Design and Synthesis of 3-D Building Blocks for Medicinal Chemistry

Andres Ricardo Gomez Angel

MSc by Research

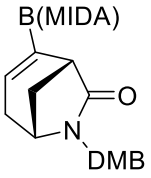
University of York

Department of Chemistry

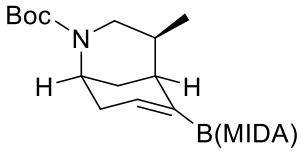
December 2019

Abstract

This thesis describes the design and synthesis of two 3-D building blocks for potential use in medicinal chemistry. The design and synthesis of normorphan-derived 3-D building block **A** and morphan-derived 3-D building block **B** is outlined. Further functionalisation of the normorphan-derived 3-D building block into lead-like compounds is also presented.



A

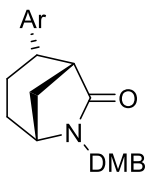


B

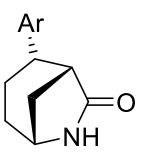
Section 2.1 describes the design consideration, vector analysis and proposed route for the synthesis of normorphan-derived 3-D building block **A**. Section 2.2 presents the racemic synthesis of normorphan-derived building block **A** which was achieved with a 30% overall yield on a multi-gram scale *via* a seven-step sequence. Section 2.3 describes the investigation of routes for the synthesis of enantioenriched normorphan-derived 3-D building block **A** by asymmetric cyclisation and diastereomeric resolution approaches.

The design, vector analysis and proposed route for morphan-derived 3-D building block **B** are presented in Section 3.1. Initial approaches for the synthesis of morphan-derived building block **B** using sulfonamide protecting groups are presented in Section 3.2. Further approaches for the synthesis of morphan-derived building block **B** using an *N*-Boc protecting group are then outlined in Section 3.3. However, unfortunately, both these routes were ultimately unsuccessful in providing the desired 3-D building block **B**.

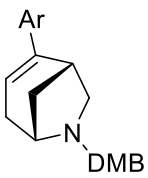
Finally, Chapter 4 showcases the functionalisation potential of normorphan-derived building block **A** for the synthesis of medicinally-relevant lead-like compounds. Section 4.1 presents the Suzuki-Miyaura arylation of 3-D building block **A** with a variety of aryl bromides while Section 4.2 shows further functionalisation of the building block into compounds such as normorphan lactams **C** and **D** and amine-based scaffold **E**.



C



D



E

List of Contents

List of Tables

List of Figures

Acknowledgments

I would like to thank my supervisor Professor Peter O'Brien for taking me into the group, for his help, guidance, support and ideas. It is thanks to him that this research was possible and as successful and enlightening as it was. A big thank you as well to Professor Richard Taylor for being my internal panel member and for his encouragement and advice.

A special thank you must go to James Firth who was instrumental in starting the project, for being my mentor and teaching me the bits and pieces that would help me undertake this project. I would also like to thank all past and current POB group members for making this year such an invaluable, joyous and enlightening experience. These include Alex, Giordaina, Hanna, Tom, Rebecca, Sophie, Nico, Kevin, Jonathan, James D, Kleo, Ben, Stephen and Hannah. I could never leave out a big thank you to Matthew who provided me with both sanity and insanity in equal measure when I needed them.

Next, I would like to thank the staff of the Department of Chemistry at York. Graeme McAllister for making sure everything ran smoothly, Heather for her impeccable work running the NMR service and Karl for the mass spectrometry service.

Finally, I would like to thank my parents and partner, Paula, for their love, infinite support in everything I do and their never-ending patience.

Author's Declaration

I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as references.

Andres Ricardo Gomez Angel

Chapter 1 Introduction

1.1. Building Blocks in Medicinal Chemistry

With the advent of high-throughput screening (HTS), pharmaceutical research and development (R&D) has begun to research different approaches for the exploration of chemical space.[1] On top of this, concepts such as "lead-oriented synthesis",[2] "escape from flatland",[3] "conformational restriction"[4] and "scaffold hopping"[5] have turned chemists' attention into developing high quality and more diverse sets of building blocks.[6-9]

Building blocks represent one of the main toolkits that medicinal chemists use to access lead compounds and to increase the diversity of lead-like structures.[10] Building blocks often constitute the main backbone of lead-like scaffolds and it is common for the same building block to be incorporated into varied lead structures across different projects.[10] Thus, the idea that higher quality and more diverse building blocks can improve the overall quality and success of discovery projects has been widely presented and adopted by various pharmaceutical companies such as AstraZeneca[11] and Pfizer.[12] In particular, the desired features in building blocks for medicinal chemistry have been outlined by AstraZeneca.[11] The presence of chemical functionality for easy incorporation into the lead structure, the 'Rule of 2' (MW <200, clogP <2, H-bond donors ≤2 and H-bond acceptors ≤4) and the lack of redox-active functionality once incorporated into the structure were initially selected as high quality hallmarks for a building block.[11]

Additional analyses into the impact of aromatic ring counts on compound developability suggested that increasing numbers of aromatic rings present in lead compounds had detrimental effects on the physicochemical properties of compounds thus lowering their applicability in discovery projects.[13] On top of this, the "escape from flatland" concept was introduced by Lovering *et al*.[3] This concept explored the correlation between the progression of molecules through drug development stages and clinical trials and the fraction of sp^3 hybridised carbon atoms (Fsp^3, number of sp^3 hybridised carbon atoms divided by the total number of carbon atoms) as well as stereogenic centres present within the molecule. Lovering *et al.* analysed compounds that had reported biological activity or were described in a medicinal chemistry patent between 1980 and 2009 and they found that a correlation existed between increased Fsp^3 and the progression of a drug through the drug development stages. The paper also found a 33% increase in the stereogenic centre count from discovery molecules to drugs. They also found that increased saturation had a beneficial effect on the

physical properties of drug candidates such as increased solubility and decreased melting points. These studies are taken as examples in support of the idea that increased 3-D shape of drug candidates and their building blocks can increase the likelihood of successful progression through clinical trials.

Following this and the widespread presence of diverse cyclic systems in drug-like molecules,[14] the concepts of "conformational restriction" and "scaffold hopping" have come into play for lead-oriented synthesis.[2] In this context, the use of conformationally restricted cyclic systems as surrogates for flexible rings (*e.g.* piperidines, morpholines, azepanes) has become popular.[6] Selected examples of said types of building blocks are presented below.

Carreira and co-workers[15] developed a series of azaspirocycles as surrogates for piperazine-like motifs (Figure 1.1). During their studies, Carreira *et al*. found that these azaspirocycles showed favourable pharmacokinetic properties with respect to their parent ring systems allowing for the synthesis of a ciprofloxacin analogue (Figure 1.1) with a better pharmacokinetic profile.

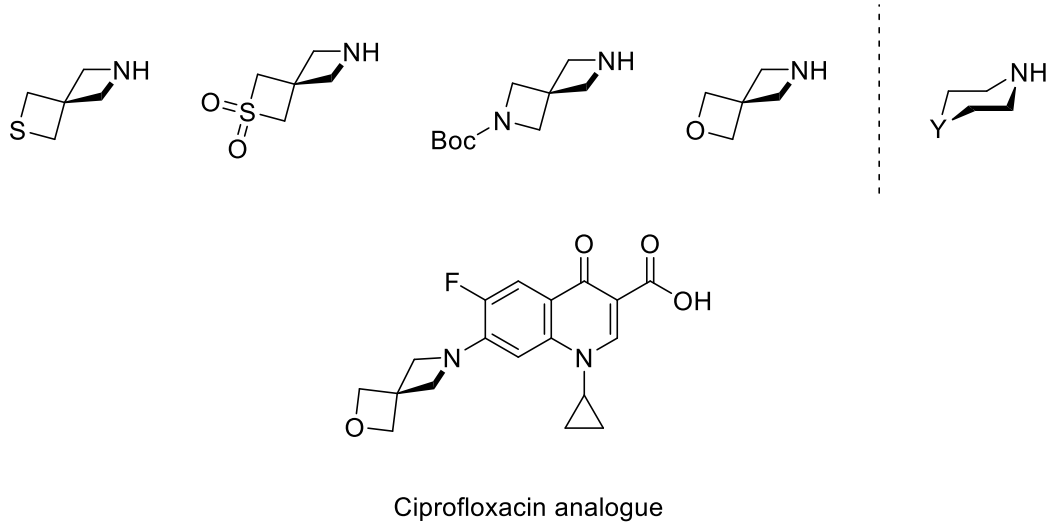


Figure 1.1 - Carreira's azaspirocycles and a ciprofloxacin analogue

Mykhailiuk and co-workers[16,17] presented in 2017 an extensive set of spirocyclic pyrrolidines with either two or three diversity points as building blocks for medicinal chemistry. These spirocyclic pyrrolidines showed comparable physicochemical properties to their analogous piperidine and morpholine systems with slightly increased lipophilicity but significantly improved metabolic stability. Some selected examples are presented in Figure 1.2. One of the spirocyclic pyrrolidines was also studied as a substituent in a ciprofloxacin-derived antibacterial agent DV-7751.

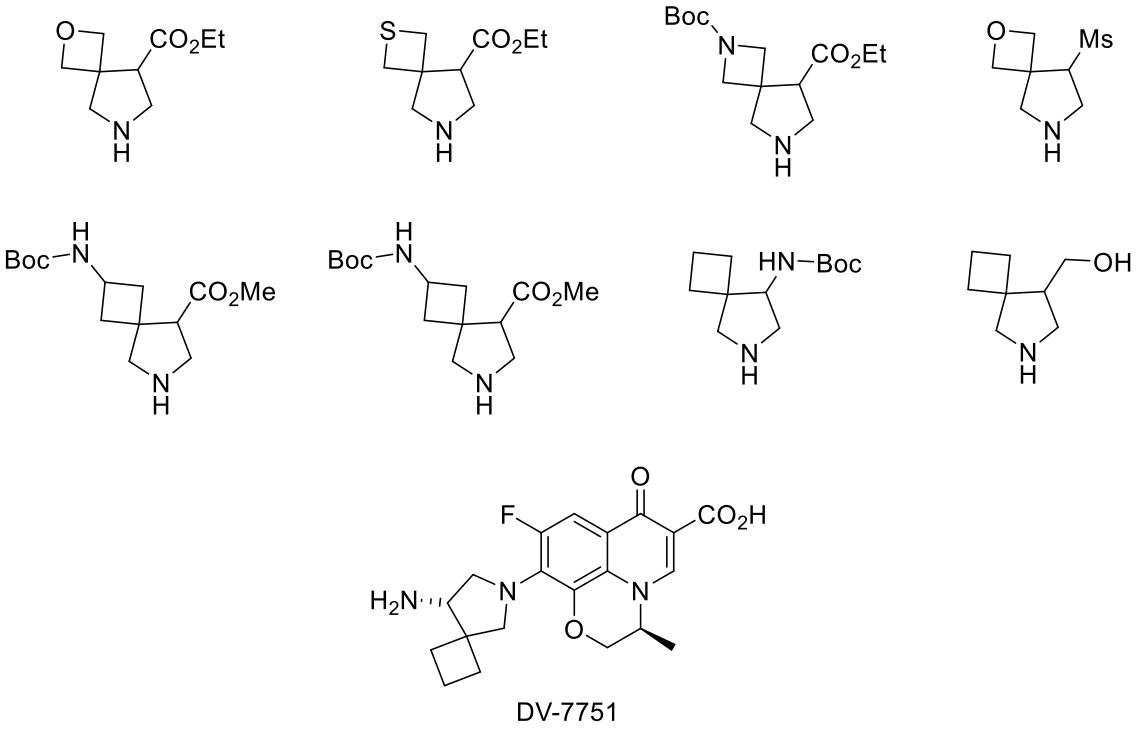


Figure 1.2 - Mykhailiuk's spirocyclic pyrrolidine building blocks

Also in 2017, Miykhailiuk and co-workers[6] reported the synthesis of 3-azabicyclo[3.2.0]heptane building blocks as surrogates for piperidine motifs. These bicyclic building blocks had similar physicochemical properties to their parent piperidines but occupied a slightly different part of chemical space according to their exit vectors (see Section 1.2). Some examples of these scaffolds are shown in Figure 1.3 together with Belaperidone, an antischizophrenia agent, which was prepared using one of the building blocks.

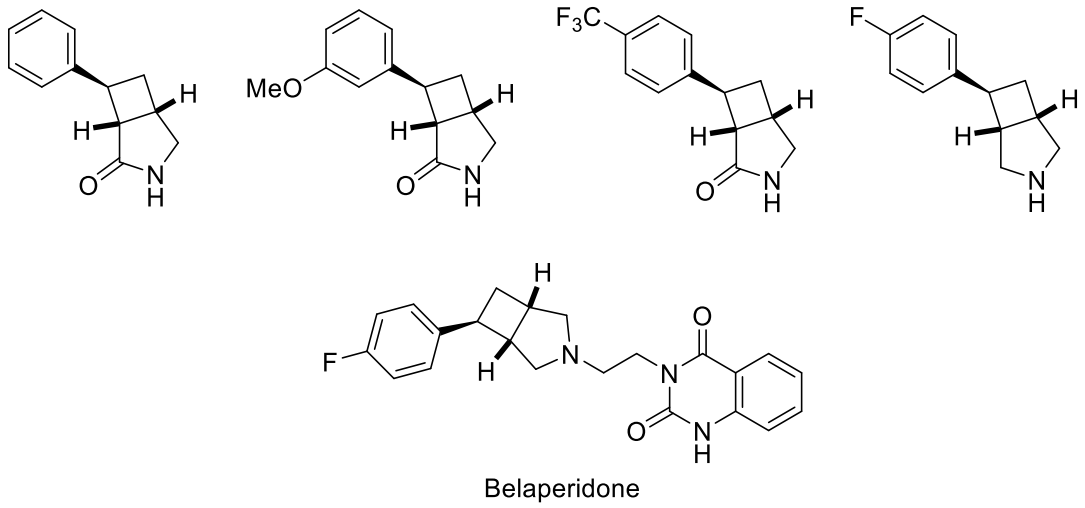


Figure 1.3 - Miykhailiuk's azabicyclo[3.2.0]heptane building blocks

It is finally worth noting that Pfizer[12] has recently developed a building block library in collaboration with various chemical companies that contains various high Fsp^3 and conformationally restricted building blocks (Figure 1.4). This set of building blocks has been incorporated into the company's discovery pipeline in recent years.

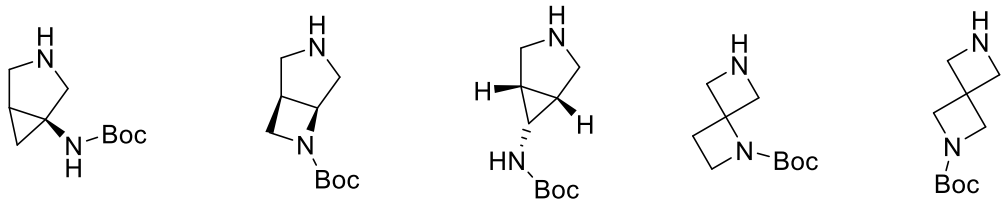


Figure 1.4 - Selected examples from Pfizer's *quick building block* library

1.2 Exit Vector Analysis

Exit vector analysis is a way of visualizing chemical space, originally introduced for CAVEAT software in the 1990s,[18] and recently popularised by Grygorenko and co-workers[19] for the geometric description of functionalisation vectors for bifunctional scaffolds. Exit vector analysis uses the relative orientation of the two diversity vectors n_1 and n_2 that can be described according to four geometric parameters. For example, in the case of a 1,4-disubstituted cyclohexane (Figure 1.5): the distance between the variation points C1 and C2, r, the plane angles Φ_1 (between vector n_1 and C1-C2) and Φ_2 (between vector n_2 and C1-C2) and the dihedral angle θ defined by the vectors n_1, C1-C2 and n_2. These parameters can be determined from the atomic coordinates and allow for the construction of Ramachandran-like plots.[19]

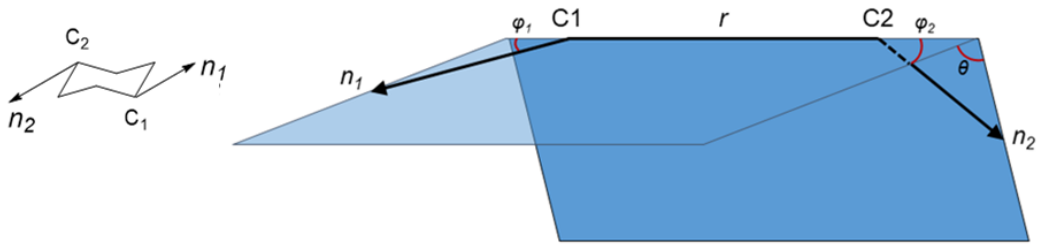


Figure 1.5 - Visual representation of variation vectors.

Extensive work has been performed by Grygorenko and coworkers[19,20] in the classification of simple saturated carbo- and heterocyclic systems. Initial studies by Grygorenko into simple 3- to 7-membered carbocyclic compounds showed clustering that allowed for systematic categorisation of these structures into four distinct regions (Figure 1.6).[19] Region α mainly comprises *cis*- and *trans*-1,2 systems. *Cis*-1,3 scaffolds as well as *cis*-1,4 6-membered rings form the β region. On the other hand, the γ region is formed by *trans*-1,4 6-membered rings while region δ includes *trans*-1,3 6-membered rings alongside some *trans*-1,3 5-membered scaffolds. Within this initial analysis by Grygorenko, there were only two *trans*-1,4 7-membered rings which lie outside the defined regions.

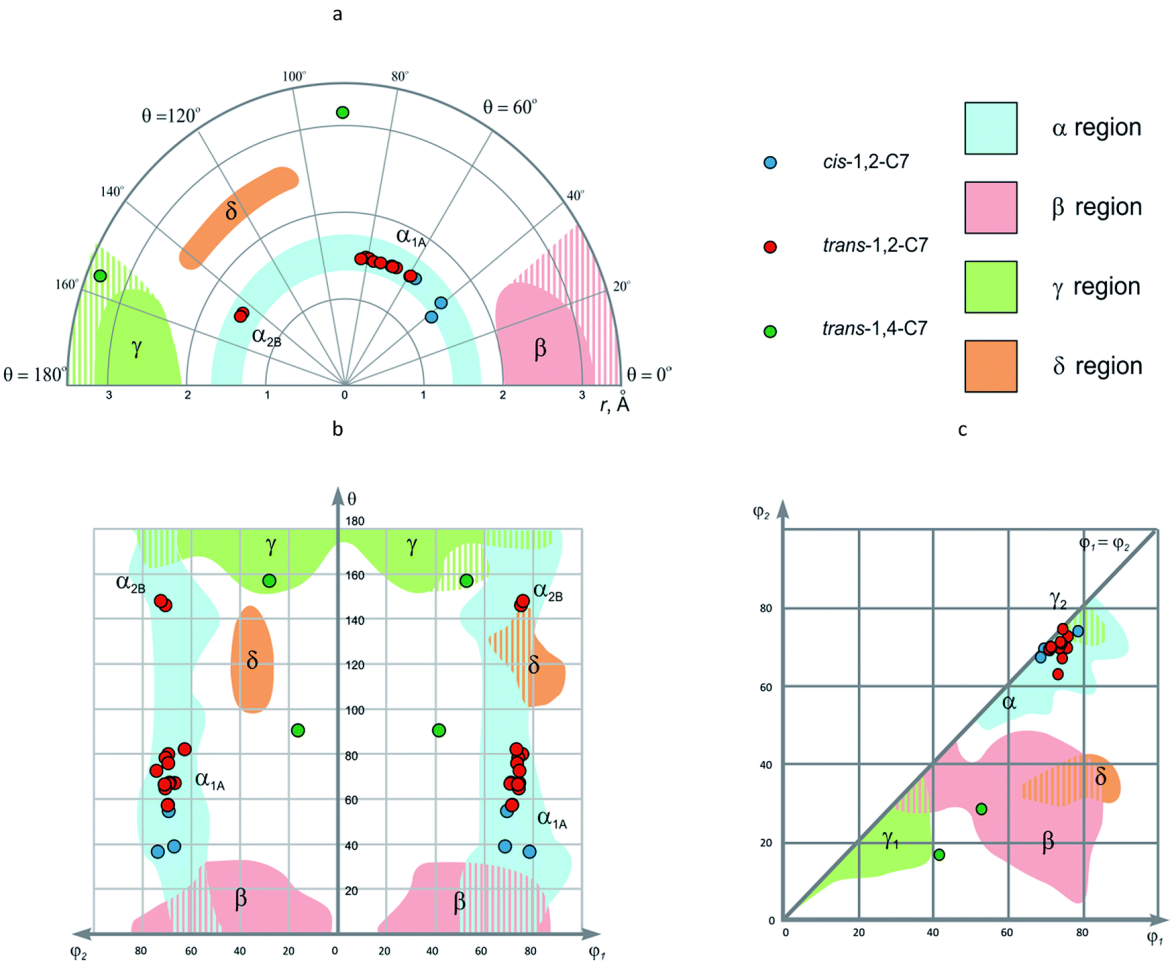


Figure 1.6 - Grygorenko's 4- to 7-membered ring carbocycle exit vector analysis[19]

Further studies by Grygorenko and co-workers[20] on heterocyclic scaffolds demonstrated that, despite their apparent similarities to their carbocyclic counterparts, the plane and dihedral angles for these scaffolds differed significantly. Particularly, it was found that 1,3-substituted scaffolds occupied an area previously unoccupied at r = 2.5 Å between the β and δ regions in the dihedral angle plot (Figure 1.7a) while still occupying a distinct region in plane angle plots (Figure 1.7b,c). This led to the definition of a new region ε for these 1,3-disubstituted heterocycles. Region β was also extended to encompass some 1,4- and some outlying 1,3- disubstituted scaffolds.

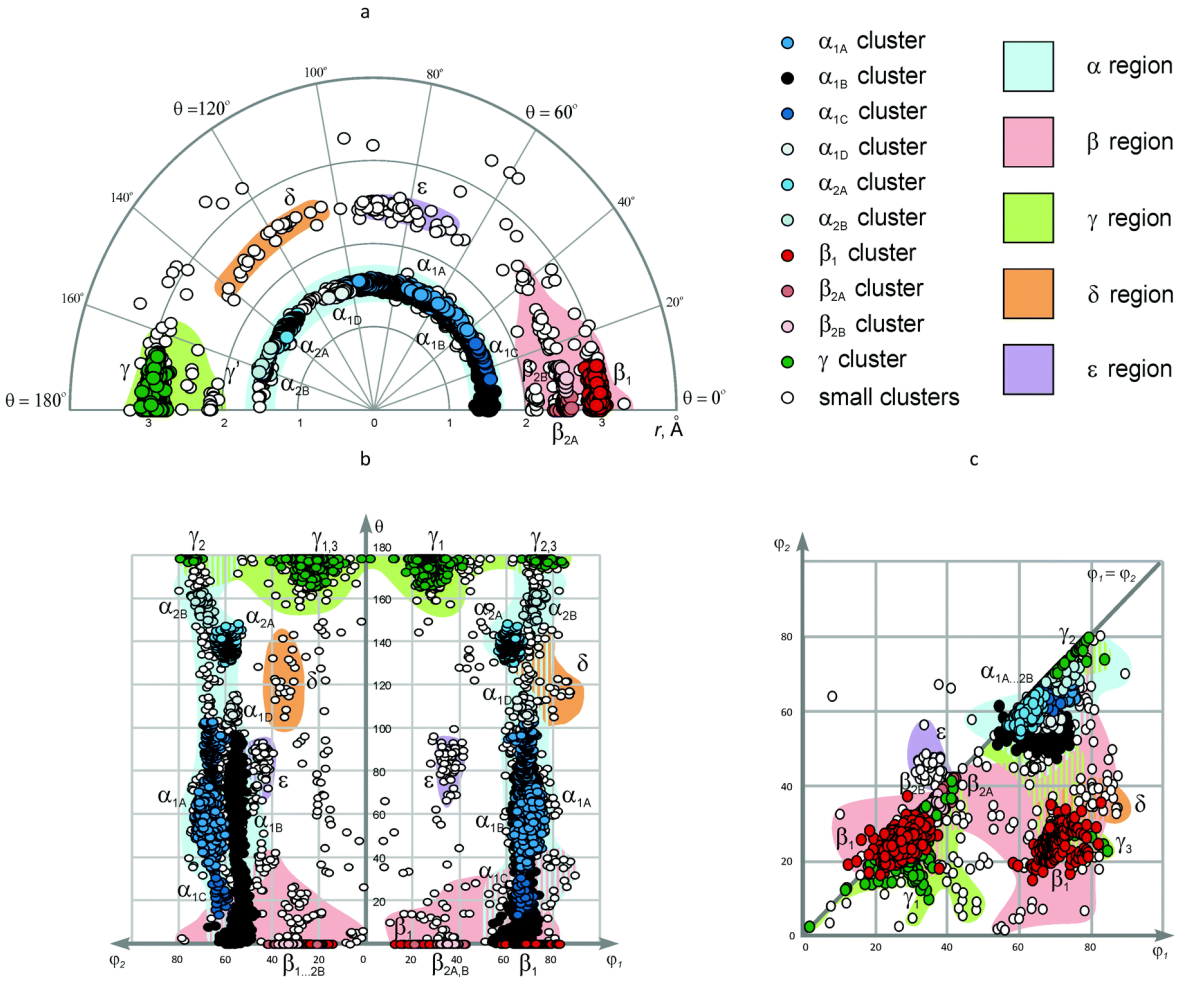


Figure 1.7 - Grygorenko's heterocycle exit vector analysis a) r-θ plot (polar coordinates); b) θ-Φ_1/Φ_2 plot; c) Φ_1-Φ_2 plot.[20]

Grygorenko and co-workers[20,21] have also extended their exit vector analysis to a series of conformationally restricted, bicyclic amines (Figure 1.8). In this analysis, it was found that bicyclic scaffolds could access previously untapped areas of chemical space. In particular, they found that larger values of r could be easily accessed with these scaffolds. Grygorenko also found that the variety of structures encompassed in this set allowed for access to a wide variety of predictable elaboration vectors outside the areas previously stablished (Figure 1.9).

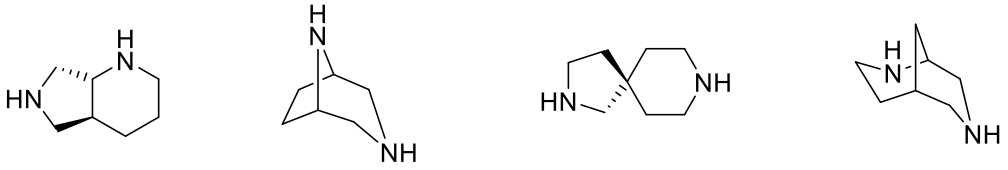


Figure 1.8 - Examples of bicyclic diamines analysed by Grygorenko and co-workers

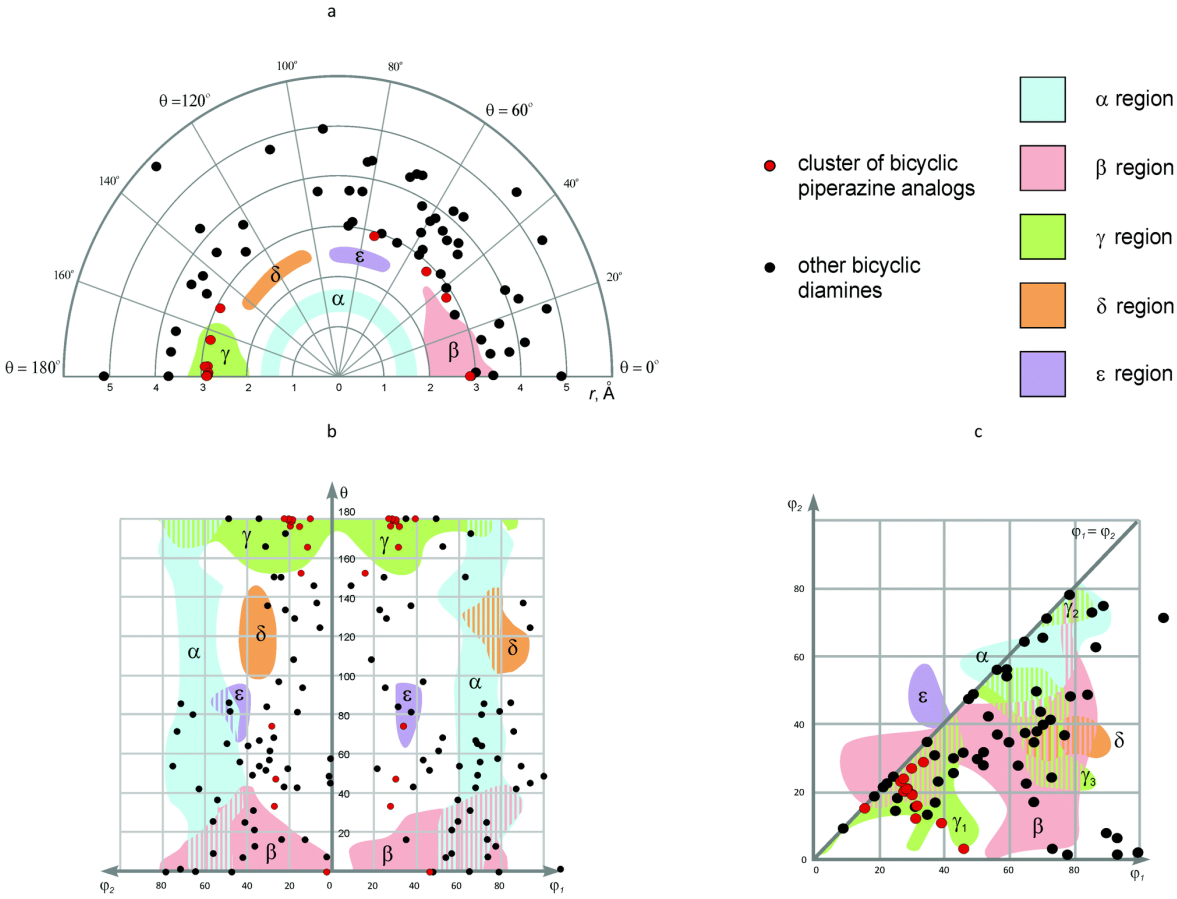


Figure 1.9 - Grygorenko's bicyclic diamine exit vector analysis a) r-θ plot (polar coordinates); b) θ-Φ_1/Φ_2 plot; b) Φ_1-Φ_2 plot

Exit vector analysis has also been applied to various other compounds such as 3-((hetera)cyclobutyl)azetidines,[22] propellanes[23] and sultams[24] and it has become an easy, well regarded and predictable method for the characterisation of the 3-D shape of medicinally-relevant scaffolds.[1]

1.3 Normorphan 6-Azabicyclo[3.2.1]octane Scaffold

1.3.1 Introduction to the Normorphan Scaffold

In recent years, normorphan-derived scaffolds have been a focus of interest in synthetic chemistry mainly due to their applications in the pharmaceutical industry[25] and their wide presence in diverse natural products.[26-29] Consequently, attention towards the synthesis and applications of this bicyclic scaffold has been continuously expanding. The normorphan scaffold has as its core a bicyclic [3.2.1]octane structure where the 6-position of the scaffold has been replaced with an amino group (Figure 1.10). This amine or amide, alongside the variety of substitution patterns that emerge from the different synthetic approaches, allow for a diverse set of functionalisation vectors in pharmaceutical space. The normorphan core also shows potential for scaffold hoping, which alongside its 3-dimensionality make it a suitable candidate as a medicinal chemistry building block.

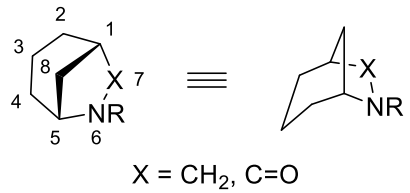


Figure 1.10 - Normorphan bicyclo[3.2.1]octane scaffold

In the context of pharmaceutical applications, 2,3-disubstituted normorphans have been investigated as novel dopamine transporter (DAT) inhibitors by Bonjoch and co-workers.[25] During their studies, it was found that normorphan **1** showed comparable potency to that of currently-used DAT inhibitors while showing less potential side-effects. Likewise, normorphan **2** is currently being investigated as a potential antitumor agent against diffuse large B-celllymphomas.[30] Azaprophen **3** has been widely investigated for the treatment of Alzheimer's disease due to its high potency as a muscarinic acetylcholine receptor antagonist.[31-33] Finally, normorphan CGP48506 has been investigated as a calcium-sensitizing agent (Figure 1.11).[34]

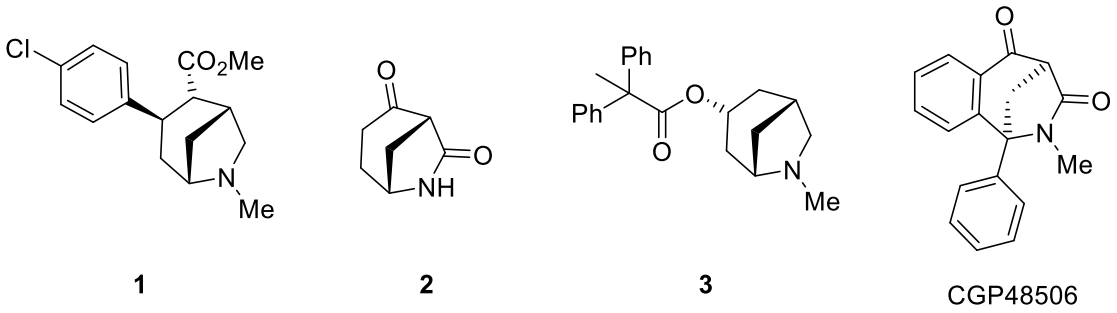


Figure 1.11 - Pharmaceutically-relevant normorphans

On the other hand, several natural products also contain the normorphan 6-azabicyclo[3.2.1]octane scaffold (Figure 1.12). For example, peduncularine **4** has been a synthetic target of notable interest with seven formal and total syntheses published so far.[27] Additionally, actinobolamine **5** has also been a relevant synthetic target for chemists since its structural elucidation by Munk and co-workers in 1967.[28,35]

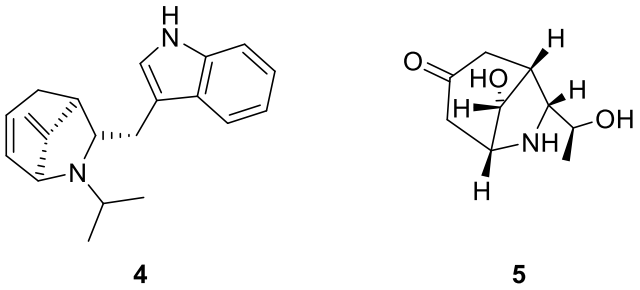


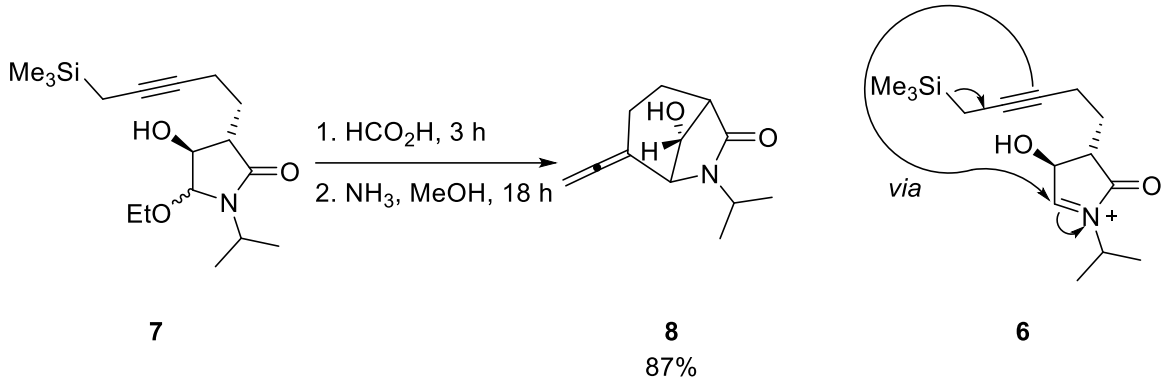
Figure 1.12 - Penduncularine **4** and Actinobolamine **5**

1.3.2 Overview of Racemic Approaches for the Synthesis of the Normorphan Scaffold

In this Section, an overview of previously reported racemic approaches for the synthesis of the normorphan and structurally related scaffolds is presented. Among the first approaches for the synthesis of the normorphan core were the thermal lactamisation of 1,3 aminoacids,[36] Beckmann rearrangements of bicyclo[2.2.1]hetan-2-one oximes,[37] amide alkylation,[38] Hofmann-Loeffler-Freytag reactions[39] and aza-Michael additions.[40] However, while these reactions afforded the desired normorphan cores in moderate to good yields, many of them had poor functional group tolerance and/or required lengthy syntheses for their starting materials. Many of them also required the installation of a precursor bicyclic scaffold.[41]

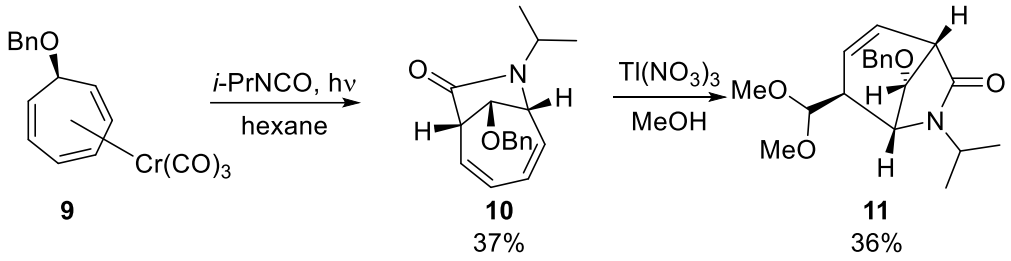
While investigating the synthesis of peduncularine **4**, Speckamp and co-workers[42] generated an electrophilic *N*-acyliminium cation **6** by acid treatment of lactam **7** which subsequently cyclised to give normorphan **8** in 87% yield (Scheme 1.1). However, while this methodology

showed a good functional group tolerance and excellent yield, it required a six-step sequence to obtain precursor lactam **7.**



Scheme 1.1

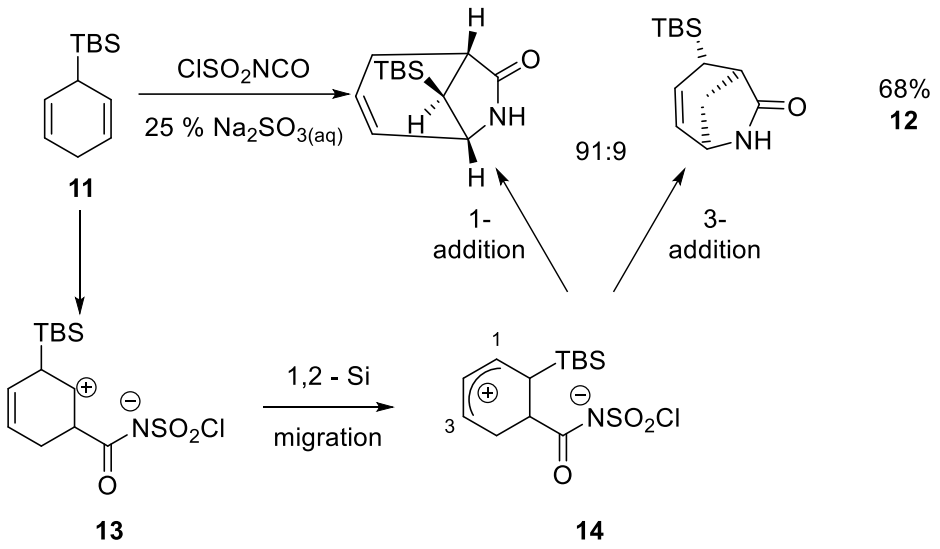
A somewhat curious approach to the synthesis of the normorphan scaffold was developed by Hoyt Meyer and co-workers[43] for the synthesis of peduncularine **4**. In it, they utilised a Cr(0)-mediated [6+2] cycloaddition under photochemical conditions between isopropyl isocyanate and cycloheptatriene **9** to give bicyclic scaffold **10** as a single diastereomer in 37% yield. Bicycle **10** was then treated with $Tl(NO_3)_3$ to give normorphan **11** in 13% yield over the two-step sequence (Scheme 1.2). Nonetheless, it is evident that the low yields and use of toxic metals render this methodology unattractive.



Scheme 1.2

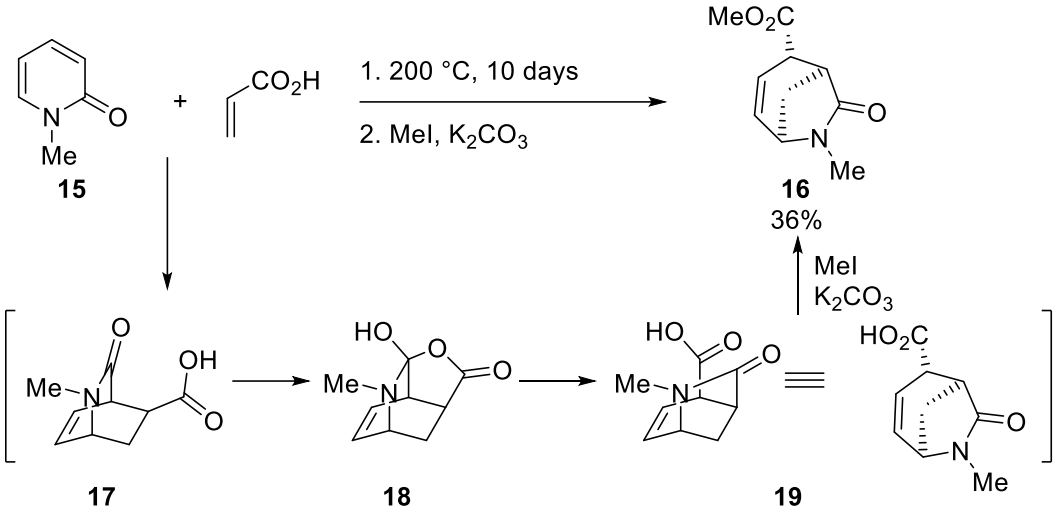
Other approaches have also been used to synthesise the normorphan core during the synthesis of peduncularine **4** such as ring closing metathesis between the 3- and 4- positions of the ring,[44] radical cyclisation of oximes,[45] [3+2] annulation of allylic silanes[46] and iminium ion-promoted rearrengements.[27] However, only the [3+2] annulation of allylic silanes was studied beyond the synthesis of their target. For example, Woerpel and co-workers[26] used silylated cyclohexadiene **11** to access normorphan **12** by treatment with chlorosulfonyl isocyanate. Here, the allylic silyl species adds to the isocyanate to generate the zwitterionic intermediate **13** which undergoes 1,2-silyl migration to give allylic cation

14. Cation **14** then rapidly cyclises to give a 91:9 mixture of regioisomers with addition at the 1-position being the main product (Scheme 1.3).[46] This approach was one of the first approaches to normorphans that required few steps towards the synthesis of its starting materials while achieving high yields and a high possibility for diversification of normorphan **12**.



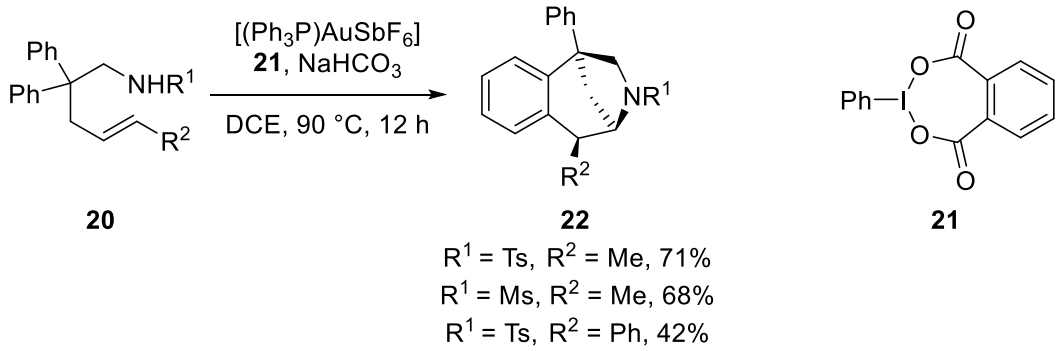
Scheme 1.3

In 2004, Johnson and co-workers[25] developed a method to quickly access simple normorphans. By using a Diels-Alder reaction between *N*-Me-pyridone **15** and acrylic acid at 200 °C for 10 days and forming the methyl ester, normorphan **16** was obtained in 36% yield over the two-step sequence (Scheme 1.4). This was achieved by initial formation of the Diels-Alder adduct **17** which rearranged *via* tricyclic intermediate **18** to give normorphan **19**. Normorphan **19** was finally methylated using MeI and K_2CO_3 to give normorphan **16**. Even though the starting materials for the methodology are readily available, the high temperature and long reaction times required are a significant drawback of this approach.



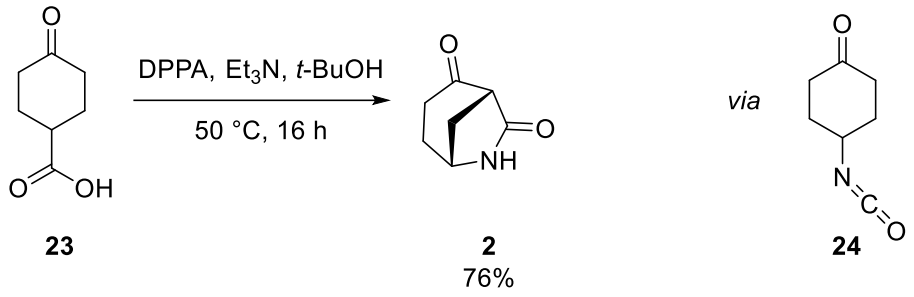
Scheme 1.4

In 2011, Nevado and co-workers[47] developed a methodology for the regioselective oxidative difunctionalisation of unactivated alkenes. However, while their methodology was not aimed at the synthesis of the normorphan scaffold, they found that while using sulfonamides **20**, a gold catalyst and hypervalent iodine compound **21**, their substrates rearranged to form benzo-fused normorphans **22** in moderate to good yields as single diastereomers (Scheme 1.5). Due to the need for the electron rich phenyl groups in the starting material, this methodology has a very limited substrate scope.



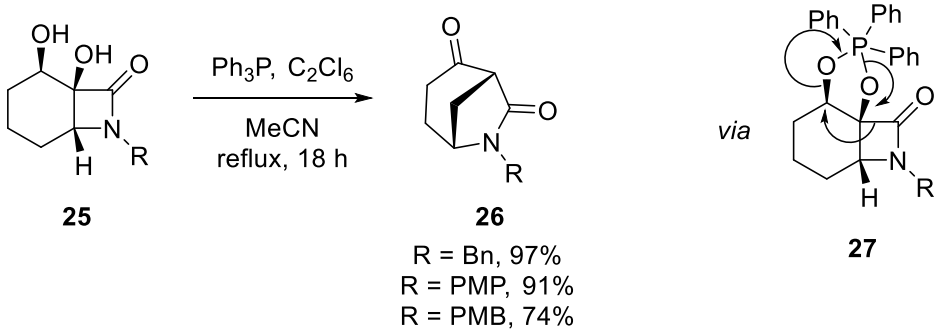
Scheme 1.5

Another racemic approach for the synthesis of the normorphan core was reported in 2014 by Xue and co-workers.[48] Here, they found that treating cyclohexanone **23** with DPPA and Et_3N gave normorphan **2** in 76% yield *via* a Curtius rearrangement into isocyanate **24** which was trapped by an enolate generated from the ketone in **23** (Scheme 1.6). Unfortunately, no further exploration into the scope of this reaction was carried out.



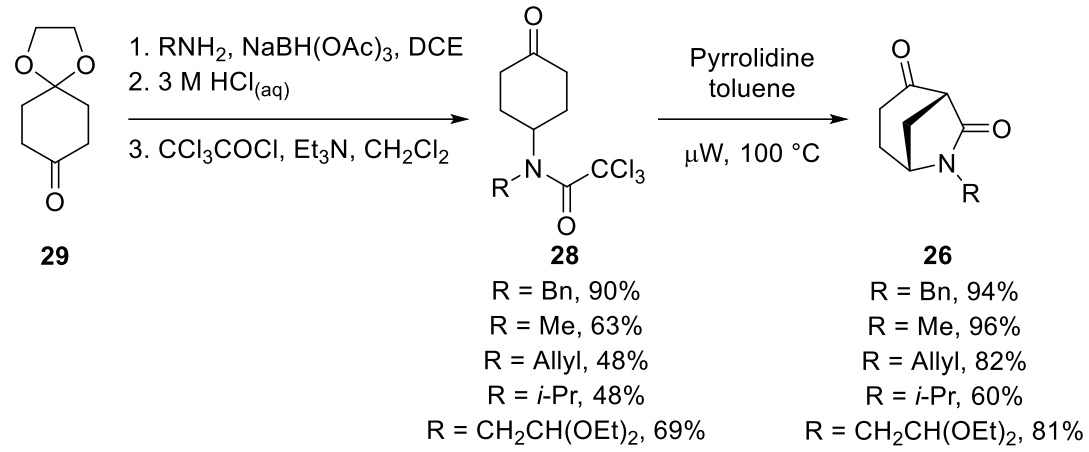
Scheme 1.6

On the other hand, Grainger and co-workers[29,49] studied the semipinacol rearrangement of *cis*-fused β-lactam diols as a way to access bridged bicyclic lactams such as normorphans. In their work, β-lactam **25** was treated with triphenylphosphine and C_2Cl_6 at reflux to afford normorphans **26** in good to excellent yields (Scheme 1.7). This transformation occurs *via* a cyclic phosphorane **27** formed from the diol present in lactam **25** and *in situ* generated Ph_2PCl_2 which undergoes migration to release Ph_3PO and form the ketone in the 2-position. However, even though this methodology gave normorphans **26** in good to excellent yields with different protecting groups, the lengthy five-step sequence required to access β-lactam **25** is its main drawback.



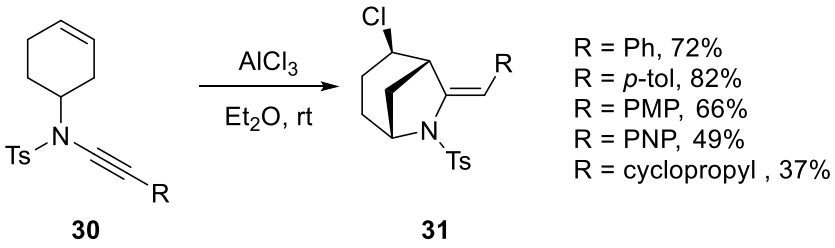
Scheme 1.7

A concise and flexible route to access normorphan **26** was reported by Bonjoch and co-workers[50] in 2015. Thus, trichloroamidoketones **28** were treated with pyrrolidine in toluene under μW irradiation to give normorphans **26** respectively in moderate to excellent yields (Scheme 1.8). Additionally, trichloroamidoketones **28** were easily obtained in a three-step sequence with a single purification from cyclohexanone **29** and the corresponding amine. Of note, Bonjoch's methodology tolerated different functionalities both in the 3- and 5-positions of the normorphan scaffold making this methodology an easy and reliable way to access diverse normorphans.



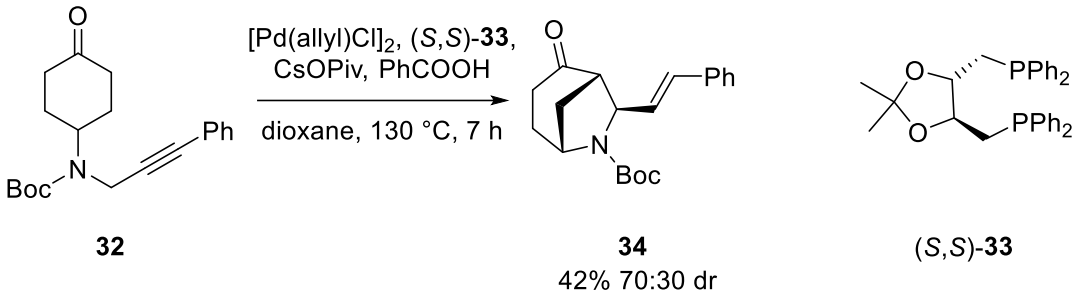
Scheme 1.8

A different approach for the synthesis of the normorphan scaffold was reported in 2017 by Lin and co-workers.[51] Treatment of *N*-Ts enynamides **30** with $AlCl_3$ afforded a wide variety of 2-chloro normorphans **31** in moderate to good yields (Scheme 1.9).



Scheme 1.9

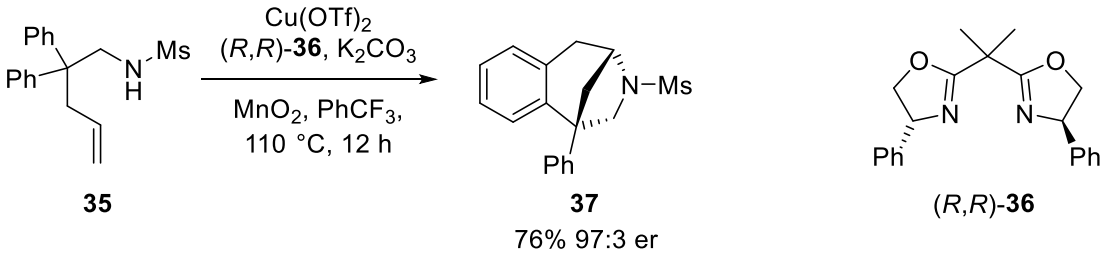
As a final example, Dong and co-workers[52] described a Pd-catalysed cyclisation of alkyne-linked cyclohexanones into normorphans in 2019. While mostly applicable to 6-oxa-bicyclo[3.2.1]octanes, they reported that when cyclohexanone **32** was treated with $[Pd(allyl)Cl]_2$ and bis-phosphine (*S*,*S*)-**33**, CsOPiv and benzoic acid at 130 °C, normorphan **34** was obtained in 42% yield as a 70:30 mixture of diastereomers (Scheme 1.10). Of note is the use of enantiomerically pure ligand (*S*,*S*)-**33** which was required for the sole purpose of increasing the diastereoselectivity of the reaction. Accordingly, no enantioselectivities were described by the authors.



Scheme 1.10

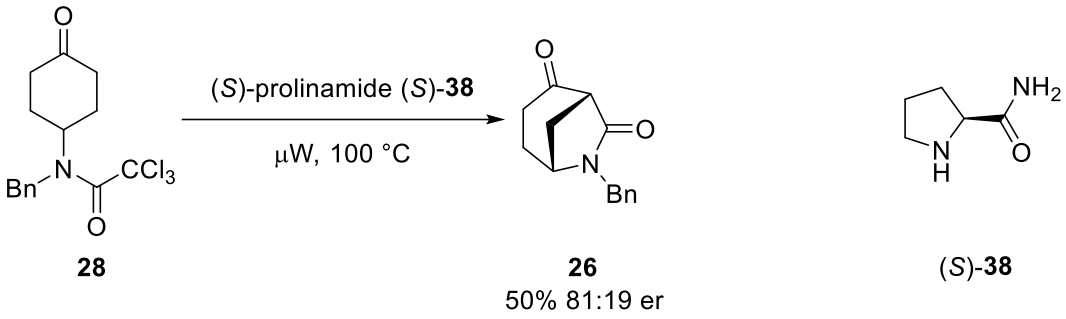
1.3.3 Overview of Asymmetric Approaches to the Normorphan Scaffold

Successful examples of the asymmetric synthesis of normorphans are quite scarce.[53] In 2014, Chemler and co-workers[54] reported a methodology for asymmetric normorphan synthesis similar to that of Nevado and co-workers (see Scheme 1.5) which proceeded *via* a Cu-catalysed carboamination. Use of sulfonamide **35**, $Cu(OTf)_2$, a chiral bisoxazoline ligand (*R*,*R*)-**36**, K_2CO_3 and MnO_2 at 110 °C afforded the benzo-fused normorphan **37** in 76% yield and 97:3 er (Scheme 1.11). Unfortunately, however, only a modest diversity of substituents in the aromatic ring could be accommodated, with substitution outside the aromatic ring causing complete inhibition of the reaction.



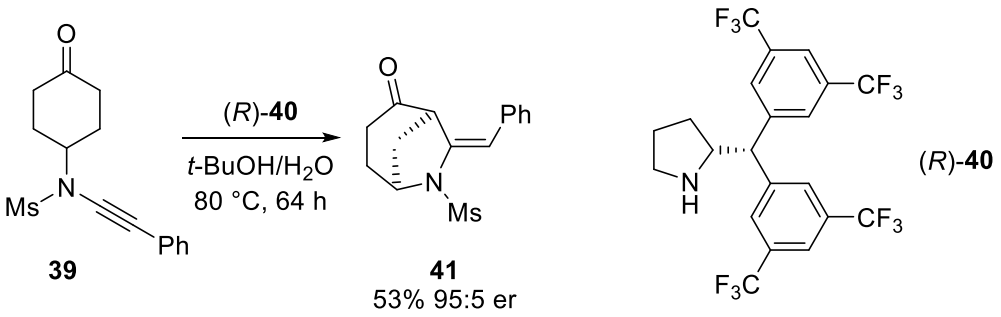
Scheme 1.11

During their studies into the racemic synthesis of normorphans, Bonjoch and co-workers[50] briefly explored the use of chiral amino acid-derived organocatalysts for the cyclisation step. However, they found that while (*S*)-prolinamide (*S*)-**38** gave the best result, normorphan **26** was obtained in only 50% yield and 81:19 er (Scheme 1.12). Several other (*S*)-proline and amino acid-derived organocatalysts were explored with little to no success. Due to the poor results obtained, no effort was made into determining the identity of the major enantiomer obtained.



Scheme 1.12

Finally, in 2019 whilst the work described in this thesis was being carried out, Ye and co-workers[53] reported an asymmetric variant of a Conia-Ene type carbocyclisation for the synthesis of normorphans. Alkyne-linked cyclohexanones such as **39** were treated with chiral amine (*R*)-**40** to give normorphan **41** in 53% yield and 95:5 er (Scheme 1.13). This represents one of the only examples of the successful asymmetric synthesis of the normorphan scaffold. This methodology could accommodate diverse substitution on the aromatic ring. However, non-aromatic substituents on the alkyne led to the production of a [3.3.1]nonane scaffold instead of the [3.2.1]octane (see Section 1.4.3). Diverse functionalisation of the normorphan scaffold was explored such as hydrogenation of the alkene, oxidative cleavage of the alkene and deoxygenation of the 2-position carbonyl.



Scheme 1.13

1.4 Morphan 2-Azabicyclo[3.3.1]nonane Scaffold

1.4.1 Introduction to the Morphan Scaffold

Morphan-derived scaffolds have long been of great interest in synthetic chemistry primarily due to their extensive presence in natural products such as those from the daphniphyllum and strychnos alkaloid families,[55-57] and their presence in diverse compounds of pharmaceutical interest.[58-61] Accordingly, the investigation of synthetic methods and applications for the morphan scaffold are continuously on the rise. The morphan scaffold has as its core a bicyclic [3.3.1]nonane structure where the 2-position has been replaced with an amino group (Figure 1.13). This amine, together with the diverse substitution patterns that arise from the different synthetic approaches allow for a varied set of functionalisation vectors in pharmaceutical space. The 3-dimensionality of the morphan core along the regions of pharmaceutical space it can occupy (see Figure 1.9) make it an adequate candidate as a medicinal chemistry building block.

