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University of BRISTOL

Synthesis of medium rings through ring expansion reactions of metallated ureas containing non-aromatic anion stabilising groups.

Makenzie Jade Millward

A dissertation submitted to the University of Bristol in accordance with the requirements for award of the degree of Doctor of Philosophy in the Faculty of Science

School of Chemistry

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Abstract

Synthesis of medium rings through ring expansion reactions of metallated ureas containing non-aromatic anion stabilising groups

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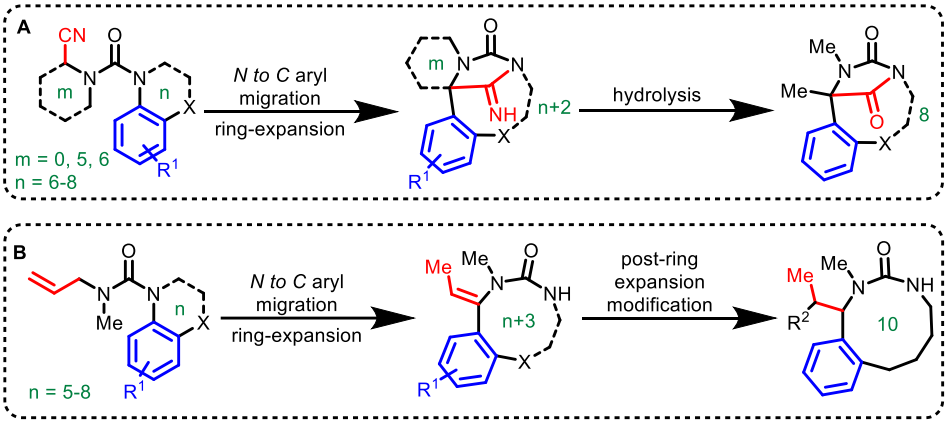
Cyclic structures containing between 8- and 12-members are classified as medium rings. Various bioactive natural products have been isolated containing these cyclic scaffolds, hence they are attractive targets for medicinal chemistry. Despite their promise the number of medium ring motifs in marketed pharmaceuticals is very limited, which is most likely attributed to the difficulties of synthesising them. Many pre-existing routes towards their synthesis use end-to-end cyclisation reactions, which are often limited in scope. Ring expansion reactions are becoming increasingly common as an alternative route towards medium rings as they avoid many of the problems associated with cyclisation reactions.



The Clayden group have reported the used of *N to C* aryl migrations of *N*-aryl-*N'*-benzyl ureas to form enantioenriched α-substituted quaternary amines. More recently they showed that tethering the aryl migrating ring to the nitrogen results in *n to n+3* ring expansion reactions under basic conditions forming benzannulated medium rings. The work reported in this thesis aims to utilise this *N to C* aryl migration chemistry producing alternative benzannulated medium rings from ureas with various anion stabilising groups other than benzyl. Firstly, this concept was successfully applied towards the synthesis of a variety of iminohydantoin bridging medium rings through *n to n+2* ring expansion using nitrile stabilised anions (**A**). These medium rings could then by hydrolysed under acidic conditions forming hydantoin bridging medium rings. This methodology was also applied toward the synthesis of vinylic medium rings from allyl ureas (**B**). A range of 8-11-membered benzannulated medium rings were isolated. These medium rings were then modified post-ring expansion by exploiting the reactivity of the enamide group through carbolithiation reactions, radical addition and hydrogenation.

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Finally, I want to thank my family whose support and encouragement has kept me going throughout my time. Mum and dad I don't think I can express in words how much you've helped me throughout this whole process, always there encouraging me to be my best. Auntie Pauline and Uncle Barry two of the most thoughtful and generous people I know, thank you.

Authors declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with or with the assistance of others, is indicated as such. Any views expressed in the dissertation are others of the author.

SIGNED: Makenzie Jade Millward. Data: 3/3/2022.

Contents

1,2-DCB	1,2-Dichlorobenzene
4CzIPN	1,2,3,5-Tetrakis(carbazole-9-yl)-4,6-dicyanobenzene
Ac	Acetyl
AIBN	Azobisisobutyonitrile
Ala	Alanine
aq.	Aqueous
Ar	Aryl
BARF	Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
^{n}Bu	Butyl
^{t}Bu	*tert*-Butyl
^{n}BuLi	Butyl lithium
^{s}BuLi	*sec*-Butyl lithium
^{t}BuLi	*tert*-Butyl lithium
^{n}BuOH	Butanol
^{t}BuONO	*tert*-Butyl nitrite
Boc	*tert*-Butyloxycarbonyl
CAN	Ceric ammonium nitrate
Cbz	*N*-carboxybenzyl
cod	1,5-cyclooctadiene
Cy	Cyclohexyl
d	Doublet
d.r	Diastereomeric ratio
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
Δ	Chemical shift
DFT	Density functional theory
DIBAL	Diisobutylaluminium hydride
diff.	Difference
DIPEA	Diisopropyl ethylamine

DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMPU	*N,N'*-dimethylpropyleneurea
DMSO	Dimethyl sulfoxide
dtbbpy	4,4-Di-*tert*-butyl-2,2-dipyridyl
e.r	Enantiomeric ratio
E^+	Electrophile
EB	Erythrosine B
ee	Enantiomeric excess
eq.	Equivalents
ESI	Electron spray ionisation
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
Fmoc	Fluorenylmethyloxycarbonyl
GI	Grubb's 1st generation catalyst
GII	Grubb's 2nd generation catalyst
Gly	Glycine
h	Hour
HFIP	Hexafluoroisopropanol
HGII	Hoveyda-Grubb's 2nd generation catalyst
HMDS	Bis(trimethylsilyl)amide
HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography
HRMS	High-resonance mass spectrometry
Hz	Hertz
IR	Infrared
J	Coupling constant
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
KHMDS	Potassium bis(trimethylsilyl)amide

L	Ligand
LDA	Lithium diisopropyl amide
LED	Light-emitting diode
Leu	Leucine
LiHMDS	Lithium bis(trimethylsilyl)amide
liq.	Liquid
µW	Microwave
m	Multiplet
m.p	Melting point
M	Molar
m-CPBA	*meta*-Chloro perbenzoic acid
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
Mes	Mesitylene
MHz	Mega hertz
min	Minute
MOM	Methoxymethyl
Ms	Trimethylsilyl
NaHMDS	Sodium bis(hexamethylsilyl)amide
NMR	Nuclear magnetic resonance
ODRE	Oxidative dearomatisation-ring-expansion rearomatisation
ON	Overnight
p-cymene	4-Methyl-1-*iso*-propylbenzene
PE	Petroleum ether
PG	Protecting group
Ph	Phenyl
Phe	Phenylalanine
Phg	Phenylglycine
PMP	*Para*-methoxyphenyl
PPA	Polyphosphoric acid
ppm	Parts per million

ppy	2-Phenylpyridine
^{i}Pr	*iso*-Propyl
^{n}Pr	Propyl
Py	Pyridyl
quant.	Quantitative
quint.	Quintet
RCM	Ring closing metathesis
R_f	Retention factor
rt	Room temperature
rxn	Reaction
s	Singlet
Sat.	Saturated
SET	Single electron transfer
SnAP	Tin amino protocol
S_NAr	Nucleophilic aromatic substitution
Sol	Solvent
T	Temperature
t	Triplet
T3P	Propylphosphoric anhydride
TBAB	Tetrabutylammonium bromide
TBS	*tert*-Butyldimethylsilyl ester
Tf	Triflate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic acid anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Tol	Tolyl
t_R	Retention time
Trp	Tryptophan
Ts	Tosyl
Tyr	Valine
X	Halogen

Xantphos	(9,9-Dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphane)
Z	Anion stabilising group

1. Introduction

1.1 Medium rings in natural products

Medium rings are a class of cyclic structures containing between 8 and 12 members. They have been found as the core for various biologically active natural products, hence are a medicinally important class of molecules (*figure 1-1*).

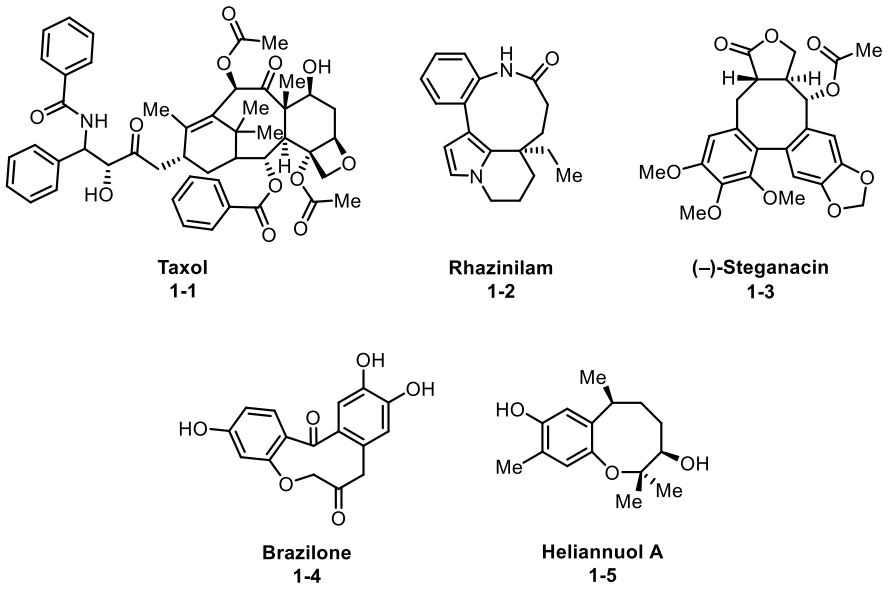


Figure 1-1: Medium ring containing natural products.

Taxol **1-1** isolated from Pacific yew trees and rhazinilam **1-2** found in *Rhazya stricta* plants have both been shown to interfere with microtubule polymerisation, stopping cancer cell division.[1–4] Taxol **1-1** is licensed for treatment against ovarian, lung and breast cancer, whereas rhazinilam **1-2** is being studied as a potential new anticancer treatment. (–)-Steganacin **1-3,** isolated from *Steganotaenia araliacea,* has shown to be an antileukemic compound.[5,6] Other natural product examples include brazilone **1-4,** an anticoagulant, and heliannuol A **1-5**.[7] Whilst not medicinally relevant heliannuol A has shown allelopathic activity, inhibiting plant growth. Many of these natural products are benzannulated medium rings (**1-2**, **1-3**, **1-4**, and **1-5**).

The conformational constraints of medium-sized rings helps with pre-organising functional groups for binding to biological targets and has been shown to enhance the binding affinity compared to the equivalent linear scaffold.[7,8]

1.2 Conformation of medium rings

Despite the evidence from natural products that medium rings are beneficial to medicinal chemistry, there remains a very limited number of medium ring motifs in marketed pharmaceuticals. Compared to smaller 5- and 6-membered rings, which are easily synthesised through numerous reactions, medium ring synthesis is hindered by entropic and enthalpic factors. The limited number of medium rings in medicinal chemistry is generally associated with the difficulties of synthesising them.

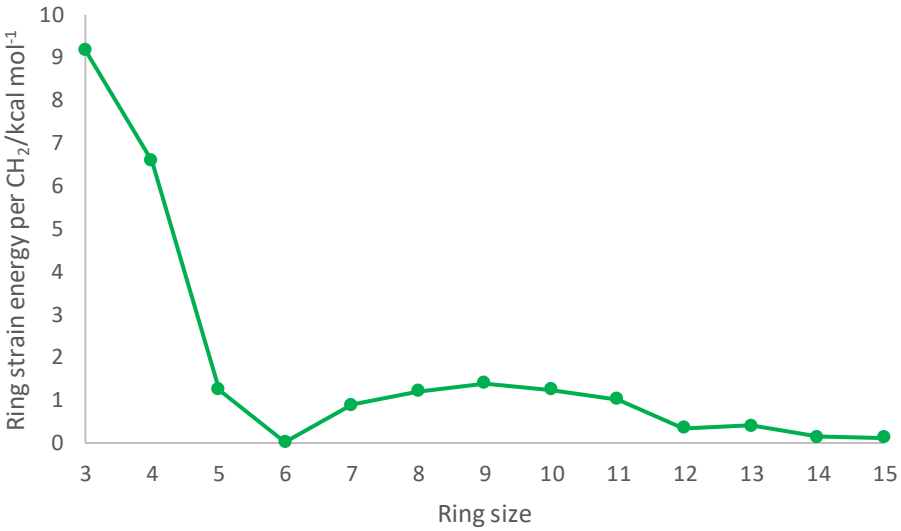


Figure 1-2: Ring strain energy per CH_2 for cycloalkanes from small rings (3-4) to macrocycles (13^+).

Besides 3 and 4 membered rings, medium rings have the highest total ring strain energy; a graphic example is shown in *figure 1-2* which shows the ring strain energy per CH_2 for 3-15-membered cycloalkanes.[9] In small and large rings angle and torsional strain are the main contributors to the strain energy experienced by the molecules, but for medium rings these strain energies are relatively low as the molecule can adopt conformations to avoid them but transannular strain dominates. This strain arises due to substituents usually hydrogens pointing into the ring, bringing them in close proximity to one another (*figure 1-3*). The presence of transannular strain means it is unlikely that medium rings will adopt one low energy conformation. Instead, there are several low energy conformations which are in equilibrium with each through low energy barriers.

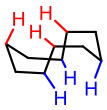


Figure 1-3: A low energy conformer of cyclodecane. Red and blue internal hydrogens experience transannular strain.

A more general route towards the synthesis of medium rings is therefore advantageous to allow the exploration of an underdeveloped area of chemical space.

1.3 Benzannulated medium ring synthesis

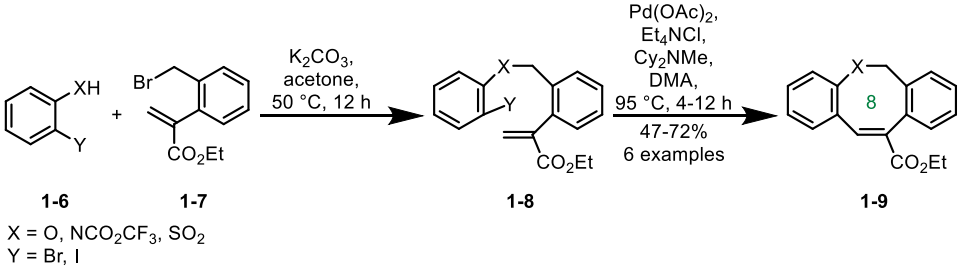
The existence of a variety of natural products containing the medium ring motif and their related biological activity has prompted chemists to study their synthesis, despite the associated difficulties. There are numerous examples within the literature and here we shall explore a range of examples broadly categorised into two main categories. The first is cyclisation reactions in which a linear structure is bound end-to-end. The second is ring expansion reactions in which the bond between fused smaller bicyclic rings is cleaved. Special attention is focused on the synthesis of benzannulated medium rings due to their presence in medicinally relevant natural products.

1.3.1 End-to-end cyclisations

1.3.1.1 Palladium mediated cyclisations

Palladium has been used in a range of cross-coupling reactions forming benzannulated macrocycles through Sonogashira, Stille, Suzuki-Miyaura and Buchwald-Hartwig cross-couplings to name a few, but for medium ring synthesis the most commonly used cross-coupling reaction is the Heck reaction.[7]

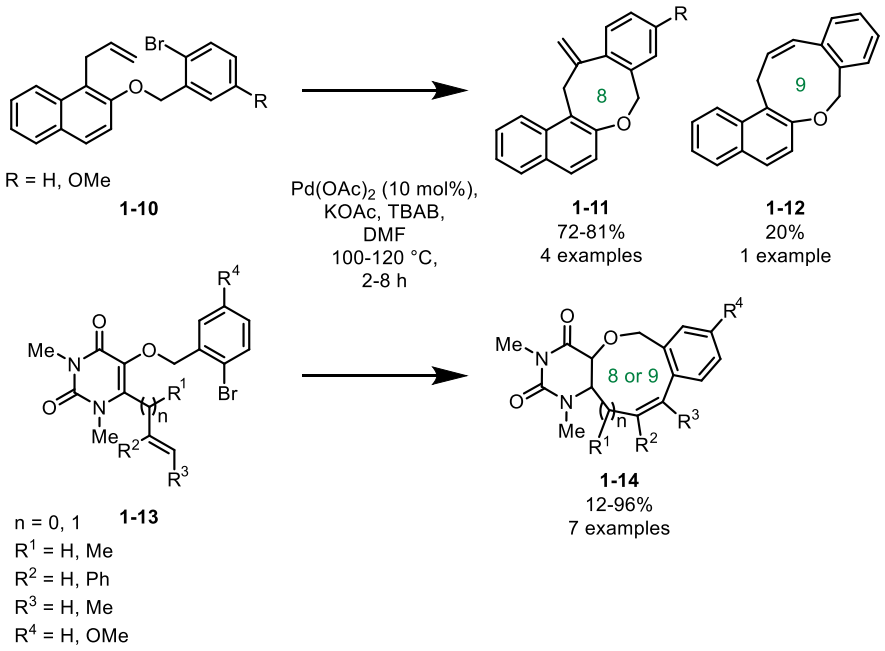
Intramolecular Heck reactions have been used as the key step in the synthesis of a range of cyclic natural products. The intramolecular Heck reaction was used to synthesis dibenzo[*b,f*]azocine, -oxocine and -thiocine derived rings **1-9** (*scheme 1-1*).[10]



Scheme 1-1: Intramolecular Heck reaction synthesising dibenzo[*b,f*]azocine, -oxocine and -thiocine derived rings.

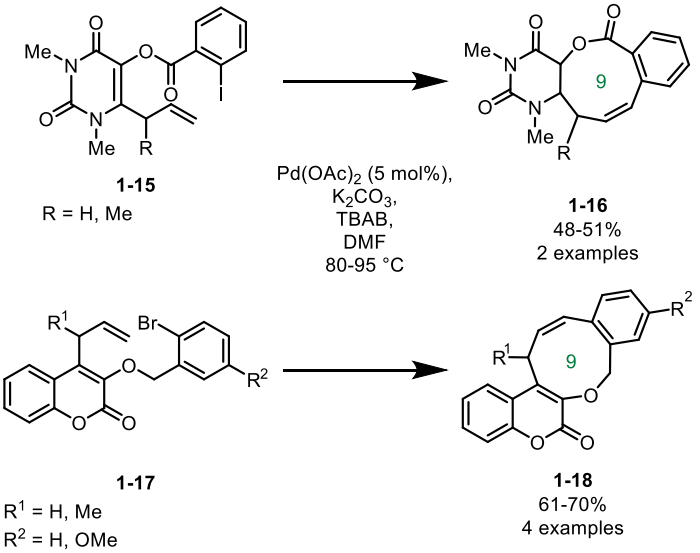
Guy *et al.* reported a novel alkylation-Heck reaction sequence. α-Aryl-substituted acrylates **1-7** were coupled to substituted benzyl halides **1-6**. Using previously developed phosphine-free conditions reported by Buchwald and co-workers,[11] the diaryl **1-8** underwent an intramolecular Heck reaction affording the 8-endo products **1-9**.

Majumdar *et al.* reported the synthesis of 8- and 9-membered oxa-heterocycles **1-11** and **1-12** using similar phosphine-free conditions (*scheme 1-2*).[12,13] The 8-*exo* products **1-11** were obtained through an intramolecular Heck reaction of **1-10** with $Pd(OAc)_2$ (10 mol%), KOAc and TBAB (tetrabutylammonium bromide) in DMF at 120 °C for 4-6 hours.[12] The products **1-11** were obtained in high yields. When R = H the 9-*endo* Heck product **1-12** was isolated as a minor product in 20% yield.



Scheme 1-2: Intramolecular Heck reactions by Majumdar using 10 mol% $Pd(OAc)_2$.

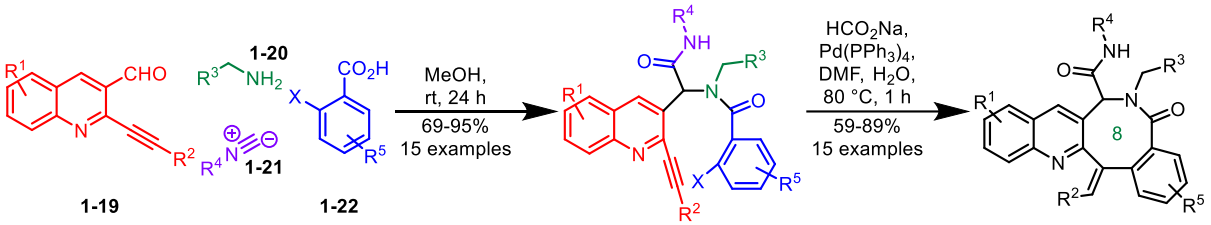
Uracil-derived starting materials **1-13** were treated under almost identical conditions ($Pd(OAc)_2$ (10 mol%), KOAc, TBAB, DMF, 100 °C, 2-3.5 hours) affording the 8- or 9-*endo* products **1-14** as the sole products in good to excellent yields through an 8- or 9-*endo* cyclisation.[13]



Scheme 1-3: Intramolecular Heck reaction forming 9-membered benzannulated rings by Majumdar using 5 mol% $Pd(OAc)_2$.

In 2009 Majumdar *et al.* showed that a reduced catalyst loading (5 mol%) and slight alterations in the conditions (K_2CO_3, TBAB, DMF, 95 °C) could be successfully implemented (*scheme 1-3*). Two derivatives of **1-14** bearing a carbonyl group α to the oxygen atom on the 9-membered ring **1-16** were synthesised in moderate yields.[14] 9-*Endo* products **1-18** were also synthesised using these conditions in good yields from **1-17**.

The Heck reaction has also been used extensively for coupling alkynes instead of alkenes to aryl halides to form medium ring heterocycles.[15] In the catalytic process a vinyl-palladium species is formed that can either be trapped by reduction or cross-coupling such as Suzuki-Miyaura. Both *endo*- and *exo*-double bond products can be synthesised. Balalaie and co-workers recently reported the synthesis of highly functionalised medium ring-fused azocinoquinoline scaffolds **1-24** in two steps (*scheme 1-4*).[16]



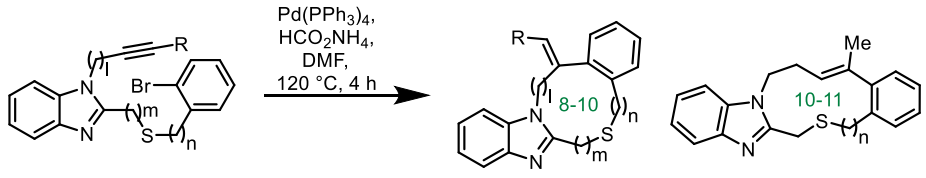
1-19 **1-22** **1-23** **1-24**

R^1 = H, 5-Me, 5-Et, 4,5-diMe, 4,6-diMe
R^2 = Ph, $4CH_3(CH_2)_4C_6H_4$, cyclopropyl
R^3 = Bn, Ph, 2-furan
R^4 = ^{t}Bu, cyclohexyl
R^5 = H, 5-OH
X = Br, I

Scheme 1-4: Post-Ugi multicomponent reaction reductive-Heck cyclisation forming benzannulated 8-membered rings.

The Ugi four component reaction was used to synthesise the acyclic precursors **1-23** which were subjected to palladium-catalysed reductive-Heck conditions, $Pd(PPh_3)_4$, HCO_2Na (as the reducing agent) in DMF/H_2O at 80 °C for 1-5 hours. The 8-*exo* products **1-24** were obtained exclusively in good to excellent yields.

Synthesis of heterocycles containing sulfur through palladium-catalysis is more challenging and less common because sulfur species are known to deactivate palladium catalysts.[15] Nonetheless Gulea *et al.* reported the synthesis of benzimidazole-fused medium rings containing nitrogen and sulfur (*scheme 1-5*).[17]



1-25
l = 1,2
m/n = 0, 1
R = Me, Et, Ph, CH_2OH, 4-$CF_3C_6H_4$, 3-FC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-thiophene

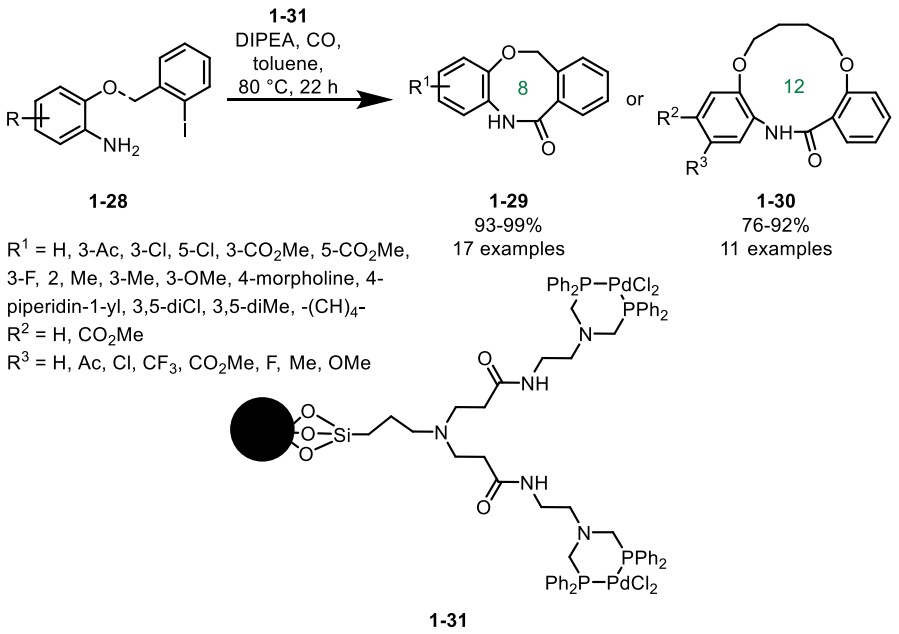
1-26
18-57%
21 example

1-27
1-26:1-27
n = 0; 1:3 (17%)
n = 1; 1:1 (24%)

Scheme 1-5: Reductive-Heck coupling forming sulfur containing benzimidazole-fused medium rings.

The synthesis of benzimidazole-fused thiazocine and thiazonine **1-26** was accomplished via 8-, 9- and 10-*exo* cyclocarbopalladation cyclisations followed by reduction in moderate yields. All the products **1-26** were obtained with Z-geometry and for all but two no evidence of the *endo*-products **1-27** were seen. For both the 9- and 10-*exo* products (when R = Me) **1-26** a mixture with the 10-/11-*endo* products **1-27** were isolated in low yields.

Separation of palladium catalysts from homogenous reaction mixtures is often tedious and can lead to ecological and economic problems, therefore easily recoverable catalysts are desirable.[18] Alper and Lu reported the use of palladium-complexed dendrimers on silica **1-31** as examples of easily recoverable catalysts for carbonylation reactions producing 8- and 12-membered benzannulated lactams **1-29** and **1-30** (*scheme 1-6*).[18,19]

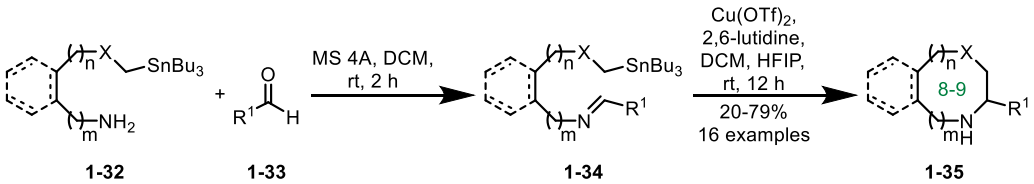


Scheme 1-6: Cyclocarbonylation reaction forming 8- and 12-membered lactams using palladium-complexed dendrimers on silica for easy catalyst recovery.

Treatment of the iodinated arylamines **1-28** with **1-31** and DIPEA under an atmosphere of carbon monoxide resulted in intramolecular cyclocarbonylation reaction, forming the 8- and 12-membered lactams **1-29** and **1-30** in high yields. Alper and Lu showed that after eight cycles the catalyst **1-31** still produced high yielding products with only slight loss of activity.

1.3.1.2 Alternative transition metal mediated cyclisations

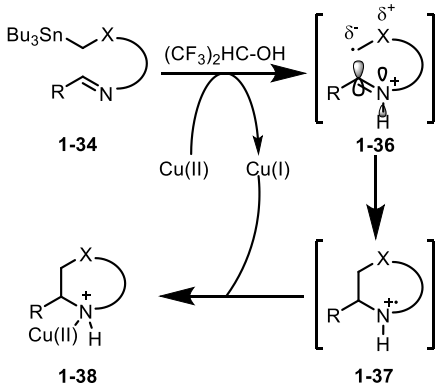
Various other metals including gold, silver, copper, chromium and nickel are also common in the synthesis of medium rings through intramolecular cyclisation. In 2014, Bode and co-workers published a radical-based approach towards the synthesis of 8- and 9-membered nitrogen heterocycles (*scheme 1-7*).[20]



X = O, NBoc
n = 0, 1
m = 1, 3
R^1 = ^{t}Bu, CO_2Et, 3-BrC_6H_4, 4-$CO_2MeC_6H_4$, 4-$CF_3C_6H_4$, 3-pyridyl, 5-pyrazole, 2-Cl-4-FC_6H_3, 3,4-benzodioxole, 4-quinoline

Scheme 1-7: SnAP reagents used to synthesis benzannulated medium rings.

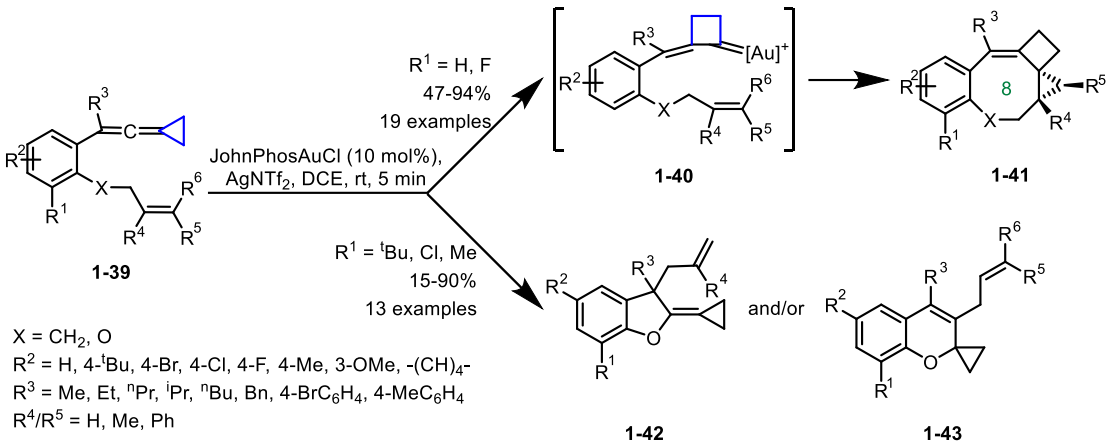
Aldehydes **1-33** and **1-32** were used to make SnAP (tin amino protocol) reagents **1-34** which underwent a copper-mediated radical cyclisation forming 8- and 9-membered nitrogen heterocycles **1-35** in low to good yields. The reaction tolerated a broad range of substrates and proceeded under relatively mild conditions.



Scheme 1-8: Radical mechanism for copper-catalysed cyclisation using SnAP reagents.

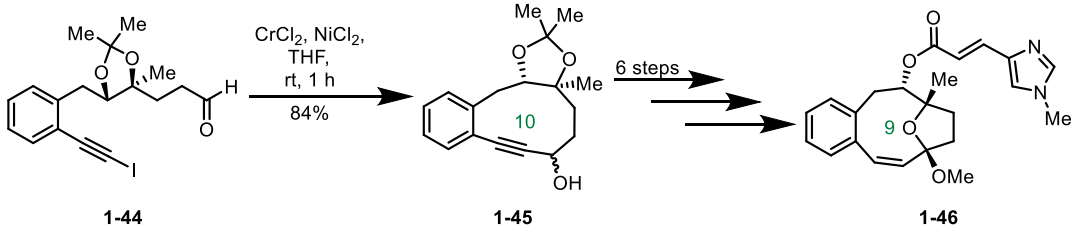
The cyclisation proceeded by copper-mediated oxidation of the Sn-C bond forming a heteroatom-stabilised primary radical **1-36** (*scheme 1-8*). This primary radical **1-36** then reacts intramolecularly with the imine forming **1-37**. The radical cation **1-37** is reduced by copper(I) generating complex **1-38**.[20,21]

Gold has also been used for the synthesis of benzannulated 8-membered rings **1-41** (*scheme 1-9*).[22] The gold(I)-catalysed rearrangement of vinylidenecyclopropanes **1-39** (R^1 = H or F) resulted in 8-membered rings **1-41** in generally good to high yields. This reaction proceeds through gold-carbene formation **1-40** before subsequent cyclopropanation giving the heterocycle **1-41**. An alternative non-carbene pathway occurs when R^1 = ^{t}Bu, Me or Cl affording 5- or 6-membered rings **1-42** and **1-43** resulting from allyl group migration.



Scheme 1-9: Gold-catalysed formation of 8-membered rings or 5- and 6-membered cyclic ethers. R^1 = H or F leads to gold-carbene formation and 8-membered ring synthesis. R^1 = ^{t}Bu, Me or Cl leads to non-carbene pathway forming cyclic ethers.

A combination of nickel and chromium were used in the key cyclisation step reported by Bermejo *et al.* forming **1-46** an aromatic analogue of eleutherobin (*scheme 1-10*).[23] Eleutherobin is an oxacyclic diterpene found in Australian soft corals and has shown to stabilise microtubules, acting as a potential anticancer agent. The linear scaffold **1-44** was treated with $CrCl_2$/$NiCl_2$ undergoing a Nozaki-Hiyama-Kishi cyclisation forming the key 10-membered ring **1-45** in good yield.



Scheme 1-10: Nozaki-Hiyama-Kishi cyclisation under chromium/nickel catalysis forming 10-membered ring **1-45** during the synthesis of eleutherobin analogues.

1.3.1.3 Ring-closing metathesis

Ring-closing metathesis (RCM) is one of the most widely used reactions for the formation of medium rings due to its compatibility with a wide range of functional groups and produces products that can be further functionalised post-RCM.[7] The common catalysts used for RCM reaction are shown in *figure 1-4*.

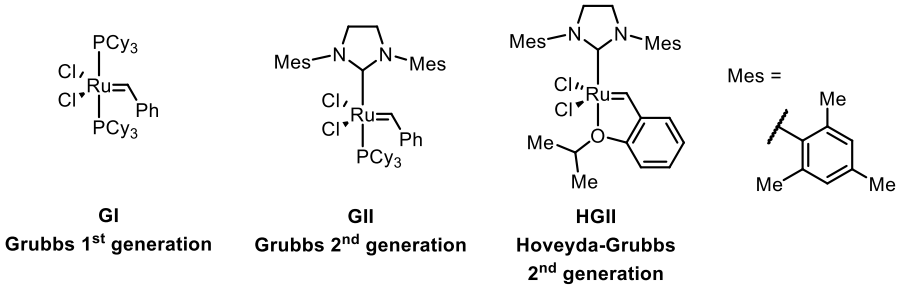
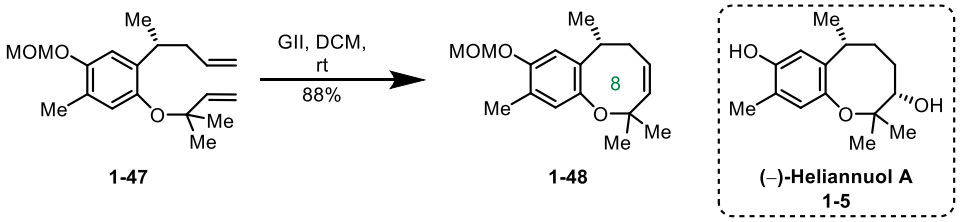


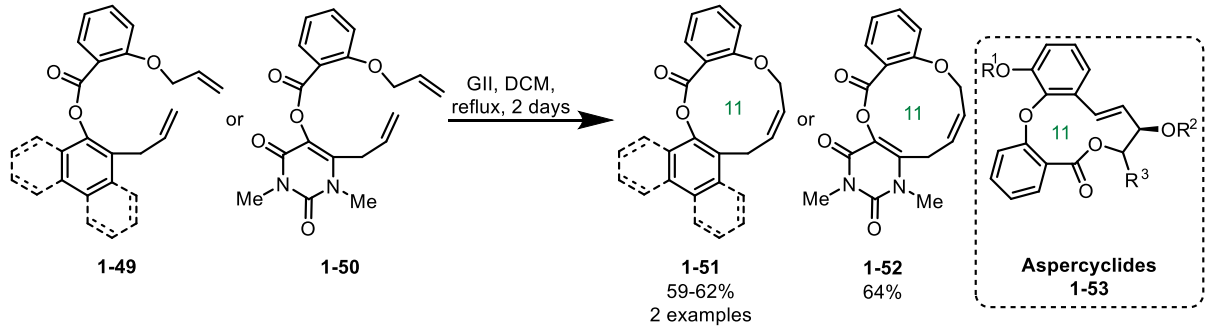
Figure 1-4: Common ring closing metathesis catalysts.

Shishido *et al.* showed that RCM could be used as the key cyclisation step forming the 8-membered ring **1-48** during the synthesis of (–)-heliannuol A, **1-5** (*scheme 1-11*).[24] The diene **1-47** underwent RCM upon treatment with **GII** affording the 8-membered ring **1-48** in good yield.



Scheme 1-9: Ring-closing metathesis forming the key 8-membered ring structure towards the synthesis of (–)-heliannuol A, **1-5**.

In 2009 Majumdar *et al.* reported the synthesis of 11-membered benzannulated lactones **1-51** and **1-52** using RCM reaction during the synthesis of derivatives of naturally occurring aspercyclides **1-53** reported to have various biological activity (*scheme 1-12*).[25] The diallyls **1-49** and **1-50** underwent RCM forming the 11-membered lactones **1-51** and **1-52** respectively in moderate yields. The reactions were performed under high dilution in DCM with **GII** and were refluxed for two days. When using **GI** only catalyst decomposition was seen.



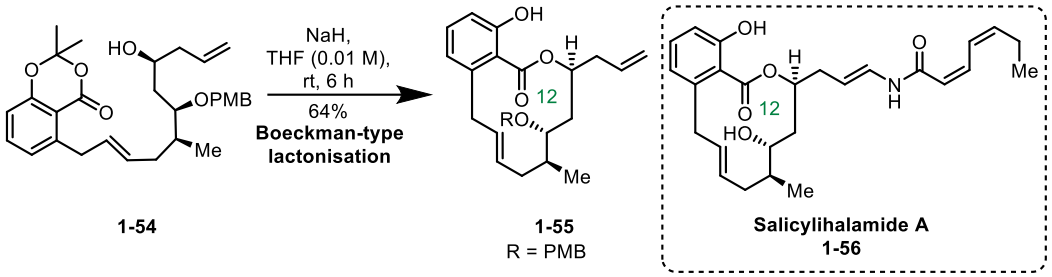
Scheme 1-10: RCM forming 11-membered lactones **1-51** and **1-52**.

1.3.1.4 Lactonisation

Synthetic and naturally occurring benzannulated lactone medium rings are reported in the literature and shown to have a diverse range of biological activity, therefore being able to synthesise them is important.[7,26] Lactonisation reactions are key cyclisation reactions and have been used as the crucial step in the synthesis of many natural products. Lactonisation involves direct reaction between carboxylic acids and alcohol groups, usually requiring some form of activation.

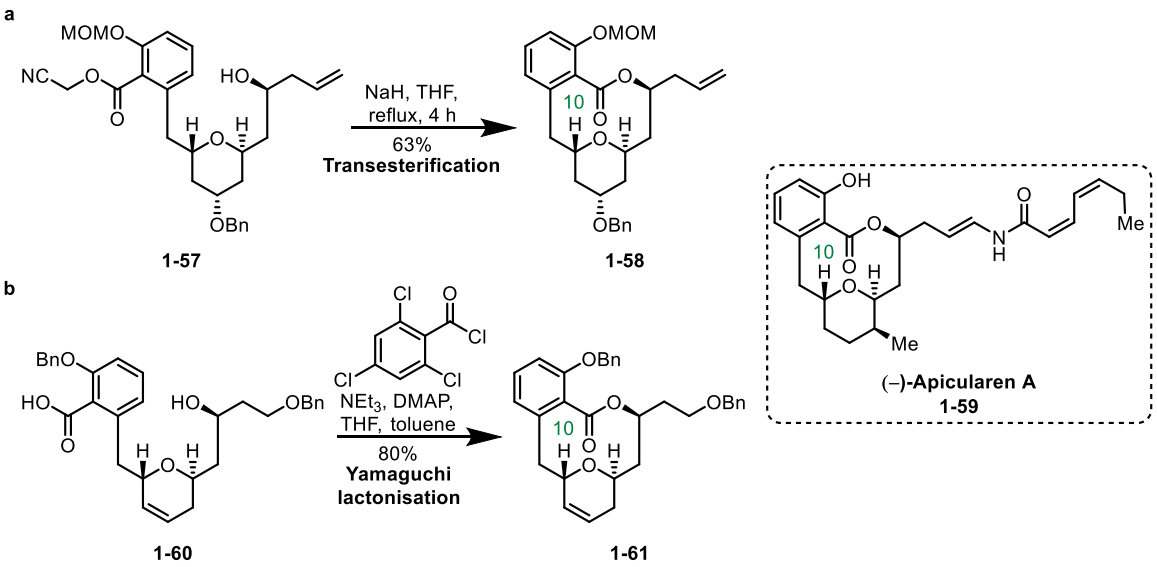
Rizzacasa *et al.* used a Boeckman-type lactonisation as the key cyclisation step in synthesising salicylihalamide A **1-56** a natural product isolated from marine sponges which showed potential antitumour properties (*scheme 1-13*).[27] The 12-memebered lactone **1-55** was formed from **1-54** by treatment with NaH in a diluted solution of THF, where **1-54** underwent Boeckman-type lactonisation

through *in situ* formation of a β-acyl ketene.[28] The desired 12-memebered lactone **1-55** was isolated in good yield.



Scheme 1-11: Lactonisation under Boeckman-type reaction forming 12-memebered lactone **1-55** during the synthesis of salicylihalamide A.

(–)-Apicularen A **1-59** is a natural product isolated from myxobacterial genus *Chondromyces* which showed potent activity against human cancer cell lines and contains a 10-membered lactone at the core.[29] Two alternative reactions utilising lactonisation as the key step to form the 10-membered benzannulated ring **1-58**/**1-61** were undertaken by Panek and Uenishi (*scheme 1-14*).[29,30] Panek *et al.* utilised a transesterification lactonisation using cyanomethyl ester **1-57** (*scheme 1-14a*), promoted using NaH.[30] A similar salicylic cyanomethyl ester was reported by Porco *et al.* for an efficient intermolecular transesterification.[31]



Scheme 1-12: Lactonisation forming the core 10-membered lactone during the synthesis of (–)-apicularen A. **a** – Transesterification cyclisation by Panek *et al*. **b** – Yamaguchi lactonisation by Uenishi *et al.*

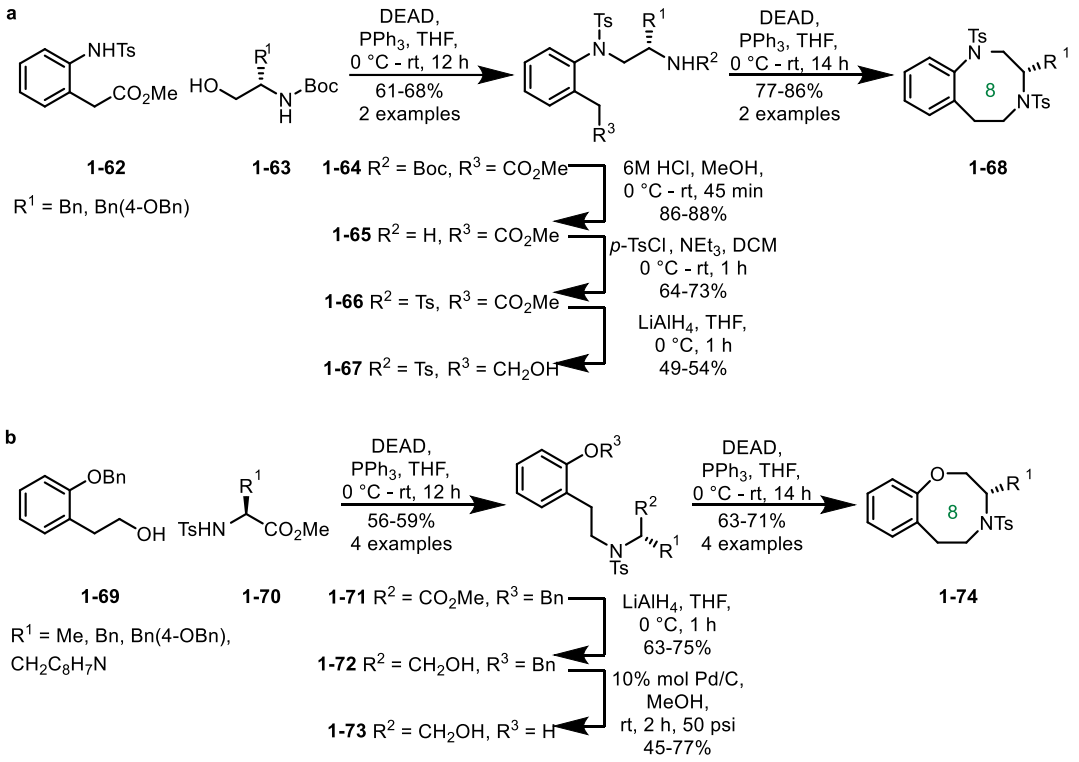
An alternative Yamaguchi macrolactonisation reaction of **1-60** was used by Uenishi *et al.* in 2012, as the key cyclisation step during the synthesis of (–)-apicularen A **1-59** and analogues (*scheme 1-14b*).[29] The 10-membered lactone **1-61** was achieved in high yield.

1.3.1.5 Mitsunobu cyclisation

The Mitsunobu reaction involves a dehydrative coupling between a pronucleophile and a primary or secondary alcohol; if a chiral secondary alcohol is used the stereochemistry is inverted.[32] This

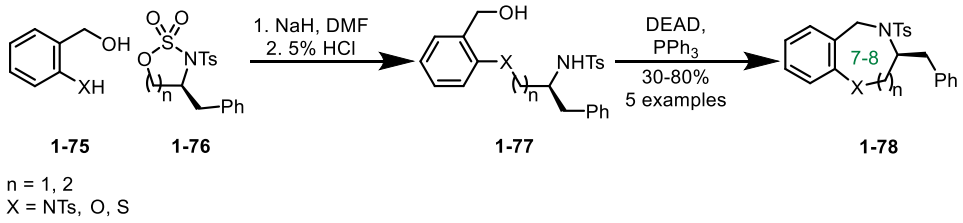
versatile reaction proceeds under mild conditions and is one of the most useful reactions in organic chemistry.[7] Unsurprisingly, this reaction has been used to synthesise medium rings.

Panda and Mishra reported the synthesis of 8-membered benzannulated rings **1-68** containing nitrogen and oxygen heteroatoms, derived from *S*-amino acids **1-63** and substituted benzene derivatives **1-62** (*scheme 1-15a*).[33] The benzodiazocines **1-68** were synthesised as shown in *scheme 1-15*; the *S*-amino alcohol derivatives **1-63** underwent an intermolecular Mitsunobu reaction with **1-62**. The acyclic chain was transformed into **1-67** through a multistep route. Intramolecular Mitsunobu reaction of **1-67** afforded the benzodiazocine products **1-68** in good yields.



Scheme 1-13: Multistep sequence with key Misunobu cyclisation reactions forming benzannulated 8-membered rings containing nitrogen and oxygen heteroatoms. **a** – Benzodiazocine synthesis. **b** – Benzooxacine synthesis.

A similar stepwise route was used to synthesis benzooxazocines **1-74** (*scheme 1-15b*). An initial intermolecular Mitsunobu reaction afforded **1-71** which then underwent reduction and benzyl group cleavage to afford the precursor **1-73**. Under Mitsunobu conditions (DEAD, PPh_3, THF, 0 °C – rt) the 8-membered rings **1-74** were isolated in good yields.



Scheme 1-14: Alternative Mitsunobu cyclisaiton synthesising 7- and 8-membered benzannulated heterocycles.

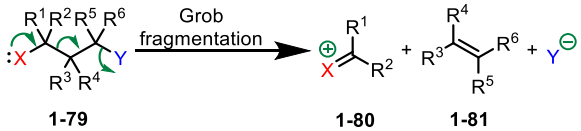
In 2009 Gallagher *et al.* reported the synthesis of similar 7- and 8-membered heterocycles **1-78**, using a Mitsunobu reaction as the key cyclisation step (*scheme 1-16*).[34] *N*-Sulfonyl cyclic sulfamidates **1-76** were used as the source of the chiral amine rather than *S*-amino acids **1-63** forming the starting materials **1-77** for the Mitsunobu cyclisation. Treatment of **1-77** with DEAD and PPh_3 afforded the cyclic products **1-78** in moderate to good yields over the two steps.

1.3.2 Ring expansion reactions

Whilst there is a variety of end-to-end cyclisation reactions that can form medium rings, most suffer from limited scope and often require high dilutions to prevent competing intermolecular reactions. On the other hand, ring expansion reactions can help negate some of the problems associated with entropic cost because they only require the synthesis of 5-7-membered ring precursors.[35–37] There are a plethora of reliable methods to synthesise 5-7-membered rings in the literature. Ring expansion reactions are categorised as fragmentation reactions of fused bicyclic compounds.

1.3.2.1 Fragmentation of fused bicyclic scaffolds

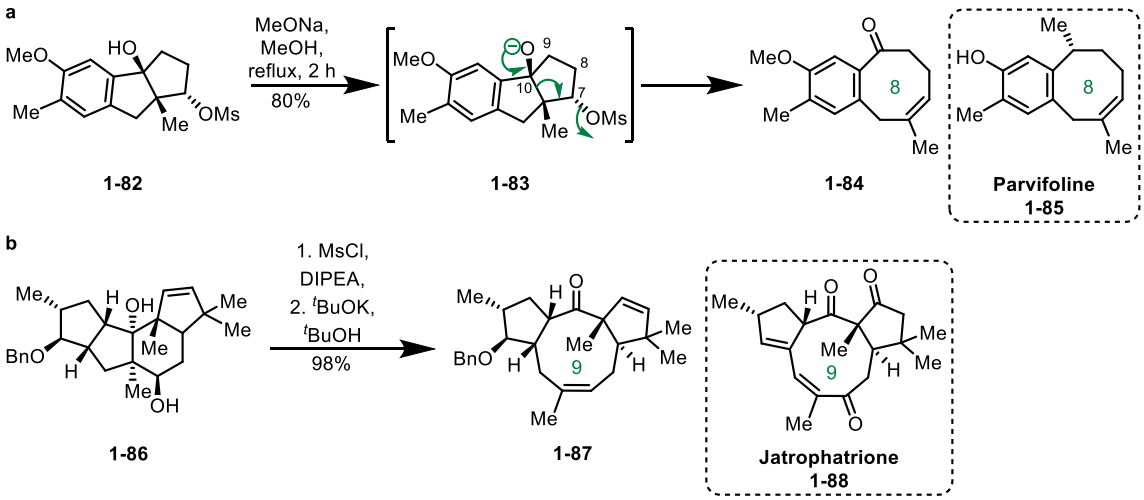
One of the most famous fragmentation reactions is the Grob fragmentation (*scheme 1-17*).[35,36,38,39] In this reaction the precursor **1-79** is heterolytically cleaved into three parts (**1-80**, **1-81**, and $\mathbf{Y}^-$). The leaving group **Y** is key to the reaction providing a strong thermodynamic driving force for the fragmentation of **1-79**, making this reaction an effective synthetic route towards the synthesis of medium rings as these are generally thermodynamically unfavourable processes. In many fragmentation reactions the extrusion of the leaving group makes the reaction irreversible.



1-79 **1-80** **1-81**

Scheme 1-15: Grob fragmentation mechanism. X – Electron donating group. Y – Electron withdrawing leaving group.

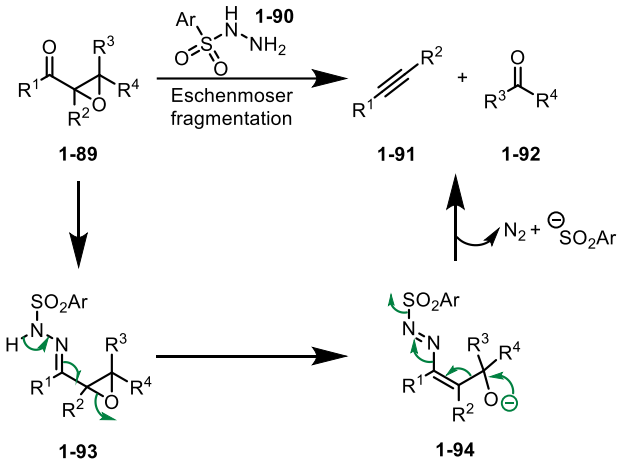
Joseph-Nathan *et al.* employed the principles of the Grob fragmentation to synthesis (±)-parvifoline **1-85**, a potential anticancer agent (*scheme 1-18a*).[40] The key benzannulated 8-membered core was formed under Grob fragmentation. The diol was selectively mesylated at the least sterically hindered secondary alcohol giving **1-82**. The mesylated product **1-82** contains the required relative *anti*-stereochemistry at the C-7 and C-10 positions required for fragmentation of **1-83** giving the *Z*-isomer **1-84** in 80% under basic conditions.



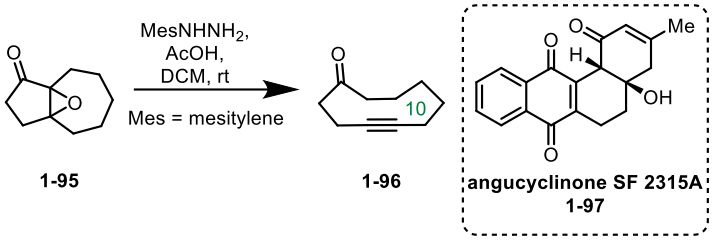
Scheme 1-16: Grob-type fragmentation reactions forming medium rings. **a** – Grob-type fragmentation during the synthesis of (±)-parvifoline. **b** – Grob-type fragmentation during the synthesis of jatrophatrione.

More recently Paquette *et al.* utilised the Grob fragmentation to install the 9-membered ring during the synthesis of jatrophatrione **1-88**, a potential antileukemic natural product (*scheme 1-18b*).[41] Again the medium ring **1-87** was formed by selective mesylation of the less sterically hindered secondary alcohol of tetracyclic 1,3-diol **1-86** followed by treatment with ^{t}BuOK to initiate the Grob fragmentation, giving **1-87** in excellent yield.

Another similar fragmentation reaction is the Eschenmoser fragmentation proceeding as shown in *scheme 1-19*.[42,43] Condensation of the aryl sulfonyl hydrazine **1-90** onto the α,β-epoxyketone **1-89** gives **1-93**. Proton loss initiates the fragmentation of **1-94** leading to alkyne **1-91** formation and the ketone **1-92**. A molecule of nitrogen and aryl sulfinate are the by-products; the formation of these highly stabilised by-products are stronger driving forces than the loss of the leaving group in the related Grob fragmentation ring expansion.

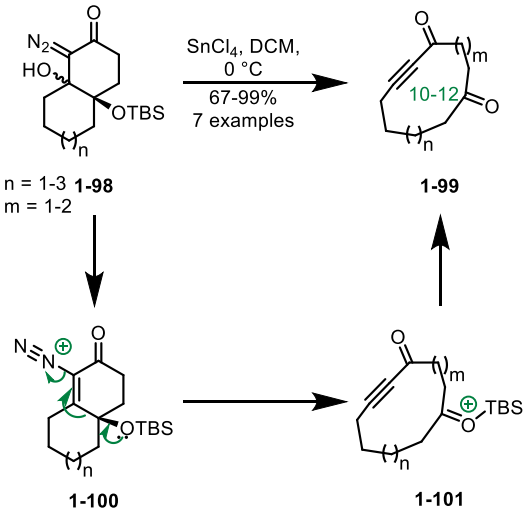


Scheme 1-17: Eschenmoser fragmentation reaction.



Scheme 1-18: Eschenmoser-type fragmentation reported by Reese and Danishefsky.

Whilst synthesising derivatives of an angucyclinone **1-97**, shown to exhibit both mild antibacterial and moderate antiviral activity in 1992 Danishefsky *et al.* reported the synthesis of 10-membered ring ynone **1-96** (*scheme 1-20*).[44] This work was based on previously reported results by Reese *et al.* in 1981, where epoxy-ketone **1-95** was treated with mesitylene-2-sulfonyl hydrazine in acetic acid and DCM undergoing Eschenmoser-type fragmentation to produce 10-membered ring **1-96**.[45]



Scheme 1-19: Grob-type fragmentation-ring expansion reported by Brewer *et al.*

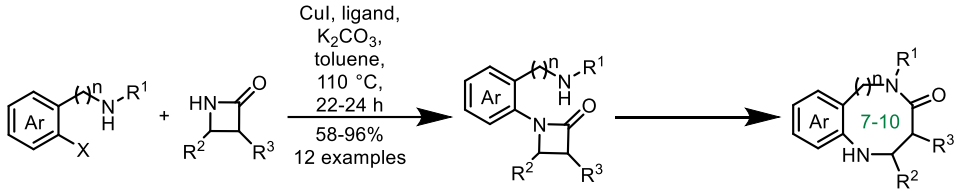
An alternative fragmentation reaction forming 10-12-membered rings **1-99** was reported by Brewer *et al.* in 2012 (*scheme 1-21*).[46] The Lewis acid-promoted fragmentation of bicyclic γ-silyloxy-β-hydroxy-α-diazoketones **1-98** give cyclic 2-alkynones **1-99** in high yields. The proposed reaction mechanism is shown in *scheme 1-21*. Under Lewis acidic conditions the β-hydroxyl is eliminated giving vinyl diazonium intermediate **1-100**. This intermediate can then undergo a Grob-type fragmentation resulting in the loss of nitrogen gas and subsequent loss of the *tert*-butyldimethylsilyl protecting group gives the medium ring **1-99**. As seen before the formation of a molecule of nitrogen is the thermodynamic driving force for the reaction.

In all these fragmentation ring expansion reactions a good choice of leaving group is essential to the fragmentation occurring. It both provides a good thermodynamic driving force for the reaction and also makes the reaction irreversible.[35] Whilst these reactions are generally very successful once the starting material is synthesised. Synthesising the starting material containing the right relative stereochemistry for the elimination is often not as straightforward.

1.3.2.2 Side-chain insertion fragmentation

An alternative approach to ring expansions is to have side-chain insertions, forming the fused bicyclic structure *in situ*, which then undergoes ring expansion by fragmentation. Side-chain insertion reactions often have starting materials which are simpler to access than the fused bicyclic compounds shown above, however the reactions can be reversible making the ring expansion reaction more challenging.

A tandem copper-catalysed C-N bond formation and ring expansion cascade was reported by Buchwald *et al.* in 2004 (*scheme 1-22*).[48] *N*-Arylated-β-lactam **1-104** was formed *in situ* by heating the aryl bromide/iodide **1-102** and β-lactam **1-103** in toluene with a catalyst, which then undergoes a transamidation reaction opening the β-lactam ring to afford **1-105**. The relief of the ring strain in the β-lactam is presumably the main driving force for the reaction.

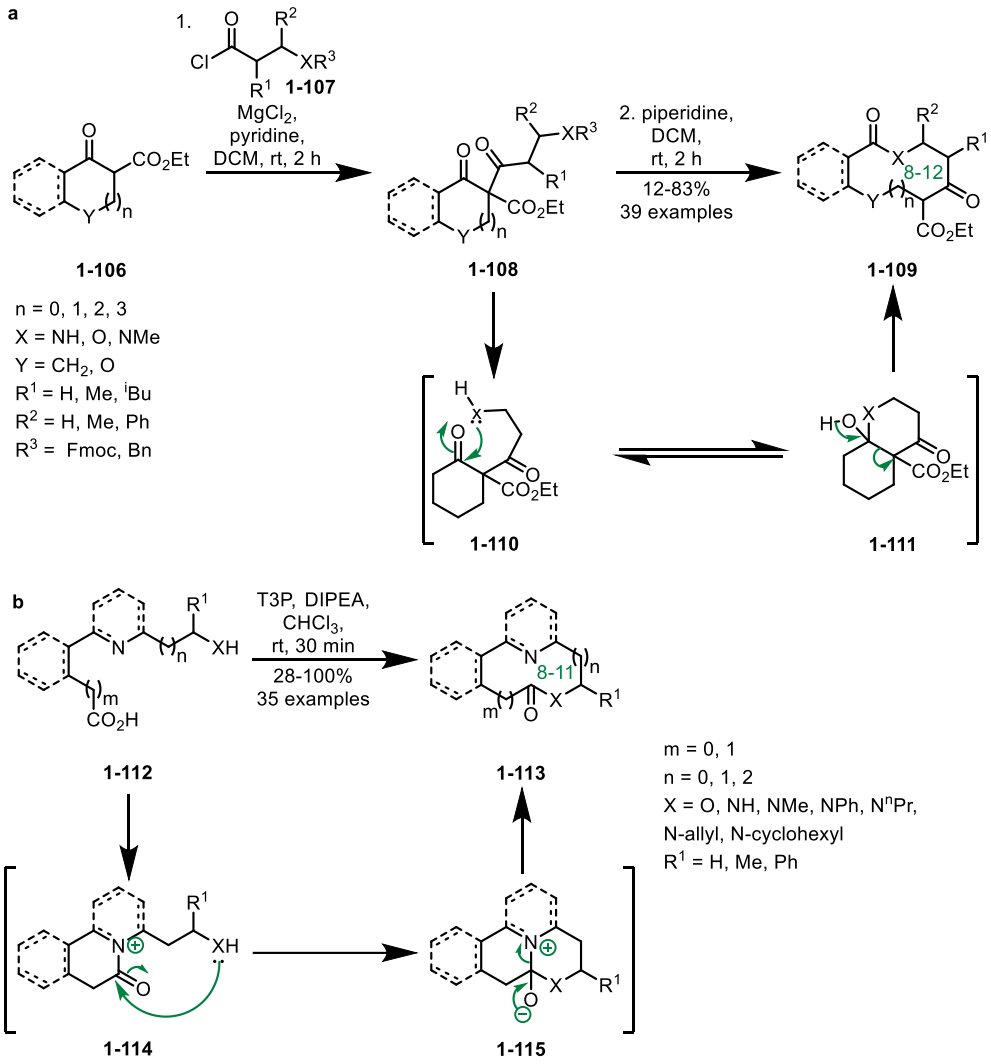


1-102 **1-103** **1-104** **1-105**

n = 0-3
X = Br, I
R^1 = H, Bn, $(CH_2)_5OH$, CH(Me)CH(OH)Ph
R^2 = H, Ph
R^3 = H, $CH(CH_3)_2$

Scheme 1-20: Tandem copper-catalysed C-N bond formation and ring expansion.

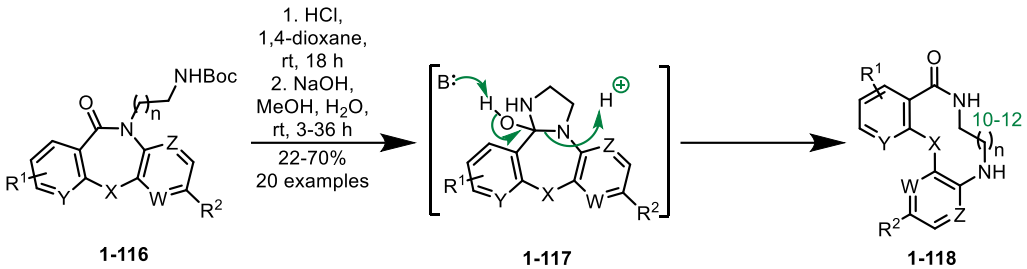
Unsworth *et al.* reported the synthesis of 8-12-membered lactams and lactones **1-109** (*scheme 1-23a*).[49,50] A two-step process involving initial formation of **1-108** by acylation of the cyclic β-keto ester **1-106** with **1-107** then treatment of intermediate **1-108** with piperidine in DCM resulted in the medium ring products **1-109** in 12-83% yields. Cleavage of the Fmoc protecting group of **1-108** forming **1-110** initiated the spontaneous ring expansion through intermediate **1-111**. The driving force for the reaction is likely to be the formation of a stabilised enolate and an amide group. The product **1-109** contains the same β-keto ester functionality required for acylation/ring expansion as the starting material **1-106** and can undergo another acylation/ring expansion cascade forming larger macrocycles **1-109**.



Scheme 1-21: Ring expansion reactions reported by the Unsworth group. **a** – Ring expansion by side-chain insertion. **b** – Ring expansion reaction by *in situ* formed 5-6-membered ring followed by side-chain insertion.

More recently the Unsworth group have reported an alternative route towards medium ring lactones and lactams **1-113** from linear starting materials **1-112** (*scheme 1-23b*).[51] Under the reaction conditions (T3P, DIPEA, $CHCl_3$, rt) the carboxylic acid **1-112** is activated and cyclises to form **1-114** which can then undergo side-chain insertion-ring expansion forming the medium ring **1-113** in low to excellent yields.

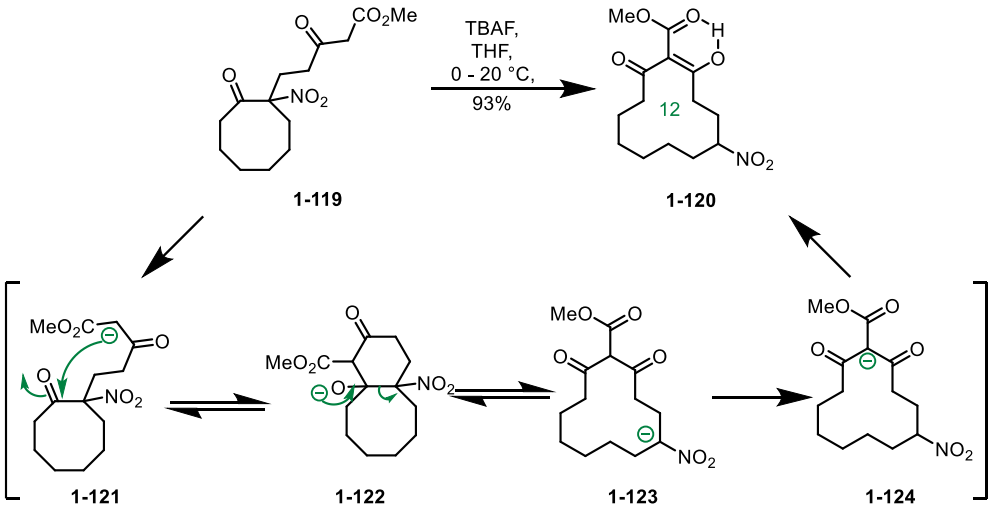
An alternative route towards the synthesis of medium ring lactams **1-118** using HIRE (hydrated imidazoline ring expansion) reaction was reported by Krasavin *et al.* (*scheme 1-24*).[52] Under acidic conditions the Boc group was cleaved from **1-116**. This lactam then cyclises forming the proposed hydrated-imidazoline intermediate **1-117** which then fragments forming the 10-12-membered benzannulated lactams **1-118** in moderate to good yields. The irreversible formation of an amide bond with the more nucleophilic amine is proposed to drive the reaction towards medium ring synthesis, expelling the less nucleophilic anilinic amino group.



n = 1, 2, 3
X = O, S
W/Y/Z = CH, N
R^1 = H, 4-Cl, 2-Me
R^2 = H, CF_3, CN, NO_2, SO_2NMe_2

Scheme 1-22: Hydrated imidazoline ring expansion reaction.

Hesse *et al.* reported the C-C bond forming ring expansion reaction of β-ketoester **1-119** to 12-membered ring **1-120** in high yield through a carbanion exchange cascade (*scheme 1-25*).[53]



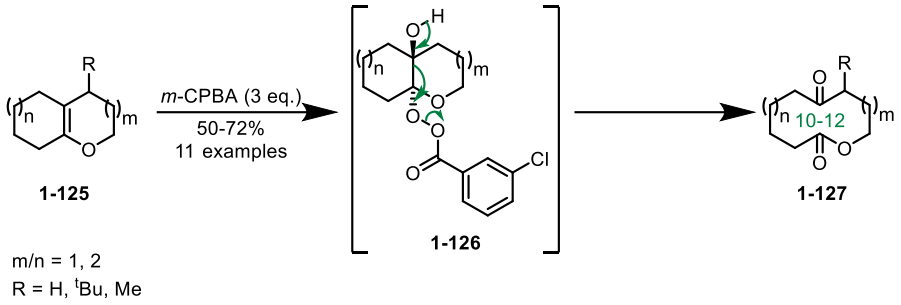
Scheme 1-23: Ring expansion of cyclic ketone **1-119** forming medium ring **1-120** through C-C bond formation.

Under basic conditions **1-119** is deprotonated forming **1-121** and adds to the ketone α to the nitro group forming **1-122** which ring opens forming anion **1-123**. Proton exchange forms tricarbonyl anion **1-124** which is highly stabilised and protonation then forms the product **1-120**. The driving force for the reaction is the formation of highly stabilised anion **1-124** and ring strain relief going from an 8-membered ring to a 12-membered ring.

1.3.2.3 Redox-mediated fragmentation

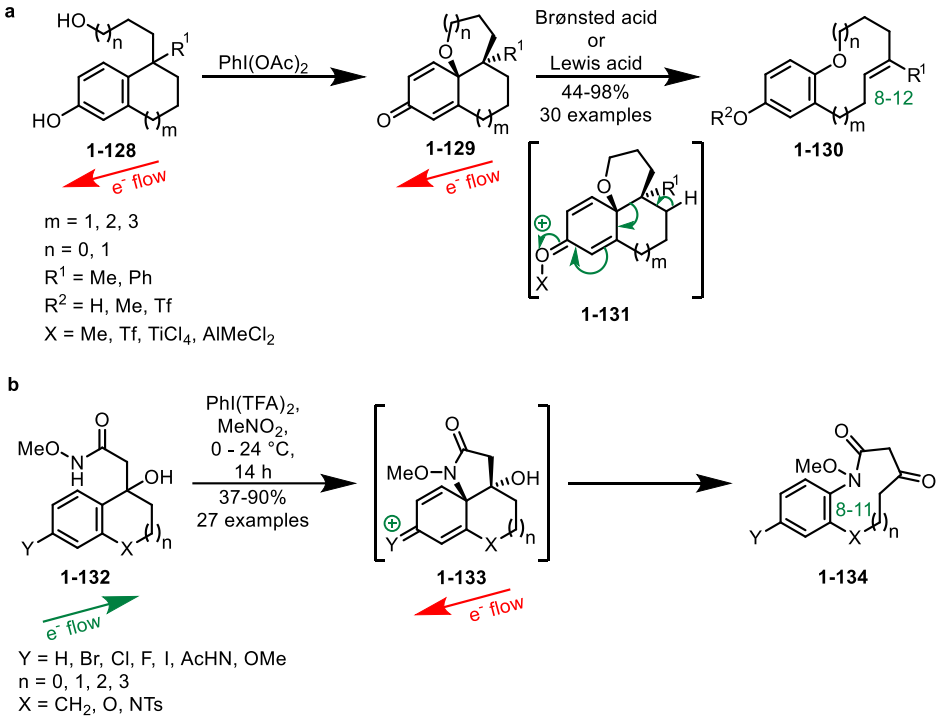
Redox processes can also be used to implement fragmentation-type ring expansions, such as oxidative cleavage of a double bond in a fused bicyclic compound. This process of oxidative cleavage is similar to that of the Grob fragmentation reaction shown above, with the oxidation of the double bond providing the precursor to the Grob fragmentation reaction.

Borowitz *et al.* reported the synthesis of 10-12-membered lactones **1-127** by oxidative ring expansion (*scheme 1-26*).[54] Treatment of bicyclic enol ether **1-125** with *m*-CPBA (3 eq.) resulted in oxidation of the double bond forming **1-126**. Ring expansion occurred by fragmentation of **1-126** eliminating the *meta*-chlorobenzoic acid to afford the medium ring lactones **1-127** in 50-72% yields.



Scheme 1-24: Oxidative ring opening using *meta*-chloroperbenzoic acid

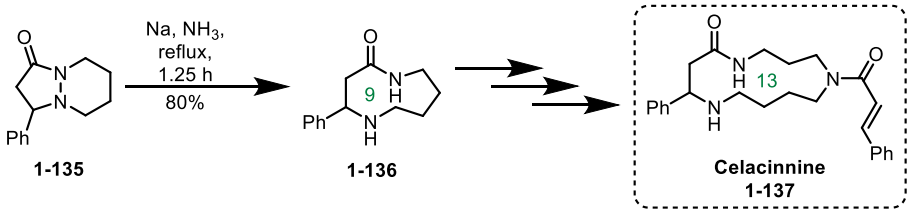
An alternative oxidative ring opening was reported by Tan *et al.* using an oxidative dearomatisation-ring expansion rearomatisation (ODRE) sequence which resulted in natural product-based benzannulated medium rings **1-130** (*scheme 1-27a*).[55] In this two-step process bicyclic phenols **1-128** are oxidatively dearomatised affording the polycyclic cyclohexadienone substrates **1-129** for the ring expansion. A subsequent rearomatisation-driven ring expansion **1-131** under Lewis or Brønsted acid conditions produced the benzannulated medium rings **1-130** in good to excellent yields. This reaction is principally an oxidative fragmentation reaction, but the oxidation takes place on a distal phenol group in **1-128**.



Scheme 1-25: Oxidative Dearomatisation-ring expansion rearomatisation forming medium rings. **a** – Formation of benzannulated medium ring ethers. Brønsted acid or Lewis acid: TsOH, $Cu(BF_4)_2$, Tf_2O. **b** – Formation of benzannulated medium ring lactams.

Whilst the yield of the products **1-130** overall were good, some products were formed as a mixture of olefin isomers and solvent adducts and only phenol products could be formed. In 2018 Tan *et al.* reported an alternative umpolung approach to the tandem ODRE reaction accessing a wider range of benzannulated lactam medium rings **1-134** (*scheme 1-27b*).[47]

Cation intermediate **1-133** is formed by attack of the electron rich arene onto the activated *N*-methoxyamide. The initial dearomatisation step (**1-132** to **1-133**) involves the opposite flow of electrons compared to the previously reported tandem ODRE (**1-128** to **1-129**) in *scheme 1-27a*. The C1-hydroxyl group then facilities the spontaneous rearomatisation causing C-C bond cleavage resulting in benzannulated lactams **1-134** in moderate to good yield.

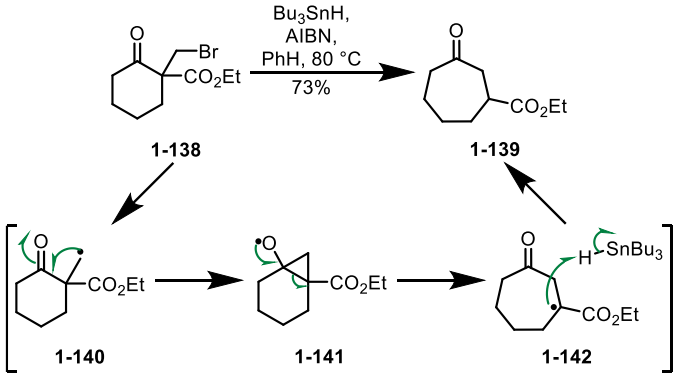


Scheme 1-26: Reductive cleavage of N-N bond in the synthesis of celacinnine.

Reductively cleaving a single bond is also an alternative ring expansion fragmentation route to synthesising medium rings. During the synthesis of celacinnine **1-137** a spermidine alkaloid found in *Maytenus arbutifolia,* Wassermann *et al.* reported the use of N-N reductive bond cleavage (*scheme 1-28*).[56] Treatment of **1-135** with Na/NH_3 resulted in the reductive cleavage of the N-N single bond forming **1-136** in 80% yield.

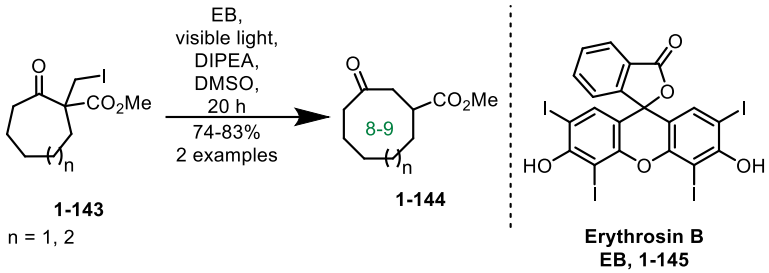
1.3.3 Radical-mediated fragmentation

Radical reactions using high-energy reactive intermediates have been used to synthesise medium rings through ring expansion reactions.[35,57] The radical based ring expansion reaction using alkoxy radicals in the Dowd-Beckwith rearrangement is one of the most common radical based ring expansions (*scheme 1-29*).[58–63]



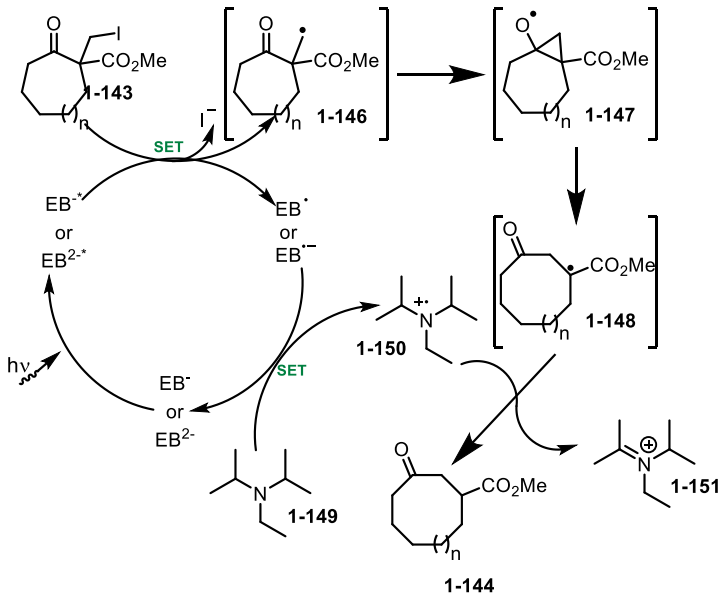
Scheme 1-27: Dowd-Beckwith radical ring expansion.

Dowd first demonstrated this radical based synthesis of medium rings **1-139** in 1987.[58] In this reaction the primary alkyl radical **1-140** on a pendant chain reversibly adds into the ketone forming the high energy oxyradical **1-141**. Rearrangement of this radical **1-141** forms the tertiary radical **1-142** which abstracts a hydride from the tributyltin hydride forming the desired medium ring product **1-139**. The formation of the more stable tertiary radical **1-142** stabilised by the ester over the primary radical **1-140** is the thermodynamic driving force for the reaction.



Scheme 1-28: Organic-dye catalysed Dowd-Beckwith radical ring expansion.

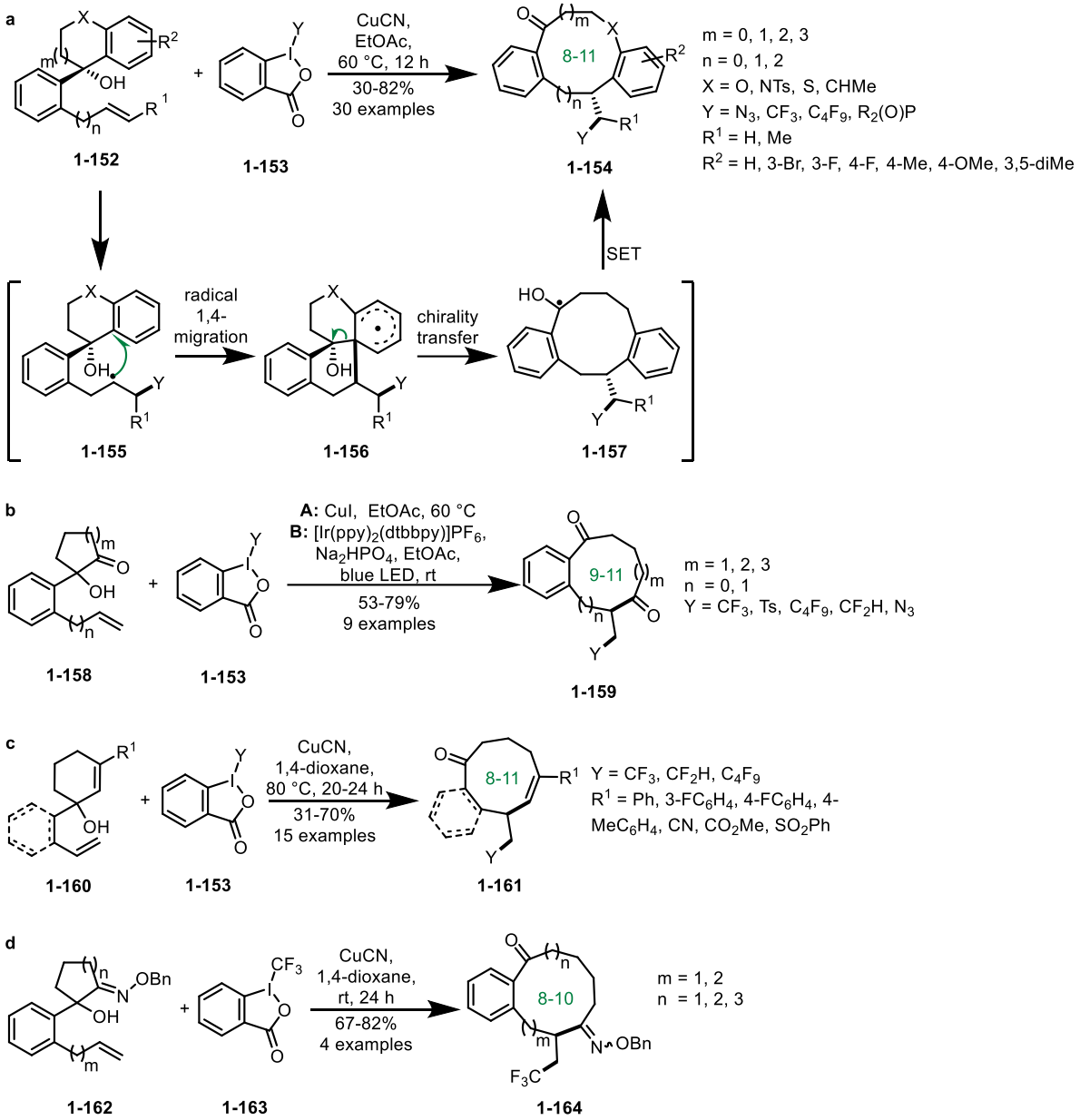
Almost 30 years after it was first published Itoh *et al.* reported an organic dye-catalysed Dowd-Beckwith radical ring expansion reaction using environmentally friendly reagents in place of AIBN and tributyltin hydride (*scheme 1-30*).[64] The photocatalyst **1-145** is required to initiate the reaction by SET (single electron transfer) to **1-146** cleaving the C-I bond (*scheme 1-31*). The reaction then proceeds as above, during which time the oxidised EB catalyst (**1-145**) is reduced by the sacrificial amine **1-149**, completing the catalytic cycle. The radical cation **1-150** provides the hydride to produce the medium ring **1-144**.



Scheme 1-29: Proposed organic-dye catalysed Dowd-Beckwith radical ring expansion mechanism.

Unactivated alkenes represent one of the most abundant feedstocks for chemical synthesis and their conversion into medium rings through radical-based reactions represents an underexplored area of organic chemistry.[65] In 2016 Liu *et al.* reported a new synthetic protocol in which radicals add to

unactivated alkenes **1-152** leading to aryl migration and medium ring synthesis forming products **1-154** in moderate to good yields (*scheme 1-32a*).



Scheme 1-32: Radical mediated ring expansions with unactivated alkenes.

Under copper catalysis the radical from **1-153** adds to the unactivated alkene **1-152** forming **1-155** with a carbon-centred alkyl radical. This radical intermediate then undergoes *ipso* attack on the aryl ring **1-156** resulting in intramolecular 1,4- or 1,5-aryl migration to form the neutral ketyl radical **1-157**. The benzannulated medium ring **1-154** is obtained by SET to the ketyl radical **1-157**. The neutral ketyl radical **1-157** is lower energy than the high-energy sp^3 carbon centred radical **1-155** providing the thermodynamic driving force for the reaction.

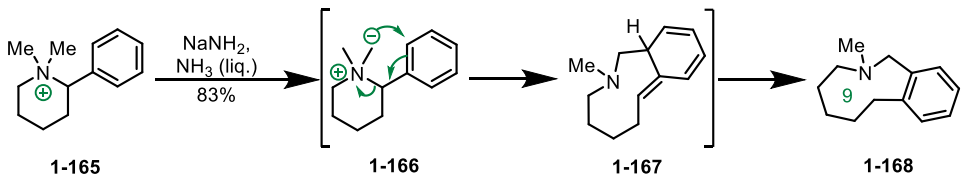
In 2016 Liu *et al.* also reported 1,4- and 1,5-formyl migrations resulting in benzannulated medium rings **1-159** in good yields from unactivated alkene **1-158** (*scheme 1-32b*).[66] The reactions proceed under a similar radical based mechanism as the aryl migration reaction above in *scheme 1-32a*.

Medium-sized cyclic ketones **1-161** were also accessed via similar chemistry following 1,3- and 1,4-vinyl migrations from starting material **1-160** (*scheme 1-32c*).[67] The products **1-161** were formed in moderate to good yields. In this reaction both benzannulated and unsubstituted alkenes **1-160** could be used to form the medium rings.

Most recently in 2018 the Liu group reported the formation of β-trifluoromethylated oxime medium rings **1-164** in good yields (*scheme 1-32d*).[68] The reaction proceeded via 1,4- and 1,5-oximino migration initiated by trifluoromethyl radical addition onto unactivated alkene **1-162** in a similar manner to that shown in *scheme 1-32a*.

1.3.4 Sigmatropic rearrangements resulting in medium ring formation

Sigmatropic rearrangements have found utility in the synthesis of medium rings in several different applications. Often there exists an equilibrium between the starting materials and the medium ring products, therefore a thermodynamic driving force favouring the medium ring product is required.[35] The driving forces often include formation of stronger bonds or ring strain relief. Many of these rearrangements use charged starting materials or intermediates forming neutral products, as a driving force for the reaction. Such an example is shown in *scheme 1-33*, a reaction reported by Hauser *et al.*[69]

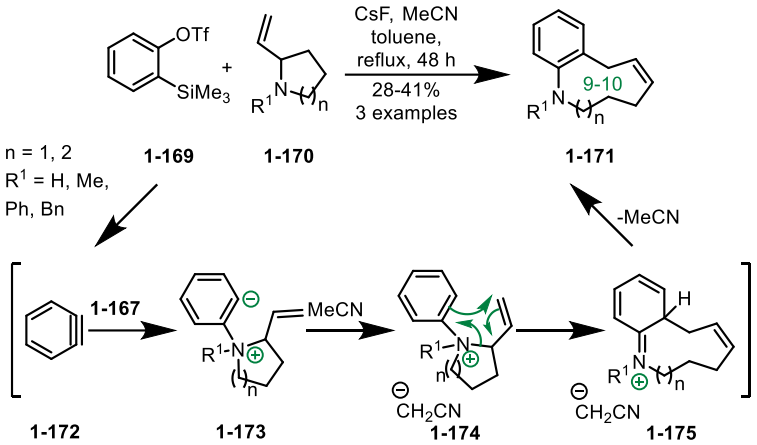


Scheme 1-33: [2,3]-Sigmatropic rearrangement reported by Hauser *et. al.*

The rearrangement of ammonium salt **1-165** is initiated by deprotonation with sodium amide in liquid ammonia leading to ylide **1-166** formation. [2,3]-Sigmatropic rearrangement affords **1-167** which results in the 9-membered benzannulated ring **1-168** after rearomatisation.

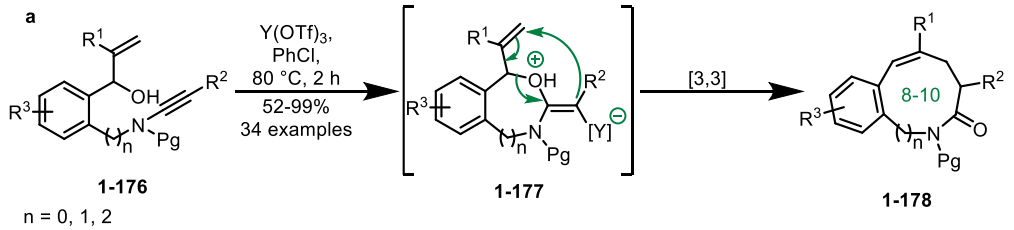
More common in the literature are [3,3]-sigmatropic rearrangements forming medium ring products. An example of this was reported by Greaney *et al.* in 2009 in which cyclic amine **1-170** undergoes a benzyne aza-Claisen rearrangement (*scheme 1-34*).[70] Unlike neutral rearrangements with allylenamines this reaction did not require very high temperatures (>200 °C). The *in situ* formed electrophilic benzyne **1-172** by reaction of **1-169** with CsF at elevated temperatures (110 °C) reacted rapidly with the nucleophilic nitrogen in **1-170** affording the zwitterion **1-173**, which is protonated by

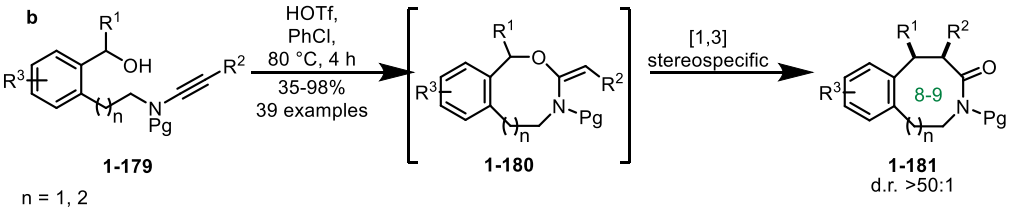
the solution giving **1-174**. This intermediate **1-174** then underwent an aza-Claisen rearrangement forming dearomatized **1-175** which rearomatises to form the product **1-171**. Reaction of the acyclic amines with substituted benzynes showed the reaction went via an aza-Claisen rearrangement and not an S_N2' pathway.



Scheme 1-34: Benzyne aza-Claisen rearrangement forming 9-10 membered benzannulated heterocycles.

Tandem intramolecular alkoxylation/Claisen rearrangement catalysed by transition metals are currently of high interest due to the high atom economy and bond-forming efficiency for synthesising functionalised cyclic compounds.[71] Ye *et al.* reported in 2017 a yttrium-catalysed intramolecular hydroalkoxylation/Claisen rearrangement cascade for the synthesis of benzannulated 8-12-membered lactams **1-178** (*scheme 1-35a*).





Scheme 1-35: Lactam synthesis through alkoxylation/Sigmatropic rearrangements. **a** – Alkoxylation/Claisen rearrangement. b – Hydroalkoxylation/[1,3]-sigmatropic rearrangement.

Sulfonyl-protected ynamide **1-176** was treated with yttrium triflate in toluene at 80 °C. The hydroxyl group attacks the yttrium triflate-activated ynamide forming the vinyl-yttrium intermediate **1-177** through a keteniminum intermediate. After proton transfer intermediate **1-177** undergoes [3,3] Claisen rearrangement forming the medium ring lactams **1-178** in moderate to excellent yields. The authors note that low concentrations are necessary to prevent intermolecular reactions for some of the larger ring sizes. The formation of the strong amide C=O bond is predicted to contribute to the progression of the reaction.

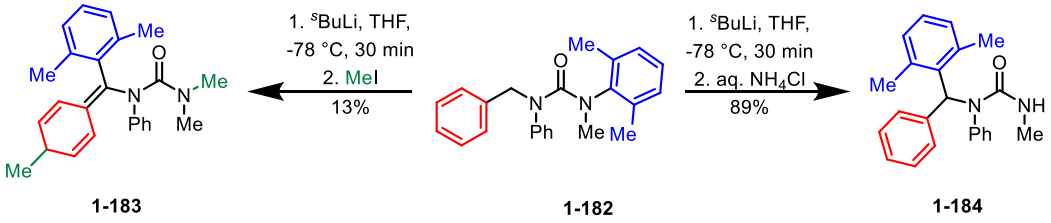
Ye *et al.* also reported the synthesis of 8-membered lactams **1-181** through a metal-free hydroalkoxylation/[1,3]-sigmatropic rearrangement (*scheme 1-35b*).[72] The benzyl alcohol-tethered ynamides **1-179** were treated with triflic acid in toluene and heated to 80 °C affording the 8-membered lactams **1-180** in generally high yields, with all product produced in high diastereoselectivity (>50:1).

A variety of different methods can be used to synthesis medium rings through both cyclisation and ring expansion reactions. Many of the cyclisation reactions shown have a limited scope. Ring expansion reactions generally offer an alternative and more successful route towards medium rings. These reactions have become increasing common in the literature of the last decade and have shown wider utility, with larger scopes and more available ring sizes accessed. Despite the increased success of ring expansion reactions, the requirement for a good leaving group as the thermodynamic driving force for the reaction often makes the synthesis of the starting materials more challenging. There needs to be a more generalised route towards medium ring synthesis where the synthesis of the starting materials is straightforward and the reactions can be easily scaled-up whilst maintaining high yields.

