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2018

Jessica Hill

School of Chemistry

A thesis submitted to the University of Bristol for the degree of Doctor of Philosophy in the Faculty of Science

Abstract

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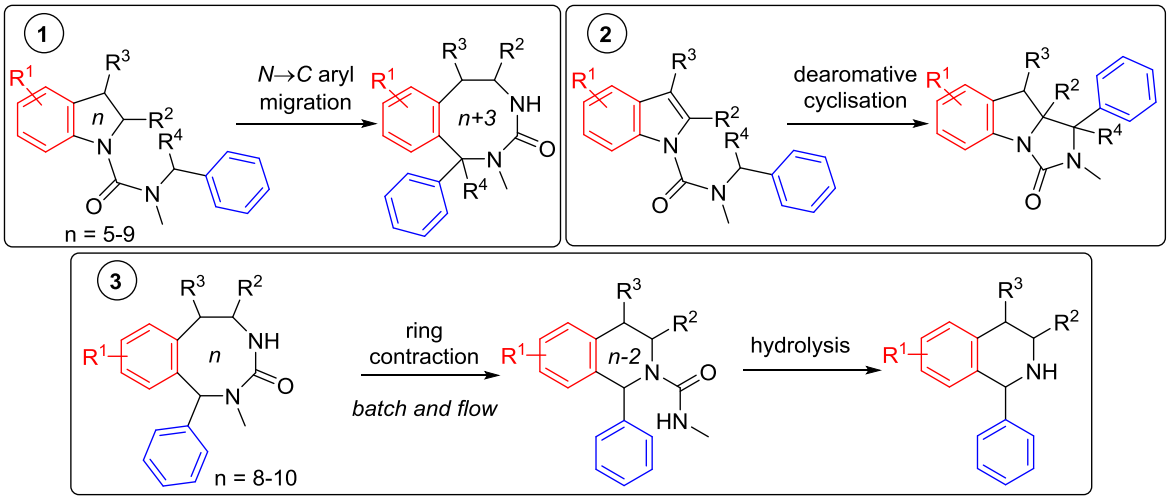
Medium ring (8-12 members) and benzannulated medium heterocycles represent a class of synthetically challenging targets. Although natural products containing medium ring *N*- and *O*- heterocycles offer beneficial biological properties, there is a stark absence of medium rings in active pharmaceutical ingredients, potentially highlighting the difficulties associated with their synthesis. Typical methods of synthesis include transition metal-catalysed processes, such as ring closing metathesis and ring expansion techniques, which require pre-organisation of the precursors to ensure a thermodynamic driving force.

Research by the Clayden group has shown that the poor reactivity between carbanions and unactivated Csp^2 'electrophiles' can be overcome by tethering the two through a urea linkage. The principles of this unique protocol have been applied to the research within this thesis. Firstly, the *N*→*C* rearrangement chemistry has been applied to cyclic systems where the urea nitrogen is tethered as part of a ring, ultimately resulting in ring expansion after aryl migration, as shown in 1. This ring expansion methodology has been optimised and applied to a wide range of urea precursors, allowing access to complex structural architectures in few steps from simple starting materials.



Secondly, when benzylic indole precursors were investigated, rather than obtaining the expected ring expansion products from the *N*→*C* aryl migration route, lithiation instead resulted in dearomative cyclisation, generating a range of polycyclic indoline structures, shown in 2. Finally, an *n* to *n-2* ring contraction protocol has been developed to access privileged tetrahydroisoquinoline and tetrahydrobenzazepine structures from medium ring nitrogen heterocycles, shown in 3. Furthermore, this ring contraction methodology has been developed for applications in flow, for the efficient multi-gram synthesis of 1-aryl tetrahydrobenzazepine.

The different synthetic methods disclosed within this thesis enables rapid access to a wide range of biologically and medicinally relevant scaffolds, from which further diversification is possible for potential library design.

Dedication and Acknowledgments

Firstly, I would like to thank Jonathan for allowing me this amazing opportunity to work on such an exciting project within his group. Your support and guidance have been first class throughout the full of my PhD and I can't thank you enough for that.

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So many others that deserve a thanks too, Josep, Mary, Louise, Laura, Frank, Mike, Dan, David, Romy, Bryden, Cath, Kathi, Julien, Hugo and Sam. Thank you to you all.

My close friend Krishna, I could not have done this without you. I will always appreciate our catch-ups which usually included gin or wine and cooking dinner each week. I have no doubts that we will be friends for life. I wish you all the luck in your next chapter!

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Finally, and most importantly, I want to finish off by thanking my nearest and dearest who I really couldn't have done this without; Mam, Dad, Nadine, Scott and Harper. Your constant support and regular visits to Bristol from Hartlepool made all the lonely times worth it. Thank you for always encouraging me to be the best I can be. The most important thing I learnt from doing this PhD here in Bristol was that nothing is more important to me than family and I am so happy to be back up North with you all! I love you all endlessly.

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So, Andrew this is for you and our son Harlen. You two are my greatest achievements!

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 those of the author.

SIGNED: Jessica Hill…… DATE: 06/09/18……

Table of Contents

Abbreviations

Ac	Acyl
AIBN	Azobisisobutyronitrile
Aq	Aqueous
Ar	Aryl
BMR	Benzannulated medium rings
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bu	Butyl
^{n}Bu	Butyl
^{t}Bu	*tert*-Butyl
^{s}Bu	*sec*-Butyl
Bz	Benzoyl
CAN	Cerium (IV) Ammonium Nitrate
Cb	Carbamate
CBz	Carboxybenzyl
COSY	Correlation Spectroscopy
Cy	Cyclohexyl
δ	Chemical shift
d	Doublet
dba	Dibenzylideneacteone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DFT	Density Functional Theory
DIBAL	Diisobutylaluminium Hydride
DIPA	Diisopropylamine
DMA	*N,N*-Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DMF	*N,N*-Dimethylformamide

DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone
DMSO	Dimethylsulfoxide
dr	Diastereomeric Ratio
E^+	Electrophile
ee	Enantiomeric Excess
eq	Equivalents
er	Enantiomeric Ratio
ESI	Electrospray Ionisation
Et	Ethyl
EWG	Electron-Withdrawing Group
Fmoc	Fluorenylmethyloxycarbonyl
Gly	Glycine
h	Hour
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
IPA	Isopropanol
^{i}Pr	*Iso*-Propyl
IR	Infrared
J	Coupling Constant
KHMDS	Potassium hexamethyldisilazide
L	Ligand
LDA	Lithium diisopropylamide
LiHMDS	Lithium Bis(trimethylsilyl) amide
LiTMP	Lithium tetramethylpiperidide
m	Multiplet
m	*meta*
M	Molar
maj	Major rotamer/ diastereomer
Me	Methyl
MHz	Mega hertz
min	Minor rotamer/ diastereomer

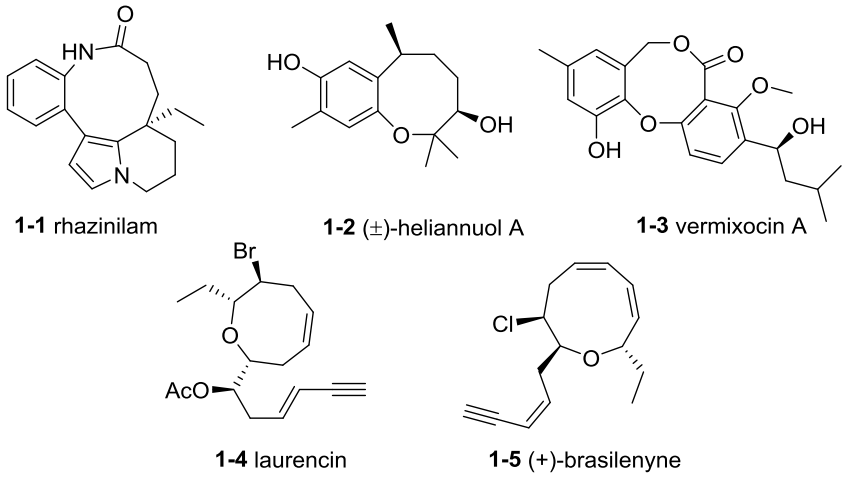
µw	Microwave
MP	Melting point
MS	Molecular sieves
NaHMDS	Sodium Bis(trimethylsilyl)amide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
Nu	Nucleophile
MOM	Methoxymethyl ether
o	*Ortho*
OAc	Acetate
p	*Para*
Petrol	Petroleum ether
PG	Protecting group
Ph	Phenyl
Piv	Pivaloyl
PMB	*para*-Methoxybenzyl
PPA	Polyphosphoric acid
ppm	Parts per millions
Pr	propyl
PTSA	*para*-Toluenesulfonic acid
py	Pyridine
q	Quartet
Quin.	Quintet
R^1	Substituent
RCM	Ring closing metathesis
R_f	Retention factor
RBF	Round bottom flask
RT	Room temperature
s	Singlet
Sat.	Saturated
SM	Starting material
S_NAr	Nucleophilic aromatic substitution

T	Temperature
t	Triplet
TBAB	Tetrabutylammonium bromide
TBDMS	*tert*-Butyldimethylsilyl
TEAC	Tetraethylammonium chloride
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Tol	Toluene
Ts	Tosylate
UV	Ultraviolet
VT	Variable temperature
X	Halogen

1. Introduction

1.1 Importance of Medium-Sized Rings

Medium-sized rings (8-12 members), particularly benzannulated medium rings (BMR) are important scaffolds in medicinal chemistry and are prevalent in a number of natural products, figure 1-1.[1]



1-1 rhazinilam **1-2** (±)-heliannuol A **1-3** vermixocin A

1-4 laurencin **1-5** (+)-brasilenyne

Figure 1-1. Medium-sized rings in natural products.

This class of compounds have been investigated as potential drug candidates. For example, rhazinilam **1-1** has been shown to demonstrate anti-cancer properties[2] and heliannuol A **1-2** exhibits allelopathic activity.[3] These positive biological properties have been attributed to the conformational constraints imposed by the cyclic structures. Such conformational restriction can offer enhanced binding affinities[4] that may correlate with improved bioavailability, and in some cases enhanced cell permeability.[5] This effect is observed because of the high degree of structural pre-organisation that facilitates the interaction of functional groups across binding sites in proteins, without a significant entropic loss upon binding.

1.2 Conformational Analysis of Medium-Sized Rings

The main challenge with the exploration of these scaffolds as therapeutic agents is the difficulties associated with their syntheses. Whilst the corresponding 5- and 6- membered ring derivatives can be readily accessed from relatively simple cyclisation and cycloaddition strategies, methods to generate medium-sized rings are obstructed by unfavourable enthalpic and entropic effects, which is reflected in the high levels of strain exhibited by these structures, table 1-1.[6]

Table 1-1. Ring strain of cycloalkanes.[6]

Ring Size	Strain per CH_2/ kJ mol^{-1}
6	0.08
7	3.72
8	5.06
9	5.86
10	5.19
11	4.27
12	1.42
13	1.67

Unlike smaller ring sizes (5-, 6- and 7- membered rings) conformational analysis of medium-sized rings is complicated.[6] In the majority of cyclic compounds strain is a compromise between minimising angle and torsional strain. However, in medium-sized rings angle and torsional strain are relatively low as the molecule can adopt a conformation to avoid these, instead introducing transannular strain. This is where substitutents, usually methylene hydrogen atoms, point "into" the ring consequently bringing them into proximity to one another causing unfavourable van der Waals interactions, figure 1-2.

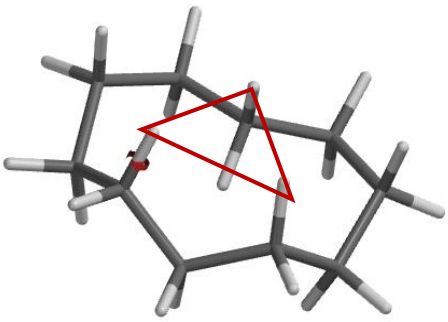


Figure 1-2. Transannular strain shown in cyclodecane. Unfavourable interactions highlighted by the triangle.

Overall, the strain of medium-sized rings is a combination of transannular strain, bond angle distortion and partial eclipsing of hydrogen atoms.[7] Minimising the strain from a single conformation is not possible, hence it is unlikely that medium-sized rings have a single low energy conformation. As a result, they usually have several conformations in equilibrium which are separated by low energy barriers. As a ring size gets larger, strain is reduced as the molecule can adopt a conformation like that of an acyclic linear alkane, avoiding eclipsing hydrogen atoms.

There is a clear absence of medium-sized rings in the database of FDA approved pharmaceuticals, owing in great deal to the difficulties associated with their synthesis.[7] Therefore, a general method for

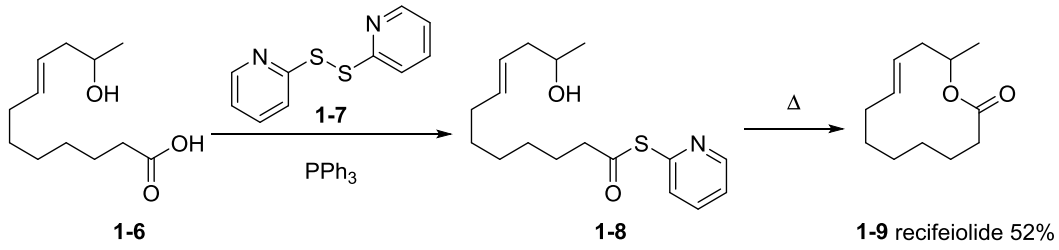
the preparation of these molecular frameworks would be highly desirable as it would permit access to unexplored chemical space.

1.3 Synthesis of Medium Rings and Benzannulated Medium Rings

Despite the challenges associated with the synthesis of medium rings, the prevalence of such structures in natural products with positive biological activities has driven chemists to explore ways of accessing these structural motifs. The examples discussed below show some of the methods developed to access these challenging molecular architectures.

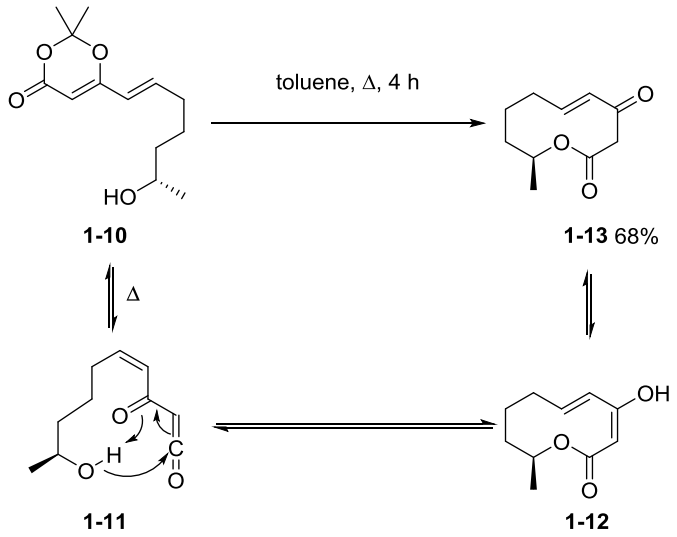
1.3.1 Medium Rings by Lactonisation

The generation of medium ring lactones by intramolecular attack of a hydroxyl group on an activated carbonyl has been investigated thoroughly. Early pioneering work by Corey and Nicolaou demonstrated that an *S*-pyridyl ester such as **1-8** could be used to activate the molecule towards lactonisation, scheme 1-1.[8,9]



Scheme 1-1. Corey-Nicolaou lactonisation to synthesise recifeiolide **1-9**.[9]

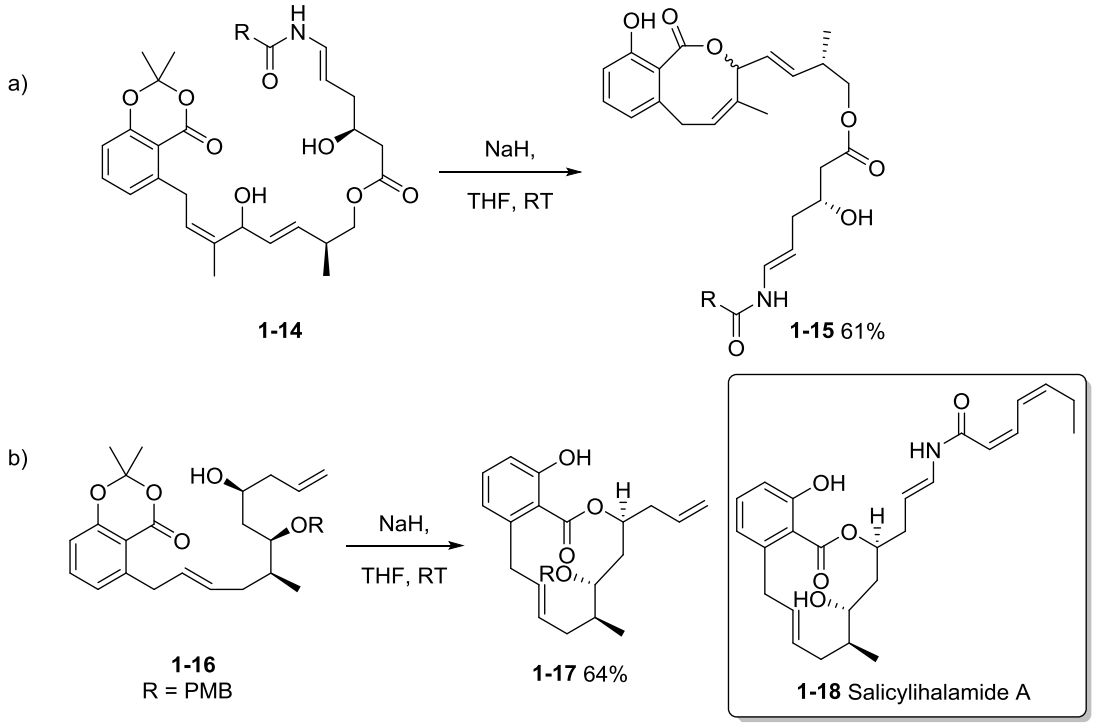
Using this cyclisation protocol as the key step, the total synthesis of 12-membered macrolide recifeiolide **1-9** was successfully carried out in only a few steps.[9] Since then, numerous other methods of carbonyl activation have been employed for the synthesis of medium ring lactones by lactonisation. An alternative method of lactonisation *via* intramolecular trapping of a ketene intermediate was developed by Boeckman *et al.* scheme 1-2.[10]



Scheme 1-2. Boeckman lactonisation *via* trapping of a ketene intermediate.[10]

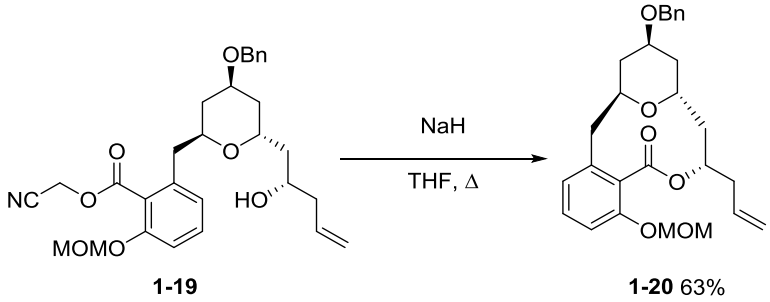
This method, which exploits dioxolenones **1-10** as masked activated carbonyls allows the formation of β-acyl ketenes **1-11** upon heating. The ketene is then trapped by the nucleophilic hydroxyl group under mild, neutral conditions to generate 10-membered lactone **1-13** in 68% yield.

Utilising a similar Boeckman lactonisation procedure, Porco *et al.* reported the synthesis of 8-membered benzolactone **1-15**, scheme 1-3 a.[11]



Scheme 1-3. 'Boeckman-type' lactonisation to synthesise benzannulated medium rings.[11,12]

In contrast to the neutral conditions initially employed by Boeckman, Porco *et al.* used basic conditions to promote the lactonisation. Similarly, the same conditions were applied to the synthesis of salicylihalamide A **1-18**, a highly cytotoxic macrolide, scheme 1-3 b.[12] When using these conditions, it was particularly important to run the reaction at high dilution to avoid competing intermolecular reactions. Likewise, in 2004 Paneck *et al.* demonstrated that the same base-promoted lactonisation could be applied to the synthesis of 10-membered lactone **1-20**, scheme 1-4.[13]



Scheme 1-20. Lactonisation utilising cyanomethyl ester to activate carbonyl.[13]

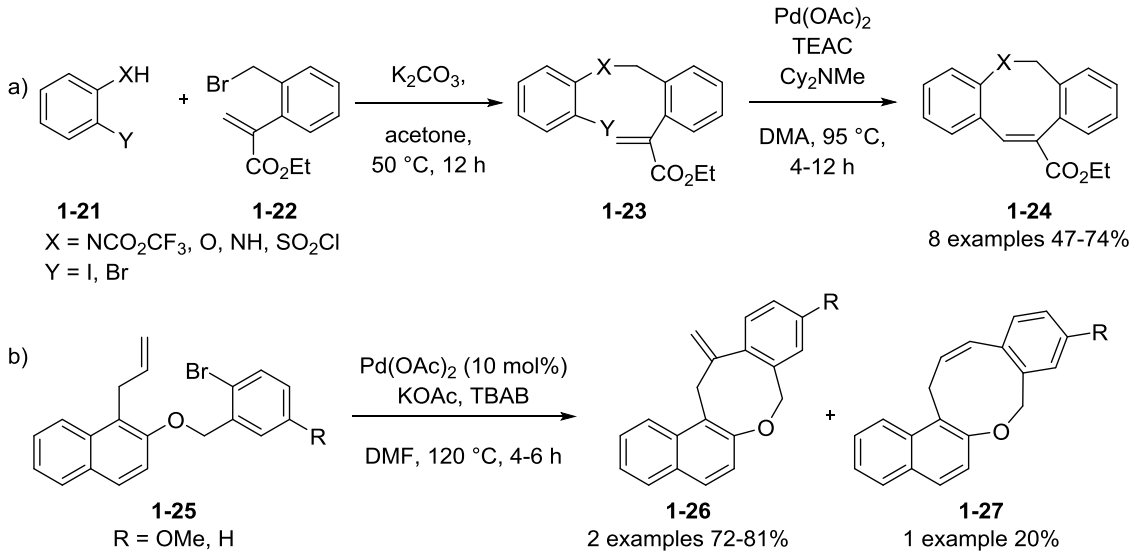
The use of a cyanomethyl ester **1-19**, which has previously been reported in transesterification reactions, was effective in activating the carbonyl towards nucleophilic attack by the hydroxyl group. Using this strategy, lactone **1-20** was synthesised in 63% yield and was used as an intermediate in the synthesis of (-)-apicularen A, a powerful inhibitor of human cancer cells.[13]

1.3.2 Medium Rings by Transition Metal-Catalysed Couplings

Transition metal-catalysed cross coupling reactions are an essential synthetic tool for generating new carbon-carbon, carbon-oxygen and carbon-nitrogen bonds.[1] Of all the transition metals, palladium is arguably the most versatile with regard to the synthesis of medium ring and benzannulated medium ring structures.

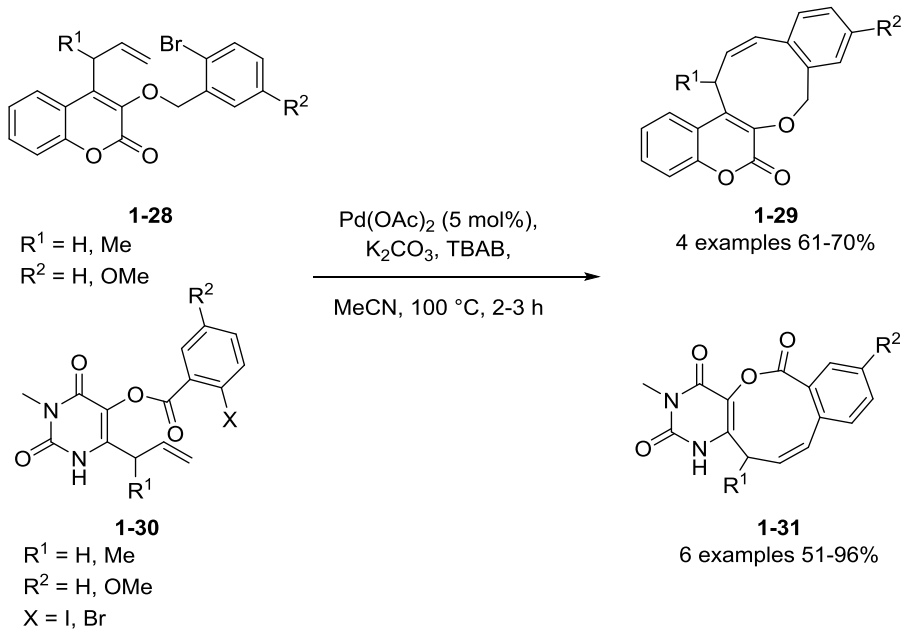
1.3.2.1 Heck Reaction

Although there is a plethora of palladium-catalysed Suzuki-Miyaura couplings applied to the synthesis of benzannulated macrocycles,[14-16] Heck coupling appears to be the method of choice for the synthesis of medium-sized rings. The Heck reaction involves the coupling of an aryl or vinyl halide with an alkene in the presence of a palladium catalyst and base. The reaction can be both inter- and intramolecular, with intramolecular Heck reactions being most successful for the synthesis of medium rings.
The synthesis of 8-membered dibenzo[*b,f*]azepines, -oxacine and -thiocine **1-24** was achieved by the intramolecular Heck coupling of an α-aryl substituted acrylates and aryl halides as in **1-23**, scheme 1-21 a.[17]



Scheme 1-21. Intramolecular Heck coupling to form benzannulated medium rings.[17,19]

Guy *et al.* demonstrated that alkylation followed by Heck coupling using the general phosphine-free reaction conditions developed by Buchwald,[18] allowed access to a range of tricyclic 8-*endo* products **1-24** exclusively in moderate to good yields. Similar phosphine-free conditions were employed for the synthesis of medium ring oxa-heterocycles **1-26** and **1-27**, scheme 1-21 b.[19] The optimal conditions were reported to be 10 mol% $Pd(OAc)_2$, KOAc and tetrabutylammonium bromide (TBAB) as an additive in DMF for 4-6 hours at 120 °C. The 8-*exo* cyclised products **1-26** were isolated as the major products with only one substrate (where R = H) giving the 9-*endo* Heck product **1-27** *via* 9-*endo-trig* cyclisation. The same authors later reported that milder conditions and lower catalyst loadings could be used to achieve cyclisation by intramolecular Heck reaction to access different medium ring oxa-heterocycles and lactone derivatives **1-29** and **1-31**, scheme 1-22.[20]



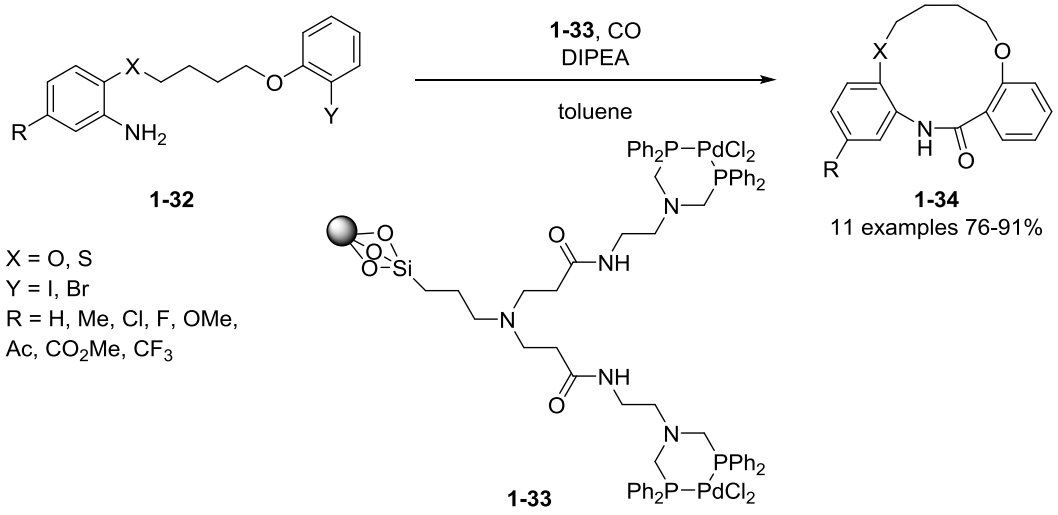
Scheme 1-22. Synthesis of benzannulated 9-membered oxa-heterocyclic ring systems and lactone derivatives *via* intramolecular Heck reaction.[20]

In all examples, the 9-*endo-trig* products were isolated exclusively with no conversion to the 8-*exo* Heck products. This phosphine-free method offers a convergent synthesis of tricyclic scaffolds.

1.3.2.2 Cyclocarbonylation

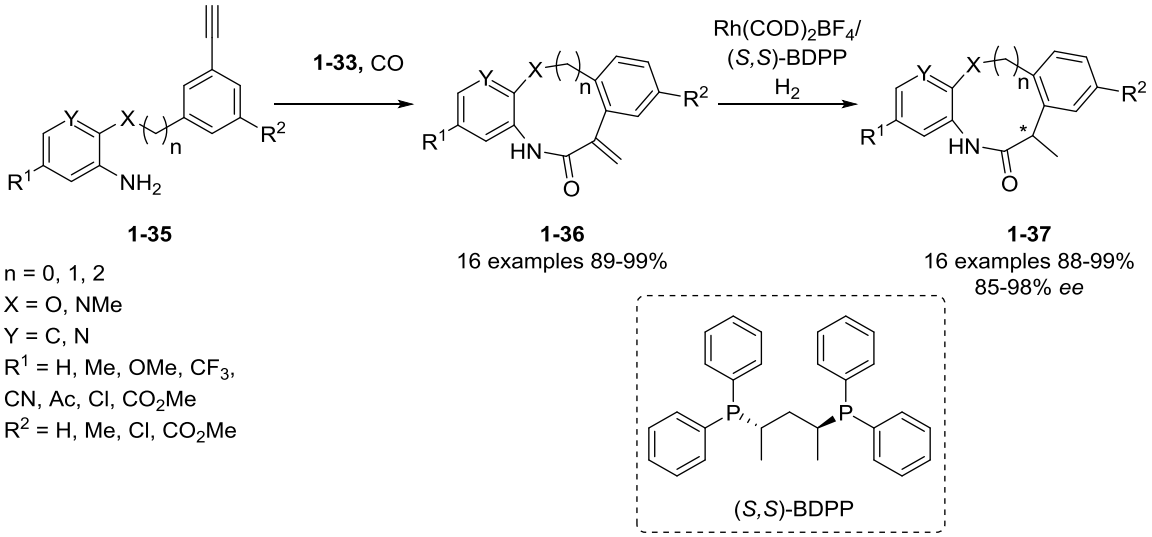
It is widely recognised that the catalytic cyclocarbonylation reaction is an important synthetic strategy for accessing cyclic carbonyl compounds from their acyclic precursors.[21] As a result, the palladium-catalysed cyclocarbonylation reaction has been applied to the synthesis of many benzannulated medium ring structures.

Homogeneous catalysis often displays excellent activity; however, the main disadvantage is the difficulty associated with the separation of the resulting product from the catalyst. Lu *et al.* addressed this issue by reporting the synthesis of 12-membered ring scaffolds **1-34** utilising recyclable palladium complexed dendrimers on silica gel, scheme 1-23.[22]



Scheme 1-23 Palladium-catalysed intramolecular cyclocarbonylation using dendritic catalyst.[22]

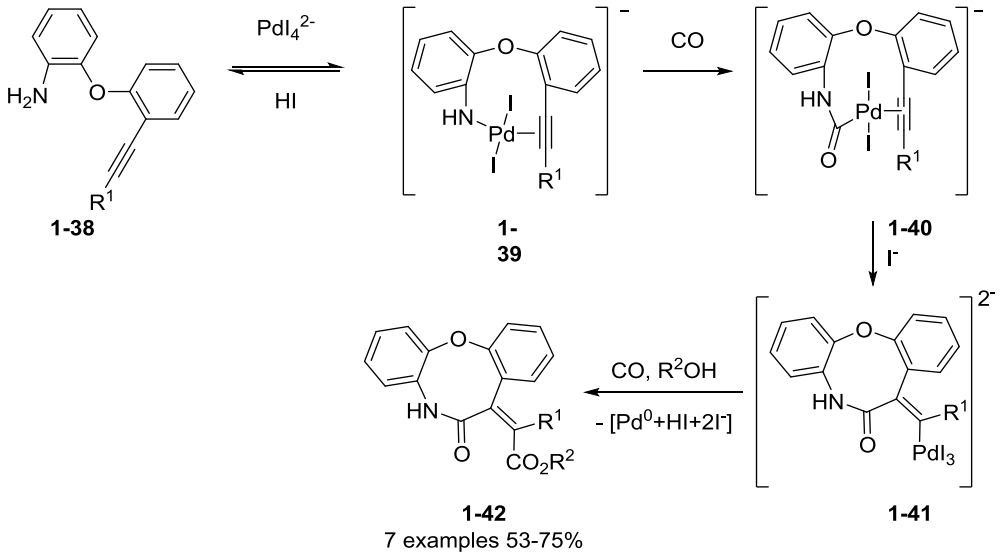
The authors reported that the heterogeneous dendritic catalyst **1-33** not only enhances the substrate's reactivity but is also able to tolerate a wide array of functional groups. Various oxygen-, nitrogen- and sulfur-containing heterocycles were afforded in good to excellent yields. Use of this heterogeneous dendritic catalyst is particularly appealing due to facile isolation of products and recyclability of the catalyst without significant loss of activity. This methodology was later applied to the asymmetric synthesis of 8- 9- and 10-membered lactams **1-37** with high regioselectivity, scheme 1-24.[23]



Scheme 1-24. Intramolecular carbonylation-asymmetric hydrogenation to form medium ring tricyclic lactams.[23]

Using the dendritic palladium catalyst **1-33** to promote an intramolecular regioselective cyclocarbonylation followed by asymmetric hydrogenation of the resulting *exo*-methylene with a rhodium catalyst gave a range of 8-, 9- and 10-membered rings **1-37**. The resulting tricyclic products were obtained in excellent yields and enantioselectivities irrespective of the electronic nature of the aromatic rings. Again, the dendritic palladium catalyst was easily recovered after the reaction was complete by filtration, demonstrating its potential for industrial use.

More recently, Gabriele *et al.* reported a palladium-catalysed oxidative carbonylation route to medium-ring lactam derivatives.[24] A series of 2-(2-ethynylphenoxy)anilines **1-38** were subjected to PdI_2/KI catalytic oxidative carbonylation conditions to yield the desired tricyclic medium ring lactams **1-42** in moderate to good yields, scheme 1-25.

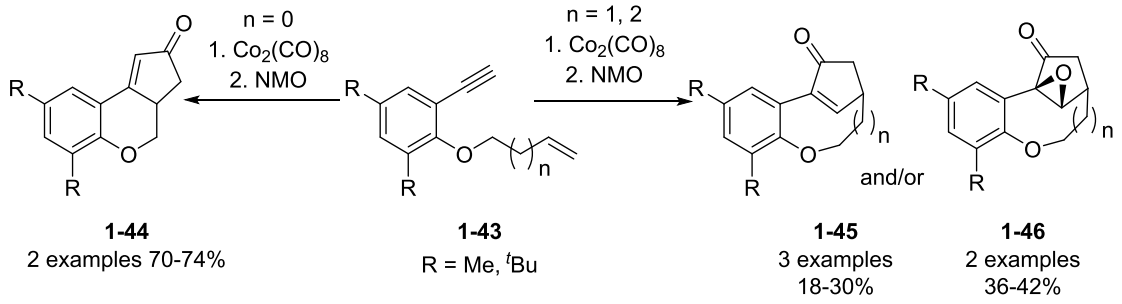


Scheme 1-25. Proposed mechanism for oxidative-carbonylation.[24]

The mechanism is proposed to start with *N*-palladation, which is stabilised by coordination to the pendant alkyne chain, followed by CO insertion to give carbamoyl-palladium iodide intermediate **1-40**. **1-40** could then evolve through an intramolecular *syn* 8-*exo-dig* triple bond insertion to yield vinylpalladium iodide intermediate **1-41**. Finally, alkoxycarbonylation of this intermediate delivers the desired 8-membered lactam derivatives **1-42**. These benzo-fused medium ring structures have shown antitumor activity against oestrogen receptor-positive (MCF-7) and triple negative (MDA-MB-231) breast cancer cell lines.

1.3.2.3 Miscellaneous Metal-Catalysed Coupling Reactions

Cobalt, copper, nickel, chromium and gold have also been used in coupling reactions to synthesise benzannulated medium-sized rings.[25-29] Lovely *et al.* reported the synthesis of bridged medium rings *via* an intramolecular *N*-methylmorpholine oxide (NMO)-mediated Pauson-Khand reaction.[25] Conversion of enynes **1-43** to their cobalt complexes was firstly achieved by addition of $Co_2(CO)_8$. These complexes were then treated with NMO which allowed the generation of medium rings **1-45** and **1-46** scheme 1-26.

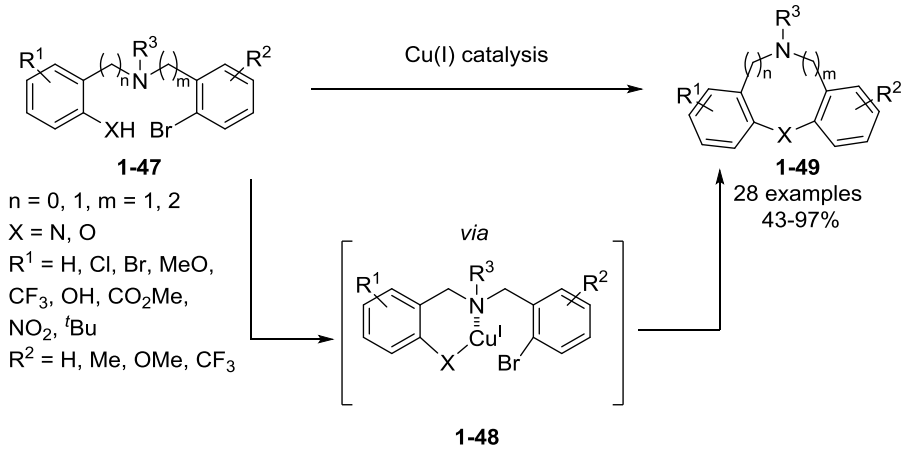


Scheme 1-26. NMO-mediated intramolecular Pauson-Khand reaction for the synthesis of medium rings.[25]

The authors noted that the *O*-allyl substrates delivered the desired fused products **1-44**, whereas the *O*-butenyl and *O*-pentenyl derivatives resulted in bridged systems **1-45** and/or **1-46.** 'Steric buttressing', the introduction of substituents *ortho* to a conformationally flexible side chain in aromatic systems, was reported to aid in the formation of medium rings by mitigating the entropic cost to cycloaddition.

Copper has also been used to synthesise benzannulated medium rings, scheme 1-27. Spring *et al.* demonstrated that copper (I) catalysis could be used to synthesise 7-, 8- and 9-membered nitrogen linked

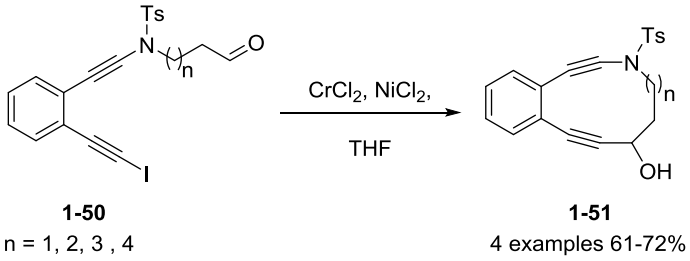
diaryls[26] and later applied this methodology to the synthesis of C-O bonds in the formation of cyclic diaryl ethers.[27]



Scheme 1-27. Synthesis of *N*- and *O*- linked tricyclic scaffolds by copper-catalysed coupling.[26,27]

The authors proposed a mechanism involving activation of the catalyst through chelation of the nitrogen, thereby acting as a ligand to copper, **1-48**. This chelation was thought to assist in the oxidative addition step of the catalytic cycle by bringing the copper in close proximity to the aryl halide, facilitating ring closure.[27] The reaction was able to tolerate many different functional groups, allowing the synthesis of an array of nitrogen- and oxygen- linked tricyclic structures **1-49**.

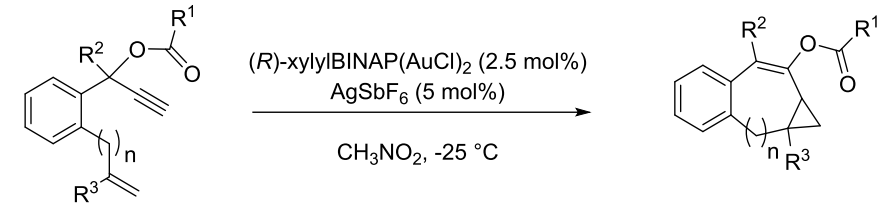
In contrast, a mixture of two transition metals was used by Popik *et al*. for the synthesis of medium ring aza-enediynes **1-51**, scheme 1-28.[28]



Scheme 1-28. Synthesis of aza-enediynes **1-51** *via* the Nozaki-Hiyama-Kishi reaction.[28]

Subjecting aldehyde **1-50** to standard Nozaki-Hiyama-Kishi conditions,[30] $CrCl_2$ and $NiCl_2$, allowed the generation of the 10-, 11-, 12- and 13-membered benzannulated rings **1-51** in good yields.

Gold has been utilised successfully in the synthesis of medium-sized rings. Toste *et al.* reported the asymmetric synthesis of 7- and 8-membered rings by an intramolecular Au(I)-catalysed cyclopropanation, scheme 1-29.[31]

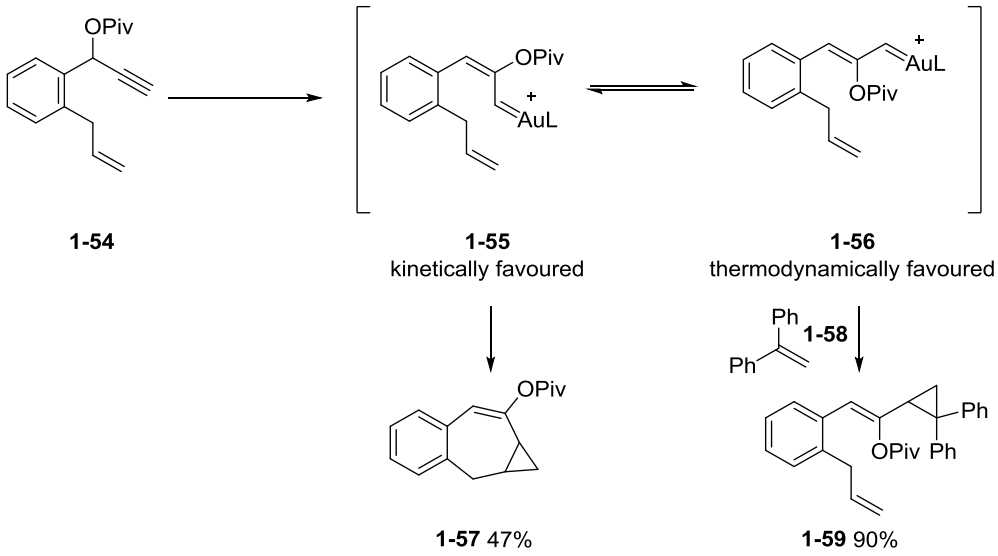


1-52
n = 0, 1, 2, 3
R^1 = Ac, Piv
R^2 = Me, Et, allyl, $(CH_2)_2Ph$
R^3 = H, Me

1-53
9 examples 44-96%
15-92% *ee*

Scheme 1-29. Asymmetric intramolecular Au(I)-catalysed cyclopropanation.[31]

Treatment of acetate **1-52** with the optimal conditions of $AuCl_2$, xylyl-BINAP in nitromethane at −25 °C gave products **1-53** with the highest enantioselectivities. The reaction tolerated substitution at the propargylic position, however substitution at the internal position of the alkene gave products with diminished enantioselectivities. It was stated that this could be overcome by substituting the catalyst for difluorophos$(AuCl)_2$.



1-54

1-55
kinetically favoured

1-56
thermodynamically favoured

1-57 47%

1-59 90%

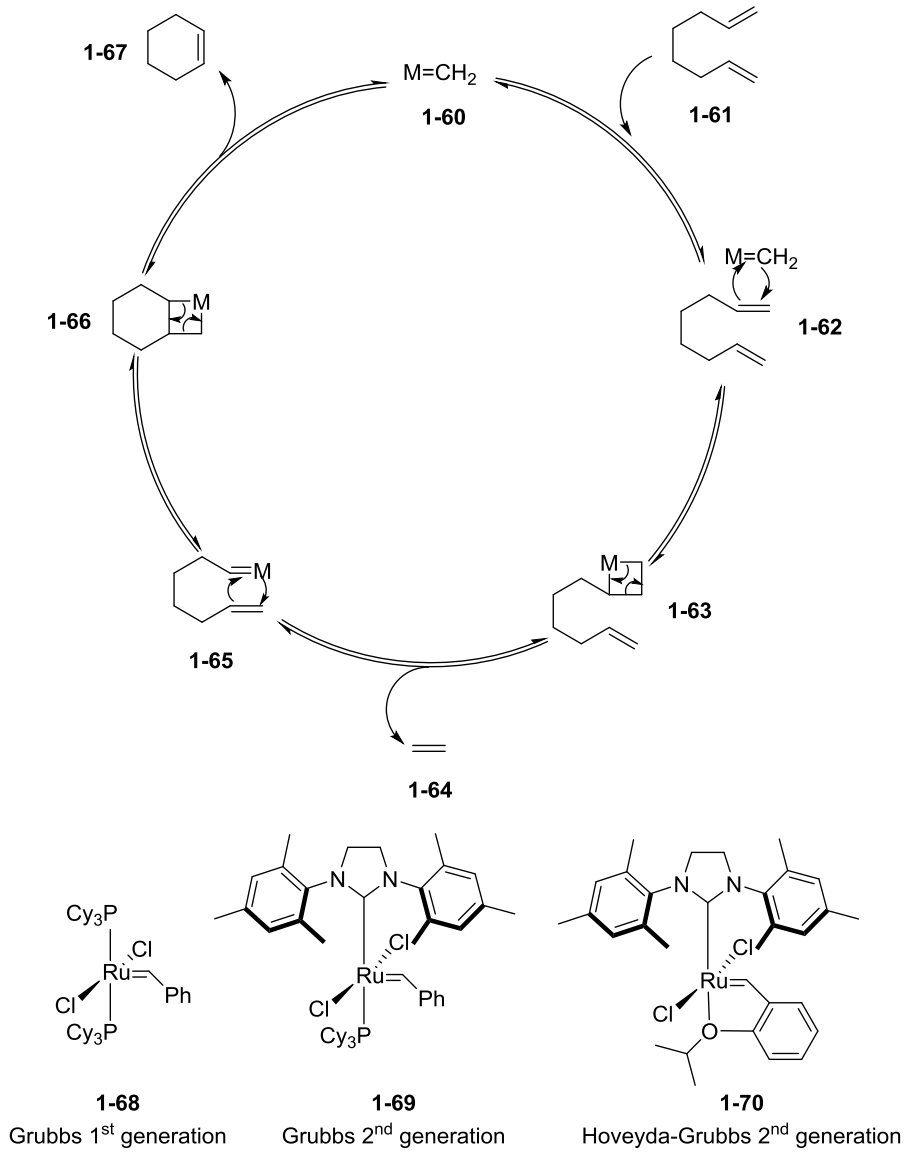
Scheme 1-30. Proposed mechanism for Au-catalysed cyclopropanation showing isomeric carbenoid intermediates.[31]

The mechanism is suspected to proceed through isomeric Au-stabilised vinyl carbenoid intermediates **1-55** or **1-56**, scheme 1-30, which are generated following a 1,2- shift of the propargyl ester. Previously published computational studies indicate that under kinetic control the *syn*-intermediate is formed, while the *anti*-intermediate is thermodynamically more favourable.[31] It is suggested that an equilibrium may exist between the two intermediates as the stereochemical outcome of the reaction is dependent on the nucleophile used. To test this hypothesis the reaction was conducted in the presence and absence of 1,1-diphenylethylene **1-58**. In the absence of 1,1-diphenylethylene the intramolecular reaction occurred to give the desired 7- membered product as the *E*-isomer **1-57**, which was expected to proceed through intermediate **1-55**. However, in the presence of 1,1-diphenylethylene an intermolecular cyclopropanation reaction occurred to form **1-59** as the *Z*-isomer. This suggests that the gold (I)-stabilised vinyl carbenoids are fluxional.

1.3.3 Ring-Closing Metathesis

Since Grubbs first published conditions for the ring closing metathesis (RCM) in 1995,[32] there has been a plethora of literature demonstrating its use as a powerful synthetic tool for the formation of new C=C bonds. Indeed, it is often the key step in the synthesis of natural products containing medium-sized rings.[1] RCM is highly attractive due to its broad functional group tolerance and the possibility of further functionalisation of the products. Consequently, many have employed RCM in the synthesis of benzannulated medium ring structures.

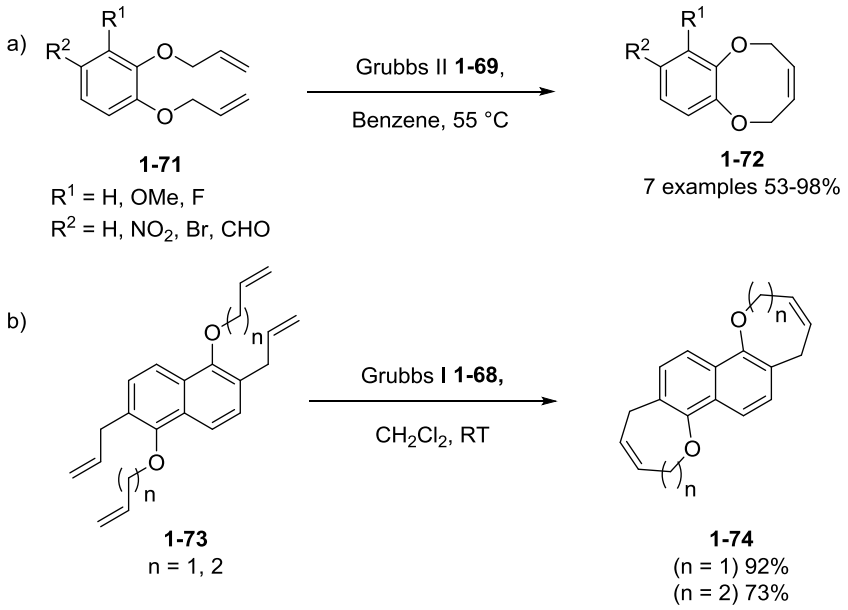
The mechanism of ring-closing metathesis has been extensively studied and proceeds as shown in scheme 1-31.[33]



Scheme 1-31. RCM catalytic scheme and common catalysts.[33]

First, the catalytically active metallocarbenoid complex **1-60** undergoes a [2+2] cycloaddition with the diene precursor **1-61**. A metallocyclobutane intermediate **1-63** is formed and is then opened in a retro [2+2] manner, generating metallocarbenoid **1-65** as an intermediate. This then undergoes re-cyclisation to form a new metallacyclobutane **1-66** that opens to deliver the desired cycloalkene product **1-67** and regenerates the catalyst. The reaction is fully reversible and entropically driven due to the release of an alkene, usually ethylene **1-64**.[33]

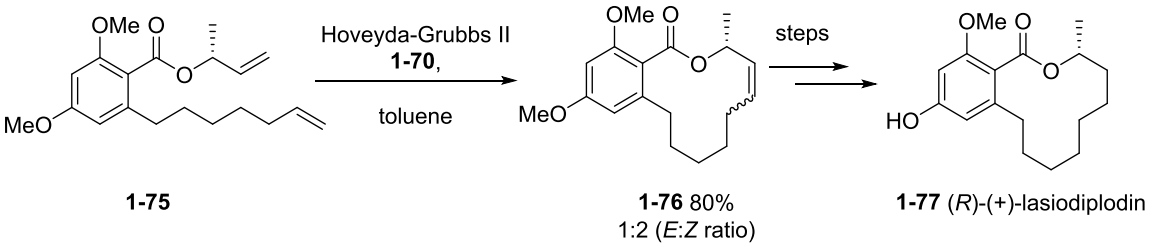
In 2004, Guillaumet *et al.* reported the synthesis of 2,5-dihydro-1,6-benzodioxocin derivatives **1-72**, scheme 1-32 a.[34] Subjecting bis-allyl ether derivatives **1-71** to RCM conditions afforded the corresponding benzannulated medium ring in good to excellent yields. Grubbs II **1-69** catalyst was found to give enhanced activity over Grubbs I **1-68**.



Scheme 1-32. RCM to form 2,5-dihydro-1,6-benzodioxocin derivatives and bisoxepine and bisoxocines.[34, 35]

In contrast, Grubbs I catalyst **1-68** was proven to be the most effective catalyst for the RCM of bisdienes **1-73**, when stirred in dichloromethane at room temperature, scheme 1-32, b.[35] The authors described a sequential double-Claisen rearrangement and two-directional RCM to generate bisoxepine and bisoxocine derivatives **1-74** in good to excellent yields.

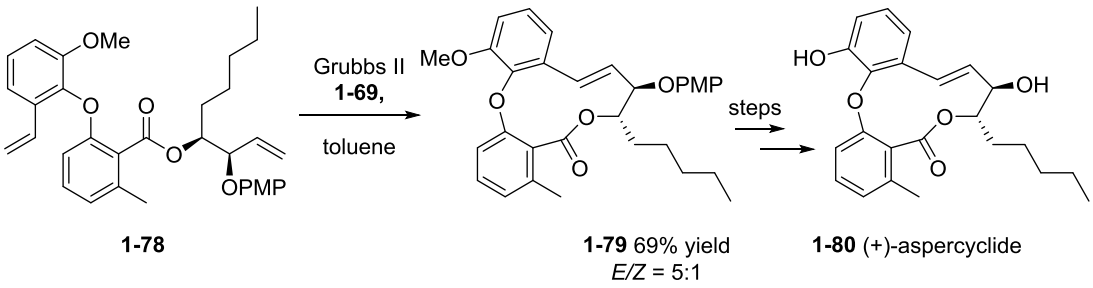
Due to the simplicity and excellent functional group tolerance of the ring closing metathesis reaction, many have exploited RCM in the synthesis of natural products.[36,37,38] In particular, RCM was used as a key step in the synthesis of (*R*)-(+)-lasiodiplodin **1-77,** which exhibits antileukemic properties, scheme 1-33.



Scheme 1-33. RCM applied in the synthesis of (*R*)-(+)-lasiodiplodin by Feringa *et al.*[36]

Fürstner[37], Feringa[36] and Faber[38] all found that using Hoveyda-Grubbs second generation catalyst **1-70** in toluene gave the desired benzannulated medium ring **1-76** with varying *E*:*Z* ratios.

Furthermore, Fürstner *et al.* reported the first total synthesis of (+)-aspercyclide **1-80** with the key step being a kinetically controlled RCM, scheme 1-34.[39]

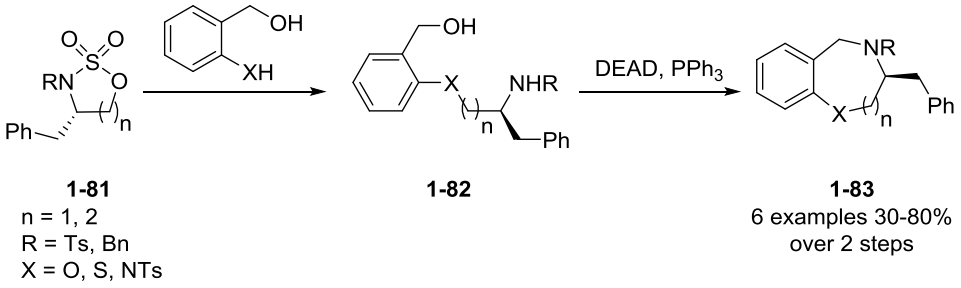


Scheme 1-34. RCM employed in total synthesis of (+)-aspercyclide.[39]

With the knowledge that the less active first-generation catalyst **1-68** will most likely deliver the kinetic isomer provided the isomers are sufficiently different in energy, this catalyst was trialled first. Although the reaction did not go to completion (<50% conversion after 5 days), analysis of the crude product revealed that the *E*-isomer **1-79** had selectively formed, indicating that this must be kinetically favoured. Grubbs second-generation catalyst **1-69** was also investigated. Despite the potential for forming the thermodynamically favoured isomer, the reaction proceeded with good selectivity suggesting a high-kinetic barrier towards isomerisation.

1.3.4 Mitsunobu Reaction

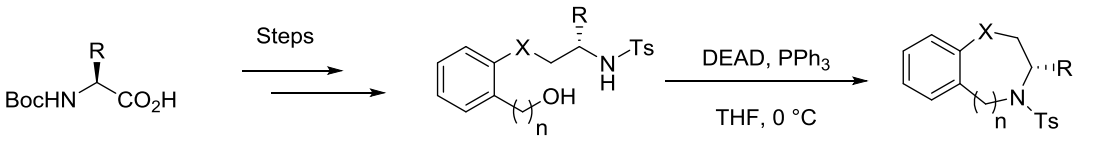
The Mitsunobu reaction is another powerful synthetic method that has been studied and applied to the synthesis of benzannulated medium rings. In 2009, Gallagher *et al.* reported the synthesis of substituted 1,4-tetrahydrobenzoxazepines, benzothiazepines, and benzodiazepines **1-83** by nucleophilic cleavage of enantiomerically enriched 1,2-cyclic sulfamidates **1-81,** followed by a Mitsunobu reaction, scheme 1-35.[40]



Scheme 1-35. Synthesis of medium rings *via* Mitsunobu reaction.[40]

Ring opening of the sulfamidates with phenol, aniline and thiophenol nucleophiles allowed the successful formation of products **1-82**. Treatment of **1-82** with PPh_3 and diethyl azodicarboxylate (DEAD) permitted the cyclisation, providing access to the medium rings **1-83** in moderate to excellent yields. This methodology was further applied to 1,3-cyclic sulfamidates to afford the analogous substituted 1,5-benzoxazocines and 1,5-benzodiazocines.

Similar 7- and 8-membered medium ring core structures were synthesised in an asymmetric fashion from their *S*-amino acid derivatives 1-84, scheme 1-36.[41]



1-84
X = O, N, S
R = Me, ^{i}Pr, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $CH_2C_6H_5$, $CH_2C_6H_4$(*p*-OH), $CH_2C_7H_6N$, $CH_2C_6H_4$(*p*-OBn)

1-85
n = 1, 2

1-86
16 examples 62-77%
>99% *ee*

Scheme 1-36. Asymmetric synthesis of benzannulated medium rings *via* Mitsunobu reaction.[41]

These scaffolds are particularly interesting due to their prevalence as core structural motifs in many biologically active molecules. The intramolecular cyclisation under standard Mitsunobu conditions generated the enantiomerically enriched bicyclic structures **1-86** in good yields and excellent enantioselectivities.

Herb *et al*. employed a Mitsunobu lactonisation as the key step in the total synthesis of salicylihalamides **1-88**, a family of natural products with potent activity against human cancer cell lines, scheme 1-37.[42]

1-87

1-88 43%

Scheme 1-37 Synthesis of salicylihalamides **1-88**.[42]

Due to the steric encumbrance around the carboxylic acid group and the presence of the alkene in **1-87** a classic lactonisation procedure was expected to be difficult. As a result, a Mitsunobu macrolactonisation was chosen due to literature precedence.[43-45] Performing the Mitsunobu macrolactonisation under high dilution gave a 25% yield of the 12-membered lactone **1-88**. However, the yield was significantly improved by utilising immobilised triphenylphosphine. This allowed the reaction to be performed at a higher concentration and subsequently resulted in an improved yield of 43%.

1.3.5 Medium Rings by Ring Expansion

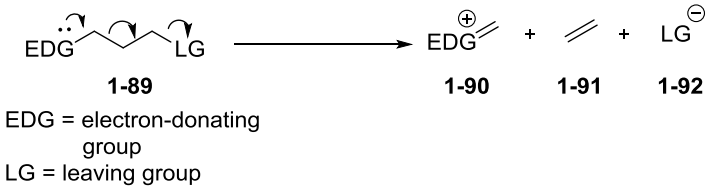
Ring expansion reactions are a popular way of forming larger ring sizes as they avoid the difficulties associated with cyclisation strategies. For a ring expansion reaction, the cyclised precursors required are often small ring sizes, e.g. 5- and 6-membered rings, which are significantly easier to form. Typically, the medium rings are then formed from the smaller rings in one of three ways; fragmentation of fused bicyclic systems, radical ring expansions or pericyclic reactions.[46]

1.3.5.1 Fragmentation of Fused Bicyclic Systems

Provided that the appropriate fused bicyclic system can be readily synthesised, subsequent access to the medium ring structures can be obtained by a fragmentation reaction.[46] The reactions tend to be irreversible processes meaning they are suitable for the synthesis of unstable systems such as medium rings, as the unfavourable transannular interactions are only experienced after fragmentation has occurred.

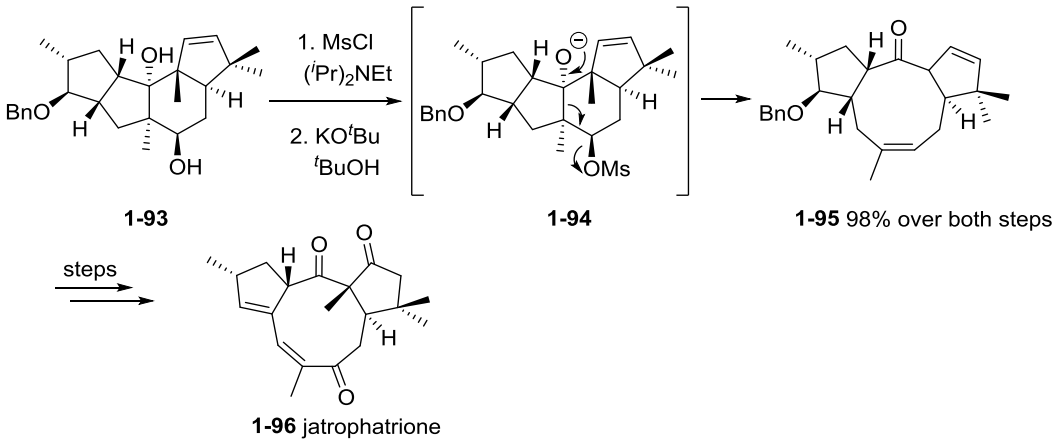
1.3.5.1.1 Elimination Fragmentation Reactions

Pioneering work by Grob[47] and Wharton[48] showed that molecules of type **1-89** with electron donating groups and leaving groups can undergo fragmentation, scheme 1-38.



Scheme 1-38. Grob/Wharton-type fragmentation.

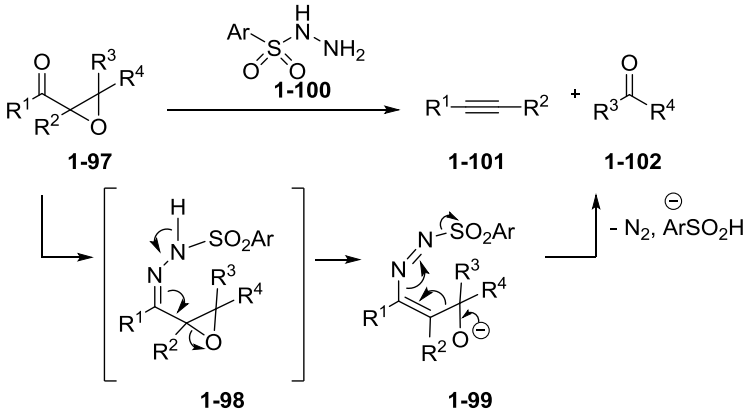
This fragmentation protocol can be applied to the fragmentation of smaller ring bicycles to generate larger rings by ring expansion. For example, Paquette *et al.* exploited a Grob/Wharton type fragmentation in the total synthesis of jatrophatrione **1-96**, a medium ring compound with anti-leukemic properties, scheme 1-39.[49]



Scheme 1-39. Synthesis of jatrophatrione by Grob fragmentation.[49]

To affect the ring expansion, polycyclic diol **1-93** was treated with mesyl chloride to selectively mesylate the secondary alcohol. Subsequent treatment with potassium *tert*-butoxide caused deprotonation of the tertiary alcohol initiating fragmentation and subsequent elimination of the *O*-mesylate generating 9-membered tricycle **1-95** in near quantitative yield.

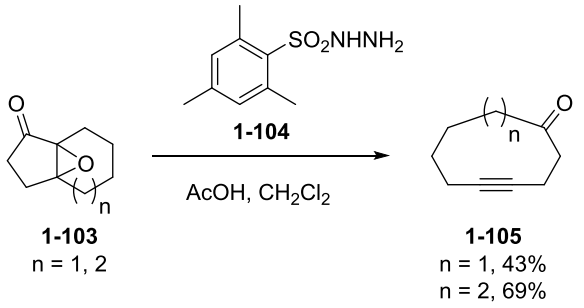
Similar to the Grob/Wharton-type fragmentations are the Eschenmoser fragmentation reactions, typically called the Eschenmoser-Tanabe fragmentations.[50] The Eschenmoser-Tanabe fragmentation describes the reaction of α,β-epoxyketones **1-97** with aryl sulfonylhydrazines **1-100** to synthesise alkynes **1-101** and ketones **1-102**, scheme 1-40.



Scheme 1-40. Eschenmoser-Tanabe fragmentation.

Both Grob/Wharton type fragmentations and Eschenmoser-Tanabe fragmentations rely on the extrusion of a stable leaving group as the thermodynamic driving force for the ring expansion reaction. Due to the elimination of nitrogen gas and a stabilised arylsulfinate, the Eschenmoser fragmentation has a stronger thermodynamic driving force than the Grob fragmentation. Consequently, this driving force can counteract the destabilising effects of forming a medium ring with a strained alkyne within its structure, allowing efficient ring expansion.

Reese,[51] and later Danishefsky,[52] exploited an Eschenmoser-Tanabe fragmentation for the synthesis of medium ring alknyl ketones **1-105**, scheme 1-41.



Scheme 1-41. Eschenmoser fragmentation of epoxy ketones **1-103** to synthesise 9- and 10-membered alkynyl ketones **1-105**.[51]

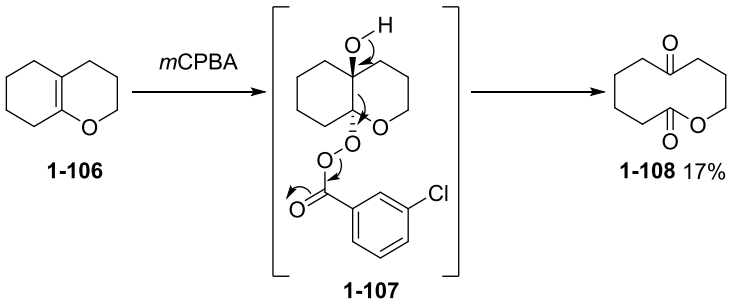
Treatment of epoxy ketone **1-103** with mesitylene-2-sulfonyl hydrazide **1-104** under acidic conditions allowed the formation of **1-105** by ring expansion *via* fragmentation.

Elimination fragmentation reactions offer a powerful technique for the synthesis of medium ring structures providing they have a strong thermodynamic driving force for ring expansion. However, it is worth noting that although these reactions have their benefits, the fragmentation precursors must be pre-organised to undergo facile fragmentation. The synthesis of the requisite starting materials is not always a simple procedure and therefore should be considered.

1.3.5.1.2 Redox-Mediated Fragmentation Reactions

Oxidative cleavage of a double bond across a fused bicyclic system is an alternative way of achieving ring expansion by fragmentation. The fragmentation process is closely related to those of the Grob and Eschenmoser fragmentations previously discussed, however the fragmentation precursor is formed by a redox process.

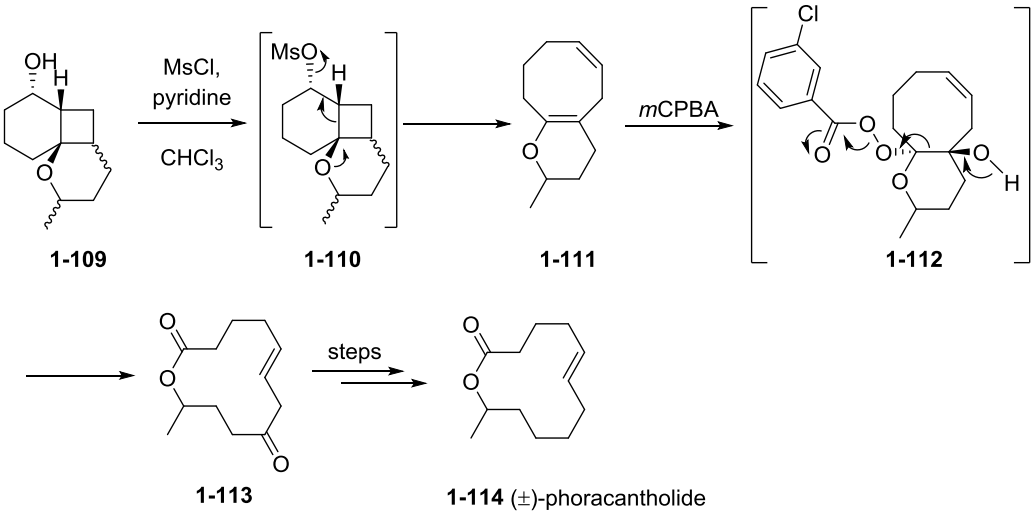
Borowitz *et al.* described the use of *meta*-chloroperbenzoic acid (*m*CPBA) to activate bicyclic enol ether **1-106** towards fragmentation, scheme 1-42.[53]



Scheme 1-42. Oxidative fragmentation of bicyclic enol ether **1-106**.[53]

Oxidation of **1-106** by treatment with *m*CPBA allowed the generation of intermediate **1-107** *in situ*, which underwent fragmentation to generate 10-membered ring lactone **1-108** in low yield. Others have reported the use of ozonolysis to oxidise the alkene bridges in bicyclic systems to give the ring expansion product.[54] This methodology has been applied to the synthesis of complex macrocyclic systems.[55]

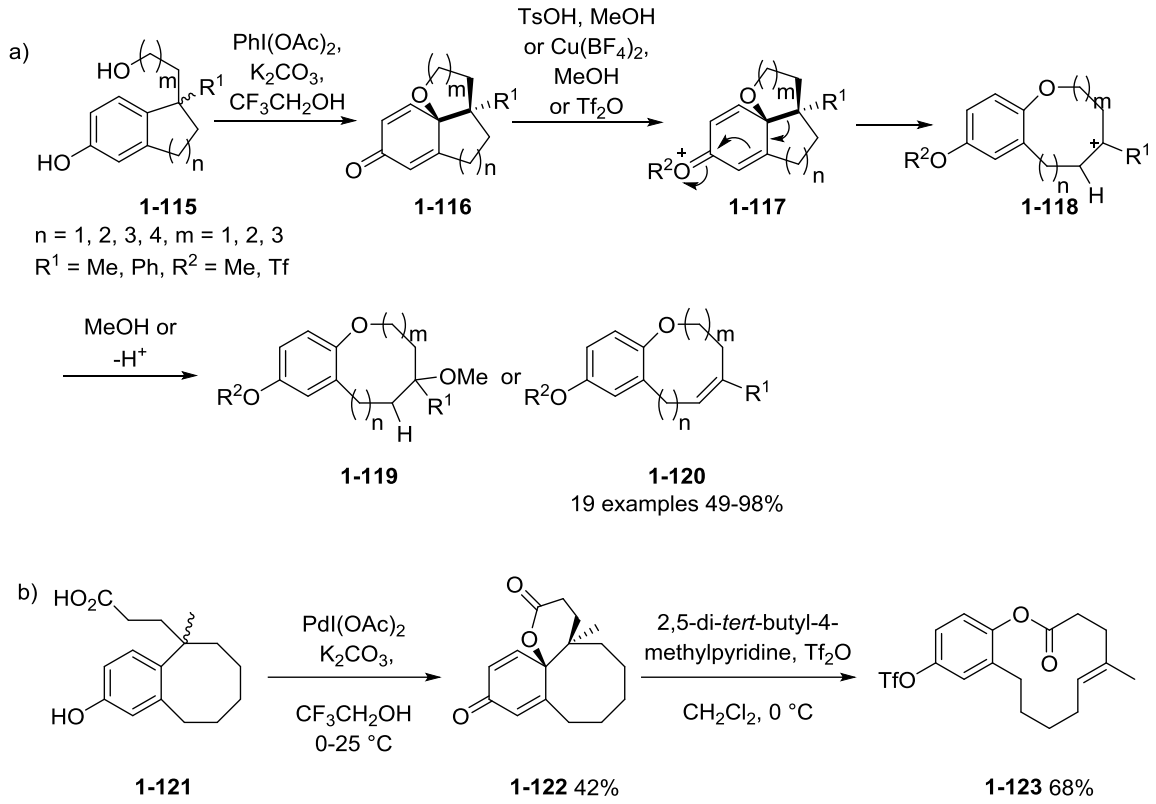
Ikeda *et al.* demonstrated the application of sequential ring expansions, involving first a Grob-type fragmentation followed by an oxidative fragmentation in the synthesis of natural product (±)-phoracantholide **1-114**, scheme 1-43.[56]



Scheme 1-43. Sequential Grob fragmentation and oxidative fragmentation for in the synthesis of (±)-phoracantholide **1-114**.[56]

Treatment of cyclobutane **1-109** with mesyl chloride allowed mesylation at the secondary alcohol. This initiated a Grob-type fragmentation to generate 6-8 fused enol ether **1-111** that was subsequently oxidised upon addition of *m*CPBA. Oxidation of the bridged alkene promoted fragmentation and ring expansion generating 12-membered lactone **1-113**, an intermediate in the synthesis of (±)-phoracantholide.[56]

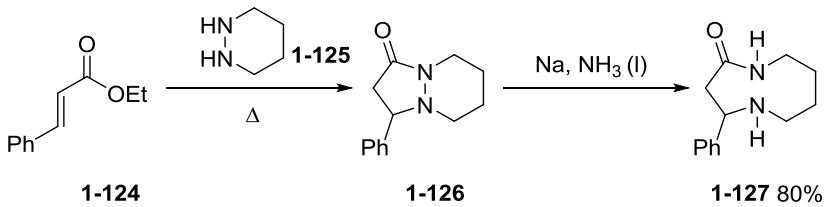
A different oxidative fragmentation approach was reported by Brauer *et al.* with the aim of creating a novel medium-ring library for drug discovery.[57] In contrast to oxidising the bond which is cleaved in the fragmentation, such as has been discussed previously, the authors reported a strategy involving oxidation of a remote phenol group, scheme 1-44 a.



Scheme 1-44. Synthesis of benzannulated medium ring ethers and lactones *via* oxidative ring expansions.[57]

Oxidation of phenol by treatment with (diacetoxyiodo)benzene initiates cyclisation to generate **1-116**, which undergoes fragmentation on addition of an appropriate Brønsted or Lewis acid to yield benzannulated rings **1-118**. Quenching with MeOH or deprotonation allowed cyclic ether scaffolds **1-119** or **1-120** to be isolated in good to excellent yields. To avoid the undesired competing dienone-phenol rearrangement, three reagent classes (Brønsted acid, Lewis acid and sulfonyl anhydride) were chosen to facilitate the desired ring expansion. The driving force was the rearomatisation of a phenol adjacent to the scissile bond. This methodology was applied to the synthesis of cyclic benzolactones of type **1-123**, scheme 1-44 b. To investigate the potential for further functionalisation of the scaffolds, the synthesis of the BMR was performed on gram scale, highlighting the industrial potential of these scaffolds. Cheminformatic analysis showed that these benzannulated medium rings had structural and physicochemical properties mimicking those found in natural products containing similar cores.

In contrast, ring expansions of bicyclic systems *via* a reductive method have also be reported. In 1980 Wasserman demonstrated the synthesis of 9-membered lactam **1-127** by reductive cleavage of an N-N bond, scheme 1-45.[58]



Scheme 1-45. Reductive fragmentation to synthesis medium ring lactam **1-127**.[58]

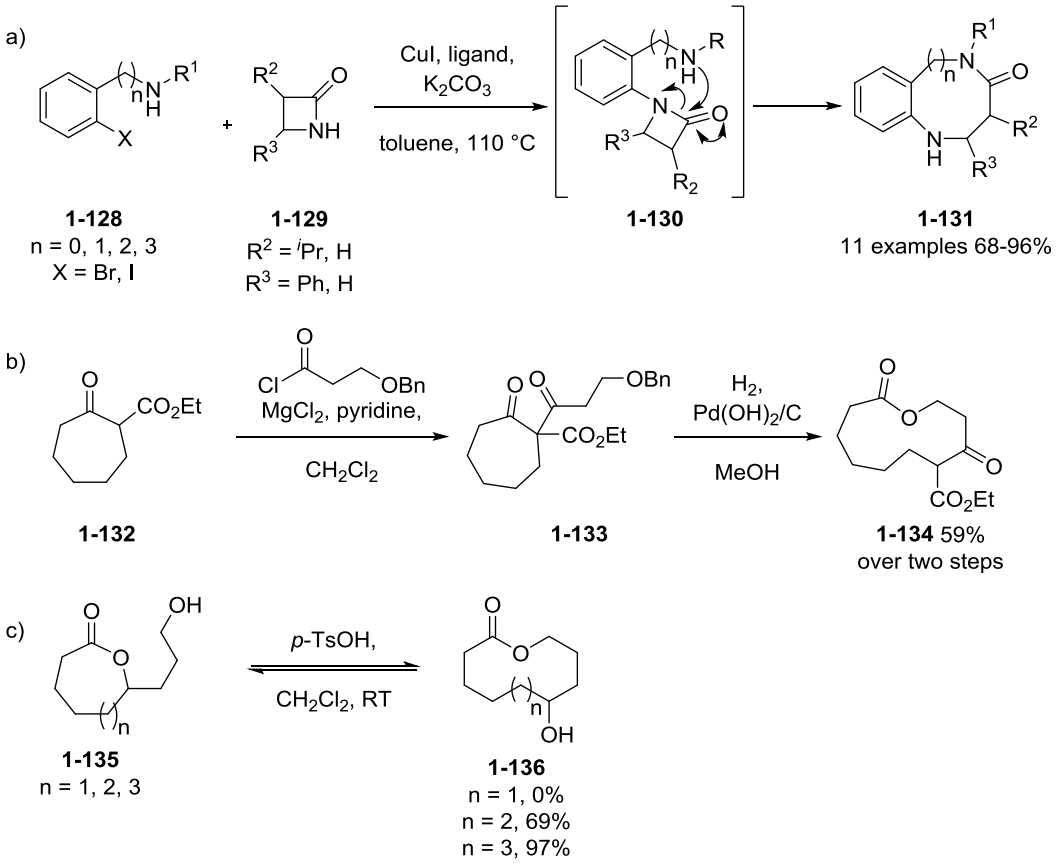
The reaction of ethyl cinnamate **1-124** and cyclic hydrazine **1-125** allowed the generation of bicycle **1-126** which underwent reductive cleavage of the N-N bond on addition of sodium and liquid ammonia.

The desired 9-membered lactam was isolated in excellent yield. A similar reductive fragmentation procedure was demonstrated by Bonjoch and co-workers for the synthesis of core structures of alkaloid natural products.[59] For this transformation the authors employed lithium instead of sodium for the reductive cleavage. Alongside the synthesis of medium ring structures, reductive fragmentation reactions have also been applied to the synthesis of macrocycles.[60]

1.3.5.1.3 Ring Expansion by Side-Chain Insertion

The synthesis of medium-sized rings by ring expansion *via* side-chain insertion can be a challenging strategy due to the reversibility of the reaction. Therefore, a strong thermodynamic driving force is necessary to ensure successful ring expansion. This has been achieved in several ingenious ways, some of which are described below.

Buchwald reported a tandem copper-catalysed C-N bond formation/ ring expansion sequence for the synthesis of 7-10 membered rings **1-131**, scheme 1-46 a.[61]



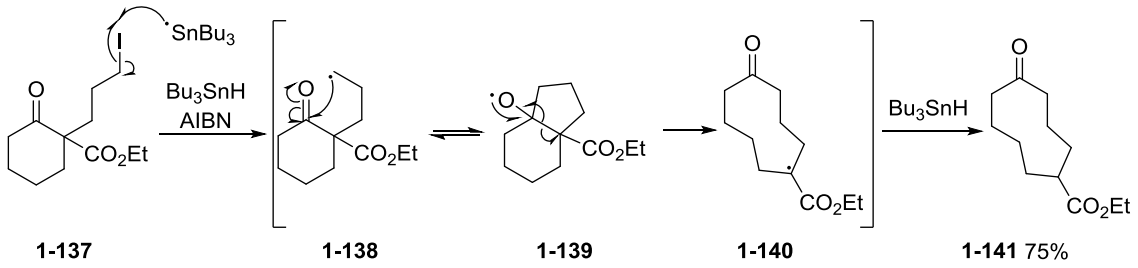
Scheme 1-46. Ring expansion by side-chain insertion to synthesise medium ring structures.[61-63]

Aryl bromides/iodides containing pendant amines **1-128** were heated with β-lactams **1-129** in the presence of a copper catalyst, scheme 1-46 a. The strong thermodynamic driving force due to relieving Baeyer strain in the β-lactam was sufficient to yield benzannulated medium ring products in good to excellent yields. Alternatively, Unsworth *et al*. reported the ring expansion of cyclic β-keto esters under neutral hydrogenation conditions, scheme 1-46 b.[62] The sequence consists of first tethering on the pendant protected alcohol giving **1-133** which then undergoes ring expansion under hydrogenative conditions. Also using a pendant alcohol for ring expansion, Corey and co-workers demonstrated that a ring expansion transesterification reaction could be used to access medium ring structures, scheme 1-46 c.[63] Unlike the other examples discussed, there is no overall change of functional group composition rendering the reactions reversible. As a result, the outcome of the reactions is a direct reflection on the

stability of the ring size being generated. For the ring expansion of 9-memebered lactone **1-135** (n=3), the reaction proceeded well and yielded the desired 12-membered ring in near quantitative yield. This can be rationalised due to the release of Pitzer strain present in the 9-membered ring on going to a larger ring system. For the 8-membered lactone (n=2), the ring expansion was significantly slower and resulted in a lower yield of 11-membered ring **1-136**, presumably due to a weaker thermodynamic driving force. Finally, the ring expansion of 7-membered lactone **1-135** (n=1) was unsuccessful with no 10-membered ring being observed. The 10-membered lactone would be significantly more strained than the 7-membered starting material, therefore making the ring expansion energetically unfavourable.

1.3.6 Ring Expansions by Radical Reactions

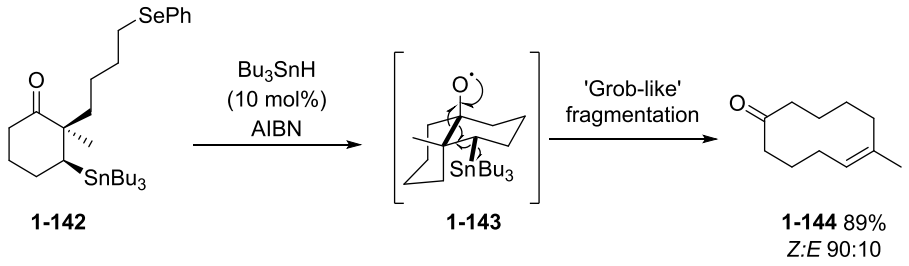
Ring expansions exploiting high energy radical intermediates has been investigated in the synthesis of medium ring structures.[64] One of the most common methods for ring expansion by radical reaction is the Dowd-Beckwith reaction.[65-69] The Dowd-Beckwith reaction describes a ring expansion of a cyclic β-keto ester by up to four carbons *via* a free radical intermediate through an α-alkylhalo substituent, scheme 1-47.



Scheme 1-47. Ring expansion by the Dowd-Beckwith reaction.[46]

This reaction was exemplified by early pioneering work by Dowd, where he demonstrated that a primary alkyl radical on a chain pendant to a β-keto ester allowed reversible cyclisation to a high energy oxyradical **1-139**. This radical initiates fragmentation leading to ring expanded structure **1-140,** where the radical is now both tertiary and stabilised by conjugation with the ester, providing a driving force for the fragmentation. Finally, C-H abstraction from Bu_3SnH yields the desired medium ring structure **1-141** in 75% yield.

Like the Grob-fragmentation described previously (see section 1.3.5.1.1), Baldwin reported a radical fragmentation reaction to stereoselectively access alkene containing medium ring structures, scheme 1-48.[70]

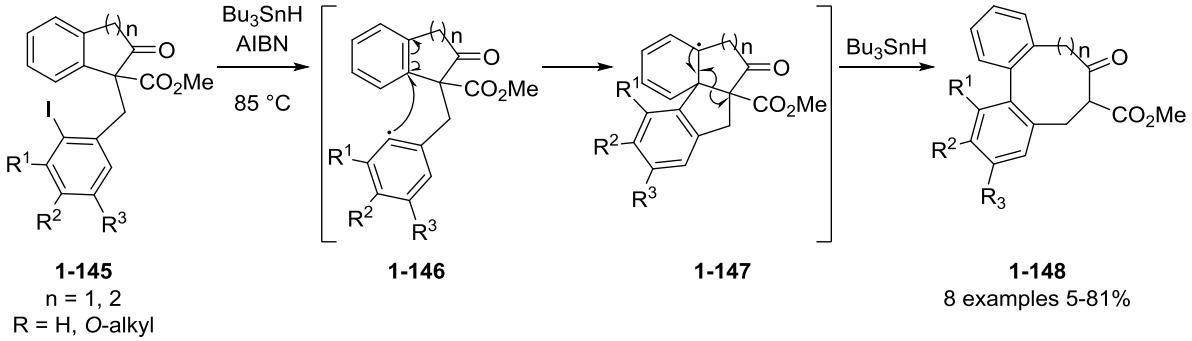


Scheme 1-48. Ring expansion by 'Grob-like' fragmentation using radicals.[70]

The alkene geometries obtained in the products are dictated by the stereochemistry of the starting materials. Homolytic cleavage of the C-Se bond upon addition of Bu_3SnH and AIBN results in cyclisation onto the cyclic ketone to give oxyradical **1-143**. This then initiates a fragmentation process similar to the Grob-fragmentation leading to medium ring structure **1-144** with a *Z*:*E* ratio of 90:10. The defined geometry is formed due to the bulky Bu_3Sn group preferentially adopting an equatorial position

on the *cis*-decalin framework, **1-143**. An advantage of this strategy is the ability to use only catalytic quantities of Bu_3SnH due to the generation of a tributylstannyl radical following fragmentation.

The synthesis of medium rings by radical reactions is not limited to the attack of a radical at a carbonyl group. Harrowven *et al.* demonstrated the synthesis of dibenzo- 8- and 9-membered rings by a radical *ipso*-substitution process, scheme 1-49.[71]



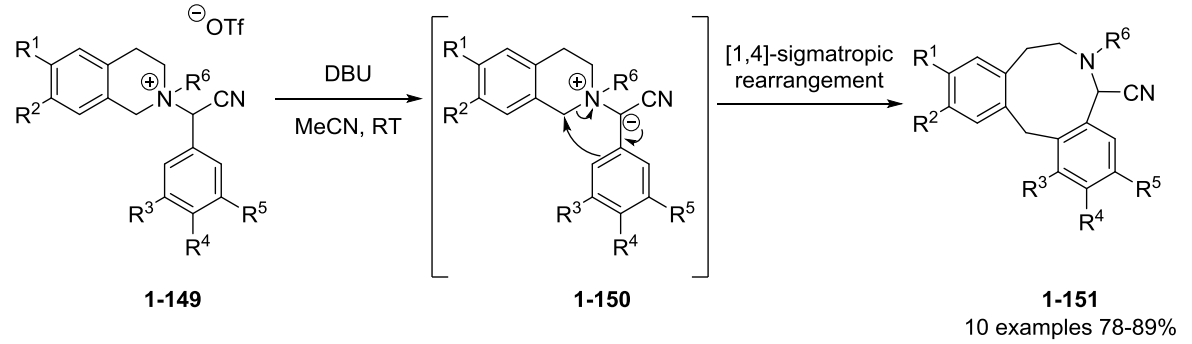
Scheme 1-49. Synthesis of medium rings **1-148** by radical *ipso*-substitution.[71]

The driving force for the reaction is based on the increasing stability of the radical species generated. The high energy aryl radical species **1-146** initiates cyclisation and subsequent rearomatisation which forms a more stable α-keto, α'-carboxy radical. C-H abstraction from Bu_3SnH gives the benzannulated medium rings **1-148** in varying yields. Importantly, the highest yields obtained were for the 8-membered products from the indanone (n=1) precursors. It was noted that for the tetralone (n=2) precursors, a competing *ortho*-cyclisation pathway was active, leading to lower yields of the desired 9-membered products. Although not discussed here, ring expansion reactions initiated by oxygen[72,73] and nitrogen[74,75] centred radicals have also been investigated for the synthesis of medium ring structures.

1.3.7 Ring Expansions by Sigmatropic Rearrangements

For the synthesis of medium-sized rings and macrocyclic structures, the most common pericyclic reaction employed is ring expansion by sigmatropic rearrangement.[46] Similarly to other ring expansion methodologies described previously, the success of the reaction depends greatly on the thermodynamic driving force. As a result, the most common pericyclic mediated ring expansions result from rearrangements of charged intermediates, where quenching of the charge to form a neutral species offers the driving force for the reaction.

