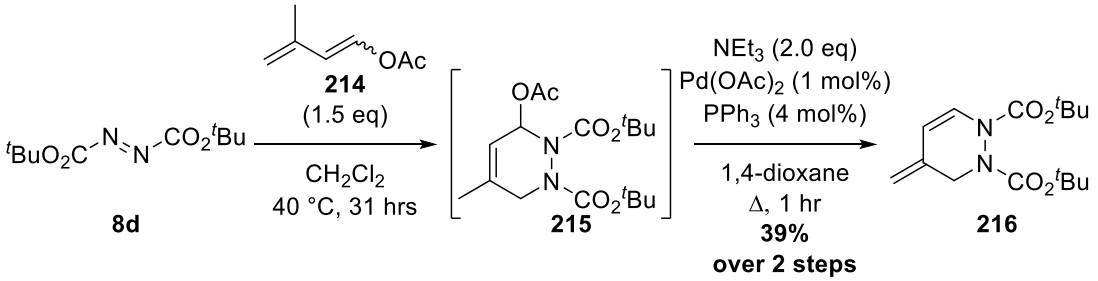
2.3.2.4.4 Palladium-Catalysed Elimination Reactions

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.



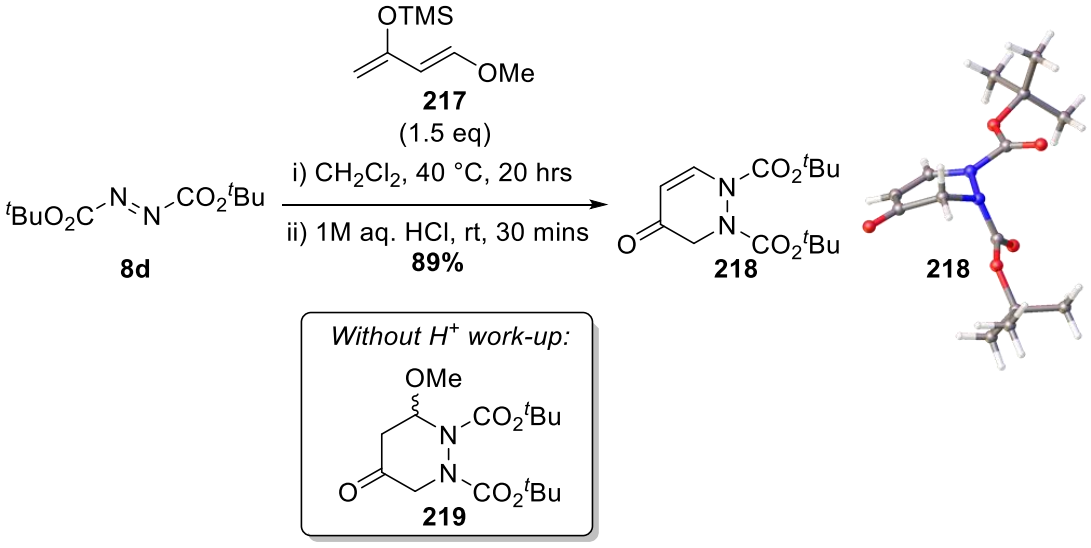
Scheme 2.28 [a] Over three steps from hydrazine with iodobenzene diacetate (1.0 eq); [b] Over two steps; [c] 2 mol% $Pd(OAc)_2$ used; [d] 34% isomerised starting material **209f**; [e] 22% isomerised starting material **209g**

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.[238] 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).[262] 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.[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.[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.

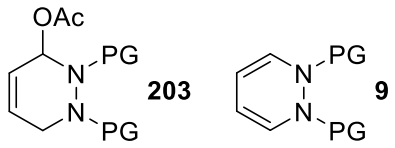


Figure 2.6

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**.[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.

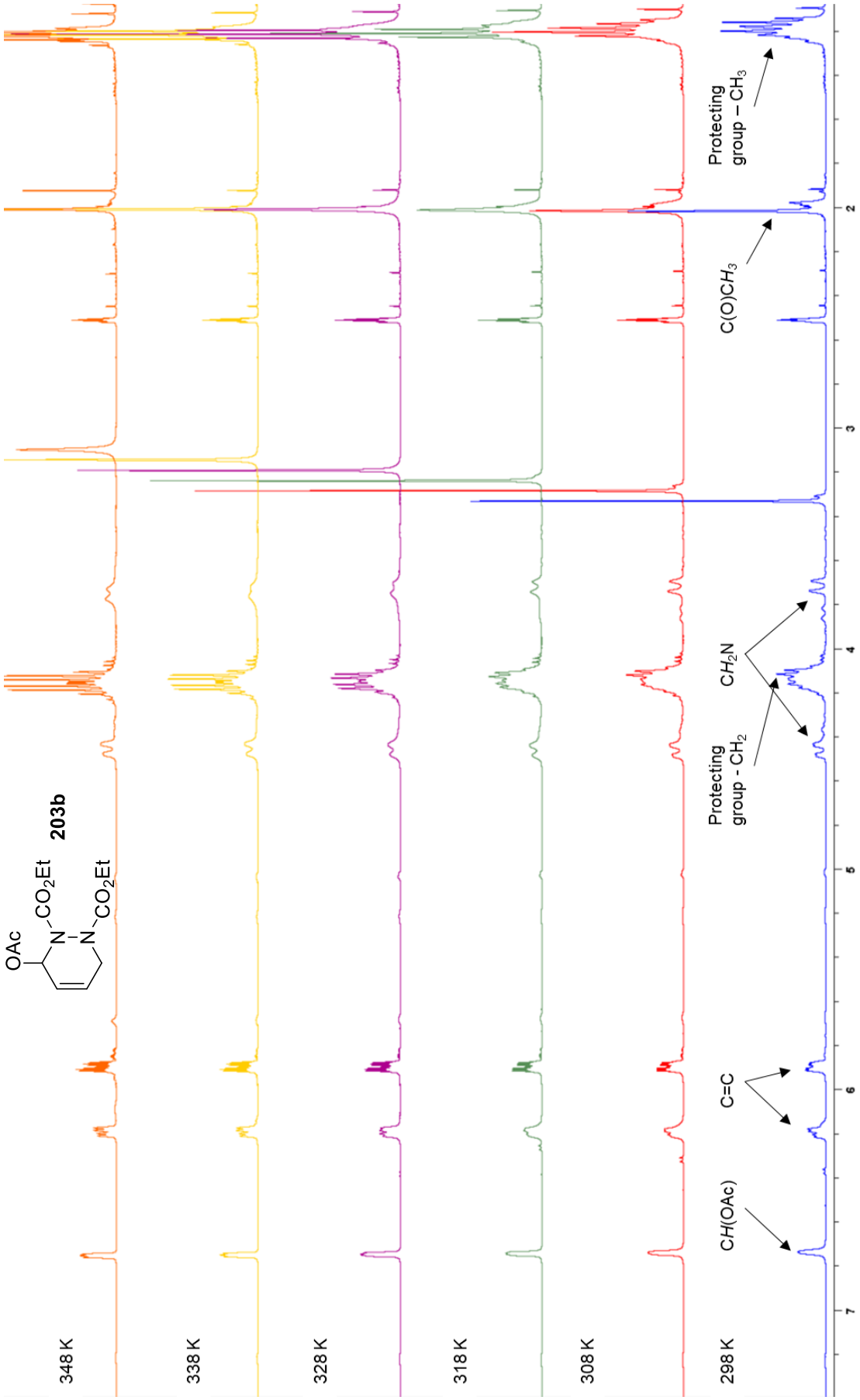


Figure 2.7 ^{1}H VT-NMR in d_6-DMSO of cycloadduct **203b**

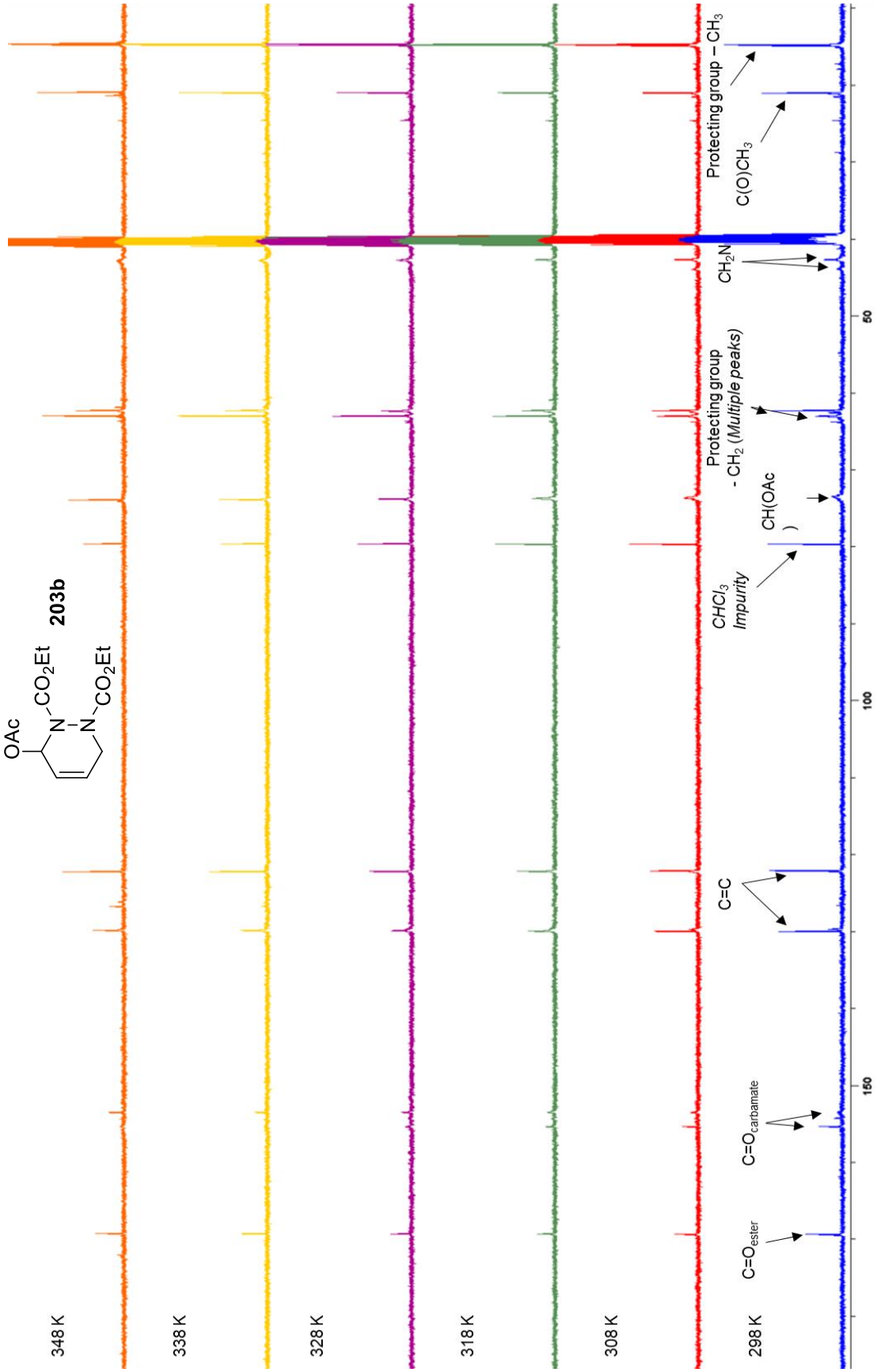


Figure 2.8 ^{13}C VT-NMR in d_6-DMSO of cycloadduct **203b**

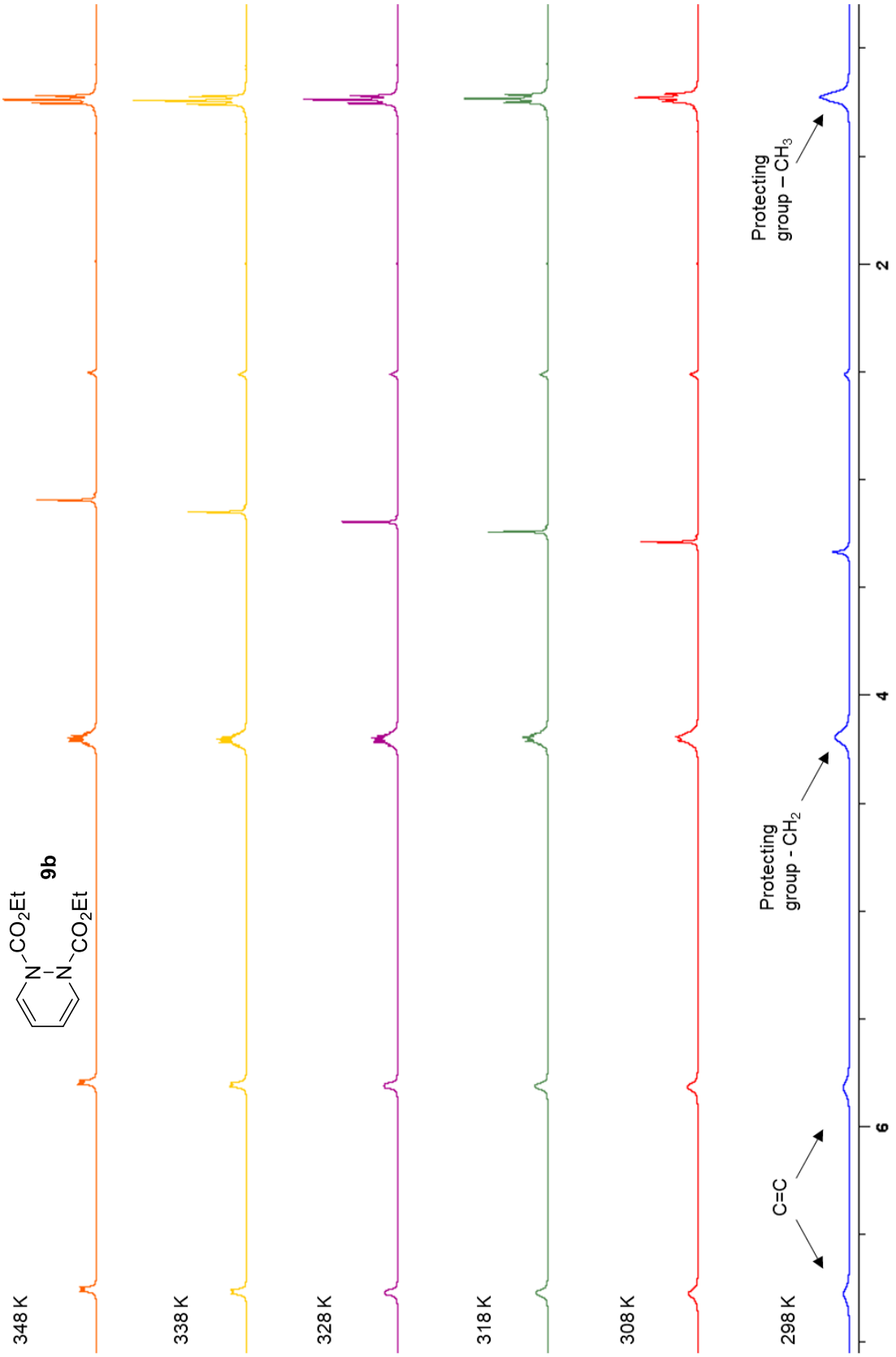


Figure 2.9 ^{1}H VT-NMR in d_6-DMSO of 1,2-dihydropyridazine **9b**

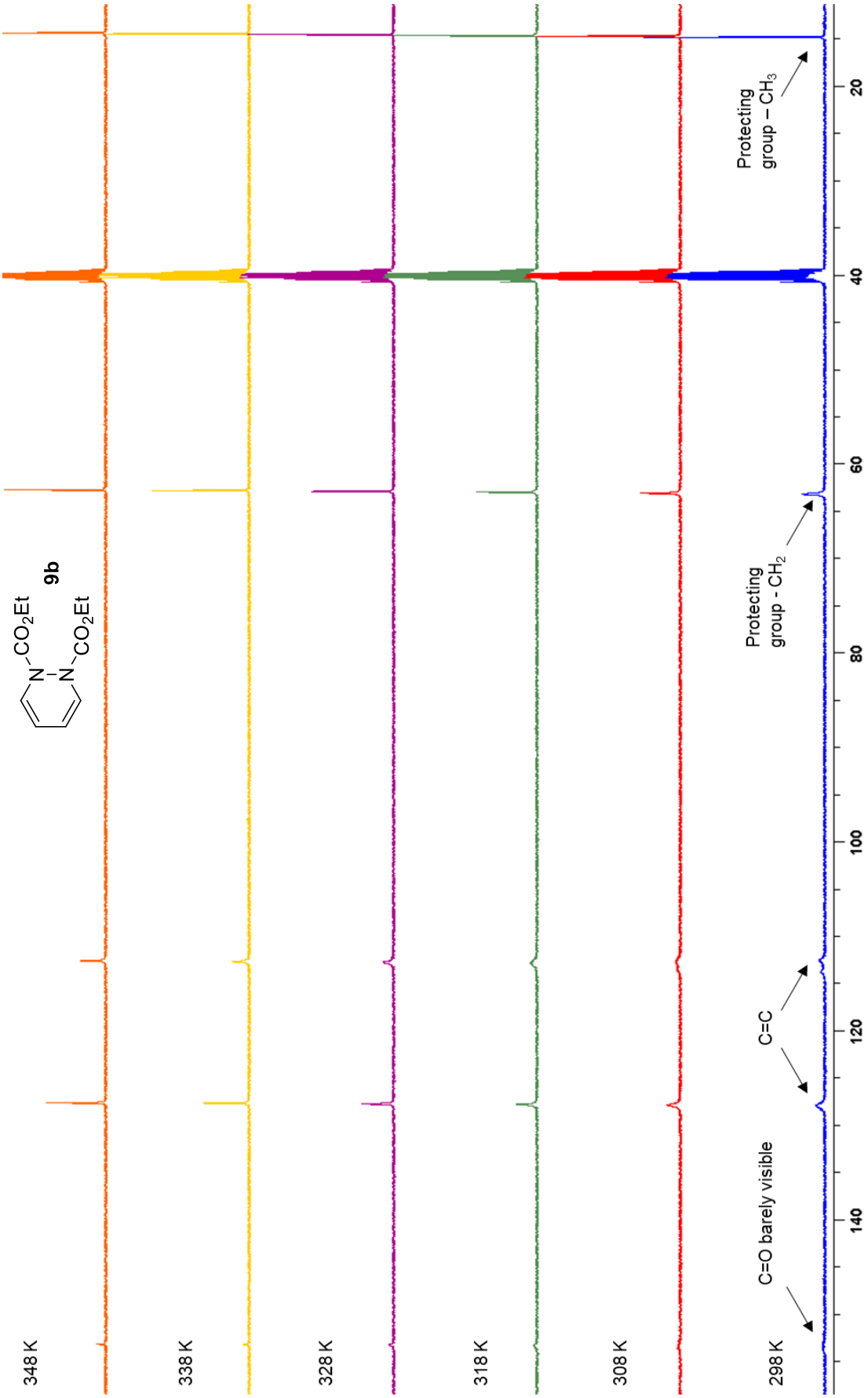
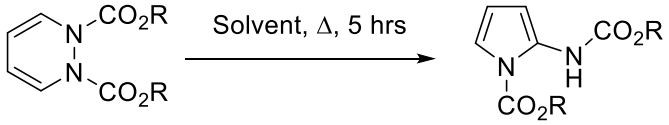


Figure 2.10 ^{13}C VT-NMR in d_6-DMSO of 1,2-dihydropyridazine **9b**

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 pyrroles **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 pyrroles **210a-d** anyway, it is likely that this is the cause of degradation and lower yields for this substrate.



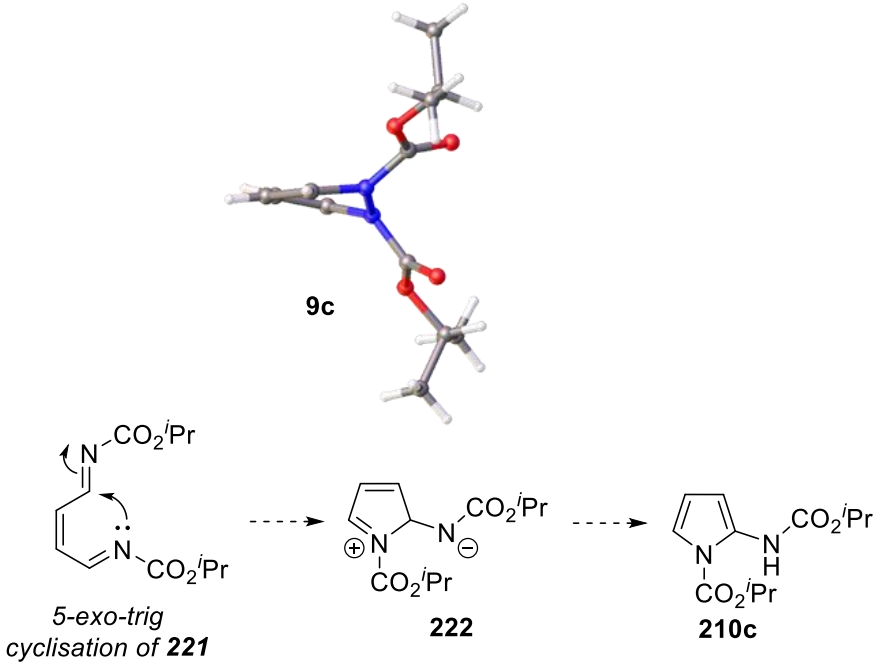
9a-d **210a-d**

Entry	R	Solvent	Yield 210a-d (%)
1	^{i}Pr	PhMe	46 (**210c**)[a]
2	^{i}Pr	DMF	52 (**210c**)[b]
3	^{i}Pr	*o*-xylene	52 (**210c**)[b]
4	^{i}Pr	*o*-xylene	90 (**210c**)
5	Me	*o*-xylene	62 (**210a**)
6	Et	*o*-xylene	86 (**210b**)
7	^{t}Bu	*o*-xylene	28 (**210d**),11 (**220d**)[c]

Table 2.15 [a] Reaction run for 19 hours; [b] Reaction run for 2 hours; [c] Product bearing one carbamate protecting group

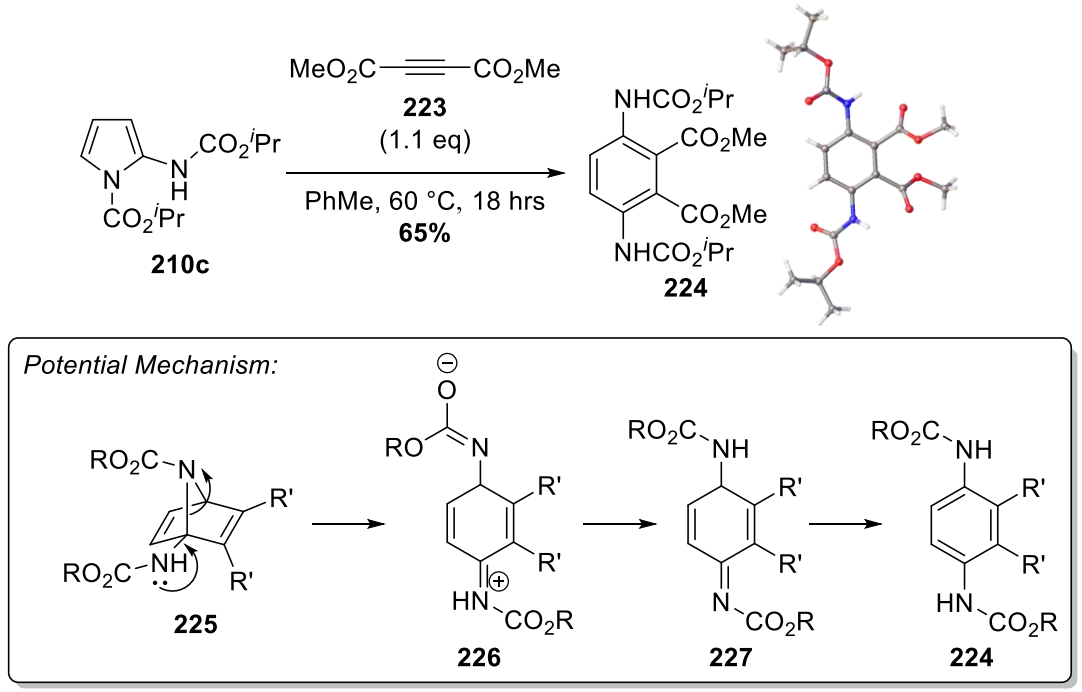
From the crystal structure of **9c**, the 1,2-dihydropyridazine ring is puckered and potentially the p-orbitals are not able to overlap as extensively as found for other 1,3-dienes, such as 1,3-butadiene, which could prevent any Diels-Alder reactions from happening (Scheme 2.31). In

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 $_{\pi}4_{s}$ + $_{\pi}2_{a}$ 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 $_{\pi}4_{s}$ + $_{\pi}2_{s}$ 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.



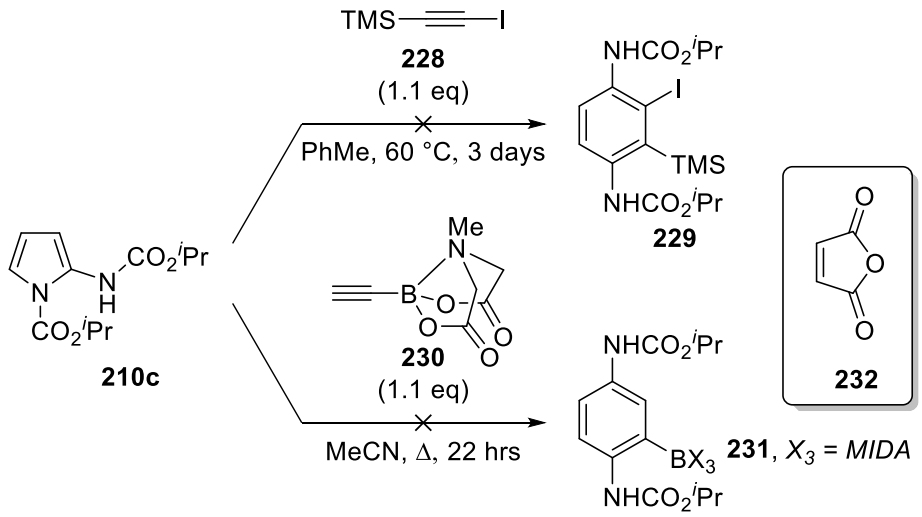
Scheme 2.31 X-ray crystal structure for 1,2-dihydropyridazine **9c** (top); mechanism (bottom)

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**.[173] 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.



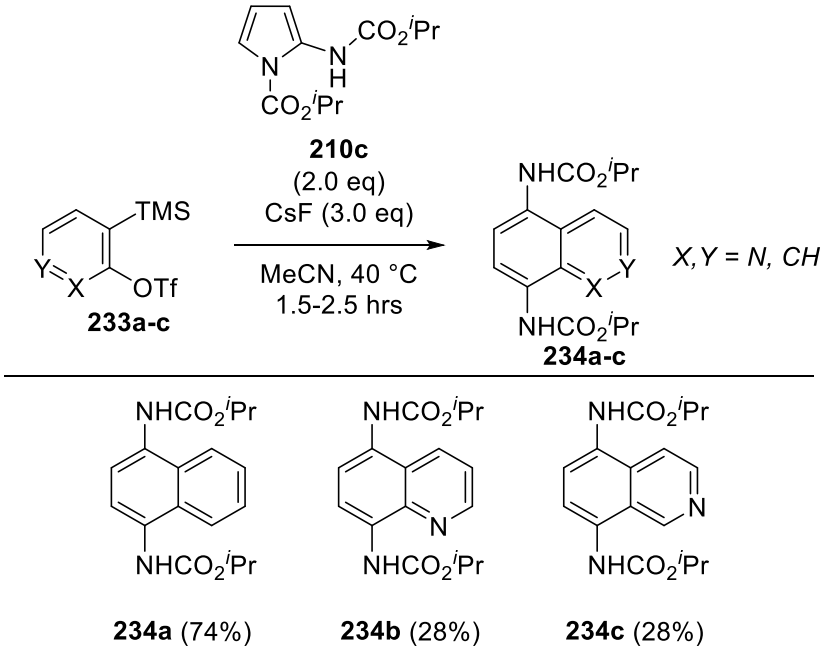
Scheme 2.32

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]



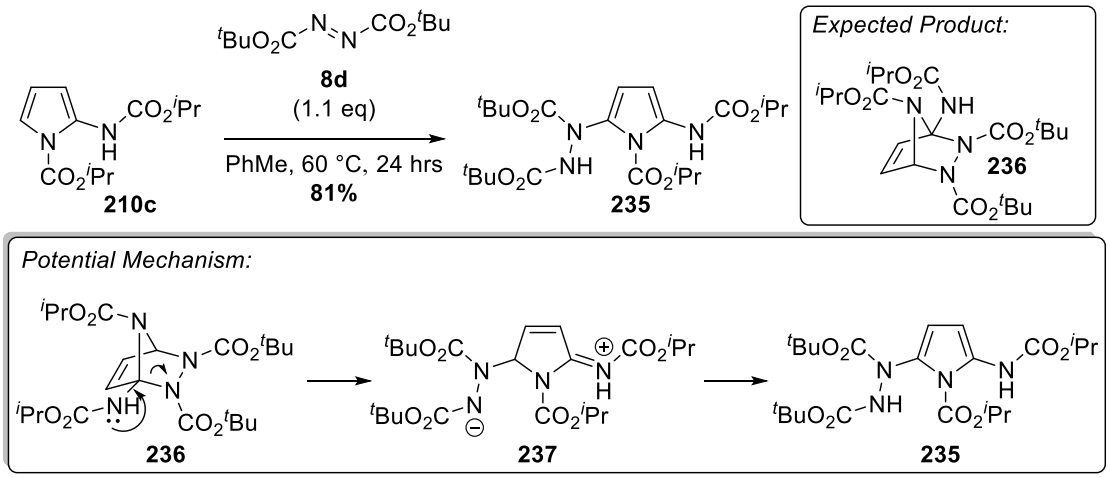
Scheme 2.33 MIDA = methyliminodiacetic acid

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.



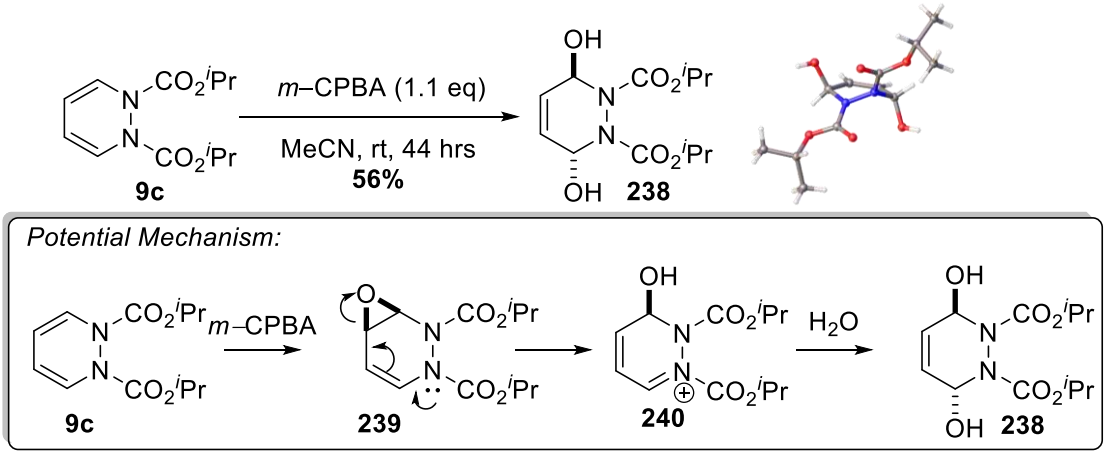
Scheme 2.34

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.



Scheme 2.35

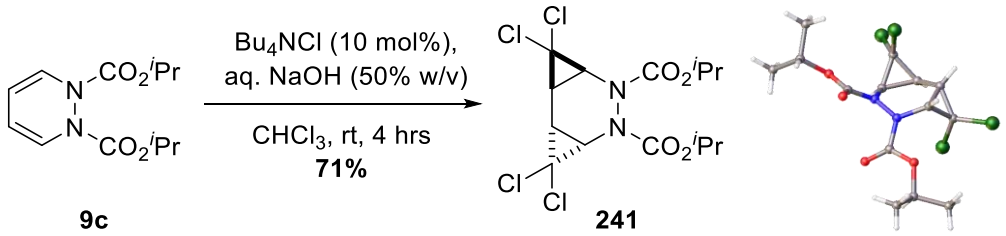
An attempted monoepoxidation of 1,2-dihydropyridazine **9c** using *m*-CPBA (*meta*-chloroperoxybenzoic acid) showed no sign of epoxide formation and poor conversions. The major product was the *trans*-diol **238** isolated in 56% yield, and the structure was confirmed by X-ray crystallography (Scheme 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.[271] 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.



Scheme 2.36

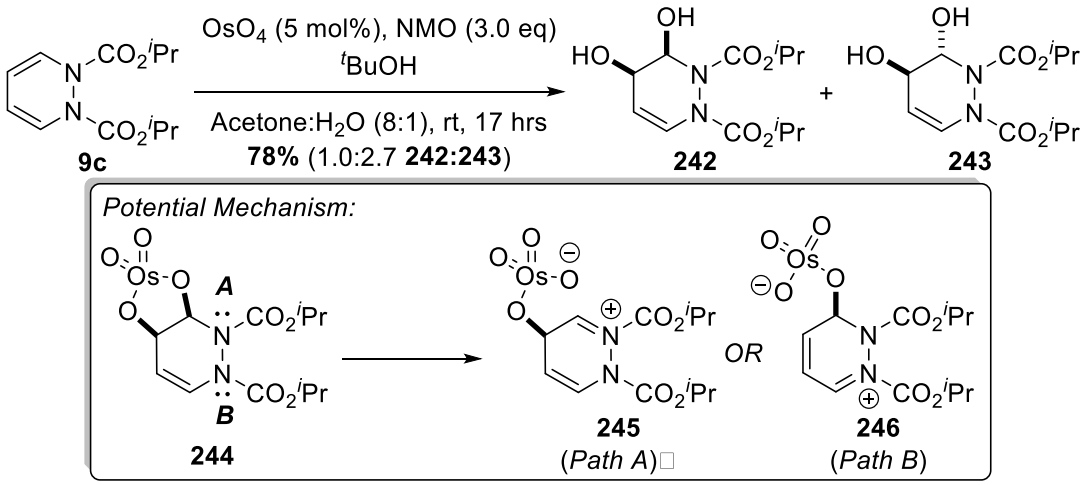
It was hoped that it should be possible to carry out a cyclopropanation of the double bonds in **9c** (Scheme 2.37). When treated under conditions that formed dichlorocarbene *in situ*, tricycle **241** was isolated in good yield and possessed two cyclopropane rings that were positioned *anti* with respect 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 mono-cyclopropanation is not feasible. Tricycle **241** showed surprising thermal stability and remained unchanged after heating at reflux in xylene for six hours.



Scheme 2.37

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 ^{1}H-^{1}H 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.



Scheme 2.38

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 identitites 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.

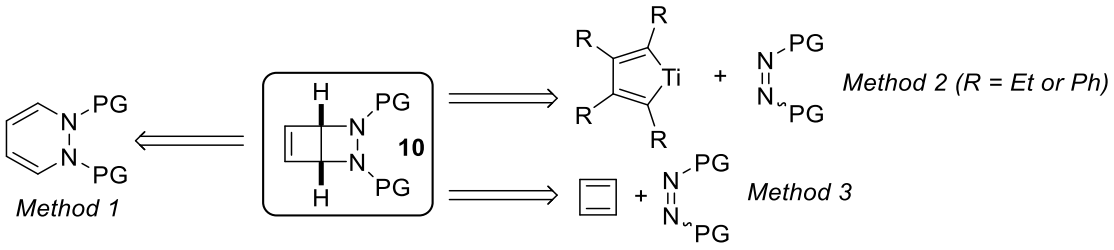
The reactions of 1,2-dihydropyridazines have shown interesting results. When 1,2-dihydropyridazines are heated at high temperatures, a clean rearrangement reaction to 2-aminopyrroles **210** took place in high yields. From the attempted Diels-Alder reactions of 1,2-dihydropyridazines **9**, it was found 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-dihydropyrdazine **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 *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

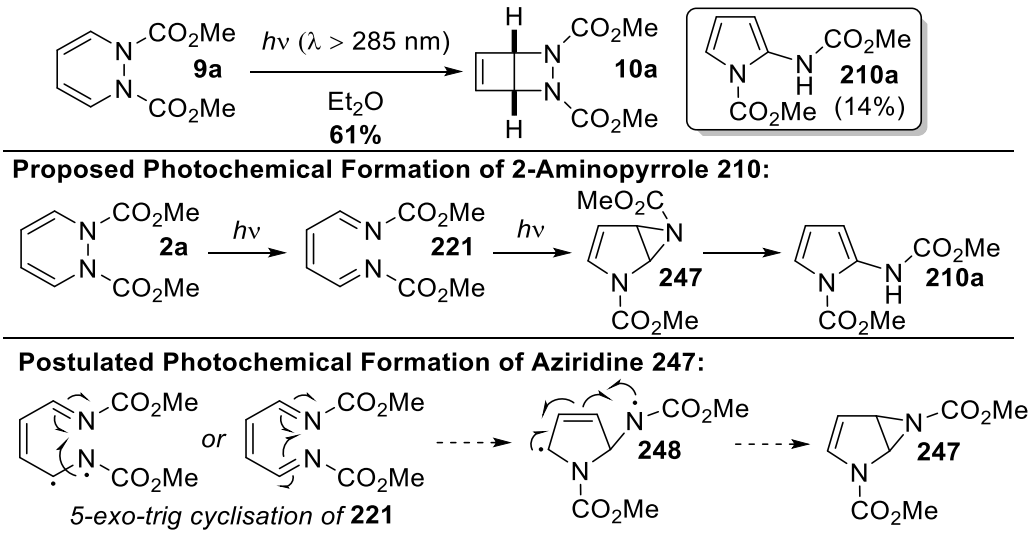
To date, there are limited literature examples for the synthesis of bicyclic 1,2-diazetidines **10** (Scheme 3.1).[33,35,36,272–275] The current ways to synthesise bicyclic 1,2-diazetidines can be divided into: the 4-π photocyclisation of 1,2-dihydropyridazines (Method 1), reaction of metal complexes 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

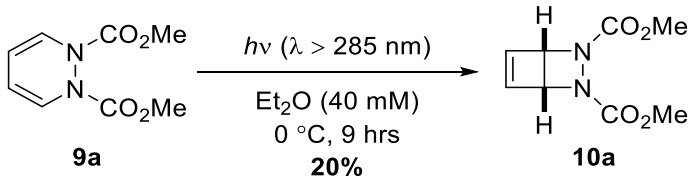
3.1.1 4-π Photocyclisation of 1,2-Dihydropyridazines

Altman *et al.* published the first 4-π photocyclisation of 1,2-dihydropyridazines in 1968.[33] 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 $_{\pi}4_{s} + _{\pi}2_{a}$ 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**.[263–269]



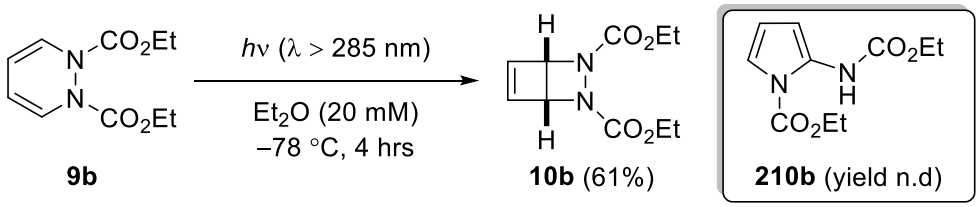
Scheme 3.2

Since this pioneering work, the synthesis of the bicyclic 1,2-diazetidine **10a** has been repeated and further experimental details have been reported.[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

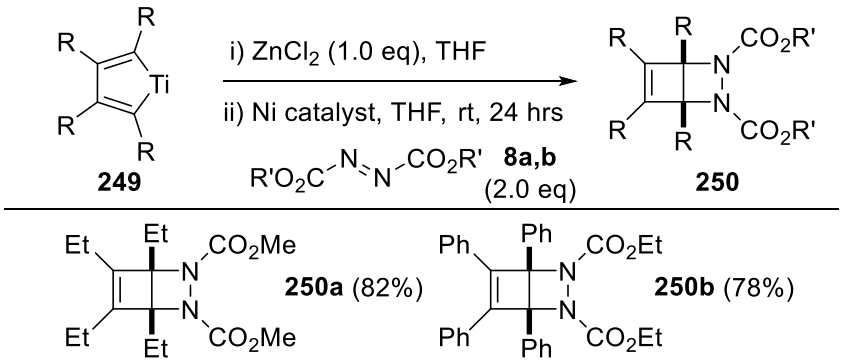
More recently, Stearns and Ortiz de Montellano developed a multigram synthesis to access bicyclic 1,2-diazetidine **10b** for biological testing.[36] Low temperatures were employed for the 4-π photocyclisation and bicyclic 1,2-diazetidine **10b** was isolated in 61% yield and again 2-aminopyrrole **210b** 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.[36]



Scheme 3.4 n.d = not determined

3.1.2 Organometallic Complexes with Azo Compounds

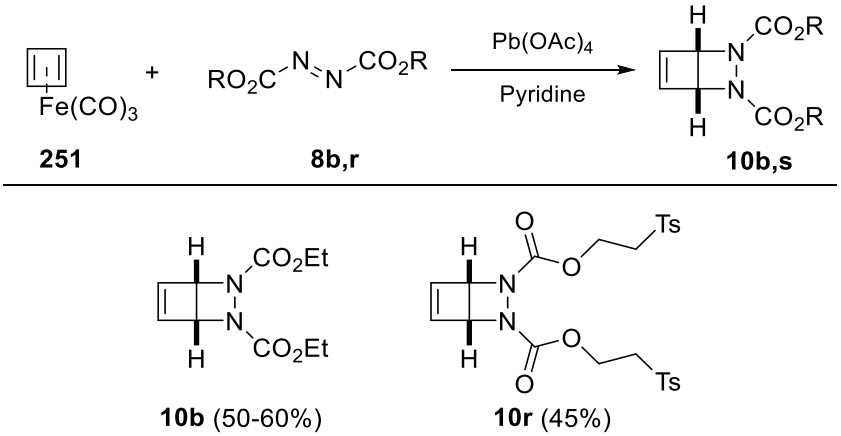
Feng employed an alternative synthesis to access substituted bicyclic 1,2-diazetidines using metal complexes (Scheme 3.5).[272] Titanium complexes **249** were treated with a Lewis acid, followed by the addition of azo compounds **8a,b** in the presence of a nickel catalyst to give tetra-substituted 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

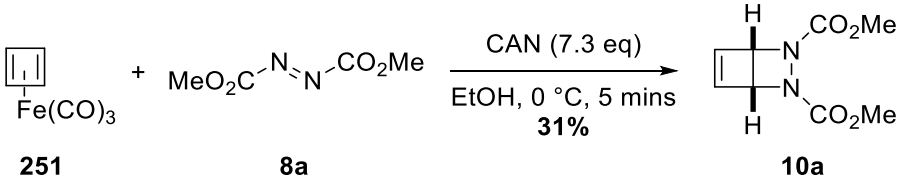
3.1.3 Cyclobutadiene and Azo Compounds

Alternatively, bicyclic 1,2-diazetidines have been synthesised through a Diels-Alder reaction between azo compounds and cyclobutadiene.[35,273–275] Masamune and co-workers first reported the use of cyclobutadieneiron tricarbonyl complex **251** to access bicyclic 1,2-diazetidines **10**.[273] 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).



