Cyclic and Spirocyclic α-Tertiary Amines by Organolithium Rearrangement

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Abbreviations

Ac	Acetate
aq	Aqueous
Ar	Aryl
Bn	Benzyl
Boc	*tert*-Butyl Carbamate
Bu	Butyl
Cat.	Catalytic
COSY	Correlation Spectroscopy
DCE	Dichloroethane
DCM	Dichloromethane
DIBAL	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
d.r	Diastereomeric ratio
e.e	Enantiomeric excess
e.r	Enantiomeric ratio
Et	Ethyl
Et_2O	Diethyl Ether
EtOAc	Ethyl acetate
EDG	Electron Donating Group
EWG	Electron Withdrawing Group
g	Grams
h	Hour
HCl	Hydrochloric Acid
HRMS	High Resolution Mass Spectroscopy
Hz	Hertz
LRMS	Low Resolution Mass Spectroscopy
LDA	Lithium diisopropylamide
Me	Methyl
MeI	Methyl iodide

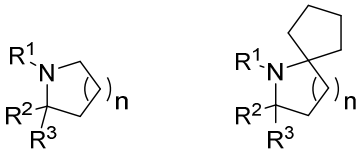
min	Minute
mL	Millilitres
mmol	Millimole
mol	Mole
MS	Mass spectrometry
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
Nu	Nucleophile
Ph	Phenyl
Py	Pyridine
*p*TSA	para-Toluenesulfonic acid
R_f	Retention Factor
r.t.	Room Temperature
S. M.	Starting Material
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
Tol	Tolyl
TMEDA	Tetramethylethylenediamine

Contents

1. Introduction

1.1. Cyclic & Spirocyclic α-Tertiary Amines

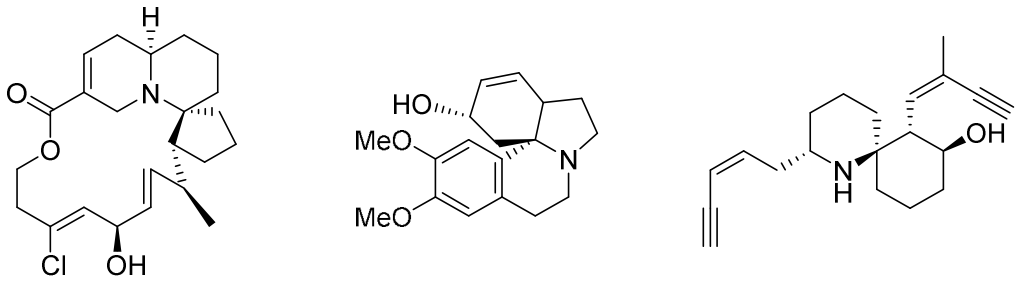
Cyclic **1** & Spirocyclic **2** α-tertiary amines are frequent motifs in naturally occurring and synthetic bioactive molecules (**Figure 1**).[1] They represent a significant challenge in modern organic synthesis and despite their ubiquity in nature there is a paucity of effective methods for the synthesis of these molecules.[2]



1 **2**

Figure 1: Cyclic & Spirocyclic α-tertiary amines (where n = 1,2,3 etc)

It is widely known that quaternary carbons bearing a nitrogen atom play a vital role in both natural and unnatural bioactive compounds.[3,4] This amino group is present in pharmaceutical drug candidates such as anti-inflammatory Halochlorine **3**,[5] and anxiolytic drug Erythravine **4**,[6] but also in naturally occurring alkaloids alike Histrionicotoxin 283A **5**.[7] It is therefore surprising that there are relatively few methods available for the direct synthesis of α-tertiary amines of this specific class, in either racemic or enantioselective forms.



3 **4** **5**

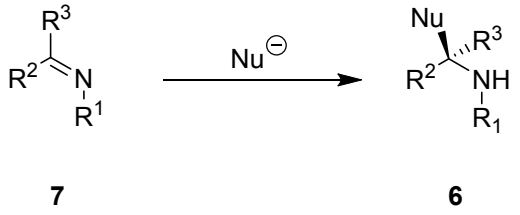
Figure 2: Various cyclic & spirocyclic α-tertiary amines

Synthetic routes that allow a concise, direct route to the construction of these compounds are of high value in organic synthesis.

1.2. Synthesis of α-Tertiary amines

1.2.1. Ketimines & Imines

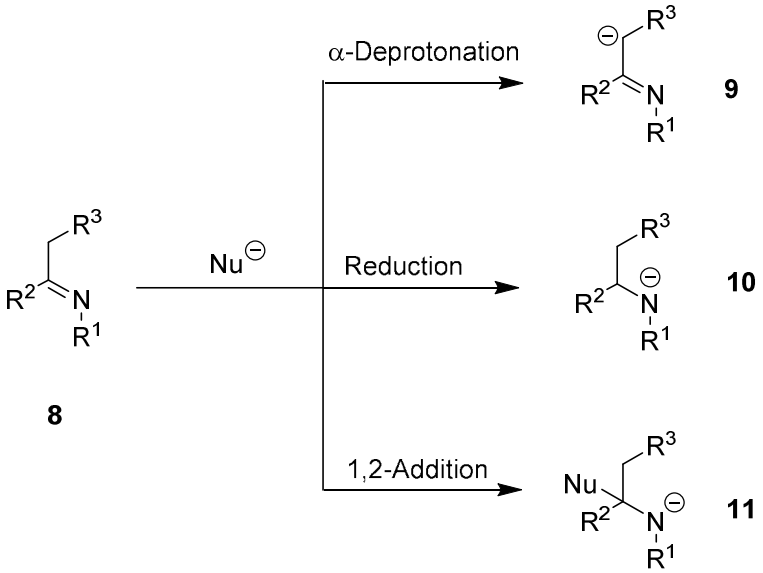
An established method for the direct synthesis of chiral α-tertiary amines **6,** involves the enantioselective 1,2 addition of a nucleophilic species to a ketimine species **7**, in which a variety of different amine classes can be accessed (**Scheme 1**).[8, 9]



7 **6**

Scheme 1: Nucleophilic addition to ketimines

A drawback of this method results from the poorly electrophilic nature of the ketimine carbon and as a result of this, side reactions are predictable. It is vital to control the electronic nature of the nitrogen substituent of **8** in order to circumvent the formation undesired by-products, such as **9** from α-deprotonation, and **10** by reduction, which can accompany the desired product **11** (**Scheme 2**).[10]



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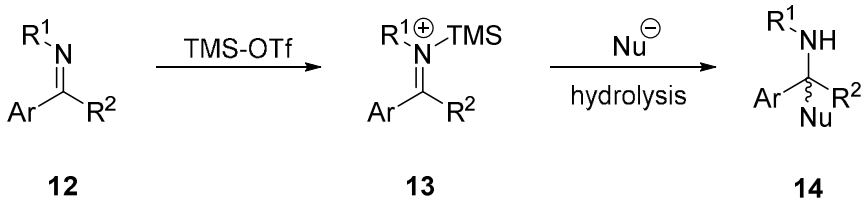
Scheme 2: Potential side reactions

A number of methods can be used to control the nucleophilic addition in a stereochemical fashion by using external control with the use of catalysts[11], ligands[12] and Lewis acids[13] or by auxiliary control.[14]

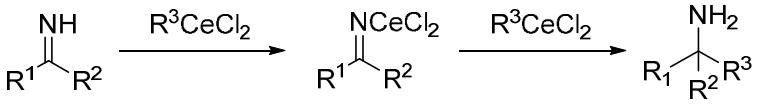
Pioneering work by Brook *et. al.*,[13] utilises activation control of the imines towards nucleophilic addition, by converting various aryl imines **12** to iminium salts **13** by addition of trimethylsilyl triflate, in which nucleophilic attack and subsequent hydrolysis of the auxiliary, releases the desired amine **14** (**Scheme 3**). It is a prime example whereby α-deprotonation is avoided by activating the imine towards nucleophilic attack, by installing an electron withdrawing group at the nitrogen position thus increasing the electrophilic nature of the imine carbonyl carbon.



12 **13** **14**

Scheme 3: Imine activation and nucleophilic addition

Du Pont[15] exemplified the use of Lewis acids to activate unsubstituted ketimines by coordination with organocerium reagents. Theoretically, the proposed mechanism occurs by coordination of ketimine **15** to an organocerium reagent, to give *N*-metalloimine **16,** in which addition of the same reagent followed by subsequent hydrolysis, allows the synthesis α-tertiary amines **17** (**Scheme 4**).



15 **16** **17**

Scheme 4: Organocerium addition to ketimines

A variety of different α-tertiary amines can be made using these approaches however, more specifically the construction of cyclic and spirocyclic α-tertiary

amines using these methods is scarce due to the requirement for a pre-existing carbon framework (R^1 and R^2 would have to be connected via a carbon chain) to exist, which in turn induces issues of the coordination to the organocerium additive. [15]

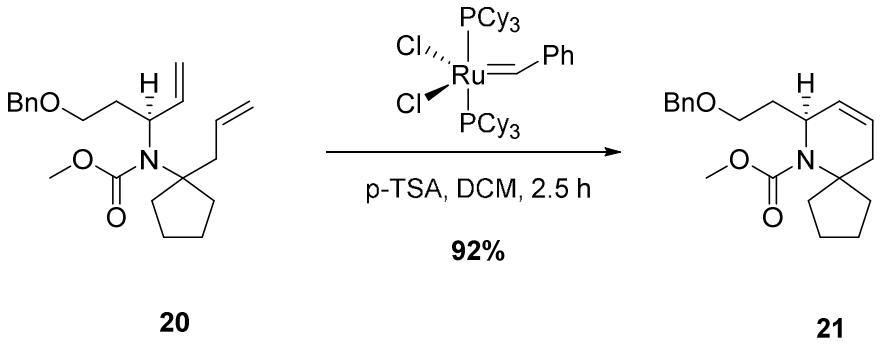
Alternatively, it is easier and more efficient to assemble the desired carbon-carbon bond by other methods such as ring closing metathesis, radical ring closure and various rearrangements.

1.3. Synthesis of Cyclic & Spirocyclic & α-Tertiary amines

1.3.1 Ring Closing Metathesis

Ring closing metathesis (RCM) is a very efficient method in which both terminal and internal double bonds can be cross-coupled to afford a closed ring system.[16] It has emerged as one of the most popular methods for carbon-carbon bond formation and has been used extensively in the synthesis of many natural products. [17,18]

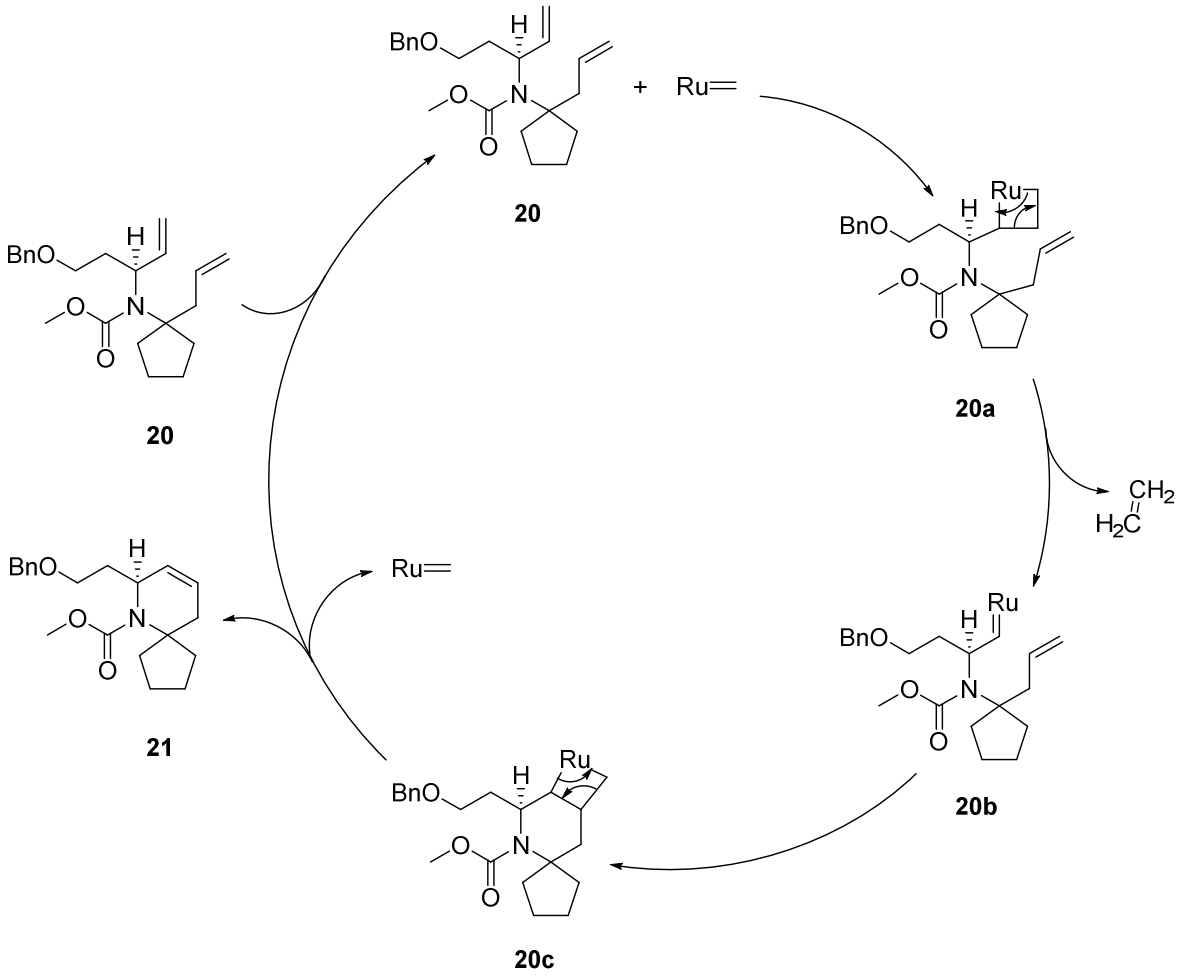
An excellent example is displayed by Wright[19] in their efforts to synthesis the spirocyclic α-tertiary amine Halochlorine (**3**, **Figure 2**). By the use of Grubbs' 1st generation catalyst accompanied with tosic acid, they presented the efficient closing of **20** to afford **21 (Scheme 5)**. [20]



20 **21**

Scheme 5: Ring closing metathesis to give a spirocyclic α-tertiary amine

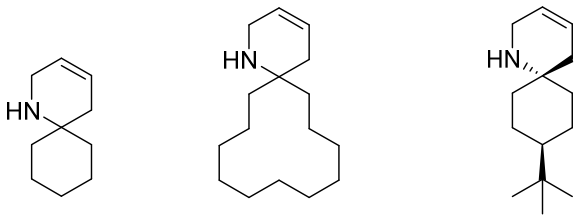
The pathway by which the ring closing metathesis occurs is proposed by the Chauvin mechanism.[21] Starting material **20** coordinates with the ruthenium based catalyst (which can be a variety of catalysts[22] and is written shorthand as Ru= for simplicity) to give the metallocyclobutane **23** that collapses to eject ethylene as a by-product along with ruthenium bound intermediate **24** that then coordinates again to the other double bond to give the second metallocyclobutane **25,** that collapses with the ejection of the ruthenium complex and the desired ring closed product **21**, completing the catalytic cycle (**Scheme 6**).



Scheme 6: Chauvin catalytic cycle for ring closing metathesis reaction

The thermodynamic driving force of the reaction is the release of ethylene from the reaction mixture;[23] however the catalytic cycle is reversible.

In their attempts to demonstrate the capability of the RCM reaction to assemble a variety of different spirocyclic α-tertiary amines, compounds **22**, **23** and **24** were synthesised in good yield, with the latter exemplifying the capacity of the RCM reaction to leave enantiopure starting materials intact (**Figure 3**). [19]



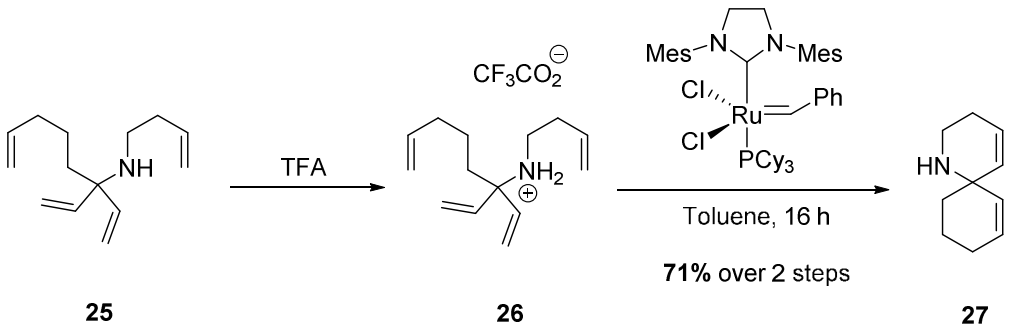
22 **23** **24**

75% **75%** **72%**

Figure 3: A few select spirocyclic α-tertiary amines synthesised using RCM reactions

It has been widely reported that free amines aren't generally compatible with metathesis reactions due to catalyst poisoning by nitrogen coordination if left unprotected.[24] The use of p-toluenesulfonic acid plays a vital role in the reaction as an *in-situ* acid salt is formed that avoids catalyst poisoning. In addition to this, it was shown that by using the protecting groups tert-butyl and methyl-carbamate, reaction times for multiple RCM reactions (which initially ranged from 8-20 days), could be dramatically reduced to a maximum of 24 hours, as the protecting groups on nitrogen not only increases both the rate of cyclisation but decreased catalyst posioning.[19]

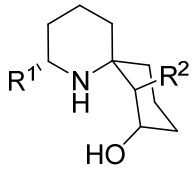
This strategy was also used in a very similar fashion by Harrity *et. al.,*[25] in the synthesis of functionalised spiropiperidines via tandem RCM, whereby commercially available tetraene **25** is treated with trifluoroacetic anhydride to yield TFA salt **26**, which upon ring closure using a Grubb's 2nd generation catalyst[26] affords the spiropiperidine **27** in good yield in a one pot reaction (**Scheme 7**).



25 **26** **27**

Scheme 7: Synthesis of spirocyclic α-tertiary amine piperidines

This methodology was developed as part of an overall strategy to access various Histrionicotoxin analogues **28** by exploiting the remaining unsaturated bond in the second ring system (**Figure 4**).



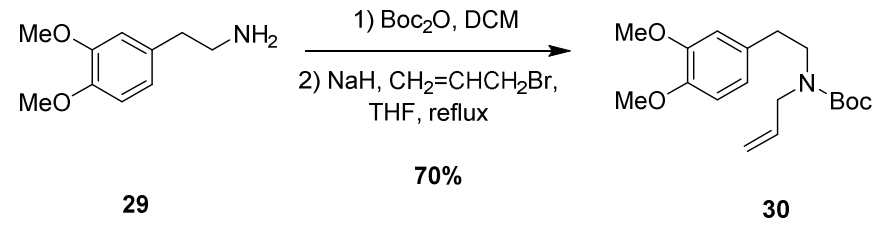
28

Figure 4: Histrionicotoxin analogues via RCM methodology

Thus it can be seen that work developed by both groups is efficient in forming cyclic structures of this type,[27] and that both cyclic and spirocyclic α-tertiary amines are made with relative ease.

In the first 14 step total synthesis of the Erythravine (**4**, **Figure 2**) by Hatakeyama *et. al.*,[28] the tetracyclic core is formed by an intramolecular ring closing metathesis reaction between an alkene and an alkyne[29] that is commonly referred to as an enyne metathesis reaction (RCEYM). Many different methods have been used to synthesise this specific family of alkaloids, as they display anti-xylotic properties and present a challenging set of targets in natural product synthesis.[30,31] The use of a ring-closing metathesis in the synthesis provides the shortest route that is currently known and showcases the utility of metathesis reactions in the synthesis of biologically important spirocyclic α-tertiary amines.[32]

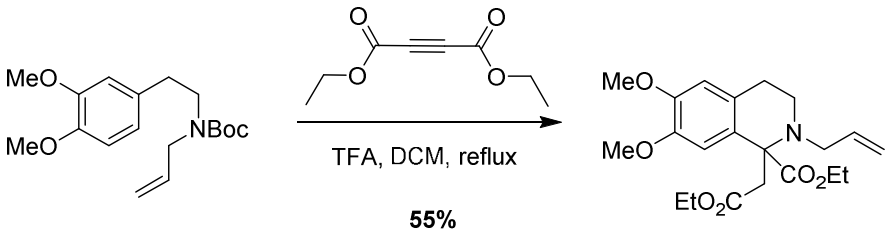
Interestingly the synthesis involves the construction of the 1st ring non-aromatic ring system by a Pictet-Spengler reaction.[33] By first protecting the commercially available starting material **29,** base-initiated alkylation followed, to give **30** in good yield over the 2 steps (**Scheme 8**).



29 30

Scheme 8: Boc protection and alkylation of dimethoxy phenylethylamine

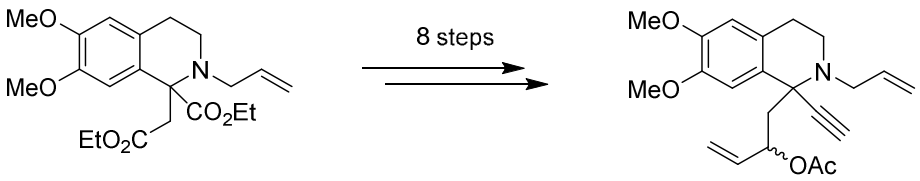
Upon refluxing **30** with trifluoroacetic acid and diethyl propiolate triggered the Pictet-Spengler type reaction[33] and afforded the cyclic α-tertiary amine **31** in moderate yield (**Scheme 9**).



30 31

Scheme 9: Pictet-Spengler type reaction

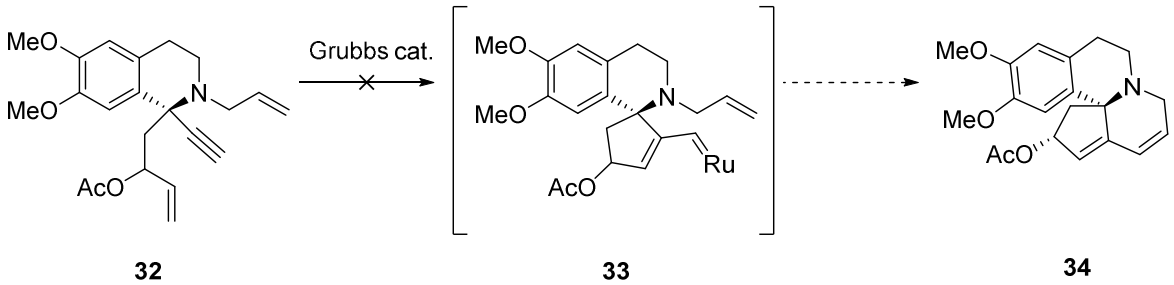
Over the course of 8 steps from diester **31**, the correct dialkene-alkyne configuration for the RCM reaction was complete, leaving **32** ready for the key step (**Scheme 10**).



31 32

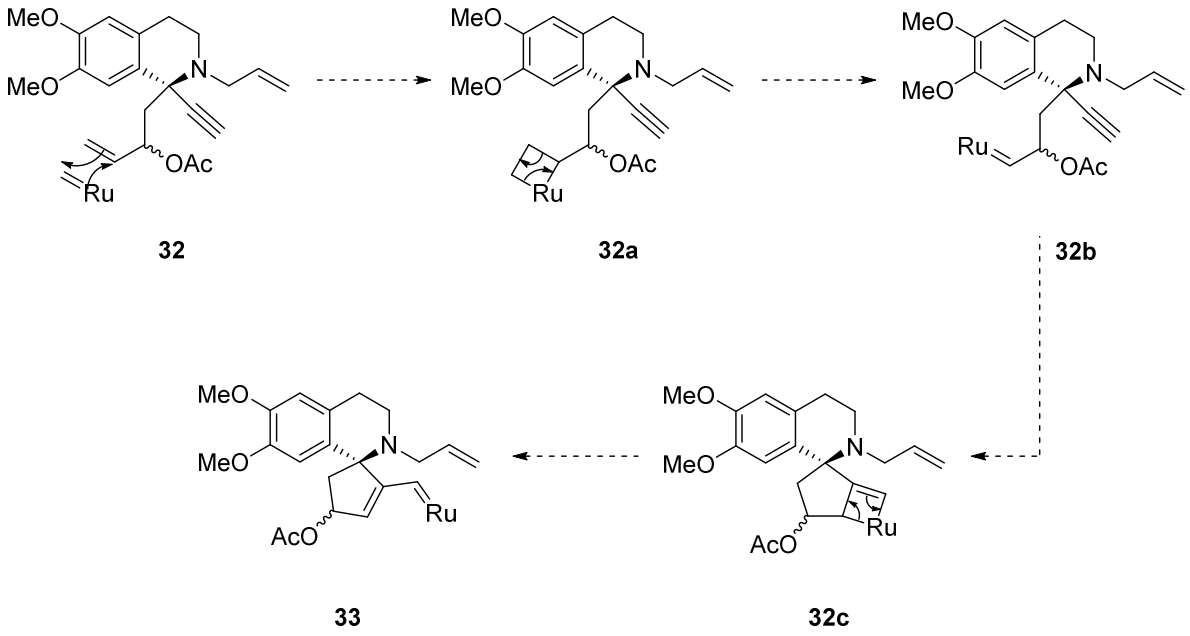
Scheme 10: Synthesis of pre-RCEYM starting material

In the paper and in related work by Mori et. al.,[34] the order by which the alkenes undergo ring chain metathesis was discovered - when **32** was treated with Grubb's 1st gen catalyst, metathesis of the allyl alcohol olefin and the alkyne to give **33** which would have led to the formation of **34**, was not observed (**Scheme 11**).



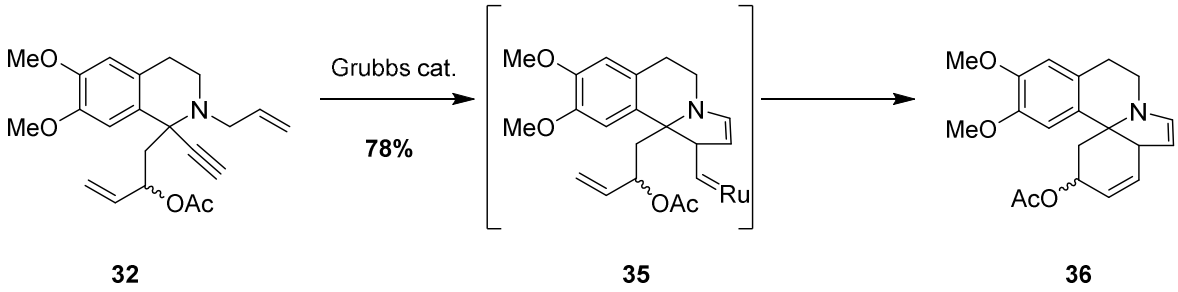
Scheme 11: Unobserved metathesis pathway and product

The two groups postulate that due to steric hindrance between the two double bonds and the constraint of the 5-membered ring, **34** is not formed.[28, 34] A Chauvin-based mechanism can rationalise these postulations; whereby if coordination of **32** to the ruthenium catalyst forms intermediate **32a**, cycloeliminating to form **32b,** where it can be seen that steric hindrance possibly prevents this pathway. If the constrained metallocyclobutane intermediate **32c** collapses, it would give spirocyclic ruthenium species **33** (**Scheme 12**).



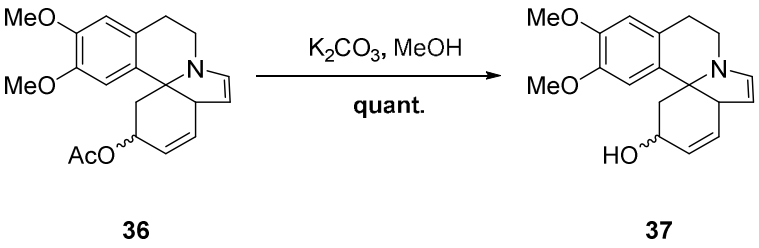
Scheme 12: Proposed mechanism rationalising why both steric hindrance and ring strain may prevent the formation of **34**

However, it was found that the other alkene bond undergoes a similar mechanism to form **35** instead, which upon refluxing with Grubbs 1st generation catalyst undergoes a standard ring closing reaction to form the desired erythravine skeleton **376** in good yield (**Scheme 13**).



Scheme 13: RCM reaction affording tetracyclic erythravine core

Simple hydrolysis of the acetyl protected compound **36** afforded the desired spirocyclic α-tertiary amine, (±)-erythravine in superb yield (**Scheme 14**).



Scheme 14: Quantitative hydrolysis to afford (±)-erythravine

The groups of Hatakeyama[28] and Mori[34] managed to show that by using RCM reactions the synthesis of both cyclic and spirocyclic α-tertiary amines in a concise and efficient manner is possible, as compared to pre-existing routes without ring closing metathesis steps originally took 24 steps to complete.[30]

1.3.2. Radical Ring Closures

In a 21 step total synthesis of (+)-Aspidofractinine **38** (**Figure 5**) by Spino, ring closing metathesis and radical ring closing reactions have been used with great efficiency to form the cyclic functionality that the structure contains.[35] The complex alkaloid along with many of its related family members; shows the ability to reverse multidrug resistance in vincristine-resistant KB cells,[36] and thus synthetic methods for its synthesis are of high value and interest.

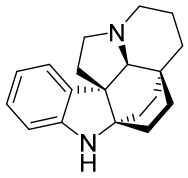


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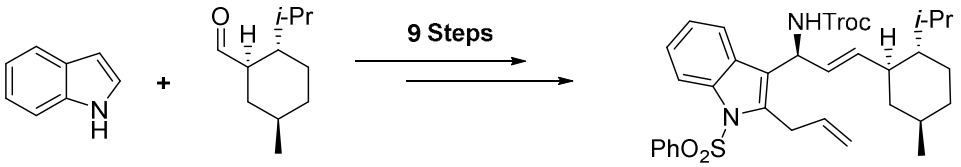
Figure 5: Indole based spirocyclic α-tertiary amine, (+)-Aspidofractinine

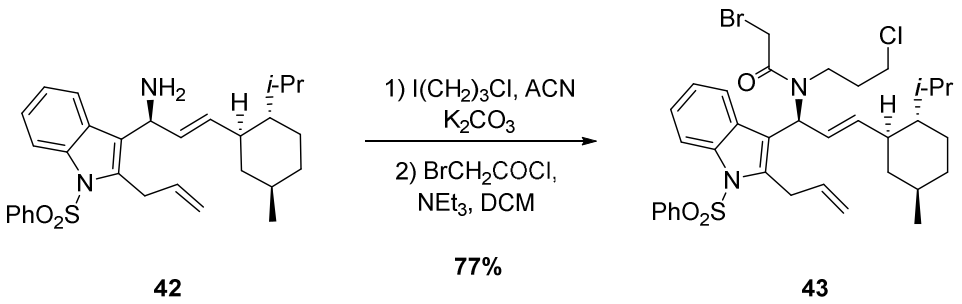
The synthetic route utilises cheap and readily available indole **39**, along with premade chiral auxiliary **40**, from which 9 relatively uneventful steps gave the main substrate **41** from which a number of crucial reactions were performed (**Scheme 15**).