1.4 *N to C* aryl migration and vinyl migration

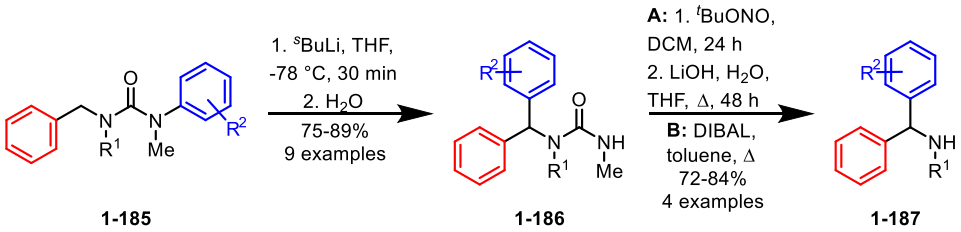
1.4.1 Initial discovery

Whilst investigating the regioselective lithiation of *N*-aryl ureas in 2007 the Clayden group discovered a stereospecific intramolecular aryl transfer;[73] this new reaction involved the migration of an aryl ring from a urea nitrogen to a sp^3 benzylic carbon (*scheme 1-36*).



Scheme 1-36: Initial discovery of the *N to C* aryl migration of *N*-aryl-*N'*-benzyl ureas when treated with base whilst investigating lithiation of *N*-aryl ureas.

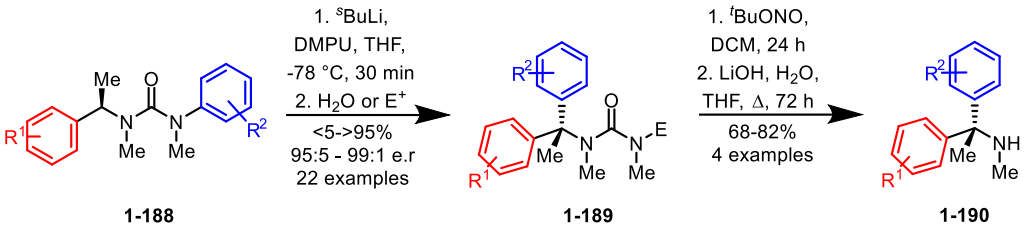
To identify the site of deprotonation *N*-aryl-*N'*-benzyl urea **1-182** was treated with ^{s}BuLi at -78 °C then quenched with MeI. Purification of the reaction mixture resulted in the isolation of an unstable compound identified as urea **1-183** in low yield. Urea **1-183** originates from the *N to C* migration of the dimethyl aryl ring. Replacement of the methylation step for quenching with aqueous NH_4Cl resulted in isolation of urea **1-184** in high yield.



R^1 = Me, Ph or *p*-Tol
R^2 = H, 4-Cl, 2-Me, 4-Me, 2-OMe, 4-OMe, 2,6-diMe

Scheme 1-37: N to C aryl migration of a range of *N*-aryl-*N'*-benzyl ureas under basic conditions followed by cleavage of the urea moiety forming diaryl methylamines.

A range of *N*-aryl-*N'*-benzyl ureas **1-185** were subjected to similar conditions resulting in rearranged ureas **1-186** in good yields (*scheme 1-37*). Interestingly the rearrangement took place irrespective of the electronic or steric nature of the substituents on the aryl migrating ring. The aryl migration was determined by analysis of the reaction products to be an *ipso* S_NAr displacement by attack of the benzylic anion formed by benzylic lithiation of urea **1-185** with ^{s}BuLi. The diarylmethyl amine derivatives **1-187** were accessed through hydrolysis of the *N*-nitroso derivative of the urea **1-186** or by reductive cleavage of the urea with DIBAL.



R^1 = H, 4-Cl, 2-F, 3-F, 4-F, 2-Me, 4-Me, 2-OMe, 4-OMe, 2,3-benzo, 3,4-benzo, 3-Cl/4-F, 3,4-OMe
R^1 = H, Cl, OMe
E = H, Me, NO

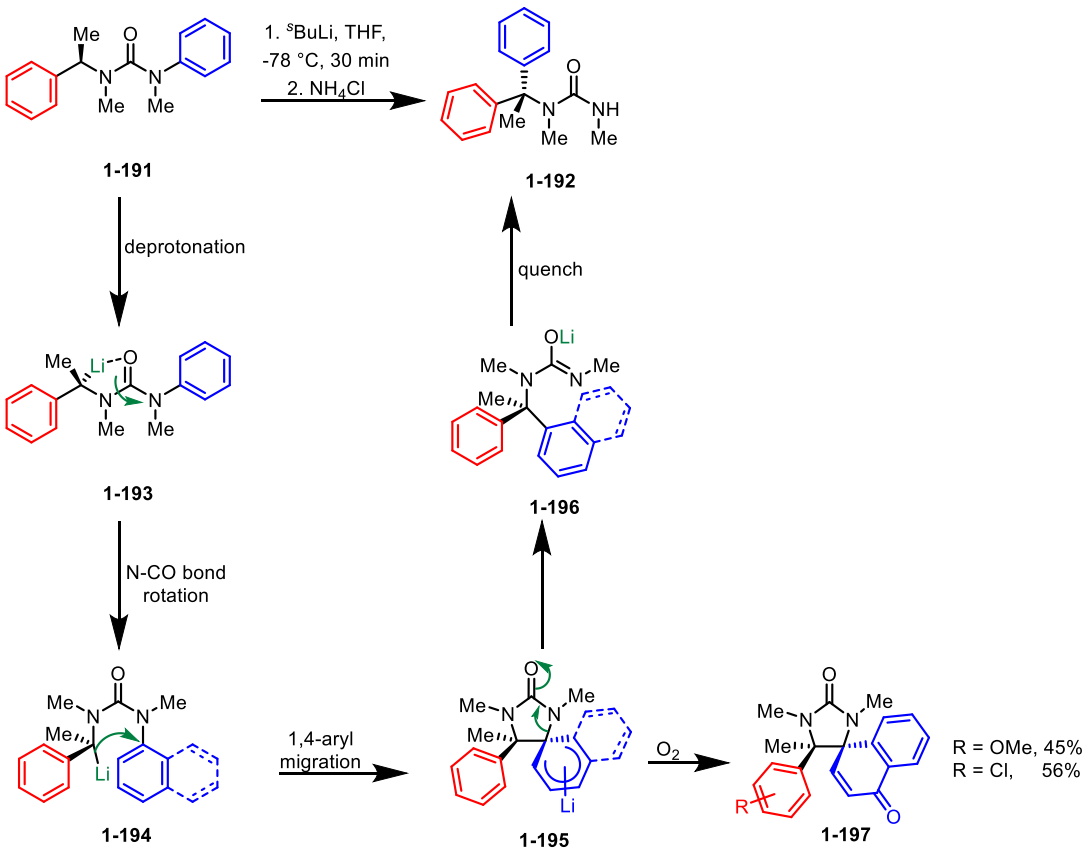
Scheme 1-38: Aryl migration of α-methylbenzylureas under basic conditions followed by cleavage of the urea moiety.

Similar rearrangements were achieved using tertiary benzyl lithium intermediate formed from treatment of ureas **1-188** with ^{s}BuLi (*scheme 1-38*). Although the migration was much slower than previous examples (*scheme 1-37*) resulting in significant amounts of starting material remaining after 2 hours. Attempts to increase the yield of **1-189** included warming the reaction above -78 °C and increasing the reaction time, however, both resulted in olefinic products, a result of urea elimination.

To improve the rate of reaction DMPU, a lithium chelating agent was added to the reaction mixture before ^{s}BuLi addition. The reaction rate was improved and **1-189** was isolated in high yields irrespective of the electronic nature of the migrating ring. When enantioenriched starting ureas **1-188** were used little to no loss of enantiomeric purity was seen after rearrangement, suggesting that the *N to C* aryl migration proceeds with almost complete stereospecificity through a configurationally stable organolithium intermediate. The urea moiety was once again cleaved by hydrolysis of the *N*-nitroso derivative to form **1-190**.

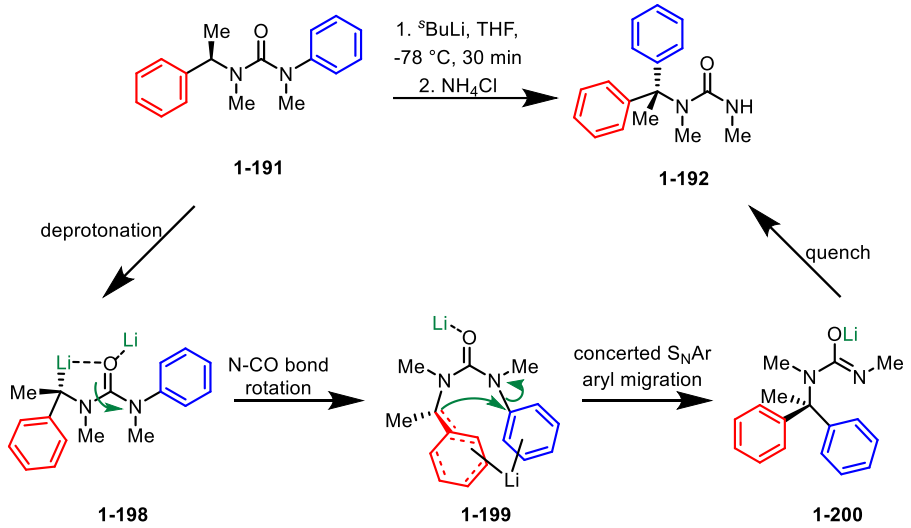
1.4.2 The reaction mechanism

The initial proposed mechanism for the *N to C* aryl migration is shown in *scheme 1-39*.[73,74] Lithiation at the benzylic position forms **1-193**. Bond rotation about the N-CO bond brings the carbanion in close proximity to the migrating aryl ring forming **1-194**. The carbanion then attacks the distal aryl ring at the *ipso* position and anion **1-195** is formed. The N-C bond is cleaved and the anion of the product **1-196** is protonated by NH_4Cl addition forming the *N to C* aryl migrated product **1-192**. The formation of intermediate **1-195** is supported by the isolation of **1-197** containing the naphthyl migrating ring under air oxidation.



Scheme 1-39: Proposed mechanism for *N to C* aryl migration based on the isolation of oxidised **1-197**.

However, following on from this report the mechanism was further investigated using a combination of *in situ* NMR and infrared spectroscopy studies and computational DFT calculations.[74] The conversion of the lithiated starting material **1-193** could be followed to the product anion **1-196** by NMR spectroscopy. The exact intermediate species were not characterised. Whilst NMR studies suggested the presence of **1-195** when the naphthyl group migrated, there was no evidence of a similar intermediate when the phenyl group migrated. Due to this a new mechanism was proposed (*scheme 1-40*).



Scheme 1-40: Proposed mechanism based on studies using *in situ* NMR and infrared spectroscopy and DFT calculation. Solvation of the lithium cations with THF not shown.

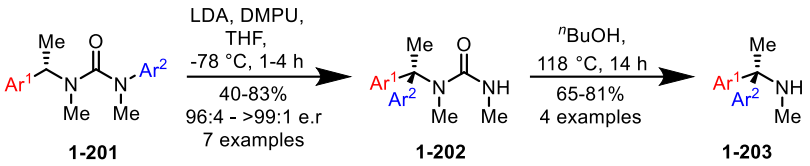
Similar results were seen when the reaction was followed by *in situ* infrared spectroscopy. After ^{s}BuLi addition two peaks were formed which were assigned to anions **1-198** and **1-199**, these then decayed over time and upon warming the product anion **1-200** was seen.

DFT studies confirmed that the mechanism in *scheme 1-40* was more probable than the mechanism in *scheme 1-39* containing intermediate **1-195**. It was proposed that the conformation of the urea is important in facilitating the reaction. Bond rotation about the N-CO bond forming intermediate **1-199** occurs to minimise the repulsion experienced between the oxygen lone pairs and the carbanion. This rotation also brings together the carbanion and the distal aryl ring. The coordinated lithium cations and their movement throughout the reaction were also highlighted as important. Movement of the solvated lithium cation in **1-198** to in between the two aryl rings in **1-199** helps with the negative charge transfer from the carbanion to the aryl ring, resulting in retentive aryl migration. A second equivalent of the base is proposed to be necessary for good yield by coordinating to the carbonyl of the urea but not actually participating in the reaction itself.

The reaction is a concerted 'S_NAr-type' reaction where no intermediates are formed during the migration of the aryl ring. Normal S_NAr reactions involve addition-elimination steps and the formation of a formal Meisenheimer intermediate (similar to **1-192**). Due to the formation of the Meisenheimer intermediate electron withdrawing groups in the *orthro*- or *para*-position are required to stabilise the build-up of negative charge. In this reaction *para*-methoxybenzene can be used as the migrating aryl ring resulting in the product **1-189** in 84% yield. Unlike standard S_NAr reactions, concerted S_NAr reactions do not require an electron withdrawing group on the migrating ring as there is no build-up of charge, allowing non-activated aryl rings to partake in S_NAr reactions.[75–77]

1.4.3 Aryl anion stabilisation for *N to C* aryl migration

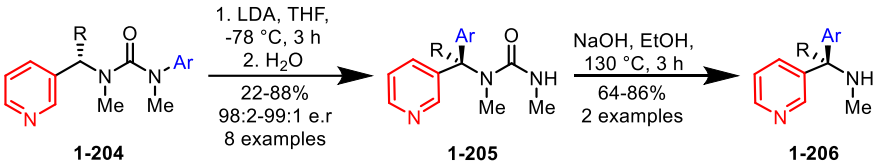
After establishing that *N to C* aryl migrations of *N*-aryl-*N'*-benzyl ureas were possible, pyridyl migrating groups were investigated.[78,79] Replacement of ^{s}BuLi with less nucleophilic LDA was required to access products **1-202** from ureas **1-201** and prevent alkylation of the pyridine ring (*scheme 1-41*).[78] DMPU addition was required to prevent racemisation of the benzyl lithium intermediate when enantiomerically pure ureas **1-201** were used. A similar mechanism to above (*scheme 1-40*) was proposed. 3-Pyridyl substituents were also formed from *ipso* attack overriding the usual regiochemistry of nucleophilic attack on a pyridine ring.



Ar^1 = Ph, *p*-Cl
Ar^2 = Ph, 2-Py, 3-Py, 4-Py, 5-Me-2-Py, 6-OMe-2-Py, 6-OMe-3-Py, 3-quinolyl, 4-isoquinolyl, 4-$NO_2C_6H_4$, 4-CNC_6H_4

Scheme 1-41: Synthesis rearrangement and urea cleavage of *N*-pyridyl-*N'*-benzyl ureas forming quaternary amines bearing an α-pyridyl group in high enantiopurity.

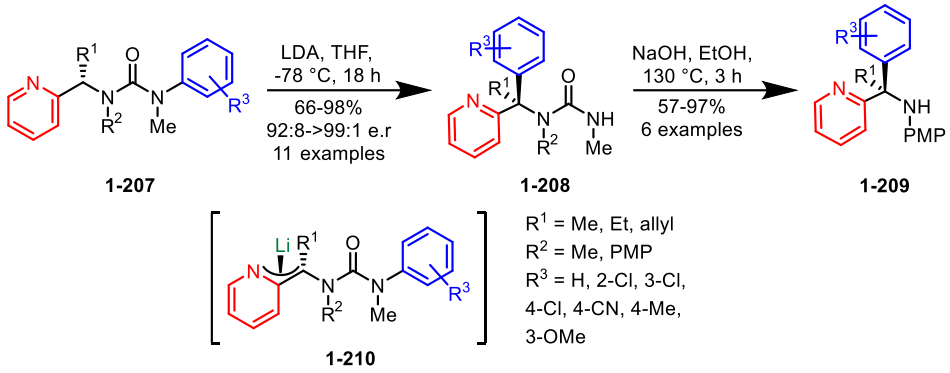
Cleavage of ureas **1-202** was accomplished by heating **1-202** in ^{n}BuOH overnight resulting in methyl isocyanate elimination giving the amine **1-203** with a quaternary stereogenic center adjacent to a pyridine ring.



R = Me, Bn
Ar = Ph, 2-Py, 4-ClC_6H_4, 4-FC_6H_4, 3-$MeOC_6H_4$

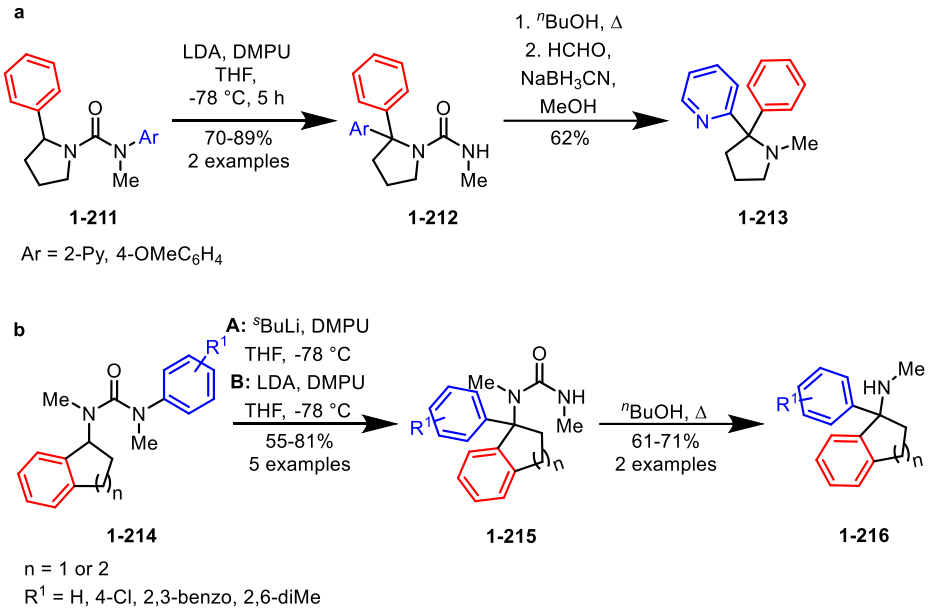
Scheme 1-42: 3-Pyridyl anion stabilised aryl migration.

α-Pyridyl amines similar to **1-203** were also synthesised using pyridyl groups to stabilise the anion.[79] 3-Pyridyl ureas **1-204** were treated with LDA in THF at -78 °C resulting in products **1-205** (*scheme 1-42*). In general, the products **1-205** were accessed in high yields without loss of enantiomeric purity and without the need for DMPU. The reaction was also tolerant of steric hindrance observed by replacing R = methyl with R = benzyl. The ureas **1-205** could also be cleaved by hydrolysis under basic conditions giving the α-quaternary amines **1-206** in good yields.



Scheme 1-43: 2-Pyridyl anion stabilised aryl migration.

The 3-pyridyl ureas **1-204** are lithiated at the carbon α to the pyridyl group but when the 2-pyridyl ureas **1-207** are lithiated, intermediate **1-210** is formed where the anion is delocalised (*scheme 1-43*). The migrated products **1-208** were isolated with retention of stereochemistry and in good to excellent yields. Both electron-donating and electron-withdrawing substituents in all positions on the aryl ring migrated, although the *ortho*-substituents led to lower yields. Similar to before the urea was hydrolysed under basic conditions affording the amines **1-209** in good to excellent yields.



Scheme 1-44: Aryl migration with cyclic amines.

This rearrangement chemistry was not limited to acyclic amines. Both heterocyclic and carbocyclic amines underwent the aryl migration (*scheme 1-44*).[80] 2-Phenylpyrrolidine derived ureas **1-211** were successfully rearranged using LDA/DMPU affording quaternary arylated pyrrolidines **1-212** in good yield. The *N*-methyl pyrrolidine **1-213**, an arylated regioisomer of nicotine was accessed in good yield through urea cleavage by heating in ^{n}BuOH followed by methylation via reductive amination. The authors note that the rearrangements of the cyclic ureas were slower than the acyclic ureas above, most likely due to the more constrained bicyclic transition state. It was also stated that due to the

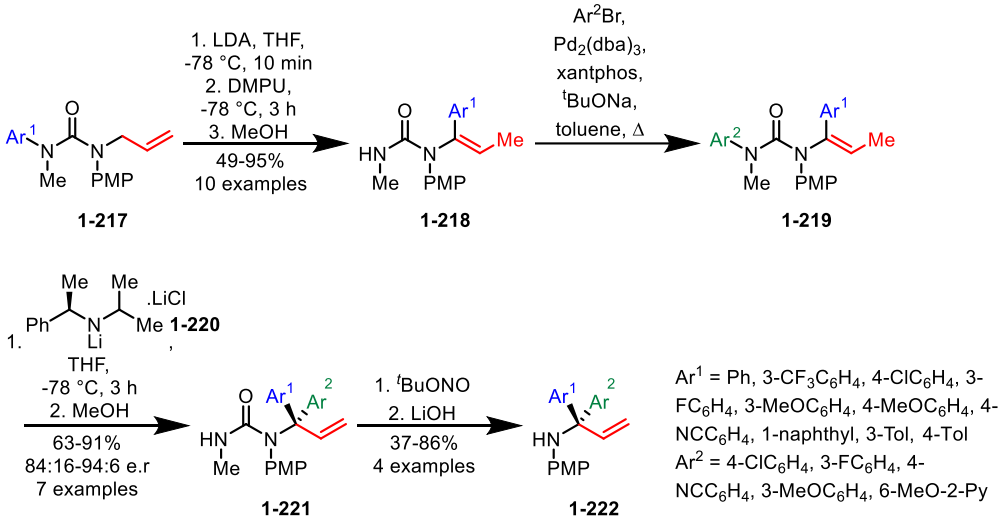
slow aryl migration competing poorly with racemisation of the organolithium intermediate no enantioenriched products **1-212** were formed.

Movement of the nitrogen to an exocyclic benzylic position as in ureas **1-214** was also successfully implemented in aryl migration, resulting in **1-215** in 55-81% yields (*scheme 1-44b*). As before the ureas could be cleaved accessing amines **1-216** in good yields.

1.4.4 *N to C* aryl migration with allyl anion stabilising groups

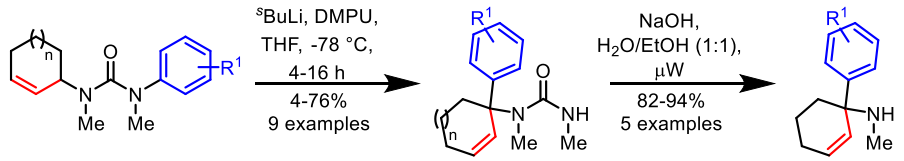
After the successful exploration of aryl anion stabilising groups, the Clayden group explored the use of alternative anion stabilising groups both carbon and heteroatom based which would promote *N to C* aryl migration.

The *N to C* aryl migration chemistry was extended to use *N*-allylureas **1-217** (*scheme 1-45*).[81] Treatment of ureas **1-217** with LDA and then addition of DMPU resulted in deprotonation of the allyl group α to the nitrogen and rapid *N to C* aryl migration affording the *N*-vinyl ureas **1-218** in moderate to excellent yields. The mechanism is proposed to occur in a similar manner to above with lithiation of the allyl group promoting *N to C* aryl migration before a second deprotonation of the allyl group and subsequent re-protonation at the γ-position affording vinyl products **1-218**.



Scheme 1-45: Consecutive double α-arylation of *N*-allyl ureas.

These urea products could then be used to synthesise vinyl amines **1-222** with quaternary stereogenic centres α to the nitrogen. Ureas **1-218** were *N*-arylated by coupling with aryl bromides to obtain compounds **1-219**. Treatment of ureas **1-219** with a chiral base **1-220** in the presence of LiCl resulted in enantiomerically enriched vinyl ureas **1-221** in good to excellent yields and high e.r. Cleavage of the urea resulted in vinyl amines **1-222** in 37-86% yields.



n = 0, 1

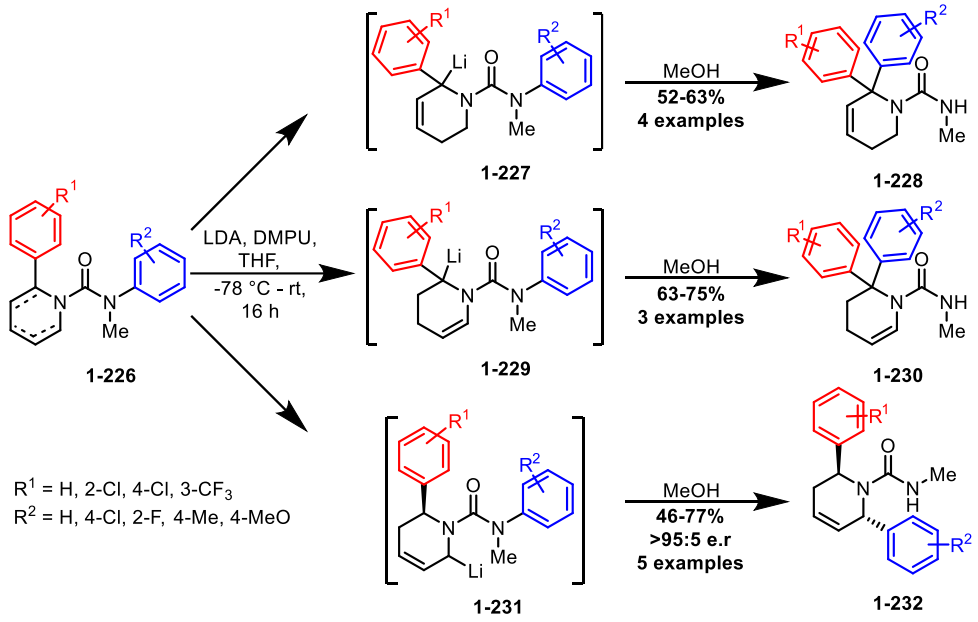
R^1 = H, 4-Cl, 3-F, 3-OMe, 4-OMe 3,5-diF

Scheme1-46: N to C aryl migration forming 1-arylcycloalkenamine ureas.

Ureas **1-223** with a cyclic allyl substituent were also successful in *N to C* aryl migration (*scheme 1-46*).[82] Treatment of cyclohexenylureas **1-223** (n = 1) with ^{s}BuLi/DMPU at -78 °C resulted in the isolation of rearranged ureas **1-224** in generally good yields (14-76%). Basic hydrolysis of ureas **1-224** under microwave irradiation afforded the 1-arylcyclohexen-1-ylamines **1-225** in good yields.

The smaller cyclopentenylamine ureas **1-223** (n = 0) also underwent *N to C* aryl migration under basic conditions forming products **1-224** although in much lower yields (4-30%).

By varying the placement of a double bond in the tetrahydropyridine derived ureas **1-226** (2,3-, 5,6- and 4,5-position) three different products **1-228**, **1-230** and **1-232** were formed (*scheme 1-47*). [83]



R^1 = H, 2-Cl, 4-Cl, 3-CF_3

R^2 = H, 4-Cl, 2-F, 4-Me, 4-MeO

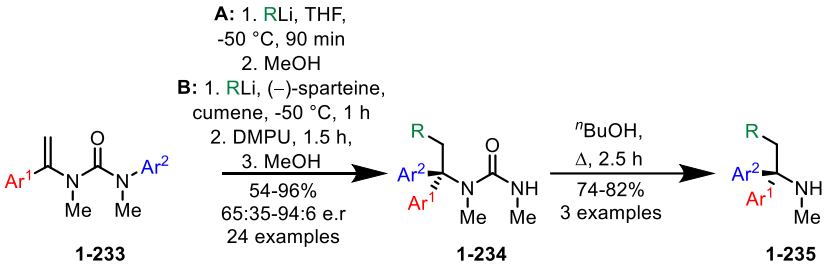
Scheme 30-47: Aryl migration of a range of tetrahydropyridine derived ureas resulting in 2,2- and 2,6-diaryltetrahydropyridines.

Treatment of tetrahydropyridine derived ureas **1-226** with the alkene at the 2,3- and 5,6-position with LDA/DMPU in THF at -78°C resulted in isolation of 2,2-diaryltetrahydropyridine products **1-228** and **1-230**, respectively in moderate yields.

By contrast ureas **1-226** with the alkene in the 4,5-position resulted in formation of 2,6-diaryltetrahydropyridines **1-232** in moderate yields. Kinetically controlled deprotonation with the relative rates being allylic 2-CH > benzylic 2-CH > allylic 4-CH controlled the outcome of the products.

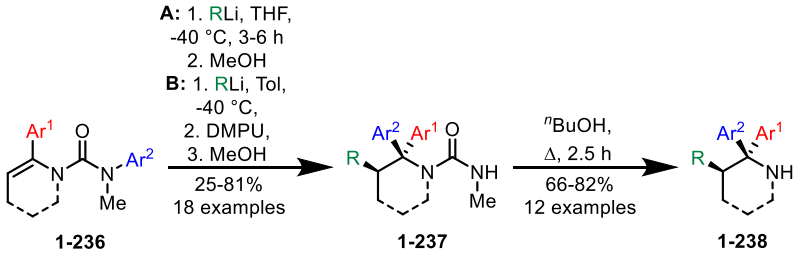
1.4.5 Tandem alkylation-rearrangement cascades

The addition of a urea moiety to vinyl amines results in vinyl groups susceptible to nucleophilic addition at the β-carbon by organolithium reagents. This umpolung reactivity was exploited by the Clayden group resulting in a tandem carbolithiation-*N to C* aryl migration cascade.[84–86] Treatment of *N*-vinyl ureas **1-233** with an organolithium in THF at -50 °C, afforded rearranged products **1-234** with two new carbon substituents added to the vinyl group (*scheme 1-48,* method **A**). A range of alkyl-, aryl- and vinyl lithium compounds were successfully incorporated into *N*-vinyl **1-233**. The urea moiety was successfully cleaved by refluxing ureas **1-235** in ^{n}BuOH for 2.5 hours.



Scheme 1-48: Tandem carbolithiation-*N to C* aryl migration of *N*-vinyl ureas. **A** – Racemic product formation. **B**- Enantioselective carbolithiation-rearrangement achieved using (–)-sparteine.

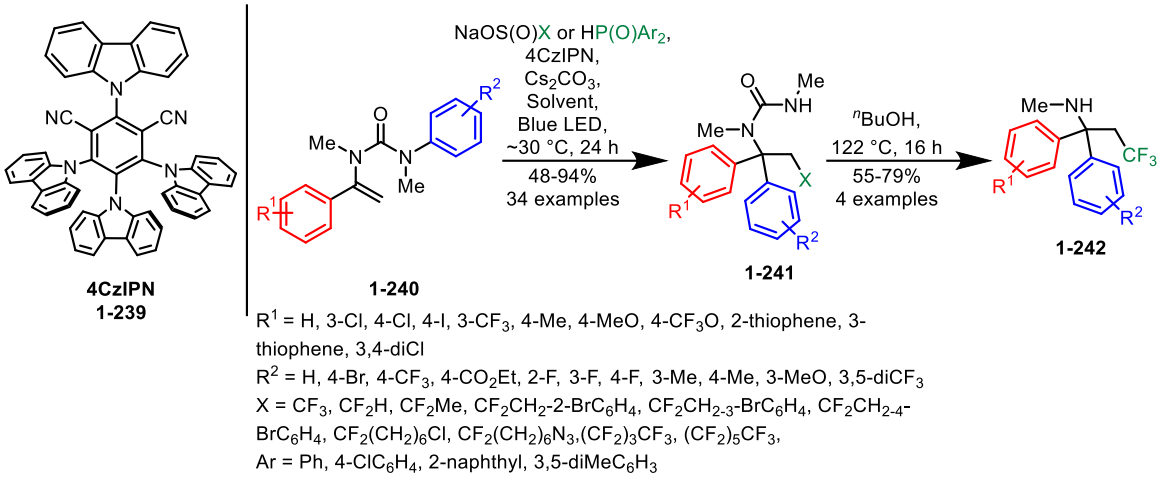
Adapting the reaction shown in *scheme 1-48* (method ***A***) by addition of (–)-sparteine and DMPU produced an asymmetric carbolithiation-rearrangement cascade variant with achiral *N*-vinyl ureas **1-233** (*scheme 1-48,* method **B**).[87] The addition of DMPU to the reaction was delayed by 6 hours to allow complete asymmetric carbolithiation. A range of ureas **1-234** were synthesised in good yields with moderate to good e.r.



Scheme 1-49: Stereospecific carbolithiation-rearrangement cascades of acyclic and cyclic ureas..

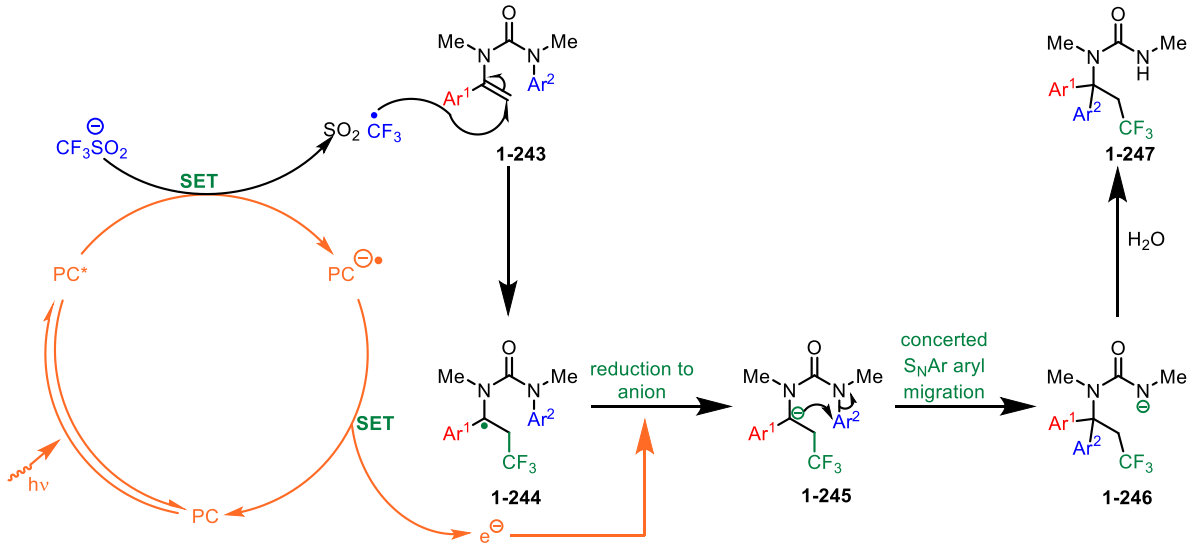
Ureas **1-236** with both acyclic and cyclic *N*-vinyl groups underwent tandem carbolithiation-aryl migration affording the *syn*-addition products **1-237** in generally good yields (*scheme 1-49*).[83,84] When ^{t}BuLi was used the yields were lower which was presumably due to increased steric hindrance. The cyclic ureas **1-236** afforded products as single diastereoisomers (>95:5 er). Access to the amines **1-238** was achieved by heating the ureas **1-237** in ^{n}BuOH.

1.4.6 Reductive radical-polar-crossover sequence



Scheme 1-5031: Difunctionalisation of vinyl ureas by Photoredox catalysis. Solvent – MeCN, acetone or DMF.

More recently this *N to C* aryl migration chemistry has been adapted for use with radicals in a reductive radical-polar crossover cascade (*scheme 1-50*).[88] The reaction shown in *scheme 1-50* is equivalent to the carbolithiation-rearrangement seen above in section 1.4.5 affording 1,2-difuntionalised vinyl urea **1-241**, but the carbolithiation step is replaced with radical addition. An extensive array of substituent ureas **1-241** were synthesis in good to excellent yields. Halogens were also successfully incorporated that would otherwise be difficult to incorporate under normal carbolithiation-rearrangement conditions. Solvolysis of the urea **1-241** with ^{n}BuOH afforded the amines **1-242**.



Scheme 1-51: Mechanism for the radical-polar crossover forming trisubstituted vinyl ureas **1-257**.

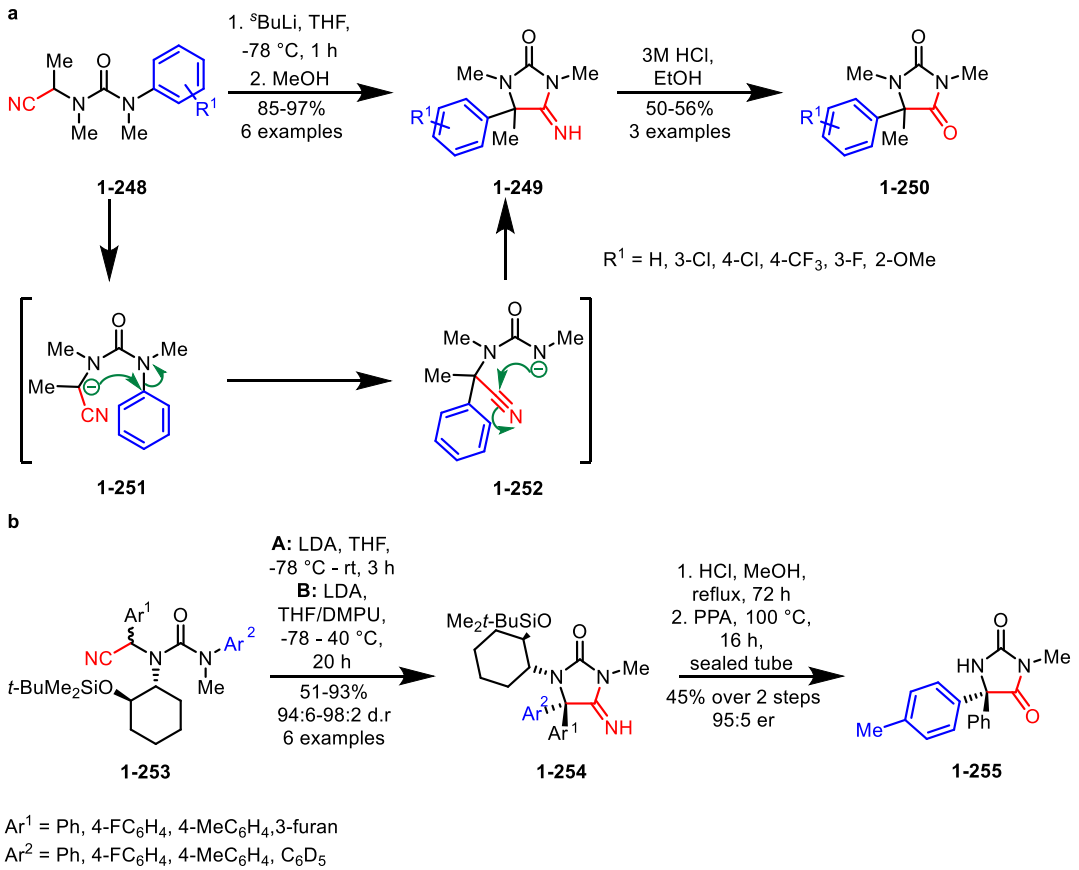
The mechanism is shown in *scheme 1-51*. The excited photocatalyst (PC*) oxidises the radical precursor by SET generating the CF_3 radical that adds to the β-position of the vinyl group **1-243**. The radical urea **1-244** is then reduced by SET from the reduced photocatalyst ($PC^{\cdot-}$) forming anion **1-245**.

This anion **1-245** undergoes the usual *N to C* aryl migration forming the product **1-257** upon protonation with water.

1.4.7 Enolate anion *N to C* aryl migrations

As well as investigating the use of carbanion stabilising groups shown above the Clayden group studied heteroatom-based anion stabilisation to promote *N to C* aryl migrations.

Amino acid arylation forming quaternary amino acids was accomplished using ureas **1-248** containing an aminonitrile tethered urea (*scheme 1-52a*).[89] Treatment of the ureas **1-248** with ^{s}BuLi and quenching with MeOH resulted in isolation of iminohydantoins **1-249** in excellent yields regardless of the electronics on the migrating aryl ring. The reaction proceeds by initial deprotonation α to the nitrile forming an 'enolate-type' anion **1-251**, which then undergoes *N to C* aryl migration forming anion **1-252**. The nitrogen anion cyclises onto the nitrile forming **1-249** upon quenching. Hydrolysis of the iminohydantoin **1-249** afforded the hydantoins **1-250** in moderate yields.

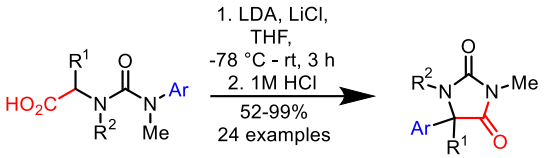


Scheme 1-52: (Imino)hydantoin synthesis through *N to C* aryl migration of aminonitrile ureas. **a** – Racemic synthesis. **b** – Enantioselective functionalisation.

Replacement of the *N*-methyl group in **1-248** with *N-trans*-2-aminocyclohexanol, a chiral auxiliary resulted in enantioselective diarylated hydantoins **1-255** (*scheme 1-52b*).[90] Under basic conditions urea **1-253** underwent *N to C* aryl migration and cyclisation forming iminohydantoins **1-254** in 51-93% yields and high diastereoselectivity. The hydantoins **1-255** were accessed through a two-step process

involving hydrolysis of the imine and cleavage of the silyl group followed by cleavage of the chiral auxiliary.

The nitrile ureas **1-248** are derived from alanine and Clayden *et al.* showed that simple amino acid enolates from ureas **1-256** could be used to promote *N to C* aryl migration forming the hydantoins **1-257** in one-step (*scheme 1-53*).[89] Both natural and unnatural amino acid were used to synthesise ureas **1-256** which when subjected to the optimised conditions (LDA, LiCl in THF) gave the hydantoin products **1-257** in good to excellent yields.

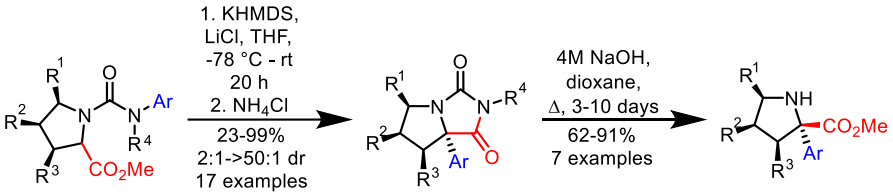


1-256 **1-257**

Ar = Ph, 3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-FC$_6$H$_4$, 2-MeC$_6$H$_4$, 2-MeOC$_6$H$_4$, 1-naphthyl, 2-pyridyl
R^1 = H, Me, ^{n}Pr, ^{i}Pr, CH$_2$CH(CH$_3$)$_2$, (CH$_2$)$_2$SCH$_3$, (CH$_2$)$_4$N(Me)Boc, -(CH$_2$)$_3$-, 3-CH$_2$-*N*-Me-indole
R^2 = Me, -(CH$_2$)$_3$-

Scheme 1-53: Hydantoin synthesis through *N to C* aryl migration of enolate stabilised ureas **1-256**.

The aryl migration of a range of 3-, 4- and 5-substituteted proline derived ureas **1-258** was also explored giving access to a range of enantioenriched α-quaternary proline derivatives **1-259** (*scheme 1-54*).[91]



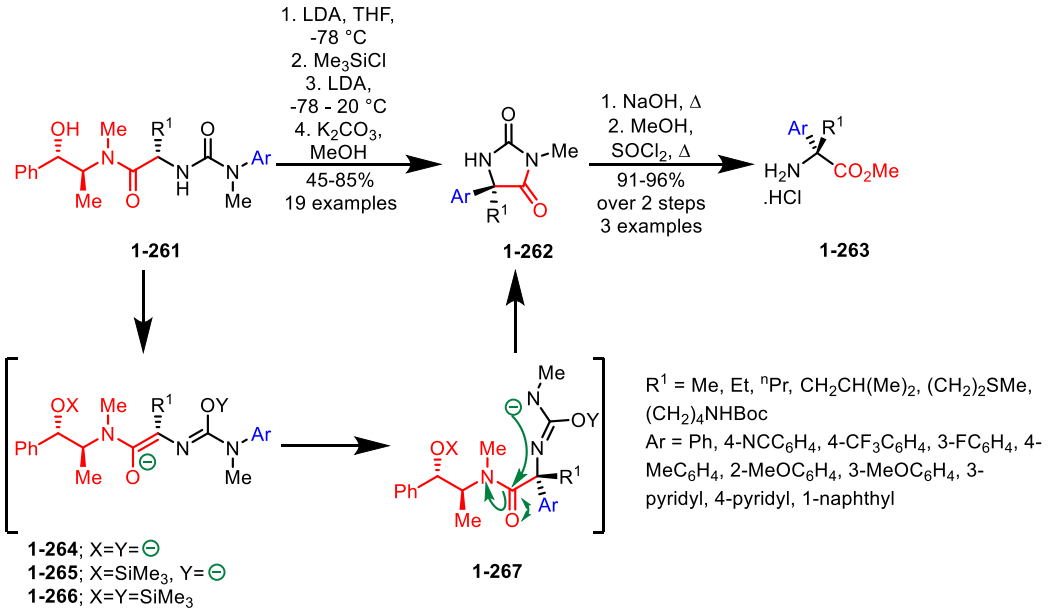
1-258 **1-259** **1-260**

Ar = Ph, 3-BrC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-CNC$_6$H$_4$, 3-FC$_6$H$_4$, 4-FC$_6$H$_4$, 2-MeC$_6$H$_4$, 3-MeOC$_6$H$_4$, 2-pyridyl, 1-naphthyl
R^1 = H, Me, -(CH$_2$)$_4$-
R^2 = H, OH, -(CH$_2$)$_4$-
R^3 = H, Me, Bn
R^4 = Me, Et, MOM

Scheme 1-54: Enantioenriched α-quaternary proline derivatives synthesised by intramolecular diastereoselective arylation.

Substitution at the 4-position resulted in a range of products **1-259** in high yields with moderate diastereoselectivity. Whereas substitution at the 4,5-positions with cyclohexane resulted in greater diastereoselectivity with the hydantoins **1-259** isolated in moderate to good yields. When the proline ureas **1-258** were substituted at the 3-position the products **1-259** were formed in almost complete diastereoselectivity and generally high yield. Hydrolysis of the urea moiety was achieved by heating **1-259** in NaOH and dioxane for several days.

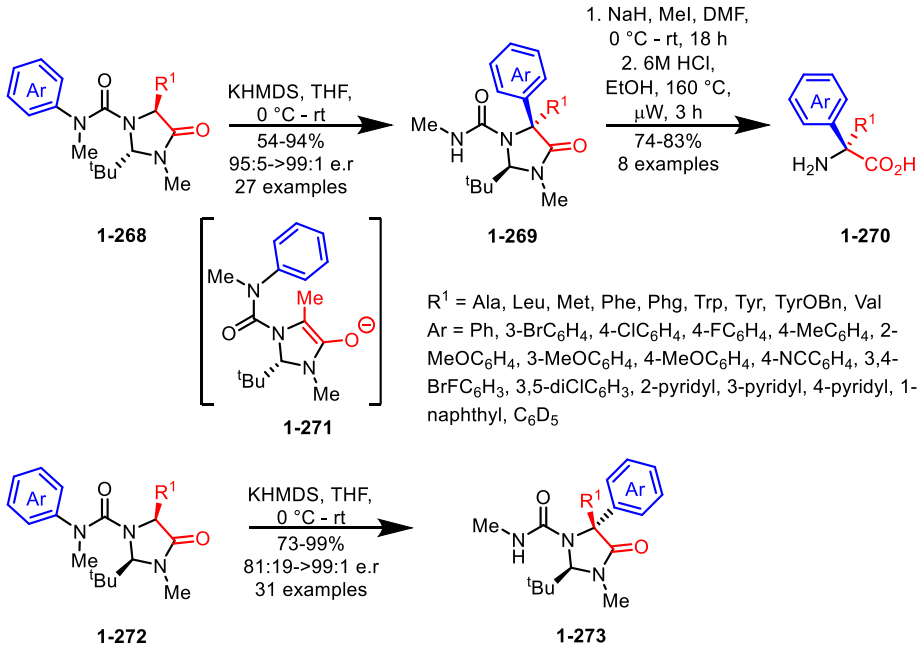
An alternative route towards the asymmetric α-arylation of amino acids was reported in 2015 by Clayden *et al.* utilising (S,S)-pseudoephedrine as a chiral auxiliary group in ureas **1-261** (*scheme 1-55*).[92] The hydantoin products **1-262** were isolated in moderate to good yields and good e.r.



Scheme 1-55: (S,S)-Pseudoephedrine-directed *N to C* aryl migration forming asymmetric quaternary amino acid synthesis.

The reaction proceeds through a multistep cascade of deprotonation-silylation-enolisation-aryl migration-cyclisation and auxiliary cleavage (**1-264** to **1-267**). TMS-Cl was essential to trap the anions formed at the hydroxyl group (OX) and the urea anion (OY) **1-266**, without which a racemic mixture of products was formed. The hydantoins **1-262** were converted into the methyl ester quaternary amino acids **1-263** in two-steps.

A more general approach to the synthesis of enantiopure quaternary amino acids bearing an aryl group was reported in 2018 using the principles of Seebach's 'self-regeneration of stereocenters' (*scheme 1-56*).[93,94]



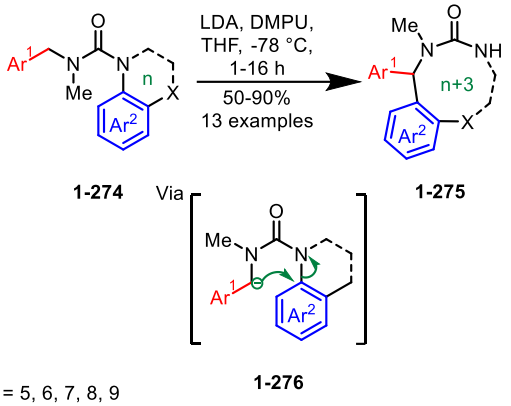
Scheme 1-56: Asymmetric quaternary amino acid synthesis exploiting 'Seebach's self-regeneration of stereocenters.'

L-Amino acids were used to synthesise both diastereoisomers of the ureas **1-268** and **1-272**. Treatment of either diastereoisomers **1-268** or **1-272** under the optimised conditions (KHMDS in THF) resulted in isolation of the rearranged products **1-269** and **1-273** respectively, in high yields and excellent diastereoselectivity, irrespective of electronic or steric factors on the aryl migrating group. Both product enantiomers **1-269** and **1-273** were easily accessed from L-amino acids. In many cases the alternative diastereoisomer was not detected making the reaction essentially enantiomerically pure (>99:1 e.r). The mechanism of the reaction is similar to above, deprotonation forms enolate **1-271** where the chirality at this center is lost, however the imidazolidinone contains a second stereocenter (*tert*-butyl group) which is retained under the reaction conditions and directs the arylation of the enolate forming a new quaternary stereocenter.

After methylation of the free NH in **1-275** the quaternary amino acids **1-276** were accessible by hydrolysis with HCl in EtOH under microwave irradiation.

1.4.8 Medium ring synthesis through *N to C* aryl migration

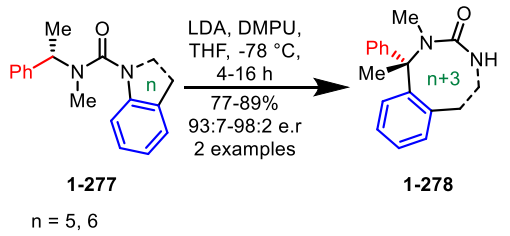
After establishing an extensive list of acyclic and cyclic anion stabilising groups for *N to C* aryl migration the Clayden group investigated the effects of tethering the migrating aryl group onto the nitrogen (*scheme 1-57*).[95]



n = 5, 6, 7, 8, 9
Ar^1 = Ph, 2-pyridyl, 2-thiophene
Ar^2 = Ph, 4-ClC_6H_3, 4-FC_6H_3, 2-MeC_6H_3, 4-$MeOC_6H_3$, C_5NH_3
X = CH_2, O

Scheme 1-57: N to C aryl migration forming medium rings. Ar^1 = 2-Pyridyl or 2-thiophene required elevated temperatures and for 2-thiophene the reaction proceeds in the absence of DMPU.

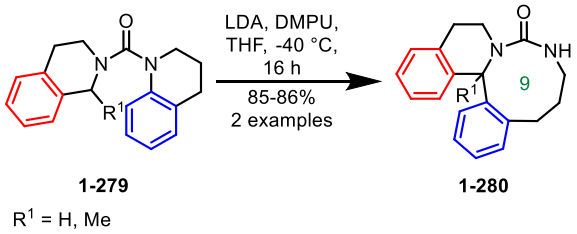
Treatment of ureas **1-274** with LDA/DMPU resulted in benzylic lithiation and *N to C* aryl migration through intermediate **1-276** in a similar manner to before. The tether between the aryl group and the nitrogen produces the medium rings **1-275** in an *n to n+3* ring expansion. The medium rings (8-12-membered) **1-275** were synthesised in good to excellent yields irrespective of the electronic or steric demand on the aryl migrating ring. Alternative heteroaryl rings were also successful in promoting ring expansion when used as the anion stabilising group but required elevated temperatures to reach completion and when Ar^1 = 2-thiophene no DMPU was required.



n = 5, 6

Scheme 1-58: Ring expansion forming enantiopure medium rings.

Enantiopure medium rings **1-278** were also synthesised in excellent yields and high enantiopurity from enantiopure starting ureas **1-277** (*scheme 1-58*). Retention of the stereochemistry was observed similar to before with the acyclic aryl migrations (*scheme 1-38*).

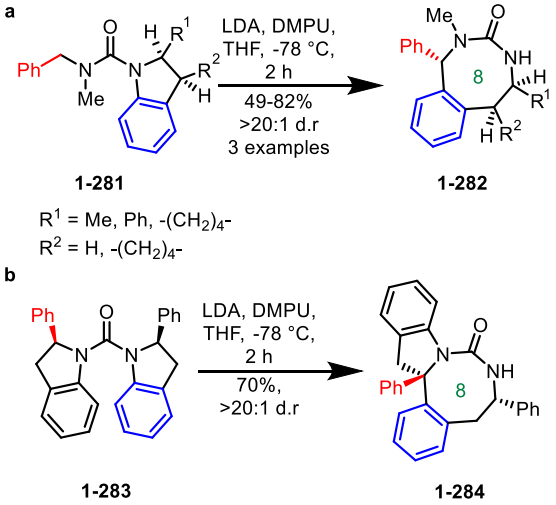


R^1 = H, Me

Scheme 1-59: Ring expansion forming fused bicyclic medium rings.

The bicyclic ureas **1-279**, synthesised by coupling two isomers of tetrahydroquinoline were successfully implemented in the ring expansion reaction forming fused polycyclic products **1-280** in high yields (*scheme 1-59*).

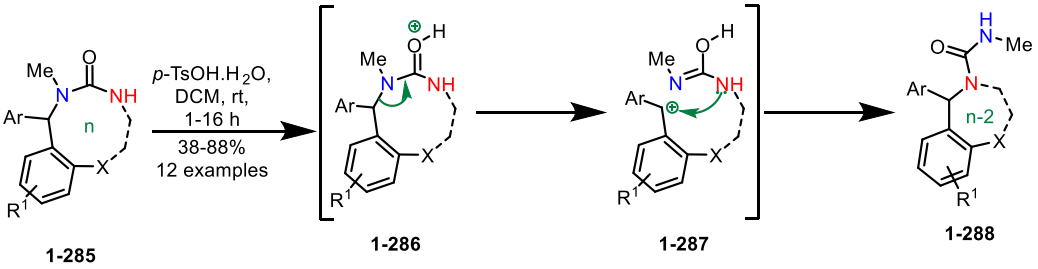
Under basic conditions chiral ureas **1-281** containing substituents on the alkyl tether formed the 8-membered rings **1-282** in moderate to good yields with complete diastereoselectivity (*scheme 1-60-a*).



Scheme 1-60: Diastereoselective ring expansion of substituted ureas.

Similar to this, symmetrical urea **1-283**, synthesised as a single diastereoisomer with a phenyl ring on the alkyl tether also underwent ring expansion (*scheme 1-60b*). The 8-memebered ring **1-284** was formed as a single diastereoisomer with the two phenyl groups having an anti-relationship.

The medium rings **1-285** synthesised above (*schemes 1-57 to 1-60*) can be transformed into 1-aryltetrahydroisoquinoline and 1-aryltetrahydrobenzazepines **1-288** (*scheme 1-61*).[96] When the medium rings **1-285** were treated with *p*-TsOH.H_2O the resultant ring contracted products **1-288** were isolated in moderate to good yield, resulting in an overall *n to n-2* ring contraction.

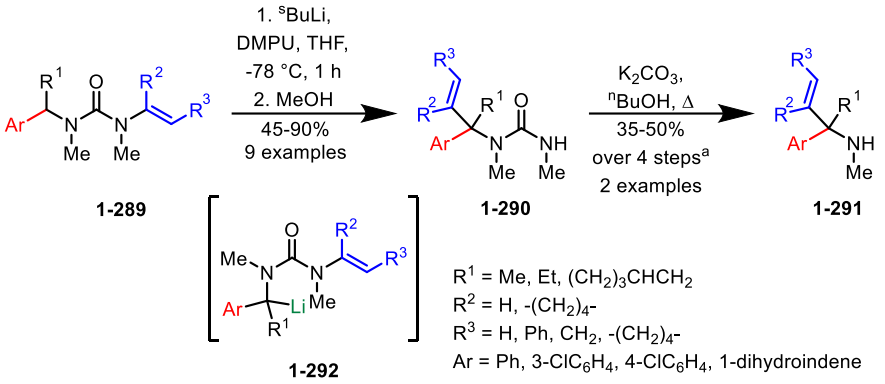


Scheme 1-6132: Ring contraction of medium rings by treatment with catalytic acid.

Upon treatment with acid the carbonyl is protonated to form **1-286** and the ring opens forming carbocation **1-287**. The nitrogen distal to the carbocation of **1-287** then traps it forming the ring contracted product **1-288**.

1.4.9 *N to C* vinyl migration

As well as developing routes towards the migration of aryl rings forming both racemic and enantioselective quaternary amino acids, α-substituted tertiary and quaternary amines and hydantoins the Clayden group also investigated alternative migrating groups, namely vinyl groups. The *N to C* vinyl migration of ureas **1-289** forming products **1-290** was reported in 2012 (*scheme 1-62*).[97]

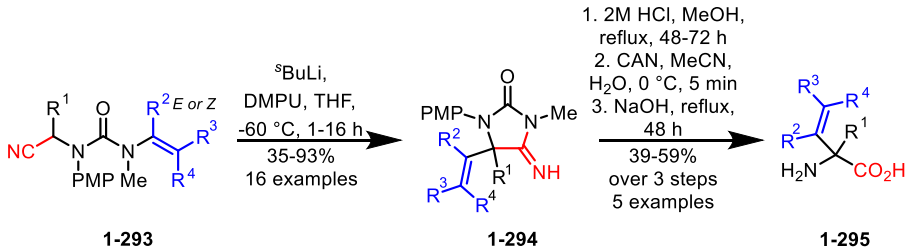


Scheme 1-62: N to C vinyl migration. a – Yields a result of one-pot synthesis from urea synthesis, through vinyl migration and urea cleavage.

A range of vinyl groups were migrated in generally good yields. Where enantiomerically pure starting materials **1-289** (>99:1 e.r) were used the products **1-290** were formed in enantiomerically pure form (>99:1 e.r), indicating that the intermediate benzyl lithium **1-292** must be configurationally stable under the reaction conditions and timescale.

The products **1-290** were acid sensitive resulting in reduced yields for some examples. However, a tandem sequence involving urea **1-289** synthesis, aryl migration and urea cleavage afforded the amine products **1-291** in good yields over four steps.

Ureas bearing nitrile groups were used above (*scheme 1-52*) to synthesise (imino)hydantoin **1-249** under basic conditions.[89,90] The Clayden group have also reported the synthesis of similar (imino)hydantoins **1-294** using vinyl migration (*scheme 1-63*).[98]

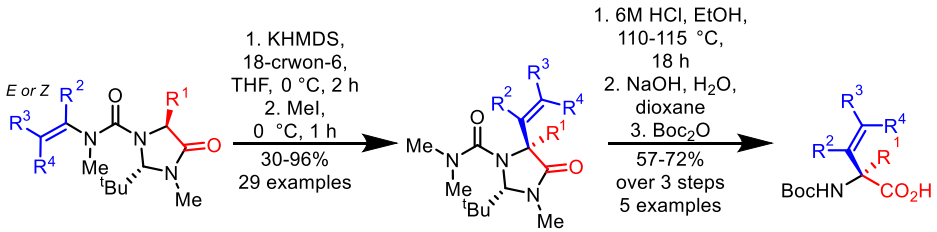


Scheme 1-63: Vinyl migration using amino nitrile stabilised anions forming quaternary amino acids in four-steps.

Under basic conditions ureas **1-293** underwent *N to C* vinyl migration and cyclisation affording the iminohydantoin products **1-294** in moderate to good yields, irrespective of the steric hindrance around

the vinyl migrating group. The vinyl migration proceeded with retention of the double bond geometry, resulting in the formation of both *E*- and *Z*-alkenyl amino acids **1-295**. The iminohydantoins **1-294** were converted to the hydantoins by hydrolysis of the imine in acidic conditions, then oxidative removal of the PMP (*p*-methoxybenzene) group by CAN (ceric ammonium nitrate). The quaternary amino acid derivatives **1-295** were accessed by treatment of the hydantoins in refluxing NaOH.

Enantiopure quaternary amino acids **1-298** bearing a vinyl group were synthesised from *N to C* vinyl migration of imidazolidinone ureas **1-296** followed by hydrolysis of the imidazolidinone (*scheme 1-64*).[99]



1-296 **1-297** **1-298**

R^1 = ally, Me, ^{n}Pr, Bn, $(CH_2)_2Ph$, CH_2CHMe_2, $(CH_2)_2SMe$, 3,4-di$MeOC_6H_3$, $CH_{2\text{-}4}$-$BnOC_6H_4$, $CH_{2\text{-}3}$-FC_6H_4, 3-*N*-Me-indoline
R^2 = H, -$(CH_2)_4$-
R^3 = H, Me, Bn, -$(CH_2)_4$-, -$(CH_2)_5$-,$CHMeCH_2CH_2CHCMe_2$
R^4 = H, Me, -$(CH_2)_5$-, estrone

Scheme 1-64: Enantioselective quaternary amino acid synthesis through vinyl migration.

A range of imidazolidinones **1-296** derived from natural and non-natural amino acids were treated with base leading to vinyl migration, where the vinyl group migrates *anti* to the *tert*-butyl group forming **1-297**. Remarkably in this reaction both the double bond geometry and the absolute configuration of the stereogenic center are controlled during the reaction.

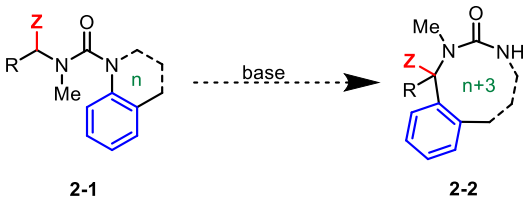
The desired quaternary amino acids **1-298** were obtained in high yields without loss in enantiomeric purity or isomerisation of the double bond through hydrolysis of the imidazolidinone products **1-297** in acid and subsequent Boc-protection of the amine.

Since 2007 the Clayden group have reported the synthesis of a range of racemic and enantioenriched α-substituted tertiary and quaternary amines, hydantoins and amino acids, including medium rings. These reactions are *N to C* migrations through urea moieties using aryl, enolate-type and allyl anion stabilising groups formed under basic conditions. The reactions were shown to occur through a concerted S_NAr reaction with both electron withdrawing and electron donating aryl rings migrated in high yields.

2. (Imino)hydantoin-bridging medium ring synthesis

2.1 Aims

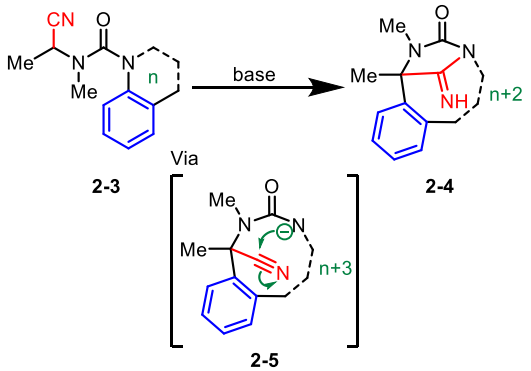
The Clayden group has shown the utility of the *N to C* migration of both aryl and vinyl groups through urea moieties, forming a range of α-substituted tertiary and quaternary amines, hydantoins and amino acids, including enantioselective rearrangements (see section 1.4). More recently they highlighted the utility of these reactions in forming nitrogen containing medium rings (section 1.4.8) by aryl migration using aryl groups tethered to the nitrogen by alkyl chains.[100] Until now the group have only explored the ring expansion forming medium rings using carbanions stabilised by aryl rings. To expand on this, we aim to investigate the use of alternative heteroatom based stabilising groups (**Z** in *scheme 2-1*) which would give access to a more diverse range of scaffolds.



2-1 **2-2**

Scheme 2-1: Ring expansion through an *N to C* aryl migration with heteroatom stabilised carbanion formed by treatment with base. Z – heteroatom stabilising group.

Initial studies aim to use the nitrile functionality as the stabilising group **Z**. Preliminary work showed that treatment of urea **2-3,** with base lead to *N to C* aryl migration expanding the ring from *n to n+3* (*scheme 2-2*). The non-innocent nitrile participates in the reaction by attack from the nitrogen anion **2-5** formed after aryl migration leading to iminohydantoin-bridging medium rings **2-4** in an overall *n to n+2* ring expansion.



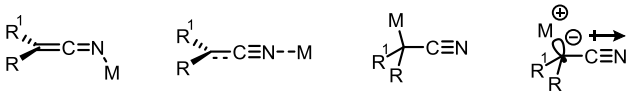
2-3 **2-4** **2-5**

Scheme 2-2: Preliminary results showed ring expansion forming iminohydantoin-bridging medium rings through *N to C* aryl migration of ureas **2-3** was possible.

The scope of the reaction was probed using predominantly commercially available 5-8-membered nitrogen heterocycles, exploring both steric and electronic effects on medium ring formation. The effect of changing the alkyl chains around the nitrile was also explored using cyclic and acyclic nitriles.

Alternative heteroatom-based anion stabilising groups which varied between resonance and inductive stabilised anions were then explored. The formation of enantioenriched medium ring amino acid derivatives was also explored using previously established chemistry for acyclic aryl migration products (see *scheme 1-52* in section 1.4.7).[93]

2.2 Nitrile anion structure



N-metalated ketenimine **2-6** | *N*-metalated nitrile **2-7** | *C*-metalated nitrile **2-8** | Nitrile anion (solution) **2-9**

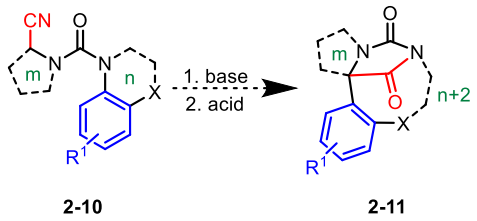
Figure 2-1: Metalated nitriles occupy a range of structures from ketenimine extreme to solvent-separated nitrile anion in solution.

The use of nitriles to stabilise carbanions in the formation of new C-C bonds is very well precedented in the literature, but the exact nature of the nitrile anions is variable.[101–104] Analysis of NMR and crystallographic data showed that metalated nitriles exist as distinct organometallics but the structure of which varies across a continuum; from one extreme *N*-metalated ketenimine **2-6** through *N*-metalated nitrile **2-7** and *C*-metalated nitrile **2-8** to another extreme solvent-separated nitrile anion **2-9** (*figure 2-1*). The site of metalation depends predominantly on the solvent, counterion, temperature of the reaction and the use of cation binding ligands (such as HMPA and 18-crown-6). Deprotonation of alkylnitriles leads to a metalated nitrile that is generally stabilised by inductive electron withdrawal rather than through resonance. The excellent nucleophilicity of the nitrile anions comes from a mixture of high electron density on the nucleophilic carbon and the small size of the nitrile functional group.

2.3 Nitrile stabilised anion aryl migration

2.3.1 Previous work

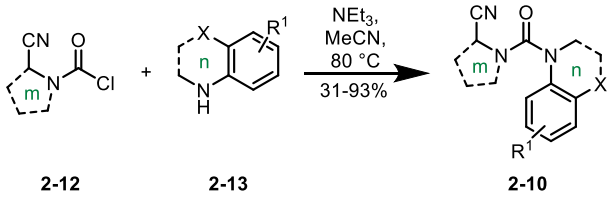
Preliminary work by Emily Ellis (during her MChem project) found that *N to C* aryl migration of α-cyanoureas was possible forming iminohydantoin-bridging medium rings.[105] A range of 8-9-membered rings were synthesised in poor to moderate yields. Hydrolysis of these iminohydantoins under acidic conditions formed desirable hydantoin-bridging medium rings **2-11** (see *scheme 2-3*).



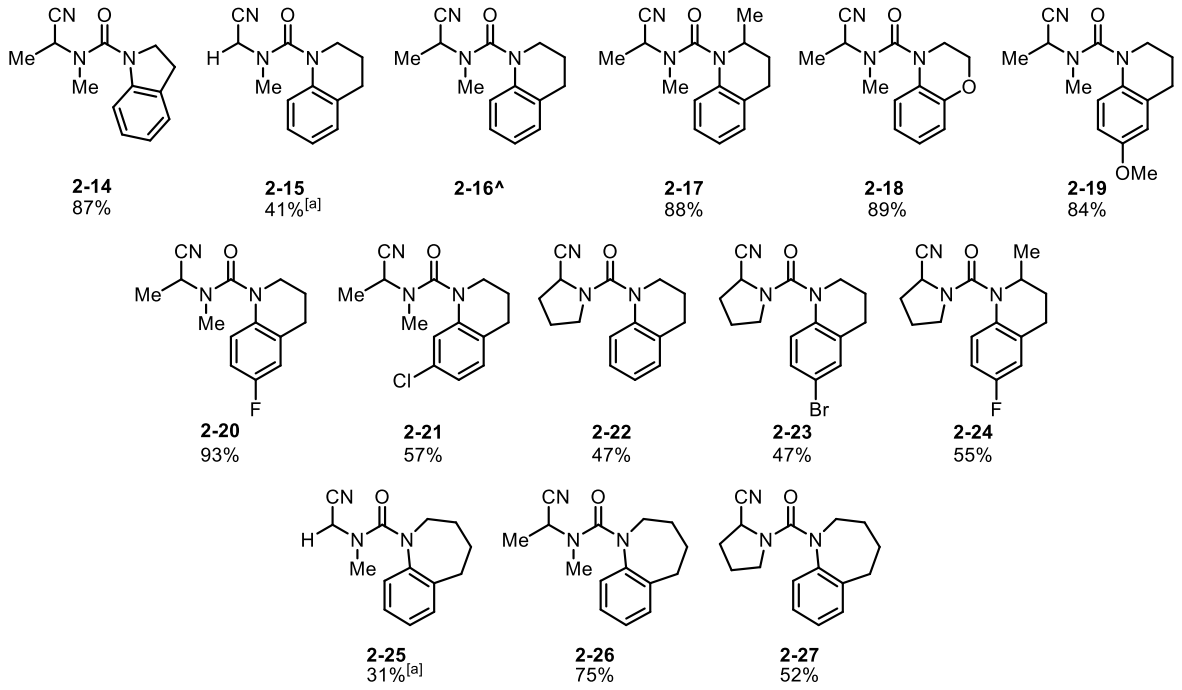
2-10 **2-11**

Scheme 2-3: Proposed ring expansion of nitrile ureas forming (imino)hydantoin-bridging medium rings.*

A variety of ureas were synthesised in generally good yield by coupling of commercially available nitrogen heterocycles with aminonitrile-derived carbamoyl chlorides (see *scheme 2-4*). Some lower yields were seen due to reactions not going to completion.



2-12 **2-13** **2-10**

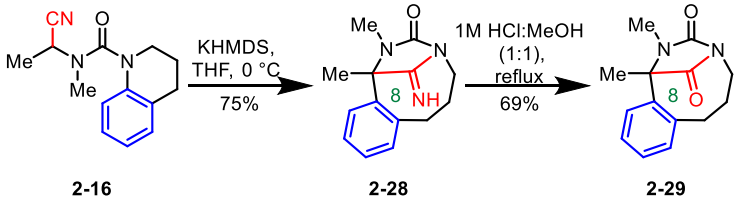


Scheme 2-4: Aminonitrile urea synthesis. [a] – Reaction not to completion.*

* Experiments carried out by Emily Ellis.

^ Experiment carried out by Dr John Ward, no yield available.

Previous work within the Clayden group involving *N to C* aryl migration of benzannulated ureas required either ^{S}BuLi/DMPU or LDA/DMPU to deprotonate the benzylic position of the urea, however, the more acidic nature of the proton α to the nitrile meant milder conditions could be used. Treatment of urea **2-16** with KHMDS resulted in formation and isolation of medium ring **2-28** in high yield (*scheme 2-5*). Iminohydantoin **2-28** was then hydrolysed with acid to give the hydantoin-bridging medium ring **2-29** in 69%.

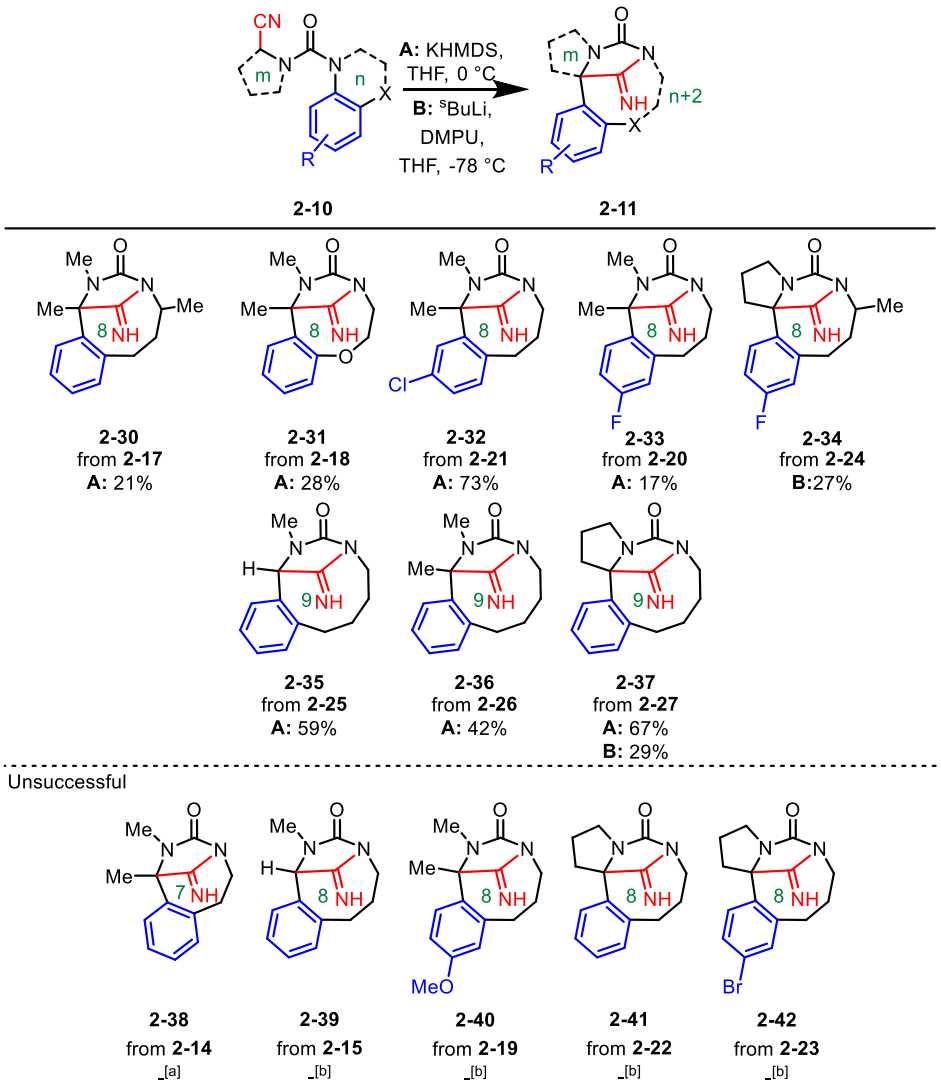


2-16 **2-28** **2-29**

Scheme 2-533: Proof of concept ring expansion and hydrolysis affording the hydantoin-bridging medium ring.*

Following on from the success within *scheme 2-5*, other 5- and 6-membered nitrogen heterocycle-derived ureas were treated under the same conditions (*scheme 2-6*). Attempted ring expansion of indoline derivative **2-14** gave only oxidative decomposition of the urea. The reaction was repeated at -40 ˚C in an effort to slow down the rate of oxidative decomposition, although only decomposition of the urea was seen in the ^{1}H NMR. A complex mix of products from the decomposition of urea **2-15**, containing no substitution at the site of deprotonation, was seen when treated with KHMDS. Treatment of urea **2-17**, with a methyl group on the alkyl tether afforded the desired product **2-30** with only one diastereoisomer isolated suggesting that mild steric hindrance was tolerated. Addition of an oxygen atom into the backbone were also tolerated as shown by the formation of **2-31**. The effects of electronics on the migrating aryl ring were investigated using ureas **2-19-2-21** and showed that electron withdrawing groups were tolerated by the formation of *meta*-chloro product **2-32** and *para*-fluoro product **2-33** although in low yield. The electron donating *para*-methoxy group in **2-19** was not tolerated resulting in a complex mixture of products in the crude ^{1}H NMR.

* Experiments carried out by Emily Ellis.



Scheme 2-634: Ring expansion products. [a] – Product from reaction was oxidative decomposition of the urea. [b] - Complex mixture of product after treatment of urea **2-10** with base.

2-Cyanopyrrolidine-derived ureas **2-22–2-24** were treated under the same conditions as above and resulted in a complex mixture of products with no detectable product seen by ^{1}H NMR. The increased steric hindrance around the site of deprotonation most likely hindered the aryl migration allowing urea decomposition to take place instead. Using alternative conditions ^{s}BuLi/DMPU, 8-membered ring **2-34** containing both a methyl group on the alkyl tether and a para-fluoro substituent on the aryl migrating group was successfully isolated in 27%; although, these conditions were not successful for the ring expansion of unsubstituted urea **2-22** and *para*-bromo urea **2-23**.

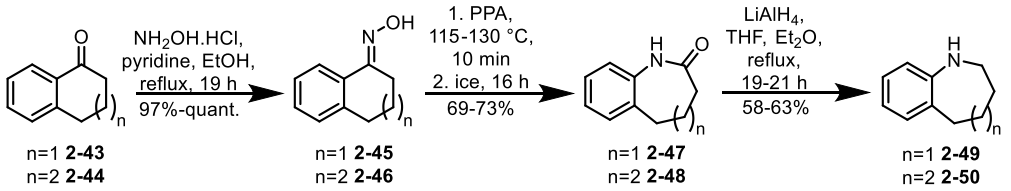
The synthesis of larger 9-membered nitrogen heterocycles was also explored with the various acyclic and cyclic nitrile ureas **2-25–2-27**. Treatment of all three ureas **2-25–2-27** with KHMDS resulted in 9-membered rings **2-35–2-37** in good yields.

* Experiments carried out by Emily Ellis.

2.3.2 Urea precursor synthesis

The preliminary work highlighted the potential of this chemistry to form complex polycyclic 8- and 9-membered rings through *N to C* aryl migration, however, larger ring systems still had not been accessed. Whilst there is a plethora of commercially available tetrahydroquinolines, larger 7- and 8-membered urea precursors require a multistep synthesis.

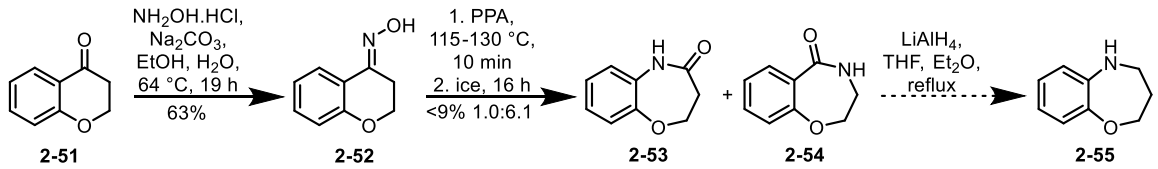
2.3.2.1 Starting material synthesis utilising the Beckmann rearrangement



Scheme 2-7: Synthesis of 7- and 8-membered ring urea precursors.

The larger 7- and 8-membered urea precursors were synthesised from commercially available ketones employing the Beckmann rearrangement (*scheme 2-7*). Oximes **2-45** and **2-46** were successfully synthesised from α-tetralone **2-43** and benzosuberone **2-44** respectively in high yield using literature procedures.[106] The oximes underwent Beckmann rearrangement upon addition to hot PPA (polyphosphoric acid)(heated to reduce viscosity) affording amides **2-47** and **2-48** in good yield.[106,107] Reduction of the amide with $LiAlH_4$ yielded the desired urea precursors **2-49** and **2-50**.[108]

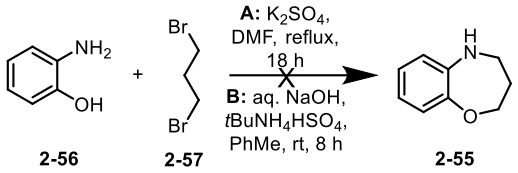
After the successful synthesis of amines **2-49** and **2-50** attention was focused on using this method to synthesise other urea precursors. The synthesis of **2-55** was attempted (*scheme 2-8*).



Scheme 2-835: Attempted synthesis of amine **2-55**.

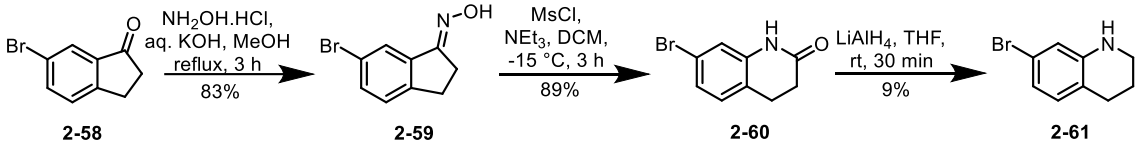
Initial formation of the oxime **2-52** was successful affording the desired product in good yield. However, under the Beckmann rearrangement conditions <9% of the rearranged product was isolated as a mixture of two regioisomers **2-53** and **2-54**. The desired amide **2-53** was obtained in <1%, a search of the literature found attempts to synthesise amide **2-53** previously under these conditions have only led to very low yields.[109]

An alternative route to amine **2-55** was sought using 2-aminophenol **2-56** and 1,3-dibromopropane **2-57** (see *scheme 2-9*). Two alternative conditions were trialled but both resulted in a complex mixture of products by ^1H NMR with no product formation detected.[110]



Scheme 2-9: Attempted synthesis towards 2,3,4,5-tetrahydrobenzo[*b*][1,4]oxapane using two different conditions, both unsuccessful.

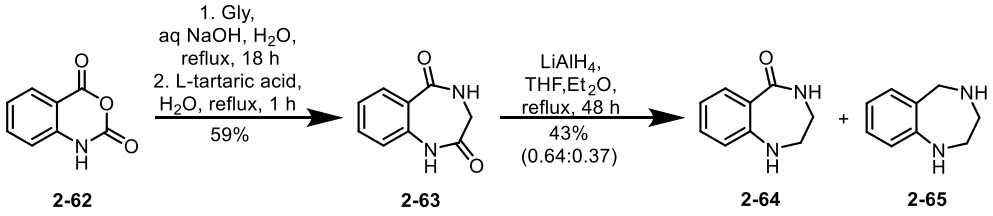
Another target amine **2-61** was proposed to investigate the formation of medium rings with substitution on the aryl migrating ring (*scheme 2-10*). Treatment of commercially available precursor 6-bromoindanone **2-58** with hydroxylamine.HCl afforded the oxime **2-59** in high yield. Beckmann rearrangement using the above conditions gave the amide **2-60** as a mixture of regioisomers in low yield. Swapping PPA for MsCl gave amide **2-60** in 89% yield as one regioisomer.[111] Reduction of the amide afforded the amine **2-61** in low yield.



Scheme 2-10: Synthesis of 7-bromo tetrahydroquinoline.

2.3.2.2 Synthesising substituted benzoazepines

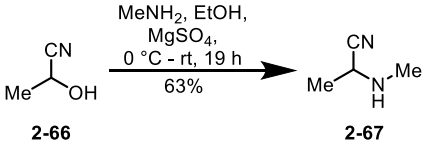
Alternative derivatives of tetrahydrobenzoazepine are not commercially available but are preferential to allow access to a wider scope of medium rings. A recent publication by Chen et. al. demonstrated a route to diamide **2-63** from commercially available glycine and isatoic anhydride (*scheme 2-11*).[112] Reduction of the diamide **2-63** with $LiAlH_4$ was achieved but resulted in a 0.64:0.37 ratio of mono- and fully-reduced amines **2-64** and **2-65** after 48 h refluxing.



Scheme 2-11: Synthesis of amide **2-59** and diamine **2-60** from isatoic anhydride and glycine.

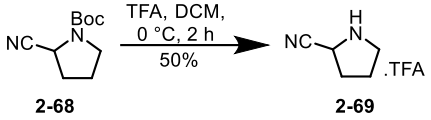
2.3.2.3 Carbamoyl chloride synthesis

With various nitrogen heterocycle precursors synthesised and sourced commercially attention turned towards synthesising the carbamoyl chlorides to couple with the nitrogen heterocycles forming the ureas.



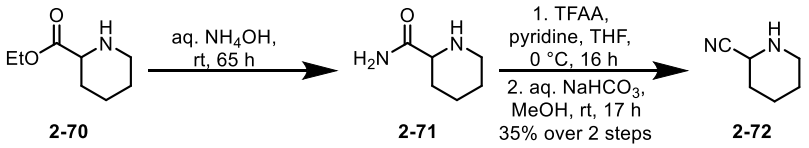
Scheme 2-12: Synthesis of 2-(methylamino)propanenitrile.

Most of the aminonitriles required to synthesise the urea starting materials are not commercially available but can be easily accessed from various starting points. Lactonitrile **2-66** was reacted with methylamine in EtOH affording 2-(methylamino)propanenitrile **2-67** in good yield (*scheme 2-12*).



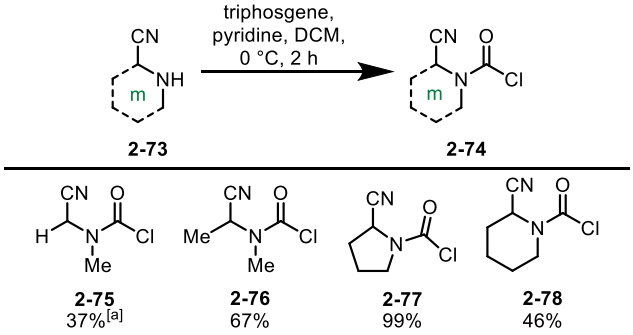
Scheme 2-13: Boc deprotection forming 2-cyano pyrrolidine.TFA salt.

Cyclic amino nitriles were readily accessed from commercially available precursors. 2-cyano pyrrolidine **2-69** was accessed by Boc deprotection of the precursor **2-68** with TFA (*scheme 2-13*).



Scheme 2-14: Synthesis of 2-cyano piperidine via dehydration of primary amide **2-71**.

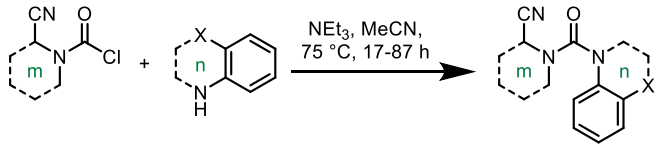
2-Cyano piperidine **2-72** was accessed from ester **2-70** via dehydration of primary amide **2-71** with TFAA (*scheme 2-14*).[113] Primary amide **2-71** was synthesised by stirring ester **2-70** in ammonium hydroxide.



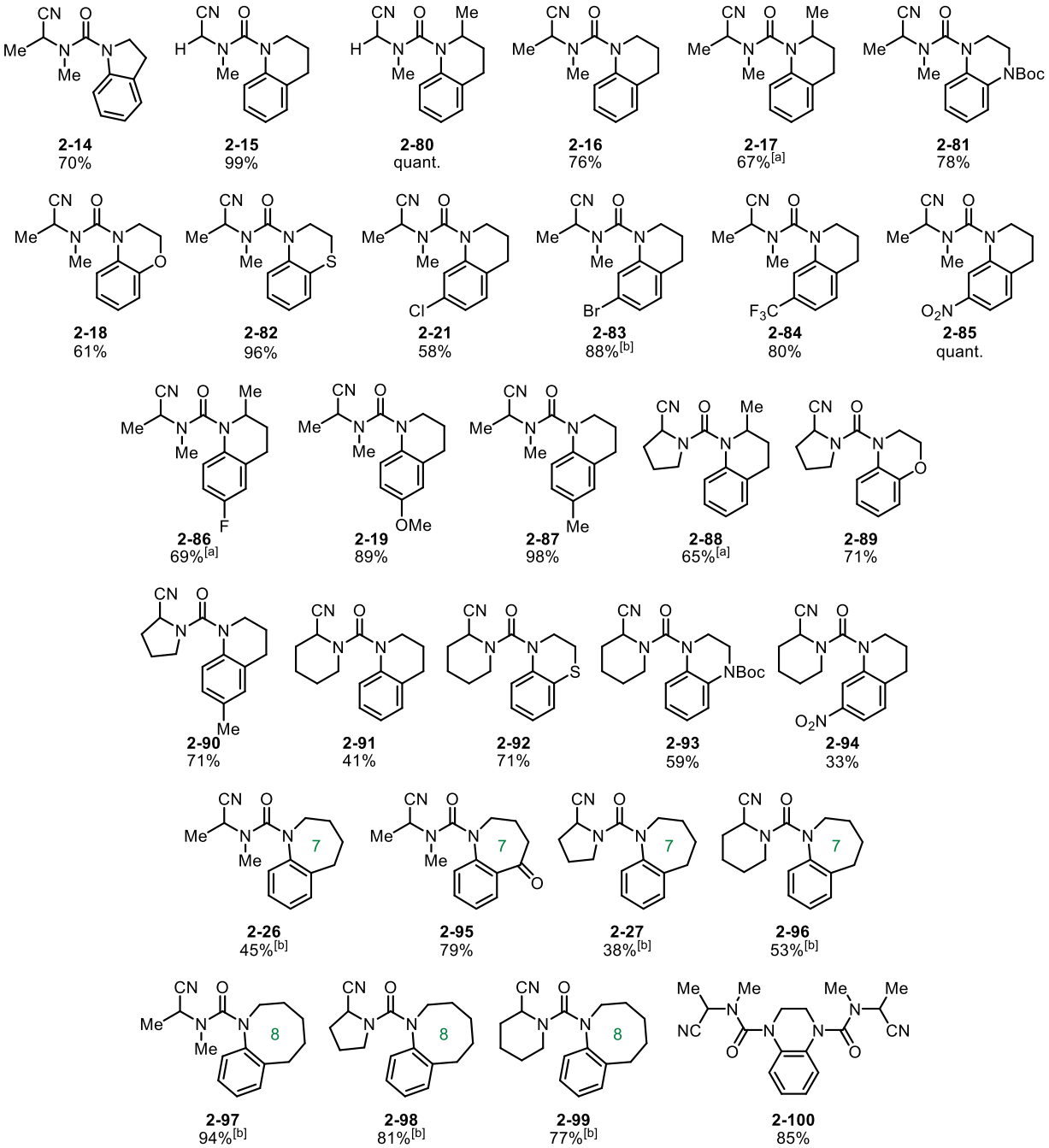
Scheme 2-15: Amino nitrile carbamoyl chloride synthesis.[a] – Formed as a 1:1 mixture with the symmetrical urea.

Various different carbamoyl chlorides were accessed through treatment of the aminonitrile with triphosgene and pyridine (*scheme 2-15*). Subjecting 2-(methylamino)acetonitrile to the reaction conditions afforded the desired carbamoyl chloride **2-75** as a 1:1 mixture with the symmetrical urea, resulting from the coupling of the *in situ* formed carbamoyl chloride **2-75** with another equivalent of the aminonitrile. Carbamoyl chlorides **2-76**, **2-77** and **2-78** were all formed in good yield from the corresponding aminonitriles.

2.3.3 Urea synthesis



2-74 **2-13** **2-79**



Scheme 2-16: Aminonitrile urea synthesis. [a]-Mixture of diastereoisomers not separated. [b] – Nitrogen heterocycle synthesised in section 2.3.2.

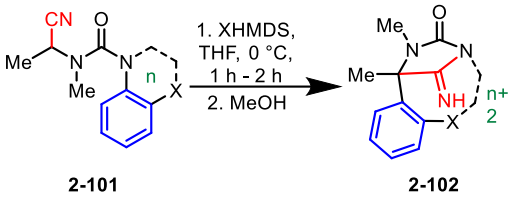
A range of commercially available 5-7-membered nitrogen heterocycles with varying steric and electronic factors and the nitrogen heterocycles synthesised above (section 2.3.2) were coupled with the carbamoyl chlorides **2-75–2-78** (*scheme 2-16*). Ureas **2-18** and **2-82** containing additional heteroatoms were also synthesised from commercially available sources. Urea **2-81** was synthesised by first mono-Boc protecting tetrahydroquinoxaline before coupling to the carbamoyl chloride **2-76**. Ureas **2-17**, **2-80**, **2-86** and **2-88** were synthesised as a mixture of diastereoisomers. The protection of the ketone in urea **2-95** was attempted with ethylene glycol however only starting material was recovered. Diurea **2-100** was synthesised from the unprotected tetrahydroquinoxaline and two equivalents of the carbamoyl chloride **2-76**.