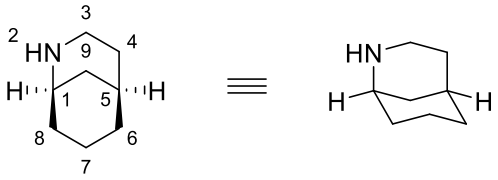


Figure 1.13 - Morphan bicyclo[3.3.1]nonane scaffold

In the context of natural products, the morphan core is present in a wide variety of alkaloids such as daphniyunnine A which is a potent cytotoxic agent[55] and morphine which is widely known for its therapeutic and anaesthetic properties.[62] Meanwhile, FR901483 has found application as an immunosupressant[59] while morphan **42** and derivatives were reported by Thomas and co-workers[61] as opioid receptor antagonists. During their studies, Thomas found that morphan **42** in particular showed similar potency to Naloxone® for the treatment of opioid overdoses without some of the potential side effects associated with it (Figure 1.14). Several other natural products contain the morphan scaffold in their structure and have been relevant synthetic targets throughout the years. Worthy of mention is strychnine and other alkaloids of the strychnos family such as kopsone as well as macrocyclic natural products such as Madangamine A.[58]

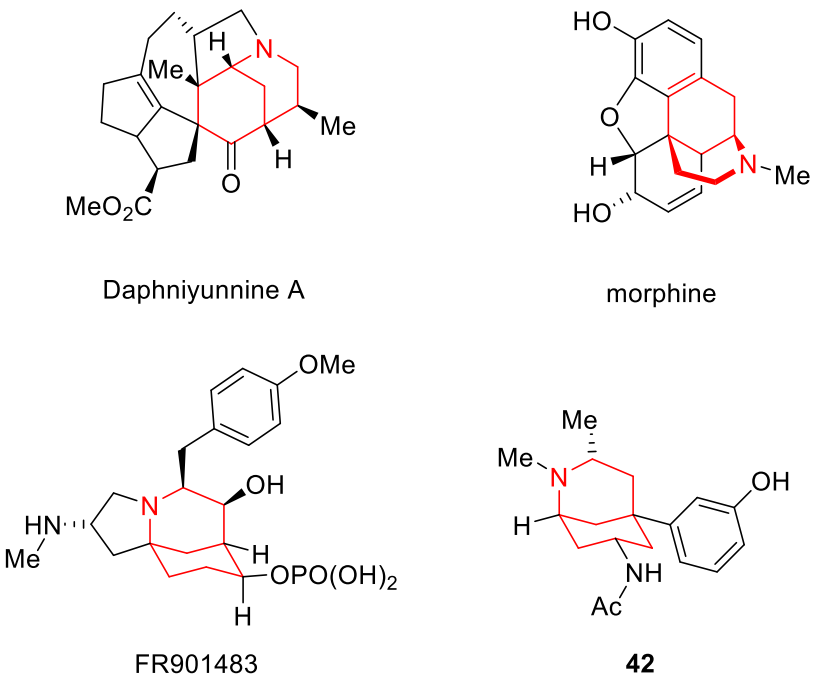
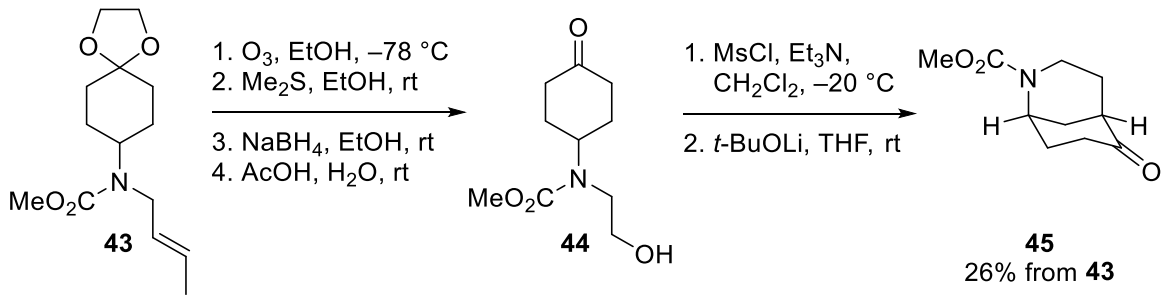


Figure 1.14 - Relevant morphans

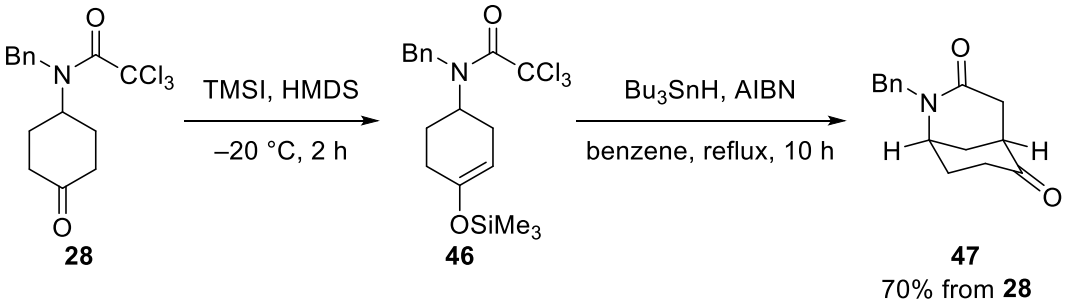
1.4.2 Overview of Racemic Approaches for the Synthesis of the Morphan Scaffold

A wide variety of synthetic methods for the synthesis of the morphan core have been described and the topic has been the focus of various reviews.[56] As such, a non-exhaustive list of some of the most recent and/or relevant methods to the current work will be presented in this Section. In 1982, Mullican and co-workers[63] reported a method for the synthesis of simple morphans by intramolecular enolate alkylation. In this work, the alkene in allylamine **43** was cleaved *via* ozonolysis to give an aldehyde which was reduced to give keto alcohol **44** after ketal deprotection. Keto alcohol **44** was then mesylated and treated with base to give morphan **45** in 26% yield from allylamine **43** (Scheme 1.14). This method has the major drawback of requiring a lengthy five-step sequence to access morphan **45** on top of the required synthesis for allylamine **43**.



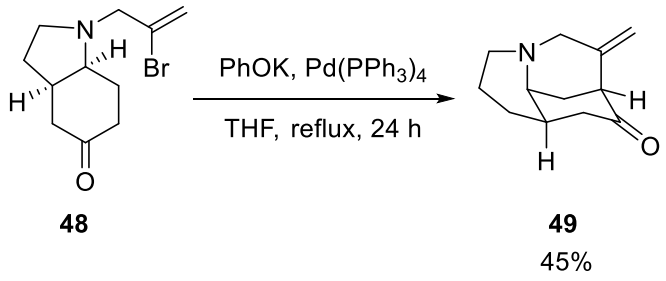
Scheme 1.14

In 1999, Bonjoch and co-workers[64] reported a radical ring closure to access morphan scaffolds. Treating trichloroamidoketone **28** with TMSI and HMDS at –20 °C gave silyl enol ether **46** which was cyclised and de-chlorinated by treatment with Bu_3SnH and AIBN at reflux to give morphan **47** in 70% yield from **28** (Scheme 1.15). This work represented a significant improvement over previous methods for the synthesis of morphans. However, the harsh conditions necessary for the cyclisation presumably meant that no additional substitution was explored by Bonjoch.



Scheme 1.15

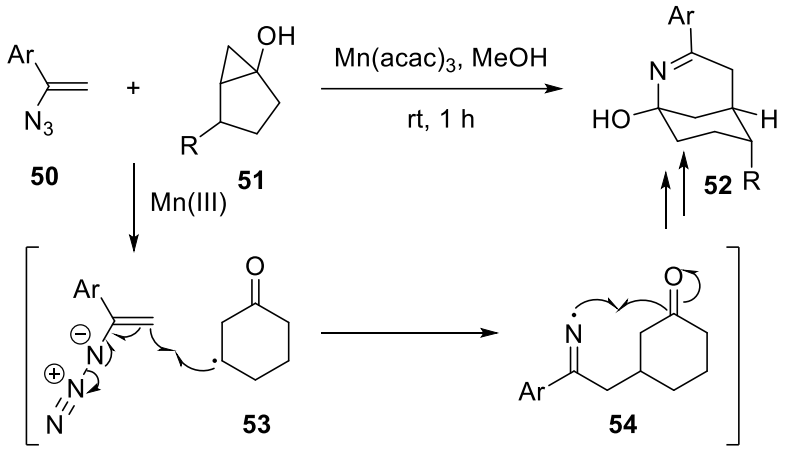
Another racemic route to access the morphan scaffold was described by Bonjoch and co-workers in 2005.[65] In this work, Bonjoch used a Pd-catalysed enolate alkenylation to generate the morphan core from the Daphniphyllum alkaloid family (see Figure 1.14). Use of ketone **48**, PhOK and $Pd(PPh_3)_4$ in THF at reflux gave morphan **49** in 45% yield (Scheme 1.16). However, since the development of this methodology was made in the context of synthesising the morphan core for the Daphniphyllum alkaloid family, no further exploration of the scope was performed.



Scheme 1.16

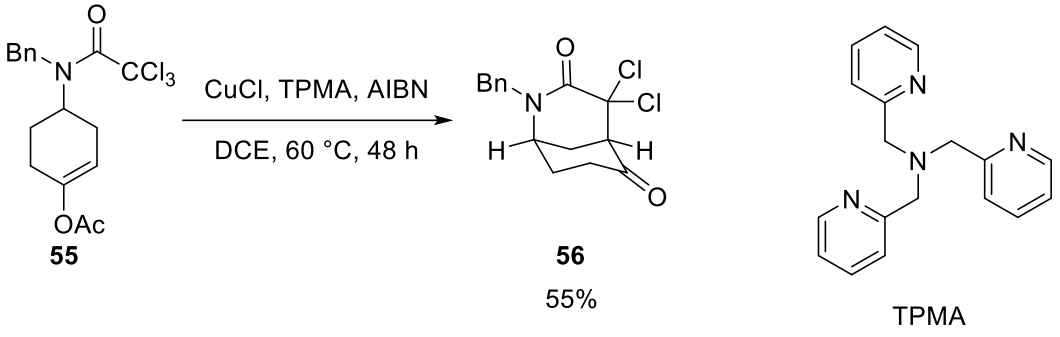
On the other hand, Chiba and coworkers[66] described the synthesis of diverse morphan scaffolds *via* Mn(III)-mediated reactions of cyclopropanols with vinyl azides. In this work, it was found that when vinyl azides **50** were reacted with cyclopropyl fused cyclopentanols **51** in the presence of Mn(III), 1-hydroxy-morphans **52** were formed in moderate to excellent

yields and diastereoselectivities (Scheme 1.17). The reaction proceeds *via* formation of cyclohexanone carbon-centred radical **53** which adds to the vinyl azide with loss of N_2 to form a nitrogen-centred radical **54**. This nitrogen-centred radical then adds to the ketone to form the 1-hydroxy-morphan. Despite the somewhat limited functionality this methodology offers, it was demonstrated that further functionalisation such as deoxygenation, reduction of the imine or substitution of the hydroxyl group was easily carried out.



Scheme 1.17

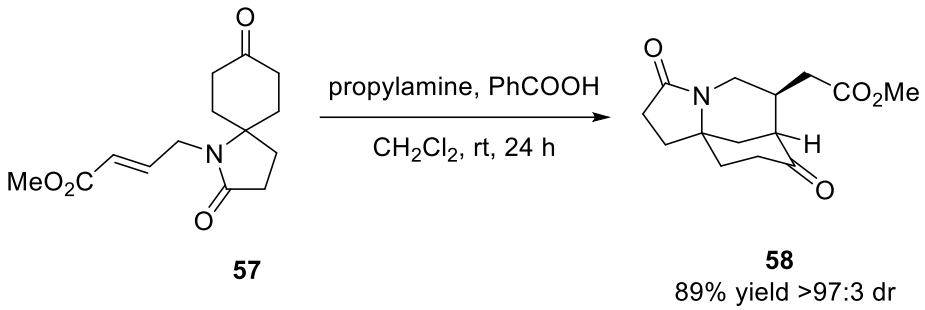
Based on Bonjoch's work (see Scheme 1.15), Belderrain and co-workers[67] described a Cu-catalysed radical cyclisation of trichloroacetamide **55** into a highly substituted morphan. Use of trichloroacetamide **55** with CuCl, TPMA and AIBN in DCE at 60 °C gave morphan **56** in 55% yield (Scheme 1.18). It is notable that, under these conditions, full de-chlorination did not occur. Little substrate scope was investigated by Belderrain, but further functionalisation such as diastereoselective de-chlorination, and substitution was described.



Scheme 1.18

In their effort to develop an asymmetric synthesis for the morphan scaffold, Dixon and co-workers[68] described the use of an organocatalytic intramolecular Michael addition of a 4-substituted cyclohexanone to obtain the morphan scaffold. Thus, treatment of α,β-

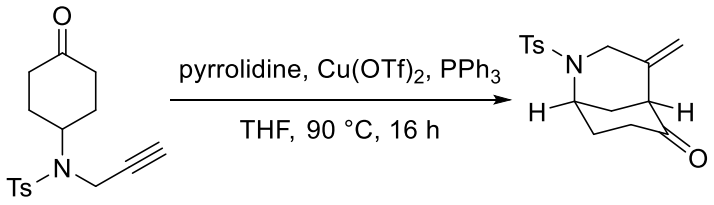
unsaturated ester **57** with propylamine and benzoic acid in CH_2Cl_2 afforded morphan **58** in 89% yield as a single diastereomer (Scheme 1.19). α,β-Unsaturated esters similar to **57** were obtained in good yields in three- to four-step sequences with a single purification. However, the scope of the reaction was only explored for the developed asymmetric variant which is discussed in detail in Section 1.4.3.



57 **58**
89% yield >97:3 dr

Scheme 1.19

Dixon and co-workers[69] reported another approach for the synthesis of morphans from 4-substituted cyclohexanones in 2017. In this work, use of an alkyne-linked cyclohexanone **59**, pyrrolidine, $Cu(OTf)_2$ and PPh_3 in THF led to the formation of morphan **60** in 78% yield (Scheme 1.20). The scope of this reaction was only explored further for the asymmetric variant (see Section 1.4.3).

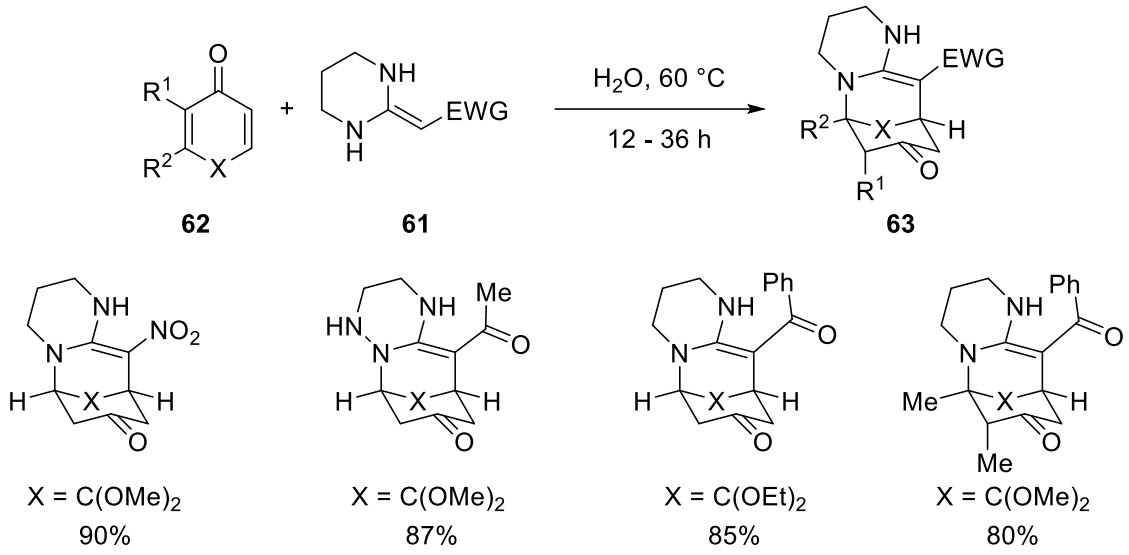


59 **60**
78%

Scheme 1.20

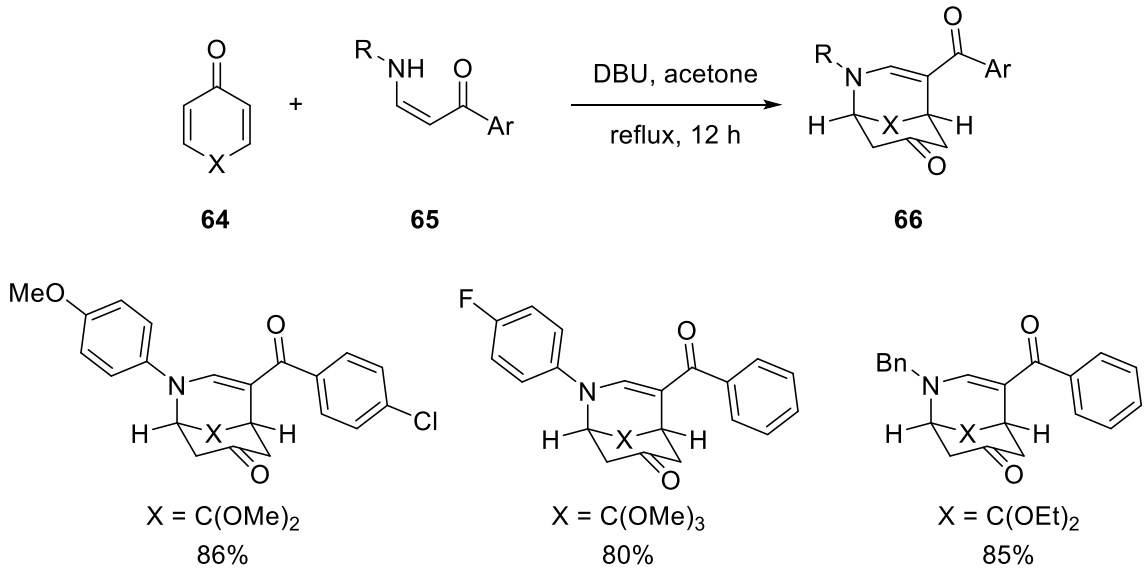
Another method for the synthesis of morphans *via* Michael addition was described by Yan and co-workers[70] in 2017. Thus, the reaction between ketene aminals **61** and quinone monoketals **62** in water at 60 °C led to the formation of morphans **63** in good to excellent yields (Scheme 1.21). This occurs *via* a Michael addition of the aminal **61** to the quinone **62** followed by an aza-Michael addition of the aminal nitrogen into the quinone's second alkene. An attractive feature of this reaction is that it is carried out in water with no other reagents. The methodology was able to accommodate different electron withdrawing groups in the aminal **61** such as NO_2, methyl ketone and acetophenone. The method could also

accommodate methyl substituents in the 1- and 2-positions of the quinone and different ketal protecting groups. However, it has the major drawback of being limited to cyclic ketene aminals with no further functionalisation of the product being explored.



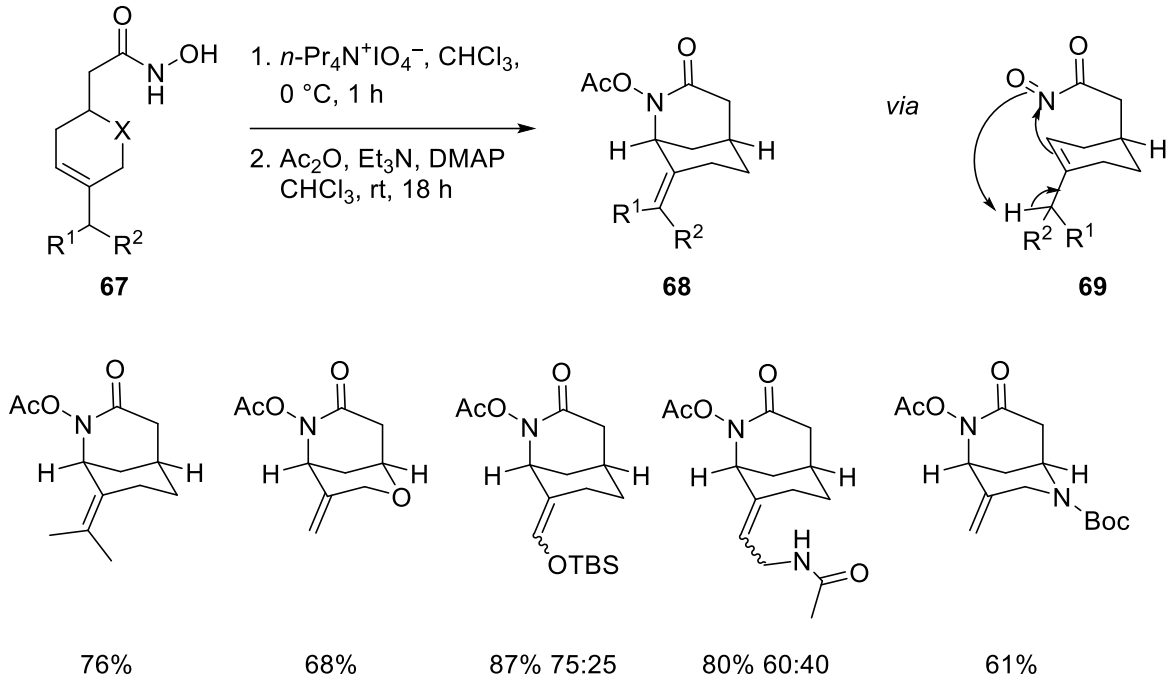
Scheme 1.21

Yan and co-workers[71] made use of a similar approach to their ketene aminal variant (see Scheme 1.21) by using monoacetal protected quinones **64** and a enaminones **65**. As such, treating quinones **64** with enaminones **65** and DBU in acetone at reflux afforded morphans **66** in good to excellent yields (Scheme 1.22). However, their scope was limited to *N*-Ar and *N*-Bn substituents as well as 4-substituted acetophenones in the 4-position of the morphan scaffold.



Scheme 1.22

As a final example of a racemic approach for the morphan scaffold, the nitroso-ene cyclisation reaction has also been used as a way to synthesise morphan cores. In 2017, Hong and co-workers[72] described a way of accessing the morphan core from an *in situ* generated *N*-acyl nitroso compound. Amide **67** was treated with *n*-$PrN^+IO_4^-$ to generate acyl nitroso compound **68** which spontaneously cyclised *via* a nitroso-ene reaction of **68** to give an *N*-hydroxy morphan. The *N*-hydroxy morphan was then acetylated to give morphan **69** in 85% yield and moderate selectivity for the two-step sequence (Scheme 1.23). Different functionality in the 8-position of the morphan scaffold was explored such as silyl ethers and acyl protected amines. The 6-position of the scaffold could also be replaced by an ether or a protected amine motif. Of note, the synthesis of alkaloid (±)-kospone, which is one of the simplest alkaloids from the Daphniphyllum family, was achieved using this methodology.

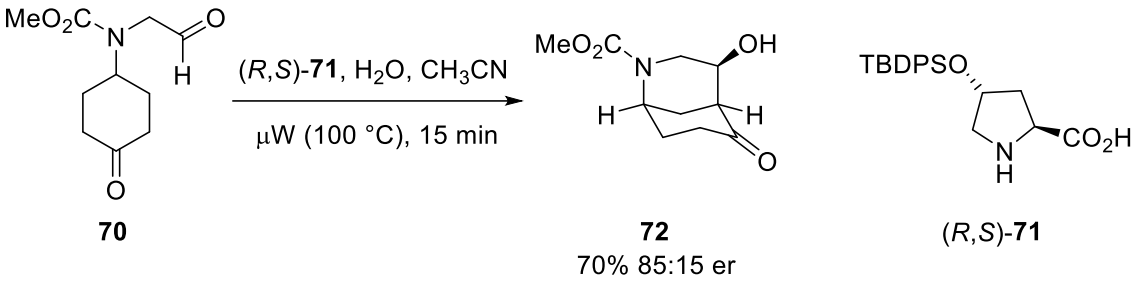


Scheme 1.23

1.4.3 Overview of Asymmetric Approaches for the Synthesis of the Morphan Scaffold

Since many of the synthetic methodologies for the morphan scaffold have been developed with a view to the total synthesis of one of the many natural products that contain them, there are more asymmetric methodologies for the synthesis of this scaffold compared to normorphans. In 2009, Bonjoch and co-workers[73] developed an organocatalytic desymmetrisation of a 4-substituted cyclohexanone under μW irradiation to access the morphan scaffold. The approach used cyclohexanone **70**, proline-derived organocatalyst (*R*-*S*)-**71** and water in CH_3CN under μW irradiation to give morphan **72** in 70% yield and 85:15

er (Scheme 1.24). Multiple proline-derived catalysts were explored with little success. However, the use of catalyst **71** with water as additive gave a good yield and adequate enantioselectivity. Unfortunately, the scope of the reaction to access different substitution patterns on the morphan scaffold was not further explored.

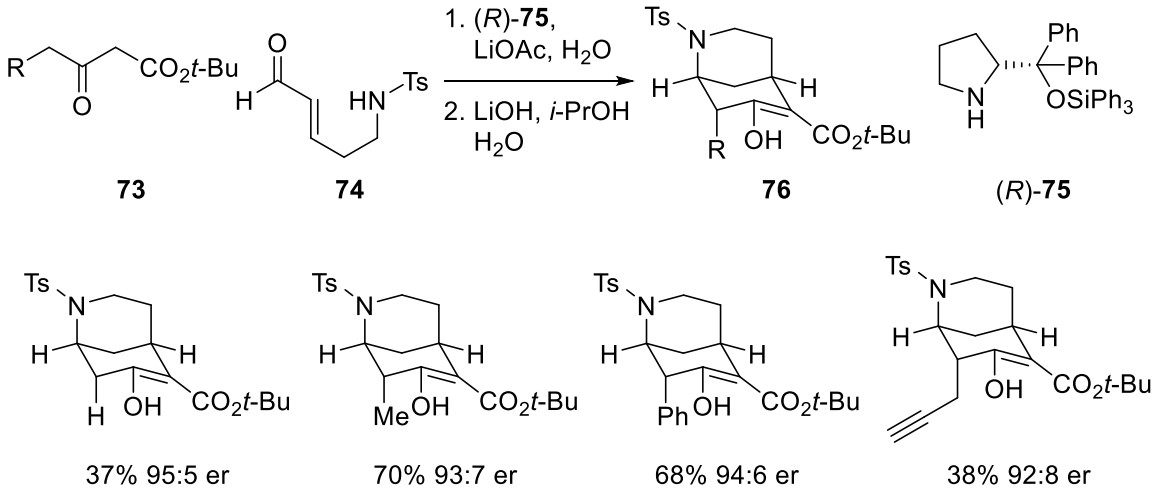


70 **72** (*R*,*S*)-**71**

70% 85:15 er

Scheme 1.24

Following this, the same group developed an alternative organocatalysed asymmetric synthesis of morphans by making use of a Robinson-type annulation.[74] Treatment of ketoesters **73** and aldehyde **74** with proline-derived catalyst (*R*)-**75** and water with LiOH gave morphans **76** in moderate to good yields and excellent enantioselectivities (Scheme 1.25). Some exploration was made into different substituents on the 8-position of the morphan scaffold.



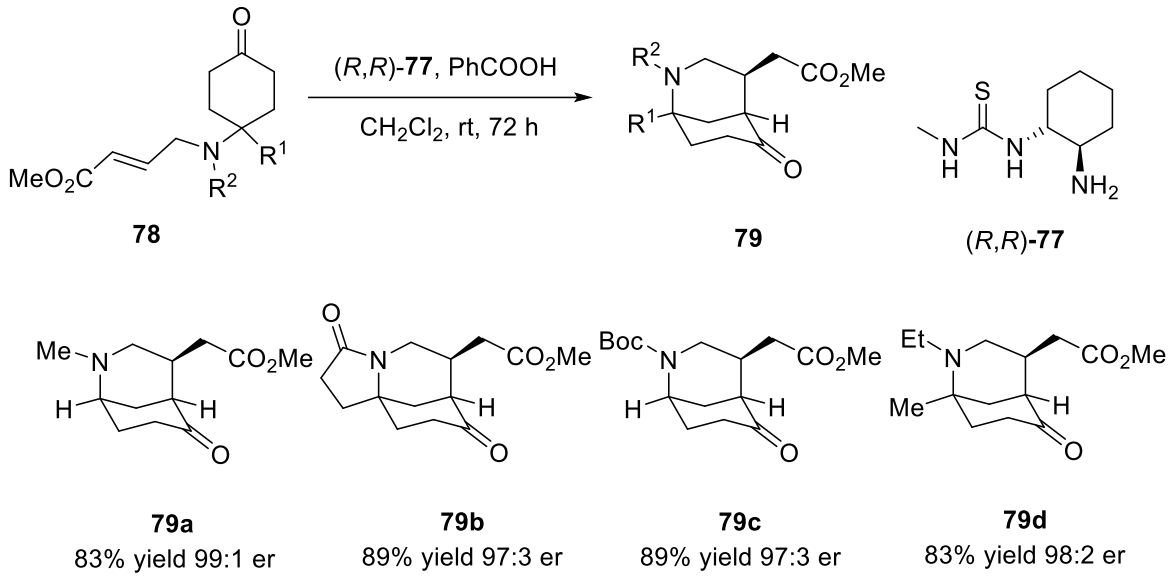
73 **74** **76** (*R*)-**75**

37% 95:5 er 70% 93:7 er 68% 94:6 er 38% 92:8 er

Scheme 1.25

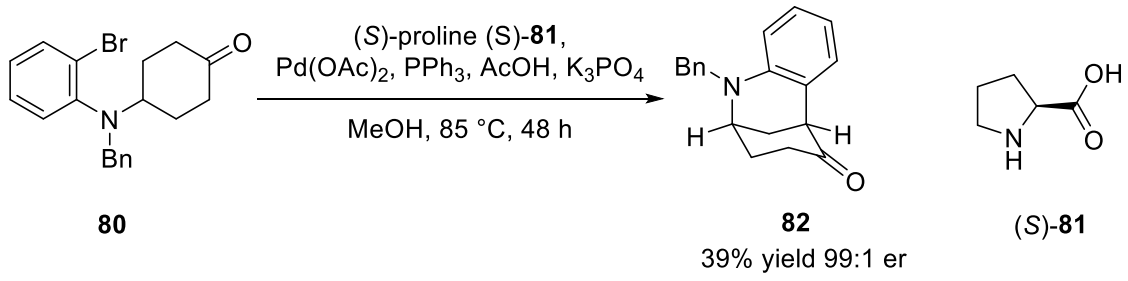
Expanding the methodology previously proposed (see Scheme 1.19), Dixon and co-workers[68] developed an asymmetric variant of their organocatalysed Michael addition. Replacing propylamine with thiourea (*R*,*R*)-**77** and using cyclohexanones **78** in CH_2Cl_2 in a sealed tube at 50 °C gave morphans **79** in good to excellent yields with good enantioselectivities as single diastereomers (Scheme 1.26). Computational analysis of the

organocatalyst used identified relatively simple thiourea (*R*,*R*)-**77** as a suitable catalyst. Some substitution in the 1-position of the morphan scaffold was investigated with overall good results.



Scheme 1.26

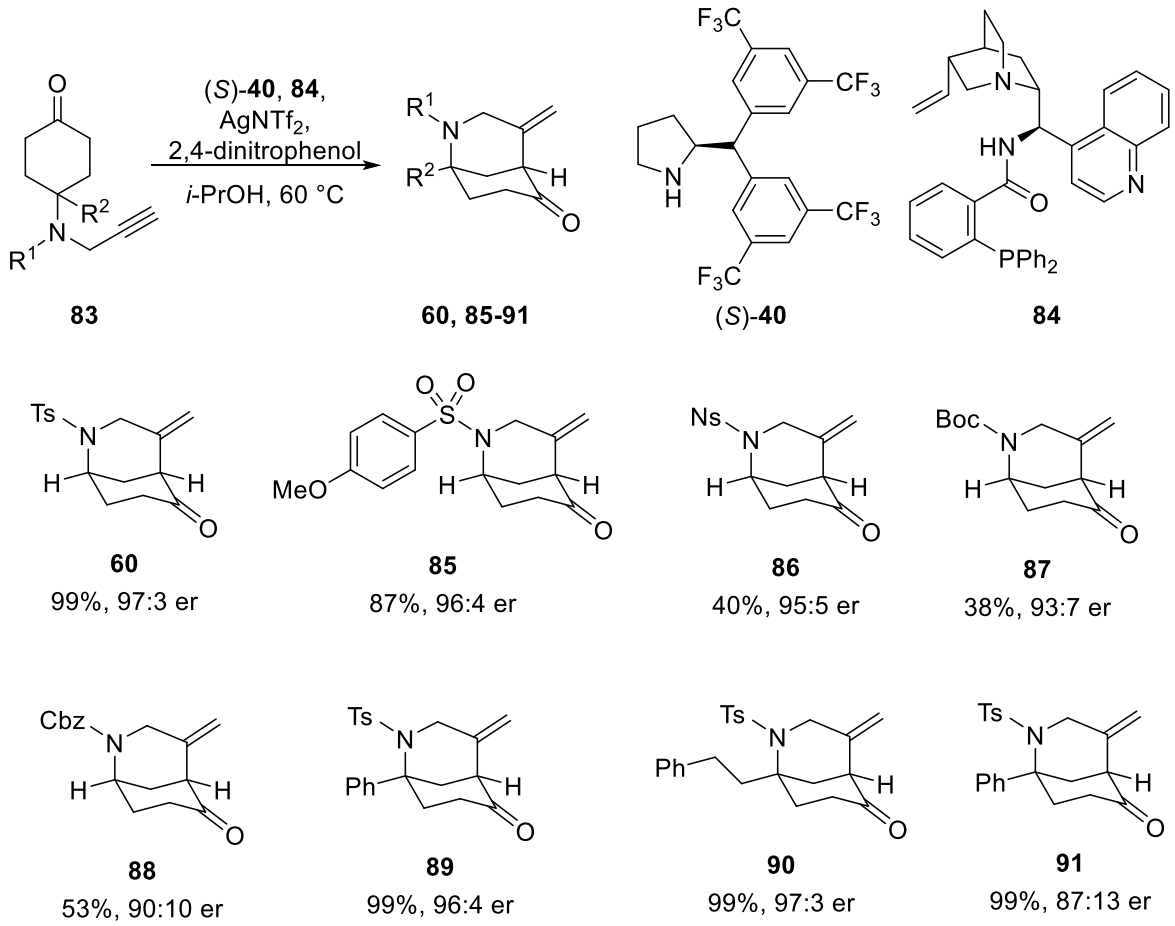
Another example of the asymmetric synthesis of morphans was described by Jia and co-workers[75] in 2016. Jia developed a Pd/proline- co-catalysed asymmetric arylative desymmetrisation of cyclohexanones. For example, treatment of cyclohexanone **80** with (*S*)-proline (*S*)-**81**, $Pd(OAc)_2$, PPh_3, AcOH and K_3PO_4 in MeOH at 85 °C afforded morphan **82** in 91% yield and 99:1 er (Scheme 1.27). However, this methodology could only accommodate limited substitution in the 4- and 5-positions of the aromatic ring.



Scheme 1.27

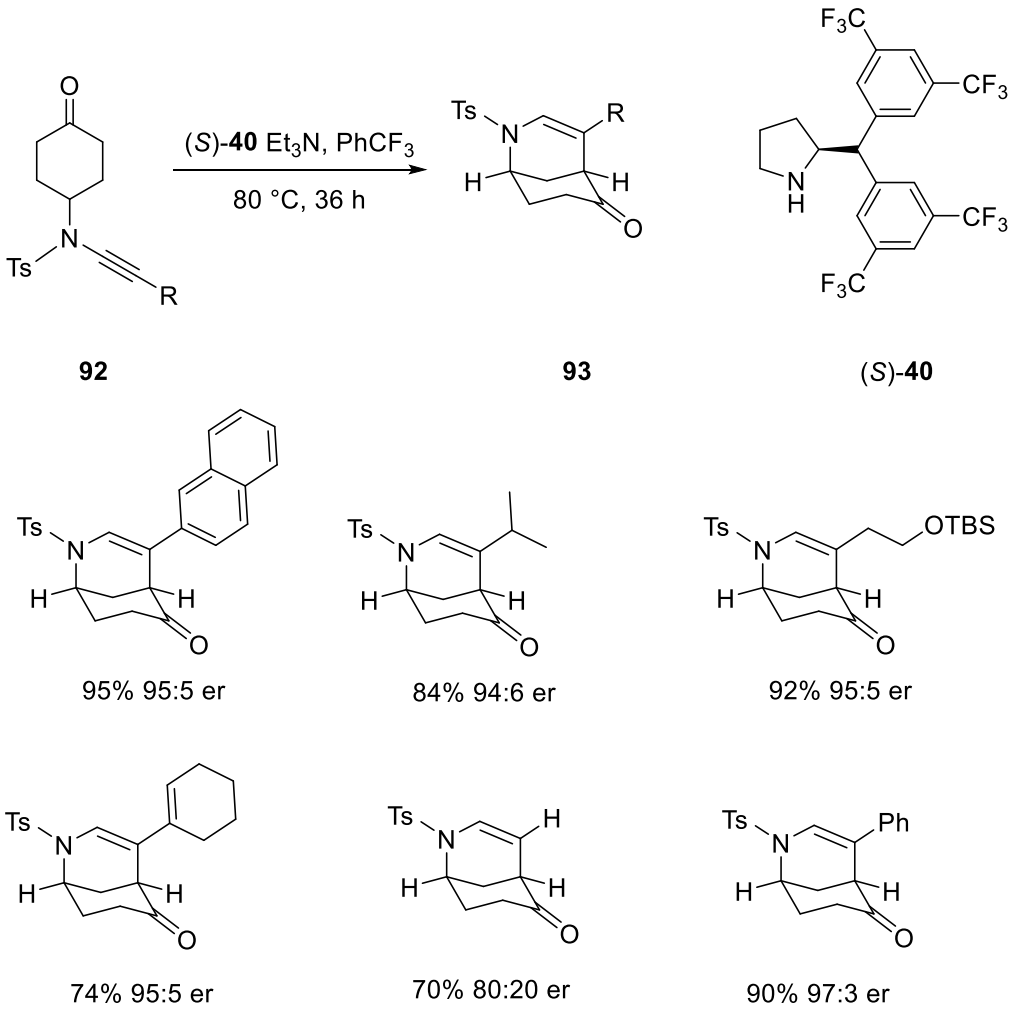
As a complement to their racemic methodology (see Scheme 1.20), Dixon and co-workers[69] described the asymmetric synthesis of morphans using cooperative silver and amine catalysis. Thus, treatment of alkyne-linked cyclohexanones **83** with $AgNTf_2$, chiral amine (*S*)-**40**, chiral phosphine **84** and 2,4-dinitrophenol in *i*-PrOH gave morphans **60**, **85**-**91** in moderate to excellent yields and good to excellent enantioselectivities (Scheme 1.28). It was

found that sulfonamides attached to electron releasing groups such as Ts and 4-$MeOC_6H_4SO_2$ gave their corresponding morphans **60** and **85** in excellent yields and enantioselectivities. Sulfonamides with electron withdrawing groups such as 4-Ns gave moderate yields with slightly decreased enantioselectivities (**86**). By contrast carbamate protecting groups such as *N*-Boc (**87**) and *N*-Cbz (**88**) suffered from diminished yields and enantioselectivities. There was also a strong match/mismatch effect between the chiral amine and phosphine components of the reaction.



Scheme 1.28

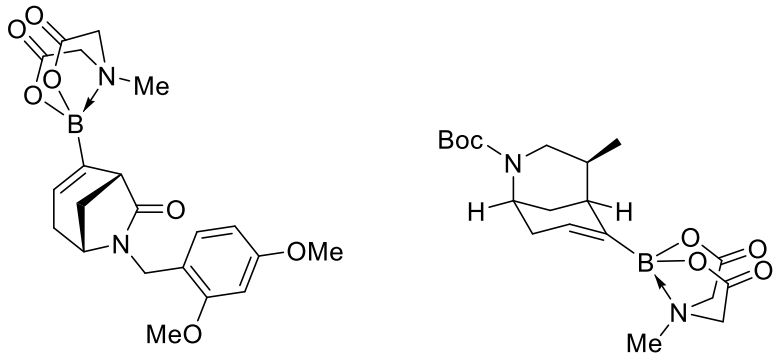
As a final example, the methodology described by Ye and co-workers[53] (see Scheme 1.13) could be easily adapted for the asymmetric synthesis of the morphan core. Use of cyclohexanones **92** with amine (*S*)-**40** and Et_3N in benzotrifluoride afforded morphans **93** in good to excellent yields and moderate to excellent enantioselectivities (Scheme 1.29). The reaction could easily accommodate a variety of alkyl, alkenyl and aryl substituents in the 4-position of the morphan core.


(S)-40 Et3N, PhCF3
80 °C, 36 h
92
93
(S)-40
95% 95:5 er
84% 94:6 er
92% 95:5 er
74% 95:5 er
70% 80:20 er
90% 97:3 er

Scheme 1.29

1.5 Project Outline

Over recent years, the use of 3-D shaped building blocks in medicinal chemistry has received increased interest. Therefore, there is a need to explore the design and development of synthetic methodology to obtain complex, bifunctional, high Fsp^3 building blocks for use in medicinal chemistry. The synthesis of medicinally-relevant compounds and the development of methodology for medicinal chemistry has long been of interest to the O'Brien group. It was planned that this project would focus on the design and synthesis of novel bifunctional 3-D building blocks **94** (normorphan scaffold) and **95** (morphan scaffold) containing a vinyl MIDA boronate and an amine or amide functionality for use in medicinal chemistry (Figure 1.15). It was decided that the development of synthetic methodology for the synthesis of 3-D building blocks **94** and **95** as both racemic samples and single enantiomers would be investigated. Previous work by Bonjoch[50] was envisaged as a way to obtain the racemic normorphan scaffold in building block **94** and the development of an enantioselective variant would be investigated. On the other hand, methodology developed by Dixon[69] would be utilised to access both the racemic and enantioenriched morphan scaffold in building block **95**. The results of these investigations are presented in Chapters 2 and 3.



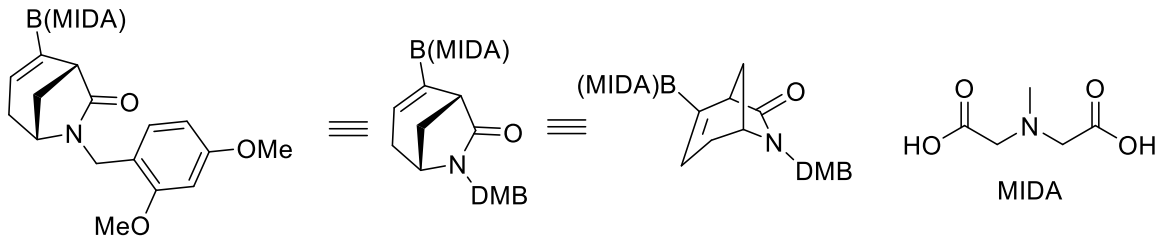
94 **95**

Figure 1.15 - Envisaged normorphan and morphan 3-D building blocks **94** and **95**

It was also planned to showcase the potential of the building blocks by outlining different functionalisation reactions that could be achieved with them. This would be done by exploring the scope of Suzuki-Miyaura cross couplings on the vinyl MIDA boronate functionality, demonstrating the diastereoselective hydrogenation of the building block as well as deprotection for the amide or amine protecting group. In the end, these studies were carried out only on building block **94** and the results are presented in Chapter 4.

Chapter 2 Design and Synthesis of a Normorphan-Derived 3-D Building Block

In this Chapter, the design and development of synthetic methodology required to access 3-D building block **94** (Figure 2.1) is described. Section 2.1 covers the design considerations and the vector analysis of various derivatives of **94** as well as the proposed synthetic strategy towards the 3-D building block. Section 2.2 discusses the synthesis of the building block, alongside optimisation of the cyclisation, enol triflate formation and borylation reactions. Section 2.3 outlines different approaches for the synthesis of enantioenriched building block **94** including studies on an organocatalytic cyclisation approach as well as a resolution approach with chiral MIDA boronate derivatives. Finally, Section 2.4 provides an overview of the results presented in this chapter.

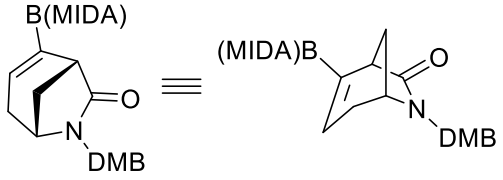


94

Figure 2.1 - Normorphan building block **94**.

2.1 Design Considerations, Vector Analysis and Proposed Route for the Synthesis of a Normorphan-Derived 3-D Building Block

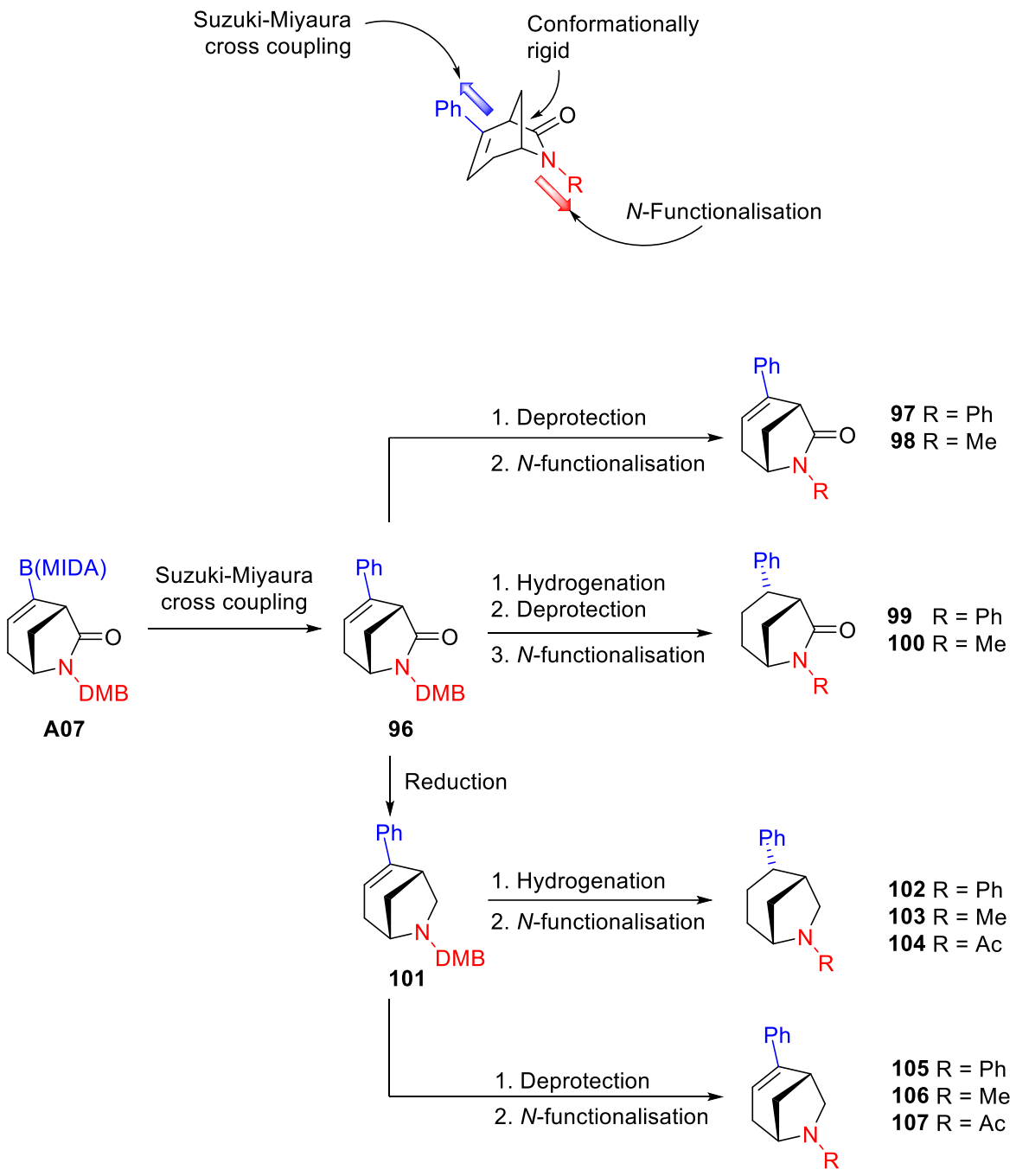
With the prominence of the bicyclo[3.2.1]octane core in the medicinal chemistry literature[25,41,76] and the available synthetic routes to diverse substitution patterns on these normorphan bicyclic cores presented in Section 1.3, our attention turned to a 6-aza-bicyclo[3.2.1] bifunctional building block **94** with a 2-substituent as our first target (Figure 2.2). It was envisaged that building block **94** could be obtained based on previous work by Bonjoch *et al*.[50] as presented in Section 1.3.2.



94

Figure 2.2 - Normorphan building block **94**.

It was expected that the bicyclic structure in building block **94** would provide conformational rigidity to allow for a set of predictable vectors from the functionalisation handles. With this in mind, the set of elaboration vectors were calculated for a group of structures which we hypothesised could be easily accessed by simple, reliable reactions. For example, Suzuki-Miyaura cross-coupling on building block **94** should give arylated normorphan **96** which could be: (i) immediately deprotected and *N*-functionalised to give amides **97** and **98**; (ii) hydrogenated diastereoselectively then deprotected and *N*-functionalised to give amides **99** and **100**; (iii) reduced into amine **101** then hydrogenated and functionalised to give amines **102**, **103** and **104** or (iv) reduced into amine **101** then deprotected and functionalised to give amines **105**, **106** and **107** (Scheme 2.1). For the hydrogenation steps, we predicted that hydrogenation on the *exo*-face of the bicyclic scaffold should occur selectively to give the diastereomers shown.



Scheme 2.1

The set of structures shown in Scheme 2.1 gives an idea of the different elaboration vectors that can be achieved with building block **94**. Using a Pipeline Pilot protocol previously developed in the O'Brien group,[77] the lowest energy conformer for each molecule was generated using molecular mechanics. On these conformers, the set of variation vectors for each molecule was selected and then calculated using an algorithm developed by Grygorenko and co-workers[19] to give the results shown in Figure 2.3. Figure 2.3a defines the vectors for the case of a 1,4 disubstituted cyclohexane, namely, the distance between the

variation points C1 and C2, r, the plane angles Φ_1 (between vector n_1 and C1-C2) and Φ_2 (between vector n_2 and C1-C2) and the dihedral angle θ defined by the vectors n_1, C1-C2 and n_2.

Comparing our set of vectors to those calculated by Grygorenko and co-workers[19,20] for a variety of cyclic compounds reveals that building block **94** has vectors that lie outside the clusters normally associated with simple 3- to 7-membered cyclic scaffolds (see Section 1.2). They also have distinct vectors compared to a diverse set of [3.3.n]propellanes[23] and cyclobutyl-azetidine-based scaffolds synthesised by the same group.[22] Our set also shows a good level of conformational rigidity where most of the structures are clustered together in the *r*-θ plot (Figure 2.3b). However, some changes are observed between the hydrogenated products and their parent compounds with distinct clusters differing mainly by the Φ_1 angle due to the change in hybridisation on the variation point C1. Additionally, *N*-methyl derivatives of the amine-based scaffold **103** and **106** seem to be outliers with regards to angles θ, Φ_1 and Φ_2 (Figure 2.3b,c,d), This, due to the sp^3 hybridization of nitrogen and its protonation during the conformer generation.

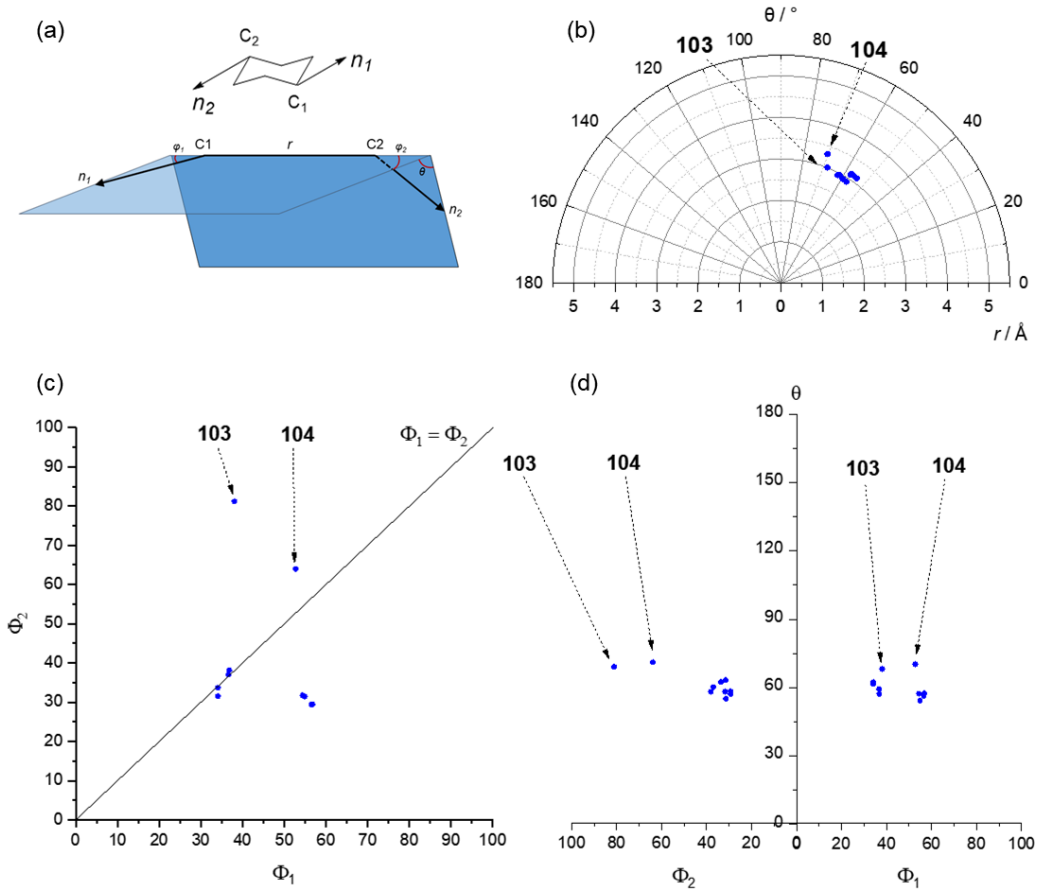
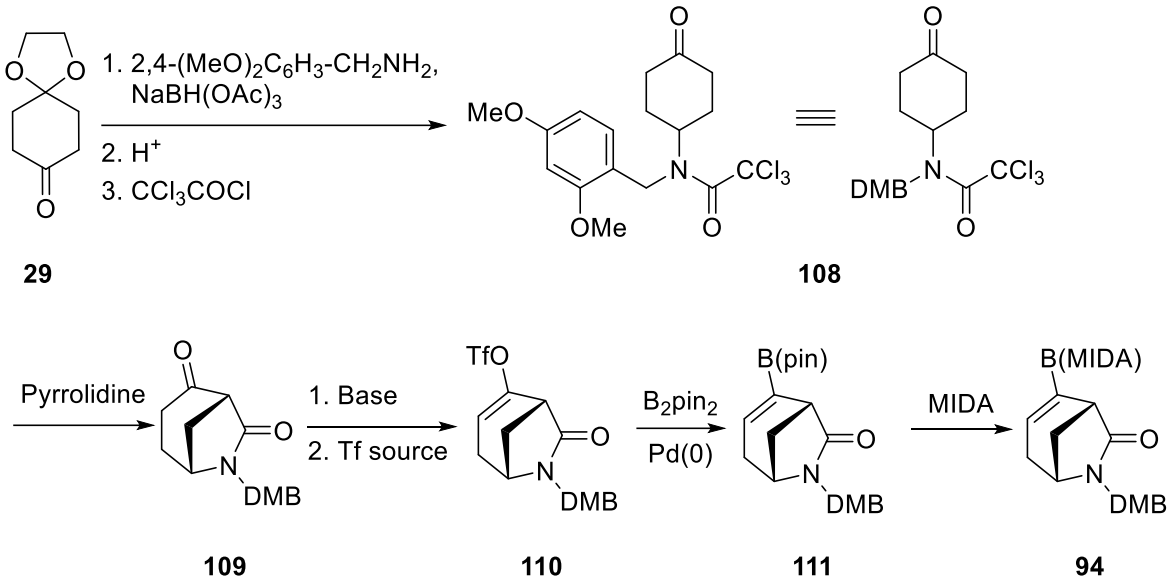


Figure 2.3 - Vector analysis for building block **94** in: a) *r-θ* plot (polar coordinates); b) visual representation of variation vectors; c) Φ_1-Φ_2 plot; c) θ-Φ_1/Φ_2 plot.

Our initial proposed route for the synthesis of 3-D building block **94** is outlined in Scheme 2.2. As previously mentioned, the scaffold construction is based on previous work by Bonjoch *et al.*[50] and the route reported by Bonjoch appeared to offer a quick and reliable way to access the racemic normorphan scaffold from an organocatalytic cyclisation of a trichloroacetamide (see Scheme 1.8). Using this approach, we envisaged that trichloroamidoketone **108** could be obtained from monoprotected cyclohexadione **29** in three steps and then, using Bonjoch's organocatalytic cyclisation, we could obtain normorphan scaffold **109**. After the cyclisation, elaboration into vinyl MIDA boronate **94** was envisioned *via* vinyl triflate formation to give **110**, followed by a Pd-catalysed Miyaura borylation[78] using B_2pin_2 to give vinyl pinacol boronate **111** and transesterification sequence to introduce the MIDA group. Additionally, it was hoped that an asymmetric organocatalytic variant of the cyclisation could be developed to access the enantioenriched building block **94**.

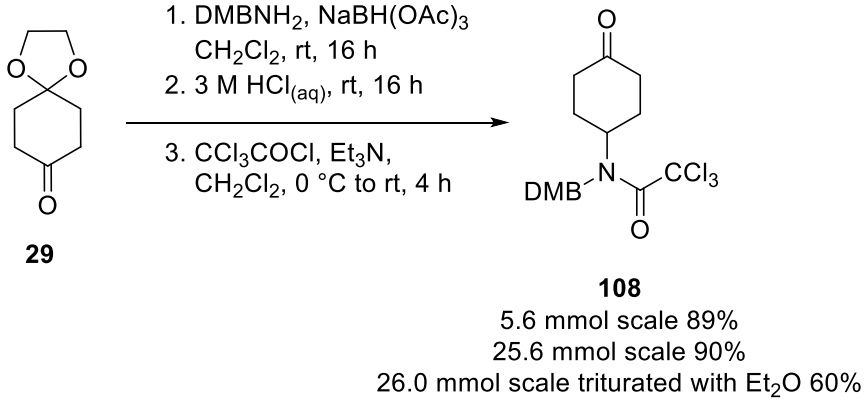


Scheme 2.2

In Bonjoch's work, a benzyl group was used as the protecting group for the amine (see Scheme 1.8). However, in the case of amides, benzyl groups are notoriously hard to deprotect.[79] Therefore, we proposed the use of 2,4-dimethoxybenzyl (DMB) protection since it should be more easily removed under either acidic or oxidative conditions during further functionalisation of the building block. A different protecting group such as Boc was not selected as we were unsure of the effect of an imide in the pyrrolidine-catalysed cyclisation. Finally, it is worth noting that the decision of using a vinyl MIDA boronate in the finalised building **94** block arose from the fact that MIDA boronates, popularised by Burke and co-workers,[80-82] tend to be easy to handle, bench-stable, crystalline solids, that are easily hydrolysed to coupling active boronic acids under traditional aqueous Suzuki-Miyaura conditions.[82]

2.2 Development of a Racemic Synthesis of a Normorphan-Derived 3-D Building Block

To begin the studies towards the synthesis of the desired building block, it was necessary to access trichloroacetamide **108**. To this end, the previously reported synthesis for the *N*-Bn variant of the trichloroacetamide **28** by Bonjoch and co-workers[50] (see Scheme 1.8) was used as a model to obtain the *N*-DMB derivative **108**. Reductive amination of 1,4-cyclohexadione monoethylene acetal **29** (5.6 mmol scale) with a stoichiometric amount of 2,4-dimethoxybenzylamine and using $NaBH(OAc)_3$ (1.4 eq.) as a reducing agent quantitatively afforded the crude amine that was, after work-up, sufficiently pure for the next reaction. Hydrolysis of the ketal with 3 M $HCl_{(aq)}$ quantitatively gave the crude ketone as a sufficiently pure product that was taken on to amide formation using an excess (1.8 eq.) of trichloroacetyl chloride in the presence of Et_3N (1.9 eq.). After purification by chromatography, trichloroacetamide **108** was obtained in 89% yield over the three-step sequence (Scheme 2.3).