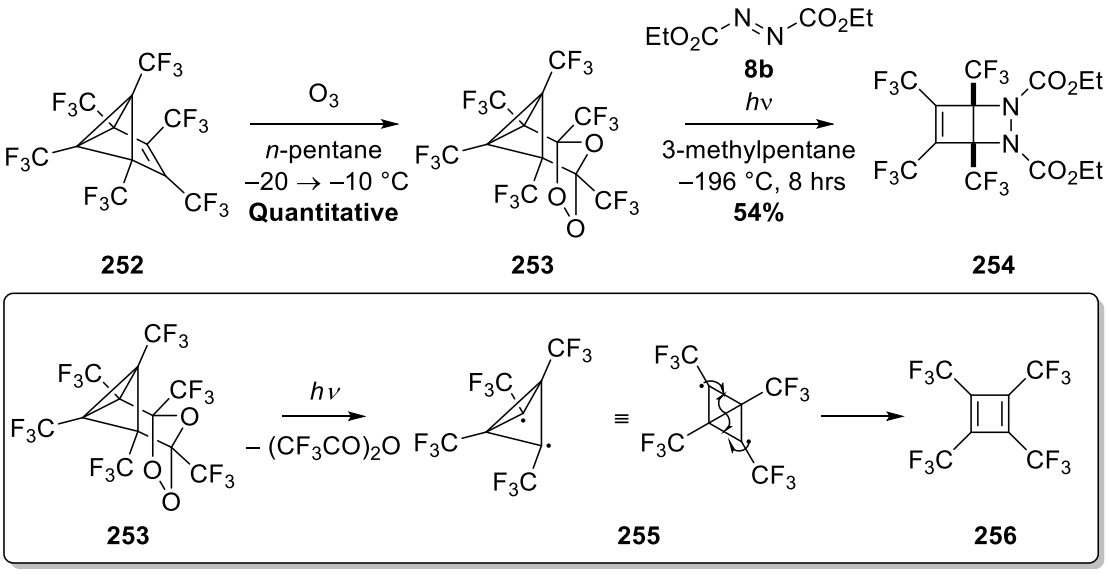
Scheme 3.6

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).[35]



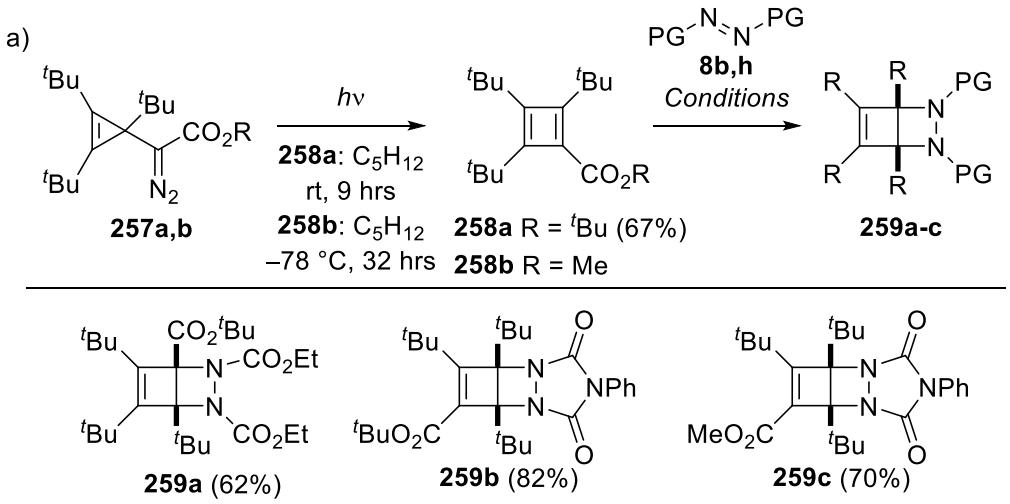
Scheme 3.7

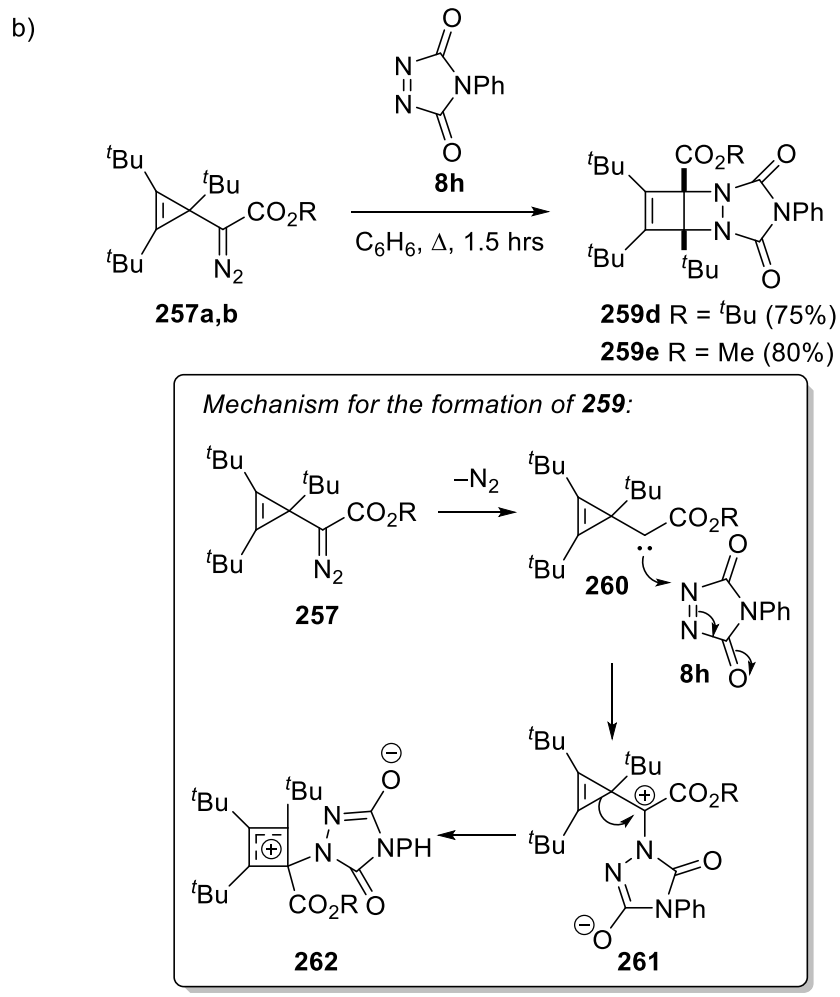
Kobayashi and co-workers have exploited hexa-substituted fluorinated benzvalene **252** as another route to make a substituted cyclobutadiene and form substituted bicyclic 1,2-diazetidines (Scheme 3.8).[274] Benzvalene **252** can be accessed through irradiation of hexa(trifluoromethyl)benzene in reasonable yields, and was found to be stable in comparison to other benzvalenes.[276–279] 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.



Scheme 3.8

Eisenbarth and Regitz have explored the photolysis of diazo compound **257** to access cyclobutadiene **258**, which bares large substituents (Scheme 3.9).[275] 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**.

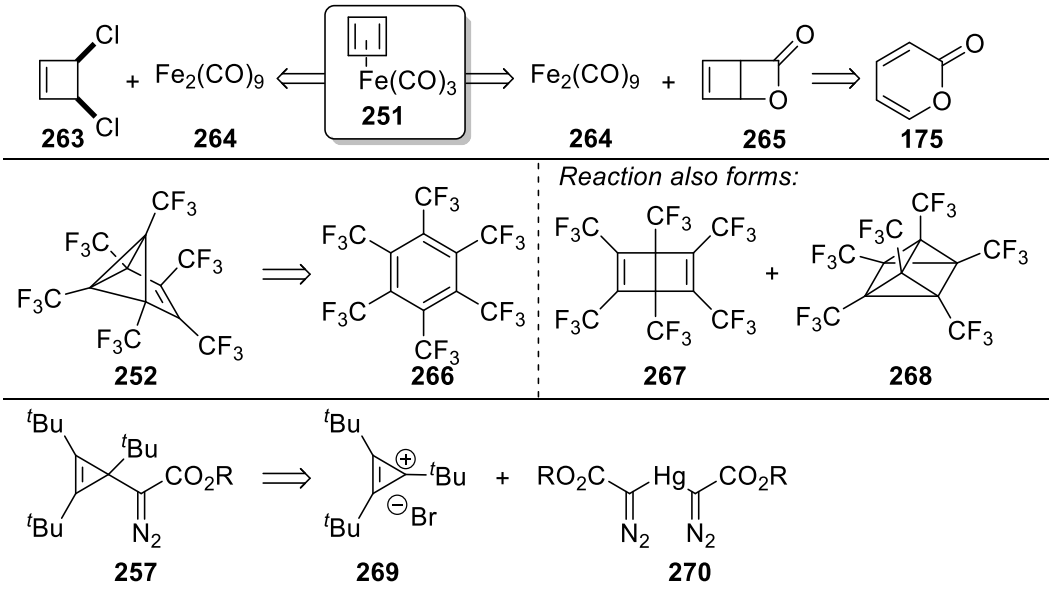




Scheme 3.9 Diels-Alder Conditions with DEAD **8b**: 1.0:1.0 **258**:**8b**, Et_2O, rt, 12 hrs; Diels-Alder Conditions with PTAD **8h**: 1.0:1.0 **258**:**8h**, C_6H_6, −5 °C, 12 hrs.

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

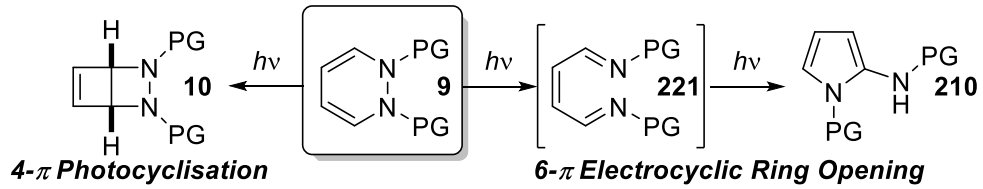
chlorine gas.[282] Bicyclic lactone **265** must be first synthesised from 2-pyrone **175** through a 4-π photocyclisation, though bicycle **265** is not that stable and has been found to be pyrophoric in air.[283] Benzvalene **252** was synthesised through irradiation of hexa(trifluoromethyl)benzene **266**, which in the process formed two other products **267** and **268**.[278] 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.



Scheme 3.10

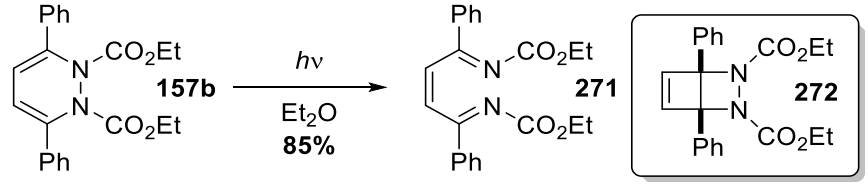
3.1.4 Photochemistry of Other 1,2-Dihydropyridazines

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).[33,35,36] In this next section the photochemistry of 1,2-dihydropyridazines that do not give any products from the 4-π photocyclisation shall be discussed.



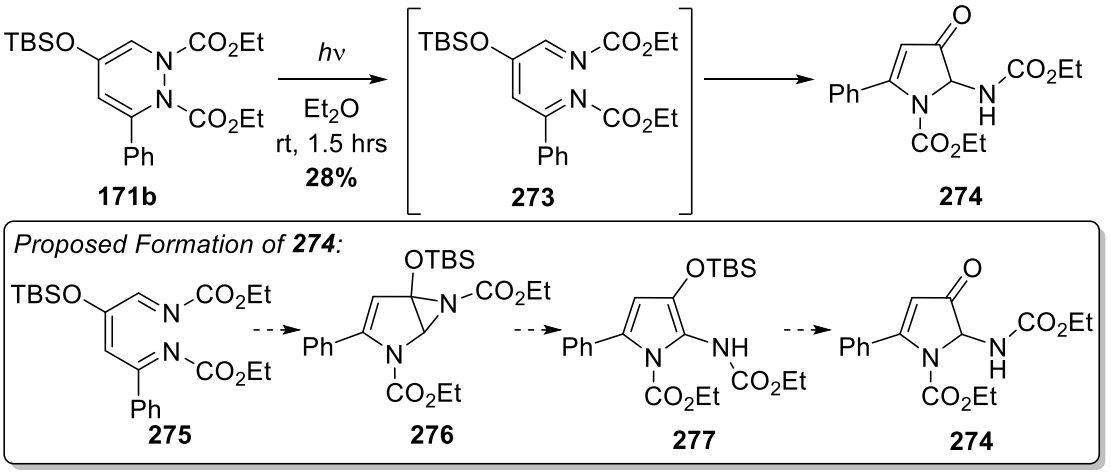
Scheme 3.11

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).[212] 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.



Scheme 3.12

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)**.**[169] 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.



Scheme 3.13

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).[165,166,174] 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.[163]

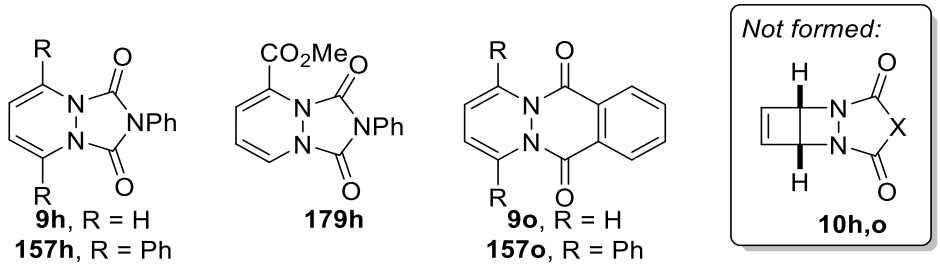
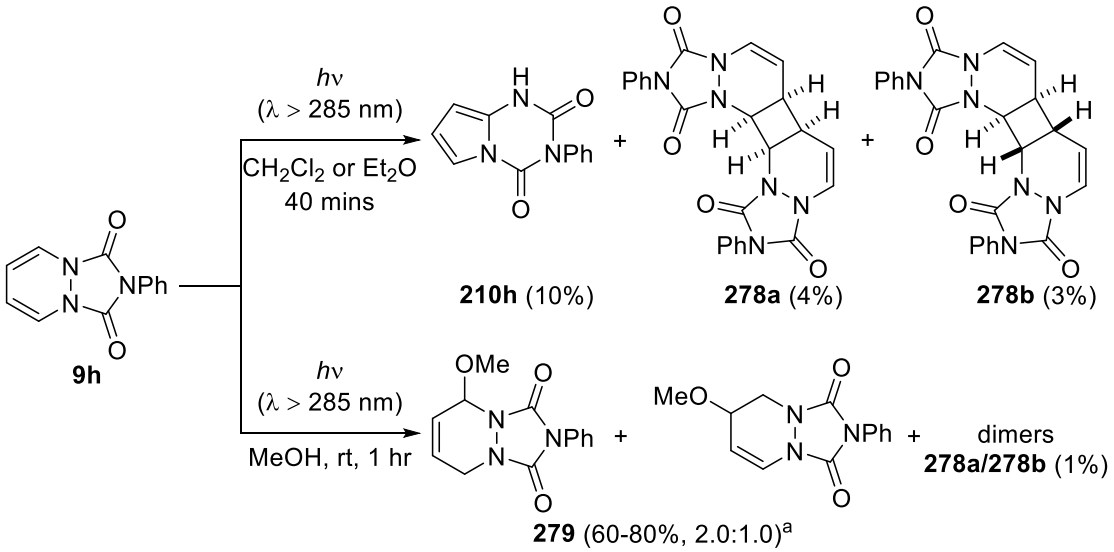


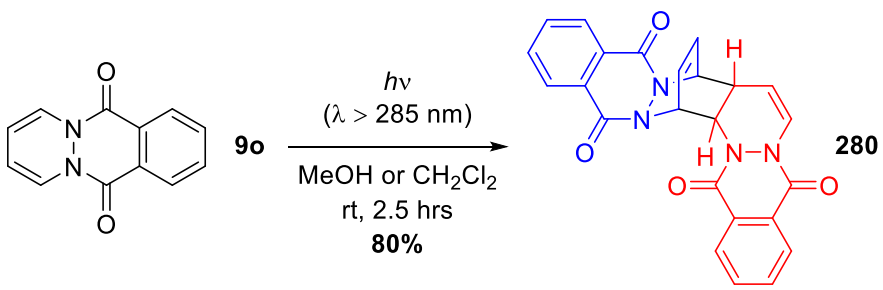
Figure 3.1

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).[165] 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.



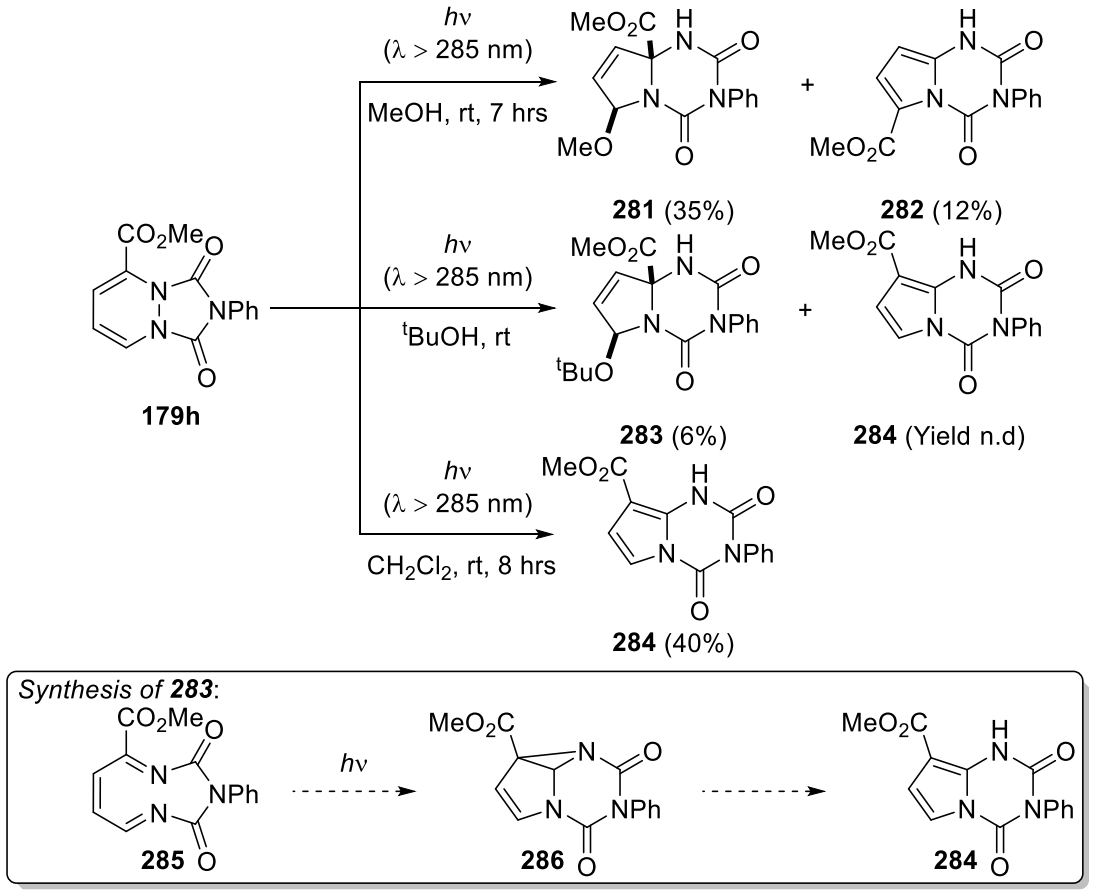
Scheme 3.14 [a] Major product not determined

In comparison, the photochemistry of the phthalazine-1,4-dione-1,2-dihydropyridazines **9o** gave completely different results (Scheme 3.15).[165] 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 $_{\pi}4_{s}$ + $_{\pi}2_{a}$ Diels-Alder reaction with another molecule of 1,2-dihydropyridazine **9o**.[284–286] Alternatively, a direct photochemical $_{\pi}4_{s}$ + $_{\pi}2_{a}$ Diels-Alder reaction between two 1,2-dihydropyridazine compounds would also lead to the expected product.[287]



Scheme 3.15

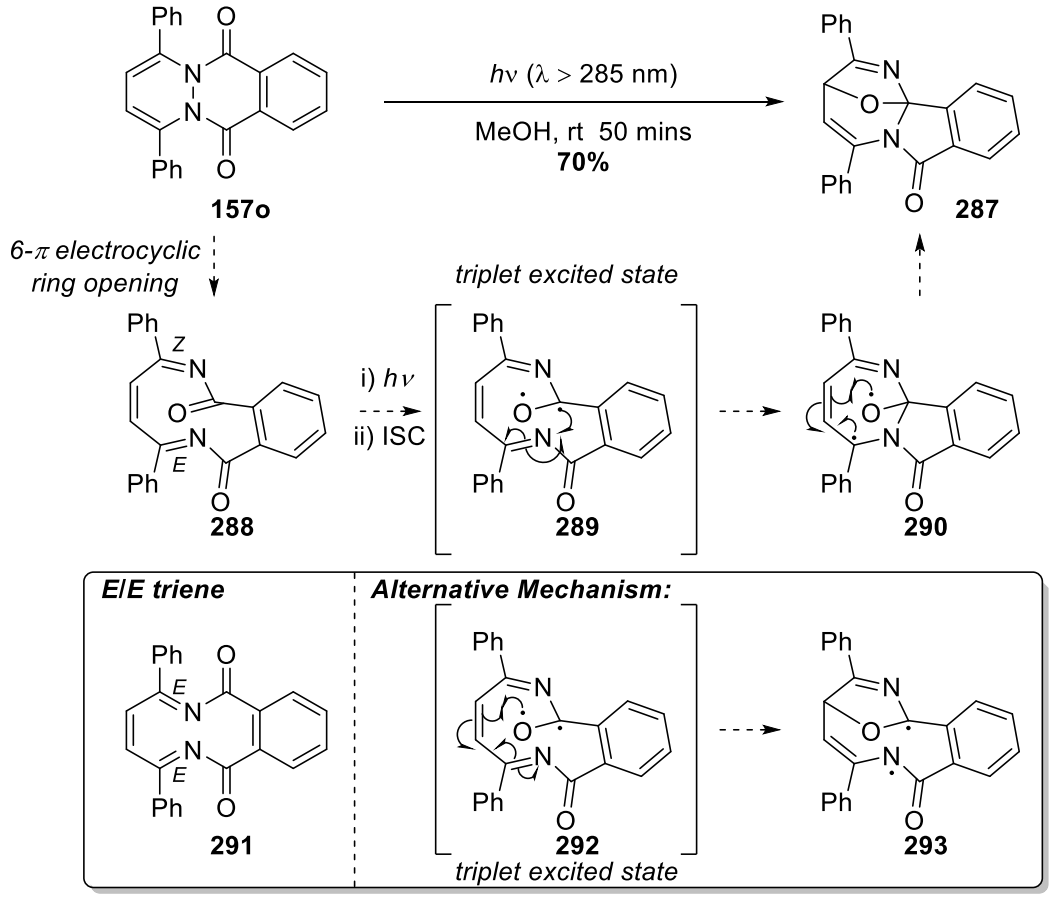
Sheradsky and Moshenberg have also studied the photochemistry of the ester substituted 1,2-dihydropyridazine **179h**, which gave products derived from a triene intermediate **285** (Scheme 3.16).[174] Irradiation of 1,2-dihydropyridazine **179h** in alcohols (methanol and *tert*-butanol) gave bicycles **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 $\pi 4_s + \pi 2_a$ cycloaddition.



Scheme 3.16

The modification of **9o** through the addition of two phenyl groups had another unexpected effect on the photochemistry (Scheme 3.17).[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

293) 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

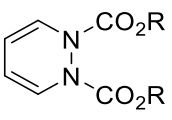
In summary, it is possible to synthesise bicyclic 1,2-diazetidines **10** but currently there is no general route to access them. As mentioned above, the 4-π photocyclisation of 1,2-dihydropyridazines **9** is currently the most practical route to access bicyclic 1,2-diazetidines **10** and for the limited 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:

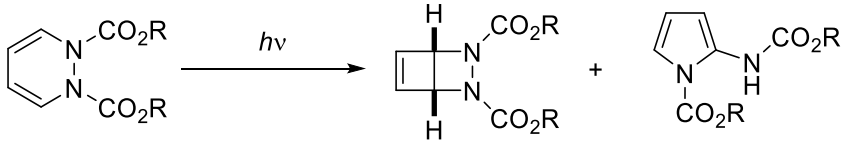


- *UV/Vis spectroscopy in different solvents*
- *Optimisation in batch and flow photoreactor*
- *Investigation of various substrates*
- *Scale-up to multigram quantities*

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).[33,35,36] It was hoped that the yield of and selectivity for the bicycle **10** could be improved with optimisation.



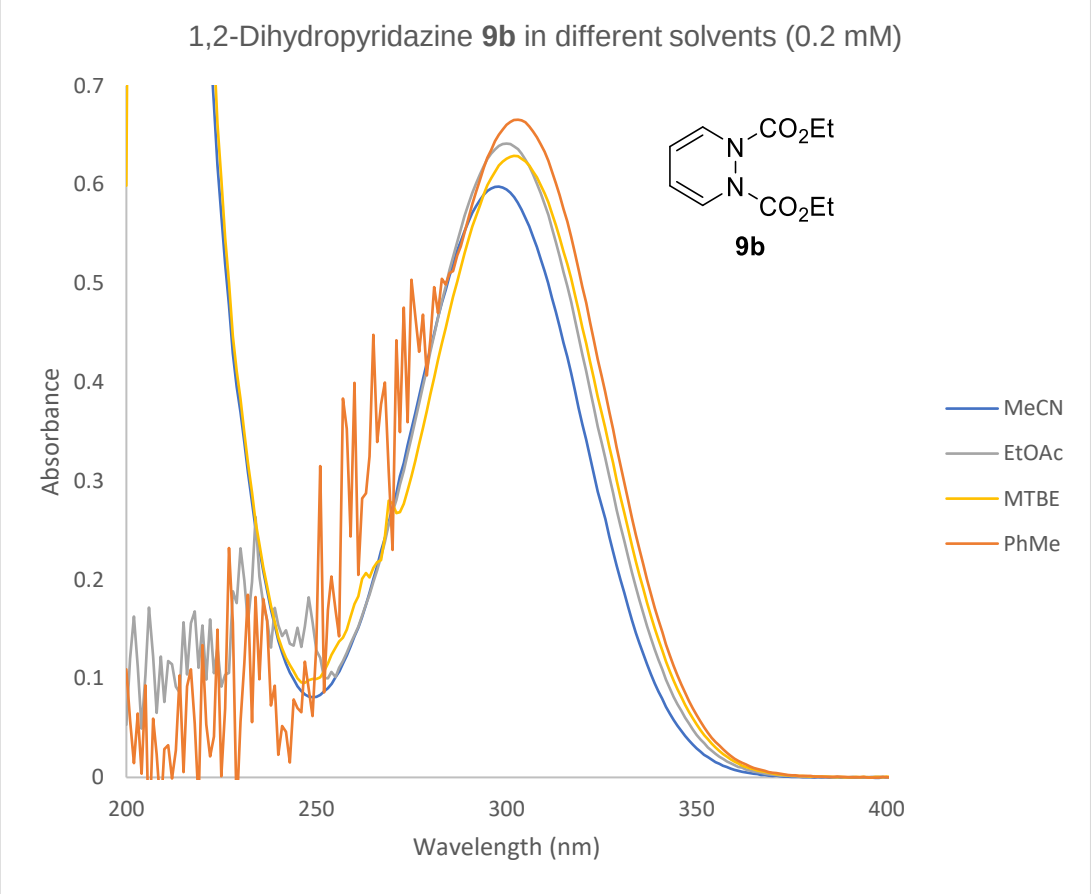
9 **10** **210**

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 λ_{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).



Entry	Solvent	Cut-off Wavelength (nm)	λ_{max} (nm)
1	MeCN	190	298
2	MTBE	210	302
3	EtOAc	255	300
4	PhMe	285	303
5	Acetone	330	327

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.

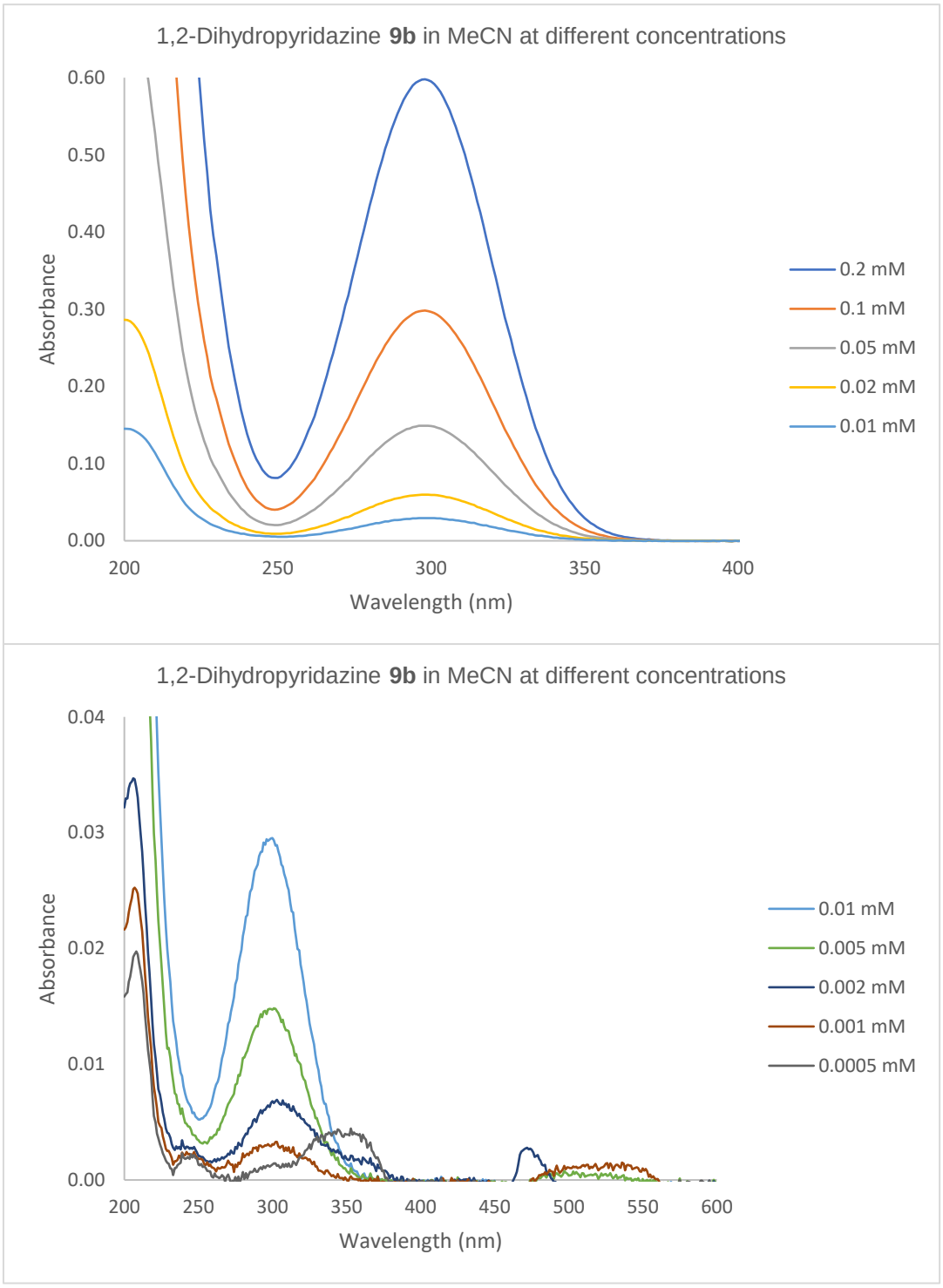
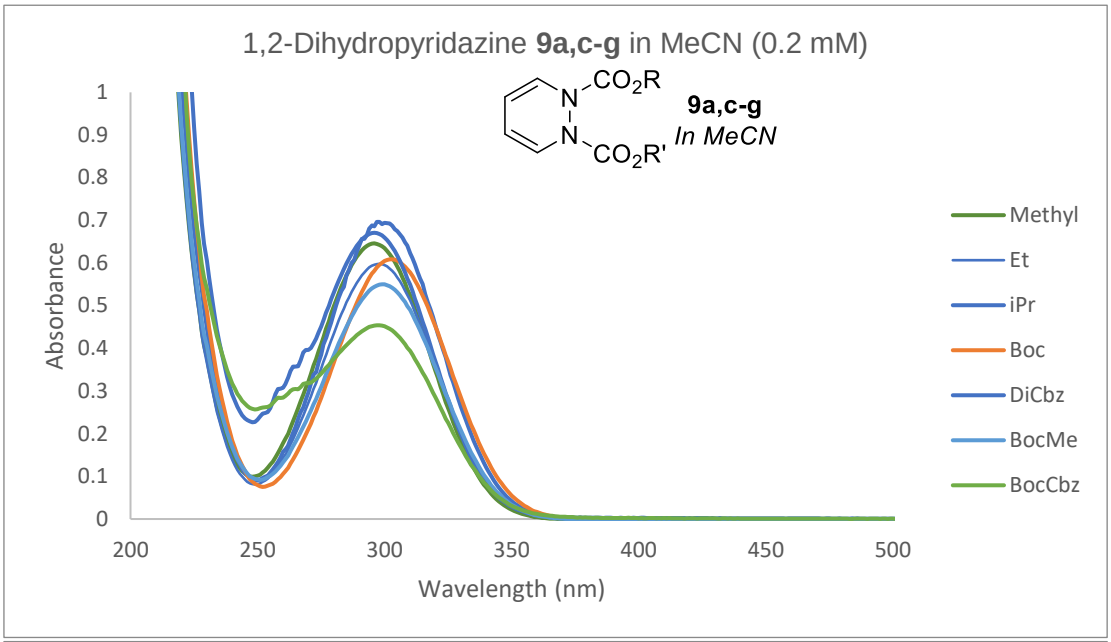
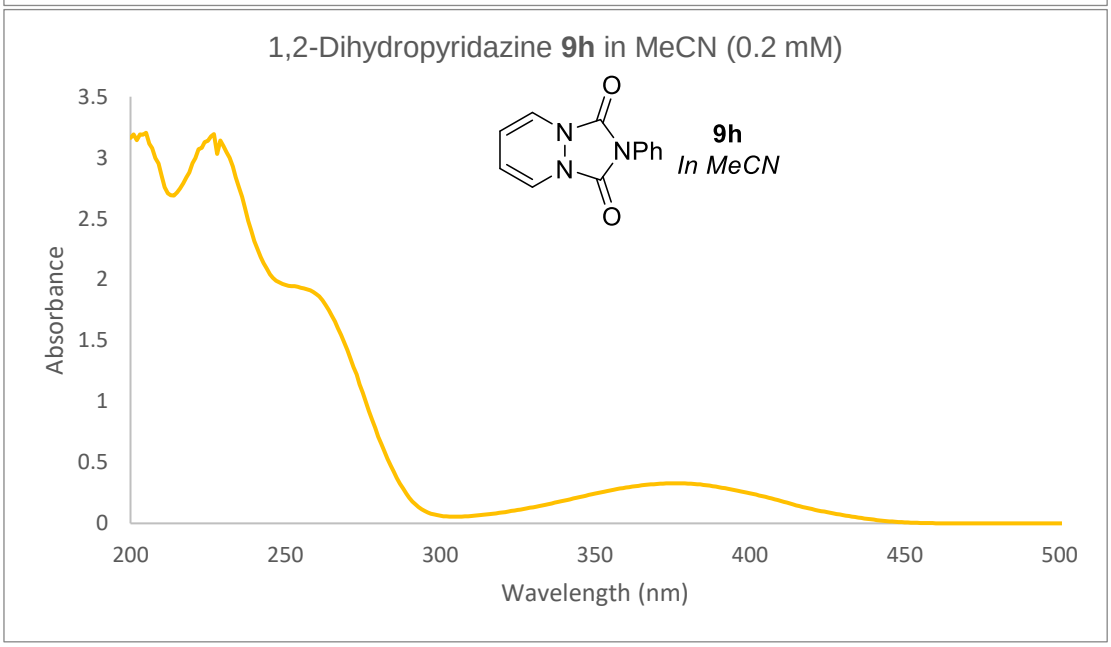


Figure 3.3

The λ_{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 λ_{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 λ_{max} is currently unknown as previous studies did not report UV-Vis data.





Entry	R	R'	1,2-Dihydropyridazine 9	λ_{max} (nm)
1	OMe	OMe	**9a**	296
2	O^{i}Pr	O^{i}Pr	**9c**	298
3	O^{t}Bu	O^{t}Bu	**9d**	303
4	OBn	OBn	**9e**	296
5	O^{t}Bu	OMe	**9f**	299
6	O^{t}Bu	OBn	**9g**	298
7	-N(Ph)-		**9h**	377

Table 3.2

3.3.2 Optimisation in a Batch Photoreactor

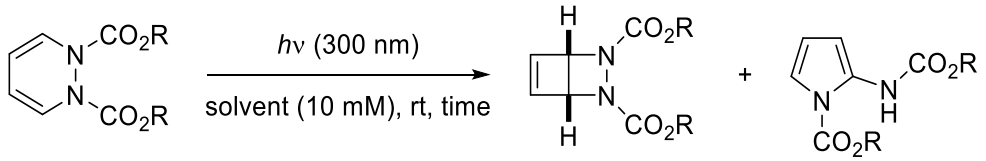
Initially, the 4-π photocyclisation was studied in a commercially available batch photoreactor (Rayonet RPR-100) and 1,2-dihydropyridazine **9b** was chosen for optimisation (Figure 3.4). The

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.

Figure 3.4 Rayonet RPR-100

In the literature, the irradiation of 1,2-dihydropyridazine **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**.[36] From UV-Vis studies, it was found that 1,2-dihydropyridazine **9b** has an absorption around 300 nm in a variety of solvents, therefore irradiation of 1,2-dihydropyridazine **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-dihydropyridazine **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 λ_{max} increased, using different solvents and protecting groups, the overall yield of and selectivity

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 λ_{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.



9 **10** **210**

Entry	R	Solvent	λ_{max} **9**	Time (hours)	10:210[a]	Bicycle 10 (%)[b]	Pyrrole 210 (%)[b]
1	Et **9b**	MeCN	298	1.75	2.8:1.0	56	9
2	Et **9b**	EtOAc	300	1	1.1:1.0	42	35
3	Et **9b**	MTBE	302	2	1.3:1.0	45	24
4	Et **9b**	PhMe	303	1	1.2:1.0	39	29
5	Et **9b**	Acetone	327	1	-	traces	-
6	^{i}Pr **9c**	MeCN	298	1	1.2:1.0	42	21
7	^{t}Bu **9d**	MeCN	303	1	1.2:1.0	42	30

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.