Opatz *et al.* reported a ring expansion method utilising a [1,4]-sigmatropic rearrangement to synthesise benzannulated medium rings **1-151**, scheme 1-50.[76]

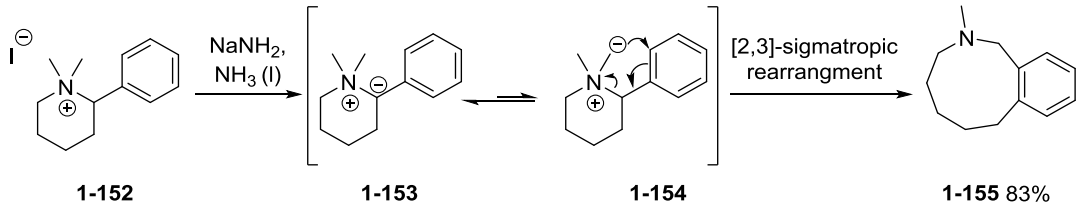


Scheme 1-50. Benzannulated medium rings by [1,4]-sigmatropic rearrangement.[76]

Deprotonation of 1,2,3,4-tetrahydroisoquinolinium salts **1-149** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) resulted in ammonium ylides **1-150**. Instead of undergoing the expected [1,2]-Stevens

rearrangement, ammonium ylide **1-150** participated in a [1,4]-sigmatropic rearrangement yielding **1-151** after rearomatisation.

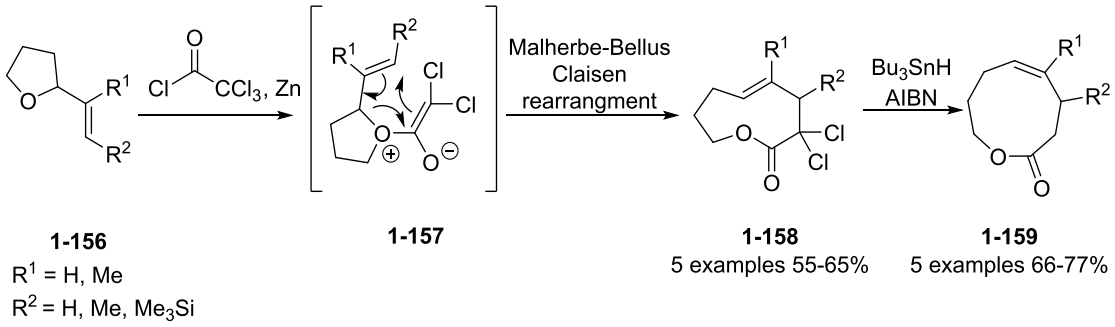
Ring expansion by a [2,3]-sigmatropic rearrangement was reported by Hauser *et al.* for the synthesis of 9-membered benzannulated ring **1-155**, scheme 1-51.[77]



Scheme 1-51. Ring expansion by Sommelet-Hauser [2,3]-sigmatropic rearrangement.[77]

This strategy, commonly known as the Sommelet–Hauser rearrangement, involved the deprotonation of quaternary ammonium salt **1-152** by treatment with sodium amide in liquid ammonia to yield a benzylic ylide **1-153**. This is in equilibrium with a second ylide **1-154** that is formed by deprotonation of one of the methyl groups. Despite this ylide being present in lower concentrations, it participates in a [2,3]-sigmatropic rearrangement, yielding the 9-membered ring after rearomatisation.

[3,3]-Sigmatropic rearrangements have also been exploited in ring expansion reactions to synthesise medium ring structures. In 1993, the Taylor group utilised the zwitterionic Malherbe–Bellus–Claisen rearrangement in a ring expansion reaction, enabling access to 9-membered cyclic lactones containing an *E*-alkene, scheme 1-52.[78]



Scheme 1-52. Medium ring lactones by [3,3]-sigmatropic rearrangement.[78]

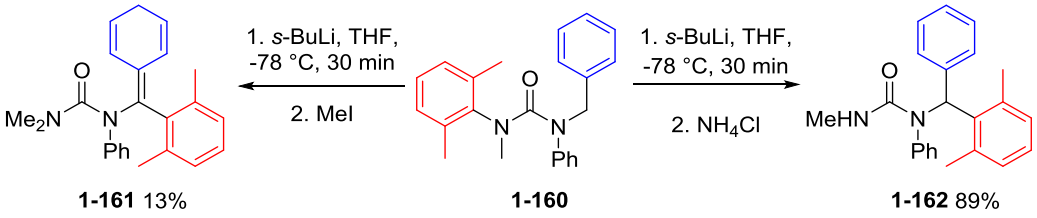
The authors noted that dechlorination of **1-158** with Bu_3SnH and AIBN also resulted in *trans-cis* isomerism affording the *Z*-alkene exclusively. A similar [3,3]-sigmatropic rearrangement of tertiary cyclic α-vinylamines was reported by Back and co-workers.[79] The authors demonstrated a 3-aza-Cope rearrangement under mild conditions for the synthesis of medium ring and macrocyclic structures.

Despite the many methods reported for the synthesis of medium rings by ring expansion and other strategies, the key disadvantage associated with all the methods described is the synthesis of the requisite starting materials. For the transformations to be successful there needs to be a strong driving force for the reaction to proceed, and this typically necessitates the synthesis of appropriate precursors containing carefully arranged functional groups. This is not always a trivial process and in some cases the synthesis of the starting materials is the most challenging part of the process. As a result, a general system which allows access to medium ring structures from simple, easily synthetically accessible starting materials is highly desirable.

1.4 Intramolecular *N*→*C* Aryl and Vinyl Migration

1.4.1 Initial Discovery and Mechanistic Insight

In 2007, whilst studying the regioselective lithiation of *N*-aryl ureas, the Clayden group discovered a new reaction which involved a stereospecific aryl transfer from a urea nitrogen to an sp^3 carbon centre, scheme 1-53.[80]

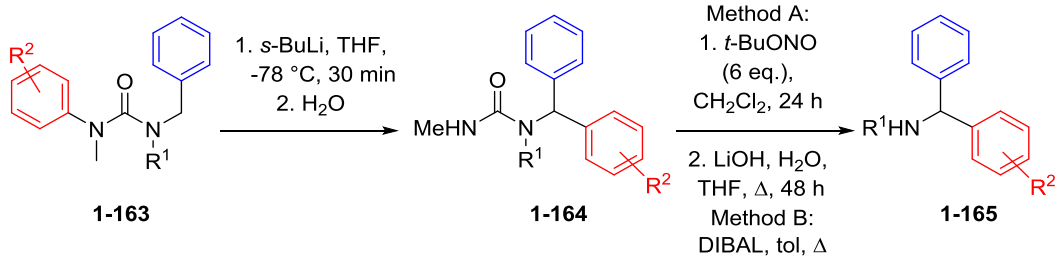


Scheme 1-53: Aryl migration from a lithiated urea.

The discovery was made whilst investigating the site of deprotonation of **1-160**. To probe the deprotonation, *N*-benzyl urea **1-160** was treated with *s*-BuLi and methyl iodide. Purification of the reaction mixture yielded an unstable compound identified as **1-161**, where the 2,6-dimethylphenyl aromatic ring had migrated to the benzylic carbon position. On replacing the methylation with an aqueous ammonium chloride quench the rearranged product **1-162** was isolated in excellent yield.

The rearrangement of a series of *N*-benzyl ureas, **1-163** was performed under similar conditions to demonstrate the generality of the method, table 1-2.

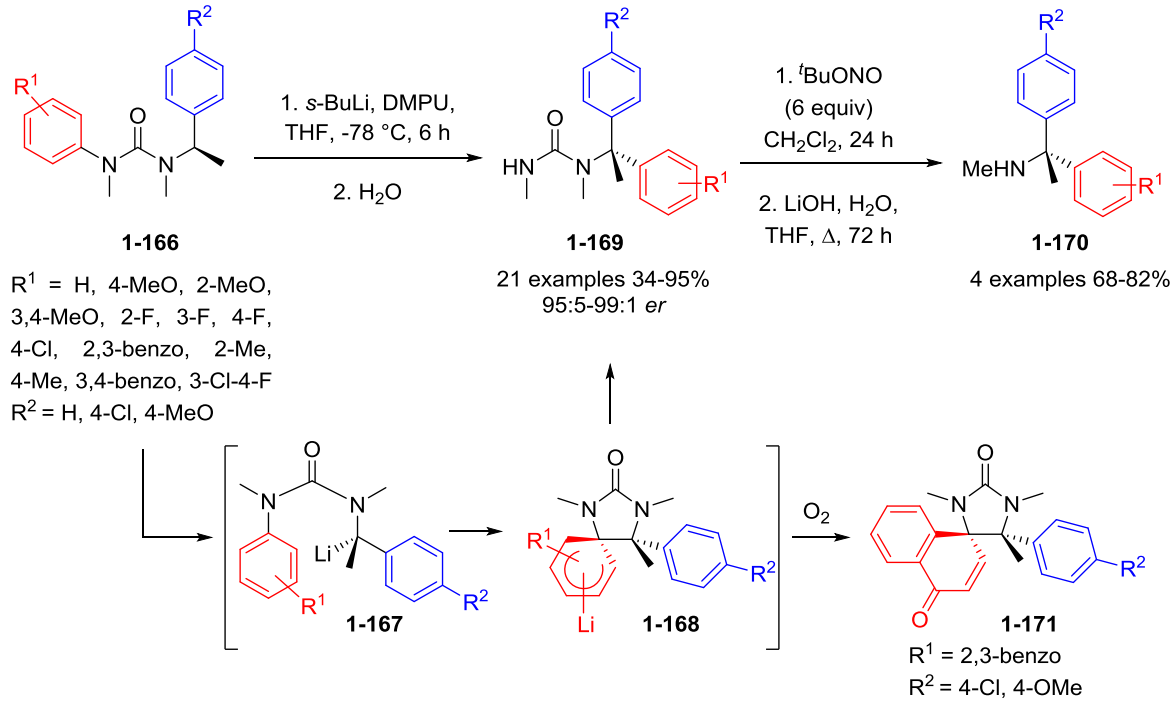
Table 1-2. Aryl migration in lithiated *N*-benzyl ureas, **1-163**.[80]



Entry	R^1	R^2	1-164 yield, %	1-165 yield, % (method)
1	Ph	2,6-diMe	89	-
2	Ph	4-Me	85	-
3	*p*-Tol	H	85	-
4	Me	H	78	84 (B)
5	Me	2-Me	76	72 (A)
6	Me	2-OMe	75	78 (A)
7	Me	2,6-di-Me	82	84 (A)
8	Me	4-Cl	69	-
9	Me	4-OMe	76	-

The results showed that the reaction proceeds in good to excellent yields irrespective of the steric and electronic nature of the substituents on the migrating ring. Subjecting compound **1-164** to DIBAL or hydrolysis of its *N*-nitroso derivative allowed cleavage of the urea yielding the diarylmethylamines **1-165** in good to excellent yields**.**

With the optimal conditions in hand, the efforts of the group turned to the synthesis of quaternary stereocenters through the rearrangement of tertiary lithiated ureas, scheme 1-54.

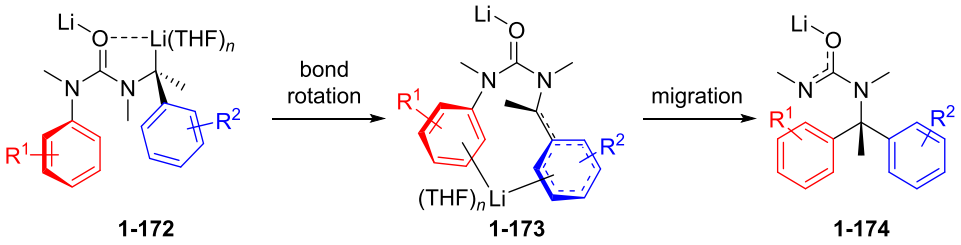


Scheme 1-54. Enantioenriched α-tertiary amines by aryl migration.[80]

Subjecting enantioenriched *α*-methylbenzylurea **1-166** to the optimal conditions resulted in a slower reaction with significant amounts of the starting material still present after 2 hours at –78 °C. With the aim of driving the reaction to completion, the temperature was raised, and the reaction time was lengthened. However, this resulted in the formation of olefinic products arising from elimination of the urea. The addition of additives to deprotonations with organolithium bases can dramatically alter their resulting reactivity.[81,82] Therefore, DMPU (*N,N'*-dimethylpropylene urea) was chosen as an additive to increase the reactivity of the resulting organolithium, as DMPU is a lithium-coordinating solvent which is assumed to work by promoting dissociation of the organolithium to an ion pair.[83] Reactions were accelerated and the resulting migrated ureas **1-169** were isolated in good to excellent yields. Substrates with electron-donating and electron-withdrawing substituents on the aromatic rings migrated in good to excellent yields, including more sterically hindered substrates. In all cases there was minimal loss of enantiopurity demonstrating that the reaction proceeds through a configurationally stable organolithium intermediate **1-167**. Cleavage of the urea afforded the enantioenriched amines **1-170** in good to excellent yields.

Clayden *et al*. offered a mechanism to rationalise the stereospecificity of the aryl migration reaction.[84] They proposed that on treatment of enantioenriched α-methyl urea **1-166** with *s*-BuLi an unusual intramolecular *ipso* S_NAr reaction takes place, proceeding through a 5-membered Meisenheimer complex **1-168**. Evidence of a dearomatised intermediate was supported by the isolation and crystallisation of enone **1-171** when the reaction was carried out under aerobic conditions. Most importantly, the authors reasoned that the highly stereospecific aryl migration was a consequence of proceeding through a configurationally stable organolithium with respect to the timescale of the reaction.

Since then, further mechanistic studies have been carried out, including *in situ* NMR and IR and computational DFT calculations.[85] *In situ* NMR analysis of the aryl migration when using a naphthyl migrating group supported the theory of proceeding through a transient dearomatised intermediate. Despite this, results from the ReactIR performed in the absence of DMPU did not show any observable dearomatised intermediate. DFT calculations provided key information regarding the mechanism, notably highlighting the importance of the coordinated lithium cations, and their migration from one site to another during the reaction. The conformation of the urea is also thought to assist in the unusual reactivity observed. It is suggested that for reaction to occur the dipole-stabilised organolithium **1-172** rotates, adopting a conformation where the carbanion is in close proximity to the remote aromatic ring **1-173**. This rotation allows much of the electronic repulsion to be bypassed, which would prevent an analogous intermolecular arylation from occurring. The solvated lithium cation sandwiches itself between the two aromatic rings, allowing it to stabilise the transfer of negative charge to the migrating aromatic ring, permitting retentive migration.



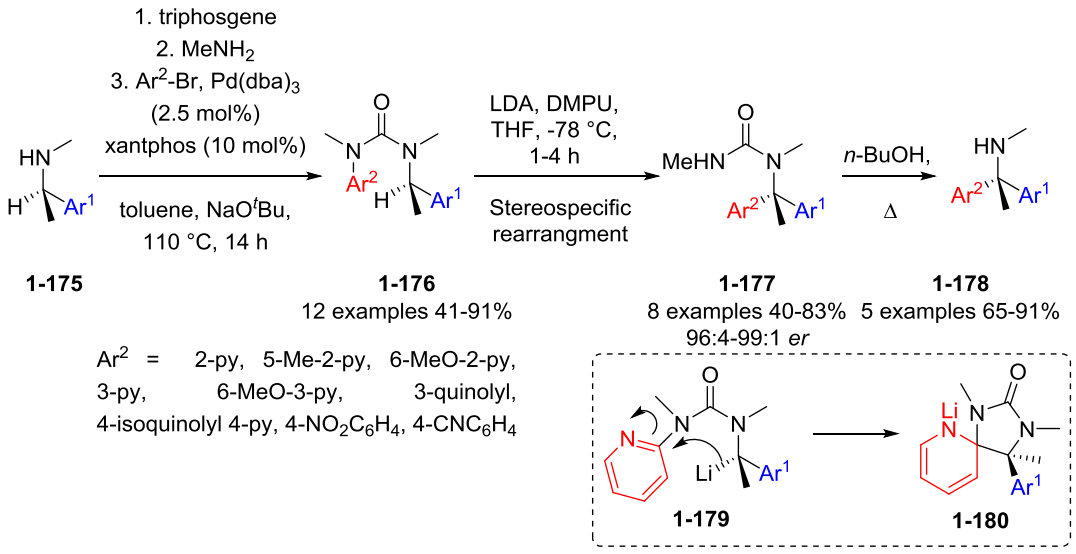
Scheme 1-55. Bond rotation in benzyl ureas allowing retentive migration of aryl group.

Further calculations also revealed that the 1,4-aryl shift was preferred over a 1,2-acyl shift due to having a lower energy transition state.

1.4.2 Substrate Scope

1.4.2.1 N→C Aryl migration Utilising Benzylic Anions

With the knowledge that *N→C* aryl migration is possible utilising benzylic anions, the scope was extended to other systems bearing benzylic centres. The methodology was applied to the *α*-pyridylation of chiral amines by substituting the migrating ring with a pyridine, scheme 1-56.[86]

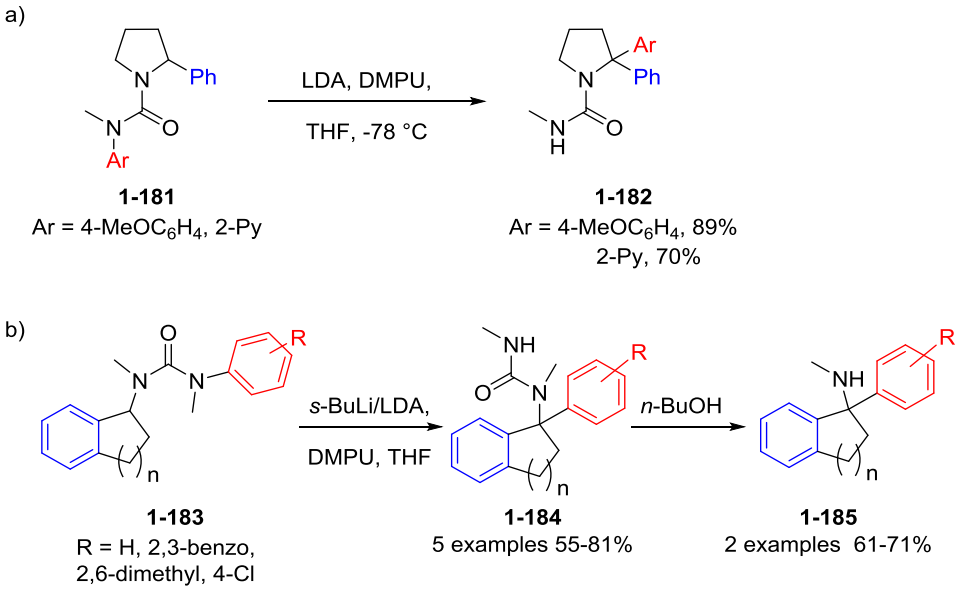


Scheme 1-56. Synthesis and rearrangement of *N*-pyridyl ureas **1-176**.[86]

Synthesis of the *N*-pyridyl ureas **1-176** was achieved by initial phosgenation and treatment with methylamine. Subsequent palladium-catalysed coupling of the bromopyridine with the urea using standard conditions reported for amides[87] afforded the pyridyl ureas **1-176** in good to excellent yields.

Under the conditions previously reported, treatment with *s*-BuLi in THF did not lead to successful rearrangement. Instead, nucleophilic attack of the organolithium base onto the pyridyl ring was observed. To circumvent this issue, LDA, a bulkier less nucleophilic base was chosen, and the reaction proceeded cleanly with excellent stereospecificity. The rearrangement was proposed to occur through a mechanism like that shown in scheme 1-56, where the Li cation 'sits' on the pyridine nitrogen in the intermediate **1-180.** The absence of regioisomeric pyridine products demonstrates that even the 3-pyridyl substitutents are attacked at the *ipso* position, overriding the usual regiochemistry of nucleophilic attack on the pyridine ring. Attempts at removing the urea using conditions previously reported failed to deliver the desired amines **1-178**. However, an alternative strategy of heating the mixture in *n*-butanol proved successful and yielded the desired aminopyridines **1-178** in good yields.

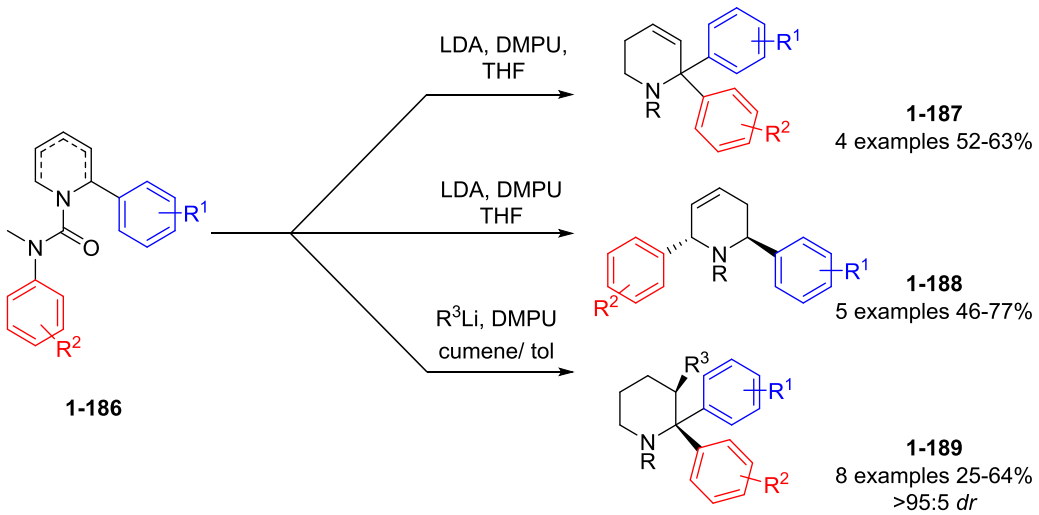
Studies were reported on the application of this aryl migration reaction to cyclic amines, both heterocyclic and carbocyclic.[88] *α*-Aryl pyrrolidines **1-181** were shown to undergo the desired aryl transfer under standard lithiation conditions with DMPU, generating the desired quaternary arylated pyrrolidine **1-182** in excellent yields, scheme 1-57 a.



Scheme 1-57. Aryl migration of pyrrolidine derivatives.[88]

The stereospecific migration of enantiomerically enriched pyrrolidine derivatives **1-181** failed, giving only racemic products. The authors stated that the rearrangement of these substrates was notably slower than the acyclic systems because of a more constrained bicyclic transition state for aryl migration, which allowed racemisation of the organolithium intermediate. A series of carbocyclic compounds with the nitrogen in an exocyclic benzylic position were also trialled using the aryl migration conditions, scheme 1-57 b. Aminoindane (n=1) and aminotetralin (n=2) were converted to the ureas *via* standard methods of coupling with an isocyanate followed by methylation. All ureas trialled gave the desired rearranged products when subjected to either *s*-BuLi or LDA in a THF/DMPU mixture in good to excellent yields.

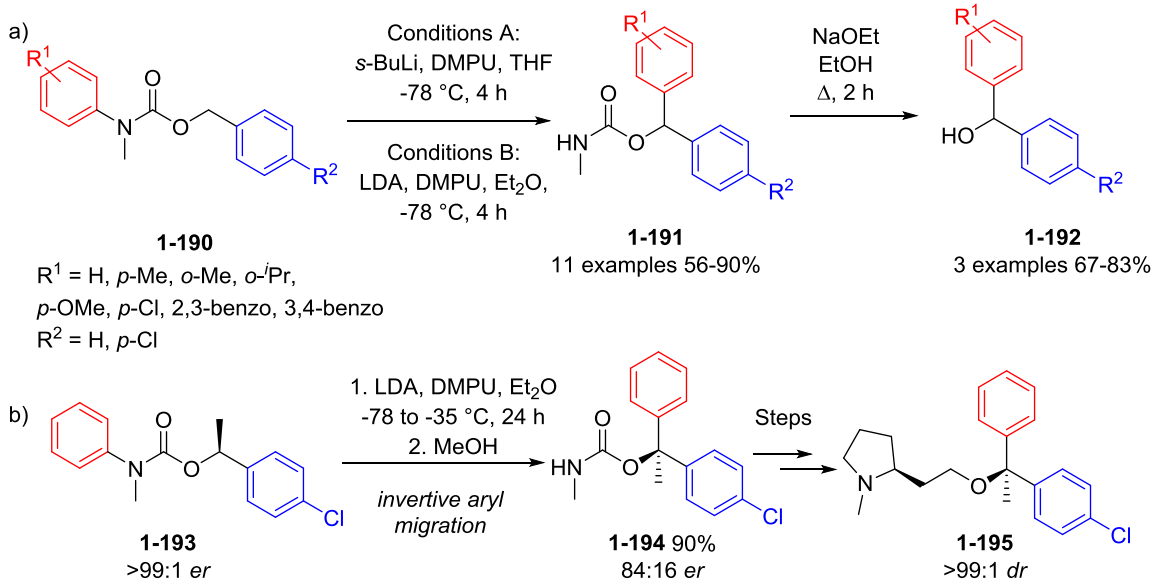
The methodology was then extended to 2-acyltetrahydropyridines, scheme 1-58.[89]



Scheme 1-58. Synthesis of 2,2- and 2,6- diarylpiperidines by *N*→*C* aryl migration.[89]

Depending on the position of unsaturation within the tetrahydropyridine ring **1-186**, *N*→*C* aryl migration by either deprotonation of the benzylic proton, allylic proton or carbolithiation across the alkene double bond led to a range of polysubstituted piperidine derivatives.

This methodology is not limited to ureas and can be applied to alternative heteroatoms *α*- to the benzylic position. Carbamates[90, 91] and thiocarbamates[92] have also been extensively studied, allowing access to arylated alcohols and thiols respectively. As with their urea counterparts, benzylic carbamates undergo facile *N*→*C* aryl migration, providing an alternative synthetic route to α,α-arylated secondary or tertiary alcohols **1-192** in good to excellent yields, scheme 1-59 a.[90]

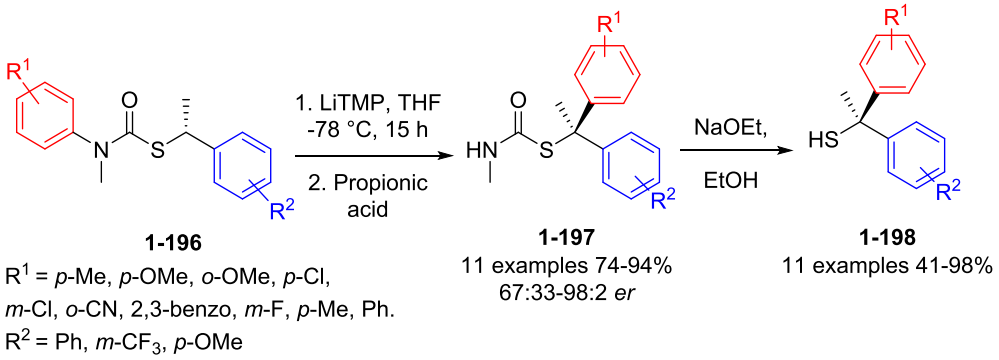


Scheme 1-59. Aryl migration of benzylic carbamates.[90, 91]

The results were similar in the sense that migration occurred irrespective of the electronic or steric nature of the migrating ring. The authors noted that the decreased stability of the intermediate *O*-substituted benzyllithium in strongly lithium coordinating solvents led to diminished enantioselectivity in the products. Therefore, THF was replaced with Et_2O, which led to a significant improvement in the product *er*. In contrast to ureas, carbamates undergo the rearrangement with overall inversion of stereochemistry. DFT calculations showed that due to the high affinity of lithium for oxygen, the lithium cation remains bonded to the carbamate oxygen in the lowest energy transition state. Consequently, the

carbamate O-Li bond positions itself away from the incoming arene, resulting in aryl migration and inversion of stereochemistry. To highlight the utility of the methodology, it was used in the first enantioselective synthesis of antihistamine agent (-)-(*S*,*S*)-clemastine **1-195**, scheme 1-59 b.[91]

The aryl transfer reaction has also been extended to analogous thiocarbamates utilising benzylic anions.[92] Lithiation of *N*-aryl *S*-*α*-alkylated thiocarbamates led to *N*→*C* migration of the aryl ring to the carbon centre *α* to sulfur. Like ureas, the migration proceeded with retention of overall stereochemistry and delivered chiral benzylic tertiary thiols **1-198** in good to excellent enantioselectivities, scheme 1-60.

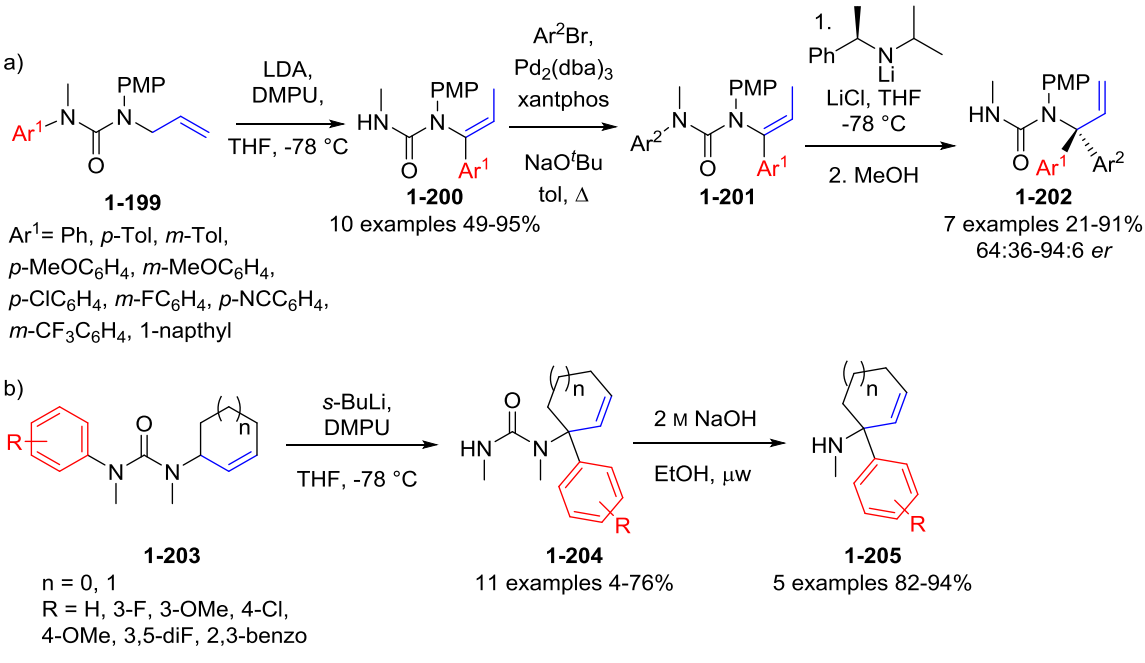


Scheme 1-60. Aryl migration in benzylic thiocarbamates to synthesise tertiary thiols.[92]

Similar to carbamates, the benzyllithium intermediate is less configurationally stable than the urea analogue leading to poor *er*s when lithiating with *s*-BuLi/LDA in THF/DMPU. This problem was overcome by replacing the organolithium base with a bulkier base, LiTMP and lithiating in the absence of DMPU, which resulted in almost complete stereospecific rearrangement.

1.4.2.2 Aryl Migration Utilising Other Nucleophiles

With regards to the anion stabilising group, groups other than benzyl groups have been shown to be successful in the rearrangement. Allyl groups have also shown promise as anion stabilising groups for the *N*→*C* aryl migration reaction, scheme 1-61.[93, 94]

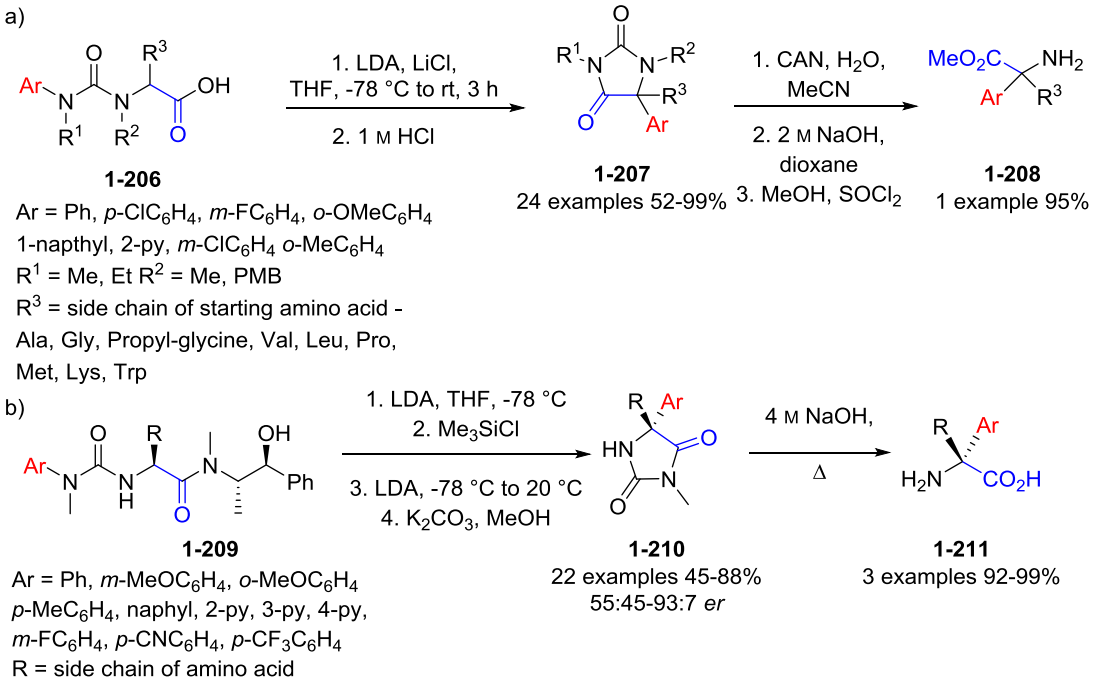


Scheme 1-61. *N*→*C* aryl migration exploiting allyl ureas.[93, 94]

1,1-Diarylallyamine derivatives were generated exploiting a sequential double α-arylation starting from *N*-allyl-*N*′-aryl ureas **1-199**.[93] *N*-Allyl-*N*′-aryl ureas were deprotonated on addition of LDA yielding an allyl lithium which rapidly rearranged by intramolecular *N*→*C* aryl transfer generating arylated vinyl ureas **1-200**. The products, after introducing a new aryl group *via* Buckwald Hartwig amination can then undergo a second *N*→*C* aryl migration reaction yielding 1,1-diarylallylamine products **1-202** after γ-protonation of the allylic anion.

It was also possible to make the second aryl transfer enantioselective using a chiral lithium amide, which generated highly enantioenriched diarylallyl ureas **1-202**. Allyl ureas **1-203** were also shown to undergo *N*→*C* aryl migration, scheme 1-61 b.[94] Lithiation at the allylic carbon allowed access to a range of α-quaternary urea derivatives **1-204** in varying yields. The utility of the method was demonstrated by performing the reaction on a multi-gram scale.

Dianionic enolates formed from *N*-aryl urea derivatives of amino acids undergo the same intramolecular *N*→*C* migration, scheme 1-62 a.[95, 96]



Scheme 1-62. Aryl migration in amino acid enolates.[95, 96]

In the cases reported, aryl migration was quickly followed by cyclisation to the corresponding hydantoin **1-207**, which could then be converted to biologically important quaternary amino acids. Interestingly, the reaction used a non-stabilised enolate nucleophile, unlike the previous work which required a group to stabilise the anion prior to rearrangement. A series of natural and unnatural amino acids were derivatised as ureas and subjected to the optimised conditions for the aryl migration. Quenching with dilute HCl solution delivered the desired hydantoins **1-207**. Hydrolysis of a hydantoin allowed the isolation of a quaternary amino acids as its methyl esters **1-208**. Since the deprotonation to form an enolate proceeds through a planar enolate anion, the previously reported migration generated only racemic products **1-207**.

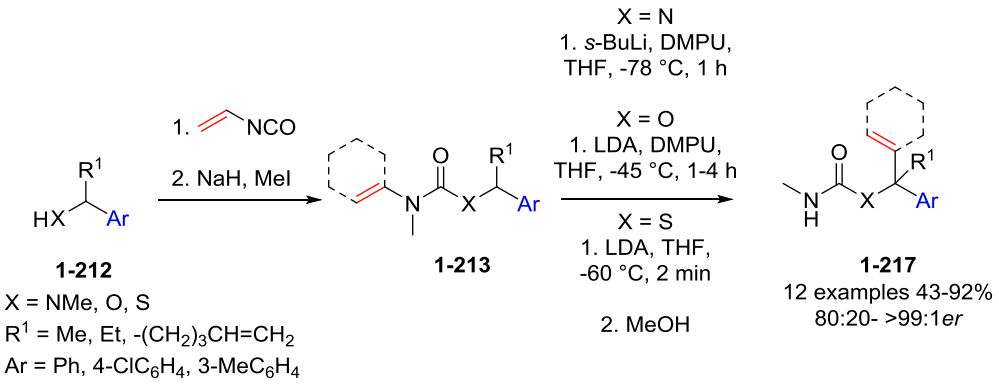
In 2015, Atkinson *et al.* reported the asymmetric *α*-arylation of *α*-amino acid derivatives using a pseudoephedrine chiral auxiliary, scheme 1-62 b.[96] *In situ* silylation and enolisation induced the diastereoselective migration of an aryl group to the *α*-amino acid carbon. This was rapidly followed by ring closure to the hydantoin, which expelled the auxiliary. The enantiomerically enriched hydantoins were then hydrolysed affording the *α*-arylated quaternary amino acids **1-211** in good enantiomeric

ratios. This method provides an alternative to metal-catalysed α-arylation of amino acids which has potential industrial importance.

The efforts of the group then turned to applying this chemistry to the asymmetric synthesis of α-aryl proline derivatives.[97] The synthesis of *α*-aryl proline derivatives has not been widely explored and those that have investigated it have scopes limited to electron-deficient aryl rings.[98] Prolines substituted in positions 3- or 5- underwent successful aryl migration, delivering the desired bicyclic or tricyclic hydantoin derivatives in high diastereoselectivity. Aryl migrations were successful for both electron-rich and electron-deficient aryl rings. Subsequent hydrolysis of the hydantoins with 4 M sodium hydroxide generated the enantiopure quaternary proline derivatives which hold potential as scaffolds for medicinal chemistry.

1.4.3 *N*→*C* Vinyl Migration

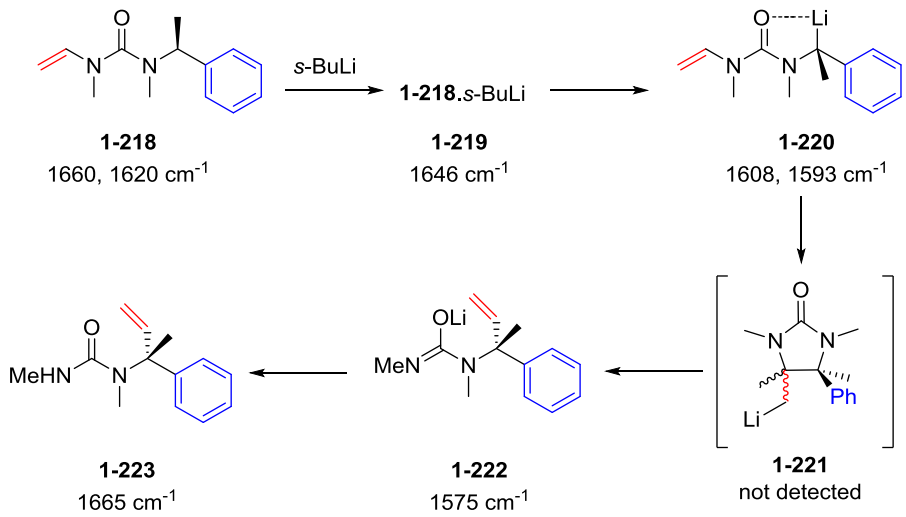
Due to the *N*→*C* aryl migration working efficiently even with the most electron-rich aromatic rings, investigations were carried out to see if the analogues vinyl migration was possible. Indeed, successful vinyl migration was achieved on lithiated benzylic ureas, carbamates and thiocarbamates, scheme 1-63.[99]



Scheme 1-63. Vinyl migration of ureas, carbamates and thiocarbamates.[99]

For urea substrates the migration was possible with *s*-BuLi. However, LDA was needed for both carbamates and thiocarbamates to avoid nucleophilic attack of the organolithium base. A one-pot reaction (urea formation, rearrangement and deprotection) for the urea analogues was carried out, followed by crystallisation of the resulting amine by addition of anhydrous HCl. This allowed the determination of stereochemistry by X-ray crystallography and showed that the migration had occurred with retention of stereochemistry.

ReactIR was used to probe the reaction mechanism further, scheme 1-64. To avoid obscuring the carbonyl region of the spectrum, the reactions were carried out in the absence of DMPU.[99]

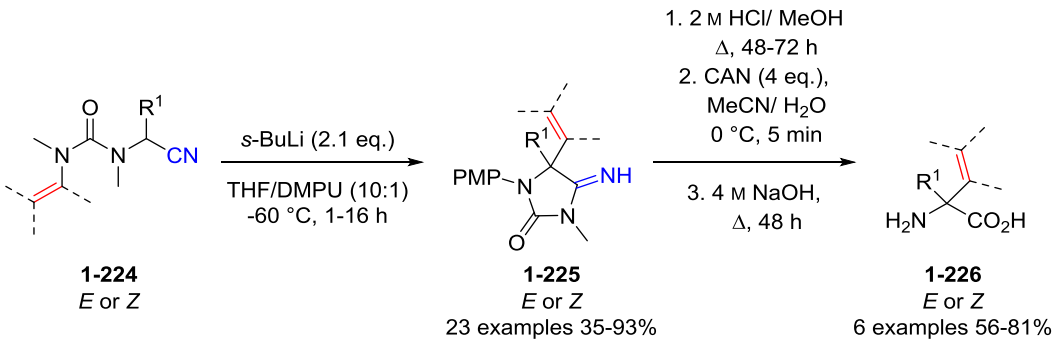


Scheme 1-64. Proposed intermediates in vinyl migration probed by ReactIR.[99]

The starting urea **1-218** displayed two absorptions at ν =1660 and 1620 cm^{-1} at −78 °C in THF. On lithiation with *s*-BuLi, these absorptions disappeared and were replaced with an absorption at ν = 1575 cm^{-1}, which was assigned to rearranged product **1-222**. No obvious intermediates were detectable. Knowing that the migration reactions were slower in Et_2O, experiments were conducted in Et_2O with or without LiCl as an additive. Addition of *s*-BuLi to **1-218** gave a transient absorption at ν = 1646 cm^{-1}, which disappeared over a period of seconds to a new intermediate with two absorptions at ν = 1608 and 1593 cm^{-1}. Quenching at this point returned starting material, so it was assumed that this intermediate may be a pre-lithiated complex **1-219**, which is converted to an intermediate lithiated urea **1-220**. The authors stated that slow warming of the reaction mixture to room temperature encouraged the rearrangement and the ν = 1608 and 1593 cm^{-1} absorptions decreased in intensity. At −15 °C a new absorption appeared at ν = 1575 cm^{-1}, which was previously assigned to **1-222** due to confirmation by treating the product **1-223** with *s*-BuLi and obtaining the same spectrum. It was suggested that the mechanism proceeded through a cyclic structure **1-221**, although there was no evidence for this by ReactIR.

DFT calculations showed the coordination of the Li cation to the π system of the phenyl ring. On formation of the carbon-carbon bond the transition state is proposed to have the Li cation on the terminal carbon of the vinyl group to help stabilise the build-up of negative charge resulting in retention of stereochemistry. Following this, it is proposed that the breakage of the carbon-nitrogen bond has the Li cation coordinating to the urea functionality to stabilise the negative charge.

More recently, the group extended the vinylation to tertiary amino nitriles, allowing the synthesis of alkenylated hydantoins, scheme 1-65.[100]

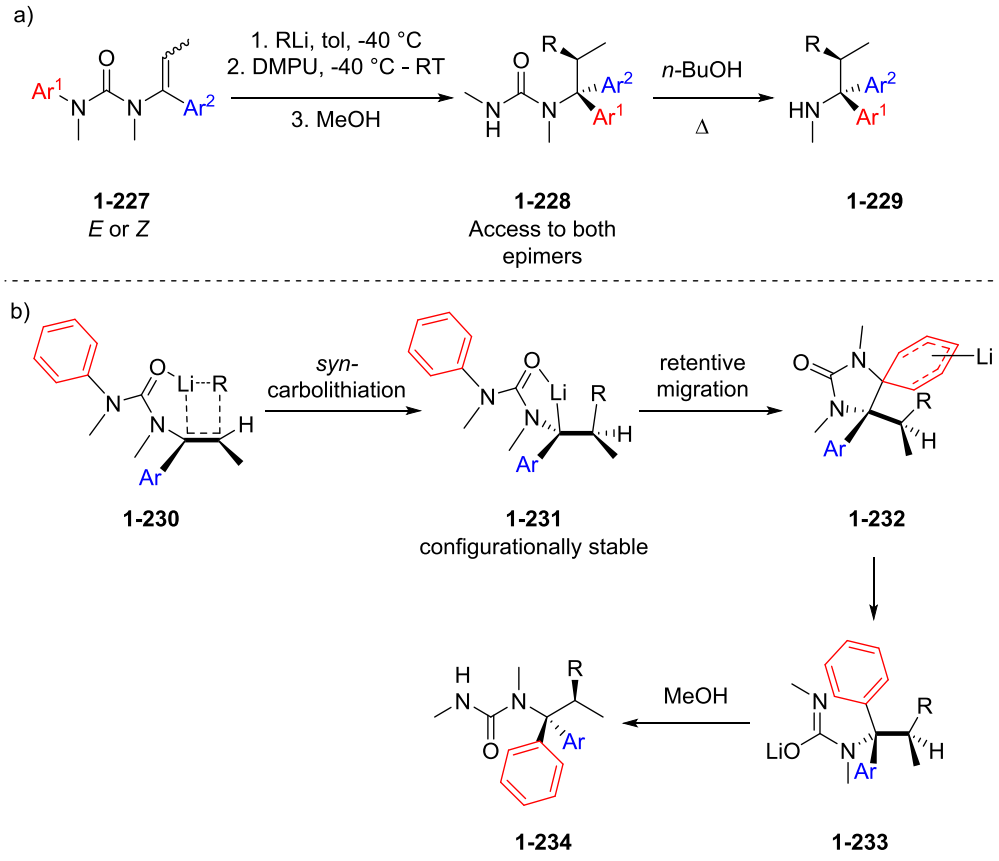


Scheme 1-65. Stereodivergent alkenylation by *N*→*C* vinyl migration.[100]

Lithiation of ureidonitrile **1-224** with *s*-BuLi in DMPU and THF promoted migration of the *N*'-alkenyl group with retention of double bond geometry. The method is stereodivergent with both the *E* and *Z* isomers being accessed from the same allyl starting material by alkene isomerisation. Upon basic hydrolysis of the hydantoin products **1-225**, quaternary α-alkenyl amino acids **1-226** were afforded as single *E* or *Z* isomers.

1.4.4 Tandem Carbolithiation – Rearrangement

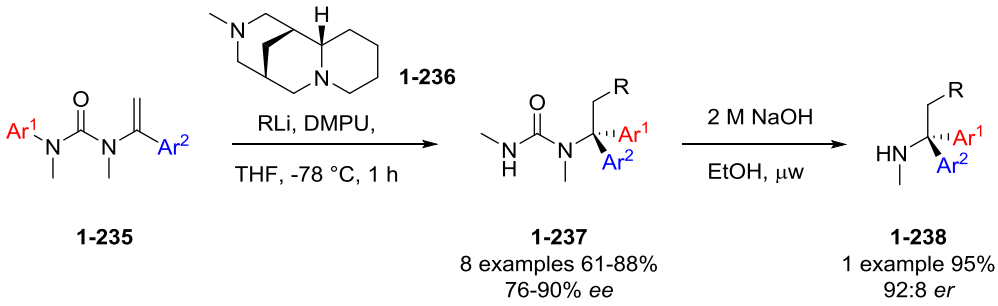
N-Alkenyl ureas **1-227** possess umpolung reactivity, undergoing addition of organolithiums to their otherwise nucleophilic β-carbons.[101] This carbolithiation step can be coupled with the *N*→*C* aryl migration reaction generating two new C-C bonds in a single pot, scheme 1-66. Products were isolated in good to excellent yields with diastereoselectivities greater than 95:5. Both the carbolithiation and rearrangement steps were stereospecific, since inverting the double bond geometry in the starting material or exchanging the aromatic rings changed the configuration of the product.



Scheme 1-66. Carbolithiation-rearrangement of *N*-vinyl ureas **1-227** and potential reaction mechanism.[101]

The reaction was presumed to occur by *syn*-carbolithiation, which forms a configurationally stable organolithium **1-231**. This undergoes retentive migration of the aryl ring from *N*→*C*, delivering rearranged product **1-234** after a methanol quench scheme 1-66 b. This methodology has been applied to both alkenylcarbamates[102] and alkenylthiocarbamates[103] for the synthesis of heavily substituted alcohols and thiols respectively.

This tandem carbolithiation-rearrangement methodology has been applied to β-unsubstituted ureas **1-235** for the asymmetric synthesis of tertiary amines **1-238**, scheme 1-67.[104]



Scheme 1-67. Asymmetric tandem carbolithiation-rearrangement using (+)-sparteine surrogate.[104]

The initial carbolithiation proceeded stereoselectively by employing (-)-sparteine or (+)-sparteine surrogate as a chiral diamine ligand. The subsequent stereospecific retentive aryl migration allowed access to the enantiomerically enriched ureas **1-237** in high yields. The corresponding amines **1-238** were isolated basic hydrolysis.

In summary, Clayden and co-workers have developed an efficient method for the synthesis of racemic and heavily substituted and enantioenriched amines, alcohols and thiols. Nucleophiles such as benzylic and allylic anions, enolates and nitrile anions were successful in achieving migration of an aryl or vinyl group from nitrogen to an sp^3 carbon centre. This unique method overcomes the challenge of coupling an anion with an unactivated aryl or vinyl 'electrophile'.

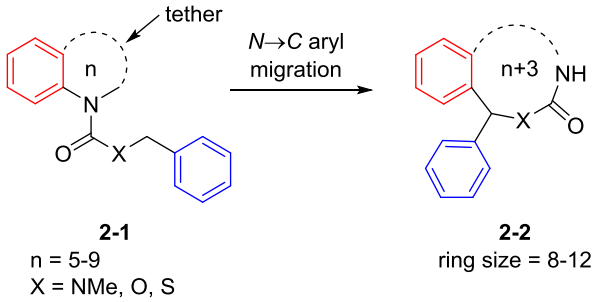
Due to the vast array of substrates this *N→C* aryl migration protocol has been successfully applied to, it was hoped that an extension of this methodology would allow a general approach towards synthesising medium ring products by a novel ring expansion reaction.

2. Results and Discussion

2.1 Aims of the Project

As described in section 1.4, Clayden and co-workers have developed an intramolecular *N→C* aryl migration reaction on ureas, carbamates and thiocarbamates, utilising different nucleophiles. However, until now only acyclic systems have been investigated, where the migrating aromatic ring is bonded solely to the urea nitrogen and the urea nitrogen is typically substituted with a methyl.

The aim of this project was to investigate the possibility of using this *N→C* aryl migration protocol for the synthesis of medium ring structures by tethering the urea nitrogen as part of a ring, scheme 2-1. It was hypothesised that *N→C* aryl migration by *ipso* S_NAr at the migrating ring and cleavage of the aryl carbon-nitrogen bond would lead to a *n+3* ring expansion of the starting ring size.



Scheme 2-1. Potential ring expansion exploiting *N→C* aryl migration.

If viable, it was hoped that this would offer an efficient and general synthesis of benzannulated medium ring structures, while addressing the challenges facing other ring expansion methods, where pre-organisation of the fragmentation precursors through typically lengthy syntheses is essential for successful ring expansion (see section 1.3.5).

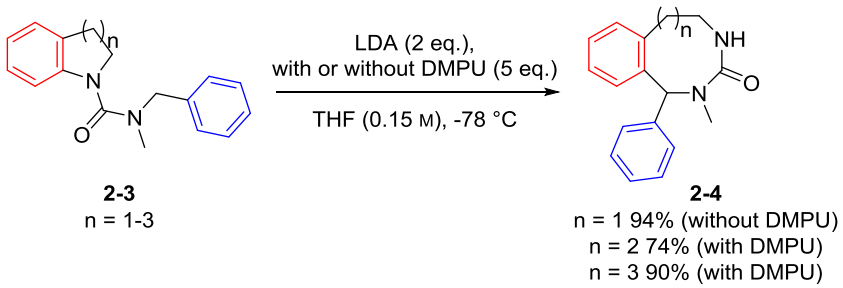
The initial aim of the project was to utilise benzylic anions for the ring expansion before exploring alternative nucleophiles. Firstly, a simple general method for the synthesis of the ring expansion precursors would need to be developed, where possible exploiting commercially available nitrogen heterocycles with varying electronic and steric parameters. The ring expansion of more complex structures would also be studied, allowing factors such as diastereoselectivity and stereospecificity of the reaction to be investigated. It was hoped that if possible, the ring expansion could be applied to both carbamate and thiocarbamate precursors, allowing a range of benzannulated medium ring structures to be accessed.

2.2 Medium Ring Nitrogen Heterocycles by Migratory Ring Expansion of Lithiated Ureas

N.B. The work described herein (section 2.2) is documented in the first author publication, J. E. Hall.; J. V. Matlock.; J. W. Ward.; K. V. Gray, J. Clayden. Angew. Chem. Int. Ed.* ***2016****, 55, 11153.*

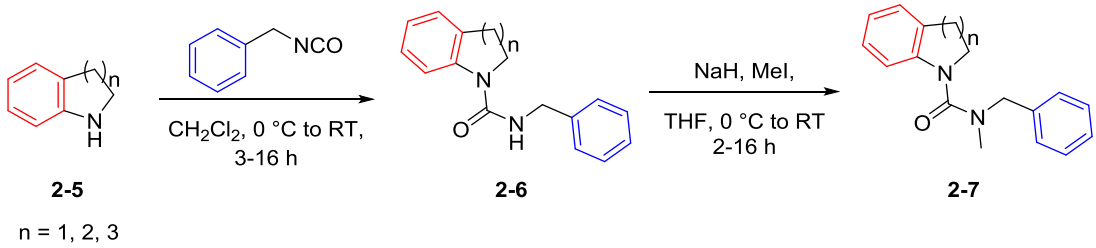
2.2.1 Previous Work

Preliminary work investigating the ring expansion of nitrogen heterocycles by *N*→*C* aryl migration showed that this route was viable and yielded medium rings in good to excellent yields, scheme 2-2.



Scheme 2-2. Preliminary ring expansion results.[*]

5- To 7-membered commercially available nitrogen heterocycles were transformed into their benzyl urea counterparts by a two-step procedure involving coupling of the parent nitrogen heterocycles with isocyanate followed by *N*-methylation, scheme 2-3. The yield of the methylation step significantly reduced on increasing the size of the nitrogen heterocycle and therefore presented a problem for using this synthetic procedure for the synthesis of larger ring sizes.

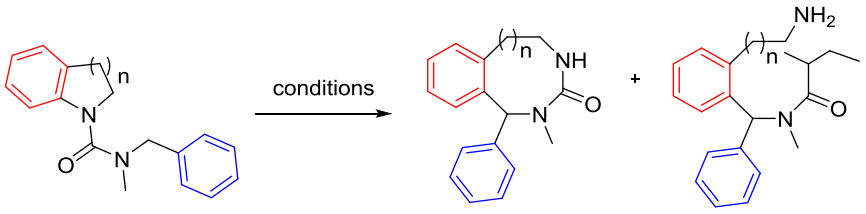


Entry	n	Yield 2-6 %	Yield 2-7 %
1	1	60	99
2	2	93	65
3	3	86	33

Scheme 2-3. Synthesis of urea starting materials *via* isocyanate coupling and methylation.

Due to the ease of synthesis, indoline urea **2-7** was chosen as a model substrate to explore optimisation of the reaction conditions. Using the reported conditions for the *N*→*C* aryl migration in acyclic systems, *s*-BuLi in THF at −78 °C for two hours, the desired 8-membered ring was isolated in 62% yield, (scheme 2-4, entry 1).

[*] Experiments carried out by Katharine Gray and Dr John Ward



2-7 **2-4** **2-8**

Entry	n	Base, eq.	Additive, eq.	Temp °C	Time, h	2-4, %[a]	2-8, %[a]
1	1	*s*-BuLi, 2	-	−78	2	62	25
2	1	*s*-BuLi, 2	-	−78	4	12	69
3	1	LDA, 2	-	−78	4	94	-
4	2	LDA, 2	DMPU, 5	−78	4	74	-
5	3	LDA, 2	DMPU, 5	−78	4	90	-

[a]Ratios reported as observed in the ^{1}H NMR of the crude material.

Scheme 2-4. Ring expansion of 5-membered indoline precursor **2-7** and optimisation of conditions.

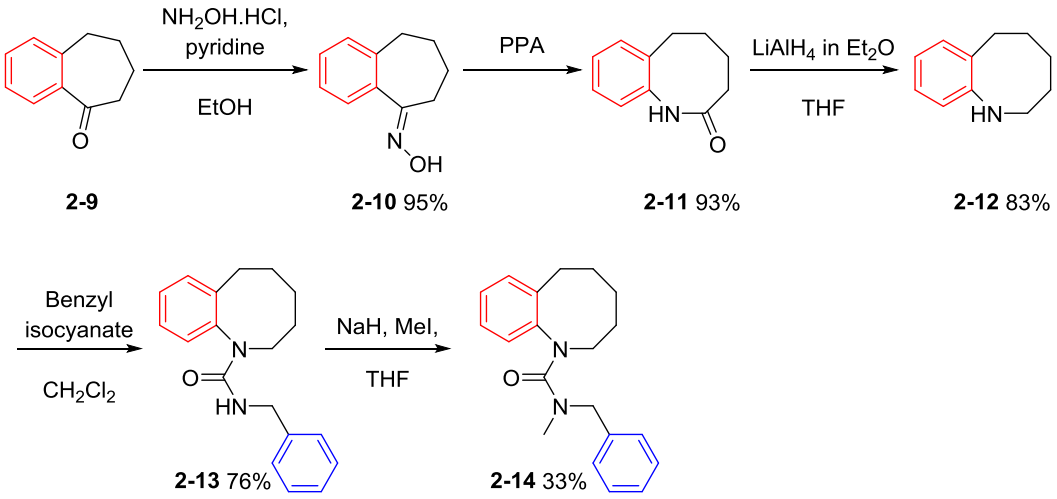
Analysis of the ^{1}H NMR spectrum of the crude material showed that a side product arising from initial ring expansion and subsequent nucleophilic attack of the *s*-BuLi at the carbonyl was also present in the reaction mixture (scheme 2-4, entry 1). Leaving the reaction for longer only increased the amount of this side product thereby reducing the amount of the desired 8-membered ring **2-4** (scheme 2-4, entry 2). Pleasingly, on replacing *s*-BuLi with LDA, a bulkier non-nucleophilic base, the undesired ring opened side product was not observed and the reaction gave the desired 8-membered ring expansion product in 94% as a ratio from the ^{1}H NMR of the crude material (scheme 2-4, entry 3). Subjecting 6- and 7-membered urea precursors to the optimised reaction conditions gave the corresponding 9- and 10-membered rings in good yields, albeit requiring longer reaction times. With the knowledge that DMPU can increase the reactivity of the organolithium by aiding deaggregation of the LDA,[81] DMPU was added to the reaction mixture. The desired 9- and 10-membered rings were isolated in 74% and 90% respectively, (scheme 2-4 entries 4 and 5).

2.2.2 Synthesis of Ring Expansion Urea Precursors

Having already showed that 8-, 9- and 10-membered nitrogen heterocycles were accessible by this methodology (see section 2.2.1), it was hoped that we could extend this to the synthesis of the full range of medium sized rings (8- to 12-members). Hence, it was essential to synthesise the 8- and 9- membered urea precursors, which after *N→C* aryl migration would allow access to the previously unexplored 11- and 12- membered cyclic ureas. In contrast to the smaller ring precursors investigated thus far, the 8- and 9-membered cyclic precursors are not commercially available and therefore needed to be synthesised prior to attempting the ring expansion.

2.2.2.1 Synthesis of 8-Membered Ring Expansion Precursor

A synthetic strategy commencing from commercially available benzosuberone **2-9** utilising a Beckmann rearrangement as the key step was devised, scheme 2-5.

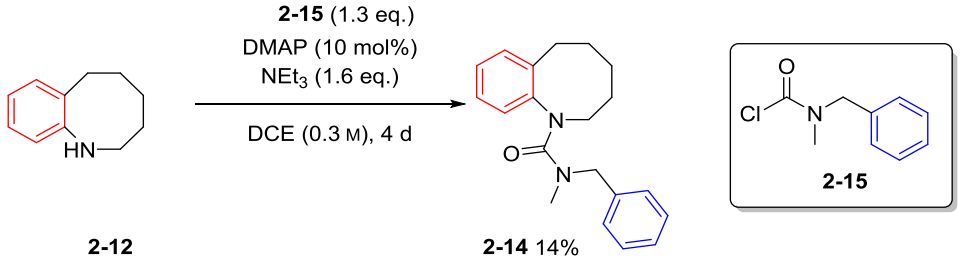


Scheme 2-5. Synthesis of 8-membered rearrangement precursor, **2-14**.

Following a literature procedure,[105] treatment of benzosuberone **2-9** with hydroxylamine hydrochloride and pyridine in ethanol resulted in oxime **2-10** in near quantitative yield. Heating oxime **2-10** in polyphosphoric acid (PPA) gave the desired Beckmann rearrangement lactam product **2-11**, which was reduced to the corresponding amine upon treatment with lithium aluminium hydride, with both reactions proceeding in good yields. Coupling of the 8-membered cyclic amine **2-12** with benzyl isocyanate afforded the desired urea in 76% yield. However, as anticipated, the methylation step was low yielding. This prompted us to investigate an alternative, more efficient strategy for tethering on the urea that could then be applied to all substrates, regardless of ring size.

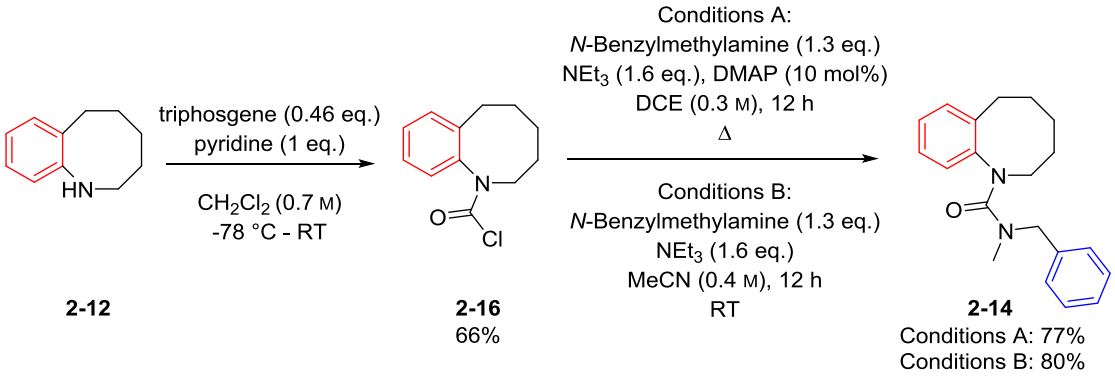
2.2.2.2 Devising a General Strategy for Tethering on Urea

With the prior knowledge that the methylation of the urea nitrogen after isocyanate coupling is significantly hindered by ring size of the starting precursor, an alternative route to the urea starting materials was of interest. 8-Membered cyclic amine **2-12** was chosen as the model substrate for these studies. It was thought that reacting amine **2-12** with benzyl(methyl)carbamoyl chloride **2-15** would generate the urea precursor in one step, scheme 2-6.



Scheme 2-6. Alternative strategy to precursor **2-14**.

Unfortunately, subjecting amine **2-12** to carbamoyl chloride **2-15** in the presence of triethylamine and 4-dimethylaminopyridine (DMAP) in dichloroethane, resulted in the desired urea in a disappointing yield of 14% after four days. This can be attributed to the reduced nucleophilicity of the 8-membered amine ring **2-12**, due to steric hindrance. To overcome this, the synthetic strategy was modified, and the carbamoyl chloride of the 8-membered cyclic amine **2-16** was synthesised, scheme 2-7.

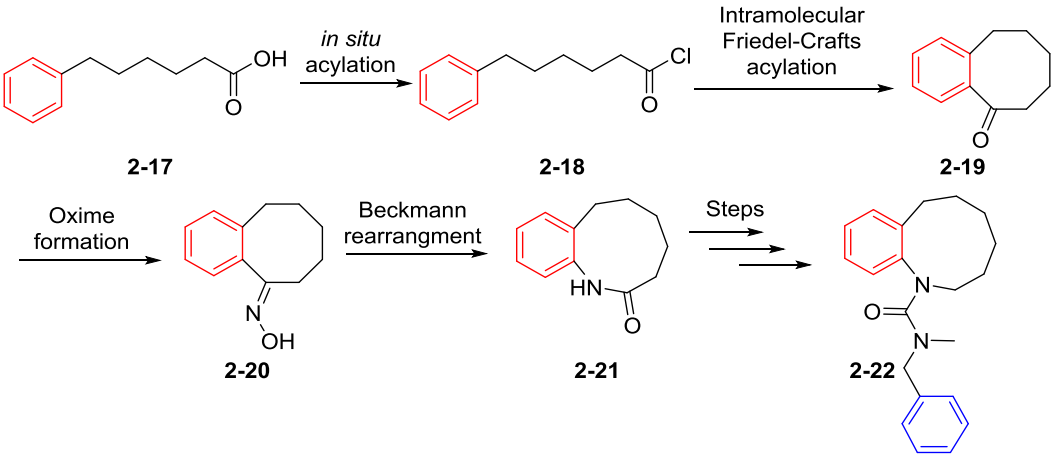


Scheme 2-7. Modified strategy for synthesis of 8-membered ring expansion precursor **2-14**.

Urea formation was achieved in two steps from **2-12**. Phosgenation with triphosgene and pyridine gave carbamoyl chloride **2-16** in good yield without the need for further purification. The resulting carbamoyl chloride was reacted with *N*-benzylmethylamine in the presence of triethylamine and catalytic DMAP in dichloroethane (conditions A, scheme 2-7). Pleasingly, the desired cyclic urea precursor was afforded in 77% yield. The amination step was further modified by removing DMAP and dichloroethane and using acetonitrile as the solvent at room temperature (conditions B, scheme 2-7). This gave the desired urea in a slightly higher yield of 80%. As a result, conditions B were chosen for tethering on the urea to the cyclic amine precursors.

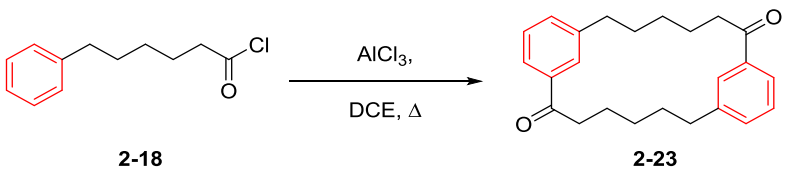
2.2.2.3 Synthesis of 9-Membered Ring Expansion Precursor

As was the case with the 8-membered cyclic amine, the 9-membered cyclic amine was not commercially available and therefore needed to be synthesised prior to ring expansion to access the 12-membered ring. Unfortunately, the 8-membered cyclic ketone analogous to benzosuberone **2-9** was also not available from commercial sources. Given that the Beckmann rearrangement proved to be an efficient strategy, synthesis of the corresponding 9-membered cyclic ketone was undertaken, scheme 2-8.



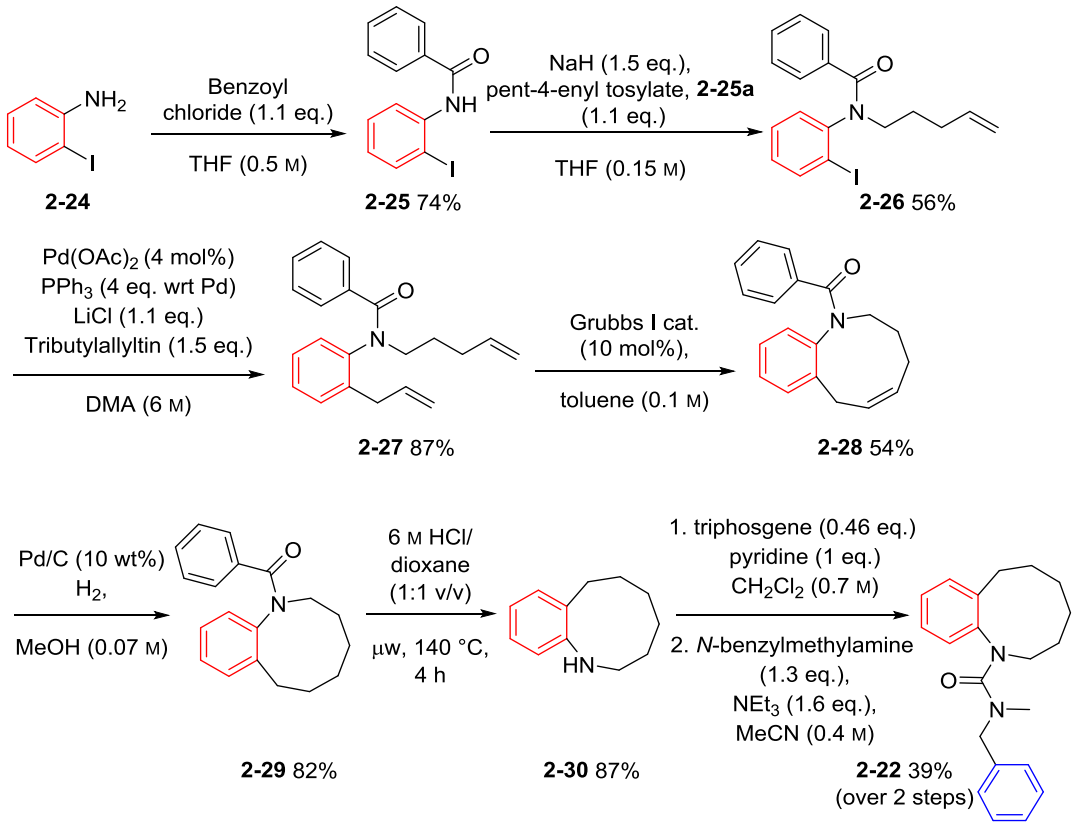
Scheme 2-8. Planned synthetic strategy to access 9-membered ring expansion precursor **2-22**.

The first step involved *in situ* formation of an acyl chloride by subjecting 6-phenylhexanoic acid **2-17** to oxalyl chloride in dichloromethane. Attempts were made towards the intramolecular Friedel-Crafts acylation to form cyclic ketone **2-19**. Aluminium trichloride was added to the acyl chloride in dichloroethane and heated to reflux. Unfortunately, the desired 8-membered cyclic ketone was not isolated and mass spectrometry suggested the formation of a dimeric species **2-23**, scheme 2-9.



Scheme 2-9. Dimer formation under Friedel-Crafts acylation conditions.

Although repeating the reaction at high dilution and using syringe pump addition of the acyl chloride avoided the formation of a dimeric species, mass balance was poor, and the product was isolated in a 15% yield. The work-up procedure was altered in the hope of gaining an improved yield as it was speculated that the formation of aluminium salts hindered product isolation. The water quench was replaced with pouring the reaction mixture onto an ice and concentrated HCl mixture. Despite this, the yield for the desired product was 20% by examination of the ^{1}H NMR spectrum with an internal standard. As a result, this route was abandoned and an alternative synthetic strategy exploiting ring closing metathesis as a key step was devised, scheme 2-10.

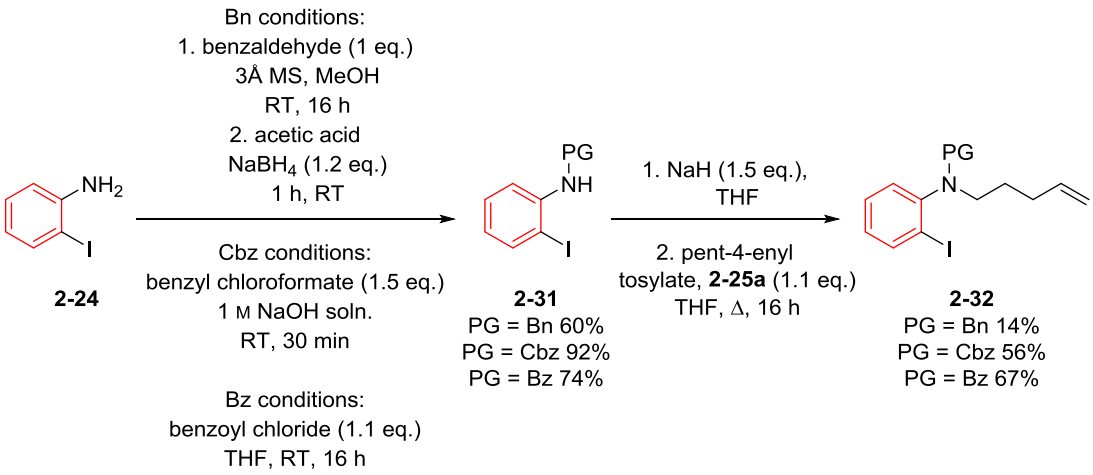


Scheme 2-10. Synthesis of 9-membered ring expansion precursor **2-22**.

The lengthy synthesis required to access **2-22** highlights the difficulties associated with the synthesis of medium-sized rings. The first steps towards the synthesis of **2-22** involved amine protection of 2-iodoaniline **2-24**, followed by alkylation to append the first alkene tether. Stille coupling allowed the introduction of another alkene tether to prepare the di-alkene compound **2-27**, which is then set up for the ring closing metathesis step. Treatment of the alkene **2-27** with Grubbs' first-generation catalyst led to cyclic amine **2-28**, which after hydrogenation resulted in the protected 9-membered cyclic amine **2-29**. Finally, a deprotection step was needed to afford the desired cyclic amine, to which the urea could then be attached.

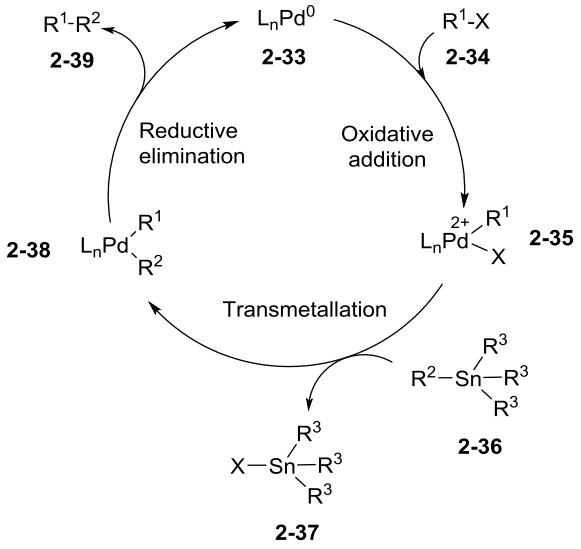
Careful choice of a protecting group at the start of the synthesis was required to avoid unnecessary deprotection steps. As a result, a benzyl group was selected to protect the aniline nitrogen as it was

envisaged that this would be removed under hydrogenation conditions needed to reduce the internal alkene later in the synthesis.



Scheme 2-11. Alternative amine protecting groups and subsequent alkylation.

Although protection proceeded cleanly following literature procedure,[106] the alkylation that followed was problematic and efficient separation of the desired product **2-32** from unreacted starting material was not possible. As a result, 2-iodoaniline was protected with an alternative protecting group, carboxybenzyl (Cbz), which can also be cleaved by hydrogenation. As before, the protection step proceeded smoothly[107], however once more the alkylation was found to be low yielding and the alkylated product **2-32** was unable to be isolated cleanly. Lastly, a benzoyl protecting group was utilised. Facile protection[108] was followed by alkylation resulting in the formation of **2-32** in a higher yield of 67%, which was separable from starting material. Although the benzoyl group cannot be cleaved by hydrogenation, it was hoped that it could be easily removed by acidic or basic hydrolysis. With alkylated product **2-32** in hand, effort was directed towards the Stille coupling to install the second alkene tether. The Stille reaction involves the coupling of an organohalide with an organostannane to obtain a coupled product *via* the use of a palladium catalyst. Subjecting **2-32** to Stille conditions, $Pd(OAc)_2$, PPh_3, LiCl and finally tributylallyltin allowed successful generation of di-alkene **2-27** in excellent yield. It was found that the optimal work-up technique involved washing the reaction mixture with 1 M KF solution,[109] which promoted the precipitation of tin by-products, allowing the mixture to be further purified by flash column chromatography. The Stille cross-coupling catalytic cycle is shown in scheme 2-12.



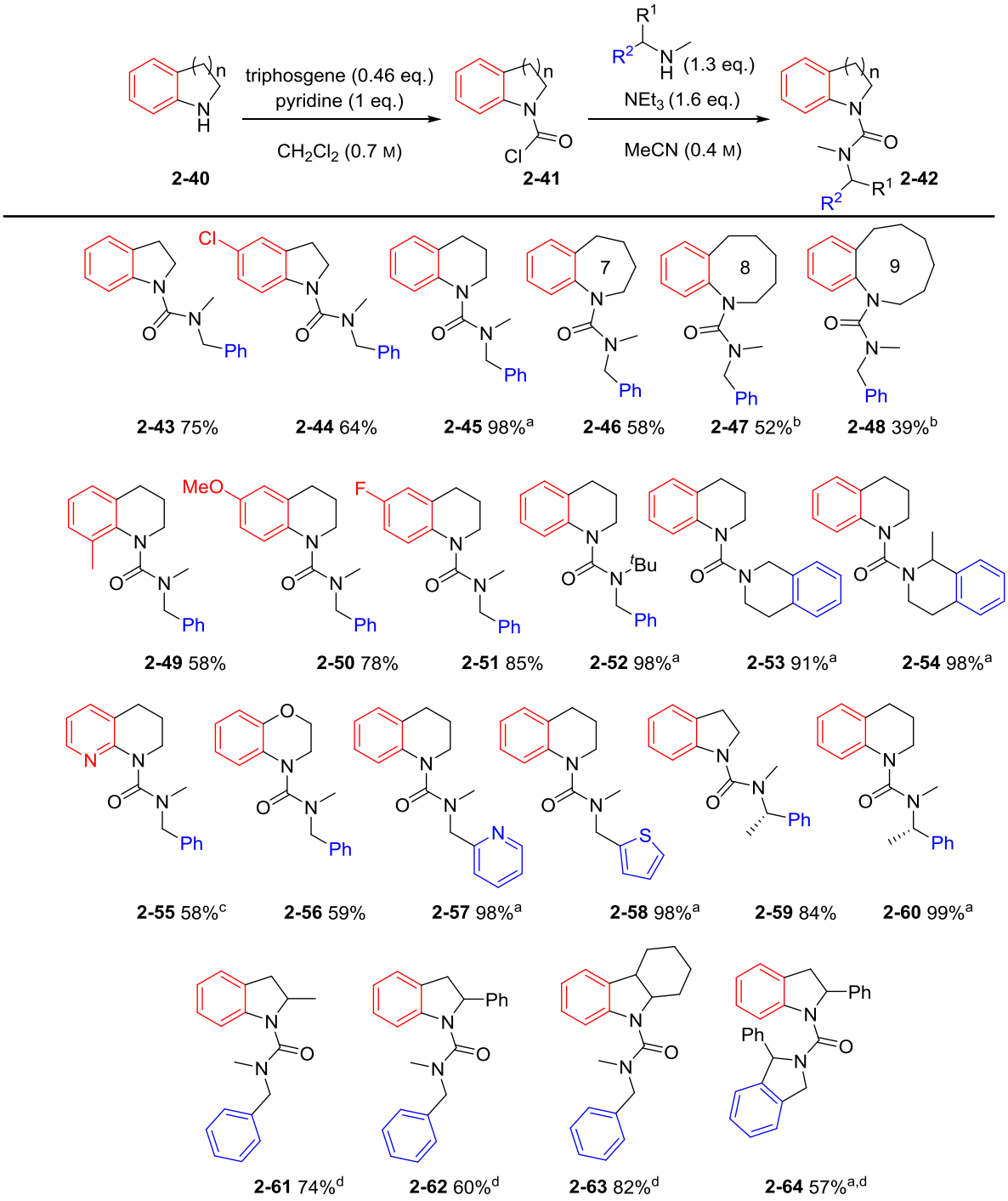
Scheme 2-12. Mechanism of Stille coupling.

The reaction proceeds with initial oxidative addition of the organohalide **2-34** to the Pd^0 species **2-33** to form Pd^{2+} complex **2-35**. Subsequent transmetallation of **2-35** with the organostannane allows the formation of species **2-38**, where the alkyl group of the organostannane has replaced the halide anion on the palladium complex. Reductive elimination delivers the desired cross-coupled product **2-39** and regenerates the palladium catalyst.

Having appended the allyl group onto the aromatic ring, the ring closing metathesis of **2-37** was explored. The optimal conditions were reported in the literature to be 10 mol% Grubbs' first-generation catalyst in toluene.[110] Subjecting diene **2-27** to these conditions allowed the formation of cyclic amine **2-28** in 54% yield. Successful hydrogenation of the alkene resulted in protected 9-membered amine **2-29**, which was hydrolysed under acidic conditions to yield the desired unprotected 9-membered cyclic amine **2-30**. Urea formation was achieved by subjecting **2-30** to the general procedure described in section 2.2.2.2.

2.2.2.4 Starting Material Substrate Scope

With the advantage of the ring expansion methodology being that complex scaffolds can be generated from simple starting materials, efforts were directed towards selecting simple commercially available starting materials. Starting materials with varying electronic and steric parameters on the migrating aromatic ring, including examples that incorporated heteroatoms were selected. The scope of the starting materials is highlighted in scheme 2-13.



Scheme 2-13. Ring expansion starting material scope.*

N.B. Yields calculated over two steps of phosgenation and amination. [a]Yield calculated over amination step only. [b]Starting cyclic amines not commercially available and synthesised according to procedures in section 2.2.2.1 and 2.2.2.3. [c]Alternative method of isocyanate coupling and methylation used. [d]From indole starting materials.

Several different indoline and tetrahydroquinoline derivatives were available with varying electronic and steric demands. Substrate **2-53** where the benzyl group is part of a ring was synthesised simply by coupling two isomers of the same molecule together (tetrahydroquinoline and tetrahydroisoquinoline). A methyl group at the benzylic centre can be introduced by coupling the tetrahydroquinoline carbamoyl

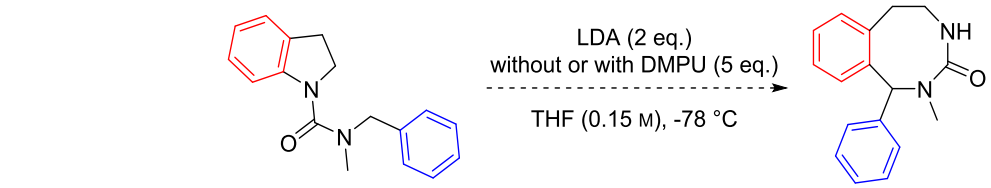
* Experiments performed in collaboration with Dr Johnathan Matlock.

chloride with 1-methyl-1,2,3,4-tetrahydroisoquinoline. Structures with additional heteroatoms in their structures were also obtained **2-55**-**2-57** from commercial sources. Two examples where the anion stabilising group was not benzyl but instead a heterocycle, 2-pyridyl and 2-thiophenyl (substrates **2-57** and **2-58**), were also synthesised to study their effect on migration.

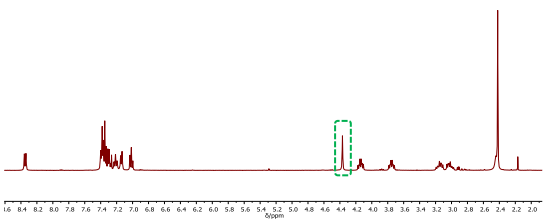
For enantioenriched examples **2-59** and **2-60**, the general procedure for urea formation was modified by reacting the appropriate carbamoyl chloride with enantioenriched (*S*)-*N*-methyl-1-phenylethan-1-amine. Racemic indoline substrates with substituents on the tether **2-61**-**2-64** were synthesised by Sn/HCl reduction of their parent 2-substituted indoles.[111] All substrates were converted into their urea counterparts in good yields over both steps, scheme 2-13.

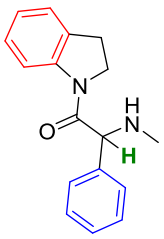
2.2.3 Ring Expansion Substrate Scope

Initial studies focused on repeating the preliminary work carried out previously (see section 2.2.1). Indoline urea **2-65** was treated with LDA (2 eq.) in THF at −78 °C and allowed to react for 2 hours. The ring expansion reaction was also repeated with DMPU in the reaction mixture. Interestingly, both reactions gave different products as determined by ^{1}H NMR analysis of the isolated compounds, although HRMS analysis indicated that both had the same mass. A key difference in the ^{1}H NMR spectra was a singlet corresponding to the benzylic proton in the ^{1}H NMR spectrum of the product isolated in the reaction without DMPU, this singlet appeared at δ = 4.27 ppm compared to δ = 6.25 ppm when the reaction was run with DMPU, see figure 2-1.

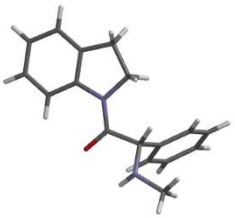


2-65 **2-66**

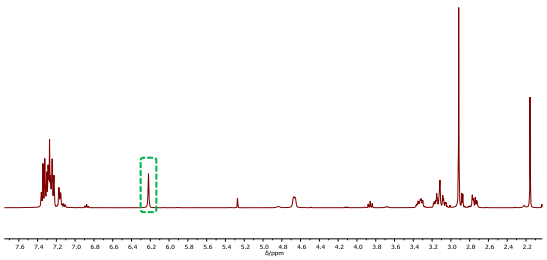


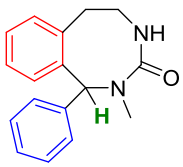


2-67



X-ray crystal structure of **2-67**

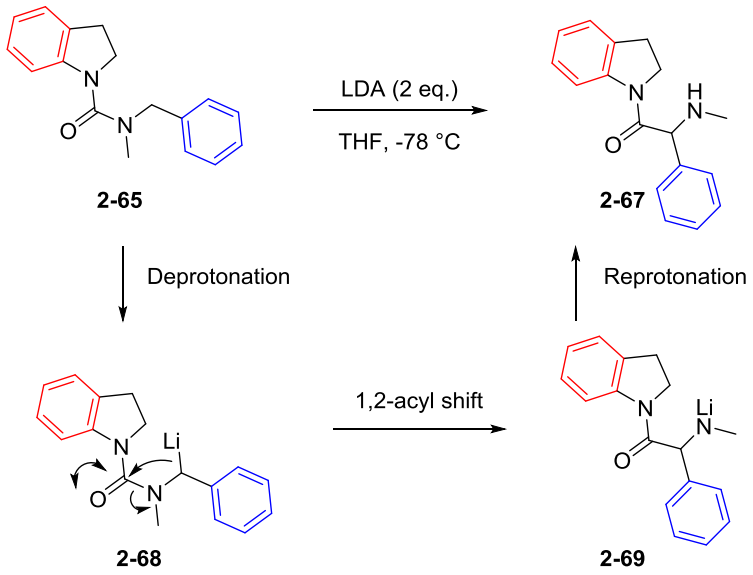




2-66

Figure 2-1. ^{1}H NMR spectra of product from rearrangement of **2-65:** without DMPU (top) with DMPU (bottom). Highlighted resonance of suspected benzylic proton.

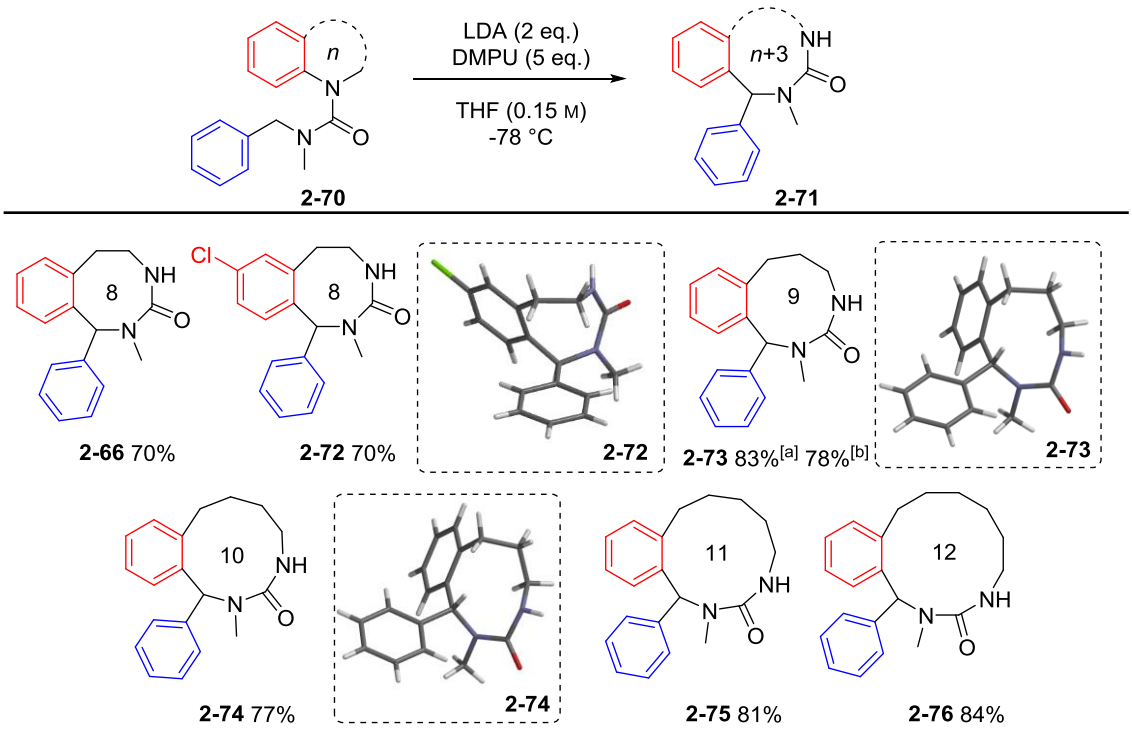
In both reactions, when run with and without DMPU, diastereotopic protons were observed indicating the formation of a chiral centre. Crystallisation of the product isolated from the reaction in the absence of DMPU allowed for X-ray analysis and the unambiguous assignment of the product as **2-67**. It was proposed that product **2-67** results from initial deprotonation at the benzylic position to form organolithium **2-68**, followed by nucleophilic attack at the urea carbonyl carbon centre, leading to a 1,2-acyl shift which after protonation delivers the secondary amine, scheme 2-14.



