

**Design, Synthesis and Functionalisation of
3-D Building Blocks for Fragment-Based
Drug Discovery & Studies Towards the
Synthesis of Quinine**

Andres R. Gomez Angel

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University of York

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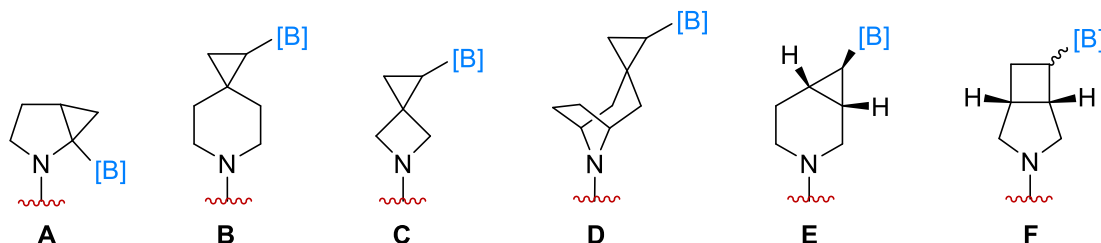
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Abstract

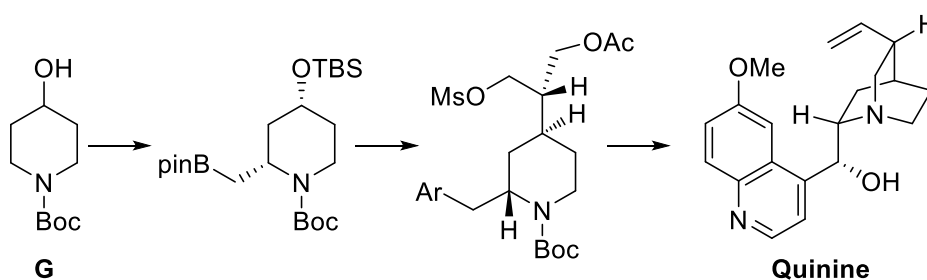
This thesis presents a novel approach for the three-dimensional elaboration of fragments and a new strategy for the total synthesis of quinine. The fragment elaboration approach introduces new bifunctional 3-D building blocks, specifically designed to overcome synthetic bottlenecks in fragment elaboration within the context of fragment-based drug discovery. It emphasizes functionalization methodology to address these challenges.

Chapter 1 provides an introduction to saturated nitrogen heterocycles, highlighting their utility and prevalence in medicinal and natural product chemistry. Chapter 2 introduces fragment-based drug discovery and the concept of fragment elaboration, showcasing prior group efforts in designing and synthesizing cyclopropyl-containing bifunctional 3-D building blocks for fragment elaboration. It also details the development of robust methodology for using cyclopropyl-containing 3-D building blocks **A-E** in fragment elaboration through Suzuki-Miyaura cross-coupling and *N*-functionalization. Chapter 3 focuses on the design, synthesis, and development of cross-coupling methodology for a new generation of cyclobutyl-containing 3-D building blocks exemplified by **F**.

Bifunctional Building Blocks



Chapter 4 explores a novel synthesis of quinine, starting from piperidine **G**. It investigates the synthesis of quinine *via* an unprecedented lithiation-trapping approach, followed by Suzuki-Miyaura cross-coupling and a late-stage N1-C2 bond formation to assemble the quinuclidine motif.



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Author's Declaration

The research presented in this thesis is, to the best of my knowledge, original unless clearly indicated by citation. This work has not previously been presented for an award at this or any other university.

Andres R. Gomez-Angel
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Abbreviations

3-D	Three-dimensional
9-BBN	9-Borabicyclo[3.3.1]nonane
Ac	Acetyl group
Ala	Alanine
API	Active pharmaceutical ingredient
Aq	Aqueous
Ar	Aryl group
AT	Aminotransferase
ATAD2	ATPase family AAA domain-containing protein 2
ATP	Adenosine triphosphate
BCB	Bicyclo[1.1.0]butane
BINAP	(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl group
Boc	<i>tert</i> -Butyloxycarbonyl
BOP	Benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate
br	Broad
BRD4	Bromodomain-containing protein 4
BuLi	Butyllithium
Cbz	Benzyloxycarbonyl
CDI	Carbonyldiimidazole
CDK	Cyclin-dependent kinase

ClogP	Calculated logP
cm ⁻¹	Wavenumber
cod	Cyclooctadiene
COSY	2-D Correlated Spectroscopy
COVID-19	Coronavirus disease 2019
CSP	Chiral Stationary Phase
Cy	Cyclohexyl group
Cys	Cysteine
<i>D</i> or <i>d</i>	Deuterium or Deuterated
Da	Dalton
DEAD	Diethyl azodicarboxylate
DFT	Density functional theory
DIBAL-H	Diisobutylaluminium hydride
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMA(c)	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess Martin periodinane
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPP	Dipeptidyl peptidase
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio

dtbbpy	4,4'-Di- <i>tert</i> -butyl-2,2'-dipyridyl
E1 _C B	Elimination unimolecular conjugate base
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	Electron donating group
ee	Enantiomeric excess
EM	Electron microscopy
Enz	Enzyme
eq	Equivalent
er	Enantiomeric ratio
ESI	Electron spray ionisation
Et	Ethyl group
EVP	Exit vector plot
EWG	Electron withdrawing group
FBDD	Fragment-based drug discovery
FBLD	Fragment-based ligand discovery
FDA	U.S. Food and Drug Administration
Fsp ³	Fraction of <i>sp</i> ³ carbons
GABA	Gamma aminobutyric acid
Glu	Glutamic acid
H ⁺ / K ⁺ ATPase	Hydrogen potassium adenosine triphosphatase
HAC	Heavy atom count
HATU	Hexafluorophosphate azabenzotriazole aetramethyl aronium
HBA	Hydrogen bond acceptor

HBD	Hydrogen bond donator
His	Histidine
HMDS	Hexamethyldisilazane
HRMS	High resolution mass spectrometry
HTS	High-throughput screening
Hz	Hertz
IBX	2-Iodoxybenzoic acid
IC ₅₀	The half maximal inhibitory concentration
<i>i</i> -Pr	Isopropyl group
IR	Infrared
ITC	Isothermal titration calorimetry
JAK	Janus kinase
JAKnib	Janus kinase inhibitor
<i>K_D</i>	Dissociation constant
LDA	Lithium diisopropylamide
LED	Light-emitting diode
Leu	Leucine
LG	Leaving group
Lys	Lysine
M	Molar concentration
<i>m</i> -	Meta position on a phenyl ring
<i>m/z</i>	Mass to charge ratio
M ⁺	Molecular ion
Me	Methyl group

MIDA	<i>N</i> -Methylimidodiacetic acid
MNEC	maximal non-effective concentration
Mpro	Main protease
Ms	Methanesulfonate
MS	Mass spectrometry
MTBE	Methyl tert-butyl ether
MW	Molecular weight
NBS	<i>N</i> -Bromosuccinimide
NHCs	<i>N</i> -heterocyclic carbenes
NHNP	Nitrogen heterocyclic natural products
nM	Nanomolar concentration
NMO	<i>N</i> -Methylmorpholine <i>N</i> -oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
NROT	Number of rotatable bonds
Ns	<i>o</i> -Nitrobenzenesulfonamide
<i>o</i> -	Ortho position on a phenyl ring
<i>p</i> -	Para position on a phenyl ring
P-450	Cytochrome P-450
<i>pan</i> -	Non-selective
PG	Protecting group
Ph	Phenyl
pin	Pinacol
Piv	2,2-Dimethylpropanoate
PMB	<i>p</i> -Methoxybenzyl

PMI	Principal moments of inertia
PMP	p-Methoxyphenyl
ppm	Parts per million
ppy	2-Phenylpyridine
R_F	Retention factor
Rgt	Reagent
RO3 or RO5	Rule of three or Rule of five
rt	Room temperature
SAR	Structure activity relationship
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
<i>sec</i>	Secondary
Ser	Serine
SMCC	Suzuki-Miyaura cross-coupling
S_N2	Nucleophilic substitution bimolecular
S_NAr	Nucleophilic aromatic substitution
sp	Species
SPR	Surface plasmon resonance
T3P	Propylphosphonic anhydride
TBDPS	<i>tert</i> -Butyldiphenylsilyl
TBS	<i>tert</i> -Butyldimethylsilyl
<i>tert</i>	Tertiary
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyranyl

Thr	Threonine
TLC	Thin layer chromatography
TM	Transition metal
TMPhen	3,4,7,8-Tetramethyl-1,10-phenanthroline
TMS	Trimethylsilyl
Ts	Toluenesulfonyl group
TSA	Thermal Shift assay
TYK	Tyrosine kinase
Tyr	Tyrosine
UV	Ultraviolet
Val	Valine
δ	Chemical shift in ppm

Chapter 1 Introduction

Saturated nitrogen heterocycles are integral scaffolds in both medicinal chemistry and natural products.¹ An analysis of FDA databases in 2020 revealed that about 60% of unique small-molecule drugs comprise nitrogen-based heterocycles.² Additionally, saturated nitrogen heterocycles appear in a wide range of natural products.³⁻⁵ Unlike their aromatic or unsaturated counterparts, the full saturation of the nitrogen-containing ring imparts unique three-dimensionality and conformational flexibility,⁶ which have become essential considerations in drug discovery and development.⁷ As a result, the development of new methodology around the use and synthesis of saturated nitrogen heterocycles is of current interest.

This thesis covers two distinct projects centred around saturated nitrogen heterocycles. The first of these projects, covered in Chapters 2 and 3, focuses on developing a technology platform designed to enable the modular conversion of 2-D fragments into 3-D lead-like compounds using a set of bifunctional *N*-containing building blocks (Figure 1.1).

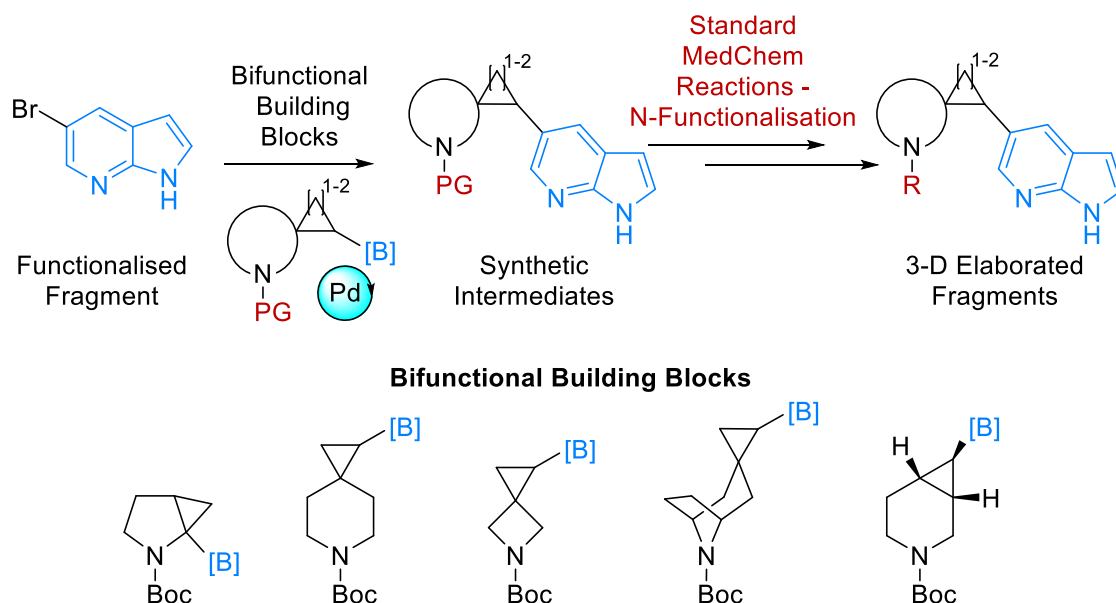
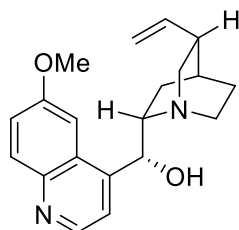


Figure 1.1 – General synthetic workflow for the modular elaboration of fragments.

Specifically, Chapter 2 details the continuation of efforts by past members of the O'Brien group to establish this platform, developing the methodology for using cyclopropyl O'Brien building blocks in a fragment elaboration context. Chapter 3 introduces a new set of cyclobutane-containing building blocks, including their synthesis and elaboration methodologies.

On the other hand, Chapter 4 describes efforts towards a novel synthesis of quinine (Figure 1.2) using methodology previously outlined by the O'Brien group, namely the lithiation-trapping of *N*-Boc heterocycles, and Suzuki-Miyaura cross-coupling.



(-)-Quinine

Figure 1.2 – (-)-Quinine.

Due to the inherent differences between the themes of these two projects, each chapter provides its own dedicated introduction. This chapter offers a brief overview of saturated *N*-heterocycles and their significance in medicinal and natural product chemistry. Section 1.1 introduces saturated *N*-heterocycles, highlighting the relevant properties that their saturation and 3-D shape impart to their utility, and prevalence in medicinal chemistry and Section 1.2 examines their occurrence in natural products.

1.1 Saturated Nitrogen Heterocycles in Medicinal Chemistry

Saturated *N*-heterocycles play a crucial role in modern medicinal chemistry due to their wide spectrum of pharmacological and physical properties.⁸ Saturated *N*-heterocycles such as piperidine, piperazine, pyrrolidine, tropane and azetidine represent some of the most prominent structural features in pharmaceutical molecules, featuring in over 190 FDA-approved drugs up to 2014,¹ with seven drugs approved in 2023 containing them.⁹ Some examples of FDA-approved drugs containing saturated *N*-heterocycles are shown in Figure 1.3.

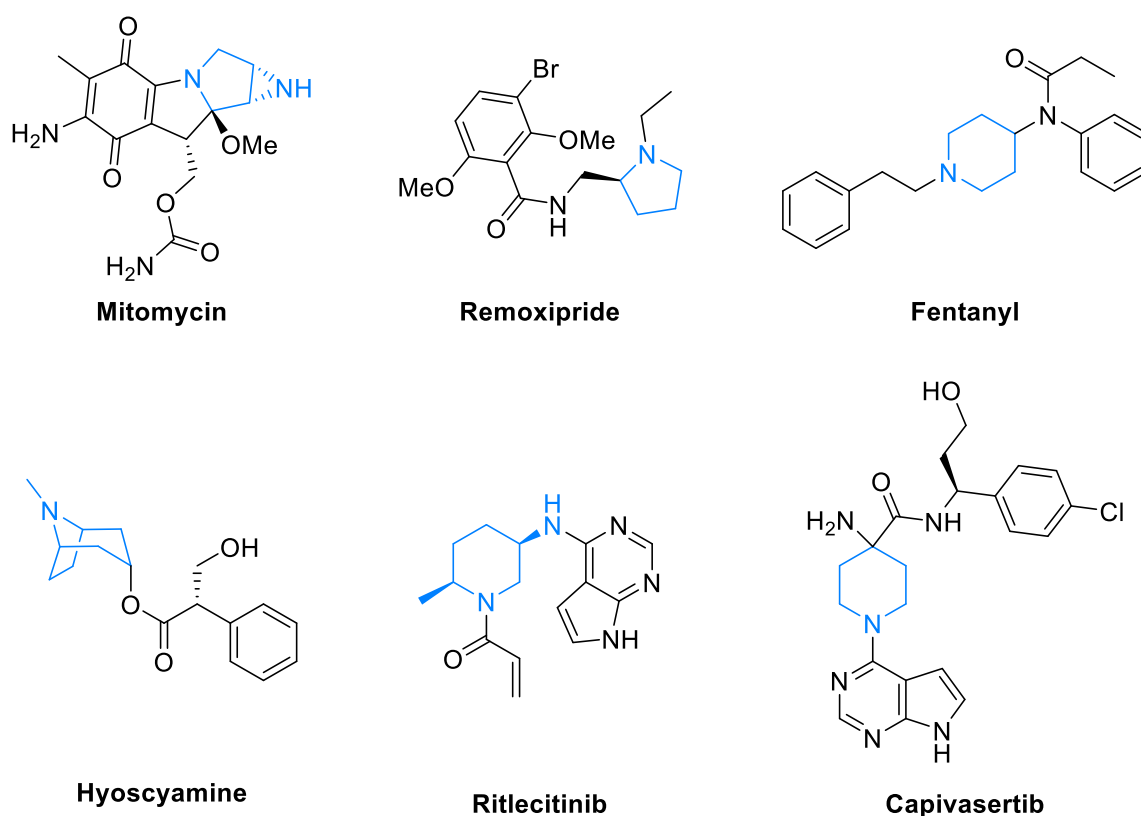


Figure 1.3 – Saturated *N*-heterocycles (blue) in medicinal chemistry.

One of the key reasons for the widespread use of *N*-heterocycles is their ability to enhance the pharmacokinetics and pharmacodynamics of drug molecules. The electron-rich nitrogen atoms in *N*-heterocycles can facilitate hydrogen bonding and electrostatic interactions with biological targets, improving binding affinity and specificity.¹⁰ This versatility in interactions is critical for targeting a broad range of receptors, enzymes, and ion channels, making *N*-heterocycles highly effective scaffolds for therapeutic agents in the treatment of various diseases, including cancer,^{10, 11} infectious diseases,¹² and central nervous system disorders.^{8, 13}

The incorporation of saturated *N*-heterocycles increases the fraction of sp^3 -hybridized carbons (F_{sp^3}) in drug molecules, a feature linked with improved solubility, metabolic stability, and reduced toxicity.^{7, 14} Additionally, these structures enhance a drug's "drug-likeness" by increasing molecular complexity, which improves bioavailability and target selectivity.¹⁵

Recently, saturated *N*-heterocycles have been employed as important bioisosteres for various more reactive or unstable functional groups,¹⁶⁻¹⁹ Bicyclic saturated *N*-heterocycles, in particular, have been used as bioisosteres of both unsaturated and saturated *N*-heterocycles, offering a more rigid structure with a high F_{sp^3} character.²⁰⁻²³ For instance, Mykhailiuk and co-workers developed 3-azabicyclo[3.1.1]heptanes as saturated isosteres of pyridine.²² Building on research by Anderson and co-workers on developing novel bioisosteres of arenes,²⁴ bicyclic piperidines **1** were synthesized in three steps from commercially available **2** in 51% yield (Figure 1.4). The authors observed similar geometric parameters and improved metabolic stability when used in an analogue of rupatadine, an antihistamine.²²

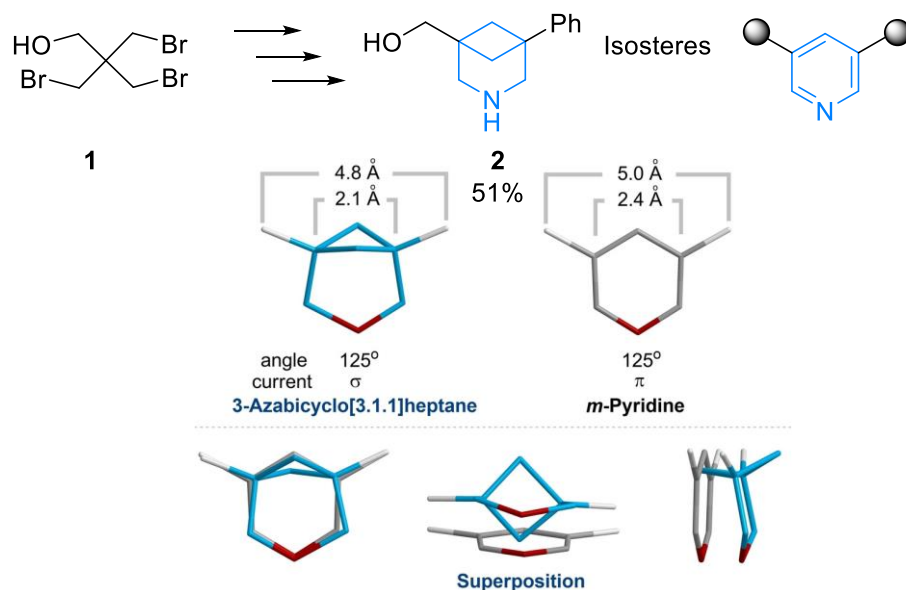


Figure 1.4 – 3-Azabicyclo[3.1.1]heptanes as potential saturated isosteres of *m*-substituted pyridines. Taken from Mykhailiuk et al.²²

Thus, saturated *N*-heterocycles have proven to be indispensable scaffolds in modern medicinal chemistry, primarily due to their ability to enhance the pharmacokinetic and pharmacodynamic profiles of drug molecules, their capacity to facilitate critical interactions with biological targets, combined with their role in increasing the sp^3 -hybridized character of drug structures and their versatility as bioisosteres for a wide range of functional groups.

1.2 Saturated Nitrogen Heterocycles in Natural Products

Saturated *N*-heterocycles are widely prevalent in natural products, and they occur in both primary and secondary metabolites.⁴ These nitrogen heterocyclic natural products (NHNPs) exhibit various bioactivities, including anti-cancer²⁵ and anti-bacterial properties.²⁶ Primary metabolite NHNPs include purines, pyrimidines, amino acids, and certain members of the vitamin B family. In contrast, secondary metabolite NHNPs encompass alkaloids, pseudoalkaloids, biogenic amine derivatives, and β -lactam antibiotics.²⁷

Up to 2017, more than 20000 NHNPs had been reported.²⁸ These compounds were isolated from both unicellular and multicellular organisms, with notable examples including penicillin, originally isolated from the fungus *P. chrysogenum*;²⁹ morphine, isolated from the opium poppy; sparteine, from *Lupinus mutabilis*;³⁰ quinine, isolated from the bark of the cinchona trees;³¹ and notoamide R, isolated from the *Aspergillus* species (Figure 1.5).²⁸ However, since isolation yields from their natural sources were often quite poor, new synthetic and biosynthetic routes have been developed to produce these compounds more efficiently.⁵

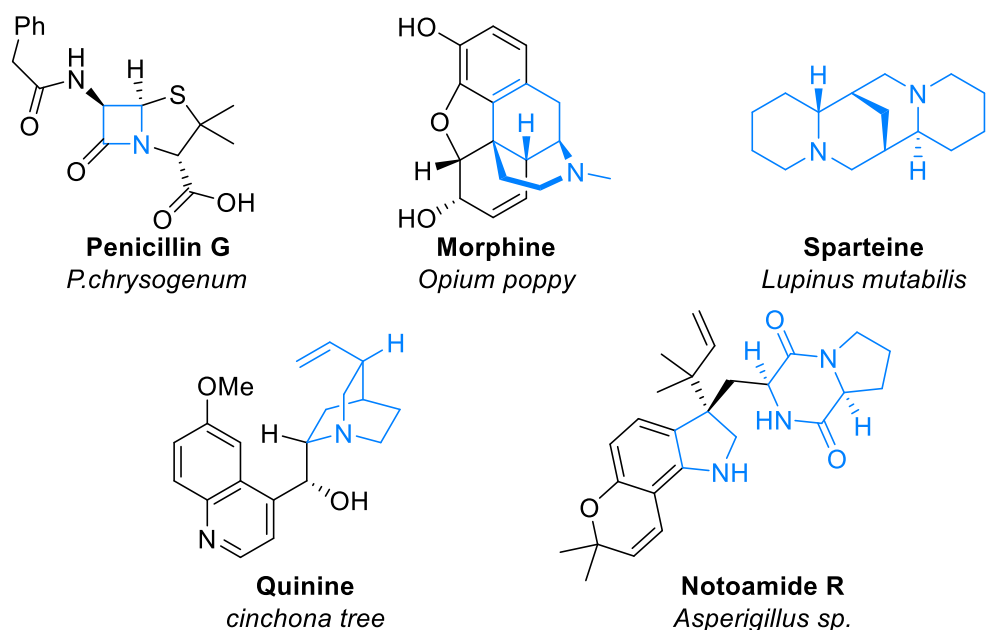


Figure 1.5 – Nitrogen heterocycle (blue) containing natural products.

Chapter 2 Cyclopropyl Building Blocks as a Modular Platform for the Elaboration of Fragments

With the advent of Fragment Based Drug Discovery (FBDD) for the efficient sampling of chemical space (see Section 2.1), the overall rate of discovery of potential drug candidates starting from fragments has increased.³² However, this increase has highlighted the need to further develop synthetic chemistry to support FBDD.³³ One of these needs is increasing the 3-D shape of current libraries due to its relationship with successful drug candidates.⁷ To solve this, several approaches have been proposed and interest in 3-D shaped fragments has emerged.³⁴ Nonetheless, recognising that current libraries already possess many compounds with low 3-D shapes³⁵ and that such compounds need to be elaborated into higher molecular weight lead compounds, we now propose a new, modular approach for the conversion of 2-D fragments into 3-D lead-like compounds.

In this chapter, we describe a synthetic platform that has been developed in the O'Brien group through the combined efforts of various past and present members. Such a synthetic platform should enable the rapid elaboration of 2-D fragments into 3-D lead-like compounds (Figure 2.1). Section 2.1 aims to provide a brief overview of FBDD. Fragment elaboration, including fragment library design and current methods for fragment elaboration, are outlined in Section 2.2. Section 2.3 then discusses cyclopropane boronates, as well as how the O'Brien group envisages their use in fragment elaboration, alongside their design and synthesis by previous members of the group. Section 2.4 outlines the aims of the current investigation (project outline). Finally, Sections 2.5-2.8 discusses the development of the necessary methodology to allow the O'Brien building blocks to be used in a fragment elaboration setting, as well as the development of a JAK3 inhibitor.

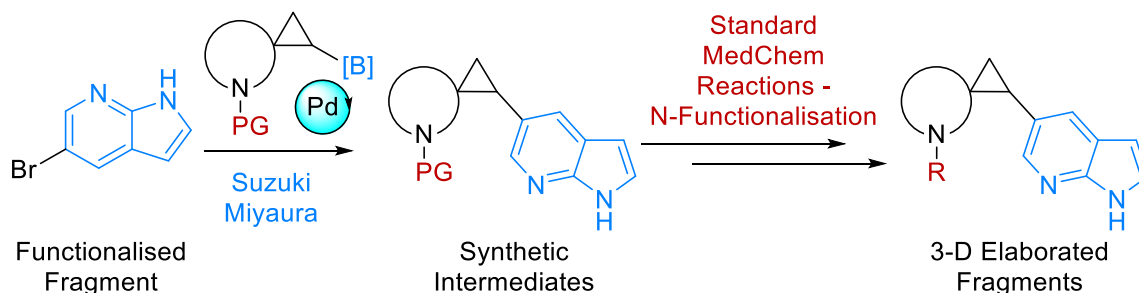


Figure 2.1 – General workflow for the use of building blocks for the elaboration of fragments. E.g. Using an azaindole as fragment hit.

2.1 Fragment-Based Drug Discovery

Fragment-based drug discovery (FBDD) is now a firmly established methodology for the design and synthesis of new active pharmaceutical ingredients (APIs). 30 years ago, high throughput screening (HTS) was the main approach for the discovery and identification of lead compounds.³² In HTS, compounds with large molecular weight (up to 500 Da) and favourable physicochemical properties, as identified by Lipinski's 'rule of five' (RO5)³⁶, are screened directly against a target. These compounds then undergo optimization studies, such as structure-activity relationship (SAR) analysis, to yield potential drug candidates. HTS achieved good success rates, particularly against highly established targets.³⁷ However, HTS faces several drawbacks, including screening artifacts such as aggregators³⁸ and low success rates, particularly when screening against newer and more challenging targets.³⁹ Additionally, there was a growing awareness of the number of compounds that could be part of the HTS chemical space. An early estimate by Guida and co-workers in 1996 put the number of possible small drug molecules well in excess of 10^{60} , with this number rising steeply with higher molecular weights.⁴⁰ Making a thorough screen of the HTS chemical space has been described as irrational and "a gamble" by industry practitioners.⁴¹

In contrast, FBDD which was first demonstrated by Fesik and co-workers in their development of a methodology to detect high affinity ligands for proteins with NMR,⁴² screens libraries with significantly smaller molecules. Such molecules are usually between 140-230 Da and have previously been guided by a set of physicochemical properties denoted as the 'rule of three'.⁴³ Notably, while libraries in HTS could theoretically possess 10^{60} compounds, libraries for FBDD would be capped at around 10^{11} , making their use much less resource-intensive.⁴⁴

This difference in the size of molecules screened in FBDD, so-called fragments, constitutes the main advantage but also one of the key challenges of FBDD. The smaller the size not only means higher efficiency in the sampling of chemical space with superior hit rates and hits for previously considered 'difficult' targets,⁴⁵ but it also means that these fragments will have significantly weaker binding affinities (mM or high μ M as opposed to nM in HTS). These affinities in turn typically require significantly more sensitive biophysical screening methods instead of bioassays.³³ In this regard, FBDD makes extensive use of virtual screening,⁴⁶⁻⁴⁸ NMR,⁴⁹⁻⁵² surface plasmon resonance (SPR),^{53, 54} thermal shift assay (TSA),^{55, 56} isothermal titration calorimetry (ITC),⁵⁷⁻⁶⁰ biolayer interferometry,⁶¹ more

recently Cryo-EM,⁶² and particularly X-ray crystallography. X-ray crystallography has the added value of allowing the elucidation of the molecular binding interactions of fragments in proteins, which provides possibilities for the identification of novel binding sites and interactions.⁶³

In contrast to HTS, fragment-based drug discovery (FBDD) relies on smaller fragments with weaker interactions. Once a fragment hit is identified and verified, it must be grown or elaborated to increase its potency, transforming it into a lead-like compound. This process is often guided by a parameter known as ligand efficiency (Figure 2.2).⁶¹ It is in this step where one of the main synthetic challenges in FBDD has been identified as “Ideally it should be possible to synthetically elaborate fragments in 3 dimensions from many different growth points/vectors using methodology that is experimentally worked out prior to fragment screening”.³³ However, this fragment elaboration stage also brings some benefits to FBDD as it allows for improved lead optimisation⁶⁴ and improved flexibility in the design of the APIs.⁶⁵

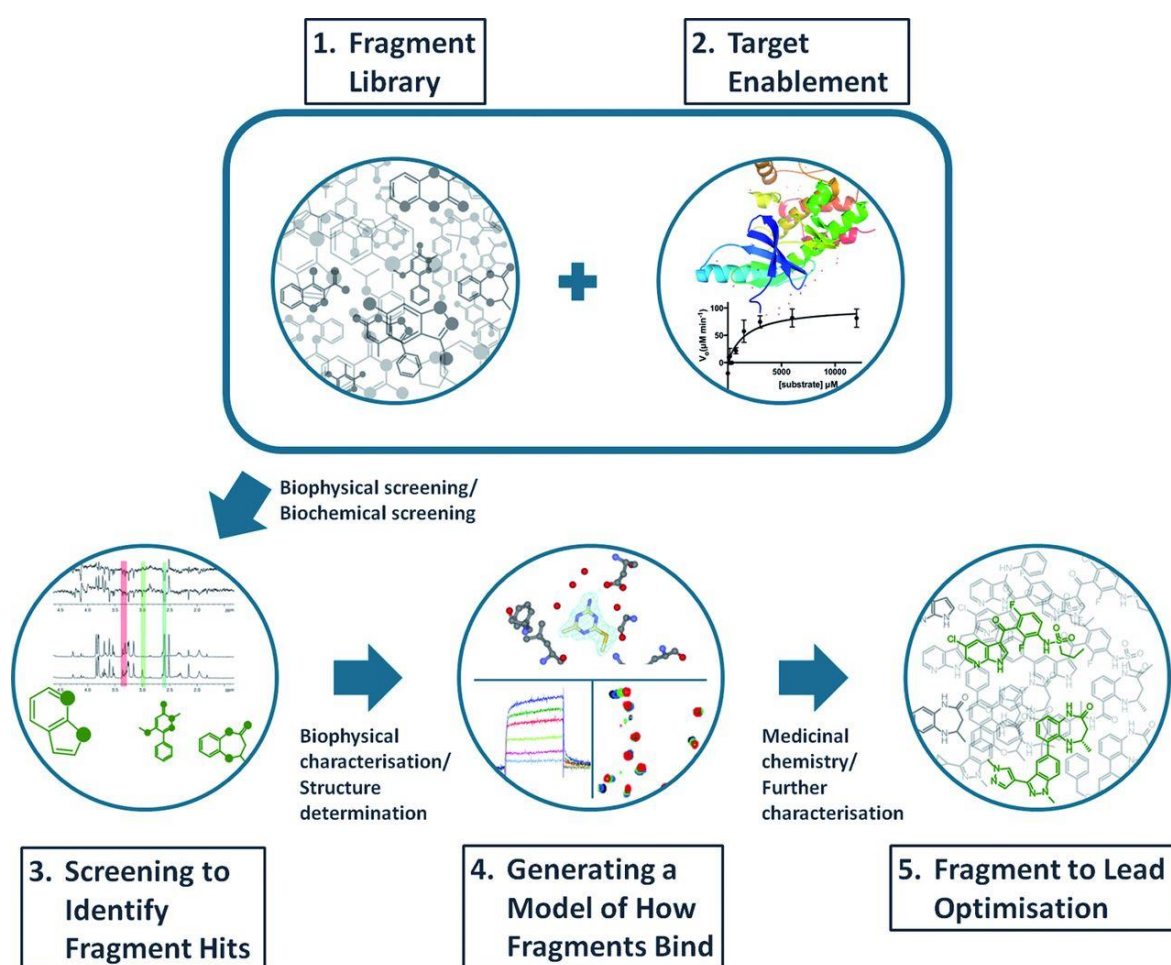


Figure 2.2 – Typical FBDD workflow. Taken from Hubbard *et al.*⁶⁶

Today, FBDD is firmly established as a methodology for the discovery and development of new drugs. Currently, seven drugs that were born out of FBDD programmes have been approved by the FDA (Figure 2.3).⁶⁷ Vemurafenib (Plexxikon) was the first API to receive approval by the FDA in 2011 for the treatment of late stage melanoma.⁶⁸ Venetoclax (AbbVie and Genentech) then received approval by the FDA in 2016 and was developed for the treatment of lymphocytic lymphoma and leukemia.⁶⁹ Pexidartinib (Plexxikon) and Erdafitinib (Astex and Johnson & Johnson) received approval in 2019 for the treatment of tenosyovial giant cell tumor,⁷⁰ and urothelial carcinoma⁷¹ respectively. Finally, both Sotorasib (Amgen) and Asciminib (Novartis) were approved by the FDA in 2021 for the treatment of non-small-cell lung cancer⁷² and Philadelphia chromosome-positive chronic myeloid leukaemia⁷³ respectively.

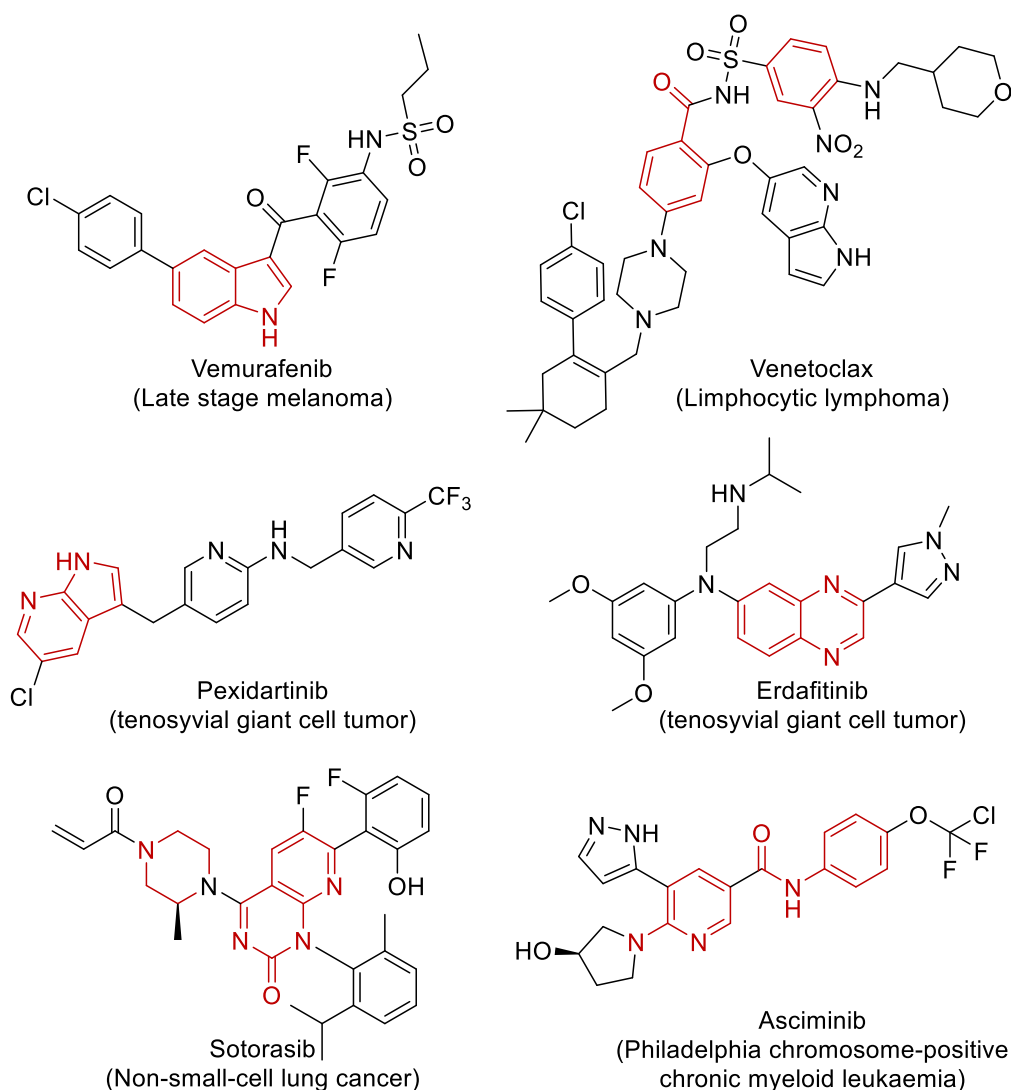


Figure 2.3 – FBDD derived APIs approved by the FDA (atoms highlighted in red represent the remainder of original fragment hits)

Over 26 lead compounds derived from FBDD compounds were also currently in phase 2 and 3 clinical trials by February 2024.^{67, 74} Additionally, efforts to deploy FBDD towards the development of pharmaceuticals to target SARS-CoV-2 have been carried out. Notably, a screening campaign on the main protease (M^{pro}) of SARS-CoV-2 was undertaken with NMR and X-ray crystallography in which a total of 1250 fragments were screened.⁷⁵ Of the potential fragments identified, two fragments had been previously designed and synthesised in the O'Brien group (Figure 2.4).



Figure 2.4 – O'Brien and co-workers hit fragments against SARS-CoV-2 M^{pro}

2.2 Fragment Libraries and Elaboration

2.2.1 Development of Fragment Libraries

The development of a fragment library is the first step in fragment-based drug discovery, and one of the most important steps.⁶⁴ Since fragments will be ultimately elaborated, the main restriction is that fragments should be significantly smaller than typical HTS compounds. Before many guidelines for the design of fragment libraries existed, Moore and co-workers at Vertex pharmaceuticals designed one of the first libraries for FBDD.⁷⁶ The team conducted a thorough analysis of the available therapeutics and examined common chemical features that made said therapeutics ‘drug-like’. With these features isolated from the parent molecules, they restricted the molecular weight (MW) in the range of 68-341 Da, a heavy atom count (HAC) of 5-22 and a ClogP of -2.2 to 5.5. Additionally, a simple but well-resolved ¹H NMR spectrum and a molecule with at least two protons within 5 Å of each other were requirements. This led to a relatively small library of 132 compounds, some of which are shown in Figure 2.5. This set of criteria was then further refined by Blommers and co-workers at Novartis. By taking the ACD1998.1 catalogue of approximately 250,000 compounds and limiting MW to <350 Da and reducing the ClogP filter to <3.5 (to aid with solubility), a hypothetical library of 64,816 compounds was created. However, by the authors’ admission, only specific diverse sets of 500 compounds are used at a time.⁷⁷

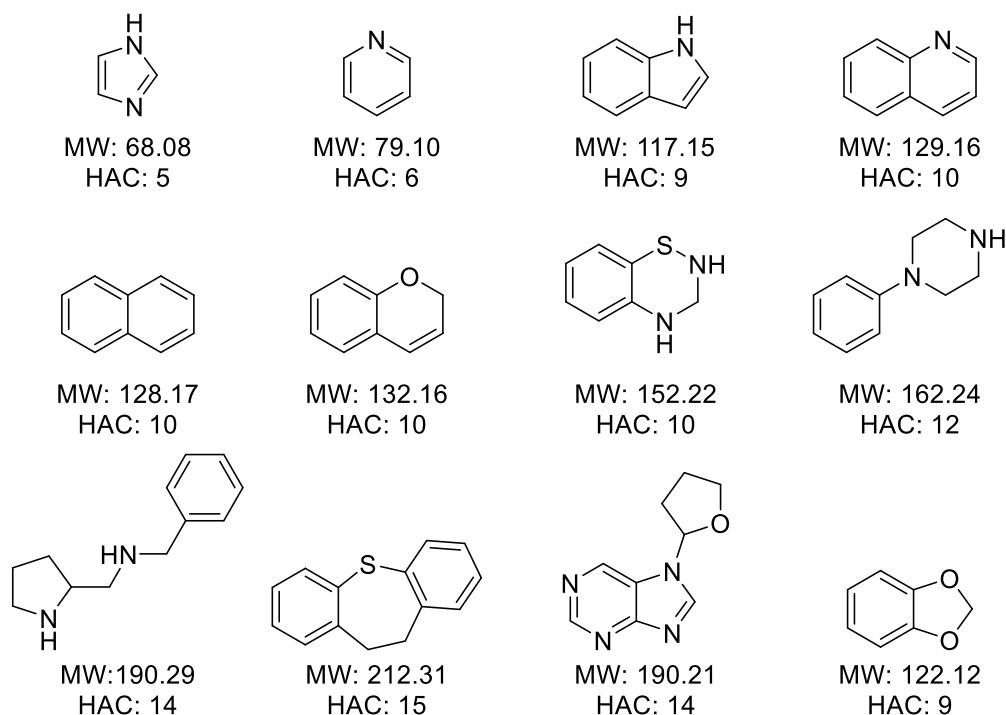


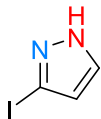
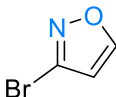
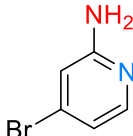
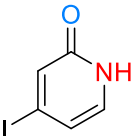
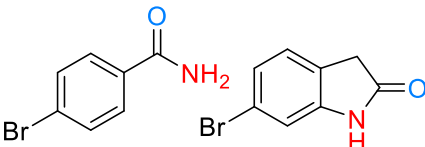
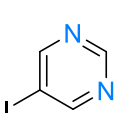
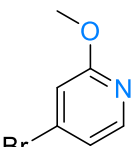
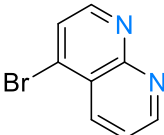
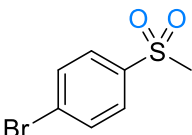
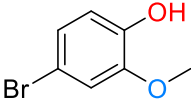
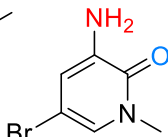
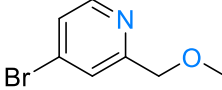
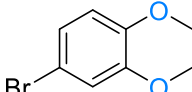
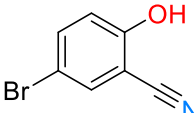
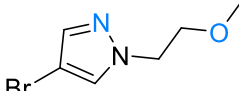
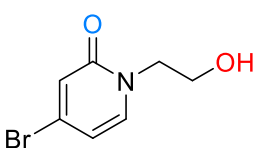
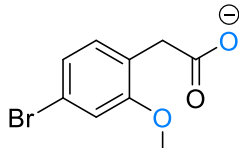
Figure 2.5 – Fragment examples from Vertex's SHAPES library

Based on these libraries and the literature at the time, Jhoti and co-workers at Astex devised the first comprehensive set of rules for fragment libraries.⁴³ Carrying out an analysis of a diverse set of fragment hits against diverse targets both inside Astex and in the literature indicated that such hits seemed to obey, on average, a ‘Rule of Three (RO3)’. Such hits, on average, had MW ≤ 3 , number of H-bond donors ≤ 3 , number of H-bond acceptors ≤ 3 and a ClogP ≤ 3 . Additionally, results suggested that the number of rotatable bonds (NROT) was usually ≤ 3 and the compounds had a polar surface area (PSA) ≤ 60 . Only the MW and the ClogP criteria have been widely adopted from the RO3. Although the RO3 is now considered outdated and newer libraries that are not strictly compatible with the RO3 have been successfully developed,⁷⁸ it still serves as a useful set of guidelines to limit molecular complexity in fragment libraries.⁷⁹

In addition to these guidelines, Pickett and co-workers at GlaxoSmithKline and Astex put out an additional set of guidelines for fragments that aimed to further increase the quality of libraries coming from academia.⁸⁰ In their work, they reintroduced the concept of NROT by capping it at ≤ 3 , introduced a limit of two chiral centres as well as an aqueous solubility guideline of ≥ 5 mM in 5% DMSO, requiring high stability for storage and lack of functional groups associated with high reactivity, aggregation or false positives. The authors also suggested a diverse set of polar binding groups, diverse scaffolds and 2- and 3-dimensional shapes as well as easily accessible and diverse vectors for fragment growth, ideally in three dimensions.

With this in mind, Waring and co-workers developed a library of minimal, halogenated fragments which they named ‘FragLites’.⁸¹ Waring’s library was designed around the idea of having a combination of two functionalities capable of forming H-bond interactions in different proximities and spatial orientations. These pharmacophore doublets not only provided protein-ligand interactions but also conferred the FragLite a level of aqueous solubility allowing for their use in the high concentration required due to their low binding potentials. Furthermore, these pharmacophore doublets would be embedded in or around aromatic scaffolds (providing lipophilicity). Finally, incorporating a heavy halogen atom (Br or I) allowed for easy X-ray crystallographic detection and characterisation, even at low concentrations, owing to their anomalous scattering. This provided useful information on the binding mechanisms as well as the drugability of the protein and possible optimisation of the fragments. In this way, Waring devised an initial set of 31 FragLites which can be classified in their donor/acceptor characteristic and their connectivity (Table 2.1).

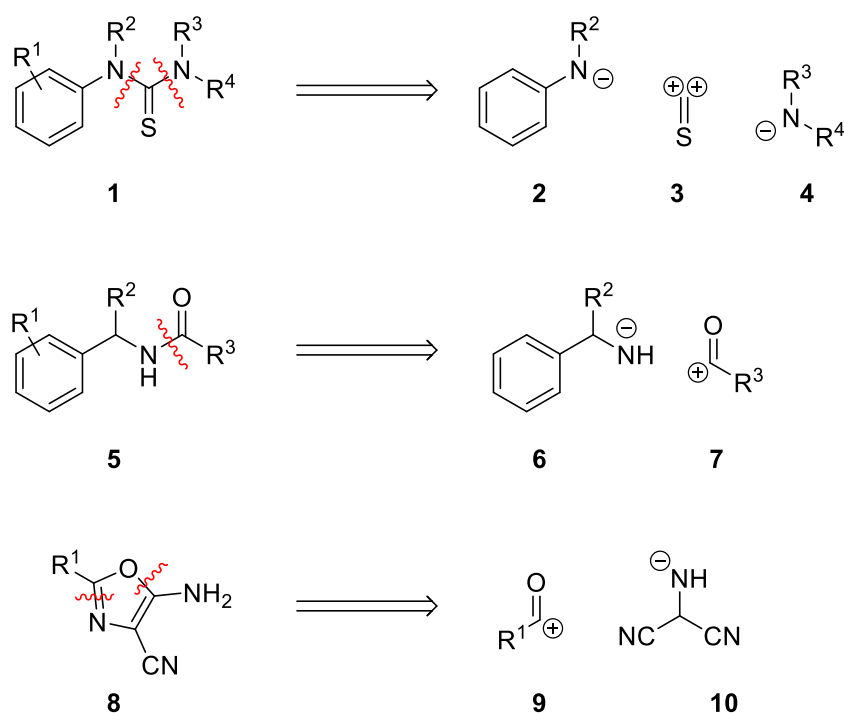
Table 2.1 – Selected examples from Waring and coworkers' FragLites. Atoms in blue are H-bond acceptors, atoms in red are H-bond donors

Connectivity	Donor / acceptor	Acceptor / acceptor
1-bond		
2-bond	  	   
3-bond	 	 
4-bond		
5-bond		

To test their library design, Waring and co-workers screened the FragLite library against cyclin-dependent kinase 2 (CDK2) due to its well known and well diffracting structure, as well as its precedent for binding small molecules at the orthosteric site.⁸¹ Of the 31 FragLites screened by X-ray crystallography, nine were observed to bind to CDK2 in six distinct sites: the orthosteric site, a previously identified allosteric site and four new allosteric sites. This represented an overall good hit rate and supported the general utility of FragLites as fragments and as a library design principle.

In particular, some of the 3-bond FragLites were introduced by Waring and co-workers during their work to map ligand interactions of bromodomain-containing proteins BRD4 and ATAD2 with FragLites.⁸² FragLites were crystallographically screened against the ATAD2 and BRD4 protein and allowed for the identification 3 novel binding sites for ATAD2 with 5 novel binding events being observed for BRD4

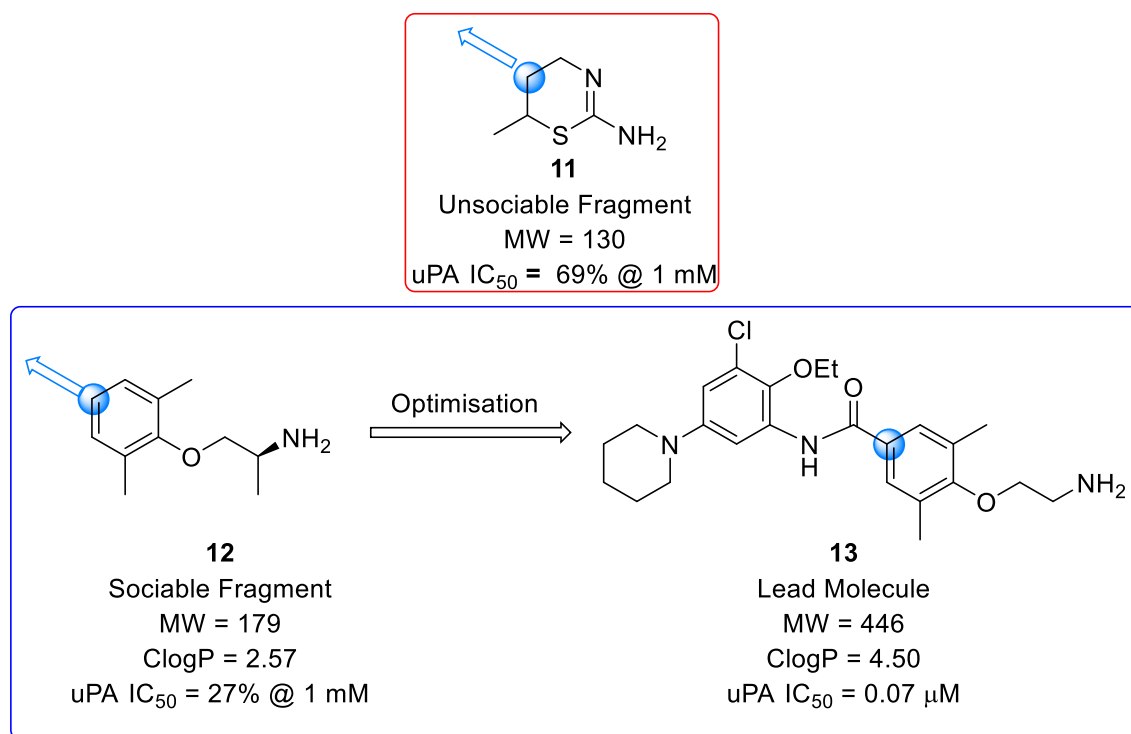
Other efforts in the research of bromodomains have brought further developments in library design principles. In their research into inhibitors of the atypical bromodomain PHIP(2), Brennan and co-workers introduced the concept of ‘poised’ fragments.⁸³ The authors defined a poised fragment as a fragment synthesised from a robust and general synthetic reaction in a way that allows for the rapid elaboration of hit fragments with parallel chemistry. As such, this methodology would facilitate the fragment optimisation and elaboration stages by rapidly allowing access to various derivatives. This would allow for improvement in binding activities and the generation of more detailed structural information. In this fashion, the authors demonstrated three simple examples (Scheme 2.1). First, the formation of thiourea **1** which can be retrosynthetically deconstructed to three distinct synthons **2-4**. Next, the synthesis of benzylamides **5**, retrosynthetically coming from synthons **6** and **7**. Finally, the synthesis of oxazoles **8**, coming from synthons **9** and **10**.



Scheme 2.1

With these design principles, Brennan and co-workers created the Diamond SGC Poised Library which is freely available in its electronic version and whose members are available for purchase from Enamine Ltd. Additionally, this library, through medium-throughput X-ray crystallographic screening allowed for the synthesis of the first reported inhibitors of PHIP(2), a protein considered a possible marker in melanoma prognosis.⁸³

Another useful concept for the design of fragment libraries was introduced in 2021 by Rees and co-workers. By reviewing previous screening campaigns at Astex, the authors developed the definition of fragment sociability.⁸⁴ The concept is that an unsociable fragment is one that has limited synthetic methodology to enable elaboration and few commercially available close analogues. In contrast, a sociable fragment has robust methodology that enable multiple growth vectors to be elaborated (ideally orthogonally) and has a significant number of commercially available analogues. An example provided was observed during a screen of the Astex fragment library against urokinase-type plasminogen activator, a protease linked to metastasis in cancer. The screen indicated that fragments **11** and **12** both had the required charged ammonium or amidine pharmacophore to interact with Gly219, Ser190 and Asp189. Notably, while fragment **11** (unsociable) had better binding efficiency (69% at 1 mM) and information about the desired growth vector (blue), the synthetic route to **11** was not reported and close analogues elaborated in the desired position were not commercially available. This meant that an early and efficient SAR would require a substantial investment in a very early stage of the project. In contrast, fragment **12**, although pharmacologically less desirable, had well-documented and substantial chemistry reported previously. Specifically, its desired growth vector was enabled by Suzuki-Miyaura cross-coupling and amide bond formation, facilitating rapid SAR and the development of lead compound **13**, a potent inhibitor of uPA (Scheme 2.2).⁸⁴



Scheme 2.2

While the previously exposed fragment libraries were developed for the purpose of identifying hits towards orthosteric and allosteric inhibition sites, other recently developed fragment libraries have been more directed to find ‘warm spots’. That is to pick up other spots in or near the protein orthosteric or allosteric sites that allow favourable interactions to be picked up for lead development.⁸⁵ The first of these, developed by Jhoti and co-workers at Astex and labelled ‘MiniFrag’, was designed as ultra-low-molecular-weight ligands to guide drug design.⁸⁶ Using a chemically diverse set of low molecular weight (HAC 3-7) and employing a novel crystallographic screen using high concentration aqueous soaks allowed the authors to identify proximal spots for fragment elaboration in a diverse set of therapeutic targets. Of note, the authors still advocated the use of traditional fragment screening for the identification of the initial fragments bound to hotspots. This MiniFrag library has also been partially incorporated into the new generation of AstraZeneca’s biophysics fragment set.⁸⁷

Following on from this, Scanlon and co-workers developed a library of ‘MicroFrag’s’.⁸⁸ With the intention of using very high concentration (1 M) X-ray crystallography assays, the authors envisioned identification of all potential polar and non-polar protein-ligand interactions within the binding hotspot. Thus, MicroFrag’s had to meet the following criteria: HAC 5-8, ClogP -2-2, have a 5- or 6-membered ring and a minimum of one heteroatom, with the library being biased towards substructures found in the DrugBank database.

Interestingly, the methodology allowed the identification of both protein's (*E. Coli*'s DsbA) hotspots and warm spots, while demonstrating a significant difference in the number of fragments bound to each. This facilitated easy identification and provided insights into potential binding sites.

2.2.2 Current Approaches for Fragment Elaboration

Evolving fragments into high affinity-lead compounds is another of the crucial stages in FBDD. In practice, three main strategies are usually applied in this optimization process: fragment growing, fragment linking and fragment merging.^{61, 89} Fragment growing, also called fragment optimisation, closely relates to standard chemical optimisation approaches and is considered the most straightforward approach.⁶⁴ The aim of this approach is to install novel target-interaction hot spots while attaching additional functionality and increasing the size of the molecule. To achieve this in a rational fashion, structural information that provides the growth vectors of the fragment is preferred. Some alternative approaches such as docking information, structural information from NMR, SAR of available analogues or fragment screening in cells can also be utilised.⁹⁰ In this regard, it is ideal to characterize the directionality, substituent size and flexibility of the attachment.⁶¹

One successful example of fragment growing was demonstrated by Mueller and co-workers at Hoffmann-La Roche in their studies to discover novel inhibitors of DNA gyrase, a well established antibacterial agent.⁹¹ A virtual screening from a pool of 350,000 fragments suggested a few hundred possible structures from where the authors performed SPR, NMR spectroscopy and X-ray crystallography analyses to narrow the initial pool to five structures from which fragment **14** had the lowest MNEC (maximal non-effective concentration). The X-ray crystallographic analysis of co-crystallised fragment **14** revealed that a DNA gyrase inhibitor necessitated additional chain stacking on a neighbouring Glu50-Arg76 salt bridge as well as, ideally, exploring lipophilic interactions with the Ile78, Pro79 and Ile94 area (Figure 2.6).⁹¹

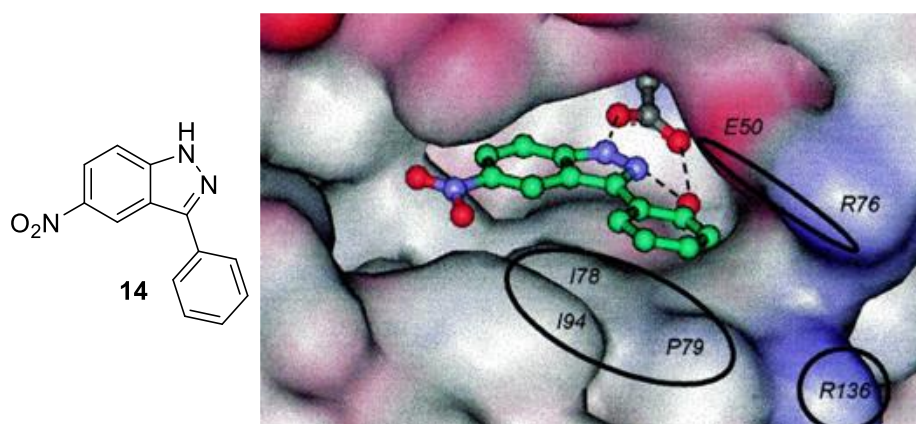
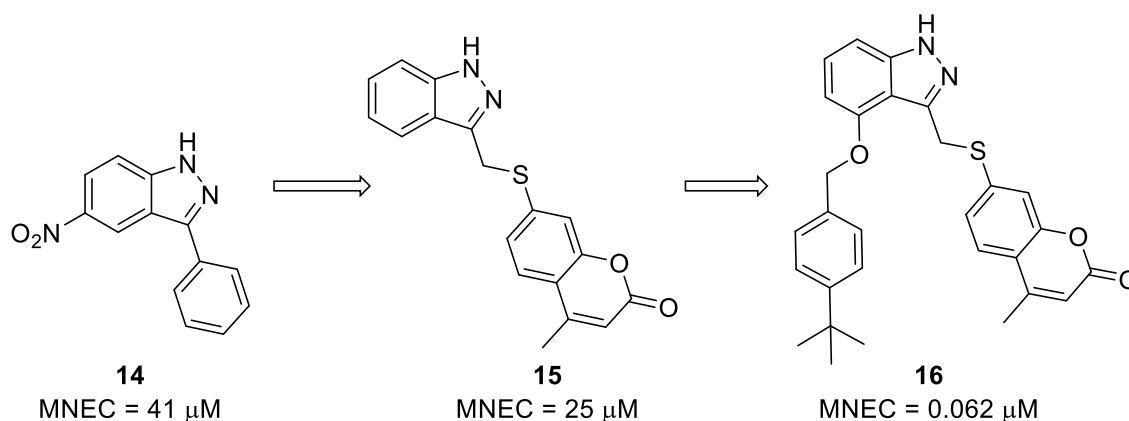


Figure 2.6 – Refined binding model of **14**. Taken from Mueller and co-workers.⁹¹ Depicted is indazole fragment **14** with observed H-bonds (dotted lines) to Asp73 side chain and a conserved water (red).

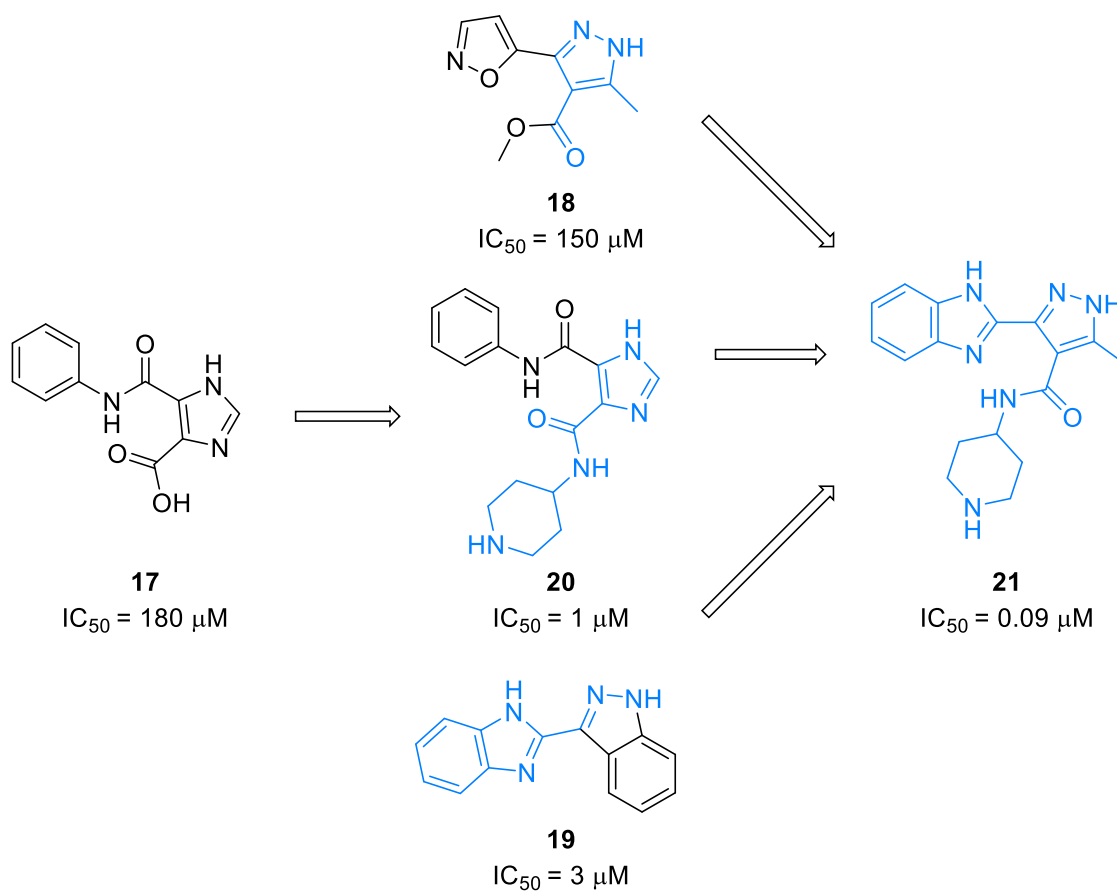
From the first hypothesis, the 3-position of indazole **14** was modified by combinatorial chemistry and screened until thiocumarin-substituted indazole **15** was found to pick up the desired interactions, yielding a MNEC of 25 μM . From here, exploration of substitution around the 4-position of the indazole moiety yielded indazole **16** which leveraged both the stacking and the lipophilic interactions to give an inhibitor with a MNEC of 0.062 μM in an in-vitro supercoiling assay (Scheme 2.3).⁹¹ This exemplifies the fragment growing approach.



Scheme 2.3

An alternative elaboration approach is that of fragment merging. Fragment merging is an approach that combines information from multiple chemical hits that bind in partially overlapping space by designing compounds that incorporate substructural features of each. In this sense, it relies on multiple crystal structures from a variety of chemotypes and careful structure-based design.^{66, 92} This approach was utilised by Hubbard and co-workers at Vernalis in their studies towards finding selective inhibitors against the protein kinase PDPK1.⁹³ Initial NMR screening gave fragment hits **17**, **18** and **19** (IC_{50} = 180 μM , 150 μM

and 3 μM respectively) with subsequent SAR of a variety of analogues of imidazole **17** yielding optimised imidazole **20** ($\text{IC}_{50} = 1 \mu\text{M}$) as a hit. Using X-ray crystallography and NMR studies, structural motifs from **18**, **19** and **20** were combined into compound **21** with an IC_{50} of 0.09 μM (Scheme 2.4). Unfortunately, the authors reported that despite the successful and selective inhibition of PDPK1, no therapeutic benefit was observed. Notably, while fragment merging has been historically poorly served by *in silico* approaches, recent developments in computational methods have improved this with studies showing successful *in silico* fragment merging approaches to identify SARS-CoV-2 MPro inhibitors.⁹⁴

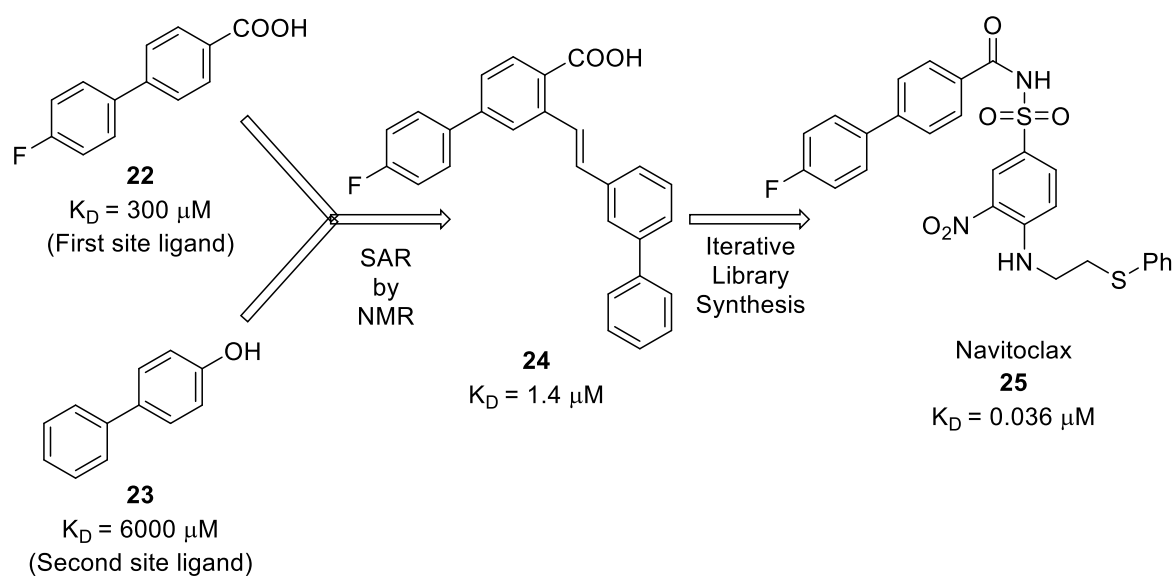


Scheme 2.4

Finally, fragment linking, widely regarded as a powerful yet challenging strategy in fragment elaboration, involves connecting two or more fragments that bind to different but adjacent sites within the active site, incorporating an additional linker moiety.^{64, 95} In this regard, fragment linking has the challenge of both finding the distinct fragments that occupy the protein hot and warm spots whilst also finding the right linker motif. This linker should orient the individual fragment units in a favourable geometry in relation to each other

without introducing too much flexibility whilst maintaining the binding poses of both fragments.^{96, 97}

Notably, Venetoclax, one of the seven marketed drugs that have their origins in FBDD (see Section 2.1, Figure 2.3), emerged from the previously developed API navitoclax, which resulted from a fragment linking campaign. This was one of the first approaches to FBDD by Fesik and co-workers, utilizing SAR by NMR.^{98, 99} The authors screened a library of compounds against BCL-2 and BCL-X_L from which biaryls **22** ($K_D = 300 \mu\text{M}$) and **23** ($K_D = 6000 \mu\text{M}$) arose as fragment hits in adjacent sites of the protein. The fragments were then linked together using an alkene moiety to yield alkene **24** ($K_I = 1.4 \mu\text{M}$) and structural information was collected using ^{15}N - ^{13}C -filtered protein-ligand NOE NMR experiments. Following this, change of linker to a sulfonamide and iterative library synthesis yielded navitoclax **25** with a K_I of $0.036 \mu\text{M}$ (Scheme 2.5), marking the first successful use of fragment linking and eventually yielding one of the first FBDD derived pharmaceuticals.

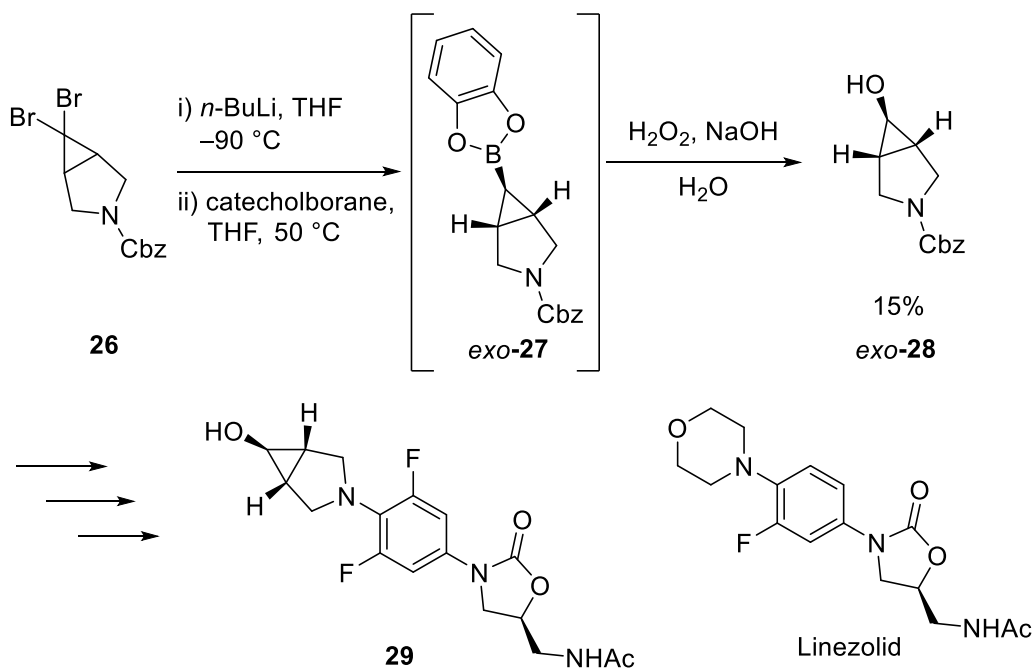


Scheme 2.5

2.3 Cyclopropyl Building Blocks for Use in Drug Discovery

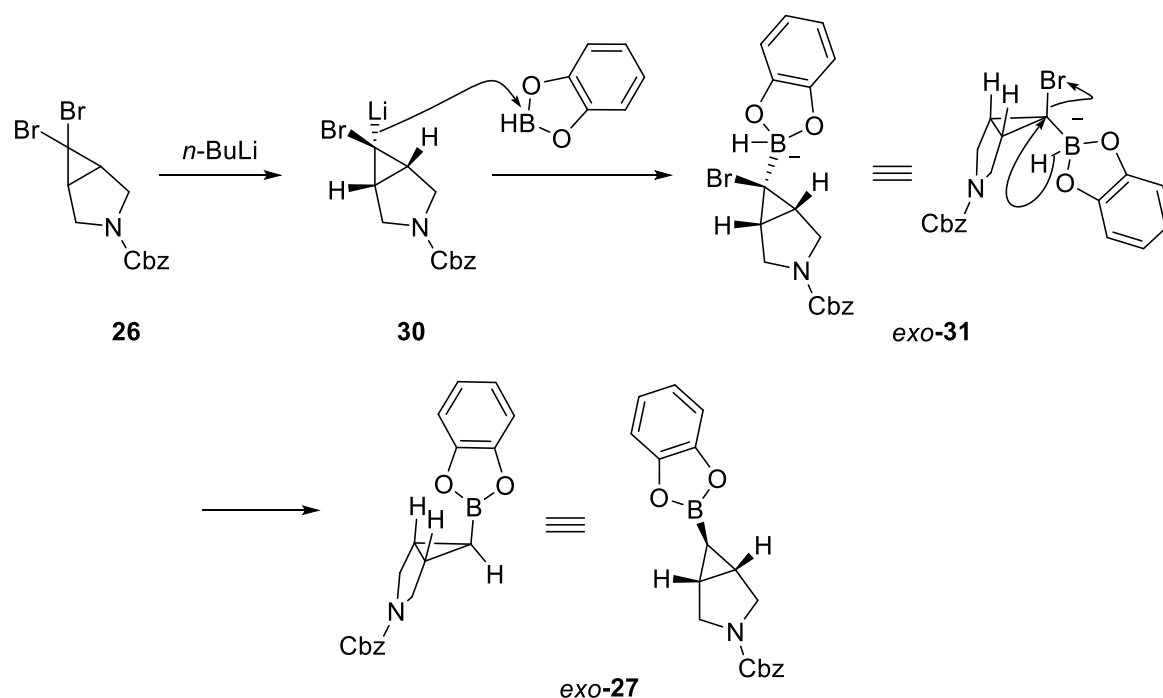
2.3.1 Recent Relevant Examples of Cyclopropyl Boronates in Medicinal Chemistry

Cyclopropyl boronates have long been valuable synthetic intermediates in medicinal chemistry, particularly as useful building blocks for cyclopropane chemistry,^{100, 101} including Suzuki-Miyaura cross-couplings¹⁰²⁻¹⁰⁵ and oxidation to cyclopropanols¹⁰⁶ among others. In this sense, Gordeev and co-workers approached a SAR campaign for the development of new antibacterials via the design of conformationally constrained analogues of Linezolid by introducing the cyclopropane moiety into their compounds.¹⁰⁷ In their campaign, analogue **exo-29** was elaborated from bicyclic cyclopropanol **exo-28** which was in turn synthesised from dibromocyclopropane **26** by reacting it with *n*-BuLi and catecholborane using methodology previously reported by Savoca and co-workers.¹⁰⁰ This yielded intermediate boronate **exo-27** which was oxidised *in situ* to alcohol **exo-28** using alkaline H₂O₂ (Scheme 2.6). This methodology was utilised by Proia and co-workers in their synthesis of tricyclic ligands for the degradation of ikzf2 and ikzf4.¹⁰⁸



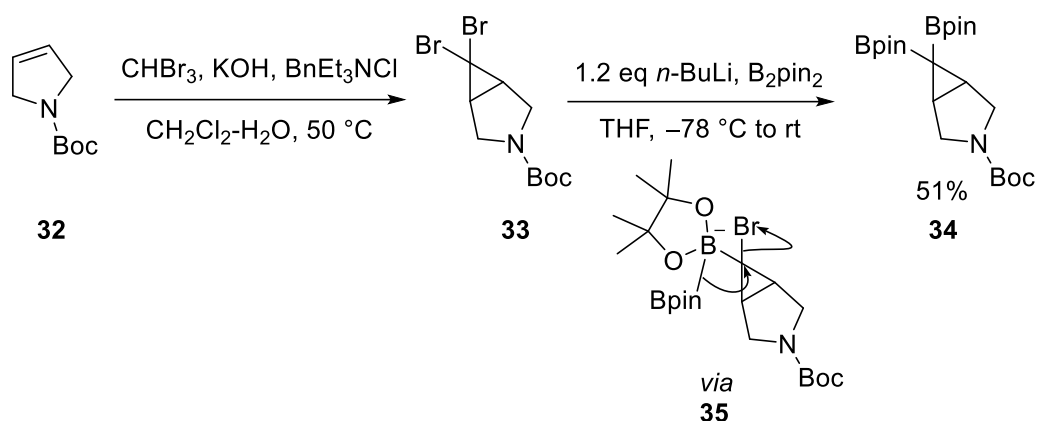
Scheme 2.6

The mechanism and stereochemical outcome of this transformation are highlighted in Scheme 2.7. Namely, dibromocyclopropane **26** undergoes *endo*-selective halogen-lithium exchange to give lithiated species **30**. Organolithium **30** is then trapped by catecholborane forming ate-complex **exo-31** which then undergoes invertive Matteson-Pasto 1,2 rearrangement to give cyclopropylboronate **exo-27**.¹⁰⁰



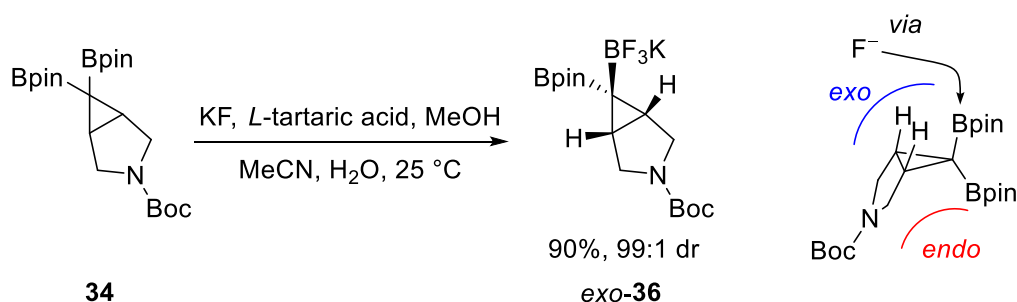
Scheme 2.7

Another example of a similar substrate was developed by Harris and co-workers during the exploration towards a modular approach to the synthesis of gem-disubstituted cyclopropanes.¹⁰⁹ Although not with a primary focus in medicinal chemistry, their work demonstrated the synthesis of cyclopropyl pyrrolidine **34** via a dibromocyclopropanation-borylation sequence from the corresponding alkene **32**. Here, alkene **32** was reacted with bromoform and KOH in the presence of a phase transfer catalyst to give crude dibromocyclopropane **33**. **33** then underwent Br-Li exchange followed by trapping with B_2pin_2 to form ate-complex **35**. This intermediate underwent a 1,2-Matteson-Pastor rearrangement resulting in bis-boronate pyrrolidine **34** with a yield of 51% over the two steps (Scheme 2.8).



Scheme 2.8

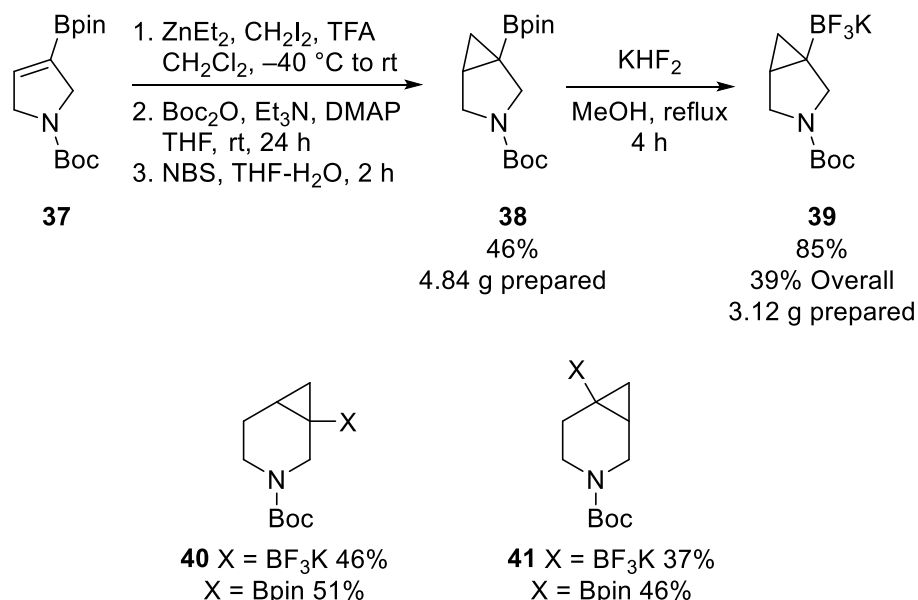
Bicyclic system **34** was also showcased by Masarwa and co-workers in their studies of a diastereoselective desymmetrising potassium trifluoroborate formation.¹¹⁰ Here, bis-boronate **34** was synthesised following the same method as Harris and co-workers (see Scheme 2.8). It was then reacted with KF and *L*-tartaric acid to produce BF_3K *exo*-**26** in 90% yield and 99:1 dr. The diastereoselectivity is achieved by the selective approach of the fluoride to the less sterically hindered boronate on the *exo* face of bicycle **34** (Scheme 2.9).



Scheme 2.9

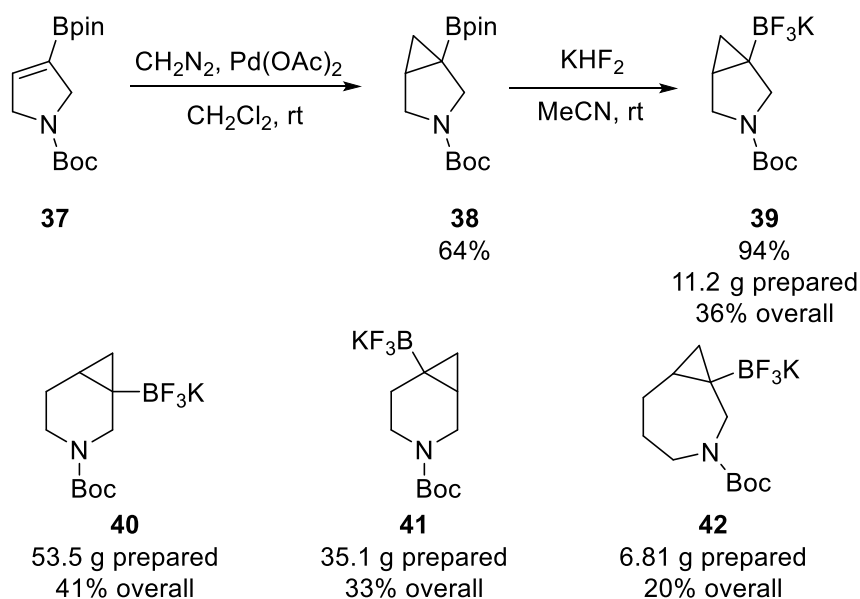
Although not developed for the specific purpose of fragment elaboration, Harris and co-workers at Pfizer have reported the synthesis and Suzuki-Miyaura cross-coupling of a set of pyrrolidine and piperidine-derived cyclopropane boronates.¹¹¹ Harris' route started from vinyl pinacol boronate **37** which was transformed into cyclopropyl pinacol boronate **38** using Simmons-Smith cyclopropanation conditions. However, this set of conditions needed the use of TFA which removed the *N*-Boc protecting group from the pyrrolidine, requiring an additional re-protection step. Moreover, Simmons-Smith cyclopropanation of vinyl boronate **37** yielded a mixture of the cyclopropyl boronate **38** and starting material **37** which were inseparable by chromatography. This further necessitated the formation of a bromohydrin from the alkene in vinyl pinacol boronate **37** using NBS and H_2O which allowed successful

purification of cyclopropyl pinacol boronate **38** which was isolated in 46% yield over the three steps. Boronate **38** was then converted into its corresponding trifluoroborate salt by treatment with KHF_2 to yield cyclopropyl trifluoroborate **39** in 85% yield. This methodology was scaled up with a 3.12 g batch obtained. Likewise, this approach was also applied to the synthesis of cyclopropyl trifluoroborates **40** and **41** (Scheme 2.10).



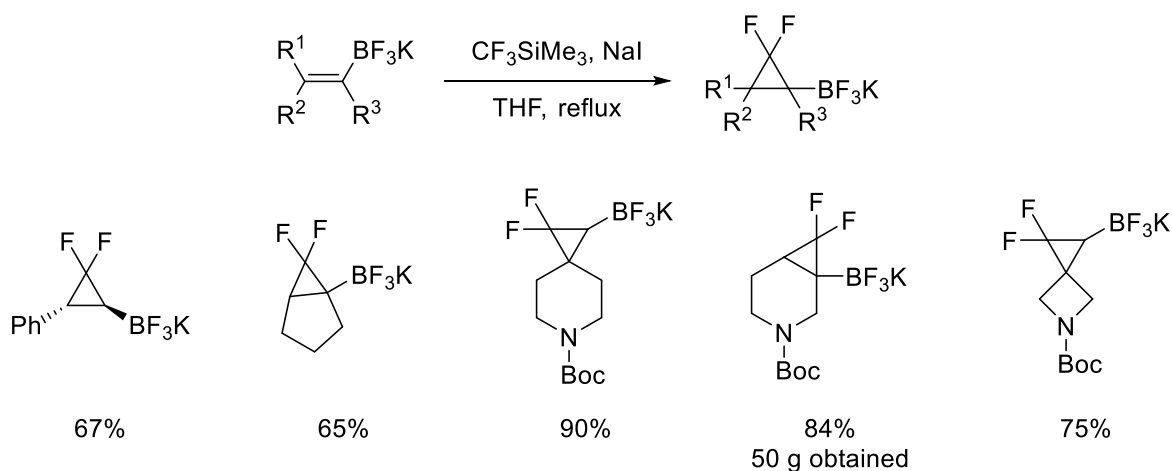
Scheme 2.10

Grygorenko and co-workers at Enamine utilised a similar route to access fused cyclopropyl trifluoroborate scaffolds.¹¹² Similar to the work of Harris and co-workers, Grygorenko started from vinyl pinacol boronate **37** which underwent a Pd-catalysed cyclopropanation using diazomethane to give cyclopropyl pinacol boronate **38** in 64% yield. Pinacol boronate **38** was then turned into cyclopropyl trifluoroborate **39** by treatment with KHF_2 . Notably, this route avoids the reprotection step used by Harris while maintaining a cleaner reaction profile that allowed for purification of cyclopropyl boronate **39** without additional steps. In this manner, Grygorenko and co-workers were able to scale the methodology to provide 11–53 g batches of scaffolds **40–42** (Scheme 2.11). This methodology was also utilised in their 2023 work on the [3+2] cycloaddition of alkynyl boronates.¹¹³ This approach employs diazomethane as a carbene precursor which is potentially explosive in solution. However, the authors comment that recent advances in flow chemistry and *in situ* generation allow for the safe generation and handling of diazomethane solutions.¹¹⁴⁻¹¹⁶



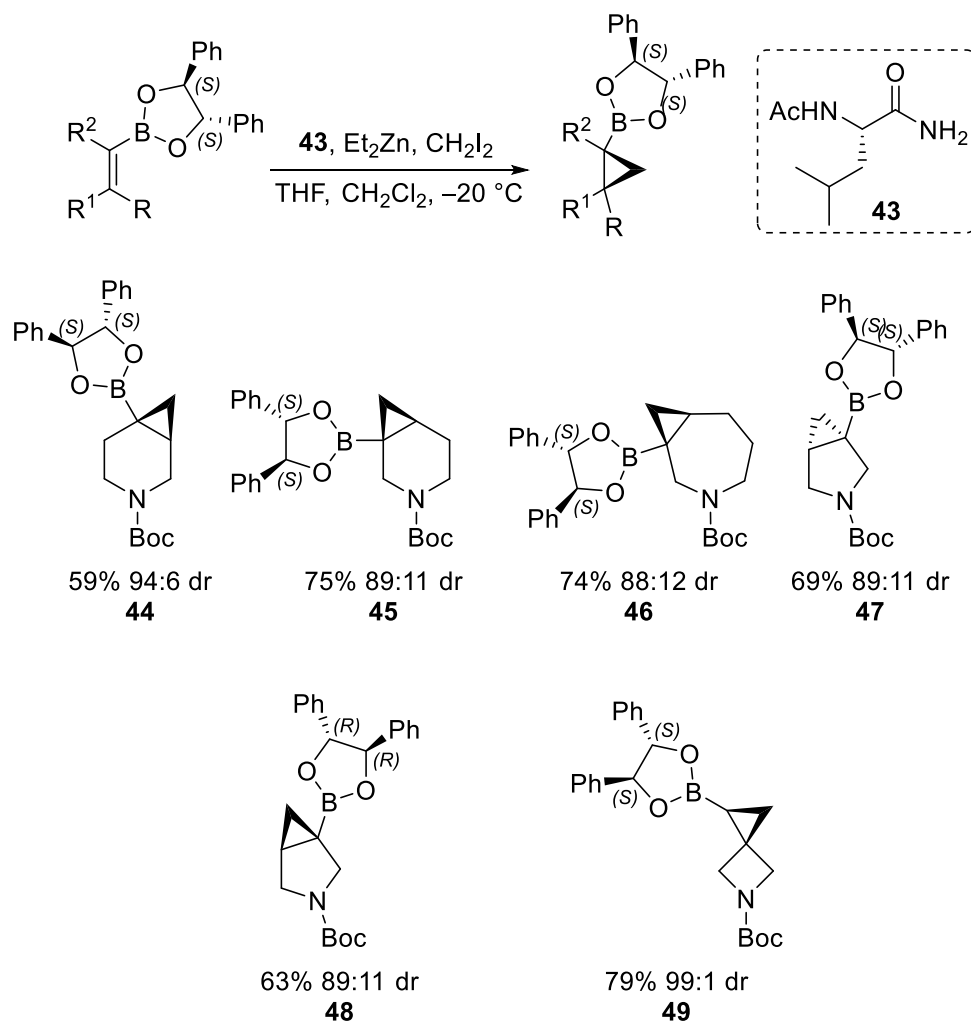
Scheme 2.11

Furthermore, Grygorenko and co-workers developed another methodology that allowed access to difluorocyclopropanated scaffolds.¹¹⁷ Using a $\text{CF}_3\text{SiMe}_3\text{-NaI}$ system, vinyl trifluoroborates were difluorocyclopropanated in good to excellent yields (Scheme 2.12). This methodology allowed access to a diverse set of spirocyclic and fused cyclopropanes with a diverse set of substitution patterns. The conditions were successfully applied on up to a 50 g scale without detrimental effect on the yield. The methodologies described by Grygorenko and co-workers were also applied in the context of medicinal chemistry, where the cyclopropyl boronates were used in the parallel synthesis of sp^3 -enriched compound libraries.¹¹⁸



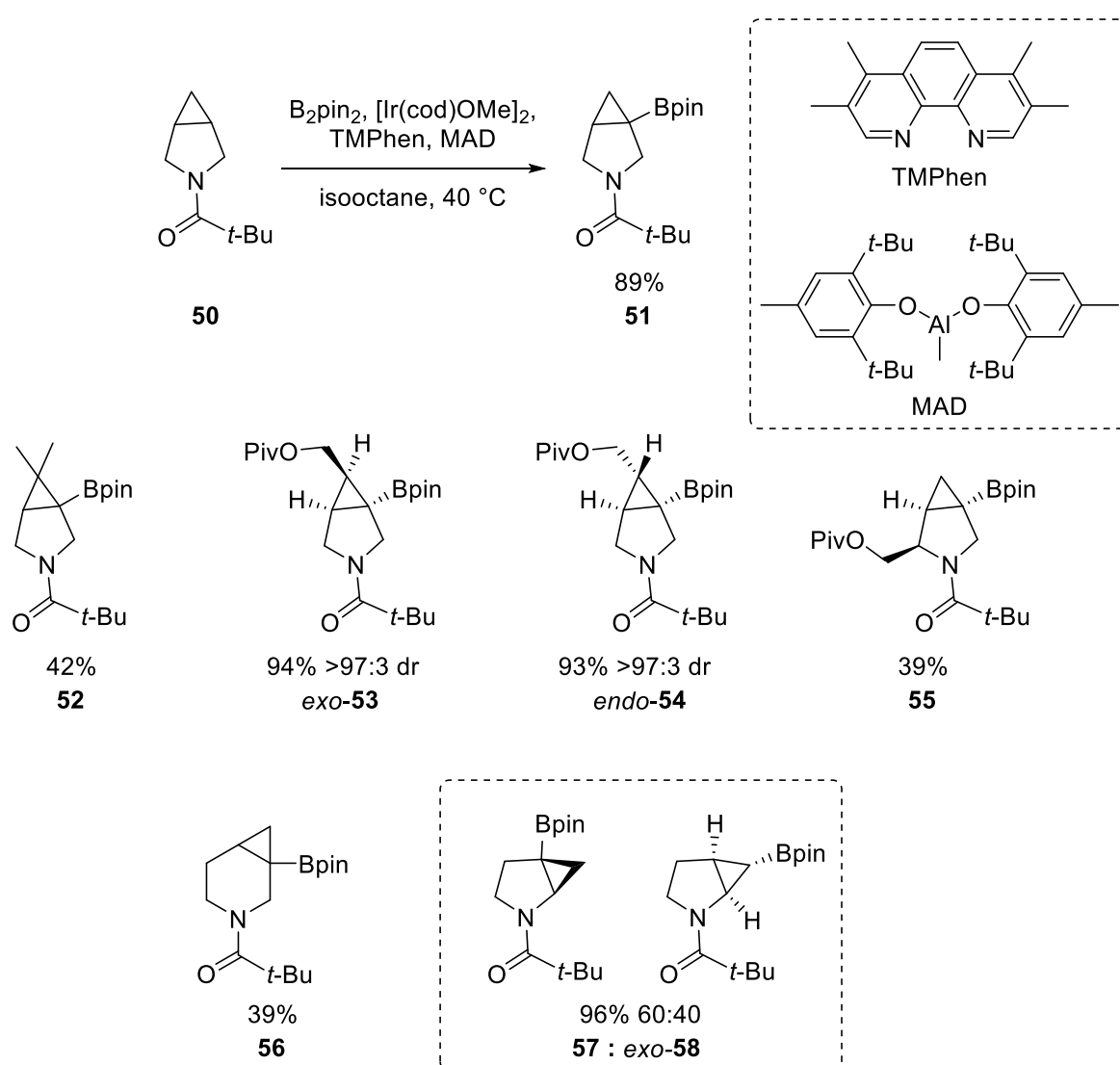
Scheme 2.12

The ongoing interest in synthesising these boronates has led to the development of new asymmetric methods for producing cyclopropyl boronates. In 2022, Wang and co-workers from Merck developed a methodology for the asymmetric synthesis of tertiary and secondary cyclopropyl boronates.¹¹⁹ By introducing a chiral diol on the vinyl boronate and under Simmons-Smith conditions with the aid of a chiral amide **43**, the authors described the synthesis of a diverse set of hetero and carbocyclic boronates **44-49** in good yields and diastereoselectivity (Scheme 2.13). Notably, the introduction of chiral amide **43** was crucial, as it facilitated chirality transfer, presumably through the addition to the boron's empty *p*-orbital and chelation of the Lewis-acidic Zn centre. Buono and co-workers reported another asymmetric methodology for the cyclopropanation of unsubstituted vinyl trifluoroborate using ethyl diazoacetate and a chiral Rh catalyst.¹²⁰ However, despite successful scale-up to 50 g, its applicability is limited to a single substrate, reducing its overall usefulness.