2.3.4 Iminohydantoin-bridging medium ring synthesis

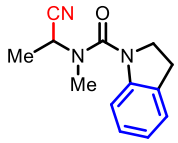
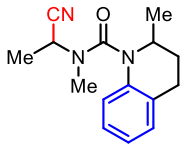
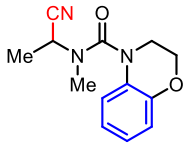
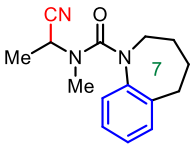
2.3.4.1 Reaction optimisation

Preliminary work indicated milder conditions (KHMDS, pka ~26 in DMSO, 0 °C) were sufficient to deprotonate the more acidic proton α to the nitrile (pka ~17 in DMSO) compared to the more traditionally used ^{s}BuLi/DMPU (pka 51 in DMSO) or LDA/DMPU (pka 35.7 in DMSO) at -78 °C. To explore the effect of different counterions for the HMDS anion, four ureas were chosen (see *table 2-1*) with varying levels of successful rearrangement during initial studies.

Table 2-1: Comparison of alternative counterions for the HMDS anion base in the ring expansion of various nitrile ureas.



2-101 **2-102**

Urea	KHMDS	NaHMDS	LiHMDS
 **2-14**	Complex mixture	Complex mixture	68% SM recovery
 **2-17**	66%[a] Product **2-102**	48%[a] Product **2-102** Decomposition products	12%[b] Product **2-102** 4% SM recovery Decomposition products
 **2-18**	29% Product **2-102** Decomposition products	6% Product **2-102** 17% SM recovery Decomposition products	18% Product **2-102** 7% SM recovery Decomposition products
 **2-26**	91%[c] Product **2-102**	-[d]	70%[c] Product **2-102**

a- Mixture of diastereoisomers isolated. b- Only major diastereoisomer isolated. c- No further purification required. d- Material lost during work-up.

Overall KHMDS proved to be the most effective affording the highest yields for three out of the four ureas trialled. From $K^+ < Na^+ < Li^+$ the strength of the coordination between the HMDS anion and the cation increases, for this *N to C* aryl migration to work it seems that a more weakly coordinating cation was preferential.

Indoline-derived urea **2-14** was unsuccessful with all three bases. A complex mixture of products was seen in the crude ^{1}H NMR for both KHMDS and NaHMDS, with LiHMDS only starting material was recovered.

Urea **2-17** proved to be highly yielding resulting in **2-30** in 66% yield as a 2.1:1.0 mixture of diastereoisomers with KHMDS; an improvement over the initial 21% isolated yield previously (see section 2.3.1). This medium ring highlighted mild steric hindrance was well tolerated during the *N to C* aryl migration. Alongside the desired product isolated from the NaHMDS and LiHMDS reactions, evidence of urea decomposition was seen by recovery of 2-methyl tetrahydroquinoline.

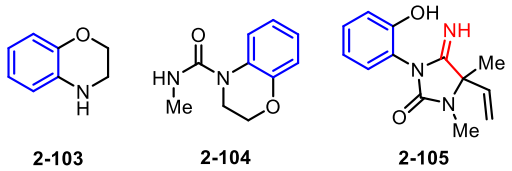
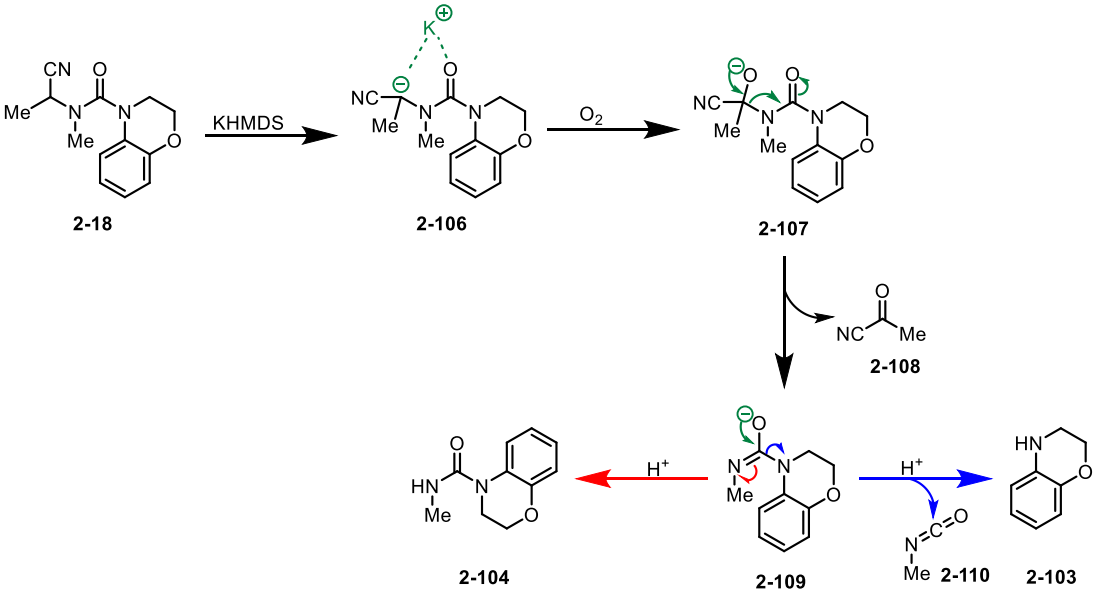


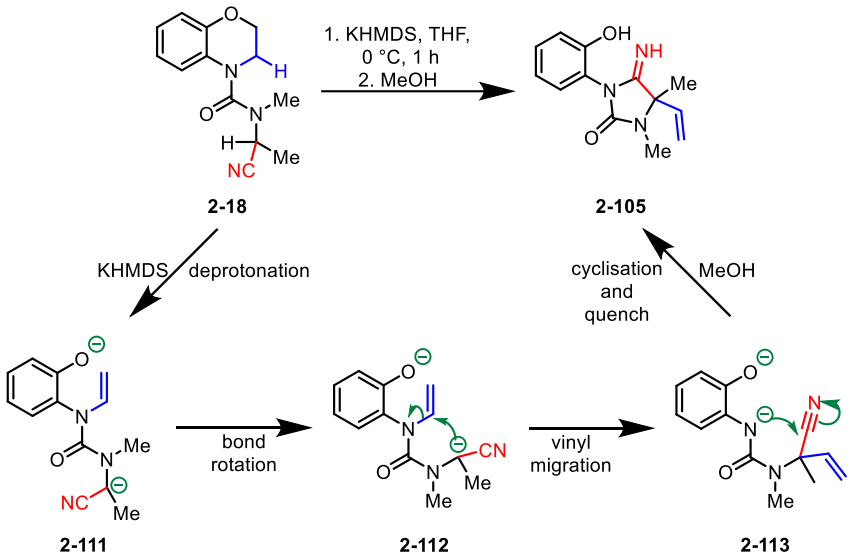
Figure 2-2: Decomposition products isolated from urea **2-18** when treated with K/Na/LiHMDS.

Treatment of urea **2-18** containing an oxygen atom in the alkyl tether with KHMDS gave the highest yield of **2-31**. Urea decomposition products **2-103**, **2-104** and **2-105** were isolated from the reaction (*figure 2-2*). Decomposition products **2-103** and **2-104** were most likely the result of oxidative cleavage of the urea, a proposed mechanism is shown in *scheme 2-17*.[114] Iminohydantoin **2-105** was previously reported by the Clayden group in 2017.[115] The proposed mechanism is shown in *scheme 2-18*. Treating urea **2-18** with base led to deprotonation both α to the nitrile and α to the nitrogen of the tetrahydroquinoxaline forming dianion **2-111**. Migration of the vinyl group to the carbanion gave **2-112**. Analogously to the cyclisation forming medium ring products **2-102** the nitrogen anion attacked the nitrile group forming iminohydantoin **2-105** upon quenching with MeOH.



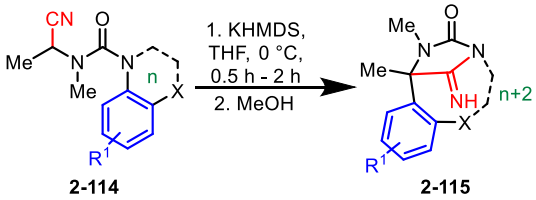
Scheme 2-17: Proposed oxidative decomposition of urea **2-18** leading to two different products.

Treatment of the 7-membered urea **2-26** with both KHMDS and LiHMDS gave the desired 9-membered ring **2-36** in high yield, with the KHMDS giving the best result. Based on these results the use of KHMDS as the base was continued and the reaction scope forming these iminohydantoin-bridging medium rings was investigated.

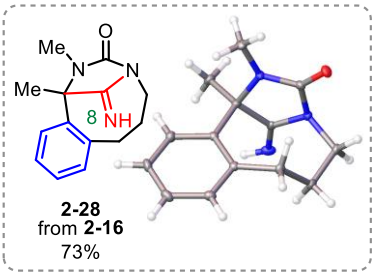


Scheme 2-18: Proposed mechanism forming iminohydantoin.

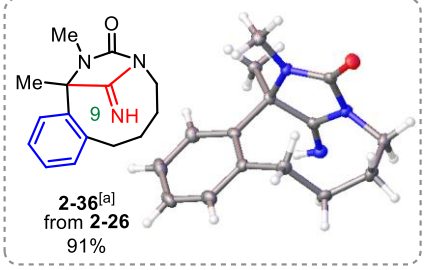
2.3.4.2 Methyl aminonitrile urea ring expansion



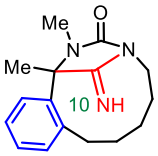
2-114 **2-115**



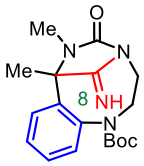
2-28
from **2-16**
73%



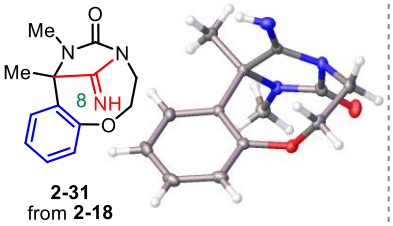
2-36[a]
from **2-26**
91%



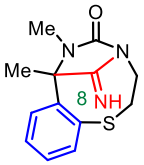
2-116[a]
from **2-97**
90%



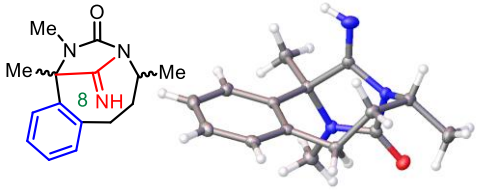
2-117
from **2-81**
64%



2-31
from **2-18**
29%

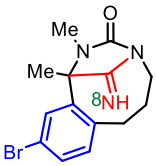


2-118
from **2-82**
54%

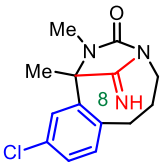


2-30
from **2-17**
66% [2:1 dr]

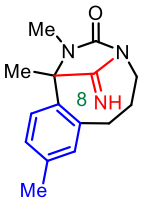
major diastereoisomer



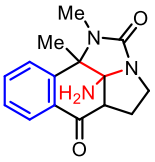
2-119
from **2-83**
49%



2-32
from **2-21**
69%

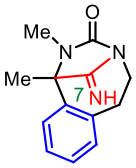


2-120
from **2-87**
35%

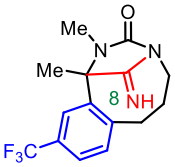


2-121
from **2-95**
55%

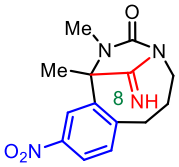
Unsuccessful



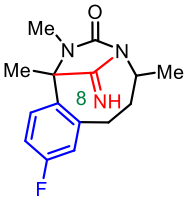
2-122
from **2-14**
[b]



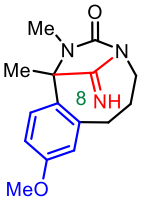
2-123
from **2-84**
[c]



2-124
from **2-85**
[b]



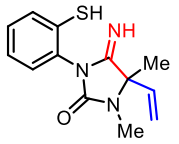
2-125
from **2-86**
[b]



2-126
from **2-19**
[b,d]

Scheme 2-19: Ring expansion products from methyl cyanoureas. [a] – No further purification required. [b] – Complex mixture of decomposition products seen after the urea was treated with KHMDS. [c] – *tele*-Substitution reaction occurred forming defluorinated product **2-128**. [d] – Intermolecular coupling of two equivalents of urea **2-19** formed product **2-132**.

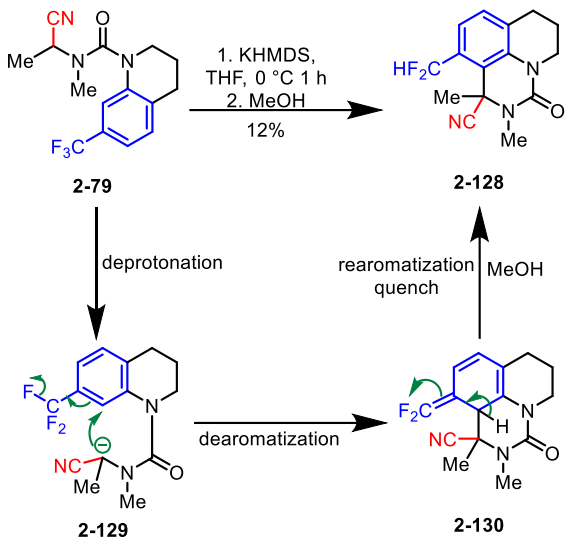
The methyl cyanoureas synthesised in section 2.3.3 were subjected to the optimised conditions affording the iminohydantoin-bridging medium rings shown in *scheme 2-19*. The unsubstituted 8-10-membered rings (**2-28**, **2-36**, **2-116**) were synthesised in high yield, crystal structures of **2-28** and **2-36** were obtained confirming the structure. Medium ring **2-117** was obtained in good yield despite containing a bulky Boc group on the tether of urea **2-81**. Ring expansion of urea **2-81** was also attempted with 18-crown-6 addition with the aim of improving the yield above 65%. Addition of 18-crown-6 resulted in only 25% product **2-117** isolated and evidence of urea decomposition was seen by ^{1}H NMR. Sulfur-containing urea **2-82** gave rise to 8-membered ring **2-118** in good yield along with **2-127** (*figure 2-3*) presumably formed through a similar route as **2-105**.



2-127
12%

Figure 2-3: Iminohydantoin by-product formed when urea **2-82** was treated with KHMDS.

After establishing that 8-10-membered rings were easily accessible and substitutions on the alkyl tether were tolerated investigations focused on the effect of varying the electronics on the migrating aryl ring using various *meta*- and *para*-electron withdrawing and electron donating substituted ureas **2-19**, **2-21** and **2-83–2-87**. Electron withdrawing groups in the *meta*-position were tolerated affording *meta*-chloro **2-32** and *meta*-bromo **2-119** medium rings in high to moderate yields, respectively. Reaction of *meta*-trifluoromethyl urea **2-84** resulted in isolation of tricyclic urea **2-128** as the major product, a result of *tele*-substitution. A proposed mechanism is shown in *scheme 2-20.* The initial anion **2-129** formed from deprotonation attacks the aryl ring *ortho* to the CF_3 moiety resulting in defluorination giving intermediate **2-130**. This dearomatized intermediate then rearomatizes upon quenching with MeOH affording the isolated product **2-128**. Similar *tele*-substitutions have been seen recently in the group looking into aryl migrations of amides.[116]



Scheme 2-20: Proposed *tele*-substitution mechanism forming **2-128**.

The strongly electron withdrawing nitro group in urea **2-85** was not tolerated affording only a complex mixture of products by ^{1}H NMR. The reaction was repeated at -20 °C to try and slow down the rate of decomposition allowing the *N to C* aryl migration to take place. Again, only a complex mixture of products was seen by ^{1}H NMR. A more substituted urea **2-86** bearing a *para*-fluoride and a methyl group on the alkyl tether was also treated with KHMDS to promote aryl migration. No desired product was isolated only decomposition of the urea was seen by isolation of the starting tetrahydroquinoline.

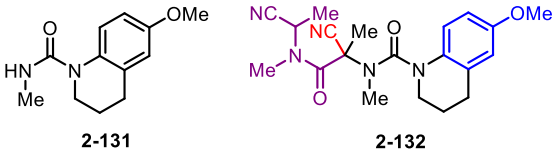
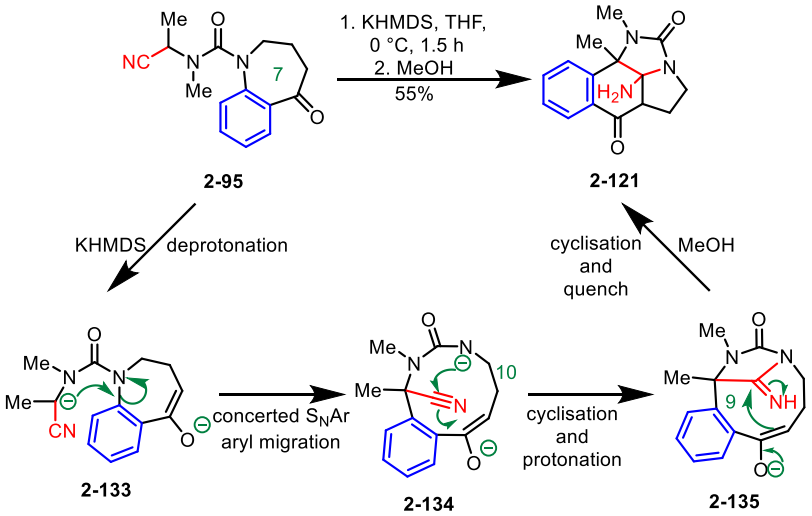


Figure 2-4: Product of urea decomposition and intermolecular coupling of two equivalents of urea **2-19**. Purple section of urea **2-132** from the second urea.

The effects of electron donating substituents on *N to C* aryl migration was investigated using *para*-methoxy urea, **2-19** and *para*-methyl urea, **2-82**. When *para*-methoxy urea **2-19** was treated with KHMDS urea decomposition was seen affording **2-131** and the product of intermolecular coupling of two equivalents of urea **2-132** (*figure 2-4*). The reaction was repeated with the solvent exchanged for Et_2O. The urea **2-19** was only sparingly soluble in Et_2O and THF (0.31 M) was added to aid solubility. After treatment with KHMDS the starting material **2-19** was recovered along with trace decomposition products.

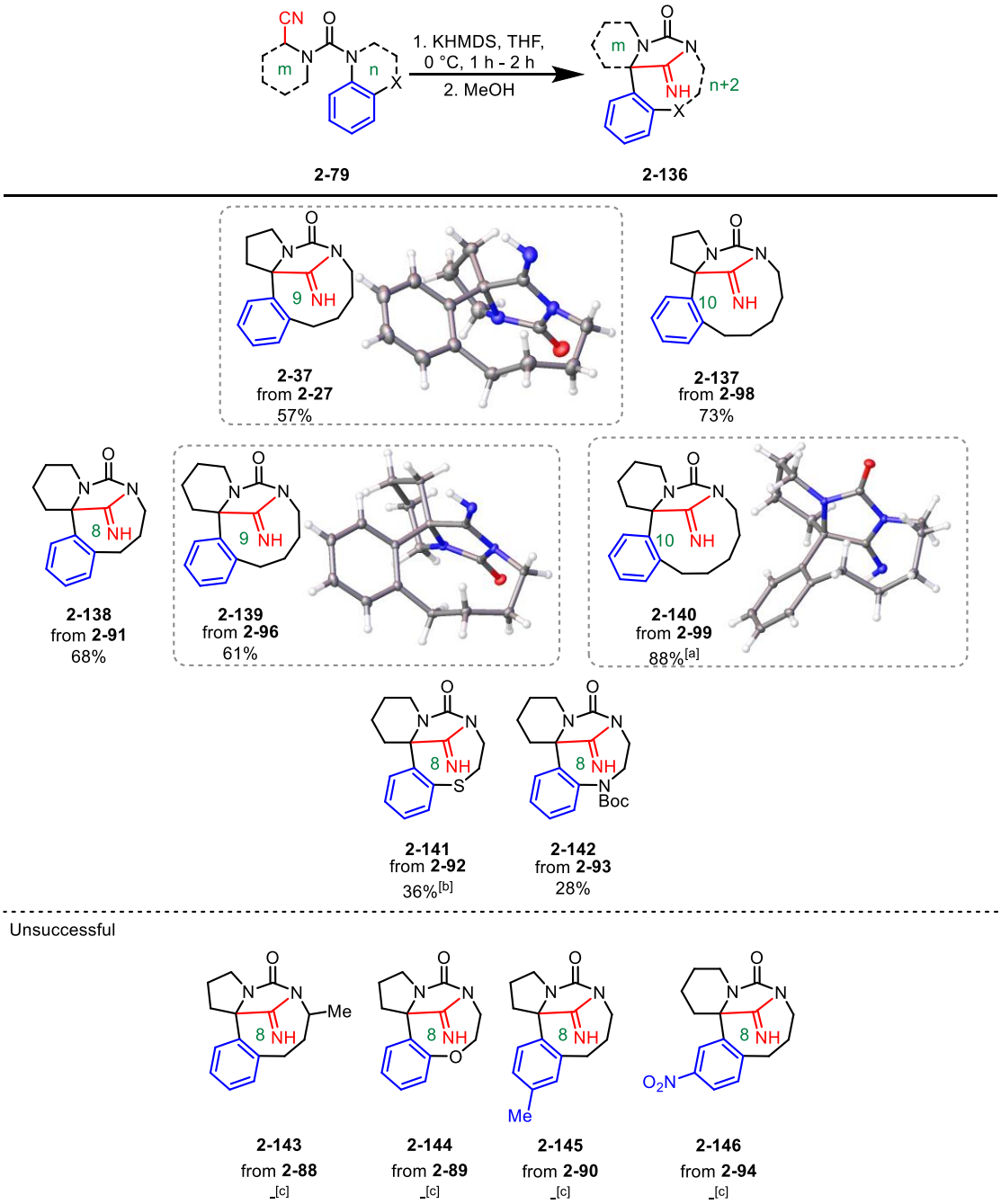
Para-methyl urea **2-87** was subjected to the optimised conditions (KHMDS in THF) resulting in the desired medium ring product **2-120** in moderate yield highlighting the reaction's tolerance to mild electron donating groups on the aryl migrating ring.



Scheme 2-21: Proposed mechanism for the formation of 6,5,5-tricyclic urea **2-121**.

Urea **2-96** containing a carbonyl group on the alkyl tether was treated with KHMDS, affording the 6,5,5-tricyclic urea, **2-121** (*scheme 2-21*). It is proposed to have a bowl like structure with the amine extruding from the top, this is based on the X-ray crystal structure obtained for **2-165** (see section 2.3.5 later). Under basic conditions the proton α to the nitrile is removed along with enolate formation, giving **2-133**. The dianion **2-133** then proceeds through the usual steps, aryl migration-cyclisation forming anion **2-135**. The presence of the iminohydantoin-bridging the medium ring constrains the usually flexible structure bringing the imine in close proximity to the enolate; a stable bond is formed affording product **2-121** as the sole product of the reaction after quenching with MeOH. Protection of the ketone using ethylene glycol was attempted to prevent the second cyclisation however only starting material was recovered from the reaction.

2.3.4.3 Cyclic aminonitrile urea ring expansion



Scheme 2-22: Ring expansion reaction forming polycyclic medium rings. [a] - No further purification required. [b] – Oxidation by-product **2-147** isolated alongside **2-141**. [c] – Complex mixture of decomposition products seen after the urea was treated with KHMDS.

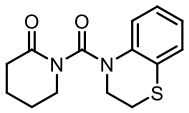
After investigating the limitations on the aryl migrating ring and the alkyl tether attention turned to forming more complex medium ring scaffolds by incorporating another ring using 2-cyanopyrrolidine and 2-piperidine carbamoyl chlorides (*scheme 2-22*).

Pyrrolidine-derived urea **2-88** bearing a methyl group on the alkyl tether was subjected to the standard KHMDS conditions affording only a complex mixture of compounds by ^{1}H NMR. Urea **2-89** containing an oxygen heteroatom in the alkyl tether was treated at 0 °C and at -5 °C again affording only complex

mixture of products. To try and slow down the rate of urea decomposition *para*-methyl urea **2-90** was cooled to -20 °C before KHMDS addition. After 3 hours at -20 °C TLC still showed the presence of starting material and the reaction mixture was warmed to -10 °C and held overnight. The reaction was quenched once TLC showed the absence of starting material. The crude ^{1}H NMR showed only a complex mixture of products.

The larger 9- and 10-membered rings **2-37** and **2-137** were synthesised in good yield from the corresponding 7- and 8-membered ureas **2-27** and **2-98** respectively. X-ray crystal data for **2-37** confirmed the structure of the product.

Unsubstituted 8-10-membered rings **2-138–2-140** containing piperidine nitrile were synthesised in good to high yield and no evidence of urea decomposition was seen. Ring expansion of ureas **2-92** and **2-93** containing heteroatoms led to 9-membered rings **2-141** and **2-142** respectively in moderate yield. The crude yield of **2-142** was low presumably due to lose of material in the aqueous layer. Alongside **2-141** oxidised urea **2-147** (26%) (*figure 2-5*) was also isolated. The reaction was repeat but first the urea/THF mixture was degassed for 1 hour to remove any trapped sources of oxygen to prevent oxidation. However, upon purification the oxidised product **2-147** was recovered in similar yield. *Para*-nitro urea **2-94** was also subjected to KHMDS affording only a complex mixture of products by ^{1}H NMR.



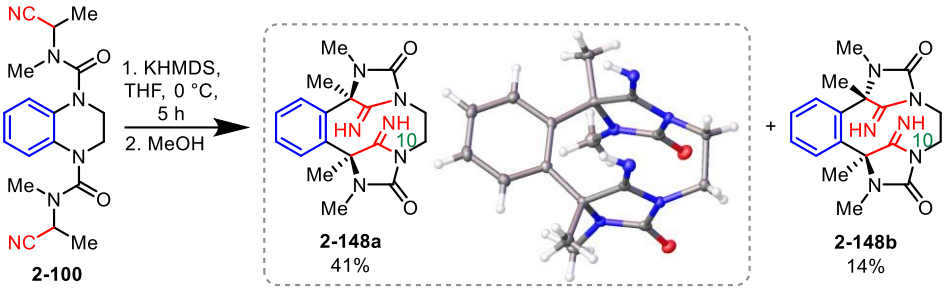
2-147

Figure 2-5: Oxidation product formed from urea **2-92** treated with KHMDS.

Comparing the yields for the methyl and cyclic aminonitrile urea products the yields generally increased as the ring size increases when there is no substitution on the rings; this is most likely due to the decrease in ring strain as the ring size increases.

2.3.4.4 Double ring expansion

In sections 2.3.4.2 and 2.3.4.3 a single aryl migration occurred for each urea resulting in a range of 8-10-membered rings with one bridging iminohydantoin including varying levels of complexity. Extending this, urea **2-100** was synthesised containing two ureas from the unprotected tetrahydroquinoxaline and two equivalents of the carbamoyl chloride **2-76** (see section 2.3.3).

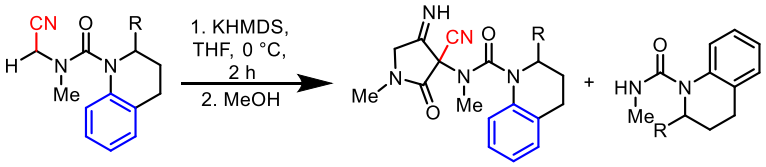


Scheme 2-23: Ring expansion of diurea **2-100** was KHMDS affording two diastereoisomers. The major *meso*-diastereoisomer (**2-148a**) and the minor C_2-symmetric diastereoisomer (**2-148b**).

The diurea **2-100** was treated with four equivalents of KHMDS and quenched after 3 hours resulting in isolation of **2-148** with two bridging iminohydantoins on a 12-membered ring in 25% yield. Purification of this molecule was difficult due to the high polarity, resulting in loss of material within the aqueous layer during work-up. Repetition of this reaction without the aqueous work-up afforded the product **2-148** in 55% overall yield (*scheme 2-23*). Two diastereoisomers were isolated during purification; the major diastereoisomer **2-148a** identified by X-ray crystallography as the *meso*-diastereoisomer. The minor diastereoisomer was determined to be the C_2-symmetric diastereoisomer **2-148b** by chiral HPLC.

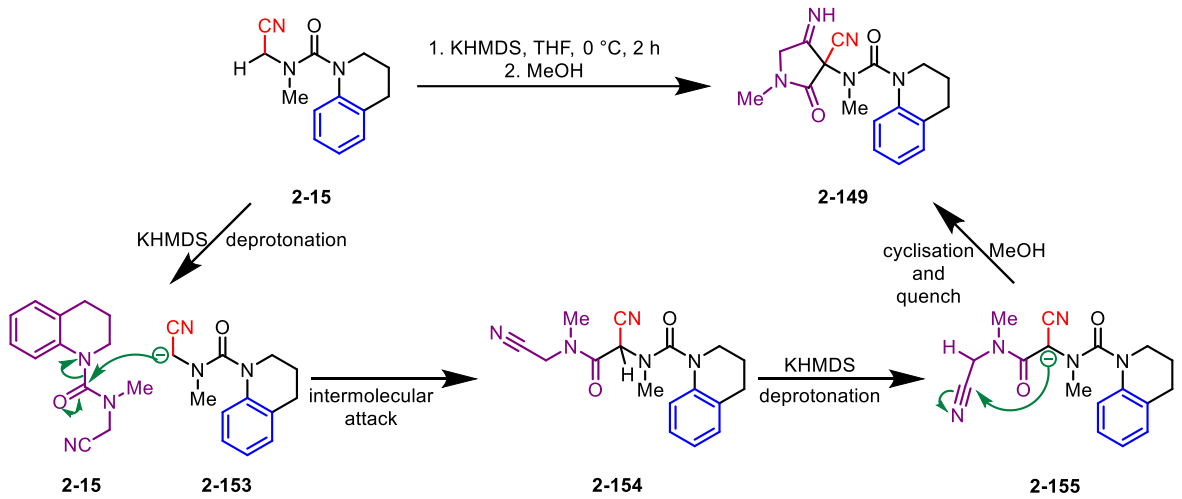
2.3.4.5 Glycine-derived urea ring expansion

Exploring whether an alkyl group α to the nitrile is required ureas **2-15** and **2-80** were synthesised. Successful ring expansion of these ureas these would form medium rings with a benzylic proton, a site for further functionalisation post-ring expansion.



Scheme 2-24: Synthesis of **2-149** and **2-150** and decomposition product **2-151**/**2-152** resulting from oxidative decomposition of the urea.

Urea **2-15** was treated under the standard conditions affording **2-149** (49%) and urea decomposition product **2-151**, however no desired medium ring product was observed (*scheme 2-24*). Urea **2-80** also afforded a similar compound, **2-150** in good yield when treated with KHMDS.



Scheme 2-25: Proposed mechanism for the formation of **2-149** and **2-150**.

The lack of steric hindrance α to the nitrile allows an intermolecular reaction between 2 equivalents of the urea forming **2-149** and **2-150** proceeding via the proposed mechanism shown in *scheme 2-25*. Initial deprotonation α to the nitrile gives **2-153**. This anion then attacks a second equivalent of the urea releasing tetrahydroquinoline. This newly formed urea **2-154** is deprotonated a second time at the most acidic site in between the amide and the urea. Anion **2-155** then undergoes an intramolecular cyclisation forming **2-149** upon quenching with MeOH.

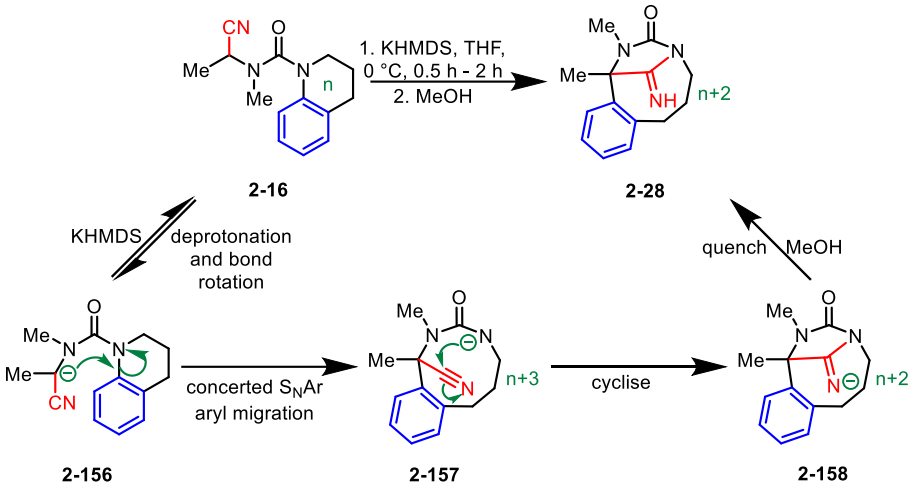
To try and suppress/limit the formation of the intermolecular attack product **2-149** alternative reaction conditions were trialled. The use of less equivalents of KHMDS proved ineffective. The reaction mixture was also diluted 10-fold to try and prevent the undesirable intermolecular reaction and promote the *N to C* aryl migration, again only **2-149** was formed in similar yield to previously. Although the use of 18-crown-6 as a potassium chelating agent was detrimental to the yield in section 2.3.4.2, addition of 18-crown-6 had no effect on the reaction and **2-150** was isolated in comparable yield to above.

Based on the discoveries in sections 2.3.4.2 – 2.3.4.5 at least a methyl group is required at the site of deprotonation to act as steric hindrance preventing intermolecular reactions and facilitate intramolecular *N to C* aryl migration.

2.3.4.6 Mechanism studies using *in situ* infra-red spectroscopy

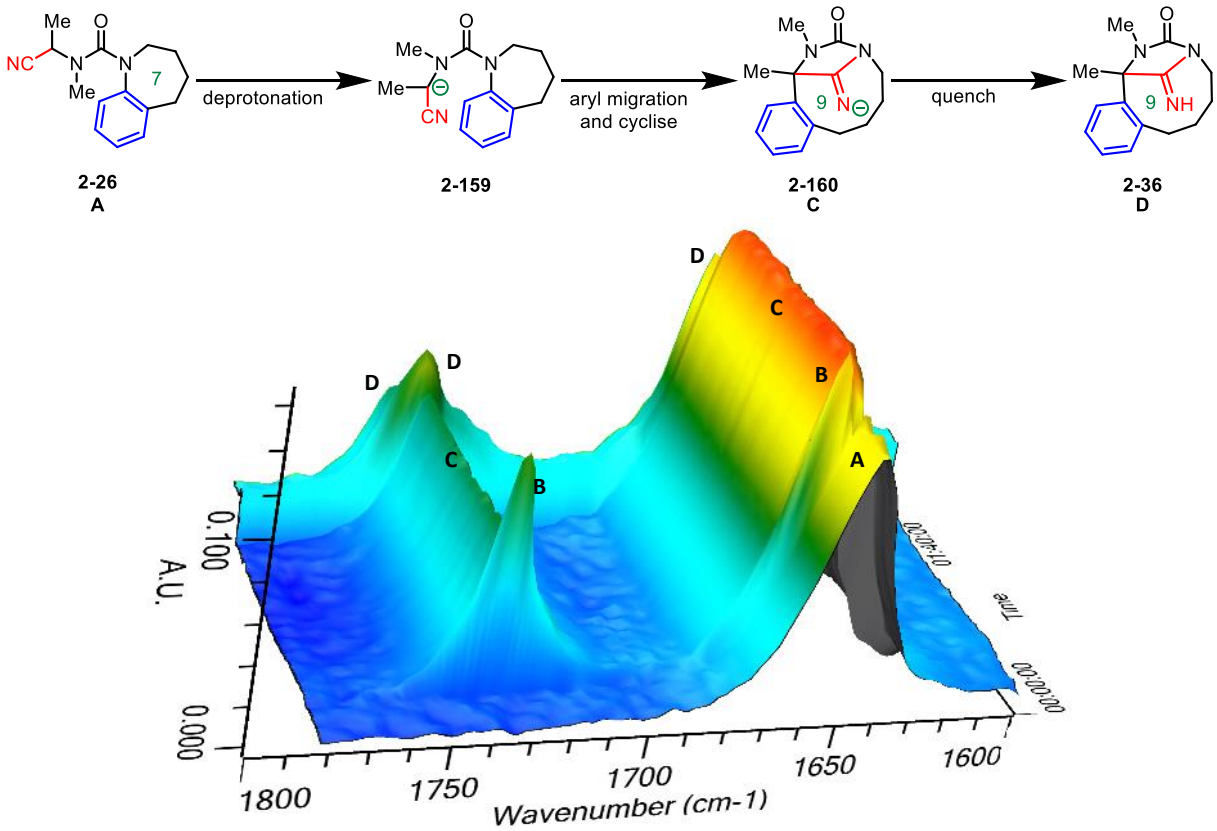
A proposed mechanism for the formation of iminohydantoin-bridging medium rings is shown in *scheme 2-26,* comprising a deprotonation-rearrangement-cyclisation cascade. Initial deprotonation of the urea and bond rotation about the N-CO bond breaks the interaction between the potassium cation and the carbonyl, resulting in anion **2-156**. The bond rotation brings together the anion and the electrophilic aryl migrating group. An 'S_NAr-type' aryl migration occurs by *ipso* attack of the anion onto

the aryl ring, breaking the Ar-N bond and establishing a new C-C bond in a concerted step forming the medium ring **2-157** in a *n to n+3* ring expansion. The nitrogen anion **2-157** then attacks the nitrile group cyclising to form the iminohydantoin-bridging medium ring upon quenching, reducing the ring size to *n+2*. Anion **2-156** was proposed to be in equilibrium with urea **2-16** after initial deprotonation from KHMDS, the equilibrium is driven by consumption of anion **2-156** forming **2-157** through *N to C* aryl migration.



Scheme 2-26: Proposed mechanism for the formation of iminohydantoin-bridging medium rings.

The reaction mechanism was probed for urea **2-26** leading to **2-36** using *in situ* infra-red spectroscopy (ReactIR) at -5 °C in THF. The ReactIR used detected absorptions between 1900 and 650 cm^{-1}; due to technical difficulties the absorptions above 1900 cm^{-1} were not monitorable which meant the disappearance of the nitrile group in **2-26** (which absorbs around 2239 cm^{-1}) was not detectable. The reaction was performed in a more concentrated solution (0.3 M vs. 0.1 M) to help with detection of short-lived intermediates. The IR spectra of the starting material in THF before KHMDS addition was recorded (**A** on *scheme 2-27*) and showed an absorption at 1654 cm^{-1} assigned to the carbonyl of the urea. Addition of KHMDS resulted in a shift to 1663 cm^{-1} (**B**), which shifted almost immediately (within 15 seconds) to 1660 cm^{-1} (**C**). For the remaining time (90 min) the spectra remained unchanged. Both shifts (**B** and **C**) were accompanied by the appearance of an absorption at 1737 cm^{-1} with only the intensity of the peak changing between these two steps. This peak was assumed to correspond to the imine anion. The reaction was quenched with MeOH after 90 min resulting in product **2-36** with absorptions at 1662, 1736, 1743 cm^{-1}, these were assumed to correspond to the carbonyl and imine of product **2-36**.



Scheme 2-27: Infra-red spectroscopy of urea **2-26** in the presence of KHMDS leading to the formation of **2-36** at -5 °C in THF. **A** – Starting urea **2-26** at -5 °C absorption at 1654 cm^{-1}. **B** – (*t* = 18 min) KHMDS (2 eq.) added at -5 °C, absorptions at 1663 & 1737 cm^{-1}. **C** – Reaction mixture at -5 °C, absorptions at 1660 & 1737 cm^{-1}. **D** – (*t* = 108 min) Reaction quenched with MeOH at -5 °C, absorptions at 1662, 1736 & 1743 cm^{-1}. The peaks are tentatively assigned as shown.

The absorptions at **C** were assigned to product anion **2-160** by comparison of the spectrum with the spectrum of product **2-36** treated with KHMDS in THF (see *figure 2-6*). The absorptions are similar to those seen for unbridged iminohydantoin anions reported previously but about 15 cm^{-1} higher.[98] It appears that the deprotonation of **2-26**, rearrangement and cyclisation leading to **2-160** are essentially instantaneous, at least for this urea. Reducing the temperature of the reaction to -38 °C (dry ice/MeCN bath) had no effect on the reaction rate leading to an almost identical ReactIR spectrum. No intermediate **2-159** was seen in the IR spectrum nor isolated as the protonated form in any of the substrate scope in section 2.3.4.

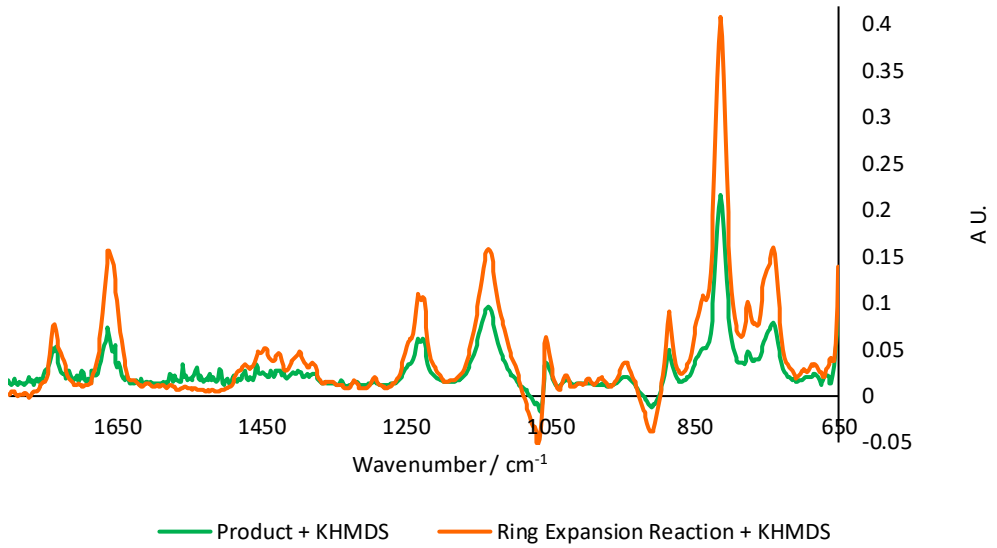
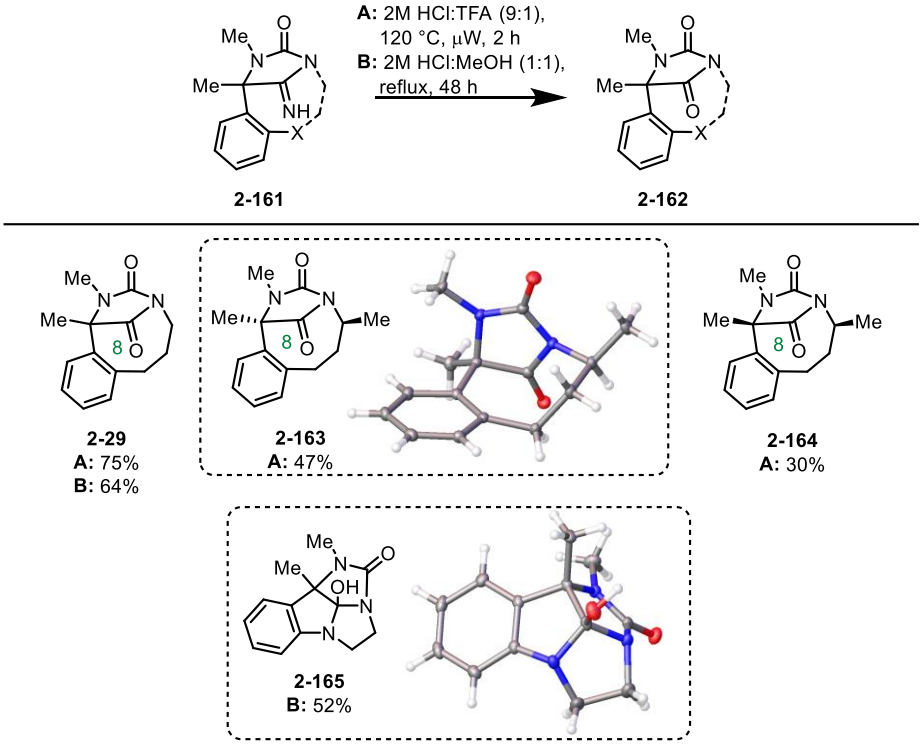


Figure 2-65: Comparison of the product **2-36** with KHMDS forming product anion **2-160** with section **C** of urea **2-26** treated with KHMDS forming product **2-36**.

2.3.5 Hydrolysis forming hydantoin-bridging medium rings

In section 2.3.4 a range of polycyclic iminohydantoin-bridging medium rings (8-10-membered) were synthesised with varying steric and electronic factors in generally good to high yields. Investigations next focused on hydrolysing a selection of these medium rings, forming the hydantoin-bridging medium rings. Whilst the iminohydantoins have the potential for biological activity, access to the hydantoin would be beneficial considering the vast number of hydantoin motifs in approved pharmaceuticals.[117,118]

In the preliminary study refluxing the unsubstituted 8-membered ring **2-28** in 1 M HCl in MeOH afforded the desired hydantoin product **2-29** in good yield (*scheme 2-5*). This reaction was repeated using 2 M HCl affording the product **2-29** in similar yield (see *scheme 2-28*). In an attempt to improve the yield, the hydrolysis was performed in the microwave. MeOH was substituted for TFA allowing higher temperatures to be used without highly pressurising the microwave vial but still keeping the iminohydantoin in solution.[119,120] Medium ring **2-28** was irradiated in the microwave for 2 hours in a 9:1 ratio of 2 M HCl:TFA resulting in the hydantoin product **2-29** in higher yield.



Scheme 2-28: Hydrolysis of iminohydantoin-bridging 8-membered rings.

The separated diastereoisomers of 8-membered ring **2-30** and **2-30'** containing a methyl group on the alkyl tether were also subjected to microwave irradiation with HCl:TFA resulting in moderate yields of **2-163** and **2-164**. No starting material or decomposition was seen in the crude ^{1}H NMRs and so the low yields were assumed to be due to material loss during work-up.

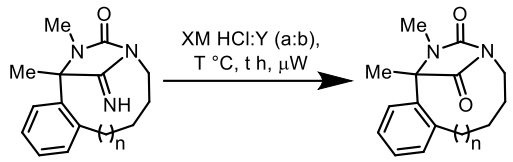
Under the acidic conditions it was presumed that the iminohydantoin of **2-117** would hydrolyse and the N-Boc protecting group cleaved in one step. Subjecting **2-117** in 2 M HCl:TFA (9:1) to microwave irradiation resulted in a complex mixture of products. However, refluxing medium ring **2-117** in 2 M HCl:MeOH (1:1) for 48 hours afforded 5,5,5-tricyclic urea **2-165**; X-ray crystallography irrefutably confirmed the structure as a bowl-like molecule with the hydroxyl group protruding from the top.

The hydrolysis of larger rings **2-36** and **2-116** were also attempted as shown in *table 2-2*. Various conditions were employed to hydrolyse these medium rings both thermally and under microwave irradiation. Initially thermal hydrolysis was attempted using previously successful conditions (entry 1, *table* 2-2) but only starting material **2-36** was recovered. Increasing the concentration of HCl had no effect.

Microwave irradiation of **2-36** was then tested using previously successful conditions (entry 4). Again, only starting material was recovered. The larger rings are more lipophilic and were possibly not fully dissolved in solution; to overcome this problem, the volume of TFA was increased (entry 6), resulting in recovery of the starting material. Next investigations focused on the overall molarity of the reaction

mixture. The molarity was halved and the reaction trialled with various ratios of HCl:TFA (entries 6-9) but only starting material was recovered. The same was found for 10-membered **2-111** (entries 10-14).

Table 2-2: Attempted hydrolysis of iminohydantoin-bridging medium rings **2-36** and **2-116**. [a] – Ratio of X M HCl:Y. [b] – Reactions performed under microwave irradiation in sealed tube. [c] – Reaction performed thermally on bench.

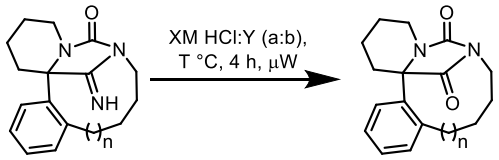


2-166 **2-167**

Entry	n	Molarity	X M HCl	Y (a:b)[a]	Temperature[b]/ °C	Time /h	Comment
1	1	0.05	1	MeOH (1:1)	70[c]	48	Starting material recovery
2		0.05	2	MeOH (1:1)	70[c]	48	Starting material recovery
3		0.05	6	MeOH (1:1)	70[c]	48	Starting material recovery
4		0.05	2	TFA (9:1)	120	4	Starting material recovery
5		0.05	6	TFA (6:4)	120	4	Starting material recovery
6		0.025	2	TFA (1:1)	120	1	Starting material recovery
7		0.025	6	TFA (1:1)	120	1	Starting material recovery
8		0.025	2	TFA (2:8)	120	1	Starting material recovery
9		0.025	6	TFA (1:1)	150	2	Starting material recovery
10	2	0.05	2	MeOH (1:1)	70[c]	48	Starting material recovery
11		0.05	2	TFA (9:1)	120	4	Starting material recovery
12		0.025	2	TFA (1:1)	120	2	Starting material recovery
13		0.025	6	TFA (1:1)	120	2	Starting material recovery
14		0.025	2	TFA (1:1)	150	2	Starting material recovery

Polycyclic medium rings **2-139** and **2-140** were also subjected to a range of hydrolysis conditions. These medium rings contain larger lipophilic areas requiring at least 40% TFA to prevent precipitation of the medium ring once aq. HCl was added (entries 1, 4, 5). A range of conditions were trialled (entries 2-3, 6-8) but only starting material was recovered. Polycyclic medium ring **2-140** was subjected to microwave irradiation at 170 °C for 4 hours, but no evidence of hydrolysis or decomposition was seen in the crude ^{1}H NMR, highlighting how robust these molecules are to harsh conditions.

Table 2-3: Attempted hydrolysis of iminohydantoin-bridging medium rings **2-139** and **2-140**. [a] – Ratio of X M HCl:Y. [b] – Reactions performed under microwave irradiation in sealed tube. [c] – Starting material poorly soluble once HCl added.



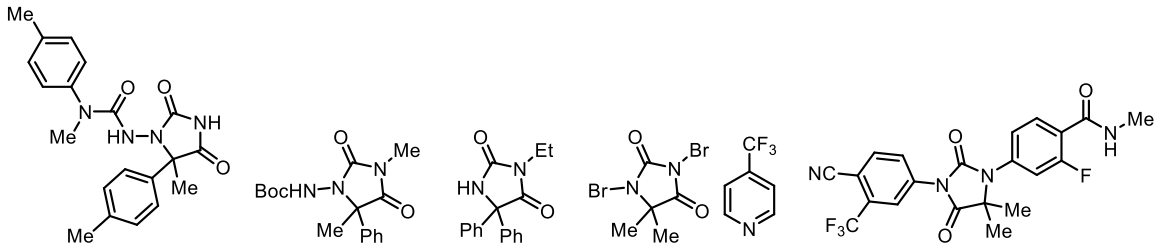
2-168 **2-169**

Entry	n	Molarity	X M HCl	Y (a:b)[a]	Temperature[b]/°C	Comment
1	1	0.05	2	TFA (8:2)[c]	120	Starting material recovery
2		0.05	2	TFA (6:4)	120	Starting material recovery
3		0.025	6	TFA (6:4)	120	Starting material recovery
4	2	0.05	2	TFA (9:1)[c]	120	Starting material recovery
5		0.05	6	TFA (9:1)[c]	120	Starting material recovery
6		0.05	6	TFA (6:4)	120	Starting material recovery
7		0.025	2	TFA (1:1)	150	Starting material recovery
8		0.025	2	TFA (1:1)	170	Starting material recovery

The 12-membered ring **2-148a** with two bridging iminohydantoins was also irradiated in the microwave in 2 M HCl:TFA ((1:1), 0.025 M, 120 °C, 4 h) again resulting in only starting material recovery.

2.3.6 Analysis of the X-ray crystal structures of (imino)hydantoins

A possible explanation for the lack of reactivity seen under acidic conditions with the larger iminohydantoin-bridging medium rings can be found by analysing the X-ray crystal structures of the (imino)hydantoins synthesised above (in section 2.3.4) and comparing them to literature monocyclic hydantoins **2-170 – 2-174** in *figure2-7*.

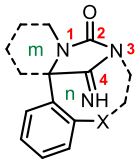


2-170 2-171 2-172 2-173 2-174

Figure 2-7: Literature hydantoins.

Monocyclic hydantoins **2-170–2-174** were used; from their literature X-ray crystal structures, their bond angles were extracted and subsequent deviations from planarity Calculated[121–124] Hydantoins are fairly stable, more or less planar rings with very little to no deviation from planarity seen in *table 2-4*.[125]

Table 2-4: Structural parameters comparison table. [a] – **ΔΣθ** = deviation from planarity = 360° - sum of bond angles. [b] – ***Δδ*** = Change in chemical shift from average value of two representative hydantoins (**2-170** & **2-171**). [c] – Values for representative monocyclic hydantoins (**2-170-2-171**).[121–124] [d] – δ = 155.3 ppm (average of two values[121]). [e] – δ = 173.7 ppm for iminohydantoins only (average of two values[121]). [f] – Data taken from X-ray crystal structures of **2-140** and **2-148**. [g] – Excluding structures where this atom lies at a ring junction. [h] – Data taken from X-ray crystal structures of **2-36**, **2-37**, 2-139. [i] – Data taken from X-ray crystal structures of 2-**28**, **2-30** and **2-31**.



2-175

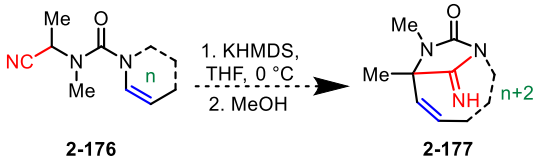
Ring size, n	N1 ΔΣθ[a]	C2 ΔΣθ[a]	C2 Δδ[b]	N3 ΔΣθ[a]	C4 ΔΣθ[a]	C4 Δδ[b]
-[c]	1.2	0.0	0.0[d]	0.1	0.0	0.0[e]
10[f]	2.9[g]	0.0	-0.9	2.4	0.2	4.6
9[h]	2.1[g]	0.0	-3.9	4.6	0.1	1.3
8[i]	2.1	0.0	-5.9	13.4	0.0	0.6

Although the molecules synthesised above contain a bridgehead nitrogen atom, formally sp^2-hybridised, for these (imino)hydantoins to be fully planar would be a contradiction of Bredt's rule.[126,127] The bond angles and subsequently the deviation from planarity were calculated for each of the X-ray crystal structures shown above and summarised in *table 2-4*. Generally, the larger the ring, the less derivation from planarity was seen. The largest structural change was seen at **N3** where the smaller 8-membered rings deviated on average 13.4° from planar making them more pyramidalised, whereas the monocyclic hydantoins were planar. This increased pyramidalization makes **C4** more electrophilic and susceptible to hydrolysis. No substantial difference was seen at **N1**

nor **C1**/**C4**. The change in planarity as the ring size increases and the ring strain decreases, plus the additional steric bulk of the piperidine-derived medium rings (**2-139** and **2-140**) is a possible explanation for the lack of reactivity seen above (*table 2-2* and *2-3*). It is noteworthy that the ^{13}C NMR shift for **C2** became more upfield as the ring size decreased.

2.3.7 Vinyl migration forming iminohydantoin-bridging medium rings

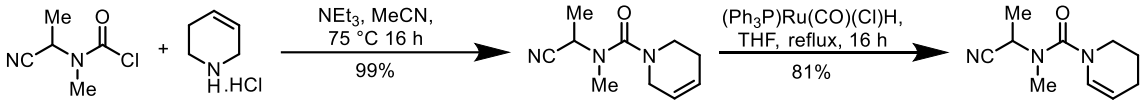
Aryl migrations forming acyclic and cyclic structures have been well studied but to date there are no literature reports of *N to C* vinyl migrations forming medium rings. These medium rings would have increased flexibility and be able to be functionalised post-ring expansion.



2-176 **2-177**

Scheme 2-29: Proposed synthesis of iminohydantoin-bridging vinyl medium rings

In section 2.3.4 we showed that polycyclic medium rings containing a bridging (imino)hydantoin could be synthesised in generally good to high yields, these medium rings contain benzyl groups which imposes some structural rigidity. Replacement of the aryl migrating group with a vinyl group (urea **2-176**) would lead to medium rings **2-177** after base promoted *N to C* vinyl migration (*scheme 2-29*). Based on previous acyclic vinyl migrations retention of alkene geometry is predicted.[98,128]



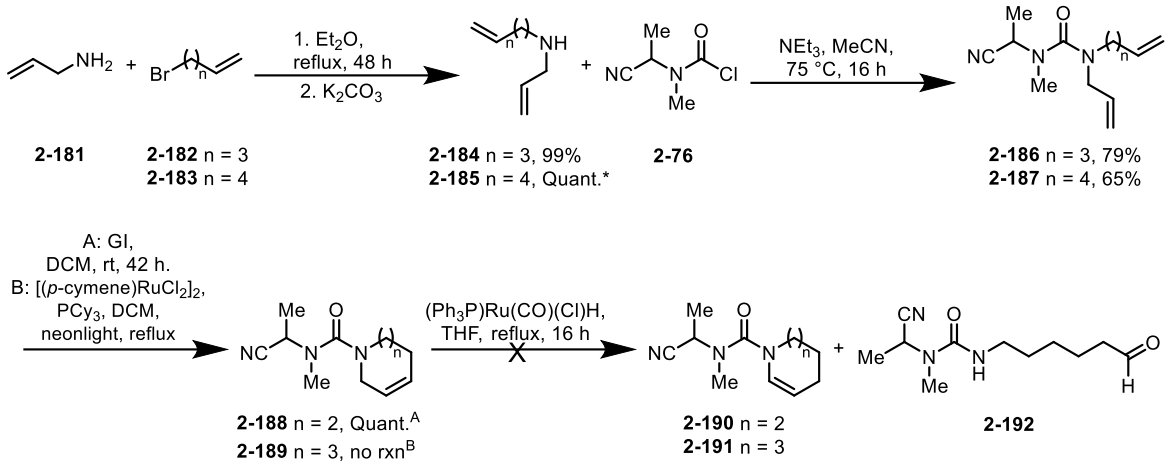
2-76 **2-178** **2-179** **2-180**

Scheme 2-30: Synthesis of urea **2-166**.

To explore the potential for vinyl migration using nitrile stabilisation, the tetrahydropyridine-derived urea **2-180** were synthesised (*scheme 2-30*). Urea **2-179** was synthesised by coupling carbamoyl chloride **2-76** with tetrahydropyridine.HCl **2-178**. The allyl group was then isomerised with [Ru] catalyst forming the desired cyanoalkyl urea **2-180** in excellent yield over two steps.

The synthesis of the larger 7- and 8-membered ring ureas **2-190** and **2-191** was attempted. The starting cyclic amines were not commercially available. A synthesis route was devised (*scheme 2-31*) starting

from commercially available allylamine **2-181** and the corresponding bromoalkene **2-182**/**2-183**, utilising a key RCM reaction to form the 7- and 8-membered rings.



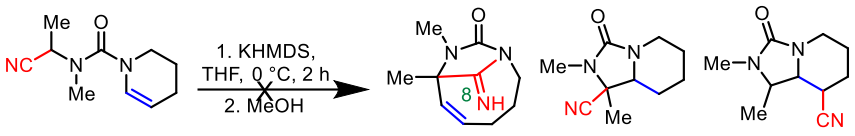
2-181 **2-182** n = 3, **2-183** n = 4 **2-184** n = 3, 99%, **2-185** n = 4, Quant.* **2-76** **2-186** n = 3, 79%, **2-187** n = 4, 65%

2-188 n = 2, Quant.[A], **2-189** n = 3, no rxn[B] **2-190** n = 2, **2-191** n = 3 **2-192**

Scheme 2-31: Attempted synthesis of vinyl ureas **2-176** and **2-177**.

Allylamine **2-181** was reacted with bromo-pentene **2-182** and bromo-hexene **2-183** affording the allylamines **2-184** and **2-185** respectively in excellent yields.[129] The allylamines **2-184** and **2-185** were coupled with the carbamoyl chloride **2-76** giving the RCM precursors **2-186**/**2-187** in high yields. The RCM of urea **2-186** afforded the 7-membered-allyl urea **2-188** in quantitative yield. Isomerisation of the urea **2-188** afforded a mixture 1.00:0.82 **2-192**:**2-190**. Aldehyde **2-192** is formed from the hydrolysis of the isomerised urea **2-190**. The aldehyde **2-192** and vinyl urea **2-190** were inseparable in all TLC conditions trialled.

For urea **2-189** the RCM using the standard condition (**A**, *scheme 2-31*) was unsuccessful and the starting material **2-189** was recovered. Heating to reflux only returned starting material. Substituting GI for GII and heating to reflux similarly resulted in no product formation. A literature search revealed that using [(*p*-cymene)$RuCl_2$] as the pre-catalyst alongside PCy_3 and exposing the reaction mixture to standard laboratory lighting should lead to RCM forming 8-membered ring **2-191**.[130] However, after leaving the reaction mixture refluxing for several days only starting material **2-189** was present in the crude ^{1}H NMR.



2-180 **2-193** **2-194** **2-195**

Scheme 2-3236: Treatment of urea **2-180** with KHMDS.

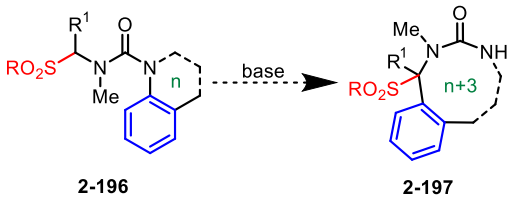
N to C vinyl migration of urea **2-180** was attempted using the conditions developed in section 2.3.4 (*scheme 2-32*). After two hours TLC analysis showed consumption of the starting material and the reaction was quenched with MeOH. Purification of the crude complex mixture of products afforded

* Experiment carried out by Madeline Townley.

trace amount of **2-194** and **2-195** along with other unidentified compounds. Bicyclic product **2-195** results from migration of the nitrile group after cyclisation. In the crude ^{1}H NMR no peaks above 4.00 ppm were seen indicating no alkenes were remaining in the reaction.

In summary application of the nitrile anion stabilised aryl migration ring expansion forming iminohydantoins was not applicable to vinyl migration. As well as a complex mixture of products, ureas **2-194** and **2-195** were isolated in trace amounts suggesting that the carbanion does attack the vinyl group, however the 5,6-bicyclic urea is more stable and is preferentially formed. Synthesis of larger 7- and 8-membered vinyl rings was also problematic resulting in hydrolysis of the 7-membered ring to the aldehyde and for the larger ring the RCM step was unsuccessful only returning starting material.

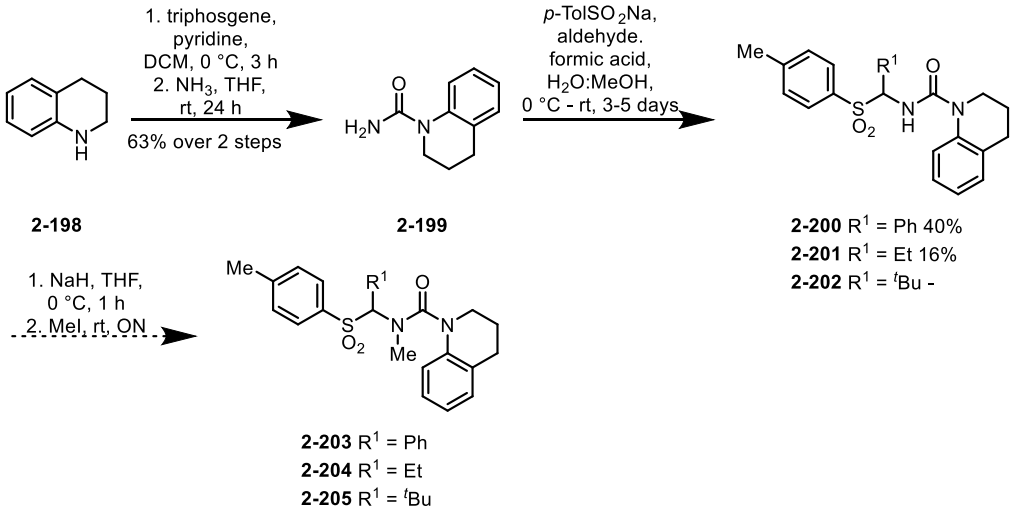
2.4 Sulfone stabilised anions forming medium rings



2-196 **2-197**

Scheme 2-33: Proposed ring expansion to sulfone containing medium rings.

The use of heteroatoms as anion stabilising groups is an underdeveloped area of aryl migration chemistry both with acyclic and cyclic products. Investigating the use of alternative anion stabilising groups sulfones were chosen using ureas **2-196** (*scheme 2-33*). It was predicted that under basic conditions an *n to n+3* ring expansion would form medium rings **2-197**, similar to that seen previously (see sections 1.4.8 and 2.3).



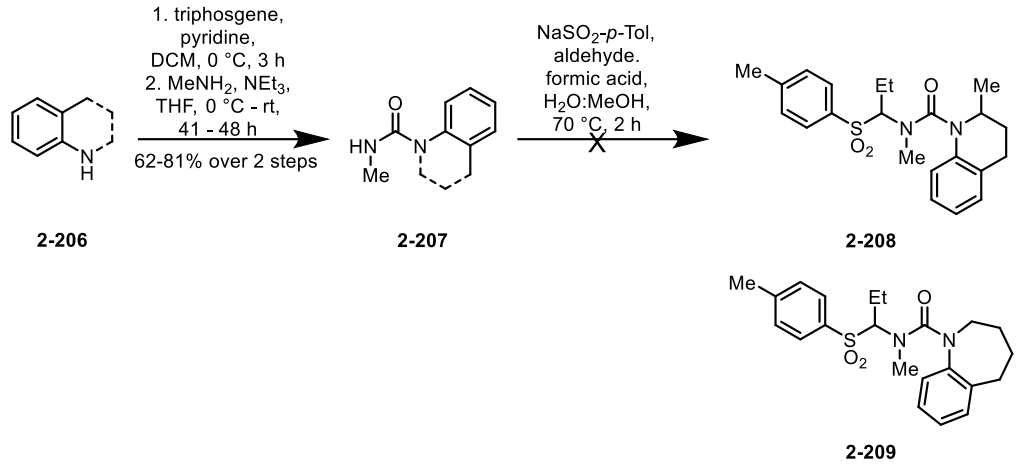
2-198 **2-199**

2-200 R^1 = Ph 40%
2-201 R^1 = Et 16%
2-202 R^1 = ^{t}Bu -

2-203 R^1 = Ph
2-204 R^1 = Et
2-205 R^1 = ^{t}Bu

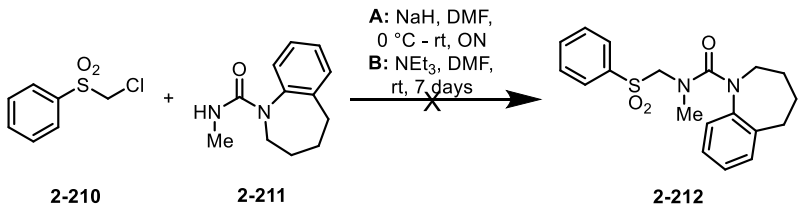
Scheme 2-34: Synthesis of sulfone anion stabilising ureas.

The sulfone starting materials are not commercially available but a stepwise route related to previous work in the group was devised starting from commercially available tetrahydroquinoline.[99,131,132] The tetrahydroquinoline **2-198** was treated with triphosgene forming the carbamoyl chloride, which was then converted into the primary urea **2-199** by reacting with ammonia in THF (*scheme 2-34*). The primary urea was converted into sulfone ureas **2-200** and **2-201**, through condensation of the aldehyde onto the urea then nucleophilic addition of the sodium sulfinate salt using a Mannich-type reaction affording the ureas in low to moderate yield. The instability of the ureas **2-200** and **2-201** in solvents may have resulted in lower yields. Decomposition of the ureas **2-186** and **2-187** resulted in loss of the sulfone and imine formation. The reaction with pivaldehyde returned only unreacted starting material, most likely due to the bulkiness of the *tert*-butyl group. Due to the instability of the sulfone ureas the methylation step was not attempted.



Scheme 2-35: Attempted synthesis of ureas **2-208** and **2-209**.

In an attempt to overcome the issues with stability of ureas **2-208** and **2-209**, the secondary ureas **2-207** were synthesised in similar way to above (*scheme 2-35*). Formation of the carbamoyl chloride then coupling with methylamine gave ureas **2-207** in good yield over two steps. The ureas were then subjected to the Mannich-type reaction used above with propionaldehyde, but with heating to 70 °C based on previous work in the literature.[133] After 2 hours only starting material was seen by TLC and ^{1}H NMR. The boiling point of propionaldehyde is 49 °C so it is possible that the aldehyde boiled off, however these conditions are reported for sulfone synthesis using propionaldehyde.

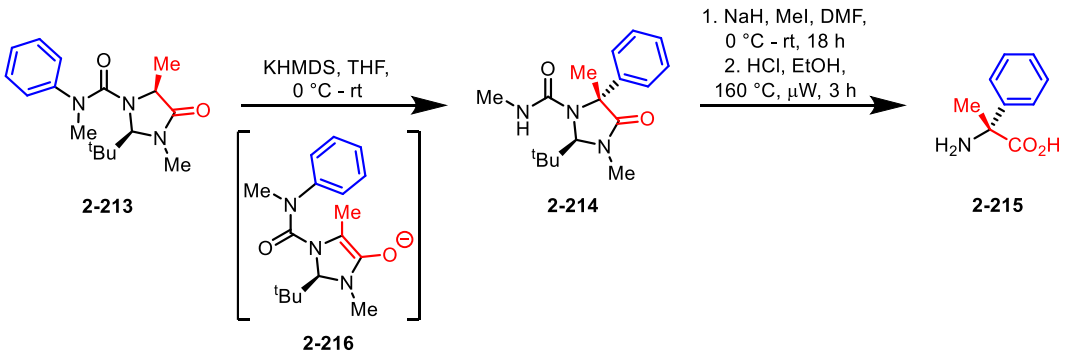


Scheme 2-36: Alternative route towards the synthesis of sulfone ureas.

An alternative approach using commercially available **2-210** was also devised. Coupling of the alkyl chloride with the urea was attempted initially using sodium hydride then using triethylamine as the base. In both cases only starting material was isolated after the reactions.

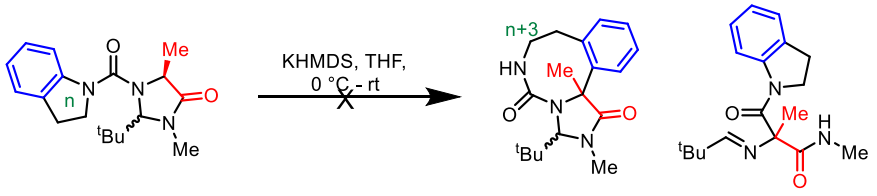
In summary the synthesis of sulfone-containing ureas was attempted, however the ureas synthesised containing an NH were unstable in solvent resulting in decomposition of the urea by loss of the sulfone and imine formation. Alternative routes to synthesising the sulfone ureas were attempted however both these attempts resulted in only starting material recovery. Due to the instability of the ureas it was not possible to test them as substrates for ring expansion forming medium rings through *N to C* aryl migration.

2.5 Diastereoselective aryl migration forming medium rings using enolate-type anion stabilising groups



Scheme 2-37: Diastereoselective aryl migration using Seebach's 'self-regeneration of stereocenters' principal followed by hydrolysis forming enantiopure α-quaternary amino acids.*

Previously work within the group found that applying Seebach's principal of 'self-regeneration of stereocenters' enantiopure α-arylated amino acids **2-215** could be generated through aryl migration of imidazolidinone **2-213** (*scheme 2-37*)(see section 1.4.7).[93] Imidazolidinone **2-213** was treated with base leading to loss of the stereocenter at the enolate **2-216**, however the presence of the bulky *tert*-butyl group at the stereogenic centre directs the aryl migrating ring to the back face. Hydrolysis of the imidazolidinone **2-214** forms the enantiopure α-arylated amino acid **2-215**.



2-217 n = 5
2-218 n = 6

2-219 n = 5
2-220 n = 6

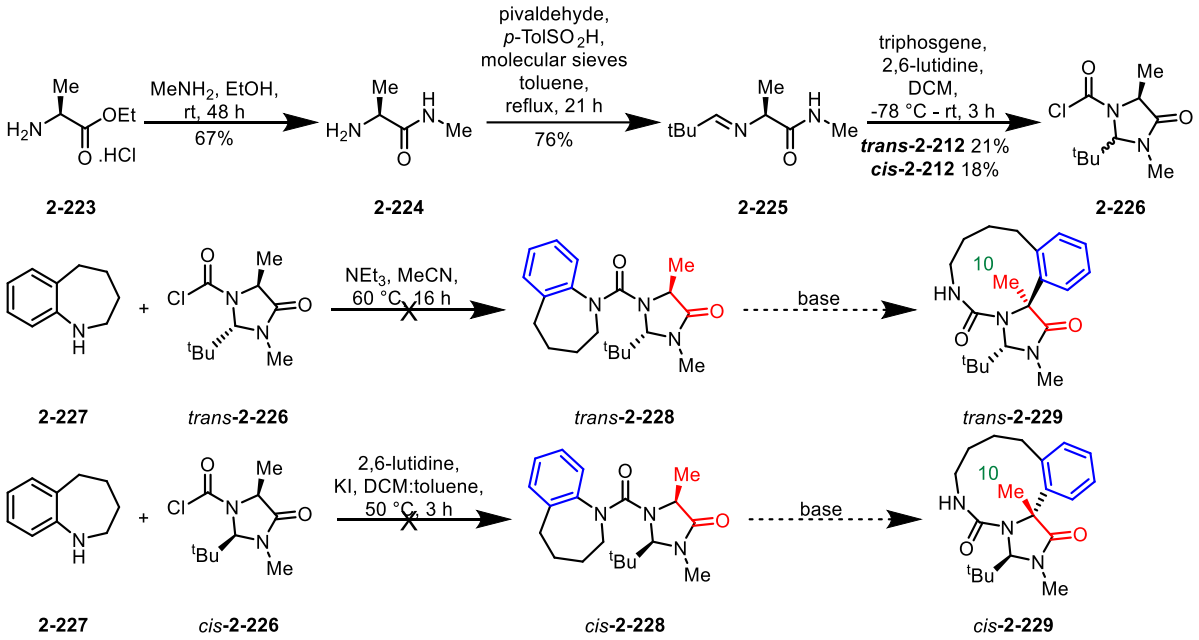
2-221 n = 5, 60-90%*^
2-222 n = 6*

Scheme 2-38: Attempted ring expansion of imidazolidinone ureas from alanine-derived amino acid.

* Experiments carried out by Dr Daniel J. Leonard
^ Experiments carried out by Dr Jessica Hill

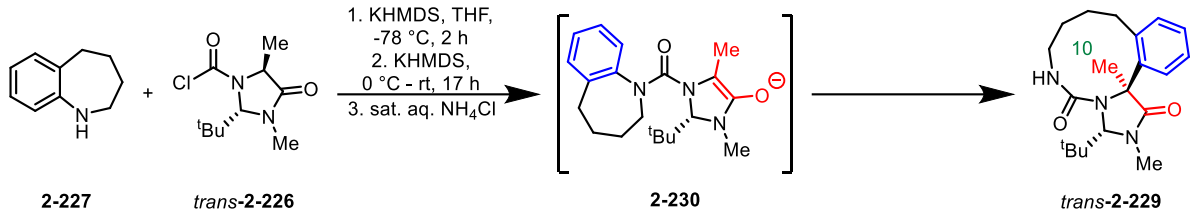
Applications of this chemistry towards the synthesis of medium rings have been investigated using ureas **2-217** and **2-218** (*scheme 2-38*).[134,135] For the smaller indoline-derived imidazolidinone **2-217**, treating either diastereomer with KHMDS (with and without 18-crown-6) led to the formation of 1,2-acyl shifted imine product **2-221**. The *cis*-tetrahydroquinoline-derived imidazolidinone *cis*-**2-218** was also treated with KHMDS but only unreacted starting material was isolated. The formation of the 8-membered ring is most likely hindered by larger transannular ring strain.

In sections 1.4.8 and 2.3 the ring expansion forming the larger rings resulted in higher yields, proposed to be due to the decrease in transannular ring strain seen as the ring size is increased. It was postulated that ring expansion of the larger benzoazepine-derived imidazolidinone **2-228** could be possible using the previously developed conditions providing a good starting point for further optimisation.



Scheme 2-39: Synthesis of imidazolidinone ureas for *N to C* aryl migration forming medium ring products.

Following the previously reported methodology the attempted synthesis of ureas *trans*-**2-229** and *cis*-**2-229** are shown in *scheme 2-39*.[93] L-alanine ethyl ester.HCl **2-223** was transformed into the amide **2-224** by reacting with methylamine. Condensation of pivaldehyde with the amide **2-224** formed the imine **2-225** in good yield. The imine was then treated with triphosgene forming imidazolidinone **2-226** as a mixture of *cis* and *trans* isomers, and the isomers were separated through column chromatography. The coupling of both carbamoyl chlorides *trans*-**2-226** and *cis*-**2-226** with benzo tetrahydroazepine **2-227** using previously reported methods was attempted but only unreacted starting material was isolated after purification.

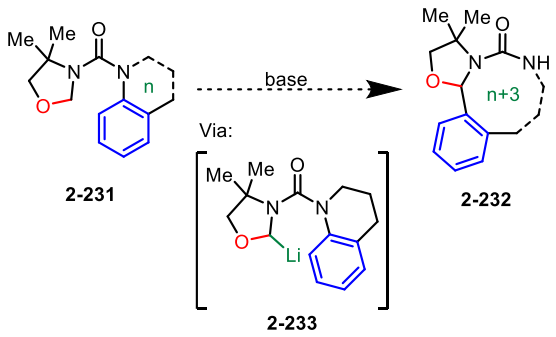


Scheme 2-40: Imidazolidinone ring expanded product formed via *in situ* formation of the urea enolate.

An alternative approach involved both the coupling of the benzotetrahydroazepine **2-227** with the carbamoyl chloride *trans*-**2-226** and the aryl migration in one-pot (*scheme 2-40*). Treating a mixture of *trans*-**2-226** and amine **2-227** with KHMDS at -78 °C for 2 hours then warming to 0 °C before a second addition of KHMDS and warming to room temperature overnight afforded a complex mix of products by ^{1}H NMR. Traces amounts of the product *trans*-**2-229** were isolated from the crude mixture after flash column chromatography.

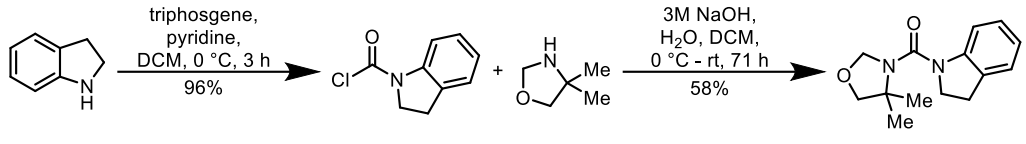
In summary the use of Seebach's 'self-regeneration of stereocenters' to form medium ring amino acid derivatives shows potential. However, difficulties synthesising the starting materials prohibited an in-depth investigation into the potential for medium ring synthesis.

2.6 Oxazolidine stabilising groups forming medium rings



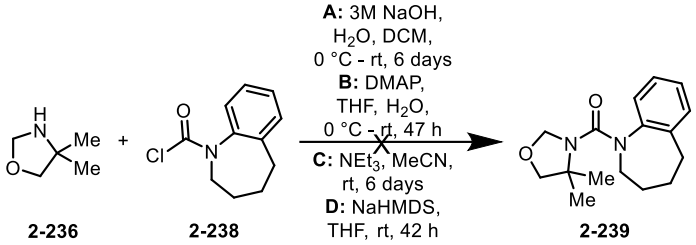
Scheme 2-41: Proposed ring expansion via inductively stabilised lithiated urea **2-233**.

Thus far only anions stabilised through resonance structures have been studied for both acyclic and cyclic aryl migration reactions. Lithiation of oxazolidine between the nitrogen and the oxygen atom, stabilised through induction, was used in dearomatising disrotatory electrocyclic ring closing reactions with *N*-benzoyloxazolidines.[136] To investigate the possibility of using these inductively stabilised groups for aryl migration forming medium rings **2-232**, ureas **2-231** were designed (*scheme 2-41*).



Scheme 2-42: Synthesis of urea **2-237**.

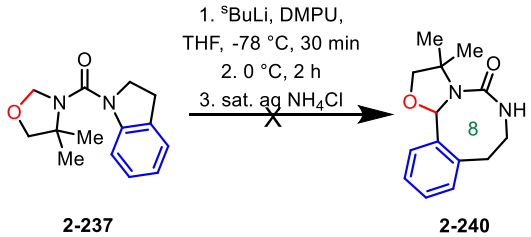
4,4-Dimethyloxazolidine **2-236** is commercially available in water, therefore an alternative synthesis route to above (section 2.3.3) was required, using previously developed Schotten-Baunmann conditions (*scheme 2-42*).[136] The indoline carbamoyl chloride **2-235** was synthesised in nearly quantitative yield by reacting **2-234** with triphosgene in the presence of pyridine. This carbamoyl chloride **2-235** was added to a mixture of the oxazolidine **2-236** in water and DCM along with NaOH, after stirring for 3 days the urea **2-237** was isolated by flash column chromatography.



Scheme 2-43: Attempted synthesis of urea **2-239**.

These conditions were then taken forward for synthesising larger 7-membered ring urea **2-239** (*Scheme 2-43*). Under the above conditions no reaction was seen after the reaction mixture was left stirring for 6 days. Switching to DMAP in THF instead of NaOH in DCM gave no product after stirring for 47 hours at room temperature.[137]

The oxazolidine **2-236** was extracted from the water using EtOAc then used in the standard urea synthesis conditions above (section 2.3.3). After stirring for 6 days no product was seen by ^{1}H NMR. A stronger base (NaHMDS) was also used in the synthesis of urea **2-239**, however after purification a low mass recovery (<25%) of products was obtained. Within the mixture benzotetrahydroazepine **2-227** (19%) and the carbamoyl chloride **2-238** (<5%) were identified. Trace amounts of the product **2-239** were also seen by ^{1}H NMR.



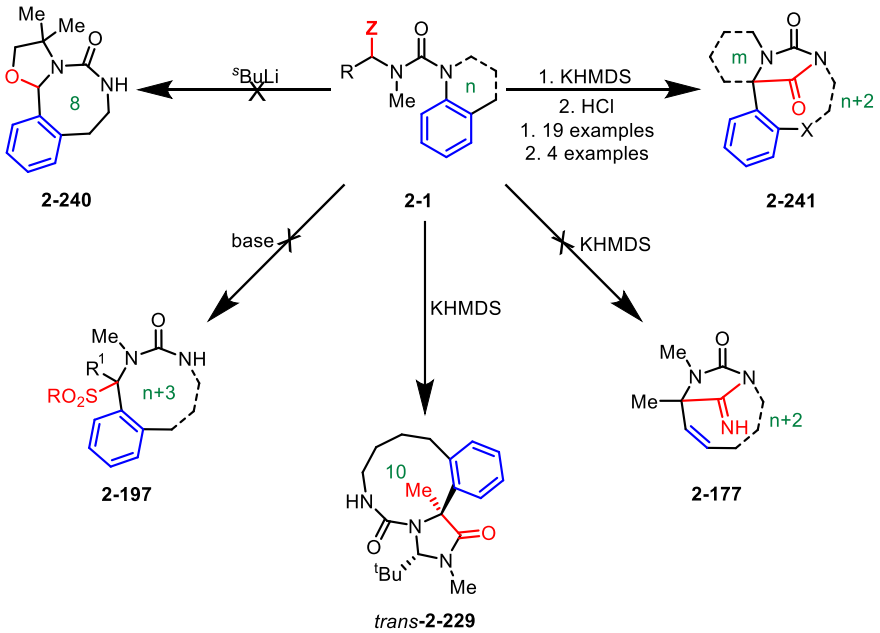
Scheme 2-44: N to C aryl migration forming medium ring **2-240**.

The *N to C* aryl migration of urea **2-237** was attempted using ^{s}BuLi/DMPU held at -78 °C for 30 min before warming to 0 °C for 2 hours (*scheme 2-44*). Analysis of the crude mixture by ^{1}H NMR showed unreacted starting material along with trace amounts of unidentified compounds, possibly trace product **2-240**. The synthesis of 8-membered rings is more challenging than the larger rings due to

increased ring strain; with this urea the increased ring strain and high sterics of the anion stabilising group could offer an explanation to the low reactivity seen.

In summary the use of oxazolidine ureas for inductively stabilised carbanion in the aryl migration forming medium rings shows potential to be successful. The synthesis of indoline urea **2-237** was successful and treatment with base led to starting material recovery and trace unknown, possibly product. Synthesis of the larger urea was more challenging but the use of NaHMDS led to trace urea synthesis. Future work in this area needs to initially focus on improving the synthesis of the ureas before optimisation of the ring expansion.

2.7 Conclusion and future work



Scheme 2-45: Summary of ring expansion reactions in chapter 2 using heteroatom-based anion stabilising groups.

A summary of the ring expansion results in chapter 2 are shown in *scheme 2-45*. In summary we have shown that under basic conditions alkylnitriles with an acyclic or cyclic tether through a urea to nitrogen heterocycles will undergo *n to n+2* ring expansion via *N to C* aryl migration forming iminohydantoin-bridging medium rings. Generally, the yields were moderate to high, with both electron withdrawing and mildly electron donating substituents tolerated on the migrating aryl ring. Both heteroatom substitution and mild steric hindrance on the alkyl tether were tolerated. Addition of a ketone on the alkyl tether resulted in a 6,5,5-tricyclic scaffold formed in good yield. Molecules containing two urea moieties underwent double ring expansion resulting in two bridging iminohydantoins with a peripheral 12-memebered ring in good yield.

For the *N to C* aryl migration to occur at least a methyl group is required at the site of deprotonation to supress intermolecular attack, as removal of the methyl group at the site of deprotonation led to

the formation of **2-149** and **2-150** under basic conditions. Various reaction conditions were trialed but unfortunately, they were unable to supress the intermolecular reaction and promote the intramolecular reaction.

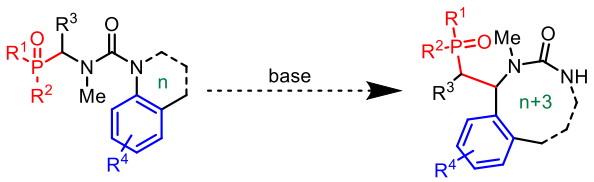
Hydrolysis of the iminohydantoin through either microwave irradiation in HCl:TFA or thermally in HCl:MeOH resulted in hydantoin-bridging 8-membered rings. Hydrolysis of Boc-protected **2-117** also resulted in deprotection and cyclisation forming 5,5,5-tricyclic bowl like structure **2-165**. However, hydrolysis of larger and more complex medium rings was not possible despite a myriad of alternative conditions trialled, most likely due to the decrease in pyramidalization as the larger rings become more planar and the imine becomes less electrophilic.

Extending this chemistry to vinyl migration was unsuccessful. Ring expansion of the 6-membered ring resulted in cyclisation and nitrile migration. The synthesis of the larger 7-membered ring was unsuccessful due to hydrolysis of the vinyl group. RCM of the 8-memebered ring was also unsuccessful.

Ureas containing alternative heteroatom anion stabilising group, sulfones, were synthesised, although the ureas proved unstable resulting in imine formation and loss of sulfone. Alternative routes towards their synthesis were attempted but were unsuccessful.

Diastereoselective synthesis of medium ring-derived amino acids were attempted using Seebach's 'self-regeneration of stereocenters'. Synthesis of the ureas proved challenging, but an alternative route was trialled in which both the urea synthesis and aryl migration were performed in one-pot through successive additions of KHMDS, resulting in trace amounts of product. Future work should first develop a route towards the synthesis of 7-membered ring imidazolidinone urea.

Urea **2-237** containing oxazolidine as the inductive anion stabilising group was synthesised. Treatment of the urea with base to promote ring expansion resulted in starting material recovery with trace amount of unknown compound, possibly the desired product. Synthesis of the larger 7-membered ring urea was attempted with only trace amounts of the urea seen when coupling of the carbamoyl chloride with the amine using NaHMDS.



2-242 **2-243**

Scheme 2-46: Proposed medium ring synthesis through *N to C* aryl migration using phosphonate and phosphine oxide anion stabilising groups.

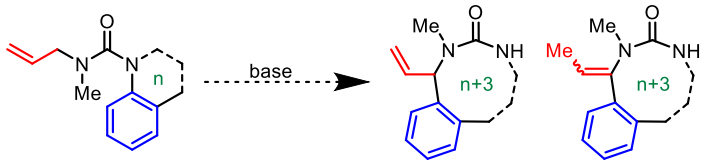
Phosphine oxides and phosphonates are interesting alternative anion stabilising groups and are underrepresented in medicinal chemistry. Ureas **2-242** containing a phosphine oxide or a

phosphonate group α to the urea are predicted to give medium ring products **2-243** in an *n to n+3* ring expansion under basic conditions (*scheme 2-46*). Future work exploring the formation of these medium rings **2-243** could provide access to useful scaffolds containing two underrepresented structural features in medicinal chemistry.

3. Vinylic medium ring synthesis

3.1 Aims

Both *N*-benzyl and *N*-nitrile anion stabilising groups were successfully used in the synthesis of medium ring nitrogen heterocycles through ring expansion reactions. However, this limits the scope of the products formed from these reactions after ring expansion. Substitution for an *N*-allyl group would give access to ureas **3-1** (*scheme 3-1*). The allyl group has been used previously promoting aryl migration of acyclic ureas (see section 1.4.4).[81,82] It was proposed that treatment with base would lead to *N to C* aryl migration forming medium rings **3-2** or **3-3** in an *n to n+3* ring expansion as seen previously (see sections 1.4.8 and 2.3). The products of the reaction would provide either **3-2** or **3-3** containing an alkene where post-ring expansion modifications could be possible.



3-1 **3-2** **3-3**

Scheme 3-1: Proposed ring expansion of allyl anion stabilising groups forming medium rings in an *n to n+3* ring expansion reaction.

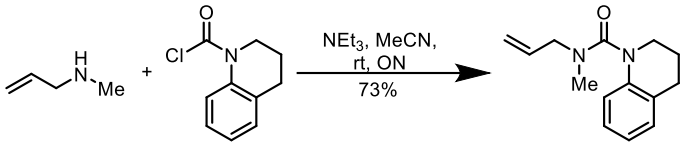
Preliminary work showed the potential of these allyl anion stabilising groups to facilitated medium ring synthesis via ring expansion after further optimisation. The initial aim was to develop an efficient route to medium ring **3-2** or **3-3** from allyl urea **3-1**. A range of commercially available tetrahydroquinoline derivatives and larger rings synthesised previously in section 2.3.2 would then be used to explore the scope of the reaction.

Post-ring expansion modifications could then be explored, giving access to a more diverse library of medium rings. Various modifications including carbolithiation, hydrogenation and cycloaddition would be possible with the medium ring products.

3.2 Allyl anion stabilising group

3.2.1 Previous work

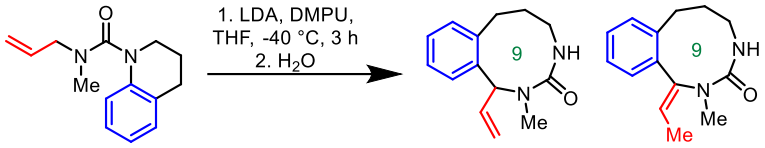
Preliminary work was carried out by Dr Jess Hill (during her PhD) and Emily Ellis (during her MChem project).[105,135] Urea **3-6** was synthesised as shown in *scheme 3-2* from *N*-allylmethylamine **3-4** and carbamoyl chloride **3-5** in high yield.



3-4 **3-5** **3-6**

Scheme 3-2: Synthesis of urea **3-6**.*

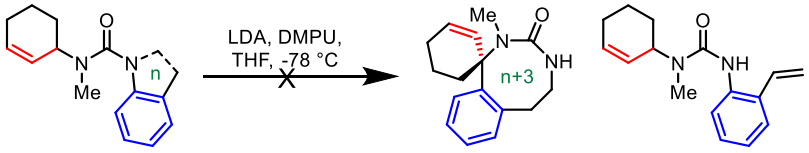
Urea **3-6** was then treated with previously optimised conditions (LDA/DMPU, -78 °C, see section 1.4.8) resulting in isolation of trace amounts of products **3-7** and **3-8** along with some starting material and a complex mixture of unidentified compounds.[135] The reaction was repeated at -40 °C as there was starting material **3-6** remaining after the reaction was quenched (*scheme 3-3*).[105]Treatment of urea **3-6** with LDA/DMPU at -40 °C resulted in isolation of a mixture of isomers of **3-7** and **3-8** in low yield (*scheme 3-3*), due to a combination of purification difficulties and other unidentified compounds seen by ^{1}H NMR. 9-Membered ring **3-7** was isolated as a mixture of conformational isomers. Previously, ring expansion with the 2-thiophene anion stabilising group proceeded in the absence of DMPU (see section 1.4.8, *scheme 1-57*), therefore the ring expansion of *N*-allylurea **3-6** was repeated at -78 °C without DMPU. **3-8** Was isolated along with a mixture of unidentified compounds after purification.



3-6 **3-7** 15% **3-8** 8%

Scheme 3-3: Ring expansion of allyl urea **3-6** with LDA/DMPU.^

To explore the effect that the organolithium base may have on the reaction, ^{s}BuLi replaced LDA and the reaction was repeated. ^{s}BuLi was added at -78 °C before warming to -40 °C, but only trace amounts of products **3-7** and **3-8** and a complex mixture of unidentified compounds were isolated after purification.