Scheme 2-14. Proposed mechanism for formation of acyl shift product **2-67**.

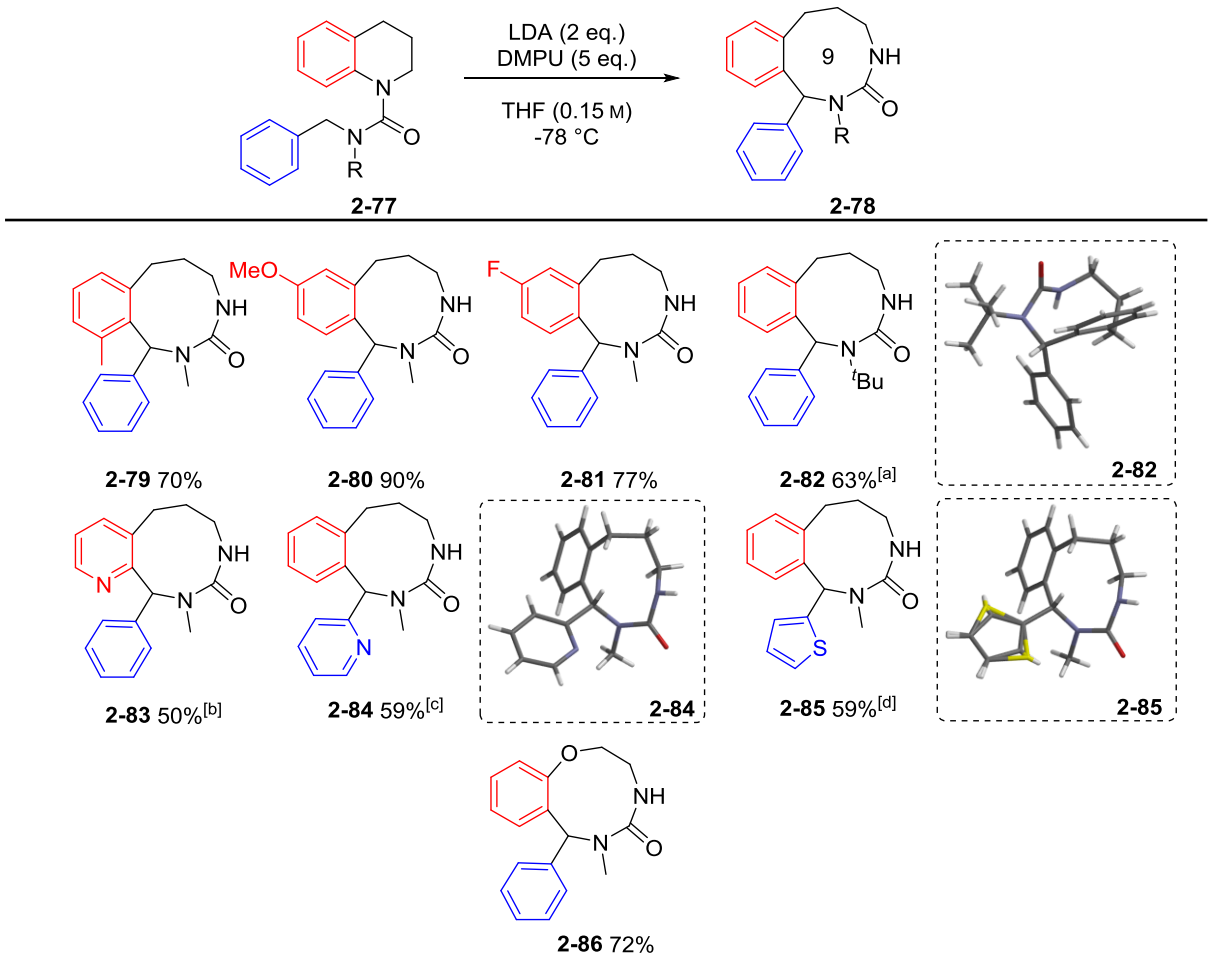
Pleasingly, the addition of DMPU in the reaction mixture completely suppressed the formation of the acyl shift product **2-67** and the desired ring expansion occurred resulting 8-membered ring product **2-66** in 70% yield. The ring expansion of tetrahydroquinoline and tetrahydrobenzazepine ureas **2-45** and **2-46** were also repeated in good to excellent yields.

The ring expansion was attempted on all the precursors synthesised (see section 2.2.2.4). Excellent yields were obtained for the 11- and 12-membered cyclic ureas **2-75** and **2-76**, demonstrating that this methodology is applicable to the synthesis of the full range of medium-sized rings, scheme 2-15.



Scheme 2-15. Migratory ring expansion to synthesise 8- to 12-membered rings.[a]Reaction conducted on 0.4 mmol scale. [b]Reaction conducted on 3 mmol scale.

The optimised conditions (LDA, 2 eq.; DMPU, 5 eq.; THF, –78 °C, 1-16 h) were applied successfully to a series of ureas **2-77** derived from commercially available 6-membered heterocycles, yielding a variety of substituted 9-membered benzannulated nitrogen heterocycles **2-79**-**2-86** in good to excellent yield**,** scheme 2-16. Ring expansion of tetrahydroquinoline benzyl urea **2-45** generated **2-73** in good yield on a scale of both 0.4 mmol and 3 mmol, with X-ray crystallography confirming the structure of **2-73**, scheme 2-15. The ring expansion reaction appears to be insensitive to both electronic and steric demands, giving the ring expansion products with electronically diverse (**2-80, 2-81**) and *ortho*-substituted hindered (**2-79**) migrating substituents in good to excellent yields, scheme 2-16.

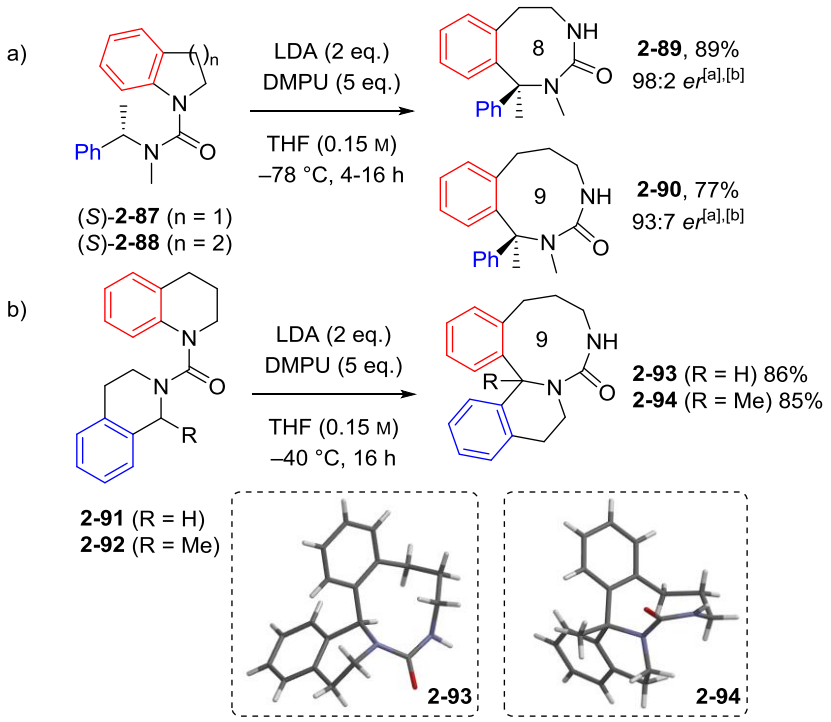


Scheme 2-16. Ring expansion to yield 9-membered nitrogen heterocycles.*
[a]Reaction run at −10 °C. [b]Reaction run at −60 °C. [c]Reaction run at −30 °C.[d]Reaction run at −40 °C without DMPU.

Heteroaromatic (2-pyridyl and 2-thiophenyl) rings may be incorporated into the migrating aryl ring (**2-83**) or alpha to the benzylic anions (**2-84**, **2-85**). For the pyridyl-containing substrates **2-55** and **2-57,** higher temperatures were required for the reaction to reach completion. By contrast, the 2-thiophenyl-stabilised anion derived from **2-58** rearranged successfully to **2-85** in the absence of DMPU. Incorporation of a heteroatom into the tether by expansion of a urea **2-56** derived from commercially available benzomorpholine gave the benzoxadiazonine **2-86** in good yield. Although a substantial decrease in the rate of reaction was observed when replacing the *N*-methyl with a *tert*-butyl group in **2-53**, a good yield of ring expanded product **2-82** was obtained when warming the temperature to −10 °C.

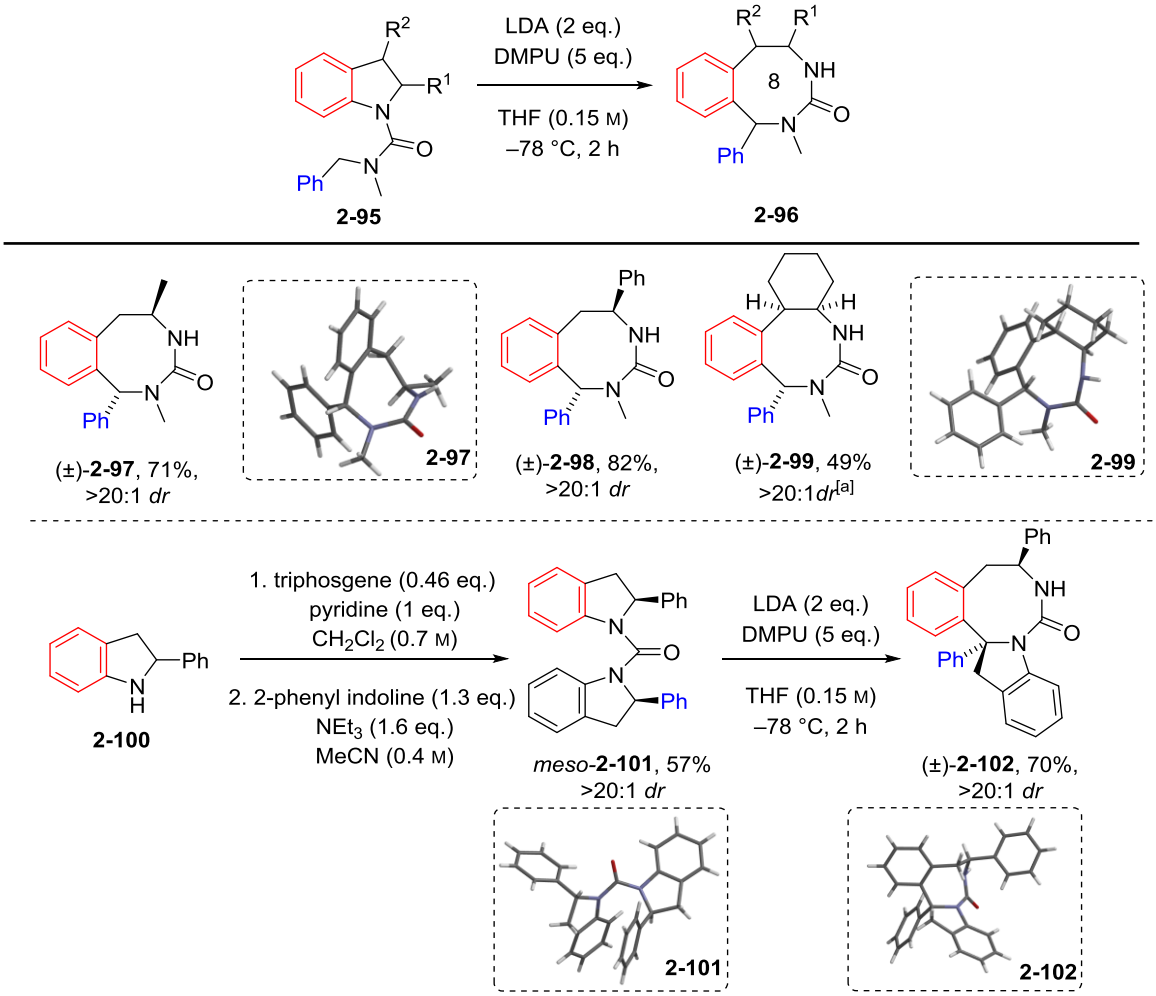
Chiral substrates **2-59** and **2-60** were made from enantiopure (*S*)-α-methylbenzylamine and underwent ring expansion under the same conditions, each giving products, **2-89** and **2-90**, with a new quaternary centre within the expanded 8- or 9-membered ring, scheme 2-17.

* Experiments performed in collaboration with Dr Johnathan Matlock.



Scheme 2-17. Ring expansion products with quaternary centres and fused rings.
[a]*er* determined by HPLC on chiral stationary phase. [b]Starting material (*S*)-**2-87** (99:1 *er*), (*S*)-**2-88** (99:1 *er*).

Like previous *N*→*C* aryl migrations studied in the group, both rearrangements were stereospecific, with only slight erosion of *er* in the case of **2-90** and must proceed through a configurationally stable organolithium intermediate.[80, 85] The ring expansion methodology was also amenable to the synthesis of bicyclic structures by migratory ring fusion, scheme 2-17 b. Ureas **2-91** and **2-92**, formed by coupling two isomeric 6-membered nitrogen heterocycles, underwent ring expansion by insertion of the tetrahydroisoquinoline ring into the tetrahydroquinoline. For the ring expansion to be successful, it was essential to warm to the reaction mixture to –40 °C. This allowed access to diazabicyclo[7.4.0]tetradecane products **2-93** and **2-94** in excellent yields. Chiral starting materials with substituents on the tether of the expanding ring **2-61**-**2-64** underwent migratory ring expansion with complete diastereoselectivity, scheme 2-18.



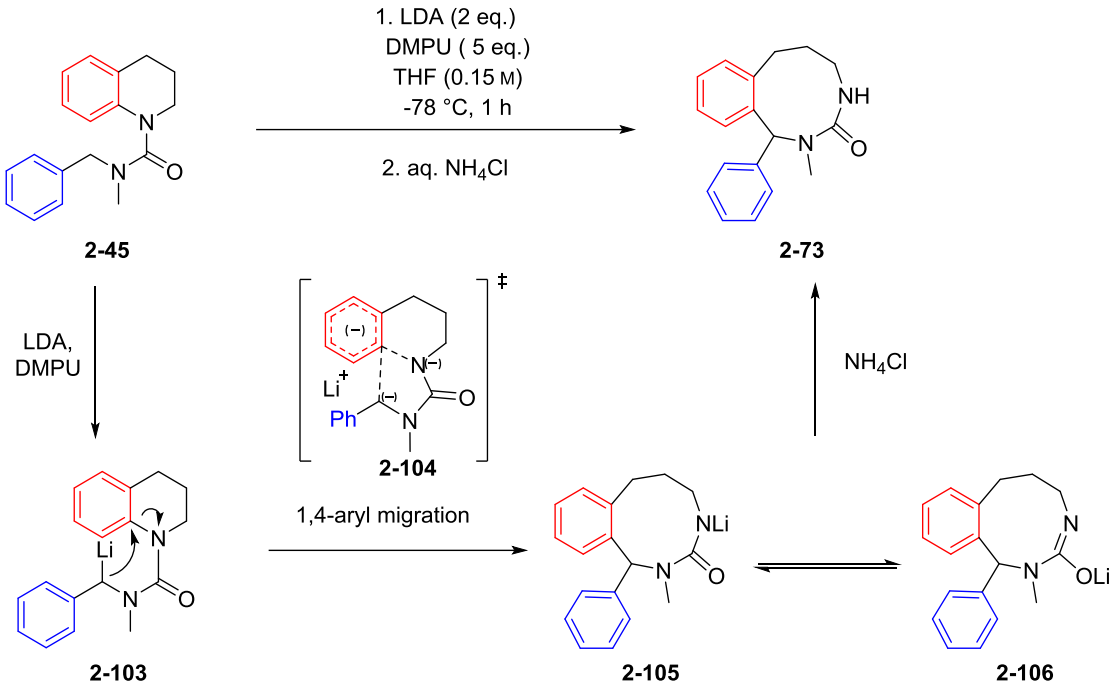
Scheme 2-18. Diastereoselective ring expansions.*
[a]Reaction run without DMPU.

Ring expansion of methyl-substituted **2-61** gave **2-97** in good yield of 71% and as a single diastereomer. X-ray crystallography showed a 1,5-*anti* relationship between the phenyl ring and methyl group on the tether. The related substrates **2-62** and **2-63** also underwent ring expansion to a single diastereomer of the 8-membered products. A fourth indoline-derived substrate **2-101** was formed by coupling of racemic 2-phenylindoline with its own carbamoyl chloride derivative, scheme 2-18. Interestingly, although potential for four diastereomers, a single diastereomer of the symmetrical urea was formed, which X-ray crystallography showed to be the *meso* diastereomer **2-101**. Migratory ring-fusion of **2-101** allowed one indoline ring to insert into the other, resulting the diazabicyclo[6.3.0]undecane **2-102** as a single diastereomer, with an *anti*- relationship between the two phenyl rings determined by X-ray crystallography, scheme 2-18.

2.2.4 Mechanistic Insight

Although there have been investigations reported into the mechanism of the rearrangement of acyclic systems in the Clayden group,[85] prior to this work no insight has been gained into the ring expansion reaction. Assuming the reaction proceeds in a similar way to the acyclic systems, the proposed mechanism is outlined in scheme 2-19.

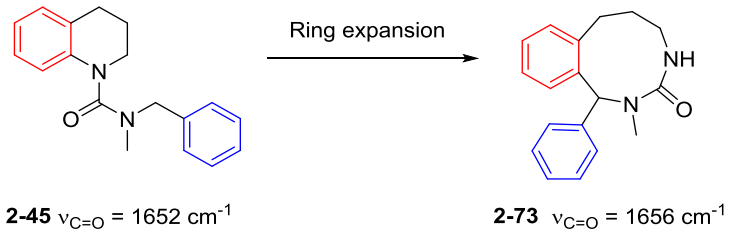
* Experiments performed in collaboration with Dr Johnathan Matlock.



Scheme 2-19. Proposed mechanism for the ring expansion of benzylic ureas.

Initial deprotonation at the benzylic position of **2-45** generates a dipole stabilised organolithium. It can be postulated that the presence of DMPU and clustering of LDA forces the breakage of the lithium-oxygen interaction, allowing the molecule to adopt a conformation where the Li cation is sandwiched between the two aromatic rings, with the naked anion situated in close proximity to the migrating ring. Carbanion attack at the *ipso*- position of the aromatic ring in a 'S_NAr-type' fashion and ring opening generates the ring expanded products **2-105** and **2-106**. A possible transition state **2-104** for the reaction is shown in scheme 2-19, which resembles an associative substitution mechanism. Quenching the reaction with a proton source generates the desired ring expanded product **2-73**.

In attempt to study the mechanism of the ring expansion of **2-45**, the reaction was followed by *in situ* infrared spectroscopy (ReactIR). It was hoped that the intermediates of the ring expansion reaction could be followed by monitoring changes in the carbonyl stretching frequencies.



Scheme 2-20. Carbonyl stretching frequencies of rearrangement precursor and product.

With the carbonyl stretching frequencies of the starting material **2-45** (1652 cm^{-1}) and product **2-73** (1656 cm^{-1}) being extremely similar it was important to run the experiments at high concentration, so any slight changes could be monitored. Unfortunately, the presence of DMPU caused issues due to having a carbonyl stretching frequency like that of the starting material and the product.

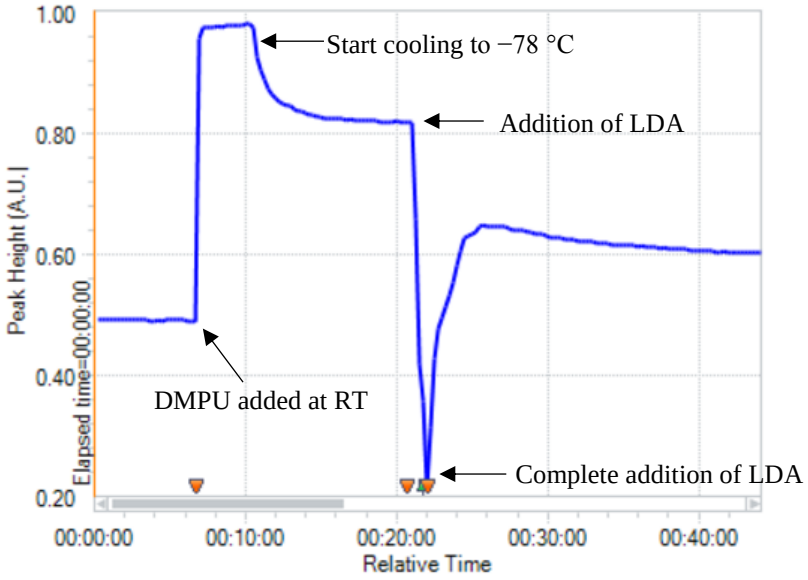


Figure 2-2. Monitoring of carbonyl stretching frequency at ν = 1652 cm^{-1} of starting material **2-45** throughout reaction.

Figure 2-2 illustrates how the carbonyl stretching frequency at ν = 1652 cm^{-1}, which corresponds to the C=O stretch in the starting material **2-45** changes over the course of the reaction. Upon addition of DMPU the frequency at ν = 1652 cm^{-1} becomes more intense due to the overlap in carbonyl stretching frequencies of DMPU and the starting material. The reaction mixture was then cooled to −78 °C. Once a stable IR spectrum had been obtained LDA was added dropwise at −78 °C resulting in rapid consumption of the starting material within less than a minute, evidenced by the loss of the IR signal at ν = 1652 cm^{-1}. Due to the close carbonyl stretching frequency of the product, *in situ* IR spectrometry was unable to distinguish between that of the product and starting material and as a result it appeared that the starting material is being regenerated. However, the starting material was not being regenerated and it is likely that **2-105** or **2-106** was observed.

After analysing a narrow wavelength window, the carbonyl stretching frequency between ν = 1500-1700 cm^{-1} was monitored over the course of the reaction. Figure 2-3 shows the IR spectrum, from two angles.

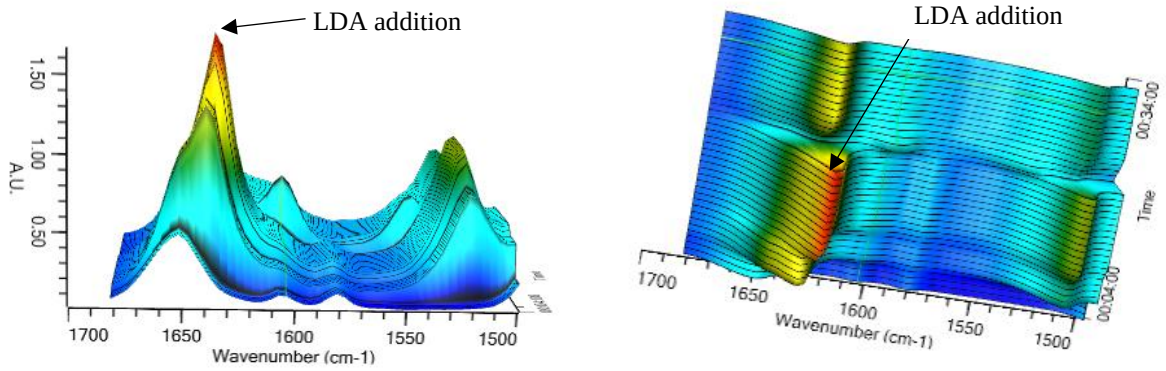
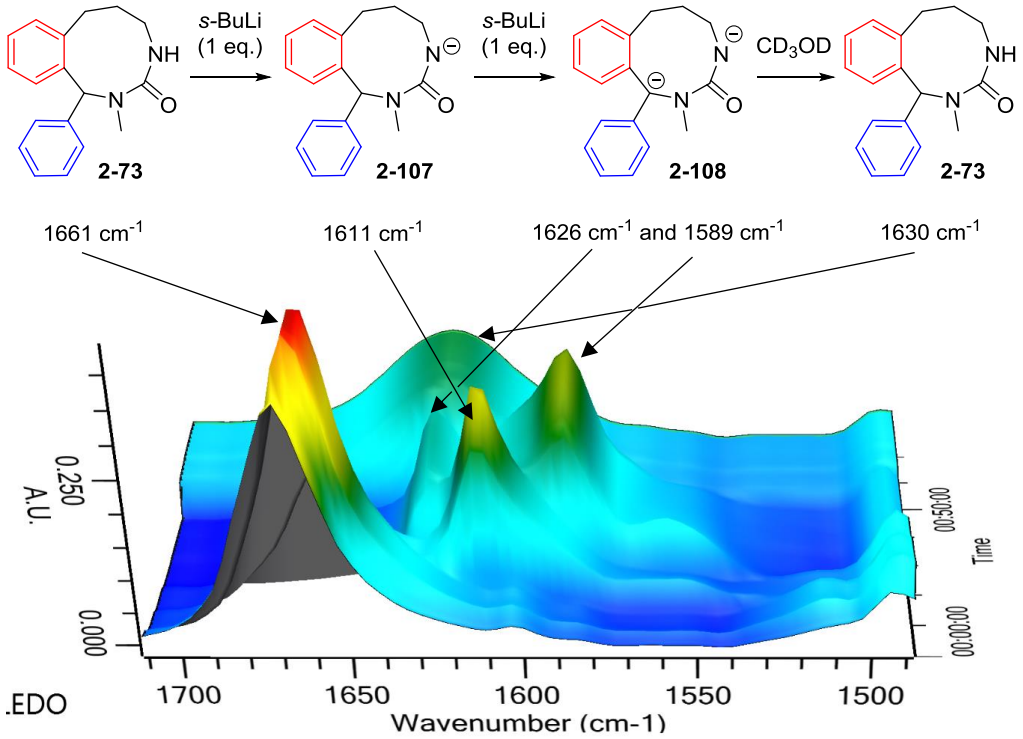


Figure 2-3. IR spectrum of the ring expansion reaction mixture over time shown from a front view (left) and birds-eye view (right).

Upon addition of LDA there is a dip in the spectrum where the starting material is consumed, and a peak appears briefly at ν = 1604 cm^{-1}. Within a minute this disappears and forms a new peak at ν = 1634 cm^{-1} which remains until the ReactIR probe was removed and the reaction mixture was quenched with

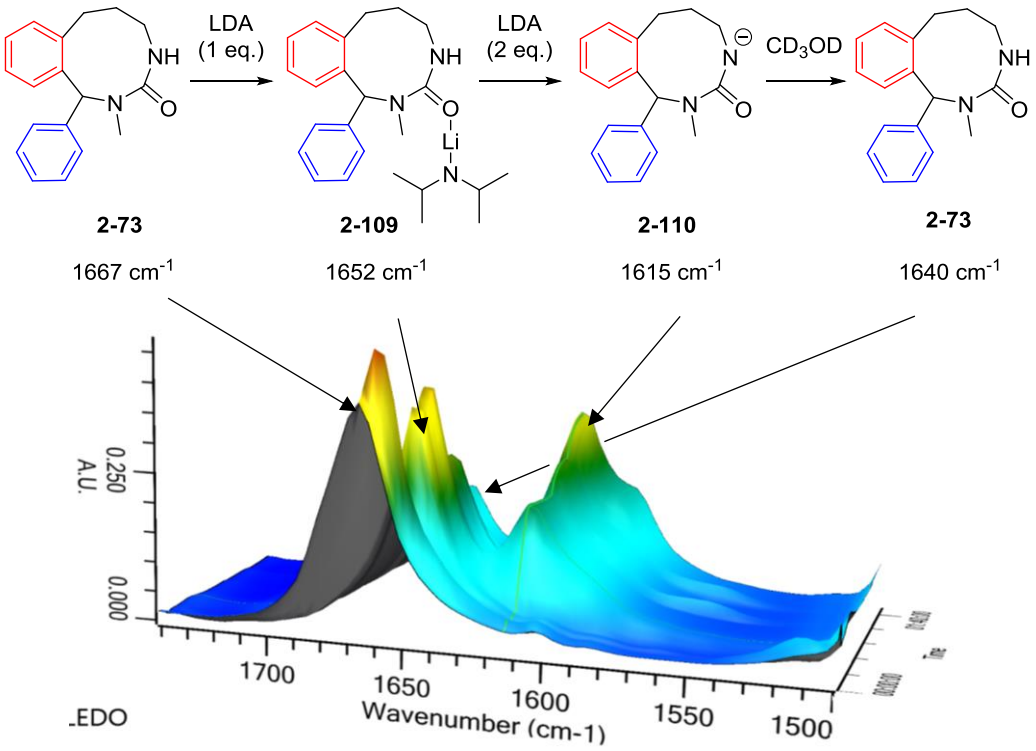
ammonium chloride. It can be postulated that the peak at ν = 1604 cm^{-1} corresponds to the lithiated starting material **2-103**, which rapidly reacts, and forms ring expanded products **2-105** and **2-106**. Alternatively, the peak at ν = 1604 cm^{-1} might correspond to the anion formed after ring expansion, which either shuttles the anion to the doubly benzylic position to give the peak at 1634 cm^{-1} or forms a dianion.

Additional *in situ* IR experiments were carried out analysing the deprotonation of the product with *s*-BuLi and LDA, in the absence of DMPU to prevent overlap of carbonyl stretching frequencies, as this would provide insight into the IR spectrum of the anion formed after ring expansion.



Scheme 2-21. 3D ReactIR trace monitoring peaks at various wavenumbers over the course of the deprotonation with *s*-BuLi. Peaks are tentatively assigned to the intermediates shown.

Prior to deprotonation, the absorption at ν = 1661 cm^{-1} was assigned to the $\nu_{C=O}$ of the urea of **2-73**. Treatment of **2-73** with 1 eq. of *s*-BuLi gave a new absorption at ν = 1611 cm^{-1} which is assigned to the $\nu_{C=O}$ of the deprotonated species **2-107**, scheme 2-21. The shifting of the urea carbonyl absorption to a lower wavenumber is indicative of a resonance stabilisation of the negative charge on nitrogen by the adjacent carbonyl group, which would be greater than in the case with the uncharged urea. This observation is consistent with previously reported work on related systems.[95] Given that complete deprotonation of the urea nitrogen was not achieved with only 1 eq. of base, a second equivalent of *s*-BuLi was introduced, with complete deprotonation of **2-73** being confirmed by the disappearance of the absorption at ν = 1661 cm^{-1}, **2-108**. The absorption at ν = 1611 cm^{-1} then begins to decrease in intensity with the appearance of two new absorptions at ν = 1626 cm^{-1} and 1589 cm^{-1} respectively, scheme 2-21. Assignment of these two absorptions to the dianion **2-108** is consistent with related acyclic systems previously studied.[84] Despite dianion formation, no deuterium was incorporated when deuterated methanol was added at −78 °C.

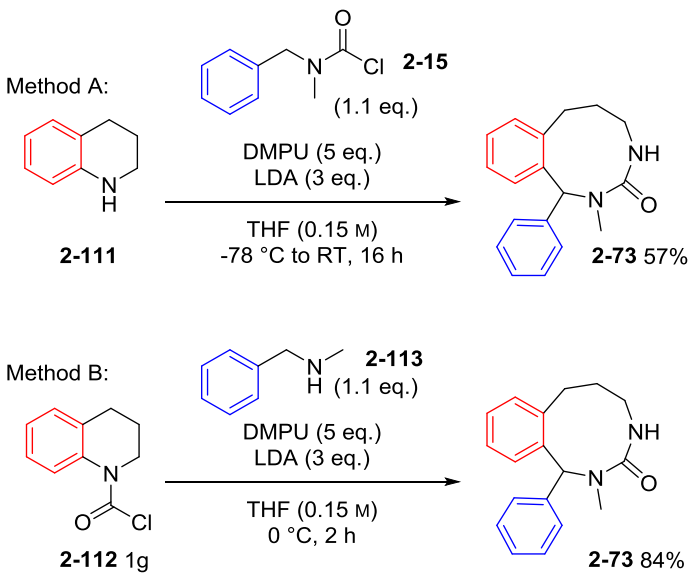


Scheme 2-22. 3D ReactIR trace monitoring peaks at various wavenumbers over the course of the deprotonation with LDA. Peaks are tentatively assigned to the intermediates shown.

Monitoring the deprotonation of **2-73** with *s*-BuLi allowed us to assign absorptions observed by *in situ* IR to specific mono- and dianion species **2-107** and **2-108**. With this in mind, the same was repeated with LDA as base. Deprotonation of **2-73** with 1 eq. of LDA led to complete consumption of the absorption at ν = 1667 cm^{-1} with a new absorption appearing immediately at ν = 1652 cm^{-1}. Since monoanion formation on addition of *s*-BuLi entailed a much larger shift in wavenumber to ν = 1611 cm^{-1} (see scheme 2-21) we tentatively assigned this peak as a pre-lithiation complex **2-109**. This type of pre-lithiated species and the associated shift of the carbonyl absorption is like those reported by O'Brien and co-workers during the lithiation of *N*-Boc piperidines.[112] A peak at ν = 1615 cm^{-1} gradually forms, which was assigned to the monoanion **2-110**, based on the wavenumber of the absorption being similar to that observed on deprotonation by *s*-BuLi. The formation of a pre-lithiated species and gradual but incomplete appearance of **2-110** is indicative of a slower rate of deprotonation with LDA. Unlike with *s*-BuLi, complete monoanion formation **2-110** was not achieved with LDA even after 3 eq. were added. Importantly, no dianion was observed with 3 eq. of LDA at −78 °C, suggesting that the brief absorption at ν = 1604 cm^{-1} observed when monitoring the ring expansion reaction is likely to correspond to lithiated starting material **2-103** and not anion of the product **2-105** or **2-106**. Again, no deuterium was incorporated when quenching the anion at –78 °C with deuterated methanol.

2.2.5. Investigating the Practicality and Robustness of the Methodology

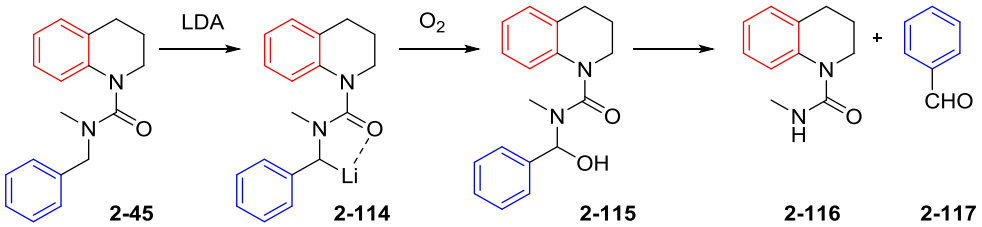
To improve the practicality of the methodology it was hoped that the urea formation and ring expansion procedures could be streamlined into an even simpler protocol. A 'one-pot' urea formation/ring expansion procedure would allow access to complex molecular architectures in a single step from simple starting materials, scheme 2-23.



Scheme 2-23. 'One-pot' urea formation/ring expansion.

Initial experiments focused on the reaction of commercially available tetrahydroquinoline **2-111** with benzyl(methyl)carbamoyl chloride **2-15** in the presence of 3 eq. LDA. To encourage the reaction to go to completion the reaction mixture was warmed to room temperature after deprotonation at −78 °C, affording the desired ring expansion product **2-73,** albeit in moderate yield. An alternative strategy of reacting tetrahydroquinoline carbamoyl chloride **2-112** with *N*-benzylmethylamine **2-113** and 3 eq. LDA was also attempted and yielded the desired ring expansion product in excellent yield after 2 hours on a gram scale.

The effect of using non-distilled reagents and solvents was examined on the ring expansion of tetrahydroquinoline urea **2-45**. Interestingly, no difference in yield was observed when using commercial LDA, DMPU and THF on a small scale. Furthermore, the reaction was attempted without DMPU in the reaction mixture. Again, no difference in yield was observed when the reaction was carried out in the absence of DMPU, although the reaction did appear to take longer to reach completion, which contrasts with the 5-membered indoline urea **2-43** that does require DMPU to suppress the acyl shift pathway to allow ring expansion (see section 2.2.3). Although many industrial processes run reactions at cryogenic temperatures on scale, it would be advantageous to avoid these temperatures, making the process more applicable to standard laboratory-based apparatus and plant vessels. As a result, the reaction was repeated in a jacketed vessel at −10 °C with and without DMPU, giving the products in lower yields of 47% and 40% respectively. In both cases, when run with and without DMPU, a side product was isolated from the reaction mixture and identified to be **2-116,** potentially arising from oxidation of the benzylic carbanion, as the reaction was not carried out in strictly inert conditions, scheme 2-24.[113]



Scheme 2-24. Potential oxidative pathway to generate **2-116**.[113]

On addition of LDA to **2-45** a dipole stabilised carbanion is generated **2-114**. However, if oxidation is quicker than ring expansion, the carbanion can be oxidised to the hemi-aminal which fragments resulting in a formal dealkylation of **2-45**.

Finally, whilst in a process chemistry laboratory the potential of scaling up the ring expansion reaction in a jacketed vessel was explored. With the knowledge that the warmer reaction temperature of −10 °C facilitates the formation of oxidative side products, the reaction was carried at −50 °C, this being the maximum cooling capacity of the vessel chiller. The reaction was performed on a six-gram scale using all commercial, non-distilled reagents. It was found that simple filtration of the crude reaction mixture through a pad of silica was enough to obtain pure compound after the reaction, therefore eliminating the need for flash column chromatography. The ring expansion product **2-73** was isolated in a good yield of 67%, highlighting the robustness of the methodology and its potential to be used on an industrial scale.

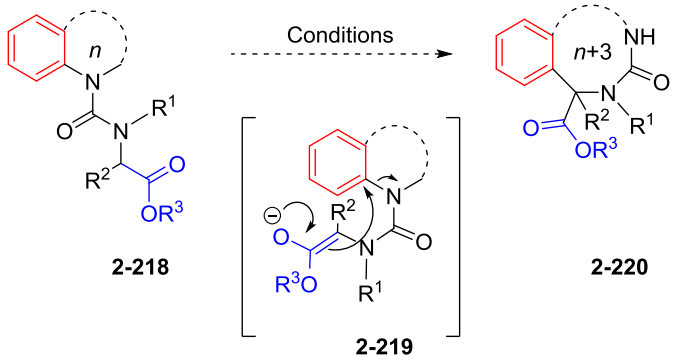
2.2.6. Investigating Alternative Nucleophiles for Ring Expansion

It has been demonstrated in this work that benzylic anions are suitable nucleophiles for the ring expansion reaction. To further extend the substrate scope, the possibility of alternative nucleophiles was explored. Nucleophiles containing different functionalities would deliver products containing alternative synthetic handles for further functionalisation.

2.2.6.1 Amino Acid Enolates

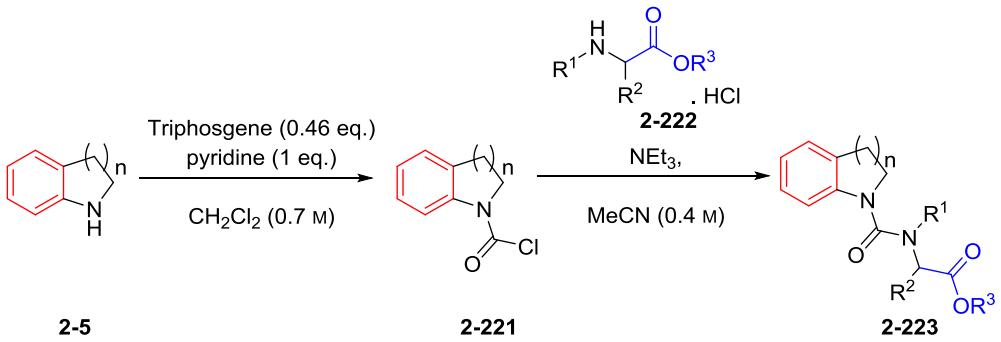
2.2.6.1.1 Tethered Amino Esters

Amino acid enolates have previously shown to be successful nucleophiles in the urea-mediated intramolecular *N→C* aryl transfer, which followed by cyclisation yields synthetically useful hydantoins.[95, 96] Subsequent hydrolysis of the hydantoins allows access to quaternary amino acids. With this basis, it was decided to investigate amino acid enolates as nucleophiles for our ring expansion, scheme 2-25.



Scheme 2-25. Potential ring expansion using tethered amino acid enolates.

If successful, this ring expansion reaction would involve the transformation of natural amino acids into complex medium ring structures. Studies within the group have demonstrated that high yields can be obtained for the *N→C* aryl migration using amino esters as precursors, as such our initial studies focused on the ring expansion of amino esters.[114] Similar to the method devised for the synthesis of benzyl ureas (see section 2.2.2.2), the synthesis of the ring expansion precursors was achieved by coupling of the carbamoyl chloride with the appropriate amino ester salt, scheme 2-26.

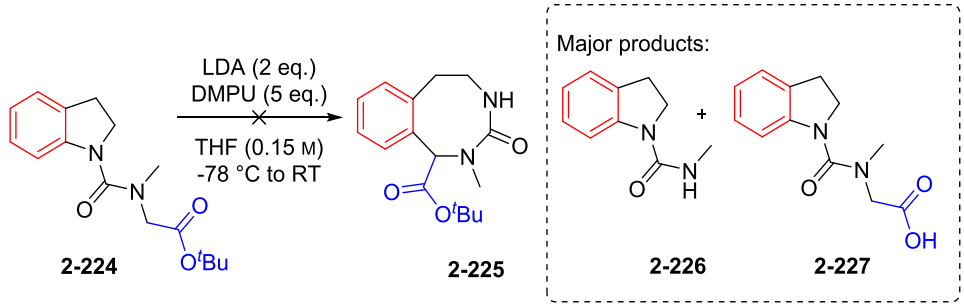


Entry	n	R^1	R^2	R^3	Yield, %
1	1	Me	H	^{t}Bu	**2-223a**, 73
2	2	Me	H	^{t}Bu	**2-223b**, 93
3	2	Me	H	Et	**2-223c**, 80
4	2	H	Me	Et	**2-223d**, 78
5	2	Me	Me	Me	**2-223e**, 67

Scheme 2-26. Synthesis of amino ester ring expansion precursors.

The coupling was achieved in good to excellent yields for all substrates and allowed access to glycine (scheme 2-26, entries 1-3) and alanine amino acid derivatives (scheme 2-26, entries 4-5).

The first substrate trialled in the ring expansion was *tert*-butyl glycine derivative **2-224**. The milder base potassium bis(trimethylsilyl)amide (KHMDS) was found to be successful for the *N*→*C* aryl migration of linear amino acid esters,[114] and thus it was our starting point for optimisation. Treatment of **2-224** with KHMDS in THF at 0 °C and warming to room temperature resulted in small amounts of unreacted starting material and a complex mixture of products, none of which appeared to be the desired ring expansion product. Additionally, mass balance was poor after purification. Next, the optimised conditions for the ring expansion of benzyl ureas were attempted, i.e. LDA (2 eq.) and DMPU (5 eq.) in THF, scheme 2-27.

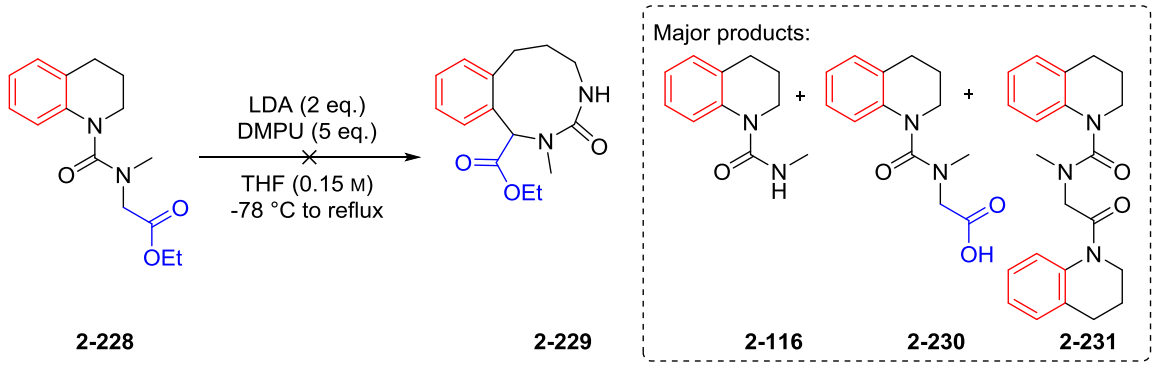


Scheme 2-27. Attempted ring expansion of *tert*-butyl ester glycine amino acid derivative.

LDA was added to the urea **2-224** and DMPU in THF at −78°C and the reaction mixture was gradually warmed to RT, scheme 2-27. Analysis of the reaction progression by TLC analysis showed only starting material at −78 °C. Warming the reaction mixture to room temperature did not lead to ring expansion and only unreacted starting material and products **2-226** and **2-227** were observed.

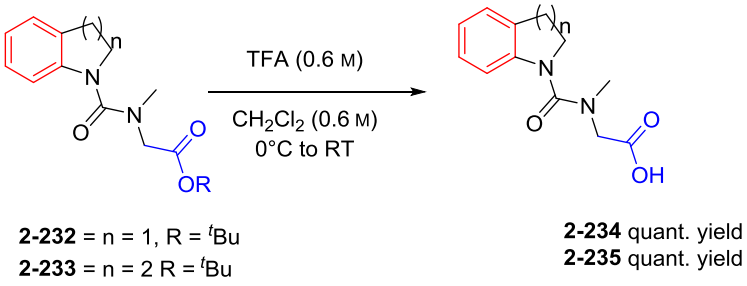
Hypothesising that the sterically bulky *tert*-butyl group was hindering the attack of the enolate at the *ipso*-position of the migrating aromatic ring, attention was turned to the less bulky tetrahydroquinoline ethyl ester derivative **2-228**. However, treatment of **2-228** with LDA and DMPU in THF showed similar

results to the ^{t}Bu derivative, with no consumption of starting material below room temperature, scheme 2-28. The reaction mixture was therefore heated to reflux and allowed to stir for four hours until TLC analysis indicated consumption of starting material. Despite the use of anhydrous solvents and reagents, the previously observed hydrolysed and fragmented products were isolated together with traces of the intermolecular acyl transfer product **2-231**, scheme 2-28.



Scheme 2-28. Attempted ring expansion of ethyl ester glycine amino acid derivative.

Previous work in the group has shown that *N*→*C* aryl migration is possible from free urea acids using LDA and LiCl as an additive.[96, 114] Acid hydrolysis of **2-232** and **2-233** using TFA afforded the corresponding acids in excellent yields, scheme 2-29.



Scheme 2-29. Acidic hydrolysis of esters

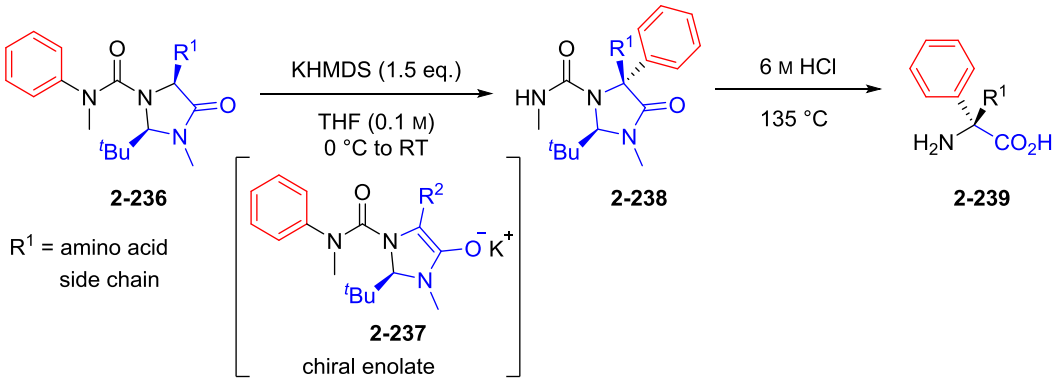
However, subsequent treatment of urea acids **2-234** and **2-235** with LDA and LiCl gave only unreacted starting material and traces of fragmented products arising from oxidation of the anion, highlighting that ring expansion is not possible utilising enolates derived from glycine amino acids under these conditions. It can be postulated that the lack of substitution at the α-position means that the molecule is unable to adopt a 'reactive conformation' where the enolate is in close proximity to the migrating aromatic ring. In attempt to overcome this limitation, efforts turned towards investigating alanine ester derivatives **2-223d** and **2-223e**, where a methyl group is at the α-position. Unfortunately, for both the ethyl and methyl esters explored, the major products isolated were the hydrolysed starting materials.

In summary, it can be concluded that tethered amino acid enolates are not appropriate nucleophiles for ring expansion. Despite using anhydrous conditions, the esters are either hydrolysed to the corresponding acids or remain as unreacted starting material. It appears that in the case for amino acid enolates the tether between the migrating aromatic ring and the urea nitrogen has a considerable effect on reactivity.

2.2.6.1.2 Imidazolidinones

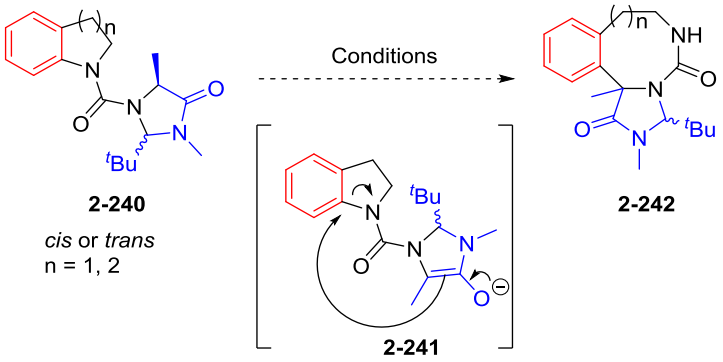
Recent work within the group has demonstrated an efficient asymmetric arylation of amino acids exploiting the principles of Seebach's self-regeneration of stereocentres strategy.[115-118] This methodology uses imidazolidinones **2-236** as enolate precursors for the *N*→*C* aryl migration reaction

and has been applied to a range of amino acid derivatives.[115] The introduction of a chiral centre in the starting material allowed for a highly diastereoselective arylation, proceeding through chiral enolate **2-237**. Subsequent hydrolysis of the imidazolidinone resulted in chiral quaternary amino acids **2-239**, scheme 2-30.



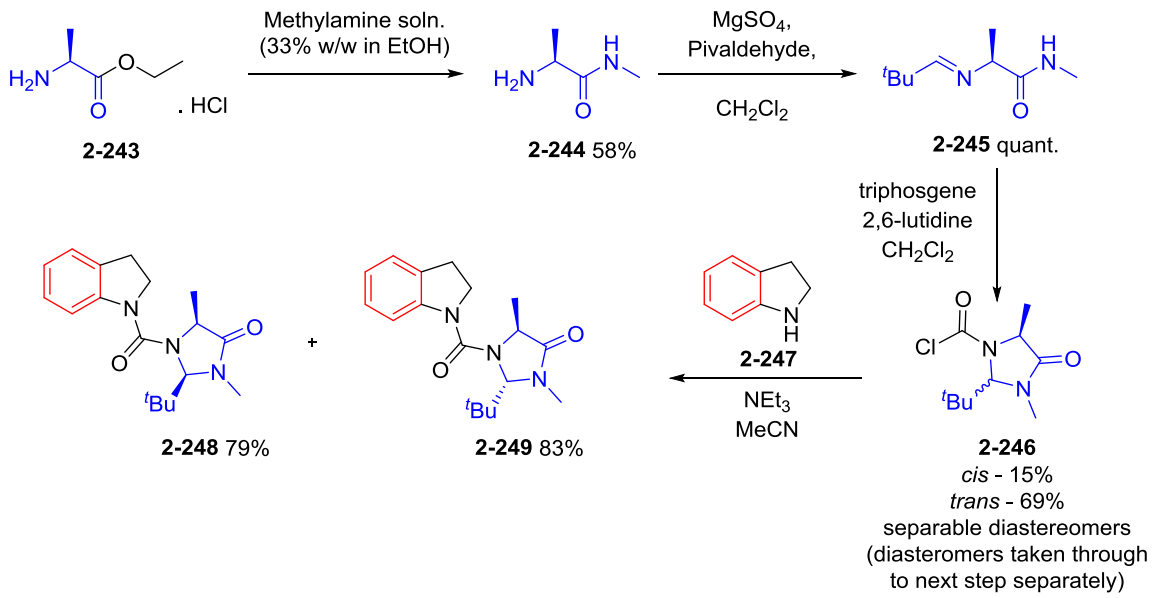
Scheme 2-30. α-Arylation of amino acids using imidazolidinones.[115]

Relatively little attention had been placed on extending this methodology to ureas where the nitrogen is tethered as part of a ring, such as in indoline and tetrahydroquinoline derivatives. Proposing that conformational restriction prevented the ring expansion reaction on tethered amino acid enolates (see section 2.2.6.1.1), it was reasoned that imidazolidinones could be alternative precursors for the ring expansion of amino acid-based substrates. If successful, this migration would permit access to fused tricyclic ring systems of the type **2-242**, scheme 2-31.



Scheme 2-31. Potential ring expansion using imidazolidinones.

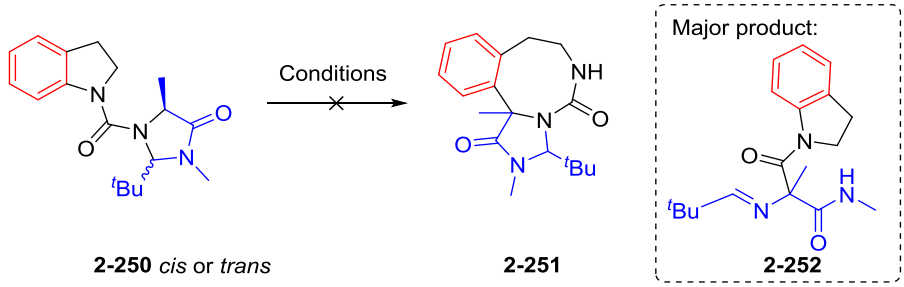
The synthesis of *cis* and *trans* imidazolidinones **2-248** and **2-249** was achieved following literature procedures, scheme 2-32.[115] The synthesis started with conversion of commercially available *L*-alanine ethyl ester hydrochloride **2-243** to its corresponding *N*-methylamide, **2-244**.[119]



Scheme 2-32. Synthesis of imidazolidinone indoline ureas **2-248** and **2-249**.

2-244 Underwent condensation with pivaldehyde to yield imine **2-245**, which was isolated and subsequently treated with triphosgene to effect acylative cyclisation. This resulted in a mixture of *cis* and *trans* diastereomers, which were separable by flash column chromatography. The carbamoyl chlorides **2-246** were then coupled separately with indoline **2-247** resulting in the desired *cis* and *trans* indoline imidazolidinone ureas **2-248** and **2-249**.

Once in hand, imidazolidinone **2-250** was subjected to basic conditions to attempt the ring expansion, scheme 2-33.

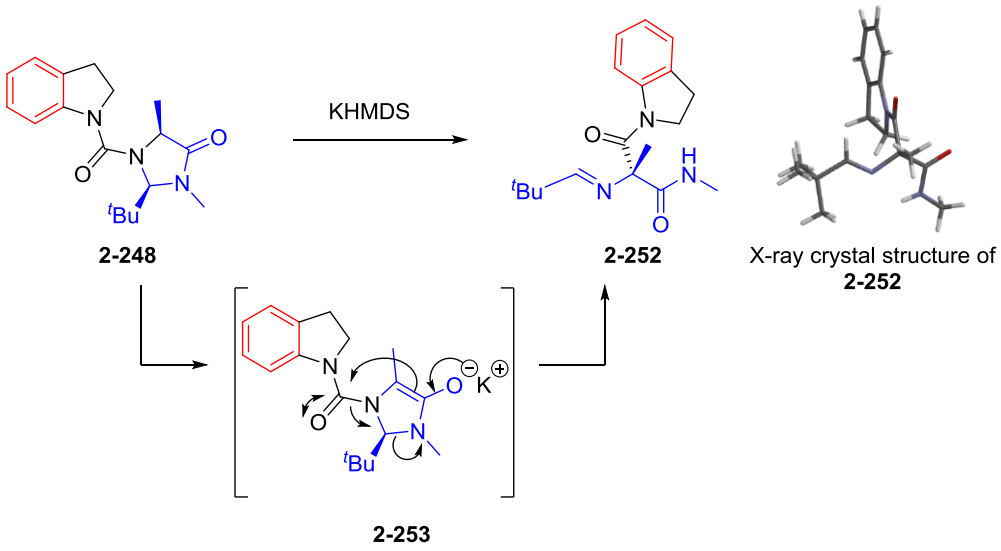


Entry	2-250	Base (eq.)	Additive (eq.)	Temp, °C	Yield 2-252, %	Comment
1	*cis*	KHMDS (1.5)	-	0-RT	90	-
2	*trans*	KHMDS (2)	18-Crown-6 (10)	0-RT	60	-
3	*cis*	LDA (2)	DMPU (5)	−78-RT	traces	Complex mixture of products
4	*cis*	LDA (2)	-	0-RT	20	Complex mixture of products

Scheme 2-33. Attempted ring expansion using imidazolidinones.

On treatment of *cis*-**2-248** with KHMDS in THF, urea **2-248** failed to undergo the desired ring expansion and imine **2-252** was generated in 90% yield with retention of stereochemistry (scheme 2-

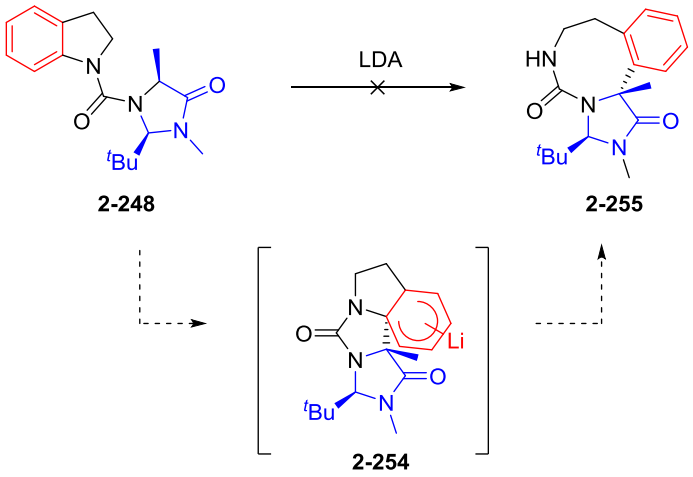
33, entry 1). The formation of imine **2-252** is suspected to proceed by the mechanism shown below, scheme 2-34.



Scheme 2-34. Possible mechanism for the generation of imine **2-252**.

Upon formation, the potassium enolate attacks the urea carbonyl performing a 1,2-acyl shift. This transformation leads to concomitant opening of the imidazolidinone, giving imine **2-252**. 18-Crown-6 was chosen as a suitable additive as it has recently proven to supress the 1,2-acyl shift pathway for a related aryl migration reaction. Although imine **2-252** was isolated in a lower yield, the ring expansion product **2-251** was not observed (scheme 2-33, entry 2).

The optimised conditions for the ring expansion of benzyl ureas were then trialled. Addition of LDA to a solution of the substrate in THF at –78 °C in the presence of DMPU did not lead to any reaction. The reaction mixture was gradually warmed to room temperature. Once TLC analysis indicated consumption of starting material, the reaction was quenched. Unfortunately, ^{1}H NMR of the crude reaction mixture showed a complex mixture of products with trace amounts of imine **2-252** being isolated after purification. Despite our best attempts, the desired ring expansion product was not observed in all cases. It can be assumed that the ring expansion is particularly unfavourable for this substrate class, perhaps due to having to proceed through a highly strained tetracyclic intermediate **2-254**, scheme 2-35.

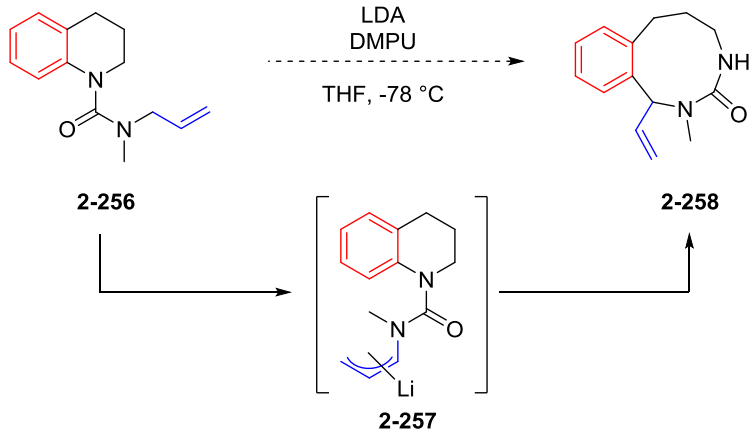


Scheme 2-35. Potential unfavourable intermediate for the ring expansion reaction.

In summary, imidazolidinones are not appropriate amino acid enolate precursors for the ring expansion reaction. In most cases a 1,2-acyl shift pathway dominated leading to imine **2-252**. Unlike benzyl ureas (see section 2.2.3), LDA and DMPU did not supress this pathway and the imine was isolated along with a complex mixture of unidentified products.

2.2.6.2 Allyl Anions

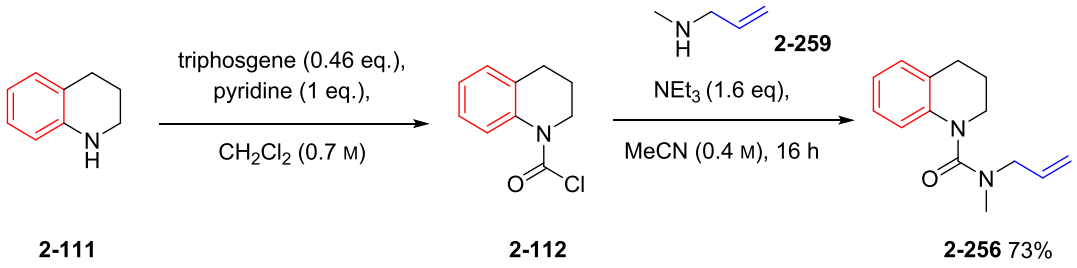
With the previous success of allyl organolithiums as nucleophiles for the rearrangement of linear acyclic systems,[93, 120] it was anticipated that an allyl group could replace the benzyl group in the ring expansion reaction, scheme 2-36.



Scheme 2-36. Ring expansion using an allyl organolithium nucleophile.

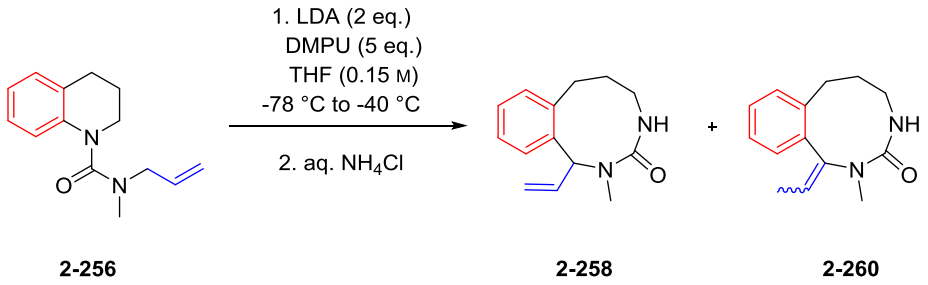
Deprotonation of *N*-allyl urea **2-256** would result in a configurationally stable allyl lithium **2-257**, which after *N*→*C* aryl migration would generate ring expanded product **2-258**.

N-allyl urea **2-256** was synthesised from commercially available tetrahydroquinoline **2-111** using the standard method for tethering on a urea (see section 2.2.2.2), scheme 2-37.



Scheme 2-37. Synthesis of *N*-allyl urea **2-256**.

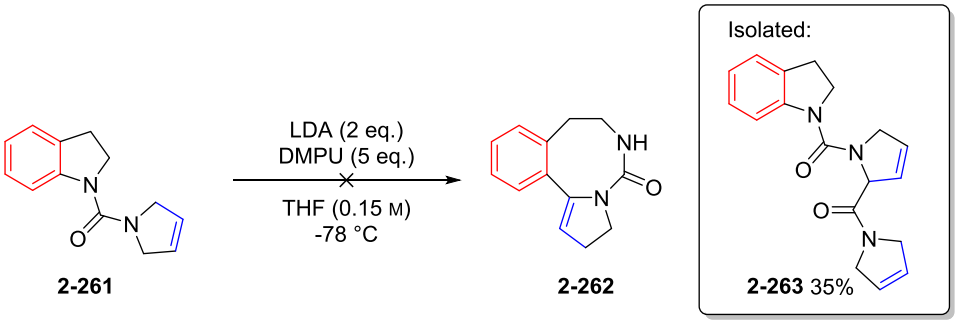
Replacing *N*-benzylmethylamine with *N*-allylmethylamine **2-259** allowed for the generation of allyl urea **2-256** in 73% yield. Subjecting **2-256** to the optimal ring expansion conditions of LDA (2 eq.), DMPU (5 eq.) in THF at –78 °C for 1 hour resulted in a complex mixture of products and only trace amounts of the desired ring expansion product was isolated after purification. Due to the isolation of a small amount of starting material following purification, the reaction time was extended to 16 hours. Although the product was observed in trace amount by ^{1}H NMR analysis of the crude reaction mixture, isolation of the product from an unknown impurity proved problematic. The effect of temperature was then explored, and a reaction was conducted which involved initial deprotonation at −78 °C followed by warming to −40 °C for 16 hours, scheme 2-38.



Scheme 2-38. Ring expansion of allyl urea **2-256**.

^{1}H NMR Analysis of the crude reaction mixture showed a mixture of isomers **2-258** and **2-260** along with other unidentified impurities. Despite our best attempts, separation of the ring expanded products from the unidentified compounds was unsuccessful. Previously it was observed that the ring expansion of thiophene substrate **2-58** only proceeded in the absence of DMPU, therefore the allyl anion-mediated ring expansion reaction was then repeated on **2-256** at −78 °C without the addition of DMPU. However, purification proved problematic, with isomer **2-260** and a mixture of unidentified side products being isolated. Speculating that the nature of the organolithium base might be influencing the outcome of the reaction, *N*-allyl urea **2-256** was then treated with *s*-BuLi in place of LDA at –78 °C and slowly warming to –40 °C. However, this resulted in only trace amounts of products **2-258** and **2-260** with a complex mixture of side products.

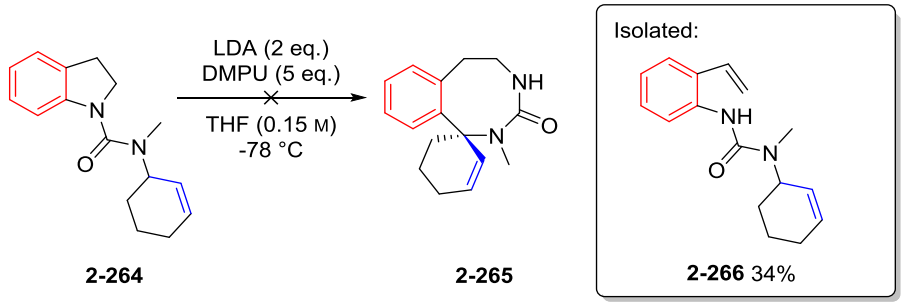
Knowing that allyl anions were potentially suitable nucleophiles for the ring expansion if the products could be separated from side products, other allyl systems were subsequently tried. Pyrolline substrate **2-261** was reacted under the optimised conditions for the ring expansion. TLC analysis of the reaction mixture showed full consumption of starting material and the presence of many new compounds. Purification by flash column chromatography revealed that **2-263**, which was isolated in a 35% yield, was the major product of the reaction, scheme 2-39.



Scheme 2-39. Attempted ring expansion of indoline substrate **2-261**.

The formation of **2-263** presumably arises from deprotonation of **2-261** to generate an allyl organolithium that reacts intermolecularly with another molecule of **2-261**. Nucleophilic attack of the allyl organolithium at the carbonyl of **2-261** and subsequent elimination of indoline gives product **2-263**.

The final substrate trialled was allyl substrate **2-264**. The ring expansion of indoline substrate **2-264** would be particularly interesting due to the potential of making spirocyclic compound **2-265**, scheme 2-40.



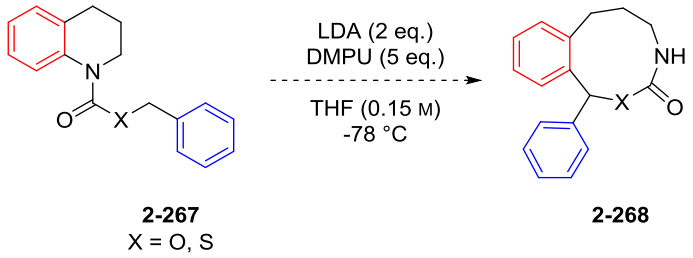
Scheme 2-40. Attempted ring expansion of indoline substrate **2-264** to access spirocyclic compounds.

Although full consumption of starting material **2-264** was observed at –78 °C after 2 hours, analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a complex mixture of products. Purification allowed the isolation of **2-266** as the major product, which results from deprotonation at the benzylic position of the indoline ring followed by ring opening.

In summary, allyl anions have shown potential to be used as alternative nucleophiles for the ring expansion reaction. However, reactivity appears to be substrate specific and therefore not general to different model systems. Future work on investigating allyl anions as nucleophiles should avoid the use of the indoline system where benzylic deprotonation and elimination competes with ring expansion.

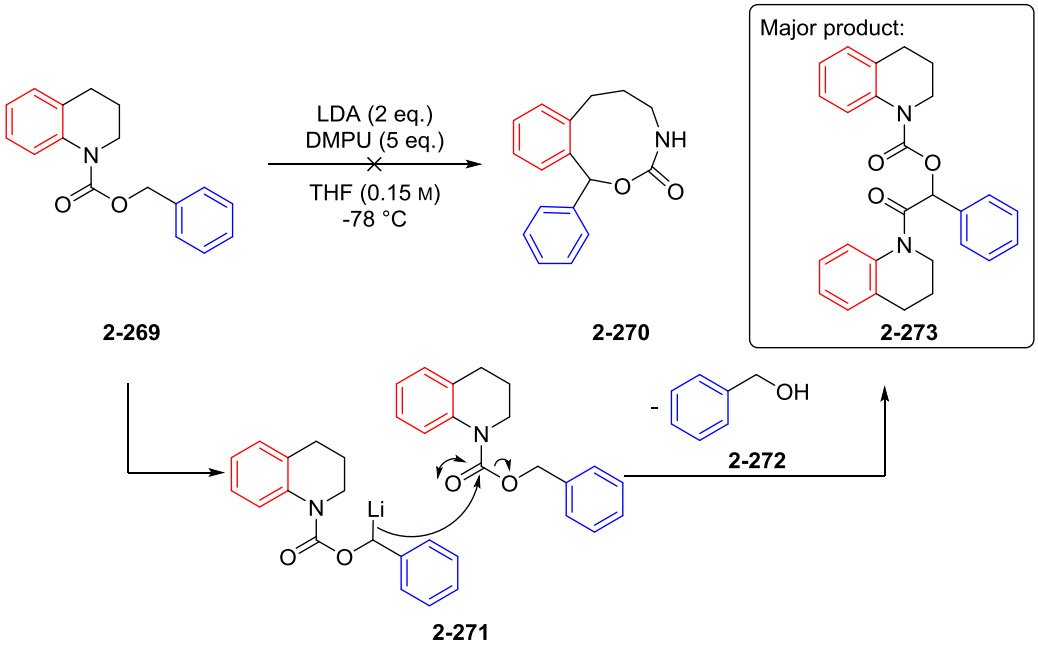
2.2.6.3 Benzylic Anions of Carbamates and Thiocarbamates

Previous work in the Clayden group has shown that *N*→*C* aryl migration on acyclic systems is possible utilising benzylic carbamates and thiocarbamates, allowing access to tertiary arylated alcohols and thiols.[90-92] Consequently, we were interested to see whether the ring expansion methodology was applicable to carbamates and thiocarbamates, scheme 2-41.



Scheme 2-41. Potential ring expansion utilising benzylic carbamates and thiocarbamates.

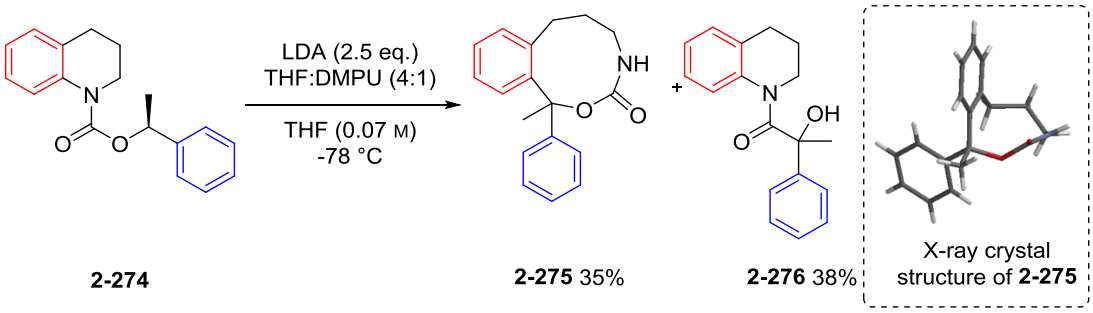
Initial studies focused on the ring expansion of benzyl carbamates. Tetrahydroquinoline carbamate **2-269** was chosen as the model substrate and was synthesised in good yield from tetrahydroquinoline carbamoyl chloride and benzyl alcohol. The ring expansion reaction was then attempted using the optimised conditions for the ring expansion of benzyl ureas, scheme 2-42. Unfortunately, the desired ring expansion product **2-270** was not observed, instead carbamate **2-269** was found to react in an intermolecular manner to generate dimer **2-273** in 30% yield. Alongside dimer formation, unreacted starting material, benzyl alcohol and traces of unknown side products were isolated after purification.



Scheme 2-42. Attempted ring expansion of tetrahydroquinoline benzyl carbamate **2-269**.

Due to the differing outcomes of reactions of the benzyl ureas with and without DMPU (see section 2.2.3), the reaction was repeated in the absence of DMPU, to see if this had an effect on the reactivity. However, the dimerised product **2-273** was observed, in 23% yield, with no sign of the ring expansion product **2-270**. The reaction was repeated with the optimised conditions for *N*→*C* aryl migration of carbamates previously reported in the group,[90] LDA (2.5 eq.) in THF:DMPU 4:1 v/v; however, these conditions generated dimeric product **2-273** in similar yield. The use of different organolithium bases was explored, however both *s*-BuLi as well as the bulkier base Li-TMP did not affect the outcome of the reaction. In an attempt to avoid the undesired intermolecular dimerisation reaction, the reaction was carried out with inverse addition of reagents. Carbamate **2-269** and DMPU were added dropwise by syringe pump over an hour to a solution of LDA in THF at −78 °C, ensuring a high concentration of LDA with respect to the concentration of carbamate. Disappointingly, this did not prevent the intermolecular reaction and **2-273** was formed preferentially in 40% yield. As a final attempt to avoid the intermolecular reaction the reaction was run at a more dilute concentration of 0.015 M. Despite this, **2-273** formed with no signs of the desired ring expansion product.

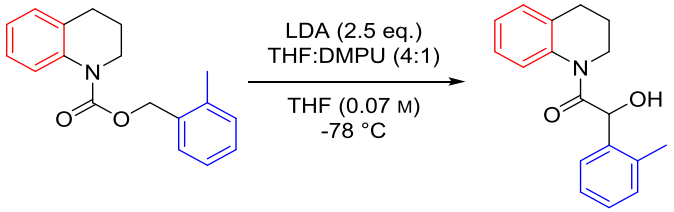
Unlike the benzyl ureas that have a methyl group bonded to the urea nitrogen, the corresponding carbamates lack any form of steric bulk at the oxygen centre. Given the markedly different reactivity observed between ureas and carbamates, it can be postulated that for ureas, the methyl group on nitrogen is essential for achieving the 'reactive conformation' necessary for ring expansion. Therefore, it was proposed that introducing steric hindrance adjacent to the oxygen atom may help firstly in allowing the molecule to adopt the correct conformation for ring expansion, but also by making the anion less reactive for the competing intermolecular reaction. To test this hypothesis, carbamate **2-274** was synthesised according to literature procedure and the ring expansion was attempted using the conditions previously reported for aryl migration using lithiated carbamates, scheme 2-43.[90]



2-274 **2-275** 35% **2-276** 38%

Scheme 2-43. Ring expansion of α-methyl benzyl carbamate **2-274**.

Treatment of α-methyl benzyl carbamate **2-274** with LDA and DMPU in THF afforded the desired ring expansion product **2-275**, albeit in low yield. The acyl shift product **2-276** was also isolated from the reaction mixture, in a slightly higher yield of 38%. Installing the α-methyl group completely suppressed the intermolecular reaction, instead favouring the intramolecular reaction, indicating that steric bulk adjacent to the oxygen is essential for ring expansion of carbamates. The reaction was then repeated with *s*-BuLi in THF, however the yield of ring expansion product **2-275** was reduced to 25%. With a low yield for the ring expansion it was wondered if it was possible to incorporate steric hindrance on the anion stabilising ring instead of alpha to the oxygen atom. Therefore, *ortho*- methyl carbamate **2-277** was synthesised by coupling of tetrahydroquinoline carbamoyl chloride with 2-methylbenzyl alcohol. Carbamate **2-277** was subjected to the conditions for ring expansion, scheme 2-44.



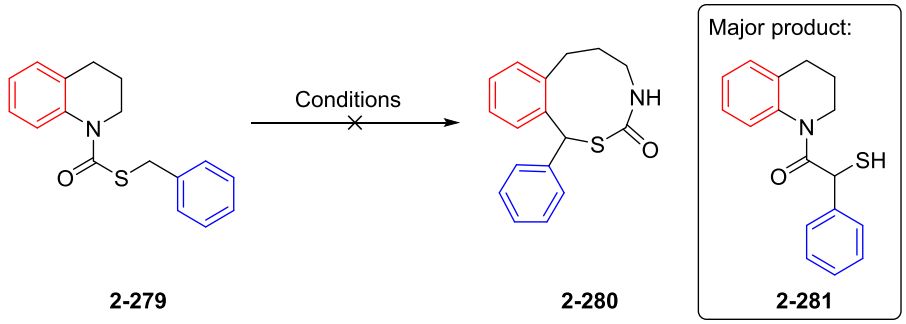
2-277 **2-278** 45%

Scheme 2-44. Attempted ring expansion of **2-277**.

Unfortunately, for carbamate **2-277** the acyl shift pathway dominated and resulted in acyl shift product **2-278** being isolated in 45% yield, along with cleaved tetrahydroquinoline. No signs of the dimeric product were observed, suggesting that there was enough steric hindrance to avoid the intermolecular reaction. This result also highlights the necessity of substitution adjacent to the oxygen atom for the ring expansion to occur.

In summary, the ring expansion methodology developed for benzyl ureas is not applicable to carbamates. It appears that there are alternative reaction pathways depending on the steric environment near the anionic centre. Installing a methyl group adjacent to oxygen suppresses the formation of dimer **2-273** and does allow access to the ring expanded product **2-275**. However, the outcome of the reaction is substrate dependent and therefore does not allow a general method for the access of medium ring carbamate structures.

To explore the feasibility of thiocarbamates being utilised in the ring expansion reaction, tetrahydroquinoline benzyl thiocarbamate **2-279** was synthesised in a similar manner to the analogous carbamates and ureas. Thiocarbamate **2-279** was then subjected to various conditions for the ring expansion, scheme 2-45.



2-279 **2-280** **2-281**

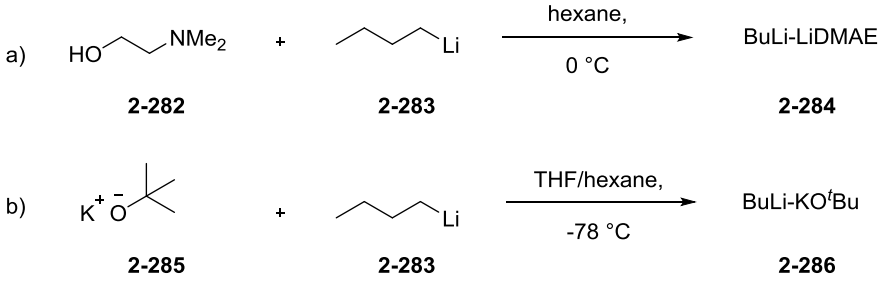
Entry	Base (eq.)	Additive (eq.)	Temp, °C	Time, h	Yield 2-281, %	Comment
1	LDA (2)	DMPU (5)	−78	2	-	Unreacted SM
2	LDA (2)	DMPU (5)	−78	16	-	Unreacted SM
3	LDA (2)	DMPU (5)	−78 - −60	2	41	Remaining unreacted SM
4	LDA (2)	-	−78 - −60	16	95	-
5	LDA (5)	-	−78	16	-	Unreacted SM
6	LDA (2.5)	DMPU (5)	0	16	55	Traces of unknown side products
7	LDA (2.5)	-	0	16	42	Traces of unknown side products
8	s-BuLi (2.5)	DMPU (4:1 THF: DMPU)	−60	16	28	Unreacted SM and THQ isolated

Scheme 2-45. Attempted ring expansion of thiocarbamate **2-279**.

The reaction was first attempted using the optimised conditions for the ring expansion of benzyl ureas, (scheme 2-45, entry 1). After leaving the reaction for 2 hours at −78 °C before being quenched with ammonium chloride, no reaction had occurred, and unreacted starting material remained. The reaction was repeated and left overnight at −78 °C to identify if longer reaction times would yield the ring expansion product **2-280** (scheme 2-45, entry 2). Unfortunately, unreacted starting material remained. The reaction was repeated but with warming of the reaction to −60 °C after deprotonation at −78 °C (scheme 2-45, entry 3). Although starting material remained, TLC analysis of the reaction mixture showed an additional product after the temperature was increased to −60 °C. After purification acyl shift product **2-281** was isolated in 41% yield, with no signs of the desired ring expansion product. The reaction was repeated in the absence of DMPU, (scheme 2-45, entry 4) and left overnight. The longer reaction time and warmer temperature allowed the acyl shift product **2-281** to be isolated in 95%, even in the absence of DMPU. It was hypothesised that similarly to carbamates, thiocarbamates did not adopt the reactive conformation for ring expansion and instead the molecule prefers to adopt the conformation where the anion is in close proximity to the carbonyl, giving rise to the acyl shift product **2-281**. It was reasoned that a large excess of LDA may assist in achieving the correct conformation by coordinating to the thiocarbamate carbonyl and anionic centre, causing a bond rotation to avoid steric clash, hence putting the anion near the migrating aromatic ring. However, treatment of **2-279** with five equivalents of LDA at −78 °C in THF resulted in no reaction (scheme 2-45, entry 5). Carrying out the reaction at 0 °C with and without DMPU resulted in a reduced yield of **2-281** along with a complex mixture of unknown side products (scheme 2-45, entries 6 and 7). **2-281** was isolated in a further reduced yield of 28% when subjecting **2-279** to the conditions used for the *N*→*C* aryl migration of lithiated carbamates

(scheme 2-45, entry 8).[90] Acyl shift product **2-281** was isolated along with unreacted starting material and tetrahydroquinoline. The formation of the acyl shift product was only observed at temperatures above −78 °C, as such we decided to avoid increasing the temperature of the reaction and opted to explore the use of other stronger bases which would affect deprotonation at −78 °C.

Superbases are extremely basic compounds that lead to irreversible proton abstraction.[121, 122] Two examples of super bases commonly used in organic synthesis are butyllithium-lithium dimethylaminoethanol (BuLi-LiDMAE) **2-284** and Schlosser's base (LICKOR) **2-286**. The synthesis of which are shown in scheme 2-46.



Scheme 2-46. Synthesis of superbases.

Butyllithium-lithium dimethylaminoethanol **2-284** is a unimetal superbase and is commonly used for the deprotonation of aromatic heterocycles.[123] It is synthesised by the addition of dimethylaminoethanol **2-282** to *n*-BuLi **2-283** in hexane at 0 °C. LICKOR describes various super basic mixtures of a potassium alkoxide with an alkyl lithium species. The most commonly used mixture is Schlosser's base **2-286** which is formed by the combination of potassium *tert*-butoxide **2-285** with *n*-BuLi **2-283** in a one to one ratio.

The ring expansion of **2-279** was first investigated with BuLi-LiDMAE **2-284**. BuLi-LiDMAE was formed *in situ* and then added to the reaction mixture at −78 °C. The reaction was monitored by TLC analysis and showed only starting material at −78 °C. The reaction mixture was gradually warmed to room temperature and monitored by TLC at the different temperature increments. Unfortunately, only unreacted starting material remained.

The reaction was repeated with Schlosser's base **2-286**. LICKOR was generated *in situ* and added to the reaction mixture at −78 °C. The reaction mixture turned a deep red colour on addition of the first drop of base, suggesting deprotonation. After leaving the reaction mixture to stir at −60 °C overnight, TLC analysis revealed complete consumption of starting material. However, poor mass balance was achieved after purification with no major product isolated. Traces of tetrahydroquinoline was observed along with a complex mixture of products.

In summary, as was the case for the benzyl carbamates, benzyl thiocarbamates are not appropriate precursors for the ring expansion reaction. Reactivity was only observed on warming of the reaction mixture above −78 °C, with the acyl shift product **2-281** dominating when LDA was used as the base. Superbases proved unsuccessful, with LICKOR leading to the formation of a complex mixture of products. These results further highlight the need for substitution on the heteroatom or steric bulk adjacent to the heteroatom for ring expansion to be successful.

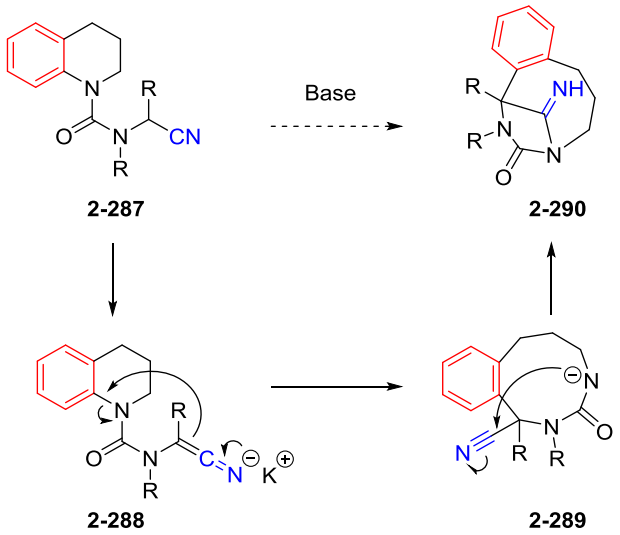
2.2.7 Conclusions & Future Work

A method for the synthesis of benzannulated medium ring nitrogen heterocycles utilising an *n* to *n+3* ring expansion of benzyl ureas has been developed. The reaction appears to be insensitive to steric and electronic factors on the migrating aromatic ring and heteroatoms can be incorporated in the aromatic rings or on the tether. The migration is stereospecific when enantioenriched urea precursors are used and proceeds with complete diastereoselectivity when substitutents are placed on the tether.

Changing the nucleophile from benzyl anions to enolates proved challenging with no ring expansion being observed in all cases. Allyl anions showed potential as suitable nucleophiles although further optimisation is required. Future work should avoid indoline precursors due to additional elimination pathways being active.

Despite the success when using benzyl anions of ureas as nucleophiles, benzyl anions of the related carbamates and thiocarbmates were unsuccessful. It can be postulated that the additional steric bulk of the methyl group at the nitrogen centre of the urea precursors aided in achieveing the correct conformation for ring expansion. Ring expansion was not observed on the carbamate and thiocarbamate derivatives which of course lack steric bulk adjacent to the anionic centre. Only in the case were steric hindrance was introduced at the anionic centre in carbamates was ring expansion observed, albeit in low yield.

Nitrile groups pose as an attractive alternative to the previously used benzyl group for the ring expansion reaction and would allow access to iminohydantoin bicycles **2-290**, scheme 2-47. Preliminary studies within the group have shown this approach to be viable and future work will explore this further.*



Scheme 2-47. Ring expansion utilising nitriles as nucleophiles.

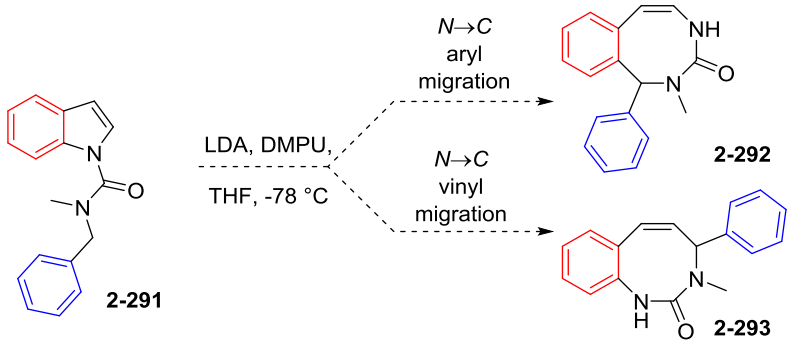
* Preliminary nitrile ring expansion experiments carried out by Emily Ellis (MChem) and Dr John Ward.

2.3 Dearomatising Anionic Cyclisation of Indoles

N.B. The work described herein (section 2.3) is documented in the first author publication, J. E. Hill.; Q. L. Lefebvre.; L. A. Fraser.; J. Clayden. Org. Lett.* ***2018****, 20, 5770.*

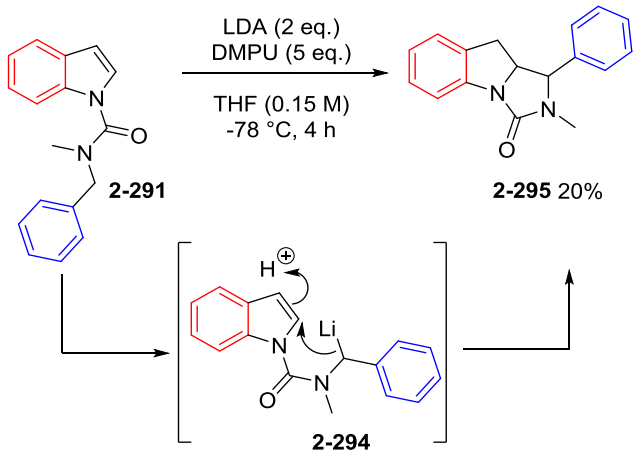
2.3.1 Initial Discovery

Whilst exploring the scope of the ring expansion reaction it was thought that indoles would be an interesting substrate class to investigate. Not only are they readily accessible from commercial sources, but they also possess both an aryl and a vinyl group, both of which have the potential to migrate under the reaction conditions. Both pathways would allow access to desirable medium ring structures, scheme 2-48.