39 **40** **41**

Scheme 15: 8 step strategy to main chiral substrate

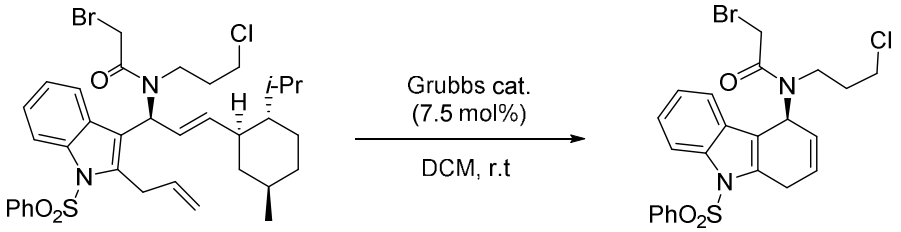
After cleaving the Troc protecting group to liberate free amine **42**, a simple alkylation via an S_N2 reaction with the dihaloalkane, in basic conditions, allowed the installation of the alkyl group. Subsequent reaction with bromoacetyl chloride furnished amide **43** in high yield over the 2 steps (**Scheme 16**).



42 **43**

Scheme 16: Two step alkylation and acylation reactions

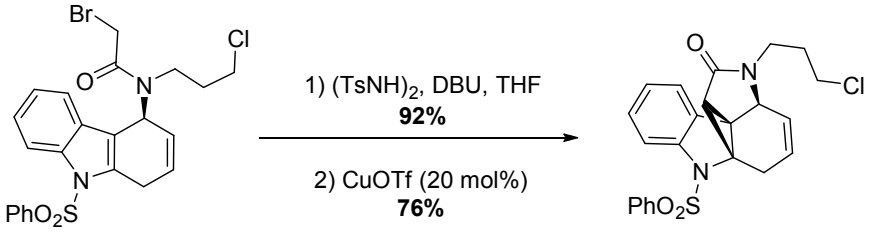
Spino then employed the use of Grubbs 2nd generation catalyst to form the 3rd ring in the synthesis. The RCM reaction of **43** proved very successful, affording the ring closed product **44** in high yield (**Scheme 17**).



43 **44**

Scheme 17: RCM reaction

Conversion of the α-bromoamide **44** to its α-diazoketone analogue occurred in a single step, from which a noteworthy Cu(I)-catalysed cyclopropanation reaction[37] occurred with complete chemoselectivity, giving **45** (**Scheme 18**).

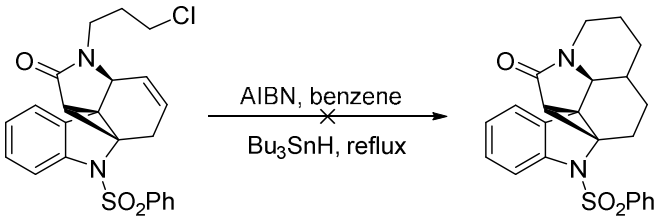


44 **45**

Scheme 18: Chemoselective cyclopropanation

Initially, Spino attempted to utilise the key radical ring closure at this stage, whereby treatment of **45** under radical initiating conditions (tributyltin hydride

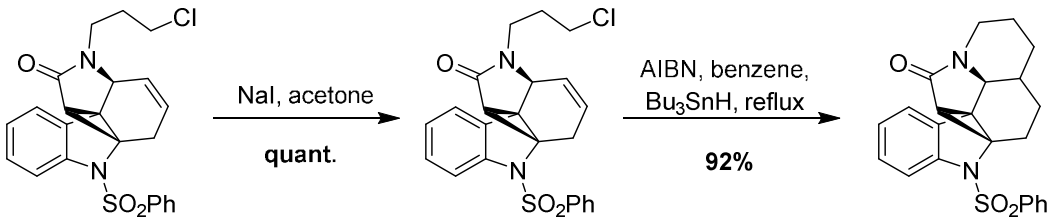
with azobisisobutryonitrile) was unsuccessful in the formation of the 5th ring system in complex compound **46**.



45 **46**

Scheme 19: Failed attempt at radical cyclisation

A number of radical cyclisation conditions were attempted, with multiple methods from the research groups of Magnus,[38] Rodriguez,[39] Heathcock[40] and Rawal[41] reporting similar successful closures in other natural product syntheses.[42] The success of *6-exo-trig* cyclisation was found to be dependent on a carbon-iodine bond rather than either carbon-chloro bond present in **45**. This conversion was easily performed by a Finkelstein reaction, and allowed the radical ring closure to occur, affording the cyclised product **46** in very high yield over the two steps (**Scheme 20**).

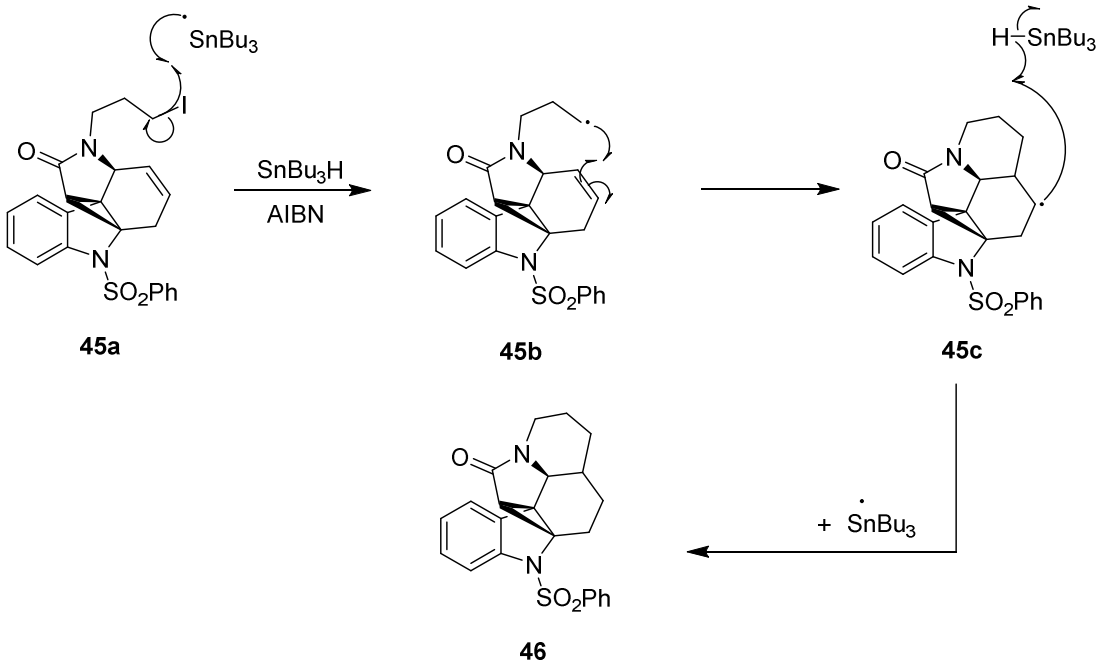


45 **47** **46**

Scheme 20: Finkelstein reaction and radical ring closure

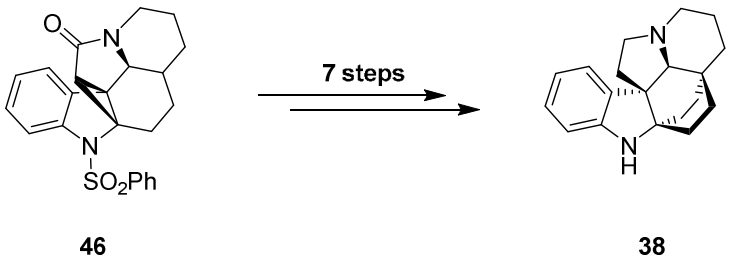
The ring closing reaction is thought to proceed via a radical mechanism presumably by initial carbon radical formation to give **45a** by homolytic cleavage, which upon reaction with the nearby alkene forms **45b** that in which intermediate **45c** regenerates the tin chain radical carrier and the ring closed product **46** (**Scheme 21**). The use of carbon-iodide bond was imperative

presumably due to the increased strength compared to either carbon-bromide/carbon-chloride bonds.



Scheme 21: Mechanism for radical ring closure

From there, a further 7 steps finished the synthetic route, arriving at the target spirocyclic α-tertiary amine, (+)-Aspidofractinine **39,** with an overall yield of 2.1%, with an average of 83% per step. It is clear that the use of both RCM and radical ring closures in this total synthesis allow the construction of this complex spirocyclic amine in a concise manner (**Scheme 22**).



Scheme 22: Further steps in the Aspidofractinine synthesis

Such radical cyclisations have been applied in the synthesis of other spirocyclic α-tertiary amines such as the Erthyrina alkaloid family and has been showcased by Banwell[43] in their synthesis of alkaloid skeleton **48** (**Figure 6**). This family of compounds with the methylenedioxy unit show curare-like and hypnotic activity, in addition to displaying interesting insecticidal properties.[44,45]

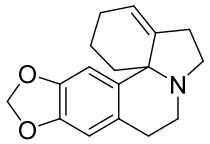


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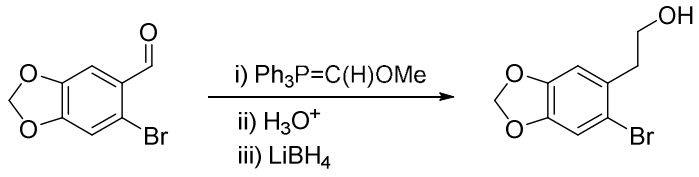
Figure 6: A member of the Erthyrina alkaloid family

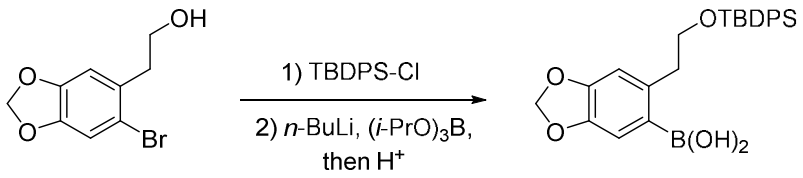
The synthetic approach started with a Wittig reaction of commercially available aldehyde **49**, which after protic workup and reduction with lithium borohydride under previously reported conditions afforded the desired alcohol **50** in high yield (**Scheme 23**).[46]



49 **50**

Scheme 23: Wittig reaction and subsequent protic reduction

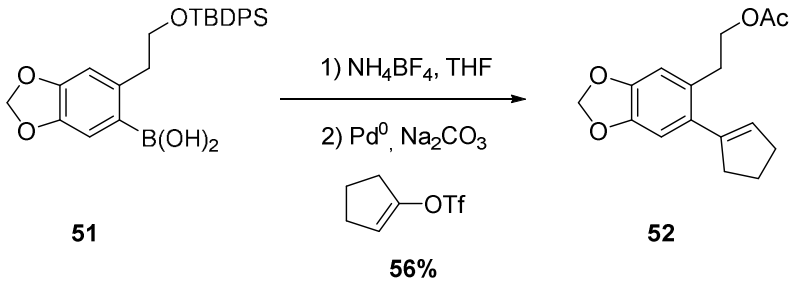
Treatment of **50** with TBDPS-Cl afforded the silyl protected ether**,** allowing the use of *n*-BuLi in efforts to exploit the bromide functionality by forming the boronic acid **51** (**Scheme 24**).



50 **51**

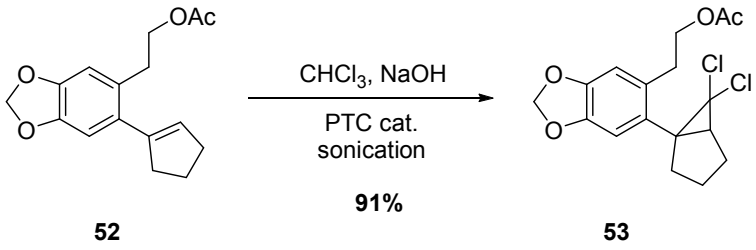
Scheme 24: Formation of protected boronic acid

With **51** in hand, the group employed an Suzuki-Miyaura cross coupling[47] with the premade enol triflate of cyclopentanone,[48] constructing the desired C-C bond. Hydrolysis of the resulting silyl ether and subsequent acetylation afforded **52** in good yield over the 3 steps (**Scheme 25**).



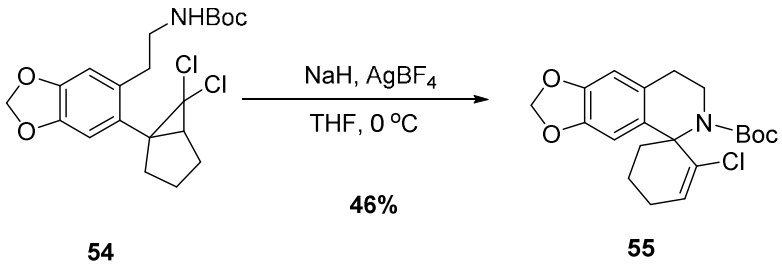
Scheme 25: Palladium cross-coupling reaction

An interesting reaction was implemented whereby the installation of a *gem*-dihalocyclopropane moiety was performed to set up the necessary platform for a spirocyclisation that the group reports as the first of its kind.[43] With **52** in hand, the dichlorocarbene insertion reaction was initiated using Makosza's phase transfer catalyst (PTC) conditions[49,50] and promoted by ultrasonication reported by Xu & Brinker[51] to give **53** in excellent yield (**Scheme 26**). Whilst the mechanism has not been properly investigated, the formation of a carbene intermediate has been excluded, and the implication of a metal complex has been suggested.[52,53]



Scheme 26: Dichlorocarbenation reaction

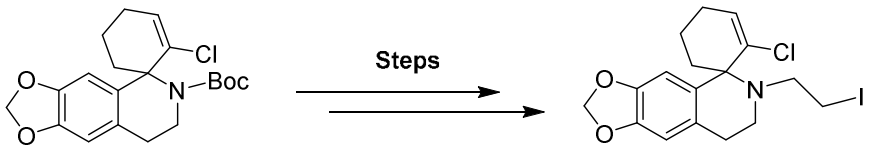
From there, after a few simple functional group introversions, the synthetic route arrived at a spirocyclisation step,[54] whereby **54** upon treatment with sodium hydride followed by silver tetrafluoroborate led to the formation of **55** in moderate yield (**Scheme 27**).



54 55

Scheme 27: Base-promoted spirocyclisation

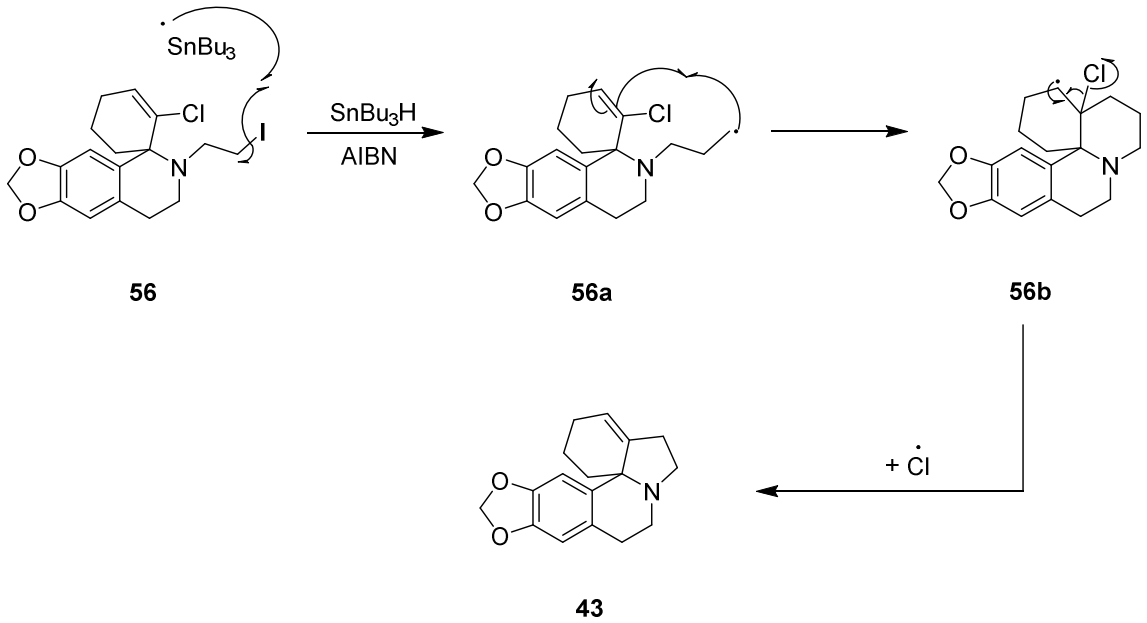
Further chemical manipulations established the required set up for the second cyclisation, this time utilising a similar approach as Spino's work, whereby a distal halide undergoes a radical cyclisation with a vinylic halide - a radical addition/elimination sequence (**Scheme 28**). This carbon radical cyclisation/Cl ejection reaction sequence is a very effective way of bridging an otherwise challenging gap, whereby other methods of S_N2 elimination and RCM are prohibited.[55]



55 56

Scheme 28: Further chemical manipulations to pre-radical cyclisation precursor

The mechanism is thought to proceed via a very similar route (**Scheme 29**) as in the ring closure before, by homolytic cleaving the carbon-iodide bond of **56** leading to the formation of carbon radical **56a**, that cyclises to give **56b,** but instead of hydride abstraction, chlorine radical ejection occurs as the last step leading to the cyclised product **43** (**Scheme 29**).



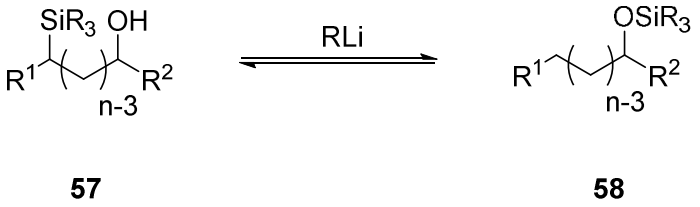
Scheme 29: Radical cyclisation/Cl radical elimination

The work of these aforementioned groups serves as an excellent demonstration whereby having distal hydrocarbon chains bearing carbon-halide terminals, nearby to an alkene, be it functionalised with a halogen or unfunctionalised, holds the possibility for radical cyclisation to occur with relative ease.

1.3.3. Organolithium Rearrangements

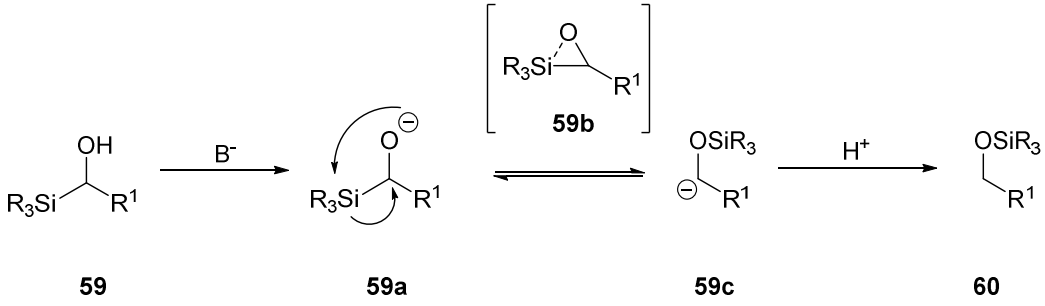
Brook Rearrangement

The 1,2-Brook rearrangement is an intramolecular 1,2-migration of an organosilyl group from carbon to oxygen promoted by an organolithium reagent acting as a base.[56] The scope has been expanded so silyl carbinol analogues **57** can undergo a 1,n-migration, allowing a variety of rearranged products **58** to be synthesised (**Scheme 30**).



Scheme 30: 1,2- and 1,n-Brook and Retro-Brook rearrangements

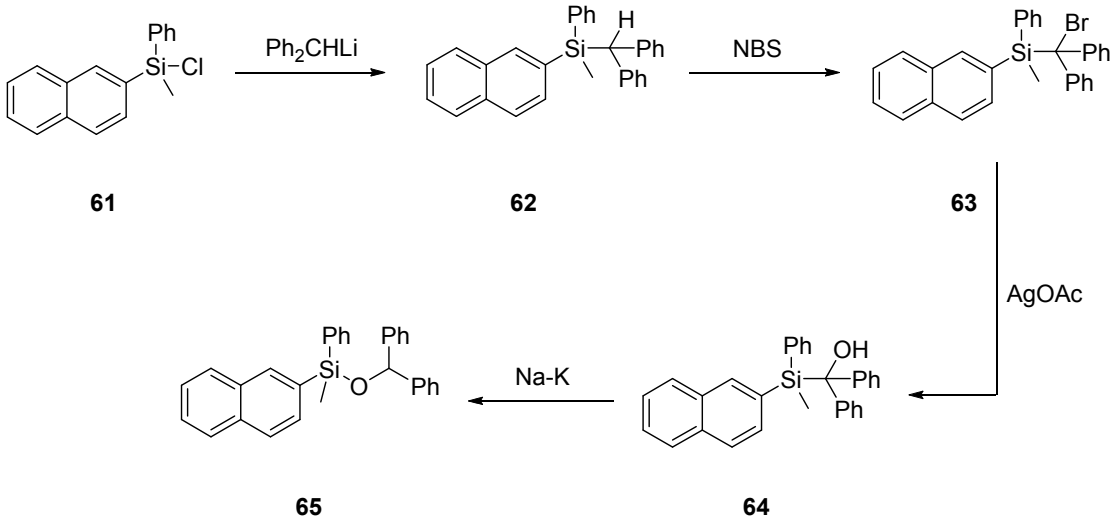
The mechanism proceeds by the deprotonation of the alcohol **59**, forming nucleophilic species **59a** that attacks the adjacent silyl position forming an transitional cyclic pentavalent silicon species **59b**. Subsequent ring opening of **59b** and protonation of carbanion **59c** by either the starting alcohol or its conjugate base produces the silyl ether **60** (
Scheme 31).



Scheme 31: Mechanism of the Brook rearrangement

The thermodynamic driving force of the reaction is the formation of O-Si bond over the existing C-Si bond, due to the increased bond strength by stronger orbital overlap between the two atoms involved.

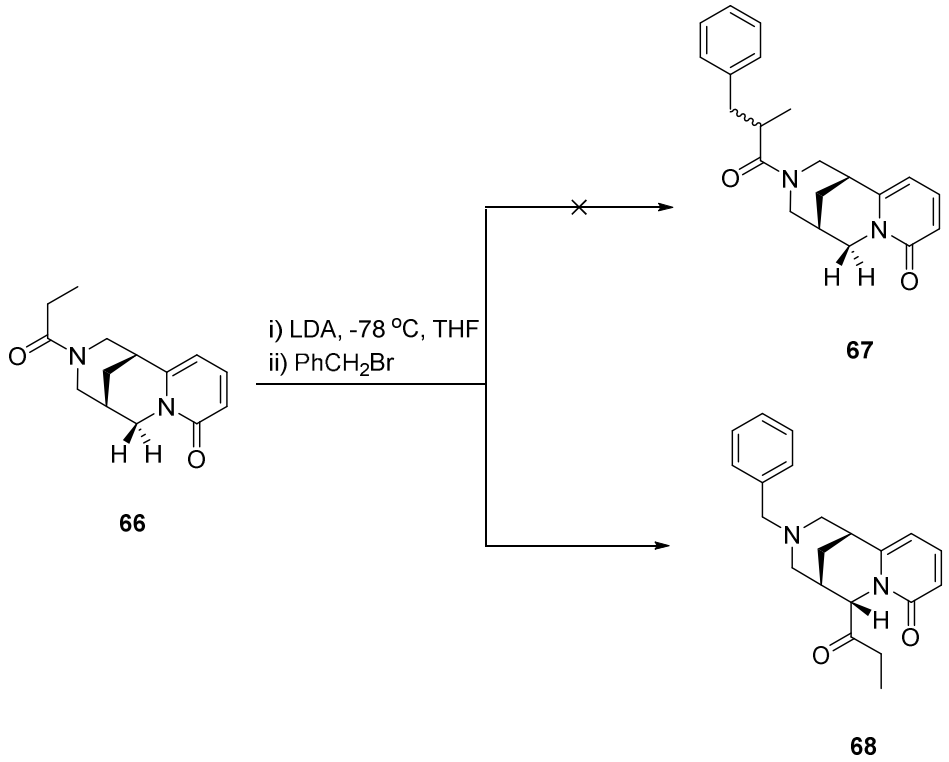
The Walden cycle (**Scheme 32**) is a key demonstration of the Brook rearrangement,[56] whereby silyl complex **61** is treated with benzhydrllithium causing the displacement of a chloride ion to give **62**, which upon reaction with NBS installs the bromine functionality, affording **63**. By then using silver (II) acetate, the hydroxyl partner **64** is formed, from which the Brook rearrangement is triggered to give the silyl ether **65**.



Scheme 32: The Walden Cycle demonstrating the Brook rearrangement

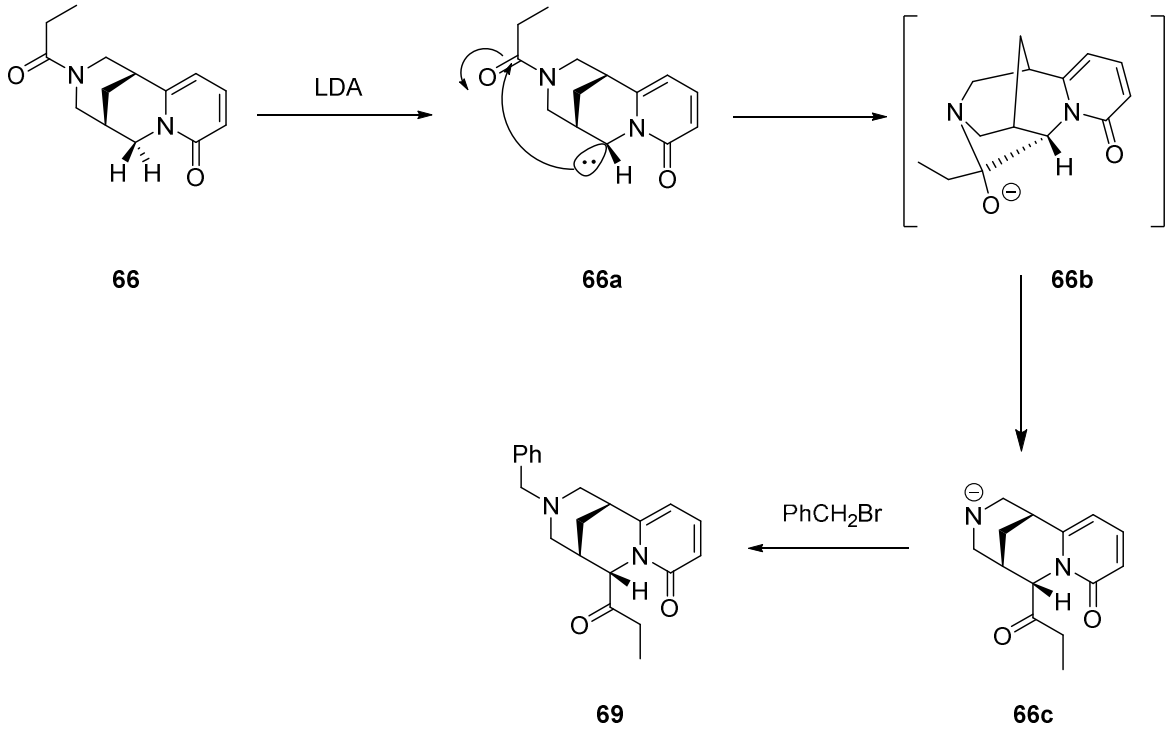
N-C Acyl Migration

During research by Rouden *et. al*.[57] into the use of chiral inducing agents for use in enantioselective alkylations, an unexpected result was found when the starting material (-)-cystisine **66** failed to alkylate to yield **67**, but rather N-C acyl migration occurred in quantitative yield to give rearranged product **68** with LDA and benzyl bromide (**Scheme 33**).



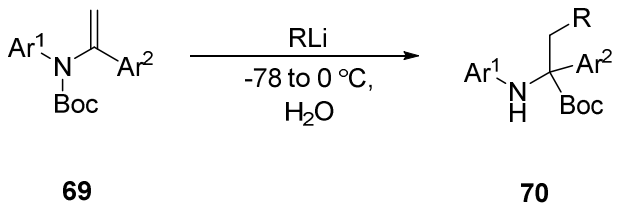
Scheme 33: Unexpected N-C acyl migration

The unexpected rearrangement is proposed to occur by initial α-deprotonation of **66** by LDA, leading to an intramolecular cyclisation of **66a** with the distal amide carbonyl, in which the transition state **66b** collapses yielding anion **66c,** in which simple S_N2 alkylation with benzylbromide presents the rearranged final product **69** (**Scheme 34**).



Scheme 34: Proposed mechanism for N-C acyl migration

Work by Coudert *et. al.,*[58] displayed a similar rearrangement involving the N-C migration of a Boc protecting group when carrying out carbolithiations of acyclic starting materials **69** which gave rearranged α-tertiary amines **70** (**Scheme 35**).



Scheme 35: N-C migration of the Boc group

The reaction was further investigated to reveal that it occurs not only with satisfactory yields and a toleration of different aromatic substituents, but also allows the use of a variety of commercial organolithium reagents (**Table 1**).