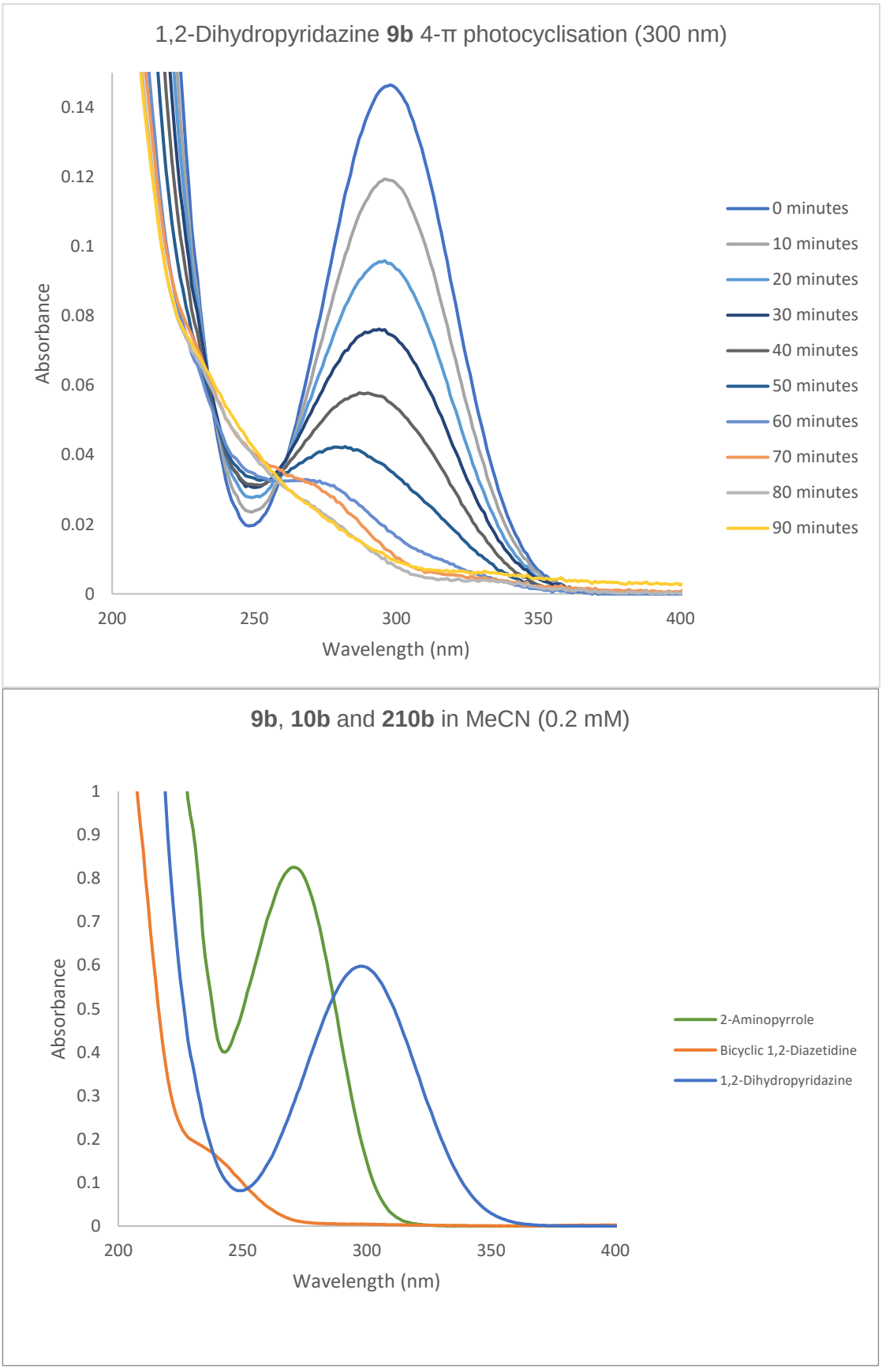

1,2-Dihydropyridazine 9b 4-π photocyclisation (300 nm)
Absorbance
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
200
250
300
350
400
Wavelength (nm)
0 minutes
10 minutes
20 minutes
30 minutes
40 minutes
50 minutes
60 minutes
70 minutes
80 minutes
90 minutes
9b, 10b and 210b in MeCN (0.2 mM)
Absorbance
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
200
250
300
350
400
Wavelength (nm)
2-Aminopyrrole
Bicyclic 1,2-Diazetidine
1,2-Dihydropyridazine

Figure 3.5

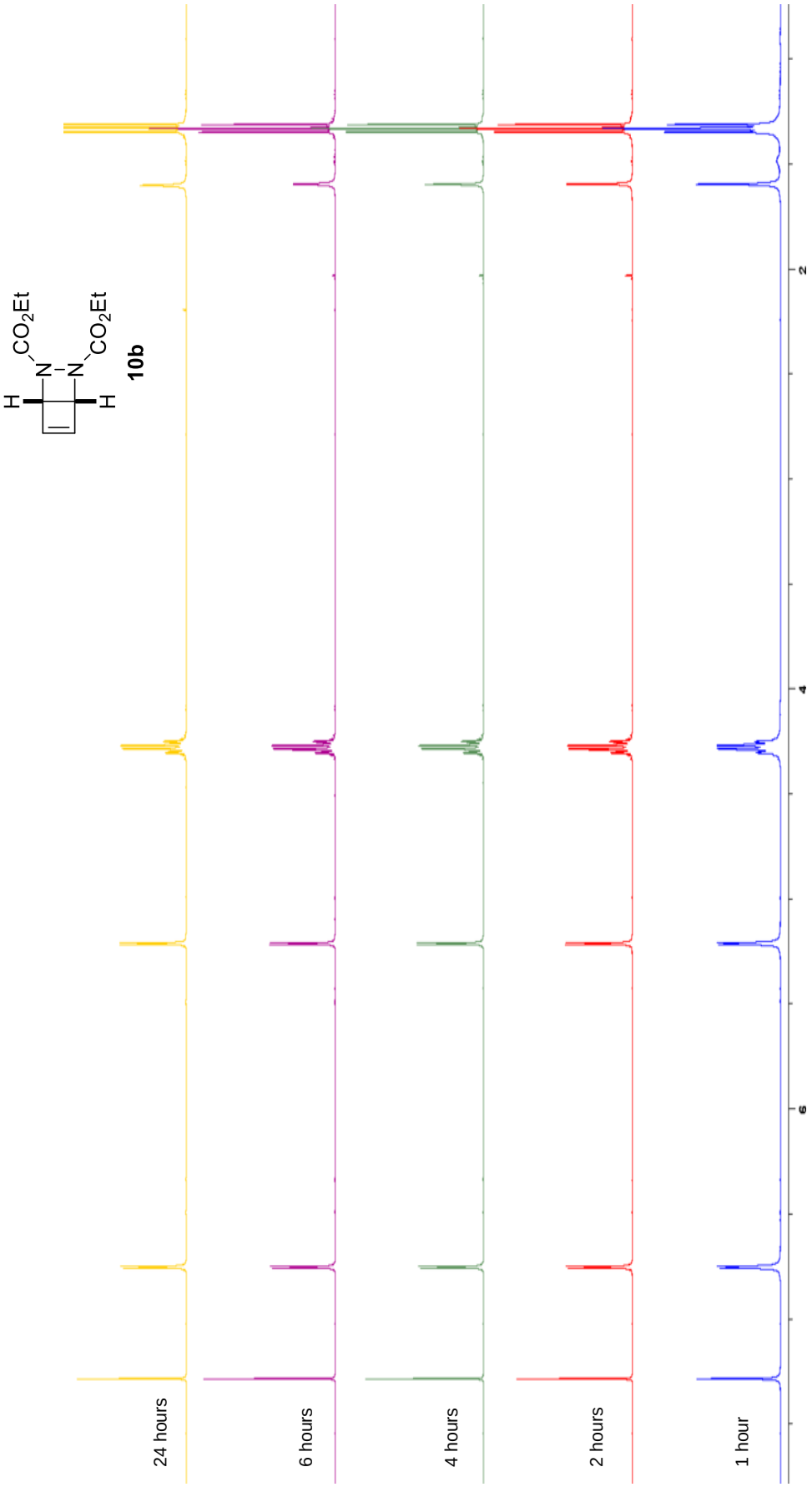


Figure 3.6 ^{1}H NMR in $CDCl_3$ of bicyclic 1,2-diazetidine **10b**, irradiated at 300 nm over a 24 hour period

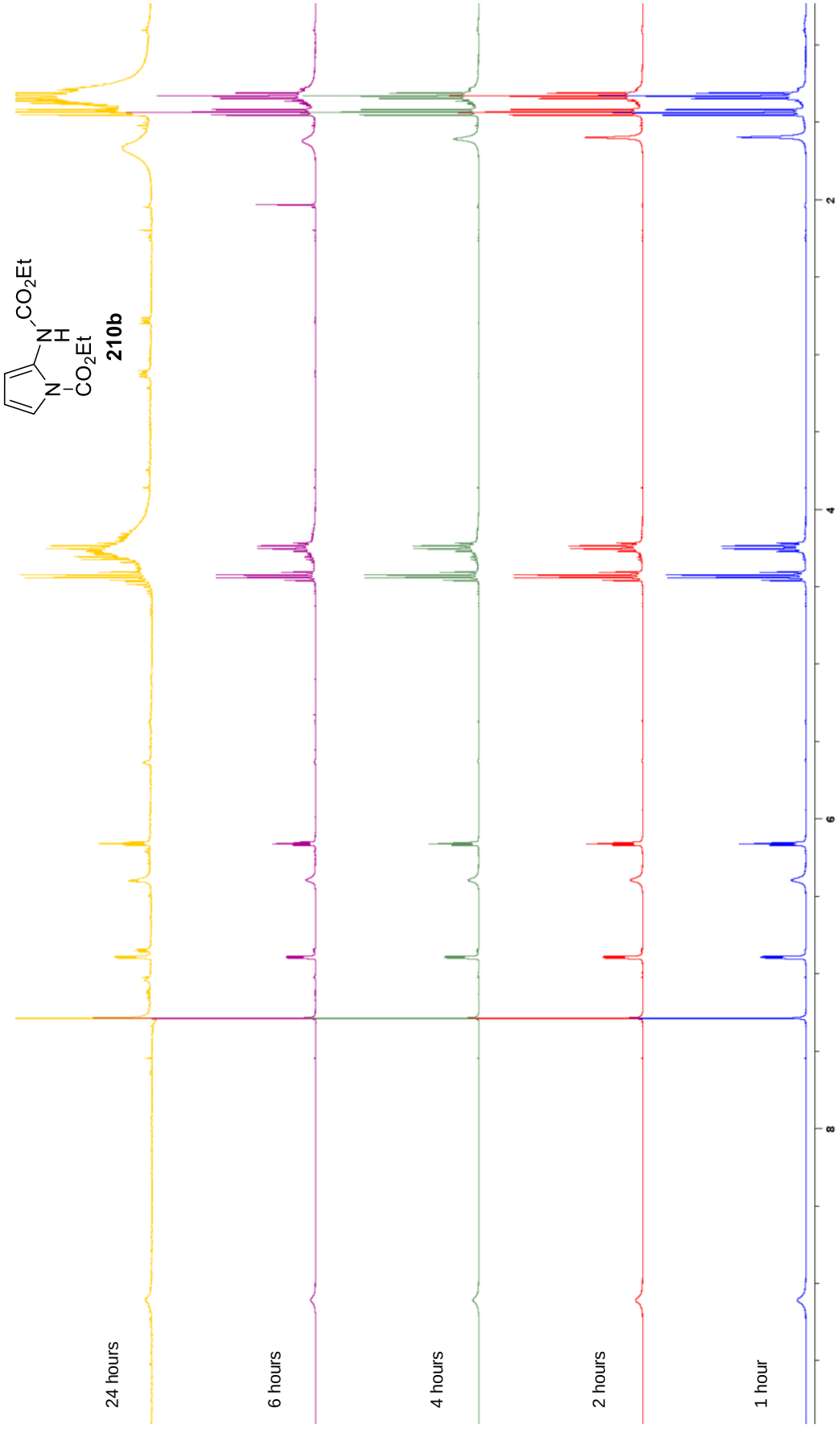


Figure 3.7 ^{1}H NMR in $CDCl_3$ of 2-aminopyrrole **210b**, irradiated at 300 nm over a 24 hour period

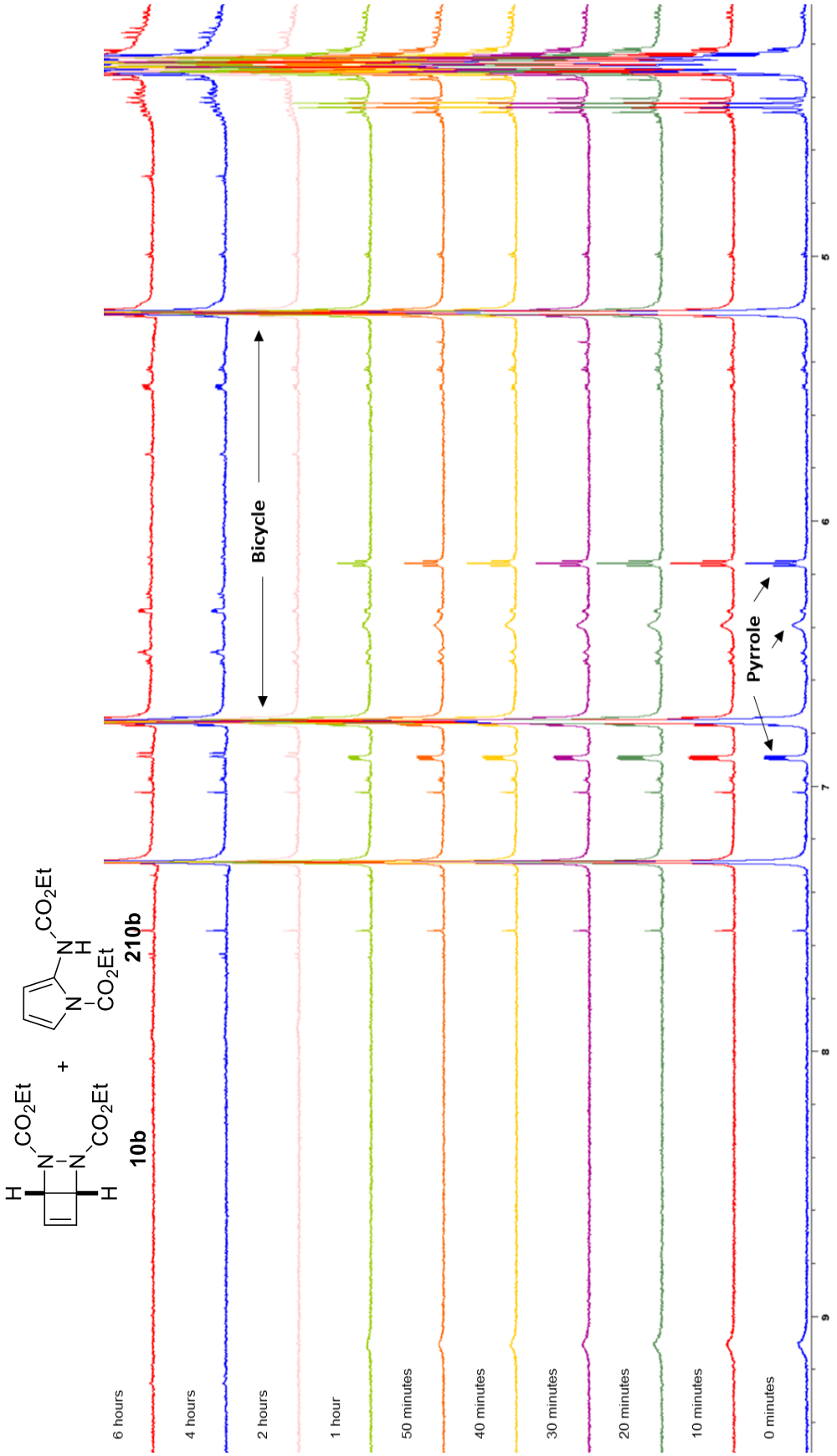


Figure 3.8 ^{1}H NMR in $CDCl_3$ of bicyclic 1,2-diazetidine **10b** with 10 mol% 2-aminopyrrole **210b**, irradiated at 300 nm over a 6 hour period

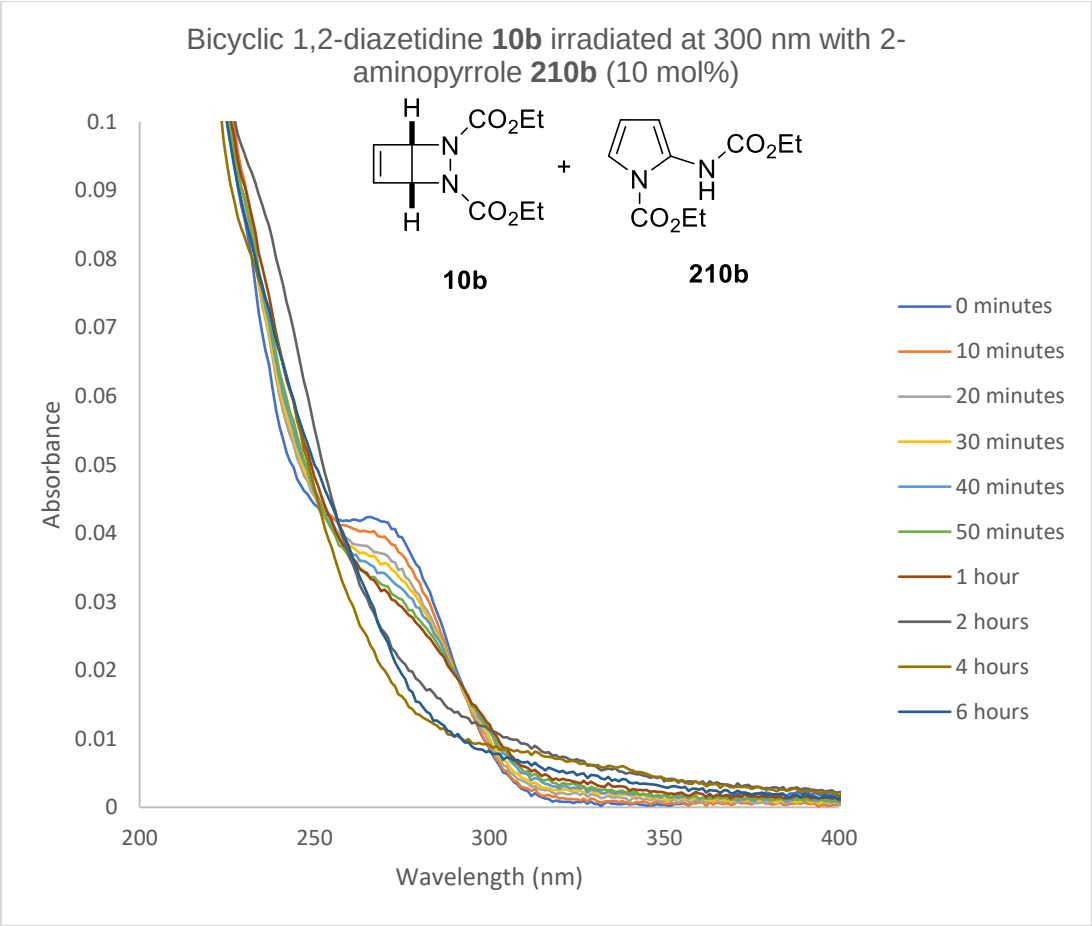


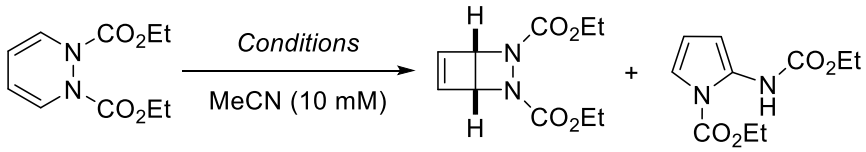
Figure 3.9

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.

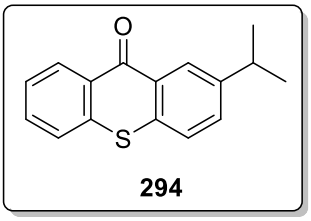
Irradiation at 350 nm (on the opposite edge of the absorption peak) completely changed the bicycle:pyrrole selectivity (entry 3). The reaction was slower compared to 300 nm (20 hours compared to 1 hour), but now only trace amounts of pyrrole **210b** were formed, and the desired bicycle **10b** was isolated 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 ($A = \varepsilon cl$; 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 (300 nm, ε = 2975; 350 nm, ε = 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→π* absorption band at the edge of the main π-π* absorption peak, which leads to the promotion of the 4-π photocyclisation pathway. In addition, this explanation further supports the suggestion that irradiation on the longer wavelength side of the λ_{max} resulted in less of the 6-π 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.



9b **10b** **210b**



294

Entry	Wavelength (nm)	Time (hours)	10b (%)	210b (%)
1	300	1	56	9
2	254	2.5	15	7
3	350	20	77	traces
4	419	1	-	-
5	419	1	-[a]	-

Table 3.4 [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.

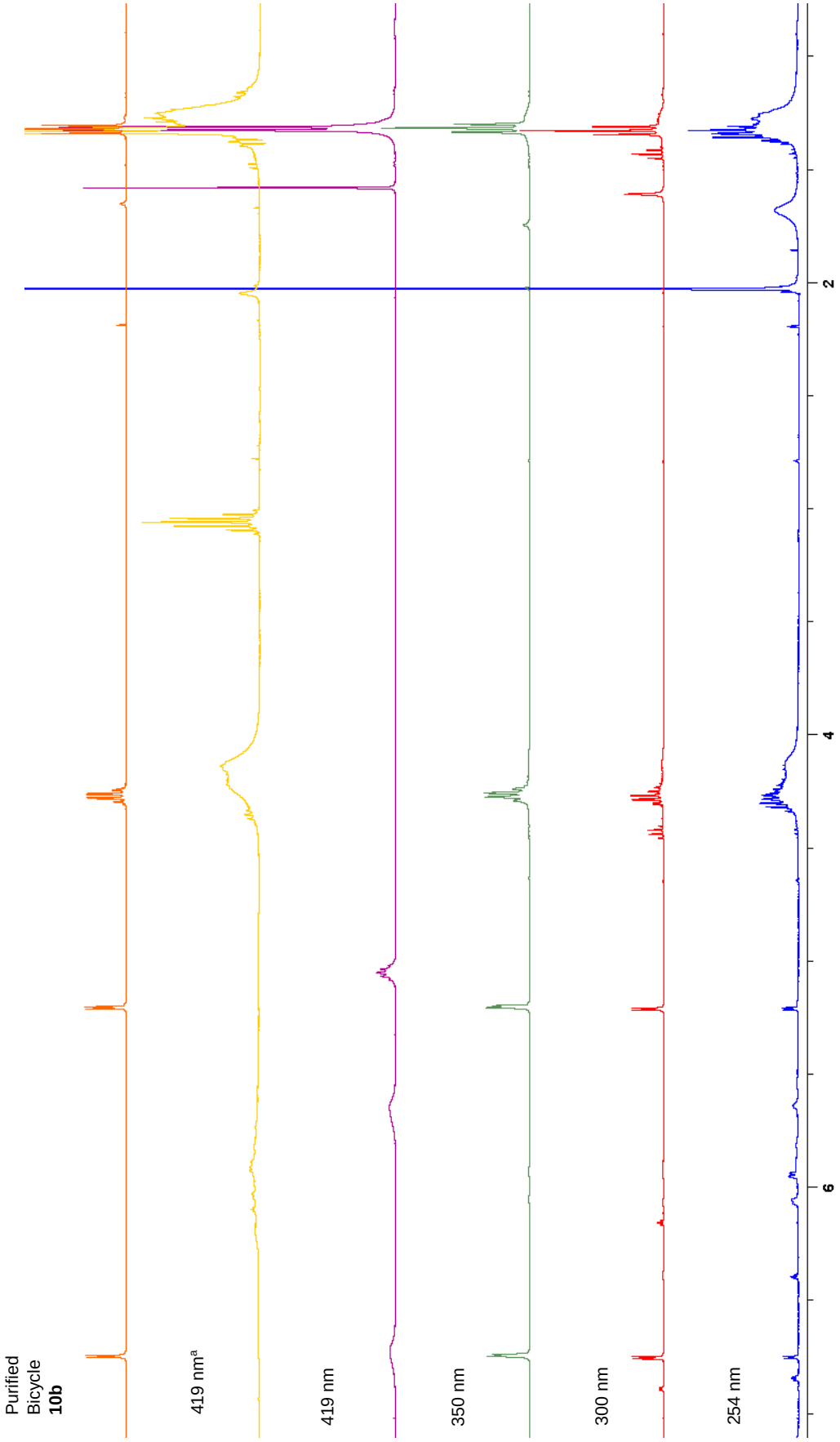
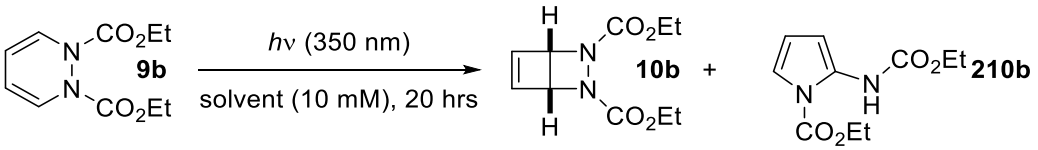


Figure 3.10 ^{1}H NMR for irradiation of 1,2-dihydropyridazine **9b** at different wavelengths; [a] Isopropylthioxanthone **294** used as a photosensitiser

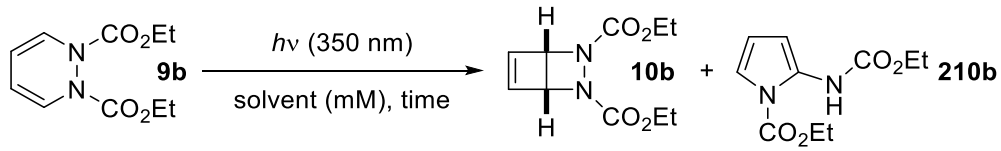
With the optimal wavelength settled upon, another solvent screen was judged worthwhile (Table 3.5). In all cases only trace amounts of the pyrrole were observed and good yields for the bicycle **10b** were obtained (entries 1-5). The change in wavelength meant that it was now possible to use acetone 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.



Entry	Solvent	Bicycle 10b (%)	Pyrrole 210b (%)
1	MeCN	77	traces
2	MTBE	77	traces
3	EtOAc	65	traces
4	PhMe	71	traces
5	Acetone	62	traces

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.

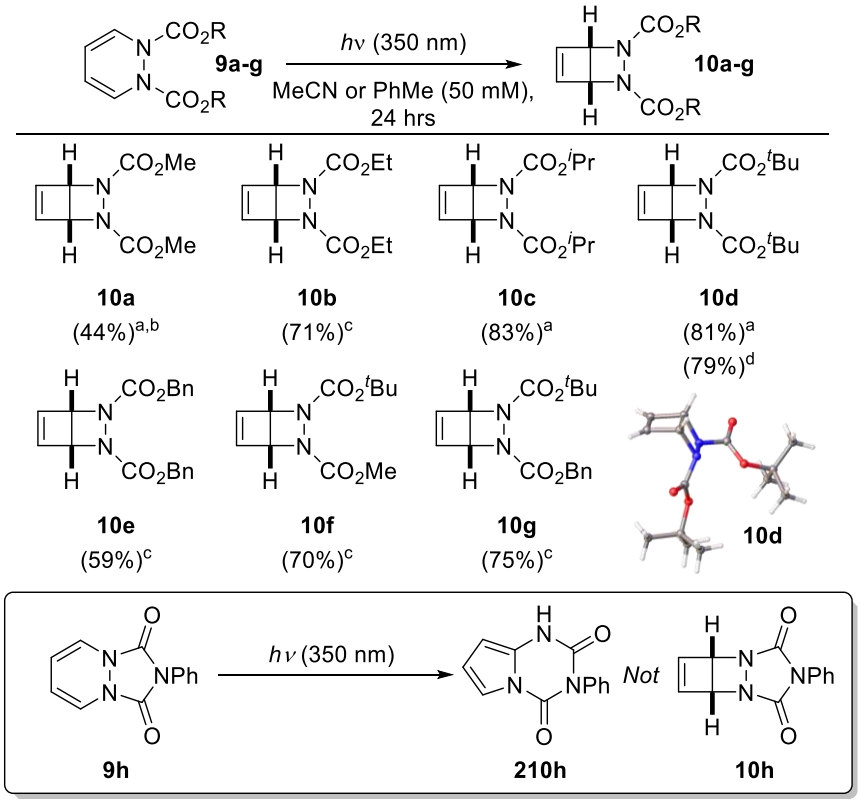


Entry	Solvent	Concentration (mM)	Time (hrs)	Bicycle 10b (%)	Pyrrole 210b (%)
1	MeCN	20	24	80	traces
2	MeCN	50	44	69	traces
3	PhMe	20	24	71	traces
4	PhMe	50	24	71	traces

Table 3.6

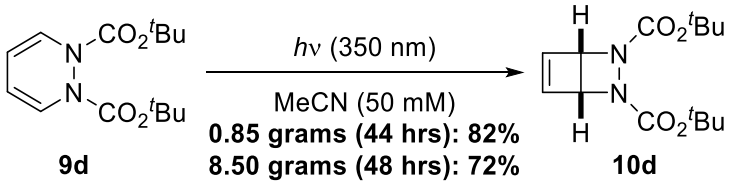
The 4-π photocyclisation has now been applied to the other 1,2-dihydropyridazines **9a-g** in either acetonitrile or toluene to give the bicycles **10a-g** in good yields (Scheme 3.19). In most cases, the bicycle yields in acetonitrile and toluene were similar and only the best yields are shown. The reason for this observed improvement is thought to have been from a slight

bathochromic shift in the λ_{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 [a] 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.[288–291] The penetration of light into a solution is governed by the Beer-Lambert Law ($A = \varepsilon c l$; 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.[292]

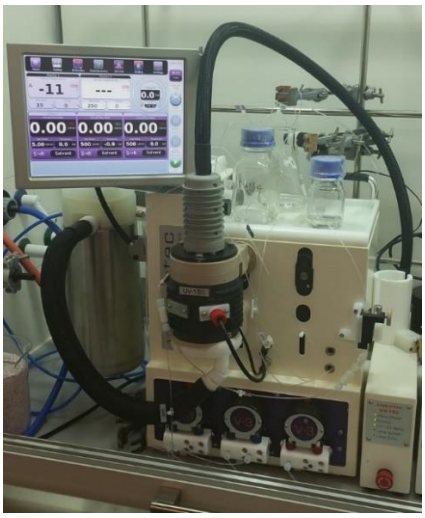


Figure 3.11 E-series Vapourtec flow system equipped with a photoreactor (UV-150)

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.

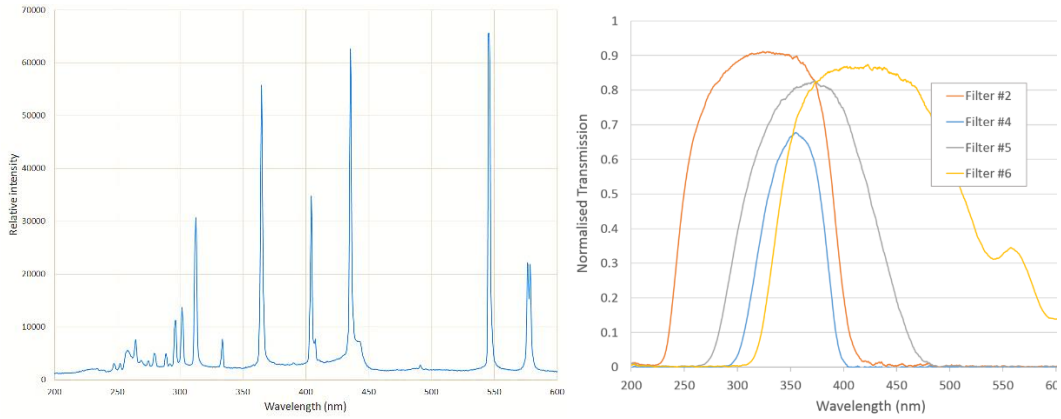
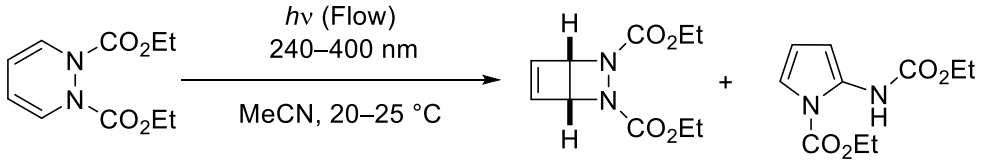


Figure 3.12 Images supplied and used with permission from Vapourtec Ltd

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.



9b **10b** **210b**

Entry	Flow rate (mL/min)	Concentration (mM)	Conversion 9b (%)[a]	Product ratio (10b:210b)[a]
1	5	20	25	1.7:1.0
2	2	20	100	3.0:1.0
3	1	20	100	5.5:1.0
4	0.5	20	100	19:1.0
5	5	10	57	2.3:1.0
6	2	10	100	5.4:1.0
7	1	10	100	18:1.0
8	0.5	10	100	No pyrrole
9	5	5	18	3.4:1.0
10	2	5	57	15:1.0
11	1	5	100	No pyrrole
12	0.5	5	100	14:1.0
13[b]	5	10	48	4.0:1.0
14[b]	2	10	100	6.9:1.0
15[b]	1	10	100	13:1.0
16[b]	0.5	10	100	No pyrrole
17[c]	5	10	18	1.9:1.0
18[c]	2	10	57	2.4:1.0
19[c]	1	10	100	8.6:1.0
20[c]	0.5	10	100	No pyrrole
21[d]	5	10	4	-[e]
22[d]	2	10	9	-[e]
23[d]	1	10	22	-[e]
24[d]	0.5	10	48	-[e]
25[f]	5	5	1	-
26[f]	2	5	2	-
27[f]	1	5	4	-
28[f]	0.5	5	7	-

Table 3.7 [a] 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; [b] Completed at lower temperature (ranged between: -4 and 0 °C); [c] Completed at 50% lamp power; [d] Type 4 filter used instead of Type 2; [e] Not possible to calculate ratio due to presence of starting material; [f] 365 nm LED used instead of medium pressure mercury lamp

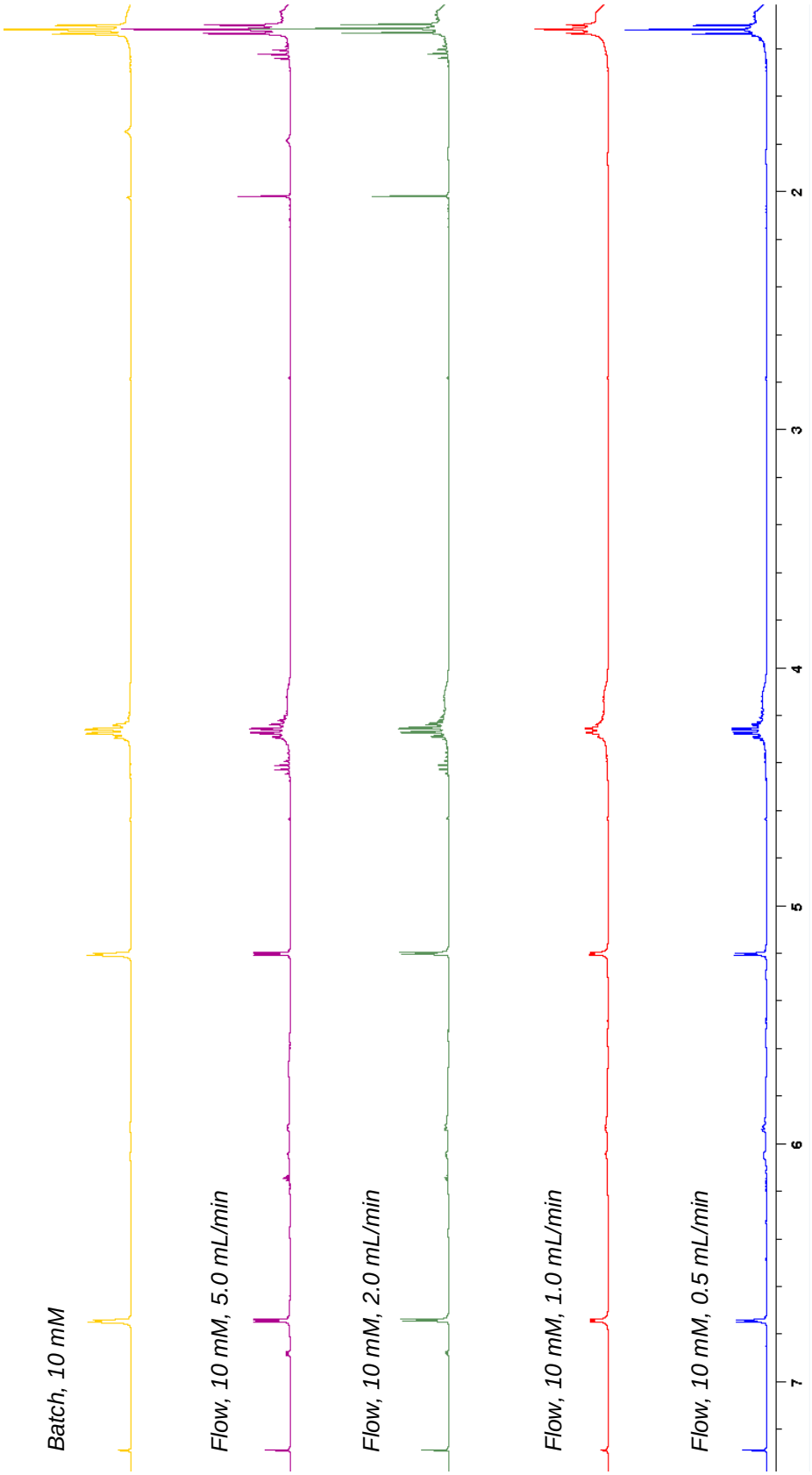


Figure 3.13 Batch vs Flow comparison for 4-π photocyclisation of 1,2-dihydropyridazine **9b**

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.

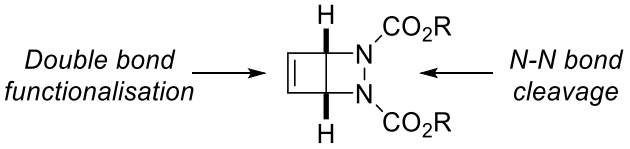
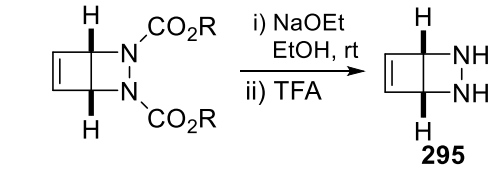


Figure 4.1

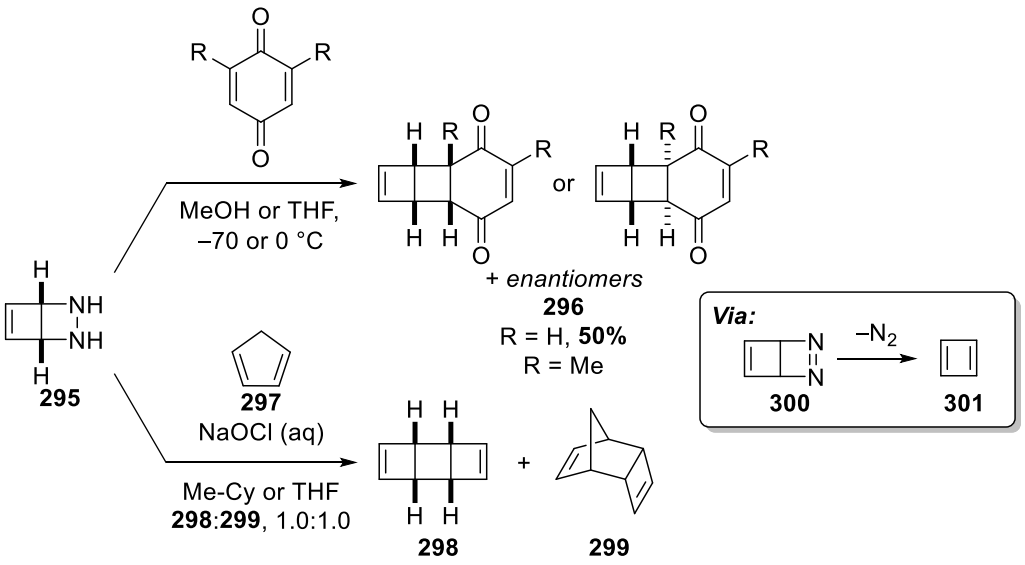
Most of the current literature has focused on the deprotection of the carbamate protecting groups attached to the nitrogen atoms under basic conditions and oxidation of the diamine to access cyclobutadiene.[162,273] The successful removal of the ethyl carbamate protecting groups from bicyclic 1,2-diazetidine **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]



10b, R = Et
10r, R = CH_2CH_2Ts

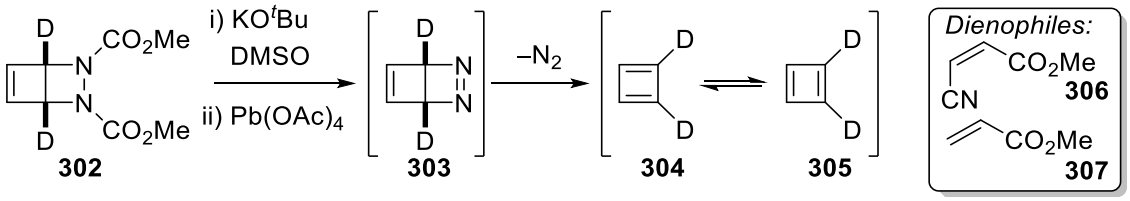
Scheme 4.1

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.