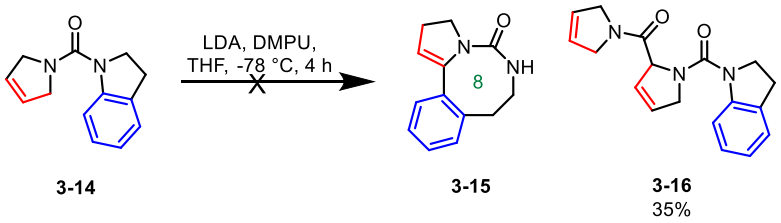


3-9 n = 5*
3-10 n = 6^
3-11 n = 5
3-12 n = 6
3-13 34%

Scheme 3-4: Attempted ring expansion of cyclic allyl ureas.

* Experiments carried out by Dr Jessica Hill
^ Experiments carried out by Emily Ellis

To explore the possibility of other allyl anion systems in the ring expansion reaction forming medium rings, ureas **3-9** and **3-10** were synthesised in an analogous manner to urea **3-6**. Treatment of indoline-derived urea **3-9** with LDA/DMPU led to complete consumption of the starting material (*scheme 3-4*). Ring opened product **3-13** was isolated as the major product from the reaction along with a complex mixture of unidentified compounds and the desired product **3-11** was not seen by ^{1}H NMR. **3-13** Is proposed to result from benzylic deprotonation on the indoline followed by ring opening. Treatment of the larger tetrahydroquinoline derived urea **3-10** with both LDA/DMPU and ^{s}BuLi/DMPU resulted in no reaction with only starting material observed in the crude ^{1}H NMR.



3-14 **3-15** **3-16** 35%

Scheme 3-5: Attempted ring expansion of cyclic allyl urea **3-14**.*

An alternative allyl urea **3-14** was synthesised and subjected to the LDA/DMPU conditions (*scheme 3-5*). TLC analysis showed complete consumption of the starting material in 4 hours and the reaction was quenched. After purification product **3-16** was isolated as the major product along a mixture of unidentified compounds and no medium ring product **3-15** was observed in the ^{1}H NMR. Urea **3-16** is presumably a result of intermolecular attack of an allyl organolithium compound (a result of deprotonation) at the carbonyl of another urea **3-16** molecule resulting in substitution of indoline.

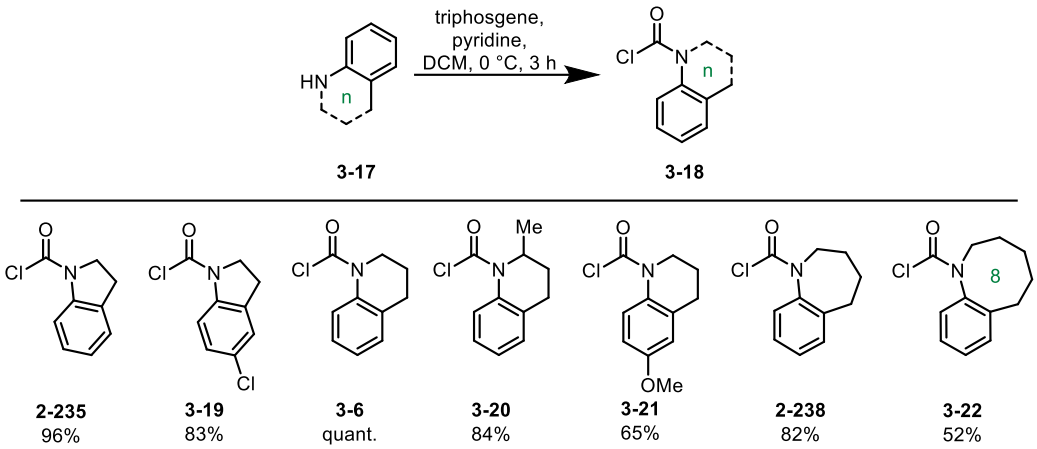
3.2.2 Starting material synthesis

The synthesis of a range of allyl ureas were carried out using commercially available tetrahydroquinolines and indolines and the larger 7- and 8-membered nitrogen heterocycles synthesised in section 2.3.2.1. Different commercially available allyl amines were also coupled to 7-membered benzotetrahydroazepine **2-227**. Generally, for the synthesis of these allyl amines the carbamoyl chloride of the nitrogen heterocycle was formed using triphosgene and then coupled to the allyl amine.

3.2.2.1 Carbamoyl chloride synthesis

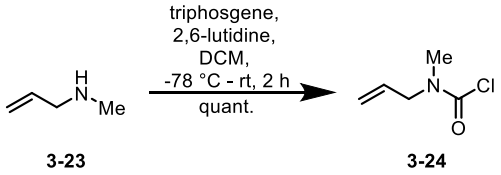
The carbamoyl chlorides of a range of commercially available nitrogen heterocycle derivatives and those synthesised in section 2.3.2.1 were synthesised (*scheme 3-6*). The nitrogen heterocycles **3-17** were added to a solution of triphosgene and pyridine. After stirring for 3 hours at 0 °C, the reaction was quenched with HCl affording the carbamoyl chlorides **3-18** in moderate to excellent yield.

* Experiments carried out by Dr Jessica Hill



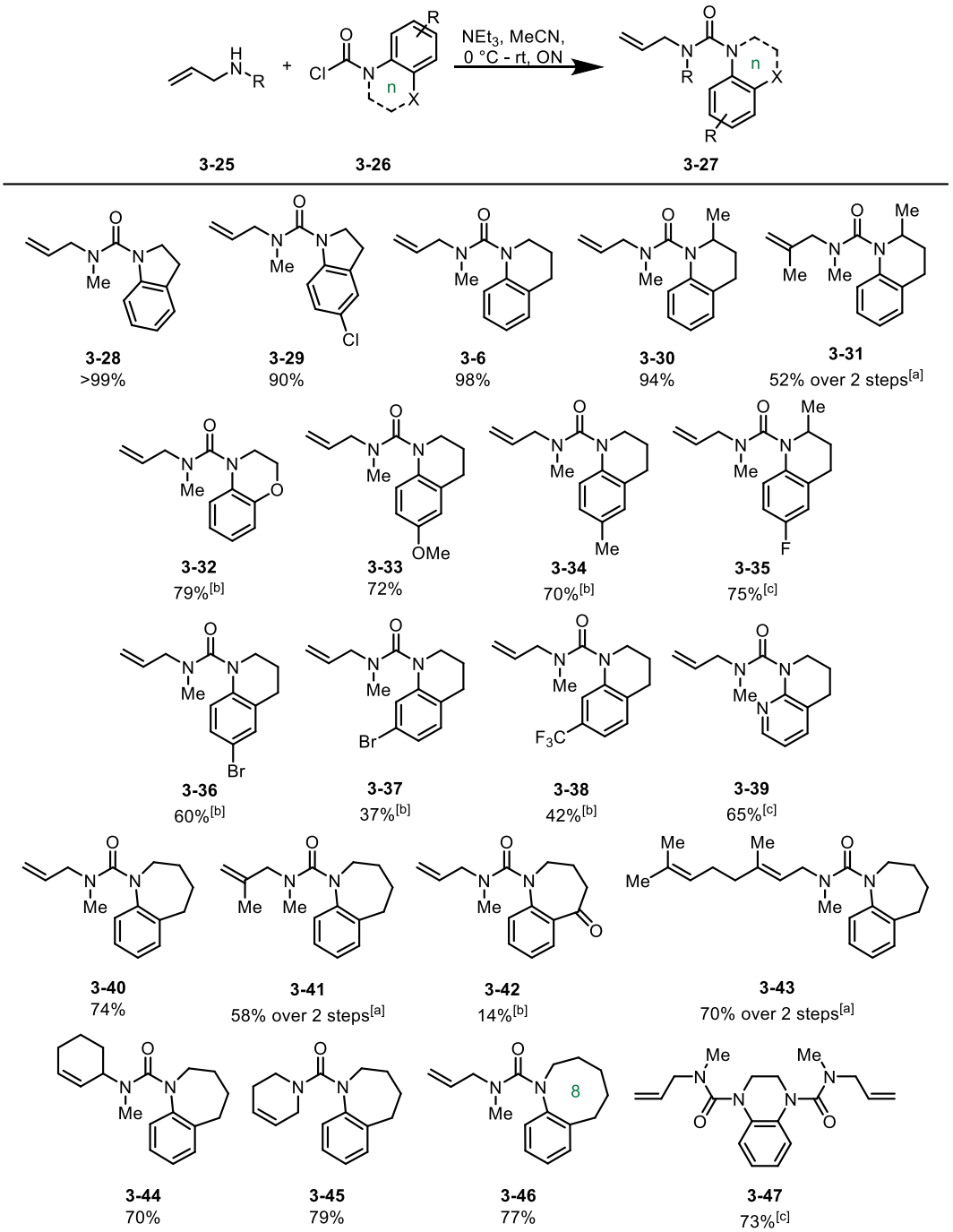
Scheme 3-6: Synthesis of a range of nitrogen heterocycle carbamoyl chlorides.

An alternative approach to synthesising the ureas required the synthesis of carbamoyl chloride **3-24** (*scheme 3-7*). *N*-allylmethylamine **3-23** was added to a solution of triphosgene and 2,6-lutidine at -78 °C before warming to room temperature and stirring for 2 hours affording carbamoyl chloride **3-24** in quantitative yield.[99]



Scheme 3-7: Synthesis of carbamoyl chloride **3-24**.

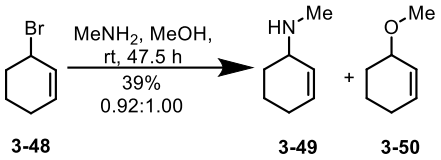
3.2.2.2 Urea synthesis



Scheme 3-8: Synthesis of *N*-allyl ureas. [a] – Two-step synthesis; 1. NEt_3, MeCN, 0 ˚C – rt, ON. 2.i. NaH, THF, 0 ˚C, 1 h. ii. MeI, rt, ON. [b] – Allyl(methyl)carbamic chloride **3-24** and nitrogen heterocycle used instead; NEt_3, MeCN, 75 ˚C, 17-75 h. [c] – Alternative conditions; NaHMDS, THF, rt, ON.

A range of *N*-allyl ureas **3-27** were synthesised with various steric and electronic demands on the aryl migrating group and the alkyl tether between the aryl ring and the nitrogen (*scheme 3-8*). A variety of acyclic and cyclic allyl groups were also used in the synthesis of ureas **3-27**. Nitrogen-derived heterocycle carbamoyl chlorides **3-18** synthesised above (*scheme 3-6*) were coupled to allylmethylamine, affording the desired ureas in excellent yields. Carbamoyl chlorides **3-20** and **2-238** were also coupled to extended acyclic allylamines and subsequent *N*-methylation gave the ureas **3-31**

and **3-41** in good yields over two steps. The allylamine precursor **3-49** for urea **3-44** was synthesised from the commercially available bromo cyclohexene (*scheme 3-9*) in low yield as a mixture with **3-50** derived from MeOH reaction with **3-48**.



Scheme 3-9: Synthesis of allylamine **3-49** from 3-bromo-cyclohexane.

Some of the ureas were synthesised using the carbamoyl chloride of allylmethylamine **3-24** instead, these reactions required heating to 75 °C affording a variety of ureas in 14-70% yield (*scheme 3-8*).

Synthesis of ureas **3-35**, **3-39** and diurea **3-47** from the coupling of carbamoyl chloride **3-24** and the corresponding nitrogen heterocycle using triethylamine were very low yielding. The use of a stronger base (NaHMDS) resulted in isolation of the ureas (**3-35**, **3-39**, **3-47**) in good yield.

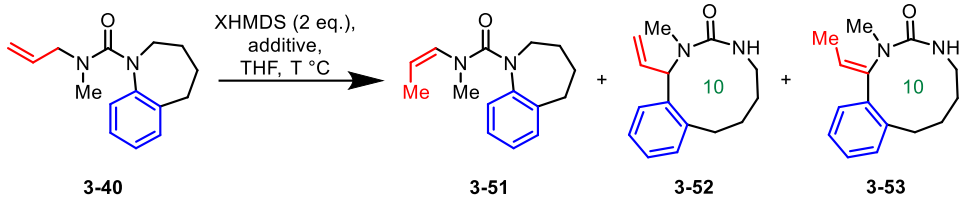
3.2.3 Vinyl urea medium ring synthesis

Preliminary investigations suggested that the use of allyl anions to promote *N to C* aryl migration forming medium ring nitrogen heterocycles was possible. However, only low yields of the medium rings were achieved. Mixtures of conformational isomers were formed that were difficult to separate from unidentified side products. Initial studies focused on optimising the reaction.

3.2.3.1 Reaction optimisation

Urea **3-40** was chosen as the model substrate for optimisation of the formation of 10-membered rings **3-52** and/or **3-53** under basic conditions (*table 3-1*). Preliminary work showed the use of LDA/^{s}BuLi only resulted in low yields of medium rings **3-52** and **3-53**. Recent unpublished work within the Clayden group suggested that KHMDS was sufficiently basic to deprotonate the *N*-allyl urea.[138] To explore this, urea **3-40** was subjected to the optimised KHMDS conditions above (section 2.3). After 22.5 hours the crude ^{1}H NMR contained both the unreacted starting material **3-40** and the *cis*-isomerised urea **3-51** in a 13.6:1.0 ratio (*table 3-1,* entry 1).

Table 3-1: Optimisation of *N to C* aryl migration of urea **3-40** forming 10-membered nitrogen heterocycles.



3-40 **3-51** **3-52** **3-53**

Entry	XHMDS	18-crown-6	T / °C	Time / h	Crude NMR % ratio 3-40 : 3-51 : 3-52 : 3-53	Isolated 3-53/%
1	K	-	0 - rt	22.5	93 : 7 : 0 : 0	-
2	K	2 eq.	0	38	-	44[a]
3	**K**	**2 eq.**	**0 - rt**	**21**	**-**	**64**
4	K[b]	1 eq.	0 - rt	20	0 : 24 : 0 : 76	51[c]
5	K[d]	1.5 eq.	0 - rt	20	0 : 4 : 0 : 96	22
6	K	-	100[e]	0.5	0 : 32 : 0 : 68[f]	-
7	K	2 eq.	100[e]	0.75	-[f,g]	-
8	Na	-	0 - rt	21	27 : 67 : 0 : 6	-
9	Li	-	0 - rt	21	77 : 14 : 0 : 9	-

[a] – 60:40 %Ratio of product **3-53** to decomposition product **2-211** (36% isolated yield). [b] – 1 Equivalent KHMDS used. [c] – 1.00:0.28 *Cis:trans* isomer ratio. [d] – 1.5 Equivalents of KHMDS used. [e] – Reaction performed under microwave irradiation. [f] – Complex mixture of unidentified decomposition products seen in the crude ^{1}H NMR. [g] – Decomposition products of 18-crown-6 seen in ^{1}H NMR. Bold shows optimised conditions taken forward.

Previous aryl migration reactions (see section 1.4) found that lithium cation chelating additives were required to achieve the desired reaction. Although there is a plethora of chelating agents for lithium cations, for potassium cations the options are very limited. The core motif for most is a crown ether, especially 18-crown-6. The reaction was repeated at 0 °C but with the addition of 18-crown-6 (entry 2). After 38 hours, TLC analysis showed complete consumption of the starting material and the reaction mixture was quenched. Purification of the reaction mixture afforded medium ring **3-53** as the *cis*-isomer (confirmed by X-ray crystallography, *figure 3-1*) in 44% yield along with secondary urea **2-**

211 (section 2.4) in 36% yield resulting from loss of the allyl group. Warming the reaction to room temperature after KHMDS addition resulted in a shorter reaction time (*entry 3*) and an increase in the yield to 64%. No decomposition products were seen in the crude ^{1}H NMR.

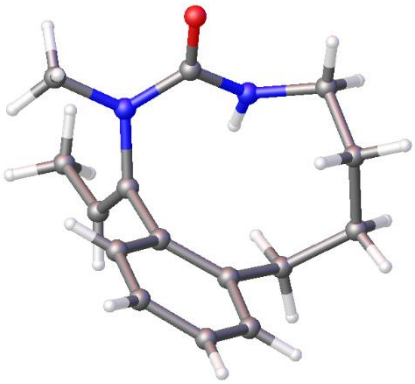


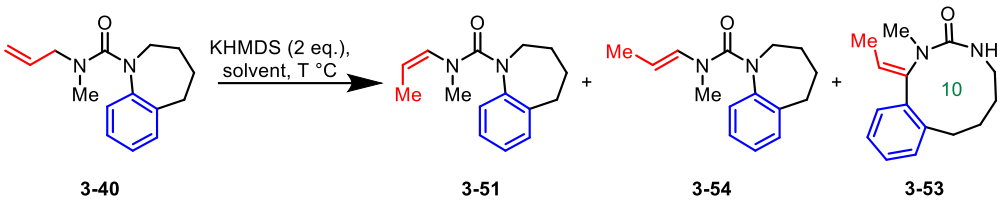
Figure 3-1: X-ray crystal structure of **3-53** confirming *cis*-isomer configuration.

The reactions in *table 3-1* used two equivalents of KHMDS/18-crown-6; entries 4 and 5 show that reducing the number of equivalents of both had a negative effect on the yield of the reaction, with both reactions leading to *cis*-isomerised starting material **3-51** present in the crude ^{1}H NMR after 20 hours.

Although no other major product was isolated with **3-53** in entry 3, there were trace amounts of decomposition products in the crude ^{1}H NMR. To try and improve the yield and reduce the reaction time the reaction was repeated under microwave irradiation (entries 6 and 7). In the absence of 18-crown-6 the product **3-53** was formed. However, after 30 minutes there was still *cis*-isomerised starting material **3-51** remaining along with a significantly large amount of decomposition products. The reaction was repeated with the addition of 18-crown-6, but only a complex mixture of unidentified decomposition products and 18-crown-6 decomposition products were seen in the crude ^{1}H NMR.

NaHMDS and LiHMDS were used in place of KHMDS (entries 8 and 9) without additive addition. After 21 hours the reactions were quenched and showed low conversion to the product **3-53**.

Table 3-2: Exploration of 1,4-dioxane as an alternative solvent for the *N to C* aryl migration forming medium rings.



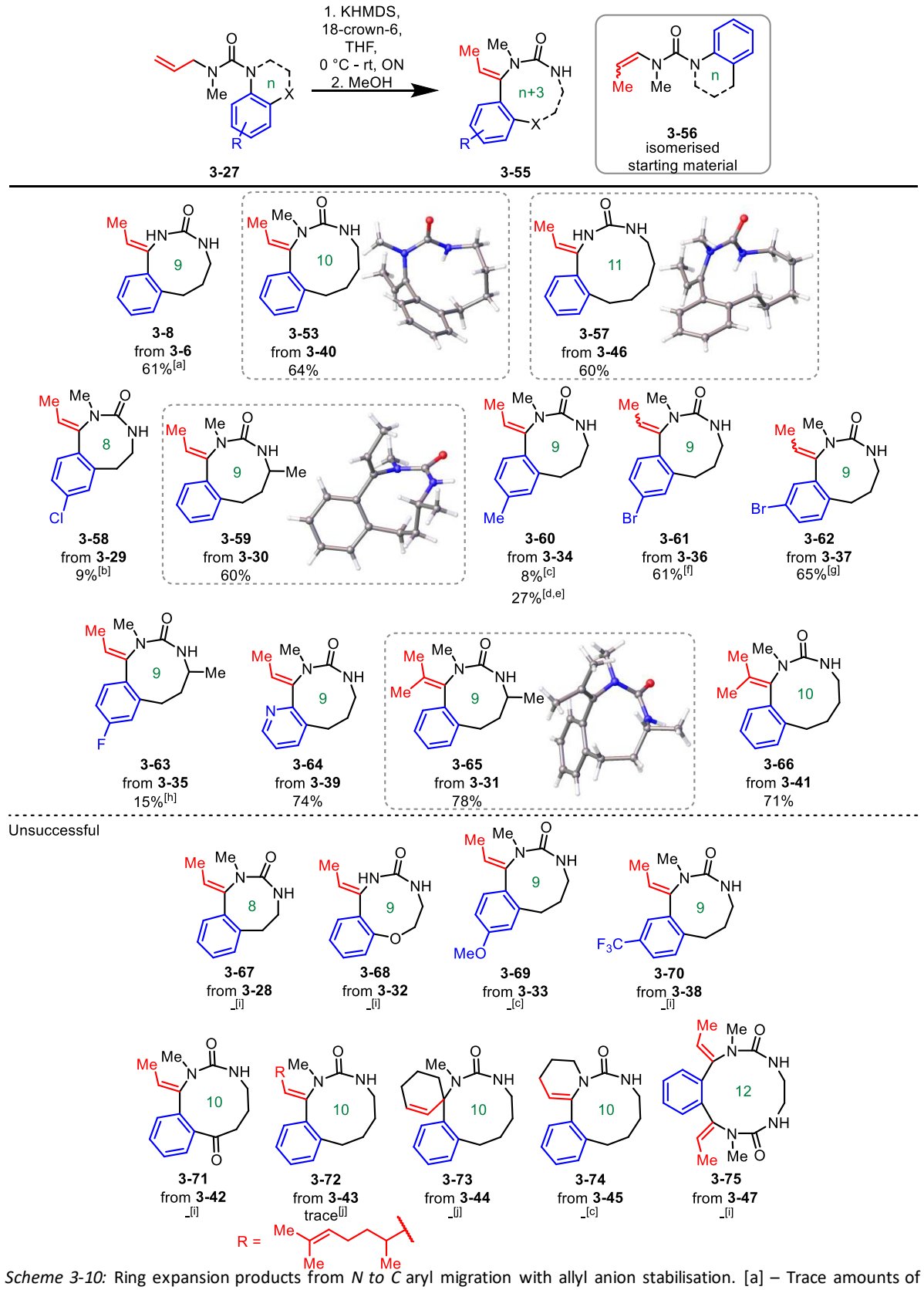
3-40 3-51 3-54 3-53

Entry	Solvent	T/ °C	Time/ h	Crude NMR %ratio 3-51 : 3-54 : 3-53	Isolated yield of 3-53/%
1	1,4-dioxane	rt	48	4 : 76 : 20	-
2	1,4-dioxane	60	46	13 : 11 : 76[a]	48
3	1,4-dioxane:THF (9:1)	100[b]	2	0 : 19 : 81[c]	-

[a] – Secondary urea **2-211** isolated in 8% yield. [b] – Reaction performed under microwave irradiation. [c] – Complex mixture of unidentified decomposition products also seen in the crude ^{1}H NMR.

Substitution of THF for 1,4-dioxane could also remove the need for 18-crown-6 as the potassium chelating agent. To test this hypothesis urea **3-51** was treated with KHMDS in 1,4-dioxane and stirred at room temperature for 48 h (*table 3-2*, entry 1). Analysis of the crude ^{1}H NMR showed the presence of the product **3-53** along with both *cis* and *trans* isomers of the urea starting material, **3-51** and **3-54**. Repetition of the reaction but with heating to 60 °C resulted in the vinylic isomer **3-53** isolated in a 48% yield, along with trace amounts of **3-51** and **3-54** (entry 2). The reaction was also performed under microwave irradiation at 100 °C (entry 3). Upon addition of KHMDS, a white precipitate formed. Addition of KHMDS to urea **3-40** in a solution of 1,4-dioxane and THF (9:1 ratio) was required to prevent precipitation formation, allowing the reaction to be irradiated in the microwave. The product **3-53** was formed along with a small amount of *trans* isomerised urea **3-54** and trace amounts of unidentified decomposition products.

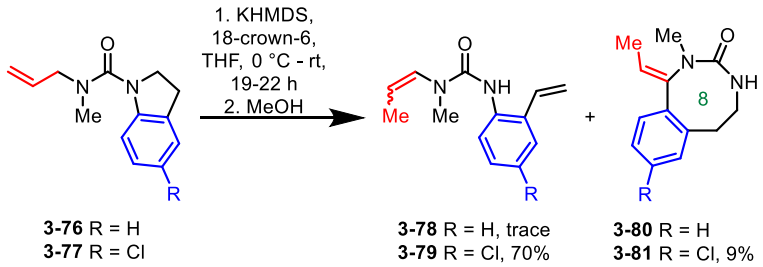
3.2.3.2 Ring expansion scope



Scheme 3-10: Ring expansion products from *N to C* aryl migration with allyl anion stabilisation. [a] – Trace amounts of isomerised starting urea seen in crude ^{1}H NMR. [b] – Decomposed *cis*-isomerised urea **3-79** isolated as major product. [c] – Isomerised starting urea **3-56** major product of the reaction. [d] – Reaction mixture heated to 60 ˚C. [e] – Product isolated with 18-crown-6 decomposition products. [f] – Product isolated as a 1.00:0.47 ratio of *cis:trans* vinyl group. [g] – Product isolated as a 1.0:0.2 ratio of *cis:trans* vinyl group. [h] – Crude ^{1}H NMR shows substantial amount of decomposed starting urea. [i] – Complex mixture of decomposed urea. [j] – Major product was *N*-methyl secondary urea **2-211** resulting from loss of the allyl group.

With the optimised ring expansion conditions (KHMDS (2 eq.), 18-crown-6 (2 eq.), THF, 0 °C – rt, ON) in hand, ureas synthesised above (*scheme 3-8*) were subjected to these conditions (*scheme 3-10*). The unsubstituted 6- and 8-membered ring starting materials **3-6** and **3-46** were subjected to the optimised conditions, affording the desired 9- and 11-membered vinyl urea products **3-8** and **3-57** in good yield. For urea **3-6**, trace amounts of both *cis*- and *trans*-isomerised starting materials **3-56** were seen in the crude ^{1}H NMR after 50 hours of stirring at room temperature. No other products were seen in the crude ^{1}H NMR for 11-membered ring **3-57**.

Indoline-derived urea **3-28** gave only a complex mixture of products by crude ^{1}H NMR, along with trace amounts of ring opened isomerised urea **3-78** (*scheme 3-11*). The ring opened urea **3-78** is presumably formed through benzylic deprotonation of the indoline. Substitution at the *para*-position with a chloride gave urea **3-29** which resulted in the 8-membered ring **3-58** being isolated in low yield after treatment with KHMDS. Together with the product **3-58**, ring opened urea **3-79** was isolated. Increasing the number of equivalents of KHMDS and 18-crown-6 from 2 to 4 resulted in no change in product yield and the decomposed urea **3-79** was isolated in 70% as a 2.02:1.00 ratio of *cis*:*trans*.



3-76 R = H
3-77 R = Cl

3-78 R = H, trace
3-79 R = Cl, 70%

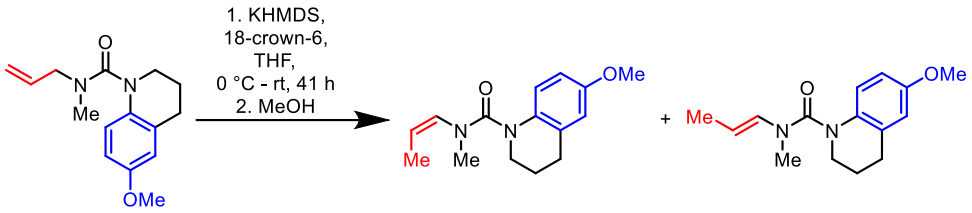
3-80 R = H
3-81 R = Cl, 9%

Scheme 3-11: Ring expansion of 5-membered ureas.

Substitution on the alkyl tether that joins the aryl migrating ring to the nitrogen of the urea with a methyl group resulted in 9-membered ring **3-59** in moderate yield (*scheme 3-10*). Increasing the scale of the reaction 10-fold resulted in isolation of the medium ring **3-59** in comparable yield (55%).

Previously, replacing a carbon in the tether with a heteroatom resulted in formation of the desired medium rings (section 2.3.4.2 and 2.3.4.3). Replacing a carbon atom with an oxygen atom (urea **3-32**) and treating with KHMDS resulted in a complex mixture of products, with the *cis*-isomerised starting material **3-56** seen in trace amounts along with other unidentified products.

Next, investigations focused on the effect of changing the electronics of the migration aryl ring using ureas **3-33–3-38**. Treatment of electron-rich *para*-methoxy urea **3-33** with the optimised conditions resulted in isolation of isomerised urea starting materials **3-82** and **3-83** along with trace amounts of unidentified products (*scheme 3-12*).



Scheme 3-12: Treatment of urea **3-33** with KHMDS.

Substitution of the strongly electron donating *para*-methoxy group for the mildly electron donating *para*-methyl group **3-34** resulted in isolation of 9-membered ring **3-60** in 8% yield (*scheme 3-10*), along with isolation of *trans*-isomerised starting material **3-85** in 20% yield and 17% of amine **3-84** resulting from urea decomposition (*figure 3-2*).

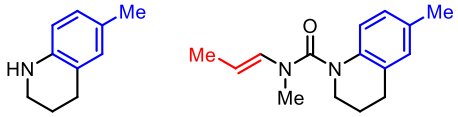


Figure 3-2: Decomposition product **3-84** and isomerised urea **3-85** isolated alongside medium ring product **3-60** when urea **3-34** was treated with KHMDS.

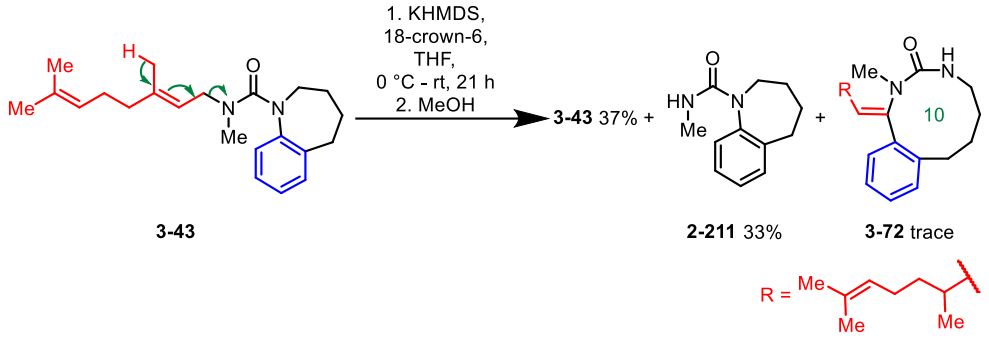
The use of electron withdrawing bromide at the *para*- and *meta*-positions on the aryl migrating ring resulted in products **3-61** and **3-62** respectively in similar yield (*scheme 3-10*). Medium ring **3-61** was isolated in 1.00:0.47 ratio of *cis:trans* products and **3-62** was isolated in a 1.0:0.2 ratio of *cis:trans* products. Doubling the equivalents of KHMDS and 18-crown-6 (4 eq.) had no effect on the yield of *para*-bromide **3-61** isolated, however the ratio of *cis:trans* products changed from 1.00:0.46 to 1.00:0.75.

meta-Trifluoromethyl substituted urea **3-38** resulted in a complex mixture of unidentified products along with trace amounts of *cis*-isomerised starting urea **3-56** when treatment with KHMDS. Treatment of urea **3-35** containing both a *para*-fluoride substituent on the aryl ring and a methyl group on the alkyl tether with KHMDS resulted in isolation of the desired medium ring **3-63** in 15% yield. Decomposition of the urea **3-35**, forming a complex mixture of products including 6-fluoro-2-methyltetrahydroquinoline starting material, accounted for the remaining products seen in the crude ^{1}H NMR.

A pyridyl migrating group was successfully substituted for the benzyl group resulting in isolation of 9-membered ring **3-64** in excellent yield from urea **3-39**.

Ketone urea **3-42** was synthesised and treated with base, having been successfully used in a previous ring expansion reaction (see section 2.3.4.2). Crude ^{1}H NMR showed a complex mixture of unidentified products including trace amounts of *cis*-isomerised starting material.

Dimethyl vinylic 9- and 10-membered rings **3-65** and **3-66** were isolated in high yield through addition of an additional methyl group onto the allyl anion stabilising group. X-ray crystallography confirmed the formation of 9-membered ring **3-65**.

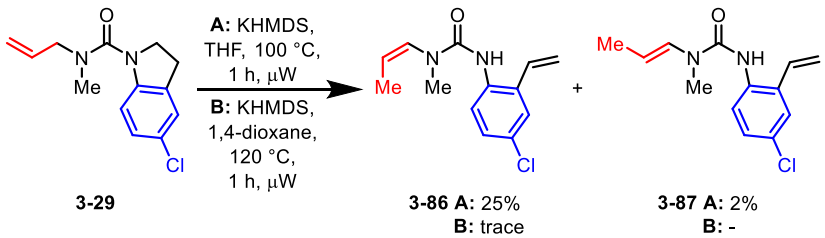


Scheme 3-13: Ring expansion of 7-membered urea **3-43**. Green arrows show δ-elimination pathway.

Extension of the allyl group using geranyl amine resulted in urea **3-43**. Treatment of this urea **3-43** with base resulted in a mixture of products (*scheme 3-13*). Medium ring **3-72** was isolated in trace amounts alongside secondary urea **2-211** in 33% yield and 37% recovered starting material **3-43**. Decomposition product **2-211** resulted from δ-elimination of the allyl chain (*scheme 3-13*, green arrows); similar elimination pathways have been seen in ongoing projects within the Clayden group.

Cyclic allyl groups were used in the synthesis of ureas **3-44** and **3-45**. Treatment of both of these ureas did not lead to the desired ring expansion medium ring formation. For urea **3-44**, 69% of the starting material was isolated along with 19% decomposition product **2-211**. Tetrahydropyridine urea **3-45** resulted in isolation of the isomerised starting material **3-56** in 43% yield.

Previously (see section 2.3.4.4) diurea **2-100** was treated with base leading to two successive ring expansions, similar reaction was predicted for diurea **3-47**. However, after treatment with KHMDS in the presence of 18-crown-6, only a complex mixture of products was seen in the crude ^{1}H NMR; attempts at isolating the multiple spots seen by TLC failed.

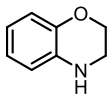


Scheme 3-14: Microwave irradiation of urea **3-29** in the presence of KHMDS with different solvents.

During the optimisation it was found that microwave irradiation of unsubstituted 7-membered urea **3-40** in the presence of KHMDS in either THF or 1,4-dioxane resulted in the product **3-53**. To try and improve some of the low yielding reactions, they were repeated under microwave irradiation. *Para*-chloro indoline derived urea **3-29** was irradiated in THF and 1,4-dioxane resulting in ring opened products **3-86** and **3-87** (*scheme 3-14*). When THF was used the *cis*-ring opened product **3-86** was

isolated in 25% yield and the *trans*-ring opened product **3-87** was isolated in 2%. When using 1,4-dioxane the crude ^{1}H NMR showed trace presence of the *cis*-ring opened product **3-86**.

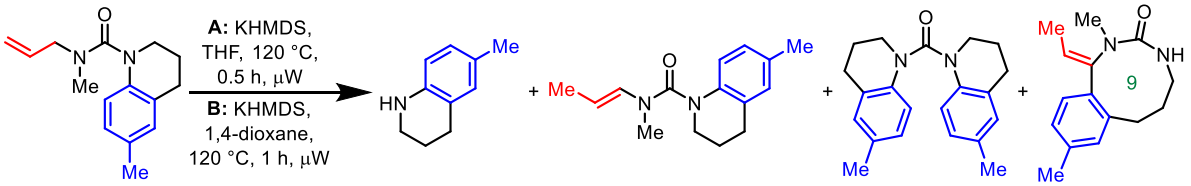
The oxygen substituted urea **3-32** was heated under reflux in 1,4-dioxane. Analysis of the crude reaction mixture by ^{1}H NMR contained no allyl/vinyl products and the major product was dihydrobenzoxazine **3-88** (*figure 3-3*).



3-88

Figure 3-3: Major product identified by ^{1}H NMR when urea **3-32** was heated under reflux in 1,4-dioxane.

Para-methyl substituted urea **3-34** was heated to 60 °C in the optimised conditions above. Amine **3-84,** resulting from the decomposition of urea **3-34,** was isolated in 27% yield and *trans*-isomerised starting urea **3-85** was isolated in 8%. Although decomposition of 18-crown-6 was observed the yield of the product **3-60** increased to ~27%. However, difficulties in purifying the product **3-60** from 18-crown-6 decomposition meant the product was not isolated.



Scheme 3-15: Microwave irradiation of urea **3-34** forming medium ring **3-60**.

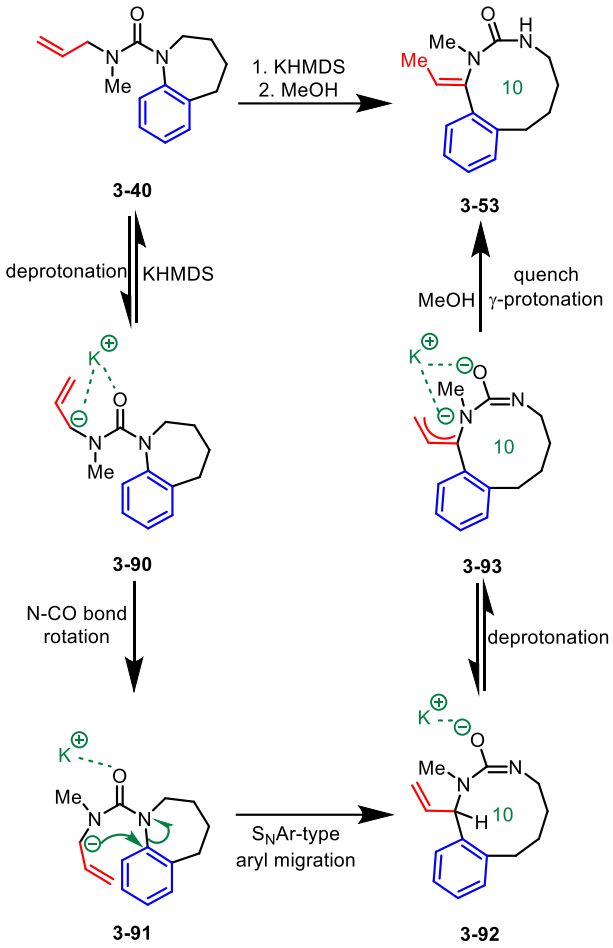
Irradiating the *para*-methyl substituted urea **3-34** in the microwave with KHMDS in THF and in 1,4-dioxane resulted in a mixture of decomposition products (*scheme 3-15*). Using THF the product **3-60** was isolated in 7% yield along with 17% *trans*-isomerised starting urea **3-85**. Alongside the starting material and product, decomposition amine **3-84** was isolated in 16% and symmetrical urea **3-89** in 9%.

Substitution of THF for 1,4-dioxane resulted in only trace amounts of the product **3-60** seen by ^{1}H NMR of the crude. Amine **3-84** was isolated in the same yield as before. *Trans*-isomerised urea **3-85** was isolated in 12% yield and the symmetrical urea **3-89** was isolated in almost double the yield. Repeating this reaction but heating under reflux resulted in only decomposition products and trace amounts of isomerised starting material **3-85** in the crude ^{1}H NMR.

Repeating the ring expansion reaction with urea **3-45** but thermally heating to 69 °C also resulted in no product formation. Crude ^{1}H NMR showed mainly unidentifiable decomposition products and isomerised starting material.

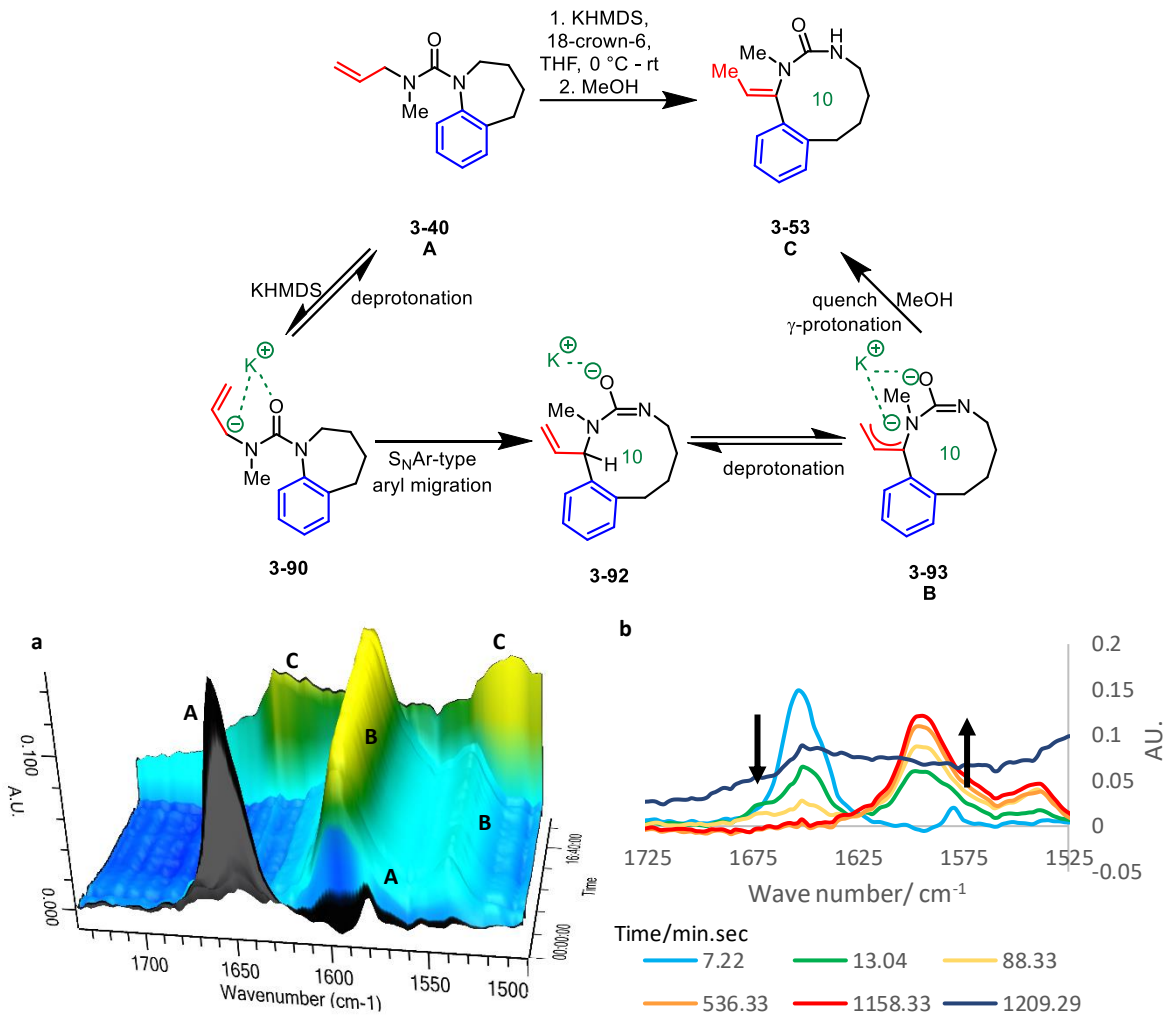
3.2.3.3 Mechanistic studies using *in situ* ReactIR and deuterium labelling

Although the mechanism by which the aryl rings migrates when tether through ureas has been well studied, the use of allyl anion stabilising groups are less well explored.[74,79,93,95,139,140] To investigate the mechanism of this ring expansion reaction ReactIR and deuterium labelling studies were undertaken.



Scheme 3-16: A proposed mechanism for the formation of medium ring **3-53** by treatment of urea **3-40** with KHMDS in the presence of 18-crown-6.

A proposed mechanism is shown in *scheme 3-16*. Initial deprotonation α to the nitrogen results in anion **3-90**. Rotation of the N-CO bond breaks the coordination of the allyl anion to the potassium cation bringing the allyl anion in close contact with the aryl ring, **3-91**. *N to C* aryl migration occurs by *ipso* attack of the allyl anion **3-91** on the aryl ring expanding the ring from *n to n+3*, forming **3-92**. It was then proposed that dianion **3-93** is formed; by a second deprotonation with KHMDS, similar to that reported earlier by Clayden *et.* al.[81] Upon treatment with MeOH γ-protonation occurs forming vinylic isomer, **3-53**.



Scheme 3-17: Probing the mechanism of **3-53** formation with *in situ* ReactIR from urea **3-40** in a THF solution with 18-crown-6 when treated with KHMDS at 0 ˚C and allowed to warm to rom temperature. **a.** Surface spectrum over the entire reaction timescale. **A** – Starting urea **3-40** with 18-crown-6 at 0 ˚C, absorptions at 1651 & 1579 cm^{-1}. *t* = 9 min KHMDS (2 eq.) addition at 0 ˚C. **B** – Reaction mixture, absorptions at 1595 & 1539 cm^{-1}. **C** – (*t* = 1174 min) Reaction Quench with MeOH at room temperature forming product **3-53**, absorptions at 1649 & 1514 cm^{-1}. **b.** Graph of ReactIR at various points throughout the course of the reaction. Decreasing arrow represents the starting material, **3-40** and the increasing arrow represents the product anion, **3-93**. The peaks are tentatively assigned as shown.

To probe the proposed mechanism (*scheme 3-16*) the reaction of urea **3-40** in the presence of KHMDS and 18-crown-6 in THF was investigated using ReactIR (*scheme 3-17a*). KHMDS addition was at 0 °C and then allowed to warm to room temperature over the course of 20 hours. Similar to before the reaction was performed in a more concentrated solution (0.3 M vs 0.1 M) to help with short-lived intermediate detection. An IR of the starting urea **3-40** with 18-crown-6 was acquired before KHMDS addition (**A** in *scheme 3-17a*) and showed absorptions at 1651 and 1579 cm^{-1} assigned to the carbonyl of the urea and the allyl group respectively. KHMDS addition was accompanied by a decrease of urea **3-40** absorptions and the appearance of two new absorptions at 1595 and 1539 cm^{-1} (**B**). The starting material peaks decreased over 5 hours and the absorptions at **B** continued to increase overnight

(*scheme 3-17b*). Quenching the reaction with MeOH after 19 hours led to a broadening of the spectrum (**C**) with weak absorptions at 1649 and 1514 cm^{-1}.

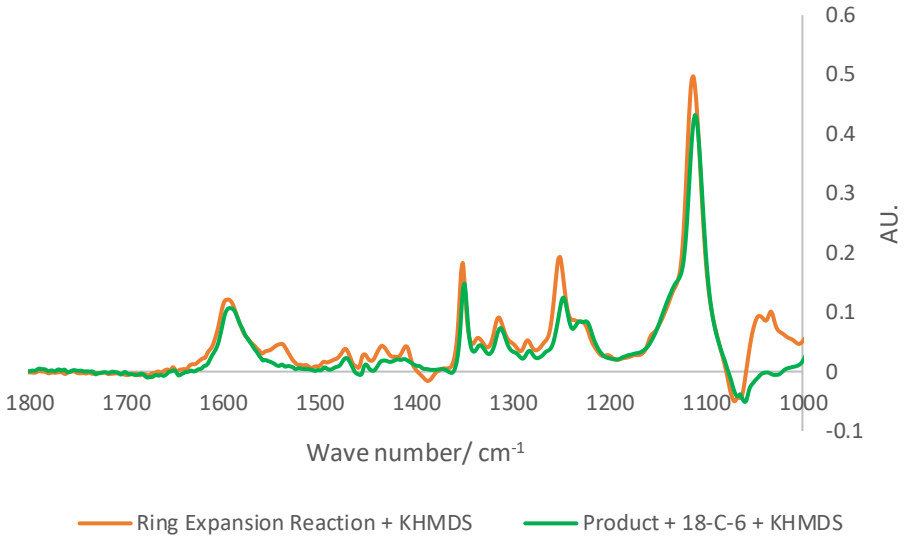
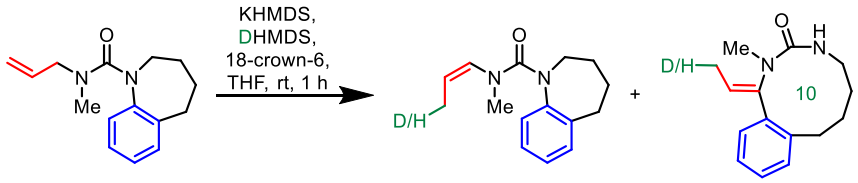


Figure 3-4: Comparison spectra of the reaction mixture (urea **3-40** and 18-crown-6 in THF) treated with KHMDS and the product **3-53** and 18-crown-6 treated with KHMDS.

The IR spectrum of the product **3-53** with 18-crown-6 in THF at room temperature was recorded and showed absorptions at 1686 and 1659 cm^{-1} assigned to the vinyl group and the carbonyl of the urea respectively by comparison with the literature.[98] Treatment of the mixture with KHMDS resulted in loss of the absorptions at 1686 and 1659 cm^{-1} and appearance of a new absorption at 1597 cm^{-1} assigned to the deprotonation of the product NH. Comparison of the spectrum recorded in *scheme 3-17* and the spectrum acquired of product **3-53** with 18-crown-6 treated with KHMDS (*figure 3-4*) showed that the peaks at **B** were assigned to dianion **3-93**. When the product **3-53** was treated with KHMDS no deprotonation at the γ-position was seen because the base was not strong enough.



3-40 | **3-94** 30% 0% D | **3-95** 42% 0% D

Scheme 3-18: Deuterium labelling study using urea **3-40** treated with a 1:1 mixture of KHMDS and D-HMDS.

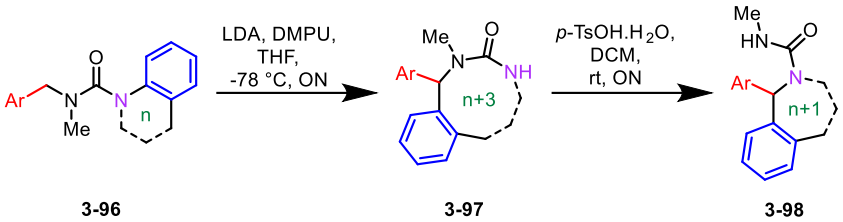
Deuterium labelling studies were next used to investigate the reaction mechanism. Based on the above proposal (*scheme 3-18*) it was assumed that the deprotonation of the urea **3-40** forming anion **3-90** were in equilibrium with each other. To investigate this and trap intermediates in the reaction a solution of urea **3-40** with 18-crown-6 in THF was treated with a 1:1 mixture of KHMDS and D-HMDS (deuterated HMDS). The reaction was quenched after one hour with MeOH and the products were isolated by column chromatography. 10-Membered ring **3-95** and *cis*-isomerised starting material **3-**

94 were isolated; ^{2}H and ^{1}H NMR showed no incorporation of deuterium. To account for the lack of deuterium incorporation it was proposed that there was a slow equilibrium between the dissociation of the H-HMDS from coordination with the potassium cation and the allyl anion and association of the D-HMDS. This dissociation of H-HMDS and association of D-HMDS was slower than the protonation of the isomerised urea and the aryl migration.

3.2.4 Post-ring expansion modifications

After probing the formation of medium rings through *N to C* aryl migration investigations focused on diversifying the medium ring products by post-ring expansion modifications. The medium ring product **3-55** contains a reactive enamide (*scheme 3-10*). This enamide was predicted to react with nucleophilic bases in carbolithiation reactions, radical addition reactions and possibly in both [4+2] and [2+2] cycloaddition reactions. Alongside addition reactions, it was also postulated that the enamide could also be used in vinyl migration reactions. Initial focus looked at ring contraction reactions with acid.

3.2.4.1 Ring contraction by treatment with acid

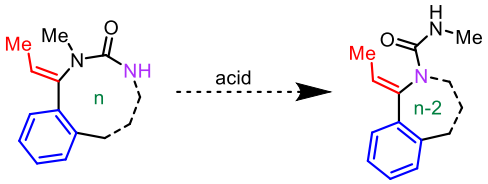


3-96 **3-97** **3-98**

Scheme 3-19: Ring expansion of the aryl ureas under basic conditions then ring contraction under acidic conditions leading to an overall *n to n+1* ring expansion.

Previously (see section 1.4.8) a two-step process was implemented forming **3-98** (*scheme 3-19*). Initially tetrahydroquinoline derived urea **3-96** was treated with base resulting in medium ring **3-97**.[95] The medium ring was subsequently treated with acid undergoing a ring contraction leading to an overall *n to n+1* ring expansion forming tetrahydroazepines, **3-98**.[96]

It was proposed that this ring contraction could be implemented for the enamide medium rings **3-99** synthesised above (section 3.2.3.2) undergoing a similar mechanism to that shown in *scheme 1-61* forming contracted rings **3-100** (*scheme 3-20*).

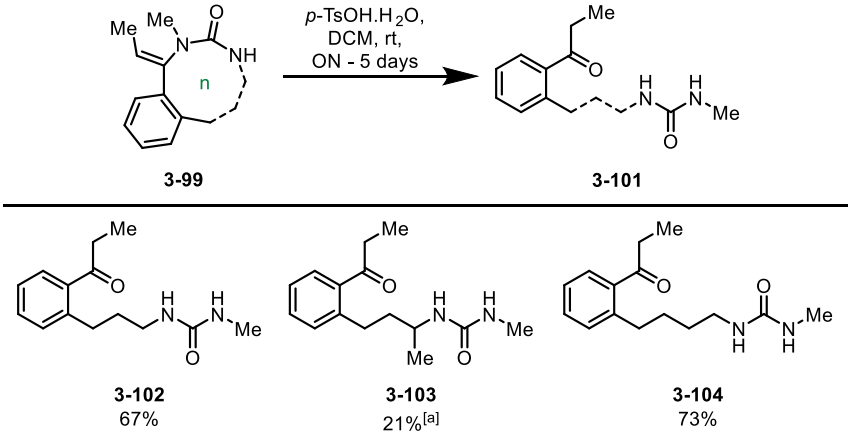


3-99 **3-100**

Scheme 3-20: Proposed acid ring contraction of enamide medium rings.

Using the conditions in the literature 10-membered ring **3-53** (*scheme 3-10*) was stirred in DCM with *para*-toluenesulfonic acid hydrate (*scheme 3-21*). Purification resulted in isolation of the ring opened

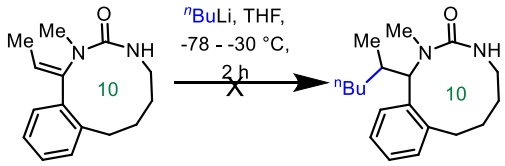
product **3-104** in 73% yield. **3-104** Was formed through hydrolysis of the enamide. Similar results were seen when 9-membered ring **3-8** and 9-membered ring containing a methyl group on the tether, **3-59** were treated under the same conditions affording the hydrolysed products **3-102** and **3-103** in 67% and 21% respectively.



Scheme 3-21: Hydrolysis of enamide medium rings **3-99**. [a] – 48% Recovered starting material **3-59**.

Repeating the reaction for 10-membered ring, **3-53** but reducing the equivalents of acid from 2 to 0.1 equivalents resulted in mainly starting material **3-53** after stirring overnight. To try and prevent the hydrolysis the reaction with 10-membered ring **3-53** was performed under nitrogen using camphor sulfonic acid instead of *para*-toluene sulfonic acid hydrate to eliminate the water. Upon purification only the hydrolysed product **3-104** was isolated in 68%.

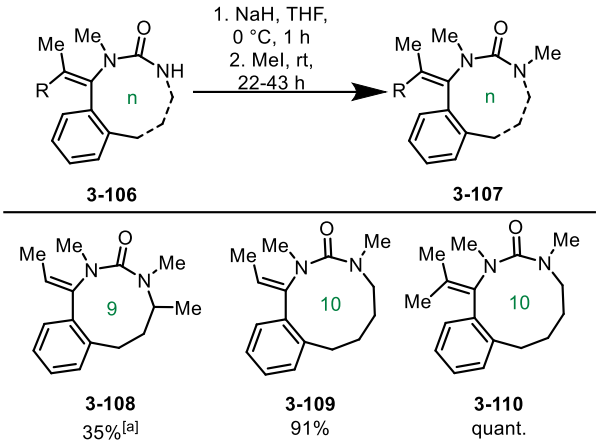
3.2.4.2 Carbolithiation onto the enamide



Scheme 3-22: Attempted carbolithiation of enamide medium ring **3-53** with ^{n}BuLi.

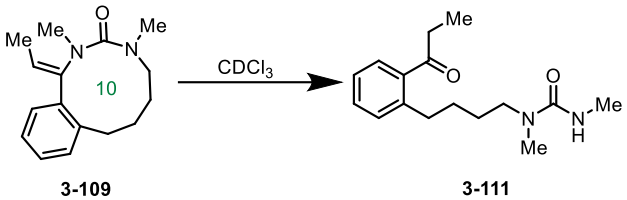
Alternative routes to functionalising these enamide medium rings avoiding acid were predicted to be more successful as the medium rings would not be able to undergo hydrolysis. To test this hypothesis carbolithiation with ^{n}BuLi was attempted with 10-membered ring **3-53** (*scheme 3-22*). Initially **3-53** in THF was cooled to -78 °C before ^{n}BuLi was added. After 2 hours the reaction was quenched and ^{1}H NMR showed only the presence of starting material **3-53** in the crude.

The reaction was repeated but the temperature was increased to -30 °C. Again, only starting material **3-53** was seen by TLC and ^{1}H NMR after the reaction mixture was quenched. 9-Membered ring bearing a methyl group on the tether, **3-59** was also treated with ^{n}BuLi at -40 °C but no reaction was seen by ^{1}H NMR. Under the reaction conditions the free NH is most likely deprotonated, the formation of this anion presumably prevents the addition of the *n*-butyl anion.



Scheme 3-23: Methylation of enamide medium rings. [a] – 39% starting material **3-59** recovered.

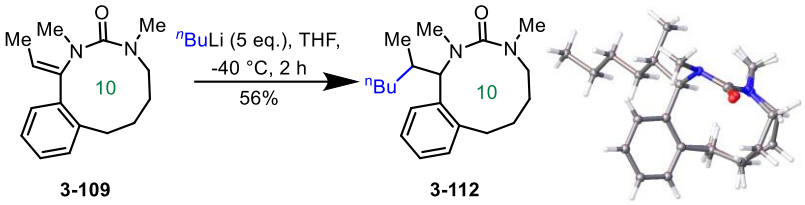
To prevent the NH from being deprotonated under the reaction conditions they were methylated (*scheme 3-23*). 10-Membered rings **3-53** and **3-66** and 9-membered ring **3-59** were methylated with iodomethane in the presence of sodium hydride. 10-Membered rings **3-53** and **3-66** were methylated in excellent yield affording **3-109** and **3-110** respectively. 9-Membered ring **3-108** was isolated in lower yield with 39% of the unreacted starting material **3-59** recovered. The steric hindrance caused by the additional methyl group α to the nitrogen most likely resulted in the slower reaction. Methylation of the NH made the medium ring **3-109** acid sensitive and the hydrolysed product **3-111** was seen in the ^{1}H NMR spectrum when run in $CDCl_3$ (*scheme 3-24*).



Scheme 3-24: Hydrolysis of methylated enamide medium ring **3-109** in deuterated chloroform.

Repetition of the reaction above (*scheme 3-22*) with the methylated urea **3-109** at -78 °C resulted in the isolation of product **3-112** in 52% yield as a mixture of diastereoisomers in a 1.53:1.00 ratio, the starting material **3-109** was also isolated in 9% yield. X-ray crystal data of the major diastereoisomer confirmed the structure of **3-112** (*scheme 3-25*).

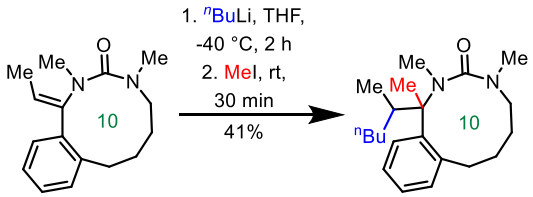
The reaction was repeated but the reaction length doubled to 4 hours to allow the remaining starting material to react. However, only a 31% yield of the product **3-112** was isolated after purification and starting material **3-109** was still present in the crude ^{1}H NMR. Due to the lower yield of product **3-112**, it was assumed that the anion of the product **3-112** is not stable over longer periods of time. To prevent the decomposition of the product anion the reaction was repeated using five equivalents of ^{n}BuLi instead of two equivalents and quenched after one hour. Analysis of the crude ^{1}H NMR showed it to be mostly starting material **3-109**. Repeating the reaction but with DMPU added resulted in no reaction and the starting material **3-109** was recovered.



3-109 3-112

Scheme 3-25: Carbolithiation of medium ring **3-109** with ^{n}BuLi.

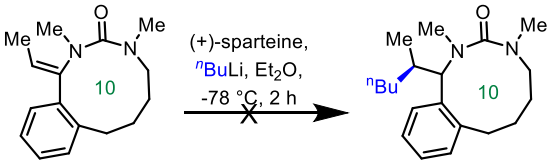
The temperature was increased to -40 °C (*scheme 3-25*) and 5 equivalents of ^{n}BuLi were added. Purification of the crude mixture resulted in isolation of medium ring **3-112** in 56% yield and trace amounts of starting material **3-109** were seen in the crude ^{1}H NMR.



3-109 3-113

Scheme 3-26: Carbolithiation of medium ring **3-109** with ^{n}BuLi quenched with MeI.

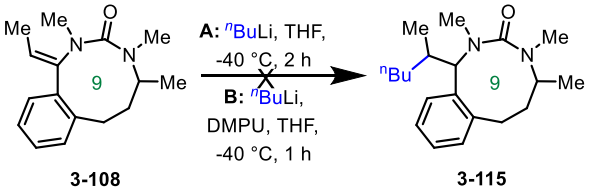
The carbolithiation reactions above (*scheme 3-25*) were quenched with MeOH and sat. aq. NH_4Cl. Repetition of the reaction quenching with iodomethane resulted in medium ring **3-113** with a quaternary centre α to the nitrogen (*scheme 3-26*). Product **3-113** was isolated in 41% as 4:1 mixture of diastereoisomers.



3-109 3-114

Scheme 3-27: Attempted enantioselective carbolithiation of medium ring **3-109**.

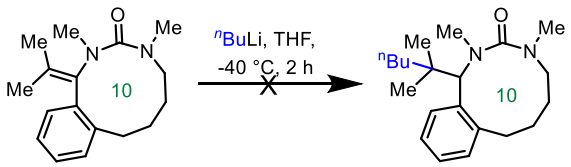
After the successful synthesis of racemic **3-112**, the asymmetric carbolithiation of **3-109** was attempted using (+)-sparteine (*scheme 3-27*).[87] To use sparteine, a solvent switch from THF to Et_2O was required. The medium ring starting material **3-109** was only sparingly soluble in Et_2O at low temperatures. ^{n}BuLi was added and the reaction mixture was left to stir for 2 hours at -78 °C before being quenched. Analysis of the crude ^{1}H NMR showed only starting material **3-109** present.



3-108 3-115

Scheme 3-28: Attempted carbolithiation of 9-membered ring **3-108** using ^{n}BuLi with and without DMPU.

After the successful synthesis of 10-membered ring **3-112** the carbolithiation of 9-membered ring **3-108** was attempted using previously successful conditions (5 equivalents of ^{n}BuLi, -40 °C, 2 h), however, no reaction was seen in ^{1}H NMR (*scheme 3-28*). Addition of DMPU to the reaction was also unsuccessful.



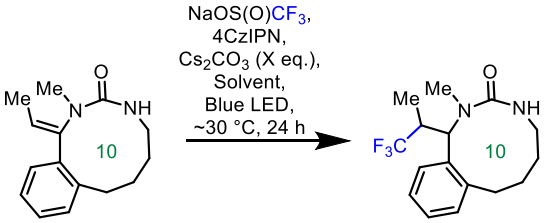
3-110 **3-116**

Scheme 3-29: Attempted carbolithiation of 10-membered ring **3-110**.

10-Membered ring **3-110** was also treated under the above conditions and resulted in no reaction (*scheme 3-29*). Both medium rings **3-108** and **3-110** contain extra steric hindrance which may contribute to the lack of reactivity seen when ^{n}BuLi was added.

3.2.4.3 Photoredox initiated radical addition to the enamide

After establishing that functionalisation of 10-membered ring **3-109** was possible using carbolithiation, alternative routes to functionalise enamides under non-acidic conditions were sought. Previously within the group photoredox-catalysed enamide difunctionalisation was achieved through *N to C* aryl migration of urea-substituted carbanions generated by reductive radical-polar crossover cascade reaction (*scheme 3-30, see section 1.4.6 for more detail*).[88]

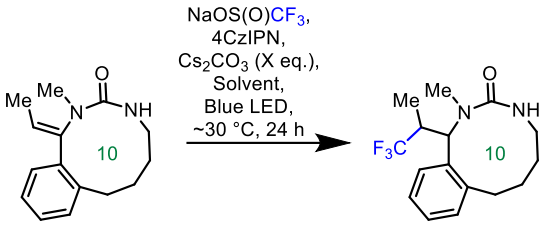


3-53 **3-117**

Scheme 3-30: N to C aryl migration using reductive radical-polar crossover cascade. Solvent: acetone, MeCN or DMF.

Although confined to a ring, the medium ring products in *scheme 3-10* are reasonably similar (vinylic urea) to the acyclic ureas **1-240** in *scheme 3-30* but not capable of aryl migration. To test this theory 10-membered ring **3-53** was subjected to the optimised conditions (*scheme 3-30*) using Langlois reagent (NaOS(O)CF$_3$) as the radical precursor (*table 3-3*).

Table 3-3: Attempted radical addition using 10-membered ring **3-53** containing a free NH, and Langlois reagent as the radical precursor.



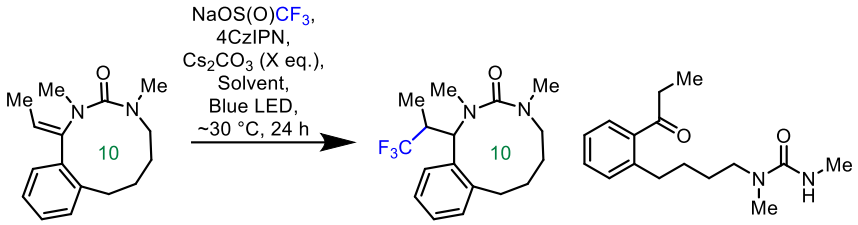
3-53 **3-117**

Entry	Solvent	Cs_2CO_3 X eq.	3-117 yield/%	Comment
1	MeCN	1.5	Trace	Starting material **3-53** recovered
2	acetone	1.5	Trace	Starting material **3-53** recovered
3	DMF	1.5	-	Starting material **3-53** recovered
4	MeCN	-	-	Starting material **3-53** recovered

The radical addition reaction was performed with Cs_2CO_3 in MeCN (*table 3-3,* entry 1), after 24 hours only trace amounts of product **3-117** was seen by ^{1}H NMR along with unreacted starting material **3-53**. During optimisation of the literature work it was found that both acetone and DMF could also be used successfully as solvents often leading to improved yields.[88] The reaction was repeated using acetone and DMF (entries 2 & 3). In both cases unreacted starting material **3-53** was seen in the crude ^{1}H NMR after an aqueous work-up, trace amounts of the product **3-117** was seen when using acetone (entry 2).

The use of Cs_2CO_3 was required to sequester the SO_2 preventing hydrolytic cleavage of the uronium species generated *in situ.*[88] SO_2 is formed during the initial oxidation of Langlois reagent generating the CF_3 radical. Removal of Cs_2CO_3 led to no improvement in yield with only starting material **3-53** recovered after an aqueous work-up (entry 4).

Table 3-4: Radical addition to 10-membered ring **3-109** using Langlois reagent as the radical precursor.



3-109 **3-118** **3-111**

Entry	Solvent	Cs_2CO_3 X eq.	3-118 yield/%	3-109 : 3-118 ratio[a]	Comment
1	MeCN	1.5	-[b]	1.00 : 0.81	Not isolated
2	acetone	1.5	62	0.72 : 1.52[c]	Starting material **3-109** not isolated
3	DMF	1.5	-	-	Starting material **3-109** recovered
4	MeCN	-	-	-	1.00 : 0.39 - Starting material **3-109** and hydrolysed **3-111** in crude ^{1}H NMR

[a] – Ratio determined from crude ^{1}H NMR. [b] – Product not isolated. [c] – Product **3-118** isolated as a mixture of two diastereoisomers (d.r 1.00:0.52).

In the carbolithiation reactions methylation of the free NH was required for reactivity, the methylated 10-membered ring **3-109** was then subjected to the radical-polar crossover conditions above (*table 3-4*). When using MeCN as the solvent, product **3-118** was observed in the crude ^{1}H NMR in a 1.00:0.81 ratio of starting material **3-109** to product **3-118** (entry 1). The product was not isolated.

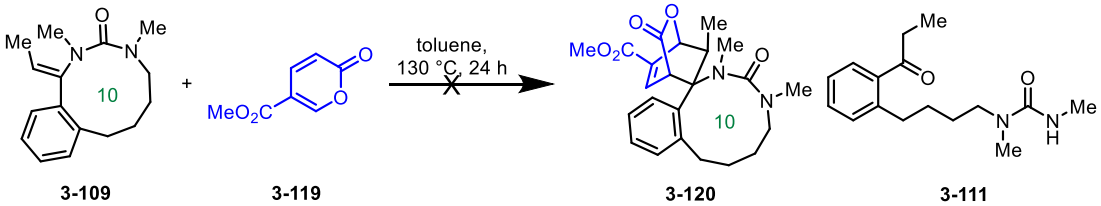
Changing the solvent to acetone resulted in isolation of the desired product **3-118** in 62% yield as a 1.00:0.52 ratio of two diastereoisomers together with unreacted starting material **3-109**, which was no isolated (entry 2). Switching the solvent to DMF resulted in no reaction and only starting material **3-109** was seen by ^{1}H NMR (entry 3).

Removal of the Cs_2CO_3 had a detrimental effect on the reaction resulting in no product **3-118** formation, but some hydrolysed starting material **3-111** was seen in crude ^{1}H NMR (entry 4).

3.2.4.4 Cycloadditions onto the enamide

Having established that both carbanions and carbon centred radicals can add into the vinyl group, investigations focused on the reactivity of the enamide through cycloaddition reactions. There is a wealth of cycloaddition reactions reported in the literature for tertiary enamides, although very few if any contain a urea enamide.[141]

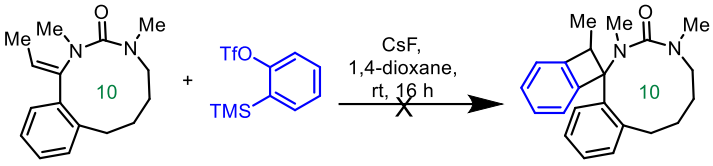
To test the ability of the enamide medium rings synthesised in *scheme 3-10*, 10-membered ring **3-109** was subjected to reported conditions for the inverse electron-demand Diels-Alder reaction of diene **3-119** with enamide dienophiles (*scheme 3-31*).[142–144]



3-109 **3-119** **3-120** **3-111**

Scheme 3-31: Attempted inverse electron-demand Diels-Alder reaction of 10-membered ring **3-109** with **3-119**.

After heating the reaction mixture under inert conditions in a sealed microwave vial for 24 hours analysis of the crude mixture by ^{1}H NMR showed no evidence of the desired product **3-120**. Hydrolysed product **3-111** was the major product. The diene **3-119** and trace amounts of the starting material **3-109** were also identified.

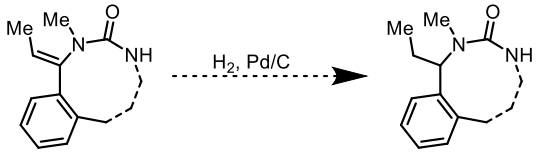


3-109 **3-121** **3-122**

Scheme 3-32: Attempted [2+2] cycloaddition reaction via benzyne formation.

[2+2] Cycloaddition reaction of **3-109** with **3-121** via *in situ* benzyne formation with caesium fluoride in 1,4-dioxane was attempted (*scheme 3-32*). The reaction mixture was stirred at room temperature overnight. After purification only unreacted starting material **3-109** was isolated. Unreacted **3-121** was also seen in the crude ^{1}H NMR, indicating that no/very little benzyne was formed during the reaction.

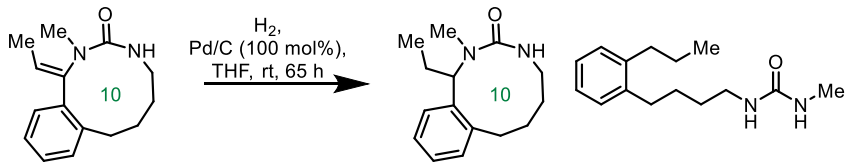
3.2.4.5 Hydrogenation of the enamide



3-99 **3-123**

Scheme 3-33: Proposed hydrogenation of the enamide medium rings.

Hydrogenation of the alkene forming medium ring **3-123**, would provide a medium ring that is more stable towards acidic conditions and represents another post-ring expansion modification (*scheme 3-33*).

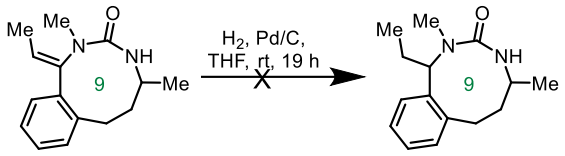


3-53 **3-124** **3-125** 48%

Scheme 3-34: Hydrogenation of medium ring **3-53**.

Model substrate **3-53** was stirred under an atmosphere of hydrogen with Pd/C in THF for 65 hours (*scheme 3-34*). After purification urea **3-125** was isolated in a 48% yield, which is predicted to be formed through further hydrogenation of **3-124** cleaving the C-N bond. Trace amounts of the product **3-124** was seen in the crude ^{1}H NMR.

The reaction was repeated but left under an atmosphere of hydrogen for 19 hours. After purification over hydrogenated urea **3-125** was isolated in 5% yield. A mixture of starting material **3-53** and the desired reduced medium ring **3-124** were isolated as a 0.45:1.00 mixture of **3-124** : **3-53**. Attempts at separating product **3-124** from starting material **3-53** using preparative TLC were unsuccessful.



3-59 **3-126**

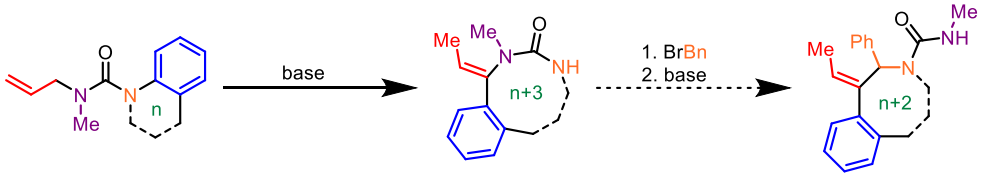
Scheme 3-35: Attempted hydrogenation of enamide **3-59**.

After proving hydrogenation of the alkene in **3-53** was possible, 9-membered ring **3-59** was also stirred under an atmosphere of hydrogen along with Pd/C in THF, using 10 mol% of the catalyst (*scheme 3-35*). After 19 hours, analysis of the crude ^{1}H NMR showed only trace amounts of the desired product **3-126** along with the unreacted starting material **3-59**.

3.2.4.6 Alkenyl migration in medium-ring nitrogen heterocycles

Exploration of the post-ring modifications of 10-membered ring **3-53** proved that radical addition and carbolithiation were possible. Hydrogenation of the enamide was also possible although medium ring **3-53** was further reduced, cleaving the C-N bond which resulted in ring opening product **3-125**. Treatment of the medium rings with acid resulted only in hydrolysis of the enamide and ring opening. Previous work using ureas to conformationally induce the formation of new C-C bonds using carbanions showed that both aryl and vinyl groups could be migrated (see section 1.4).

3.2.4.6.1 Benzyl stabilised anion

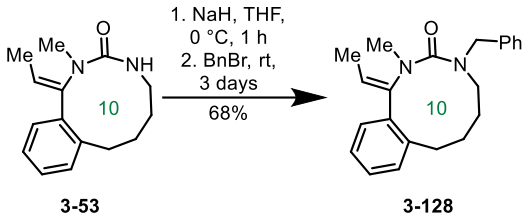


3-1 **3-99** **3-127**

Scheme 3-36: Multistep process resulting in an overall *n to n+2* ring expansion through aryl migration then benzylation and subsequent alkenyl migration.

The medium rings synthesised above (section 3.2.3.2) contain a vinyl group attached through a urea to an NH. It was proposed that benzylation of the free NH would provide cyclic ureas equivalent to

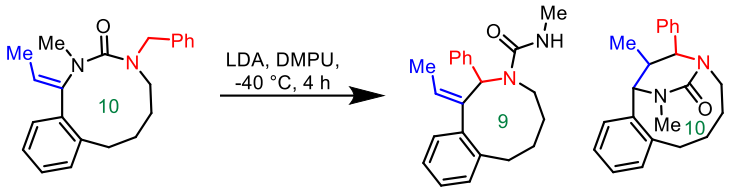
those used previously for vinyl migration.[97] Under basic conditions, a second migration (vinyl) was predicted to occur resulting in reduction of the ring size by 1, leading to **3-127** in an overall *n to n+2* (*scheme 3-36*).



3-53 **3-128**

Scheme 3-37: Benzylation of 10-membered ring **3-53**.

Benzylation of 10-membered ring **3-53** using sodium hydride and benzyl bromide resulted in isolation of product **3-128** in 68% yield, unreacted starting material **3-53** was also isolated in 26% yield (*scheme 3-37*). The benzylated medium ring **3-128** was also found to be very sensitive to acid and would hydrolyse in deuterated chloroform.



3-128 **3-129** **3-130** 13%

Scheme 3-38: Attempted alkenyl migration using a benzyl stabilised anion.

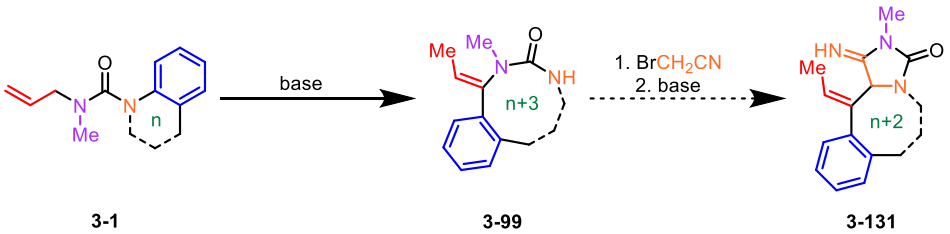
Based on previous work, LDA was used for benzylic deprotonation and DMPU was added as a lithium cation coordinating agent. Initially, benzylated medium ring **3-128** was treated with LDA at -78 °C in the presence of DMPU. After 4 hours TLC analysis showed starting material **3-128** was present and the reaction mixture was held at -78 °C overnight. Purification of the crude mixture resulted in isolation of 52% unreacted starting material **3-128** and a complex mixture of products containing trace amounts of **3-130**. The ring contracted product **3-129** was not observed in the crude ^{1}H NMR. Bridging medium ring **3-130** is formed through carbanion attack on the β-carbon of the vinyl group.

Efforts to try and push the reaction to one major product included increasing the temperature from -78 °C to -40 °C (*scheme 3-38*). Analysis of the crude mixture showed starting material **3-128** was still remaining. Purification of the crude mixture resulted in clean isolation of **3-130** in 13% yield as the major product. The remaining mixture was a complex mix of unidentified compounds. Removal of DMPU from the crude mixture proved difficult and isolation of unidentified compounds through column chromatography from the coeluting DMPU was unsuccessful.

The reaction was repeated but with the temperature increased to -20 °C for 4 hours. TLC analysis showed starting material **3-128** remaining; the reaction temperature was increased to -10 °C and held overnight. Starting material **3-128** was still present in the reaction mixture. Purification of the crude mixture resulted in isolation of trace amounts of **3-130** and trace amounts of unidentified compounds.

Due to the difficulties of removing DMPU from the rest of the reaction mixture, the reaction was repeated in the absence of DMPU. Medium ring **3-128** was treated with LDA in THF at -40 °C for 3 hours, after which TLC analysis showed the presence of starting material **3-128**. The reaction temperature was increased to -20 °C and left overnight. Purification of the crude reaction mixture resulted in isolation of starting material **3-128** in 50% yield. A complex mixture of unidentified products was also isolated along with trace amounts of **3-130**.

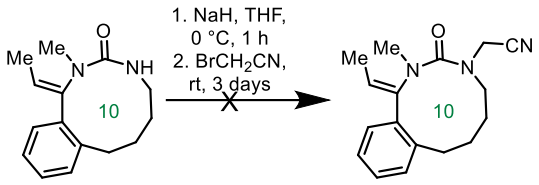
3.2.4.6.2 Nitrile stabilised anion



3-1 **3-99** **3-131**

Scheme 3-39: Proposed iminohydantoin bicycle synthesis through ring expansion of allylureas forming vinylic products. Coupling of these with acetonitrile derivative and alkenyl migration under basic conditions.

Nitrile groups were used above in section 2.3 as anion stabilising groups for aryl migration forming medium rings with (imino)hydantoins bridging them.[140] Nitrile anion stabilising groups have also been used for acyclic aryl and vinyl migrations.[90,98,139] A proposed synthesis of iminohydantoin **3-131** was suggested from coupling of methylnitrile onto the free NH of **3-99** then treatment of the resulting medium ring with base (*scheme 3-39*).

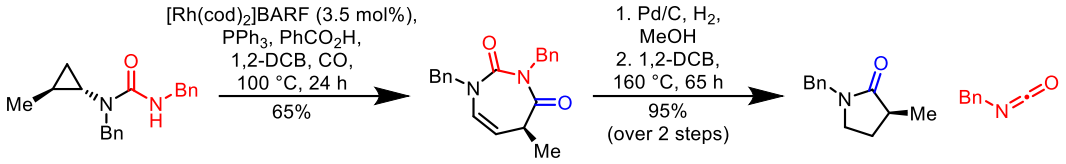


3-53 **3-132**

Scheme 3-40: Attempted alkylation of 1-membered ring **3-53** with bromoacetonitrile.

Similar to previous alkylation reactions on the NH, 10-memebred ring **3-53** was treated with sodium hydride in THF for 1 hour then bromoacetonitrile was added and the reaction mixture was stirred at room temperature for 3 days (*scheme 3-40*). Analysis of the crude ^{1}H NMR showed that no reaction had taken place and both starting materials were recovered.

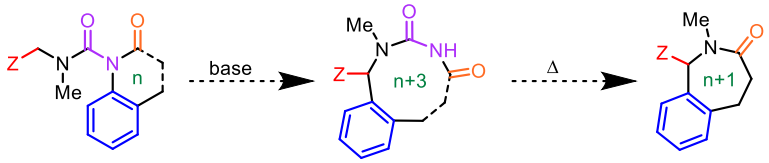
3.3 Lactam urea ring expansion and extrusion of the urea moiety



3-133 >99:1 e.r. **3-134** **3-135** 98:2 e.r. **3-136**

Scheme 3-41: γ-Lactams synthesis by isocyanate-derived transient directing group ring expansion of cyclopropanes and subsequent ring contraction extruding the isocyanate transient directing group.

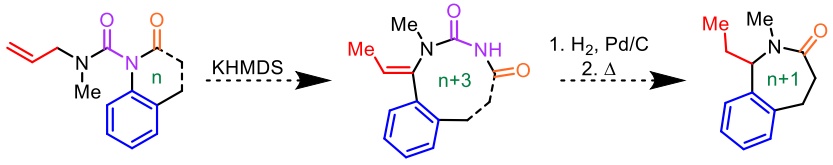
Recently, Bower and co-workers reported a unique strategy for synthesising γ-lactams **3-135** from cyclopropane derived ureas **3-133** (*scheme 3-41*).[145] Initially, unsaturated 7-membered ring **3-134** was synthesised through previously reported, directing group activated carbonylative C-C bond cleavage of the aminocyclopropane.[146] Cyclic urea **3-134** was then reduced under an atmosphere of hydrogen. When the reduced cyclic urea was heated at 160 °C in 1,2-DCB the benzyl isocyanate directing group **3-136** was extruded forming the desired γ-lactam **3-135** in high yield with complete enantiopurity retained.



3-137 **3-138** **3-139**

Scheme 3-42: Proposed ring expansion forming medium rings followed by ring contraction extruding the urea moiety forming benzolactams.

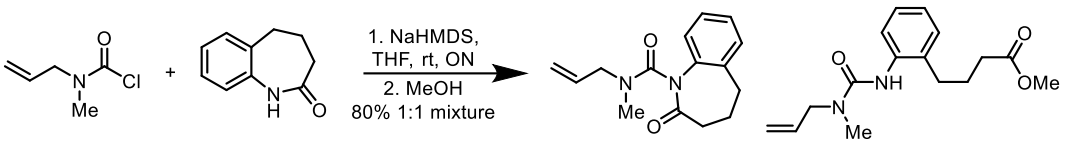
Based on the literature report,[145] it was proposed that a similar approach could be adapted for the synthesis of nitrogen heterocycles **3-139** by extruding the urea moiety (*scheme 3-42*). However, in order to promote this ring contraction, medium ring **3-138** synthesis from lactam **3-137** would be required which have not been attempted before.



3-140 **3-141** **3-142**

Scheme 3-43: Proposed allyl anion stabilised ring expansion of lactam urea **3-140** then hydrogenation of the double bond and ring contraction extruding the urea moiety forming benzolactam **3-142**.

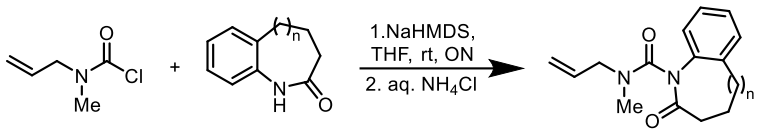
An allyl anion stabilising group was chosen for the ring expansion-ring contraction forming lactam **3-140** (*scheme 3-43*). Based on the work above, it was proposed that treatment of lactam ureas **3-140** with base would promote *N to C* aryl migration forming medium ring **3-141**. Before ring contraction the double bond would most likely need to be hydrogenated to increase the nucleophilicity of the amine similar to that found in the literature (see *scheme 3-42*).[145]



3-24 **3-143** **3-144** **3-145**

Scheme 3-44: Coupling of carbamoyl chloride and lactam, quenched with MeOH forming the desired urea **3-144** and amide hydrolysis.

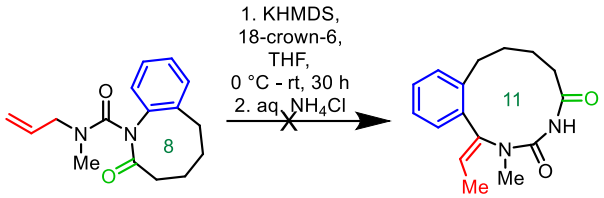
Synthesis of urea **3-143** by coupling of carbamoyl chloride **3-24** with benzolactam **3-143** using NaHMDS as the base resulted in a 1:1 mixture of desired urea **3-144** and **3-145** (*scheme 3-44*). **3-145** Resulted from the hydrolysis of the lactam amide in **3-144** by MeOH used for quenching the reaction.



3-24 **3-146** **3-147** n = 1 52%
3-148 n = 2 67%

Scheme 3-45: Synthesis of lactam ureas.

Repeating the reaction but quenching the reaction with aqueous NH_4Cl resulted in successful isolation of the desired lactam urea **3-147** in 52% yield with no evidence of lactam hydrolysis (*scheme 3-45*). The larger 8-membered lactam urea **3-148** was also successfully synthesised and isolated in 67% yield.

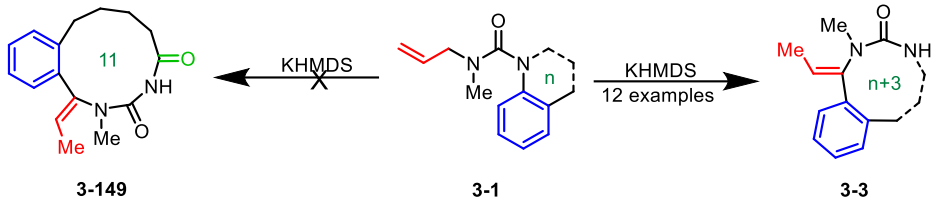


3-148 **3-149**

Scheme 3-46: Attempted ring expansion of lactam urea **3-148** with KHMDS and 18-crown-6.

8-Membered lactam **3-148** was treated with KHMDS in the presence of 18-crown-6 (*scheme 3-46*). Analysis of the crude ^1H NMR showed a complex mixture of products, no starting material **3-148** was remaining. Column chromatography was attempted on the crude mixture to separate the spots seen by TLC however some of the spots co-eluted making identification difficult.

3.4 Conclusion and future work



3-149 **3-1** **3-3**

Scheme 3-47: Summary of the medium ring synthesis in chapter 3 using allyl-anion stabilising groups.

A summary of the ring expansion reactions in chapter 3 are shown in *scheme 3-47*. Allylamines tethered through a urea to nitrogen heterocycles rearrange into medium rings **3-3** containing an enamide under basic conditions. The yields for this *N to C* aryl migration were generally moderate to high. Competing urea decomposition reactions were seen for some ureas **3-1**, especially those containing electron rich aryl migrating groups which resulted in low yields of **3-3** or no product at all.

Modifications of the medium ring scaffold **3-3** through post-ring expansion modifications were explored predominantly using 10-membered ring **3-53**. Treatment with acid led to hydrolysis of the enamide, opening the ring. Methylation of the medium ring was key to any successful post-ring expansion modifications. Carbolithiation with ^{n}BuLi resulted in the incorporation of a *n*-butyl chain into the enamide. Quenching the reaction with MeI resulted in the formation of a quaternary center α to the nitrogen in the medium ring scaffold.

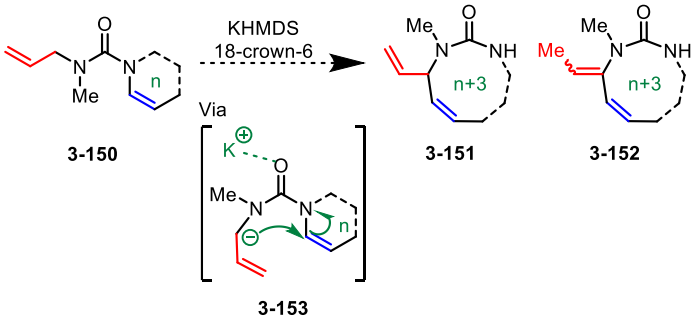
A trifluoromethyl radical was also successfully added to the enamide under blue LED irradiation using Langlois reagent as the radical precursor and an organic photocatalyst. The double bond was also hydrogenated, although under the reaction conditions the C-N bond was cleaved leading to ring opening.

[2+2] And [4+2] cycloaddition reactions on 10-membered ring **3-109** were also attempted but were unsuccessful, leading to recovery of the starting material.

An attempt at performing an alkenyl migration using benzannulated medium ring **3-126** was trialled by treatment with LDA in the presence and absence of DMPU, which resulted in cyclisation onto the β position of the double bond. An alternative alkenyl migration using a nitrile anion stabilising was also proposed, however formation of the precursor by coupling 10-membered ring **3-53** with bromomethylnitrile was unsuccessful.

Alternative ureas **3-138** containing an additional carbonyl group were also synthesised to probe medium ring formation. The attempted ring expansion of the 8-membered lactam urea **3-148** was trialled with KHMDS and 18-crown-6. Purification of the complex mixture of products seen in the crude ^{1}H NMR was unsuccessful and no identifiable products were isolated.

Replacement of the aryl ring in **3-1** with an alkene would form ureas **3-150** and treatment of these ureas with base is predicted to afford medium rings **3-151** or **3-152** (*scheme 3-48*). These medium rings would contain an additional alkene group in the ring which could also be used to functionalise the medium ring scaffold after ring expansion. Future work should be concerned with exploring the possibility of this reaction using allyl anion stabilising groups.



Scheme 3-48: Proposed future work involving vinyl migration using an allyl anion stabilising group.

4. Experimental

4.1 General directions

Chemicals were purchased and used without purification. Dry solvents were obtained by passage through a column of anhydrous alumina using equipment from Anhydrous Engineering (University of Bristol). Anhydrous Et_2O was stored over 3 Å molecular sieves and purchased from Acros and used as received. Anhydrous 1,4-dioxane was purchased from Sigma-Aldrich and used as received. Triethylamine was purchased from Fischer scientific and stored over KOH. Reactions requiring anhydrous conditions were performed under N_2 and in vacuum and flame or oven-dried glassware. Liquid reagents, solutions or solvents were added via syringe through rubber suba-seal. All reactions were stirred magnetically. Reactions performed microwave irradiation were performed in the Biotage Initiator+.

Chromatography: Flash column chromatography was performed on an automated Biotage Isolera™ Spektra Four using gradient elution on prepacked silica gel Biotage SNAP Ultra columns/Biotage Sfär columns or manual methods using silica gel [Merck, 230-400 mesh (40-63 µm)]. Solvents for flash column chromatography and TLC are listed as volume:volume percentages.

TLC analysis: Reactions were monitored by TLC on alumina backed silica plates, Kieselgel $60F_{254}$ (Merck). Visualisation was under UV light (254 and 366 nm) and either by staining with potassium permanganate solution, ninhydrin solution or Seebach stain then heating.

^{1}H NMR: Spectra were recorded on Bruker (400 or 500 MHz), Jeol ECS or ECZ (400 MHz) or Varian VNMR (500 MHz). All NMR experiments were performed at 25 ˚C unless otherwise stated. Spectra collected were analysed and processed using MestReNova. Chemical shifts (δ_H) are quoted in parts per million (ppm) and are referenced to the residual proton signals of acetone, $CHCl_3$, CH_2Cl_2, DMSO or MeOH. ^{1}H coupling constants are reported in Hz. Data are reported as follows: chemical shift multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qunit. = quintet, m = multiplet, dd = double of doublets, br = broad etc …), coupling constants, integration and assignment. 2D experiments of COSY, HSQC and HMBC were used in the assignment of NMR spectra.

^{13}C NMR: Spectra were recorded on Bruker (100 or 125 MHz), Jeol ECS or ECZ (100 MHz) or Varian (125 MHz). All NMR experiments were performed at 25 ˚C unless otherwise stated. Chemical shifts (δ_C) are quoted in parts per million (ppm) and are referenced to the residual proton signals of acetone, $CHCl_3$, CH_2Cl_2, DMSO or MeOH. ^{13}C coupling constants are reported in Hz. Data are reported as follows: chemical shift and assignment or chemical shift, multiplicity (d = doublet, q = quartet, dd = doublet of doublets), coupling constant and assignment.