Scheme 2-48. Possible migratory pathways for indole.

Surprisingly, treatment of indole urea **2-291** with the optimised ring expansion conditions of LDA (2 eq.), DMPU (5 eq.) in THF at −78 °C did not follow either of these pathways, and instead polycyclic indoline **2-295** was formed in 20% yield as a single diastereomer, through a dearomatising anionic cyclisation, scheme 2-49.



Scheme 2-49. Dearomatising anionic cyclisation of indole urea **2-291**.[*]

Given the generation of structurally interesting heterocyclic 6,5,5 ring systems, we decided to investigate this dearomatising cyclisation methodology further.

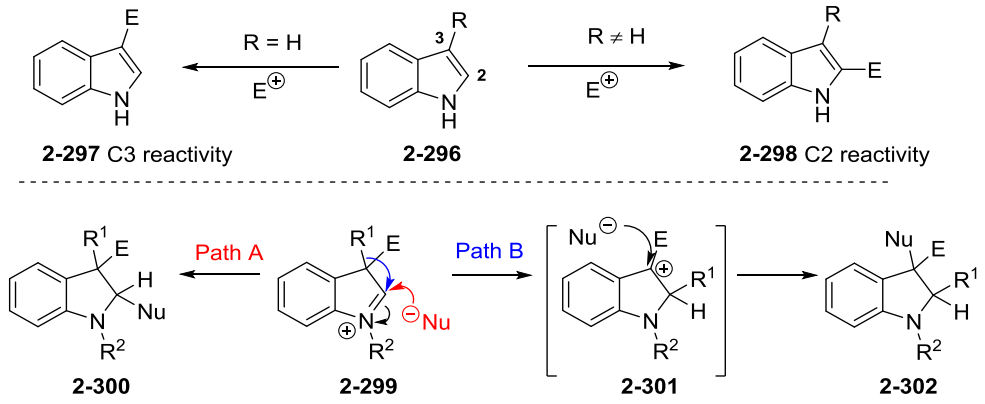
[*] Experiment carried out in collaboration with Dr Johnathan Matlock.

2.3.2 Strategies for Dearomatising Indoles

2.3.2.1 Background

Indole dearomatisation is an important strategy for the synthesis of alkaloids which have known positive biological properties. Indoline and indolenine have shown promise as therapeutic agents due to their biological activity against inflammation, hypertension and cancer.[124-129] It therefore comes as no surprise that many groups have devoted their research towards the functionalisation of indoles, tryptamines and β-carboline building blocks.[130]

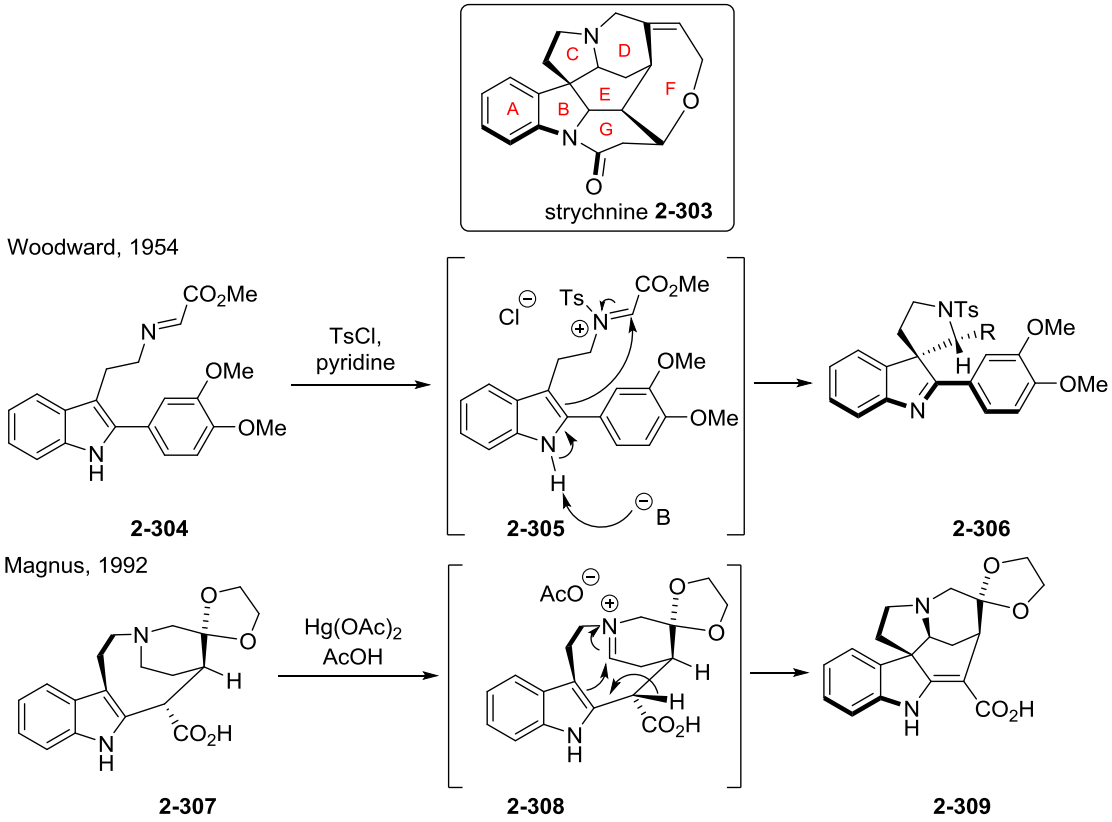
Functionalisation at the C3 position of indole is most commonly achieved following the reaction of the parent indole with suitable electrophiles by enamine type reactivity. Although functionalisation at C2 is possible, this is typically attained when the C3 position is blocked, scheme 2-50. When dearomatisation occurs at the C3 position, the resulting indolenium **2-299** can be attacked by a nucleophile at the C2 position resulting in indolenine **2-300** (scheme 2-50, path A). Alternatively, the indolenium **2-299** can undergo an intramolecular [1,2]-shift of a C3 substituent to the C2 position, followed by trapping of the benzylic carbocation by nucleophilic addition at C3 (scheme 2-50, path B).



Scheme 2-50. Indole reactivity.[130]

The dearomatisation reactivity of indole has sparked a vast amount of interest in the field as it enables the formation of interesting ring systems, with different substitution patterns obtainable dependent on the regioselectivity.

The usefulness of indole dearomatisation has been demonstrated in the context of natural product synthesis and was successfully implemented into the synthesis of the indole alkaloid, Strychnine **2-303**. Of the many syntheses published, five include an indole dearomatisation strategy at some stage in their synthesis. For example, in 1954, Woodward exploited such a dearomative strategy *via* a 'Pictet–Spengler-type' reaction of an activated tryptamine-derived iminium **2-305** for the construction of the C ring of Strychnine, scheme 2-51.[131]



Scheme 2-51. Dearomatising indole as the key steps in the synthesis of strychnine **2-303**.[131, 132]

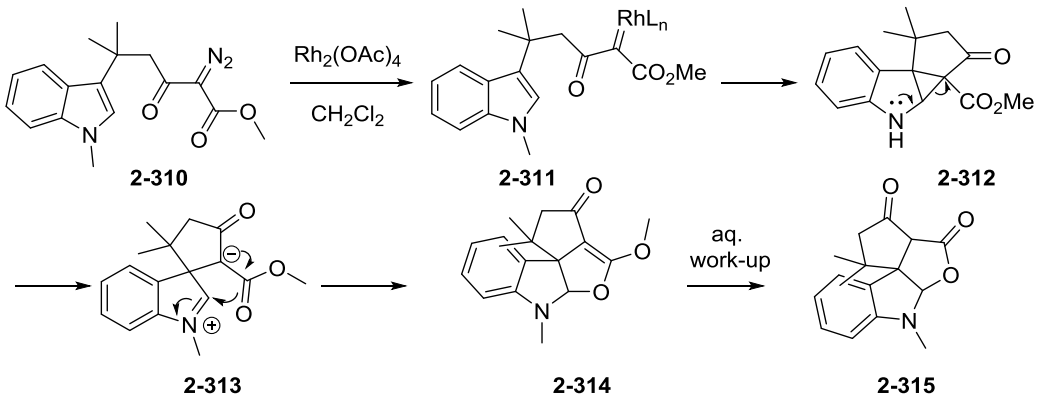
Further studies by Magnus showed that a dearomative strategy by a transannular Mannich reaction was feasible.[132, 133] The use of mercury acetate was reported for the dehydrogenation of tetracyclic indole **2-307** to produce iminium **2-308** which was subsequently attacked intramolecularly by the nucleophilic C3 position to synthesise the pentacyclic indoline scaffold, scheme 2-51. Others have also demonstrated dearomative transformations of indole for the synthesis of Strychnine both racemically[134] and asymmetrically,[135] clearly highlighting the importance of this method for accessing useful alkaloid structures.

2.3.2.2 Indole Dearomatisation by Cycloadditions

Cycloadditions are powerful synthetic methods for the construction of complex molecular architectures with concomitant control of the resulting stereocentres. Many cycloaddition strategies have been exploited as an alternative method to effect dearomatisation of indole to access polycyclic structures, such as cyclopropanations, 1-3-dipolar cycloadditions, [2+2] cycloadditions followed by retro-Mannich fragmentations and Diels–Alder reactions.[130]

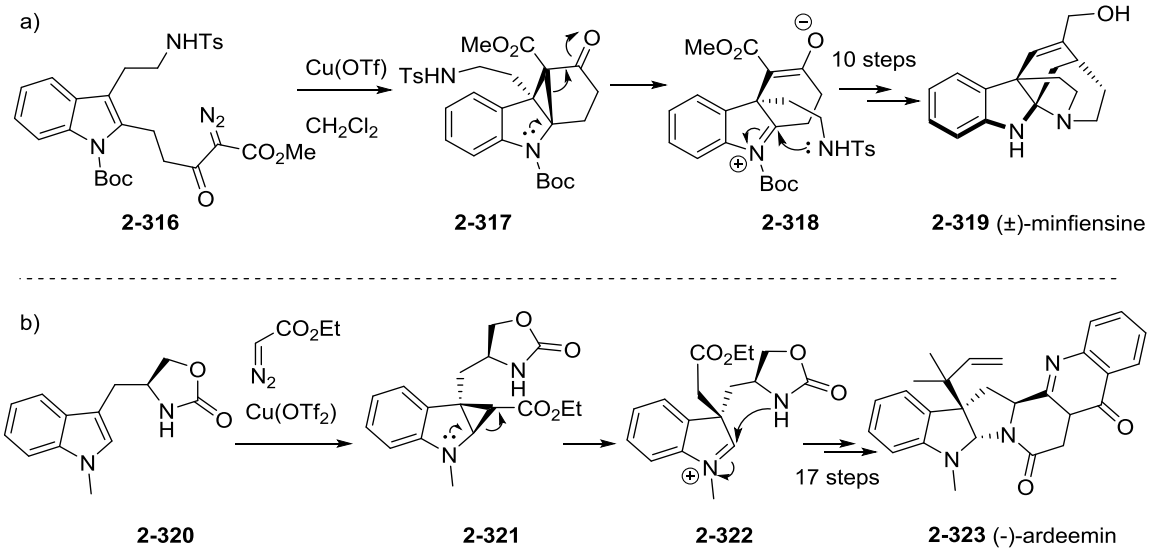
2.3.2.2.1 Cyclopropanations

Due to the ability of indole to undergo cyclopropanation, together with the known tendency of cyclopropanes to undergo fragmentation, coupling both reactivities has allowed an effective method for the synthesis of polycyclic indoline structures. Metals such as rhodium and copper have been reported to catalyse these processes by formation of carbenoid species. Jung *et al.* studied the use of rhodium acetate to generate a rhodium carbenoid of 3-substituted indole esters **2-311**, followed by cyclopropanation yielding **2-312**.[136] Spontaneous ring opening of the cyclopropane afforded iminium **2-313**, which underwent cyclisation initiated by the ester enolate, yielding **2-315** as the minor product after hydrolysis.



Scheme 2-52. Indole dearomatisation *via* cyclopropanation.[136]

Similarly, Qin *et al*. investigated a dearomatising cyclopropanation procedure in the synthesis of natural products (±)-minfiensine and (-)-ardeemin.[137, 138] In contrast to the work by Jung, Qin and co-workers used copper (II) triflate as the catalyst to aid the reaction. Initially, Qin focused on developing an achiral dearomatisation/rearrangement sequence using tryptamine derivative **2-316**, scheme 2-53 a.



Scheme 2-53. Copper catalysed cyclopropanation for indole dearomatisation.[137, 138]

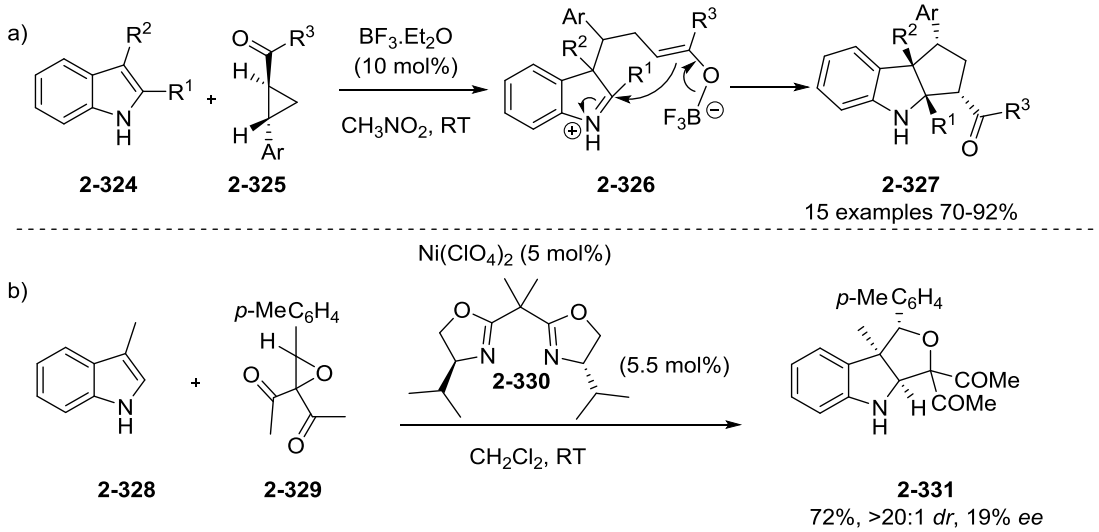
The cyclopropanation-ring opening generated indolenium **2-318** which was subsequently trapped intramolecularly by the pendant amine, scheme 2-53 a. Shortly after, Qin reported a diastereoselective dearomatisation of tryptophan derivative **2-320**, for the synthesis of (-)-ardeemin **2-323**.[138] The procedure involved a 'one-pot' three step cascade reaction including an intermolecular cyclopropanation, ring opening and ring closure sequence which proceeded in good yield and diastereoselectivity, scheme 2-53 b. An asymmetric cyclopropanation, ring opening sequence was later developed by Davies[139] exploiting rhodium carbenoids derived from 4-aryl-1-sulfonyl-1,2,3-triazoles. The pyrroloindoline products produced using this methodology were accessed in moderate to excellent yields and enantioselectivites using methyl protected indoles. Unprotected indoles were also successful in the reaction, although the products were isolated with lower enantiomeric excess.

2.3.2.2.2 1,3-Dipolar Cycloadditions

1,3-Dipolar cycloadditions offer an alternative route to alkaloid frameworks by dearomatisation of indoles using two key methods. The first is mediated by Lewis acids, enabling the opening of ring systems (cyclopropanes, epoxides), thereby generating 1,3-dipoles that trigger the cycloadditions. The

second approach uses metal catalysis for the generation of carbonyl ylides as dipolarophiles for cycloadditions.

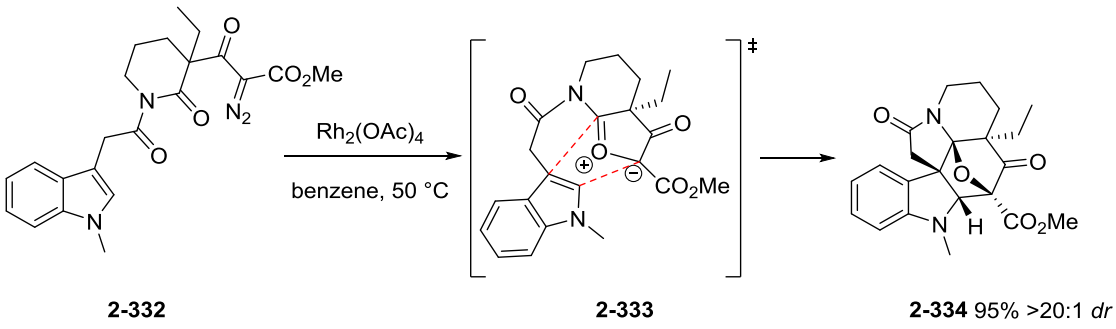
Whilst older studies focused on the use of ytterbium triflate for the dearomatisation of 3-methyl indoles,[140-142] a more recent study by Venkatesh reported a [3+2] cyclopenta[*b*]annulation for the synthesis of polycyclic indoline **2-327**, using boron trifluoride as Lewis acid, scheme 2-54 a.[143]



Scheme 2-54. Lewis acid-mediated [3+2] cycloaddition.[143, 144]

Electron-rich arylated cyclopropanes were necessary to promote ring opening on addition of boron trifluoride to generate a stable zwitterionic intermediate. This allowed a facile [3+2] cycloaddition yielding indoline products **2-327** *via* an iminium intermediate **2-326**, scheme 2-54 a. An array of tricyclic indoline products **2-327** were obtained in good to excellent yields. Similarly, Wu *et al.* published the synthesis of oxygenated indoline **2-331**, opening an epoxide instead of a cyclopropane, scheme 2-54 b.[144] Nickel perchlorate was chosen as a suitable catalyst for the transformation along with BOX ligand **2-330** to induce enantioselectivity. Although the desired indoline product **2-331** was isolated in good yield as a single diastereomer, the enantiomeric excess was poor.

The most common metal employed for indole dearomatisation using 1,3-dipolar cycloadditions is rhodium. In 1995, Padwa *et al.* reported a rhodium (II)-catalysed cyclisation-cycloaddition sequence in the total synthesis of *Aspidosperma* alkaloids, scheme 2-55.[145]

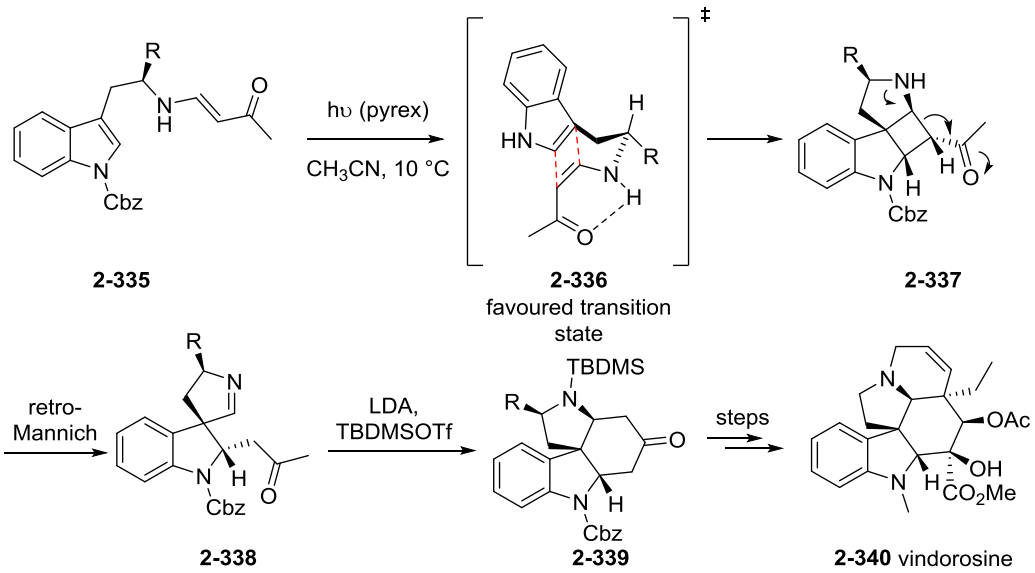


Scheme 2-55. Rhodium (II)-catalysed cyclisation and 1-3-dipolar cycloaddition.

In this strategy the 1,4-diazo imide **2-332** undergoes cyclisation, generating 1,3-carbonyl ylide **2-333** which encourages the C2-C3 indole double bond to react as a 2π component in the 1,3-dipolar cycloaddition. The resulting hexacyclic indoline **2-334** was isolated in 95% yield with excellent diastereoselectivity.

2.3.2.2.3 [2+2] Photocycloadditions Followed by Retro-Mannich Fragmentation

[2+2] Photocycloadditions followed by a retro-Mannich fragmentation have also been used for indole dearomatisation. Winkler and co-workers investigated this sequence as a key step in the synthesis of vindorosine **2-340**, scheme 2-56.[146]



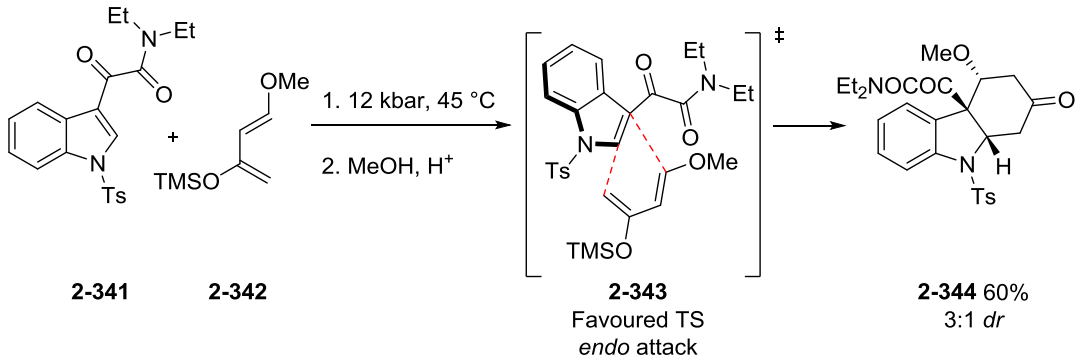
Scheme 2-56. [2+2] Photocycloaddition followed by retro-Mannich fragmentation as a key step in the synthesis of vindorosine **2-340**.[146]

Irradiation of indole **2-335** using a 450 W medium pressure Hg lamp gave cyclobutane **2-337** which subsequently underwent a retro-Mannich fragmentation yielding photoadduct **2-338** in excellent yield and diastereoselectivity. Treatment of spirocyclic cycloadduct **2-338** with LDA and silyl triflate allowed ring closure to the tetracyclic structure **2-339**. Using the same method of photocycloaddition followed by retro-Mannich fragmentation, White *et al.* reported the synthesis of many β-carbolines and oxindole natural products.[147]

2.3.2.2.4 Diels–Alder Cycloadditions

Diels-Alder [4+2] cycloaddition is a powerful synthetic method in an organic chemist's toolbox for the synthesis of ring systems. Not only does it allow access to 6-membered rings, but it simultaneously sets stereogenic centres and functional groups.[148] Indole substrates can participate in Diels–Alder cycloadditions in two ways, either as dienophiles using the C2-C3 double bond, or as dienes when substituted at the C2 or C3 positions with a pendent alkene.

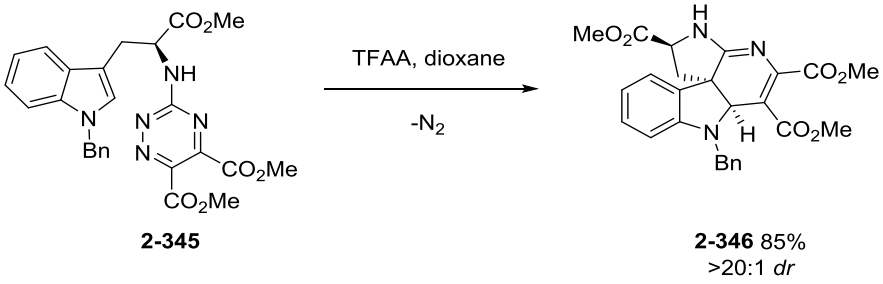
Due to indole's low tendency to act as a dienophile, normal electron-demand Diels–Alder reactions are challenging, often requiring specific substitution on indole and harsh reaction conditions. It is essential for the indole to be substituted at nitrogen and the C3 position with electron-withdrawing groups to ensure reactivity. Early work by Wenkert showed that indole dearomatisation using a normal demand Diels–Alder [4+2] cycloaddition was possible when using high pressures.[149] They reported the synthesis of tricyclic indoline **2-344** by normal-demand Diels-Alder cycloaddition with Danishefsky's diene **2-342**, scheme 2-57.



Scheme 2-57. Diels–Alder [4+2] cycloaddition using high pressure.[149]

Pressures as high as 12 kbar at 45 °C for 48 hours were required to access polycyclic indole **2-344** in good yield after hydrolysis of the silyl enol ether. The product was isolated as a 3:1 mixture of *endo:exo* products which were separable by column chromatography.

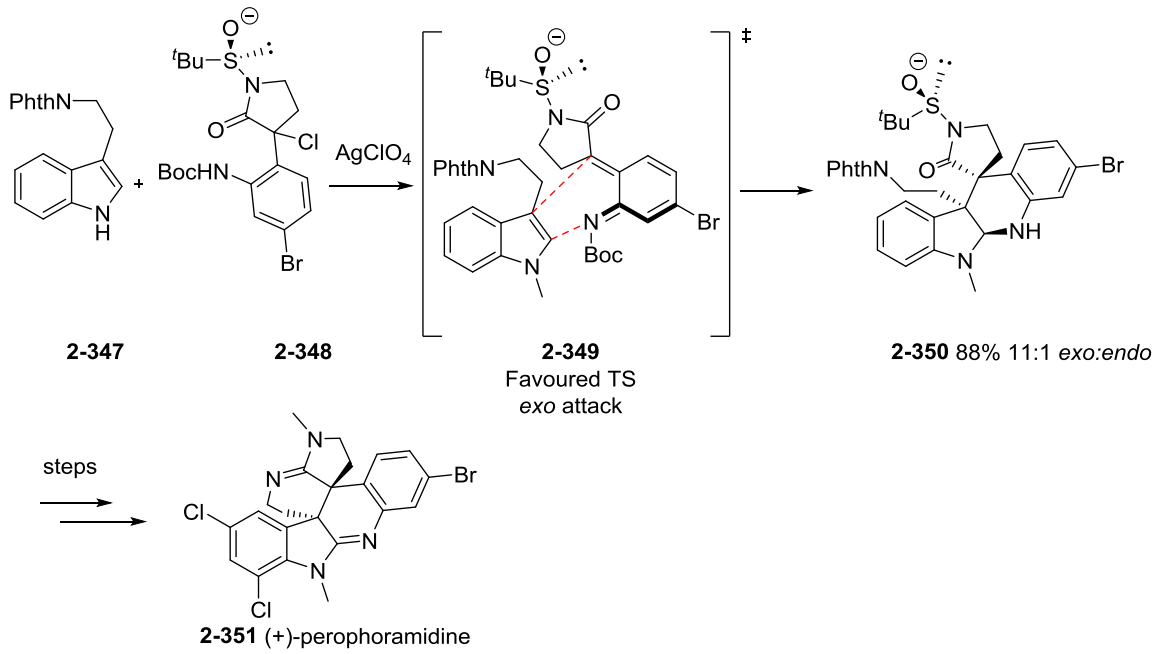
Inverse electron-demand Diels–Alder cycloadditions for the dearomatisation of indoles are also possible, exploiting the indole C2-C3 double bond as a dienophile and reacting it with an electron-poor diene. Pioneering work by Snyder showed that indoles can react with 1,2,4,5-tetrazines, 1,2,4-triazines and pyridazines in [4+2] cycloadditions to yield the desired polycyclic indoline scaffolds.[150-156] An example is shown in scheme 2-58.



Scheme 2-58. Inverse electron-demand Diels–Alder cycloaddition for the synthesis of tetracyclic indoline **2-346**.[150-156]

Subjecting tryptophan triazine derivative **2-345** to trifluoroacetic anhydride in dioxane led to an intramolecular inverse electron-demand Diels–Alder cycloaddition yielding **2-346** as a single diastereomer after extrusion of nitrogen and deacylation of the *N*-trifluoroacetate adduct. The fact that no other diastereomer was detected indicates that the chiral centre present in **2-345** imparts excellent stereocontrol in the facial approach of the azadiene to the indole dienophile. Tetracyclic indoline **2-346** is of importance due to being an aza-analog of *Aspidosperma* alkaloids.

Hetero-Diels–Alder cycloadditions are predominantly inverse electron-demand reactions and occur typically between (aza) quinone methide dipolarophiles and the 2π electrons of the C2-C3 double bond of indole. In 2010, Qin *et al.* reported an intermolecular hetero-Diels–Alder cycloaddition as the key step in the asymmetric total synthesis of (+)-perophoramidine **2-351**.[157]

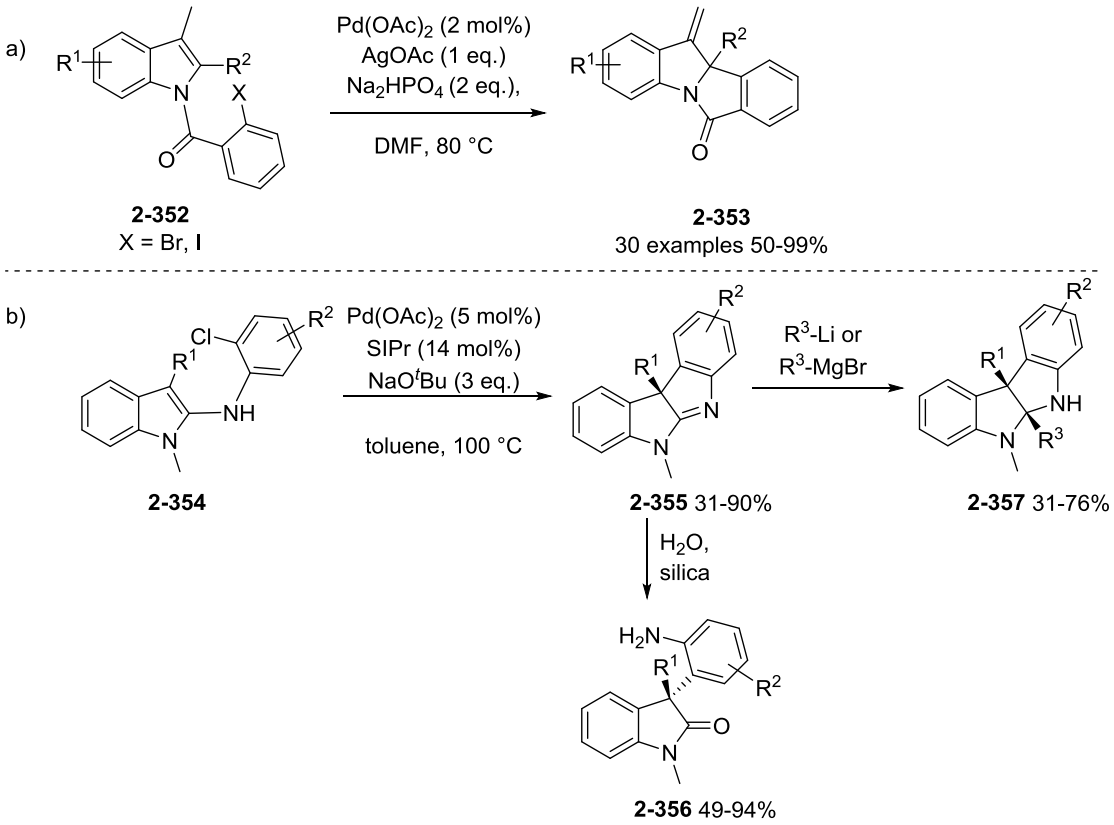


Scheme 2-59. Hetero-Diels–Alder cycloaddition as the key step in the synthesis of (+)-perophoramidine.[157]

In this work a silver (I) Lewis acid was needed to assist in the formation of a reactive aza-quinone methide intermediate **2-349**, which underwent an inverse electron-demand [4+2] cycloaddition with indole **2-347**, generating the complex spirocyclic indoline core **2-350** in 88% yield. Although there is potential for multiple isomers, the reaction proceeded with high *exo* selectivity *via* an *in situ* generated trans/trans diene, **2-349**.

2.3.2.3 Indole Dearomatisation by Palladium-Catalysed Reactions

Despite their widespread use in synthetic organic chemistry for the formation of new C-C bonds, palladium-catalysed cross coupling reactions have not been extensively studied in the context of dearomatisation of indoles. As a rare example, in 2012 Wu and co-workers devised a method of accessing fused indoline structures **2-353** *via* an intramolecular Heck reaction, scheme 2-60 a.[158]

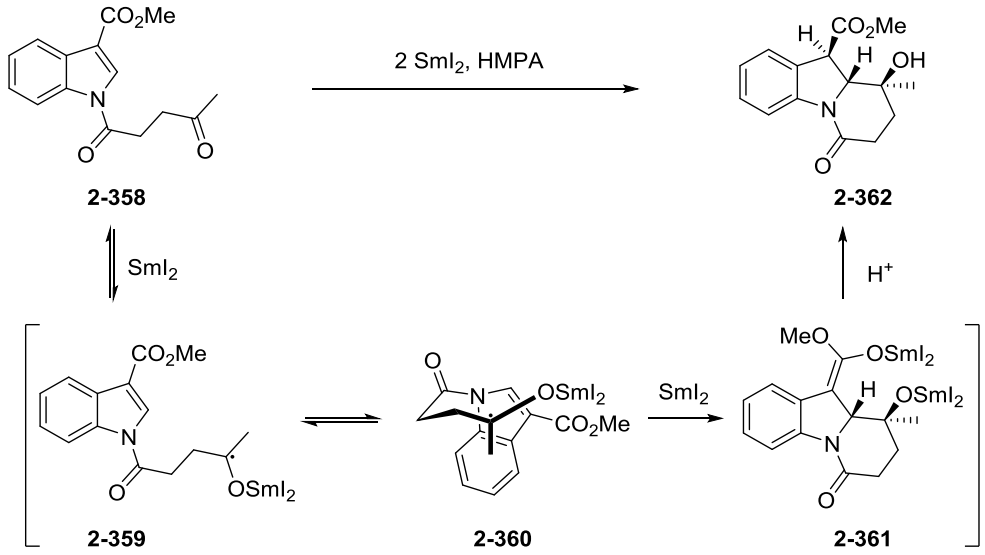


Scheme 2-60. Palladium-catalysed dearomatisation of indoles.[158, 159]

The authors used palladium (II) in conjugation with silver acetate to enable a Heck reaction followed by β-hydride elimination to yield structure **2-353** in moderate to excellent yields. In a similar fashion, Bedford *et al.* demonstrated an alternative palladium-catalysed dearomatisation procedure also using palladium acetate.[159] The catalyst was formed *in situ* by palladium acetate and *N*-heterocyclic carbene ligand SIPr, and subjected to indole starting material and potassium *tert*-butoxide in toluene at 100 °C, scheme 2-60 b. The desired indoloindole structures **2-355** were generated in moderate to excellent yields and could be further modified into oxindoles **2-356** or reduced to tetracyclic indolines **2-357**.

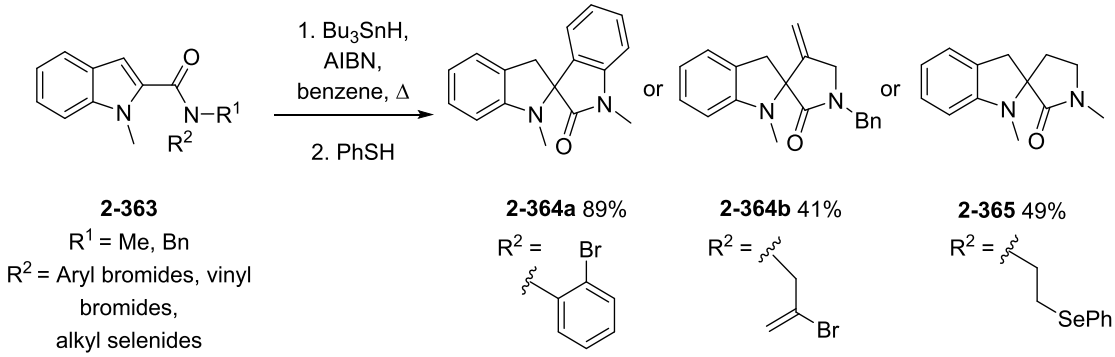
2.3.2.4 Indole Dearomatisation by Radical Cyclisation

Radical cyclisations are an important method for dearomatising indoles and allow access to complex polycyclic frameworks. Reissig *et al.* reported a diastereoselective intramolecular indole dearomatisation by addition of a ketyl radical to indole, scheme 2-61.[160, 161] The reaction is promoted by a samarium diiodide-HMPA complex which transfers an electron to a carbonyl group, therefore generating a radical anion that reacts with the aromatic system through a 6-membered transition state, scheme 2-61.



Scheme 2-61. Indole dearomatisation by radical cyclisation.

It was hypothesised that the bulky samarium alkoxide prefers an equatorial position in the transition state due to steric and electronic reasons, positioning the methyl group in an axial position, **2-360**. Subsequent protonation of the enolate generates tricyclic indoline **2-362**. This methodology was later applied to the total synthesis of Strychnine.[162] In 2004, Baldwin *et al.* reported a dearomatising spirocyclisation to generate spirolactam structures **2-364a**, **2-364b**, **2-365**, scheme 2-62.[163]



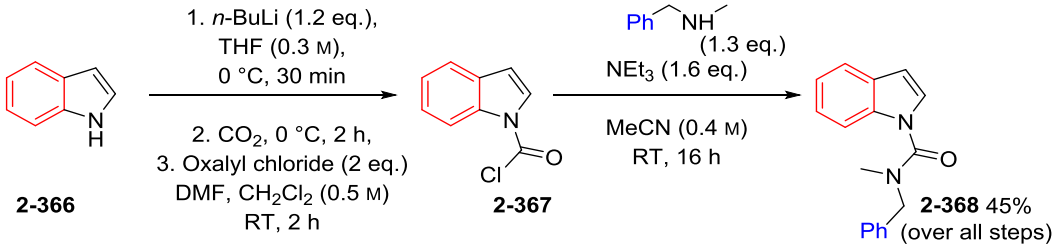
Scheme 2-62. Indole dearomatisation *via* spirocyclisation using aryl, vinyl and alkyl radicals.[163]

This work demonstrated that aryl, vinyl and alkyl radicals could be used in this *ipso*-substitution to give full dearomatisation of indole. Subjecting each precursor to the same cyclisation conditions of Bu_3SnH, AIBN in benzene allowed access to the spirocyclic compounds in varying yields. When the high energy aryl radicals were used, yields of the desired product were excellent. However, yields were much lower for the products isolated using vinyl radicals, despite the fact that no reduced starting material was observed. Yields for the spirocycles obtained using alkyl radicals derived from alkyl selenides were also moderate, with the remaining mass being reduced starting material.

Despite the indole dearomatisation methods described above, there is still scope to investigate new methods for the synthesis of novel polycyclic indoline structures. A method which utilises commercially available indoles and increases the complexity of the molecular architecture using only a few simple steps is highly desirable. As a result, employing the simple and transition metal free conditions previously developed for the ring expansion of benzyl ureas (see section 2.2) offers an attractive method for the synthesis of polycyclic indoline frameworks through indole dearomatisation.

2.3.3 Indole Urea Precursor Synthesis

Initial studies focused on developing a general method for precursor synthesis. Indole urea **2-368** was synthesised in two steps following a literature procedure, scheme 2-63.[164]

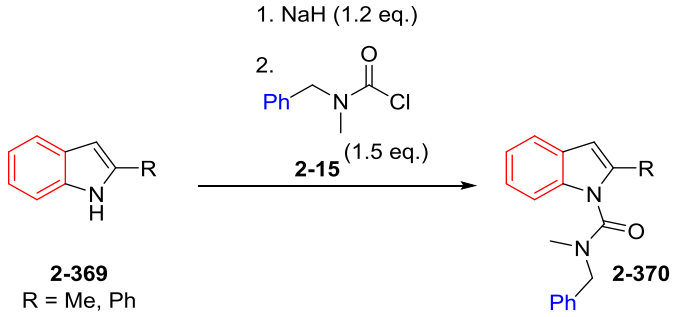


Scheme 2-63. Synthesis of indole urea precursor **2-368**.*

The method involves the synthesis of indoline carbamic acid and subsequent treatment with oxalyl chloride to afford the carbamoyl chloride **2-367**. Coupling of **2-367** with *N*-benzylmethylamine using the standard conditions (see section 2.2.2.2) yields the indole benzyl urea **2-368** in 45% yield over all steps.

With the knowledge that treatment of indole urea **2-368** with the standard conditions for ring expansion leads to the generation of polycyclic indoline **2-295**, it was postulated that blocking the 2-position on the indole would favour ring expansion over dearomatising cyclisation. As a result, 2-methyl indole and 2-phenyl indole were chosen as suitable precursors to test this hypothesis. Despite the fact that indole urea **2-368** was synthesised successfully using the CO_2 method describe above, this method was not applicable to the synthesis of 2-methyl and 2-phenyl indole ureas **2-370**. As a result, an alternative, general method was investigated for precursor synthesis.

Firstly, a one-step procedure involving treatment of indole **2-369** with benzyl(methyl)carbamoyl chloride **2-15** was attempted, scheme 2-64.



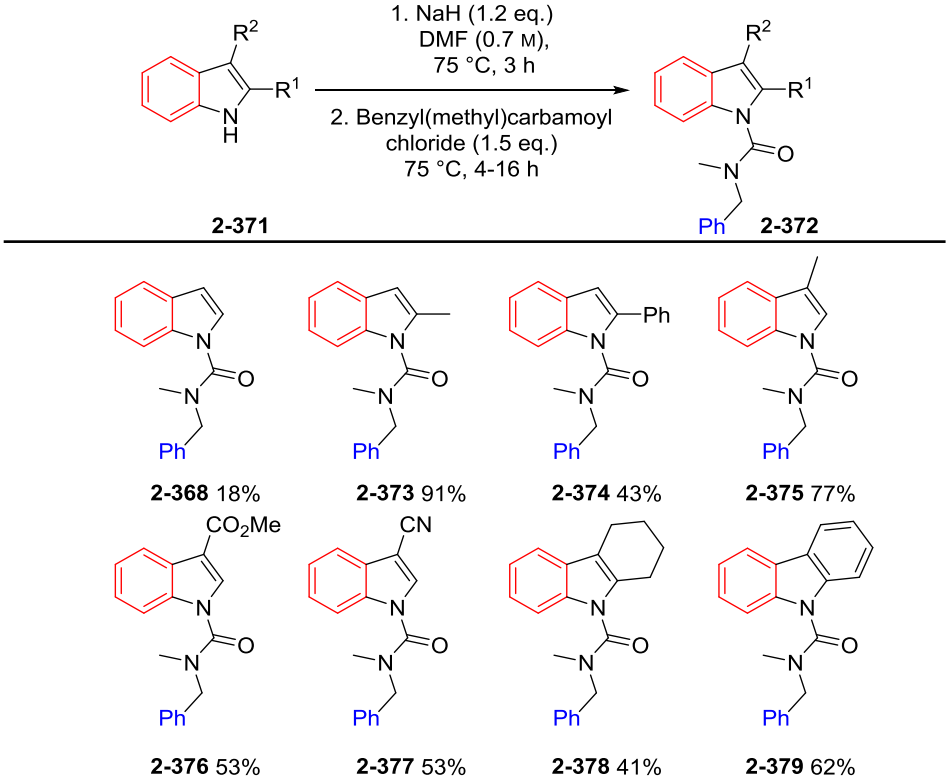
Entry	R	Solvent	Temp, °C	Yield 2-370, %
1	Me	THF	RT	6
2	Ph	THF	RT	33
3	Me	DMF	75	91
4	Ph	DMF	75	43

Scheme 2-64. Synthesis of 2-substituted indole ureas **2-370**.•

* Experiment carried out by Johnathan Matlock.
• Experiments carried out by Laura Fraser (MChem)

Although this method is simpler from a practical perspective, indoles **2-369** had poor solubility in THF and the desired 2-substituted indole ureas **2-370** were isolated in low yields (scheme 2-64 entries 1 and 2). To circumvent this issue, the solvent was replaced with DMF to aid solubility and allow higher reaction temperatures.[165] Pleasingly, the 2-substituted indole ureas **2-370** were isolated in improved yields (scheme 2-64 entries 3 and 4). As a result, this was chosen as the optimised method for precursor synthesis.

With a method for precursor synthesis in hand our focus turned to synthesising a range of indole benzyl ureas. Scheme 2-65 shows the ureas synthesised from commercially available indoles.



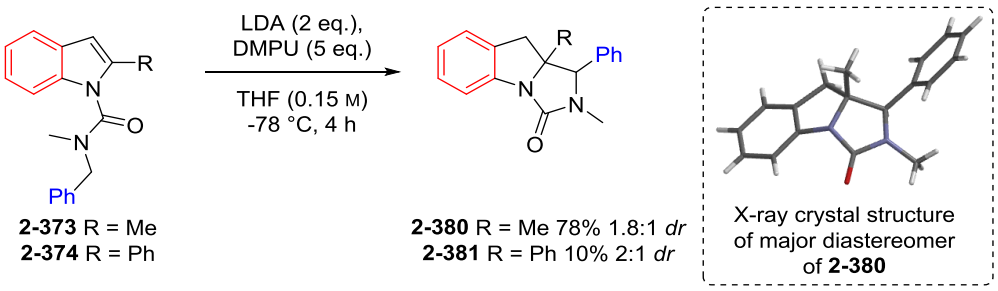
Scheme 2-65. Synthesis of indole benzyl ureas from commercial indoles.*

Using the methodology outlined above, a range of 2- and 3-substituted indoles were converted into their benzyl urea counterparts in moderate to excellent yields.

2.3.4 Dearomatising Anionic Cyclisation of Indole Ureas Derived from Commercial Indoles

As stated previously we were interested in investigating whether substitution at the 2-position of indole would block the dearomatising cyclisation, instead favouring the ring expansion. To test this hypothesis, indole urea substrates **2-373** and **2-374** were trialled using the conditions previously optimised for ring expansion, scheme 2-66.

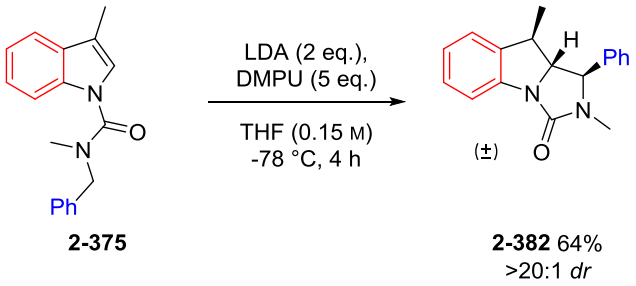
* Experiments carried out in collaboration with Laura Fraser (MChem).



Scheme 2-66. Dearomatising cyclisation of 2-substituted indole benzyl ureas.•

Interestingly, despite introducing substitution at the 2-position of indole, the dearomatising cyclisation pathway dominated, with no ring expansion products observed. When R=Me the polycyclic indoline product **2-380** was isolated in 78% yield as a mixture of separable diastereomers. X-Ray crystallography revealed the major diastereomer as having a *cis*- relationship between the phenyl and methyl groups, scheme 2-66. The reaction was repeated in the absence of DMPU to assess its necessity in the reaction. TLC analysis of the reaction mixture without DMPU after four hours showed predominantly starting material, indicating that DMPU is essential for increasing the rate of reaction, presumably due to deaggregation of the LDA solution. The phenyl-substituted substrate **2-374** also gave a polycyclic product **2-381**, in only 10% yield as an inseparable mixture of diastereomers in a 2:1 ratio.

3-Substituted indoles were then investigated in the dearomatising cyclisation reaction. The cyclisation of 3-substituted indoles would give rise to three stereocentres, hence the possibility for the formation of four diastereomers. 3-Methyl indole urea **2-375** was subjected to the cyclisation conditions and yielded polycyclic indoline **2-382** as a single diastereomer in 64% yield, scheme 2-67. Nuclear Overhauser Effect (NOE) NMR experiments confirmed that the phenyl, the proton and the methyl group had a 1,2,3-all-*syn*-relationship.

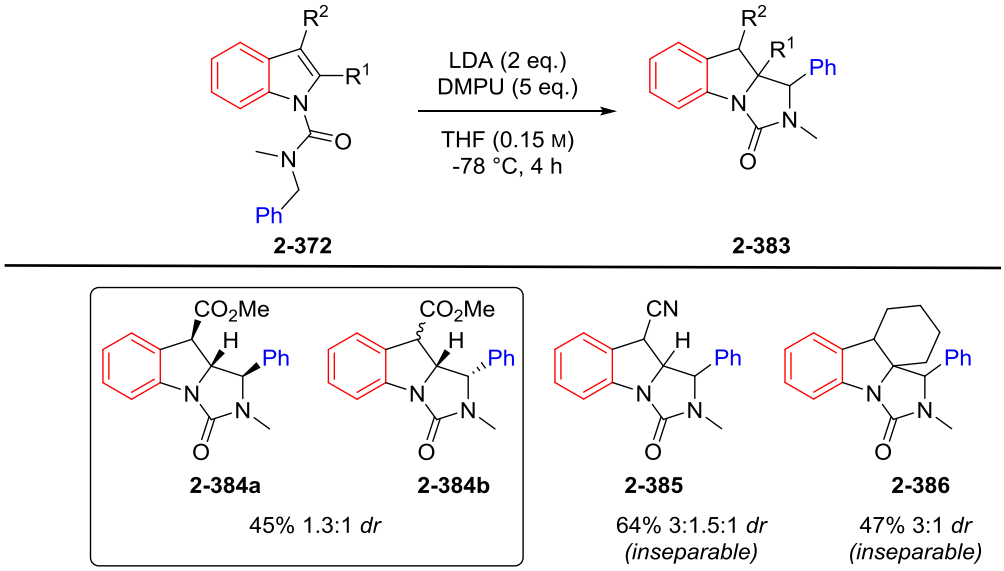


Scheme 2-67. Dearomatising cyclisation of 3-substituted indole urea **2-375**.

The reaction was then repeated using *s*-BuLi in THF in attempt to improve the yield of **2-382**. The desired product was isolated in a lower yield of 36% as a single diastereomer along with several unwanted side products, which suggested alkylation by the nucleophilic *s*-BuLi. As a result, in all subsequent reactions LDA was chosen as the base.

The remaining indole ureas (see scheme 2-65) were subjected to the optimised conditions for dearomatising cyclisation, LDA (2 eq.), DMPU (5 eq.) in THF (0.15 M) at −78 °C and allowed to react for 2-4 hours, scheme 2-68.

• Experiment carried out by Laura Fraser (MChem).



Scheme 2-68. Dearomatising anionic cyclisation of indole ureas.*

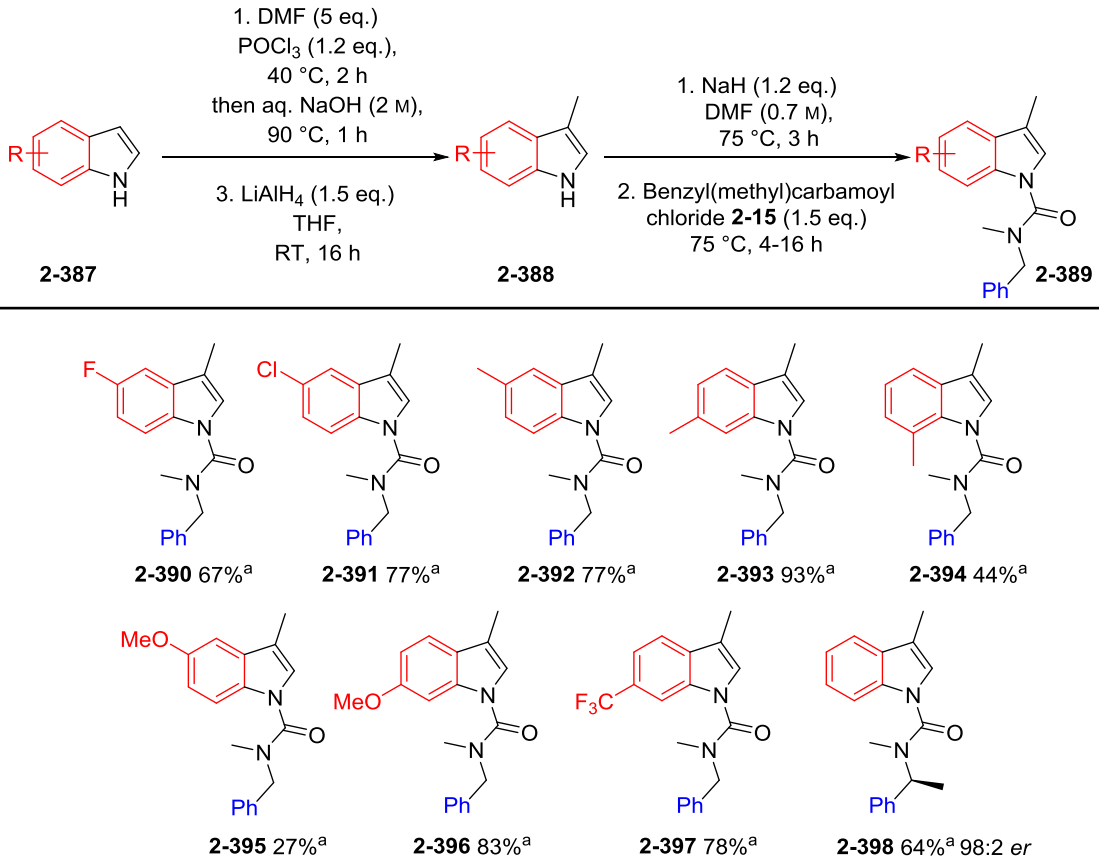
Methyl ester substrate **2-376** underwent cyclisation successfully in 45% yield with a diastereoselectivity of 1.3:1. The diastereomers were separable by flash column chromatography and NOE analysis allowed the configuration of the major diastereomer to be assigned as **2-384a**. Unfortunately, NOE analysis of the minor diastereomer was not enough to unambiguously assign the stereochemistry. Cyano indole urea **2-377** cyclised in a higher yield of 64%, however the 3:1.5:1 mixture of diastereomers was inseparable by flash column chromatography. As a result, the configuration of the stereocentres was difficult to elucidate. Pleasingly, tetrahydrocarbazole derivative **2-378** underwent cyclisation in a moderate yield of 47% yielding an inseparable 3:1 mixture of diastereomers. It can be assumed that for both observed diastereomers of **2-386** a *cis* relationship between the indoline scaffold and cyclohexane ring will be favoured due to being less strained than the *trans* analogues.[166-167] Unsurprisingly, carbazole urea **2-379** failed to cyclise under the reaction conditions. This was a particularly ambitious substrate due to the possibility of multiple pathways, dearomatising cyclisation and ring expansion. Dearomatising cyclisation would not only dearomatise the indole but also the fused phenyl ring. Unfortunately, subjecting this material to the reaction conditions led to a complex mixture of unidentified products with no ring expansion or dearomatising cyclisation products observed.

2.3.5 3-Methyl Indole Urea Precursor Synthesis

With the knowledge that cyclisation of 3-methyl indole urea **2-375** gave the desired polycyclic indoline product **2-382** in good yield with excellent diastereoselectivity, our effort turned towards extending the scope of 3-substituted indoles. However, in contrast to the simple 3-methyl indole, 3-methyl indoles bearing additional substitution on the aromatic ring are not commercially available and therefore needed to be synthesised prior to tethering on the benzyl urea.

A variety of 3-methyl indoles were synthesised from their parent indoles with varying electronic and steric properties, scheme 2-69.

* Experiment carried out by Laura Fraser (MChem).

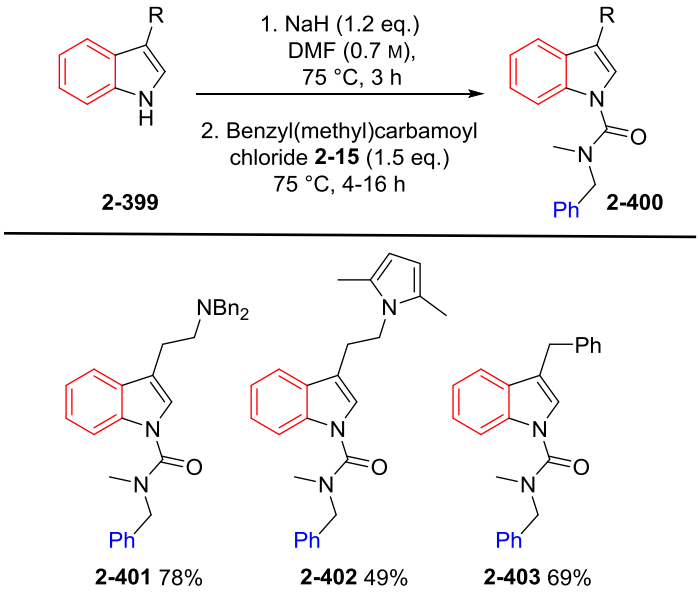


Scheme 2-69. 3-Methyl indole urea precursor synthesis. [a]Yields quoted refer to the attaching of the urea step.[*]

Indoles were converted into their 3-methyl analogues by a Vilsmeier-Haack reaction.[168] This involved reaction of the indole with the 'Vilsmeier reagent' which is generated *in situ* after initial treatment of DMF with $POCl_3$. After an aqueous work-up the indole aldehyde is isolated, which can then be reduced to the desired methyl derivative upon treatment with $LiAlH_4$. The 3-methyl indoles were transformed into their benzyl urea counterparts in moderate to excellent yields following the general procedure (see section 2.3.3). To investigate the stereospecificity of the cyclisation reaction urea **2-398** was synthesised by reaction of 3-methyl indole with (*S*)-methyl(1-phenylethyl)carbamoyl chloride.

Alongside 3-methyl indoles, other 3-substituted indoles were studied to investigate the effect the nature of the 3-substitutent has on both reactivity and diastereoselectivity, scheme 2-70.

[*] Experiments carried out in collaboration with Dr Quentin Lefebvre.



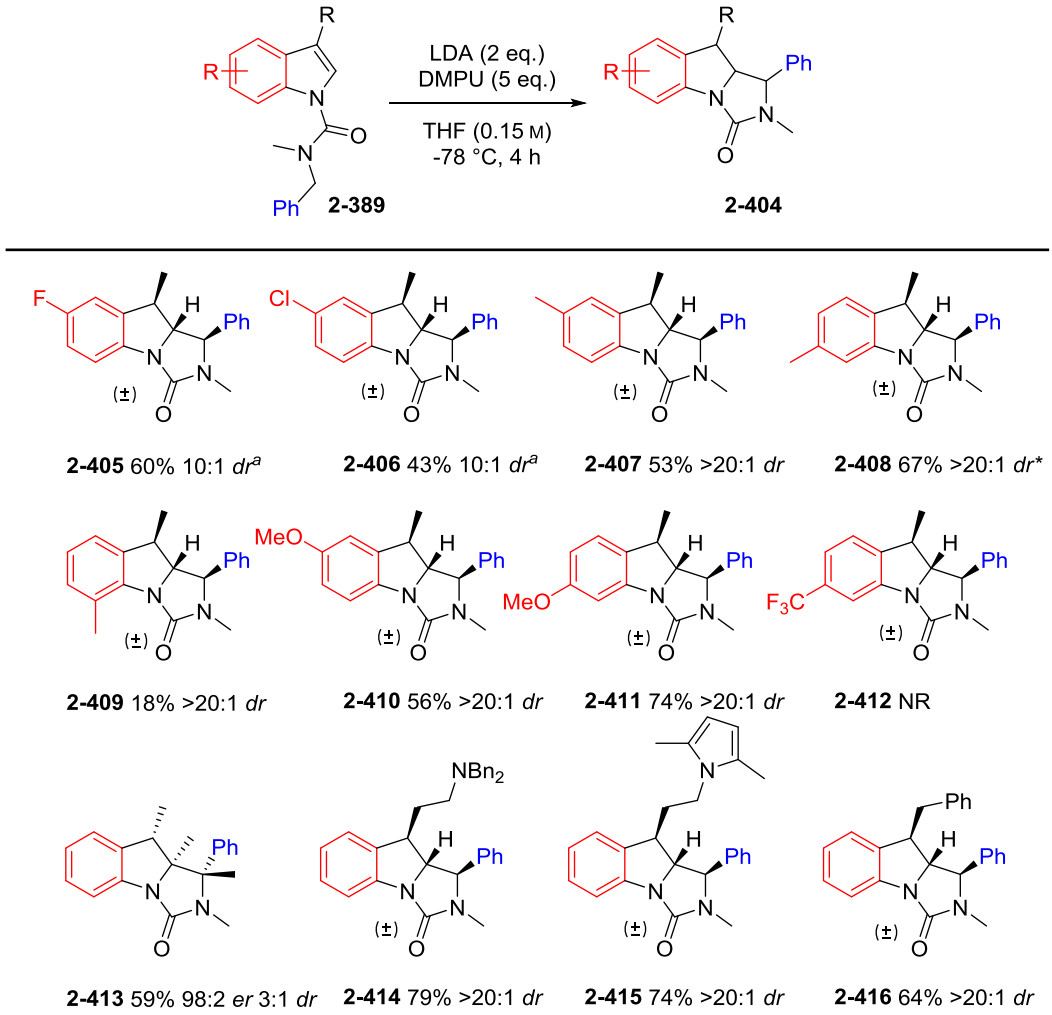
Scheme 2-70. Additional 3-substituted indole urea precursors synthesised.*

Tryptamine posed as an interesting substrate to explore due to its useful biological properties.[169] Therefore, protected tryptamines **2-401** and **2-402** were synthesised according to literature procedures.[170, 171] 3-Benzyl indole **2-403** was synthesised *via* a literature procedure exploiting 'borrowing hydrogen' chemistry.[172] We were curious to investigate whether the incorporation of a benzyl group would affect the reactivity due to potential for competing deprotonation. With a variety of 3-substituted indoles synthesised our focus turned towards attempting the dearomatising anionic cyclisation.

2.3.6 Dearomatising Cyclisation Substrate Scope of 3-Substituted Indoles

Treatment of 3-substituted indoles **2-389** under the optimised conditions for dearomatising cyclisation allowed a range of polycyclic indoline structures to be synthesised in moderate to excellent yields and high diastereoselectivity, scheme 2-71.

* Experiments carried out in collaboration with Dr Quenitin Lefebvre.



Scheme 2-71. Dearomatising cyclisation substrate scope of 3-substituted indole urea precursors. [a]Configuration of major diastereomer shown based on stereochemistry of major diastereomer of analogues 3-methyl indole ring closure product **2-407**.*

Heterocyclic 6,5,5 ring systems **2-405** to **2-416** were accessed following the dearomatising cyclisation methodology. Pleasingly, fluorine and chlorine atoms were tolerated at the 5-position, yielding the corresponding polycyclic indoline products **2-405** and **2-406** with good diastereoselectivity. A methyl group can be introduced at the 5-, 6- and 7-positions to gain access to structure **2-407**-**2-409** as single diastereomers. NOE experiments and an X-ray crystal structure of **2-407** allowed confirmation of an all *cis* relative stereochemistry, figure 2-5.

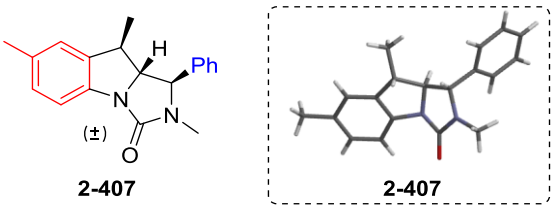


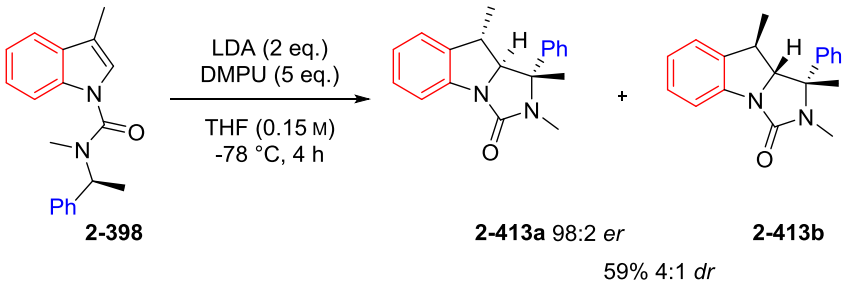
Figure 2-5. X-Ray crystal structure of **2-407** showing all *cis* relative stereochemistry.

A lower yield was obtained for **2-409** suggesting that the presence of a methyl group at the *ortho*-position of the aromatic ring hinders the reaction. The electron-donating methoxy substituent was well

* Experiment carried out by Dr Quenitin Lefebvre

tolerated, giving good yields of the corresponding polycyclic structures **2-410** and **2-411** as single diastereomers. A higher yield of 74% was obtained when the methoxy group was present at the 6-position. This behaviour was tentatively attributed to the increased basicity of the post-addition organolithium intermediate, thereby promoting a cleaner reaction by favouring proton transfer from diisopropylamine. Unfortunately, indole urea **2-397** bearing a 6-CF_3 group failed to undergo the desired cyclisation reaction. Instead, a complex mixture of unidentified products and decomposition was observed. Tryptamine urea precursors **2-401** and **2-402** cyclised successfully under the reaction conditions and delivered **2-414** and **2-415** cleanly as single diastereomers. Despite the potential for competing deprotonation at the 3-benzyl position of indole **2-403**, efficient dearomatising cyclisation occurred delivering the desired polycyclic indoline **2-416** in good yield as a single diastereomer.

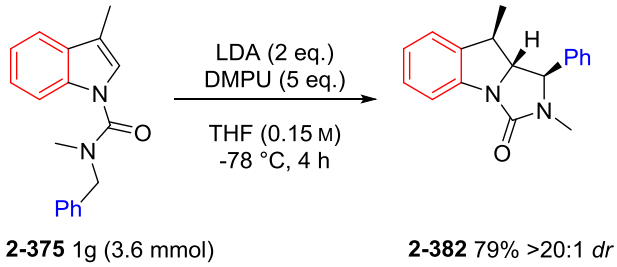
To investigate the stereospecificity of the reaction, urea **2-398** containing an enantioenriched α-methyl group was investigated. Treatment of urea **2-398** with LDA (2 eq.), DMPU (5 eq.) in THF at −78 °C for four hours yielded the desired cyclised product with no erosion of enantiopurity and as a 4:1 mixture of diastereomers, scheme 2-72.



Scheme 2-72. Stereospecific dearomatising cyclisation of urea precursor **2-398**.

The diastereomers were separable by flash column chromatography and NOE NMR experiments were used to assign the relative stereochemistry of the stereocentres. Like the analogous 3-methyl indole substrates, the major diastereomer has an all *cis* relative stereochemistry between the methyl, proton and phenyl ring **2-413a**. Unfortunately, attempts to grow crystals suitable for X-ray diffraction were unsuccessful, therefore we were unable to determine the absolute stereochemistry of the enantioenriched centre. Nonetheless, it is reasonable to postulate that the reaction proceeds with retention of configuration based on the outcomes observed in other rearrangements utilising benzylic anions previously reported in the Clayden group.[80, 173]

To assess the scalability of the dearomatising cyclisation reaction, indole urea **2-375** was cyclised on a gram scale, scheme 2-73.

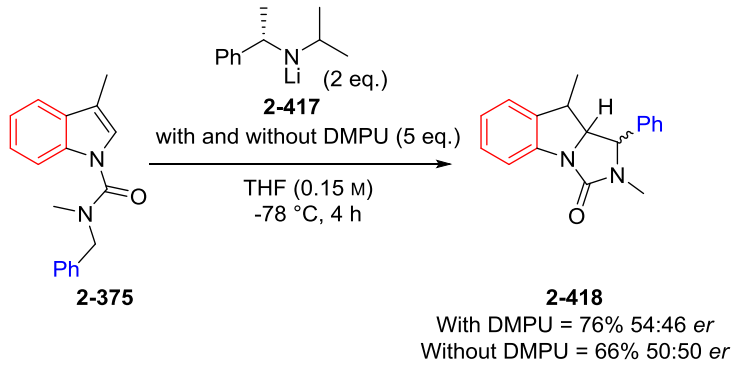


Scheme 2-73. Gram scale dearomatising cyclisation of indole urea **2-375**.

Pleasingly, the desired product **2-382** was isolated in a higher yield of 79% compared to 64% which was achieved on a 0.7 mmol scale. This highlights the potential applications of this methodology in industrial research and development.

2.3.7 Attempted Stereoselective Deprotonation

Although the cyclised product **2-413** with an enantioenriched centre can be achieved by stereospecific reaction from enantiopure precursor **2-398**, the possibility of stereoselective deprotonations had not been investigated. This would allow access to products with enantioenriched centres from racemic starting materials. To determine whether this would be feasible, the deprotonation of 3-methyl indole urea **2-375** was attempted with chiral LDA derivative **2-417**. LDA derivative **2-417** was chosen as a suitable chiral base due to previous work in the group demonstrating its potential for asymmetric induction.[93] The reaction was attempted in the presence and absence of DMPU, scheme 2-74.

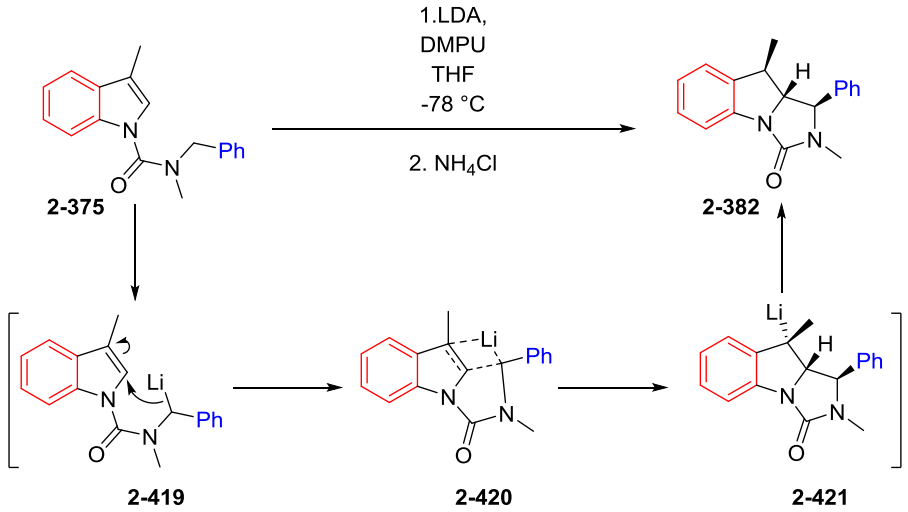


Scheme 2-74. Attempted asymmetric deprotonation of indole benzyl urea **2-375**.

Chiral HPLC analysis showed that the reaction carried out in the presence of DMPU gave slight asymmetric induction with an enantiomeric ratio of 54:46 *er* (see supporting information). In the absence of DMPU the desired cyclised product was isolated as a perfect racemate with a 50:50 enantiomeric ratio. Therefore, although deprotonation with chiral lithium amide **2-417** shows promise for asymmetric induction, further work is needed to optimise the reaction to obtain improved enantioselectivities.

2.3.8 Mechanistic Insight

A proposed mechanism for the dearomatising cyclisation reaction is depicted in scheme 2-75.

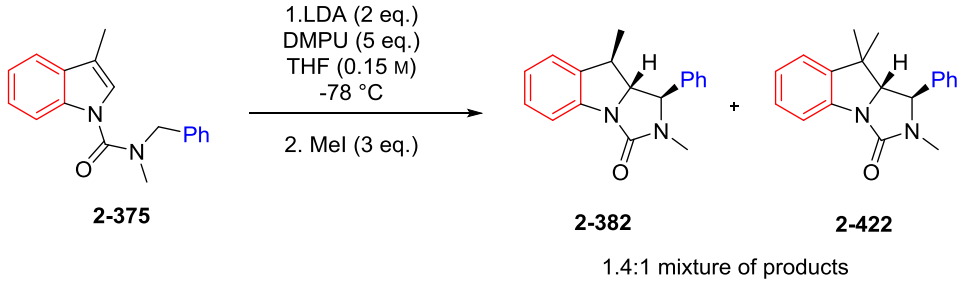


Scheme 2-75. Potential cyclisation mechanism of indole ureas.

Deprotonation at the benzylic position generates organolithium **2-419** which subsequently attacks the indole at the 2-position. The cyclisation is proposed to proceed *via* a *syn*-carbolithiation step where both

the carbon and lithium add to the same face of the vinyl group through a 4-membered transition state **2-420**. Polycyclic indoline **2-382** is afforded after protonation of the resulting anion, either *in situ* from diisopropylamine or on quench with aqueous saturated NH_4Cl solution.

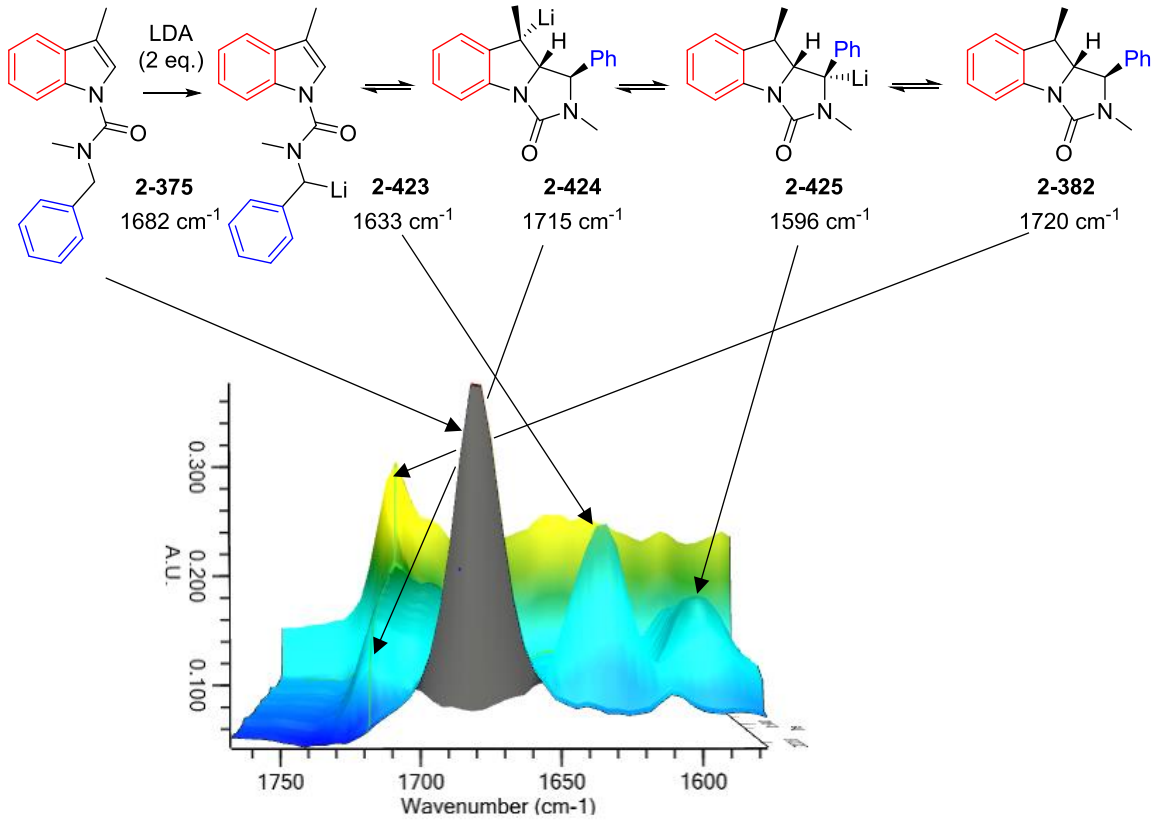
Interestingly, when repeating the reaction with methyl iodide as a quenching agent, full methylation was not observed, scheme 2-76.



Scheme 2-76. Dearomatising cyclisation of 3-methyl indole with methyl iodide quench.*

Analysis of the crude reaction mixture by ^1H NMR showed a 1.4:1 mixture of non-methylated **2-382** to methylated product **2-422**. Since LDA gives reversible deprotonation, it is reasonable to suggest that reprotonation occurs *in situ* by diisopropylamine before the reaction is quenched with an external source.

To better understand the origins of the substrate dependent diastereoselectivity, the reaction mechanism was probed further using *in situ* ReactIR, scheme 2-77.



Scheme 2-77. 3D ReactIR trace monitoring peaks at various wavenumbers over the course of the reaction. Peaks are tentatively assigned to the intermediates shown.

* Experiment carried out in collaboration with Laura Fraser (MChem).

Due to the presence of strong carbonyl stretching frequencies in DMPU, we opted to run the reaction in the absence of DMPU to ensure any slight shifts in wavenumber would be observed. Starting material **2-375** in THF showed a clear carbonyl peak at ν =1682 cm^{-1}. Upon addition of two equivalents of LDA at −78 °C, the starting material peak at ν =1682 cm^{-1} disappeared and a transient species with a carbonyl stretch of ν =1633 cm^{-1} appeared. This most likely corresponds to the lithiated starting material **2-423**, possibly in a more solvated/aggregated state. This species rapidly disappears and gives rise to three new signals at ν =1596 cm^{-1}, 1715 cm^{-1} and 1720 cm^{-1} respectively. Over the course of 70 minutes the peak at ν =1596 cm^{-1} slowly decreased in intensity whilst the other two at ν = 1715cm^{-1} and 1720 cm^{-1} increased in intensity. After 70 minutes the reaction was quenched with aq. saturated NH_4Cl solution, which led to the disappearance of the signals at ν = 1596 cm^{-1} and 1715 cm^{-1}, tentatively assigned as lithiated products **2-424** and **2-425**. Simultaneously, the peak at ν =1720 cm^{-1} increased and was identified as product by comparison with the spectrum of an authentic sample. The desired product **2-382** was isolated in 52% yield after purification. These results support the proposed mechanism of benzylic lithiation, *syn*-carbolithiation followed by partial *in situ* protonation mediated by diisopropylamine.

2.3.9 Conclusions & Future Work

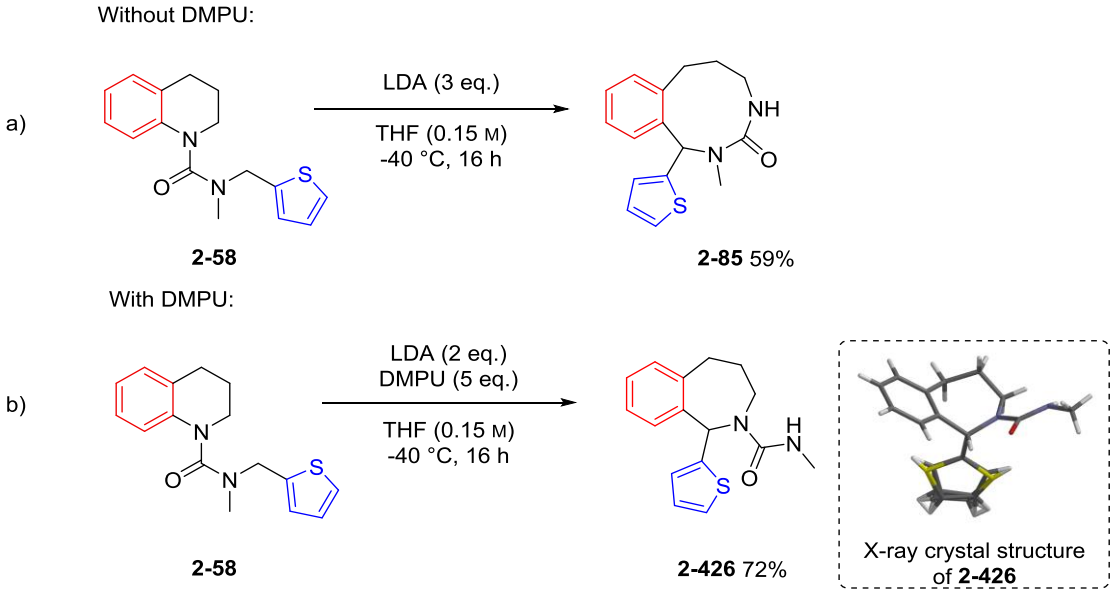
A method has been developed for the synthesis of heterocyclic 6,5,5 systems exploiting a dearomatising anionic cyclisation of lithiated indole benzyl ureas using lithium diisopropylamide. The products of this cyclisation reaction are polycyclic indoline structures which have potential to be further functionalised. The reaction proceeds with excellent diastereoselectivity when 3-substituted indoles are used, yielding products with all *cis* relative stereochemistry confirmed where possible by NOESY experiments and X-ray crystal structures. However, the cyclisation was less selective when electron-withdrawing groups (CO_2Me, CN) were substituted at the 3-position, presumably due to the stabilisation of the resulting anion leading to less rapid reprotonation. The structurally interesting tryptamine derivatives cyclised in good yields with excellent selectivity and could be later deprotected to access the free amines. Substrates with substitution at the 2-position gave varying yields and poor selectivity, highlighting that the diastereoselectivity is substrate specific. The reaction is stereospecific when enantioenriched starting materials are used, indicating the reaction proceeds through a configurationally stable organolithium. Additionally, the reaction can be performed on a gram scale, yielding the desired polycyclic indoline scaffold in a higher yield than what was reported on smaller scale, increasing its industrial potential. Future work will focus on further derivatisation of the products and investigating alternative nucleophiles for the cyclisation.

2.4 Ring Contraction of Medium Ring Nitrogen Heterocycles

N.B. The work described herein (section 2.4) is documented in the first author publication, J. E. Hill.; J. V. Matlock.; Q. Lefebvre.; K. G. Cooper.; J. Clayden. Angew. Chem. Int. Ed. 2018, 57, 5788.*

2.4.1 Initial Discovery

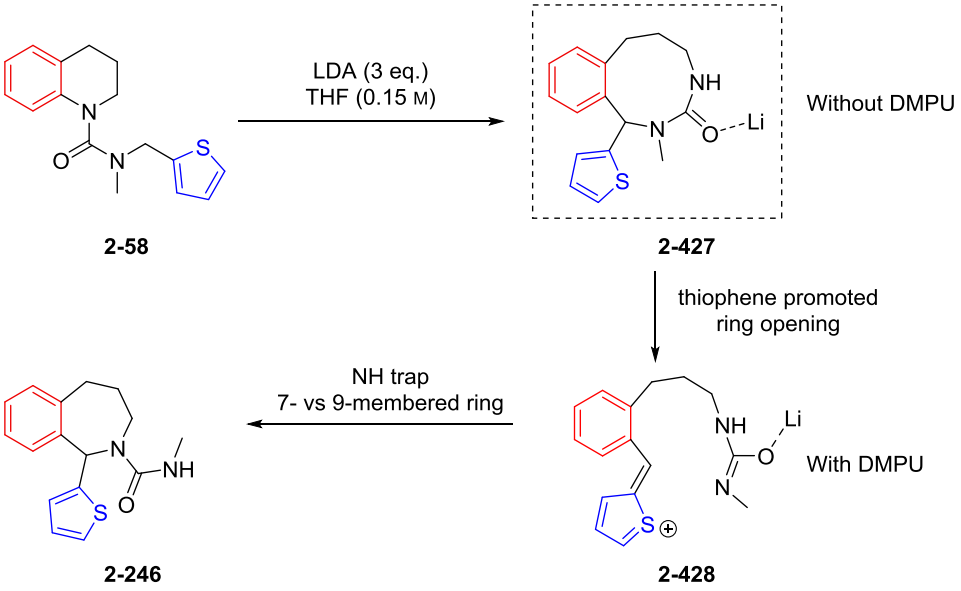
Whilst investigating the substrate scope for the ring expansion of benzyl ureas (see section 2.2.3) it was shown that thiophene substrate **2-58** could undergo the ring expansion only in the absence of DMPU, scheme 2-78 a.



Scheme 2-78. Discovery of *n* to *n*-2 ring contraction of thiophene substrate **2-58**.[*]

This contrasted with the other substrates which required DMPU to favour the 1,4-aryl migration over the 1,2-acyl shift. It was concluded at the time that when using DMPU the product isolated was that of the acyl shift, where the anion attacks the urea carbonyl instead of the aromatic ring. However, analysis of a crystal by X-ray crystallography allowed the product to be unambiguously assigned as 7-membered ring **2-426**, where the more heavily substituted benzylic carbon atom had migrated from one urea nitrogen to the other, scheme 2-78 b. A possible mechanism for the ring contraction is shown in scheme 2-79.

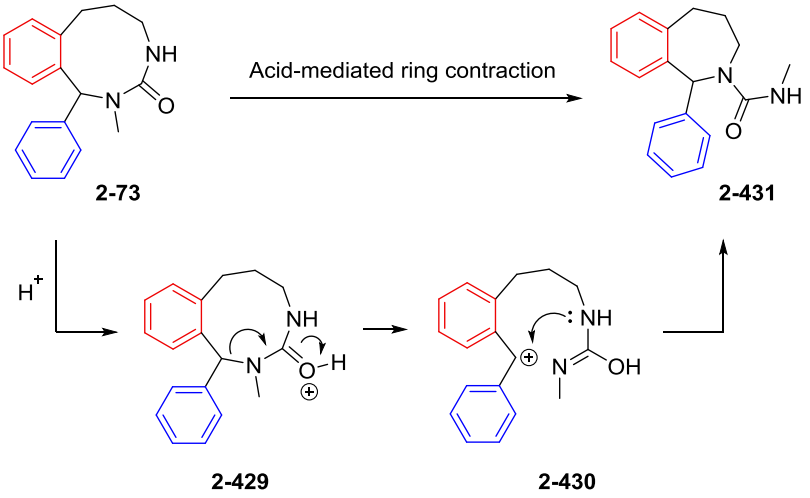
[*] Experiment carried out by Dr Johnathan Matlock.



Scheme 2-79. Possible mechanism for ring contraction of thiophene substrate.

The reaction is suspected to begin with the reported *n* to *n+3* ring expansion on addition of two equivalents of LDA. When DMPU is in the reaction mixture, this is rapidly followed by a thiophene promoted ring opening and a final ring closure to form the 9- or 7-membered ring. Due to the reduced strain in the 7-membered ring compared to the 9-, the 7-membered ring was formed preferentially.

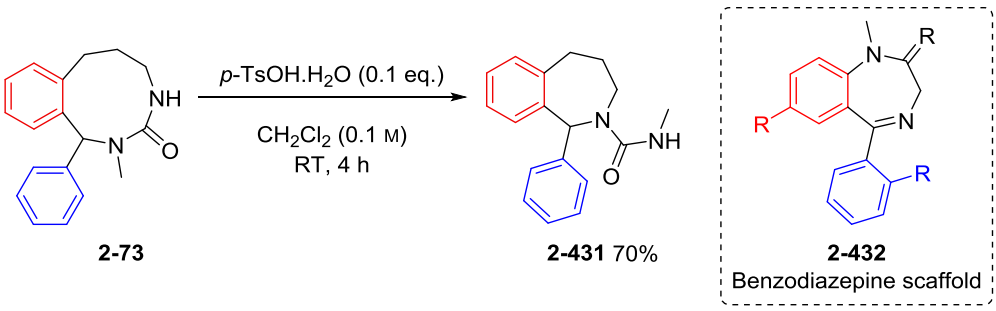
Although this reactivity was only observed with the thiophene substrate, we reasoned that treatment of the medium ring precursors with a strong acid might promote a 'S_N1 type' ring opening, scheme 2-80.



Scheme 2-80. Acid-mediated ring contraction.

The proposed mechanism starts with protonation of the urea carbonyl **2-429**, followed by ring opening to form a benzhydryl cation **2-430**. This carbocation can then be quenched by intramolecular cyclisation to form the 7-membered ring **2-431.**

Initial studies showed that treatment of 9-membered precursor **2-73** with 0.1 equivalents of *p*-toluenesulfonic acid monohydrate (*p*-TsOH.H_2O) in dichloromethane resulted in the desired ring contracted product **2-431** in 70% yield, scheme 2-81. These tetrahydrobenzazepine structures are particularly interesting due to their similarities to the biologically active benzodiazepines **2-432**.[174]



Scheme 2-81. Ring contraction of 9-membered ring **2-73**.

It was anticipated that this ring contraction methodology could also be applied to 8-membered rings, offering access to privileged tetrahydroisoquinoline structures.