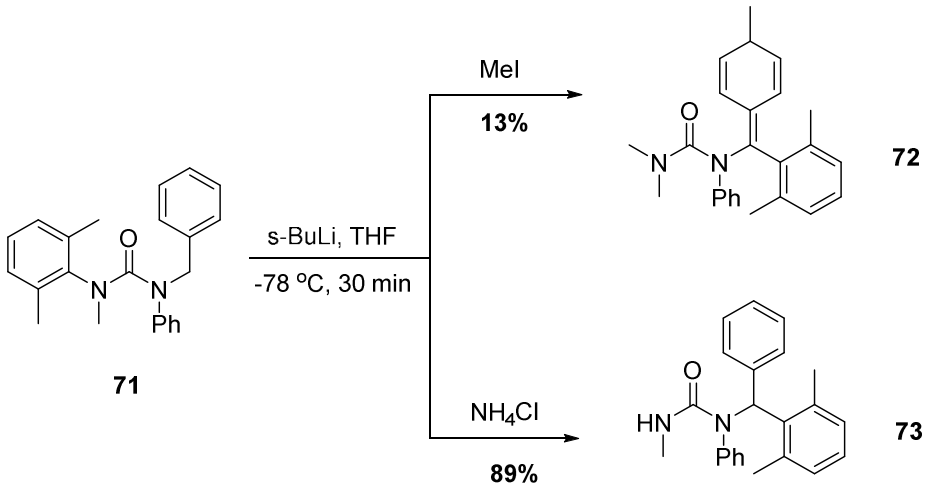
Entry	Ar^1	Ar^2	RLi	Yield 70 (%)
1	Ph	Ph	Me	75
2	Ph	Ph	Ph	78
3	Ph	Ph	LDA	89
4	Ph	Ph	$N(PhCH_2)(Me)$	50
5	2-Me-Ph	Ph	Me	80
6	2-Me-Ph	Ph	Ph	81
7	3-MeO-Ph	Ph	Me	68
8	3-MeO-Ph	2-Napthyl	Me	56
9	3-MeO-Ph	Ph	*n*-Bu	89
10	3-MeO-Ph	Ph	LDA	86
11	3-MeO-Ph	2-Benzo-furyl	*n*-Bu	26
12	3-MeO-Ph	2-Furyl	*n*-Bu	14

Table 1: Scope of N-C migration

Rearrangement of Benzylic Ureas

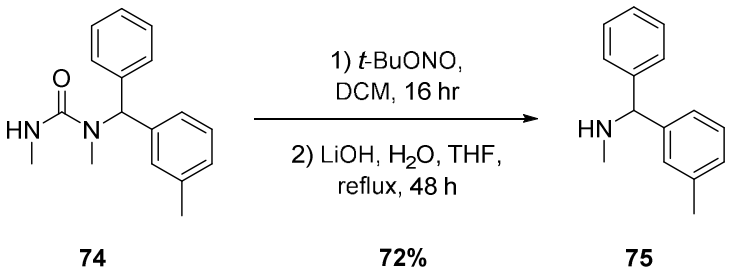
Experimental work with the aim of investigating the site of lithiation of benzylic ureas by Clayden *et. al.,*[59] led to the beginning of a multitude of different organolithium rearrangements, opening up many avenues into the synthesis of various primary, secondary and tertiary α-amines.

It was discovered that when urea **71** was treated with sec-BuLi, lithiation occurred at the benzylic position and induced a unique N-C aryl transfer to the α-carbon of the urea. Different quenching agents were used to trap the products that were formed, discovering that when quenched with methyl iodide **72** was produced in poor yield, presumably due to the instability of dearomatisation of the secondary aryl ring, but when quenched with ammonium chloride rearranged urea **73** was formed in very high yield (**Scheme 36**).[60]



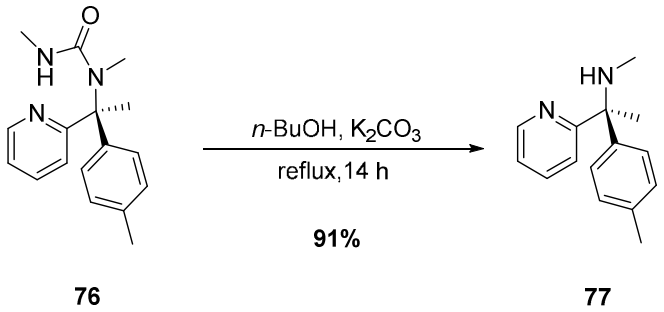
Scheme 36: Rearrangement of benzylic ureas

A range of benzylic ureas were subjected to similar conditions and were found to be successful candidates in the organolithium rearrangement, regardless of the steric or electronic nature of the migrating aryl ring. Deprotection of one of the examples **74** was performed by first converting the urea into a nitroso intermediate and refluxing in lithium hydroxide that allowed the synthesis of α-secondary aryl amine **75** in good yield (**Scheme 37**).



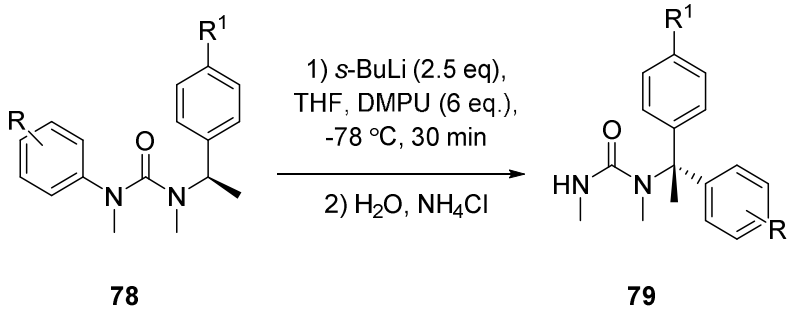
Scheme 37: Urea deprotection

The use of n-butanol over prolonged refluxing with lithium hydroxide was also found to be extremely beneficial for not just these examples but for the majority of all previous work on ureas,[61] when work on N-pyridyl urea **76** providing a clean, concise way to free amine **77** in excellent yield (**Scheme 38**).[59]



Scheme 38: Modified conditions for urea hydrolysis

The scope of the rearrangement of benzylic ureas was broadened to include a stereospecific version of this N-C aryl migration, and was performed using enantiomerically pure α-methylbenzylureas **78** that highlights that the reaction not only tolerates both electron donating and withdrawing substituents on the migrating aryl ring but also occurs with minimal loss of enantiomeric purity,[59] affording ureas **79** which upon deprotection liberate the expected α-tertiary amines. (**Scheme 39**, **Table 2**).



78 79

Scheme 39: Stereospecific rearrangement of enantiomerically pure starting materials

Entry	(*R*)-/(*S*)- 78	R	R¹	Yield 79 (%)	er 79
1	(*R*)-	4-MeO-Ph	H	(*R*)-82	97:3
2	(*S*)-	4-F-Ph	H	(*S*)-34	99:1
3	(*S*)-	4-Cl-Ph	H	(*S*)-51	98:2
4	(*S*)-	3-Cl, 4-F-Ph	H	(*S*)-69	>99:1
5	(*S*)-	2,3-Napthyl	H	(*S*)-n.d.	95:5
6	(*S*)-	3,4-Napthyl	H	(*S*)-88	>97:3
7	(*S*)-	H	4-MeO-Ph	(*S*)-73	>98:2
8	(*S*)-	2-Me	4-MeO-Ph	(*S*)-64	99:1

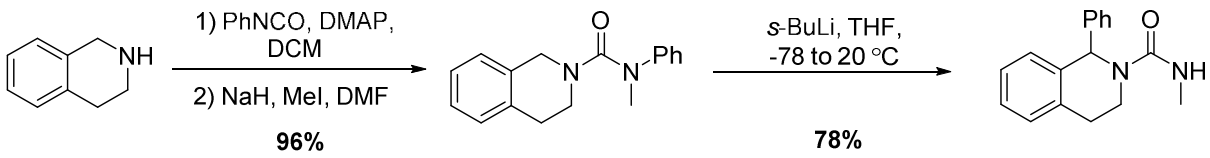
Table 2: Scope of stereospecific rearrangement

These findings heavily suggest that the migration proceeds *via* a lithiated intermediate that is stabilised, as the products of the reaction are formed with retention of configuration. Work in this field has deepened, with the use of (-)-sparteine or a (+)-sparteine surrogate allowing the construction of amines bearing tertiary substituents in an asymmetric manner.[62]

Rearrangement of Cyclic substrates

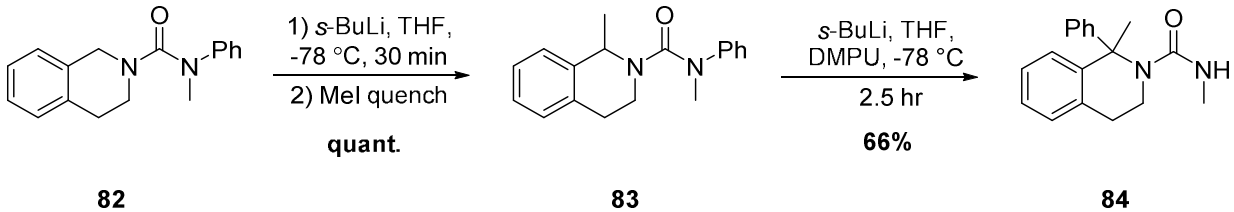
The scope of the rearrangement has also been broadened to include cyclic starting materials, tuning the methodology to being able to specifically make cyclic α-tertiary amines.[63] Tetrahydroisoquinoline substrates were found to successfully rearrange, showing that cyclic substrates can provide the necessary platform by which cyclic and spirocyclic α-tertiary amines can be constructed.

The stage for rearrangement was established by the initial condensation of phenylisocyanate with tetrahydroisoquinoline followed by *N*-methylation to give **80**, which under the usual lithiation conditions (but without DMPU) yielded the rearranged product **81** in good yield (**Scheme 40**).



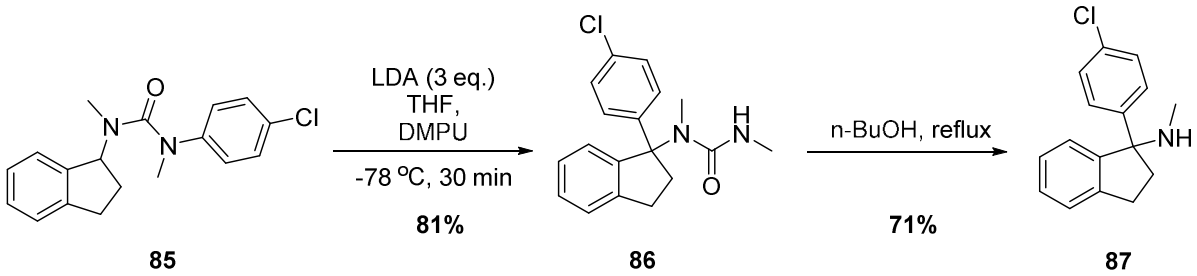
Scheme 40: Rearrangement of unsubstituted tetrahydroisoquinoline substrate

The rearrangement was also successful on substituted tetrahydroisoquinoline substrates. First **82** was deprotonated and methylated to give **83**, then under standard lithiation conditions and phenyl migration occurred via the tertiary carbanion to afford the rearranged product **84** in good yield. (**Scheme 41**).



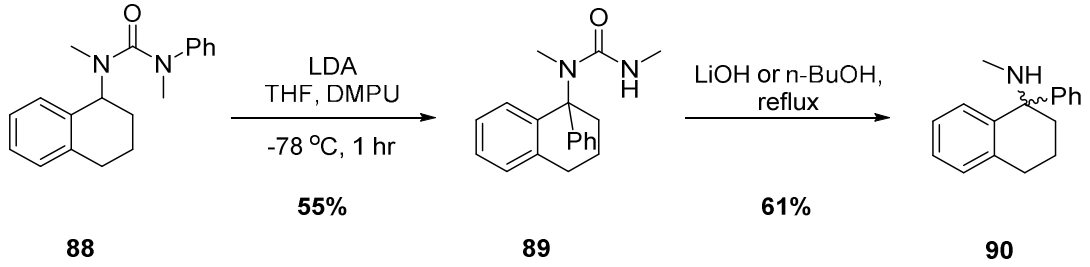
Scheme 41: Rearrangement of α-substituted tetrahydroisoquinoline substrate

In addition to this, a number of carbocyclic substrates were also found to successfully rearrange. The 5-membered carbocycle **85** rearranged to give **86** and upon deprotection by refluxing in n-butanol afforded the carbocyclic α-tertiary amine **87** in good yield (**Scheme 42**)



Scheme 42: Synthesis of carbocyclic α-tertiary amines

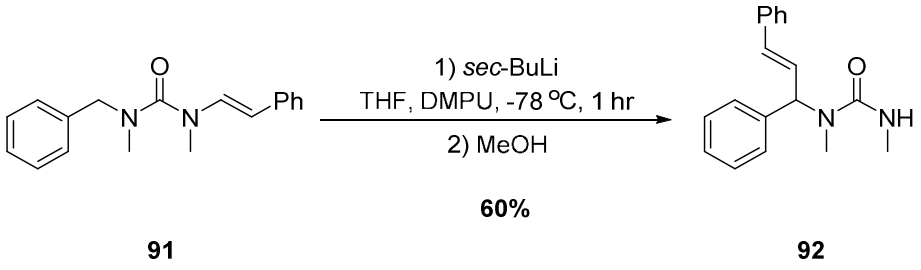
Alongside these findings, 6-membered carbocycle analogue **88** was lithiated under usual conditions, forming rearranged urea **89**. The free amine **90** was acquired by refluxing **89** in either LiOH or *n*-butanol (**Scheme 43**).[64]



Scheme 43: Rearrangement of carbocyclic substrates

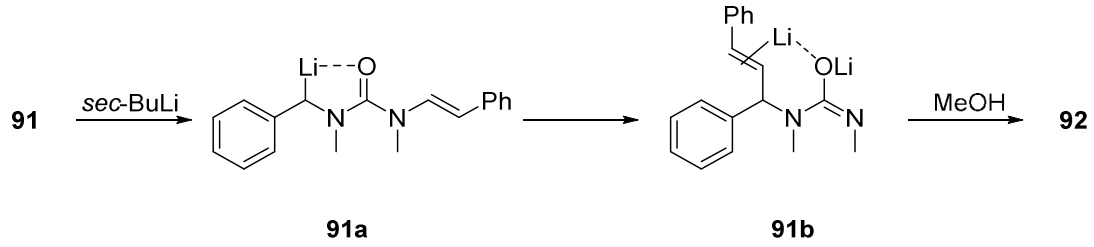
Following these findings that even electron rich aryl groups migrate, further work by Clayden *et. al.*[65] discovered an N-C migration of alkenyl groups by vinylation of a tertiary carbanion, allowing the synthesis of functionalised quaternary centres bearing alkenyl substituents, in addition to aryl or simple non-branched alkyl groups previously reported.[59]

Initial experiments found that styrenyl urea **91** was lithiated under usual conditions with *sec*-BuLi and quenched with methanol to afford urea **92** as a single *Z*-alkene geometrical isomer (**Scheme 44**).



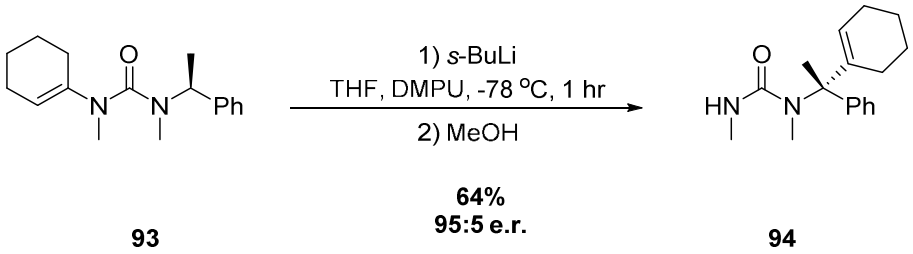
Scheme 44: Rearrangement of styrenyl urea

The mechanism proposed proceeds by α-deprotonation of urea **91** to give benzyllithium **91a,**[59] following which migration of the styrenyl group occurs via the tertiary carbanionic centre. A second deprotonation would result in a chelated cinnamyllithium **91b**[66] that is quenched to afford the rearranged urea **92** (**Scheme 45**).



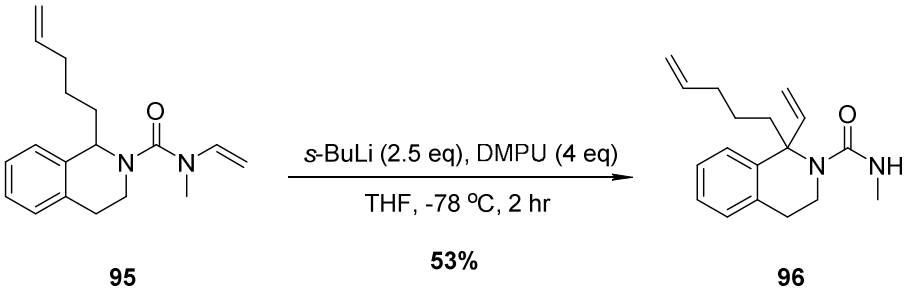
Scheme 45: Proposed mechanism of the intramolecular vinyl migration

The methodology was used to synthesise a number of different vinyl migrated products with retention of stereochemistry when enantiomerically pure starting materials were used. An excellent example is the lithiation of **93** to give the rearranged urea **94**, as it occurs not only with an electron rich, bulky cyclohexenyl substituent but also with minimal loss of e.r. (**Scheme 46**).



Scheme 46: Rearrangement of cyclohexenyl urea

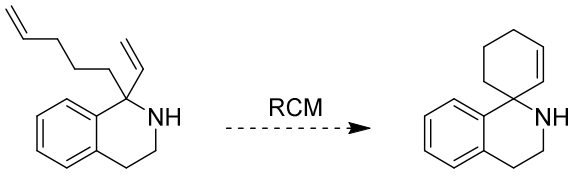
Using the same methodology, the paper reports the construction of a urea based on a tetrahydroisoquinoline core, and poses the ability to construct cyclic and potentially spirocyclic α-tertiary amines. When **95** was lithiated to give the rearranged urea **96**, such migration of the vinyl group[65] poses the opportunity to exploit a potential intramolecular ring closing metathesis reaction (**Scheme 47**).



95 96

Scheme 47: Intramolecular vinylation

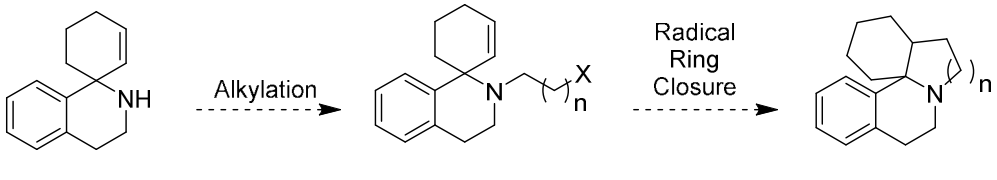
Whilst in the literature the organolithium rearrangement shows ability to tolerate a variety of other substrates and migrating groups, the specific migration of the vinyl group of **95** to give **96** poses the ability for a future RCM reaction. Hypothetically if the urea was hydrolysed using optimal conditions to give **97,** the possibility for metathesis afford spirocyclic α-tertiary amine **98** in just a few steps is promising (**Scheme 48**).



97 98

Scheme 48: Potential for ring closing metathesis to give spirocycle

Intramolecular vinylation followed by RCM to give **98** shows the potential to synthesis the Erythravine core in a similar fashion to both Spino[35] and Banwell's work.[43] By first alkylating spirocycle **98** installing a distal carbon-halide bond to give **99**, and then performing a radical cyclisation by under the same conditions as reported in the literature,[35, 43] potentially the tetracyclic erythravine core **100** could be constructed with relative ease**.** In addition to this, the newly formed ring could be of various sizes (n=1, 2, etc) if the corresponding alkylating agent was used (**Scheme 49**).



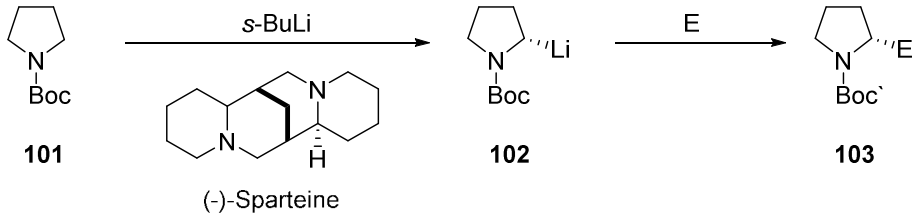
98 99 100

Scheme 49: Possible sequence to afford an Erythravine carbon framework

The rearrangement has the potential to assemble a variety of cyclic and spirocyclic α-tertiary amines, and since the intramolecular vinylation work has been shown to proceed with enantioselectivity,[59] the rearrangement of enantiomerically pure heterocyclic starting materials could give spirocycles in enantiomeric excess.

The availability of enantiopure heterocyclic starting materials is limited with most being available as only one form from the chiral pool and in many cases prohibitively expensive, however work by Peter Beak[67] holds precedent for stereoselective and enantioselective substitutions using chiral ligands such as (-)-sparteine that allows a greater range of enantiopure acyclic and cyclic starting materials.

Early work by Beak developed the asymmetric deprotonation of Boc protected pyrrolidines, whereby treating substrate **101** with sec-BuLi with (-)-sparteine creates lithiated intermediate **102**, which can then react with different electrophiles to give enantioenriched products **103** with high enantiomeric excesses (**Scheme 50**, **Table 3**).[67]

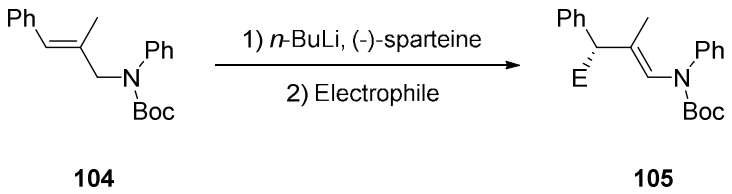


Scheme 50: Asymmetric lithiation and subsequent reaction with electrophiles

Product	(*R*)-/(*S*)-	E	Yield (%)	ee (%)
103a	(*R*)-	CO_2H	55	88
103b	(*R*)-	Ph_2COH	77	90
103c	(*S*)-	$Si(CH_3)_3$	71	94

Table 3: Range of electrophiles used in the reaction

The scope of the asymmetric deprotonation was broadened to include substrates in which alkyl groups can be installed with good enantioselectivity.[67] Boc protected allyl amine **104** was treated with n-BuLi in the presence of (-)-sparteine, that upon reaction with alkyl electrophiles afforded a variety of different products **105** in good yield and high er (**Scheme 51**, **Table 4**).



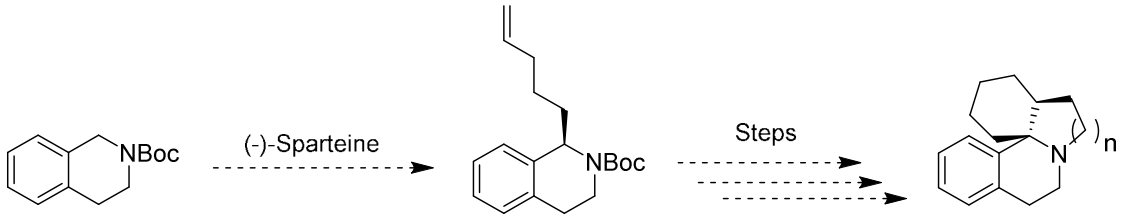
104 **105**

Scheme 51: Enantioselective alkylation reaction

Product	Electrophile	E	Yield (%)	er
105a	$PhCH_2Br$	$PhCH_2$-	86	93:7
105b	$CH_2=CHCH_2Br$	$CH_2=CHCH_2$-	85	90:10
105c	$(CH_2)_5CO$	$(CH_2)_5COH$-	77	93:7

Table 4: Various alkylations achieved using various electrophiles

Hypothetically, by combining the the two different methods, tetrahydroisoquinoline could be alkylated enantioselectively to give **106**, holding potential for an enantioselective synthesis of Erythravine's carbon framework **107** (**Scheme 52**).



106 **107**

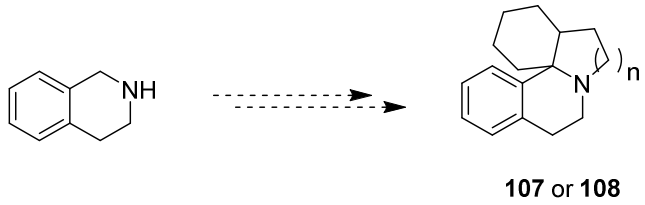
Scheme 52: Possible enantioselective synthesis of Erythravine core

If combined with the organolithium rearrangement that has been developed to make both spirocyclic and cyclic α-tertiary amines, an enantioselective synthesis could be possible.

2 Results and Discussion

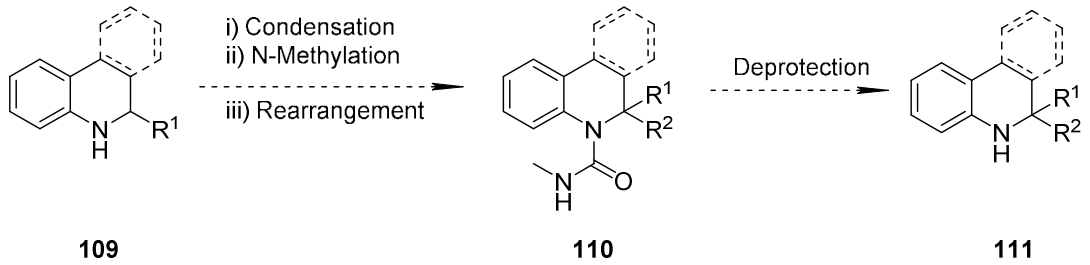
2.1 Aims of Project

The aims of the project are effectively split into two halves, with the first aim to showcase the rearrangement for utility in natural product synthesis by synthesising the saturated carbon skeleton versions of Erythravine **107** (when n = 1) and HomoErythravine **108** (when n = 2) core from tetrahydroisoquinoline, using both the ring closing metathesis[25] and radical ring closure[35,43] chemistry developed on similar systems (**Scheme 53**)



Scheme 53: Project aims Erythravine (n = 1) and Homoerythravine core (n = 2)

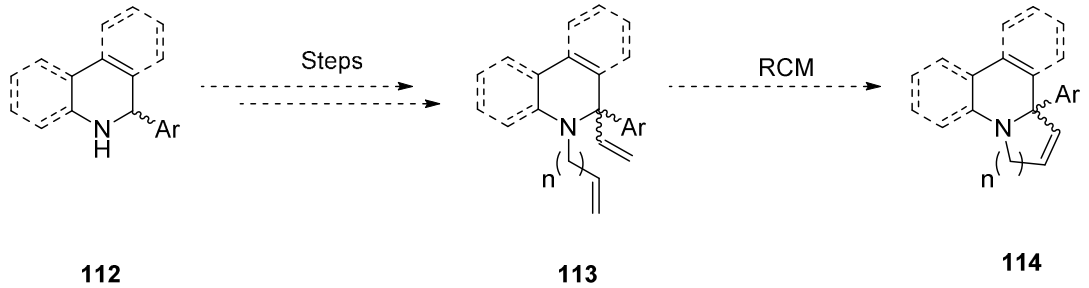
The second aim is to explore the scope of the organolithium rearrangement by using various substituted heteroaromatic systems **109**, which upon the usual 3 step process of condensation, N-methylation rearranged ureas **110** could open up a number of novel rearranged products if they were successfully deprotected to form amines **111**. A subset of these will then be selected according to their drug likeness and similarity to natural products, further showcasing the utility of the organolithium rearrangement (**Scheme 54**).



Scheme 54: Aim of expanding the scope of organolithium rearrangement

An enantiopure approach could be possible based on the work of Beak, which could furthermore allow the synthesis of these novel compounds in enantiopure form.

By using aryl substituted substrates **112** and combining urea condensation, methylation and migration of vinyl groups, followed by N-alkylation to deliver compounds **113** with two terminal alkenes, ring closing metathesis methodology could potentially form various spirocyclic and cyclic α-tertiary amines **114**. By combining these pre-existing methods, various substrates could be accessed and a range of interesting targets could potentially be accessed using this chemistry (**Scheme 55**).



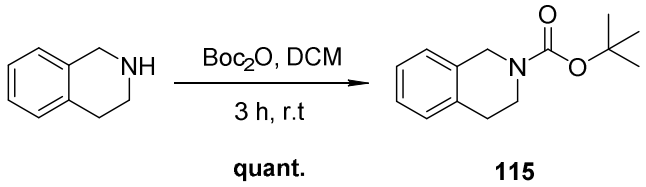
Scheme 55: Potential for this chemistry to synthesise interesting targets

If the installation of the aryl group could be performed in an enantiopure fashion, this methodology could be used to synthesise enantiopure compounds that are otherwise challenging, in a concise manner.

2.1.1. Synthesis of Erythravine Core

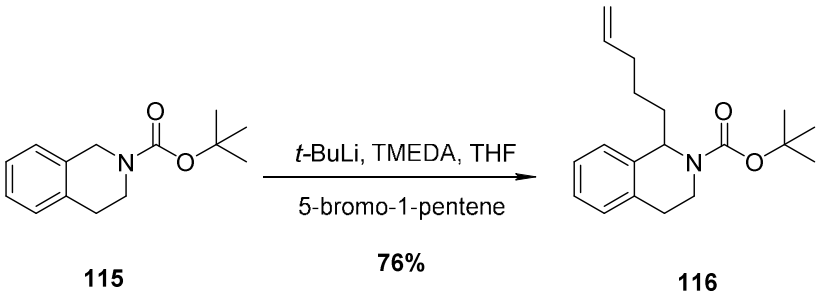
The synthetic route designed for the synthesis of Erythravine and Homoerythravine, showcasing the utility of the organolithium rearrangement, started by using commercially available tetrahydroisoquinoline, as the initial carbon framework from which the spirocyclic molecule could then be created.

Starting with a simple reaction of the secondary amine with di-*tert*-butyl dicarbonate (Boc_2O) occurred affording **115** with no issues, providing the necessary protection required for the following transformation (**Scheme 56**).



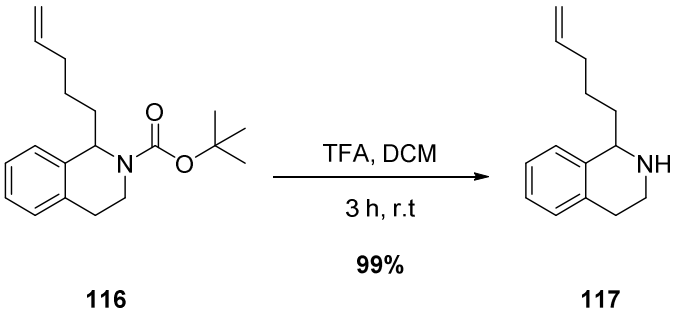
Scheme 56: Boc protection of tetrahydroisoquinoline

Treatment of **115** with *tert*-butyllithium lead to deprotonation at the α-position, that successfully reacted with electrophilic 5-bromo-1-pentene to give **116** in good yield. The alkylation established the necessary terminal olefinic side chain for the planned future metathesis reaction (**Scheme 57**).



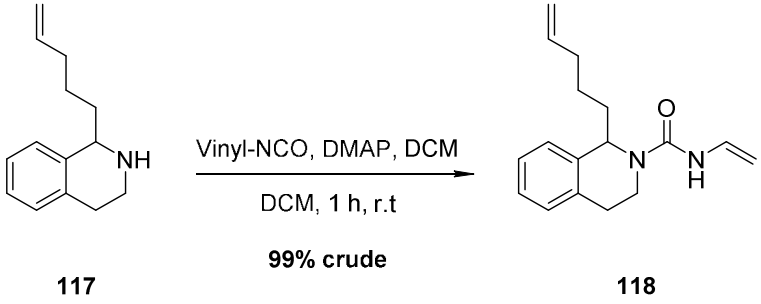
Scheme 57: *tert*-BuLi alkylation with 5-bromo-1-pentene

Deprotection of **116** using trifluoroacetic acid occurred with ease to give **117** quantitatively (**Scheme 58**).