Scheme 2.13

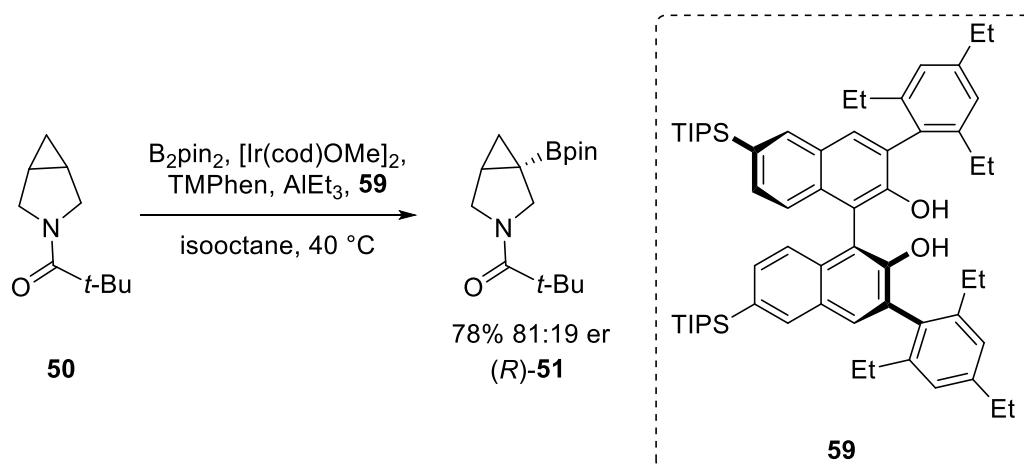
In 2023 Nakao and co-workers reported a regioselective Ir/Al-catalysed borylation of fused pyrrolidines and piperidines.¹²¹ Using the fused pyrrolidine scaffold **50**, reaction with B₂pin₂, an Ir catalyst, TMPhen and an Al cocatalyst MAD afforded the borylated cyclopropane **51** in 89% yield (Scheme 2.14). The methodology was applicable to a diverse set of cyclopropyl fused pyrrolidines and piperidines **52-58**, including some with preset stereocentres **53-55**. However, a 2,3-fused pyrrolidine afforded a 60:40 mixture of regioisomers **57** and *exo*-**58**. Additionally, the authors observed that the pivaloyl amide was essential for the methodology, as substituting it with a Boc group completely halted the reaction, thereby limiting its applicability.



Scheme 2.14

Additionally, an asymmetric variant of the methodology was developed by replacing the Al co-catalyst for one generated from AlEt₃ and BINOL derivative **59**.¹²¹ In this fashion,

borylated cyclopropane (*R*)-**51** was obtained in 78% yield and 81:19 er (Scheme 2.15). Another asymmetric synthesis of simple trifluoromethyl-substituted cyclopropane boronates using alkenes and a chiral Cu-catalyst was also reported by Carreras and co-workers.¹²² However it suffered from a dearth of structural variety.



Scheme 2.15

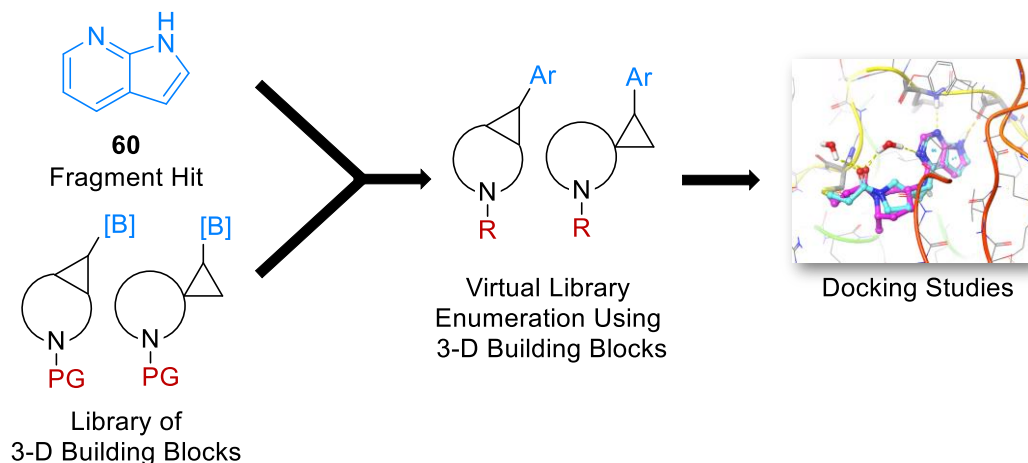
2.3.2 Overview of the York Cyclopropyl Boronate 3-D Building Blocks

The goal of this project involves the development of a synthetic platform to allow for the systematic and programmable elaboration of typically 2-D fragment hits into 3-D lead-like compounds using specially designed 3-D building blocks. Rather than the development of a complex methodology for the elaboration of fragments, we propose to leverage the power and robustness of the reliable set of reactions commonly utilised in medicinal chemistry.¹²³ This will be achieved with a newly designed set of bifunctional 3-D building blocks.

The main design element for each building block is the ability to trace unique 3-D elaboration vectors around a fragment's chemical space, ultimately forming the backbone of a drug candidate. The focus on the 3-dimensionality of the building blocks is key with regards to both the versatility and success of any active pharmaceutical ingredient that is ultimately developed around these.¹²⁴ Thus, the building blocks are designed to include a high fraction of sp^3 hybridised carbons (F_{sp^3}) due to its correlation with a higher success in clinical trials.¹²⁵ In the long term, the creation of a library of ~20 3-D building blocks which can be used to elaborate fragments is envisaged.

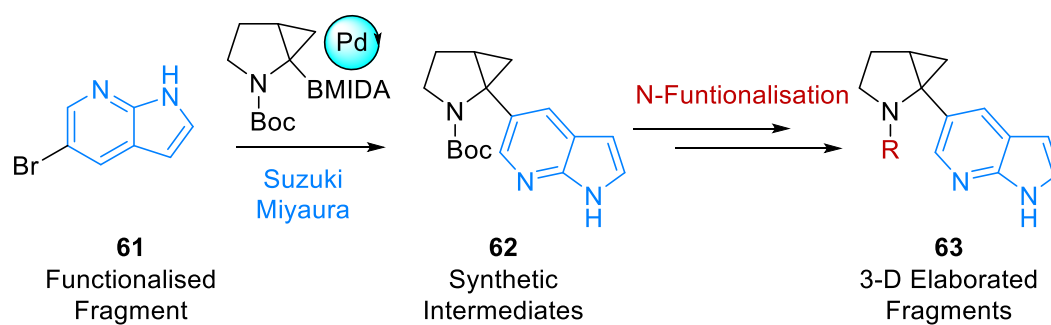
The approach, specially designed for structurally enabled proteins, starts with a fragment-identification phase. In this phase, a fragment or a collection of fragments is identified, ideally through X-ray crystallographic or virtual screening of a protein (e.g., azaindole **60**,

Scheme 2.16).¹²⁶ Then, the designed set of building blocks can be used to create a virtual library of compounds in which the fragment hit has been elaborated with the building blocks and further diversified with typical medicinal chemistry capping groups. From this virtual library, computational screening methods can illuminate a set of potential lead-like molecules for the synthesis phase.



Scheme 2.16 – General workflow for the use of building blocks for the elaboration of fragments. E.g. Using an azaindole as fragment hit.

In the synthesis phase, the fragment hit **60** can be elaborated via Suzuki-Miyaura cross-coupling. This involves reacting a halogenated derivative of the initial fragment hit **61** with the desired building block, utilizing the included cyclopropyl MIDA boronate moiety to produce **62**. Then, after Boc group removal, **62** can in turn be further functionalised by reliable *N*-functionalisation reactions into a set of lead-like compounds **63** (Scheme 2.17). Both stages of the synthesis phase utilise reactions that are robust and widely use in medicinal chemistry to minimise any barriers to uptake by FBDD practitioners. Additionally, since the synthetic methodology is established in advance and uses the same sets of reactions, the generation of 3-D lead-compounds can be achieved rapidly. It is expected that the proposed methodical and systematic approach will allow for process automation in the long term, enabling for the relief of one of the bottlenecks in the drug discovery process.¹²⁷⁻¹²⁹



Scheme 2.17

With this goal in mind, an initial set of conditions was established for the design process of the 3-D building blocks. It is proposed that the 3-D building blocks would consist of cyclopropyl boronate-substituted nitrogen heterocycles. The cyclopropane moiety's strained three-membered ring allows interactions with neighbouring π -systems resembling those of a vinyl group, thus facilitating cross-coupling.¹³⁰ In drug discovery, the cyclopropyl group presents itself as a bioisostere for saturated alkenes, while having increased metabolic stability.^{19, 131} Additional benefits that cyclopropanes have conferred to different drug molecules include enhanced potency, increased permeability of the blood-brain barrier, conformational restriction and decreased plasma clearance.¹³² Furthermore, the 3-D building blocks were designed to conform with the “rule of two” guidelines outlined by Goldberg *et al.* from AstraZeneca (MW < 200, clogP < 2, HBD $\leq$ 2 and HBA $\leq$ 4) for building blocks in medicinal chemistry.¹³³

It was decided that the defined set of elaboration vectors would comprise a cyclopropyl MIDA boronate and an *N*-Boc protected cyclic amine. The MIDA boronate, developed by Burke *et al.*, would be a suitable synthetic handle for Suzuki-Miyaura cross-coupling for the attachment of fragments.¹³⁴⁻¹³⁶ MIDA boronates possess several advantages as they are usually free-flowing bench-stable and silica-gel compatible solids; additionally, their potential use in slow-release Suzuki-Miyaura cross-couplings allows them to generate potentially unstable boronic acids *in situ* thus allowing for the cross-coupling of potentially problematic substrates.¹³⁵ On the other hand, the amine (after Boc removal) allows for coupling with medicinally-relevant substituents,¹³⁷ with known reliable chemistry such as Buchwald-Hartwig couplings, reductive amination or amide bond formation. Finally, the 3-D building blocks were designed around fused and spirocyclic systems. This, due to the recent interest and prevalence of these moieties in medicinal chemistry campaigns due to their favourable properties,^{125, 138-142} and the O'Brien's group experience in their synthesis.¹⁴³

Using these design criteria, the O'Brien group has, to date, carried out the design and synthesis of nine 3-D building blocks **64-71** (Figure 2.8). Each of these building blocks presents distinct elaboration vectors between the MIDA boronate and the amine which is key for a systematic exploration of chemical space from a 2-D fragment hit.

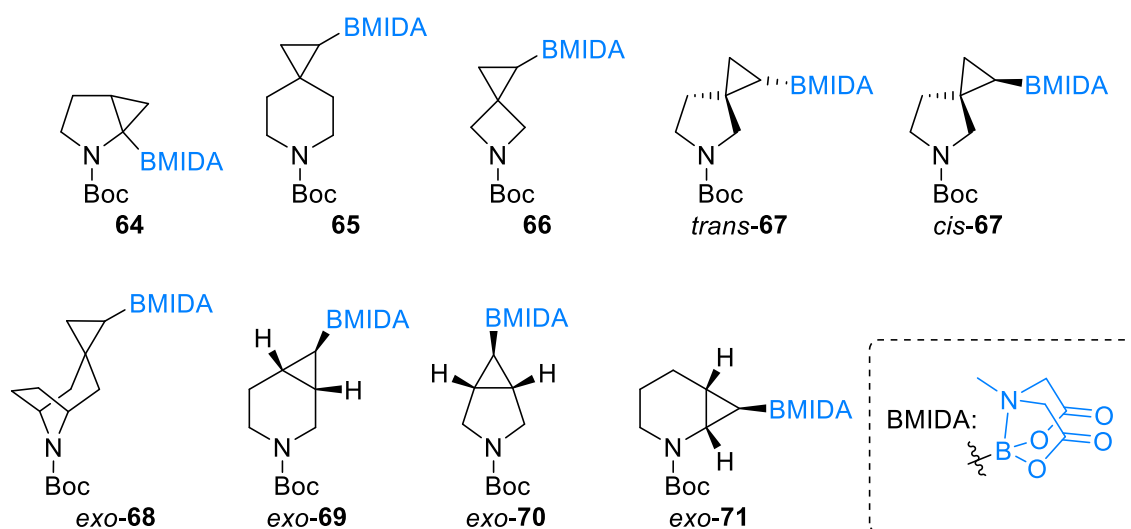


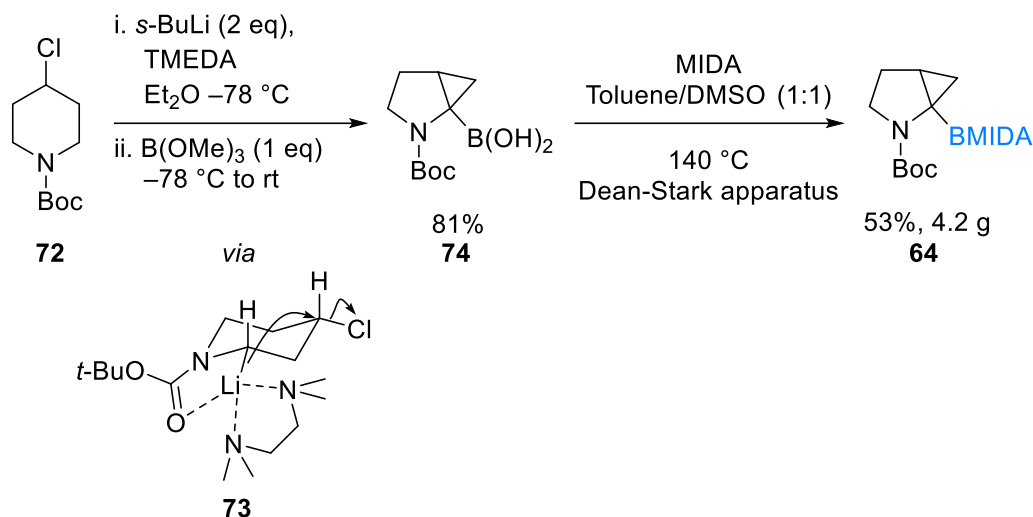
Figure 2.7 – O'Brien and coworkers bifunctional 3-D building blocks.

2.3.3 Overview of the O'Brien Group Synthetic Strategies for 3-D Building Blocks

One of the main objectives in the design aspect of the current project in the group was the synthetic tractability of the proposed 3-D building blocks **64-71**. It was desired to avoid bespoke strategies for as many of the building blocks as possible. Thus, while pyrrolidine building block **64** has a bespoke strategy involving cyclisation of a lithiated intermediate, building blocks **65**, **66** and *exo*-**68** utilise a common strategy *via* a dichlorocyclopropane and building blocks **67** and **69-71** are synthesised *via* monodebromination of a dibromocyclopropane. Full details of these three approaches to the building blocks are presented below.

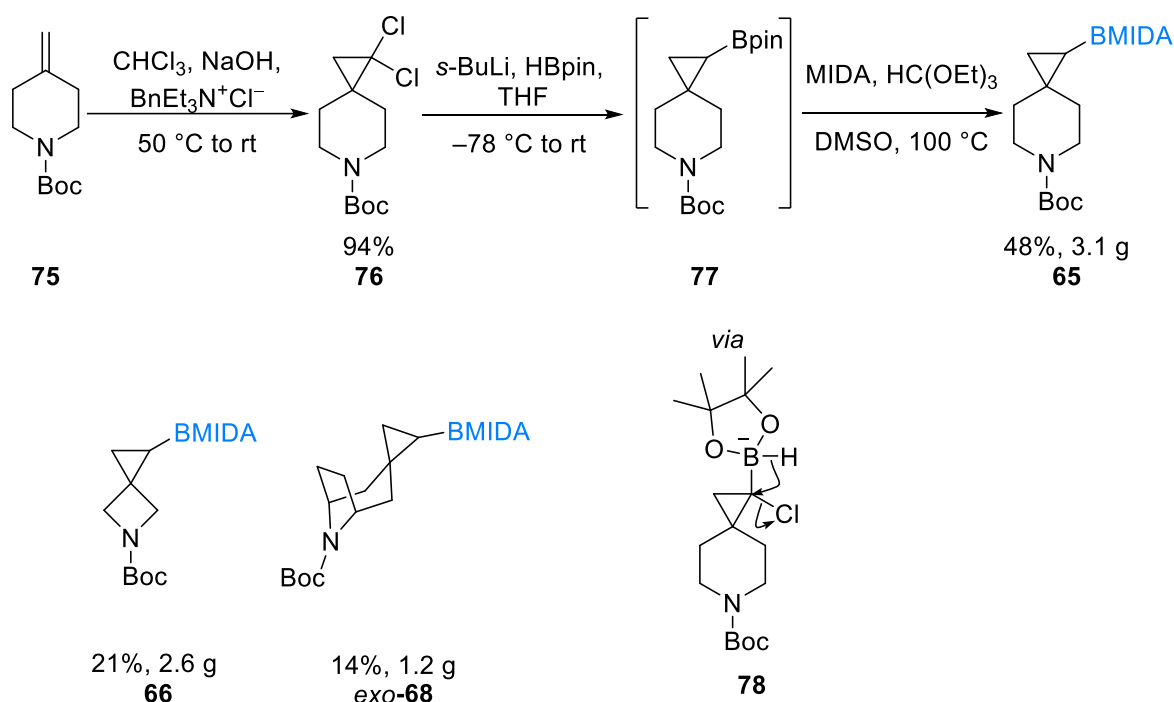
Pyrrolidine-based 3-D building block **64** is the only building block that requires a bespoke synthesis (Scheme 2.18). In this route, based on Beak's precedent,¹⁴⁴ 4-chloropiperidine **72** was lithiated in the α position using *s*-BuLi and TMEDA to generate transient lithiated species **73** which underwent cyclisation with the C–Cl σ^* orbital to generate the cyclopropyl-fused pyrrolidine. This in turn was lithiated by a second equivalent of base and trapped with trimethoxyborate to generate cyclopropyl boronic acid **74** in 81% yield (after aqueous work-up and chromatography). Boronic acid **74** was then converted into MIDA boronate **64**

in 53% yield upon treatment with MIDA. Gratifyingly, this synthesis could be scaled up to 35 mmol of chloropiperidine **72** to obtain 4.2 g of 3-D building block **64** in 43% yield overall.¹⁴⁵⁻¹⁴⁷



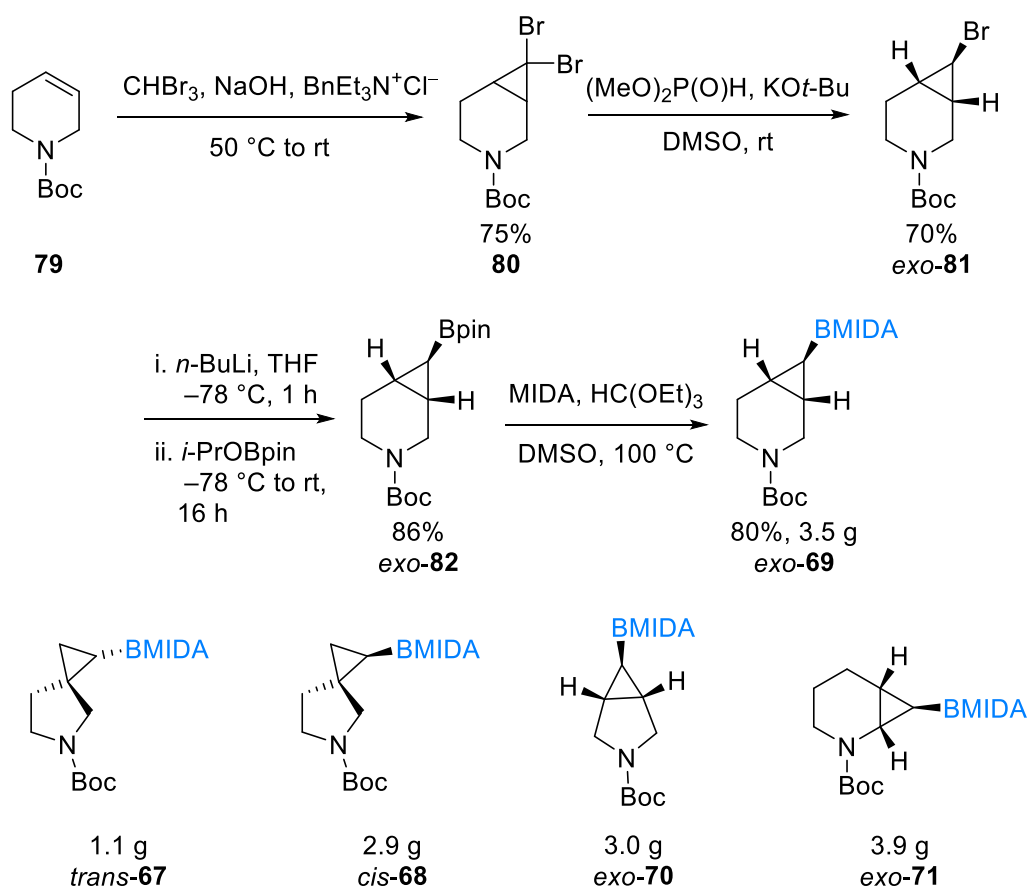
Scheme 2.18

On the other hand, building blocks **65**, **66** and *exo*-**68** share a common strategy where the alkene is converted into a dichlorocyclopropane which undergoes a boronate rearrangement into the cyclopropyl pinacol boronate.¹⁰⁰ This is exemplified in Scheme 2.19 for spirocyclic piperidine **65**. In this way, alkene **75** was dichlorocyclopropanated with CHCl₃, BnEt₃N⁺Cl⁻ and NaOH to give dichlorocyclopropane **76** in 94% yield after recrystallisation. Then, dichlorocyclopropane **76** was treated with *s*-BuLi and HBpin (*in situ*) to afford cyclopropyl pinacol boronate **77** which was used without further purification to form the MIDA boronate in 48% yield over the two steps. This boronate rearrangement proceeds by an initial halogen-lithium exchange and subsequent addition of the lithiated species to the empty *p*-orbital of the boron to form boronate **78**. **78** then undergoes a 1,2-hydride shift with substitution of the chloride to give pinacol boronate **77**. Overall, this approach was able to be scaled up to 100 mmol of alkene **75** and 18 mmol of dichlorocyclopropane **76** to afford 3.1 g of cyclopropyl MIDA boronate **65** in 45% yield. This strategy was also successfully applied to building blocks **66** and *exo*-**68** with overall yields of 21% and 14% respectively. Of note, the corresponding alkene starting materials for building blocks **66** and *exo*-**68** required separate synthesis, adding one or two steps to the route.



Scheme 2.19

Finally, a different route was used to access building blocks *trans*-**67**, *cis*-**67** and *exo*-**69**-**71**. This strategy consisted of a dibromocyclopropanation of the alkene followed by monodebromination, halogen-lithium exchange and trapping to form the desired pinacol boronate and transesterification into the MIDA boronate. This is exemplified in Scheme 2.20 for piperidine building block *exo*-**69**. In this way, alkene **79** was treated with CHBr_3 , $\text{BnEt}_3\text{N}^+\text{Cl}^-$ and NaOH to give dibromocyclopropane **80** in 75% yield after chromatography. Stereoselective debromination using trimethyl phosphite¹⁴⁸ afforded monobromide *exo*-**81** in 70% yield. The stereochemical outcome of this debromination is proposed to arise from formation of a monobromocyclopropane carbanion intermediate that places the bromide in the less sterically hindered *exo* position.¹⁴⁸ Halogen-lithium exchange using $n\text{-BuLi}$ followed by trapping with $i\text{-PrOBpin}$ successfully gave pinacol boronate *exo*-**82** in 86% yield *via* a stereospecific transformation. Finally, standard conditions for MIDA boronate formation afforded cyclopropyl MIDA boronate *exo*-**69** in 80% yield. In this case, 3.5 g of building block *exo*-**69** was afforded in a 36% yield overall. Of note, for diastereomeric building blocks *trans*-**67** and *cis*-**67**, while no steric preference was observed in the debromination reaction, their corresponding monobromides were separable by chromatography.



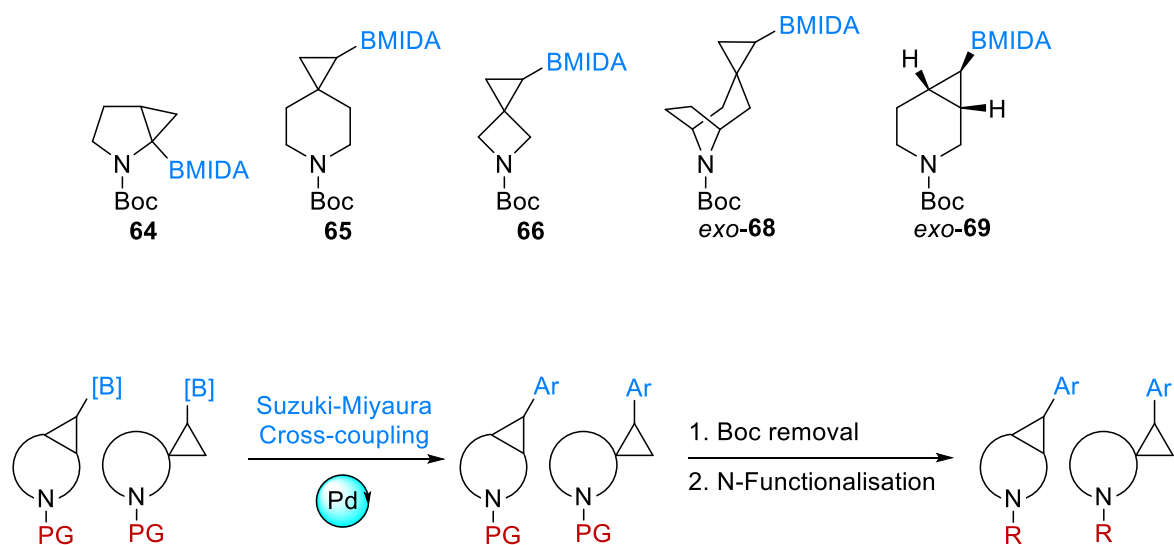
Scheme 2.20

With these three strategies, the O'Brien group has developed multi-gram scale routes to each of nine 3-D building blocks. Additionally, the building blocks are commercially available from Key Organics.

2.4 Project Outline

One of the main themes of this research project is to explore the impact of fragment-based drug discovery (FBDD) in drug development, focusing on its challenges and limitations, particularly during the fragment elaboration stage. The project aims to develop a synthetic platform to alleviate some of the bottlenecks encountered in this stage of drug development. The O'Brien group designed a library of sp^3 -rich bifunctional building blocks with defined vectors to be utilised in fragment elaboration campaigns. With building blocks **64-71** having been already synthesised by previous members of the group,^{145, 147, 149, 150} the aim of this project is to establish the methodology necessary for their utilization. As previously discussed (see Section 2.2.2), traditional fragment elaboration is often performed in stepwise fashion. On the other hand, the O'Brien bifunctional 3-D building blocks are designed to provide a platform for modular elaboration of fragments where fragments are attached by Suzuki-Miyaura cross-coupling utilising the cyclopropyl BMIDA handle and further elaborated around the amine handle.

In this way, the remainder of this Chapter centres around exploring the functionalisation potential of the five 3-D building blocks **64-66**, *exo-68* and *exo-69*, from a fragment elaboration standpoint. For this, functionalisation scope of the cyclopropyl MIDA boronate would be explored using Suzuki-Miyaura cross-coupling with a variety of aromatic and heteroaromatic aryl bromides. For *N*-functionalisation, Boc group removal and amide bond formation, reductive amination, sulfonamide formation or arylation reactions (S_NAr and Buchwald-Hartwig) with different medicinally relevant groups would be investigated. Additionally, potential alternative uses for the boronate handle will be explored. Finally, the potential of the O'Brien 3-D scaffolds in a medicinal chemistry application, with design input from medicinal chemists at AstraZeneca, is explored (Scheme 2.21).



Scheme 2.21

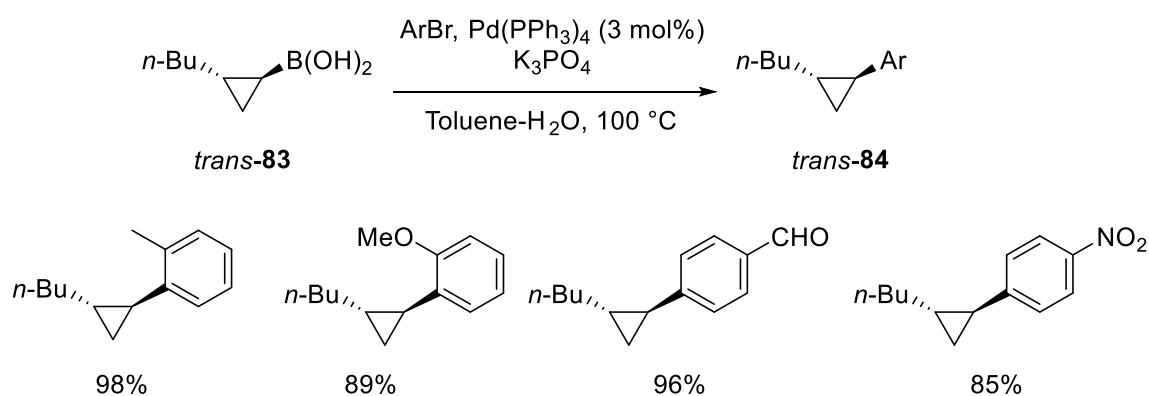
Thus, Section 2.5 delves into the Suzuki-Miyaura cross-coupling of the MIDA boronate building blocks. Section 2.6 shows some of the potential for *N*-functionalisation of the proposed building blocks by the generation of a small set of lead-like compounds. Recognising the additional synthetic potential of the 3-D building blocks, Section 2.7 briefly explores the C-B bond functionalisation of a pinacol boronate derivative of building block **65**. Finally, Section 2.8 explores the use of the O'Brien and coworkers bifunctional 3-D building blocks in the synthesis of selective JAK3 inhibitors.

2.5 Suzuki-Miyaura Cross-Coupling of Cyclopropyl Boronates

This section addresses the Suzuki-Miyaura cross coupling of cyclopropyl boronates. In Section 2.5.1 an overview of the literature around the cross-coupling of cyclopropyl organoboron compounds is provided. Section 2.5.2 addresses the previous work carried in the O'Brien group around the cross-coupling of cyclopropyl boronates. Finally, Section 2.5.3 presents our optimisation and substrate scope for the cross-coupling of four of the O'Brien group 3-D building blocks.

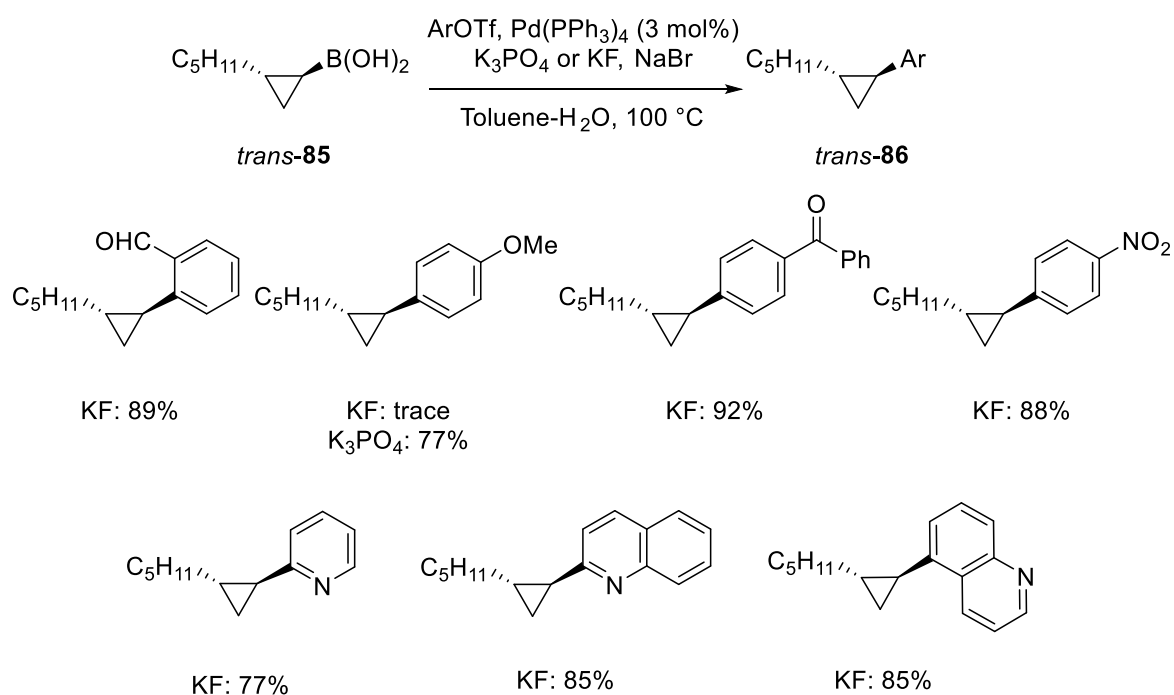
2.5.1 Overview of Suzuki-Miyaura Cross-Coupling of Cyclopropyl Organoboron Compounds

The Suzuki-Miyaura cross-coupling reaction is one of the main carbon-carbon bond forming reactions in the toolkit of synthetic chemists.¹⁵¹ Initially reported in 1979, this Pd-catalysed reaction employs an organoboron compound and organic halides or pseudohalides as handles for the cross-coupling and is currently one of the main reactions utilised in medicinal chemistry projects.¹⁵² In the case of cyclopropyl boron compounds, the first example of a Suzuki-Miyaura cross-coupling reaction was reported by Deng and Wang in 1996.¹⁵³ In their work, the cross-coupling of cyclopropyl boronic acid *trans*-**83** and a variety of aryl bromides using 3 mol% Pd(PPh₃)₄ and K₃PO₄ generated cyclopropyl arenes *trans*-**84** in good to excellent yields (Scheme 2.22). The scope was further expanded to heteroaryl bromides with good yields.¹⁵⁴ Of note, this is one of the first examples of stereospecific cross-coupling of a sp³ hybridised organoboron compound, which proceeded with overall retention of configuration. At a similar time, Marsden and Hildebrand¹⁵⁵ reported a similar methodology which used a propylene glycol boronic ester, 10 mol% Pd(PPh₃)₄ and KOt-Bu to couple a variety of aryl bromides, including 3-bromopyridine, in a stereospecific fashion albeit in considerably lower yields. Additionally, Marsden and coworkers' methodology had the drawback of requiring a high palladium loading. The conditions developed by Deng and co-workers were further leveraged by Pietruszka and co-workers in their work on the synthesis of enantiomerically pure cyclopropanes.¹⁰⁶



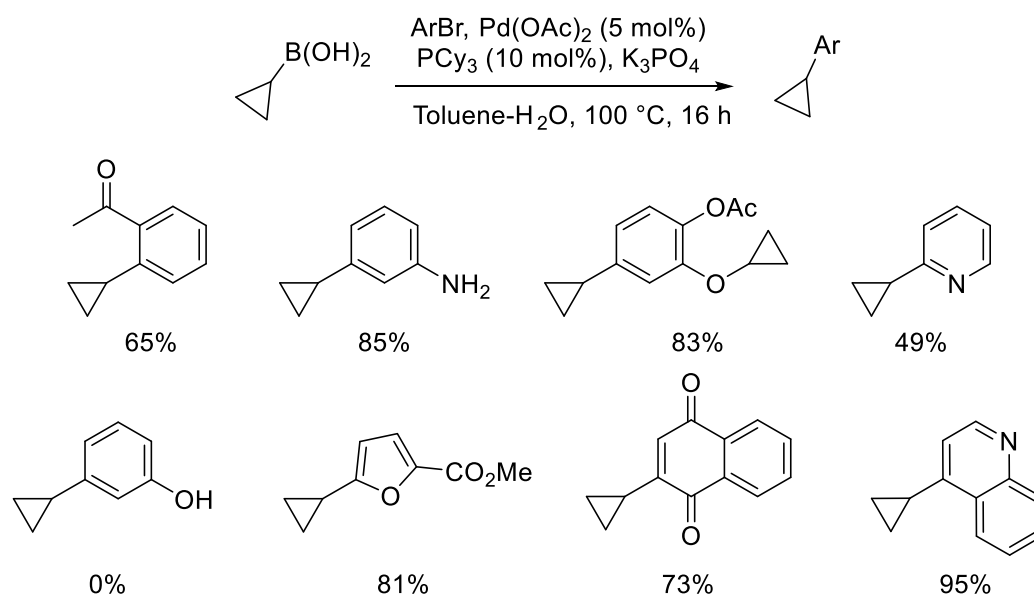
Scheme 2.22

From then onwards, a wide variety of cross-couplings from cyclopropyl boron compounds has been reported.¹⁵⁶ However, due to their relevance to the current project, only the formation of cyclopropyl arenes will be considered in this overview. In 2000, Deng and Yao¹⁵⁷ described the stereospecific Suzuki-Miyaura cross-coupling of *trans*-cyclopropyl boronic acids with aryl triflates. In this case, a 3 mol% loading of $\text{Pd(PPh}_3)_4$ as catalyst was utilised with KF as base for electron deficient arenes and K_3PO_4 for electron rich arenes. Additionally, use of 1 eq. NaBr slowed decomposition of the palladium catalyst which enabled high yields to be obtained. In this way, boronic acid *trans*-85 was successfully cross-coupled to a variety of aryl triflates to give cyclopropyl arenes *trans*-86 in good to excellent yields with cyclopropyl arenes *trans*-86 being exclusively obtained. Subsequently, the use of these conditions for the cross-coupling of heteroaryl triflates was described (Scheme 2.23).¹⁵⁸



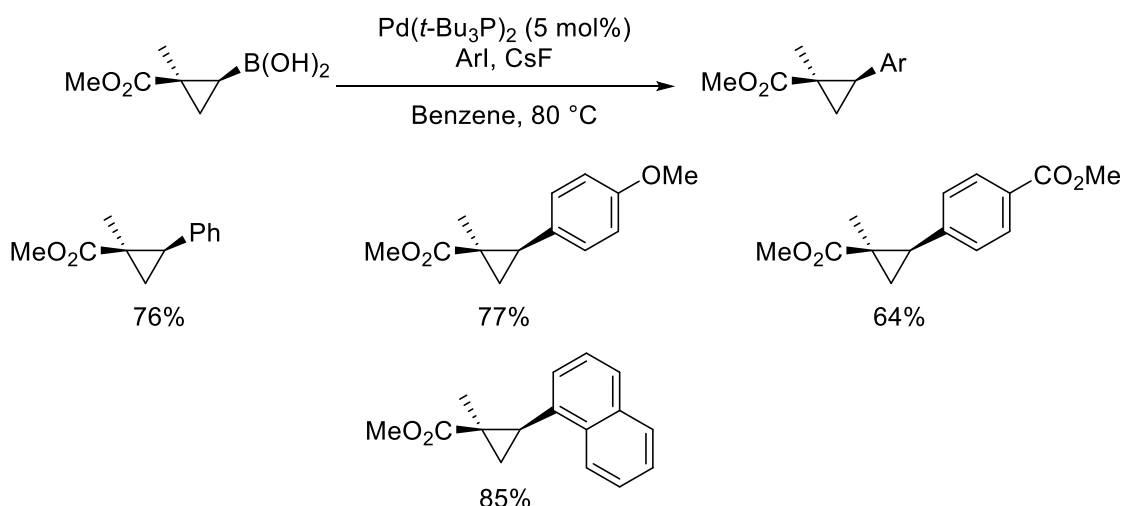
Scheme 2.23

The previously shown examples utilised Pd(PPh₃)₄ which, despite being commercially, is sensitive to air, making it less than ideal for handling.¹⁵⁷ However, it is known that catalytically competent Pd(0) species can be generated *in situ* by reaction of a Pd(II) precatalyst and a phosphine.¹⁵⁹ In the case of cyclopropyl boron compounds, the first successful example of this implementation was showcased by Chen and Wallace in 2002.¹⁶⁰ Cyclopropyl boronic acid was cross-coupled with a variety of aromatic and heteroaromatic bromides using 5 mol% Pd(OAc)₂ and 10 mol% PCy₃ in the presence of K₃PO₄. A variety of substrates, including furan derived and vinyl bromides, was successfully cross-coupled in good to excellent yields (Scheme 2.24). The methodology was selective for aryl bromides over aryl chlorides, and it was found that acidic phenolic protons shut the reaction down. Furthermore, a similar catalytic system but using Pd₂dba₃ as the Pd source was also reported by Carreras and coworkers in 2021.¹²²



Scheme 2.24

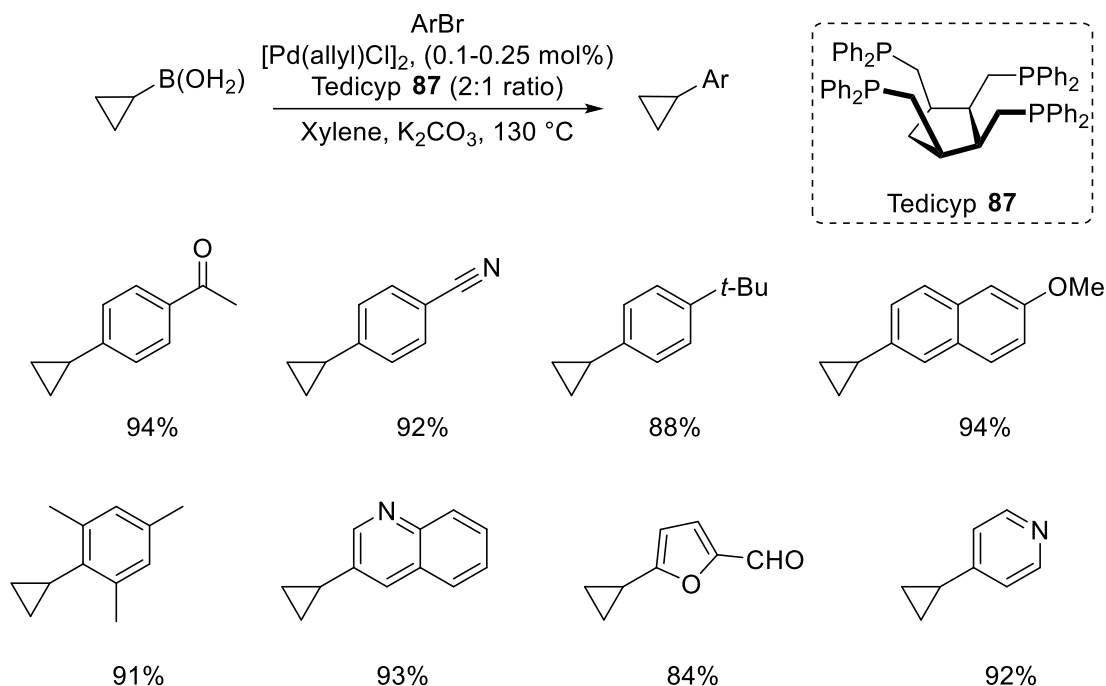
Another catalytic system was demonstrated by Gevorgyan and coworkers in 2003 during their research into the catalytic enantioselective hydroboration of cyclopropenes. Here the authors described the Suzuki-Miyaura cross-coupling of 2,2-disubstituted cyclopropyl boronic acids with aryl iodides utilising $\text{Pd}(t\text{-Bu}_3\text{P})_2$ as the active catalytic species and CsF in anhydrous conditions (Scheme 2.25).¹⁶¹ Importantly, this allowed the cross-coupling of labile methyl esters with a selection of aryl bromides in high yields without ester hydrolysis.



Scheme 2.25

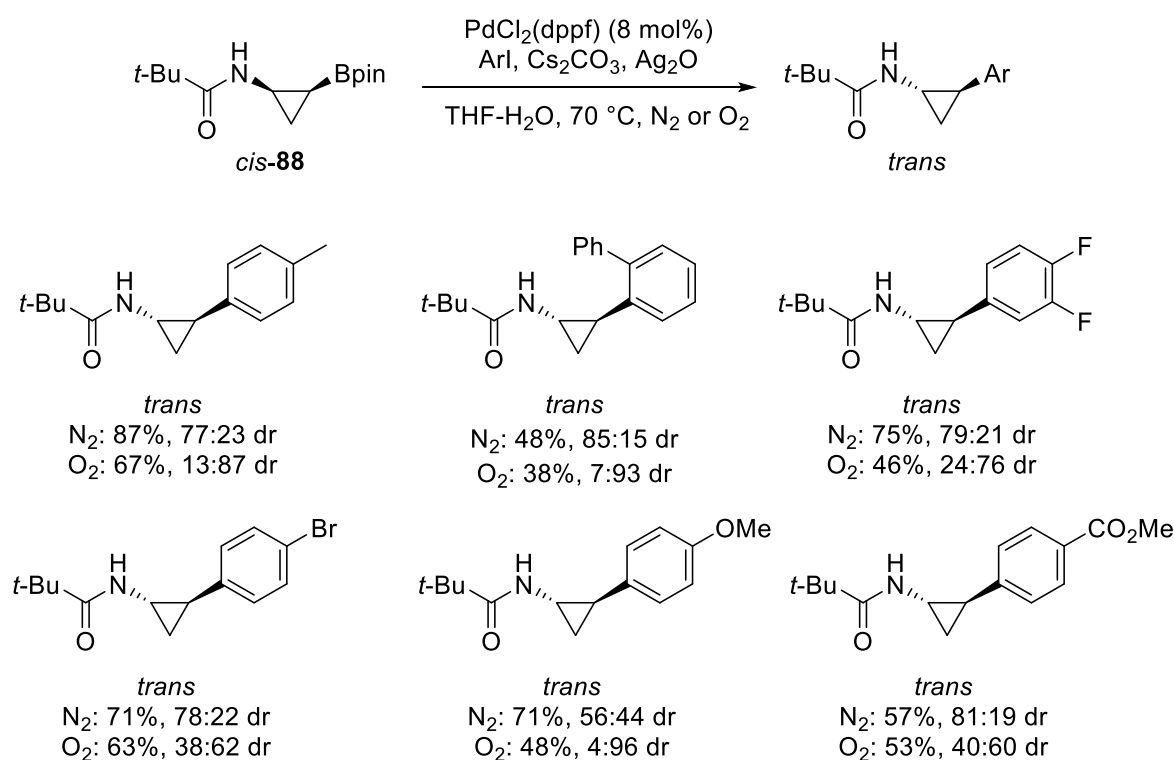
A catalytic system that enabled very low-loading cyclopropyl cross-couplings was reported by Doucet and co-workers.¹⁶² Using $[\text{Pd}(\text{allyl})\text{Cl}]_2$ and in-house developed tetraphosphine Tedicyp **87** in a 2:1 ratio, cross-coupling of cyclopropyl boronic acid to a variety of aryl and

heteroaryl bromides proceeded in good to excellent yields using 0.1-0.25 mol% loading of their catalyst (Scheme 2.26). Notably, this methodology could be applied to aryl chlorides by increasing the catalyst loading to 0.25-0.4 mol%. Despite the low loadings utilised by this methodology, the five-step sequence to access tetraphosphine **87** and high temperature requirements undermine its appeal.



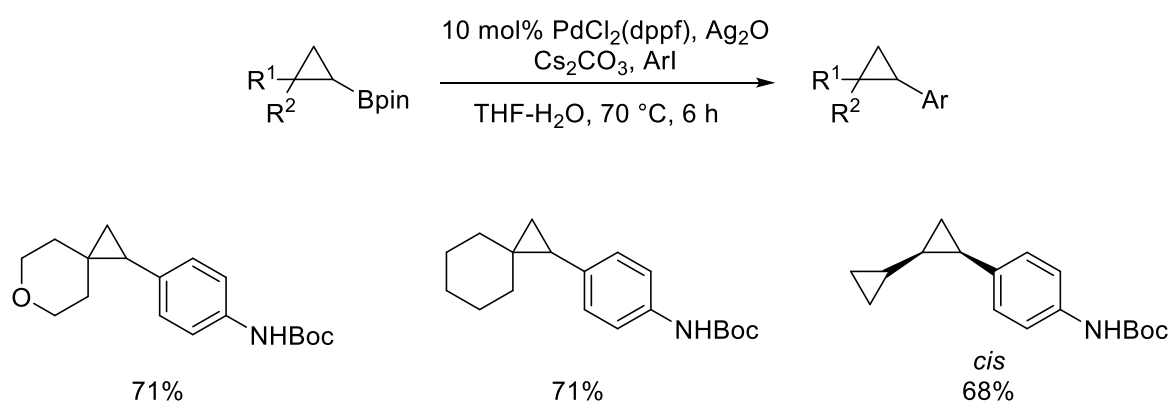
Scheme 2.26

Pinacol boronates (Bpin) are one of the most used compounds in Suzuki-Miyaura cross-couplings due to their easier handling and higher stability than boronic acids.¹⁶³ In 2015, Itami and co-workers reported the cross-coupled of *N*-substituted cyclopropyl pinacol boronate **88** with diverse aromatic and heteroaromatic bromides using $\text{PdCl}_2(\text{dppf})$ alongside Ag_2O and Cs_2CO_3 (Scheme 2.27).¹⁶⁴ Of note, it was found that use of Ag_2O , which is hypothesised to speed up the transmetallation process, was essential to obtain the coupled products in good yields. However, it was also discovered that the cross-coupling produced a mixture of diastereomers where the *trans* isomer was preferred under N_2 atmosphere and the *cis* under O_2 atmosphere. Further investigation revealed that this was due to the epimerization of the C-N bond *via* an unknown mechanism, although the cross-coupling itself proceeded in a completely stereoretentive manner. Furthermore, the problem with C-N bond isomerisation was not observed in a separate work in 2006 by Solduga and co-workers who used a phthalimide protecting group coupled with an alternative boronic ester.¹⁶⁵



Scheme 2.27

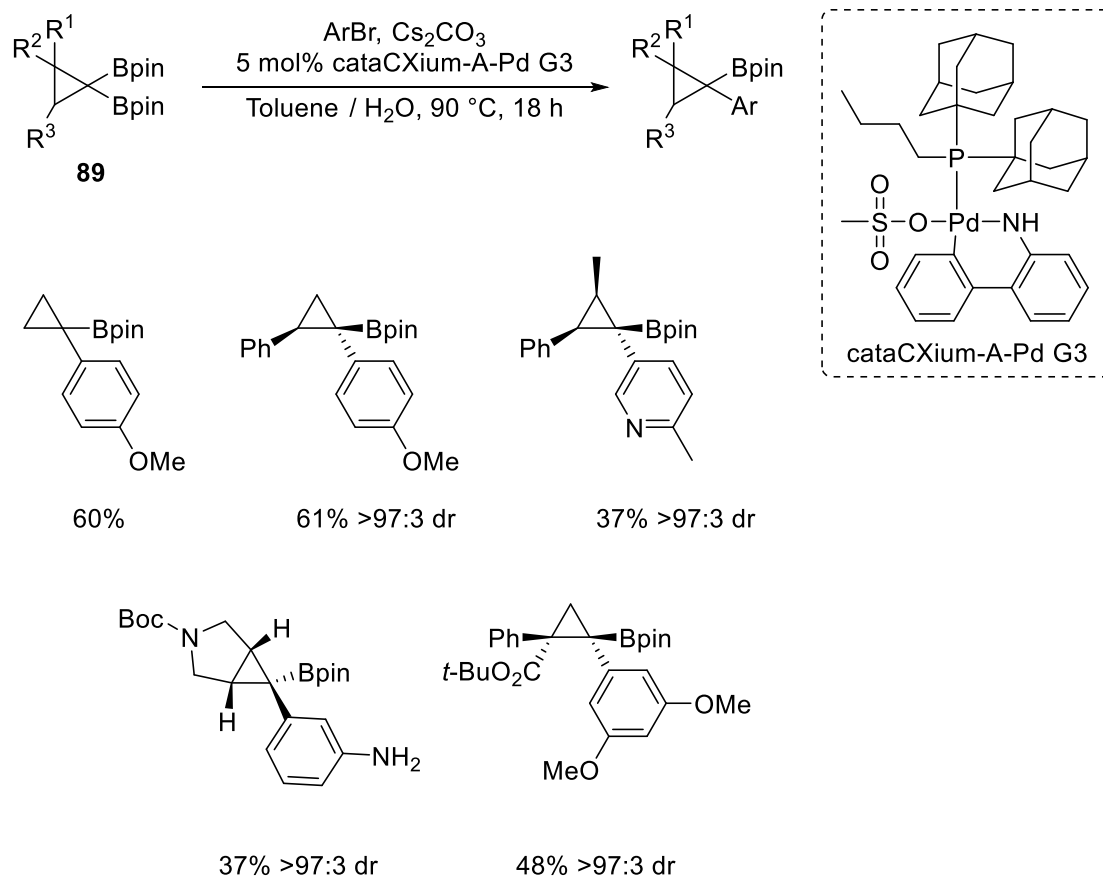
In 2017, Talbot and co-workers¹³⁴ utilised the same catalytic system (10 mol% PdCl₂(dppf) alongside Ag₂O and Cs₂CO₃) to couple diverse cyclopropyl pinacol boronates to a small set of aryl bromides (Scheme 2.28). Of note, without the adjacent N atom, no epimerization was observed.



Scheme 2.28

Alternative catalytic systems with the use of Buchwald-type phosphines SPhos¹⁶⁶, XPhos¹⁶⁷ and RuPhos¹⁶⁸ have also been reported in the cross-coupling of cyclopropyl pinacol boronates. However, a ligand that has recently received increased attention is cataCXium A. In 2018, Harris and co-workers¹¹¹ described the diastereoselective Suzuki-Miyaura cross-

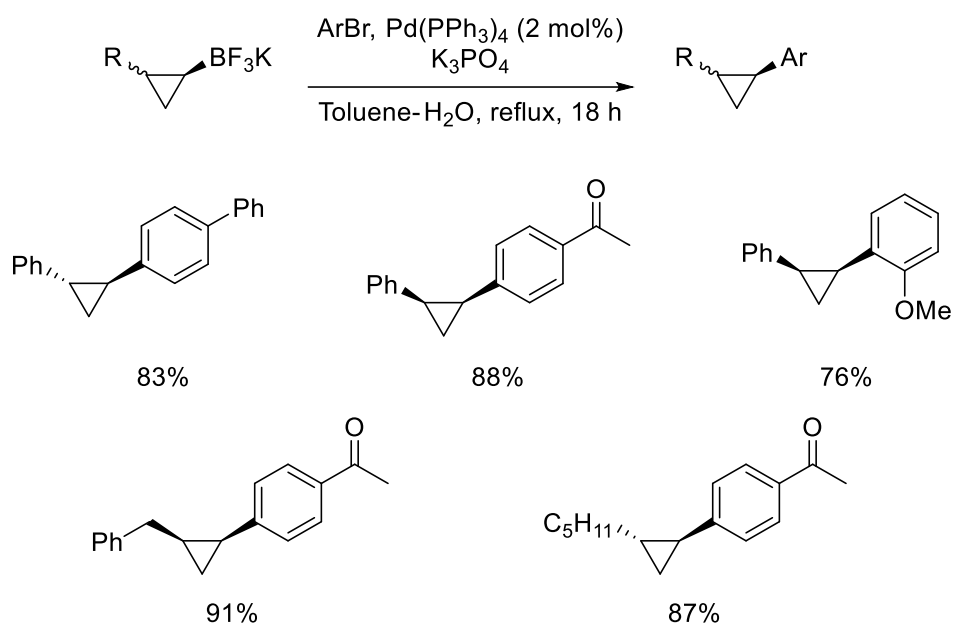
coupling of geminal bis-boronates **89**. After extensive optimisation, it was found that use of 5 mol% cataCXium A Pd G3 in the presence of Cs_2CO_3 allowed for cross-coupling to occur in only the least sterically-hindered pinacol boronate with a variety of aromatic and heteroaromatic bromides to give monoarylated cyclopropanes in good yields and diastereoselectivities (Scheme 2.29).



Scheme 2.29

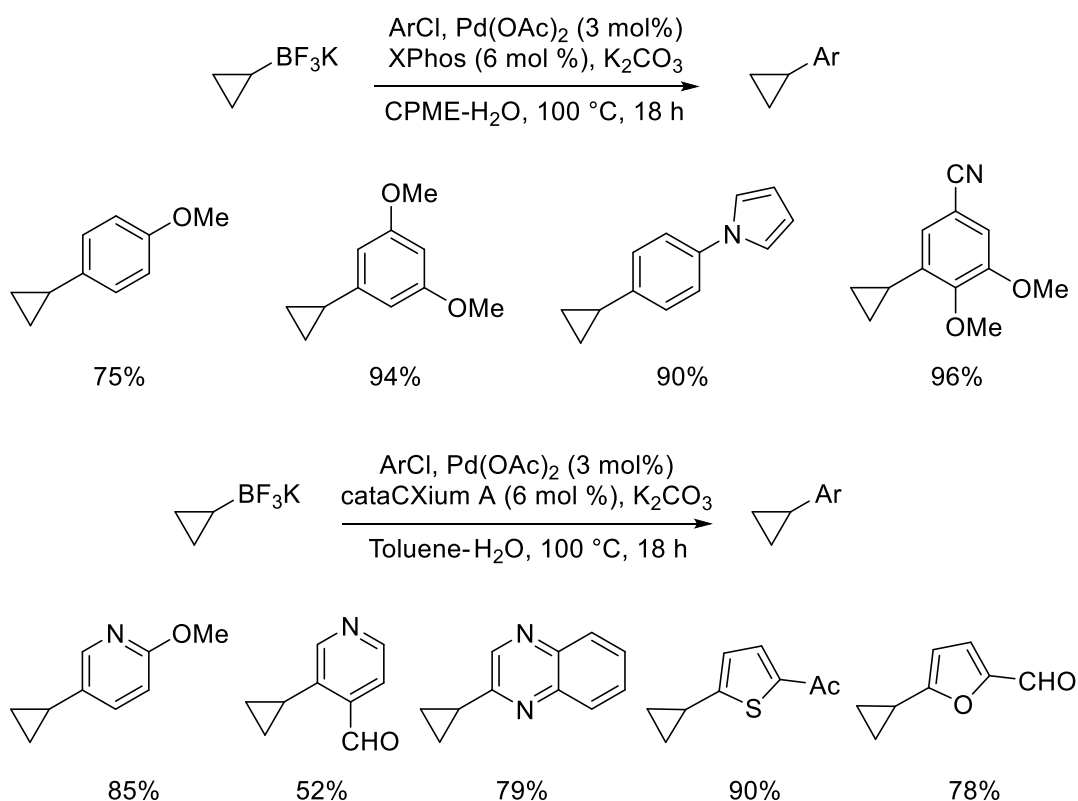
In addition to boronic acids, several other organoboron compounds can be used in Suzuki-Miyaura cross-coupling. Among these, potassium trifluoroborate (BF_3K) salts, introduced by Molander,¹⁶⁹ have gathered considerable interest. Trifluoroborate salts are typically free-flowing solids and are stable to air and moisture which makes them convenient for handling and storage. The trifluoroborate group can be hydrolysed *in situ* under aqueous conditions to generate the boronic acid which participates in the cross-coupling. The rate of hydrolysis for the BF_3K group has been shown to depend on multiple factors such as pH, the attached organic group and the reaction vessel shape, material and size as well as the stirring rate.¹⁷⁰ Thus, reactions involving potassium trifluoroborate salts often require extensive optimisation.

In 2004, Deng and co-workers reported the first synthesis of cyclopropyl BF_3K salts and their use in Suzuki-Miyaura cross-coupling.¹⁷¹ Despite finding several suitable conditions for the cross-coupling of cyclopropyl potassium trifluoroborates using a variety of Pd(II) sources and bases, use of 2 mol% $\text{Pd(PPh}_3)_4$ and K_3PO_4 in toluene gave sufficiently good results while keeping reaction costs low. In this manner, several cyclopropyl BF_3K substrates were successfully coupled to aryl bromides in good to excellent yields (Scheme 2.30). With examples of both *cis* and *trans*-trifluoroborates examined, it was confirmed that the Suzuki-Miyaura cross-coupling of cyclopropyl organoboron compounds proceeds stereospecifically with retention of configuration. A similar example was published in 2005 by Fournier and co-workers,¹⁷² where 1,2,3-trisubstituted cyclopropyl trifluoroborates were coupled to aryl bromides using 3 mol% Pd(OAc)_2 and 6 mol% (biphenyl) PCy_2 as a catalyst system. However, the examined scope was limited.



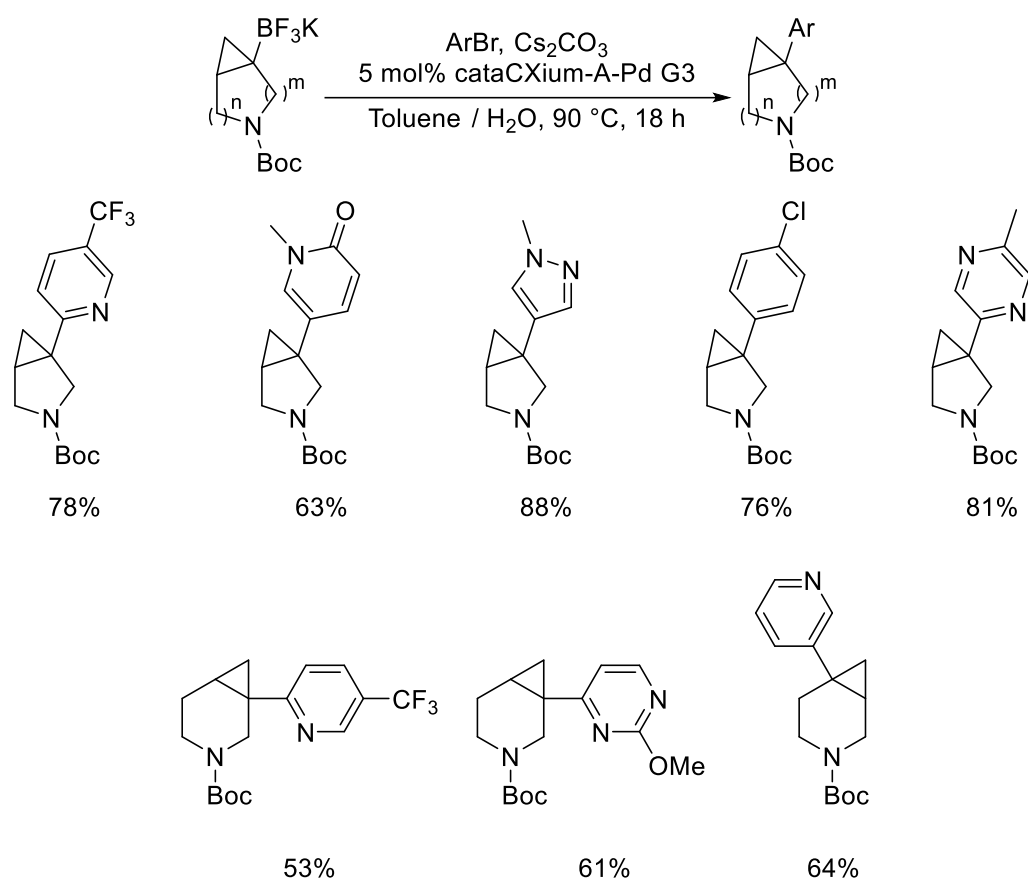
Scheme 2.30

In 2008, Molander and co-workers reported a methodology for the cross-coupling of cyclopropyl and cyclobutyl BF_3K substrates to aryl chlorides.¹⁷³ For the cross-coupling of cyclopropyl BF_3K , 2 mol% Pd(OAc)_2 in combination with 6 mol% XPhos worked as the best catalytic system in conjunction with K_2CO_3 . However, it was found that with heteroaryl chlorides, 3 mol% cataCXium A and Cs_2CO_3 provided significantly better results compared to the XPhos- K_2CO_3 combination (Scheme 2.31). In subsequent work, suitable ligands that allowed cross-couplings to aryl mesylates¹⁷⁴ and benzyl chlorides were identified.¹⁷⁵



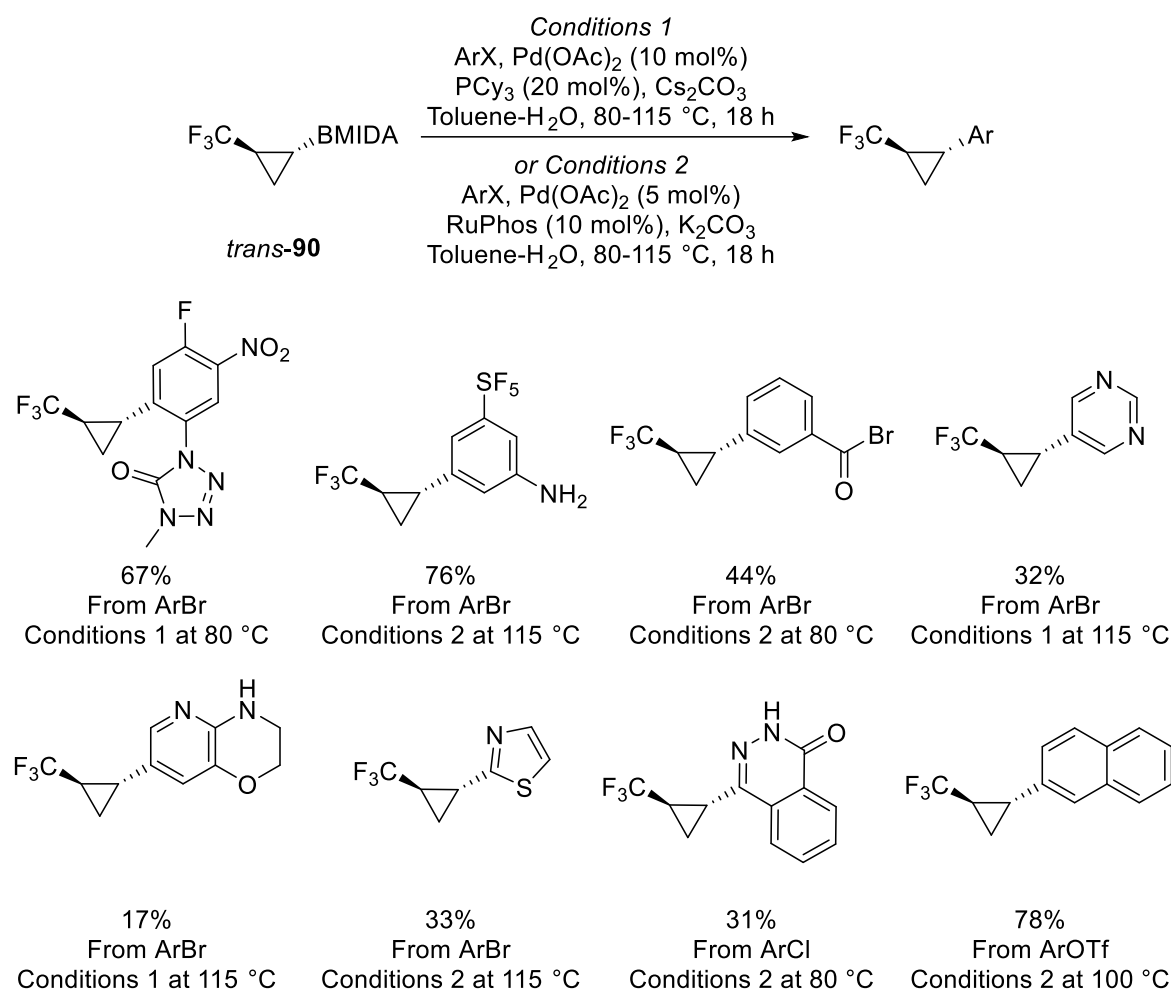
Scheme 2.31

During Harris and co-workers¹¹¹ studies on potassium trifluoroborate building blocks presented in Section 2.3.1 (see Scheme 2.10), a range of Suzuki-Miyaura cross-coupling examples was explored to generate a small library of arylated compounds. Following optimisation, it was found that use of 5 mol% pre-catalyst cataCXium-A-Pd G3 and Cs_2CO_3 in toluene- H_2O allowed for the effective cross-coupling of various aryl bromides (Scheme 2.32). Using this same catalytic system, Grygorenko and co-workers¹⁰¹ cross-coupled a variety of substituted cyclopropyl BF_3K substrates to aromatic and heteroaromatic aryl bromides. Following this, the methodology was applied for the synthesis of a library of sp^3 -enriched compounds.¹¹⁸ Sterically congested cyclopropyl trifluoroborates have also been successfully coupled with the use of $\text{PdCl}_2(\text{dppf})$ albeit in diminished yields.¹²¹



Scheme 2.32

Extensive use of MIDA boronates in cyclopropyl Suzuki-Miyaura cross-coupling was reported in 2013 by Singh and co-workers.¹⁷⁶ It was found that the use of either 5 mol% Pd(OAc)₂, 10 mol% PCy₃ and Cs₂CO₃ or 10 mol% Pd(OAc)₂, 20 mol% RuPhos and K₂CO₃ allowed for the stereospecific cross-coupling of cyclopropyl MIDA boronate *trans*-**90** to a wide variety of aromatic and heteroaromatic aryl chlorides, bromides, iodides and triflates (Scheme 2.33). This methodology showcases a very ample scope between the two catalytic systems. However, the authors do not give a reasoning for the selection of conditions in function of the substrate with the temperature being varied from 80 to 115 °C between substrates without an apparent trend. With this set of conditions and using an increased Pd loading of 15 mol% (30 mol% PCy₃), Singh and co-workers reported the synthesis of tetrazolones as protein kinase C inhibitors in a patent.¹⁷⁷



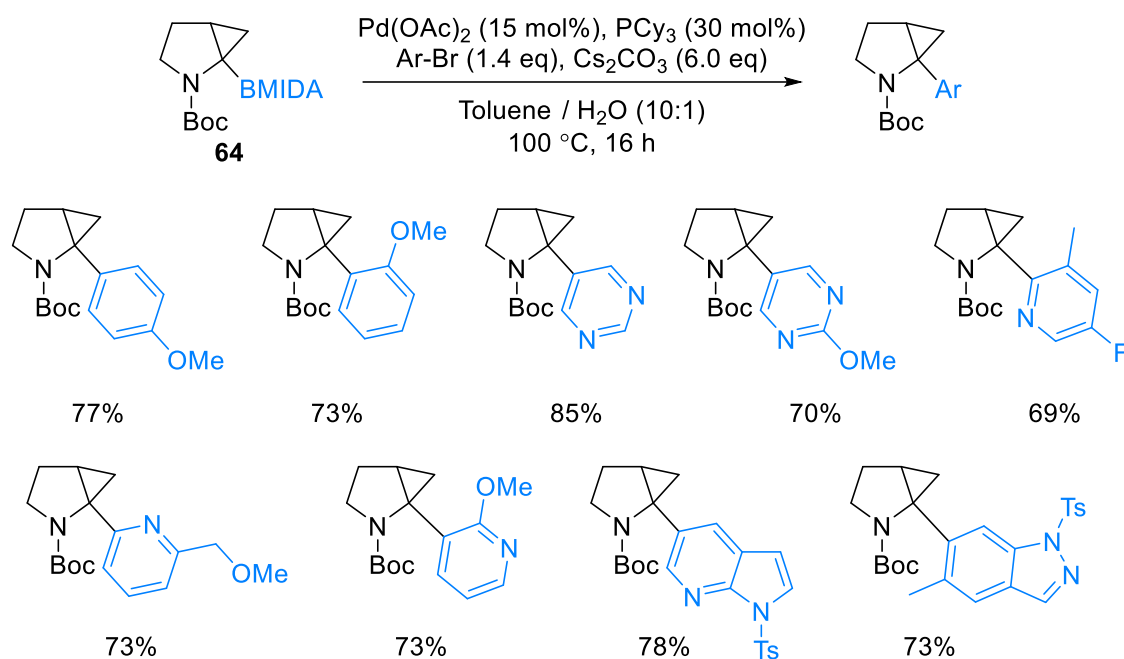
Scheme 2.33

Alternative B-containing compounds such as 9-BBN¹⁷⁸ and propylene glycol boronic ester¹⁰⁴ have also been successfully used in the Suzuki-Miyaura cross-coupling of cyclopropyl boronate albeit with significantly less prevalence.

In conclusion, while the Suzuki-Miyaura cross-coupling of cyclopropyl organoboron compounds is well preceded, the use of MIDA boronates is less well known. From the exhibited examples, Pd(OAc)₂ was a popular choice of pre-catalyst with a diverse set of monophosphine ligands such as PCy₃, SPhos, RuPhos, XPhos and cataCXium A. Use of bisphosphine ligands such as dppf was also observed, particularly for pinacol boronates. Finally, the Pd loading was usually high, between 3-15 mol% except for specially designed ligands which allowed for lower catalyst loadings.

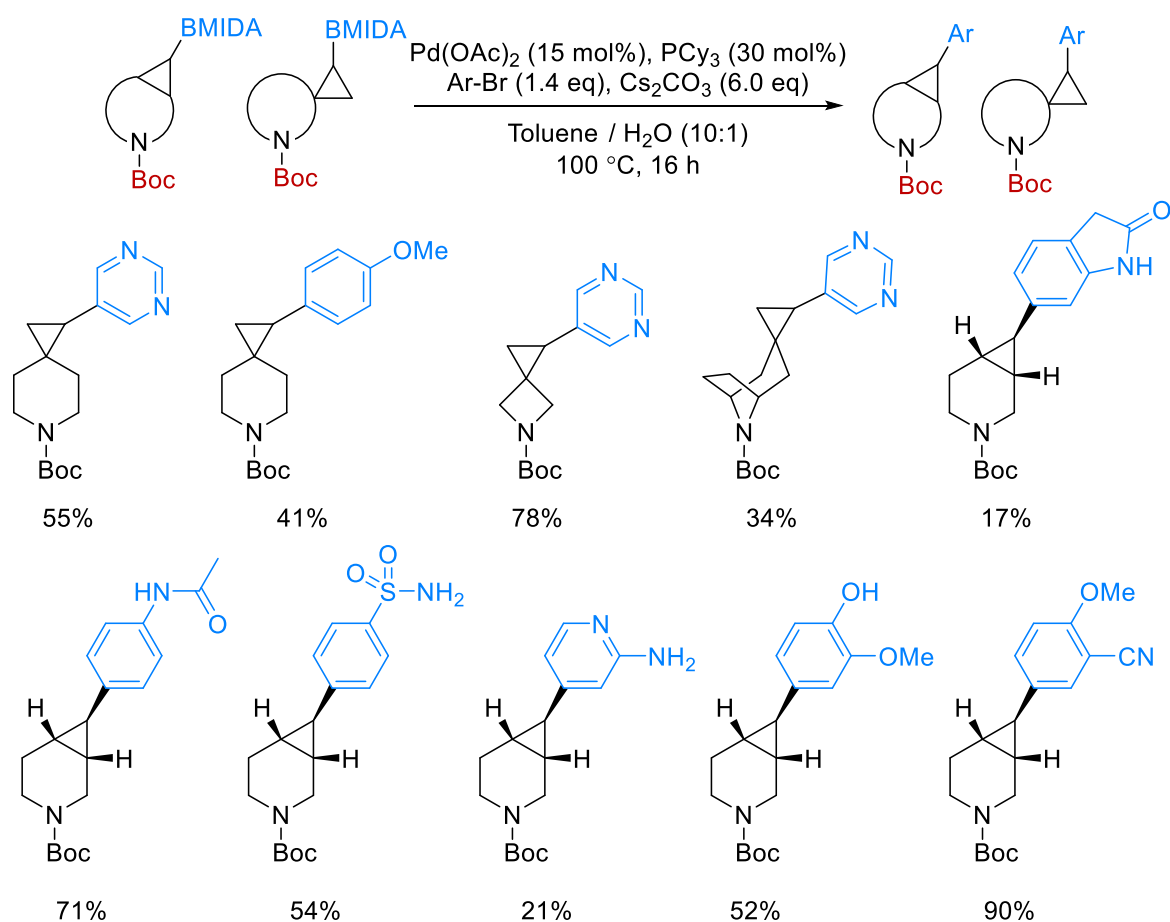
2.5.2 Previous Examples of Cross-Coupling of Cyclopropyl MIDA Boronates in the O'Brien Group

Previously in the O'Brien group,^{146, 147} an adequate set of conditions for the Suzuki-Miyaura cross-coupling of cyclopropyl MIDA boronates such as **64** was identified. This set of conditions, based on the work by Singh and co-workers introduced in section 2.5.1 (see Scheme 2.23),¹⁷⁷ and work by De Man and co-workers,¹⁷⁹ utilised 15 mol% Pd(OAc)₂, 30 mol% PCy₃ and 6 eq Cs₂CO₃ in toluene-H₂O and were successfully applied to a variety of aromatic and heteroaromatic bromides (Scheme 2.34).



Scheme 2.34

This same set of conditions was also utilised in initial studies for some of the O'Brien building blocks, including piperidine **65**, azetidine **66**, tropane *exo*-**68** and piperidine *exo*-**69**. Previous results are shown in Scheme 2.35. However, while these conditions proved adequate for the cross-coupling with a variety of aromatic and heteroaromatic aryl bromides on these substrates, concerns about the high Pd loading led to the conclusion that further optimisation was required.



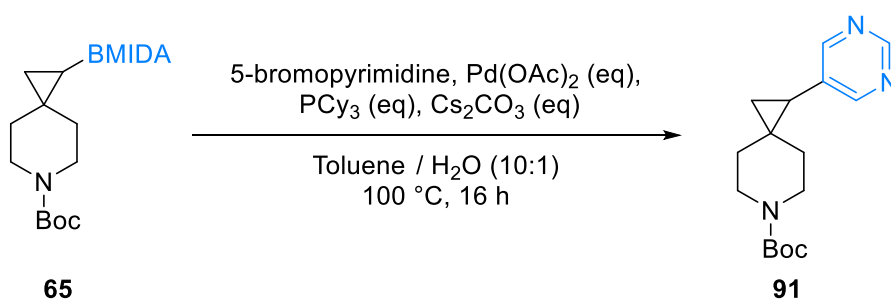
Scheme 2.35

2.5.3 Suzuki-Miyaura Cross-Coupling of Cyclopropyl MIDA Boronate Building Blocks

Initially, the plan was to focus on the cross coupling of spiropiperidine building block **65** with a view to identifying conditions that used a lower Pd loading. The cross-coupling with 5-bromopyrimidine was selected as a representative medicinal chemistry relevant aryl bromide. To start, a reaction was performed using 15 mol% $\text{Pd}(\text{OAc})_2$ and 30 mol% PCy_3 which gave cyclopropyl pyrimidine **81** in 55% yield (Table 2.2, Entry 1). Use of 10 mol% $\text{Pd}(\text{OAc})_2$ and 20 mol% PCy_3 gave cyclopropyl pyrimidine **81** in 30% yield (Entry 2) while further lowering the $\text{Pd}(\text{OAc})_2$ loading to 5 mol% gave cyclopropyl pyrimidine **81** in 59% yield (Entry 3). With this result being comparable to that obtained using 15 mol% $\text{Pd}(\text{OAc})_2$ loading, the conclusion that the result using 10 mol% $\text{Pd}(\text{OAc})_2$ (Entry 2) could be considered an outlier was reached. Performing the cross-coupling using a 2.5 mol% Pd loading had no detrimental effect on the yield, giving cyclopropyl pyrimidine **81** in 62%

yield (Entry 4). Despite these results, it was evident that the reaction could be further optimised as incomplete hydrolysis of the MIDA boronate and recovery of 13-19% of the MIDA boronate starting material **65** was being observed. It has been observed by Lloyd-Jones and Burke,¹⁸⁰ that hydrolysis of MIDA boronates into the reactive boronic acids is highly dependent on base concentrations. Thus, it was decided to repeat the lower 5 and 2.5 mol% Pd(OAc)₂ loading reactions with 3 eq of base. Gratifyingly, this gave cyclopropyl pyrimidine **81** in 70% and 68% yield respectively (Entries 5 and 6). We hypothesise that, similarly to the observations by Lloyd-Jones and coworkers,¹⁸⁰ the lower conversions in the hydrolysis of the MIDA boronates in entries 1-4 are likely due to partial dehydration of the organic layer caused by excess Cs₂CO₃ in the cross-coupling mixture slowing the hydrolysis. Ultimately, due to more consistent higher yields across other substrates being investigated in the group,¹⁵⁰ the conditions utilising 5 mol% Pd(OAc)₂, 10 mol% PCy₃ and 3 eq Cs₂CO₃ were selected as our standard cross-coupling conditions.

Table 2.2 – Optimization of the Suzuki-Miyaura cross-coupling of building block **65**

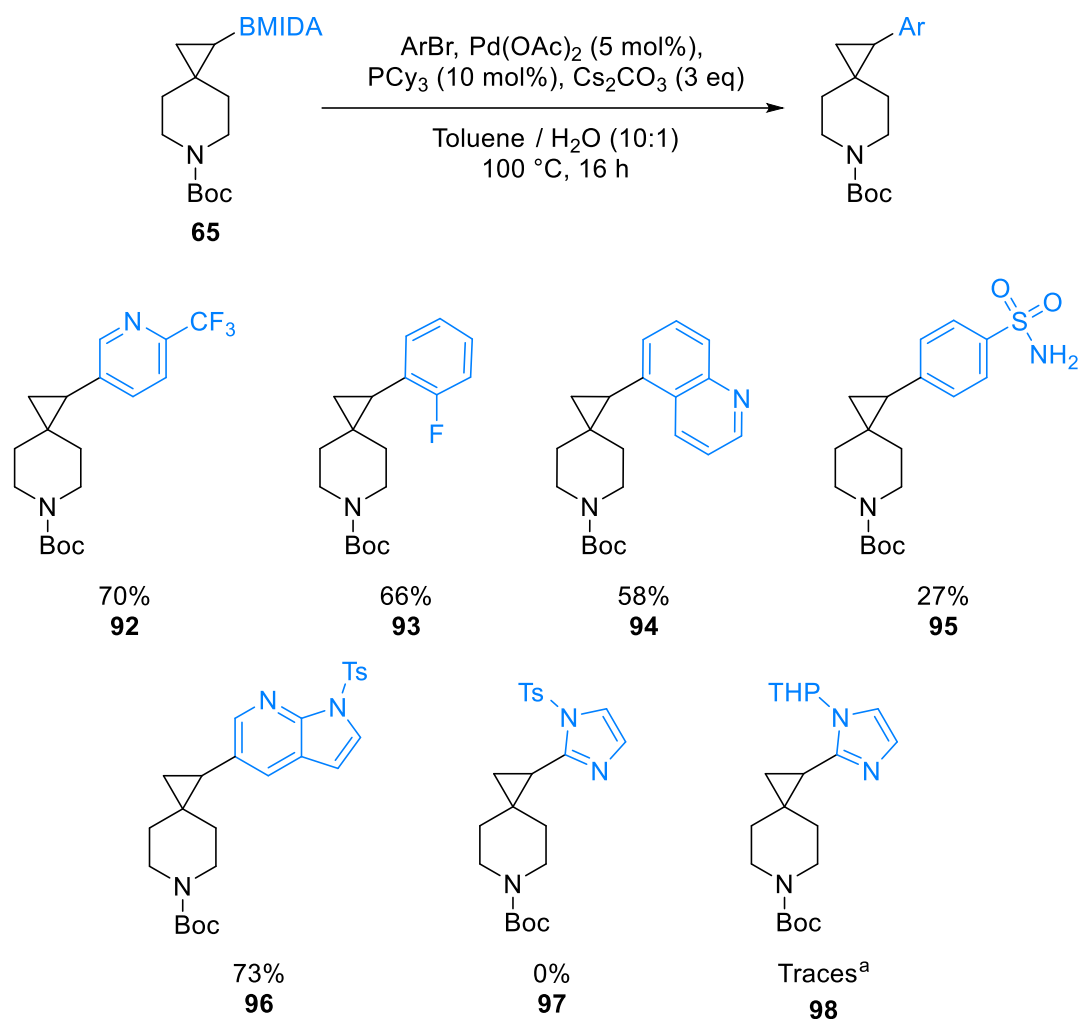


Entry	Pd(OAc) ₂ (mol%)	PCy ₃ (mol%)	Cs ₂ CO ₃ (eq.)	Yield (%) ^a	SM recovery (%) ^a
1	15	30	6	55	17
2	10	20	6	30	13
3	5	10	6	59	19
4	2.5	5	6	62	13
5	5	10	3	70	0
6	2.5	5	3	68	0

^a % yield after chromatography

With this result in hand, we moved on to explore the scope of aryl bromides for the Suzuki-Miyaura cross-coupling in 3-D building blocks **64-69**. A range of medically relevant aryl and heteroaryl bromides, partly inspired by Harris and co-workers from Pfizer, was selected.^{109, 111} Initially, the scope was explored using spiroperidine 3-D building block **65**.

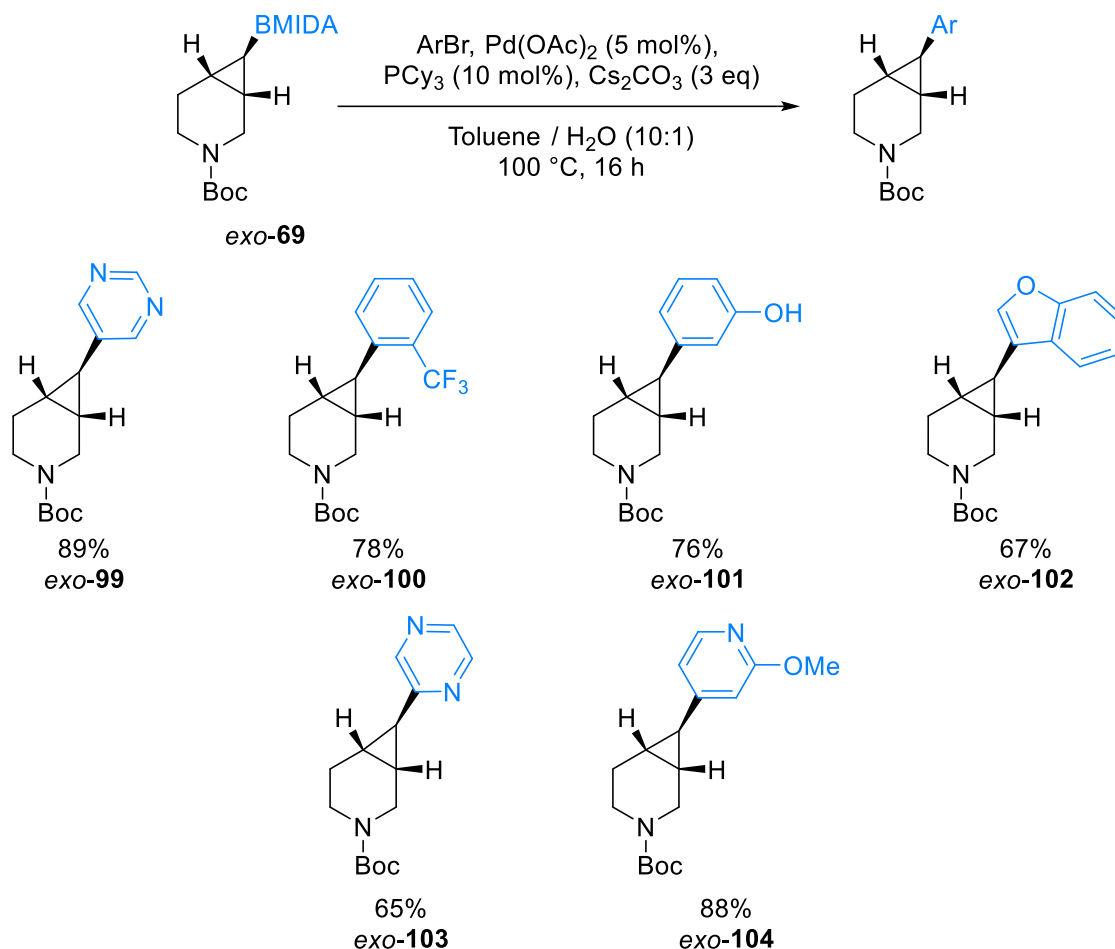
Pleasingly, arylated spiropiperidines **92-94** and **96** were obtained in good yields (Scheme 2.36). However, using 4-bromobenzene sulfonamide to give arylated spiropiperidine **95**, a lower yield (27%) was observed. Use of *N*-Ts protected imidazole gave none of desired arylated spiropiperidine **97**, but evidence of tosyl removal from the imidazole coupled product was observed. Thus, another attempt was made changing the nitrogen protecting group to a 2-tetrahydropyranyl (THP)¹⁸¹ group but, unfortunately, only traces of arylated spiropiperidine **98** were observed by mass spectrometry.