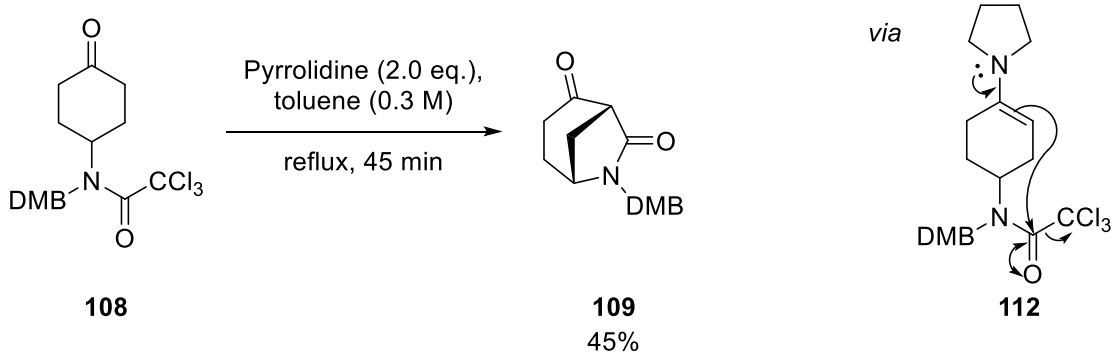
Scheme 2.3

Formation of trichloroacetamide **108** was confirmed by HRMS and both ^1H and ^{13}C NMR spectroscopy where, despite the presence of rotamers (65:35 ratio) about the amide's C–N bond, diastereotopic signals were observed for the attached DMB group (δ_H 4.60–4.52 (m, 1.3H, ArCHN), 4.04–3.92 (m, 0.35H, ArCHN), 3.84–3.74 (m, 6.35H, ArCHN, OMe)). Additionally, the ^{13}C NMR spectrum showed signals at δ_C 93.8 and 160.7 that were assigned, by analogy with the *N*-Bn variant **28** (δ_C 93.5, 160.5),[64] as the CCl_3 and C(O)N signals respectively.

Scale-up of the procedure to 26 mmol of substrate gave a 90% yield of amidoketone **108** when purified by chromatography (Scheme 2.3). However, since it was desired to achieve a

more efficient purification, avoiding the large amounts of solvent and silica required for chromatography, an alternative purification was attempted on a 26 mmol scale. With the knowledge that the *N*-Bn variant can be purified by recrystallisation from Et_2O, purification by triturating the crude product with Et_2O was attempted. This gave trichloroacetamide **108** in 60% yield which, despite being significantly lower than that obtained using chromatography, provides a useful alternative when purifying this early-stage product in large quantities.

Next, trichloroacetamide **108** was subjected to an organocatalytic cyclisation using Bonjoch's conditions[50] with pyrrolidine to afford normorphan **109**. This reaction proceeds *via* formation of enamine **112** from pyrrolidine and the ketone, with enamine **112** adding to the trichloroacetamide with concomitant elimination of $^{-}CCl_3$. However, initial results using toluene as a solvent at reflux gave normorphan **109** in only 45% yield (Scheme 2.4). The ^1H NMR spectrum of normorphan **109** showed the expected signal of the newly formed CH α to the two carbonyl groups as a doublet at δ_H 3.18, having only one significant coupling (^3J = 5.0 Hz) to one of the methylene bridge protons and a negligible coupling to the other.



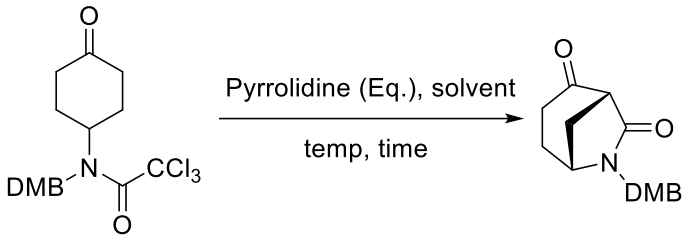
108 **109** 45% **112**

Scheme 2.4

With this result in hand, we set out to find an adequate set of conditions for this cyclisation reaction (Table 2.1). Increasing the reaction time from 45 min to 3 h at reflux in toluene had a detrimental effect on the yield (33% of **109**, Entry 2). Thus, using the alternative method proposed by Bonjoch, a change into neat, sealed tube conditions and lowering the pyrrolidine equivalents was made. In this way, a good yield (63%) of normorphan **109** was obtained (Entry 3). Finally, since solubility problems were observed in the early stages of the reaction, we wondered whether increasing the equivalents of pyrrolidine to 1.0 and adding a small amount of toluene (4.0 M concentration) could prove beneficial. To our delight, this set of conditions afforded the best, most reproducible result (80% of **109,** Entry 4). Using these

conditions, normorphan **109** was isolated in 80% yield on a 1.22 mmol scale with no erosion of the yield when scaled up to 17.1 mmol scale (Entry 5).

Table 2.1 - Optimisation of racemic cyclisation to give normorphan **109**

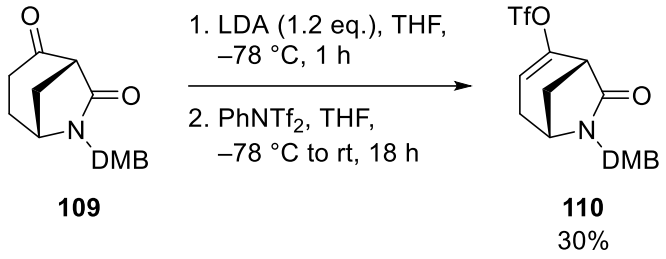


108 **109**

Entry	Pyrrolidine Eq.	Solvent	C[a] (M)	Temp[b] (°C)	Time	Scale (mmol)	Yield[c] (%)	Vessel
1	2.0	Toluene	0.3	Reflux	45 min	0.49	45	RBF[d]
2	2.0	Toluene	0.3	Reflux	3 h	0.98	33	RBF[d]
3	0.5	Neat		100	1 h	1.22	63	Sealed tube
4	1.0	Toluene	4.0	100	1 h	1.22	80	Sealed tube
5	1.0	Toluene	4.0	100	1h	17.1	80	Sealed tube

a) Concentration of substrate (mmol/mL); b) Temperature measured in oil bath; c) Isolated % yield; d) RBF = round-bottomed flask.

With an optimised cyclisation in hand, vinyl triflate formation from the ketone in normorphan **109** was the next step to be investigated. Relying on Bredt's rule for regioselectivity and a reported literature procedure[83] for a similar normorphan that lacked the amide, use of LDA as a base and $PhNTf_2$ as a triflate source was attempted. Thus, normorphan **109** was treated with LDA at –78 °C in THF to give the enolate which was trapped with $PhNTf_2$ to give vinyl triflate **110** in 30% yield after purification by chromatography (Scheme 2.5). Vinyl triflate formation was confirmed by ^{1}H NMR spectroscopy, in which a narrow 1H multiplet was observed at δ_H 5.56–5.51 and assigned to the alkene CH. ^{13}C NMR spectroscopy also showed a quartet (J = 320.0 Hz) at δ_C 118.6 corresponding to the CF_3 carbon. Signals corresponding to the newly-formed alkene at δ_C 148.4 and 114.8 were also observed.

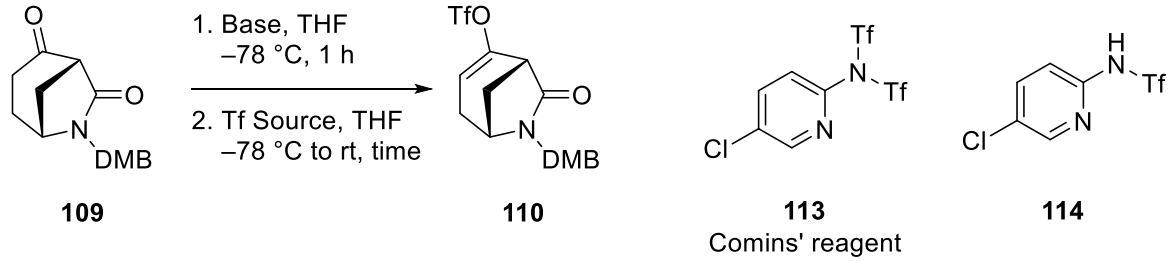


109 **110** 30%

Scheme 2.5

A range of conditions were then explored with the aim to increasing the yield for the formation of vinyl triflate **110** (Table 2.2). We first attempted to change the triflate source to a more reactive triflimide (Comins' reagent **113**) which has shown use with unreactive substrates in previous studies.[84] However, only a marginal increase in yield was observed (33% of **110**, Entry 2) suggesting issues with deprotonation of ketone **109** rather than problems with trapping the formed enolate. Thus, a brief screen of bases was performed. Using LiHMDS and Comins' reagent gave only traces of enol triflate **110** (Entry 3). Changing to NaHMDS showed promise giving **110** in 54% yield (Entry 4). However, the product from this reaction was isolated as an 85:15 mixture with triflamide **114**, derived from Comin's reagent, that proved impossible to separate by chromatography. On the other hand, using KHMDS as a base and returning to $PhNTf_2$ as the triflate source gave only traces of product (Entry 5). It has been suggested[85] that a wash with cold 1 M $NaOH_{(aq)}$ in the work-up can be effective at removing side-products from the triflating agent. Following this, using NaHMDS with both $PhNTf_2$ and Comins' reagent **113** gave vinyl triflate **110** as a pure product albeit in a diminished yield suggesting decomposition of **110** in the work-up (Entries 6 and 7). Finally, using NaHMDS and $PhNTf_2$ as a triflate source without the NaOH wash gave vinyl triflate **110** in a moderate and consistent yield (Entry 8) but increasing the reaction time proved detrimental to the yield (Entry 9). Thus, using NaHMDS as a base and $PhNTf_2$ as the triflate source with a trapping time of 18 h and without a NaOH wash in the work-up proved to be the most effective way to obtain vinyl triflate **110**. These conditions also allowed the reaction to be scaled up to 12.3 mmol scale without any detrimental effect on the yield (61% of **110)**.

Table 2.2 - Formation of vinyl triflate **110**

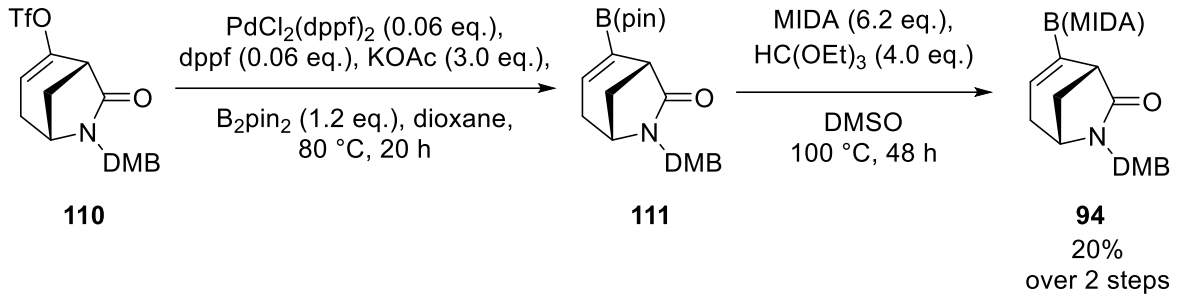


109 **110** **113** Comins' reagent **114**

Entry	Base	Eq.	Tf Source	Eq.	Time (h)	Yield[a] (%)
1	LDA[b]	1.2	$PhNTf_2$	1.4	18	30
2	LDA[b]	1.2	**113**	1.3	72	33[c]
3	LiHMDS	1.4	**113**	1.3	18	10[d]
4	NaHMDS	1.3	**113**	1.3	18	54[e]
5	KHMDS	1.3	$PhNTf_2$	1.4	18	8
6	NaHMDS	1.8	$PhNTf_2$	1.3	18	45[f]
7	NaHMDS	1.8	**113**	1.3	18	36[f]
8	NaHMDS	1.8	$PhNTf_2$	1.3	18	61[g]
9	NaHMDS	1.8	$PhNTf_2$	1.3	48	33

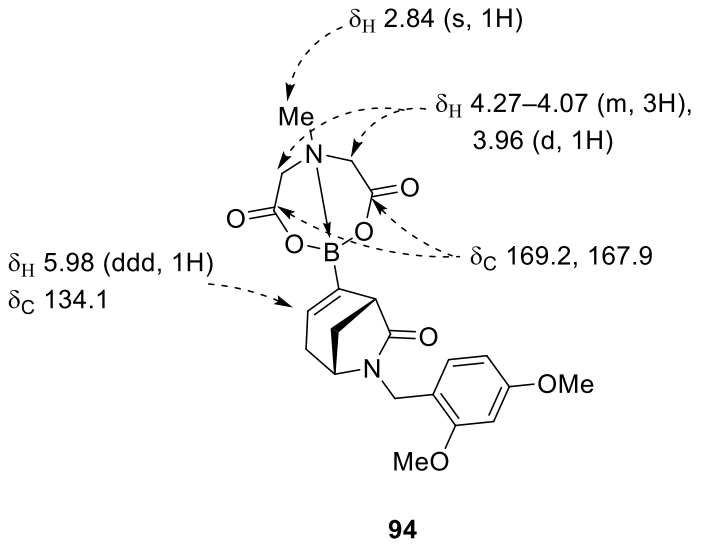
a) Isolated % yield; b) Prepared *in situ* by the addition of *n*-BuLi to *i*-Pr_2NH; c) Isolated as an 80:20 mixture with **114**; d) Estimated by ^1H NMR spectroscopy; e) Isolated as an 85:15 mixture with **114**; f) cold 1 M $NaOH_{(aq)}$ wash; g) 12.3 mmol scale

The next step involved converting vinyl triflate **110** into vinyl pinacol boronate intermediate **111** and then into the desired vinyl MIDA boronate **94**. This was initially attempted using a literature procedure,[78] with dppf as a ligand for the Pd and KOAc as base, which gave vinyl pinacol boronate **111** as an inseparable mixture with B_2pin_2 derived impurities which was submitted to vinyl MIDA boronate formation. This was carried out using a large excess of MIDA and $HC(OEt)_3$ at 100 °C in DMSO,[86] giving vinyl MIDA boronate **94** in 20% yield over the two steps (Scheme 2.6).



Scheme 2.6

Formation of both vinyl pinacol boronate **111** and vinyl MIDA boronate **94** was confirmed by HRMS and NMR spectroscopy. Particularly, for vinyl pinacol boronate **111,** the signal corresponding to the alkene proton shifted downfield from δ_H 5.56–5.51 in vinyl triflate **110** to δ_H 6.40–6.37 in vinyl pinacol boronate **111**. Additionally, the signal corresponding to the C–OTf carbon resonance in vinyl triflate **110** which was observed at δ_C 148.4 disappeared for the newly formed C–Bpin in vinyl pinacol boronate **111**. This is due to coupling between the carbon and the quadrupolar boron atom which gives rise to signals that occasionally are not well resolved in the ^{13}C NMR spectrum.[87] On the other hand, for vinyl MIDA boronate **94**, the signal corresponding to the alkene signal was observed at δ_H 5.98 (ddd, J = 3.0, 3.0, 3.0 Hz). Additionally, the incorporation of the MIDA moiety on building block **94** was confirmed with the proton signals corresponding to the two diastereotopic CH_2 groups. Three of these protons appeared alongside one of the benzylic protons at δ_H 4.27–4.07 (m, 4H), with the other one coming at δ_H 3.96 (d, J = 17.0 Hz, 1H). The *N*-Me signal was also observed as a 3H singlet at δ_H 2.84. Finally, the ^{13}C NMR spectrum showed the alkene CH signal at δ_C 134.1 with signals for quaternary protons appearing at δ_C 169.2 and 167.9 which were assigned as the two diastereotopic C=O groups in the MIDA group (Figure 2.4).



94

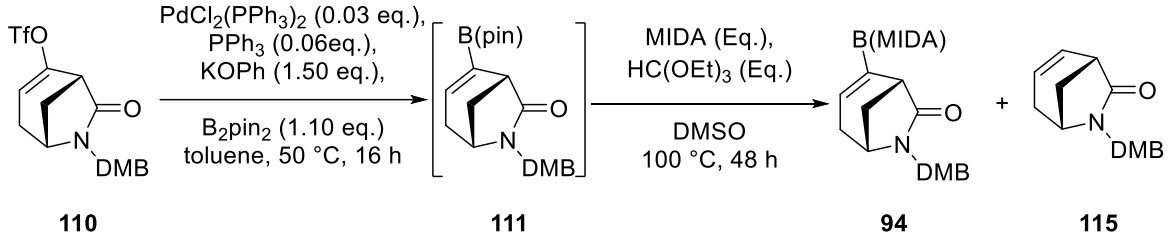
Figure 2.4 - Key ^{1}H and ^{13}C NMR spectroscopic signals for building block **94**.

With building block **94** in hand and the observed problems in the formation of vinyl pinacol boronate **111**, our attention turned to finding conditions suitable for the synthesis of vinyl MIDA boronate **94** in higher yield. It has been reported[88] that for challenging substrates changing the ligand in Miyaura's borylation to PPh_3 and the base to KOPh can give better results. However, use of these conditions in toluene with vinyl triflate **110** gave only impure vinyl pinacol boronate **111** after chromatographic separation. With this result and upon performing 2-D TLC analysis of the impure pinacol boronate **111**, it was concluded that decomposition under chromatography conditions was occurring. Nonetheless, this impure product was submitted to the previously used MIDA boronate formation conditions, affording a 54% yield of vinyl MIDA boronate **94** over the two steps (Table 2.3, Entry 1).

With these results in hand, and the evidence of vinyl pinacol boronate **111** decomposition under column chromatography conditions, Miyaura's borylation was once more attempted and the crude product directly submitted to MIDA boronate formation. This gave a 70% yield of vinyl MIDA boronate **94** over the two steps. However, a significant amount of alkene **115** (17%) was also observed for reactions in which vinyl pinacol boronate **111** was not purified (Entry 2). Additionally, since the formation of vinyl MIDA boronate **94** required a large excess of both of the reagents used, an attempt at diminishing the equivalents of MIDA from 6.5 to 4.0 and of $HC(OEt)_3$ from 4.5 to 4.0 was made. However, a decrease in the yield of vinyl MIDA boronate **94** to 60% was observed while the isolated quantity of alkene **115** remained mostly similar (Entry 3). The formation of alkene **115** was determined from its characteristic alkene signals. Namely, two signals were observed at δ_H 6.07 (dddd,

J = 9.0, 7.5, 1.0, 1.0 Hz, 1H) and 5.51 (dddd, J = 9.0, 3.5, 3.0, 1.5 Hz, 1H) which were consistent with the two alkene protons in **115**. Likewise, the ^{13}C NMR spectrum showed two signals corresponding to =CH carbons at δ_C 129.2 and 126.0.

Table 2.3 - Optimisation of vinyl MIDA boronate formation



110 **111** **94** **115**

Entry	Eq. MIDA	Eq. $HC(OEt)_3$	Yield of 94[a] (%)	Yield of 115[a] (%)
1	6.2	4.0	54	N.D.[b]
2[c]	6.5	4.5	70	15
3[c]	3.0	4.0	60	17

a) % yield after chromatography; b) not determined; c) no intermediate purification of pinacol boronate **111** was attempted.

Additional ^{1}H NMR spectroscopic analysis of the crude mixtures for both the intermediate vinyl pinacol boronate **111** and the vinyl MIDA boronate **94** indicate that alkene **115** seems to be generated primarily as a by-product of Miyaura's borylation step, presumably by a protodeborylation-type process. This is evidenced by the appearance of the signals associated with the alkene protons in **115**, and their ratios with respect to the alkene signals in both **111** and **94** in the crude spectra for both reactions (Figure 2.5). This together with the fact that Entry 4 (Table 2.3) gave a diminished yield for MIDA boronate **94** but a similar yield for alkene **115** when compared to Entry 3, leads us to conclude that alkene **115** is mainly a product that arises from the Miyaura borylation of vinyl triflate **110** into vinyl pinacol boronate **111**.

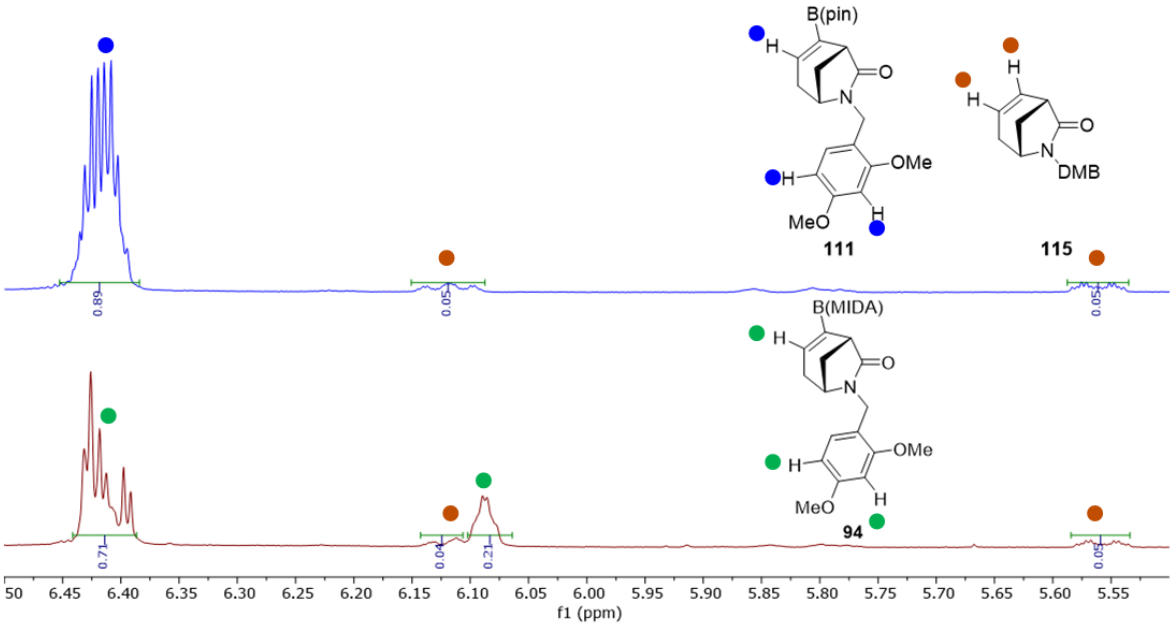
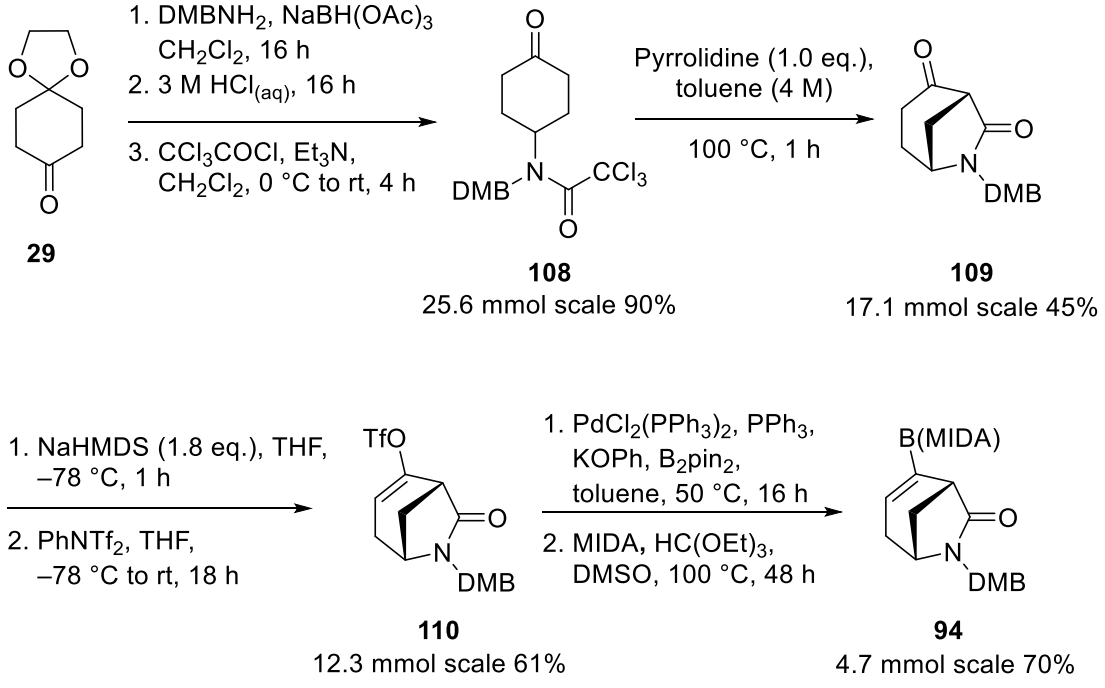


Figure 2.5 - ^{1}H NMR spectrum of the crude product of the Miyaura borylation reaction (blue) and subsequent MIDA transesterification (red).

Thus, the synthesis of vinyl MIDA boronate building block **94** was achieved with a 30% overall yield on a multigram-scale from ketone **29** (Scheme 2.7). This was accomplished using a three-step sequence to give amidoketone **108**, followed by an organocatalytic cyclisation into normorphan **109** and finishing with a vinyl triflate formation to give **110** and borylation-transesterification to give vinyl MIDA boronate **94**.

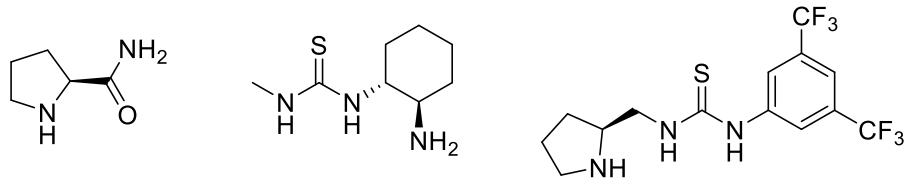


Scheme 2.7

2.3 Investigation of Routes for the Synthesis of Enantioenriched Normorphan-Derived 3-D Building Block

With the need to obtain enantioenriched building block **94**, two alternative and complementary strategies to achieve this were envisaged. Based on the literature precedent presented in Section 1.3.3, we hypothesised that an asymmetric variant for the organocatalytic cyclisation could be developed to access the enantioenriched normorphan scaffold. The second strategy would be based on a resolution approach based on chiral MIDA derivatives.

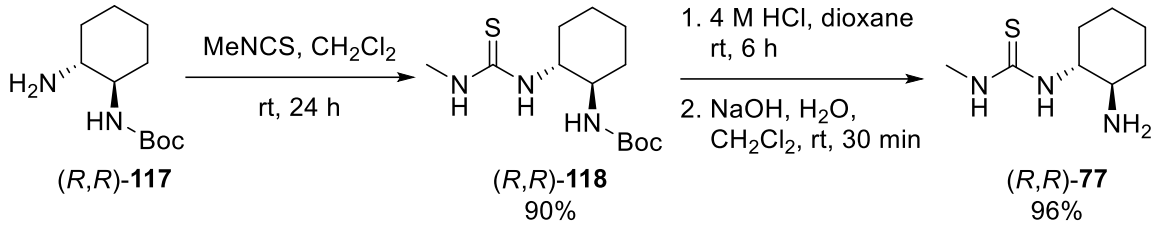
The organocatalytic cyclisation approach would require the exploration of different organocatalysts to those tried by Bonjoch[50] to improve both the yield and enantioselectivity. Thus, we set out to find a small set of catalysts which could prove adequate to allow the asymmetric cyclisation of **108** into **109**. Previous research by Bonjoch and co-workers[50] identified commercially available (*S*)-prolinamide (*S*)-**38** as a possible catalyst for this transformation (see Scheme 1.12). On the other hand, Dixon's[68] thiourea (*R*,*R*)-**77** (see Scheme 1.26) presented itself as a suitable option that could be synthesised in two steps with a single purification. Finally, Tang-and coworkers[89] outlined the use of thiourea (*S*)-**116** which could be also be obtained in two steps with a single purification (Figure 2.6).



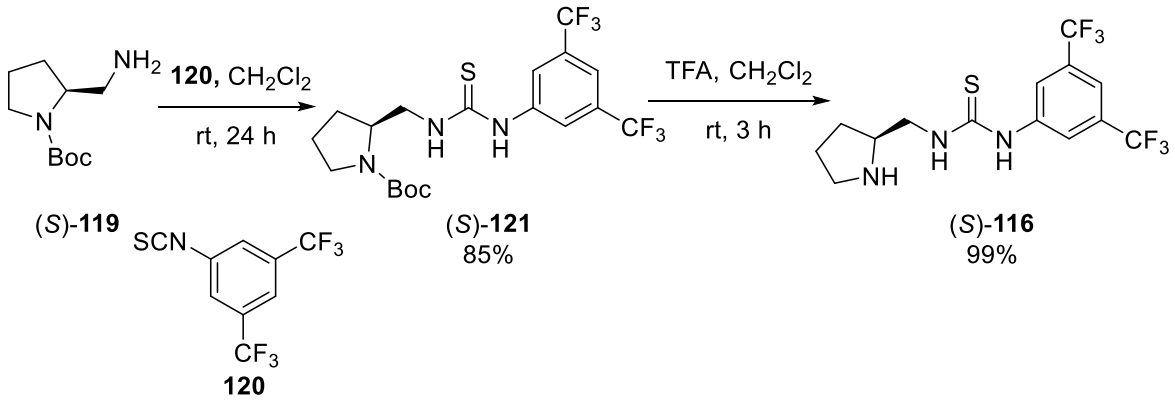
(*S*)-**38** (*R*,*R*)-**77** (*S*)-**116**

Figure 2.6 - Possible organocatalysts identified for the asymmetric cyclisation

Having assembled this short list of possible catalysts, we set out to synthesise them. As previously mentioned, catalyst (*R*,*R*)-**77** could be synthesised in two steps from commercially available *N*-Boc-diamine (*R*,*R*)-**117** and methyl isothiocyanate, which in our hands gave a 90% yield of (*R*,*R*)-**118**. Subsequent deprotection and free-basing of the hydrochloride salt afforded thiourea (*R*,*R*)-**77** in an 86% overall yield (Scheme 2.8). Likewise, thiourea (*S*)-**116** was prepared in two steps by using *N*-Boc pyrrolidine (*S*)-**119** and the appropriate isothiocyanate **120** to afford (*S*)-**121** in 85% yield which was deprotected and free-based quantitatively to afford thiourea (*S*)-**116** (Scheme 2.9). Data for both synthesised catalysts matched those reported in the literature.[68,89]

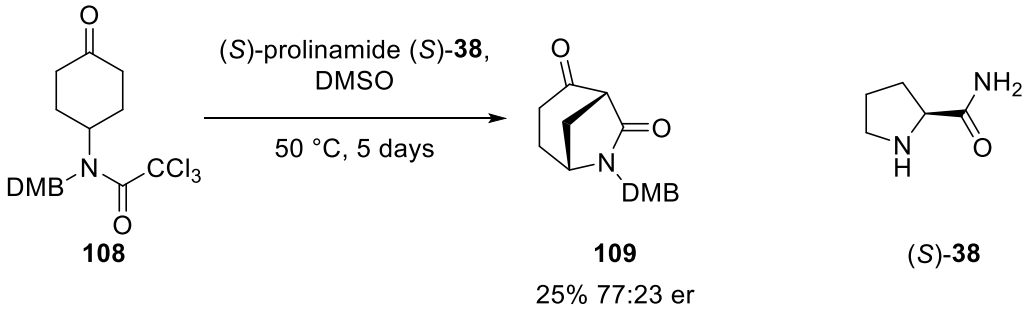


Scheme 2.8



Scheme 2.9

With our catalysts in hand and Bonjoch's precedent, we first attempted the asymmetric cyclisation of **108** into **109** using (*S*)-prolinamide (*S*)-**38**. Thus, use of trichloroamidoketone **108** with (*S*)-prolinamide (*S*)-**38** in DMSO at 50 °C for 5 days gave normorphan **109** in 25% yield and 77:23 er (Scheme 2.10). This was consistent the result previously obtained by Bonjoch[50] with the *N*-Bn analogue (see Scheme 1.12). The er was determined using chiral stationary phase HPLC in comparison with a racemic standard. Unfortunately, we were not able to determine the absolute configuration of the major enantiomer.

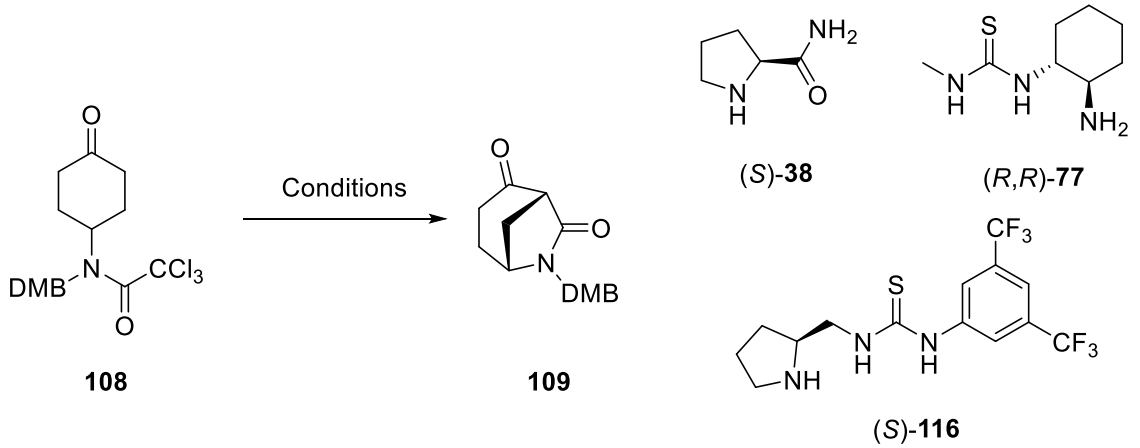


Scheme 2.10

Following this, use of Dixon's thiourea (*R*,*R*)-**77** under the reported conditions[68] was attempted. However, using trichloroamidoketone **108** with thiourea (*R*,*R*)-**77** and PhCOOH in CH_2Cl_2 in a sealed tube at 50 °C for 7 days gave no product (Entry 2). Using our initial conditions of trichloroamidoketone **108** in DMSO with thiourea (*R*,*R*)-**77** at 50 °C for 5 days,

normorphan **109** was obtained in 12% yield and 60:40 er (Entry 3). Finally, use of thiourea (*S*)-**116** as catalyst in DMSO at 50 °C for 5 days gave a 30% yield of normorphan **109** in only 55:45 er (Entry 4). Due to these disappointing yields and enantioselectivities, no further work was carried out on this approach.

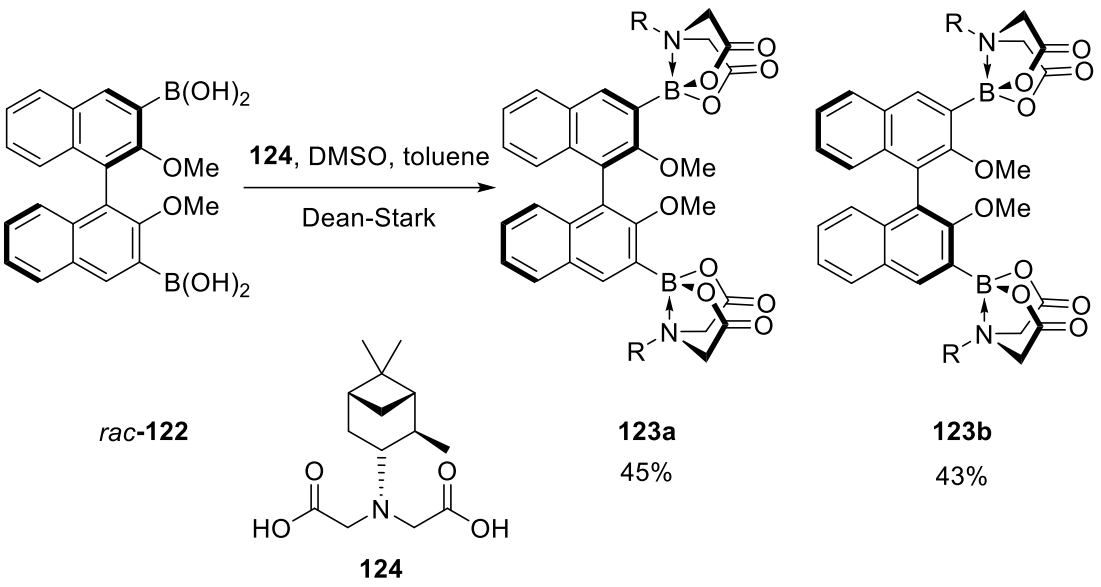
Table 2.4 - Asymmetric cyclisation of **108** into **109**



Entry	Catalyst	Conditions	Time	Yield[a] (%)	er[b]
1	(*S*)-**38** (50 mol%)	DMSO, 50 °C	5 days	25	77:23
2	(*R*,*R*)-**77** (10 mol%)	PhCOOH (0.05 eq.), CH_2Cl_2, 50 °C	7 days	No Reaction	
3	(*R*,*R*)-**77** (50 mol%)	DMSO, 50 °C	5 days	12	60:40
4	(*S*)-**116** (50 mol%)	DMSO, 50 °C	5 days	30	55:45

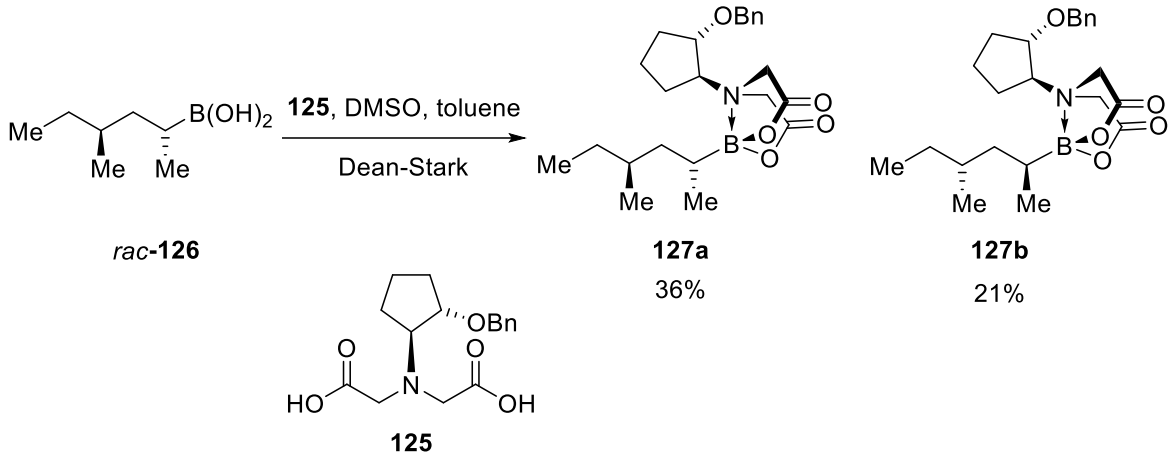
a) % yield after chromatography; b) er determined using chiral stationary phase HPLC

Next, we considered the resolution approach using chiral MIDA derivatives. Previous research by Cheon and co-workers[90] had shown that racemic BINOL-derived boronic acid **122** could be resolved by converting it into their diastereomeric MIDA* boronates **123a** and **123b** with chiral MIDA derivative **124** and separating them by chromatography (Scheme 2.11).



Scheme 2.11

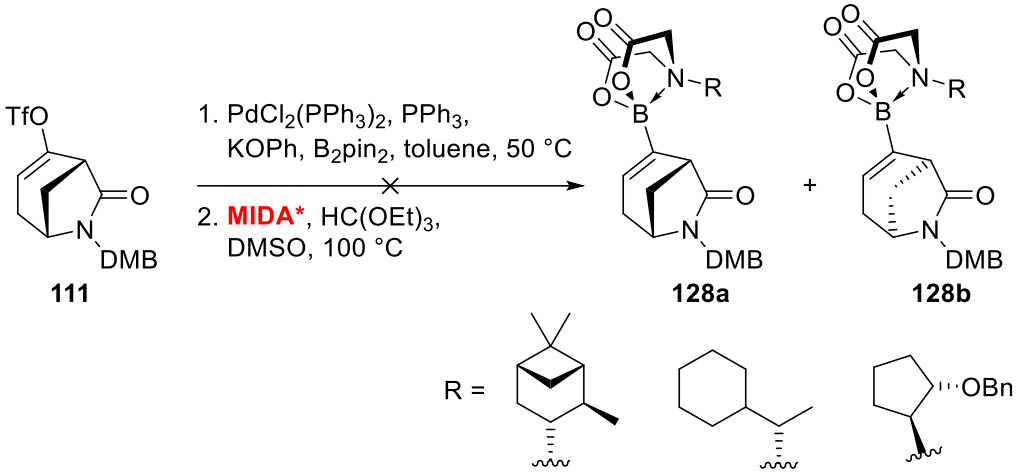
Likewise, Burke and co-workers[81] described the resolution of racemic carbon-centred sp^3 boronic acids using chiral MIDA derivative **125**. In one example, racemic boronic acid *rac*-**126** was reacted with chiral MIDA **125** to give separable B(MIDA*) derivatives **127a** and **127b** in good yields (Scheme 2.12). In Burke's approach, the produced chiral MIDA* boronates **127a**/**127b** were hydrolysed *in situ* in order to perform a stereoretentive Suzuki-Miyaura cross-coupling reaction.



Scheme 2.12

As such, we planned to explore different chiral MIDA* derivatives that would allow us to obtain diastereomeric vinyl MIDA* boronates which we could then separate using chromatography. The chiral MIDA* derivatives utilised by Cheon and Burke were proposed alongside a simpler α-methyl-cyclohexylamine derived MIDA*. However, in our hands, when attempting the transesterification reaction for this substrate with the chiral MIDA

derivatives, negligible formation of the desired vinyl MIDA* boronates **128a** and **128b** was observed. Instead, we observed mainly the formation of alkene **115** (Scheme 2.13). At this point, our attempts at the synthesis of enantioenriched building block **94** were halted.



Scheme 2.13

2.4 Overview

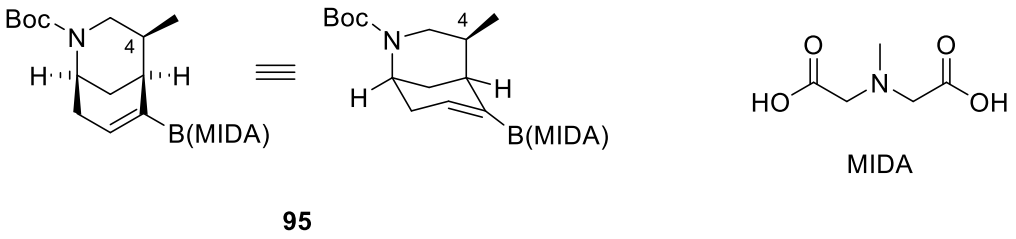
To summarise, the racemic synthesis of normorphan 3-D building block **94** was achieved in 30% overall yield over seven steps. This was achieved *via* a three-step sequence to form amidoketone **108** that was submitted to an organocatalytic cyclisation with pyrrolidine to give the normorphan scaffold. Normorphan **109** was converted into the vinyl triflate **110** and finally into the MIDA boronate **94** by a telescoped borylation-transesterification sequence.

Two different approaches for the synthesis of enantioenriched 3-D building block **94** were also explored. Initial approaches exploiting the organocatalytic cyclisation with three chiral catalysts attempted with little success, with (*S*)-prolinamide (*S*)-**38** affording the best results giving the desired scaffold **109** in 25% yield and 77:23 er. Chiral thioureas developed by Dixon and Tang were also explored with little success. Likewise, attempting to resolve the formed diastereomers of the chiral derived MIDA* boronates was not fruitful since alkene **115** was the main product.

Suzuki-Miyaura cross coupling alongside further functionalisation of the synthesised normorphan 3-D building block towards lead-like compounds is described in Chapter 4.

Chapter 3 Design and Studies Towards the Synthesis of a Morphan-Derived 3-D Building Block

The design and development of synthetic methodology towards accessing 3-D building block **95** (Figure 3.1) is described in this chapter. The design considerations and vector analysis of various derivatives of **95** as well as the proposed synthetic strategy towards the 3-D building block are discussed in Section 3.1. Section 3.2 discusses initial approaches for the synthesis of the building block using *N*-sulfonamide protected derivatives while Section 3.3 describes the synthesis of the normorphan building block **95** from an *N*-Boc protected amine. Finally, an overview of the results presented in this chapter and future work are discussed in Section 3.4.

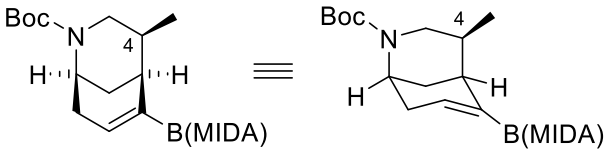


95

Figure 3.1 - Morphan building block **95**.

3.1 Design Considerations, Vector Analysis and Proposed Route for the Synthesis of a Morphan-Derived 3-D Building Block

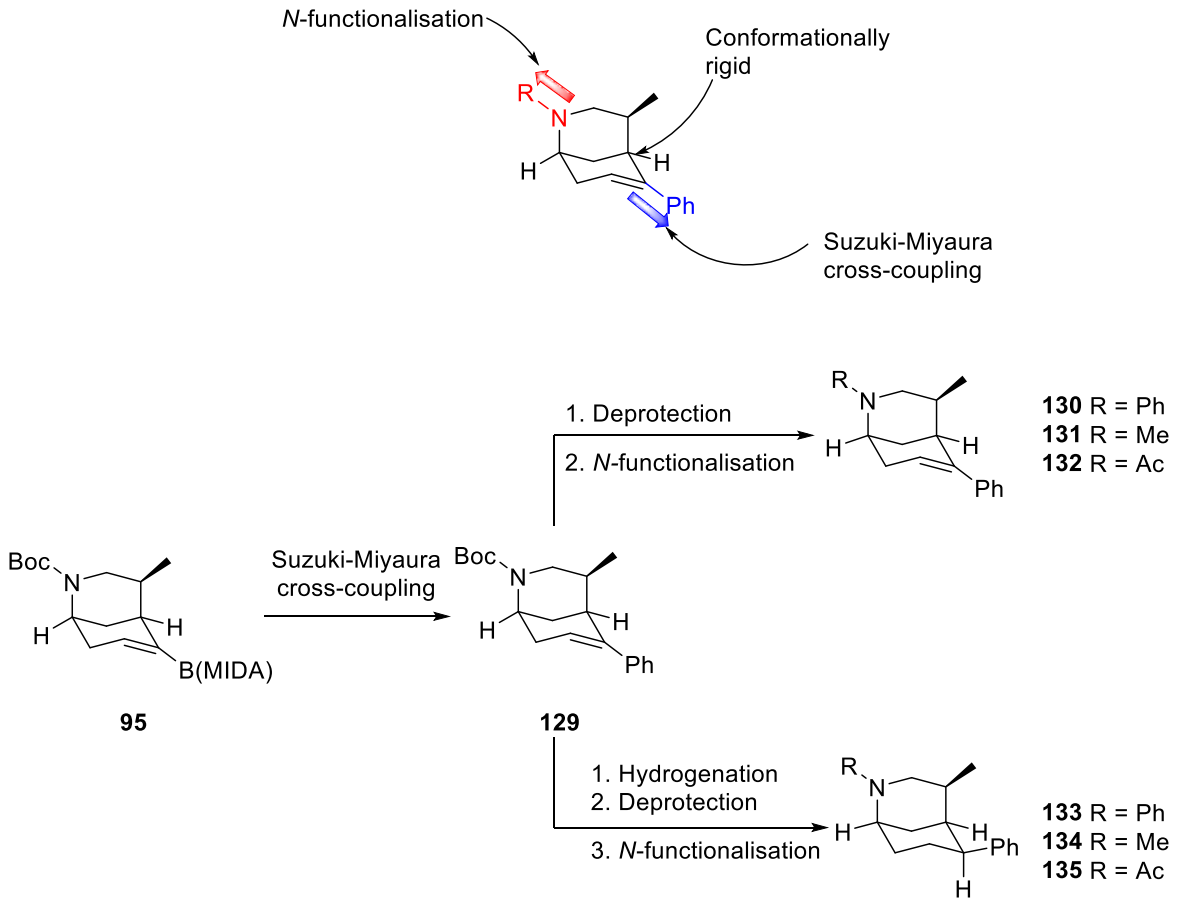
The bicyclo[3.3.1]nonane core is an important structural motif that is found in a diverse range of bioactive molecules and natural products.[55,59,91] As such, many synthetic routes for different substitution patterns on these morphan bicyclic cores have been developed (see Section 1.4). With this in mind, our attention turned to 2-aza-bicyclo[3.3.1]nonane bifunctional building block **95** with a 4-methyl substituent as our next target (Figure 2.2). It was envisaged that building block **95** could be obtained based on some of the previous work developed by Dixon *et al*.[69] which was presented in Section 1.4.2.



95

Figure 3.2 - Morphan building block **95**.

As in the case of normorphan building block **94** (see Section 2.1), it was expected that the bicyclic structure in building block **95** would provide conformational rigidity and a set of predictable functionalisation vectors. With this in mind, the set of elaboration vectors was calculated for a group of structures which we hypothesised could be easily accessed by simple, reliable reactions as previously established for building block **94**. For example, Suzuki-Miyaura cross-coupling on building block **95** should give arylated morphan **129** which could be: (i) immediately deprotected and *N*-functionalised to give amines **130-132** (ii) hydrogenated diastereoselectively then deprotected and *N*-functionalised to give amines **133-135** (Scheme 3.1). Similar to normorphan scaffold **94**, we predicted that hydrogenation on the *exo*-face of the bicyclic scaffold should occur selectively to give the diastereomers shown.



Scheme 3.1

The set of structures shown in Scheme 3.1 gives an idea of the different elaboration vectors that could be achieved with 3-D building block **95**. By following the same procedure as that for normorphan 3-D **94** (see Section 2.1), the set of variation vectors for each molecule was selected and then calculated using Grygorenko and co-workers'[19] algorithm to give the results shown in Figure 3.3.

Similar to the case of normorphan building block **94**, morphan building block **95** has a set of elaboration vectors that lie outside the clusters normally associated with simple 3- to 7-membered ring cyclic scaffolds (see Section 1.2) whilst also having distinct vectors from the set of [3.3.n]propellanes[23] and cyclobutyl-azetidine based scaffolds synthesised by the same group.[19,20,22] The set shows slightly lower conformational rigidity where the structures appear to be more loosely clustered than those previously calculated for normorphan **94** in the *r*-θ plot (Figure 3.3b). This is likely due to the larger ring sizes in the morphan **95**

[3.3.1]nonane bicyclic core compared to the [3.2.1]octane in the normorphan **94**. Just as observed for normorphan **94**, some changes are observed between the hydrogenated products and their parent compounds which are observed by distinct clusters differing mainly by the Φ_1 angle due to the change in hybridisation on the variation point C_1. Additionally, *N*-phenyl derivatives of the scaffold, **130** and **133**, seem to be outliers with regards to angles θ, Φ_1 and Φ_2 (Figure 3.3b,c,d). It is noteworthy that, similar to normorphan **94**, the *N*-Me derivatives of scaffold **95** are ionized at the pH at which the conformer generation is performed (7.4) stopping inversion at the sp^3 nitrogen.

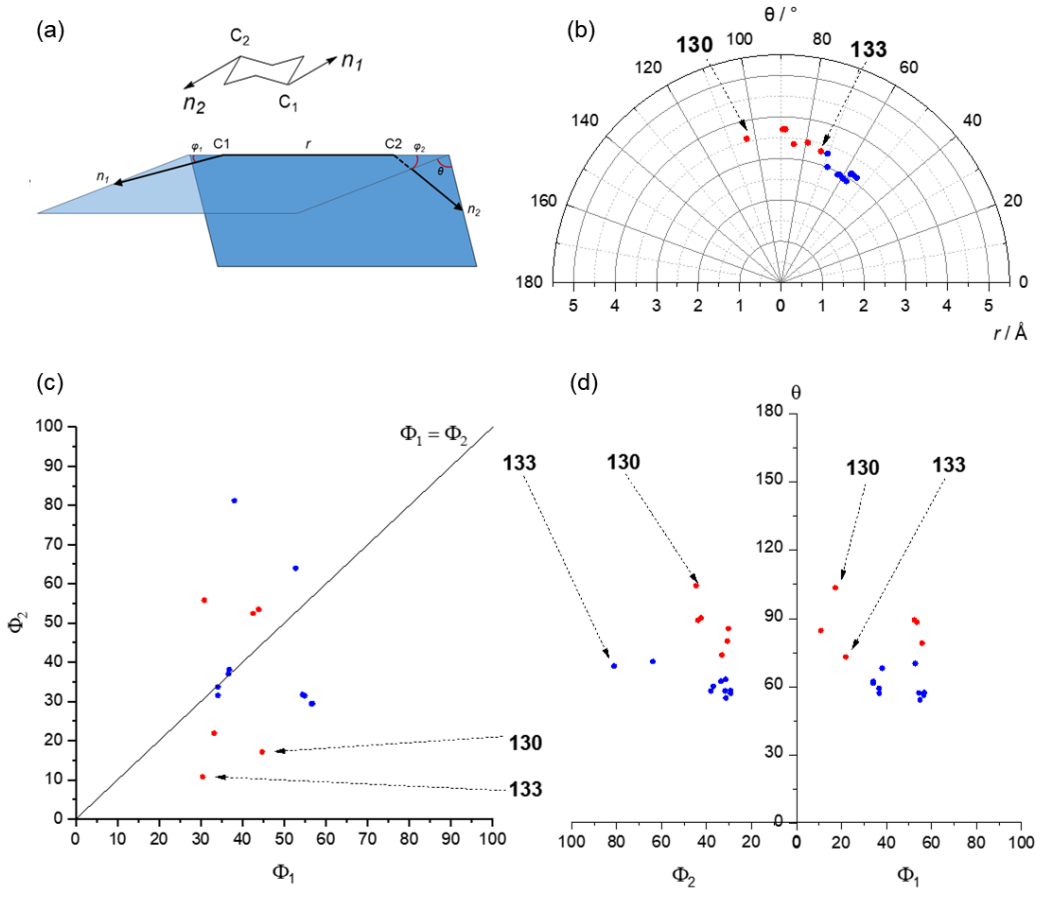
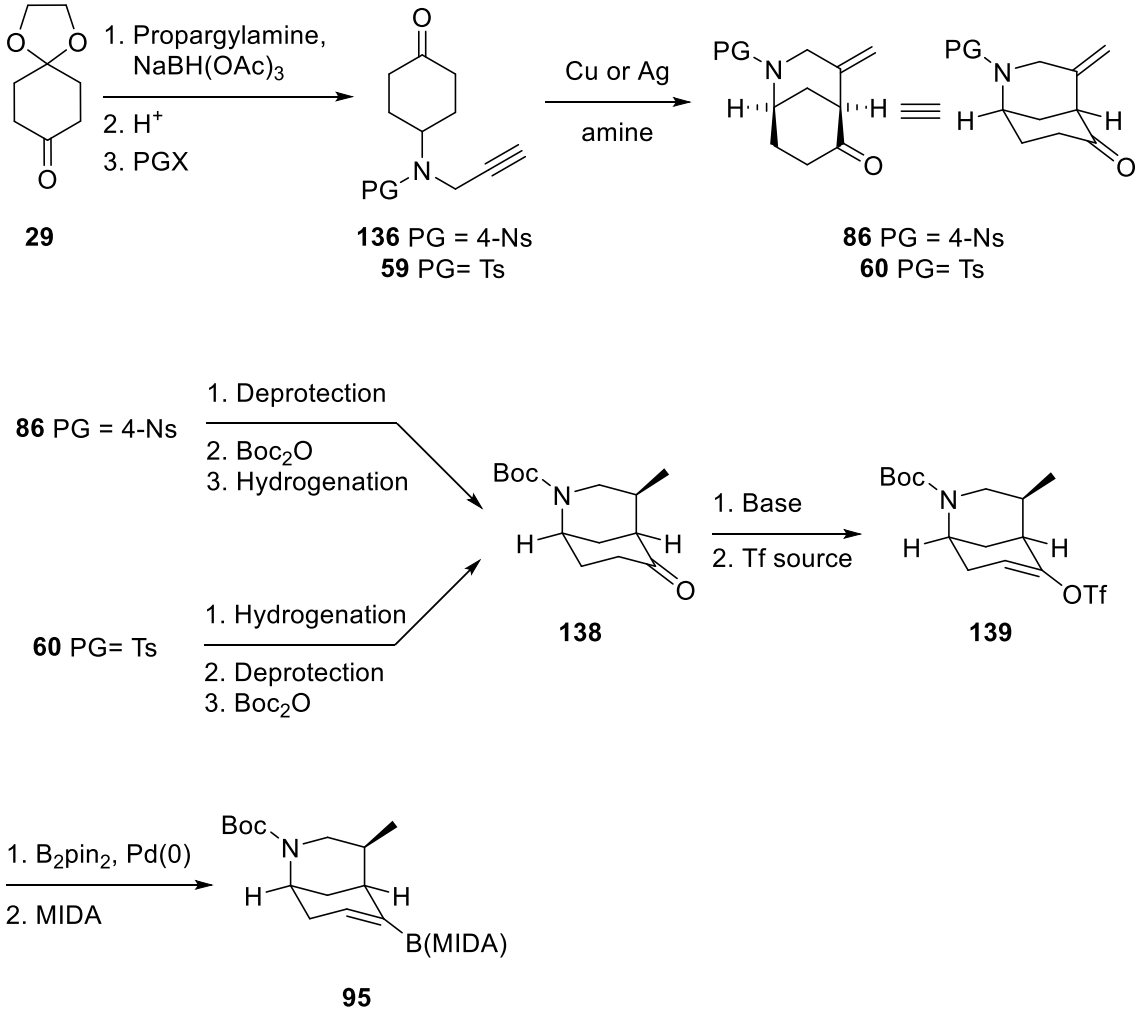


Figure 3.3 - Vector analysis for morphan building block **95** (red) and normorphan **94** (blue) in: a) visual representation of variation vectors; b) *r*-*θ* plot (polar coordinates); c) Φ_1-Φ_2 plot; d) θ-Φ_1/Φ_2 plot.

Our proposed plans to obtain 3-D building block **95** are presented in Scheme 3.2. The scaffold construction is based on previous work by Dixon *et al.*[69] and appeared to offer a quick and reliable way to access both the racemic and the enantioenriched normorphan scaffold from a Ag or Cu and amine co-catalysed cycloisomerisation of an alkyne-linked cyclohexanone (see Scheme 1.20). Following Dixons's approach, we envisaged that amino ketones **136**/**59** could be obtained from monoprotected cyclohexadione **29** in three steps and

then, using the organocatalytic cycloisomerisation, we could obtain morphan scaffolds **137/60**. After the cyclisation, hydrogenation of the exocyclic alkene and sulfonamide protecting group exchange into a *tert*-butyl carbamate to give morphan **138** was proposed for *N*-Ts morphan **60**. For *N*-(4-Ns) morphan **86**, in order to avoid hydrogenation of the NO_2 functionality in the sulfonamide, protecting group exchange and then hydrogenation would be performed. Finally, elaboration into vinyl MIDA boronate **95** was envisioned *via* vinyl triflate formation to give **139**, followed by a Pd-catalysed Miyaura borylation[78] using B_2pin_2 and transesterification sequence to introduce the MIDA group. Additionally, it was expected that our developed route could be applied to enantioenriched morphans **86/60** produced by Dixon's asymmetric variant of the cycloisomerisation to access the enantioenriched building block **95**.



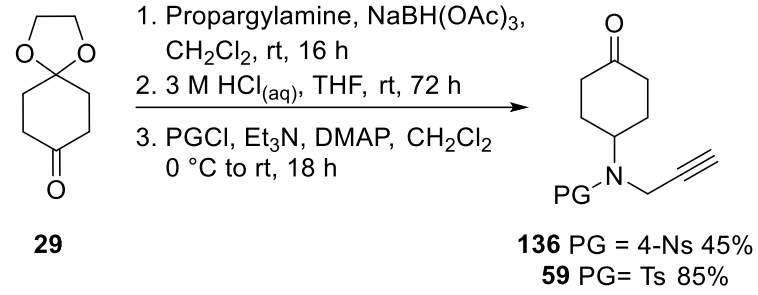
Scheme 3.2

In Dixons's work, sulfonamide protected amines afforded higher yields and better enantioselectivities than carbamate or acetyl protected ones in the enantioselective variant

(see Scheme 1.28). Additionally, it was reported that enantioenriched sulfonamide protected morphans such as **86** and **60** could be easily recrystallised to enantiopurity.[69] As such, despite the possibility of needing harsher conditions for the deprotection of these sulfonamides, we proposed exploring the route starting with an *N*-Ts protected amine and exchanging it to a Boc after the enantiopure building block had been obtained. The use of an *N*-(4-Ns) protected amine was also proposed as it can be more easily removed *via* a S_NAr reaction.[92] It was also ultimately necessary to explore the *N*-Boc protected series of compounds.

3.2 Initial Approaches for the Synthesis of a Morphan-Derived 3-D Building Block Using Sulfonamide Protecting Groups

The first step in the synthesis of the desired building block involved accessing amino ketones **136** and **59**. To this end, the previously reported synthesis by Dixon and co-workers[69] was used. Reductive amination of 1,4-cyclohexadione monoethylene acetal **29** with propargylamine and using $NaBH(OAc)_3$ as a reducing agent quantitatively afforded the crude amine that was, after work-up, sufficiently pure for the next reaction. Hydrolysis of the ketal with 3 M $HCl_{(aq)}$ in THF gave the crude ketone as a sufficiently pure product. This ketone was the diversification point for the protecting group. As such, it was used in sulfonamide formation using either *p*-toluenesulfonyl chloride or 4-nitrobenzenesulfonyl chloride in the presence of Et_3N and catalytic DMAP. After purification by chromatography, *N*-Ts-amino ketone **59** was obtained in 85% yield over the three-step sequence whereas *N*-(4-Ns)-amino ketone **136** was obtained in 45% yield (Scheme 3.3).