2.4.2 Strategies for the Synthesis of Tetrahydroisoquinolines and Benzazepines

Tetrahydroisoquinolines, benzazepines and related benzo-fused nitrogen heterocycles are privileged scaffolds in medicinal chemistry for library design and drug discovery.[7, 175-180] There are a multitude of isoquinoline alkaloids that display diverse pharmacological and biological properties. The benzazepine scaffold forms the key motif for many active pharmaceutical ingredients which specifically target the central nervous system.[181] Several examples are shown in figure 2-7.[175-180]

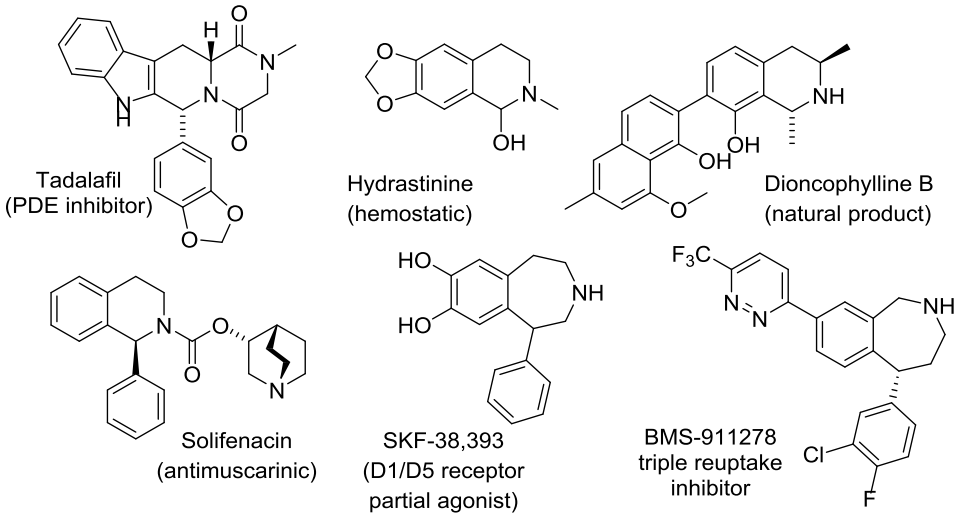
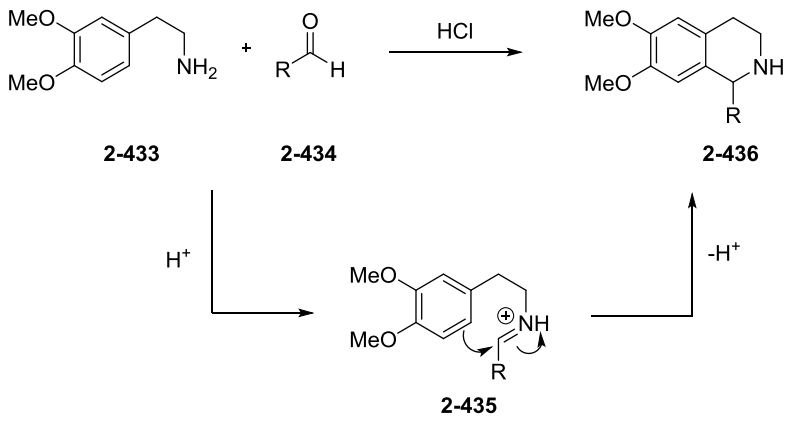


Figure 2-7. Tetrahydroisoquinoline, benzazepine and related motifs in molecules with biological activity.[175-180]

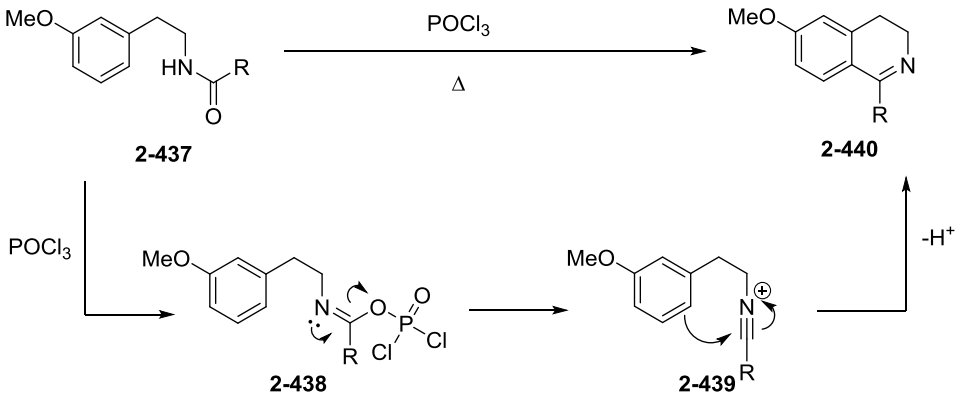
The most practical methods for the synthesis of tetrahydroisoquinolines are the Pictet-Spengler[182-187] and Bischler-Napieralski reactions.[188-190] The Pictet–Spengler reaction involves the condensation of a β-arylethylamine **2-433** with a carbonyl compound **2-434** to generate tetrahydroisoquinoline **2-436**, scheme 2-82.



Scheme 2-82. Pictet–Spengler reaction for the synthesis of tetrahydroisoquinolines.

The mechanism begins with protonation of the carbonyl, which is subsequently attacked by amine **2-433**. A sequence of proton transfer steps and the release of a water molecule generates iminium intermediate **2-435**. This then undergoes a 6-*endo-trig* cyclisation with loss of aromaticity of the aryl ring. The aromaticity is then restored by a final deprotonation step, resulting in tetrahydroisoquinoline product **2-436**.

The Bischler–Napieralski reaction is an intramolecular electrophilic substitution reaction that allows for the cyclisation of β-ethylamides. The reaction requires a dehydrating agent such as phosphorus oxychloride ($POCl_3$), phosphorus pentoxide (P_2O_5) or zinc chloride ($ZnCl_2$) for the synthesis of 3,4-dihydroisoquinoline derivatives, scheme 2-83.



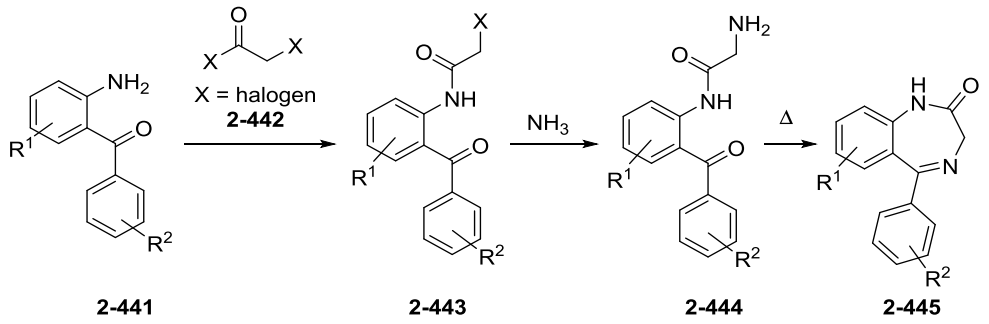
Scheme 2-83. Bischler–Napieralski reaction for the synthesis of tetrahydroisoquinolines.

The reaction is suspected to proceed by dehydration of the amide to form nitrilium ion **2-439** which is then attacked by the electron-rich arene in by an electrophilic substitution reaction. Deprotonation regains aromaticity of the aromatic ring giving imine **2-440**, scheme 2-83. Imine **2-440** can then be reduced yielding tetrahydroisoquinoline derivatives. An alternative mechanism involving a dichlorophosphoryl imine-ester intermediate may also be plausible.[191]

Despite recent advances in the field,[192] both reactions are limited by the need for electron-donating groups on the aromatic ring and harsh reaction conditions, such as refluxing the substrate in strong acid. Additionally, neither reaction works well for the formation of ring sizes other than 6.

The most common synthetic routes to benzodiazepine structures start with an *ortho*-aminobenzophenone **2-441**, scheme 2-84. This reacts with a haloacetyl halide **2-442**, affording the

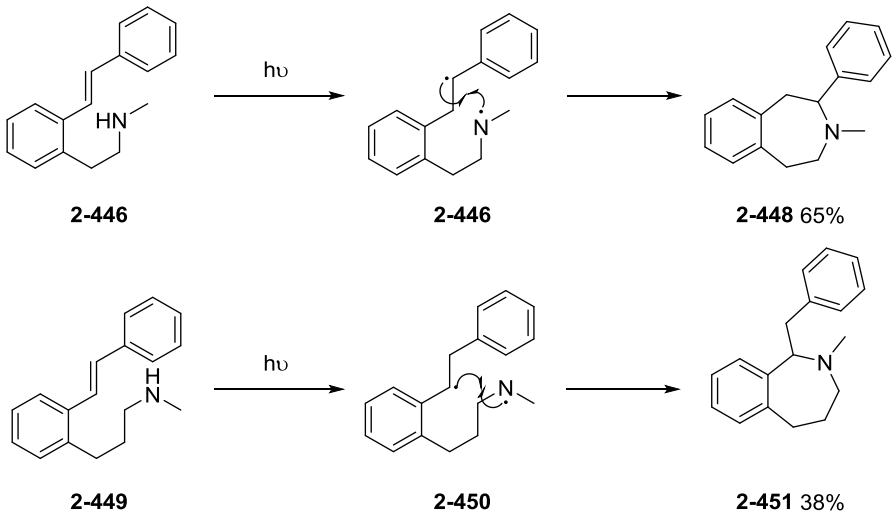
corresponding amide **2-443**. The halogen is then displaced with ammonia generating the glycinamine **2-444** which cyclises to form the imine **2-445**.[193]



Scheme 2-84. Synthesis of benzodiazepine **2-445**.[193]

Due to the lack of functionalised 2-amino benzophenone structures commercially available, other methods have been developed to increase the diversity, usually employing metal catalysis.[194]

Photochemistry has also been utilised in the synthesis of benzazepine structures.[195] 2- and 3-benzazepines were synthesised *via* a regioselective intramolecular photoamination of *ortho*-(aminoethyl)- and *ortho*-(aminopropyl)stilbenes, scheme 2-85.



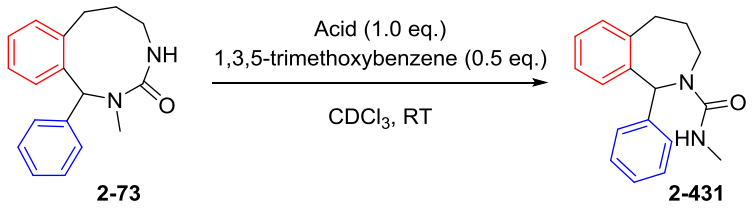
Scheme 2-85. Photochemical synthesis of benzazepines **2-448** and **2-451**.[195]

Direct irradiation of stilbenes **2-446** and **2-449** using 300 nm light resulted in the formation of benzazepines **2-448** and **2-451**. Despite the moderate yields achieved, the reaction requires deoxygenated solvents and a photochemical reactor, limiting its practicality.

Therefore, development of a practically simple and inexpensive method for the synthesis of tetrahydroisoquinoline and 'benzazepine-like' structures is of interest.

2.4.3 Optimisation of Ring Contraction Conditions

With a range of starting materials synthesised *via* the ring expansion methodology (see section 2.2.3), our initial studies focused on screening acids with the aim of improving the yield. 9-Membered nitrogen heterocycle **2-73** was chosen as the model substrate for optimisation, with the reactions run in the presence of an internal standard, scheme 2-86.



2-73 **2-431**

Entry	Acid	Yield 2-431, %[a]
1	*p*-TsOH.H_2O	98
2	HCl in Et_2O	81
3	TFA in $CDCl_3$	91

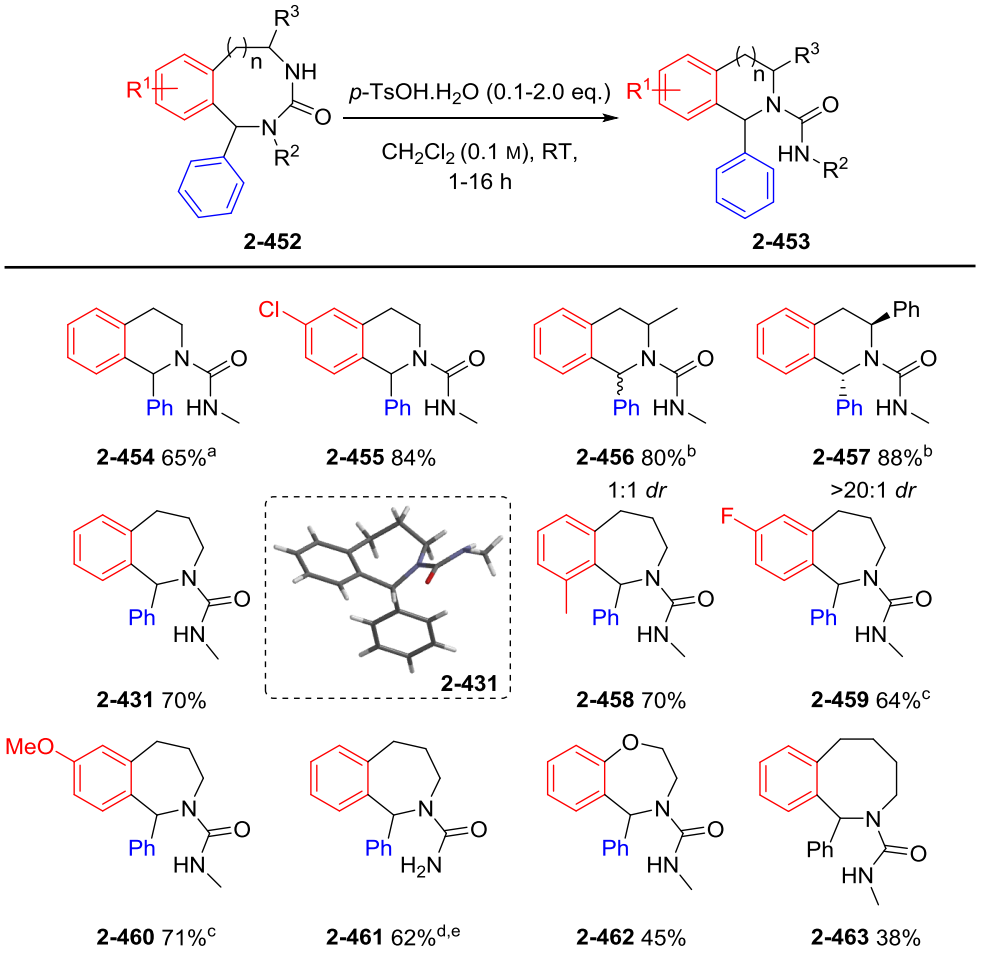
Scheme 2-86. Ring contraction of **2-73** with different Brønsted acids. [a]Yields calculated from ^{1}H NMR using internal standard.[*]

The highest yields were obtained when using *p*-toluenesulfonic acid to promote the reaction (scheme 2-86, entry 1). Although still highly yielding, a reduction in yield was observed when using HCl and TFA (scheme 2-86, entries 2 and 3). As a result, *p*-toluenesulfonic acid was chosen as the acid for all subsequent ring contraction studies. It was found that loadings as low as 0.1 equivalents were sufficient to deliver the desired product in good yield.

2.4.4 Substrate Scope

With the aim of exploring this consecutive ring expansion and contraction strategy as a general way of accessing tetrahydroisoquinolines and related compounds, these conditions were then applied to a series of substrates **2-452**, each made by ring expansion of the appropriate urea.[196] The results are summarised in scheme 2-87.

[*] Experiments carried out in collaboration with Dr Johnathan Matlock.



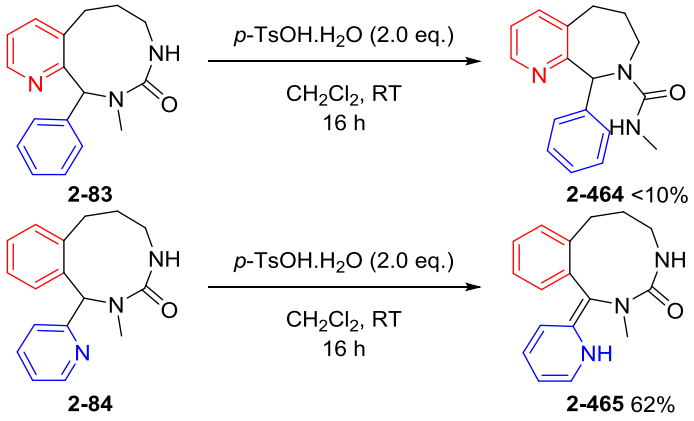
Scheme 2-87. Substrate scope of the ring contraction. [a]Using 2.0 eq. of *p*-TsOH.H_2O. [b]From a single diastereomer of the starting material. [c]Product formed from tetrahydroquinoline benzyl urea **2-45** by a one-pot ring expansion-contraction using 10 eq. *p*-TsOH.H_2O. [d]Using 2.5 eq. methanesulfonic acid at 0 °C. [e]From **2-82**, in which R^2 = ^{t}Bu, the ^{t}Bu is lost in the reaction.

The reaction was successful when using alternatively substituted 8-membered starting materials (n=1), giving the tetrahydroisoquinolines **2-454**-**2-457** in good yield. Single diastereomers of ring expanded starting materials **2-97** and **2-98** produced a diastereoisomeric mixture of products when R^3 = Me in **2-456**, but a single diastereomer of phenyl-substituted **2-457**. After repeating the ring contraction of **2-97** at 0 °C in hope of improving the diastereoselectivity, analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a mixture of unreacted starting material and product **2-456** as a single diastereomer. Leaving the reaction for longer at 0 °C did not drive the reaction to completion and the same ratio of starting material to product was observed. This indicated that although the reaction was more selective at lower temperatures, it was less reactive and warmer temperatures were needed for full conversion. It was postulated that the reaction is under thermodynamic control and the product can ring open and close unselectively, leading to epimerisation which may account for the observed 1:1 diastereomeric ratio when R^3 = Me. These results were particularly pleasing as 1-aryl tetrahydroisoquinolines represent a class of biologically relevant compounds which display pharmacological activity, indeed **2-454** is a precursor to the drug solifenacin.[197]

9-Membered ring expansion starting materials (n=2), which are available[196] from tetrahydroquinoline benzyl ureas or morpholine (see section 2.2.3) likewise underwent the ring contraction, giving the otherwise problematic 1-substituted 2,3,4,5-tetrahydro-1H-benzo-[c]azepines **2-431**, **2-458**-**2-461** and the oxa analogue **2-462**. **2-461** was formed from precursor **2-82**, in which R^2 is ^{t}Bu, which was removed under the conditions of the reaction, thereby allowing access to alternatively substituted urea products.

The ring contraction reaction was tolerant of variously substituted rings, with electronically diverse **2-455, 2-459, 2-460** and sterically hindered **2-458** all being formed successfully. 7-Membered ring contracted products **2-459** and **2-460** were accessed exploiting a one-pot ring-expansion-contraction method using 10 eq. *p*-toluenesulfonic acid, highlighting the practicality of the method. Unsurprisingly, the 8-membered ring contracted product **2-463** was isolated in a lower yield of 38%. This can be explained due to the formation of another medium-sized ring, which will have unfavourable transannular interactions. 11- and 12-Membered ring expansion products **2-75** and **2-76** were also trialled in the ring contraction. Subjecting them to the optimised conditions for the ring contraction *p*-toluenesulfonic acid (0.1 eq.), CH_2Cl_2 (0.1 M) at RT resulted in no conversion. Therefore, both substrates heated in the microwave at 100 °C for 15 minutes. Unfortunately, decomposition was observed. For the ring contraction of **2-75** and **2-76** to be successful a carbocation would need to form and be quenched by an intramolecular cyclisation to give a 9- or 10-membered ring. It can be reasoned that the transannular strain present in the products of the 9- and 10-membered rings would be too high for the cyclisation to occur.

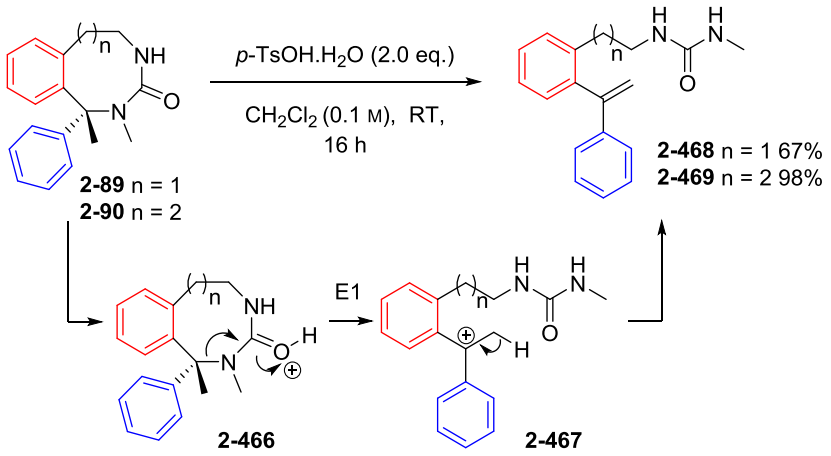
Pyridine analogues **2-83** and **2-84** were also attempted in the ring contraction with stoichiometric amounts of *p*-toluenesulfonic acid. Treatment of **2-83** with *p*-toluenesulfonic acid (2 eq.) in CH_2Cl_2 at room temperature gave trace amounts of ring contracted product **2-464** along with other unidentified products. Unlike **2-83**, subjecting **2-84** to the ring contraction conditions resulted in a bright yellow fluorescent solution. After purification, the major product was identified to be **2-465** in 62% yield, where protonation of the pyridine nitrogen had occurred followed by tautomerisation, scheme 2-88.



Scheme 2-88. Attempted ring contraction of pyridine analogues **2-83** and **2-84**.

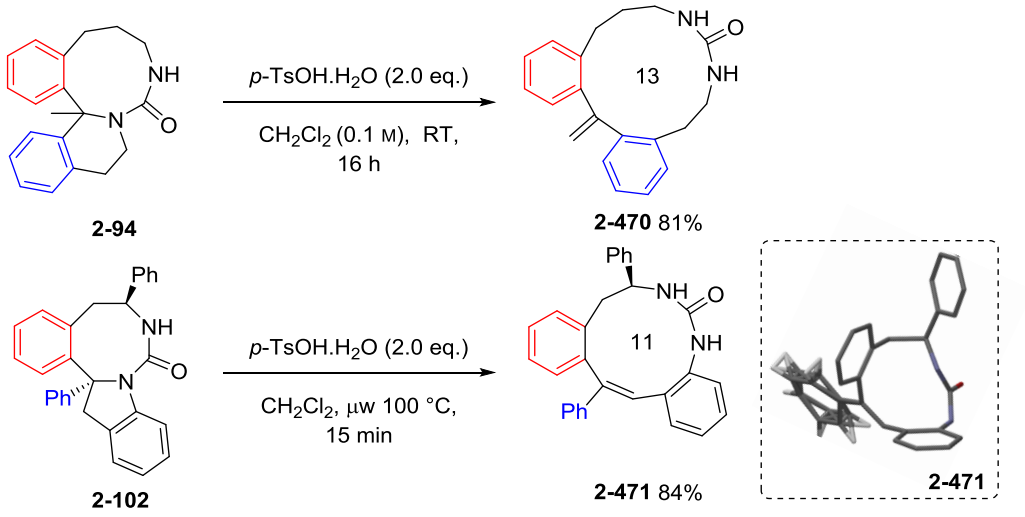
Presumably, this tautomer is formed preferentially as it minimises transannular interactions across the ring.

Medium ring substrates in which an alternative E1 elimination pathway is available did not undergo ring contraction. Instead, treatment with acid promoted elimination, giving alkene products, scheme 2-89.



Scheme 2-89. E1 elimination pathway of substrates with adjacent abstractable protons.

Compounds **2-89**, **2-90**, **2-94** and **2-102** underwent elimination on treatment with acid, rather than ring contraction, yielding olefinic products, scheme 2-89. The monocyclic compounds **2-89** and **2-90** ring opened on elimination to yield the simple 1,1-diarylethylenes **2-468** and **2-469**, scheme 2-89. In contrast, elimination of bicyclic **2-94** and **2-102** generated 13- and 11- membered cyclic alkenes **2-470** and **2-471**, scheme 2-90. X-Ray crystallography confirmed the *Z*-alkene geometry of the 11-membered ring **2-471**.

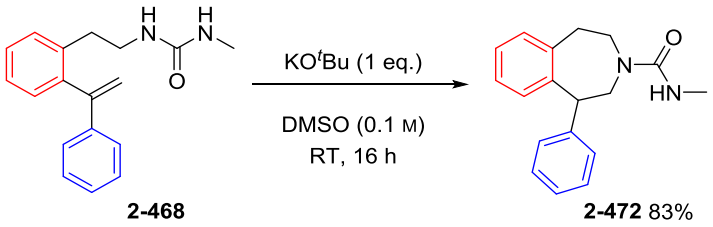


Scheme 2-90. Elimination pathway leading to generation of larger rings.*

These results suggest a common mechanism in which protonation of the electron-rich oxygen atom of the urea initiates the formation of a carbocation. This carbocation either provides the intermediate for E1 elimination when a β-proton is lost, or alternatively is trapped by the remote urea nitrogen in an intramolecular S_N1 substitution that leads to ring contraction.

The formation of alkene **2-468** makes an alternative pathway for ring contraction possible where base is used, rather than acid. **2-468** is electrophilic towards attack by a nitrogen nucleophile and treatment of **2-468** with potassium *tert*-butoxide promotes intramolecular hydroamination to form 7-membered ring **2-472** in 83% yield, scheme 2-91.[198]

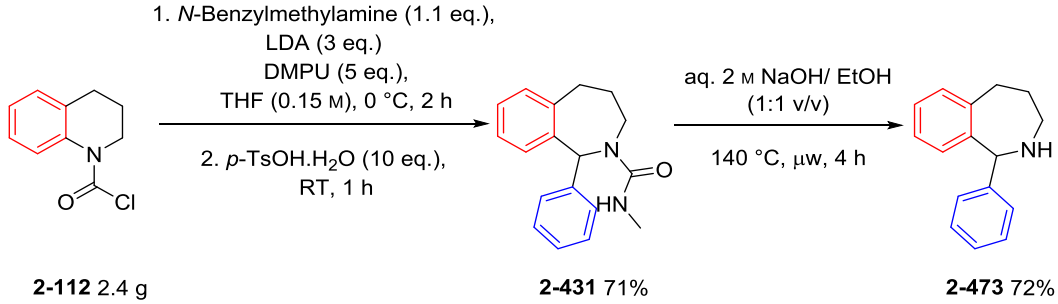
* Experiments carried out in collaboration with Dr Johnathan Matlock.



Scheme 2-91. Intramolecular hydroamination to generate 7-membered ring **2-472**.

This method of formation of 7-membered ring **2-472** from diarylalkene **2-468** and hence from the indoline benzyl urea precursor **2-59** represents an alternative "n+3−1" ring expansion-recontraction strategy for the synthesis of this alternatively substituted class of 1-aryl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepines. Unfortunately, similar reactions to form the 8-membered ring from diarylalkene **2-469** were unsuccessful.

To assess the scalability and demonstrate the practical utility of the method, a 'one-pot' urea formation, ring expansion and ring contraction was performed using tetrahydroquinoline carbamoyl chloride **2-112** on a 2.4 g scale, scheme 2-92.



Scheme 2-92. 'One-pot' urea formation, ring expansion, ring contraction and subsequent hydrolysis.

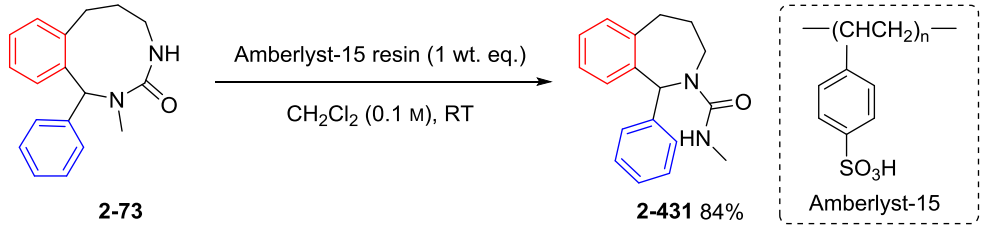
Carbamoyl chloride **2-112**, which is synthesised in one step from commercially available tetrahydroquinoline, was converted into its corresponding benzyl urea counterpart, then ring expanded with LDA and DMPU and finally re-contracted to product **2-431** on addition of an excess of *p*-TsOH.H_2O. The urea tether was then removed by basic hydrolysis under microwave conditions giving 7-membered ring **2-473** in 72% yield, which can be further functionalised.

2.4.5 Ring Contraction in Flow

Flow chemistry offers many advantages over traditional batch chemistry, especially when considering scale-up. As a result, there has been a large amount of research into the development of flow systems, both in academia and industry.[199, 200] A major advantage with a continuous flow set up is safety. The system allows only small amounts of hazardous material to be reacting or generated at any one time and the high surface area allows for excellent control of exotherms. Additionally, flow systems can result in faster reaction times due to the ease at which they are pressurised. This allows solvents to be heated significantly higher than their boiling points, achieving faster rates of reaction. Scaling up from small scale to large scale can be a simple procedure due to inherently translatable mixing and heat transfer. Higher flow rates and correspondingly larger flow reactors can be used to scale up to industrially relevant quantities. Despite these advantages, not all synthetic procedures can be performed in flow. For example, reactions which involve suspensions are challenging due to the risk of blockages. As a result, they are usually performed under much more dilute conditions compared to batch, making it difficult to generally define the benefits of flow over batch.

Due to the simplicity of the ring contraction methodology, we were interested in investigating if it was applicable to flow chemistry. Exploiting a solid-supported acid instead of *p*-toluenesulfonic acid would allow elimination of work-up and purification steps, making the whole procedure more industrially relevant.

Amberlyst-15, a polystyrene based ion exchange resin with strongly acidic sulfonic acid groups on the surface, was chosen as a suitable alternative to *p*-toluenesulfonic acid. Initial studies focused on replacing *p*-toluenesulfonic acid with amberlyst resin in batch for the ring contraction of 9-membered ring expansion product **2-73**, scheme 2-93.



Scheme 2-93. Acid promoted ring contraction using amberlyst-15 resin.

The reaction was monitored by liquid chromatography mass spectrometry (LCMS) and showed full consumption of starting material to the desired product **2-431** after 1 hour and 45 minutes. Before transferring to flow, the reaction was first optimised under microwave conditions. Indeed, microwave and flow reactions share many similarities. For example, microwave reactions typically have short reaction times due to the high temperatures attainable under pressurised conditions. This directly relates to short residence times in flow. In addition, the possibility to use flow reactors fitted with backpressure regulators allows straightforward replication of the high temperatures and pressures achievable in microwave batch experiments.[201] The optimal conditions were found to be one weight equivalent of amberlyst-15 resin, 60 °C for ten minutes in the microwave. With these conditions in hand our efforts turned to transferring the ring contraction to flow.

Flow reactions were performed using a Uniqsis FlowSyn module, figure 2-8. The instrument uses a PTFE flow path and the OMNIFIT® glass column, was manually packed with amberlyst-15 resin (height 1.3 cm).

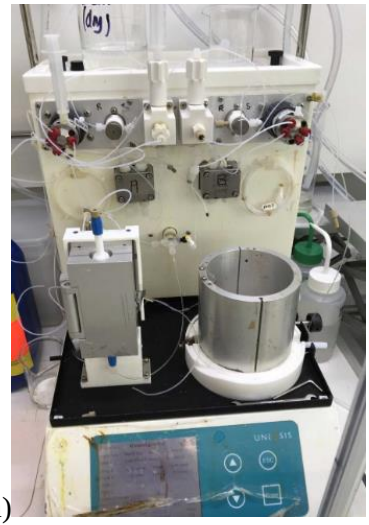
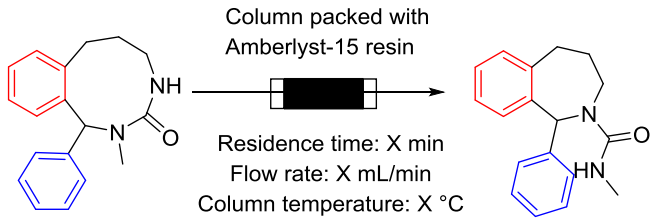
a)  b) 

Figure 2-8. a) Uniqsis FlowSyn module b) OMNIFIT® glass column packed with amberlyst-15 resin.

The height of packed amberlyst resin was selected to be 1.3 cm as this was the smallest amount of resin required to achieve a ten minute residence time using the slowest flow rate of 0.1 mL/min. The starting material, as a 1.8 M solution in CH_2Cl_2, was delivered to the system *via* tubing from a Schott bottle

placed on top of the instrument. A second Schott bottle containing anhydrous dichloromethane was used to carry the starting material through the system, ensuring all substrate passes through the column. The packed column was connected to the system and secured into the Uniqsis heating block to ensure efficient heating. Once the temperature and flow rate were programmed into the system, the run was started. After passing through the column, the solvent was collected in a round bottom flask and the solvent was removed under reduced pressure.

The optimised microwave conditions were trialled in the first flow run, 60 °C, 10 minute reaction time, 0.1 mL/min flow rate, (scheme 2-94, entry 1).



2-73 0.1 g scale **2-431**

Entry	Flow rate, mL/min	Column temp, °C	Residence time, min	2-73, %	2-431, %
1	0.1	60	10	-	11
2	0.2	RT	5	-	51
3	1.0	RT	1	38	60
4	0.5	RT	2	11	80
5	1.0	60	1	-	67
6	0.4	60	2.5	-	86
7	5.0	RT	0.2	68	17
8	0.4	60	2.5	-	92[a]

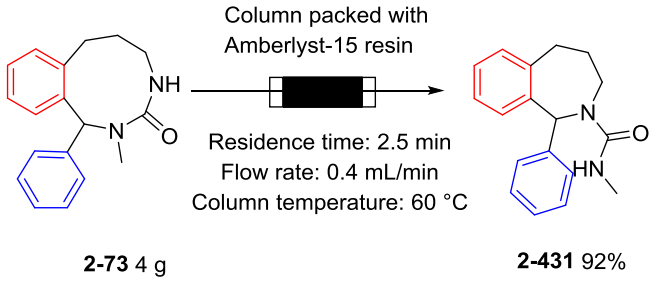
Scheme 2-94. Optimisation of ring contraction in flow. [a]Reaction performed on a 4 gram scale.

Although the desired ring contracted product **2-431** was isolated in 11% yield, mass balance was poor. It could be speculated that due to the slow flow rate, high temperature and increased amberlyst resin compared to the microwave run, decomposition could occur, and the resulting products could bind to the column. To circumvent this issue, the reaction was repeated with a higher flow rate of 0.2 mL/min and performed at room temperature (scheme 2-94, entry 2). Pleasingly, the desired product was isolated in a higher yield of 51% albeit lower than what was obtained in batch. With the thought that shorter residence times were resulting in higher yields of the tetrahydrobenzazepine **2-431**, the flow rate was increased to 1.0 mL/min (scheme 2-94, entry 3). Unfortunately, the shorter residence time of 1 minute meant that full consumption of starting material was not observed, despite **2-431** being present in 60%. As a result, the flow rate was reduced to 0.5 mL/min, giving a two minute residence time. Although a higher yield of product **2-431** was achieved, starting material **2-73** was present in 11% (scheme 2-94, entry 4). With the aim of keeping a quick flow rate and driving the reaction to completion, a flow run was conducted with a 1.0 mL/min flow rate at 60 °C (scheme 2-94, entry 5). Product **2-431** was isolated in 67% yield with no signs of starting material, indicating that temperature is beneficial for the ring contraction in flow. On review of the previous runs the highest yield of **2-431** was obtained when 0.5 mL/min flow rate was used at room temperature (scheme 2-94, entry 4). However, unreacted starting

material remained, and it has been shown that higher temperatures are beneficial to drive the reaction to completion. Therefore, with the aim of achieving a high yield of **2-431** without any unreacted starting material, 0.4 mL flow rate at 60 °C was trialled (scheme 2-94, entry 6). The desired product was isolated cleanly in 86% and required no further purification.

As a final run to investigate the effect of quicker flow rates at room temperature the reaction was repeated with 5.0 mL/min flow rate. As anticipated, starting material remained in 68% along with 17% product (scheme 2-94, entry 7). A recycling strategy, where the mixture is passed through the column again until starting material is consumed, could be used to allow quicker flow rates.

To demonstrate the scalability of ring contraction in flow, the reaction was repeated using the optimised conditions on a four gram scale, scheme 2-95.



Scheme 2-95. Scale-up of ring contraction in flow.

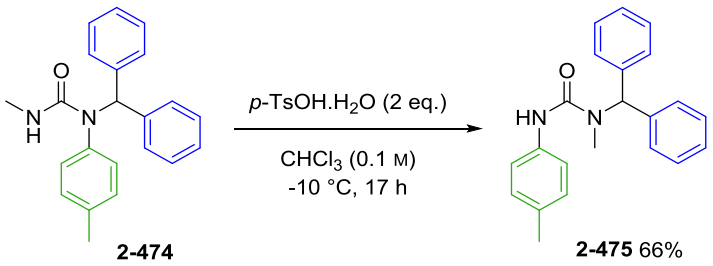
7-Membered nitrogen heterocycle **2-431** was isolated in excellent yield of 92% without the need for work-up or purification, therefore highlighting the scalability and practicality of the flow method. This extremely simple flow method offers an attractive alternative to the batch procedure for the synthesis of 1-aryl tetrahydrobenzazepines.

2.4.5 Conclusions & Future Work

In summary, an acid-mediated *n* to *n*−2 ring contraction of medium ring cyclic ureas has been developed in batch and in flow. Many acids promote the ring contraction reaction but *p*-toluenesulfonic acid monohydrate was shown to give the highest yields in batch and amberlyst-15 resin was chosen as a suitable solid-supported alternative for flow studies. This method, coupled in tandem to the practical synthesis of starting materials from readily available heterocycles (see section 2.2.3) allows the rapid and scalable synthesis of potentially bioactive 1-aryl tetrahydroisoquinoline and tetrahydrobenzazepine derivatives. Alternatively substituted 1-aryl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepines can be accessed *via* an acid-promoted E1 elimination pathway of appropriate precursors resulting in 1,2-diarylalkenes that can undergo intramolecular hydroamination.

Future work will investigate the potential of chiral Brønsted acids for inducing chirality in the ring contraction. Additionally, chiral Lewis acids can be screened to identify if any enantioselectivity is obtained in the products.

Current work within the group is focusing on extending this methodology to linear acyclic systems, scheme 2-96.



Scheme 2-96. *N*→*N*' migration in linear acyclic systems.*

If chirality could be incorporated into the system this would offer an alternative route towards chiral amines. Preliminary work has shown that the migration is stereospecific when enantioenriched starting materials are used, supporting the presence of a concerted mechanism rather than carbocation formation. However, additional studies need to be carried out to investigate the mechanism and scope further.

* Experiments carried out by RBS students Jamie Cadge, Beth Donnelly and Hannah Steeds.

3. Experimental

3.1 General Directions

Reactions requiring anhydrous conditions (where specified) were executed under dry nitrogen or argon atmospheres in glassware that was dried using either a combination of vacuum and heat-gun, oven, or flame drying. Reaction mixtures were stirred magnetically. Air- and moisture-sensitive liquids and solutions were transferred *via* syringe or cannula into the reaction vessels through rubber septa. All reagents were purchased (unless specified) at highest commercial quality and used as received. Non-anhydrous solvents were purchased (unless specified) at the highest commercial quality and used as received. Anhydrous CH_2Cl_2 and Et_2O, THF and MeCN were stored over 3 Å were purchased from Acros and used as received. Anhydrous pyridine stored over 3 Å molecular sieves was purchased from Acros. DMPU was distilled from CaH_2 and stored under nitrogen in a Young's tube. Triethylamine was distilled from CaH_2 and stored under nitrogen in a Young's tube. All temperatures described below −10 °C were achieved using a Julabo cryostat.

3.2 Analytical Directions

R$_f$: TLC was performed on aluminium backed silica plates (0.2 mm, 60 F_{254}) which were developed using standard visualising agents: UV fluorescence (254 & 366 nm), phosphomolybdic acid / Δ, vanillin / Δ, potassium permanganate / Δ and Seebach / Δ

Chromatography: Flash chromatography was performed on an automated Biotage Isolera™ Spektra Four using gradient elution on pre-packed silica gel Biotage® SNAP Ultra columns or by manual means using Fluorochem 60 silica (40-60 µm particle size). Solvents for flash chromatography and TLC are reported in volume:volume percentages.

Enantiomeric excess was determined by HPLC on an Agilent Infinity 1260 system with UV detection at 254, 230 and 210 nm using either a ChiralPak AD-H or Chiralcel OD-H column and hexane/IPA as the eluent for all separations unless otherwise stated.

Mp: Melting points were measured on a Kofler hotstage melting point apparatus and are uncorrected.

IR: IR spectra were recorded on neat compounds using a Perkin Elmer (Spectrum One) FT-IR spectrometer (ATR sampling accessory). Only strong and selected absorbances (ν_{max} expressed in cm^{-1}) are reported.

^{1}H NMR: Spectra were recorded on Jeol ECS (400 MHz), Bruker (400 or 500 MHz) or Varian VNMR (400 MHz or 500 MHz) instruments. Chemical shifts (δ_H) are quoted in parts per million (ppm) and referenced to the appropriate NMR solvent peak(s). 2D NMR experiments COSY, HSQC and HMBC were used where necessary in assigning NMR spectra. Spin-spin coupling constants (*J*) are reported in Hertz (Hz).

^{13}C NMR: Spectra were recorded on Jeol ECS (100 MHz), Bruker (100 MHz or 125 MHz) or Varian VNMR (100 MHz or 125 MHz) instruments. Chemical shifts (δ_C) are quoted in parts per million (ppm) and referenced to the appropriate solvent peak(s). Spin-spin coupling constants (*J*) are reported in Hertz (Hz).

^{19}F NMR: Spectra were recorded on Jeol ECS (376 MHz) or Varian VNMR (376 MHz) instruments. Chemical shifts (δ_F) are quoted in parts per million (ppm) and referenced to an external standard. Spin-spin coupling constants (*J*) are reported in Hertz (Hz).

m/z: Low resolution mass spectra (m/z) were recorded on a Bruker Daltronics MicrOTOF 2 mass spectrometer (ESI), with only molecular ions ($[M]^+$, $[M+H]^+$, $[M+Na]^+$) and major peaks reported.

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

Optical Rotations: ($[\alpha]_D^T$) Optical rotations were measured on a Bellingham and Stanley Ltd. ADP220 polarimeter where *c* is given in g/100 mL.

X-ray Sample Preparation: Crystals suitable for X-ray were grown by dissolving the sample in a dense solvent (CH_2Cl_2) in which it is reasonably soluble and a second chamber placed outside containing a less dense solvent (Et_2O or *n*-Pentane). The solvents slowly mixed together, altering the polarity of the solution in which the sample is dissolved, leading to crystallisation, figure 3-1.

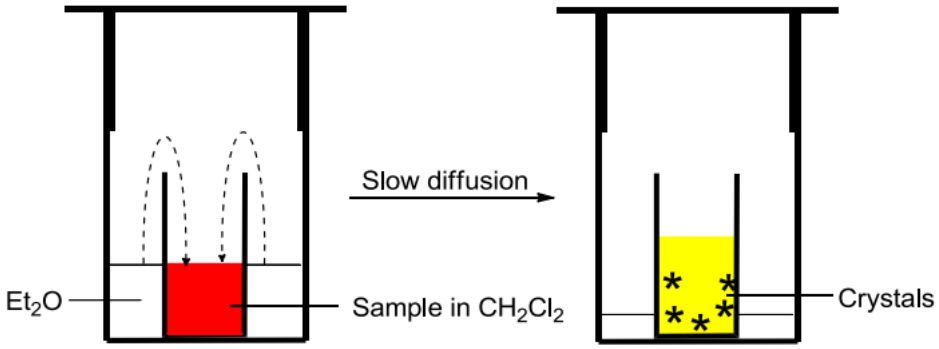


Figure 3-1. Crystallisation by slow diffusion.

3.3 General Procedures

General Procedure 1 (GP1): Carbamoyl Chloride Synthesis for Cyclic Amines

A flame-dried two-necked round bottom flask cooled to RT under vacuum. Triphosgene (0.46 eq.) was added and the flask was subsequently nitrogen/vacuum cycled three times. Anhydrous CH_2Cl_2 (0.7 M) was added and the reaction was cooled to −78 °C. Pyridine (1 eq.) was added dropwise and the reaction was stirred for 5 min at −78 °C. Cyclic amine (1 eq.) was added to the reaction mixture dropwise and stirred for 5 min. The reaction mixture was warmed to RT until consumption of the cyclic amine was observed by TLC. The reaction mixture was quenched with 1 M HCl and extracted three times with CH_2Cl_2. The combined organic phases were washed with sat. $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude carbamoyl chloride. Purification through a pad of silica eluting with 20% EtOAc/petrol gave the desired carbamoyl chloride, which could be used directly in the next step or stored in the freezer at −20 °C until required.

General Procedure 2 (GP2): Urea Synthesis using Cyclic Amine Carbamoyl Chlorides

A solution of carbamoyl chloride (1.0 eq.) in anhydrous MeCN was added dropwise under an atmosphere of nitrogen to a solution of amine (1.3 eq.) and freshly distilled triethylamine (1.6 eq.) in anhydrous MeCN (0.4 M). The reaction was stirred at RT until the consumption of the carbamoyl chloride was observed by TLC. The reaction mixture was quenched with sat. $NaHCO_3$ and extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude urea. The crude urea was purified using flash column chromatography on silica gel to give the desired compound.

General Procedure 3 (GP3): Fresh Preparation of Lithium Diisopropylamide (LDA)

A flame-dried flask was nitrogen/vacuum cycled three times. Freshly distilled diisopropylamine (2 eq.) was added to the flask under nitrogen followed by THF (0.6 M). The solution was cooled to 0 °C and *n*-butyllithium (2 eq., 1.6 M in hexanes) was added dropwise. The solution was stirred at 0 °C for 20 min prior to use.

General Procedure 4 (GP4): Ring Expansion/ *N*→*C* Aryl Migration

To a flame-dried Schlenk tube was added urea (1 eq.) followed by THF (0.15 M). DMPU (5 eq.) was added to the solution at RT and stirred for 5 min. The Schlenk tube was cooled to −78 °C and a solution of freshly prepared LDA (2 eq.)/ commercial LDA solution (2 M in THF/heptane/ethylbenzene) was added dropwise to the reaction mixture. The reaction mixture was stirred for 4 h at −78 °C or until complete consumption of urea was observed by TLC. The reaction mixture was quenched with sat. NH_4Cl and warmed to RT. The reaction mixture was then extracted three times with EtOAc and the combined organic phases were washed three times with water and once with brine. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a crude residue. The crude ring expansion/aryl migration products were purified by flash column chromatography on silica gel to give the desired compounds.

General Procedure 5 (GP5): Synthesis of Amino Acid Esters from Carbamoyl Chlorides

To a solution of amino acid ester hydrochloride (1.1 eq.) in MeCN (0.4 M) was added freshly distilled triethylamine (2.6 eq.) at RT. Carbamoyl chloride (1 eq.) was added over 5 min at RT and the reaction mixture was stirred at RT until consumption of the carbamoyl chloride was observed by TLC. CH_2Cl_2 was added to the reaction mixture and the organic phase was washed twice with 1 M HCl and once with sat. $NaHCO_3$. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a crude residue. The crude urea was purified by flash column chromatography on silica gel to give the desired compound.

General procedure 6 (GP6): Synthesis of Benzylic Carbamates from Carbamoyl Chlorides

To a suspension of NaH (60% dispersion in mineral oil, 2 eq.) in CH_2Cl_2 (0.2 M) was added benzyl alcohol (2 eq.) at 0 °C. The solution was warmed to RT and carbamoyl chloride (1 eq.) was added dropwise. The reaction mixture was stirred until consumption of carbamoyl chloride was observed by TLC. The reaction was quenched by slow addition of water, followed by sat. NH_4Cl. The organic phase was washed with once with water and once with brine. The combined organic phases were then dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a crude residue. The crude carbamate was purified by flash column chromatography on silica gel to give the desired compound.

General procedure 7 (GP7): Synthesis of 3-Methyl Indoles

By the method of H. G. Cheng *et al.*,[168] to a three-necked flask was added indole (1 eq.) and DMF (5 eq.). The mixture was cooled to 0 °C, then $POCl_3$ (1.2 eq.) was added dropwise. The solution was heated at 40 °C for 2 h. The mixture was cooled to RT and 2 M NaOH solution was added slowly. The resultant mixture was heated to 90 °C for a further 1 h. The reaction mixture was cooled to RT and EtOAc was added to dissolve the solid. The aqueous phase was extracted three times with EtOAc and the combined organics were washed once with brine. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The corresponding 1*H*-indole-3-carbaldehyde was used in the next step without further purification.

To a flame-dried flask was added $LiAlH_4$ (1.5 eq.) followed by THF (4 mL $mmol^{-1}$ indole) under an atmosphere of nitrogen. The solution was cooled to 0 °C before dropwise addition of the above aldehyde in THF (4 mL $mmol^{-1}$ indole). The mixture was stirred overnight at RT. Upon reaction completion, H_2O (1 mL/ 0.5 g indole) was added dropwise followed by NaOH (1 g/ 0.5 g indole) and H_2O (3 mL/ 0.5 g indole). The mixture was stirred for 15 min, then the solid was removed by filtration and washed with Et_2O. The combined organic phases were dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude residue was purified by flash column chromatography on silica gel to afford the corresponding 3-methyl-1*H*-indole.

General procedure 8 (GP8): Indole Urea Synthesis using Benzyl(methyl)carbamoyl chloride

By the method of B. Li *et al.*[165], to a suspension of NaH (60% dispersion in mineral oil, 2 eq.) in DMF (0.7 M), a solution of indole (1 eq.) was added dropwise at 0 °C. The reaction mixture was warmed to RT and then heated at 75 °C for 3 h. The reaction mixture was cooled to 0 °C and a solution of benzyl(methyl)carbamoyl chloride **2-15** (1.5 eq.) was added dropwise. The reaction mixture was then heated to 75 °C for 16 h or until TLC showed reaction completion. The reaction mixture was cooled to RT, quenched with sat. NH_4Cl and extracted three times with EtOAc. The combined organics were washed three times with 5% LiCl, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude urea was purified by flash column chromatography on silica gel to yield the desired indole urea.

General Procedure 9 (GP9): Dearomatising Cyclisation of Indole Ureas

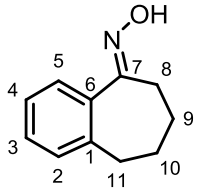
To a flame-dried Schlenk tube was added indole urea (1 eq.) followed by THF (0.15 M) under an atmosphere of nitrogen. DMPU (5 eq.) was added at RT and the reaction mixture was stirred for 5 min. The mixture was cooled to −78 °C and then LDA (2 M in THF/heptane/ethylbenzene, 2 eq.,) was added dropwise. The reaction mixture was stirred for 2 h at −78 °C or until TLC showed reaction completion. The reaction mixture was quenched with sat. NH_4Cl and extracted three times with EtOAc. The combined organic phases were washed twice with water and once with brine, before being dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel to afford the desired cyclisation products.

General procedure 10 (GP10): Ring Contraction of Medium Ring Nitrogen Heterocycles

To a flask containing the corresponding cyclic urea (1 eq.) in CH_2Cl_2 (0.1 M) in air was added *p*-toluenesulfonic acid monohydrate (0.1 - 2 eq.). The reaction mixture was stirred for 1-16 h at RT or 15 min in the microwave at 100 °C, until complete consumption of starting material was observed by TLC (*N.B.* for some substrates both starting material and product have the same R_f). Once complete, the reaction mixture was quenched with sat. $NaHCO_3$. The aqueous phase was extracted three times with CH_2Cl_2 and the organic phases were washed three times with water. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a crude residue. The crude product was purified by flash column chromatography on silica gel to give the ring contracted product.

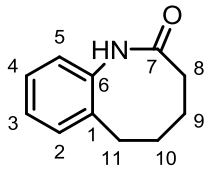
3.4 Characterisation Data

(*E*)- 6,7,8,9-Tetrahydro-5*H*-benzo[7]annulen-5-one oxime (2-10)



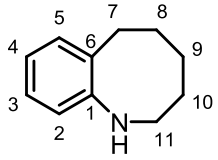
To a stirred solution of 1-benzosuberone (4.0 g, 25 mmol) and hydroxylamine hydrochloride (3.5 g, 50 mmol) in EtOH (125 mL) was added pyridine (3.5 mL, 44 mmol). The reaction mixture was heated to reflux and stirred overnight. The solvent was removed *in vacuo* and the crude product was purified *via* flash column chromatography (10 to 15% EtOAc in petrol) affording **2-10** as a white solid (4.0 g, 92%).**^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.20 (1 H, br s, OH), 7.41 (1 H, dd, *J* 7.5, 1.5, H5), 7.30 (1 H, td, *J* 7.5, 1.5, H3), 7.23 (1 H, dt, *J* 7.5, 1.0, H4), 7.13 (1 H, dd, *J* 7.5, 1.0, H2), 2.77–2.71 (4 H, m, H8, H11), 1.78 (2 H, quin, *J* 6.5, H9/H10), 1.64 (2 H, quin, *J* 6.5, H9/ H10). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 162.9 (C7), 139.6 (C6), 136.2 (C1), 129.4 (C3), 129.0 (C2), 127.5 (C4), 126.7 (C5), 32.1 (C11), 26.2 (C8), 26.1 (C10), 21.7 (C9). *Data in accordance with literature.*[105]

3,4,5,6-Tetrahydrobenzo[*b*]azocin-2(1*H*)-one (2-11)



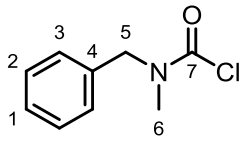
Polyphosphoric acid (10 g) was added to a 100 mL RB flask and heated to 115 °C. (*E*)-6,7,8,9-Tetrahydro-5*H*-benzo[7]annulen-5-one oxime **2-10** (3.5 g, 20 mmol) was added in one portion and the reaction mixture was heated to 130 °C and kept at this temperature for 10 min. Ice was then added to the reaction mixture and a fine white precipitate formed. CH_2Cl_2 (20 mL) was added and the organic phase was separated and washed with sat. $NaHCO_3$. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* affording **2-11** as a white solid (3.0 g, 86%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.14 (1 H, br s, NH), 7.28–7.17 (3 H, m, H2, H3, H4), 7.08 (1 H, dd, *J* 7.5 1.0, H5), 2.80–2.60 (2 H, br, H11), 2.3–1.5 (6 H, br, H9, H10, H11). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 177.1 (C7), 140.0 (C1), 136.0 (C6), 131.0 (C3/C4), 127.9 (C3/C4), 127.1 (C2), 125.3 (C5), 32.7 (C11), 31.3 (C8), 29.7 (C10), 25.0 (C9). *Data in accordance with literature.*[105, 202]

1,2,3,4,5,6-Hexahydrobenzo[*b*]azocine (2-12)



A solution of 3,4,5,6-tetrahydrobenzo[*b*]azocin-2(1*H*)-one **2-11** (1.5 g, 8.6 mmol) in THF (20 mL) was added dropwise to a suspension of $LiAlH_4$ (0.98 g, 26 mmol) in Et_2O (116 mL). The reaction mixture was stirred at reflux for 20 h. Water (1 mL) was added to quench the reaction, followed by 2 M NaOH (1 mL) and water (3 mL). The reaction mixture was stirred for 1 h before the granular salt was filtered and washed with Et_2O. The solvent was removed *in vacuo* and the crude material was purified by flash column chromatography (50% EtOAc in petrol) yielding **2-12** as a yellow oil (1.1 g, 82%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.10 (1 H, td, *J* 7.5, 1.5, H3), 7.06 (1 H, dd, *J* 7.5, 1.5, H5), 6.92 (1 H, dt, *J* 7.5, 1.0, H4), 6.88 (1 H, dd, *J* 7.5, 1.0, H2), 3.2–3.17 (2 H, m, H11), 3.03 (1 H, br s, NH), 2.85–2.82 (2 H, m, H7), 1.76–1.68 (2 H, m, H10/ H8), 1.56–1.49 (4 H, m, H10/H8, H9); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 147.7 (C1), 135.1 (C5), 130.5 (C3), 127.4 (C6), 122.9 (C4), 122.8 (C2), 51.5 (C11), 32.1 (C6), 31.4 (C10), 28.8 (C9), 25.4 (C8). *Data in accordance with literature.*[203]

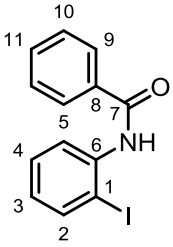
Benzyl(methyl)carbamoyl chloride (2-15)



According to **GP1**, *N*-benzylmethylamine (4.7 mL, 37 mmol), triphosgene (5.0 g, 17 mmol) and pyridine (3.0 mL, 37 mmol) in CH_2Cl_2 (52 mL) gave the *titled compound* **2-15** as a colourless oil (5.74 g, 93%). *N.B. Compound exists as a mixture of rotamers in a 1:1.3 ratio.* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.29 (5 H, m, H1, H2, H3^{rotA+B}), 4.75 (2 H, s, H5^{rotA}), 4.61 (2 H, s, H5^{rotB}) 3.1 (3 H, s, H6^{rotB}), 3.0 (3 H, s, H6^{rotA}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.6 (C7), 135.6 and 135.3 (C4^{rotA+B}), 129.1 and 129.0

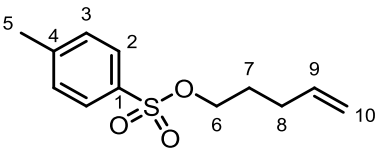
(C2/C3^{rotA+B}), 128.3 and 128.2 (C2/C3^{rotA+B}), 127.3 (C1), 56.5 (C5^{rotA}) and 54.6 (C5^{rotB}), 38.0 (C6^{rotB}) and 36.5 (C6^{rotA}). *Data in accordance with literature.*[204]

_N_-(2-Iodophenyl)benzamide, 2-25:



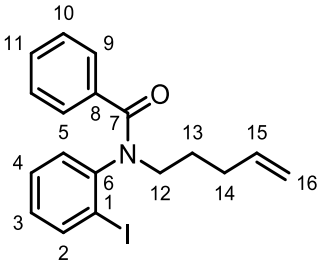
To a stirred solution of 2-iodoaniline (2.0 g, 9.1 mmol) in THF (20 mL) was added benzoyl chloride (1.2 mL, 10 mmol) at RT. The reaction mixture was stirred at RT for 16 hours or until TLC showed consumption of starting material. The reaction mixture was diluted with EtOAc, washed twice with 5% $NaHCO_3$ and once with brine. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10% EtOAc in petrol) to yield *N*-(2-iodophenyl)benzamide **2-25** as a white solid (2.2 g, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.47 (1 H, dd, *J* 8.2, 1.5, H5), 8.30 (1 H, br s, NH), 8.0–7.97 (2 H, m, H9), 7.83 (1 H, dd, *J* 8.0, 1.5, H2), 7.65–7.51 (3 H, m, H4, H10), 7.44–7.39 (1H, m, H11), 6.89 (1 H, td, *J* 7.7, 1.6, H3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 165.4 (C7), 139.0 (C6), 138.4 (C2), 134.7 (C8), 132.3 (C11), 129.6 (C4), 129.1 (C10), 127.3 (C9), 126.2 (C3), 121.9 (C5), 90.3 (C1). *Data in accordance with literature.*[205]

Pent-4-en-1-yl 4-methylbenzenesulfonate (2-25a)



To a solution of 4-penten-1-ol (1.0 g, 12 mmol) and pyridine (1.9 mL, 23 mmol) in CH_2Cl_2 (12 mL) was added *p*-toluenesulfonyl chloride (3.3 g, 17 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h then at RT for a further 1 h. H_2O (9 mL) was added and the mixture was extracted with Et_2O (20 mL). The organic phase was subsequently extracted with 2 M HCl, 5% Na_2CO_3 and H_2O. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (10% Et_2O in petrol) to yield **2-25a** (2.7 g, 96%) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.79 (2 H, d, *J* 8.2, H2), 7.35 (2 H, d, *J* 8.2, H3), 5.69 (1 H, ddt, *J* 18.2, 9.6, 6.7, H9), 4.99–4.96 (1 H, m, H10), 4.95–4.93 (1 H, m, H10), 4.04 (2 H, t, *J* 6.4, H6), 2.45 (3 H, s, H5), 2.11–2.06 (2 H, m, H8), 1.78–1.71 (2 H, m, H7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 144.8 (C1), 136.7 (C4), 133.3 (C9), 129.9 (C3), 128.0 (C2), 115.6 (C10), 69.9 (C6), 29.5 (C8), 28.1 (C7), 21.8 (C5). *Data in accordance with literature.*[206]

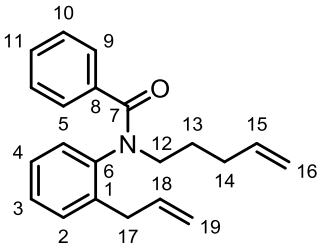
_N_-(2-Iodophenyl)-_N_-(pent-en-1-yl)benzamide (2-26)



To a flame-dried Schlenk tube was added NaH (0.19 g, 60% dispersion in mineral oil, 4.6 mmol) and THF (20 mL). The suspension was cooled to 0 °C and *N*-(2-iodophenyl)benzamide **2-25** (1.0 g, 3.1 mmol) was added dropwise as a solution in THF (10 mL). The reaction was warmed to RT and stirred for 3 h. A solution of pent-4-enyl tosylate **2-25a** (0.82 g, 3.4 mmol) in THF (2 mL) was added to the mixture and stirred at reflux for 16 h. The reaction was quenched by the slow addition of H_2O (5 mL) and diluted with EtOAc. The aqueous phase was extracted three times with EtOAc and the organic phases were washed with brine. The combined organic phases were dried over $MgSO_4$, filtered through celite and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (5 to 40% EtOAc in petrol) yielding *N*-(2-iodophenyl)-*N*-(pent-en-1-yl)benzamide **2-26** (0.68 g, 56%). *Product exists as rotamers in a 1:1 ratio.* **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.83 (1 H, d, *J* 7.9, H2), 7.34–7.01 (7 H, m, ArH), 6.89 (1 H, t, J 7.8, ArH), 5.87–5.72 (1H, m, H15), 5.04–4.93 (2 H, m, H16), 4.33–4.24 (1 H, m, H12$_{rot}$), 3.41–3.34 (1 H, m, H12$_{rot}$), 2.19–2.06 (2 H, m, CH_2), 1.93–1.83 (1 H, m, H13$_{rot}$), 1.78–1.66 (1 H, m, H13$_{rot}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 170.5 (C7), 145.3 (C6) 140.5 (C2), 137.9 (C15), 136.2 (C6) 131.6 (C8), 129.7 (C11$_{rot}$), 129.6 (C11$_{rot}$), 129.2 (C10$_{rot}$), 129.1 (C10$_{rot}$), 128.8 (C9$_{rot}$), 128.3 (C9$_{rot}$), 127.9 (C4$_{rot}$), 127.8 (C3), 127.7 (C5),

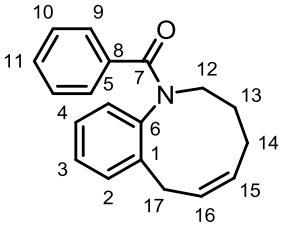
115.3 (C16), 100.2 (C1), 49.4 (C12), 31.4 ($C14_{rot}$), 31.3 ($C14_{rot}$), 27.0 ($C13_{rot}$), 26.5 ($C13_{rot}$). *Data in accordance with literature.*[207]

_N_-(2-Allylphenyl)-_N_-pent-4-en-1-yl)benzamide (2-27)



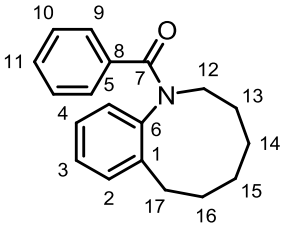
To a flame-dried Young's tube was added $Pd(OAc)_2$ (0.02 g, 0.1 mmol, 4 mol%), PPh_3 (0.11 g, 0.41 mmol, 4 eq. with respect to Pd) and LiCl (0.12 g, 2.8 mmol). Dimethylacetamide (2 mL) was added and the mixture was stirred at RT for 20 min to generate the catalyst. To the yellow solution was added *N*-(2-iodophenyl)-*N*-(pent-en-1-yl)benzamide **2-26** (1 g, 2.6 mmol) as a solution in dimethylacetamide (2 mL), followed by tributylallyltin (1.2 mL, 3.8 mmol). The Young's tube was sealed and heated to 100 °C for 24 h. The reaction mixture was filtered through celite and washed three times with 5% LiCl solution and three times with 1 M KF solution. The combined organic phases were filtered through celite and washed once with brine. The organic phase was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10 to 40% EtOAc in petrol) yielding *N*-(2-allylphenyl)-*N*-pent-4-en-1-yl)benzamide **2-27** as a yellow oil (0.68 g, 87%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.28–7.01 (9 H, m, ArH), 5.84–5.65 (2 H, m, H15, H18), 5.10–4.93 (4 H, m, H16, H19), 4.12 (1 H, ddd, *J* 13.1, 10.4, 5.6, $H12_a$), 3.49 (1 H, ddd, *J* 13.1, 10.4, 5.3, $H12_b$), 3.34 (1 H, dd, *J* 15.9, 6.8, $H17_a$), 3.17 (1 H, dd, *J* 15.9, 6.4, $H17_b$), 2.15–2.05 (2 H, m, H14), 1.85–1.67 (2 H, m, H13); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 170.4 (C7), 141.6 (C6), 137.9 (C15), 137.1 (C8), 136.3 (C1), 135.9 (C18), 130.6 (CH), 129.9 (CH), 129.6 (CH), 129.2 (CH), 128.5 (CH), 127.9 (CH), 127.6 (CH), 117.2 (C19), 115.2 (C16), 50.1 (C12), 35.0 (C17), 31.4 (C14), 26.5 (C13). *Data in accordance with literature.*[110, 207]

(*Z*)-Phenyl(2,3,4,7-tetrahydro-1*H*-benzo[*b*]azonin-1-yl)methanone (2-28)



To a flame-dried Young's tube was added Grubbs I catalyst (0.12 g, 0.14 mmol, 10 mol%) and *N*-(2-allylphenyl)-*N*-pent-4-en-1-yl)benzamide **2-27** (0.43 g, 1.4 mmol) as a solution in toluene (14 mL, 0.1 M). The solution was stirred at RT for 10 min. The Young's tube was then sealed and heated to 60 °C for 48 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (5 to 20% EtOAc in petrol). The product was then recrystallised from Et_2O to yield **2-28** as colourless prisms (0.21 g, 54%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.39–7.38 (2 H, m, ArH), 7.24–7.22 (2 H, m, ArH), 7.18–7.11 (3 H, m, ArH), 6.98 (1 H, td, *J* 7.6, 1.6, ArH), 6.75 (1 H, dd, *J* 7.8, 1.3, ArH), 5.75 (1 H, td, *J* 10.7, 6.0, H16), 5.55 (1 H, td, *J* 10.7, 6.0, H15), 4.30–4.26 (1 H, m, $H17_a$), 4.19 (1 H, ddd, *J* 13.2, 4.4, 2.1, $H12_a$), 3.06–2.19 (3 H, m, $H17_b$, $H12_b$, $H14_a$), 2.87–2.79 (1 H, m, $H13_a$), 2.13–2.06 (1 H, m, $H14_b$), 1.48 (1 H, ttd, *J* 13.7, 4.3, 2.0 $H13_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 172.5 (C7), 145.5 (C6), 137.4 (C8), 136.5 (C1), 131.1 (ArCH), 129.9 (ArCH), 129.85 (ArCH), 129.1 (C16), 128.8 (C15), 128.11 (ArCH), 128.08 (ArCH), 127.9 (ArCH), 127.6 (ArCH), 51.6 (C12), 31.5 (C17), 26.1 (C13), 22.6 (C14). *Data in accordance with literature.*[110, 207]

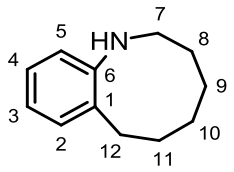
(2,3,4,5,6,7-Hexahydro-1H-benzo[b]azonin-1-yl)(phenyl)methanone (2-29)



To a solution of **2-28** (173 mg, 0.62 mmol), in MeOH (8 mL) was added Pd/C (18 mg, 10 wt%). The suspension was stirred at RT under a hydrogen atmosphere for 16 h. The reaction mixture was then filtered through celite and washed with a mixture of EtOAc and MeOH. The filtrate was concentrated *in vacuo* and the crude product was purified by recrystallisation from Et_2O giving **2-29** as colourless prisms (142 mg, 82%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.23–7.11 (6 H, m, ArH), 7.11–7.05 (2 H, m, ArH), 6.99–

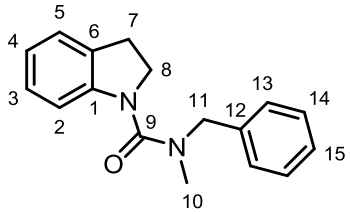
6.96 (1 H, m, ArH), 4.68 (1 H, ddd, *J* 13.7, 5.9, 4.2, H12$_a$), 3.18 (1 H, ddd, *J* 13.7, 8.6, 4.2, H12$_b$), 2.76 (1 H, ddd, *J* 13.6, 11.6, 4.2, H17$_a$), 2.32–2.15 (2 H, m, H17$_a$, H13$_a$), 1.78–1.63 (2 H, m, H13$_b$, H16$_a$), 1.62–1.36 (5 H, m, H16b, H14, H15). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 170.4 (C7), 143.9 (C8), 140.2 (C6), 136.7 (C1), 130.7 (ArCH), 129.2 (ArCH), 128.5 (ArCH), 128.3 (ArCH), 128.1 (ArCH), 127.5 (ArCH), 127.3 (ArCH), 50.5 (C12), 30.1 (C17), 28.9 (C16), 26.4 (C13), 23.9 (C14), 22.2 (C15). *Data in accordance with literature.*[110]

2,3,4,5,6,7-Hexahydro-1*H*-benzo[b]azonine (2-30)



A solution of (2,3,4,5,6,7-hexahydro-1*H*-benzo[b]azonin-1-yl)(phenyl)methanone **2-29** (0.16 g, 0.58 mmol) in dioxane (2 mL) and 6 M HCl (2 mL) was stirred in a microwave at 140 °C for 4 h. Once cooled the reaction was quenched with 2 M NaOH (2 mL). CH_2Cl_2 was added and the organic phase was separated. The aqueous phase was extracted three times with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography eluting with (5% to 20% EtOAc in petrol) gave the *title compound* **2-30** as a yellow oil (90 mg, 87%). $\mathbf{R_f}$ 0.35 (10% EtOAc/petrol). $\boldsymbol{\nu_{max}}$ **/cm^{-1}** (film) 2922, 2800, 1462; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.15 (1 H, td, *J* 7.6, 1.6, H4), 7.05 (1 H, dd, *J* 7.6, 1.6, H2), 7.9 (1 H, dd, *J* 7.6, 1.2, H5), 6.88 (1 H, td, *J* 7.6, 1.2, H3), 3.37–3.35 (2 H, br, H7), 2.79–2.76 (2 H, m, H12), 1.76–1.71 (2 H, br, H11), 1.55–1.51 (6 H, br, H8, H9, H10); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.4 (C6), 133.8 (C1), 130.5 (C2), 127.4 (C4), 121.5 (C3), 121.2 (C5), 50.0 (C7), 31.9 (C12), 28.9 (C11), 27.4 (C8), 27.0 (C10), 25.2 (C9); **HRMS** m/z (ESI$^+$) $C_{12}H_{18}N^+$ requires: 176.1433; found: 176.1433.

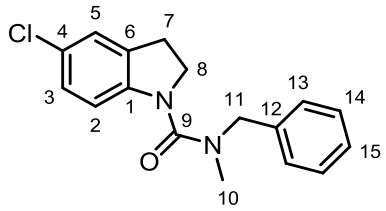
***N*-Benzyl-*N*-methylindoline-1-carboxamide (2-43)**



Benzyl isocyanate (0.54 mL, 3.8 mmol) was added to indoline (0.53 mL, 4.2 mmol) in CH_2Cl_2 (4.2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then warmed to RT and stirred overnight. The reaction was quenched with 1 M HCl (4 mL) and the organic phase was washed three times with 1 M HCl. The combined aqueous phases were re-extracted with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude urea which was used directly in the next step without further purification.

A suspension of sodium hydride (0.15 g, 3.8 mmol, 60% dispersion in mineral oil) was added to a suspension of the urea (0.80 g, 3.2 mmol) in THF (21 mL) at 0 °C. Iodomethane (0.30 mL, 4.8 mmol) was added dropwise to the resulting solution and stirred for 24 h at RT. H_2O (10 mL) and 1 M NaOH (10 mL) were added and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a crude residue. Purification by flash column chromatography eluting with (20% EtOAc in petrol) gave the *title compound* **2-43** as a colourless oil (0.63 g, 75%). $\mathbf{R_f}$ 0.21 (20% EtOAc/petrol); $\boldsymbol{\nu_{max}}$ **/cm^{-1}** (film) 3029, 2922, 1651; *The title compound was obtained as a mixture of rotamers in a 10:1 ratio, only peaks corresponding to the major rotamer are reported.* **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.39–7.29 (5 H, m, H13, H14, H15), 7.18 (1 H, d, *J* 7.4, H5), 7.14 (1 H, t, *J* 7.8, H4), 7.00 (1 H, d, *J* 8.0, H2), 6.90 (1 H, t, *J* 7.4, H3), 4.53 (2 H, s, H11), 3.95 (2 H, t, *J* 8.3, H8), 3.05 (2 H, t, *J* 8.3, H7), 2.85 (3 H, s, H10); **^{13}C NMR** (101 MHz; $CDCl_3$) δ 160.3 (C9), 144.5 (C1), 137.5 (C12), 131.5 (C6), 128.8 (ArCH), 128.2 (ArCH), 127.6 (ArCH), 127.2 (C4), 125.0 (C5), 121.6 (C3), 113.6 (C2), 53.9 (C11), 50.7 (C8), 36.2 (C10), 28.3 (C7); **HRMS** (ESI$^+$) m/z $C_{17}H_{19}N_2O^+$ requires: 267.1491; found: 267.1499.

***N*-Benzyl-5-chloro-*N*-methylindoline-1-carboxamide (2-44)**



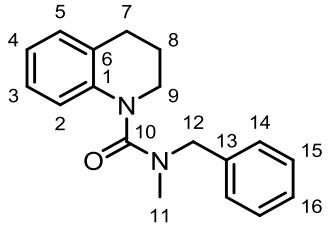
Carbamoyl chloride formation:

According to **GP1,** 5-chloroindoline (0.50 g, 3.3 mmol), triphosgene (0.44 g, 1.5 mmol) and pyridine (0.25 mL, 3.3 mmol) in CH_2Cl_2 (4.7 mL) gave the carbamoyl chloride. $\mathbf{R}_f$ 0.52 (30% Et_2O/*n*-pentane).

Urea formation:

According to **GP2,** 5-chloroindoline-1-carbamoyl chloride (0.51 g, 2.3 mmol), *N*-methylbenzylamine (0.35 mL, 3.0 mmol) and triethylamine (0.52 mL, 3.8 mmol) in MeCN (5.9 mL) was stirred at RT for 1 h. Purification by flash column chromatography eluting with (10% to 60% Et_2O in *n*-hexane) gave the *title compound* **2-44** as white solid (0.62 g, 64% over 2 steps). $\mathbf{R}_f$ 0.17 (30% Et_2O/*n*-pentane); **Mp** 84–86 °C (CH_2Cl_2/*n*-pentane); $\boldsymbol{\nu_{max}}$ **/cm^{-1}** (film) 2918, 1725, 1651; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.38–7.26 (5 H, m, H13, H14, H15), 7.12 (1 H, d, *J* 2.1, H5), 7.08 (1 H, dd, *J* 8.5, 2.1, H3), 6.92 (1 H, d, *J* 8.5, H2), 4.49 (2 H, s, H11), 3.94 (2 H, t, *J* 8.3, H8), 3.02 (2 H, t, *J* 8.3, H7), 2.82 (3 H, s, H10); **^{13}C NMR** (101 MHz; $CDCl_3$) δ 160.2 (C9), 143.4 (C12), 137.3 (C1), 133.4 (C6), 128.8 (C13/C14), 128.1 (C13/C14), 127.7 (C4), 127.1 (C15), 126.5 (C3), 125.1 (C5), 114.7 (C2), 53.8 (C11), 50.9 (C8), 36.1 (C10), 28.3 (C7); **HRMS** (ESI^+) m/z $C_{17}H_{18}{}^{35}ClN_2O^+$ requires: 301.1102; found: 301.1102. $C_{17}H_{18}{}^{37}ClN_2O^+$ requires: 303.1073; found: 303.1075.

***N*-Benzyl-*N*-methyl-3,4-tetrahydroquinoline-1(2*H*)-carboxamide (2-45)**



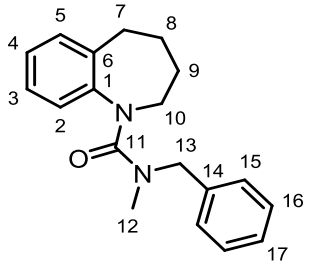
Carbamoyl chloride formation:

According to **GP1,** 1,2,3,4-tetrahydroquinoline (3.7 mL, 29 mmol), triphosgene (4.0 g, 14 mmol) and pyridine (2.4 mL, 29 mmol) in CH_2Cl_2 (42 mL) gave the carbamoyl chloride. $\mathbf{R}_f$ 0.46 (30% Et_2O/*n*-pentane) (*N.B.* The amounts described here were used to prepare a batch stock of the carbamoyl chloride, which was subsequently used for the synthesis of several urea substrates on smaller scales described below)

Urea formation:

According to **GP2,** 3,4-Tetrahydroquinoline-1(2*H*)-carbamoyl chloride (0.93 g, 4.8 mmol), *N*-methylbenzylamine (0.70 mL, 6.2 mmol) and triethylamine (1.0 mL, 7.6 mmol) in MeCN (12 mL) were stirred at RT for 4 h. Purification by flash column chromatography eluting with (3% to 20% EtOAc in petrol) gave the *title compound* **2-45** as a yellow oil (1.3 g, 98%). $\mathbf{R}_f$ 0.23 (20% EtOAc/petrol); $\boldsymbol{\nu_{max}}$ **/cm^{-1}** (film) 3026, 2932, 1643; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.37–7.32 (2 H, m, ArH), 7.31–7.26 (3 H, m, ArH), 7.10–7.05 (2 H, m, ArH), 6.95–6.92 (1 H, m, H2), 6.89 (1 H, td, *J* 7.4, 1.2, H4), 4.45 (2 H, s, H12), 3.62 (2 H, t, *J* 6.5, H9), 2.74 (2 H, t, *J* 6.5, H7), 2.70 (3 H, s, H11), 1.95 (2 H, p, *J* 6.5, H8); **^{13}C NMR** (101 MHz; $CDCl_3$) δ 161.1 (C10), 140.9 (C13), 137.6 (C1), 129.2 (ArCH), 128.7 (C14/C15), 128.2 (C14/C15), 127.9 (ArCH), 127.5 (C6), 126.6 (ArCH), 121.9 (ArCH), 119.5 (C2), 53.7 (C12), 45.8 (C9), 36.0 (C11), 27.1 (C7), 23.5 (C8); **HRMS** (ESI^+) m/z $C_{18}H_{22}N_2O^+$ requires: 281.1648; found: 281.1649.

***N*-Benzyl-*N*-methyl-2,3,4,5-tetrahydro-1*H*-benzo[b]azepine-1-carboxamide (2-46)**



Carbamoyl chloride formation:

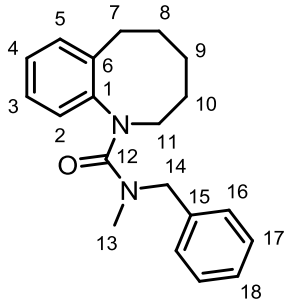
According to **GP1**, 2,3,4,5-tetrahydro-1*H*-benzo[b]azepine (0.50 g, 3.4 mmol), triphosgene (0.46 g, 1.6 mmol) and pyridine (0.26 mL, 3.4 mmol) in CH_2Cl_2 (4.9 mL) gave the carbamoyl chloride. $\mathbf{R}_f$ 0.41 (10% EtOAc/petrol).

Urea formation:

According to **GP2**, 2,3,4,5-tetrahydro-1*H*-benzo[b]azepine-1-carbamoyl chloride (0.51 g, 2.4 mmol), *N*-methylbenzylamine (0.36 mL, 3.2 mmol) and triethylamine (0.54 mL,

3.9 mmol) in MeCN (6.0 mL) was stirred at RT for 3 h. Purification by flash column chromatography eluting with (10% to 20% EtOAc in petrol) gave the *title compound* **2-46** as white solid (0.58 g, 58% over 2 steps). $\mathbf{R_f}$ 0.18 (10% EtOAc/petrol); **Mp** 105-106 °C (CH_2Cl_2/*n*-pentane); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 3026, 2923, 1726, 1644; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.33–7.28 (2 H, m, H15), 7.26–7.23 (1 H, m, H17), 7.22–7.16 (3 H, m, H5, H16), 7.12 (1 H, td, *J* 7.5, 1.6, H3), 7.06 (1 H, td, *J* 7.5, 1.6, H4), 6.95 (1 H, dd, *J* 7.5, 1.5, H2), 4.31 (2 H, s, H13), 3.72 (2 H, br, H10), 2.76–2.72 (2 H, m, H7), 2.35 (3 H, s, H12), 1.80–1.74 (2 H, m, H9), 1.69–1.60 (2 H, m, H8); **^{13}C NMR** (101 MHz; $CDCl_3$) δ 161.6 (C11), 146.2 (C14), 138.3 (C1), 138.0 (C6), 130.5 (C5), 128.6 (C15), 128.1 (C16), 127.28 (C17), 127.27 (C3), 125.7 (C4), 124.8 (C2), 53.8 (C13), 48.8 (C10), 35.8 (C12), 25.3 (C7), 30.9 (C9), 26.0 (C8); **HRMS** (ESI^+) m/z $C_{19}H_{23}N_2O^+$ requires: 295.1805; found: 295.1811.

***N*-Benzyl-*N*-methyl-3,4,5,6-tetrahydrobenzo[b]azocine-1(2*H*)-carboxamide (2-47)**



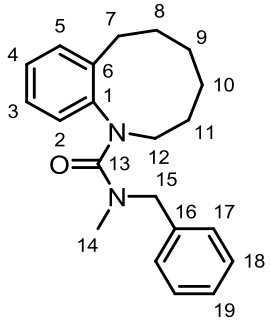
Carbamoyl chloride formation:

According to **GP1**, 1,2,3,4,5,6-hexahydrobenzo[b]azocine (0.50 g, 3.1 mmol), triphosgene (0.42 g, 1.4 mmol) and pyridine (0.24 mL, 3.1 mmol) in CH_2Cl_2 (4.4 mL) gave the carbamoyl chloride. $\mathbf{R_f}$ 0.58 (10% EtOAc/petrol).

Urea formation:

3,4,5,6-tetrahydrobenzo[b]azocine-1(2*H*)-carbamoyl chloride (0.43 g, 1.9 mmol) and 4-dimethylaminopyridine (20 mg, 0.19 mmol) were added to a solution of *N*-methylbenzylamine (0.22 mL, 1.9 mmol) and triethylamine (0.43 mL, 3.1 mmol) in dichloroethane (6.4 mL). The reaction mixture was stirred at reflux for 12 h. After cooling, the mixture was quenched with $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography eluting with (20% EtOAc in petrol) gave the *title compound* **2-47** as a yellow oil (0.45 g, 52% over 2 steps). $\mathbf{R_f}$ 0.21 (20% EtOAc/petrol); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 2922, 2852, 1634; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.28–7.18 (6 H, m, ArH), 7.12–7.09 (2 H, m, H16), 7.04–7.00 (1 H, m, H4), 4.35 (2 H, s, H14), 3.67–3.58 (2 H, br, H11), 2.76–2.71 (2 H, m, H7), 2.40 (3 H, s, H13), 1.75–1.67 (2 H, br, H10), 1.59–1.44 (4 H, br, H8, H9); **^{13}C NMR** (101 MHz; $CDCl_3$) δ 163.6 (C12), 143.6 (C15), 142.0 (C1), 138.2 (C6), 130.3 (ArC), 128.4 (C17), 127.8 (C16), 127.69 (ArCH), 127.66 (ArCH), 127.5 (ArCH), 127.1 (ArCH), 54.6 (C11), 54.0 (C14), 35.8 (C13), 31.9 (C7), 31.8 (C10), 27.1 (C8/C9), 26.3 (C8/C9); **HRMS** (ESI^+) m/z $C_{20}H_{25}N_2O^+$ requires: 309.1961; found: 309.1965.

***N*-Benzyl-*N*-methyl-2,3,4,5,6,7-hexahydro-1*H*-benzo[b]azonine-1-carboxamide (2-48)**



Carbamoyl chloride formation:

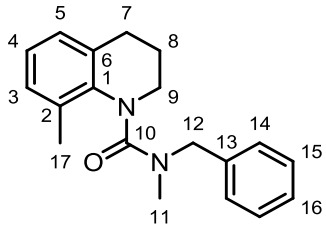
According to **GP1**, 2,3,4,5,6,7-hexahydro-1*H*-benzo[b]azonine (0.13 g, 0.76 mmol), triphosgene (0.10 g, 0.35 mmol) and pyridine (60 μL, 0.76 mmol) in CH_2Cl_2 (1.1 mL) gave the carbamoyl chloride. $\mathbf{R_f}$ 0.58 (10% EtOAc/petrol).

Urea formation:

According to **GP2**, 2,3,4,5,6,7-hexahydro-1*H*-benzo[*b*]azonine-1-carbamoyl chloride (0.11 g, 0.45 mmol) *N*-methylbenzylamine (70 μL, 0.59 mmol) and triethylamine (0.10 mL, 0.73 mmol) in MeCN (1.2 mL) was stirred at RT for 16 h. Purification by flash column chromatography eluting with (5% to 20% EtOAc in petrol) gave the *title compound* **2-48** as a colourless oil (0.10 g, 39% over 2 steps). $\mathbf{R_f}$ 0.36 (20% EtOAc/petrol); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 2922, 1637, 1450, 1392; **^{1}H NMR** (500 MHz, DMSO-d_6, 373 K/100 °C) δ 7.27–7.23 (2 H, m, ArH), 7.21–7.13 (4 H, m, ArH), 7.10–7.08 (2 H, m, ArH), 7.05–7.02 (1 H, m, ArH), 4.21 (2 H, s, H15), 3.67–3.64 (2 H, br m, H12), 2.72 (2 H, t, *J* 6.0, H7), 2.33 (3 H, s, H14), 1.72–1.67 (2 H, m, H8/H11), 1.65–1.60 (2 H, m, H8/H11), 1.51–1.46 (2 H, m, H9/H10), 1.34–1.28 (2 H, m, H9/H10); **^{13}C NMR** (126 MHz, DMSO-d_6, 373 K/100 °C) δ 160.5 (C13), 144.4 (C16),

139.7 (C1), 137.8 (C6), 130.2 (ArCH), 127.5 (ArCH), 126.9 (ArCH), 126.8 (ArCH), 126.7 (ArCH), 126.22 (ArCH), 126.17 (ArCH), 53.0 (C15), 50.8 (C12), 35.1 (C14), 29.0 (C8), 27.4 (C7), 26.4 (C9), 23.8 (C11), 22.4 (C10); **HRMS** (ESI^+) m/z $C_{21}H_{27}N_2O^+$ requires: 323.2118; found: 323.2119.

***N*-Benzyl-*N*,8-dimethyl-3,4-tetrahydroquinoline-1(2*H*)-carboxamide (2-49)**



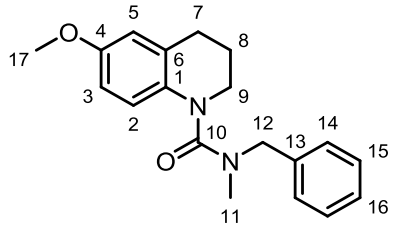
Carbamoyl chloride formation:

According to **GP1**, 8-methyl-1,2,3,4-tetrahydroquinoline (0.50 g, 3.4 mmol), triphosgene (0.46 g, 1.6 mmol) and pyridine (0.26 mL, 3.4 mmol) in CH_2Cl_2 (4.9 mL) gave the carbamoyl chloride. $\mathbf{R_f}$ 0.58 (30% EtOAc/petrol).

Urea formation:

According to **GP2**, 8-methyl-3,4-Tetrahydroquinoline-1(2*H*)-carbamoyl chloride (0.58 g, 2.7 mmol), *N*-methylbenzylamine (0.40 mL, 3.6 mmol) and triethylamine (0.61 mL, 4.4 mmol) in MeCN (6.9 mL) was stirred at RT for 1 h. Purification by flash column chromatography eluting with (15% to 80% Et_2O in *n*-pentane) gave the *title compound* **2-49** as a white solid (0.64 g, 58% over 2 steps). $\mathbf{R_f}$ 0.11 (30% Et_2O/*n*-pentane); **Mp** 111-112 °C (CH_2Cl_2/*n*-pentane); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 2920, 1724, 1651; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.34–7.22 (5 H, m, H14, H15, H16), 7.04–7.00 (1 H, m, H4), 6.98–6.93 (2 H, m, H3, H5), 4.38 (2 H, br m, H12), 3.65–3.55 (2 H, br, H9), 2.73–2.61 (5 H, m, H11, H7), 2.12 (3 H, s, H17), 1.98–1.87 (2 H, br m, H8); **^{13}C NMR** (101 MHz; $CDCl_3$) δ 162.0 (C10), 140.2 (C1), 137.9 (C13), 132.5 (C2), 131.9 (C5), 128.9 (C6), 128.7 (C15), 128.2 (C14), 127.4 (C3), 126.3 (C16), 124.0 (C4), 53.4 (C12), 46.6 (C9), 35.5 (C11), 27.3 (C7), 24.3 (C8), 18.2 (C17); **HRMS** (ESI^+) m/z $C_{19}H_{23}N_2O^+$ requires: 295.1805; found: 295.1804.

***N*-Benzyl-6-methoxy-*N*-methyl-3,4-tetrahydroquinoline-1(2*H*)-carboxamide (2-50)**



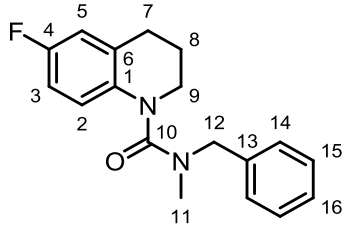
Carbamoyl chloride formation:

According to **GP1,** 6-methoxy-1,2,3,4-tetrahydroquinoline (0.50 g, 3.1 mmol), triphosgene (0.42 g, 1.4 mmol) and pyridine (0.25 mL, 3.1 mmol) in CH_2Cl_2 (4.4 mL) gave the carbamoyl chloride. $\mathbf{R_f}$ 0.39 (20% EtOAc/*n*-pentane).