^{19}F NMR: Spectra were recorded on Bruker (376 MHz) or Jeol ECS (376 MHz). All experiments were recorded at 25 ˚C. Chemical shifts (δ_F) are quoted in parts per million (ppm). ^{19}F coupling constants are reported in Hz. Data are reported as follows: chemical shift, multiplicity (s = single, d = doublet, m = multiplet, dd = doublet of doublets), coupling constant and assignment.

HRMS: High resolution mass spectra were recorded on a Bruker Daltronics MicrOTOF 2 mass spectrometer (ESI).

IR: IR spectra were recorded using a Perkin Elmer (Spectrum One) FT-IR spectrometer (ART sampling accessory) and were recorded neat. Only strong and selected absorbances are reported.

m.p: Melting points were measured on a Kofler hotstage melting point apparatus and are uncorrected. Samples were recrystalised from DCM unless otherwise stated.

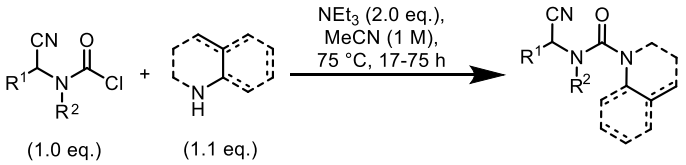
X-ray crystallography sample formation: Crystals for x-ray crystallography were grown by slow diffusion. The sample was dissolved in a suitable solvent (DCM/acetone/$CHCl_3$/$CDCl_3$/MeOH) in a small vial. A second less polar solvent (Et_2O/*n*-pentane/hexane/heptane) was placed outside the vial and allowed to diffuse in causing crystallisation.

4.2 General procedures:

General Procedure 1 (GP1) – Carbamoyl chloride synthesis:

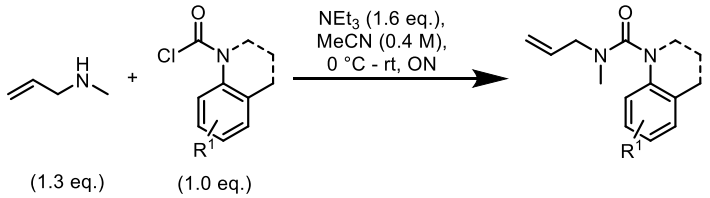
Under an atmosphere of N_2 a solution of triphosgene (0.46 eq.) in anhydrous DCM (1 M) was cooled to 0 °C. Anhydrous pyridine (1.0 eq.) was added dropwise followed by the amine (1.0 eq.) whilst maintaining 0 °C. The reaction mixture was stirred at 0 °C for 2 h then quenched with aq. HCl (1 M) and allowed to warm to room temperature. The reaction mixture was diluted with DCM (30 mL) and washed with aq. HCl (1 M, 2 x 30 mL). The combined aqueous layers were extracted into DCM (2 x 30 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (15 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to afford the crude carbamoyl chloride which was used without further purification.

General Procedure 2A (GP2A) – Nitrile urea synthesis:



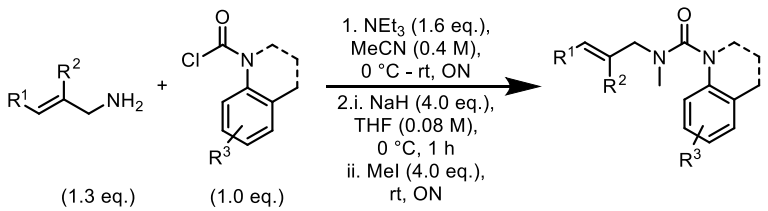
Under an atmosphere of N_2 the amine (1.1 eq.) and anhydrous triethylamine (2.0 eq.) were added to a solution of the carbamoyl chloride (1.0 eq.) in anhydrous MeCN (1 M). The reaction mixture was heated to 75 °C and stirred for the stated amount of time. The reaction mixture was cooled to room temperature and sat. aq. $NaHCO_3$ (5 mL) was added. The reaction mixture was extracted into DCM (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography afforded the title compound.

General Procedure 2B (GP2B) – Allyl urea synthesis at room temperature:



Under an atmosphere of N_2, anhydrous triethylamine (1.6 eq.) was added to a solution of the carbamoyl chloride (1.0 eq.) in anhydrous MeCN (0.4 M). The reaction mixture was cooled to 0 °C. The amine (1.3 eq.) was added dropwise. The reaction mixture was stirred for the stated amount of time, whilst warming to room temperature. To the reaction mixture sat. aq. $NaHCO_3$ (5 mL) was added. The reaction mixture was extracted into DCM (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography afforded the title compound.

General Procedure 2C (GP2C) – Urea synthesis followed by NH methylation:

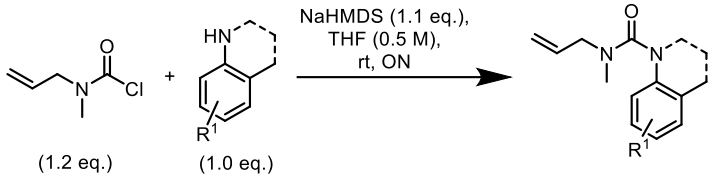


Under an atmosphere of N_2, anhydrous triethylamine (1.6 eq.) was added to a solution of the carbamoyl chloride (1.0 eq.) in anhydrous MeCN (0.4 M). The reaction mixture was cooled to 0 °C. The amine (1.3 eq.) was added dropwise. The reaction mixture was stirred for the stated amount of time, whilst warming to room temperature. To the reaction mixture sat. aq. $NaHCO_3$ (5 mL) was added. The

reaction mixture was extracted into DCM (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography afforded the secondary urea.

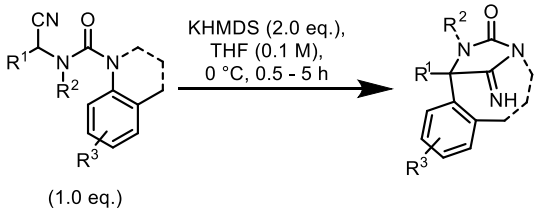
Under an atmosphere of N_2, NaH (60% in mineral oil, 4.0 eq.) was added portion wise to a solution of the secondary urea (1.0 eq.) in anhydrous THF (0.08 M) cooled to 0 °C. The reaction mixture was stirred at 0 °C for 1 h. To the reaction mixture iodomethane (4.0 eq.) was added dropwise. The reaction mixture was stirred for the stated amount of time, whilst warming to room temperature. To the reaction mixture H_2O (30 mL) was added. The aqueous layer was extracted into EtOAc (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography afforded the title compound.

General Procedure 2D (GP2D) – NaHMDS urea synthesis:



Under an atmosphere of N_2, NaHMDS (1 M in THF. 1.1 eq.) was added dropwise to a solution of allyl(methyl)carbamic chloride (1.2 eq.) and the amine (1.0 eq.) in anhydrous THF (0.5 M). The reaction mixture was stirred at room temperature for the stated amount of time. The reaction mixture was quenched with sat. aq. NH_4Cl (1 mL) and diluted with EtOAc (20 mL). The organic layer was washed with sat. aq. NH_4Cl (20 mL) and the aqueous layer extracted into EtOAc (20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced. Purification via flash column chromatography afforded the title compound.

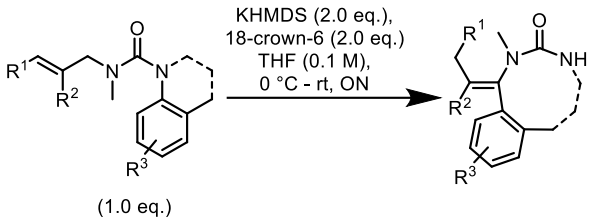
General Procedure 3A (GP3A) – KHMDS promoted ring-expansion:



Under an atmosphere of N_2, the urea (1.0 eq.) was dissolved in anhydrous THF (0. 1 M) and cooled to 0 °C. KHMDS (1 M in THF, 2 eq.) was added dropwise whilst maintaining 0 °C. The reaction mixture was stirred at 0 °C and stirred for the stated amount of time. The reaction mixture was quenched with MeOH (0.5 mL), allowed to warm to room temperature and diluted with EtOAc (20 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (15 mL) and the aqueous layer was further extracted into EtOAc (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent

removed under reduced pressure. Purification via flash column chromatography afforded the title compound.

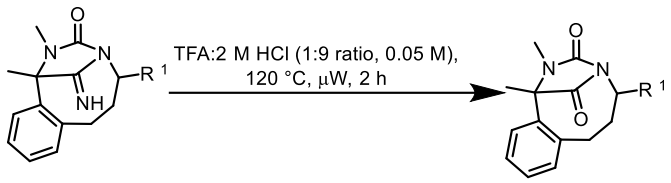
General Procedure 3B (GP3B) – KHMDS/18-crown-6 promoted ring-expansion:



(1.0 eq.)

Under an atmosphere of N_2, the urea (1.0 eq.) and 18-crown-6 (2.0 eq.) were dissolved in anhydrous THF (0.1 M) and cooled to 0 °C. KHMDS (1 M in THF, 2.0 eq.) was added dropwise whilst maintaining 0 °C. The reaction mixture was stirred for the stated amount of time, whilst warming to room temperature. The reaction mixture was quenched with MeOH (1 mL) and diluted with EtOAc (20 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (15 mL) and the aqueous layer was further extracted into EtOAc (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to afford the crude ring expanded product. Purification via flash column chromatography afforded the desired compound.

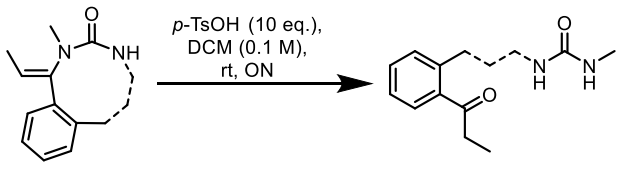
General Procedure 4 (GP4) – Hydrolysis of iminohydantoin:



(1.0 eq.)

The medium ring (1.0 eq.) was dissolved in TFA:2 M HCl (1:9 ratio, 0.05 M) in a microwave vial. The vial was sealed and heated in a microwave reactor at 120 °C for 2 h. The reaction was basified (pH > 7) with sat. aq. $NaHCO_3$. The reaction mixture was extracted into DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure, affording the title compound.

General Procedure 5 (GP5) – Enamide medium ring hydrolysis:

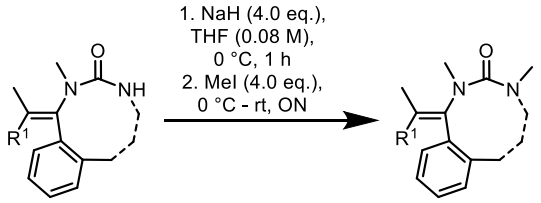


(1.0 eq.)

To a solution of the medium ring (1.0 eq.) in DCM (0.1 M) was added *para*-toluene sulfonic acid (10 eq.). The reaction mixture was stirred at room temperature for the stated amount of time. The

reaction mixture was washed with sat. aq. $NaHCO_3$. The aqueous layer was extracted into DCM (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography afforded the title compound.

General Procedure 6 (GP6) – *N*-methyl with iodomethane:



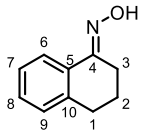
(1.0 eq.)

Under an atmosphere of N_2, the urea (1.0 eq.) was dissolved in anhydrous THF (0.08 M) and cooled to 0 °C. NaH (60% in mineral oil, 4.0 eq.) was added portion wise whilst maintaining 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Iodomethane (4.0 eq.) was added dropwise. The reaction mixture was stirred overnight whilst warming to room temperature. The reaction mixture was quenched with H_2O (30 mL). The reaction mixture was extracted into EtOAc (3 x 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to afford the title product.

N.B. Methylated medium ring unstable in weak acid (including $CHCl_3$/$CDCl_3$) and will hydrolyse.

4.3 Experimental data

3,4-Dihydronaphthalen-1(2*H*)-one oxime (2-45):

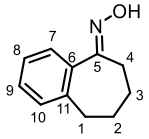


3,4-Dihydronaphthalen-1(2*H*)-one oxime synthesised according to the literature.[106]

α-Tetralone (0.91 mL, 6.84 mmol) and hydroxylamine.HCl (989 mg, 14.2 mmol) were suspended in EtOH (35 mL). Pyridine (0.96 mL, 12.0 mmol) was added. The reaction mixture was heated under reflux and stirred for 19 h. The reaction mixture was cooled to room temperature and the volatiles removed under reduced pressure. Purification via flash column chromatography eluting with EtOAc:PE (1:9 – 1:4) afforded the title compound (1.13 g, quant.) as a colourless solid. $\mathbf{R_f}$ = 0.76 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.85 (s, br, 1H, OH), 7.89 (dd, *J* = 7.7, 1.2, 1H, ArH), 7.58 (td, *J* = 7.5, 1.5, 1H, ArH), 7.22 (td, *J* = 7.7, 1.5, 1H, ArH), 7.17-7.15 (m, 1H, ArH), 2.86-2.83 (m, 2H, H3), 2.79-2.76 (m, 2H, H1), 1.93-1.86 (m, 2H, H2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 155.6 (C4), 139.9 (Ar), 130.7 (Ar), 129.3 (ArH), 128.8 (ArH), 126.6 (ArH), 124.1 (ArH), 30.0 (C1), 23.9 (C3), 21.5 (C2).

Data in accordance with the literature.[107]

6,7,8,9-Tetrahydro-5*H*-benzo-[7]annulen-5-one oxime (2-46):

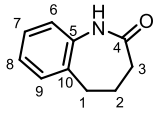


6,7,8,9-Tetrahydro-5*H*-benzo[7]-annulen-5-one oxime synthesised according to the literature.[106]

1-Benzosuberone (0.93 mL, 6.24 mmol) and hydroxylamine.HCl (934 mg, 13.5 mmol) were suspended in EtOH (33 mL). Pyridine (0.88 mL, 10.9 mmol) was added. The reaction mixture was heated under reflux and stirred for 18 h. The reaction mixture was cooled to room temperature and the volatiles removed under reduced pressure. Purification via flash column chromatography eluting with EtOAc:PE (1:9 – 1:4) afforded the title compound (1.06 g, 97%) as a colourless solid. $\mathbf{R_f}$ = 0.48 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.06 (s, br, 1H, OH), 7.39 (dd, *J* = 7.4, 1.4, 1H, ArH), 7.30 (td, *J* = 7.4, 1.6, 1H, ArH), 7.23 (td, *J* = 7.4, 1.4, 1H, ArH), 7.13 (dd, *J* = 7.4, 0.9, 1H, ArH), 2.77-2.72 (m, 4H, H1/4), 1.78 (quint., *J* = 6.5, 2H, H3), 1.68-1.62 (m, 2H, H2).

Data in accordance with the literature.[147]

1,3,4,5-Tetrahydro-2*H*-benzo[*b*]azepine-2-one (2-47):

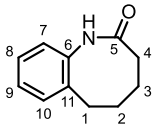


1,3,4,5-Tetrahydro-2*H*-benzo[*b*]azepine-2-one synthesised according to the literature.[107]

Polyphosphoric acid (3.71 g, 11.0 mmol) was heated to 115 °C to decrease the viscosity. 3,4-Dihydronaphthalen-1(2*H*)-one oxime (1.13 g, 7.02 mmol) was added in one portion. The reaction mixture was heated to 120 °C and stirred for 10 min. The reaction mixture was cooled and ice was added to the stirred mixture. The reaction mixture was stirred for 16 h at room temperature where a precipitate formed. The reaction mixture was diluted with DCM (20 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to afford the title compound (776 mg, 69%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.53 (s, 1H, NH), 7.32-7.26 (m, 2H, ArH), 7.18 (td, *J* = 7.5, 1.5, 1H, ArH), 7.07 (d, br, *J* = 8.0, 1H, ArH), 2.86 (t, *J* = 7.0, 2H, H4), 2.42 (t, *J* = 7.0, 2H, H2), 2.33-2.25 (m, 2H, H3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 175.7 (C1), 138.1 (Ar), 134.4 (Ar), 129.9 (ArH), 127.6 (ArH), 125.7 (ArH), 122.0 (ArH), 32.9 (C2), 30.5 (C4), 28.7 (C3).

Data in accordance with the literature.[107]

3,4,5,6-Tetrahydrobenzo[*b*]azocin-2(1*H*)-one (2-48):

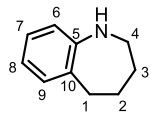


3,4,5,6-Tetrahydrobenzo[*b*]azocin-2(1*H*)-one synthesised in accordance with the literature.[107]

Polyphosphoric acid (3.90 g, 11.6 mmol) was heated to 115 °C to decrease the viscosity. 6,7,8,9-Tetrahydro-5*H*-benzo[7]annulen-5-one oxime (1.06 g, 6.07 mmol) was added in one portion. The reaction mixture was heated to 130 °C and stirred for 10 min. The reaction mixture was cooled and ice was added to the stirred mixture. The reaction mixture was stirred for 16 h at room temperature where a precipitate formed. The reaction mixture was diluted with DCM (20 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to afford the title compound (773 mg, 73%) as a brown solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.40 (s, 1H, NH), 7.26-7.15 (m, 3H, ArH), 7.08-7.06 (m, 1H, ArH), 2.87-1.41 (m, br, 8H, H2/3/4/5). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 177.3 (C1), 139.9 (Ar), 136.1 (Ar), 131.0 (ArH), 127.9 (ArH), 127.1 (ArH), 125.3 (ArH), 32.6 (C2), 31.3 (C5), 29.7 (C3 or 4), 24.9 (C3 or 4).

Data in accordance with the literature.[148]

2,3,4,5-Tetrahydro-1*H*-benzo[*b*]azepine (2-49):



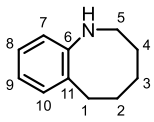
2,3,4,5-Tetrahydro-1*H*-benzo[*b*]azepine synthesised in accordance with the literature.[108]

Under an atmosphere of N_2, lithium aluminium hydride (439 mg, 11.6 mmol) was suspended in anhydrous Et_2O (50 mL). A solution of 1,3,4,5-tetrahydro-2*H*-benzo[*b*]azepin-2-one (600 mg, 3.76 mmol) in anhydrous THF (9 mL) was added dropwise to the suspension. The reaction mixture was heated under reflux and stirred for 19 h. The reaction mixture was cooled to room temperature and quenched by dropwise addition of H_2O (1 mL), then aq. NaOH (2 M, 1 mL) then H_2O (3 mL). The reaction mixture was stirred at room temperature for 1 h where a white precipitate formed. The precipitate was filtered off and washed with Et_2O. The solvent was removed under reduced pressure and the residue dissolved in DCM (20 mL). The organic layer was washed with brine (20 mL). The aqueous layer was extracted into DCM (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 3:7) afforded the title compound (346 mg, 63%) as an orange oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.18 (dd, *J* = 7.5, 1.0, 1H, ArH), 7.10 (td, *J* = 7.5, 1.5, 1H, ArH), 6.90 (td, *J* = 7.2, 1.5, 1H,

ArH), 6.78 (dd, *J* = 7.5, 1.0, 1H, ArH), 3.73 (s, br, 1H, NH), 3.11-3.08 (m, 2H, H1), 2.86-2.83 (m, 2H, H4), 1.90-1.84 (m, 2H, H2), 1.74-1.69 (m, 2H, H3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 150.8 (Ar), 134.0 (Ar), 131.1 (ArH), 126.9 (ArH), 121.1 (ArH), 119.7 (ArH), 49.2 (C1), 36.4 (C4), 32.4 (C2), 27.3 (C3).

Data in accordance with the literature.[108]

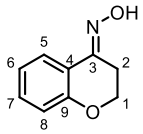
1,2,3,4,5,6-Hexahydrobenzo[*b*]azocine (2-50):



1,2,3,4,5,6-Hexahydrobenzo[*b*]azocine synthesised in accordance with the literature.[108]

Under an atmosphere of N_2, lithium aluminium hydride (389 mg, 10.2 mmol) was suspended in anhydrous Et_2O (48 mL). A solution of 3,4,5,6-tetrahydrobenzo[*b*]azocin-2(1*H*)-one (595 mg, 3.40 mmol) in anhydrous THF (8 mL) was added dropwise to the suspension. The reaction mixture was heated under reflux and stirred for 21 h. The reaction mixture was cooled to room temperature and quenched by dropwise addition of H_2O (1 mL), then aq. NaOH (2 M, 1 mL) then H_2O (3 mL). The reaction mixture was stirred at room temperature for 1 h where a white precipitate formed. The precipitate was filtered off and washed with Et_2O. The solvent was removed under reduced pressure and the residue dissolved in DCM (20 mL). The organic layer was washed with brine (20 mL). The aqueous layer was extracted into DCM (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography eluting with EtOAc:PE (7:13 – 9:11) afforded the title compound (319 mg, 58%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.95 (td, *J* = 7.5, 1.5, 1H, ArH), 6.91 (dd, *J* = 7.5, 1.5, 1H, ArH), 6.78 (td, *J* = 7.5, 1.0, 1H, ArH), 6.74 (dd, *J* = 7.5, 1.0, 1H, ArH), 3.07-3.04 (m, 2H, H1), 2.85 (s, br, 1H, NH), 2.71-2.68 (m, 2H, H5), 1.61-1.55 (m, 2H, H4), 1.42-1.35 (m, 4H, H2/3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 147.8 (Ar), 135.1 (Ar), 130.5 (ArH), 127.3 (ArH), 123.0 (ArH), 122.8 (ArH), 51.5 (C1), 32.1 (C5), 31.4 (C4), 28.8 (C2 or 3), 25.4 (C2 or 3).

Chroman-4-one oxime (2-52):



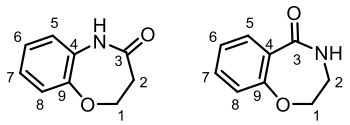
Chroman-4-one oxime synthesised in accordance with the literature.[149]

To a suspension of hydroxylamine.HCl (1.39 g, 20.0 mmol) in EtOH (50 mL) was added a solution of 4-chromanone (1.48 g, 10.0 mmol) in EtOH (10 mL). Na_2CO_3 (1.06 g, 10.0 mmol) was dissolved in H_2O (10 mL) and added dropwise to the reaction mixture. The reaction mixture was heated to 64 °C and stirred for 18 h. The reaction mixture was cooled to room temperature and the volatiles removed

under reduced pressure. H_2O (60 mL) was added to the residue and the solution extracted into Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure affording the title compound (1.13 g, 69%) as a white solid. **^{1}H NMR** (400 MHz; $CDCl_3$): δ_H 7.83 (ddd, *J* = 8.0, 1.5, 0.5, 1H, ArH), 7.78 (s, br, 1H, OH), 7.29-7.24 (m, 1H, ArH), 6.95 (ddd, *J* = 8.0, 7.0, 1.0, 1H, ArH), 6.91 (ddd, *J* = 8.0, 1.0, 0.5, 1H, ArH), 4.25 (t, *J* = 6.0, 2H, H1), 2.99 (t, *J* = 6.0, 2H, H2). **^{13}C NMR** (101 MHz; $CDCl_3$): δ_C 156.8 (C3), 150.2 (Ar), 131.3 (ArH), 124.2 (ArH), 121.6 (ArH), 118.5 (Ar), 117.9 (ArH), 65.1 (C1), 23.6 (C2). **HRMS m/z** (ESI^+): calcd. For. $C_9H_{10}NO_2$ [M+H] Calculated 164.0633. Found 164.0722.

Data in accordance with the literature.[149]

2,3-Dihydrobenzo[*b*][1,4]oxazepin-4-(5*H*)-one (2-53) and 3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one (2-54):



2,3-Dihydrobenzo[*b*][1,4]oxazepin-4-(5*H*)-one and 3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one synthesised in accordance with the literature. [107]

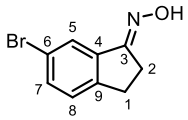
Polyphosphoric acid (3.37 g, 9.97 mmol) was heated to 115 °C to decrease the viscosity. Chroman-4-one oxime (1.03 g, 6.30 mmol) was added in one portion. The reaction mixture was heated to 125 °C and stirred for 10 min. The reaction mixture was cooled and ice was added to the stirred mixture. The reaction mixture was stirred for 16 h at room temperature where a precipitate formed. The reaction mixture was diluted with DCM (20 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography eluting with EtOAc:PE (3:17 – 1:0) afforded the title compounds.

2,3-Dihydrobenzo[*b*][1,4]oxazepin-4-(5*H*)-one (2-53) (13.2 mg, <1%) as a yellow oil. **^{1}H NMR** (400 MHz; $CDCl_3$): δ_H 8.46 (s, br, 1H, NH), 7.08-6.96 (m, 4H, ArH), 4.46 (t, *J* = 5.5, 2H, H1), 2.87 (t, *J* = 5.5, 2H, H2). **^{13}C NMR** (101 MHz; $CDCl_3$): δ_C 173.2 (C3), 148.8 (Ar), 129.1 (Ar), 125.6 (ArH), 123.9 (ArH), 122.3 (ArH), 121.9 (ArH), 69.0 (C1), 37.2 (C2).

3,4-Dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one (2-54) (82 mg, 8%) as orange solid. **^{1}H NMR** (400 MHz; $CDCl_3$): δ_H 7.94 (dd, *J* = 7.9, 1.8, 1H, ArH), 7.86 (s, br, 1H, NH), 7.41 (ddd, *J* = 8.2, 7.2, 1.8, 1H, ArH), 7.12 (ddd, *J* = 7.9, 7.2, 1.2, 1H, ArH), 7.01 (dd, *J* = 8.2, 1.2, 1H, ArH), 4.45-4.35 (m, 2H, H1), 3.48 (td, *J* = 5.5, 4.2, 2H, H2). **^{13}C NMR** (101 MHz; $CDCl_3$): δ_C 170.6 (C3), 155.2 (Ar), 133.2 (ArH), 131.6 (ArH), 123.7 (Ar), 122.6 (ArH), 121.1 (ArH), 73.0 (C1), 41.2 (C2).

Data in accordance with the literature.[150,151]

(*E*)-6-Bromo-2,3-dihydro-1*H*-inden-1-one oxime (2-59):

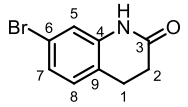


(*E*)-6-Bromo-2,3-dihydro-1*H*-inden-1-one oxime synthesised in accordance with the literature.[152]

To a solution of indanone (1.61 g, 7.63 mmol) in MeOH (30mL) was added hydroxylamine.HCl (760 mg, 10.9 mmol) and aq. KOH (8.9 M, 2.5 mL). The reaction mixture was heated under reflux and stirred for 3 h. The reaction mixture was cooled to room temperature and acidified to pH 1 with aq. HCl (1 M) where a precipitate formed. The precipitate was filtered and washed with H_2O affording the title compound (1.41 g, 82%) as a brown solid. **^{1}H NMR** (400 MHz, DMSO-d_6): δ_H 11.07 (s, 1H, OH), 7.63 (d, *J* = 1.5, 1H, ArH), 7.49 (dd, *J* = 8.1, 1.5, 1H, ArH), 7.33 (d, br, *J* = 8.1, 1H, ArH), 2.98-2.93 (m, 2H, H1 or 2), 2.81-2.74 (m, 2H, H1 or 2).

Data in accordance with the literature.[152]

7-Bromo-3,4-dihydroquinolin-2-(1*H*)-one (2-60):

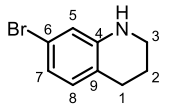


7-Bromo-3,4-dihydroquinolin-2-(1*H*)-one synthesised in accordance with the literature.[111]

Under an atmosphere of N_2, (*E*)-6-bromo-2,3-dihydro-1*H*-inden-1-one oxime (1.00 g, 4.44 mmol) and triethylamine (0.41 mL, 5.33 mmol) were dissolved in anhydrous DCM (13.5 mL) and cooled to -15 °C. Methanesulfonyl chloride (1.24 mL, 8.88 mmol) was added dropwise whilst maintaining -15 °C. The reaction mixture was stirred for 3 h at -15 °C. The reaction mixture was warmed to room temperature and diluted with DCM (30 mL), washed with ice cold aq. HCl (1 M, 30 mL) and sat. aq. $NaHCO_3$ (30 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography eluting with EtOAc:PE (0:1 – 2:3) afforded the title compound (886 mg, 89%) as a beige solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.93 (dd, *J* = 1.9, 0.6, 1H, ArH), 7.57 (dd, *J* = 1.9, 8.2, 1H, ArH), 7.27-7.24 (m, 1H, ArH), 3.13-3.03 (m, 4H, H1/2).

Data in accordance with the literature.[111]

7-Bromo-1,2,3,4-tetrahydroquinoline (2-61):

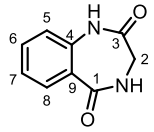


7-Bromo-1,2,3,4-tetrahydroquinoline synthesised in accordance with the literature.[111]

Under an atmosphere of N_2, lithium aluminium hydride (139 mg, 3.67 mmol) was suspended in anhydrous THF (6 mL). 7-Bromo-3,4-dihydroquinolin-2-(1*H*)-one (550 mg, 2.45 mmol) dissolved in anhydrous THF (5 mL) was added dropwise to the suspension. The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was cooled to 0 °C and quenched with sat. aq. $NaHCO_3$ (15 mL). The precipitate was filtered and the aqueous layer extracted into EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography eluting with EtOAc:PE (0:1 – 1:0) afforded the title compound (47 mg, 9%) as a brown solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.78 (dt, *J* = 8.0, 1.1, 1H, ArH), 6.68 (dd, *J* = 8.0, 2.0, 1H, ArH), 6.59 (d, *J* = 2.0, 1H, ArH), 3.35-3.24 (m, 2H, H1), 2.69 (t, *J* = 6.4, 2H, H1), 1.96-1.85 (m, 2H, H2).

Data in accordance with the literature.[111]

3,4-Dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (2-63):

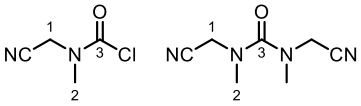


3,4-Dihydro-1*H*-[*e*][1,4]diazepine-2,5-dione synthesised in accordance with literature.[112]

To a solution of glycine (1.00 g, 13.3 mmol) in H_2O (13 mL) was added isatoic anhydride (2.18 g, 13.3 mmol) portion wise whilst stirring. The pH of the reaction mixture was adjusted to pH >8 by addition of aq. NaOH (6 M). The reaction was heated under reflux and stirred for 19 h. The reaction mixture was cooled to room temperature. A suspension of L-tartaric acid (5.00 g, 33.3 mmol) in H_2O (15.2 mL) was added to the reaction mixture. The reaction mixture was heated under reflux and stirred for 1 h. The reaction mixture was cooled to room temperature. Aq. NH_3 was added to the reaction mixture until pH 9 was reached. The reaction mixture was filtered under vacuum filtration and washed with ice cold H_2O to afford the title compound (1.37 mg, 59%) as a brown solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 10.33 (s, 1H, NH), 8.52 (t, *J* = 6.0, 1H, NH), 7.75 (dd, *J* = 7.7, 1.0, 1H, ArH), 7.50 (td, *J* = 7.9, 1.3, 1H, ArH), 7.21 (t, *J* = 7.7, 1H, ArH), 7.11 (d, *J* = 7.9, 1H, ArH), 3.59 (d, *J* = 6.0, 2H, H2). **^{13}C NMR** (101 MHz; $CDCl_3$): δ_C 171.1 (CO), 168.0 (CO), 137.1 (Ar), 132.2 (ArH), 130.8 (ArH), 135.5 (Ar), 123.8 (ArH), 120.9 (ArH), 44.5 (C2).

Data in accordance with the literature.[112]

(Cyanomethyl)(methyl)carbamic chloride (2-75) and 1,3-bis(cyanomethyl)-1,3-dimethylurea:

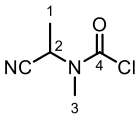


According to **GP1**, triphosgene (1.28 g, 4.32 mmol), anhydrous pyridine (1.51 mL, 9.39 mmol) and 2-(methylamino)acetonitrile.HCl (569 mg, 5.34 mmol) were stirred at 0 °C for 2 h affording the crude title products (523 mg) as an orange oil in a 1:1 mixture.

(Cyanomethyl)(methyl)carbamic chloride (2-75): (261 mg, 37%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.43 (s, 2H, H1), 3.15 (s, 3H, H2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 148.9 (C3), 114.2 (CN), 41.3 (C1), 37.4 (C2).

1,3-Bis(cyanomethyl)-1,3-dimethylurea: (261 mg, 30%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.32 (s, 4H, H1), 3.26 (s, 6H, H2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 151.0 (C3), 114.2 (CN), 38.8 (C2), 38.5 (C1).

(1-Cyanoethyl)(methyl)carbamic chloride (2-76):

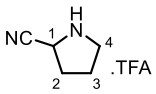


DL-Lactonitrile (1.00 mL, 14.1 mmol) and excess $MgSO_4$ were cooled to 0 °C. Methylamine (5.20 mL, 42.2 mmol, 33 wt% in EtOH), was added and the reaction mixture was stirred for 19 h whilst warming to room temperature. The reaction mixture was filtered and the volatiles removed under reduced pressure to afford the crude 2-(methylamino)propanenitrile (745 mg, 63%) as a yellow oil.

Data in accordance with the literature.[115]

According to **GP1**, triphosgene (1.01 g, 3.40 mmol), anhydrous pyridine (0.63 mL, 7.82 mmol) and 2-(methylamino)propanenitrile (658 mg, 7.82 mmol) afforded the crude title product (765 mg, 42% over 2 steps) as an orange oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.33 (q, *J* = 7.2, 1H, H2), 3.20 (s, 3H, H3), 1.56 (d, *J* = 7.2, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 150.0 (C4), 116.5 (CN), 44.3 (C2), 33.9 (C3), 17.0 (C1).

Pyrrolidine-2-carbonitrile.TFA (2-69):



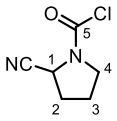
Pyrrolidine-2-carbonitrile.TFA synthesised in accordance with the literature.[98]

Under an atmosphere of N_2, 1-*tert*-butoxycarbonyl-2-cyanopyrrolidine (5.00 g, 25.5 mmol) was dissolved in anhydrous DCM (100 mL) and cooled to 0 °C. Trifluoroacetic acid (30.0 mL, 44.7 mmol) was added. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was warmed to room temperature and the volatiles removed under reduced pressure. The residue was suspended in toluene (3 x 50 mL) and the solvent removed under reduced pressure. The crude product was

recrystallised from Et_2O, affording pyrrolidine-2-carbonitrile.TFA (2.70 g, 50%) as a colourless solid. **^{1}H NMR** (400 MHz, DMSO-d_6): δ_H 9.85 (s, br, 1H, NH), 4.70 (t, *J* = 7.4, 1H, H1), 3.34-3.18 (m, 2H, H4), 2.34 (dtd, *J* = 13.5, 7.8, 5.7, 1H, H2a or 3a), 2.20-2.09 (m, 1H, H2b or 3b), 2.08-1.84 (m, 2H, H2 or 3).

Data in accordance with the literature.[98]

2-Cyanopyrrolidine-1-carbonyl chloride (2-77):

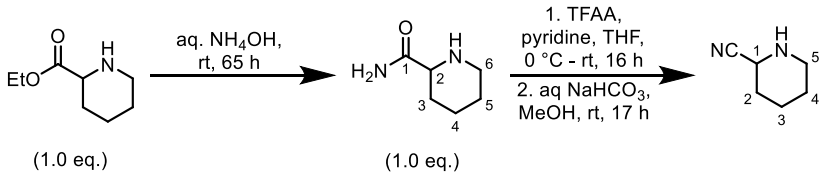


2-Cyanopyrrolidine-1-carbonyl chloride synthesised in accordance with the literature.[98]

Under an atmosphere of N_2 triphosgene (1.13 g, 3.81 mmol) was dissolved in anhydrous DCM (20 mL) and cooled to -78 °C. 2,6-lutidine (1.32 mL, 11.4 mmol) was added dropwise whilst maintaining -78 °C. The reaction mixture was stirred at -78 °C for 10 min. Pyrrolidine-2-carbonitrile.TFA (2.00 g, 9.52 mmol) was suspended in DCM (4 mL) and 2,6-lutidine (1.10 mL, 9.52 mmol) was added and stirred at room temperature for 10 min. The pyrrolidine-2-carbonitrile solution was added dropwise to the triphosgene solution dropwise whilst maintaining -78 °C. The reaction mixture was stirred for 17 h whilst warming to room temperature. The reaction mixture was cooled to 0 °C and quenched with aq. HCl (1 M). The reaction mixture was warmed to room temperature, diluted with DCM (30 mL) and washed with aq. HCl (1 M, 2 x 30 mL). The combined aqueous layers were extracted into DCM (2 x 30 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (15 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to afford the crude title compound (1.49 g, 99%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$)(Mixture of rotamers A:B 0.57:0.43): δ_H 4.78 (dd, *J* = 7.1, 2.6, 0.57H, H1, rot. A), 4.61 (dd, *J* = 7.5, 3.2, 0.43 H, H1, rot. B), 3.92-3.38 (m, 2H, H4 rot. A+B), 2.40-2.07 (m, 4H, H2/3, rot. A+B).

Data in accordance with the literature.[98]

Piperidine-2-carbonitrile (2-72):



Piperidine-2-carbonitrile synthesised according to the literature.[113]

2-Carboxymethyl piperidine.HCl (4.09 g, 22.8 mmol) was dissolved in aq. ammonia (54 mL). The reaction mixture was stirred at room temperature for 65 h. The volatiles were removed under reduced pressure to afford the crude amide. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.72 (s, br, 1H, NH), 7.93 (s, 1H, NH),

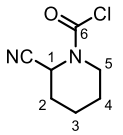
7.53 (s, 1H, NH), 3.66 (dd, J = 11.5, 3.3, 1H, H2), 3.17 (d, br, *J* = 12.5, 1H, H6a), 2.86 (td, *J* = 12.5, 3.6, 1H, H6b), 2.11 (d, br, *J* = 11.5, 1H, H3a), 1.85-1.35 (m, 5H, H3b/4/5).

Under an atmosphere of N_2 the crude amide (3.50 g, 27.3 mmol) was dissolved in anhydrous THF (80 mL) and pyridine (4.40 mL, 54.6 mmol) was added. The reaction mixture was cooled to 0 °C. Trifluoroacetic anhydride (4.24 mL, 30.0 mmol) was added dropwise whilst maintaining 0 °C. The reaction mixture was stirred for 16 h whilst warming to room temperature. The volatiles were removed under reduced pressure. The residue was dissolved in $CHCl_3$ (20 mL) and washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure, affording the crude amide (2.71 g, 77%).

The crude amide was dissolved in MeOH (42 mL) and sat. aq. $NaHCO_3$ (42 mL) was added. The reaction mixture was stirred at room temperature for 17 h. The solvents were removed under reduced pressure. H_2O (30 mL) was added to the residue and extracted into Et_2O (3 x 30 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure, affording the crude piperidine-2-carbonitrile (1.39 g, 35% over 2 steps). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.00 (t, *J* = 4.2, 1H, H1), 3.00 (ddd, *J* = 12.1, 10.2, 3.1, 1H, H5a), 2.89 (dt, *J* = 12.1, 4.2, 1H, H5b), 1.91-1.45 (m, 6H, H2/3/4). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 120.1 (CN), 46.8 (C1), 43.5 (C5), 29.1 (C2), 25.3 (C4), 21.6 (C3).

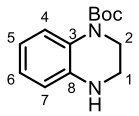
Data in accordance with the literature.[113]

2-Cyanopiperidine-1-carbonyl chloride (2-78):



According to **GP1**, triphosgene (1.80 g, 6.07 mmol), anhydrous pyridine (1.06 mL, 13.2 mmol) and crude piperidine-2-carbonitrile (1.45 g, 13.2 mmol) were stirred for 3 h at 0 °C, affording the crude title product (1.55 g, 68%) as a brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.49-5.46 (m, 1H, H1), 4.36 (ddd, *J* = 13.6, 4.4, 2.3, 1H, H5a), 3.35 (td, *J* = 13.6, 2.7, 1H, H5b), 2.09-1.77 (m, 5H, H2/3/4a), 1.58-1.50 (m, 1H, H4b). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 149.7 (C6), 116.2 (CN), 46.6 (C5), 45.8 (C1), 28.6 (C2), 24.9 (C4), 20.3 (C3).

***tert*-Butyl 3,4-dihydroquinoxaline-1(2*H*)-carboxylate:**

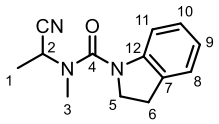


tert-Butyl 3,4,-dihydroquinoxaline-1(2*H*)-carboxylate synthesised in accordance with the literature.[153]

1,2,3,4-tetrahydroquinoxaline (307 mg, 2.29 mmol) was dissolved in THF (2 mL) and H_2O (0.5 mL). NaOH (183 mg, 4.58 mmol) was added in one portion. Di-*tert*-butyl dicarbonate (549 mg, 2.52 mmol) was added portion wise to the stirred mixture. The reaction mixture was stirred at room temperature for 16 h. H_2O (10 mL) was added and the mixture was extracted into DCM (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 7:13) afforded the title product (444 mg, 83%) as a yellow oil. **^{1}H NMR** (400 MHz; $CDCl_3$): δ_H 7.49 (d, *J* = 7.4 Hz, 1H, ArH), 6.91-6.87 (m, 1H, ArH), 6.67-6.63 (m, 1H, ArH), 6.56 (dd, J = 8.0, 1.4 Hz, 1H, ArH), 3.95 (s, 1H, NH), 3.48-3.75 (m, 2H, H1 or 2), 3.42-3.39 (m, 2H, H1 or 2), 1.52 (s, 9H, Boc). **^{13}C NMR** (101 MHz; $CDCl_3$): δ_C 153.5 (CO), 136.9 ArH, 124.9 (Ar), 124.8 (ArH), 124.7 (ArH), 116.8 (ArH), 114.7 (ArH), 81.1 ($C(CH_3)_3$), 42.2 (C1 or 2), 41.6 (C1 or 2), 28.5 (Boc).

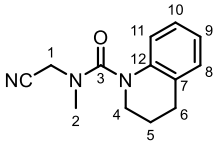
Data in accordance with the literature.[154]

***N*-(1-Cyanoethyl)-*N*-methylindoline-1-carboxamide (2-14):**



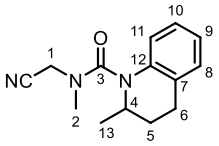
According to **GP2A**, (1-cyanoethyl)(methyl)carbamic chloride (200 mg, 1.37 mmol), indoline (0.17 mL, 1.50 mmol) and triethylamine (0.38 mL, 2.73 mmol) were heated under reflux at 75 °C for 70 h. Purification via flash column chromatography eluting with EtOAc:PE (2:3 – 3:1) afforded the title compound (219 mg, 70%) as a purple oil. $\mathbf{R_f}$ = 0.68 (1:1 EtOAc:PE). **^{1}H NMR** (400 MHz; $CDCl_3$): δ_H 7.21-7.15 (m, 2H, ArH), 7.04-7.01 (m, 1H, ArH), 6.95 (td, *J* = 7.4, 1.0, 1H, ArH), 5.06 (q, *J* = 7.2, 1H, H2), 3.97-3.93 (m, 2H, H5), 3.07 (td, *J* = 8.2, 2.9, 2H, H6), 2.97 (s, 3H, H3), 1.62 (d, *J* = 7.2, 3H, H1). **^{13}C NMR** (101 MHz; $CDCl_3$): δ_C 159.2 (C4), 143.1 (Ar), 131.9 (Ar), 127.4 (ArH), 125.3 (ArH), 122.6 (ArH), 118.8 (CN), 114.0 (ArH), 50.6 (C5), 44.4 (C2), 33.2 (C3), 28.2 (C6), 17.3 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{13}H_6N_3O$ [M+H] Calculated 230.1215. Found 230.1293. **IR υ_{max}** (ATR)/cm^{-1}: 3071, 3051, 2998, 2946, 2897, 2853, 2237, 1650.

***N*-(Cyanomethyl)-*N*-methyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (2-15):**



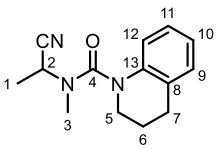
According to **GP2A**, (cyanomethyl)(methyl)carbamic chloride (116 mg, 0.879 mmol), 1,2,3,4-tatrahydroquinoline (0.12 mL, 0.967 mmol) and triethylamine (0.25 mL, 1.76 mmol) were heated under reflux at 75 °C for 44 h. Purification via flash column chromatography eluting with EtOAc:PE (11:9 – 13:7) afforded the title compound (200 mg, 99%) as an orange oil. $\mathbf{R_f}$ = 0.83 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz; $CDCl_3$): δ_H 7.16-7.12 (m, 2H, ArH), 7.01-6.96 (m, 2H, ArH), 4.18 (s, 2H, H1), 3.64 (m, 2H, H4), 2.78-2.74 (m, 2H, H6), 2.76 (s, 3H, H2), 1.99 (quint., *J* = 6.6, 2H, H5). **^{13}C NMR** (101 MHz; $CDCl_3$): δ_C 160.1 (C3), 139.8 (Ar), 129.5 (Ar), 129.2 (ArH), 127.0 (ArH), 123.5 (ArH), 120.5 (ArH), 15.7 (CN), 45.6 (C4), 38.4 (C1), 37.2 (C2), 27.0 (C6), 23.9 (C5). **HRMS m/z** (ESI^+): calcd. for. $C_{13}H_{15}N_3NaO$ [M+Na] Calculated 252.1215. Found 252.1104. **IR υ_{max}** (ATR)/cm^{-1}: 3025, 2919, 2843, 2248, 1656.

***N*-(Cyanomethyl)-*N*,2-dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (2-80):**



According to **GP2A**, (cyanomethyl)(methyl)carbamic chloride (262 mg, 0.879 mmol), 2-methyl-1,2,3,4-tetrahydroquinoline (0.14 mL, 0.967 mmol) and triethylamine (0.25 mL, 1.76 mmol) were heated under reflux at 75 °C for 30 h. Purification via flash column chromatography eluting with EtOAc:Petrol (7:13 – 2:3) afforded the title compound (215 mg, quant.) as a yellow oil. $\mathbf{R_f}$ 0.19 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz; $CDCl_3$): δ_H 7.16-7.13 (m, 2H, ArH), 7.02-6.94 (m, 2H, ArH), 4.34 (quint. d, *J* = 6.6, 4.4, 1H, H4), 4.14 (s, 2H, H1), 2.67 (s, 3H, H2), 2.19 (ddt, *J* = 13.1, 6.2, 4.4, 1H, H5a), 1.64 (dtd, *J* = 13.1, 8.6, 6.6, 1H, H5b), 1.19 (d, *J* = 7.0 Hz, 3H, H13). **^{13}C NMR** (101 MHz; $CDCl_3$): δ_C 159.8 (C3), 138.2 (Ar), 130.0 (Ar), 128.8 (ArH), 127.2 (ArH), 123.5 (ArH), 121.4 (ArH), 115.8 (CN), 50.4 (C4), 38.4 (C1), 37.0 (C2), 30.8 (C5), 24.7 (C6), 19.4 (C13). **HRMS m/z** (ESI^+): calcd. for. $C_{14}H_{17}N_3NaO$ [M+Na] Calculated 266.1372. Found 266.1260. **IR υ_{max}** (ATR)/cm^{-1}: 3080, 2944, 2867, 2248, 1642.

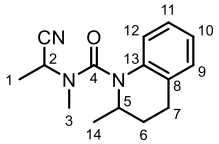
***N*-(1-Cyanoethyl)-*N*-methyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (2-16):**



According to **GP2A**, (1-cyanoethyl)(methyl)carbamic chloride (357 mg, 2.44 mmol), 1,2,3,4-tetrahydroquinoline (0.34 mL, 2.68 mmol) and triethylamine (0.68 mL, 4.87 mmol) were heated under

reflux at 75 °C for 42 h. Purification via flash column chromatography eluting with EtOAc:PE (3:10 – 2:3) afforded the title compound (448 mg, 76%) as a brown solid. $\mathbf{R_f}$ = 0.19 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.15-7.11 (m, 2H, ArH), 7.00-6.95 (m, 2H, ArH), 5.21 (q, *J* = 7.3, 1H, H2), 3.67 (ddd, *J* = 12.6, 6.7, 5.9, 1H, H5a), 3.57 (ddd, *J* = 12.6, 6.9, 5.9, 1H, H5b), 2.76 (t, *J* = 6.7, 2H, H7), 2.69 (s, 3H, H3), 2.02-1.95 (m, 2H, H6), 1.54 (d, *J* = 7.3, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.3 (C4), 140.3 (C13), 129.7 (C8), 129.5 (ArH), 127.2 (ArH), 123.6 (ArH), 120.7 (ArH), 119.0 (CN), 46.0 (C5), 44.5 (C2), 330 (C3), 27.3 (C7), 24.2 (C6), 17.5 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{14}H_{18}N_3O$ [M+H] Calculated 244.1444. Found 244.1455. **IR ν_{max}** (ATR)/cm^{-1}: 2995, 2930, 2855, 2239, 1633. **m.p.** 84-88 °C.

***N*-(1-Cyanoethyl)-*N*,2-dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (2-17):**



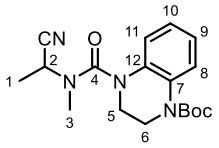
According to **GP2A**, (1-cyanoethyl)(methyl)carbamic chloride (181 mg, 1.24 mmol), 2-methyl-1,2,3,4-tetrahydroquinoline (0.20 mL, 1.36 mmol) and triethylamine (0.34 mL, 2.47 mmol) were heated under reflux at 75 °C for 41 h. Purification via flash column chromatography eluting with EtOAc:PE (7:13 – 2:3) afforded the title compound (212 mg, 67%) as a mixture of 2 diastereoisomers as a yellow oil. $\mathbf{R_f}$ = 0.71/0.62 (3:7 EtOAc:PE). **d.r** = 1.0:1.5.

Diastereoisomer 1: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.18-7.11 (m, 2H, ArH), 7.01-6.97 (m, 1H, ArH), 6.93-6.89 (m, 1H, ArH), 5.20 (q, *J* = 7.1, 1H, H2), 4.28 (qd, *J* = 6.5, 4.0, 1H, H5), 2.79-2.64 (m, 2H, H7), 2.58 (s, 3H, H3), 2.24-2.11 (m, 1H, H6a), 1.72-1.61 (m, 1H, H6b), 1.54 (d, *J* = 7.1, 3H, 1H), 1.18 (d, *J* = 6.5, 1H, H14). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 159.5 (C4), 138.4 (Ar), 129.6 (Ar), 128.9 (ArH), 127.0 (ArH), 123.3 (ArH), 121.1 (ArH), 118.5 (CN), 50.3 (C5), 44.1 (C2), 32.8 (C3), 306 (C6), 24.6 (C7), 19.4 (C14), 16.9 (C1). **IR ν_{max}** (ATR)/cm^{-1}: 2953, 2870, 2852, 2263, 1642.

Diastereoisomer 2: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.18-7.11 (m, 2H, ArH), 7.01-6.97 (m, 1H, ArH), 6.93-6.89 (m, 1H, ArH), 5.21 (q, *J* = 7.4, 1H, H2), 4.35 (qd, *J* = 6.5, 4.5, 1H, H5), 2.79-2.64 (m, 2H, H7), 2.62 (s, 3H, H3), 2.24-2.11 (m, 1H, H6a), 1.72-1.61 (m, 1H, H6b), 1.51 (d, *J* = 7.4, 3H, H1), 1.19 (d, *J* = 6.5, 3H, H14). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 158.2 (C4), 138.4 (Ar), 130.0 (Ar), 128.9 (ArH), 127.2 (ArH), 123.4 (ArH), 121.3 (ArH), 118.5 (CN), 50.3 (C5), 44.1 (C2), 32.2 (C3), 30.8 (C6), 24.8 (C7), 19.4 (C14), 17.4 (C1). **IR ν_{max}** (ATR)/cm^{-1}: 3080, 2970, 2870, 2242, 1642.

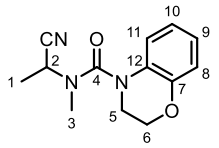
HRMS m/z (ESI^+): calcd. for $C_{15}H_{19}N_3NaO$ [M+Na] Calculated 280.1528. Found 280.1420.

***tert*-Butyl 4-((1-cyanoethyl)(methyl)carbamoyl)-3,4-dihydroquinoxaline-1(2*H*)-carboxylate (2-81):**



According to **GP2A**, (1-cyanoethyl)(methyl)carbamic chloride (59.0 mg, 0.400 mmol), *tert*-butyl-3,4-dihydroquinoxaline-1(2*H*)-carboxylate (103 mg, 0.555 mmol) and triethylamine (0.11 mL, 0.800 mmol) were heated under reflux at 75 °C for 27 h. Purification via flash column chromatography eluting with EtOAc:PE (2:3 – 9:11) afforded the title compound (108 mg, 78%) as a yellow oil. $\mathbf{R_f}$ = 0.20 (1:3 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.87 (d, br, *J* = 8.1, 1H, ArH), 7.06 (td, *J* = 8.1, 1.8, 1H, ArH), 7.01 (td, *J* = 7.7, 1.8, 1H, ArH), 6.93 (dd, *J* = 7.7, 1.7, 1H, ArH), 5.226 (q, *J* = 7.3, 1H, H2), 3.89-3.82 (m, 2H, H6), 3.82-3.77 (m, 1H, H5a), 3.65 (dt, *J* = 12.6, 6.1, 1H, H5b), 2.74 (s, 3H, H3), 1.59-1.53 (m, 12H, H1/Boc-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 158.6 (C4), 153.3 (Boc-CO), 133.4 (Ar), 131.0 (Ar), 124.4 (ArH), 124.1 (ArH), 124.0 (ArH), 119.6 (ArH), 118.4 (CN), 81.8 (Boc-$C(Me)_3$), 47.4 (C6), 45.4 (C5), 44.2 (C2), 33.1 (C3), 28.5 (Boc-CH_3), 17.2 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{18}H_{24}N_4NaO_3$ [M+Na] Calculated 367.1848. Found 367.1731. **IR ν_{max}** (ATR)/cm^{-1}: 2958, 2923, 2852, 2239, 1706, 1652.

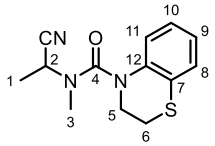
***N*-(1-Cyanoethyl)-*N*-methyl-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxamide (2-18):**



According to **GP2A**, (1-cyanoethyl)(methyl)carbamic chloride (200 mg, 1.37 mmol), 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (0.18 mL, 1.50 mmol) and triethylamine (0.38 mL, 2.73 mmol) were heated under reflux at 75 °C for 70 h. Purification via flash column chromatography eluting with EtOAc:PE (2:3 – 1:0) afforded the title compound (203 mg, 61%) as a brown solid. $\mathbf{R_f}$ 0.56 (1:1 EtOAc:PE). **^{1}H NMR** (400 MHz; $CDCl_3$): δ_H 7.02-6.84 (m, 4H, ArH), 5.19 (q, *J* = 7.3, 1H, H2), 4.39-4.29 (m, 2H, H6), 3.80 (ddd, *J* = 13.3, 5.4, 3.2, 1H, H5a), 3.66 (ddd, *J* = 13.3, 6.6, 3.4, 1H, H5b), 2.89 (s, 3H, H3), 1.60 (d, *J* = 7.3, 3H, H1). **^{13}C NMR** (101 MHz; $CDCl_3$): δ_C 158.4 (C4), 145.2 (Ar), 126.9 (Ar), 124.4 (ArH), 121.0 (ArH), 119.9 (ArH), 118.5 (CN), 117.7 (ArH), 66.5 (C6), 44.4 (C2), 43.5 (C5), 33.1 (C3), 17.7 (C1). **m.p.** 89-93 °C. **IR υ_{max}** (ATR)/cm^{-1}: 2998, 2970, 2938, 2889, 2841, 2232, 1651.

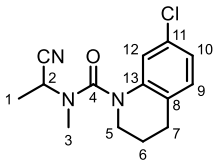
Data is in accordance with the literature.[115]

***N*-(1-Cyanoethyl)-*N*-methyl-2,3-dihydro-4*H*-benzo[*b*][1,4]thiazine-4-carboxamide (2-82):**



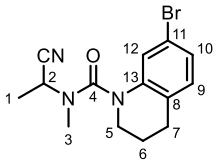
According to **GP2A**, (1-cyanoethyl)(methyl)carbamic chloride (110 mg, 0.751 mmol), 3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine (125 mg, 0.827 mmol) and triethylamine (0.21 mL, 1.50 mmol) were heated under reflux at 75 °C for 40 h. Purification via flash column chromatography eluting with EtOAc:PE (0:1 – 1:0) afforded the title compound (189 mg, 96%) as a yellow oil. $\mathbf{R_f}$ = 0.34 (3:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.26-7.24 (m, 1H, ArH), 7.11-7.00 (m, 2H, ArH), 6.94 (ddd, *J* = 8.0, 1.5, 0.5, 1H, ArH), 5.18 (q, *J* = 7.2, 1H, H2), 4.02 (ddd, *J* = 13.2, 6.4, 5.3, 1H, H6a), 3.81 (ddd, *J* = 13.2, 7.0, 5.3, 1H, H6b), 3.27-3.17 (m, 2H, H5), 2.58 (s, 3H, H3), 1.52 (d, *J* = 7.2, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 159.5 (C4), 140.0 (Ar), 128.5 (ArH), 127.9 (Ar), 126.1 (ArH), 125.2 (ArH), 122.6 (ArH), 118.8 (CN), 44.8 (C6), 44.4 (C2), 33.1 (C3), 30.9 (C5), 17.5 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{13}H_{15}N_3NaOS$ [M+Na] Calculated 284.0936. Found 284.0829. **IR ν_{max}** (ATR)/cm^{-1}: 2979, 2928, 2852, 2242, 1642.

7-Chloro-*N*-(1-cyanoethyl)-*N*-methyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (2-21):



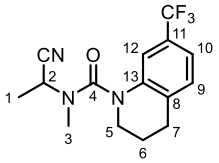
According to **GP2A**, (1-cyanoethyl)(methyl)carbamic chloride (131 mg, 0.894 mmol), 7-chloro-1,2,3,4-tetrahydroquinoline (150 mg, 0.895 mmol) and triethylamine (0.25 mL, 1.82 mmol) were heated under reflux at 75 °C for 63 h. Purification via flash column chromatography eluting with EtOAc:PE (1:3 – 1:0) afforded the title compound (144 mg, 58%) as a pink solid. $\mathbf{R_f}$ = 0.50 (3:7 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.10-6.98 (m, 1H, ArH), 6.98-6.88 (m, 2H, ArH), 5.18 (q, *J* = 7.2, 1H, H2), 3.66 (ddd, *J* = 12.4, 6.9, 5.4, 1H, H5a), 3.53 (ddd, *J* = 12.4, 7.2, 5.3, 1H, H5b), 2.76 (s, 3H, H3), 2.76-2.72 (m, 2H, H7), 2.06-1.88 (m, 2H, H6), 1.57 (d, *J* = 7.2, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 159.8 (C4), 140.8 (Ar), 132.2 (Ar). 130.4 (ArH), 127.0 (Ar), 123.1 (ArH), 120.2 (ArH), 118.5 (CN). 45.8 (C5), 44.2 (C2), 32.8 (C3), 26.6 (C7), 23.4 (C6), 17.2 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{14}H_{17}ClN_3O$ [M+H] Calculated 278.1055. Found 278.1058. **IR ν_{max}** (ATR)/cm^{-1}: 2972, 2919, 2843, 2236, 1649. **m.p** 119-122 °C.

7-Bromo-*N*-(1-cyanoethyl)-*N*-methyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (2-83):



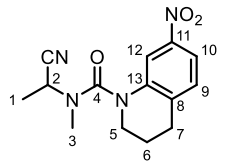
According to **GP2A**, (1-cyanoethyl)(methyl)carbamic chloride (23.0 mg, 0.156 mmol), 7-bromo-1,2,3,4-tetrahydroquinoline (33.0 mg, 0.156 mmol) and triethylamine (0.03 mL, 0.212 mmol) were heated under reflux at 75 °C for 42 h. Purification via flash column chromatography eluting with EtOAc:PE (1:3 – 1:0) afforded the title compound (44 mg, 88%) as a brown oil. $\mathbf{R_f}$ = 0.52 (1:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.11-7.06 (m, 2H, ArH), 6.98 (d, *J* = 8.1, 1H, ArH), 5.17 (q, *J* = 7.3, 1H, H2), 3.66 (ddd, *J* = 12.4, 6.8, 5.5, 1H, H5a), 3.52 (ddd, *J* = 12.4, 7.2, 5.3, 1H, H5b), 2.75 (s, 3H, H3), 2.72 (td, *J* = 6.8, 2.4, 2H, H7), 2.01-1.90 (m, 2H, H6), 1.57 (d, *J* = 7.3, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 159.8 (C4), 141.0 (Ar), 130.7 (ArH), 127.5 (Ar), 125.9 (ArH), 123.1 (ArH), 119.9 (Ar), 118.4 (CN), 45.8 (C5), 44.2 (C2), 32.8 (C3), 26.6 (C7), 23.3 (C6), 17.2 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{14}H_{17}BrN_3O$ [M+H] Calculated 322.0550. Found 322.0556. **IR ν_{max}** (ATR)/cm^{-1}: 2975, 2921, 2850, 2238, 1645.

***N*-(1-Cyanoethyl)-*N*-methyl-7-(trifluoromethyl)-3,4-dihydroquinoline-1(2*H*)-carboxamide (2-84):**



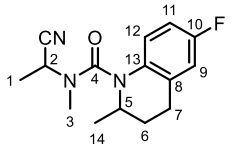
According to **GP2A**, (1-cyanoethyl)(methyl)carbamic acid (70 mg, 0.478 mmol), 7-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline (108 mg, 0.537 mmol) and triethylamine (0.13 mL, 0.904 mmol) were heated under reflux at 75 °C for 70 h. Purification via flash column chromatography eluting with EtOAc:PE (2:3 – 3:1) afforded the title compound (119 mg, 80%) as a yellow oil. $\mathbf{R_f}$ = 0.63 (1:1 EtOAc:PE). **^{1}H NMR** (500 MHz; $CDCl_3$): δ_H 7.24-7.19 (m, 3H, ArH), 5.22 (q, *J* = 7.3 Hz, 1H, H2), 3.73 (ddd, *J* = 12.4, 6.9, 5.3, 1H, H5), 3.56 (ddd, *J* = 12.4, 7.5, 5.0, 1H, H5), 2.83 (q, *J* = 6.4, 2H, H7), 2.72 (s, 3H, H3), 2.09-1.94 (m, 2H, H6), 1.57 (d, *J* = 7.3, 3H, H1). **^{13}C NMR** (125 MHz; $CDCl_3$): δ_C 159.8 (C4), 140.1 (Ar), 132.4 (Ar), 129.9 (C9), 129.3 (q, *J* = 32.5, C11), 124.0 (q, *J* = 272.1, CF_3), 119.35 (C10 or 12, *J* = 3.8), 118.4 (CN), 117.0 (C10 or 12, q, *J* = 3.8), 45.8 (C5), 44.1 (C2), 32.8 (C3), 27.1 (C7), 23.2 (C6), 17.1 (C1). **^{19}F NMR** (376 MHz; $CDCl_3$): δ_F -62.7 (s, 3F, CF_3. **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{17}F_3N_3O$ [M+H] Calculated 312.1245. Found 312.1322. **IR υ_{max}** (ATR)/cm^{-1}: 2998, 2949, 2882, 2847, 2246, 1652.

***N*-(1-Cyanoethyl)-*N*-methyl-7-nitro-3,4-dihydroquinoline-1(2*H*)-carboxamide (2-85):**



According to **GP2A**, (1-cyanoethyl)(methyl)carbamic chloride (200 mg, 1.37 mmol), 7-nitro-1,2,3,4-tetrahydroquinoline (268 mg, 1.50 mmol) and triethylamine (0.38 mL, 2.73 mmol) were heated under reflux at 75 °C for 87 h. Purification via flash column chromatography eluting with EtOAc:PE (1:9 – 1:0) afforded the title compound (393 mg, quant.) as an orange solid. $\mathbf{R_f}$ = 0.38 (1:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.85 (d, *J* = 2.3, 1H, ArH), 7.78 (dd, *J* = 8.4, 2.3, 1H, ArH), 7.26 (d, *J* = 8.4, 1H, ArH), 5.23 (q, *J* = 7.3, 1H, H2), 3.74 (ddd, *J* = 12.3, 6.8, 5.0, 1H, H5a), 3.56 (ddd, *J* = 12.3, 7.6, 4.7, 1H, H5b), 2.93-2.86 (m, 2H, H7), 2.81 (s, 3H, H3), 2.12-1.94 (m, 2H, H6), 1.62 (d, *J* = 7.3, 3H, H1). **^{13}C NMR** (101 MHz; $CDCl_3$): δ_C 159.8 (C4), 147.0 (Ar), 104.5 (Ar), 135.2 (Ar), 130.2 (ArH), 118.3 (CN), 117.3 (ArH), 115.0 (ArH), 46.0 (C5), 44.2 (C2), 32.9 (C3), 27.3 (C7), 22.6 (C6), 17.2 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{14}H_{16}N_4O$ [M+H] Calculated 289.1295. Found 289.1296. **IR ν_{max}** (ATR)/cm^{-1}: 2996, 2923, 2838, 2238, 1664.

***N*-(1-Cyanoethyl)-6-fluoro-*N*,2-dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (2-86):**



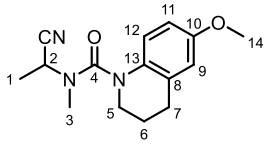
According to **GP2A**, (1-cyanoethyl)(methyl)carbamic chloride (100 mg, 0.682 mmol), 6-fluoro-2-methyl-1,2,3,4-tatrahydroquinoline (124 mg, 0.750 mmol) and triethylamine (0.19 mL, 1.36 mmol) were heated under reflux at 75 °C for 40 h. Purification via flash column chromatography eluting with EtOAc:PE (2:3 – 7:3) afforded the title compound as a mixture of 2 diastereomers (129 mg, 69%) as a yellow oil. **R** = 0.63/0.56 (1:1 EtOAc:PE). **d.r** =1.0:1.0.

Diastereoisomer 1: ^{1}H NMR (400 MHz; $CDCl_3$): δ_H 6.91-6.82 (m, 3H, ArH), 5.16 (q, *J* = 7.0, 1H, H2), 4.33 (qt, *J* = 7.2, 3.2, 1H, H5), 2.77-2.69 (m, 1H, H7a), 2.67-2.59 (m, 1H, H7b), 2.57 (s, 3H, H3), 2.21 (ddt, *J* = 13.3, 8.1, 6.5, 1H, H6a), 1.64-1.57 (m, 1H, H6b), 1.50 (d, *J* = 7.2, 3H, H14), 1.17 (d, *J* = 7.0, 3H, H1). **13C NMR (101 MHz; $CDCl_3$): δ_C** 159.9 (C4), 158.8 (d, *J* = 242.5, C10), 134.3 (d, *J* = 3.0, C13), 132.4 (d, *J* = 7.5, C8), 122.7 (d, *J* = 8.0, C12), 118.8 (CN), 115.2 (d, *J* = 22.5, C9), 113.8 (d, *J* = 23.0, C11), 50.2 (C5), 44.1 (C2), 32.7 (C3), 30.4 (C6), 24.8 (d, *J* = 1.5, C7), 19.2 (C1), 17.3 (C14). **^{19}F NMR** (376 MHz; $CDCl_3$): δ_F – 119.5-119.7 (m, 1F, ArF). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{18}FN_3NaO$ [M+Na] Calculated 298.1434. Found 298.1334.

Diastereoisomer 2: **^{1}H NMR** (400 MHz; $CDCl_3$): δ_H 6.88-6.86 (m, 3H, ArH), 5.16 (q, *J* = 6.8 Hz, 1H, H2), 4.31-4.24 (m, 1H, H5), 2.77-2.70 (m, 1H, H7a), 2.67-2.63 (m, 1H, H7b), 2.60 (s, 3H, H3), 2.22-2.13 (m, 1H, H6a), 1.69-1.59 (m, 1H, H6b), 1.54 (d, *J* = 7.1 Hz, 3H, H14), 1.17 (d, *J* = 6.8 Hz, 3H, H1). **^{13}C NMR** (101 MHz; $CDCl_3$): δ_C 159.5 (C4), 158.9 (d, *J* = 243.5, C10), 134.3 (d, *J* = 3.0, C13), 131.9 (d, *J* = 7.0, C8), 122.8 (d, *J* = 8.0, C12), 118.4 (CN), 115.3 (d, *J* = 22.5, C9), 114.0 (d, *J* = 23.0, C11), 50.3 (C5), 44.2 (C2), 32.2 (C3), 30.5 (C6), 24.9 (d, *J* = 1.0 Hz, C7), 19.3 (C1), 16.9 (C14). **^{19}F NMR** (376 MHz; $CDCl_3$): δ_F – 119.5-119.6 (m, 1F, ArF). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{18}FN_3NaO$ [M+Na] Calculated 298.1434. Found 298.1339.

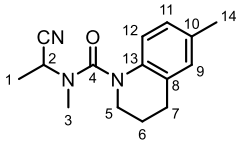
IR υ_{max} (ATR)/cm^{-1}: 3070, 2956, 2876, 2239, 1643.

***N*-(1-Cyanoethyl)-6-methoxy-*N*-methyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (2-19):**



According to **GP2A**, (1-cyanoethyl)(methyl)carbamic chloride (200 mg, 1.37 mmol), 6-methoxy-1,2,3,4-tetrahydroquinoline (245 mg, 1.50 mmol) and triethylamine (0.38 mL, 2.73 mmol) were heated under reflux at 75 °C for 40 h. Purification via flash column chromatography eluting with EtOAc:PE (3:7 – 1:0) afforded the title compound (332 mg, 89%) as a purple solid. R_f = 0.25 (3:1EtOAc:PE). **^{1}H NMR** (400 MHz; $CDCl_3$): δ_H 6.92 (d, *J* = 8.5, 1H, ArH), 6.72-6.68 (m, 2H, ArH), 5.17 (q, *J* = 7.0, 1H, H2), 3.78 (s, 3H, H14), 3.66 (dt, *J* = 12.5, 6.8, 1H, H5), 3.55 (dt, *J* = 12.5, 6.8, 1H, H7a), 2.73 (t, *J* = 6.8, 2H, H7b), 2.66 (s, 3H, H3), 1.95 (dquint., *J* = 13.5, 6.8, 2H, H6), 1.53 (d, *J* = 7.3, 3H, H1). **^{13}C NMR** (101 MHz; $CDCl_3$): δ_C 160.1 (C4), 155.8 (C10), 133.2 (Ar), 131.2 (Ar), 121.8 (ArH), 118.8 (CN), 114.0 (ArH), 112.06 (ArH), 55.6 (C14), 45.5 (C5), 44.2 (C2), 32.7 (C3), 27.3 (C7). 24.0 (C6), 17.2 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{19}N_2O_2$ [M+H] Calculated 274.1550. Found 274.1544. **IR υ_{max}** (ATR)/cm^{-1}: 2998, 2930, 2902, 2833, 2244, 1625. **m.p.** 117-121 °C.

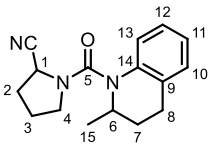
***N*-(1-Cyanoethyl)-*N*,6-dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (2-87):**



According to **GP2A**, (1-cyanoethyl)(methyl)carbamic chloride (200 mg, 1.37 mmol), 6-methyl-1,2,3,4-tetrahydroquinoline (221 mg, 1.50 mmol) and triethylamine (0.38 mL, 2.73 mmol) were heated under reflux at 75 °C for 60 h. Purification via flash column chromatography eluting with EtOAc:PE (1:9 – 3:2) afforded the title compound (343 mg, 98%) as a brown oil. R_f = 0.11 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.95-6.93 (m, 2H, ArH), 6.87-6.85 (m, 1H, ArH), 5.19 (q, *J* = 7.3, 1H, H2), 3.66 (ddd, *J* = 12.6,

6.9, 5.9, 1H, H5a), 3.55 (ddd, *J* = 12.6, 6.8, 6.0, 1H, H5b), 2.71 (t, *J* = 6.7, 2H, H7), 2.67 (s, 3H, H3), 2.28 (s, 3H, H14), 2.02-1.91 (m, 2H, H6), 1.54 (d, *J* = 7.3, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.0 (C4), 137.4 (Ar), 132.9 (Ar), 129.7 (ArH), 129.3 (Ar), 127.6 (ArH), 120.4 (ArH), 118.8 (CN), 45.6 (C5), 44.2 (C2), 32.7 (C3), 26.9 (C7), 24.0 (C6), 20.8 (C14), 17.2 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{20}N_3O$ [M+H] Calculated 258.1601. Found 258.1599. **IR ν_{max}** (ATR)/cm^{-1}: 2979, 2941, 2871, 2236, 1643.

1-(2-Methyl-1,2,3,4-tetrahydroquinoline-1-carbonyl)pyrrolidine-2-carbonitrile (2-88):



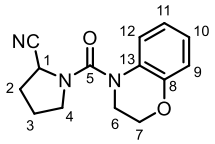
According to **GP2A**, 2-cyanopyrrolidine-1-carbonyl chloride (200 mg, 1.27 mmol), tetrahydroquinaldine (0.22 mL, 1.52 mmol) and triethylamine (0.55 mL, 2.53 mmol) were heated under reflux at 75 °C for 64 h. Purification via flash column chromatography eluting with EtOAc:PE (1:9 – 1:0) afforded the title compound as a mixture of 2 diastereoisomers (221 mg, 65%) as a yellow oil. **R_f** = 0.56/0.50 (1:1 EtOAc:PE). **d.r** = 1.0:1.0.

Diastereoisomer 1: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.18-7.09 (m, 2H, ArH), 7.02-6.94 (m, 1H, ArH), 6.94-6.89 (m, 1H, ArH), 4.60-4.54 (m, 1H, H1), 4.41 (quint. d, *J* = 6.5, 4.2, 1H, H6), 3.05-2.90 (m, 2H, H4), 2.76-2.55 (m, 2H, H8), 2.34-2.00 (m, 4H, H7a/3a/2), 1.97-1.84 (m, 1H, H3b), 1.71-1.55 (m, 1H, H7b), 1.20 (d, *J* = 6.5, 3H, H15). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 157.8 (C5), 138.2 (Ar), 131.6 (Ar), 128.3 (ArH), 126.9 (ArH), 123.2 (ArH), 121.4 (ArH), 119.4 (CN), 50.1 (C6), 48.8 (C4), 47.3 (C1), 31.3 (C7), 30.6 (C2), 25.2 (C3), 24.7 (C8), 20.2 (C15). **IR ν_{max}** (ATR)/cm^{-1}: 2966, 2926, 2245, 1640.

Diastereoisomer 2: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.19-7.11 (m, 2H, ArH), 7.07 (dd, *J* = 8.0, 1.3, 1H, ArH), 7.00 (td, *J* = 7.3, 1.3, 1H, ArH), 4.82 (t, *J* = 7.2, 1H, H1), 4.38 (quint. d, *J* = 6.6, 4.9, 1H,H6), 3.06-2.83 (m, 2H, H4), 2.76-2.54 (m,2H, H8), 2.36-2.19 (m, 2H, H7a/2a), 2.10 (ddt, *J* = 12.8, 8.6, 6.8, 1H, H2b), 1.96-1.85 (m, 1H,H3a), 1.77 (ddtd, *J* = 12.6, 8.6, 7.8, 6.9, 1H, H3b), 1.56 (dddd, *J* = 13.4, 7.4, 6.2, 4.9, 1H, H7b), 1.19 (d, *J* = 6.6, 3H, H15). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 158.1 (C5), 137.8 (Ar), 131.2 (Ar), 128.5 (ArH), 127.0 (ArH), 123.7 (ArH), 122.6 (ArH), 119.5 (CN), 50.0 (C6), 48.9 (C4), 47.5 (C1), 31.3 (C7), 30.7 (C2), 25.1 (C3), 25.0 (C8), 19.6 (C15). **IR ν_{max}** (ATR)/cm^{-1}: 2971, 2922, 2887, 2901, 2244, 1637.

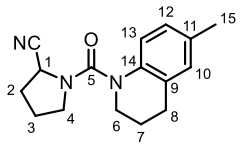
HRMS m/z (ESI^+): calcd. for $C_{16}H_{19}N_3NaO$ [M+Na] Calculated 292.1420. Found 292.1424.

1-(3,4-Dihydro-2*H*-benzo[*b*][1,4]oxazine-4-carbonyl)pyrrolidine-2-carbonitrile (2-89):



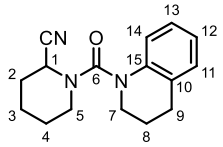
According to **GP2A**, 2-cyanopyrrolidine-1-carbonyl chloride (200 mg, 1.27 mmol), 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (0.19 mL, 1.52 mmol) and triethylamine (0.55 mL, 2.53 mmol) were heated under reflux at 75 °C for 64 h. Purification via flash column chromatography eluting with EtOAc:PE (1:9 – 1:0) afforded the title compound (231 mg, 71%) as a yellow oil. $\mathbf{R_f}$ = 0.37 (1:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.07 (dd, *J* = 8.0, 1.6, 1H, ArH), 6.96 (ddd, *J* = 8.2, 7.1, 1.6, 1H, ArH), 6.90-6.84 (m, 2H, ArH), 4.86-4.83 (m, 1H, H1), 4.42 (ddd, *J* = 10.9, 3.7, 3.1, 1H, H7a), 4.31 (ddd, *J* = 10.9, 9.1, 3.0, 1H, H7b), 4.00 (ddd, *J* = 13.3, 3.7, 3.0, 1H, H6a), 3.56 (ddd, *J* = 13.3, 9.1, 3.1, 1H, H6b), 3.45-3.39 (m, 1H, H4a), 3.30 (ddd, *J* = 10.5, 7.5, 5.6, 1H, H4b), 2.35-2.19 (m, 2H, H2), 2.09 (ddd, *J* = 12.7, 7.0, 5.6, 1H, H3a), 1.98-1.87 (m, 1H, H3b). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 156.6 (C5), 145.6 (Ar), 124.5 (Ar), 120.8 (ArH), 120.5 (ArH), 119.2 (CN), 117.6 (ArH), 66.9 (C7), 49.1 (C4), 48.1 (C1), 42.9 (C6), 30.8 (C2), 25.0 (C3). **HRMS m/z** (ESI^+): calcd. for $C_{14}H_{15}N_3NaO$ [M+Na] Calculated 280.1056. Found 280.1053. **IR ν_{max}** (ATR)/cm^{-1}: 2976, 2900, 2243, 1645.

1-(6-Methyl-1,2,3,4-tetrahydroquinoline-1-carbonyl)pyrrolidine-2-carbonitrile (2-90):



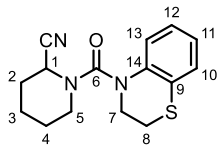
According to **GP2A**, 2-cyanopyrrolidine-1-carbonyl chloride (200 mg, 1.27 mmol), 6-methyl-1,2,3,4-tetrahydroquinoline (223 mg, 1.52 mmol) and triethylamine (0.55 mL, 2.53 mmol) were heated under reflux at 75 °C for 64 h. Purification via flash column chromatography eluting with 10% MeOH in DCM:DCM (1:9 – 1:0) afforded the title compound (241 mg, 71%) as an orange oil. $\mathbf{R_f}$ = 0.53 (1:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.98-6.91 (m, 3H, ArH), 4.77 (dd, *J* = 7.5, 5.8, 1H, H1), 3.82 (dt, *J* = 12.4, 6.5, 1H, CH_2), 3.52-3.43 (m, 1H, CH_2), 3.13 (dt, *J* = 10.5, 7.1, 1H, CH_2), 3.04 (ddd, *J* = 10.5, 7.5, 5.4, 1H, CH_2), 2.69 (q, *J* = 6.5, 2H, CH_2), 2.28 (s, 3H, H15), 2.27-2.19 (m, 1H, CH_2), 2.19-2.10 (m, 1H, CH_2), 2.09-1.83 (m, 2H, CH_2), 1.93-1.77 (m, 2H, CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 158.3 (C5), 137.0 (Ar), 133.0 (Ar), 130.6 (Ar), 129.4 (ArH), 127.5 (ArH), 121.1 (ArH), 119.4 (CN), 48.7 (CH_2), 47.9 (CH_2), 44.9 (CH_2), 30.8 (CH_2), 26.9 (CH_2), 25.0 (CH_2), 24.2 (CH_2), 20.9 (C15). **HRMS m/z** (ESI^+): calcd. for $C_{16}H_{19}N_3NaO$ [M+Na] Calculated 292.1420. Found 292.1429. **IR ν_{max}** (ATR)/cm^{-1}: 2991, 2939, 2885, 2242, 1640.

1-(1,2,3,4-Tetrahydroquinoline-1-carbonyl)-piperidine-2-carbonitrile (2-91):



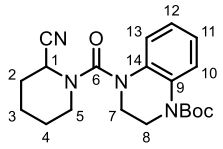
According to **GP2A**, 2-cyanopiperidine-1-carbonyl chloride (118 mg, 0.683 mmol), 1,2,3,4-tetrahydroquinoline (0.10 mL, 0.751 mmol) and triethylamine (0.19 mL, 1.37 mmol) were heated under reflux at 75 °C for 48 h. Purification via flash column chromatography eluting with EtOAc:PE (1:9 – 7:3) afforded the title compound (75 mg, 41%) as an orange solid. $\mathbf{R_f}$ = 0.34 (1:3 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.15-7.08 (m, 3H, ArH), 6.97 (td, *J* = 7.2, 1.5, 1H, ArH), 5.13 (m, 1H, H1), 3.68 (dt, *J* = 12.6, 6.5, 1H, H7a), 3.58 (dt, *J* = 12.6, 6.5, 1H, H7b), 3.41 (d, br, *J* = 13.6, 1H, H2a), 2.97-2.89 (m, 1H, H2b), 2.75 (t, *J* = 6.5, 2H, H9), 2.00-1.91 (m, 3H, H5a/8), 1.83-1.63 (m, 3H, H4/5b), 1.53 (d, br, *J* = 13.5, 1H, H3a), 1.35 (qt, *J* = 13.5, 3.4, 1H, H3b). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 159.8 (C6), 140.0 (Ar), 129.2 (ArH), 129.1 (Ar), 126.8 (ArH), 123.4 (ArH), 120.4 (ArH), 117.8 (CN), 45.7 (C1), 45.6 (C7), 44.8 (C2), 28.5 (C5), 27.0 (C9), 24.5 (C3), 23.9 (C8), 20.6 (C4). **HRMS m/z** (ESI^+): calcd. for $C_{16}H_{20}N_3O$ [M+H] Calculated 270.1528. Found 270.1613. **IR ν_{max}** (ATR)/cm^{-1}: 2948, 2865, 2233, 1652. **m.p** 138-140 °C.

1-(3,4-Dihydro-2*H*-benzo[*b*][1,4]thiazine-4-carbonyl)piperidine-2-carbonitrile (2-92):



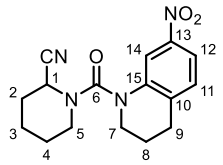
According to **GP2A**, 2-cyanopiperidine-1-carbonyl chloride (214 mg, 1.24 mmol), 3,4-dihydro-2*H*-1,4-benzothiazine (200 mg, 1.37 mmol) and triethylamine (0.35 mL, 2.48 mmol) were heated under reflux at 75 °C for 21 h. Purification via flash column chromatography eluting with EtOAc:PE (5:95 – 2:3) afforded the title compound (252 mg, 71%) as an orange oil. $\mathbf{R_f}$ = 0.29 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.23 (ddd, *J* = 7.7, 1.6, 0.6, 1H, ArH), 7.10-6.99 (m, 3H, ArH), 5.14-5.09 (m, 1H, H1), 3.99 (ddd, *J* = 13.3, 6.4, 5.4, 1H, H7 or 8), 3.82 (ddd, *J* = 13.3, 6.5, 5.4, 1H, H7 or 8), 3.30 (dddd, *J* = 13.6, 5.8, 2.6, 1.3, 1H, CH_2), 3.20 (ddd, *J* = 6.4, 5.4, 1.1, 2H, H7 or 8), 2.84 (ddd, *J* = 13.6, 12.7, 2.8, 1H, CH_2), 1.97-1.91 (m, 1H, CH_2), 1.79-1.59 (m, 3H, CH_2), 1.50-1.44 (m, 1H, CH_2), 1.31-1.19 (m, 1H, CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 158.9 (C6), 139.4 (Ar), 127.9 (ArH), 126.9 (Ar), 125.4 (ArH), 124.8 (ArH), 122.3 (ArH), 117.4 (CN), 45.7 (C1), 44.7 (C 7 or 8), 44.0 (C7 or 8). 28.3 (CH_2), 24.2 (CH_2), 20.4 (CH_2). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{17}N_3NaOS$ [M+Na] Calculated 310.0985. Found 310.0988. **IR ν_{max}** (ATR)/cm^{-1}: 2944, 2853, 2238, 1646.

***tert*-Butyl 4-(2-cyanopiperidine-1-carbonyl)-3,4-dihydroquinoxaline-1(2*H*)-carbonxylate (2-93):**



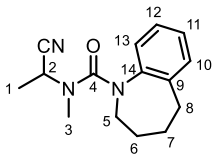
According to **GP2A**, 2-cyanopiperidine-1-carbonyl chloride (201 mg, 1.16 mmol), *tert*-butyl-3,4-dihydroquinoxaline-1(2*H*)-carboxylate (295 mg, 1.28 mmol) and triethylamine (0.32 mL, 2.33 mmol) were heated under reflux at 75 °C for 21 h. Purification via flash column chromatography eluting with EtOAc:PE (5:95 – 2:3) afforded the title compound (253 mg, 59%) as an orange oil. $\mathbf{R_f}$ = 0.29 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.89 (d, *J* = 7.7, 1H, ArH), 7.09-6.99 (m, 3H, ArH), 5.22-5.17 (m, 1H, H1), 3.87-3.83 (m, 2H, H8), 3.82-3.78 (m, 1H, H7a), 3.70-3.62 (m, 1H, H7b), 3.54-3.51 (m, br, 1H, CH_2), 2.96 (td, *J* = 13.2, 2.8, 1H, CH_2), 1.99-1.95 (m, 1H, CH_2), 1.84-1.68 (m, 3H, CH_2), 1.61-1.57 (m, 1H, CH_2), 1.54 (s, 9H, Boc-CH_3), 1.42-1.30 (m, 1H, CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 158.4 (C6), 153.4 (Boc-CO), 133.4 (Ar), 130.47 (Ar), 124.3 (2xArH), 123.9 (ArH), 119.6 (ArH), 117.6 (CN), 81.8 (Boc-$C(Me)_3$), 47.4 (C8), 45.7 (C1), 45.2 (C7), 45.1 (CH_2), 28.5 (CH_2/Boc-CH_3), 24.4 (CH_2), 20.6 (CH_2). **HRMS m/z** (ESI^+): calcd. for $C_{20}H_{27}N_4O_3$ [M+H] Calculated 371.2078. Found 371.2077. **IR ν_{max}** (ATR)/cm^{-1}: 2978, 2940, 2862, 2238, 1699, 1651.

1-(7-Nitro-1,2,3,4-tetrahydroquinoline-1-carbonyl)piperidine-2-carbonitrile (2-94):



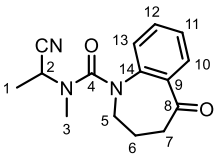
According to **GP2A**, 2-cyanopiperidine-1-carbonyl chloride (200 mg, 1.16 mmol), 7-nitro-1,2,3,4-tetrahydroquinoline (188 mg, 1.05 mmol) and triethylamine (0.32 mL, 2.31 mmol) were heated under reflux at 75 °C for 63 h. Purification via flash column chromatography eluting with EtOAc:PE (1:9 – 1:0) afforded the title compound (122 mg, 33%) as a yellow solid. $\mathbf{R_f}$ = 0.39 (1:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.06 (d, *J* = 2.3, 1H, ArH), 7.79 (dd, *J* = 8.4, 2.3, 1H, ArH), 7.26 (d, *J* = 8.4, 1H, ArH), 5.11-5.10 (m, 1H, H1), 3.77 (ddd, *J* = 12.3, 6.9, 4.9, 1H, H7a), 3.54 (ddd, *J* = 12.3, 76, 4.6, 1H, H7b), 3.50-3.45 (m, 1H, H5a), 3.09 (td, *J* = 13.2, 2.8, 1H, H5b), 2.95-2.82 (m, 2H, H9), 2.10-1.85 (m, 5H, H8/3a/2), 1.79-1.68 (m, 1H, H3b), 1.60-1.57 (m, 1H, H4a), 1.47-1.36 (m, 1H, H4b). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 159.8 (C6), 146.8 (Ar), 140.7 (Ar), 135.1 (ArH), 130.3 (ArH), 117.6 (CN), 117.4 (ArH), 115.2 (ArH), 46.0 (C7), 45.9 (C1), 45.2 (C5), 28.5 (C2), 27.4 (C9), 24.3 (C4), 22.7 (C8), 20.6 (C3). **HRMS m/z** (ESI^+): calcd. for $C_{16}H_{18}N_4O_3$ [M+H] Calculated 315.1452. Found 315.1452. **IR ν_{max}** (ATR)/cm^{-1}: 2945, 2865, 2241, 1664.

***N*-(1-Cyanoethyl-*N*-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (2-26):**



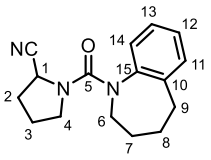
According to **GP2A**, (1-cyanoethyl)(methyl)carbamic chloride (166 mg, 1.13 mmol), 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine (183 mg, 1.24 mmol) and triethylamine (0.31 mL, 2.26 mmol) were heated under reflux at 75 °C for 43 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 2:3) afforded the title compound (131 mg, 45%) as a purple solid. $\mathbf{R_f}$ = 0.34 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.24-7.11 (m, 3H, ArH), 6.92 (dd, *J* = 7.6, 1.6, 1H, ArH), 5.18 (q, *J* = 7.3, 1H, H2), 3.92-3.42 (m, br, 2H, H5), 2.81-2.78 (m, 2H, H7), 2.36 (s, 3H, H3), 1.80-10.74 (m, 2H, H6 or 7), 1.73-1.56 (m, 2H, H6 or 7), 1.41 (d, *J* = 7.3, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.3 (C4), 144.8 (Ar), 138.5 (Ar), 130.7 (ArH, br), 127.7 (ArH), 126.6 (ArH), 124.9 (ArH), 48.9 (C5), 44.3 (C2, br), 35.2 (C8), 32.0 (C6 or 7, br), 30.5 (C6 or 7), 17.1 (C1, br). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{20}N_3O$ [M+H] Calculated 258.1601. Found 258.1590. **IR ν_{max}** (ATR)/cm^{-1}: 2995, 2930, 2855, 2239, 1633. **m.p** 114-116 °C.

***N*-(1-Cyanoethyl)-*N*-methyl5-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (2-95):**



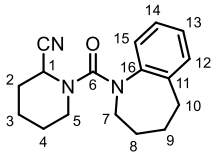
According to **GP2A**, (1-cyanoethyl)(methyl)carbamic chloride (200 mg, 1.37 mmol), 1,2,3,4-tetrahydro-5*H*-benzo[*b*]azepine-5-one (200 mg, 1.34 mmol) and triethylamine (0.38 mL, 2.73 mmol) were heated under reflux at 75 °C for 75 h. Purification via flash column chromatography eluting with EtOAc:PE (3:7 – 3:2) afforded the title compound (267 mg, 79%) as a white solid. $\mathbf{R_f}$ = 0.51 (1:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.81 (dd, *J* = 7.8, 1.7, 1H, ArH), 7.52 (td, *J* = 7.8, 1.7, 1H, ArH), 7.33 (td, *J* = 7.8, 1.1, 1H, ArH), 7.01 (dd, *J* = 7.8, 1.1, 1H, ArH), 5.25 (q, *J* = 7.2, 1H, H2), 3.78 (dt, *J* = 13.5, 6.8, 1H, H5a), 3.70 (dt, *J* = 13.5, 6.7, 1H, H5b), 2.76-2.73 (m, 2H, H7), 2.39 (s, 3H, H3), 2.07-1.96 (m, 2H, H6), 1.45 (d, *J* = 7.2, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 203.4 (C8), 160.9 (C4), 143.4 (Ar), 134.7 (Ar), 130.3 (ArH), 127.2 (ArH), 125.5 (ArH), 118.6 (CN), 49.6 (C5), 44.4 (C2), 40.3 (C7), 32.6 (C3), 23.1 (C6), 17.4 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{18}N_3O_2$ [M+H] Calculated 272.1321. Found 272.1394. **IR ν_{max}** (ATR)/cm^{-1}: 3080, 2967, 2885, 2239, 1675, 1646. **m.p** 114-117 °C.