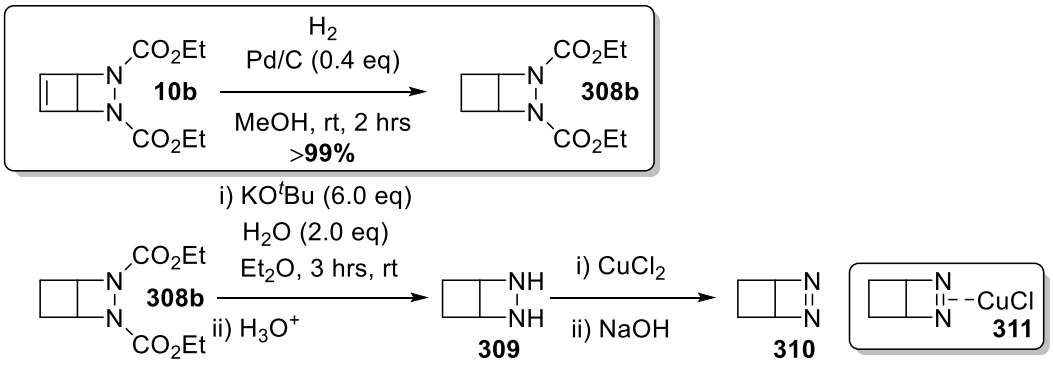
Scheme 4.2

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).[162] 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, cycloadducts 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.



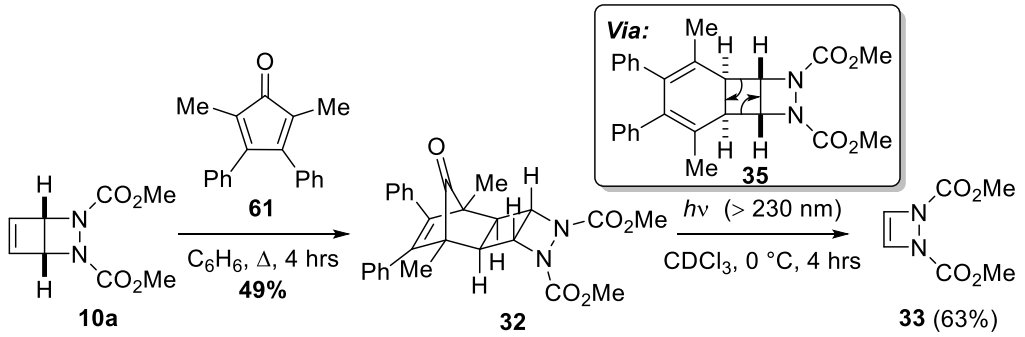
Scheme 4.3

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).[33,36,294] Removal of the ethyl carbamate protecting groups from saturated bicycle **308b** was then achieved under modified conditions developed for the deprotection of amides.[295] Diamine **309** was oxidised with copper(II) salts to give azo compound **310**, which could be isolated as the copper complex **311**.



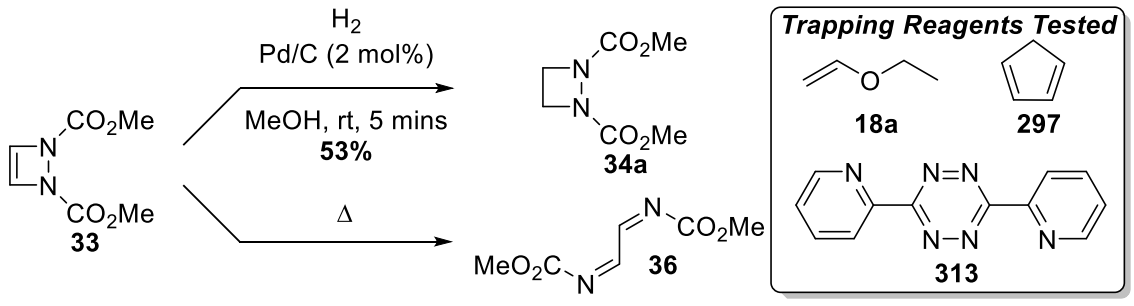
Scheme 4.4

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).[35,80] 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.



Scheme 4.5

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.



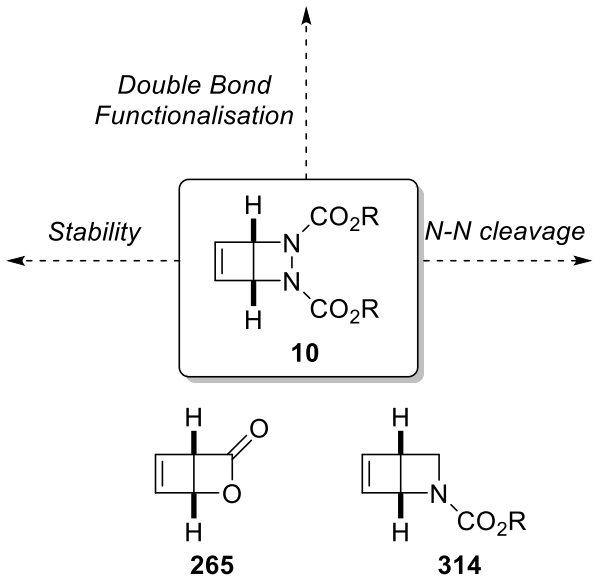
Scheme 4.6

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/NH_3 or SmI_2) 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]

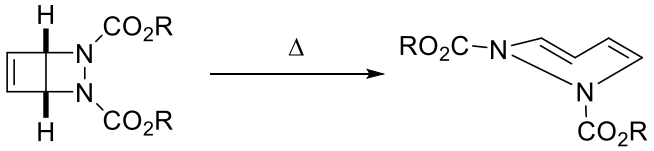


Scheme 4.7

4.3 Results and Discussion

4.3.1 Thermal Stability of Bicyclic 1,2-Diazetidines

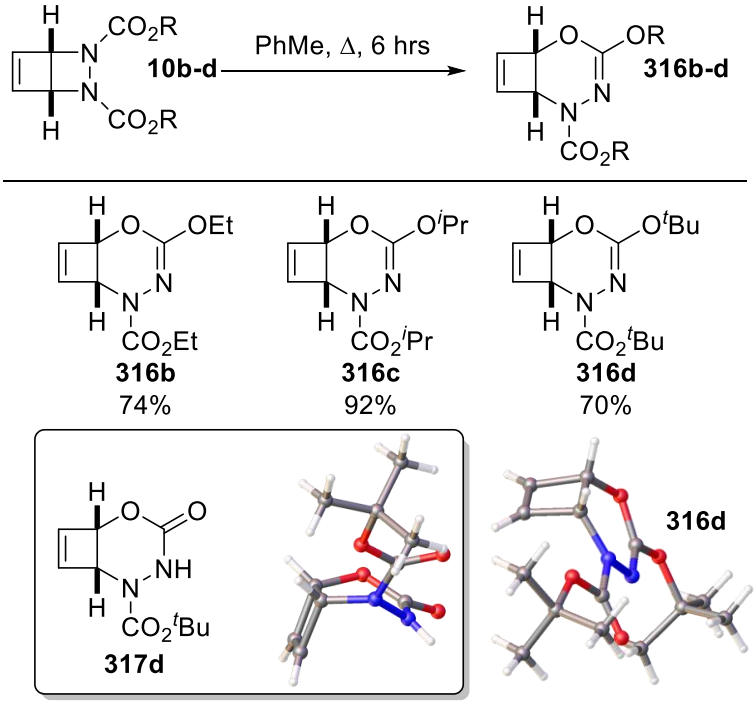
From the knowledge of the thermal rearrangement reactions of 1,2-dihydropyridazine **9** combined with the newly formed strained rings in the bicyclic-1,2-diazetidines **10**, the first step was to investigate their thermal stabilities. It should be not possible under thermal conditions for bicyclic-1,2-diazetidines **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.



10 **315**

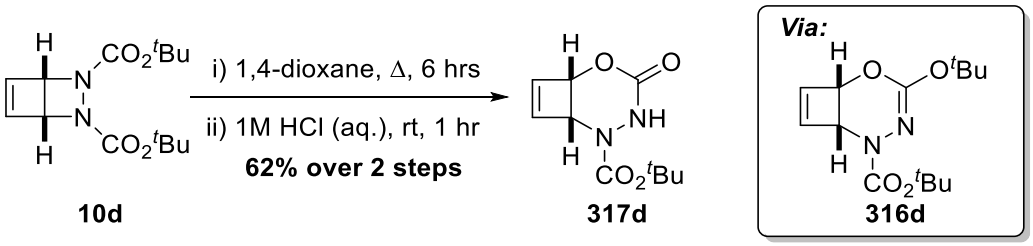
Scheme 4.8

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 ^{13}C and 2-D NMR spectroscopy. The carbons adjacent to nitrogen in **10** appear as a single peak at 66.7 ppm in the ^{13}C 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.



Scheme 4.9

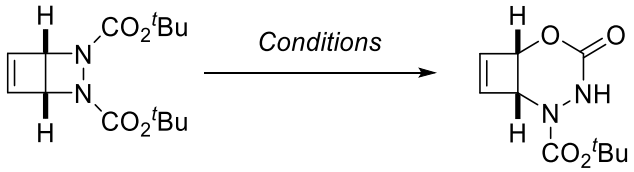
Attempts to drive the conversion of **316d** into **317d** at high temperatures and prolonged reaction times only resulted in degradation. Instead, inspiration was taken from the acidic conditions required to access enone **218** (from the Diels-Alder reaction with Danishefsky's diene). It was postulated 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.



Scheme 4.10

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). The

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*).



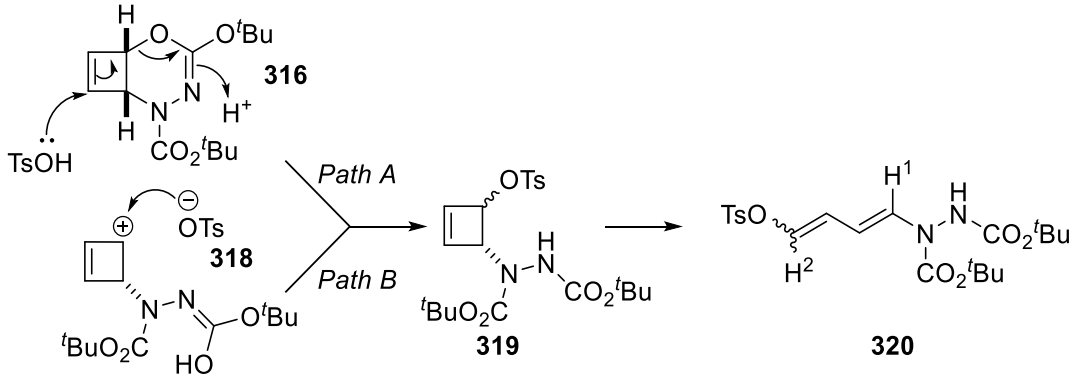
10d **317d**

Entry	Conditions	Time (hours)	Yield 317d (%)
1	1M aqueous HCl, 1,4-dioxane:HCl (1:1)	1	50
2	0.1M aqueous HCl, MeOH:HCl (1:1)	2	47
3	0.1M aqueous HCl, MeOH:HCl (2:1)	2	53
4	0.1M aqueous HCl, MeOH:HCl (4:1)	2	51
5	0.1M aqueous HCl, MeOH:HCl (8:1)	2	41
6	Dowex H^+ resin, MeOH	2	45
7	*p*-TsOH (1.1 eq), CH_2Cl_2	0.2	50
8	TFA (10 eq), CH_2Cl_2	2	n.i[a]
9	*p*-TsOH (0.1 eq), CH_2Cl_2	5	0
10	Silica gel, CH_2Cl_2	72	0
11	I_2 (1.1 eq), CH_2Cl_2	0.2	38
12	1,4-dioxane:1M aqueous NaOH (1:1)	7	0

Table 4.1 [a] Not isolated

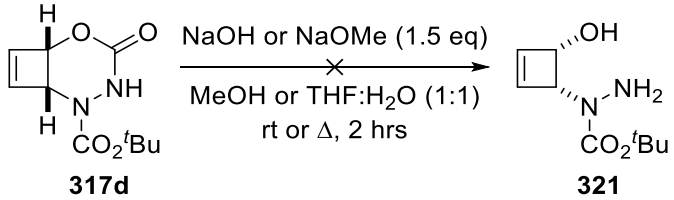
The major side product from the reaction of bicyclic-1,2-diazetidine **10d** with *p*-toluenesulfonic acid was diene **320**, which was obtained in 35% yield (Scheme 4.11). From ^{1}H NMR analysis, a *trans*-configuration was determined for the double bond attached to the hydrazine from the coupling constant of the hydrogen attached to the same carbon as the hydrazine fragment (13.6 Hz, H^1 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, H^2 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 S_N2' 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_N1 cleavage of the C-O bond, to give an allylic 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-π 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_N2' reaction.



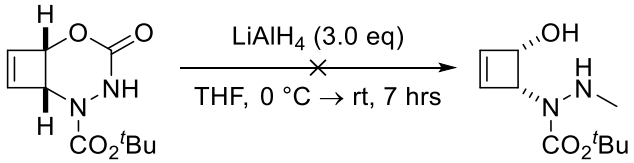
Scheme 4.11

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.



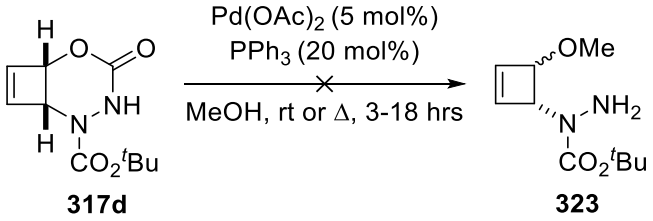
Scheme 4.12

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.



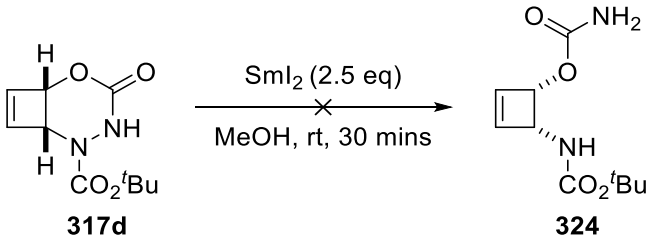
Scheme 4.13

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).



Scheme 4.14

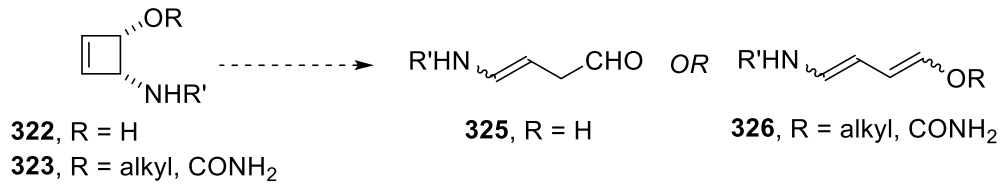
Treatment of bicycle **317d** with freshly prepared and titrated samarium(II) iodide, which was prepared according to a previously published procedure,[305] resulted in a large loss in material and the isolation of the starting material in 14% yield (Scheme 4.15).



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,[112] 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,[113–115] it is not known whether the oxygen or the nitrogen substituent will preferentially favour outward rotation.



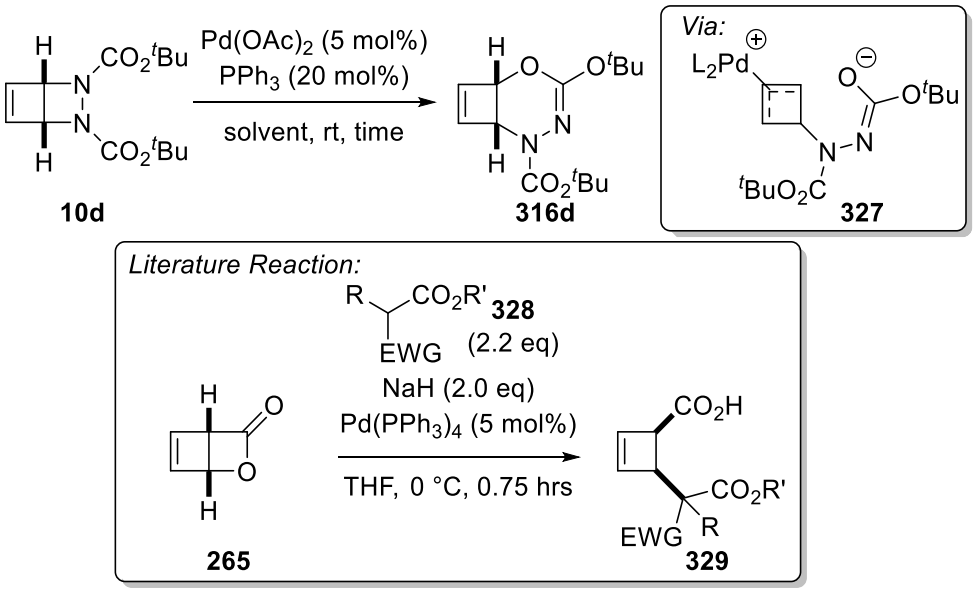
322, R = H
323, R = alkyl, $CONH_2$

325, R = H

326, R = alkyl, $CONH_2$

Scheme 4.16

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).

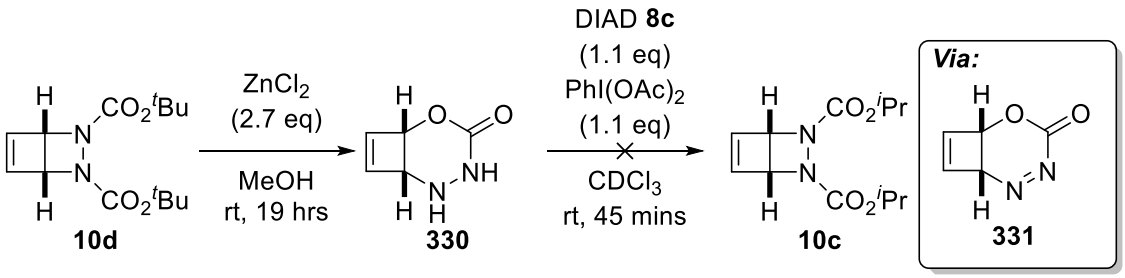


Entry	Solvent	Time (hours)	Yield 316d (%)
1	THF	29	72
2	MeOH	2	60

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 ^{1}H NMR peaks to those

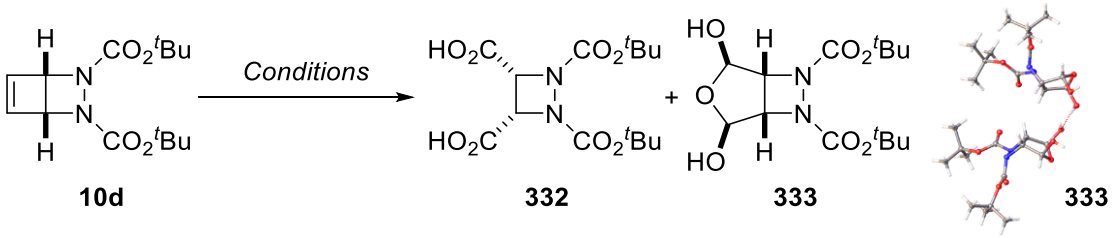
found for bicyclic 1,2-diazetidine **10**. Due to the very small scale and time constraints, it was unfortunately not possible to identify this new product.



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).

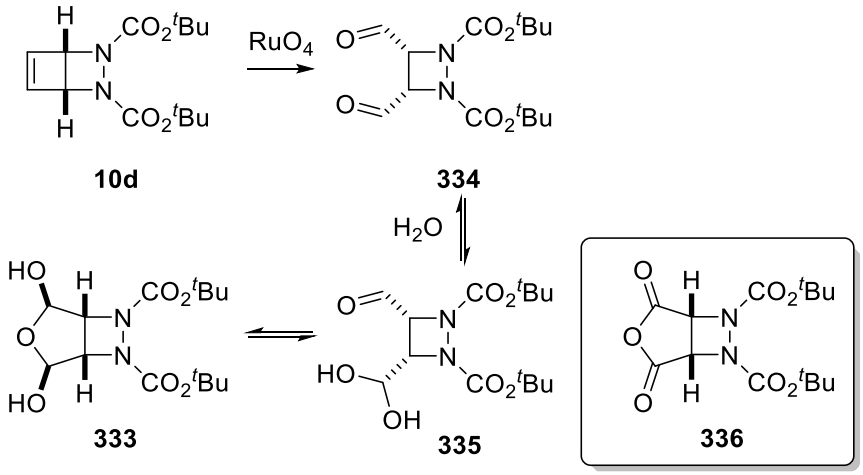


Entry	Conditions	Yield 332 (%)	Yield 333 (%)
1	$RuO_2.xH_2O$ (5 mol%), 10% aqueous $NaIO_4$, EtOAc, rt, 20 mins	0	85
2	OsO_4 (5 mol%), $NaIO_4$ (4.0 eq), 2,6-lutidine (2.0 eq) 1,4-dioxane:H_2O (3:1), rt, 24 hrs	0	80
3	OsO_4 (5 mol%), NMO (3.0 eq), acetone:H_2O (8:1), rt, 50 hrs	0	68
4	$RuO_2.xH_2O$ (5 mol%), 10% aqueous $NaIO_4$, EtOAc, rt, 41 hrs	76	0

Table 4.3 NMO: *N*-methylmorpholine *N*-oxide

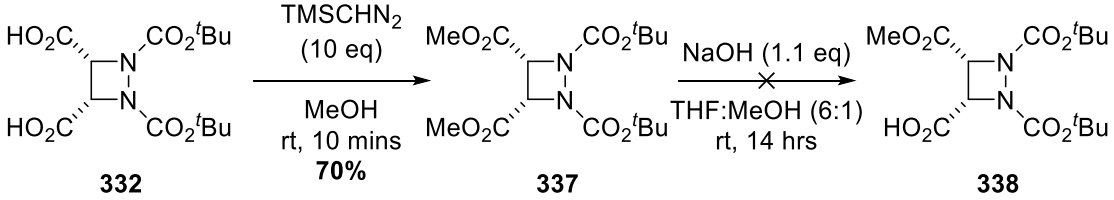
Formation of bicycle **333** was thought to have started with formation of dialdehyde **334**, which in the presence of water (from the reaction mixture) resulted in the hydration of one of the aldehydes **335**, followed by cyclisation to give bicycle **333** (Scheme 4.18). The bicyclic 1,2-diazetidine **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.



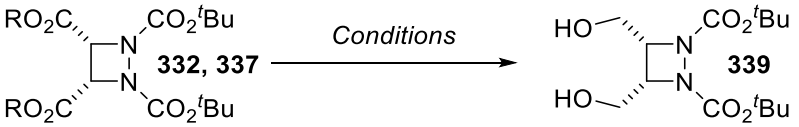
Scheme 4.18

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

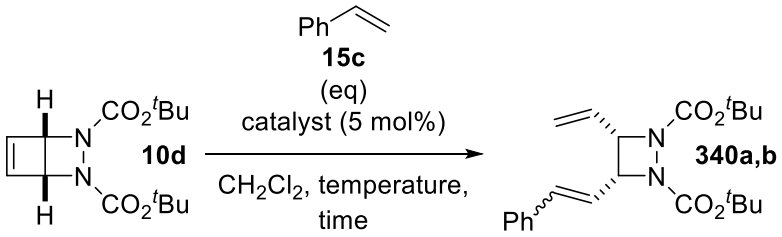
It was thought that 1,2-diazetidines **332** and **337** would be ideal precursors to the alcohol **339** (Table 4.4). The attempted reduction of diacid **332** led to the formation of complex mixtures (entries 1 and 2), likely caused by competition reactions between the reduction of the acid and the 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.



Entry	R	Conditions	Yield 339 (%)
1	H	$LiAlH_4$ (3.0 eq), THF, 0 °C → rt, 30 mins	0
2	H	BH_3•THF (3.0 eq), THF, 0 °C → rt, 24 hrs	0
3	Me	$LiBH_4$ (2.5 eq), THF, 0 °C → rt, 4 hrs	0

Table 4.4

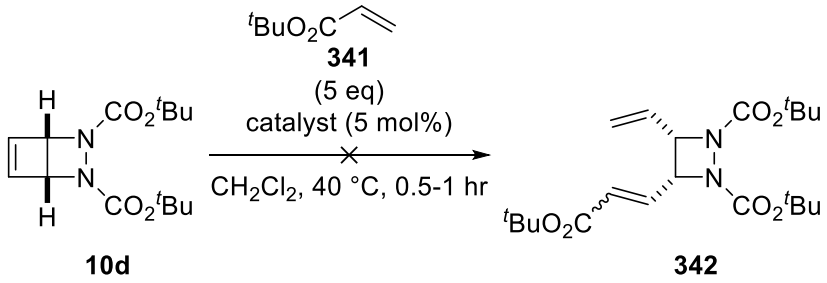
The double bond in bicyclic 1,2-diazetidines **10d** was expected to undergo a ring opening cross metathesis sequence in the presence of a suitable alkene (Table 4.5). Styrene **15c** was chosen as the alkene for optimisation and both catalysts **75** and **76** were investigated (See Scheme 1.21 for 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).



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

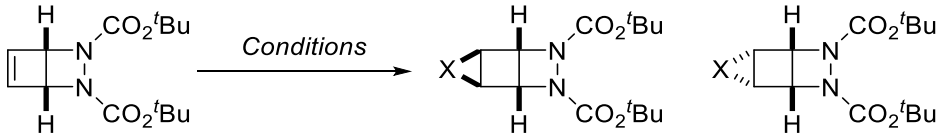
Table 4.5 [a] Calculated from ^{1}H NMR spectra in d_6-DMSO through comparison of *Z*-isomer **340a** and *E*-isomer **340b** peaks. No internal standard used

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

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**.

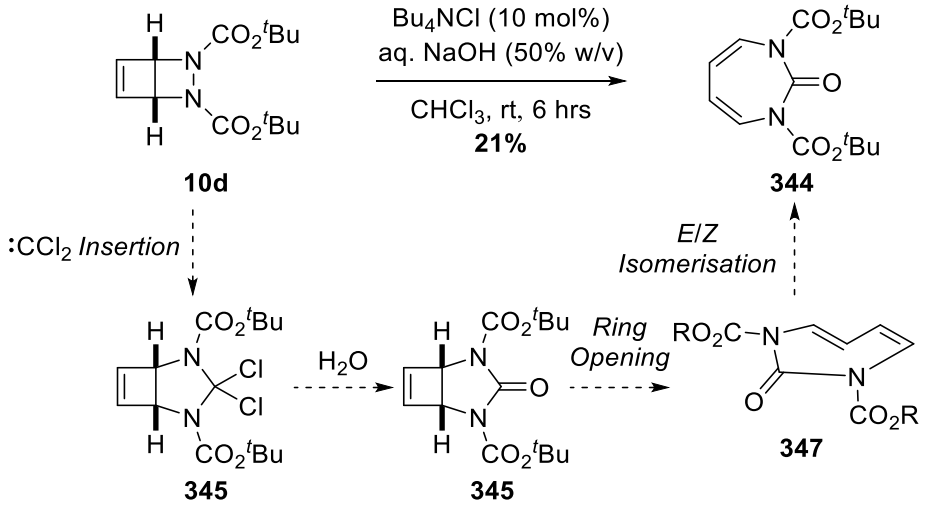


Entry	Conditions	X	Yield 343 (%)
1	$PhMe_3NBr_3$ (0.1 eq), $TsNClNa.3H_2O$ (1.2 eq), MeCN, rt or 40 °C, 24 hrs	NTs	0
2	Bu_4NCl (10 mol%), aq. NaOH (50% w/v), $CHCl_3$, rt, 6 hrs	CCl_2	0
3	*m*-CPBA (1.2 eq), CH_2Cl_2, rt or 40 °C, 24 hrs	O	0

Table 4.6

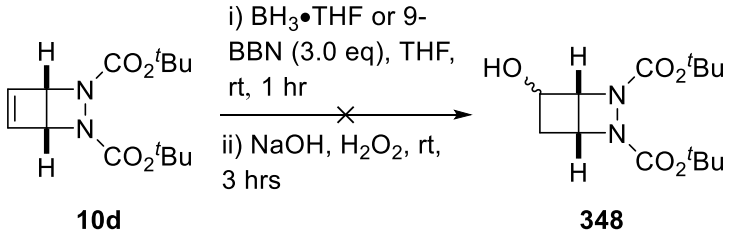
The major product from the cyclopropanation reaction contained no chlorine atoms (from mass spectrometry analysis) and relatively simple ^{1}H and ^{13}C NMR spectra, which suggested the presence of a symmetrical diene. From this information it has been tentatively suggested the product formed is diazepine **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.[91] 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-π electrocyclic

ring opening would give a highly strained diene **347** that could undergo *E*/*Z* isomerisation to give diazepine **344**.



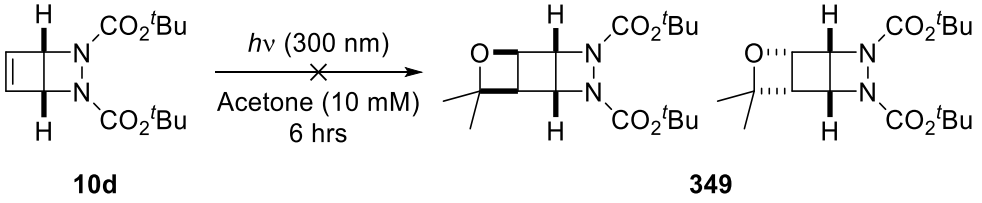
Scheme 4.21

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.



Scheme 4.22

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).

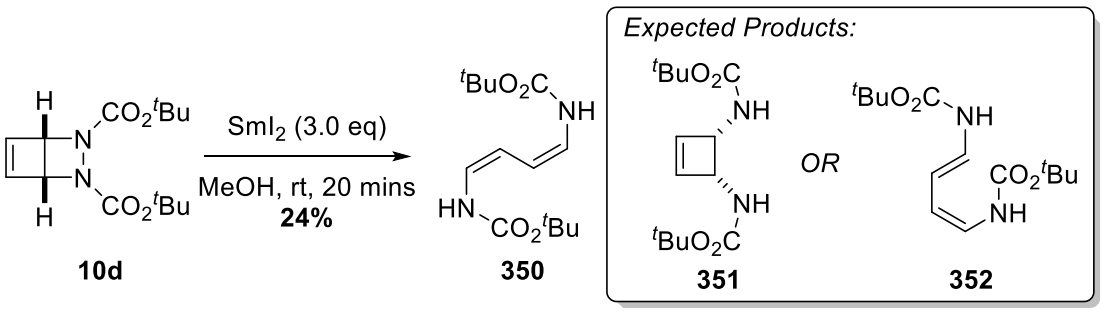


Scheme 4.23

4.3.3 Synthesis of Functionalised Cyclobutenes

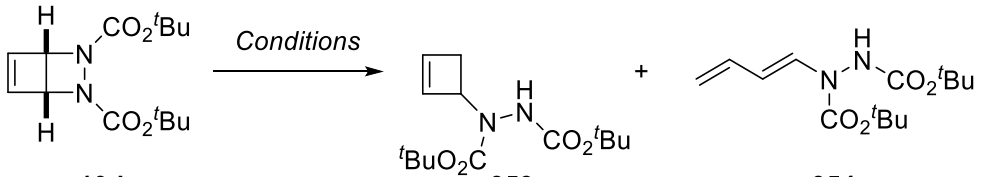
The efficient cleavage of the N-N bond in bicycle **10d** would enable access to *cis*-diaminocyclobutenes **351**, which were expected to undergo a spontaneous electrocyclic ring opening to give functionalised dienes (Scheme 4.24).

Samarium(II) iodide was freshly prepared, titrated and used according to a literature procedure.[305] 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.[112] 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.



Scheme 4.24

There have been a variety of other methods described for the cleavage of N-N bonds published in the literature,[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.[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 cyclobutanes. 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).[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.



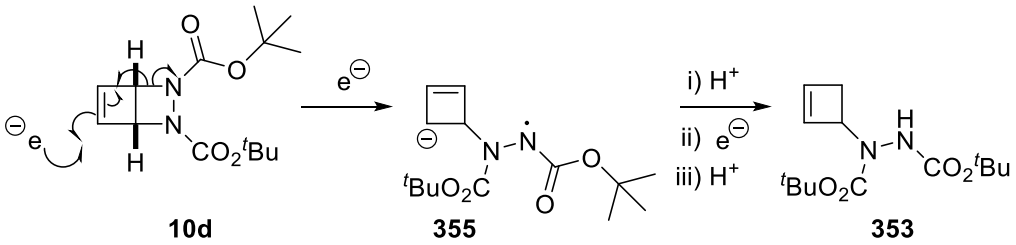
10d **353** **354**

Entry	Conditions	Yield 353 and 354 (%)	Ratio 353:354[a]
1	LiDBB (2.5 eq), THF, −78 °C, 10 mins	35	n.d
2	Na/NH_3, THF, −78 °C → rt	87	2.4:1.0
3	Zn (10 eq), NH_4OAc (1.1 eq), MeOH, rt, 22 hrs	69	1.3:1.0
4	Zn (10 eq), NH_4Cl (1.1 eq), MeOH, rt, 22 hrs	79	1.0:1.4

Table 4.7 [a] Calculated by ^1H NMR in d_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**.

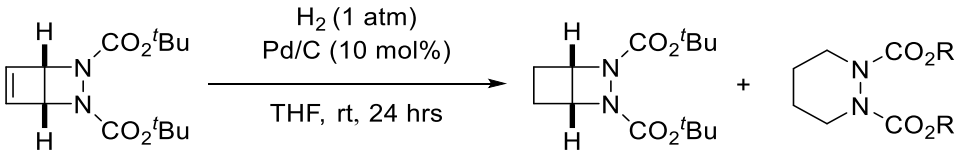


10d **355** **353**

Scheme 4.25

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.[90,308] 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 diazinane **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.



10d **308d** (6%) **356** (85%)

Scheme 4.26

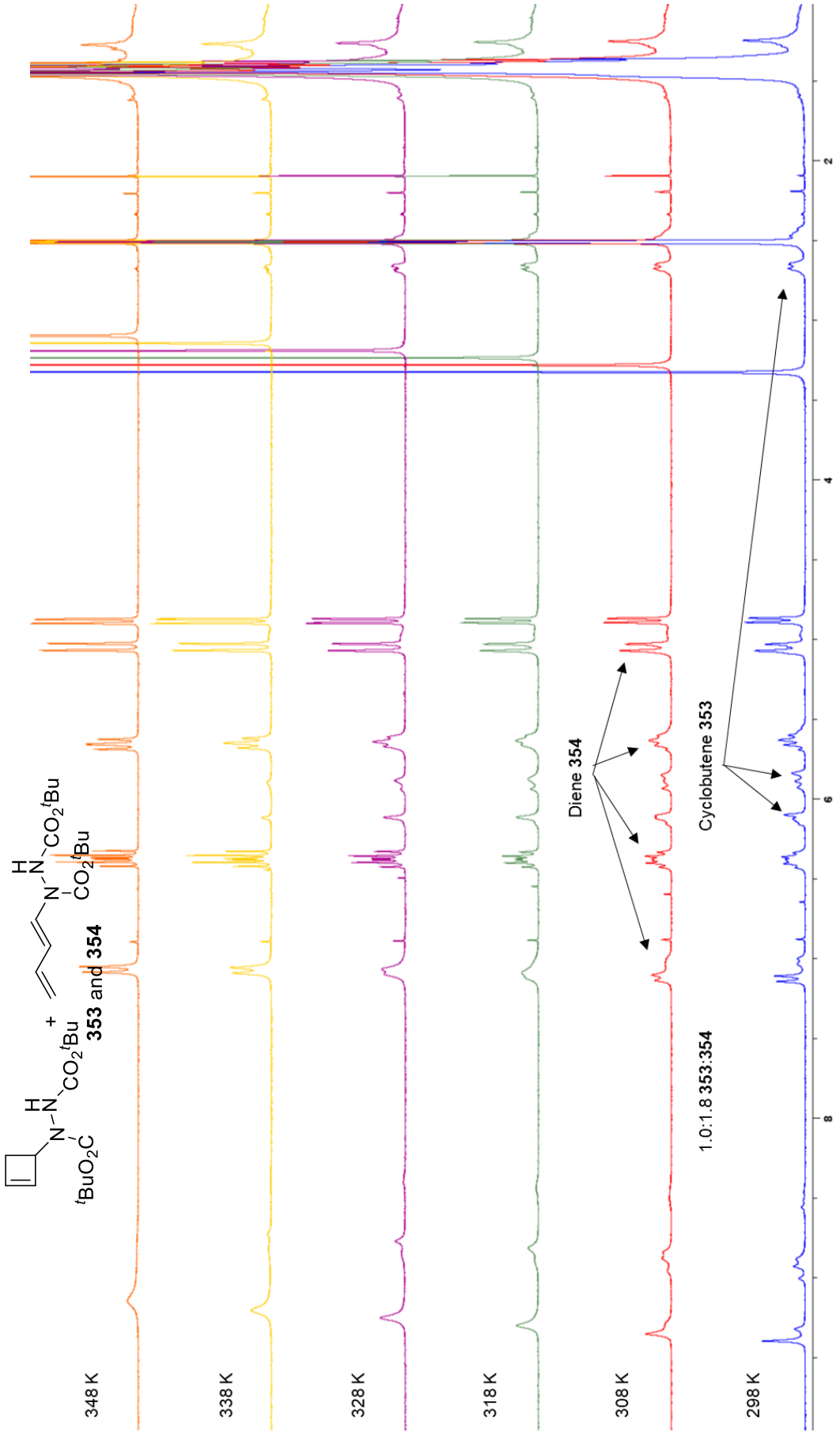
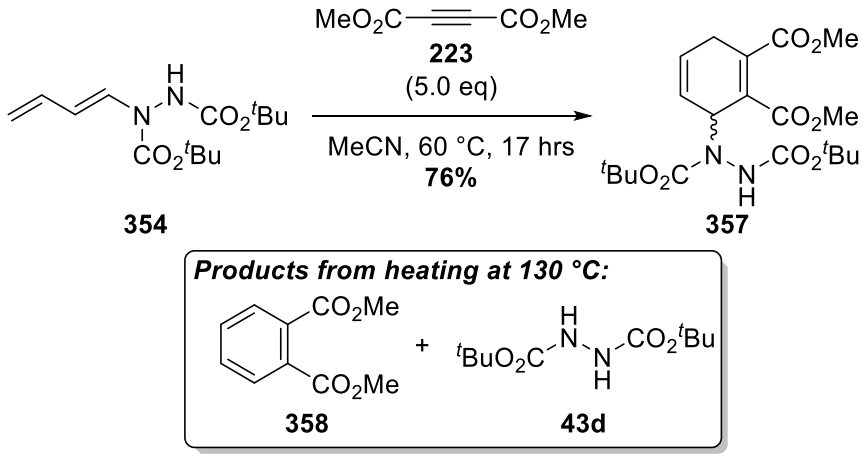


Figure 4.2 Variable Temperature ^{1}H NMR in d_6-DMSO of cyclobutene **353** and diene **354**

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

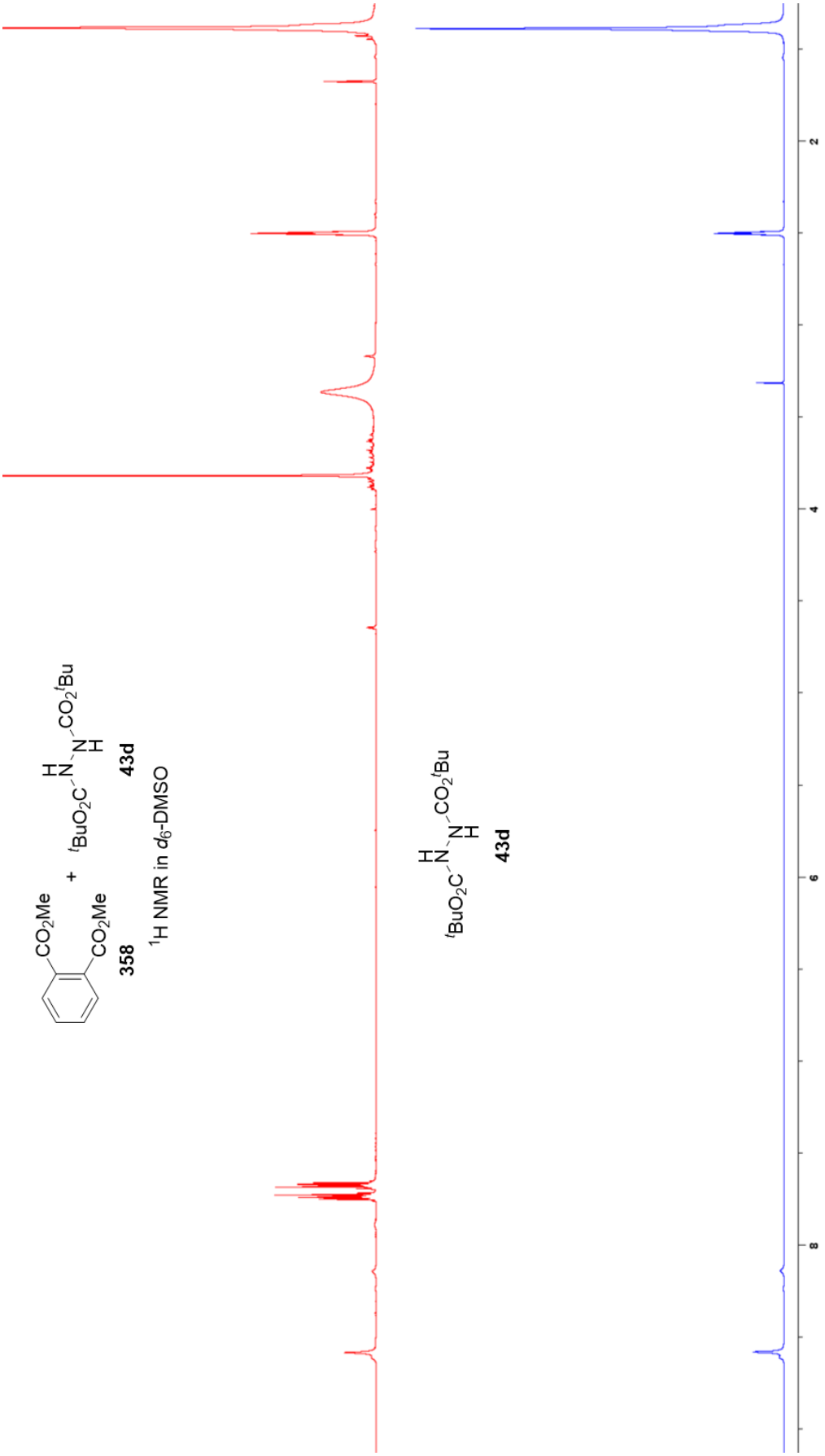


Figure 4.3 ^{1}H NMR of cycloadduct **357** after heating at 130 °C

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 halohydration 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-likeness 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.