Urea formation:

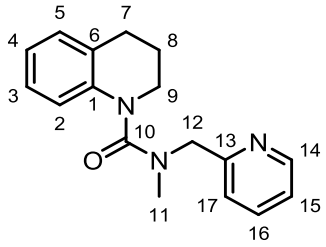
According to **GP2,** 6-methoxy-3,4-tetrahydroquinoline-1(2*H*)-carbamoyl chloride (0.70 g, 3.1 mmol), *N*-methylbenzylamine (0.46 mL, 4.0 mmol) and triethylamine (0.69 mL, 5.0 mmol) in MeCN (8 mL) were stirred at RT for 12 h. Purification by flash column chromatography eluting with (10% to 80% Et_2O in petrol) gave the *title compound* **2-50** as a yellow oil (0.75 g, 78% over 2 steps). $\mathbf{R_f}$ 0.13 (40% Et_2O/*n*-pentane); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 1636, 1498, 1387, 1198, 701; **^{1}H NMR** (500 MHz; $CDCl_3$) δ 7.37–7.31 (2 H, m, H14), 7.30–7.23 (3 H, m, H15, H16), 6.90 (1 H, d, *J* 8.5, H2), 6.70–6.61 (2 H, m, H3, H5), 4.42 (2 H, s, H12), 3.76 (3 H, s, H17), 3.60 (2 H, t, *J* 6.6, H9), 2.70 (3 H, t, *J* 6.6, H7), 2.67 (3 H, s, H11), 1.92 (2 H, p, *J* 6.6, H8); **^{13}C NMR** (126 MHz; $CDCl_3$) δ 161.3 (C10), 154.9 (C4), 137.9 (C13), 134.4 (C6), 129.8 (C1), 128.7 (C15), 128.1 (C14), 127.4 (C16), 121.3 (C2), 113.8 (C3), 112.4 (C5), 55.5 (C17), 53.8 (C12), 45.7 (C9), 36.1 (C11), 27.3 (C7), 23.7 (C8); **HRMS** (ESI^+) m/z $C_{19}H_{22}N_2NaO_2^+$ requires: 333.1573; found: 333.1572.

***N*-Benzyl-6-fluoro-*N*-methyl-3,4-tetrahydroquinoline-1(2*H*)-carboxamide (2-51)**



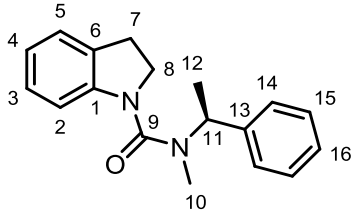
Carbamoyl chloride formation:
According to **GP1**, 6-fluoro-1,2,3,4-tetrahydroquinoline (0.25 g, 1.7 mmol), triphosgene (0.23 g, 0.76 mmol) and pyridine (0.13 mL, 1.7 mmol) in CH_2Cl_2 (2.4 mL) gave the carbamoyl chloride. $\mathbf{R}_f$ 0.53 (20% EtOAc/*n*-pentane).
Urea formation:
According to **GP2**, 6-fluoro-3,4-tetrahydroquinoline-1(2*H*)-carbamoyl chloride (0.36 g, 1.7 mmol), *N*-methylbenzylamine (0.25 mL, 2.2 mmol) and triethylamine (0.37 mL, 2.7 mmol) in MeCN (4.2 mL) was stirred at RT for 12 h. Purification by flash column chromatography eluting with (10% to 80% Et_2O in petrol) gave the *title compound* **2-51** as a yellow oil (0.42 g, 85% over 2 steps). $\mathbf{R}_f$ 0.11 (40% Et_2O/*n*-pentane); $\boldsymbol{\nu_{max}}$**/cm^{-1}** (film) 2931, 1642, 1496, 1482, 1390, **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.41–7.32 (2 H, m, H14), 7.32–7.23 (3 H, m, H15, H16), 6.90 (1 H, dd, *J* 8.6, 5.0, H3), 6.82–6.74 (2 H, m, H2, H5), 4.44 (2 H, s, H12), 3.59 (2 H, t, *J* 6.7, H9), 2.71 (2 H, t, *J* 6.7, H7), 2.70 (3 H, s, H11), 1.97–1.88 (2 H, m, H8); **^{13}C NMR** (101 MHz; $CDCl_3$) δ 161.2 (C10), 158.0 (d, J_{CF} 241, C4), 137.5 (C13), 136.9 (C1), 129.8 (d, J_{CF} 7, C6), 128.7 (C14), 128.1 (C15/C16), 127.5 (C15/C16), 121.2 (d, J_{CF} 8, C2), 115.3 (d, J_{CF} 22, C3/C5), 113.3 (d, J_{CF} 23, C3/C5), 53.7 (C12), 45.8 (C9), 36.0 (C11), 27.1 (C7), 23.2 (C8); **^{19}F NMR** (376 MHz; $CDCl_3$) δ −121.7 (td, *J* 8.6, 5.0, F); **HRMS** (ESI^+) m/z $C_{18}H_{19}FN_2NaO^+$ requires: 321.1371; found: 321.1374.

***N*-Methyl-*N*-(pyridin-2-ylmethyl)-3,4-tetrahydroquinoline-1(2*H*)-carboxamide (2-57)**



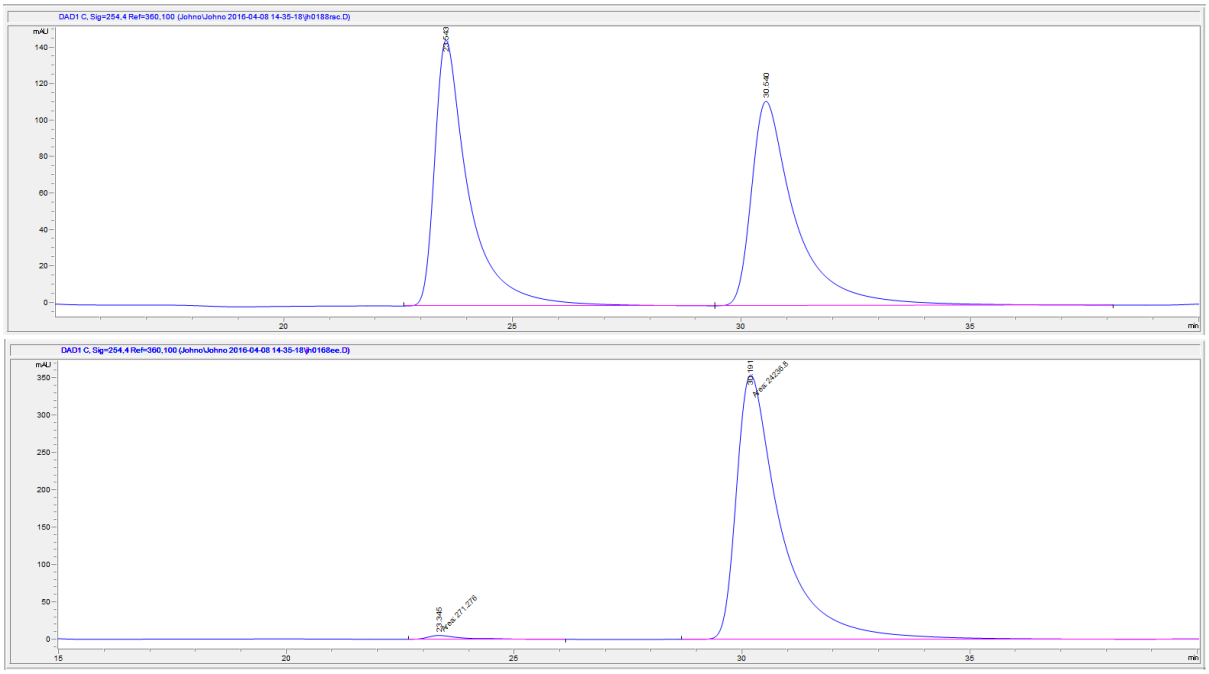
Carbamoyl chloride formation:
According to **GP1**, 1,2,3,4-tetrahydroquinoline (3.7 mL, 29 mmol), triphosgene (4.0 g, 14 mmol) and pyridine (2.4 mL, 29 mmol) in CH_2Cl_2 (42 mL) gave the carbamoyl chloride. $\mathbf{R}_f$ 0.46 (30% Et_2O/*n*-pentane). (*N.B.* The amounts described here were used to prepare a batch stock of the carbamoyl chloride).
Urea formation:
According to **GP2**, 3,4-tetrahydroquinoline-1(2*H*)-carbamoyl chloride (0.30 g, 1.5 mmol), *N*-methyl-1-(pyridin-2-yl)methanamine (0.25 mL, 2.0 mmol) and triethylamine (0.34 mL, 2.5 mmol) in MeCN (4 mL) was stirred at RT for 12 h. Purification by flash column chromatography eluting with (10% to 100% EtOAc in petrol) gave the *title compound* **2-57** as a yellow oil (0.42 g, 98%). $\mathbf{R}_f$ 0.09 (60% EtOAc/*n*-pentane); $\boldsymbol{\nu_{max}}$**/cm^{-1}** (film) 1636, 1491, 1389, 1248, 749; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 8.55 (1 H, ddd, *J* 4.9, 1.8, 1.0, H14), 7.67 (1 H, td, *J* 7.8, 1.8, H16), 7.33 (1 H, td, *J* 7.5. 1.0, H3), 7.21–7.15 (1 H, m, H15), 7.10–7.05 (2 H, m, H5, H17), 7.04–7.00 (1 H, m, H2), 6.89 (1 H, td, *J* 7.5, 1.4, H4), 4.57 (2 H, s, H12), 3.68–3.56 (2 H, m, H9), 2.79 (3 H, s, H11), 2.73 (2 H, t, *J* 6.7, H7), 1.99–1.89 (2 H, m, H8); **^{13}C NMR** (101 MHz; $CDCl_3$) δ 161.2 (C10), 157.9 (C13), 149.4 (C14), 140.9 (C1), 136.9 (C16), 129.1 (C5/C17), 128.0 (C6), 126.6 (C5/C17), 122.4 (C15), 122.3 (C3), 122.0 (C4), 119.8 (C2), 55.5 (C12), 45.8 (C9), 36.9 (C11), 27.1 (C7), 23.6 (C8); **HRMS** (ESI^+) m/z $C_{17}H_{19}N_3NaO^+$ requires: 304.1420; found: 304.1424.

(−)-(*S*)-*N*-Methyl-*N*-(1-phenylethyl)indoline-1-carboxamide (2-59)



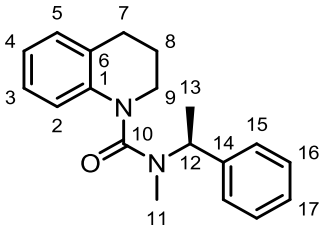
Carbamoyl chloride formation:
According to **GP1**, indoline (0.50 g, 4.2 mmol), triphosgene (0.57 g, 1.9 mmol) and pyridine (0.33 mL, 4.2 mmol) in CH_2Cl_2 (6.0 mL) gave the carbamoyl chloride. $\mathbf{R}_f$ 0.42 (10% EtOAc/petrol).
Urea formation:

According to **GP2**, indoline-1-carbamoyl chloride (0.66 g, 3.6 mmol), (*S*)-*N*-methyl-1-phenylethan-1-amine (0.59 mL, 4.7 mmol) and triethylamine (0.81 mL, 5.8 mmol) in MeCN (9.1 mL) was stirred at RT for 3 h. Purification by flash column chromatography eluting with (10% to 20% EtOAc in petrol) gave the *title compound* **2-59** as a yellow oil (0.95 g, 84% over 2 steps). $\mathbf{R}_f$ 0.16 (10% EtOAc/petrol); $\boldsymbol{\nu}_{\mathbf{max}}$**/cm**$^{-1}$ (film) 2971, 2901, 1644; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.45–7.36 (4 H, m, H14, H15), 7.32–7.27 (1 H, m, H16), 7.17 (1 H, dd, *J* 7.4, 1.3, H5), 7.11 (1 H, td, *J* 7.7, 1.3, H3), 6.92 (1 H, d, *J* 7.7, H2), 6.87 (1 H, td, *J* 7.4, 1.3, H4), 5.53 (1 H, q, *J* 7.0, H11), 3.99–3.88 (2 H, m, H8), 3.04 (2 H, t, *J* 8.2, H7), 2.64 (3 H, s, H10), 1.65 (3 H, d, *J* 7.1, H12); **^{13}C NMR** (101 MHz; $CDCl_3$) δ 160.3 (C9), 144.7 (C13), 141.0 (C1), 131.5 (C6), 128.6 (C14), 127.7 (C15), 127.4 (C16), 127.1 (C3), 124.9 (C5), 121.5 (C4), 113.6 (C2), 54.0 (C11), 50.8 (C8), 30.9 (C10), 28.4 (C7), 16.1 (C12); **HRMS** (ESI^+) m/z $C_{18}H_{21}N_2O^+$ requires: 281.1648; found: 281.1643; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ −57 (*c*. 1.0, $CHCl_3$); **HPLC** Racemic sample was prepared in an analogous manner using (±)-*N*-methyl-1-phenylethan-1-amine[211] which was prepared according to literature procedures.
ChiralPak AD-H column, 1 mL/min, 25 °C, 2% *i*PrOH/*n*-hexane; t_R: 23.4 min (minor), 30.2 min (major), *er* = 99:1



Peak #	Time / min	Area	Height	Width	Area / %	Symmetry
1	23.345	271.3	5.1	0.8846	1.107	0.439
2	30.191	24236.8	355.1	1.1374	98.893	0.448

(−)-(*S*)-*N*-Methyl-*N*-(1-phenylethyl)-3,4-tetrahydroquinoline-1(2*H*)-carboxamide (2-60)

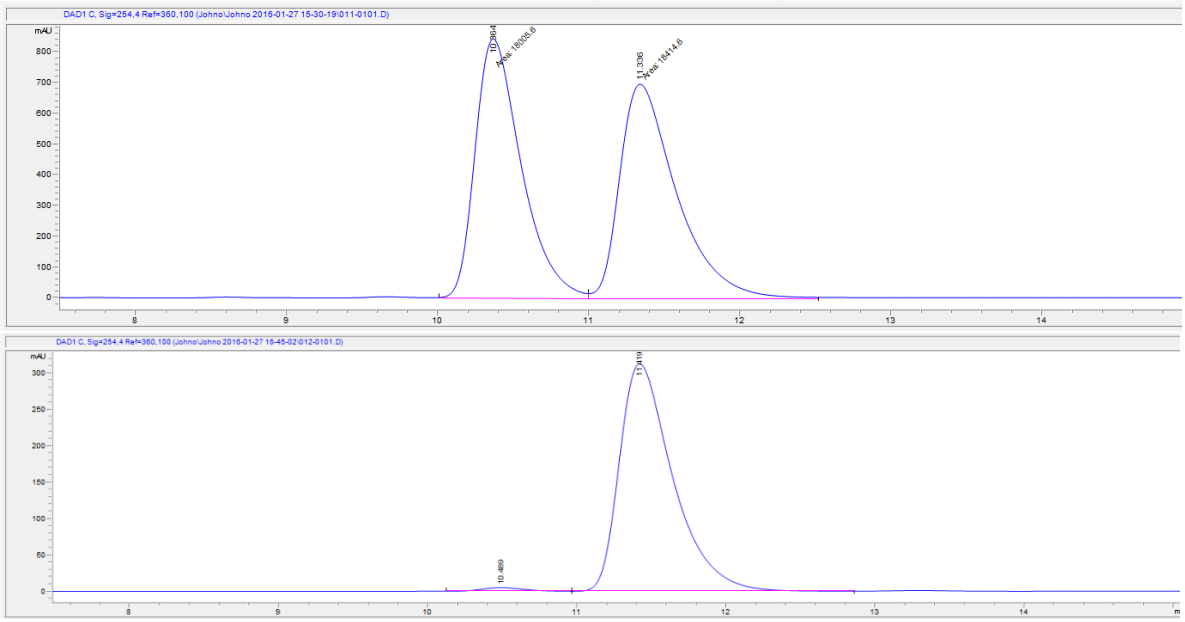


Carbamoyl chloride formation:

According to **GP1**, 1,2,3,4-tetrahydroquinoline (3.7 mL, 29 mmol), triphosgene (4.0 g, 14 mmol) and pyridine (2.4 mL, 29 mmol) in CH_2Cl_2 (42 mL) gave the carbamoyl chloride. $\mathbf{R_f}$ 0.46 (30% Et_2O/*n*-pentane). (*N.B.* The amounts described here were used to prepare a batch stock of the carbamoyl chloride).

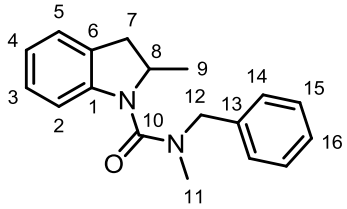
Urea formation:

According to **GP2**, 3,4-tetrahydroquinoline-1(2*H*)-carbamoyl chloride (0.30 g, 1.5 mmol), (*S*)-*N*-methyl-1-phenylethan-1-amine (0.29 mL, 2.0 mmol) and triethylamine (0.34 mL, 2.5 mmol) in MeCN (4 mL) was stirred at RT for 12 h. Purification by flash column chromatography eluting with (7% to 60% Et_2O in petrol) gave the *title compound* **2-60** as a colourless oil (0.44 g, 99%). $\mathbf{R_f}$ 0.20 (30% Et_2O/*n*-pentane); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 2971, 2901, 1637; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.41−7.32 (4 H, m, H15, H16), 7.32–7.24 (1 H, m, H17), 7.11–7.02 (2 H, m, H3, H2), 6.93 (1 H, dd, *J* 8.1, 0.8, H5), 6.88 (1 H, td, *J* 7.4, 1.3, H4) 5.59 (1 H, q, *J* 7.0, H12), 3.68–3.54 (2 H, m, H9), 2.76 (2 H, t, *J* 6.7, H7), 2.44 (3 H, s, H11), 2.06–1.92 (2 H, m, H8), 1.57 (3 H, d, *J* 7.0, H13); **^{13}C NMR** (101 MHz; $CDCl_3$) δ 161.3 (C10), 141.1 (C14), 141.0 (C1), 129.1 (C5), 128.5 (C16), 128.0 (C6), 127.5 (C15), 127.4 (C4), 126.5 (C17), 121.8 (C3), 119.5 (C2), 54.1 (C12), 45.9 (C9), 30.7 (C11), 27.1 (C7), 23.6 (C8), 16.0 (C13); **HRMS m/z** (ESI^+) m/z $C_{19}H_{23}N_2O^+$ requires: 295.1805; found: 295.1791; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ −19 (*c.* 0.8, $CHCl_3$); **HPLC** Racemic sample was prepared in an analogous manner using (±)-*N*-methyl-1-phenylethan-1-amine[211] which was prepared according to literature procedures. ChiralPak OD-H column, 1 mL/min, 25 °C, 3% *i*PrOH/*n*-hexane; t_R: 10.5 min (minor), 11.4 min (major), *er* = 99:1



Peak #	Time / min	Area	Height	Width	Area / %	Symmetry
1	10.489	91.7	4.8	0.2964	1.168	0.804
2	11.419	7759.3	312.5	0.3757	98.832	0.57

(±)-*N*-Benzyl-*N*,2-dimethylindoline-1-carboxamide (2-61)



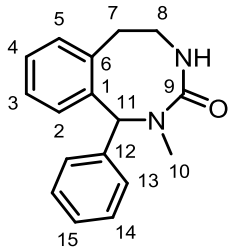
Carbamoyl chloride formation:

According to **GP1**, 2-methylindoline (0.15 g, 1.1 mmol), triphosgene (0.15 g, 0.52 mmol) and pyridine (90 μL, 1.1 mmol) in CH_2Cl_2 (1.6 mL) gave the carbamoyl chloride. $\mathbf{R}_f$ 0.23 (5% EtOAc/petrol).

Urea formation:

According to **GP2**, 2-methylindoline-1-carbamoyl chloride (0.18 g, 0.92 mmol), *N*-methylbenzylamine (0.15 mL, 1.2 mmol) and triethylamine (0.21 mL, 1.3 mmol) in MeCN (2.3 mL) was stirred at RT for 12 h. Purification by flash column chromatography eluting with (10% to 80% Et_2O in petrol) gave the *title compound* **2-61** as a yellow oil (0.22 g, 74% over 2 steps). $\mathbf{R}_f$ 0.25 (40% Et_2O/*n*-pentane); $\boldsymbol{\nu}_{max}$ **/cm^{-1}** (film) 2931, 1643, 1491, 1380, 750; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.38–7.27 (5 H, m, ArH), 7.15–7.07 (2 H, m, ArH), 6.85 (1 H, td, *J* 7.6, 1.0, H3), 6.75 (1 H, d, *J* 7.6, H2), 4.71 (1 H, d, *J* 14.9, H12$_a$), 4.58–4.49 (1 H, m, H8), 4.37 (1 H, d, *J* 14.9, H12$_b$), 3.18 (1 H, dd, *J* 15.4, 8.6, H7$_a$), 2.86 (3 H, s, H11), 2.67 (1 H, dd, *J* 15.4, 8.6, H7$_b$), 1.42 (3 H, d, *J* 6.0, H9); **^{13}C NMR** (101 MHz; $CDCl_3$) δ 159.6 (C10), 145.0 (C1), 137.5 (C6), 130.3 (C13), 128.8 (ArCH), 128.2 (ArCH), 127.6 (ArCH), 127.2 (ArCH), 125.1 (ArCH), 121.1 (C3), 111.7 (C2), 58.4 (C12), 53.9 (C8), 36.6 (C7), 35.7 (C11), 20.0 (C9); **HRMS** (ESI^+) m/z $C_{18}H_{21}N_2O^+$ requires: 281.158; found: 281.1648.

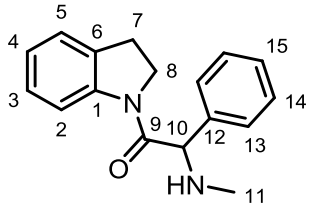
(±)-2-Methyl-1-phenyl-1,4,5,6-tetrahydrobenzo[*e*][1,3]diazocin-3(2*H*)-one (2-66)



Ring Expansion:

According to **GP4** *N*-benzyl-*N*-methylindoline-1-carboxamide **2-43** (0.07 g, 0.26 mmol), DMPU (0.17 mL, 1.3 mmol) LDA (0.27 mL, 0.53 mmol, 2.0 M) in THF (1.8 mL) were kept at −78 °C for 4 h. Purification by flash column chromatography eluting with (20% to 100% EtOAc in petrol) gave the *title compound* **2-66** as a white solid (49 mg, 70%). $\mathbf{R}_f$ 0.22 (80% EtOAc in petrol); **Mp** 180-183 °C ($CHCl_3$); $\boldsymbol{\nu}_{max}$ **/cm^{-1}** (film) 3299, 2931, 1645, 1483, 907, 723; **^{1}H NMR** (500 MHz; $CDCl_3$) δ 7.38–7.24 (8 H, m, ArH), 7.18 (1 H, dd, *J* 7.0, 1.9, H2), 6.25 (1 H, s, H11), 4.50 (1 H, br, NH), 3.38–3.33 (1 H, m, H8$_a$), 3.20–3.09 (2 H, m, H8$_b$, H7$_a$), 2.93 (3 H, s, H10), 2.80–2.75 (1H, m, H7$_a$); **^{13}C NMR** (126 MHz; $CDCl_3$) δ 165.3 (C9), 140.7 (C1), 138.9 (C12), 136.7 (C6), 131.2 (ArCH), 130.1 (ArCH), 128.4 (ArCH), 128.3 (ArCH), 127.2 (ArCH), 127.0 (ArCH), 126.6 (C2), 65.6 (C11), 44.0 (C8), 36.8 (C7), 33.9 (C10); **HRMS** (ESI^+) m/z $C_{17}H_{19}N_2O^+$ requires: 267.1492; found: 267.1491.

(±)-1-(Indolin-1-yl)-2-(methylamino)-2-phenylethan-1-one (2-67)



LDA preparation:

According to **GP3**, diisopropylamine (0.16 mL, 1.1 mmol), *n*-butyllithium (0.81 mL, 1.1 mmol, 1.4 M in THF) and THF (1.9 mL).

Acyl shift:

(*N.B.* No DMPU was required for this transformation)

According to **GP4**, *N*-benzyl-*N*-methylindoline-1-carboxamide **2-43** (0.15 g, 0.56 mmol), and LDA (see above) in THF (3.8 mL) were kept at −78 °C for 3 h. Purification by flash column chromatography eluting with (20% to 100% EtOAc in petrol) gave the *title compound* **2-67** as a yellow solid (99 mg, 66%). $\mathbf{R}_f$ 0.18 (80% EtOAc/petrol); **Mp** 151-153 °C (CH_2Cl_2/*n*-pentane); $\boldsymbol{\nu}_{max}$ **/cm^{-1}** (film); 2925, 1653, 1598, 1481, 1399; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.35 (1 H, d, *J* 7.8, H2), 7.41–7.34 (4 H, m, ArH), 7.32–7.28 (1 H, m, ArH), 7.22 (1 H, t, *J* 7.8, H3), 7.15 (1 H, d, *J* 7.8, H5), 7.03 (1 H, td, *J* 7.8, 1.1, H4), 4.37 (1 H, s, H10), 4.15 (1 H, td, *J* 10.3, 6.4, H8$_a$), 3.76 (1 H, td, *J* 10.3, 6.4, H8$_b$), 3.17 (1 H, ddd, *J* 16.5, 10.4, 6.4, H7$_a$), 3.03 (1 H, ddd, *J* 16.5, 10.4, 6.4, H7$_b$), 2.43 (3 H, s, H11). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.6 (C9), 143.4 (C1), 138.2 (C12), 131.4 (C6), 129.4 (ArC),

128.5 (ArC), 128.4 (ArC), 128.0 (C3), 124.9 (C5), 124.4 (C4), 117.7 (C2), 67.6 (C10), 47.6 (C8), 35.1 (C11), 28.5 (C7); **HRMS** (ESI$^+$) m/z $C_{17}H_{19}N_2O^+$ requires: 267.1491; found: 267.1493; **X-ray** crystallography data:

Bond precision: C-C = 0.0021 A Wavelength=0.71073

Cell: a=7.5225(10) b=16.146(3) c=11.6628(17)
alpha=90 beta=103.779(10) gamma=90

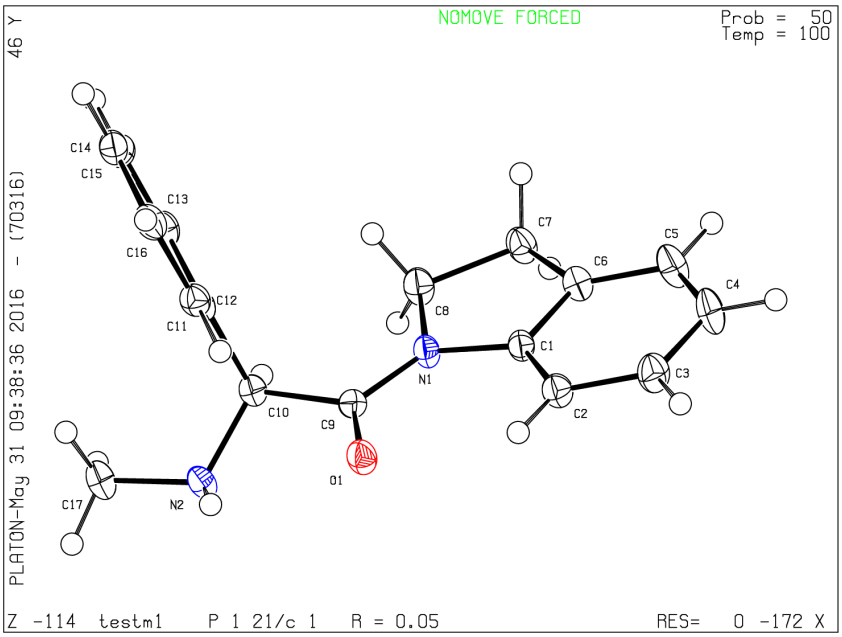
Temperature: 100 K

	Calculated	Reported
Volume	1375.8(4)	1375.8(4)
Space group	P 21/c	P 1 21/c 1
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C17 H18 N2 O	C17 H18 N2 O
Sum formula	C17 H18 N2 O	C17 H18 N2 O
Mr	266.33	266.33
Dx,g cm-3	1.286	1.286
Z	4	4
Mu (mm-1)	0.081	0.081
F000	568.0	568.0
F000'	568.21	
h,k,lmax	9,21,15	9,21,15
Nref	3351	3307
Tmin,Tmax	0.956,0.976	0.597,0.746
Tmin'	0.956	

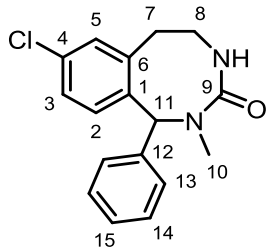
Correction method= # Reported T Limits: Tmin=0.597 Tmax=0.746 AbsCorr = MULTI-SCAN

Data completeness= 0.987 Theta(max)= 28.120

R(reflections)= 0.0465(2371) wR2(reflections)= 0.1210(3307)



(±)-8-Chloro-2-methyl-1-phenyl-1,4,5,6-tetrahydrobenzo[*e*][1,3]diazocin-3(2*H*)-one (2-72)

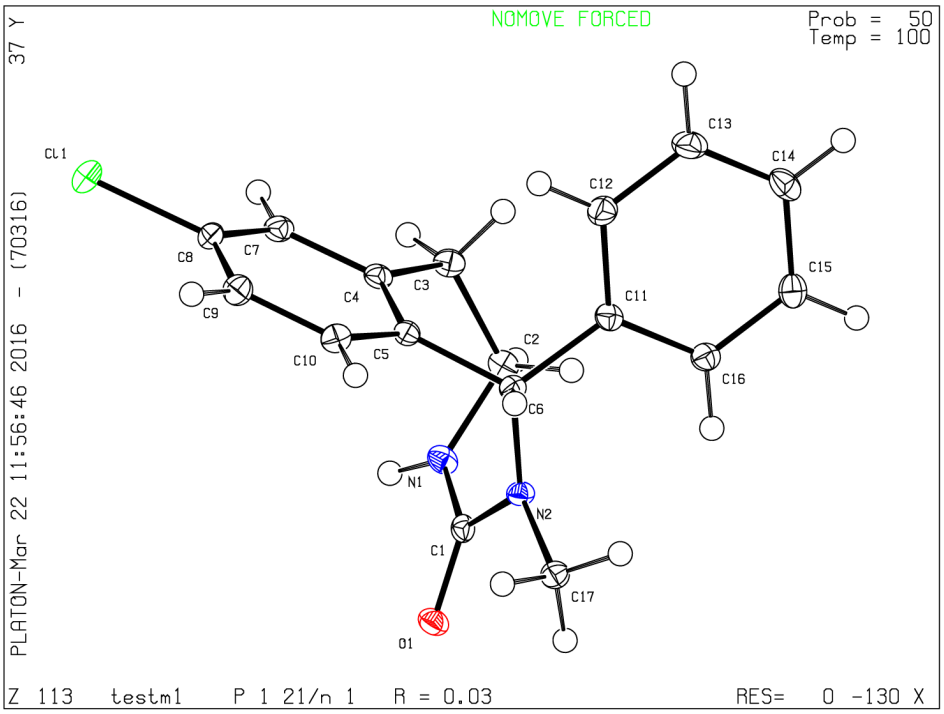


LDA preparation:
According to **GP3**, diisopropylamine (0.09 mL, 0.66 mmol), *n*-butyllithium (0.47 mL, 0.71 mmol, 1.4 M in THF) and THF (1.1 mL).
Ring Expansion:
According to **GP4**, *N*-benzyl-5-chloro-*N*-methylindoline-1-carboxamide **2-44** (0.10 g, 0.33 mmol), DMPU (0.20 mL, 1.7 mmol) and LDA (see above) in THF (2.2 mL) were kept at −78 °C for 1 h. Purification by flash column chromatography eluting with (0% to 10% MeOH in CH_2Cl_2) gave the *title compound* **2-72** as a white solid (88 mg, 88%). $\mathbf{R_f}$ 0.16 (70% EtOAc/petrol); **Mp** 219–220 °C (CH_2Cl_2/*n*-pentane); $\mathbf{\nu_{max}}$ **/cm^{-1}** (film); 3302, 2930, 1646, 1491, 1029. **^{1}H NMR** (500 MHz; $CDCl_3$) δ 7.37 (2 H, t, *J* 7.5, H14), 7.32–7.25 (3 H, m, H3, H2, H15), 7.22 (2 H, d, *J* 8.3, H13), 7.19 (1 H, s, H5), 6.19 (1 H, s, H11), 4.45 (1 H, br, NH), 3.38–3.31 (1 H, m, H8$_a$), 3.20–3.14 (1 H, m, H8$_b$), 3.10–3.04 (1 H, m, H7$_a$), 2.91 (3 H, s, H10), 2.73 (1 H, ddd, *J* 15.6, 5.7, 3.2, H7$_b$); **^{13}C NMR** (126 MHz; $CDCl_3$) δ 165.1 (C9), 142.7 (C1), 138.6 (C12), 135.4 (C6), 134.0 (C4), 131.6 (C2), 131.3 (C14), 128.7 (C13), 127.3 (C5), 127.1 (C3), 126.8 (C15), 65.2 (C11), 43.7 (C8), 36.7 (C7), 34.1 (C10); **HRMS** (ESI$^+$) m/z $C_{17}H_{17}{}^{35}ClN_2NaO^+$ requires: 323.0922; found: 323.0917. $C_{17}H_{17}{}^{37}ClN_2NaO^+$ requires: 325.0892; found: 325.0890; **X-ray** crystallography data:

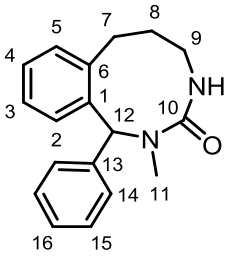
Bond precision: C-C = 0.0017 A Wavelength=0.71073
Cell: a=6.7936(2) b=28.5203(8) c=7.6673(2)
alpha=90 beta=103.0208(16) gamma=90
Temperature: 100 K

	Calculated	Reported
Volume	1447.39(7)	1447.38(7)
Space group	P 21/n	P 1 21/n 1
Hall group	-P 2yn	-P 2yn
Moiety formula	C17 H17 Cl N2 O	C17 H17 Cl N2 O
Sum formula	C17 H17 Cl N2 O	C17 H17 Cl N2 O
Mr	300.78	300.77
Dx,g cm^{-3}	1.380	1.380
Z	4	4
Mu (mm^{-1})	0.264	0.264
F000	632.0	632.0
F000'	632.81	
h,k,lmax	8,37,10	8,37,10
Nref	3464	3462
Tmin,Tmax	0.874,0.926	0.695,0.746
Tmin'	0.874	

Correction method= # Reported T Limits: Tmin=0.695 Tmax=0.746 AbsCorr = MULTI-SCAN
Data completeness= 0.999 Theta(max)= 27.947
R(reflections)= 0.0327(3201) wR2(reflections)= 0.0855(3462)
S = 1.060 Npar= 191



(±)-2-Methyl-1-phenyl-1,2,4,5,6,7-hexahydro-3*H*-benzo[e][1,3]diazonin-3-one (2-73)



Ring Expansion:

According to **GP4** *N*-benzyl-*N*-methyl-3,4-dihydroquinoline-1(*2H*)-carboxamide **2-45** (0.11 g, 0.39 mmol), DMPU (0.24 mL, 2.0 mmol) and LDA (0.39 mL, 0.78 mmol, 2.0 M) in THF (2.6 mL) were kept at −78 °C for 1 h. Purification by flash column chromatography eluting with (40% to 100% EtOAc in petrol) gave the *title compound* **2-73** as a white solid (91 mg, 83%). $\mathbf{R_f}$ 0.11 (90% Et_2O/*n*-pentane); **Mp** 151–152 °C (CH_2Cl_2/*n*-pentane); $\mathbf{\nu_{max}}$ **/cm^{-1}** (film) 3297, 2927, 1656; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.43–7.40 (1 H, m, ArH), 7.37–7.33 (2 H, m, ArH), 7.33–7.30 (2 H, m, ArH), 7.29–7.23 (2 H, m, ArH), 7.12 (2 H, d, *J* 7.5, H14), 6.84 (1 H, s, H12), 4.03 (1 H, t, *J* 8.2, NH), 3.32–3.24 (1 H, m, $H9_a$), 3.22–3.13 (1 H, m, $H9_b$), 2.91–2.85 (1 H, m, $H7_a$), 2.83 (3 H, s, H11), 2.76–2.71 (1 H, m, $H7_b$), 2.04-1.96 (1 H, m, $H8_a$), 1.60-1.49 (1 H, m, $H8_b$); **^{13}C NMR** (101 MHz; $CDCl_3$) δ 168.6 (C10), 139.8 (C1), 138.7 (C13), 138.7 (C6), 130.5 (ArCH), 128.7 (C14), 128.5 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 127.2 (ArCH), 127.0 (ArCH), 61.5 (C12), 43.5 (C9), 31.7 (C8), 31.5 (C11), 29.6 (C7); **HRMS** (ESI^+) m/z $C_{18}H_{21}N_2O^+$ requires: 281.1648; found: 281.1649; **X-ray** crystallography data:

Bond precision:	C-C = 0.0019 A		Wavelength=0.71073
Cell:	a=8.2085(6)	b=8.9895(6)	c=11.0786(7)
	alpha=87.681(5)	beta=83.866(5)	gamma=67.212(5)
Temperature:	100 K		

	Calculated	Reported
Volume	749.37(9)	749.37(9)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C18 H20 N2 O	C18 H20 N2 O
Sum formula	C18 H20 N2 O	C18 H20 N2 O
Mr	280.36	280.36
Dx,g cm^{-3}	1.242	1.243

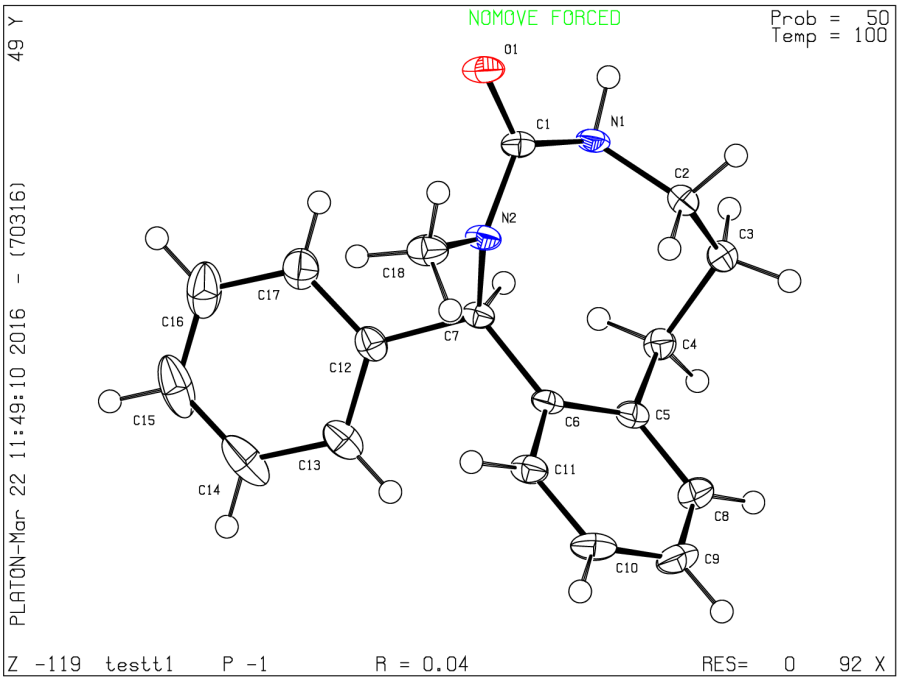
Z	2	2
Mu (mm^{-1})	0.078	0.078
F000	300.0	300.0
F000'	300.11	
h,k,lmax	10,11,14	10,11,14
Nref	3642	3599
Tmin,Tmax	0.975,0.981	0.675,0.746
Tmin'	0.975	

Correction method= # Reported T Limits: Tmin=0.675 Tmax=0.746 AbsCorr = MULTI-SCAN

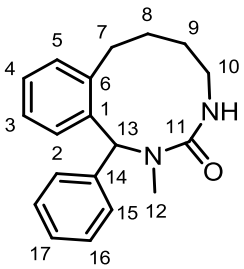
Data completeness= 0.988 Theta(max)= 28.081

R(reflections)= 0.0440(2727) wR2(reflections)= 0.1214(3599)

S = 1.029 Npar= 195



(±)-2-Methyl-1-phenyl-1,4,5,6,7,8-hexahydrobenzo[*e*][1,3]diazecin-3(2*H*)-one (2-74)



LDA preparation:

According to **GP3**, diisopropylamine (0.10 mL, 0.68 mmol), *n*-butyllithium (0.49 mL, 0.68 mmol, 1.4 M in THF) and THF (1.1 mL).

Ring Expansion:

According to **GP4**, *N*-benzyl-*N*-methyl-2,3,4,5-tetrahydro-1*H*-benzo[b]azepine-1-carboxamide **2-46** (0.10 g, 0.34 mmol), DMPU (0.21 mL, 1.7 mmol) and LDA (see above) in THF (2.3 mL) were kept at −78 °C for 1 h. Purification by flash column chromatography eluting with (50% EtOAc in petrol) gave the *title compound* **2-74** as a white solid (77 mg, 77%). $\mathbf{R_f}$ 0.41 (80% EtOAc/petrol); **Mp** 229–230 °C (CH_2Cl_2/*n*-pentane); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 3352, 2925, 1611; **^{1}H NMR** (400 MHz; DMSO-d_6) δ 7.36–7.33 (2 H, t, *J* 7.5, ArH), 7.29–7.22 (3 H, m, ArH), 7.17–7.12 (3 H, m, H2, H15), 6.95 (1 H, d, *J* 7.8, H5), 6.71 (1 H, s, H13), 3.63–3.54 (1 H, br, H10$_a$), 3.17–3.09 (1 H, br, H7$_a$), 2.83–2.75 (1 H, br, H10$_b$), 2.74–2.64 (1 H, br, H7$_b$), 2.38 (3 H, s, H12), 1.92–1.80 (1 H, br, H9$_a$), 1.44–1.33 (1 H, br, H9$_b$), 1.29–1.20 (2 H, br, H8); **^{13}C NMR** (101 MHz; DMSO-d_6) δ 161.1 (C11), 141.6 (C1), 140.4 (C14), 135.7 (C6), 129.8 (C5), 129.6 (ArCH), 128.1 (ArCH), 127.6 (C14), 127.5 (ArCH), 126.5 (ArCH), 124.9

(C2), 60.0 (C13), 40.9 (C10), 31.1 (C7), 29.7 (C12), 28.3 (C9), 25.8 (C8); **HRMS** (ESI^+) m/z $C_{19}H_{23}N_2O^+$ requires: 295.1805; found: 295.1801; **X-ray** crystallography data:

Bond precision: C-C = 0.0030 A Wavelength=0.71073

Cell: a=18.2387(5) b=36.1019(11) c=9.4070(3)
alpha=90 beta=90 gamma=90

Temperature: 100 K

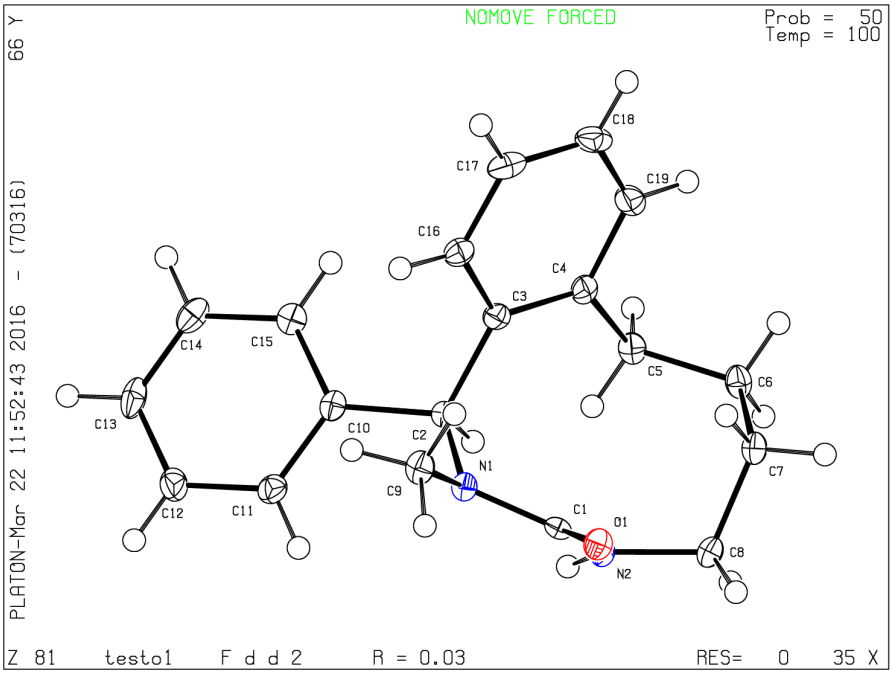
	Calculated	Reported
Volume	6194.1(3)	6194.0(3)
Space group	F d d 2	F d d 2
Hall group	F 2 -2d	F 2 -2d
Moiety formula	C19 H22 N2 O	C19 H22 N2 O
Sum formula	C19 H22 N2 O	C19 H22 N2 O
Mr	294.39	294.38
Dx,g cm^{-3}	1.263	1.263
Z	16	16
Mu (mm^{-1})	0.079	0.079
F000	2528.0	2528.0
F000'	2528.92	
h,k,lmax	24,47,12	24,47,12
Nref	3719[1971]	3697
Tmin,Tmax	0.970,0.982	0.679,0.746
Tmin'	0.970	

Correction method= # Reported T Limits: Tmin=0.679 Tmax=0.746 AbsCorr = MULTI-SCAN

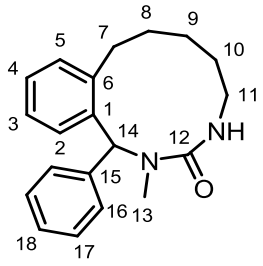
Data completeness= 1.88/0.99 Theta(max)= 27.919

R(reflections)= 0.0340(3467) wR2(reflections)= 0.0824(3697)

S = 1.045 Npar= 200

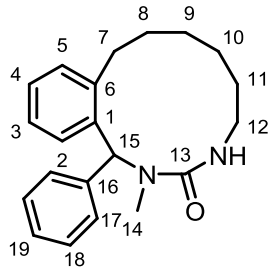


(±)-2-Methyl-1-phenyl-1,2,4,5,6,7,8,9-octahydro-3*H*-benzo[*e*][1,3]diazacycloundecin-3-one (2-75)



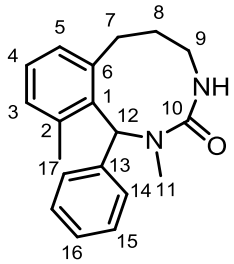
LDA preparation:
According to **GP3**, diisopropylamine (0.91 mL, 0.65 mmol), *n*-butyllithium (0.47 mL, 0.65 mmol, 1.4 M in THF) and THF (1.1 mL).
Ring Expansion:
According to **GP4**, *N*-benzyl-*N*-methyl-3,4,5,6-tetrahydrobenzo[*b*]azocine-1(2*H*)carboxamide **2-47** (0.10 g, 0.32 mmol), DMPU (0.21 mL, 1.6 mmol) and LDA (see above) in THF (2.2 mL) were kept at −78 °C for 1 h. Purification by flash column chromatography eluting with (50% to 100% EtOAc in petrol) gave the *title compound* **2-75** as a white solid (81 mg, 81%). $\mathbf{R}_f$ 0.30 (60% EtOAc/petrol); **Mp** 230–231 °C (CH_2Cl_2/*n*-pentane); $\boldsymbol{\nu_{max}}$ **/cm^{-1}** (film) 3675, 3335, 2922, 1727, 1621; **^{1}H NMR** (500 MHz, DMSO-d_6, 373 K/100 °C) δ 7.36 (2 H, t, *J* 7.7, H17), 7.29–7.25 (2 H, m, H2/H18), 7.21 (1 H, td, *J* 7.5, 1.5, H3), 7.17–7.14 (2 H, d, *J* 7.1, H16), 7.09 (1 H, td, *J* 7.5, 1.5, H4), 6.86 (1 H, d, *J* 7.5, H5), 6.82 (1 H, s, H14), 6.68 (1 H, br, NH), 3.53–3.47 (1 H, m, H11$_a$), 3.24–3.19 (1 H, m, H7$_a$), 3.12–3.09 (1 H, br, H11$_b$), 2.48 (3 H, s, H13), 2.43 (1 H, td, *J* 12.7, 6.1, H7$_b$), 1.90–1.81 (1 H, br, H9$_a$), 1.69–1.56 (3 H, br, H8$_a$, H10), 1.54–1.46 (1 H, br, H9$_b$), 1.29–1.21 (1 H, br, H8$_b$); **^{13}C NMR (126 MHz, DMSO-d_6, 373 K/100 °C)** δ 158.8 (C12), 143.0 (C1), 140.6 (C15), 136.8 (C6) 129.9 (C5), 129.8 (C18), 127.5 (C17), 126.90 (C16), 126.88 (C3), 125.8 (C2), 124.3 (C4), 58.9 (C14), 40.6 (C11), 31.1 (C13), 30.2 (C7), 29.2 (C8), 27.0 (C10), 26.0 (C9); **HRMS** (ESI$^+$) m/z $C_{20}H_{25}N_2O^+$ requires: 309.1961; found 309.1964.

(±)-2-Methyl-1-phenyl-1,4,5,6,7,8,9,10-octahydrobenzo[e][1,3]diazacyclododecin-3(2*H*)-one (2-76)



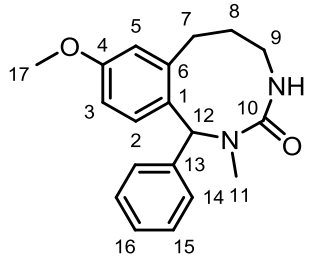
Ring Expansion:
According to **GP4**, *N*-benzyl-*N*-methyl-2,3,4,5,6,7-hexahydro-1H-benzo[b]azonine-1-carboxamide **2-48** (50 mg, 0.16 mmol), DMPU (0.10 mL, 0.78 mmol) and LDA (0.16 mL, 0.32 mmol, 2.0 M) in THF (1.0 mL) were kept at −78 °C for 1 h. Purification by flash column chromatography eluting with (10% to 100% EtOAc in petrol) gave the *title compound* **2-76** as a white solid (42 mg, 84%). $\mathbf{R}_f$ 0.36 (50% EtOAc/petrol); **Mp** 205–206 °C (CH_2Cl_2/*n*-pentane); $\boldsymbol{\nu_{max}}$ **/cm^{-1}** (film) 3300, 2925, 1621, 1539; **^{1}H NMR** (500 MHz, DMSO-d_6, 373 K/100 °C) δ 7.34 (2 H, t, *J* 7.5, H18), 7.29–7.24 (2 H, m, H2, H19), 7.20 (1 H, t, *J* 7.4, H3), 7.12 (2 H, d, *J* 7.5, H17), 7.06 (1 H, t, *J* 7.4, H4), 6.81–6.77 (2 H, m, H5, H15), 6.50 (1 H, br s, NH), 3.30–3.23 (1 H, br, H12$_a$), 3.09 (1 H, td, *J* 12.5, 4.4, H7$_a$), 2.93–2.90 (1 H, br, H12$_b$), 2.53 (3 H, s, H14), 2.37 (1 H, td, *J* 12.5, 5.1, H7$_b$), 1.69–1.46 (5 H, br, H8$_a$, H9$_a$, H11$_a$, H10), 1.42–1.29 (3 H, br, H8$_b$, H9$_b$, H11$_b$);
^{13}C NMR (100 MHz, DMSO-d_6, 373 K/100 °C) δ 157.7 (C13), 142.6 (C1), 140.7 (C16), 137.3 (C6), 130.0 (C18), 129.7 (C5), 127.5 (C18), 126.9 (C3), 126.7 (C17), 125.8 (C2), 124.4 (C4), 57.8 (C15), 40.1 (C12), 31.3 (C7), 29.4 (C14), 28.9 (C8/C9/C11), 28.4 (C8/C9/C11), 27.7 (C8/C9/C11), 21.6 (C10); **HRMS** (ESI$^+$) m/z $C_{21}H_{27}N_2O^+$ requires: 323.2118; found 323.2127.

(±)-2,11-Dimethyl-1-phenyl-1,2,4,5,6,7-hexahydro-3*H*-benzo[*e*][1,3]diazonin-3-one (2-79)



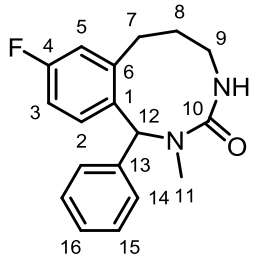
LDA preparation:
According to **GP3**, diisopropylamine (0.10 mL, 0.68 mmol), *n*-butyllithium (0.49 mL, 0.68 mmol, 1.4 M in THF) and THF (1.1 mL).
Ring Expansion:
According to **GP4**, *N*-benzyl-*N*,8-dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxamide **2-49** (0.10 g, 0.34 mmol), DMPU (0.21 mL, 1.7 mmol) and LDA (see above) in THF (2.3 mL) were kept at −78 °C for 1 h. Purification by flash column chromatography eluting with (15% to 100% EtOAc in petrol) gave the *title compound* **2-79** as a white solid (68 mg, 68%). $\mathbf{R_f}$ 0.37 (70% EtOAc/petrol); **Mp** 134–135 °C (CH_2Cl_2/*n*-pentane); $\mathbf{\nu_{max}}$ **/cm^{-1}** (film) 3310, 2920, 1658, 1448, 781; **^{1}H NMR** (500 MHz; DMSO-d_6, 373 K/100 °C) δ 7.34 (2 H, t, *J* 7.5, H15), 7.28–7.22 (3 H, m, H14, H16), 7.12 (1 H, t, *J* 7.4, H4), 7.04 (1 H, d, *J* 7.4, H3), 6.98 (1 H, d, *J* 7.4, H5), 6.02 (1 H, br, NH), 5.92 (1 H, s, H12), 3.53–3.43 (1 H, m, H9$_a$), 3.01–2.95 (1 H, m, H9$_b$), 2.83 (1 H, ddd, *J* 13.3, 9.9, 2.8, H7$_a$), 2.71–2.69 (3 H, m, H11), 2.61–2.55 (1 H, m, H7$_b$), 2.33 (3 H, s, H17), 1.74–1.67 (1 H, m, H8$_a$), 1.64–1.55 (1 H, m, H8$_b$); **^{13}C NMR** (126 MHz; DMSO-d_6, 373 K/ 100 °C) δ 165.3 (C10), 142.6 (C1), 140.1 (C13), 136.9 (C6), 136.7 (C2), 129.0 (C5), 128.2 (C3), 127.8 (C4, ArCH), 127.1 (C14), 126.0 (C16), 64.5 (C12), 42.4 (C9), 36.6 (C11), 32.6 (C7), 31.5 (C8), 21.0 (C17); *1 × aromatic (C) signal is not observed due to overlapping peaks, a HSQC confirms this.* **HRMS** (ESI$^+$) m/z $C_{19}H_{22}N_2NaO^+$ requires: 317.1624; found: 317.1625.

(±)-9-Methoxy-2-methyl-1-phenyl-1,2,4,5,6,7-hexahydro-3*H*-benzo[*e*][1,3]diazonin-3-one (2-80)



Ring Expansion:
According to **GP4** *N*-benzyl-6-methoxy-*N*-methyl-3,4-dihydroquinoline-1(2*H*)-carboxamide **2-50** (0.10 g, 0.32 mmol), DMPU (0.19 mL, 1.6 mmol) LDA (0.32 mL, 0.64 mmol, 2.0 M) in THF (2.2 mL) were kept at −78 °C for 1 h. Purification by flash column chromatography eluting with (20% to 100% EtOAc in petrol) gave the *title compound* **2-80** as a white solid (90 mg, 90%).
$\mathbf{R_f}$ 0.20 (70% EtOAc/petrol); **Mp** 195–196 °C (CH_2Cl_2/*n*-pentane); $\mathbf{\nu_{max}}$ **/cm^{-1}** (film) 3321, 2923, 1646, 1607, 1447; **^{1}H NMR** (500 MHz, DMSO-d_6, 373 K/100 °C) δ 7.31 (2 H, t, *J* 7.0, H15), 7.22 (1 H, t, *J* 7.0, H16), 7.01–6.98 (3 H, m, ArH), 6.78 (1 H, d, *J* 2.6, H5), 6.74–6.69 (1 H, m, ArH), 6.51 (1 H, s, H12), 6.16 (1 H, br, NH), 3.82–3.77 (1 H, m, H9$_a$), 3.76–3.75 (3 H, br, H17), 3.02–2.95 (1 H, m, H9$_b$), 2.72–2.64 (2 H, br, H7), 2.63–2.61 (3 H, br, H11), 1.71–1.62 (1 H, br, H8$_a$), 1.62–1.55 (1 H, br, H8$_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.0 (C10), 158.8 (C4), 142.8 (C1), 141.4 (C13), 132.0 (C6), 128.7 (C15), 127.9 (C14), 127.0 (C16), 116.8 (C5), 111.3 (C3), 62.5 (C12), 55.6 (C17), 43.5 (C9), 34.6 (C7), 27.8 (C11), 27.6 (C8). **HRMS** (ESI$^+$) m/z $C_{19}H_{23}N_2O_2^+$ requires: 311.1754; found 311.1739.

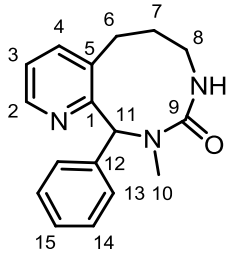
(±)-9-Fluoro-2-methyl-1-phenyl-1,2,4,5,6,7-hexahydro-3*H*-benzo[e][1,3]diazonin-3-one (2-81)



Ring Expansion:
According to **GP4**, *N*-benzyl-6-fluoro-*N*-methyl-3,4-dihydroquinoline-1(2*H*)-carboxamide **2-51** (0.10 g, 0.34 mmol), DMPU (0.21 mL, 1.7 mmol) LDA (0.34 mL, 0.67 mmol, 2.0 M) in THF (2.2 mL) were kept at −78 °C for 1 h. Purification by flash column chromatography eluting with (17% to 100% EtOAc in petrol) gave the *title compound* **2-81** as a white solid (77 mg, 77%). $\mathbf{R_f}$ 0.32 (30% EtOAc/petrol); **Mp** 160-161 °C (CH_2Cl_2/*n*-pentane); $\mathbf{\nu_{max}}$ **/cm^{-1}** (film) 3305, 2950, 1650, 1493, 1394, 729. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (1 H, dd, *J* 8.6, 5.8, H2), 7.34–7.30 (2 H, m, H15), 7.28–7.22 (1 H, m, H16), 7.13–7.06 (2 H, m, H14), 7.03 (1 H, td, *J* 8.4, 2.8, H5), 6.95 (1 H, dd, *J* 9.6, 2.8, H3), 6.78 (1 H, s, H12), 4.16 (1 H, t, *J* 8.0, NH),

3.32–3.13 (2 H, m, H7$_a$, H9$_a$), 2.89–2.80 (1 H, m, H9$_b$), 2.79 (3 H, s, H11), 2.70 (1 H, ddd, *J* 14.1, 6.2, 2.5, H7$_b$), 2.09–1.92 (1 H, m, H8$_a$), 1.62–1.49 (1 H, m, H8$_b$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.4 (C10), 162.5 (d, J_{CF} 248, C4), 142.4 (d, J_{CF} 7, C6), 138.5 (C13), 134.6 (d, J_{CF} 3.2, C1), 130.0 (d, J_{CF} 6.9, C2), 128.6 (C15/C16), 128.5 (C15/C16), 127.3 (C14), 116.8 (d, J_{CF} 20, C3), 114.0 (d, J_{CF} 21, C5), 61.0 (C12), 43.4 (C9), 31.5 (C8), 31.3 (C11), 29.8 (C7); **^{19}F NMR** (376 MHz, $CDCl_3$) −113.8 (m, CF_3); **HRMS** (ESI^+) m/z $C_{18}H_{19}FN_2ONa^+$ requires: 321.1374; found: 321.1363.

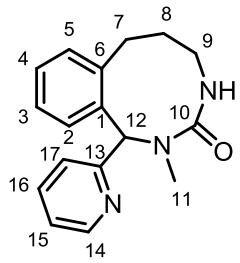
(±)-11-Phenyl-5,6,7,8,10,11-hexahydro-9*H*-pyrido[2,3-e][1,3]diazonin-9-one (2-83)



Ring Expansion:

According to **GP4**, *N*-benzyl-*N*-methyl-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide **2-55** (0.10 g, 0.36 mmol), DMPU (0.21 mL, 1.8 mmol) and LDA (0.36 mL, 0.71 mmol, 2.0 M) in THF (2.4 mL) were kept at −60 °C for 16 h. Purification by flash column chromatography eluting with (0% to 3% MeOH in CH_2Cl_2) gave the *title compound* **2-83** as an colourless oil (50 mg, 50%). **R_f** 0.39 (5% MeOH/CH_2Cl_2); **ν_{max}/cm^{-1}** (film) 1646, 1427, 1393, 726, 698; **^{1}H NMR** (500 MHz; $CDCl_3$) δ 8.64 (1 H, br, H2), 7.51 (1 H, d, *J* 7.7, H4), 7.38–7.14 (6 H, m, ArH), 6.88 (1 H, s, H11), 4.07 (1 H, t, *J* 8.2, NH), 3.34 (1 H, td, *J* 13.9, 5.6, H6$_a$), 3.26–3.11 (1 H, m, H8$_a$), 2.90 (3 H, s, H10), 2.80–2.65 (2 H, m, H8$_b$, H6$_b$), 2.06 (1 H, t, *J* 14.9, H7$_a$), 1.51 (1 H, t, *J* 14.9, H7$_b$); **^{13}C NMR** (126 MHz; $CDCl_3$) δ 168.4 (C9), 158.8 (C1), 148.2 (C2), 137.9 (C4), 137.7 (C12), 134.5 (C6), 129.2 (ArCH), 128.4 (ArCH), 127.3 (ArCH), 123.3 (ArCH), 60.9 (C11), 43.3 (C8), 31.7 (C10), 31.4 (C6), 29.1 (C7); **HRMS** (ESI^+) m/z $C_{17}H_{19}N_3NaO^+$ requires: 304.120; found: 304.1423.

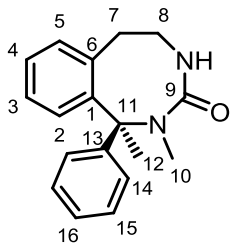
(±)-2-Methyl-1-(pyridin-2-yl)-1,2,4,5,6,7-hexahydro-3H-benzo[e][1,3]diazonin-3-one (2-84)



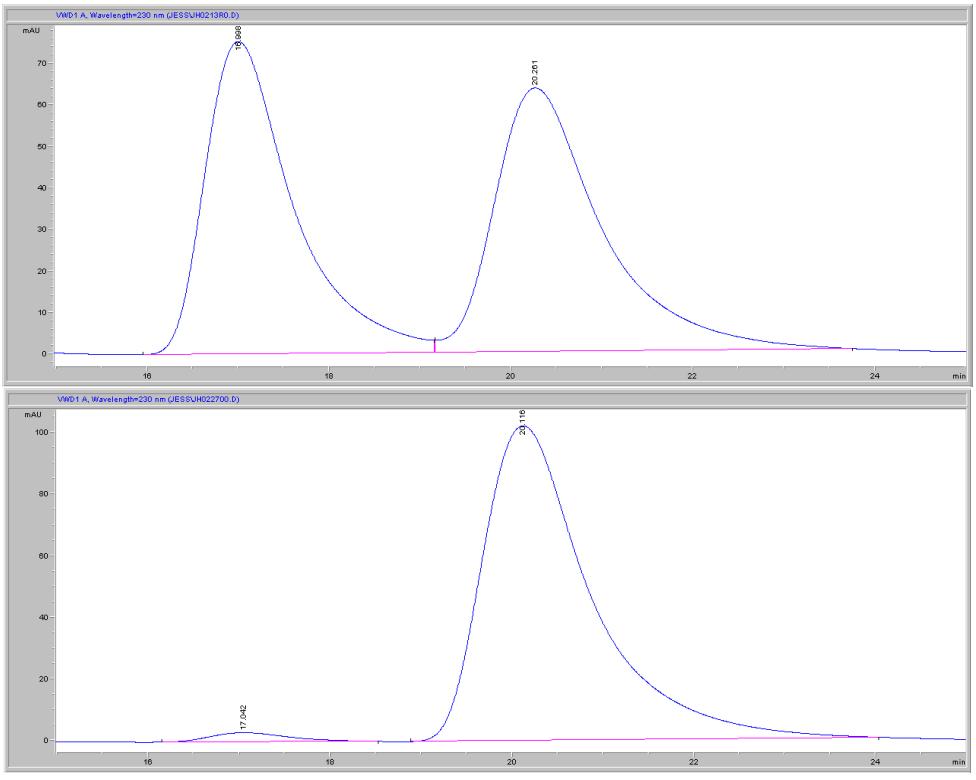
Ring Expansion:

According to a modified procedure of **GP4**, *N*-Methyl-*N*-(pyridin-2-ylmethyl)-3,4-dihydroquinoline-1(2*H*)-carboxamide **2-57** (0.10 g, 0.36 mmol), DMPU (0.20 mL, 1.6 mmol) and LDA (0.34 mL, 0.68 mmol, 2.0 M) in THF (2.3 mL) were kept at −78 °C for 30 min, before warming to −30 °C for 16 h. Purification by flash column chromatography eluting with (0% to 4% MeOH in CH_2Cl_2) gave the *title compound* **2-84** as a yellow solid (59 mg, 59%). **R_f** 0.37 (70% EtOAc/petrol); Mp 175–176 °C (CH_2Cl_2/*n*-pentane); **ν_{max}/cm^{-1}** (film) 3243, 2935, 1659, 1428, 1392; **^{1}H NMR** (500 MHz; $CDCl_3$) δ 8.64 (1 H, ddd, *J* 4.9, 1.9, 1.0, H14), 7.63 (1 H, td, *J* 7.5, 1.9, H16), 7.53–7.47 (1 H, m, H17), 7.35–7.29 (2 H, m, ArH), 7.25–7.19 (2 H, m, ArH), 7.19–7.16 (1 H, m, ArH), 6.80 (1 H, br s, H12), 4.11 (1 H, s, NH), 3.35–3.22 (1 H, m, H7$_a$), 3.22–3.16 (1 H, m, H9$_a$), 2.97–2.85 (1 H, m, H9$_b$), 2.81 (3 H, s, H11), 2.78–2.68 (1 H, m, H7$_b$), 2.08–1.96 (1 H, m, H8$_a$), 1.58 (1 H, ddddd, *J* 14.5, 12.5, 6.2, 4.3, 2.3, H8$_b$); **^{13}C NMR** (126 MHz; $CDCl_3$) δ 168.3 (C10), 158.3 (C13), 149.6 (C14), 139.9 (C1), 138.2 (C6), 136.5 (C16), 130.5 (ArCH), 129.2 (ArCH), 128.5 (ArCH), 126.8 (ArCH), 123.7 (ArCH), 122.1 (ArCH), 63.6 (C12), 43.4 (C9), 32.1 (C11), 31.9 (C8), 29.8 (C9); **HRMS** (ESI^+) m/z $C_{17}H_{19}N_3NaO^+$ requires: 304.1420; found: 304.1414.

(+)-(*S*)-1,2-Dimethyl-1-phenyl-1,4,5,6-tetrahydrobenzo[*e*][1,3]diazocin-(2*H*)-one (2-89)

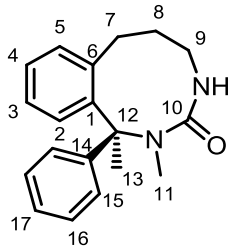


LDA preparation:
According to **GP3**, diisopropylamine (0.10 mL, 0.71 mmol), *n*-butyllithium (0.51 mL, 0.71 mmol, 1.4 M in THF) and THF (1.2 mL).
Ring Expansion:
According to **GP4**, (*S*)-*N*-methyl-*N*-(1-phenylethyl)indoline-1-carboxamide **2-59** (0.10 g, 0.36 mmol), DMPU (0.22 mL, 1.8 mmol) and LDA (see above) in THF (1.2 mL) were kept at −78 °C for 4 h. Purification by flash column chromatography eluting with (20% to 100% EtOAc in petrol) gave the *title compound* **2-89** as a colourless oil (89 mg, 89%). $\mathbf{R_f}$ 0.11 (30% EtOAc/petrol); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 3331, 2972, 1623, 1522, 1244; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.25–7.22 (4 H, m, ArH), 7.20–7.15 (4 H, m, ArH), 4.66 (1 H, br, NH), 3.18–3.02 (2 H, m, H8), 2.99–2.90 (1 H, m, $H7_a$), 2.76 (3 H, s, H10), 2.74–2.68 (1 H, m, $H7_b$), 1.96 (3 H, s, H12); **^{13}C NMR** (101 MHz; $CDCl_3$) δ. 164.4 (C9), 147.0 (C13), 142.7 (C1), 139.2 (C6), 131.8 (ArCH), 129.2 (ArCH), 127.6 (ArCH), 126.9 (ArCH), 126.7 (ArCH), 126.3 (ArCH), 68.8 (C11), 43.5 (C8), 35.6 (C7), 33.5 (C10), 32.7 (C12); **HRMS** (ESI^+) m/z $C_{18}H_{21}N_2O^+$requires: 281.1648; found: 281.1644; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ +41 (*c*. 0.27, $CHCl_3$); **HPLC** Racemic sample was prepared in an analogous manner using (±)-*N*-methyl-*N*-(1-phenylethyl)indoline-1-carboxamide (±)-**8**.
ChiralPak OD-H column, 1 mL/min, 25 °C, 230 nm, 5% *i*PrOH/*n*-hexane; t_R: 17.0 min (minor), 20.1 min (major), *er* = 98:2



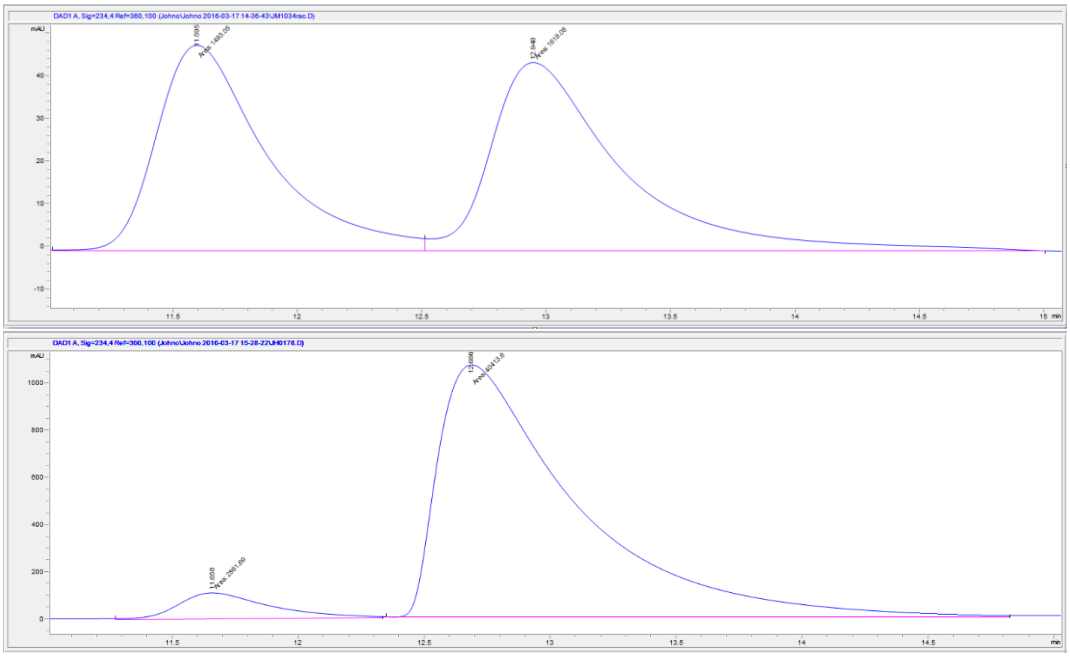
Peak #	Time / min	Area	Height	Width	Area / %	Symmetry
1	17.042	181.7	3	0.85	2.103	0.672
2	20.116	8457	102.1	1.2368	97.897	0.543

(+)-(*S*)-1,2-Dimethyl-1-phenyl-1,2,4,5,6,7-hexahydro-3*H*-benzo[e][1,3]diazonin-3-one (2-90)



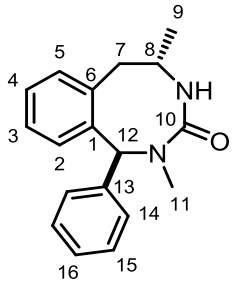
Ring Expansion:

According to **GP4**, (−)-(*S*)-*N*-Methyl-*N*-(1-phenylethyl)-3,4-dihydroquinoline-1(2*H*)-carboxamide **2-60** (0.10 g, 0.34 mmol), DMPU (0.21 mL, 1.7 mmol) and LDA (0.34 mL, 0.68 mmol, 2.0 M) in THF (1.2 mL) were kept at −78 °C for 16 h. Purification by flash column chromatography eluting with (12% to 100% EtOAc in petrol) gave the *title compound* **2-90** as a white solid (77 mg, 77%). $\mathbf{R_f}$ 0.21 (50% EtOAc/petrol); **Mp** 125–127 °C (CH_2Cl_2/*n*-pentane); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 1681, 1643, 1082, 1067, 1034; **^{1}H NMR** (500 MHz; DMSO-d_6, 373 K/100 °C) δ 7.41–7.34 (3 H, m, H16, H17), 7.33–7.28 (2 H, m, H15) 7.24–7.10 (2 H, m, ArH), 7.10–7.00 (2 H, m, ArH), 6.09 (1 H, br, NH), 3.67–3.29 (1 H, br, H9$_a$), 3.10–2.93 (2 H, m, H9$_b$, H7$_a$), 2.82 (3 H, s, H11), 2.51–2.34 (1 H, br, H7$_b$), 2.02 (3 H, s, H13), 1.90–1.67 (2 H, m, H8);
^{13}C NMR (126 MHz; DMSO-d_6, 373 K/100 °C) δ 165.1 (C10), 145.8 (C14), 143.1 (C1), 142.4 (C6), 131.6 (ArCH), 127.3 (ArCH), 127.0 (ArCH), 126.9 (ArCH), 126.5 (ArCH), 125.2 (ArCH), 124.2 (ArCH), 66.3 (C12), 42.8 (C9), 34.0 (C7), 33.9 (C11), 31.8 (C8), 25.9 (C13); **HRMS** (ESI$^+$) m/z $C_{18}H_{20}N_2NaO^+$ requires: 303.1468; found: 303.1466; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ +41 (*c*. 0.27, $CHCl_3$); **HPLC** Racemic sample was prepared in an analogous manner using (±)-*N*-methyl-*N*-(1-phenylethyl)-3,4-dihydroquinoline-1(2*H*)-carboxamide (±)-**9**. ChiralPak OD-H column, 1 mL/min, 25 °C, 230 nm, 5% *i*PrOH/*n*-hexane; t_R: 11.7 min (minor), 12.7 min (major), *er* = 93:7



Peak #	Time / min	Area	Height	Width	Area / %	Symmetry
1	11.658	2861.7	111.1	0.4294	6.613	0.579
2	12.686	40413.6	1066.8	0.6314	93.387	0.311

(1*S*,5*S*)-2,5-dimethyl-1-phenyl-1,4,5,6-tetrahydrobenzo[*e*][1,3]diazocin-3(2*H*)-one (2-97)



Ring Expansion:

According to **GP4**, *N*-benzyl-*N*,2-dimethylindoline-1-carboxamide **2-61** (0.06 g, 0.22 mmol), DMPU (0.14 mL, 1.1 mmol) and LDA (0.22 mL, 0.44 mmol, 2.0 M) in THF (1.5 mL) were kept at −78 °C for 2 h. Purification by flash column chromatography eluting with (40% to 100% EtOAc in petrol) gave the *title compound* **2-97** as a white solid (43 mg, 71%). $\mathbf{R}_f$ 0.28 (70% EtOAc/petrol); **Mp** 184–186 °C (CH_2Cl_2/*n*-pentane); $\boldsymbol{\nu_{max}}$**/cm^{-1}** (film) 3210, 3070, 2893, 1648, 1481; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.36–7.24 (6 H, m, ArH), 7.21 (2 H, d, *J* 7.6, ArH), 7.13–7.11 (1 H, m, ArH), 6.03 (1 H, s, H12), 3.99 (1 H, br, NH), 3.51–3.43 (1 H, br, H8), 2.99 (3 H, s, H11), 2.82–2.72 (1 H, br, $H7_a$), 2.63 (1 H, dd, *J* 15.5, 4.3, $H7_b$), 1.20 (3 H, d, *J* 6.5, H9). **^{13}C NMR** (101 MHz; $CDCl_3$) δ 163.9 (C10), 140.2 (C1), 139.8 (C13), 136.3 (C6), 131.5 (ArCH), 131.3 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 127.0 (ArCH), 126.9 (ArCH), 126.6 (ArCH), 67.6 (C12), 49.5 (C8), 44.6 (C7), 35.0 (C11), 24.6 (C9); **HRMS** (ESI^+) m/z $C_{18}H_{21}N_2O^+$ requires: 281.1648; found: 281.1647; **X-ray** crystallography data:

Bond precision: C-C = 0.0041 A Wavelength=0.71073

Cell: a=18.6703(10) b=9.6103(5) c=18.5204(11)
alpha=90 beta=112.274(3) gamma=90

Temperature: 100 K

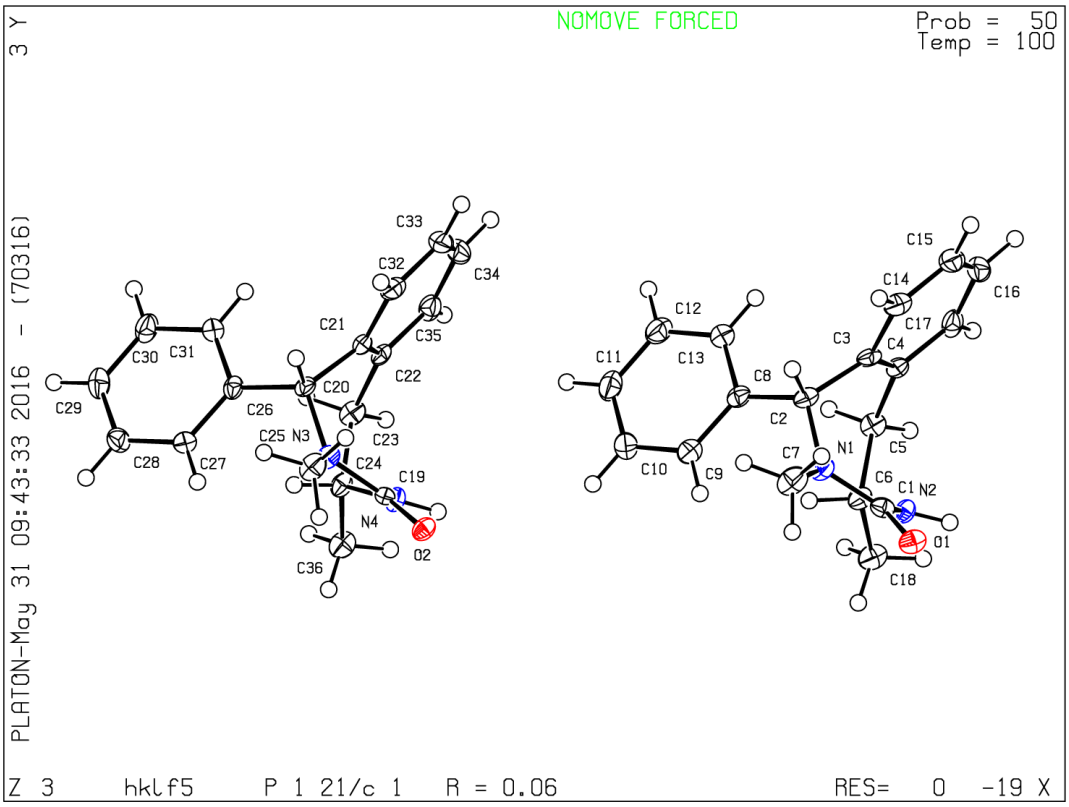
	Calculated	Reported
Volume	3075.1(3)	3075.1(3)
Space group	P 21/c	P 1 21/c 1
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C18 H20 N2 O	C18 H20 N2 O
Sum formula	C18 H20 N2 O	C18 H20 N2 O
Mr	280.36	280.36
Dx,g cm-3	1.211	1.211
Z	8	8
Mu (mm-1)	0.076	0.076
F000	1200.0	1200.0
F000'	1200.44	
h,k,lmax	24,12,24	24,12,24
Nref	7344	7202
Tmin,Tmax	0.957,0.985	0.621,0.746
Tmin'	0.957	

Correction method= # Reported T Limits: Tmin=0.621 Tmax=0.746 AbsCorr = MULTI-SCAN

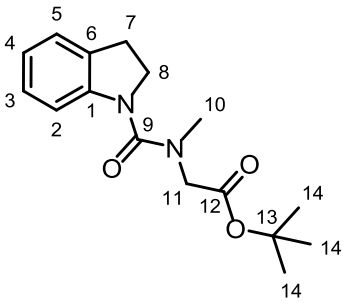
Data completeness= 0.981 Theta(max)= 27.868

R(reflections)= 0.0620(4758) wR2(reflections)= 0.1240(7202)

S = 1.043 Npar= 384

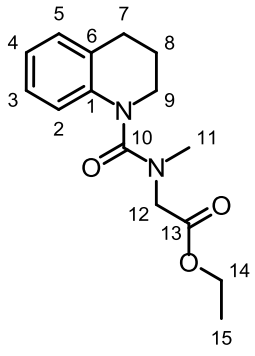


***tert*-Butyl *N*-(indoline-1-carbonyl)-*N*-methylglycinate (2-224)**



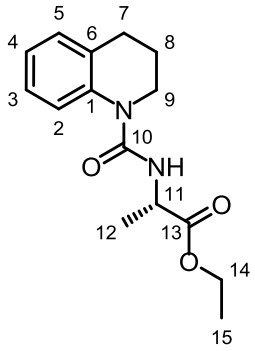
According to **GP5**, sarcosine *tert*-butyl ester hydrochloride (0.55 g, 3.0 mmol) was dissolved in MeCN (6.9 mL) and triethylamine (1.0 mL, 7.2 mmol) was added dropwise. Indoline-1-carbamoyl chloride **2-41** (0.5 g, 2.8 mmol) was dissolved in a small amount of MeCN and added dropwise to the reaction mixture at RT. The mixture was stirred at reflux for 2 h. Purification by flash column chromatography eluting with (10 to 40% EtOAc in petrol) gave the *title compound* **2-224** as a colourless oil (0.58 g, 73%). $\mathbf{R_f}$ 0.48 (40% EtOAC/petrol); $\mathbf{\nu_{max}}$ **/cm^{-1}** (film) 2974, 1739, 1654, 1482; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19–7.10 (3 H, m, ArH), 6.91–6.85 (1 H, m, ArH), 3.98 (2 H, s, H11), 3.91 (2 H, t, *J* 8.2, H8), 3.04–3.00 (2 H, m, H7), 2.99 (3 H, s, H10), 1.49 (9 H, s, H14); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.9 (C12), 159.8 (C9), 144.1 (C1), 131.4 (C6), 127.1 (ArCH), 124.8 (ArCH), 121.5 (ArCH), 113.6 (ArCH), 81.8 (C13), 52.0 (C11), 50.4 (C8), 37.7 (C10), 28.2 (C7), 28.1 (C14); **HRMS** (ESI$^+$) m/z $C_{16}H_{23}N_2O^+$ requires: 291.1703; found: 291.1703.

Ethyl *N*-methyl-*N*-(1,2,3,4-tetrahydroquinoline-1-carbonyl)glycinate (2-228)



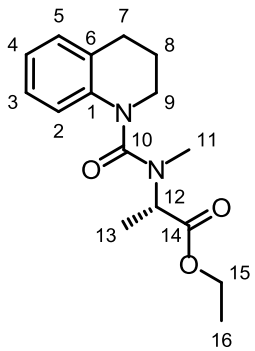
According to **GP5**, sarcosine ethyl ester hydrochloride (0.26 g, 1.7 mmol) was dissolved in MeCN (3.8 mL) and triethylamine (0.56 mL, 4.0 mmol) was added dropwise. 3,4-Tetrahydroquinoline-1(2*H*)-carbamoyl chloride **2-112** (0.3 g, 1.5 mmol) was dissolved in a small amount of MeCN and added dropwise to the reaction mixture at RT. The mixture was stirred at RT for 16 h. Purification by flash column chromatography eluting with (10 to 40% EtOAc in petrol) gave the *title compound* **2-228** as a colourless oil (0.34 g, 80%). $\mathbf{R}_f$ 0.16 (20% EtOAc/ petrol); $\boldsymbol{\nu}_{max}$ **/cm^{-1}** (film) 2935, 1744, 1649, 1493; **^{1}H** NMR (400 MHz, $CDCl_3$) δ 7.20 (1 H, d, *J* 8.1, H2), 7.13–7.08 (2 H, m, H3, H5), 6.91 (1 H, td, *J* 7.4, 1.3, H4), 4.21 (2 H, q, *J* 7.1, H14), 4.05 (2 H, s, H12), 3.60 (2 H, t, *J* 6.5, H9), 2.79 (3 H, s, H11), 2.75 (2 H, t, *J* 6.5, H7), 1.97 (2 H, p, *J* 6.5, H8), 1.29 (3 H, t, *J* 7.1, H15); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.9 (C13), 160.7 (C10), 140.5 (C1), 128.9 (C5), 128.2 (C9), 126.6 (C3), 122.1 (C4), 120.2 (C2), 61.1 (C14), 51.3 (C12), 45.5 (C9), 37.9 (C7), 26.9 (C11), 23.6 (C8), 14.2 (C15); **HRMS** (ESI^+) m/z $C_{15}H_{21}N_2O_3^+$ requires: 277.1547; found: 277.1559.

Ethyl (1,2,3,4-tetrahydroquinoline-1-carbonyl)-L-alaninate (2-223d)



According to **GP5**, L-alanine ethyl ester hydrochloride (0.86 g, 5.6 mmol) was dissolved in MeCN (13 mL) and triethylamine (1.9 mL, 13 mmol) was added dropwise. 3,4-Tetrahydroquinoline-1(2*H*)-carbamoyl chloride **2-112** (1.0 g, 5.1 mmol) was dissolved in a small amount of MeCN and added dropwise to the reaction mixture at RT. The mixture was stirred to reflux for 2 h. Purification by flash column chromatography eluting with (10 to 50% EtOAc in petrol) gave the *title compound* **2-223d** as a colourless oil (1.1 g, 78%). $\mathbf{R}_f$ 0.19 (30% EtOAc/ petrol); $\boldsymbol{\nu}_{max}$ **/cm^{-1}** (film) 2937, 1737, 1659, 1492, 1197; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (1 H, d, *J* 8.0, H2), 7.23–7.14 (2 H, m, H3, H5), 7.07–7.01 (1 H, m H4), 5.66 (1 H, d, *J* 7.5, NH), 4.54 (1 H, p, *J* 7.2, H11), 4.20–4.15 (2 H, m, H14), 3.80 (1 H, dt, *J* 12.5, 6.2, H9$_a$), 3.66 (1 H, dt, *J* 12.5, 6.2, H9$_b$), 2.74 (2 H, t, *J* 6.5, H7), 1.97–1.86 (2 H, m, H8), 1.37 (3 H, d, *J* 7.2, H12), 1.27 (3 H, t, *J* 7.1, H15); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.8 (C13), 155.8 (C10), 139.0 (C1), 132.2 (C6), 129.5 (C3/C5), 126.6 (C3/C5), 124.3 (C4), 123.1 (C2), 61.3 (C14), 49.5 (C11), 43.4 (C9), 27.0 (C7), 23.9 (C8), 18.7 (C12), 14.1 (C15); **HRMS** (ESI^+) m/z $C_{15}H_{21}N_2O_3^+$ requires: 277.1546; found: 277.1542; $[\boldsymbol{\alpha}]_D^{21}$ +83 (*c.* 0.21, $CHCl_3$).

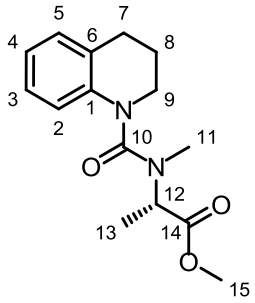
Ethyl *N*-methyl-*N*-(1,2,3,4-tetrahydroquinoline-1-carbonyl)-*L*-alaninate (2-223)



To a solution of ethyl (1,2,3,4-tetrahydroquinoline-1-carbonyl)-*L*-alaninate, (1.1 g, 3.8 mmol) in THF (19 mL) was added NaH (0.30 g, 7.6 mmol, 60% dispersion in mineral oil) at 0 °C. Methyl iodide (0.71 mL, 11 mmol) was added dropwise and the reaction was stirred at RT for 16 h. The reaction was quenched with water (5 mL) followed by 1 M NaOH (5 mL). The aqueous phase was extracted three times with EtOAc and the combined organic phases were dried over $MgSO_4$ and filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography, eluting with (10 to 40% EtOAc in petrol) to give the *title compound* **2-223** as a yellow oil (0.64 g, 58%). $\mathbf{R}_f$ 0.25 (30% EtOAc/petrol) $\boldsymbol{\nu}_{max}$ **/cm^{-1}** (film) 2987, 1738, 1646, 1375, 1066; *Product exists as rotamers in a 2:1 ratio. Rotamers will be assigned as major and minor (maj+min)* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (1 H, dd, *J* 8.3, 1.2, H2^{min}), 7.14–7.06 (3 H, m, H2^{maj}, H3, H5), 6.90 (1 H, ddd, *J* 8.2, 6.7, 2.0, H4), 4.73 (1 H, q, *J* 7.2, H11^{maj}), 4.24–4.16 (3 H, m, H11^{min}, H15), 3.62–3.55 (2 H, m, H9), 2.79–2.72 (2 H, m, H7), 2.67 (3 H, s, H11^{maj}), 2.62 (3 H, s, H11^{min}),

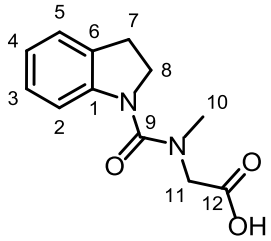
2.01–1.94 (2 H, m, H8), 1.44 (3 H, d, *J* 7.3, H13), 1.30 (3 H, t, *J* 7.1, H16^{maj}), 1.27 (3 H, t, *J* 7.2, H16^{min}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.6 (C14^{min}), 172.1 (C14^{maj}), 160.8 (C10^{maj}), 160.4 (C10^{min}), 140.7 (C1^{min}), 140.6 (C1^{maj}), 128.9 (ArCH^{maj}), 128.8 (ArCH^{min}), 128.1 (C6^{min}), 128.0 (C6^{maj}), 126.6 (ArCH^{min}), 126.4 (ArCH^{maj}), 122.0 (C4^{maj}), 121.9(C4^{min}), 120.2 (C2^{min}), 119.9 (C2^{maj}), 61.2 (H11^{min}), 61.1 (H15^{maj}), 61.0 (H15^{min}), 55.0 (H11^{maj}), 45.5 (H9^{maj}), 45.0 (H9^{min}), 32.8 (H11^{maj}), 32.5 (H11^{min}), 27.0 (H9^{min}), 27.95 (H9^{maj}), 26.7 (H7^{min}), 23.6 (H7^{maj}), 23.1 (H13^{maj}), 14.5 (H13^{min}), 14.2 (H16^{maj}), 14.2 (H16^{min}); **HRMS** (ESI$^+$) m/z $C_{16}H_{23}N_2O_3^+$ requires: 291.1703; found: 291.1701.