1-(2,3,4,5-Tetrahydro-1*H*-benzo[*b*]azepine-1-carbonyl)pyrrolidine-2-carbonitrile (2-27):



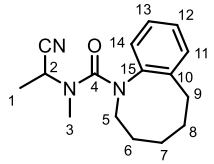
According to **GP2A**, 2-cyanopyrrolidine-1-carbonyl chloride (181 mg, 1.15 mmol), 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine (185 mg, 1.26 mmol) and triethylamine (0.32 mL, 2.29 mmol) were heated under reflux at 75 °C for 45 h. Purification via flash column chromatography eluting with acetone:DCM (0:1 – 1:4) afforded the title compound (118 mg, 38%) as a colourless solid. $\mathbf{R_f}$ = 0.76 (1:9 Acetone:DCM). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.21-7.10 (m, 3H, ArH), 7.06 (dd, *J* = 7.4, 1.5, 1H, ArH), 4.70-4.67 (m, br, 1H, H1), 4.52-3.92 (m, br, 1H, CH_2), 3.53-3.02 (m, br, 1H, CH_2), 2.79-2.74 (m, 2H, CH_2), 2.71 (s, br, 1H, CH_2), 2.52 (s, br, 1H, CH_2), 2.15-1.98 (m, 2H, CH_2), 1.91-1.67 (m, br, 5H, 3xCH_2), 1.64-1.50 (m, br, 1H, CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 158.0 (C5), 144.1 (Ar), 139.2 (Ar), 130.4 (ArH), 127.6 (ArH), 126.6 (ArH), 125.9 (ArH), 119.6 (CN), 48.4 (C1), 47.8 (CH_2), 35.0 (CH_2), 30.4 (CH_2), 30.3 (CH_2), 28.7 (CH_2), 25.9 (CH_2), 25.2 (CH_2). **HRMS m/z** (ESI^+): calcd. for $C_{16}H_{19}N_3NaO$ [M+Na] Calculated 292.1420. Found 292.1423. **IR ν_{max}** (ATR)/cm^{-1}: 2980, 2932, 2940, 2248, 1639. **m.p** 131-134 °C.

1-(2,3,4,5-Tetrahydro-1*H*-benzo[*b*]azepine-1-carbonyl)piperidine-2-carbonitrile (2-96):



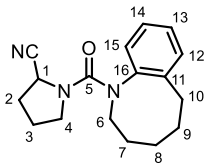
According to **GP2A**, 2-cyanopiperidine-1-carbonyl chloride (101 mg, 0.587 mmol), 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine (95 mg, 0.645 mmol) and triethylamine (0.16 mL, 1.17 mmol) were heated under reflux at 75 °C for 21 h. Purification via flash column chromatography eluting with EtOAc:PE (5:95 – 2:3) afforded the title compound (88 mg, 53%) as an orange oil. $\mathbf{R_f}$ = 0.30 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.24-7.11 (m, 3H, ArH), 6.99 (dd, *J* = 7.7, 1.5, 1H, ArH), 5.06 (s, 1H, H1), 4.06-3.36 (m, br, 2H, H7), 3.17-3.13 (m, 1H, CH_2), 2.79-2.76 (m, 2H, H9), 2.68 (t, *J* = 12.4, 1H, CH_2), 1.89-1.52 (m, 8H, CH_2), 1.33 (d, br, *J* = 14.0, 1H, CH_2), 1.08-0.95 (m, 1H, CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.4 (C6), 145.2 (Ar), 138.5 (Ar), 131.0 (ArH), 127.9 (ArH), 127.0 (ArH), 125.5 (ArH), 118.2 (CN), 49.1 (C1), 46.1 (C7), 44.4 (CH_2), 35.5 (C9), 30.8 (CH_2), 28.7 (CH_2), 26.1 (CH), 24.4 (CH_2), 21.0 (CH_2). **HRMS m/z** (ESI^+): calcd. for $C_{17}H_{22}N_3O$ [M+H] Calculated 284.1757. Found 284.1757. **IR ν_{max}** (ATR)/cm^{-1}: 2928, 2856, 2235, 1645.

***N*-(1-Cyanoethyl)-*N*-methyl-3,4,5,6-tetrahydrobenzo[*b*]azocine-1(2*H*)-carboxamide (2-97):**



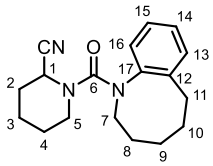
According to **GP2A**, (1-cyanoethyl)(methyl)carbamic chloride (124 mg, 0.846 mmol), 1,2,3,4,5,6-hexahydrobenzo[*b*]azocine (150 mg, 0.930 mmol) and triethylamine (0.26 mL, 1.86 mmol) were heated under reflux at 75 °C for 23 h. The title product (215 mg, 94%) was obtained as a brown oil. $\mathbf{R_f}$ = 0.58 (1:3 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.27-7.21 (m, 3H, ArH), 7.01-6.97 (m, 1H, ArH), 5.17 (q, *J* = 7.2, 1H, H2), 3.71-3.48 (m, br, 2H, H5), 2.69 (td, *J* = 6.1, 2.0, 2H, H9), 2.43 (s, 3H, H3), 1.76-1.66 (m, br, 2H, H8), 1.55-1.43 (m, br, 4H, H6/7), 1.31 (d, *J* = 7.2, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 161.9 (C4), 142.4 (Ar), 141.9 (Ar), 130.6 (ArH), 128.2 (ArH), 128.0 (ArH), 127.6 (ArH), 118.9 (CN), 54.5 (C5), 44.6 (C2), 32.0 (C3), 31.8 (C9), 31.7 (C8), 26.9 (C6 or 7), 26.1 (C6 or 7), 17.3 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{16}H_{22}N_3O$ [M+H] Calculated 272.1682. Found 272.1748. **IR ν_{max}** (ATR)/cm^{-1}: 2925, 2855, 2239, 1641.

1-(1,2,3,4,5,6-Hexahydrobenzo[*b*]azocine-1-carbonyl)pyrrolidine-2-carbonitrile (2-98):



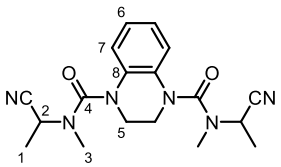
According to **GP2A**, 2-cyanopyrrolidine-1-carbonyl chloride (89.1 mg, 0.564 mmol), 1,2,3,4,5,6-hexahydrobenzo[*b*]azocine (100 mg, 0.620 mmol) and triethylamine (0.16 mL, 1.13 mmol) were heated under reflux at 75 °C for 17 h. Purification via flash column chromatography eluting with acetone:DCM (0:1 – 1:4) afforded the title compound (129 mg, 81%) as a yellow oil. $\mathbf{R_f}$ = 0.63 (1:9 Acetone:DCM). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.30-7.20 (m, 3H, ArH), 7.12-7.08 (m, 1H, ArH), 4.72 (t, *J* = 6.0, 1H, H1), 4.45-3.00 (m, br, 2H, CH_2), 2.78-2.64 (m, br, 3H, 2xCH_2), 2.09-1.98 (m, 2H, CH_2), 1.95-1.84 (m, 1H, CH_2), 1.82-1.73 (m, br, 2H, CH_2), 1.69-1.38 (m, br, 5H, 3xCH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 159.1 (C5), 142.5 (Ar), 141.6 (Ar), 130.3 (ArH), 128.5 (ArH), 128.3 (ArH), 127.8 (ArH), 119.7 (CN), 53.8 (CH_2), 49.0 (C1), 47.6 (CH_2), 31.7 (CH_2), 31.5 (CH_2), 30.0 (CH_2), 26.6 (CH_2), 26.2 (CH_2), 25.4 (CH_2). **HRMS m/z** (ESI^+): calcd. for $C_{17}H_{21}N_3NaO$ [M+Na] Calculated 306.1577. Found 306.1578. **IR ν_{max}** (ATR)/cm^{-1}: 2924, 2854, 2242, 1633.

1-(1,2,3,4,5,6-Hexahydrobenzo[*b*]azocine-1-carbonyl)piperidine-2-carbonitrile (2-99):



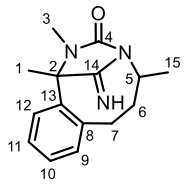
According to **GP2A**, 2-cyanopiperidine-1-carbonyl chloride (97.0 mg, 0.564 mmol), 1,2,3,4,5,6-hexahydrobenzo[*b*]azocine (100 mg, 0.620 mmol) and triethylamine (0.16 mL, 1.17 mmol) were heated under reflux at 75 °C for 48 h. Purification via flash column chromatography eluting with EtOAc:PE (0:1 – 1:1) afforded the title compound (129 mg, 77%) as a yellow oil. $\mathbf{R_f}$ = 0.59 (1:3 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.30-7.25 (m, 3H, ArH), 7.04-7.02 (m, 1H, ArH), 5.05 (s, br, 1H, H1), 3.62 (s, br, 2H, H7), 3.48 (d, br, *J* = 14.8, 1H, H2a), 2.77-2.62 (m, 3H, H2b/CH_2), 1.82-1.49 (m, 10H, 5 x CH_2), 1.31 (d, br, *J* = 13.9, 1H, H3a), 0.88-0.73 (m, 1H, H3b). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 161.8 (C6), 142.4 (Ar), 141.4 (Ar), 130.5 (ArH), 128.0 (ArH), 127.8 (ArH), 127.5 (ArH), 117.9 (CN), 54.0 (C7), 45.9 (C1), 44.0 (C2), 31.6 (CH_2), 31.5 (CH_2), 28.4 (CH_2), 26.6 (CH_2), 25.9 (CH_2), 24.0 (C3), 20.5 (CH_2). **HRMS m/z** (ESI^+): calcd. for $C_{18}H_{24}N_3O$ [M+H] Calculated 298.1841. Found 298.1923. **IR ν_{max}** (ATR)/cm^{-1}: 2924, 2861, 2242, 1645.

***N*^{1},*N*^{4}-bis(1-cyanoethyl)-*N*^{1},*N*^{4}-dimethyl-2,3-dihydroquinoxaline-1,4-dicarboxamide (2-100):**



According to **GP2A**, (1-cyanoethyl)(methyl)carbamic chloride (1.35 g, 9.21 mmol), 1,2,3,4-tetrahydroquinoxaline (450 mg, 3.35 mmol) and triethylamine (2.56 mL, 18.4 mmol) were heated under reflux at 75 °C for 60 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 1:0) afforded the title compound (1.01 g, 85%) as a pink solid. $\mathbf{R_f}$ = 0.63 (1:0 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.09-7.01 (m, 4H, ArH), 5.33-5.24 (m, 2H, H2), 3.87-3.74 (m, 4H, H5), 2.73 (s, 3H, H3), 2.72 (s, 3H, H3), 1.58 (d, *J* = 7.3, 3H, H1), 1.58 (d, *J* = 7.3, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 159.9 (C4), 132.8 (Ar), 124.7 (ArH), 120.9 (ArH), 118.3 (CN), 46.9 (C5), 44.2 (C2), 32.9 (C3), 17.1 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{18}H_{22}N_6NaO_2$ [M+Na] Calculated 377.1804. Found 377.1707. **IR ν_{max}** (ATR)/cm^{-1}: 2971, 2880, 2244, 1652. **m.p** 166-168 °C.

12-Imino-1,2,5-trimethyl-1,5,6,7-tetrahydro-1,4-methanobenzo[*e*][1,3]diazonin-3(2H)-one (2-30):

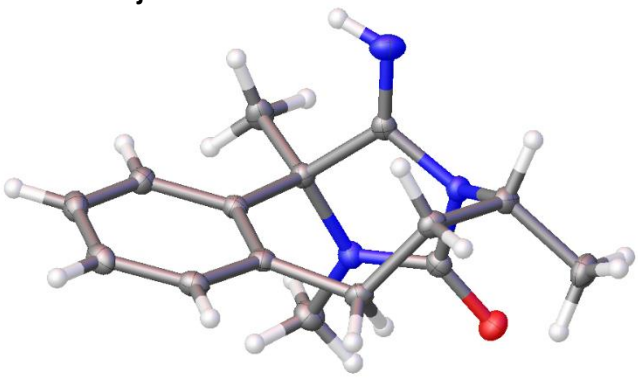


According to **GP3A**, *N*-(1-cyanoethyl)-*N*,2-dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (53.0 mg, 0.206 mmol) and KHMDS (1 M in THF, 0.41 mL, 0.412 mmol) in anhydrous THF were stirred at 0 °C for 2 h. Purification via column chromatography eluting with EtOAc:PE (1:4 – 1:0) afforded the title compound (35 mg, 0.136 mmol, 66%) as a mixture of 2 isolated diastereoisomers.

Major-diastereoisomer: (24 mg, 45%) as a white solid. $\mathbf{R_f}$ = 0.33 (3:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.90 (s, br, 1H, NH), 7.34 (d, br, *J* = 7.5, 1H, ArH), 7.25 (td, *J* = 7.5, 1.7, 1H, ArH), 7.20 (td, *J* = 7.5, 1.5, 1H, ArH), 7.12 (dd, *J* = 7.5, 1.5, 1H, ArH), 4.62-4.31 (m, 1H, H5), 3.39-2.96 (m, br, 1H, H7a), 2.78 (dd, *J* = 15.8, 9.6, 1H, H7b), 2.58 (s, 3H, H3), 2.27-2.17 (m, br, 1H, H6a), 2.03-1.93 (m, br, 1H, H6b), 1.86 (s, 3H, H1), 1.70 (d, *J* = 7.3, 3H, H15). **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 173.4 (C14), 162.0 (C4), 140.7 (Ar), 138.6 (Ar), 135.4 (ArH), 129.2 (ArH), 126.8 (ArH), 126.7 (ArH), 65.8 (C2), 53.6 (C5), 32.7 (C6), 32.5 (C7), 25.8 (C3), 21.1 (C1), 20.5 (C15). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{20}N_3O$ [M+H] Calculated 258.1601. Found 258.1603. **IR ν_{max}** (ATR)/cm^{-1}: 3241, 2923, 2856, 1720, 1658.

Minor-diastereoisomer: (11 mg, 21%) as a white solid. $\mathbf{R_f}$ = 0.43 (3:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.40-7.38 (m, 1H, ArH), 7.25-7.22 (m, 2H, ArH), 7.12-7.10 (m, 1H, ArH), 4.33-4.23 (m, 1H, H5), 2.84-2.77 (m, 1H, H7a), 2.66 (s, 3H, H3), 2.51 (dd, *J* = 16.2, 9.2, 1H, H7b), 2.19-2.11 (m, br, 1H, H6a), 2.04 (ddd, *J* = 14.7, 9.9, 4.6, 1H, H6b), 1.85 (s, 3H, H1), 1.57 (d, *J* = 7.0, 3H, H15). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 173.1 (C14), 162.0 (C4), 140.7 (Ar), 138.6 (Ar), 135.4 (ArH), 129.2 (ArH), 126.8 (ArH), 126.7 (ArH), 65.8 (C2), 53.6 (C5), 32.7 (C6), 32.5 (C7), 25.8 (C3), 21.1 (C1), 20.5 (C15). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{20}N_3O$ [M+H] Calculated 258.1601. Found 258.1600. **IR ν_{max}** (ATR)/cm^{-1}: 3244, 2926, 2853, 1732, 1653.

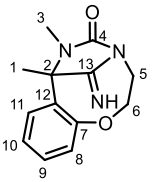
X-ray crystallography data for major-diastereoisomer:



Empirical formula	$C_{15}H_{21}N_3O_2$
Formula weight	275.35
Temperature/K	100(2)
Crystal system	triclinic
Space group	P-1
a/Å	7.1405(3)
b/Å	8.5770(4)
c/Å	11.9704(6)
α/°	73.957(3)
β/°	88.399(3)
γ/°	78.976(3)
Volume/Å^3	691.32(6)
Z	2
ρ_{calc}g/cm^3	1.323
μ/mm^{-1}	0.090
F(000)	296.0
Crystal size/mm^3	0.382 x 0.326 x 0.149
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	3.542 to 55.856
Index ranges	-8 ≤ h ≤ 9, -11 ≤ k ≤ 11, -15 ≤ l ≤ 15
Reflections collected	12697
Independent reflections	3308 [R_{int} = 0.0270, R_{sigma} = 0.0248]
Data/restraints/parameters	3308/1/196
Goodness-of-fit on F^2	1.045
Final R indexes [I>=2σ (I)]	R_1 = 0.0395, wR_2 = 0.0994
Final R indexes [all data]	R_1 = 0.0471, wR_2 = 0.1040
Largest diff. peak/hole/ eÅ^{-3}	0.41/-0.23

CCDC number: 1993729.

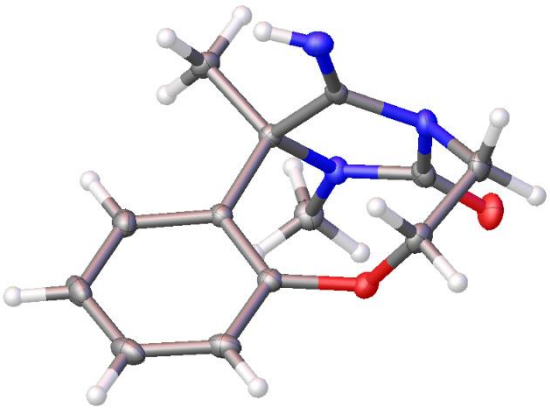
12-Imino-6-dimethyl-2,3,6,7-tetrahydro-5*H*-4,7-methanobenzo[*h*][1,4,6]oxadiazonin-5-one (2-31):



According to **GP3A**, *N*-(1-cyanoethyl)-*N*-methyl-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxamide (55.0 mg, 0.224 mmol) and KHMDS (1 M in THF, 0.45 mL, 0.448 mmol) in anhydrous THF were stirred at 0 °C for 1 h. Purification via flash column chromatography eluting with EtOAc:PE (1:3 – 1:0) afforded

the title compound (16 mg, 29%) as a yellow oil. **R_f** = 0.15 (3:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.78 (s, br, 1H, NH), 7.35 (d, *J* = 7.7, 1H, ArH), 7.31 (td, *J* = 7.8, 1.7, 1H, ArH), 7.16 (td, *J* = 7.7, 1.4, 1H, ArH), 7.06 (dd, *J* = 7.8, 1.4, 1H, ArH), 4.40 (dd, *J* = 11.1, 5.9, 1H, H6a), 4.25 (ddd, *J* = 13.7, 11.9, 5.9, 1H, H5a), 4.00-3.87 (m, br, 1H, H6b), 3.55-2.75 (m, br, 1H, H5b), 2.62 (s, br, 3H, H3), 1.86 (s, br, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 173.9 (C13), 162.6 (C4), 159.0 (C7), 133.4 (C12), 130.7 (ArH), 126.9 (ArH), 125.7 (ArH), 124.8 (ArH), 69.2 (C6), 65.2 (C2), 44.4 (C5), 25.8 (C3), 19.1 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{13}H_{16}N_3O_2$ [M+H] Calculated 246.1164. Found 246.1258. **IR ν_{max}** (ATR)/cm^{-1}: 3555, 3349, 3260, 3204, 2966, 2926, 1740, 1667.

X-ray crystal data:

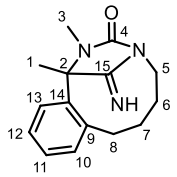


Empirical formula	$C_{13}H_{17}N_3O_3$
Formula weight	263.29
Temperature/K	99.97
Crystal system	monoclinic
Space group	$P2_{1/c}$
a/Å	8.0314(2)
b/Å	8.1488(2)
c/Å	19.2027(5)
α/°	90
β/°	90.5479917)
γ/°	90
Volume/Å^3	1256.69(5)
Z	4
ρ_{calc}g/cm^3	1.392
μ/mm^{-1}	0.101
F(000)	560.0
Crystal size/mm^3	0.394 x 0.347 x 0.144
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	4.242 to 59.146
Index ranges	-11 ≤ h ≤ 11, -11 ≤ k ≤ 11, -26 ≤ l ≤ 26
Reflections collected	26526
Independent reflections	3522 [R_{int} = 0.0329, R_{sigma} = 0.0184]
Data/restraints/parameters	3522/0/186
Goodness-of-fit on F^2	1.049
Final R indexes [I>=2σ (I)]	R_1 = 0.0378, wR_2 = 0.0952

Final R indexes [all data]	R_1 = 0.0449, wR_2 = 0.0998
Largest diff. peak/hole/ eÅ^{-3}	0.40/-0.22

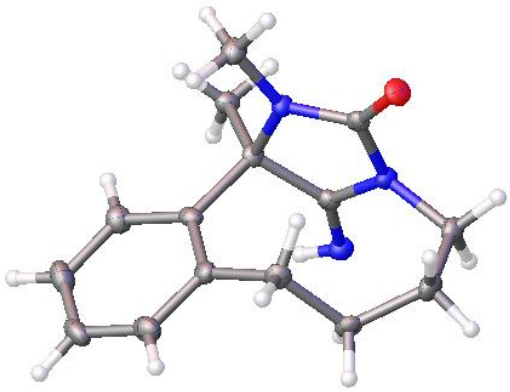
CCDC number: 1993728.

13-Imino-1,2-dimethyl-1,2,5,6,7,8-hexahydro-3*H*-1,4-methanobenzo[*e*][1,3]diazecine-3-one (2-36):



According to **GP3A**, *N*-(1-cyanoethyl)-*N*-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (63.0 mg, 0.245 mmol) and KHMDS (1 M in THF, 0.47 mL, 0.466 mmol) in anhydrous THF were stirred at 0 °C for 1.5 h. The title compound (57 mg, 91%) was obtained as a yellow solid without any further purification. **R_f** = 0.12 (7:3 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.43-7.41 (m, 1H, ArH), 7.24-7.22 (m, 2H, ArH), 7.09-7.07 (m, 1H, ArH), 4.03 (ddd, *J* = 13.9, 12.3, 5.7 Hz, 1H, H5a), 3.80 (dd, *J* = 13.9, 6.0, 1H, H5b), 2.79 (ddd, *J* = 15.4, 12.7, 6.7, 1H, H8a), 2.71 (s, 3H, H3), 2.43 (ddd, *J* = 15.4, 6.4, 1.8, 1H, H8b), 2.10-1.98 (m, 1H, H6a), 1.92-1.74 (m, 2H, H7a/H6b), 1.83 (s, 3H, H1), 1.62-1.53 (m, 1H, H7b). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 172.1 (C15), 158.6 (C4), 142.3 (Ar), 136.2 (Ar), 133.9 (ArH), 129.2 (ArH), 127.4 (ArH), 126.5 (ArH), 66.7 (C2), 39.9 (C5), 33.9 (C8), 28.7 (C6), 25.4 (C3), 24.0 (C7), 22.7 (C1). **HRMS m/z** (ESI$^+$): calcd. for $C_{15}H_{20}N_3O$ [M+H] Calculated 258.1528. Found 258.1612. **IR ν_{max}** (ATR)/cm^{-1}: 3275, 2953, 2921, 2897, 2858, 1721, 1651. **m.p** 170-173 °C (Recrystallised from DCM:Et_2O).

X-ray crystal data:

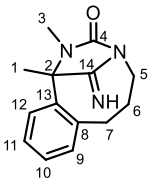


Empirical formula	$C_{15}H_{19}N_3O$
Formula weight	257.33
Temperature/K	10092)
Crystal system	trigonal
Space group	$P3_1$
a/Å	22.0392(6)
b/Å	22.0392(6)
c/Å	7.1184(2)
α/°	90
β/°	90
γ/°	120
Volume/Å^3	2994.36(18)

Z	9
ρ_{calc}g/cm^3	1.284
μ/mm^{-1}	0.0831242.0
F(000)	1242.0
Crystal size/mm^3	0.389 x 0.323 x 0.234
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	3.696 to 51.362
Index ranges	-26 ≤ h ≤ 26, -24 ≤ k ≤ 26, -8 ≤ l ≤ 8
Reflections collected	22901
Independent reflections	7518 [R_{int} = 0.0614, R_{sigma} = 0.0705]
Data/restraints/parameters	7518/1/532
Goodness-of-fit on F^2	1.023
Final R indexes [I>=2σ (I)]	R_1 = 0.0444, wR_2 = 0.0831
Final R indexes [all data]	R_1 = 0.0623, wR_2 = 0.0905
Largest diff. peak/hole/ eÅ^{-3}	0.16/-0.21

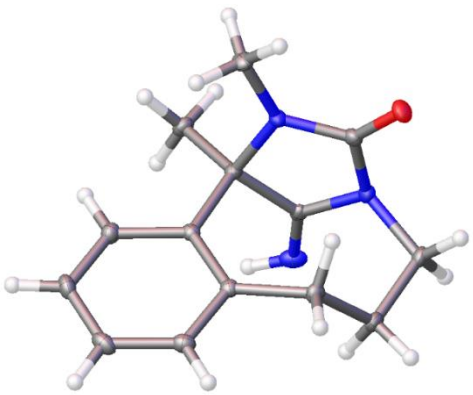
CCDC number: 1993727.

12-Imino-1,2-dimethyl-1,5,6,7-tetrahydro-1,4-methanobenzo[*e*][1,3]diazonin-3(2*H*)-one (2-28):



According to **GP3A**, *N*-(1-cyanoethyl)-*N*-methyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (102 mg, 0.419 mmol) and KHMDS (1 M in THF, 0.82 mL, 0.822 mmol) in anhydrous THF were stirred at 0 °C for 30 min. Purification via flash column chromatography eluting with EtOAc:PE (7:3 – 4:1) afforded the title compound (74 mg, 73%) as a yellow solid. **R_f** = 0.15 (3:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.39-7.37 (m, 1H, ArH), 7.24-7.19 (m, 2H, ArH), 7.12-7.09 (m, 1H, ArH), 3.88 (ddd, *J* = 13.7, 12.0, 5.8, 1H, H5a), 3.69-3.58 (m, br, 1H, H5b), 2.83-2.72 (m, br, 1H, H7a), 2.66 (s, 3H, H3), 2.53 (dd, *J* = 16.3, 9.2, 1H, H7b), 2.27-2.15 (m, br, 1H, H6a), 1.95 (ddd, *J* = 15.0, 10.1, 5.8, 1H, H6b), 1.87 (s, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 172.0 (C14), 161.2 (C4), 140.0 (Ar), 138.4 (Ar), 135.3 (ArH), 128.9 (ArH), 126.5 (ArH), 126.4 (ArH), 65.2 (C2, br), 42.1 (C5, br), 31.5 (C7, br), 25.3 (C3), 24.6 (C6, br), 20.2 (C1, br). **HRMS m/z** (ESI$^+$): calcd. for $C_{14}H_{17}N_3NaO$ [M+Na] Calculated 266.1269. Found 266.1276. **IR ν_{max}** (ATR)/cm^{-1}: 3210, 2996, 2954, 2923, 2887, 1732, 1668. **m.p** 129-133 °C (Recrystallised from DCM:Et_2O).

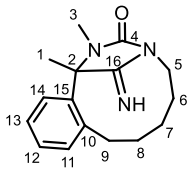
X-ray crystal data:



Empirical formula	$C_{14}H_{19}N_3O_2$
Formula weight	261.32
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_{1/c}$
a/Å	8.1323(2)
b/Å	8.1695(2)
c/Å	19.3253(4)
α/°	90
β/°	90.8030(10)
γ/°	90
Volume/Å^3	1283.79(5)
Z	4
ρ_{calc}g/cm^3	1.352
μ/mm^{-1}	0.092
F(000)	560.0
Crystal size/mm^3	0.492 x 0.406 x 0.373
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	5.01 to 55.804
Index ranges	$-10 \leq h \leq 10$, $-10 \leq k \leq 7$, $-21 \leq l \leq 25$
Reflections collected	11411
Independent reflections	3068 [R_{int} = 0.0225, R_{sigma} = 0.0217]
Data/restraints/parameters	3068/1/181
Goodness-of-fit on F^2	1.119
Final R indexes [I>=2σ (I)]	R_1 = 0.0448, wR_2 = 0.1036
Final R indexes [all data]	R_1 = 0.0507, wR_2 = 0.1067
Largest diff. peak/hole/ eÅ^{-3}	0.45/-0.35

CCDC number: 1993726.

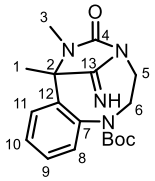
14-Imino-1,2-dimethyl-1,5,6,7,8,9-hexahydro-1,4-methanobenzo[*e*][1,3]diazacycloundecin-3(2*H*)-one (2-116):



According to **GP3A**, *N*-(1-cyanoethyl)-*N*-methyl-3,4,5,6-tetrahydrobenzo[*b*]azocine-1(2*H*)-carboxamide (50.0 mg, 0.184 mmol) and KHMDS (1 M in THF, 0.37 mL, 0.369 mmol) in anhydrous THF were stirred at 0 °C for 1 h. The title compound (45 mg, 90%) was obtained as a yellow oil without any further purification. $\mathbf{R_f}$ = 0.18 (7:3 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.45 (dd, *J* = 7.5, 1.6, 1H, ArH), 7.29-7.21 (m, 2H, ArH), 7.13 (dd, *J* = 7.1, 1.9, 1H, ArH), 3.78 (m, 2H, H5), 2.64 (s, 3H, H3), 2.48-2.38 (m, br, 1H, H9a), 2.38-2.32 (m, br, 1H, H9b), 2.26-2.12 (m, br, 1H, H6a), 1.90-1.85 (m, br, 1H, H6b), 1.82 (s, 3H, H1), 1.71-1.59 (m, br, 3H, H7a/8), 1.52-1.42 (m, br, 1H, H7b). **^{13}C NMR** (101 MHz, $CDCl_3$):

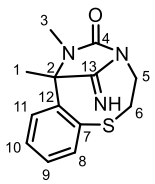
δ_C 169.7 (C16), 157.0 (C4), 143.3 (Ar), 134.8 (Ar), 133.2 (ArH), 129.3 (ArH), 128.1 (ArH), 126.2 (ArH), 65.5 (C2), 39.8 (C5), 31.2 (C9), 28.6 (C8), 25.5 (C7), 25.2 (C3), 24.0 (C1), 23.5 (C6). **HRMS m/z** (ESI^+): calcd. for $C_{16}H_{22}N_3O$ [M+H] Calculated 272.1685. Found 272.1754. **IR ν_{max}** (ATR)/cm^{-1}: 3281, 2925, 2852, 1727, 1650.

***tert*-Butyl 12-imino-6,7-dimethyl-5-oxo-2,3,6,7-tetrahydro-4,7-methanobenzo[*gi*][1,3,6]triazonine-1(5*H*)-carboxylate (2-117):**



According to **GP3A**, *tert*-butyl 4-((1-cyanoethyl)(methyl)carbamoyl)-3,4-dihydroquinoxaline-1(2*H*)-carboxylate (49.0 mg, 0.145 mmol) and KHMDS (1 M in THF, 0.29 mL, 0.290 mmol) in anhydrous THF were stirred at 0 °C for 1 h. Purification via flash column chromatography eluting with MeOH:DCM (0:1 – 1:9) afforded the title compound (32 mg, 64%) as an orange oil. $\mathbf{R_f}$ = 0.65 (1:9 MeOH:DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) (mixture of rotamers A:B in a 0.67:0.33 ratio): δ_H 7.43-7.40 (m, 1H, ArH, rot. A+B), 7.37-7.28 (m, 2H, ArH, rot. A+B), 7.12 (dd, *J* = 7.4, 1.8, 0.33H, ArH, rot. B), 7.02-6.98 (m, 0.67H, ArH, rot. A), 4.34-4.23 (m, 1H, CH_2, rot A+B), 4.13-4.06 (m, 0.67H, CH_2, rot. A), 3.89 (dd, *J* = 14.3, 4.9, 0.33H, CH_2, rot. B), 3.60-3.48 (m, 1H, CH_2, rot. A+B), 3.35-3.30 (m, 0.33H, CH_2, rot. B), 3.28-3.17 (m, 0.67H, CH_2, rot. A), 2.64 (s, 2H, H3, rot. A), 2.62 (s, 1H, H3, rot. B), 1.86 (s, 3H, H3, rot. A+B), 1.53 (s, 3H, Boc-CH_3, rot. B), 1.30 (s, 6H, Boc-CH_3, rot. A). **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 172.2 (C4, rot. B), 171.2 (C4, rot. A), 160.6 (C13, rot. B), 160.4 (C13, rot. A), 155.0 (Boc-CO, rot. B), 154.6 (Boc-CO, rot. A), 142.3 (Ar, rot. B), 142.2 (Ar, rot. A), 136.8 (Ar, rot. B), 136.1 (Ar, rot. A), 133.3 (ArH, rot B), 132.6 (ArH, rot. A), 130.3 (ArH, rot. B), 129.7 (ArH, rot. A), 128.0 (ArH, rot. B), 127.7 (ArH, rot. A), 127.0 (ArH, rot. A+B), 81.7 (Boc-$C(Me)_3$, rot. B), 80.9 (Boc-$C(Me)_3$, rot. A), 65.2 (C2, rot. B), 65.1 (C2, rot. A), 46.8 (CH_2, rot. B), 46.1 (CH_2, rot. A), 43.9 (CH_2, rot. B), 43.0 (CH_2, rot. A), 28.3 (Boc-CH_3, rot. A), 28.2 (Boc-CH_3, rot. B), 25.6 (C3, rot. A+B), 20.0 (C1, rot. B), 19.9 (C1, rot. A). **HRMS m/z** (ESI^+): calcd. for $C_{18}H_{24}N_4O_3$ [M+H] Calculated 345.1921. Found 345.1919. **IR ν_{max}** (ATR)/cm^{-1}: 3191, 2978, 2932, 1741, 1707, 1665.

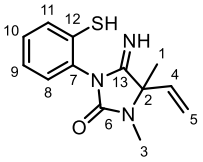
12-Imino-6,7-dimethyl-2,3,6,7-tetrahydro-5*H*-4,7-methanobenzo[*h*][1,4,6]thiadiazonin-5-one (2-118):



According to **GP3A**, *N*-(1-cyanoethyl)-*N*-methyl-2,3-dihydro-4*H*-benzo[*b*][1,4]thiazine-4-carboxamide (50.0 mg, 0.192 mmol) and KHMDS (1 M in THF, 0.38 mL, 0.384 mmol) in anhydrous THF were stirred

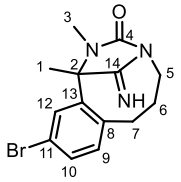
at 0 °C for 1 h. Purification via flash column chromatography eluting with MeOH:DCM (0:1 – 1:9) afforded the title compound (27 mg, 54%) as a yellow oil. $\mathbf{R_f}$ = 0.68 (1:9 MeOH:DCM). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.70-7.68 (m, 1H, ArH), 7.50 (d, br, *J* = 7.7, 1H, ArH), 7.40 (td, *J* = 8.9, 7.7, 1H, ArH), 7.28-7.25 (m, 1H, ArH), 4.00 (td, *J* = 13.1, 5.0, 1H, H5a), 3.87-3.83 (m, br, 1H, H5b), 3.56-3.42 (m, br, 1H, H6a), 3.03 (dd, *J* = 14.8, 5.0, 1H, H6b), 2.64 (s, 3H, H3), 1.91 (s, 3H, H1). **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 172.8 (C13), 160.9 (C4), 143.1 (Ar), 141.4 (ArH), 133.1 (Ar), 129.6 (ArH), 129.4 (ArH), 127.6 (ArH), 65.7 (C2), 42.9 (C5), 34.4 (H6), 26.3 (C3), 21.4 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{13}H_{16}N_3OS$ [M+H] Calculated 262.0936. Found 262.1000. **IR ν_{max}** (ATR)/cm^{-1}: 3256, 3059, 2934, 2857, 1733, 1660.

N.B. Vinyl migration product 5-imino-1-(2-mercaptophenyl)-3,4-dimethyl-4-vinylimidazolidin-2-one, **2-127** (6 mg, 12%) was isolated as an orange oil.



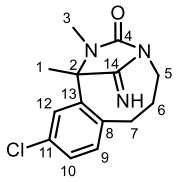
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.50-7.47 (m, 1H, ArH), 7.40-7.22 (m, 3H, 2 x ArH/NH), 7.18-7.10 (m, 1H, ArH), 6.36 (dd, *J* = 16.5, 9.5, 1H, H4), 5.41-5.37 (m, 2H, H5), 2.61 (s, 3H, H3), 1.82 (s, 3H, H1). **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 180.6 (C13), 166.2 (C6), 132.4 (ArH), 131.0 (C4), 129.9 (ArH), 129.2 (ArH), 128.4 (Ar), 127.1 (ArH), 125.4 (Ar), 118.8 (C5), 68.2 (C2), 25.1 (C3), 24.8 (C1).

10-Bromo-12-imino-1,2-dimethyl-1,5,6,7-tetrahydro-1,4-methanobenzo[*e*][1,3]diazonin-3(2*H*)-one (2-119):



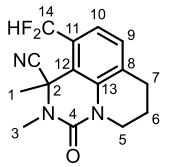
According to **GP3A**, 7-bromo-*N*-(1-cyanoethyl)-*N*-methyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (25.0 mg, 0.0779 mmol) and KHMDS (1 M in THF, 0.19 mL, 0.187 mmol) in anhydrous THF were stirred at 0 °C for 1 h. Purification via flash column chromatography eluting with EtOAc:PE (1:9 – 1:0) afforded the title compound (12 mg, 49%) as a white solid. $\mathbf{R_f}$ = 0.45 (1:0 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.56 (s, br, 1H, NH), 7.50 (s, br, 1H, ArH), 7.35 (dd, *J* = 8.2, 2.2, 1H, ArH), 6.99 (d, *J* = 8.2, 1H, ArH), 3.93-3.85 (m, 1H, H5a), 3.75-3.49 (m, br, 1H, H5b), 2.84-2.70 (m, br, 1H, H7a), 2.69 (s, 3H, H3), 2.49 (dd, *J* = 16.3, 9.1, 1H, H7b), 2.26-2.11 (m, br, 1H, H6a), 1.96 (ddd, *J* = 15.3, 10.1, 5.8, 1H, H6b), 1.88 (s, br, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 171.9 (C4), 161.3 (C14), 140.9 (Ar), 139.3 (Ar), 137.0 (ArH), 132.0 (ArH), 129.8 (ArH), 120.8 (Ar), 65.5 (C2), 42.1 (C5), 31.1 (C7), 25.6 (C3), 24.6 (C6), 20.5 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{14}H_{17}{}^{79}BrN_3O$ [M+H] Calculated 322.0550. Found 322.0560. **IR ν_{max}** (ATR)/cm^{-1}: 3265, 2919, 2858, 1723, 1659. **m.p** 175-178 °C.

10-Chloro-12-imino-1,2-dimethyl-1,5,6,7-tetrahydro-1,4-methanobenzo[*e*][1,3]diazonin-3(2*H*)-one (2-32):



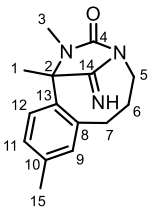
According to **GP3A**, 7-chloro-*N*-(1-cyanoethyl)-*N*-methyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (62.0 mg, 0.224 mmol) and KHMDS (1 M in THF, 0.45 mL, 0.448 mmol) in anhydrous THF were stirred at 0 °C for 1 h. Purification via flash column chromatography eluting with EtOAc:PE (1:9 – 1:0) afforded the title compound (43 mg, 69%) as a colourless solid. $\mathbf{R_f}$ = 0.24 (7:3 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.36 (d, *J* = 2.3, 1H, ArH), 7.20 (dd, *J* = 8.2, 2.3, 1H, ArH), 7.05 (d, *J* = 8.2, 1H, ArH), 3.88 (ddd, *J* = 13.9, 12.0, 5.8, 1H, H5a), 3.63 (dd, *J* = 13.9, 6.3, 1H, H5b), 2.83-2.72 (m, br, 1H, H7a), 2.68 (s, 3H, H3), 2.49 (dd, *J* = 16.3, 9.1, 1H, H7b), 2.26-2.10 (m, br, 1H, H6a), 1.96 (dddt, *J* = 14.9, 10.1, 5.7, 1.0, 1H, H6b), 1.88 (s, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 171.4 (C4), 161.3 (C14), 140.6 (Ar), 138.8 (Ar), 136.9 (ArH), 132.7 (Ar), 129.0 (ArH), 127.1 (ArH), 65.7 (C2), 42.2 (C5), 31.2 (C7), 25. (C3), 24.8 (C6), 20.5 (C1). **HRMS m/z** (ESI$^+$): calcd. for $C_{14}H_{17}ClN_3$ [M+H] Calculated 278.1055. Found 278.1060. **IR ν_{max}** (ATR)/cm^{-1}: 3263, 2957, 2850, 1732, 1662. **m.p** 155-157 °C (Recrystallised fromacetone:Et_2O).

1-(Difluoromethyl)-1,2-dimethyl-3-oxo-2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinazoline-1-carbonitrile (2-128):



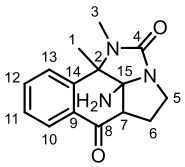
According to **GP3A**, *N*-(1-cyanoethyl)-*N*-methyl-7-(trifluoromethyl)-3,4-dihydronquinoline-1(2*H*)-carboxamide (60.0 mg, 0.193 mmol) and KHMDS (1 M in THF, 0.43 mL, 0.426 mmol) in dry THF were stirred at 0 °C for 1h. Purification via flash column chromatography eluting with EtOAc:*n*-pentane (1:9 – 1:0) afforded the title compound (7 mg, 12%) as a purple oil. **^{1}H NMR** (500 MHz; $CDCl_3$): δ_H 7.52 (t, *J* = 54.5, 1H, H14), 7.37 (dd, *J* = 8.0, 1.4, 1H, H10), 7.24 (d, *J* = 8.0, 1H, H9), 4.05 (dddd, *J* = 13.0, 9.2, 3.9, 0.6, 1H, H5a), 3.73 (dddd, *J* = 13.0, 6.8, 3.7, 1.2, 1H, H5b), 3.28 (s, 3H, H3), 2.89-2.77 (m, 2H, H7), 2.02 (ddddd, *J* = 10.6, 6.7, 5.1, 4.4, 2.6, 1H, H6a), 1.94-1.88 (m, 1H, H6b), 1.83 (s, 3H, H1). **^{13}C NMR** (125 MHz; $CDCl_3$): δ_C 163.1 (C4), 151.8 (C13), 134.2 (C8), 131.0 (C9), 129.8 (dd, *J* = 23.4, 22.4, C11), 127.9 (dd, *J* = 2.7, 1.6, C12), 120.9 (dd, *J* = 12.9, 5.2, C10), 118.8 (CN), 111.4 (dd, *J* = 239.6, 235.3, C14), 57.8 (C2), 43.3 (C5), 32.4 (C3), 28.2 (C7), 26.7 (C1), 20.9 (C6). **^{19}F NMR** (376 MHz; $CDCl_3$): δ_F -91.8 (d, *J* = 247.5, CF_2H), -122.5 (d, *J* = 247.5, CF_2H). **HRMS m/z** (ESI$^+$): calcd. for $C_{15}H_{16}F_2N_3O$ [M+H] Calculated 292.1183. Found 292.1256. **IR ν_{max}** (ATR)/cm^{-1}: 2962, 2250, 1659.

12-Imino-1,2,9-trimethyl-1,5,6,7-tetrahydro-1,4-methanobenzo[*e*][1,3]diazonin-3(2*H*)-one (2-120):



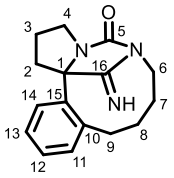
According to **GP3A**, *N*-(1-cyanoethyl)-*N*,6-dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (100 mg, 0.389 mmol) and KHMDS (1 M in THF, 0.78 mL, 0.778 mmol) in anhydrous THF were stirred at 0 °C for 2 h. Purification via flash column chromatography eluting with MeOH:DCM (0:1 – 1:9) afforded the title compound (35 mg, 35%) as a yellow gum. $\mathbf{R_f}$ = 0.41 (5:95 MeOH:DCM). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.51 (s, br, 1H, NH), 7.27 (d, *J* = 7.8, 1H, ArH), 7.04 (dd, *J* = 7.8, 1.5, 1H, ArH), 6.93 (d, *J* = 1.5, 1H, ArH), 3.89 (ddd, *J* = 13.7, 12.0, 5.7, 1H, H5a), 3.67-3.60 (m, 1H, H5b), 2.80-2.69 (m, 1H, H7a), 2.67 (s, 3H, H3), 2.50 (dd, *J* = 16.2, 9.1, 1H, H7b), 2.28 (s, 3H, H15), 2.23-2.19 (m, 1H, H6a), 1.99-1.91 (m, 1H, H6b), 1.86 (s, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 173.0 (C4), 161.6 (C14), 140.3 (Ar), 139.4 (Ar), 136.9 (ArH), 135.9 (Ar), 127.6 (ArH), 127.1 (ArH), 66.1 (C2), 42.8 (C5), 31.9 (C7), 25.9 (C3), 25.2 (C6), 21.2 (C15), 20.7 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{20}N_3O$ [M+H] Calculated 258.1528. Found 258.1607. **IR ν_{max}** (ATR)/cm^{-1}: 3233, 2923, 2852, 1726, 1664.

3^1-Amino-1,10b-dimethyl-1,3^1,4,5,5a,10b-hexahydrobenzo[*f*]imidazo[4,5,1-*hi*]indole-2,6-dione (2-121):



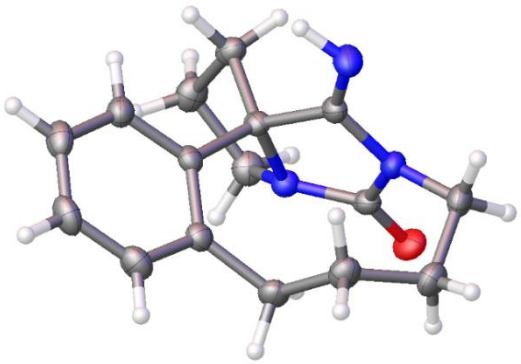
According to **GP3A**, *N*-(1-cyanoethyl)-*N*-methyl-5-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (29.0 mg, 0.107 mmol) and KHMDS (1 M in THF, 0.22 mL, 0.222 mmol) in anhydrous THF were stirred at 0 °C for 1.5 h. Purification via flash column chromatography eluting with MeOH:DCM (2:98 – 1:9) afforded the title compound (16 mg, 55%) as a colourless solid. $\mathbf{R_f}$ = 0.54 (1:9 MeOH:DCM). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.73 (ddd, *J* = 7.5, 1.5, 0.6, 1H, ArH), 7.63-7.54 (m, 2H, ArH), 7.49 (td, *J* = 7.3, 1.4, 1H, ArH), 4.07 (dddd, *J* = 12.2, 9.2, 2.2, 0.7, 1H, H5a), 3.21 (ddd, *J* = 12.2, 9.9, 8.0, 1H, H5b), 2.73-2.68 (m, 1H, H7), 2.57-2.47 (m, 1H, H6a), 2.25 (s, 3H, H3), 2.13 (dddd, *J* = 13.6, 9.9, 8.0, 2.2, 1H, H6b), 1.79 (s, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 197.6 (C8), 160.4 (C4), 139.7 (Ar), 134.2 (Ar), 132.6 (ArH), 129.2 (ArH), 127.1 (ArH), 126.4 (ArH), 83.7 (C15), 61.4 (C2), 56.0 (C7), 44.7 (C5), 25.1 (C3), 23.8 (C6), 15.0 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{17}N_3NaO_2$ [M+Na] Calculated 294.1213. Found 294.1204. **IR ν_{max}** (ATR)/cm^{-1}: 3391, 3316, 2973, 2923, 2850, 1682. **m.p** 157-160 °C.

15-Imino-2,3,7,8,9,10-hexahydro-1*H*,5*H*-6,14b-methanobenzo[*e*]pyrrolo[1,2-*c*]diazecine-5-one (2-37):



According to **GP3A**, 1-(2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carbonyl)pyrrolidine-2-carbonitrile (68.0 mg, 0.253 mmol) and KHMDS (1 M in THF, 0.51 mL, 0.506 mmol) in anhydrous THF were stirred at 0 °C for 1 h. Purification via flash column chromatography eluting with MeOH:DCM (0:1 – 1:9) affording the title compound (39 mg, 57%) as a white solid. $\mathbf{R_f}$ = 0.33 (25:75 MeOH:DCM). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.41-7.35 (m, 1H, ArH), 7.26-7.18 (m, 2H, ArH), 7.15-7.09 (m, 1H, ArH), 3.93 (ddd, *J* = 13.9, 11.6, 5.4, 1H, CH_2), 3.79 (ddd, *J* = 13.9, 5.9, 1.9, 1H, CH_2), 3.70 (dt, *J* = 11.1, 7.1, 1H, CH_2), 3.19 (ddd, *J* = 11.1, 6.9, 5.7, 1H, CH_2), 3.04 (ddd, *J* = 15.3, 6.4, 2.7, 1H, CH_2), 2.94-2.76 (m, 2H, 2xCH_2), 2.15-1.83 (m, 5H, 4xCH_2), 1.82-1.72 (m, 1H, CH_2), 1.51 (ddddd, *J* = 15.1, 10.2, 3.7, 2.7, 1.2, 1H, CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 172.7 (C5), 162.0 (C16), 143.4 (Ar), 137.0 (Ar), 134.2 (ArH), 129.0 (ArH), 126.4 (ArH), 125.6 (ArH), 74.5 (C1), 45.1 (CH_2), 40.7 (CH_2), 33.8 (CH_2), 32.2 (CH_2), 28.8 (CH_2), 26.8 (CH_2), 24.5 (CH_2). **HRMS m/z** (ESI^+): calcd. for $C_{16}H_{20}N_3O$ [M+H] Calculated 270.1601. Found 270.1609. **IR ν_{max}** (ATR)/cm^{-1}: 3270, 2953, 2869, 1723, 1645. **m.p** 173-175 °C (Recrystallised from $CDCl_3$:*n*-pentane).

X-ray crystal data:

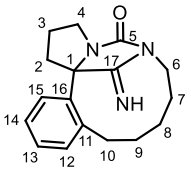


Empirical formula	$C_{16}H_{19}N_3O$
Formula weight	269.34
Temperature/K	100(2)
Crystal system	Triclinic
Space group	P-1
a/Å	6.9675(12)
b/Å	8.6877(14)
c/Å	12.0676(19)
α/°	87.020(11)
β/°	74.121(11)
γ/°	77.399(12)
Volume/Å^3	685.7(2)
Z	2
ρ_{calc}g/cm^3	1.305

μ/mm^{-1}	0.084
F(000)	288.0
Crystal size/mm^3	0.352 x 0.352 x 0.185
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	4.804 to 56.374
Index ranges	-9 ≤ h ≤ 9, -11 ≤ k ≤ 11, -15 ≤ l ≤ 15
Reflections collected	12669
Independent reflections	3290 [R_{int} = 0.0625, R_{sigma} = 0.0578]
Data/restraints/parameters	3290/0/185
Goodness-of-fit on F^2	1.034
Final R indexes [I>=2σ (I)]	R_1 = 0.0466, wR_2 = 0.1020
Final R indexes [all data]	R_1 = 0.0735, wR_2 = 0.1140
Largest diff. peak/hole/ eÅ^{-3}	0.23/-0.24

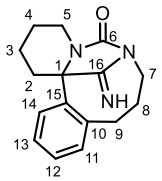
CCDC number: 1993730.

16-Imino-2,3,8,9,10,11-hexahydro-1*H*,5*H*,7*H*-6,15b-methanobenzo[*e*]pyrrolo[1,2-*c*]diazacycloundecin-5-one (2-137):



According to **GP3A**, 1-(1,2,3,4,5,6-hexahydrobenzo[*b*]azocine-1-carbonyl)pyrrolidine-2-carbonitrile (45.0 mg, 0.159 mmol) and KHMDS (1 M in THF, 0.32 mL, 0.318 mmol) in anhydrous THF were stirred at 0 °C for 1 h. Purification via flash column chromatography eluting with MeOH:DCM (0:1 – 1:9) afforded the title compound (33 mg, 73%) as a yellow gum. $\mathbf{R_f}$ = 0.44 (25:75 MeOH:DCM). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.39 (dd, *J* = 7.8, 1.5, 1H,ArH), 7.29-7.24 (m, 1H, ArH), 7.22 (dd, *J* = 7.5, 1.9, 1H, ArH), 7.20-7.15 (m, 1H, ArH), 3.84-8.62 (m, 3H, 2xCH_2), 3.16 (ddd, *J* = 11.1, 8.6, 3.5, 1H, CH_2), 3.04-2.86 (m, 2H, 2xCH_2), 2.46-2.32 (m, 1H, CH_2), 2.25-2.05 (m, 3H, 2xCH_2), 1.88-1.77 (m, 2H, 2xCH_2), 1.73-1.55 (m, 3H, 2xCH_2), 1.50 (ddt, *J* = 11.5, 9.7, 5.0, 1H, CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 170.0 (C5), 160.9 (C17), 144.6 (Ar), 134.9 (Ar), 133.5 (ArH), 129.0 (ArH), 126.3 (ArH), 126.0 (ArH), 73.4 (C1), 44.3 (CH_2), 39.8 (CH_2), 33.1 (CH_2), 30.7 (CH_2), 28.3 (CH_2), 26.5 (CH_2), 25.5 (CH_2), 23.5 (CH_2). **HRMS m/z** (ESI^+): calcd. for $C_{17}H_{22}N_3O$ [M+H] Calculated 284.1757. Found 284.1764. **IR ν_{max}** (ATR)/cm^{-1}: 3247, 2923, 1722, 1654.

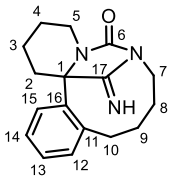
15-Imino-1,2,3,4,9,10-hexanhydro-6*H*,8*H*-7,14b-methanobenzo[*e*]pyrido[1,2-*c*]diazonin-6-one (2-138):



According to **GP3A**, 1-(1,2,3,4-tetrahydroquinoline-1-carbonyl)piperidine-2-carbonitrile (50.0 mg, 0.186 mol) and KHMDS (1 M in THF, 0.37 mL, 0.372 mmol) in anhydrous THF were stirred at 0 °C for 1

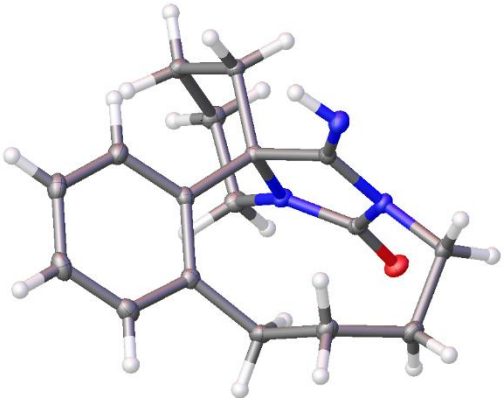
h. Purification via flash column chromatography eluting with EtOAc:PE (3:7 – 1:0) afforded the title compound (34 mg, 68%) as a yellow oil. $\mathbf{R_f}$ = 0.23 (1:0 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.46 (d, *J* = 7.6, 1H, ArH), 7.28-7.20 (m, 2H, ArH), 7.12 (d, *J* = 7.4, 1H, ArH), 4.04 (dd, *J* = 13.5, 4.7, 1H, H2a), 3.85 (td, *J* = 13.2, 5.9, 1H, H5a), 3.62-3.53 (m, br, 1H, H5b), 2.93 (d, br, *J* = 13.4, 1H, CH_2), 2.79-2.64 (m, 2H, CH_2), 2.55 (td, *J* = 13.2, 3.4, 1H, H2b), 2.22-2.10 (m, br, 1H, CH_2), 2.04-1.95 (m, 2H, CH_2), 1.91-1.76 (m, 2H, CH_2), 1.72 (d, br, *J* = 13.2, 1H, CH_2), 1.56-1.44 (m, 1H, CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 171.2 (C6), 159.6 (C16), 141.5 (Ar), 137.5 (Ar), 135.7 (ArH), 128.9 (ArH), 127.5 (ArH), 126.7 (ArH), 63.7 (C1), 41.9 (C5), 37.5 (C2), 31.4 (CH_2), 30.6 (CH_2), 25.7 (CH_2), 21.2 (CH_2). **HRMS m/z** (ESI^+): calcd. for $C_{16}H_{20}N_3O$ [M+H] Calculated 270.3480. Found 270.1601. **IR ν_{max}** (ATR)/cm^{-1}: 3244, 2950, 2851, 1728, 1666.

16-Imino-1,2,3,4,8,9,10,11-octahydro-6*H*-7,15b-methanobenzo[*e*]pyrido[1,2-*c*][1,3]diazecine-6-one (2-139):



According to **GP3A**, 1-(2,3,4,5,-tetrahydro-1*H*-benzo[*b*]azepine-1-carbonyl)piperidine-2-carbonitrile (70.0 mg, 0.247 mmol) and KHMDS (1 M in THF, 0.49 mL, 0.494 mmol) in anhydrous THF were stirred at 0 °c for 1.5 h. Purification via flash column chromatography eluting with MeOH:DCM (1:99 – 1:9) afforded the title compound (43 mg, 61%) as a yellow foam. $\mathbf{R_f}$ = 0.59 (5:95 MeOH:DCM). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.7-7.43 (m, 1H, ArH), 7.27-7.20 (m, 2H, ArH), 7.12-7.08 (m, 1H, ArH), 6.84 (s, br, 1H, NH), 4.10 (ddt, *J* = 13.6, 5.1, 1.6, 1H, CH_2), 4.05-3.93 (m, 1H, CH_2), 3.80 (ddd, *J* = 1.8, 6.0, 1.4, 1H, CH_2), 2.89 (d, br, *J* = 14.1, 1H, CH_2), 2.77 (ddd, *J* = 15.4, 12.4, 6.5, 1H, CH_2), 2.70-2.57 (m, 2H, CH_2), 2.06-1.91 (m, 2H, CH_2), 1.89-1.73 (m, 3H, CH_2), 1.70-1.62 (m, 2H, CH_2), 1.57-1.43 (m, 2H, CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 172.2 (C6), 156.9 (C17), 143.5 (Ar), 134.9 (Ar), 134.4 l(ArH), 129.0 (ArH), 128.2 (ArH), 126.4 (ArH), 64.8 (C1), 40.2 (CH_2), 37.5 (CH_2), 33.7 (CH_2), 32.5 (CH_2), 29.3 (CH_2), 25.8 (CH_2), 24.4 (CH_2), 21.1 (CH_2). **HRMS m/z** (ESI^+): calcd. for $C_{17}H_{22}N_3O$ [M+H] Calculated 284.1685. Found 284.1756. **IR ν_{max}** (ATR)/cm^{-1}: 3272, 2937, 2891, 2856, 1722, 1735, 1651.

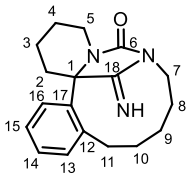
X-ray crystal data:



Empirical formula	$C_{17}H_{21}N_3O$
Formula weight	283.37
Temperature/K	100(2)
Crystal system	Triclinic
Space group	P-1
a/Å	7.0488(2)
b/Å	8.6329(3)
c/Å	12.6463(5)
α/°	88.989(2)
β/°	74.751(2)
γ/°	77.777(2)
Volume/Å^3	725.03(4)
Z	2
ρ_{calc}g/cm^3	1.298
μ/mm^{-1}	0.083
F(000)	304.0
Crystal size/mm^3	0.428 x 0.329 x 0.322
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	3.34 to 56.23
Index ranges	$-9 \le h \le 9$, $-11 \le k \le 11$, $-16 \le l \le 16$
Reflections collected	13480
Independent reflections	3531 [R_{int} = 0.0223, R_{sigma} = 0.0203]
Data/restraints/parameters	3531/0/194
Goodness-of-fit on F^2	1.034
Final R indexes [I>=2σ (I)]	R_1 = 0.0378, wR_2 = 0.0899
Final R indexes [all data]	R_1 = 0.0433, wR_2 = 0.0940
Largest diff. peak/hole/ eÅ^{-3}	0.33/-0.22

CCDC number: 1993731.

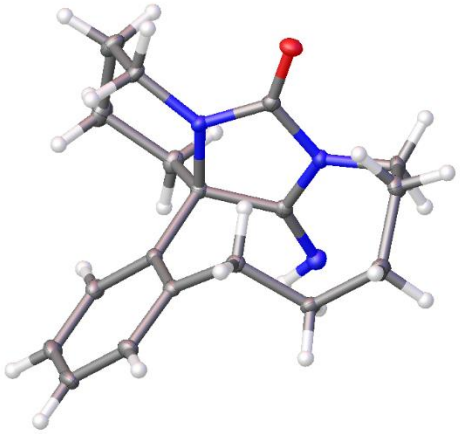
17-Imino-1,2,3,4,9,10,11,12-octahydro-6*H*,8*H*-7,16b-methanobenzo[*e*]pyrido[1,2-*c*][1,3]diazacycloundecin-6-one (2-140):



According to **GP3A**, 1-(1,2,3,4,5,6-hexahydrobenzo[*b*]azocine-1-carbonyl)piperidine-2-carbonitrile (185 mg, 0.622 mmol) and KHMDS (1 M in THF, 1.24 mL, 1.24 mmol) in anhydrous THF were stirred at 0 °C for 1.5 h. The title compound (163 mg, 88%) was obtained without any further purification as a yellow oil. $\mathbf{R_f}$ = 0.24 (1:0 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.51-7.46 (m, 1H, ArH), 7.28-7.22 (m, 2H, ArH), 7.18-7.13 (m, 1H, ArH), 6.74 (s, br, 1H, NH), 4.07 (ddt, br, *J* = 13.5, 4.9, 1.6, 1H, H2a), 3.81-3.71 (m, br, 2H, H7), 2.87 (d, br, *J* = 14.1, 1H, CH_2), 2.65-2.58 (m, 1H, CH_2), 2.53 (m, 1H, H2b), 2.36 (dt, *J* = 14.1, 9.6, 1H, CH_2), 2.23-2.12 (m, 1H, CH_2), 1.94-1.78 (m, 3H, 2 x CH_2), 1.67-1.58 (m, 5H, 3 x CH_2), 1.53-1.40 (m, 2H, CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 170.7 (C6), 156.2 (C18), 144.8 (Ar), 133.9 (ArH), 133.8 (Ar), 129.3 (ArH), 129.2 (ArH), 126.3 (ArH), 64.3 (C1), 40.0 (C7), 37.9 (C2), 34.2 (CH_2), 31.2 (CH_2),

29.4 (CH_2), 26.1 (CH_2), 25.8 (CH_2), 24.1 (CH_2), 21.5 (CH_2). **HRMS m/z** (ESI^+): calcd. for $C_{18}H_{24}N_3O$ [M+H] Calculated 298.1841. Found 298.1913. **IR ν_{max}** (ATR)/cm^{-1}: 3551, 3493, 3283, 3252, 3824, 2835, 1717, 1648.

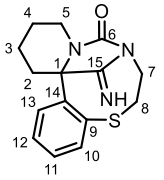
X-ray crystal data:



Empirical formula	$C_{18}H_{26}N_3O_{2.5}$
Formula weight	324.42
Temperature/K	100.01
Crystal system	triclinic
Space group	P-1
a/Å	7.6118(2)
b/Å	9.3656(3)
c/Å	12.1634(4)
α/°	93.7306(19)
β/°	95.390(2)
γ/°	108.1269(18)
Volume/Å^3	816.35(4)
Z	2
ρ_{calc}g/cm^3	1.320
μ/mm^{-1}	0.089
F(000)	350.0
Crystal size/mm^3	0.534 x 0.264 x 0.196
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	3.38 to 61.014
Index ranges	$-10 \le h \le 10$, $-13 \le k \le 13$, $-17 \le l \le 17$
Reflections collected	18692
Independent reflections	4993 [R_{int} = 0.0296, R_{sigma} = 0.0292]
Data/restraints/parameters	4993/0/232
Goodness-of-fit on F^2	1.039
Final R indexes [I>=2σ (I)]	R_1 = 0.0428, wR_2 = 0.1072
Final R indexes [all data]	R_1 = 0.0557, wR_2 = 0.1150
Largest diff. peak/hole/ eÅ^{-3}	0.41/-0.36

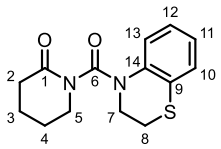
CCDC number: 1993732.

15-Imino-1,2,3,4,8,9-hexahydro-6*H*,7,14b-methanobenzo[*h*]pyrido[1,2-*f*][1,4,6]thiadiazonin-6-one (2-141):



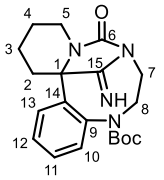
According to **GP3A**, 1-(3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine-4-carboyl)piperidine-2-carbonitrile (100 mg, 0.348 mmol) and KHMDS (1 M in THF, 0.70 mL, 0.696 mmol) in anhydrous THF were stirred at 0 °C for 1.5 h. Purification via flash column chromatography eluting with MeOH:DCM (0:1 – 1:9) afforded the title compound (36 mg, 36%) as an orange oil. $\mathbf{R_f}$ = 0.57 (5:95 MeOH:DCM). **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.69 (dd, *J* = 7.7, 1.6, 1H, ArH), 7.54 (dd, *J* = 7.9, 1.5, 1H, ArH), 7.40 (td, *J* = 7.9, 1.6, 1H, ArH), 7.24 (td, *J* = 7.7, 1.5, 1H, ArH), 4.04-4.00 (m, 1H, CH_2), 3.92 (td, *J* = 13.5, 5.0, 1H, CH_2), 3.77 (dd, *J* = 13.5, 5.5, 1H, CH_2), 3.35 (ddd, *J* = 14.9, 12.5, 5.5, 1H, CH_2), 3.05 (dd, *J* = 14.9, 5.0, 1H, CH_2), 2.90 (dd, br, *J* = 11.2, 3.9, 1H, CH_2), 2.46 (td, *J* = 1.5, 3.4, 1H, CH_2), 2.05-1.95 (m, br, 1H, CH_2), 1.87-1.77 (m, 2H, CH_2), 1.69 (d, br, *J* = 13.3, 1H, CH_2), 1.56-1.47 (m, 1H, CH_2). **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 172.9 (C6), 158.8 (C15), 142.3 (ArH), 141.5 (Ar), 133.9 (Ar), 129.5 (ArH), 129.1 (ArH), 128.4 (ArH), 63.7 (C1), 42.3 (CH_2), 37.6 (CH_2), 35.4 (CH_2), 30.9 (CH_2), 25.2 (CH_2), 21.1 (CH_2). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{18}N_3OS$ [M+H] Calculated 288.1171. Found 288.1181. **IR ν_{max}** (ATR)/cm^{-1}: 3239, 2923, 2845, 1732, 1660.

NB: Oxidation of starting urea **2-147** during the reaction resulted in isolation of 1-(3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine-4-carbonyl)piperidine-2-carbonitrile (26%).



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.48 (dd, *J* = 7.7, 1.3, 1H, ArH), 7.30 (td, *J* = 7.7, 1.6, 1H, ArH), 7.23 (td, *J* = 7.5, 1.3, 1H, ArH), 7.11 (dd, *J* = 7.5, 1.6, 1H, ArH), 3.77 (tt, *J* = 5.8, 2.2, 2H, H5), 3.34-3.30 (m, 2H, H7 or 8), 3.04-3.01 (m, 2H, H7 or 8), 2.45 (tt, *J* = 6.5, 2.2, 2H, H2), 1.88-1.82 (m, 2H, H3), 1.77-1.71 (m, 2H, H4). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 172.8 (C6), 159.2 (C15), 145.2 (Ar), 133.5 (ArH), 132.9 (Ar), 129.3 (ArH), 127.4 (ArH), 127.1 (ArH), 49.3 (C5), 40.9 (C7 or 8), 37.3 (C7 or 8), 32.2 (C2), 21.6 (C4), 19.5 (C3).

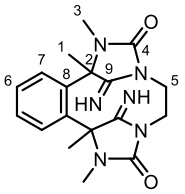
***tert*-Butyl 15-imino-6-oxo-1,2,3,4,8,9-hexahydro-6*H*,10*H*-7,14b-methanobenzo[*g*]pyrido[2,1-*i*]triazonine-10-carboxylate (2-142):**



According to **GP3A**, *tert*-butyl 4-(2-cyanopiperidine-1-carbonyl)-3,4-dihydroquinoxaline-1(2*H*)-carboxylate (50.0 mg, 0.135 mmol) and KHMDS (1 M in THF, 0.27 mL, 0.270 mmol) in anhydrous THF were stirred at 0 °C for 1.5 h. Purification via flash column chromatography with MeOH:DCM (1:99 –

1:9) afforded the title compound (14 mg, 28%) as a brown oil. $\mathbf{R_f}$ = 0.28 (5:95 MeOH:DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) (mixture of rotamers A:B in a 0.67:0.33 ratio): δ_H 7.48 (dt, *J* = 7.1, 1.7, 1H, ArH, rot. A+B), 7.38-7.30 (m, 2H, ArH, rot. A+B), 7.16-7.12 (m, 0.33H, ArH, rot. B), 7.05-7.01 (m, 0.67H, ArH, rot. A), 4.31 (ddd, *J* = 13.7, 11.9, 5.2, 0.67H, CH_2, rot. A), 4.26-4.23 (m, 0.33H, CH_2, rot. B), 4.11 (dd, *J* = 14.0, 5.2, 067H, CH_2, rot. A), 3.98 (ddt, *J* = 13.3, 5.0, 1.6, 1H, CH_2, rot. A+B), 3.94-3.90 (m, 0.66H, 2xCH_2, rot. B), 3.59-3.53 (m, 1H, CH_2, rot. A+B), 3.27 (ddd, *J* = 14.4, 12.0, 5.4, 0.33H, CH_2, rot. B), 3.17 (ddd, *J* = 14.0, 11.9, 5.4, 0.67H, CH_2, rot. A), 2.95-2.89 (m, 1H, CH_2, rot. A+B), 2.62 (td, *J* = 13.4, 3.3, 0.33H, CH_2, rot. B), 2.52 (td, *J* = 13.3, 3.3, 0.67H, CH_2, rot. A), 2.04-1.95 (m, 1H, CH_2, rot. A+B), 1.90-1.78 (m, 2, CH_2, rot. A+B), 1.67-1.64 (m, 1H, CH_2, rot. A+B), 1.50-1.44 (m, 1H, CH_2, rot. A+B), 1.53 (s, 3H, Boc-CH_3, rot. B), 1.33 (s, 6H, Boc-CH_3, ro.t A). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 173.1 (C6, rot. B), 172.6 (C6, rot. A), 158.1 (C15, rot. A), 158.0 (C15, rot. B), 154.8 (Boc-CO, rot. B), 154.5 (Boc-CO, rot. A), 143.3 (Ar, rot. B), 143.1 (Ar, rot. A), 135.5 (Ar, rot. B), 134.7 (Ar, rot. A), 133.5 (ArH, rot. B), 132.9 (ArH, rot. A), 130.1 (ArH, rot. B), 129.6 (ArH, rot. A), 127.9 (ArH, rot. A+B), 127.6 (ArH, rot. A+B), 81.6 (Boc-$C(Me)_3$, rot. A), 80.7 (Boc-$C(Me)_3$, rot. B), 63.1 (C1, rot. B), 62.9 (C1, rot. A), 47.3 (CH_2, rot. B), 46.6 (CH_2, rot. A), 43.6 (CH_2, rot. B), 42.7 (CH_2, rot. A), 37.6 (CH_2, rot. A), 37.6 (CH_2, rot. A), 37.4 (CH_2, rot. B), 29.6 (CH_2, rot. A+B), 28.4 (Boc-CH_3, rot. A), 28.1 (Boc-CH_3, rot. B), 25.0 (CH_2, rot. A+B), 24.8 (CH_2, rot. A+B), 21.0 (CH_2, rot. A+B). **HRMS m/z** (ESI$^+$): calcd. for $C_{20}H_{27}N_4O_3$ [M+H] Calculated 371.2078. Found 271.2074. **IR ν_{max}** (ATR)/cm^{-1}: 3265, 2979, 2947, 2870, 1737, 1697, 1663.

15,16-Diimino-1,2,9,10-tetramethyl-1,2,5,6,9,10-hexahydro-1,4:7,10-dimethanobenzo[*j*][1,3,6,8]tetraazacyclododecine-3,8-dione (2-148a & 2-148b):



According to a modified **GP3A**, N^1,N^4-bis(1-cyanoethyl)-N^1,N^4-dimethyl2,3-dihydroquinoxaline-1,4-dicarboxamide (306 mg, 0.863 mmol) and KHMDS (1 M in THF, 3.50 mL, 3.50 mmol) in anhydrous THF were stirred at 0 °C for 5 h. The reaction mixture was quenched with MeOH (2 mL) and the volatiles removed under reduced pressure. Purification via column chromatography eluting with MeOH:DCM (5:95 – 2:8) afforded the title compound as a mixture of diastereoisomers:

***Meso*-(major)-diastereoisomer (2-148a):**

(125 mg, 41%) as a yellow solid. $\mathbf{R_f}$ = 0.32 (1:9 MeOH:DCM). **^{1}H NMR** (500 MHz, MeOD-d_4): δ_H 7.93 (dd, *J* = 6.0. 3.6, 2H, ArH), 7.61 (dd, *J* = 6.0, 3.5, 2H, ArH), 4.22-4.14 (m, 2H, H5a), 4.10-4.02 (m, 2H, H5b), 2.60 (s, 6H, H3), 1.91 (s, 6H, H1). **^{13}C NMR** (125 MHz, MeOD-d_4): δ_C 167.4 (C4), 156.0 (C9), 135.6 (Ar),

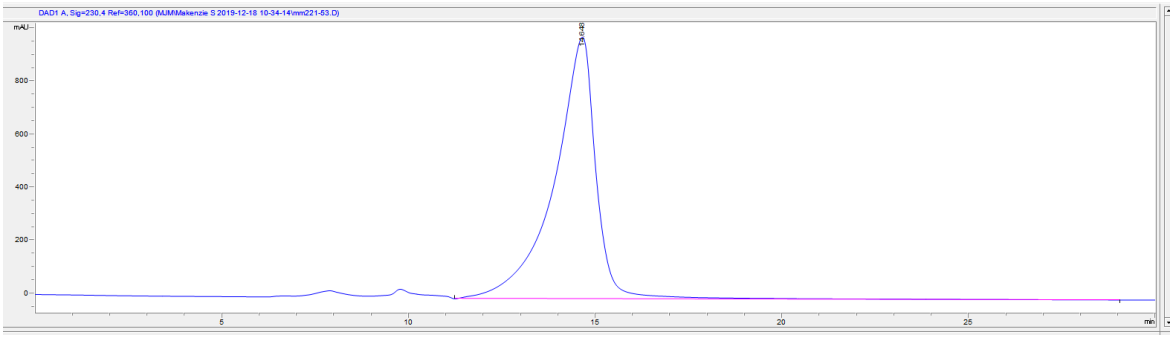
132.5 (ArH), 129.5 (ArH), 65.7 (C2), 35.8 (C5), 27.6 (C1), 24.7 (C3). **HRMS m/z** (ESI^+): calcd. for $C_{18}H_{23}N_6O_2$ [M+H] Calculated 255.1877. Found 355.1869. **IR ν_{max}** (ATR)/cm^{-1}: 3262, 2946, 1745, 1668. **m.p** 288-291 °C (Recrystallised from MeOH).

***C_2 symmetric*-(minor)-diastereoisomer (2-148b):**

(44 mg, 14%) as a yellow solid. **R_f** = 0.44 (1:9 MeOH:DCM). **^{1}H NMR** (500 MHz, MeOD-d_4): δ_H 7.96-7.93 (m, 2H, ArH), 7.58-7.55 (m, 2H, ArH), 4.18-4.05 (m, br, 2H, H5a), 3.81-3.79 (m, br, 2H, H5b), 2.63 (s, 6H, H3), 1.87 (s, 6H, H1). **^{13}C NMR** (125 MHz, MeOD-d_4): δ_C 176.9 (C4), 157.5 (C9), 137.2 (Ar), 133.8 (ArH), 130.6 (ArH), 66.7 (C2), 38.4 (C5), 29.5 (C1), 25.2 (C3). **HRMS m/z** (ESI^+): calcd. for $C_{18}H_{23}N_6O_2$ [M+H] Calculated 355.1877. Found 355.1892. **IR ν_{max}** (ATR)/cm^{-1}: 3271, 3222, 2976, 2960, 1729, 1659. **m.p** 234-236 °C (Recrystallised form MeOH).

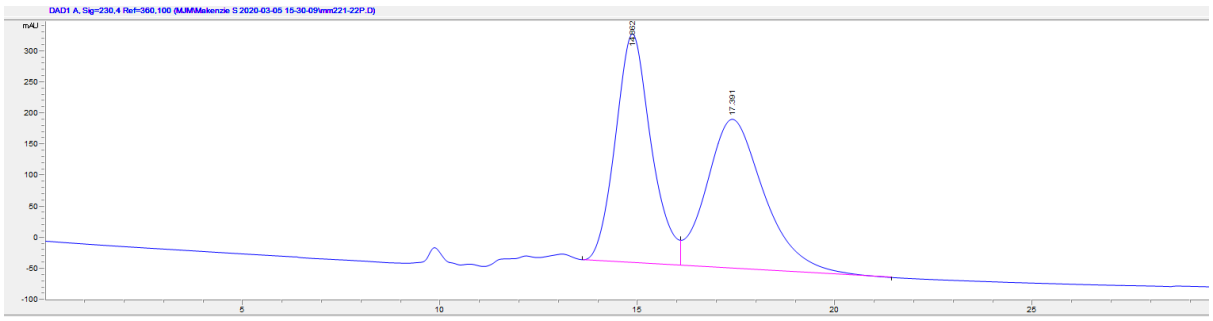
HPLC: Chiral OJ-H column, MeOH:EtOH = 5:95, flow = 0.3 mL/min, 230 nm.

***Meso*-(major)-diastereoisomer (2-148a):** t_R = 14.6 min.



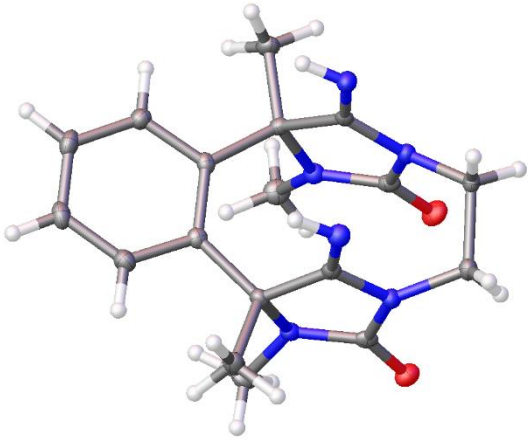
Peak #	Time / min	Area	Height	Width	Area / %	Symmetry
1	14.648	77686.2	990	1.0895	100.000	1.89

***Racemic*-(minor)-diastereoisomer (2-148b):** t_R = 14.9 min, 17.4 min, *er* = 49:51.



Peak #	Time / min	Area	Height	Width	Area / %	Symmetry
1	14.862	23223.8	367.4	0.9434	48.798	0.85
2	17.391	24367.9	239.6	1.5146	51.202	0.756

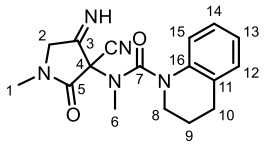
X-ray crystal data for *meso*-(major)-diastereoisomer (2-148a):



Empirical formula	$C_{18}H_{26}N_6O_4$
Formula weight	390.45
Temperature/K	100(2)
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a/Å	8.3617(3)
b/Å	13.8207(6)
c/Å	16.0698(6)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1857.10(13)
Z	4
ρ_{calc}g/cm^3	1.396
μ/mm^{-1}	0.101
F(000)	832.0
Crystal size/mm^3	0.443 x 0.367 x 0.154
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	3.886 to 55.938
Index ranges	-11 ≤ h ≤ 11, -18 ≤ k ≤ 18, -20 ≤ l ≤ 21
Reflections collected	17119
Independent reflections	4432 [R_{int} = 0.0451, R_{sigma} = 0.0416]
Data/restraints/parameters	4432/6/281
Goodness-of-fit on F^2	1.018
Final R indexes [I>=2σ (I)]	R_1 = 0.0355, wR_2 = 0.0754
Final R indexes [all data]	R_1 = 0.0444, wR_2 = 0.0800
Largest diff. peak/hole/ eÅ^{-3}	0.25/-0.18

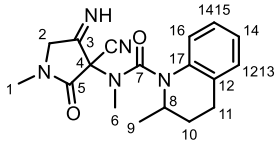
CCDC number: 1993733734.

***N*-(3-Cyano-4-imino-1-methyl-2-oxopyrrolidin-3-yl)-*N*-methyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (2-149):**



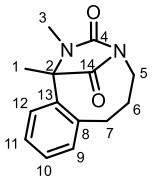
According to **GP3A**, *N*-(cyanomethyl)-*N*-methyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (60.0 mg, 0.262 mmol) and KHMDS (1 M in THF, 0.52 mL, 0.524 mmol) in anhydrous THF stirred at 0 °C for 2 h. Purification via flash column chromatography eluting with EtOAc:PE (1:3 – 1:0) afforded the title compound (21 mg, 49%) as a yellow oil. **^{1}H NMR** (400 MHz; $CDCl_3$): δ_H 8.81 (s, br, 1H, NH), 7.12-7.09 (m, 1H, ArH), 7.06-7.04 (m, 2H, ArH), 7.00-6.94 (m, 1H, ArH), 3.85 (s, 2H, H2), 3.70 (t, *J* = 6.5, 2H, H8), 2.99 (s, 3H, H6), 2.85 (s, 3H, H1), 2.77 (t, *J* = 6.5, 2H, H10), 2.01-1.98 (m, 2H, H9). **^{13}C NMR** (101 MHz; $CDCl_3$): δ_C 158.6 (C7), 156.7 (C5), 146.5 (C3), 139.7 (Ar), 131.6 (Ar), 128.5 (ArH), 126.5 (ArH), 123.8 (ArH), 121.8 (ArH), 114.9 (CN), 89.1 (C4), 50.1 (C2), 45.7 (C8), 36.7 (C6), 29.8 (C1), 26.8 (C10), 24.2 (C9). **HRMS m/z** (ESI^+): calcd. for. $C_{17}H_{19}N_5O_2H$ [M+H]. Calculated 326.1539. Found 326.1608. **IR ν_{max}** (ATR)/cm^{-1}: 2928, 2862, 2215, 1706, 1623.

***N*-(3-Cyano-4-imino-1-methyl-2-oxopyrrolidin-3-yl)-*N*,2-dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (2-150):**



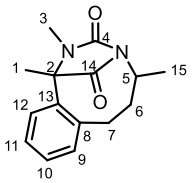
According to **GP3A**, *N*-(cyanomethyl)-*N*,2-dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (60.0 mg, 0.247 mmol) and KHMDS (1 M in THF, 0.49 mL, 0.494 mmol) in anhydrous THF were stirred at 0 °C for 2 h. Purification via flash column chromatography eluting with MeOH:DCM (0:1 – 1:9) afforded the title compound (28 mg, 67%) as an orange oil. **R_f** = 0.70 (1:9 MeOH:DCM). **^{1}H NMR** (400 MHz; $CDCl_3$): δ_H 9.49 (s, br, 1H, NH), 7.16-7.09 (m, 2H, ArH), 7.04-6.93 (m, 2H, ArH), 4.59 (d, *J* = 15.3, 1H, H2a), 4.31 (quint. d, *J* = 6.4, 4.3, 1H, H8), 3.80 (d, *J* = 15.3, 1H, H2b), 3.29 (s, 3H, H6), 2.75 (ddd, *J* = 15.6, 8.7, 6.4, 1H, H11a), 2.64 (dt, *J* = 15.6, 6.2, 1H, H11b), 2.47 (s, 3H, H1), 2.17 (ddt, *J* = 13.2, 8.7, 6.4, 1H, H10a), 1.64 (dtd, *J* = 13.2, 6.2, 4.3, 1h, H10b), 1.18 (d, *J* = 6.4, 3H, H9). **^{13}C NMR** (101 MHz; $CDCl_3$): δ_C 161.6 (C5), 152.0 (C7), 138.0 (Ar), 132.0 (C3), 129.9 (Ar), 128.9 (ArH), 127.0 (ArH), 123.6 (ArH), 121.7 (ArH), 110.8 (CN), 97.2 (C4), 50.4 (C8), 43.8 (C2), 36.5 (C1), 30.7 (C10), 28.9 (C6), 24.5 (C11), 19.3 (C9). **HRMS m/z** (ESI^+): calcd. for. $C_{18}H_{21}N_5NaO_2$ [M+Na]. Calculated 362.1593. Found 362.1609. **IR ν_{max}** (ATR)/cm^{-1}: 2955, 2897, 2218, 1698, 1635.

1,2-Dimethyl-1,5,6,7-tetrahydro-1,4-methanobenzo[*e*][1,3]diazonine-3,12(2*H*)-dione (2-29):



According to **GP4**, 12-imino-1,2-dimethyl-1,5,6,7-tetrahydro-1,4-methanobenzo[*e*][1,3]diazonin-3(2*H*)-one (37.0 mg, 0.152 mmol) dissolved in TFA:2 M HCl (1:9 ratio, 3.04 mL, 0.05 M) in a microwave vial. The sealed vial was heated in the μW at 120 °C for 2 h. The title compound (28 mg, 75%) was afforded without any further purification as a yellow oil. $\mathbf{R_f}$ = 0.71 (1:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.40 (dd, *J* = 7.3, 1.7, 1H, ArH), 7.26 (quint. d, *J* = 7.3, 1.8, 2H, ArH), 7.12 (dd, *J* = 7.3, 1.8, 1H, ArH), 3.81-3.65 (m, br, 2H, H5), 2.96-2.78 (m, br, 1H, H7a), 2.73 (s, 3H, H3), 2.57 (dd, *J* = 16.1, 9.1, 1H, H7b), 2.20-2.10 (m, 1H, H6a), 2.07-1.99 (m, 1H, H6b), 1.87 (s, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 180.9 (C14), 172.9 (C4), 139.7 (Ar), 137.0 (Ar), 135.9 (ArH), 129.5 (ArH), 127.5 (ArH), 127.1 (ArH), 66.6 (C2), 40.7 (C5), 32.0 (C7), 29.8 (C6), 25.5 (C3), 18.0 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{14}H_{16}N_2NaO_2$ [M+Na] Calculated 267.1212. Found 267.1103. **IR ν_{max}** (ATR)/cm^{-1}: 2923, 2859, 1771, 1778, 1707.

1,2,5-Trimethyl-1,5,6,7-tetrahydro-1,4-methanobenzo[*e*][1,3]diazonine-3,12(2*H*)-dione (2-163 and 2-164):



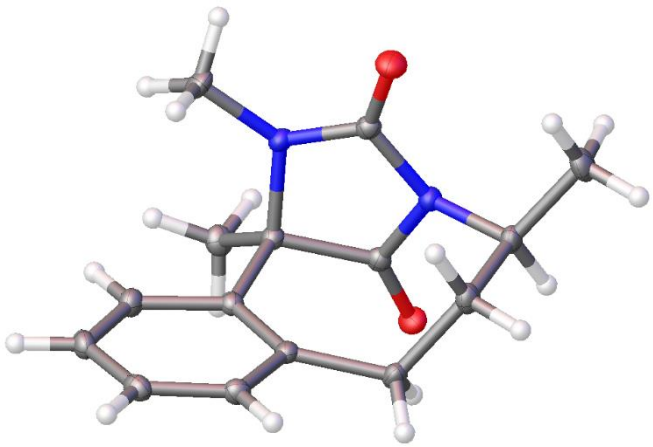
According to **GP4**, 12-imino-1,2,5-trimethyl-1,5,6,7-tetrahydro-1,4-methanobenzo[*e*][1,3]diazonin-3(2*H*)-one was dissolved in TFA:2 M HCl (1:9 ratio, 0.05 M) in a microwave vial. The sealed vial was heated in the μW at 120 °C for 2 h.

Major-diastereoisomer (2-163):

12-Imino-1,2,5-trimethyl-1,5,6,7-tetrahydro-1,4-methanobenzo[*e*][1,3]diazonin-3(2*H*)-one (15.0 mg, 0.0583 mmol) afforded the title compound (7 mg, 47%) as a yellow gum. $\mathbf{R_f}$ = 0.80 (5:95 MeOH:DCM). **^{1}H NMR** (500 MHz, $CDCl_3$, 243 K/-30 °C) (mixture of rotamers A:B in a 0.70:0.30 ratio): δ_H 7.40 (d, *J* = 7.3, 0.3 H, ArH rot. B), 7.34-7.23 (m, 2H, ArH, rot. A+B), 7.23-7.18 (m, 0.7H, ArH, rot. A), 7.13 (d, *J* = 7.6, 1H, ArH), 4.59 (sextet, *J* = 7.4, 0.7H, H5, rot. A), 4.44 (quint., *J* = 7.7, 0.3H, rot. B), 3.26-3.14 (m, 0.7H, H7, rot. A), 2.82-2.73 (m, 1H, H7, rot. A+B), 2.76-2.73 (m, 0.3H, H7, rot. B), 2.72 (s, 1H, H3, rot. B), 2.58 (s, 2H, H3, rot. A), 2.38-2.24 (m, 0.3H, H6a, rot. B), 2.17-2.05 (m, 1.7H, H6, rot. A+B), 1.84 (s, 1H, H1, rot. B), 1.83 (s, 2H, H1, rot. A), 1.68 (d, *J* = 7.6, 1H, H15, rot. B), 1.62 (d, *J* = 7.2, 2H, H15, rot. A). **^{13}C NMR** (125 MHz, $CDCl_3$, 243 K/-30 °C): δ_C 182.7 (C14, rot. A), 181.7 (C14, rot. B), 159.3 (C4, rot. B), 158.4 (C4, rot. A), 137.5 (Ar, rot. A+B), 137.4 (Ar, rot. A+B), 136.7 (ArH, rot. A+B), 129.5 (ArH, rot.

B), 128.8 (ArH, rot. A), 127.4 (ArH, rot. B), 127.1 (ArH, rot. B), 126.8 (ArH, rot. A), 126.8 (ArH, rot. A), 66.9 (C2, rot. A), 65.1 (C2, rot. B), 59.3 (C5, rot. B), 56.4 (C5, rot. A), 32.4 (C6 or 7, rot. A+B), 31.3 (C6 or 7, rot. A+B), 25.1 (C3, rot. B), 24.4 (C3, rot. A), 18.0 (C15 or 1, rot. B), 17.9 (C15 or 1, rot. B), 17.7 (C15, rot. A), 16.6 (C1, rot. A). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{18}N_2NaO_2$ [M+Na] Calculated 281.1260. Found 281.1258. **IR ν_{max}** (ATR)/cm^{-1}: 2920, 2851, 1769, 1712.

X-ray crystal data:



Empirical formula	$C_{15}H_{18}N_2O_2$
Formula weight	258.31
Temperature/K	100.01
Crystal system	Monoclinic
Space group	$P2_{1/n}$
a/Å	9.6859(2)
b/Å	8.2156(2)
c/Å	16.9618(3)
α/°	90
β/°	106.1200(10)
γ/°	90
Volume/$Å^3$	1296.67(5)
Z	4
$\rho_{calc}g/cm^3$	1.323
μ/mm^{-1}	0.089
F(000)	552.0
Crystal size/mm^3	0.543 x 0.24 x 0.163
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	4.398 to 60.116
Index ranges	$-13 \le h \le 13$, $-7 \le k \le 11$, $-23 \le l \le 23$
Reflections collected	26574
Independent reflections	3801 [R_{int} = 0.0423, R_{sigma} = 0.0276]
Data/restraints/parameters	3801/0/175
Goodness-of-fit on F^2	1.014
Final R indexes [I>=2σ (I)]	R_1 = 0.0396, wR_2 = 0.0968
Final R indexes [all data]	R_1 = 0.0530, wR_2 = 0.1047

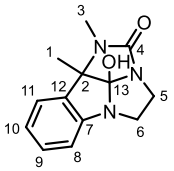
Largest diff. peak/hole/ eÅ^{-3} 0.41/-0.21

CCDC number: 1993735.

Minor-diastereoisomer (2-164):

12-Imino-1,2,5-trimethyl-1,5,6,7-tetrahydro-1,4-methanobenzo[*e*][1,3]diazonin-3(2*H*)-one (23.0 mg, 0.0894 mmol) afforded the title compound (7 mg, 30%) as an orange oil. $\mathbf{R_f}$ = 0.84 (5:95 MeOH:DCM). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.33 (dd, *J* = 7.2, 2.0, 1H, ArH), 7.22-7.15 (m, 2H, ArH), 7.05 (dd, *J* = 7.0, 2.1, 1H, ArH), 4.14-4.04 (m, 1H, H5), 2.76 (ddd, *J* = 16.4, 9.2, 2.2, 1H, H7a), 2.65 (s, 3H, H3), 2.46 (ddd, *J* = 16.4, 8.0, 1.7, 1H, H7b), 2.08-1.94 (m, 2H, H6), 1.78 (s, 3H, H1), 1.49 (d, *J* = 6.9, 3H, H15). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 181.3 (C14), 160.5 (C4), 140.0 (Ar), 137.0 (Ar), 135.7 (ArH), 129.5 (ArH), 127.6 (ArH), 127.1 (ArH), 66.3 (C2), 52.3 (C5), 33.4 (C6), 32.7 (C7), 25.6 (C3), 19.4 (C15), 18.4 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{18}N_2NaO_2$ [M+Na] Calculated 259.1441. Found 259.1436. **IR ν_{max}** (ATR)/cm^{-1}: 2932, 2852, 1771, 1706.