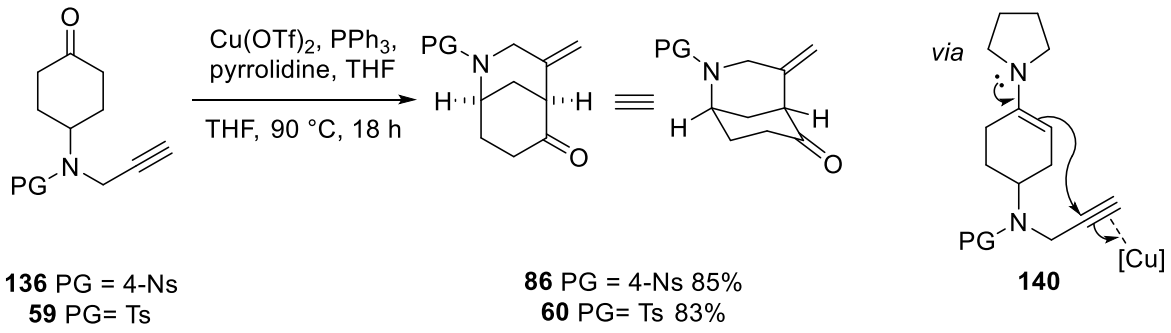


Scheme 3.3

Formation of *N*-(4-Ns)-amino ketone **136** was confirmed by HRMS and both ^1H and ^{13}C NMR spectroscopy where signals for the protons next to nitrogen were observed at δ_H 4.36–4.18 (m, 1H) and 4.18 (d, J = 2.5 Hz, 2H). The 2.5 Hz coupling of the NCH_2 protons can be explained by a long distance ^4J coupling to the alkyne proton. Furthermore, the alkyne proton was observed as a triplet at δ_H 2.17. Incorporation of the sulfonamide group was evidenced by the signals in the aromatic region at δ_H 8.41–8.31 and 8.20–8.08. Likewise, *N*-Ts protected amine **59** showed a similar ^1H NMR spectrum with the signal for the Me group overlapping with another signal at δ_H 2.46–2.33.

Next, amino ketones **136** and **59** were subjected to a copper and amine co-catalysed cycloisomerisation using Dixon's conditions.[69] Thus, reaction of each amino ketone with $Cu(OTf)_2$, PPh_3 and pyrrolidine afforded racemic morphans **86** and **60**. These reactions proceed *via* formation of enamine **140** between pyrrolidine and the ketone, with enamine

140 adding to the Cu-activated alkyne to perform a 6-*exo*-dig cyclisation. This gave racemic morphans **86** and **60** in 85% and 83% yield respectively (Scheme 3.4). In the ^{1}H NMR spectrum of morphan **86**, signals were observed in the alkene region at δ_H 5.14 and 5.07 (both doublets) which were assigned to the $=CH_2$ protons. Additionally, all data from morphans **136** and **59** were consistent with those reported in the literature.[69]



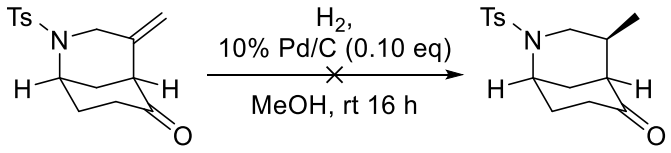
136 PG = 4-Ns
59 PG= Ts

86 PG = 4-Ns 85%
60 PG= Ts 83%

140

Scheme 3.4

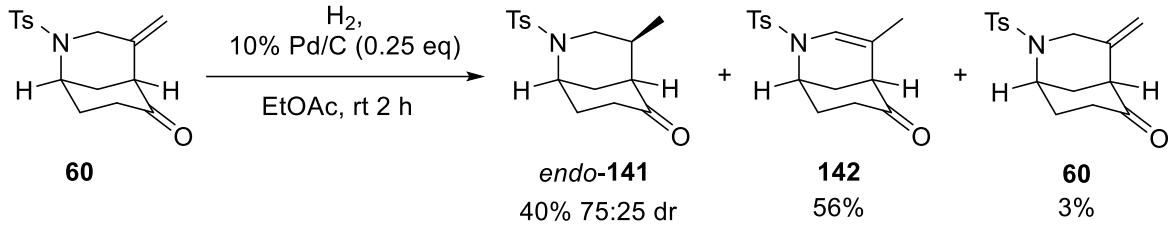
During purification, it became apparent that *N*-(4-Ns) morphan **86** showed poor solubility in most organic solvents with the exception of CH_2Cl_2. This made both purification and further handling of morphan **86** inconvenient, leading us to make the decision of discarding the 4-Ns sulfonamide protecting group in favour of the Ts sulfonamide. With this in mind, we set out to try the planned hydrogenation of the exocyclic double bond. However, our first attempt using a set of conditions reported by Bonjoch for a similar morphan,[65] using normorphan **60**, 10% Pd/C in MeOH at rt, gave a complex mixture of unidentified products (Scheme 3.5).



60 **141**

Scheme 3.5

Nonetheless, a change in solvent from MeOH to EtOAc and increasing the amount of 10% Pd/C from 0.10 eq to 0.25 eq gave a better result. In this way, a 72:25 mixture of diastereomeric morphans *endo*- and *exo*-**141** was isolated in 40% yield. However, we also found that enamine **142** appeared as a by-product of the reaction, isolated in 56% yield as a 95:5 mixture with starting morphan **60** (Scheme 3.6).



Scheme 3.6

Formation of hydrogenated morphans *endo*- and *exo*-**141** was confirmed by both HRMS and NMR spectroscopy and the diastereomeric outcome of this reaction was identified by ^{1}H NMR spectroscopy. In particular, the signals corresponding to the NCH_2 protons in each diastereomer were diagnostic. The major diastereomer showed signals at δ_H 3.83 (dd, J = 13.5, 6.0 Hz, 1H) and 2.81 (dd, J = 13.5, 12.5 Hz, 1H) (Figure 3.3). The signal at δ_H 3.83 was assigned as the equatorial proton, having one large ^{2}J = 13.5 Hz coupling and a small $^{3}J_{eq\text{-}ax}$ = 6.0 Hz coupling to the adjacent CH proton. The other signal, at δ_H 2.81, was assigned as the NCH_2 axial proton and showed two large couplings, one ^{2}J = 13.5 Hz and one $^{3}J_{ax\text{-}ax}$ = 12.5 Hz to the CH proton. These J values were consistent with assigning the major product as *endo*-**141**. In contrast, the minor diastereomer's NCH_2 signals appeared at δ_H 3.25 (dd, J = 12.5, 5.0 Hz, 1H) and 2.98 (dd, J = 12.5, 6.0 Hz, 1H). Each showed one large ^{2}J = 12.5 Hz coupling and a second small $^{3}J_{ax\text{-}eq}$ or $^{3}J_{eq\text{-}eq}$ coupling. This is consistent with the adjacent CH proton being in an equatorial position (axial methyl group) and allowed the assignment of the minor diastereomer as *exo*-**141** (Figure 3.3).

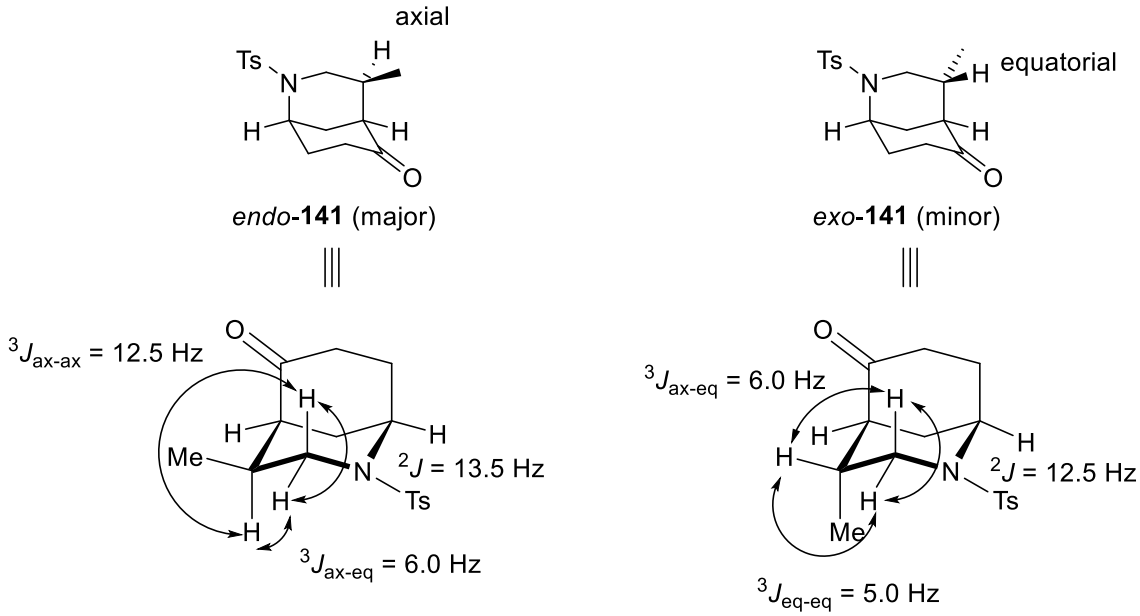
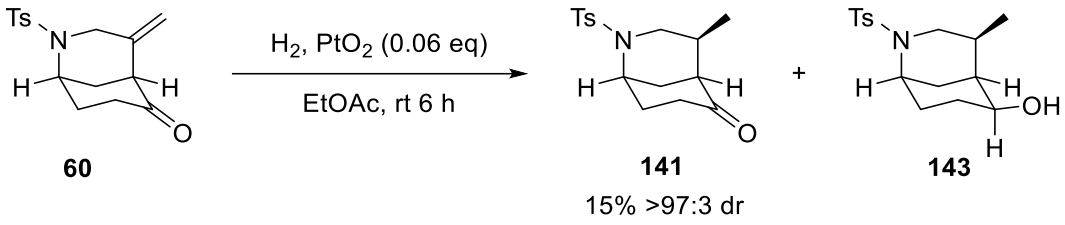


Figure 3.3 - Multiplet analysis for the diastereomeric outcome of the hydrogenation of **60** into **141**.

The major diastereomer is formed by hydrogenation on the less hindered *exo* face of the bicyclic scaffold as we had previously observed for normorphan-derived 3-D building block **94**. On the other hand, the minor diastereomer is presumably formed by a minor competing pathway of *endo* face hydrogenation.

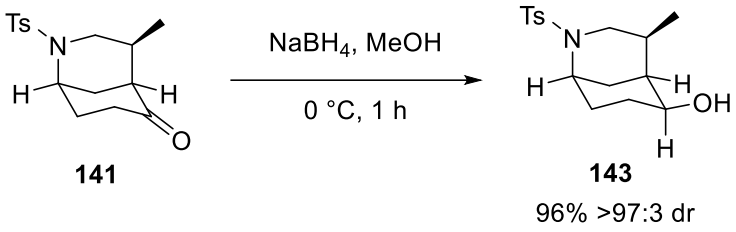
Enamine **142** was also identified by NMR spectroscopic analysis. Namely, the ^{1}H NMR spectrum of enamine **142** showed a signal in the high end of the alkene region at δ_H 6.79 (q, J = 1.5 Hz, 1H) which was assigned as the =CH proton. This had a long distance ^{4}J coupling to a methyl group δ_H 1.62 (d, J = 1.5 Hz, 3H). This, alongside reported NMR spectroscopy data for 6-membered ring *N*-Ts enamines,[93] led us to conclude that enamine **142** was the by-product formed. We hypothesise that enamine **142** is formed by Pd-mediated isomerisation of the alkene to a product stabilized by the strongly electron withdrawing effect of the sulfonamide.

Based on this, we set out to find conditions that would allow us to obtain morphan **141** with good diastereoselectivity while avoiding the formation of enamine **142**. After the conclusion of the work presented in this thesis, it was reported[53] that using high pressures (20 atm) with 10% Pd/C afforded good yields and excellent diastereoselectivity for morphans similar to **60**. Additionally, Li and co-workers[94,95] reported the use of Crabtree's catalyst for the diastereoselective hydrogenation of a diverse set of structurally complex morphans. Likewise, PtO_2 has been reported for the hydrogenation of exocyclic alkenes in sulfonamide and sulfinamide protected pyrrolidines.[96] Thus, we decided to explore the possibility of using PtO_2 for the hydrogenation of morphan **60** into **141**. Using H_2 with PtO_2 in EtOAc at rt for 6 h afforded morphan **141** in 15% yield and >97:3 dr. However, while the formation of enamine **142** was not observed, a new product, which accounted for the remaining mass, was formed (Scheme 3.7). Unfortunately, purification of this by-product was not possible, and this made full characterisation impossible. Nonetheless, HRMS analysis suggested the formation of a product from the addition of 4H to morphan **60**. Additionally, IR spectroscopic analysis of the impure product suggested that reduction of the ketone had occurred since no carbonyl bands were observed. All of this information led us to tentatively assign this by-product as alcohol **143**, formed by the hydrogenation of the exocyclic alkene and ketone moieties in morphan **60**.



Scheme 3.7

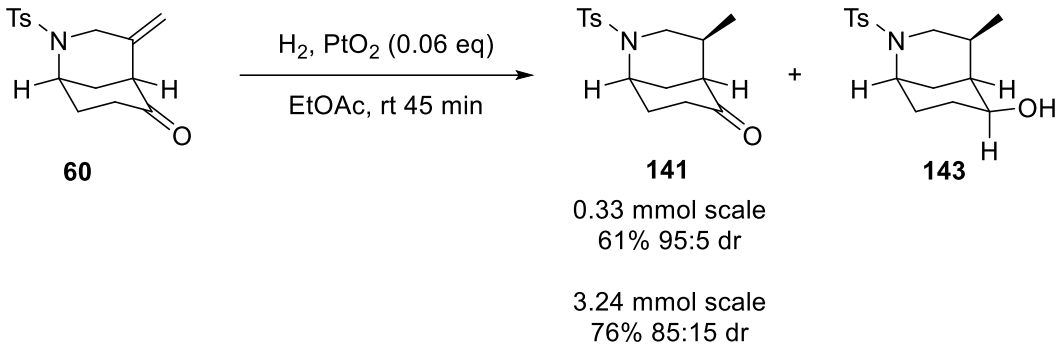
Thus, in order to correctly characterise alcohol **143**, we proposed to reduce the ketone in morphan **141** to form alcohol **143** and compare the NMR spectra of both products. Consequently, $NaBH_4$ reduction of morphan **141** in MeOH at 0 °C for 2 h was attempted. This gave alcohol **143** in 96% yield and >97:3 dr from the product of hydride addition from the *exo*-face of the bicyclic scaffold (Scheme 3.8).



Scheme 3.8

Formation of alcohol **143** was confirmed by HRMS, NMR and IR spectroscopic analysis. The ^{1}H NMR spectrum of alcohol **143** showed a signal at δ_H 3.97 (dddd, J = 11.0, 7.0, 4.5, 1.5 Hz, 1H) which, due to its chemical shift and COSY couplings, was assigned as the HOC*H* proton. Additionally, the coupling pattern, containing a large $^3J_{ax\text{-}ax}$ = 11.0 Hz, two small $^3J_{ax\text{-}eq}$ = 7.0 and 4.5 Hz and a small ^3J coupling to the OH proton led us to assign it as the product from *exo* addition of the hydride into the carbonyl group. Characterisation of alcohol **143** allowed us to confirm that this was the main constituent of the by-product isolated from the PtO_2-catalysed hydrogenation of morphan **60**. Despite this, it was not possible to determine what other compounds were observed alongside it.

We then hypothesised that hydrogenation of the carbonyl group could be slower than hydrogenation of the alkene. Therefore, a shorter reaction time was attempted. Use of PtO_2 in EtOAc at rt for 45 min on a 0.3 mmol scale gave morphan **141** in 61% yield, albeit with a slightly diminished diastereoselectivity of 95:5. Since it was hoped that the product could be recrystalised to diastereopurity, this reaction was scaled up to 3.2 mmol. Unfortunately, while morphan **141** was isolated in 76% yield, the diastereoselectivity was reduced significantly to 85:15 for no obvious reason (Scheme 3.9).



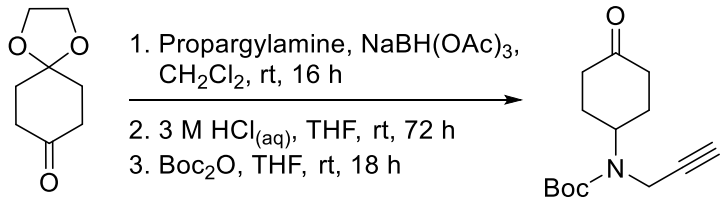
Scheme 3.9

Additionally, the expected reduction of the ketone when submitting normorphan **141** to the conditions for removal of the *N*-Ts protecting group (*i.e.* Li, naphthalene or Mg, MeOH) led us to believe that *N*-Ts protected substrates were not ideal. Consequently, we hypothesised that starting from a *N*-Boc protected substrate might prove to be a more efficient route towards 3-D building block **95**. It was expected that despite *N*-Boc protected substrates giving diminished yields and enantioselectivities in the asymmetric variant of the cyclisation, the shorter overall route would overcome the reduced yield. Additionally, we hoped that the likelihood of vinyl MIDA boronate **95** being crystalline would allow us to recrystallise the final product to enantiopurity.

3.3 Investigation of the Synthesis of a Morphan-Derived 3-D Building Block Using a Boc Protecting Group

Since sulfonamide protected morphans proved non-ideal for the synthesis of 3-D building block **95** and with the aim of streamlining the synthesis by avoiding protecting group exchanges, we moved on to investigate the *N*-Boc protecting group. We envisaged that the *N*-Boc protecting group would be carried throughout the synthesis without any need to be deprotected and, ideally, improving the diastereoselectivity issues in the hydrogenation of the exocyclic alkene.

Thus, amino ketone **144** was synthesised in a three-step synthesis using our general approach. 1,4-Cyclohexadione monoethylene acetal **29** (32.3 mmol scale) was reacted with propargylamine and $NaBH(OAc)_3$ to give the crude amine quantitatively. The ketal protecting group was deprotected with 3 M $HCl_{(aq)}$ in THF to give the crude amino ketone. This crude amino ketone was protected using Boc_2O in THF to give, after chromatography, *N*-Boc amino ketone **144** in 77% yield over the three-step sequence (Scheme 3.10).



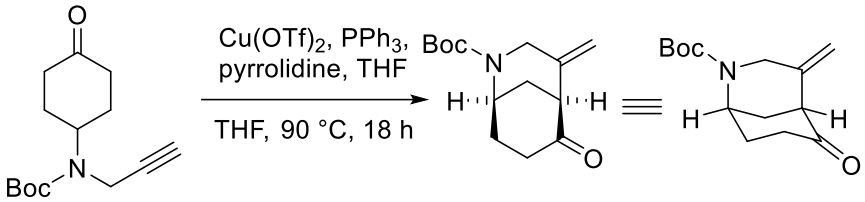
29 **144** 77%

Scheme 3.10

As in the case of amino ketones **136** and **59**, formation of amino ketone **144** was confirmed by HRMS and ^1H and ^{13}C NMR spectroscopic analysis. Namely, despite broadening due to rotamers, signals were observed at δ_H 4.59–4.16 (br m, 1H), 3.92 (br s, 2H) and 2.21–1.86 (m, 3H). These signals were assigned as the NCH, NCH_2 and ≡CH/CH_2 protons respectively. Additionally, a singlet for 9H, assigned as the *t*-Bu group, was observed at δ_H 1.48. The ^{13}C NMR spectrum of amino ketone **144** showed a signal at δ_C 154.8 which was assigned as the C=O from the Boc group with all spectroscopic data matching those reported in the literature.[69]

We then moved on to attempt the racemic cyclisation into morphan **87**. Gratifyingly, using the conditions of $Cu(OTf)_2$, PPh_3 and pyrrolidine and scaling up to 7.96 mmol scale, gave

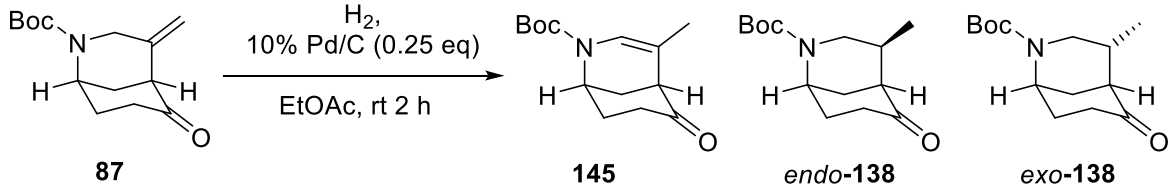
morphan **87** in 77% yield after chromatography (Scheme 3.11). Formation of morphan **87** was evidenced primarily by ^{1}H NMR spectroscopic analysis. Particularly, two rotameric signals were observed for one of the alkene's CHH' protons at δ_H 5.07 (s, 0.55H), 5.04 (s, 0.45H,). A second signal in the alkene region appeared at δ_H 4.99 (s, 1H) and was assigned as the second alkene proton. All spectroscopic data was consistent with those reported in the literature.[69]



144 **87** 77%

Scheme 3.11

Having accessed morphan scaffold **87**, our attention turned to the hydrogenation step which had presented some difficulties for *N*-Ts morphan **60**. With this in mind, the hydrogenation was initially explored using H_2 and 10% Pd/C (0.1 eq) in EtOAc. This gave the crude product which contained (by ^{1}H NMR spectroscopy) a 90:8:2 mixture of enamine **145**, morphan *endo*-**138** and morphan *exo*-**138** (Scheme 3.12). Formation of enamine **145** was evidenced primarily by ^{1}H NMR spectroscopy of the crude product. Namely, the =CH signal from the enamine appeared as two rotameric signals at δ_H 7.03–6.94 (m, 0.5H) and 6.85–6.76 (m, 0.5H). This was confirmed by isolation and characterisation from a subsequent experiment (see Table 3.1).



87 **145** *endo*-**138** *exo*-**138**

90 : 8 : 2

Scheme 3.12

Formation of morphans *endo*- and *exo*-**138** was confirmed by HRMS and NMR spectroscopic analysis. Particularly, the ^{1}H NMR spectrum of the mixture of *N*-Boc morphans *endo*- and *exo*-**138** showed very similar features to those of the *N*-Ts analogues. A 3H doublet at δ_H 0.85 for the Me group of morphan *endo*-**138** was observed. Likewise,

the signals for the NCHH' protons were observed at δ_H 4.04 (dd, *J* = 14.0, 6.5 Hz, 0.5H), 3.92 (dd, *J* = 14.0, 6.5 Hz, 0.5H) and 2.83–2.66 (m, 1H) for morphan *endo*-**138**. However, there was significant broadening of the signals due to the presence of rotamers, which made it difficult to identify the diastereomers by multiplet analysis. Nonetheless, the signals for the NCHH' protons for the minor diastereomer *exo*-**138**, observed at δ_H 3.58 (dd, *J* = 13.5, 5.5 Hz, 0.5H), 3.37 (dd, *J* = 13.5, 5.5 Hz, 0.5H), 3.27 (dd, *J* = 13.5, 5.5 Hz, 0.5H) and 3.12 (dd, *J* = 13.5, 5.5 Hz, 0.5H), point towards the adjacent CH proton being in an equatorial position (Figure 3.4). This, alongside the diastereomeric outcome of the hydrogenation of *N*-Ts protected morphan **60**, suggest that the major diastereomer from the hydrogenation was *endo*-**138**.

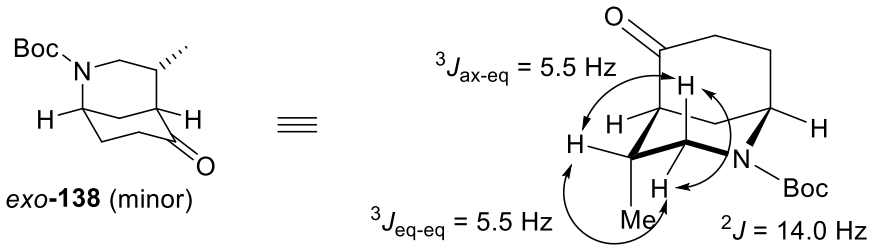
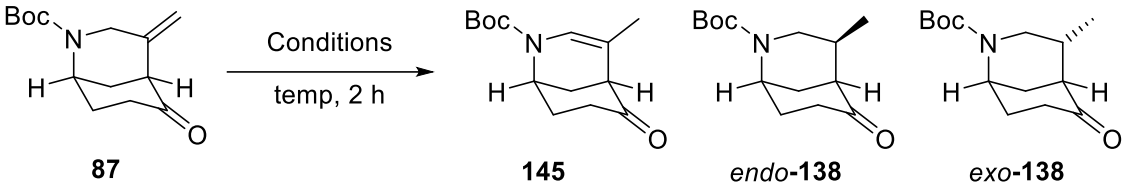


Figure 3.4 - Multiplet analysis for the diastereomeric outcome of the hydrogenation of **87** into **138**.

Since the result from this hydrogenation gave mostly enamine **145**, we moved on to explore different conditions that would allow us access to morphans **138** in good yields and selectivity. Thus, a small optimisation of the hydrogenation was attempted (Table 3.1). A change in solvent from EtOAc to EtOH using 10% Pd/C was initially made. However, after work-up, only a complex mixture of products was observed (Entry 2). Likewise, using AcOH (5 eq) as additive in the hope of protonating the enamine, with 10% Pd/C in EtOAc gave a similar outcome (Entry 3). It has been suggested that transfer hydrogenation with ammonium formate can effectively hydrogenate difficult substrates such as deactivated enamines.[97] Therefore, transfer hydrogenation conditions with $NH_4^+HCO_2^-$ and 10% Pd/C were attempted on morphan **87** but, unfortunately, only a complex mixture of products was observed after work-up (Entry 4).

Table 3.1 - Optimisation of the hydrogenation of morphan **87** into **138**

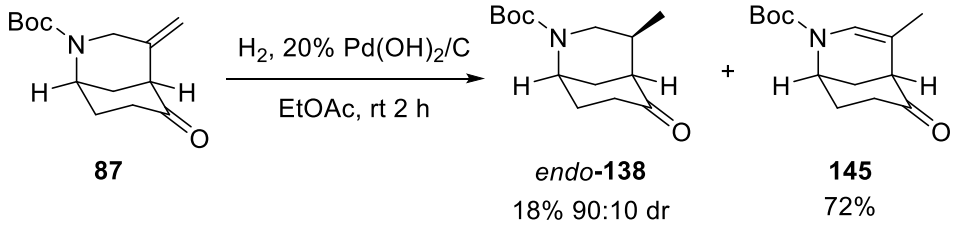


87 **145** ***endo*-138** ***exo*-138**

Entry	Conditions	Temp	**145 : *endo*-138 : *exo*-138**
1	H_2, 10 % Pd/C (0.1 eq), EtOAc	rt	90 : 8 : 2[a]
2	H_2, 10 % Pd/C (0.1 eq), EtOH	rt	Complex mixture[a]
3	H_2, 10 % Pd/C (0.1 eq), AcOH (5.0 eq), EtOAc	rt	Complex mixture[a]
4	10% Pd/C (0.02 eq), NH_4CO_2H (10 eq), MeOH	reflux	Complex mixture[a]

a) Determined by ^{1}H NMR spectroscopy

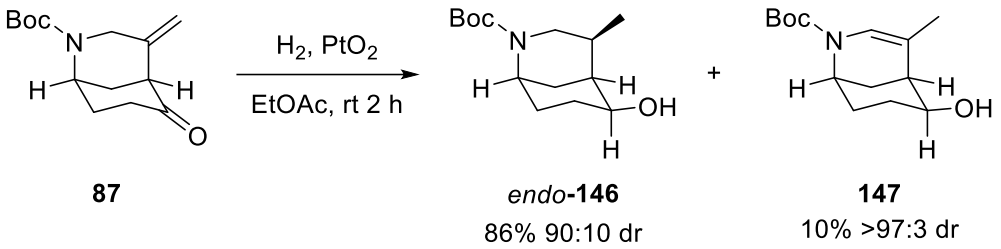
Next, a change of catalyst from 10% Pd/C to 20% $Pd(OH)_2$/C was made while keeping the equivalents constant. In this way, morphan *endo*-**138** was obtained in 18% yield and 90:10 dr with enamine **145** being obtained in 72% yield (Scheme 3.13).



87 ***endo*-138** 18% 90:10 dr **145** 72%

Scheme 3.13

With the poor results obtained with Pd catalysts, we hypothesised that, as in the case with *N*-Ts morphan **60**, hydrogenation of *N*-Boc morphan **87** using PtO_2 would afford the product from the hydrogenation of both the alkene and the ketone. This could hopefully be purified and then oxidised to give the desired morphan *endo*-**138**. Thus, morphan **87** was hydrogenated in the presence of PtO_2 in EtOAc. This gave a 90:10 mixture of alcohols *endo*- and *exo*-**146** in 86% yield, together with its corresponding enamine **147** in 10% yield as a single diastereomer (Scheme 3.14).



87 *endo*-**146** 86% 90:10 dr **147** 10% >97:3 dr

Scheme 3.14

Formation of morphans *endo*- and *exo*-**146** was confirmed by HRMS and NMR spectroscopy and the diastereomeric outcome of the reaction was identified by ^{1}H NMR spectroscopy. In particular, the signals for the NCH_2 protons in each diastereomer were diagnostic, while the CH signal adjacent to the alcohol allowed the assignment of this stereocentre. The major diastereomer showed rotameric signals at δ_H 3.81 (dd, J = 13.5, 6.0 Hz, 0.55H), 3.71 (dd, J = 13.5, 6.0 Hz, 0.45H), 3.02 (dd, J = 13.5, 13.0 Hz, 0.55H) and 2.98 (dd, J = 13.5, 13.0 Hz, 0.45H) for the NCH_2 protons (Figure 3.5). The signals at δ_H 3.81 and 3.71 correspond to the equatorial proton and have a large ^{2}J = 13.5 Hz coupling and a small $^{3}J_{eq\text{-}eq}$ = 6.0 Hz coupling to the adjacent CH. The other signals at δ_H 3.02 and 2.98 correspond to the NCH_2 axial proton and showed two large couplings, one ^{2}J = 13.5 Hz and one $^{3}J_{ax\text{-}ax}$ = 13.0 Hz. This was consistent with the proton adjacent to the NCH_2 protons being in an axial position (Me in an equatorial position) and allowed the assignment of the major diastereomer as morphan *endo*-**146** (Figure 3.5). With respect to the stereoselectivity of the carbonyl reduction, the major diastereomer showed a signal at δ_H 3.97 (ddd, J = 11.0, 5.5, 5.5 Hz, 1H) which was assigned as the C*H*OH proton. This signal shows one large $^{3}J_{ax\text{-}ax}$ = 11.0 Hz coupling to one of the adjacent CH_2 protons and two small $^{3}J_{ax\text{-}eq}$ = 5.5 Hz couplings. This is consistent with this proton being in an axial position (OH equatorial) as shown in Figure 3.5. As in the case of *N*-Ts morphan **141** (see Section 3.2), this outcome is presumably derived from a major pathway involving hydrogenation from the *exo*-face of the bicyclic core on both the alkene and the ketone functionalities. We hypothesised that the minor diastereomer in the hydrogenation of the exocyclic alkene was being formed by a minor, competing pathway of hydroxyl-directed hydrogenation.

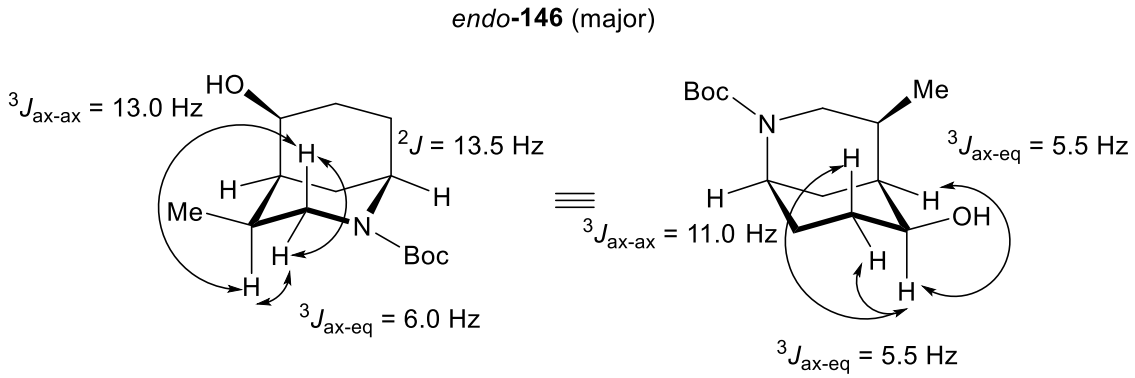
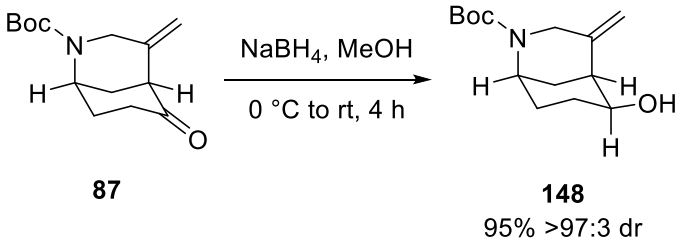


Figure 3.5 - Multiplet analysis for the diastereomeric outcome of the hydrogenation of **87** into **146**

In a similar way, the formation of enamine **147** was confirmed by NMR spectroscopic analysis. The ^{1}H NMR spectrum of enamine **147** showed characteristic signals similar to those observed for enamine **145**. Namely, rotameric signals were observed at δ_H 6.94 (s, 0.5H) and 6.77 (s, 0.5H) and were assigned as the =CH proton. The signal for the CH proton adjacent to the OH appeared at δ_H 3.86 (dddd, J = 10.0, 4.5, 4.5, 4.5 Hz, 1H) which, by the same analysis as that for morphan *endo*-**146** (see Figure 3.5), confirms that the alcohol is in an equatorial position.

In order to explore improving the diastereoselectivity, we decided to investigate reduction of the ketone into the alcohol first and then study the hydrogenation of the exocyclic alkene. In addition, protection of the alcohol and hydrogenation would allow us to explore the hypothesis of hydroxyl-directed hydrogenation. Consequently, morphan **87** was reduced with $NaBH_4$ in MeOH to give, after work-up, alcohol **148** as a sufficiently pure product in 95% yield as a single diastereomer (Scheme 3.15). The ^{1}H NMR spectrum of alcohol **148** showed the signal for the CH proton adjacent to the alcohol at δ_H 3.72–3.59 (m, 1H). However, although the diastereomeric outcome of the reduction could not be determined directly by ^{1}H NMR spectroscopy of alcohol **148**, it was possible to determine it from the product of the subsequent conversion of alcohol **148** into morphan *endo*-**146**.

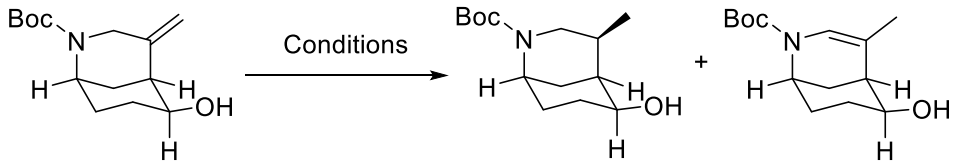


87 **148**
95% >97:3 dr

Scheme 3.15

A range of conditions was then explored for the hydrogenation of morphan **148** (Table 3.2). We first attempted the use of 10% Pd/C as a catalyst for the hydrogenation. However, when morphan **148** was hydrogenated in the presence of 10% Pd/C as catalyst in EtOH, only enamine **147** was obtained in 96% yield (Entry 1). We hypothesised that using AcOH as an additive could protonate enamine **147** thus making the overall reduction easier. Nonetheless, when morphan **148** was hydrogenated using 10% Pd/C as catalyst in the presence of AcOH only a complex mixture of products were observed after work-up (Entry 2). It was then decided to change the catalyst to 20% $Pd(OH)_2/C$. Using this catalyst, enamine **147** was obtained as the single product of the hydrogenation in 94% yield after work-up (Entry 3). As previously mentioned, it has been suggested that transfer hydrogenation conditions can be effective for unreactive alkenes.[97] Using these conditions, a 75:25 mixture of morphans *endo*- and *exo*-**146** was isolated in 42% yield and enamine **147** was isolated in 55% yield (Entry 4). It was then decided to use PtO_2 as the catalyst since it had previously shown the highest efficiency for the hydrogenation of ketone substrates (see Scheme 3.9 and Scheme 3.14). Gratifyingly, hydrogenation of morphan **148** using PtO_2 as catalyst gave morphan *endo*-**146** in 90% yield and 75:25 dr with enamine **147** being isolated in only 6% yield (Entry 5).

Table 3.2 - Hydrogenation of morphan **148**

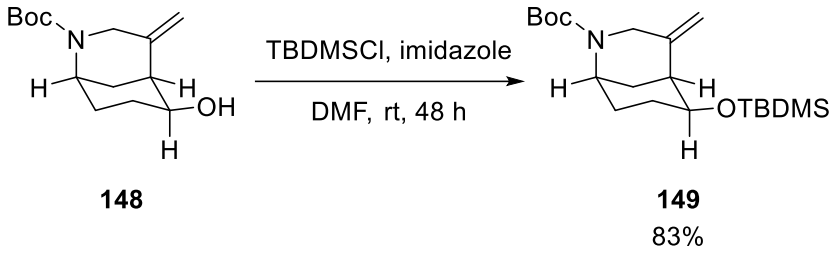


148 *endo*-**146** **147**

Entry	Conditions	Temp (°C)	146[a]	147[a]
1	H_2, 10% Pd/C, EtOH, 2 h	rt	0%	96%
2	H_2, 10% Pd/C, AcOH, EtOH, 2 h	rt	Complex mixture[b]	
3	H_2, 20% $Pd(OH)_2$, EtOAc, 2h	rt	0%	94%
4	10% Pd/C, $NH_4^+HCO_2^-$, MeOH, 2 h	reflux	42% 75:25 dr[c]	55%
5	H_2, PtO_2, EtOAc, 2 h	rt	90% 75:25 dr[c]	6%

a) isolated % yield; b) by ^{1}H NMR spectroscopy of the crude product; c) determined by ^{1}H NMR spectroscopy

The diminished diastereoselectivity in the hydrogenation of morphan **148** (Table 3.2, Entries 4 and 5) with respect to morphan **87** (Table 3.1, Entry 1) supports the hypothesis that the minor diastereomer is generated by a competing pathway of hydroxyl-directed hydrogenation. Presumably, starting from alcohol **148**, this pathway is more significant. Consequently, we decided that protecting the hydroxyl group in morphan **148** with a bulky group such as TBDMS would hinder this minor pathway both sterically and by impeding coordination of the hydroxyl group to the metal catalyst. As such, morphan **148** was *O*-protected by using TBDMS and imidazole in DMF. This gave *O*-TBDMS morphan **149** in 83% yield (Scheme 3.16).



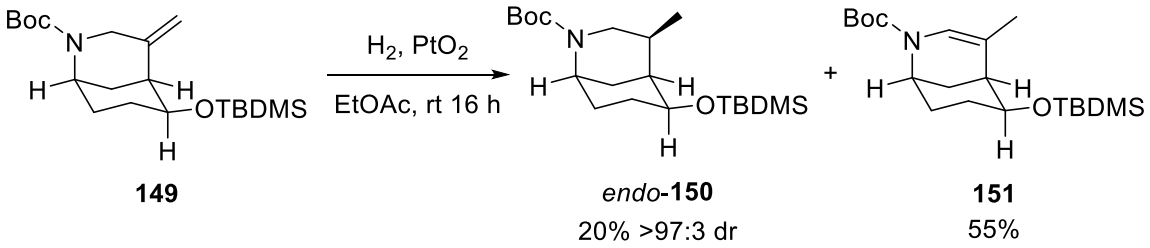
148 **149**
83%

Scheme 3.16

Formation of *O*-TBDMS morphan **149** was confirmed by HRMS and NMR spectroscopy. In particular, the ^{1}H NMR spectrum of morphan **149** showed the expected signals for the =CHH' protons at δ_H 5.02–4.96 (m, 1H) and 4.95–4.89 (m, 1H). Signals were also observed at δ_H 0.87 (s, 9H) and 0.07–0.03 (m, 6H) which were assigned as the *t*-Bu and Me groups from the TBDMS group. On the other hand, the ^{13}C NMR spectrum of morphan **149** showed four signals at δ_C –4.3 to –4.4 which were assigned to the Me groups adjacent to the Si.

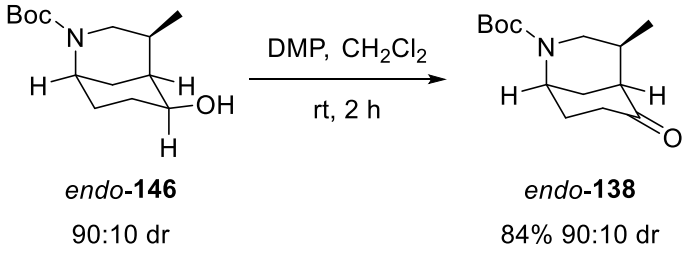
O-TBDMS morphan **149** was then hydrogenated using our previously established conditions with H_2 and PtO_2 as catalyst at rt for 16 h. Use of these conditions with morphan **149** gave hydrogenated morphan *endo*-**150** in 20% yield as a single diastereomer and enamine **151** in 55% yield (Scheme 3.17). The ^{1}H NMR spectrum of morphan **150** showed rotameric signals at δ_H 3.84 (dd, *J* = 13.5, 6.0 Hz, 0.5H), 3.73 (dd, *J* = 13.5, 6.0 Hz, 0.5H), 3.07 (dd, *J* = 13.5, 13.0 Hz, 0.5H) and 3.03 (dd, *J* = 13.5, 13.0 Hz, 0.5H) which were assigned as the NCHH' protons. Following the same analysis as that for morphans *endo*-**138** and -*endo*-**146** (see Figure 3.4 and Figure 3.6) allowed us to conclude that the diastereomer formed is the *endo* product. Formation of enamine **151** was also confirmed by HRMS and NMR analysis. Particularly, the ^{1}H NMR spectrum of enamine **151** showed characteristic rotameric signals at δ_H 6.88 (s, 0.4H) and 6.73 (s, 0.6H) which were assigned to the =CH proton of the enamine

and the Me signal was observed at δ_H 1.78–1.75 (m, 3H). On the other hand, the ^{13}C NMR spectrum showed signals at δ_C 122.2, 121.8, 115.3 and 114.4 with the first two being assigned as the =C carbon and the other two as the =CH, the signals doubling up due to rotamers.



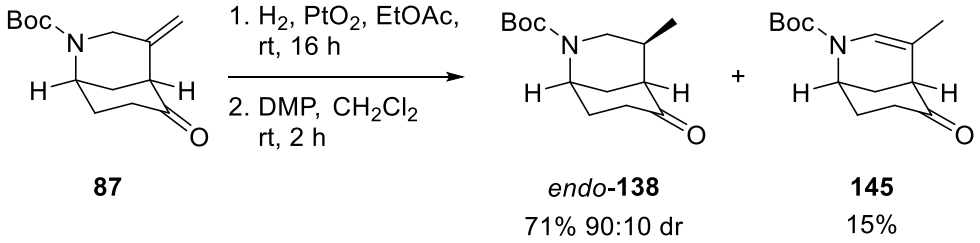
Scheme 3.17

The diastereomeric outcome of this hydrogenation, namely the formation of morphan *endo*-**150** in >97:3 dr, suggests that, due to the absence of a hydroxyl-directed pathway, the reaction is completely sterically controlled. This therefore supports our previously outlined hypothesis that the minor product, *exo*-**146**, from the hydrogenation of **148** is being formed by a minor pathway of hydroxyl-directed hydrogenation. However, our efforts to improve the outcome of the hydrogenation using TBDMS protection did not prove of much use since, despite increasing the diastereoselectivity of the reaction, increasing the steric bulk on the *endo* face of morphan **149** also led to significantly diminished yields. Thus, we decided that converting morphan **87** into a 90:10 mixture of alcohols *endo*-**146** and *exo*-**146** by hydrogenation (see Scheme 3.14) and then oxidising this mixture back into the ketone using Dess-Martin periodinane (DMP) would be the best course of action. We hypothesised that the vinyl MIDA boronate, which we expected to be a crystalline solid, could be recrystallised to diastereopurity. As such, we first attempted the oxidation of a 90:10 mixture of alcohols *endo*-**146** and *exo*-**146** using DMP in CH_2Cl_2 at rt for 2 h. This gave a 90:10 mixture of keto-morphans *endo*-**138** and *exo*-**138** in 84% yield (Scheme 3.18). Spectroscopic data for keto-morphans **138** were consistent with previously obtained samples (see Scheme 3.12).



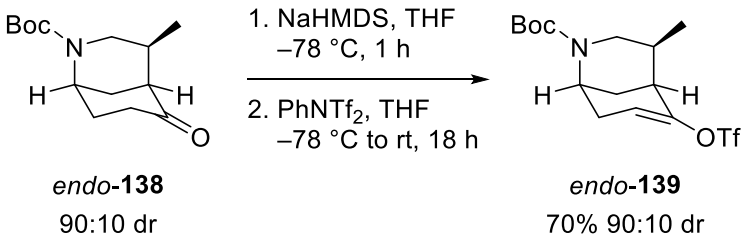
Scheme 3.18

In order to facilitate purification and increase the yield, we investigated whether this oxidation could be performed on the crude product from the hydrogenation of morphan **87**. In this way, morphan **87** was hydrogenated using H_2 and PtO_2 in EtOAc and the crude product from this reaction was treated with DMP in CH_2Cl_2. Gratifyingly, this gave morphan *endo*-**138** in 71% yield and 90:10 dr with a single purification while enamine **145** was obtained in 15% yield (Scheme 3.19). This represents a negligible decrease in yield, which on top of the easier purification constitutes a useful alternative for the synthesis of a 90:10 mixture of morphans *endo*- and *exo*-**138**.



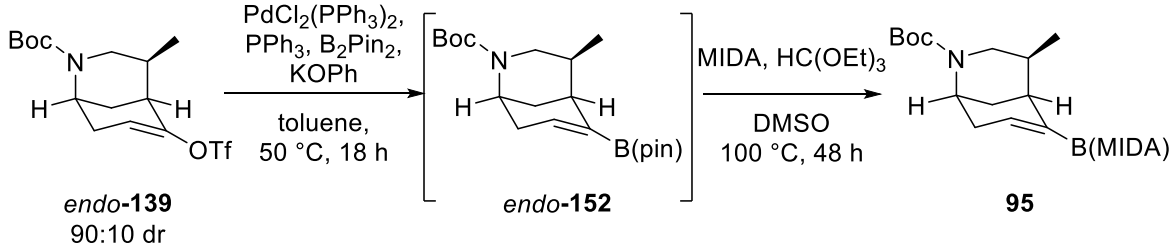
Scheme 3.19

The next step involved turning the ketone in morphans **138** into a vinyl triflate. This was attempted using NaHMDS and $PhNTf_2$, previously identified from our work on the normorphan scaffold (see Section 2.2). Thus, morphan *endo*-**138** (90:10 dr) was treated with NaHMDS in THF at –78 °C for 1 h and the formed enolate was trapped with $PhNTf_2$ from –78 °C to rt for 18 h. In this way, vinyl triflate *endo*-**139** (90:10 dr) was obtained in 70% yield after chromatography (Scheme 3.20). Formation of vinyl triflates *endo*- and *exo*-**139** was confirmed by HRMS and NMR spectroscopy. In particular, the ^{1}H NMR spectrum of vinyl triflates **139** showed a signal at δ_H 5.92 (dd, J = 4.0, 4.0 Hz) which was assigned to the =CH proton of the major diastereomer. On the other hand, the ^{13}C NMR spectrum of vinyl triflate *endo*-**139** showed a quartet at δ_C 118.6 (J = 320 Hz) which was assigned as the CF_3 carbon.



Scheme 3.20

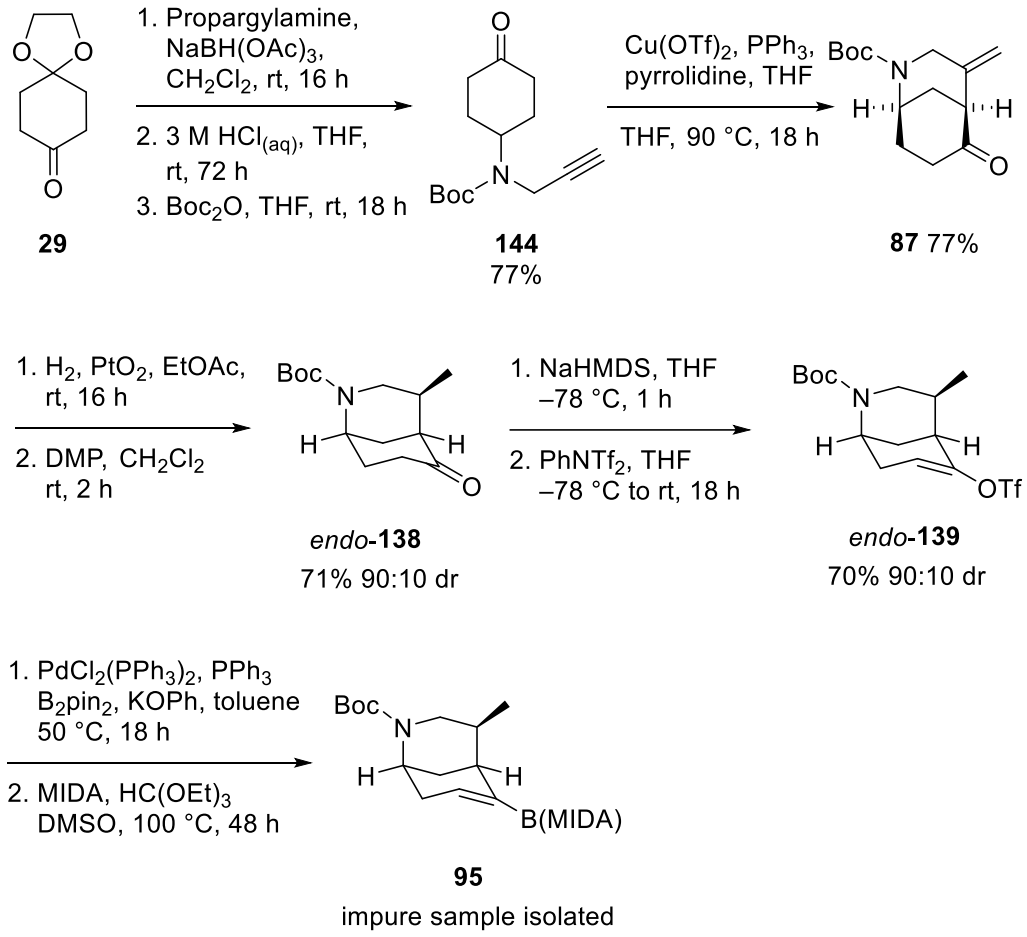
The last step involved turning vinyl triflate *endo*-**139** (90:10 dr) into vinyl pinacol boronate *endo*-**152** and this into vinyl MIDA boronate **95**. We envisaged doing this with the previously used method of a Miyaura borylation using B_2pin_2, $PdCl_2(PPh_3)_2$, PPh_3 and KOPh to form vinyl pinacol boronate *endo*-**152**. Then, based on previous experience with normorphan 3-D building block **94** (see Section 2.2), taking the crude pinacol boronate *endo*-**152** and transesterifying it into vinyl MIDA boronate **95** using MIDA and $HC(OEt)_3$. Thus, vinyl triflate *endo*-**139** (90:10 dr) was treated with B_2pin_2, $PdCl_2(PPh_3)_2$, PPh_3 and KOPh in toluene at rt for 18 h and the crude product was treated with MIDA and $HC(OEt)_3$ in DMSO at 100 °C for 48 h. However, after chromatography, vinyl MIDA boronate **95** was isolated as a mixture with unidentified products (Scheme 3.21). Nonetheless, the formation of vinyl MIDA boronate **95** was confirmed by both HRMS and NMR spectroscopy. The ^{1}H NMR spectrum of vinyl MIDA boronate **95** showed a signal at δ_H 6.22–6.17 (m, 1H) which was assigned as the =CH proton. In addition, rotameric signals for one of the NCHH' protons were observed at δ_H 4.51–4.43 (m, 0.6H), 4.35–4.30 (m, 0.4H). Unfortunately, due to time constraints and the overall impracticality of the synthesis of morphan-derived building block **95**, no further attempts at synthesising vinyl MIDA boronate **95** were made.



endo-**139** 90:10 dr — *endo*-**152** — **95**

Scheme 3.21

Thus, the synthesis of an impure sample of vinyl MIDA boronate **95** was achieved using the *N*-Boc protected series of compounds. The route was accomplished up to vinyl triflate *endo*-**139** with a 29% overall yield and 90:10 dr (Scheme 3.22). This was achieved using a three-step sequence to give amino ketone **144**, followed by a Cu/amine co-catalysed cycloisomerisation into morphan **87**, diastereoselective hydrogenation and oxidation into morphan **138** and finishing with a vinyl triflate formation to give **139**. Borylation-transesterification into vinyl MIDA boronate **95** was also attempted, but impure vinyl MIDA boronate **95** was isolated. Further exploration into the diastereoselective hydrogenation was also performed by studying alcohol and *O*-TBDMS derivatives of morphan **87.**



29 **144** 77% **87** 77%

endo-**138** 71% 90:10 dr *endo*-**139** 70% 90:10 dr

95 impure sample isolated

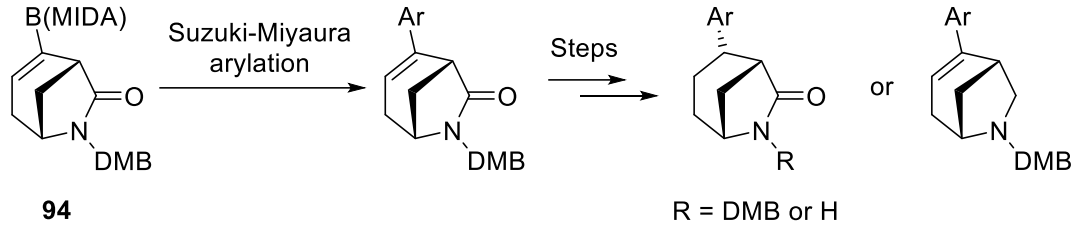
Scheme 3.22

3.4 Overview

To summarise, the synthesis of a morphan-derived 3-D building block was partially achieved. Initially, use of a sulfonamide protected series of compounds was explored with limited success. A change into the *N*-Boc protected series of compounds afforded the late-stage vinyl triflate *endo*-**139** in 29% overall yield over seven steps. This was achieved by a three-step sequence to give aminoketone **144** which was cyclised with pyrrolidine and a $Cu(OTf)_2$ catalyst to afford the morphan scaffold which was subsequently converted into vinyl triflate *endo*-**139**. Formation of the objective vinyl MIDA boronate **95** was attempted but only an impure sample was obtained. Different approaches for the hydrogenation of both the *N*-Ts and *N*-Boc substrates were investigated. Reduction of the ketone moiety and protection of the formed alcohol as an *O*-TBDMS group were explored with little success.

Chapter 4 Suzuki-Miyaura Cross-Coupling and Further Functionalisation of the Normorphan-derived 3-D Building Block

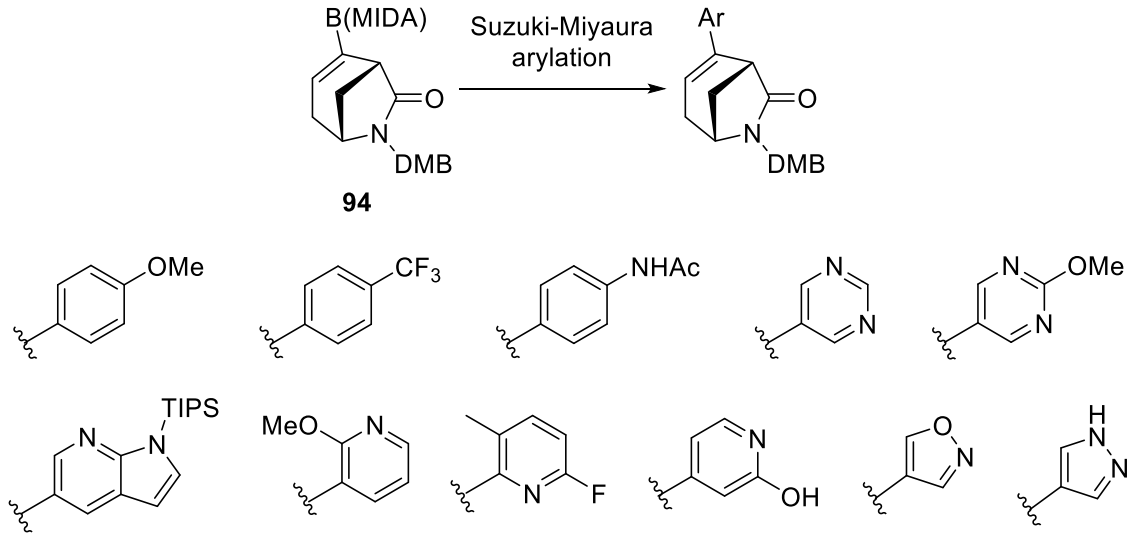
In order to demonstrate the utility of normorphan-derived building block **94** in the construction of drug-like and lead-like compounds for medicinal chemistry, this Chapter summarises some of the functionalisation possibilities that were explored (Scheme 4.1). Section 4.1 focuses on Suzuki-Miyaura cross-coupling with the vinyl MIDA boronate handle on building block **94**. Section 4.2 shows further functionalisation of the 3-D building block including hydrogenation of the alkene, reduction of the amide moiety and deprotection of the *N*-DMB group. Finally, Section 4.3 provides an overview of the functionalisation possibilities that were explored.



Scheme 4.1

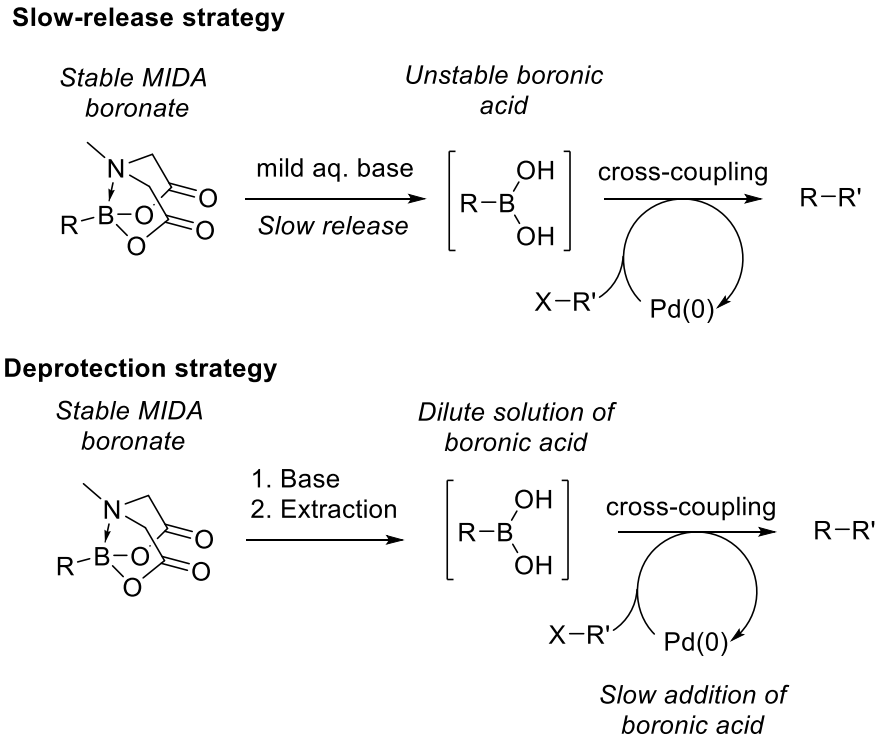
4.1 Suzuki-Miyaura Arylations of the Normorphan-Derived 3-D Building Block

With the aim to showcase the functionalisation possibilities of 3-D building block **94**, our attention turned to Suzuki-Miyaura cross-couplings using the vinyl MIDA boronate installed in the building block (Scheme 4.2). Initially, it was planned to explore conditions for the cross-coupling using 4-bromoanisole and 4-bromobenzotrifluoride as coupling partners. Then, a variety of aromatic and heteroaromatic aryl bromides would be explored. It was also desired to include a set of aryl bromides based on FragLites, introduced by Waring and co-workers, [98] as medicinally-relevant aryl groups.