Scheme 2.36 – ^{a)} by HRMS of the crude product

With the scope for spiropiperidine **65** examined, 3,4-fused piperidine 3-D building block *exo*-**69** was explored next. Using 5-bromopyrimidine as a control reaction, arylated fused piperidine *exo*-**99** was obtained in 89% yield (Scheme 2.37). Likewise, arylated fused piperidines *exo*-**100-104** were obtained in good to excellent yields. The aryl bromides contain both electron rich and deficient aromatic and heteroaromatic systems. We hypothesise that reduced steric hindrance around the C-B bond in comparison with

spiropiperidine 3-D building block **65** led to the generally higher yields in the cross-coupling reactions.



Scheme 2.37

Notably, the Suzuki-Miyaura cross-coupling of fused piperidine **exo-69** proceeded in a stereospecific fashion with overall retention of configuration. This was evidenced by the generation of diastereomerically pure products, NMR spectroscopic data and X-ray crystallographic analysis of a methanesulfonamide derivative of piperidine **exo-99**.¹⁴⁵ In particular, ^1H NMR spectroscopic analysis of arylated piperidines **exo-99**, **exo-102** and **exo-104** showed that ^3J values of the CHAr protons in the cyclopropane ring were in the 4.5-5.0 Hz range (Figure 2.8). These ^3J values are indicative of *trans* cyclopropane protons based on the observations of Hutton and Schaefer¹⁸² who reported ^3J values in the range of 2.0-7.0 Hz for *trans*-cyclopropyl protons and 7.1-11.0 Hz for ^3J coupling in *cis*-cyclopropane protons.

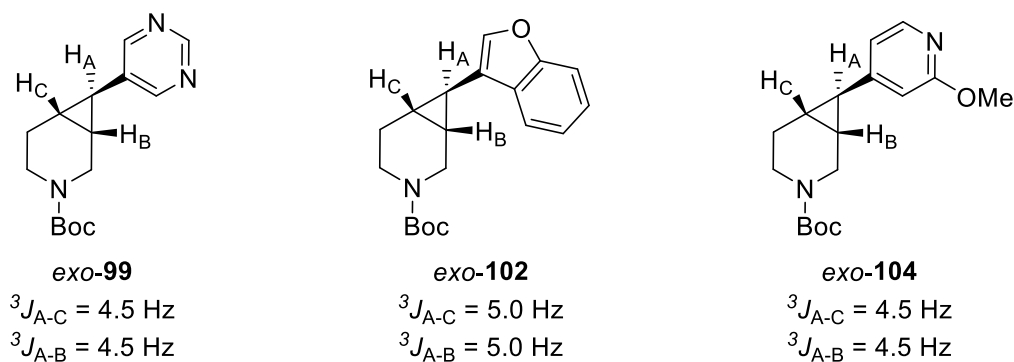
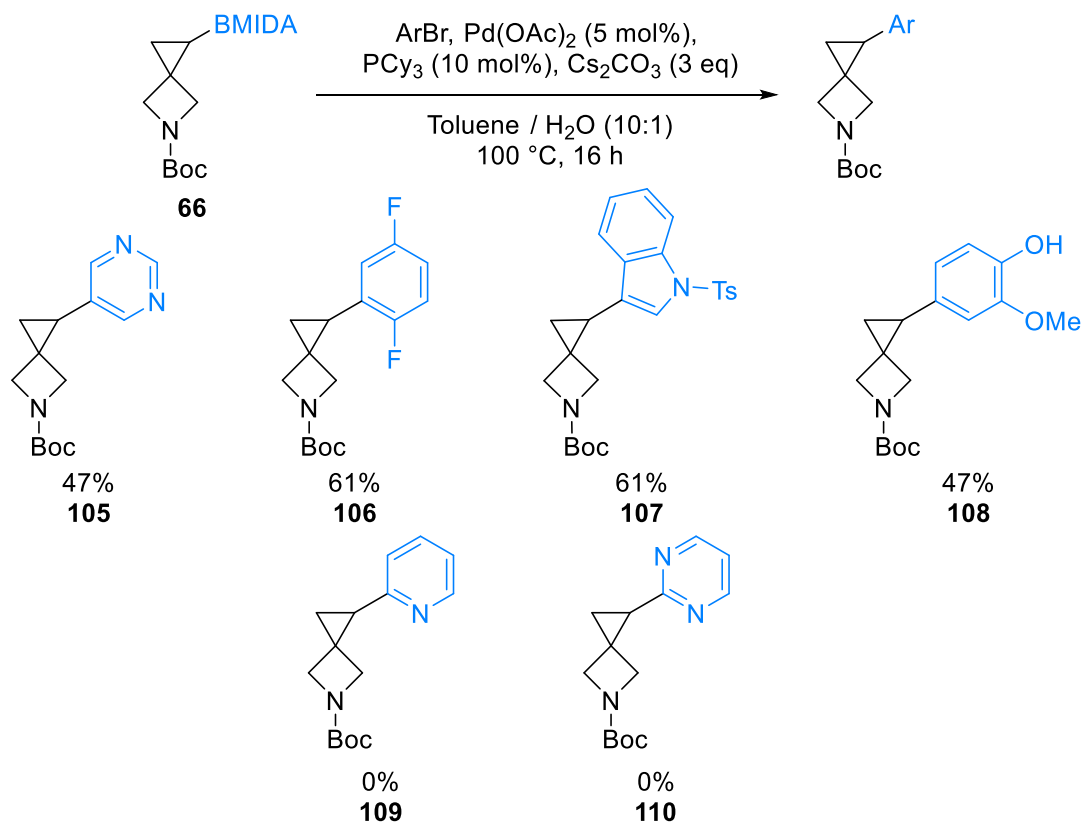


Figure 2.8 – ^3J values for arylated piperidines **exo-99**, **exo-102** and **exo-104**.

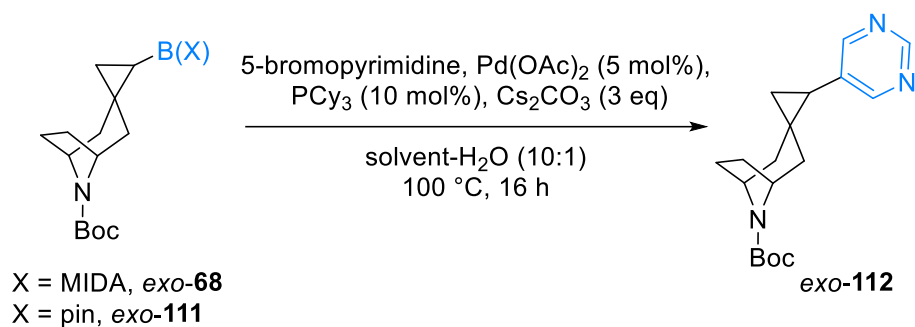
Next, cross-coupling using spirocyclic azetidine 3-D building block **66** was explored. Use of 5-bromopyrimidine gave arylated spirocyclic azetidine **105** in 47% yield (Scheme 2.38). Similarly, arylated spirocyclic azetidines **106–108** were obtained in good yields. On the other hand, although use of 2-bromopyridine afforded arylated azetidine **109** according to HRMS and ^1H NMR spectroscopy of the crude reaction product, due to poor solubility of the product in organic solvents, it could not be isolated. Finally, coupling to 2-bromopyrimidine failed to give arylated azetidine **110**; there were no traces of product by either HRMS or ^1H NMR spectroscopy of the crude reaction mixture.



Scheme 2.38

With these results in hand, we moved on to the Suzuki-Miyaura cross-coupling using tropane-derived 3-D building block *exo*-**68**. However, when attempting the reaction using 5-bromopyrimidine with 5 mol% Pd(OAc)₂, arylated spirocyclic tropane *exo*-**112** was isolated in only 29% yield with 50% of unreacted cyclopropyl MIDA boronate *exo*-**68** recovered (Table 2.3, Entry 1). We hypothesised that poor solubility of the substrate was responsible for its poor reactivity (and lack of hydrolysis to the boronic acid for reaction), so a solvent change for the Suzuki-Miyaura cross-coupling was proposed. A review on solvent effects in Pd-catalysed cross-coupling reactions¹⁵⁹ highlighted dioxane as a possible alternative solvent. Thus, use of the standard Suzuki-Miyaura conditions in 1,4-dioxane-H₂O was explored but this reaction gave no desired product by HRMS or ¹H NMR spectroscopy despite cyclopropyl MIDA boronate *exo*-**68** being completely consumed (Entry 2). Based on literature precedent, 10:1 mixtures of toluene and each of DMF or MeCN were explored but they failed to give either product or unreacted starting material (Entries 3 and 4). Use of a 10:1 mixture of toluene and dioxane gave arylated tropane *exo*-**112** in 31% yield and unreacted cyclopropyl MIDA boronate *exo*-**68** in 10% yield (Entry 5). Finally, use of the corresponding cyclopropyl pinacol boronate derivative *exo*-**111** was explored in the hope that it would be a more soluble substrate. There was some success and reaction of pinacol boronate *exo*-**111** in toluene-H₂O afforded arylated tropane *exo*-**112** in 39% yield with 20% of unreacted boronate *exo*-**111** recovered (Entry 6).

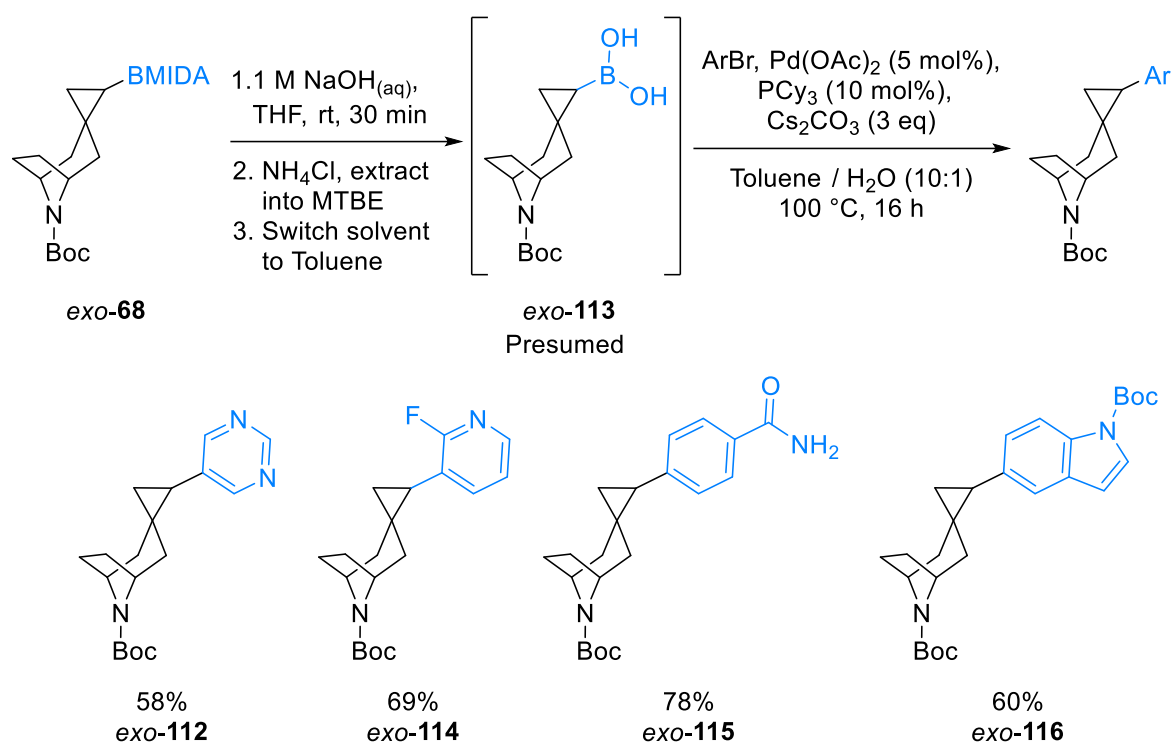
Table 2.3 – Optimisation of the Suzuki-Miyaura cross-coupling of tropane building block



Entry	(X)	Solvent	Yield (%) ^a	SM Recovery (%) ^a
1	MIDA	Toluene	29	50
2	MIDA	1,4-Dioxane	0	0
3	MIDA	Toluene / DMF 10:1	0	0
4	MIDA	Toluene / MeCN 10:1	0	0
5	MIDA	Toluene / dioxane 10:1	31	10
6	pin	Toluene	39	20

^a)% yield after chromatography

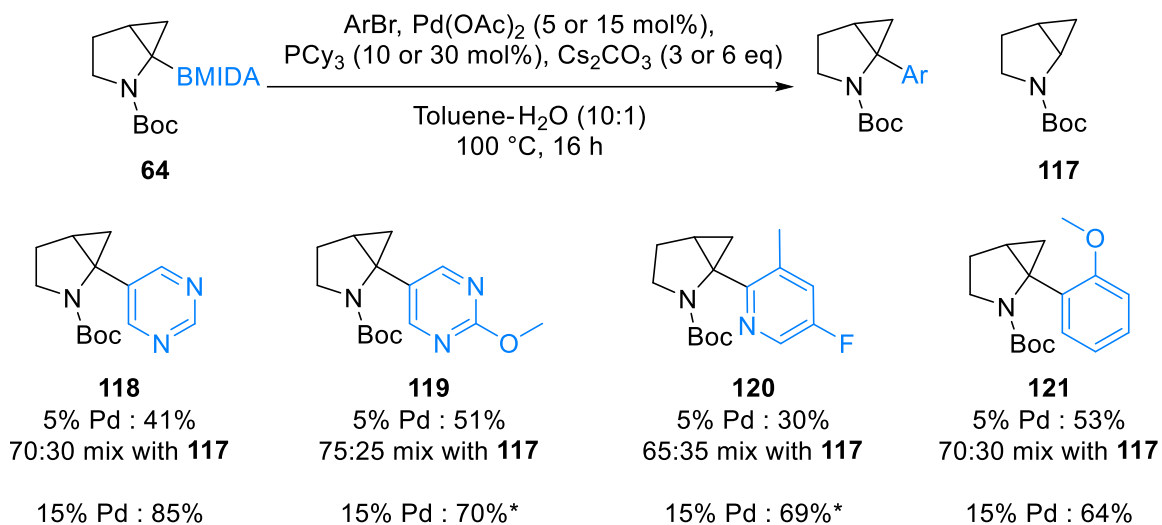
With these slightly disappointing results, the corresponding pre-formed boronic acid was explored. In 2019, Burke and co-workers reported the *ex situ* basic hydrolysis of an alkyl MIDA boronate and its subsequent use in a Suzuki-Miyaura cross-coupling reaction.¹⁸³ Following this approach, cyclopropyl MIDA boronate *exo*-**68** was hydrolysed using 1 M NaOH_(aq) in THF, followed by quenching with saturated NH₄Cl_(aq) and extraction into MTBE to presumably give boronic acid *exo*-**113**. However, since we were aware of the solvent dependency of Suzuki-Miyaura reactions, an additional solvent switch into toluene was performed and the presumed boronic acid intermediate was carried on to the cross-coupling reaction (Scheme 2.39). Gratifyingly, this afforded arylated tropane *exo*-**112** in 58% yield and the methodology could be extended to cross-coupling with a variety of aryl bromides to give arylated tropanes *exo*-**114-116** in good yields.



Scheme 2.39

The last 3-D building block to be explored was fused pyrrolidine **64**. Use of the optimised conditions with 5 mol% Pd(OAc)₂ and 5-bromopyrimidine gave arylated pyrrolidine **118** in 41% yield which was isolated as a 70:30 inseparable mixture with protodeborylated product **117** (Scheme 2.40). From previous results in the group,¹⁴⁷ arylated pyrrolidine **118** had been obtained in 85% yield when using a 15 mol% Pd(OAc)₂ loading. Thus, different aryl bromides were explored to see whether this would affect the amount of protodeborylated product **117** obtained and its separation from the desired arylated pyrrolidines. Disappointingly, both arylated pyrrolidines **119** and **120** were obtained in diminished yields of 51% and 30% and as inseparable mixtures with pyrrolidine **117**, in contrast with the results previously obtained in the group. To rule out effects from impurities in the reactants being used, parallel cross-coupling reactions using 2-bromoanisole with both 5 and 15 mol% Pd(OAc)₂ were carried out for comparison purposes. The 5 mol% Pd(OAc)₂ loading afforded arylated pyrrolidine **121** in 53% yield, isolated as a 70:30 mixture with protodeborylated **117** while the reaction carried out using 15 mol% Pd(OAc)₂ gave pure arylated pyrrolidine **121** in 64% yield. This clearly confirmed our suspicion that lower Pd loadings led to increased amounts of protodeborylated pyrrolidine **117** for this substrate. We hypothesise that increased steric hindrance around the C-B bond in cyclopropyl pyrrolidine **64** makes cross-coupling of the boronic acid slower, allowing for protodeborylation to be a competitive side

reaction. As a result, for fused pyrrolidine scaffold **64**, we decided to continue using a 15 mol% Pd(OAc)₂ loading (see Scheme 2.34).

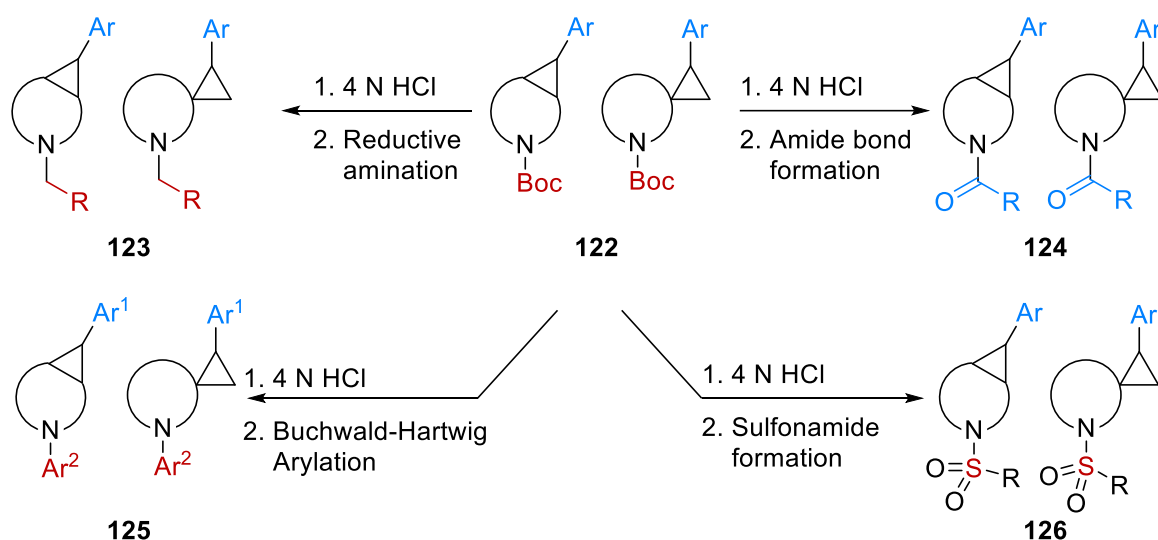


Scheme 2.40

In this manner, the optimisation and scope exploration of the Suzuki-Miyaura cross-coupling functionalisation of cyclopropyl MIDA boronate 3-D building blocks **64-69** was concluded with a wide range of medically-relevant aromatic and heteroaromatic groups being successfully cross-coupled in yields of 27-89%, with a good proportion of high yielding examples. On the other hand, notable exceptions to this success are couplings with imidazole despite a brief exploration in nitrogen protecting groups and the cross-coupling using 2-bromopyrimidine.

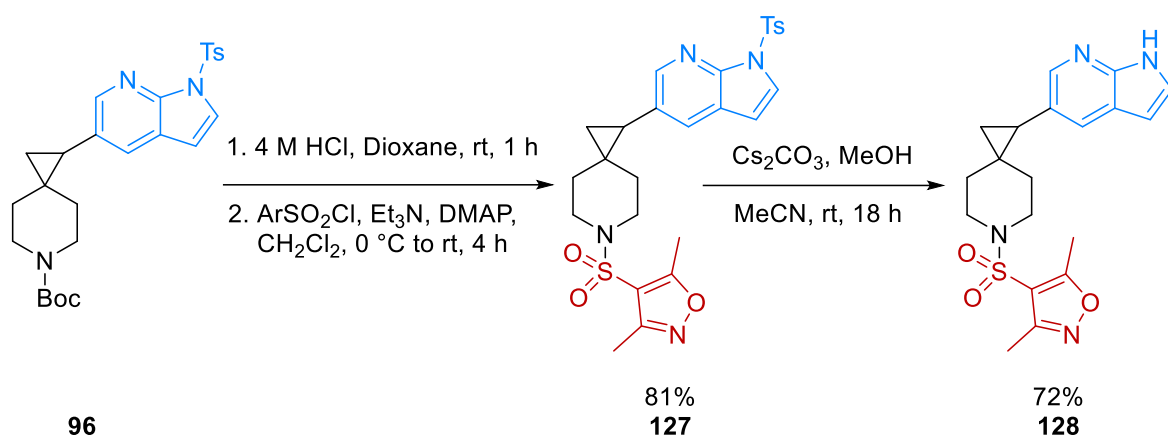
2.6 N-Functionalisation of Arylated 3-D Building Blocks

With the scope of the Suzuki-Miyaura cross-coupling for the designed 3-D building blocks explored, it was desired to showcase a variety of *N*-functionalisation reactions with medicinally relevant groups. It was envisaged that a 3-D building block **122** could be deprotected and the nitrogen functionalised in a variety of ways, such as amide bond formation, sulfonamide formation, reductive amination (S_N2 alkylation), S_NAr and Buchwald-Hartwig arylation to give compounds **123-126** (Scheme 2.41).¹²³



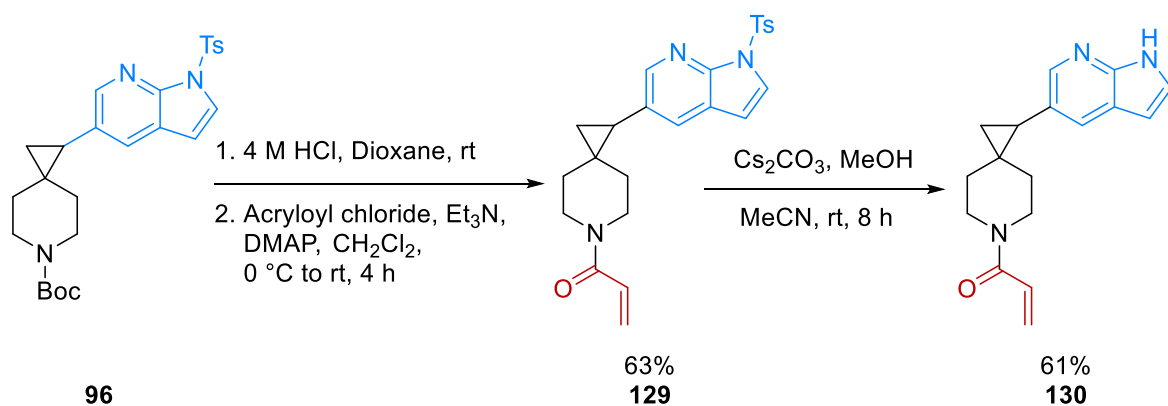
Scheme 2.41

To begin, spirocyclic piperidine **96** was selected since the aza-indole functionality is a known pharmacophore¹⁸⁴ and this would also allow us to demonstrate removal of the tosyl group. As such, removal of the Boc group in arylated spirocyclic piperidine **96** was achieved using 4 N HCl in dioxane and reaction of the so-generated hydrochloride salt with a heterocyclic sulfonyl chloride, Et₃N and DMAP afforded *N*'-Ts sulfonamide **127** in 81% yield. Subsequently, *N*'-Ts deprotection from the heteroaromatic was performed using Cs₂CO₃ and MeOH at rt for 18 h¹⁸⁵ to give sulfonamide **128** in 72% yield (Scheme 2.42). This is exactly the sort of synthetic sequence that, by varying the sulfonyl chloride, could be utilised to rapidly generate a small library of lead-like compounds from an aza-indole fragment hit.



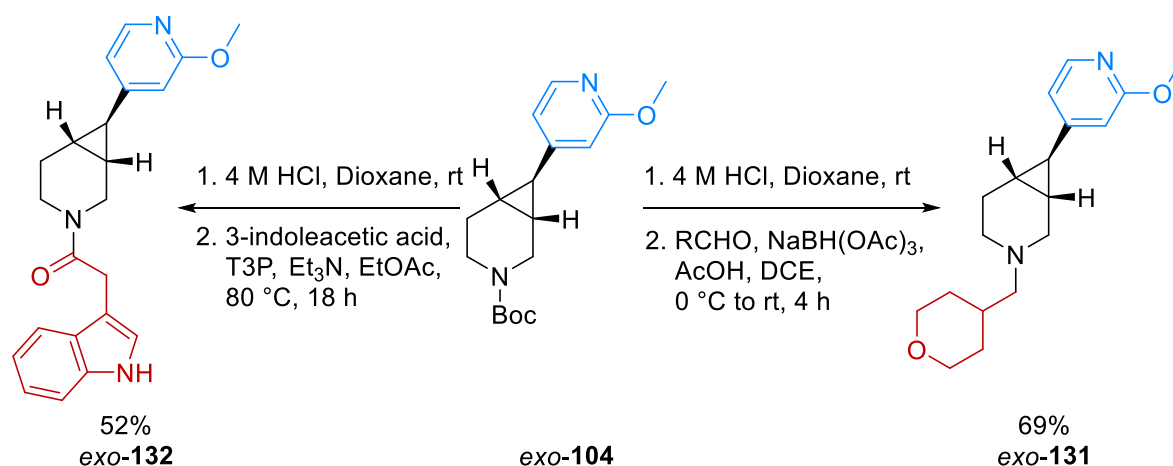
Scheme 2.42

In a similar fashion, spirocyclic piperidine **96** was functionalised in order to form a *N*-acrylamide, which is a commonly encountered covalent warhead.¹⁸⁶⁻¹⁸⁸ Deprotection of the amine in **96** using 4 N HCl in 1,4-dioxane and amidation using acryloyl chloride, Et₃N and DMAP afforded *N*'-Ts acrylamide **129** in 63% yield. Subsequent *N*'-Ts deprotection gave *N*'-H acrylamide **130** in 61% yield (Scheme 2.43).



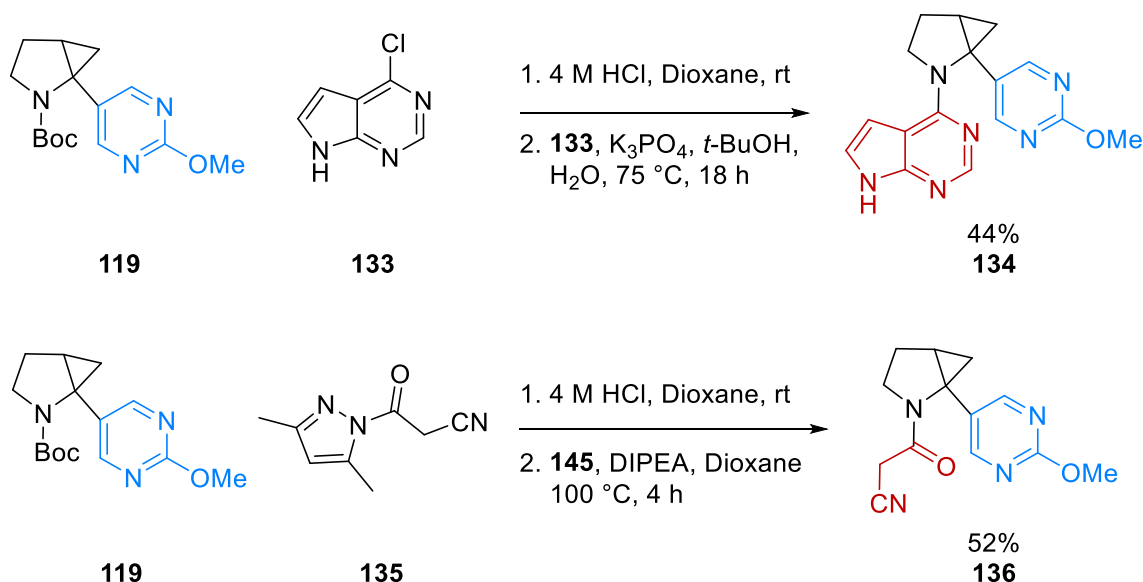
Scheme 2.43

Amidation and reductive amination were explored using cyclopropyl fused piperidine *exo*-**104** containing a methoxy pyridine substituent. Thus, standard Boc group removal was carried out and the HCl salt was submitted to reductive amination conditions (aldehyde, NaBH(OAc)₃ and acid)¹⁸⁹ to afford tetrahydropyranyl amine *exo*-**131** in 69% yield. A separate batch of piperidine *exo*-**104** was deprotected and submitted to amide formation conditions with 3-indoleacetic acid and T3P¹⁹⁰ to give indole acetamide *exo*-**132** in 52% yield (Scheme 2.44).



Scheme 2.44

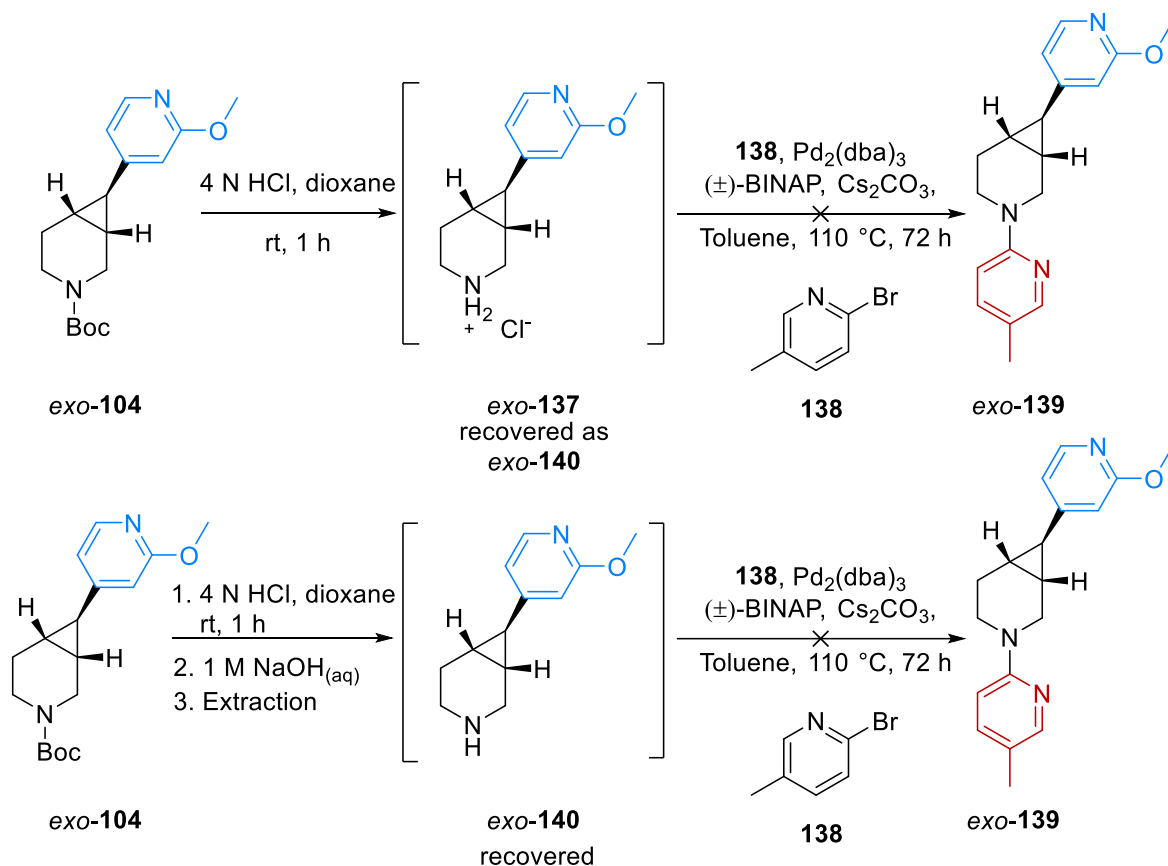
N-Functionalisation was also explored on cyclopropyl fused pyrrolidine **119**. For this scaffold, S_NAr arylation inspired by Inaba and co-workers' recent synthesis of a JAK inhibitor¹⁸⁴ and amidation with a nitrile covalent warhead were carried out. In this manner, pyrrolidine **119** was deprotected and the hydrochloride salt was reacted with aryl chloride **133** and K₃PO₄ at 75 °C to give di-arylated pyrrolidine **134** in 44% yield. Similarly, this hydrochloride salt was reacted with amide **135**, an acylating agent,¹⁸⁴ at 100 °C in 1,4-dioxane to afford amide **136** in 52% yield (Scheme 2.45).



Scheme 2.45

Having performed these examples, Buchwald-Hartwig arylation was explored. With this aim, a methodology developed by Buchwald and co-workers using Pd₂(dba)₃, (±)-BINAP and Cs₂CO₃ in toluene was utilised.¹⁹¹ Initial attempts consisted of deprotecting fused

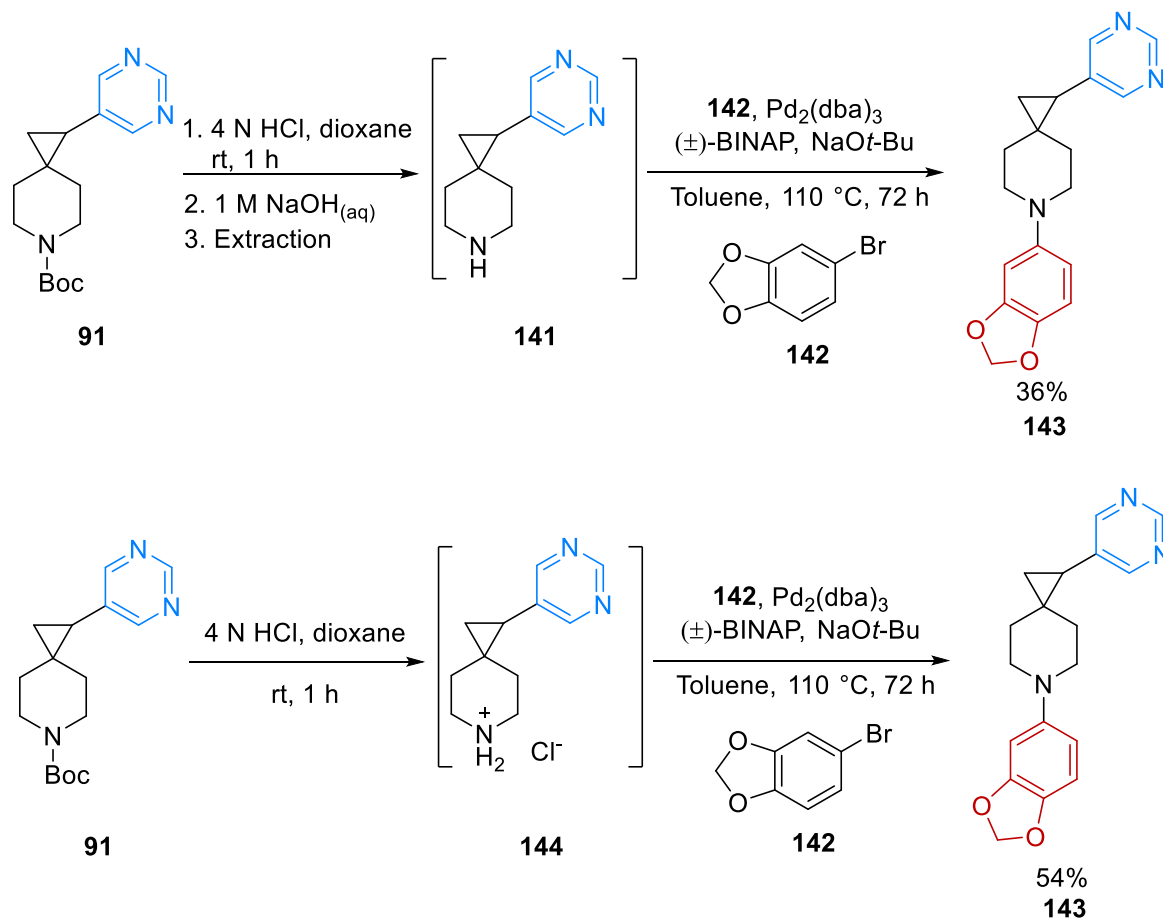
piperidine **exo-104** and using HCl salt **exo-137** for the cross-coupling with bromopyridine **138**. This afforded no arylated piperidine **exo-139**. We speculate that poor solubility of the HCl salt **exo-137** in toluene impeded deprotonation by the base to generate the reactive amine species in turn allowing for partial recovery of the amine after work-up (Scheme 2.46). Nonetheless, attempting this reaction by deprotecting, pre-generating the amine and using this for the cross-coupling was unsuccessful as no product was evidenced by HRMS of the crude product. In this case, amine **exo-140** was partially recovered.



Scheme 2.46

Thus, we decided to explore a similar set of conditions using NaOt-Bu ¹⁹² as the base instead of Cs_2CO_3 and utilising a simpler substrate and aryl substituent. Hence, spirocyclic piperidine **91** with a pyrimidine group was deprotected using 4 N HCl in dioxane and basified to generate amine **141**. This crude amine was then taken on to Buchwald-Hartwig cross-coupling using aryl bromide **142**, $\text{Pd}_2(\text{dba})_3$, (±)-BINAP and NaOt-Bu in toluene (110 °C, 72 h). This afforded arylated spirocyclic piperidine **143** in 36% yield (Scheme 2.47). However, during the free-basing process, it was evident from crude mass recovery that amine **141** was highly water soluble and this likely contributed to the low yield obtained in this

reaction. Gratifyingly, this reaction could be performed with the HCl salt **144** with a significant improvement in the yield of arylated piperidine **143** (54% yield after chromatography). We hypothesise that this is due to both increased solubility of HCl salt **144** and NaOt-Bu in toluene leading to improved generation of the reactive species for the Buchwald-Hartwig cross-coupling.

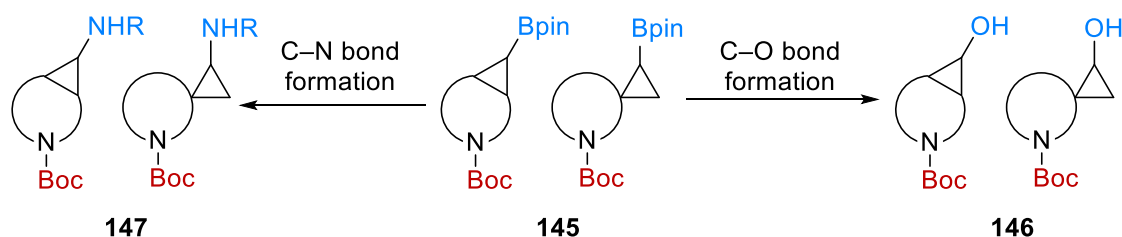


Scheme 2.47

In this way, the potential of the designed 3-D building blocks for *N*-functionalisation was demonstrated with examples of amide bond formation, sulfonamide formation, reductive amination and Buchwald-Hartwig cross coupling.

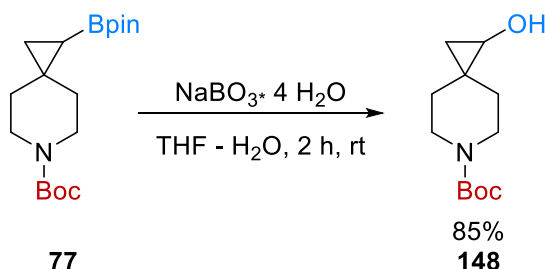
2.7 C–B bond functionalisation

Cyclopropyl pinacol boronates **145** are found as intermediates in the synthesis of the presented 3-D building blocks (see Chapter 2.3.3). With relatively easy access to these intermediates, it seemed likely that such pinacol boronates could be readily converted into alcohol and amine derivatives of the building blocks which would allow for different functionalisation potential, broadening their synthetic potential. Hence, the formulated plan consisted in utilising the obtained pinacol boronates **145** and turning them into amines **147** and alcohols **146** (Scheme 2.48).



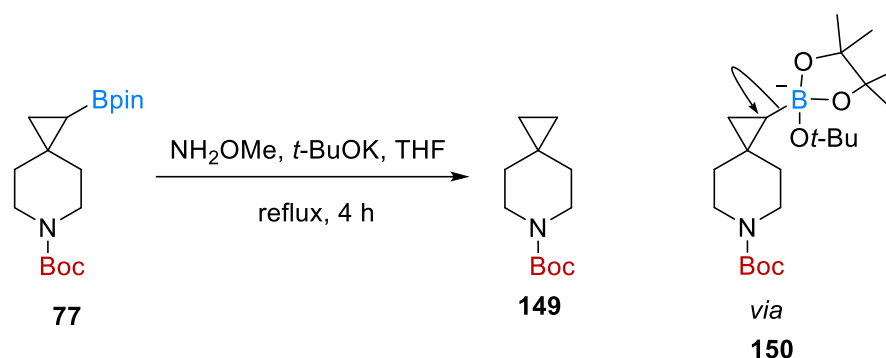
Scheme 2.48

Using a literature procedure¹⁹³ with $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ in THF-water at rt for 2 h, cyclopropyl pinacol boronate **77** was readily transformed into alcohol **148** in 85% yield (Scheme 2.49).



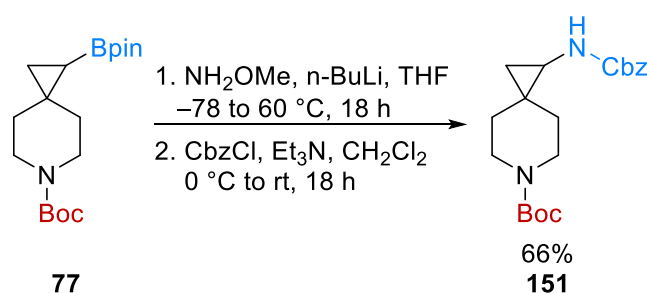
Scheme 2.49

For the synthesis of the amine, cyclopropyl pinacol boronate **77** was initially reacted with a solution of NH_2OMe and $\text{KO}t\text{-Bu}$ as per a literature procedure reported by Tortosa and co-workers for cyclobutyl pinacol boronates.¹⁹³ However, NMR spectroscopic and HRMS analysis of the crude reaction mixture showed none of the desired product. Instead, cyclopropane **149**, from protodeborylation, was observed as the only product (Scheme 2.50). We hypothesise that, for our substrates, at elevated temperatures *tert*-butoxide adds to the pinacol boronate to generate ate-species **150** which can easily deboronate to form cyclopropane **149** after protonation of the so-formed carbanion.



Scheme 2.50

An alternative procedure was attempted, where a solution of LiNHOMe was pre-generated by reacting NH_2OMe with $n\text{-BuLi}$ and this solution was then added to pinacol boronate **77**. In this fashion, the amine was generated and protected *in situ* as the Cbz carbamate to generate carbamate **151** in 66% yield over the two steps (Scheme 2.51). The Cbz protecting group was selected as it was expected that it would provide orthogonal reactivity to the already present Boc carbamate.



Scheme 2.51

In this way, it was demonstrated that the intermediate pinacol boronates from the synthesis of the 3-D building blocks have potential use by means of C–B bond functionalisation. In particular, C–O and C–N bonds could be formed in good yields. Hence, the synthetic utility of the presented building blocks is extended.

2.8 Synthesis of Covalent JAK3 Inhibitor Analogues: Case Study of the York Cyclopropyl 3-D Building Blocks in Fragment Elaboration

Having demonstrated the cross-coupling and *N*-functionalization potential of the group's cyclopropyl building blocks, we aimed to showcase the effectiveness of our modular approach in developing genuine lead compounds from our 3-D building blocks. Thus, the plan was to implement our workflow to develop selective inhibitors of Janus kinase 3 (JAK3) through a scaffold-hopping approach that can also be viewed as fragment elaboration.^{194, 195}

Janus Kinases (JAK) are a family of non-receptor protein-tyrosine kinases (PTKs) that are essential signalling mediators downstream of pro-inflammatory cytokines.¹⁹⁶ Four different enzymes, JAK1, JAK2, JAK3 and tyrosine kinase 3 (TYK2) have been identified in this family.^{197, 198} Inhibition of these kinases has gained traction in the development of efficacious therapies for rheumatic and autoimmune diseases such as rheumatoid arthritis, spondyloarthritis, psoriasis, atopic dermatitis, irritable bowel syndrome and alopecia areata.^{196, 199}

The first selective JAK inhibitor to enter clinical trials and one of the first to receive regulatory approval by the FDA in 2012 was tofacitinib (Figure 2.9),¹⁹⁹ developed by Pfizer for the treatment of rheumatoid arthritis.²⁰⁰ Tofacitinib exhibited a good level of JAK3 selectivity with IC₅₀ values of 1 nM, 20 nM and 112 nM against JAK3, JAK2 and JAK1 respectively. Delgocitinib was then developed by Matsushita and co-workers at Japan Tobacco for the treatment of atopic dermatitis and other inflammatory skin conditions.²⁰¹ In contrast to tofacitinib, delgocitinib is a pan-JAK inhibitor (inhibits similarly across the JAK family) and exhibits IC₅₀ values of 13 nM, 2.6 nM and 2.8 nM against JAK3, JAK2 and JAK1 respectively.²⁰² Expanding on tofacitinib's research, Pfizer further discovered ritlecitinib which is used for the treatment of alopecia areata.²⁰³ Ritlecitinib exhibited IC₅₀ values of 33 nM, >10,000 nM, and >10,000 nM against JAK3, JAK2 and JAK1 respectively making it the first 'truly selective' JAK3 inhibitor.²⁰⁴

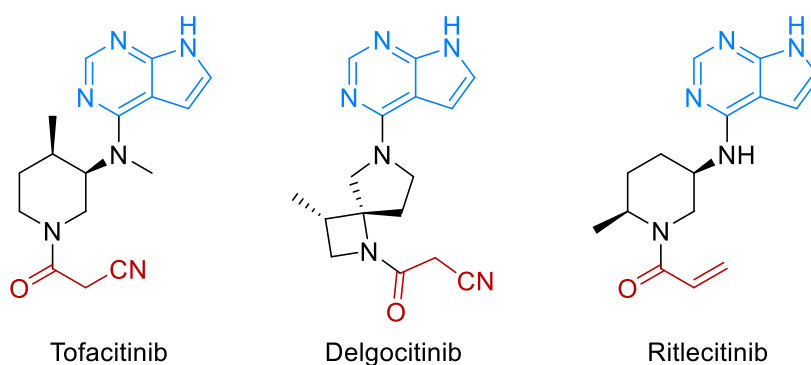


Figure 2.9 – JAK inhibitors.

It is proposed that the overall inhibition exhibited by these APIs towards the JAK family comes from the pyrazolopyrimidine system (highlighted in blue) which interacts with an ATP binding pocket present in the JAK family of cytokine kinases through hydrogen bond interactions to Glu903 and Leu905.²⁰⁵⁻²⁰⁸ Further interaction is picked up by hydrogen bond and non-covalent interactions between the amide and nitrile groups and Leu956 present in all members of the family.²⁰⁶ However, a key differentiating feature and source of selectivity towards JAK3 lies in the acrylamide moiety (a Michael acceptor), which can form irreversible covalent interactions with the Cys909 residue. This residue replaces Ser909 in JAK3, setting it apart from the rest of the JAK family.²⁰⁴ The X-ray structure of JAK3 co-crystallised with ritlecitinib is shown in Figure 2.10 and shows the above-mentioned interactions: the key pyrrolopyrimidine moiety of ritlecitinib (green) binds to the hinge region of JAK3 (Glu903 & Leu905) and the acrylamide warhead forms a covalent interaction with Cys909. Additionally, it is believed that the hydrogen-bonded water between the pyrrolopyrimidine and the acrylamide aids in the activation of the acrylamide towards interaction with Cys909.

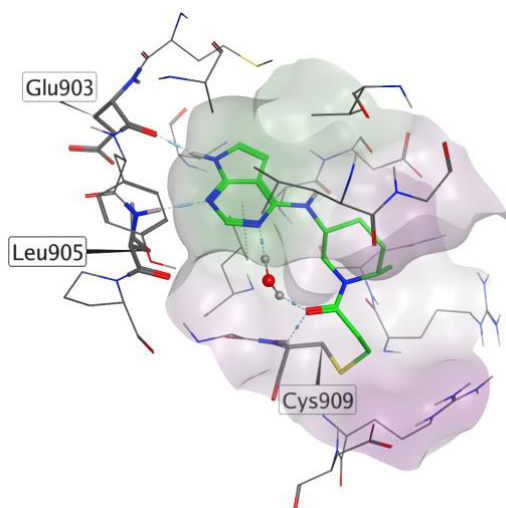


Figure 2.10 – X-ray crystal structure of JAK3 co-crystallised with ritlecitinib.

Molecular docking studies were conducted by collaborators Simon Lucas and Lucia Fusani at AstraZeneca. Following our proposed methodology, we virtually enumerated all nine of our building blocks using the pyrrolopyrimidine binding group as our initial fragment and an acrylamide covalent warhead as our capping group. Docking studies indicated that compounds (*R*)-**152** and (*R,R*)-**153** could potentially adopt docking poses similar to ritlecitinib (see Figure 2.11). With (*R,R*)-**153** more closely resembling the amide interaction and the H-bonded water of ritlecitinib with JAK3.

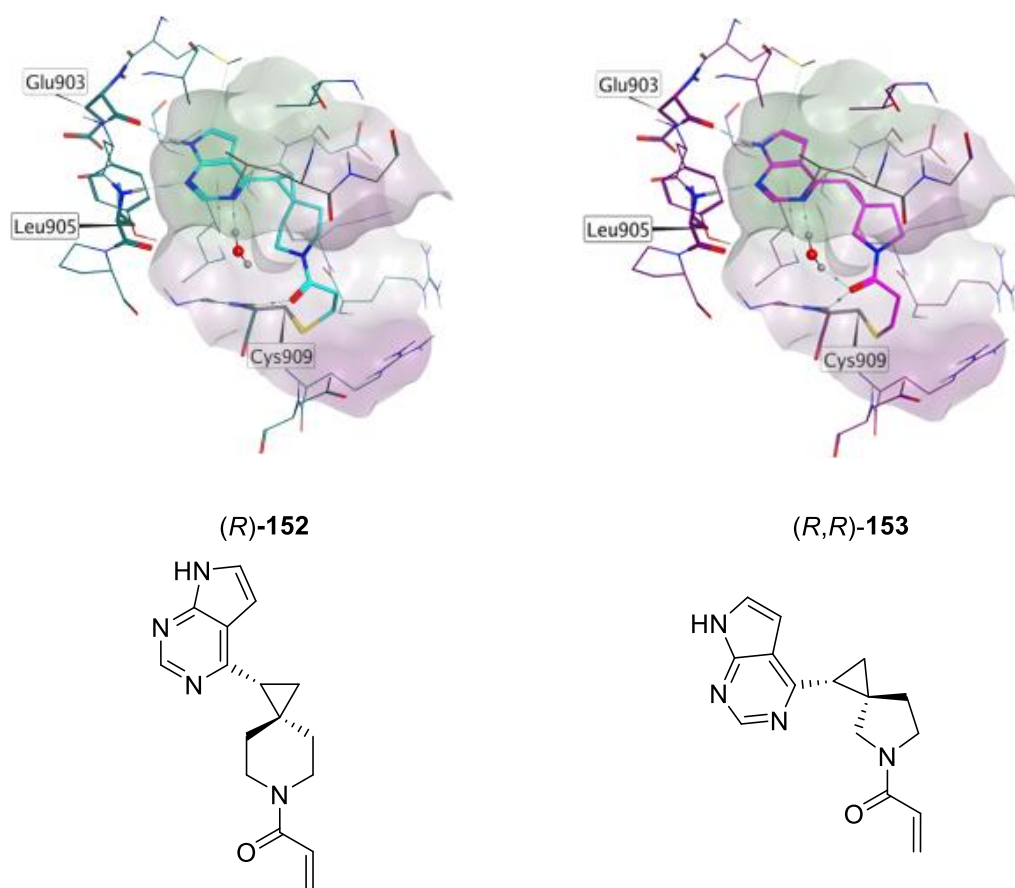


Figure 2.11 – Docking structure of *(R)*-**152** and *(R,R)*-**153** bound to JAK3.

In addition to the modelled acrylamide inhibitors **152** and **153**, the alternative covalent warheads cyanoamide and chloramide were also considered. 2,3-Fused piperidine scaffold *exo*-**71** was also proposed due to what we deemed as a comparable spatial orientation from the docking studies. With this, we proposed the synthesis of **152-160** as potential JAK3 inhibitors (Figure 2.12). Since our building blocks were available as racemic mixtures, all compounds were synthesised in their racemic form rather than as single enantiomers, which were used in the docking studies.

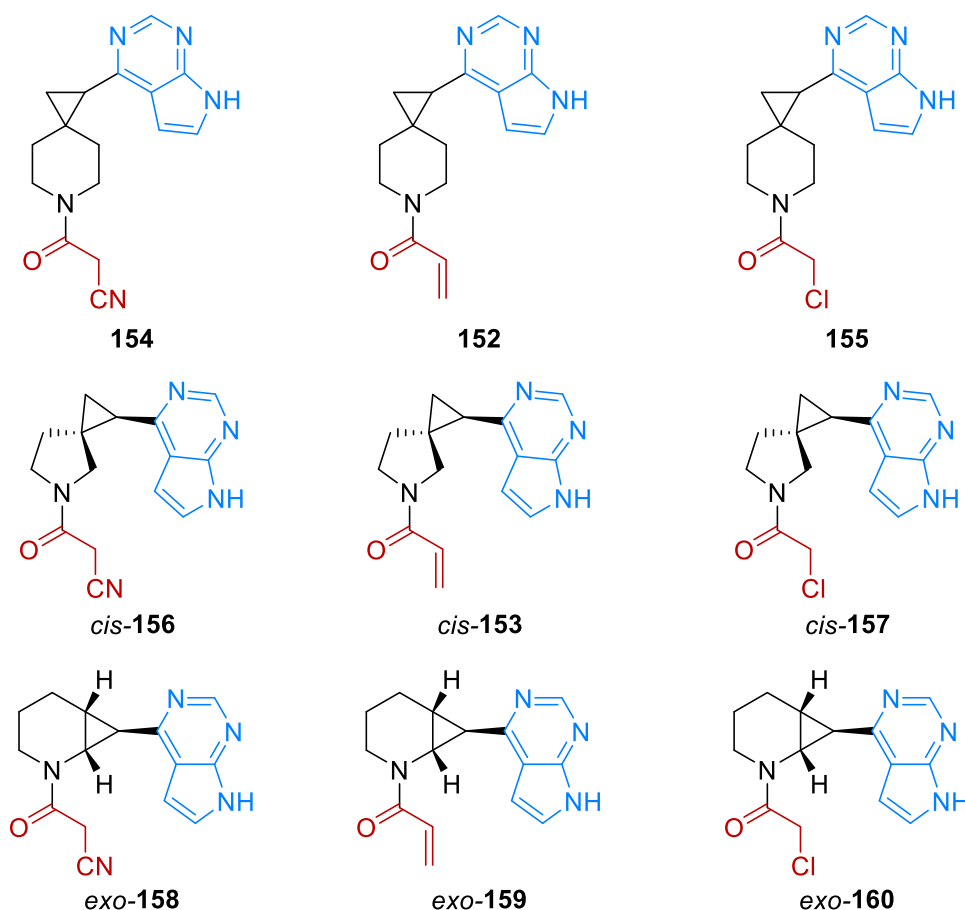
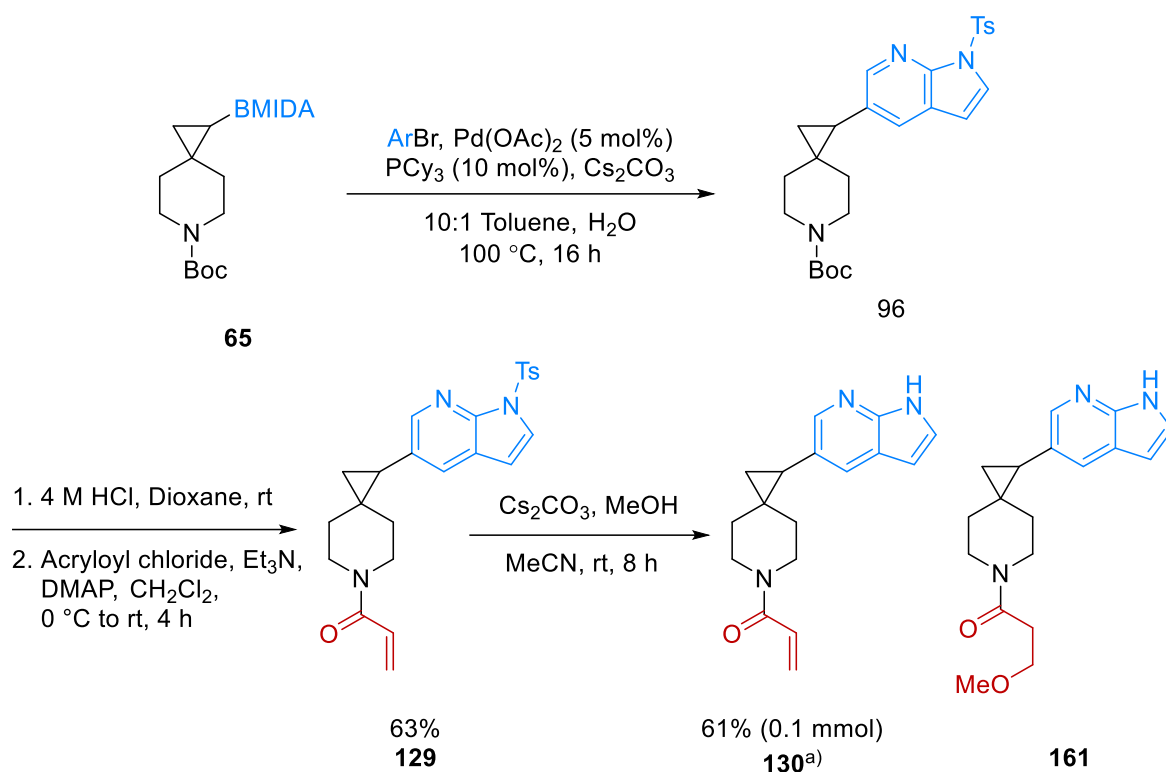


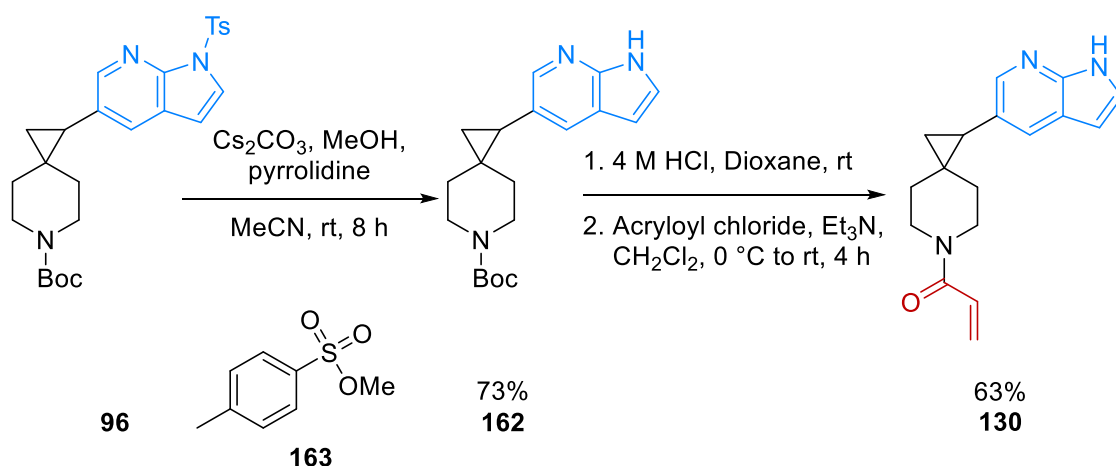
Figure 2.12 – Proposed JAK3 inhibitors.

During our previous studies on the Suzuki-Miyaura cross-coupling and *N*-functionalisation of the 3-D difunctional building blocks, a route to an analogue of compound **152** had been developed, albeit on a small scale. The route, as proposed by our methodology, consisted of an initial Suzuki-Miyaura cross coupling of MIDA building block **65** with a protected derivative of pyrrolopyridine **61** using a 5 mol% loading of palladium to yield the arylated cyclopropyl piperidine **96** in 73% yield (see Section 2.5.3, Scheme 2.36). Following this removal of the Boc group and formation of the acrylamide using acryloyl chloride, DMAP and Et₃N gave *N'*-Ts acrylamide **129** in 63% yield which was then deprotected with Cs₂CO₃ and MeOH to give *N'*-H acrylamide **130** in 69% yield (see Section 2.5.4., Scheme 2.43). However, after further exploration on this route, reproducibility issues were observed on the last deprotection step on larger scales where acrylamide **130** was isolated as an impure mixture with the product from competing addition of methoxide to the acrylamide after deprotection **161** (Scheme 2.52).



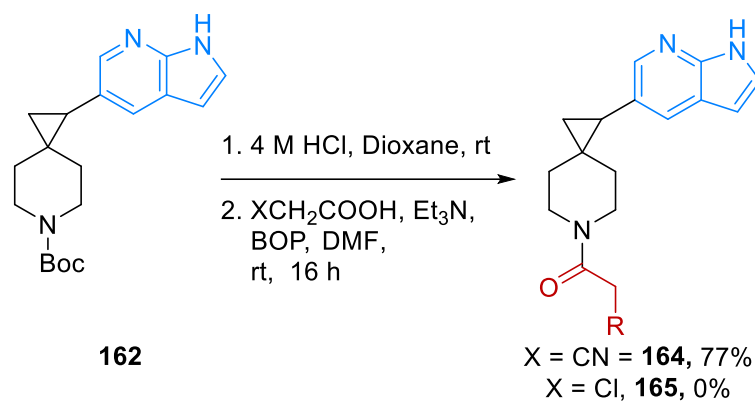
Scheme 2.52 – ^a) 0.25 mmol, isolated as an impure mixture with **161**

To solve this problem and create a slightly more convergent route into the JAK3 inhibitors, the order of the deprotection and the acylation steps was reversed while still using this model pyrrolopyridine **96** (Scheme 2.53). In this manner, *N*'-Ts arylated cyclopropyl piperidine **96** was deprotected using Cs₂CO₃ and MeOH and pyrrolidine to yield *N*'-H arylated cyclopropane **162** in 73%. The addition of an excess of pyrrolidine avoided methylation of the deprotected aromatic NH with byproduct methyltoluenesulfonate **163** formed by the removal of the Ts by MeO[−]. Then, removal of the Boc group and acylation using acryloyl chloride and Et₃N proceeded smoothly to give acrylamide **61** in 76% yield on a 0.5 mmol scale. Notably, no DMAP was added in this instance because its use led to the trace formation of the acylated indole, as observed by ¹H NMR spectroscopy of the crude product.



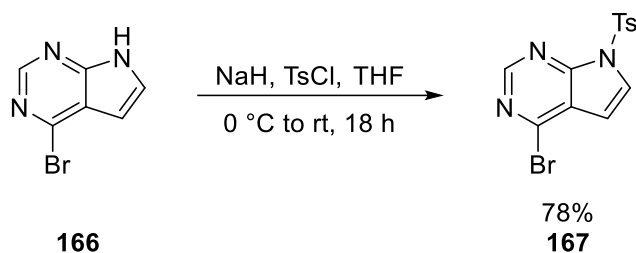
Scheme 2.53

Gratifyingly the route did prove to be more convergent as cyanoamide **164** was successfully synthesised in 77% yield from arylated cyclopropane **162** using cyanoacetic acid and BOP. However, when these conditions were attempted with chloroacetic acid as the partner, no product **165** was isolated (Scheme 2.54).



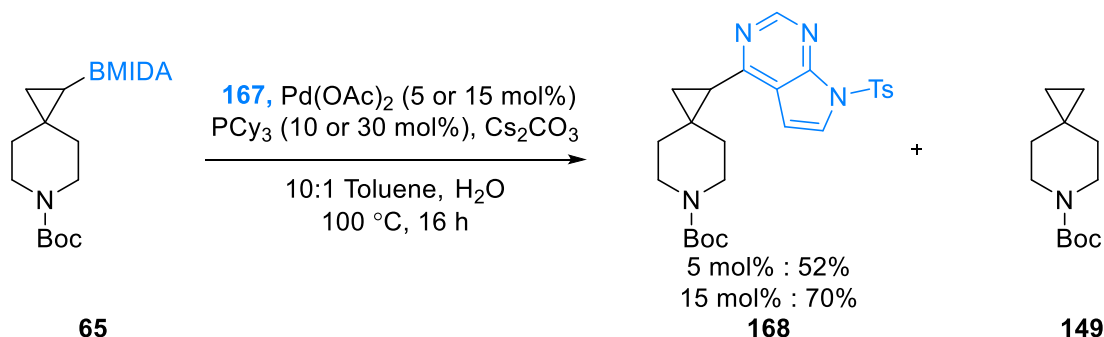
Scheme 2.54

Having established an efficient route to the desired JAK3 inhibitors with the model substrate, we then proceeded with the synthesis of amides **152-160**. Since initial attempts at cross-coupling the free bromopyrrolopyrimidine were unsuccessful, the first step involved protection of the heteroaryl bromide required for the cross-coupling. Using previously explored tosylation conditions for a pyrrolopyrimidine with NaH and TsCl in THF,²⁰⁹ *N*-H pyrrolopyrimidine **164** was protected to give *N*-Ts pyrrolopyrimidine **165** in 78% yield (Scheme 2.55).



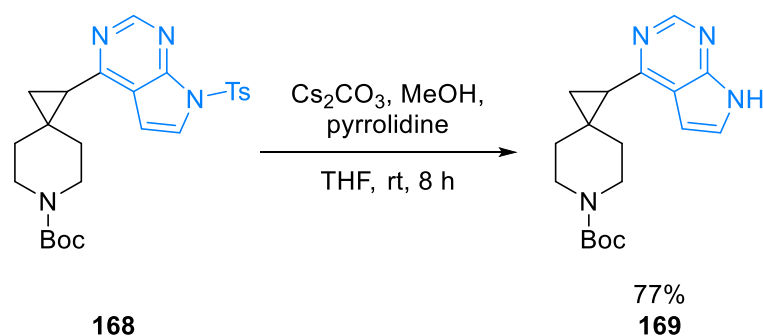
Scheme 2.55

Then, the cross-coupling of cyclopropyl MIDA boronate **65** with aryl bromide **167** was explored. Initial attempts at using our previously developed conditions with a 5 mol% loading of $\text{Pd}(\text{OAc})_2$ saw some success as arylated cyclopropane **168** was obtained in 52% yield. However, ^1H NMR spectroscopy and HRMS of the crude product evidenced the formation of significant quantities of protodeborylated product **149**. From previous studies on cyclopropyl MIDA boronate **65**, we knew that higher Pd loadings can benefit cross-couplings where protodeboronation is a problem (See section 2.5.3, Scheme 2.40). Thus, MIDA boronate **65** was cross-coupled with *N*-Ts pyrrolopyrimidine **167** using 15 mol% $\text{Pd}(\text{OAc})_2$ to give arylated cyclopropane **168** in 70% yield and no evidence of formation of protodeborylated product **149** (Scheme 2.56).



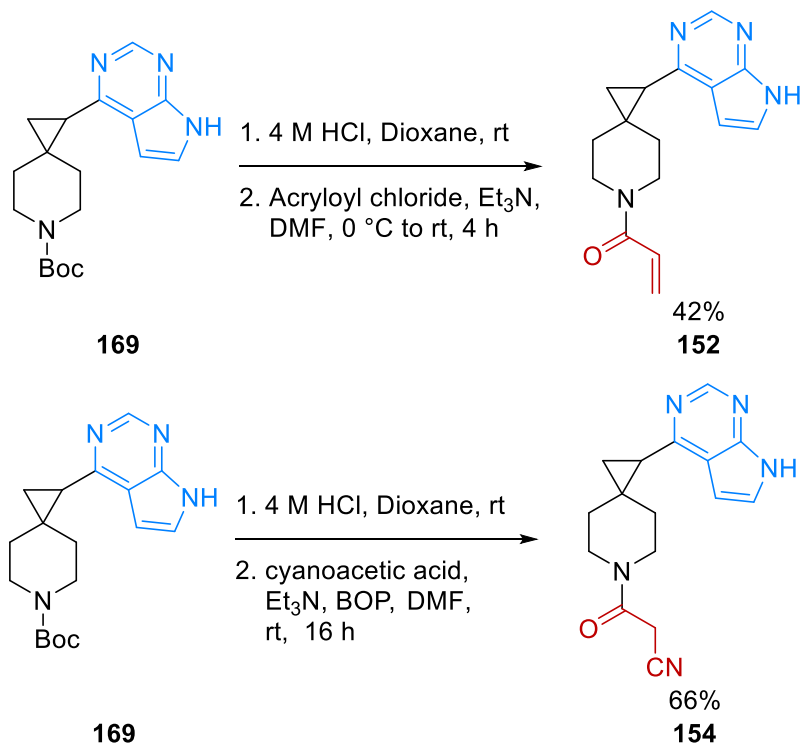
Scheme 2.56

Next, removal of the *N*-Ts group was to be carried out similarly to that achieved with pyrrolopyridine **96**. Thus, reacting *N*'-Ts arylated cyclopropane **168** with Cs_2CO_3 , and MeOH in the presence of pyrrolidine afforded *N*'-H arylated cyclopropane **169** in 77% yield with no evidence of *N*-methylation (Scheme 2.57). Of note, for this deprotection, THF was used instead of MeCN as *N*'-Ts arylated cyclopropane **168** proved completely insoluble in MeCN.



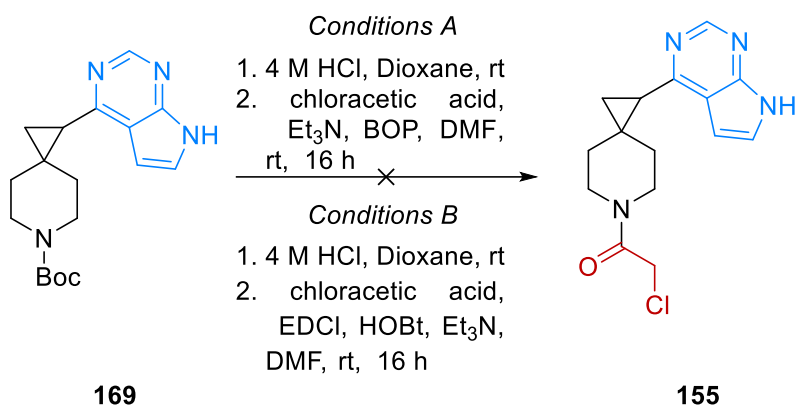
Scheme 2.57

With *N'*-H aryl cyclopropane **169** in hand, the next and final step consisted of attaching the desired covalent warheads. Formation of the acrylamide was performed using acryloyl chloride and Et_3N . In this way *N'*-H cyclopropane **169** was deprotected using 4 N HCl and dioxane and the crude hydrochloride salt amidated with acryloyl chloride and Et_3N in DMF. This gave acrylamide **152** in 42% yield after chromatography. On the other hand, formation of the cyanoamide covalent warhead was achieved with cyanoacetic acid and BOP. Thus, *N'*-H arylated cyclopropane **169** was deprotected and the hydrochloride salt reacted with cyanoacetic acid, BOP and Et_3N in DMF to give cyanoamide **154** in 66% yield (Scheme 2.58).



Scheme 2.58

Finally, formation of chloroamide **155** was attempted. Initially, we attempted the formation using our previously developed conditions for the cyanoamide, using chloroacetic acid, BOP and Et₃N. Unfortunately, only trace amounts of amide **155** were observed by HRMS of the crude product. Use of an alternative set of coupling reagents (EDCl and HOBT) also proved unsuccessful with no formation of amide **155** being observed (Scheme 2.59).



Scheme 2.59

With acrylamide **152** and cyanoamide **154** in our hands and acrylamide *cis*-**153** and cyanoamide *cis*-**157** successfully synthesised by another group member,¹⁵⁰ the samples were screened against the JAK family (JAK1, JAK2, JAK3 and TYK2). Gratifyingly, acrylamides **152** and *cis*-**153** and cyanoamide *cis*-**157** proved to be JAK3 selective with IC₅₀ values of 1230 nM, 69 nM and 1420 nM. Unfortunately, cyanoamide **154** demonstrated poor stability under the biological assay conditions. In comparison to the previously exposed JAK inhibitors (Table 2.4, Figure 2.13), tofacitinib exhibited a good level of JAK3 selectivity (IC₅₀ = 1 nM), delgocitinib is a pan-JAK inhibitor (IC₅₀ = 13 nM), and ritlecitinib is another ‘truly selective’ JAK3 inhibitor (IC₅₀ = 33 nM). Notably, although all these pharmaceuticals demonstrate better inhibition than the compounds presented here, acrylamide *cis*-**153** exhibited inhibition in the same order of magnitude. Importantly, unlike these APIs, acrylamide *cis*-**153** was synthesized and assayed as a racemate, yet it still showed a selectivity profile comparable to that of ritlecitinib, which was used as the model in the docking studies.

Table 2.4 – IC₅₀ values against JAK1, JAK2, JAK3, TYK2

Compound	JAK1 (nM)	JAK2 (nM)	JAK3 (nM)	TYK2 (nM)
Tofacitinib	112	20	1	–
Delgocitinib	2.8	2.6	13	58
Ritlecitinib	>10,000	>10,000	33	>10,000
Acrylamide 152	>10,000	>10,000	1,230	>10,000
Acrylamide <i>cis</i>-153	>10,000	>10,000	69	>10,000
Cyanoamide <i>cis</i>-157	>10,000	>10,000	1,420	>10,000

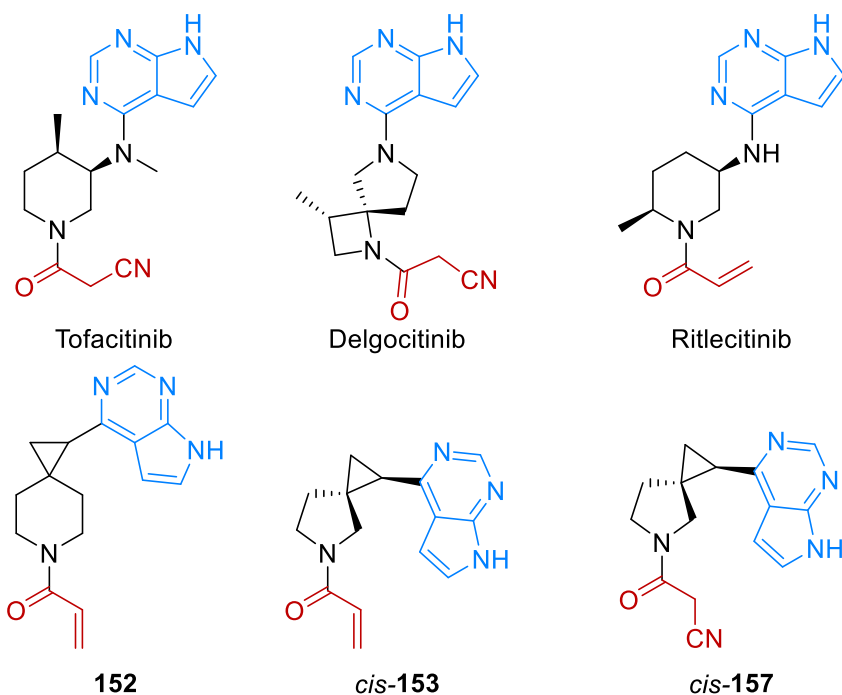
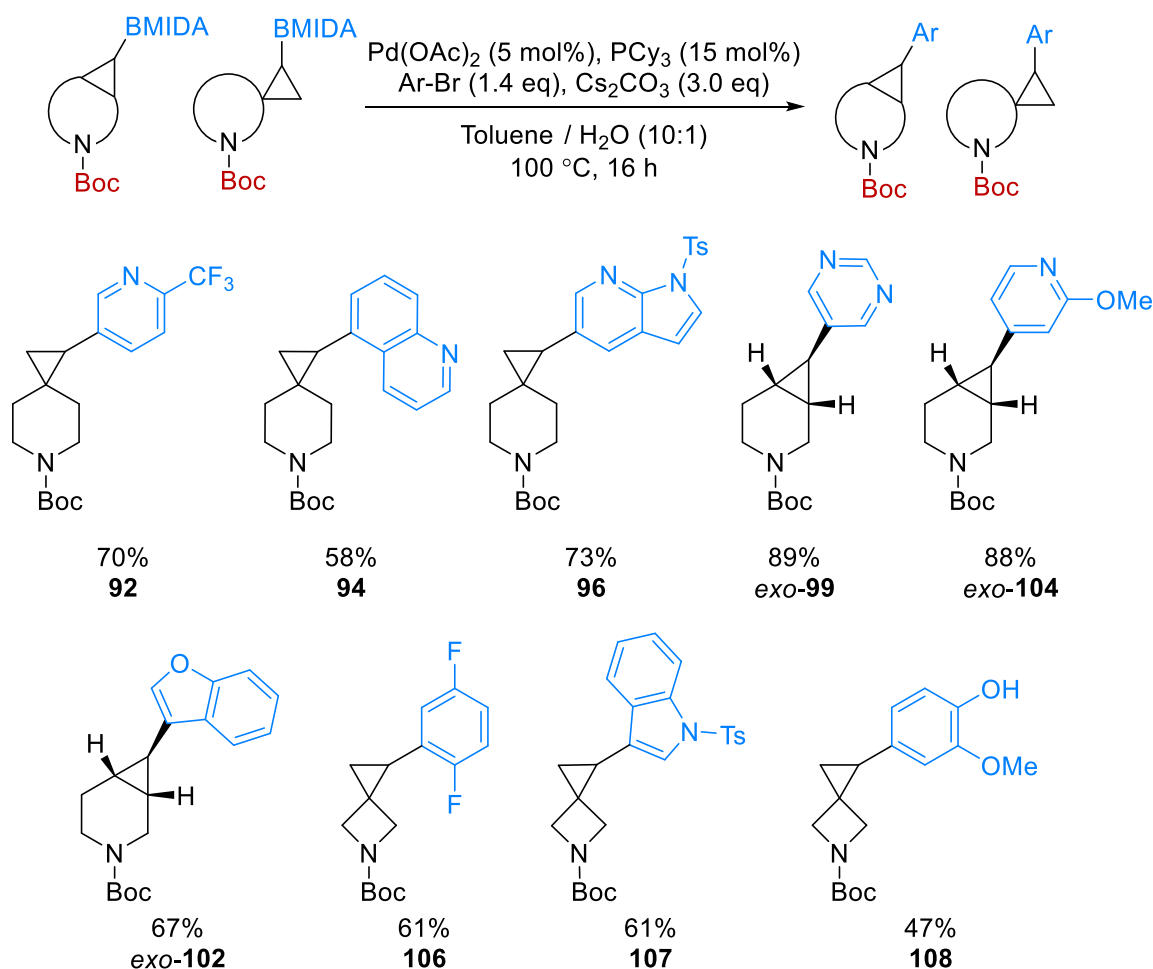


Figure 2.13 – JAK inhibitors

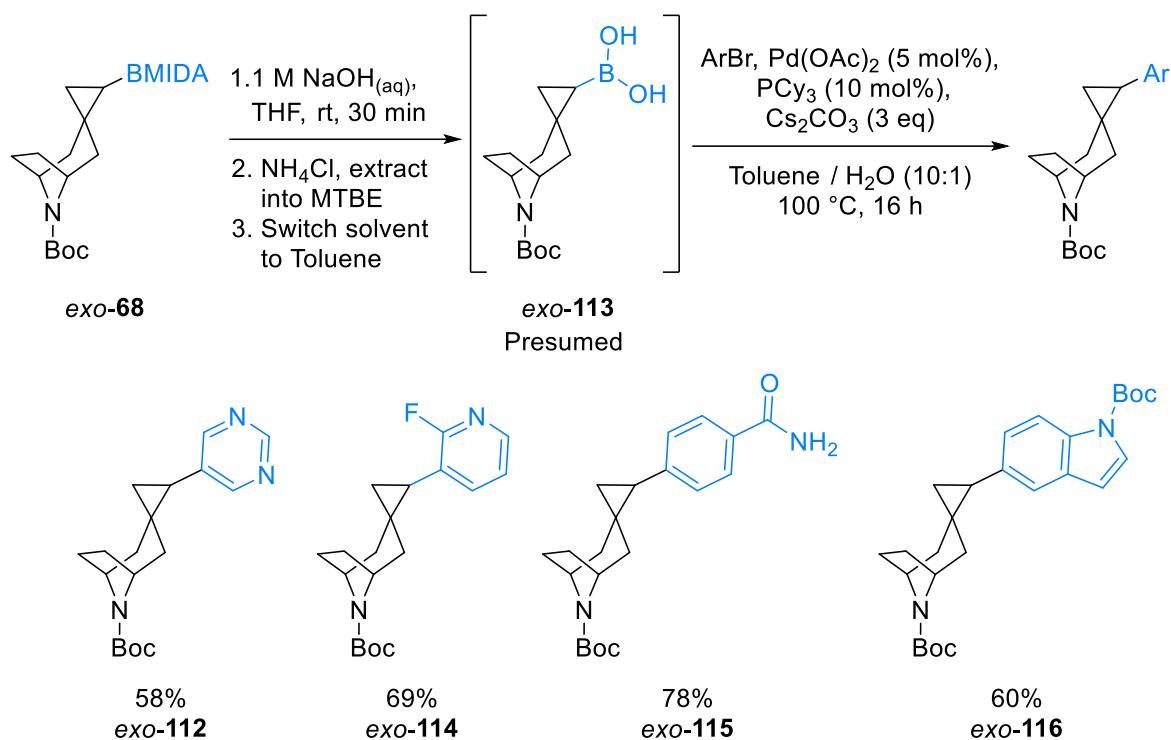
The discovery of this potent and selective JAK3 covalent inhibitors during this first iteration of a medicinal chemistry campaign demonstrate the potential of our approach. We have shown that the design of the O'Brien and coworkers building blocks and the established synthetic methodology alongside docking studies and biochemical assays allows for the rapid synthesis of lead compounds, particularly speeding up the synthesis stage which is often the bottleneck in fragment elaboration. This approach is currently being applied to other structure-guided FBDD projects.

2.9 Conclusion

In summary, we have successfully developed methodology that allows for the use of the nine cyclopropyl O'Brien building blocks (commercially available through KeyOrganics) in the fragment elaboration stage of FBDD campaigns. In this work, the Suzuki-Miyaura cross-coupling of the MIDA building blocks was optimised and a wide scope of cross-couplings with a variety of electron deficient and rich aromatic and heteroaromatic systems across five of the building blocks **64**, **65**, **66** *exo*-**68** and *exo*-**69** was demonstrated. Cross-couplings to *N* and *O*-containing heterocycles including protected indoles and benzofurans were shown (Scheme 2.60) and a special set of conditions for the successful cross-coupling of tropane building block *exo*-**68** was developed (Scheme 2.61).

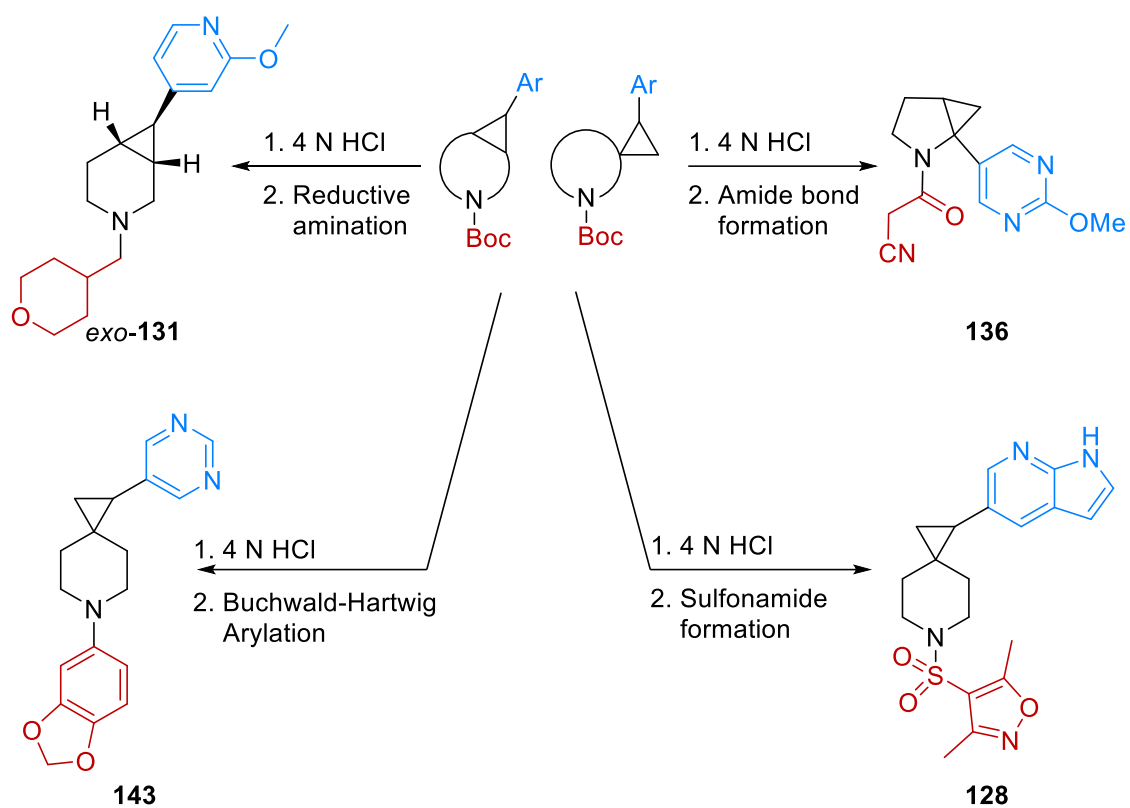


Scheme 2.60



Scheme 2.61

Additionally, *N*-functionalisation potential was demonstrated across the building blocks to easily and efficiently access a variety of lead-like compounds through some commonly used reactions in medicinal chemistry while including medically relevant motifs. Examples included reductive amination to introduce saturated oxygen heterocycles, amide bond formations introducing indoles and covalent warheads, sulfonamide formations and Buchwald-Hartwig arylations (Scheme 2.62). C-B bond functionalisation was also demonstrated by oxidation and C-N bond formation.



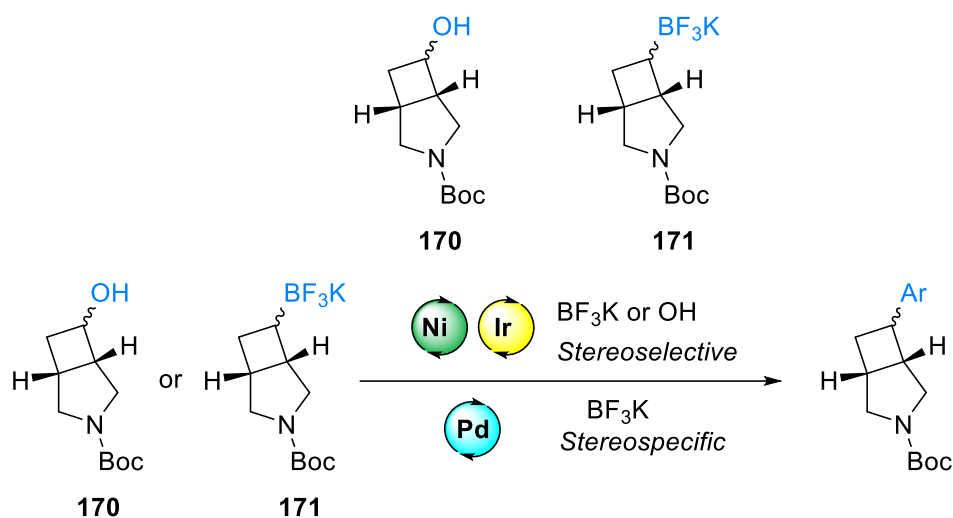
Scheme 2.62

Finally, the potential of the cyclopropyl building blocks was demonstrated by the design and synthesis of selective JAK3 inhibitors by a scaffold-hopping project based on the API ritlecitinib. Gratifyingly, the synthesised JAK inhibitors proved to be JAK3 selective with good IC_{50} values. Acrylamide *cis*-153 exhibited comparable inhibition to ritlecitinib, despite being assayed as a racemate. This is a very promising result from our first iteration of a medicinal chemistry campaign.

Chapter 3 Cyclobutyl Building Blocks as a Modular Platform for the Elaboration of Fragments: New Areas of Chemical Space

With the O'Brien methodology platform for fragment elaboration firmly established through the synthesis, development, and case study using cyclopropyl building blocks, we sought ways to expand the accessible areas of chemical space that our building blocks could cover. In this way, we envisaged the design of new 3-D building blocks to access further areas of 3-D chemical space. Recognising the value of our previously introduced design criteria but increasing the ring-size from cyclopropanes to cyclobutanes allowed for the design of a new generation of building blocks.

Cyclobutanes have flourished in recent medicinal chemistry literature owing to the increase in reliable preparative methods that allow for successful exploitation of their increased s-character and lowered reactivity when compared to cyclopropanes.^{210, 211} However, it is worth noting that while cyclopropanes facilitate Pd-mediated cross-couplings, the Pd-catalysed cross-coupling cyclobutyl boronates is lessprecedented, which in turn opens up the possibility for the development and application of novel methodology for their cross-coupling.²¹² To this end, cyclobutyl-fused pyrrolidines *endo*- and *exo*-**170** and **171** were proposed as useful scaffolds for developing the cyclobutane ring system within our methodology platform. These scaffolds would require the creation of synthetic routes to access them and the exploration of cross-coupling methodologies. This would include using metallophotoredox methods developed by MacMillan from the alcohol handle which we expected would proceed with stereoselectivity,²¹³ and developing Suzuki-Miyaura cross-coupling conditions from the BF₃K handle which we expected to proceed stereospecifically (Scheme 3.1).



Scheme 3.1

Section 3.1 introduces the concept of cyclobutanes and the scaffold for our proposed cyclobutane building blocks. Then, Section 3.2 outlines the current cyclobutyl building block project scope. In Section 3.3, recent relevant examples of cyclobutanes in synthetic and medicinal chemistry are showcased. Section 3.4 explores the synthesis of the selected cyclobutyl building blocks. The background literature and results around the cross-coupling of the cyclobutyl building blocks are discussed in Section 3.5 with Section 3.6 giving an overview of the synthesis of a methanesulfonamide derived from one of our building blocks.

3.1 Introduction and Design Considerations for the O'Brien Cyclobutyl Building Blocks

During the O'Brien group's research in the development of cyclopropyl building blocks for the elaboration of fragments, one of the main criteria for the design and selection of building blocks was the efficient and varied access to 3-D chemical space. To this end, members of the group have simulated the structures of the cyclopropyl building block-derived methanesulfonamides **172-179** and performed an exit vector plot (EVP) analysis of them (Figure 3.1).^{214, 215} For our building blocks, the exit vectors are defined by the parameters r and θ , where r corresponds to the distance between atoms C1 and C2, and θ denotes the dihedral angle between the n_1 -C1 and n_2 -C2 planes. These parameters can be determined from the atomic coordinates of the lowest energy conformers, which were calculated using quantum mechanics (DFT, B3LYP/6-31G*) by William Butler.^{214, 216-219} An important observation from this was that despite the success in reaching a wide range of chemical space with just nine building blocks, more scaffolds would be needed to access further areas of 3-D chemical space.