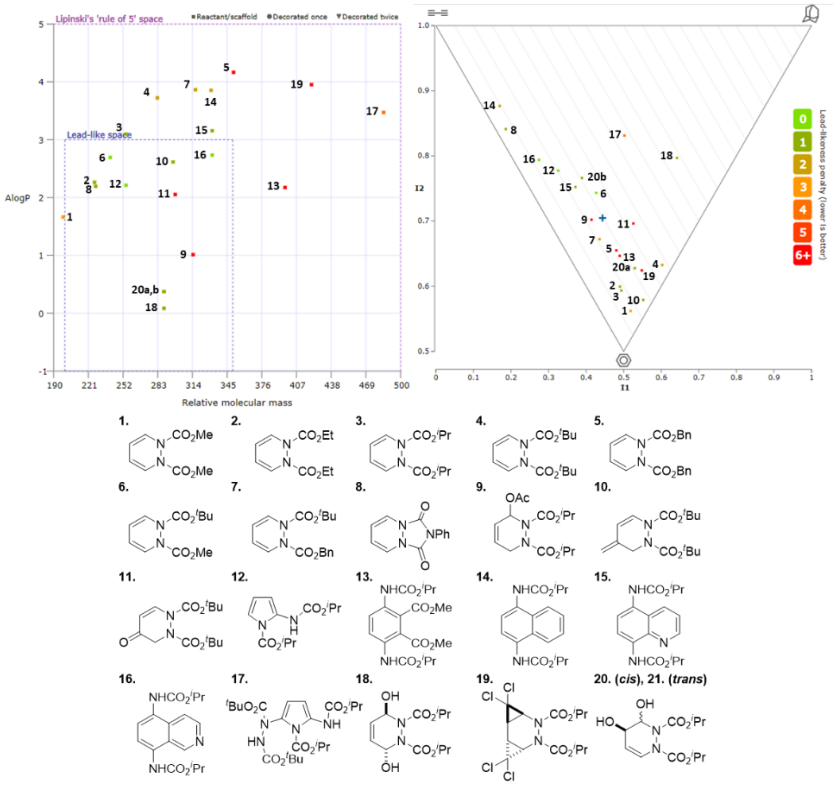


Figure 5.1 Like-likeness (top left) and shape analysis (top right) of 1,2-dihydropyridazines and products from derivatisation reactions; Like-likeness penalty = -1≤ logP≤3, 14≤ heavy atoms ≤26 e.g. molecular weight 200-350, remove reactive functional groups, decrease the amount sp^2 character e.g. 1 or 2 aromatic rings

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, λ_{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-π 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*-diene **350** was isolated in low yields (24%), presumably from 4-π electrocyclic ring opening to give *E*/*Z*-diene **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*-diene **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.

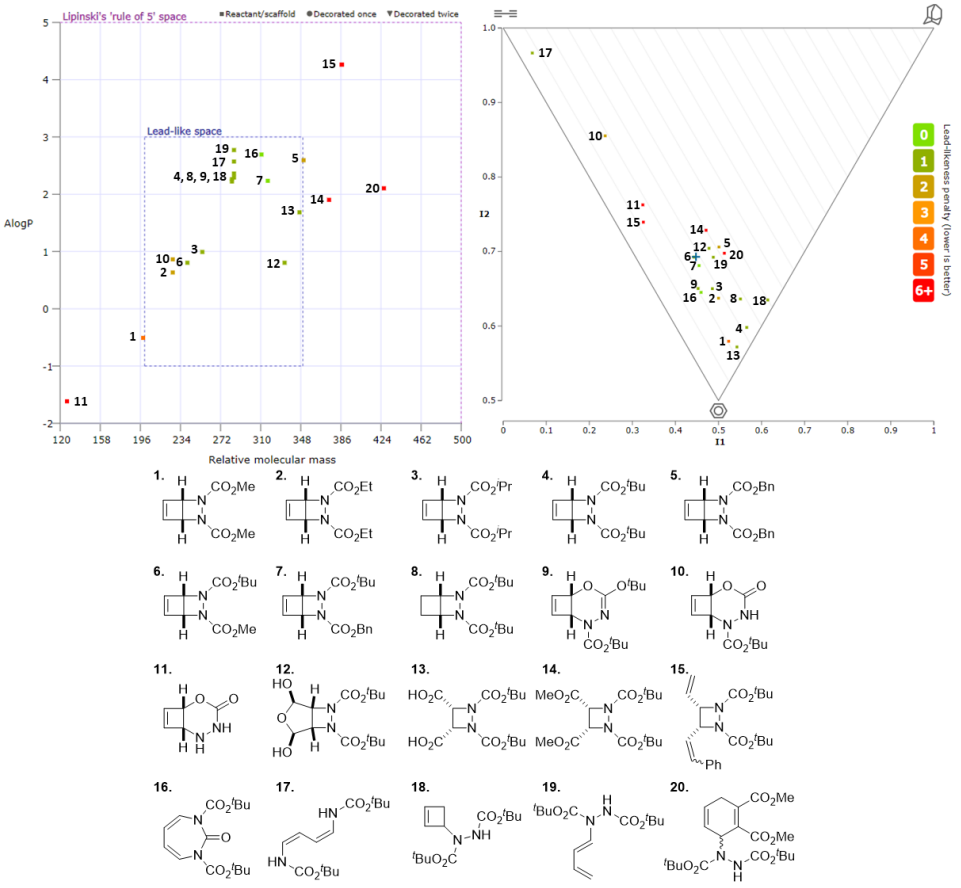


Figure 5.2 Like-likeness (top left) and shape analysis (top right) of bicyclic 1,2-diazetidines and products from derivatisation reactions

5.2 Future Work

The investigation of the 4-π 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-π photocyclisation pathway can be applied to the substituted 1,2-dihydropyridazines that favoured the 6-π 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).

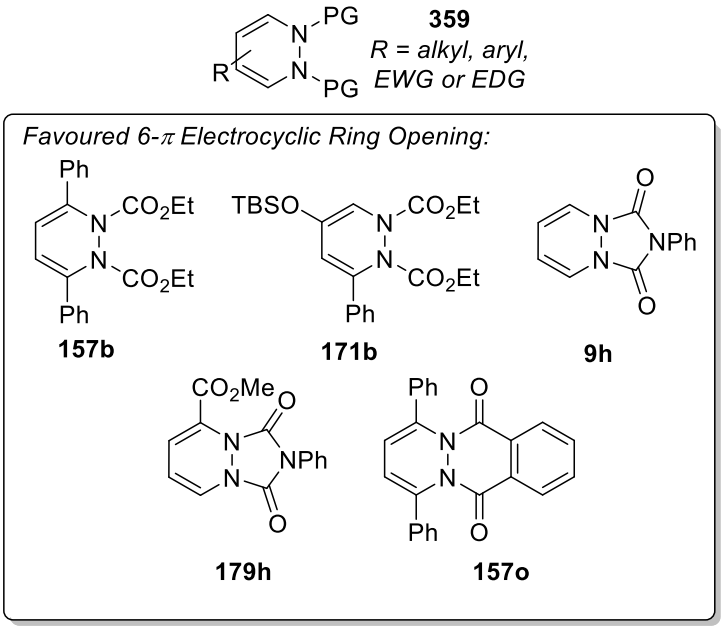
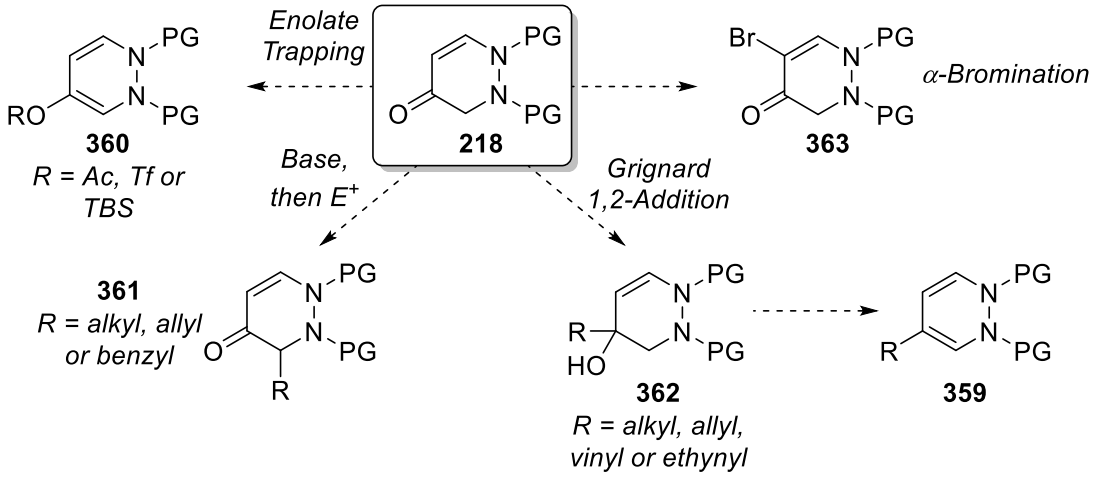


Figure 5.3

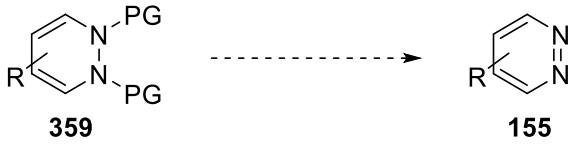
Starting from enone **218**, it should be possible to access a variety of substituted 1,2-dihydropyridazines (Scheme 5.1). Firstly, deprotonation of the acidic hydrogen in the α-position and trapping of the enolate with an electrophile would provide access to *O*-substituted 1,2-dihydropyridazines **360**. 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).[309] 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 = 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]



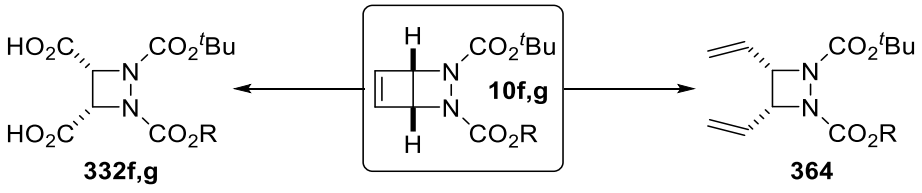
Scheme 5.1

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.



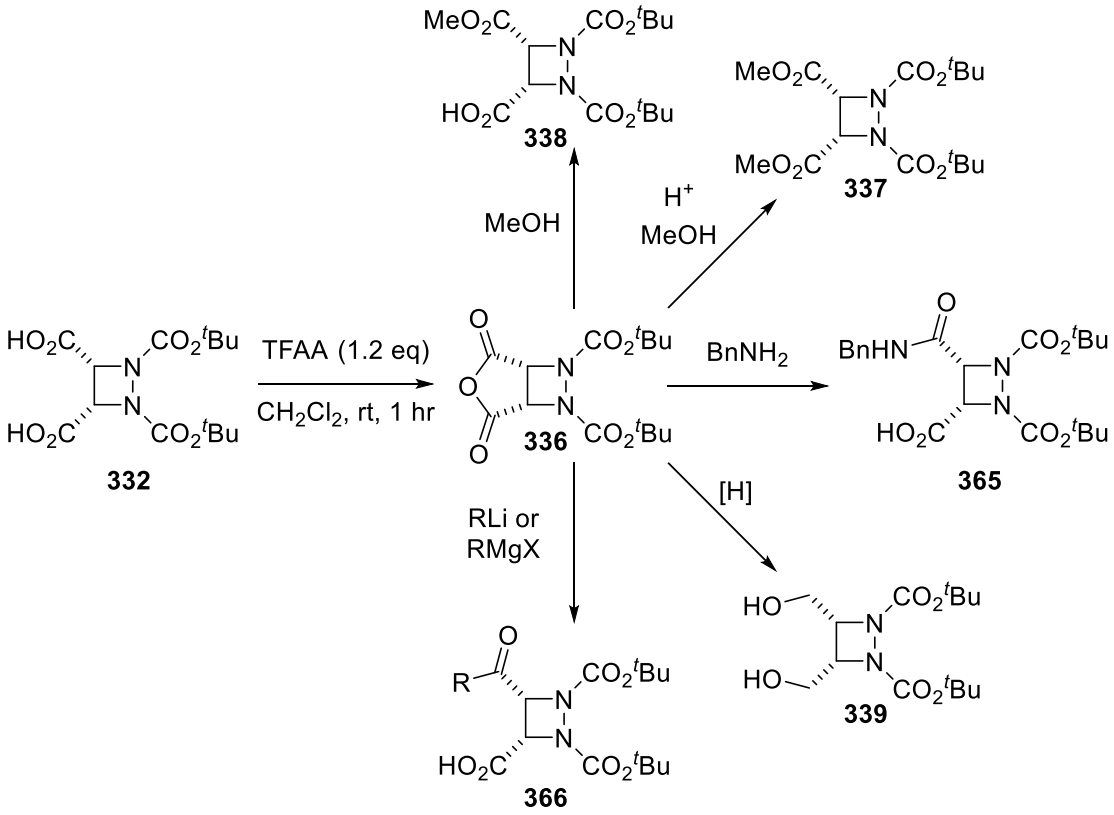
Scheme 5.2

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 selectivity 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.



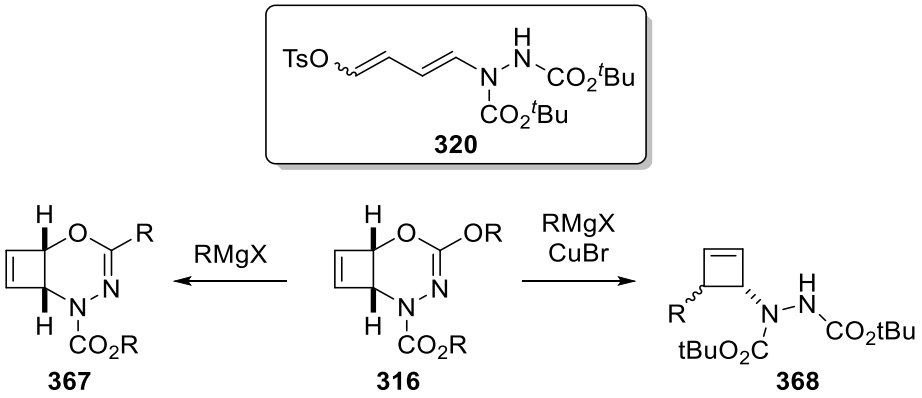
Scheme 5.3

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).[311] 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**).



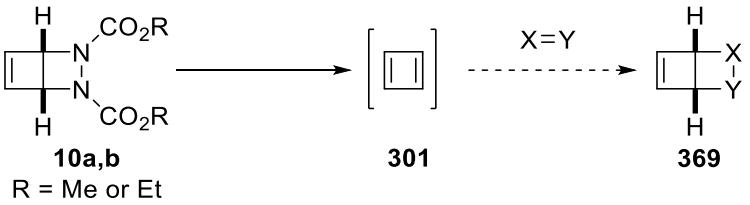
Scheme 5.4

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).



Scheme 5.5

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**.[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.



Scheme 5.6

Chapter 6: Experimental

6.1 General Information

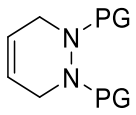
Reagents were purchased in the highest purity available from Acros Organics, Alfa Aesar, Fluorochem, Sigma Aldrich and TCI. Anhydrous solvents used in reactions were purchased from Acros Organics equipped with AcroSeal™ and all other solvents used were of reagent grade. Triphenylphosphine was recrystallized 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 ^{1}H 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).

^{1}H NMR spectroscopic data were obtained on either 300 or 400 MHz instruments and ^{13}C{^{1}H} 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 $CHCl_3$ (δ_H = 7.26 ppm) and $CDCl_3$ (δ_C = 77.16 ppm, central line), residual d_5-DMSO (δ_H = 2.50ppm) and d_6-DMSO (δ_C = 39.52 ppm, central line). The assignment of the signals in the ^{1}H and ^{13}C 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,[312] the structure was solved with the ShelXT structure solution program using direct methods and refined with the ShelXL refinement package using least squares minimisation.[313,314] Figures and tables were prepared using Olex2 software.[312]

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.

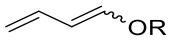
6.2 General Procedures

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



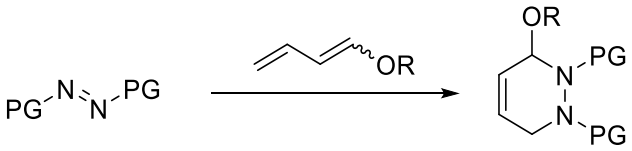
A 15% (w/v) solution of butadiene in hexane (1.0-3.0 eq) was added in one portion to a stirred solution of the desired azo compound (1.0 eq) in CH_2Cl_2 (0.2-0.6 M) in a sealed flask at room temperature. The resulting mixture was stirred either at room temperature or 40 °C for a specific length of time 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



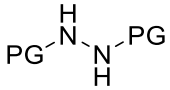
Crotonaldehyde (1.0 eq) was added dropwise to a stirred solution of potassium *tert*-butoxide (1.1 eq) in THF (1.2-1.3 M) at –78 ˚C under argon and stirred for 10 minutes. Acid chloride (1.1 eq) was added dropwise over 10 minutes and stirred at –78 ˚C for 30 minutes. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (25 mL) and extracted with Et_2O (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.

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

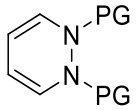


Pyridine (3.0-6.0 eq) was added dropwise to a stirred solution of carbazate (1.0 eq) and the desired chloroformate (1.1-1.2 eq) in THF or 2-MeTHF (0.1-1M) at 0 ˚C under argon. The resulting suspension was stirred at 0 ˚C for 15 minutes and then at room temperature for 1.5 hours. A 10% (v/v) aqueous solution of HCl (10 mL) was added and the mixture was extracted with CH_2Cl_2 (5 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) 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 [$AgCO_3$/Celite][258]

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 $AgNO_3$ (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 [$AgCO_3$/Celite] (2.82 g, the amount of Ag_2CO_3 per mass of Ag_2CO_3/Celite was not calculated, reported as 1 mmol per 0.57 g).

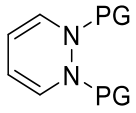
General procedure F: Synthesis of 1,2-dihydropyridazines starting from commercially available azo compounds



1-Acetoxy-1,3-butadiene (1.5 eq) was added in one portion to a solution of the azo compound (1.0 eq) in CH_2Cl_2 (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%), 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.

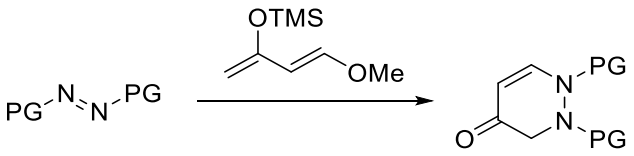
General procedure G: Synthesis of 1,2-dihydropyridazines starting from hydrazine-1,2-dicarboxylates



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_2Cl_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.

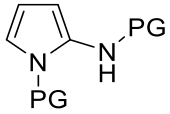
The cycloadducts were dried in a desiccator, dissolved in 1,4-dioxane (0.5 M) and added to an oven-dried vial under argon that contained $Pd(OAc)_2$ (1.0 mol%), PPh_3 (4.0 mol%) and triethylamine (2.0 eq) The vial was sealed, then heated at reflux for 1 hour. The reaction mixture was cooled to room temperature 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



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_2Cl_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 at room temperature 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_2Cl_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.

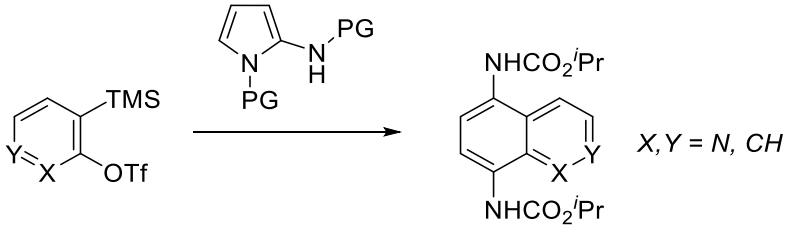
General Procedure I: Synthesis of 2-aminopyrrole from 1,2-dihydropyridazines



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.

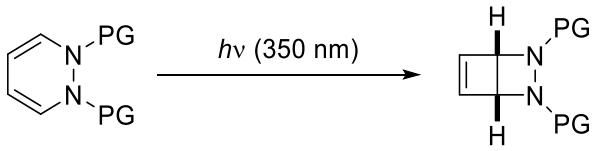
Note: 2-Aminopyrroles must be stored in the freezer under an inert atmosphere in order to prevent degradation.

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



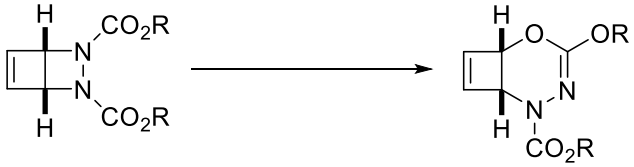
CsF (3.0 eq) was added in one portion to a stirred solution of 2-aminopyrrole (2.0 eq) and aryne precursor (1.0 eq) in MeCN (0.1 M) at room temperature under argon, then heated at 40 °C for 1.5-2.5 hours. The reaction mixture was cooled to room temperature, filtered through Celite and the solvent removed 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



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.

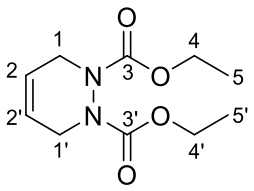
General Procedure L: Thermal rearrangement of bicyclic 1,2-diazetidines



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[36]



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 CH_2Cl_2 (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.

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

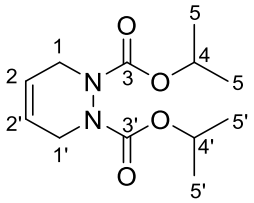
^{1}H NMR (400 MHz, $CDCl_3$); δ 5.83-5.74 (br m, 2H, **H2** and **H2'**), 4.46–4.42 (br m, 2H, $\mathbf{H1_A}$ and $\mathbf{H1'_A}$), 4.21-4.20 (br m, 4H, **H4** and **H4'**), 3.80 (br s, 2H, $\mathbf{H1_B}$ and $\mathbf{H1'_B}$), 1.26 (t, *J* = 7.0 Hz, 6H, **H5** and **H5'**).

^{13}C NMR (100 MHz, $CDCl_3$); 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).

HRMS (ESI): *m*/*z* calculated for: $C_{10}H_{16}N_2O_4$ $[M+Na]^+$ 251.1002, found 251.0991.

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



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 CH_2Cl_2 (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.

R_f (hexane-EtOAc, 4:1) = 0.25

^{1}H NMR (400 MHz, $CDCl_3$); 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, $\mathbf{H1_A}$ and $\mathbf{H1'_A}$), 3.92–3.69 (br m, 2H, $\mathbf{H1_B}$ and $\mathbf{H1'_B}$), 1.22 (d, *J* = 6.2 Hz, 12H, **H5** and **H5'**).

^{13}C NMR (100 MHz, $CDCl_3$, 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**).

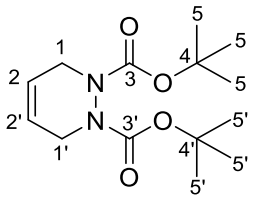
^{1}H NMR (400 MHz, 328 K, $CDCl_3$); δ 5.79-5.72 (m, 2H, **H2** and **H2'**), 4.94 (sept, *J* = 6.2 Hz, 2H, **H4** and **H4'**) 4.47–4.26 (br m, 2H, $\mathbf{H1_A}$ and $\mathbf{H1'_A}$), 3.88–3.64 (br m, 2H, $\mathbf{H1_B}$ and $\mathbf{H1'_B}$), 1.24-1.22 (m, 12H, **H5** and **H5'**).

^{13}C NMR (100 MHz, 328 K, $CDCl_3$); δ 155.3 (**C3**), 124.0 (**C2**), 70.0 (**C4**), 43.9 (**C1**), 22.2 (**C5**), 22.1 (**C5**).

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

HRMS (ESI): *m*/*z* calculated for: $C_{12}H_{20}N_2O_4$ $[M+H]^+$ 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_2Cl_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

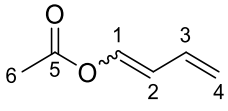
^{1}H NMR (400 MHz, $CDCl_3$); δ 5.81-5.71 (br m, 2H, **H2** and **H2'**), 4.40–4.20 (m, 2H, $\mathbf{H1_A}$ and $\mathbf{H1'_A}$), 3.77–3.66 (m, 2H, $\mathbf{H1_B}$ and $\mathbf{H1'_B}$), 1.46 (s, 18H, **H5** and **H5'**).

^{13}C NMR (100 MHz, $CDCl_3$, additional peaks due to complex rate processes denoted by an asterisk); δ 154.7 (**C3**), 124.1 (**C2**), 123.5* (**C2**), 81.1 (**C4**), 44.9* (**C1**), 43.3 (**C1**), 28.4 (**C5**).

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

HRMS (ESI): *m*/*z* calculated for: $C_{14}H_{24}N_2O_4$ $[M + K]^+$ 323.1368 and $[M + Na]^+$ 307.1628, found 323.1349 and 307.1624 respectively.

(*E*/*Z*)- 1-Acetoxy-1,3-butadiene 202a[237,238]



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.

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_2O (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_2O, 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.[237,238]

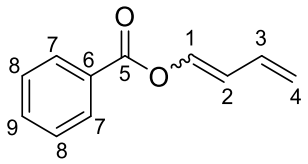
Major Isomer:

R_f (hexane-EtOAc, 2:1) = 0.58

^{1}H NMR (400 MHz, $CDCl_3$); δ 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, **H4$_A$**), 5.10–5.07 (m, 1H, **H4$_B$**), 2.14 (s, 3H, **H6**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 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[315]



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_2O (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 (eluent: petroleum ether-Et_2O, 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

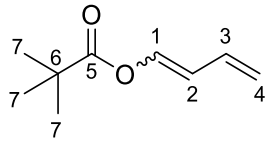
^{1}H NMR (400 MHz, $CDCl_3$); δ 8.15–8.09 (m, 2H, **H7**), 7.66 (dd, *J* = 12.2, 0.5 Hz, 1H, **H1**), 7.64–7.58 (m, 1H, **H9**), 7.51–7.45 (m, 2H, **H8**), 6.42–6.32 (m, 1H, **H3**), 6.27–6.21 (m, 1H, **H2**), 5.30–5.25 (m, 1H, $\mathbf{H4_A}$), 5.15–5.12 (m, 1H, $\mathbf{H4_B}$).

^{13}C NMR (100 MHz, $CDCl_3$); δ 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**).

FTIR (ATR) ν (cm^{-1}): 3087, 1731 (C=O), 1656, 1601.

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

(*E*/*Z*)-Buta-1,3-dien-1-yl pivalate 202c[316]



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

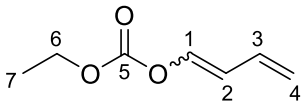
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.39 (d, *J* = 12.3 Hz, 1H, **H1**), 6.33-6.24 (m, 1H, **H3**), 6.09-6.03 (m, 1H, **H2**), 5.22-5.18 (m, 1H, $\mathbf{H4_A}$), 5.09-5.06 (m, 1H, $\mathbf{H4_B}$), 1.24 (s, 9H, **H7**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5 (**C5**), 139.3 (**C1**), 132.0 (**C3**), 117.0 (**C4**), 116.0 (**C2**), 38.9 (**C6**), 27.1 (**C7**).

FTIR (ATR) ν (cm^{-1}): 2976, 1743 (C=O).

HRMS (ESI): No mass peak found.

(*E*/*Z*)-Buta-1,3-dien-1-yl ethyl carbonate 202d[317]



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

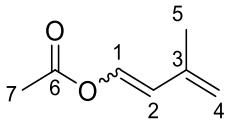
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.20 (d, *J* = 12.2 Hz, 1H, **H1**), 6.31-6.21 (m, 1H, **H3**), 6.08-6.02 (m, 1H, **H2**), 5.24-5.19 (m, 1H, **H4$_A$**), 5.11-5.08 (m, 1H, **H4$_B$**), 4.27 (q, *J* = 7.2 Hz, 2H, **H6**), 1.34 (t, *J* = 7.2 Hz, 3H, **H7**).

^{13}C NMR (100 MHz, $CDCl_3$); 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[238]



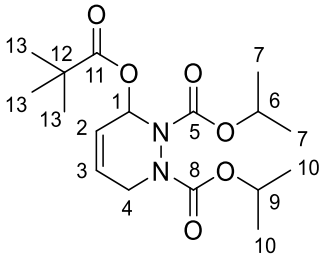
4-Dimethylaminopyridine (0.64 g, 5.24 mmol, 0.2 eq), triethylamine (25 mL, 181 mmol, 2.1 eq) and acetic anhydride (12 mL, 130 mmol, 5.0 eq) were added to 3-methyl-2-butenal (2.5 mL, 25.9 mmol, 1.0 eq) at room temperature under argon. The solution was stirred for 5 days at room temperature, then diluted with Et_2O (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 $NaHCO_3$ (5 x 20 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_2O, 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.[238]

^{1}H NMR (400 MHz, $CDCl_3$); 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$_A$** and **H4$_B$**), 2.14 (s, 3H, **H7**), 1.85-1.84 (m, 3H, **H5**).

^{13}C NMR (100 MHz, $CDCl_3$); 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



Using general procedure C, 1-pivaloyloxy-1,3-butadiene **202c** (2.03 g, 13.2 mmol, 1.6 eq) and diisopropyl 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.

R_f (Hexane-EtOAc, 2:1) = 0.40.

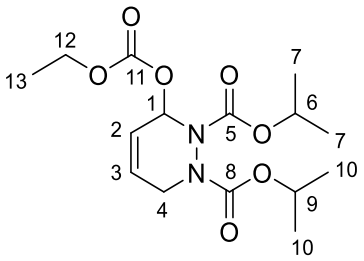
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.87-6.79 (br m, 1H, **H1**), 6.09-6.04 (br m, 1H, **H3**), 5.87-5.82 (br m, 1H, **H2**), 5.03-4.90 (br m, 2H, **H6** and **H9**), 4.60-4.43 (br m, 1H, **H4$_A$**), 3.87-3.68 (br m, 1H, **H4$_B$**), 1.27-1.22 (br m, 12H, **H7** and **H10**), 1.19 (br s, 9H, **H13**).

^{13}C NMR (100 MHz, $CDCl_3$, 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: $C_{17}H_{28}N_2O_6$ $[M+Na]^+$ 379.1840, found 379.1837.

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



Using 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.

R_f – Not stable on silica gel (streaks).

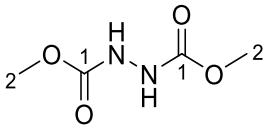
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.80-6.71 (br m, 1H, **H1**), 6.13-6.05 (br m, 1H, **H3**), 5.91-5.85 (br d, 1H, **H2**), 5.07-4.91 (m, 2H, **H6** and **H9**), 4.64-4.39 (br m, 1H, **H4$_A$**), 4.27-4.14 (m, 2H, **H12**), 3.86-3.67 (br m, 1H, **H4$_B$**), 1.31-1.21 (m, 15H, **H7**, **H10** and **H13**).

^{13}C NMR (100 MHz, $CDCl_3$, additional peaks due to complex rate processes denoted by an asterisk); δ 155.2 (**C5**, **C8** or **C11**), 153.8 (**C5**, **C8** or **C11**), 129.8 (**C3**), 121.7 (**C2**), 76.5 (**C1**), 71.0* (**C6** or **C9**), 70.2 (**C6** or **C9**), 64.3 (**C12**), 42.4 (**C4**) , 22.2* (**C7** or **C10**), 22.1 (**C7** or **C10**), 21.8* (**C7** or **C10**), 14.3 (**C13**).

FTIR (ATR) ν (cm^{-1}): 2984, 1737 (C=O), 1707 (C=O).

HRMS (ESI): *m*/*z* calculated for: $C_{12}H_{19}N_2O_4$ $[M-OCO_2Et]^+$ 255.1339, found 255.1342.

Dimethyl hydrazine-1,2-dicarboxylate 43a



Using 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.

R_f (CH_2Cl_2-EtOAc, 1:1) = 0.32

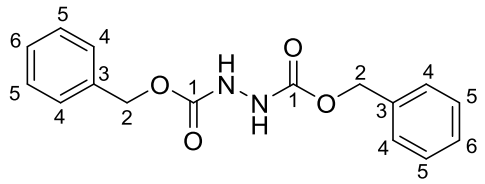
mp = 123-124 ˚C

^{1}H NMR (400 MHz, d_6-DMSO); δ 9.12-8.72 (br m, 2H, **NH**), 3.58 (s, 6H, **H2**).

^{13}C NMR (100 MHz, d_6-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[247]



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.

R_f (Hexane-EtOAc, 1:1) = 0.41

mp = 102-103 ˚C

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.38-7.30 (br m, 10H, **H4**, **H5**, **H6**), 6.67 (br s, 2H, **NH**), 5.16 (s, 4H, **H2**).

^{13}C NMR (100 MH, $CDCl_3$); 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**), 68.0 (**C2**).

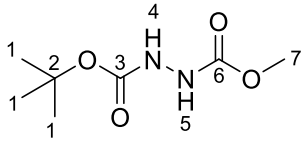
^{1}H NMR (400 MHz, d_6-DMSO); δ 9.33-8.88 (br m, 2H, **NH**), 7.40-7.33 (br m, 10H, **H4**, **H5**, **H6**), 5.09 (s, 4H, **H2**).

^{13}C NMR (100 MHz, d_6-DMSO); δ 156.5 (**C1**), 136.6 (**C3**), 128.4 (**C4**, **C5** or **C6**), 128.0 (**C4**, **C5** or **C6**), 127.9 (**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: $C_{16}H_{16}N_2O_4$ $[M-H]^-$ 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.

R_f (Hexane-EtOAc, 1:1) = 0.25

mp = 103-105 ˚C

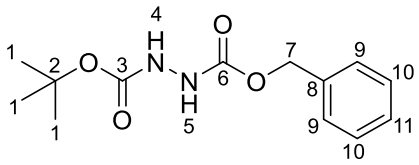
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.59 (br s, 1H, **H4** or **H5**), 6.40 (br s, 1H, **H4** or **H5**), 3.75 (s, 3H, **H7**), 1.46 (s, 9H, **H1**).

^{13}C NMR (100 MHz, $CDCl_3$); 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: $C_7H_{14}N_2O_4$ $[M-H]^-$ 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.

R_f (Hexane-EtOAc, 2:1) = 0.27

mp = 75-76 ˚C

^{1}H NMR (400 MHz, $CDCl_3$); 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**).

^{13}C NMR (100 MHz, $CDCl_3$); 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**), 82.0 (**C2**), 67.9 (**C7**), 28.2 (**C1**).

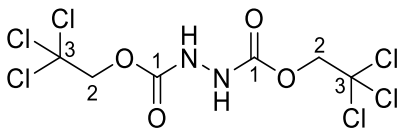
^{1}H NMR (400 MHz, d_6-DMSO); δ 9.04 (br s, 1H, **H4** or **H5**), 8.77 (br s, 1H, **H4** or **H5**), 7.38-7.34 (m, 5H, **H9**, **H10**, **H11**), 5.06 (br s, 2H, **H7**), 1.40-1.33 (m, 9H, **H1**).

^{13}C NMR (100 MHz, d_6-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: $C_{13}H_{18}N_2O_4$ $[M+Na]^+$ 289.1159, found 289.1148.

Bis(2,2,2-trichloroethyl) hydrazine-1,2-dicarboxylate 43i[246]



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_2O (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

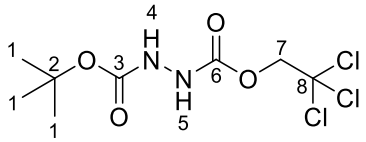
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.99-6.81 (br m, 2H, **NH**), 4.80 (s, 4H, **H2**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 154.8 (**C1**), 94.7 (**C3**), 75.4 (**C2**).

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

HRMS (APCI): *m*/*z* calculated for: $C_6H_6N_2O_4Cl_6$ $[M-H]^-$ 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, $CDCl_3$); δ 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, $CDCl_3$); δ 155.4, (**C3** or **C6**),155.2 (**C3** or **C6**), 95.0 (**C8**), 82.4 (**C2**), 75.4 (**C7**), 28.3 (**C1**).

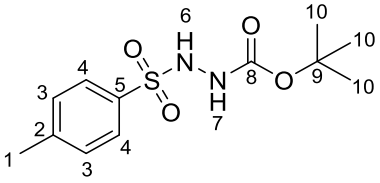
^{1}H NMR (400 MHz, d_6-DMSO); δ 9.49 (br s, 1H, **H4** or **H5**), 8.93 (br s, 1H, **H4** or **H5**), 4.84-4.80 (br m, 2H, **H7**), 1.40 (br s, 9H, **H1**).

^{13}C NMR (100 MHz, d_6-DMSO); δ 155.4 (**C3** or **C6**), 155.1 (**C3** or **C6**), 95.8 (**C8**), 79.4 (**C2**), 73.7 (**C7**), 28.1 (**C1**).

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

HRMS (ESI): *m*/*z* calculated for: $C_6H_{13}N_2O_4Cl_3$ $[M+Na]^+$ 328.9833, found 328.9827.

1-*tert*-Butyl 2-tosyl hydrazine-1-carboxylate 43k[92]



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 (Hexane-EtOAc, 1:1) = 0.38

mp = 99-101 ˚C

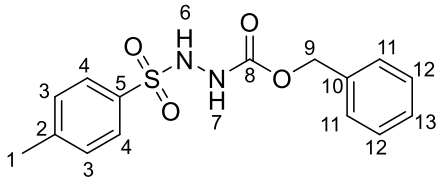
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.80 (d, *J* = 8.1 Hz, 2H, **H4**), 7.29 (d, *J* = 8.1 Hz, 2H, **H3**), 6.78 (br s, 2H, **H6** and **H7**), 2.40 (s, 3H, **H1**), 1.22 (s, 9H, **H10**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 154.3 (**C8**), 144.7 (**C2**), 133.7 (**C5**), 129.6 (**C3**), 128.9 (**C4**), 82.4 (**C9**), 27.9 (**C10**), 21.7 (**C1**).

FTIR (ATR) ν (cm^{-1}): 3308 (NH), 3232 (NH), 2976, 1716 (C=O), 1331 (SO_2), 1150 (SO_2).

HRMS (ESI): *m*/*z* calculated for: $C_{12}H_{18}N_2O_4S$ $[M-H]^-$ 285.0915, found 285.0916.

1-Benzyl 2-tosyl hydrazine-1-carboxylate 43l[92]



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_2Cl_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 (Hexane-EtOAc, 1:1) = 0.23

mp = 141-142 ˚C

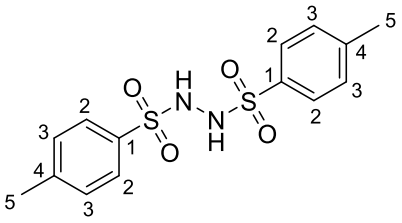
^{1}H NMR (400 MHz, d_6-DMSO); δ 9.69 (br s, 1H, **H6** or **H7**), 9.52 (br s, 1H, **H6** or **H7**), 7.66 (d, *J* = 8.1 Hz, 2H, **H4**), 7.37-7.29 (br m, 5H, **H3**, **H12**, **H13**), 7.22 (br d, *J* = 6.5 Hz, 2H, **H11**), 4.93 (br s, 2H, **H9**), 2.37 (s, 3H, **H1**).