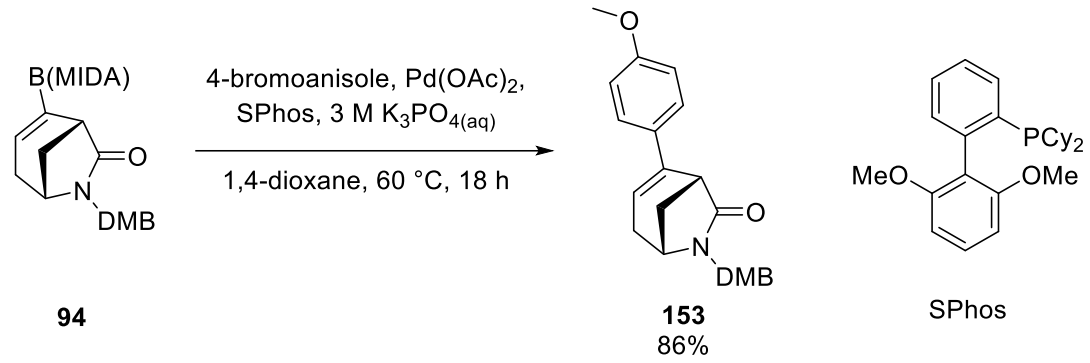
Scheme 4.2

Various sets of conditions have been developed for the use of MIDA boronates in Suzuki-Miyaura cross-couplings, which are essentially classified into those that use a slow-release strategy and a deprotection strategy.[99] The slow-release strategy, developed by Burke and coworkers,[82] hydrolyses the MIDA boronate *in situ* under standard aqueous Suzuki-Miyaura conditions to generate the free boronic acid which is subsequently transmetallated into the catalytic cycle to minimize by-products generated in the presence of large quantities of free boronic acid in the reaction media (Scheme 4.3). On the other hand, the deprotection strategy, mainly used in iterative cross-coupling[100] and anhydrous Suzuki-Miyaura cross-couplings[81] relies on the full release of the boronic acid into a dilute solution for its further use in the cross-coupling by slow addition into the reaction media (Scheme 4.3).



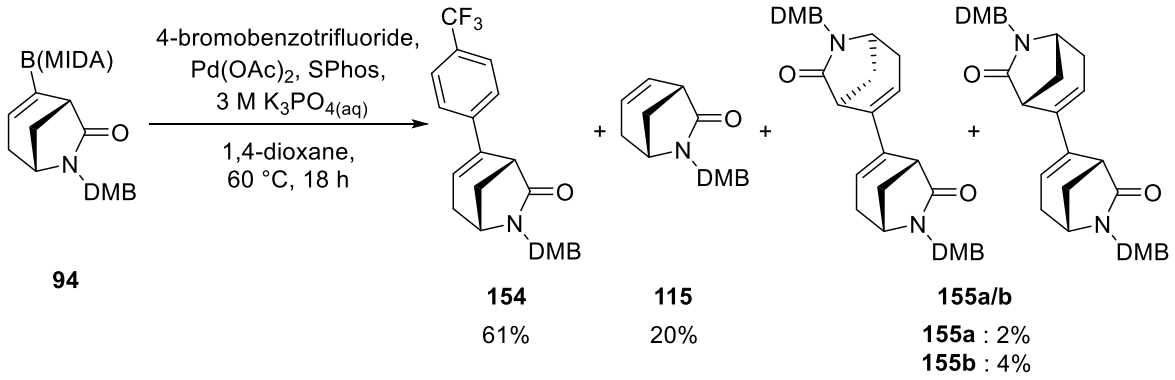
Scheme 4.3

Taking these strategies into consideration and with the idea of having a simple and reliable method for performing the Suzuki-Miyaura cross-coupling of vinyl MIDA boronate **94**, our attention turned to the slow-release method developed by Burke *et al*.[82] using $Pd(OAc)_2$ as a Pd source, SPhos as a ligand and $K_3PO_{4(aq)}$ for the release of the boronic acid. Using this set of conditions, vinyl MIDA boronate **94** was successfully coupled to 4-bromoanisole to give, after chromatography, arylated normorphan **153** in 86% yield (Scheme 4.4) as the only product. Incorporation of the 4-anisole group was confirmed by HRMS and ^{1}H NMR spectroscopy where the signal corresponding to the vinylic proton was observed at δ_H 5.67 in arylated normorphan **153**, Additionally, signals corresponding to the methoxy groups in the aromatic rings were seen as 9H multiplet at δ_H 3.78.



Scheme 4.4

With this result in hand, coupling to 4-bromobenzotrifluoride was attempted. However, ^{1}H NMR spectroscopy of the crude reaction mixture revealed the appearance of three products as well as the desired arylated normorphan **154**. Thus, after chromatography, arylated normorphan **154** was isolated in 61% yield. A second product, identified as alkene **115**, was isolated in 20% yield while another two products subsequently identified as bis-normorphans **155a** and **155b** were isolated in 2% and 4% yield as 75:25 and 95:5 mixtures with SPhos respectively (Scheme 4.5). Incorporation of the benzotrifluoride moiety in normorphan **154** was confirmed by HRMS and NMR spectroscopic analysis. Namely, signals observed in the ^{1}H NMR spectrum of normorphan **154** in the aromatic region at δ_H 7.68–7.63 and 7.60–7.55 as multiplets were assigned as those from the benzotrifluoride motif. Additionally, the ^{13}C NMR spectrum of normorphan **154** showed signals at δ_C 129.1 (q, J = 32.5 Hz) and 125.5 (q, J = 4.0 Hz) which were assigned as the *ipso* and *ortho* carbons to the CF_3 group. The CF_3 carbon appeared at δ_C 124.4 (q, J = 272.0 Hz).



Scheme 4.5

The first of the observed by-products that was isolated in 20% yield was identified as alkene **115** by comparison with previously isolated samples (see Section 2.2). We hypothesise that alkene **115** is formed by protodeborylation of the transient boronic acid species formed by

hydrolysis of vinyl MIDA boronate **94**. On the other hand, ^{1}H NMR spectroscopic analysis of the other two isolated products **155a** and **155b** (2% and 4% yield respectively) showed that they had very similar spectra. Particularly, the ^{1}H NMR spectra of both compounds contained all the signals from the normorphan core. For bis-normorphan **155a** signals appeared at δ_H 5.85 (s), 3.67 (d, J = 5.0 Hz) and 3.08 (d, J = 5.0 Hz) for the =CH, NCH and C(O)CH protons of the normorphan core respectively. For bis-normorphan **155b** these same signals were seen at δ_H 6.05–5.62 (m), 3.72–3.67 (m) and 3.16 (d, J = 5.0 Hz). This was consistent to a coupled normorphan bearing a vinyl substituent that showed no signals in the ^{1}H NMR spectrum with the exception of those belonging to the normorphan core (Figure 4.1). Additionally, the ^{13}C NMR spectra for both **155a** and **155b** showed only signals that belonged to the normorphan core.

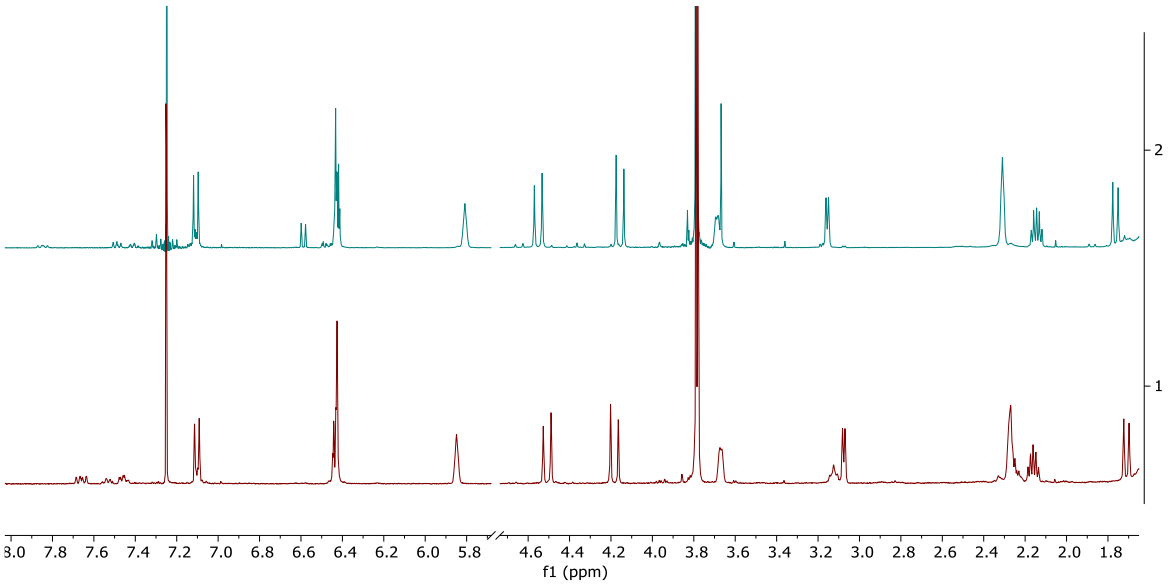
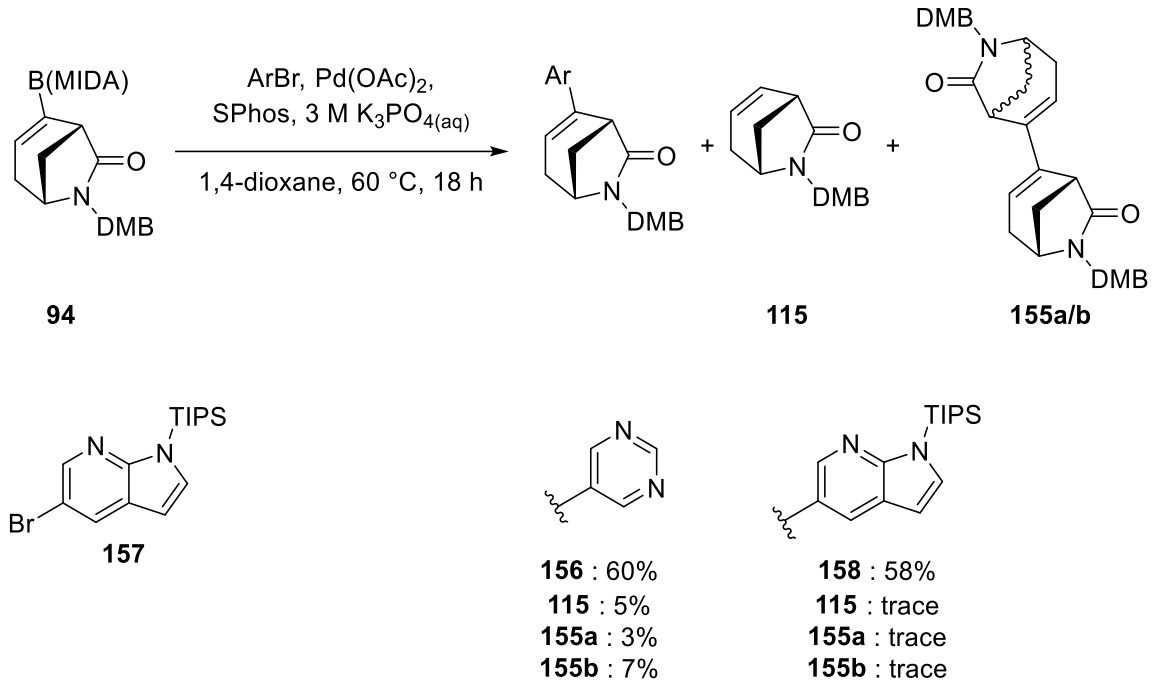


Figure 4.1 - ^{1}H NMR spectra of **155a** (blue) and **155b** (red)

Thus, we propose that a dimerisation by oxidative homocoupling of the boron-containing species had occurred giving rise to the formation diastereomeric bis-normorphans **155a/b**. This was confirmed by HRMS analysis. It is likely that these products are generated by a minor competing pathway in which small quantities of oxygen present in the reaction,[101] coupled with high concentrations of the transient boronic acid species,[102] lead to the formation of the homocoupled product.

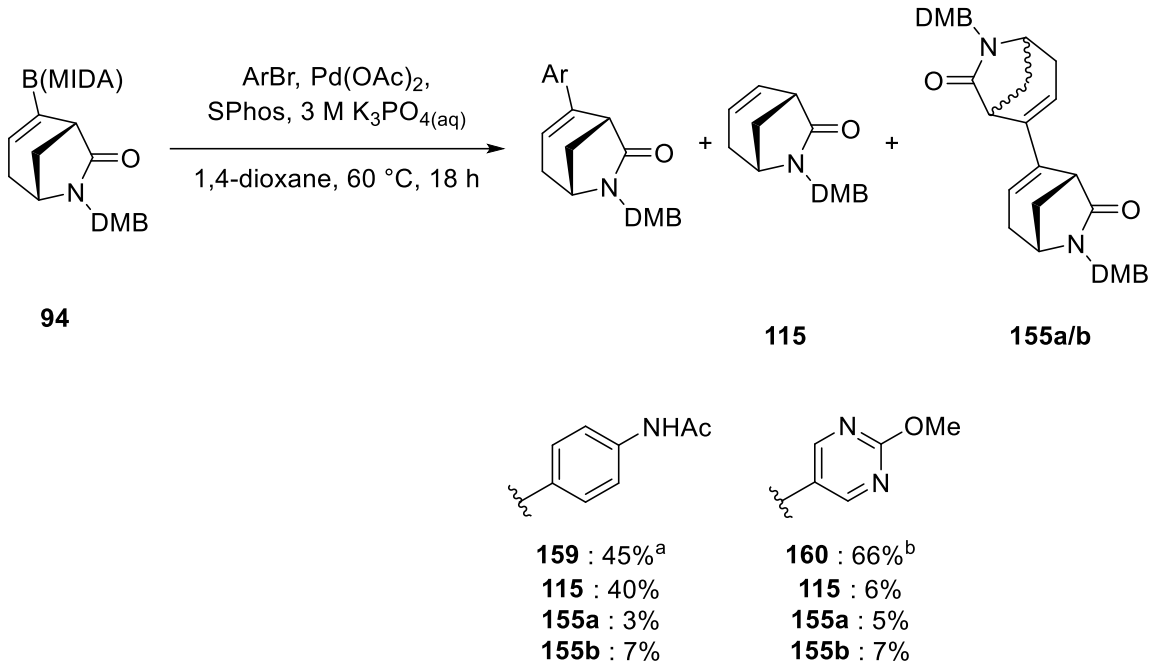
With the previous results in hand, we moved on to study the scope of aryl bromides that could be coupled to normorphan-derived 3-D building block **94**. Use of 5-bromopyrimidine gave arylated normorphan **156** in 60% yield, alkene **115** in 5% yield and bis-normorphans **155a/b** in 3% and 7% yields respectively. Likewise, use of *N*-TIPS azaindole **157** as

coupling partner afforded arylated normorphan **158** in 58% yield with only trace by-products formed (Scheme 4.6).



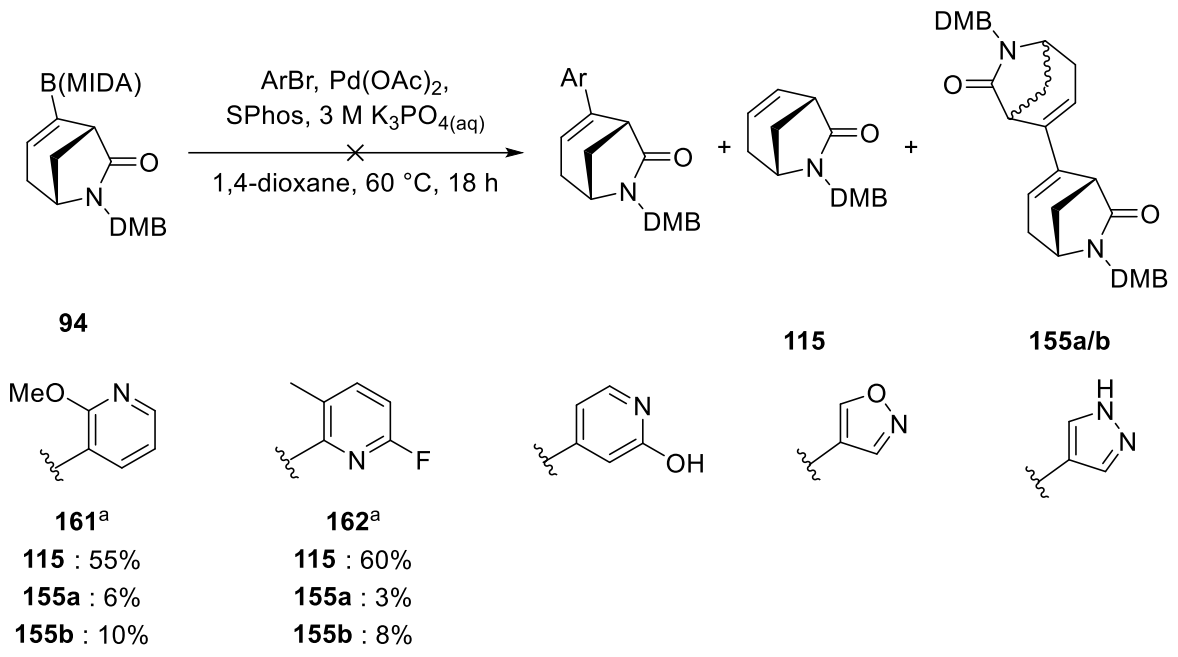
Scheme 4.6

Use of 4-bromo-acetanilide gave arylated normorphan **159** in 45% yield as a 90:10 mixture with bis-normorphan **155b** (7% yield). This coupling also afforded alkene **115** in 40% yield and bis-normorphan **155a** in 3% yield. Coupling to 2-methoxy-5-bromopyrimidine gave arylated normorphan **160** in 66% yield as a 95:5 mixture with bis-normorphan **155a** (5% yield). This coupling also gave alkene **115** and bis-normorphan **155b** in 6% and 7% yield respectively (Scheme 4.7).



Scheme 4.7 - a) Isolated as a 90:10 mixture with bis-normorphan **155b**; b) Isolated as a 95:5 mixture with bis-normorphan **155a**

A selection of less successful results is summarised in Scheme 4.8. Use of 3-bromo-2-methoxy-pyridine afforded only alkene **115** in 55% yield and bis-normorphans **155a/b** in 6% and 10% yield respectively after chromatography. However, it should be noted that formation of arylated morphan **161** was evidenced in the ^{1}H NMR spectrum of the crude product. Similarly, coupling using 2-bromo-5-fluoro-3-methylpyridine gave only alkene **115** in 60% yield and bis-normorphans **155a/b** in 3% and 8% yield respectively despite evidence of the formation or arylated normorphan **162** by ^{1}H NMR spectroscopy of the crude product. Finally, ^{1}H NMR spectroscopic analysis of the crude reaction mixtures of couplings using 4-bromo-2-hydroxypyridine, 4-bromo-isoxazole and 4-bromo-pyrazole showed formation of only trace amounts of the desired products.



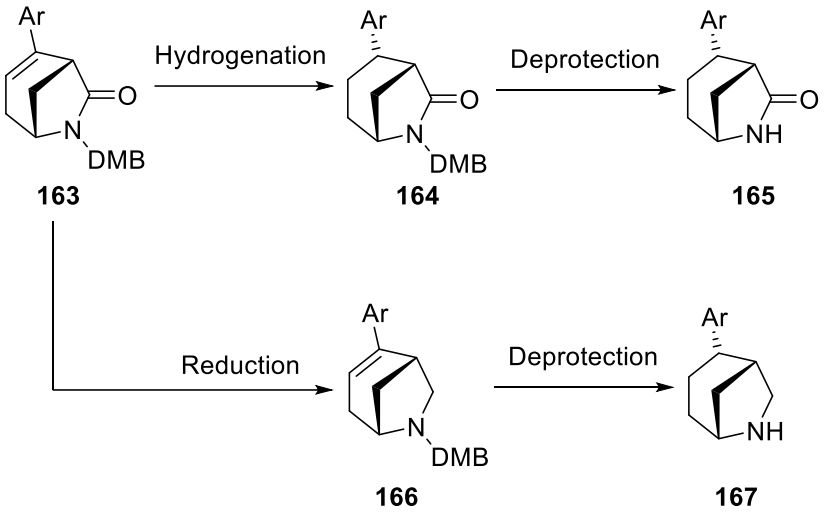
Scheme 4.8 - a) Formation of product evidenced by ^{1}H NMR spectroscopy of the crude product.

Thus, 3-D building block **94** was coupled to a variety of aryl bromides, including heteroaromatic ones, in moderate to good yields, proving the potential utility of the 3-D building block in the synthesis of lead-like compounds. However, it is important to note that non-protected groups such as free NH or OH moieties proved in many cases detrimental to the yield. Additionally, the appearance of different by-products by competing pathways was inconvenient as some of them were difficult to separate from the desired product.

It is known[99] that modifying the reaction conditions, for slower release of the boronic acid (*e.g.* lower concentrations of base), as well as utilising different precatalyst/ligand combinations[82] can have a beneficial effect by reducing the formation of the undesired products of cross-couplings. Thus, we propose that while the current conditions prove adequate for the Suzuki-Miyaura coupling of 3-D building block **94**, an optimisation of the reaction conditions could be performed to allow for coupling with the more problematic heteroaryl bromides and decrease contamination by side products of the reaction.

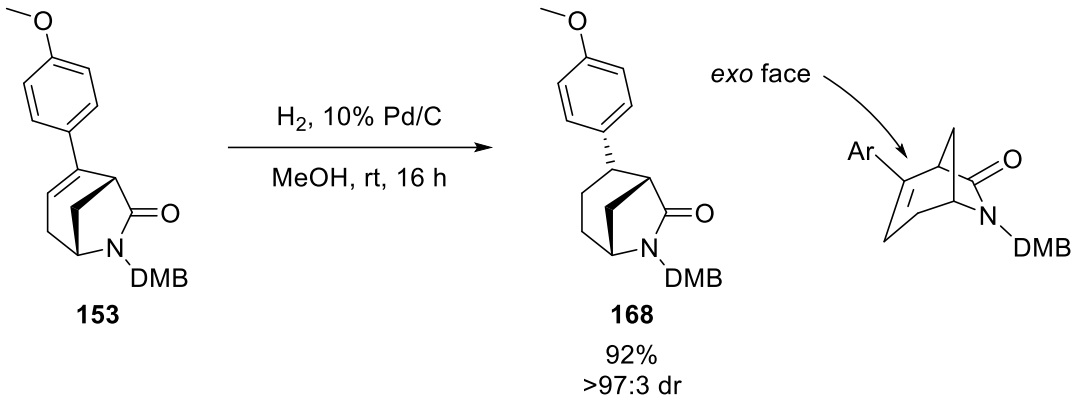
4.2 Further Functionalisation of the Normorphan-Derived 3-D Building Block

With the scope of the Suzuki-Miyaura arylation briefly explored, we moved on to the further functionalisation that was proposed for 3-D building block **94**. Once Suzuki-Miyaura functionalisation had been performed, it was envisaged that the arylated normorphan could be taken on through two distinct routes. The first involved diastereoselective hydrogenation of the alkene in **163** into normorphan **164**. Normorphan **164** could then be deprotected to give normorphan **165** upon which conditions for *N*-functionalisation could be explored. On the other hand, the amide in arylated normorphan **163** could be reduced to obtain amine **166** which could then be deprotected to obtain normorphan **167** (Scheme 4.9).



Scheme 4.9

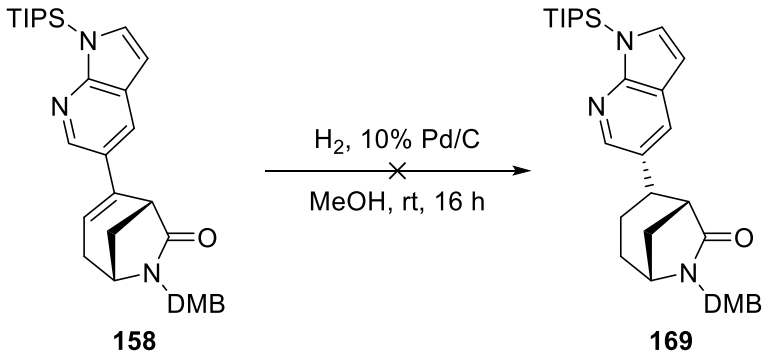
The first step investigated was the diastereoselective hydrogenation of the alkene. We expected that, due to the inherent shape of building block **94**, hydrogenation of the alkene would likely be diastereoselective due to preferential hydrogenation on the less sterically hindered *exo*-face of the bicyclic scaffold. With this in mind, we utilised standard hydrogenation conditions with 10% Pd/C as catalyst under a hydrogen atmosphere to perform the hydrogenation on arylated normorphan **153**. To our delight, using these conditions, hydrogenated normorphan **168** was isolated in 92% yield as a single diastereomer, with no purification required (Scheme 4.10).



Scheme 4.10

Formation of normorphan **168** was confirmed by HRMS and NMR spectroscopy. The ^{1}H NMR spectrum of normorphan **168** showed a signal at δ_H 2.84 (ddd, J = 12.0, 5.0, 1.5 Hz, 1H) which was assigned as the proton in the benzylic position. Another signal at δ_H 1.85 (ddd, J = 14.0, 5.0, 5.0 Hz, 1H) was assigned to one of the protons in the CHH' in the 3-position of the normorphan scaffold. The other CHH' proton signal was observed underneath other signals. Since normorphan **168** is an oil, the stereochemical outcome was assigned as the expected *exo* product from X-ray crystallographic analysis of a subsequent derivative (see Figure 4.2).

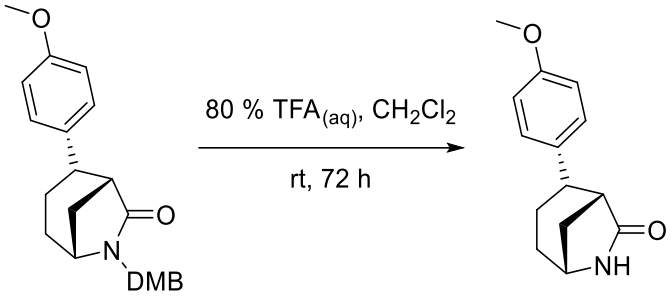
In contrast, attempted hydrogenation of aza-indole arylated normorphan **158** into normorphan **169** proved unsuccessful (Scheme 4.11), The ^{1}H NMR spectroscopic analysis of the crude product revealed a low number of aromatic signals, with new aliphatic signals appearing. This could be evidence of hydrogenation of the aza-indole aromatic ring or formation of a dearomatized unidentified product.



Scheme 4.11

We then moved on to search for deprotection conditions for the *N*-DMB protecting group that is present in arylated normorphan **168**. The majority of methods used for the

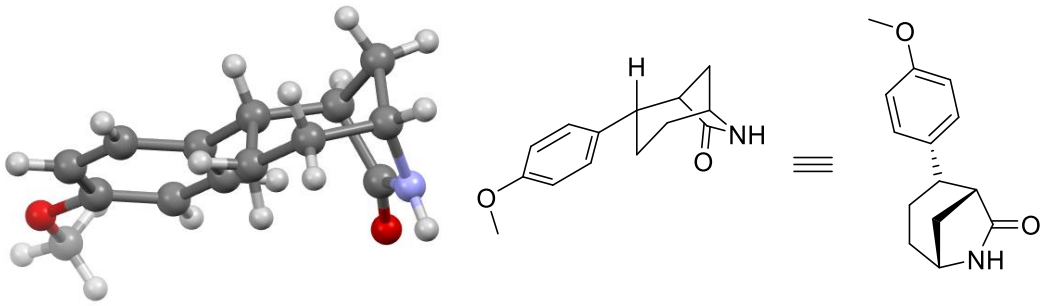
deprotection of the *N*-DMB group make use of its ability to generate a stable, benzylic carbocation. As such, many methods for deprotection use acidic conditions such as TFA with cation scavengers such as water[79] or 1,3-dimethoxybenzene,[103] or Lewis acids such as BCl_3.[104] *N*-DMB groups have also been deprotected under oxidative conditions such as DDQ[105] or ceric ammonium sulfate.[106] With this knowledge, a first set of conditions using aqueous TFA at rt was attempted. Pleasingly, this gave amide **170** in 68% yield after 72 h (Scheme 4.12).



168 **170** 68%

Scheme 4.12

Removal of the *N*-DMB group to give NH amide **170** was confirmed by HRMS and by ^{1}H NMR spectroscopic analysis. Particularly, the ^{1}H NMR spectrum of amide **170** showed a broad singlet at δ_H 6.69, which had no carbons attached and was assigned as the NH proton. This was evidence of the removal of the *N*-DMB group. Gratifyingly, amide **170** proved to be a solid and analysis by X-ray crystallography (Figure 4.2) allowed us to confirm the stereochemical outcome of the hydrogenation of arylated normorphan **94**. As expected, the relative stereochemistry of the stereocentre generated at the benzylic position was that from hydrogenation from the least sterically hindered *exo* face of the alkene.

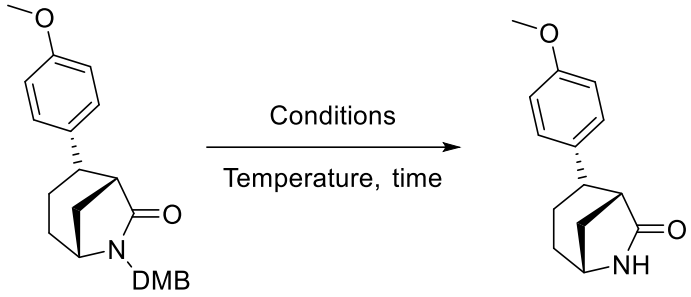


170

Figure 4.2 - X-ray crystal structure of amide **170**

However, since the deprotection of the *N*-DMB group in amide **168** proved to be slow, with some starting material observed after 72 h, we moved on to finding conditions which could provide amide **170** more quickly and efficiently. Making use of the different ways to deprotect *N*-DMB groups, oxidative conditions were employed. In this manner, using DDQ as oxidant and water as scavenger gave amide **168** in 25% yield with significant formation of unidentified by-products observed (Entry 2). Thus, we returned to the use of acidic conditions while heating to speed the reaction up and hopefully achieve full conversion. Accordingly, using 80% $TFA_{(aq)}$ at 60 °C afforded amide **170** in 73% yield after 18 h (Entry 3). However, while these conditions proved adequate for the deprotection of amide **168**, we thought that some functionalities that could be introduced in previous steps of the synthesis, such as the BMIDA,[107] could be labile to aqueous acid. As such, we turned our attention to a different cation scavenger to use with our acidic conditions. Use of anhydrous TFA and 1,3-dimethoxybenzene as scavenger[103] gave amide **170** in 52% yield. However, the reaction proved to be slow, taking 72 h with presence of some starting material remaining in the crude product (Entry 4).

Table 4.1 - Optimisation of *N*-DMB deprotection.



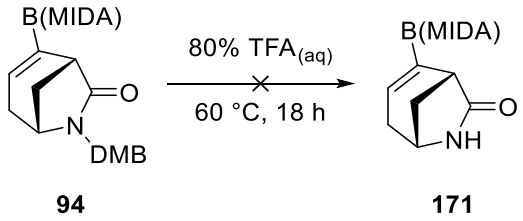
168 **170**

Entry	Conditions	Temp (°C)	Time (h)	Yield[a] (%)
1	80% $TFA_{(aq)}$, CH_2Cl_2	rt	72	68
2	DDQ, H_2O, CH_2Cl_2	rt	24	25
3	80% $TFA_{(aq)}$	60	18	73
4	TFA, 1,3-dimethoxybenzene, CH_2Cl_2	rt	72	52

a) % isolated yield

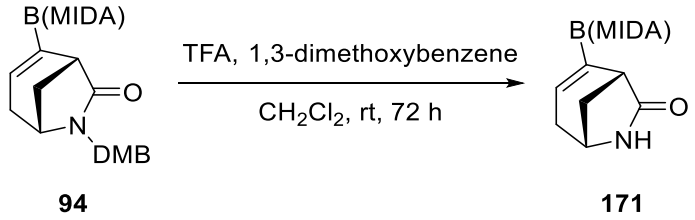
With different conditions for the deprotection of the *N*-DMB group in hand, we were interested in exploring whether the *N*-DMB group could be removed from vinyl MIDA boronate **94** and if the product from this deprotection could be selectively functionalised in

the presence of the *N*-H amide. Initially, attempting the deprotection of the *N*-DMB in vinyl MIDA boronate **94** by using our highest yielding conditions (80% $TFA_{(aq)}$ at 60 °C) failed to give *N*-H-amide **171**, giving a complex mixture of unidentified products (Scheme 4.13). This, we hypothesise, was partly due to hydrolysis of the MIDA boronate moiety under the acidic conditions.



Scheme 4.13

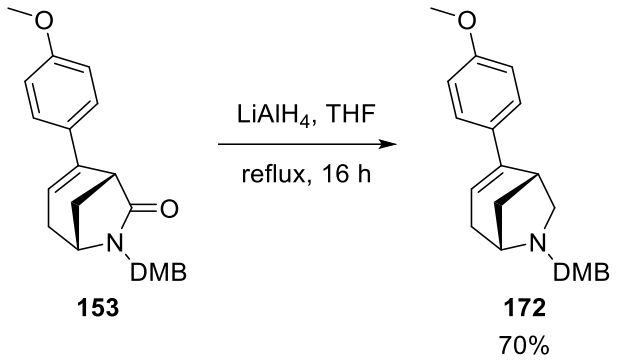
Therefore, we changed the cation scavenger to 1,3-dimethoxybenzene in the absence of water. Pleasingly, using anhydrous TFA with 1,3-dimethoxybenzene in CH_2Cl_2 at rt, amide **171** was generated in 60% yield (Scheme 4.14). The formation of amide **171** was confirmed by both HRMS and NMR spectroscopy. Namely, the ^{1}H NMR spectrum of amide **171** showed a singlet at δ_H 7.55 which was assigned to the newly formed *N*-H. Likewise, the proton signals expected for the NCH_2 protons from the MIDA group were observed at δ_H 4.25, 4.13, 3.91 and 3.90 as doublets due to their diastereomeric nature. Likewise, the ^{13}C NMR spectrum of amide **171** showed signals for the MIDA boronate being observed at δ_C 170.4 (C=O, ester), 169.2 (C=O, ester) and 46.6 (NMe). Nevertheless, despite success at obtaining deprotected 3-D building block **171**, it suffered from extremely low solubility in most common organic solvents, which makes amide **171** inconvenient as a building block for further elaboration.



Scheme 4.14

Finally, we explored whether we could obtain an amine version of our building block. This would allow us to expand the accessible set of elaboration vectors by changing the hybridisation of the nitrogen and thus the geometry of the bicyclic scaffold (see Section 2.1). Hence, it was envisaged that reduction of the amide in arylated normorphan **153** would allow

easy access into the desired amine. This could, in principle, be achieved by using a variety of reducing agents such as $LiAlH_4$,[108] DIBAlH,[109] BH_3 complexes,[110] or even transition metal hydride complexes[111] with varying degrees of selectivity. However, since arylated normorphan **153** did not contain particularly reactive functionalities, $LiAlH_4$ was used. Reduction of arylated normorphan **153** with $LiAlH_4$ in THF at reflux afforded amine **172** in 70% yield after chromatography (Scheme 4.15).



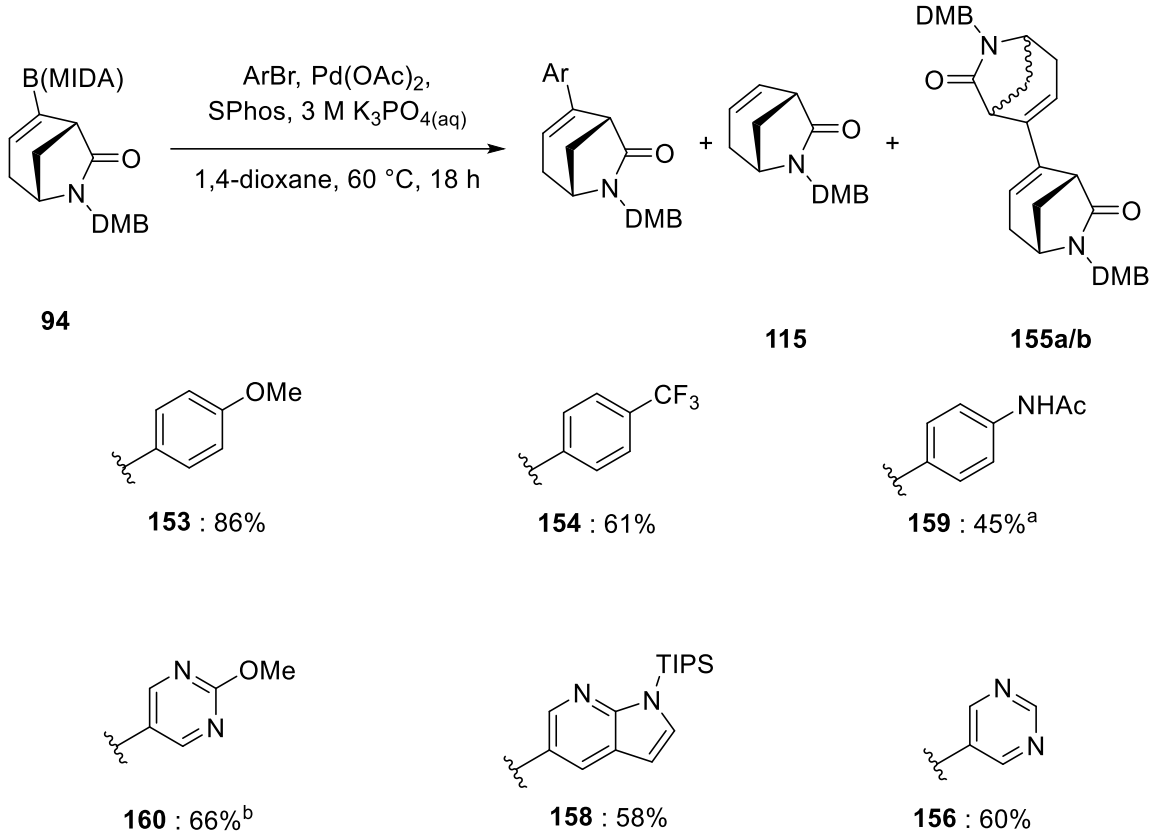
153 **172** 70%

Scheme 4.15

Successful reduction of the amide **153** to give amine **172** was confirmed by HRMS, NMR and IR spectroscopy. The ^{1}H NMR spectrum of amine **172** showed a 2H multiplet δ_H 3.12–3.02 which is the region expected for a CH_2 next to a heteroatom. This led us to assign this signal as the newly formed CH_2 in amine **172**. Additionally, the signal for the proton at the 7-position of the normorphan scaffold in amine **172** was observed as a doublet of doublets at δ_H 3.00. Finally, the IR spectrum of amine **172** showed no bands in the carbonyl region.

4.3 Overview

To summarise, we have shown that 3-D building block **94** can be functionalised in diverse ways. Namely, we have shown that Suzuki-Miyaura cross-coupling on **94** can be performed with a variety of aryl bromides, including some heteroaromatics in moderate to good yields (Scheme 4.16).

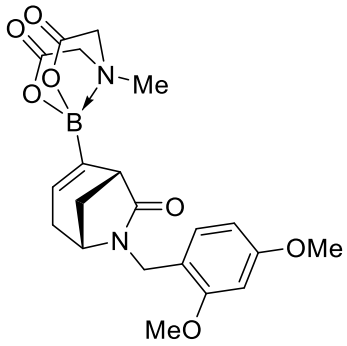


Scheme 4.16 - a) Isolated as a 90:10 mixture with bis-normorphan **155b**; b) Isolated as a 95:5 mixture with bis-normorphan **155a**

Diastereoselective hydrogenation of the alkene in normorphan **153** was also exemplified obtaining an excellent yield and complete diastereoselectivity towards the product from hydrogenation from the *exo* face. This was confirmed by X-ray crystallographic analysis. Deprotection conditions for the *N*-DMB group were also identified by using aqueous TFA at 60 °C. Likewise, for hydrolysis-sensitive groups, anhydrous deprotection conditions were also found by using 1,3-dimethoxybenzene as a cation scavenger. Gratifyingly, these last conditions were successfully applied to the deprotection of 3-D building block **94** which unfortunately proved inadequate for further functionalisation due to solubility problems. Finally, we were able to access a different set of elaboration vectors by converting the amide into an amine by reduction with $LiAlH_4$ in good yield.

Chapter 5 Conclusions and Future Work

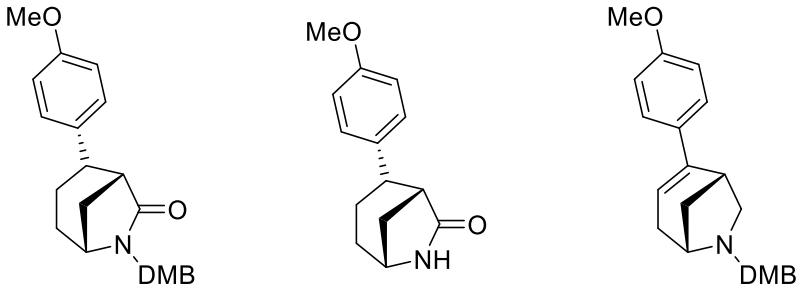
In conclusion, normorphan-derived building block **94** was synthesised in its racemic form in an overall 30% yield *via* a seven-step sequence (Figure 5.1). This sequence consisted of a three-step synthesis of an aminoketone that was then cyclised to give the normorphan. This was then converted into the vinyl triflate to enable a Miyaura borylation and transesterification sequence to give normorphan-derived building block **94**. Two approaches for the enantioenriched synthesis of building block **94** were also explored, namely, an organocatalytic asymmetric cyclisation and a diastereomeric resolution approach. However, both approaches ultimately proved unsuccessful.



94

Figure 5.1 - Normorphan-derived building block **94**

Suzuki-Miyaura arylations of 3-D building block **94** were showcased with a variety of aryl bromides including heteroaromatic ones in yields of 46-86%. Further functionalisation of building block **94** such as diastereoselective hydrogenation of the alkene, *N*-deprotection and reduction of the amide were also successful to give the products shown in Figure 5.2.



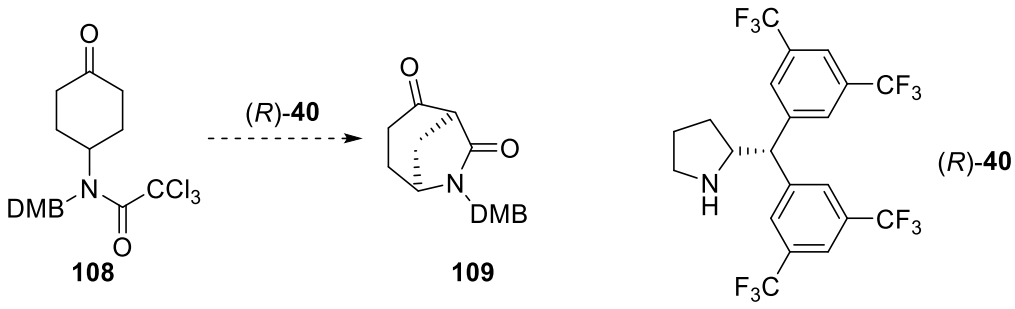
153
92% >97:3 dr

170
73%

172
70%

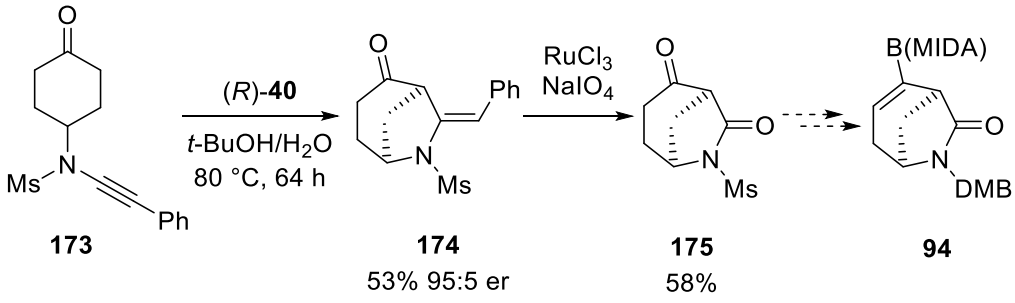
Figure 5.2 - Products from further functionalisation of building block **94**

Future work on the synthesis of building block **94** could include the exploration of alternative routes for the synthesis of enantioenriched building block **94**. For example, a more in-depth study into the organocatalytic cyclisation of trichloroacetamide **108** into normorphan **109** could be carried out. In this study, catalysts such as (*R*)-**40** utilised by Ye and co-workers[53] in their Conia-ene methodology, could be explored (Scheme 5.1).



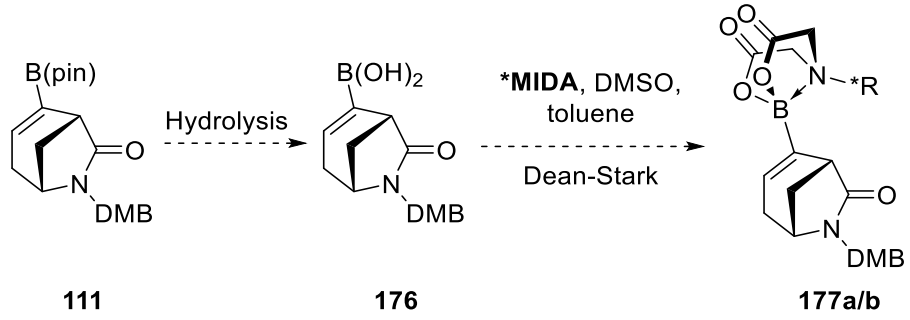
Scheme 5.1

Ye and co-workers[53] also explored the cleavage of the alkene in the products of their asymmetric Conia-ene type reaction (**173** to **174** to **175**). This could be utilised to obtain a sulfonamide protected version of the normorphan scaffold **175**. Then, selective conditions for the deprotection of the sulfonamide group could be explored to afford enantioenriched building block **94** or a derivative (Scheme 5.2).



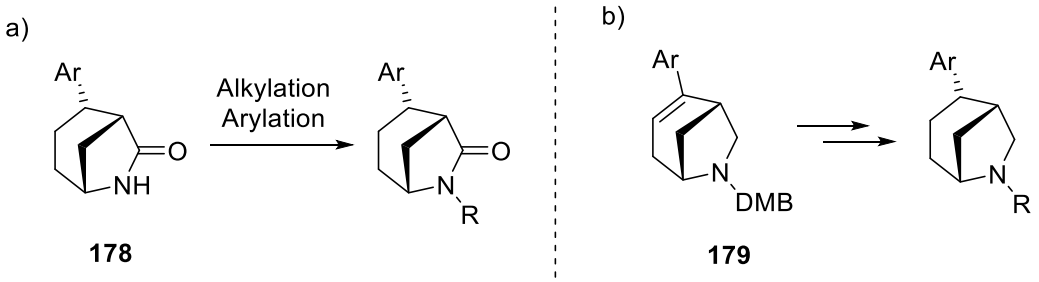
Scheme 5.2

Alternatively, different conditions for the formation of the vinyl MIDA boronate could be explored to allow for the formation and resolution of the diastereomeric MIDA* boronates. Namely, hydrolysis of the pinacol boronate **111** into boronic acid **176** and installation of the chiral MIDA derivatives using the conditions reported by Burke and co-workers[81] could be explored with the aim to avoid formation of alkene **115** (Scheme 5.3).



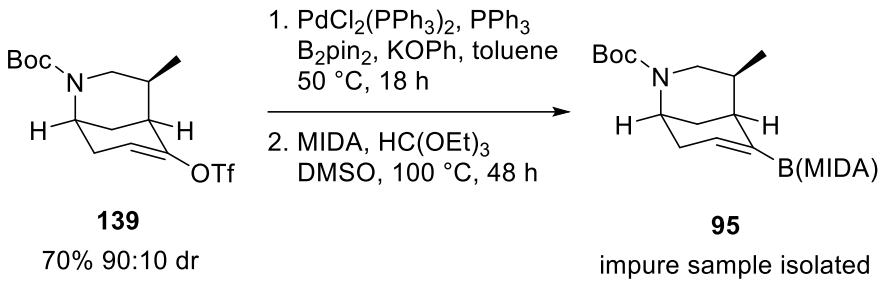
Scheme 5.3

On the other hand, further work on the functionalisation of normorphan-derived scaffold **94** could include further exploration of the scope and conditions for Suzuki-Miyaura cross-coupling of the vinyl MIDA boronate **94** to enable coupling with a more diverse and medicinally-relevant set of heteroaromatic aryl bromides. *N*-Functionalisation of the building block such as *N*-alkylation and *N*-arylation could also be explored on amide-based scaffold **178** (Scheme 5.4a). Furthermore, conditions for hydrogenation, deprotection and *N*-functionalisation of amine-based scaffold **179** could also be explored (Scheme 5.4b).



Scheme 5.4

With regards to morphan-derived building block **95**, the synthesis of this building block proved more challenging. Late-stage enol triflate **139** was obtained in 29% overall yield and only 90:10 dr. However, formation of vinyl MIDA boronate **956** from enol triflate **169** failed to give a pure sample of vinyl MIDA boronate **95** (Scheme 5.5). Different routes involving sulfonamide and *N*-Boc protected series of substrates were studied for the synthesis of building block **95** with the *N*-Boc protected series of compounds chosen for the overall route.

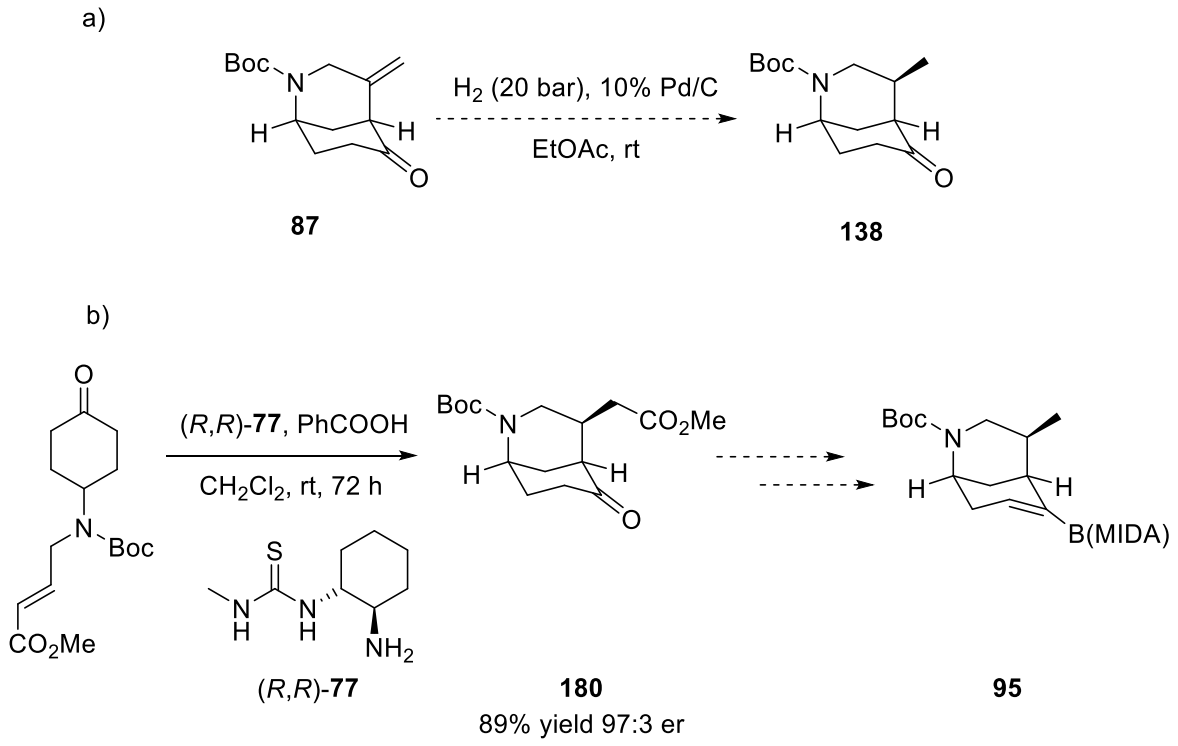


139
70% 90:10 dr

95
impure sample isolated

Scheme 5.5

Further work in this scaffold should involve the synthesis and characterisation of a pure sample of vinyl MIDA boronate **95** which could be achieved by attempting purification of the intermediate vinyl pinacol boronate instead of using the crude product. Development of a route into diastereopure building block **95** is also important. A possible approach would be to use the hydrogenation conditions reported by Ye and co-workers[53] (10% Pd/C with H_2 at 20 bar) (Scheme 5.6). Alternatively, a different approach to access a morphan scaffold without the methylene group could be investigated. For example Dixon and co-workers[68] reported the synthesis of **180** after which decarboxylation could be performed to access the diastereopure morphan building block **95** (Scheme 5.6). Finally, Suzuki-Miyaura functionalisation of the vinyl MIDA boronate, hydrogenation of the alkene, and *N*-functionalisation could be explored.



87

138

(*R*,*R*)-**77**

180
89% yield 97:3 er

95

Scheme 5.6

Chapter 6 Experimental

6.1 Computational Methods

Computational vector analysis was performed by generating the lowest energy conformer of the compound of interest using a Pipeline Pilot protocol developed in the O'Brien group.[77] Prior to conformer generation a wash step was performed, which involved stripping salts and ionising the molecule at pH 7.4. Any stereocentre created here was left with undefined stereochemistry. SMILES strings were converted to their canonical representation. A list of allowed chirality at each centre is generated and a SMILES file with all possible stereoisomers was written. Conformers were generated using the BEST method in Catalyst using the rel option, run directly on the server and not through the built-in Conformation Generator component with a chosen maximum relative energy threshold of 20 kcal mol^{-1}, maximum of 255 conformers for each compound. Conformations were read, ones that cannot be represented by the canonical SMILES are discarded, with the remaining ones standardised to a single enantiomer. Duplicates were filtered with a RMSD threshold of 0.1. Minimisation with 200 steps of Conjugate Gradient minimisation with an RMS gradient tolerance of 0.1 was performed using the CHARMm forcefield with Momany-Rone partial charge estimation and a Generalised Born implicit solvent model. Duplicates were filtered again with a RMSD threshold of 0.1.

Following this, the lowest energy conformer was selected for each compound and a MDL Molfile containing the 3-D coordinates of atoms was generated. The variation points and vectors were individually defined and the file was inputted into Grygorenko's[19] Python™ protocol which gave the processed data for r, Φ_1, Φ_2, and θ.

6.2 Synthetic Methods

6.2.1 General Methods

All non-aqueous reactions were carried out under oxygen-free Ar atmosphere using flame-dried glassware. THF was freshly distilled from sodium and benzophenone. Alkyllithiums were titrated against *N*-benzylbenzamide before use.[112] Et_3N, *i*-Pr_2NH and pyrrolidine were distilled over CaH_2 before use. Brine refers to a saturated $NaCl_{(aq)}$ solution. Water is distilled water. Flash column chromatography was carried out using Fluka Chemie GmbH silica (220-440 mesh). Thin layer chromatography was carried out using commercially available Merck

F_{254} aluminium backed silica plates. Proton (400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument using an internal deuterium lock. For samples recorded in $CDCl_3$, chemical shifts are quoted in parts per million relative to $CHCl_3$ (δ_H 7.26) and $CDCl_3$ (δ_C 77.0, central line of triplet). For samples recorded in d_6-DMSO, chemical shifts are quoted in parts per million relative to DMSO (δ_H 2.50, central line of quintet) and d_6-DMSO (δ_C 39.5, central line of septet). For samples recorded in d_6-acetone, chemical shifts are quoted in parts per million relative to acetone (δ_H 2.05, central line of quintet) and d_6-acetone (δ_C 29.8, central line of septet). Carbon NMR spectra were recorded with broad band proton decoupling and assigned using DEPT experiments. Coupling constants (*J*) are quoted in Hertz. Melting points were carried out on a Gallenkamp melting point apparatus. Infrared spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer. Electrospray high and low resonance mass spectra were recorded at room temperature on a Bruker Daltronics microOTOF spectrometer.

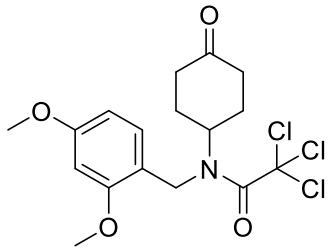
6.2.2 General Procedures

General Procedure A: Suzuki-Miyaura cross coupling of vinyl MIDA boronate 94

A solution of vinyl MIDA boronate **94** (100 mg, 0.234 mmol, 1.0 eq), $Pd(OAc)_2$ (3 mg, 0.012 mmol, 0.05 eq), SPhos (10 mg, 0.023 mmol, 0.1 eq) and the aryl bromide (0.28 mmol, 1.2 eq) in dioxane (2.35 mL) in a sealed tube was stirred at rt for 15 min under Ar. 3 M $K_3PO_{4(aq)}$ (0.59 mL, 1.755 mmol, 7.5 eq), degassed by sparging with Ar, was added and the resulting mixture was stirred and heated at 60 °C in a sealed tube for 20 h. H_2O (5 mL) was added and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

6.2.3 Experimental Procedures and Characterisation Data

2,2,2-Trichloro-*N*-(2,4-dimethoxybenzyl)-*N*-(4-oxocyclohexyl)acetamide 108



108

A solution of 1,4-cyclohexadione monoethylene acetal **29** (4.00 g, 25.6 mmol, 1.0 eq), 2,4-dimethoxybenzylamine (3.9 mL, 25.6 mmol, 1.0 eq) and $NaBH(OAc)_3$ (7.60 g, 35.9 mmol, 1.4 eq) in CH_2Cl_2 (100 mL) was stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (10mL) was added. Then, 1 M $NaOH_{(aq)}$ was added until pH ≈ 10 was reached. The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (50 mL) dried (Na_2SO_4) and evaporated under reduced pressure to give the crude amine as a pale yellow oil. To the crude amine was added 3 M $HCl_{(aq)}$ (140 mL) and the resulting solution was stirred at rt for 48 h. Solid Na_2CO_3 was added until pH ≈ 9 was reached and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude amino ketone as a pale yellow oil. The crude amino ketone was dissolved in CH_2Cl_2 (80 mL). The resulting solution was cooled to 0 °C and Et_3N (6.8 mL, 48.6 mmol, 1.9 eq) was added under Ar. Then, trichloroacetyl chloride (5.2 mL, 45.0 mmol, 1.8 eq) was added dropwise and the solution was allowed to warm to rt. The resulting solution was stirred at rt for 4 h and then poured into water (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:6 to 7:3 Et_2O-hexane as eluent gave trichloroacetamide **108** (9.45 g, 90%) as a white solid, mp 122-124 °C; R_F (4:6 Et_2O-hexane) 0.22; IR (ATR) 2956, 1717 (C=O, ketone), 1674 (C=O, amide), 1615, 1507, 1417, 1259, 1208, 1157, 1123, 1036, 825, 812, 730, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 7.25–7.15 (m, 0.35H, Ar), 6.96 (d, J = 8.5 Hz, 0.65H, Ar), 6.52–6.35 (m, 2H, Ar), 5.00 (br t, J = 12.0 Hz, 0.65H, NCH), 4.93–4.79 (m, 0.35H, NCH), 4.60–4.52 (m, 1.3H, NCHAr), 4.04–3.92 (m, 0.35H, NCHAr), 3.84–3.74 (m, 6.35H, NCHAr, OMe), 2.49–2.37 (m, 3.3H, CH), 2.36–2.21 (m, 0.7H, CH), 2.21–2.10 (m, 2.05H, CH), 2.10–1.91 (m, 1.95H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 208.4 (C=O, ketone), 160.7 (C=O, amide),

160.1 (*ipso*-Ar), 157.2 (*ipso*-Ar), 128.7 (Ar, only resolved in HMQC), 127.1 (Ar), 117.4 (*ipso*-Ar), 104.3 (*ipso*-Ar), 98.5 (Ar), 93.8 (CCl_3), 57.2 (NCH), 55.5 (OMe), 46.9 (NCH), 42.1 (NCH_2), 39.8 (CH_2), 29.3 (CH_2) (1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{17}H_{20}{}^{35}Cl_3NO_4$ $(M + Na)^+$ 430.0350, found 430.0344 (+1.4 ppm error).