Methyl *N*-methyl-*N*-(1,2,3,4-tetrahydroquinoline-1-carbonyl)-*L*-alaninate (2-223e)



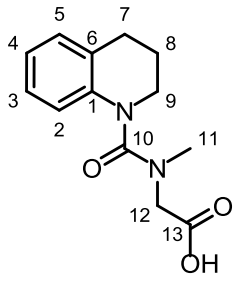
According to **GP5**, methyl *N*-methyl-L-alaninate hydrochloride (0.6 g, 3.9 mmol) was dissolved in MeCN (9 mL) and triethylamine (1.3 mL, 9.3 mmol) was added dropwise. 3,4-Tetrahydroquinoline-1(2*H*)-carbamoyl chloride **2-112** (0.7 g, 3.6 mmol) was dissolved in a small amount of MeCN and added dropwise to the reaction mixture at RT. The mixture was stirred at RT for 16 h. Purification by flash column chromatography eluting with (10 to 50% EtOAc in petrol) gave the *title compound* **2-223e** as a colourless oil (0.66 g, 67%). **R_f** 0.17 (30% EtOAc/petrol); **ν_{max} /cm^{-1}** (film) 2987, 1647, 1393, 1066; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.12–7.05 (3 H, m, H2, H3, H5), 6.90 (1 H, ddd, *J* 7.4, 5.7, 2.6, H4), 4.72 (1 H, q, *J* 7.2, H12), 3.74 (3 H, s, H15), 3.64–3.53 (2 H, m, H9), 2.76 (2 H, t, *J* 6.7, H7), 2.67 (3 H, s, H11), 2.01–1.93 (2 H, m, H8), 1.45 (3 H, d, *J* 7.2, H13); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.7 (C14), 160.8 (C16), 140.5 (C1), 128.9 (C5), 128.2 (C6), 126.5 (C3), 122.1 (C4), 119.9 (C2), 54.9 (C12), 52.2 (C15), 45.5 (C9), 33.0 (C11), 26.9 (C7), 23.6 (C8), 14.6 (C13); **HRMS** (ESI$^+$) m/z $C_{15}H_{21}N_2O_3^+$ requires: 277.1547; found: 277.1557; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ -38 (*c*. 0.5, $CHCl_3$)

***N*-(Indoline-1-carbonyl)-*N*-methylglycine (2-234)**



To a solution of *tert*-butyl *N*-(indoline-1-carbonyl)-*N*-methylglycinate **2-224** (0.43 g, 1.5 mmol) in CH_2Cl_2 (2.5 mL) was added TFA (2.5 mL) at 0 °C. The reaction mixture warmed to RT and stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 (8 mL) and washed three times with water. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography eluting with (10 to 100% EtOAc in petrol) yielding the *title compound* **2-234** as an orange oil (0.33 g, 99%). **R_f** 0.09 (5% MeOH/CH_2Cl_2); **ν_{max} /cm^{-1}** (film) 2925, 1650, 1484, 1390; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (1 H, br s, OH), 7.19–7.10 (3 H, m, H2, H3, H5), 6.93 (1 H, td, *J* 7.3, 1.3, H4), 4.07 (2 H, s, H11), 3.96 (2 H, t, *J* 8.2, H8), 3.06 (2 H, t, *J* 8.2, H7), 3.02 (3 H, s, H10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.9 (C12), 160.7 (C9), 143.2 (C1), 131.7 (C6), 127.2 (C5), 125.0 (C3), 122.4 (C4), 114.2 (C2), 51.9 (C11), 50.6 (C8), 38.1 (C10), 28.2 (C7); **HRMS** (ESI$^+$) m/z $C_{12}H_{14}N_2NaO_3^+$ requires: 257.0897; found: 257.0893.

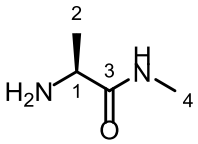
***N*-Methyl-*N*-(1,2,3,4-tetrahydroquinoline-1-carbonyl)glycine (2-235)**



According to **GP5**, sarcosine *tert*-butyl ester hydrochloride (0.51 g, 2.8 mmol) was dissolved in MeCN (6.4 mL) and triethylamine (0.93 mL, 6.6 mmol) was added dropwise. 3,4-Tetrahydroquinoline-1(2*H*)-carbamoyl chloride **2-112** (0.5 g, 2.6 mmol) was dissolved in a small amount of MeCN and added dropwise to the reaction mixture at RT. The mixture was stirred at reflux for 3 h. Purification by flash column chromatography eluting with (10 to 40% EtOAc in petrol) gave the *tert*-butyl ester as a colourless oil.

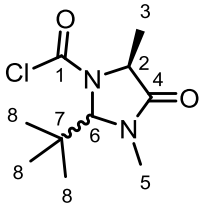
To a solution of the *tert*-butyl ester (0.6 g, 2.0 mmol) in CH_2Cl_2 (3.3 mL) was added TFA (3.3 mL) at 0 °C. The reaction mixture warmed to RT and stirred for 3 h. The reaction mixture was diluted with CH_2Cl_2 (9 mL) and washed three times with water. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography eluting with (10 to 100% EtOAc in petrol) yielding the *title compound* **2-235** as an off-white sticky oil (0.35 g, 71%). $\mathbf{R_f}$ 0.13 (5% MeOH/CH_2Cl_2); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 2933, 1738, 1601, 1492, 1397; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16–7.07 (3 H, m, H2, H3, H5), 6.97 (1 H, td, *J* 7.3, 1.4, H4), 6.74 (1 H, br, OH), 4.02 (2H, s, H12), 3.65 (2 H, t, *J* 6.6, H9), 2.76 (2 H, t, *J* 6.6, H7), 2.73 (3 H, s, H11), 1.99 (2 H, p, *J* 6.6, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.3 (C13), 161.9 (C10), 139.5 (C1), 129.1 (C6), 129.0 (C5), 126.7 (C3), 123.2 (C4), 120.5 (C2), 52.4 (C12), 45.6 (C9), 38.2 (C11), 26.8 (C7), 23.7 (C8); **HRMS** (ESI^+) m/z $C_{13}H_{17}N_2O_3^+$ requires: 249.1233; found: 249.1239.

(*S*)-2-Amino-*N*-methylpropanamide (2-244)



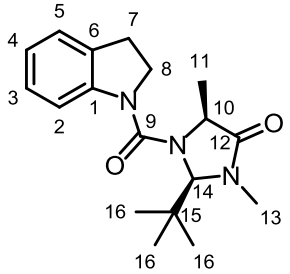
Following literature procedure,[115] ethanolic $MeNH_2$ (57 mL, 460 mmol) was added to L-alanine ethyl ester hydrochloride (10 g, 65 mmol) and the reaction mixture was stirred at RT for 16 h. The solvent was removed *in vacuo* and the crude product was dissolved in $CHCl_3$ and washed with aq. 3.8 M K_2CO_3 solution. The aqueous phase was extracted three times with chloroform and the combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* yielding the *title compound* **2-244** as pale yellow oil (3.8 g, 58%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (1 H, br s, NH), 3.30 (1 H, q, *J* 7.0, H1), 2.62 (3 H, d, *J* 5.0, H4), 1.43 (2 H, br s, NH_2), 1.14 (3 H, d, *J* 7.0, H2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.5 (C3), 50.6 (C1), 25.6 (C4), 21.6 (C2). *Data in accordance with literature.*[208]

(5*S*)-2-(*tert*-Butyl)-3,5-dimethyl-4-oxoimidazolidine-1-carbamoyl chloride (2-246)



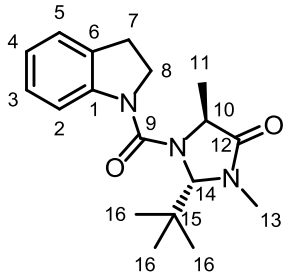
To a solution of (*S*)-2-amino-*N*-methylpropanamide **2-244** (2.0 g, 20 mmol) in anhydrous toluene (30 mL) was added molecular sieves (3 Å), pivalaldehyde (2.3 mL, 22 mmol) and *p*-toluenesulfonic acid monohydrate (0.56 g, 2.9 mmol). The reaction mixture was stirred at reflux overnight. The reaction mixture was filtered and quenched by slow addition of sat. $NaHCO_3$ until pH >9. The organic phase was separated, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was dissolved in anhydrous CH_2Cl_2 (3.3 mL) and added dropwise to a solution of triphosgene (1.8 g, 6.0 mmol) and 2,6-lutidine (1.9 mL, 16 mmol) in anhydrous CH_2Cl_2 (6.7 mL) at −78 °C. After 15 min, the reaction mixture was warmed to RT and stirred for 3 h. The reaction was quenched by addition of 1 M HCl. The organic phase was separated, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (eluting with 1% Acetone in CH_2Cl_2) gave isolated diastereomers: *cis*- **2-246** (0.78 g, 15%) as a yellow oil; $\mathbf{R_f}$ 0.24 (1% Acetone/CH_2Cl_2); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 2976, 2880, 1747, 1710; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.10 (1 H, s, H6), 4.39 (1 H, q, *J* 7.0, H2), 3.01 (3 H, s, H5), 1.61 (3 H, d, *J* 7.0, H3), 1.04 (9 H, s, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.2 (C4), 150.3 (C1), 83. 8 (C6), 58.5 (C2), 38.0 (C7), 31.6 (C5), 26.6 (C8), 17.5 (C3); **HRMS m/z** (ESI^+) $C_{10}H_{18}ClO_2N_2^+$ requires: 233.1051; found: 233.1049. *trans*- **2-246** (3.6 g, 69%) as a white solid; $\mathbf{R_f}$ 0.42 (1% Acetone/ CH_2Cl_2); $\mathbf{\nu_{max}/cm^{-1}}$ **(film)**; 2972, 2875, 1746, 1713; *Product exists as rotamers in a 55:45 ratio. Rotamers will be assigned as major and minor (maj+min)* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.17 (1 H, br s, $H6^{min}$), 5.13 (1 H, br s, $H6^{maj}$), 4.14 (1 H, br, H2), 3.05 (3 H, s, H5), 1.75 (3 H, br, $H3^{min}$), 1.61 (3 H, br, $H3^{maj}$), 1.06 (9 H, s, $H8^{maj}$), 1.01 (9 H, s, $H8^{min}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.1 (C4), 148.7 (C1), 83.7 ($C6^{maj}$), 82.6 ($C6^{min}$), 58.4 ($C2^{maj/min}$), 57.3 ($C2^{maj/min}$), 41.1 (C7), 32.2 (C5), 26.7 ($C8^{maj}$), 26.3 ($C8^{min}$), 19.7 ($C3^{min}$), 15.9 ($C3^{maj}$); **HRMS** (ESI^+) m/z $C_{10}H_{18}ClO_2N_2^+$ requires: 233.1051; found: 233.1049.

(2*R*,5*S*)-2-(*tert*-Butyl)-1-(indoline-1-carbonyl)-3,5-dimethylimidazolidin-4-one (2-248)



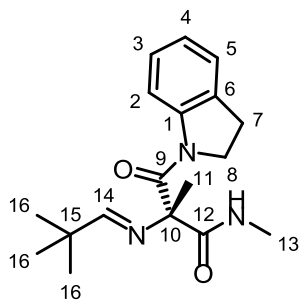
Cis- **2-246** (0.2 g, 0.86 mmol), indoline (0.48 mL, 4.3 mmol), 2,6-lutidine (0.2 mL, 1.7 mmol) and KI (0.16 mg, 0.95 mmol) were reacted in CH_2Cl_2/toluene (2.5 mL, 4:1 v/v) at 60 °C for 3 h. The reaction was quenched with 1 M HCl and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography, eluting with (30 to 100% EtOAc in petrol) to give the *title compound* **2-248** as an off-white solid (0.22 g, 79%); $\mathbf{R_f}$ 0.23 (40% EtOAc/petrol); **Mp** 134–135 °C (CH_2Cl_2/*n*-pentane); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 2917, 2901, 1704, 1658, 1381; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (1 H, d, *J* 8.0, H2), 7.21–7.15 (2 H, m, H3, H5), 6.97 (1 H, t, *J* 7.4, H4), 5.68 (1 H, s, H14), 4.09–4.03 (3 H, m, H10, H8), 3.30–3.20 (1 H, m, $H7_a$), 3.11–3.04 (1 H, m, $H7_b$), 3.05 (3 H, s, H15), 1.68 (3 H, d, *J* 6.8, H11), 1.03 (9 H, s, H16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.7 (C12), 161.4 (C9), 144.0 (C1), 131.2 (C6), 127.2 (C3/C5), 124.7 (C3/C5), 123.1 (C4), 116.7 (C2), 82.2 (C14), 58.4 (C10), 51.3 (C8), 36.3 (C15), 31.6 (C13), 29.1 (C7), 26.6 (C16), 20.2 (C11); **HRMS** (ESI^+) m/z $C_{18}H_{26}N_3O_2^+$ requires: 316.2020; found: 316.2020

(2S,5S)-2-(*tert*-Butyl)-1-(indoline-1-carbonyl)-3,5-dimethylimidazolidin-4-one (2-249)



Trans- **2-246** (0.3 g, 1.3 mmol), indoline (0.29 mL, 2.1 mmol) and triethylamine (0.29 mL, 2.1 mmol) were reacted in MeCN (3.2 mL) at 60 °C for 16 h. The reaction was quenched with sat. $NaHCO_3$ and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography, eluting with (10 to 100% EtOAc in petrol) to give the *title compound* **2-249** as a white solid (0.34 g, 83%). $\mathbf{R_f}$ 0.18 (40% EtOAC/petrol); **Mp** 195–196 °C (CH_2Cl_2/*n*-pentane); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 2917, 2901, 1704, 1658, 1381; *Product exists as rotamers in a 58:42 ratio. Rotamers will be assigned as major and minor (maj+min)*; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68–7.64 (1 H, br, $H2^{maj}$), 7.26–7.17 (2 H, m, H3, H5), 7.06 (1 H, d, *J* 7.8, $H2^{min}$), 7.00–6.96 (1 H, m, H4), 5.58 (1 H, s, $H14^{min}$), 5.44 (1 H, s, $H14^{maj}$), 4.08–3.90 (3 H, m, H16, H8), 3.34–2.95 (5 H, m, H7, H13), 1.39 (3 H, d, *J* 6.7, $H11^{maj}$), 1.14 (3 H, d, *J* 6.7, $H11^{min}$), 1.04 (9 H, s, $H16^{min}$), 0.96 (9 H, s, $H9^{maj}$); **^{13}C** NMR (101 MHz, $CDCl_3$) δ 172.4 (C12), 159.9 (C9), 142.8 (C1), 132.4 (C6), 127.6 ($C3^{maj}$/$C5^{maj}$), 127.5 ($C3^{maj}$/$C5^{maj}$), 125.7($C3^{min}$/$C5^{min}$), 124.7 ($C3^{min}$/$C5^{min}$), 123.1 ($C4^{maj}$), 122.5 ($C4^{min}$), 116.2 ($C2^{maj}$), 112.5 ($C2^{min}$), 81.1 ($C14^{min}$), 80.6 ($C14^{maj}$), 56.0 (C10), 49.8 ($C8^{maj}$), 48.6 ($C8^{min}$), 39.5 (C15) 31.9 ($C13^{maj}$), 31.7 ($C13^{min}$), 28.5 ($C7^{maj}$), 27.3 ($C7^{min}$), 26.1 ($C16^{min}$), 25.7 ($C16^{maj}$), 17.3 ($C11^{maj}$), 16.7 ($C11^{min}$); **HRMS** (ESI^+) m/z $C_{18}H_{26}N_3O_2^+$ requires: 316.2020; found: 316.2020.

(*R*,*E*)-2-((2,2-Dimethylpropylidene)amino)-3-(indolin-1-yl)-*N*,2-dimethyl-3-oxopropanamide (2-252)



To a solution of *cis*- **2-246** (0.05 g, 0.16 mmol) in THF (1.6 mL) was added KHMDS (0.24 mL, 0.24 mmol, 1 M in THF) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 15 min before being warmed to RT and stirred for 4 h. The reaction was quenched with NH_4Cl and stirred for 15 min. The aqueous phase was extracted three times with EtOAc, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography, eluting with (30 to 80% EtOAc in petrol) to give the *title compound* **2-252** as white solid (0.45 g, 90%). $\mathbf{R_f}$ 0.26 (40% EtOAc/petrol) **Mp** 167–168 °C (CH_2Cl_2/*n*-pentane); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 2924,

2867, 1729, 1663, 1461. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (1 H, d, *J* 8.0, H2), 7.72 (1 H, br, NH), 7.53 (1 H, s, H14), 7.17 (1 H, t, *J* 7.5, H3), 7.11 (1 H, d, *J* 7.5, H5), 6.99 (1 H, t, *J* 7.5, H4), 3.77–3.61 (2 H, m, H8), 3.0–2.89 (5 H, m, H7, H13), 1.53 (3 H, s, H11), 1.03 (9 H, s, H16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.9 (C14), 172.7 (C12), 167.7 (C9), 143.3 (C1), 131.2 (C6), 127.4 (C3), 124.3 (C5), 124.1 (C4), 117.8 (C2), 73.5 (C10), 46.8 (C8), 37.0 (C15), 28.4 (C7), 26.6 (C11), 26.3 (C16), 26.1 (C13). **HRMS** (ESI^+) m/z $C_{18}H_{26}N_3O_2^+$ requires: 316.2020; found: 316.2025; **X-ray** crystallography data:

Bond precision: C-C = 0.0033 A Wavelength=0.71073

Cell: a=10.4437(4) b=12.4907(4) c=13.5222(4)
alpha=90 beta=90 gamma=90

Temperature: 100 K

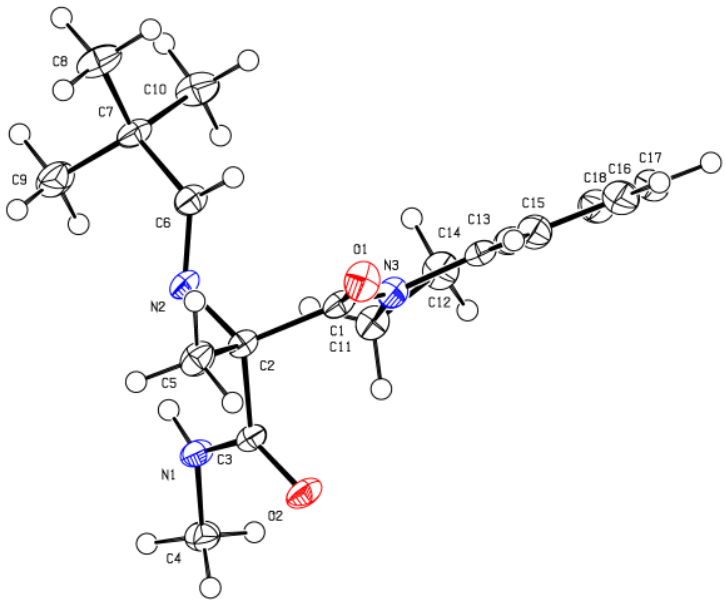
	Calculated	Reported
Volume	1763.96(10)	1763.96(10)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C18 H25 N3 O2	C18 H25 N3 O2
Sum formula	C18 H25 N3 O2	C18 H25 N3 O2
Mr	315.41	315.41
Dx,g cm-3	1.188	1.188
Z	4	4
Mu (mm-1)	0.079	0.079
F000	680.0	680.0
F000'	680.26	
h,k,lmax	13,16,17	13,16,17
Nref	4250[2414]	3205
Tmin,Tmax	0.958,0.982	0.597,0.746
Tmin'	0.954	

Correction method= # Reported T Limits: Tmin=0.597 Tmax=0.746 AbsCorr = MULTI-SCAN

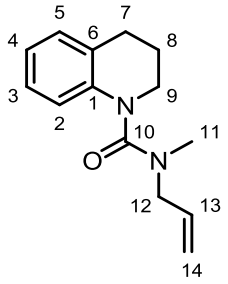
Data completeness= 1.33/0.75 Theta(max)= 27.987

R(reflections)= 0.0392(2951) wR2(reflections)= 0.0950(3205)

S = 1.085 Npar= 218

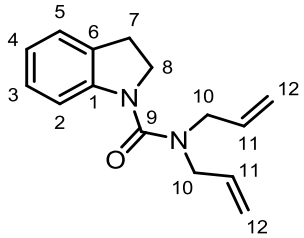


***N*-Allyl-*N*-methyl-3,4-tetrahydroquinoline-1(2*H*)-carboxamide (2-256)**



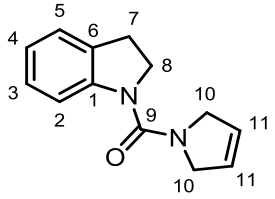
Carbamoyl chloride formation:
According to **GP1**, 1,2,3,4-tetrahydroquinoline (3.7 mL, 29 mmol), triphosgene (4.0 g, 14 mmol, 0.46) and pyridine (2.4 mL, 29 mmol) in CH_2Cl_2 (42 mL) gave the carbamoyl chloride. $\boldsymbol{R_f}$ 0.46 (30% Et_2O/*n*-pentane).
Urea formation:
According to a modified **GP2**, 3,4-Tetrahydroquinoline-1(2*H*)-carbamoyl chloride **2-112** (0.50 g, 2.56 mmol), *N*-Allylmethylamine (0.18 mL, 3.3 mmol) and triethylamine (0.57 mL, 4.1 mmol) in MeCN (6.4 mL) as stirred at RT for 16 h. Purification by flash column chromatography eluting with (10% to 80% Et_2O in *n*-Pentane) gave the *title compound* **2-256** as a yellow oil (0.43 g, 73%). $\mathbf{R_f}$ 0.20 (30% Et_2O/*n*-pentane); $\boldsymbol{\nu_{max}}$ **/cm^{-1}** (film) 2925, 1645, 1492, 1387, 752. **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.11–7.06 (2 H, m, ArH), 6.95–6.86 (2 H, m, ArH), 5.82 (1 H, ddt, *J* 16.8, 10.8, 6.1, H13), 5.21–5.19 (1 H, m, $H14_a$), 5.18–5.14 (1 H, m, $H14_b$), 3.86–3.83 (2 H, m, H12), 3.60–3.56 (2 H, m, H9), 2.76 (2 H, t, *J* 6.7, H7), 2.72 (3 H, s, H11), 2.00–1.93 (2 H, m, H7); **^{13}C NMR** (101 MHz; $CDCl_3$) δ 161.0 (C10), 141.0 (C1), 133.7 (C13), 129.2 (ArCH), 127.9 (C6), 126.6 (ArCH), 121.9 (ArCH), 119.7 (ArCH), 117.9 (C14), 52.7 (C12), 45.7 (C9), 35.6 (C11), 27.1 (7), 23.6 (C8); **HRMS** (ESI^+) m/z $C_{14}H_{19}N_2O^+$ requires: 231.1419; found: 281.1814.

***N*,*N*-Diallylindoline-1-carboxamide**



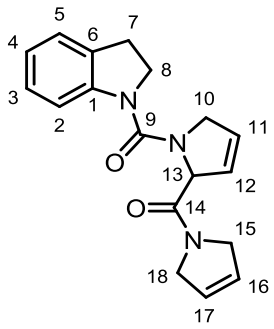
According to a modified **GP2**, indoline-1-carbamoyl chloride **2-41** (0.40 g, 2.2 mmol), diallylamine (0.22 mL, 2.9 mmol) and triethylamine (0.49 mL, 3.5 mmol) in MeCN (5.5 mL) was stirred at RT for 12 h. Purification by flash column chromatography eluting with (10% to 100% EtOAc in petrol) gave the *title compound* as a yellow oil (0.43 g, 80%). $\mathbf{R_f}$ 0.51 (10% EtOAc/petrol); $\boldsymbol{\nu_{max}}$ **/cm^{-1}** (film) 2921, 1650, 1481, 1396, 1242; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.20–7.14 (2 H, m, H5, H3), 7.10 (1 H, dd, *J* 7.5, 1.0, H2), 6.91 (1 H, td, *J* 7.5, 1.1, H4), 5.87 (2 H, ddt, *J* 17.9, 9.7, 6.0, H11), 5.27–5.20 (4 H, m, H12), 3.95–3.90 (6 H, H8, H10), 3.06 (2 H, t, *J* 8.3, H7); **^{13}C NMR** (101 MHz; $CDCl_3$) δ 160.0 (C9), 144.5 (C1), 134.0 (C11), 131.6 (C6), 127.2 (C3/C5), 125.0 (C5/C3), 121.8 (C4), 118.0 (C12), 113.8 (C2), 50.7 (C10), 50.0 (C8), 28.4 (C7); **HRMS** (ESI^+) m/z $C_{15}H_{19}N_{2O}^+$ requires: 243.1492; found: 243.1496.

(2,5-Dihydro-1*H*-pyrrol-1-yl)(indolin-1-yl)methanone (2-261)



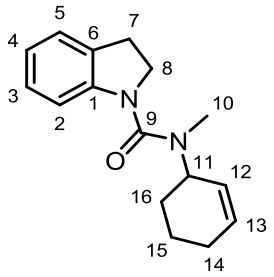
To a flame-dried Schlenk tube was added *N*,*N*-diallylindoline-1-carboxamide (0.40 g, 1.7 mmol), Grubbs' 1st generation catalyst (0.07 g, 0.08 mmol) and CH_2Cl_2 (33 mL). The reaction mixture was stirred at RT for 16 h. The solvent was removed *in vacuo* leaving the crude residue. Purification by flash column chromatography eluting with (10% to 100% EtOAc in petrol) gave the *title compound* **2-261** as a yellow oil (0.28 g, 78%). $\mathbf{R_f}$ 0.24 (20% EtOAc/petrol); $\boldsymbol{\nu_{max}}$ **/cm^{-1}** (film) 2857, 1647, 1623, 1482, 1385; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.20–7.15 (3 H, m, H2, H3, H5), 6.94–6.89 (1 H, m, H4), 5.87–5.84 (2 H, m, H11), 4.35–4.33 (4 H, m, H10), 3.98 (2 H, t, *J* 8.3, H8), 3.11 (2 H, t, *J* 8.3, H7); **^{13}C NMR** (101 MHz; $CDCl_3$) δ 158.5 (C9), 144.3 (C1), 131.4 (C6), 127.1 (C3/C5), 125.7 (C11), 124.8 (C3/C5), 121.7 (C4), 114.9 (C2), 54.7 (C10), 50.3 (C8), 28.8 (C7). **HRMS** (ESI^+) m/z $C_{13}H_{15}N_2O^+$ requires: 215.1179; found: 215.1178.

(2,5-Dihydro-1H-pyrrol-1-yl)(1-(indoline-1-carbonyl)-2,5-dihydro-1*H*-pyrrol-2-yl)methanone (2-263)



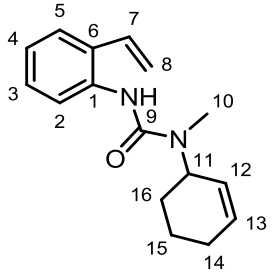
LDA preparation:
According to **GP3**, diisopropylamine (0.13 mL, 0.93 mmol), *n*-butyllithium (0.58 mL, 0.93 mmol, 1.6 M in THF) and THF (1.5 mL).
Attempted ring Expansion:
According to **GP4**, (2,5-dihydro-1*H*-pyrrol-1-yl)(indolin-1-yl)methanone **2-261** (0.10 g, 0.47 mmol), DMPU (0.20 mL, 2.4 mmol) and LDA (see above) in THF (3.1 mL) were kept at −78 °C for 4 h. Purification by flash column chromatography eluting with (10% to 100% EtOAc in petrol) gave the *title compound* **2-263** as a colourless oil (32 mg, 22%). $\mathbf{R_f}$ 0.14 (90% EtOAc/petrol); $\mathbf{\nu_{max}\ /cm^{-1}}$ (film) 2861, 1643, 1620, 1482, 1389; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.27–7.24 (1 H, m, H2), 7.11–7.06 (2 H, m, H3, H5), 6.82 (1 H, td, *J* 7.4, 1.1, H4) 5.96–5.92 (1 H, m, H11/H12), 5.80–5.66 (4 H, m, H11/H12, H13, H16, H17), 4.58–4.50 (2 H, m, H15$_a$, H10$_a$), 4.32–4.20 (2 H, m, H15$_b$, H16$_a$) 4.15–4.06 (2 H, m, H16$_b$, H10$_b$), 3.95–3.88 (2 H, m, H8), 3.11–3.02 (1 H, m, H7$_a$), 2.95–2.88 (1 H, m, H7$_b$); **^{13}C NMR** (101 MHz; $CDCl_3$) δ 168.5 (C14), 157.7 (C9), 144.0 (C1), 131.5 (C6), 128.6 (C11/C12), 127.3 (C3/C5), 126.0 (C11/C12/C16/C17), 125.0 (C16/C17), 124.7 (C16/C17), 124.5 (C3/C5), 121.9 (C4), 115.1 (C2), 66.1 (C13), 55.6 (C10), 53.6 (C16), 53.1 (C15), 50.3 (C8), 28.7 (C7); **HRMS** (ESI$^+$) m/z $C_{18}H_{20}N_3O_2^+$ requires: 310.1550; found: 310.1554.

***N*-(Cyclohex-2-en-1-yl)-N-methylindoline-1-carboxamide (2-264)**



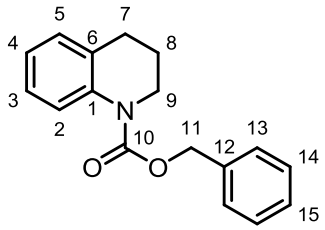
3-bromocyclohexene (1.4 g, 8.7 mmol) was added to a 50 mL RBF and cooled to 0 °C. Methylamine (10.8 mL, 87 mmol, 10 wt %) was added slowly and the reaction mixture was warmed to RT and stirred for 16 h. The reaction was quenched with 2 M NaOH and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* yielding *N*-methylcyclohex-2-en-1-amine which was used in the next step without further purification.
According to a modified **GP2**, indoline-1-carbamoyl chloride **2-41** (0.20 g, 1.1 mmol), *N*-methylcyclohex-2-en-1-amine (0.16 mg, 1.4 mmol) and triethylamine (0.25 mL, 1.8 mmol) in MeCN (2.8 mL) were stirred at RT for 4 h. Purification by flash column chromatography eluting with (10% to 100% EtOAc in petrol) gave the *title compound* **2-264** as a yellow oil (0.15 g, 38%). $\mathbf{R_f}$ 0.20 (10% EtOAc/petrol); $\mathbf{\nu_{max}\ /cm^{-1}}$ (film) 3021, 2928, 1644, 1603, 1480; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.20–7.12 (2 H, m, H3, H5), 6.99–6.96 (1 H, m, H2), 6.89 (1 H, td, *J* 7.4, 1.1, H4), 5.99–5.94 (1 H, m, H12/H13), 5.66–5.62 (1 H, m, H12/H13), 4.70–4.64 (1 H, m, H11), 3.98–3.87 (2 H, m, H8), 3.07–3.03 (2 H, m, H7), 2.81 (3 H, s, H10), 2.09–2.02 (2 H, m, H14), 2.01–1.95 (1 H, m, H16$_a$), 1.90–1.83 (1 H, m, H15$_a$), 1.76–1.64 (2 H, m, H15$_b$, H16$_b$); **^{13}C NMR** (101 MHz; $CDCl_3$) δ 160.4 (C9), 144.7 (C1), 131.7 (C12/C13), 131.6 (C6), 128.9 (C12/C13), 127.1 (C3/C5), 124.9 (C3/C5), 121.4 (C4), 113.4 (C2), 53.9 (C11), 50.7 (C8), 31.4 (C10), 28.3 (C7), 26.5 (C16), 24.8 (C14), 21.7 (C15); **HRMS** (ESI$^+$) m/z $C_{16}H_{21}N_2O^+$ requires: 257.1648; found: 257.1648.

1-(Cyclohex-2-en-1-yl)-1-methyl-3-(2-vinylphenyl)urea (2-266)



According to **GP4**, *N*-(cyclohex-2-en-1-yl)-*N*-methylindoline-1-carboxamide **2-264** (35 mg, 0.14 mmol), DMPU (0.08 mL, 0.68 mmol) and LDA (0.15 mL, 0.3 mmol, 2.0 M) in THF (1.0 mL) were kept at −78 °C for 16 h. Purification by flash column chromatography eluting with (10% to 100% EtOAc in petrol) gave the *title compound* **2-266** as a colourless oil (12 mg, 34%). $\mathbf{R_f}$ 0.46 (20% EtOAc/petrol); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 3021, 2930, 1632, 1513, 1479; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.82 (1 H, d, *J* 8.1, H2), 7.36 (1 H, dd, *J* 7.7, 1.6, H5), 7.27–7.23 (1 H, m, H3), 7.05 (1 H, t, *J* 7.5, H4), 6.80 (1 H, dd, *J* 17.4, 11.1, H7), 6.45 (1 H, br s, NH), 5.99–5.93 (1 H, m, H12/H13), 5.65 (1 H, dd, *J* 17.4, 1.4, $H8_a$), 5.60–5.55 (1 H, m, H12/H13), 5.39 (1 H, dd, *J* 11.1, 1.4, $H8_b$), 4.84–4.76 (1 H, m, H11), 2.90 (3 H, s, H10), 2.07–2.01 (2 H, m, H14), 1.98–1.91 (1 H, m, $H16_a$), 1.87–1.80 (1 H, m, $H15_a$), 1.73–1.54 (2 H, m, $H15_b$, $H16_b$); **^{13}C NMR** (101 MHz; $CDCl_3$) δ; 155.6 (C9), 136.3 (C1), 132.9 (C7), 132.1 (C12/C13), 129.8 (C6), 128.9 (C12/C13), 128.6 (C3), 127.0 (C5), 123.8 (C4), 122.9 (C2), 117.8 (C8), 52.8 (C11), 30.7 (C10), 27.0 (C16), 24.7 (C14), 21.6 (C15); **HRMS** (ESI^+) m/z $C_{16}H_{21}N_2O^+$ requires: 257.1648; found: 257.1660.

Benzyl 3,4-tetrahydroquinoline-1-(2*H*)-carboxylate (2-269)



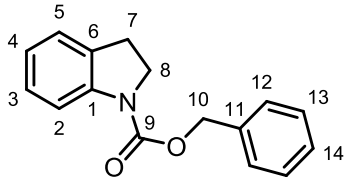
Carbamoyl chloride formation:

According to **GP1**, 1,2,3,4-tetrahydroquinoline (3.7 mL, 29 mmol), triphosgene (4.0 g, 14 mmol) and pyridine (2.4 mL, 29 mmol) in CH_2Cl_2 (42 mL) gave the carbamoyl chloride. $\mathbf{R_f}$ 0.46 (30% Et_2O/*n*-pentane) (*N.B.* The amounts described here were used to prepare a batch stock of the carbamoyl chloride).

Carbamate formation

According to **GP6**, to a suspension of NaH (0.41 g, 10 mmol) in CH_2Cl_2 (26 mL) was added benzyl alcohol (1.1 mL, 10 mmol) at 0 °C. 3,4-Tetrahydroquinoline-1(2*H*)-carbamoyl chloride **2-112** (1.0 g, 5.1 mmol) was added at RT and the mixture was stirred at RT for 16 h. Purification by flash column chromatography eluting with (0 to 10% EtOAc in petrol) gave the *title compound* **2-269** (1.1 g, 81%). $\mathbf{R_f}$ 0.20 (5% EtOAc/petrol); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 2945, 1702, 1492, 1392; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (1 H, d, *J* 8.3, H2), 7.43–7.32 (5 H, m, ArH), 7.17 (1 H, td, *J* 7.8, 1.2, H3), 7.10 (1 H, dd, *J* 7.3, 1.2, H5), 7.02 (1 H, td, *J* 7.3, 1.2, H4), 5.26 (2 H, s, H11), 3.83–3.80 (2 H, m, H9), 2.79 (2 H, t, *J* 6.5, H7), 1.96 (2 H, p, *J* 6.5, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.8 (C10), 138.2 (C12), 136.6 (C1), 130.1 (C6), 128.7 (C5), 128.6 (ArCH), 128.2 (ArCH), 128.1 (ArCH), 126.1 (C3), 124.0 (C2), 123.8 (C4), 67.6 (C11), 45.0 (C9), 27.4 (C7), 23.6 (C8); **HRMS** (ESI^+) m/z $C_{17}H_{17}NNaO_2^+$ requires: 290.1151; found: 290.1161.

Benzyl indoline-1-carboxylate



Carbamoyl chloride formation:

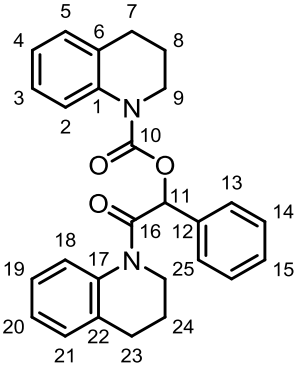
According to **GP1**, indoline (0.50 g, 4.2 mmol), triphosgene (0.57 g, 1.9 mmol) and pyridine (0.33 mL, 4.2 mmol) in CH_2Cl_2 (6.0 mL) gave the carbamoyl chloride. $\mathbf{R_f}$ 0.42 (10% EtOAc/Petrol).

Carbamate formation

According to **GP6**, to a suspension of NaH (0.13 g, 3.3 mmol) in CH_2Cl_2 (8.3 mL) was added benzyl alcohol (0.37 mL, 10.2 mmol) at 0 °C. Indoline-1-carbamoyl chloride (0.3 g, 1.6 mmol) was added at RT and the mixture was stirred at RT for 16 h. Purification by flash column chromatography eluting with (0 to 10% EtOAc in petrol) gave the *title compound* (0.3 g, 72%). $\mathbf{R_f}$ 0.17 (5% EtOAc/petrol); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 2919, 1704, 1602, 1487, 1408; **^{1}H NMR** (500 MHz, DMSO-d_6, 373 K/100 °C) δ 7.66 (1 H, d, *J* 7.9, H2), 7.46–7.42 (2 H, m, H12), 7.42–7.37 (2 H, m, H13), 7.36–7.31 (1 H, m, H14), 7.20 (1

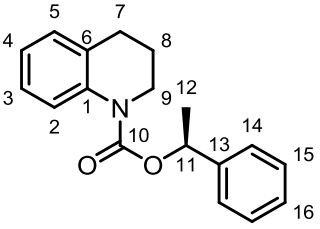
H, d, *J* 7.4, H5), 7.14 (1 H, t, *J* 7.9, H3), 6.96–6.93 (1 H, m, H4), 5.26 (2 H, s, H10), 4.01 (2 H, t, *J* 8.7, H8), 3.11 (2 H, t, *J* 8.7, H7); **^{13}C NMR** (126 MHz, DMSO-d_6, 373 K/100 °C) δ 152.0 (C9), 141.6 (C11), 136.2 (C1), 130.9 (C6), 127.8 (C13), 127.3 (C14), 127.1 (C12), 126.5 (C3), 124.3 (C5), 121.9 (C4), 113.6 (C2), 66.0 (C10), 46.9 (C8), 26.4 (C7); **HRMS** (ESI$^+$) m/z $C_{16}H_{15}NNaO_2^+$ requires: 276.0994; found: 27.0991.

2-(3,4-tetrahydroquinolin-1(2H)-yl)-2-oxo-1-phenylethyl 3,4-dihydroquinoline-1(2H)-carboxylate (2-273)



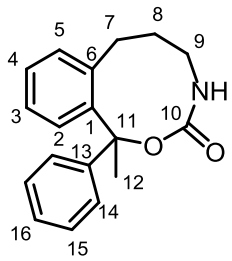
According to **GP4**, benzyl 3,4-dihydroquinoline-1-(2*H*)-carboxylate **2-269** (0.10 g, 0.37 mmol), DMPU (0.22 mL, 1.9 mmol), LDA (0.37 mL, 0.75 mmol, 2.0 M) in THF (2.5 mL) were kept at −78 °C for 5 h. Purification by flash column chromatography eluting with (10 to 40% EtOAc in petrol) gave the *title compound* **2-273** as a colourless oil (46 mg, 29%). **R_f** 0.40 (20% EtOAc/petrol); **ν_{max} /cm^{-1}** (film) 2923, 1671, 1492, 1391.**^{1}H NMR** (500 MHz; DMSO-d_6, 373 K/100 °C) δ 7.81 (1 H, d, *J* 8.2, H2), 7.56 (1 H, d, *J* 7.5, H18), 7.34–7.09 (10 H, m, ArH), 6.98 (1 H, td, *J* 7.4, 1.2, ArH), 6.54 (1 H, s, H11), 3.97 (1 H, dt, *J* 12.9, 6.5, H25$_a$), 3.90 (1 H, ddd, *J* 12.4, 7.1, 4.9, H9$_a$), 3.54 (1 H, ddd, *J* 12.4, 7.8, 4.5, H9$_b$), 3.36–3.30 (1 H, m, H25$_b$), 2.77–2.66 (2 H, m, H7), 2.55 (1 H, dt, *J* 15.8, 6.2, H23$_a$), 2.25–2.11 (1 H, br, H23$_b$), 1.95–1.88 (1 H, m, H8$_a$), 1.87–1.81 (1 H, m, H8$_b$), 1.78–1.73 (1 H, m, H24$_a$), 1.59 (1 H, dp, *J* 13.4, 6.5, H24$_b$); **^{13}C NMR** (126 MHz; DMSO-d_6, 373 K/ 100 °C) δ 168.5 (C16), 154.1 (C10), 139.0 (ArC), 138.4 (ArC), 134.8 (ArC), 133.8 (ArC), 130.5 (ArC), 129.2 (ArCH), 128.9 (ArCH), 128.85 (ArCH), 128.84 (ArCH), 128.2 (ArCH), 126.4 (ArCH), 126.0 (ArCH), 124.85 (ArCH), 124.84 (C18), 123.99 (ArCH), 123.98 (C2), 75.0 (C11), 45.2 (C9), 43.9 (C25), 27.1 (C7), 26.0 (C23), 23.6 (C24), 23.4 (C8); **HRMS** (ESI$^+$) m/z $C_{27}H_{27}N_2O_3^+$ requires: 427.2016; found: 427.2018.

(*S*)-1-Phenylethyl 3,4-tetrahydroquinoline-2(*2H*)-carboxylate (2-274)



According to **GP6**, to a suspension of NaH (0.16 g, 4.1 mmol) in CH_2Cl_2 (10 mL) was added (*S*)-(-)-1-phenylethanol (0.5 mL, 4.1 mmol) at 0 °C. 3,4-Tetrahydroquinoline-1(2*H*)-carbamoyl chloride **2-112** (0.4 g, 2.0 mmol) was added at RT and the mixture was stirred at RT for 16 h. Purification by flash column chromatography eluting with (0 to 10% EtOAc in petrol) gave the *title compound* **2-274** (0.47 g, 82%). **R_f** 0.20 (5% EtOAc/petrol); **ν_{max} /cm^{-1}** (film) 2930, 1700, 1492, 1383; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (1 H, d, *J* 8.3, H2) 7.38–7.27 (5 H, m, ArH), 7.17–7.13 (1 H, m, H3), 7.09 (1 H, d, *J* 7.4, H5), 7.01 (1 H, t, *J* 7.4, H4), 5.94 (1 H, q, *J* 6.6, H11), 3.83–3.77 (2 H, m, H9), 2.77 (2 H, t, *J* 6.5, H7), 1.94 (2 H, p, *J* 6.5, H8), 1.61 (3 H, d, *J* 6.6, H12); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.3 (C10), 142.3 (C13), 138.3 (C1), 130.2 (C6), 128.7 (C5), 128.6 (C14/C15), 127.9 (C16), 126.1 (C14/C15), 126.0 (C3), 124.2 (C2), 123.7 (C4), 74.2 (C11), 45.0 (C9), 27.5 (C7), 23.6 (C8), 23.0 (C12); **HRMS** (ESI$^+$) m/z $C_{18}H_{19}NNaO_2^+$ requires: 304.1308; found: 304.1311.

1-Methyl-1-phenyl-4,5,6,7-tetrahydrobenzo[*g*][1,3]oxazonin-3(1*H*)-one (2-275)



According to a modified **GP4**, to a solution of (*S*)-1-phenylethyl 3,4-dihydroquinoline-2(*2H*)-carboxylate **2-274** (0.1 g, 0.36 mmol), in THF (4.1 mL) and DMPU (1.02 mL, 1:4 DMPU:THF) was added LDA (0.45 mL, 0.89 mmol, 2.0 M) dropwise at −78 °C. The reaction mixture was stirred for 2 h. Purification by flash column chromatography, eluting with (10 to 60% EtOAc in petrol) gave the *title compound* **2-275** as a white solid (35 mg, 35%). $\mathbf{R_f}$ 0.24 (30% EtOAc/petrol); **Mp** 130-131 °C (CH_2Cl_2/*n*-pentane); $\boldsymbol{\nu_{max}}$**/cm^{-1}** (film) 2936, 1717, 1447, 1391, 1057; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (1 H, dd, *J* 7.6, 1.6, H2), 7.34–7.22 (7 H, m, H3, H4, H14, H15, H16), 7.19 (1 H, dd, *J* 7.4, 1.7, H5), 4.88 (1 H, t, *J* 6.9, NH), 3.61 (1 H, dddd, *J* 14.5, 12.4, 7.5, 1.7, H9$_a$), 2.90 (1 H, dddd, *J* 14.5, 6.2, 4.1, 2.6, H9$_b$), 2.46 (1 H, ddd, *J* 13.8, 11.0, 1.6, H7$_a$), 2.40–2.34 (1 H, m, H7$_b$), 2.30 (3 H, s, H12), 1.91 (1 H, dddt, *J* 13.8, 7.5, 3.5, 1.7, H8$_a$), 1.73–1.62 (1 H, m, H8$_b$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.7 (C10), 148.1 (C13), 143.1 (C1), 140.1 (C6), 132.8 (C5), 128.7 (C2), 128.3 (ArCH), 128.1 (ArCH), 126.7 (ArCH), 125.5 (ArCH), 124.9 (ArCH), 85.5 (C11), 43.8 (C9), 35.6 (C8), 33.2 (C7), 32.0 (C12); **HRMS** (ESI$^+$) m/z $C_{18}H_{20}NO_2^+$ requires: 282.1488; found: 282.1493; **X-ray** crystallography data:

Bond precision: C-C = 0.0030 A Wavelength=0.71073

Cell: a=18.0471(4) b=13.5717(3) c=12.2289(3)
alpha=90 beta=90 gamma=90

Temperature: 100 K

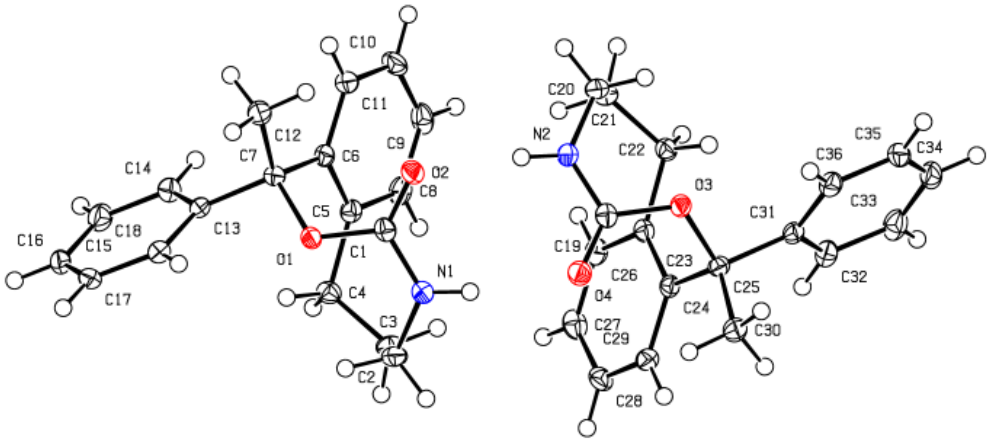
	Calculated	Reported
Volume	2995.22(12)	2995.22(12)
Space group	P c a 21	P c a 21
Hall group	P 2c -2ac	P 2c -2ac
Moiety formula	C18 H19 N O2	C18 H19 N O2
Sum formula	C18 H19 N O2	C18 H19 N O2
Mr	281.34	281.34
Dx,g cm-3	1.248	1.248
Z	8	8
Mu (mm-1)	0.081	0.081
F000	1200.0	1200.0
F000'	1200.52	
h,k,lmax	23,17,16	23,17,16
Nref	7204[3772]	7146
Tmin,Tmax	0.961,0.973	0.643,0.746
Tmin'	0.961	

Correction method= # Reported T Limits: Tmin=0.643 Tmax=0.746 AbsCorr = MULTI-SCAN

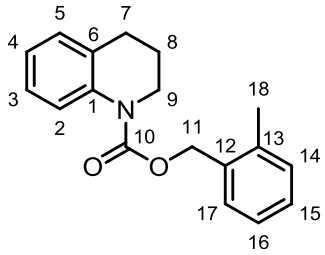
Data completeness= 1.89/0.99 Theta(max)= 28.000

R(reflections)= 0.0345(6407) wR2(reflections)= 0.0800(7146)

S = 1.023 Npar= 389

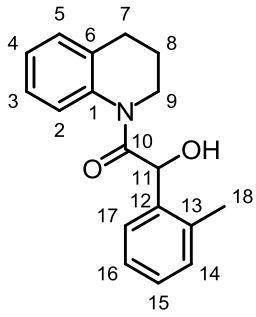


2-Methylbenzyl 3,4-tetrahydroquinoline-1(*2H*)-carboxylate (2-277)



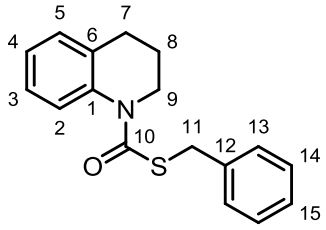
According to **GP6**, to a suspension of NaH (0.16 g, 4.1 mmol) in CH_2Cl_2 (10 mL) was added 2-methylbenzyl alcohol (0.5 g, 4.1 mmol) at 0 °C. 3,4-Tetrahydroquinoline-1(2*H*)-carbamoyl chloride **2-112** (0.4 g, 2.0 mmol) was added at RT and the mixture was stirred at RT for 16 h. Purification by flash column chromatography eluting with (0 to 10% EtOAc in petrol) gave the *title compound* **2-277** (0.45 g, 78%). $\mathbf{R_f}$ 0.17 (5% EtOAc/petrol); $\mathbf{\nu_{max}}$ **/cm^{-1}** (film) 2987, 2901, 1699, 1393, 1065; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (1 H, d, *J* 8.3, H2), 7.39–7.36 (1 H, m, H14), 7.27–7.19 (3 H, m, H15, H16, H17), 7.17–7.13 (1 H, m, H3), 7.09 (1 H, d, *J* 7.5, H5), 7.01 (1 H, td, *J* 7.5, 1.2, H4), 5.26 (2 H, s, H11), 3.81–3.77 (2 H, m, H9), 2.78 (2 H, t, *J* 6.5, H7), 2.38 (3 H, s, H18), 1.95 (2 H, p, *J* 6.5, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.8 (C10), 138.3 (C12), 136.9 (C1), 134.5 (C6), 130.4 (ArC), 130.1 (C13), 129.1 (C14), 128.7 (C5), 128.5 (ArC), 126.1 (ArC), 126.1 (C3), 124.0 (C2), 123.8 (C4), 66.0 (C11), 45.1 (C9), 27.5 (C7), 23.6 (C8), 19.1 (C18); **HRMS** (ESI$^+$) m/z $C_{18}H_{19}NNaO_2^+$ requires: 304.1308; found: 304.1307.

1-(3,4-Tetrahydroquinolin-1(2H)-yl)-2-hydroxy-2-(o-tolyl)ethan-1-one (2-278)



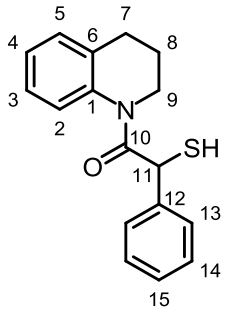
According to a modified **GP4**, to a solution of 2-methylbenzyl 3,4-Tetrahydroquinoline-1(*2H*)-carboxylate **2-277** (0.1 g, 0.36 mmol) in THF (5 mL) and DMPU (1.25 mL, 1:4 DMPU:THF) was added LDA (0.36 mL, 0.71 mmol, 2.0 M) dropwise at −78 °C. The reaction stirred for 2 h at −78 °C. Purification by flash column chromatography, eluting with (10 to 60% EtOAc in petrol) gave the *title compound* **2-278** as a colourless oil (45 mg, 45%). $\mathbf{R_f}$ 0.48 (30% EtOAc/petrol); $\mathbf{\nu_{max}}$ **/cm^{-1}** (film) 3399, 1652, 1023, 998; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (1 H, d, *J* 8.0, H2), 7.29–7.27 (1 H, m, ArH), 7.19–7.07 (6 H, m, ArH), 5.67 (1 H, d, *J* 6.7, H11), 5.39 (1 H, d, *J* 6.7, OH), 3.85 (1 H, dt, *J* 12.7, 6.4, H9$_a$), 3.32 (1 H, dt, *J* 12.7, 6.4, H9$_b$), 2.62 (1 H, dt, *J* 15.9, 6.4, H7$_a$), 2.48–2.41 (1 H, m, H7$_b$), 2.12 (3 H, s, H18), 1.87 (1 H, dp, *J* 13.0, 6.4, H8$_a$), 1.63 (1 H, dp, *J* 13.0, 6.4, H8$_b$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.0 (C10), 143.6 (C1), 143.58 (C13), 140.7 (C12), 135.3 (ArCH), 133.7 (ArCH), 132.8 (ArCH), 132.1 (ArCH), 131.0 (ArCH), 130.9 (ArCH), 130.2 (ArCH), 129.2 (C2), 73.8 (C11), 48.5 (C9), 31.0 (C7), 28.3 (C8), 23.5 (C18); **HRMS** (ESI$^+$) m/z $C_{18}H_{19}NNaO_2^+$ requires: 304.1308; found: 304.1309.

_S_-Benzyl 3,4-tetrahydroquinoline-1(2H)-carbothioate (2-279)



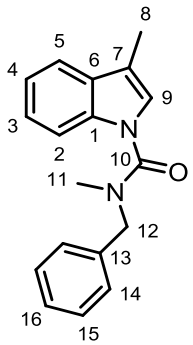
To a solution of benzyl thiol (0.58 mL, 4.9 mmol) in CH_2Cl_2 (10 mL) was added triethylamine (0.68 mL, 4.9 mmol). 3,4-hydroquinoline-1(2*H*)-carbamoyl chloride **2-112** (0.8 g, 4.1 mmol) was added and the reaction mixture was stirred at reflux for 16 h. The mixture was washed twice with aq. 1 M HCl, dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography, eluting with (5% EtOAc in petrol) to give the *title compound* **2-279** as colourless oil (1.0 g, 93%). $\mathbf{R_f}$ 0.48 (5% EtOAc/petrol); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 2929, 1654, 1489, 1296. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (1 H, d, *J* 8.1, H2), 7.39–7.36 (2 H, m, H13), 7.33–7.29 (2 H, m, H14), 7.26–7.22 (1 H, m, H15), 7.18 (1 H, td, *J* 7.5, 1.9, H3), 7.15–7.07 (2 H, m, H4, H5), 4.20 (2 H, s, H11), 3.82–3.78 (2 H, m, H9), 2.76 (2 H, t, *J* 6.6, H7), 1.99 (2 H, p, *J* 6.6, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.2 (C10), 138.0 (C12), 137.9 (C1), 131.8 (C6), 129.2 (C13), 128.8 (C4/C5), 128.7 (C14), 127.3 (C15), 126.1 (C3), 125.3 (C4/C5), 124.9 (C2), 45.3 (C9), 35.4 (C11), 27.0 (C7), 23.8 (C8); **HRMS** (ESI^+) m/z $C_{17}H_{17}NNaOS^+$ requires: 306.0923; found: 306.0922.

1-(3,4-Tetrahydroquinolin-1(2H)-yl)-2-mercapto-2-phenylethan-1-one (2-281)



To a solution of *S*-benzyl 3,4-dihydroquinoline-1(2H)-carbothioate **2-279** (0.1 g, 0.35 mmol) in THF (2.35 mL) and DMPU (0.22 mL, 1.8 mmol) was added LDA (0.36 mL, 0.71 mmol, 2.0 M) dropwise at −78 °C. The mixture was warmed to −60 °C and left to stir for 2 h. The reaction was quenched with propionic acid (0.08 mL, 1.1 mmol), followed by sat. NH_4Cl and warmed to RT. The aqueous phase was extracted three times with Et_2O and the combined organic phases were washed three times with water and once with brine. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography, eluting with (0 to 20% EtOAc in petrol) to give the *title compound* **2-281** as a colourless oil (41 mg, 41%). $\mathbf{R_f}$ 0.19 (5% EtOAc/petrol); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 2926, 2561, 1650, 1490, 1380; **^{1}H NMR** (500 MHz; DMSO-d_6, 373 K/100 °C) δ 7.40 (1 H, d, *J* 8.0, H2), 7.32–7.12 (8 H, m, ArH), 5.41 (1 H, d, *J* 7.7, H11), 3.85–3.80 (1 H, m, $H9_a$), 3.61 (1 H, dt, *J* 15.5, 6.6, $H9_b$), 3.20 (1 H, d, *J* 7.7, SH), 2.66–2.60 (1 H, m, $H7_a$), 2.49–2.44 (1 H, m, $H7_b$), 1.89–1.82 (1 H, m $H8_a$), 1.81–1.74 (1 H, m, $H8_b$); **^{13}C NMR** (126 MHz; DMSO-d_6, 373 K/ 100 °C) δ 170.3 (C10), 140.7 (C1), 139.4 (C12), 133.6 (C6), 128.9 (ArCH), 128.7 (ArCH), 128.0 (ArCH), 127.7 (ArCH), 126.4 (ArCH), 125.9 (ArCH), 124.8 (C2), 44.3 (C11), 44.3 (C9), 26.2 (C7), 23.8 (C8); **HRMS** (ESI^+) m/z $C_{17}H_{18}NOS^+$ requires: 284.1103; found: 284.1104.

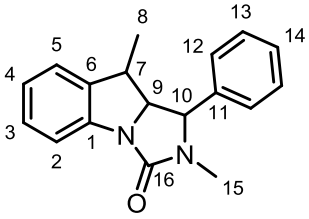
***N*-Benzyl-*N*,3-dimethyl-1*H*-indole-1-carboxamide (2-375)**



According to **GP8**, 3-methylindole (0.25 g, 1.9 mmol) in DMF (1 ml) was added to a suspension of NaH (0.15 g, 3.8 mmol) in DMF (1.0 mL) at 0 °C and stirred at 75 °C for 3 h. Addition of benzyl(methyl)carbamoyl chloride (0.53 g, 2.9 mmol) in DMF (0.7 mL) and purification by flash column chromatography eluting with (5 to 20% EtOAc in petrol) gave the *title compound* **2-375** as a pale yellow solid (0.35 g, 66%). $\mathbf{R_f}$ 0.26 (10% EtOAc/petrol); **Mp** 80-81 °C (CH_2Cl_2/*n*-pentane); $\mathbf{\nu_{max}/cm^{-1}}$ (film) 2917, 1673, 1451, 1394, 1336; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (1 H, br d, *J* 8.2, H2), 7.54 (1H, d, *J* 7.6, H5), 7.41–7.21 (6 H, m, H3, H14, H15, H16), 7.22 (1 H, td, *J* 7.6, 1.5, H4), 7.12 (1 H, br, H9), 4.67 (2 H, s, H12), 2.98 (3 H, s, H11), 2.29 (3 H, s, H8). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.6 (C10), 136.6 (C13), 136.2 (C1), 130.4 (C6), 129.0 (C15), 128.1 (C14), 128.0 (C16), 123.8 (C3), 123.4 (C9), 121.6 (C4), 119.2 (C5), 115.3

(C7), 113.8 (C2), 54.3 (C12), 35.5 (C11), 9.8 (C8); **HRMS** (ESI$^+$) m/z $C_{18}H_{19}N_2O^+$ requires: 279.1492; found: 279.1479.

2,9-Dimethyl-1-phenyl-1,2,9,9a-tetrahydro-3*H*-imidazo[1,5-a]indol-3-one (2-382)



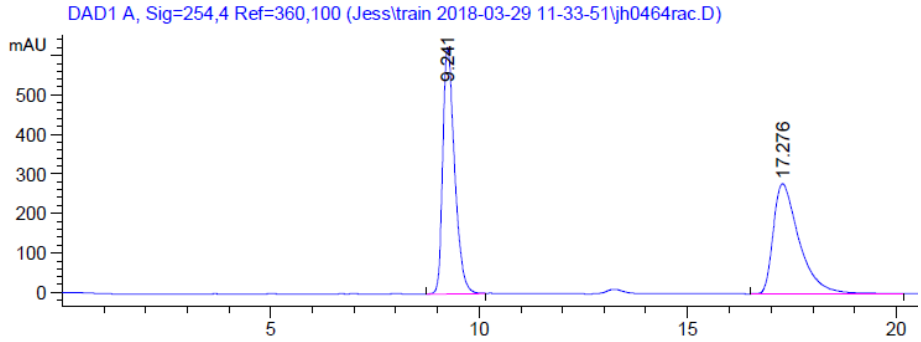
According to general procedure **GP9,** *N*-benzyl-*N*,3-dimethyl-1*H*-indole-1-carboxamide **2-375** (0.2 g, 0.72 mmol), DMPU (0.43 mL, 3.6 mmol) and LDA (0.72 mL, 1.4 mmol, 2.0 M) in THF (4.8 mL) were kept at −78 °C for 2 h. Purification by flash column chromatography eluting with (3 to 30% EtOAc in petrol) afforded the *title compound* **2-382** as a white solid as a single diastereomer (0.13 g, 64%) *d.r.* >20:1. $\mathbf{R_f}$ 0.24 (20% EtOAc/petrol); **Mp** 132 °C (CH_2Cl_2/*n*-pentane); $\boldsymbol{\nu_{max}}$ **/cm^{-1}** (film) 2959, 1709, 1478, 1390, 758; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 (1 H, br d, *J* 7.8, H2), 7.47–7.43 (2 H, m, H13), 7.40–7.36 (3 H, m, H12, H14), 7.27–7.23 (1 H, m, *J* 7.4, H3), 7.13 (1 H, br d, *J* 7.5, H5), 7.05 (1 H, td *J* 7.2, 1.0, H4), 4.42 (1 H, d, *J* 6.3, H10), 3.89 (1 H, dd, *J* 8.7, 6.3, H9), 3.48 (1 H, p, *J* 7.0, H7), 2.69 (3 H, s, H15), 1.31 (3 H, d, *J* 7.0, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.6 (C16), 142.6 (C1), 139.8 (C11), 136.7 (C6), 129.4 (C13), 128.7 (C14), 128.1 (C3), 126.9 (C12), 123.9 (C4), 123.5 (C5), 115.9 (C2), 73.6 (C9), 69.5 (C10), 44.2 (C7), 29.2 (C15), 18.0 (C8); **HRMS** (ESI$^+$) m/z $C_{18}H_{19}N_2O^+$, requires: 279.1492; found: 279.1497.

Following **GP9** on a 3.6 mmol scale, the *title compound* **2-382** was obtained as a white solid (0.79 g, 79%). *Spectroscopic data of **2-382** matches that previously stated for **2-382**.*

Attempted asymmetric deprotonation with chiral LDA derivative **2-417**:

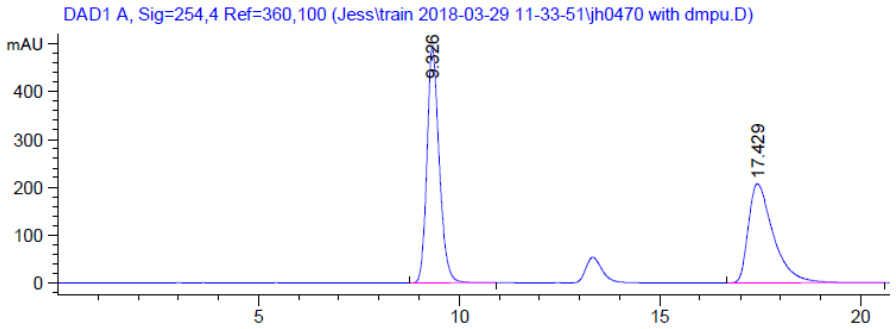
To a flame-dried flask was added (*S*)-(-)-*N*-Isopropyl-1-phenylethylamine hydrochloride (0.09 g, 0.43 mmol) and THF (0.72 mL). The solution was cooled to 0 °C and *n*-BuLi (0.54 mL, 0.86 mmol, 1.6 M in hexanes) was added dropwise and stirred at 0 °C for 20 mins before immediate use. According to general procedure **GP9,** *N*-Benzyl-*N*,3-dimethyl-1*H*-indole-1-carboxamide **2-375** (0.06 g, 0.22 mmol), DMPU (0.13 mL, 1.1 mmol) and chiral LDA derivative **2-417** (as above) in THF (1.43 mL) were kept at −78 °C for 2 h. Purification by flash column chromatography (eluting with 3% to 30% EtOAc in petrol) afforded the *title compound* **2-382** as a white solid (0.46 g, 76%). *Spectroscopic data of **2-382** matches that previously stated for **2-382**.* **HPLC** Racemic sample was prepared according to **GP9**. ChiralPak OD-H column, 1 mL/min, 25 °C, 230 nm, 10% *i*PrOH/*n*-hexane; t_R: 9.2 min, 17.3 min, *er* = 54:46

Racemic **2-382**:



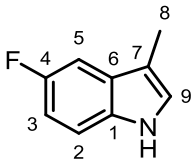
Peak #	Time / min	Area	Height	Width	Area / %
1	9.241	12261	623.55	0.299	50.6
2	17.276	11989	278.32	0.648	49.4

Reaction with chiral LDA derivative **2-417**:



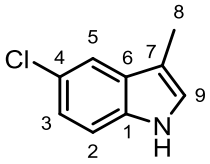
Peak #	Time / min	Area	Height	Width	Area / %
1	9.3	10461	494.55	0.3188	53.8
2	17.4	8971.4	207.05	0.6495	46.2

5-Fluoro-3-methyl-1*H*-indole (2-388)



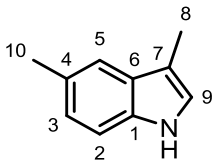
According to **GP7**, 5-fluoroindole (0.5 g, 3.7 mmol), DMF (1.4 mL, 19 mmol) and $POCl_3$ (0.42 mL, 4.4 mmol) were stirred at 40 °C for 2 h. 2 M NaOH solution (20 mL) was added and the solution was stirred at 90 °C for 1 h. The crude aldehyde was used in the next step without purification. To a solution of $LiAlH_4$ (0.21 g, 5.6 mmol) in THF (13.5 mL) was added the above crude aldehyde in THF (13.5 mL) dropwise at 0 °C. The reaction mixture was stirred at RT overnight. Purification by flash column chromatography eluting with (5 to 20% EtOAc in petrol) gave the *title compound* **2-388** (0.37 g, 66% over two steps).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (1 H, br s, NH), 7.29–7.23 (2 H, m, H2, H5), 7.05–7.02 (1 H, m, H9), 6.96 (1 H, td, *J* 9.0, 2.5, H3), 2.33 (3 H, d, *J* 1.1, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.9 (d, J_{CF} 234, C4) 132.9 (C1), 128.8 (d, J_{CF} 9.5, C6), 123.5 (C9), 112.1 (d, J_{CF} 4.8, C7), 111.6 (C3), 110.3 (C3), 103.9 (C5), 9.76 (C8); **^{19}F NMR** (376 MHz; $CDCl_3$) δ −125.2 (td, *J* 9.4, 4.3, F). *Data in accordance with literature.*[168]

5-Chloro-3-methyl-1*H*-indole (2-388)



According to **GP7**, 5-chloroindole (1.0 g, 6.6 mmol), DMF (2.6 mL, 33 mmol) and $POCl_3$ (0.74 mL, 8.0 mmol) were stirred at 40 °C for 2 h. 2 M NaOH solution (40 mL) was added and the solution was stirred at 90 °C for 1 h. The crude aldehyde was used in the next step without purification. To a solution of $LiAlH_4$ (0.38 g, 9.9 mmol) in THF (27 mL) was added the above crude aldehyde in THF (27 mL) dropwise at 0 °C. The reaction mixture was stirred at RT overnight. Purification by flash column chromatography eluting with (5 to 20% EtOAc in petrol) gave the *title compound* **2-388** (0.56 g, 51% over two steps). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (1 H, br s, NH), 7.58 (1 H, d, *J* 2.0, H5), 7.28 (1 H, d, *J* 8.5, H2), 7.17 (1 H, dd, *J* 8.5, 2.0, H3), 7.03–7.0 (1 H, m, H9), 2.33 (3 H, d, *J* 1.1, H8); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 134.7 (C1), 129.6 (C6), 125.0 (C4), 123.1 (C9), 122.3 (C3), 118.5 (C5), 112.0 (C2), 111.7 (C7), 9.67 (C8). *Data in accordance with literature.*[168]

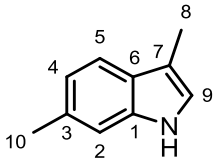
3,5-Dimethyl-1H-indole (2-388)



According to **GP7**, 5-methylindole (0.5 g, 3.8 mmol), DMF (1.5 mL, 19 mmol) and $POCl_3$ (0.3 mL, 4.6 mmol) were stirred at 40 °C for 2 h. 2 M NaOH solution (20 mL) was added and the solution stirred at 90 °C for 1 h. The crude aldehyde was used in the next step without purification. To a solution of $LiAlH_4$ (0.22 g, 5.7 mmol) in THF (13.5 mL) was added the above

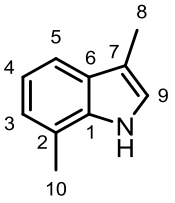
crude aldehyde in THF (13.5 mL) dropwise at 0 °C. The reaction mixture was stirred at RT overnight. Purification by flash column chromatography eluting with (5 to 20% EtOAc in petrol) gave the *title compound* **2-388** (0.28 g, 51% over two steps). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (1 H, br s, NH), 7.42–7.41 (1 H, m, H5), 7.28–7.25 (1 H, m, H2), 7.06 (1 H, dd, *J* 8.2, 1.6, H3), 6.97–6.95 (1 H, m, H9), 2.52 (3 H, s, H10), 2.36 (3 H, d, *J* 1.1, H8);**^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.7 (C1), 128.7 (C4), 128.5 (C6), 123.6 (C3), 121.9 (C9), 118.6 (C5), 111.4 (C4), 110.7 (C2), 21.6 (C10), 9.79 (C8). *Data in accordance with literature.*[168]

3,6-Dimethyl-1*H*-indole (2-388)



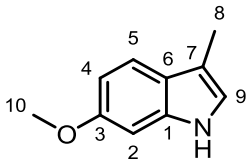
According to **GP7**, 5-methylindole (0.5 g, 3.8 mmol), DMF (1.5 mL, 19 mmol) and $POCl_3$ (0.43 mL, 4.6 mmol) were stirred at 40 °C for 2 h. 2 M NaOH solution (20 mL) was added and the solution stirred at 90 °C for 1 h. The crude aldehyde was used in the next step without purification.
To a solution of $LiAlH_4$ (0.21 g, 5.7 mmol) in THF (13.5 mL) was added the above crude aldehyde in THF (13.5 mL) dropwise at 0 °C. The reaction mixture was stirred at RT overnight. Purification by flash column chromatography eluting with (5 to 20% EtOAc in petrol) gave the *title compound* **2-388** (0.23 g, 41% over two steps). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (1 H, br s, NH), 7.47 (1 H, d, *J* 8.0, H5), 7.15–7.13 (1 H, m, H2), 6.99–6.96 (1 H, m, H4), 6.90–6.88 (1 H, m, H9), 2.48 (3 H, s, H10), 2.33 (3 H, d, *J* 0.8, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.9 (C1), 131.8 (C3), 126.3 (C6), 121.0 (C4, C9), 118.6 (C5), 111.7 (C7), 111.0 (C2), 21.9 (C10), 9.86 (C8). *Data in accordance with literature.*[168]

3,7-Dimethyl-1*H*-indole (2-388)



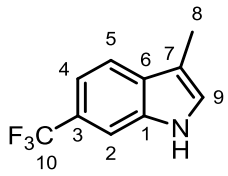
According to **GP7**, 5-methylindole (0.5 g, 3.3 mmol), DMF (1.5 mL, 19 mmol) and $POCl_3$ (0.43 mL, 4.6 mmol) were stirred at 40 °C for 2 h. 2 M NaOH solution (20 mL) was added and the solution stirred at 90 °C for 1 h. The crude aldehyde was used in the next step without purification.
To a solution of $LiAlH_4$ (0.22 g, 5.7 mmol) in THF (13.5 mL) was added the above crude aldehyde in THF (13.5 mL) dropwise at 0 °C. The reaction mixture was stirred at RT overnight. Purification by flash column chromatography eluting with (5 to 20% EtOAc in petrol) gave the *title compound* **2-388** (0.12 g, 22% over two steps).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (1 H, br s, NH), 7.38–7.36 (1 H, m, H5), 6.97 (1 H, t, *J* 7.4, H4), 6.93–6.90 (1 H, m, H3), 6.89–6.87 (1 H, m, H9), 2.39 (3 H, s, H10), 2.26 (3 H, d, *J* 1.1, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.0 (C1), 128.0 (C6), 122.5 (C3), 121.4 (C9), 120.2 (C2), 119.5 (C4), 116.7 (C5), 112.4 (C7), 16.7 (C10), 9.94 (C8). *Data in accordance with literature.*[209]

6-Methoxy-3-methyl-1*H*-indole (2-388)



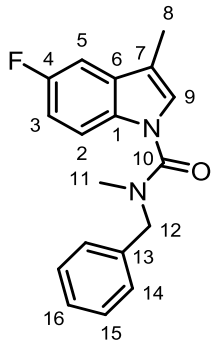
According to **GP7**, 6-methoxyindole (0.5 g, 3.4 mmol), DMF (1.3 mL, 17 mmol) and $POCl_3$ (0.38 mL, 4.1 mmol) were stirred at 40 °C for 2 h. 2 M NaOH solution (20 mL) was added and the solution was stirred at 90 °C for 1 h. The crude aldehyde was used in the next step without purification.
To a solution of $LiAlH_4$ (0.19 g, 5.1 mmol) in THF (13.5 mL) was added the above crude aldehyde in THF (13.5 mL) dropwise at 0 °C. The reaction mixture was stirred at RT overnight. Purification by flash column chromatography eluting with (5 to 20% EtOAc in petrol) gave the *title compound* **2-388** (0.30 g, 55% over two steps). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (1 H, br s, NH), 7.49–7.46 (1 H, m, H5), 6.89–6.82 (3 H, m, H2, H4, H9), 3.88 (3 H, s, H10), 2.34 (3 H, d, *J* 1.2, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.6 (C3), 137.7 (C1), 123.0 (C6), 120.4 (C9), 119.5 (C5), 111.8 (C7), 109.2 (C4), 94.7 (C2), 55.9 (C10), 9.86 (C8). *Data in accordance with literature.*[210]

3-Methyl-6-(trifluoromethyl)-1*H*-indole (2-388)



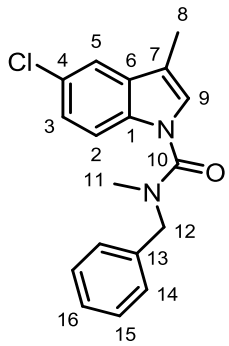
According to **GP7**, 6-(trifluoromethyl)-1*H*-indole (0.5 g, 2.7 mmol), DMF (1.1 mL, 14 mmol) and $POCl_3$ (0.30 mL, 3.2 mmol) were stirred at 40 °C for 2 h. 2 M NaOH solution (20 mL) was added and the solution was stirred at 90 °C for 1 h. The crude aldehyde was used in the next step without purification. To a solution of $LiAlH_4$ (0.15 g, 4.1 mmol) in THF (13.5 mL) was added the above crude aldehyde in THF (13.5 mL) dropwise at 0 °C. The reaction mixture was stirred at RT overnight. Purification by flash column chromatography eluting with (5 to 20% EtOAc in petrol) gave the *title compound* **2-388** (0.19 g, 35% over two steps). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (1 H, br s, NH), 7.67–7.63 (2 H, m, H4, H5), 7.38–7.34 (1 H, m, H2), 7.13–7.11 (1 H, m, H9), 2.36 (3 H, d, *J* 1.1, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.2 (C1), 130.7 (C6), 125.5 (q, J_{CF} 271, C10) 124.4 (C9), 124.1 (q, J_{CF} 31.6, C3) 119.4 (C5), 116.0 (q, J_{CF} 3.6, C2), 112.3 (C7), 108.6 (q, J_{CF} 4.4, C4), 9.68 (C8); **^{19}F NMR** (376 MHz; $CDCl_3$) δ −60.5 (s, CF_3). *Data in accordance with literature.*[3]

***N*-Benzyl-5-fluoro-N,3-dimethyl-1*H*-indole-1-carboxamide (2-390)**



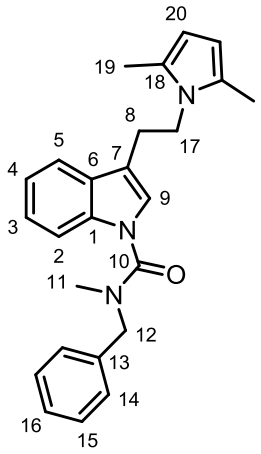
According to **GP8**, 5-fluoro-3-methyl-1*H*-indole (0.25 g, 1.7 mmol) in DMF (1 mL) was added to a suspension of NaH (0.13 g, 3.4 mmol) in DMF (1.0 mL) at 0 °C and stirred at 75 °C for 3 h. Addition of benzyl(methyl)carbamoyl chloride **2-15** (0.46 g, 2.5 mmol) in DMF (0.3 mL) and purification by flash column chromatography eluting with (10 to 60% EtOAc in petrol) gave the *title compound* **2-390** as a white solid (0.33 g, 67%). **R_f** 0.28 (20% EtOAc/petrol); **Mp** 116-117 °C (CH_2Cl_2/*n*-pentane); **ν_{max}/cm^{-1}** (film) 2918, 2855, 1674, 1446, 1394; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (1 H, dd, *J* 8.9, 4.5, H2), 7.42–7.32 (5 H, m, H14, H15, H16), 7.17 (1 H, dd, *J* 9.0, 2.6, H5), 7.14–7.13 (1 H, br, H9), 7.03 (1 H, td, *J* 9.0, 2.6, H3), 4.66 (2 H, s, H12), 2.98 (3 H, s, H11), 2.24 (3 H, d, *J* 1.2, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.9 (d, J_{CF} 238, C4), 155.3 (C10), 136.4 (C13), 132.7 (C1), 131.2 (d, J_{CF} 9.5, C6), 129.1 (C14/C15), 128.03 (C14/C15), 128.02 (C16), 124.8 (C9), 115.2 (d, J_{CF} 4.3, H7), 114.8 (d J_{CF} 9.3, C2), 111.8 (d J_{CF} 26, C3), 104.5 (d J_{CF} 24, C5), 54.3 (C12), 36.5 (C11), 9.7 (C8); **^{19}F NMR** (376 MHz; $CDCl_3$) δ −122.1 (1 H, td, *J* 9.1, 4.5, F); **HRMS** (ESI^+) m/z $C_{18}H_{18}FN_2O^+$, requires: 297.1398; found 297.1400.

***N*-Benzyl-5-chloro-N,3-dimethyl-1*H*-indole-1-carboxamide (2-391)**



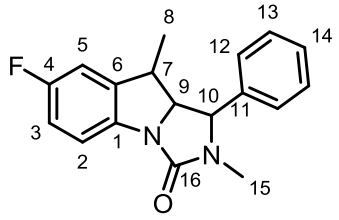
According to **GP8**, 5-chloro-3-methyl-1*H*-indole (0.25 g, 1.5 mmol) in DMF (1 mL) was added to a suspension of NaH (0.12 g, 3.0 mmol) in DMF (1.0 mL) at 0 °C and stirred at 75 °C for 3 h. Addition of benzyl(methyl)carbamoyl chloride **2-15** (0.45 g, 2.3 mmol) in DMF (0.2 mL) and purification by flash column chromatography eluting with (10 to 60% EtOAc in petrol) gave the *title compound* **2-391** as an orange oil (0.36 g, 77%). **R_f** 0.59 (30% EtOAc/petrol); **ν_{max}/cm^{-1}** (film) 2921, 2852, 1683, 1449, 1396; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (1 H, dd, *J* 8.8, 0.6, H2), 7.49 (1 H, dd, *J* 2.2, 0.6, H5), 7.41–7.30 (5 H, m, H14, H15, H16), 7.25 (1 H, dd, *J* 8.8, 2.2, H3), 7.12 (1 H, br q, *J* 1.2, H9), 4.65 (2 H, s, H12), 2.97 (3 H, s, H11), 2.24 (3 H, d, *J* 1.2, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.1 (C10), 136.3 (C13), 134.7 (C1), 131.6 (C6), 129.1 (C14/C15), 128.1 (C16), 128.0 (C14/C15), 127.4 (C4), 124.5 (C9), 124.1 (C3), 118.9 (C5), 114.89 (C7), 114.86 (C2), 54.3 (C12), 36.5 (C11), 9.7 (C8); **HRMS** (ESI^+) m/z $C_{18}H_{18}ClN_2O^+$, requires: 313.1102; found: 313.1116.

***N*-Benzyl-3-(2-(2,5-dimethyl-1*H*-pyrrol-1-yl)ethyl)-*N*-methyl-1*H*-indole-1-carboxamide (2-402)**



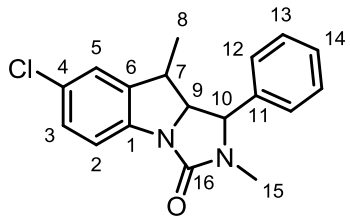
According to **GP8**, 3-(2-(2,5-dimethyl-1*H*-pyrrol-1-yl)ethyl)-1*H*-indole (0.17 g, 0.71 mmol) in DMF (0.5 mL) was added to a suspension of NaH (0.057 g, 1.4 mmol) in DMF (0.4 mL) at 0 °C and stirred at 75 °C for 3 h. Addition of benzyl(methyl)carbamoyl chloride **2-15** (0.196 g, 1.07 mmol) in DMF (0.2 mL) and purification by flash column chromatography eluting with (10 to 60% EtOAc in petrol) gave the *title compound* **2-402** as a colourless oil (0.13 g, 49%). $\mathbf{R_f}$ 0.38 (20% EtOAc/petrol); $\boldsymbol{\nu_{max}}$ **/cm^{-1}** (film) 2919, 1676, 1452, 1394, 1079; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (1 H, d, *J* 8.2, H2), 7.52 (1 H, d, *J* 7.8, H5), 7.42–7.30 (6 H, m, H3, H14, H15, H16), 7.26–7.21 (1 H, m H4), 6.99 (1 H, s, H9), 5.74 (2 H, s, H20), 4.63 (2 H, s, H12), 4.01 (2 H, t, *J* 7.6, H17), 3.00 (2 H, t, *J* 7.6, H8), 2.94 (3 H, s, H11), 2.13 (6 H, s, H19); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.2 (C10), 136.4 (C1), 136.1 (C13), 129.3 (C16), 129.0 (C14/C15), 128.1 (C14/C15), 128.0 (C18), 127.5 (C6), 124.1 (C3), 123.9 (C9), 121.9 (C4), 118.8 (C5), 115.9 (C7), 113.9 (C2), 105.5 (C20), 54.3 (C12), 43.7 (C17), 36.4 (C11), 26.7 (C8), 12.6 (C19); **HRMS** (ESI^+) m/z $C_{25}H_{28}N_3O^+$, requires; 386.2227 found 386.2233.

7-Fluoro-2,9-dimethyl-1-phenyl-1,2,9,9a-tetrahydro-3H-imidazo[1,5-a]indol-3-one (2-405)



According to **GP9,** *N*-benzyl-5-chloro-N,3-dimethyl-1*H*-indole-1-carboxamide **2-390** (0.15 g, 0.51 mmol), DMPU (0.31 mL, 2.6 mmol) and LDA (0.51 mL, 1.0 mmol, 2.0 M) in THF (3.4 mL) were kept at −78 °C for 2 h. Purification by flash column chromatography eluting with (10 to 50% EtOAc in petrol) afforded the *title compound* **2-405** as an inseparable mixture of diastereomers (89 mg, 60%) *d.r.* 10:1. $\mathbf{R_f}$ 0.19 (20% EtOAc/petrol); $\boldsymbol{\nu_{max}}$ **/cm^{-1}** (film) 2965, 2906, 1710, 1483, 1392; *Diastereomers are assigned as major diastereomer and minor diastereomer (Dia^{maj}/Dia^{min})* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47–7.35 (6 H, m, H2, H12, H13, H14), 6.95–6.90 (1 H, m, H3), 6.83 (1 H, ddd, *J* 8.3, 2.6, 1.2, H5), 4.60 (0.09 H, d, *J* 6.2, H10 Dia^{min}), 4.53 (0.09 H, dd, *J* 8.8, 6.2, H9 Dia^{min}), 4.42 (0.91 H, d, *J* 5.7, H10 Dia^{maj}), 3.91 (0.91 H, dd, *J* 8.9, 5.7, H9 Dia^{maj}), 3.47 (0.91 H, p, *J* 7.4, H7 Dia^{maj}), 3.36 (0.09 H, p, *J* 7.7, H7 Dia^{min}), 2.69 (2.7 H, s, H15 Dia^{maj}), 2.67 (0.27 H, s, H15 Dia^{min}), 1.31 (3 H, d, *J* 6.9, H8 Dia$^{maj+min}$); *Signals reported are for the major diastereomer only.* **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.1 (d, J_{CF} 241, C4), 159.6 (C16), 139.6 (C11), 138.68 (d, J_{CF} 2.0, C1), 138.62 (d, J_{CF} 8.0, C6), 128.7 (C14) 126.7 (C12/C13) 116.8 (d, J_{CF} 8.6, C2) 114.4 (d, J_{CF} 24, C3) 110.8 (d, J_{CF} 24, C5) 73.9 (C9), 68.8 (C10), 44.4 (C7), 29.0 (C15), 17.5 (C8); **^{19}F NMR** (376 MHz; $CDCl_3$) δ −119.3 (1 H, td, *J* 8.5, 4.5, F); **HRMS** (ESI^+) m/z $C_{18}H_{18}FN_2O^+$ requires: 297.1398; found: 297.1419.

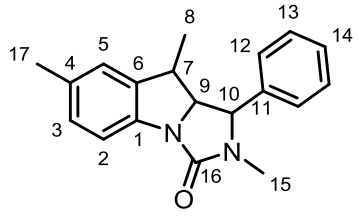
7-Chloro-2,9-dimethyl-1-phenyl-1,2,9,9a-tetrahydro-3H-imidazo[1,5-a]indol-3-one (2-406)



According to **GP9,** *N*-benzyl-5-chloro-N,3-dimethyl-1*H*-indole-1-carboxamide **2-391** (0.15 g, 0.48 mmol), DMPU (0.29 mL, 2.4 mmol) and LDA (0.48 mL, 0.96 mmol, 2.0 M) in THF (3.2 mL) were kept at −78 °C for 2 h. Purification by flash column chromatography eluting with (10 to 60% EtOAc in petrol) afforded the *title compound* **2-406** as a white solid as an inseparable mixture of diastereomers (65 mg, 43%) *d.r.* 10:1. $\mathbf{R_f}$ 0.19 (20% EtOAc/petrol); **Mp** 136-137 °C (CH_2Cl_2/*n*-pentane); $\boldsymbol{\nu_{max}}$ **/cm^{-1}** (film) 2961, 2910, 1711, 1476, 1390; *Diastereomers are assigned as major diastereomer and minor diastereomer (Dia^{maj}/Dia^{min}).* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46–7.36 (6 H, m, H2, H12, H13, H14), 7.20 (1 H, dd, *J* 8.4, 2.1, H3), 7.12–7.11 (0.09 H, br, H5 Dia^{min}), 7.11–7.08 (0.91, br, H5 Dia^{maj}), 4.61 (0.09 H, d, *J* 6.8, H10 Dia^{min}), 4.52 (0.09 H, dd, *J* 8.9, 6.7, H9 Dia^{min}), 4.42 (0.91 H, d, *J* 6.1, H10 Dia^{maj}), 3.90 (0.91 H, dd, *J* 8.8, 6.1, H9 Dia^{maj}), 3.46 (0.91 H, p, *J* 7.0, H7 Dia^{maj}), 3.36 (0.09 H, p, *J* 7.8, H7 Dia^{min}), 2.68 (2.73 H, s, H15 Dia^{maj}), 2.67 (0.27 H, s, H15 Dia^{min}), 1.30 (3 H,

d, *J* 7.0, H8 Dia^{min}+Dia^{maj}). *Signals reported are for the major diastereomer only*. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3 (C16), 141.4 (C11), 139.5 (C1), 138.7 (C6), 129.5 (C12/C13), 129.1 (C4), 128.9 (C14), 128.1 (C3), 126.8 (C12/C13), 123.9 (C5), 116.8 (C2), 73.7 (C9), 69.3 (C10), 44.3 (C7), 29.2 (C15), 17.8 (C8); **HRMS** (ESI$^+$) m/z $C_{18}H_{18}ClN_2O^+$ requires: 313.1102; found: 313.1108.