^{13}C NMR (100 MHz, d_6-DMSO); δ 155.7 (**C8**), 143.2 (**C2**), 136.4 (**C5** or **C10**), 136.1 (**C5** or **C10**), 129.4 (**C3**), 128.3 (**C4**, **C11**, **C12** or **C13**), 127.9 (**C4**, **C11**, **C12** or **C13**), 127.6 (**C4**, **C11**, **C12** or **C13**), 65.9 (**C9**), 21.1 (**C1**).

FTIR (ATR) ν (cm^{-1}): 3338 (NH), 3181 (NH), 1722 (C=O), 1340 (SO_2), 1163 (SO_2).

HRMS (APCI): *m*/*z* calculated for: $C_{15}H_{16}N_2O_4S$ $[M-H]^-$ 319.0758, found 319.0770.

***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_2Cl_2 (10 mL) at room temperature under argon. The resulting solution was stirred at room temperature for 2.5 hours, then Et_2O (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_2O (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_2O (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.

mp = 210-212 ˚C (decomposition)

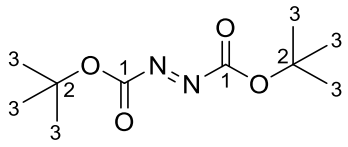
^{1}H NMR (400 MHz, d_6-DMSO); δ 9.58 (s, 2H, **NH**), 7.64 (d, *J* = 8.0 Hz, 4H, **H2**), 7.38 (d, *J* = 8.0 Hz, 4H, **H3**), 2.39 (s, 6H, **H5**)

^{13}C NMR (100 MHz, d_6-DMSO); δ 143.6 (**C4**), 135.5 (**C1**), 129.6 (**C3**), 127.9 (**C2**), 21.1 (**C5**).

FTIR (ATR) ν (cm^{-1}): 3230 (NH), 3204 (NH), 1331 (SO_2), 1164 (SO_2).

HRMS (ESI): No mass peak found.

Di-*tert*-butyl azodicarboxylate 8d



Fétizon's Reagent Oxidation: Fétizon'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.[247]

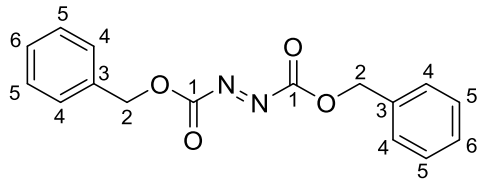
R_f (Hexane-EtOAc, 1:1) = 0.67.

^{1}H NMR (400 MHz, $CDCl_3$); δ 1.61 (s, 18H, **H3**).

^{13}C NMR (75 MHz, $CDCl_3$); δ 159.4 (**C1**), 86.9 (**C2**), 27.8 (**C3**).

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

Dibenzyl azodicarboxylate 8e



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_2Cl_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 (Hexane-EtOAc, 1:1) = 0.65

mp = 43-45 ˚C

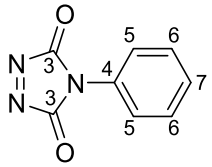
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.44-7.37 (m, 10H, **H4**, **H5**, **H6**), 5.43 (s, 4H, **H2**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 160.2 (**C1**), 133.7 (**C3**), 129.4 (**C6**), 129.0 (**C4** or **C5**), 129.0 (**C4** or **C5**), 71.0 (**C2**).

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

HRMS (ESI): No mass peak found.

4-Phenyl-1,2,4-triazoline-3,5-dione 8h[318]



Iodobenzene diacetate (2.82 g, 8.76 mmol, 1.3 eq) was added in one portion to a stirred suspension of 4-phenylurazole **43h** (1.15 g, 6.49 mmol, 1.0 eq) in CH_2Cl_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)

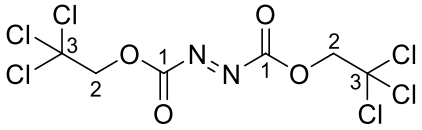
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.57-7.54 (m, 2H, **H5** or **H6**), 7.51-7.45 (m, 3H, **H5** or **H6** and **H7**)

^{13}C NMR (100 MHz, $CDCl_3$, **C4** not visible); δ 157.9 (**C3**), 130.0 (**C5** or **C6**), 129.6 (**C7**), 124.1 (**C5** or **C6**).

FTIR (ATR) ν (cm^{-1}): 1737 (C=O).

HRMS (ESI): *m*/*z* calculated for: $C_8H_5N_3O_2$ 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_2Cl_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_f - Not stable on silica gel

mp = 98-100 ˚C

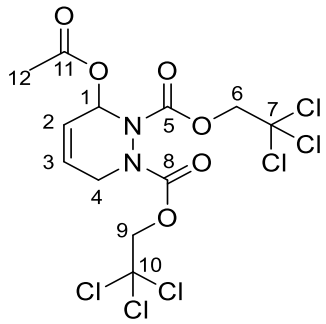
^{1}H NMR (400 MHz, $CDCl_3$); δ 5.06 (s, 4H, **H2**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 158.6 (**C1**), 93.3 (**C3**), 77.1 (**C2**).

FTIR (ATR) ν (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_f (Hexane-EtOAc, 2:1) = 0.29

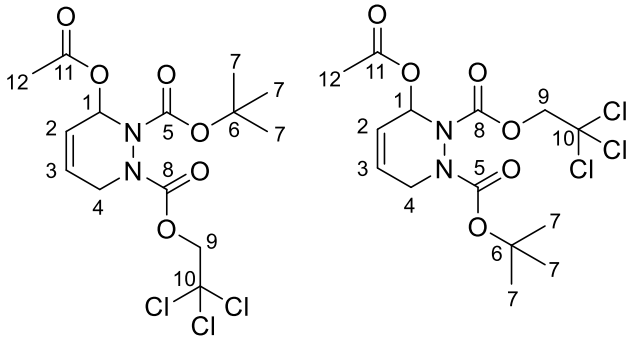
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.96-6.91 (br m, 1H, **H1**), 6.16-6.09 (br m, 1H, **H3**), 5.98-5.89 (br m, 1H, **H2**), 4.99-4.57 (br m, 5H, **H4$_A$**, **H6** and **H9**), 4.08-3.88 (m, 1H, **H4$_B$**), 2.07-2.04 (br m, 3H, **H12**).

^{13}C NMR (100 MHz, $CDCl_3$, additional peaks due to complex rate processes denoted by an asterisk); δ 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) ν (cm^{-1}): 2958, 1724 (C=O).

HRMS (ESI): *m*/*z* calculated for: $C_{12}H_{12}N_2O_6Cl_6$ $[M+Na]^+$ 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 µL, 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_2Cl_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 cycloadduct **203j** (607 mg, 1.45 mmol, 96%, unable to determine major regioisomer) as a colourless oil.

R_f (Hexane-EtOAc, 2:1) = 0.38

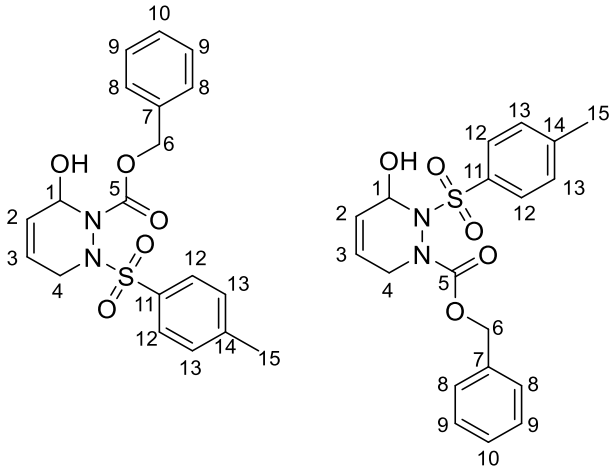
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.92-6.85 (br m, 1H, **H1**), 6.14-6.07 (br m, 1H, **H3**), 5.94-5.84 (br m, 1H, **H2**), 4.92-4.4.45 (br m, 3H, **H9** and $\mathbf{H4_A}$), 3.93-3.88 (br m, 1H, $\mathbf{H4_B}$), 2.09-2.04 (br m, 3H, **H12**), 1.50-1.43 (br m, 9H, **H7**).

^{13}C NMR (100 MHz, $CDCl_3$, additional peaks due to complex rate processes denoted by an asterisk); δ 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) ν (cm^{-1}): 2980, 1713 (C=O).

HRMS (ESI): *m*/*z* calculated for: $C_{14}H_{16}N_2O_6Cl_3$ $[M+Na]^+$ 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 **43l** (42 mg, 0.13 mmol, 1.0 eq) in CH_2Cl_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

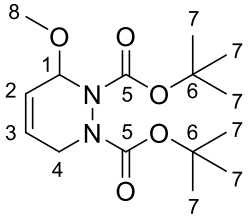
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.80-7.73 (br m, 2H, **H12**), 7.39-7.33 (br m, 3H, **H9**, **H10**), 7.24-7.21 (br m, 2H, **H8**), 7.19-7.13 (br m, 2H, **H13**), 6.07-6.03 (br m, 1H, **H3**), 5.93-5.87 (br m, 1H, **H2**), 5.83-5.78 (br m, 1H, **H1**), 5.05-4.81 (br m, 2H, **H6**), 4.43-4.37 (m, 1H, **H4$_A$**), 4.16-4.09 (m, 1H, **OH**), 3.73-3.66 (br m, 1H, **H4$_B$**), 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) ν (cm^{-1}): 3485 (OH), 3032, 1711 (C=O), 1340 (SO_2), 1157 (SO_2).

HRMS (ESI): *m/z* calculated for: $C_{19}H_{20}N_2O_5S$ $[M+Na]^+$ 411.0985, found 411.0977.

Di-*tert*-butyl 3-methoxy-3,6-dihydropyridazine-1,2-dicarboxylate 212d



K_2CO_3 (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.

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

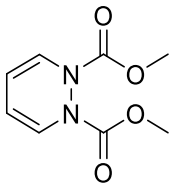
^{1}H NMR (400 MHz, $CDCl_3$); δ 5.95-5.86 (br m, 1H, **H3**), 5.84-5.77 (br m, 1H, **H2**), 5.46-5.25 (br m, 1H, **H1**), 4.48-4.24 (br m, 1H, **H4$_A$**), 3.73-3.56 (br m, 1H, **H4$_B$**), 3.48-3.45 (br m, 3H, **H8**), 1.48-1.43 (br m, 18H, **H7**).

^{13}C NMR (100 MHz, $CDCl_3$, 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).

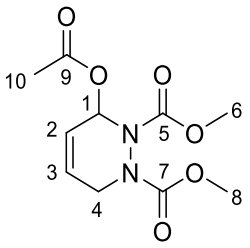
HRMS (APCI): *m/z* calculated for: $C_{15}H_{26}N_2O_5$ $[M+Na]^+$ 337.1734, found 337.1719.

Dimethyl-1,2-dihydropyridazine-1,2-dicarboxylate 9a[33–35]



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 CH_2Cl_2 (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**



R_f (Hexane-EtOAc, 1:1) = 0.21

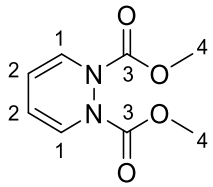
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.88-6.76 (br m, 1H, **H1**), 6.08-6.05 (br m, 1H, **H3**), 5.90-5.79 (br m, 1H, **H2**), 4.61-4.41 (br m, 1H, **H4$_A$**), 3.89-3.71 (br m, 7H, **H6**, **H8** and **H4$_B$**), 2.01 (br s, 3H, **H10**).

^{13}C NMR (100 MHz, $CDCl_3$, 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**), 128.6* (**C3**), 122.5* (**C2**), 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) ν (cm^{-1}): 2957, 1711 (C=O), 1655 (C=O).

HRMS (ESI): *m*/*z* calculated for: $C_{10}H_{14}N_2O_6$ $[M+Na]^+$ 281.0744, found 281.0730.

1,2-Dihydropyridazine **9a**



R_f (Hexane-EtOAc, 2:1) = 0.26

mp = 62-64 ˚C

^{1}H NMR (400 MHz, 298 K, d_6-DMSO); δ 6.92-6.66 (br m, 2H, **H1**), 5.92-5.70 (br m, 2H, **H2**), 3.74 (s, 6H, **H4**).

^{1}H NMR (400 MHz, 348 K, d_6-DMSO); δ 6.76 (dd, *J* = 5.2, 2.5 Hz, 2H, **H1**), 5.81 (dd, *J* = 5.2, 2.5 Hz, 2H, **H**), 3.76 (s, 6H, **H4**).

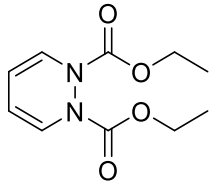
^{13}C NMR (100 MHz, 298 K, d_6-DMSO, additional peaks due to complex rate processes denoted by an asterisk); δ 153.8 (**C3**), 127.3 (**C1**), 113.4* (**C2**), 112.1 (**C2**), 53.7 (**C4**).

^{13}C NMR (100 MHz, 348 K, d_6-DMSO); δ 153.2 (**C3**), 127.0 (**C1**), 112.2 (**C2**), 53.2 (**C4**).

FTIR (ATR) ν (cm^{-1}): 2958, 1715 (C=O).

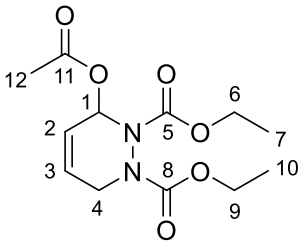
HRMS (APCI): *m*/*z* calculated for: $C_8H_{10}N_2O_4$ $[M+H]^+$ 199.0713, found 199.0719.

Diethyl 1,2-dihydropyridazine-1,2-dicarboxylate 9b[36]



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 CH_2Cl_2 (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**



R_f (hexane-EtOAc, 1:1) = 0.24

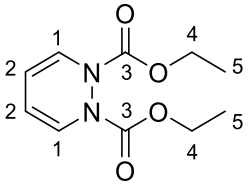
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.90-6.82 (br m, 1H, **H1**), 6.09 (br dd, *J* = 9.5, 3.8 Hz, 1H, **H3**) 5.92-5.83 (br m, 1H, **H2**), 4.64-4.44 (m, 1H, **H4$_A$**), 4.29-4.17 (m, 4H, **H6** and **H9**), 3.89-3.73 (m, 1H, **H4$_B$**), 2.04 (br s, 3H, **H12**), 1.29-1.23 (m, 6H, **H7** and **H10**).

^{13}C NMR (100 MHz, $CDCl_3$, additional peaks due to complex rate processes denoted by an asterisk); δ 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) ν (cm^{-1}): 2984, 2937, 1733 (C=O), 1709 (C=O).

HRMS (ESI): *m*/*z* calculated for: $C_{12}H_{18}N_2O_6$ $[M+Na]^+$ 309.1057, found 309.1051.

1,2-Dihydropyridazine **9b**



R_f (hexane-EtOAc, 1:1) = 0.51

mp = 56-58 ˚C

^{1}H NMR (400 MHz, 298 K, d_6-DMSO); δ 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); δ 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**).

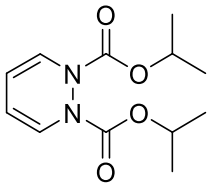
^{13}C NMR (100 MHz, 298 K, d_6-DMSO, additional peaks due to complex rate processes denoted by an asterisk); δ 153.2 (**C3**), 127.3 (**C1**), 113.2* (**C2**), 111.9 (**C2**), 62.6 (**C4**), 14.2 (**C5**).

^{13}C NMR (100 MHz, 348 K, d_6-DMSO); δ 152.6 (**C3**), 127.0 (**C1**), 112.0 (**C2**), 62.2 (**C4**), 13.8 (**C5**).

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

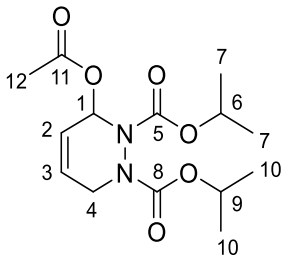
HRMS (ESI): *m*/*z* calculated for: $C_{10}H_{14}N_2O_4$ $[M+Na]^+$ 249.0846, found 249.0847.

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 CH_2Cl_2 (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 (Hexane-EtOAc, 1:1) = 0.40

mp = 54-58 ˚C

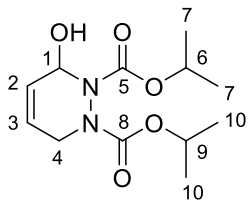
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.90-6.83 (br m, 1H, **H1**), 6.09-6.05 (br m, 1H, **H3**), 5.89-5.82 (br m, 1H, **H2**), 4.99-4.94 (m, 2H, **H6** and **H9**), 4.62-4.39 (br m, 1H, **H4$_A$**), 3.85-3.67 (br m, 1H, **H4$_B$**), 2.02 (br s, 3H, **H12**), 1.25-1.21 (br m, 12H, **H7** and **H10**).

^{13}C NMR (100 MHz, $CDCl_3$, additional peaks due to complex rate processes denoted by an asterisk); δ 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) ν (cm^{-1}): 2984, 1731 (C=O), 1698 (C=O).

HRMS (APCI): *m/z* calculated for:$C_{14}H_{22}N_2O_6$ $[M+Na]^+$ 337.1370, found 337.1370; $C_{12}H_{19}N_2O_4$ $[M-OAc]^+$ 255.1339, found 255.1337; $C_{12}H_{19}N_2O_5$ $[M-CH_3CO]^-$ 271.1299, found 271.1295.

Alcohol **208c**



R_f (Hexane-EtOAc, 1:1) = 0.25.

mp = 73-76 ˚C

^{1}H NMR (400 MHz, d_6-DMSO); δ 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, **H4$_A$**), 3.72-3.55 (br m, 1H, **H4$_B$**), 1.23-1.12 (br m, 12H, **H7** and **H10**).

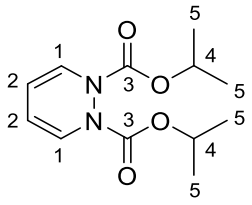
^{13}C NMR (100 MHz, d_6-DMSO, additional peaks due to complex rate processes denoted by an asterisk); δ 154.8 (**C5** or **C8**), 153.6* (**C5** or **C8**), 153.2* (**C5** or **C8**), 126.2* (**C2**), 126.1 (**C2**),

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).

HRMS (APCI): *m*/*z* calculated for: $C_{12}H_{20}N_2O_5$ $[M+Na]^+$ 295.1264, found 295.1247.

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



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

mp = 93-94 ˚C

^{1}H NMR (400 MHz, 298 K, d_6-DMSO); δ 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**).

^{1}H NMR (400 MHz, 348 K, d_6-DMSO); δ 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**).

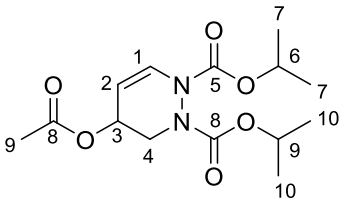
^{13}C NMR (100 MHz, 298 K, d6 -DMSO, additional peaks due to complex rate processes denoted by an asterisk); δ 152.6* (**C3**), 151.9 (**C3**), 127.4 (**C1**), 113.0* (**C2**), 111.7 (**C2**), 70.5 (**C4**), 21.6 (**C5**).

^{13}C NMR (100 MHz, 348 K, d_6-DMSO); δ 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: $C_{12}H_{18}N_2O_4$ $[M+H]^+$ 255.1339, found 255.1329.

Rearranged Allylic Acetate **209c**



R_f (Hexane-EtOAc, 2:1) = 0.34

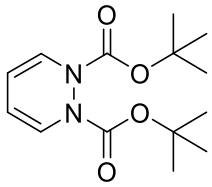
^{1}H NMR (400 MHz, d_6-DMSO); δ 7.23-7.19 (br m, 1H, **H1**), 5.22-5.15 (br m, 1H, **H2**), 5.02-4.99 (br m, 1H, **H3**), 4.93-4.78 (m, 2H, **H6**), 4.45-4.29 (br m, 1H, $\mathbf{H4_A}$), 3.47-3.26 (br m, 1H, $\mathbf{H4_B}$), 2.03-1.91 (m, 3H, **H9**), 1.24-1.17 (br m, 12H, **H7**).

^{13}C NMR (100 MHz, d_6-DMSO, additional peaks due to complex rate processes denoted by an asterisk); δ 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: $C_{14}H_{22}N_2O_6$ $[M+Na]^+$ 337.1357, found 337.1370.

Di-*tert*-butyl 1,2-dihydropyridazine-1,2-dicarboxylate 9d

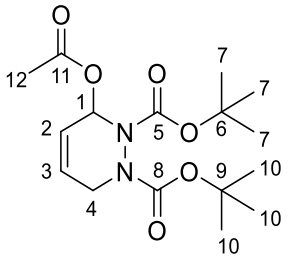


Using general procedure F, di-*tert*-butyl azodicarboxylate **8d** (1.00 g, 4.35 mmol) and 1-acetoxy-1,3-butadiene **202a** (0.8 mL, 6.53 mmol) in CH_2Cl_2 (1.7 mL) was stirred at 40 °C for 2 days. After the addition of hexane (20 mL), filtration and drying, cycloadduct (1.45 g, 4.23 mmol), $Pd(OAc)_2$ (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 CH_2Cl_2 (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 CH_2Cl_2 (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 (Hexane-EtOAc, 2:1) = 0.36

mp = 119-121 ˚C

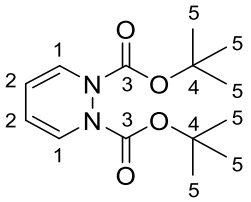
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.87-6.72 (br m, 1H, **H1**), 6.08-6.00 (br m, 1H, **H3**), 5.89-5.75 (br m, 1H, **H2**), 4.57-4.34 (br m, 1H, **H4$_A$**), 3.85-3.60 (br m, 1H, **H4$_B$**), 2.04 (br s, 3H, **H12**), 1.46-1.43 (br m, 18H, **H7** and **H10**).

^{13}C NMR (100 MHz, $CDCl_3$, additional peaks due to complex rate processes denoted by an asterisk); δ 169.9* (**C11**), 169.4 (**C11**), 154.4 (**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).

HRMS (ESI): *m*/*z* calculated for: $C_{16}H_{26}N_2O_6$ $[M+Na]^+$ 365.1683, found 365.1681.

1,2-Dihydropyridazine **9d**



R_f (Hexane-EtOAc, 1:1) = 0.64

mp = 94-95 ˚C

^{1}H NMR (400 MHz, 298 K, d_6-DMSO); δ 6.81-6.60 (br m, 2H, **H1**), 5.84-5.62 (br m, 2H, **H2**), 1.44 (s, 18H, **H5**).

^{1}H NMR (400 MHz, 348 K, d_6-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**).

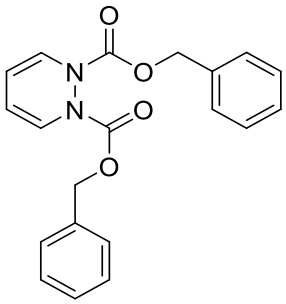
^{13}C NMR (100 MHz, 298 K, d6 -DMSO, additional peaks due to complex rate processes denoted by an asterisk); δ 151.8* (**C3**), 150.8 (**C3**), 127.6 (**C1**), 111.9* (**C2**), 111.6 (**C2**), 111.1* (**C2**), 81.9 (**C4**), 27.6 (**C5**).

^{13}C NMR (100 MHz, 348 K, d_6-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: $C_{14}H_{22}N_2O_4$ $[M+Na]^+$ 305.1472, found 305.1469.

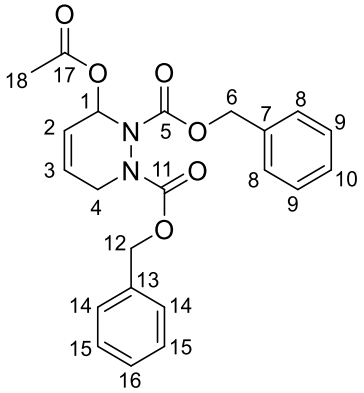
Dibenzyl-1,2-dihydropyridazine-1,2-dicarboxylate 9e



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 CH_2Cl_2 (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**



R_f (Hexane-EtOAc, 2:1) = 0.22

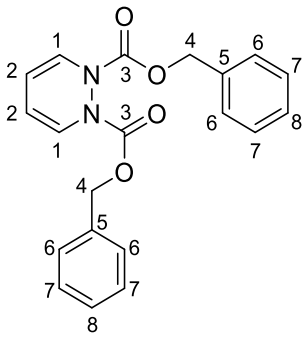
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.34-7.29 (br m, 10H, **H8**, **H9**, **H10**, **H14**, **H15** and **H16**), 6.94-6.87 (br m, 1H, **H1**), 6.10 (br dd, *J* = 9.9, 4.1 Hz, 1H, **H3**), 5.92-5.84 (br m, 1H, **H2**), 5.25-5.01 (br m, 4H, **H6** and **H12**), 4.68-4.48 (m, 1H, **H4$_A$**), 3.98-3.69 (br 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); δ 169.6 (**C17**), 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**), 128.1 (**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) ν (cm^{-1}): 3032, 1709 (C=O).

HRMS (ESI): *m*/*z* calculated for: $C_{22}H_{22}N_2O_6$ $[M+Na]^+$ 433.1370, found 433.1349.

1,2-Dihydropyridazine **9e**



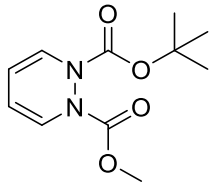
R_f (Hexane-EtOAc, 2:1) = 0.37

^{1}H NMR (400 MHz, 298 K, d_6-DMSO); δ 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, d_6-DMSO); δ 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**).

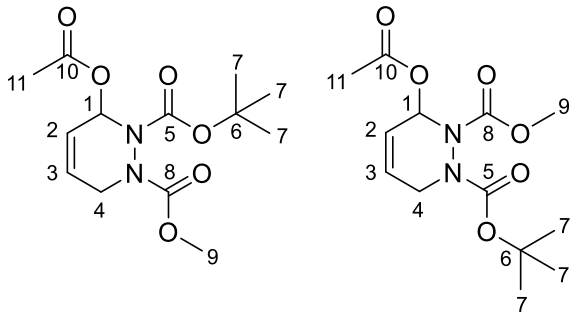
^{13}C NMR (100 MHz, 298 K, d6 -DMSO, additional peaks due to complex rate processes denoted by an asterisk); δ 153.2 (**C3**), 152.4* (**C3**), 135.6 (**C5**), 128.5 (**C6**, **C7** or **C8**), 128.2 (**C6**, **C7** or **C8**), 127.7 (**C6**, **C7**, **C8** or **C1**), 127.2 (**C6**, **C7**, **C8** or **C1**), 113.4* (**C2**), 112.2 (**C2**), 67.8 (**C4**).
^{13}C NMR (100 MHz, 348 K, d_6-DMSO); δ 152.6 (**C3**), 135.3 (**C5**), 128.0 (**C6**, **C7** or **C8**), 127.7 (**C6**, **C7** or **C8**), 127.2 (**C6**, **C7**, **C8**), 127.0 (**C1**), 112.3 (**C2**), 67.4 (**C4**).
FTIR (ATR) ν (cm^{-1}): 3032, 2954, 1716 (C=O).
HRMS (ESI): *m/z* calculated for: $C_{20}H_{18}N_2O_4$ $[M+Na]^+$ 373.1159, found 373.1148.

1-t*ert*-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 CH_2Cl_2 (5.3 mL) was stirred at 40 °C for 24 hours. After being passed through a short silica gel column (eluent: hexane-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-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-EtOAc, 2:1) = 0.24

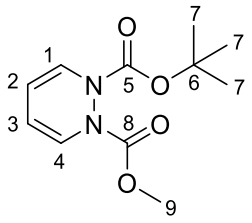
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.88-6.75 (br m, 1H, **H1**), 6.11-6.02 (br m, 1H, **H3**), 5.92-5.81 (br m, 1H, **H2**), 4.61-4.38 (br m, 1H, **H4$_A$**), 3.81-3.66 (m, 4H, **H4$_B$**, **H9**), 2.08-2.00 (m, 3H, **H11**), 1.48-1.44 (br m, 9H, **H7**).

^{13}C NMR (100 MHz, $CDCl_3$, additional peaks due to regioisomers and complex rate processes denoted by an asterisk); δ 169.6* (**C10**), 169.6 (**C10**), 154.3 (**C5**, **C8**), 129.4 (**C3**), 122.1 (**C2**), 81.9* (**C6**), 81.4 (**C6**), 73.7 (**C1**), 53.8 (**C8**), 53.4* (**C8**), 42.6* (**C4**), 42.2 (**C4**), 28.3 (**C7**), 28.2* (**C7**), 21.0 (**C11**), 21.0* (**C11**), 20.6* (**C11**).

FTIR (ATR) ν (cm^{-1}): 2980, 1709 (C=O).

HRMS (ESI): *m/z* calculated for: $C_{13}H_{20}N_2O_6$ $[M+Na]^+$ 323.1214, found 323.1203.

1,2-Dihydropyridazine **9f**



R_f (Hexane-EtOAc, 2:1) = 0.37

mp = 70-72 ˚C

^{1}H NMR (400 MHz, 298 K, d_6-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**).

^{1}H NMR (400 MHz, 348 K, d_6-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**).

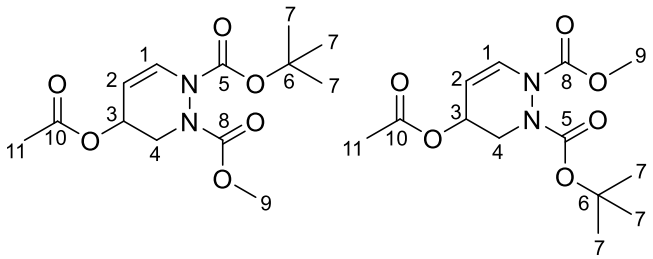
^{13}C NMR (100 MHz, 298 K, d6 -DMSO, additional peaks due to complex rate processes denoted by an asterisk); δ 153.7 (**C5** or **C8**), 152.8* (**C5** or **C8**), 151.8 (**C5** or **C8**), 127.8 (**C1** or **C4**), 127.0 (**C1** or **C4**), 113.0* (**C2** or **C3**), 112.1 (**C2** or **C3**), 111.1 (**C2** or **C3**), 82.3 (**C6**), 53.5 (**C9**), 27.6 (**C7**).

^{13}C NMR (100 MHz, 348 K, d_6-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**).

FTIR (ATR) ν (cm^{-1}): 2984, 1748 (C=O), 1716 (C=O).

HRMS (APCI): *m/z* calculated for: $C_{11}H_{16}N_2O_4$ $[M-H]^-$ 239.1037, found 239.1029.

Rearranged Allylic Acetate **209f**



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

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

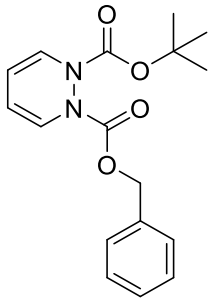
^{1}H NMR (400 MHz, 348 K, d_6-DMSO); δ 7.22-7.14 (br m, 1H, **H1**), 5.21-5.12 (br m, 1H **H2**), 5.06-5.00 (br m, 1H, **H3**), 4.52-4.26 (br m, 1H, **H4$_A$**), 3.75-3.71 (b m, 3H, **H9**), 3.47-3.22 (br m, 1H, **H4$_B$**), 2.04-1.90 (br m, 3H, **H11**), 1.46-1.43 (br m, 9H, **H7**).

^{13}C NMR (100 MHz, 348 K, d_6-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) ν (cm^{-1}): 2958, 1718 (C=O), 1648 (C=O).

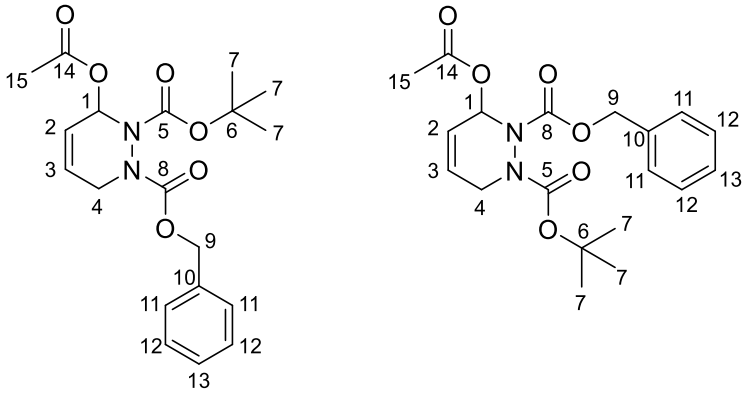
HRMS (ESI): *m*/*z* calculated for: $C_{13}H_{20}N_2O_6$ $[M+Na]^+$ 323.1214, found 323.1205.

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 CH_2Cl_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), $Pd(OAc)_2$ (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.

Cycloadduct **203g**



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

R_f (Hexane-EtOAc, 2:1) = 0.28

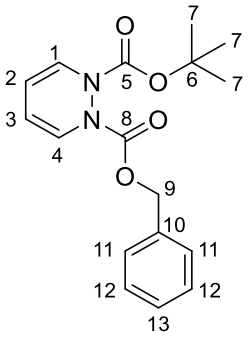
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.36-7.28 (br m, 10H, **H11**, **H12**, **H13**), 6.92-6.80 (br m, 1H, **H1**), 6.09-6.02 (br m, 1H, **H3**), 5.93-5.79 (br m, 1H, **H2**), 5.28-5.11 (br m, 2H, **H9**), 4.63-4.38 (m, 1H, $\mathbf{H4_A}$), 3.91-3.66 (br m, 1H, $\mathbf{H4_B}$), 2.06-1.79 (br m, 3H, **H15**), 1.47-1.34 (br m, 9H, **H7**).

^{13}C NMR (100 MHz, $CDCl_3$, additional peaks due to regioisomers and complex rate processes denoted by an asterisk); δ 169.6 (**C14**), 169.4* (**C14**), 155.4* (**C5** or **C8**), 154.4 (**C5** or **C8**), 136.1* (**C10**), 135.7 (**C10**), 129.4 (**C3**), 128.6 (**C11, C12** or **C13**), 128.5 (**C11, C12** or **C13**), 128.4* (**C11, C12** or **C13**), 128.2* (**C11, C12** or **C13**), 127.7 (**C11, C12** or **C13**), 122.1 (**C2**), 81.4 (**C6**), 73.8 (**C1**), 68.3 (**C9**), 67.9* (**C9**), 42.7 (**C4**), 42.3* (**C4**), 28.1 (**C7**), 21.0 (**C15**), 20.7* (**C15**).

FTIR (ATR) ν (cm^{-1}): 2978, 1735 (C=O), 1707 (C=O).

HRMS (ESI): *m/z* calculated for: $C_{19}H_{24}N_2O_6$ $[M+Na]^+$ 399.1527, found 399.1516.

1,2-Dihydropyridazine **9g**



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

^{1}H NMR (400 MHz, 298 K, d_6-DMSO); δ 7.43-7.27 (br m, 5H, **H11**, **H12**, **H13**), 6.86-6.68 (br m, 2H, **H1**, **H4**), 5.89-5.67 (br m, 2H, **H2**, **H3**), 5.37-5.04 (br m, 2H, **H9**), 1.50-1.19z (br s, 9H, **H7**).

^{1}H NMR (400 MHz, 348 K, d_6-DMSO); δ 7.40-7.31 (br m, 5H, **H11**, **H12**, **H13**), 6.78-6.72 (m, 2H, **H1**, **H4**), 5.81-5.73 (m, 2H, **H2**, **H3**), 5.26-5.18 (m, 2H, **H9**), 1.41 (s, 9H, **H7**).

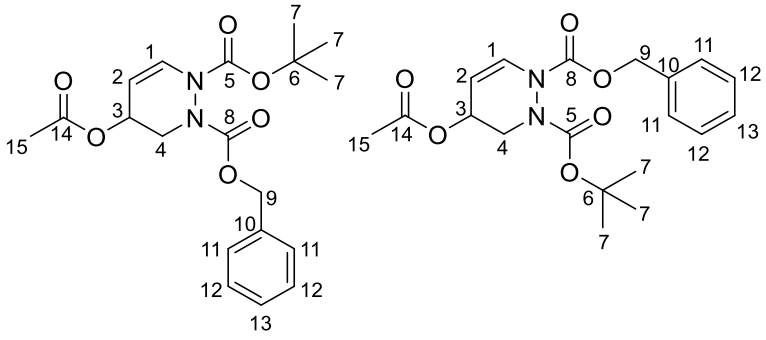
^{13}C NMR (100 MHz, 298 K, d6 -DMSO, additional peaks due to complex rate processes denoted by an asterisk); δ 153.2 (**C5** or **C8**), 152.3 (**C5** or **C8**), 135.7 (**C10**), 128.4 (**C11, C12** or **C13**), 128.2 (**C11, C12** or **C13**), 127.8 (**C11, C12** or **C13**), 127.4 (**C1** or **C4**), 126.9 (**C1** or **C4**), 113.1* (**C2** or **C3**), 112.3 (**C2** or **C3**), 111.2* (**C2** or **C3**), 82.4 (**C6**), 67.5 (**C9**), 27.6 (**C7**).

^{13}C NMR (100 MHz, 348 K, d_6-DMSO); δ 152.5 (**C8**), 151.3 (**C5**), 135.4 (**C10**), 128.0 (**C11, C12** or **C13**), 127.7 (**C11, C12** or **C13**), 127.5 (**C1** or **C4**), 127.3 (**C11, C12** or **C13**), 126.7 (**C1** or **C4**), 112.2 (**C2** or **C3**), 111.5 (**C2** or **C3**), 82.0 (**C6**), 67.2 (**C9**), 27.3 (**C7**).

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

HRMS (ESI): *m/z* calculated for: $C_{17}H_{20}N_2O_4$ $[M+Na]^+$ 339.1315, found 339.1316.

Rearranged Allylic Acetate **209g**



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

R_f (Hexane-EtOAc, 2:1) = 0.34

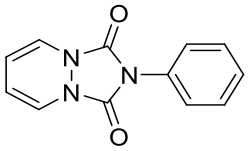
^{1}H NMR (400 MHz, 348 K, d_6-DMSO); δ 7.39-7.18 (br m, 6H, **H1**, **H11**, **H12**, **H13**), 5.27-5.13 (br m, 3H, **H2**, **H9**), 5.05-5.01 (br m, 1H, **H3**), 4.53-4.33 (br m, 1H, $\mathbf{H4_A}$), 3.54-3.23 (br m, 1H, $\mathbf{H4_B}$), 2.04-1.84 (br m, 3H, **H15**), 1.48-1.27 (br m, 9H, **H7**).

^{13}C NMR (100 MHz, 348 K, d_6-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).

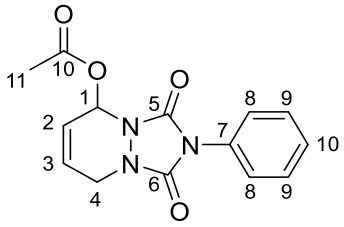
HRMS (ESI): *m*/*z* calculated for: $C_{19}H_{24}N_2O_6$ $[M+Na]^+$ 399.1527, found 399.1521.

2-Phenyl-[1,2,4]triazolo[1,2-a]pyridazine-1,3-dione 9h[165]



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 CH_2Cl_2 (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**



R_f (Hexane-EtOAc, 1:1) = 0.23

mp = 130-132 ˚C

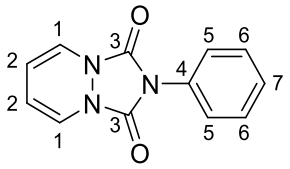
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.55-7.45 (m, 4H, **H7**, **H8**), 7.41-7.37 (m, 1H, **H9**), 6.82-6.81 (m, 1H, **H1**), 6.26-6.22 (m, 1H, **H3**), 6.16-6.12 (m, 1H, **H2**), 4.52 (ddd, *J* = 17.2, 4.6, 1.7, 1H, **H4$_A$**), 4.07-4.02 (m, 1H, **H4$_B$**), 2.08 (s, 3H, **H11**).

^{13}C NMR (100 MHz, $CDCl_3$); 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:$C_{12}H_{10}N_3O_2$ $[M-OAc]^+$ 228.0768, found 228.0775.

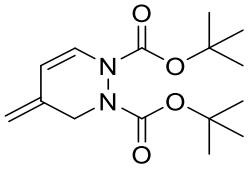
1,2-Dihydropyridazine **9h**



^{1}H NMR (400 MHz, $CDCl_3$); δ 7.54-7.38 (br m, 5H, **H5**, **H6**, **H7**), 6.88 (br dd, *J* = 6.1, 2.7 Hz, 2H, **H1**), 5.34 (br dd, *J* = 6.1, 2.7 Hz, 2H, **H2**).

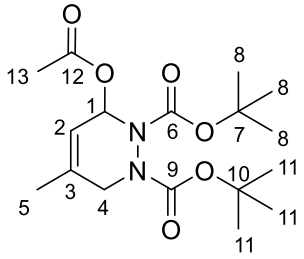
^{13}C NMR (100 MHz, $CDCl_3$); δ 142.7 (**C3**), 131.0 (**C4**), 129.4 (**C5**), 128.7 (**C7**), 125.8 (**C6**), 120.9 (**C1**), 105.2 (**C2**).