Lab book reference: ARG-1-007

A solution of 1,4-cyclohexadione monoethylene acetal **29** (875 mg, 5.62 mmol, 1.0 eq), 2,4-dimethoxybenzylamine (0.9 mL, 5.84 mmol, 1.0 eq) and $NaBH(OAc)_3$ (1.70 g, 7.86 mmol, 1.4 eq) in CH_2Cl_2 (25 mL) was stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (5mL) was added. Then, 1 M $NaOH_{(aq)}$ was added until pH ≈ 10 was reached. The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude amine as a pale-yellow oil. To the crude amine was added 3 M $HCl_{(aq)}$ (40 mL) and the resulting solution was stirred at rt for 48 h. Solid Na_2CO_3 was added until pH ≈ 9 was reached and the solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude amino ketone as a pale-yellow oil. The crude amino ketone was dissolved in CH_2Cl_2 (20 mL). The resulting solution was cooled to 0 °C and Et_3N (1.5 mL, 10.8 mmol, 1.9 eq) was added. Then, trichloroacetyl chloride (1.1 mL, 9.80 mmol, 1.8 eq) was added dropwise and the solution was allowed to warm to rt. The resulting solution was stirred at rt for 4 h and then poured into water (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:6 to 7:3 Et_2O-hexane as eluent gave trichloroacetamide **108** (2.04 g, 89%) as a white solid, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above.

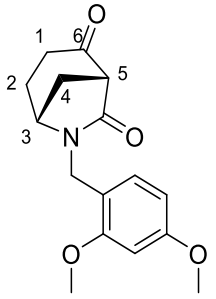
Lab book reference: ARG-1-003

A solution of 1,4-cyclohexadione monoethylene acetal **29** (4.06 g, 26.0 mmol, 1.0 eq), 2,4-dimethoxybenzylamine (4.0 mL, 26.0 mmol, 1.0 eq) and $NaBH(OAc)_3$ (7.70 g, 36.4 mmol, 1.4 eq) in CH_2Cl_2 (107 mL) was stirred at rt for 12 h. Saturated $NH_4Cl_{(aq)}$ (10mL) was added. Then, 1 M $NaOH_{(aq)}$ was added until pH ≈ 10 was reached. The mixture was extracted with

CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude amine as a pale-yellow oil. To the crude amine was added 3 M $HCl_{(aq)}$ (140 mL) and the resulting solution was stirred at rt for 48 h. Solid Na_2CO_3 was added until pH ≈ 9 was reached and the solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude amino-ketone as a pale-yellow oil. The crude amino-ketone was dissolved in CH_2Cl_2 (80 mL). The resulting solution was cooled to 0 °C and Et_3N (7.0 mL, 49.4 mmol, 1.9 eq) was added. Then, trichloroacetyl chloride (5.3 mL, 46.8 mmol, 1.8 eq) was added dropwise and the solution was allowed to warm to rt. The resulting solution was stirred at rt for 4 h and then poured into water (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by triturating the crude solid with Et_2O (2 × 50 mL) gave trichloroacetamide **108** (6.38 g, 60%) as a white solid, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-2-108

6-(2,4-Dimethoxybenzyl)-6-azabicyclo[3.2.1]octane-2,7-dione 109



109

A mixture of trichloroacetamide **108** (501 mg, 1.22 mmol, 1.0 eq) and pyrrolidine (0.11 mL, 1.22 mmol, 1.0 eq) in toluene (0.3 mL) was stirred and heated at 100 °C in a sealed vial for 1 h. The crude mixture was directly purified by flash column chromatography on silica with 1:1 to 4:1 EtOAc-hexane as eluent to give normorphan **109** (281 mg, 80%) as a red oil, R_F (1:1 EtOAc-hexane) 0.17; IR (ATR) 2953, 1723 (C=O, ketone), 1689 (C=O, amide), 1613, 1588, 1508, 1418, 1295, 1209, 1158, 1125, 1034, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.21 (m, 1H, Ar), 6.48–6.44 (m, 2H, Ar), 4.60 (d, *J* = 14.5 Hz, 1H, NC*H*H'), 4.43 (d, *J* = 14.5 Hz, 1H, NCH*H'*), 3.85–3.78 (m, 7H, OMe, NCH), 3.18 (d, *J* = 5.0 Hz, 1H, C(O)CH),

2.56 (dddd, *J* = 11.5, 5.0, 5.0, 2.5 Hz, 1H, CH-4), 2.45–2.32 (m, 2H, C(O)CHH'), 2.08–2.00 (m, 1H, CH-2), 1.98 (d, *J* = 11.5 Hz, 1H, CH-4), 1.79 (dddd, *J* = 13.5, 8.5, 8.5, 1.5 Hz, 1H, CH-2). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 203.0 (C=O, ketone), 170.8 (C=O, amide), 160.9 (*ipso*-Ar), 158.7 (*ipso*-Ar), 131.3 (Ar), 116.8 (*ipso*-Ar), 104.4 (Ar), 98.6 (Ar), 58.3 (*C*HCO), 55.5 (OMe), 54.8 (NCH), 39.5 (NCH_2), 36.2 (CH_2-4), 35.1 (*C*H_2CO), 27.6 (CH_2-2) (1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{16}H_{19}NO_4$ $(M + H)^+$ 290.1383, found 290.1387 (+1.4 ppm error).

Lab book reference: ARG-1-019

A mixture of trichloroacetamide **108** (200 mg, 0.49 mmol, 1.0 eq) and pyrrolidine (0.1 mL, 0.98 mmol, 2.0 eq) in toluene (2 mL) was stirred and heated at reflux for 45 min. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 4:1 EtOAc-hexane as eluent gave normorphan **109** (63 mg, 45%) as a red oil, identical (by ^{1}H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-1-006

A mixture of trichloroacetamide **108** (400 mg, 0.98 mmol, 1.0 eq) and pyrrolidine (0.2 mL, 1.96 mmol, 2.0 eq) in toluene (3 mL) was stirred and heated at reflux for 3 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 4:1 EtOAc-hexane as eluent gave normorphan **109** (93 mg, 33%) as a red oil, identical (by ^{1}H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-1-008

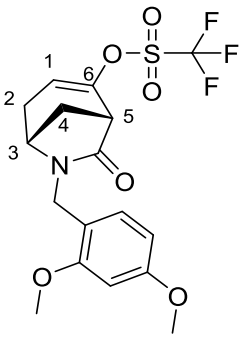
A mixture of trichloroacetamide **108** (500 mg, 1.22 mmol, 1.0 eq) and pyrrolidine (51 µL, 0.61 mmol, 0.5 eq) was stirred and heated at 100 °C in a sealed vial for 1 h. The crude mixture was directly purified by flash column chromatography on silica with 1:1 to 4:1 EtOAc-hexane as eluent to give normorphan **109** (222 mg, 63%) as a red oil, identical (by ^{1}H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-1-010

A mixture of trichloroacetamide **108** (7.00 g, 17.1 mmol, 1.0 eq) and pyrrolidine (1.43 mL, 17.1 mmol, 1.0 eq) in toluene (4.3 mL) was stirred and heated at 100 °C in a sealed tube for 1 h. The crude mixture was directly purified by flash column chromatography on silica with 1:1 to 4:1 EtOAc-hexane as eluent to give normorphan **109** (3.96 g, 80%) as a red oil, identical (by ^{1}H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-2-109

6-(2,4-Dimethoxybenzyl)-7-oxo-6-azabicyclo[3.2.1]oct-2-en-2-yl trifluoromethanesulfonate 110



110

NaHMDS (4.0 mL of a 2 M solution in THF, 8.0 mmol, 1.6 eq) was added dropwise to a stirred solution of normorphan **109** (1.44 g, 4.97 mmol, 1.0 eq) in THF (12 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, a solution of $PhNTf_2$ (2.30 g, 6.46 mmol, 1.3 eq) in THF (8 mL) was added and the resulting solution was allowed to warm slowly to rt. The solution was stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (15 mL) was added and the mixture was extracted with Et_2O (4 × 15 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 4:1 Et_2O-hexane as eluent gave vinyl triflate **110** (1.25 g, 60%) as a clear oil, R_F (3:2 Et_2O-hexane) 0.22; IR (ATR) 2959, 1703 (C=O), 1662 (C=C), 1589, 1508, 1415, 1206, 1138, 878, 834, 609 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.08 (m, 1H, Ar), 6.47–6.40 (m, 2H, Ar), 5.56–5.51 (m, 1H, =CH), 4.50 (d, *J* = 14.5 Hz, 1H, NC*H*H'), 4.29 (d, *J* = 14.5 Hz, 1H, NCH*H'*), 3.83–3.77 (m, 6H, OMe), 3.76–3.71 (m, 1H, NCH), 2.98–2.94 (m, 1H, CH-5), 2.36–2.23 (m, 3H, CH_2-2, CH-4), 1.90 (d, *J* = 10.5 Hz, 1H, CH_2-4); ^{13}C NMR (100.6 MHz,

$CDCl_3$) δ 173.6 (C=O), 160.8 (*ipso*-Ar), 158.5 (*ipso*-Ar), 148.4 (=C), 130.9 (Ar), 118.6 (q, J = 320.0 Hz, CF_3), 117.2 (*ipso*-Ar), 114.8 (=CH) , 104.5 (Ar), 98.6 (Ar), 55.5 (OMe), 55.4 (OMe), 53.0 (NCH), 44.7 (*C*HCO), 38.4 (NCH_2), 34.1 (CH_2-4), 28.3 (CH_2-2); HRMS (ESI) *m/z* calcd for $C_{17}H_{18}F_3NO_6S$ $(M + Na)^+$ 444.0699, found 444.0706 (–1.8 ppm error).

Lab book reference: ARG-1-048

n-BuLi (0.19 mL of a 2.2 M solution in THF, 0.41 mmol, 1.2 eq) was added dropwise to a stirred solution of *i*-Pr_2NH (61 µL, 0.41 mmol, 1.2 eq) in THF (1 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 10 min. Then, a solution of normorphan **109** (100 mg, 0.35 mmol, 1.0 eq) in THF (0.8 mL) was added. The solution was stirred for 1 h. Then, a solution of $PhNTf_2$ (172 mg, 0.48 mmol, 1.4 eq) in THF (1 mL) was added and the resulting solution was allowed to warm slowly to rt. The solution was stirred at rt for 18 h. Saturated $NH_4Cl_{(aq)}$ (2 mL) was added and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 4:1 Et_2O-hexane as eluent gave vinyl triflate **110** (44 mg, 30%) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-1-021

LiHMDS (1.0 mL of a 1 M solution in THF, 1.01 mmol, 1.4 eq) was added dropwise to a stirred solution of normorphan **109** (210 mg, 0.72 mmol, 1.0 eq) in THF (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, a solution of Comins' reagent **113** (370 mg, 0.94 mmol, 1.3 eq) in THF (2 mL) was added and the resulting solution was allowed to warm slowly to rt. The solution was stirred at rt for 18 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product which contained <10% of vinyl triflate **110** by ^1H NMR spectroscopy.

Lab book reference: ARG-1-027

KHMDS (0.31 mL of a 1 M solution in THF, 0.31 mmol, 1.3 eq) was added dropwise to a stirred solution of normorphan **109** (100 mg, 0.30 mmol, 1.0 eq) in THF (1.5 mL) at –78 °C under Ar. After stirring at –78 °C for 1 h, a solution of $PhNTf_2$ (122 mg, 0.34 mmol, 1.4 eq) in THF (1.5 mL) was added and resulting the solution was allowed to warm slowly to rt. The solution was stirred at rt for 18 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 4:1 Et_2O-hexane as eluent gave vinyl triflate **110** (8 mg, 8%) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-1-020

NaHMDS (0.76 mL of a 2 M solution in THF, 1.53 mmol, 1.8 eq) was added dropwise to a stirred solution of normorphan **109** (245 mg, 0.85 mmol, 1.0 eq) in THF (3 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, a solution of $PhNTf_2$ (395 mg, 1.11 mmol, 1.3 eq) in THF (2.5 mL) was added and the resulting solution was allowed to warm slowly to rt. The solution was stirred at rt for 18 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with cold 10% $NaOH_{(aq)}$ (10 mL) and brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 4:1 Et_2O-hexane as eluent gave vinyl triflate **110** (150 mg, 45%) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-1-031

NaHMDS (0.76 mL of a 2 M solution in THF, 1.53 mmol, 1.8 eq) was added dropwise to a stirred solution of normorphan **109** (245 mg, 0.85 mmol, 1.0 eq) in THF (3 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, a solution of Comins' reagent **113** (435 mg, 1.11 mmol, 1.3 eq) in THF (2.5 mL) was added and resulting the solution was allowed to warm slowly to rt. The solution was stirred at rt for 18 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the mixture was extracted with Et_2O (3 × 15 mL). The

combined organic extracts were washed with cold 10% $NaOH_{(aq)}$ (10 mL) and brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 4:1 Et_2O-hexane as eluent gave vinyl triflate **110** (130 mg, 36%) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-1-032

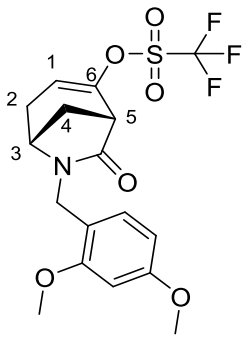
NaHMDS (2.8 mL of a 2 M solution in THF, 1.52 mmol, 1.8 eq) was added dropwise to a stirred solution of normorphan **109** (230 mg, 0.79 mmol, 1.0 eq) in THF (2.8 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, a solution of $PhNTf_2$ (367 mg, 1.23 mmol, 1.3 eq) in THF (2.2 mL) was added and the resulting solution was allowed to warm slowly to rt. The solution was stirred at rt for 48 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 4:1 Et_2O-hexane as eluent gave vinyl triflate **110** (113 mg, 33%) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-1-038

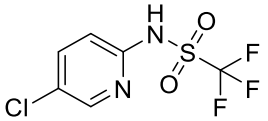
NaHMDS (9.2 mL of a 2 M solution in THF, 18.4 mmol, 1.6 eq) was added dropwise to a stirred solution of normorphan **109** (3.55 g, 12.3 mmol, 1.0 eq) in THF (30 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, a solution of $PhNTf_2$ (5.70 g, 15.9 mmol, 1.3 eq) in THF (20 mL) was added and resulting the solution was allowed to warm slowly to rt. The solution was stirred at rt for 18 h. Saturated $NH_4Cl_{(aq)}$ (30 mL) was added and the mixture was extracted with Et_2O (5 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 4:1 Et_2O-hexane as eluent gave vinyl triflate **110** (3.20 g, 61%) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-2-111

6-(2,4-Dimethoxybenzyl)-7-oxo-6-azabicyclo[3.2.1]oct-2-en-2-yl trifluoromethanesulfonate 110 and *N*-(5-chloropyridin-2-yl)-1,1,1-trifluoromethanesulfonamide 114



110



114

n-BuLi (0.25 mL of a 2.2 M solution in THF, 0.53 mmol, 1.3 eq) was added dropwise to a stirred solution of *i*-Pr_2NH (75 µL, 0.53 mmol, 1.3 eq) in THF (1 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 10 min. Then, a solution of normorphan **109** (118 mg, 0.41 mmol, 1.0 eq) in THF (1 mL) was added. The resulting solution was stirred at –78 °C for 1 h. Then, solution of Comins' reagent **113** (208 mg, 0.53 mmol, 1.3 eq) in THF (1 mL) was added and the resulting solution was allowed to warm slowly to rt. The solution was stirred at rt for 18 h. Saturated $NH_4Cl_{(aq)}$ (2 mL) was added and the mixture extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and the evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 4:1 Et_2O-hexane as eluent gave an 80:20 mixture of vinyl triflate **110** and sulfonamide **114** (69 mg, i.e. 56.6 mg (33%) of vinyl triflate **110**) as a clear oil. Diagnostic signals for sulfonamide **114**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15–8.10 (m, 1H), 7.82–7.75 (m, 1H), 7.72–7.64 (m, 1H).

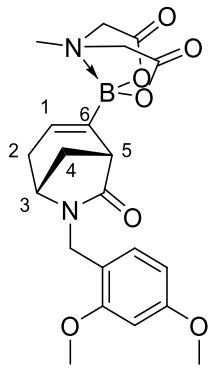
Lab book reference: ARG-1-022

NaHMDS (0.53 mL of a 2 M solution in THF, 1.08 mmol, 1.3 eq) was added dropwise to a stirred solution of normorphan **109** (240 mg, 0.83 mmol, 1.0 eq) in THF (1.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, a solution of Comins' reagent **113** (424 mg, 1.08 mmol, 1.3 eq) in THF (2.5 mL) was added and the resulting solution was allowed to warm slowly to rt. The solution was stirred at rt for 18 h. Saturated

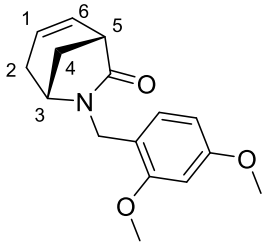
$NH_4Cl_{(aq)}$ (5 mL) was added and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 4:1 Et_2O-hexane as eluent an 85:15 mixture of vinyl triflate **110** and sulfonamide **114** (219 mg, i.e. 190 mg (54%) of vinyl triflate **110**) as a clear oil.

Lab book reference: ARG-1-025

8-(6-(2,4-Dimethoxybenzyl)-7-oxo-6-azabicyclo[3.2.1]oct-2-en-2-yl)-4-methyldihydro-4λ⁴,8λ⁴-[1,3,2]oxazaborolo[2,3-*b*][1,3,2]oxazaborole-2,6(3*H*,5*H*)-dione 94 and 6-(2,4-dimethoxybenzyl)-6-azabicyclo[3.2.1]oct-2-en-7-one 115



94



115

A solution of vinyl triflate **110** (1.98 g, 4.70 mmol, 1.0 eq), $PdCl_2(PPh_3)_2$ (97 mg, 0.14 mmol, 0.03 eq), PPh_3 (73 mg, 0.28 mmol, 0.06 eq), KOPh (931 mg, 7.05 mmol, 1.5 eq) and B_2pin_2 (1.31 g, 5.17 mmol, 1.1 eq) in toluene (30 mL) under Ar was stirred and heated at 50 °C for 16 h. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude pinacol boronate. The crude pinacol boronate was dissolved in DMSO (24 mL) and MIDA (4.49 g, 30.54 mmol, 6.5 eq) and $HC(OEt)_3$ (3.70 mL, 21.14 mmol, 4.5 eq) were added. The resulting mixture was stirred and heated at 100 °C under Ar for 48 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the mixture was extracted with EtOAc (4 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 to 7:3 CH_2Cl_2-acetone as eluent gave alkene **115** (192 mg, 15%) as a clear oil, R_F (9:1 hexane-acetone) 0.1; IR (ATR) 2940, 2835, 1685 (C=O), 1612, 1587, 1506, 1411, 1206, 1031, 832, 669 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$) δ 7.09–7.03 (m, 1H, Ar), 6.42–6.34 (m, 2H, Ar), 6.07 (dddd, *J* = 9.0, 7.0, 1.0, 1.0 Hz, 1H, =CH-6), 5.51 (dddd, *J* = 9.0, 3.5, 3.0, 1.5 Hz, 1H, =CH-1), 4.50 (d, *J* = 15.0 Hz, 1H, NC*H*H'), 4.16 (d, *J* = 15.0 Hz, 1H, NCH*H'*), 3.76–3.71 (m, 6H, OMe), 3.66–3.62 (m, 1H, NCH), 2.75 (dd, *J* = 7.0, 4.5 Hz, 1H, CH-5), 2.17 – 2.04 (m, 3H, CHH'-2, C*H*H'-4), 1.71 (d, *J* = 10.0 Hz, 1H, CH*H'*-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.5 (C=O), 160.4 (*ipso*-Ar), 158.5 (*ipso*-Ar), 130.3 (Ar), 129.2 (=CH-6), 126.0 (=CH-1), 117.8 (*ipso*-Ar), 104.3 (Ar), 98.4 (Ar), 55.4 (OMe), 54.3 (NCH), 40.8 (CH-5), 37.8 (NCH_2), 33.9 (CH_2-4), 28.3 (CH_2-2) (1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{16}H_{19}NO_3$ $(M+Na)^+$ 296.1257, found 296.1250 (+2.7 ppm error) and vinyl MIDA boronate **94** (1.40 g, 70%) as an off-white crystalline solid, mp 80-82 °C; R_F (4:1 CH_2Cl_2-acetone) 0.29; IR (ATR) 2958, 1760 (C=O, ester), 1673 (C=O, amide), 1614, 1508, 1457, 1292, 1180, 1036, 823 cm^{-1}; ^{1}H NMR (400 MHz, d_6-acetone) δ 7.08 (d, *J* = 8.5 Hz, 1H, Ar), 6.53 (d, *J* = 2.5 Hz, 1H, Ar), 6.45 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar), 5.98 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H, =CH), 4.41 (d, *J* = 15.0 Hz, 1H, NC*H*H'), 4.27–4.07 (m, 4H, NCH*H'*, CHH'CO_2), 3.96 (d, *J* = 17.0 Hz, 1H, CH*H'*CO_2), 3.81 (s, 3H, OMe), 3.78–3.71 (m, 4H, OMe, NCH), 2.84 (s, 3H, NMe), 2.64 (d, *J* = 4.5 Hz, 1H, CH-5), 2.24–2.17 (m, 2H, CHH'-2), 2.16 (ddd, *J* = 10.5, 5.5, 4.5 Hz, 1H, C*H*H'-4), 1.67 (d, *J* = 10.5 Hz, 1H, CH*H'*-4); ^{13}C NMR (100.6 MHz, d_6-acetone) δ 177.0 (C=O, amide), 169.2 (C=O, ester), 167.9 (C=O, ester), 160.7 (*ipso*-Ar), 158.6 (*ipso*-Ar), 134.1 (=CH), 130.0 (Ar), 117.8 (*ipso*-Ar), 104.6 (Ar), 98.2 (Ar), 62.0 (*C*H_2CO_2), 61.3 (*C*H_2CO_2), 55.0 (OMe), 54.8 (OMe), 54.3 (NCH), 45.8 (NMe), 41.8 (CH-5), 37.6 (NCH_2), 33.7 (CH_2-4), 28.8 (CH_2-2, only resolved in DEPT-135) (=C-B resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{21}H_{25}BN_2O_7$ $(M + Na)^+$ 451.1647, found 451.1654 (–0.2 ppm error)

Lab book reference: ARG-2-114

$PdCl_2$(dppf) (22 mg, 0.03 mmol, 0.06 eq), dppf (17 mg, 0.03 mmol, 0.06 eq), KOAc (134 mg, 1.37 mmol, 3.0 eq) and B_2pin_2 (137 mg, 0.54 mmol, 1.2 eq) were added to a stirred solution of vinyl triflate **110** (193 mg, 0.46 mmol, 1.0 eq) in dioxane (3 mL) at rt under Ar. The resulting mixture was stirred and heated at 80 °C under Ar for 16 h. H_2O (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude pinacol boronate. Purification by flash column chromatography

on silica with 4:6 EtOAc-hexane as eluent gave impure pinacol boronate **111** (100 mg) which was dissolved in DMSO (1.2 mL). MIDA (228.5 mg, 1.55 mmol, 6.2 eq) and $HC(OEt)_3$ (0.17 mL, 1.0 mmol, 4.0 eq) were added. The resulting mixture was stirred and heated at 100 °C under Ar for 48 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 to 7:3 CH_2Cl_2-acetone as eluent gave vinyl MIDA boronate **94** (49 mg, 25%) as an off-white crystalline solid identical (by ^1H and ^{13}C NMR spectroscopy) to that described above. Diagnostic signals for pinacol boronate **111**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.11–7.07 (m, 1H, Ar), 6.43–6.39 (m, 2H, Ar), 6.39–6.37 (m, 1H, =CH), 4.52 (d, *J* = 15.0 Hz, 1H, NC*H*H'), 4.14 (d, *J* = 15.0 Hz, 1H, NCH*H'*), 3.84–3.74 (m, 6H, OMe), 3.66–3.60 (m, 1H, NCH), 3.07 (d, *J* = 4.5 Hz, 1H, C(O)CH), 2.11 (ddd, *J* = 10.5, 5.5, 5.5 Hz, 1H, C*H*H'), 1.64 (d, *J* = 10.5 Hz, 1H, CH*H'*); HRMS (ESI) *m/z* calcd for $C_{22}H_{30}BNO_5$ $(M + Na)^+$ 422.2109, found 422.2117 (–1.0 ppm error).

Lab book reference: ARG-1-015

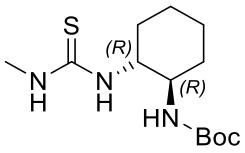
A solution of vinyl triflate **110** (219 mg, 0.52 mmol, 1.0 eq), $PdCl_2(PPh_3)_2$ (15 mg, 0.02 mmol, 0.03 eq), PPh_3 (8 mg, 0.03 mmol, 0.06 eq), KOPh (103 mg, 0.78 mmol, 1.5 eq) and B_2pin_2 (145 mg, 0.57 mmol, 1.1 eq) in toluene (3 mL)was stirred and heated at 50 °C under Ar for 16 h. H_2O (15 mL) was added, and the mixture was extracted with EtOAc (4 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude pinacol boronate. Purification by flash column chromatography on silica with 4:6 EtOAc-hexane as eluent gave impure pinacol boronate **111** (158 mg) which was dissolved in DMSO (1.8 mL). MIDA (343 mg, 2.33 mmol, 6.2 eq) and $HC(OEt)_3$ (0.25 mL, 1.50 mmol, 4.0 eq) were added. The reaction mixture was heated and stirred at 100 °C under Ar for 48 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the mixture was extracted with EtOAc (4 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 to 7:3 CH_2Cl_2-acetone as eluent gave vinyl MIDA boronate **94** (122 mg, 54%) as an off-white crystalline solid, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-1-028

A solution of vinyl triflate **110** (1.45 g, 3.44 mmol, 1.0 eq), $PdCl_2(PPh_3)_2$ (72 mg, 0.10 mmol, 3 mol%), PPh_3 (54 mg, 0.21 mmol, 6 mol%), KOPh (682 mg, 5.16 mmol, 1.5 eq) and B_2pin_2 (961 mg, 3.78 mmol, 1.1 eq) in toluene (22 mL) was stirred and heated at 50 °C under Ar for 16 h. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude pinacol boronate **111**. The crude pinacol boronate was dissolved in DMSO (18 mL) and MIDA (1.52 g, 10.32 mmol, 3.0 eq) and $HC(OEt)_3$ (2.4 mL, 13.76 mmol, 4.0 eq) were added. The reaction mixture was stirred and heated to 100 °C under Ar for 48 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the mixture extracted with EtOAc (4 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 to 7:3 CH_2Cl_2-acetone as eluent gave alkene **115** (150 mg, 17%) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above and vinyl MIDA boronate **94** (850 mg, 60%) as an off-white crystalline solid, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-2-120

tert-Butyl ((1*R*,2*R*)-2-(3-methylthioureido)cyclohexyl)carbamate (*R*,*R*)-118



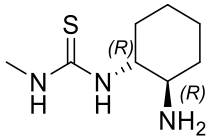
(*R*,*R*)-**118**

Methyl isothiocyanate (419 mg, 5.60 mmol, 3 eq) was added to a stirred solution of *tert*-butyl ((1*R*,2*R*)-2-aminocyclohexyl)carbamate (*R*,*R*)-**117** (400 mg, 1.87 mmol, 1.0 eq) in CH_2Cl_2 (8.5 mL) under Ar at rt. The solution was stirred at rt for 24 h. 1 M $NaOH_{(aq)}$ (10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:6 EtOAc-hexane as eluent gave *N*-Boc-thiourea (*R*,*R*)-**118** (484 mg, 90%) as a white gum, $[\alpha]_D$ –4.1 (*c* 2.1 $CHCl_3$) (lit.,[68] $[\alpha]_D$ –4.3 (*c* 2.1 $CHCl_3$)); R_F (1:1 EtOAc-hexane)

0.32; IR (ATR) 3332 (NH), 2933, 1674 (C=O), 1504, 1414, 1165 cm^{-1}; ^{1}H NMR (400 MHz, d_4-methanol) δ 4.13–3.97 (m, 1H, NCH), 2.87 (br s, 3H, NMe), 2.10–1.87 (m, 2H), 1.77–1.62 (m, 2H), 1.47–1.36 (m, 10H), 1.33–1.19 (m, 5H); ^{13}C NMR (100.6 MHz, d_4-methanol) δ 157.2 (C=O), 78.7 (O*C*Me_3), 60.2, 54.0, 32.3, 32.0, 27.4, 24.7, 24.5, 13.2 (C=S resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{13}H_{25}N_3O_2S$ $(M + Na)^+$ 310.1560, found 310.1561 (–0.4 ppm error). Spectroscopic data consistent with those reported in the literature.[68]

Lab book reference: ARG-1-074

1-((1*R*,2*R*)-2-Aminocyclohexyl)-3-methylthiourea (*R*,*R*)-77

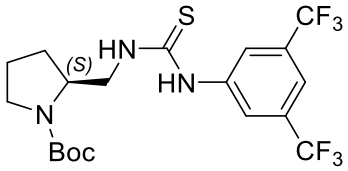


(*R*,*R*)-**77**

4 M HCl in dioxane (1.79 mL, 7.18 mmol, 9.6 eq) was added to a stirred solution of *N*-Boc-thiourea (*R*,*R*)-**118** (215 mg, 0.748 mmol, 1.0 eq) in CH_2Cl_2 (4.7 mL) at rt under Ar. The resulting solution was stirred at rt for 6 h. The solvent was evaporated under reduced pressure. CH_2Cl_2 (5 mL) was added. Then 1 M $NaOH_{(aq)}$ (10 mL) was added and brine (5 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (6 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the thiourea (*R*,*R*)-**77** (180 mg, 96%) as a white gum, $[\alpha]_D$ +7.5 (*c* 3.0 $CHCl_3$) (lit.,[68] $[\alpha]_D$ +7.3 (*c* 3.0 $CHCl_3$)); IR (ATR) 2933, 1515, 1414 cm^{-1}; ^{1}H NMR (400 MHz, d_4-methanol) δ 4.18–3.63 (m, 1H, NCH), 2.95 (s, 3H, NMe), 2.59–2.46 (m, 1H, NCH), 2.00–1.93 (m, 2H), 1.84–1.67 (m, 2H), 1.50–1.16 (m, 4H); ^{13}C NMR (100.3 MHz, d_4-methanol) δ 55.8, 35.2, 33.0, 26.7, 26.0 (C=S, NMe, NCH resonances not resolved); HRMS (ESI) *m/z* calcd for $C_8H_{17}N_3S$ $(M + H)^+$ 188.1216, found 188.1213 (+1.5 ppm error). Spectroscopic data consistent with those reported in the literature.[68]

Lab book reference: ARG-2-094

***tert*-Butyl (*S*)-2-((3-(3,5-bis(trifluoromethyl)phenyl)thioureido)methyl)pyrrolidine-1-carboxylate (*S*)-121**

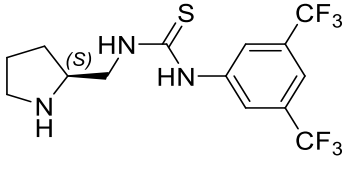


(*S*)-121

1-Isothiocyanato-3,5-bis(trifluoromethyl)benzene **120** (938 mg, 3.46 mmol, 1.4 eq) was added to a stirred solution of *tert*-butyl (*S*)-2-(aminomethyl)pyrrolidine-1-carboxylate (*S*)-**119** (630 mg, 3.46 mmol, 1.0 eq) in CH_2Cl_2 (21 mL) at rt under Ar. The resulting solution was stirred at rt for 24 h. 1 M $NaOH_{(aq)}$ (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 EtOAc-hexane as eluent gave *N*-Boc-thiourea (*S*)-**121** (1.27 g, 85%) as an off-white solid, mp 94-96 °C; R_F (1:1 EtOAc-hexane) 0.22; IR (ATR) 2978, 1658 (C=O), 1368, 1274, 681 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO, 120 °C) δ 9.87 (br s, 1H, NH), 8.30 (s, 2H, Ar), 8.04 (br s, 1H, NH), 7.64 (s, 1H, Ar), 4.05–3.97 (m, 1H, NCH), 3.83 – 3.74 (m, 1H, NC*H*H'), 3.64–3.55 (m, 1H, NCH*H'*), 3.42–3.24 (m, 2H, C(O)NCHH'), 2.02–1.76 (m, 4H, CH_2), 1.43 (s, 9H, CMe3); ^{13}C NMR (100.6 MHz, d_6-DMSO, 120 °C) δ 181.9 (C=S), 154.8 (C=O), 142.7 (*ipso*-Ar), 130.9 (q, *J* = 33.0 Hz, *ipso*-Ar), 125.2, 122.5, 79.4 (*C*Me_3), 56.8, 47.5, 46.9, 28.7 (C*Me*$_3$) (Ar, CF_3 resonances not resolved) HRMS (ESI) *m/z* calcd for $C_{19}H_{23}F_6N_3O_2S$ $(M + Na)^+$ 494.1307, found 494.1296 (+2.4 ppm error).

Lab book reference: ARG-1-077

(*S*)-1-(3,5-bis(Trifluoromethyl)phenyl)-3-(pyrrolidin-2-ylmethyl)thiourea (*S*)-116



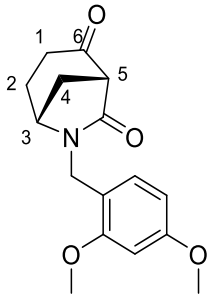
(*S*)-116

TFA (4.0 mL, 47.7 mmol, 150 eq) was added to a stirred solution of *N*-Boc-thiourea (*S*)-**121** (150 mg, 0.32 mmol, 1.0 eq) in CH_2Cl_2 (4 mL) at rt under Ar. The resulting solution was stirred at rt for 2 h. 1 M $NaOH_{(aq)}$ (4 mL) was added and the mixture was extracted with

CH_2Cl_2 (4 × 10 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give thiourea (*S*)-**116** (117 mg, 99%) as an off-white solid, $[\alpha]_D$ –26.3 (*c* 0.70 $CHCl_3$) (lit.,[89] $[\alpha]_D$ –26.7 (*c* 0.695 $CHCl_3$)); mp 102-104 °C (lit.,[89] 102 °C); IR (ATR) 3246 (NH), 2958, 1550, 1276, 681 cm^{-1}; ^1H NMR (400 MHz, d_4-methanol) δ 8.10 (s, 2H, Ar), 7.50 (s, 1H, Ar), 3.89–3.79 (m, 3H, NCH, NCH_2), 3.24 (ddd, *J* = 11.5, 7.5, 7.5 Hz, 1H, C(O)NC*H*H'), 3.18–3.11 (m, 1H, C(O)NCH*H'*), 2.11–2.01 (m, 1H, CH), 2.00–1.86 (m, 2H, CH), 1.75–1.64 (m, 1H, CH); ^{13}C NMR (100.6 MHz, d_4-methanol) δ 184.2 (C=S), 142.8 (*ipso*-Ar), 132.7 (q, *J* = 33.5 Hz, *ipso*-Ar), 124.7 (q, *J* = 272.0 Hz, CF_3), 124.2 (br, Ar), 118.3 (br, Ar), 61.8 (NCH), 46.5 (NCH_2), 45.5 (NCH_2), 28.6 (CH_2), 24.2 (CH_2); HRMS (ESI) *m/z* calcd for $C_{14}H_{15}F_6N_3S$ $(M + H)^+$ 372.0964, found 372.0962 (+0.4 ppm error). Spectroscopic data consistent with those reported in the literature.[89]

Lab book reference: ARG-2-121

6-(2,4-Dimethoxybenzyl)-6-azabicyclo[3.2.1]octane-2,7-dione 109



109

A solution of trichloroacetamide **108** (200 mg, 0.49 mmol, 1.0 eq) and (*S*)-prolinamide (*S*)-**38** (28 mg, 0.24 mmol, 0.5 eq) in DMSO (2.0 mL) was stirred and heated at 50 °C in a sealed tube for 5 days. Water (5 mL) was added and the mixture extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 4:1 EtOAc-hexane as eluent gave enantioenriched normorphan **109** (33 mg, 25%, 77:23 er by CSP-HPLC) as a red oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above; CSP-HPLC: Chiracel IC (1 *i*-PrOH, 0.5 mL min^{-1}) 40.4 min (major), 56.5 min (minor) (Figure 6.1).

Lab book reference: ARG-1-009

A solution of trichloroacetamide **108** (200 mg, 0.49 mmol, 1.0 eq), thiourea (*R*,*R*)-**77** (6 mg, 0.02 mmol, 0.05 eq) and benzoic acid (1.5 mg, 0.01 mmol, 0.02 eq) in CH_2Cl_2 (2.5 mL) was stirred and heated at 50 °C in a sealed tube for 7 days. The solvent was evaporated under reduced pressure to give the crude product which contained (by ^{1}H and ^{13}C NMR spectroscopy) no trace of product.

Lab book reference: ARG-1-044

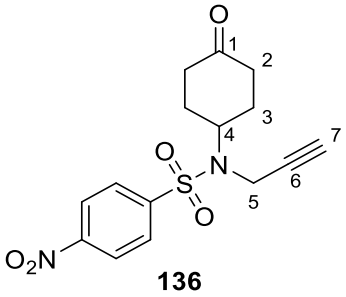
A solution of trichloroacetamide **108** (100 mg, 0.24 mmol, 1.0 eq) and thiourea (*R*,*R*)-**77** (20 mg, 0.12 mmol, 0.5 eq) in DMSO (1.0 mL) was stirred and heated at 50 °C in a sealed tube for 5 days. Water (5 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 4:1 EtOAc-hexane as eluent gave enantioenriched normorphan **109** (9 mg, 12%, 60:40 er by CSP-HPLC) as a red oil, identical (by ^{1}H and ^{13}C NMR spectroscopy) to that described above. CSP-HPLC: Chiracel IC (1 *i*-PrOH, 0.5 mL min^{-1}) 35.6 min (major), 49.4 min (minor) (Figure 6.2).

Lab book reference: ARG-1-065

A solution of trichloroacetamide **108** (100 mg, 0.24 mmol, 1.0 eq) and thiourea (*S*)-**116** (45 mg, 0.12 mmol, 0.5 eq) in DMSO (1.0 mL) was stirred and heated at 50 °C in a sealed tube for 5 days. Water (5 mL) was added and the mixture extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 4:1 EtOAc-hexane as eluent gave enantioenriched normorphan **109** (21 mg, 30%, 55:45 er by CSP-HPLC) as a red oil, identical (by ^{1}H and ^{13}C NMR spectroscopy) to that described above. CSP-HPLC: Chiracel IC (1 *i*-PrOH, 0.5 mL min^{-1}) 35.7 min (major), 49.1 min (minor) (Figure 6.3).

Lab book reference: ARG-1-061

4-Nitro-*N*-(4-oxocyclohexyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide 136



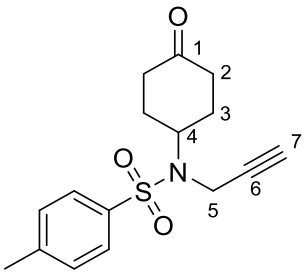
136

A solution of 1,4-cyclohexadione monoethylene acetal **29** (1.73 g, 7.51 mmol, 1.0 eq), propargylamine (0.5 mL, 7.81 mmol, 1.04 eq) and $NaBH(OAc)_3$ (2.23 g, 10.51 mmol, 1.4 eq) in CH_2Cl_2 (25 mL) was stirred at rt for 24 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added. Then, 1 M $NaOH_{(aq)}$ was added until pH ≈ 10 was reached. The mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude amine as a pale yellow oil. To a solution of the crude amine in THF (18 mL) was added 3 M $HCl_{(aq)}$ (18 mL) and the resulting solution was stirred at rt for 72 h. Solid Na_2CO_3 was added until pH ≈ 9 was reached and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude amino ketone as a red oil. The crude amino ketone and DMAP (88 mg, 0.72 mmol, 0.1 eq) were dissolved in CH_2Cl_2 (36 mL). The resulting solution was cooled to 0 °C and Et_3N (1.25 mL, 9.01 mmol, 1.25 eq) was added under Ar. Then, a solution of 4-nitrobenzenesulfonyl chloride (2.00 g, 9.01 mmol, 1.25 eq) in CH_2Cl_2 (4.5 mL) was added dropwise and the solution was allowed to warm to rt. The resulting solution was stirred at rt for 18 h and then 1 M $HCl_{(aq)}$ (10 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with CH_2Cl_2 as eluent gave alkynyl amino ketone **136** (2.51 g, 45%) as an off-white solid, mp 146-148 °C (lit.,[69] 147-148 °C); R_F (CH_2Cl_2) 0.32; IR (ATR) 2954, 1716 (C=O), 1529 (NO_2), 1350 (S=O), 1163, 735, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41–8.31 (m, 2H, Ar), 8.20–8.08 (m, 2H, Ar), 4.36–4.18 (m, 1H, NCH), 4.18 (d, *J* = 2.5 Hz, 2H, NCH_2), 2.51–2.35 (m, 4H, CH_2-2), 2.17 (t, *J* = 2.5 Hz, 1H, ≡CH), 2.11–1.94 (m, 4H, CH_2-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 207.9 (C=O), 150.2 (*ipso*-Ar), 146.4 (*ipso*-Ar), 128.7 (Ar), 124.4 (Ar), 78.8 (≡C-6), 73.9 (≡CH-7), 56.3 (NCH), 39.8 (NCH_2), 32.8 (CH_2-2), 30.2 (CH_2-3); HRMS (ESI) *m/z* calcd for $C_{15}H_{16}N_2O_5S$

$(M + Na)^+$ 359.0672, found 359.0676 (–1.1 ppm error). Spectroscopic data consistent with those reported in the literature.[69]

Lab book reference: ARG-1-085

4-Methyl-*N*-(4-oxocyclohexyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide 59



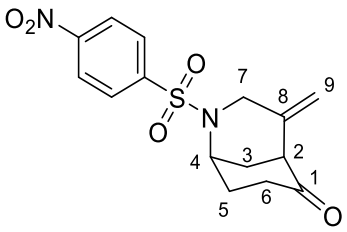
59

A solution of 1,4-cyclohexadione monoethylene acetal **29** (5.05 g, 32.3 mmol, 1.0 eq), propargylamine (2.2 mL, 32.6 mmol, 1.04 eq) and $NaBH(OAc)_3$ (9.59 g, 42.3 mmol, 1.4 eq) in CH_2Cl_2 (108 mL) was stirred at rt for 24 h. Saturated $NH_4Cl_{(aq)}$ (25 mL) was added. Then, 1 M $NaOH_{(aq)}$ was added until pH ≈ 10 was reached. The mixture was extracted with CH_2Cl_2 (4 × 25 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude amine as a pale yellow oil. To a solution of the crude amine in THF (40 mL) was added 3 M $HCl_{(aq)}$ (120 mL) and the resulting solution was stirred at rt for 72 h. Solid Na_2CO_3 was added until pH ≈ 9 was reached and the mixture was extracted with EtOAc (4 × 25 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude amino ketone as red oil. The crude amino ketone and DMAP (394 mg, 3.23 mmol, 0.1 eq) were dissolved in CH_2Cl_2 (160 mL). The resulting solution was cooled to 0 °C and Et_3N (5.63 mL, 40.4 mmol, 1.25 eq) was added under Ar. Then, a solution of *p*-toluenesulfonyl chloride (7.70 g, 40.4 mmol, 1.25 eq) in CH_2Cl_2 (20 mL) was added dropwise and the mixture was allowed to warm to rt. The resulting solution was stirred at rt for 18 h and then 1 M $HCl_{(aq)}$ (25 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (4 × 20 mL) and the combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:3 EtOAc-hexane as eluent gave alkynyl amino ketone **59** (8.44 g, 85%) as an off-white solid, mp 125-127 °C (lit.,[69] 126-127 °C); R_F (1:3 EtOAc-hexane) 0.21; IR (ATR) 2954, 1714 (C=O), 1326 (S=O), 1157,

1044, 656, 571 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.78 (m, 2H, Ar), 7.32–7.27 (m, 2H, Ar), 4.26–4.12 (m, 1H, NCH), 4.10 (d, *J* = 2.5 Hz, 2H, NCH_2), 2.46–2.33 (m, 7H, Me, CH_2-2), 2.16 (t, *J* = 2.5 Hz, 1H, ≡CH), 2.12–1.90 (m, 4H, CH_2-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.7 (C=O), 143.8 (*ipso*-Ar), 137.6 (*ipso*-Ar), 129.8 (Ar), 127.4 (Ar), 79.8 (≡CH), 73.1 (≡C), 55.7 (NCH), 40.0 (CH_2-2), 32.6 (NCH_2), 30.1 (CH_2-3), 21.7 (Me); HRMS (ESI) *m/z* calcd for $C_{16}H_{19}NO_3S$ $(M + Na)^+$ 238.0978, found 328.0978 (–0.1 ppm error). Spectroscopic data consistent with those reported in the literature.[69]

Lab book reference: ARG-2-038

4-Methylene-2-((4-nitrophenyl)sulfonyl)-2-azabicyclo[3.3.1]nonan-6-one 86



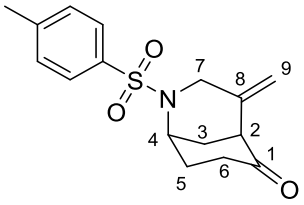
86

$Cu(OTf)_2$ (11 mg, 0.03 mmol, 0.05 eq), PPh_3 (31 mg, 0.12 mmol, 0.20 eq) and pyrrolidine (10 µL, 0.12 mmol, 0.2 eq) were added to a stirred solution of amino ketone **136** (200 mg, 0.60 mmol, 1.0 eq) in THF (3 mL) in a sealed tube at rt under Ar. The resulting mixture was stirred at rt for 15 min and then stirred and heated at 90 °C for 18 h. The mixture was allowed to cool to rt and the solids were removed by filtration through Celite®. The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with CH_2Cl_2 as eluent gave morphan **86** (170 mg, 85%) as an off-white solid, mp 172-174 °C; R_F (CH_2Cl_2) 0.32; IR (ATR) 2954, 1714 (C=O), 1529, (NO_2), 1650, 1164 (S=O), 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43–8.38 (m, 2H, Ar), 8.07–8.02 (m, 2H, Ar), 5.14 (d, *J* = 1.5 Hz, 1H, =C*H*H'), 5.07 (d, *J* = 1.5 Hz, 1H, =CH*H'*), 4.24 (d, *J* = 14.5 Hz, 1H, NC*H*H'), 4.13 (dd, *J* = 3.0, 3.0 Hz, 1H, NCH), 3.83 (dd, *J* = 14.5, 1.0 Hz, 1H, NCH*H'*), 3.30–3.23 (m, 1H, CH-2), 2.78 (ddd, *J* = 16.0, 13.0, 8.0 Hz, 1H, C*H*H'-6), 2.42–2.30 (m, 2H, CH*H'*-6, C*H*H'-5), 2.02–1.88 (m, 3H, CH*H'*-5, CHH'-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 207.4 (C=O), 150.3 (*ipso*-Ar), 143.8 (*ipso*-Ar), 137.2 (=C), 128.6 (Ar), 124.7 (Ar), 115.9 (=CH_2), 50.1 (CH-2), 48.4 (NCH), 47.4 (NCH_2), 34.8 (CH_2-6), 32.3 (CH_2-5), 30.7 (CH_2-3); HRMS (ESI) *m/z* calcd for $C_{15}H_{16}N_2O_5S$ $(M + Na)^+$ 359.0672, found

359.0672 (–0.1 ppm error). Spectroscopic data consistent with those reported in the literature.[69]

Lab book reference: ARG-2-003

4-Methylene-2-toluenesulfonyl-2-azabicyclo[3.3.1]nonan-6-one 60

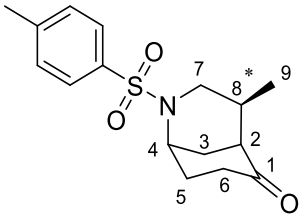


60

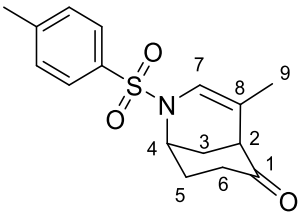
$Cu(OTf)_2$ (89 mg, 0.25 mmol, 0.05 eq), PPh_3 (258 mg, 0.98 mmol, 0.20 eq) and pyrrolidine (82 µL, 0.982 mmol, 0.20 eq) were added to a stirred solution of amino ketone **59** (1.5 g, 4.91 mmol, 1.0 eq) in THF (25 mL) in a sealed tube at rt under Ar. The resulting mixture was stirred at rt for 15 min and then stirred and heated at 90 °C for 18 h. The mixture was allowed to cool to rt and the solids were removed by filtration through Celite®. The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:4 to 1:1 EtOAc-hexane as eluent gave morphan **60** (1.25 g, 83%) as an off-white solid, mp 138-140 °C (lit.,[69] 136-138 °C); R_F (1:4 EtOAc-hexane) 0.08; IR (ATR) 2952, 1713 (C=O), 1342, 1160 (S=O), 1095, 547 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75–7.70 (m, 2H, Ar), 7.35–7.31 (m, 2H, Ar), 5.10 (d, *J* = 2.0 Hz, 1H, =C*H*H'), 5.01 (d, *J* = 2.0 Hz, 1H, =CH*H'*), 4.16 (d, *J* = 14.0 Hz, 1H, NC*H*H'), 4.09 (dd, *J* = 3.5, 3.0 Hz, 1H, NCH), 3.75 (d, *J* = 14.0 Hz, 1H, NCH*H'*), 3.22 (br s, 1H, CH-2), 2.80 (ddd, *J* = 16.0, 13.0, 7.5 Hz, 1H, C*H*H'-6), 2.43 (s, 3H, Me), 2.40–2.31 (m, 1H,C*H*H'-5), 2.27 (dd, *J* = 16.0, 6.0 Hz, 1H, CH*H'*-6), 1.96 (dddd, *J* = 14.0, 3.5, 3.5, 3.5 Hz, 1H, C*H*H'-3), 1.87 (ddd, *J* = 14.0, 3.0, 3.0 Hz, 1H, CH*H'*-3), 1.90–1.80 (m, 1H, CH*H'*-5); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.3 (C=O), 143.0 (*ipso*-Ar), 138.2 (=C), 134.8 (*ipso*-Ar), 130.0 (Ar), 127.4 (Ar), 115.2 ($=CH_2$), 50.2 (CH-2), 48.0 (NCH), 47.2 (NCH_2), 34.8 (CH_2-6), 32.5 (CH_2-5), 30.5 (CH_2-3), 21.6 (Me).; HRMS (ESI) *m/z* calcd for $C_{16}H_{19}NO_3S$ $(M + Na)^+$ 329.0978, found 328.0971 (+2.2 ppm error). Spectroscopic data consistent with those reported in the literature.[69]

Lab book reference: ARG-2-023

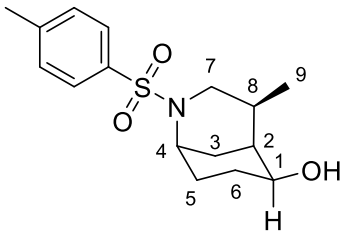
4-Methyl-2-toluenesulfonyl-2-azabicyclo[3.3.1]nonan-6-one *endo*-141, 4-methyl-2-toluenesulfonyl-2-azabicyclo[3.3.1]non-3-en-6-one 142 and 4-methyl-2-toluenesulfonyl-2-azabicyclo[3.3.1]nonan-6-ol 143



endo-**141**



142



143

PtO_2 (39 mg, 0.17 mmol, 0.06 eq) was added to a stirred solution of morphan **60** (846 mg, 2.77 mmol, 1 eq) in EtOAc (14 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and then with H_2 three times. The mixture was stirred under a balloon of H_2 (760 mmHg) for 6 h. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:4 to 3:2 Et_2O-hexane as eluent gave hydrogenated morphan *endo*-**141** (124 mg, 15%, >97:3 dr) as a white solid, mp 146-148 °C; R_F (2:3 Et_2O-hexane) 0.15; IR (ATR) 2929, 1702 (C=O), 1338, 1158 (S=O), 546 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73–7.68 (m, 2H, Ar), 7.34–7.29 (m, 2H, Ar), 4.29 (dd, *J* = 3.5, 3.0 Hz, 1H, NCH), 3.83 (dd, *J* = 13.5, 6.0 Hz, 1H, NC*H*H'), 2.81 (dd, *J* = 13.5, 12.5 Hz, 1H, NCH*H'*), 2.48–2.38 (m, 5H, Ar*Me*, CH-2, C*H*H'-6), 2.10 (ddd, *J* = 18.0, 10.5, 8.5 Hz, 1H, CH*H'*-6), 2.04–1.84 (m, 5H, CHH'-5, CHH'-3, CH-8), 0.84 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 211.0 (C=O), 143.6 (*ipso*-Ar), 137.3 (*ipso*-Ar), 130.0 (Ar), 127.1 (Ar), 49.0 (CH-2), 47.4 (NCH_2), 46.1 (NCH), 39.3 (CH_2-6), 32.8 (CH_2-5), 32.7 (CH-8), 28.6 (CH-3), 21.6 (Ar*Me*), 16.8 (CH*Me*); HRMS (ESI) *m/z* calcd for $C_{16}H_{21}NO_3S$ $(M + Na)^+$ 330.1164, found 330.1129 (+1.6 ppm error) and impure alcohol **143** (670 mg) as an off-white solid.

Lab book reference: ARG-2-024

10 % Pd/C (49 mg, 0.04 mmol, 0.10 eq) was added to a stirred solution of morphan **60** (150 mg, 0.49 mmol, 1 eq) in MeOH (20 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and then with H_2 three times. The mixture was stirred under a balloon of H_2 (760 mmHg) for 16 h. The solids were

removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude product which contained (by ^{1}H NMR spectroscopy) a complex mixture of products.

Lab book reference: ARG-2-007

10 % Pd/C (100 mg, 0.08 mmol, 0.25 eq) was added to a stirred solution of morphan **60** (100 mg, 0.33 mmol, 1 eq) in EtOAc (16 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and then with H_2 three times. The mixture was stirred under a balloon of H_2 (760 mmHg) for 2 h. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:4 to 3:2 Et_2O-hexane as eluent gave a 75:25 mixture (by ^{1}H NMR spectroscopy) of hydrogenated morphans *endo*-**141** and *exo*-**141** (43 mg, 40%) as a white solid and a 95:5 mixture (by ^{1}H NMR spectroscopy) of enamine **142** and morphan **60** (59 mg, i.e. 56 mg (56%) of **142** and 3 mg (3%) of **60**) as an off-white solid, R_F (3:2 Et_2O-hexane) 0.52; IR (ATR) 2932, 1706 (C=O), 1358, 1158 (S=O), 944, 663 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) for **142**: δ 7.68–7.64 (m, 2H, Ar), 7.28 (m, 2H, Ar), 6.79 (q, *J* = 1.5 Hz, 1H, =CH-7), 4.12–4.09 (m, 1H, NCH), 2.69 (dd, *J* = 1.5, 1.5 Hz, 1H, CH-2), 2.54 (ddd, *J* = 15.5, 13.5, 7.5 Hz, 1H, C*H*H'-6), 2.38 (s, 3H, Ar*Me*), 2.35–2.28 (m, 1H, C*H*H'-5), 2.12 (dd, *J* = 15.5, 6.0 Hz, 1H, CH*H'*-6), 1.87 (ddd, *J* = 13.5, 6.0, 3.0 Hz, 1H, CH*H'*-5), 1.80 (ddd, *J* = 13.0, 2.5, 2.5 Hz, 1H, C*H*H'-3), 1.62 (d, *J* = 1.5 Hz, 3H, =CMe), 1.27 (dddd, *J* = 13.0, 3.5, 3.5, 3.0 Hz, 1H CH*H'*-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) for **142**: δ 208.3 (C=O), 144.0 (*ipso*-Ar), 135.8 (*ipso*-Ar), 130.0 (Ar), 126.9 (Ar), 122.8 (=CH-7), 113.6 (=C-8), 49.7 (CH-2), 47.6 (NCH), 34.5 (CH_2-5), 33.7 (CH_2-6), 27.7 (CH_2-3), 21.6 (Ar*Me*), 19.5 (=C*Me*); HRMS (ESI) *m/z* calcd for $C_{16}H_{19}NO_3S$ $(M + Na)^+$ 328.0978, found 328.0971 (+1.2 ppm error). Diagnostic signals for morphan *exo*-**141**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20–4.12 (m, 1H, NCH), 3.25 (dd, *J* = 12.5, 5.0 Hz, 1H, NC*H*H'), 2.98 (dd, *J* = 12.5, 6.0 Hz, 1H, NCH*H'*), 1.07 (d, *J* = 7.0 Hz, 3H, CH*Me*).

Lab book reference: ARG-2-012

PtO_2 (3.3 mg, 0.01 mmol, 0.05 eq) was added to a stirred solution of morphan **60** (100 mg, 0.33 mmol, 1 eq) in EtOAc (2 mL) at rt under Ar. The reaction flask was evacuated under

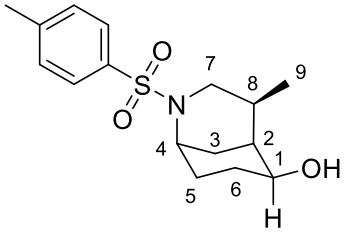
reduced pressure and back-filled with Ar three times and then with H_2 three times. The mixture was stirred under a balloon of H_2 (760 mmHg) for 45 min. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:4 to 3:2 Et_2O-hexane as eluent gave a 95:5 mixture (by ^1H NMR spectroscopy) of hydrogenated morphans *endo*-**141** and *exo*-**141** (61 mg, 61%) as a white solid and impure alcohol **143** (35 mg) as an off-white solid.

Lab book reference: ARG-2-029

PtO_2 (32 mg, 0.36 mmol, 0.05 eq) was added to a stirred solution of morphan **60** (991 mg, 3.24 mmol, 1 eq) in EtOAc (16 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and then with H_2 three times. The mixture was stirred under a balloon of H_2 (760 mmHg) for 45 min. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:4 to 3:2 Et_2O-hexane as eluent gave a 85:15 mixture (by ^1H NMR spectroscopy) of hydrogenated morphans *endo*-**141** and *exo*-**141** (760 mg, 76%) as a white solid and impure alcohol **143** (210 mg) as an off-white solid.

Lab book reference: ARG-2-029

4-Methyl-2-toluenesulfonyl-2-azabicyclo[3.3.1]nonan-6-ol 143



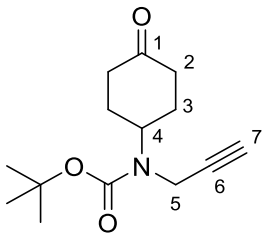
143

$NaBH_4$ (62 mg, 1.63 mmol, 5.0 eq) was added to a stirred solution of morphan endo-**141** (100 mg, 0.33 mmol, 1 eq) in MeOH (2 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 1 h. EtOAc (10 mL) and water (10 mL) were added. The layers were separated and the organic layer was washed with brine (10 mL), dried ($MgSO_4$) and

evaporated under reduced pressure to give alcohol **143** (97 mg, 96%, >97:3 dr) as a white solid, mp 90-92 °C; R_F (3:2 Et_2O-hexane) 0.18; IR (ATR) 3521 (OH), 2925, 1327, 1154 (S=O), 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.65 (m, 2H, Ar), 7.28–7.24 (m, 2H, Ar), 4.02 (dddd, *J* = 3.0, 3.0, 3.0, 3.0 Hz, 1H, NCH), 3.97 (dddd, *J* = 11.0, 7.0, 5.0, 1.5 Hz, 1H, HOC*H*), 3.69 (dd, *J* = 12.5, 7.0 Hz, 1H, NC*H*H'), 3.18 (dd, *J* = 12.5, 12.5 Hz, 1H, NCH*H'*), 2.40 (s, 3H, Ar*Me*), 2.06–1.93 (m, 2H, CH-2, CH-8), 1.86 (ddd, *J* = 13.5, 5.0, 3.0 Hz, 1H, C*H*H'-6), 1.82–1.74 (m, 1H, CHH'), 1.71–1.47 (m, 5H, CH*H'*-6, CH*H'*, CH_2, OH), 1.15 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.1 (Ar), 137.0 (Ar), 129.8 (*ipso*-Ar), 127.0 (*ipso*-Ar), 74.4 (HOCH), 49.7 (NCH_2), 46.6 (NCH), 37.7 (CH-2), 34.9 (CH_2), 34.3 (CH-8), 31.0 (CH_2), 29.7 (CH_2-6), 21.6 (Ar*Me*), 18.6 (C*Me*$_3$); HRMS (ESI) *m/z* calcd for $C_{16}H_{23}NO_3S$ $(M + Na)^+$ 332.1291, found 333.1288 (+0.4 ppm error).