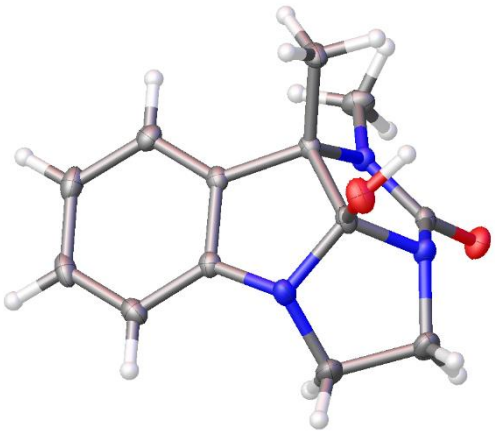
2a^1-Hydroxy-1,8b-dimethyl-2a^1,3,4,8b-tetrahydro-1,2a,4a-triazapentaleno[1,6-*b*]inden-2(1*H*)-one (2-165):



tert-Butyl 6,7-dimethyl-5,12-dioxo-2,3,6,7-tetrahydro-4,7-methanobenzo[*g*][1,3,6]triazonine-1(5*H*)-carboxylate (49.0 mg, 0.142 mmol) was dissolved in 2 M HCl:MeOH (1:1 ratio, 0.05 M). The solution was heated under reflux and stirred for 44 h. The reaction mixture was cooled to room temperature and extracted into DCM (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography eluting with MeOH:DCM (1:99 – 1:9) afforded the title compound (18 mg, 52%) as a yellow solid. $\mathbf{R_f}$ = 0.17 (1:20 MeOH:DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) (mixture of rotamers A:B in a 0.78:0.22 ratio): δ_H 7.23-7.18 (m, 1H, ArH, rot. A+B), 7.11-7.08 (m, 1H, ArH, rot. A+B), 6.94-6.87 (m, 1H, ArH, rot. A+B), 6.74 (d, *J* = 7.7, 1H, ArH, rot. A+B), 4.07 (ddd, *J* = 11.8, 8.0, 3.7, 1H, H5a, rot. A+B), 3.96 (s, br, 1H, OH, rot. A+B), 3.80-3.70 (m, 1H, H6a, rot. A+B), 3.61-3.54 (m, 1H, H5b, rot. A+B), 3.22 (dt, *J* = 9.7, 8.0, 1H, H6b, rot. A+B), 2.74 (s, 2.34H, H3, rot. A), 2.72 (s, 0.66H, H3, rot. B), 1.67 (s, 2.34H, H1, rot. A), 1.66 (s, 0.66H, H1, rot. B). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 161.0 (C4, rot. B), 160.3 (C4, rot. A), 150.8 (Ar, rot. B), 150.4 (Ar, rot. A), 132.7 (Ar, rot. A), 132.5 (Ar, rot. B), 130.2 (ArH, rot. A), 130.2 (ArH, rot. B), 123.5 (ArH, rot. B), 123.4 (ArH, rot. A), 121.9 (ArH, rot. A), 121.5 (ArH, rot. B), 113.9 (ArH, rot. A), 113.9 (ArH, rot. B), 102.7 (C13, rot. B), 102.6 (C13, rot. A), 68.7 (C2, rot. B), 68.3 (C2, rot A), 53.0 (C6, rot. A), 52.6 (C6, rot. B), 47.7 (C5, rot. B) 47.7 (C5, rot. A), 25.5 (C3, rot. B), 25.4 (C3, rot. A), 17.0 (C1, rot. B), 16.4

(C1, rot. A). **HRMS m/z** (ESI^+): calcd. for $C_{13}H_{16}N_3O_2$ [M+H] Calculated 246.1164. Found 246.1257. **IR** ν_{max} (ATR)/cm^{-1}: 3292 (br), 2968, 2932, 2871, 1674, 1603. **m.p** 186-188 °C (Recrystallised from $CHCl_3$:Et_2O).

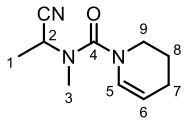
X-ray crystal data:



Empirical formula	$C_{13}H_{15}N_3O_2$
Formula weight	245.28
Temperature/K	100(2)
Crystal system	orthorhombic
Space group	Pbca
a/Å	13.4226(6)
b/Å	7.6316(4)
c/Å	22.4832(11)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2303.09(19)
Z	8
ρ_{calc}g/cm^3	1.415
μ/mm^{-1}	0.098
F(000)	1040.0
Crystal size/mm^3	0.461 x 0.284 x 0.24
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	3.624 to 55.97
Index ranges	$-17 \le h \le 17$, $-10 \le k \le 10$, $-29 \le l \le 28$
Reflections collected	19730
Independent reflections	2763 [R_{int} = 0.0432, R_{sigma} = 0.0251]
Data/restraints/parameters	2763/0/169
Goodness-of-fit on F^2	1.047
Final R indexes [I>=2σ (I)]	R_1 = 0.0413, wR_2 = 0.0977
Final R indexes [all data]	R_1 = 0.0543, wR_2 = 0.1046
Largest diff. peak/hole/ eÅ^{-3}	0.33/-0.25

CCDC number: 1993733.

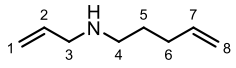
***N*-(1-Cyanoethyl)-*N*-methyl-3,4-dihydropyridine-1(2*H*)-carboxamide (2-180):**



According to **GP2**, (1-cyanoethyl)(methyl)carbamic chloride (700 mg, 4.78 mmol), 1,2,3,6-tetrahydropyridine.HCl (572 mg, 4.78 mmol) and triethylamine (1.33 mL, 9.56 mmol) were heated under reflux at 75 °C for 25 h. The crude allyl urea (910 mg, 99%) was taken forward without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.87-5.79 (m, 1H, H6), 5.64 (ddt, *J* = 8.4, 3.3, 1.6, 1H, H7), 4.86-4.78 (m, 1H, H2), 3.78-3.73 (m, 2H, H5), 3.44 (dt, *J* = 13.2, 5.3, 1H, H9a), 3.30-3.21 (m, 1H, H9b), 2.88 (d, *J* = 1.1, 3H, H3), 2.30-2.08 (m, 2H, H8), 1.49 (dd, *J* = 7.4, 1.1, 3H, H1). **HRMS m/z** (ESI^+): calcd. for $C_{10}H_{15}N_3ONa$ [M+Na] Calculated 216.1107. Found 216.1115.

Under an atmosphere of N_2 the crude allyl urea (900 mg, 4.66 mmol) and chlorocarbonylhydridotris(triphenylphosphine) (444 mg, 0.466 mmol) were dissolved in anhydrous THF (47 mL). The reaction mixture was heated to 66 °C and stirred for 21 h. The reaction mixture was cooled to room temperature and the volatiles removed under reduced pressure. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 1:0) afforded the title compound (730 mg, 81%) as an orange oil. **R_f** = 0.84 (7:3 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.33 (dt, *J* = 8.3, 1.9, 1H, H5), 4.91 (dt, *J* = 8.3, 3.7, 1H, H6), 4.84 (q, *J* = 7.3, 1H, H2), 3.57 (ddd, *J* = 12.4, 6.5, 3.7, 1H, H7a), 3.40 (ddd, *J* = 12.4, 8.36, 3.7, 1H H7b), 2.92 (s, 3H, H3), 2.12-2.05 (m, 2H, H9), 1.94-1.78 (m, 2H, H8), 1.53 (d, *J* = 7.3, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.3 (C4), 127.4 (C5), 118.9 (CN), 106.7 (C6), 44.9 (C2), 43.8 (C7), 34.7 (C3), 22.4 (C8), 21.1 (C9), 17.3 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{10}H_{15}N_3NaO$ [M+Na] Calculated 216.1107. Found 216.1110. . **IR ν_{max}** (ATR)/cm^{-1}: 2931, 2863, 2241, 1704.

***N*-Allylpent-4-en-1-amine (2-184):**



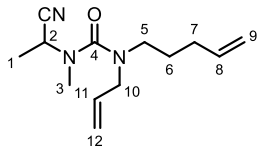
N-allylpent-4-en-1-amine synthesised in accordance with the literature.[129]

Under an atmosphere of N_2, a solution of allylamine (5.02 mL, 67.1 mmol) in anhydrous Et_2O (4 mL) was added to a solution of 5-bromo-1-pentene (0.78 mL, 6.71 mmol) in anhydrous Et_2O (4 mL). The reaction mixture was heated to 36 °C and stirred for 64 h. The reaction mixture was cooled to room temperature and poured onto sat. aq. K_2CO_3 (20 mL), the pH was made up to pH 14 with aq. NaOH (1 M). The aqueous layer was extracted into Et_2O (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure affording the title compound (831 mg, 99%) as an orange oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.96-5.76 (m, 2H, C2/7), 5.16 (dq, *J* =

17.2, 1.7, 1H, H1a or 7a), 5.08 (dq, *J* = 10.2, 1.4, 1H, H1a or 8a), 5.02 (dq, *J* = 17.1, 1.7, 1H, H1b or 8b), 4.95 (ddt, *J* = 10.2, 2.4, 1.3, 1H, H1b or 8b), 3.24 (dt, *J* = 6.0, 1.5, H3), 2.66-2.59 (m, 2H, H4), 2.10 (tdd, *J* = 8.1, 6.0, 1.5, 2H, H6), 1.59 (quint. *J* =7.4, 2H, H5), 1.02 (s, br, 1H, NH).

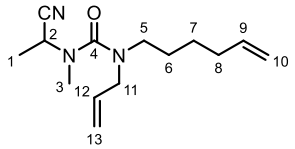
Data in accordance with the literature.[155]

1-Allyl-3-(1-cyanoethyl)-3-methyl-1-(pent-4-en-1-yl)urea (2-186):



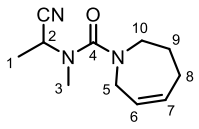
According to **GP2**, (1-cyanoethyl)(methyl)carbamic chloride (530 mg, 3.62 mmol), *N*-allylpent-4-en-1-amine (448 mg, 3.58 mmol) and triethylamine (1.01 mL, 7.26 mmol) were heated under reflux at 75 °C for 21 h. Purification via flash column chromatography eluting with EtOAc:PE (3:20 – 1:0) afforded the title compound (674 mg, 79%) as a colourless oil. $\mathbf{R_f}$ = 0.82 (100% EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.85-5.71 (m, 2H, H8/11), 5.24-5.20 (m, 1H, H12a), 5.19 (t, br, *J* =1.5, 1H, H12b), 5.06-4.94 (m, 2H, H9), 4.79 (q, *J* =7.3, 1H, H2), 3.81-3.75 (m, 2H, H10), 3.21-3.07 (m, 2H, H5), 2.87 (s, 3H, H3), 2.06-1.98 (m, 2H, H7), 1.70-1.57 (m, 2H, H6), 1.50 (d, *J* =7.3, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 163.8 (C4), 137.8 (C8), 133.8 (C11), 119.1 (CN), 117.7 (C12), 115.3 (C9), 51.0 (C10), 47.2 (C5), 45.0 (C2), 33.9 (C3), 31.1 (C7), 26.6 (C6), 17.3 (C1). **IR ν_{max}** (ATR)/cm^{-1}: 2958, 2242, 1643.

1-Allyl-3-(1-cyanoethyl)-1-(hex-5-en-1-yl)-3-methylurea (2-187):



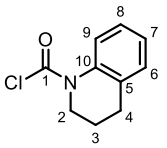
According to **GP2**, (1-cyanoethyl)(methyl)carbamic chloride (200 mg, 1.37 mmol), *N*-allylhex-5-en-1-amine (180 mg, 1.37 mmol) and triethylamine (0.38 mL, 2.73 mmol) were heated under reflux at 75 °C for 69 h. Purification via flash column chromatography eluting with EtOAc:PE (3:20 – 1:0) afforded the title compound (220 mg, 64%) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.85-5.71 (m, 2H, H9/12), 5.24-5.20 (m, 1H, H13a), 5.19-5.18 (m, 1H, H13b), 5.03-4.92 (m, 2H, H10), 4.79 (q, *J* = 7.3, 1H, H2), 3.80-3.75 (m, 2H, H11), 3.18-3.09 (m, 2H, H5), 2.87 (s, 3H, H3), 2.09-2.02 (m, 2H, H8), 1.60-1.51 (m, 2H, H6), 1.50 (d, *J* = 7.3, 3H,H1), 1.40-1.30 (m, 2H, H7). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 163.8 (C4), 138.5 (C9), 133.9 (C12), 119.2 (CN), 117.6 (C13), 114.9 (C10), 50.9 (C11), 47.5 (C5), 45.0 (C2), 33.9 (C3), 33.5 (C8), 26.9 (C6), 26.3 (C7), 17.3 (C1). **HRMS m/z** (ESI$^+$): calcd. for $C_{14}H_{23}N_3NaO$ [M+Na] Calculated 272.1733. Found 272.1740. **IR ν_{max}** (ATR)/cm^{-1}: 2976, 2930, 2863, 2238, 1643.

***N*-(1-Cyanoethyl)-*N*-methyl-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxamide (2-188):**



Under an atmosphere of N_2, 1-Allyl-3-(1-cyanoethyl)-3-methyl-1-(pent-4-en-1-yl)urea (166 mg, 0.706 mmol) and Grubb's 1st generation catalyst (29.0 mg, 0.0353 mmol) were dissolved in anhydrous DCM (14 mL). The reaction mixture was stirred at room temperature for 42 h. The volatiles were removed under reduced pressure. Purification via flash column chromatography eluting with EtOAc:PE (3:7 – 1:0) afforded the title compound (146 mg, quant.) as an orange oil. $\mathbf{R_f}$ = 0.68 (1:0 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.82 (dtt, *J* = 10.7, 4.6, 1.1, 1H, H7), 5.75 (dtt, *J* = 10.7, 4.6, 1.2, 1H, H6), 4.79 (q, *J* = 7.3, 1H, H2), 3.88-3.71 (m, 2H, H5), 3.56-3.38 (m, 2H, H10), 2.87 (s, 3H, H3), 2.23 (dddd, *J* = 7.6, 6.1, 2.7, 1.4, 2H, H8), 1.98-1.81 (m, 2H,H9), 1.51 (d, *J* = 73, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 163.9 (C4), 132.7 (C7), 127.9 (C6), 119.3 (CN), 49.9 (C10), 47.2 (C5), 45.1 (C2), 33.8 (C3), 27.1 (C8), 26.7 (C9), 17.3 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{11}H_{17}N_3NaO$ [M+Na] Calculated 230.1264. Found 230.1271. **IR ν_{max}** (ATR)/cm^{-1}: 2934, 2881, 2238, 1630.

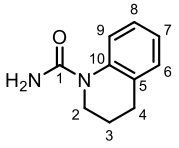
3,4-Dihydroquinoline-1(2*H*)-carbonyl chloride (3-6):



According to **GP1**, triphosgene (513 mg, 1.73 mmol), anhydrous pyridine (0.300 mL, 3.75 mmol) and 1,2,3,4-tetrahydroquinoline (0.47 mL, 3.75 mmol) were stirred at room temperature for 18 h, affording the crude title product (731 mg, quant.) as an orange oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.66 (d, br, *J* = 8.1, 1H, ArH), 7.24-7.18 (m, 1H, ArH), 7.17-7.10 (m, 2H, ArH), 3.95 (t, *J* = 6.3 2H, H2), 2.82 (t, *J* = 6.7, 2H, H4), 2.14-1.97 (m, 2H, H3).

Data in accordance with the literature.[156]

3,4-Dihydroquinoline-1(2*H*)-carboxamide (2-199):



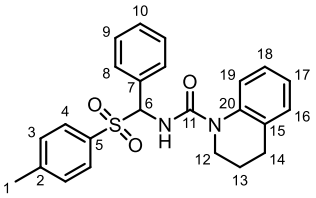
3,4-Dihydroquinoline-1(2*H*)-carboxamide synthesis adapted from the literature.[99]

Under an atmosphere of N_2, 3,4-dihydroquinoline-1(2*H*)-carbonyl chloride (573 mg, 2.94 mmol) was dissolved in ammonia (0.5 M in THF, 29.4 mL, 14.7 mmol). The reaction mixture was stirred at room

temperature for 24 h. The volatiles were removed under reduced pressure. The residue with dissolved in EtOAc (20 mL) and washed with H_2O (3 x 20 mL), and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford the title compound (325 mg, 63%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.38 (dd, *J* = 7.8, 1.1, 1H, ArH), 7.22-7.16 (m, 2H, ArH), 7.08 (td, *J* = 7.4, 1.3, 1H, ArH), 5.01 (s, br, 2H, NH), 3.79-3.75 (m, 2H, H2), 2.76 (t, *J* = 6.7, 2H, H4), 1.96 (quint. J = 6.7, 2H, H3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.2 (C1), 139.0 (Ar), 132.8 (Ar), 129.6 (ArH), 126.9 (ArH), 125.0 (ArH0, 123.2 (ArH), 43.7 (C2), 27.1 (C4), 24.0 (3).

Data in accordance with the literature.[157]

***N*-(Phenyl(tosyl)methyl)-3,4-dihydroquinoline-12*H*)-carboxamide (2-200):**

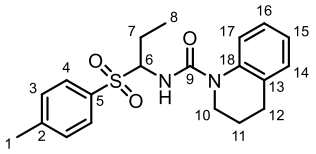


N-(Phenyl(tosyl)methyl)-3,4-dihydroquinoline-12*H*)-carboxamide (**2-200**) synthesis adapted from the literature.[131]

To a solution of 3,4-dihydroquinoline-1(2*H*)-carboxamide (200 mg, 1.14 mmol) and sodium *para*-toluenesulfinate (443 mg, 2.28 mmol) in MeOH:H_2O (1:2, 3.35 mL) was added benzaldehyde (0.17 mL, 1.71 mmol) and formic acid (0.09 mL, 2.28 mmol). The reaction mixture was stirred at room temperature for 93 h. The reaction mixture was filtered and washed with diethyl ether (20 mL). The filtrate was dissolved in DCM (20 mL) and dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The title compound (192 mg, 40%) as an off-white solid. **^{1}H NMR** (400 MHz, DMSO-*d*$_6$): δ_H 7.95 (d, *J* = 10.3, 1H, NH), 7.79-7.74 (m, 2H, ArH), 7.67 (dd, *J* = 6.7, 3.0, 2H, ArH), 7.48-7.41 (m, 5H, ArH), 7.06 (dd, *J* = 7.5, 1.7, 1H, ArH), 7.00 (td, *J* = 7.7, 1.7, 1H, ArH), 6.92 (td, *J* = 7.3, 1.4, 1H, ArH), 6.85 (dd, *J* = 8.2, 1.3, 1H, ArH), 6.35 (d, *J* = 10.3, 1H, H6), 3.58 (ddd, *J* = 12.2, 6.9, 4.7, 1H, H12a), 3.51 (ddd, *J* = 12.2, 6.7, 4.6, 1H, H12b), 2.64-2.59 (m, 2H, ArH), 2H, H14), 2.42 (s, 3H, H1), 1.71 (ddd, *J* = 13.3, 6.7, 4.7, 1H, H13a), 1.67-1.57 (m, 1H, H13b). **^{13}C NMR** (101 MHz, DMSO-*d*$_6$): δ_C 155.4 (C11), 144.7 (Ar), 138.4 (Ar), 134.2 (Ar), 130.9 (Ar), 129.8 (ArH), 129.6 (ArH), 129.4 (ArH), 129.3 (Ar), 129.1 (ArH), 128.7 (ArH), 128.2 (ArH), 125.5 (ArH), 123.3 (ArH), 122.8 (ArH), 74.2 (C6), 45.1 (C12), 26.3 (C14), 23.0 (C13) 21.1 (C1). **IR ν_{max}** (ATR)/cm^{-1}: 3344, 3032, 2965, 2931, 2847, 1650.

N.B. Compounds unstable with prolonged exposure to solvent.

***N*-(1-Tosylpropyl)-3,4-dihydroquinoline-1(2*H*)-carboxamide (2-201):**

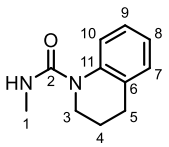


N(-1-Tosylpropyl)-3,4-dihydroquinoline-1(2*H*)-carboxamide (**2-201**) synthesis adapted from the literature.[131]

To a solution of 3,4-dihydroquinoline-1(2*H*)-carboxamide (200 mg, 1.14 mmol) and sodium *para*-toluenesulfinate (443 mg, 2.28 mmol) in MeOH:H_2O (1:2, 3.36 mL) was added propionaldehyde (0.12 mL, 1.71 mmol) and formic acid (0.09 mL, 2.28 mmol). The reaction mixture was stirred at room temperature for 117 h. The reaction mixture was placed in the freezer for 16 h, the resulting crystals were filtered under vacuum filtration and washed with ice cold Et_2O affording the title compound (67 mg, 16%) as colourless crystals. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.76-7.69 (m, 2H, ArH), 7.38-7.30 (m, 2H, ArH), 7.25-7.20 (m, 1H, ArH), 7.20-7.16 (m, 2H, ArH), 7.12 (td, *J* = 7.4, 1.4, 1H, ArH), 5.51 (d, *J* = 10.5, 1H, NH), 5.21 (td, *J* = 10.5, 3.7, 1H, H6), 3.58-3.49 (m, 2H, H10), 2.76-2.64 (m, 2H, H12), 2.44 (s, 3H, H1), 2.23 (dqd, *J* = 14.9, 7.5, 3.7, 1H, H7a), 1.86-1.77 (m, 1H, H7b), 1.77-1.67 (m, 2H, H11), 1.06 (t, *J* = 7.5, 3H, H8). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 154.8 (C9), 145.0 (Ar), 138.3 (Ar), 134.4 (Ar), 132.8 (Ar), 129.9 (ArH), 129.8 (ArH), 129.2 (ArH), 127.2 (ArH), 125.4 (ArH), 123.3 (ArH), 72.1 (C6), 43.8 (C10), 26.9 (C12), 23.7 (C11), 21.9 (C1), 21.0 (C7), 10.3 (C8). **IR ν_{max}** (ATR)/cm^{-1}: 3326, 2964, 2877, 1647.

N.B. Compounds unstable with prolonged exposure to solvent.

***N*,2-Dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxamide:**

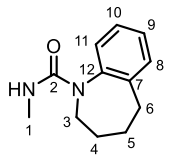


N,2-dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxamide synthesis adapted from the literature.[158]

Under an atmosphere of N_2, a solution of 2-methyl-3,4-dihydroquinoline-1(2*H*)-carbonyl chloride (1.00 g, 4.78 mmol) in anhydrous THF (5 mL) was cooled to 0 °C. Triethylamine (0.87 mL, 6.21 mmol) and $MeNH_2$ (2 M in THF, 2.87 mL, 5.74 mmol) were added dropwise whilst maintaining 0 °C. The reaction mixture was stirred for 41 h whilst warming to room temperature. The reaction mixture was washed with H_2O (20 mL) and aq. HCl (1 M, 20 mL). The aqueous layer was extracted into EtOAc (20 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure affording the title compound (951 mg, 97%) as a cream solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.24-7.12 (m, 3H, ArH), 7.07 (ddd, *J* = 7.6, 6.8, 1.7, 1H, ArH), 4.96 (s, br, 1H, NH), 4.74 (sextet, *J* = 6.6, 1H, H3), 2.79 (s, 3H, H1), 2.68-2.50 (m, 2H, H5), 2.25 (dtd, *J* = 13.3, 6.8, 5.4, 1H, H4a), 1.43

(dddd, *J* = 13.3, 8.7, 6.8, 5.6, 1H, H4b), 1.14 (d, *J* = 6.6, 3H, H12). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 157.4 (C2), 137.8 (Ar), 134.8 (Ar), 128.8 (ArH), 126.9 (ArH), 124.7 (ArH), 124.7 (ArH), 48.5 (C3), 32.1 (C4), 27.5 (C1), 25.7 (C5), 20.5 (C12).

***N*-Methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (2-211):**

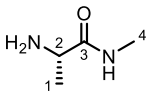


N-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide synthesis adapted from the literature.[158]

Under an atmosphere of N_2, a solution of 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carbonyl chloride (1.00 g, 4.78 mmol) in anhydrous THF (5 mL) was cooled to 0 °C. Triethylamine (0.87 mL, 6.21 mmol) and $MeNH_2$ (2 M in THF, 2.87 mL, 5.74 mmol) were added dropwise whilst maintaining 0 °C. The reaction mixture was stirred for 48 h whilst warming to room temperature. The reaction mixture was washed with H_2O (20 mL) and aq. HCl (1 M , 20 mL). The aqueous layer was extracted into EtOAc (20 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure affording the title compound (737 mg, 76%) as a cream solid. **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.34-7.11 (m, 4H, ArH), 4.62 (s, br, 1H, H3a), 4.19 (s, br, 1H, NH), 2.99-2.42 (m, br, 3H, H3b/6), 2.74 (s, 3H, H1), 2.09-1.57 (m, br, 3H, H4/5), 1.34 (s, br, 1H, H4b or 5b). **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 157.0 (C2), 142.3 (Ar), 142.2 (Ar), 130.8 (ArH), 128.2 (ArH), 128.0 (ArH), 127.6 (ArH), 47.4 (C3), 34.8 (C6), 29.9 (C4 or 5), 27.5 (C1), 26.3 (C4 or 5). **IR ν_{max}** (ATR)/cm^{-1}: 3356, 2961, 2937, 2899, 2850, 1638. **m.p.** 107-108 °C.

Data in accordance with the literature.[159]

(S)-2-Amino-*N*-methylpropanamide (2-224):



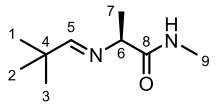
(S)-2-amino-*N*-methylpropanamide synthesised in accordance with the literature.[93]

L-alanine ethyl ester.HCl (5.00 g, 32.5 mmol) was added $MeNH_2$ (33 %wt in EtOH, 27 mL, 228 mmol). The reaction mixture was stirred at room temperature for 48 h. The volatiles were removed under reduced pressure and the residue dissolved in $CHCl_3$ (30 mL) and washed with aq. K_2CO_3 (3.8 M, 20 mL). The aqueous layer was extracted into $CHCl_3$ (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure affording the crude title product (2.24 g, 67%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.26 (s, br, 1H, NH), 3.47 (q, *J* = 7.0,

1H, H2), 2.79 (d, *J* = 5.0, 3H, H4), 1.48 (s, br, 2H, NH), 1.31 (d, *J* = 7.0, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 176.4 (C3), 50.8 (C2), 25.8 (C4), 21.9 (C1).

Data in accordance with the literature.[93]

(S,E)-2-((2,2-Dimethylpropylidene)amino-*N*-methylpropanamide (2-225):

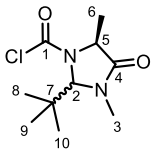


(S,E)-2-((2,2-dimethylpropylidene)amino-*N*-methylpropanamide synthesised in accordance with the literature.[93]

Under an atmosphere of N_2, pivaldehyde (1.84 mL, 17.0 mmol) and *para*-toluene sulfinic acid (392 mg, 2.06 mmol) were added to a solution of (S)-2-amino-*N*-methylpropanamide (1.45 g, 14.2 mmol) and molecular sieves in anhydrous toluene (21 mL). The reaction mixture was heated under reflux and stirred for 21 h. The reaction mixture was cooled to room temperature and filtered. The filtered reaction mixture was quenched by slow addition of sat. aq $NaHCO_3$ until pH >9. The organic layer was separated and the aqueous layer was extracted into DCM (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure affording the crude title compound (1.84 g, 76%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.51 (dd, *J* = 2.2, 1.1, 1H, H5), 6.90 (s, br, 1H, NH), 3.67 (qd, *J* = 7.1, 2.3, 1H, H6), 2.94-2.75 (m, 3H, H9), 1.38-1.23 (m, 3H, H7), 1.19-0.98 (m, 9H, H1/2/3).

Data in accordance with the literature. [93]

(5S)-2-(*tert*-Butyl)-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride (2-226):



(5S)-2-(*tert*-butyl)-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride synthesised in accordance with the literature.[93]

Under an atmosphere of N_2, triphosgene (697 mg, 2.35 mmol) was dissolved in anhydrous DCM (4.5 mL) and cooled to -78 °C. 2,6-Lutidine (0.82 mL, 7.06 mmol) was added dropwise. The reaction mixture was stirred for 5 min whilst maintaining -78 °C. A solution of the crude (S,E)-2-((2,2-dimethylpropylidene)amino-*N*-methylpropanamide (1.00 g, 5.88 mmol) in anhydrous DCM (1.5 mL) was added dropwise to the triphosgene solution. The reaction mixture was stirred at -78 °C for 15 min before warming to room temperature and stirring for 3 h. The reaction mixture was quenched with aq. HCl (1 M) and stirred for 1 h. The reaction mixture was diluted with DCM (20 mL) and washed with

aq. HCl (1 M, 3 x 20 mL). The combined aqueous layers were extracted into DCM (3 x 20 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (20 mL), dried over Na_2SO_3, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography eluting with acetone:DCM (0:1 – 1:99) afforded the title compound as a mixture of isolated diastereoisomers.

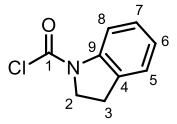
***Trans*-(5S)-2-(*tert*-butyl)-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride (*trans*-2-226):** (233 mg, 17%) as a white solid. . **^{1}H NMR** (400 MHz, $CDCl_3$)(mixture of rotamers A:B in a 0.56:0.44 ratio): δ_H 5.18 (s, 0.44H, H2, rot. B), 5.14 (s, 0.56H, H2, rot. A), 4.15 (s, br, 1H, H5, rot. A+B), 3.05 (s, br, 3H, H3, rot. A+B), 1.76 (s, br, 1.32H, H6, rot. B), 1.61 (d, *J* = 7.0, 1.68H, H6, rot. A), 1.21-0.94 (m, 9H, H8/9/10, rot. A+B).

***Cis*-(5S)-2-(*tert*-butyl)-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride (*cis*-2-226):** (122 mg, 9%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.04 (s, 1H, H2), 4.32 (q, *J* = 7.0, 1H, H5), 2.95 (d, *J* = 0.5, 3H, H3), 1.55 (d, *J* = 7.0, 3H, H6), 0.97 (s, 9H, H8/9/10).

Mixed fraction: (174 mg, 13%) as yellow oil.

Data in accordance with the literature.[93]

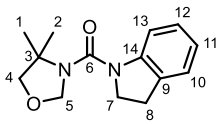
Indoline-1-carbonyl chloride (2-235):



According to **GP1**, triphosgene (573 mg, 1.93 mmol), anhydrous pyridine (0.34 mL, 4.20 mL) and indoline (500 mg, 4.20 mmol) were stirred at 0 °C for 3 h, affording the crude title compound (727 mg, 96%) as a purple solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.87 (d, *J* = 8.0, 1H, ArH), 7.34-7.16 (m, 2H, ArH), 7.10 (td, *J* = 7.4, 1.1, 1H, ArH), 4.25 (t, *J* = 8.5, 2H, H2), 3.20 (t, *J* = 8.5, 2H, H3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 145.0 (C1), 141.3 (Ar), 132.2 (Ar), 128.0 (ArH), 125.3 (ArH), 125.3 (ArH), 116.4 (ArH), 51.7 (C2), 27.2 (C3).

Data in accordance with the literature.[160]

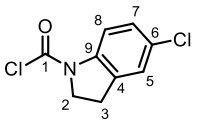
(4,4-Dimethyloxazolidin-3-yl)(indolin-1-yl)methanone (2-237):



To a solution of 4,4-dimethyloxazolidine (75% wt in H_2O, 0.23 mL, 1.62 mmol) in aq. NaOH (3 M, 0.73 mL) and DCM (0.76 mL) cooled to 0 °C was added a solution of indoline-1-carbonyl chloride (200 mg,

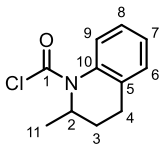
1.10 mmol) in DCM (0.5 mL). The reaction mixture was stirred for 71 h whilst warming to room temperature. The aqueous layer was extracted into DCM (3 x 20 mL). The combined organic layers were washed with water (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford the crude urea product. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 1:0) afforded the title compound (156 mg, 58%) as a purple oil. $\mathbf{R_f}$ = 0.63 (1:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.19-7.04 (m, 3H, ArH), 6.89 (td, *J* = 7.3, 1.3, 1H, ArH), 4.95 (s, 2H, H5), 3.84 (t, *J* = 8.3, 2H, H7), 3.79 (s, 2H, H4), 3.05 (t, *J* = 8.3, 2H, H8), 1.57 (s, 6H, H1/2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 155.2 (C6), 144.2 (Ar), 131.4 (Ar), 127.2 (ArH), 125.0 (ArH), 121.9 (ArH), 114.1 (ArH), 80.7 (C4), 80.5 (C5), 50.0 (C7), 28.6 (C8), 23.5 (C1/2). **HRMS m/z** (ESI^+): calcd. for $C_{14}H_{18}N_2NaO_2$ [M+Na] Calculated 269.1260. found 269.1257. **IR ν_{max}** (ATR)/cm^{-1}: 2966, 2934, 2864, 1650.

5-Chloroindoline-1-carbonyl chloride (3-19):



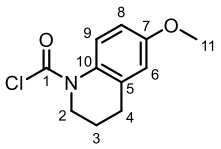
According to **GP1**, triphosgene (445 mg, 1.50 mmol), anhydrous pyridine (0.27 mL, 3.25 mmol) and 5-chloroindoline (0.35 mL, 3.25 mmol) were stirred at 0 °C for 3 h, affording the crude title compound (583 mg, 83%) as a pink solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.81 (dd, *J* = 8.4, 0.6, 1H, ArH), 7.24-7.10 (m, 2H, ArH), 4.30-4.26 (m, 2H, H2), 3.19 (t, *J* = 8.5, 2H, H3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 145.2 (C1), 140.1 (Ar), 134.0 (Ar), 130.3 (Ar), 128.0 (ArH), 125.4 (ArH), 117.4 (ArH), 51.9 (C2), 27.1 (C3).

2-Methyl-3,4-dihydroquinoline-1(2*H*)-carbonyl chloride (3-20):



According to **GP1**, triphosgene (278 mg, 0.938 mmol), anhydrous pyridine (0.17 mL, 2.04 mmol) and 2-methyl-1,2,3,4-tetrahydroquinoline (0.29 mL, 2.04 mmol) were stirred at 0 °C for 3 h, affording the crude title product (359 mg, 84%) as an orange oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.51 (d, *J* = 8.0, 1H, ArH), 7.26-7.19 (m, 1H, ArH), 7.19-7.14 (m, 2H, ArH), 4.77 (sextet, *J* = 6.7, 1H, H2), 2.75-2.58 (m, 2H, H4), 2.39 (ddt, *J* = 13.0, 7.2, 5.5, 1H, H3a), 1.54-1.38 (m, 1H, H3b), 1.21 (d, *J* = 6.7, 3H, H11) . **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 148.7 (C1), 136.1 (Ar), 134.3 (Ar), 127.7 (ArH), 126.9 (ArH), 126.6 (ArH), 126.5 (ArH), 54.2 (C2), 32.2 (C3), 25.6 (C4), 19.8 (C11).

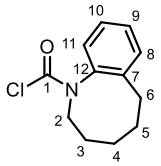
6-Methoxy-3,4-dihydroquinoline-1(2*H*)-carbonyl chloride (3-21):



According to **GP1**, triphosgene (434 mg, 1.46 mmol), anhydrous pyridine (0.26 mL, 3.20 mmol) and 6-methoxy-1,2,3,4-tetrahydroquinoline (522 mg, 3.20 mmol) were stirred at 0 °C for 3 h, affording the crude title product (466 mg, 65%) as a purple solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.56 (s, br, 1H, H6), 6.75 (ddt, *J* = 8.9, 2.9, 0.7, 1H, ArH), 6.70-6.64 (m, 1H, ArH), 3.98-3.85 (m, 2H, H2), 3.79 (s, 3H, H11), 2.78 (t, *J* = 6.7, 2H, H4), 2.12-1.98 (m, 2H, H3).

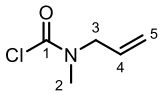
Data in accordance with the literature.[161]

3,4,5,6-Tetrahydro[*b*]azocine-1(2*H*)-carbonyl chloride (3-22):



According to **GP1**, triphosgene (254 mg, 0.857 mmol), anhydrous pyridine (0.15 mL, 1.86 mmol) and 1,2,3,4,5,6-hexahydro[*b*]azocine (300 mg, 1.86 mmol) were stirred at 0 °C for 3 h, affording the crude title compound (215 mg, 52%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.39-7.21 (m, 3H, ArH), 7.13 (dd, *J* = 7.7, 1.5, 1H, ArH), 4.49 (ddd, *J* = 13.5, 8.7, 3.5, 1H, H2a), 3.08 (ddd, *J* = 13.5, 7.1, 3.2, 1H, H2b), 2.80-2.63 (m, 2H, H6), 2.00-1.87 (m, 1H, CH_2), 1.82-1.70 (m, 1H, CH_2), 1.65-1.34 (m, 4H, 2 x CH_2).

Allyl(methyl)carbamic chloride (3-24):



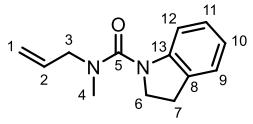
Allyl(methyl)carbamic chloride synthesised in accordance with the literature.[99]

Under an atmosphere of N_2, triphosgene (1.48 g, 5.00 mmol) was dissolved in anhydrous DCM (31 mL) and cooled to -78 °C. 2,6-Lutidine (1.74 mL, 15.0 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 10 min. To the reaction mixture was added *N*-allylmethylamine (1.20 mL, 12.6 mmol) in anhydrous DCM (3 mL) dropwise. The reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was quenched with aq. HCl (1 M) and allowed to stir for 30 min. The reaction mixture was diluted with DCM (20 mL) and washed with aq. HCl (1 M, 2 x 30 mL). The combined aqueous layers were extracted into DCM (2 x 20 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (20 mL), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford the title compound (1.66 g, quant.) as an orange oil. **^{1}H NMR** (400 MHz, $CDCl_3$) (mixture of rotamers A:B in a 0.53:0.47 ratio): δ_H 5.88-5.69 (m, 1H, H4, rot. A+B), 5.30-5.19 (m,

2H, H5, rot. A+B), 4.08 (dt, *J* = 5.8, 1.5, 0.94H, H3, rot. B), 4.00 (dt, *J* = 6.0, 1.4, 1.06H, H3, rot. A), 3.09 (s, 1.6H, H2, rot. A), 3.02 (s, 1.4H, H2, rot. B).

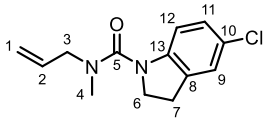
Data in accordance with the literature.[99]

***N*-Allyl-*N*-methylindoline-1-carboxamide (3-26):**



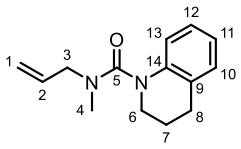
According to **GP2B**, indoline-1-carbonyl chloride (300 mg, 1.66 mmol), *N*-allylmethylamine (0.21 mL, 2.16 mmol) and triethylamine (0.37 mL, 2.66 mmol) were stirred at room temperature for 19.5 h. Purification via flash column chromatography eluting with EtOAc:PE (1:9 – 4:1) afforded the title compound (359 mg, quant.) as brown oil. $\mathbf{R_f}$ = 0.63 (2:3 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.20-7.09 (m, 2H, ArH), 7.00 (ddd, *J* = 8.0, 1.1, 0.3, 1H, ArH), 6.88 (td, *J* = 7.4, 1.1, 1H, ArH), 5.95-5.81 (m, 1H, H2), 5.26 (dq, *J* = 8.9, 1.4, 1H, H1a), 5.24-5.20 (m, 1H, H1b), 3.95-3.86 (m, 4H, H3/6), 3.09-2.98 (m, 2H, H7), 2.88 (s, 3H, H4). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.5 (C5), 144.8 (Ar), 134.2 (C2), 131.9 (Ar), 127.5 (ArH), 125.3 (ArH), 121.9 (ArH), 118.4 (C1), 114.1 (ArH), 53.3 (C3), 51.0 (C6), 36.2 (C4), 28.7 (C7). **HRMS m/z** (ESI^+): calcd. for $C_{13}H_{16}N_2NaO$ [M+Na] Calculated 239.1155. Found 239.1159. **IR ν_{max}** (ATR)/cm^{-1}: 2960, 2910, 2852, 1650.

***N*-Allyl-5-chloro-*N*-methylindoline-1-carboxamide (3-29):**



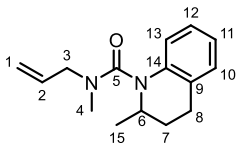
According to **GP2B**, 5-chloroindoline-1-carbonyl chloride (500 mg, 2.33 mmol), *N*-allylmethylamine (0.29 mL, 3.03 mmol) and triethylamine (0.52 mL, 3.73 mmol) were stirred at room temperature for 1 h. Purification via flash column chromatography eluting with EtOAc:PE (2:8 – 8:2) afforded the title compound (558 mg, 90%) as an orange oil. $\mathbf{R_f}$ = 0.63 (1:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.14-7.06 (m, 2H, ArH), 6.94 (d, *J* = 8.4, 1H, ArH), 5.92-5.81 (m, 1H, H2), 5.27-5.25 (m, 1H, H1a), 5.24-5.22 (m, 1H, H1b), 3.91 (t, *J* = 8.3, 2H, H6), 3.88 (dt, *J* = 6.1, 1.4, 2H, H3), 3.05-2.98 (m, 2H, H7), 2.86 (s, 3H, H4). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.1 (C5), 143.3 (Ar), 134.0 (C2), 133.4 (Ar), 127.1 (ArH), 126.5 (Ar), 125.1 (ArH), 118.2 (C1), 114.8 (ArH), 52.9 (C3), 50.8 (C6), 35.8 (C4), 28.3 (C7). **HRMS m/z** (ESI^+): calcd. for $C_{13}H1_{15}ClN_2NaO$ [M+Na] Calculated 273.0765. Found 273.0776. **IR ν_{max}** (ATR)/cm^{-1}: 2971, 2901, 1651.

***N*-Allyl-*N*-methyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (3-6):**



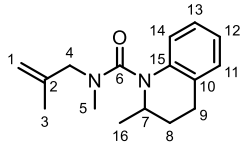
According to **GP2B**, 3,4-dihydroquinoline-1(2*H*)-carbonyl chloride (500 mg, 2.56 mmol), *N*-allylmethylamine (0.32 mL, 3.33 mmol) and triethylamine (0.57 mL, 4.10 mmol) were stirred at room temperature for 21 h. Purification via flash column chromatography eluting with EtOAc:PE (1:9 – 4:1) afforded the title compound (580 mg, 98%) as a yellow oil. $\mathbf{R_f}$ = 0.61 (2:3 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.12-7.04 (m, 2H, ArH), 6.93 (dd, *J* = 8.6, 1.2, 1H, ArH), 6.89 (td, *J* = 7.4, 1.3, 1H, ArH), 5.90-5.75 (m, 1H, H2), 5.23-5.17 (m, 1H, H1a), 5.18-5.15 (m, 1H, H1b), 3.84 (dt, *J* = 6.1, 1.4, 2H, H3), 3.65-3.54 (m, 2H, H6), 2.76 (t, *J* = 6.7 , 2H, H8), 2.72 (s, 3H, H4), 2.02-1.91 (m, 2H, H7). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 161.0 (C5), 141.0 (Ar), 133.7 (C2), 129.2 (ArH), 128.0 (Ar), 126.6 (ArH), 122.0 (ArH), 119.7 (ArH), 118.0 (C1), 52.8 (C3), 45.8 (C6), 35.7 (C4), 27.1 (C8), 23.7 (C7). **HRMS m/z** (ESI^+): calcd. for $C_{14}H_{19}N_2O$ [M+H] Calculated 231.1492. Found 231.11493. **IR ν_{max}** (ATR)/cm^{-1}: 2930, 2886, 1643.

***N*-Allyl-*N*,2-dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (3-30):**



According to **GP2B**, 2-methyl-3,4-dihydroquinoline-1(2*H*)-carbonyl chloride (253 mg, 1.21 mmol), *N*-allylmethylamine (0.15 mL, 1.57 mmol) and triethylamine (0.27 mL, 1.64 mmol) were stirred at room temperature for 21 h. Purification via flash column chromatography eluting with EtOAc:PE (1:9 – 4:1) afforded the title compound (276 mg, 94%) as a yellow oil. $\mathbf{R_f}$ = 0.68 (2:3 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.08 (ddt, *J* = 7.9, 6.3, 0.9, 2H, ArH), 6.94-6.81 (m, 2H, ArH), 5.87-5.73 (m, 1H, H2), 5.21-5.16 (m, 1H, H1a), 5.16-5.12 (m, 1H, H1b), 4.24 (quint. d, *J* = 6.5, 3.7, 1H, H6), 3.82 (dqt, *J* = 15.1, 6.1, 1.4, 2H, H3), 2.81-2.67 (m, 2H, H8), 2.67 (s, 3H, H4), 2.10-1.98 (m, 1H, H7a), 1.72 (dddd, *J* = 13.2, 6.0, 5.0, 3.7, 1H, H7b), 1.20 (d, *J* = 6.5, 3H, H15). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.6 (C5), 139.6 (Ar), 133.7 (C2), 128.9 (ArH), 126.8 (ArH), 121.6 (ArH), 119.9 (ArH), 117.9 (C1), 52.7 (C3), 49.8 (C6), 35.5 (C4), 30.0 (C7), 24.4 (C8), 19.3 (C3). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{21}N_2O$ [M+H] Calculated 245.1648. Found 245.1645. **IR ν_{max}** (ATR)/cm^{-1}: 2968, 2931, 2848, 1639.

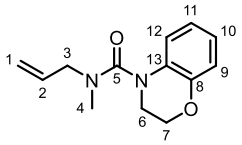
***N*,2-Dimethyl-*N*-(2-methylallyl)-3,4-dihydroquinoline-1(2*H*)-carboxamide (3-21):**



According to **GP2C**, 2-methyl-3,4-dihydroquinoline-1(2*H*)-carbonyl chloride (200 mg, 0.957 mmol), 1,2-methylallylamine (0.08 mL, 1.24 mmol) and triethylamine (0.21 mL, 1.53 mmol) were stirred at room temperature for 22 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 3:2) afforded the secondary urea (146 mg, 62%) as a colourless oil. $\mathbf{R_f}$ = 0.64 (1:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.29-7.25 (m, 1H, ArH), 7.23-7.14 (m, 2H, ArH), 7.08 (td, *J* = 7.6, 1.4, 1H, ArH), 5.17-5.01 (m, br, 1H, NH), 4.83-4.70 (m, 3H, H7/1), 3.88 (dd, *J* = 16.0, 6.1, 1H, H4a), 3.71 (dd, *J* = 16.0, 5.4, 1H, H4b), 2.70-2.53 (m, 2H, H9), 2.26 (dtd, *J* = 13.4, 6.7, 5.4, 1H, H8a), 1.73 (dd, *J* = 1.5, 0.8, 3H, H3), 1.44 (dddd, *J* = 13.3, 8.8, 6.7, 5.6, 1H, H8b), 1.14 (d, *J* = 6.5, 3H, H16). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 156.6 (C6), 143.2 (C2), 137.7 (Ar), 134.9 (Ar), 128.8 (ArH), 126.9 (ArH), 124.9 (ArH), 124.9 (ArH), 110.3 (C1), 48.5 (C7), 46.5 (C4), 32.1 (C8), 25.8 (C9), 20.6 (C3), 20.4 (C16).

A solution of the secondary urea (134 mg, 0.549 mmol) and NaH (60 % in mineral oil, 88 mg, 2.20 mmol) was added and stirred for 1 h at 0 °C. Iodomethane (0.14 mL, 2.20 mmol) was added to the reaction mixture and stirred at room temperature for 20.5 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 4:1) afforded the title compound (131 mg, 92%) as a yellow oil. $\mathbf{R_f}$ = 0.48 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.13-7.03 (m, 2H, ArH), 6.91-6.80 (m, 2H, ArH), 4.93-4.86 (m, 1H, H1a), 4.82-4.75 (m, 1H, H1b), 4.23 (quint. d, *J* = 6.5, 3.6, 1H, H7), 3.89 (d, *J* = 15.1, 1H, H4a), 3.63 (d, *J* = 15.1, 1H, H4b), 2.81-2.69 (m, 2H, H9), 2.67 (s, 3H, H5), 2.10-1.99 (m, 1H, H8a), 1.78-1.71 (m, 1H, H8b), 1.69 (d, *J* = 1.2, 3H, H3), 1.21 (d, *J* = 6.5, 3H, H16). **HRMS m/z** (ESI^+): calcd. for $C_{16}H_{23}N_2O$ [M+H] 259.1805. Found 259.1808. **IR ν_{max}** (ATR)/cm^{-1}: 3081, 2970, 2934, 2846, 1642.

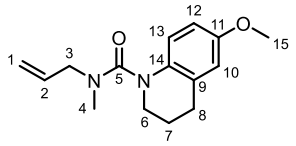
***N*-Allyl-*N*-methyl-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxamide (3-32):**



According to a modified **GP2B**, allyl(methyl)carbamic chloride (306 mg, 2.30 mmol), 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (0.37 mL, 2.99 mmol) and triethylamine (0.51 mL, 3.68 mmol) were heated under reflux at 70 °C for 47 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 4:1) afforded the title compound (422 mg, 79%) as an orange solid. $\mathbf{R_f}$ = 0.44 (4:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.99 (ddd, *J* = 8.0, 1.6, 0.6, 1H, ArH), 6.90-6.80 (m, 3H, ArH), 5.90-5.79 (m, 1H, H2), 5.25-5.22 (m, 1H, H1a), 5.21-5.18 (m, 1H, H1b), 4.36-4.24 (m, 2H, H7), 3.90 (dt, *J* = 6.2, 1.5, 2H,

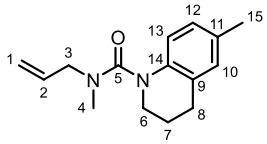
H3), 3.72-3.62 (m, 2H, H6), 2.85 (s, 3H, H4). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 159.3 (C5), 145.0 (Ar), 133.4 (C2), 128.2 (Ar), 123.2 (ArH), 120.7 (ArH), 119.6 (ArH), 118.3 (C1), 117.3 (ArH), 66.4 (C7), 52.9 (C3), 43.8 (C6), 35.9 (C4). **HRMS m/z** (ESI^+): calcd. for $C_{13}H_{17}N_2O_2$ [M+H] Calculated 233.1285. Found 233.1286. **IR ν_{max}** (ATR)/cm^{-1}: 2990, 2917, 1874, 1652. **m.p.** 60-61 °C.

***N*-Allyl-6-methoxy-*N*-methyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (3-33):**



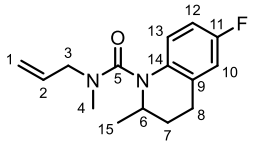
According to **GP2A**, 6-methoxy-3,4-dihydroquinoline-1(2*H*)-carbonyl chloride (213 mg, 0.946 mmol), *N*-allylmethylamine (0.12 mL, 1.23 mmol) and triethylamine (0.21 mL, 1.51 mmol) were stirred at room temperature for 20 h. Purification via flash column chromatography eluting with EtOAc:PE (1:9 – 4:1) afforded the title compound (177 mg, 72%) as a yellow oil. **R_f** = 0.30 (2:3 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.90 (d, J = 8.7, 1H, ArH), 6.71-6.62 (m, 2H, ArH), 5.88-5.74 (m, 1H, H2), 5.20-5.17 (m, 1H, H1a), 5.16-5.13 (m, 1H, H1b), 3.81 (dt, *J* = 6.1, 1.4, 2H, H3), 3.76 (s, 3H, H4), 3.56 (dd, *J* = 6.6, 5.9, 2H, H6), 2.72 (t, *J* = 5.8, 2H, H8), 2.68 (s, 3H, H15), 1.98-1.90 (m, 2H, H7). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 161.2 (C5), 154.9 (Ar), 134.5 (Ar), 133.9 (C2), 129.9 (Ar), 121.4 (ArH), 117.8 (C1), 113.8 (ArH), 112.4 (ArH), 55.6 (C4), 52.9 (C3), 45.6 (C6), 35.7 (C15), 27.4 (C8), 23.9 (C7). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{21}N_2O_2$ [M+H] Calculated 261.1598. Found 261.1599. **IR ν_{max}** (ATR)/cm^{-1}: 2936, 2837, 1635.

***N*-Allyl-*N*,6-dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (3-34):**



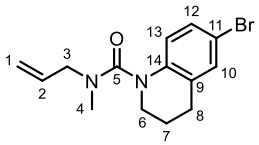
According to a modified **GP2B**, allyl(methyl)carbamic chloride (200 mg, 1.50 mmol), 1,2,3,4-tetrahydro-6-methylquinoline (287 mg, 1.95 mmol) and triethylamine (0.33 mL, 2.40 mmol) were heated at 50 °C for 23.5 h. Purification via flash column chromatography eluting with (0:1 – 1:1) afforded the title compound (257 mg, 70%) as a yellow oil. **R_f** = 0.67 (2:3 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.93-6.87 (m, 2H, ArH), 6.86-6.81 (m, 1H, ArH), 5.89-5.75 (m, 1H, H2), 5.19-5.18 (m, 1H, H1a), 5.17-5.14 (m, 1H, H1b), 3.83 (dt, *J* = 6.3, 1.4, 2H, H3), 3.59-3.53 (m, 2H, H6), 2.70 (s, 3H, H4), 2.71-2.66 (m, 2H, H8), 2.25 (s, 3H, H15), 2.00-1.90)m, 2H, H7). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 161.1 (C5), 138.5 (Ar), 133.9 (C2), 131.4 (C11), 129.6 (ArH), 128.0 (Ar), 127.2 (ArH), 119.8 (ArH), 117.8 (C1), 52.8 (C3), 45.7 (C6), 35.7 (C4), 27.0 (C8), 23.8 (C7), 20.7 (C15). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{21}N_2O$ [M+H] 245.1648. Found 245.1646. **IR ν_{max}** (ATR)/cm^{-1}: 2991, 2928, 2863, 1642.

***N*-Allyl-6-fluoro-*N*,2-dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (3-35):**



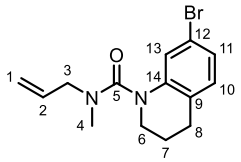
According to **GP2D**, allyl(methyl)carbamic chloride (300 mg, 2.26 mmol), 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (0.30 mL, 1.88 mmol) and NaHMDS (1 M in THF, 2.1 mL, 2.07 mmol) were stirred at room temperature for 24 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 4:1) afforded the title compound (371 mg, 75%) as an orange oil. $\mathbf{R_f}$ = 0.32 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.86-6.74 (m, 3H, ArH), 5.87-5.72 (m, 1H, H2), 5.19-5.11 (m, 2H, H1), 4.22 (quint. d, *J* = 6.5, 3.8, 1H, H6), 3.86-3.70 (m, 2H, H3), 2.77-2.66 (m, 2H, H8), 2.65 (s, 3H, H4), 2.12-1.99 (m, 1H, H7a), 1.68 (dddd, *J* = 13.3, 6.2, 5.3, 3.8, 1H, H7b), 1.17 (d, *J* = 6.5, 3H, H15). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.8 (C5), 158.1 (d, *J* = 241.2, C11), 135.6 (d, *J* = 2.5, C14), 133.6 (C2), 130.2 (d, *J* = 7.2, C9), 121.7 (d, *J* = 8.1, C13), 117.9 (C1), 115.1 (d, *J* = 22.0, C10 or 12), 113.5 (d, *J* = 22.4, C10 or 12), 52.7 (C3), 49.8 (C6), 35.5 (C4), 29.9 (C7), 24.6 (C8), 19.1 (C15). **^{19}F NMR** (376 MHz, $CDCl_3$): δ_F -122.0-122.1 (m, 1F, ArF). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{20}FN_2O$ [M+H] Calculated 263.1554. found 263.1560. **IR ν_{max}** (ATR)/cm^{-1}: 3080, 2934, 2845, 1640.

***N*-Allyl-6-bromo-*N*-methyl-3,4-dihydroquinoine-1(2*H*)-carboxamide (3-36):**



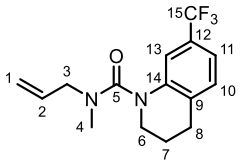
According to a modified **GP2B**, allyl(methyl)carbamic chloride (299 mg, 2.12 mmol), 6-bromo-1,2,3,4-tetrahydroquinoline (583 mg, 2.75 mmol) and triethylamine (0.47 mL, 3.39 mL) were heated under reflux at 70 °C for 44 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 3:2) afforded the title compound (395 mg, 60%) as a yellow oil. $\mathbf{R_f}$ = 0.51 (1:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.21 (dt, *J* = 2.1, 1.0, 1H, ArH), 7.19-7.14 (m, 1H, ArH), 6.80 (d, *J* = 8.7, 1H, ArH), 5.88-5.74 (m, 1H, H2), 5.24-5.13 (m, 2H, H1), 3.83 (dt, *J* = 6.2, 1.4, 2H, H3), 3.60-3.50 (m, 2H, H6), 2.73 (s, 3H, H4), 2.80-2.68 (m, 2H, H8), 2.00-1.89 (m, 2H, H7). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 16.8 (C5), 140.1 (Ar), 133.4 (C2), 131.9 (ArH), 129.7 (Ar), 129.5 (ArH), 121.1 (ArH), 118.2 (C1), 114.2 (Ar), 52.7 (C3), 45.8 (C6), 35.6 (C4), 27.0 (C8), 23.2 (C7). **HRMS m/z** (ESI^+): calcd. $C_{14}H_{18}{}^{79}BrN_2O$ [M+H] Calculated 309.0597. Found 309.0611. **IR ν_{max}** (ATR)/cm^{-1}: 3077, 2933, 2850, 1645.

***N*-Allyl-7-bromo-*N*-methyl-3,4-dihydroquinoine-1(2*H*)-carboxamide (3-37):**



According to a modified **GP2B**, allyl(methyl)carbamic chloride (145 mg, 1.09 mmol), 7-bromo-1,2,3,4-tetrahydroquinoline (254 mg, 1.20 mmol) and triethylamine (0.24 mL, 1.74 mmol) were heated under reflux at 70 °C for 44 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 3:2) afforded the title compound (123 mg, 37%) as a colourless oil. $\mathbf{R_f}$ = 0.26 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$)(mixture of rotamers A:B 0.66:0.33): δ_H 7.09-7.06 (m, 1H, ArH, rot. A+B), 7.00 (d, *J* = 1.9, 0.33H, ArH, rot. B), 6.98 (d, *J* = 1.9, 0.66H, ArH, rot. A), 6.94 (d, *J* = 0.9, 0.66H, ArH, rot. A), 6.92 (d, *J* = 0.9, 0.33H, ArH, rot. B), 5.95-5.72 (m, 1H, H2, rot. A+B), 5.26-5.08 (m, 2H, H1, rot. A+B), 3.86 (dt, *J* = 6.1, 1.4, 1.34 H, H3, rot. A), 3.74 (dt, *J* = 5.6, 1.6, 0.66 H, H3, rot. B), 3.61-3.46 (m, 2H, H6, rot. A+B), 2.77 (s, 2H, H4, rot. A), 2.76 (s, br, 1H, H4, rot. B), 2.71 (td, *J* = 6.6, 0.9, 2H, H7, rot. A+B), 2.00-1.90 (m, 2H, H8, rot. A+B). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.6 (C5, rot. A+B), 142.1 (Ar, rot. A+B), 134.2 (C2, rot. B), 133.3 (C2, rot. A), 130.6 (ArH, rot. A), 130.6 (ArH, rot. B), 126.1 (Ar, rot. A+B), 124.5 (ArH, rot. A), 124.5 (ArH, rot. B), 122.1 (ArH, rot. A+B), 119.8 (Ar, rot. A+B), 118.3 (C1, rot. A), 117.1 (C1, rot. B), 53.6 (C3, rot. B), 52.8 (C3, rot. A), 45.9 (C6, rot. A+B), 36.2 (C4, rot. A), 35.6 (C4, rot. B), 26.8 (C7, rot. A+B), 23.1 (C8, rot. A+B). **HRMS m/z** (ESI^+): calcd. $C_{14}H_{18}{}^{79}BrN_2O$ [M+H] Calculated 309.0597. Found 209.0607. **IR ν_{max}** (ATR)/cm^{-1}: 3078, 2933, 2858, 1648.

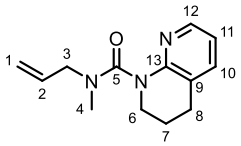
***N*-Allyl-*N*-methyl-7-(trifluoromethyl)-3,4-dihydroquinoline-1(2*H*)-carboxamide (3-38):**



According to a modified **GP2B**, allyl(methyl)carbamic chloride (200 mg, 1.50 mmol), 7-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline (392 mg, 1.95 mmol) and triethylamine (0.33 mL, 2.40 mmol) were heated under reflux at 73 °C for 4 days. Purification via flash column chromatography eluting with EtOAc:PE (0:1 – 4:1) afforded the title compound (186 mg, 42%) as an orange oil. $\mathbf{R_f}$ = 0.67 (2:3 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.19-7.13 (m, 2H, ArH), 7.12-7.07 (m, 1H, ArH), 5.87-5.75 (m, 1H, H2), 5.24-5.14 (m, 2H, H1), 3.87 (dt, *J* = 6.2, 1.4, 2H, H3), 3.61-3.56 (m, 2H, H6), 2.80 (td, *J* = 6.9, 1.3, 2H, H8), 2.73 (s, 3H, H4), 2.01-1.93 (m, 2H, H7). **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 160.1 (C5), 141.2 (Ar), 133.1 (C2), 130.9 (q, *J* = 1.2, Ar), 129.7 (C10), 129.0 (q, *J* = 32.3, C12), 124.2 (q, *J* = 272.0, C15), 118.0 (q, *J* = 3.9, C11 or 13), 117.8 (C1), 116.1 (q, *J* = 4.0, C11 or 13), 52.7 (C3), 46.0 (C6), 35.8 (C4), 27.9 (C8), 22.9 (C7). **^{19}F NMR** (376 MHz, $CDCl_3$): δ_F -62.6 (s, 3F, CF_3). **HRMS m/z** (ESI^+): calcd. for

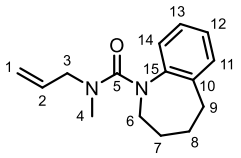
$C_{15}H_{17}F_3N_2NaO$ [M+Na] Calculated 321.1185. Found 321.1180. **IR ν_{max}** (ATR)/cm^{-1}: 3088, 2933, 2864, 1653.

***N*-Allyl-*N*-methyl-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (3-39):**



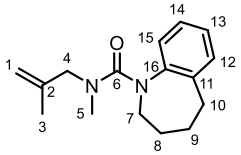
According to **GP2D**, allyl(methyl)carbamic chloride (297 mg, 2.23 mmol), 1,2,3,4-tetrahydro-1,8-naphthyridine (250 mg, 1.86 mmol) and NaHMDS (1 M in THF, 2.05 mL, 2.05 mmol) were stirred at room temperature for 43 h. Purification via flash column chromatography eluting with acetone:PE (2:8 – 1:0) afforded the title compound (278 mg, 65%) as an orange oil. $\mathbf{R_f}$ = 0.55 (2:3 acetone:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.97 (ddd, *J* = 4.9, 1.9, 0.9, 1H, ArH), 7.20 (ddt, *J* = 6.5, 2.0, 1.0, 1H, ArH), 6.63 (dd, *J* = 7.3, 4.9, 1H, ArH), 5.79 (ddt, *J* = 17.2, 10.3, 5.9, 1H, H2), 5.22-5.17 (m, 1H, H1a), 5.13-5.09 (m, 1H, H1b), 3.91 (dt, *J* = 5.9, 1.6, 2H, H3), 3.58-3.50 (m, 2H, H6), 2.81 (s, 3H, H4), 2.71 (t, *J* = 6.6, 2H, H8), 1.97-1.89 (m, 2H, H7). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.1 (C5), 153.7 (Ar), 146.0 (ArH), 137.0 (ArH), 133.8 (C2), 119.4 (Ar), 117.2 (C1), 115.9 (ArH), 52.4 (C3), 46.0 (C6), 35.1 (C4), 26.7 (C8), 22.1 (C7). **HRMS m/z** (ESI^+): calcd. for $C_{13}H_{17}N_3NaO$ [M+Na] Calculated 254.1264. Found 254.1260. **IR ν_{max}** (ATR)/cm^{-1}: 2931, 2864, 1654.

***N*-Allyl-*N*-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (3-40):**



According to **GP2B**, 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carbonyl chloride (886 mg, 4.24 mmol), *N*-allylmethylamine (0.53 mL, 5.51 mmol) and triethylamine (0.94 mL, 6.78 mmol) were stirred at room temperature for 22 h. Purification via flash column chromatography eluting with EtOAc:PE (1:9 - 4:1) afforded the title compound (765 mg, 74%) as a colourless oil. $\mathbf{R_f}$ = 0.66 (2:3 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.19 (dd, *J* = 7.5, 1.6, 1H, ArH), 7.14 (td, *J* = 7.5, 1.8, 1H, ArH), 7.07 (td, *J* = 7.5, 1.4, 1H, ArH), 6.96 (dd, *J* = 7.7, 1.4, 1H, ArH), 5.65-5.52 (m, 1H, H2), 5.10-5.07 (m, 1H, H1a), 5.06-5.03 (m, 1H, H1b), 3.67 (dt, *J* = 6.1, 1.4, 2H, H3), 3.85-3.53 (m, br, 2H, H6), 2.81-2.75 (m, 2H, H9), 2.42 (s, 3H, H4), 1.79-1.70 (m, 2H, H7 or 8), 1.61-1.69 (m, br, 2H, H7 or 8). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 161.5 (C5), 146.3 (Ar), 138.4 (Ar), 133.9 (C2), 130.5 (ArH), 127.3 (ArH), 125.7 (ArH), 124.9 (ArH), 117.4 (C1), 53.0 (C3), 48.7 (C6), 35.4 (C4), 35.3 (C9), 30.8 (C7 or 8), 26.0 (C7 or 8). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{20}N_2ONa$ Calculated 267.1468. Found 267.1465. **IR ν_{max}** (ATR)/cm^{-1}: 2981, 2924, 2855, 1640.

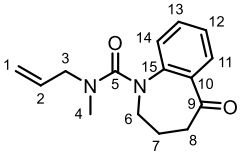
***N*-Methyl-*N*-(2-methylallyl)-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (3-41):**



According to **GP2C**, 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carbonyl chloride (200 mg, 0.957 mmol), 2-methylallylamine (0.08 mL, 1.24 mmol) and triethylamine (0.21 mL, 1.53 mmol) were stirred at room temperature for 21 h. Purification via flash column chromatography eluting with EtOAc:PE (1:9 – 7:3) afforded the secondary urea (190 mg, 81%) as a colourless solid. $\mathbf{R_f}$ = 0.56 (1:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.33-7.20 (m, 4H, ArH), 4.76-4.75 (m, 1H, H1a), 4.72-.4.69 (m, 1H, H1b), 4.65 (s, br, 1H, H6a), 4.44-4.32 (m, br, 1H, H6b), 3.76 (s, br, 2H, H4), 2.77 (s, br, 2H, H9), 2.65 (s, 1H, H7 or 8), 2.13-1.75 (m, br, 3H, H7/8), 1.70 (dd, *J* = 1.5, 0.8, 3H, H3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 156.1 (C5), 143.6 (C2), 142.2 (Ar), 142.2 (Ar), 130.9 (ArH), 128.2 (ArH), 128.1 (ArH), 127.7 (ArH), 109.7 (C1), 47.4 (C6), 46.2 (C4), 34.8 (C9), 29.9 (C7 or 8), 26.4 (C7 or 8), 20.4 (C3). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{20}N_2NaO$ [M+Na] Calculated 267.1468. Found 267.1470. **IR ν_{max}** (ATR)/cm^{-1}: 3290, 2965, 2931, 2912, 2853, 1645.

A solution of the secondary urea (300 mg, 1.23 mmol) and NaH (60% in mineral oil, 197 mg, 4.92 mmol) were stirred at 0 °C for 1 h. Iodomethane (0.31 mL, 4.92 mmol) was added to the reaction mixture and stirred at room temperature for 52 h. Purification via flash column chromatography eluting with EtOAc:PE (1:9 – 4:1) afforded the title compound (230 mg, 72%) as a colourless oil. $\mathbf{R_f}$ = 0.47 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.21-7.17 (m, 1H, ArH), 7.14 (td, *J* = 7.6, 1.8, 1H, ArH), 7.07 (td, *J* = 7.4, 1.4, 1H, ArH), 6.97 (dd, *J* = 7.7, 1.4, 1H, ArH), 4.85-4.79 (m, 1H, H1a), 4.75-4.70 (m, 1H, H1b), 3.80-3.52 (m, 2H, H7), 3.63 (s, 2H, H4), 2.84-2.74 (m, 2H, H10), 2.38 (s, 3H, H5), 1.79-1.70 (m, 2H, H8 or 9), 1.68-1.63 (m, 2H, H8 or 9), 1.62 (s, 3H, H3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 161.7 (C6), 146.3 (Ar), 141.7 (C2), 138.3 (Ar), 130.5 (ArH), 127.3 (ArH), 125.7 (ArH), 124.8 (ArH), 112.5 (C1), 55.9 (C4), 48.8 (C7), 35.3 (C10), 35.3 (C5), 30.9 (C8 or 9), 26.0 (C8 or 9), 20.2 (C3). **HRMS m/z** (ESI^+): calcd. for $C_{16}H_{22}N_2NaO$ [M+Na] Calculated 281.1624. Found 281.1626. **IR ν_{max}** (ATR)/cm^{-1}: 2981, 2924, 2855, 1640.

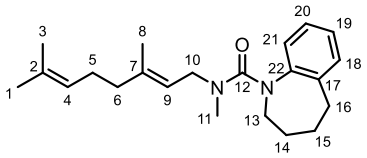
***N*-Allyl-*N*-methyl-5-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (3-42):**



According to a modified **GP2B**, allyl(methyl)carbamic chloride (200 mg, 1.50 mmol), 1,2,3,4-tetrahydro[*b*]azepin-5-one (314 mg, 1.95 mmol) and triethylamine (0.33 mL, 2.40 mmol) were heated

under reflux at 75 °C for 3 days. Purification via flash column chromatography eluting with (1:4 – 1:0) afforded the title compound (56 mg, 14%) as an orange oil. $\mathbf{R_f}$ = 0.44 (2:3 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.81 (dd, *J* = 7.8, 1.7, 1H, ArH), 7.45 (ddd, *J* = 8.0, 7.3, 1.7, 1H, ArH), 7.23 (td, *J* = 7.6, 1.1, 1H, ArH), 7.04 (dd, *J* = 8.1, 1.1, 1H, ArH), 5.62 (ddt, *J* = 17.1, 10.3, 6.0, 1H, H2), 5.14-5.02 (m, 2H, H1), 3.77-3.67 (m, 4H, H3/6), 2.77-2.69 (m, 2H, H8), 2.51 (s, 3H, H4), 2.06-1.93 (m, 2H, H7). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 203.1 (C9), 161.2 (C5), 145.3 (Ar), 133.7 (ArH), 133.4 (Ar), 133.1 (C2), 129.8 (ArH), 125.7 (ArH), 124.8 (ArH), 117.9 (C1), 52.8 (C3), 49.3 (C6), 40.3 (C8), 35.7 (C4), 23.9 (C7). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{18}N_2NaO_2$ [M+Na] Calculated 281.1260. Found 281.1265. **IR ν_{max}** (ATR)/cm^{-1}: 2932, 1714, 1648.

(*E*)-*N*-(3,7-Dimethylocta-2,6-dien-1-yl)-*N*-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (3-43):

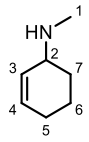


According to **GP2C**, 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carbonyl chloride (200 mg, 0.957 mmol), geranylamine (0.23 mL, 1.24 mmol) and triethylamine (0.21 mL, 1.53 mmol) were stirred at room temperature for 22 h. Purification via flash column chromatography eluting with EtOAc;PE (0:1 – 1:1) afforded the secondary urea (298 mg, 95%) as a yellow oil. $\mathbf{R_f}$ = 0.67 (1:1 EtOAc:PE). **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.35-7.15 (m, 4H, ArH), 5.16-4.96 (m, 2H, H9/4), 4.84-4.45 (m, 1H, H13a), 4.23-4.09 (m, 1H, NH), 3.77 (s, br, 2H, H10), 2.88-2.38 (m, br, 3H, H13b/CH_2), 2.07-1.76 (m, br, 7H, 4 x CH_2), 1.64 (s, 3H, H1 or 3), 1.59 (s, 3H, H8), 1.56 (s, 3H, H1 or 3), 1.40-1.23 (m, br, 1H, CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 156.3 (C12), 142.4 (Ar), 142.2 (Ar), 138.5 (C7), 131.7 (C2), 130.8 (ArH), 128.2 (ArH), 127.9 (ArH), 127.6 (ArH), 124.1 (C4 or 9), 121.7 (C4 or 9), 47.4 (C13), 39.6 (CH_2), 38.8 (C10), 34.8 (CH_2), 29.9 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 25.8 (C1 or 3), 17.8 (C1 or 3), 16.4 (C8).

A solution of the secondary urea (490 mg, 1.50 mmol) and NaH (60% in mineral oil, 240 mg, 6.00 mmol) were stirred at 0 °C for 1 h. Iodomethane (0.57 mL, 6.00 mmol) was added to the reaction mixture and stirred at room temperature for 6 days. Purification via flash column chromatography eluting with EtOAc:PE (0:1 – 3:2) afforded the title compound (377 mg, 74%) as a colourless oil. $\mathbf{R_f}$ = 0.73 (1:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.18 (dd, *J* = 7.4, 1.8, 1H, ArH), 7.13 (td, *J* = 7.7, 1.8, 1H, ArH), 7.06 (td, *J* = 7.4, 1.4, 1H, ArH), 6.94 (dd, *J* = 7.7, 1.4, 1H, ArH), 5.04 (tdq, *J* = 7.1, 2.9, 1.4, 1H, H4), 4.97 (tq, *J* = 6.9, 1.4, 1H, H9), 3.86-3.48 (m, br, 2H, H13), 3.67 (d, *J* = 6.9, 2H, H10), 2.84-2.73 (m, 2H, H16), 2.39 (s, 3H, H11), 2.07-1.90 (m, 4H, H5/6), 1.79-1.69 (m, 2H, H14 or 15), 1.69-1.61 (m, 2H, H14 or 15), 1.65 (d, *J* = 0.9, 3H, H1 or 3), 1.58 (d, *J* = 1.4, 3H, H1 or 3), 1.57 (d, *J* = 1.4, 3H, H8). **^{13}C NMR**

(101 MHz, $CDCl_3$): δ_C 161.5 (C12), 146.4 (Ar), 139.1 (C7), 138.3 (Ar), 131.7 (C2), 130.4 (ArH), 127.2 (ArH), 125.5 (ArH), 124.9 (ArH), 124.1 (C4), 120.0 (C9), 48.6 (C13), 47.6 (C10), 39.7 (C5 or 6), 35.4 (C16), 35.1 (C11), 30.9 (C14 or 15), 26.5 (C5 or 6), 26.0 (C14 or 15), 25.8 (C1 or 3), 17.8 (C1 or 3), 16.2 (C8). **HRMS m/z** (ESI^+): calcd. for $C_{22}H_{33}N_2O$ [M+H] Calculated 341.2587. Found 341.2595. **IR ν_{max}** (ATR)/cm^{-1}: 2972, 2923, 2854, 1644.

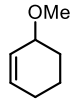
***N*-Methylcyclohex-2-en-1-amine (3-49):**



N-methylcyclohex-2-en-1-amine synthesised in accordance with the literature.[82]

Under an atmosphere of N_2, 3-bromo-cyclohexene (1.00 mL, 8.65 mmol) was added to methylamine (2 M in MeOH, 21.6 mL, 43.3 mmol). The reaction mixture was stirred at room temperature for 47.5 h. The reaction mixture was quenched with aq. NaOH (0.7 M, 35 mL). The reaction mixture was diluted with DCM (10 mL). The aqueous layer was extracted into DCM (2 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure affording the crude title product as a mixture with **3-50** in 0.92:1.00 ratio (761 mg, 39%) as an orange oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.81-5.62 (m, 2H, H3/4), 3.05 (ddt, *J* = 7.0, 5.2, 3.4, 1H, H2), 2.45 (d, *J* = 1.0, 3H, H1), 2.10-1.28 (m, 6H, H5/6/7).

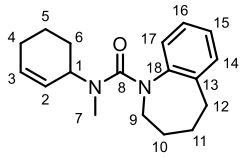
Data in accordance with the literature.[162]



3-50

N.B. Methoxy adduct 3-50 formed through MeOH attack on 3-bromo-cyclohexene.

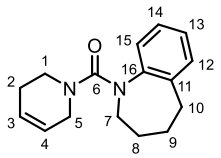
***N*-(Cyclohex-2-en-1-yl)-*N*-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (3-44):**



According to **GP2A**, 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carbonyl chloride (541 mg, 2.58 mmol), *N*-methylcyclohex-2-en-1-amine (as a 0.92:1.00 mixture with 3-methoxycyclohex-1-ene, 619 mg, 2.77 mmol) and triethylamine (0.58 mL, 4.13 mmol) were stirred at room temperature for 23 h. Purification via flash column chromatography eluting with EtOAC:PE (0:1 – 7:3) afforded the title compound (515 mg, 70%) as a white solid. **R_f** = 0.39 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.20-7.17 (m, 1H, ArH), 7.13 (td, *J* = 7.6, 1.8, 1H, ArH), 7.06 (td, *J* = 7.4, 1.4, 1H, ArH), 6.97 (dd, *J* = 7.7, 1.4, 1H, ArH), 5.81-5.71 (m, 1H, H2), 5.31 (ddd, *J* = 10.2, 2.2, 1.3, 1H, H3), 4.60 (ddt, *J* = 8.0, 5.2, 2.7, 1H, H1), 4.06-3.17 (m, br, 2H, H9), 2.88-2.69 (m, 2H, H12), 2.27 (s, 3H, H7), 1.92 (ddt, *J* = 9.6, 6.0, 2.4, 2H, CH_2), 1.83-1.38 (m,

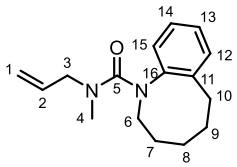
8H, 4 x CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 161.9 (C8), 146.5 (Ar), 138.4 (Ar), 131.0 (C2), 130.4 (ArH), 129.0 (C3), 127.2 (ArH), 125.5 (ArH), 124.7 (ArH), 53.8 (C1), 48.5 (C9), 35.4 (C12), 30.9 (C7), 3.9 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 24.7 (CH_2), 21.7 (CH_2). **HRMS m/z** (ESI^+): calcd. for $C_{18}H_{25}N_2O$ [M+H] Calculated 285.1961. Found 285.1965. **IR ν_{max}** (ATR)/cm^{-1}: 3045, 2917, 2847, 1634. **m.p** 118-120 °C.

(3,6-Dihydropyridin-1(2*H*)-yl)(2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-1-yl)methanone (3-45):



According to **GP2A**, 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carbonyl chloride (200 mg, 0.957 mmol), 1,2,3,6-tetrahydropyridine hydrochloride (148 mg, 1.24 mmol) and triethylamine (0.21 mL, 1.53 mmol) were stirred at room temperature for 21.5 h affording the title compound (194 mg, 79%) as an orange oil without further purification. **R_f** = 0.63 (1:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.20 (dd, *J* = 7.4, 1.8, 1H, ArH), 7.13 (td, *J* = 7.7, 1.8, 1H, ArH), 7.07 (td, *J* = 7.4, 1.5, 1H, ArH), 6.98 (dd, *J* = 7.7, 1.5, 1H, ArH), 5.69 (dtt, *J* = 10.1, 4.0, 2.2, 1H, H3 or 4), 5.51 (dtd, *J* = 10.1, 3.2, 1.6, 1H, H3 or 4), 3.87-3.55 (m, br, 2H, H7), 3.49 (quint., *J* = 2.8, 2H, H1), 3.28-3.12 (m, br, 2H, H5), 2.86-2.75 (m, 2H, H10), 1.87-1.77 (m, 2H, H2), 1.77-1.70 (m, 2H, H8 or 9), 1.70-1.57 (m, br, 2H, H8 or 9). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.8 (C6), 146.2 (Ar), 138.2 (Ar), 130.4 (ArH), 127.3 (ArH), 125.7 (ArH), 125.6 (C3 or 4), 124.9 (ArH), 124.7 (C3 or 4), 48.4 (C7), 45.5 (C1), 42.8 (C5), 35.4 (C10), 30.7 (C8 or 9), 25.9 (C8 or 9), 24.8 (C2). **HRMS m/z** (ESI^+): calcd. for $C_{16}H_{21}N_2O$ [M+H] Calculated 257.1648. Found 257.1655. **IR ν_{max}** (ATR)/cm^{-1}: 2916, 2935, 2853, 2827, 1633.

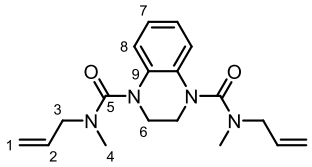
***N*-Allyl-*N*-methyl-3,4,5,6-tetrahydrobenzo[*b*]azocine-1(2*H*)-carboxamide (3-46):**



According to **GP2A**, 3,4,5,6-tetrahydro[*b*]azocine-1(2*H*)-carbonyl chloride (204 mg, 0.914 mmol), *N*-allylmethylamine (0.11 mL, 1.19 mmol) and triethylamine (0.20 mL, 1.46 mmol) were stirred at room temperature for 21 h. Purification via flash column chromatography eluting with EtOAc:PE (1:9 – 4:1) afforded the title compound (181 mg, 77%) as a yellow oil. **R_f** = 0.68 (2:3 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.23-7.14 (m, 3H, ArH), 7.03-6.95 (m, 1H, ArH), 5.31 (ddt, *J* = 17.7, 9.8, 5.6, 1H, H2), 5.01-4.96 (m, 1H, H1a), 4.95-4.93 (m, 1H, H1b), 3.66 (dt, *J* = 6.0, 1.5, 2H, H6), 2.78-2.65 (m, 2H, H10), 2.45 (s, 3H, H4), 1.68 (tt, *J* = 6.8, 3.7, 2H, H7 or 9), 1.56-1.47 (m, br, 2H, H7 or 9), 1.47-1.37 (m, br, 2H, H8). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 163.2 (C5), 143.7 (Ar), 142.0 (Ar), 133.9 (C2), 130.3 (ArH), 127.7 (ArH), 127.7 (ArH), 127.5 (ArH), 116.9 (C1), 53.3 (C6), 35.2 (C4), 31.8 (C10), 31.8 (C7 or 9), 27.0 (C7 or 9), 26.2

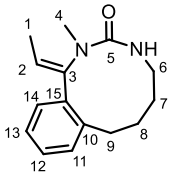
(C8). **HRMS m/z** (ESI^+): calcd. for $C_{16}H_{23}N_2O$ [M+H] Calculated 259.1805. Found 259.1802. **IR ν_{max}** (ATR)/cm^{-1}: 2921, 2853, 1637.

N^1,N^4-Diallyl-N^1,N^4-dimethyl-2,3-dihydroquinoxaline-1,4-dicarboxamide (3-47):



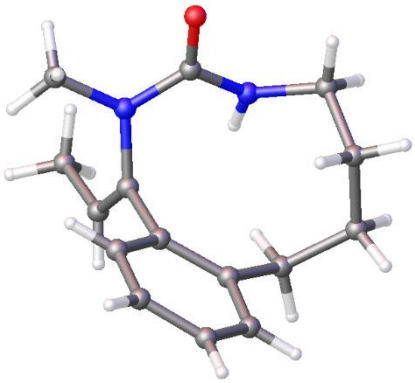
According to **GP2D,** allyl(methyl)carbamic chloride (658 mg, 4.95 mmol), 1,2,3,4-tetrahydroquinoxaline (300 mg, 2.24 mmol) and NaHMDS (1 M in THF, 4.70 mL, 4.70 mmol) were stirred at room temperature for 26 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 1:0) afforded the title compound (533 mg, 73%) as an orange solid. R_f = 0.45 (1:O EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.20-6.89 (m, 4H, ArH), 5.81 (ddt, *J* = 16.6, 10.4, 6.2, 2H, H2), 5.23-5.19 (m, 2H, H1a), 5.19-5.14 (m, 2H, H1b), 3.86 (dt, *J* = 6.2, 1.4, 4H, H3), 3.74 (s, 4H, H6), 2.71 (s, 6H, H4). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 159.6 (C5), 133.0 (C2), 132.7 (C9), 122.7 (ArH), 119.8 (ArH), 117.9 (C1), 52.5 (C3), 46.3 (C6), 35.4 (C4). **HRMS m/z** (ESI^+): calcd. for $C_{18}H_{24}N_4NaO_2$ [M+Na] Calculated 351.1791. Found 351.1788. **IR ν_{max}** (ATR)/cm^{-1}: 3081, 2939, 2876, 1648, 1634. **m.p** 58-60 °C.

(*Z*)-1-Ethylidene-2-methyl-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecine-3(2*H*)-one (3-53):



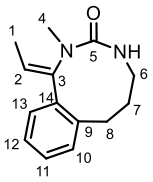
According to **GP3B**, *N*-allyl-*N*-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (200 mg, 0.819 mmol), 18-crown-6 (433 mg, 1.64 mmol) and KHMDS (1 M in THF, 1.64 mL, 1.64 mmol) in anhydrous THF were stirred at room temperature for 21 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 1:0) afforded the title compound (128 mg, 64%) as a colourless solid. R_f = 0.50 (8:2 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.26-7.10 (m, 4H, ArH), 5.64 (q, *J* = 6.8, 1H, H2), 5.12 (s, br, 1H, NH), 3.38-3.22 (m, br, 2H, H6), 3.08 (s, 3H, H4), 2.80 (t, *J* = 7.3, 2H, H9), 1.85 (d, *J* = 6.8, 3H, H1), 1.84-1.76 (m, 2H, H7 or 8), 1.32-1.20 (m, 2H, H7 or 8). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 159.0 (C5), 141.3 (C3), 138.6 (Ar), 138.3 (Ar), 130.1 (ArH), 129.8 (ArH), 128.3 (C2), 128.3 (ArH), 125.8 (ArH), 42.5 (C6), 34.8 (C4), 32.2 (C9), 28.8 (C7 or 8), 26.0 (C7 or 8), 13.1 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{21}N_2O$ [M+H] Calculated 245.1648. Found 245.1645. **IR ν_{max}** (ATR)/cm^{-1}: 3387, 2929, 2905, 2882, 2851, 1650. **m.p** 142-144 °C (recrystallised from acetone:Et_2O).

X-ray crystal data:



Empirical formula	$C_{15}H_{20}N_2O$
Formula weight	244.33
Temperature/K	99.99
Crystal system	Orthorhombic
Space group	$Pna2_1$
a/Å	10.6094(3)
b/Å	7.9990(2)
c/Å	15.6062(5)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1324.41(7)
Z	4
P_{calc}g/cm^3	1.225
μ/mm^{-1}	0.078
F(000)	528.0
Crystal size/mm^3	0.528 x 0.274 x 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	5.22 to 54.97
Index ranges	$-13 \le h \le 13$, $-10 \le k \le 10$, $-20 \le l \le 20$
Reflections collected	16542
Independent reflections	3038 [R_{int} = 0.0426, R_{sigma} = 0.0309]
Data/restraints/parameters	3038/1/169
Goodness-of-fit on F^2	1.046
Final R indexes [I>=2σ (I)]	R_1 = 0.0323, wR2 = 0.0726
Final R indexes [all data]	R_1 = 0.0381, wR_2 = 0.0753
Largest diff. peak/hole/eÅ^{-3}	0.18/-0.17

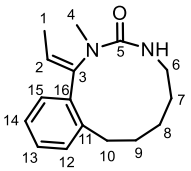
(*Z*)-1-Ethylidene-2-methyl-1,2,4,5,6,7-hexahydro-3*H*-benzo[*e*][1,3]diazonin-3-one (3-8):



According to **GP3B**, *N*-allyl-*N*-methyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (100 mg, 0.435 mmol), 18-crown-6 (230 mg, 0.870 mmol) and KHMDS (1 M in THF, 0.87 mL, 0.870 mmol) in anhydrous THF were stirred at room temperature for 50 h. Purification via flash column chromatography eluting with

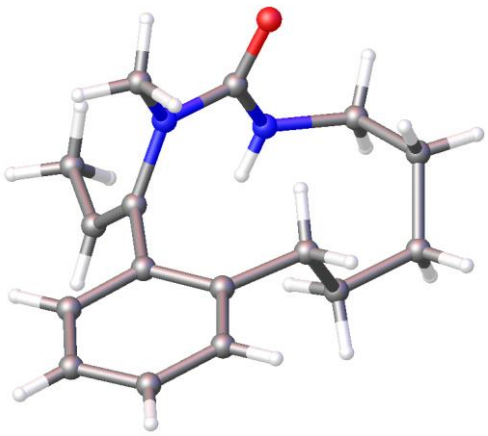
EtOAc:PE (1:4 – 1:0) afforded the title compound (61 mg, 61%) as a colourless solid. $\mathbf{R_f}$ = 0.36 (100% EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.37-7.30 (m, 1H, ArH), 7.25-7.19 (m, 2H, ArH), 7.14-7.08 (m, 1H, ArH), 5.73 (q, *J* = 6.9, 1H, H2), 4.76 (s, br, 1H, NH), 2.91 (s, 3H, H4), 3.19-2.67 (m, br, 4H, H6/8), 1.77 (d, *J* = 6.9, 3H, H1), 1.95-1.67 (m, br, 2H, H7). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.5 (C5), 143.1 (C3), 139.7 (Ar), 136.4 (Ar), 131.8 (ArH), 129.6 (ArH), 128.7 (ArH), 127.1 (ArH), 125.7 (C2), 41.4 (C6), 35.6 (C4), 33.9 (C7), 31.3 (C8), 13.1 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{14}H_{18}N_2NaO$ [M+H] Calculated 253.1311. Found 253.1320. **IR ν_{max}** (ATR)/cm^{-1}: 3231, 2972, 2933, 1673. **m.p.** 179-181 °C (recrystallised from DCM:hexane).

(*Z*)-1-Ethylidene-2-methyl-1,2,4,5,6,7,8,9-octahydro-3*H*-benzo[*e*][1,3]diazacycloundecin-3-one (3-57):



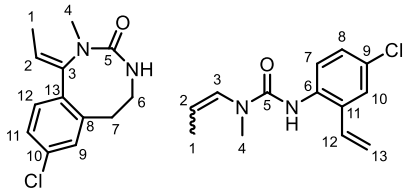
According to **GP3B**, *N*-allyl-*N*-methyl-3,4,5,6-tetrahydrobenzo[*b*]azocine-1(2*H*)-carboxamide (60.0 mg, 0.232 mmol), 18-crown-6 (123 mg, 0.464 mmol) and KHMDS (1 M in THF, 0.46 mL, 0.464 mmol) in anhydrous THF were stirred at room temperature for 21 h. Purification via flash column chromatography eluting with EtOAc:PE (1:9 – 1:0) afforded the title compound (36 mg, 60%) as a yellow solid. $\mathbf{R_f}$ = 0.68 (100% EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.28-7.15 (m, 3H, ArH), 7.12 (dd, *J* = 7.4, 1.4, 1H, ArH), 5.71 (q, *J* = 6.9, 1H, H2), 5.44-5.28 (m, br, 1H, NH), 3.98-3.00 (m, br, 2H, H6), 2.80 (s, 3H, H4), 2.71-2.37 (m, br, 2H, H10), 1.81 (d, *J* = 6.9, 3H, H1), 1.91-1.61 (m, br, 2H, CH_2), 1.69-1.52 (m, 4H, 2 x CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 157.0 (C5), 143.6 (C3), 141.4 (Ar), 136.7 (Ar), 132.6 (ArH), 130.9 (ArH), 128.8 (ArH), 126.7 (C2), 126.3 (ArH), 43.2 (C6), 33.0 (C4), 31.7 (C10), 31.5 (CH_2), 27.6 (CH_2), 24.1 (CH_2), 13.9 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{16}H_{22}N_2NaO$ [M+Na] Calculated 281.1624. Found 281.1635. **IR ν_{max}** (ATR)/cm^{-1}: 3439, 2967, 2916, 2873, 1657. **m.p** 145-146 °C (recrystallised from DCM:Et_2O).

X-ray crystal data:



Empirical formula	$C_{16}H_{22}N_2O$
Formula weight	258.35
Temperature/K	100.04
Crystal system	Monoclinic
Space group	$P2_1/n$
a/Å	11.0502(6)
b/Å	7.5872(4)
c/Å	16.4784(9)
α/°	90
β/°	93.644(4)
γ/°	90
Volume/Å^3	1378.76(13)
Z	4
P_{calc}g/cm^3	1.245
μ/mm^{-1}	0.078
F(000)	560.0
Crystal size/mm^3	0.566 x 0.447 x 0.16
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	4.314 to 56.106
Index ranges	$-14 \le h \le 14$, $-9 \le k \le 9$, $-21 \le l \le 21$
Reflections collected	18435
Independent reflections	3322 [R_{int} = 0.0316, R_{sigma} = 0.0229]
Data/restraints/parameters	3322/0/178
Goodness-of-fit on F^2	1.034
Final R indexes [I>=2σ (I)]	R_1 = 0.0360, wR2 = 0.0862
Final R indexes [all data]	R_1 = 0.0423, wR_2 = 0.0902
Largest diff. peak/hole/eÅ^{-3}	0.32/-0.19

(*Z*)-8-Chloro-1-ethylidene-2-methyl-1,4,5,6-tetrahydrobenzo[*e*][1,3]diazocine-3(2*H*)-one (3-58) and 3-(4-chloro-2-vinylphenyl)-1-methyl-1-(prop-1-en-1-yl)urea (3-79):



According to a modified **GP3B**, *N*-allyl-5-chloro-*N*-methylindoline-1-carboxamide (53.0 mg, 0.212 mmol), 18-crown-6 (224 mg, 0.845 mmol) and KHMDS (1 M in THF, 0.85 mL, 0.850 mmol) in anhydrous THF were stirred at room temperature for 22 h. Purification via flash column chromatography eluting with EtOAc:PE (2:8 – 1:0) afforded the title compounds.