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_2Cl_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), $Pd(OAc)_2$ (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**



R_f (Hexane-EtOAc, 2:1) = 0.35

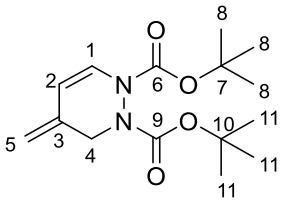
^{1}H NMR (400 MHz, d_6-DMSO); δ 6.69-6.62 (m, 1H, **H1**), 5.62-5.54 (m, 1H, **H2**), 4.27-4.09 (m, 1H, $\mathbf{H4_A}$), 3.72-3.53 (m, 1H, $\mathbf{H4_B}$), 2.01 (br s, 3H, **H13**), 1.73 (br s, 3H, **H5**), 1.46-1.35 (m, 18H, **H8** and **H11**).

^{13}C NMR (100 MHz, d_6-DMSO, additional peaks due to complex rate processes denoted by an asterisk); δ 168.8 (**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**).

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

HRMS (ESI): *m/z* calculated for: $C_{17}H_{28}N_2O_6$ $[M+Na]^+$ 379.1840, found 379.1825.

Diene **216**



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

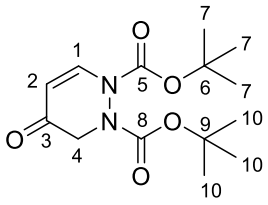
^{1}H NMR (400 MHz, 348 K, d_6-DMSO); δ 6.98 (br d, J = 8.0 Hz, 1H, **H1**), 5.63 (br d, J = 8.0 Hz, 1H, **H2**), 4.91-4.88 (br m, 1H, **H5$_A$**), 4.77-4.74 (br m, 1H, **H5$_B$**), 4.57 (br d, J = 15.3 Hz, 1H, **H4$_A$**), 3.74 (br d, J = 15.3 Hz, 1H, **H4$_B$**), 1.47-1.39 (br m, 18H, **H8** and **H11**).

^{13}C NMR (100 MHz, 348 K, d_6-DMSO); δ 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) ν (cm^{-1}): 2978, 2933, 1713 (C=O).

HRMS (APCI): *m/z* calculated for: $C_{15}H_{24}N_2O_4$ $[M+Na]^+$ 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_2Cl_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 ˚C

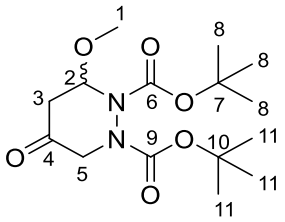
^{1}H NMR (400 MHz, 348 K, d_6-DMSO); δ 8.11 (br d, J = 8.6 Hz, 1H, **H1**), 5.40 (br d, J = 8.6 Hz, 1H, **H2**), 4.41-3.95 (br m, 2H, **H4$_A$** and **H4$_B$**), 1.51 (s, 9H, **H7** or **H9**), 1.42 (s, 9H, **H7** or **H9**).

^{13}C NMR (100 MHz, 348 K, d_6-DMSO); δ 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) ν (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



R_f (Hexane-EtOAc, 2:1) = 0.39

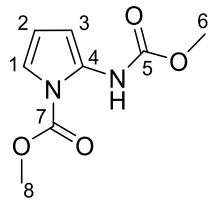
^{1}H NMR (400 MHz, 348 K, d_6-DMSO); δ 5.49-5.45 (br m, 1H, **H2**), 4.41-4.30 (br m, 1H, **H5$_A$**), 3.68-3.59 (br m, 1H, **H5$_B$**), 3.37 (br s, 3H, **H1**), 2.89 (br dd, *J* = 16.1, 6.4 Hz, **H3$_A$**), 2.56 (br dd, *J* = 16.1, 3.9 Hz, **H3$_B$**), 1.47-1.42 (br m, 18H, **H8** and **H11**).

^{13}C NMR (100 MHz, 348 K, d_6-DMSO); δ 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**).

FTIR (ATR) ν (cm^{-1}): 2978, 2933, 1730 (C=O), 1708 (C=O).

HRMS (APCI): *m*/*z* calculated for: $C_{15}H_{26}N_2O_6$ $[M+Na]^+$ 353.1683, found 353.1697.

Methyl 2-[(methoxycarbonyl)amino]-1*H*-pyrrole-1-carboxylate 210a[33]



Using general procedure I, a solution of 1,2-dihydropyridazine **9a** (520 mg, 2.62 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→9:1) gave 2-aminopyrrole **210a** (320 mg, 1.61 mmol, 62%) as a colourless solid.

R_f (Hexane-EtOAc, 2:1) = 0.35

mp = 46-47 ˚C

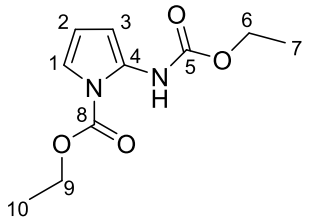
^{1}H NMR (400 MHz, $CDCl_3$); δ 9.05 (br s, 1H, **NH**), 6.85 (dd, *J* = 3.6, 1.8 Hz, 1H, **H1**), 6.42-6.32 (br m, 1H, **H3**), 6.13 (t, *J* = 3.6 Hz, 1H, **H2**), 3.95 (s, 3H, **H8**), 3.77 (s, 3H, **H6**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 153.1 (**C5**), 152.4 (**C7**), 130.5 (**C4**), 114.0 (**C1**), 111.6 (**C2**), 98.4 (**C3**), 54.2 (**C8**), 52.6 (**C6**).

FTIR (ATR) ν (cm^{-1}): 3349 (NH), 2950, 1724 (C=O).

HRMS (APCI): *m*/*z* calculated for: $C_8H_{10}N_2O_4$ $[M+H]^+$ 199.0713, found 199.0712.

Ethyl 2-[(ethoxycarbonyl)amino]-*1H*-pyrrole-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, $CDCl_3$) δ 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, $CDCl_3$) δ 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**).

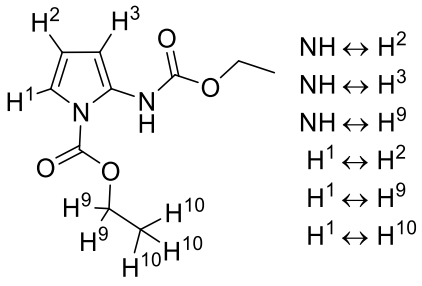
^{1}H NMR (400 MHz, d_6-DMSO) δ 8.92 (br s, 1H, **NH**), 7.07 (dd, *J* = 3.6, 1.9 Hz, 1H, **H1**), 6.15 (t, *J* = 3.6 Hz, 1H, **H2**), 6.10-6.06 (br m, 1H, **H3**), 4.32 (q, *J* = 7.1 Hz, 2H, **H9**), 4.08 (q, *J* = 7.1 Hz, 2H, **H6**), 1.30 (t, *J* = 7.1 Hz, 3H, **H10**), 1.20 (t, *J* = 7.1 Hz, 3H, **H7**).

^{13}C NMR (100 MHz, d_6-DMSO) δ 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**).

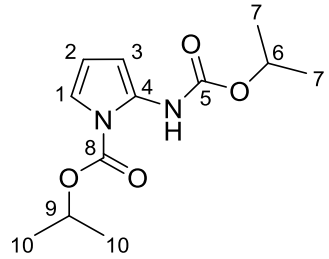
FTIR (ATR) ν (cm^{-1}): 3345 (NH), 3145 (NH), 2980, 1718 (C=O).

HRMS (ESI): *m*/*z* calculated for: $C_{10}H_{14}N_2O_4$ $[M+H]^+$ 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 (Hexane-EtOAc, 2:1) = 0.58

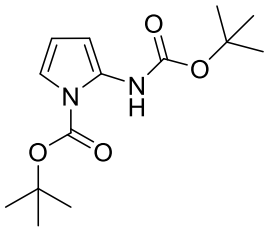
^{1}H NMR (400 MHz, $CDCl_3$); δ 9.08 (br s, 1H, **NH**), 6.85 (dd, *J* = 3.6, 1.8 Hz, 1H, **H1**), 6.40-6.32 (br m, 1H, **H3**), 6.12 (t, *J* = 3.5 Hz, 1H, **H2**), 5.16 (sept, *J* = 6.2 Hz, 1H, **H9**), 5.00 (sept, *J* = 6.2 Hz, 1H, **H6**), 1.39 (d, *J* = 6.2 Hz, 6H, **H10**), 1.29 (d, *J* = 6.2 Hz, 6H, **H7**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 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) ν (cm^{-1}): 3366 (NH), 2982, 1720 (C=O).

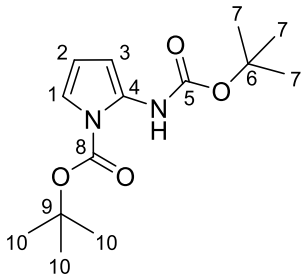
HRMS (APCI): *m*/*z* calculated for: $C_{12}H_{18}N_2O_4$ $[M+Na]^+$ 277.1159, found 277.1154.

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



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 (Hexane-EtOAc, 2:1) = 0.58

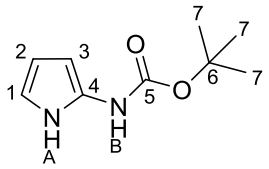
^{1}H NMR (400 MHz, $CDCl_3$); δ 9.00 (br s, 1H, **NH**), 6.79 (dd, *J* = 3.5, 1.8 Hz, 1H, **H1**), 6.35-6.29 (br m, 1H, **H3**), 6.08 (t, *J* = 3.5 Hz, 1H, **H2**), 1.59 (s, 9H, **H7** or **H10**), 1.50 (s, 9H, **H7** or **H10**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 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) ν (cm^{-1}): 3366 (NH), 2982, 1720 (C=O).

HRMS (APCI): *m*/*z* calculated for: $C_{12}H_{18}N_2O_4$ $[M+Na]^+$ 277.1159, found 277.1154.

2-Aminopyrrole **220d**



R_f (Hexane-EtOAc, 2:1) = 0.50

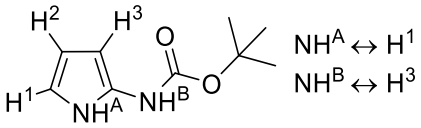
^{1}H NMR (400 MHz, $CDCl_3$); δ 9.60 (br s, 1H, **NH_A**), 7.26 (br s, 1H, **NH_B**), 6.50-6.45 (m, 1H, **H1**), 6.07 (m, 1H, **H2**), 5.61-5.51 (m, 1H, **H3**), 1.52 (s, 9H, **H7**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 153.4 (**C5**), 128.1 (**C4**), 112.1 (**C1**), 107.0 (**C2**), 92.5 (**C3**), 81.1 (**C6**), 28.4 (**C**).

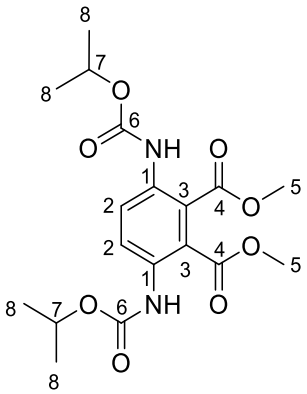
FTIR (ATR) ν (cm^{-1}): 3452 (NH), 3314 (NH), 2980, 1679 (C=O).

HRMS (ESI): *m/z* calculated for: $C_9H_{14}N_2O_2$ $[M+H]^+$ 183.1128, found 183.1127.

Important NOE Contacts



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 (Hexane-EtOAc, 2:1) = 0.4

Mp = 118-120 °C

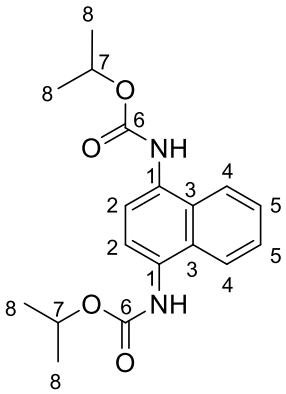
^{1}H NMR (400 MHz, $CDCl_3$); δ 8.42 (br s, 2H, **NH**), 8.31 (s, 2H, **H2**), 4.99 (sept, *J* = 6.3 Hz, 2H, **H7**), 3.87 (s, 6H, **H5**), 1.29 (d, *J* = 6.3 Hz, 12H, **H8**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 167.9 (**C4**), 153.4 (**C6**), 133.6 (**C1**), 124.7 (**C2**), 119.4z (**C3**), 69.3 (**C7**), 53.0 (**C5**), 22.2 (**C8**).

FTIR (ATR) ν (cm^{-1}): 3343 (NH), 3308 (NH), 2984, 1720 ($C=O_{ester}$), 1705 ($C=O_{carbamate}$).

HRMS (APCI): *m/z* calculated for: $C_{18}H_{24}N_2O_8$ $[M-H]^-$ 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.

R_f (Hexane-EtOAc, 2:1) = 0.26

mp = 187-189 ˚C (decomposition)

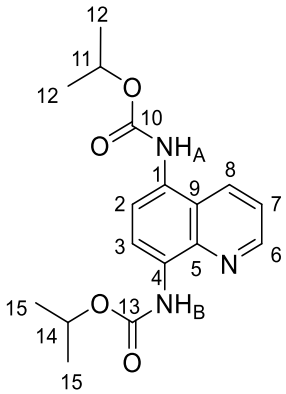
^{1}H NMR (400 MHz, d_6-DMSO); δ 9.37 (br s, 2H, **NH**), 8.02 (br dd, *J* = 6.5, 3.3 Hz, 2H, **H4**), 7.54 (br dd, *J* = 6.5, 3.3 Hz, 2H, **H5**) 7.51-7.49 (m, 2H, **H2**), 4.91 (sept, *J* = 6.2 Hz, 2H, **H7**), 1.28 (br d, *J* = 6.2 Hz, 12H, **H8**).

^{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).

HRMS (ESI): *m/z* calculated for: $C_{18}H_{22}N_2O_4$ $[M+Na]^+$ 353.1472, found 353.1458.

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

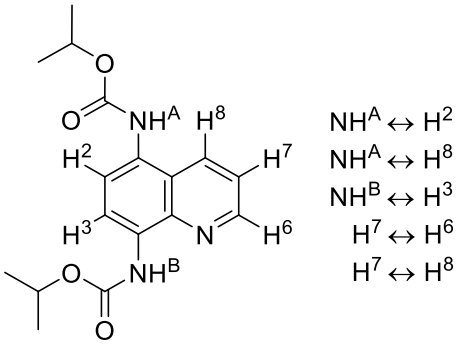
^{1}H NMR (400 MHz, d_6-DMSO); δ 9.44 (br s, 1H, **NH_A**), 9.05 (br s, 1H, **NH_B**), 8.89 (dd, *J* = 4.2, 1.6 Hz, 1H, **H6**), 8.44 (dd, *J* = 8.6, 1.6 Hz, 1H, **H8**), 8.21 (d, *J* = 8.4 Hz, 1H, **H3**), 7.65 (dd, *J* = 8.6, 4.2 Hz, 1H, **H7**), 7.60 (d, *J* = 8.4 Hz, 1H, **H2**), 5.01-4.86 (m, 2H, **H11** and **H14**), 1.33-1.24 (m, 12H, **H12** and **H15**).

^{13}C NMR (100 MHz, d_6-DMSO); δ 154.6 (**C10** or **C13**), 152.5 (**C10** or **C13**), 148.8 (**C6**), 137.7 (**C5**), 132.3 (**C8**), 131.5 (**C4**), 127.8 (**C1**), 123.3 (**C9**), 122.1 (**C2**), 121.8 (**C7**), 114.2 (**C3**), 68.3 (**C11** or **C14**), 67.8 (**C11** or **C14**), 22.0 (**C12** or **C15**), 21.9 (**C12** or **C15**).

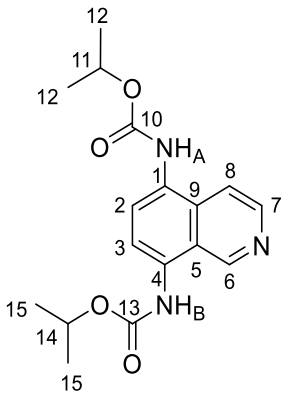
FTIR (ATR) ν (cm^{-1}): 3375 (NH), 3278 (NH), 2978, 1724 (C=O), 1689 (C=O).

HRMS (ESI): *m*/*z* calculated for: $C_{17}H_{21}N_3O_4$ $[M+H]^+$ 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

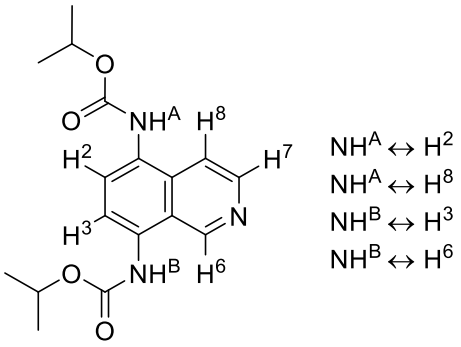
^{1}H NMR (400 MHz, d_6-DMSO); δ 9.73 (br s, 1H, **NH_B**), 9.52 (br s, 1H, **NH_A**), 9.39 (br s, 1H, **H6**), 8.51 (d, *J* = 5.8 Hz, 1H, **H7**), 7.88 (dd, *J* = 5.8, 0.6 Hz, 1H, **H8**), 7.80 (d, *J* = 8.3 Hz, 1H, **H2**), 7.67 (d, *J* = 8.3 Hz, 1H, **H3**), 4.98-4.87 (m, 2H, **H11** and **H14**), 1.31-1.25 (m, 2H, **H12** and **H15**).

^{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**).

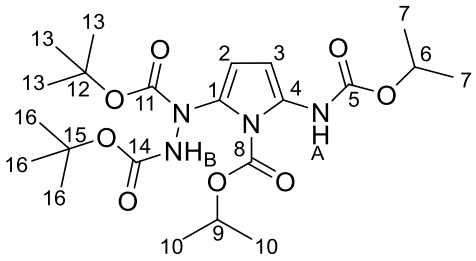
FTIR (ATR) ν (cm^{-1}): 3269 (NH), 2978, 1728 (C=O), 1694 (C=O).

HRMS (ESI): *m*/*z* calculated for: $C_{17}H_{21}N_3O_4$ $[M+H]^+$ 332.1605, found 332.1591.

Important NOE Contacts



Di-*tert*-butyl-1-{1-(isopropyloxy)carbonyl-5-[(isopropyloxycarbonyl)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, 2H, **NH$_A$** and **NH$_B$**), 6.10-6.05 (br m, 1H, **H2**), 5.98-5.90 (br m, 1H, **H3**), 5.01-4.95 (m, 1H, **H6** or **H9**), 4.83-4.77 (m, 1H, **H6** or **H9**), 1.47-1.17 (m, 30H, **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**), 153.2* (**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**).

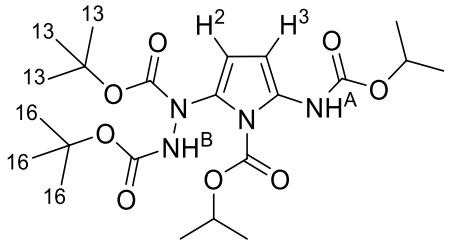
^{1}H NMR (400 MHz, 348 K, d_6-DMSO); δ 8.72 (s, 1H, **NH_A**), 8.38 (br s, 1H, **NH_B**), 6.11 (d, *J* = 3.7 Hz, 1H, **H2**), 5.97 (br dd, *J* = 3.7, 0.4 Hz, 1H, **H3**), 5.03 (sept, *J* = 6.3 Hz, 1H, **H6** or **H9**), 4.84 (sept, *J* = 6.3 Hz, 1H, **H6** or **H9**), 1.45-1.35 (m, 18H, **H13** and **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_6-DMSO, additional peaks due to rotamers denoted by an asterisk); δ 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**), 27.7 (**C13** or **C16**), 27.4 (**C13** or **C16**), 21.4 (**C7** or **C10**), 20.8 (**C7** or **C10**).

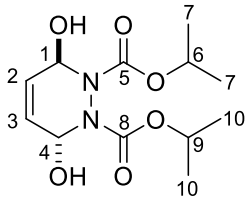
FTIR (ATR) ν (cm^{-1}): 3364 (NH), 2980, 1718 (C=O).

HRMS (ESI): *m*/*z* calculated for: $C_{22}H_{36}N_4O_8$ $[M+H]^+$ 485.2606 and $[M+Na]^+$ 507.2425, found 485.2585 and 507.2401, respectively.

Important NOE contacts



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

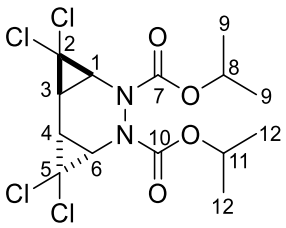
^{1}H NMR (400 MHz, 328 K, $CDCl_3$); δ 6.03-5.98 (m, 2H, **H2** and **H3**), 5.94-5.85 (br m, 2H, **H1** and **H4**), 4.97 (sept, *J* = 6.3 Hz, 2H, **H6** and **H9**), 1.26 (br d, *J* = 6.3 Hz, 12H, **H7** and **H10**).

^{13}C NMR (100 MHz, 328 K, $CDCl_3$); δ 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) ν (cm^{-1}): 3416 (OH), 2982, 1679 (C=O).

HRMS (ESI): *m*/*z* calculated for: $C_{12}H_{20}N_2O_6$ $[M+Na]^+$ 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_4Cl (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

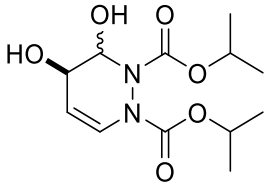
^{1}H NMR (400 MHz, $CDCl_3$); δ 5.04-4.94 (m, 2H, **H8** and **H11**), 3.63-3.54 (m, 2H, **H1** and **H6**), 2.15-2.11 (m, 2H, **H3** and **H4**), 1.35-1.23 (m, 12H, **H9** and **H12**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 153.2 (**C7** and **C10**), 71.5 (**C8** and **C11**), 63.0 (**C2** and **C5**), 42.2 (**C1** and **C6**), 25.8 (**C3** and **C4**), 22.3 (**C8** or **C11**), 21.8 (**C8** or **C11**).

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

HRMS (APCI): *m*/*z* calculated for: $C_{14}H_{18}N_2O_4Cl_4$ $[M+H]^+$ 419.0093, found 419.0079.

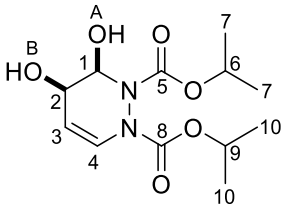
Diisopropyl 3,4-dihydroxy-3,4-dihydropyridazine-1,2-dicarboxylate 242 and 243



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 ^{t}BuOH, 0.2 mL, 0.02 mmol, 0.05 eq) in acetone:H_2O (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 $Na_2S_2O_3$ (5 mL) and extracted with CH_2Cl_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**



R_f (Hexane-EtOAc, 1:1) = 0.14

mp = 104-106˚C

^{1}H NMR (400 MHz, d_6-DMSO); δ 6.81-6.44 (br m, 2H, **H4** and **OH$_A$**), 5.51-5.38 (br m, 1H, **H1**), 4.99-4.93 (br m, 1H, **OH$_B$**), 4.87-4.71 (br m, 3H, **H3**, **H6** and **H9**), 4.10-4.04 (br m, 1H, **H2**), 1.24-1.19 (m, 12H, **H7** and **H10**).

^{13}C NMR (100 MHz, d_6-DMSO, **C1** not visible, additional peaks due to complex rate processes denoted by an asterisk); δ 152.6 (**C5** or **C8**), 151.3 (**C5** or **C8**), 123.7 (**C4**), 108.4 (**C3**), 70.1* (**C6** or **C9**), 69.9 (**C6** or **C9**), 62.6* (**C2**), 62.4 (**C2**), 21.7* (**C7** or **C10**), 21.6 (**C7** or **C10**), 21.6 (**C7** or **C10**).

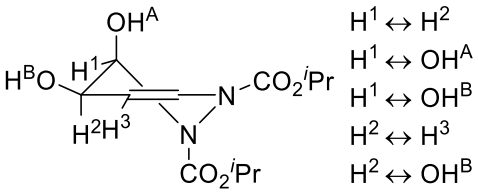
^{1}H NMR (400 MHz, 348 K, d_6-DMSO); δ 6.77 (br d, J = 8.0 Hz, 1H, **H4**), 6.22-6.11 (br m, 1H, **OH$_A$**), 5.50-5.47 (br m, 1H, **H**), 4.91-4.77 (br m, 3H, **H3**, **H6** and **H9**), 4.66 (br d, J = 7.7 Hz, 1H, **OH$_B$**), 4.13-4.09 (br m, 1H, **H2**), 1.25-1.20 (m, 12H, **H7** and **H10**).

^{13}C NMR (100 MHz, 348 K, d_6-DMSO, additional peaks due to complex rate processes denoted by an asterisk); δ 152.9 (**C5** or **C8**), 123.7 (**C4**), 108.2 (**C3**), 74.1 (**C1**), 69.6 (**C6** or **C9**), 69.3 (**C6** or **C9**), 62.2 (**C2**), 21.4* (**C7** or **C10**), 21.3* (**C7** or **C10**), 21.3 (**C7** or **C10**), 21.2* (**C7** or **C10**), 21.2* (**C7** or **C10**), 21.2 (**C7** or **C10**).

FTIR (ATR) ν (cm^{-1}): 3424 (OH), 2980, 1687 (C=O).

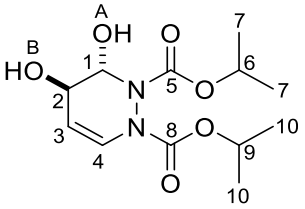
HRMS (APCI): *m/z* calculated for: $C_{12}H_{20}N_2O_6$ $[M+Na]^+$ 311.1214, found 311.1199.

Important NOE Contacts



No cross peak between H^2 ↔ OH^A

trans-Diol **243**



R_f (Hexane-EtOAc, 1:1) = 0.08

mp = 104-106˚C

^{1}H NMR (400 MHz, d_6-DMSO); δ 7.02-6.88 (br m, 1H, **H4**) 6.52-6.35 (br m, 1H **OH_A**), 5.59-5.44 (br m, 1H, **H1**), 5.11-5.08 (br m, 1H, **OH_B**), 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, d_6-DMSO, additional peaks due to complex rate processes denoted by an asterisk); δ 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**).

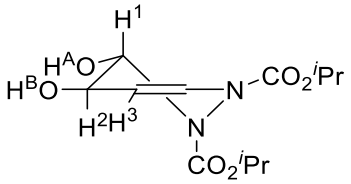
^{1}H NMR (400 MHz, 348 K, d_6-DMSO); δ 6.95 (br d, J = 7.9 Hz, 1H, **H4**), 6.18-6.12 (br m, 1H, **OH_A**), 5.60-5.52 (br m, 1H, **H1**), 5.07-5.00 (br m, 1H, **H3**), 4.89-4.79 (br m, 3H, **H6**, **H9** and **OH_B**), 3.75-3.71 (br m, 1H, **H2**), 1.29-1.17 (m, 12H, **H7** and **H10**).

^{13}C NMR (100 MHz, 348 K, d_6-DMSO, additional peaks due to complex rate processes denoted by an asterisk); δ 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) ν (cm^{-1}): 3422 (OH), 2984, 1702 (C=O), 1649 (C=O).

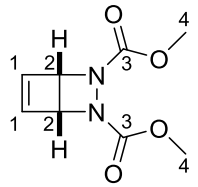
HRMS (APCI): *m/z* calculated for: $C_{12}H_{20}N_2O_6$ $[M+Na]^+$ 311.1214, found 311.1199.

Important NOE Contacts



$H^1 \leftrightarrow H^2$
$H^1 \leftrightarrow OH^A$
$H^1 \leftrightarrow OH^B$
$H^2 \leftrightarrow H^3$
$H^2 \leftrightarrow OH^A$
$H^2 \leftrightarrow OH^B$

Dimethyl 2,3-diazabicyclo[2.2.0]hex-5-ene-2,3-dicarboxylate 10a[33,35]



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_f (Hexane-EtOAc, 2:1) = 0.1

mp = 76-78 ˚C

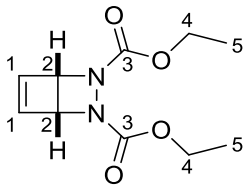
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.74-6.71 (m, 2H, **H1**), 5.21-5.18 (m, 2H, **H2**), 3.81 (s, 6H, **H4**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 160.6 (**C3**), 143.7 (**C1**), 67.5 (**C2**), 53.7 (**C4**).

FTIR (ATR) ν (cm^{-1}): 2961, 1743 (C=O), 1720 (C=O).

HRMS (ESI): *m*/*z* calculated for: $C_8H_{10}N_2O_4$ $[M+Na]^+$ 221.0533, found 221.0532.

Diethyl 2,3-diazabicyclo[2.2.0]hex-5-ene-2,3-dicarboxylate 10b[36]



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 (eulent: hexane-EtOAc, 7:1→4:1) gave the bicycle **10b** (121 mg, 0.54 mmol, 71%) as a pale yellow oil.

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

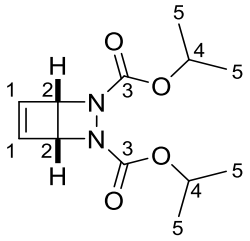
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76-6.68 (m, 2H, **H1**), 5.22-5.14 (m, 2H, **H2**), 4.31-4.17 (m, 4H, **H4**), 1.30 (t, *J* = 7.1 Hz, 6H, **H5**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1 (**C3**), 143.6 (**C1**), 67.3 (**C2**), 62.8 (**C4**), 14.6 (**C5**).

FTIR (ATR) ν (cm^{-1}): 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 (Hexane-EtOAc, 1:1) = 0.35

mp = 48-50 ˚C

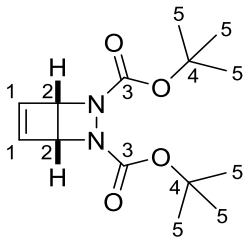
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.72-6.69 (m, 2H, **H1**), 5.17-5.14 (m, 2H, **H2**), 5.00 (sept, *J* = 6.3 Hz, 2H, **H4**), 1.29-1.27 (m, 12H, **H5**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 159.7 (**C3**), 143.5 (**C1**), 70.6 (**C4**), 67.1 (**C2**), 22.11 (**C5**), 22.09 (**C5**).

FTIR (ATR) ν (cm^{-1}): 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 (Hexane-EtOAc, 1:1) = 0.46

mp = 81-83 ˚C

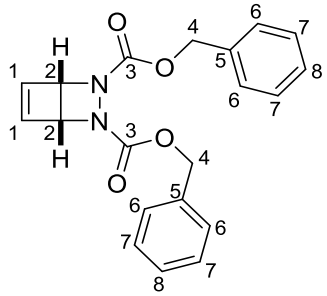
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.71-6.70 (m, 2H, **H1**), 5.09-5.08 (m, 2H, **H2**), 1.49 (s, 18H, **H5**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 159.0 (**C3**), 143.5 (**C1**), 82.1 (**C4**), 66.7 (**C2**), 28.3 (**C5**).

FTIR (ATR) ν (cm^{-1}): 2982, 2937, 1694 (C=O).

HRMS (APCI): *m/z* calculated for: $C_{14}H_{22}N_2O_4$ $[M+Na]^+$ 305.1472, 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 (Hexane-EtOAc, 2:1) = 0.28

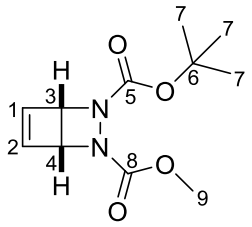
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.36-7.31 (m, 10H, **H6**, **H7**, **H8**), 6.66-6.63 (m, 2H, **H1**), 5.26-5.18 (m, 4H, **H2**, **H4**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 159.9 (**C3**), 143.6 (**C1**), 135.7 (**C5**), 128.6 (**C6** or **C7**), 128.4 (**C8**), 128.2 (**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: $C_{20}H_{18}N_2O_4$ $[M+Na]^+$ 373.1159, found 373.1142.

tert-Butyl methyl 2,3-diazabicyclo[2.2.0]hex-5-ene-2,3-dicarboxylate 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.

R_f (Hexane-EtOAc, 2:1) = 0.18

mp = 79-81 ˚C

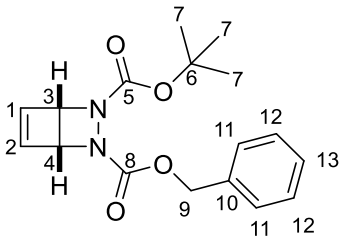
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.74-6.72 (m, 1H, **H1** or **H2**), 6.70-6.69 (m, 1H, **H1** or **H2**), 5.17-5.16 (m, 1H, **H3** or **H4**), 5.12-5.10 (m, 1H, **H3** or **H4**), 3.79 (s, 3H, **H9**), 1.49 (s, 9H, **H7**).

^{13}C NMR (100 MHz, $CDCl_3$); 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: $C_{11}H_{16}N_2O_4$ $[M+Na]^+$ 263.1002, found 263.0991.

Benzyl _tert_-butyl 2,3-diazabicyclo[2.2.0]hex-5-ene-2,3-dicarboxylate 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.

R_f (Hexane-EtOAc, 2:1) = 0.26

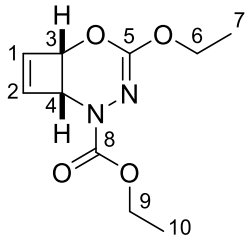
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.36-7.29 (m, 5H, **H11**, **H12**, **H13**), 6.70-6.69 (m, 1H, **H1** or **H2**), 6.67-6.65 (m, 1H, **H1** or **H2**), 5.25-5.21 (m, 2H, **H9**), 5.18-5.16 (m, 1H, **H3** or **H4**), 5.12-5.11 (m, 1H, **H3** or **H4**), 1.46 (s, 9H, **H7**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 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) ν (cm^{-1}): 2978, 2932, 1735 (C=O), 1702 (C=O).

HRMS (ESI): *m*/*z* calculated for: $C_{17}H_{20}N_2O_4$ $[M+Na]^+$ 339.1315, found 339.1310.

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 (Hexane-EtOAc, 1:1) = 0.34

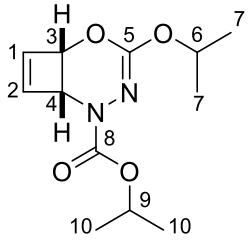
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.47-6.45 (br m, 1H, **H1**), 6.31-6.29 (br m, 1H, **H2**), 5.46 (br dd, *J* = 4.3, 2.4 Hz, 1H, **H3**), 5.18-5.11 (br m, 1H, **H4**), 4.30-4.17 (br m, 4H, **H6** and **H9**), 1.34-1.30 (br m, 6H, **H7** or **H10**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 154.1 (**C8**), 150.4 (**C5**), 142.0 (**C1**), 138.8 (**C2**), 79.4 (**C3**), 64.7 (**C6** or **C9**), 62.3 (**C6** or **C9**), 55.7 (**C4**), 14.7 (**C7** or **C10**), 14.2 (**C7** or **C10**).

FTIR (ATR) ν (cm^{-1}): 2982, 1735 (C=O), 1666 (C=N).

HRMS (APCI): *m*/*z* calculated for: $C_{10}H_{14}N_2O_4$ $[M+H]^+$ 227.1026, found 227.1017.

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 (Hexane-EtOAc, 2:1) = 0.25

mp = 48-50 ˚C

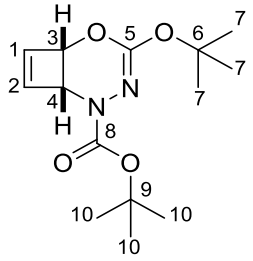
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.46-6.44 (br m, 1H, **H1**), 6.30-6.29 (br m, 1H, **H2**), 5.43 (br dd, *J* = 4.3, 2.4 Hz, 1H, **H3**), 5.15-5.11 (br m, 1H, **H4**), 5.04-4.93 (br m, 2H, **H6** and **H9**), 1.33-1.28 (br m, 6H, **H7** or **H10**).

^{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}): 2980, 1731 (C=O), 1657 (C=N).

HRMS (ESI): *m*/*z* calculated for: $C_{12}H_{18}N_2O_4$ $[M+Na]^+$ 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_f (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**).

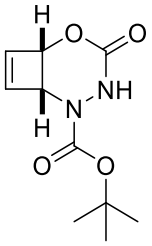
^{1}H NMR (400 MHz, d_6-DMSO); δ 6.57-6.38 (br m, 2H, **H1** and **H2**), 5.47-5.44 (br m, 1H, **H3**), 5.02-4.94 (br m, 1H, **H4**), 1.53-1.43 (br m, 18H, **H7** or **H10**).

^{13}C NMR (100 MHz, d_6-DMSO); δ 152.1 (**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: $C_{14}H_{22}N_2O_4$ $[M+Na]^+$ 305.1472, found 305.1469.

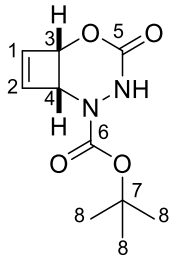
***tert*-Butyl 4-oxo-5-oxa-2,3-diazabicyclo[4.2.0]oct-7-ene-2-carboxylate 317d**



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 CH_2Cl_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. 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 CH_2Cl_2 (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 CH_2Cl_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. 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 (Hexane-EtOAc, 2:1) = 0.07

mp = 134-136 ˚C

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.21 (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}C NMR (100 MHz, $CDCl_3$); δ 153.6 (**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**).

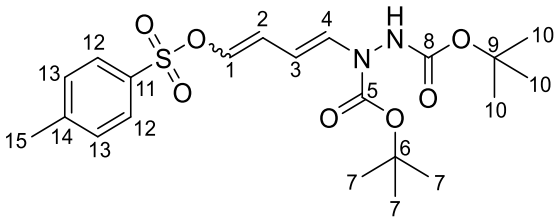
^{1}H NMR (400 MHz, d_6-DMSO); δ 9.84 (br s, 1H, **NH**), 6.55-6.52 (br m, 1H, **H1**), 5.41-5.39 (br m, 1H, **H2**), 5.43-5.41 (br m, 1H, **H3**), 5.33-5.31 (br m, 1H, **H4**), 1.44 (br s, 18H, **H8**).

^{13}C NMR (100 MHz, d_6-DMSO); δ 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) ν (cm^{-1}): 3293 (NH), 2982, 2933, 1728 (C=O), 1683 (C=O).

HRMS (ESI): *m*/*z* calculated for: $C_{10}H_{14}N_2O_4$ $[M+Na]^+$ 249.0846, found 249.0839.

Diene **320**



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

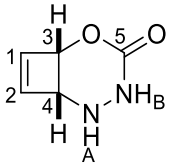
^{1}H NMR (400 MHz, 348 K, d_6-DMSO); δ 9.19-8.69 (br m, 1H, **NH**), 7.79 (d, *J* = 8.2 Hz, 2H, **H12**), 7.49 (d, *J* = 8.2 Hz, 2H, **H13**), 7.05 (br d, *J* = 13.6 Hz, 1H, **H4**), 6.72 (br d, *J* = 11.7 Hz, 1H, **H1**), 6.16 (br t, *J* = 11.4 Hz, 1H, **H2**), 5.55 (br t, *J* = 12.5 Hz, 1H, **H3**), 2.43 (s, 3H, **H15**), 1.49-1.38 (br m, 18H, **H7** and **H10**).

^{13}C NMR (100 MHz, 348 K, d_6-DMSO, additional peaks due to complex rate processes denoted by an asterisk); δ 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**), 78.6* (**C5** or **C9**), 27.8* (**C7** or **C10**), 27.7 (**C7** or **C10**), 27.3 (**C7** or **C10**), 20.7 (**C15**).

FTIR (ATR) ν (cm^{-1}): 3326 (NH), 2978, 1721 (C=O), 1709 (C=O), 1367 (SO_2), 1145 (SO_2).

HRMS (ESI): *m*/*z* calculated for: $C_{21}H_{30}N_2O_7S$ $[M+Na]^+$ 477.1666 and $[M-H]^-$ 453.1701, found 477.1669 and 453.1714, respectively.

5-oxa-2,3-diazabicyclo[4.2.0]oct-7-en-4-one 330



$ZnCl_2$ (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_2Cl_2-MeOH, 100:0→99:1→98:1) gave the bicycle **330** as an orange oil with impurities.

R_f (CH_2Cl_2-MeOH, 96:4) = 0.11

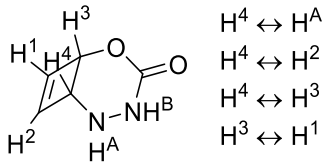
^{1}H NMR (400 MHz, d_6-DMSO); δ 8.45 (br s, 2H, **NH_B**), 6.41-6.38 (br m, 1H, **H1**), 6.31-6.28 (br m, 1H, **H2**), 5.48-5.45 (br m, H, **NH_A**), 5.20-5.16 (br m, H, **H3**), 4.22-4.18 (br m, 1H, **H4**).

^{13}C NMR (100 MHz, d_6-DMSO); δ 154.2 (**C5**), 142.3 (**C1**), 138.9 (**C2**), 80.3 (**C3**), 61.0 (**C4**).

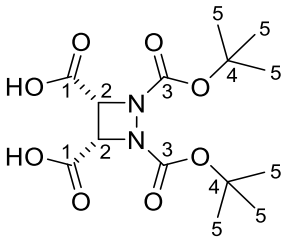
FTIR (ATR) ν (cm^{-1}): 3319 (NH), 1655 (C=O).

HRMS (APCI): *m*/*z* calculated for: $C_5H_6N_2O_2$ $[M+H]^+$ 127.0502, found 127.0509.

Important NOE contacts:



1,2-Bis(*tert*-butoxycarbonyl)-1,2-diazetidine-3,4-dicarboxylic acid 332



An aqueous 10% $NaIO_4$ 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 $RuO_2.xH_2O$ (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 ($MgSO_4$), filtered through Celite and evaporated under reduced pressure to give diacid **332** (374 mg, 1.08 mmol, 76%) as a grey solid.