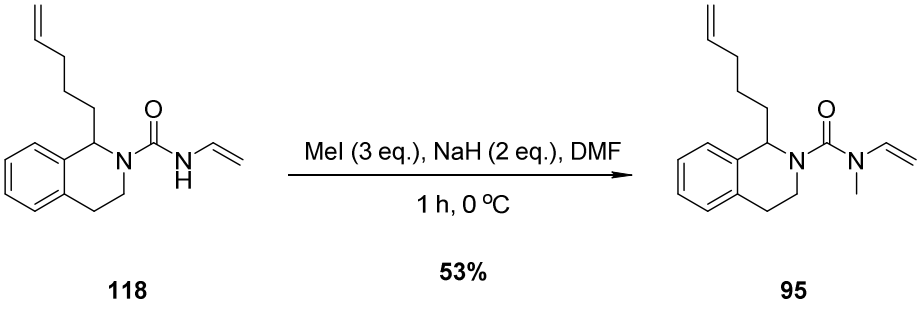
Scheme 58: Acid deprotection to give the free alkylated amine

With the deprotected secondary amine in hand, condensation of **117** with vinyl isocyanate (Vinyl-NCO) afforded the unstable intermediate **118** that was taken forth to the next step without purification (**Scheme 59**).



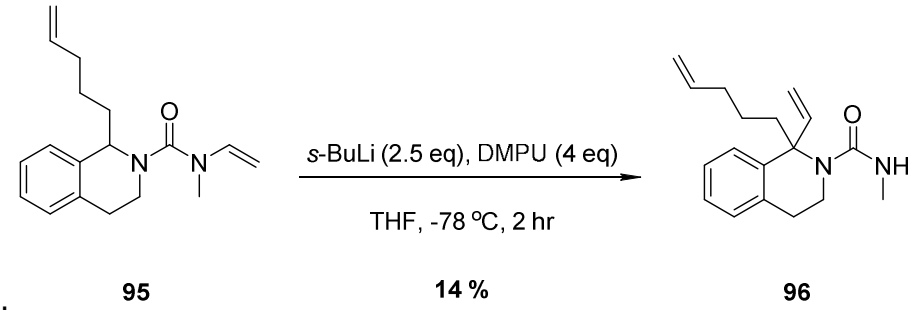
Scheme 59: Condensation reaction with Vinyl isocyanate

The unstable compound was then *N*-methylated by treatment with sodium hydride and methyl iodide to afford **95**, which wasn't purified prior to the rearrangement reaction planned. The intermediate was made and used on the same day as the rearrangement, as it was previously reported in a short report by Simon Herbert that the compounds were especially susceptible to decomposition (**Scheme 60**).



Scheme 60: N-methylation under standard conditions

The rearrangement reaction was then attempted according to the literature published by the group. Initially, the addition of *sec*-BuLi to **95** in THF and DMPU led to the migration of the vinyl group to establish the α-tertiary amine **96**, albeit in very poor yield (**Scheme 61**)



Scheme 61: Migration of vinyl group

The purification of the crude rearranged product often proved difficult, isolating much less material than was evident in the crude ^{1}H NMR spectroscopy and often impurities associated with its decomposition coeluting and hampering the purity of the final product.

Numerous attempts were made to optimise the reaction to obtain product in any appreciable yield. Such changes were made to the procedure based upon observations on crude ^{1}H NMR spectra, with the main finding being the order of reagent addition. DMPU was added an hour after the initial injection of *sec*-butyllithium as it could be seen from crude ^{1}H NMR spectroscopy that DMPU degradation products were forming, presumably from having a high local concentration of DMPU upon addition of the organolithium reagent to the reaction mixture. With such changes, a significant difference was seen between the two proton spectra, potentially providing evidence for this theory. Secondly, the reaction time was increased as starting material could be seen easily via ^{1}H NMR that starting material was present, deduced by the unchanged position of the distinctive methyl proton alpha to the urea nitrogen, and took on average 3-4 hours more than the literature procedures for rearrangement of aryl substituents.

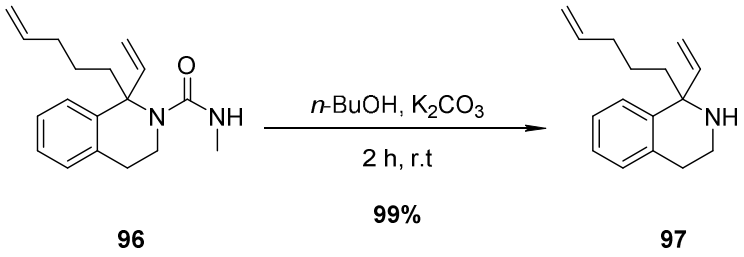
Despite these changes, the maximum yield that was obtained for this product was still 34%, causing a severe pinch in the synthesis, resulting in both a considerable loss of material and the rapid consumption of vinyl isocyanate - a significant issue of this project.

Before attempting the rearrangement chemistry, a total of 0.1 g vinyl isocyanate was leftover from various colleague's experiments. The ease of obtaining more became the bottleneck in the synthesis due to Sigma-Aldrich being the sole commercial supplier, whose stock continued to be backordered 6-7 months at a time. Eventually 5.0 g of vinyl isocyanate was obtained, however it had polymerised into a white solid prior to even being opened for use in the rearrangement.

Alternatively, synthesising vinyl isocyanate in the laboratory was not a viable solution to the problem, due to the inherent characteristics of vinyl isocyanate being a very volatile and toxic compound combined with a lack of methods by which it can be made in the laboratory. A single industrial based procedure was found that involved the use of complex industrial apparatus, in which theoretical attempts to scale down to a laboratory level induced multiple issues in order circumvent industrial machinery such that it was not viable.

Despite this issue, which only became problematic later on in the project when the rearranged product and stock of vinyl isocyanate was depleted, a total of 150 mg was available to carry forth for further synthetic steps.

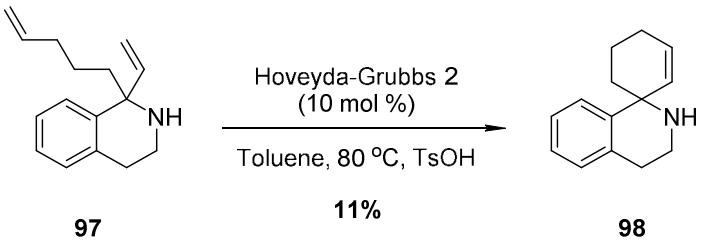
The synthesis continued with the hydrolysis of the rearranged urea **96** which fortunately occurred in quantitative yield giving **97** that required no further purification (**Scheme 62**).



96 97

Scheme 62: Hydrolysis of urea under standard conditions

The ring closing metathesis reaction of **97** had previously been investigated briefly by Simon Herbert during his time in the group. In a short report written by him, it was found the use of p-toluenesulfonic acid (pTSA) was imperative for the success of the metathesis reaction. This was not a surprising result due to the similar tactics used by Harrity *et al.,*[25] as it plays a crucial role in forming an *in situ* acid salt that prevents nitrogen from poisoning the catalyst. With **97** in hand, the unpublished protocol Simon developed was implemented by using Hoveyda-Grubb's 2nd generation catalyst, with pTSA present prior to the addition of the catalyst to the system, and was successful, forming **98**, albeit in very low yield after extensive purification (**Scheme 63**).



97 98

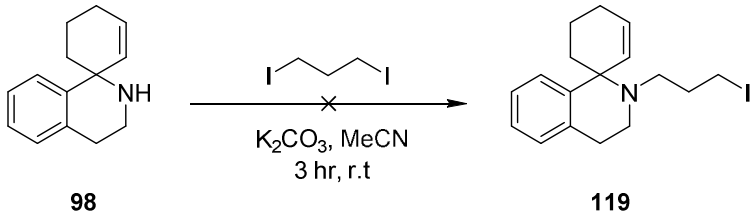
Scheme 63: Ring closing metathesis reaction

In line with Simon Herbert's observations, the product of the metathesis reaction was very difficult to purify. From crude ^{1}H NMR spectra, it could be seen that the desired product was present albeit accompanied by a multitude of impurities that coeluted with the spirocyclic compound. After repeated flash column chromatography in an attempt to remove the impurities, it mainly served to reduce the yield rather than aid the isolation of the pure product.

Due to the limited supply of starting material, the extensive purification became increasingly less beneficial and resource wasting, and so the synthetic route

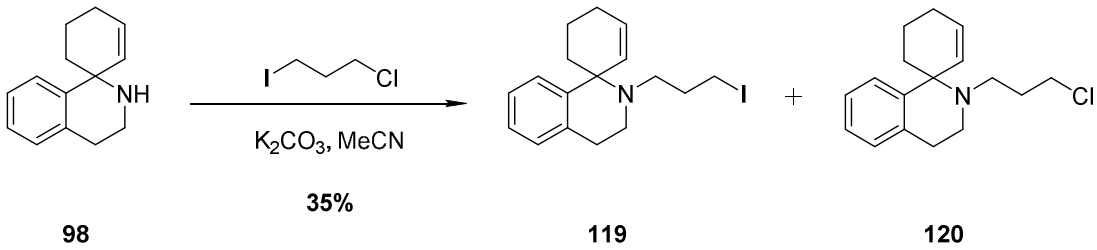
was continued by attempting the alkylation of the RCM product, a transformation that Simon Herbert had partially achieved in his previous efforts to synthesis the erythravine core.

Continuing with the synthesis, in an attempt to alkylate spirocycle **98**, 1,3-diiodopropane was used as the alkylation agent in efforts to synthesise alkylated product **119**, but proved unsuccessful, returning starting material (**Scheme 64**).



Scheme 64: Attempted alkylation with 1-chloro-3-iodopropane

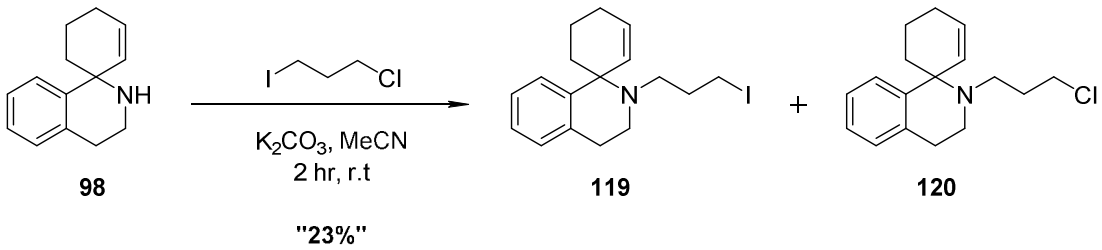
This procedure was used instead of a protocol developed by Simon Herbert in which he used 1-chloro-3-iodopropane as the alkylating agent, that gave a mixture of both chloro/iodo alkylated products **119** and **120** (**Scheme 65**). It was envisaged that by using 1,3-diodopropane this could circumvent the issue of chemoselectivity, thus the sole formation of **119** could be possible.



Scheme 65: Simon's reported alkylation giving mixture of products

Whilst both products still being useful, the issue of having a mixture of chloro/iodo products invokes the necessity for a Finkelstein transformation to convert the chloro-alkylated product into the iodo-alkylated product, further reducing the amount of a very limited and thus valuable starting material.

With the less than 25 mg of starting material left, it was decided to repeat Simon's procedure of using the 1-chloro-3-iodopropane despite the issues stated, in which **98** alkylated to give a mixture of alkylated products **119** and **120**, in line with Simon's results albeit in lower yield, affording a total of 12 mg prior to purification (**Scheme 66**).



98 **119** **120**

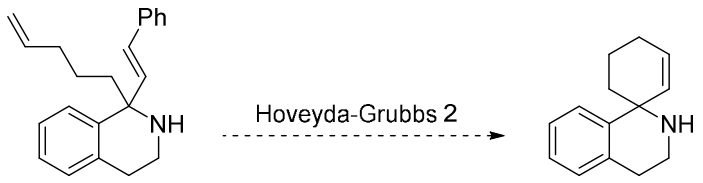
"23%"

Scheme 66: Attempted alkylation using 1-chloro-3-iodopropane

The remaining amount (from which the 'yield' was calculated) was a mixture of chloro/iodo alkylated products, as deduced from the MS of the 'product' and observed in ^{1}H NMR as a roughly 50:50 mixture. Upon purification via flash column chromatography, a number of different fractions were obtained that presented no use for further transformations, only a trivial amount of potential product was obtained and this was used in attempts to characterise the product, in which no thorough proton or carbon NMRs were obtained. Only HRMS accurate mass and IR spectra data could be collected.

At this point in the project, progress effectively came to a standstill due to the unavailability of vinyl isocyanate and possessing no more material for repeat experiments to generate a larger amount.

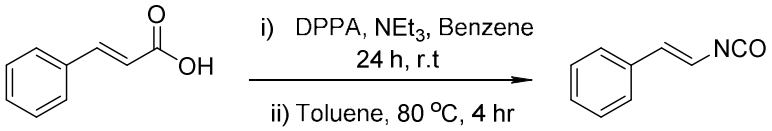
Within the group it had previously been reported that the styrenyl moiety had been migrated on similar substrates, and so it was envisaged that if the styrenyl group could be migrated and subsequent rearranged urea hydrolysed to give **121**, then the metathesis reaction for this could be performed to give the same starting material **98** as before (**Scheme 67**).



121 98

Scheme 67: Envisaged RCM reaction

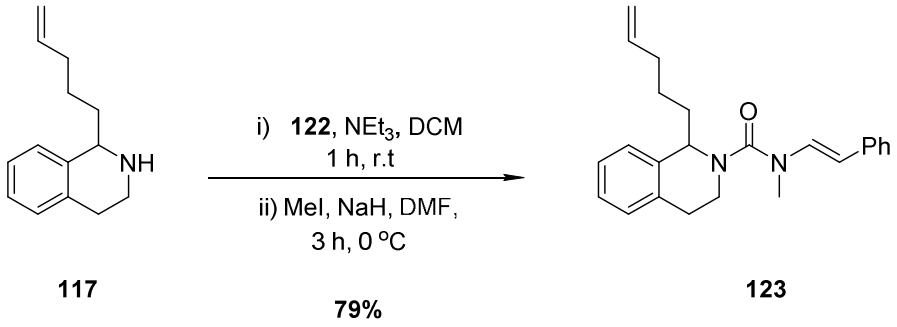
The initial drawback of this alternative approach lies within the certainty that RCM by-products will result, however the limitation of vinyl isocyanate and the existing knowledge that stryenyl isocyanate can undergo migration reactions of this type invoked this strategy. By following a general procedure, stryenyl isocyanate **122** was made by using trans-cinnamic acid with diphenylphosphoryl azide (DPPA), followed by heat promoted Curtius rearrangement of the acyl azide,[68] to afford the desired isocyanate that was used immediately but could not be purified by column chromatography due to its sensitivity to decomposition (**Scheme 68**).



89% 122

Scheme 68: Synthetic approach to styrenyl isocyanate

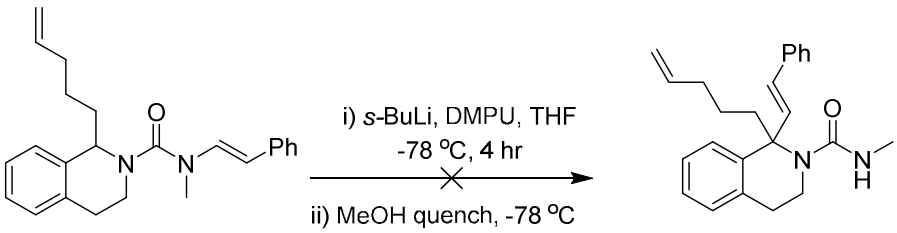
Condensation of isocyanate **122** with **117** was successful, and the urea formed was taken forth as a crude product and methylated, yielding urea **123.** Unlike the vinyl group containing substrates, purification of the *N*-methylated product **123** was possible, and after extensive purification the reaction proved to be reliably high yielding (**Scheme 69**).



117 **79%** **123**

Scheme 69: Condensation followed by *N*-methylation

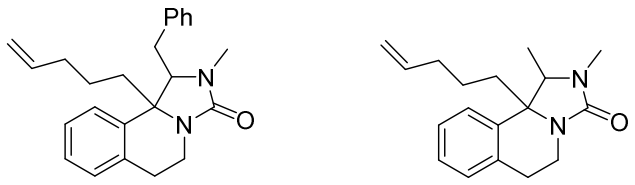
With the *N*-methylated product **123** in hand, the rearrangement was then attempted using the same conditions previously used in migration of the vinyl group to synthesise **124**. This proved unsuccessful, returning a solution in which the TLC indicated the presence of many impurities and remaining starting material. Based on these observations, the reaction was performed again, keeping the temperature at -78 °C for the duration of the reaction, including the methanol quench, potentially avoiding by-products forming and increasing the time of the reaction to promote the consumption of the starting material (**Scheme 70**).



123 **124**

Scheme 70: Attempted rearrangement of styrenyl isocyanate

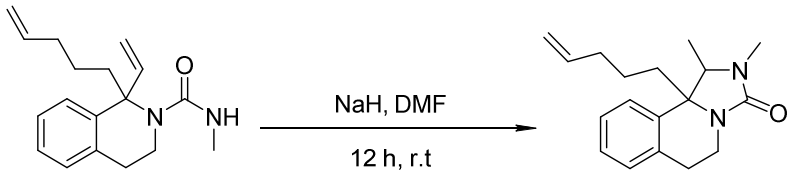
Whilst the increase in reaction time allowed the consumption of the starting material to occur, and maintaining the temperature of the reaction, especially during the quench, also fulfilled its purpose to reduce the number of impurities obtained, unfortunately by-product **125** was observed in large amounts (up to 45 %) that also matched a very similar by-product **126** Simon Herbert had noted the presence of in the migration of the vinyl group (**Figure 7**).



125 126

Figure 7: Observed by-products in the migration of stryenyl and vinyl groups.

Simon Herbert had upon observing this by-product, found that when **96** was treated with sodium hydride for an extended period of time, it resulted in almost quantitative conversion to the undesired by-product **126**.



96 126

Scheme 71: Observed formation of by-product as potential proof of concept

Despite the conditions for this being quite forcing, it served as potential proof of concept in which the rearranged product could be degrading with extended reaction times.

To explore if this was the same case with migration of the styrenyl group, first the rearranged product would have to be isolated in it's pure form and then be subjected to the same protocol (**Scheme 72**).

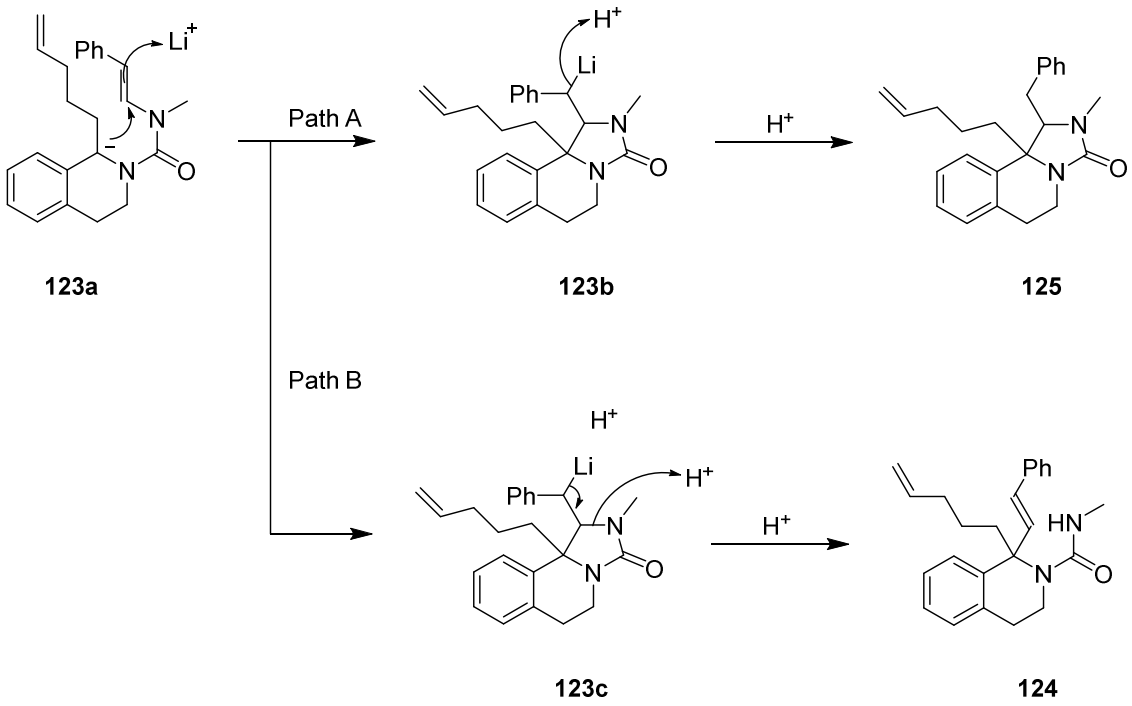
96 125

Scheme 72: Potential reaction to provide evidence for cyclic material

However, because short reaction times led to an incomplete reaction leaving starting material **123** (R_f = 0.1) and longer reaction times induced the formation of the cyclic urea **125** (R_f = 0.1-0.15 it meant that in both cases the desired product could not be isolated easily as it was accompanied by these impurities, causing a satisfactory level of purity difficult to achieve. Optimisation of this reaction was attempted to gauge a middle point whereby potentially the product could be isolated without both contaminants, however this proved futile.

At this point, it was hypothesised that a different styrenyl isocyanate in which various functional groups on the benzene ring could potentially be used to disfavour the formation of this product.

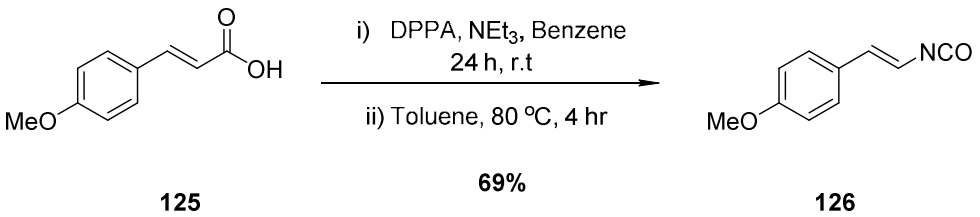
Based on mechanisms previously proposed, it was postulated that upon deprotonation of **123** with sec-BuLi to give **123a**, two mechanistic pathways, A and B, in which the by-product **125** and desired product **124** were being formed. Path A could arise due to the increased stability of the benzylic position, as a result of localised charge in conjugation with the benzene ring and so protonation of **123b** at the benzylic position could explain the formation of by-product **125**. Thus, if the benzylic position could be destabilised by changing the electronic nature of the styrenyl aromatic ring, the intermediate **123b** could collapse in the desired fashion leading to the formation of the desired urea **124** (**Scheme 73**).



Scheme 73: Hypothesised intermediate in the formation of cyclised by-product

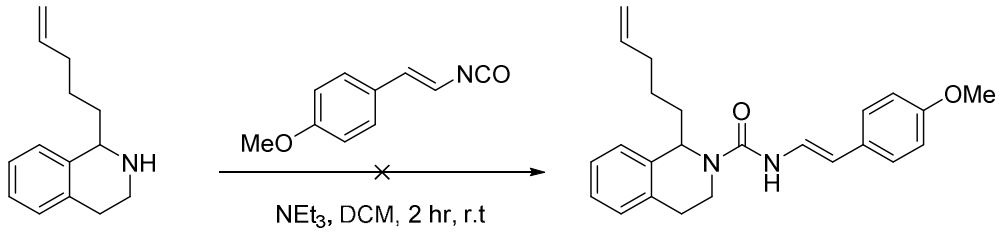
By using a stryenyl isocyanate with an electron donating group such as methoxy group installed on the benzene ring, the benzylic position could tuned to disfavour localised charge, which in turn would consequentially lead to the formation of the desired compound rather than forming a more stable intermediate, that can give the cyclised by-product.

Initially, using the same procedure, 4-methyoxy styrenyl isocyanate **125** was synthesised from the corresponding trans-cinnamic acid **126** with ease and used in its crude form, due unavoidable decomposition if purification was attempted (**Scheme 74**).



Scheme 74: Synthesis of new styrenyl isocyanate

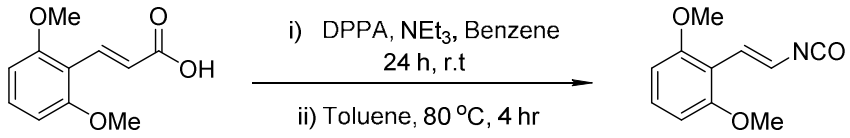
Following this, the condensation of the freshly made styrenyl isocyanate **126** with the core starting material **117** was attempted, with the aim of synthesising the crude urea **127**. The reaction was found to proceed with the numerous undesired by-products, which upon individual isolation concluded that the reaction had failed to synthesis the correct condensed product (**Scheme 75**).



117 **127**

Scheme 75: Condensation of styrenyl isocyanates with core building block

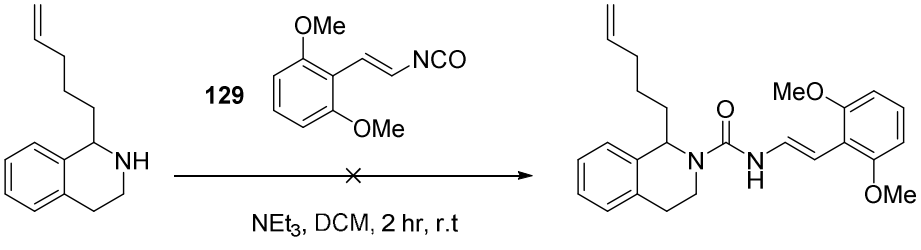
In further attempts to explore other isocyanates, compound **128** was treated under the same conditions, affording **129** that was taken forth as a crude product due to the aforementioned instability of isocyanates (**Scheme 76**).



128 **69%** **129**

Scheme 76: Synthesis of 2,6-dimethyoxy styrenyl isocyanate

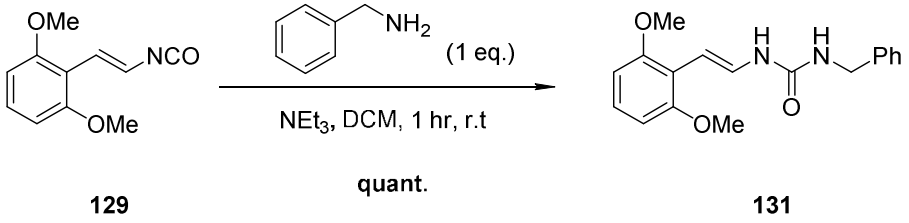
Unfortunately, achieving a satisfactory level of purification of compound **130** when attempted to condense styrenyl isocyanate **129** with **117** was not possible (**Scheme 77**).



117 **130**

Scheme 77: Attempted condensation reaction

In an experiment to double check these styrenyl isocyanates were not decomposing during the reaction with **117**, the slowest to react of the stryenyl isocyanates **129** (as deduced by consumption via TLC analysis), was reacted with benzylamine. The reaction was found to successfully condense to give **131**, in quantitative yield, providing evidence that the isocyanate was not decomposing and could form a condensed product[i] (**Scheme 78**).



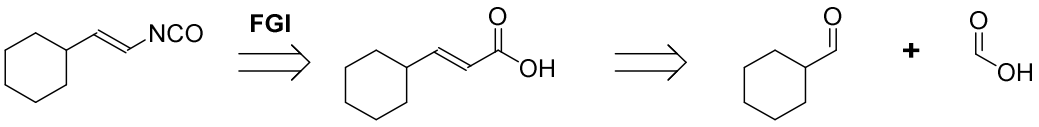
Scheme 78: Condensation reaction with benzylamine to test reactivity

This evidence did however give an indication that the issue of reactivity was with the core starting material amine **117** instead. With **117** being cyclic and 2° in nature reduced reactivity is not unexpected, and so further exploration into the use of different isocyanates was performed, concentrating on those which were more reactive than previously attempted. The importance for isocyanates that could rearrange without formation of an undesired cyclic intermediate during the rearrangement step was of paramount importance, with the requirement for a clean metathesis reaction cleanly being less important at this stage.

With a general trend that the various stryenyl isocyanates used were not forming the condensed products, it was deduced that the functional groups present on the ring system bared no overall change on electronic nature and thus reactivity. With this in mind, a comparison between styrenyl isocyanate and its non-aromatic analogue **132** was targeted. Despite not being

[i] Product was confirmed by ^{1}H NMR and m/s analysis, no further characterisation was performed.

commercially available, a retrosynthetic plan was devised whereby an FGI transformation of **132** could give the corresponding acid **133**, from which construction of the double bond would be the last step in the retrosynthetic analysis (**Scheme 79**).

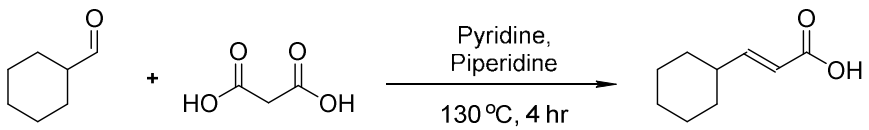


132 **133** **134**

Scheme 79: Retrosynthetic analysis of target isocyanate

A number of methods were evaluated with the aim of constructing the α,β-unsaturated acid, with work by Concellón using samarium chemistry,[69] and other groups work involving various Wadsworth-Horner-Emmons reactions being considered.[70,71] However the most appealing procedure that was found, was work by Nishizawa *et al.*,[72] that involved the use of a Knoevenagel reaction[73] to afford α,β-unsaturated acids, which was extensively shown to occur with minimal purification requirements, and with exclusive *E*-selectivity.

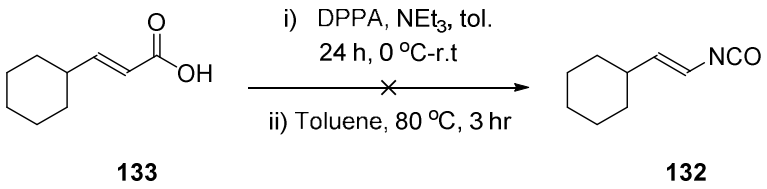
With this knowledge, aldehyde **134** was treated under the reported conditions with malonic acid to give the α,β-unsaturated acid **133** in excellent yield as a single isomer (**Scheme 80**).