(*Z*)-8-Chloro-1-ethylidene-2-methyl-1,4,5,6-tetrahydrobenzo[*e*][1,3]diazocine-3(2*H*)-one (3-58): Afforded compound (5.0 mg, 9%) as an orange oil. **R_f** = 0.24 (100 % EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.20 (dd, *J* = 8.1, 1.2, 1H, ArH), 7.16-7.13 (m, 1H, ArH), 7.10 (dd, *J* = 2.1, 1.0, 1H, ArH), 5.70 (q, *J* = 6.9, 1H, H2), 4.94-4.88 (m, br, 1H, NH), 3.51-3.40 (m, br, 2H, H6), 3.09-3.02 (m, br, 2H, H7), 2.91 (s, 3H,

H4), 1.79 (d, *J* = 6.9, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 159.5 (C5), 140.5 (C3), 139.8 (Ar), 135.8 (Ar), 133.6 (Ar), 130.9 (ArH), 129.7 (ArH), 127.1 (C2), 126.5 (ArH), 41.6 (C6), 36.2 (C7), 35.1 (C4), 12.6 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{13}H_{15}ClN_2O$ [M+H] Calculated 251.0946. Found 251.0944. **IR ν_{max}** (ATR)/cm^{-1}: 2969, 2912, 1644.

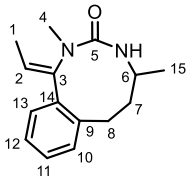
3-(4-Chloro-2-vinylphenyl)-1-methyl-1-(prop-1-en-1-yl)urea (3-79): Afforded compound (37 mg, 70%) as a mixture of 2 stereoisomers as a white solid. ***Cis:Trans*** 2.02:1.00.

***Cis*-major: R_f** = 0.26 (1:9 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.89 (d, *J* = 8.8, 1H, ArH), 7.34-7.29 (m, 1H, ArH), 7.21 (dd, *J* = 8.8, 2.5, 1H, ArH), 6.73 (s, br, 1H, NH), 6.62 (dd, *J* = 17.4, 11.0, 1H, H12), 6.12 (dq, *J* = 7.6, 1.8, 1H, H3), 5.69-5.55 (m, 2H, H2/13a), 5.42 (dd, *J* = 11.0, 1.1, 1H, H13b), 3.07 (s, 3H, H4), 1.72 (dd, *J* = 7.0, 1.8, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 154.1 (C5), 134.7 (Ar), 131.4 (C12), 130.7 (Ar), 129.4 (C3), 128.8 (Ar), 128.5 (ArH), 126.8 (C2), 126.8 (ArH), 123.2 (ArH), 119.2 (C13), 34.9 (C4), 12.6 (C1).

***Trans*-minor: R_f** = 0.41 (1:9 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.65 (d, *J* = 8.7, 1H, ArH), 7.36 (d, *J* = 2.5, 1H, ArH), 7.24-7.21 (m, 1H, ArH), 6.74-6.67 (m, 1H, H2), 6.71 (dd, *J* = 17.5, 11.0, 1H, H12), 6.53-6.46 (m, br, 1H, NH), 5.71-5.65 (m, 1H, H13a), 5.46 (dd, *J* = 11.0, 1.1, 1H, H13b), 5.16 (dq, *J* = 13.4, 6.7, 1H, H2), 3.12 (s, 3H, H4), 1.76 (dd, *J* = 6.7, 1.6, 3H,H1). **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 131.8 (C12), 131.4 (C3), 128.5 (ArH), 124.6 (ArH), 123.2 (ArH), 32.4 (C4), 15.4 (C1). Remaining ^{13}C NMR of *trans*-minor not identifiable due to very weak signals and overlapping with *cis*-major peaks.

Mix: HRMS m/z (ESI^+): calcd. for $C_{13}H_{15}N_2OCl$ [M+H] Calculated 251.0946. Found 251.0943. **IR ν_{max}** (ATR)/cm^{-1}: 3417, 2971, 2913, 1671, 1648. **m.p** 87-89 °C (mix of stereoisomers).

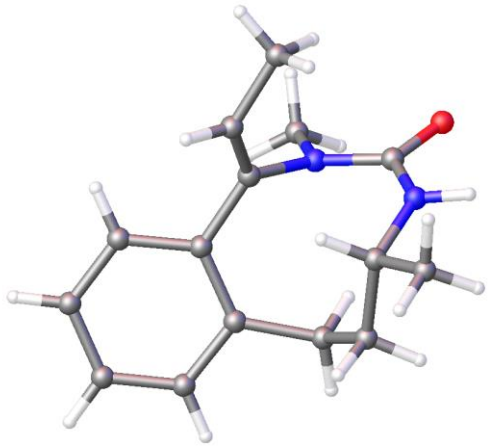
(*Z*)-1-Ethylidene-2,5-dimethyl-1,2,4,5,6,7-hexahydro-3*H*-benzo[*e*][1,3]diazonin-3-one (3-59):



According to **GP3B**, *N*-allyl-*N*,2-dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (78.0 mg, 0.319 mmol), 18-crown-6 (169 mg, 0.639 mmol) and KHMDS (1 M in THF, 0.64 mL, 0.639 mmol) in anhydrous THF were stirred at room temperature for 21 h. Purification via flash column chromatography eluting with EtOAc:PE (1:9 – 1:0) afforded the title compound (47 mg, 60%) as a colourless gum. **R_f** = 0.44 (100% EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.39-7.31 (m, 1H, ArH), 7.26-7.20 (m, 2H, ArH), 7.14-7.08 (m, 1H, ArH), 5.76 (q, *J* = 6.9, 1H, H2), 4.27 (d, *J* = 8.7, 1H, NH), 4.02-3.89 (m, br, 1H, H6), 3.27-3.12 (m, 1H, H8a), 2.88 (s, 3H, H4), 2.63 (dt, *J* = 14.5, 4.4, 1H, H8b), 1.76 (d, *J* = 6.9, 3H, H1), 1.73-1.65 (m, 2H, H7), 1.01 (d, *J* = 6.4, 3H, H15). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 159.6 (C5), 143.3 (C3), 139.9 (Ar), 136.5

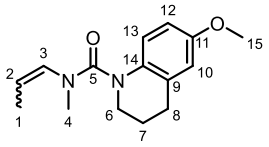
(Ar), 131.9 (ArH), 129.7 (ArH), 128.7 (ArH), 127.1 (ArH), 126.0 (C2), 47.0 (C6), 41.9 (C7), 35.3 (C4), 31.6 (C8), 23.6 (C15), 12.9 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{20}N_2NaO$ [M+Na] Calculated 267.1468. Found 267.1477. **IR ν_{max}** (ATR)/cm^{-1}: 3320, 3205, 3076, 2978, 2929, 2894, 1643.

X-ray crystal data:



Empirical formula	$C_{15}H_{20}N_2O$
Formula weight	244.33
Temperature/K	100.0
Crystal system	Monoclinic
Space group	$P2_1/n$
a/Å	11.7679(5)
b/Å	8.8023(3)
c/Å	12.9805(5)
α/°	90
β/°	99.6660(10)
γ/°	90
Volume/$Å^3$	1325.49(9)
Z	4
$P_{calc}g/cm^3$	1.224
μ/mm^{-1}	0.077
F(000)	528.0
Crystal size/mm^3	0.316 x 0.241 x 0.199
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	4.326 to 57.534
Index ranges	$-15 \leq h \leq 15$, $-11 \leq k \leq 11$, $-17 \leq l \leq 17$
Reflections collected	38073
Independent reflections	3430 [R_{int} = 0.0565, R_{sigma} = 0.0336]
Data/restraints/parameters	3430/0/170
Goodness-of-fit on F^2	1.031
Final R indexes [I>=2σ (I)]	R_1 = 0.0404, wR2 = 0.0924
Final R indexes [all data]	R_1 = 0.0609, wR_2 = 0.1007
Largest diff. peak/hole/$eÅ^{-3}$	0.30/-0.23

6-Methoxy-*N*-methyl-*N*-(prop-1-en-1-yl)-3,4-dihydroquinoline-1(2*H*)-carboxamide (3-82 & 3-83):

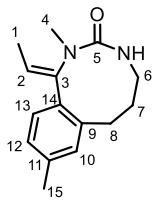


According to **GP3B**, *N*-allyl-6-methoxy-*N*-methyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (85.0 mg, 0.327 mmol), 18-crown-6 (173 mg, 0.654 mmol) and KHMDS (1 M in THF, 0.65 mL, 0.654 mmol) in anhydrous THF were stirred at room temperature for 41 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 4:1) afforded the title compounds as a mixture of 2 stereoisomers as yellow oils. ***Cis:Trans*** 1.00:0.20.

***Trans*-major (3-82):** (34 mg, 40%). $\mathbf{R_f}$ = 0.68 (3:7 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.80-6.74 (m, 1H, ArH), 6.71-6.63 (m, 3H, H3/ArH), 4.77 (dq, *J* = 14.2, 6.6, 1H, H2), 3.76 (s, 3H, H4), 3.62-3.52 (m, 2H, H6), 2.85 (s, 3H, H15), 2.75 (t, *J* = 6.7, 2H, H8), 2.02-1.88 (m, 2H, H7), 1.64 (dd, *J* = 6.6, 1.6, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 159.0 (C5), 155.3 (C11), 133.8 (Ar), 131.0 (C3), 129.9 (Ar), 122.3 (ArH), 113.8 (ArH), 112.5 (ArH), 103.0 (C2), 55.6 (C4), 46.0 (C6), 33.7 (C15), 27.3 (C8), 23.8 (C7), 15.5 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{20}N_2O_2$ [M+H] Calculated 261.1598. Found 261.1596. **IR ν_{max}** (ATR)/cm^{-1}: 2936, 1646.

***Cis*-minor (3-83):** (14 mg, 16%). $\mathbf{R_f}$ = 0.39 (3:7 EtOAc:PE). **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 6.99 (d, *J* = 8.8, 1H, ArH), 6.67-6.54 (m, 2H, ArH), 5.85 (dq, *J* = 8.2, 1.7, 1H, h3), 4.87 (dq, *J* = 8.2, 7.1, 1H, H2), 3.72 (s, 3H, H4), 3.63-6.52 (m, 2H, H6), 3.04 (s, 3H, H15), 2.70 (t, *J* = 6.7, 2H, H9), 2.01-1.82 (m, 2H, H7), 1.59 (dd, *J* = 7.1, 1.7, 3H, H1). **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 160.4 (C5), 155.1 (Ar), 133.7 (Ar), 131.8 C3), 130.3 (Ar), 123.1 (ArH), 116.0 (C2), 113.3 (ArH), 112.2 (ArH), 55.6 (C4), 46.0 (C6), 36.9 (C15), 27.3 (C9), 24.0 (C7), 12.9 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{20}N_2O_2$ [M+H] Calculated 261.1598. Found 261.1594. **IR ν_{max}** (ATR)/cm^{-1}: 2984, 2944, 2904, 1642.

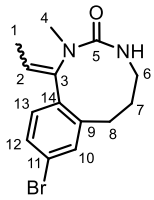
(*Z*)-1-Ethylidene-2,9-dimethyl-1,2,4,5,6,7-hexahydro-3*H*-benzo[*e*][1,3]diazonin-3-one (3-60):



According to **GP3B**, *N*-allyl-*N*,6-dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (100 mg, 0.410 mmol), 18-crown-6 (217 mg, 0.820 mmol) and KHMDS (1 M in THF, 0.82 mL, 0.820 mmol) in anhydrous THF were stirred at room temperature for 19 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 1:0) afforded the title compound (8 mg, 8%) as an orange oil. $\mathbf{R_f}$ = 0.37 (100% EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.24 (d, *J* = 7.7, 1H, H13), 7.04 (ddd, *J* = 7.7, 1.9, 0.8, 1H, H12),

6.93 (d, *J* = 1.9, 1H, H10), 5.70 (q, *J* = 6.9, 1H, H2), 4.83-4.55 (br, 1H, NH), 3.87-3.44 (m, br, 1H, H6a), 3.23-2.53 (m, br, 3H, H6a/8), 2.89 (s, 3H, H4), 2.32 (s, 3H, H15), 1.99-1.54 (m, br, 2H, H7), 1.75 (d, J = 6.9, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.2 (C5), 142.9 (C3), 139.2 (Ar), 138.1 (Ar), 133.4 (Ar), 132.2 (C10), 129.3 (C13), 127.4 (C12), 124.6 (C2), 41.0 (C6), 35.2 (C4), 33.7 (C7), 30.9 (C8), 20.8 (C15), 12.7 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{20}N_2NaO$ [M+Na] Calculated 267.1468. Found 267.1480. **IR** ν_{max} (ATR)/cm^{-1}: 3300, 3228, 3087, 2959, 2924, 1660.

9-Bromo-1-ethylidene-2-methyl-1,2,4,5,6,7-hexahydro-3*H*-benzo[*e*][1,3]diazonin-3-one (3-61):



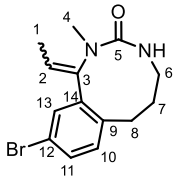
According to **GP3B**, *N*-allyl-6-bromo-*N*-methyl-3,4-dihydroquinoine-1(2*H*)-carboxamide (100 mg, 0.325 mmol), 18-crown-6 (172 mg, 0.650 mmol) and KHMDS (0.91 M in THF, 0.71 mL, 0.650 mmol) in anhydrous THF were stirred at room temperature for 22 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 1:0) afforded the title compound (61 mg, 61%) as a mixture of 2 isomers as a yellow solid. ***Cis:Trans*** 1.00:0.47.

***Cis*-major: R_f** = 0.29 (100% EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.28 (dd, *J* = 8.2, 2.1, 1H, ArH), 7.21 (d, *J* = 2.1, 1H, ArH), 7.12 (d, *J* = 8.2, 1H, ArH), 5.65 (q, *J* = 6.9, 1H, H2), 4.64 (s, br, 1H, NH), 3.70-3.35 (m, br, 1H, H6a), 3.18-2.45 (m, br, 3H, H6b/8), 2.84 (s, 3H, H4), 2.02-1.42 (m, br, 2H, H7), 1.70 (d, *J* = 6.9, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.1 (C5), 142.2 (C3), 141.8 (Ar), 135.6 (Ar), 134.2 (ArH), 130.8 (ArH), 130.0 (ArH), 125.8 (C2), 122.2 (Ar), 41.3 (C6), 35.6 (C4), 33.5 (C7), 31.0 (C8), 13.0 (C1). **IR** ν_{max} (ATR)/cm^{-1}: 3307, 3228, 3093, 2931, 2865, 1674, 1651. **m.p** decomposes.

***Trans*-minor: R_f** = 0.38 (100% EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.33-7.27 (m, 2H, ArH), 6.89 (d, *J* = 8.0, 1H, ArH), 5.64 (q, *J* = 7.1, 1H, H2), 4.11 (t, br, *J* = 8.1, 1H, NH), 3.80-3.46 (m, br, 1H, H6a), 3.28 (s, 3H, H4), 3.38-3.10 (m, br, 1H, H6b), 3.01-2.55 (m, br, 2H, H8), 1.84-1.45 (m, br, 2H, H7), 1.59 (d, *J* = 7.1, 3H, H1). **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 161.1 (C5), 143.1 (C3), 142.7 (Ar), 134.9 (Ar), 132.0 (ArH), 129.9 (ArH), 129.6 (ArH), 122.1 (Ar), 118.1 (C2), 44.1 (C6), 39.9 (C4), 32.8 (C8), 31.6 (C7), 13.8 (C1). **IR** ν_{max} (ATR)/cm^{-1}: 3221, 3084, 2921, 2855, 1672, 1647.

HRMS m/z (ESI^+): calcd. for $C_{14}H_{17}N_2O^{79}Br$ [M+H] Calculated 309.0597. Found 309.0600.

10-Bromo-1-ethylidene-2-methyl-1,2,4,5,6,7-hexahydro-3*H*-benzo[*e*][1,3]diazonin-3-one (3-62):



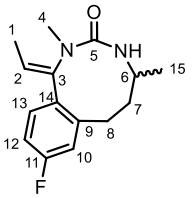
According to **GP3B**, *N*-allyl-7-bromo-*N*-methyl-3,4-dihydroquinoine-1(2*H*)-carboxamide (83.0 mg, 0.269 mmol), 18-crown-6 (172 mg, 0.650 mmol) and KHMDS (0.91 M in THF, 0.71 mL, 0.650 mmol) in anhydrous THF were stirred at room temperature for 22 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 1:0) afforded the title compound (54 mg, 65%) as a mixture of 2 isomers as an off-white solid. ***Cis:Trans**:* 1.0:0.2.

***Cis*-major: R_f** = 0.32 (100% EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.47 (d, *J* = 2.2, 1H, ArH), 7.34 (dd, *J* = 8.1, 2.2, 1H, ArH), 6.98 (d, *J* = 8.1, 1H, ArH), 5.76 (q, *J* = 7.0, 1H, H2), 4.74 (s, br, 1H, NH), 3.79-3.39 (m, br, 1H, H6a), 3.26-2.52 (m, br, 3H, H6b/8), 2.89 (s, 3H, H4), 2.12-1.55 (m, br, 2H, H7), 1.77 (d, *J* = 7.0, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.2 (C5), 142.1 (C3), 138.7 (Ar), 133.4 (ArH), 132.1 (Ar), 131.9 (ArH), 131.4 (ArH), 126.7 (C2), 120.6 (Ar), 41.3 (C6), 35.6 (C4), 33.7 (C7), 30.8 (C8), 13.1 (C1). **IR ν_{max}** (ATR)/cm^{-1}: 3298, 3234, 3082, 2963, 2941, 2902, 1649. **m.p** decomposes.

***Trans*-minor: R_f** = 0.40 (100% EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.32 (dd, *J* = 8.1, 2.2, 1H, ArH), 7.15 (d, J = 2.2, 1H, ArH), 7.00 (d, *J* = 8.1, 1H, ArH), 5.65 (q, *J* = 7.2, 1H, H2), 4.10 (t, br, *J* = 8.0, 1H, NH), 3.76-3.42 (m, br, 1H, H6a), 3.29 (s, 3H, H4), 3.38-3.08 (m, br, 1H, H6b), 2.96-2.50 (m, br, 2H, H8), 1.66-1.57 (m, br, 2H, H7), 1.59 (d, *J* = 7.2, 3H, H1). **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 161.0 (C5), 142.4 (C3), 139.9 (Ar), 137.8 (Ar), 131.5 (ArH), 130.8 (ArH), 130.8 (ArH), 120.3 (Ar), 118.6 (C2), 44.2 (C6), 39.9 (C4), 32.6 (C8), 31.6 (C7), 13.8 (C1). **IR ν_{max}** (ATR)/cm^{-1}: 3294, 3239, 2954, 2923, 2853, 4667, 1644.

HRMS m/z (ESI$^+$): calcd. for $C_{14}H_{17}N_2O^{79}Br$ [M+H] Calculated 309.0597. Found 309.0599.

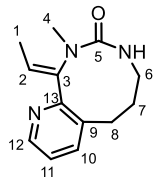
(*Z*)-1-Ethylidene-9-fluoro-2,5-dimethyl-1,2,4,5,6,7-hexahydro-3*H*-benzo[*e*][1,3]diazenin-3-one (3-63):



According to **GP3**, *N*-allyl-6-fluoro-*N*,2-dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (100 mg, 0.381 mmol), 18-crown-6 (201 mg, 0.762 mmol) and KHMDS (1 M in THF, 0.76 mL, 0.762 mmol) in anhydrous THF were stirred at room temperature for 17 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 1:0) afforded the title compound (15 mg, 15%) as a brown solid. **R_f** = 0.47 (100% EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.29 (dd, *J* = 8.5, 6.0, 1H, H13), 6.90 (ddd, *J* = 8.5, 8.3, 2.8, 1H, H12), 6.81 (dd, *J* = 9.8, 2.7, 1H, H10), 5.68 (q, *J* = 6.9, 1H, H2), 4.24 (d, br, *J* =

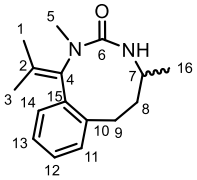
8.6, 1H, NH), 3.99-3.84 (m, 1H, H6), 3.20-3.08 (m, 1H, H8a), 2.87 (s, 3H, H4), 2.60 (dt, *J* = 14.4, 4.5, 1H, H8b), 1.75 (d, *J* = 6.9, 3H, H1), 1.72-1.61 (m, 2H, H7), 1.02 (dd, J = 6.4, 3H, H15). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 162.6 (d, *J* = 247.7, C11), 159.4 (C5), 142.4 (d, *J* = 7.4, C9), 142.4 (C3), 132.6 (d, *J* = 2.4, C14), 131.2 (d, *J* = 8.2, C13), 125.7 (C2), 118.3 (d, *J* = 20.8, C10), 113.7 (d, *J* = 20.9, C12), 47.1 (C6), 41.6 (C7), 35.3 (C4), 31.6 (C8), 23.6 (C15), 12.9 (C1). **^{19}F NMR** (376 MHz, $CDCl_3$): δ_F -114.3 (ddd, *J* = 9.8, 8.3, 6.0, 1F, ArF). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{19}FN_2NaO$ [M+Na] Calculated 285.1374. Found 285.1383. **IR ν_{max}** (ATR)/cm^{-1}: 3227, 2974, 2934, 1673, 1651. **m.p** 173-175 °C.

(*Z*)-11-Ethylidene-10-methyl-5,6,7,8,10,11-hexahydro-9*H*-pyrido[2,3-*e*][1,3]diazonin-9-one (3-64):



According to **GP3B**, *N*-allyl-*N*-methyl-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (100 mg, 0.433 mmol), 18-crown-6 (229 mg, 0.866 mmol) and KHMDS (0.91 M in THF, 0.95 mL, 0.866 mmol) in anhydrous THF were stirred at room temperature for 22 h. Purification via column chromatography eluting with EtOAc:PE then EtOAc:MeOH (3:7 – 1:0 then 1:0 – 9:1) afforded the title compound (74 mg, 74%) as an orange solid. $\mathbf{R_f}$ = 0.28 (6:94 MeOH:DCM). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.49 (dd, *J* = 4.7, 1.7, 1H, ArH), 7.44 (dd, *J* = 7.7, 1.7, 1H, ArH), 7.17 (dd, *J* = 7.6, 4.7, 1H, ArH), 6.37 (q, *J* = 7.1, 1H, H2), 4.69 (t, br, *J* = 7.9, 1H, NH), 3.65 (s, br, 1H, H6a), 3.40-3.17 (m, br, 1H, H8a), 3.02-2.82 (m, br, 1H, H6b), 2.94 (s, 3H, H4), 2.72 (s, br, 1H, H8b), 2.15-1.92 (m, br, 1H, H7a), 1.82 (d, *J* = 7.1, 3H, H1), 1.75-1.53 (m, br, 1H, H7b). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.6 (C5), 153.8 (Ar), 147.8 (ArH), 142.2 (C3), 140.2 (ArH), 134.7 (Ar), 129.4 (C2), 123.2 (ArH), 40.8 (C6), 35.8 (C4), 33.8 (C7), 30.8 (C8), 12.9 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{13}H_{18}N_3O$ [M+H]. Calculated 232.1444. Found 232.1447. **IR ν_{max}** (ATR)/cm^{-1}: 3294, 3213, 3053, 2930, 1648. **m.p** 161-163 °C (recrystallised from acetone:hexane).

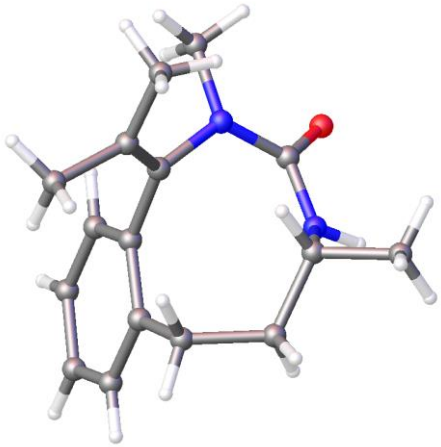
2,5-Dimethyl-1-(propan-2-ylidene)-1,2,4,5,6,7-hexahydro-3*H*-benzo[*e*][1,3]diazonin-3-one (3-65):



According to **GP3B**, *N*,2-dimethyl-*N*-(2-methylallyl)-3,4-dihydroquinoline-1(2*H*)-carboxamide (165 mg, 0.639 mmol), 18-crown-6 (338 mg, 1.28 mmol) and KHMDS (1 M in THF, 1.28 mL, 1.28 mmol) in anhydrous THF stirred at room temperature for 21 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 1:0) afforded the title compound (128 mg, 78%) as a white solid. $\mathbf{R_f}$ = 0.53 (100% EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.14-7.21 (m, 2H, ArH), 7.13-7.07 (m, 2H, ArH), 3.85 (d, br, *J* = 9.6, 1H, NH), 3.74-3.60 (m, 1H, H7), 3.05 (s, 3H, H5), 2.79 (dt, *J* = 9.6, 4.1, 2H, H9), 1.86 (s, 3H,

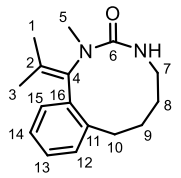
H1 or 3), 1.68 (s, 3H, H1 or 3), 1.76-1.65 (m, 1H, H8a), 1.56-1.42 (m, 1H, H8b), 1.08 (d, *J* = 6.5, 3H, H16). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.3 (C6), 140.9 (Ar), 137.4 (C4), 136.3 (Ar), 130.3 (ArH), 129.3 (ArH), 128.2 (ArH), 126.6 (ArH/C2), 49.3 (C7), 39.9 (C8), 37.6 (C5), 32.8 (C9), 25.3 (C16), 20.9 (C1 or 3), 20.1 (C1 or 3). **HRMS m/z** (ESI^+): calcd. for $C_{16}H_{22}N_2NaO$ [M+Na] Calculated 281.1624. Found 281.1615. **IR** ν_{max} (ATR)/cm^{-1}: 3230, 2985, 2929, 2894, 1647. **m.p** 161-163 °C.

X-ray crystal data:



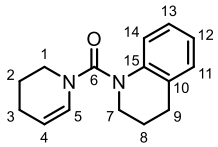
Empirical formula	$C_{16}H_{22}N_2O$
Formula weight	258.35
Temperature/K	100.0
Crystal system	Orthorhombic
Space group	Pbca
a/Å	8.1453(6)
b/Å	14.3133(10)
c/Å	24.0604(16)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2805.1(3)
Z	8
P_{calc}g/cm^3	1.224
μ/mm^{-1}	0.077
F(000)	1120.0
Crystal size/mm^3	0.495 x 0.3 x 0.16
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	5.692 to 55.848
Index ranges	$-10 \le h \le 10$, $-18 \le k \le 18$, $-31 \le l \le 31$
Reflections collected	71752
Independent reflections	3361 [R_{int} = 0.0550, R_{sigma} = 0.0183]
Data/restraints/parameters	3361/0/180
Goodness-of-fit on F^2	1.037
Final R indexes [I>=2σ (I)]	R_1 = 0.0372, wR2 = 0.0913
Final R indexes [all data]	R_1 = 0.0445, wR_2 = 0.0956
Largest diff. peak/hole/eÅ^{-3}	0.34/-0.22

2-Methyl-1-(propan-2-ylidene)-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecine-3(2*H*)-one (3-66):



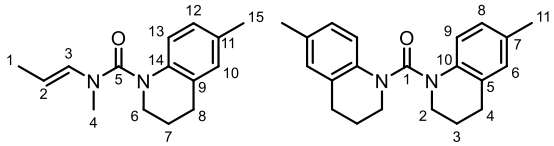
According to **GP3B**, *N*-methyl-*N*-(2-methylallyl)-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (150 mg, 0.581 mmol), 18-crown-6 (307 mg, 1.16 mmol) and KHMDS (1 M in THF, 1.16 mL, 1.16 mmol) in anhydrous THF stirred at room temperature for 17 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 1:0) afforded the title compound (107 mg, 71%) as a white solid. $\mathbf{R_f}$ = 0.57 (100% EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.25-7.18 (m, 2H, ArH), 7.18-7.08 (m, 2H, ArH), 5.05 (d, br, *J* = 11.3, 1H, NH), 3.83-3.71 (m, 1H, H7a), 3.09 (s, 3H, H5), 2.89-2.72 (m, 2H, H7b/10a), 2.64 (ddd, *J* = 14.4, 12.3, 5.5, 1H, H10b), 2.08-1.91 (m, 1H, H8 or 9), 1.90 (s, 3H, H1 or 3), 1.83 (tdt, *J* = 11.8, 5.5, 3.0, 1H, H8 or 9), 1.51 (s, 3H, H1 or 3), 1.34-1.24 (m, 1H, H8 or 9), 1.15-1.01 (m, 1H, H8 or 9). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 159.1 (C6), 138.1 (Ar), 137.7 (Ar), 135.3 (C2), 134.6 (C4), 129.4 (ArH), 129.2 (ArH), 127.9 (ArH), 126.1 (ArH), 43.3 (C7), 35.0 (C5), 32.0 (C10), 29.4 (C8 or 9), 28.9 (C1 or 3), 26.1 (C8 or 9), 20.3 (C1 or 3). **HRMS m/z** (ESI^+): calcd. for $C_{16}H_{23}N_2O$ [M+H] Calculated 259.1805. Found 259.1795. **IR ν_{max}** (ATR)/cm^{-1}: 3350, 2927, 2905, 2849, 1647. **m.p** 154-155 °C (recrystallised from acetone:heptane).

(3,4-Dihydropyridin-1(2*H*)-yl)(2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-1-yl)methanone:



According to **GP3B**, (3,6-dihydropyridin-1(2*H*)-yl)(2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-1-yl)methanone (70.0 mg, 0.273 mmol), 18-crown-6 (155 mg, 0.586 mmol) and KHMDS (1 M in THF, 0.82 mL, 0.819 mmol) in anhydrous THF were stirred at room temperature for 19 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 4:1) afforded the title compound (30 mg, 43%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.19 (dd, *J* = 7.4, 1.8, 1H, ArH), 7.13 (td, *J* = 7.7, 1.8, 1H, ArH), 7.07 (td, *J* = 7.4, 1.5, 1H,ArH), 6.87 (dd, *J* = 7.7, 1.5, 1H, ArH), 6.36 (dt, *J* = 8.4, 2.0, 1H, H5), 4.63 (dt, *J* = 8.4, 3.8, 1H, H4), 4.04-3.39 (m, br, 2H, H7), 3.20-3.00 (m, br, 2H, H1), 2.82-2.75 (m, 2H, H10), 1.88 (tdd, *J* = 6.1, 3.8, 2.0, 2H, H3), 1.81-1.71 (m, 2H, H8), 1.70-1.60 (m, 4H, H2/9). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 158.1 (C6), 145.6 (Ar), 138.1 (Ar), 130.5 (ArH), 127.4 (ArH), 127.3 (C5), 125.8 (ArH), 125.1 (ArH), 105.0 (C4), 48.6 (C7), 44.3 (C1), 35.3 (C10), 30.6 (C8), 25.8 (C9), 22.0 (C2), 21.7 (C3). **HRMS m/z** (ESI^+): calcd. for $C_{16}H_{20}N_2O$ [M+H] Calculated 257.1648. Found 257.1644. **IR ν_{max}** (ATR)/cm^{-1}: 2928, 2852, 1638. **m.p** 117-120 °C.

(*E*)-*N*,6-Dimethyl-*N*-(prop-1-en-1-yl)-3,4-dihydroquinoline-1(2*H*)-carboxamide (3-85) & bis(6-methyl-3,4-dihydroquinolin-1(2*H*)-yl)methanone (3-89):

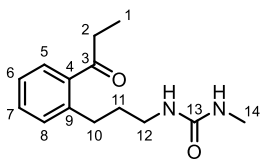


Under an atmosphere of N_2, *N*-allyl-*N*,6-dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (41.0 mg, 0.170 mmol) and KHMDS (1 M in THF, 0.34 mL, 0.340 mmol) in anhydrous 1,4-dioxane (1.70 mL) were sealed in a flame dried microwave vial. The reaction mixture was heated under microwave irradiation at 120 °C for 1 h. The reaction mixture was quenched with MeOH (0.5 mL) and diluted with EtOAc (10 mL) and washed with sat. aq. $NaHCO_3$ (10 mL). The aqueous layer was extracted into EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography eluting with EtOAc (0:1 -1:0) afforded the title compounds.

(*E*)-*N*,6-Dimethyl-*N*-(prop-1-en-1-yl)-3,4-dihydroquinoline-1(2*H*)-carboxamide (3-85): Afforded compound (5 mg, 12%) as a yellow oil. $\mathbf{R_f}$ = 0.39 (1:9 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.94-6.85 (m, 2H, ArH), 6.74-6.66 (m, 2H, H3/ArH), 4.79 (dq, *J* = 14.3, 6.6, 1H, H2), 3.64-3.56 (m, 2H, H6), 2.86 (s, 3H, H4), 2.74 (t, *J* = 6.9, 2H, H8), 2.26 (s, 3H, H15), 2.00-1.93 (m, 2H, H7), 1.65 (dd, *J* = 6.6, 1.6, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 159.0 (C5), 137.9 (Ar), 132.1 (Ar), 130.9 (C3), 129.6 (ArH), 128.2 (Ar), 127.3 (ArH), 120.8 (ArH), 103.3 (C2), 46.0 (C6), 33.7 (C4), 27.0 (C8), 23.8 (C7), 20.8 (C15), 15.5 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{20}N_2O$ [M+H] Calculated 245.1648. Found 245.1641. **IR ν_{max}** (ATR)/cm^{-1}: 2987, 2929, 2897, 1646.

Bis(6-methyl-3,4-dihydroquinolin-1(2*H*)-yl)methanone (3-89): Afforded compound (9 mg, 17%) as an orange gum. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.14 (d, *J* = 8.3, 2H, ArH), 6.95-6.78 (m, 4H, ArH), 3.65-3.41 (m, br, 4H, H2), 2.72 (t, *J* = 6.7, 4H, H4), 2.24 (s, 6H, H11), 1.92 (quint., *J* = 6.5, 4H, H3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 159.3 (C1), 137.2 (Ar), 1323 (Ar), 129.6 (ArH), 128.3 (Ar), 127.2 (ArH), 121.2 (ArH), 46.0 (C2), 27.1 (C4), 23.7 (C3), 20.8 (C11). **HRMS m/z** (ESI^+): calcd. for $C_{21}H_{24}N_2O$ [M+H] Calculated 321.1961. Found 321.1962. **IR ν_{max}** (ATR)/cm^{-1}: 2987, 2935, 2857, 1644.

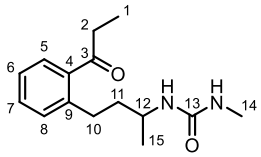
1-Methyl-3-(3-(2-propionylphenyl)propyl)urea (3-102):



According to **GP5**, (Z)-1-ethylidene-2-methyl-1,2,4,5,6,7-hexahydro-3*H*-benzo[*e*][1,3]diazonin-3-one (154 mg, 0.669 mmol) and *para*-toluenesulfonic acid (1.27 g, 6.69 mmol) were stirred for 5 days.

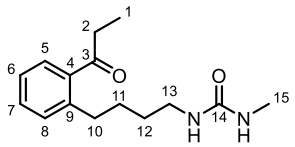
Purification via flash column chromatography eluting with EtOAc:PE (0:1 – 1:0) afforded the title compound (111 mg, 67%) as a pale-yellow gum. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.62 (dd, *J* = 8.3, 1.4, 1H, ArH), 7.45-7.38 (m, 1H, ArH), 7.31-7.19 (m, 2H, ArH), 5.18 (s, br, 1H, NH), 4.48 (s, br, 1H, NH), 3.21 (t, *J* = 6.4, 2H, H12), 2.93 (q, *J* = 7.3, 2H, H2), 2.85-2.76 (m, 5H, H10/14), 1.93-1.75 (m, 2H, H11), 1.18 (t, *J* = 7.3, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 206.2 (C3), 159.6 (C13), 141.6 (Ar), 138.1 (Ar), 131.4 (ArH), 131.3 (ArH), 128.5 (ArH), 126.0 (ArH), 39.9 (C12), 35.2 (C2), 32.0 (C11), 30.9 (C10), 27.3 (C14), 8.5 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{14}H_{21}N_2O_2$ [M+H] Calculated 249.1598 Found 249.1598. **IR ν_{max}** (ATR)/cm^{-1}: 3327, 3229, 2969, 2933, 2873, 1674, 1623.

1-Methyl-3-(4-(2-propionylphenyl)butan-2-yl)urea (3-103):



According to **GP5**, (Z)-1-ethylidene-2,9-dimethyl-1,2,4,5,6,7-hexahydro-3*H*-benzo[*e*][1,3]diazonin-3-one (200 mg, 0.819 mmol) and *para*-toluenesulfonic acid (1.56 g, 8.20 mmol) were stirred for 45 h. Purification via flash column chromatography eluting with acetone:PE (0:1 -2:3) afforded the title compound (44 mg, 21%) as yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.65 (dd, *J* = 8.2, 1.4, 1H, ArH), 7.41-7.33 (m, 1H, ArH), 7.30-7.14 (m, 2H, ArH), 5.39-4.03 (m, br, 2H, NH), 3.85-3.73 (m, 1H, H12), 3.05-2.83 (m, 3H, H2/10a), 2.82 (s, 3H, H14), 2.66 (ddd, *J* = 12.7, 10.7, 6.3, 1H, H10b), 1.81-1.54 (m, 2H, H11), 1.27-1.12 (m, 6H, H1/15). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 205.7 (C3), 159.1 (C13), 142.5 (Ar), 137.4 (Ar), 131.7 (ArH), 131.6 (ArH), 129.0 (ArH), 126.1 (ArH), 46.7 (C12), 39.5 (C11), 35.0 (C2), 31.2 (C10), 27.4 (C14), 22.1 (C15), 8.6 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{23}N_2O_2$ [M+H] Calculated 263.1754. Found 263.1747. **IR ν_{max}** (ATR)/cm^{-1}: 3328, 2976, 2928, 1686, 1621. **m.p** 101-102 °C.

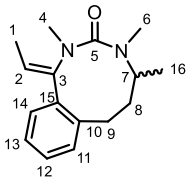
1-Methyl-3-(4-(2-propionylphenyl)butyl)urea (3-104):



According to **GP5**, (Z)-1-ethylidene-2-methyl-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecine-3(2*H*)-one (100 mg, 0.410 mmol) and *para*-toluene sulfonic acid (154 mg, 0.820 mmol) were stirred for 17 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 4:1) afforded the title compound (78 mg, 73%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.60 (dd, *J* = 7.5, 1.8, 1H, ArH), 7.46-7.33 (m, 1H, ArH), 7.32-7.19 (m, 2H, ArH), 5.26 (s, br, 1H, NH), 4.92 (s, br, 1H, NH), 3.22 (t, *J* = 6.5, 2H, H13), 2.93 (q, *J* = 7.2, 2H, H2), 2.76 (s, 3H, H15), 2.87-2.70 (m, 2H, H10), 1.72-1.48 (m, 4H, H11/12), 1.19 (t, *J* = 7.2, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 206.0 (C3), 159.6 (C14), 142.2 (Ar), 138.0 (Ar),

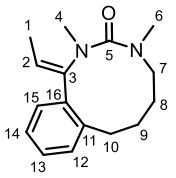
131.3 (ArH), 131.3 (ArH), 128.4 (ArH), 125.9 (ArH), 39.8 (C13), 35.2 (C2), 33.5 (C10), 29.8 (C11 or 12), 29.0 (C11 or 12), 27.2 (C15), 8.5 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{22}N_2NaO_2$ [M+Na] Calculated 285.1573 Found 285.1578. **IR ν_{max}** (ATR)/cm^{-1}: 3323, 2971, 2935, 2902, 1683, 1619. **m.p** 105-106 °C.

(*Z*)-1-Ethylidene-2,4,5-trimethyl-1,2,4,5,6,7-hexahydro-3*H*-benzo[*e*][1,3]diazonin-3-one (3-107):



According to **GP6**, (Z)-1-ethylidene-2,5-dimethyl-1,2,4,5,6,7-hexahydro-3*H*-benzo[*e*][1,3]diazonin-3-one (240 mg, 0.983 mmol) and NaH (60% dispersion in mineral oil, 157 mg, 3.93 mmol) in anhydrous THF and stirred at 0 °C for 1.5 h. Iodomethane (0.24 mL, 3.93 mmol) was added to the reaction mixture stirred at room temperature for 42.5 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 4:1) afforded the title compound (89 mg, 35%) as a colourless oil. $\mathbf{R_f}$ = 0.25 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, CD_2Cl_2): δ_H 7.17-7.05 (m, 3H, ArH), 6.95 (dt, *J* = 6.7, 1.5, 1H, ArH), 5.10 (q, *J* = 7.0, 1H, H2), 4.21-4.06 (m, 1H, H7), 3.54 (td, *J* = 13.2, 4.1, 1H, H9a), 3.17 (s, 3H, H4 or 6), 2.43 (dt, *J* = 13.4, 3.9, 1H, H9b), 2.07 (s, 3H, H4 or 6), 1.85 (d, *J* = 7.0, 3H, H1), 1.75-1.59 (m, 1H, H8a), 1.53-1.41 (m, 1H, H8b), 1.03 (d, *J* = 6.8, 3H, H16). **^{13}C NMR** (101 MHz, CD_2Cl_2): δ_C 162.1 (C5), 144.4 (C3), 140.4 (Ar), 140.3 (ArH) 129.2 (ArH), 128.2 (ArH), 126.7 (ArH), 126.3 (ArH), 118.4 (C2), 53.8 (C7), 38.8 (C4 or 6), 33.2 (C8), 32.2 (C9), 26.9 (C4 or 6), 21.9 (C16), 14.4 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{16}H_{23}N_2O$ [M+H] Calculated 259.1805. Found 259.1801. **IR ν_{max}** (ATR)/cm^{-1}: 3015, 2924, 2865, 1635.

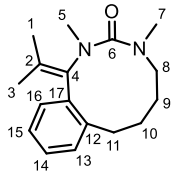
(*Z*)-1-Ethylidene-2,4-dimethyl-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecine-3(2*H*)-one (3-108):



According to **GP6**, (*Z*)-1-ethylidene-2-methyl-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecine-3(2*H*)-one (500 mg, 2.05 mmol) and NaH (60% dispersion in mineral oil, 197 mg, 8.20 mmol) were stirred in anhydrous THF at 0 °C for 1 h. Iodomethane (0.51 mL, 8.20 mmol) was added to the reaction mixture and stirred at room temperature for 22 h affording the title compound (484 mg, 91%) as a yellow gum. $\mathbf{R_f}$ = 0.56 (1:1 EtOAc:PE). **^{1}H NMR** (400 MHz, CD_2Cl_2): δ_H 7.18-7.11 (m, 2H, ArH), 7.10-7.04 (m, 2H, ArH), 5.21 (q, *J* = 7.0, 1H, H2), 3.39-3.24 (m, 2H, H7), 3.23 (s, 3H, H4 or 6), 2.89 (s, br, 2H, H10), 2.45 (s, 3H, H4 or 6), 1.84 (d, *J* = 7.0, 3H, H1), 1.69-1.52 (m, 2H, H8 or 9), 1.43 (quint., *J* = 6.3, 2H, H8 or 9). **^{13}C NMR** (101 MHz, CD_2Cl_2): δ_C 162.1 (C5), 143.3 (C3), 142.6 (Ar), 139.6 (Ar), 130.4 (ArH), 128.1 (ArH), 127.3 (ArH), 125.6 (ArH), 121.5 (C2), 46.5 (C7), 40.6 (C4 or 6), 33.6 (C4 or 6), 28.9 (C10), 27.6 (C8 or 9), 27.4

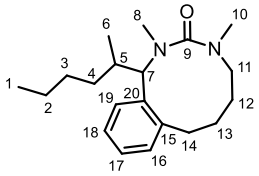
(C8 or 9), 14.3 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{16}H_{22}N_2NaO$ [M+Na] Calculated 281.1624. Found 281.1631. **IR ν_{max}** (ATR)/cm^{-1}: 3014, 2936, 2856, 1619.

2,4-Dimethyl-1-(propan-2-ylidene)-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecine-3(2*H*)-one (3-109):



According to **GP6**, 2-methyl-1-(propan-2-ylidene)-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecine-3(2*H*)-one (150 mg, 0.581 mmol) and NaH (60% dispersion in mineral oil, 93.0 mg, 2.32 mmol) in anhydrous THF stirred at 0 °C for 1 h. Iodomethane (0.14 mL, 2.32 mmol) was added and the reaction mixture stirred at room temperature for 21 h affording the title compound (158 mg, quant.) as a white gum. **R_f** = 0.62 (7:3 EtOAc:PE). **^{1}H NMR** (400 MHz, CD_2Cl_2): δ_H 7.21-7.15 (m, 1H, ArH), 7.14-7.09 (m, 2H, ArH), 7.07-7.01 (m, 1H, ArH), 3.82-3.58 (m, br, 1H, H8a), 3.13 (s, 3H, H5 or 7), 3.01-2.81 (m, br, 1H, H8b), 2.72-2.53 (m, br, 2H, H11), 2.47 (s, 3H, H5 or 7), 2.06-1.91 (m, br, 1H, H9a), 1.90 (s, 3H, H1 or 3), 1.66-1.40 (m, br, 1H, H9b), 1.51 (s, 3H, H1 or 3), 0.93-0.81 (m, br, 2H, H10). **^{13}C NMR** (101 MHz, CD_2Cl_2): δ_C 163.3 (C6), 143.8 (Ar), 137.8 (C4), 137.7 (Ar), 129.6 (ArH), 128.1 (ArH), 128.0 (ArH), 128.0 (C2), 125.9 (ArH), 46.8 (C8), 40.4 (C5 or 7), 34.1 (C5 or 7), 29.3 (C11), 27.3 (C9), 27.2 (C10), 20.6 (C1 or 3), 20.3 (C1 or 3). **HRMS m/z** (ESI^+): calcd. for $C_{17}H_{24}N_2O$ [M+H] Calculated 273.1961. Found 273.1957. **IR ν_{max}** (ATR)/cm^{-1}: 2955, 2927, 2871, 2820, 1626.

1-(Hexan-2-yl)-2,4-dimethyl-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecine-3(2*H*)-one (3-111):



Under an atmosphere of N_2, (*Z*)-1-ethylidene-2,4-dimethyl-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecine-3(2*H*)-one (100 mg, 0.387 mmol) was dissolved in anhydrous THF (9.7 mL) and cooled to -40 °C. ^{n}BuLi (2.5 M in hexane, 0.78 mL, 1.95 mmol) was added dropwise whilst maintaining -40 °C. The reaction mixture was stirred at -40 °C for 2 h. The reaction mixture was quenched with MeOH (1 mL) and sat. aq. NH_4Cl (1 mL). The aqueous layer was extracted into EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 3:2) afforded the title compound (69 mg, 56%) as a white gum. **d.r** = 1.53:1.00.

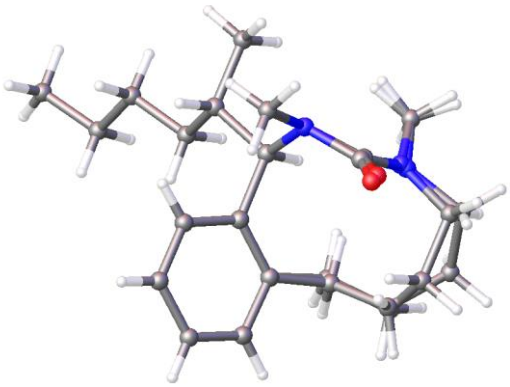
Major-diastereoisomer: R_f = 0.33 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, CD_3Cl): δ_H 7.26-7.10 (m, 4H, ArH), 4.73 (d, *J* = 11.2, 1H, H7), 3.85-3.74 (m, 1H, H11a), 2.97 (tdd, *J* = 9.3, 6.9, 3.6, 1H, H14a), 2.92 (s, 3H,

H10), 2.72-2.64 (m, 1H, H14b), 2.66 (s, 3H, H8), 2.49-2.38 (m, 1H, H11b), 2.28-2.10 (m, 1H, H5), 1.97-1.86 (m, 1H, H12a), 1.86-1.73 (m, 1H, H12b), 1.12 (d, *J* = 6.5, 3H, H6), 1.55-1.02 (m, 7H, H2/3/4a/13), 0.92-0.84 (m, 1H, H4b), 0.77 (t, *J* = 7.0, 3H, H1). **^{13}C NMR** (101 MHz, CD_3Cl): δ_C 166.9 (C9), 140.7 (Ar), 137.2 (Ar), 130.1 (ArH), 127.1 (ArH), 126.4 (ArH), 125.5 (ArH), 61.3 (C7), 52.3 (C11), 40.1 (C10), 33.5 (C5), 33.2 (C4), 30.3 (C12), 30.1 (C14), 28.9 (C2 or 3), 28.7 (C8), 24.2 (C13), 22.8 (C2 or 3), 16.7 (C6), 14.1 (C1).

Minor-diastereoisomer: **R_f** = 0.40 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, CD_3Cl): δ_H 7.26-7.10 (m, 4H, ArH), 4.70 (d, *J* = 11.2, 1H, H7), 3.85-3.74 (m, 1H, H11a), 2.97 (tdd, *J* = 9.3, 6.9, 3.6, 1H, H14a), 2.89 (s, 3H, H10), 2.72-2.64 (m, 1H, H14b), 2.68 (s, 3H, H8), 2.49-2.38 (m, 1H, H11b), 2.28-2.10 (m, 1H, H5), 1.97-1.86 (m, 1H, H12a), 1.86-1.73 (m, 1H, H12b), 1.55-1.02 (m, 7H, H2/3/4a/13), 0.94 (t, *J* = 7.0, 3H, H1), 0.92-0.84 (m, 1H, H4b), 0.66 (d, *J* = 6.5, 3H, H6). **^{13}C NMR** (101 MHz, CD_3Cl): δ_C 166.9 (C9), 140.7 (Ar), 137.7 (Ar), 130.1 (ArH), 127.1 (ArH), 126.5 (ArH), 125.6 (ArH), 61.8 (C7), 52.1 (C11, B), 39.8 (C10), 34.0 (C5), 33.1 (C4), 30.2 (C12), 29.7 (C14), 29.0 (C2 or 3), 28.7 (C8), 24.6 (C13), 23.1 (C2 or 3), 17.0 (C6), 14.3 (C1).

HRMS m/z (ESI^+): calcd. for $C_{20}H_{32}N_2NaO$ [M+Na] Calculated 339.2407. Found 339.2423. **IR ν_{max}** (ATR)/cm^{-1}: 2921, 2856, 1646.

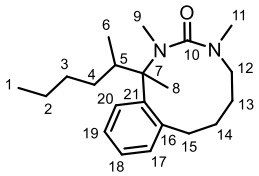
X-ray crystal data:



Empirical formula	$C_{20}H_{32}N_2O$
Formula weight	316.47
Temperature/K	100.0
Crystal system	Monoclinic
Space group	$P2_1/n$
a/Å	11.9480(5)
b/Å	10.6335(4)
c/Å	15.0281(6)
α/°	90
β/°	108.7580(10)
γ/°	90
Volume/Å^3	1807.89(13)
Z	4
P_{calc}g/cm^3	1.163
μ/mm^{-1}	0.071

F(000)	696.0
Crystal size/mm^3	0.34 x 0.197 x 0.167
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	5.258 to 54.23
Index ranges	-15 ≤ h ≤ 15, -13 ≤ k ≤ 13, -19 ≤ l ≤ 19
Reflections collected	48202
Independent reflections	4003 [R_{int} = 0.0332, R_{sigma} = 0.0170]
Data/restraints/parameters	4003/196/276
Goodness-of-fit on F^2	1.026
Final R indexes [I>=2σ (I)]	R_1 = 0.0355, wR2 = 0.0856
Final R indexes [all data]	R_1 = 0.0433, wR_2 = 0.0905
Largest diff. peak/hole/eÅ^{-3}	0.29/-0.18

1-(Hexan-2-yl)-1,2,4-trimethyl-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecine-3(2*H*)-one (3-112):



Under an atmosphere of N_2, (*Z*)-1-ethylidene-2,4-dimethyl-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecine-3(2*H*)-one (50.0 mg, 0.194 mmol) was dissolved in anhydrous THF (4.9 mL) and cooled to -40 °C. ^{n}BuLi (2.5 M in hexane, 0.39 mL, 0.980 mmol) was added dropwise whilst maintaining -40 °C. The reaction mixture was stirred at -40 °C for 2 h. The reaction mixture was quenched with iodomethane (0.06 mL, 0.970 mmol) and stirred at room temperature for 30 min. MeOH (1 mL) was added to the reaction mixture. The reaction mixture was diluted with H_2O (20 mL) and extracted into EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography eluting with EtOAc:PE (0:1 – 7:3) afforded the title compound (26 mg, 41%) as a mixture of 2 diastereoisomers as a colourless oil. **d.r** 1.00:0.25.

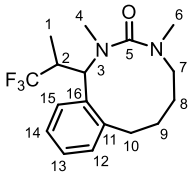
Major-diastereoisomer: R_f = 0.48 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.31-7.27 (m, 1H, ArH), 7.11-7.06 (m, 2H, ArH), 7.04-7.00 (m, 1H, ArH), 3.86 (ddd, *J* = 14.4, 12.0, 4.8, 1H, H12a), 3.47 (dd, *J* = 13.1, 9.0, 1H, H15a), 3.04 (dd, *J* = 14.4, 5.3, 1H,H12b), 2.99 (s, 3H, H9), 2.53 (s, 3H, H11), 2.46-2.34 (m, 1H, H15b), 1.90 (s, 3H, H8), 1.89-1.78 (m, 2H, H13a/H14a), 1.79-1.70 (m, 1H, H5), 1.67-1.04 (m, 6H, H2/3/4a/14b), 0.93-0.80 (m, 7H, H1/6/13b), 0.20 (dtd, *J* = 13.7, 9.6, 4.0, 1H, H4b). **^{13}C NMR** (101 MHz, CD_3Cl): δ_C 166.9 (C10), 141.5 (Ar), 139.5 (Ar), 131.2 (ArH), 129.1 (ArH), 126.0 (ArH), 125.1 (ArH), 67.8 (C7), 47.3 (C12), 42.8 (C5), 34.6 (C9), 33.8 (C11), 32.4 (C4), 31.0 (C2 or 3), 30.8 (C15), 26.2 (C13), 25.8 (C14), 23.0 (C2 or 3), 20.8 (C8), 17.6 (C6), 14.3 (C1).

Minor-diastereoisomer: R_f = 0.58 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.46-7.38 (m, 1H, ArH), 7.20-7.14 (m, 1H, ArH), 7.12-7.05 (m, 2H, ArH), 3.60-3.39 (m, br, 1H, C5), 3.22-3.09 (m, 1H, H12a), 3.12

(s, 3H, H9), 2.92-2.75 (m, 2H, H12b/CH_2), 2.71-2.63 (m, 1H, CH_2), 2.43 (s, 3H, H11), 1.36-1.17 (m, 10H, 5 x CH_2), 1.00 (d, *J* = 6.7, 3H, H6), 0.95-0.87 (m, 3H, H1). **^{13}C NMR** (101 MHz, CD_3Cl): δ_C 164.8 (C10), 141.2 (Ar), 139.2 (Ar), 130.4 (ArH), 128.1 (ArH), 126.0 (ArH), 124.9 (ArH), 65.5 (C7), 48.3 (C12), 39.5 (C5), 37.1 (C9), 36.2 (C11), 31.6 (CH_2), 30.3 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 23.7 (CH_2), 23.4 (CH_2), 17.5 (C6), 14.3 (C1).

HRMS m/z (ESI^+): calcd. for $C_{21}H_{35}N_2O$ [M+H] Calculated 331.2744. Found 331.2744. **IR ν_{max}** (ATR)/cm^{-1}: 2951, 2927, 2858, 1650.

2,4-Dimethyl-1-(1,1,1-trifluoropropan-2-yl)-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecine-3(2*H*)-one (3-117):



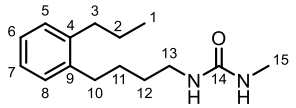
In a flame-dried 5 mL microwave vial under an atmosphere of N_2, (*Z*)-1-ethylidene-2,4-dimethyl-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecine-3(2*H*)-one (52.0 mg, 0.200 mmol), sodium triflinate (94 mg, 0.600 mmol), caesium carbonate (98 mg, 0.300 mmol) and 1,2,3,5-tetrakis(carbazole-9-yl)-4,6-dicyanobenzene (8.0 mg, 0.0100 mmol) were suspended in anhydrous acetone (2 mL). The reaction mixture was degassed using N_2 delivered via syringe needle for 10 min with stirring. The vial was sealed and the reaction mixture was exposed to 24 W blue LED irradiation and stirred for 29 h at ~30 °C. The reaction mixture was quenched with H_2O (5 mL) and extracted into EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 1:0) afforded the title compound (41 mg, 62%) as a mixture of 2 diastereoisomers as yellow oils. **d.r** 1.92:1.00.

Major-diastereoisomer: **R_f** = 0.20 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, acetone-d_6): δ_H 7.45 (dd, *J* = 7.7, 1.6, 1H, ArH), 7.29-7.13 (m, 3H, ArH), 5.26 (d, *J* = 11.5, 1H, H3), 3.83-3.73 (m, 1H, H7a), 3.51-3.36 (m, 1H, H2), 2.98 (s, 3H, H4 or 6), 3.03-2.91 (m, 1H, H10a), 2.70 (dt, *J* = 14.1, 5.3, 1H, H10b), 2.58 (s, 3H, H4 or 6), 2.56-2.48 (m, 1H, H7b), 2.01-1.77 (m, 2H, CH_2), 1.40 (dd, *J* = 6.8, 0.8, 3H, H1), 1.25 (tdt, *J* = 6.8, 4.8, 2.6, 2H, CH_2). **^{13}C NMR** (101 MHz, acetone-d_6): δ_C 166.3 (C5), 140.6 (Ar), 136.3 (Ar), 130.7 (ArH), 128.9 (q, *J* = 280.5, CF_3), 128.4 (ArH), 128.3 (ArH), 125.6 (ArH), 56.1 (q, *J* = 2.3, C3), 52.7 (C7), 40.1 (q, *J* = 24.2, C2), 40.1 (C4 or 6), 29.7 (CH_2), 29.3 (C10), 28.7 (C4 or 6), 24.3 (CH_2), 11.9 (q, *J* = 3.3, C1). **^{19}F NMR** (376 MHz, acetone-d_6): δ_F -68.1 (d, *J* = 7.9, 3F, CF_3). **HRMS m/z** (ESI^+): calcd. for $C_{17}H_{24}F_3N_2O$ [M+H] Calculated 329.1835. Found 329.1831. **IR ν_{max}** (ATR)/cm^{-1}: 2979, 2921, 2861, 1648.

Minor-diastereoisomer: **R_f** = 0.30 (1:4 EtOAc:PE). **^{1}H NMR** (500 MHz, acetone-d_6): δ_H 7.40 (dd, *J* = 7.7, 1.7, 1H, ArH), 7.32 (dd, *J* = 7.5, 1.7, 1H, ArH), 7.26 (td, *J* = 7.6, 1.7, 1H, ArH), 7.24-7.20 (m, 1H, ArH),

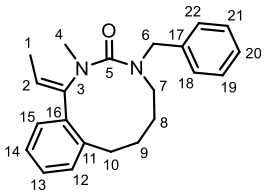
5.43 (d, *J* = 11.5, 1H, H3), 3.67 (dddd, *J* = 12.8, 5.1, 2.8, 1.0, 1H, H7a), 3.54-3.43 (m, 1H, H2), 3.17-3.07 (m, 1H, H10a), 2.87 (s, 3H, H4 or 6), 2.72 (dt, *J* = 14.2, 5.1, 1H, H10b), 2.68 (s, 3H, H4 or 6), 2.48 (ddd, *J* = 12.9, 10.2, 2.8, 1H, H7b), 1.99-1.80 (m, 2H, H9), 1.25-1.15 (m, 2H, H8), 0.84 (d, *J* = 6.8, 3H, H1). **^{13}C NMR** (125 MHz, acetone-d_6): δ_C 166.5 (C5), 141.2 (Ar), 136.1 (Ar), 131.1 (ArH), 129.3 (q, *J* = 279.9, CF_3), 128.5 (ArH), 127.6 (ArH), 126.4 (ArH), 56.8 (C3), 53.3 (C7), 40.1 (C4 or 6), 38.2 (q, *J* = 24.7, C2), 31.2 (C9), 24.1 (C8), 12.8 (q, *J* = 3.3, C1). C4 or 6 and C10 missing, residing under acetone peak. **^{19}F NMR** (376 MHz, acetone-d_6): δ_F -69.5 (d, *J* = 8.2, 3F, CF_3). **HRMS m/z** (ESI^+): calcd. for $C_{17}H_{24}F_3N_2O$ [M+H] Calculated 329.1835. Found 329.1846. **IR ν_{max}** (ATR)/cm^{-1}: 3023, 2927, 2860, 1649.

1-Methyl-3-(4-(2-propylphenyl)butyl)urea 3-124):



Under an atmosphere of H_2, (Z)-1-ethylidene-2-methyl-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecine-3(2*H*)-one (100 mg, 0.410 mmol) and Pd/C (10 wt%, 44 mg, 0.410 mmol) were suspended in anhydrous THF (3 mL) and stirred at room temperature for 65 h. The reaction mixture was filtered through celite and the product eluted with EtOAc. The solvent was removed under reduced pressure. Purification via flash column chromatography eluting with EtOAc:PE (1:1 – 1:0) afforded the title compound (49 mg, 48%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.17-7.0 (m, 4H, ArH), 4.44-4.21 (m, br, 2H, NH), 3.19 (td, *J* = 6.7, 5.7, 2H, H13), 2.76 (d, *J* = 4.9, 3H, H15), 2.66-2.60 (m, 2H, H10), 2.60-2.53 (m, 2H, H3), 1.66-1.54 (m, 6H, H2/11/12), 0.68 (t, *J* = 7.3, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 159.0 (C14), 140.5 (Ar), 140.0 (Ar), 129.4 (ArH), 129.2 (ArH), 126.1 (ArH), 126.0 (ArH), 40.7 (C13), 34.9 (C4), 32.4 (C10), 30.4 (C11 or 12), 28.6 (C11 or 12), 27.4 (C15), 24.5 (C2), 14.4 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{24}N_2O$ [M+H] Calculated 249.1961. Found 249.1955. **IR ν_{max}** (ATR)/cm^{-1}: 3336, 2956, 2939, 2867, 1621. **m.p** 90-91 °C.

(*Z*)-4-Benzyl-1-ethylidene-2-methyl-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecine-3(2*H*)-one (3-127):

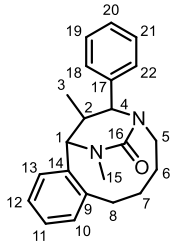


Under an atmosphere of N_2, (Z)-1-ethylidene-2-methyl-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecine-3(2*H*)-one (526 mg, 2.15 mmol) was dissolved in anhydrous THF (27 mL) and cooled to 0 °C. NaH (60% dispersion in mineral oil, 172 mg, 4.30 mmol) was added portion wise whilst maintaining 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Benzyl bromide (0.77 mL, 6.45 mmol) was added dropwise

to the reaction mixture. The reaction mixture was warmed to room temperature and stirred for 3 days. The reaction mixture was quenched with H_2O (10 mL). The reaction mixture was extracted into EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Purification via column chromatography eluting with EtOAc:PE (0:1 – 1:0) afforded the title compound (488 mg, 68%) as a white solid. $\mathbf{R_f}$ = 0.39 (1:4 EtOAc:PE). **^{1}H NMR** (400 MHz, CD_2Cl_2): δ_H 7.28-7.20 (m, 1H, ArH), 7.19-7.08 (m, 6H, ArH), 6.68-6.79 (m, 2H, ArH), 5.27 (q, *J* = 7.0, 1H, H2), 4.15 (s, 2H, H6), 3.46-3.31 (m, br, 2H, H7), 3.28 (s, 3H, H4), 3.04-2.84 (s, br, 2H, H10), 1.87 (d, *J* = 7.0, 3H, H1), 1.64-1.53 (m, br, 2H, H8 or 9), 1.44-1.34 (m, br, 2H, H8 or 9). **^{13}C NMR** (101 MHz, CD_2Cl_2): δ_C 161.7 (C5), 143.2 (C3), 142.3 (Ar), 139.8 (Ar), 139.4 (C17), 130.7 (ArH), 128.4 (ArH), 128.3 (ArH), 127.7 (ArH), 127.7 (ArH), 126.6 (ArH), 125.8 (ArH), 121.8 (C2), 50.0 (C6), 44.7 (C7), 40.9 (C4), 28.8 (C10), 27.7 (C8 or 9), 27.3 (C8 or 9), 14.4 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{22}H_{26}N_2NaO$ [M+Na] calculated 357.1937. Found 357.1943. **IR ν_{max}** (ATR)/cm^{-1}: 3020, 2931, 2907, 2854, 1631.

N.B Benzylated medium ring unstable in weak acid (including $CHCl_3$/$CDCl_3$) and will hydrolyse.

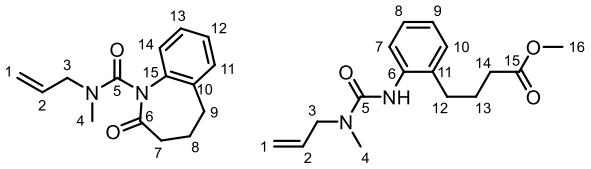
2,14-Dimethyl-3-phenyl-2,3,4,5,6,7,8-hexahydro-1*H*-1,4-(epiminomethano)benzo[*e*]azecin-13-one (3-129):



Under an atmosphere of N_2, (Z)-4-benzyl-1-ethylidene-2-methyl-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecine-3(2*H*)-one (53.0 mg, 0.159 mmol) and *N*,*N'*-dimethylpropyleneurea (0.10 mL, 0.800 mmol) were dissolved in anhydrous THF (2.1 mL) and stirred at room temperature for 10 min. The reaction mixture was cooled to -40 °C and LDA (2 M in THF/heptane/ethyl benzene, 0.16 mL, 0.318 mmol) was added dropwise. The reaction mixture was stirred at -40 °C for 4 h. The reaction mixture was quenched with sat. aq. NH_4Cl (1 mL) and diluted with EtOAc (20 mL). The aqueous layer was extracted into EtOAc (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography eluting with EtOAc:*n*-pentane (1:4 – 1:0) afforded the title compound (7 mg, 13%) as an orange oil. **^{1}H NMR** (500 MHz, CD_2Cl_2): δ_H 7.33-7.19 (m, 6H, ArH), 7.18-7.09 (m, 2H, ArH), 7.05 (d, *J* = 7.8, 1H, ArH), 4.38 (d, *J* = 3.9, 1H, H1 or 4), 3.82 (ddd, *J* = 14.2, 6.7, 4.0, 1H, H5a), 3.70 (d, *J* = 11.4, 1H, H1 or 4), 3.08 (s, 3H, H15), 2.73-2.68 (m, 2H, H8), 2.48-2.35 (m, 2H, H2/5b), 2.09-1.98 (m, 1H, H6a or 7a), 1.74-1.47 (m, 3H, H6/7), 0.73 (d, *J* = 7.0, 3H, H3). **^{13}C NMR** (125 MHz, CD_2Cl_2): δ_C 158.5

(C16), 141.9 (Ar), 141.8 (Ar), 133.6 (Ar), 133.5 (ArH), 132.4 (ArH), 132.4 (ArH), 128.8 (ArH), 128.0 (ArH), 127.6 (ArH), 124.9 (ArH), 68.4 (C1 or 4), 65.0 (C1 or 4), 45.9 (C5), 43.7 (C2), 35.5 (C15), 30.1 (C8), 28.8 (C6 or 7), 24.2 (C6 or 7), 16.6 (C3). **HRMS m/z** (ESI^+): calcd. for $C_{22}H_{26}N_2O$ [M+H] Calculated 335.2118. Found 335.2110. **IR ν_{max}** (ATR)/cm^{-1}: 2969, 2922, 2870, 1634.

***N*-Allyl-*N*-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (3-143) & methyl 4-(2-(3-allyl-3-methylureido)phenyl)butanoate (3-144):**

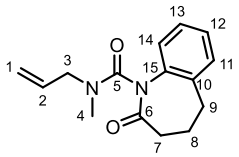


Under an atmosphere of N_2, NaHMDS (1 M, in THF, 5.0 mL, 4.97 mmol) was added dropwise to a solution of 1,3,4,5-tetrahydro-2*H*-benzo[*b*]azepin-2-one (727 mg, 4.52 mmol) and allylcarbamic chloride (721 mg, 5.42 mmol) in anhydrous THF (9.9 mL). The reaction mixture was stirred at room temperature for 22 h. The reaction mixture was quenched with MeOH (3 mL) and diluted with EtOAc (20 mL). The reaction mixture was washed with sat. aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted into EtOAc (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography eluting with acetone:PE (0:1 – 1:0) afforded the title compounds as a 1:1 mixture as a colourless oil.

***N*-allyl-*N*-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (3-143):** (499 mg, 43%). Data in accordance with below.

Methyl 4-(2-(3-allyl-3-methylureido)phenyl)butanoate (3-144): (499 mg, 42%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.67 (dd, *J* = 8.1, 1.3, 1H, ArH), 7.21-7.14 (m, 1H, ArH), 7.11 (dd, *J* = 7.7, 1.7, 1H, ArH), 7.01 (td, *J* = 7.5, 1.3, 1H, ArH), 6.48 (s, br, 1H, NH), 5.89 (ddt, *J* = 17.2, 10.4, 5.3, 1H, H2), 5.35-5.19 (m, 2H, H1), 4.01 (dt, *J* = 5.3, 1.7, 2H, H3), 3.66 (s, 3H, H16), 3.05 (s, 3H, H4), 2.67-2.5. (m, 2H, H14), 2.35 (t, *J* = 6.9, 2H, H12), 1.93-1.82 (m, 2H, H13). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 174.2 (C15), 156.3 (C5), 137.0 (Ar), 133.8 (C2), 132.0 (Ar), 129.6 (ArH), 127.1 (ArH), 124.1 (ArH), 123.9 (ArH), 117.2 (C1), 51.7 (C3), 51.7 (C16), 34.8 (C4), 33.1 (C12), 30.8 (C14), 25.1 (C13). **HRMS m/z** (ESI^+): calcd. for $C_{16}H_{22}N_2O_3$ [M+H] Calculated 291.1703. Found 291.1707.

***N*-Allyl-*N*-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (3-143):**

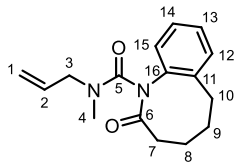


According to **GP2D**, allyl(methyl)carbamic chloride (396 mg, 2.98 mmol), 13,4,5-tetrahydro-2*H*-1-benzazin-2-one (400 mg, 2.48 mmol) and NaHMDS (1 M in THF, 2.73 mL, 2.73 mmol) were stirred at room temperature for 24 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 1:0) afforded the title compound (331 mg, 52%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$)(mixture of rotamers A:B 0.60:0.40): δ_H 7.35-7.17 (m, 3H, ArH, rot. A+B), 7.12 (dd, *J* = 7.6, 1.8, 0.4H, ArH, rot. B), 7.10-7.05 (m, 0.6H, ArH, rot. A), 5.83 (ddt, *J* = 17.3, 10.3, 5.7, 0.6H, H2, rot. A), 5.63 (ddt, *J* = 17.3, 10.0, 5.9, 0.4H, H2, rot. B), 5.36-5.26 (m, 0.6H, H1a, rot. A), 5.25-5.21 (m, 0.6H, H1b, rot. A), 5.20-5.17 (m, 0.4H, H1a, rot. B), 5.16-5.13 (m, 0.4H, H1b, rot. B), 4.10 (dd, *J* = 10.3, 6.4, 1.2H, H3, rot. A), 3.86 (s, br, 0.8H, H3, rot. B), 3.02 (s, 1.2H, H4, rot. B), 2.96 (s, 1.8H, H4, rot. A), 2.95-2.66 (m, 2H, H7, rot. A+B), 2.37 (t, *J* = 7.4, 2H, H9, rot. A+B), 2.29-2.16 (m, 2H, H8, rot. A+B). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 173.2 (C6, rot. B), 172.8 (C6, rot. A), 155.5 (C5, rot. A), 155.3 (C5, rot. B), 139.0 (Ar, rot. B), 138.9 (Ar, rot. A), 135.7 (Ar, rot. A), 135.4 (Ar, rot. B), 132.7 (C2, rot. B), 131.9 (C2, rot. A), 130.2 (ArH, rot. A+B), 128.0 (ArH, rot. A+B), 127.4 (ArH, rot. A), 127.4 (ArH, rot. B), 122.7 (ArH, rot. B), 122.6 (ArH, rot. A), 118.8 (C1, rot. B), 118.1 (C1, rot. A), 53.4 (C3, rot. B), 51.9 (C3, rot. A), 35.4 (C4, rot. A), 34.2 (C4, rot. B), 33.5 (C9, rot. B), 33.4 (C9, rot. A), 30.2 (C7, rot. B), 30.1 (C7, rot. A), 28.8 (C8, rot A+B). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{18}N_2NaO_2$ [M+Na] Calculated 281.1260. Found 281.1267. **IR ν_{max}** (ATR)/cm^{-1}: 2942, 2866, 1673.

N.B. Upon standing at room temperature decomposes by amide cleavage.

***N*-Allyl-*N*-methyl-2-oxo-3,4,5,6-tetrahydrobenzo[*b*]azocine-1(2*H*)-carboxamide (3-144):**

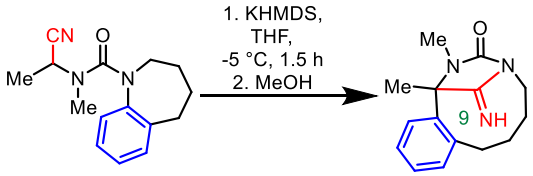


According to **GP2D**, allyl(methyl)carbamic chloride (456 mg, 3.43 mmol), 3,4,5,6-tetrahydro[*b*]azocin-2(1*H*)-one (500 mg, 2.86 mmol) and NaHMDS (1 M in THF, 3.15 mL, 3.15 mmol) in anhydrous THF were stirred at room temperature for 20 h. Purification via flash column chromatography eluting with EtOAc:PE (1:4 – 9:1) afforded the title compound (525 mg, 67%) as an off-white solid. $\mathbf{R_f}$ = 0.43 (1:1 EtOAc:PE). **^{1}H NMR** (400 MHz, $CDCl_3$)(mixture of rotamers A:B 0.64:0.36): δ_H 7.36-7.27 (m, 2H, ArH, rot. A+B), 7.25-7.18 (m, br, 1H, ArH, rot. A+B), 7.17-7.00 (m, br, 1H, ArH, rot. A+B), 5.93-5.73 (m, 1H, H2, rot. A+B), 5.34 (d, *J* = 17.2, 0.64H, H1a, rot. A), 5.29-5.18 (m, 1.36H, H1, rot. A+B), 4.19-4.08 (m,

0.64H, H3a, rot. A), 4.07-3.95 (m, 1.36H, H3, rot. A+B), 3.10 (s, br, 1.92H, H4, rot. A), 3.01 (s, br, 1.08H, H4, rot. B), 2.89 (dd, *J* = 14.0, 7.5, 1H, H7a, rot. A+B), 2.66 (t, br, *J* = 13.1, 1H, H7b, rot. A+B), 2.33 (ddd, *J* = 12.3, 7.3, 2.2, 1H, H10a, rot. A+B), 2.20-2.13 (m, 1H, H8a or 9a, rot. A+B), 2.13-2.05 (m, 1H, H10b, rot. A+B), 1.99-1.78 (m, 2H, H8 or 9, rot. A+B), 1.49-1.34 (m, 1H, H8b or 9b, rot,. A+B). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 175.3 (C6, rot. B), 174.7 (C6, rot. A), 142.4 (Ar, rot. A+B), 137.8 (Ar, rot. A+B), 132.0 (C2, rot. A+B), 131.4 (ArH, rot. A+B), 129.1 (ArH, rot. A+B), 127.3 (ArH, rot. A+B), 125.2 (ArH, rot. A+B), 118.6 (C1, rot. B), 117.8 (C1, rot. A), 53.5 (C3, rot. B), 51.9 (C3, rot. A), 35.6 (C4, rot. A), 34.1 (C4, rot. B), 33.3 (C10, rot. A+B), 30.7 (C7, rot. B), 30.6 (C7, rot. A), 29.4 (C8 or 9, rot. A+B), 25.7 (C8 or 9, rot. A+B). **HRMS m/z** (ESI$^+$): calcd. for $C_{16}H_{20}N_2NaO_2$ [M+Na] Calculated 295.1417. Found 295.1416. **IR ν_{max}** (ATR)/cm^{-1}: 2924, 2868, 1671. **m.p** 71-73 °C.

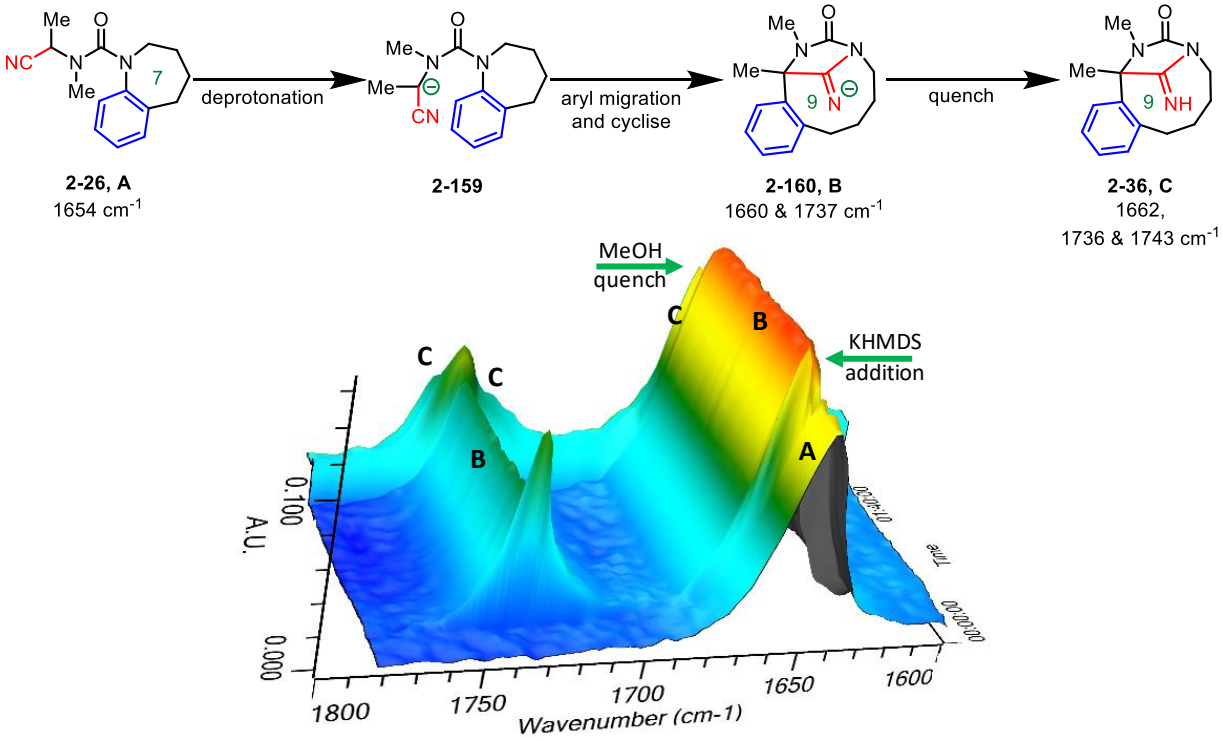
4.4 Mechanistic investigations

4.4.1 Iminohydantoin-bridging medium ring synthesis *in situ* ReactIR experiment



2-26 **2-36**

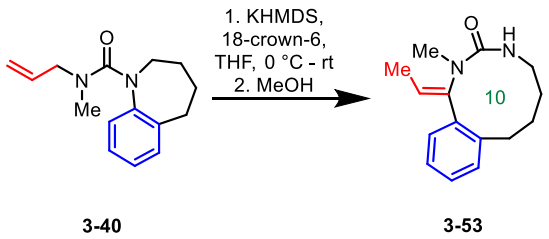
A ReactIR probe was fixed into a flame-dried three-necked round bottom flask, which was cooled to room temperature under vacuum. Under an atmosphere of N_2, anhydrous THF (2.6 mL) was added and the reaction flask cooled to -5 ˚C for 30 min before an IR solvent background spectrum was taken. The solvent was removed via a syringe and the flask placed under vacuum to remove the remaining solvent. In a separate flask, under an atmosphere of N_2, *N*-(1-cyanoethyl)-*N*-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (100 mg, 0.389 mmol) was dissolved in anhydrous THF (2.6 mL, 0.3 M). The solution was transferred into the three-necked flask via a syringe. The reaction flask was cooled to -5 ˚C for 30 min before the ReactIR was started. After 5 min the scan rate was set to record a spectra every 15 seconds. KHMDS (1 M in THF, 0.79 mL, 0.778 mmol) was added dropwise over 90 seconds. The reaction mixture was allowed to stir for a further 1.5 h at -5 ˚C. The reaction was quenched with MeOH (1 mL) and the spectra were recorded for a further 10 min.



Scheme 4-1: 3D *in situ* ReactIR trace monitoring for the formation of 9-membered ring **2-36** from urea **2-26** in THF under basic conditions. Peaks are tentatively assigned as shown.

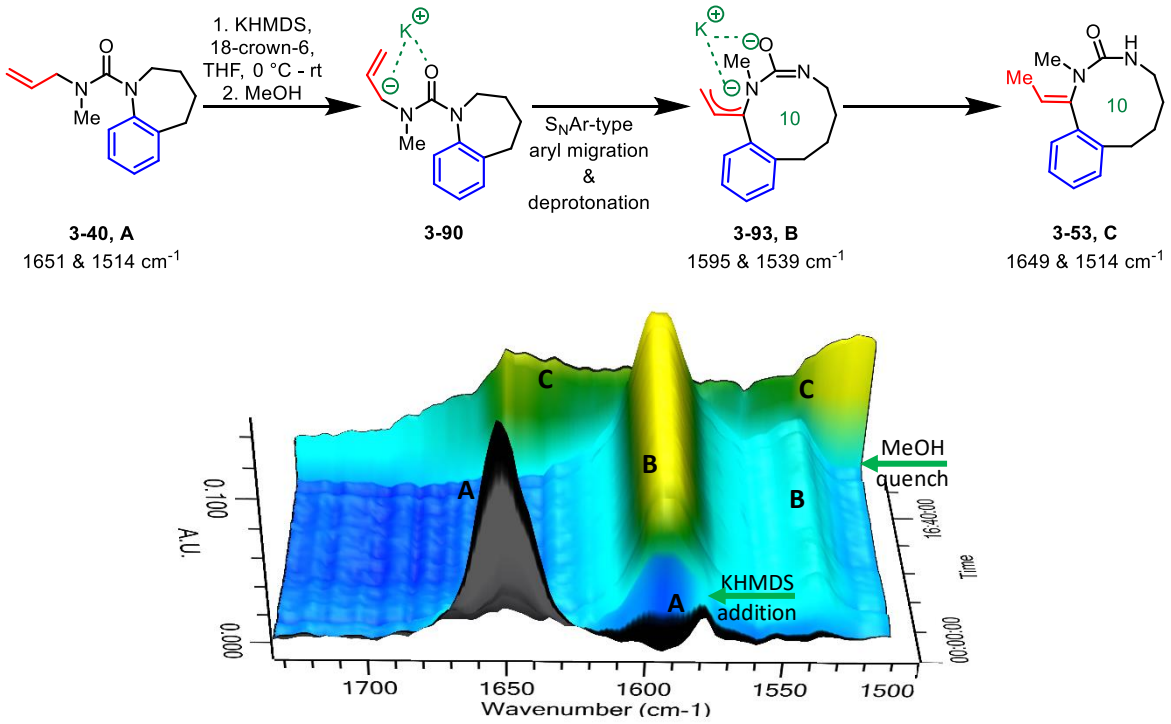
4.4.2 Vinylic medium ring synthesis

4.4.2.1 *In situ* ReactIR experiment



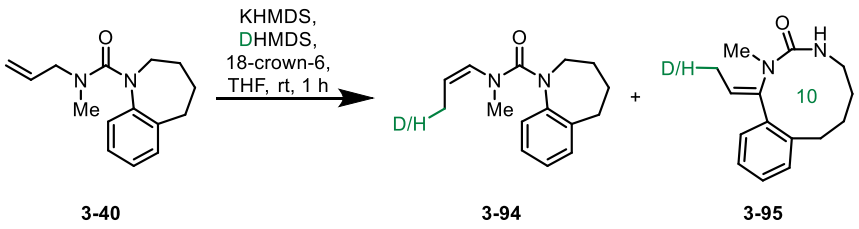
A ReactIR probe was fixed into an oven-dried three-necked round bottom flask, which was cooled to room temperature under vacuum. Under an atmosphere of N_2, anhydrous THF (2.7 mL) was added and the reaction flask cooled to 0 ˚C for 30 min, before an IR solvent background spectrum was taken. The solvent was removed via a syringe and the flask placed under vacuum to remove the remaining solvent. In a separate flask, under an atmosphere of N_2, *N*-Allyl-*N*-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (100 mg, 0.410 mmol) and 18-crown-6 (217 mg, 0.820 mmol) were dissolved in anhydrous THF (2.7 mL, 0.3 M). The solution was transferred into the three-necked flask via a syringe. The reaction mixture was cooled to 0 ˚C for 30 min before the ReactIR was started. After 9 min the scan rate was set to record a spectra every 15 seconds. KHMDS (1 M in THF, 0.82 mL, 0.820 mmol) was added dropwise over 30 seconds. The reaction mixture was allowed to stir for a further 19 hours whilst warming to room temperature and the scan rate was increased to 1 min. The scan rate

was changed to 30 seconds and the reaction mixture was quenched with MeOH (1 mL) and the spectra recorded for a further 45 min.



Scheme 4-2: 3D *in situ* ReactIR trace for the formation of 10-membered ring **3-53** from urea **3-40** with 18-crown-6 in THF under basic conditions. Peaks are tentatively assigned as shown.

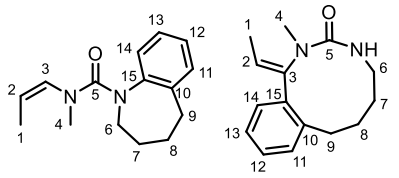
4.4.2.2 Deuterium labelling experiment



Formation of 0.5 M solution of DHMDS and KHMDS (1:1 ratio):

Under an atmosphere of N_2, D_2O (36 µL) was added to KHMDS (1 M in THF, 4.00 mL, 4.00 mmol) at room temperature forming a solution of KHMDS (0.5 M) and DHMDS (0.5 M) in THF. The solution was filtered through a PTFE syringe filter.

(Z)-*N*-Methyl-*N*-(prop-1-en-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (3-94) and (Z)-1-Ethylidene-2-methyl-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecine-3(2*H*)-one (3-53):



Under an atmosphere of N_2, *N*-allyl-*N*-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (50.0 mg, 0.205 mmol) and 18-crown-6 (108 mg, 0.410 mmol) were dissolved in anhydrous THF (10 mL) and stirred at room temperature. KHMDS/DHMDS (0.5 M in THF, 2.06 mL, 1.03 mmol) solution was added to the reaction mixture. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with MeOH (1 mL). The reaction mixture was diluted with EtOAc (20 mL) and washed with sat. aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted into EtOAc (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification via flash column chromatography eluting with EtOAc:PE (0:1 – 1:0) afforded the title compounds.

(*Z*)-*N*-Methyl-*N*-(prop-1-en-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-carboxamide (3-94): (15 mg, 30%) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.15-7.10 (m, 1H, ArH), 7.09-6.99 (m, 2H, ArH), 6.96 (dd, J = 7.2, 2.0, 1H, ArH), 5.53 (dq, *J* = 7.8, 1.7, 1H, H3), 4.61 (dq, *J* = 7.8, 7.0, 1H, H2), 3.67 (s, br, 2H, H6), 2.91 (s, 3H, H4), 2.74-2.66 (m, 2H, H9), 1.78-1.70 (m, 2H, H7), 1.63 (s, br, 2H, H8), 1.37 (dd, *J* = 7.0, 1.7, 3H, H1). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 160.2 (C5), 145.7 (Ar), 139.0 (Ar), 131.6 (C3), 130.0 (ArH), 127.0 (ArH), 125.7 (ArH), 125.5 (ArH), 117.5 (C2), 48.4 (C6), 37.1 (C4), 35.1 (C9), 30.9 (C7), 26.0 (C8), 12.6 (C1). **HRMS m/z** (ESI^+): calcd. for $C_{15}H_{20}N_2O$ [M+H] Calculated 245.1648. Found 245.1646. **IR ν_{max}** (ATR)/cm^{-1}: 2976, 2926, 2851, 1641.

(*Z*)-1-Ethylidene-2-methyl-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecine-3(2*H*)-one (3-53): (21 mg, 42%) Data in accordance with above.

^{2}H NMR and ^{1}H NMR showed no incorporation of deuterium into either **3-94** or **3-95**.

5. Appendices

5.1 Appendix 1 - Structural parameters raw data for (imino)hydantoins

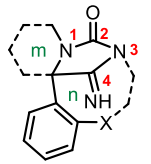


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Table A1: Data from X-ray crystallography for (imino)hydantoins both monocyclic and polycyclic. Yellow – 8-membered ring data. Blue – 9-membered ring data. Pink – Excluded data due to atom **4** in ring junction or carbonyl not imine. Orange – 10-membered ring data. Green – Representative monocyclic hydantoin data taken from the literature.[121–124] [a] – ΔΣθ = Deviation from planarity = 360 ˚ - sum of bond angles. [b] – Average deviation form planarity for ring size. [c] – Δδ = Change in chemical shift from the average value of two representative hydantoins.

Compound Number	2-28	2-31	2-30	2-163	2-36'	2-36''	2-36'''	2-37	2-139	2-140	2-148a'	2-148a''	2-170	2-171	2-172	2-173	2-174
N1/°	112.06 123.49 123.66	112.06 123.29 123.29	112.72 123.44 123.83	110.16 119.67 124.02	112.60 122.90 124.30	112.10 122.40 123.00	112.30 121.90 122.25	110.83 123.26 112.53	112.67 126.06 120.95	111.94 123.65 120.70	112.54 122.84 123.09	111.41 121.59 122.74	122.71 122.63 114.05	121.48 122.53 113.91	113.45	114.80 120.90 123.90	113.60 123.10 121.60
N1 ΔΣθ[a]	0.79	1.36	0.01	6.15	0.20	2.50	3.55	13.38	0.32	3.71	1.53	4.26	0.61	2.08		0.40	1.70
Average ΔΣθ[b]	**2.08**				**2.08**						**2.89**		**1.20**				
C2/°	124.62 127.38 108.00	124.14 127.33 108.51	126.44 125.21 108.33	125.55 126.68 107.73	124.20 126.90 108.80	124.20 126.90 108.80	124.30 127.30 108.40	126.76 124.93 108.31	127.40 124.85 107.74	127.90 124.19 107.90	124.10 128.30 107.62	124.90 127.50 107.58	128.60 125.60 105.80	125.80 127.76 106.44	124.41 128.77 106.81	125.30 129.30 105.40	106.60 128.00 125.40
C2 ΔΣθ[a]	0.00	0.02	0.02	0.04	0.10	0.10	0.00	0.00	0.01	0.01	-0.02	0.02	0.00	0.00	0.01	0.00	0.00
Average ΔΣθ [b]	**0.02**				**0.04**					**0.00**			**0.00**				

^{13}C C=O (C2)/ppm	161.20	162.60	162.00	158.80	158.40			162.00	156.90	156.20	156.00		155.90	154.60			
Average	161.15				159.10					156.10			155.25				
Δδ[c]	**-5.90**				**-3.85**					**-0.85**							
N3/°	110.19	109.07	109.17	109.55	111.20	110.80	111.00	111.29	111.51	111.06	111.42	111.44	124.85	124.36	125.81	112.60	110.90
	117.73	117.05	115.63	118.69	122.80	120.60	122.40	123.84	123.26	126.98	124.39	123.41	111.80	123.48	122.45	127.10	124.50
	117.92	115.57	122.92	122.95	121.00	122.70	121.60	122.00	121.21	121.21	120.65	122.18	123.04	112.13	111.69	120.10	124.50
N3 ΔΣθ[a]	14.16	18.31	12.28	8.81	5.00	5.90	5.00	2.87	4.02	0.75	3.54	2.97	0.31	0.03	0.05	0.20	0.10
Average ΔΣθ[b]	**13.39**				**4.56**					**2.42**			**0.14**				
C4/°	127.62	123.78	123.22	126.60	123.10	123.70	130.10	130.31	129.78	128.49	129.28	123.60	125.48	107.52	125.42	124.60	108.10
	125.13	128.32	129.45	126.30	129.80	129.30	123.10	123.52	123.87	124.48	124.30	129.50	126.58	125.75	126.86	127.90	125.30
	107.15	107.72	107.57	107.05	107.00	106.90	106.80	106.15	106.34	107.00	106.20	106.60	107.94	126.73	107.72	107.40	126.60
C4 ΔΣθ[a]	0.10	0.18	-0.24	0.05	0.10	0.10	0.00	0.02	0.01	0.03	0.22	0.30	0.00	0.00	0.00	0.10	0.00
Average ΔΣθ[b]	**0.02**				**0.05**					**0.18**			**0.02**				
^{13}C C=NH (C4)/ppm	172.00	173.90	173.40	182.30	172.10			172.70	172.20	170.70	167.40		173.90	173.40			
Average	173.10				172.33					169.05			173.65				
Δδ [c]	**0.55**				**1.32**					**4.60**							
Dihedral Angle 1234/°	1.79	3.95	5.63	2.99	0.48	0.39	1.50	10.61	3.86	9.82	5.74	5.87	6.14	1.52	0.22	1.67	2.80

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