R_f (CH_2Cl_2-MeOH, 9:1) = baseline

mp = 168-170 ˚C (decomposition)

^{1}H NMR (400 MHz, d_4-MeOD); δ 5.05 (s, 2H, **H2**), 1.48 (s, 18H, **H5**).

^{13}C NMR (100 MHz, d_4-MeOD); δ 170.2 (**C1**), 159.9 (**C3**), 84.0 (**C4**), 63.2 (**C2**), 28.3 (**C5**).

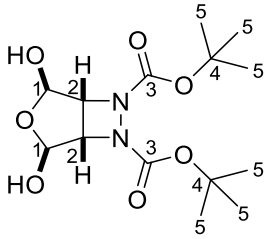
^{1}H NMR (400 MHz, $CDCl_3$); δ 10.6 (br s, 2H, **OH**), 5.00 (br s, 2H, **H2**), 1.46 (s, 18H, **H5**).

^{13}C NMR (100 MHz, $CDCl_3$); 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).

HRMS (ESI): *m*/*z* calculated for: $C_{14}H_{22}N_2O_8$ $[M+Na]^+$ 369.1268, found 369.1254.

Di-*tert*-butyl 2,4-dihydroxy-3-oxa-6,7-diazabicyclo[3.2.0]heptane-6,7-dicarboxylate 333



An aqueous 10% $NaIO_4$ 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 $RuO_2.xH_2O$ (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 ($MgSO_4$), 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 (Hexane-EtOAc, 1:1) = 0.11

mp = 38-40 ˚C

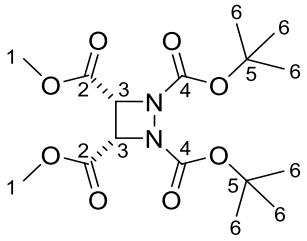
^{1}H NMR (400 MHz, d_6-DMSO); δ 6.63 (d, J = 5.5 Hz, 2H, **OH**), 5.50 (d, J = 5.5 Hz, 2H, **H1**), 4.60 (br s, 2H, **H2**), 1.41 (s, 18H, **H5**).

^{13}C NMR (100 MHz, d_6-DMSO); δ 157.0 (**C3**), 99.1 (**C1**), 81.4 (**C4**), 69.1 (**C2**), 27.7 (**C5**).

FTIR (ATR) ν (cm^{-1}): 3407 (OH), 2980, 2935, 1702 (C=O)

HRMS (ESI): *m*/*z* calculated for: $C_{14}H_{24}N_2O_7$ $[M+Na]^+$ 355.1476, found 355.1468.

1,2-Di-*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 $CHCl_3$ (2 mL), washed with a saturated solution of sodium thiosulfate (5 mL), dried (Na_2SO_4) 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 (Hexane-EtOAc, 1:1) = 0.48

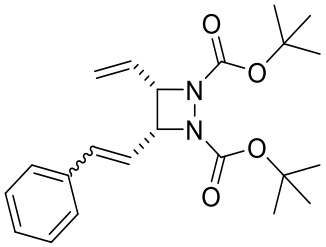
^{1}H NMR (400 MHz, $CDCl_3$); δ 4.94 (s, 2H, **H3**), 3.76 (s, 6H, **H1**) 1.47 (s, 18H, **H6**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 167.7 (**C2**), 158.0 (**C4**), 83.2 (**C5**), 61.4 (**C3**), 52.9 (**C1**), 28.1 (**C6**).

FTIR (ATR) ν (cm^{-1}): 2980, 1752 ($C=O_{ester}$), 1709 ($C=O_{carbamate}$).

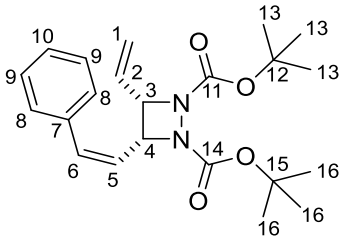
HRMS (ESI): *m*/*z* calculated for: $C_{16}H_{26}N_2O_8$ $[M+Na]^+$ 397.1581, found 397.1585; $[2M+Na]^+$ 771.3271, found 771.3271.

Di-*tert*-butyl 3-ethenyl-4-[(*E*/*Z*)-2-phenylethenyl]-1,2-diazetidine-1,2-dicarboxylate 340a,b



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 CH_2Cl_2 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 (eluent: 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

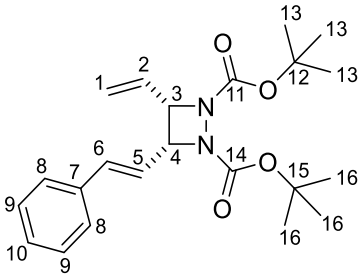
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.36-7.27 (m, 3H, **H9** and **H10**), 7.21-7.18 (m, 2H, **H8**), 6.80 (d, *J* = 11.5 Hz, 1H, **H6**), 5.99-5.84 (m, 2H, **H2** and **H5**), 5.47-5.36 (m, 3H, **H1$_A$**, **H1$_B$** and **H4**), 4.90-4.84 (m, 1H, **H3**), 1.47 (br s, 9H, **H13**), 1.44 (br s, 9H, **H16**).

^{13}C NMR (100 MHz, $CDCl_3$); 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 (**C12** 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).

HRMS (ESI): *m*/*z* calculated for: $C_{22}H_{30}N_2O_4$ $[M+Na]^+$ 409.2098, found 409.2096; $[2M+Na]^+$ 795.4303, found 795.4299.

E-isomer **340b**



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

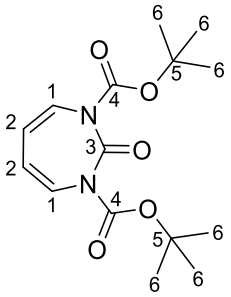
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.40-7.25 (m, 5H, **H8**, **H9**, **H10**), 6.65 (d, *J* = 15.7 Hz, 1H, **H6**), 6.24 (dd, *J* = 15.7, 8.6 Hz, 1H, **H5**), 5.97-5.88 (m, 1H, **H2**), 5.45-5.34 (m, 2H, $\mathbf{H1_A}$ and $\mathbf{H1_B}$), 5.07-5.01 (m, 1H, **H4**), 4.97-4.91 (m, 1H, **H3**), 1.49-4.40 (m, 18H, **H13** and **H16**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 158.9 (**C**), 158.6 (**C**), 136.1 (**C7**), 135.9 (**C6**), 132.5 (**C2**), 128.8 (**C9**), 128.4 (**C10**), 126.8 (**C8**), 123.5 (**C5**), 120.8 (**C1**), 82.1 (**C12** or **C15**), 81.9 (**C12** or **C15**), 66.8 (**C3**), 66.5 (**C4**), 28.3 (**C13** or **C16**), 28.2 (**C13** or **C16**).

FTIR (ATR) ν (cm^{-1}): 2980, 2932, 1709 (C=O).

HRMS (ESI): *m*/*z* calculated for: $C_{22}H_{30}N_2O_4$ $[M+Na]^+$ 409.2098, found 409.2092; $[2M+Na]^+$ 795.4303, found 795.4296.

Di-*tert*-butyl 2-oxo-1,3-diazepine-1,3-dicarboxylate 344



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 $CHCl_3$ (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 NH_4Cl (2 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_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, 9:1) gave diazepine **344** (13 mg, 0.04 mmol, 21%) as a colourless film.

R_f (Hexane-EtOAc, 2:1) = 0.52

^{1}H NMR (400 MHz, $CDCl_3$); δ 6.50-6.47 (m, 2H, **H1**), 5.88-5.85 (m, 2H, **H2**), 1.52 (s, 18H, **H6**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 155.6 (**C3**), 151.5 (**C4**), 131.8 (**C1**), 128.0 (**C2**), 84.3 (**C5**), 28.1 (**C6**).

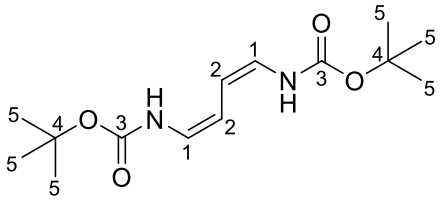
^{1}H NMR (400 MHz, d_6-DMSO); δ 6.51-6.48 (m, 2H, **H1**), 6.04-6.00 (m, 2H, **H2**), 1.45 (m, 2H, **H6**).

^{13}C NMR (100 MHz, d_6-DMSO); δ 154.3 (**C3**), 150.6 (**C4**), 127.5 (**C1**), 118.5 (**C2**), 83.7 (**C5**), 27.4 (**C6**).

FTIR (ATR) ν (cm^{-1}): 2980, 2933, 1718 (C=O).

HRMS (ESI): *m*/*z* calculated for: $C_{15}H_{22}N_2O_5$ $[M+Na]^+$ 333.1421, found 333.1404.

Di-*tert*-butyl (1*Z*,3*Z*)-buta-1,3-diene-1,4-diylbiscarbamate 350



SmI_2 prepared according to a previously reported procedure.[305]

Note: It was essential for dry THF without stabilisers to be used for the preparation of SmI_2.

A solution of SmI_2 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 (Hexane-EtOAc, 2:1) = 0.48

mp = 206-208 ˚C (decomposition)

^{1}H NMR (400 MHz, $CDCl_3$); δ 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, $CDCl_3$); δ 152.6 (**C3**), 122.3 (**C1**), 100.2 (**C2**), 81.3 (**C4**), 28.4 (**C5**).

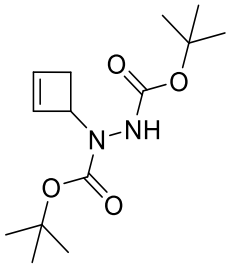
^{1}H NMR (400 MHz, d_6-DMSO); δ 9.07-8.77 (br m, 2H, **NH**), 6.14-6.04 (br m, 2H, **H1**), 5.66-5.49 (br m, 2H, **H2**), 1.43 (br s, 18H, **H5**).

^{13}C NMR (100 MHz, d_6-DMSO); δ 153.1 (**C3**), 121.0 (**C1**), 102.2 (**C2**), 79.2 (**C4**), 28.0 (**C5**).

FTIR (ATR) ν (cm^{-1}): 3325 (NH), 2980, 2935, 1690 (C=O), 1621 (C=O).

HRMS (ESI): *m*/*z* calculated for: $C_{14}H_{24}N_2O_4$ $[M+Na]^+$ 307.1628, found 307.1628.

Di-*tert*-butyl 1-(cyclobut-2-en-1-yl)hydrazine-1,2-dicarboxylate 353



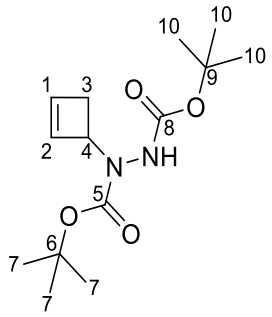
Na/NH_3(l) Reaction: A solution of bicyclic 1,2-diazetidine **10d** (50 mg, 0.18 mmol, 1.0 eq) in THF (3 mL) was added to a stirred solution of distilled ammonia (3 mL) at –78 °C under argon. Sodium metal (41 mg, 1.77 mmol, 10 eq) was added portion wise at –78 °C, then the reaction mixture was warmed 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 ($MgSO_4$) 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: NH_4Cl (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 (Hexane-EtOAc, 2:1) = 0.46

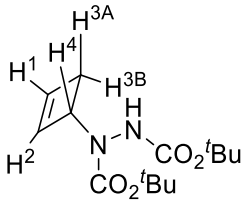
^{1}H NMR (400 MHz, d_6-DMSO); δ 8.92-8.51 (br m, 1H, **NH**), 6.16-6.08 (br m, 1H, **H1**), 5.94-5.80 (br m, 1H, **H2**), 5.10-4.84 (br m, 1H, **H4**), 2.69-2.40 (br m, 2H, **H3**), 1.43-1.38 (br m, 18H, **H7** and **H10**).

^{13}C NMR (100 MHz, d_6-DMSO, additional peaks due to rotamers annotated by an asterisk); δ 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) ν (cm^{-1}): 3301 (NH), 2976, 2928, 1702 (C=O).

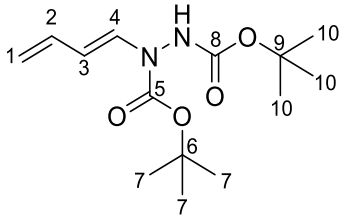
HRMS (ESI): *m*/*z* calculated for: $C_{14}H_{24}N_2O_4$ $[M+Na]^+$ 307.1628, found 307.1637.

Important NOE contacts:



$H^1 \leftrightarrow H^{3A}$
$H^1 \leftrightarrow H^{3B}$
$H^4 \leftrightarrow H^{3A}$

Diene **354**



R_f (Hexane-EtOAc, 2:1) = 0.52

mp = 96-98 ˚C

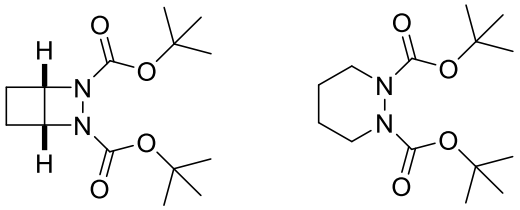
^{1}H NMR (400 MHz, 348 K, d_6-DMSO); δ 9.24-8.70 (br m, 1H, **NH**), 7.06 (br d, *J* = 13.6 Hz, 1H, **H4**), 6.42-6.32 (m, 1H, **H2**), 5.68-5.62 (m, 1H, **H3**), 5.06-5.01 (m, 1H, **H1$_A$**), 4.89-4.86 (m, H, **H1$_B$**), 1.47-1.41 (br m, 18H, **H7** and **H10**).

^{13}C NMR (100 MHz, 348 K, d_6-DMSO); δ 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) ν (cm^{-1}): 3289 (NH), 2978, 2932, 1715 (C=O), 1649 (C=O).

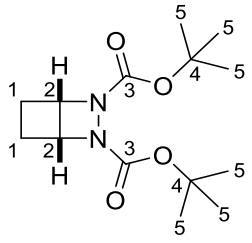
HRMS (ESI or APCI): target mass not found.

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**



R_f (Hexane-EtOAc, 4:1) = 0.17

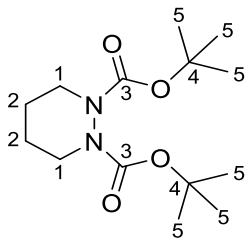
^{1}H NMR (400 MHz, $CDCl_3$); δ 4.68-4.66 (br m, 2H, **H2**), 2.55-2.52 (br m, 4H, **H1**), 1.50 (br s, 18H, **H5**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 158.7 (**C3**), 81.9 (**C4**), 64.1 (**C2**), 28.3 (**C5**), 27.4 (**C1**).

FTIR (ATR) ν (cm^{-1}): 2976, 2932, 1739 (C=O), 1700 (C=O).

HRMS (ESI and APCI): Target mass not found.

Diazinane **356**



R_f (Hexane-EtOAc, 4:1) = 0.24

mp = 56-58 ˚C

^{1}H NMR (400 MHz, $CDCl_3$); δ 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); δ 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); δ 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); δ 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**).

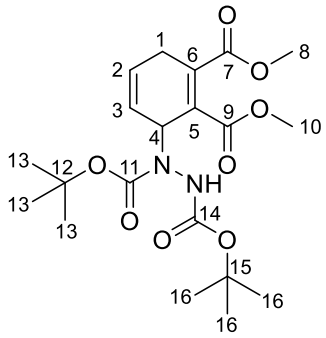
^{1}H NMR (400 MHz, 348 K, d_6-DMSO); δ 4.01-3.89 (br m, 2H, **H1$_A$**), 2.88-2.79 (br m, 2H, **H1$_B$**), 1.63-1.42 (br m, 22H, **H2** and **H5**).

^{13}C NMR (100 MHz, 348 K, d_6-DMSO); δ 153.1 (**C3**), 79.5 (**C4**), 44.4 (**C1**), 27.6 (**C5**), 22.8 (**C2**).

FTIR (ATR) ν (cm^{-1}): 2982, 2932, 1690 (C=O).

HRMS (APCI): *m/z* calculated for: $C_{14}H_{26}N_2O_4$ $[M+Na]^+$ 309.1785, found 309.1794.

Di-*tert*-butyl-1-[2,3-bis(methoxycarbonyl)cyclohexa-2,5-dien-1-yl]hydrazine-1,2-dicarboxylate 357



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: CH_2Cl_2-MeOH, 100:0→99:1) gave cycloadduct **357** (42 mg, 0.10 mmol, 76%) as a colourless oil.

R_f (Hexane-EtOAc, 1:1) = 0.48

^{1}H NMR (400 MHz, 378 K, d_6-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, $\mathbf{H1_A}$ and $\mathbf{H1_B}$), 1.42 (s, 9H, **H13** or **H16**), 1.40 (s, 9H, **H13** or **H16**).

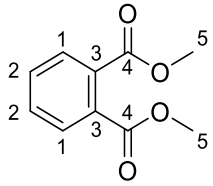
^{13}C NMR (100 MHz, 378 K, d_6-DMSO, **C4** not visible, additional peaks due to complex rate processes annotated by an asterisk); δ 166.6 (**C8** or **C10**), 165.7 (**C8** or **C10**), 154.7 (**C11** or **C14**), 153.3 (**C11** or **C14**), 125.4 (**C2**), 122.4 (**C3**), 79.9 (**C12** or **C15**), 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) ν (cm^{-1}): 3330 (NH), 2978, 1720 (C=O).

HRMS (ESI or APCI): *m/z* calculated for: $C_{20}H_{30}N_2O_8$ $[M+Na]^+$ 449.1894, found 449.1890.

*Note: When the NMR sample of **357** (in d_6-DMSO) was heated at temperatures above 130 °C, dimethyl benzene-1,2-dicarboxylate **358** and di-tert-butyl hydrazodicarboxylate **43d** were formed.*

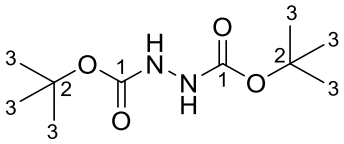
Dimethyl benzene-1,2-dicarboxylate 358



^{1}H NMR (400 MHz, d_6-DMSO); δ 7.75-7.72 (m, 2H, **H1**), 7.69-7.66 (m, 2H, **H2**), 3.82 (s, 6H, **H5**).

^{13}C NMR (100 MHz, d_6-DMSO); δ 167.4 (**C4**), 131.7 (**C2**), 131.4 (**C3**), 128.7 (**C1**), 52.6 (**C5**).

Di-tert-butyl hydrazodicarboxylate 43d



^{1}H NMR (400 MHz, d_6-DMSO); δ 8.61-8.14 (br m, 2H, **NH**), 1.38 (br s, 18H, **H3**).

^{13}C NMR (100 MHz, d_6-DMSO, additional peaks due to rotamers denoted by an asterisk); δ 155.6 (**C1**), 79.0* (**C2**), 78.9 (**C2**), 28.2* (**C3**), 28.1 (**C3**), 27.9* (**C3**).

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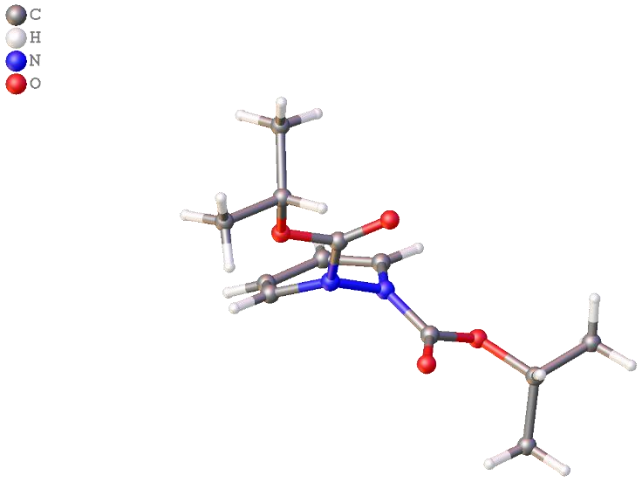
Chapter 8: Appendix

8.1 X-Ray Data

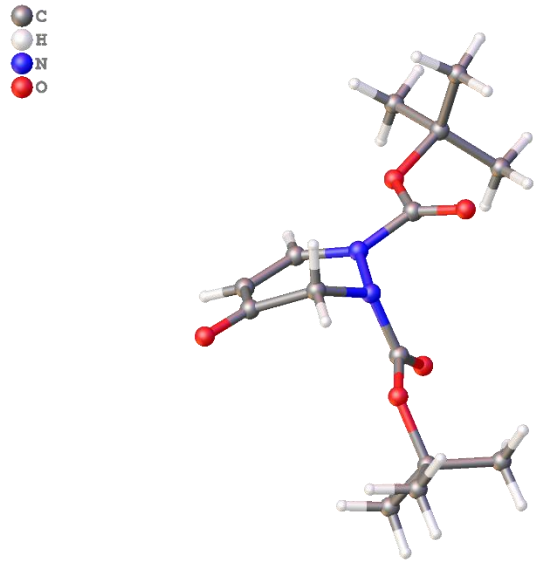
1. X-Ray Crystal Structure Data for **9c**



Identification code	SC104
Empirical formula	$C_{12}H_{18}N_2O_4$
Formula weight	254.28
Temperature/K	100.2(5)
Crystal system	monoclinic
Space group	C2/c
a/Å	18.4345(2)
b/Å	7.62687(9)
c/Å	19.5917(3)
α/°	90
β/°	108.8812(15)
γ/°	90
Volume/Å^3	2606.32(6)
Z	8
ρ_{calc}g/cm^3	1.296
μ/mm^{-1}	0.814
F(000)	1088.0
Crystal size/mm^3	0.348 × 0.149 × 0.078
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.542 to 153.332

Index ranges	-23 ≤ h ≤ 17, -9 ≤ k ≤ 9, -23 ≤ l ≤ 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

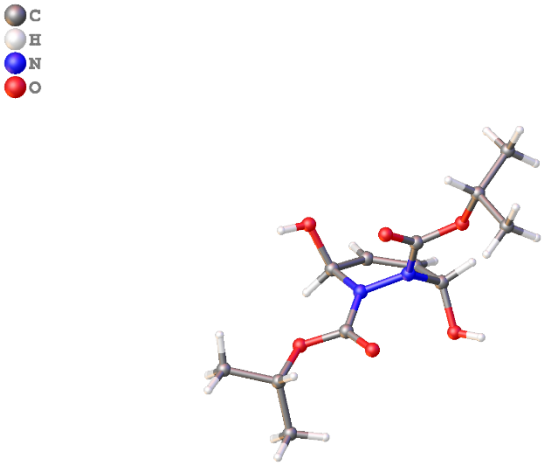
2. X-Ray Crystal Structure Data for **218**



Identification code	MC231-new
Empirical formula	$C_{14}H_{22}N_2O_5$
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/Å^3	828.55(6)
Z	2
ρ_{calc}g/cm^3	1.196
μ/mm^{-1}	0.758
F(000)	320.0
Crystal size/mm^3	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 F^2	1.048
Final R indexes [I>=2σ (I)]	R_1 = 0.0449, wR_2 = 0.1273
Final R indexes [all data]	R_1 = 0.0491, wR_2 = 0.1323
Largest diff. peak/hole / e Å^{-3}	0.20/-0.20

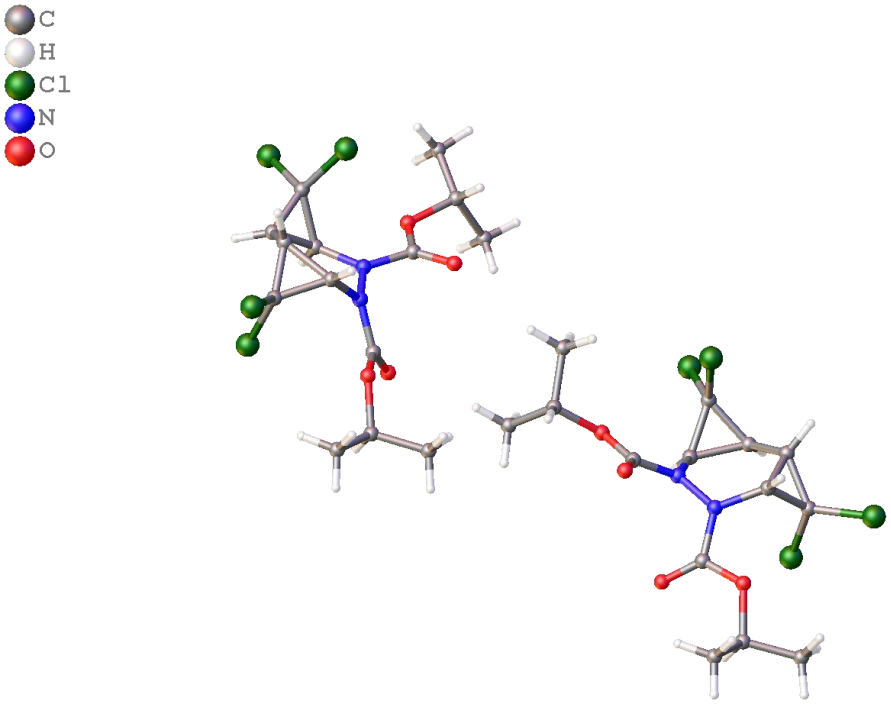
3. X-Ray Crystal Structure Data for **238**



Identification code	SC106
Empirical formula	$C_{12}H_{20}N_2O_6$
Formula weight	288.30
Temperature/K	100
Crystal system	monoclinic

Space group	$P2_1/c$
a/Å	10.0193(3)
b/Å	14.8599(4)
c/Å	9.9341(3)
α/°	90
β/°	110.451(3)
γ/°	90
Volume/Å^3	1385.83(7)
Z	4
ρ_{calc}g/cm^3	1.382
μ/mm^{-1}	0.942
F(000)	616.0
Crystal size/mm^3	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 F^2	1.073
Final R indexes [I>=2σ (I)]	R_1 = 0.0399, wR_2 = 0.1049
Final R indexes [all data]	R_1 = 0.0420, wR_2 = 0.1065
Largest diff. peak/hole / e Å^{-3}	0.38/-0.30

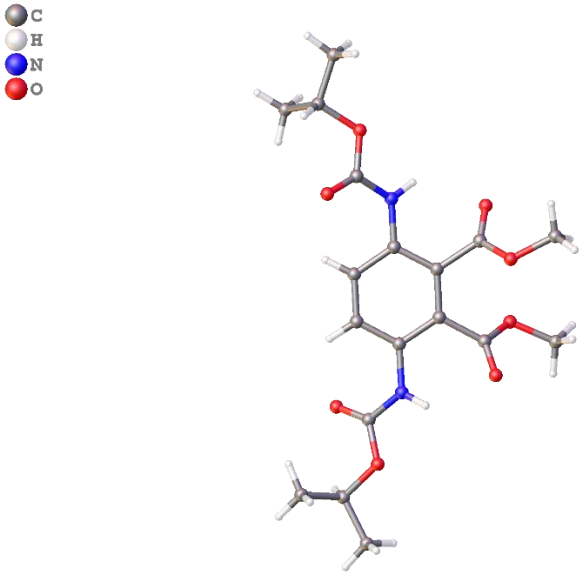
4. X-Ray Crystal Structure Data for **241**



Identification code	SC105
Empirical formula	$C_{28}H_{36}Cl_8N_4O_8$
Formula weight	840.21
Temperature/K	100.00(10)
Crystal system	triclinic
Space group	P-1
a/Å	10.2631(2)
b/Å	11.9194(3)
c/Å	15.8919(4)
α/°	89.4160(18)
β/°	89.8269(18)
γ/°	77.4429(18)
Volume/Å^3	1897.44(7)
Z	2
ρ_{calc}g/cm^3	1.471
μ/mm^{-1}	5.859
F(000)	864.0
Crystal size/mm^3	0.433 × 0.247 × 0.18

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 F^2	1.175
Final R indexes [I>=2σ (I)]	R_1 = 0.0470, wR_2 = 0.1223
Final R indexes [all data]	R_1 = 0.0473, wR_2 = 0.1224
Largest diff. peak/hole / e $Å^{-3}$	0.61/-0.38

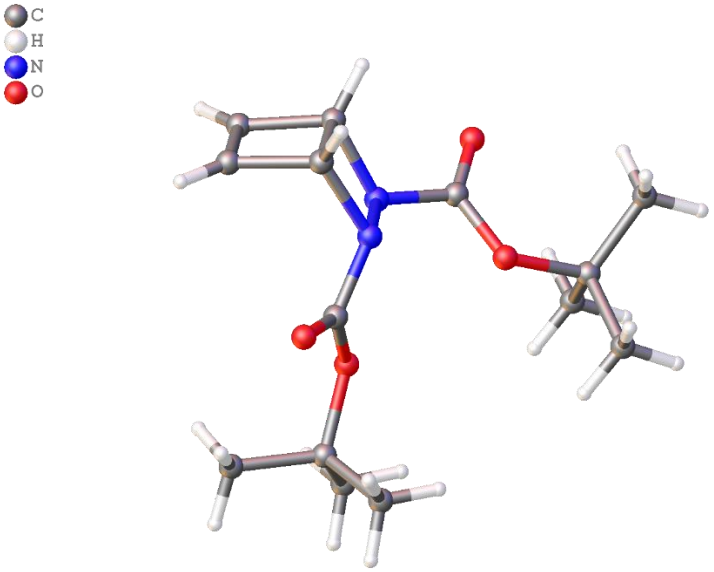
5. X-Ray Crystal Structure Data for **224**



Identification code	pre_MC201
Empirical formula	$C_{18}H_{24}N_2O_8$
Formula weight	396.39
Temperature/K	292.52(10)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	9.8453(3)
b/Å	7.5243(2)
c/Å	26.0993(11)

α/°	90
β/°	98.958(3)
γ/°	90
Volume/Å^3	1909.82(11)
Z	4
ρ_{calc}g/cm^3	1.379
μ/mm^{-1}	0.924
F(000)	840.0
Crystal size/mm^3	0.203 × 0.036 × 0.024
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.206 to 147.368
Index ranges	-12 ≤ h ≤ 11, -9 ≤ k ≤ 6, -31 ≤ l ≤ 31
Reflections collected	13128
Independent reflections	3805 [R_{int} = 0.0411, R_{sigma} = 0.0393]
Data/restraints/parameters	3805/0/259
Goodness-of-fit on F^2	1.045
Final R indexes [I>=2σ (I)]	R_1 = 0.0384, wR_2 = 0.0876
Final R indexes [all data]	R_1 = 0.0512, wR_2 = 0.0933
Largest diff. peak/hole / e Å^{-3}	0.28/-0.26

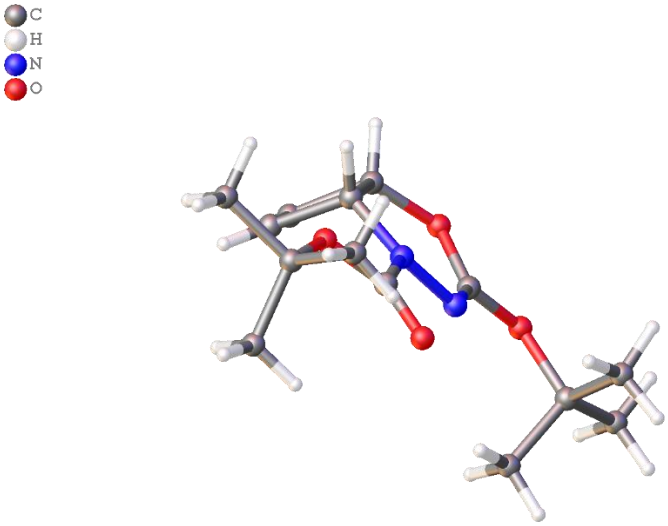
6. X-Ray Crystal Structure Data for **10d**



Identification code	SC107
Empirical formula	$C_{14}H_{22}N_2O_4$
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 × 0.309 × 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

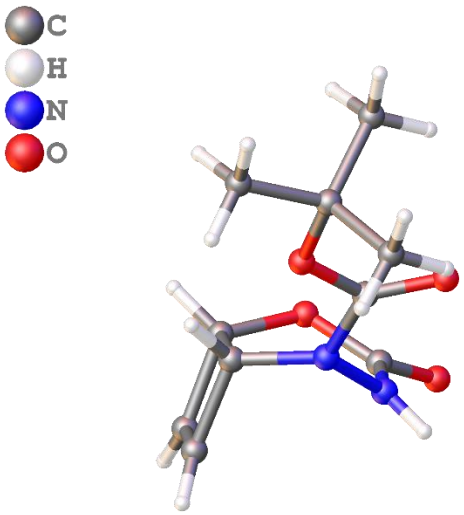
7. X-Ray Crystal Structure Data for **316d**



Identification code	SC112
Empirical formula	$C_{14}H_{22}N_2O_4$
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

Volume/Å^3	1487.5(3)
Z	4
ρ_{calc}g/cm^3	1.261
μ/mm^{-1}	0.762
F(000)	608.0
Crystal size/mm^3	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 [R_{int} = 0.0489, R_{sigma} = 0.0302]
Data/restraints/parameters	3103/0/187
Goodness-of-fit on F^2	1.156
Final R indexes [I>=2σ (I)]	R_1 = 0.0871, wR_2 = 0.1955
Final R indexes [all data]	R_1 = 0.0891, wR_2 = 0.1962
Largest diff. peak/hole / e Å^{-3}	0.57/-0.41

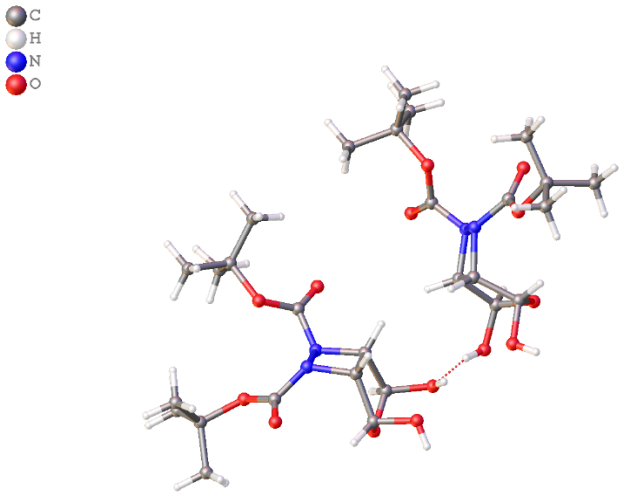
8. X-Ray Crystal Structure Data for **317d**



Identification code	SC108
Empirical formula	$C_{10}H_{14}N_2O_4$
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/Å^3	1106.26(11)
Z	4
ρ_{calc}g/cm^3	1.358
μ/mm^{-1}	0.893
F(000)	480.0
Crystal size/mm^3	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 F^2	1.056
Final R indexes [I>=2σ (I)]	R_1 = 0.0545, wR_2 = 0.1455
Final R indexes [all data]	R_1 = 0.0604, wR_2 = 0.1504
Largest diff. peak/hole / e Å^{-3}	0.65/-0.28

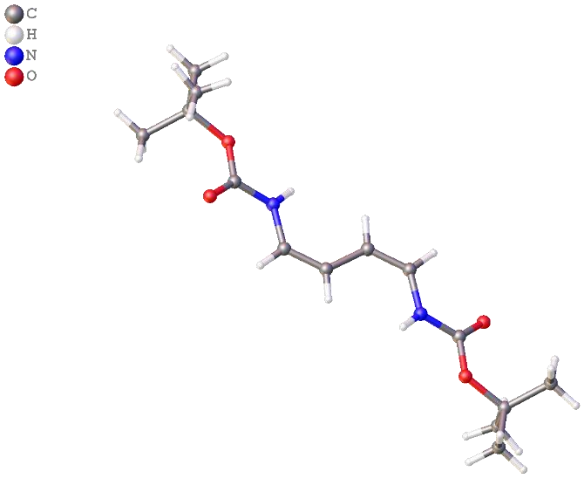
X-Ray Crystal Structure Data for **333**



Identification code	SC111
Empirical formula	$C_{28}H_{48}N_4O_{14}$
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/Å^3	3407.9(2)
Z	4
ρ_{calc}g/cm^3	1.296
μ/mm^{-1}	0.880
F(000)	1424.0
Crystal size/mm^3	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

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>=2σ (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 $Å^{-3}$	0.36/-0.23

9. X-Ray Crystal Structure Data for **350**

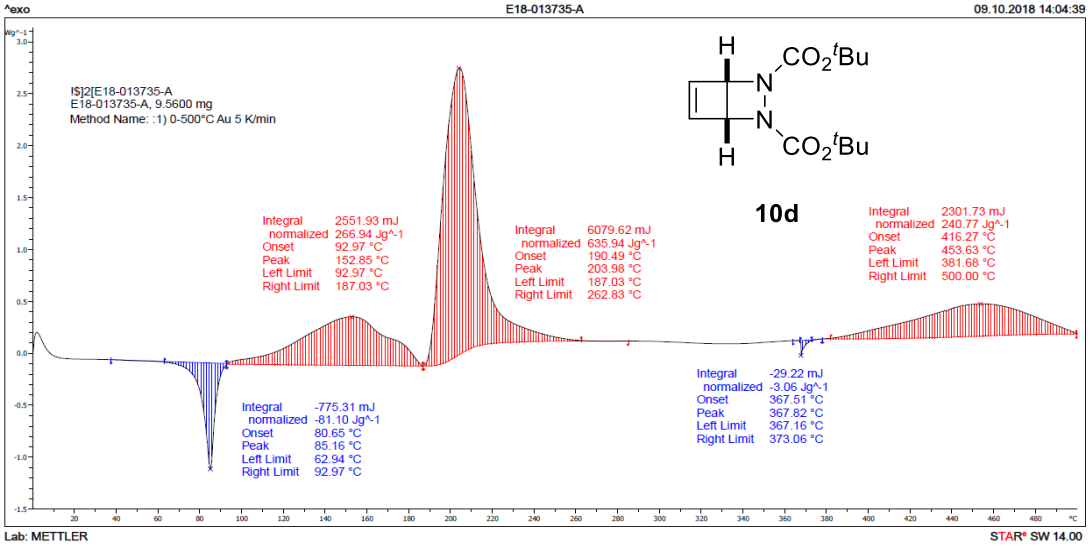


Identification code	SC117
Empirical formula	$C_{14}H_{24}N_2O_4$
Formula weight	284.35
Temperature/K	99.9(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	5.23750(9)
b/Å	8.83307(15)
c/Å	16.5180(3)
α/°	90
β/°	92.6082(17)
γ/°	90
Volume/$Å^3$	763.39(2)
Z	2

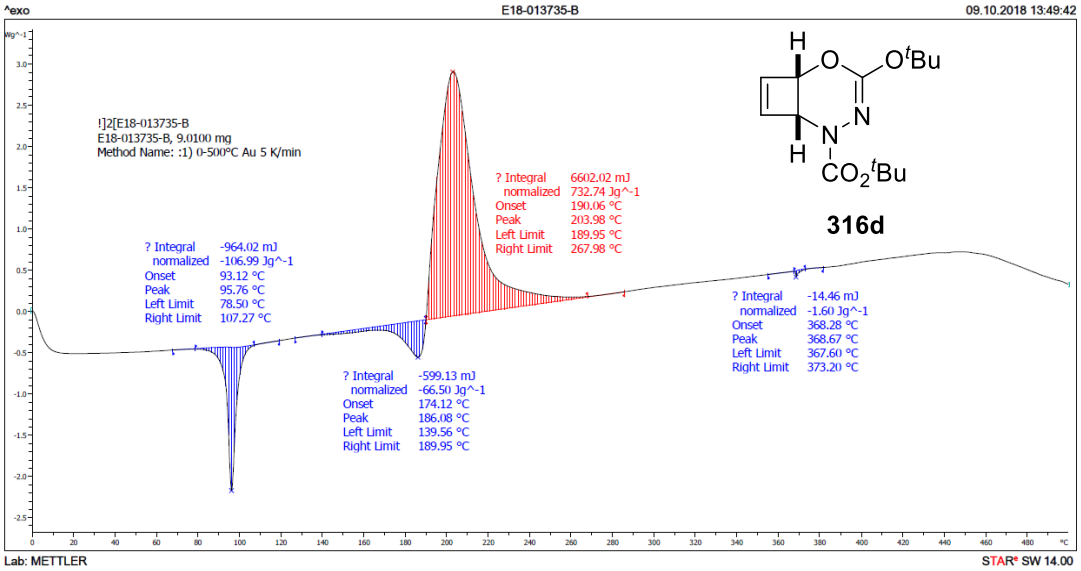
ρ_{calc}g/cm^3	1.237
μ/mm^{-1}	0.743
F(000)	308.0
Crystal size/mm^3	0.109 × 0.098 × 0.082
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	10.724 to 153
Index ranges	-6 ≤ h ≤ 6, -11 ≤ k ≤ 11, -17 ≤ l ≤ 20
Reflections collected	9639
Independent reflections	1589 [R_{int} = 0.0415, R_{sigma} = 0.0201]
Data/restraints/parameters	1589/0/94
Goodness-of-fit on F^2	1.058
Final R indexes [I>=2σ (I)]	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 Å^{-3}	0.21/-0.23

8.2 Differential Scanning Calorimetry (DSC) Traces

1. Bicyclic 1,2-Diazetidine **10d**



2. Rearranged Bicycle **316d**



3. Degraded Bicycle **317d**