Lab book reference: ARG-2-030

***tert*-Butyl (4-oxocyclohexyl)(prop-2-yn-1-yl)carbamate 144**



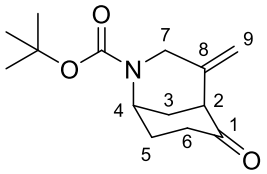
144

A solution of 1,4-cyclohexadione monoethylene acetal **29** (5.05 g, 32.3 mmol, 1.0 eq), propargylamine (2.2 mL, 32.6 mmol, 1.04 eq) and $NaBH(OAc)_3$ (9.59 g, 42.3 mmol, 1.4 eq) in CH_2Cl_2 (108 mL) was stirred at rt for 24 h. Saturated $NH_4Cl_{(aq)}$ (25 mL) was added. Then, 1 M $NaOH_{(aq)}$ was added until pH ≈ 10 was reached. The mixture was extracted with CH_2Cl_2 (4 × 25 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude amine as a pale yellow oil. To a solution of the crude amine in THF (40 mL) was added 3 M $HCl_{(aq)}$ (120 mL) and the resulting solution was stirred at rt for 72 h. Solid Na_2CO_3 was added until pH ≈ 9 was reached and the mixture was extracted with EtOAc (4 × 25 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude amino ketone as a red oil. The crude amino ketone was dissolved in THF (34 mL) and Boc_2O (8.487 g, 37.2 mmol, 1.2 eq) was added at rt. The resulting solution was stirred at rt for 18 h and then water (25 mL) was added. The resulting mixture

was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:5 EtOAc-hexane as eluent gave alkynyl amino ketone **144** (6.21 g, 77%) as a white solid, mp 72-74 °C (lit.,[69] 71-72 °C); R_F (1:4 EtOAc-hexane) 0.20; IR (ATR) 2973, 1717 (C=O), 1689 (C=O), 1165, 681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.59–4.16 (br m, 1H, NCH), 3.92 (br s, 2H, NCH_2), 2.53–2.31 (m, 4H, CH_2-2), 2.21–1.86 (m, 3H, ≡CH, CH_2-3), 1.48 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 209.6 (C=O, ketone), 154.8 (C=O, Boc), 81.1 (*C*Me_3), 80.8 (≡C), 70.8 (≡CH), 53.7 (NCH), 40.1 (CH_2-2), 32.5 (NCH_2), 29.8 (CH_2-3), 28.5 (C*Me*$_3$); HRMS (ESI) *m/z* calcd for $C_{14}H_{21}NO_3$ $(M + Na)^+$ 274.1414, found 274.1415 (–0.5 ppm error). Spectroscopic data consistent with those reported in the literature.[69]

Lab book reference: ARG-2-086

***tert*-Butyl 4-methylene-6-oxo-2-azabicyclo[3.3.1]nonane-2-carboxylate 87**



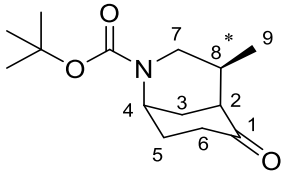
87

$Cu(OTf)_2$ (144 mg, 0.398 mmol, 0.05 eq), PPh_3 (419 mg, 1.59 mmol, 0.20 eq) and pyrrolidine (130 μL, 1.59 mmol, 0.20 eq) were added to a stirred solution of amino ketone **144** (2.0 g, 7.96 mmol, 1.0 eq) in THF (30 mL) in a sealed tube at rt under Ar. The resulting mixture was stirred at rt for 15 min and then stirred and heated at 90 °C for 18 h. The mixture was allowed to cool to rt and the solids were removed by filtration through Celite®. The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:9 to 1:1 EtOAc-hexane as eluent gave morphan **87** (1.54 g, 77%) as a white solid, mp 78-80 °C; R_F (1:2 EtOAc-hexane) 0.2; IR (ATR) 2972, 1716 (C=O, ketone), 1686 (C=O, Boc), 1389, 1164, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 5.07 (s, 0.55H, =C*H*H'), 5.04 (s, 0.45H, =C*H*H'), 4.99 (s, 1H, =CH*H′*), 4.38 (d, *J* = 16.0 Hz, 0.55H, NC*H*H'), 4.32 (dd, *J* = 3.5, 3.0 Hz, 0.45H, NCH), 4.24 (d, *J* = 16.0 Hz, 0.45H, NC*H*H'), 4.19 (dd, *J* = 3.5, 3.0 Hz, 0.55H, NCH), 4.07 (d, *J* = 16.0 Hz, 0.45H, NCH*H′*), 4.01 (d, *J* = 16.0 Hz, 0.55H, NCH*H′*), 3.33 (s, 1H, CH-2), 2.74–2.54 (m, 1H, C*H*H'-6), 2.42–2.19 (m, 3H, CH*H′*-6, C*H*H'-5, C*H*H'-3), 2.00 (ddd, *J* =

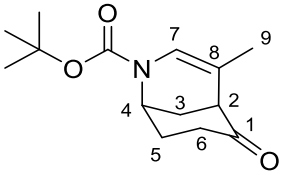
14.0, 13.5, 3.0 Hz, 1H, CH*H'*-3), 1.85–1.73 (m, 1H, CH*H'*-5), 1.53–1.45 (m, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 209.3 (C=O, ketone), 209.0 (C=O, ketone), 155.2 (C=O, Boc), 154.9 (C=O, Boc), 139.8 (=C), 139.6 (=C), 114.2 (=CH_2), 113.8 (=CH_2), 80.2 (*C*Me_3), 51.3 (CH-2), 50.8 (CH-2), 46.3 (NCH_2), 46.3 (NCH), 45.6 (NCH_2), 45.4 (NCH), 35.3 (CH_2-6), 34.9 (CH_2-6), 31.4 (CH_2), 31.2 (CH_2), 30.6 (CH_2), 28.6 (C*Me*$_3$); HRMS (ESI) *m/z* calcd for $C_{14}H_{21}NO_3$ $(M + Na)^+$ 274.1414, found 274.1412 (+0.6 ppm error). Spectroscopic data consistent with those reported in the literature.[69]

Lab book reference: ARG-2-052

tert-Butyl 4-methyl-6-oxo-2-azabicyclo[3.3.1]nonane-2-carboxylate _endo_-138 and _tert_-Butyl 4-methyl-6-oxo-2-azabicyclo[3.3.1]non-3-ene-2-carboxylate 145



138



145

PtO_2 (213 mg, 0.936 mmol, 0.1 eq) was added to a stirred solution of morphan **87** (2.35 g, 7.36 mmol, 1 eq) in EtOAc (47 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and then with H_2 three times. The mixture was stirred under a balloon of H_2 (760 mmHg) for 16 h. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude product. The crude product was dissolved in CH_2Cl_2 (100 mL) and Dess-Martin periodinane (5.95 g, 14.0 mmol, 1.5 eq) was added at rt under Ar. The resulting mixture was stirred at rt for 2 h. Saturated $NaHCO_{3(aq)}$ (50 mL) was added and the mixture was stirred for 30 min. The layers were separated and the organic layer was washed with saturated $Na_2S_2O_{3(aq)}$ (15 mL) and brine (25 mL), dried ($MgSO_4$) and the evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:9 to 2:3 Et_2O-hexane as eluent gave enamine **145** (360 mg, 15%) as a clear oil, R_F (2:3 Et_2O-hexane) 0.24; IR (ATR) 2933, 1693 (C=O, ketone), 1665 (C=O, Boc), 1392, 1152, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.03–6.94 (m, 0.5H, =CH), 6.85–6.76 (m, 0.5H, =CH), 4.46–4.38 (m, 0.5H, NCH), 4.32–4.24 (m, 0.5H, NCH), 2.83–2.76 (m, 1H, CH-2), 2.62–2.46 (m, 1H, C*H*H'-6), 2.35–2.18 (m, 1H, CH*H'*-6), 2.20–2.07 (m, 1H, CHH'), 2.07–1.94 (m, 1H, CHH'), 1.98–1.75 (m, 2H, CHH', CHH'), 1.62 (d, *J*

= 1.5 Hz, 3H, =CMe), 1.52–1.45 (m, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 209.4 (C=O, ketone), 209.3 (C=O, ketone), 152.1 (C=O, Boc), 151.5 (C=O, Boc), 123.5 (=CH), 123.3 (=CH), 111.6 (=C), 110.7 (=C), 81.2 (*C*Me_3), 81.0 (*C*Me_3), 50.3 (CH-2), 50.0 (CH-2), 45.6 (NCH), 44.7 (NCH), 33.7 (br, CH_2-6), 33.4 (CH_2), 32.8 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.35 (C*Me*$_3$), 28.3 (C*Me*$_3$), 19.4 (Me), 19.3 (Me); HRMS (ESI) *m/z* calcd for $C_{14}H_{21}NO_3$ $(M + Na)^+$ 374.1414, found 374.1406 (+2.9 ppm error) and a 90:10 mixture (by ^1H NMR spectroscopy) of hydrogenated morphans *endo*-**138** and *exo*-**138** (1.67 g, 71%) as an off-white solid, R_F (2:3 Et_2O-hexane) 0.17; IR (ATR) 2930, 1684 (C=O), 1402, 1339, 1167, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) for *endo*-**138** (50:50 mixture of rotamers): δ 4.52–4.28 (m, 1H, NCH), 4.04 (dd, *J* = 14.0, 6.5 Hz, 0.5H, NC*H*H'), 3.92 (dd, *J* = 14.0, 6.5 Hz, 0.5H, NC*H*H'), 2.83–2.66 (m, 1H, NCH*H'*), 2.56–2.46 (m, 2H, CH-2, C*H*H'-6), 2.29–2.16 (m, 1H, CH*H'*-6), 2.14–1.89 (m, 5H, CH_2-3, CH_2-5, CH-8), 1.44 (s, 9H, CMe_3), 0.85 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) for *endo*-**141** (rotamers): δ 212.0 (C=O, ketone), 211.8 (C=O, ketone), 155.1 (C=O, Boc), 155.0 (C=O, Boc), 80.0 (*C*Me_3), 49.7 (CH-2), 49.6 (CH-2), 47.3 (NCH_2), 46.6 (NCH_2), 44.4 (NCH), 43.3 (NCH), 39.6 (CH_2-6), 33.0 (CH_2), 32.8 (CH_2), 32.6 (CH-8), 30.5 (CH_2), 29.9 (CH_2), 28.5 (C*Me*$_3$), 17.1 (CH*Me*); $C_{14}H_{23}NO_3$ $(M + Na)^+$ 276.1570, found 276.1570 (0.0 ppm error). Diagnostic signals for *exo*-**138**: ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 3.58 (dd, *J* = 13.5, 5.5 Hz, 0.5H, NC*H*H'), 3.37 (dd, *J* = 13.5, 5.5 Hz, 0.5H, NC*H*H'), 3.27 (dd, *J* = 13.5, 5.5 Hz, 0.5H, NCH*H'*), 3.12 (dd, *J* = 13.5, 5.5 Hz, 0.5H, NCH*H'*).

Lab book reference: ARG-2-090

Dess-Martin periodinane (365 mg, 0.86 mmol, 2.0 eq) was added to a stirred solution of a 90:10 mixture of morphans *endo*-**146** and *exo*-**146** (110 mg, 0.43 mmol, 1.0 eq) in CH_2Cl_2 (7 mL) at rt under Ar. The resulting mixture was stirred at rt for 2 h. Saturated $NaHCO_{3(aq)}$ (10 mL) was added and the mixture was stirred for 30 min. The layers were separated and the organic layer was washed with saturated $Na_2S_2O_{3(aq)}$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:9 to 2:3 Et_2O-hexane as eluent gave a 90:10 mixture (by ^1H NMR spectroscopy) of hydrogenated morphans *endo*-**138** and *exo*-**138** (89 mg, 84%) as an off-white solid, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-2-079

10% Pd/C (40 mg, 0.04 mmol, 0.1 eq) was added to a stirred solution of morphan **87** (100 mg, 0.40 mmol, 1.0 eq) in EtOAc (2 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and then with H_2 three times. The mixture was stirred under a balloon of H_2 (760 mmHg) for 2 h. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude product which contained (by ^{1}H NMR spectroscopy) a 90:8:2 mixture of enamine **145**, morphan *endo*-**138** and morphan *exo*-**138**

Lab book reference: ARG-2-041

10% Pd/C (21 mg, 0.02 mmol, 0.1 eq) was added to a stirred solution of morphan **87** (50 mg, 0.20 mmol, 1.0 eq) in EtOH (1 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and then with H_2 three times. The mixture was stirred under a balloon of H_2 (760 mmHg) for 2 h. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude product which contained (by ^{1}H NMR spectroscopy) a complex mixture of products.

Lab book reference: ARG-2-053

10% Pd/C (21 mg, 0.02 mmol, 0.1 eq) was added to a stirred solution of morphan **87** (50 mg, 0.20 mmol, 1.0 eq) and AcOH (56 µL, 1.0 mmol, 5 eq) in EtOAc (1 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and then with H_2 three times. The mixture was stirred under a balloon of H_2 (760 mmHg) for 2 h. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude product which contained (by ^{1}H NMR spectroscopy) a complex mixture of products.

Lab book reference: ARG-2-053

20% $Pd(OH)_2/C$ (14 mg, 0.02 mmol, 0.1 eq) was added to a stirred solution of morphan **87** (50 mg, 0.20 mmol, 1.0 eq) in EtOAc (1 mL) at rt under Ar. The reaction flask was evacuated

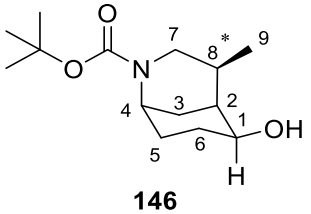
under reduced pressure and back-filled with Ar three times and then with H_2 three times. The mixture was stirred under a balloon of H_2 (760 mmHg) for 2 h. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:9 to 2:3 Et_2O-hexane as eluent gave enamine **145** (36 mg, 72%) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above and a 90:10 mixture (by ^1H NMR spectroscopy) of hydrogenated morphans *endo*-**138** and *exo*-**138** (9 mg, 18%) as an off-white solid, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-2-057

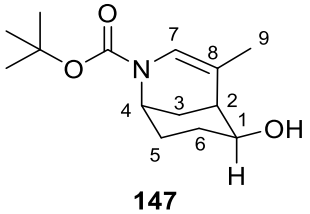
10% Pd/C (10 mg, 0.01 mmol, 0.02 eq) was added to a stirred solution of morphan **87** (100 mg, 0.40 mmol, 1.0 eq) and $NH_4^+HCO_2^-$ (251 µL, 3.98 mmol, 10 eq) in MeOH (2 mL) at rt under Ar. The resulting mixture was stirred and heated at reflux for 2 h under Ar. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude product which contained (by ^1H NMR spectroscopy) a complex mixture of products.

Lab book reference: ARG-2-064

***tert*-Butyl 6-hydroxy-4-methyl-2-azabicyclo[3.3.1]nonane-2-carboxylate *endo*-146 and *tert*-butyl 6-hydroxy-4-methyl-2-azabicyclo[3.3.1]non-3-ene-2-carboxylate 147**



146



147

PtO_2 (9.0 mg, 0.04 mmol, 0.1 eq) was added to a stirred solution of morphan **87** (100 mg, 0.40 mmol, 1.0 eq) in EtOAc (2 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and then with H_2 three times. The mixture was stirred under a balloon of H_2 (760 mmHg) for 16 h. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:9 to 1:4

EtOAc-hexane as eluent gave enamine **147** (10 mg, 10%, >97:3 dr) as an off-white solid, mp 140-142 °C; R_F (2:3 EtOAc-hexane) 0.20; IR (ATR) 3440 (OH), 2934, 1665 (C=O), 1392, 1156 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 6.94 (s, 0.5H, =CH-7), 6.77 (s, 0.5H, =CH-7), 4.18–4.14 (m, 0.5H, NCH), 4.05–4.02 (m, 0.5H, NCH), 3.86 (dddd, *J* = 10.0, 4.5, 4.5, 4.5 Hz, 1H, HOC*H*), 2.38 (ddd, *J* = 4.5, 3.5, 3.5 Hz, 1H, CH-2), 1.98–1.84 (m, 1H, C*H*H'), 1.79 (s, 3H, Me), 1.74–1.51 (m, 4H, CHH', CHH'), 1.49–1.38 (m, 10H, CH*H'*, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 152.3 (C=O, Boc), 151.7 (C=O, Boc), 123.0 (=CH-7), 122.7 (=CH-7), 113.7 (=C), 113.1 (=C), 80.6 (*C*Me_3), 80.3 (*C*Me_3), 74.8 (HOCH), 74.7 (HOCH), 45.7 (NCH), 44.9 (NCH), 39.8 (CH-2), 39.5 (CH-2), 31.3 (CH_2), 30.7 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 28.5 (C*Me*$_3$), 28.4 (C*Me*$_3$), 27.8 (CH_2), 27.7 (CH_2), 22.5 (CH_2), 22.4 (CH_2); HRMS (ESI) *m/z* calcd for $C_{14}H_{23}NO_3$ $(M + Na)^+$ 276.1570, found 276.1568 (+0.9 ppm error) and a 90:10 mixture (by ^1H NMR spectroscopy) of hydrogenated morphans *endo*-**146** and *exo*-**146** (86 mg, 86%) as an off-white solid, R_F (2:3 EtOAc-hexane) 0.18; IR (ATR) 3436 (OH), 2928, 1662 (C=O), 1402, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) for *endo*-**146** δ 4.17–4.12 (m, 0.45H, NCH), 4.03–4.00 (m, 0.55H, NCH), 3.97 (ddd, *J* = 11.0, 5.5, 5.5 Hz, 1H, HOC*H*), 3.81 (dd, *J* = 13.5, 6.0 Hz, 0.55H, NC*H*H'), 3.71 (dd, *J* = 13.5, 6.0 Hz, 0.45H, NC*H*H'), 3.02 (dd, *J* = 13.5, 13.0 Hz, 0.55H, NCH*H'*), 2.98 (dd, *J* = 13.5, 13.0 Hz, 0.45H, NCH*H'*), 2.18 (s, 1H, OH), 2.05–1.95 (m, 2H, CH-2, CH-8), 1.92–1.80 (m, 2H, CHH'), 1.77–1.63 (m, 2H, CHH'), 1.59–1.47 (m, 2H, CHH'), 1.44–1.36 (m, 9H, CMe_3), 1.16 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 155.4 (C=O), 155.8 (C=O), 79.4 (*C*Me_3), 79.3 (*C*Me_3), 74.7 (HOCH), 74.67 (HOCH), 49.6 (NCH_2), 49.0 (NCH_2), 44.8 (NCH), 43.8 (NCH), 38.2 (CH), 38.0 (CH), 34.5 (CH_2), 34.46 (CH_2), 34.2 (CH), 34.0 (CH), 30.9 (CH_2), 30.8 (CH_2), 30.6 (CH_2), 30.0 (CH_2), 28.5 (C*Me*$_3$), 18.9 (CH*Me*), 18.8 (CH*Me*); HRMS (ESI) *m/z* calcd for $C_{14}H_{25}NO_3$ $(M + Na)^+$ 278.1727, found 278.1721 (+2.0 ppm error). Diagnostic signals for *exo*-**146**: ^1H NMR (400 MHz, $CDCl_3$) δ 2.65–2.50 (m, 1H, NCH*H'*), 0.91 (d, *J* = 7.0 Hz, 3H, CH*Me*).

Lab book reference: ARG-2-067

10% Pd/C (28 mg, 0.03 mmol, 0.1 eq) was added to a stirred solution of morphan **148** (65 mg, 0.25 mmol, 1.0 eq) in EtOH (1.3 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and then with H_2 three times.

The mixture was stirred under a balloon of H_2 (760 mmHg) for 2 h. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give enamine **147** (63 mg, 96%) as an off white solid, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-2-047

10% Pd/C (21 mg, 0.02 mmol, 0.1 eq) was added to a stirred solution of morphan **148** (50 mg, 0.20 mmol, 1.0 eq) and AcOH (56 µL, 1.0 mmol, 5.0 eq) in EtOH (1 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and then with H_2 three times. The mixture was stirred under a balloon of H_2 (760 mmHg) for 2 h. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude product which contained (by ^1H NMR spectroscopy) a complex mixture of products.

Lab book reference: ARG-2-055

20% $Pd(OH)_2/C$ (14 mg, 0.02 mmol, 0.1 eq) was added to a stirred solution of morphan **148** (50 mg, 0.20 mmol, 1.0 eq) in EtOAc (1 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and then with H_2 three times. The mixture was stirred under a balloon of H_2 (760 mmHg) for 2 h. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give enamine **147** (47 mg, 94%) as an off white solid, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-2-057

10% Pd/C (10 mg, 0.01 mmol, 0.02 eq) was added to a stirred solution of morphan **148** (100 mg, 0.40 mmol, 1.0 eq) and $NH_4^+HCO_2^-$ (251 mg, 3.98 mmol, 10 eq) in MeOH (2 mL) at rt under Ar. The resulting mixture was stirred and heated at reflux for 2 h. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:9 to 1:4 EtOAc-hexane as eluent gave enamine **147** (55 mg, 55%) as an off-white solid, identical

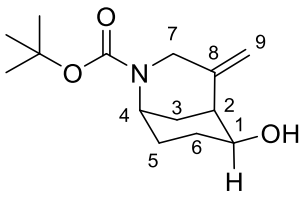
(by ^{1}H and ^{13}C NMR spectroscopy) to that described above and a 75:25 mixture (by ^{1}H NMR spectroscopy) of hydrogenated morphans *endo*-**146** and *exo*-**146** (42 mg, 42%) as an off-white solid.

Lab book reference: ARG-2-065

PtO_2 (4 mg, 0.02 mmol, 0.1 eq) was added to a stirred solution of morphan **148** (50 mg, 0.2 mmol, 1.0 eq) in EtOAc (1 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and then with H_2 three times. The mixture was stirred under a balloon of H_2 (760 mmHg) for 2 h. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:9 to 1:4 EtOAc-hexane as eluent gave enamine **147** (3 mg, 6%) as an off-white solid, identical (by ^{1}H and ^{13}C NMR spectroscopy) to that described above and a 75:25 mixture (by ^{1}H NMR spectroscopy) of hydrogenated morphans *endo*-**146** and *exo*-**146** (40 mg, 90%) as an off-white solid.

Lab book reference: ARG-2-050

***tert*-Butyl 6-hydroxy-4-methylene-2-azabicyclo[3.3.1]nonane-2-carboxylate 148**



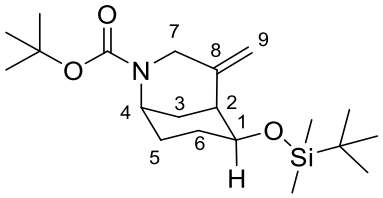
148

$NaBH_4$ (1.04 g, 27.6 mmol, 5.0 eq) was added to a stirred solution of morphan **87** (1.39 g, 5.52 mmol, 1.0 eq) in MeOH (28 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt. The mixture was stirred at rt for 4 h. EtOAc (10 mL) and water (10 mL) were added. The layers were separated and the organic layer was washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give alcohol **148** (1.33 g, 95%, >97:3 dr) as a white solid, mp 112-114 °C; R_F (3:2 EtOAc-hexane) 0.23; IR (ATR) 3432 (OH), 2935, 1670 (C=O), 1395, 1168 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09–5.05 (m, 1H, =C*H*H'), 4.96–4.91 (m, 1H, CH*H'*), 4.26–3.95 (m, 3H, NCH, NCHH'), 3.72–3.59 (m,

1H, HOCH), 2.72 (br dd, *J* = 4.0, 4.0 Hz, 1H, CH-2), 2.06–1.91 (m, 2H, CHH'), 1.86–1.61 (m, 3H, CHH', OH), 1.48–1.37 (m, 10H, CMe_3, CH*H'*), 1.34–1.20 (m, 1H, CH*H'*); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 155.2 (C=O), 154.9 (C=O), 142.0 (=C), 141.8 (=C), 112.9 (=CH_2), 112.8 (=CH_2), 79.6 (*C*Me_3), 71.0 (HOCH), 47.6 (NCH_2), 46.7 (NCH_2), 45.8 (NCH), 44.9 (NCH), 41.8 (CH-2), 41.3 (CH-2), 30.3 (CH_2), 30.1 (br, CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.8 (CH_2), 28.6 (br, C*Me*$_3$); HRMS (ESI) *m/z* calcd for $C_{14}H_{23}NO_3$ $(M + Na)^+$ 276.1570, found 276.1564 (+2.4 ppm error).

Lab book reference: ARG-2-049

tert-Butyl 6-((_tert_-butyldimethylsilyl)oxy)-4-methylene-2-azabicyclo[3.3.1]nonane-2-carboxylate 149



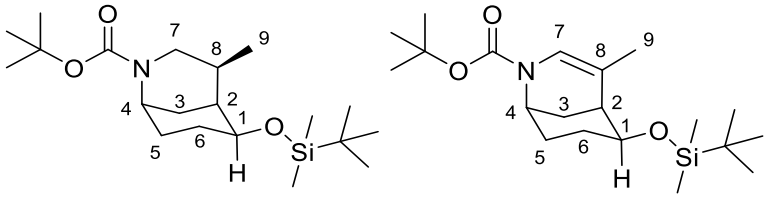
149

TBDMSCl (144 mg, 0.96 mmol, 1.2 eq) was added to a stirred solution of morphan **148** (200 mg, 0.79 mmol, 1.0 eq) and imidazole (134 mg, 1.97 mmol, 2.5 eq) in DMF (3 mL) at rt under Ar. The resulting solution was stirred at rt for 48 h. Saturated $NaHCO_{3(aq)}$ (15 mL) was added and the resulting mixture was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed brine (3 × 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 to 9:1 hexane-Et_2O gave morphan **149** (240 mg, 83%) as a clear oil, R_F (9:1 hexane-Et_2O) 0.25; IR (ATR) 2930, 1692 (C=O), 1391, 1095, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.02–4.96 (m, 1H, =C*H*H'), 4.95–4.89 (m, 1H, =CH*H'*), 4.21–3.91 (m, 3H, NCH, NCHH'), 3.73–3.64 (m, 1H, OCH), 2.61 (s, 1H, CH-2), 2.04–1.88 (m, 2H, CHH'), 1.67–1.48 (m, 3H, CHH', C*H*H'), 1.48–1.31 (m, 10H, $OCMe_3$, CH*H'*), 0.87 (s, 9H, $SiCMe_3$), 0.07–0.03 (m, 6H, $SiMe_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 155.3 (C=O), 155.2 (C=O), 141.5 (=C), 141.0 (=C), 113.4 (=CH_2), 113.1 (=CH_2), 79.6 (*C*Me_3), 79.5 (*C*Me_3), 73.0 (OCH), 72.95 (OCH), 48.1 (NCH_2), 47.2 (NCH_2), 46.1 (NCH), 45.4 (NCH), 42.1 (CH-2), 41.7 (CH-2), 30.8 (CH_2), 30.7 (CH_2), 30.3 (CH_2), 29.5 (CH_2), 29.1 (CH_2), 28.8 (OC*Me*$_3$),

26.1 (SiC*Me*$_3$), –4.30 (SiMe), –4.32 (SiMe), –4.40 (SiMe), –4.42 (SiMe); HRMS (ESI) *m/z* calcd for $C_{20}H_{37}NO_3Si$ $(M + Na)^+$ 390.2435, found 390.2428 (+1.8 ppm error).

Lab book reference: ARG-2-063

tert-Butyl 6-((_tert_-butyldimethylsilyl)oxy)-4-methyl-2-azabicyclo[3.3.1]nonane-2-carboxylate _endo_-150 and _tert_-butyl 6-((_tert_-butyldimethylsilyl)oxy)-4-methyl-2-azabicyclo[3.3.1]non-3-ene-2-carboxylate 151



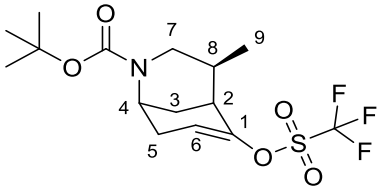
endo-**150** **151**

PtO_2 (13 mg, 0.06 mmol, 0.1 eq) was added to a stirred solution of morphan **149** (150 mg, 0.41 mmol, 1.0 eq) in EtOAc (2 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and then with H_2 three times. The mixture was stirred under a balloon of H_2 (760 mmHg) for 16 h. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 to 95:5 hexane-Et_2O as eluent gave enamine **151** (82 mg, 55%) as a clear oil, R_F (9:1 hexane-Et_2O) 0.34; IR (ATR) 2930, 1697 (C=O), 1390, 1156, 1083, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 6.88 (s, 0.4H, =CH), 6.73 (s, 0.6H, =CH), 4.16–4.11 (m, 0.6H, NCH), 4.03–3.96 (m, 0.4H, NCH), 3.84–3.77 (m, 1H, OCH), 2.27–2.22 (m, 1H, CH-2), 1.94–1.78 (m, 1H, C*H*H'), 1.78–1.75 (m, 3H, =CMe), 1.69–1.50 (m, 4H, CHH', CHH'), 1.48–1.37 (m, 10H, CHH', OCMe$_3$), 0.88–0.82 (m, 9H, SiCMe$_3$), 0.05–0.00 (m, 6H, SiMe$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 152.3 (C=O), 151.7 (C=O), 122.2 (=CH), 121.8 (=CH), 115.3 (=C), 114.4 (=C), 80.3 (O*C*Me$_3$), 80.0 (O*C*Me$_3$), 75.4 (OCH), 75.2 (OCH), 45.8 (NCH), 44.9 (NCH), 40.2 (CH-2), 40.0 (CH-2), 31.3 (CH_2), 30.7 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.4 (OC*Me$_3$*), 28.3 (CH_2), 28.1 (CH_2), 26.0 (SiC*Me$_3$*), 22.4 (=C*Me*), 22.2 (=C*Me*), 18.2 (Si*C*Me$_3$), 18.17 (Si*C*Me$_3$), –4.61 (SiMe), –4.64 (SiMe), –4.7 (SiMe).; HRMS (ESI) *m/z* calcd for $C_{20}H_{37}NO_3Si$ $(M + Na)^+$ 390.2435, found 390.2434 (+0.2 ppm error) hydrogenated morphan *endo*-**150** (30 mg, 20% >97:3 dr) as a clear oil, R_F (9:1 hexane-Et_2O) 0.27; IR (ATR) 2928, 1689 (C=O), 1092, 834, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50

mixture of rotamers) δ 4.18 (br dd, *J* = 3.0, 3.0 Hz, 0.5H, NCH), 4.04 (br dd, *J* = 3.0, 3.0 Hz, 0.5H, NCH), 3.97–3.90 (m, 1H, OCH), 3.84 (dd, *J* = 13.5, 6.0 Hz, 0.5H, NC*H*H'), 3.73 (dd, *J* = 13.5, 6.0 Hz, 0.5H, NC*H*H'), 3.07 (dd, *J* = 13.5, 13.0 Hz, 0.5H, NCH*H'*), 3.03 (dd, *J* = 13.5, 13.0 Hz, 0.5H, NCH*H'*), 2.10–1.96 (m, 1H, CH-2), 1.95–1.89 (m, 1H, C*H*Me), 1.79–1.65 (m, 4H, CHH', CHH'), 1.61–1.50 (m, 1H, CHH'), 1.51–1.41 (m, 9H, $OCMe_3$), 1.17 (d, *J* = 7.0 Hz, 3H, CH*Me*), 0.87 (s, 9H, $SiCMe_3$), 0.08– -0.06 (m, 6H, $SiMe_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 155.5 (C=O), 79.25 ($OCMe_3$), 79.2 ($OCMe_3$), 75.2 (OCH), 75.17 (OCH), 49.8 (NCH_2), 49.1 (NCH_2), 45.0 (NCH), 44.0 (NCH), 38.5 (*C*HMe), 38.3 (*C*HMe), 34.8 (CH_2), 34.7 (CH_2), 34.5 (CH-2), 34.4 (CH-2), 32.0 (CH_2), 31.9 (CH_2), 30.8 (CH_2), 30.2 (CH_2), 28.65 ($OCMe_3$), 26.0 ($SiCMe_3$), 19.2 (CH*Me*), 18.2 (CH*Me*), –4.68 (SiMe), –4.7 (SiMe); HRMS (ESI) *m/z* calcd for $C_{20}H_{39}NO_3Si$ $(M + Na)^+$ 392.2591, found 392.2592 (–0.1 ppm error).

Lab book reference: ARG-2-068

tert-Butyl 4-methyl-6-(((trifluoromethyl)sulfonyl)oxy)-2-azabicyclo[3.3.1]non-6-ene-2-carboxylate _endo_-139



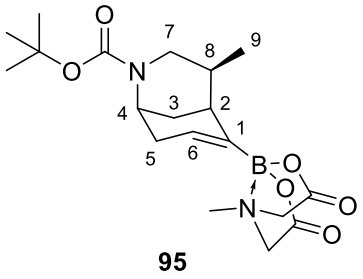
139

NaHMDS (0.95 mL of a 2 M solution in THF, 1.90 mmol, 1.6 eq) was added dropwise to a stirred solution of a 90:10 mixture of morphans *endo*-**138** and *exo*-**138** (300 mg, 1.18 mmol, 1.0 eq) in THF (3 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, a solution of $PhNTf_2$ (550 mg, 1.54 mmol, 1.3 eq) in THF (2 mL) was added and the resulting solution was allowed to warm slowly to rt. The mixture was stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 to 9:1 hexane-acetone as eluent gave a 90:10 mixture (by ^1H NMR spectroscopy) of vinyl triflates *endo*-**139** and *exo*-**139** (320 mg, 70%) as a clear oil, R_F (98:2 hexane-acetone) 0.14; IR (ATR) 2972, 1691 (C=O), 1414, 1209, 1143, 847, 611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) for *endo*-**139** (55:45 mixture of rotamers) δ 5.92 (dd, *J* =

4.0, 4.0 Hz, 1H, =CH), 4.55–4.49 (m, 0.55H, NC*H*H'), 4.38–4.32 (m, 0.45H, NC*H*H'), 3.99–3.90 (m, 0.45H, NCH*H'*), 3.84–3.75 (m, 0.55H, NCH*H'*), 2.64–2.45 (m, 3H, NCH, CH-2, C*H*H'), 2.18–2.07 (m, 1H, CH*H'*), 1.94–1.84 (m, 3H, CHH', C*H*Me), 1.49–1.41 (m, 9H, CMe_3), 0.92 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) for *endo*-**139** (rotamers) δ 154.8 (C=O), 148.2 (=C), 119.5 (br, =CH), 118.6 (q, *J* = 320.0 Hz, CF_3), 80.1 (*C*Me_3), 44.3 (NCH_2), 43.4 (NCH_2), 42.3 (br, NCH), 37.9 (CH-2), 33.6 (*C*HMe), 33.4 (*C*HMe), 32.2 (CH_2), 32.0 (CH_2), 31.2 (br, CH_2), 28.6 (C*Me*$_3$), 17.2 (CH*Me*); HRMS (ESI) *m/z* calcd for $C_{15}H_{22}F_3NO_5S$ $(M + Na)^+$ 408.1063, found 408.1064 (–0.3 ppm error). Diagnostic signals for ***exo*-139** ^1H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 5.90–5.84 (m, 1H, =CH), 3.71 (br d, *J* = 13.5 Hz, 0.45H, NC*H*H'), 3.62 (br d, *J* = 13.5 Hz, 0.55H, NC*H*H'), 3.20 (dd, *J* = 13.5, 4.5 Hz, 0.55H, NCH*H'*), 3.11 (dd, *J* = 13.5, 4.5 Hz, 0.45H, NCH*H'*), 1.11 (d, *J* = 7.0 Hz, 3H, CH*Me*).

Lab book reference: ARG-2-088

***tert*-Butyl 4-methyl-6-(4-methyl-2,6-dioxotetrahydro-2*H*-4λ⁴,8λ⁴-[1,3,2]oxazaborolo[2,3-*b*][1,3,2]oxazaborol-8-yl)-2-azabicyclo[3.3.1]non-6-ene-2-carboxylate 95**



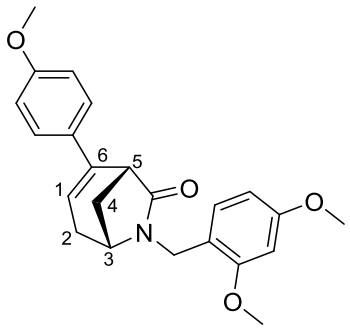
95

A solution of enol triflate **139** (318 mg, 0.82 mmol, 1.0 eq), $PdCl_2(PPh_3)_2$ (17 mg, 0.025 mmol, 3 mol%), PPh_3 (13 mg, 0.05 mmol, 6 mol%), KOPh (164 mg, 1.24 mmol, 1.5 eq) and B_2Pin_2 (230 mg, 0.91 mmol, 1.1 eq) in toluene (6 mL) under Ar was stirred and heated at 50 °C and stirred for 16 h. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude pinacol boronate. The crude pinacol boronate was dissolved in DMSO (5 mL) and MIDA (607 mg, 4.12 mmol, 5.0 eq) and $HC(OEt)_3$ (0.62 mL, 3.71 mmol, 4.5 eq) were added. The resulting mixture was stirred and heated at 100 °C under Ar for 48 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the mixture was extracted with EtOAc (4 × 30 mL). The combined organic extracts were washed with

brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:4 to 1:1 hexane-acetone as eluent gave impure vinyl MIDA boronate **95** (150 mg) as a white solid, R_F (6:4 hexane-acetone) 0.26; ^{1}H NMR (400 MHz $CDCl_3$) diagnostic signals for *endo*-**95** (60:40 mixture of rotamers) δ 6.22–6.17 (m, 1H, =CH), 4.51–4.43 (m, 0.6H, NCHH'), 4.35–4.30 (m, 0.4H, NCHH'), 2.78 (s, 1.4H, NMe), 2.75 (s, 1.6H, NMe), 1.40 (s, 9H, CMe_3), 1.00 (d, J = 7.0 Hz, 1.4H, CH*Me*), 0.80 (d, J = 7.0 Hz, 1.6H, CH*Me*); HRMS (ESI) m/z calcd for $C_{19}H_{29}BN_2O_6$ (M + Na)+ 415.2011, found 415.2015 (+0.9 ppm error)

Lab book reference: ARG-2-092

6-(2,4-Dimethoxybenzyl)-2-(4-methoxyphenyl)-6-azabicyclo[3.2.1]oct-2-en-7-one 153



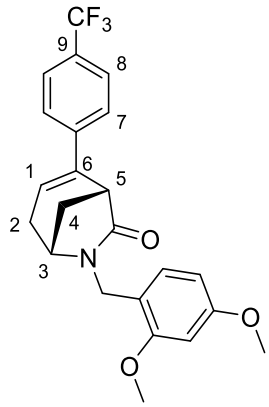
153

Using general procedure A, MIDA boronate **94** (750 mg, 1.75 mmol, 1.0 eq), $Pd(OAc)_2$ (20 mg, 0.09 mmol, 5 mol%), SPhos (72 mg, 0.17 mmol, 10 mol%), 4-bromoanisole (0.27 mL, 2.11 mmol, 1.2 eq) and 3 M $K_3PO_{4(aq)}$ (5.74 mL, 17.2 mmol, 7.5 eq), in dioxane (28 mL) gave the crude product. Purification by flash column chromatography on silica with 1:1 EtOAc-hexane as eluent gave arylated normorphan **153** (565 mg, 86%) as a clear oil, R_F (3:2 EtOAc-hexane) 0.49; IR (ATR) 2938, 2835, 1686 (C=O), 1609, 1508, 1244, 1032, 835, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.44 (m, 2H, Ar), 7.15–7.11 (m, 1H, Ar), 6.89–6.84 (m, 2H, Ar), 6.45–6.41 (m, 2H, Ar), 5.70–5.63 (m, 1H, =CH), 4.57 (d, J = 15.0 Hz, 1H, NC*H*H'), 4.25 (d, J = 15.0 Hz, 1H, NCH*H'*), 3.81–3.76 (m, 9H, OMe), 3.76– 3.73 (m, 1H, NCH-3), 3.23 (d, J = 5.0 Hz, 1H, CH-5), 2.63–2.27 (m, 2H, CH_2-2), 2.24 (ddd, J = 10.0, 5.0, 5.0 Hz, 1H, C*H*H'-4), 1.84 (d, J = 10.0 Hz, 1H, CH*H'*-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.8 (C=O), 160.4 (*ipso*-Ar), 158.9 (*ipso*-Ar), 158.6 (*ipso*-Ar), 139.8 (=C), 133.5 (*ipso*-Ar), 130.5 (Ar), 126.5 (Ar), 119.7 (=CH), 118.0 (*ipso*-Ar), 113.9 (Ar), 104.3 (Ar), 98.5 (Ar), 55.5 (OMe), 55.4 (OMe), 53.9 (NCH), 44.3 (*C*HCO), 38.0 (NCH_2), 34.1 (CH_2-4), 28.8 (CH_2-2)

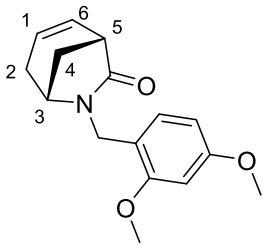
(1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{23}H_{25}NO_4$ $(M + H)^+$ 380.1856, found 380.1858 (–0.4 ppm error).

Lab book reference: ARG-1-070

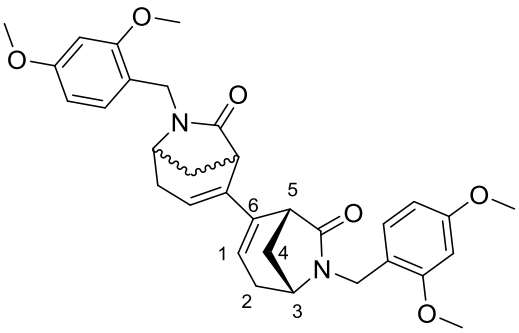
6-(2,4-Dimethoxybenzyl)-2-(4-(trifluoromethyl)phenyl)-6-azabicyclo[3.2.1]oct-2-en-7-one 154, 6-(2,4-dimethoxybenzyl)-6-azabicyclo[3.2.1]oct-2-en-7-one 115 and 6,6'-bis(2,4-dimethoxybenzyl)-6,6'-diaza[2,2'-bi(bicyclo[3.2.1]octane)]-2,2'-diene-7,7'-dione 155a/B



154



115



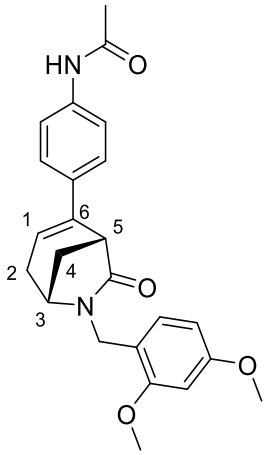
155a/b

Using general procedure A, vinyl MIDA boronate **94** (100 mg, 0.234 mmol, 1.0 eq), $Pd(OAc)_2$ (3 mg, 0.012 mmol, 0.05 eq), SPhos (10 mg, 0.023 mmol, 0.1 eq), 4-bromobenzotrifluoride (63 mg, 0.280 mmol, 1.2 eq) and 3 M $K_3PO_{4(aq)}$ (0.59 mL, 1.755 mmol, 7.5 eq) in dioxane (2.34 mL) gave the crude product. Purification by flash column chromatography on silica with 4:1 to 3:2 hexane-EtOAc as eluent gave alkene **115** (12 mg, 20%) as a clear oil, identical (by ^{1}H and ^{13}C NMR spectroscopy) to that described above, arylated normorphan **154** (60 mg, 61%) as a clear oil, R_F (3:2 hexane-EtOAc) 0.32; IR (ATR) 2941, 2837, 1687 (C=O), 1613, 1588, 1507, 1322, 1109, 818, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.63 (m, 2H, Ar), 7.60–7.55 (m, 2H, Ar), 7.16–7.11 (m, 1H, Ar), 6.47–6.39 (m, 2H, Ar), 5.85 (ddd, *J* = 3.5, 3.0, 1.5 Hz, 1H, =CH-1), 4.57 (d, *J* = 15.0 Hz, 1H, NC*H*H'), 4.26 (d, *J* = 15.0 Hz, 1H, NCH*H'*), 3.83–3.67 (m, 7H, OMe, NCH), 3.24 (d, *J* = 4.5 Hz, 1H, CH-5), 2.42–2.31 (m, 2H, CHH'-2), 2.27 (ddd, *J* = 10.0, 5.0, 4.5 Hz, 1H, C*H*H'-4), 1.86 (d, *J* = 10.0 Hz, 1H, CH*H'*-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.4 (C=O), 160.6 (*ipso*-Ar), 158.6 (*ipso*-Ar), 144.2 (*ipso*-Ar), 139.6 (=C), 130.7 (Ar), 129.1 (q, *J* = 32.5 Hz, *ipso*-Ar), 125.6 (Ar), 125.5 (q, *J* = 4.0 Hz, Ar), 124.4 (q, *J* = 272.0 Hz, CF_3), 123.8 (=CH), 117.8 (*ipso*-

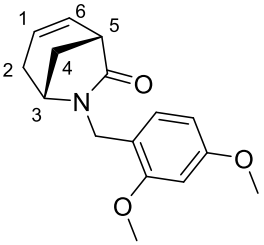
Ar), 104.3 (Ar), 98.5 (Ar), 55.5 (OMe), 53.7 (NCH), 44.2 (CH-5), 38.2 (NCH_2), 34.0 (CH_2-4), 29.1 (CH_2-2) (1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{23}H_{22}F_3NO_3$ $(M + Na)^+$ 440.1444, found 440.1442 (+0.4 ppm error), a 75:25 mixture (by ^1H NMR spectroscopy) of bis-normorphan **155a** and SPhos (2 mg, i.e. 1.5 mg (2%) of **155a**) as a clear oil, R_F (3:2 hexane-acetone) 0.2; IR (ATR) 2928, 1689 (C=O), 1613, 1588, 1508, 1208, 1034, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) for **155a** δ 7.14–7.06 (m, 2H, Ar), 6.48–6.39 (m, 4H, Ar), 5.85 (s, 2H, =CH), 4.51 (d, *J* = 15.0 Hz, 2H, NC*H*H'), 4.18 (d, *J* = 15.0 Hz, 2H, NCH*H'*), 3.82–3.75 (m, 12H, OMe), 3.67 (d, *J* = 5.0 Hz, 2H, NCH), 3.08 (d, *J* = 5.0 Hz, 2H, CH-5), 2.36–2.20 (m, 4H, CHH'-2), 2.16 (ddd, *J* = 10.5, 5.0, 5.0 Hz, 2H, C*H*H'-4), 1.71 (d, *J* = 10.5 Hz, 2H, CH*H'*-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) for **155a** δ 176.4 (C=O), 160.4 (*ipso*-Ar), 158.7 (*ipso*-Ar), 139.2 (=C), 130.5 (Ar), 119.4 (=CH), 118.0 (*ipso*-Ar), 104.2 (Ar), 98.5 (Ar), 55.5 (OMe), 53.5 (NCH), 42.3 (CH-5), 38.1 (NCH_2), 34.1 (CH_2-4), 28.5 (CH_2-2) (1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{32}H_{36}N_2O_6$ $(M + Na)^+$ 567.2466, found 567.2455 (+1.9 ppm error) and a 95:5 mixture (by ^1H NMR spectroscopy) of bis-normorphan **155b** and SPhos (3 mg i.e. 2.85 mg (4%) of **155b**) as a clear oil, R_F (3:2 hexane-acetone) 0.09; IR (ATR) 2929, 1764, 1678 (C=O), 1613, 1508, 1208, 1035, 835, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) for **155b** δ 7.13–7.09 (m, 2H, Ar), 6.46–6.40 (m, 4H, Ar), 6.05–5.62 (m, 2H, =CH), 4.55 (d, *J* = 15.0 Hz, 2H, NC*H*H'), 4.16 (d, *J* = 15.0 Hz, 2H, NCH*H'*), 3.84–3.76 (m, 12H, OMe), 3.72–3.67 (m, 2H, NCH), 3.16 (d, *J* = 5.0 Hz, 2H, CH-5), 2.35–2.30 (m, 4H, CHH'-2), 2.14 (ddd, *J* = 10.0, 5.0, 5.0 Hz, 2H, C*H*H'-4), 1.76 (d, *J* = 10.0 Hz, 2H, CH*H'*-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) for **155b** δ 176.6 (C=O), 160.4 (*ipso*-Ar), 158.6 (*ipso*-Ar), 138.0 (=C), 130.6 (Ar), 120.1 (=CH), 117.9 (*ipso*-Ar), 104.3 (Ar), 98.5 (Ar), 55.5 (OMe), 53.7 (NCH), 41.2 (CH-5), 37.9 (NCH_2), 33.6 (CH_2-4), 28.7 (CH_2-2) (1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{32}H_{36}N_2O_6$ $(M + Na)^+$ 567.2466, found 567.2466 (0 ppm error).

Lab book reference: ARG-2-123

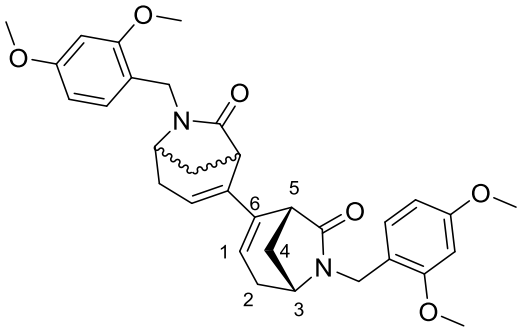
***N*-(4-(-6-(2,4-Dimethoxybenzyl)-7-oxo-6-azabicyclo[3.2.1]oct-2-en-2-yl)phenyl)acetamide 159 6-(2,4-dimethoxybenzyl)-6-azabicyclo[3.2.1]oct-2-en-7-one 115 and 6,6'-bis(2,4-dimethoxybenzyl)-6,6'-diaza[2,2'-bi(bicyclo[3.2.1]octane)]-2,2'-diene-7,7'-dione 155a/b**



159



115



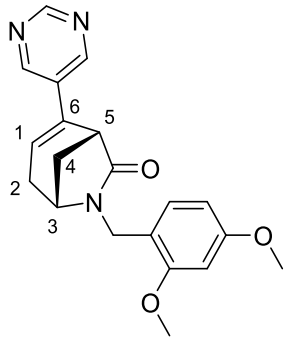
155a/b

Using general procedure A, vinyl MIDA boronate **94** (100 mg, 0.234 mmol, 1.0 eq), $Pd(OAc)_2$ (3 mg, 0.012 mmol, 0.05 eq), SPhos (10 mg, 0.023 mmol, 0.1 eq), 4-bromoacetanilide (63 mg, 0.280 mmol, 1.2 eq) and 3 M $K_3PO_{4(aq)}$ (0.59 mL, 1.755 mmol, 7.5 eq) in dioxane (2.34 mL) gave the crude product. Purification by flash column chromatography on silica with 2:8 to 1:99 hexane-EtOAc as eluent gave alkene **115** (26 mg, 40%) as a clear oil, identical (by ^{1}H and ^{13}C NMR spectroscopy) to that described above, a 75:25 mixture (by ^{1}H NMR spectroscopy) of bis-normorphan **155a** and SPhos (3 mg, i.e. 2.3 mg (3%) of **155a**) as a clear oil, identical (by ^{1}H and ^{13}C NMR spectroscopy) to that described above and a 90:10 mixture (by ^{1}H NMR spectroscopy) of arylated normorphan **159** and bis-normorphan **155b** (48 mg, i.e. 43.2 mg (45%) of **159** and 4.8 mg (7%) of **155b**) as a clear oil, R_F (1:99 hexane-EtOAc) 0.3; IR (ATR) 3309 (NH), 2939, 2836, 1669 (C=O), 1613, 1591, 1508, 1208, 1035, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) for **159** δ 8.82 (br s, 1H, NH), 7.52–7.49 (m, 2H, Ar), 7.43–7.39 (m, 2H, Ar), 7.09 (d, *J* = 8.5 Hz, 1H, Ar), 6.47–6.40 (m, 2H, Ar), 5.77–5.74 (m, 1H, =CH), 4.59 (d, *J* = 15.0 Hz, 1H, NC*H*H'), 4.25 (d, *J* = 15.0 Hz, 1H, NCH*H'*), 3.84–3.73 (m, 7H, OMe, NCH), 3.27 (d, *J* = 4.5 Hz, 1H, CH-5), 2.38–2.22 (m, 3H, CHH'-2, C*H*H'-4), 2.07 (s, 3H, Me), 1.88 (d, *J* = 10.5 Hz, 1H, CH*H'*-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.1 (C=O, lactam), 169.1 (C=O, NHC(O)), 160.6 (*ipso*-Ar), 158.6 (*ipso*-Ar), 139.7 (*ipso*-Ar), 138.0 (*ipso*-Ar), 135.6 (=C), 130.2 (Ar), 125.7 (Ar), 120.5 (=CH), 120.0 (Ar), 117.6 (*ipso*-Ar), 104.3 (Ar), 98.6 (Ar), 55.5 (OMe), 55.4 (OMe), 54.0

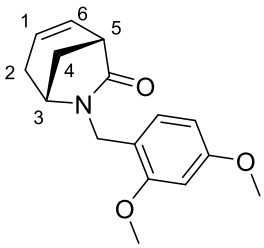
(NCH), 44.1 (C-5), 38.3 (NCH_2), 34.1 (CH_2-4), 28.8 (CH_2-2), 24.4 (Me); HRMS (ESI) *m/z* calcd for $C_{24}H_{26}N_2O_4$ $(M + Na)^+$ 429.1785, found 429.1782 (+0.7 ppm error).