134 **94%** **133**

Scheme 80: Knoevenagel Condensation

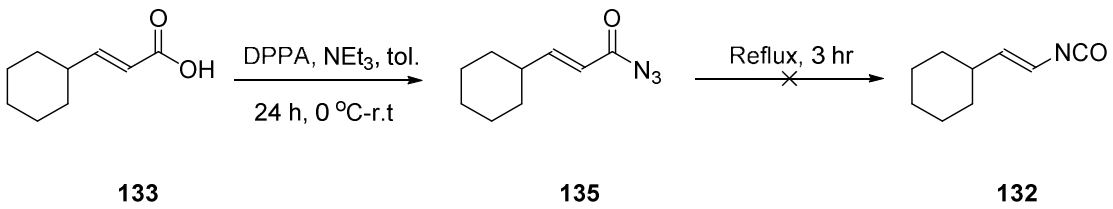
Initially, conversion of α,β-unsaturated acid **133** to isocyanate **132** proved troublesome, with the reaction conditions resulting in decomposition of the final product. The reaction was attempted numerous times and despite taking meticulous care with water and oxygen free solvents, decomposition of the desired isocyanate still occurred (**Scheme 81**).



133 132

Scheme 81: Curtius rearrangement forming desired isocyanate

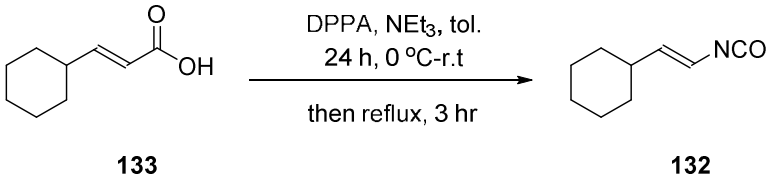
Up until this point, the reaction had always been performed as a two part conversion, as denoted in the schemes. Between these points, the acyl azide was always checked by ^{1}H NMR, TLC methods but mainly IR due to the very diagnostic changes that could be seen. It could be seen that the acyl azide **135** was being formed with no issue, but during the second part involving refluxing for various times, the result was complete decomposition (**Scheme 82**).



133 135 132

Scheme 82: 2 step procedure

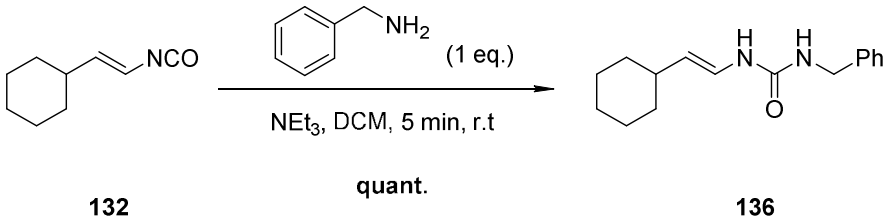
Thinking that acyl azide was decomposing during the reflux after being treated as a second step, the reaction was combined to give a one pot procedure instead and refluxed as usual to afford the desired isocyanate **132** with no signs of decomposition (**Scheme 83**).



133 132

Scheme 83: Successful one-pot synthesis

With the crude product in hand and wishing to double check its reactivity towards amines, a test reaction with benzylamine was performed (as previously practised) in which the reactivity was confirmed, by the near quantitative formation of **136** within 5 minutes (**Scheme 84**)

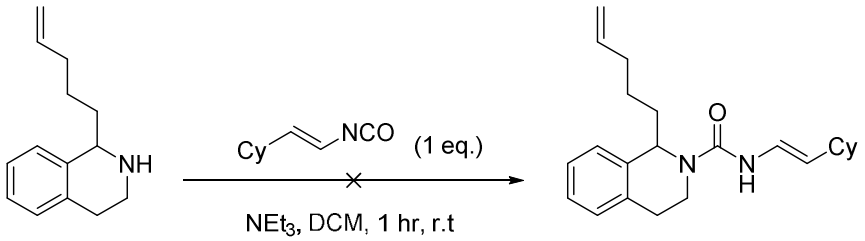


132 136

Scheme 84: Successful condensation with benzylamine

Like all previous isocyanates made, it was taken forth as the crude product. Condensation with benzylamine[ii] proved that any of the DPPA decomposition products present did not interfere with the condensation.

In light of this information, **117** was combined with the isocyanate **132** under standard conditions and rather disappointingly, the final reaction mixture was rich in various unwanted by-products, and with no remaining isocyanate being identified (**Scheme 85**).



117 137

Scheme 85: Unsuccessful condensation with cyclohexenyl isocyanate

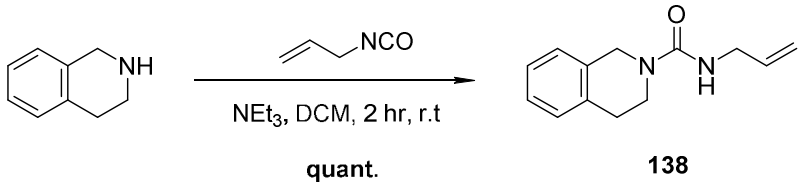
At this point in the project it was decided that there was no further time to attempt exploring other isocyanates, and rather than wait in hope for a chemical supplier to restock vinyl isocyanate, a different strategy was taken.

Rather than working with the core starting material **117** that is relatively precious, tetrahydroisoquinoline was used as the basis for the following reactions due to the abundance of it that allowed large scale reactions to be performed. If the strategy was to prove successful, then it was envisaged that

[ii] Product was confirmed by ^{1}H NMR and m/s analysis, no further characterisation was performed.

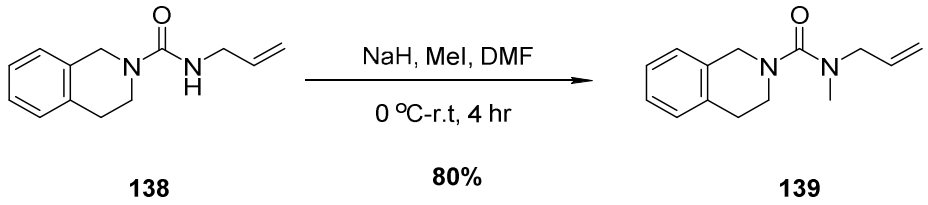
simple substitution of **117** instead should have little to no effect on the success of the reaction, as the incorporation of the alkyl chain should have no bearing on the ability for the same reactions to occur.

The new strategy involved the condensation of allyl isocyanate with tetrahydroisoquinoline, forming urea **138** in quantitative yield (**Scheme 86**).



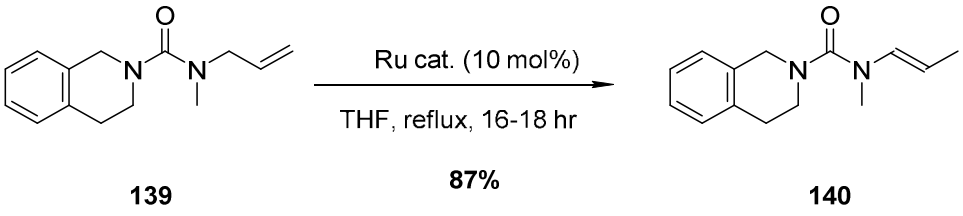
Scheme 86: Condensation with allyl isocyanate

Standard methylation afforded the N-methylated product **139** in good yield, and was produced on a multigram scale for the coming steps (**Scheme 87).**



Scheme 87: N-methylation under standard conditions

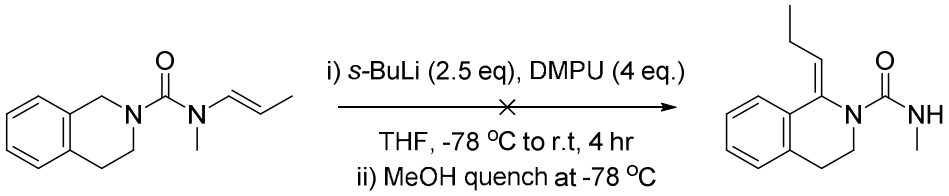
With the methylation complete, isomerisation of the terminal double bond in **139** to give **140** was planned. This type of chemistry had been reported within the group by Julien Lefranc on similar ureas and so, by treating **139** with catalyst carbonylchlorohydridotris(triphenylphosphine)ruthenium(II) under the reported conditions, the vinyl compound **140** was formed in excellent yield (**Scheme 88**).



Scheme 88: Ruthenium catalysed alkene isomerisation reaction

With the isomerisation being a complete success, the migration of the alkenyl group was planned by lithiating under the same conditions that was successful in the early vinyl migration reactions performed, and reported by the group (**Scheme 89**). A number of attempts were made with hopes to rearrange **140** to give **141**, but no successful set of conditions were found for the migration of the alkenyl group (

Table 5).



140 **141**

Scheme 89: Attempted rearrangement

Entry	sec-BuLi /eq	DMPU /eq	Time /h	Quench /°C	Yield 141 /%
1	2.5	4	4	-78	-
2	2.5	4	12	-78	-
3	2.5	0	4	-78	-
4	2.5	0	12	-78	-

Table 5: Various conditions used in attempted rearrangement reactions

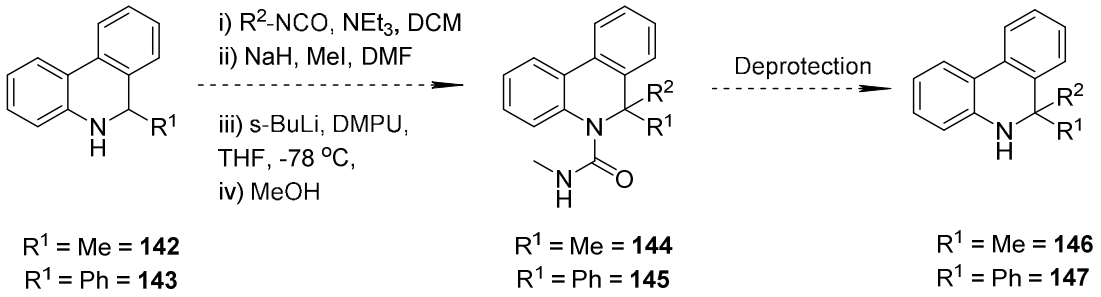
Applying the same conditions that worked for the migration of the vinyl group, proved unsuccessful (Entries 1-2), a discouraging result due to the similarity between the vinyl migrating group and alkenyl group used in this strategy. The use of sec-BuLi alone, in a short space of time, returned starting material (Entry 3) and so increasing the duration of the reaction afforded a decomposed mess (Entry 4), in which both experiments highlighted the requirement for DMPU and the fact prolonged times resulted in unwanted sec-BuLi addition products.

Further exploration of this was not attempted due to time constraints near to the end of the experimental time, but it can be seen from the entries listed that

the reaction doesn't hold much promise considering the very similar alkenyl group would not migrate under the same conditions as for the vinyl group that were successful.

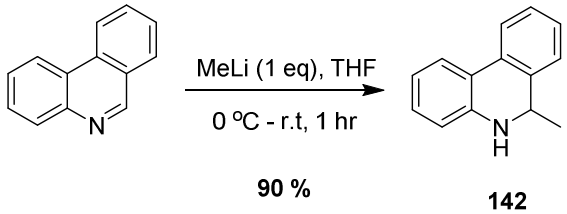
2.1.2. Phenanthridine Chemistry

As stated in the project aims, one of the proposed set of substrates selected to explore and potentially broaden the scope of the organolithium rearrangement were compounds 6-methyl-5,6-dihydrophenanthridine **142** and 6-phenyl-5,6-dihydrophenanthridine **143** as both starting materials represented a class of compounds that had never previously been used in the organolithium rearrangement. Lithiation and subsequent rearrangement of aryl substituents of *N*-methylated ureas **144** & **145** could be feasible, upon which deprotection could yield cyclic α-tertiary amines **146** & **147 (Scheme 90)**.



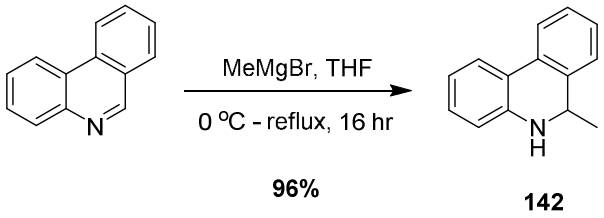
Scheme 90: Planned substrate examination for scope expansion

By implementing an established protocol[74] that originally used quinoline, phenanthridine was reacted with methylithium to form 6-methyl-5,6-dihydrophenanthridine **142** in high yield, requiring (**Scheme 91**).



Scheme 91: Methyllithium addition to phenanthridine

This reaction provided a slight advantage (due to shorter reaction times) over an alternative approach involving Grignard addition of methylmagnesium bromide that required longer reaction times and more forcing conditions, although this method did result in slightly higher yield (**Scheme 92**).



Scheme 92: Grignard addition to phenanthridine

In addition to **142**, 6-phenyl-5,6-dihydrophenanthridine **143 (Figure 8)** was also synthesised using both organolithium and Grignard addition procedures, although it was decided to focus on the 6-methyl-5,6-dihydrophenanthridine **142** substrate due to the increased ability for **143** to stablise a negative charge upon deprotonation when treated with sec-BuLi or LDA by conjunction with the phenyl ring and subsequently fail to rearrange the aryl group.

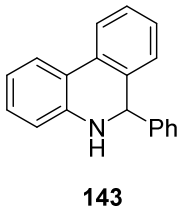
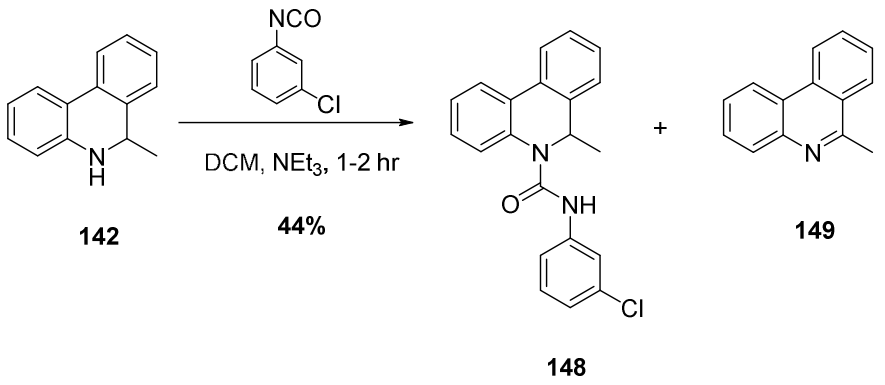


Figure 8: 2-phenylphenanthridine substrate

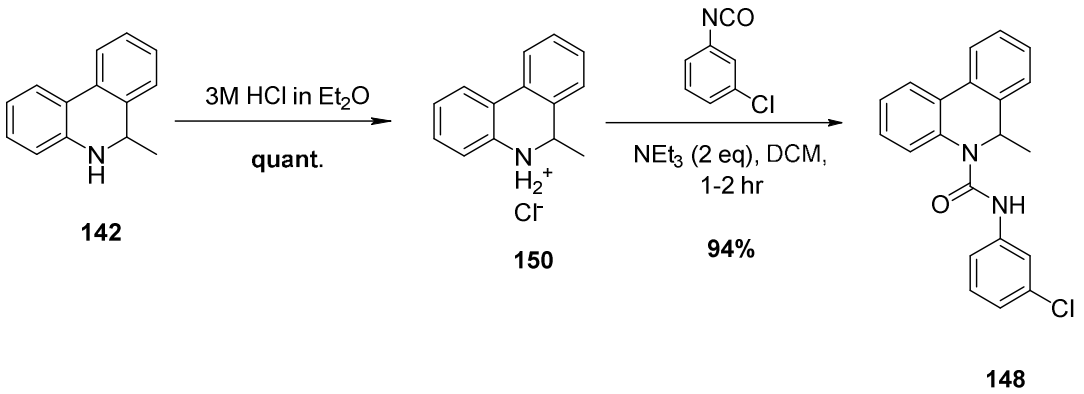
With the methylithium addition product **142** in hand, condensation with 3-chloroisocyanate was to proceed. The decision to utilise this compound out of a variety of possible isocyanates came from previous evidence gathered by the group regarding its success in aryl migrations. A secondary reason for choosing this over an unfunctionalised option such as phenylisocyanate was because of the distinctly different aromatic peaks that 3-chlorophenyl has in ^{1}H and MS spectra compared to phenylisocyanate, allowing a quick identification whether the group had first been installed and successfully migrated.

Initially, condensation of **142** with 3-chlorophenylisocyanate under standard conditions (although with the absence of DMAP) occurred successfully to give urea **148**, albeit in low yield due to the formation of rearomatised starting material **149** (**Scheme 93**).



Scheme 93: Condensation of 2-methylphenanthridine with 3-chlorophenyl isocyanate

Despite using freshly prepared 6-methyl-5,6-dihydrophenanthridine **142**, the formation of rearomatised product **149** during the synthesis of **148** occurred, accounting for over half the yield. Although its removal via flash column chromatography proved facile, the reaction was further optimised by converting the starting material **142** to the hydrochloride salt **150** using ethereal hydrochloric acid (**Scheme 94**). The reaction occurred with ease to give **150** in almost quantitative yield. Liberation of the original starting material by using 2 equivalents of base allowed the synthesis of the desired urea in excellent yield.

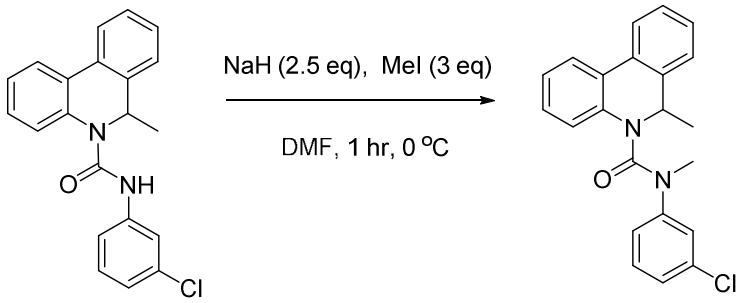


Scheme 94: Formation of hydrochloride salt followed by condensation

With this slight issue circumvented, a large amount of starting material could be made efficiently by effectively doubling the yield. Progressing forth, *N*-Methylation was then performed using the same conditions as implemented in

the successful methylation of the vinyl condensed product during the erythravine synthesis.

Preliminary attempts at the *N*-methylation of **148** in the hope of affording **151** were unsuccessful and often returned degraded starting material. A significant amount of time was spent in the pursuit of acquiring a successful set of conditions, changing the equivalents of sodium hydride and methyl iodide, time and some solvent variation (**Scheme 95**, **Table 6**). Eventually after exhausting a variety of conditions, the reagents were put to question and it was gallingly found that replacement of the sodium hydride with a new source (Entry 9) gave a small amount of the desired product. The reaction time was subsequently increased (Entry 10) and methylation was achieved in good yield. The reaction was repeated on larger scales (Entries 11 and 12) also in good yield but required longer reactions times as deduced by TLC analysis.



148 **151**

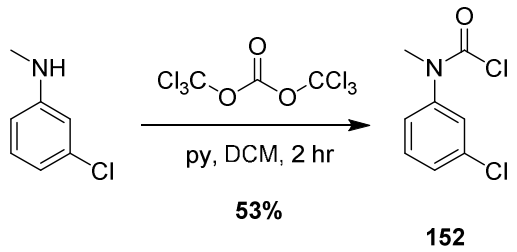
Scheme 95: Initial N-methylation attempt

Entry	NaH /eq	MeI /eq	Solvent	Time /h	Yield 151 /%
1	1	1	DMF	1	-
2	1	1	DMF	3	-
3	1	1	DMF	12	-
4	2.5	2	DMF	1	-
5	2.5	2	THF	1	-
6	2.5	3	Dioxane	3	-
7	2.5	3	DMF	12	-
8	2.5	3	DMF	1	-
9	2.5	3	DMF	1	33

10	3	3	DMF	3	67
11	2.5	3	DMF	5	62
12	2.5	3	DMF	5	60

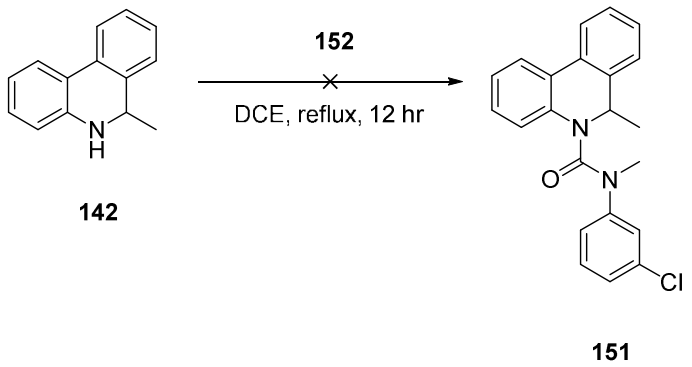
Table 6: Various conditions attempted for N-methylation

Whilst optimisation of the *N*-methylation reaction was performed, another approach to using established carbamoyl chloride methodology was utilised as an alternative way of synthesising the methylated compound **151.** The appropriate 3-chloro-N-methylaniline was treated with triphosgene in pyridine according to a standard procedure, affording the carbamoyl chloride **152** in moderate yield (**Scheme 96**).



Scheme 96: Synthesis of carbamoyl chloride

Carbamoyl chloride **152** was used in a coupling reaction trialling conditions developed by Mike Tait which had been successful for other substrates (**Scheme 97**). Upon the return of a complex mixture of products, a number of coupling reactions were attempted to gauge whether the reaction could be optimised (**Table 7**). None of the reactions attempted at elevated or high temperatures were successful, with the majority of these attempts resulting in very messy complicated mixtures as deduced by TLC analysis and ^{1}H NMR spectra. Extended reaction times only increased this result, but it was found on the opposite scale that stirring at milder temperatures resulted in no consumption of starting material, even with prolonged reaction times.



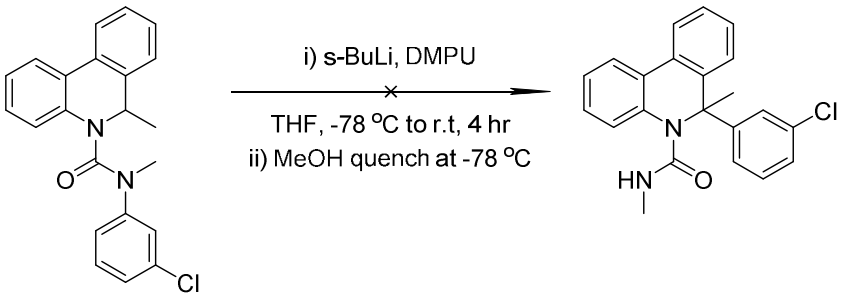
Scheme 97: Initial carbamoyl chloride coupling attempt

Entry	Temperature /°C	Solvent	Time /h	Yield 151 /%
1	25	DCM	48	-
2	40	DCM	48	-
3	60	DCE	12	-
4	100	DCE	12	-
5	100	DCE	24	-

Table 7: Various reaction conditions attempted

At this point it was decided that although there could be potential to cut out 2 synthetic steps (hydrochloride salt formation, condensation with isocyanate) if the carbamoyl chloride was synthesised, proceeding via the original optimised strategy was preferable and thus concluded experimentation using the carbamoyl chloride methodology.

With the purified *N*-methylated compound available the rearrangement was attempted using the same conditions that were successful for rearranging the vinyl group during the synthetic approach to erythravine (**Scheme 98**). Treatment of **151** with *sec*-BuLi prior to the addition of DMPU afforded no trace of **153** but rather a mixture of starting material and various by-products, subsequently a number of optimisation experiments were attempted to synthesise **153** (**Table 8**).



151 153

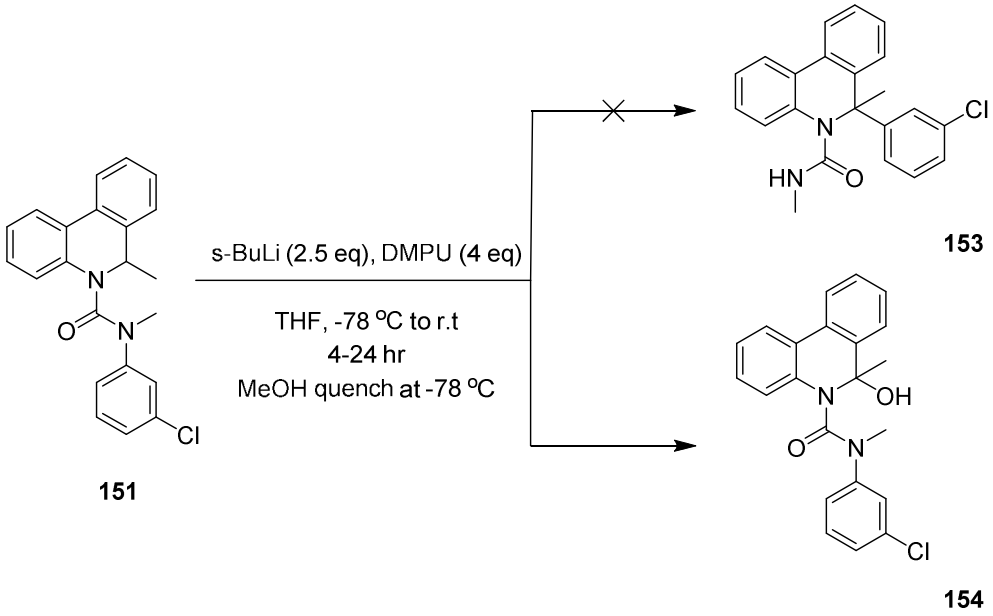
Scheme 98: First rearrangement attempt using previously successful conditions

Entry	sec-BuLi /eq	DMPU /eq	Time /h	Quench /°C	Yield 153 /%
1	2.5	4	4	-78	-
2	2.5	4	6	-78	-
3	2.5	4	14	-78	-
4	2.5	4	24	-78	-
5	2.5	8	2	-78	-
6	2.5	8	6	-78	-
7	2.5	8	14	-78	-
8	2.5	8	24	-78	-
9	2.5	0	2	-78	-
10	2.5	0	6	-78	-
11	2.5	0	14	-78	-
12	2.5	4	14	-78	-
13	2.5	4	14	-40	-
14	2.5	4	14	0	-
15	2.5	4	14	20	-

Table 8: Conditions trialled in rearrangement

All reactions (Entries 1-15) were all were carried out in dry THF, with the addition of sec-BuLi at -78 °C prior to the addition of DMPU an hour later, which was then kept at -78 °C for a further hour before being allowed to warmed to room temperature prior to the quench.

The rearrangement was performed using the same reaction conditions but with prolonged reaction times (Entry 1-4) in order to allow consumption of the starting material, however these attempts still returned starting material and a number of by-products. One major by-product, **154**, was isolated and characterised, with its formation being a suspected result of an oxygen source present in the reaction (**Scheme 99**).



Scheme 99: Formation of α-hydroxylated compound during rearrangement attempt

A limited number of variables were identified and by process of elimination it was deduced that potentially DMPU was harbouring oxygen and that if degassed the reaction may proceed without the formation of this undesired α-hydroxylated compound. Following this, the first attempted reactions (Entries 1-4) were repeated with degassed DMPU but still returned starting material. The formation of this by-product served as an important indication as to what was occurring with the rearrangement, as it helps prove that α-deprotonation was occurring. Deprotonation at this point was also supported by quenching with deuterated methanol (CH_3OD) and upon analysis, no signal for the methine proton could be seen, confirming a deuteron had been abstracted.

After such findings, it was deduced that prolonging the time of the was not the crucial factor in the rearrangement, logically the next step was to increase the equivalents of DMPU (Entries 5-8) in order to promote the rearrangement, with prolonged reaction times additionally. No rearranged product was observed, and neither was any starting material but rather DMPU degradation products.

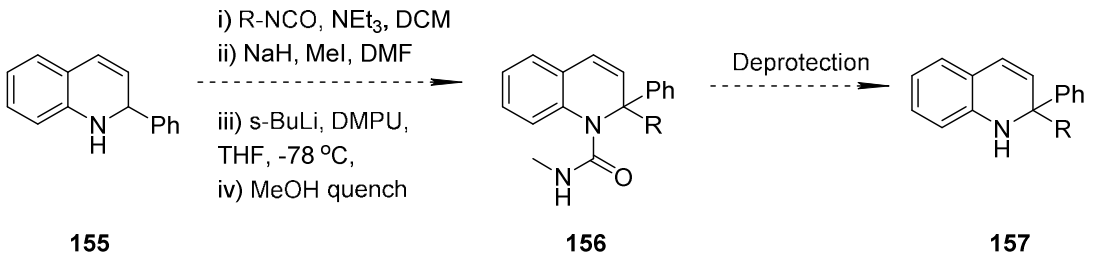
It was further investigated that without the addition of DMPU (Entries 9-11), no reaction was observed and degraded starting material was returned. This was not a surprising result as it had previously been noted within the group that without the addition of DMPU the rearrangement was largely unsuccessful but was performed to eliminate this potential variable.

Having controlled both the time, amount of DMPU and sec-BuLi, investigation into the nature of the quenching temperature was performed as work within the group on the rearrangement with different substrates had given evidence that the rearrangement may be occurring during the quench, and thus, the temperature at which it was performed at could be imperative to the success of the reaction. Unfortunately quenching at different temperatures (Entries 12-15) resulted in no rearranged product, but importantly showed that at -40 ^{o}C, no starting material was seen and that at higher temperatures complex mixtures of degraded products were obtained.

At this point it was reasonably concluded that 6-methyl-5,6-dihydrophenanthridine can be α-deprotonated but is too stable to undergo the desired aryl migration and will hydroxylate where oxygen is available, or reforming starting material upon methanol quench at low temperatures.

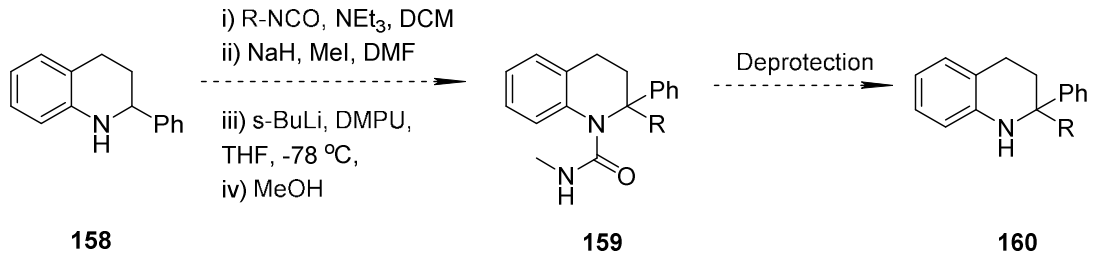
2.1.3. Dihydroquinoline & Tetrahydroquinoline Chemistry

In the aim of expanding the scope of the organolithium reaction, dihydroquinoline and tetrahydroquinoline substrates were also selected as targets, because their capacity to undergo the organolithium rearrangement could also be explored using the same methodology as with phenanthridine. By following the same route as before, conversion of amine **155** to the corresponding urea, *N*-methylation prior to the aryl migration, in hope of synthesising migrated urea **156**, finally followed by deprotection would allow the synthesis of unsaturated cyclic α-tertiary amines **157** (**Scheme 100**).