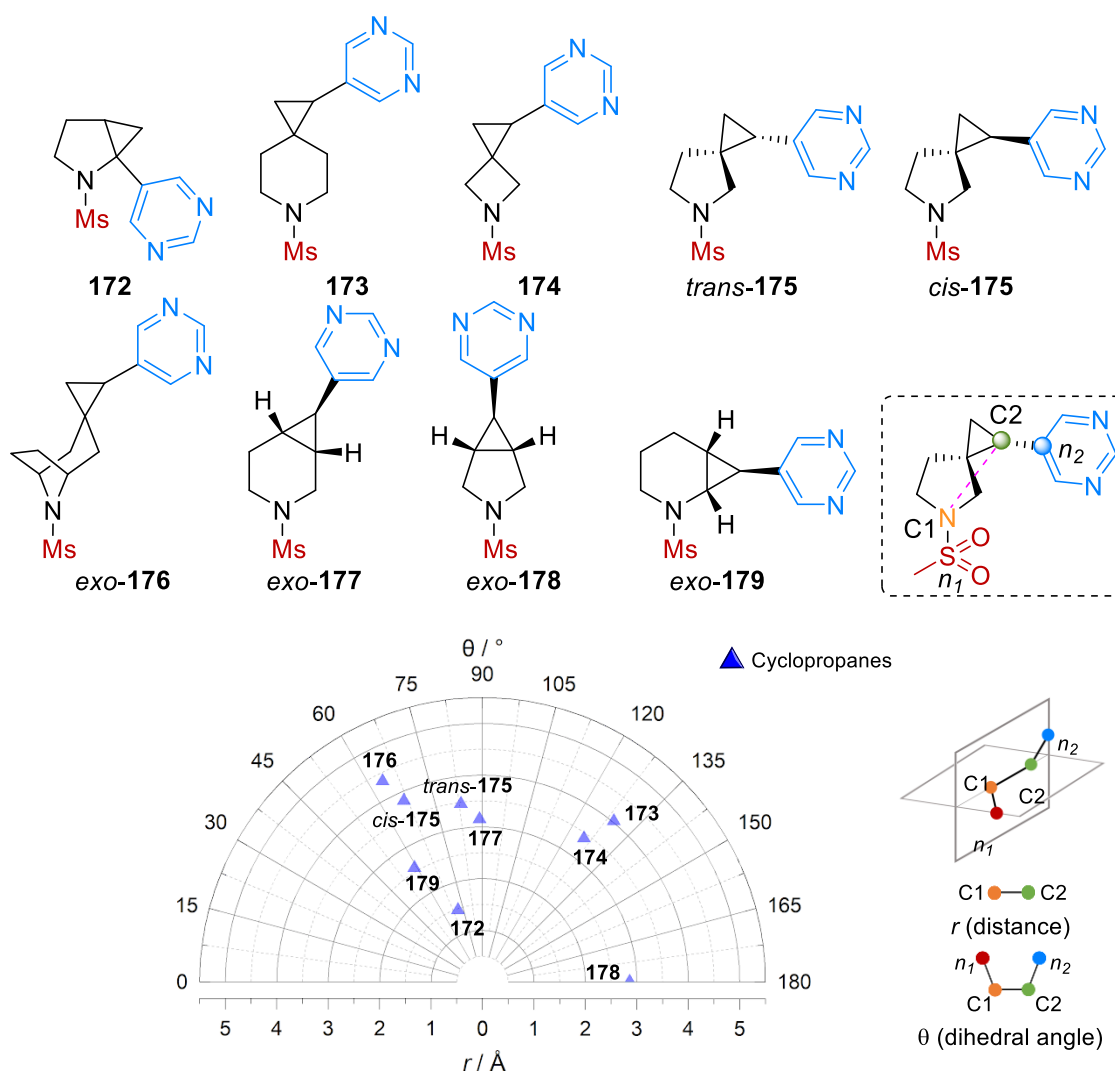


Figure 3.1 – EVP analysis of the O'Brien cyclopropyl pyrimidine sulfonamides. r is the distance in Å from C1 (orange) to C2 (green); θ is the dihedral angle made across the imaginary bond system amongst n_1 (red), C1 (orange), C2 (green) and n_2 (blue).

Four-membered rings are witnessing a significant increase in their prominence in medicinal chemistry programs.²²⁰ One of the reasons for this is the advancing synthetic methodology that has allowed for expedited and reliable access to these motifs with a variety of functionality,²²¹⁻²²³ as well as advances in their cross-coupling methodology.^{213, 224-226} Additionally, in contrast to the cyclopropyl ring, the cyclobutyl motif is not planar but puckered, conveying further structural variety and allowing for significantly less reactivity.²¹⁰ This has allowed for its use in rigidifying linear alkyl chains that link two pendant functionalities,^{227, 228} in replacing gem-dimethyl moieties²²⁹ and in the introduction of chain branching.²³⁰ Additionally, fused and spirocyclic cyclobutanes have seen extensive use as scaffold-hopping and bioisostere analogues of larger rings while allowing for conformational restriction and lower entropic costs to binding.^{21, 139, 211, 231, 232}

Indeed, over 300 patents were filed in 2019 for drug substances containing four membered rings (cyclobutane, oxetane and azetidine) with 9 FDA-approved drugs containing a cyclobutane group.²¹⁰ The structures of notable cyclobutane containing compounds are presented in Figure 3.2. Belaperidone, developed by Knoll, contains the bicyclo[3.2.0]heptane core and was developed for the treatment of schizophrenia.²³³ Ecenofloxacin, containing the same core, was developed by Nishino and co-workers as a wide spectrum antibiotic from a scaffold-hopping campaign from enrofloxacin.²³⁴ US2015/34489, containing a spiro[3.3]heptane core, was patented by AbbVie as an antivasopressin agent.²³⁵ Finally, spiropiperidine **180**, with a spiro[4.3]octane core, was explored as an analgesic by Pfizer.²³⁶

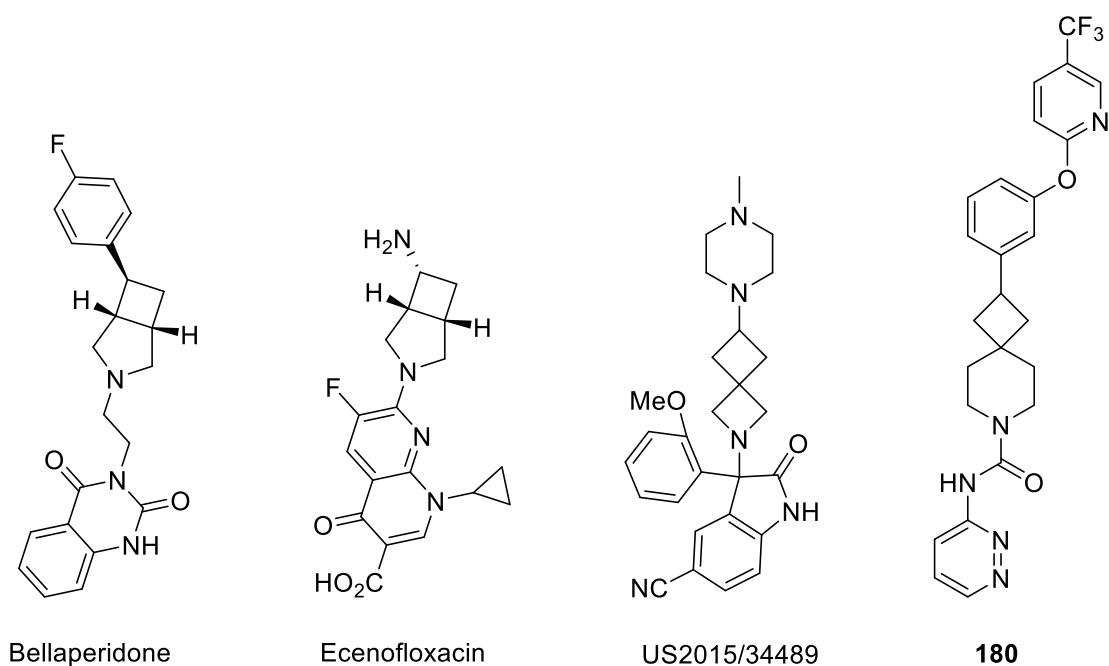


Figure 3.2 – Medicinally-relevant examples of fused and spiro-cyclobutanes.

Following similar design criteria to the O'Brien group cyclopropyl building blocks, it was decided that the new set of bifunctional 3-D building blocks would comprise a cross-coupling enabled cyclobutyl group and an *N*-Boc protected amine. Based on reports from Molander,^{173, 174} it was envisaged that a cyclobutyl BF_3K moiety could participate in Ni-catalysed photoredox cross-couplings as well as Pd-catalysed cross-couplings.¹⁷⁴ Additionally, recent reports by MacMillan and co-workers signalled the possibility to use alcohols which are usually intermediates in the synthesis of the cyclobutyl trifluoroborates as cross-coupling partners in photoredox cross-couplings.^{237, 238} These include

deoxygenative arylation,^{213, 224} deoxygenative Csp³-Csp³ cross couplings,²³⁹⁻²⁴² deoxygenative Buchwald-Hartwig-type cross-couplings,²⁴³ fluoromethylations^{9, 244} and others.²⁴⁵⁻²⁴⁷

An initial exploration into the cyclobutyl space was proposed by exploring hydroxycyclobutanes **170**, **181** and **182** and cyclobutyl trifluoroborates **171**, **183** and **184** as potential new building blocks. Prior to the synthesis of the proposed cyclobutyl 3-D building blocks, exit vector analysis was performed by William Butler²¹⁴ to ensure that the building blocks were able to access novel chemical space (Figure 3.3). Pleasingly, exit vector analysis indicated that the proposed structures do allow for access to new areas of chemical space.

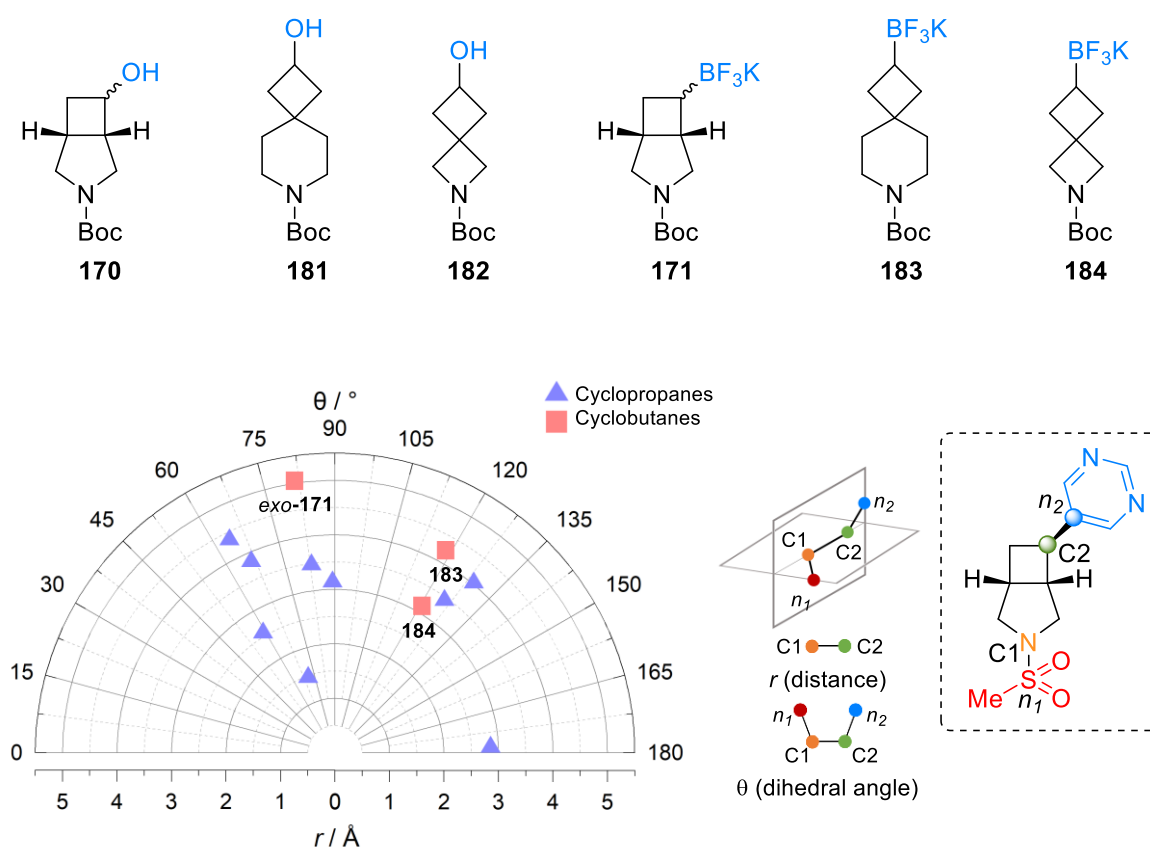
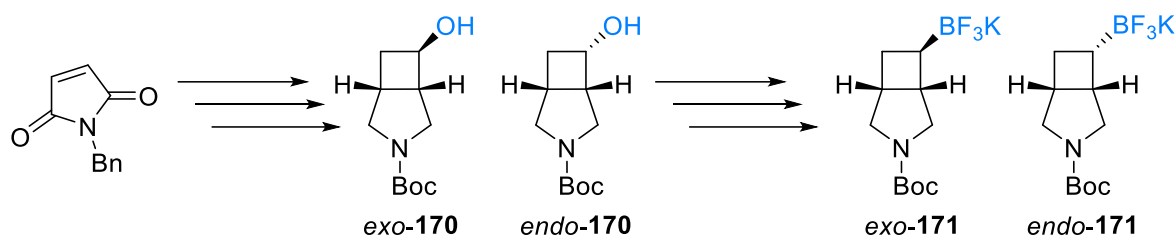


Figure 3.3 – EVP analysis of the cyclobutane pyrimidine methanesulfonamides. Red squares highlighted in EVP represent the sulfonamides synthesised virtually from cyclobutyl boronates **171**, **183** and **184**.

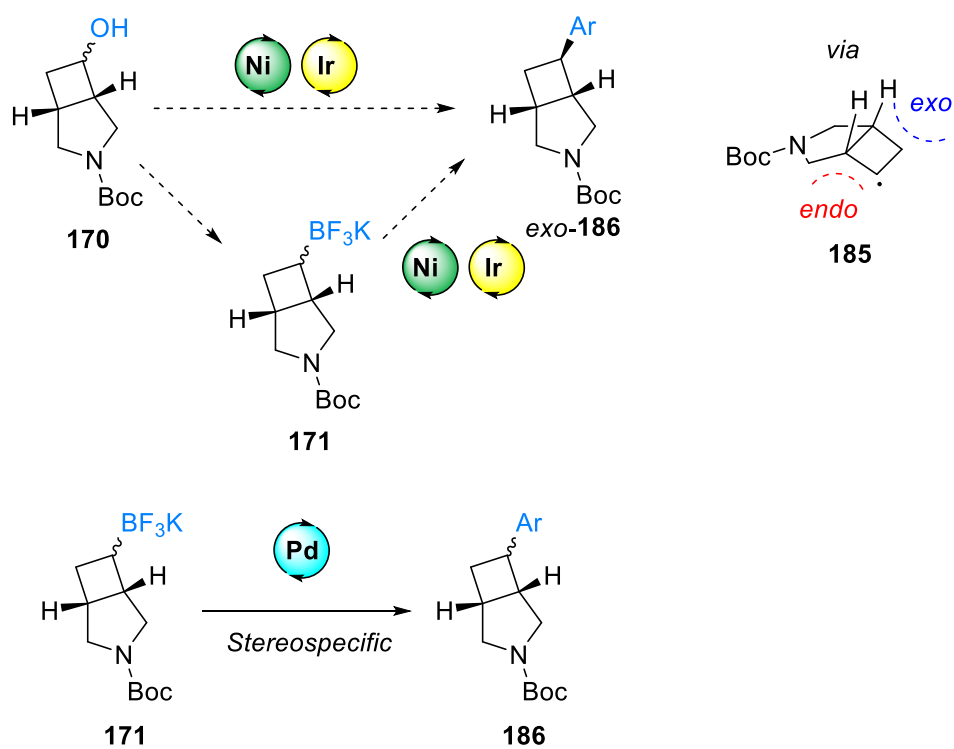
With a methodology platform for the programmed elaboration of fragments successfully established using the O'Brien cyclopropyl building blocks (Chapter 2) and recognizing the need to develop new building blocks to cover additional areas of chemical space, building blocks **171**, **172** and **181-184** were designed. From this, fused hydroxy pyrrolidines **170** and BF₃K pyrrolidines **171** were selected as the first scaffold to explore the development of

potentially stereoselective routes into the *endo* and *exo* diastereomers of each building block. Likewise, the stereochemical information provided by the bicyclo[3.2.0]heptane core would allow for exploring Ni-catalysed and Pd-catalysed cross-couplings as well as their stereochemical outcomes.



Scheme 3.2

In this way, the current chapter explores the stereoselective synthesis of hydroxy pyrrolidines *endo*- and *exo*-**170** according to a previously reported methodology developed by Grygorenko and co-workers.²⁴⁸ From alcohols **170**, the goal would be to develop methodology that allows the stereoselective synthesis of boronates *endo*- and *exo*-**171** (Scheme 3.2). Then, with building blocks **170** and **171** in hand, Ni-catalysed photoredox will be explored using the hydroxy and BF_3K synthetic handles (Scheme 3.3). Particularly, since both cross-couplings proceed by the formation of carbon-centred radical **185**, it was expected that the fused bicyclic structure in **185** would induce preferential trapping on the less-hindered *exo* face to give arylated pyrrolidines *exo*-**186**. Finally, with access to BF_3K pyrrolidines **171**, we aimed to develop conditions for Suzuki-Miyaura cross-coupling which we envisaged would proceed stereospecifically with retention of stereochemistry (Scheme 3.3).

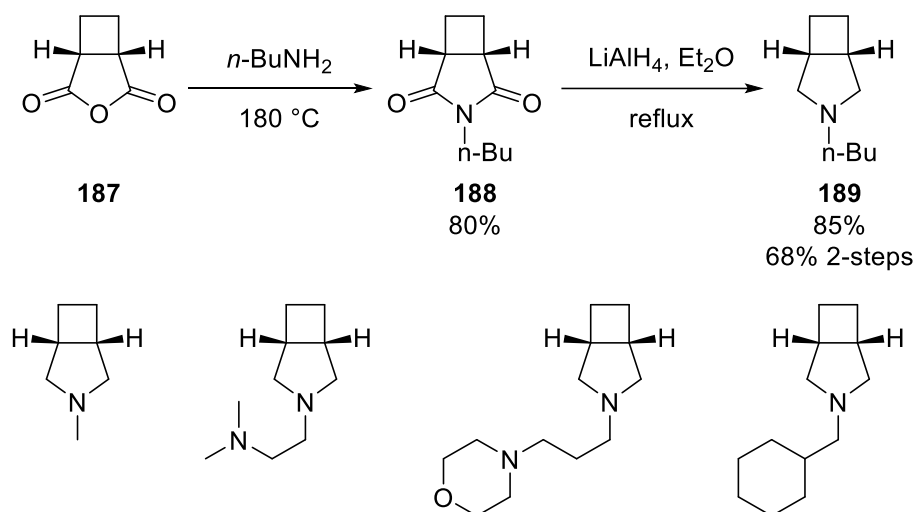


Scheme 3.3

3.3 Synthetic Overview of Relevant Bicyclo[3.2.0]heptane Scaffolds

Cyclobutanes have recently received increased interest in both synthetic and medicinal chemistry as they provide valuable scaffolds and provide an opportunity to uniquely tune the physicochemical and biochemical properties of compounds²⁴⁹ whilst also allowing for the exploration of novel chemical and medicinal chemistry space.²⁵⁰ In particular, the bicyclo[3.2.0]heptane core has received increased interest due to its presence in biologically active compounds such as Belaperidone and Ecenofloxacin (see Figure 3.2) as well as its possibility to act as a bioisostere of 6-membered rings such as piperidine.²⁵¹ Herein a brief overview of the synthesis and use of relevant examples of the bicyclo[3.2.0]heptane core are presented.

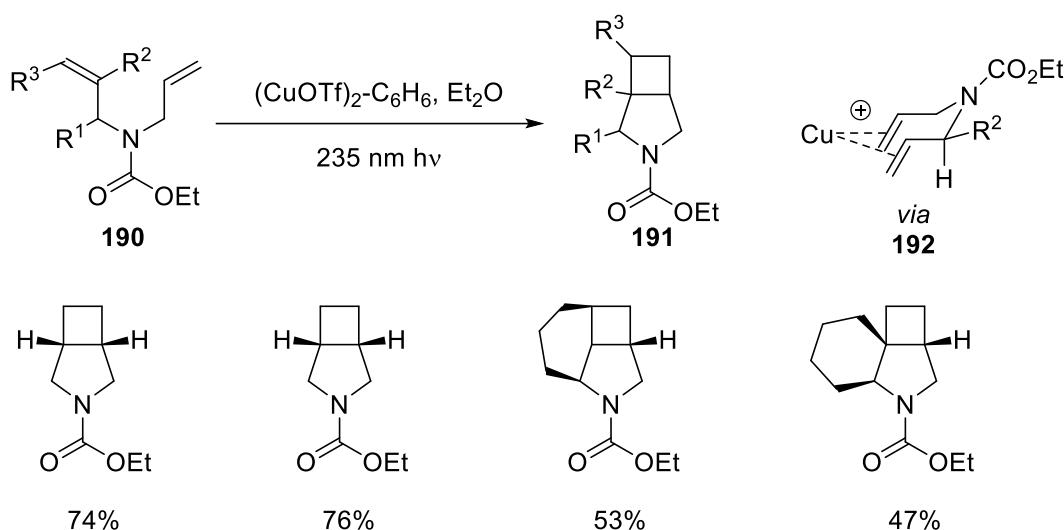
One of the earliest examples on the synthesis of the bicyclo[3.2.0]heptane bicyclic core was published by Grogan and co-workers while researching the synthesis of 3-azabicyclo[3.2.0]heptanes as potential hypotensive agents.²⁵² Starting from cyclobutyl dicarboxylic anhydride **187**, a condensation with neat butylamine at 180 °C afforded *N*-butyl cyclobutane imide **188** in 80% yield. Following this, reduction with LiAlH₄ in refluxing ether afforded *N*-butyl pyrrolidine cyclobutane **189** in 85% yield (Scheme 3.4). This methodology allowed for diverse *N*-substitution but no substitution around the cyclobutane ring was explored.



Scheme 3.4

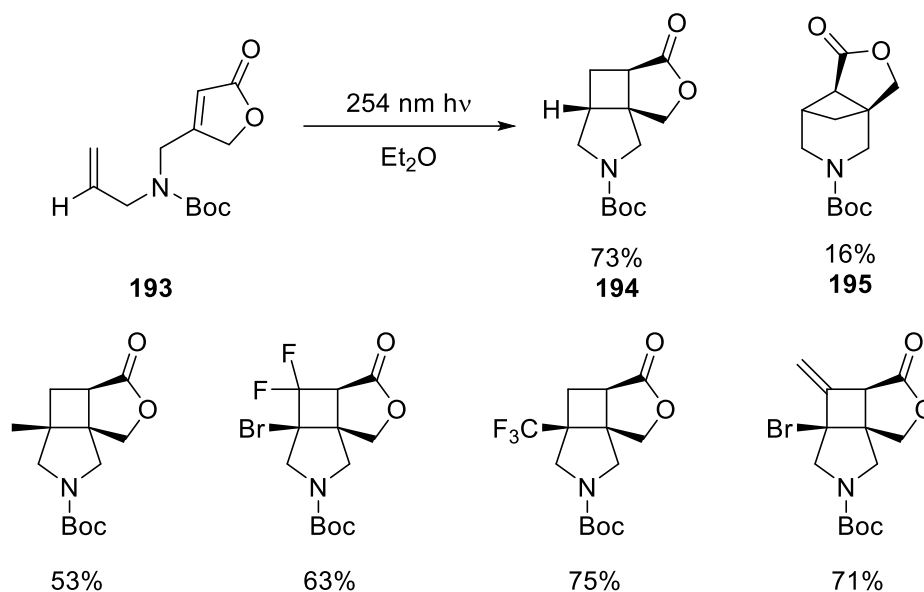
The formation of an imide of the type **188** followed by reduction to the amine is a common methodology to the azabicyclo[3.2.0]heptane core. Other methodology that is often used, even in combination with imide reduction, is [2+2] cycloaddition. This cycloaddition approach was introduced by Miranti and co-workers.²⁵³ In their work, they introduce a Cu-

catalysed photoinduced [2+2] cycloaddition of *N,N*-diallyl carbamates. Reacting *N,N*-diallyl carbamates **190** with CuOTf under 235 nm irradiation afforded pyrrolidine bicycles **191** in good yields. Some substitution around the 2-position of the pyrrolidine as well as the bridgehead and the cyclobutane was tolerated including an additional ring system. The authors propose the selectivity comes from the chair-like transition state assumed by the copper ligated olefins in **192** (Scheme 3.5). Of note, the use of the ethyl carbamate group in the amine would allow for potential amine deprotection and further functionalisation of the nitrogen.



Scheme 3.5

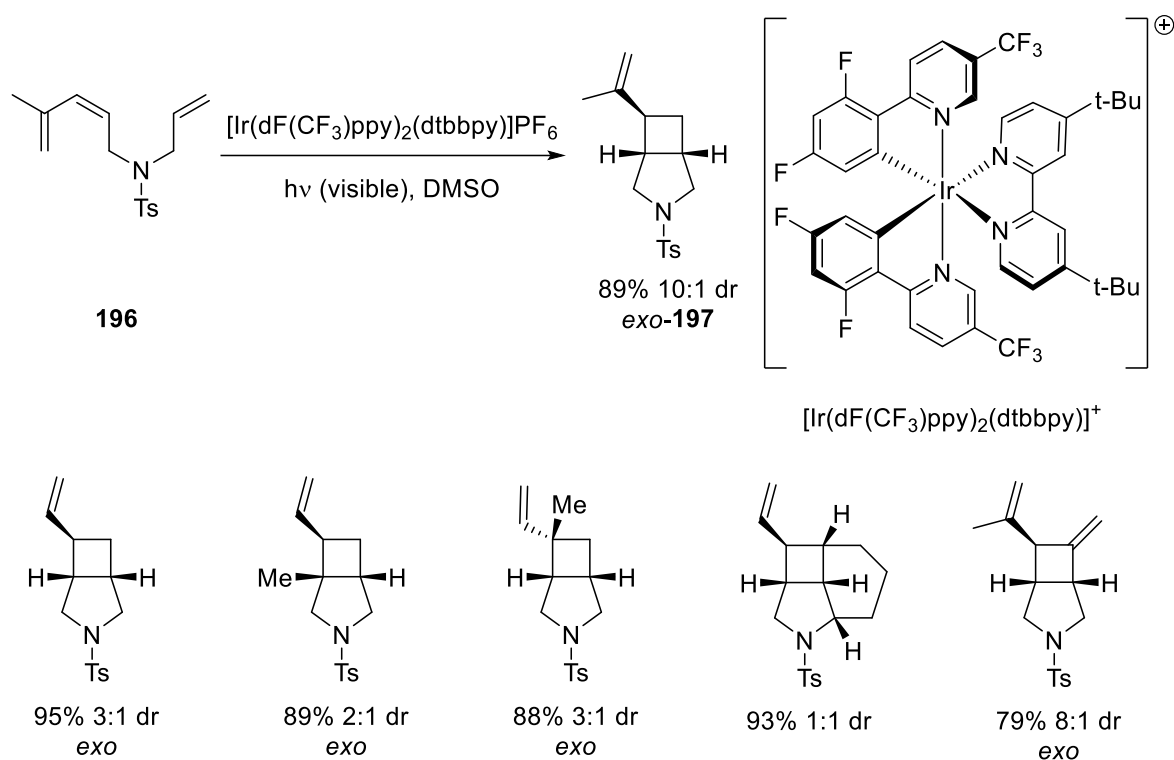
This methodology was also used by del Pozo and co-workers while using chiral *N*-capping groups to deliver enantiopure 3-azabicyclo[3.2.0]heptanes.²⁵⁴ Similarly, Bach and co-workers leveraged an UV photoinduced [2+2] cycloaddition of allylamines to access conformationally restricted pyrrolidines.²⁵⁵ In their work, irradiation of *N*-Boc diallylamine **193** with 254 nm UV light led to the formation of fused pyrrolidine cyclobutane **194** in 73% yield with some substitution on the bridgehead and cyclobutane positions tolerated (Scheme 3.6). Notably, a regioisomeric byproduct **195**, resulting from head-to-tail [2+2] cycloaddition of the olefins, was also observed in significant quantities.



Scheme 3.6

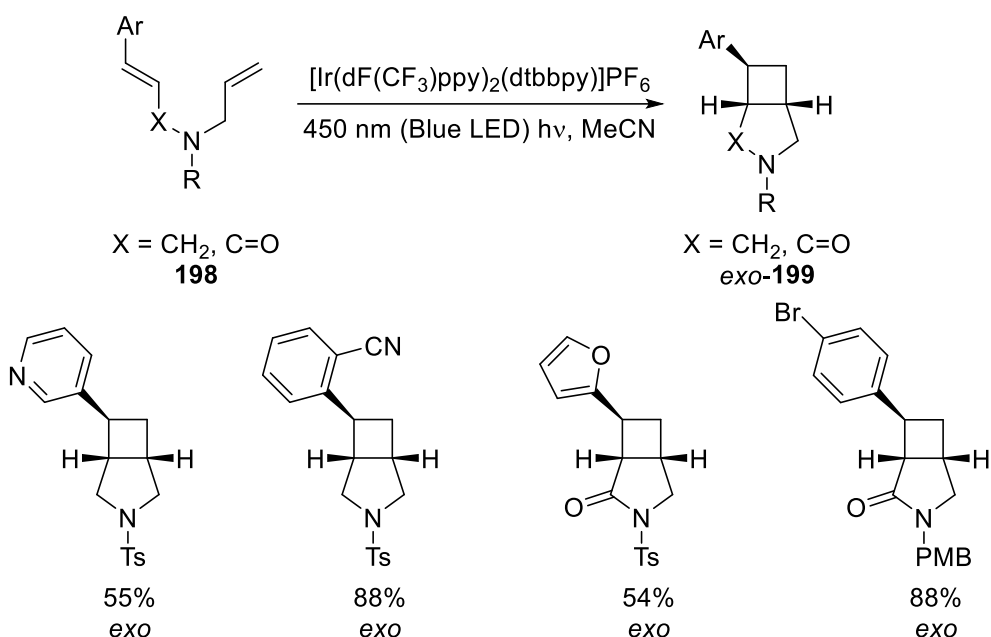
This methodology was also used by Mykhailiuk and co-workers in 2017.²⁵⁶ Substituting one of the allyl amine branches for a cinnamic acid amide allowed the irradiation wavelength required for the reaction to be increased whilst allowing for substitution of the cyclobutane-position with a diverse range of aromatics. Additionally, Yoon and co-workers reported a modification of this methodology using cooperative Ru/V-catalysis under visible light to give 3-oxabicyclo[3.2.0]heptanes.²⁵⁷

This modification was further developed by Yoon and co-workers in 2014 where it allowed for the [2+2] cycloaddition of dienes that would have otherwise decomposed under UV irradiation.²⁵⁸ In their work, the authors reacted *N*-Ts diallyl amines **196** in the presence of [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ under visible light irradiation to give pyrrolidine cyclobutane *exo*-**197** in 89% yield and 10:1 dr (Scheme 3.7). This methodology had good tolerance for substitution around the bicyclic ring and some derivatization of the products was showcased.



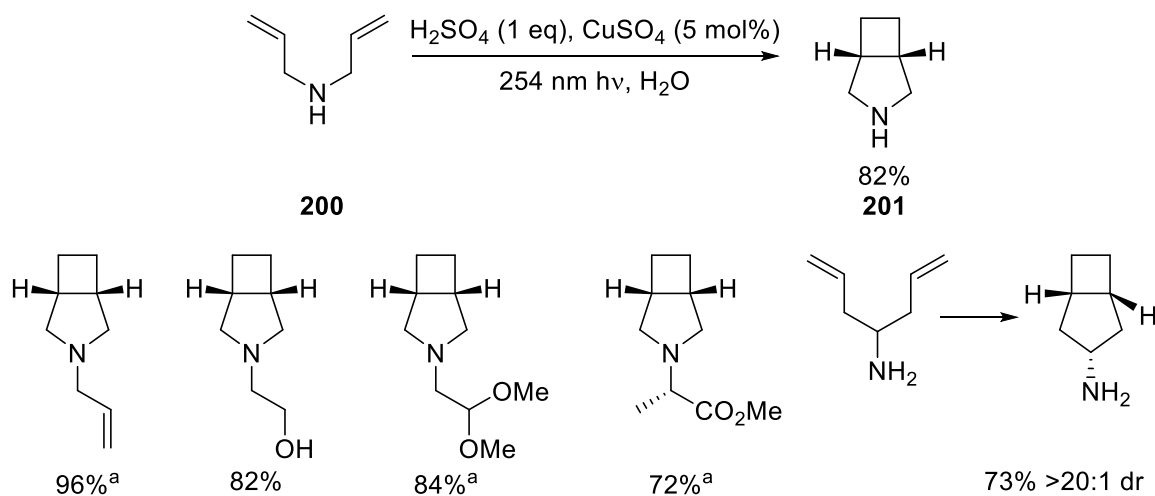
Scheme 3.7

Further development of this single component [2+2] cycloaddition methodology was reported by Mathur and co-workers in 2020.²⁵¹ Combining the introduction of the cinnamic acid amide by Mykhailiuk²⁵⁶ and the catalytic approach by Yoon²⁵⁸ allowed the synthesis of a diverse set of aryl-substituted cyclobutyl pyrrolidines and pyrrolidones **exo-199** from diallylamines **198** under visible light photoinduced Ir-catalysis in good to excellent yields (Scheme 3.8). Diverse substitution around the aromatic position, including heteroaromatics, was well tolerated as well as different *N*-protecting groups such as Boc, Ts, Bn and PMB.



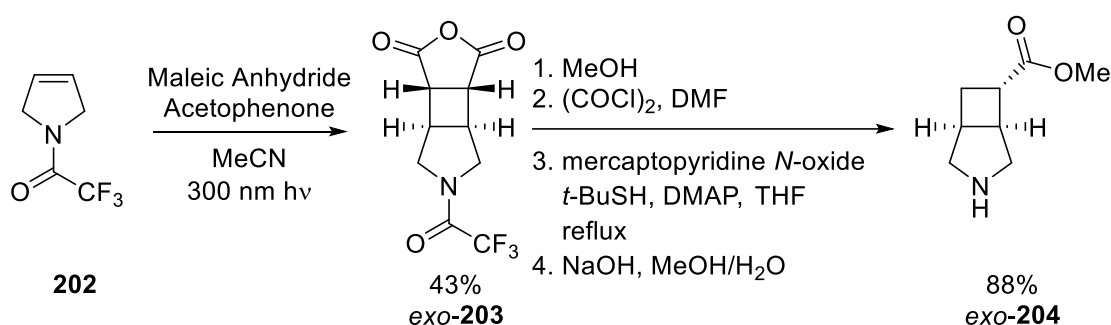
Scheme 3.8

The intramolecular [2+2] cycloaddition is a useful approach for the synthesis of cyclobutanes. However, all the methodologies previously reported are incompatible with the presence of unprotected amines. In contrast, in 2022, Burns and co-workers reported a new aqueous amine-tolerant [2+2] photocycloaddition of unactivated olefins for the synthesis of the bicyclo[3.2.1]heptane core.²⁵⁹ In their work, treatment of diallylamine **200** with H_2SO_4 , catalytic CuSO_4 and 254 nm irradiation in water afforded *N*-H cyclobutylpyrrolidine **201** in 82% yield (Scheme 3.9). This methodology showed extensive tolerance to *N*-substitution as well as for the presence of an exocyclic amine. However, no substitution around the cyclobutane system was explored.



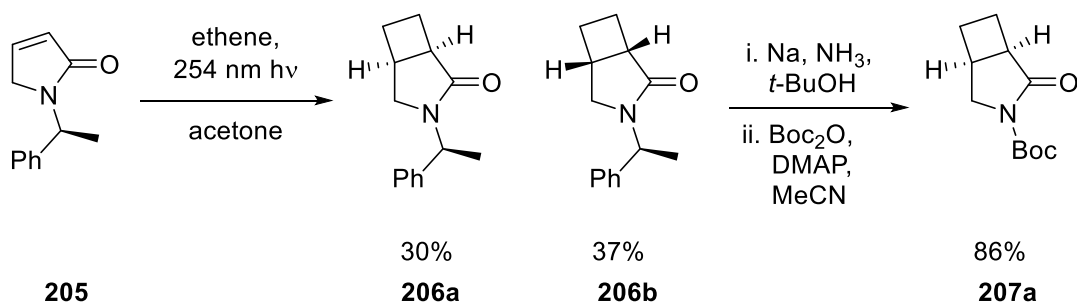
Scheme 3.9 ^a) Using AcOH in place of H_2SO_4

Although the intramolecular [2+2] cycloaddition has been established as a robust methodology for synthesizing bicyclo[3.2.0]heptanes, it often necessitates the installation of functionality prior to cyclization, making it a very linear approach. In contrast, an intermolecular [2+2] cycloaddition methodology should allow for the direct formation of bicyclo[3.2.0]heptanes with diverse functionality. One of the first examples of this approach was reported by Wanner and co-workers.²⁶⁰ Reaction of *N*-trifluoroacetyl-3-pyrroline **202** with maleic anhydride in the presence of acetophenone under 300 nm irradiation afforded cyclobutane *exo*-**203** in 43% yield. Anhydride *exo*-**203** could in turn be ring-opened with MeOH, singly decarboxylated and the *N*-trifluoroacetamide group removed under basic conditions to afford cyclobutane *exo*-**204** in 88% yield (Scheme 3.10).



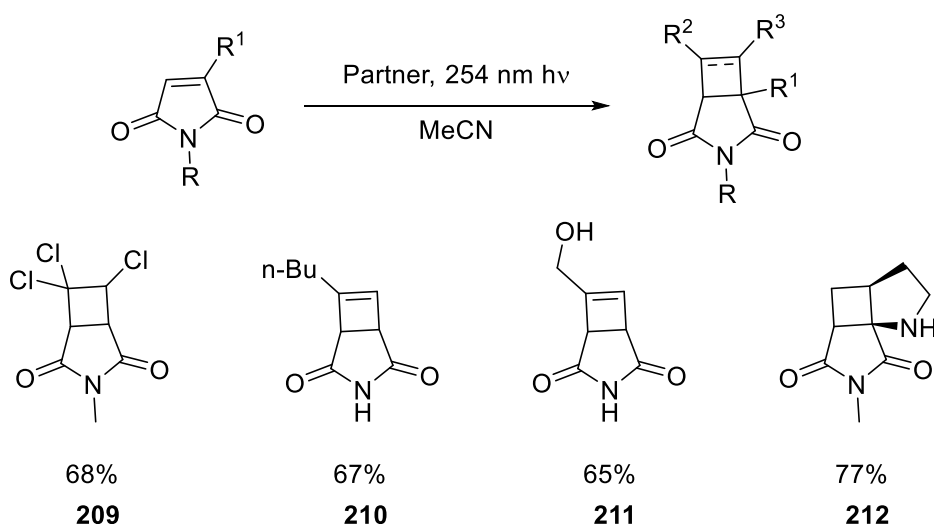
Scheme 3.10

In a similar fashion, Aitken and co-workers reported the [2+2] cycloaddition of unsaturated lactam **205** with ethene under UV irradiation to yield cyclobutyl lactams **206a** and **206b** in 30% and 37% yield respectively (Scheme 3.11).²⁶¹ The α -methylbenzyl group could then be subsequently cleaved using Na in NH₃ and the resulting lactam *N*-Boc protected to yield lactam **207a** in 86% yield. This methodology was used to access a diverse set of enantiomerically pure cyclobutyl amino acid derivatives.^{262, 263} This same approach was utilised by De Silva and co-workers by using further functionalised lactam starting materials and following the cycloaddition by a ring expansion to yield enantiopure azepanes.²⁶⁴



Scheme 3.11

Other substrates that have been widely explored in intermolecular [2+2] cycloadditions for the synthesis of 3-azabicyclo[3.2.0]heptanes are maleimides.²⁶⁵⁻²⁷² Notably, Booker-Milburn and co-workers explored the batch and flow behaviour of a variety of photochemical reactions.²⁷³ Amongst these, the authors explored the [2+2] cycloaddition of maleimide derivatives using 245 nm UV light (Scheme 3.12). Despite the main purpose of the work being the comparison between batch and flow conditions, the methodology demonstrated good tolerance to substitution around the cyclobutyl moiety. Cycloadditions demonstrated included trichloroethylene to yield cyclobutane **209** in 68% yield, hexyne to yield cyclobutene **210** in 67% yield, propargyl alcohol to yield alcohol **211** in 65% yield and even a tethered allylamine to yield tricyclic cyclobutane **212** in 77% yield.

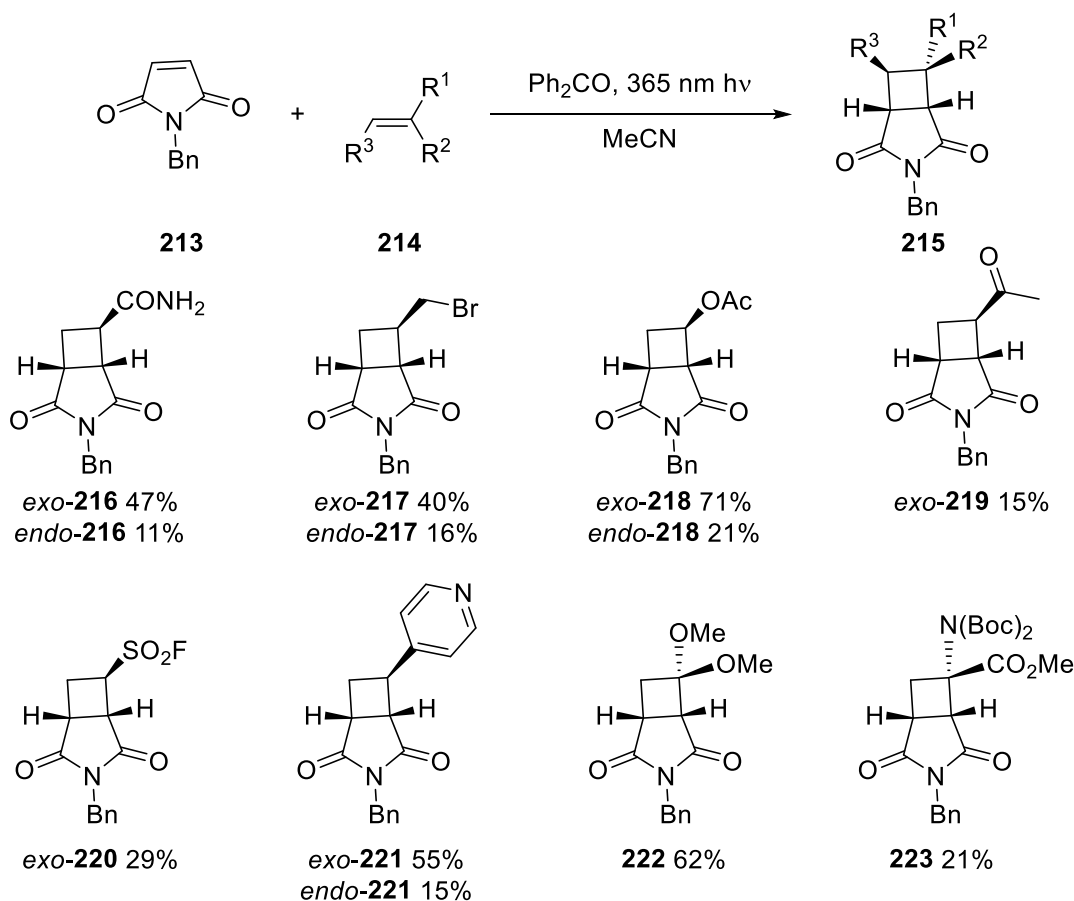


Scheme 3.12

One of the main limitations of the photochemically initiated [2+2] cycloaddition route to cyclobutanes lies in the short wavelengths required for the excitation of the substrate which in turn induces poor functional group tolerance.²⁵⁸ In order to address this issue, several approaches such as the use of catalysis or photosensitisers has been explored.

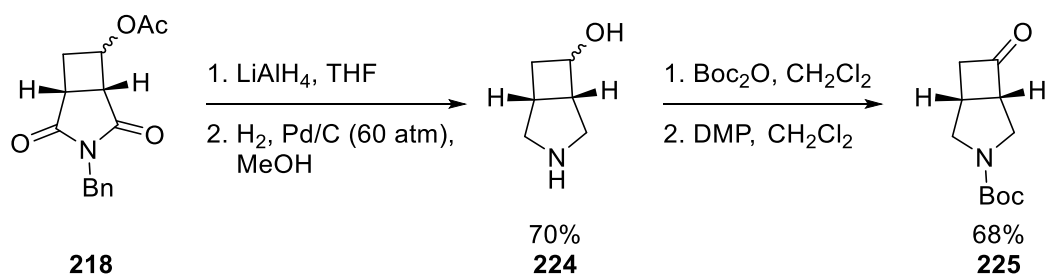
An example of photosensitization was reported Mykhailiuk and co-workers at Enamine in their work on the [2+2] photocycloaddition of *N*-Bn maleimide for synthesis of 3-azabicyclo[3.2.1]heptanes.²⁴⁸ [2+2]-Cycloadditions of *N*-Bn maleimide **213** with a diverse set of alkenes **214** using 366 nm light and benzophenone as a sensitizer were carried out to give 3-azabicyclo[3.2.1]heptanes **215** with diverse functionality around the cyclobutane and very good functional group tolerance (Scheme 3.13). Examples included cycloaddition with alkenes bearing functional groups such as amides **216**, allyl bromides **217**, vinyl esters **218**,

ketones **219**, sulfonyl fluorides **220**, heteroaromatics **221** and some disubstituted examples **222-223**. Notably, in all cases where a diastereomeric mixture was obtained, pure diastereomers were isolated and the configurations were assigned by analogy to X-ray crystal structures of a methyl ester and bromide **217**.



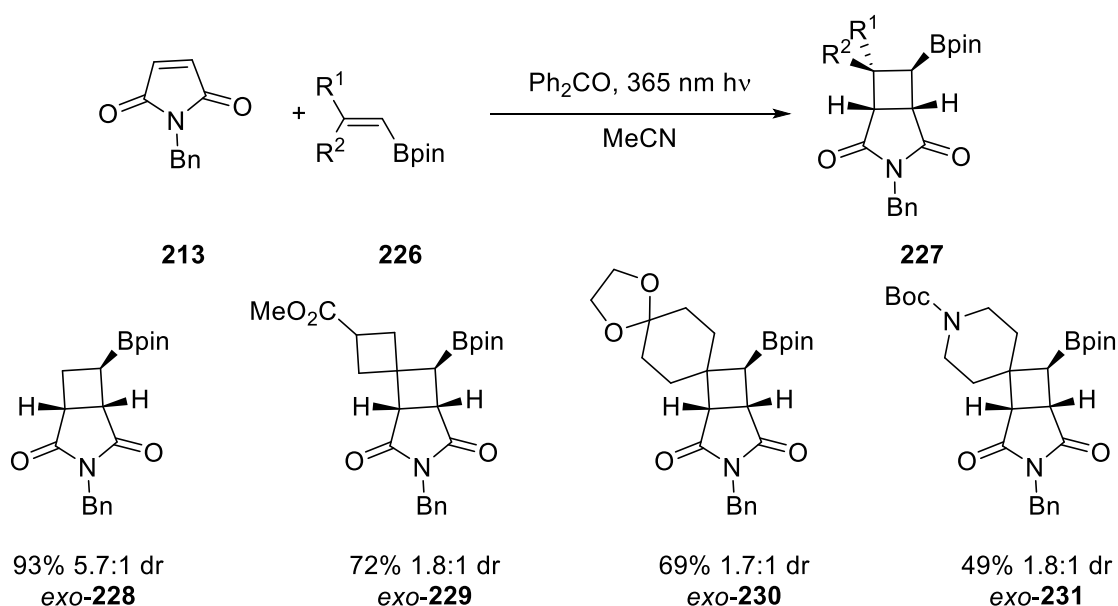
Scheme 3.13

As an example of further functionalisation, Mykhailiuk and co-workers took acetates **218** and performed a LiAlH₄ reduction followed by a high-pressure Pd-catalysed debenzoylation to afford amino alcohols **224** in 70% yield. Following this, Boc protection and oxidation of the alcohols using DMP afforded *N*-Boc ketone **225** in 68% yield (Scheme 3.14).²⁴⁸



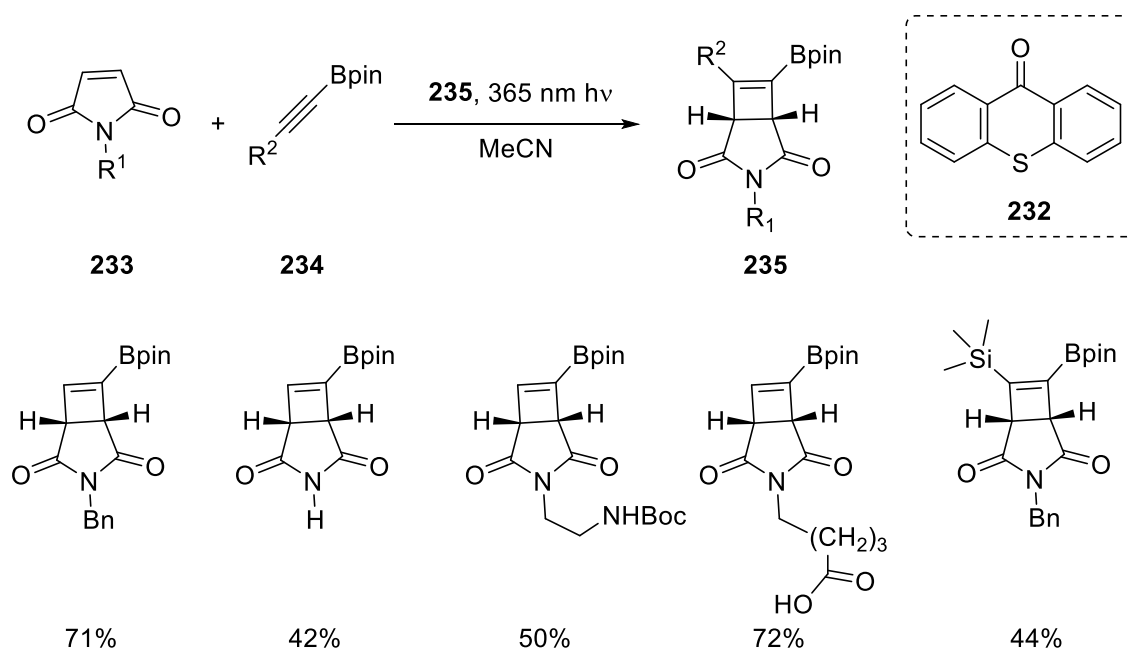
Scheme 3.14

Expanding on their colleague's methodology, Grygorenko and co-workers carried out [2+2] cycloadditions of *N*-Bn maleimide **213** with alkenyl pinacol boronates.²⁷⁴ By modifying the stoichiometry of the reaction, the [2+2] cycloaddition of a diverse set of alkenyl pinacol boronates **226** with *N*-Bn maleimide **213** to give cyclobutyl pinacol boronates **227** was achieved in good yields albeit in poor diastereomeric ratios (Scheme 3.15). Notably, only the piperidine-substituted cyclobutyl pinacol boronate **231** allowed for the separation of its diastereomers, even when using specialized 2-cyanoethyl-modified silica gel semipreparative columns thus diminishing the applicability of the methodology.



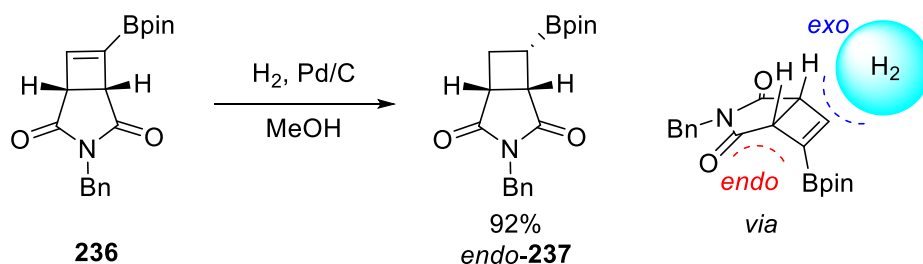
Scheme 3.15

Further development on their methodology was reported by Grygorenko and co-workers in 2023 an exploration into using alkynyl pinacol boronates in the [2+2] cycloaddition for the synthesis of 3-azabicyclo[3.2.0]heptanes.²⁷⁵ By using thioxanthone **232** as a photosensitizer, [2+2] photoinitiated cycloaddition of *N*-substituted maleimides **233** with diversely substituted alkynyl pinacol boronates **234** gave unsaturated 3-azabicyclo[3.2.0]heptanes **235** (Scheme 3.16). Functionalities tolerated included Boc protected amines, carboxylic acids, and some silicon functionalities.



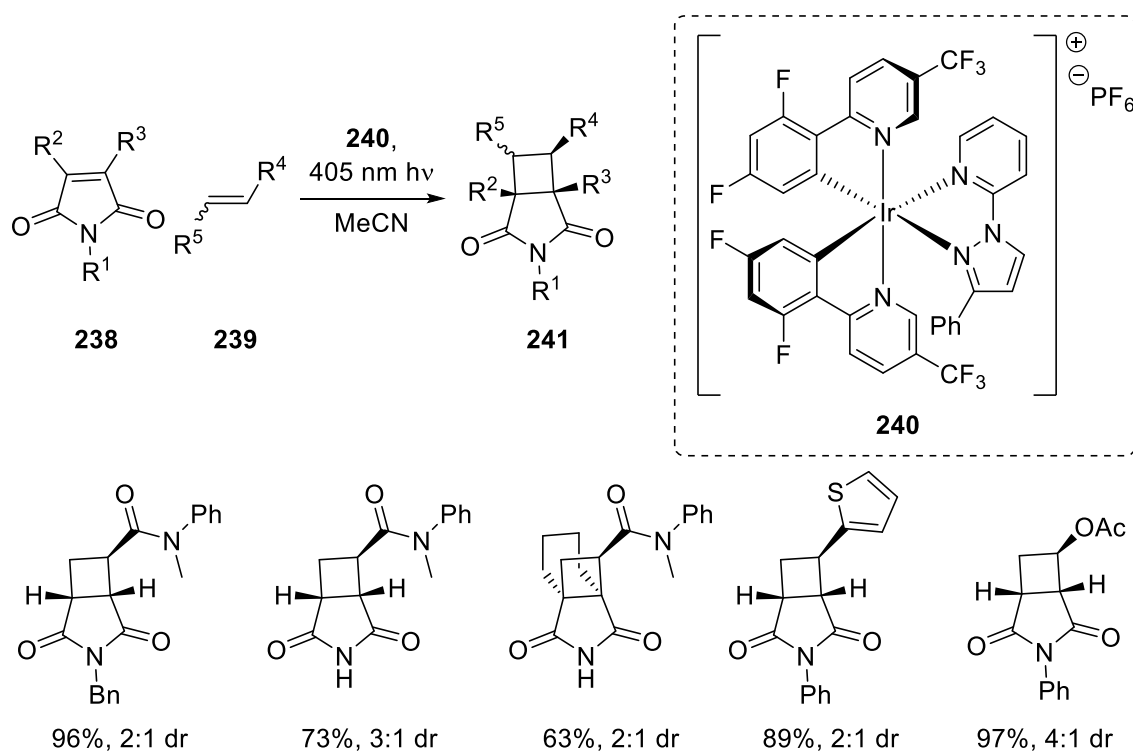
Scheme 3.16

Grygorenko and co-workers also explored a diverse range of functionalisation possibilities for the pinacol boronates **236**.²⁷⁵ One example is shown in Scheme 3.17. Hydrogenation of pinacol boronate **236** gave cyclobutyl boronate *endo*-**237** in 92% yield, with stereoselectivity coming from preferential approach of the hydrogenation catalyst over the least hindered *exo*-face of the alkene.



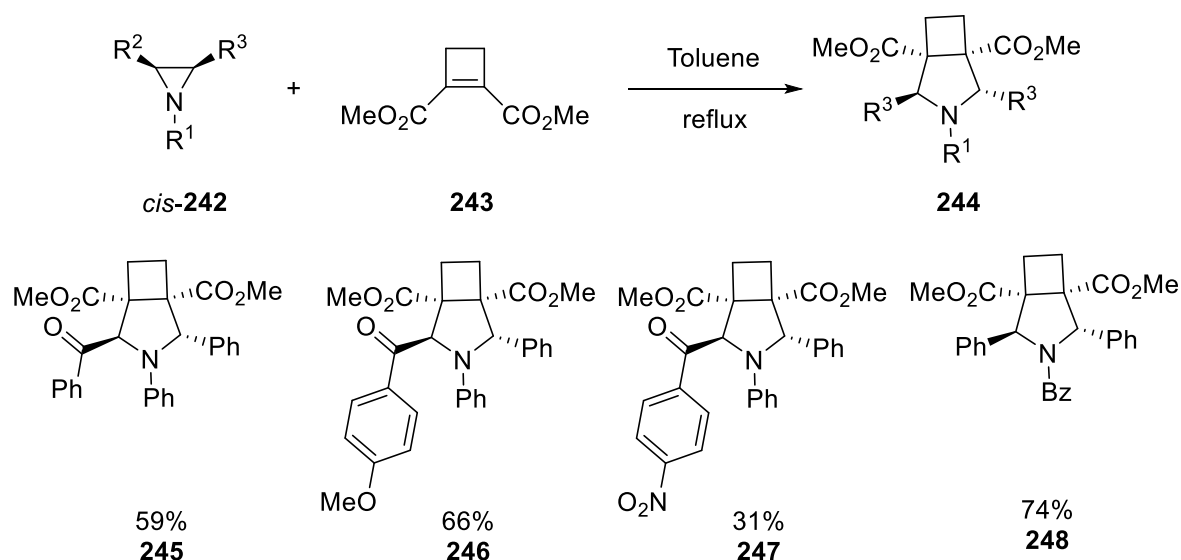
Scheme 3.17

Using a similar [2+2] cycloaddition methodology, Liu and co-workers also reported the cycloaddition of maleimide derivatives with diverse olefins for the synthesis of the 3-azabicyclo[3.2.0]heptane core.²⁷⁶ Using maleimides **238**, olefins **239** and Ir-catalyst **240**, a range of substituted cyclobutanes **241** were prepared in excellent yields and variable diastereoselectivity (Scheme 3.18). The Ir-catalyst allowed for the use of longer wavelengths in the photoinitiation, and this enabled a broader range of functionality around the amino and cyclobutane motifs.



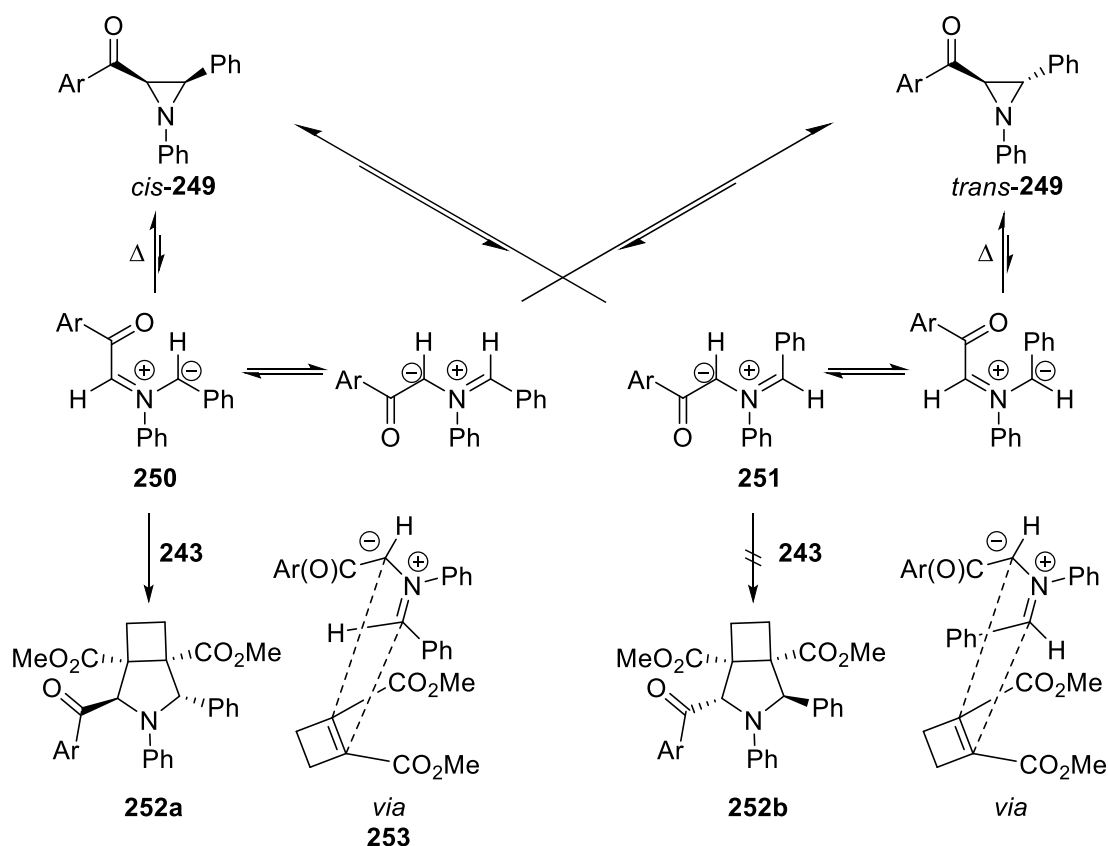
Scheme 3.18

In contrast to the [2+2] cycloadditions where the cyclobutane system is the one formed, [3+2] cycloadditions where the pyrrolidine system is formed are significantly less prevalent. In the synthesis of 3-azabicyclo[3.2.0]heptanes, these approaches consist primarily in 1,3-dipolar cycloadditions of a variety of *in situ*-generated dipoles to diversely substituted activated cyclobutenes.²⁷⁷ This approach was first reported by Lown and co-workers in 1994 in their studies into 1,3-dipolar cycloadditions of monocyclic aziridines.²⁷⁷ Reaction of aziridines *cis*-**242** with cyclobutene dicarboxylate **243** in refluxing toluene yielded fused cyclobutyl pyrrolidines **244** in good yields and as single diastereomers (Scheme 3.19). This methodology proceeds via ring opening of the aziridines to generate a 1,3-dipole which undergoes a cycloaddition with the alkene. This incurs in poor functional group tolerance due to the instability of the azomethine ylide generated by thermal ring opening of the aziridine.



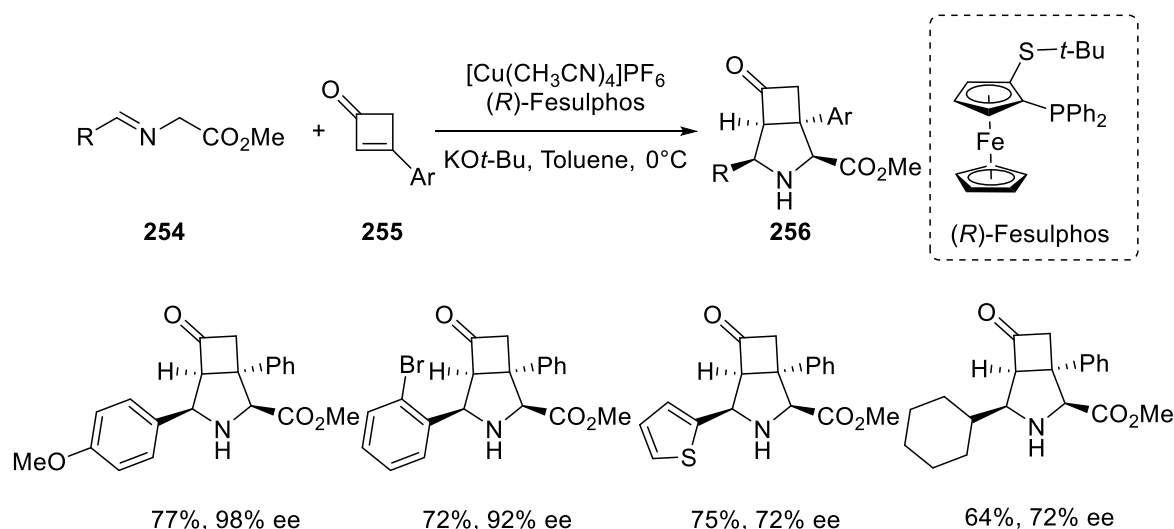
Scheme 3.19

Of note, for benzoyl-substituted aziridines **249**, both the *cis* and *trans* isomers yielded the same diastereomeric cyclobutanes **252a**. This is explained by both a preferential addition guided by sterics and secondary orbital interactions and the possibility of this aziridines to interconvert by a ring opening, isomerisation, electrocyclization sequence. Importantly, aziridines *cis* and *trans*-**249** undergo thermal conrotatory ring opening to yield azomethine ylides **250** and **251** respectively. Here, only ylide **250** (from aziridine *cis*-**249**) can successfully give fused cyclobutane **252a** via transition state **253** where the Ph group has secondary orbital interactions with the cyclobutyl carboxylate and avoids steric clash with the cyclobutyl protons. However, ylide **251** (from aziridine *trans*-**249**) can undergo disrotatory thermal 4π electrocyclisation to yield aziridine *cis*-**249** and in turn fused cyclobutane **252a** (Scheme 3.20).²⁷⁸



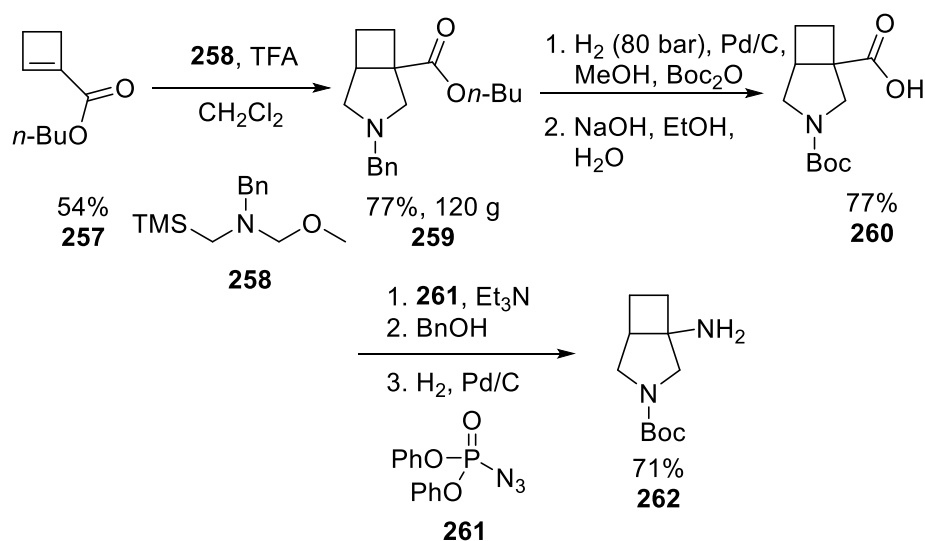
Scheme 3.20

The use of azomethine ylides in [3+2] cycloadditions for the synthesis of bicyclo[3.2.0]heptanes was also investigated by Carretero and co-workers in 2018.²⁷⁹ The azomethine ylides were generated by reacting iminoesters **254** with KO*t*-Bu in the presence of a Cu-catalyst. The ylide then undergoes [3+2] cycloaddition with cyclobutenones **255** to yield fused cyclobutanes **256** in good yields and enantioselectivities (Scheme 3.21). Although this methodology allows for the synthesis of diversely substituted fused cyclobutanes with good enantioselectivity and functionalisation potential due to the ketone, the necessary aromatic substitution in the bridgehead position presents a significant drawback.



Scheme 3.21

Grygorenko and co-workers at Enamine have also utilised [3+2] cycloadditions with azomethine ylides for the synthesis of 3-azabicyclo[3.2.0]heptanes.²⁷⁷ Cyclobutene **257** underwent [3+2] cycloaddition with an ylide derived from amine **258** to yield fused cyclobutyl pyrrolidine **259** in 77% in up to 120 g batches. The *N*-Bn group in cyclobutyl pyrrolidine **259** was then removed by high-pressure hydrogenation and then Boc protected to give an *N*-Boc pyrrolidine which after saponification of the ester yielded *N*-Boc aminoacid **260** in 77% yield (Scheme 3.22). The synthesis of a range of building blocks derived from it was then explored.²⁷⁷ Namely monoprotected amine **262** was made by a modified Curtius rearrangement followed by Pd-catalysed hydrogenolysis of the *N*-Bn group into diamine **262** in 71% overall yield.



Scheme 3.22

Markedly, Grygorenko and co-workers performed vector analysis on the cyclobutyl pyrrolidines.²⁷⁷ Similarly to the results obtained by the O'Brien group (see Figure 2.3), Grygorenko found that the cyclobutyl pyrrolidines occupied the area of $100^\circ > \theta > 120^\circ$ and $2 > r > 3$ Å in an area they designated as δ which is usually occupied by trans-1,3-disubstituted cyclopentanes and cyclohexanes (Figure 3.4).

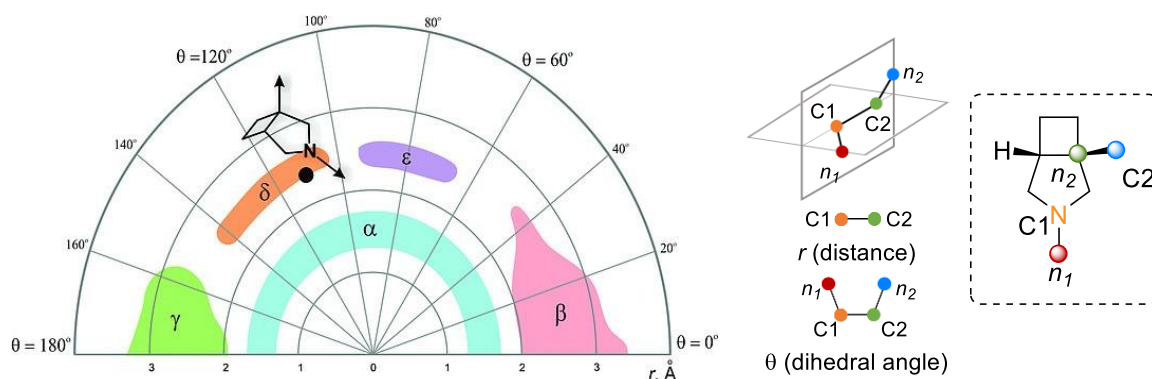
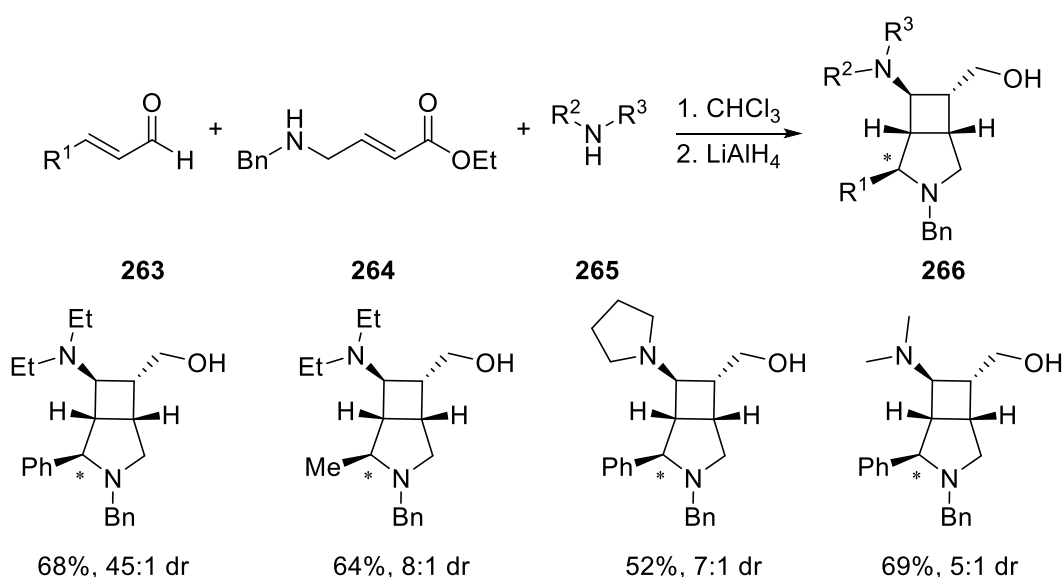


Figure 3.4 – EVP analysis of the Grygorenko cyclobutyl pyrrolidines. Taken from Grygorenko²⁷⁷

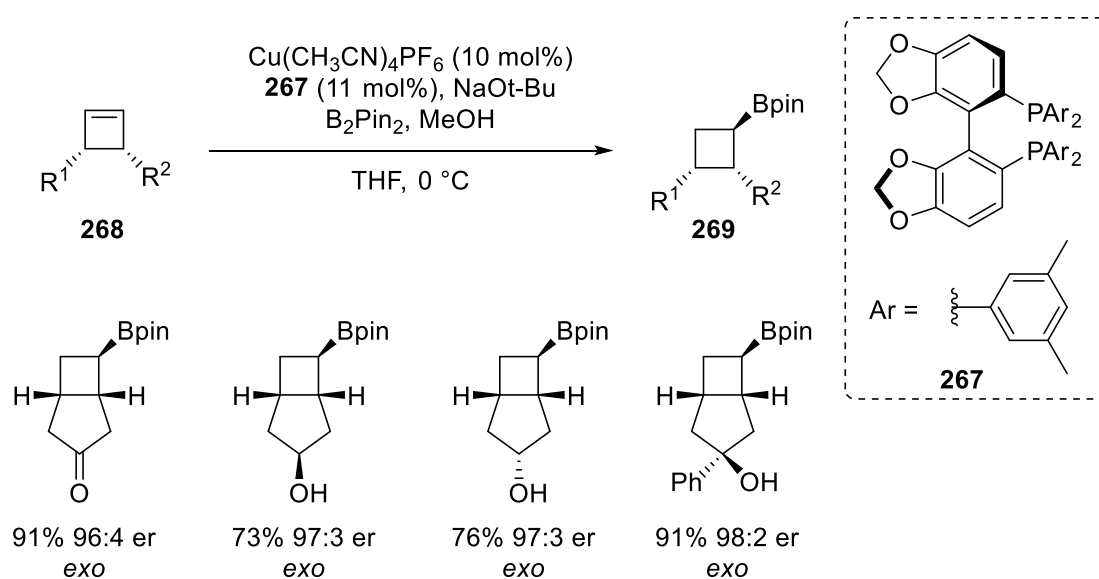
An alternative uncommon approach for the synthesis of 3-azabicyclo[3.2.0]heptanes was reported by Kanger and co-workers in 2010, namely the use of a multicomponent reaction.²⁸⁰ By reacting unsaturated aldehydes **263** with α,β -unsaturated- γ -aminoester **264** and a secondary amine **265** to give 3-azabicyclo[3.2.0]heptane esters, the ester was then reduced with LiAlH_4 to give diaminoalcohols **266** in good yields and diastereoselectivities with respect to the C-R¹ bond (Scheme 3.23).



Scheme 3.23

Additionally to the methods so far exposed, other alternatives such as Ghosez's keteneiminium cycloadditions²⁸¹, intramolecular cyclisations in cycloheptanes²¹¹ and multi-step syntheses²⁸²⁻²⁸⁴ are available for different isomers of bicyclo[3.2.0]heptanes. However, these isomers lie outside the scope of this overview. Nonetheless, methodologies that rely on the functionalisation of the cyclobutane motif in preformed bicyclo[3.2.0]heptanes are of relevance and will be briefly addressed. Most of these functionalisations can be classified in two different types: functionalisation that relies on the reactivity of cyclobutenes and that which relies on C-H activation in cyclobutanes.²⁸⁵

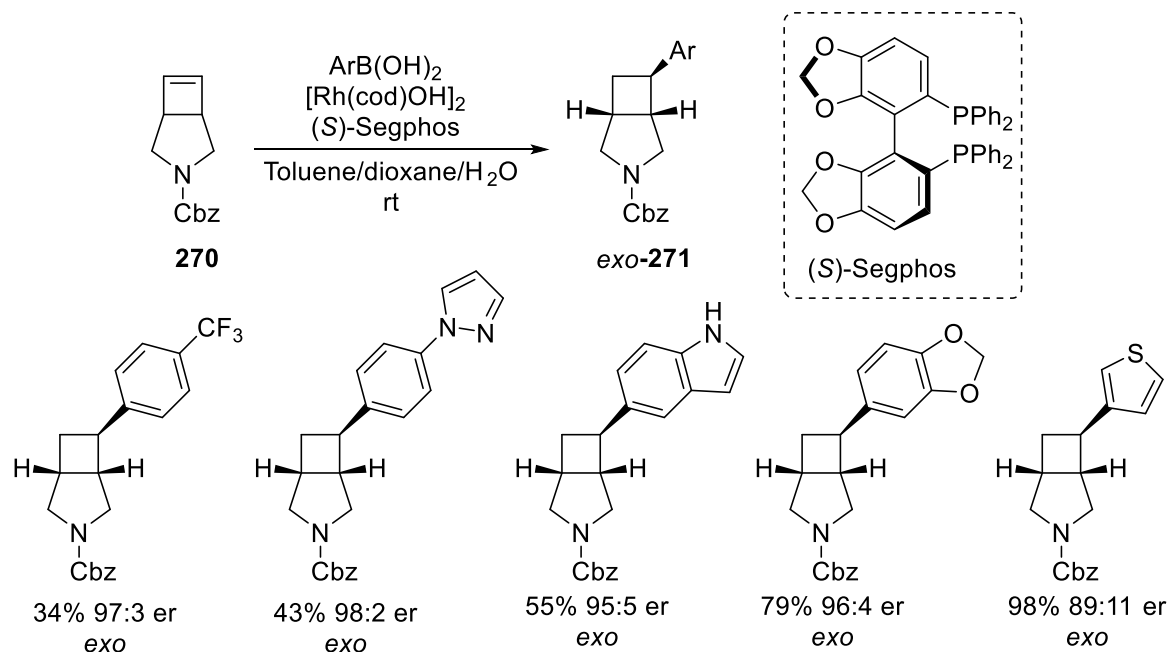
In the functionalisation of cyclobutenes, a methodology that stands out is Cu-catalysed borylations developed by Tortosa and co-workers.^{193, 286, 287} Use of catalytic $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$, ligand **267**, NaOt-Bu and MeOH enabled the borylation of cyclobutenes **268** to give cyclobutyl boronates **269** in excellent yields and enantioselectivities (Scheme 3.24).²⁸⁶ This methodology was also applied to an interesting set of bicyclo[3.2.0]heptanes.



Scheme 3.24

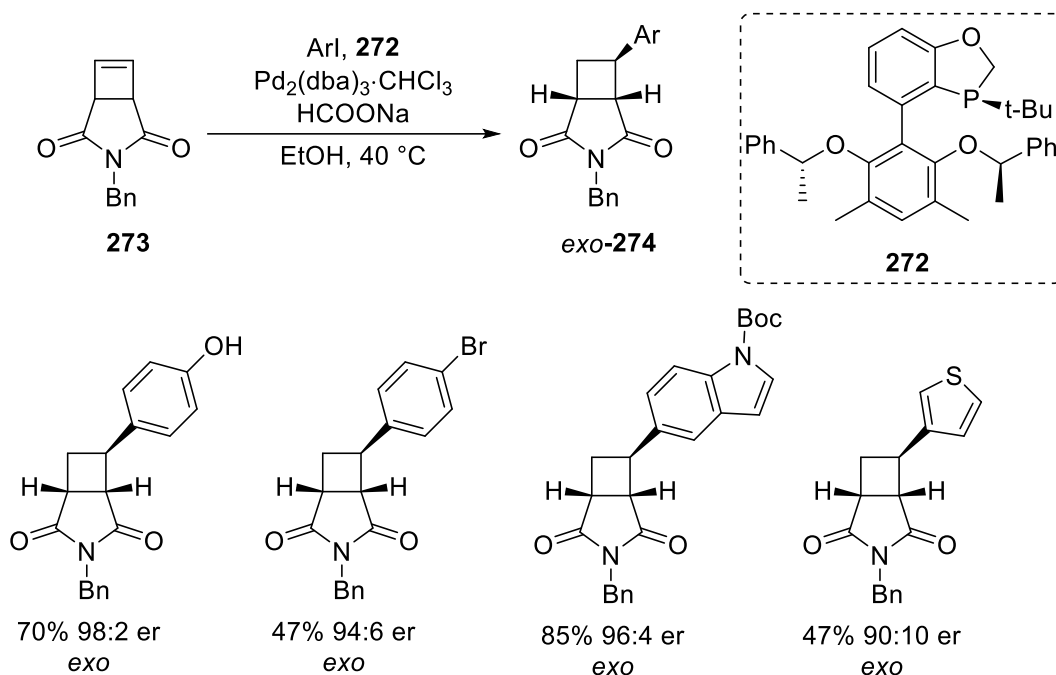
Further functionalisation of cyclobutenes was developed by Fletcher and co-workers in the exploration of Rh-catalysed hydroarylations of cyclobutenes.²²⁵ Using a Rh precatalyst and (S)-Segphos, the enantioselective hydroarylation of unsaturated bicyclo[3.2.0]heptanes **270** with diverse aromatic and heteroaromatic boronic acids was accomplished to give arylated cyclobutanes **271** in good yields and excellent enantioselectivities (Scheme 3.25). This methodology could also be applied to spirocyclic and non-fused cyclobutanes albeit with diminished enantioselectivities. Additionally, in subsequent work, Fletcher and co-workers

expanded their methodology to include the catalytic asymmetric hydrometallation of bicyclo[3.2.0]heptanes with salicylaldehydes.²²⁶



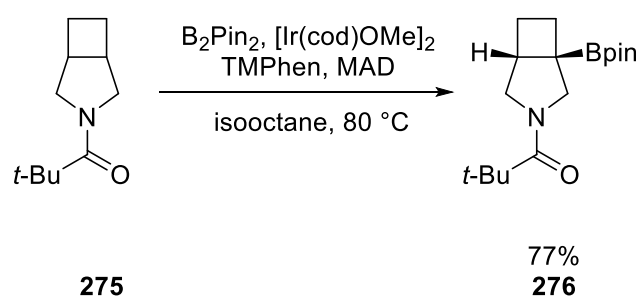
Scheme 3.25

Similar to Fletcher's methodology, Lu and co-workers developed a Pd-catalysed hydroarylation of unsaturated bicyclo[3.2.0]heptanes.²⁸⁸ Under reductive Heck conditions, use of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$, ligand **272** and HCOONa allowed for the hydroarylation of cyclobutene **273** with aryl iodides to yield arylated cyclobutanes *exo*-**274** in good yields and enantioselectivities (Scheme 3.26). With this methodology, a good scope of aryl iodides was demonstrated.



Scheme 3.26

Finally, a methodology worth mentioning is Nakao and co-workers' C-H borylation by Ir/Al-catalysis (see Section 2.3, Scheme 2.14).¹²¹ Although most of the examples are on cyclopropanes, $[\text{Ir}(\text{cod})\text{OMe}]_2$, TMPhen and MAD were used for the borylation of *N*-Piv bicyclo[3.2.1]heptane **275** in the bridgehead position to yield borylated cyclobutane **276** in 77% yield (Scheme 3.27).

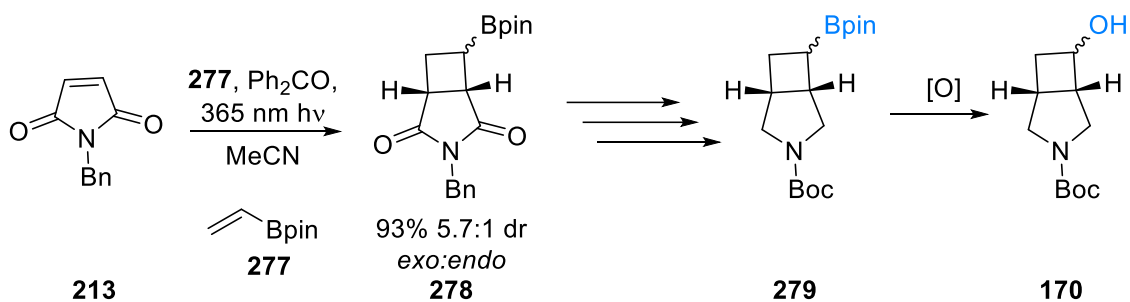


Scheme 3.27

3.4 Synthesis of Cyclobutyl Building Blocks

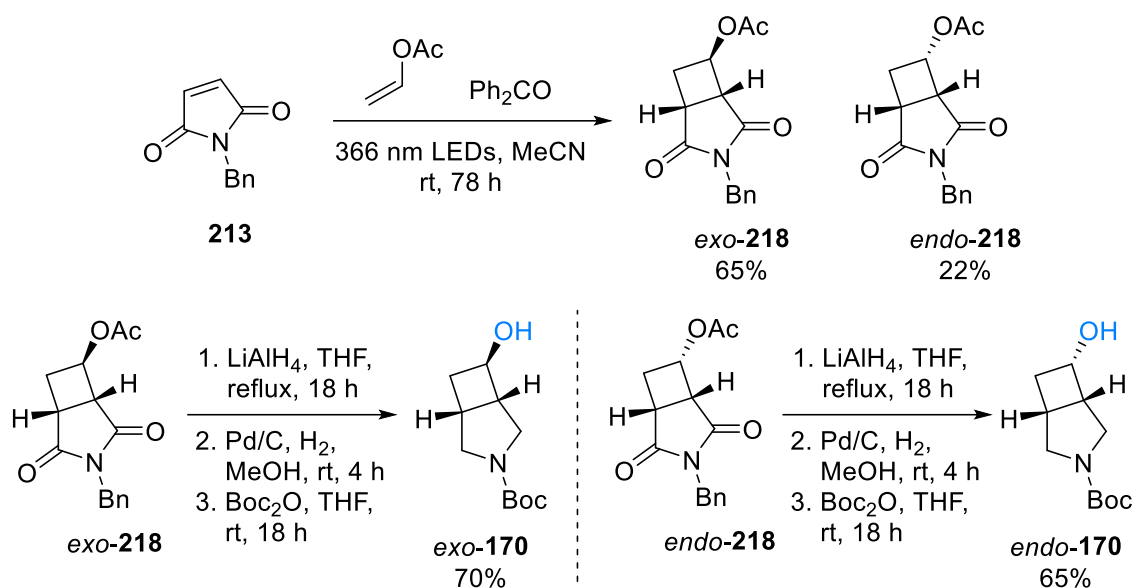
3.4.1 Synthesis of Hydroxy-containing Cyclobutane Building Blocks

Based on previous work by Grygorenko and co-workers, two possibilities for the synthesis of cyclobutyl building blocks **170** and **171** were apparent (see Section 3.3, Schemes 3.13, 3.15). The first would involve photosensitized [2+2] cycloaddition of *N*-Bn maleimide **213** with vinyl pinacol boronate **277** to give pinacol boronates **278**, which was reported to proceed in 93% yield with *exo* diastereoselectivity. Then, reduction, debenzylation and Boc protection should give pinacol boronates **279** which could subsequently be oxidised into alcohols **170** (Scheme 3.28). However, while this route would allow for the expedient synthesis of both boron and oxygen-containing building blocks, from Grygorenko's observations, separation of the diastereomers of this series of compounds could prove difficult.²⁷⁴



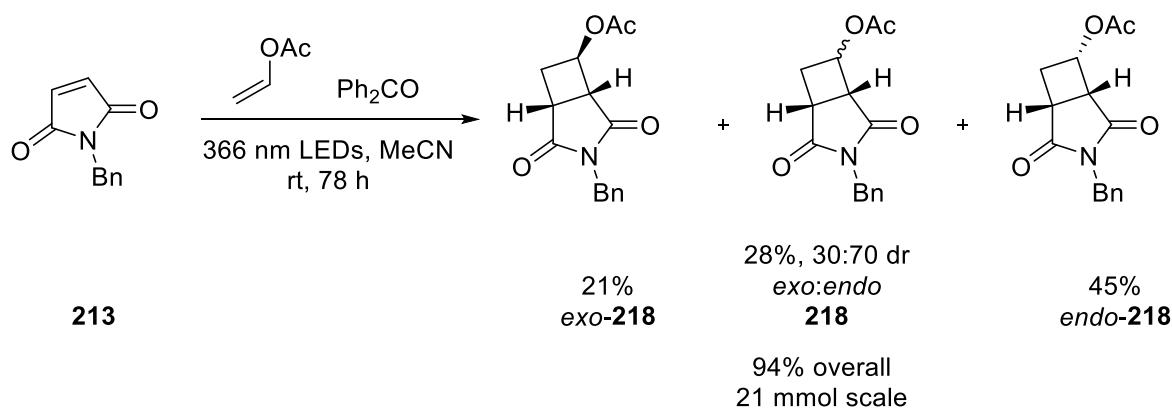
Scheme 3.28

Alternatively, Grygorenko and co-workers' photosensitized [2+2] cycloaddition methodology would allow for expedited access to diastereomeric alcohols *endo*- and *exo*-**170** via imides *endo*- and *exo*-**218** (Scheme 3.29).²⁴⁸ In their work, *N*-benzylmaleimide **213** was reacted with vinyl acetate using benzophenone as photosensitizer. This afforded maleimides *exo*- and *endo*-**218** in 65% and 22% yield respectively. Maleimides *exo*- and *endo*-**218** were then separately reduced with LiAlH_4 , the *N*-Bn group removed by hydrogenolysis, and the amine Boc protected to give alcohols *exo*- and *endo*-**170** in 70% and 65% yield respectively.



Scheme 3.29

From this, the initial goal involved reaching a reproducible way to access alcohols *endo*- and *exo*-170 in a sufficiently large scale to be able to access significant quantities of them for exploration of cross-coupling and accessing BF_3K salts *endo*- and *exo*-171 via a route that is outlined later. Thus, *N*-benzylmaleimide **213** was reacted with vinyl acetate and benzophenone by irradiation with a 365 nm LED lamp. This afforded imide *exo*-218 in 45% yield, imide *endo*-218 in 21% yield and a 70:30 mixture of imides *exo* and *endo*-218 in 28% yield (Scheme 3.30). This methodology was able to be scaled to up to 21 mmol (27.5 g) in 94% overall yields.



Scheme 3.30

In our results, despite the characterization of the major and minor products coinciding with those reported by Grygorenko and co-workers,²⁴⁸ our efforts to confirm the stereochemistry of the products by oxidation of the vinyl boronates (see Section 3.4.2, Scheme 3.42)

contradicted Grygorenko's assignments. Thus, a crystal was grown from the minor product which after X-ray crystallographic analysis confirmed it as imide **exo-218** (Figure 3.5).