Lab book reference: ARG-2-117

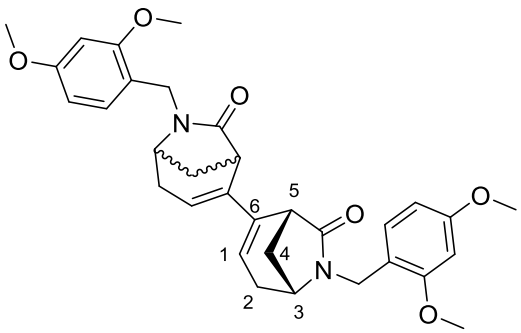
6-(2,4-Dimethoxybenzyl)-2-(pyrimidin-5-yl)-6-azabicyclo[3.2.1]oct-2-en-7-one 156, 6-(2,4-dimethoxybenzyl)-6-azabicyclo[3.2.1]oct-2-en-7-one 115 and 6,6'-bis(2,4-dimethoxybenzyl)-6,6'-diaza[2,2'-bi(bicyclo[3.2.1]octane)]-2,2'-diene-7,7'-dione 155a/b



156



115



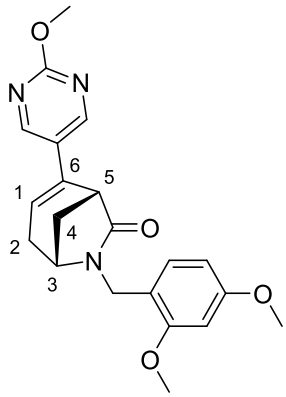
155a/b

Using general procedure A, vinyl MIDA boronate **94** (100 mg, 0.234 mmol, 1.0 eq), $Pd(OAc)_2$ (3 mg, 0.012 mmol, 0.05 eq), SPhos (10 mg, 0.023 mmol, 0.1 eq), 5-bromo-pyrimidine (45 mg, 0.280 mmol, 1.2 eq) and 3 M $K_3PO_{4(aq)}$ (0.59 mL, 1.755 mmol, 7.5 eq) in dioxane (3.9 mL) gave the crude product. Purification by flash column chromatography on silica with 99:1 to 9:1 Et_2O-MeOH as eluent gave alkene **115** (3 mg, 5%) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above, arylated normorphan **156** (50 mg, 60%) as a clear oil, R_F (9:1 Et_2O-MeOH) 0.27; IR (ATR) 2942, 2866, 1687 (C=O), 1613, 1507, 1412, 1208, 1033, 903, 823, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H, Ar), 8.85 (s, 2H, Ar), 7.15–7.07 (m, 1H, Ar), 6.45–6.37 (m, 2H, Ar), 5.90 (dd, *J* = 3.5, 3.5 Hz, 1H, =CH), 4.54 (d, *J* = 15.0 Hz, 1H, NC*H*H'), 4.23 (d, *J* = 15.0 Hz, 1H, NCH*H'*), 3.77 (s, 7H, OMe, NCH), 3.19 (d, *J* = 5.0 Hz, 1H, CH-5), 2.41–2.32 (m, 2H, CHH'-2), 2.28 (ddd, *J* = 10.5, 5.0, 5.0 Hz, 1H, C*H*H'-4), 1.86 (d, *J* = 10.5 Hz, 1H, CH*H'*-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.8 (C=O), 160.6 (*ipso*-Ar), 158.6 (*ipso*-Ar), 157.3 (Ar), 153.5 (Ar), 135.0 (=C), 133.8 (*ipso*-Ar), 130.7 (Ar), 125.6 (=CH), 117.5 (*ipso*-Ar), 104.4 (Ar), 98.5 (Ar), 55.5 (OMe), 53.4 (NCH), 43.6 (CH-5), 38.2 (NCH_2), 33.8 (CH_2-4), 29.1 (CH_2-2) (1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{20}H_{21}N_3O_3$ $(M + Na)^+$ 374.1475, found 374.1471 (+0.9 ppm error), a 75:25 mixture (by ^1H NMR

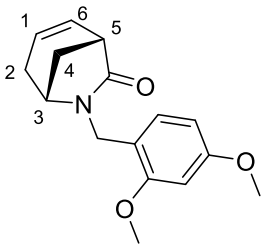
spectroscopy) of bis-normorphan **155a** and SPhos (2 mg, i.e. 1.5 mg (3%) of **155a**) as a clear oil, identical (by ^{1}H and ^{13}C NMR spectroscopy) to that described above and a 90:10 mixture (by ^{1}H and ^{13}C NMR spectroscopy) of bis-normorphan **155b** and SPhos (4 mg, i.e. 3.6 mg (7%) of **155b**) as a clear oil, identical (by ^{1}H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-2-106

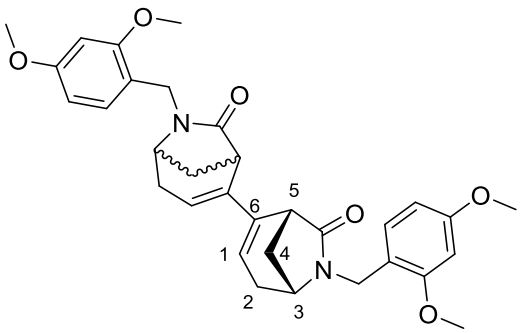
6-(2,4-Dimethoxybenzyl)-2-(2-methoxypyrimidin-5-yl)-6-azabicyclo[3.2.1]oct-2-en-7-one 160, 6-(2,4-dimethoxybenzyl)-6-azabicyclo[3.2.1]oct-2-en-7-one 115 and 6,6'-bis(2,4-dimethoxybenzyl)-6,6'-diaza[2,2'-bi(bicyclo[3.2.1]octane)]-2,2'-diene-7,7'-dione 155a/b



160



115



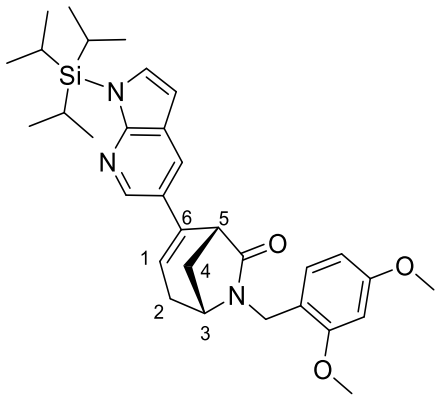
155a/b

Using general procedure A, vinyl MIDA boronate **94** (100 mg, 0.234 mmol, 1.0 eq), $Pd(OAc)_2$ (3 mg, 0.012 mmol, 0.05 eq), SPhos (10 mg, 0.023 mmol, 0.1 eq), 5-bromo-2-methoxy-pyrimidine (53 mg, 0.280 mmol, 1.2 eq) and 3 M $K_3PO_{4(aq)}$ (0.59 mL, 1.755 mmol, 7.5 eq) in dioxane (2.34 mL) gave the crude product. Purification by flash column chromatography on silica with 99:1 to 9:1 Et_2O-MeOH as eluent gave alkene **115** (4 mg, 6%) as a clear oil, identical (by ^{1}H and ^{13}C NMR spectroscopy) to that described above, a 95:5 mixture (by ^{1}H NMR spectroscopy) of arylated normorphan **160** and bis-normorphan **155a** (62 mg, i.e. 58.9 mg (66%) of **160** and 3.1 mg (5%) of **155a**) as a clear oil, R_F (95:5 Et_2O-MeOH) 0.46; IR (ATR) 2955, 2836, 1686 (C=O), 1613, 1589, 1471, 1412, 1207, 1032, 823 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) for **160** δ 8.60 (s, 2H, Ar), 7.08 (d, *J* = 8.0 Hz, 1H, Ar), 6.46–6.35 (m, 2H, Ar), 5.78 (dd, *J* = 3.5, 2.5 Hz, 1H, =CH), 4.49 (d, *J* = 15.0 Hz, 1H, NC*H*H'), 4.19 (d, *J* = 15.0 Hz, 1H, NCH*H'*), 3.95 (s, 3H, OMe), 3.81–3.71 (m, 7H, OMe, NCH), 3.10 (dd, *J* = 5.0, 1.0 Hz, 1H, CH-5), 2.38–2.29 (m, 2H, CHH'-2), 2.25 (dddd, *J* =

10.0, 5.5, 4.5, 1.0 Hz, 1H, C*H*H'-4), 1.85 (d, *J* = 10.5 Hz, 1H, CH*H'*-4); ^{13}C NMR (100.6 MHz, CD_2Cl_2) δ 175.8 (C=O), 164.9 (*ipso*-Ar), 160.6 (*ipso*-Ar), 158.6 (*ipso*-Ar), 155.9 (Ar), 134.6 (*ipso*-Ar), 130.2 (Ar), 128.0 (=C), 122.9 (=CH), 117.8 (*ipso*-Ar), 104.3 (Ar), 98.3 (Ar), 55.41 (OMe), 55.36 (OMe), 54.8 (NCH), 43.7 (CH-5), 38.0 (NCH_2), 33.6 (CH_2-4), 28.8 (CH_2-2) (1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{21}H_{23}N_3O_4$ (M + Na)$^+$ 404.1581, found 404.1583 (–0.4 ppm error) and a 90:10 mixture (by ^{1}H NMR spectroscopy) of bis-normorphan **155b** and SPhos (5 mg, i.e. 4.5 mg of **155b**, 7%) as a clear oil, identical (by ^{1}H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-2-107

6-(2,4-Dimethoxybenzyl)-2-(1-(triisopropylsilyl)-1*H*-pyrrolo[2,3-b]pyridin-5-yl)-6-azabicyclo[3.2.1]oct-2-en-7-one 158



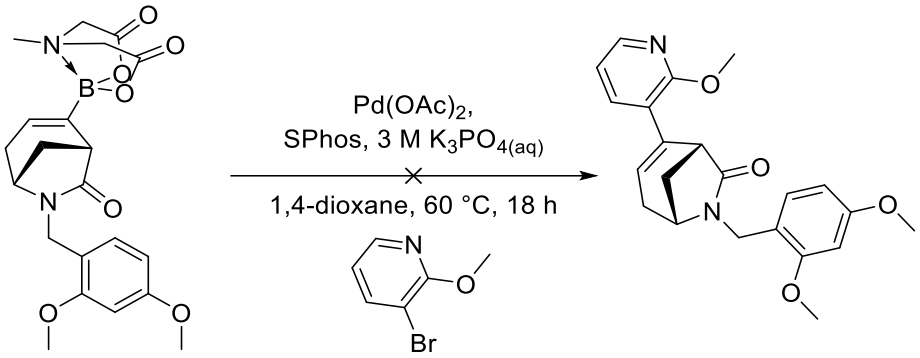
158

Using general procedure A, MIDA boronate **94** (200 mg, 1.47 mmol, 1.0 eq), $Pd(OAc)_2$ (6 mg, 0.025 mmol, 0.05 eq), SPhos (20 mg, 0.047 mmol, 0.1 eq), 5-bromo-1-triisopropylsilanyl-1*H*-pyrrolo[2,3-b]pyridine **157** (198 mg, 0.56 mmol, 1.2 eq) and 3 M $K_3PO_{4(aq)}$ (1.52 mL, 4.59 mmol, 7.5 eq) in dioxane (7.5 mL) gave the crude product. Purification by flash column chromatography on silica with 1:4 EtOAc-hexane as eluent gave arylated normorphan **158** (178 mg, 58%) as a clear oil, R_F (1:4 EtOAc-hexane) 0.15; IR (ATR) 2945, 2866, 2244, 1686 (C=O), 1613, 1507, 1465, 1385, 1207, 1154, 906, 726, 648 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.0 Hz, 1H, Ar), 8.10 (d, *J* = 2.0 Hz, 1H, Ar), 7.27 (d, *J* = 3.5 Hz, 1H, Ar), 7.21–7.13 (m, 1H, Ar), 6.55 (d, *J* = 3.5 Hz, 1H, Ar), 6.49–6.40 (m, 2H, Ar), 5.78 (dd, *J* = 3.5, 3.5 Hz, 1H, =CH), 4.61 (d, *J* = 15.0 Hz, 1H, NC*H*H'), 4.29 (d, *J* = 15.0 Hz, 1H, NC*H*H'), 3.91–3.72 (m, 7H, OMe, NCH), 3.33 (d, *J* = 5.0

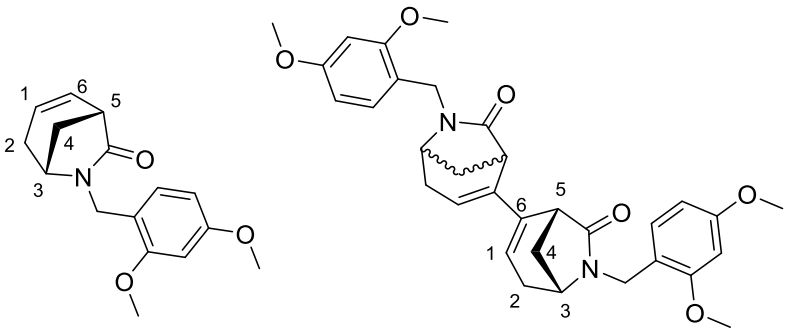
Hz, 1H, CH-5), 2.43–2.30 (m, 2H, CHH'-2), 2.29 (ddd, *J* = 10.0, 5.0, 5.0 Hz, 1H, C*H*H'-4), 1.91 (d, *J* = 10.0 Hz, 1H, CH*H'*-4), 1.85 (sept, *J* = 7.5 Hz, 3H, SiCH), 1.121 (d, *J* = 7.5 Hz, 9H, SiCH*Me*$_2$), 1.117 (d, J = 7.5 Hz, 9H, SiCH*Me*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.8 (C=O), 160.5 (*ipso*-Ar), 158.6 (*ipso*-Ar), 153.4 (*ipso*-Ar), 140.3 (Ar), 139.0 (=C), 131.6 (Ar), 130.6 (Ar), 129.1 (*ipso*-Ar), 124.7 (Ar), 122.0 (*ipso*-Ar), 120.5 (=CH), 118.0 (*ipso*-Ar), 104.3 (Ar), 103.4 (Ar), 98.5 (Ar), 55.5 (OMe), 53.9 (NCH), 44.6 (CH-5), 38.0 (NCH_2), 34.2 (CH_2-4), 29.0 (CH_2-2), 18.3 (SiCH*Me*$_2$), 12.4 (SiCH) (1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{32}H_{44}N_3O_3$ $(M + H)^+$ 546.3146, found 546.3147 (–0.1 ppm error).

Lab book reference: ARG-1-069

Attempted synthesis of 6-(2,4-Dimethoxybenzyl)-2-(2-methoxypyridin-3-yl)-6-azabicyclo[3.2.1]oct-2-en-7-one 161. 6-(2,4-Dimethoxybenzyl)-6-azabicyclo[3.2.1]oct-2-en-7-one 115 and 6,6'-bis(2,4-dimethoxybenzyl)-6,6'-diaza[2,2'-bi(bicyclo[3.2.1]octane)]-2,2'-diene-7,7'-dione 155a/b



94 **161**

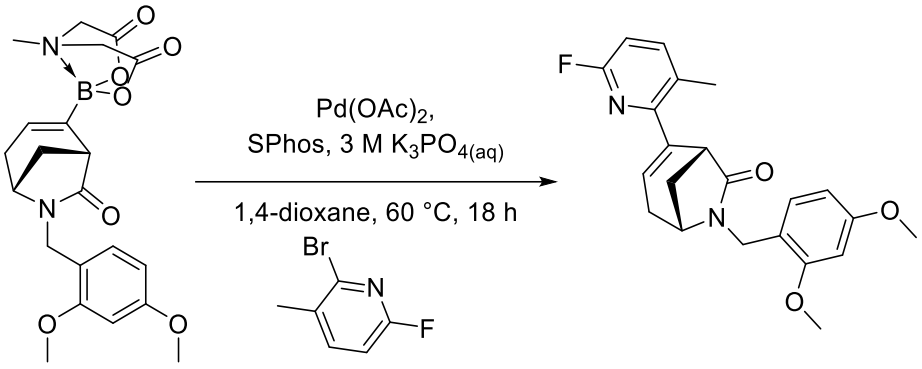


115 **155a/b**

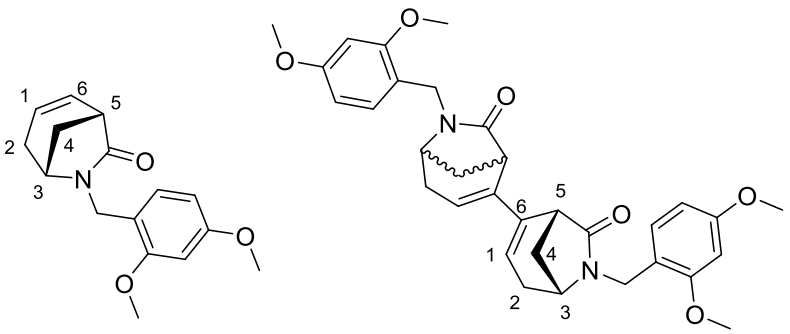
Using general procedure A, vinyl MIDA boronate **94** (100 mg, 0.234 mmol, 1.0 eq), $Pd(OAc)_2$ (3 mg, 0.012 mmol, 0.05 eq), SPhos (10 mg, 0.023 mmol, 0.1 eq), 3-bromo-2-methoxy-pyridine (53 mg, 0.280 mmol, 1.2 eq) and 3 M $K_3PO_{4(aq)}$ (0.59 mL, 1.755 mmol, 7.5 eq) in dioxane (2.34 mL) gave the crude product. Purification by flash column chromatography on silica with 99:1 to 9:1 Et_2O-MeOH as eluent gave alkene **115** (37 mg, 55%) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above, a 75:25 mixture (by ^1H NMR spectroscopy) of bis-normorphan **155a** and SPhos (4 mg, i.e. 3 mg (6%) of **155a**) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above and an 85:15 mixture (by ^1H and ^{13}C NMR spectroscopy) of bis-normorphan **155b** and SPhos (6 mg, i.e. 5 mg (10%) of **155b**) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above. There was evidence in the ^1H NMR spectrum of the crude product for the formation of arylated normorphan **161** but none was isolated after chromatography.

Lab book reference: ARG-2-118

Attempted synthesis of 6-(2,4-dimethoxybenzyl)-2-(6-fluoro-3-methylpyridin-2-yl)-6-azabicyclo[3.2.1]oct-2-en-7-one 162. 6-(2,4-Dimethoxybenzyl)-6-azabicyclo[3.2.1]oct-2-en-7-one 115 and 6,6'-bis(2,4-dimethoxybenzyl)-6,6'-diaza[2,2'-bi(bicyclo[3.2.1]octane)]-2,2'-diene-7,7'-dione 155a/b



94 **162**



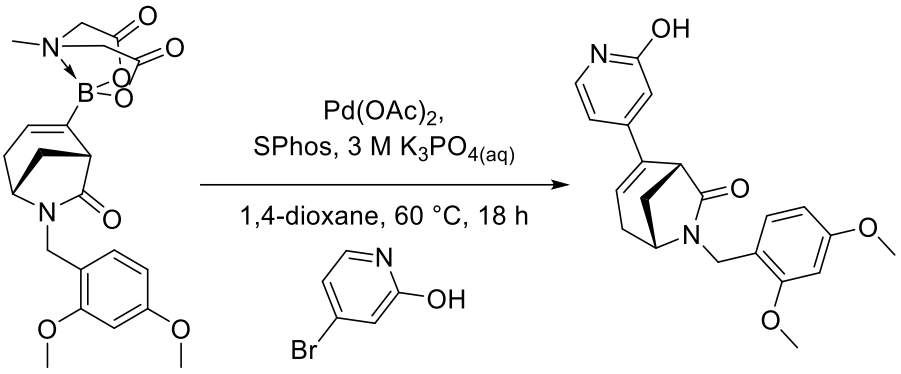
115 **155a/b**

Using general procedure A, vinyl MIDA boronate **94** (100 mg, 0.234 mmol, 1.0 eq), $Pd(OAc)_2$ (3 mg, 0.012 mmol, 0.05 eq), SPhos (10 mg, 0.023 mmol, 0.1 eq), 2-bromo-5-fluoro-3-methylpyridine (33 µL, 0.280 mmol, 1.2 eq) and 3 M $K_3PO_{4(aq)}$ (0.59 mL, 1.755 mmol, 7.5 eq) in dioxane (2.34 mL) gave the crude product. Purification by flash column chromatography on silica with 99:1 to 9:1 Et_2O-MeOH as eluent gave alkene **115** (40 mg, 60%) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above, a 80:20 mixture (by ^1H NMR spectroscopy) of bis-normorphan **155a** and SPhos (2 mg, i.e. 1.5 mg (3%) of **155a**) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above and an 85:15 mixture (by ^1H and ^{13}C NMR spectroscopy) of bis-normorphan **155b** and SPhos (5 mg, i.e. 4 mg (8%) of **155b**) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above. There was evidence in the ^1H NMR

spectrum of the crude product for the formation of arylated normorphan **162** but none was isolated after chromatography.

Lab book reference: ARG-2-124

Attempted synthesis of 6-(2,4-dimethoxybenzyl)-2-(2-hydroxypyridin-4-yl)-6-azabicyclo[3.2.1]oct-2-en-7-one

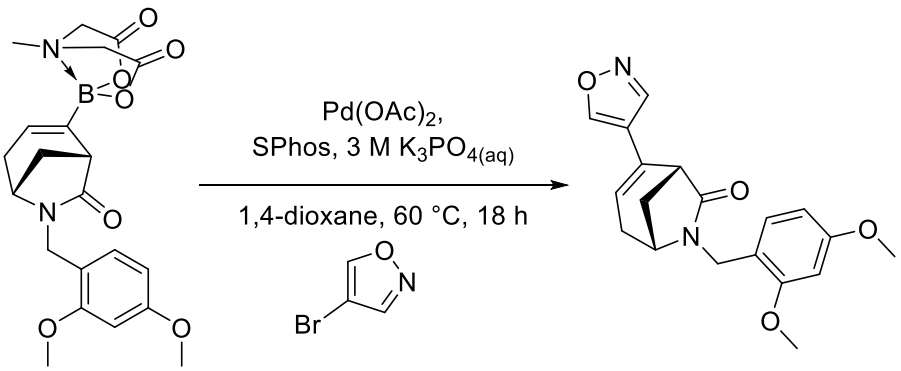


94

Using general procedure A, vinyl MIDA boronate **94** (100 mg, 0.234 mmol, 1.0 eq), $Pd(OAc)_2$ (3 mg, 0.012 mmol, 0.05 eq), SPhos (10 mg, 0.023 mmol, 0.1 eq), 4-bromo-2-hydroxypyridine (49 mg, 0.280 mmol, 1.2 eq) and 3 M $K_3PO_{4(aq)}$ (0.59 mL, 1.755 mmol, 7.5 eq) in dioxane (2.34 mL) gave the crude product which contained (by ^1H NMR spectroscopy) only traces of arylated normorphan**.**

Lab book reference: ARG-2-116

Attempted synthesis of 6-(2,4-dimethoxybenzyl)-2-(isoxazol-4-yl)-6-azabicyclo[3.2.1]oct-2-en-7-one

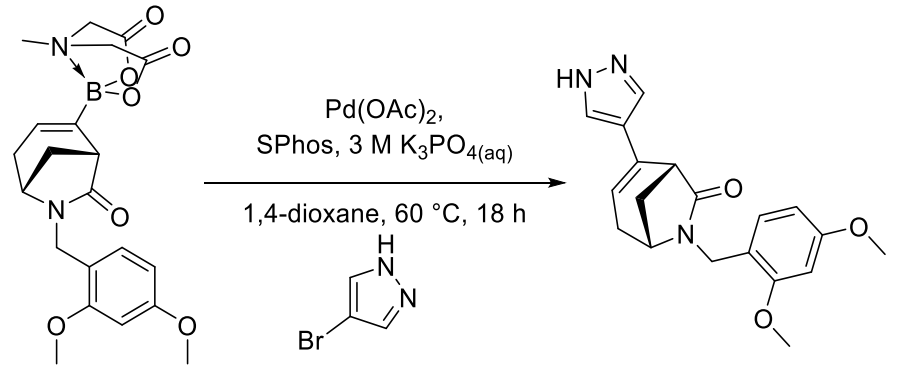


94

Using general procedure A, vinyl MIDA boronate **94** (100 mg, 0.234 mmol, 1.0 eq), $Pd(OAc)_2$ (3 mg, 0.012 mmol, 0.05 eq), SPhos (10 mg, 0.023 mmol, 0.1 eq), 4-bromo-isoxazole (41 mg, 0.280 mmol, 1.2 eq) and 3 M $K_3PO_{4(aq)}$ (0.59 mL, 1.755 mmol, 7.5 eq) in dioxane (2.34 mL) gave the crude product which contained (by ^1H NMR spectroscopy) only traces of arylated normorphan.

Lab book reference: ARG-2-105

Attempted synthesis of 6-(2,4-dimethoxybenzyl)-2-(1H-pyrazol-4-yl)-6-azabicyclo[3.2.1]oct-2-en-7-one



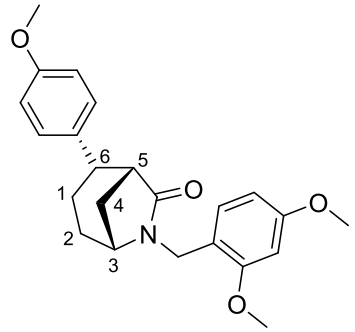
94

Using general procedure A, vinyl MIDA boronate **94** (100 mg, 0.234 mmol, 1.0 eq), $Pd(OAc)_2$ (3 mg, 0.012 mmol, 0.05 eq), SPhos (10 mg, 0.023 mmol, 0.1 eq), 4-bromo-pyrazole (41 mg, 0.280 mmol, 1.2 eq) and 3 M $K_3PO_{4(aq)}$ (0.59 mL, 1.755 mmol, 7.5 eq) in

dioxane (2.34 mL) gave the crude product which contained (by ^{1}H NMR spectroscopy) only traces of arylated normorphan.

Lab book reference: ARG-2-104

6-(2,4-Dimethoxybenzyl)-2-(4-methoxyphenyl)-6-azabicyclo[3.2.1]octan-7-one 168

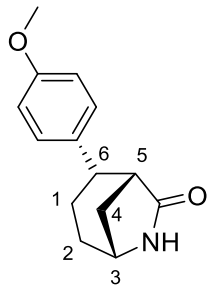


168

10% Pd/C (61 mg, 0.057 mmol, 10 mol%) was added to a stirred solution of arylated normorphan **153** (215 mg, 0.57 mmol, 1 eq) in MeOH (3 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and then with H_2 three times. The resulting mixture was stirred under a balloon of H_2 (760 mmHg) for 18 h. The solids were removed by filtration through Celite® and washed with MeOH (10 mL). The filtrate was evaporated under reduced pressure to give hydrogenated normorphan **168** (200 mg, 92%, >97:3 dr) as a clear oil, R_F (3:2 EtOAc-hexane) 0.49; IR (ATR) 2936, 2835, 1680 (C=O), 1611, 1587, 1508, 1243, 1032, 825, 728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.33 (m, 2H, Ar), 7.22 (d, *J* = 8.5 Hz, 1H, Ar), 6.87–6.82 (m, 2H, Ar), 6.47–6.42 (m, 2H, Ar), 4.64 (d, *J* = 14.5 Hz, 1H, NC*H*H'), 4.30 (d, *J* = 14.5 Hz, 1H, NCH*H'*), 3.84–3.74 (m, 9H, OMe), 3.61 (dd, *J* = 5.5, 4.5 Hz, 1H, NCH), 2.84 (ddd, *J* = 12.0, 5.0, 1.5 Hz, 1H, CH-6), 2.64 (d, *J* = 5.5 Hz, 1H, CH-5), 2.28 (dddd, *J* = 11.0, 5.5, 5.5, 1.5 Hz, 1H, C*H*H'-4), 1.85 (ddd, *J* = 14.0, 5.0, 5.0 Hz, 1H, C*H*H'-1), 1.79–1.61 (m, 3H, CH*H'*-1, C*H*H'-2, CH*H'*-4), 1.52 (ddd, *J* = 12.0, 11.5, 5.0 Hz, 1H, CH*H'*-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.3 (C=O), 160.5 (*ipso*-Ar), 158.7 (*ipso*-Ar), 158.2 (*ipso*-Ar), 136.5 (*ipso*-Ar), 131.0 (Ar), 128.7 (Ar), 117.9 (*ipso*-Ar), 113.7 (Ar), 104.2 (Ar), 98.4 (Ar), 55.5 (OMe), 55.4 (OMe), 55.3 (OMe), 54.8 (NCH), 46.2 (CH-5), 44.0 (CH-6), 39.7 (CH_2-4), 38.6 (NCH_2), 27.5 (CH_2-1), 26.4 (CH_2-2); HRMS (ESI) *m/z* calcd for $C_{23}H_{27}NO_4$ $(M + Na)^+$ 404.1832, found 404.1837 (–1.2 ppm error).

Lab book reference: ARG-1-054

2-(4-Methoxyphenyl)-6-azabicyclo[3.2.1]octan-7-one 170



170

80% v/v $TFA_{(aq)}$ (8 mL) was added to a stirred solution of *N*-DMB-amide **168** (100 mg, 0.26 mmol, 1.0 eq) in CH_2Cl_2 (1 mL) at rt. The resulting mixture was stirred and heated at 60 °C for 18 h. The solvent was evaporated under reduced pressure. The residue was suspended in toluene (10 mL) and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 7:3 EtOAc-hexane as eluent gave amide **170** (44 mg, 73%) as an off-white crystalline solid, mp 140-142 °C; R_F (7:3 EtOAc-hexane) 0.20; IR (ATR) 3231 (NH), 2934, 1693 (C=O), 1611, 1514, 1247, 1181, 1035, 835, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.27 (m, 2H, Ar), 6.88–6.79 (m, 2H, Ar), 6.69 (br s, 1H, NH), 3.85–3.69 (m, 4H, OMe, NCH), 2.88 (ddd, *J* = 12.5, 6.0, 2.0 Hz, 1H, CH-6), 2.53 (d, *J* = 5.5 Hz, 1H, CH-5), 2.44 (dddd, *J* = 11.5, 6.0, 5.5, 2.0 Hz, 1H, C*H*H'-4), 2.09–1.88 (m, 2H, C*H*H'-1, C*H*H'-2), 1.88–1.73 (m, 2H, CH*H'*-1, CH*H'*-4), 1.68 (ddd, *J* = 12.5, 12.5, 6.0 Hz, 1H, CH*H'*-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 179.0 (C=O), 158.2 (*ipso*-Ar), 136.2 (*ipso*-Ar), 128.5 (Ar), 113.8 (Ar), 55.3 (OMe), 51.2 (NCH), 45.8 (CH-5), 43.8 (CH-6), 41.0 (CH_2-4), 29.1 (CH_2-1), 26.8 (CH_2-2); HRMS (ESI) *m/z* calcd for $C_{14}H_{17}NO_2$ $(M + H)^+$ 232.1332, found 232.1334 (–0.8 ppm error).

Lab book reference: ARG-1-062

80% v/v $TFA_{(aq)}$ (5 mL) was added to a stirred solution of *N*-DMB-amide **168** (70 mg, 0.18 mmol, 1.0 eq) in CH_2Cl_2 (1 mL) at rt. The resulting mixture was stirred at rt for 72 h. The solvent was evaporated under reduced pressure. The residue was suspended in toluene (10 mL) and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 7:3 EtOAc-hexane as

eluent gave amide **170** (27 mg, 68%) as an off-white crystalline solid, identical (by ^{1}H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-1-057

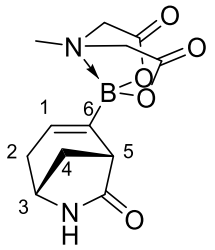
DDQ (71 mg, 0.31 mmol, 1.5 eq) was added to a stirred solution of *N*-DMB-amide **168** (79 mg, 0.21 mmol, 1.0 eq) in CH_2Cl_2 (1 mL) and H_2O (0.1 mL) at rt. The resulting mixture was stirred at rt for 24 h. Saturated $NaHCO_{3(aq)}$ (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 7:3 EtOAc-hexane as eluent gave amide **170** (12 mg, 25%) as an off-white crystalline solid, identical (by ^{1}H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-1-058

TFA (596 µL, 7.8 mmol, 30 eq) was added to a stirred solution of *N*-DMB-amide **168** (100 mg, 0.26 mmol, 1.0 eq) and *m*-dimethoxybenzene (68 µL, 0.52 mmol, 2 eq) in CH_2Cl_2 (1.3 mL) at rt. The resulting solution stirred at rt for 72 h. Saturated $NaHCO_{3(aq)}$ (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 7:3 EtOAc-hexane as eluent gave amide **170** (31 mg, 52%) as an off-white crystalline solid, identical (by ^{1}H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-1-084

4-Methyl-8-(-7-oxo-6-azabicyclo[3.2.1]oct-2-en-2-yl)dihydro-4λ⁴,8λ⁴-[1,3,2]oxazaborolo[2,3-*b*][1,3,2]oxazaborole-2,6(3*H*,5*H*)-dione 171



171

TFA (800 µL, 7.01 mmol, 30 eq) was added to a stirred solution of vinyl MIDA boronate **94** (100 mg, 0.23 mmol, 1.0 eq) and *m*-dimethoxybenzene (60 µL, 0.46 mmol, 2 eq) in CH_2Cl_2 (1.15 mL) at rt. The resulting mixture was stirred at rt for 72 h. The solvent was evaporated under reduced pressured. The residue was suspended in toluene (5 mL) and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 8:2 CH_2Cl_2-acetone as eluent gave free amide **171** (39 mg, 60%) as a white crystalline solid. mp 280-282 °C (decomposition); R_F (2:8 CH_2Cl_2-acetone) 0.31; IR (ATR) 3388 (NH), 1755 (C=O, ester), 1671 (C=O, amide), 1322, 110, 1039, 558 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.55 (s, 1H, NH), 5.86 (ddd, *J* = 3.0, 3.0, 1.5 Hz, 1H, =CH-1), 4.25 (d, *J* = 17.5 Hz, 1H, C(O)C*H*H'), 4.13 (d, *J* = 16.5 Hz, 1H, C(O)C*H*H'), 3.91 (d, *J* = 17.5 Hz, 1H, C(O)CH*H'*), 3.90 (d, *J* = 16.5 Hz, 1H, C(O)CH*H'*), 3.68–3.65 (m, 1H, NCH), 2.64 (s, 3H, NMe), 2.41 (d, *J* = 5.0 Hz, 1H, CH-5), 2.32 (ddd, *J* = 19.0, 3.0, 3.0 Hz, 1H, C*H*H'-2), 2.07 (ddd, *J* = 10.5, 5.0, 5.0 Hz, 1H, C*H*H'-4), 2.02 (ddd, *J* = 19.0, 3.0, 1.5 Hz, 1H, CH*H'*-2), 1.52 (d, *J* = 10.5 Hz, 1H, CH*H'*-4); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 179.7 (C=O, amide), 170.4 (C=O, ester), 169.2 (C=O, ester), 134.1 (=CH), 62.2 (*C*H_2CO_2), 61.6 (*C*H_2CO_2), 49.8 (NCH), 46.6 (NMe), 41.5 (CH-5), 34.9 (CH_2-4), 33.2 (CH_2-2) (=C-B resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{12}H_{15}BN_2O_5$ $(M + H)^+$ 301.0966, found 301.0966 (+0.8 ppm error).

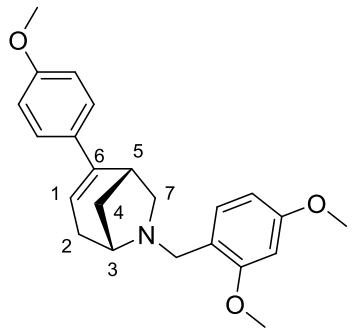
Lab book reference: ARG-1-094

80% v/v $TFA_{(aq)}$ (7 mL) was added to a stirred solution of vinyl MIDA boronate **94** (100 mg, 0.23 mmol, 1.0 eq) in CH_2Cl_2 (1.5 mL) at rt. The resulting mixture was stirred and heated at 60 °C for 18 h. The solvent was evaporated under reduced pressure. The residue was suspended in toluene (5 mL) and the solvent was evaporated under reduced pressure to

give the crude product which contained (by ^{1}H NMR spectroscopy) an unidentified mixture of products

Lab book reference: ARG-1-093

6-(2,4-Dimethoxybenzyl)-2-(4-methoxyphenyl)-6-azabicyclo[3.2.1]oct-2-ene 172



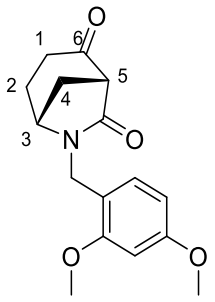
172

A solution of arylated normorphan **153** (200 mg, 0.53 mmol, 1.0 eq) in THF (7.5 mL), was added dropwise to a stirred suspension of $LiAlH_4$ (80 mg, 2.11 mmol, 4 eq) in THF (3.5 mL) at rt under Ar. The resulting mixture was stirred and heated at reflux for 16 h under Ar. After allowing the mixture to cool to rt, H_2O (0.15 mL), 2 M $NaOH_{(aq)}$ (0.32 mL) and $MgSO_4$ (250 mg) were added and the resulting mixture was stirred for 15 min. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 to 9:1 EtOAc-MeOH as eluent gave amine **172** (136 mg, 70%) as a clear oil, R_F (9:1 EtOAc-MeOH) 0.3; IR (ATR) 2934, 2832, 1607, 1507, 1240, 1152, 1032, 819 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.5 Hz, 1H, Ar), 7.31–7.27 (m, 2H, Ar), 6.87–6.82 (m, 2H, Ar), 6.48 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar), 6.44 (d, *J* = 2.5 Hz, 1H, Ar), 5.72 (ddd, *J* = 3.5, 3.5, 1.5 Hz, 1H, =CH), 3.87–3.80 (m, 2H, NCHH'Ar), 3.81–3.79 (m, 9H, OMe), 3.48–3.42 (m, 1H, NCH), 3.12–3.02 (m, 2H, NCHH'-7), 3.00 (dd, *J* = 5.0, 4.5 Hz, 1H, CH-5), 2.48 (ddd, *J* = 18.5, 3.5, 2.0 Hz, 1H, C*H*H'-2), 2.30 (ddd, *J* = 18.5, 3.5, 3.5 Hz, 1H, CH*H'*-2), 2.04 (ddd, *J* = 10.5, 5.0, 5.0 Hz, 1H, C*H*H'-4), 1.84 (d, *J* = 10.5 Hz, 1H, CH*H'*-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.6 (*ipso*-Ar), 158.6 (*ipso*-Ar), 158.2 (*ipso*-Ar), 144.2 (=C), 134.1 (*ipso*-Ar), 130.2 (Ar), 126.2 (Ar), 121.3 (*ipso*-Ar), 119.6 (=CH), 113.8 (Ar), 103.9 (Ar), 98.4 (Ar), 63.2 (NCH_2-7), 58.2 (NCH), 55.45 (OMe), 55.43 (OMe), 55.38 (OMe), 52.6 (NCH_2Ar), 38.6 (CH-5), 34.3 (CH_2-2), 33.6 (CH_2-4); HRMS (ESI) *m/z* calcd for $C_{23}H_{27}NO_3$ $(M + H)^+$ 366.2064, found 366.2066 (–0.5 ppm error).

Lab book reference: ARG-1-071

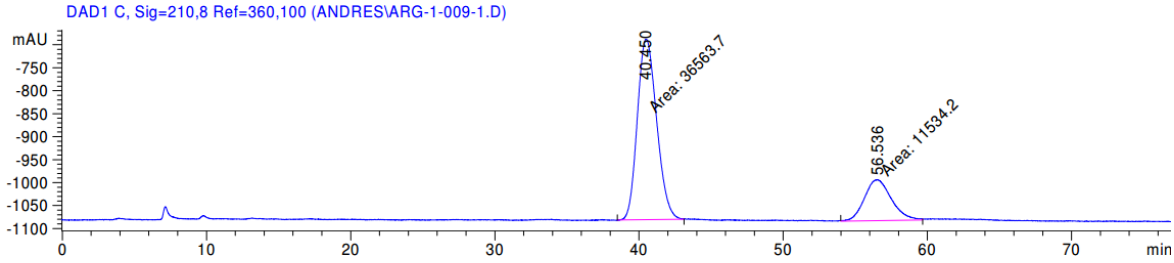
6.2.4 HPLC Traces

HPLC Traces for enantioenriched 109



109

ARG-1-009

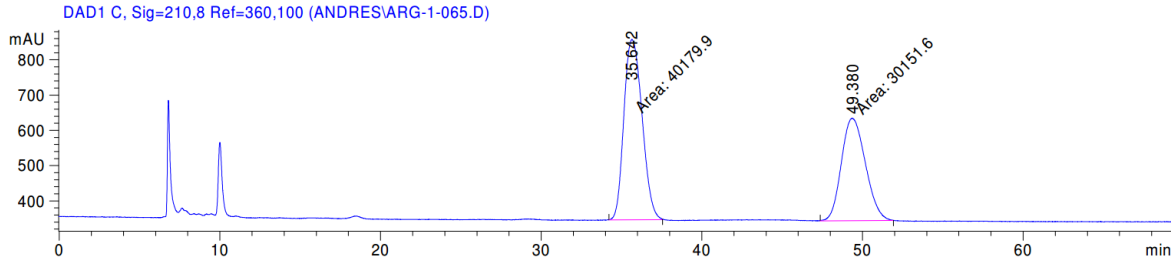


Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.450	MM	1.5508	3.65637e4	392.96259	76.0194
2	56.536	MM	2.1532	1.15342e4	89.28035	23.9806
Totals :				4.80979e4	482.24294	

Figure 6.1 - HPLC Trace for ARG-1-009

ARG-1-065

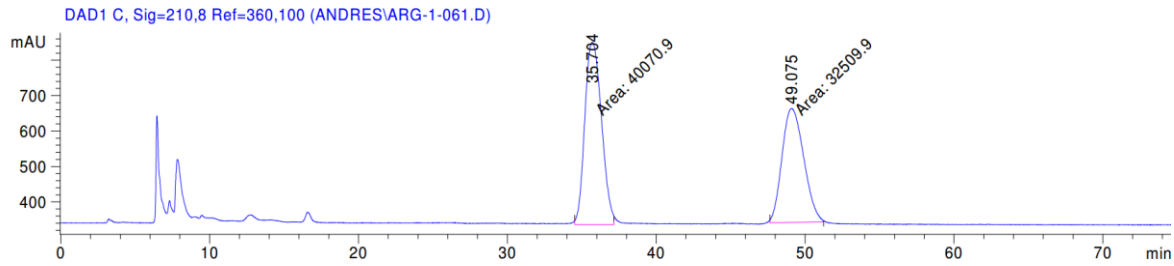


Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.642	MM	1.3076	4.01799e4	512.13098	57.1293
2	49.380	MM	1.7289	3.01516e4	290.67096	42.8707
Totals :				7.03315e4	802.80194	

Figure 6.2 - HPLC Trace for ARG-1-065

ARG-1-061



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.704	MM	1.2960	4.00709e4	515.31061	55.2087
2	49.075	MM	1.6863	3.25099e4	321.30942	44.7913
Totals :				7.25809e4	836.62003	

Figure 6.3 - HPLC Trace for ARG-1-061

6.2.5 Crystal Data

Crystal data for 170

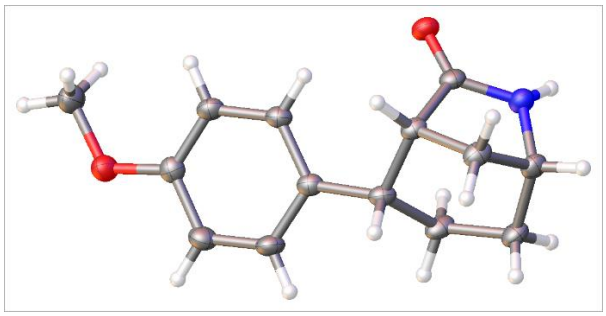


Table 6.1 - Crystal data and structure refinement for paob1911

Identification code	**paob1911**
Empirical formula	$C_{14}H_{17}NO_2$
Formula weight	231.28
Temperature/K	109.95(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	16.7674(7)
b/Å	6.2020(2)
c/Å	11.4525(4)
α/°	90
β/°	97.971(4)
γ/°	90
Volume/Å^3	1179.45(8)
Z	4
ρ_{calc}g/cm^3	1.302
μ/mm^{-1}	0.695
F(000)	496.0
Crystal size/mm^3	0.157 × 0.138 × 0.03
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	10.656 to 141.988
Index ranges	$-20 \leq h \leq 20$, $-6 \leq k \leq 7$, $-14 \leq l \leq 13$
Reflections collected	8760
Independent reflections	2251 [R_{int} = 0.0333, R_{sigma} = 0.0340]
Data/restraints/parameters	2251/0/159
Goodness-of-fit on F^2	1.048
Final R indexes [I>=2σ (I)]	R_1 = 0.0547, wR_2 = 0.1437
Final R indexes [all data]	R_1 = 0.0645, wR_2 = 0.1522
Largest diff. peak/hole / e Å^{-3}	0.57/-0.28

Data collected, solved and refined by Sam Hart

Abbreviations

Ac - Acetyl

Acac - Acetylacetone

AIBN - Azobisisobutyronitrile

Aq - Aqueous

Ar - Aryl

Bn - Benzyl

Boc - *tert*-butoxycarbonyl

Br - Broad

Cbz - Carboxybenzyl

cm^{-1} - Wavenumber

CSP - Chiral stationary phase

d - Doublet

DAT - Dopamine transporter

DBU - 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCE - 1,2-dichlorethane

DDQ - 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DMAP - 4-Dimethylaminopyridine

DMB - 2,4-Dimethoxybenzyl

DMF - Dimethylformamide

DMP - Dess-Martin peridinane

DMSO - Dimethylsulfoxide

DPPA - Diphenyl phosphoryl azide

Dppf - 1,1′-Bis(diphenylphosphino)ferrocene

Eq - Equivalents

ESI - Electrospray ionisation

Et - Ethyl

EWG - Electron withdrawing group

Fsp^3 - Fraction of sp^3 carbons

g - Gram(s)

h - Hour(s)

H bond - Hydrogen bond

HMDS - hexamethyldisilazane

HPLC - High performance liquid chromatography

HRMS - High resolution mass spectrometry

HTS - High throughput screening

Hz - Hertz

IR - Infra-red

i-Pr - *iso*-propyl

J - Coupling constant in Hz

kcal mol^{-1} - Kilocalories per mole

LDA - Lithium diisopropylamine

m - Multiplet

M - Molar

m/z - Mass to charge ratio

M+ - Molecular ion

Me - Methyl

mg - Milligrams

μM - Micromolar

MIDA - Methyliminodiacetic acid

min - Minute(s)

mL - Millilitre(s)

mmol - Millimole(s)

MS - Mass spectrometry

Ms - Mesyl

MW - Molecular weight

NMR - Nuclear Magnetic Resonance

Ns - 4-Nosyl

PG - Protecting group

Ph - Phenyl

Pin - Pinacolato

Piv - Pivaloyl

PMP - *para*-methoxyphenyl

PNP - *para*-nitrophenyl

ppm - Parts per million

p-tol - *para*-tolyl

q - Quartet

R*f*- Retention Factor

R&D – Research and development

rt - Room Temperature

s - Singlet

SMILES - Simplified molecular-input line-entry system

t - Triplet

t-Bu - *tert*-butyl

TBS - *tert*-butyldimethylsilyl

TBDMS - *tert*-butyldimethylsilyl

TBDPS - *tert*-butyldiphenylsilyl

TIPS - Triisopropylsilyl

Tf - Triflate

TFA - Trifluoroacetic acid

THF - Tetrahydrofuran

TPMA - Tris(2-pyridylmethyl)amine

Ts - Tosyl

μW - Microwave

References

1. Grygorenko, O. O.; Volochnyuk, D. M.; Ryabukhin, S. V.; Judd, D. B., *Chem. - Eur. J.* **2019**, 10.1002/chem.201903232.
2. Doveston, R.; Marsden, S.; Nelson, A., *Drug Discov. Today* **2014**, *19*, 813-819.
3. Lovering, F.; Bikker, J.; Humblet, C., *J. Med. Chem.* **2009**, *52*, 6752-6756.
4. Mann, A., Chapter 17 - Conformational Restriction and/or Steric Hindrance in Medicinal Chemistry. In *The Practice of Medicinal Chemistry (Third Edition)*, Wermuth, C. G., Ed. Academic Press: New York, 2008; pp 363-379.
5. Böhm, H.-J.; Flohr, A.; Stahl, M., *Drug. Discov. Today Techno.l* **2004**, *1*, 217-224.
6. Denisenko, A. V.; Druzhenko, T.; Skalenko, Y.; Samoilenko, M.; Grygorenko, O. O.; Zozulya, S.; Mykhailiuk, P. K., *J. Org. Chem.* **2017**, *82*, 9627-9636.
7. Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M., *Angew. Chem. Int. Ed.* **2010**, *49*, 9052-9067.
8. Wlochal, J.; Davies, R. D. M.; Burton, J., *Org. Lett.* **2014**, *16*, 4094-4097.
9. Druzhenko, T.; Denisenko, O.; Kheylik, Y.; Zozulya, S.; Shishkina, S. S.; Tolmachev, A.; Mykhailiuk, P. K., *Org. Lett.* **2015**, *17*, 1922-1925.
10. Helal, C. J.; Bartolozzi, A.; Goble, S. D.; Mani, N. S.; Guzman-Perez, A.; Ohri, A. K.; Shi, Z.-C.; Subramanyam, C., *Drug Discov. Today* **2018**, *23*, 1458-1462.
11. Goldberg, F. W.; Kettle, J. G.; Kogej, T.; Perry, M. W. D.; Tomkinson, N. P., *Drug Discov. Today* **2015**, *20*, 11-17.
12. Helal, C. J.; Bundesmann, M.; Hammond, S.; Holmstrom, M.; Klug-Mcleod, J.; Lefker, B. A.; McLeod, D.; Subramanyam, C.; Zakaryants, O.; Sakata, S., *ACS Med. Chem. Lett.* **2019**, *10*, 1104-1109.
13. Ritchie, T. J.; Macdonald, S. J. F., *Drug Discov. Today* **2009**, *14*, 1011-1020.
14. Aldeghi, M.; Malhotra, S.; Selwood, D. L.; Chan, A. W. E., *Chem. Biol. Drug. Des.* **2014**, *83*, 450-461.
15. Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M., *Angew. Chem. Int. Ed.* **2010**, *49*, 3524-3527.
16. Chalyk, B. A.; Butko, M. V.; Yanshyna, O. O.; Gavrilenko, K. S.; Druzhenko, T. V.; Mykhailiuk, P. K., *Chem. - Eur. J.* **2017**, *23*, 16782-16786.
17. Chalyk, B.; Isakov, A.; Butko, M.; Hrebeniuk, K.; Savych, O.; Kucher, O.; Gavrilenko, K.; Druzhenko, T.; Yarmolchuk, V.; Zozulya, S.; Mykhailiuk, P., *Eur. J. Org. Chem.* **2017**, 4530-4542.

18. Lauri, G.; Bartlett, P. A., *J. Comput. Aided Mol. Des.* **1994**, *8*, 51-66.
19. Grygorenko, O. O.; Babenko, P.; Volochnyuk, D. M.; Raievskyi, O.; Komarov, I. V., *RSC Adv.* **2016**, *6*, 17595-17605.
20. Grygorenko, O. O.; Demenko, D.; Volochnyuk, D. M.; Komarov, I. V., *New J. Chem.* **2018**, *42*, 8355-8365.
21. Grygorenko, O. O.; Prytulyak, R.; Volochnyuk, D. M.; Kudrya, V.; Khavryuchenko, O. V.; Komarov, I. V., *Mol. Divers.* **2012**, *16*, 477-487.
22. Feskov, I. O.; Chernykh, A. V.; Kuchkovska, Y. O.; Daniliuc, C. G.; Kondratov, I. S.; Grygorenko, O. O., *J. Org. Chem.* **2019**, *84*, 1363-1371.
23. Sokolenko, Y. M.; Yurov, Y. Y.; Vashchenko, B. V.; Hryshchuk, O. V.; Filimonova, Y.; Ostapchuk, E. N.; Artemenko, A.; Zaremba, O. V.; Grygorenko, O. O., *J. Org. Chem.* **2019**, *84*, 13908-13921.
24. Dibchak, D.; Shcherbacova, V.; Denisenko, A. V.; Mykhailiuk, P. K., *Org. Lett.* **2019**, *21*, 8909-8914.
25. Quirante, J.; Vila, X.; Bonjoch, J.; Kozikowski, A. P.; Johnson, K. M., *Bioorg. Med. Chem.* **2004**, *12*, 1383-1391.
26. Roberson, C. W.; Woerpel, K. A., *J. Am. Chem. Soc* **2002**, *124*, 11342-11348.
27. Hodgson, D. M.; Shelton, R. E.; Moss, T. A.; Dekhane, M., *Org. Lett.* **2010**, *12*, 2834-2837.
28. Holmes, A. B.; Kee, A.; Ladduwahetty, T.; Smith, D. F., *J. Chem. Soc., Chem. Commun.* **1990**, *0*, 1412-1414.
29. Betou, M.; Male, L.; Steed, J. W.; Grainger, R. S., *Chem. - Eur. J.* **2014**, *20*, 6505-6517.
30. Melnick, A.; Cerchietti, L. C.; Cardenas, M.; Xue, F.; MAcKerell, A. D. BCL6 Inhibitors as Anticancer Agents. US20160166549A1, 2016.
31. Genovese, R. F.; Elsmore, T. F., *Pharmacol. Biochem. Behav.* **1989**, *32*, 495-498.
32. Genovese, R. F., *Eur. J. Pharmacol.* **1990**, *176*, 271-279.
33. Triggle, D. J.; Kwon, Y. W.; Abraham, P.; Pitner, J. B.; Mascarella, S. W.; Carroll, F. I., *J. Med. Chem.* **1991**, *34*, 3164-3171.
34. Herold, P.; Herzig, J. W.; Wenk, P.; Leutert, T.; Zbinden, P.; Fuhrer, W.; Stutz, S.; Schenker, K.; Meier, M.; Rihs, G., *J. Med. Chem.* **1995**, *38*, 2946-2954.
35. Munk, M. E.; Sodano, C. S.; McLean, R. L.; Haskell, T. H., *J. Am. Chem. Soc* **1967**, *89*, 4158-4165.
36. Schneider, W.; Hoyer, J., *Arch. Pharm.* **1971**, *304*, 637-648.

37. Hunt, P. A.; Moody, C. J.; Slawin, A. M. Z.; Williams, D. J.; Myers, P. L.; Smith, C., *J. Chem. Soc. Perk. T. 1*. **1992**, 831-837.
38. Takeda, M.; Inoue, H.; Noguchi, K.; Honma, Y.; Kawamori, M.; Tsukamoto, G.; Saito, S., *Chem. Pharm. Bull.* **1976**, *24*, 1002-1012.
39. Gassman, P. G.; Fox, B. L., *J. Org. Chem.* **1967**, *32*, 3679-3680.
40. Furstoss, R.; Teissier, P.; Waegell, B., *J. Chem. Soc. Chem. Comm.* **1970**, 384.
41. Bonjoch, J.; Mestre, E.; Cortes, R.; Granados, R.; Bosch, J., *Tetrahedron* **1983**, *39*, 1723-1728.
42. Klaver, W. J.; Hiemstra, H.; Speckamp, W. N., *J. Am. Chem. Soc* **1989**, *111*, 2588-2595.
43. Rigby, J. H.; Meyer, J. H., *Synlett* **1999**, *1999*, 860-862.
44. Washburn, D. G.; Heidebrecht, R. W.; Martin, S. F., *Org. Lett.* **2003**, *5*, 3523-3525.
45. Kitamura, M.; Ihara, Y.; Uera, K.; Narasaka, K., *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1552-1560.
46. Roberson, C. W.; Woerpel, K. A., *Org. Lett.* **2000**, *2*, 621-623.
47. De Haro, T.; Nevado, C., *Angew. Chem. Int. Ed.* **2011**, *50*, 906-910.
48. Sun, X.; Rai, R.; Deschamps, J. R.; Mackerell, A. D.; Faden, A. I.; Xue, F., *Tetrahedron Lett.* **2014**, *55*, 842-844.
49. Grainger, R. S.; Betou, M.; Male, L.; Pitak, M. B.; Coles, S. J., *Org. Lett.* **2012**, *14*, 2234-2237.
50. Diaba, F.; Montiel, J. A.; Serban, G.; Bonjoch, J., *Org. Lett.* **2015**, *17*, 3860-3863.
51. Yeh, M.-C. P.; Chang, Y.-M.; Lin, H.-H., *Adv. Synth. Catal.* **2017**, *359*, 2196-2201.
52. Zheng, P.; Wang, C.; Chen, Y.-C.; Dong, G., *ACS Catal.* **2019**, *9*, 5515-5521.
53. Xu, Y.; Sun, Q.; Tan, T.-D.; Yang, M.-Y.; Yuan, P.; Wu, S.-Q.; Lu, X.; Hong, X.; Ye, L.-W., *Angew. Chem. Int. Ed.* **2019**, *58*, 16252-16259.
54. Casavant, B. J.; Hosseini, A. S.; Chemler, S. R., *Adv. Synth. Catal.* **2014**, *356*, 2697-2702.
55. Kang, B.; Jakubec, P.; Dixon, D. J., *Nat. Prod. Rep.* **2014**, *31*, 550-562.
56. Bonjoch, J.; Diaba, F.; Bradshaw, B., *Synthesis* **2011**, 993-1018.
57. Cannon, J. S.; Overman, L. E., *Angew. Chem. Int. Ed.* **2012**, *51*, 4288-4311.
58. Ballette, R.; Pérez, M.; Proto, S.; Amat, M.; Bosch, J., *Angew. Chem. Int. Ed.* **2014**, *53*, 6202-6205.
59. Snider, B. B.; Lin, H., *J. Am. Chem. Soc* **1999**, *121*, 7778-7786.

60. Kibayashi, C.; Miyata, T.; Takahama, K.; Fukushima, H. Morphan derivatives or salts thereof and medicinal compositions containing the same. US6608080B1, 2000.
61. Carroll, F. I.; Melvin, M. S.; Nuckols, M. C.; Mascarella, S. W.; Navarro, H. A.; Thomas, J. B., *J. Med. Chem.* **2006**, *49*, 1781-1791.
62. Xie, C.; Luo, J.; Zhang, Y.; Huang, S.-H.; Zhu, L.; Hong, R., *Org. Lett.* **2018**, *20*, 2386-2390.
63. Boger, D. L.; Patel, M.; Mullican, M. D., *Tetrahedron Lett.* **1982**, *23*, 4559-4562.
64. Quirante, J.; Scolano, C.; Diaba, F.; Bonjoch, J., *Heterocycles* **1999**, *50*, 731-738.
65. Solé, D.; Urbaneja, X.; Bonjoch, J., *Org. Lett.* **2005**, *7*, 5461-5464.
66. Wang, Y.-F.; Chiba, S., *J. Am. Chem. Soc* **2009**, *131*, 12570-12572.
67. Diaba, F.; Martínez-Laporta, A.; Bonjoch, J.; Pereira, A.; Muñoz-Molina, J. M.; Pérez, P. J.; Belderrain, T. R., *Chem. Commun.* **2012**, *48*, 8799-8801.
68. Gammack Yamagata, A. D.; Datta, S.; Jackson, K. E.; Stegbauer, L.; Paton, R. S.; Dixon, D. J., *Angew. Chem. Int. Ed.* **2015**, *54*, 4899-4903.
69. Manzano, R.; Datta, S.; Paton, R. S.; Dixon, D. J., *Angew. Chem. Int. Ed.* **2017**, *56*, 5834-5838.
70. Ma, Y.-L.; Wang, K.-M.; Huang, R.; Lin, J.; Yan, S.-J., *Green Chem.* **2017**, *19*, 3574-3584.
71. Hu, X.-M.; Zhou, B.; Yang, C.-L.; Lin, J.; Yan, S.-J., *ACS Omega* **2018**, *3*, 5994-6005.
72. Zhai, L.; Tian, X.; Wang, C.; Cui, Q.; Li, W.; Huang, S.-H.; Yu, Z.-X.; Hong, R., *Angew. Chem. Int. Ed.* **2017**, *56*, 11599-11603.
73. Diaba, F.; Bonjoch, J., *Org. Biomol. Chem.* **2009**, *7*, 2517.
74. Bradshaw, B.; Parra, C.; Bonjoch, J., *Org. Lett.* **2013**, *15*, 2458-2461.
75. Liu, R.-R.; Li, B.-L.; Lu, J.; Shen, C.; Gao, J.-R.; Jia, Y.-X., *J. Am. Chem. Soc* **2016**, *138*, 5198-5201.
76. Kallepu, S.; Gollapelli, K. K.; Nanubolu, J. B.; Chegondi, R., *Chem. Commun.* **2015**, *51*, 16840-16843.
77. Wheldon, M. C. Design and Synthesis of 3-Dimensional Fragments to Explore Pharmaceutical Space. University of York, 2016.
78. Ishiyama, T.; Murata, M.; Miyaura, N., *J. Org. Chem.* **1995**, *60*, 7508-7510.
79. Muranaka, K.; Ichikawa, S.; Matsuda, A., *J. Org. Chem.* **2011**, *76*, 9278-9293.
80. Gillis, E. P.; Burke, M. D., *Aldrichimica Acta.* **2009**, *42*, 17-27.

81. Lehmann, J. W.; Crouch, I. T.; Blair, D. J.; Trobe, M.; Wang, P.; Li, J.; Burke, M. D., *Nat. Commun.* **2019**, *10*, doi:10.1038/s41467-019-09249-z.
82. Knapp, D. M.; Gillis, E. P.; Burke, M. D., *J. Am. Chem. Soc* **2009**, *131*, 6961-6963.
83. Tessier, P. E.; Nguyen, N.; Clay, M. D.; Fallis, A. G., *Org. Lett.* **2005**, *7*, 767-770.
84. Comins, D. L.; Dehghani, A., *Tetrahedron Lett.* **1992**, *33*, 6299-6302.
85. Ritter, K., *Synthesis* **1993**, 735-762.
86. Lv, W.-X.; Li, Q.; Li, J.-L.; Li, Z.; Lin, E.; Tan, D.-H.; Cai, Y.-H.; Fan, W.-X.; Wang, H., *Angew. Chem. Int. Ed.* **2018**, *57*, 16544-16548.
87. Wrackmeyer, B., *Prog. Nucl. Magn. Reson. Spectrosc.* **1979**, *12*, 227-259.
88. Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N., *J. Am. Chem. Soc* **2002**, *124*, 8001-8006.
89. Cao, C.-L.; Sun, X.-L.; Kang, Y.-B.; Tang, Y., *Org. Lett.* **2007**, *9*, 4151-4154.
90. Lee, C.-Y.; Cheon, C.-H., *J. Org. Chem.* **2013**, *78*, 7086-7092.
91. Zhang, H.; Yang, S.-P.; Fan, C.-Q.; Ding, J.; Yue, J.-M., *J. Nat. Prod.* **2006**, *69*, 553-557.
92. Miller, S. P.; Zhong, Y.-L.; Liu, Z.; Simeone, M.; Yasuda, N.; Limanto, J.; Chen, Z.; Lynch, J.; Capodanno, V., *Org. Lett.* **2014**, *16*, 174-177.
93. Åhman, J.; Somfai, P., *J. Chem. Soc., Perkin Trans. 1* **1994**, 1079-1082.
94. Chen, Y.; Zhang, W.; Ren, L.; Li, J.; Li, A., *Angew. Chem. Int. Ed.* **2018**, *57*, 952-956.
95. Lu, Z.; Li, Y.; Deng, J.; Li, A., *Nat. Chem.* **2013**, *5*, 679-684.
96. Procopiou, G.; Lewis, W.; Harbottle, G.; Stockman, R. A., *Org. Lett.* **2013**, *15*, 2030-2033.
97. Paryzek, Z.; Koenig, H.; Tabaczka, B., *Synthesis* **2003**, 2023-2026.
98. Wood, D. J.; Lopez-Fernandez, J. D.; Knight, L. E.; Al-Khawaldeh, I.; Gai, C.; Lin, S.; Martin, M. P.; Miller, D. C.; Cano, C.; Endicott, J. A.; Hardcastle, I. R.; Noble, M. E. M.; Waring, M. J., *J. Med. Chem.* **2019**, *62*, 3741-3752.
99. Lennox, A. J. J.; Lloyd-Jones, G. C., *Isr. J. Chem.* **2010**, *50*, 664-674.
100. Gillis, E. P.; Burke, M. D., *J. Am. Chem. Soc* **2007**, *129*, 6716-6717.
101. Adamo, C.; Amatore, C.; Ciofini, I.; Jutand, A.; Lakmini, H., *J. Am. Chem. Soc* **2006**, *128*, 6829-6836.
102. Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lloyd-Jones, G. C.; Murray, P. M., *Angew. Chem. Int. Ed.* **2010**, *49*, 5156-5160.

103. Mitsumori, S.; Tsuri, T.; Honma, T.; Hiramatsu, Y.; Okada, T.; Hashizume, H.; Kida, S.; Inagaki, M.; Arimura, A.; Yasui, K.; Asanuma, F.; Kishino, J.; Ohtani, M., *J. Med. Chem.* **2003**, *46*, 2446-2455.
104. Chiba, T.; Kitahata, S.; Matsuda, A.; Ichikawa, S., *Chem. Pharm. Bull.* **2016**, *64*, 811-816.
105. Gupta, R.; Sogi, K. M.; Bernard, S. E.; Decatur, J. D.; Rojas, C. M., *Org. Lett.* **2009**, *11*, 1527-1530.
106. Maduskuie, T. P.; McNamara, K. J.; Ru, Y.; Knabb, R. M.; Stouten, P. F. W., *J. Med. Chem.* **1998**, *41*, 53-62.
107. Gonzalez, J. A.; Ogba, O. M.; Morehouse, G. F.; Rosson, N.; Houk, K. N.; Leach, A. G.; Cheong, P. H. Y.; Burke, M. D.; Lloyd-Jones, G. C., *Nat. Chem.* **2016**, *8*, 1067-1075.
108. Mazurov, A. A.; Miao, L.; Bhatti, B. S.; Strachan, J.-P.; Akireddy, S.; Murthy, S.; Kombo, D.; Xiao, Y.-D.; Hammond, P.; Zhang, J.; Hauser, T. A.; Jordan, K. G.; Miller, C. H.; Speake, J. D.; Gatto, G. J.; Yohannes, D., *J. Med. Chem.* **2012**, *55*, 9181-9194.
109. Fukuyama, T.; Liu, G., *J. Am. Chem. Soc* **1996**, *118*, 7426-7427.
110. Gray, D.; Gallagher, T., *Angew. Chem. Int. Ed.* **2006**, *45*, 2419-2423.
111. Wang, X.; Xia, D.; Qin, W.; Zhou, R.; Zhou, X.; Zhou, Q.; Liu, W.; Dai, X.; Wang, H.; Wang, S.; Tan, L.; Zhang, D.; Song, H.; Liu, X.-Y.; Qin, Y., *Chem* **2017**, *2*, 803-816.
112. Burchat, A. F.; Chong, J. M.; Nielsen, N., *J. Organomet. Chem* **1997**, *542*, 281-283.