Scheme 100: Planned steps in rearrangement of 2-phenyl-1,2-dihydroquinoline **155**

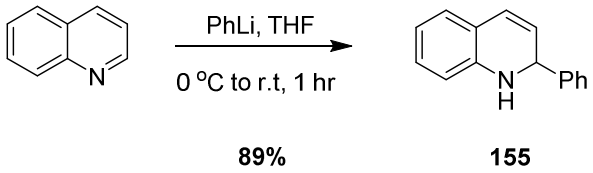
In the exact same way, the fully reduced version 2-phenyl-1,2,3,4-tetrahydroquinoline **158** could potentially follow the same line of chemistry in the aim of synthesising rearranged urea **159**, which upon deprotection would afford saturated cyclic α-tertiary amines **160** (**Scheme 101**).



Scheme 101: Planned steps for the rearrangement of **158**

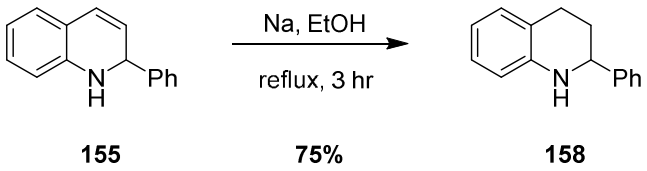
To begin the planned syntheses, the literature procedure used in the phenanthridine substrate chemistry was implemented by reacting quinoline

with phenyllithium to afford 2-phenyl-1,2-dihydroquinoline **155** in high yield, (**Scheme 102**).



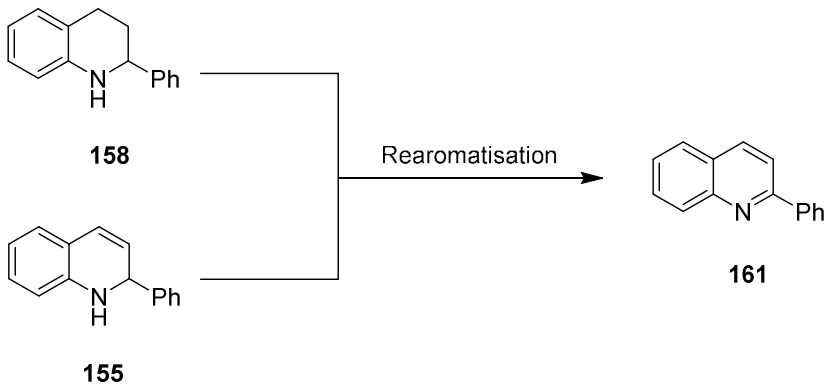
Scheme 102: PhLi addition to quinoline

Initially, in order to explore both compounds, a portion of **155** was taken and was dissolved in dry ethanol before performing a Birch-type reduction using solid sodium, synthesising **158** easily with a high degree of purity (**Scheme 103**).[74]



Scheme 103: Birch-type reduction

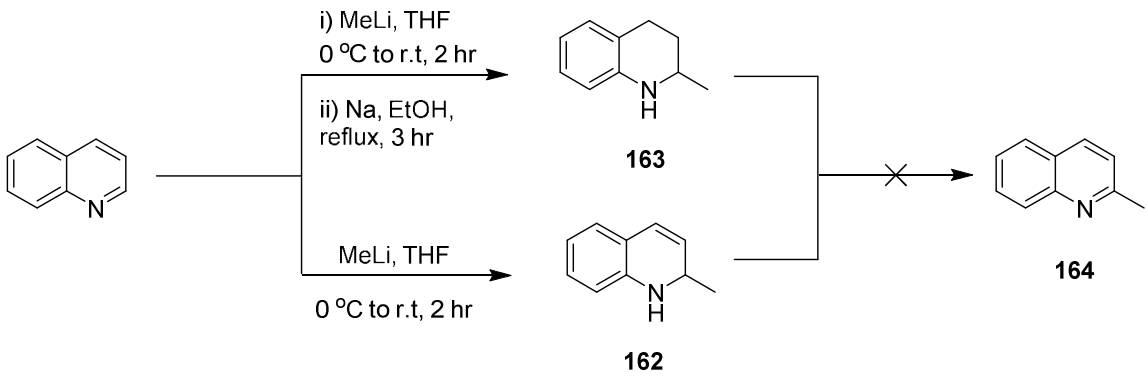
It was found that with time, both the 2-phenyl-1,2-dihydroquinoline **155** and 2-phenyl-1,2,3,4-tetrahydroquinoline **158** compounds rearomatised if exposed to air or if purified by silica column chromatography despite basification yielded **161**. Purification via alumina column chromatography proved futile (**Scheme 104**).



Scheme 104: Rearomatisation of starting materials if exposed to air or purified

From the experience gained with the 6-methyl-5,6-dihydrophenanthridine substrate, simple conversion to the hydrochloride salt allowed the storage of both dihydroquinoline **155** and tetrahydroquinoline **158** substrates for prolonged amounts of time, meaning their preparation and further chemistry to be performed on the same day was not essential.

It was noteworthy however that 2-phenyl-1,2,3,4-tetrahydroquinoline **158** was considerably less susceptible to rearomatisation, presumably due to the requirement for two oxidations to occur rather than a single oxidation with the dihydroquinoline **155**, in which conjugation with another benzylic ring increased the likelyhood of rearomatisation. This was easily observed as when the liquid dihydroquinoline **255** was exposed for 1-2 hours, solid **161** was obtained, whereas when a portion of liquid **158** was deliberately exposed to air for 1 week, only then was solid **161** obtained. Interestingly, 2-methyl-1,2-dihydroquinoline **162** and 2-methyl-1,2,3,4-tetrahydroquinoline **163** were synthesised for potential rearrangements, but these were abandoned as the α-carbon position would not be capable of stabilising an anionic charge with methyl substituents. It was found that they did not rearomatise to give **164** if exposed to air, or purified via flash column chromatography (**Scheme 105**).

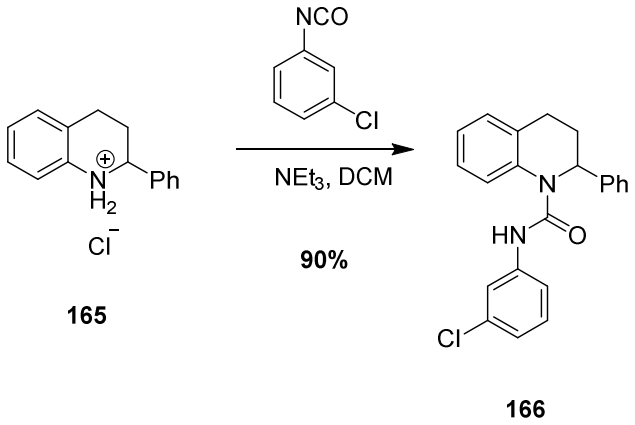


Scheme 105: Synthesis of **162** and **163**

Due to the ease of working with 2-phenyl-1,2,3,4-tetrahydroquinoline **158**, focus was aimed primarily on attempting to explore the possibility for the it to

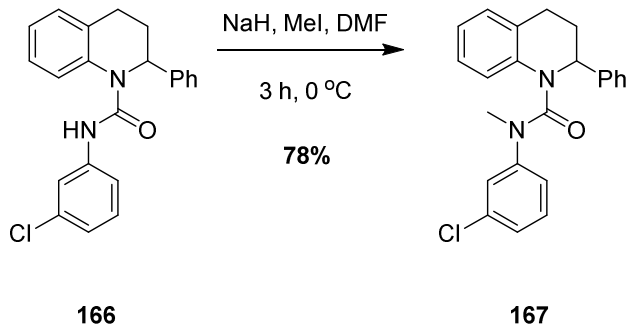
undergo aryl migration rather than 2-phenyl-1,2-dihydroquinoline **155** – but remains an area of future exploration.

Condensation of **158** with 3-chlorophenylisocyanate, under the same conditions as previously used occurred with similar issues of obtaining some rearomatised starting material alongside the desired urea, and so the amine salt **165** was used alternatively, as same strategy during the phenanthridine chemistry proved successful, and once again served as a useful synthetic manipulation to avoid such rearomatisation since the desired urea **166** was obtained in excellent yield (**Scheme 106**).



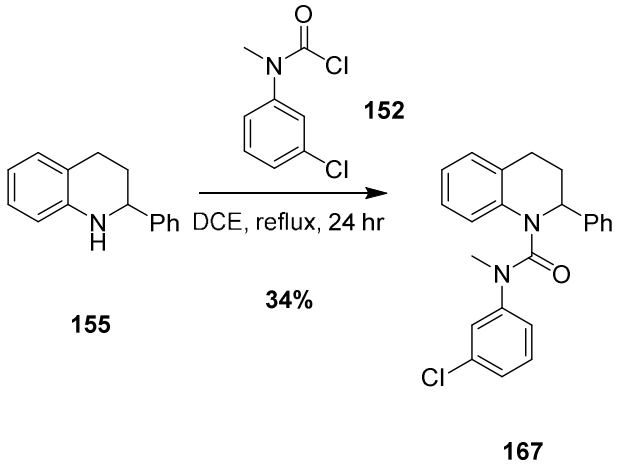
Scheme 106: Condensation with hydrochloride salt

Following on, N-methylation of **166** under the same conditions as used in the phenanthridine chemistry afforded the *N*-methylated product **167** in good yield (**Scheme 107**).



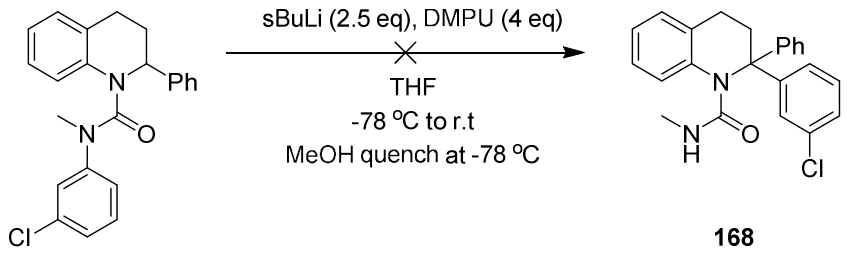
Scheme 107: N-Methylation of urea under standard conditions

Initially the ^{1}H spectra for this compound appeared misleading, with 3 of the alkyl protons converging underneath one signal, leaving the 5th alkyl proton as doublet triplet due to being flanked by 2 protons and 1 methine proton. A COSY experiment confirmed coupling of the alkyl protons and confirmed the synthesis of **167**, a rerun of this sample to be performed in deuterated benzene to cause a change in the chemical shifts. Additionally, to confirm that the correct starting material had been made, the alternative carbamoyl chloride methodology was utilised by reacting **155** with the 3-chlorocarbamoyl chloride to afford **167,** which despite being particularly difficult to isolate gave spectra that was in good agreement of that *N*-methylation product (**Scheme 108**).



Scheme 108: Carbamoyl chloride coupling

Rearrangement of **167** was then attempted using the successful conditions from the erythravine synthesis, and thus was treated with sec-BuLi at -78 ^{o}C in THF before the addition of degassed DMPU an hour later, which was then left for a further hour as usual before being allowed to warm to room temperature before the methanol quench. The rearrangement was unsuccessful, returning degraded starting material, with none of the distinctive signs of a successful rearrangement, mainly the disappearance of the methine proton. A number of reactions in attempt to synthesise **168** were then undertaken (**Table 9**).



167 168

Scheme 109: First attempted rearrangement

Entry	sec-BuLi /eq	DMPU /eq	Time /h	Quench /°C	Yield 168 /%
1	2.5	4	12	-78	-
2	2.5	4	24	-78	-
3	2.5	4	12	-40	-
4	2.5	4	12	-40	-
5	2.5	8	12	-40	-
3	2.5	4	12	0	-
4	2.5	4	12	25	-

Table 9: Conditions trialled in rearrangement

From the experience gained with the phenanthridine substrate where it was found that the nature of quench was crucial to the outcome of the reaction, the rearrangement was repeated and quenched at a number of temperatures.

First the reaction was quenched at -78 °C but repeatedly returned starting material (Entries 1-2) and so, slightly more forcing conditions were implemented by quenching at -40 °C (Entries 3-5) in which this temperature difference seemed to have a definite effect on the consumption of the starting material as none was observed in these reactions, indicating that at -78 °C the rearrangement is too slow for the aryl migration to occur.

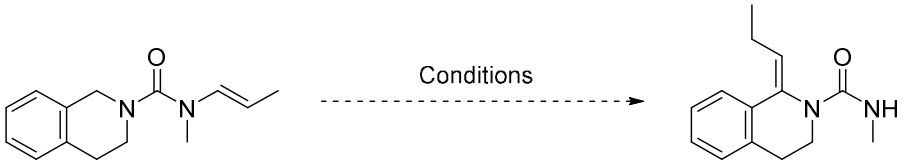
Reactions quenched at -40 °C showed some promise, with ^{1}H spectra displaying signals similar to quartets which could potentially represent the expected NH-

methyl proton, however upon isolation and characterisation of these fractions it was concluded that these were undesired by-products that were lacked characteristic features of a successful rearrangement: NH-methyl as a doublet; disappearance of the methine proton; N-methyl as a quartet.

Reactions quenched at temperatures higher than -40 ^{o}C (Entries 3-4) gave crude mixtures of which TLC and ^{1}H analysis confirmed the presence of at least 10-11 other by-products in the reaction.

3. Future Work

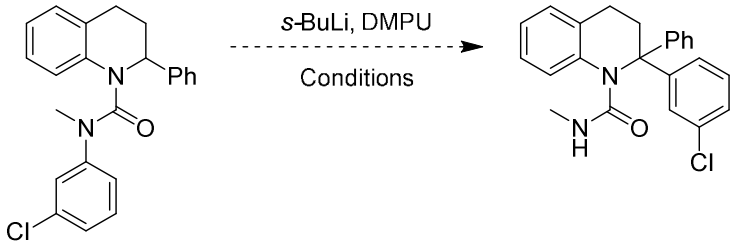
Further work regarding the development of the erythravine chemistry lies with exploring the use of different isocyanates. The search for an isocyanate which can rearrange without cyclisation may be a lengthy process, however the reward for the synthesising the target molecule will serve as an excellent showcase of the organolithium rearrangement. Due to time constraints, the rearrangement of **140** to **141** was not fully explored and thus future work based on finding a good set of conditions would serve as a good starting point, before rethinking a new overall strategy (**Scheme 110**).



140 **141**

Scheme 110: Future work regarding the exploration of rearrangement conditions

Additionally, further work focusing on optimising conditions used in the rearrangement of the **167**, as this has been relatively unexplored in comparison to the 6-methyl-1,2-dihydrophenanthridine substrates (**Scheme 111**).

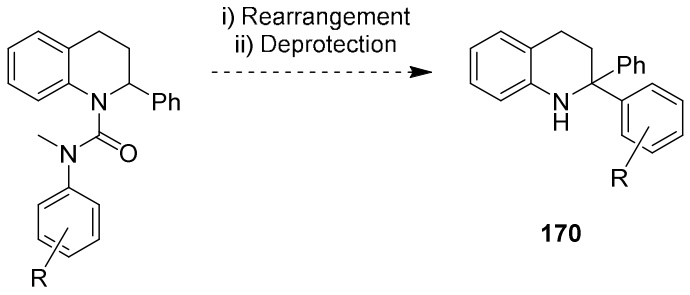


167 **168**

Scheme 111: Further rearrangement attempts to perform

If a set of successful conditions are found then a variety of different substrates **169** could be formed in which the aryl group could possess a range of either electron withdrawing or electron donating groups. These could then be trialled in the rearrangement in attempt to synthesise cyclic & spirocyclic α-tertiary

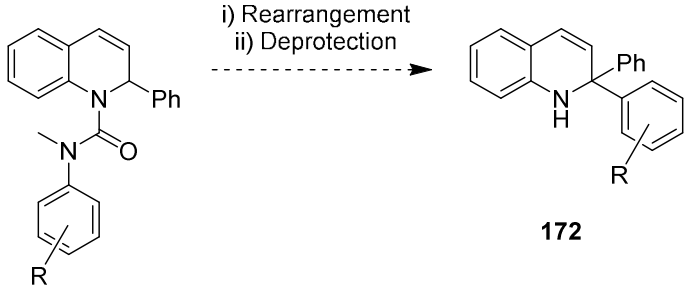
amines **170** whilst simultaneously expanding the scope of the organolithium reaction (**Scheme 112**).



169 **170**

Scheme 112: Further reactions to attempt with different aryl substituents, where R = EDG/EWG.

If a success set of conditions are found, then simple application to 2-phenyl-1,2-dihydroquinoline substrates **171** will be investigated. This could potentially open up a set of novel rearranged compounds **172 (Scheme 113)**.



171 **172**

Scheme 113: Future reactions for dihydroquinoline substrate chemistry

Revisiting the phenanthridine substrate chemistry will also be attempted if conditions can be achieved for successful rearrangements for both 2-phenyl-1,2,3,4-tetrahydroquinoline and 2-phenyl-1,2-dihydroquinoline chemistry.

4. Experimental

4.1. General Information

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Ultrashield 300, 400 or 500 spectrometer (300, 400 or 500 MHz respectively) with residual non-deuterated solvent as the internal standard. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian a Bruker Ultrashield 300, 400 or 500 spectrometer (75, 100 or 125 MHz respectively). NMR data are presented as follows: chemical shift δ (in parts per million (ppm) down-field from tetramethylsilane), integration, multiplicity, coupling constant J (in Hz) and assignment (based on chemical shift, integration, coupling pattern and COSY, DEPT, HSQC and HMBC NMR experiments when necessary). Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), or a combination of these. The solvents used were deuterated chloroform (δ H: $CDCl_3$ 7.27 ppm; δ C: $CDCl_3$ 77.0 ppm) and dimethylsulfoxide, (δ H: $(CD_3)_2SO$ 2.50 ppm; δ C: $(CD_3)_2SO$ 39/52 ppm)

Low and high resolution mass spectra were recorded by staff at the University of Manchester. ES spectra were recorded on a Micromass Platform II; High resolution mass spectra (accurate mass measurement) were recorded on a Thermo Finnigan MAT 95XP mass spectrometer, and are accurate to ± 0.001 Da.

Infrared spectra were recorded on an ATi Perkin Elmer Spectrum RX1 FTIR spectrometer and only absorption maxima (υ_{max}) of interest are reported and quoted as wavenumbers (cm^{-1}). All samples were run as evaporated films from chloroform.

Melting points were determined on a Kofler microscope melting point machine and are uncorrected. Decomposition is noted when the compound changed from its original form to a black substance without a gradual change.

Analytical TLC was carried out on pre-coated UV_{254} plates (Macherey-Nagel alugram. Sil $G/_{UV254}$ or Machery-Nagel polygram. Alox $N/_{UV254}$), with visualisation by UV light at 254 nm, and/or stained using either phosphomolybdic acid, potassium permanganate, Seebach dips.

Flash column chromatography was carried out using Fluorochem Davisil 40 – 63 μm 60 Å silica or Fluka Basic 0.05-0.15 mm Aluminium Oxide, under a positive pressure by means of compressed air, followed by removal of the solvent *in vacuo* after purification.

Reagents and solvents were purified by standard means. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium wire and benzophenone under nitrogen. Dichloromethane (DCM) was obtained by distillation from calcium hydride under nitrogen. Triethylamine used was from a commercial source and stored over potassium hydroxide. DMPU was distilled, under reduced pressure, from calcium hydride, and stored over molecular sieves. It was also degassed by freeze-thaw techniques and sonication under vacuum. All other chemicals were used as received, except where otherwise noted in the experimental text.

Petrol refers to the fraction of light petroleum ether boiling between 40 °C and 60 °C. All other solvents and commercially obtained reagents were used as received or purified using standard procedures. *n*-Butyl lithium was used as a solution in hexanes (2.6M), *i*-propyl lithium as a solution in pentane (0.7 M), *s*-butyl lithium as a solution in cyclohexane/hexane (92/8) (1.3 M), *t*-butyl lithium as a solution in pentane (1.7 M), methyl lithium as a solution in diethylether (2.0 M) and phenyl lithium as a solution in *n*-butylether (2.0 M). All the above organolithium solutions were titrated prior to use, by using a solution of *N*-benzylbenzamide although a solution of diphenylacetic acid was also used. Cooling baths used are acetone/dry ice for –78 °C and acetonitrile/dry ice for –40 °C.

All experiments were performed in anhydrous conditions under an atmosphere of argon, unless otherwise noted in the experimental text. Apparatus was oven-dried and standard techniques were employed in handling air-sensitive materials.

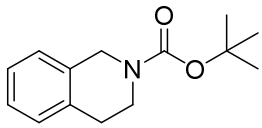
4.3. General Procedures

General Procedure 1 – *Synthesis of Stryenyl Isocyanates*

The appropriate cinnamic acid (1 eq.) was dissolved in dry benzene (10 mL) and triethylamine (1 eq.) and cooled to 0 ^{o}C. Diphenylphosphoryl azide (1 eq.) was added dropwise over 10 min and allowed to stir and warm to r.t for 24 h. The reaction mixture was poured into excess saturated aqueous NH_4Cl (25 mL), and extracted with EtOAc (2 × 20 mL). The organic phase was then sequentially washed with $KHSO_4$ (1 M, 20 mL), H_2O (20 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (50 mL). The organic phase was then dried (Na_2SO_4), filtered and concentrated *in vacuo* at room temperature to afford the corresponding stryenyl acyl azide that was dissolved in dry toluene (75 mL) and heated under reflux for 3 h. The reaction mixture was concentrated *in vacuo* to afford the corresponding stryenyl isocyanate, and was used without purification.

4.4. Experimental Data

***tert*-Butyl 3,4-dihydroisoquinoline-2-(1*H*)-carboxylate (115)**



Di-*tert*-butyl dicarbonate (0.74 g, 3.3 mmol) was added dropwise to a solution of tetrahydroisoquinoline (0.46 mL, 3.3 mmol) in dry DCM (10 mL) and stirred at room temperature for 3 h. The mixture was then concentrated *in vacuo* to give the title product **115** (0.77 g, 99 %) as a yellow oil which was used without further purification.

R_f: 0.65 (EtOAc/PE: 1/3)

IR υ_{max} (film)/cm^{-1}: 2974, 2945 and 2371

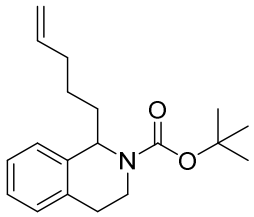
^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.20-7.17 (m, 4H, 4 × Ar*H*), 4.60 (s, 2H, C*H*$_2$-N), 3.68 (t, *J*=9.7, 3.5, 2H, CH_2-N-C*H*$_2$-CH_2), 2.86 (t, *J*=9.5, 3.4, 2H, CH_2-N-CH_2-C*H*$_2$), 1.52 (s, 9H, C(C*H*$_3$)$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ_C 154.93 (C=O), 134.8 (C_{Ar}), 128.7 (C_{Ar}), 126.3 (CH_{Ar}), 126.2 (CH_{Ar}), 125.1 (CH_{Ar}), 124.9 (CH_{Ar}), 79.7 (*C*-$(CH_3)_3$), 45.2 (*C*H_2-N), 40.6 (*N*-*C*H_2-CH), 28.51 (3 × C(*C*H_3)$_3$), and 27.4 (N-CH_2-*C*H_2).

NMR File: 2012-10-09-jpc-14 (500)

Data consistent with that reported in the literature.[75]

tert-Butyl 1-(pent-4-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (116)



tert-Butyl 3,4-dihydroisoquinoline-2-(1*H*)-carboxylate **115** (0.52 g, 2.25 mmol) was dissolved in dry THF (20 mL) under argon atmosphere of argon. TMEDA (0.40 mL, 4.5 mmol) was added to the solution over 5 min and the reaction mixture was cooled to -78 °C. *tert*-BuLi (1.53 mL, 2.32 mmol) was added dropwise and the reaction was stirred for 40 min at -78 °C. To the solution, 5-Bromo-1-pentene (0.5 mL, 2.7 mmol) was then added and the reaction allowed to warm to r.t. overnight. The reaction was slowly quenched with MeOH (20 mL). The reaction mixture was washed with H_2O (2 × 20 mL) and extracted with EtOAc (3 × 20 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil, which was purified by flash column chromatography (EtOAc/PE: 5/95) to give the title compound **116** (0.47 g, 69 %) as a colourless oil.

R_f: 0.6 (EtOAc/PE: 1/3)

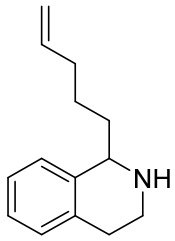
IR υ_{max} (film)/cm^{-1}: 2972, 2931, 2360 and 1692

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.33-7.30 (m, 4H, 4 × Ar*H*), 6.00 (ddt, *J*= 17.1, 10.3 and 6.6 Hz, 1H, C*H*=CH_2), 5.22-5.17 (m, 2H, C*H*$_2$=CH), 5.14 (ddt, *J*=10.4, 2.4 and 1.2, 1H, C*H*-N), 4.12 (dddd, *J*=13.2, 6.0, 4.0 and 0.2, 1H, C*H*$_2$-N), 3.42 (ddd, *J*=15.2, 10.0, and 5.2, 1H, C*H*$_2$-N), 3.04-2.90 (m, 2H, C*H*$_2$-CH_2-N), 2.34-2.23 (m, 2H, C*H*$_2$-CH=CH_2), 2.01-1.85 (m, 2H, C*H*$_2$-CH), 1.70-1.58 (m, 2H, C*H*$_2$-CH_2-CH=CH_2) and 1.63 (s, 9H, C-(C*H*$_3$)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C 153.7 (C=O), 138.0 (*C*H=CH_2), 137.6 (C_{Ar}), 133.4 (C_{Ar}), 128.1 (CH_{Ar}), 126.2 (CH_{Ar}), 125.7 (CH_{Ar}), 125.2 (CH_{Ar}), 113.9 (*C*H$_2$=CH), 78.3 (*C*-$(CH_3)_3$), 53.5 (CH-N), 37.0 (CH_2-N), 35.3(*C*H$_2$-CH_2-CH=CH_2), 32.1 (*C*H$_2$-CH=CH_2), 27.6 (3 × C(*C*H_3)$_3$), 27.2 (*C*H$_2$-CH_2-N) and 24.7 (*C*H$_2$-CH)

Data consistent with that reported in the literature.[65]

1-(Pent-4-en-1-yl)-1,2,3,4-tetrahydroisoquinoline (117)



Carbamate **116** (0.17 g, 5.14 mmol) was solubilised in dry DCM (10 mL) and treated with trifluoroacetic acid (0.96 mL, 51.5 mmol) and stirred for 3 h at r.t. The solvent then removed under reduced pressure and NaOH (1 M, 10 mL) was added to the crude mixture. The reaction was extracted with *tert*-butyl methyl ether (3 × 20 mL) and then DCM (2 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound **117** (0.11 g, 93 %) as a colourless oil, used without further purification.

R_f: 0.3 (EtOAc/PE: 7/3).

IR υ_{max} (film)/cm^{-1}: 2925, 2854 and 1639.

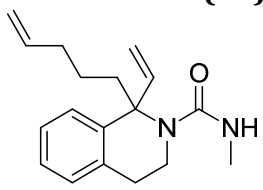
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.17-7.06 (m, 4H, 4 × Ar*H*), 5.83 (ddt, *J*=17.5, 10.3 and 6.9 Hz, 1H, C*H*=CH_2), 5.08-5.01 (m, 1H, CH_2=CH), 4.95 (ddt, *J*=10.3, 2.2 and 1.1, 1H, CH_2=CH), 3.95 (dd, *J*=9.0 and 3.6, 1H, C*H*-N), 3.24 (dt, *J*=12.5 and 5.5, 1H, CH_2-N), 2.99 (ddd, *J*= 12.5, 7.2 and 5.1, 1H, CH_2-N), 2.89-2.70 (m, 2H, CH_2-CH_2-N), 2.18-2.06 (m, 2H, CH_2-CH=CH_2) and 1.91-1.47 (m, 5H, 2 × CH_2 and NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C 139.7 (C_{Ar}), 138.7 (<u>C</u>H=CH_2), 135.1 (C_{Ar}), 129.2 (CH_{Ar}), 126.1 (CH_{Ar}), 125.8 (CH_{Ar}), 125.7 (CH_{Ar}) 114.7 (<u>C</u>H_2=CH), 55.6 (CH-N), 41.0 (CH_2-N), 35.9 (CH_2), 33.8 (<u>C</u>H_2-CH=CH_2), 30.0 (<u>C</u>H_2-CH_2-N) and 25.4 (CH_2).

Data consistent with that reported in the literature.[65]

NMR file: 2012-10-09-jpc-15

1-Ethenyl-*N*-methyl-1-(pent-4-en-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (96)



Amine **117** (0.27 g, 2.11 mmol) was dissolved in DCM (20 mL) and reacted with vinyl isocyanate (0.15 mL, 2.11 mmol) and DMAP (25.7 mg, 0.21 mmol.). The reaction mixture was stirred for 1 h at r.t. The mixture was concentrated *in vacuo* and the crude urea dissolved in dry DMF (12 mL). Methyl iodide (0.89 mL, 6.33 mmol) was added and the reaction was cooled to 0 °C. Sodium hydride (0.11 g, 4.22 mmol, 60 % in mineral oil) was then quickly but cautiously added and the reaction was stirred for 3 h at 0 °C. The reaction was then diluted with Et_2O (20 mL) and quenched slowly with H_2O (20 mL). The reaction was washed with H_2O (3 × 20 mL) and then washed with a 5 % LiCl solution (3 × 20 mL) and the organic phase dried ($MgSO_4$) and concentrated *in vacuo* to give a crude mixture that was dissolved in dry THF (1.4 mL). The resulting solution was cooled to -78°C and treated with *s*-BuLi (4.12 mL, 5.27 mmol). The reaction was stirred for 1 h and DMPU (0.14 mL, 12.66 mmol) was added and stirred for a further 2 h. The reaction mixture was then quenched with MeOH (20 mL), diluted with Et_2O (20 mL) and washed with H_2O (2 × 20 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil, which upon flash column chromatography (EtOAc/PE: 1/1) afforded the title compound **96** (0.32 g, 53 %) as a colourless oil.