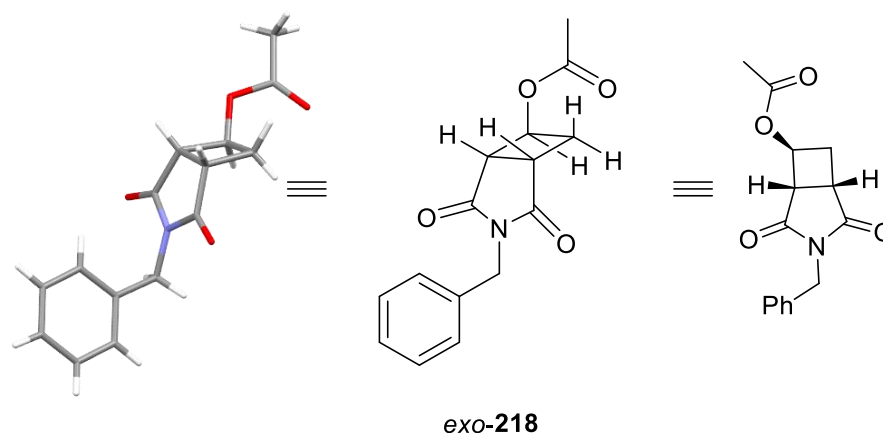
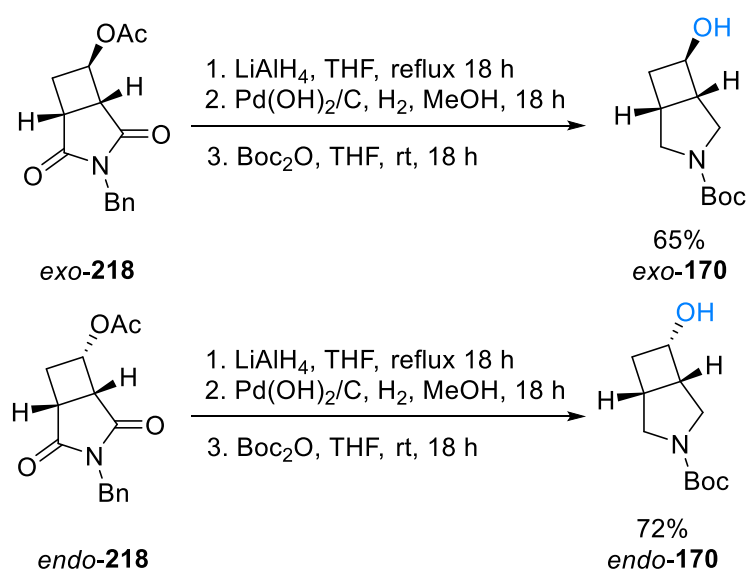


Figure 3.5 – X-Ray crystal structure of imide **exo-218**

In a manner similar to that previously outlined by Grygorenko and co-workers (see Scheme 7), imides **exo-** and **endo-218** were separately reduced with LiAlH_4 , the *N*-Bn group removed by hydrogenolysis, and the amine protected with Boc_2O to give alcohols **exo-** and **endo-170** in 65% yield and 72% yield respectively over 3 steps with a single purification at the final step (Scheme 3.31). A combined 30:70 mixture of imides **exo-** and **endo-218** was also submitted to these conditions to yield a 30:70 mixture of alcohols **exo-** and **endo-170** in 65% yield. Of note, when attempting the hydrogenolysis by using Pd/C at atmospheric pressure no conversion was observed, whereas the use of $\text{Pd}(\text{OH})_2$ gave complete debenzylation even at atmospheric pressure.

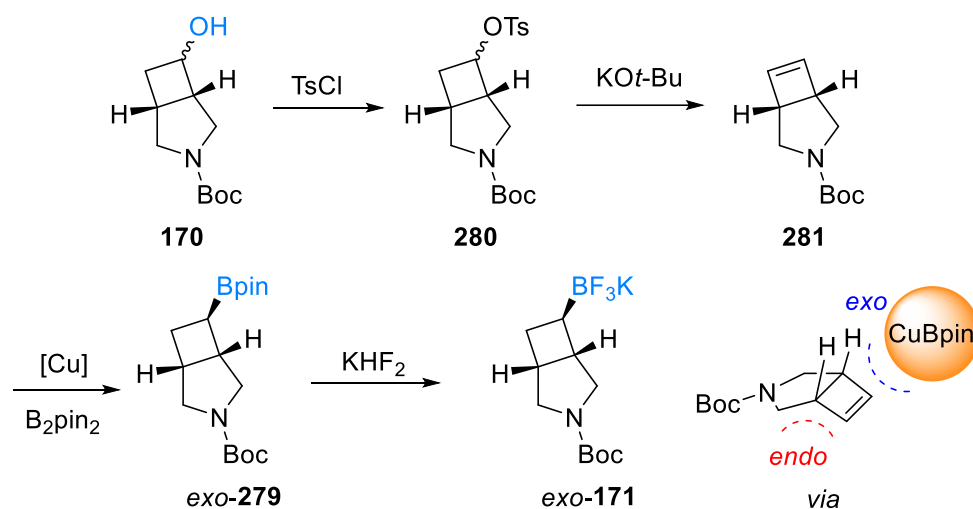


Scheme 3.31

From here, diastereomerically pure alcohols *exo*- and *endo*-**170** were utilised for studying the direct photoredox cross-coupling (see Section 3.5.1). The 30:70 mixture of alcohols *exo*- and *endo*-**170** was used for the synthesis of cyclobutyl trifluoroborates *exo*- and *endo*-**171**.

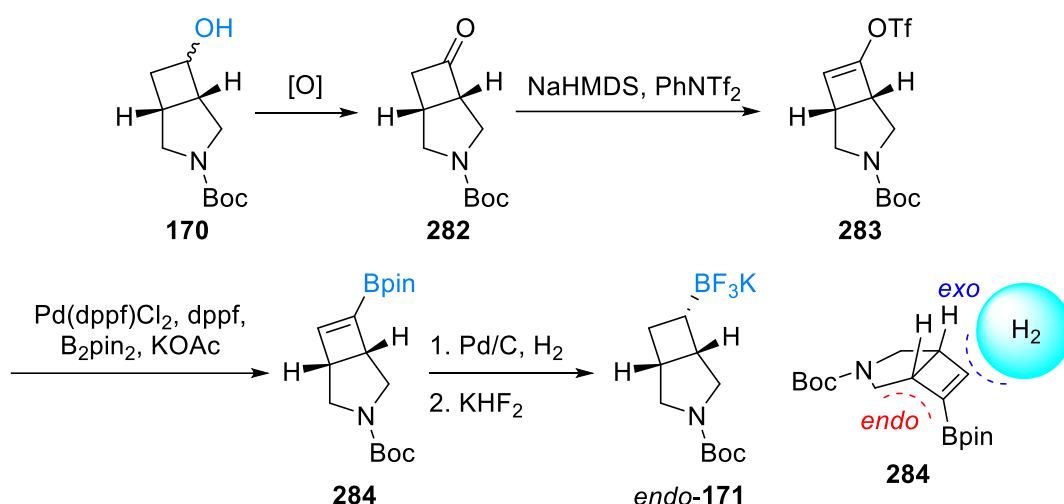
3.4.2 Synthesis of BF₃K-containing Cyclobutane Building Blocks

We envisaged that, using a previously reported route by Tortosa and co-workers,²⁸⁷ alcohols **170** could be utilised to access cyclobutyl trifluoroborate *exo*-**171** by tosylation into sulfonates **280**, elimination to give alkene **281** and sterically-driven diastereoselective Cu-catalysed borylation (on the *exo* face) to give pinacol boronate *exo*-**279**. Finally, BF₃K salt formation would give access to cyclobutyl trifluoroborate *exo*-**171** (Scheme 3.32).



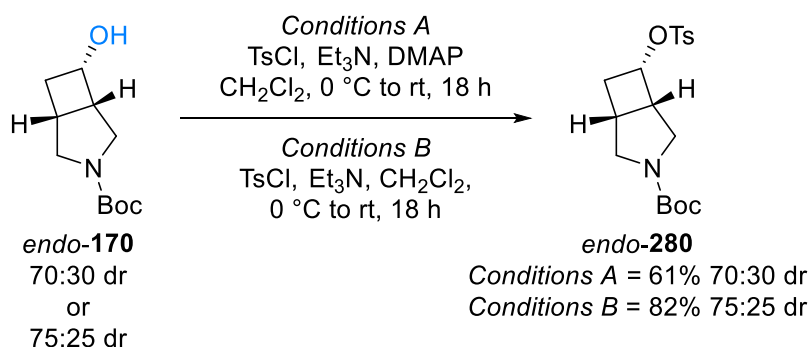
Scheme 3.32

On the other hand, we proposed that access to cyclobutyl trifluoroborate *endo*-**171** could be achieved by an in-group developed methodology.¹⁴³ Oxidation of alcohols **170** would afford cyclobutanone **282** from which enolisation and triflation to give vinyl triflate **283** could be carried out. Then, Miyaura borylation should give vinyl pinacol boronate **284**. Subsequent hydrogenation and BF₃K formation should deliver cyclobutyl trifluoroborate *endo*-**171** (Scheme 3.33). Stereoselectivity was expected from preferential hydrogenation of vinyl pinacol boronate **284** from the least-hindered *exo*-face as was observed by Grygorenko and co-workers for a structurally related compound (see Section 3.3, Scheme 3.17).²⁷⁵



Scheme 3.33

For the route to cyclobutyl trifluoroborate *exo*-**171** (see Scheme 3.32), it was necessary to prepare cyclobutene **281** as an intermediate. Initially, starting from a 70:30 mixture of alcohols *endo*- and *exo*-**170**, tosylation using TsCl, Et₃N and DMAP afforded a 70:30 mixture of sulfonates *endo*- and *exo*-**280** in 61% yield. However, purification of tosylates *endo*- and *exo*-**280** proved difficult as an impurity which eluted between the two diastereomers was observed. Thus, a second attempt was made without using DMAP. A 75:25 mixture of alcohols *endo*- and *exo*-**170** was reacted with TsCl and Et₃N to give a 75:25 mixture of tosylates *endo*- and *exo*-**280** in 82% yield (Scheme 3.34). Gratifyingly, not using DMAP gave a significantly cleaner reaction with an easier purification.



Scheme 3.34

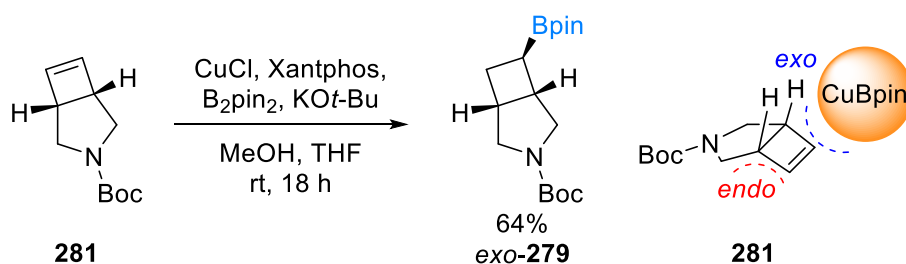
The next step involved elimination of the tosylate using KOT-Bu as reported by Tortosa and co-workers for related cyclobutane systems.²⁸⁶ Thus, a 70:30 mixture of tosylates *endo*- and *exo*-**280** in DMSO was treated with KOT-Bu at 25 °C to give cyclobutene **281** in 40% yield (Scheme 3.35). Variable yields of cyclobutene **281** were observed during repetitions of the elimination step which, upon further assessment, were attributed to its high volatility. This

is a characteristic that Tortosa and co-workers also noted for structurally related compounds²⁸⁷ and that we have noticed with different low molecular weight *N*-Boc compounds in the group.



Scheme 3.35

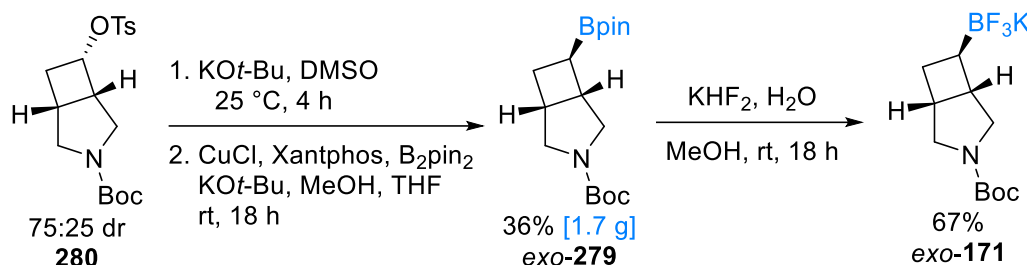
With cyclobutene **281** in hand, we moved on to explore the *exo*-selective borylation with conditions adapted from Tortosa and co-workers' borylation of spirocyclobutenes.²⁸⁷ Reacting the alkene in cyclobutene **281** with B₂pin₂, CuCl, Xantphos and KOt-Bu gave cyclobutyl pinacol boronate *exo*-**279** in 64% yield (Scheme 3.36). The diastereoselectivity of the borylation arises from the preferential addition of the CuBpin complex to the less-hindered *exo*-face of alkene **281**. As discussed later (see Scheme 3.42), the stereochemistry of the diastereomeric cyclobutyl pinacol boronate *endo*-**279** was established by conversion into the corresponding alcohol *endo*-**279**, which also confirms the stereochemistry of cyclobutyl pinacol boronate *exo*-**279**.



Scheme 3.36

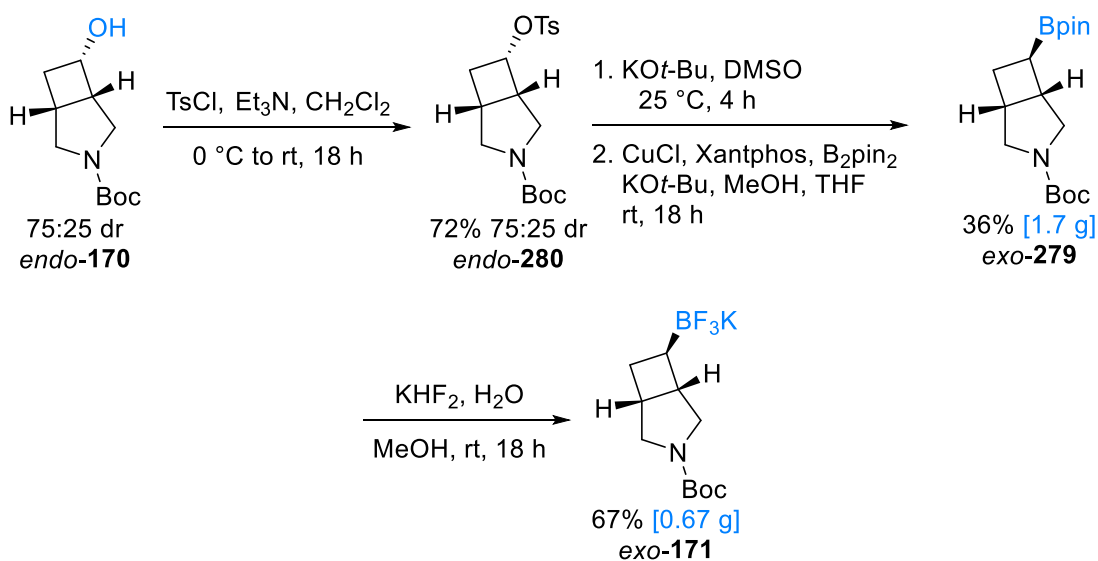
Gratifyingly, the borylation of the alkene could also be performed on the crude alkene **281** generated from tosylate elimination. Thus a 75:25 mixture of tosylates *endo*- and *exo*-**280** was treated with KOt-Bu in DMSO at 25 °C and the solids in the reaction mixture removed by filtration through a pad of silica eluting with Et₂O (least volatile solvent available). The filtrate was partially evaporated (due to the volatility of this intermediate, cyclobutene **281**) and reacted with B₂pin₂, CuCl, Xantphos and KOt-Bu in THF to give cyclobutyl pinacol boronate *exo*-**279** in 36% yield over the two steps (Scheme 2.37). In this way, cyclobutyl

pinacol boronate *exo*-**279** could be synthesised in up to 1.7 g quantities. Finally, synthesis of the trifluoroborate salt proceeded smoothly using general conditions reported by Molander and co-workers.¹⁷³ Reaction of pinacol boronate *exo*-**279** with KHF₂ in MeOH and H₂O gave cyclobutyl trifluoroborate *exo*-**171** in 67% yield.



Scheme 3.37

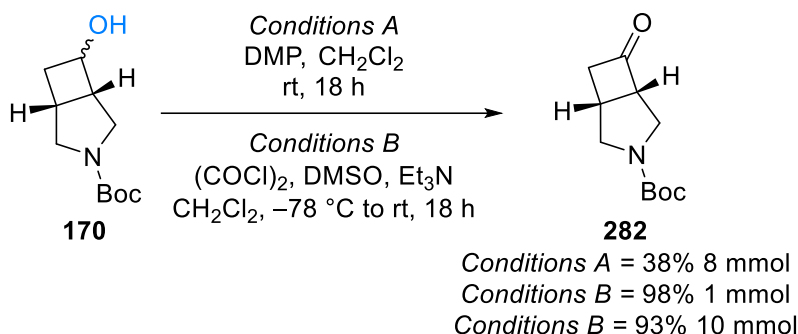
In this way, the synthesis of cyclobutyl trifluoroborate building block *exo*-**171** was completed in four steps and 17% overall yield from cyclobutyl alcohols **170** with 0.67 g of cyclobutyl building block *exo*-**171** synthesised (Scheme 3.38).



Scheme 3.38

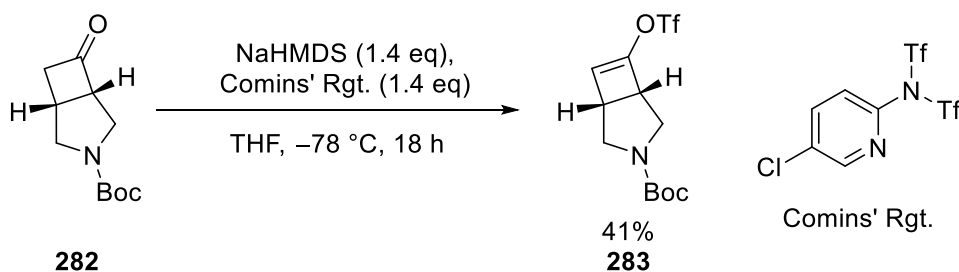
With cyclobutyl building block *exo*-**171** in hand, we next explored the synthesis of cyclobutyl building block *endo*-**171** according to the route proposed previously (see Scheme 3.33). The first step involved oxidation of alcohols **170** into ketone **282** which we attempted doing using DMP as previously reported by Grygorenko and co-workers.²⁴⁸ However, reacting a 75:25 mixture of alcohols *endo*- and *exo*-**170** with DMP in CH₂Cl₂ afforded ketone **282** in a low 38% yield after multiple chromatographic purifications. Therefore, Swern oxidation conditions were attempted. Gratifyingly, reacting a 70:30 mixture of alcohols

endo- and *exo*-**170** with (COCl)₂, DMSO and Et₃N in CH₂Cl₂ afforded ketone **282** in 98% after a single chromatographic purification on a 1 mmol scale. Likewise, performing the Swern oxidation on a 20 mmol scale afforded ketone **282** in 91% yield (Scheme 3.39).



Scheme 3.39

Formation of a vinyl triflate from ketone **282** was the next step. From conditions previously utilised for spirocyclic cyclobutanes in the group,²⁸⁹ initial conditions utilising NaHMDS and Comins' reagent²⁹⁰ were attempted. Thus, ketone **282** was reacted with NaHMDS and the formed enolate trapped with Comins' reagent to give vinyl triflate **283** in 41% yield (Scheme 3.40). In addition to the low yields, difficulty in the chromatographic purification coupled with irreproducibility made it necessary to explore alternative conditions.

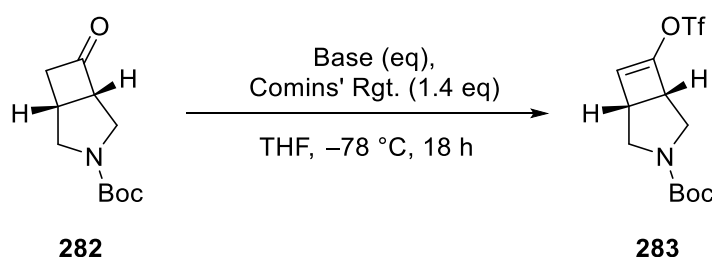


Scheme 3.40

Our attempts to optimise the vinyl triflate formation are summarised in Table 3.1, including the initial example (Entry 1). KHMDS is an alternative base that has been reported as useful in vinyl triflate formation for structurally related compounds.²⁹¹ Thus, reaction of ketone **282** with KHMDS and Comins' reagent in THF afforded enol triflate **283** in 39% yield, with significantly increased reproducibility and an easier chromatographic separation (Entry 2). From analysis of the ¹H NMR spectra of the crude reaction mixture, it suggested that formation of the enolate seemed to be the issue. Thus, a brief screening of alternative bases was performed. A change to LiHMDS²⁹² afforded vinyl triflate **283** in 23% yield (Entry 3). Alternatively, LDA afforded vinyl triflate **283** in under 10% yield as determined by ¹H NMR

spectroscopic analysis of the crude reaction mixture (Entry 4). From these results, KHMDS was selected as the best base. With this, increasing the equivalents from 1.4 eq to 2.0 eq to hopefully increase the degree of deprotonation of ketone **282** was attempted. In this way, reaction of ketone **282** with 2.0 eq of KHMDS and 1.4 eq of Comins' reagent afforded vinyl triflate **283** in 37% yield (Table 1, Entry 5). With these results, optimal reaction conditions settled on using 1.4 eq of KHMDS and 1.4 eq of Comins' reagent. Gratifyingly, on scale-up of the vinyl triflate formation to 15 mmol, vinyl triflate **283** was obtained in 53% yield using these conditions (Table 1, Entry 6).

Table 3.1 – Optimisation of vinyl triflate **283** formation

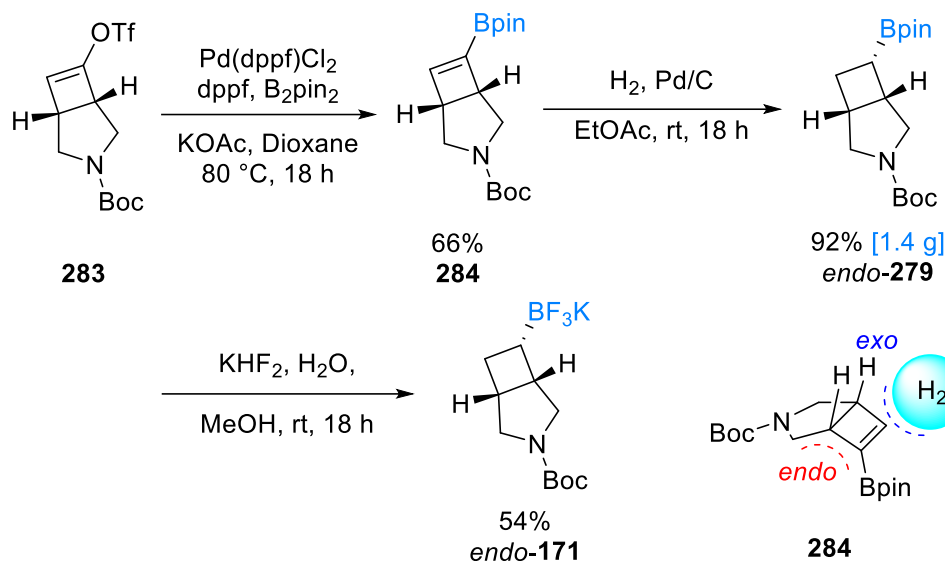


Entry	Base	Eq	Yield 283 (%) ^a
1	NaHMDS	1.4	41
2	KHMDS	1.4	39
3	LiHMDS	1.4	23
4	LDA	1.4	<10 ^b
5	KHMDS	2.0	37
6	KHMDS	1.4	53

^a % yield after chromatography; ^b from analysis of the ¹H NMR spectrum of the crude reaction mixture

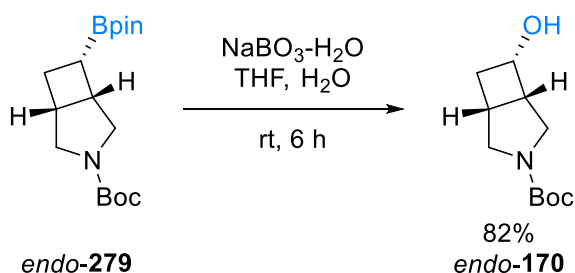
Next, Miyaura borylation of vinyl triflate **283** into vinyl pinacol boronate **284** followed by diastereoselective hydrogenation to give pinacol boronate *endo*-**279** were investigated. Using standard Miyaura borylation conditions,²⁹³ vinyl triflate **283** was reacted with B₂pin₂, PdCl₂dppf, additional dppf and KOAc in dioxane at 80 °C to yield vinyl pinacol boronate **284** in 66% yield. Vinyl pinacol boronate **284** was subsequently hydrogenated with H₂ and Pd/C to give pinacol boronate *endo*-**279** in 92% yield to obtain up to 1.4 g of product. The diastereoselectivity of this reaction comes from the preferential hydrogenation from the less hindered *exo* face of the alkene (Scheme 3.41). From here, the final step involved the formation of a BF₃K salt from pinacol boronate *endo*-**279**. Similarly to *exo*-**279**, pinacol

boronate *endo*-**279** was reacted with KHF_2 in MeOH and H_2O to give cyclobutyl trifluoroborate *endo*-**171** in 54% yield.



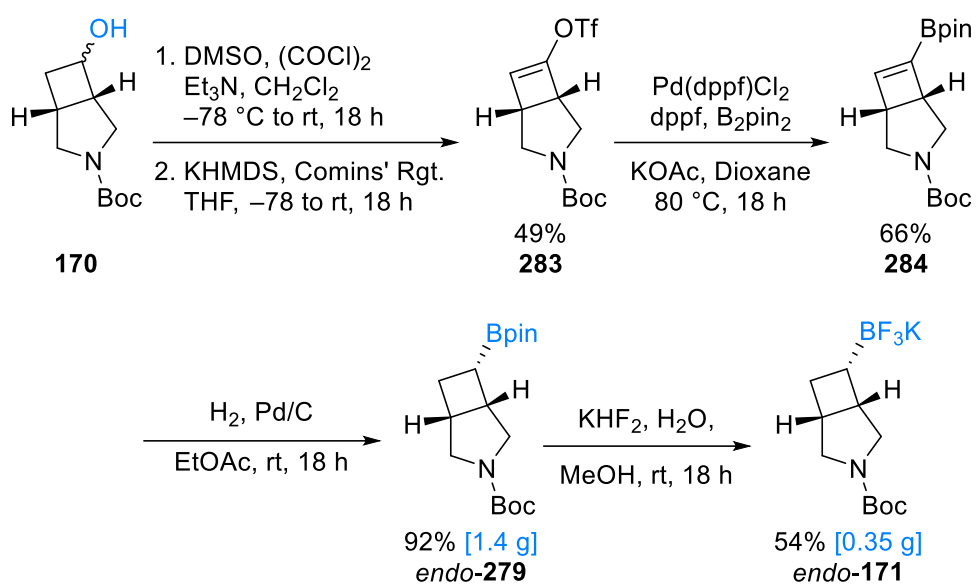
Scheme 3.41

With pinacol boronate *endo*-**279** in hand, we aimed to provide further evidence of the stereochemical identity of building blocks *endo* and *exo*-**170**. Thus, stereoretentive $\text{NaBO}_3\text{-H}_2\text{O}$ mediated oxidation of pinacol boronate *endo*-**279** gave cyclobutyl alcohol *endo*-**170** in 82% (Scheme 3.42). The ^1H NMR spectrum of this alcohol clearly matched that of alcohol *endo*-**171** prepared previously (see Scheme 3.31) and was actually the point at which we realised Grygorenko's erroneous stereochemical assignment.²⁴⁸



Scheme 3.42

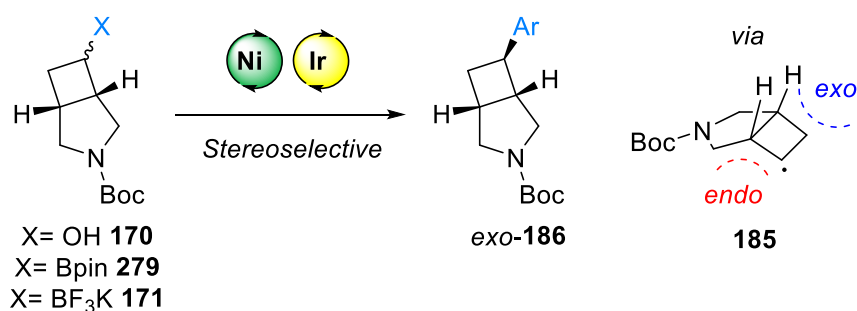
In this way, the synthesis of cyclobutyl trifluoroborate building block *endo*-**171** was completed in five steps and 16% overall yield from cyclobutyl alcohols **170** with 0.35 g of cyclobutyl building block *endo*-**171** synthesised (Scheme 3.43).



Scheme 3.43

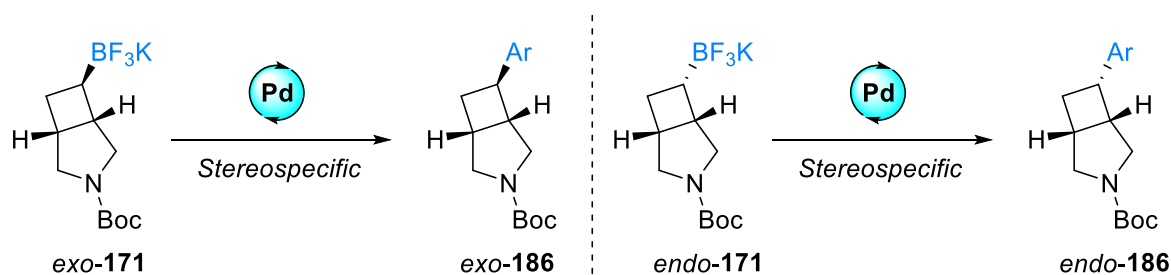
3.5 Cross-Coupling of Cyclobutyl Building Blocks

With hydroxy, pinacol boronate and BF_3K building blocks *endo*- and *exo*-**170**, **171** and **279** in hand, the stage was set to explore the cross-coupling potential of the cyclobutyl building blocks. We envisaged that hydroxy building blocks *endo*- and *exo*-**170** could participate in the recently developed alcohol metallophotoredox cross-coupling developed by MacMillan and co-workers²¹³ to give arylated cyclobutanes *exo*-**186** in a stereoselective fashion. Similarly, inspired by work from Maier and co-workers²⁹⁴ and Molander and co-workers,²⁹⁵ we envisaged that pinacol boronates *endo*- and *exo*-**279** and trifluoroborates *endo*- and *exo*-**171** could also participate in metallophotoredox cross-couplings to give arylated cyclobutanes *exo*-**186** in a stereoselective fashion (Scheme 3.44). Since these cross-couplings should all proceed by the formation of carbon-centred radical **185**, it was expected that the fused bicyclic structure in **185** would induce preferential trapping on the less-hindered *exo*- face to give arylated cyclobutanes *exo*-**186**.



Scheme 3.44

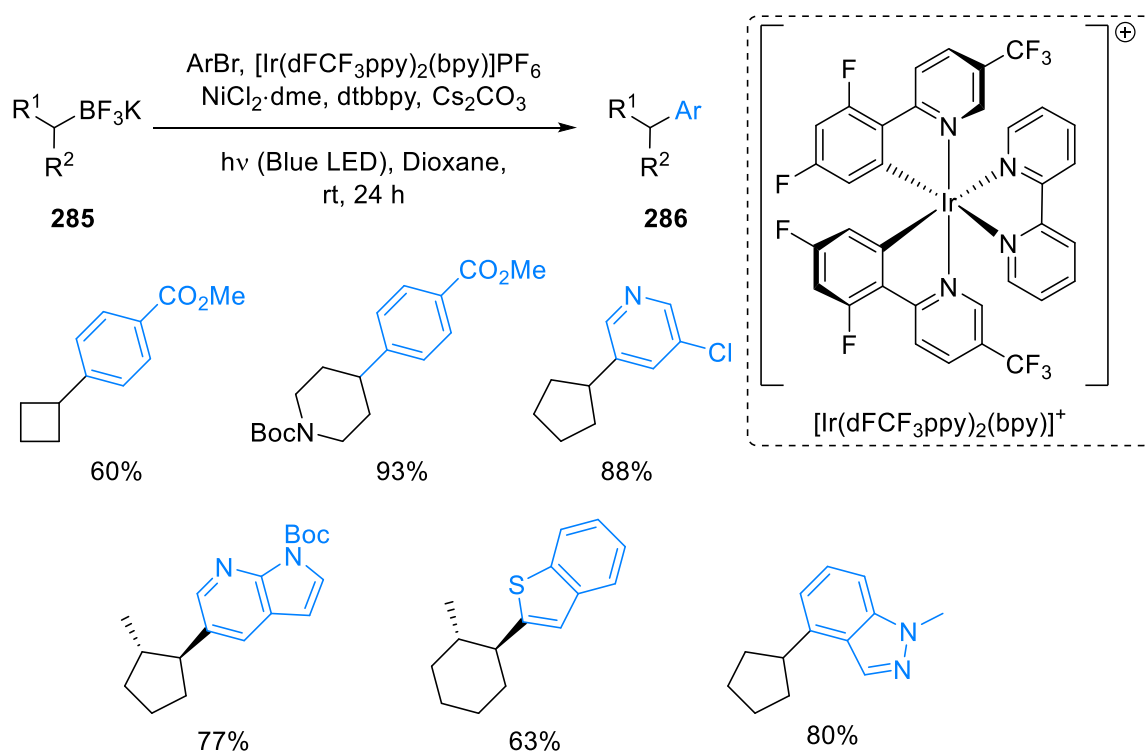
Alternatively, we envisaged that cyclobutyl trifluoroborates *endo*- and *exo*-**171** could participate in Suzuki-Miyaura cross-couplings to give arylated cyclobutanes **186** in a stereospecific fashion, with expected stereoretentive cross-coupling (Scheme 3.45). However, some methodology development was expected for this cross-coupling as there is less precedent for the Pd-catalysed sp^3 - sp^2 cross-coupling of cyclobutyl boronates.^{173, 212, 296}



Scheme 3.45

3.5.1 Photoredox Cross-Coupling of Cyclobutyl Building Blocks

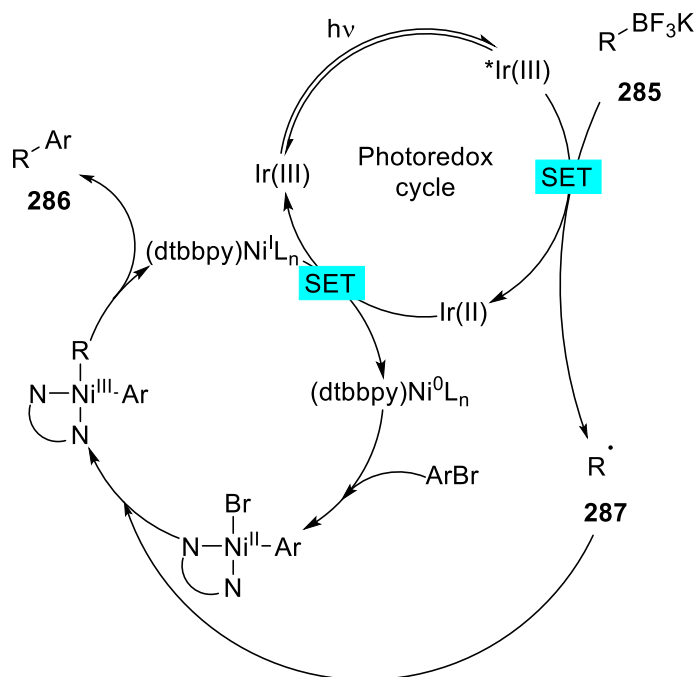
One of the main methods for the sp^3 - sp^2 cross-coupling is the Ni-catalysed photoredox cross-coupling of trifluoroborates with aryl halides developed by Molander and co-workers.²⁹⁵ In their work, the Ni-catalysed photoredox cross-coupling of secondary trifluoroborates with aryl bromides by “single-electron transmetalation” was developed. Use of secondary trifluoroborates **285**, $[\text{Ir}(\text{dFCF}_3\text{ppy})_2(\text{bpy})]\text{PF}_6$, $\text{NiCl}_2\cdot\text{dme}$, dtbbpy and Cs_2CO_3 in dioxane with visible-light irradiation afforded arylated compounds **286** in good to excellent yields and good functional group compatibility (Scheme 3.46). Notably, the cross-coupling of a cyclobutyl boronate and a *N*-Boc piperidine boronate were showcased as well as cross-coupling other cycloalkanes with diverse medicinally relevant aryl and heteroaryl bromides.



Scheme 3.46

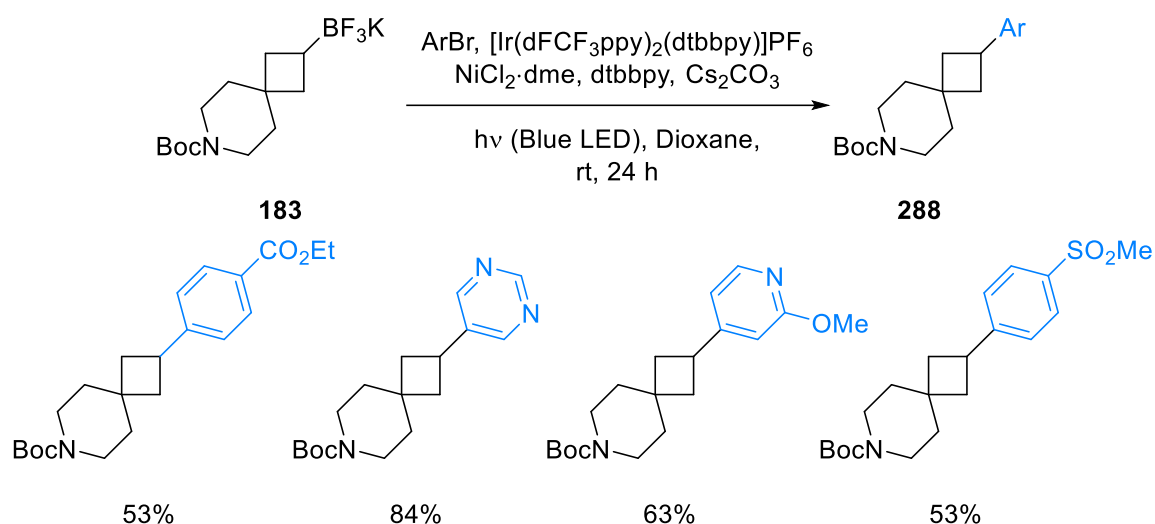
Mechanistically, Molander’s BF_3K cross-coupling works by direct SET activation of trifluoroborate **285** by an activated Ir(III) species to generate a C-centred radical **287**.

Radical **287** is then able to participate in the Ni catalytic cycle by a substitution and reductive elimination process to yield cross-coupled product **286** (Scheme 3.47).



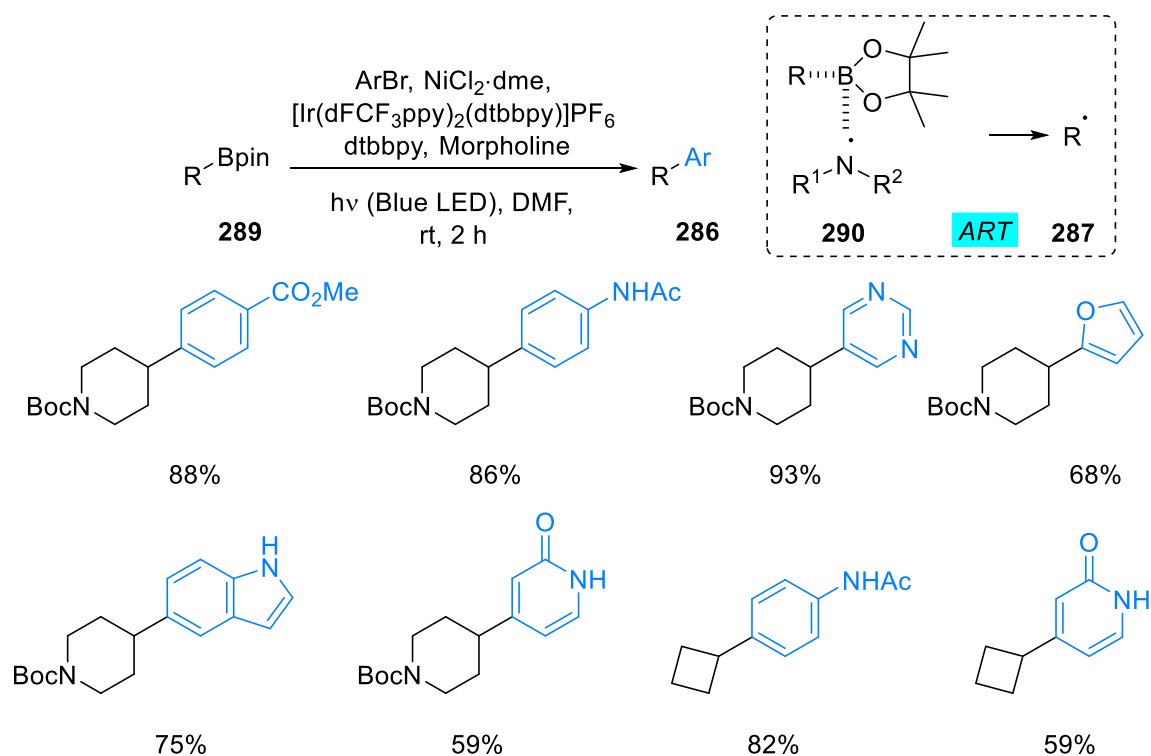
Scheme 3.47

Variations of the Molander methodology have been further used for the cross-coupling of a diverse set of cyclobutyl BF_3K boronates.²⁹⁷⁻³⁰⁰ Notably, in a related O'Brien group project, Hannah Kemp successfully applied Molander and co-workers' conditions for the cross-coupling of a spirocyclic cyclobutyl piperidine trifluoroborate. In this way, cyclobutyl trifluoroborate **183** was reacted with $[Ir(dFCF_3dtbbpy)_2(dtbbpy)]PF_6$, $NiCl_2 \cdot dme$, $dtbbpy$, Cs_2CO_3 and diverse aryl and heteroaryl bromides to give arylated cyclobutanes **288** in good to acceptable yields (Scheme 3.48).²⁸⁹



Scheme 3.48

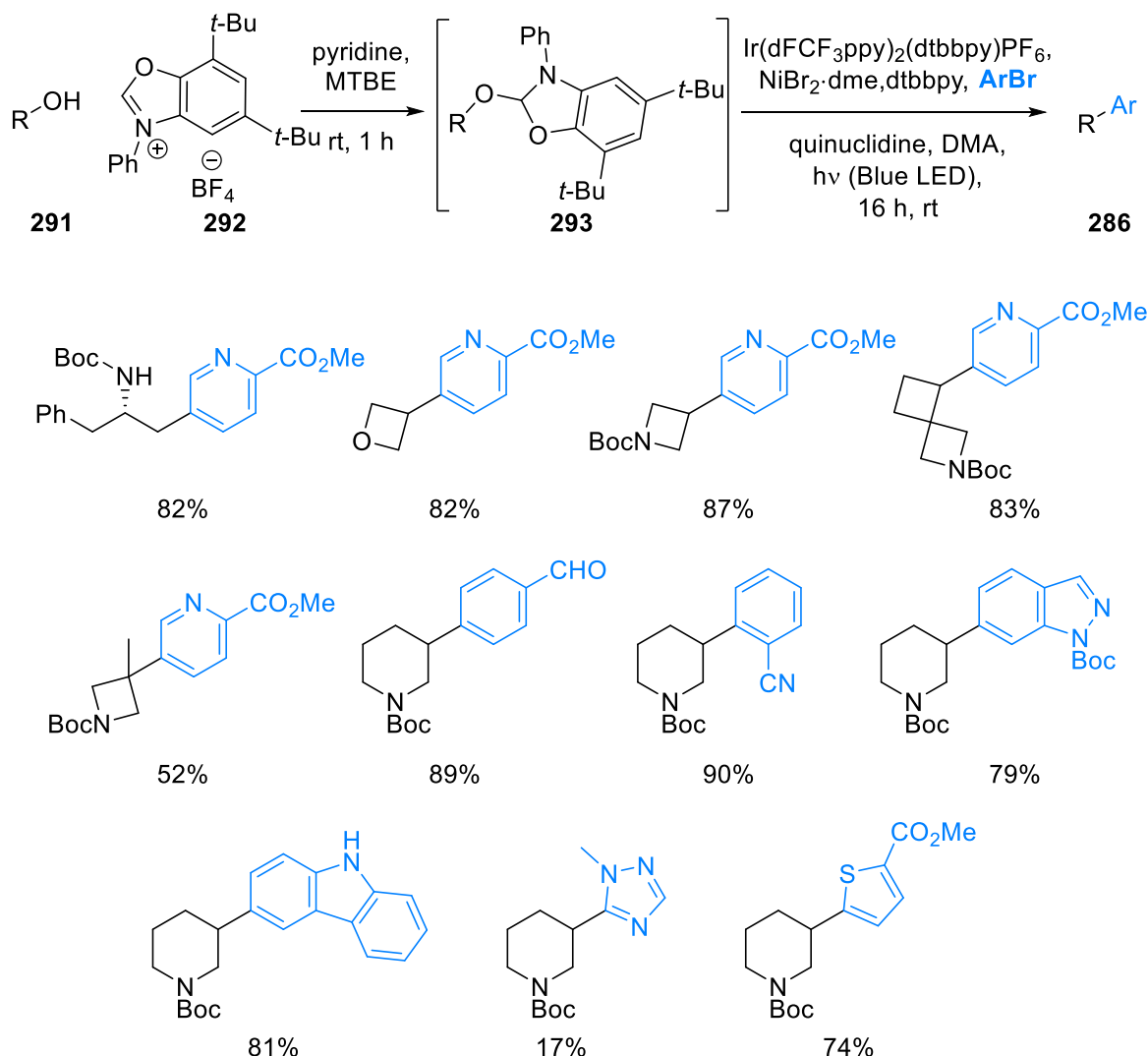
While the photoredox cross-coupling of BF_3K boronates is well preceded, the higher oxidation potentials of pinacol boronates makes them more difficult to use in photoredox methodology.³⁰¹ However, this limitation has recently been overcome by the use of Lewis base activation of the boronate.³⁰² Using this, Maier and co-workers reported a series of photoredox cross-coupling of pinacol boronates with aryl bromides mediated by an amino radical transfer (ART) process.²⁹⁴ In their work, reaction of alkyl pinacol boronates **289** with $[\text{Ir}(\text{dFCF}_3\text{dtbbpy})_2(\text{dtbbpy})]\text{PF}_6$, $\text{NiCl}_2 \cdot \text{dme}$, dtbbpy , an aryl bromide and morpholine as ART agent in DMF under visible light irradiation afforded cross-coupled products **286** in good yields (Scheme 3.49). ART, the main development in this methodology consists on using a pregenerated amino radical **290** to activate the pinacol boronate generating the C-centred radical **287** active in the Ni-catalysed cross coupling. Two examples with a cyclobutyl boronate were described. Since pinacol boronates are widely used and are intermediates in the synthesis of BF_3K salts, this methodology could facilitate wider adoption of photoredox methods in the synthetic community.



Scheme 3.49

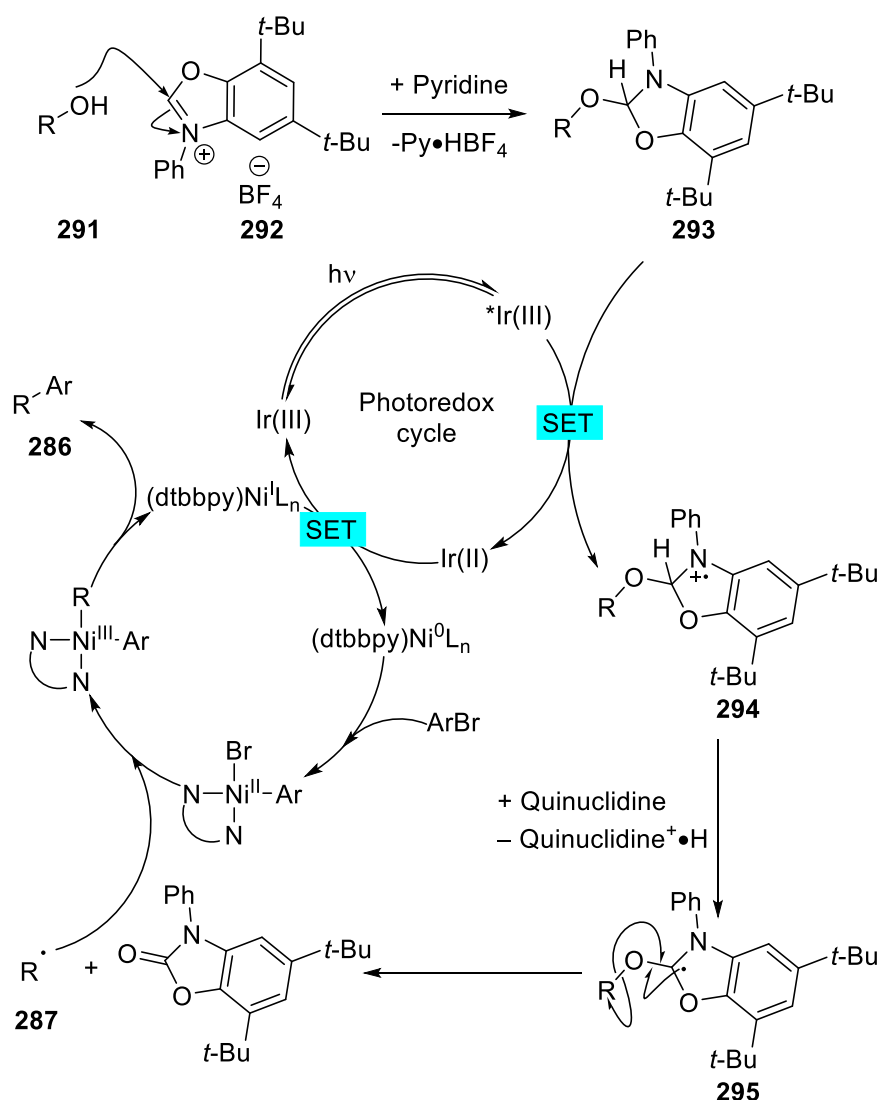
Alcohols have also recently been developed as alternative substrates for photoredox cross-couplings. Initially, development of alcohols in cross-couplings centred around the prior formation of photoredox active species such as oxalates²²⁴ and xanthates.³⁰³ However, MacMillan and co-workers have recently developed conditions for the direct participation of alcohols in a variety of photoredox cross-couplings by reaction with a benzoxazolium salt.^{239, 243}

Notably, MacMillan and co-workers developed the direct deoxygenative arylation of alcohols mediated by benzoxazolium adduct formation.²¹³ Thus, alcohols **291** were reacted with benzoxazolium salt **292** (and other related variants) and pyridine to *in situ* generate adduct **293**. This adduct was then reacted with $[\text{Ir}(\text{dFCF}_3\text{dtbbpy})_2(\text{dtbbpy})]\text{PF}_6$, $\text{NiBr}_2 \cdot \text{dme}$, dtbbpy , an aryl bromide and quinuclidine in DMA under visible light irradiation to afford cross-coupled products **286** in excellent yields (Scheme 3.50). This methodology demonstrated broad tolerance for a variety of alcohol substrates, including 4-membered rings such as *N*-Boc azetidines, oxetanes, and fused spirocyclic cyclobutanes. A diverse set of aryl and heteroaryl bromides were explored, including benzaldehydes, nitriles, pyridines, *N*-Boc and *N*-H heterocycles, as well as *N*- and *S*-containing 5-membered aromatics.



Scheme 3.50

One of MacMillan and co-workers' principal contributions in this work was the introduction of benzoxazolium adduct **293** as a redox-active species. Adduct **293** is formed from nucleophilic addition of alcohol **291** to benzoxazolium salt **292** followed by deprotonation with pyridine. Following this, adduct **293** can participate in the Ir-photoredox cycle to give *N*-centred radical cation **294** which, after deprotonation by quinuclidine, gives *C*-centred radical **295**. *C*-centred radical **295** can then undergo homolytic cleavage of the C-O bond to give *C*-centred radical **287**, the active species in the Ni-catalysed cross-coupling (Scheme 3.51).²¹³

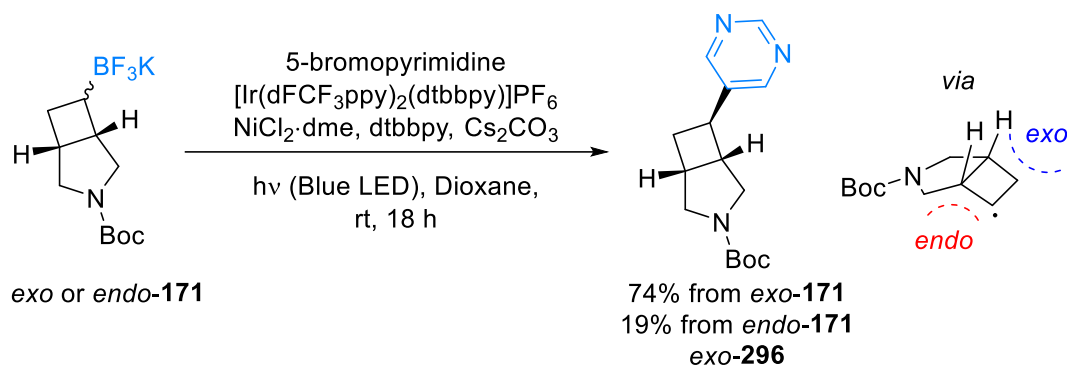


Scheme 3.51

Overall, the photoredox cross-coupling of cyclobutanes is well preceded with a variety of possible substrates including, but not limited to, pinacol boronates, BF_3K salts and more recently alcohols. However, due to the closeness of the examples discussed herein and the availability of the substrates utilised in the synthesis of our building blocks, these three methodologies were the ones that were selected for further studies with our newly synthesised cyclobutane building blocks.

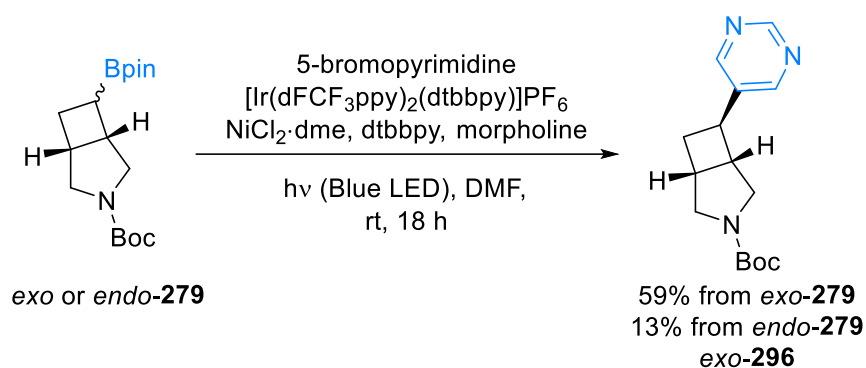
From this, we moved on to explore the different photoredox cross-couplings on building blocks *exo*- and *endo*-**170**, **171** and **279** with the aim to determine the best photoredox cross-coupling methodology for our substrates and their stereochemical implications. Initially, we started exploring the well-precedented Molander photoredox cross-coupling on cyclobutyl BF_3K building blocks *exo*- and *endo*-**171**. Thus, reaction of cyclobutyl trifluoroborate *exo*-

171 with $[\text{Ir}(\text{dFCF}_3\text{dtbbpy})_2(\text{dtbbpy})]\text{PF}_6$, $\text{NiCl}_2\cdot\text{dme}$, dtbbpy , Cs_2CO_3 and 5-bromopyrimidine in dioxane under visible light irradiation yielded arylated cyclobutane *exo*-**296** in 74% as a single diastereomer (Scheme 3.52). The proof of stereochemistry is discussed later in Section 3.6. Expectedly, based on the proposed formation of the same radical intermediate, reaction of cyclobutyl trifluoroborate *endo*-**171** under the same conditions yielded the same arylated cyclobutyl *exo*-**296** as a single diastereomer, albeit in a significantly diminished 19% yield. We hypothesise that the difference in yield comes from the additional steric hindrance in cyclobutyl trifluoroborate *endo*-**171** making SET from the excited Ir catalyst to the trifluoroborate salt more difficult. Additionally, from the obtained results alongside observations by Hannah Kemp,²⁸⁹ it became apparent that this methodology suffered from reproducibility issues and was not as robust in our hands as we had hoped.



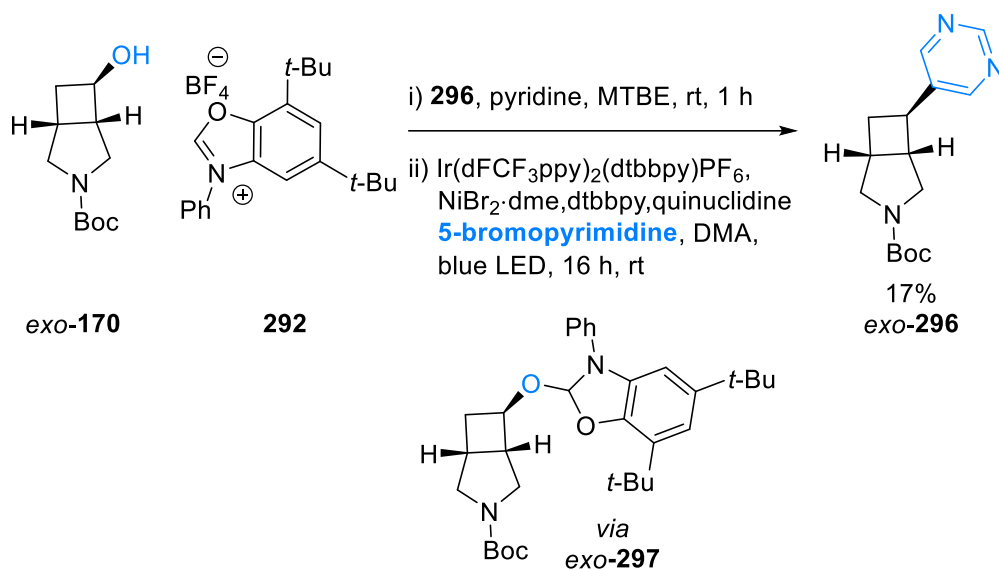
Scheme 3.52

Then, we explored Maier and co-workers' photoredox cross-coupling on cyclobutyl pinacol boronates *exo*- and *endo*-**279**. Reaction of pinacol boronate *exo*-**279** with $[\text{Ir}(\text{dFCF}_3\text{dtbbpy})_2(\text{dtbbpy})]\text{PF}_6$, $\text{NiCl}_2\cdot\text{dme}$, dtbbpy , morpholine and 5-bromopyrimidine in DMF under visible light irradiation yielded arylated cyclobutane *exo*-**296** in 59% yield as a single diastereomer (Scheme 3.53). Conversely, reaction of cyclobutyl pinacol boronate *endo*-**279** under the same conditions gave arylated cyclobutane *exo*-**296** in 13% yield as a single diastereomer. We hypothesise that the diminished yield comes from a more difficult SET to the more sterically hindered *exo* boronate.



Scheme 3.53

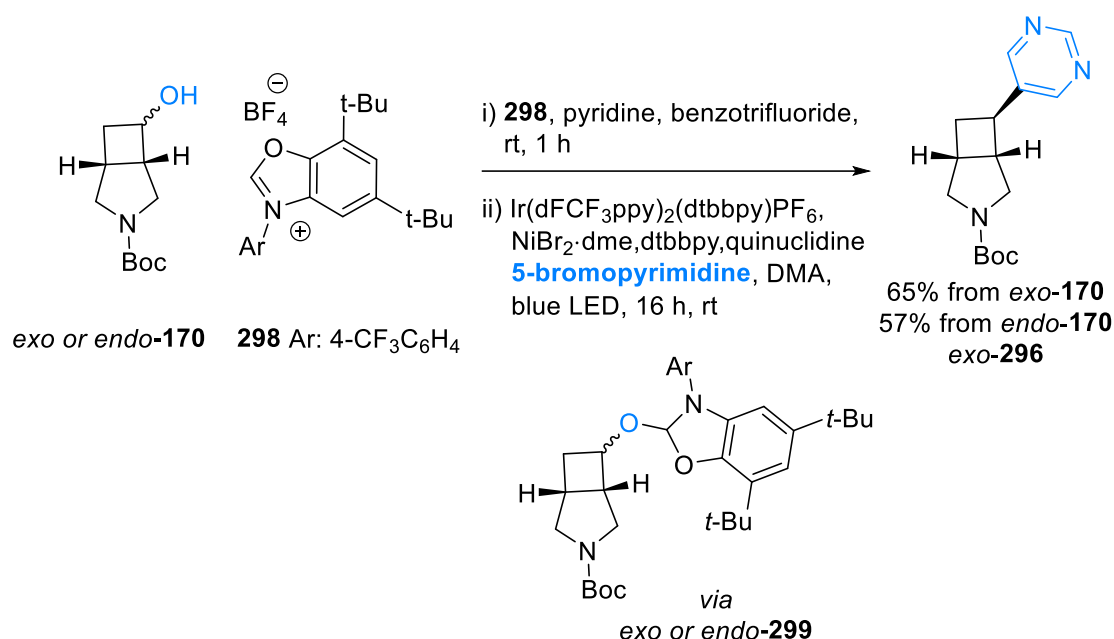
Finally, attention turned to the use of the alcohol cross-coupling methodology developed by MacMillan and co-workers. This was applied to the cross-coupling of cyclobutanols *exo*- and *endo*-**170**. However, initial reaction of cyclobutanol *exo*-**170** with benzoxazolium salt **292**, pyridine, $[\text{Ir}(\text{dFCF}_3\text{dtbbpy})_2(\text{dtbbpy})]\text{PF}_6$, $\text{NiBr}_2 \cdot \text{dme}$, dtbbpy , 5-bromopyrimidine and quinuclidine under visible light irradiation afforded arylated cyclobutane *exo*-**296** in a low 17% yield as a single diastereomer (Scheme 3.54).



Scheme 3.54

One of the observations during MacMillan's work was that more sterically hindered alcohols were less efficient at forming the redox-active adduct *exo*-**297**. Thus, for such substrates, it was proposed that introducing an electron withdrawing group onto the aromatic ring in the *N*-Ph motif in benzoxazolium salt **292** could alleviate this issue by making the formation of adduct **292** more favourable at the cost of some efficiency in SET step.²¹³ Therefore, based on MacMillan and co-workers' guidance, a *N*-4- $\text{CF}_3\text{C}_6\text{H}_4$ group on the benzoxazolium salt

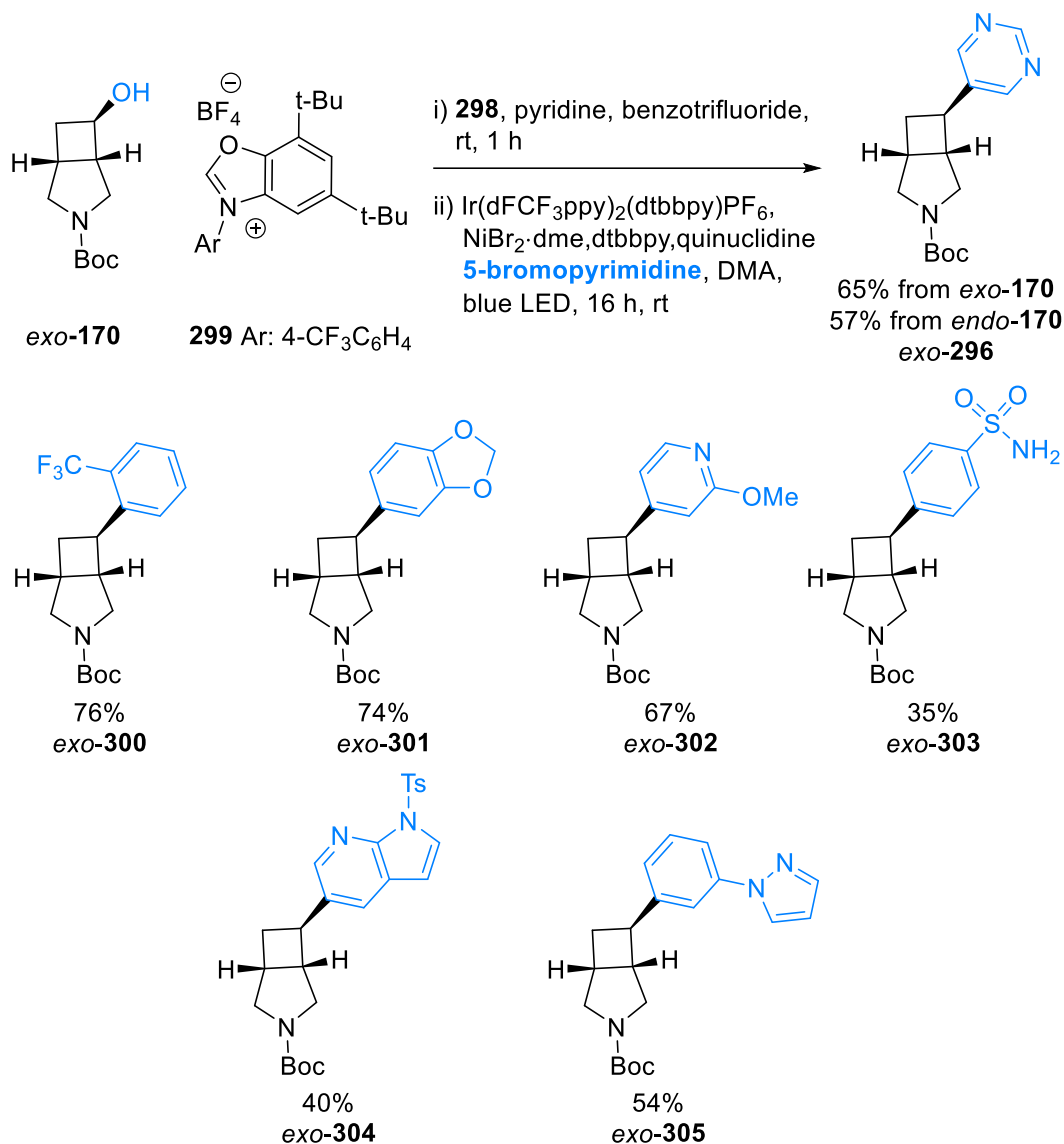
was explored. In this way, reaction of cyclobutanol *exo*-**170** with benzoxazolium salt **298** (with a *N*-4-CF₃C₆H₄ group), pyridine, [Ir(dFCF₃dtbbpy)₂(dtbbpy)]PF₆, NiBr₂·dme, dtbbpy, 5-bromopyrimidine and quinuclidine under visible light irradiation gratifyingly afforded arylated cyclobutane *exo*-**296** in a much improved 65% yield (Scheme 3.55). Conversely, reaction of cyclobutanol *endo*-**170** under the same conditions gave arylated cyclobutane *exo*-**296** in 57% yield as a single diastereomer. We hypothesise that SET to the more distant benzoxazolium nitrogen bypasses some of the steric hindrance around the C-O bond, thereby enabling higher yields.



Scheme 3.55

From the previous results, alongside the reported functional group tolerance, we selected MacMillan and co-workers' methodology for the photoredox cross-coupling of our cyclobutane building blocks. Due to the slightly higher overall yield in its formation, cyclobutanol *exo*-**170** was selected to be cross-coupled with a range of medically relevant aryl and heteroaryl bromides. Pleasingly, six cross-couplings were attempted and, in all cases, arylated cyclobutanes *exo*-**300-305** were obtained in good yields (Scheme 3.56). Additionally, while sulfonamide *exo*-**303** was obtained in a diminished 35% yield, more medically relevant aryl groups such as those in arylated cyclobutanes *exo*-**304** and *exo*-**305** were not only tolerated but also obtained in acceptable yields. Of note, it should be pointed out that products from this methodology come with difficult purifications due to the range of reagents and by-products present. Nevertheless, its functional group tolerance and

reliability make it a powerful synthetic tool for fragment elaboration using our modular synthetic platform.

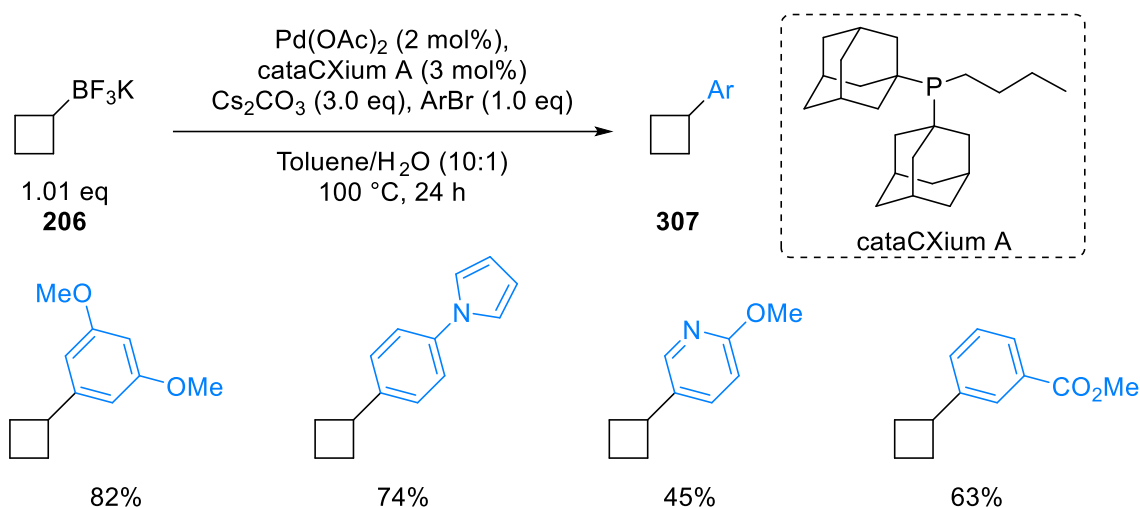


Scheme 3.56

3.5.2 Suzuki-Miyaura Cross-Coupling of Cyclobutyl Building Blocks

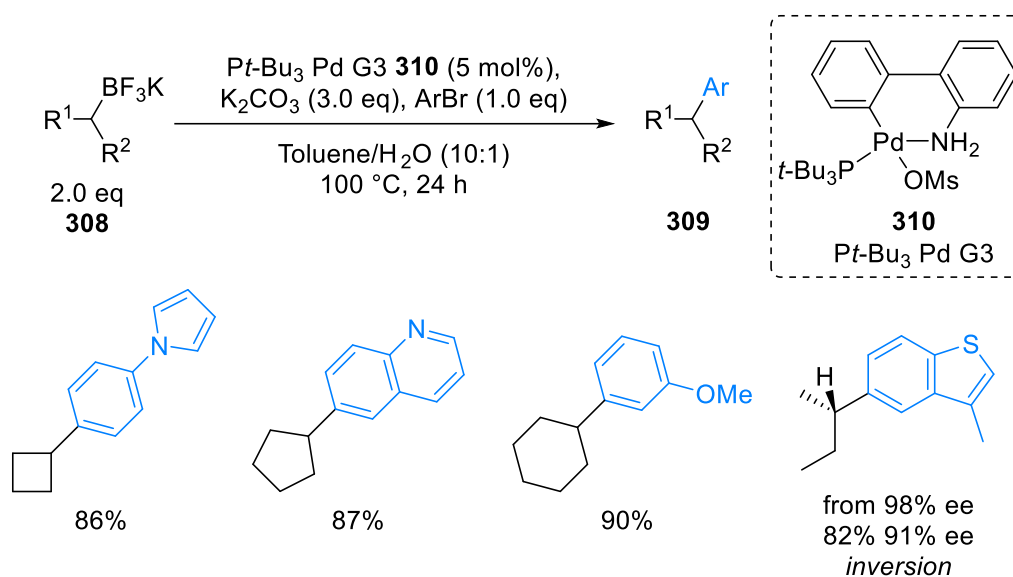
In contrast to photoredox sp^2 - sp^3 cross-couplings the Pd-catalysed sp^2 - sp^3 Suzuki-Miyaura cross-coupling (SMCC) is somewhat less precededented.²¹² However, there are a few prior examples of sp^2 - sp^3 cross-coupling of cyclobutyl trifluoroborate salts. Gormisky and Molander reported one of the earlier examples of this methodology in 2008 where it was found that use of the sterically bulky and electron rich cataCXium A ligand was the key.¹⁷³ In their work, reaction of cyclobutyl trifluoroborate **206** with Pd(OAc)₂, cataCXium A,

Cs_2CO_3 and an aryl chloride in toluene and water at 100 °C afforded cross-coupled products **307** in good yields (Scheme 3.57). Although the authors were able to cross-couple some heteroaromatics, the reported scope is narrow and was showcased with only four examples.



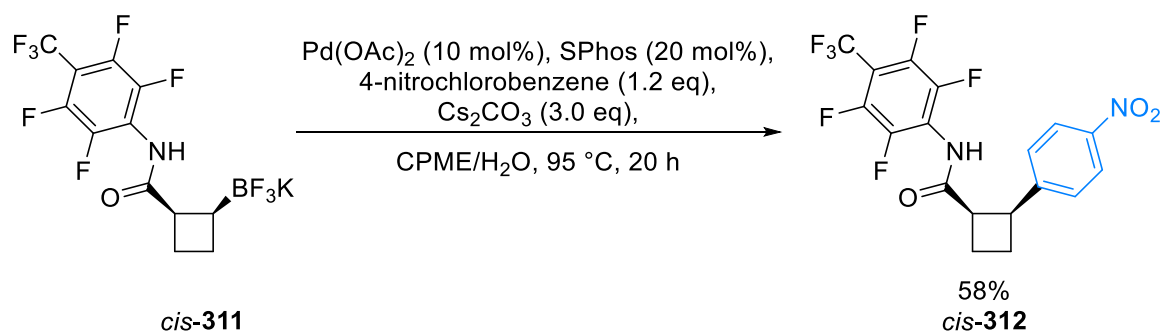
Scheme 3.57

Further refinement of Gromisky and Molander's methodology was reported by Biscoe and co-workers in the development of stereospecific Pd-catalysed $\text{sp}^2\text{-sp}^3$ cross-couplings by replacing the $\text{Pd}(\text{OAc})_2$ and cataCXium A combination with a Pt-Bu_3 Pd G3 Buchwald precatalyst **310** and switching the base to K_2CO_3 .²¹² In this fashion, trifluoroborates **308** were reacted with precatalyst **310**, K_2CO_3 and an aryl chloride in toluene and water at 100 °C to give cross-coupled products **309** in good yield (Scheme 3.58). While the focus of their studies was not on the cross-coupling of cyclic systems, one of the examples was a cyclobutane previously reported by Gromisky and Molander and it was reported to proceed in similar yield (86% vs 74%, see Scheme 58). Additionally, it was reported that the use of this specific set of conditions with an acyclic trifluoroborate led to almost complete inversion of configuration (*via* an invertive transmetallation) when done on enantioenriched substrates.



Scheme 3.58

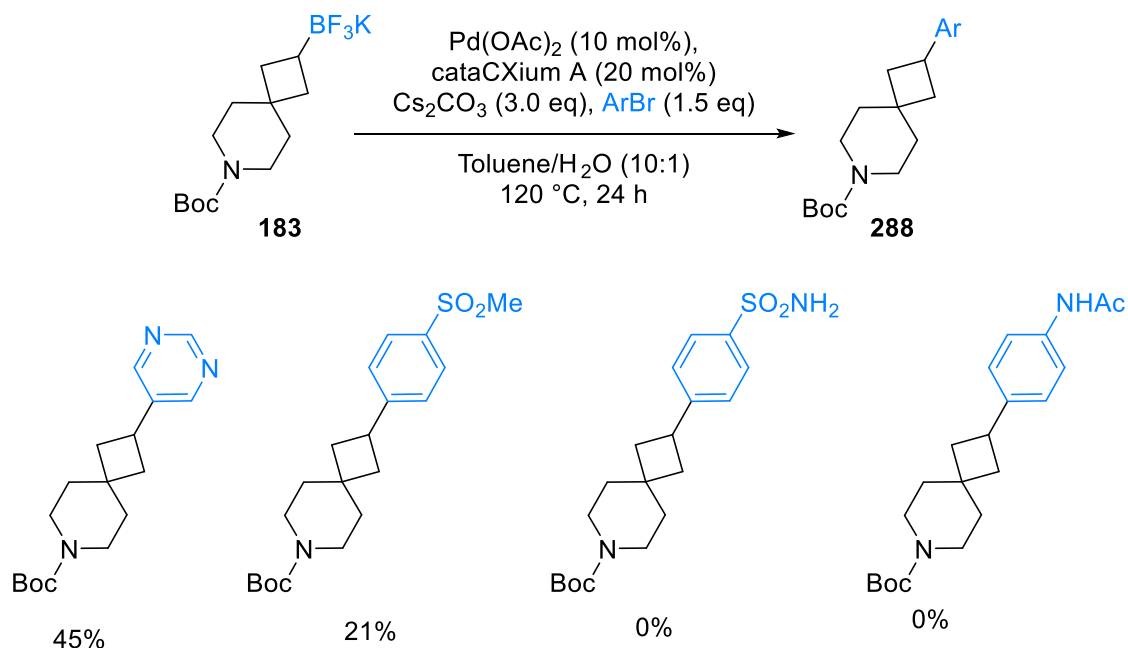
Yu and co-workers also reported the cross-coupling of a cyclobutyl trifluoroborate during their studies into asymmetric Pd-catalysed borylations of sp^3 -H bonds.³⁰⁴ For example, cyclobutyl trifluoroborate *cis*-**311** was reacted with $\text{Pd}(\text{OAc})_2$, SPhos, Cs_2CO_3 and 4-nitrochlorobenzene to give arylated cyclobutane *cis*-**312** in 58% yield with complete retention of stereochemistry (Scheme 3.59). It was hypothesised that the cross-coupling is assisted by the adjacent amide group which both facilitates the cross-coupling and guides the stereochemistry by a retentive process.



Scheme 3.59

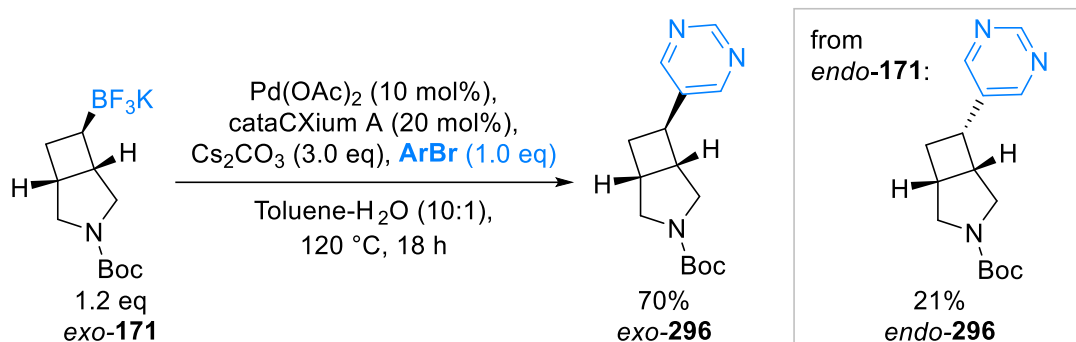
Finally, the O'Brien group has an ongoing interest in the Suzuki-Miyaura cross-coupling of sp^3 boronates.³⁰⁵ During initial optimisation studies performed on α -Bpin-*N*-Boc-pyrrolidine, a combination of $\text{Pd}(\text{OAc})_2$, cataCXium A, Cs_2CO_3 and an aryl bromide in toluene/water at 120°C was found to be a privileged set for the cross-coupling of this substrate as well as other diverse heterocyclic boronates.^{305, 306} Indeed, these conditions were adapted by Hannah Kemp for the cross-coupling of a spirocyclic cyclobutyl piperidine

building block **183**.²⁸⁹ In this way, reaction of cyclobutyl trifluoroborate **183** with Pd(OAc)₂, cataCXium A, Cs₂CO₃ and an aryl bromide in toluene/water at 120 °C afforded arylated cyclobutanes **288** in acceptable yields (Scheme 3.60). Of note, despite the apparent scope of the methodology being quite narrow, further developments by Will Butler by changing the equivalents of trifluoroborate salt to 1.2 eq and those of the aryl bromide to 1.0 eq have improved the yields and expanded the scope with spirocyclic cyclobutyl trifluoroborate **183**.²¹⁴



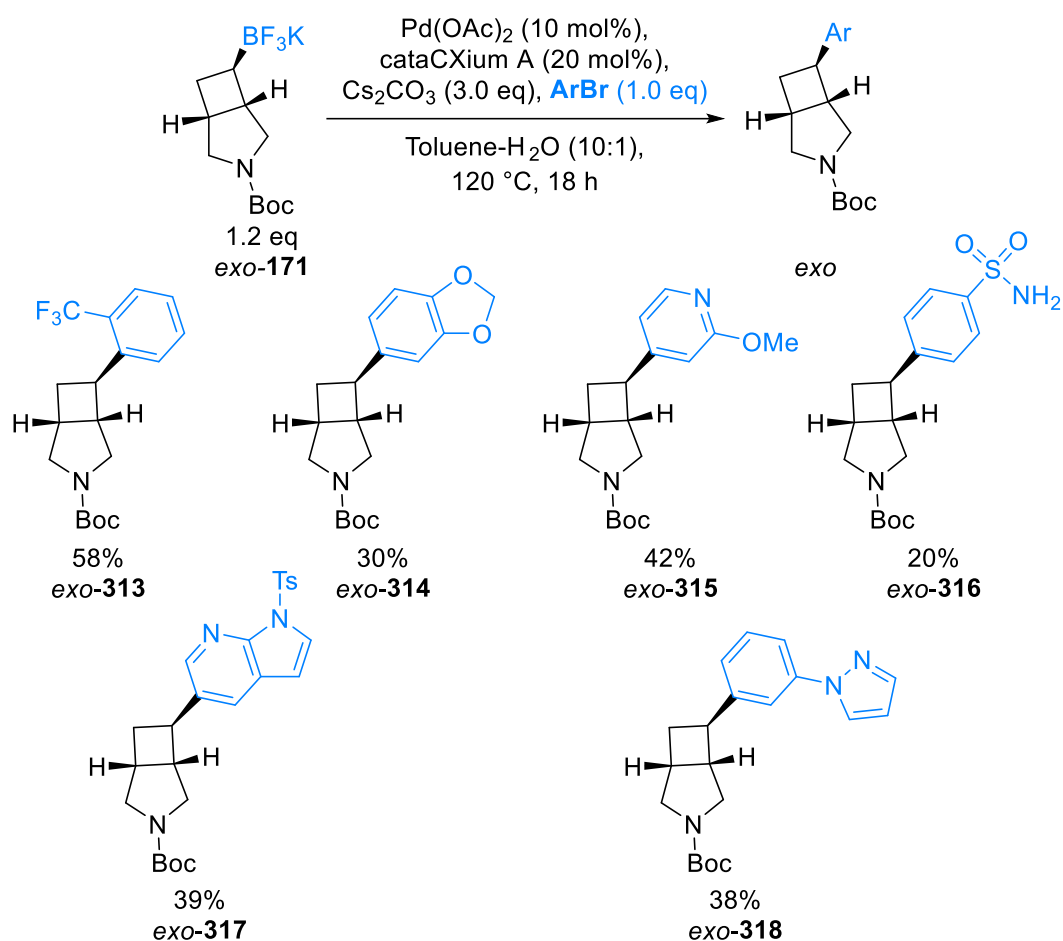
Scheme 3.60

With these O'Brien group conditions in mind, we moved on to explore the Suzuki-Miyaura cross-coupling of cyclobutyl trifluoroborates *exo*- and *endo*-**171**. Thus, cyclobutyl trifluoroborate *exo*-**171** (1.2 eq) was reacted with Pd(OAc)₂, cataCXium A, Cs₂CO₃ and 5-bromopyrimidine (1.0 eq) in toluene-water at 120 °C to give arylated cyclobutane *exo*-**296** in 70% yield as a single diastereomer (Scheme 3.61). In contrast, cyclobutyl trifluoroborate *endo*-**171** under the same conditions gave arylated cyclobutane *endo*-**296** in 21% yield as a single diastereomer. These two reactions clearly gave two diastereomeric products based on their ¹H and ¹³C NMR spectra, and both reactions proceeded with overall retention of stereochemistry. Notably, we were surprised to obtain a positive result from the cross-coupling of *endo*-**171**, as previous research by other group members has shown that steric hindrance around the C-B bond can significantly hinder cross-coupling by slowing down the transmetallation step.^{305, 306}



Scheme 3.61

The scope of the Suzuki-Miyaura cross-coupling of cyclobutyl trifluoroborate **exo-171** was then explored by utilising the same aryl bromides used for the photoredox cross-coupling scope (see Scheme 3.56). Pleasingly, arylated cyclobutanes **exo-313**, **315**, **317**, **318** were obtained in acceptable yields with benzodioxole **exo-314** being obtained in a low 30% yield (Scheme 3.62). Nonetheless, it is noteworthy that medically relevant aryl groups such as **exo-317** and **exo-318** were tolerated albeit in lower yields than those observed with photoredox cross-coupling.



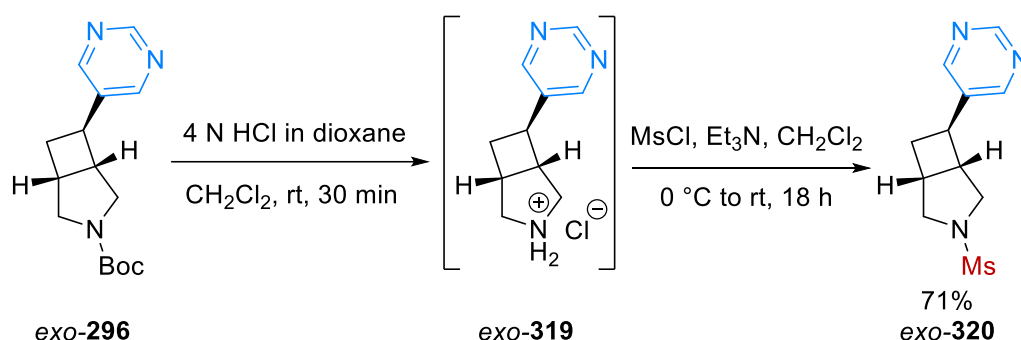
Scheme 3.62

While the Suzuki-Miyaura cross-coupling of cyclobutane building block *exo*-171 proved lower yielding overall than the photoredox cross-coupling, it requires a less-specialised set-up than that of the photoredox cross-coupling. This, coupled with overall easier purifications and the fact that all products were successfully obtained with complete stereospecificity make it a very valuable tool in the fragment elaboration landscape.

3.6 Synthesis of a Methanesulfonamide

To conclude our studies on this new generation of cyclobutyl building blocks, we aimed to synthesize a methanesulfonamide derivative of one of the arylated cyclobutanes. This would enable us to determine the stereochemistry of the cross-couplings and add to our collection of sulfonamides derived from cyclopropyl building blocks. These derivatives have been used to compare calculated exit vectors with those determined experimentally and to gather further structural information on our cyclobutane building block **170**.

Pyrimidine cyclobutane *exo*-**296** was selected for this transformation. In this way, reaction of pyrimidine cyclobutane *exo*-**296** with 4 N HCl in dioxane gave HCl salt *exo*-**319** which was immediately reacted with MsCl and Et₃N to give methanesulfonamide *exo*-**320** in 71% yield (Scheme 3.63).



Scheme 3.63

With methanesulfonamide *exo*-**320** in hand, a crystal was grown and analysed by X-ray crystallography which confirmed the stereochemistry as sulfonamide *exo*-**320** (Figure 3.6). This confirmed all of our previous assumptions around the stereoselectivity and stereospecificity of both classes of cross-couplings that we have used in this project.

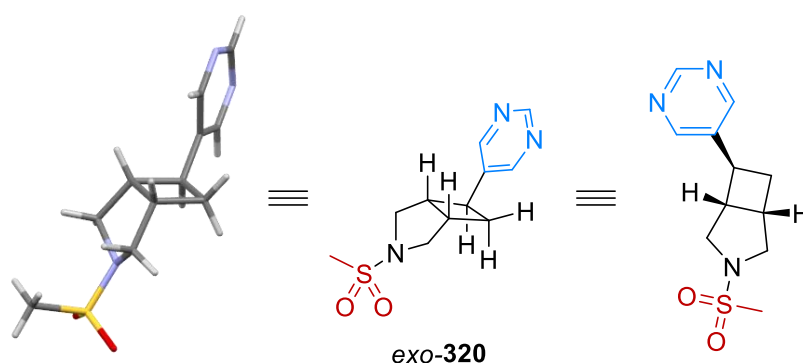
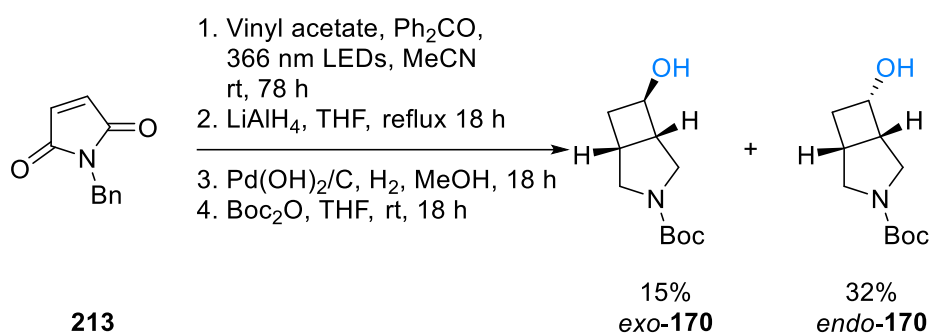


Figure 3.6 – X-Ray crystal structure of methanesulfonamide *exo*-**320**

3.7 Conclusions and Future Work

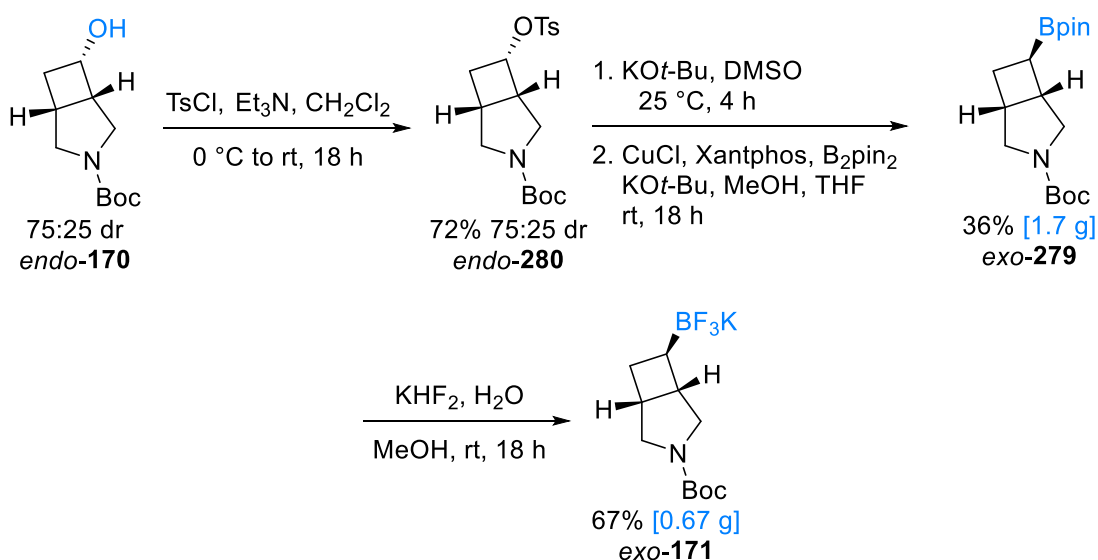
In summary, we have successfully developed the start of a new generation of building blocks for the fragment elaboration stage of FBDD campaigns. In this work, we have introduced four new building blocks *endo*- and *exo*-**170** and **171** and have demonstrated both their syntheses and their potential in photoredox and Suzuki-Miyaura cross-coupling methodology.

Following methodology adapted from Grygorenko and co-workers, the synthesis of hydroxy building blocks *endo* and *exo*-**170** was achieved from *N*-Bn maleimide **213** in 32% and 15% overall yield respectively (Scheme 3.64).