2,7,9-Trimethyl-1-phenyl-1,2,9,9a-tetrahydro-*3H*-imidazo[1,5-*a*]indol-3-one (2-407)



According to **GP9,** *N*-benzyl-N,3,5-trimethyl-1H-indole-1-carboxamide **2-392** (0.15 g, 0.51 mmol), DMPU (0.31 mL, 2.6 mmol) and LDA (0.52 mL, 1.0 mmol, 2.0 M) in THF (3.4 mL) were kept at −78 °C for 2 h. Purification by flash column chromatography eluting with (5 to 50% EtOAc in petrol) afforded the *title compound* **2-407** as a white solid as a single diastereomer (80 mg, 53%) *d.r.* >20:1. **R_f** 0.19 (20% EtOAc/petrol); **Mp** 112–113 °C (CH_2Cl_2/*n*-pentane); **ν_{max} /cm^{-1}** (film) 2924, 1708, 1612, 1489, 1390; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46–7.37 (6 H, m, H2, H12, H13, H14), 7.05 (1 H, d, *J* 8.0, H3), 6.95 (1 H, s, H5), 4.42 (1 H, d, *J* 6.0, H10), 3.87 (1 H, dd, *J* 8.8, 6.0, H9), 3.44 (1 H, p, *J* 7.0, H7), 2.68 (3 H, s, H15), 2.32 (3 H, s, H17), 1.30 (3 H, d, *J* 7.0, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.8 (C16), 140.3 (C11), 139.9 (C1), 136.8 (C4), 133.5 (C6), 129.4 (C12/C13), 128.7 (C14), 128.5 (C3), 126.8 (C12/C13), 124.1 (C5), 115.6 (C2), 73.8 (C9), 69.2 (C10), 44.3 (C7), 29.1 (C15), 21.3 (C17), 17.8 (C8); **HRMS** (ESI$^+$) m/z $C_{19}H_{21}N_2O^+$ requires: 293.1648; found: 293.1647; **X-ray** crystallography data:

Bond precision: C-C = 0.0040 A Wavelength=0.71073

Cell: a=12.3834(11) b=9.0000(9) c=14.3130(13)
alpha=90 beta=102.337(6) gamma=90

Temperature: 100 K

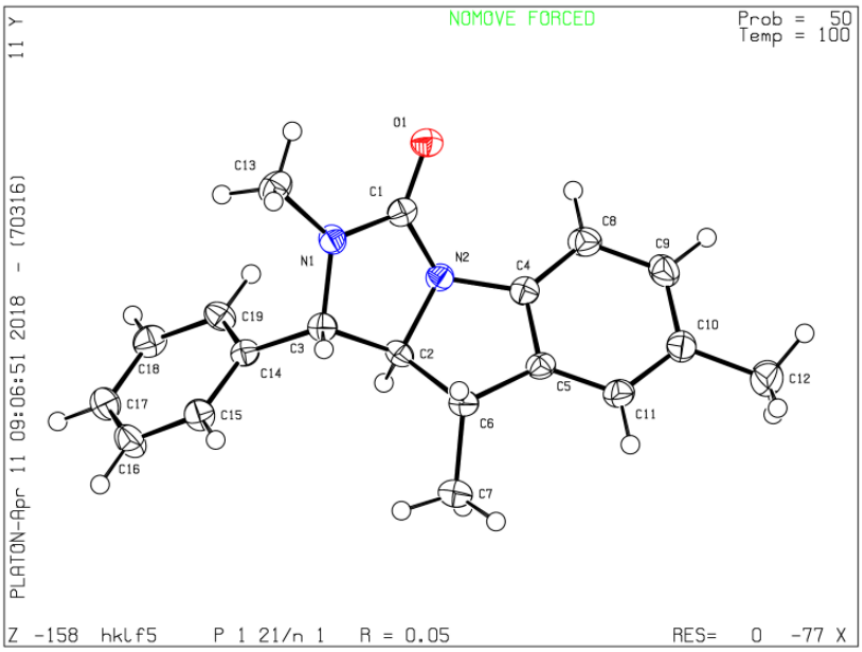
	Calculated	Reported
Volume	1558.4(3)	1558.4(3)
Space group	P 21/n	P 1 21/n 1
Hall group	-P 2yn	-P 2yn
Moiety formula	C19 H20 N2 O	C19 H20 N2 O
Sum formula	C19 H20 N2 O	C19 H20 N2 O
Mr	292.37	292.37
Dx,g cm-3	1.246	1.246
Z	4	4
Mu (mm-1)	0.078	0.078
F000	624.0	624.0
F000'	624.23	
h,k,lmax	14,10,17	14,10,17
Nref	2852	2853
Tmin,Tmax	0.975,0.986	0.557,0.745
Tmin'	0.975	

Correction method= # Reported T Limits: Tmin=0.557 Tmax=0.745 AbsCorr = MULTI-SCAN

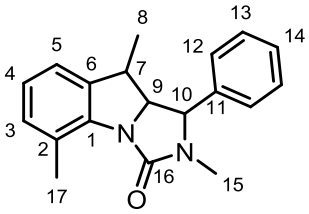
Data completeness= 1.000 Theta(max)= 25.349

R(reflections)= 0.0529(1913) wR2(reflections)= 0.1200(2853)

S = 1.031 Npar= 203

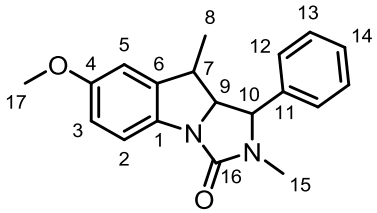


2,5,9-Trimethyl-1-phenyl-1,2,9,9a-tetrahydro-3H-imidazo[1,5-a]indol-3-one (2-409)



According to **GP9,** *N*-benzyl-*N*,3,7-trimethyl-1*H*-indole-1-carboxamide **2-394,** (85 mg, 0.29 mmol), DMPU (0.18 mL, 1.5 mmol) and LDA (0.29 mL, 0.58 mmol, 2.0 M) in THF (1.9 mL) were kept at −78 °C for 2 h. Purification by flash column chromatography eluting with (10 to 40% EtOAc in petrol) afforded the *title compound* **2-409** as a colourless oil as a single diastereomer (15 mg, 18%) *d.r.* >20:1. $\mathbf{R_f}$ 0.23 (20% EtOAc/petrol); $\boldsymbol{\nu_{max}}$ **/cm^{-1}** (film) 3029, 2957, 2921, 1708, 1391; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48–7.39 (5 H, m, H12, H13, H14), 7.11–7.09 (1 H, br m, H5), 7.05 (1 H, t, *J* 7.4, H4), 6.97 (1 H, d, *J* 7.4, H3), 4.45 (1 H, d, *J* 3.2, H10), 3.84 (1 H, dd, *J* 9.9, 3.2, H9), 3.52–3.44 (1 H, m, H7), 2.76 (3 H, s, H15), 2.63 (3 H, s, H17), 1.36 (3 H, d, *J* 6.8, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.5 (C16), 142.4 (C11), 140.7 (C1), 138.0 (C6), 130.1 (C5), 129.4 (C12/C13), 129.3 (C2), 128.6 (C14), 126.7 (C12/C13), 125.3 (C4), 120.2 (C3), 75.0 (C9), 66.0 (C10), 44.5 (C7), 29.2 (C15), 19.0 (C17), 16.4 (C8); **HRMS** (ESI^+) m/z $C_{19}H_{20}N_2NaO^+$ requires: 315.1468; found: 315.1476.

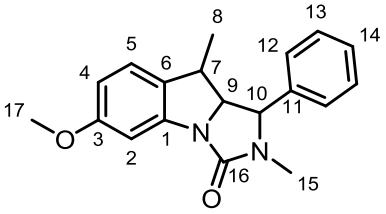
7-Methoxy-2,9-dimethyl-1-phenyl-1,2,9,9a-tetrahydro-3*H*-imidazo[1,5-*a*]indol-3-one (2-410)



According to **GP9,** *N*-benzyl-5-methoxy-*N*,3-dimethyl-1H-indole-1-carboxamide **2-395,** (97 mg, 0.31 mmol), DMPU (0.19 mL, 1.6 mmol) and LDA (0.32 mL, 0.63 mmol, 2.0 M) in THF (2.1 mL) were kept at −78 °C for 2 h. Purification by flash column chromatography eluting with (10 to 60% EtOAc in petrol) afforded the *title compound* **2-410** as a colourless oil as a single diastereomer (54 mg, 56%) *d.r.* >20:1. $\mathbf{R_f}$ 0.16 (30% EtOAc/petrol); $\boldsymbol{\nu_{max}}$ **/cm^{-1}** (film) 2957, 1708, 1488, 1274, 1232; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45–7.36 (6 H, m, H2, H12, H13, H14), 6.79–6.57 (1 H, m, H3), 6.71–6.68 (1 H, m, H5), 4.41 (1 H, d, *J* 5.5, H10), 3.89–3.85 (1 H, m, H9), 3.78 (3 H, s, H17), 3.44 (1 H, p, *J* 7.4, H7), 2.68 (3 H, s, H15), 1.30 (3 H, d, *J* 7.0, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.1 (C16), 157.1 (C4), 140.1 (C11), 138.3 (C6), 136.4 (C1), 129.4 (C12/C13), 128.7 (C14), 126.8

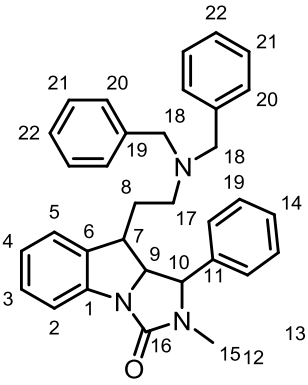
(C12/C13), 116.7 (C2), 112.6 (C3), 110.1 (C5), 74.1 (C9), 68.8 (C10), 55.9 (C17), 44.6 (C7), 29.1 (C15), 17.6 (C8); **HRMS** (ESI$^+$) m/z $C_{19}H_{21}N_2O_2^+$ requires: 309.1598; found: 309.1613.

6-Methoxy-2,9-dimethyl-1-phenyl-1,2,9,9a-tetrahydro-3*H*-imidazo[1,5-a]indol-3-one (2-411)



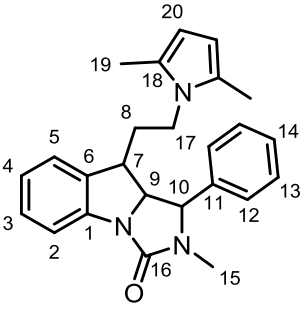
According to **GP9**, *N*-benzyl-6-methoxy-N,3-dimethyl-1H-indole-1-carboxamide X, (155 mg, 0.5 mmol), DMPU (0.30 mL, 2.5 mmol) and LDA (0.51 mL, 1.0 mmol, 2.0 M) in THF (3.4 mL) were kept at −78 °C for 2 h. Purification by flash column chromatography eluting with (10 to 60% EtOAc in petrol) afforded the *title compound* **2-411** as a white solid as a single diastereomer (115 mg, 74%) *d.r.* >20:1. $\mathbf{R}_f$ 0.21 (20% EtOAc/petrol); **Mp** 124–125 °C (CH_2Cl_2/*n*-pentane); ν_{max} **/cm^{-1}** (film) 2958, 1711, 1615, 1591, 1494; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46–7.42 (2 H, m, ArH), 7.40–7.35 (3 H, m, ArH), 7.10 (1 H, d, *J* 2.4, H2), 7.01–6.98 (1 H, m, H5), 6.59 (1 H, dd, *J* 8.2, 2.4, H4), 4.41 (1 H, d, *J* 6.5, H10), 3.88 (1 H, dd, *J* 8.5, 6.5, H9), 3.82 (3 H, s, H17), 3.41 (1 H, p, *J* 7.0, H7), 2.67 (3 H, s, H15), 1.26 (3 H, d, *J* 7.0, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.2 (C16), 159.5 (C3), 143.7 (C1), 139.6 (C11), 129.4 (C12/C13), 128.7, (C14) 128.5 (C6), 126.9 (C12/C13), 123.8 (C5), 110.1 (C4), 101.5 (C2), 74.2 (C9), 69.7 (C10), 55.8 (C17), 43.6 (C7), 29.2 (C15), 18.3 (C8); **HRMS** (ESI$^+$) m/z $C_{19}H_{21}N_2O_2^+$ requires: 309.1597; found: 309.1608.

9-(2-(Dibenzylamino)ethyl)-2-methyl-1-phenyl-1,2,9,9a-tetrahydro-3*H*-imidazo[1,5-*a*]indol-3-one (2-414)



According to **GP9,** *N*-benzyl-3-(2-(dibenzylamino)ethyl)-*N*-methyl-1H-indole-1-carboxamide **2-401,** (60 mg, 0.12 mmol), DMPU (0.075 mL, 0.62 mmol) and LDA (0.125 mL, 0.25 mmol, 2.0 M) in THF (0.8 mL) were kept at −78 °C for 2 h. Purification by flash column chromatography eluting with (10 to 50% EtOAc in petrol) afforded the *title compound* **2-414** as a white solid as a single diastereomer (46 mg, 79%) *d.r.* >20:1. $\mathbf{R}_f$ 0.25 (20% EtOAc/petrol); **Mp** 143–144 °C (CH_2Cl_2/*n*-pentane); ν_{max} **/cm^{-1}** (film) 3027, 2923, 2798, 2244, 1709; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (1 H, d, *J* 7.9, H2), 7.39–7.18 (17 H, m, ArH), 6.96 (1 H, t, *J* 7.3, ArH), 6.86 (1 H, d, *J* 7.5, ArH), 4.18–4.16 (1 H, m, H10), 3.94–3.90 (1 H, m, H9), 3.54–3.39 (5 H, m, H7, H18), 2.59 (3 H, s, H15), 2.41–2.34 (1 H, m, H17$_a$), 2.29–2.20 (1 H, m, H17$_b$), 2.14–2.04 (1 H, m, H8$_a$), 1.69–1.57 (1 H, m, H8$_b$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.7 (C16), 143.0 (C11), 139.5 (C1), 139.1 (C19), 135.5 (C6), 129.3, 128.8, 128.4, 128.1, 127.4, 127.1, 124.0, 123.8 (ArC), 115.7 (C2), 72.6 (C9), 69.7 (C10), 58.5 (C18), 51.7 (C17), 46.9 (C7), 32.1 (C8), 29.0 (C15); **HRMS** (ESI$^+$) m/z $C_{33}H_{34}N_3O^+$ requires: 488.2696; found: 488.2700.

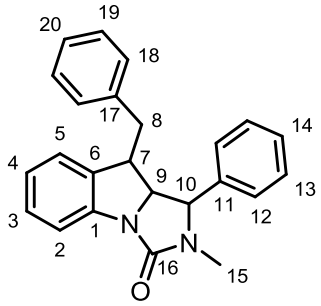
9-(2-(2,5-dimethyl-1*H*-pyrrol-1-yl)ethyl)-2-methyl-1-phenyl-1,2,9,9a-tetrahydro-3*H*-imidazo[1,5-*a*]indol-3-one (2-415)



According to **GP9**, *N*-benzyl-3-(2-(2,5-dimethyl-1*H*-pyrrol-1-yl)ethyl)-*N*-methyl-1*H*-indole-1-carboxamide **2-402**, (80 mg, 0.21 mmol), DMPU (0.13 mL, 1.04 mmol) and LDA (0.21 mL, 0.42 mmol, 2.0 M) in THF (1.4 mL) were kept at −78 °C for 2 h. Purification by flash column chromatography eluting with (10 to 60% EtOAc in petrol) afforded the *title compound* **2-415** as a colourless oil a single diastereomer (59 mg, 74%) *d.r.* >20:1. $\mathbf{R}_f$ 0.15 (20% EtOAc/petrol); ν_{max} **/cm^{-1}** (film) 2913, 2237, 1709, 1602, 1480; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56–7.53 (1 H, m, H2), 7.48–7.40 (5 H, m ArH), 7.30–7.26 (1 H, m, H4), 7.14 (1 H, d, *J* 7.4, H5), 7.05 (1 H, td, *J* 7.5, 1.1, H4), 5.69 (2 H, s, H20), 4.40 (1 H, d, *J* 7.1, H10), 4.17–4.12 (1 H, m, H9), 3.60 (1 H, ddd, *J* 14.2, 12.2, 4.8, H17$_a$), 3.46 (1 H, td, *J* 8.9, 3.8, H7), 3.28 (1 H, ddd, *J* 14.2, 12.5, 4.8, H17$_b$),

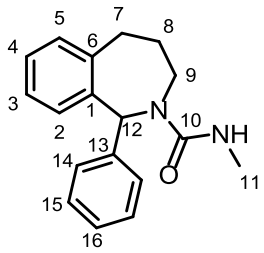
2.66 (3 H, s, H15), 2.23–2.16 (1 H, m, H8$_a$), 1.94 (6 H, s, H19), 1.76–1.66 (1 H, m, H8$_b$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3 (C16), 142.6 (C1), 138.8 (C11), 134.0 (C6), 129.7 (C12/C13), 129.4 (C14), 128.7 (C3), 127.6 (C12/C13), 127.0 (C18), 123.9 (C4), 123.8 (C5), 115.6 (C2), 105.4 (C20), 72.4 (C9), 70.1 (C10), 47.3 (C7), 41.6 (C17), 35.0 (C8), 29.1 (C15), 12.2 (C19); **HRMS** (ESI$^+$) m/z $C_{25}H_{28}N_3O^+$ requires: 386.2227; found: 386.2244.

9-Benzyl-2-methyl-1-phenyl-1,2,9,9a-tetrahydro-3*H*-imidazo[1,5-a]indol-3-one (2-416)



According to **GP9**, *N*,3-dibenzyl-*N*-methyl-1*H*-indole-1-carboxamide **2-403**, (50 mg, 0.14 mmol), DMPU (0.09 mL, 0.71 mmol) and LDA (0.14 mL, 0.28 mmol, 2.0 M) in THF (0.94 mL) were kept at −78 °C for 2 h. Purification by flash column chromatography (eluting with 10 to 60% EtOAc in petrol) afforded the *title compound* **2-416** as a colourless oil as an inseparable mixture of diastereomers (32 mg, 64%) *d.r*. 10:1. **R$_f$** 0.27 (20% EtOAc/petrol); **ν$_{max}$ /cm^{-1}** (film) 3028, 2912, 1708, 1602, 1478. *Diastereomers are assigned as major diastereomer and minor diastereomer (Dia^{maj}/Dia^{min}).* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (1 H, d, *J* 7.8, H2), 7.29–7.01 (11 H, m, ArH), 6.84 (2 H, d, *J* 6.5, H18/H19), 4.69 (0.09 H, d, *J* 6.2, H10 Dia^{min}), 4.64–4.61 (0.09 H, m, H9 Dia^{min}) 4.12 (0.91 H, dd, *J* 8.4, 5.4, H9 Dia^{maj}), 4.01 (0.91 H, d, *J* 5.4, H10 Dia^{maj}), 3.81 (0.91 H, td, *J* 9.1, 5.1, H7 Dia^{maj}), 3.70–3.62 (0.09 H, m, H7 Dia^{min}), 3.36 (1 H, dd, *J* 14.0, 5.1, H8$_a$), 2.64 (1 H, dd, *J* 14.0, 9.8, H8$_b$), 2.53 (3 H, s, H15). *Signals reported are for the major diastereomer only.* **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.7 (C16), 143.4 (C1), 138.9 (C11), 138.4 (C17), 135.1 (C6), 1291 (ArCH), 128.9 (ArCH), 128.9 (ArCH), 128.4 (ArCH), 128.3 (ArCH), 127.0 (ArCH), 126.7 (C18/C19), 124.1 (ArCH), 123.8 (ArCH), 116.5 (C2), 72.0 (C10), 68.8 (C9), 51.9 (C7), 40.1 (C8), 28.8 (C15); **HRMS** (ESI$^+$) m/z $C_{24}H_{23}N_2O^+$ requires: 355.1805; found: 355.1816.

(±)-*N*-Methyl-1-phenyl-1,3,4,5-tetrahydro-2*H*-benzo[c]azepine-2-carboxamide (2-431)



According to **GP10**, 2-methyl-1-phenyl-1,2,4,5,6,7-hexahydro-3*H*-benzo[e][1,3]diazonin-3-one **2-73** (100 mg, 0.36 mmol) and *p*-toluenesulfonic acid monohydrate (6.8 mg, 36 μmol) in CH_2Cl_2 (3.6 mL) were stirred for 1 h at RT. Purification by flash column chromatography eluting (15 to 100% EtOAc in petrol) gave the *title compound* **2-431** as a white solid (70 mg, 70%). **R$_f$** 0.20 (60% EtOAc/petrol); **Mp** 200–201 °C (CH_2Cl_2/*n*-pentane); **ν$_{max}$ /cm^{-1}** (film) 3290, 2933, 1608, 1538, 1284; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.39–7.09 (8 H, m, ArH), 6.95 (1 H, d, *J* 7.4, ArH), 6.35 (1 H, br s, H12), 4.44 (1 H, q, *J* 4.4, NH), 3.85 (1 H, dt, *J* 14.8, 3.5, H9$_a$), 3.15 (1 H, br t, *J* 14.8, H9$_b$), 2.80 (2 H, br t, *J* 6.2, H7), 2.77 (3 H, d, *J* 4.4, H11), 2.00–1.80 (1 H, m, H8$_a$), 1.67–1.53 (1 H, m, H8$_b$); **^{13}C NMR** (101 MHz; $CDCl_3$) δ 159.0 (C10), 140.8 (C1), 140.1 (C13), 138.9 (C6), 130.5 (ArCH), 130.1 (ArCH), 128.9 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 127.5 (ArCH), 126.6 (ArCH), 64.1 (C12), 43.5 (C9), 34.0 (C7), 28.0 (C11), 27.3 (C8); **HRMS** (ESI$^+$) m/z $C_{18}H_{20}N_2NaO^+$ requires: 303.1468; found: 303.1467; **X-ray** crystallography data:

Bond precision:	C-C = 0.0015 A		Wavelength=0.71073
Cell:	a=8.3785(2)	b=16.8762(4)	c=20.7555(6)
	alpha=90	beta=90	gamma=90
Temperature:	100 K		
	Calculated		Reported
Volume	2934.77(13)		2934.77(13)
Space group	P b c a		P b c a
Hall group	-P 2ac 2ab		-P 2ac 2ab
Moiety formula	C18 H20 N2 O		C18 H20 N2 O
Sum formula	C18 H20 N2 O		C18 H20 N2 O
Mr	280.36		280.36

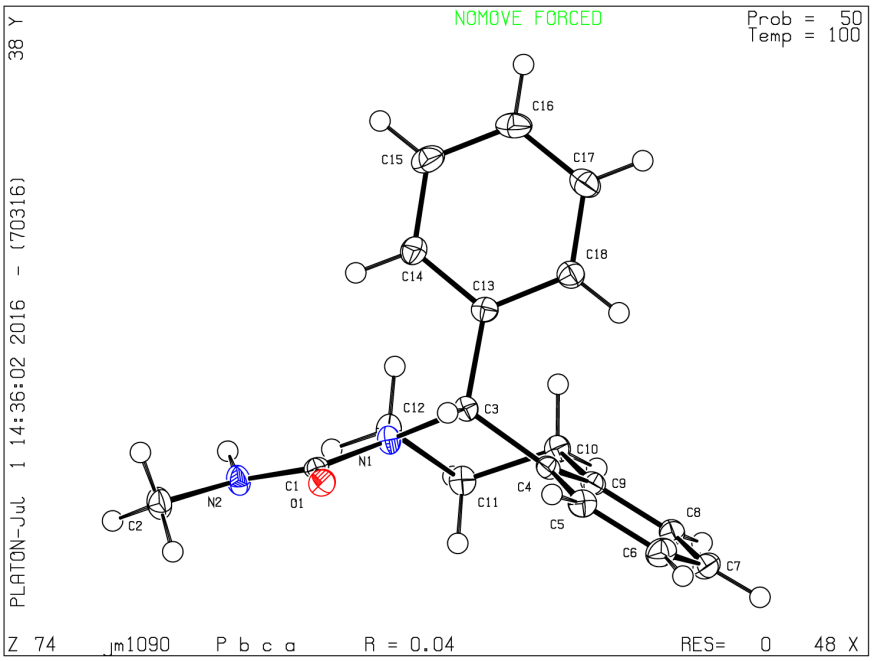
Dx,g cm^{-3}	1.269	1.269
Z	8	8
Mu (mm^{-1})	0.079	0.079
F000	1200.0	1200.0
F000'	1200.44	
h,k,lmax	11,23,29	11,23,29
Nref	4322	4321
Tmin,Tmax	0.961,0.979	0.674,0.746
Tmin'	0.961	

Correction method= # Reported T Limits: Tmin=0.674 Tmax=0.746 AbsCorr = MULTI-SCAN

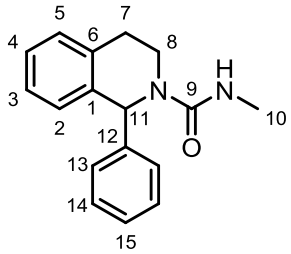
Data completeness= 1.000 Theta(max)= 30.107

R(reflections)= 0.0390(3537) wR2(reflections)= 0.1044(4321)

S = 1.014 Npar= 195

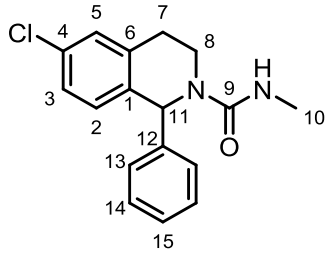


(±)-*N*-Methyl-1-phenyl-3,4-tetrahydroisoquinoline-2(1*H*)-carboxamide (2-454)



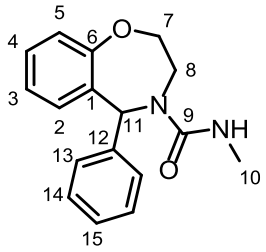
According to **GP10**, *N*-benzyl-*N*-methylindoline-1-carboxamide **2-66** (25 mg, 9 μmol) and *p*-toluenesulfonic acid monohydrate (36 mg, 18 μmol) in CH_2Cl_2 (0.9 mL) were stirred for 12 h at RT. Purification by flash column chromatography eluting (15 to 100% EtOAc in petrol) gave the *title compound* **2-454** as a white solid (13 mg, 52%). $\mathbf{R_f}$ 0.20 (60% EtOAc/petrol); **Mp** 164–165 °C (CH_2Cl_2/*n*-pentane); $\mathbf{\nu_{max}}$ **/cm^{-1}** (film) 3368, 1615, 1540, 1487, 1242, 702; **^{1}H NMR** (500 MHz; $CDCl_3$) δ 7.31–7.12 (9 H, m, ArH), 6.35 (1 H, s, H11), 4.49 (1 H, q, *J* 4.5, NH), 3.64–3.52 (2 H, m, H8), 2.89 (1 H, ddd, *J* 15.8, 6.9, 5.4, $H7_a$), 2.83 (3 H, d, *J* 4.5, H10), 2.79 (3 H, ddd, *J* 15.8, 6.6, 5.5, $H7_b$); **^{13}C NMR** (126 MHz; $CDCl_3$) δ 158.5 (C9), 143.0 (C1), 136.8 (C12), 135.3 (C6), 128.6 (ArCH), 128.5 (ArCH), 128.3 (ArCH), 127.6 (ArCH), 127.29 (ArCH), 127.25 (C4), 126.5 (C2), 57.9 (C11), 40.3 (C8), 28.4 (C7), 27.9 (C10); **HRMS** (ESI^+) m/z $C_{17}H_{18}N_2NaO^+$ requires: 289.1311; found: 289.1317.

(±)-6-Chloro-*N*-methyl-1-phenyl-3,4-tetrahydroisoquinoline-2(1*H*)-carboxamide (2-455)



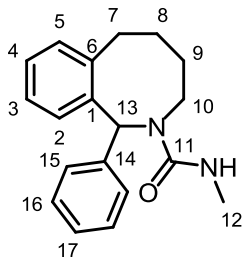
According to **GP10**, 8-chloro-2-methyl-1-phenyl-1,4,5,6-tetrahydrobenzo[e][1,3]diazocin-3(2*H*)-one **2-72** (49 mg, 0.16 mmol) and *p*-toluenesulfonic acid monohydrate (2.8 mg, 16 μmol) in CH_2Cl_2 (1.6 mL) were stirred for 1 h at RT. Purification by flash column chromatography eluting (12 to 100% EtOAc in petrol) gave the *title compound* **2-455** as a white solid (41 mg, 84%). $\mathbf{R_f}$ 0.30 (50% EtOAc/petrol); **Mp** 174–175 °C (CH_2Cl_2/*n*-pentane); $\mathbf{\nu_{max}}$ **/cm^{-1}** (film) 3359, 1620, 1539, 1487, 1242; **^{1}H NMR** (500 MHz; $CDCl_3$) δ 7.34–7.13 (7 H, m, ArH), 7.07 (1 H, d, *J* 8.8, ArH), 6.39 (1 H, s, H11), 4.75 (1 H, q, *J* 4.7, NH), 3.60 (1 H, dt, *J* 12.4, 5.8, H8$_a$), 3.48 (1 H, ddd, *J* 12.4, 8.1, 5.0, H8$_b$), 2.90–2.84 (1 H, m, H7$_a$), 2.82 (3 H, d, *J* 4.7, H10), 2.73 (1 H, dt, *J* 16.0, 5.8, H7$_b$); **^{13}C NMR** (126 MHz; $CDCl_3$) δ 158.3 (C9), 142.4 (C1), 137.1 (C12), 135.1 (C6), 132.7 (C4), 129.6 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 127.6 (ArCH), 127.4 (ArCH), 126.6 (ArCH), 57.1 (C11), 39.4 (C8), 28.2 (C7), 27.9 (C10); **HRMS** (ESI$^+$) m/z $C_{17}H_{17}{}^{35}ClN_2NaO^+$ requires: 323.0922; found: 323.0918 and $C_{17}H_{17}{}^{37}ClN_2NaO^+$ requires: 325.0892; found: 325.0895.

(±)-*N*-Methyl-5-phenyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5*H*)-carboxamide (2-462)



According to **GP10**, 6-methyl-7-phenyl-3,4,6,7-tetrahydrobenzo[h][1,4,6]oxadiazonin-5(2H)-one **2-86** (58 mg, 0.21 mmol) and *p*-toluenesulfonic acid monohydrate (4.0 mg, 21 μmol) in CH_2Cl_2 (2.0 mL) were stirred for 16 h at RT. Purification by flash column chromatography eluting (12 to 100% EtOAc in petrol) gave the *title compound* **2-462** as a white solid (26 mg, 45%). $\mathbf{R_f}$ 0.17 (50% EtOAc/petrol); **Mp** 165–166 °C (CH_2Cl_2/*n*-pentane); $\mathbf{\nu_{max}}$ **/cm^{-1}** (film) 3277, 2923, 1616, 1256, 1209; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.22 (4 H, m, ArH), 7.18–7.16 (1 H, m, ArH), 7.11 (1 H, d, *J* 7.5, H5), 7.07–7.03 (2 H, m, ArH), 6.42 (1 H, s, H11), 4.62 (1 H, br, NH), 4.11 (1 H, ddd, *J* 12.8, 5.8, 2.5, H7$_a$), 3.91–3.82 (2 H, m, H7$_b$, H8$_a$), 3.37 (1 H, ddd, *J* 14.8, 8.0, 2.5, H8$_b$), 2.80 (3 H, d, *J* 4.5, H10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.9 (C9), 158.1 (C6), 139.6 (C12), 131.2, 130.5 (C1), 129.4 (ArCH), 128.8 (ArCH), 127.7 (ArCH), 127.5 (C5), 123.6 (ArCH), 122.0 (ArCH), 70.9 (C7), 62.4 (C11), 44.6 (C8), 28.1 (C10); **HRMS** (ESI$^+$) m/z $C_{17}H_{18}N_2NaO_2^+$ requires: 305.1260; found: 305.1262.

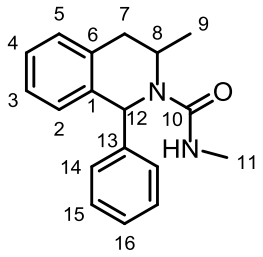
(±)-*N*-Methyl-1-phenyl-3,4,5,6-tetrahydrobenzo[c]azocine-2(1*H*)-carboxamide (2-463)



According to **GP10**, 2-methyl-1-phenyl-1,4,5,6,7,8-hexahydrobenzo[e][1,3]diazecin-3(2*H*)-one **2-74** (50 mg, 0.17 mmol) and *p*-toluenesulfonic acid monohydrate (3.2 mg, 17 μmol) in CH_2Cl_2 (1.7 mL) were stirred for 1 h at RT. Purification by flash column chromatography eluting (12 to 100% EtOAc in petrol) gave the *title compound* **2-463** as a white solid (19 mg, 38%). $\mathbf{R_f}$ 0.25 (50% EtOAc/petrol); **Mp** 136–137 °C (CH_2Cl_2/*n*-pentane); $\mathbf{\nu_{max}}$ **/cm^{-1}** (film) 3389, 2933, 1619, 1525, 729; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (2 H, t, *J* 7.0, H16), 7.38–7.19 (5 H, m, ArH), 7.03 (1 H, td, *J* 7.6, 1.8, H4), 6.59 (1 H, d, *J* 7.6, H5), 6.26 (1 H, s, H13), 4.37 (1 H, br, NH), 3.72–3.64 (1 H, m, H10$_a$), 3.10–3.04 (1 H, m, H10$_b$), 2.85 (1 H, ddd, *J* 12.8, 9.3, 2.7, H5$_a$), 2.76–2.68 (1 H, m, H5$_b$), 2.73 (3 H, d, *J* 4.5, H12), 2.02–1.85 (2 H, m, H8$_a$, H9$_a$), 1.63–1.51 (2 H, m, H8$_b$, H9$_b$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.4 (C11), 144.0 (C1), 141.5 (C14), 138.0 (C6), 130.9 (ArCH), 130.5 (C5), 129.0 (C16), 128.5 (ArCH), 127.6 (ArCH), 127.5

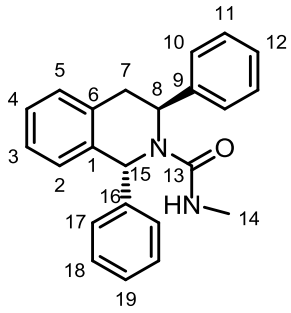
(ArCH), 126.1 (C4), 63.0 (C13), 42.3 (C10), 31.2 (C7), 28.9 (C8/C9), 27.9 (C12), 26.9 (C8/C9); **HRMS** (ESI$^+$) m/z $C_{19}H_{23}N_2O^+$ requires: 295.1805; found: 295.1798.

(±)-*N*,3-Dimethyl-1-phenyl-3,4-tetrahydroisoquinoline-2(*1H*)-carboxamide (2-456)



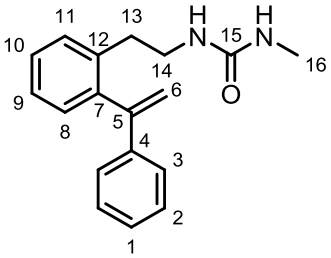
According to **GP10**, 2,5-dimethyl-1-phenyl-1,4,5,6-tetrahydrobenzo[*e*][1,3]diazocin-3(2*H*)-one **2-97** (50 mg, 0.18 mmol) and *p*-toluenesulfonic acid monohydrate (3 mg, 0.02 mmol) in CH_2Cl_2 (1.8 mL) were stirred for 16 h at RT. Purification by flash column chromatography eluting (20 to 100% EtOAc/petrol) gave the *title compound* **2-456** as a white solid as an inseparable mixture of diastereomers (40 mg, 80%) *d.r.* 1:1. $\boldsymbol{R_f}$ 0.28 (70% EtOAc/petrol); **Mp** 148–149 °C (CH_2Cl_2/*n*-pentane); $\boldsymbol{\nu_{max}}$ **/cm^{-1}** (film) 3349,2965, 1633, 1527, 1480; *Diastereomers are assigned as diastereomer A and diastereomer B (diaA/diaB);* **^{1}H NMR** (400 MHz, d_6-DMSO) δ 7.76 (1 H, d, *J* 8.0, ArH^{diaA}), 7.46 (1 H, d, *J* 7.3, ArH$^{diaA/B}$), 7.28–7.00 (10 H, m, ArH^{diaA+B}), 6.80 (1 H, t, *J* 7.4, ArH$^{diaA/B}$), 6.58–6.54 (0.5 H, m, NH^{diaA}), 6.29–6.24 (0.5 H, m, NH^{diaB}), 6.08 (1 H, s, H12^{diaA+B}), 4.56–4.50 (0.5 H, m, H8^{diaA}), 4.44–4.37 (0.5 H, m, H8^{diaB}), 3.30–3.24 (0.5 H, m, H7$_a$^{diaA}), 2.96 (0.5 H, dd, *J* 14.5, 5.6, H7$_a$^{diaB}), 2.64 (1.5 H, d, *J* 4.3, H11^{diaA}), 2.59–2.53 (2.5 H, m, H7$_b$^{diaA}, H7$_b$^{diaB}, H11^{diaB}), 1.10 (1.5 H, d, *J* 6.4, H9^{diaB}), 0.84 (1.5 H, d, *J* 6.1, H9^{diaA}); **^{13}C NMR** (101 MHz, d_6-DMSO) δ 157.2 (C10^{diaB}), 154.8 (C10^{diaA}), 144.1 (C1^{diaA}), 143.1 (C1^{diaB}), 137.9 (C13^{diaA+B}), 133.7 (C6^{diaA}), 129.2 (C6^{diaB}), 128.6, 128.0, 127.1, 126.9, 126.6, 126.1, 125.8, 124.8, 121.0, 114.6 (ArH^{diaA+B}), 57.6 (C12^{diaA+B}), 53.6 (C8^{diaB}), 46.6 (C8^{diaA}), 35.8 (C7^{diaA}), 34.5 (C7^{diaB}), 27.4 (C11^{diaB}), 26.8 (C11^{diaA}), 20.6 (C9^{diaB}), 20.3 (C9^{diaA}); **HRMS** (ESI$^+$) m/z $C_{18}H_{21}N_2O^+$ requires: 281.1648; found: 281.1630.

***(1R,3S)-N*-Methyl-1,3-diphenyl-3,4-tetrahydroisoquinoline-2(*1H*)-carboxamide (2-457)**



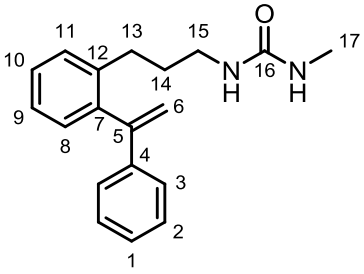
According to **GP10**, 2-methyl-1,5-diphenyl-1,4,5,6-tetrahydrobenzo[e][1,3]diazocin-3(2H)-one **2-98** (50 mg, 0.15 mmol) and *p*-toluenesulfonic acid monohydrate (3 mg, 0.02 mmol) in CH_2Cl_2 (1.5 mL) were stirred for 16 h at RT. Purification by flash column chromatography eluting (20% to 100% EtOAc/petrol) gave the *title compound* **2-457** as a white solid as a single diastereomer (44 mg, 88%) *d.r.* >20:1. $\boldsymbol{R_f}$ 0.26 (60% EtOAc/petrol); **Mp** 177-178 °C (CH_2Cl_2/*n*-pentane); $\boldsymbol{\nu_{max}}$ **/cm^{-1}** (film) 3664, 2987, 1638, 1393, 1065; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (1 H, d, *J* 7.5, ArH), 7.29–7.25 (5 H, m, ArH), 7.20–7.13 (4 H, m, ArH), 7.11–7.07 (1 H, m, ArH), 6.90 (2 H, dd, *J* 6.7, 2.9, ArH), 6.77 (1 H, d, *J* 7.4, ArH), 6.61 (1 H, s, H15), 5.34–5.31 (1 H, m, H8), 4.22 (1 H, d, *J* 5.0, NH), 3.34 (1 H, dd, *J* 14.7, 6.1, H7$_a$), 2.72–2.67 (1 H, m, H7$_b$), 2.65 (3 H, d, *J* 5.0, H14); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.8 (C13), 142.8 (C1), 142.4 (C9/C16), 138.9 (C9/C16), 132.7 (C6), 128.8, 128.7, 128.5, 127.8, 127.6, 127.2, 127.0, 126.8, 126.2, 125.8 (ArCH), 59.2 (C15), 56.9 (C8), 31.1 (C7), 28.0 (C14); **HRMS** (ESI$^+$) m/z $C_{23}H_{23}N_2O^+$ requires: 343.1805; found: 343.1820.

1-Methyl-3-(2-(1-phenylvinyl)phenethyl)urea (2-468)



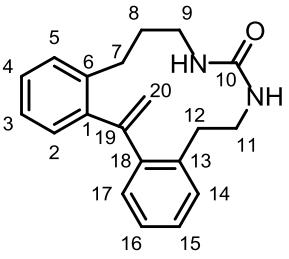
According to **GP10**, 1,2-dimethyl-1-phenyl-1,4,5,6-tetrahydrobenzo[*e*][1,3]diazocin-3(*2H*)-one **2-89** (0.45 g, 1.5 mmol) and *p*-toluenesulfonic acid monohydrate (0.58 g, 3.0 mmol) in CH_2Cl_2 (15 mL) were stirred for 16 h at RT yielding the *title compound* **2-468** as a white solid (0.3 g, 67%). No further purification was required. $\mathbf{R_f}$ 0.11 (1% MeOH/CH_2Cl_2); **Mp** 110-112 °C ($CHCl_3$); $\mathbf{\nu_{max}}$ **/cm^{-1}** (film) 3327, 2935, 1629, 1572, 1264; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.23 (9 H, m, ArH), 5.80 (1 H, d, *J* 1.4, H6$_a$), 5.22 (1 H, d, *J* 1.4, H6$_b$), 4.09 (1 H, br s, NH), 4.01 (1 H, br s, NH), 3.19 (2 H, q, *J* 7.0, H14), 2.66 (3 H, d, *J* 4.5, H16), 2.58 (2 H, t, *J* 7.0, H13); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.7 (C15), 149.1 (C5), 141.7 (C4), 140.8 (C12), 137.1 (C7), 130.7 (ArCH), 129.9 (ArCH), 128.6 (ArCH), 128.03 (ArCH), 128.0 (ArCH), 126.63 (ArCH), 126.6 (ArCH), 115.7 (C6), 41.5 (C14), 33.9 (C13), 27.3 (C16); **HRMS** (ESI$^+$) m/z $C_{18}H_{21}N_2O^+$ requires: 281.1648; found: 281.1659.

1-Methyl-3-(2-(1-phenylvinyl)phenethyl)urea (2-469)



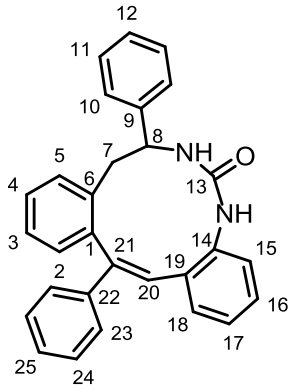
According to **GP10**, 1,2-dimethyl-1-phenyl-1,2,4,5,6,7-hexahydro-*3H*-benzo[*e*][1,3]diazonin-3-one **2-90** (0.15 g, 0.51 mmol) and *p*-toluenesulfonic acid monohydrate (0.19 g, 1.0 mmol) in CH_2Cl_2 (5.1 mL) were stirred for 16 h at RT yielding the *title compound* **2-469** as a colourless oil (147 mg, 98%). No further purification was required. $\mathbf{R_f}$ 0.13 (1% MeOH/CH_2Cl_2); $\mathbf{\nu_{max}}$ **/cm^{-1}** (film) 3054, 2305, 1422, 1264;**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29–7.18 (9 H, m, ArH), 5.75 (1 H, d, *J* 1.4, H6$_a$), 5.18 (1 H, d, *J* 1.4, H6$_b$), 4.53–4.49 (1 H, br, NH), 4.40 (1 H, t, *J* 5.6, NH), 2.96 (2 H, td, *J* 6.9, 5.6, H15), 2.66 (3 H, d, *J* 4.9, H17), 2.40–2.36 (2 H, m, H13), 1.62–1.55 (2 H, m, H14); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.9 (C16), 149.3 (C5), 141.3 (C4), 141.0 (C12), 139.6 (C7), 130.7 (ArCH), 129.3 (ArCH), 128.5 (ArCH), 128.0 (ArCH), 127.9 (ArCH), 126.6 (ArCH), 126.1 (ArCH), 115.5 (C6), 40.3 (C15), 31.2 (C14), 30.7 (C13), 27.3 (C17); **HRMS** (ESI$^+$) m/z $C_{19}H_{23}N_2O^+$ requires: 295.1805; found: 295.1806.

17-Methylene-5,6,7,9,10,11,12,17-octahydro-8*H*-dibenzo[f,i][1,3]diazacyclotridecin-8-one (2-470)



According to **GP10**, 16b-methyl-5,9,10,11,12,16b-hexahydrobenzo[7,8][1,3]diazonino[9,1-a]isoquinolin-8(6H)-one **2-94** (37 mg, 0.12 mmol) and *p*-toluenesulfonic acid monohydrate (46 mg, 0.24 mmol) in CH_2Cl_2 (1.2 mL) were stirred for 48 h at RT yielding the *title compound* **2-470** as a white solid (28 mg, 76%). No further purification was required. $\mathbf{R_f}$ 0.65 (10% MeOH/CH_2Cl_2 + 1% NEt_3); **Mp** decomposed >230 °C (CH_2Cl_2/*n*-pentane); $\mathbf{\nu_{max}}$ **/cm^{-1}** (film) 3325, 2925, 1640, 1555, 1262. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (1 H, d, *J* 7.8, ArH), 7.31–7.21 (4 H, m, ArH), 7.12–7.05 (2 H, m, ArH), 6.94 (1 H, d, *J* 7.8, ArH), 5.54 (1 H, s, H20$_a$), 5.27 (1 H, s, H20$_b$), 4.48–4.40 (1 H, br, NH), 4.30–4.25 (1 H, br, NH), 3.59 (2 H, br t, *J* 6.1, H11), 3.18 (2 H, br t, *J* 6.1, H12), 3.11 (2 H, br t, *J* 5.6, H9), 2.40–2.36 (2 H, m, H7), 1.69–1.62 (2 H, m, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.9 (C10), 148.0 (C19), 142.7(ArC), 142.6 (ArC), 139.1 (ArC), 136.3 (ArC), 131.1 (ArCH), 129.6 (ArCH), 128.8 (ArCH), 128.1 (ArCH), 127.9 (ArCH), 127.6 (ArCH), 126.1 (ArCH), 126.05 (ArCH), 121.5 (C20), 41.1 (C11), 40.2 (C9), 32.4 (C12), 30.8 (C8), 30.4 (C7). **HRMS** (ESI$^+$) m/z $C_{20}H_{23}N_2O^+$ requires: 307.1805; found: 307.1810.

(Z)-8, 14-Diphenyl-5,7,8,9-tetrahydro-6H-dibenzo[d,h][1,3]diazacycloundecin-6-one (2-471)



According to **GP10,** (6S,14aR)-6,14a-diphenyl-6,7,14,14a-tetrahydrobenzo[6,7][1,3]diazocino[1,8-a]indol-8(5H)-one **2-102** (57 mg, 0.14 mmol) and *p*-toluenesulfonic acid monohydrate (52 mg, 0.27 mmol) in CH_2Cl_2 (1.4 mL) were stirred for 15 min in a microwave at 100 °C. Purification by flash column chromatography eluting (10 to 100% EtOAc/petrol) gave the *title compound* **2-471** as a white solid (48 mg, 84%). **R_f** 0.76 (10% MeOH/CH_2Cl_2 + 1% NEt_3); **Mp** decomposed >230 °C (CH_2Cl_2/*n*-pentane); **ν_{max}/cm^{-1}** (film) 2967, 1662, 1444, 760; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53–7.52 (2 H, br m, ArH), 7.40–7.26 (8 H, br m, ArH), 7.25–7.18 (5 H, br m, ArH), 6.93 (1 H, br t, *J* 7.7, ArH), 6.87–6.80 (2 H, br m, ArH), 6.44 (1 H, br s, NH), 6.13 (1 H, br s, H20), 5.56–5.50 (1 H, br m, H8), 4.70 (1 H, d, *J* 10.8, NH), 3.07 (1 H, dd, *J* 13.4, 5.7, $H7_a$), 2.70 (1 H, dd, *J* 13.4, 2.7, $H7_b$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.2 (C13), 145.3 (ArC), 141.2 (ArC), 140.8 (ArC), 138.7 (ArC), 135.12 (ArC), 133.9 (ArC), 135.1 (ArCH), 135.0 (ArCH), 133.2 (C20), 132.7, 132.5, 129.0, 128.6, 128.0, 127.97, 127.6, 127.2, 127.1, 126.7, 126.2, 126.0 (ArCH), 51.4 (C8), 40.1 (C7); **HRMS** (ESI^+) m/z $C_{29}H_{24}N_2NaO^+$ requires: 439.1780; found: 439.1780; **X-ray** crystallography data:

Bond precision: C-C = 0.0026 A Wavelength=0.71073

Cell: a=9.7515(3) b=10.4670(3) c=13.3967(4)
alpha=88.7235(16) beta=87.0479(16) gamma=73.4928(15)

Temperature: 100 K

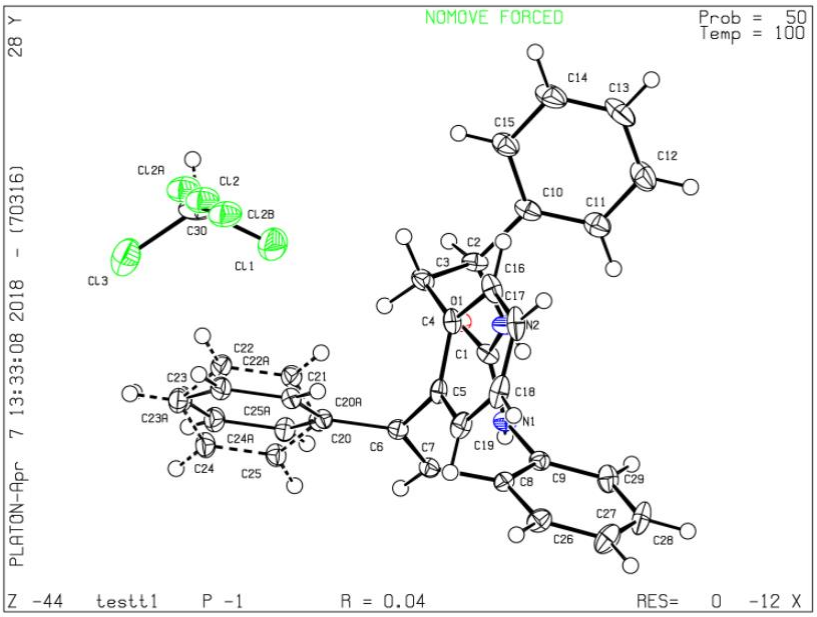
	Calculated	Reported
Volume	1309.25(7)	1309.25(7)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C29 H24 N2 O, C H Cl3	C29 H24 N2 O, C H1 Cl3
Sum formula	C30 H25 Cl3 N2 O	C30 H25 Cl3 N2 O
Mr	535.87	535.87
Dx,g cm-3	1.359	1.359
Z	2	2
Mu (mm-1)	0.377	0.377
F000	556.0	556.0
F000'	557.06	
h,k,lmax	12,13,17	12,13,17
Nref	6312	6299
Tmin,Tmax	0.816,0.917	0.672,0.746
Tmin'	0.807	

Correction method= # Reported T Limits: Tmin=0.672 Tmax=0.746 AbsCorr = MULTI-SCAN

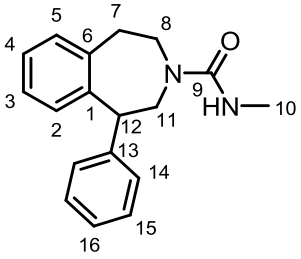
Data completeness= 0.998 Theta(max)= 27.974

R(reflections)= 0.0443(4980) wR2(reflections)= 0.1071(6299)

S = 1.026 Npar= 369

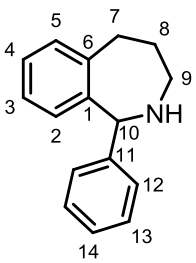


_N_-Methyl-1-phenyl-1,4,5,6-tetrahydrobenzo[_d_]azocine-3(2_H_)-carboxamide (2-472)



1-Methyl-3-(2-(1-phenylvinyl)phenethyl)urea **2-468** (0.8 g, 0.3 mmol) was added to a flame-dried flask followed by anhydrous, degassed DMSO (2.9 mL). Potassium *tert*-butoxide (32 mg, 0.3 mmol) was added to the flask at RT. The reaction mixture was stirred at RT for 16 h or until TLC showed consumption of starting material. Water (2 mL) was added to the reaction mixture and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography eluting with (1 to 10% MeOH in CH_2Cl_2) gave the *titled compound* **2-472** as a colourless oil (66 mg, 83%). $\mathbf{R}_f$ 0.13 (1% MeOH/ CH_2Cl_2); $\boldsymbol{\nu}_{max}$ **/cm^{-1}** (film) 3329, 2925, 1631, 1572, 1267; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.10 (8 H, br m, ArH), 6.93 (1 H, br d, *J* 7.4, ArH), 4.55 (1 H, br dd, *J* 9.6, 5.0, H12), 4.40 (1 H, br m, NH), 4.17 (1 H, br dd, *J* 15.0, 5.0, H11$_a$), 3.75–3.67 (2 H, br m, H11$_b$, H8$_a$), 3.51 (1 H, br m, H8$_b$), 3.31 (1 H, ddd, *J* 14.7, 10.5, 3.8, H7$_a$), 3.01–2.94 (1 H, br m, H7$_b$), 2.73 (3 H, d, *J* 4.6, H10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.7 (C9), 143.3 (C1), 141.5 (C13), 138.6 (C6), 131.2 (ArCH), 130.5 (ArCH), 128.8 (ArCH), 128.3 (ArCH), 127.1 (ArCH), 126.7 (ArCH), 126.7 (ArCH), 52.3 (C12), 49.8 (C11), 46.6 (C8), 35.5 (C7), 27.7 (C10); **HRMS** (ESI$^+$) m/z $C_{18}H_{21}N_2O^+$ requires: 281.1648; found: 281.1659.

1-Phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (2-473)

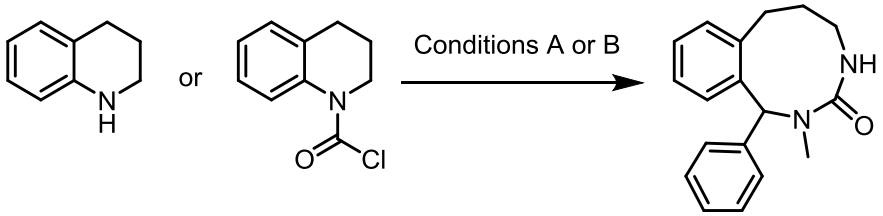


To a microwave vial was added *N*-methyl-1-phenyl-1,3,4,5-tetrahydro-2*H*-benzo[c]azepine-2-carboxamide **2-431** (100 mg, 0.36 mmol), ethanol (2 mL) and aq. 2 M NaOH (2 mL) (1:1 v/v EtOH: 2 M NaOH). The mixture was heated at 140 °C in a microwave for 4 h. Once complete, CH_2Cl_2 was added and the aqueous phase was extracted three times with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography, eluting with (1 to 4% MeOH in CH_2Cl_2) yielding the *title compound* **2-473** as a colourless oil (57 mg, 72%). $\mathbf{R}_f$ 0.12 (60% EtOAc/petrol); $\boldsymbol{\nu}_{max}$ **/cm^{-1}** (film) 3338, 2928, 1618, 1532, 1491; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41–7.29 (5 H, m, ArH),

7.21–7.19 (1 H, m, ArH), 7.16–7.12 (1 H, m, ArH), 7.03 (1 H, td, *J* 7.5, 1.5, ArH), 6.64 (1 H, d, *J* 7.5, ArH), 5.21 (1 H, s, H10), 3.40 (1 H, dt, *J* 13.8, 4.4, $H9_a$), 3.23–3.12 (2 H, m, $H9_b$, $H7_a$), 2.94 (1 H, ddd, *J* 14.5, 8.1, 2.1, $H7_b$), 1.94–1.83 (2 H, m, NH, $H8_a$), 1.75–1.65 (1 H, m, $H8_b$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.1 (C1), 142.8 (C11), 142.5 (C6), 129.8 (ArCH), 128.5 (ArCH), 127.9 (ArCH), 127.88 (ArCH), 127.0 (ArCH), 126.95 (ArCH), 126.0 (ArCH), 65.8 (C10), 51.1 (C9), 35.9 (C7), 30.1 (C8); **HRMS** (ESI^+) m/z $C_{16}H_{18}N^+$ requires: 224.1433; found: 224.1433.

3.5 *In Situ* Urea Formation/ Ring Expansion Reaction

- **Synthesis of (±)-2-Methyl-1-phenyl-1,2,4,5,6,7-hexahydro-3H-benzo[e][1,3]diazonin-3-one (2-73)**



2-111 **2-112** **2-73**

Scheme 3-1. *In situ* urea formation ring expansion to synthesise **2-73**.

Conditions A:

To a solution of 1,2,3,4-tetrahydroquinoline **2-111** (0.10 g, 0.75 mmol), DMPU (0.45 mL, 3.8 mmol) and benzyl(methyl)carbamoyl chloride **2-15** (0.15 g, 0.83 mmol) in anhydrous THF (5 mL) was added LDA (1.1 mL, 2.3 mmol, 2.0 M) dropwise at −78 °C. The reaction mixture was then warmed to RT and left for 16 h. The reaction mixture was quenched with sat. NH_4Cl and extracted three times with EtOAc. The combined organic phases were washed twice with H_2O and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the resulting residue by flash column chromatography eluting with (40% to 100% EtOAc in petrol) gave the *title compound* **2-73** as a white solid (0.12 g, 57%).

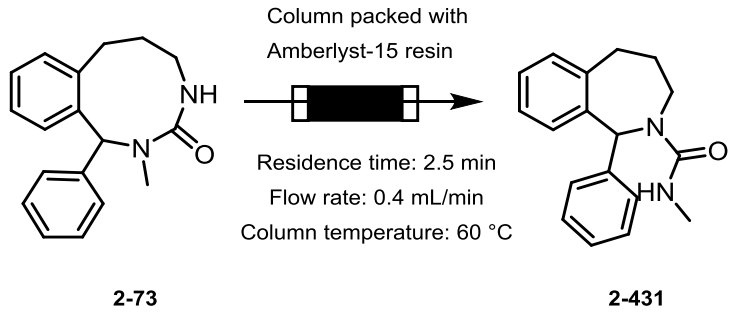
Conditions B:

To a solution of 3,4-tetrahydroquinoline-1(2*H*)-carbamoyl chloride **2-112** (1.0 g, 5.1 mmol) in anhydrous THF (34 mL) was added DMPU (3.1 mL, 26 mmol) at RT under nitrogen. *N*-Methyl-1-phenylmethanamine (0.72 mL, 5.6 mmol) was then added which lead to the formation of a thick white suspension. The suspension was then cooled to 0 °C, followed by the addition of LDA (7.7 mL, 15 mmol, 2.0 M (*N.B.* vigorous stirring is required to ensure the first drops of LDA mix into the solution, this is achieved using a large magnetic stirrer bar. The reaction mixture becomes a homogenous solution after the first few drops of LDA. The reaction mixture was light yellow initially progressing to a deep red colour after LDA addition is complete). The reaction was then stirred for 2 h at 0 °C or until consumption of urea **2-45** is observed by TLC. The reaction was then quenched with sat. NH_4Cl and extracted three times with EtOAc. The combined organic phases were washed twice with H_2O and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the resulting residue by flash column chromatography eluting with (40% to 100% EtOAc in petrol) gave the *title compound* **2-73** as a white solid (1.2 g, 84%).

*Spectroscopic data of the compounds isolated from both the procedures described above matches the data obtained for **2-73** starting from pre-isolated urea **2-45**.*

3.6 Ring Contraction in Flow

- **Synthesis of (±)-N-Methyl-1-phenyl-1,3,4,5-tetrahydro-2H-benzo[c]azepine-2-carboxamide (2-431)**

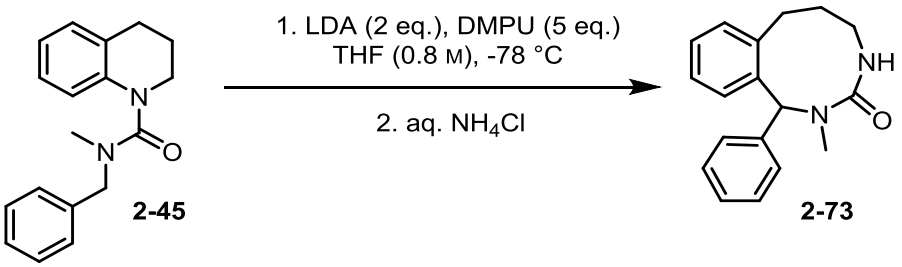


Scheme 3-2. Ring contraction of **2-73** in flow.

Flow reactions were performed using a Uniqsis FlowSyn module. The instrument used a PTFE flow path and the OMNIFIT® glass column was manually packed with amberlyst-15 resin (height 1.3 cm). (±)-2-Methyl-1-phenyl-1,2,4,5,6,7-hexahydro-3*H*-benzo[e][1,3]diazonin-3-one **2-73** (0.5 g, 1.78 mmol in 10 mL CH_2Cl_2) was delivered to the system *via* tubing from a Schott bottle. The flow rate was set to 0.4 mL/min and the column was heated to 60 °C using the Uniqsis column heater. After passing through the column, the solvent was collected in a round bottom flask and the solvent was removed *in vacuo*, resulting the *title compound* **2-431** as a white solid (0.43 g, 86%). No further purification was needed. The reaction was repeated on a 17 mmol scale yielding the *title compound* **2-431** as a white solid (4.60, 98%). *Spectroscopic data of **2-431** matches that previously stated for **2-431**.*

3.7 *In situ* ReactIR Experiments

- **Ring expansion of *N*-Benzyl-*N*-methyl-3,4-tetrahydroquinoline-1(2*H*)-carboxamide – Synthesis of (±)-2-Methyl-1-phenyl-1,2,4,5,6,7-hexahydro-3*H*-benzo[e][1,3]diazonin-3-one (2-73)**



Scheme 3-3. Ring expansion of **2-45**.

A ReactIR probe was inserted into a three-necked Schlenk tube equipped with a stirrer bar. The reaction vessel was dried *via* heat gun under vacuum. In a separate flask the urea **2-45** (0.11 g, 0.39 mmol) was dissolved in anhydrous THF (0.5 mL) which was then transferred to the reaction vessel *via* syringe. DMPU (0.2 mL, 1.9 mmol) was added to the solution and spectra was allowed to stabilise. The ReactIR was started and spectra were recorded every 15 seconds. Once the ReactIR had stabilised the mixture was cooled to –78 °C. Once the temperature had reached –78 °C and a stable IR spectrum was obtained, LDA (0.39 mL, 0.78 mmol, 2.0 M) was added dropwise *via* syringe. The reaction mixture was stirred for 30 min before quenching with aq. sat. NH_4Cl.

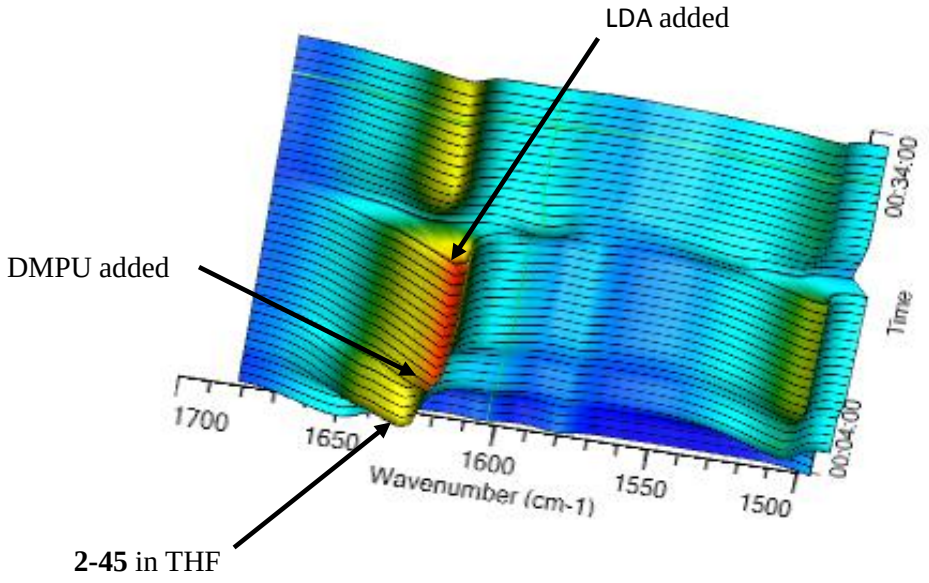


Figure 3-1. 3D ReactIR trace monitoring peaks at various wavenumbers over the course of the ring expansion reaction.

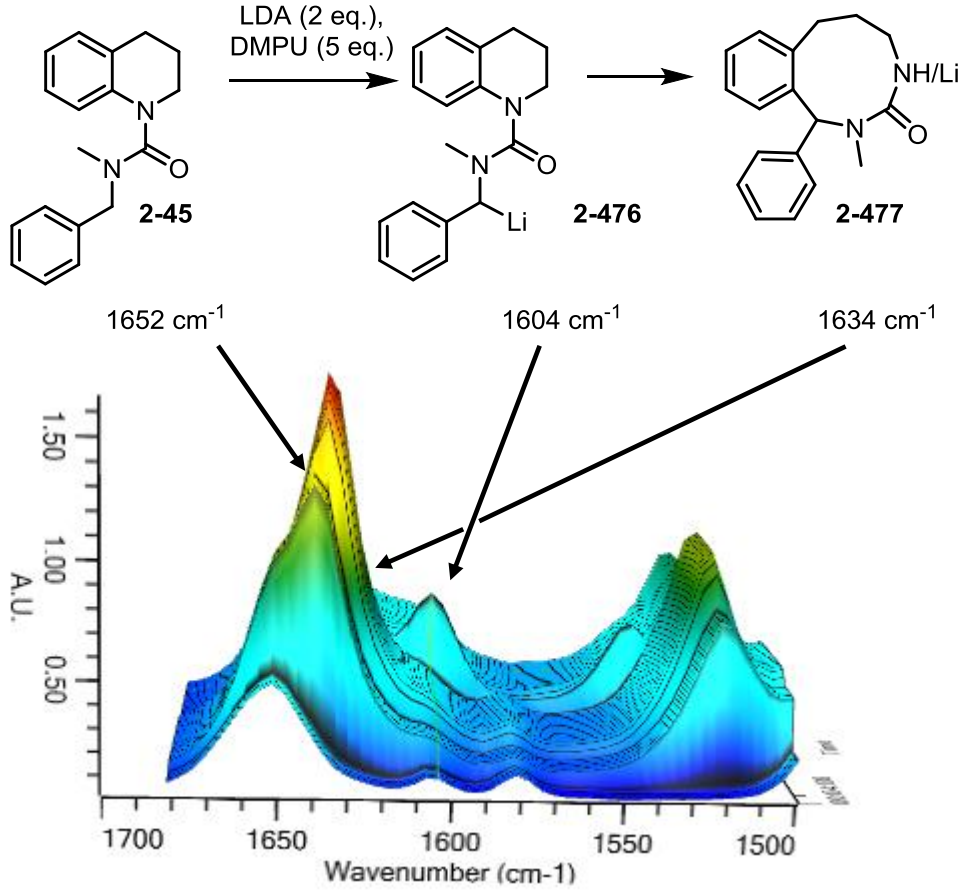
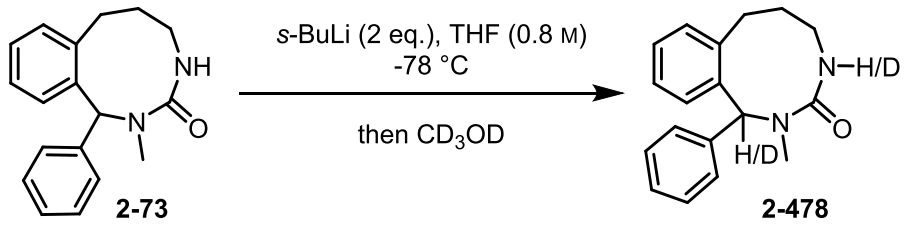


Figure 3-2. 3D ReactIR trace monitoring peaks at various wavenumbers over the course of the reaction. Peaks are tentatively assigned to the intermediates shown.

- **Deprotonation of the ring expansion product 2-73 with *s*-BuLi**



Scheme 3-4. Deprotonation of **2-73** with s-BuLi.

A ReactIR probe was inserted into a three-necked Schlenk tube equipped with a stirrer bar. The reaction vessel was dried with a heat gun, under vacuum. Anhydrous THF (0.7 mL) was added to the reaction vessel under a nitrogen atmosphere at RT and an IR solvent background spectrum was taken. The solvent was then removed *via* syringe from the reaction vessel. In a separate flask the ring expansion product **2-73** (0.15 g, 0.54 mmol) was dissolved in anhydrous THF (0.7 mL) which was then transferred to the reaction vessel *via* syringe. The ReactIR was started and spectra were recorded every 15 seconds. Once the ReactIR had stabilised the mixture was cooled to –78 °C. Once the temperature had reached –78 °C and a stable IR spectrum was obtained, *s*-BuLi (0.49 mL, 0.54 mmol, 1.1 M in hexanes) was added dropwise *via* syringe. The reaction mixture was stirred for 10 minutes. Another 1 equivalent of *s*-BuLi was added. The reaction mixture was left for a further 30 min at −78 °C before quenching with CD_3OD (0.7 mL). Spectra were recorded every 15 seconds for a further 20 min. No deuterium incorporation was observed by ^1H NMR of **2-479** after quenching the reaction with CD_3OD at −78 °C.

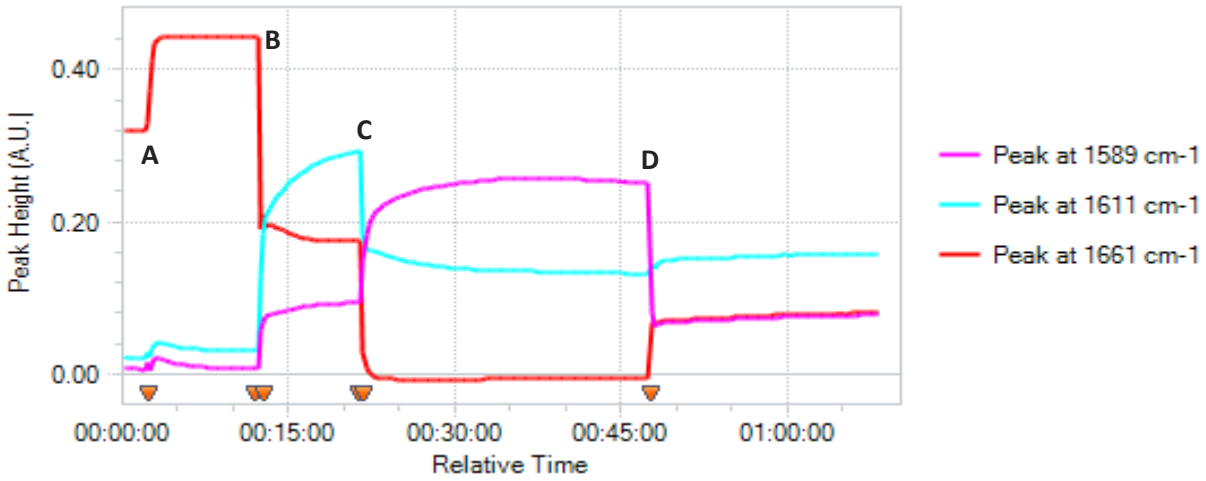


Figure 3-3. 2D ReactIR trace monitoring peaks at various wavelengths over the course of the deprotonation with *s*-BuLi. **A**: Reaction cooled to −78 °C. **B**: *s*-BuLi (1 eq.) added. **C**: *s*-BuLi (1 eq.) added. **D**: CD_3OD quench.

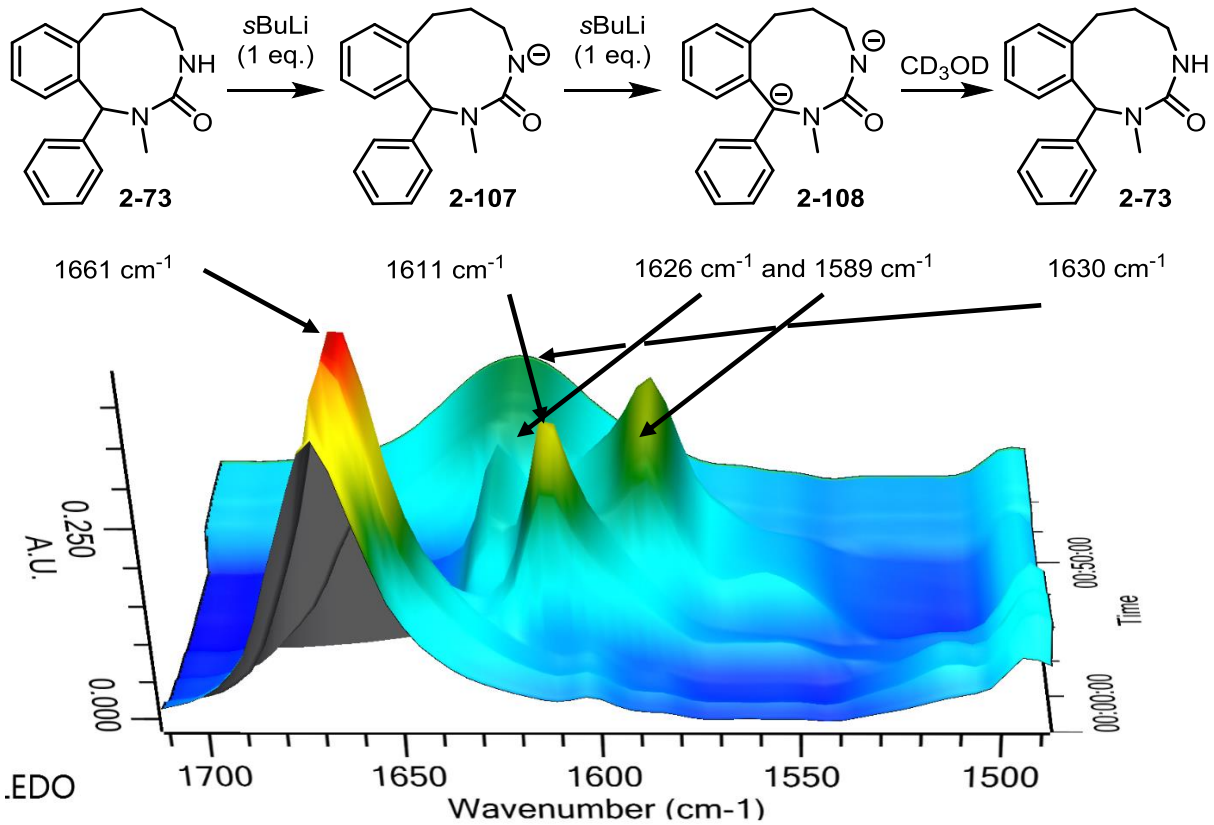
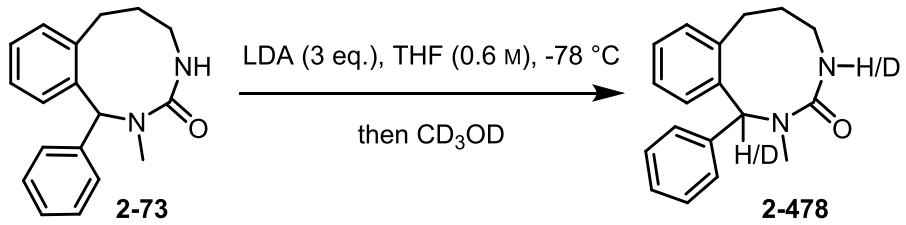


Figure 3-4. 3D ReactIR trace monitoring peaks at various wavenumbers over the course of the deprotonation with *s*-BuLi. Peaks are tentatively assigned to the intermediates shown.

- **Deprotonation of the ring expansion product 2-73 with LDA:**



Scheme 3-5. Deprotonation of **2-73** with LDA.

A ReactIR probe was inserted into a three-necked Schlenk tube equipped with a stirrer bar. The reaction vessel was dried *via* heat gun under vacuum. Anhydrous THF (0.7 mL) was added to the reaction vessel under a nitrogen atmosphere at RT and an IR solvent background spectrum was taken. The solvent was then removed *via* syringe from the reaction vessel. In a separate flask the ring expansion product **2-73** (0.11 g, 0.39 mmol) was dissolved in anhydrous THF (0.7 mL) which was then transferred to the reaction vessel *via* syringe. The ReactIR was started and spectra were recorded every 15 seconds. Once the ReactIR had stabilised the mixture was cooled to –78 °C. Once the temperature had reached –78 °C and a stable IR spectrum was obtained, LDA (0.20 mL, 0.39 mmol, 2.0 M) was added dropwise *via* syringe. The reaction mixture to stirred for 50 minutes. Another 1 equivalent of LDA was added. The reaction mixture was left for a further 20 min before another equivalent of LDA was added. The reaction was stirred for 20 min at −78 °C before quenching with CD_3OD (0.7 mL). No deuterium incorporation was observed by ^1H NMR of **2-479** after quenching the reaction with CD_3OD at −78 °C.

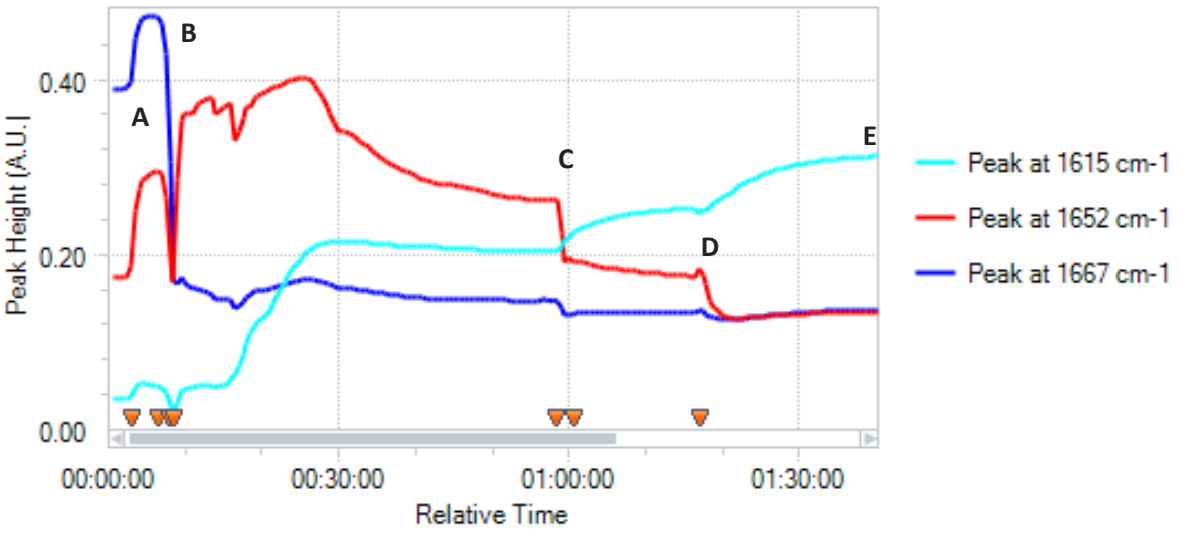


Figure 3-5. 2D ReactIR trace monitoring peaks at various wavelengths over the course of the deprotonation with LDA. **A**: Reaction cooled to −78 °C. **B**: LDA (1 eq.) added. **C**: LDA (1 eq.) added. **D**: LDA (1 eq.) added. **E**: CD_3OD quench.

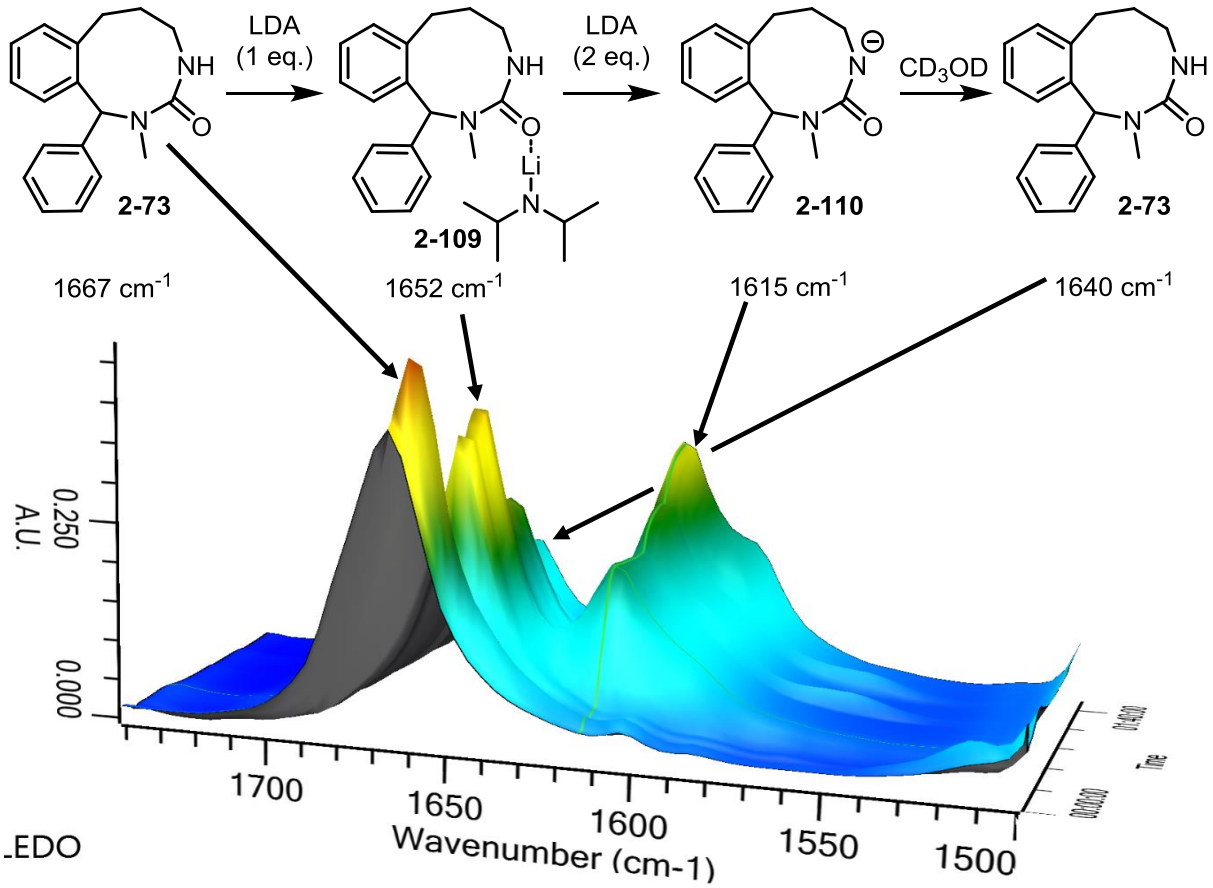
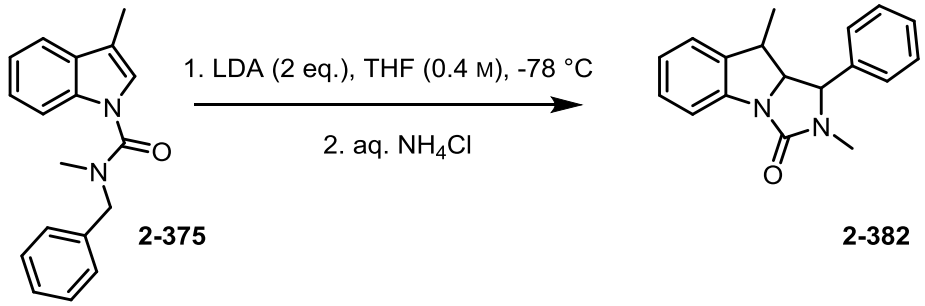


Figure 3-6. 3D ReactIR trace monitoring peaks at various wavenumbers over the course of the deprotonation with LDA. Peaks are tentatively assigned to the intermediates shown.

- **Dearomatizing cyclisation of *N*-Benzyl-*N*,3-dimethyl-1*H*-indole-1-carboxamide – synthesis of 2,9-Dimethyl-1-phenyl-1,2,9,9a-tetrahydro-3*H*-imidazo[1,5-a]indol-3-one:**



Scheme 3-6. Dearomatising cyclisation of **2-375**.

A ReactIR probe was inserted into a three-necked Schlenk tube equipped with a stirrer bar. The reaction vessel was dried *via* heat gun under vacuum. In a separate flask the indole urea **2-375** (0.1 g, 0.35 mmol) was dissolved in anhydrous THF (1.0 mL) which was then transferred to the reaction vessel *via* syringe. The ReactIR was started and spectra were recorded every 15 seconds. Once the ReactIR had stabilised the mixture was cooled to –78 °C. Once the temperature had reached –78 °C and a stable IR spectrum was obtained, LDA (0.35 mL, 0.69 mmol, 2.0 M) was added dropwise *via* syringe. The reaction mixture was stirred for 1 h before quenching with aq. sat. NH_4Cl.

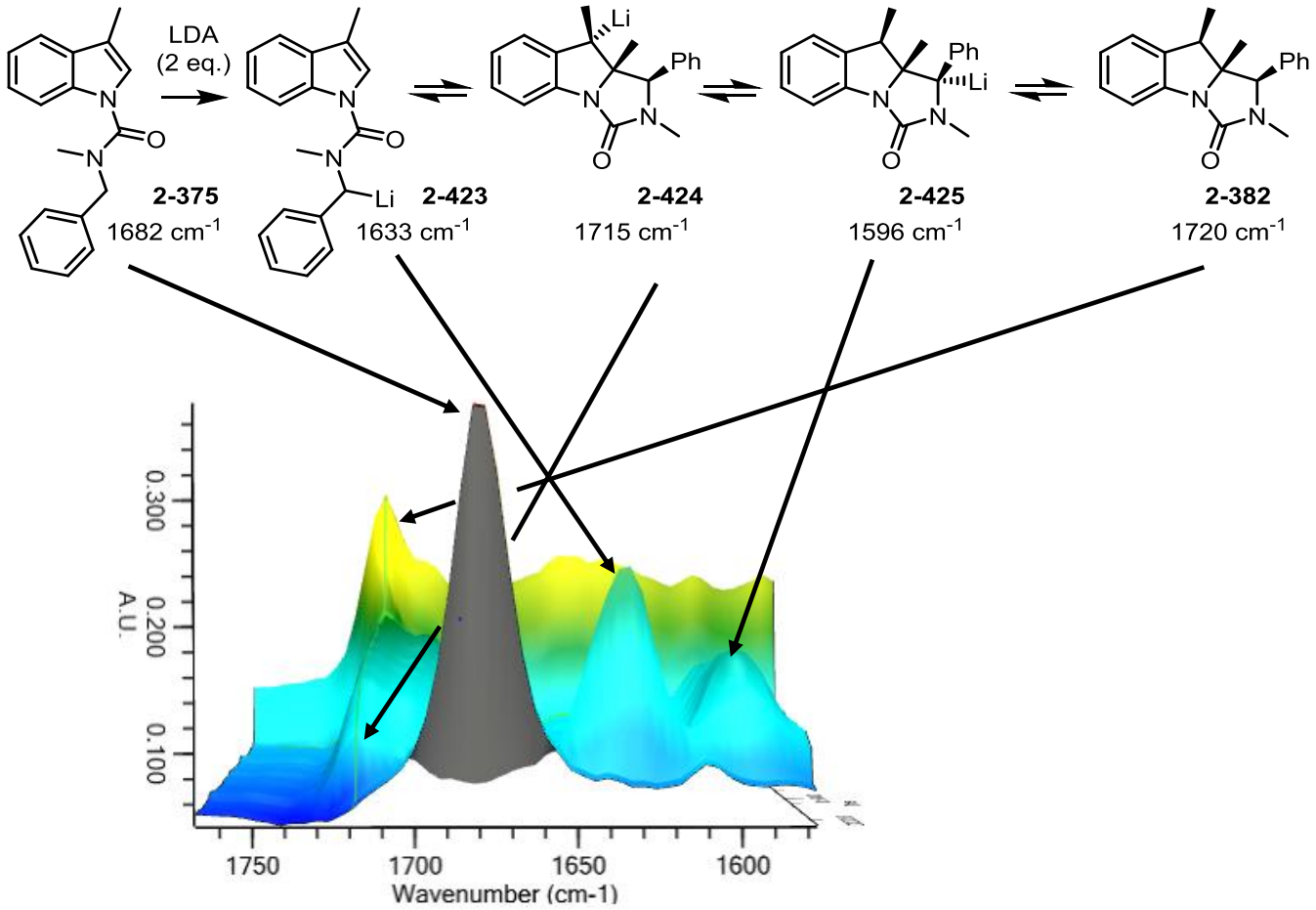


Figure 3-7. 3D ReactIR trace monitoring peaks at various wavenumbers over the course of the reaction. Peaks are tentatively assigned to the intermediates shown.

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