R_f: 0.1 (EtOAc/PE: 7/3)

IR υ_{max} (film)/cm^{-1}: 2934, 1636, 1539 and 1534.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.19-7.09 (m, 4H, 4 ×Ar*H*), 6.08 (dd, *J*=17.7 and 10.7, 1H, CH_2=C*H*-C), 5.65 (ddt, *J*=17.0, 10.3 and 6.7 Hz, 1H, CH_2=C*H*-CH_2), 5.35 (dd, *J*=17.7 and 0.5 Hz, 1H, C$H_{2(cis)}$=CH-C), 5.23 (br s, 1H, NH), 5.20 (dd, *J*=10.7 and 0.5 Hz, 1H, C$H_{2(trans)}$=CHC), 4.95-4.88 (m, 2H, CH_2=CH-CH_2), 4.20 (dt, *J*= 12.8 and 4.9 Hz, 1H, CH_2-N), 3.48 (dt, *J*=12.8 and 5.9 Hz, 1H, CH_2-N), 2.82 (t, *J*=5.9 Hz, 2H, CH_2-CH_2-N), 2.79 (d, *J*=4.6Hz, 3H, NCH_3), 2.60 (ddd, *J*=13.7, 12.5 and 4.6 Hz, 1H, CH_2-C_q), 2.09 (ddd, J=13.7, 12.6 and 4.0 Hz, 1H, CH_2-C_q), 2.03-1.88 (m, 2H, CH_2-CH=CH_2), 1.47-1.39 (m, 1H, CH_2-CH_2-C_q) and 1.09-0.98 (m, 1H, CH_2-CH_2-Cq).

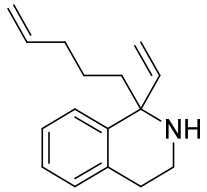
^{13}C NMR (75 MHz, $CDCl_3$): δ_C 159.1 (C=O), 146.5 (CH_2=$\underline{C}$H-C), 138.2 (CH_2=$\underline{C}$H-CH_2), 138.1 (C_{Ar}), 135.6 (C_{Ar}), 127.4 (CH_{Ar}), 126.1 (CH_{Ar}), 125.7 (CH_{Ar}), 125.1 (CH_{Ar}), 114.7 ($\underline{C}H_2$=CH-CH_2), 112.3 $\underline{C}H_2$=CH-C), 64.1 (C_q), 41.5 (CH_2-N), 35.0 (CH_2-C), 34.7 (CH_2-$\underline{C}H_2$-N), 32.6 (CH_2), 27.4 (N-CH_3) and 23.9 (CH_2).

HRMS: calcd for $C_{18}H_{25}N_2O$ 285.1962 found 285.1962 $(M^+H)^+$.

NMR file: 2012-10-21-jpc-12

Data consistent with that reported in the literature.[65]

1-(Pent-4-en-1-yl)-1-vinyl-1,2,3,4-tetrahydroisoquinoline (97)



Urea **96** (0.10 g, 0.35 mmol) and K_2CO_3 (0.05 g, 0.35 mmol) were dissolved in *n*-BuOH (10 ml) and heated under reflux for 2 h. After cooling, the mixture was quenched with H_2O (30 mL), extracted with EtOAc (2 x 20 mL), washed with H_2O (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a crude mixture which upon purification by flash column chromatography (PE/EtOAc: 9:1, 1% NEt_3) afforded the titled amine **97** (0.078 g, 99 %) as a colourless oil.

R_f: 0.1 (EtOAc/PE: 8/2)

IR υ_{max} (film)/cm^{-1}: 3078, 2930, 2356 and 1642

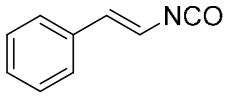
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.19-7.09 (m, 4H, 4 ×Ar*H*), 5.99 (dd, *J*=17.7 and 10.7, 1H, CH_2=C*H*-C), 5.74 (ddt, *J*=17.2, 10.6, 1H, CH_2=C*H*-CH_2), 5.10 (dd, *J*=10.6 and 0.5, 1H, C$H_{2(trans)}$=CHC), 4.98-4.89 (m, 2H, CH_2=CH-CH_2), 4.80 (dd, *J*=17.2, and 1.2, 1H, C$H_{2(cis)}$=CH-C), 3.10-3.00 (m, 2H, CH_2-CH_2-N), 2.85 (ddd, *J*=16.1, 9.6 and 6.4, 1H, CH_2-CH_2-N), 2.75 (dt, *J*=16.1 and 3.3, 1H, CH_2-CH_2-N), 2.01 (q, *J*=7.2, 2H, CH_2-CH_2=CH_2) 1.99 (ddd, *J*=13.7, 12.5 and 5.6Hz, 1H, CH_2-Cq), 1.81 (ddd, *J*=13.7, 12.6 and 4.0 Hz, 1H, CH_2-Cq), 1.51-1.44 (m, 2H, CH_2-CH=CH_2), 1.47-1.39 (m, 1H, CH_2-CH_2-Cq) and 1.19-1.12 (m, 1H, CH_2-CH_2-C_q).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C 145.5 (CH_2=<u>C</u>H-C), 139.5 (C_{Ar}), 138.9 (CH_2=<u>C</u>H-CH_2), 135.8 (C_{Ar}), 129.0 (CH_{Ar}), 127.5 (CH_{Ar}), 125.8 (CH_{Ar}), 125.5 (CH_{Ar}), 114.5 (<u>C</u>H_2=CH-CH_2), 113.3 (<u>C</u>H_2=CH-C), 62.1 (C_q), 40.4 (CH_2-C), 36.4 (CH_2-<u>C</u>H_2-N), 30.6 (CH_2), 27.4 (N-CH_3) and 22.9 (CH_2).

HRMS: Calcd for $C_{16}H_{22}N$ 228.1747 found 228.1762 $(M^+H)^+$.

NMR file: 2012-11-02-jpc-56 (300)

(*E*)-(2-isocyanatovinyl)benzene (122)



The titled isocyanate was synthesised using the general procedure 1, using the corresponding trans-cinnamic acid (1.00 g, 6.7 mmol), triethylamine (0.93 mL, 6.7 mmol) and diphenylphosphoryl azide (1.44 mL, 6.7 mmol). The desired compound was obtained (0.78 g, 78 %) as a yellow oil that was used without further purification.

R_f: 0.1 (EtOAc/PE: 0.5/9.5)

IR υ_{max} (film)/cm^{-1}: 3059, 2250 and 2170

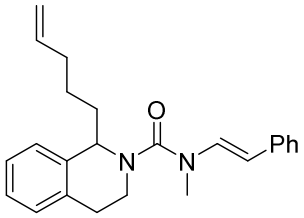
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.32-7.15 (m, 5H, ArH), 6.51-6.48 (d, *J*=15.1, 1H, Ar-C*H*=CH-NCO) and 6.35-6.33 (d, *J*=10.0, 1H, Ar-CH=C*H*-NCO).

^{13}C NMR: Compound too unstable to purify for accurate ^{13}C analysis.

LRMS: (ES) *m/z* 146 ($M + H^+$).

NMR file: 2012-12-03-jpc-16 (300)

(*E*)-N-Methyl-1-(pent-4-en-1-yl)-*N*-styryl-3,4-dihydroisoquinoline-2(1H)-carboxamide (123)



Tetrahydroisoquinoline **97** (1.00 g, 4.58 mmol) was dissolved in DCM (100 mL) and reacted with **122** (0.66 g, 4.58 mmol) and NEt_3 (1.2 mL, 9.16 mmol.). The reaction mixture was stirred for 1 h at r.t. The mixture was concentrated *in vacuo* to give a yellow solid, which was dissolved in dry DMF (25 mL) before methyl iodide (0.85 mL, 13.74 mmol) was added and the reaction was cooled to 0 °C. Sodium hydride (0.13 g, 9.16 mmol, 60 % in mineral oil) was then quickly but cautiously added and the reaction was stirred for 3 h at 0 °C. The reaction was then diluted with Et_2O (20 mL) and quenched slowly with H_2O (20 mL). The reaction was washed with H_2O (3 × 20 mL) and then washed with a 5 % LiCl solution (3 × 20 mL) and the organic phase dried ($MgSO_4$) and concentrated *in vacuo* to give a crude mixture which upon purification by flash column

chromatography (EtOAc/Pentane: 1:5 1% NEt_3) afforded the titled urea **123** (0.95 g, 79 %) as a white solid.

R_f: 0.2 (EtOAc/PE: 1/3, 1% NEt_3)

IR υ_{max} (film)/cm^{-1}: 2945, 2930, 1635 and 1542

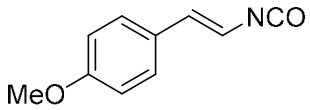
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.31-7.06 (m, 9H, 9 × Ar*H*), 6.92 (d, *J*=15.0, 1H, NCH_3C*H*=CHPh), 6.45 (d, *J*=15.7, 1H, NCH_3CH=C*H*Ph), 5.73 (ddt, *J*=16.9, 10.6 and 7.4 Hz, 1H, C*H*=CH_2), 5.43 (d, *J*=10.6, 1H, CH=C*H*$_2$), 4.95 (d, *J*=16.9, 1H, CH_2=C*H*$_2$), 4.30 (t, 1H, C*H*-N), 3.74 (t, 2H, C*H*$_2$-N), 3.17 (s, 3H, N-CH_3), 3.05 (t, *J*=4.3 and 3.1, 2H, C*H*$_2$$CH_2$-N), 2.21-2.16 (m, 2H, C*H*$_2$CH=CH_2) and 1.91-1.47 (m, 4H, 2 × C*H*$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C 155.9 (C=O), 139.1 (N<u>C</u>H=CH), 139.7 (C_{Ar}), 137.9 (<u>*C*</u>H=CH_2), 136.2 (C_{Ar}), 134.9 (C_{Ar}), 133.2 (C_{Ar}), 129.4 (CH_{Ar}), 128.9 (CH_{Ar}), 128.5 (CH_{Ar}), 128.3 (CH_{Ar}), 127.9 (CH_{Ar}), 126.7 (CH_{Ar}), 125.9 (CH_{Ar}), 119.8 (NCH=<u>C</u>H), 115.3 (<u>*C*</u>H_2=CH), 60.1 (CH-N), 40.1 (CH_2<u>C</u>H_2N), 35.1 (N-CH_3), 30.20 (CH_2-N), 34.9 (<u>*C*</u>H_2-CH=CH_2), 24.1 (<u>C</u>H_2CH_2-CH=CH_2), 28.9 (<u>*C*</u>H_2-CH_2-N) and 24.1 (CH_2).

HRMS: Calcd for $C_{24}H_{29}N_2O$ 261.1214 found 261.1213 $(M+H)^+$.

NMR file: 2012-12-10-jpc-34 (300)

(*E*)-1-(2-Isocyanatovinyl)-4-methoxybenzene (126)



The titled isocyanate was synthesised using the *general procedure 1*, using the corresponding trans-cinnamic acid (0.5 g, 2.8 mmol), triethylamine (0.4 mL, 2.8 mmol) and diphenylphosphoryl azide (0.6 mL, 2.8 mmol). The desired compound was obtained (0.34 g, 69 %) as a dark brown oil that was used without further purification.

R_f: 0.25 (EtOAc/PE: 2.5/7.5)

IR υ_{max} (film)/cm^{-1}: 2922 and 2168

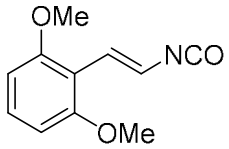
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.34 (d, *J*=2.3, 2H, 2 x ArH), 7.20 (d, J=2.1, 2H, 2 x ArH), 6.41 (d, *J*=12.2, 1H, Ar-C*H*=CH-NCO), 6.32 (d, *J*=12.2, 1H, Ar-CH=C*H*-NCO) and 3.73 (s, 3H, 3 x OCH_3).

^{13}C NMR: Compound too unstable to purify for accurate ^{13}C analysis.

LRMS: (ES) *m/z* 176 $(M + H^+)$.

NMR file: 2013-04-13-jpc-23 (300)

(*E*)-2-(2-Isocyanatovinyl)-1,3-dimethoxybenzene (129)



The titled isocyanate was synthesised using the *general procedure 1*, using the corresponding trans-cinnamic acid (1.0 g, 4.8 mmol), triethylamine (0.66 mL, 4.8 mmol) and diphenylphosphoryl azide (1.0 mL, 4.8 mmol). The desired compound was obtained (0.79 g, 80 %) as dark orange oil that was used without further purification.

R_f: 0.3 (EtOAc/PE: 3/7)

IR υ_{max} (film)/cm^{-1}: 3660 and 2259

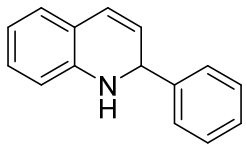
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.34 (t, *J*=7.9, 1H, Ar*H*), 7.12 (d, *J*=7.7, 2H, 2 x Ar*H*), 6.59 (d, *J*=15.3, 1H, Ar-C*H*=CH-NCO), 6.40 (d, *J*=15.1, 1H, Ar-CH=C*H*-NCO) and 3.77 (s, 6H, 2 x OCH_3).

^{13}C NMR: Compound too unstable to purify for accurate ^{13}C analysis.

LRMS: (ES) *m/z* 207 ($M+H^+$).

NMR file: 2013-04-14-jpc-54 (300)

2-Phenyl-1,2-dihydroquinoline (155)



Quinoline (3.0 mL, 21.1 mmol) in dry THF (10 mL) was added to phenyllithium (19.98 mL, 21.1 mmol) at 0 ^oC and allowed to stir for 1 h at r.t. The reaction was quenched with H_2O (20 mL) and the reaction mixture extracted with EtOAc (2 × 20 mL), dried over K_2CO_3 and concentrated *in vacuo* to give the title compound **155** (4.38 g, 83 %) as a mobile yellow oil, that was used without further purification.

R_f: 0.25 (EtOAc/PE: 1/9)

IR υ_{max} (film)/cm^{-1}: 3450, 2930, 2356, 1642 and 1540

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.45-7.41 (m, 5H, 5 x Ar*H*) 7.38-7.28 (m, 4H, 4 x Ar*H*), 6.69 (d, *J*=5.1, 1H, C*H*$_2$=CH$_2$-CH), 6.58 (dd, *J*=5.1, and 4.2 1H, CH$_2$=C*H*$_2$-CH), 4.50 (d, *J*=4.2, 1H, NH-C*H*) and 4.00 (br s, 1H, NH).

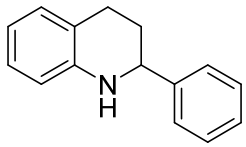
^{13}C NMR (75 MHz, $CDCl_3$): 141.2 (N-C_{Ar}), 139.1 (C_{Ar}), 133.4 (CH_{Ar}), 132.4 (CH_{Ar}), 131.7 (CH_{Ar}), 128.9 (CH_{Ar}), 128.6 (C_{Ar}), 127.9 (CH_{Ar}), 127.1 (CH_{Ar}), 126.1 (CH_{Ar}), 125.9 (CH_{Ar}), 125.5 (CH_{Ar}), 119.1 (*C*H=CH-CH-NH), 117.6 (CH=*C*H-CH-NH) and 54.9 (NH-*C*H).

LRMS: (ES) *m/z* 206 ($M+H^+$).

Data consistent with that reported in the literature.[74]

NMR file: 2012-11-23-jpc-05

2-Phenyl-1,2,3,4-tetrahydroquinoline (158)



Dihydroquinoline **155** (0.61 g, 2.96 mmol) was dissolved in dry ethanol (12 mL) and the solution heated at reflux for 1 h. Freshly cut sodium (1.25 g, 53.6 mmol) was washed with petroleum ether and added portion wise over 1 h and the mixture left to reflux for a further 1 h. The reaction was cooled and the thick reaction mixture quenched by the slow addition of H_2O (50 mL). The reaction mixture was then extracted with EtOAc (3 × 20 mL) and concentrated *in vacuo* to give the titled compound **158** (1.10 g, 75 %) as a viscous yellow oil.

R_f: 0.2 (EtOAc/PE: 1/9)

IR υ_{max} (film)/cm^{-1}: 3455, 2945, 1650 and 1542

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.45-7.26 (m, 5H, Ar*H*), 7.05 (d, *J*= 7.7, 2H, Ar*H*), 6.69 (t, *J*=7.7, 2H, Ar*H*), 6.68 (t, *J*=7.7, 1H, Ar*H*), 4.48 (t, *J*=10.3, 2.5, 1H, NH-C*H*), 4.06 (NH), 2.95 (q, *J*=3.6, 2.5, 1H, NH-C*H*-CH$_2$-C*H*$_2$), 2.78-2.75 (m, 1H, NH-CH-CH$_2$-C*H*$_2$), 2.15 (q, *J*=3.8, 2.7, 1H, NH-CH-C*H*$_2$-CH$_2$) and 2.07 (s, 1H, NH-CH-CH$_2$-C*H*$_2$).

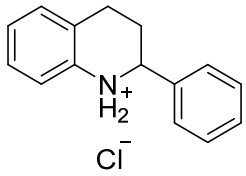
^{13}C NMR (75 MHz, $CDCl_3$): δ_C 148.0 (N-C_{Ar}), 142.3 (C_{Ar}), 129.5 (CH_{Ar}), 128.5 (CH_{Ar}), 127.6 (CH_{Ar}), 126.9 (CH_{Ar}), 126.6 (C_{Ar}), 120.9 (CH_{Ar}), 120.1 (CH_{Ar}), 119.2 (CH_{Ar}), 117.2 (CH_{Ar}), 114.0 (CH_{Ar}), 56.3 (NH-*C*H) 31.0 (*C*H$_2$-CH$_2$-CH) and 26.4 (CH$_2$-*C*H$_2$-CH).

LRMS: (ES) *m/z* 210 ($M+H^+$).

Data consistent with that reported in the literature.[74]

NMR file: 2012-11-24-jpc-19

2-Phenyl-1,2,3,4-tetrahydroquinolin-1-ium chloride (165)



Amine **164** (1.00 g, 4.78 mmol) was dissolved in an dry ethereal solution of HCl (3M, 30 mL) and stirred for 10 min. The solution was then concentrated *in vacuo* to afford the amine salt **165** (1.17 g, 99 %) as colourless prisms that was used without further purification.

R_f: 0.4 (EtOAc/PE: 1/1, 5% NEt_3)

IR υ_{max} (film)/cm^{-1}: 3495 and 1540

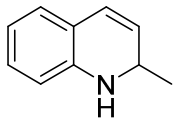
^{1}H NMR (300 MHz, D_2O): δ_H 7.13-7.10 (m, 4H, 4 x Ar*H*), 7.05-7.02 (m, 5H, 5 x Ar*H*) 4.47 (dt, *J*=9.8, 3.1, 1H, NH-C*H*), 3.00 (t, *J*=9.7, 4.6, 2H, CH_2-CH_2-CH-NH) and 2.85 (dt, *J*=9.6, 4.3, 2H, CH_2-CH_2-CH-NH).

^{13}C NMR (75 MHz, D_2O): δ_C 143.0 (N-C_{Ar}), 138.3 (C_{Ar}), 137.9 (CH_{Ar}), 126.9 (CH_{Ar}), 127.6 (C_{Ar}), 126.7 (CH_{Ar}), 126.5 (CH_{Ar}), 121.5 (CH_{Ar}), 120.2 (CH_{Ar}), 120.0 (CH_{Ar}), 118.4 (CH_{Ar}), 70.5 (NH_2-$\underline{C}$H) 32.5 ($\underline{C}H_2$-CH_2-CH) and 30.1 (CH_2-$\underline{C}H_2$-CH)

LRMS: (ES) *m/z* 210 ($M+H^+$).

NMR file: 2013-05-23-jpc-34

2-Methyl-1,2-dihydroquinoline (162)



Quinoline (1.0 mL, 7.07 mmol) in dry THF (10 mL) was added to methylithium (6.7 mL, 7.07 mmol) at 0 °C and allowed to reflux for 25 h at 70 °C. The reaction was quenched with H_2O and the reaction mixture extracted with EtOAc (2 × 20 mL), dried over K_2CO_3 and concentrated *in vacuo* to give the title compound **162** (0.98 g, 96 %) as a yellow oil, that was used without further purification.

R_f: 0.3 (EtOAc/PE: 1/9)

IR υ_{max} (film)/cm^{-1}: 3432, 2930, 2356 and 1642

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 6.86-6.60 (m, 4H, 4 x ArH), 6.42 (d, *J*=8.0, 1H, C*H*$_2$=CH$_2$-CH), 6.33 (dd, *J*=8.1, 1.1, 1H, CH$_2$=C*H*$_2$-CH), 4.43 (dq, *J*=7.2, 4.2, 1H, NH-C*H*), 3.65 (br s, 1H, NH) and 1.33 (d, *J*=4.2, 3H, CH_3).

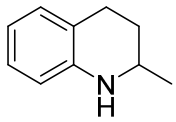
^{13}C NMR (75 MHz, $CDCl_3$): δ_C 159.0 (N-C_{Ar}), 143.8 (C_{Ar}), 136.5 (CH_{Ar}), 129.6 (CH_{Ar}), 128.6 (CH_{Ar}), 125.1 (CH_{Ar}), 117.5 (C_{Ar}*C*H=CH-CH), 112.6 (C_{Ar}CH=*C*H-CH), 48.2 (NH-*C*H) and 24.20 (C-*C*H$_3$).

LRMS: (ES) *m/z* 144 ($M+H^+$).

Data consistent with that reported in the literature.[74]

NMR file: 2012-11-23-jpc-7

2-Methyl-1,2,3,4-tetrahydroquinoline (163)



Dihydroquinoline **162** (1.11 g, 7.58 mmol) was dissolved in dry ethanol (30 mL) and the solution heated at reflux for 1 h. Freshly cut sodium (3.13 g, 136.44 mmol) was washed with petroleum ether (25 mL) and added portion wise to the solution over 1 h and the reaction heated at reflux for a further 1 h. The reaction was cooled and the thick reaction mixture quenched by the slow addition of H_2O (20 mL). The reaction mixture was then extracted with EtOAc (3 × 20 mL) and concentrated in vacuo to give the titled compound **163** (0.85 g, 82 %) as a yellow oil.

R_f: 0.3 (EtOAc/PE: 1/9)

IR υ_{max} (film)/cm^{-1}: 3450, 2953 and 1540

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.21-7.10 (m, 4H, 4 x Ar*H*), 4.45 (dt, *J*=11.5, 5.1, 1H, NH-C*H*), 4.06 (br s, 1H, NH) 2.96 (t, *J*=11.1, 2H, C*H*$_2$-CH$_2$-CH), 2.78 (dt, *J*=11.4, 3.8, 2H, CH$_2$-C*H*$_2$-CH) and 1.37 (d, *J*=3.2, 3H, CH_3).

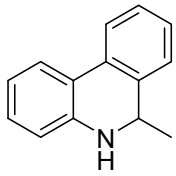
^{13}C NMR (75 MHz, $CDCl_3$): δ_C 144.0 (N-C_{Ar}), 129.3 (C_{Ar}), 136.5 (CH_{Ar}), 126.5 (CH_{Ar}), 120.6 (CH_{Ar}), 117.1 (CH_{Ar}), 57.8 (NH-*C*H) 31.7 (*C*H$_2$-CH$_2$-CH), 29.8 (CH$_2$-*C*H$_2$-CH) and 22.40 (C-*C*H$_3$).

LRMS: (ES) *m/z* 148 ($M + H^+$).

Data consistent with that reported in the literature.[74]

NMR file: 2012-11-26-jpc-19 (500)

6-Methyl-5,6-dihydrophenanthridine (142)



To a solution of phenanthridine (0.32 g, 1.79 mmol) in dry THF (30 mL) was added methylithium (2.5 mL, 1.79 mmol) at 0 °C and the mixture allowed to stir for 1 h at r.t. The reaction was quenched with H_2O (20 mL) and the reaction mixture extracted with EtOAc (2 × 20 mL), dried over K_2CO_3 and concentrated *in vacuo* to give the title compound **142** (0.33 g, 95 %) as a yellow solid that was used without further purification.

R_f: 0.30 (EtOAc/PE: 2/8)

IR υ_{max} (film)/cm^{-1}: 3330, 2945 and 1542

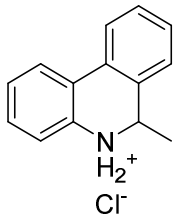
^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.65-7.60 (m, 2H, Ar*H*), 7.23 (d, *J*=7.2, 1H, Ar*H*), 7.17 (d, *J*=7.3, 1H, Ar*H*), 7.07-7.03 (m, 2H, Ar*H*), 6.75 (d, *J*=7.2 1H, Ar*H*), 6.59 (d, *J*=7.4, 1H, Ar*H*), 4.47 (q, *J*=6.9, 4.3, 1H, NH-C*H*), 4.1 (br s, 1H, N*H*) and 1.36 (d, *J*=4.3, 2H, C-CH_3)

^{13}C NMR (125 MHz, $CDCl_3$): δ_C 144.03 (C_{Ar}), 137.24 (C_{Ar}), 131.0 (C_{Ar}), 128.8 (C_{Ar}), 127.4 (CH_{Ar}), 127.3 (CH_{Ar}), 123.4 (CH_{Ar}), 122.5 (CH_{Ar}), 121.3 (CH_{Ar}), 118.9 (CH_{Ar}), 115.3 (CH_{Ar}), 50.86 (N-CH) and 22.7 (C-$\underline{C}H_3$)

LRMS: (ES) *m/z* 194 ($M + H^+$).

NMR file: 2012-01-11-jpc-69 (500)

6-Methyl-5,6-dihydrophenanthridin-5-ium chloride (150)



Amine **142** (1.00 g, 5.15 mmol) was dissolved in an dry ethereal solution of HCl (3M, 40 mL) and stirred for 10 min. The solution was then concentrated *in*

vacuo to afford the amine salt **150** (1.51 g, 99 %) as colourless prisms that was used without further purification.

R_f: 0.1 (EtOAc/PE: 2/5, 5% NEt_3)

IR υ_{max} (film)/cm^{-1}: 2950, 2948 and 1545

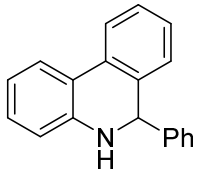
^{1}H NMR (500 MHz, D_2O): δ_H 7.64-7.60 (m, 2H, Ar*H*), 7.23 (d, *J*=7.1, 1H, Ar*H*), 7.17 (d, *J*=7.2, 1H, Ar*H*), 7.07-7.03 (m, 2H, Ar*H*), 6.78 (d, *J*=7.0, 1H, Ar*H*), 6.60 (d, *J*=7.1, 1H, Ar*H*), 4.49 (q, *J*=6.7, 3.8, 1H, NH-C*H*), 4.4 (br s, 1H, NH) and 1.38 (d, *J*=3.8, 2H, C-CH_3)

^{13}C NMR (125 MHz, D_2O): δ_C 145.0 (C_{Ar}), 138.2 (C_{Ar}), 134.0 (C_{Ar}), 129.2 (C_{Ar}), 128.4 (CH_{Ar}), 128.1 (CH_{Ar}), 124.4 (CH_{Ar}), 123.5 (CH_{Ar}), 121.3 (CH_{Ar}), 118.9 (CH_{Ar}), 115.3 (CH_{Ar}), 72.86 (N-CH_2) and 19.1 (C-$\underline{C}H_3$)

LRMS: (ES) *m/z* 196 ($M + H^+$).

NMR file: 2013-03-12-jpc-23 (500)

6-Phenyl-5,6-dihydrophenanthridine (143)



To a solution of phenanthridine (0.39 g, 2.13 mmol) in dry THF (30 mL) was added phenyllithium (2.0 mL, 2.13 mmol) at 0 °C and the mixture allowed to stir for 1 h at r.t. The reaction was quenched with H_2O (20 mL) and the reaction mixture extracted with EtOAc (2 × 20 mL), dried over K_2CO_3 and concentrated *in vacuo* to give the title compound **143** (0.43 g, 77 %) as a yellow solid that was used without further purification.

R_f: 0.30 (EtOAc/PE: 2/8)

IR υ_{max} (film)/cm^{-1}: 3330, 2945, 1610 and 1555

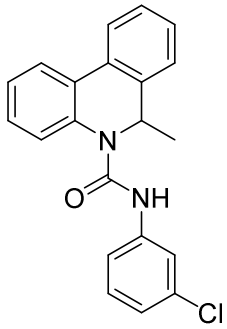
^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.71-7.60 (m, 2H, ArH), 7.52 (d, *J*=7.5, 1H, ArH), 7.32-7.27 (m, 5H, ArH) 7.17 (d, *J*=7.6, 1H, ArH), 7.07-7.06 (m, 2H, ArH), 6.78-6.57 (m, 2H, ArH), 5.50 (q, *J*=7.1, 4.5, 1H, NH-C*H*), and 3.40 (br s, 1H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ_C 179.6 (N-C_{Ar}), 144.2 (C_{Ar}), 143.4 (C_{Ar}), 135.7 (C_{Ar}), 131.4 (C_{Ar}), 129.0 (CH_{Ar}), 128.7 (CH_{Ar}), 127.8 (CH_{Ar}), 127.6 (CH_{Ar}), 127.2 (CH_{Ar}), 122.3 (CH_{Ar}), 122.0 (CH_{Ar}), 119.1 (CH_{Ar}), 114.9 (CH_{Ar}) and 60.20 (N-CH).

LRMS: (ES) *m/z* 258 ($M + H^+$).

NMR file: 2012-01-11-jpc-58 (500)

N-(3-Chlorophenyl)-6-methylphenanthridine-5(6H)-carboxamide (148)



Amine **142** (0.27 g, 2.11 mmol) was dissolved in DCM (20 mL) and reacted with 3-chlorophenyl isocyanate (0.15 mL, 2.11 mmol) and NEt_3 (0.3 mL, 2.11 mmol.). The reaction mixture was stirred for 1 h at r.t. The mixture was concentrated *in vacuo* to give a yellow solid which upon purification by flash column chromatography (EtOAc/Pentane: 1:9, 1% NEt_3) afforded the titled urea **148** (0.34 g, 99 %) as an off-white solid.

R_f: 0.35 (EtOAc/PE: 0.5/9.5)

IR υ_{max} (film)/cm^{-1}: 3341, 2948, 1641 and 1562

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.90-7.80 (m, 3H, Ar*H*), 7.50-7.1 (m, 8H, Ar*H*), 7.0 (s, 1H, Ar*H*), 5.88 (q, *J*=9.3, 3.5, 1H, NH-C*H*), 1.25 (d, *J*=3.5, 3H, C-CH_3). (NH peak not visible)

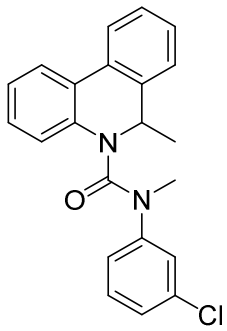
^{13}C NMR (75 MHz, $CDCl_3$): δ_C 152.2 (C=O), 139.8 (C_{Ar}), 139.6 (C_{Ar}), 134.6 (C_{Ar}), 134.5 (C_{Ar}), 129.8 (C_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 128.1 (CH_{Ar}), 127.8 (CH_{Ar}), 126.5 (CH_{Ar}), 126.0 (CH_{Ar}), 125.1 (CH_{Ar}), 124.4 (CH_{Ar}), 123.4 (CH_{Ar}), 123.2 (CH_{Ar}), 119.1 (CH_{Ar}), 117.0 (CH_{Ar}), 51.20 (N-CH) and 20.38 (C-$\underline{C}H_3$).