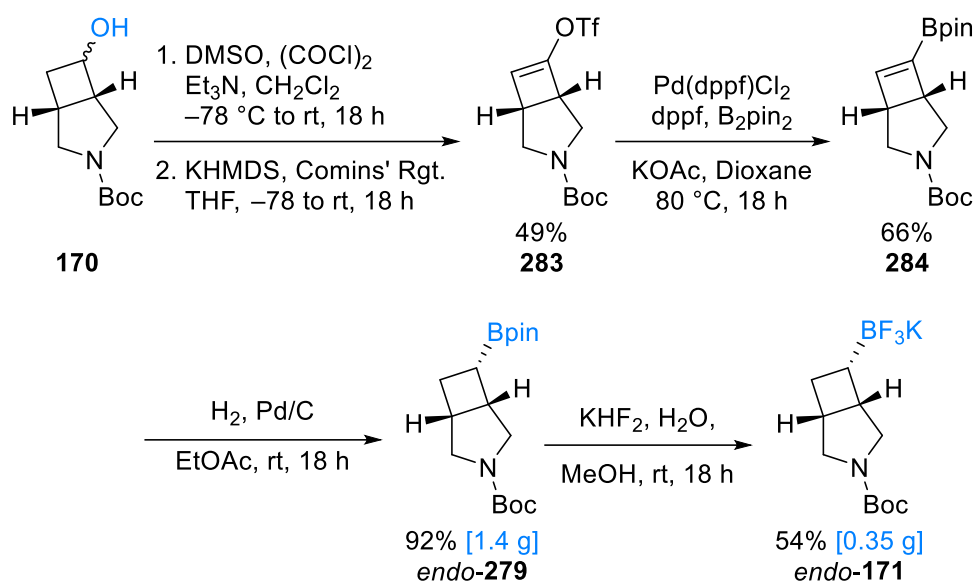
Scheme 3.64

The synthesis of cyclobutyl trifluoroborate building block *exo*-**171** was completed in four steps and 17% overall yield from cyclobutyl alcohols **170** with 0.67 g of cyclobutyl building block *exo*-**171** synthesised (Scheme 3.65).



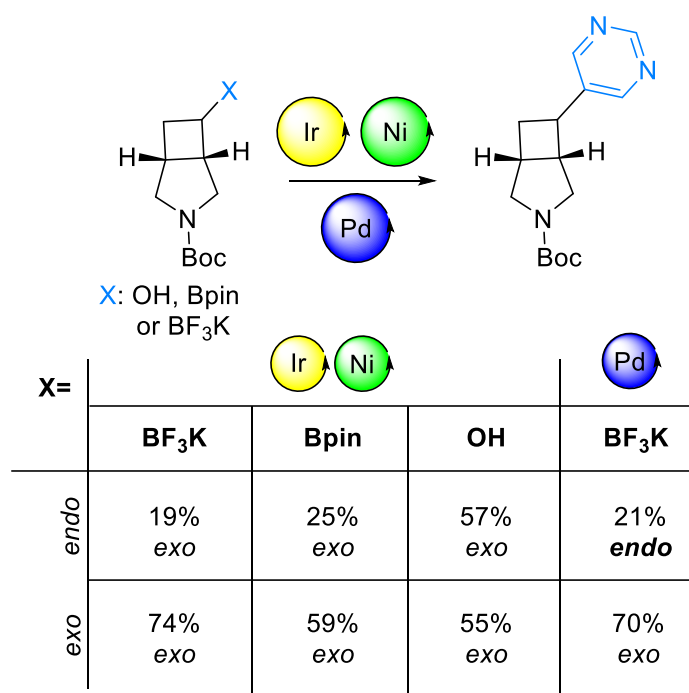
Scheme 3.65

Additionally, the synthesis of cyclobutyl trifluoroborate building block *endo*-**171** was completed in five steps and 16% overall yield from cyclobutyl alcohols **170** with 0.35 g of cyclobutyl building block *endo*-**171** synthesised (Scheme 3.66).



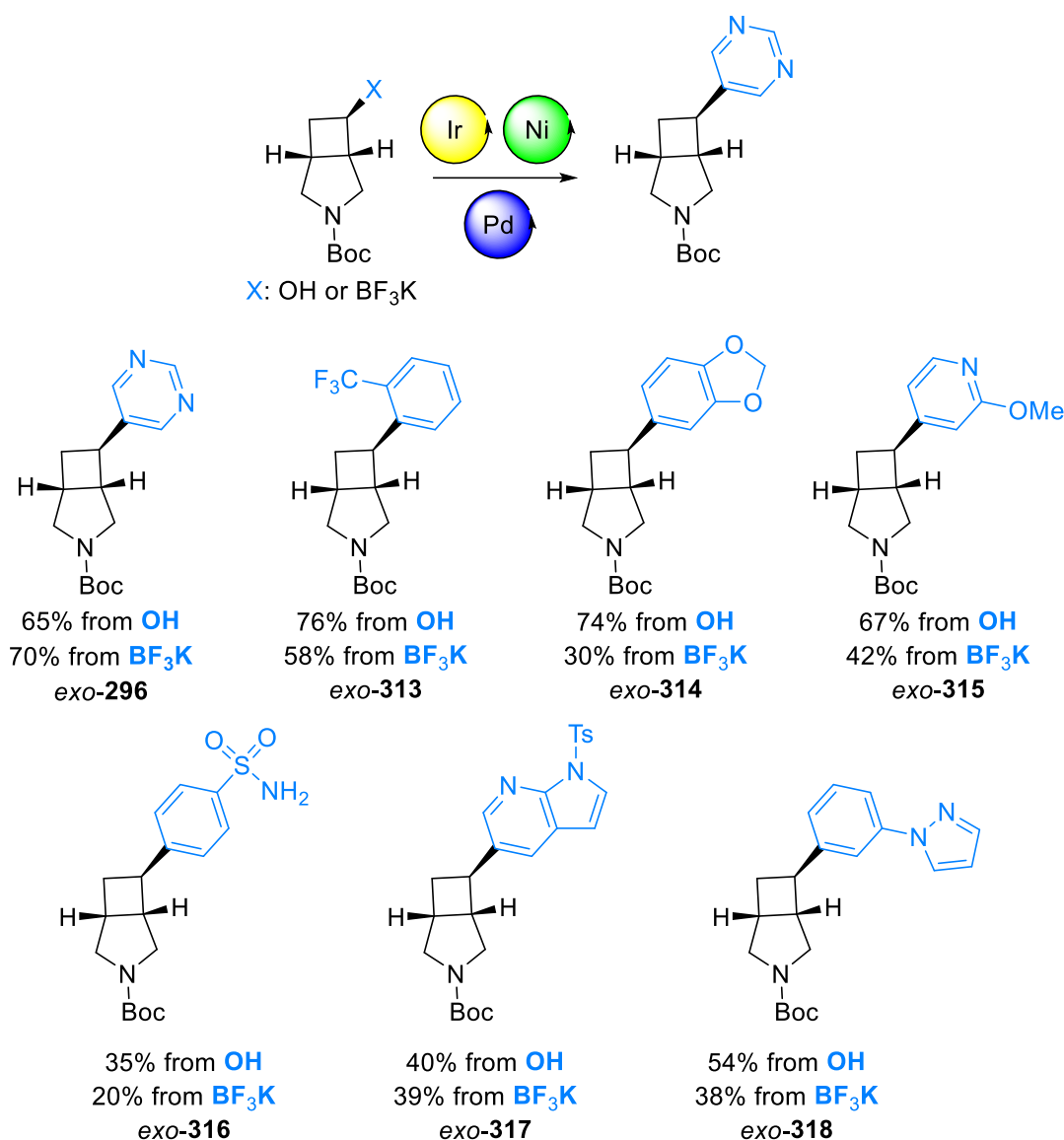
Scheme 3.66

Furthermore, both photoredox and Suzuki-Miyaura cross-couplings of the *endo*- and *exo*-building blocks **170**, **171**, and **279** were explored. MacMillan's deoxygenative photoredox cross-coupling and Suzuki-Miyaura cross-coupling emerged as the most effective strategies. The photoredox cross-couplings proceeded in a stereoselective manner, favouring the *exo*-products, while the Suzuki-Miyaura cross-coupling proceeded in a stereospecific manner with overall retention of stereochemistry (Scheme 3.67).



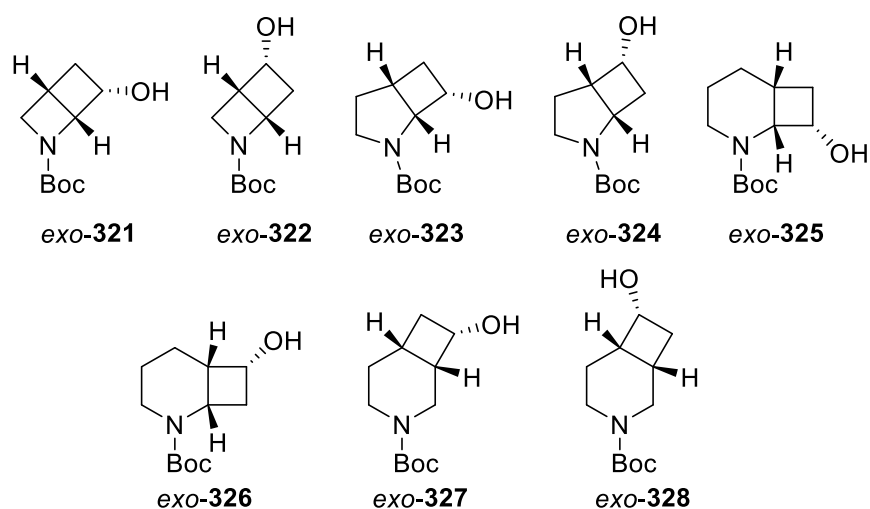
Scheme 3.67

Finally, the scope of the photoredox cross-coupling and the Suzuki-Miyaura cross-coupling was explored using a diverse selection of aryl bromides, yielding promising results and demonstrating good functional group tolerance. The MacMillan photoredox cross-coupling showed excellent functional group tolerance and achieved good yields, while the Suzuki-Miyaura cross-coupling, though it produced somewhat lower yields, remained valuable due to its stereospecificity and the ease of carrying out and purifying the reaction (Scheme 3.68).



Scheme 3.68

In terms of future work, we propose that the development a cross-coupling studies of new cyclobutyl containing building blocks **321-328** is a next logical step that would allow tis methodology platform to access new areas of chemical space while employing the methodology that has been developed and presented in this work. We have specifically selected *endo* fused cyclobutanols as we anticipate the rigid bicyclic structures would allow for more reliable access to the individual diastereomer which we envisage would come from reduction of the precursor while still allowing the photoredox cross-coupling to proceed with high yields (Scheme 3.69).



Scheme 3.69

Furthermore, once more building blocks are available, new fragment elaboration campaigns should be undertaken. These should utilise our entire set of cyclopropyl and cyclobutyl building blocks both in a manner similar to that described in Chapter 2 as scaffold-hopping or simply starting from bound fragments.

Chapter 4 Studies Towards the Total Synthesis of Quinine

(-)-Quinine is an iconic alkaloid that has attracted the attention of many chemists over the last century (Figure 4.1).^{307, 308} It is extracted from the bark of Cinchona trees³⁰⁹ and has been used since the 1600s for the treatment of malaria.³¹⁰ More recently, quinine derivatives have replaced quinine itself in the treatment of malaria and other diseases.^{311, 312} Additionally, quinine derivatives have found extensive use in asymmetric synthesis, functioning as ligands for metal catalysis,^{313, 314} and as backbones for diverse organocatalysts.³¹⁵⁻³²⁰

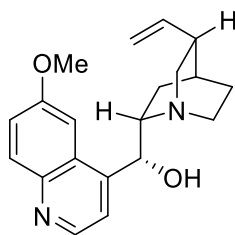
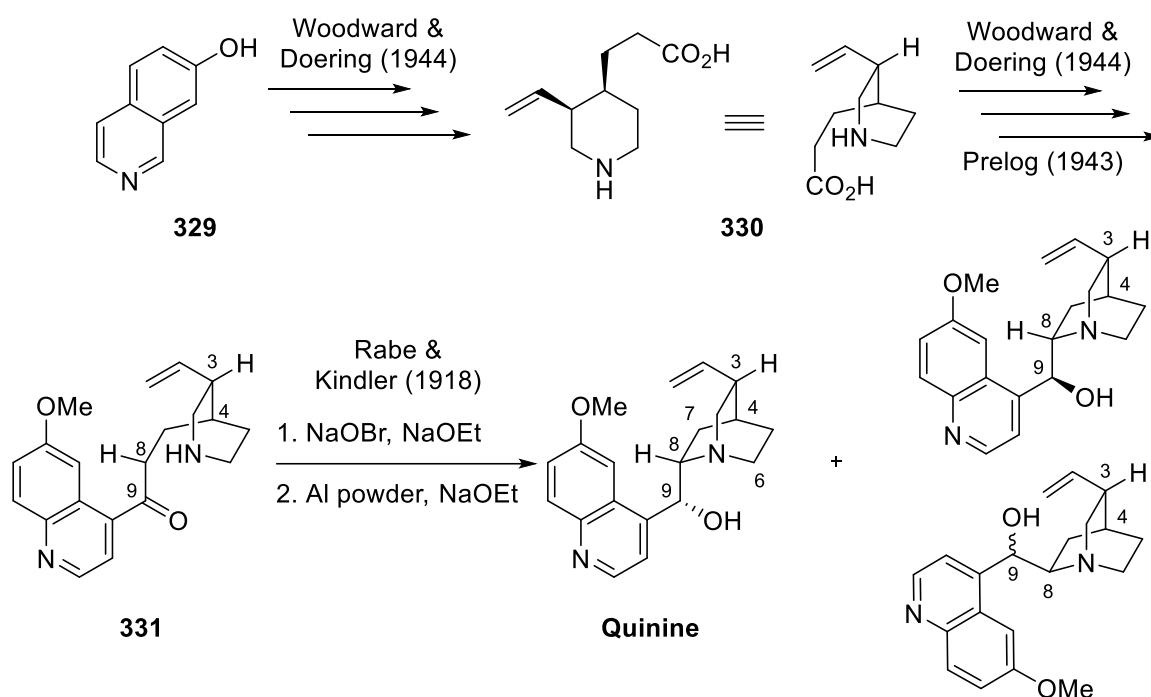


Figure 4.1 – (-)-Quinine.

Multiple synthesis of quinine have been reported up to date.³⁰⁸ Nonetheless, we envisaged that, using methodology previously outlined by the O'Brien group on the lithiation-trapping of *N*-Boc heterocycles, and a sp^3 - sp^2 Suzuki-Miyaura cross-coupling step, a concise and efficient synthetic route for the synthesis of quinine could be outlined and performed. This chapter describes the current state of said synthesis. Section 4.1 provides a brief overview of selected, previous syntheses of quinine. Section 4.2 provides the project outline, including the retrosynthetic analysis for our proposed synthesis of quinine. Section 4.3 describes the results obtained and Section 4.4 provides an overview of the work and outlines possible future work.

4.1 Overview of Previous Synthetic Strategies for Quinine

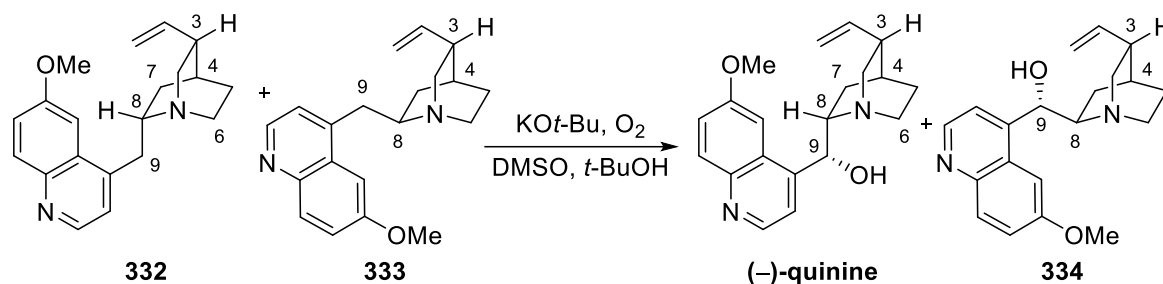
Although not without controversy,³⁰⁸ it is generally accepted that the first synthesis of quinine was the formal synthesis carried out by Woodward and Doering in 1944.³²¹⁻³²⁴ Starting from isoquinoline **329**, a route into piperidine **330** was derived. From piperidine **330**, following methodology developed by Prelog and co-workers, Woodward and Doering reached quinotoxine **331**. From here, methodology outlined by Rabe and Kindler allowed for the synthesis of quinine.³²⁵ Namely, reaction of quinotoxine **331** with NaOBr and NaOEt gives the α -bromoketone by means of the bromoamine. Following this, treatment with Al powder achieved the N-C8 cyclization to form the quinuclidine core and the subsequent reduction gave quinine alongside its other three C8 and C9 diastereomers (Scheme 4.1).



Scheme 4.1

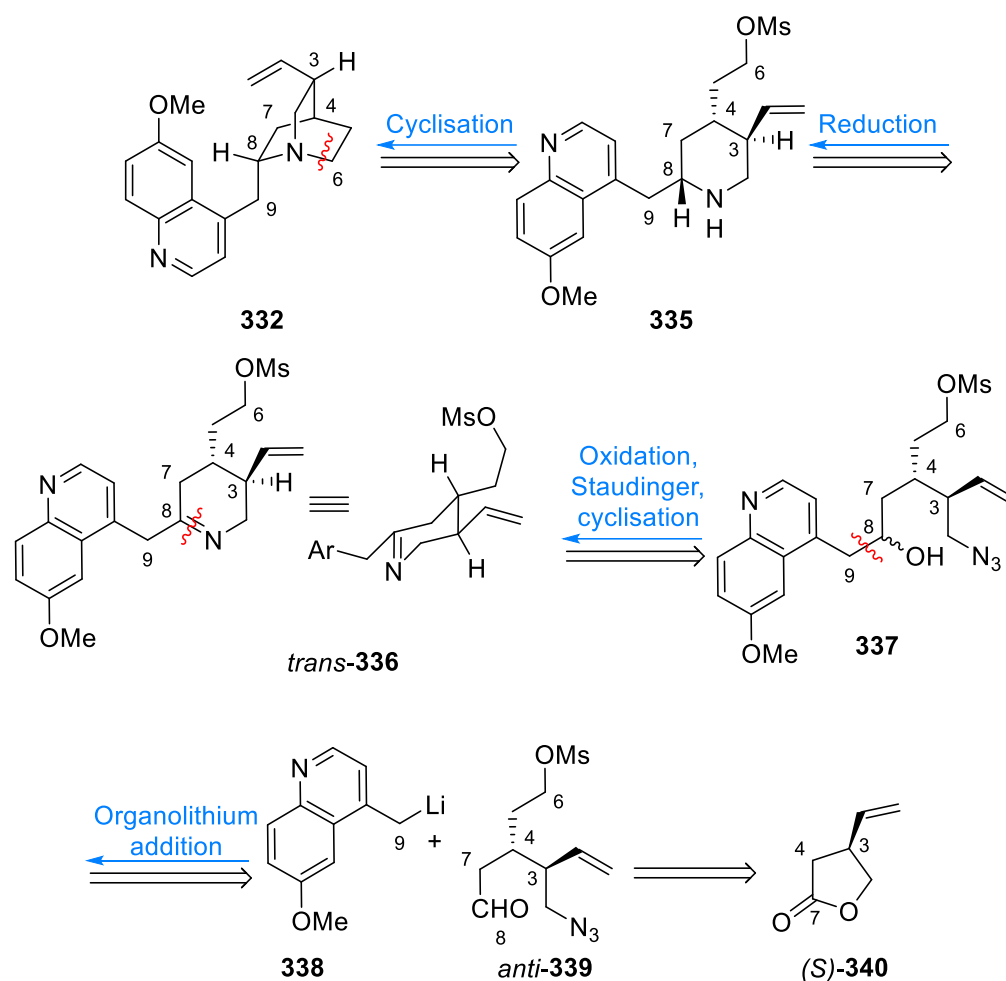
Relying on a similar key N-C8 cyclization, Uskokovic and co-workers in 1970 devised a similar synthesis of (–)-quinine and quinidine by ring opening of an epoxide formed between C8-C9. Additionally, Uskokovic and co-workers described the separation of quinine C8 and C9 diastereomers by crystallisation of their tartrate salts.³²⁶⁻³³⁰ Furthermore, it was during Uskokovic and co-workers' work at Hoffmann-La Roche that full stereoselectivity in the oxidation of the C9 centre was first observed.^{329, 330} Namely, treatment of a mixture of deoxyquinine **332** and deoxyquinidine **333** with KOt-Bu in an O₂ atmosphere led to the formation of (–)-quinine and quinidine **334** with complete diastereoselectivity (Scheme 4.2).

Further improvement of this synthesis was described by Martin and co-workers in 1972 by introducing new methodology for the formation of the C8-C9 bond before cyclisation.³³¹



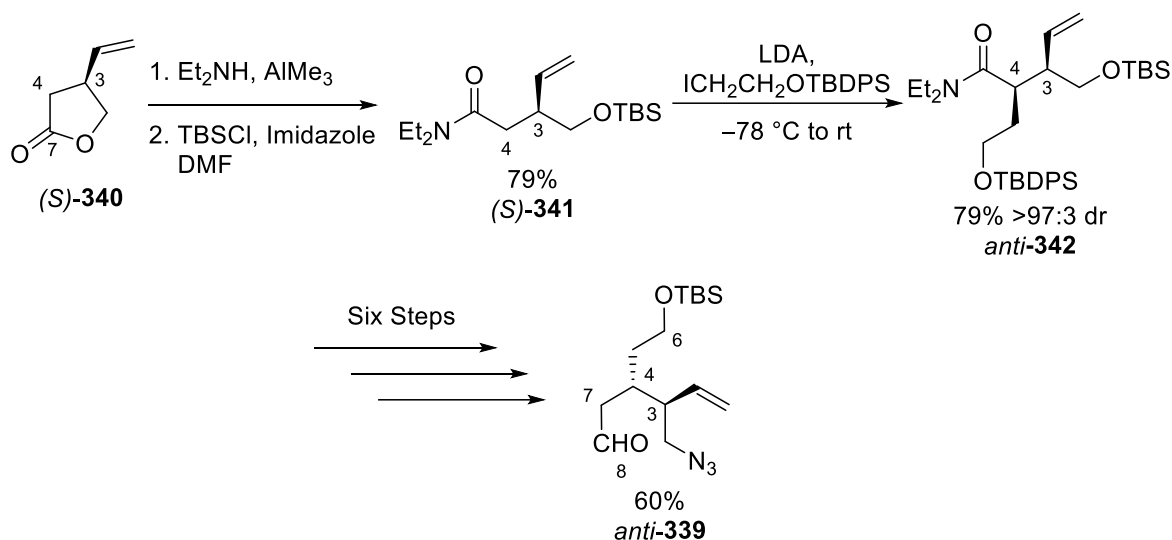
Scheme 4.2

The first fully stereoselective synthesis of (-)-Quinine was only reported in 2001 by Stork and co-workers.³³² Knowing that the C9 oxidation of deoxyquinine into quinine proceeded stereoselectively, Stork and co-workers targeted the synthesis of deoxyquinine **332** by a late N-C6 bond formation. In their analysis, deoxyquinine **332** would be formed by the intramolecular cyclisation of piperidine **335**. In turn, piperidine **335** would be prepared by reduction of cyclic imine *trans*-**336**, formed by oxidation of the C8 alcohol to the ketone and Staudinger reduction of the C6 azide in hydroxyazide **337** followed by condensation. Hydroxyazide **337** could be synthesised by addition of organolithium **338** into aldehyde *anti*-**339** which could in turn be obtained from lactone (*S*)-**340** (Scheme 4.3). It was envisaged that the configuration in the C3 centre would be provided by lactone (*S*)-**340**, the C4 stereochemistry would be dictated by a diastereoselective α -alkylation of a derivative of lactone (*S*)-**340** and the configuration of C8 by a diastereoselective reduction of imine *trans*-**336**.



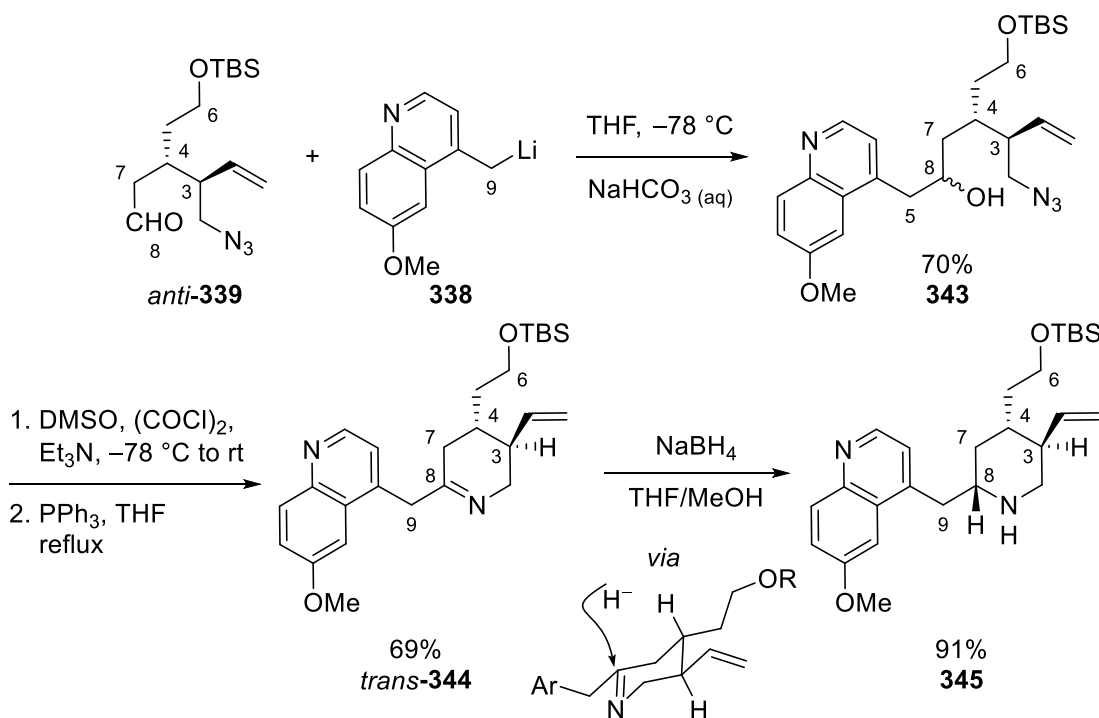
Scheme 4.3

Stork and co-workers' synthesis began with ring opening of lactone (S)-**340** with Et₂NH and AlMe₃ followed by TBS protection to give amide (S)-**241** in 79% yield. Key diastereoselective alkylation of the amide proceeded by deprotonation with LDA at –78 °C followed by trapping with a TBDPS protected alkyl iodide to give amide *anti*-**342** in 79% yield as a single diastereomer. Then, a six-step sequence consisting of removal of the TBS group, reduction to the aldehyde, Wittig olefination with a methoxymethylene phosphorane, formation of the azide and acid hydrolysis gave aldehyde *anti*-**339** in 60% yield (Scheme 4.4).³³²



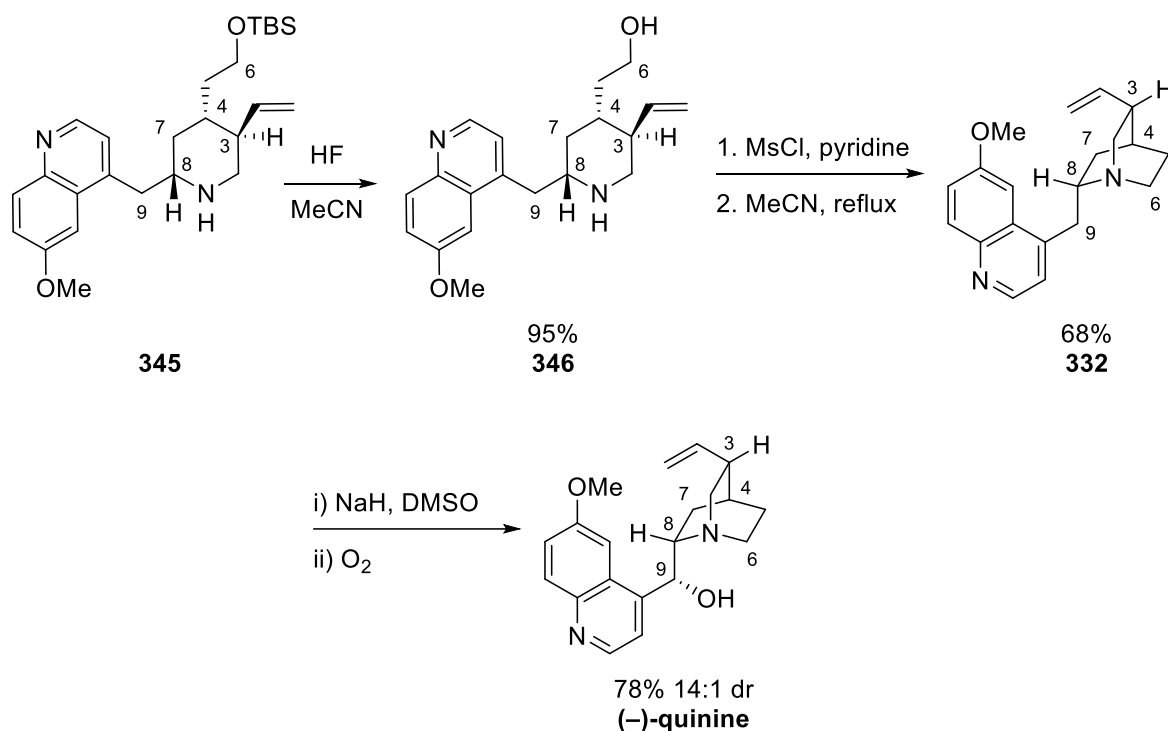
Scheme 4.4

C8-C9 bond formation was then achieved by addition of organolithium **338** into aldehyde *anti*-**339** to give alcohols **343** in 70% yield. Swern oxidation followed by Staudinger reduction of the azide gave imine *trans*-**344** in 69% yield. The next crucial step was the diastereoselective reduction of imine *trans*-**344**, achieved using NaBH_4 in 91% yield and complete diastereoselectivity, to give piperidine **345** (Scheme 4.5).³³² The reaction proceeded through axial hydride addition, positioning the aromatic group in the energetically favoured equatorial position.



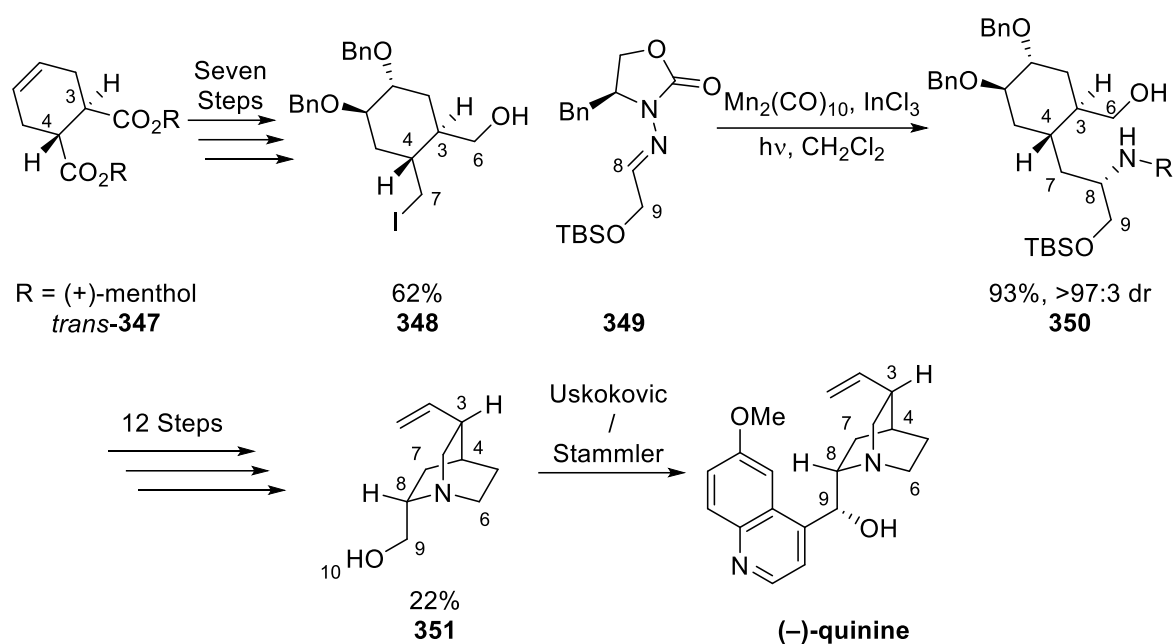
Scheme 4.5

Finally, Stork and co-workers reached deoxyquinine by deprotection of the OTBS group with HF in MeCN to give alcohol **346** in 95% followed by mesylation with MsCl and pyridine and cyclisation in refluxing MeCN to give deoxyquinine **332** in 68% yield. Following this, known oxidation using NaH and O₂ gave (–)-quinine in 78% yield and 14:1 dr (Scheme 4.6).³³²



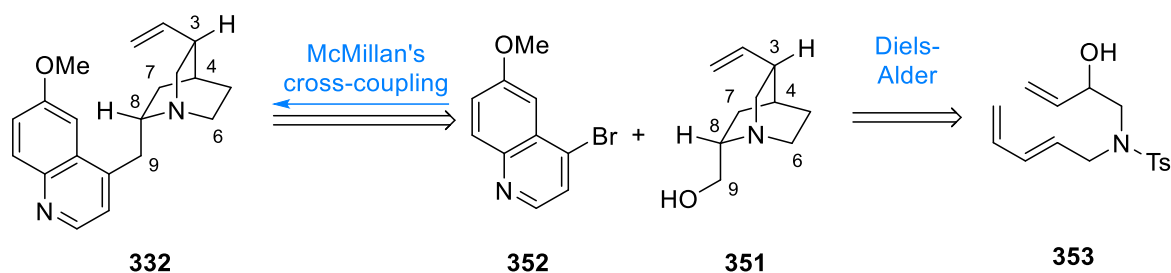
Scheme 4.6

In this way, Stork and co-workers completed their landmark synthesis of (–)-quinine in an overall 8% yield and 16 steps. This was the first example of a total linear asymmetric synthesis. Inspired by the synthesis developed by Stork and co-workers, Qin and co-workers devised a formal synthesis in 2012 that focused on the late-stage formation of the N-C6 bond.³³³ The synthesis focused around making use of previously developed methodology on Mn-mediated radical-ionic annulations to set the C8 stereocentre.³³⁴ Starting from diester *trans*-**347**, iodide **348** was accessed through a seven-step sequence in 62% yield. For the key transformation, iodide **348** was then reacted with hydrazone **349**, Mn₂(CO)₁₀ and InCl₃ under UV irradiation to give amino alcohol **350** in 93% yield as a single diastereomer. Through a 12-step sequence involving Stork's N-C6 bond formation, amino alcohol **350** was converted into quinuclidine **351** with an overall yield of 22%. From this point, using methodologies previously developed by Uskokovic³²⁹ and Stammeler,³³⁵ (–)-quinine could be synthesised (Scheme 4.7).



Scheme 4.7

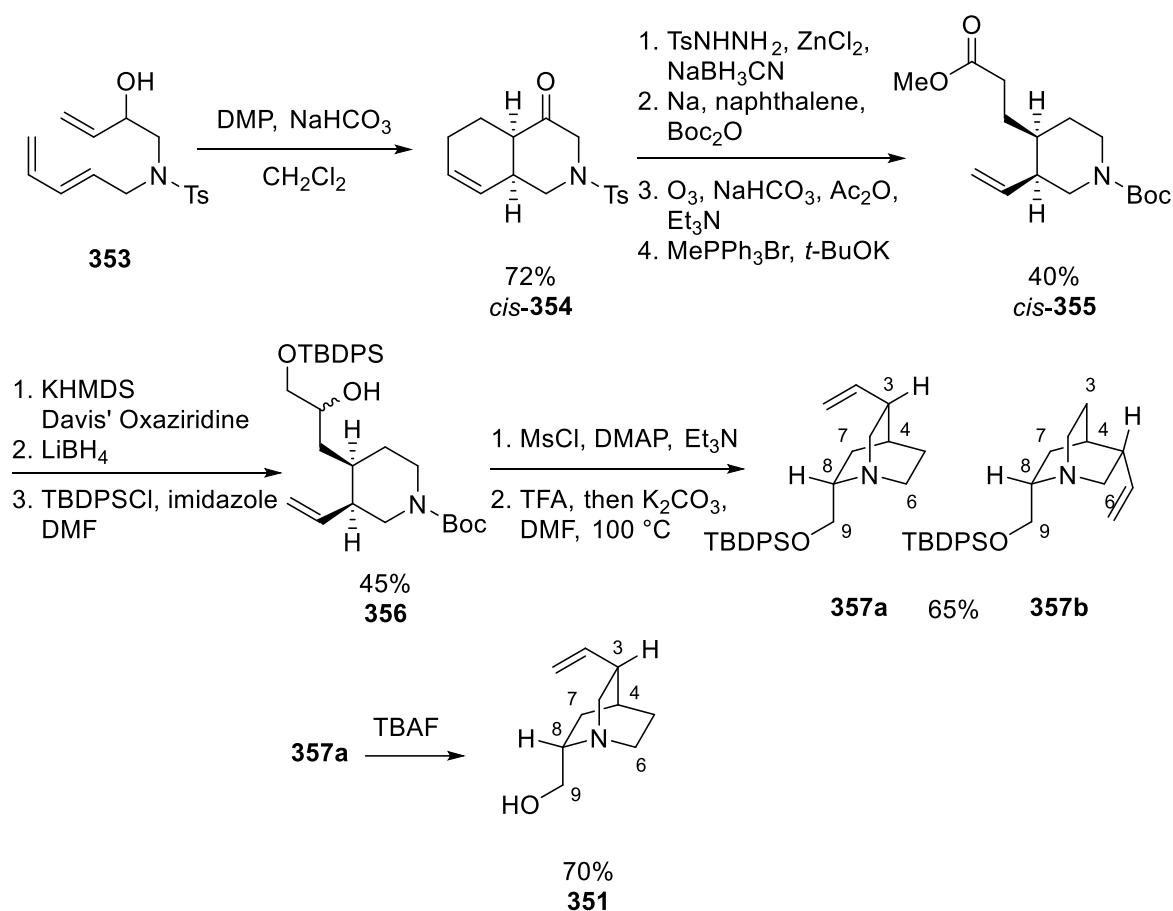
In a manner reminiscent of the synthesis by Qin and co-workers, two recent syntheses of cinchona-like alkaloids have focused on the synthesis of derivatives of quinuclidine **251** and its arylation *via* metal-catalysed cross-couplings. The first of these, published in 2023 by Yang and co-workers,³³⁶ centres on the synthesis of amino alcohol **251**, employing a key intramolecular Diels-Alder reaction from triene **353**. This intermediate was then used in a MacMillan deoxygenative photoredox cross-coupling (as discussed in Section 3.5.1) to synthesize deoxyquinine **332** (Scheme 4.8).



Scheme 4.8

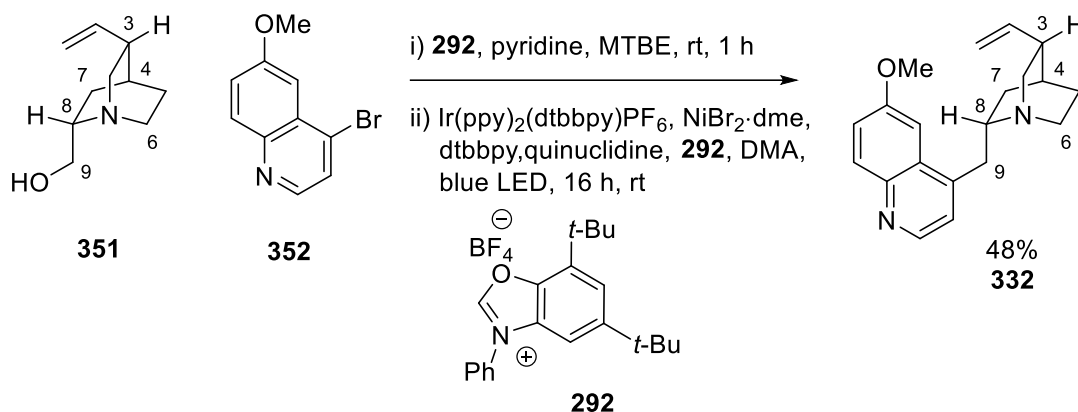
Although Yang and co-workers also developed a stereoselective route to amino alcohol **358**, their main focus was the development of a racemic synthesis as well as the cross-coupling methodology.³³⁶ Starting from sulfonamide **353**, oxidation of the alcohol produced an enone which underwent spontaneous Diels-Alder cycloaddition to furnish bicyclic lactam *cis*-**354** in 72% yield. A four-step sequence of reduction, protecting group substitution, ozonolysis and Wittig olefination then gave alkene *cis*-**355** in 40% yield. α -Oxidation using Davis's

oxaziridine followed by reduction a selective protection of the primary alcohol yielded alcohol **356** in 45% yield which after mesylation and removal of the Boc group cyclised into a 1:1 mixture of quinuclidines **357** in 65% overall yield. Removal of the TBDPS group from quinuclidine **357a** furnished desired alcohol **351** in 70% yield (Scheme 4.9).



Scheme 4.9

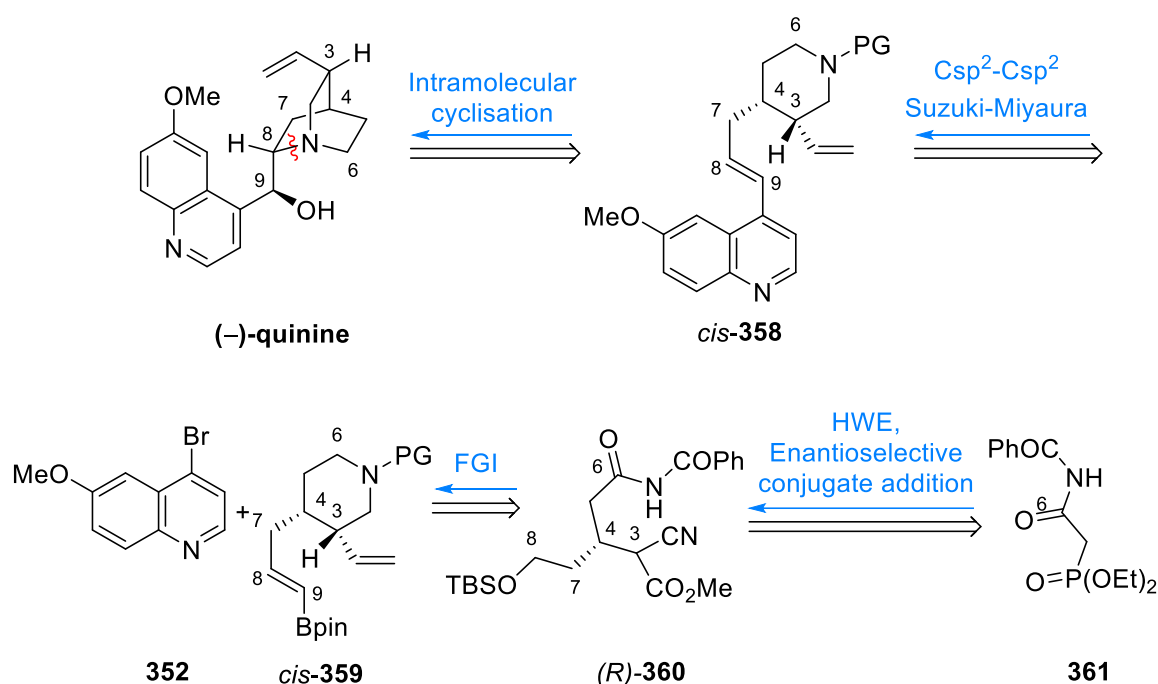
To finish their synthesis Yang and co-workers made use of MacMillan's standard conditions, reacting alcohol **351** with quinoline bromide **352**, benzoxazolium salt **292**, NiBr₂•dtbbpy and quinuclidine to give deoxyquinine **332** in 48% yield (Scheme 4.10).³³⁶



Scheme 4.10

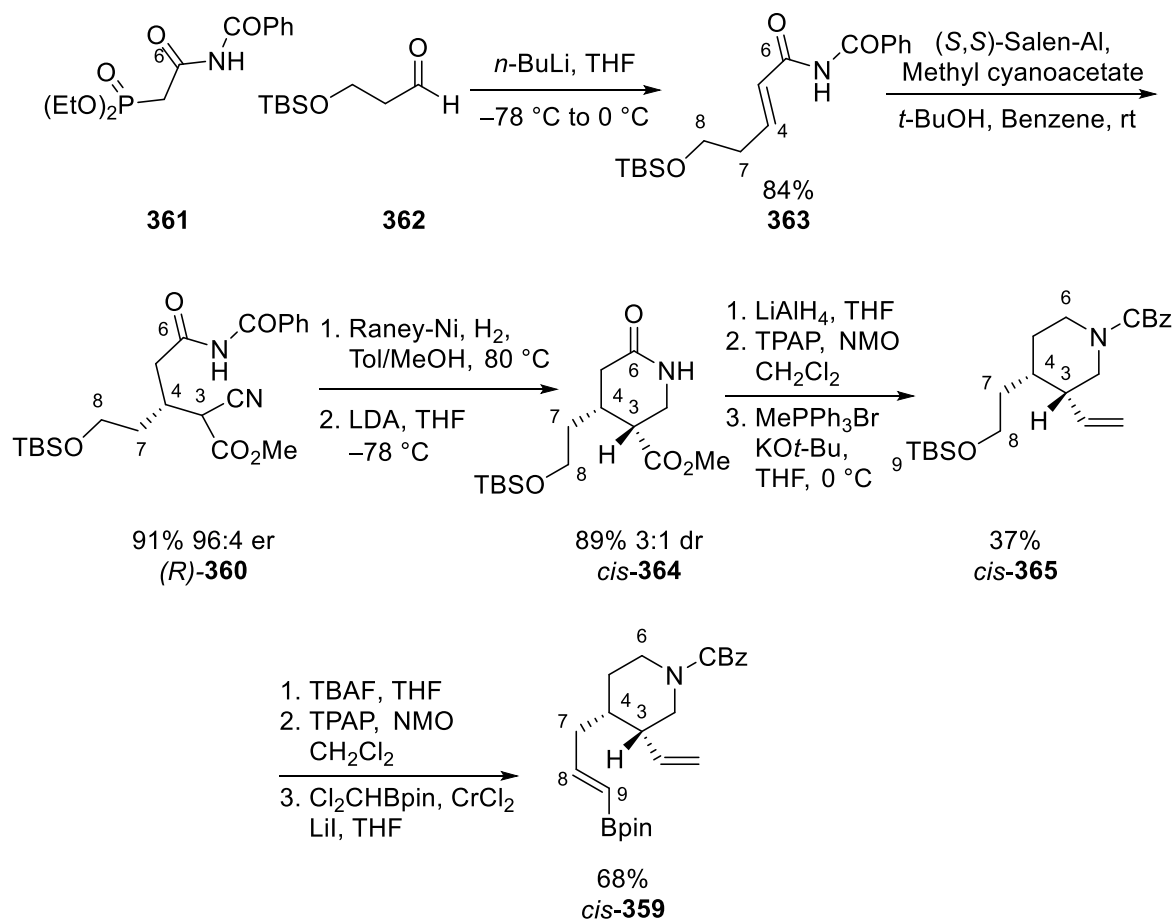
Similarly to Yang and co-workers, in 2024, Foley and co-workers reported a cross-coupling methodology for the synthesis of the C9-Ar bond in quinine-inspired compounds.³¹ In their work, a Ni-catalysed cross-electrophile cross-coupling was developed that enabled cross-coupling of bromide derivative of alcohol **351** with aryl bromide **352** in 43% yield. While this methodology is valuable for general cross-electrophile couplings, it requires a two-step process to convert alcohol **351** into the necessary bromide, all while yielding similar results to MacMillan's cross-coupling from the alcohol.

In contrast to the strategy initially developed by Stork and co-workers, the next landmark asymmetric synthesis of quinine was presented by Jacobsen and co-workers in 2003.³³⁷ Jacobsen revisited an N-C8 disconnection strategy, reminiscent of the approach used by Rabe³²⁵ and Woodward.³²² Jacobsen's retrosynthesis employed three key disconnections. The first of these afforded (–)-quinine from an intramolecular cyclisation to set up the N-C8 bond from a derivative of piperidine *cis*-**358**. This consisted of a sequence of stereoselective dihydroxylation followed by an epoxide formation and ring opening. Then the authors envisaged formation of piperidine *cis*-**358** from a $\text{sp}^2\text{-sp}^2$ Suzuki-Miyaura cross-coupling of quinoline **352** and boronate *cis*-**359** to form the Ar-C9 bond. Boronate *cis*-**359** was synthesised from a series of functional group interconversions from cyanoacetate (*R*)-**360**. Finally, cyanoacetate (*R*)-**360** can be obtained from imide **361** by a series of reactions including a Horner-Wadsworth-Emmons olefination and an enantioselective conjugate addition to set up the C4 stereocentre (Scheme 4.11).



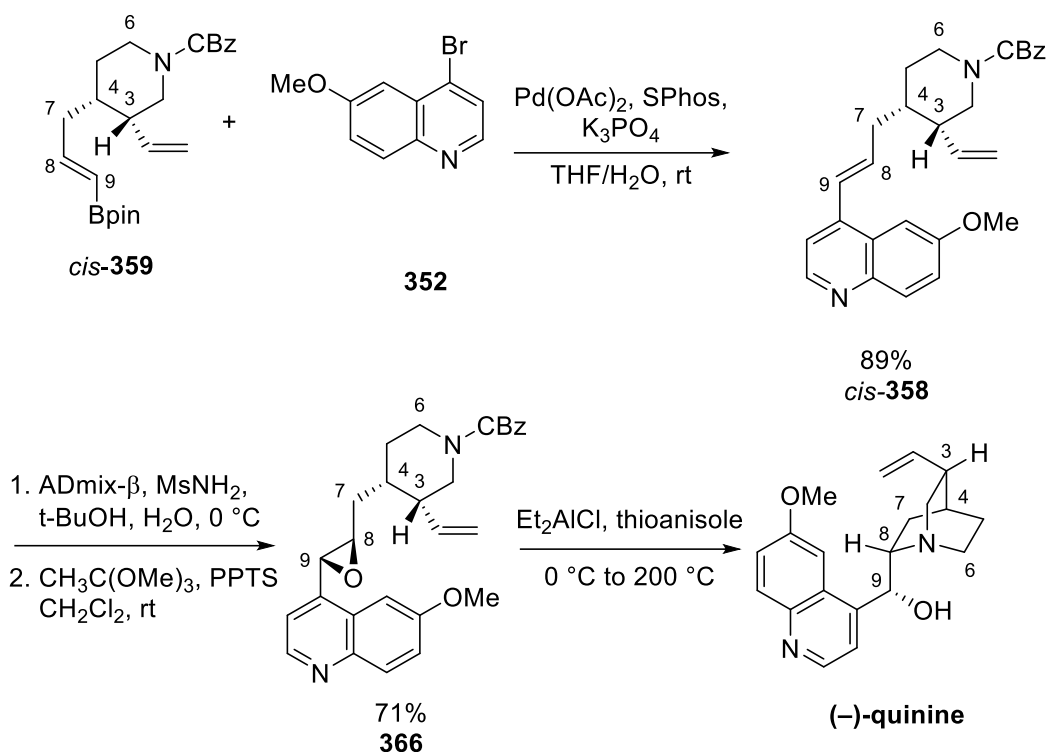
Scheme 4.11

Jacobsen and co-workers' synthesis started with a Horner-Wadsworth-Emmons olefination of imide **361** with aldehyde **362** to give olefin **363** in 84% yield. Olefin **363** then underwent one of Jacobsen's key transformations: a Salen-Al catalysed enantioselective conjugate addition with methyl cyanoacetate, yielding imide (R)-**360** in 91% yield and 96:4 er. Imide (R)-**360** was reduced with Raney-Ni and H₂ to give piperidone *cis*-**364** which, after epimerisation of C3 with LDA, was obtained in 89% yield and 3:1 dr. Piperidone *cis*-**364** was reduced with LiAlH₄, followed by protection with Cbz₂O. The resulting alcohol was then subjected to Ley-Griffith oxidation and Wittig olefination, producing piperidine *cis*-**365**. After separating the diastereomers by chromatography, piperidine *cis*-**365** was obtained as a single diastereomer in 37% yield. Finally, removal of the TBS group with TBAF, followed by Ley-Griffith oxidation and alkylation of the resulting aldehyde under modified Takai conditions, afforded pinacol boronate *cis*-**359** in 68% yield (Scheme 4.12).



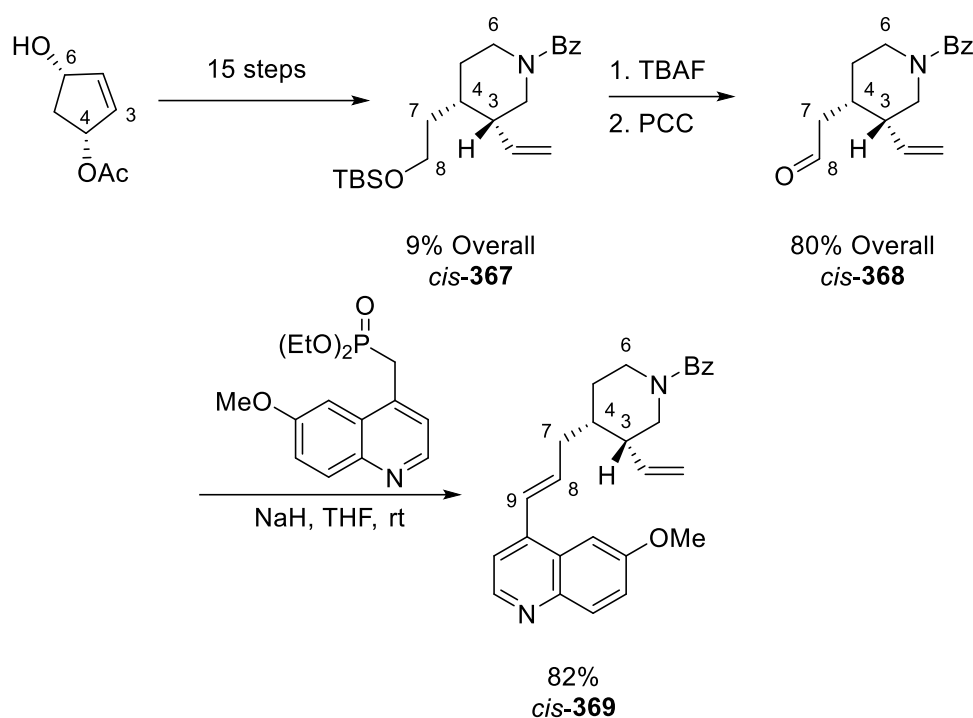
Scheme 4.12

To complete their synthesis, Jacobsen and co-workers performed a cross-coupling of boronate **cis-359** with quinoline bromide **352**, which was synthesized in four steps from p-anisidine in 54% yield. Using $\text{Pd}(\text{OAc})_2$ and SPhos, olefin **cis-358** was formed in 89% yield. Subsequently, Sharpless dihydroxylation of the secondary olefin, followed by epoxide formation under dehydrating conditions with trimethyl orthoacetate and PPTS, produced epoxide **366** in 71% yield as a single diastereomer. Finally, removal of the benzyl carbamate in epoxide **366** using Et_2AlCl and thioanisole led to an intramolecular $\text{S}_{\text{N}}2$ -like cyclisation, resulting in the formation of (–)-quinine in 68% yield (Scheme 4.13).³³⁷



Scheme 4.13

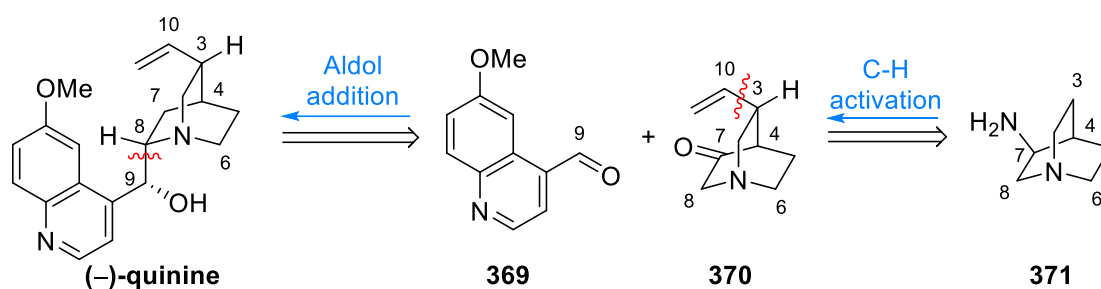
In this fashion, Jacobsen and co-workers concluded a landmark total asymmetric synthesis of (-)-quinine in a 7% overall yield over 14 steps. Parallel to Jacobsen and co-workers' synthesis and following a very similar design rationale, Kobayashi and co-workers also reported an asymmetric synthesis of (-)-quinine in 2004.³³⁸ Aiming for the same intermediate epoxide **366**, Kobayashi and co-workers synthesised alkene *cis*-**369** through a Horner-Wadsworth-Emmons olefination. The authors, however, arrived at the precursor aldehyde *cis*-**368** starting from cyclopentene *cis*-**367** (Scheme 4.14). Overall, Kobayashi and co-workers obtained (-)-quinine in 3% yield over 22 steps.



Scheme 4.14

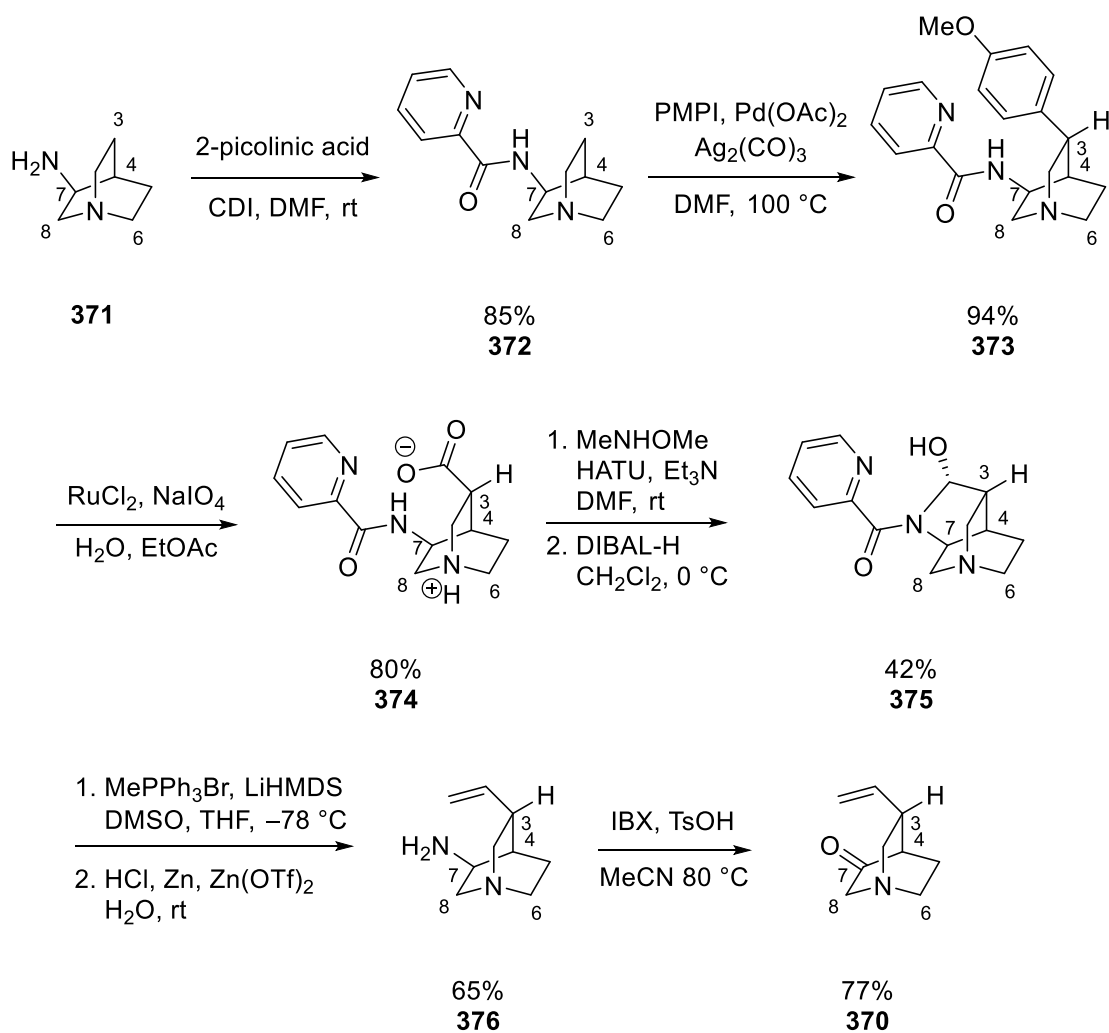
These two strategies, which focused on the synthesis of derivatives of alkene *cis*-**369**, have been widely explored in further syntheses of quinine. In 2010, Aggarwal and co-workers built on the groundwork laid by Jacobsen and Kobayashi regarding the synthesis of aldehyde *cis*-**358**, demonstrating the effectiveness of their sulfur ylide-mediated asymmetric epoxidations for the synthesis of (–)-quinine.³³⁹ In their work, a direct asymmetric Corey-Chaykovsky-type epoxidation of an *N*-Teoc derivative of aldehyde *cis*-**358** was achieved using a sulfur ylide, yielding excellent results in terms of both yield and stereoselectivity. Similarly, in 2011, Hatakeyama and co-workers developed a Jacobsen-Kobayashi-type synthesis with a focus on organocatalytic methods for producing aldehyde *cis*-**358**.³⁴⁰ Finally, in 2019, Cordova and co-workers advanced a modular organocatalytic approach to synthesising derivatives of aldehyde **358**, which enabled the creation of various epimers, enantiomers, and analogues of quinine and its related compound quinidine.³⁴¹

Alternatively, Maulide and co-workers reported an elegant C-H functionalization approach, which began with an intact quinuclidine system and featured a late-stage formation of the C8-C9 bond.³⁴² Maulide envisaged (–)-quinine coming from an aldol addition of quinuclidine ketone **370** to aldehyde **369** forming the C8-C9 bond. In turn, quinuclidine ketone **370** would be synthesised from a diastereoselective CH-activation of a derivative of amine **371** to form the C3-C10 bond (Scheme 4.15).



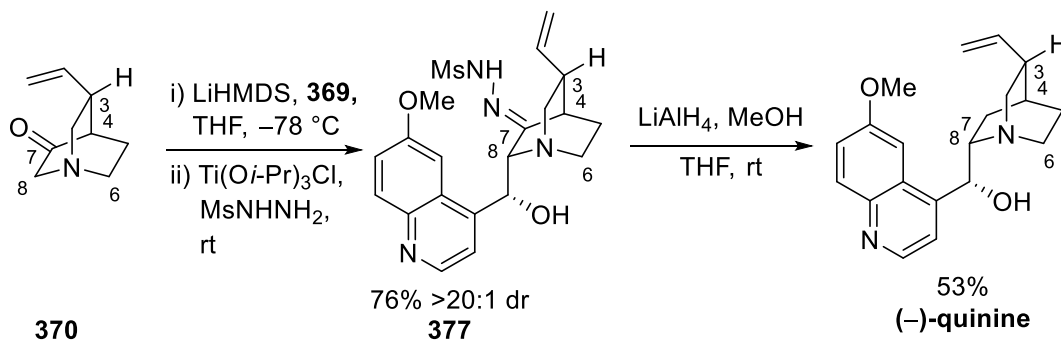
Scheme 4.15

Maulide and co-workers' synthesis began with quinuclidine diamine **371**, to which picolinic acid was appended as a directing group for the forthcoming C-H functionalisation. This step, using CDI, yielded amide **372** in 85% yield. Amide **372** then underwent CH arylation on the 3-position using *p*-methoxyiodobenzene, Pd(OAc)₂ and Ag₂CO₃ to give arylated quinuclidine **373** in 94% yield as a single diastereomer. Ruthenium-catalysed oxidative degradation of the anisole moiety then gave amino acid **374** in 80% yield. Formation of the Weinreb amide using HATU, followed by reduction with DIBAL-H, produced hemiaminal **375** in 42% yield, effectively preventing epimerisation. Hemiaminal **375** then underwent Wittig olefination and reductive cleavage of the picolinamide to give quinuclidine **376** in 65% yield. Then, amine to ketone oxidation promoted by IBX afforded ketone **370** in 77% yield (Scheme 4.16).³⁴²

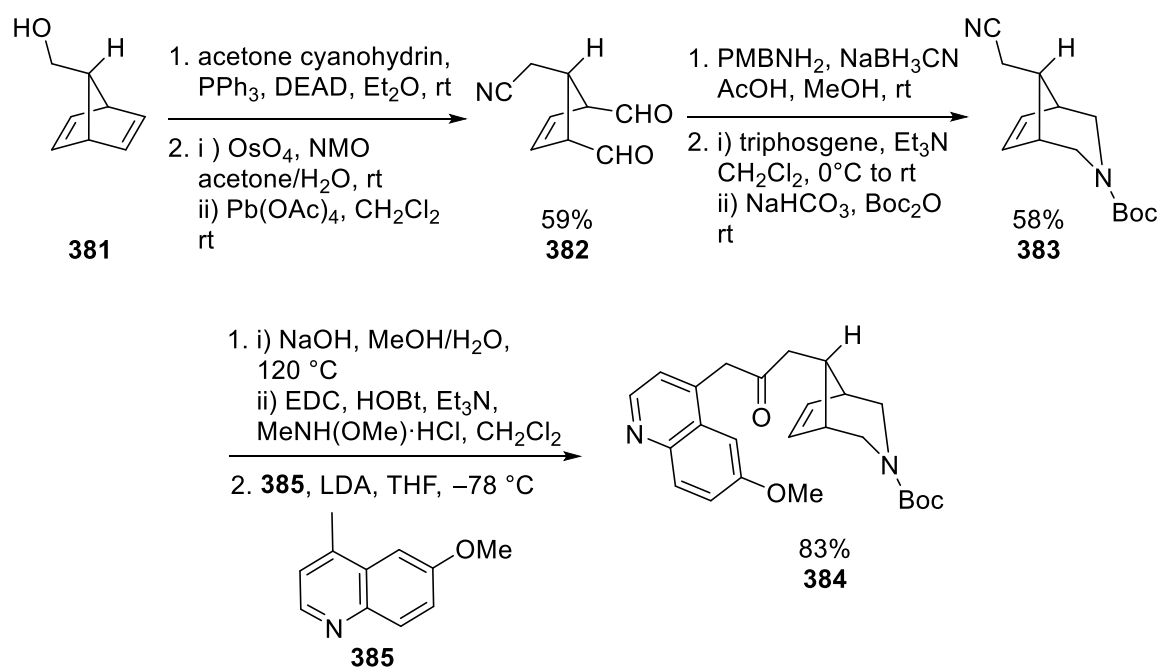


Scheme 4.16

To conclude the synthesis, ketone **370** was reacted with aldehyde **369** and LiHMDS to form the aldol product, which was immediately converted into hydrazone **377** in 76% yield and >20:1 dr to prevent C8 epimerization. Finally, reduction of the hydrazone using LiAlH₄ afforded (–)-quinine in 53% yield (Scheme 4.17). Overall, Maulide and coworkers' synthesis gave (–)-quinine in 10 steps from quinuclidine **371** and 5.4% overall yield.³⁴²

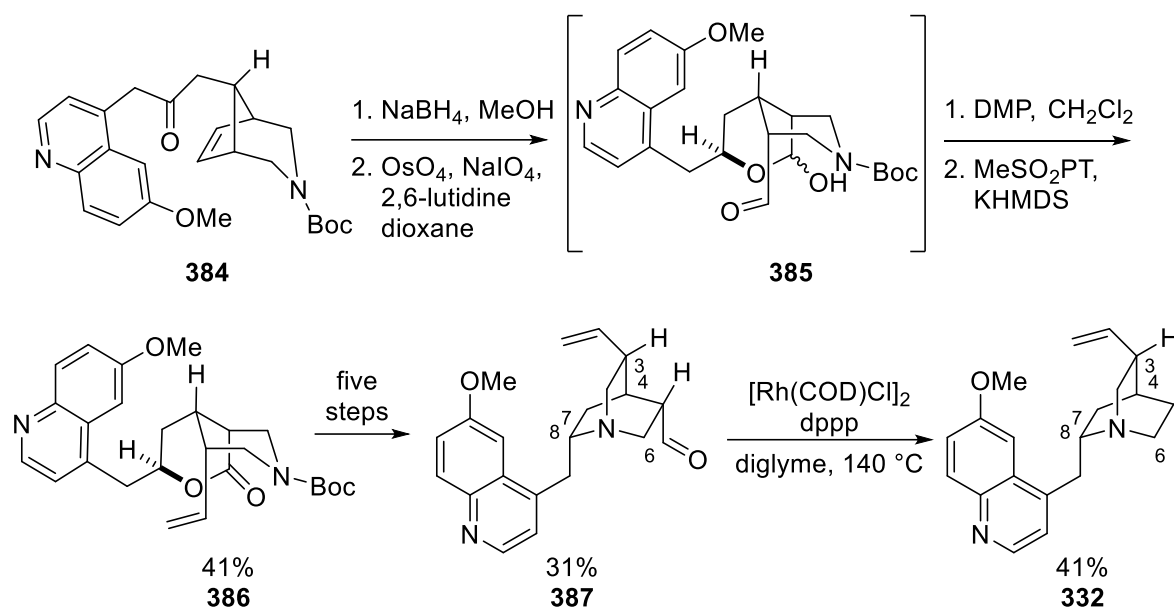


Scheme 4.17



Scheme 4.19

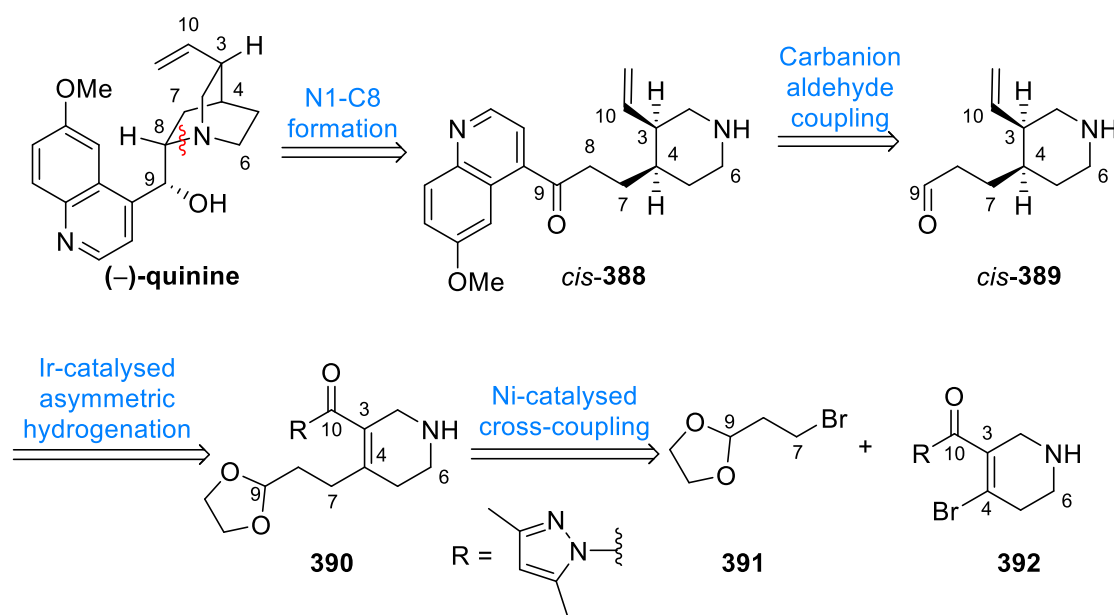
In the desymmetrisation step towards the synthesis of quinine from bicyclic amine **384**, the ketone was reduced, and the olefin underwent oxidative cleavage to yield lactol **385**, which was immediately oxidized with DMP. The leftover aldehyde then underwent a Julia-Kocienski olefination to form alkene **386** in 41% yield. Subsequently, alkene **386** was subjected to a five-step sequence, furnishing quinuclidine **387** in 37% yield. A Rh-catalysed decarbonylation of this intermediate then produced deoxyquinine **332** in 41% yield (Scheme 4.20).³⁴³



Scheme 4.20

More recently, asymmetric syntheses of quinine have focused heavily on using organocatalysis to establish the stereogenic centres around the quinuclidine core. Alongside Cordova's synthesis,³⁴¹ briefly mentioned above, syntheses by Ishikawa and co-workers,^{344, 345} and Hayashi and co-workers^{307, 346} also fall in this category.

A noteworthy recent synthesis was reported by Qin and co-workers in 2024.³⁴⁷ In a manner reminiscent of syntheses by Woodward, Uskokovic, and Martin, an N-C8 cyclization of ketone *cis*-**388** was used as the final step of their synthesis. Ketone *cis*-**388** was itself obtained by adding an aryl organolithium to aldehyde *cis*-**389**. However, Qin and co-workers applied modern methodologies throughout, including a key Ir-catalysed hydrogenation of alkene **390** to set the desired stereocentres and a Ni-catalysed cross-coupling to synthesize alkene **390** (Scheme 4.21).

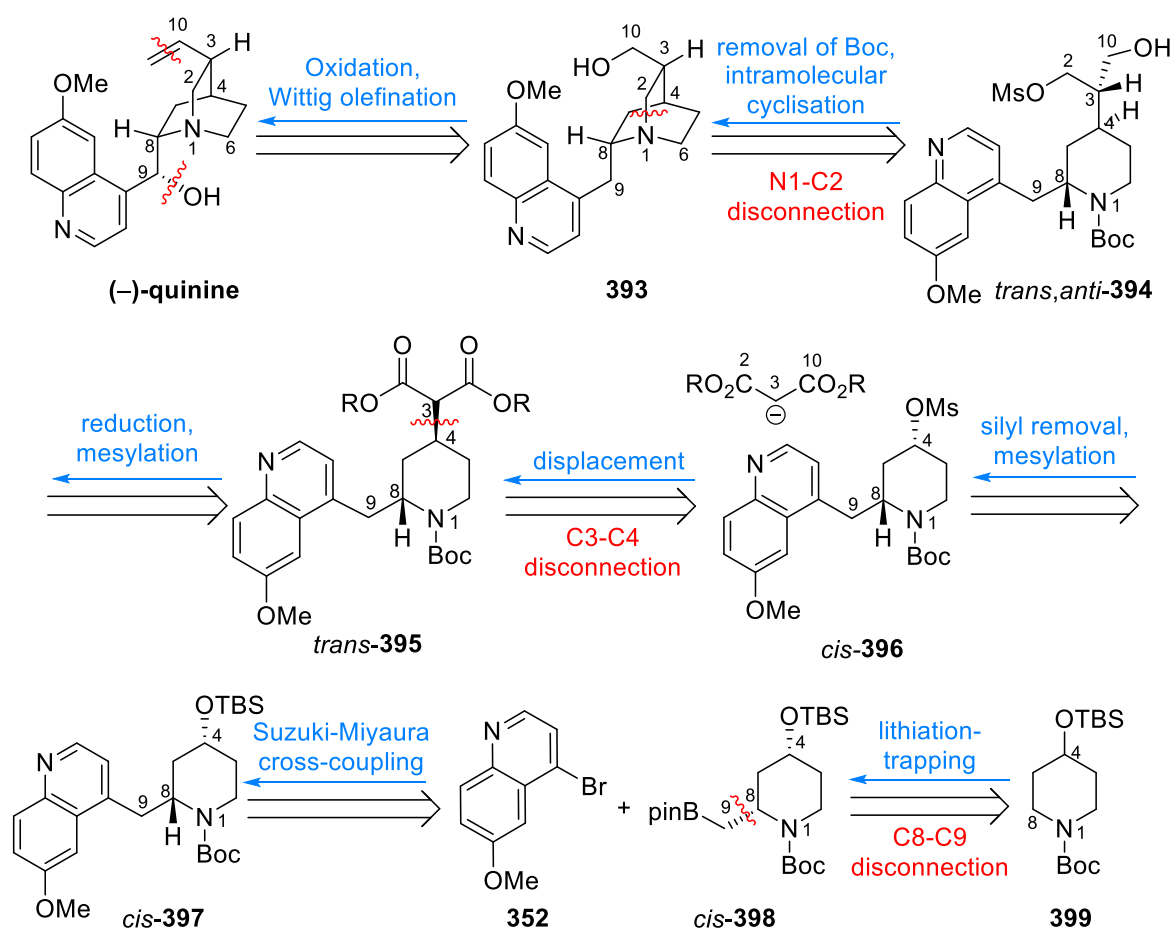


Scheme 4.21

As illustrated in this selective overview, quinine has served as a target for demonstrating diverse synthetic strategies and methodologies, which have undergone significant advancements over the years. The journey began with the formal synthesis by Woodward and Doering in 1944, which incorporated a key N-C8 cyclization developed by Rabe and Kindler. Uskokovic and co-workers further refined the N-C8 cyclization strategy, while Stork and co-workers achieved the first asymmetric synthesis, concluding with an N-C6 cyclization. Subsequent innovations include the introduction of asymmetric metal catalysis in the syntheses developed by Qin and Jacobsen, organocatalysis by Cordova, Ishikawa, and Hayashi, and modern methodologies such as C-H activation by Maulide and sp^3 - sp^3 cross-couplings by Yang and Foley.

4.3 Retrosynthetic Analysis and Project Outline

The O'Brien group has significant historical experience³⁴⁸⁻³⁵⁰ of Beak's³⁵¹ *N*-Boc lithiation-trapping methodology and has previously investigated the lithiation and trapping of 4-substituted *N*-Boc piperidines with various electrophiles.³⁰⁵ Additionally, one strand of the group's current research focuses on the Suzuki-Miyaura cross-coupling of sp^3 -hybridised boronates and their derivatives. Building on this, the aim of this project is to design and develop a synthetic route for the synthesis of quinine using both aspects of methodology highlighted above. A synthetic route was devised that applies these methodologies in a C8-C9 disconnection. Furthermore, the quinuclidine ring would be formed *via* an N1-C2 disconnection, a disconnection that has not previously been applied in any known syntheses of quinine. This route is summarised retrosynthetically in Scheme 4.22.

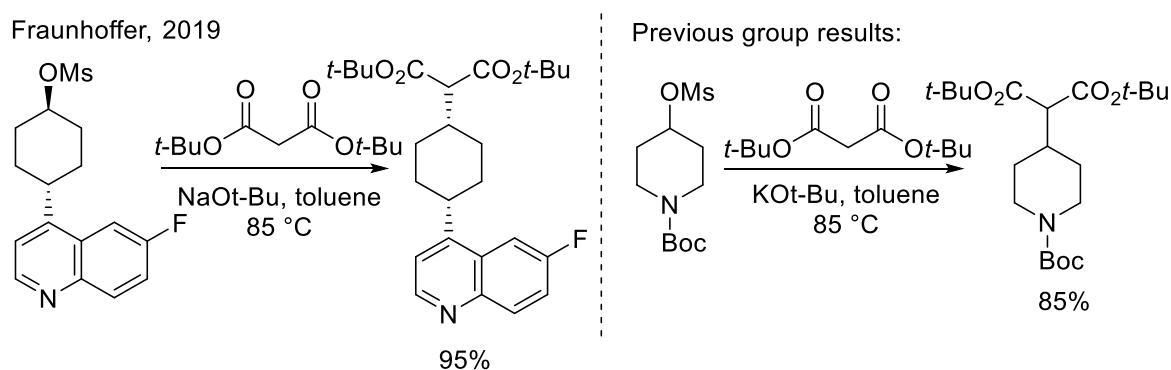


Scheme 4.22

(-)-Quinine could be derived from quinuclidine **393** from previously established methodology, namely alcohol oxidation and Wittig olefination based on methods reported by Hatakeyama on a similar compound³⁴⁰ and C9 benzylic oxidation using methods

described by Uskokovic³²⁹ and Stammer (see Scheme 4.6).³³⁵ Importantly, this approach would explore a new strategy for the formation of the quinuclidine ring, *via* a key N1-C2 disconnection to give monomesylate *trans-anti*-**394** as the starting material for this step. Monomesylate *trans,anti*-**394** could be synthesised from malonate *trans*-**395** *via* reduction and mesylation. Malonate *trans*-**395** could be obtained from displacement of mesylate *cis*-**396**, itself formed aryl piperidine *cis*-**397**. Aryl piperidine *cis*-**397** could be synthesised by Suzuki-Miyaura cross-coupling of sp^3 hybridised pinacol boronate *cis*-**398** with bromoquinoline **352**. Pinacol boronate *cis*-**398** could be formed *via* *N*-Boc α -lithiation (using *s*-BuLi and TMEDA or a chiral diamine) of piperidine **399** and trapping with chloromethyl Bpin, offering a new route to join the piperidine and quinoline moieties (C8-C9 disconnection).

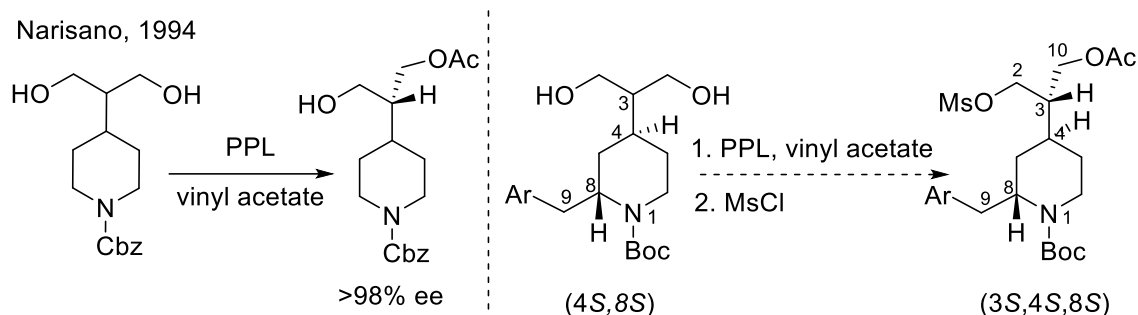
The proposed route has several key steps where stereochemistry would be set. The first of these is the asymmetric access to pinacol boronate *cis*-**398**. This would rely on methodology previously developed by Beak^{352, 353} that establishes the diastereoselective formation of *cis*-2,4-disubstituted *N*-Boc piperidines. This would be complemented by previous work from the O'Brien^{354, 355} group on the asymmetric lithiation-trapping of *N*-Boc piperidines to set the initial *cis*-(*R,S*) C8 and C4 stereochemistry of pinacol boronate *cis*-**398**. Subsequently, a precedented S_N2 malonate displacement³⁵⁶ which was also previously studied by members of the group (Scheme 4.23),³⁰⁶ would set the desired *trans*-(*S,S*) C8 and C4 stereochemistry for diester *trans*-**395**.



Scheme 4.23

Following this, we would encounter a diastereoselective monofunctionalisation of a diol intermediate (not shown). Anticipating poor substrate control of this functionalisation, we planned to employ an enzymatic kinetic resolution developed by Narisano and co-workers,³⁵⁷ which would yield a monoacetate with the desired C3 configuration that, after

mesylation, would be (*S*) (Scheme 4.24). Finally, the C9 stereochemistry would be introduced using Uskokovic's diastereoselective C9 oxidation (see Section 4.1, Scheme 4.2).

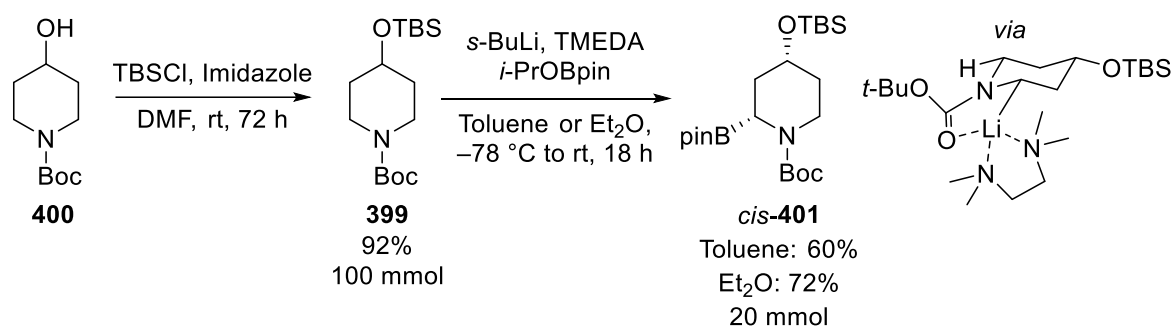


Scheme 4.24

This chapter focuses on the development of a synthetic route for quinine based on the proposed retrosynthetic analysis. The lithiation and trapping of piperidine **399** is explored, followed by the development of Suzuki-Miyaura cross-coupling methodology for boronate *cis*-**398**. Further functionalisation into piperidine *trans,anti*-**394** is also presented. From there, the cyclization of piperidine *trans,anti*-**394** into quinuclidine **393** is developed. Finally, the chapter addresses the final stages, detailing the necessary steps to advance quinuclidine **393** into (–)-quinine.

4.4 Towards a Synthesis of Quinine

With the synthetic route previously outlined and some related preliminary model studies carried out in the group,³⁰⁶ the initial plan was to develop methodology for the synthesis and Suzuki-Miyaura cross-coupling of TBS-protected piperidine pinacol boronate *cis*-**398**. Resorting to methodology previously developed in the O'Brien group,³⁰⁵ hydroxypiperidine **400** was protected using TBSCl and imidazole to yield piperidine **399** in 92% yield on a 100 mmol scale (Scheme 17). Equatorial lithiation of piperidine **399** with an equatorially disposed OTBS group using *s*-BuLi and TMEDA in toluene and trapping with *i*-PrOBpin gave pinacol boronate *cis*-**401** (97:3 dr) from which *cis*-**401** could be isolated in 60% yield as a single diastereomer after chromatography. Alternatively, using Et₂O as the solvent also gave pinacol boronate *cis*-**401** in 97:3 dr; a 72% yield of *cis*-**401** was isolated after chromatography (Scheme 4.25). This could be scaled up effectively to 20 mmol. At this stage, the *cis* stereochemistry was assigned based on Beak's previously discussed work³⁵³ and related examples in the O'Brien group.



Scheme 4.25 – All compounds in this scheme are racemic.

The next step would involve a Matteson homologation of pinacol boronate *cis*-**401** into pinacol boronate *cis*-**398** which is a stereospecific process that would proceed with overall retention of configuration.³⁵⁸ This proceeds mechanistically *via* the intermediate boronate complex *cis*-**402** (Table 4.1). Initial attempts used conditions reported by Sawamura and co-workers³⁵⁹ for an analogous pyrrolidine. Unfortunately, use of ClCH₂Br and *n*-BuLi at –78 °C to 40 °C afforded pinacol boronate *cis*-**398** (10% yield), protodeborylated piperidine **399** (42% yield) and starting pinacol boronate *cis*-**401** (30% yield) (Entry 1). With the hypothesis that protodeborylated **399** was being formed by decomposition of the boronate intermediate *cis*-**402** formed by addition of ClCH₂Li to pinacol boronate *cis*-**401** at high temperatures, the same set of conditions was attempted while trapping at rt. This gave pinacol boronate *cis*-**398** in 45% yield with protodeborylated piperidine **399** being obtained in 7% yield (Entry

2). It has been reported³⁶⁰ that addition of ZnCl₂ can facilitate formation of the intermediate boronate complex *cis*-**402**. However, use of ZnCl₂, ClCH₂Br and *n*-BuLi on pinacol boronate *cis*-**401** gave a diminished 35% yield of pinacol boronate *cis*-**398** with protodeborylated piperidine **399** being obtained in 15% yield (Entry 3). Likewise, use of CH₂Br₂ in place of ClCH₂Br proved detrimental with pinacol boronate *cis*-**398** being obtained in 30% yield (Entry 4). Finally, use of ClCH₂I³⁶¹ afforded pinacol boronate *cis*-**398** in 63% yield, protodeborylated piperidine **399** in 2% yield and starting pinacol boronate *cis*-**401** in 10% yield (Entry 5). Gratifyingly, these conditions could be applied to pinacol boronate *cis*-**401** on a 9.4 mmol scale with an increased yield of 88% (Entry 6).

Table 4.1 – Optimisation of Matteson homologation of pinacol boronate **401**.

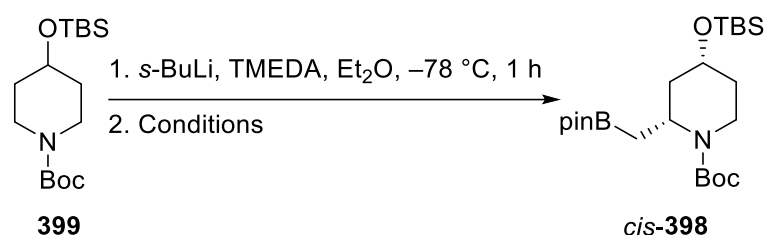
Entry	Conditions	Yield ^a 398 (%)	Yield ^a 399 (%)	Yield ^a 401 (%)	Scale (mmol)
1	ClCH ₂ Br, <i>n</i> -BuLi, THF, –78 °C to 40 °C, 18 h	10	42	30	0.30
2	ClCH ₂ Br, <i>n</i> -BuLi, THF, –78 °C to rt, 18 h	45	7	28	0.30
3	ClCH ₂ Br, <i>n</i> -BuLi, ZnCl ₂ , THF, –78 °C to rt, 18 h	35	15	32	0.30
4	CH ₂ Br ₂ , <i>n</i> -BuLi, THF, –78 °C to rt, 18 h	30	20	29	0.25
5	ClCH ₂ I, <i>n</i> -BuLi, THF, –78 °C to rt, 18 h	63	2	10	1.00
6	ClCH ₂ I, <i>n</i> -BuLi, THF, –78 °C to rt, 18 h	88	ND	ND	9.40

^a) Isolated yield after chromatography; ND: Not Determined; All compounds in this table are racemic.

Although this two-step lithiation-trapping and homologation methodology provided adequate access to pinacol boronate *cis*-**398** in 41% overall yield as a single diastereomer,

interest in accessing pinacol boronate *cis*-**398** directly from *N*-Boc piperidine **399** in a single step was still present and was thus explored (Table 4.2). Following a recent review by Aggarwal and co-workers,³⁶² a series of conditions appeared suitable for the direct lithiation-trapping transformation of *N*-Boc piperidine **399** into pinacol boronate *cis*-**398**. Conditions reported by Zawatzky and co-workers,³⁶⁰ namely lithiation using a *s*-BuLi/TMEDA complex followed by transmetallation with ZnCl₂ and trapping with chloromethyl Bpin afforded only traces of pinacol boronate *cis*-**398** (Entry 1). Our previous studies in the Matteson homologation of pinacol boronate *cis*-**398** (see Table 4.2, entry 3) suggested that the addition of ZnCl₂ had a detrimental effect on the formation of pinacol boronate *cis*-**398**. Utilising the same conditions without the addition of ZnCl₂ gave a 93:7 mixture of pinacol boronates *cis*- and *trans*-**398** in 9% yield (Entry 2). It has been suggested that addition of Mg²⁺ salts to the reaction can aid the rearrangement of the boronate complex.³⁶³ However, addition of MgBr₂ had a minimal impact on the reaction with pinacol boronate *cis*-**398** being obtained in 12% yield (93:7 dr) (Entry 3). Likewise, it has been shown³⁶⁴ that a solvent switch from Et₂O to CHCl₃ after formation of the boronate complex **402** can facilitate its rearrangement into pinacol boronate *cis*-**398**. Nonetheless, use of the solvent switch had minimal effect on the reaction with pinacol boronate *cis*-**398** being obtained in 14% yield (93:7 dr) (Entry 4). Fortunately, use of bromomethyl Bpin gave a significant improvement and pinacol boronate *cis*-**398** was isolated in 45% yield and 96:4 dr (Entry 5). Scale-up of these conditions afforded pinacol boronate *cis*-**398** in 70% as a single diastereomer after chromatography on a 1.5 mmol scale (Entry 6).

Table 4.2 – Optimisation of direct lithiation-trapping to give pinacol boronate *cis*-**398**.

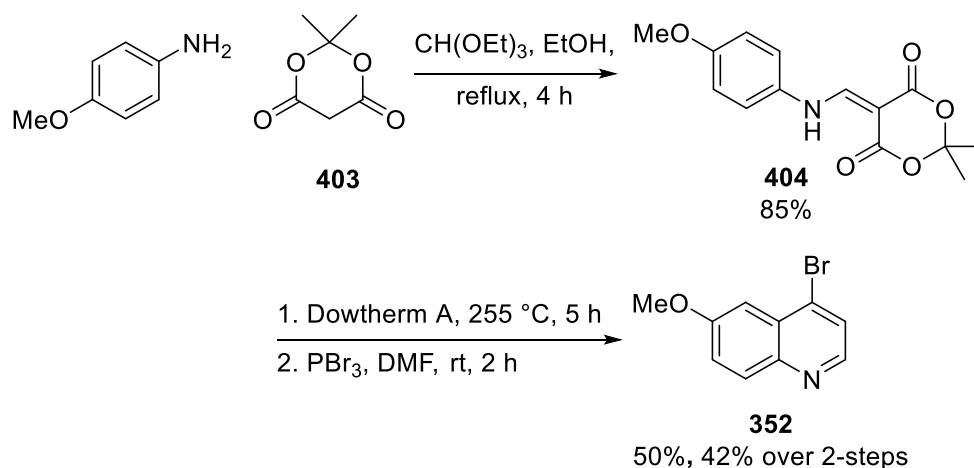


Entry	Conditions	Yield ^a 398 (%)	dr ^b (<i>cis:trans</i>)
1	ClCH ₂ Bpin, ZnCl ₂ , Et ₂ O, –78 °C to rt, 18 h	Traces ^c	ND ^d
2	ClCH ₂ Bpin, Et ₂ O, –78 °C to rt, 18 h	9	93:7
3	ClCH ₂ Bpin, MgBr ₂ , Et ₂ O, –78 °C to rt, 18 h	12	93:7
4	ClCH ₂ Bpin, Et ₂ O, –78 °C, 1 h, then solvent switch to CHCl ₃ , reflux, 18 h	14	93:7
5	BrCH ₂ Bpin, Et ₂ O, –78 °C to rt, 18 h	45	96:4
6	BrCH ₂ Bpin, Et ₂ O, –78 °C to rt, 18 h	70	>97:3

^a) Isolated yield after chromatography; ^b) Determined by ¹H NMR spectroscopy of the purified product; ^c) By HRMS of the crude product; ^d) Not determined; All compounds in this table are racemic.

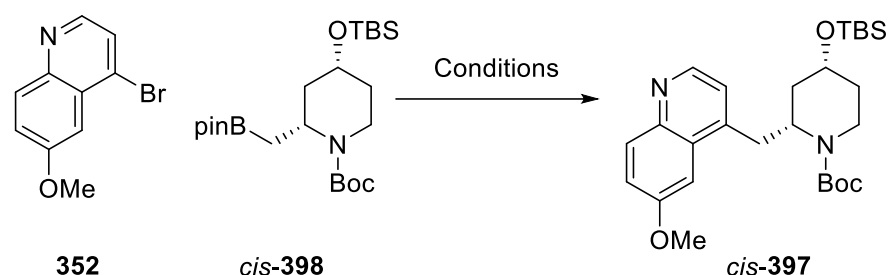
Overall, while the two-step trapping and homologation methodology affords a single diastereomer in acceptable yields, the improved yields and efficiency from the direct trapping make it a more valuable methodology. This is especially true since any quantities of pinacol boronate *trans*-**398** generated are easily removed in downstream purifications.

With two different reliable methodologies to access pinacol boronate *cis*-**398** in good yields in place, the next step involved a sp³-sp² Suzuki-Miyaura cross-coupling reaction. For this, access to bromoquinoline **352** was required. Gratifyingly, following a previously reported procedure,³³⁷ bromoquinoline **352** was easily prepared in 42% yield over 3 steps from *p*-anisidine and Meldrum's acid **403** (Scheme 4.26).



Scheme 4.26

Next, a series of conditions for the Suzuki-Miyaura-cross-coupling of CH_2Bpin compounds α to nitrogen were selected for the cross-coupling of pinacol boronate *cis*-**398** and bromoquinoline **352**. The results are summarised in Table 4.3. The first, described by Li and co-workers,³⁶⁵ used $\text{Pd}(\text{dba})_2$, dppf and $\text{CsOH} \cdot \text{H}_2\text{O}$ with an excess of aryl bromide in dioxane and gave aryl piperidine *cis*-**397** in 35% yield as a ~90% pure compound with unidentified aromatic and aliphatic impurities (Entry 1). Similarly, conditions reported by Taylor and co-workers,³⁶⁶ using $\text{Pd}(\text{dppf})\text{Cl}_2$, K_2CO_3 , Ag_2O and an excess of aryl bromide in THF and H_2O gave aryl piperidine *cis*-**397** in 45% yield (~90% purity) (Entry 2). The O'Brien group is currently exploring the Suzuki-Miyaura cross-coupling of heterocyclic sp^3 boronates.³⁰⁵ From these studies, the use of a $\text{Pd}(\text{OAc})_2$, cataCXium A and Cs_2CO_3 in a toluene- H_2O system has emerged as a particularly versatile and efficient set of conditions to effect the Suzuki-Miyaura cross-coupling of secondary sp^3 boronates and with Bpin derivatives or BF_3K salts. Thus, applying these conditions to the cross-coupling of pinacol boronate *cis*-**398** and an excess of bromoquinoline **352** in both toluene- H_2O and dioxane- H_2O afforded aryl piperidine *cis*-**397** in 55% yield (~95% purity) (Entry 3) and 65% yield (~90% purity) (Entry 4) respectively. Finally, utilising these conditions with an excess of pinacol boronate *cis*-**398** in toluene- H_2O gave aryl piperidine *cis*-**397** in 78% yield with no evidence of the previously observed impurity (Entry 5). Additionally, it was observed that scaling up this reaction to 2.5 mmol while keeping the reaction volume to a maximum of 20 mL, resulted in the cross-coupling reaction giving arylated piperidine *cis*-**397** in 93% yield (Entry 6).

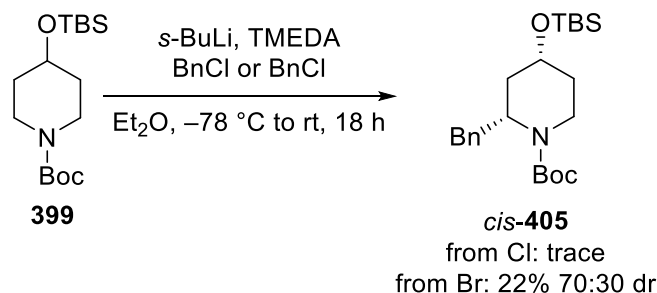
Table 4.3 – Optimisation of Suzuki-Miyaura cross-coupling of pinacol boronate *cis*-**398**.

Entry	Eq. 398	Eq. 352	Conditions	Yield ^a 397 (%)
1	1.0	1.3	Pd(dba) ₂ (10 mol%), dppf (10 mol%), CsOH·H ₂ O (4.0 eq), dioxane, 100 °C, 18 h	35 ^b
2	1.0	1.3	Pd(dppf)Cl ₂ (15 mol%), K ₂ CO ₃ (3.0 eq), Ag ₂ O (1.5 eq), THF-H ₂ O (9:1), 100 °C, 18 h	45 ^b
3	1.0	1.3	Pd(OAc) ₂ (10 mol%), cataCXium A (20 mol%), Cs ₂ CO ₃ (3.0 eq), toluene-H ₂ O (9:1) 100 °C, 18 h	55 ^c
4	1.0	1.3	Pd(OAc) ₂ (10 mol%), cataCXium A (20 mol%), Cs ₂ CO ₃ (3.0 eq), dioxane-H ₂ O (9:1), 100 °C, 18 h	65 ^b
5	1.3	1.0	Pd(OAc) ₂ (10 mol%), cataCXium A (20 mol%), Cs ₂ CO ₃ (3.0 eq), toluene-H ₂ O (9:1), 100 °C, 18 h	78
6	1.3	1.0	Pd(OAc) ₂ (10 mol%), cataCXium A (20 mol%), Cs ₂ CO ₃ (3.0 eq), toluene-H ₂ O (9:1), 100 °C, 18 h (2.5 mmol)	93

^a) Isolated yield after chromatography; ^b) ~90% pure by ¹H NMR spectroscopy of the purified product; ^c) ~95% pure by ¹H NMR spectroscopy of the purified product; All compounds in this table are racemic.

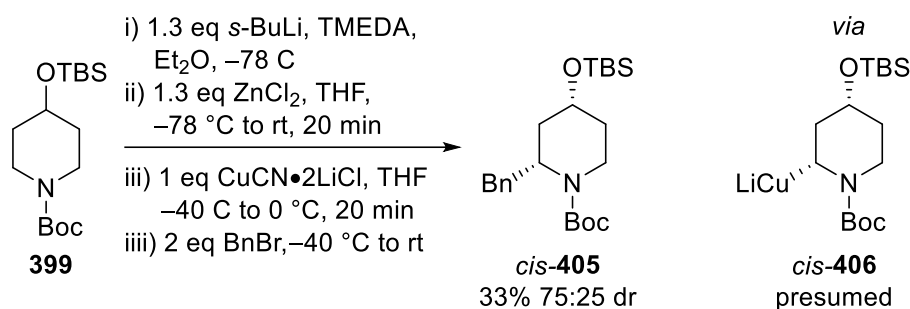
Before moving on to the next stages of the synthetic route, we decided to explore the possibility of directly trapping the lithiated species derived from piperidine **399** with a benzyl halide derived from quinoline **352**. This could in principle provide a direct synthesis of aryl piperidine *cis*-**397**. However, there is limited precedent for the lithiation and direct benzylation of *N*-Boc piperidines.³⁶⁷ Therefore, we initially attempted to apply our standard lithiation trapping conditions using benzyl bromide and benzyl chloride as model substrates. Use of *s*-BuLi and TMEDA for lithiation followed by trapping with BnCl yielded only trace amounts of benzylated piperidine *cis*-**405**. In contrast, trapping with BnBr afforded

benzylated piperidine *cis*-**405** in 22% yield (70:30 dr, *cis*-**405** assumed to be the major diastereomer) (Scheme 4.27).



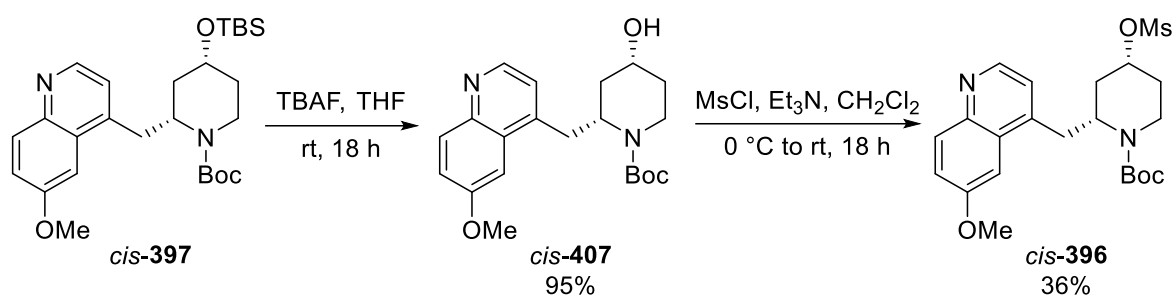
Scheme 4.27 – All compounds in this scheme are racemic.

An alternative to direct lithiation and trapping is the formation and trapping of a piperidine Gilman-type reagent.³⁶⁸ Thus, lithiation of piperidine **399** with *s*-BuLi and TMEDA, followed by transmetalation to the cuprate via an organozinc reagent using ZnCl₂ and CuCN, afforded cuprate *cis*-**406** as a presumed intermediate. Trapping this intermediate with BnBr gave benzylated piperidine *cis*-**405** in 33% yield and 75:25 dr with the same major diastereomer as observed in the direct organolithium trapping (Scheme 4.28). It was concluded that neither the organolithium trapping nor the cuprate trapping approaches looked very promising and were unlikely to work well with the more complex quinoline-based benzyl bromide required for the quinine synthesis. As a result, no further studies were conducted on this approach.



Scheme 4.28 – All compounds in this scheme are racemic.

With this direct trapping strategy into arylated piperidine *cis*-**397** discarded, we proceeded with the proposed synthesis. From aryl piperidine *cis*-**397**, removal of the TBS group was achieved in 95% yield using TBAF to give alcohol *cis*-**407** which was subsequently mesylated with MsCl and Et₃N to give sulfonate *cis*-**396** in a disappointing 36% yield (Scheme 4.29). ¹H NMR spectroscopic analysis of the crude mesylation product revealed that the low yield was primarily due to losses during chromatographic purification.



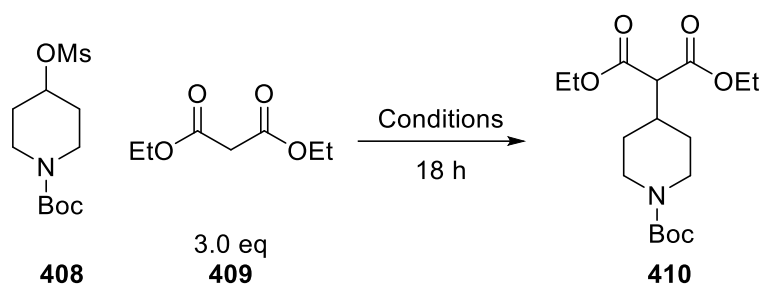
Scheme 4.29 – All compounds in this scheme are racemic.

Despite the low-yielding mesylation (which we planned to return to at a later stage), we proceeded to explore the required nucleophilic substitution on mesylated piperidine **408**. Drawing on Fraunhofer's work on malonate substitutions of substituted cyclohexane mesylates (see Scheme 4.23)³⁵⁶ and prior explorations within our group,³⁰⁶ we selected diethyl malonate **409**, anticipating that it would provide a good balance between the nucleophilicity of its anion and the ease of subsequent reduction to the diol.

The results on the diethyl malonate substitution reactions with unsubstituted piperidine mesylate **408** as a model system are shown in Table 4.4. Initial attempts to carry out the substitution using NaH in dioxane at 85 °C afforded substituted piperidine **410** in only 30% yield (Entry 1).^{369, 370} Switching to Fraunhofer's reported conditions, which utilised 3 eq of KO t -Bu in toluene at 85 °C, failed to produce any substituted piperidine **410** as the malonate and KO t -Bu mixture in toluene formed an intractable gel (Entry 2).³⁵⁶ Replacing KO t -Bu with NaO t -Bu was also unsuccessful, once again resulting in the formation of an intractable gel and yielding none of the desired piperidine **410** (Entry 3).

It has been reported that addition of 18-crown-6 can improve the solubility and nucleophilicity of some K⁺ and Na⁺ nucleophiles.³⁷¹ Therefore, we employed 3 eq of NaO t -Bu together with 0.25 eq of 18-crown-6 at 85 °C and this afforded piperidine **410** in 40% yield with no gel formation observed (Entry 4). Gratifyingly, increasing the equivalents of 18-crown-6 to 1.0 and 1.5 eq under the same conditions improved the yields, giving piperidine **410** in 63% and 71% yield respectively (Entries 5 and 6). Finally, increasing the temperature of the nucleophilic substitution step to 100 °C further increased the yield, giving piperidine **410** in 85% yield (Entry 7).

Table 4.4 – Model studies for malonate substitution



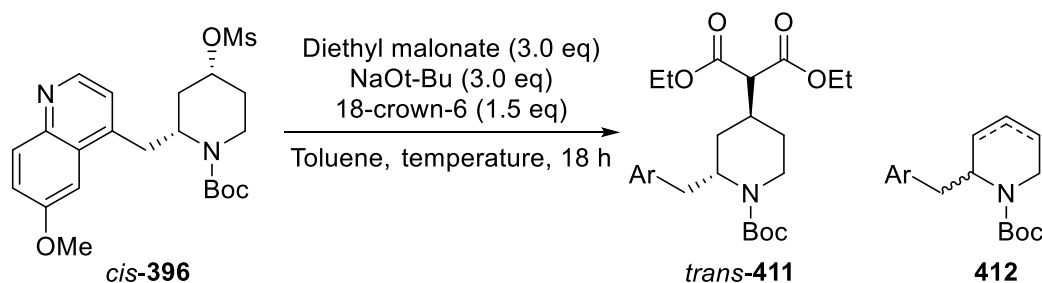
Entry	Conditions	Yield ^a 410 (%)
1	NaH (1.75 eq), dioxane, 85 °C	30%
2	KOt-Bu (3.0 eq), Toluene, 85 °C	0%
3	NaOt-Bu (3.0 eq), Toluene, 85 °C	0%
4	NaOt-Bu (3.0 eq), 18-crown-6 (0.25 eq), Toluene, 85 °C	40%
5	NaOt-Bu (3.0 eq), 18-crown-6 (1.0 eq), Toluene, 85 °C	63%
6	NaOt-Bu (3.0 eq), 18-crown-6 (1.5 eq), Toluene, 85 °C	71%
7	NaOt-Bu (3.0 eq), 18-crown-6 (1.5 eq), Toluene, 100 °C	85%

^a) Isolated yield after chromatography; All compounds in this table are racemic.

Thus, we initially settled on using 3 equivalents of NaOt-Bu and 1.5 equivalents of 18-crown-6 in toluene at 100 °C for substituting aryl piperidine mesylate *cis*-**396** by the diethyl malonate (Table 4.5). Under these conditions, reacting aryl piperidine mesylate *cis*-**396** gave piperidine diester *trans*-**411** in 59% yield as a single diastereomer. The stereochemical outcome of this S_N2 reaction was proven, as described later, by X-ray crystallography of diol *trans*-**413** (see Scheme 4.31). However, alkenes **412**, presumably formed by E2 type elimination of a proton on the β carbon and either the OMs group or the malonate, were also isolated with an overall yield of 25% (Entry 1). We hypothesized that adjusting the temperature could help strike a balance between the rates of substitution and elimination. Therefore, the reaction was attempted at 90 °C, 80 °C, and 70 °C. At 90 °C, piperidine diester *trans*-**411** was obtained in 71% yield, while alkenes **412** were isolated in 15% yield (Entry 2). At 80 °C, piperidine diester *trans*-**411** was produced in a reduced yield of 61%, with alkenes **412** isolated in 17% yield (Entry 3). Finally, at 70 °C, the yield of piperidine diester

trans-**411** was only 37%, with alkenes **412** in 12% yield (Entry 4). Thus, 90 °C was selected as the ideal temperature to perform the substitution.

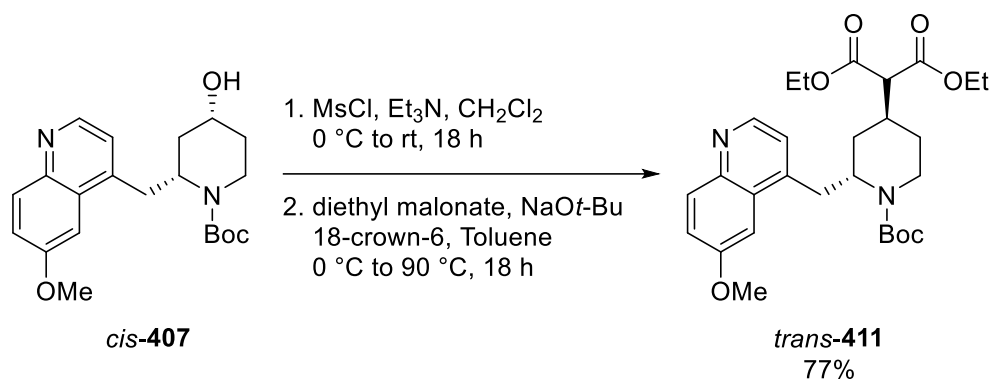
Table 4.5 – Optimisation of malonate substitution for mesylate *cis*-**396**



Entry	Temperature (°C)	Yield ^a <i>trans</i> - 411 (%)	Yield ^a 412 (%)
1	100	59%	25%
2	90	71%	15%
3	80	61%	17%
4	70	37%	12%

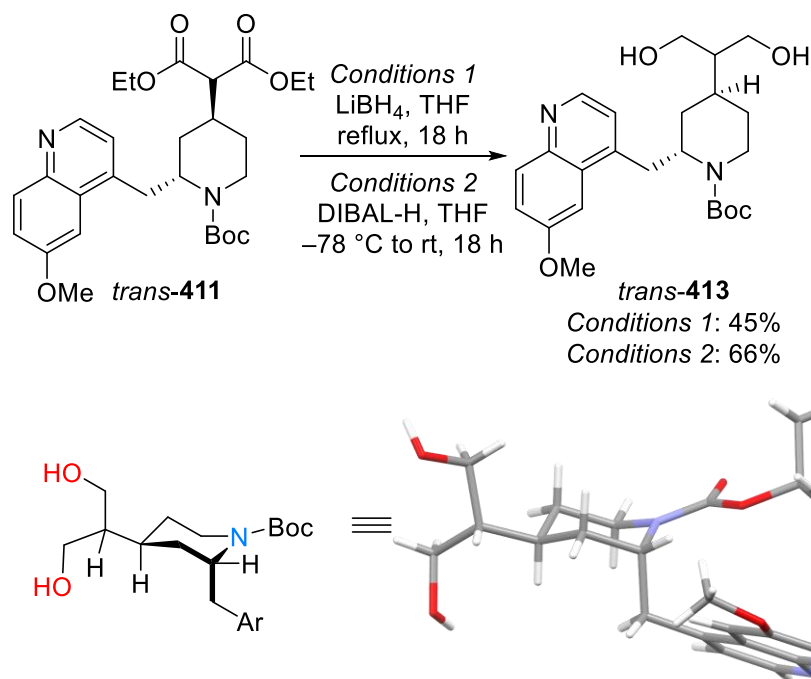
^a) Isolated yield after chromatography; All compounds in this table are racemic.

With a satisfactory set of conditions for the malonate substitution, we returned to the low yielding mesylation step (see Scheme 4.29). In particular, we sought to improve the overall mesylation and substitution sequence. As mentioned earlier, ¹H NMR spectroscopic analysis of the crude mesylation product indicated that the mesylation proceeded with complete conversion, and there were very few impurities present in the crude product. Therefore, we decided to attempt the mesylation/substitution sequence without purification of the intermediate mesylate. In this approach, hydroxy piperidine *cis*-**407** was reacted with MsCl and Et₃N to give crude piperidine mesylate *cis*-**396** after work-up, which was immediately reacted with diethyl malonate, NaOt-Bu, and 18-crown-6 at 90 °C. Pleasingly, this afforded piperidine diester *trans*-**411** in 77% yield over the two steps (Scheme 4.30). This methodology was able to be scaled up to 5.18 mmol of hydroxypiperidine *cis*-**407** to give ~2.0 g of diester *trans*-**411**.



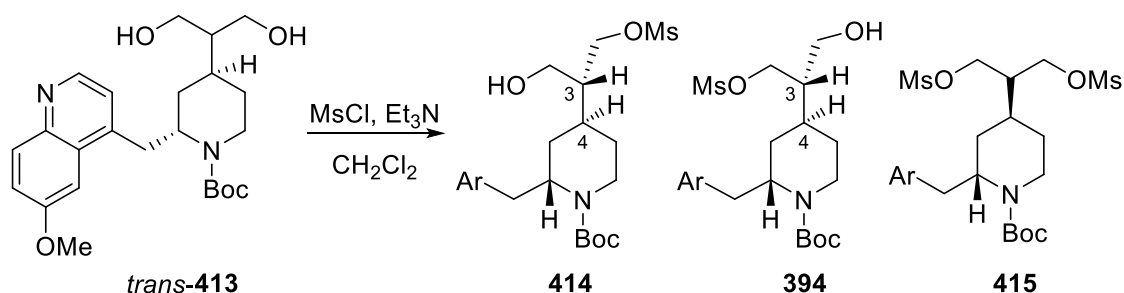
Scheme 4.30 – All compounds in this scheme are racemic.

Next, we aimed to perform the complete reduction of the diester in *trans*-**411** to the corresponding diol. Using conditions previously identified by previous members of the group on a piperidine malonate model system,³⁰⁶ reaction of piperidine diester *trans*-**411** with LiBH₄ in refluxing THF afforded diol *trans*-**413** in 45% yield (Scheme 4.31). However, reproducibility issues were encountered with these conditions where the yields and purity of the isolated products were highly variable. Alternatively, reacting diester *trans*-**411** with DIBAL-H at –78 °C to room temperature produced diol *trans*-**413** in a more reproducible 66% yield even up 3.56 mmol of diester *trans*-**411** to give ~1.0 g of diol *trans*-**413** (Scheme 4.31). Additionally, at this stage, the structure of the product was able to be confirmed as *trans*-**413** by single crystal X-ray crystallography (Scheme 4.31). This confirmed our previous assumptions of the stereochemical outcome of the lithiation-trapping and nucleophilic substitution steps. Additionally, the observed axial CH₂Ar and equatorial diol are consistent with prior observations from previous members of the group in various disubstituted piperidines.³⁷²



Scheme 4.31– All compounds in this scheme are racemic.

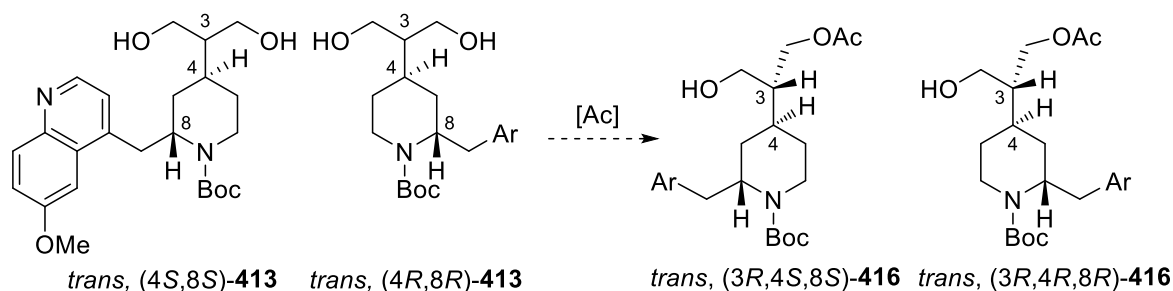
The next step involved the proposed monomesylation of diol *trans*-**413** to form mesylate *trans*-**394** (see Scheme 4.22), marking a critical divergence point in our synthesis. Employing non-selective conditions resulted in a statistical mixture of racemic diastereomeric mesylates **414**, **394**, and the dimesylate *trans*-**415** in poor yields (Scheme 4.32). To synthesize quinine, we needed to obtain a monomesylate with configurations (3*S*, 4*S*). However, there is limited precedent for the enantioselective mesylation of diols via desymmetrisation.



Scheme 4.32– All compounds in this scheme are racemic.

In contrast, the asymmetric monoacetylation of similar systems is well-documented.³⁷³⁻³⁷⁶ Therefore, we hypothesized that the use of a chiral reagent to obtain a selective monoacetylation on racemic diol *trans*-**413** would yield enantioenriched diastereomeric monoacetates *trans*,(3*R*,4*S*,8*S*)-**416** and *trans*,(3*R*,4*R*,8*R*)-**416**, which we hoped could be

separated by chromatography. Once separated, we could further convert monoacetate *trans*,(3*R*,4*S*,8*S*)-**416** into the desired monomesylate *trans*,(3*S*,4*S*,8*S*)-**394** (Scheme 4.33).



Scheme 4.33

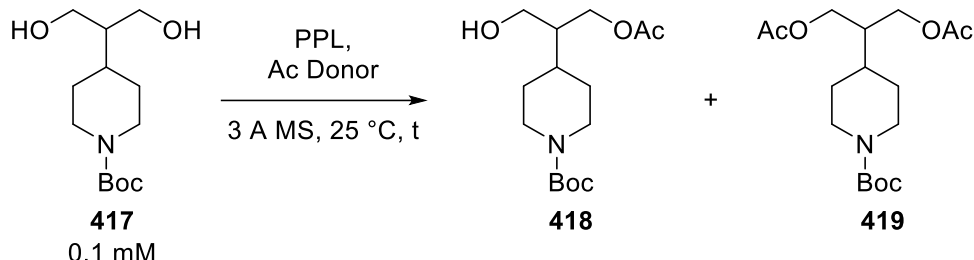
Ideally, at this stage we would start with an enantioenriched diol that would allow higher than 50% conversions to the desired monoacetate *trans*,(3*R*,4*S*,8*S*)-**413**. However, providing that the diastereomers could be separated, this approach would still yield an enantioenriched acetate that we could further advance into (–)-quinine.

Fortunately, an enzymatic method for asymmetric monoacetylation of 1,3-diols had been previously explored by Narisano and co-workers on an related piperidine diol to give the (*R*) selectivity we desired (see Section 4.3, Scheme 4.23).³⁵⁷ Starting from racemic diol *trans*-**413**, this would effectively constitute a parallel kinetic resolution³⁷⁷ that would allow us to advance the synthesis to (–)-quinine and, if desired, to another diastereomer of quinine. Thus, we adopted Narisano's reported conditions, using porcine pancreatic lipase (PPL), an acyl donor as a solvent, and molecular sieves with the diol at 0.1 mM concentration. We applied these conditions to piperidine diol **417**, which was produced by the reduction of piperidine diester **410** (see Table 4.4), to establish an initial set of reaction conditions (Table 4.6).

Our initial attempts, using 20,000 U/mmol of PPL and vinyl acetate for 24 hours, produced monoacetate **418** in 38% yield and diacetate **419** in 10% yield (Entry 1). As we were only interested in conversion to the monoacetate **418** from this reaction, no attempt to determine the *er* of monoacetate **418** was made in this or any subsequent reactions. Extending the reaction time to 48 hours under the same conditions gave monoacetate **418** in 40% yield, with diacetate **419** obtained in 8% yield (Entry 2). Further extending the time to 72 hours gave a similar result, with monoacetate **418** in 44% yield and diacetate **419** in 8% yield (Entry 3). Increasing the enzyme amount to 60,000 U/mmol had a negative effect, with the reaction stalling after 4 hours, yielding monoacetate **418** in 22% and diacetate **419** in 5% (Entry 4). Switching the acyl donor to EtOAc at both 20,000 and 60,000 U/mmol of PPL

was also ineffective, yielding monoacetate **418** in 33% and 31%, respectively, with diacetate **419** only being observed in trace amounts (Entries 5 and 6).

Table 4.6 – Model studies for enzymatic acetylation



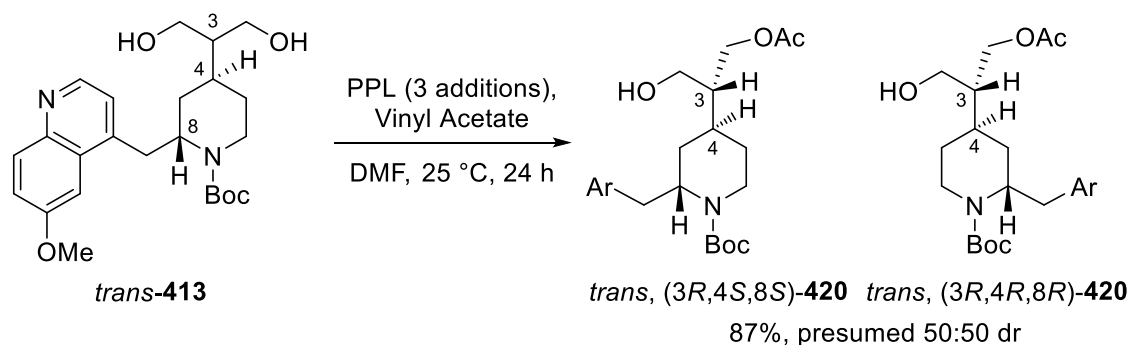
Entry	PPL Eq (U/mmol)	Ac Donor	Time (h)	Yield ^a 418 (%)	Yield ^a 419 (%)
1	20000	Vinyl Acetate	24	38	10
2	20000	Vinyl Acetate	48	40	8
3	20000	Vinyl Acetate	72	44	8
4	60000	Vinyl Acetate	4	22	5
5	20000	EtOAc	92	33	Trace
6	60000	EtOAc	24	31	Trace
7	20000 × 3 additions	Vinyl Acetate	24	64	12

^a) Isolated yield after chromatography; Reactions were run using Ac donor as solvent All compounds in this table are racemic.

The data suggested that the acetylation was stalling between the 4-hour and 24-hour marks. Therefore, we attempted three equally spaced additions of 20,000 U/mmol of PPL using vinyl acetate as the acyl donor with a 24 h reaction time. Gratifyingly, this approach afforded monoacetate **418** in 64% yield, with diacetate **419** obtained in 12% yield (Entry 7). This identified the optimal conditions to be used for diol *trans*-**413**.

These optimal conditions were successfully applied to racemic diol *trans*-**413**, with the addition of a small amount of DMF to facilitate the solubilization of diol *trans*-**413**. This resulted in the formation of diastereomeric monoacetates **420** in 87% yield, with a presumed

50:50 dr and only trace amounts of diacetylation observed. Separation of the diastereomers, however, was not possible at this stage (Scheme 4.34).

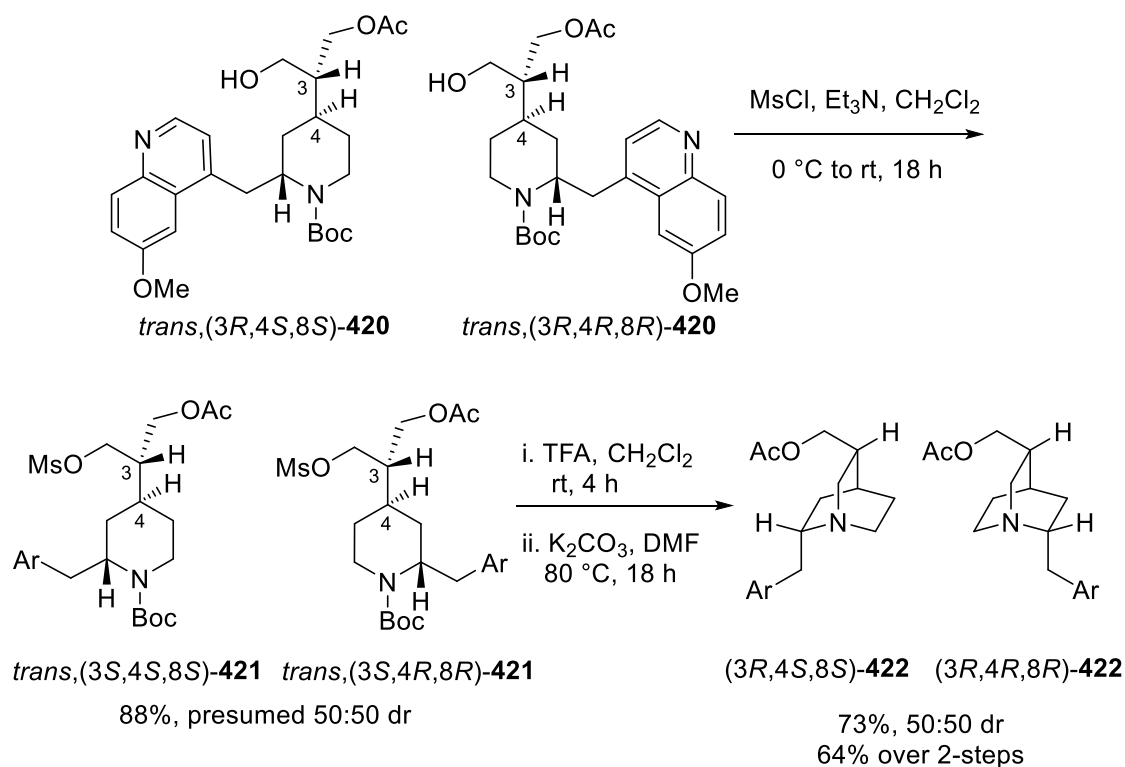


Scheme 4.34

Based on a conversion of over 50%, we concluded that both diastereomers had been formed, with our stereochemical assignment relying on the expected outcome of the enzymatic reaction, although er determination was not attempted for any of the diastereomers in this mixture nor any subsequent compounds. Due to the presence of diastereomers and complications arising from Boc group-induced rotamers, we were unable to conclusively determine the diastereomeric ratio at this stage. However, upon conversion of the monoacetates into quinuclidines (see Scheme 4.35), ¹H NMR spectroscopic analysis confirmed a 50:50 mixture of diastereomers.

Despite being unable to separate the diastereomers at this stage, we set out to explore the remaining route as we anticipated that it would still be used in the proposed asymmetric strategy since we would be able to avoid the formation of these diastereomers (see Section 4.5. Mesylation of monoacetates **420** with MsCl and Et₃N gave mesylates **421** as an inseparable mixture in 88% yield and presumed 50:50 dr. Then, using conditions similar to those reported by Jacobsen and co-workers in their synthesis of quinine,³³⁷ mesylates **412** were treated with TFA at room temperature. After solvent evaporation, the resulting TFA salt was treated with excess K₂CO₃ in DMF at 80 °C. This yielded an inseparable mixture of quinuclidine acetates **422** in 73% yield and 50:50 dr. At this point it was possible to confirm both the presence and the ratio of diastereomers from the ¹H and ¹³C NMR spectra. Namely, in the ¹H NMR spectrum, two 3H Me signals (1.97 and 1.94 ppm) corresponding to the acetate Me group were observed in a 50:50 ratio. Additionally, consistent doubling of signals

(in a ~50:50 ratio) was observed in the ^{13}C NMR spectrum for the OCH_2 , OMe , NCH_2 and CH_2Ar signals (Figure 4.2).



Scheme 4.35

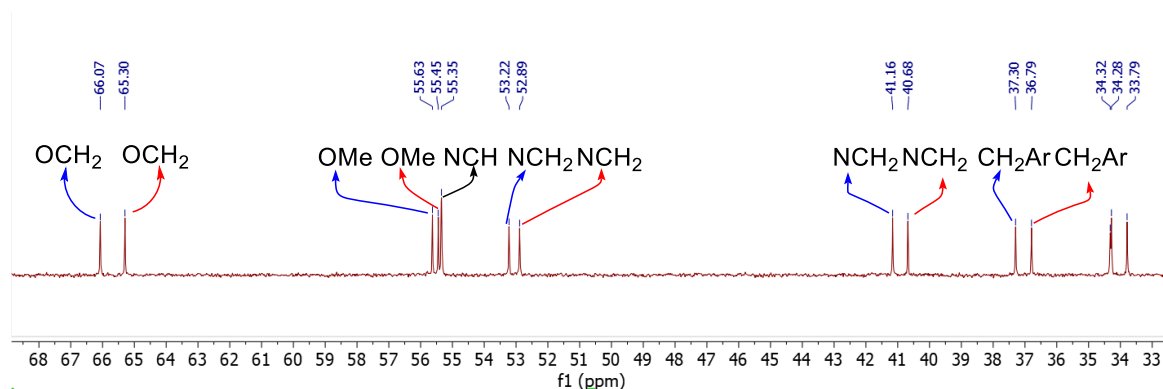
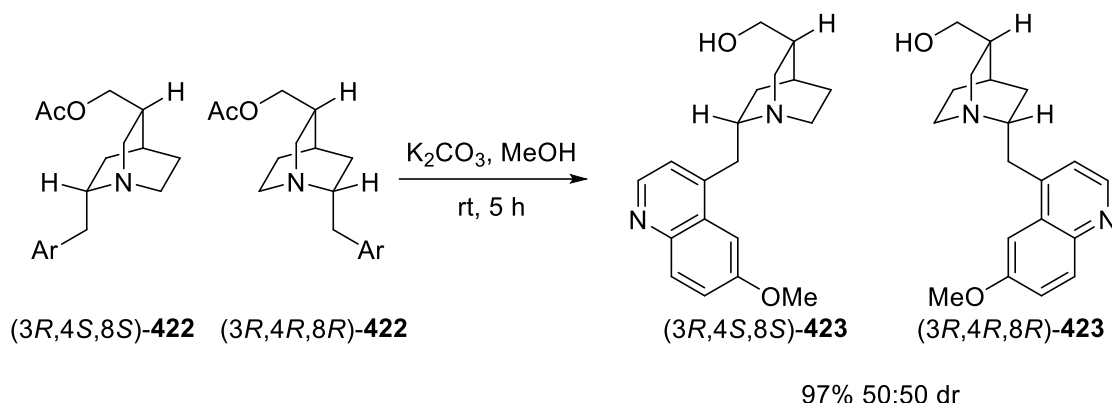


Figure 4.2 – ^{13}C NMR spectrum of quinuclidines **422**

Subsequent saponification of the acetates proceeded smoothly using K_2CO_3 in MeOH and H_2O to give an inseparable mixture of quinuclidine alcohols **423** in 97% yield and presumed 50:50 dr. (Scheme 4.36). Although direct determination of the dr from the ^1H NMR spectra

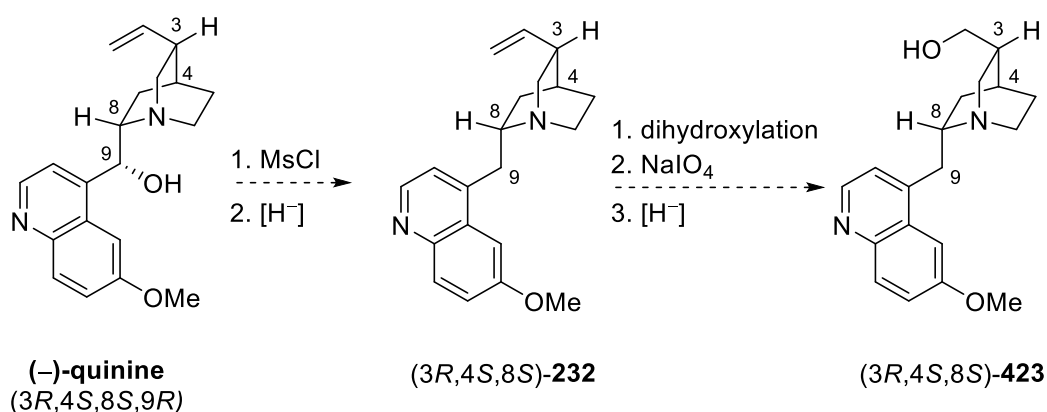
was not possible, the 70-30 ppm region in the ^{13}C NMR spectrum appeared similar to that shown in Figure 4.2 and this led us to conclude that the 50:50 dr was still present.



Scheme 4.36

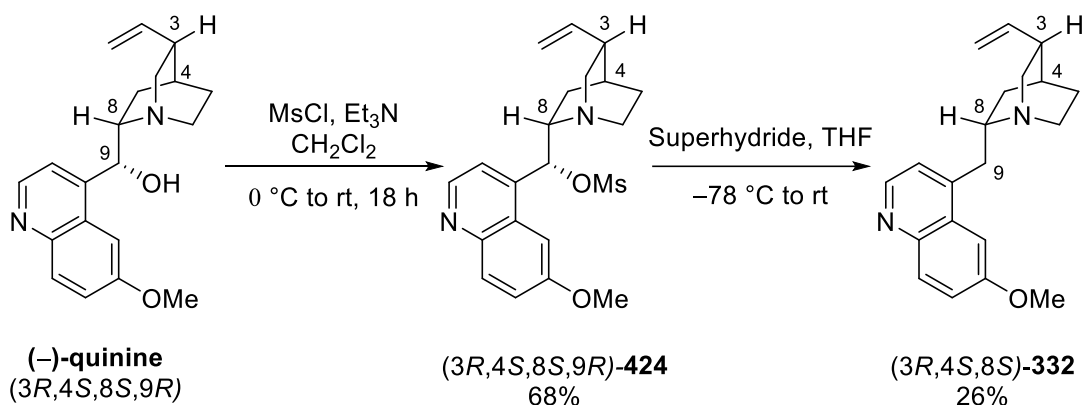
Despite attempts to separate the diastereomers at the monoacetate **420**, monomesylate **421**, quinuclidine **422** and alcohol **423** stages using selective crystallization, column chromatography, and preparative HPLC, we were unsuccessful in carrying out a separation. Therefore, at this point, we aimed to validate our end-game strategy with the mixture of alcohols (3*R*,4*S*,8*S*)- and (3*R*,4*R*,8*R*)-**423** (72 mg) that we had currently available before committing additional resources to exploring the asymmetric methodology, in particular, the proposed chiral base methodology. Furthermore, we were also keen to provide additional proof of the structure of alcohols (3*R*,4*S*,8*S*)- and (3*R*,4*R*,8*R*)-**423**. To address both of these issues, we decided to gain more structural information on our compounds and the final steps of the synthesis by intercepting our forward synthesis with an intermediate obtained starting from deconstruction of commercial (–)-quinine using reactions that have been reported previously.

It was envisaged that following methodology from Bull,³⁷⁸ starting from (–)-quinine, mesylation followed by reduction would yield deoxyquinine (3*R*,4*S*,8*S*)-**232**. Building on methodology previously explored by Hoffman³⁷⁹ and Dive,³⁸⁰ dihydroxylation followed by oxidative cleavage and reduction would yield quinuclidine (3*R*,4*S*,8*S*)-**423** (Scheme 4.37). This would allow us to compare the spectroscopic data with quinuclidine alcohols (3*R*,4*S*,8*S*)- and (3*R*,4*R*,8*R*)-**423** obtained *via* our total synthesis approach (see Scheme 4.36).



Scheme 4.37

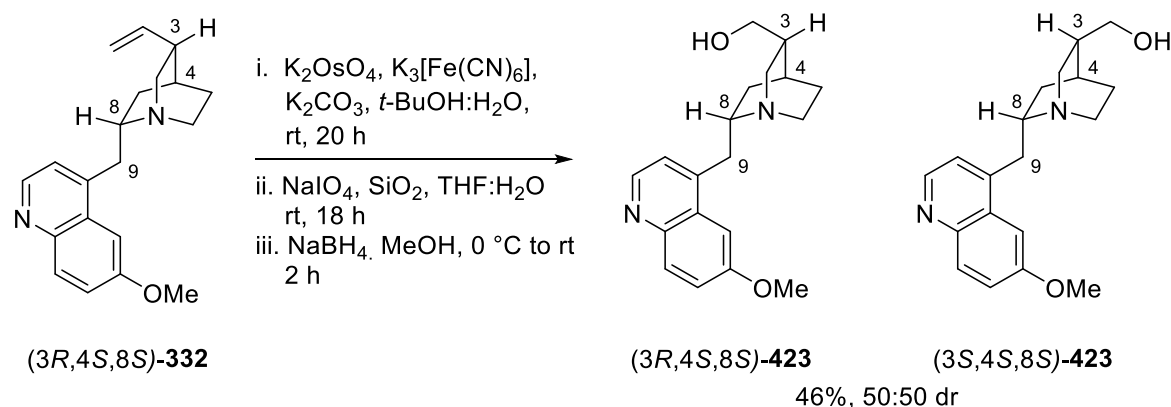
Using standard mesylation conditions,³⁷⁸ (-)-quinine was treated with MsCl and Et₃N to give quinine mesylate (3R,4S,8S,9R)-424 in 68% yield. Following this, quinine mesylate (3R,4S,8S,9R)-424 was reacted with Superhydride in THF at -78 °C, which resulted in the formation of deoxyquinine (3R,4S,8S)-232 in 26% yield (Scheme 4.38). Despite the low yield from the reduction, we were able to scale up the reaction sufficiently to produce enough material for our needs.



Scheme 4.38

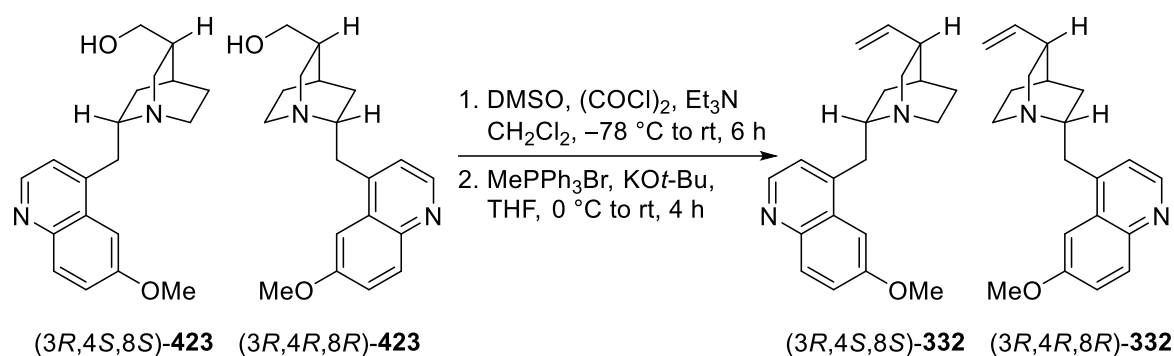
From here, following methodology reported by Hoffman³⁷⁹ and Dive,³⁸⁰ deoxyquinine (3R,4S,8S)-332 was dihydroxylated using K₂OsO₄, K₃[Fe(CN)₆], and K₂CO₃ to yield an intermediate diol, which was immediately subjected to oxidative cleavage with NaIO₄ and SiO₂, to form the corresponding aldehyde. Analysis of the crude aldehyde at this point by ¹H NMR spectroscopy indicated that epimerisation had occurred, presumably at the C-3 position. There were two signals due to the aldehyde proton at 9.72 and 9.68 ppm. This was frustrating as there are reports that the use of SiO₂ during the oxidative cleavage step should have prevented epimerisation of the intermediate aldehyde.³⁷⁹ This aldehyde mixture was

then reduced using NaBH₄ to give a presumed 50:50 mixture of epimeric hydroxy quinuclidines (3*R*,4*S*,8*S*)- and (3*S*,4*S*,8*S*)-**423** in 46% yield (Scheme 4.39). Nonetheless, we were able to confirm that the ¹H and ¹³C NMR spectra of this mixture matched those obtained from the saponification of (3*R*,4*S*,8*S*)- and (3*R*,4*R*,8*R*)-**422** (see Scheme 4.36).



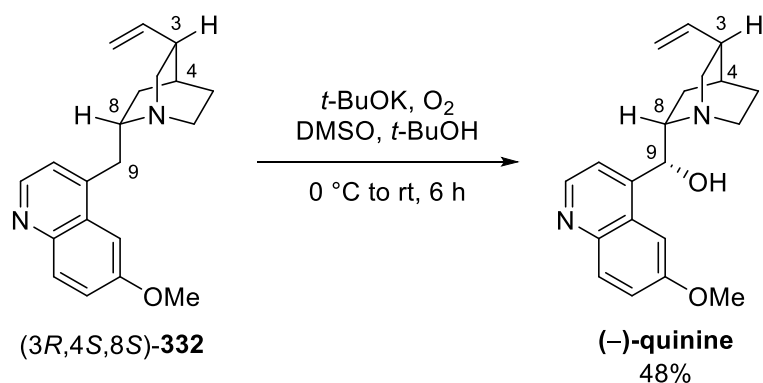
Scheme 4.39

With this information, we wished to explore the last few steps of the synthesis using the 50:50 mixture of quinuclidine alcohols (3*R*,4*S*,8*S*)- and (3*R*,4*R*,8*R*)-**423** that we had prepared *via* our total synthesis route, namely the conversion of alcohols (3*R*,4*S*,8*S*)- and (3*R*,4*R*,8*R*)-**423** into olefins (3*R*,4*S*,8*S*)- and (3*R*,4*R*,8*R*)-**332**. Building on methodology developed by Hatakeyama and co-workers during their synthesis of quinine,³⁴⁰ the mixture of alcohols (3*R*,4*S*,8*S*)- and (3*R*,4*R*,8*R*)-**423** underwent Swern oxidation to yield the corresponding aldehydes, which matched the characterisation of those previously overserved by dihydroxylation and oxidative cleavage (see Scheme 4.39). which were then subjected to Wittig olefination. This produced an impure mixture of alkenes **332** in the crude product (Scheme 4.40). Unfortunately, initial purification attempts were unsuccessful and due to time constraints, this was the only attempt at this transformation. Pleasingly, ¹H NMR spectroscopic and MS analysis of the isolated product indicated the presence of the desired olefin (3*R*,4*S*,8*S*)-**332** which was evident by comparison with the results obtained by Yang (see Section 4.1, Scheme 4.10).³³⁶



Scheme 4.40

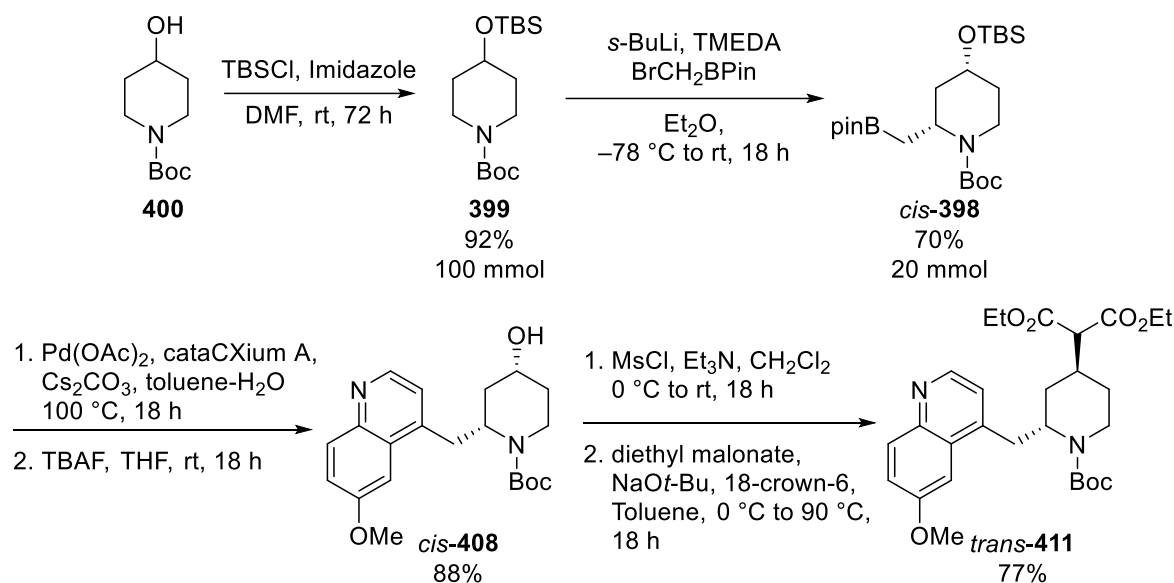
Finally, to conclude the synthesis it was necessary to perform the C9 oxidation reported by Uskokovic³²⁶ and by Stork.³³² However, we had reached the end of the line, and the crude product obtained from the oxidation/Wittig sequence could not be advanced any further. Nonetheless, we wished to demonstrate that we could reproduce the oxidation of deoxyquinine **332** to (–)-quinine demonstrated by Stork and co-workers.³³² Thus, using deoxyquinine **332** obtained from (–)-quinine, olefin **332** was treated with *t*-BuOK and O₂ to give (–)-quinine in 48% yield and complete C9 diastereoselectivity (Scheme 4.41).



Scheme 4.41

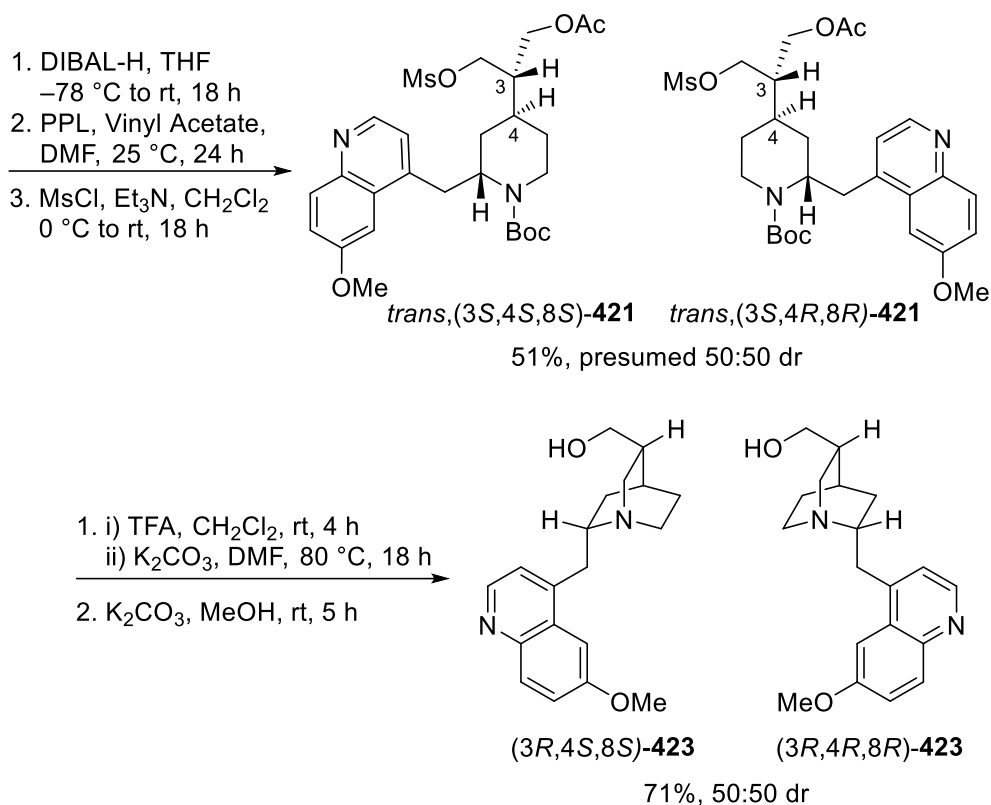
4.5 Conclusions and Future Work

In this way, we have established an initial route to quinuclidine alcohols (3*R*,4*S*,8*S*)- and (3*R*,4*R*,8*R*)-**423**, one of which is a direct precursor to quinine. This was accomplished through an 11-step sequence with an overall yield of 20%. The sequence began with TBS protection of *N*-Boc-4-hydroxypiperidine **400**, followed by α -lithiation and trapping with a CH_2Bpin electrophile to afford pinacol boronate *cis*-**398** in 64% yield over two steps. Next, Suzuki-Miyaura cross-coupling and TBS removal produced alcohol *cis*-**408** in 88% yield. Mesylation and substitution yielded diester *trans*-**411** in 77% yield (Scheme 4.42).



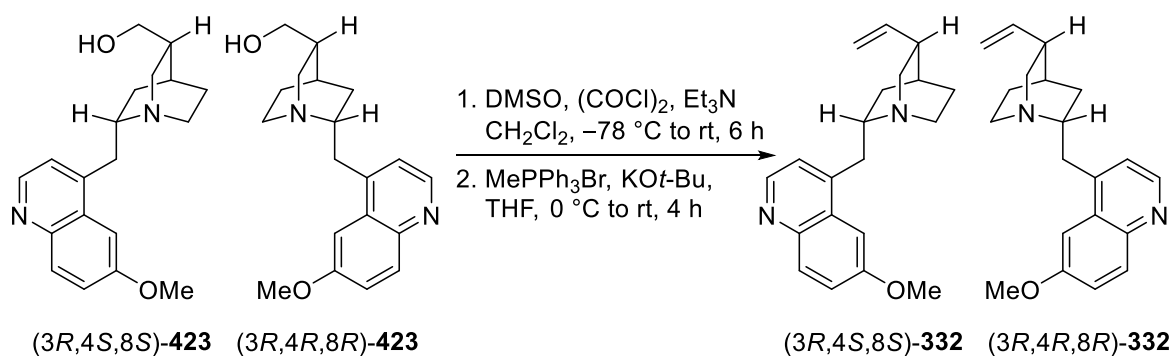
Scheme 4.42 – All compounds in this scheme are racemic.

Reduction with DIBAL-H, enzymatic parallel kinetic resolution, and mesylation afforded diastereomeric mesylates **421** in 51% yield and a 50:50 diastereomeric ratio. Finally, Boc group removal and base-promoted cyclization, followed by saponification of the esters, provided quinuclidine alcohols (3*R*,4*S*,8*S*)- and (3*R*,4*R*,8*R*)-**423** in 71% yield (Scheme 4.43).



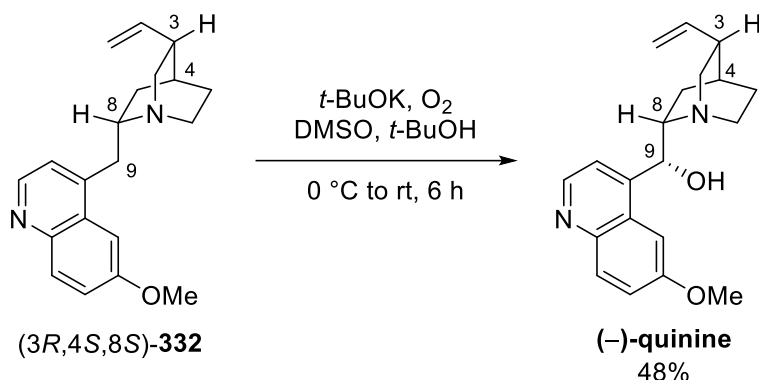
Scheme 4.43

Additionally, we have established that methodology previously developed for the oxygenated analogues of quinuclidine alcohols **423**³⁴⁰ can, in principle, be applied in the end-game of our synthesis. Quinuclidine alcohols **423** underwent Swern oxidation, followed by Wittig olefination, to yield alkenes **332** (Scheme 4.44). However, due to time constraints, it was not possible to determine the yield or confirm whether epimerization at C3 could be an issue during this sequence.

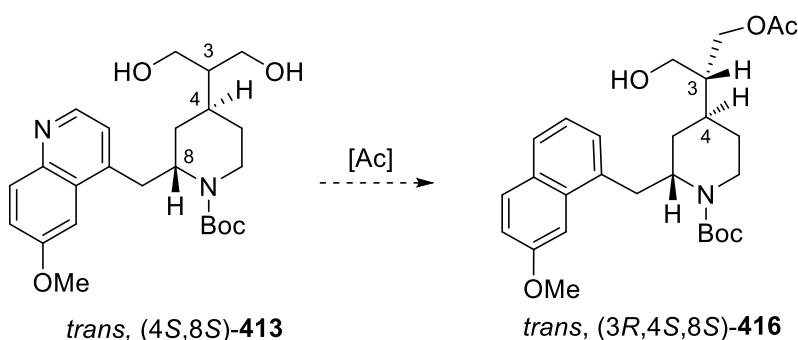


Scheme 4.44

Finally, we also demonstrated that the well preceded oxidation of C9 is effective in our hands. Here, deoxyquinine **332** was reacted with *t*-BuOK and O₂ to give (–)-quinine in 48% yield and complete diastereoselectivity (Scheme 4.45).

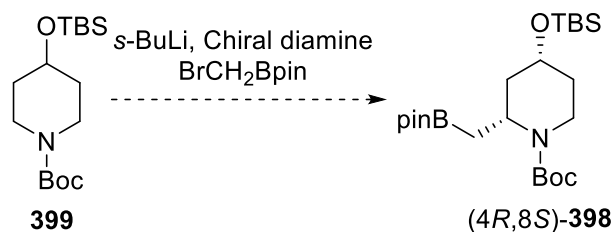


At this point, the next steps required for a successful completion of the synthesis of quinine are clear. The first step consists of establishing methodology that allows for the synthesis of acetate *trans*,(3*R*,4*S*,8*S*)-**416** diastereoselectively. Initially, we propose that coming into the asymmetric monoacetylation with an enantioenriched diol *trans*-**413** would allow for the formation of a single diastereomer at this stage (Scheme 4.45).



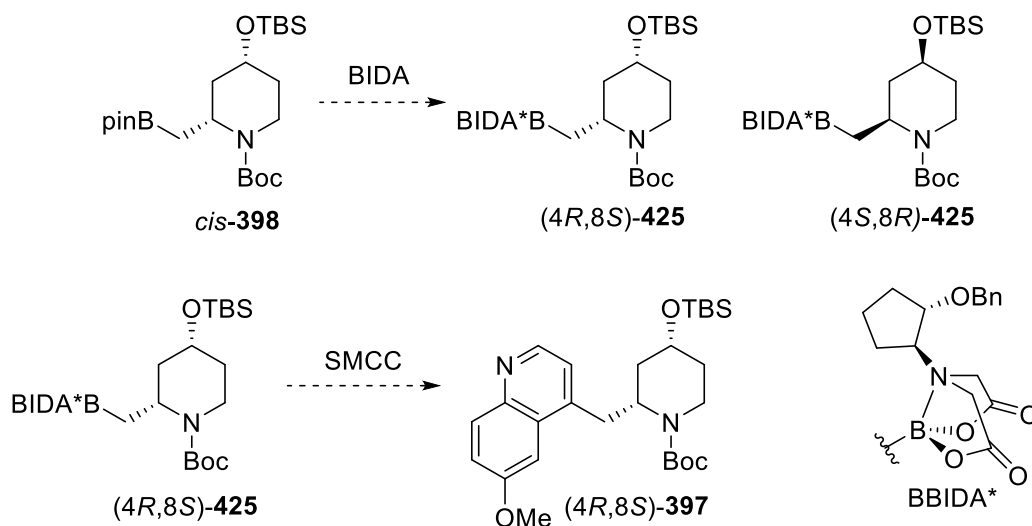
Scheme 4.45

We envisage two alternatives to achieve this. The first would consist in using asymmetric lithiation-trapping methodology using chiral diamines^{144, 305, 381, 382} to obtain an enantioenriched pinacol boronate (4*R*,8*S*)-**398** (Scheme 4.46). We hypothesize that this pinacol boronate could also be recrystallised to enantiopurity, facilitating the synthesis of a diastereopure acetate *trans*,(3*R*,4*S*,8*S*)-**416**.



Scheme 4.46

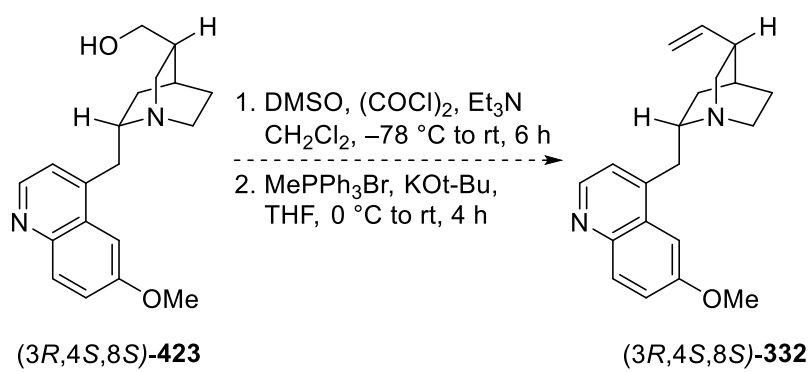
Alternatively, use of Burke's chiral MIDA boronate derivative, BIDA²⁹⁶ on a racemic sample of boronates *cis*-398 could provide access to diastereomeric BIDA boronates *cis*-425, which could be separated by chromatography. At this stage, the diastereopure BIDA boronate (4R,8S)-425 could undergo Suzuki-Miyaura cross-coupling, resulting in the formation of enantiopure arylated piperidine (4R,8S)-397 (Scheme 4.47).



Scheme 4.47

At this point, it would be necessary to assess the stereoselectivity of the lipase catalysed monoacetylation of diol (4R,8S)-413. However, since the monoacetates 420 and mesylates 421 proved to be solids, provided that a good selectivity for the *trans*,(3R,4S,8S)-420 monoacetate was observed, the product could be recrystallised to enantiopurity.

Finally, it would be necessary to re-evaluate the Swern oxidation and Wittig olefination sequence from alcohol (3R,4S,8S)-423 to olefin (3R,4S,8S)-332 to determine whether the product can be purified and if any epimerization occurs at the C3 aldehyde (Scheme 4.48). Fortunately, if this sequence proves inadequate, there are alternative methods for both oxidation and olefination of epimerization-prone aldehydes, such as the Stahl oxidation³⁸³ and Tebbe olefination³⁴⁵.



Scheme 4.48

Chapter 5 Experimental

5.1 General Information

All non-aqueous reactions were carried out under oxygen free Ar or N₂ using flame-dried glassware unless otherwise stated. Dry solvents (THF, CH₂Cl₂, DMF, toluene, Et₂O, hexane, MeCN and MeOH) were obtained and used without further purification from PureSolv 300-3-MD dry solvent dispenser unless otherwise stated. EtOAc, pyridine, DIPEA and Et₃N were freshly distilled over CaH₂. DMA and trifluoro toluene were ran through a neutral alumina column (0.25 g of alumina / mL of solvent) and stored over 3 Å MS. All other anhydrous solvents were purchased and used without further purification. Alkylolithiums were titrated against *N*-benzylbenzamide before use. *i*-PrO-Bpin was used without further purification. Brine refers to saturated aqueous sodium chloride solution and water is deionised water. Flash column chromatography was carried out according to standard techniques using silica gel (60 Å, 220-440 mesh particle size 40–63 µm) purchased from Sigma-Aldrich or Fluka silica gel, 35–70 µm, 60 Å and the solvent system as stated. Thin layer chromatography was carried out using Merck TLC Silica gel 60G F254 aluminium backed plates (100390 Supelco). Spots were visualised by UV and appropriate stains (CAM, KMnO₄, Ninhydrin, Vanillin). Melting points were carried out on a Gallenkamp melting point apparatus. Proton (400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 or a JEOL ECS400 instrument using an internal deuterium lock. Chemical shifts (δ) are recorded in parts per million (ppm) and referenced to the residual solvent peak of the stated solvent, with tetramethylsilane defined as 0 ppm. NMR spectra were analysed, assigned, and reported using recommended methods and DEPT as well as 2-D NMR techniques such as HH-COSY, HMQC, HMBC and NOESY where required. Coupling constants (*J*) are quoted in Hertz. For samples recorded in CDCl₃, chemical shifts are quoted in parts per million relative to CHCl₃ (δ_H 7.26 ppm) and CDCl₃ (δ_C 77.16 ppm, central line of triplet). For samples recorded in CD₃OD, chemical shifts are quoted in parts per million relative to CD₃OD (δ_H 3.31 ppm, central line of quintet) and CD₃OD (δ_C 49.0 ppm, central line of septet). For samples recorded in DMSO-*d*₆, chemical shifts are quoted in parts per million relative to *d*₆-DMSO (δ_H 2.50 ppm, central line of quintet) and DMSO-*d*₆ (δ_C 39.5 ppm, central line of septet). For samples recorded in acetone-*d*₆, chemical shifts are quoted in parts per million relative to *d*₆-acetone (δ_H 2.05 ppm, central line of quintet) and *d*₆-acetone (δ_C 29.8 ppm, central line of septet). Infrared spectra were recorded on a PerkinElmer UATR 2 FT-IR spectrometer.

Electrospray and atmospheric pressure chemical ionisation techniques (ESI and APCI) have been applied and mass spectra were recorded at room temperature on a Bruker Daltronics microOTOF spectrometer.

Note: Solvent systems for flash column chromatography using acetone and CHCl_3 can be explosive in the presence of trace NaOH.

5.2 General Procedures

General Procedure A: Suzuki-Miyaura cross-coupling of cyclopropyl MIDA boronates using 5 mol% Pd

A solution of Pd(OAc)₂ (8 mg, 0.04 mmol, 0.15 eq) and PCy₃ (21 mg, 0.08 mmol, 0.30 eq), Cs₂CO₃ (489 mg, 1.5 mmol, 6.0 eq) and the aryl bromide (0.35 mmol, 1.4 eq) was added to MIDA boronate (0.25 mmol, 1.0 eq) in toluene (5.0 mL) at rt in a sealed tube under Ar. H₂O (0.5 mL) was added and the suspension was degassed by sparging with Ar for 20 min. The resulting mixture was stirred and heated at 100 °C for 18 h under Ar. The mixture was then allowed to cool to rt and EtOAc (15 mL) and water (15 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (30 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product.

General Procedure B: Suzuki-Miyaura cross-coupling of cyclopropyl MIDA boronates using 15 mol% Pd

A solution of Pd(OAc)₂ (3 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7 mg, 0.02 mmol, 0.10 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq) and the aryl bromide (0.35 mmol, 1.4 eq) was added to MIDA boronate (0.25 mmol, 1.0 eq) in toluene (5.0 mL) at rt in a sealed tube under Ar. H₂O (0.5 mL) was added and the suspension was degassed by sparging with Ar for 20 min. The resulting mixture was stirred and heated at 100 °C for 18 h under Ar. The mixture was then allowed to cool to rt and EtOAc (15 mL) and water (15 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (30 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product.

General Procedure C: Suzuki-Miyaura Cross-Coupling of Cyclopropyl MIDA Boronate 1f via *ex situ* hydrolysis

1 M NaOH_(aq) (1 mL) was added to a solution of cyclopropyl MIDA boronate (0.25 mmol, 1.0 eq) in THF (1 mL) at rt and the resulting mixture was stirred at rt for 30 min. Saturated NH₄Cl_(aq) (1 mL) and MTBE (5 mL) were added and the two layers were separated. The aqueous layer was extracted with MTBE (3 × 5 mL). The combined organic layers were

washed with brine (10 mL), dried (MgSO_4) and evaporated under reduced pressure to a volume of ~5 mL. Toluene (10 mL) was added and the solvent was evaporated under reduced pressure to a volume of ~2 mL. The resulting solution was transferred to a sealed tube. Then, Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq) and the aryl bromide (0.35 mmol, 1.4 eq) were added and the sealed tube was evacuated and backfilled with Ar three times. A solution of $\text{Pd}(\text{OAc})_2$ (2.81 mg, 0.01 mmol, 0.05 eq) and PCy_3 (7.01 mg, 0.02 mmol, 0.10 eq) in toluene (2.8 mL) was added. Then, H_2O (0.5 mL), degassed by sparging with Ar for 30 min, was added and the resulting mixture was stirred and heated at 100 °C for 18 h under Ar. The mixture was then allowed to cool to rt and EtOAc (15 mL) and water (15 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (30 mL), dried (MgSO_4) and evaporated under reduced pressure to give the crude product.

General procedure D: Ni-catalysed photoredox cross-coupling of alkyltrifluoroborate salts

4,4'-Di-*tert*-butyl-2,2'-bipyridine (4 mg, 0.013 mmol, 5.0 mol%), $\text{NiCl}_2 \cdot \text{dme}$ (3 mg, 0.013 mmol, 5.0 mol%) and anhydrous THF (0.5 mL) were added to a 7 mL screw cap vial fitted with a PTFE septum and equipped with a magnetic stirrer bar. The vial was capped and the resulting suspension was heated with a heat gun until the nickel salt was fully solubilised to give a pale green solution of $\text{NiCl}_2(\text{dtbbpy})$. The solvent was evaporated under reduced pressure. Then, alkyltrifluoroborate salt (0.25 mmol, 1.0 eq), aryl bromide (0.38 mmol, 1.5 eq), $[\text{Ir}(\text{dFCF}_3\text{ppy})_2(\text{dtbpy})]\text{PF}_6$ (7 mg, 0.0063 mmol, 2.5 mol%), Cs_2CO_3 (123 mg, 0.38 mmol, 1.5 eq) and anhydrous 1,4-dioxane (5 mL) were added. The vial was capped and purged with Ar for 20 min. The screw cap was wrapped with Parafilm[®] and stirred approximately 4 cm away from a blue LED light at rt for 16 h. A fan was blown across the reaction set-up to keep the reaction at rt. Then, EtOAc (20 mL) and water (20 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General procedure E: Ni-catalysed photoredox cross-coupling of alkylpinacolboronates

4,4'-Di-*tert*-butyl-2,2'-bipyridine (3 mg, 0.010 mmol, 5 mol%), NiCl₂•dme (2 mg, 0.010 mmol, 5 mol%) and anhydrous THF (0.5 mL) were added to a 7 mL screw cap vial fitted with a PTFE septum and equipped with a magnetic stirrer bar. The vial was capped and the resulting suspension was heated with a heat gun until the nickel salt was fully solubilised to give a pale green solution of NiCl₂(dtbbpy). The solvent was evaporated under reduced pressure. Then, alkylpinacolboronate (0.40 mmol, 2.0 eq), aryl bromide (0.20 mmol, 1.0 eq), [Ir(dFCF₃ppy)₂(dtbpy)]PF₆ (2 mg, 0.0020 mmol, 1 mol%), morpholine (26 µL, 0.30 mmol, 1.5 eq) and anhydrous DMF (3 mL) were added. The screw cap was wrapped with Parafilm® and stirred approximately 4 cm away from a blue LED light at rt for 16 h. A fan was blown across the reaction set-up to keep the reaction at rt. Then, EtOAc (20 mL) and water (20 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine (7 × 20 mL), dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product.

General procedure F: Ni-catalysed photoredox cross-coupling of alcohols

Alcohol (0.44 mmol, 1.75 eq), benzoxazolium salt **298** (185 mg, 0.40 mmol, 1.60 eq), pyridine (32 µL, 0.40 mmol, 1.60 eq) and anhydrous benzotrifluoride (2.5 mL) were added to a 7 mL screw cap vial equipped with a Suba-Seal® and magnetic stirrer bar. The resulting mixture was purged with N₂ for 15 min and then stirred at rt under N₂ for 1 h to give a suspension (vial 1).

Separately, 4,4'-di-*tert*-butyl-2,2'-bipyridine (3 mg, 0.012 mmol, 5.0 mol%), NiBr₂•dme (4 mg, 0.012 mmol, 5.0 mol%) and anhydrous THF (0.5 mL) were added to a 7 mL screw cap vial fitted with a PTFE septum and equipped with a magnetic stirrer bar. The vial was capped and the resulting suspension was heated with a heat gun until the nickel salt was fully solubilised to give a bright green solution of NiBr₂(dtbbpy). The solvent was evaporated under reduced pressure. Then, [Ir(dFCF₃ppy)₂(dtbpy)]PF₆ (4 mg, 0.0038 mmol, 1.5 mol%), quinuclidine (49 mg, 0.44 mmol, 1.75 eq), aryl bromide (0.25 mmol, 1.00 eq) and anhydrous DMA (2.5 mL) were added (vial 2).

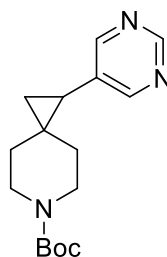
The suspension of the alcohol adduct in benzotrifluoride (vial 1) was taken up in a syringe with a 19-gauge needle attached. The 19-gauge needle was then removed and replaced by a syringe filter attached to a 21-gauge needle in order to transfer the contents into vial 2. The resulting solution was purged with N₂ for 15 min. The screw cap was wrapped with Parafilm[®] and stirred approximately 4 cm away from a 60 W blue LED light at rt for 16 h. A fan was blown across the reaction set-up. Then, EtOAc (20 mL) and water (20 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). Depending on the aryl bromide (see individual entry), the combined organics were washed with 1 M HCl_(aq) (20 mL), 15% CuSO_{4(aq)} (20 mL) and/or sat. EDTA_(aq) (20 mL) to remove some of the by-products generated. Then, the combined organics were washed with brine (3 × 20 mL), dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product.

General Procedure G: Suzuki-Miyaura cross-coupling of alkyltrifluoroborate salts

Alkyltrifluoroborate salt (0.30 mmol, 1.2 eq), aryl bromide (0.25 mmol, 1.0 eq), Pd(OAc)₂ (6 mg, 0.025 mmol, 10 mol%), cataCXium A (18 mg, 0.05 mmol, 20 mol%) and Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq) were added to a 7 mL screw cap vial fitted with a PTFE septum and equipped with a magnetic stirrer bar. The vial was capped and purged under N₂ for 20 min. Then, degassed toluene (1 mL) and degassed water (0.1 mL) were added and the resulting mixture was stirred at 1000 rpm and heated at 120 °C for 24 h. After being allowed to cool to rt, EtOAc (20 mL) and water (20 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine (20 mL), dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product.

5.3 Experimental Procedures for Chapter 2

tert-Butyl 1-(pyrimidin-5-yl)-6-azaspiro[2.5]octane-6-carboxylate **91**



91

Table 2.2, Entry 5

Using general procedure A, MIDA boronate **65** (92 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 5-bromopyrimidine (56 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 7:3 hexane-EtOAc as eluent gave arylated piperidine **91** (51 mg, 70%) as a clear oil which solidified upon standing to a white solid, mp 92-94 °C; *R*_F (7:3 hexane-EtOAc) 0.18; IR (ATR) 2931, 1687 (C=O), 1415, 1238, 1167, 1124, 1008, 730 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.03 (s, 1H, Ar), 8.56 (s, 2H, Ar), 3.62 (ddd, *J* = 13.0, 6.5, 4.0 Hz, 1H, NCH), 3.43–3.28 (m, 2H, NCH), 3.16 (ddd, *J* = 13.0, 8.0, 4.0 Hz, 1H, NCH), 1.90 (dd, *J* = 8.0, 6.5 Hz, 1H, CHAr), 1.65 (ddd, *J* = 12.5, 8.3, 3.9 Hz, 1H, CH), 1.47–1.37 (m, 10H, CMe₃, CH), 1.25–1.16 (m, 1H, CH), 1.07 (ddd, *J* = 13.5, 6.5, 4.0 Hz, 1H, CH), 1.02–0.97 (m, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 157.1 (Ar), 156.7 (Ar), 155.0 (C=O), 132.6 (*ipso*-Ar), 79.7 (OCMe₃), 42.9 (br, NCH₂), 36.5 (CH₂), 30.1 (CH₂), 28.5 (CMe₃), 25.6 (CHAr), 23.6 (C), 15.9 (CHCH₂); HRMS (ESI) *m/z* calcd for C₁₆H₂₃N₃O₂ (M + Na)⁺ 312.1682, found 312.1683 (–0.3 ppm error).

Lab book reference: ARG-2-132

Table 2.2, Entry 1

Using general procedure B, MIDA boronate **65** (92 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (488 mg, 1.50 mmol, 6.0 eq), 5-bromopyrimidine (56 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (11 mg, 0.03 mmol, 0.15 eq) and PCy₃ (21 mg, 0.06 mmol, 0.30 eq) in toluene (5 mL) and H₂O (0.5

mL) gave the crude product. Purification by flash column chromatography on silica with 7:3 hexane-EtOAc as eluent gave arylated piperidine **91** (40 mg, 55%) as a white solid. The spectroscopic data obtained were identical to those reported above.

Lab book reference: ARG-2-126

Table 2.2, Entry 2

Using modified general procedure A, MIDA boronate **65** (92 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (488 mg, 1.50 mmol, 6.0 eq), 5-bromopyrimidine (56 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (5.6 mg, 0.02 mmol, 0.10 eq) and PCy₃ (14 mg, 0.04 mmol, 0.20 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 7:3 hexane-EtOAc as eluent gave arylated piperidine **91** (21 mg, 30%) as a white solid. The spectroscopic data obtained were identical to those reported above.

Lab book reference: ARG-2-127

Table 2.2, Entry 3

Using modified general procedure A, MIDA boronate **65** (92 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (488 mg, 1.50 mmol, 6.0 eq), 5-bromopyrimidine (56 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 7:3 hexane-EtOAc as eluent gave arylated piperidine **91** (42 mg, 59%) as a white solid. The spectroscopic data obtained were identical to those reported above.

Lab book reference: ARG-2-128

Table 2.2, Entry 4

Using modified general procedure A, MIDA boronate **65** (92 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (488 mg, 1.50 mmol, 6.0 eq), 5-bromopyrimidine (56 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (1.4 mg, 0.005 mmol, 0.025 eq) and PCy₃ (3.5 mg, 0.01 mmol, 0.05 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column

chromatography on silica with 7:3 hexane-EtOAc as eluent gave arylated piperidine **91** (44 mg, 62%) as a white solid. The spectroscopic data obtained were identical to those reported above.

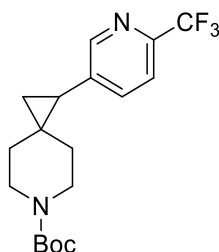
Lab book reference: ARG-2-129

Table 2.2, Entry 6

Using modified general procedure A, MIDA boronate **65** (92 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 5-bromopyrimidine (56 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (1.4 mg, 0.005 mmol, 0.025 eq) and PCy₃ (3.5 mg, 0.01 mmol, 0.05 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 7:3 hexane-EtOAc as eluent gave arylated piperidine **91** (49 mg, 68%) as a white solid. The spectroscopic data obtained were identical to those reported above.

Lab book reference: ARG-2-130

tert*-Butyl 1-(6-(trifluoromethyl)pyridin-3-yl)-6-azaspiro[2.5]octane-6-carboxylate **92*



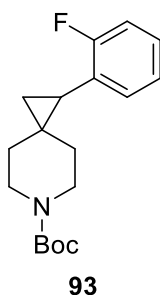
92

Using general procedure B, MIDA boronate **65** (92 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 5-bromo-2-trifluoromethylpyridine (79 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 4:1 hexane-EtOAc as eluent gave arylated piperidine **92** (63 mg, 70%) as a colourless oil which solidified upon standing to a white solid, mp 82–84 °C; R_F (4:1 hexane-EtOAc) 0.25; IR (ATR) 2928, 1684 (C=O), 1336, 1239, 1123, 1088, 732 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.54 (s, 1H, Ar), 7.63–7.42 (m, 2H, Ar), 3.72–3.52 (m, 1H,

NCH), 3.43–3.34 (m, 1H, NCH), 3.27–3.19 (m, 1H, NCH), 3.19–3.11 (m, 1H, NCH), 1.99 (dd, $J = 7.0, 7.0$ Hz, 1H, CHAr), 1.61 (ddd, $J = 12.5, 8.0, 3.5$ Hz, 1H, CH), 1.46–1.32 (m, 10H, CH, CMe₃), 1.23–1.13 (m, 1H, CH), 1.13–1.04 (m, 1H, CH), 1.04–0.96 (m, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers and conformers) δ 154.9 (C=O), 150.8 (Ar), 150.6 (Ar), 145.7 (q, $J = 35.0$ Hz, *ipso*-Ar), 138.4 (*ipso*-Ar), 137.0 (br, Ar), 136.8 (Ar), 121.8 (q, $J = 274.0$ Hz, CF₃), 119.9 (q, $J = 2.5$ Hz, Ar), 119.6 (q, $J = 2.5$ Hz, Ar), 79.6 (OCMe₃), 43.3 (br, NCH₂), 36.5 (CH₂), 29.8 (CH₂), 28.7 (CMe₃), 28.5 (CMe₃), 28.3 (CMe₃), 28.1 (CMe₃), 26.2 (CHAr), 26.0 (C), 25.8 (C), 16.5 (CHCH₂), 16.4 (CCH₂), 16.2 (CCH₂); HRMS (ESI) m/z calcd for C₁₈H₂₃F₃N₂O₂ (M + Na)⁺ 379.1604, found 379.1600 (–1.0 ppm error).

Lab book reference: ARG-2-134

tert*-Butyl 1-(2-fluorophenyl)-6-azaspiro[2.5]octane-6-carboxylate **93*

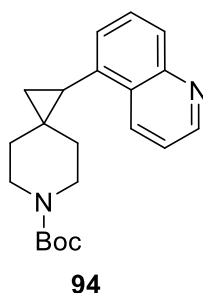


Using general procedure B, MIDA boronate **65** (92 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 1-bromo-2-fluorobenzene (61 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 96:4 hexane-EtOAc as eluent gave arylated piperidine **93** (50 mg, 66%) as a colourless oil which solidified upon standing to a white solid, mp 60–62 °C; R_F (96:4 hexane-EtOAc) 0.18; IR (ATR) 2925, 1687 (C=O), 1418, 1235, 1167, 1121, 751 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) δ 7.20–7.12 (m, 1H, Ar), 7.07–6.95 (m, 3H, Ar), 3.56–3.49 (m, 2H, NCH), 3.27 (ddd, $J = 13.0, 7.0, 4.0$ Hz, 1H, NCH), 3.11 (ddd, $J = 13.0, 7.5, 4.0$ Hz, 1H, NCH), 1.99 (dd, $J = 8.5, 5.5$ Hz, 1H, CHAr), 1.59–1.50 (m, 2H, CH), 1.43 (s, 9H, CMe₃), 1.22–1.06 (m, 2H, CH), 0.94 (dd, $J = 5.5, 5.0$ Hz, 1H, CH), 0.86 (dd, $J = 8.5, 5.0$ Hz, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 162.8 (d, $J = 245.5$ Hz, *ipso*-Ar), 155.1 (C=O), 129.6 (d, $J = 4.0$ Hz, Ar), 127.6 (d, $J = 8.0$ Hz, Ar), 126.4 (d, $J = 15.0$ Hz, *ipso*-Ar), 123.7 (d, $J = 3.5$ Hz, Ar), 115.0 (d, $J = 22.0$ Hz, Ar), 79.3 (OCMe₃), 43.3 (br, NCH₂), 36.5 (CH₂), 30.0 (CH₂), 28.6 (CMe₃),

24.6 (C), 22.7 (d, $J = 4.5$ Hz, CHAr), 15.3 (CCH₂); HRMS (ESI) m/z calcd for C₁₈H₂₄FNO₂ ($M + Na$)⁺ 328.1683, found 328.1682 (+0.5 ppm error).

Lab book reference: ARG-2-139

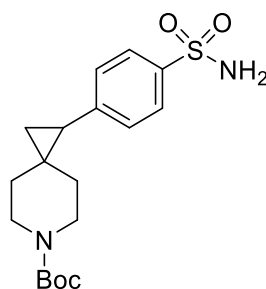
tert*-Butyl 1-(quinolin-5-yl)-6-azaspiro[2.5]octane-6-carboxylate **94*



Using general procedure A, MIDA boronate **65** (92 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 5-bromoquinoline (72 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 4:1 hexane-EtOAc as eluent gave arylated piperidine **94** (48 mg, 58%) as a colourless oil which solidified upon standing to a white solid, mp 100–102 °C; R_F (96:4 hexane-EtOAc) 0.18; IR (ATR) 2924, 1681 (C=O), 1420, 1355, 1238, 1166, 1119, 728 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.83 (dd, $J = 4.0, 1.5$ Hz, 1H, Ar), 8.06 (dd, $J = 8.5, 1.5$ Hz, 1H, Ar), 7.99 (d, $J = 9.0$ Hz, 1H, Ar), 7.60 (dd, $J = 9.0, 2.0$ Hz, 1H, Ar), 7.49 (d, $J = 2.0$ Hz, 1H, Ar), 7.35 (dd, $J = 8.5, 4.0$ Hz, 1H, Ar), 3.60–3.44 (m, 2H, NCH), 3.26–3.11 (m, 2H, NCH), 2.14 (dd, $J = 8.5, 6.0$ Hz, 1H, CHAr), 1.62–1.54 (m, 2H, CH), 1.41 (s, 9H, CMe₃), 1.18–1.14 (m, 2H, CH), 1.09 (dd, $J = 6.0, 5.5$ Hz, 1H, CH), 0.94 (dd, $J = 8.5, 5.5$ Hz, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.0 (C=O), 149.8 (Ar), 147.1 (*ipso*-Ar), 137.7 (*ipso*-Ar), 135.7 (Ar), 131.8 (Ar), 128.9 (Ar), 128.2 (*ipso*-Ar), 126.1 (Ar), 121.3 (Ar), 79.4 (OCMe₃), 43.5 (br, NCH₂), 36.8 (CH₂), 29.8 (CH₂), 28.8 (CHAr), 28.5 (CMe₃), 25.7 (C), 16.0 (CHCH₂); HRMS (ESI) m/z calcd for C₂₁H₂₆N₂O₂ ($M + H$)⁺ 339.2067, found 339.2069 (–0.5 ppm error).