LRMS: (ES) *m/z* 349 ($M + H^+$).

HRMS: Calcd for $C_{21}H_{18}ClN_2O$ 349.1145 found 349.1145 $(M^+H)^+$.

NMR file: 2013-08-15-jpc-42 (300)

N-(3-Chlorophenyl)-*N*,6-dimethylphenanthridine-5(6H)-carboxamide (151)



Urea **148** (0.56, 2.9 mmol) was dissolved in dry DMF (20 mL) before methyl iodide (0.54 mL, 8.7 mmol) was added and the reaction was cooled to 0°C. NaH (0.23 g, 5.8 mmol, 60 % in mineral oil) was then quickly but cautiously added and the reaction was stirred for 3 h at 0 °C. The reaction was then diluted with Et_2O (20 mL) and quenched slowly with H_2O (20 mL). The reaction was washed with H_2O (3 × 20 mL) and then washed with a 5 % LiCl solution (3 × 20 mL) and the organic phase dried ($MgSO_4$) and concentrated *in vacuo* to give a crude mixture which upon purification by flash column chromatography (PE/EtOAc: 9:1, 1% NEt_3) afforded the titled urea **151** (0.53 g, 94 %) as an off-white solid.

R_f: 0.5 (EtOAc/PE: 1.5/8.5, 1 % NEt_3)

IR υ_{max} (film)/cm^{-1}: 3338, 2942, 1612 and 1545

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.54 (d, *J*=7.5, 1H, Ar*H*), 7.41 (d, *J*=7.5, 1H, Ar*H*), 7.27-7.14 (m, 4H, Ar*H*), 6.99-6.88 (m, 4H, Ar*H*), 6.58 (s, 1H, Ar*H*), 6.49 (t, 1H, Ar*H*), 5.40 (q, *J*=10.1, 3.9, 1H, NH-C*H*), 3.20 (s, 3H, N-CH_3) and 1.18 (d, *J*=3.6, 3H, C-CH_3).

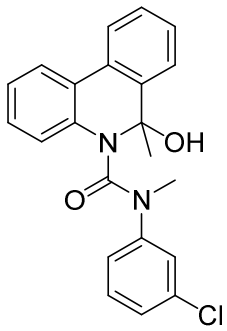
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.7 (C=O), 145.7 (C_{Ar}), 138.3 (C_{Ar}), 135.3 (C_{Ar}), 133.8 (C_{Ar}), 130.0 (C_{Ar}), 129.1 (CH_{Ar}), 128.0 (CH_{Ar}), 127.7 (CH_{Ar}), 127.3 (CH_{Ar}), 126.0 (CH_{Ar}), 125.6 (CH_{Ar}), 125.2 (CH_{Ar}), 124.2 (CH_{Ar}), 123.9 (CH_{Ar}), 123.8 (CH_{Ar}-), 123.6 (CH_{Ar}), 123.5 (CH_{Ar}), 123.3 (CH_{Ar}), 121.7 (CH_{Ar}), 53.8 (N-<u>*C*</u>H), 39.2 (N-CH_3), 20.5 (C-<u>*C*</u>H_3).

LRMS: (ES) *m/z* 363 ($M + H^+$).

HRMS: Calcd for $C_{22}H_{20}ClN_2O$ 363.1265 found 363.1265 $(M^+H)^+$.

NMR file: 2013-09-09-jpc-8 (^{1}H, 400), 2013-09-09-jpc (^{13}C, 400)

N-(3-Chlorophenyl)-6-hydroxy-*N*,6-dimethylphenanthridine-5(6H)-carboxamide (154)



Urea **151** (0.12 g, 0.34 mmol) was dissolved in dry THF (1.4 mL) and the reaction was cooled to -78 °C and treated with *s*-BuLi (0.65 mL, 0.85 mmol). The reaction was stirred for 1 h and DMPU (0.17 mL, 1.37 mmol) was added and stirred for a further 12 h at -78 °C. The reaction mixture was then quenched with MeOH (10 mL), diluted with Et_2O (20 mL) and washed with H_2O (2 × 20 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil, which upon flash column chromatography (EtOAc/Pentane: 1/1) afforded the title compound **154** (0.32 g, 53 %) as a colourless oil.

R_f: 0.30 (EtOAc/PE: 1/1, 1% NEt_3)

IR υ_{max} (film)/cm^{-1}: 3566, 2947, 1610 and 1540

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.63-6.90 (m, 11 H, ArH), 6.60 (s, 1H, ArH), 3.38 (N-CH_3) and 1.26 (s, 3H, C-CH_3). C-OH cannot be seen.

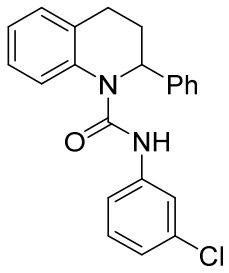
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.7 (C=O), 145.7 (C_{Ar}), 138.3 (C_{Ar}), 135.3 (C_{Ar}), 133.8 (C_{Ar}), 130.0 (C_{Ar}), 128.1 (CH_{Ar}), 127.0 (CH_{Ar}), 126.7 (CH_{Ar}), 126.3 (CH_{Ar}), 125.5 (CH_{Ar}), 125.2 (CH_{Ar}), 124.9 (CH_{Ar}), 124.7 (CH_{Ar}), 124.5 (CH_{Ar}), 124.2 (CH_{Ar}), 123.9 (CH_{Ar}), 123.8 (CH_{Ar}), 123.5 (CH_{Ar}), 121.9 (CH_{Ar}), 84.3 (C-OH) 40.2 (N-CH_3), 21.5 (C-$\underline{C}H_3$).

LRMS: (ES) *m/z* 400 ($M+Na^+$).

HRMS: Calcd for $C_{22}H_{18}ClNaO_2$ 400.1023 found 400.1023 $(M^+Na)^+$

NMR file: 2013-05-20-jpc-21 (400)

N-(3-Chlorophenyl)-2-phenyl-3,4-dihydroquinoline-1(2H)-carboxamide (166)



Amine **158** (0.27 g, 1.31 mmol) was dissolved in DCM (20 mL) and reacted with 3-chlorophenyl isocyanate (0.15 mL, 1.31 mmol) and NEt_3 (0.23 mL, 1.70 mmol). The reaction mixture was stirred for 1 h at r.t. The mixture was concentrated *in vacuo* to give the titled urea **166** (0.31 g, 62 %) as an off-white solid that was used without further purification.

R_f: 0.20 (EtOAc/Pentane: 1/9, 1% NEt_3)

IR υ_{max} (film)/cm^{-1}: 3455, 2942, 1639 and 1542

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.51 (d, *J*=7.8, 2H, ArH), 7.36-7.17 (m, 8 H, ArH), 7.04 (t, *J*=7.7, 7.5, 1H, ArH), 7.00 (d, *J*=7.7, 2H, ArH), 5.60 (t, *J*=3.9, 2.1, 1H, NH-C*H*), 2.75-2.67 (m, 3H, CH_2-C*H*(H)) and 1.90 (m, 1H, CH_2-CH(*H*)).

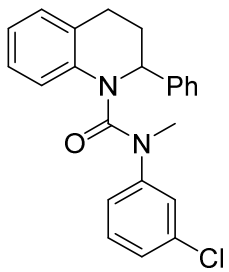
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 151.7 (C=O), 141.6 (N-C_{Ar}), 140.4 (NCH-$\underline{C}$Ar), 140.3 (NH-$\underline{C}_{Ar}$), 133.9 ($\underline{C}$-Cl), 131.7 (CH_{Ar}), 129.9 (CH_{Ar}), 129.3 (C_{Ar}), 128.9 (CH_{Ar}), 128.5 (CH_{Ar}), 126.5 (CH_{Ar}), 123.8 (C_{Ar}), 123.3 (CH_{Ar}), 121.8 (CH_{Ar}), 118.8 (CH_{Ar}), 118.3 (CH_{Ar}), 117.3 (CH_{Ar}), 59.3 (NH-$\underline{C}$H) 30.6 ($\underline{C}H_2$-CH_2-CH) and 26.9 (CH_2-$\underline{C}H_2$-CH).

LRMS: (ES) *m/z* 363 ($M + H^+$).

HRMS: Calcd for $C_{22}H_{20}ClNO_2$ 363.1378 found 363.1370 $(M^+H)^+$

NMR file: 2013-09-18-jpc-31 (400)

N-(3-Chlorophenyl)-*N*-methyl-2-phenyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (167)



Urea **166** (0.13 g, 0.35 mmol) was dissolved in dry DMF (15 mL). Methyliodide (0.06 mL, 1.05 mmol) was added and the reaction was cooled to 0 °C. NaH

(0.034 g, 0.87 mmol, 60 % in mineral oil) was then quickly but cautiously added and the reaction was stirred for 3 h at 0 °C. The reaction was then diluted with Et_2O (20 mL) and quenched slowly with H_2O (20 mL). The reaction was washed with H_2O (3 × 20 mL) and then washed with a 5 % LiCl solution (3 × 20 mL) and the organic phase dried ($MgSO_4$) and concentrated *in vacuo* to give a crude mixture which upon purification by flash column chromatography (EtOAc/Pentane: 2/9, 1% NEt_3) afforded the titled urea **166** (0.10 g, 78 %) as an off-white solid.

R_f: 0.20 (EtOAc/Pentane: 1/9, 1% NEt_3)

IR υ_{max} (film)/cm^{-1}: 3459, 2933, 1645, 1543 and 1510

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.31-7.00 (m, 10 H, ArH), 6.90-6.87 (m, 2H, ArH), 5.27-5.25 (t, *J*=3.3, 2.1, 1H, NH-C*H*), 3.23 (s, 3H, N-CH_3), 2.49-2.48 (m, 3H, CH_2-C*H*(H)) and 1.96-1.94 (m, 1H, CH_2-CH(*H*)).

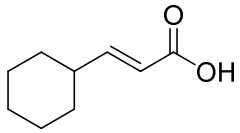
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 152.7 (C=O), 141.9 (N-C_{Ar}), 140.7 (NCH-$\underline{C}$Ar), 140.5 (NH-$\underline{C}_{Ar}$), 132.6 ($\underline{C}$-Cl), 131.4 (CH_{Ar}), 129.5 (CH_{Ar}), 129.7 (C_{Ar}), 128.6 (CH_{Ar}), 128.9 (CH_{Ar}), 126.2 (CH_{Ar}), 124.5 (C_{Ar}), 123.3 (CH_{Ar}), 121.6 (CH_{Ar}), 119.8 (CH_{Ar}), 119.3 (CH_{Ar}), 118.6 (CH_{Ar}), 59.4 (NH-$\underline{C}$H) 35.4 (NCH_3), 30.2 ($\underline{C}H_2$-CH_2-CH) and 25.1 (CH_2-$\underline{C}H_2$-CH).

LRMS: (ES) *m/z* 377 (M + H^+).

HRMS: Calcd for $C_{23}H_{20}ClN_2O$ 363.1422 found 363.1408 $(M^+H)^+$

NMR file: 2013-09-16-jpc-45 (400)

(*E*)-3-Cyclohexylacrylic acid (132)



To a mixture of malonic acid (2.08 g, 20.0 mmol) and piperidine (235 µL, 2.38 mmol) in pyridine (5.8 mL) was added cyclohexanecarboxaldehyde (1.12g, 10.0 mmol) and the mixture stirred at r.t for 5 min. The reaction mixture was then heated to 130 °C for 4 h. The reaction was cooled to room temperature and quenched with HCl (1 M, 15 mL). The aqueous layer was extracted with ether (3 x 30 mL) and the combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4 and concentrated in vacuo to give an off white solid, which

was purified by flash column chromatography (EtOAc/Pentane: 1/5) to give the titled compound **132** (1.25 g, 81%) as a colourless solid.

R_f: 0.2 (EtOAc/Pentane: 1/4)

IR υ_{max} (film)/cm^{-1}: 2963, 2945, 2920 and 1686

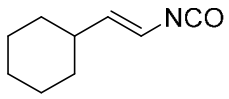
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.04 (dd, *J*=15.7, 6.9 , 1H, C*H*=CHCO$_2$H), 5.78 (dd, *J*=15.6, 1.60, 1H, CH=C*H*CO$_2$H) and 2.21-1.25 (m, 11H, Cy).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C 172.4 (C), 156.9 (CH), 118.2 (CH), 40.4 (CH), 31.4 (2 x CH_2), 25.8 (CH_2), 25.5 (2 x CH_2) and 14.0 (2 x CH_2).

Data consistent with that in the literature.[72]

NMR file: 2013-11-06-jpc-38 (500)

(*E*)-(2-Isocyanatovinyl)cyclohexane (132)



The titled isocyanate was synthesised using the *general procedure 1*, using the corresponding *trans*-cinnamic acid (0.5 g, 2.8 mmol), triethylamine (0.4 mL, 2.8 mmol) and diphenylphosphoryl azide (0.6 mL, 2.8 mmol). The desired compound was obtained (0.34 g, 69 %) as an orange oil that was used without further purification.

R_f: 0.1 (EtOAc/PE: 1/5)

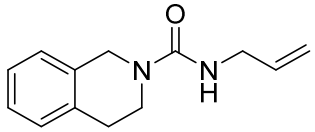
IR υ_{max} (film)/cm^{-1}: 2923, 2851, 2262 and 1488.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.15 (dd, *J*=14.9, 6.2, 1H, C*H*=CHNCO), 5.82 (dd, *J*=14.8, 1.60, 1H, CH=C*H*NCO) and 2.25-1.11 (m, 11H, Cy).

^{13}C NMR: Compound too unstable to purify for accurate ^{13}C analysis.

NMR file: 2013-11-06-jpc-04 (500)

N-Allyl-3,4-dihydroisoquinoline-2(1H)-carboxamide (138)



Tetrahydroisoquinoline (4.10 mL, 32.80 mmol) was dissolved in DCM (20 mL) and reacted with allyl isocyanate (2.70 mL, 32.80 mmol) and NEt_3 (5.40 mL,

0.00 mmol). The reaction mixture was stirred for 1 h at r.t. The mixture was concentrated *in vacuo* to give the titled urea **138** (7.00 g, 99 %) as an off-white solid that was used without further purification.

R_f: 0.30 (EtOAc/Pentane: 1/5, 1% NEt_3)

IR υ_{max} (film)/cm^{-1}: 2970, 2934, 2362 and 1696

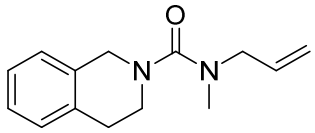
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.24-7.12 (m, 4H, 4 × Ar*H*), 5.79 (dt, *J*=17.2, 10.6, 7.0, 1H, CH_2CH=CH_2), 4.97 (dd, *J*=10.6, 1.3, 1H, CH_2CH=CH_2), 4.96 (dd, *J*=17.3, 1.3, 1H, CH_2CH=CH_2), 4.35 (s, 2H, CH_2N), 3.95 (d, *J*=7.0, 2H, $NHCH_2$) 3.54 (q, *J*=4.3, 3.5, 2H, CH_2CH_2N) and 2.99 (t, 2H, CH_2CH_2N).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C 157.9 (C=O), 135.1 (C_{Ar}), 133.2 (C_{Ar}), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 127.1 (CH_{Ar}), 126.1 (CH_{Ar}), 134.6 ($CH_2\underline{C}H$=CH_2), 116.1 (CH_2CH=$\underline{C}H_2$), 48.2 ($\underline{C}H_2CH$=CH_2), 45.5 ($\underline{C}H_2NCONH$), 42.8 ($CH_2\underline{C}H_2N$), and 29.1 ($\underline{C}H_2CH_2N$).

HRMS: Calcd for $C_{13}H_{17}N_2O$ 217.1355 found 217.1352 $(M^+H)^+$

NMR file: 2013-11-06-jpc-04 (500)

N-Allyl-*N*-methyl-3,4-dihydroisoquinoline-2(1H)-carboxamide (139)



Urea **138** (1.00 g, 4.34 mmol) was dissolved in dry DMF (20 mL). Methyliodide (0.81 mL, 13.02 mmol) was added and the reaction was cooled to 0 °C. Sodium hydride (0.15 g, 10.85 mmol, 60 % in mineral oil) was then quickly but cautiously and the reaction was stirred for 3 h at 0°C. The reaction was then diluted with Et_2O (20 mL) and quenched slowly with H_2O (20 mL). The reaction was washed with H_2O (3 × 20 mL) and then washed with a 5 % LiCl solution (3 × 20 mL) and the organic phase dried ($MgSO_4$) and concentrated *in vacuo* to give a crude mixture which upon purification by flash column chromatography (EtOAc/Pentane: 1/5, 1 % NEt_3) afforded the titled urea **139** (0.84 g, 80 %) as an off-white solid.

R_f: 0.4 (EtOAc/Pentane: 1/5, 1% NEt_3)

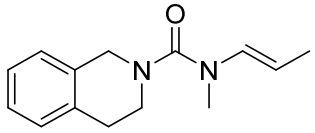
IR υ_{max} (film)/cm^{-1}: 2947, 2931, and 1692

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.23-6.8 (m, 4H, 4 × Ar*H*), 5.90 (dt, *J*=1.5, 4.7, 17.5, 1H, CH_2CH=CH_2), 4.98 (dd, *J*=1.4, 10.7, 1H, CH_2CH=CH_2), 4.97 (dd, *J*=1.5, 17.6, 1H, CH_2CH=CH_2), 4.34 (s, 2H, CH_2N), 4.01 (d, *J*=4.3, 2H, NCH_3CH_2) 3.50 (d, *J*=4.4, 2H, CH_2CH_2N), 3.03 (s, 3H, N-CH_3) and 2.98 (q, *J*=4.4, 1.3, 2H, CH_2CH_2N).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C 151.9 (C=O), 135.4 (C_{Ar}), 134.4 (C_{Ar}), 130.5 (CH_{Ar}), 130.2 (CH_{Ar}), 128.6 (CH_{Ar}), 128.3 (CH_{Ar}), 109.5 (CH_2<u>C</u>H=CH_2), 101.2 (CH_2CH=<u>C</u>H_2), 50.3 (<u>C</u>H_2CH=CH_2), 43.8 (<u>C</u>H_2NCON), 41.0 (CH_2<u>C</u>H_2N), 35.00 (N-CH_3) and 30.0 (<u>C</u>H_2CH_2N).

HRMS: Calcd for $C_{14}H_{19}N_2O$ 231.1523 found 231.1521 $(M^+H)^+$

(E)-N-methyl-N-(prop-1-en-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxamide (140)



Amine **139** (2.53 g, 11.01 mmol) was dissolved in THF (50 mL) and treated with carbonylchlorohydridotris(triphenylphosphine) ruthenium(II) (0.93 g, 1.01 mmol). The reaction mixture was heated at refluxed for 16 h. The reaction was then cooled to room temperature and concentrated *in vacuo* to give a pale brown oil. The crude mixture was purified by flash chromatography on silica gel (EtOAc/Pentane: 1/5, 1% NEt_3) affording the titled compound 140 (2.10 g, 77 %) as a yellow oil.

R_f: 0.35 (EtOAc/Pentane: 1/4, 1% NEt_3)

IR υ_{max} (film)/cm^{-1}: 2943, 2938, 1681 and 1540

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.27-7.11 (m, 4H, 4 × Ar*H*), 6.55 (dt, *J*=15.1, 7.6, 1H, C*H*=$CHCH_3$), 4.88 (dd, *J*=7.2, 15, 1H, CH=C*H*CH_3), 4.95 (s, 2H, CH_2N), 3.03 (s, 3H, N-CH_3), 3.57 (d, *J*=3.4, 2H, CH_2CH_2N), 2.99 (d, *J*=3.5, 2H, CH_2CH_2N) and 1.73 (d, *J*=7.2, 3H, CH=CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C 152 (C=O), 139.4 (C_{Ar}), 139.1 (<u>C</u>H=$CHCH_3$), 135.1 (C_{Ar}), 128.4 (CH_{Ar}), 127.7 (CH_{Ar}), 127.7 (CH_{Ar}), 126.9 (CH_{Ar}), 106.2 (CH=<u>C</u>HCH_3), 43.8 (<u>C</u>H_2NCON), 42.6 (CH_2<u>C</u>H_2N), 42.00 (N-CH_3), 28.9 (<u>C</u>H_2CH_2N) and 14.0 (CH=CH*C*H_3),

HRMS: Calcd for $C_{14}H_{19}N_2O$ 231.1523 found 231.1523 $(M^+H)^+$

5. References

1) Roy, S.; Spino, C. *Org. Lett.,* **2006**, *8*, 939.

2) Verdaguer, X.; Lauge, U.E.W.; Buchwald, S.L. *Angew. Chem. Int. Ed.,* **1998**, 37, 1103

3) Carlier, P.R.; Zhoa, H.; DeGuzman, J.; Lam, P.C-H. *J. Am. Chem. Soc*., **2003**, *125*, 11482.

4) Mashiko, T.; Hara, K.; Tanaka, D.S.; Fujiwara, Y.; Kumagai, N.; Shibasakai, M. *J. Am. Chem. Soc*., **2007**, *129*, 11342.

5) Postigo, A. A.; Teixido, J.; Sanchesmadrid, F. *Res. Immunol.* **1993**, *144*, 723.

6) Flausino O. Jr.; Santos L. Á.; Verlhi H.; Pereira A. M.; Bolzani V. S.; Luiz Nunes-de-Souza R. *J. Nat. Prod.,* **2007**, 70, 48–53.

7) Santarem M.; Vanucci-Bacqué C.; Lhommet G. *J. Org. Chem.*, **2008**, *73* (16), 6466–6469

8) Cogan, D.A.; Liu, G.; Ellman, J. *Tetrahedron*. **1999**, *55*, 8883.

9) Bloch, R. *Chem. Rev.,* **1998**, 98, 1407.

10) Ellman, J.A.; Owens, T.D.; Tang, T.P. *Acc. Chem. Res*., **2002**, *35*, 984.

11) Ciganek, E. *J. Org. Chem.,* **1992**, *57*, 4521.

12) Davis, F.A.; Reddy, R.E.; Szewozyk, J.M.; Venkat Reddy, G.; Portonovo, P.S., Zhang, H.; Faneli, D.; Thimma Reddy, R.; Zhou, P.; Carroll, P.J. *J. Org. Chem.*, **1997**, *62*, 2555.

13) Brook, M.A.; Jahangir. *Synth. Comm.* **1988**, *18*, 893.

14) Wakayama, M.; Ellman, J.A. *J. Org. Chem*., **2003**, *68*, 150.

15) Ciganek, E. *J. Org. Chem.,* **1992**, *57*, 4521.

16) Grubbs, R. H.; Chang, S. *Tetrahedron,* **1998**, *54*, 4413.

17) Fűrstner, A. *Angew., Chem. Int. Ed*., **2000**, *39*, 3013.

18) Gradillas, A.; Perez-Castells, J. *Angew. Chem. Int. Ed.,* **2006**, *45*, 6086.

19) Wright, D. L.; Schulte II, J. P.; Page, M. A. *Org. Lett*., **2000**, *2*, 1847.

20) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew*. *Chem*., *Int. Ed*. *Engl*. **1995**, 34, 2039.

21) Hérisson P. J.-L.; Chauvin Y. *Die Makromolekulare Chemie,* **1971**, *141*, (1), 161.

22) Grubbs, R. H.; Chang. S. *Tetrahedron*, **1998**, *55*, 1427.

23) H. Clavier, C. A. Urbino-Blanco, S. P. Nolan, *Organometallics*, **2009**, *28*, 2848-2854.

24) Fu, G. C.; Nguygen, S.-B.T; Grubbs, R. H. *J. Am. Chem. Soc.,* **1993**, *115*, 9856.

25) Edwards, A. S.; Wybrow, R. A. J.; Johnstone, C.; Adams, H.; Harrity, J. P. A. *Chem. Comm*., **2002**, 1542-1543.

26) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.

27) Bassindale, M. J.; Edwards, A. S.; Hamley, P.; Adams, H.; Harrity, J. P. A. *Chem Comm.,* **2000**, 1035.

28) Fukumoto, H.; Esumi T.; Ishihara J.; Hatakeyam, S. *Tetrahedron Lett.,* **2003***, 44,* (44),8047-8049

29) Kim, S.-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073–1081.

30) Tsuda, Y.; Sano, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, **1996**; Vol. 48, 249–337.

31) Rigby, J. H.; Deur, C.; Heeg, M. J. *Tetrahedron Lett*., **1999**, *40*, 6887–6890

32) Padwa, A.; Hennig, R.; Kappe, C. O.; Reger, T. S. *J. Org. Chem.* **1998**, *63*, 1144–1155.

33) Varcauteren, J.; Lavaut, C.; Levy, J.; Massiot, G. *J. Org. Chem.* **1984**, *49*, 2278–2279.

34) Shimizu, K.; Takimoto, M.; Mori, M. *Org. Lett.* **2003**, *5*, 2323–2325.

35) Gagnon, D.; Spino, C. *J. Org. Chem*., **2009**, *74*, 6035-6041.

36) Subramaniam, G.; Hiraku, O.; Hayashi, M.; Koyano, T.; Komiyana, K.; Kam, T.-S. *J. Nat. Prod.* **2008**, *71*, 53-57.

37) Toma, T.; Shimokawa, J.; Fukuyama, T. *Org. Lett*. **2007**, *9*, 3195-3197.

38) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750-4757.

39) Rodriguez, J. G.; Urrutia, A. *Tetrahedron* **1999**, *55*, 11095-11108.

40) Toczko, M. A.; Heathcock, C. H. *J. Org. Chem.* **2000,** *65*, 2642-2645.

41) Kozmin, S. A.; Iwana, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc*. **2002**, *124*, 4628-4641.

42) Zard, S. Z. *Radical Reactions in Organic Synthesis; Oxford University Press: New York*, **2003**, 224.

43) Stanislawski, P. C.; Willis, A. C.; Banwell, M. G. *Org. Lett*., **2006**, *8*, 2143-2146.

44) Lee, H. I.; Cassidy, M. P.; Rashatasakton, P.; Padwa, A. *Org. Lett.,* **2003**, *5*, 6067.

45) Kim, G.; Kim, J. H.; Lee, K. Y. *J. Org. Chem.,* **2006**, *71*, 2185.

46) Ogata, Y.; Ikeda, M.; Nomoto, S.; Okita, M.; Shimomura, N.; Kaneko, T.; Yamanaka, T.; Hishinuma, I.; Nagakawa, J.; Hirota, K.; Miyamoto, K.; Horie, T.; Wakabayashi, T. European patent EP0281098, 1988; *Chem. Abstr*. **1989**, *110*, 95206.

47) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457.

48) Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001.

49) Makosza, M.; Wawrzyniewicz, M. *Tetrahedron Lett*. **1969**, 4659.

50) Makosza M.; Fedorynski M. *Adv. Catal*. **1987**, *35* , 375

51) Xu, L.; Brinker, U. H.; *In Synthetic Organic Sonochemistry;* Luche, J.-L.; Ed.; Plenum Press; New York, **1998**, 333-335.

52) A. Voituriez, L. E. Zimmer, A. B. Charette, *J. Org. Chem.*, **2010**, *75*, 1244-1250.

53) J. C. Lorenz, J. Long, Z. Yang, S. Xue, X. Xie, Y. Shi, *J. Org. Chem.,* **2004**, *69*, 327-334.

54) Banwell, M.; Edwards, A.; Harvey, J.; Hockless D.; Willis, A. *J. Am. Chem. Soc.,* Perkin Trans. *1*, **2000**, 2175.

55) Irie, H.; Shibata, K.; Matsuno, K.; Zhang, Y. *Heterocycles.,* **1989**, *29*, 1033.

56) Brook, A.G. *Acc. Chem. Res.* **1974**, *7*, 77.

57) Rouden J.; Ragot, A.; Gouault S.; Cahard D.; Plaquevent, J-C.; Lasne, M-C. *Tetrahedron Asym*. **2002**, *13*, 1299.

58) Bouet, A.; Cieslikiewicz, M.; Lewinski, K.; Coudert, G.; Gillaizeau, I. *Tetrahedron*. **2010**, *66*, 498.

59) Clayden, J.; Dufour, J.; Grainger, D.M.; Helliwell, M. *J. Am. Chem. Soc*. **2007**, *129*, 7488.

60) Clayden, J.; Donnard, M.; Lefranc, J.; Minassi, A.; Tetlow, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 6624.

61) Clayden, J.; Hennecke, U. *Org. Lett*. **2008**, *10*, 3567.

62) Tait, M.; Donnard, M.; Minassi, A.; Lefranc, J.; Bechi, B.; Carbone, G.; O'Brien, P.; Clayden, J. *Org. Lett.* **2013**, *15*, (1), 34-37.

63) Bach, R.; Clayden, J.; Hennecke, U. *Synlett*. **2009**, *3*, 421.

64) Tetlow, D. J.; Vincent, M. A.; Hiller, I. H.; Clayden, J. *Chem. Commun*., **2013**, *49*, 1548-1550.

65) Lefranc, J.; Fournier, A. M.; Mingat, G.; Herbert, S.; Marcelli, T.; Clayden, J. *J. Am. Chem. Soc.*, **2012**, *134*, 7286–7289.

66) Tetlow, D. J.; Hennecke, U.; Raftery, J.; Waring, M. J.; Clarke, D. S.; Clayden, J. *Org. Lett.* **2010**, *12*, 5442.

67) Beak, P.; Kerrick, S. T., Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231–3239.

68) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron*, **1974**, *30*, 2151-2157

69) Concellón, J. M.; Concellón, C. *J. Org. Chem*. **2006**, *71*, 1728-1731.

70) Koppel, G. A.; Kinnick, M. D. *Tetrahedron Lett.* **1974**, 711-713

71) Denney, D. B.; Smith, L. C. *J. Org. Chem,* **1962**, *27*, 647-649.

72) Nishizawa, R.; Nishiyama, T.; Hisaich, K.; Matsunaga, N.; Minamoto, C.; Habashita, H.; Takaoka, Y.; Toda, M.; Shibayama, S.; Tada, H.; Sagawa, K.; Fukushima, D.; Maeda, K.; Mitsuya, H. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 727.

73) Jones, G. *Org. React.* **1997**, *15*, 204-213.

74) Oldham, W.; Johns, I. B. *J. Am. Chem. Soc.* **1939**, *61*, 3289.

75) Coppola, G.M. *J. Heterocycl. Chem.,* **1991**, *28*, 1769-1772.