Lab book reference: ARG-2-135

tert*-Butyl 1-(4-sulfamoylphenyl)-6-azaspiro[2.5]octane-6-carboxylate **95*

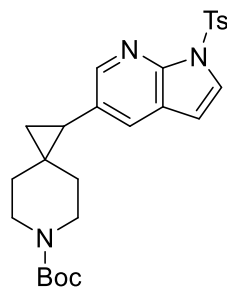


95

Using general procedure B, MIDA boronate **65** (92 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 4-bromobenzenesulfonamide (82 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 3:2 hexane-EtOAc as eluent gave arylated piperidine **95** (24 mg, 27%) as a pale-yellow oil, *R*_F (3:2 hexane-EtOAc) 0.13; IR (ATR) 3255 (NH₂) 2928, 1666 (C=O), 1427, 1331, 1241, 1158, 908, 728 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.95–7.76 (m, 2H, Ar), 7.37–7.08 (m, 2H, Ar), 5.16 (s, 2H, NH₂), 3.53 (ddd, *J* = 13.0, 7.0, 4.0 Hz, 1H, NCH), 3.46 (ddd, *J* = 13.0, 7.0, 4.0 Hz, 1H, NCH), 3.32–3.08 (m, NCH), 2.03 (dd, *J* = 8.0, 6.0 Hz, 1H, CHAr), 1.60–1.47 (m, 2H, CH), 1.42 (s, 9H, CMe₃), 1.19–1.11 (m, 2H, CH), 1.02 (dd, *J* = 6.0, 5.5 Hz, 1H, CH), 0.94 (dd, *J* = 8.0, 5.5 Hz, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.1 (C=O), 144.8 (*ipso*-Ar), 139.5 (*ipso*-Ar), 129.4 (Ar), 126.3 (Ar), 79.6 (OCMe₃), 43.5 (br, NCH₂), 36.8 (CH₂), 29.7 (CH₂), 28.7 (CHAr), 28.5 (CMe₃), 26.2 (C), 16.7 (CHCH₂); HRMS (ESI) *m/z* calcd for C₁₈H₂₆N₂O₄S (M + Na)⁺ 389.1505, found 389.1508 (–0.6 ppm error).

Lab book reference: ARG-2-136

tert*-Butyl 1-[1-(4-methylbenzenesulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-6-azaspiro[2.5]octane-6-carboxylate **96*

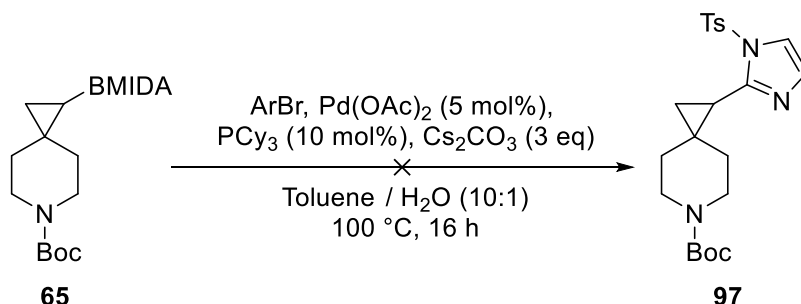


96

Using general procedure B, MIDA boronate **65** (183 mg, 0.50 mmol, 1.0 eq), Cs₂CO₃ (488 mg, 1.5 mmol, 3.0 eq), 5-bromo-*N*-tosyl-azaindole (245 mg, 0.70 mmol, 1.4 eq), Pd(OAc)₂ (5.6 mg, 0.025 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.05 mmol, 0.10 eq) in toluene (10 mL) and H₂O (1.0 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc to 7:3 hexane-EtOAc as eluent gave arylated piperidine **95** (176 mg, 73%) as a white solid, mp 74-76 °C; *R*_F (4:1 hexane-EtOAc) 0.26; IR (ATR) 2924, 1597 (C=O), 1498, 1443, 993, 768 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.31 (d, *J* = 2.0 Hz, 1H, Ar), 8.07–8.02 (m, 2H, Ar), 7.66 (d, *J* = 4.0 Hz, 1H, Ar), 7.57 (d, *J* = 2.0 Hz, 1H, Ar), 7.26–7.22 (m, 2H, Ar), 6.50 (d, *J* = 4.0 Hz, 1H, Ar), 3.58 (ddd, *J* = 13.0, 6.5, 3.5 Hz, 1H, NCH), 3.41 (ddd, *J* = 13.0, 8.0, 4.0 Hz, 1H, NCH), 3.28–3.18 (m, 1H, NCH), 3.13 (ddd, *J* = 12.0, 8.0, 4.0 Hz, 1H, NCH), 2.35 (s, 3H, Me), 2.00 (dd, *J* = 8.5, 6.0 Hz, 1H, CHAr), 1.58 (ddd, *J* = 12.0, 7.5, 3.5 Hz, 1H, CH), 1.48–1.35 (m, 10H, CMe₃, CH), 1.14 (ddd, *J* = 13.0, 8.0, 4.5 Hz, 1H, CH), 1.02 (ddd, *J* = 13.0, 6.0, 4.0 Hz, 1H, CH), 0.95–0.87 (m, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.0 (C=O), 146.4 (Ar), 145.9 (*ipso*-Ar), 145.2 (*ipso*-Ar), 135.5 (*ipso*-Ar), 129.7 (Ar), 129.2 (Ar), 128.1 (Ar), 126.8 (Ar), 122.5 (*ipso*-Ar), 105.0 (Ar), 79.5 (OCMe₃), 42.6 (br, NCH₂), 36.6 (CH₂), 30.0 (CH₂), 28.5 (CMe₃), 26.0 (CHAr), 24.9 (C), 21.7 (Me), 16.0 (CHCH₂) (1 × *ipso*-Ar resonance not resolved); HRMS (ESI) *m/z* calcd for C₂₆H₃₂N₃O₄S (M + Na)⁺ 507.1927, found 504.1929 (–0.4 ppm error).

Lab book reference: ARG-3-032

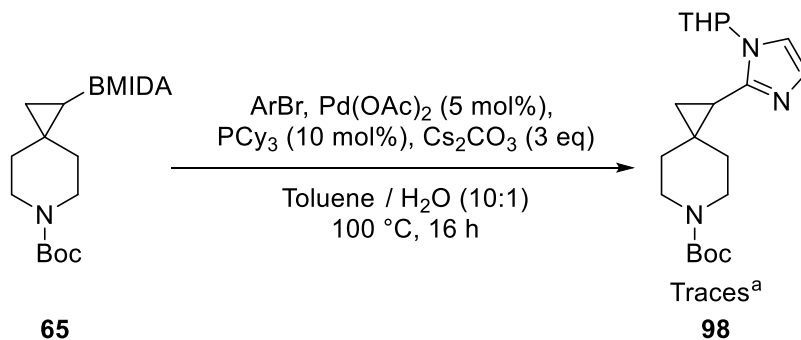
Attempted synthesis of *tert*-Butyl 1-(1-tosyl-1*H*-imidazol-2-yl)-6-azaspiro[2.5]octane-6-carboxylate **97**



Using general procedure B, MIDA boronate **65** (92 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 2-bromo-1-tosyl-1*H*-imidazole (105 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product which contained (by ¹H NMR spectroscopy and HRMS) no arylated cyclopropane **97**

Lab book reference: ARG-2-037

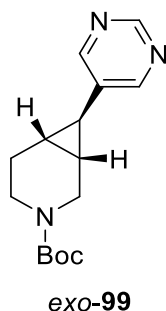
Attempted synthesis of *tert*-Butyl 1-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-imidazol-2-yl)-6-azaspiro[2.5]octane-6-carboxylate **98**



Using general procedure B, MIDA boronate **65** (92 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 2-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-imidazole (81 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product which contained (by ¹H NMR spectroscopy and HRMS) only traces arylated cyclopropane **98**

Lab book reference: ARG-3-021

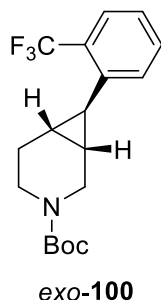
***tert*-Butyl 7-(pyrimidin-5-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate *exo*-99**



Using general procedure B, MIDA boronate *exo*-69 (88 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 5-bromopyrimidine (56 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 4:1 hexane-EtOAc as eluent gave arylated piperidine *exo*-99 (61 mg, 89%) as a white solid, mp 68–70 °C; *R*_F (7:3 hexane-EtOAc) 0.24; IR (ATR) 2975, 1684 (C=O), 1418, 1365, 1245, 1164, 727, 630 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.98 (s, 1H, Ar), 8.38 (s, 2H, Ar), 4.11–3.90 (m, 1H, NCH), 3.69–3.42 (m, 2H, NCH), 2.98 (ddd, *J* = 13.5, 9.5, 5.5 Hz, 1H, NCH), 2.05 (dddd, *J* = 14.0, 7.0, 5.5, 5.0 Hz, 1H, CH), 1.95–1.81 (m, 1H, CH), 1.59 (dd, *J* = 4.5, 4.5 Hz, 1H, CHAr), 1.51–1.38 (m, 11H, CMe₃, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 156.2 (Ar), 155.1 (C=O), 154.2 (Ar), 136.2 (*ipso*-Ar), 79.9 (OCMe₃), 41.8 (br, NCH₂), 39.8 (br, NCH₂), 28.5 (CMe₃), 22.5 (br, CH₂, CH), 22.0 (CHAr), 20.5 (CH); HRMS (ESI) *m/z* calcd for C₁₅H₂₁N₃O₂ (M + H)⁺ 276.1707, found 276.1713 (–2.5 ppm error).

Lab book reference: ARG-2-160

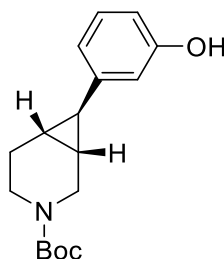
***tert*-Butyl 7-(2-(trifluoromethyl)phenyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate**
***exo*-100**



Using general procedure B, MIDA boronate *exo*-**69** (88 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 2-bromobenzotrifluoride (79 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 hexane-Et₂O as eluent gave arylated piperidine *exo*-**100** (66 mg, 78%) as a white solid, mp 98–100 °C; *R*_F (7:3 hexane-Et₂O) 0.48; IR (ATR) 2930, 1688 (C=O), 1419, 1313, 1259, 1113, 764 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (55:45 mixture of rotamers) δ 7.59 (d, *J* = 8.0 Hz, 1H, Ar), 7.41 (dd, *J* = 8.0, 7.5 Hz, 1H, Ar), 7.23 (dd, *J* = 8.0, 7.5 Hz, 1H, Ar), 7.03 (d, *J* = 8.0 Hz, 1H, Ar), 4.13–4.03 (m, 0.55H, NCH), 4.02–3.93 (m, 0.45H, NCH), 3.73–3.59 (m, 0.9H, NCH), 3.54–3.37 (m, 1.1H, NCH), 3.12–3.00 (m, 0.45H, NCH), 2.93–2.84 (m, 0.55H, NCH), 2.06–1.93 (m, 2H, CH, CHAr), 1.93–1.82 (m, 1H, CH), 1.47 (s, 9H, CMe₃), 1.53–1.39 (m, 1H, CH), 1.35–1.20 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers and conformers) δ 155.1 (C=O), 140.9 (br, *ipso*-Ar), 132.1 (Ar), 131.8 (Ar), 129.5 (Ar), 129.2 (Ar), 126.3 (Ar), 126.0 (Ar), 125.9 (Ar), 125.8 (Ar), 125.4 (Ar), 124.8 (q, *J* = 272.0 Hz, CF₃), 79.6 (OCMe₃), 42.3 (br, NCH₂), 28.8 (CMe₃), 28.5 (CMe₃), 28.3 (CMe₃), 28.1 (CMe₃), 24.1 (CHAr), 23.9 (CHAr), 22.4 (br, CH₂), 21.5 (br, CH or CH₂), 19.8 (br, CH or CH₂), 18.4 (br, CH or CH₂); HRMS (ESI) *m/z* calcd for C₁₈H₂₂F₃NO₂ (M + H)⁺ 364.1485, found 364.1485 (+2.7 ppm error).

Lab book reference: ARG-2-137

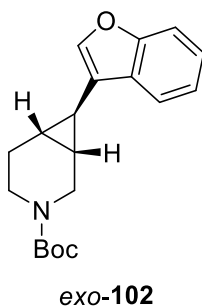
***tert*-Butyl 7-(3-hydroxyphenyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate *exo*-101**



Using general procedure B, MIDA boronate *exo*-**69** (88 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 3-bromophenol (61 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 4:1 hexane-EtOAc as eluent gave arylated piperidine *exo*-**101** (55 mg, 76%) as a white solid, mp 112-114 °C; *R*_F (3:2 hexane-EtOAc) 0.35; IR (ATR) 3315 (OH), 2929, 1657 (C=O), 1430, 1366, 1248, 1159, 730 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.07 (dd, *J* = 8.0, 7.5 Hz, 1H, Ar), 6.82 (br s, 1H, OH), 6.64 (d, *J* = 8.0 Hz, 1H, Ar), 6.53 (d, *J* = 7.5 Hz, 1H, Ar), 6.50 (s, 1H, Ar), 3.90 (br d, *J* = 13.5 Hz, 1H, NCH), 3.67–3.36 (m, 2H, NCH), 3.16–2.83 (m, 1H, NCH), 2.05–1.93 (m, 1H, CHAr), 1.87–1.74 (m, 1H, CH), 1.58–1.54 (m, 1H, CH), 1.48 (s, 9H, CMe₃), 1.40–1.27 (m, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 156.6 (C=O), 155.6 (*ipso*-Ar), 144.7 (*ipso*-Ar), 129.5 (Ar), 117.4 (br, Ar), 112.7 (Ar), 112.4 (Ar), 80.2 (OCMe₃), 42.6 (NCH₂), 41.9 (NCH₂), 41.1 (NCH₂), 40.3 (NCH₂), 28.6 (CMe₃), 27.5 (br, CHAr), 23.0 (CH₂), 22.6 (CH₂), 21.7 (br, CH), 20.2 (br, CH); HRMS (ESI) *m/z* calcd for C₁₇H₂₃NO₃ (M + Na)⁺ 312.1570, found 312.1574 (−1.2 ppm error).

Lab book reference: ARG-2-144

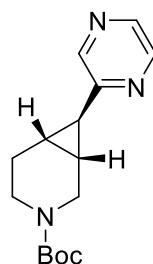
***tert*-Butyl 7-(benzofuran-3-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate *exo*-102**



Using general procedure B, MIDA boronate *exo*-**69** (88 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 3-bromobenzofuran (69 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave arylated piperidine *exo*-**102** (52 mg, 67%) as a colourless oil, *R*_F (4:1 hexane-EtOAc) 0.30; IR (ATR) 2975, 2928, 1685 (C=O), 1452, 1418, 1364, 1244, 1166, 743 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, *J* = 7.5 Hz, 1H, Ar), 7.44 (d, *J* = 7.5 Hz, 1H, Ar), 7.31 (d, *J* = 1.0 Hz, 1H, Ar), 7.29–7.21 (m, 2H, Ar), 4.05 (d, *J* = 13.5 Hz, 1H, NCH), 3.61 (dd, *J* = 13.5, 4.5 Hz, 1H, NCH), 3.57–3.43 (m, 1H, NCH), 3.10–2.97 (m, 1H, NCH), 2.07 (dddd, *J* = 14.0, 7.0, 5.5, 5.0 Hz, 1H, CH), 2.01–1.89 (m, 1H, CHAr), 1.65 (dd, *J* = 5.0, 5.0 Hz, 1H, CH), 1.49 (s, 9H, CMe₃), 1.47–1.31 (m, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 155.4 (C=O), 155.3 (*ipso*-Ar), 140.3 (Ar), 128.3 (*ipso*-Ar), 124.4 (Ar), 122.4 (Ar), 122.1 (*ipso*-Ar), 119.7 (Ar), 111.5 (Ar), 79.6 (OCMe₃), 42.6 (NCH₂), 41.7 (NCH₂), 41.0 (NCH₂), 40.0 (NCH₂), 28.6 (CMe₃), 23.0 (br, CH₂), 22.4 (br, CH₂), 18.6 (CHAr), 17.0 (br, CH), 16.6 (br, CH); HRMS (ESI) *m/z* calcd for C₁₉H₂₃NO₃ (M + Na)⁺ 336.1570, found 336.1564 (+1.9 ppm error).

Lab book reference: ARG-2-149

***tert*-Butyl 7-(pyrazin-2-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate *exo*-103**

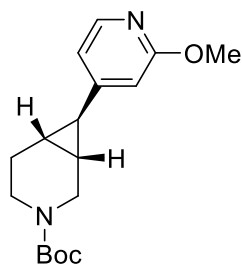


***exo*-103**

Using general procedure B, MIDA boronate *exo*-**69** (88 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 2-bromopyrazine (32 μ L, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc as eluent gave arylated piperidine *exo*-**104** (45 mg, 65%) as a colourless oil, *R*_F (1:1 hexane-EtOAc) 0.22; IR (ATR) 2975, 2928, 1686 (C=O), 1416, 1364, 1244, 1165, 1131, 769 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.42 (d, *J* = 1.5 Hz, 1H, Ar), 8.32 (dd, *J* = 2.5, 1.5 Hz, 1H, Ar), 8.25 (d, *J* = 2.5 Hz, 1H, Ar), 4.03–3.87 (m, 1H, NCH), 3.65–3.39 (m, 1H, NCH), 3.52 (dd, *J* = 13.5, 4.0 Hz, 1H, NCH), 2.98 (ddd, *J* = 13.5, 9.5, 5.5 Hz, 1H, NCH), 2.08–1.96 (m, 1H, CHAr), 1.92–1.81 (m, 1H, CH), 1.79 (dd, *J* = 4.5, 4.0 Hz, 1H, CH), 1.75–1.70 (m, 2H, CH), 1.45 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 157.7 (*ipso*-Ar), 155.2 (C=O), 144.1 (Ar), 143.7 (Ar), 141.3 (Ar), 79.7 (OCMe₃), 42.2 (NCH₂), 41.5 (NCH₂), 40.9 (NCH₂), 39.7 (NCH₂), 28.5 (CMe₃), 26.3 (br, CH), 23.2 (CHAr), 22.8 (CH₂), 22.4 (CH₂), 21.7 (br, CH); HRMS (ESI) *m/z* calcd for C₁₅H₂₁N₃O₂ (M + Na)⁺ 298.1526, found 298.1527 (–0.3 ppm error).

Lab book reference: ARG-2-146

***tert*-Butyl 7-(2-methoxypyridin-4-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate *exo*-104**

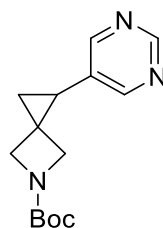


***exo*-104**

Using general procedure B, MIDA boronate *exo*-**69** (88 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 4-bromo-2-methoxypyridine (66 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 4:1 hexane-EtOAc as eluent gave arylated piperidine *exo*-**109** (67 mg, 88%) as a colourless oil, *R*_F (3:2 hexane-EtOAc) 0.38; IR (ATR) 2976, 1687 (C=O), 1611, 1417, 1390, 1245, 1162, 1129, 1045, 731 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.94 (d, *J* = 5.5 Hz, 1H, Ar), 6.45 (dd, *J* = 5.5, 1.5 Hz, 1H, Ar), 6.31 (d, *J* = 1.5 Hz, 1H, Ar), 3.92 (d, *J* = 14.0 Hz, 1H, NCH), 3.86 (s, 3H, OMe), 3.51 (dd, *J* = 14.0, 4.5 Hz, 1H, NCH), 3.58–3.38 (m, 1H, NCH), 3.01–2.89 (m, 1H, NCH), 2.03–1.93 (m, 1H, CHAr), 1.88–1.74 (br m, 1H, CH), 1.54 (dd, *J* = 4.5, 4.5 Hz, 1H, CH), 1.44 (s, 9H, CMe₃), 1.45–1.31 (m, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 164.5 (*ipso*-Ar), 155.4 (*ipso*-Ar), 155.1 (C=O), 146.6 (Ar), 114.5 (Ar), 106.8 (Ar), 79.7 (OCMe₃), 53.4 (OMe), 42.4 (NCH₂), 41.6 (NCH₂), 40.4 (NCH₂), 39.9 (NCH₂), 28.5 (CMe₃), 26.9 (br, CH), 23.0 (CHAr), 22.5 (br, CH₂), 21.4 (CH); HRMS (ESI) *m/z* calcd for C₁₇H₂₄N₂O₃ (M + H)⁺ 305.1860, found 305.1859 (+0.3 ppm error).

Lab book reference: ARG-2-147

tert*-Butyl 1-(pyrimidin-5-yl)-5-azaspiro[2.3]hexane-5-carboxylate **105*

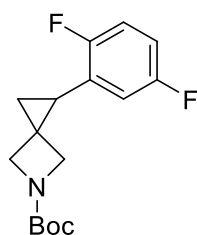


105

Using general procedure B, MIDA boronate **66** (85 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 5-bromopyrimidine (56 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 1:4 hexane-EtOAc as eluent gave arylated azetidine **105** (31 mg, 47%) as a white solid, mp 111–113 °C; *R*_F (3:7 hexane-EtOAc) 0.22; IR (ATR) 2875, 1696 (C=O), 1413, 1379, 1365, 1122, 771, 728 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.02 (s, 1H, Ar), 8.32 (s, 2H, Ar), 4.06 (d, *J* = 8.0 Hz, 1H, NCH), 4.03 (d, *J* = 8.0 Hz, 1H, NCH), 3.94 (d, *J* = 8.5 Hz, 1H, NCH), 3.68 (d, *J* = 8.5 Hz, 1H, NCH), 2.01 (dd, *J* = 9.0, 6.5 Hz, 1H, CHAr), 1.40–1.33 (m, 10H, CMe₃, CH), 1.13 (dd, *J* = 6.5, 6.5 Hz, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 156.6 (Ar), 155.9 (C=O), 155.5 (Ar), 132.8 (*ipso*-Ar), 79.8 (OCMe₃), 56.5 (br, NCH₂), 53.4 (br, NCH₂), 28.4 (CMe₃), 23.9 (C), 20.9 (CHAr), 16.9 (CHCH₂); HRMS (ESI) *m/z* calcd for C₁₄H₁₉N₃O₂ (M + Na)⁺ 284.1369, found 284.1369 (+0.2 ppm error).

Lab book reference: ARG-2-161

tert*-Butyl 1-(2,5-difluorophenyl)-5-azaspiro[2.3]hexane-5-carboxylate **106*

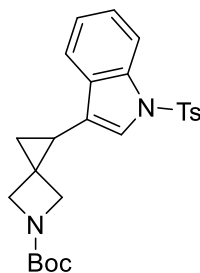


106

Using general procedure B, MIDA boronate **66** (85 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 2,5-difluorobromobenzene (68 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave arylated azetidine **106** (45 mg, 61%) as a white solid, mp 80-82 °C; *R*_F (2:3 hexane-EtOAc) 0.52; IR (ATR) 2976, 1695 (C=O), 1497, 1365, 1179, 1120, 772 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.06–6.95 (m, 1H, Ar), 6.88–6.80 (m, 1H, Ar), 6.43–6.35 (m, 1H, Ar), 4.11 (d, *J* = 8.0 Hz, 1H, NCH), 4.04 (d, *J* = 8.0 Hz, 1H, NCH), 3.89 (d, *J* = 8.5 Hz, 1H, NCH), 3.66 (d, *J* = 8.5 Hz, 1H, NCH), 2.24 (dd, *J* = 9.0, 6.5 Hz, 1H, CHAr), 1.43 (s, 9H CMe₃), 1.28 (dd, *J* = 9.0, 6.0 Hz, 1H, CH), 1.10 (dd, *J* = 6.5, 6.0 Hz, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 158.8 (d, *J* = 239.5 Hz, *ipso*-Ar), 158.0 (d, *J* = 241.5 Hz, *ipso*-Ar), 156.1 (C=O), 116.4 (dd, *J* = 24.5, 8.5 Hz, Ar), 113.8 (dd, *J* = 24.5, 8.5 Hz, Ar), 113.5 (dd, *J* = 25.0, 5.0 Hz, Ar), 79.6 (OCMe₃), 56.1 (NCH₂, only resolved in HSQC), 54.8 (NCH₂, only resolved in HSQC), 28.4 (CMe₃), 23.2 (C), 19.6 (d, *J* = 4.0 Hz, CHAr), 16.0 (CHCH₂) (1 × *ipso*-Ar resonance not resolved); HRMS (ESI) *m/z* calcd for C₁₆H₁₉F₂NO₂ (M + Na)⁺ 318.1276, found 318.1276 (+0.1 ppm error).

Lab book reference: ARG-2-151

tert*-Butyl 1-[1-(4-methylbenzenesulfonyl)-1*H*-indol-3-yl]-5-azaspiro[2.3]hexane-5-carboxylate **107*

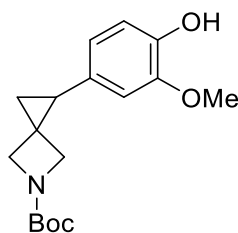


107

Using general procedure B, MIDA boronate **66** (85 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), *N*-Ts-3-bromoindole (123 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave arylated azetidine **107** (69 mg, 61%) as a pale-yellow oil, *R*_F (7:3 hexane-EtOAc) 0.38; IR (ATR) 2976, 1694 (C=O), 1365, 1172, 1118, 737, 669, 571, 537 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, *J* = 8.0 Hz, 1H, Ar), 7.71–7.67 (m, 2H, Ar), 7.57 (d, *J* = 7.5 Hz, 1H, Ar), 7.33 (dd, *J* = 8.0, 8.0 Hz, 1H, Ar), 7.26 (dd, *J* = 8.0, 7.5 Hz, 1H, Ar), 7.21–7.17 (m, 2H, Ar), 7.08 (s, 1H, Ar), 4.11 (d, *J* = 8.0 Hz, 1H, NCH), 4.07 (d, *J* = 8.0 Hz, 1H, NCH), 3.77 (d, *J* = 8.5 Hz, 1H, NCH), 3.44 (d, *J* = 8.5 Hz, 1H, NCH), 2.31 (s, 3H, Me), 2.04 (dd, *J* = 9.0, 6.0 Hz, 1H, CHAr), 1.41 (s, 9H, CMe₃), 1.26 (dd, *J* = 9.0, 6.0 Hz, 1H, CH), 1.07 (dd, *J* = 6.0, 6.0 Hz, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 156.1 (C=O), 145.0 (*ipso*-Ar), 135.4 (*ipso*-Ar), 135.0 (*ipso*-Ar), 131.5 (*ipso*-Ar), 129.9 (Ar), 126.7 (Ar), 125.1 (Ar), 123.5 (Ar), 121.9 (Ar), 121.8 (*ipso*-Ar), 119.5 (Ar), 113.9 (Ar), 79.5 (OCMe₃), 57.4 (br, NCH₂), 54.9 (br, NCH₂), 28.4 (CMe₃), 22.3 (C), 21.6 (Me), 16.2 (CHAr), 15.2 (CHCH₂); HRMS (ESI) *m/z* calcd for C₂₅H₂₉N₂O₄S (M + Na)⁺ 475.1662, found 475.1673 (–2.3 ppm error).

Lab book reference: ARG-2-152

tert*-Butyl 1-(4-hydroxy-3-methoxyphenyl)-5-azaspiro[2.3]hexane-5-carboxylate **108*

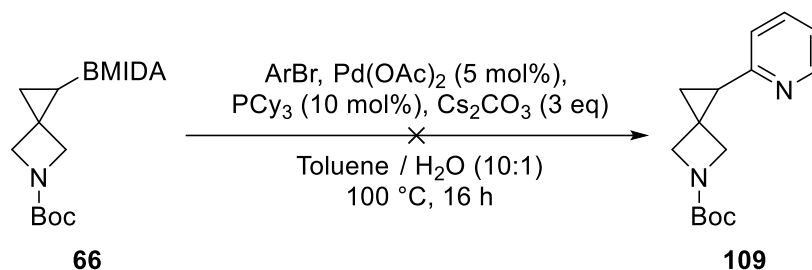


108

Using general procedure B, MIDA boronate **66** (85 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 4-bromo-2-methoxyphenol (71 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave arylated azetidine **108** (36 mg, 47%) as an off-white gum, *R*_F (4:1 hexane-EtOAc) 0.11; IR (ATR) 3331 (OH), 2934, 2251, 1681 (C=O), 1517, 1417, 1365, 1157, 1121, 729 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.83 (d, *J* = 8.0 Hz, 1H, Ar), 6.51 (d, *J* = 2.0 Hz, 1H, Ar), 6.40 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar), 5.63 (br s, 1H, OH), 4.05 (d, *J* = 8.0 Hz, 1H, NCH), 4.00 (d, *J* = 8.0 Hz, 1H, NCH), 3.89–3.85 (m, 1H, NCH), 3.87 (s, 3H, OMe), 3.71 (d, *J* = 8.5 Hz, 1H, NCH), 2.01 (dd, *J* = 9.5, 6.0 Hz, 1H, CHAr), 1.42 (s, 9H, CMe₃), 1.17 (dd, *J* = 9.5, 6.0 Hz, 1H, CH), 0.99 (dd, *J* = 6.0 Hz, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 156.2 (C=O), 146.6 (*ipso*-Ar), 144.1 (*ipso*-Ar), 130.8 (*ipso*-Ar), 119.1 (Ar), 118.9 (Ar), 114.6 (Ar), 114.4 (Ar), 110.0 (Ar), 109.8 (Ar), 79.6 (CMe₃), 57.5 (br, NCH₂), 56.1 (OMe), 55.9 (OMe), 53.1 (br, NCH₂), 28.5 (CMe₃), 28.4 (CMe₃), 25.6 (CHAr), 25.4 (CHAr), 22.6 (C), 16.4 (CHCH₂); HRMS (ESI) *m/z* calcd for C₁₇H₂₃NO₄ (M + Na)⁺ 328.1519, found 329.1518 (+0.3 ppm error).

Lab book reference: ARG-2-153

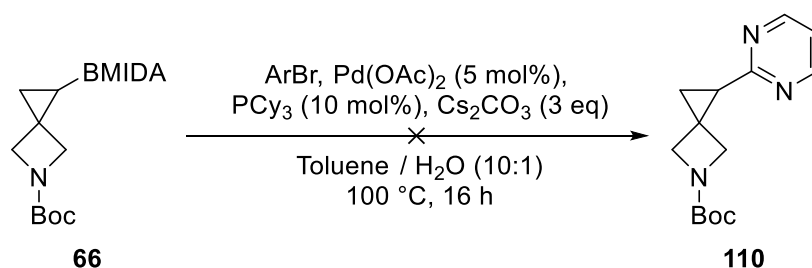
Attempted synthesis of *tert*-Butyl 1-(pyridin-2-yl)-5-azaspiro[2.3]hexane-5-carboxylate **109**



Using general procedure B, MIDA boronate **66** (85 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 2-bromopyridine (55 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product which contained (by ¹H NMR spectroscopy and HRMS) no arylated cyclopropane **109**

Lab book reference: ARG-2-154

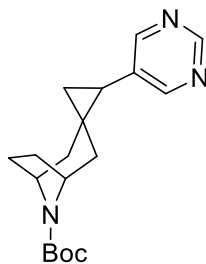
Attempted synthesis of *tert*-Butyl 1-(pyrimidin-2-yl)-5-azaspiro[2.3]hexane-5-carboxylate **110**



Using general procedure B, MIDA boronate **66** (85 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 2-bromopyrimidine (55 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product which contained (by ¹H NMR spectroscopy and HRMS) no arylated cyclopropane **110**.

Lab book reference: ARG-2-155

***tert*-Butyl 3'-(pyrimidin-5-yl)-8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-8-carboxylate *exo*-112**



***exo*-112**

Using general procedure D, MIDA boronate *exo*-**68** (98 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 5-bromopyrimidine (56 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave arylated tropane *exo*-**112** (44 mg, 58%) as a white gum, *R*_F (7:3 hexane-EtOAc) 0.36; IR (ATR) 2976, 1683 (C=O), 1413, 1158, 1099, 727 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.01 (s, 1H, Ar), 8.49 (s, 2H, Ar), 4.33–4.10 (m, 2H, NCH), 2.38–2.22 (m, 1H, CH), 1.98–1.81 (m, 4H, CH), 1.72–1.52 (m, 2H, CH, CHAr), 1.41 (s, 9H, CMe₃), 1.26–1.14 (m, 2H, CH), 1.06–0.96 (m, 1H, CH), 0.61–0.53 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 156.9 (Ar), 156.5 (Ar), 153.3 (C=O), 132.5 (*ipso*-Ar), 79.4 (OCMe₃), 54.5 (NCH), 54.0 (NCH), 53.7 (NCH), 53.3 (NCH), 42.0 (CH₂), 41.3 (CH₂), 37.4 (CH₂), 36.6 (CH₂), 28.6 (CMe₃), 28.0 (CH₂), 27.4 (CH₂), 21.4 (CHCH₂), 19.9 (C), 19.5 (CHAr); HRMS (ESI) *m/z* calcd for C₁₈H₂₅N₃O₂ (M + Na)⁺ 338.1839, found 338.1839 (–0.7 ppm error).

Lab book reference: ARG-2-167

Table 2.3, Entry 1

Using general procedure A, MIDA boronate *exo*-**68** (98 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 5-bromopyrimidine (56 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave arylated tropane *exo*-**112** (22 mg, 29%) as a white

gum And MIDA boronate *exo*-**68** (49 mg, 50%) as a white solid identical (by ^1H NMR spectroscopy) to that described above.

Lab book reference: ARG-2-162

Table 2.3, Entry 2

Using modified general procedure A, MIDA boronate *exo*-**68** (98 mg, 0.25 mmol, 1.0 eq), Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq), 5-bromopyrimidine (56 mg, 0.35 mmol, 1.4 eq), $\text{Pd}(\text{OAc})_2$ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy_3 (7.0 mg, 0.02 mmol, 0.10 eq) in dioxane (5 mL) and H_2O (0.5 mL) gave the crude product which contained (by ^1H NMR spectroscopy and HRMS) no arylated cyclopropane.

Lab book reference: ARG-2-163

Table 2.3, Entry 3

Using modified general procedure A, MIDA boronate *exo*-**68** (98 mg, 0.25 mmol, 1.0 eq), Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq), 5-bromopyrimidine (56 mg, 0.35 mmol, 1.4 eq), $\text{Pd}(\text{OAc})_2$ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy_3 (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (4.5 mL), DMF (0.5 mL) and H_2O (0.5 mL) gave the crude product which contained (by ^1H NMR spectroscopy and HRMS) no arylated cyclopropane.

Lab book reference: ARG-2-164

Table 2.3, Entry 4

Using modified general procedure A, MIDA boronate *exo*-**68** (98 mg, 0.25 mmol, 1.0 eq), Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq), 5-bromopyrimidine (56 mg, 0.35 mmol, 1.4 eq), $\text{Pd}(\text{OAc})_2$ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy_3 (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (4.5 mL), MeCN (0.5 mL) and H_2O (0.5 mL) gave the crude product which contained (by ^1H NMR spectroscopy and HRMS) no arylated cyclopropane.

Lab book reference: ARG-2-164

Table 2.3, Entry 5

Using modified general procedure A, MIDA boronate *exo*-**68** (98 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 5-bromopyrimidine (56 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (4.5 mL), dioxane (0.5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave arylated tropane *exo*-**112** (24 mg, 31%) as a white gum, and MIDA boronate *exo*-**68** (10 mg, 10%) as a white solid identical (by ¹H NMR spectroscopy) to that described above.

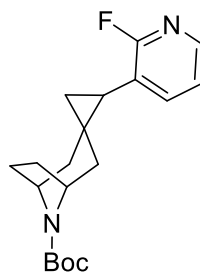
Lab book reference: ARG-2-164

Table 2.3, Entry 6

Using modified general procedure A, pinacol boronate *exo*-**111** (91 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 5-bromopyrimidine (56 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave pinacol boronate *exo*-**111** (47 mg, 52%) and arylated tropane *exo*-**112** (30 mg, 39%) as a white gum identical (by ¹H NMR spectroscopy) to that described above.

Lab book reference: ARG-2-165

***tert*-Butyl 3'-(2-fluoropyridin-3-yl)-8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-8-carboxylate *exo*-114**

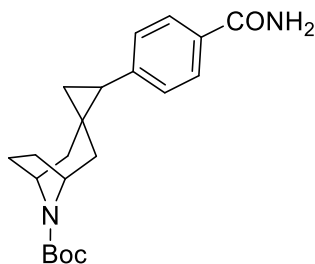


***exo*-114**

Using general procedure D, MIDA boronate *exo*-**68** (98 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 3-bromo-2-fluoropyridine (62 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave arylated tropane *exo*-**114** (57 mg, 69%) as an off-white solid, mp 136-138 °C; *R*_F (7:3 hexane-EtOAc) 0.42; IR (ATR) 2976, 1683 (C=O), 1389, 1157, 1100, 773, 729 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.11–7.94 (m, 1H, Ar), 7.47–7.37 (m, 1H, Ar), 7.11–7.00 (m, 1H, Ar), 4.36–3.96 (m, 2H, NCH), 2.47–2.29 (m, 1H, CH), 1.95–1.83 (m, 4H, CH), 1.73–1.58 (m, 2H, CH, CHAr), 1.48–1.39 (m, 9H, CMe₃), 1.18–1.09 (m, 2H, CH), 1.04–0.95 (m, 1H, CH), 0.53–0.45 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 163.7 (d, *J* = 239.5 Hz, *ipso*-Ar), 153.5 (C=O), 144.9 (d, *J* = 14.5 Hz, Ar), 139.85 (d, *J* = 48.5 Hz, Ar), 121.6 (br, *ipso*-Ar), 121.0 (Ar), 79.4 (OCMe₃), 54.6 (NCH), 54.1 (NCH), 53.9 (NCH), 53.5 (NCH), 41.6 (CH₂), 40.9 (CH₂), 36.8 (CH₂), 36.1 (CH₂), 28.6 (CMe₃), 28.1 (br, CH₂), 27.4 (br, CH₂), 21.0 (C), 19.3 (CHCH₂), 18.5 (CHAr); HRMS (ESI) *m/z* calcd for C₁₉H₂₅FN₂O₂ (M + Na)⁺ 355.1792, found 355.1797 (–1.2 ppm error).

Lab book reference: ARG-2-169

***tert*-Butyl 3'-(4-carbamoylphenyl)-8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-8-carboxylate *exo*-115**

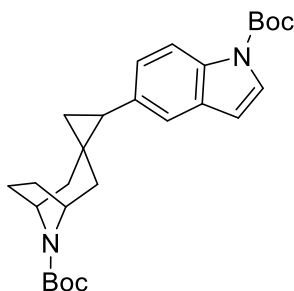


***exo*-115**

Using general procedure D, MIDA boronate *exo*-**68** (98 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), 4-bromobenzamide (70 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 3:2 hexane-EtOAc as eluent gave arylated tropane *exo*-**115** (69 mg, 78%) as an off-white solid, mp 144–146 °C; *R*_F (7:3 hexane-EtOAc) 0.42; IR (ATR) 3347 (NH), 3196 (NH), 2977, 2243, 1661 (C=O, Boc), 1611 (C=O, amide), 1390, 1159, 1102, 728 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.75–7.64 (m, 2H, Ar), 7.18–7.05 (m, 2H, Ar), 6.55–6.22 (m, 2H, NH₂), 4.32–4.09 (m, 2H, NCH), 2.38–2.20 (m, 1H, CH), 1.94–1.85 (m, 4H, CH), 1.69 (dd, *J* = 8.5, 6.0 Hz, 1H, CHAr), 1.55–1.34 (m, 10H, CMe₃, CH), 1.17 (dd, *J* = 6.0, 5.0 Hz, 1H, CH), 1.10 (dd, *J* = 8.5, 5.0 Hz, 1H, CH), 0.98 (d, *J* = 13.5 Hz, 1H, CH), 0.63–0.50 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 169.8 (C=O, amide), 153.4 (C=O, Boc), 143.4 (*ipso*-Ar), 131.0 (*ipso*-Ar), 128.7 (Ar), 127.2 (Ar), 79.2 (OCMe₃), 55.2 (br, NCH), 54.4 (br, NCH), 53.9 (br, NCH), 52.5 (br, NCH), 42.8 (br, CH₂), 41.6 (br, CH₂), 37.0 (br, CH₂), 36.5 (br, CH₂), 29.7 (CH₂), 29.3 (CH₂), 28.5 (CMe₃), 28.0 (br, CH₂), 27.4 (br, CH₂), 24.4 (CHAr), 21.8 (C), 20.0 (br, CHCH₂); HRMS (ESI) *m/z* calcd for C₂₁H₂₈N₂O₃ (M + Na)⁺ 379.1992, found 379.1986 (+1.6 ppm error).

Lab book reference: ARG-2-170

***tert*-Butyl 3'-(1-(*tert*-butoxycarbonyl)-1*H*-indol-5-yl)-8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-8-carboxylate *exo*-116**

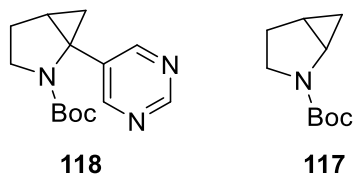


***exo*-116**

Using general procedure D, MIDA boronate *exo*-**68** (98 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq), *N*-Boc-5-bromoindole (103 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave arylated tropane *exo*-**116** (68 mg, 60%) as a colourless oil, *R*_F (95:5 hexane-EtOAc) 0.20; IR (ATR) 2977, 1732 (C=O), 1687 (C=O), 1367, 1325, 1158, 1023, 728 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.06–7.95 (m, 1H, Ar), 7.55 (d, *J* = 4.0 Hz, 1H, Ar), 7.30–7.28 (m, 1H, Ar), 7.11 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar), 6.50 (d, *J* = 4.0 Hz, 1H, Ar), 4.31–4.26 (m, 1H, NCH), 4.20–4.13 (m, 1H, NCH), 2.37–2.30 (m, 1H, CH), 1.97–1.88 (m, 4H, CH), 1.79 (dd, *J* = 8.0, 6.0 Hz, 1H, CHAr), 1.68–1.63 (m, 10H, CMe₃, CH), 1.44 (s, 9H, CMe₃), 1.18 (dd, *J* = 6.0, 5.0 Hz, 1H, CH), 1.09 (dd, *J* = 8.0, 5.0 Hz, 1H, CH), 1.01 (d, *J* = 13.5 Hz, 1H, CH), 0.57 (d, *J* = 13.5 Hz, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 153.4 (C=O), 149.9 (C=O), 135.9 (*ipso*-Ar), 133.1 (*ipso*-Ar), 130.6 (*ipso*-Ar), 126.2 (Ar), 126.1 (Ar), 125.7 (Ar), 120.6 (Ar), 114.7 (Ar), 114.6 (Ar), 107.3 (Ar), 107.2 (Ar), 83.6 (OCMe₃), 79.1 (OCMe₃), 54.4 (NCH), 54.1 (NCH), 42.0 (CH₂), 37.2 (CH₂), 28.7 (CMe₃), 28.6 (CMe₃), 28.3 (CMe₃), 28.2 (CMe₃), 27.8 (br, CH₂), 24.1 (CHAr), 24.0 (CHAr), 21.5 (br, C), 18.9 (CHCH₂) (1 × CH₂ resonance not resolved); HRMS (ESI) *m/z* calcd for C₂₇H₃₆N₂O₄ (M + Na)⁺ 475.2567, found 475.2577 (–2.0 ppm error).

Lab book reference: ARG-2-184

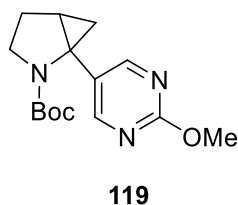
tert*-Butyl 1-(pyrimidin-5-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate **118** and *tert*-butyl 2-azabicyclo[3.1.0]hexane-2-carboxylate **117*



Using general procedure A, MIDA boronate **64** (84 mg, 0.25 mmol, 1.0 eq), 5-bromopyrimidine (56 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 7:3 hexane-EtOAc as eluent gave a 70:30 mixture arylated pyrrolidine **118** and pyrrolidine **117** (35 mg, i.e. 27 mg of **118**, 41% and 8 mg of **117**, 18%) as a clear oil. Spectroscopic data consistent with those reported in the literature.¹⁴⁹

Lab book reference: ARG-3-001

tert*-Butyl 1-(2-methoxypyrimidin-5-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate **119*

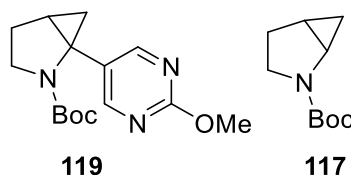


Using general procedure B, MIDA boronate **64** (194 mg, 0.57 mmol, 1.0 eq), Cs₂CO₃ (1.12 g, 3.44 mmol, 6.0 eq), 5-bromo-2-methoxypyrimidine (152 mg, 0.80 mmol, 1.4 eq), Pd(OAc)₂ (20 mg, 0.09 mmol, 0.15 eq) and PCy₃ (48 mg, 0.17 mmol, 0.30 eq) in toluene (11.5 mL) and H₂O (1.2 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 CH₂Cl₂-EtOAc as eluent gave arylated pyrrolidine **119** (112 mg, 67%) as a white solid, mp 100-102 °C; *R*_F (9:1 CH₂Cl₂-EtOAc) 0.10; IR (ATR) 2974, 1692 (C=O), 1472, 1162 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.35 (s, 2H, Ar), 3.91 (s, 3H, OMe), 3.77 (ddd, *J* = 11.5, 9.5, 5.5 Hz, 1H, NCH), 3.50–3.39 (m, 1H, NCH), 2.28 (dddd, *J* = 13.0, 9.5, 6.5, 6.5 Hz, 1H, CH), 1.94 (ddd, *J* = 13.0, 8.5, 5.5 Hz, 1H, CH), 1.58–1.53 (m, 2H, CH), 1.22 (s, 9H, CMe₃), 1.04–0.96 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 164.4 (*ipso*-Ar), 158.1 (Ar), 155.9 (C=O), 128.0 (*ipso*-Ar), 80.2 (OCMe₃), 54.9

(OMe), 49.4 (NCH₂), 45.2 (CAr), 28.7 (CH), 28.3 (CMe₃), 26.2 (CH₂), 20.7 (CH₂); HRMS *m/z* calcd for C₁₅H₂₁N₃O₃ (M + Na)⁺ 314.1475, found 314.1473 (+0.8 ppm error).

Lab book reference: ARG-3-036

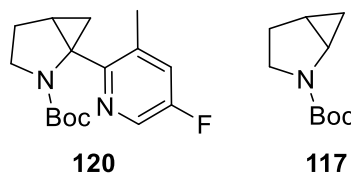
***tert*-Butyl 1-(2-methoxypyrimidin-5-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate **119**
and *tert*-butyl 2-azabicyclo[3.1.0]hexane-2-carboxylate **117****



Using general procedure A, MIDA boronate **64** (84 mg, 0.25 mmol, 1.0 eq), 5-bromo-2-methoxypyrimidine (66 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 CH₂Cl₂-EtOAc as eluent gave a 75:25 mixture arylated pyrrolidine **119** and pyrrolidine **11** (44 mg, i.e. 37 mg of **119**, 51% and 7 mg of **117**, 17%) as a clear oil. Spectroscopic data consistent with those reported in the literature.¹⁴⁹

Lab book reference: ARG-3-002

***tert*-Butyl 1-(5-fluoro-3-methylpyridin-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate **120**
and *tert*-butyl 2-azabicyclo[3.1.0]hexane-2-carboxylate **117****

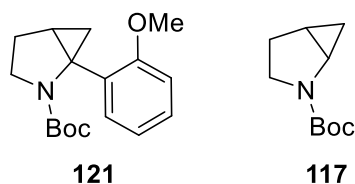


Using general procedure A, MIDA boronate **64** (84 mg, 0.25 mmol, 1.0 eq), 2-bromo-5-fluoro-3-methylpyridine (66 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 CH₂Cl₂-EtOAc as eluent gave a 65:35 mixture arylated pyrrolidine **120** and pyrrolidine **117** (29 mg,

i.e. 22 mg of **120**, 30% and 7 mg of **117**, 17%) as a clear oil. Spectroscopic data consistent with those reported in the literature.¹⁴⁹

Lab book reference: ARG-3-003

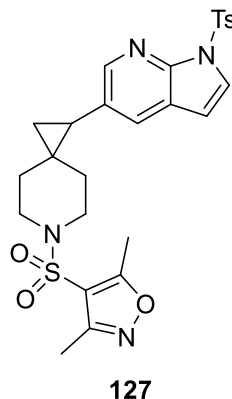
tert*-Butyl 1-(2-methoxyphenyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate **121** and *tert*-butyl 2-azabicyclo[3.1.0]hexane-2-carboxylate **117*



Using general procedure A, MIDA boronate **64** (84 mg, 0.25 mmol, 1.0 eq), 2 1-bromo-2-methoxybenzene (65 mg, 0.35 mmol, 1.4 eq), Pd(OAc)₂ (2.8 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7.0 mg, 0.02 mmol, 0.10 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 6:4 CH₂Cl₂-EtOAc as eluent gave a 70:30 mixture arylated pyrrolidine **121** and pyrrolidine **117** (48 mg, i.e. 38 mg of **121**, 53% and 10 mg of **117**, 22%) as a clear oil. Spectroscopic data consistent with those reported in the literature.¹⁴⁹

Lab book reference: ARG-3-004

3,5-Dimethyl-4-((1-(1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-6-azaspiro[2.5]octan-6-yl)sulfonyl)isoxazole **127**

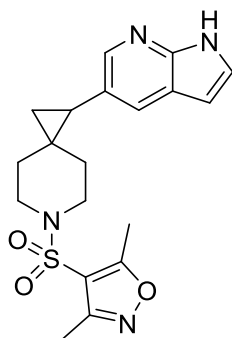


4 N HCl in dioxane (3 mL) was added to a stirred solution of arylated piperidine **96** (76 mg, 0.16 mmol, 1 eq) in dioxane (1 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h and the solvent was evaporated under reduced pressure to give the crude HCl salt. The crude HCl salt was suspended in CH₂Cl₂ and DMAP (2 mg, 0.02 mmol, 0.1 eq) and Et₃N (120 μ L, 0.8 mmol, 5.0 eq) were added under Ar. The resulting solution was cooled to 0 °C and 3,5-dimethylisoxazole-4-sulfonyl chloride (40 mg, 0.20 mmol, 1.25 eq) was added and the solution was stirred at rt for 4 h. 1 M HCl_(aq) (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 10 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 hexane-EtOAc as eluent gave sulfonamide **127** (70 mg, 81%) as a white solid, mp 90-92 °C; *R*_F (7:3 hexane-EtOAc) 0.24; IR (ATR) 2923, 1371, 1173, 908, 723, 674, 579 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.25 (d, *J* = 2.0 Hz, 1H, Ar), 8.08–8.01 (m, 2H, Ar), 7.67 (d, *J* = 4.0 Hz, 1H, Ar), 7.55 (d, *J* = 2.0 Hz, 1H, Ar), 7.29–7.23 (m, 2H, Ar), 6.51 (d, *J* = 4.0 Hz, 1H, Ar), 3.40 (ddd, *J* = 11.5, 8.5, 3.5 Hz, 1H, NCH), 3.13–3.02 (m, 2H, NCH), 2.81 (ddd, *J* = 11.5, 8.5, 3.5 Hz, 1H, NCH), 2.58 (s, 3H, Me), 2.39–2.32 (m, 6H, Me), 2.06–2.01 (m, 1H, CHAr), 1.83 (ddd, *J* = 13.5, 8.5, 3.5 Hz, 1H, CH), 1.51 (ddd, *J* = 13.5, 6.0, 3.5 Hz, 1H, CH), 1.36 (ddd, *J* = 14.0, 8.5, 4.0 Hz, 1H, CH), 1.08 (ddd, *J* = 14.0, 6.5, 3.5 Hz, 1H, CH), 0.93 – 0.86 (m, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) (conformers) δ 173.6 (*ipso*-Ar), 158.0 (*ipso*-Ar), 146.1 (Ar), 146.0 (Ar), 145.3 (*ipso*-Ar), 135.4 (*ipso*-Ar), 129.7 (Ar), 129.4 (*ipso*-Ar), 129.3 (Ar), 129.0 (*ipso*-Ar), 128.1 (Ar), 128.0 (Ar), 127.0 (Ar), 126.9 (Ar), 122.6 (*ipso*-Ar), 114.0 (*ipso*-Ar), 105.0 (Ar), 104.9 (Ar), 45.3 (NCH₂), 45.0 (NCH₂), 35.9 (CH₂), 25.9 (CHAr), 25.8 (CHAr), 23.9 (C), 21.73 (Me), 21.69 (Me), 15.9 (CHCH₂), 13.0

(Me), 11.4 (Me), 11.37 (Me); HRMS m/z calcd for $C_{26}H_{28}N_4O_5S_2$ ($M + Na$)⁺ 563.1393, found 563.1401 (−1.4 ppm error).

Lab book reference: ARG-3-035

4-((1-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)-6-azaspiro[2.5]octan-6-yl)sulfonyl)-3,5-dimethylisoxazole 128



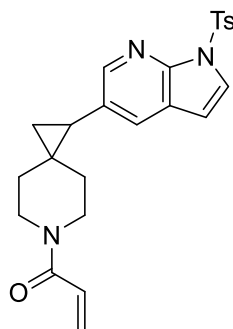
128

CS_2CO_3 (166 mg, 0.51 mmol, 3.0 eq) was added to a stirred solution of sulfonamide **127** (65 mg, 0.12 mmol, 1.0 eq) in THF (1.1 mL) and MeOH (0.6 mL) and the resulting mixture was stirred at rt for 16 h. H_2O (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 CH_2Cl_2 -EtOAc as eluent gave *N'*-H sulfonamide **128** (41 mg, 72%) as a white solid, mp 96–98 °C; R_F (4:1 CH_2Cl_2 -EtOAc) 0.14; IR (ATR) 3133 (NH), 2923, 2852, 1585, 1405, 1336, 1177, 905, 724, 624, 571 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 10.77 (s, 1H, NH), 8.22–8.12 (m, 1H, Ar), 7.78–7.61 (m, 1H, Ar), 7.46–7.34 (m, 1H, Ar), 6.61–6.37 (m, 1H, Ar), 3.42 (ddd, J = 11.0, 6.0, 4.0 Hz, 1H, NCH), 3.17–3.07 (m, 2H, NCH), 2.86 (ddd, J = 11.5, 8.5, 3.5 Hz, 1H, NCH), 2.61 (s, 3H, Me), 2.39 (s, 3H, Me), 2.13 (dd, J = 8.5, 6.0 Hz, 1H, CHAr), 1.85 (ddd, J = 13.5, 9.0, 3.5 Hz, 1H, CH), 1.58 (ddd, J = 13.5, 6.0, 3.5 Hz, 1H, CH), 1.42 (ddd, J = 13.0, 8.5, 4.0 Hz, 1H, CH), 1.21–1.14 (m, 1H, CH), 0.97 (dd, J = 6.0, 5.5 Hz, 1H, CH), 0.90 (dd, J = 8.5, 5.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.6 (*ipso*-Ar), 158.1 (*ipso*-Ar), 147.8 (Ar), 144.0 (Ar), 128.9 (*ipso*-Ar), 125.9 (Ar), 125.4 (*ipso*-Ar), 120.2 (*ipso*-Ar), 114.0 (*ipso*-Ar), 100.4 (Ar), 45.5 (NCH₂), 45.1 (NCH₂), 36.0 (CH₂),

29.8 (CH₂), 26.2 (CHAr), 23.5 (C), 15.8 (CHCH₂), 13.1 (Me), 11.5 (Me); HRMS *m/z* calcd for C₁₉H₂₂N₄O₃S (M + H)⁺ 387.1485, found 387.1489 (−1.0 ppm error).

Lab book reference: ARG-3-038

1-(1-(1-Tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-6-azaspiro[2.5]octan-6-yl)prop-2-en-1-one **129**



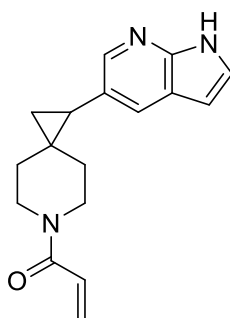
129

4 N HCl in dioxane (5 mL) was added to a stirred solution of arylated piperidine **96** (150 mg, 0.31 mmol, 1 eq) in dioxane (1 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h and the solvent was evaporated under reduced pressure to give the crude HCl salt. The crude HCl salt was suspended in CH₂Cl₂ (4 mL) and DMAP (4 mg, 0.03 mmol, 0.1 eq) and Et₃N (0.2 mL, 1.4 mmol, 4.5 eq) were added under Ar. The resulting solution was cooled to 0 °C and acryloyl chloride (88 μL, 1.09 mmol, 3.5 eq) was added and the solution was stirred at rt for 4 h. 1 M HCl_(aq) (15 mL) was added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 CH₂Cl₂-EtOAc as eluent gave acrylamide **129** (82 mg, 61%) as a white semi-solid, *R*_F (9:1 CH₂Cl₂-EtOAc) 0.10; IR (ATR) 2920, 2239, 1641 (C=O), 1442, 1372, 1163, 907, 724, 673, 579 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) (55:45 mixture of rotamers) δ 8.30 (d, *J* = 2.0 Hz, 1H, Ar), 8.09–7.96 (m, 2H, Ar), 7.66 (d, *J* = 4.0 Hz, 1H, Ar), 7.60–7.57 (m, 1H, Ar), 7.28–7.21 (m, 2H, Ar), 6.58 (dd, *J* = 16.5, 10.5 Hz, 0.45H, =CH), 6.50 (d, *J* = 4.0 Hz, 1H, Ar), 6.46 (dd, *J* = 16.5, 10.5 Hz, 0.55H, =CH), 6.27–6.17 (m, 1H, =CH), 5.69–5.55 (m, 1H, =CH), 3.91–3.81 (m, 0.55H, NCH), 3.72–3.60 (m, 1H, NCH), 3.59–3.50 (m, 0.9H, NCH), 3.39–3.21 (m, 1.55H, NCH), 2.34 (s, 3H, Me), 2.07–2.02 (m, 1H, CHAr), 1.70–1.61 (m, 1H, CH), 1.56–

1.44 (m, 1H, CH), 1.24–1.15 (m, 1.1H, CH), 1.13–1.03 (m, 0.9H, CH), 0.99–0.91 (m, 2H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) (rotamers) δ 165.6 (C=O), 146.3 (Ar), 146.2 (Ar), 146.0 (*ipso*-Ar), 145.3 (*ipso*-Ar), 135.5 (*ipso*-Ar), 129.8 (Ar), 129.5 (*ipso*-Ar), 129.3 (br, Ar), 128.1 (Ar), 128.0 (=CH), 127.5 (=CH₂), 126.9 (Ar), 122.6 (*ipso*-Ar), 105.0 (Ar), 45.9 (NCH₂), 45.4 (NCH₂), 42.7 (NCH₂), 41.6 (NCH₂), 37.4 (CH₂), 36.2 (CH₂), 31.0 (CH₂), 29.8 (CH₂), 26.1 (CHAr), 25.0 (C), 21.7 (Me), 16.1 (CHCH₂); HRMS m/z calcd for $\text{C}_{24}\text{H}_{25}\text{N}_3\text{O}_3\text{S}$ ($\text{M} + \text{Na}$)⁺ 458.1509, found 458.1513 (–0.9 ppm error).

Lab book reference: ARG-3-053

1-(1-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)-6-azaspiro[2.5]octan-6-yl)prop-2-en-1-one **130**



130

Cs_2CO_3 (110 mg, 0.34 mmol, 3.0 eq) was added to a stirred solution of sulfonamide **129** (50 mg, 0.11 mmol, 1.0 eq) in THF (1.1 mL) and MeOH (0.35 mL) and the resulting mixture was stirred at rt for 8 h. H_2O (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 $\times$ 10 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:9 CH_2Cl_2 -EtOAc as eluent gave *N'*-H acrylamide **130** (19 mg, 61%) as a clear oil, R_F (1:8 CH_2Cl_2 -EtOAc) 0.20; IR (ATR) 3203 (NH), 2923, 2853, 1640 (C=O), 1443, 1222, 729 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) (55:45 mixture of rotamers) δ 9.91–9.76 (m, 1H, NH), 8.23 (s, 1H, Ar), 7.72 (s, 1H, Ar), 7.36–7.29 (m, 1H, Ar), 6.62 (dd, J = 17.0, 10.5 Hz, 0.45H, =CH), 6.55–6.41 (m, 1.55H, =CH, Ar), 6.31–6.18 (m, 1H, =CH), 5.72–5.57 (m, 1H, =CH), 3.95–3.85 (m, 0.55H, NCH), 3.76–3.68 (m, 1H, NCH), 3.66–3.54 (m, 0.9H, NCH), 3.45–3.27 (m, 1.55H, NCH), 2.20–2.09 (m, 1H, CHAr), 1.76–1.65 (m, 1H, CH), 1.62–1.52 (m, 1H, CH), 1.34–1.22 (m, 1H, CH), 1.22–1.11 (m, 1H, CH), 1.08–0.99 (m, 1H,

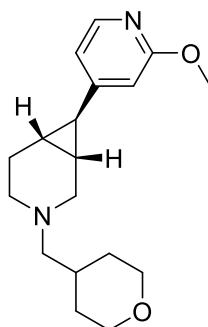
CH), 1.02–0.92 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) (rotamers) δ 165.7 (C=O), 147.6 (*ipso*-Ar), 144.5 (Ar), 128.8 (Ar), 128.2 (Ar), 128.1 (Ar), 127.4 (=CH₂), 125.5 (Ar), 120.0 (*ipso*-Ar), 100.7 (=CH), 46.1 (NCH₂), 45.6 (NCH₂), 42.3 (NCH₂), 41.8 (NCH₂), 37.6 (CH₂), 36.4 (CH₂), 31.2 (CH₂), 30.0 (CH₂), 29.8 (CH₂), 26.4 (CHAr), 24.6 (C), 16.0 (CHCH₂) (1 $\times$ *ipso*-Ar resonance not resolved); HRMS m/z calcd for $\text{C}_{17}\text{H}_{20}\text{N}_3\text{O}$ ($\text{M} + \text{H}$)⁺ 282.1601, found 282.1605 (–1.5 ppm error).

Lab book reference: ARG-3-064

4 N HCl in dioxane (5 mL) was added to a stirred solution of arylated piperidine **162** (73 mg, 0.22 mmol, 1 eq) in dioxane (1 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h and the solvent was evaporated under reduced pressure to give the crude HCl salt. The crude HCl salt was suspended in CH_2Cl_2 (2 mL) and Et_3N (0.2 mL, 1.4 mmol, 6.5 eq) were added under Ar. The resulting solution was cooled to 0 °C and acryloyl chloride (20 μL , 1.09 mmol, 3.5 eq) was added and the solution was stirred at rt for 4 h. 1 M $\text{HCl}_{(\text{aq})}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 10 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:9 CH_2Cl_2 -EtOAc as eluent gave *N'*-H acrylamide **61** (19 mg, 76%) as a clear oil. The spectroscopic data obtained were identical to those reported above.

Lab book reference: ARG-3-084

7-(2-Methoxypyridin-4-yl)-3-((tetrahydro-2H-pyran-4-yl)methyl)-3-azabicyclo[4.1.0]heptane *exo*-131

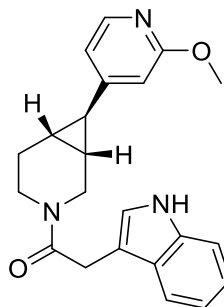


***exo*-131**

4 N HCl in dioxane (4 mL) was added stirred solution of arylated piperidine *exo*-**104** (80 mg, 0.26 mmol, 1 eq) in dioxane (1 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h under Ar and the solvent was evaporated under reduced pressure to give the crude HCl salt. The crude HCl salt was suspended in DCE (2.6 mL) and tetrahydro-2H-pyran-4-carbaldehyde (45 mg, 0.39 mmol, 1.5 eq) and AcOH (59 μ L, 1.0 mmol, 4.0 eq) were added under Ar. The resulting solution was cooled to 0 $^{\circ}$ C and NaBH(OAc)₃ (220 mg, 1.0 mmol, 4.0 eq) was added and the solution stirred at rt for 4 h. Saturated NaHCO_{3(aq)} (20 mL) was added, and the two layers separated. The aqueous layer was extracted with EtOAc (3 $\times$ 15 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 EtOAc-hexane as eluent gave amine *exo*-**131** (54 mg, 67%) as a yellow oil; *R*_F (4:1 EtOAc-hexane) 0.17; IR (ATR) 2926, 2839, 1611, 1454, 1390, 1093, 851 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃) δ 7.95 (d, *J* = 5.5 Hz, 1H, Ar), 6.49 (d, *J* = 5.5 Hz, 1H, Ar), 6.33 (s, 1H, Ar), 4.00–3.93 (m, 3H, OCH), 3.89 (s, 3H, OCH₃), 3.41–3.33 (m, 2H, OCH, NCH), 2.87 (d, *J* = 11.5 Hz, 1H, NCH), 2.56–2.51 (m, 1H, NCH), 2.38–2.32 (m, 1H, NCH), 2.15 – 1.99 (m, 4H, CHAr, NCH), 1.94–1.81 (m, 2H, CH), 1.76–1.58 (m, 4H, CH), 1.48–1.41 (m, 1H, CH), 1.40–1.33 (m, 1H, CH); ¹³C NMR (100.6 MHz, CD₂Cl₂) δ 165.0 (*ipso*-Ar), 157.2 (*ipso*-Ar), 146.8 (Ar), 114.8 (Ar), 106.8 (Ar), 68.4 (OCH₂), 65.3 (NCH₂), 53.6 (OMe), 53.4 (NCH₂), 51.2 (NCH₂), 33.2 (CH), 32.4 (CH₂), 28.0 (CHAr), 25.9 (CH), 24.9 (CH₂), 22.3 (CH); HRMS *m/z* calcd for C₁₈H₂₆N₂O₂ (M + H)⁺ 303.2067, found 303.2068 (–0.5 ppm error).

Lab book reference: ARG-3-022

2-(1H-Indol-3-yl)-1-(7-(2-methoxypyridin-4-yl)-3-azabicyclo[4.1.0]heptan-3-yl)ethan-1-one *exo*-132



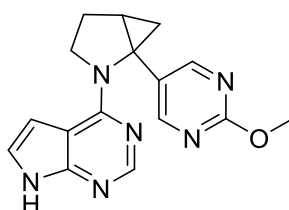
***exo*-132**

4 N HCl in dioxane (4 mL) was added to a stirred solution of arylated piperidine *exo*-**104** (103 mg, 0.34 mmol, 1 eq) in dioxane (1 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h and the solvent was evaporated under reduced pressure to give the crude HCl salt. The crude HCl salt was suspended in EtOAc (3 mL) and 3-indoleacetic acid (66 mg, 0.37 mmol, 1.1 eq) and Et₃N (0.19 mL, 1.4 mmol, 4.0 eq) were added under Ar. The resulting solution was cooled to 0 °C and a 50% solution of T3P in toluene (0.35 mL, 0.68 mmol, 2.0 eq) was added and the resulting solution was stirred and heated at 80 °C for 18 h. After being allowed to cool to rt, EtOAc (20 mL) was added and the solution was washed with saturated NaHCO_{3(aq)} (10 mL), 0.5 M HCl_(aq) (10 mL) and brine (15 mL), dried (MgSO₄) and 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 amide *exo*-**132** (62 mg, 53%) as a red solid, mp 200-202 °C (decomposition); *R*_F (19:1 EtOAc-MeOH) 0.21; IR (ATR) 3255 (NH), 2925, 1612 (C=O), 1453, 1165, 745 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (50:50 mixture of rotamers) δ 8.25 (s, 1H, NH), 7.92 (d, *J* = 5.5 Hz, 0.5H, Ar), 7.87 (d, *J* = 5.5 Hz, 0.5H, Ar), 7.72–7.66 (m, 1H, Ar), 7.37 (dd, *J* = 7.5, 7.5 Hz, 1H, Ar), 7.26–7.05 (m, 3H, Ar), 6.33 (dd, *J* = 5.5, 1.5 Hz, 0.5H, Ar), 6.18 (d, *J* = 1.5 Hz, 0.5H, Ar), 6.10 (dd, *J* = 5.5, 1.5 Hz, 0.5H, Ar), 5.99 (d, *J* = 1.5 Hz, 0.5H, Ar), 4.42 (d, *J* = 14.0 Hz, 0.5H, NCH), 4.08–4.00 (m, 1H, NCH), 3.91–3.78 (m, 5H, OMe, C(O)CH), 3.64 (dd, *J* = 14.0, 4.5 Hz, 0.5H, NCH), 3.54 (ddd, *J* = 14.0, 5.0, 5.0 Hz, 0.5H, NCH), 3.45 (dd, *J* = 14.0, 4.5 Hz, 0.5H), 3.07 (ddd, *J* = 13.0, 10.5, 5.5 Hz, 0.5H, NCH), 2.83 (ddd, *J* = 13.0, 10.5, 5.5 Hz, 0.5H, NCH), 2.06–1.95 (m, 0.5H, CHAr), 1.89–1.68 (m, 1.5H, CHAr, CH), 1.45–1.26 (m, 2.5H, CH), 1.12–1.03 (m, 0.5H, CH); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 170.8 (C=O), 170.4 (*ipso*-Ar), 154.9 (*ipso*-Ar), 146.4 (*ipso*-Ar), 122.6 (Ar), 122.5 (*ipso*-Ar), 120.0 (Ar), 119.9 (Ar), 119.2 (Ar), 119.1 (Ar), 118.3 (*ipso*-Ar), 114.5 (Ar), 114.3 (Ar), 111.4 (Ar),

109.5 (*ipso*-Ar), 109.4 (*ipso*-Ar) 106.7 (Ar), 53.5 (OMe), 44.3 (NCH₂), 43.1 (NCH₂), 40.3 (NCH₂), 39.2 (CH₂), 32.2 (CH₂Ar), 32.1 (CH₂), 29.8 (CH₂), 26.9 (CH₂), 26.5 (CH₂), 23.3 (CHAr), 23.0 (CH), 22.9 (CH), 22.5 (CH), 21.1 (CH), 20.9 (CH); HRMS *m/z* calcd for C₂₂H₂₃N₃O₂ (M + H)⁺ 362.1863, found 362.1867 (−1.2 ppm error).

Lab book reference: ARG-3-029

4-(1-(2-Methoxypyrimidin-5-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-7H-pyrrolo[2,3-d]pyrimidine **134**



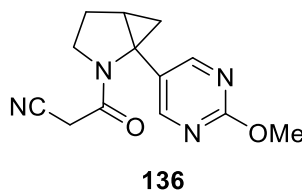
132

4 N HCl in dioxane (4 mL) was added to a stirred solution of arylated pyrrolidine **119** (55 mg, 0.19 mmol, 1 eq) in dioxane (0.5 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h and the solvent was evaporated under reduced pressure to give the crude HCl salt. The crude HCl salt was suspended in *t*-BuOH (1 mL) and H₂O (0.8 mL) and 4-chloro-7H-pyrrolo[2,3-d]pyrimidine **133** (31 mg, 0.20 mmol, 1.1 eq) and K₃PO₄ (242 mg, 1.14 mmol, 6.0 eq) were added under Ar. The resulting solution was stirred and heated at 75 °C for 18 h. After being allowed to cool to rt, 1 M HCl_(aq) (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc to 95:5 EtOAc-MeOH as eluent gave diarylated pyrrolidine **132** (23 mg, 40%) as a white semi-solid, *R*_F (95:5 EtOAc-MeOH) 0.32; IR (ATR) 3193 (NH), 2927, 1456, 1430, 1276, 1003, 726 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) δ 10.39 (s, 1H, NH), 8.39 (s, 2H, Ar), 8.28 (s, 1H, Ar), 6.97 (d, *J* = 3.5 Hz, 1H, Ar), 6.33 (d, *J* = 3.5 Hz, 1H, Ar), 4.39 (ddd, *J* = 11.0, 9.0, 7.0 Hz, 1H, NCH), 4.28–4.17 (m, 1H, NCH), 3.94 (s, 3H, OMe), 2.64–2.52 (m, 1H, CH), 2.16–2.06 (m, 1H, CH), 2.04 (dd, *J* = 9.0, 6.0 Hz, 1H, CH), 1.90 (ddd, *J* = 9.0, 7.0, 6.0 Hz, 1H, CH), 1.29 (ddd, *J* = 6.0, 6.0 Hz, 1H, CH); ¹³C NMR (100.6 MHz, Acetone-*d*₆) δ 157.1 (Ar), 151.1 (*ipso*-Ar), 143.9 (*ipso*-Ar), 129.1 (*ipso*-Ar), 120.9 (Ar), 120.1 (Ar), 108.1 (Ar), 101.5 (Ar), 54.8 (OMe), 54.0 (NCH₂), 53.2

(NCH), 47.7 (CAr), 42.0 (CH or CH₂), 30.5 (CH or CH₂), 27.9 (CH or CH₂); HRMS *m/z* calcd for C₁₆H₁₆N₆O (M + Na)⁺ 331.1283, found 331.1286 (−0.9 ppm error).

Lab book reference: ARG-3-042

3-(1-(2-Methoxypyrimidin-5-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-oxopropanenitrile
136

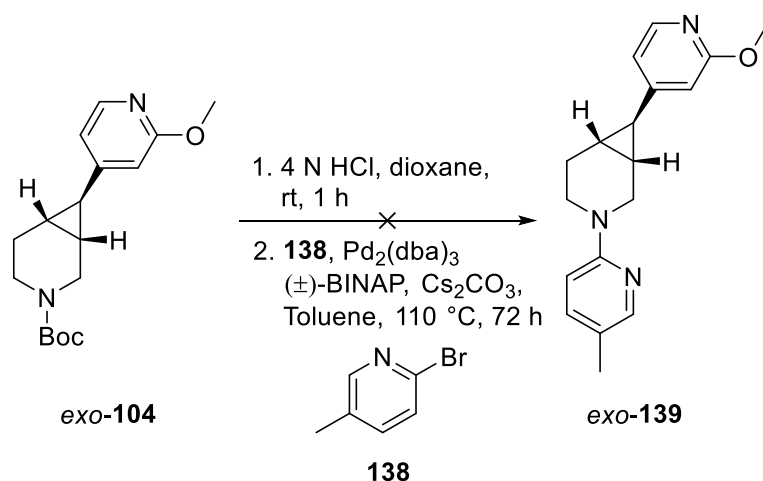


4 N HCl in dioxane (3 mL) was added to a stirred solution of arylated pyrrolidine **119** (51 mg, 0.18 mmol, 1 eq) in dioxane (0.5 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h and the solvent was evaporated under reduced pressure to give the crude HCl salt. The crude HCl salt was suspended in dioxane (1.7 mL) and 3-(3,5-dimethyl-1H-pyrazol-1-yl)-3-oxopropanenitrile **135** (72 mg, 0.44 mmol, 2.5 eq) and DIPEA (0.14 mL, 0.79 mmol, 4.5 eq) were added under Ar. The resulting solution was stirred and heated at 100 °C for 18 h. After being allowed to cool to rt, 1 M HCl_(aq) (10 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 EtOAc-hexane as eluent gave amide **136** (23 mg, 52%) as a pale-yellow semi-solid, *R_F* (4:1 EtOAc-hexane) 0.11; IR (ATR) 2937, 2258 (C≡N), 1661 (C=O), 1474, 1415, 1327, 1033, 801 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) (50:50 mixture of rotamers) δ 8.51–8.40 (m, 2H, Ar), 4.19–4.06 (m, 1H, NCH), 4.03–3.95 (m, 3.5H, OMe, NCH), 3.58–3.50 (m, 0.5H, NCH), 3.41 (s, 1H, C(O)CH), 3.34 (d, *J* = 18.0 Hz, 0.5H, C(O)CH), 3.13 (d, *J* = 18.0 Hz, 0.5H, C(O)CH), 2.61–2.51 (m, 0.5H, CH), 2.51–2.40 (m, 0.5H, CH), 2.20–2.07 (m, 1H, CH), 2.04–1.93 (m, 0.5H, CH), 1.88–1.81 (m, 0.5H, CH), 1.75–1.62 (m, 1H, CH), 1.26 (dd, *J* = 5.0, 5.0 Hz, 0.5H, CH), 1.14 (dd, *J* = 5.0, 5.0 Hz, 0.5H, CH); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 165.4 (*ipso*-Ar), 164.9 (*ipso*-Ar), 162.4 (C=O), 161.6 (C=O), 159.6 (Ar), 157.7 (Ar), 126.2 (*ipso*-Ar), 125.8 (*ipso*-Ar), 113.6 (C≡N), 113.5 (C≡N), 55.4 (OMe), 55.1 (OMe), 53.4 (NCH₂), 50.8 (NCH₂), 47.0 (NC), 45.7 (NC), 32.6 (CH), 27.1 (CH₂), 26.8

(C(O)CH₂), 26.7 (C(O)CH₂), 26.0 (CH), 25.5 (CH₂), 21.8 (CH₂); HRMS *m/z* calcd for C₁₃H₁₅N₄O₂ (M + Na)⁺ 281.1009, found 281.1003 (+2.3 ppm error).

Lab book reference: ARG-3-057

Attempted synthesis of 7-(2-methoxypyridin-4-yl)-3-(5-methylpyridin-2-yl)-3-azabicyclo[4.1.0]heptane *exo*-139



4 N HCl in dioxane (3 mL) was added to a stirred solution of arylated piperidine **exo-104** (117 mg, 0.39 mmol, 1 eq) in dioxane (1 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h and the solvent was evaporated under reduced pressure to give the crude HCl salt. The crude HCl salt was suspended in toluene (3 mL) and 2-bromo-5-methylpyridine **138** (72 mg, 0.42 mmol, 1.1 eq), Pd₂(dba)₃ (37 mg, 0.04 mmol, 0.1 eq), (±)-BINAP (37 mg, 0.06 mmol, 0.15 eq) and Cs₂CO₃ (319 mg, 0.98 mmol, 2.5 eq) were added under Ar and the resulting mixture was stirred and heated at 110 °C for 72 h. After being allowed to cool to rt, EtOAc (5 mL) and MeOH (5 mL) were added and the solids were removed by filtration through celite, eluting with EtOAc (25 mL). The filtrate was evaporated under reduced pressure to give the crude product which contained (by ¹H NMR spectroscopy and HRMS) no arylated piperidine **exo-139**.

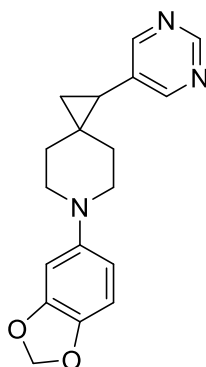
Lab book reference: ARG-3-030

4 N HCl in dioxane (3 mL) was added to a stirred solution of arylated piperidine **exo-104** (117 mg, 0.39 mmol, 1 eq) in dioxane (1 mL) at rt under Ar. The resulting mixture was

stirred at rt for 1 h and 1 M NaOH_(aq) (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude amine. The crude amine was dissolved in toluene (3 mL) and 2-bromo-5-methylpyridine **138** (72 mg, 0.42 mmol, 1.1 eq), Pd₂(dba)₃ (37 mg, 0.04 mmol, 0.1 eq), (±)-BINAP (37 mg, 0.06 mmol, 0.15 eq) and Cs₂CO₃ (319 mg, 0.98 mmol, 2.5 eq) were added under Ar and the resulting mixture was stirred and heated at 110 °C for 72 h. After being allowed to cool to rt, EtOAc (5 mL) and MeOH (5 mL) were added and the solids were removed by filtration through celite, eluting with EtOAc (25 mL). The filtrate was evaporated under reduced pressure to give the crude product which contained (by ¹H NMR spectroscopy and HRMS) no arylated piperidine *exo*-**139**.

Lab book reference: ARG-3-037

6-(Benzo[d][1,3]dioxol-5-yl)-1-(pyrimidin-5-yl)-6-azaspiro[2.5]octane **143**



143

4 N HCl in dioxane (4 mL) was added to a stirred solution of arylated piperidine **91** (115 mg, 0.40 mmol, 1 eq) in dioxane (1 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h and the solvent was evaporated under reduced pressure to give the crude HCl salt. The crude HCl salt was suspended in toluene (1.5 mL) and 3,4-methylenedioxybromobenzene (88 mg, 0.44 mmol, 1.1 eq), Pd₂(dba)₃ (37 mg, 0.04 mmol, 0.1 eq), (±)-BINAP (37 mg, 0.06 mmol, 0.15 eq) and NaOt-Bu (96 mg, 1.0 mmol, 2.5 eq) were added under Ar and the resulting mixture was stirred and heated at 110 °C for 48 h. After being allowed to cool to rt, EtOAc (5 mL) was added and the solids were removed by filtration through celite, eluting with EtOAc (25 mL). The filtrate was evaporated under

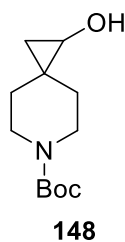
reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 hexane-EtOAc to 1:1 hexane-EtOAc as eluent gave aniline **143** (66 mg, 54%) as a clear oil, R_F (1:1 hexane-EtOAc) 0.20; IR (ATR) 2923, 1503, 1488, 1197, 1036, 729 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.05 (s, 1H, Ar), 8.59 (s, 2H, Ar), 6.69 (d, J = 8.5 Hz, 1H, Ar), 6.54 (d, J = 2.5 Hz, 1H, Ar), 6.35 (dd, J = 8.5, 2.5 Hz, 1H, Ar), 5.88 (s, 2H, OCH_2), 3.23–3.16 (m, 1H, NCH), 3.10 (ddd, J = 11.5, 8.0, 3.5 Hz, 1H, NCH), 2.90–2.86 (m, 2H, NCH), 1.93 (dd, J = 8.0, 6.0 Hz, 1H, CHAr), 1.84 (ddd, J = 12.5, 8.0, 3.5 Hz, 1H, CH), 1.64 (ddd, J = 13.5, 6.5, 3.5 Hz, 1H, CH), 1.45–1.37 (m, 1H, CH), 1.32–1.23 (m, 1H, CH), 1.06–0.99 (m, 2H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 157.2 (Ar), 156.6 (Ar), 148.2 (*ipso*-Ar), 147.9 (*ipso*-Ar), 141.7 (*ipso*-Ar), 132.9 (*ipso*-Ar), 110.0 (Ar), 108.2 (Ar), 101.0 (OCH_2), 100.9 (Ar), 51.4 (NCH_2), 50.9 (NCH_2), 36.7 (CH_2), 30.1 (CH_2), 25.5 (C), 23.5 (CHAr), 16.0 (CHCH_2); HRMS m/z calcd for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 310.1550, found 310.1555 (–1.8 ppm error).

Lab book reference: ARG-3-049

4 N HCl in dioxane (4 mL) was added to a stirred solution of arylated piperidine **91** (115 mg, 0.40 mmol, 1 eq) in dioxane (1 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h and 1 M $\text{NaOH}_{(\text{aq})}$ (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO_4) and evaporated under reduced pressure to give the crude amine. The crude amine was dissolved in toluene (1.5 mL) and 3,4-methylenedioxybromobenzene (88 mg, 0.44 mmol, 1.1 eq), $\text{Pd}_2(\text{dba})_3$ (37 mg, 0.04 mmol, 0.1 eq), ($\pm$)-BINAP (37 mg, 0.06 mmol, 0.15 eq) and NaOt-Bu (96 mg, 1.0 mmol, 2.5 eq) were added under Ar and the resulting mixture was stirred and heated at 110 $^\circ\text{C}$ for 48 h. After being allowed to cool to rt, EtOAc (5 mL) was added and the solids were removed by filtration through celite, eluting with EtOAc (25 mL). The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 hexane-EtOAc to 1:1 hexane-EtOAc as eluent gave aniline **143** (44 mg, 36%) as a clear oil. The spectroscopic data obtained were identical to those reported above.

Lab book reference: ARG-3-043

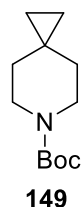
tert*-Butyl 1-hydroxy-6-azaspiro[2.5]octane-6-carboxylate **148*



NaBO₃·4H₂O (385 mg, 2.5 mmol, 5 eq) was added to a stirred solution of pinacol boronate **77** (169 mg, 0.50 mmol, 1 eq) in THF (10 mL) and H₂O (10 mL) at rt and the resulting mixture was stirred at rt for 2 h. H₂O (5 mL) and EtOAc (15 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 to 1:1 hexane-EtOAc as eluent gave alcohol **148** (98 mg, 87%) as a clear oil, *R*_F (7:3 hexane-EtOAc) 0.40; IR (ATR) 3417 (OH), 2975, 1666 (C=O), 1421, 1365, 1241, 1161, 966, 861, 769 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.46–3.32 (m, 4H, NCH), 3.28 (dd, *J* = 6.5, 3.0 Hz, 1H, CHOH), 1.67–1.58 (m, 1H, CH), 1.55–1.49 (m, 1H, CH), 1.43 (s, 9H, CMe₃), 1.28–1.13 (m, 2H, CH), 0.57–0.48 (m, 1H, CH), 0.38–0.33 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.2 (C=O), 79.6 (OCMe₃), 55.7 (OCH), 43.6 (br, NCH₂), 34.0 (br, CH₂), 28.6 (CMe₃), 23.2 (C), 19.5 (CHCH₂); HRMS *m/z* calcd for C₁₂H₂₁NO₃ (M + Na)⁺ 250.1414, found 250.1418 (–1.7 ppm error).

Lab book reference: ARG-3-052

tert*-butyl 6-azaspiro[2.5]octane-6-carboxylate **149*

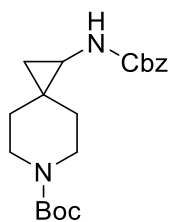


KOt-Bu (224 mg, 2 mmol, 4.0 eq) was added to a stirred suspension of pinacol boronate **77** (169 mg, 0.5 mmol, 1.0 eq) and MeONH₃Cl (125 mg, 1.5 mmol, 3.0 eq) in THF (3 mL). The resulting suspension was heated and stirred at 60 °C for 18 h under Ar. After being allowed to cool to rt, H₂O (15 mL) and EtOAc (15 mL) were added and the two layers were separated.

The aqueous layer was extracted with EtOAc (3×15 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO_4) and evaporated under reduced pressure to give the crude product which contained (by ^1H NMR spectroscopy) only protodeborylated cyclopropane **149**. Spectroscopic data consistent with those reported in the literature.³⁸⁴

Lab book reference: ARG-3-054

tert*-Butyl 1-(((benzyloxy)carbonyl)amino)-6-azaspiro[2.5]octane-6-carboxylate **151*



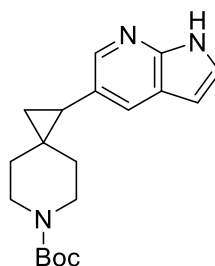
151

NaOH (3.6 g, 0.18 mol) was added to a stirred suspension of MeONH_3Cl (7.5 g, 0.18 mol) in THF (15 mL) and H_2O (0.1 mL) at rt under Ar. The resulting suspension was stirred vigorously at rt for 24 h. The supernatant was removed by syringe and added to a separate flask. CaSO_4 (10 g) was added and the mixture was stirred at rt for 48 h. The supernatant was removed by syringe and added to a separate flask. The residual solid was washed with THF (10 mL). The supernatant was removed by syringe and added to the separate flask. This gave a solution of anhydrous MeONH_2 in THF and the concentration was determined to be 0.8 M by ^1H NMR spectroscopy using toluene as an internal standard. *n*-BuLi (0.75 mL of a 2 M solution in hexane, 1.5 mmol, 3.0 eq) was added dropwise to a stirred solution of anhydrous MeONH_2 (1.87 mL of a 0.8 M solution in THF, 1.5 mmol, 3.0 eq) in THF (3.1 mL) at -78°C under Ar. The resulting solution was stirred at -78°C for 10 min and added dropwise to a stirred solution of pinacol boronate **77** (169 mg, 0.5 mmol, 1.0 eq) in THF (1.2 mL) at -78°C under Ar. The resulting solution was stirred at -78°C for 1 h and then allowed to warm to rt. Then, the solution was heated and stirred at 60°C for 16 h under Ar. After being allowed to cool to rt, H_2O (15 mL) and EtOAc (15 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3×15 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO_4) and evaporated under reduced pressure to give the crude amine. The crude amine was dissolved in CH_2Cl_2 (3 mL) and Et_3N (0.17 mL, 1.25 mmol, 2.5 eq) was added. The resulting mixture was cooled to 0

°C and CbzCl (0.34 mL, 1.00 mmol, 2.0 eq) was added dropwise. The mixture was allowed to warm to rt and was stirred at rt for 16 h. H₂O (15 mL) and CH₂Cl₂ (15 mL) were added and the two layers were separated. The organic layer was washed with 1 M HCl_(aq) (15 mL) and brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 to 1:1 hexane-EtOAc as eluent gave bis-carbamate **149** (120 mg, 66%) as a clear gum, *R*_F (4:1 hexane-EtOAc) 0.14; IR (ATR) 3318 (NH), 2929, 1690 (C=O), 1669 (C=O), 1423, 1239, 1166, 966, 736 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.31 (m, 5H, Ar), 5.21–5.05 (m, 2H, NCH₂Ar), 4.92–4.74 (m, 1H, NH), 3.60–3.13 (m, 4H, NCH), 2.59–2.38 (m, 1H, NCH), 1.48–1.43 (m, 11H, CMe₃, CH), 1.39–1.28 (m, 2H, CH), 0.86–0.71 (m, 1H, CH), 0.47–0.32 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 157.4 (C=O), 155.0 (C=O), 137.9 (*ipso*-Ar), 128.6 (Ar), 128.3 (Ar), 128.3 (Ar), 82.5 (OCMe₃), 68.0 (OCH₂Ar), 42.4 (br, NCH₂), 34.2 (NCH), 29.2 (CH₂), 28.6 (CMe₃), 23.6 (C), 18.0 (CHCH₂); HRMS *m/z* calcd for C₂₀H₂₈N₂O₄ (M + Na)⁺ 383.1941, found 383.1951 (–2.4 ppm error).

Lab book reference: ARG-3-061

tert*-Butyl 1-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-6-azaspiro[2.5]octane-6-carboxylate **162*



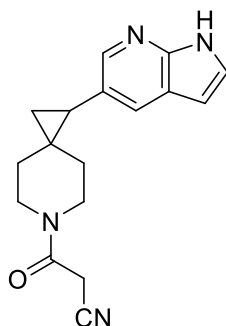
162

Cs₂CO₃ (568 mg, 1.75 mmol, 3.0 eq) was added to a stirred solution of arylated piperidine **96** (281 mg, 0.58 mmol, 1.0 eq) and pyrrolidine (0.14 mL, 1.75 mmol, 3.0 eq) in THF (5.8 mL) and MeOH (1.9 mL) and the resulting mixture was stirred at rt for 16 h. H₂O (15 mL) and EtOAc (15 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 2:3 hexane-EtOAc as eluent gave *N'*-H arylated piperidine **162** (137 mg, 73%) as a clear oil, *R*_F (2:3 hexane-EtOAc) 0.20;

^1H NMR (400 MHz, CDCl_3) δ 11.55 (s, 1H, NH), 8.26 (s, 1H, Ar), 7.73 (d, $J = 2.5$ Hz, 1H, Ar), 7.38 (dd, $J = 3.5, 2.5$ Hz, 1H, Ar), 6.44 (d, $J = 3.5$ Hz, 1H, Ar), 3.68–3.60 (m, 1H, NCH), 3.52–3.43 (m, 1H, NCH), 3.34–3.27 (m, 1H, NCH), 3.22–3.10 (m, 1H, NCH), 2.10 (dd, $J = 8.5, 5.5$ Hz, 1H, CHAr), 1.63 (ddd, $J = 12.5, 7.5, 4.0$ Hz, 1H, CH), 1.52–1.40 (m, 10H, CH, CMe_3), 1.27–1.20 (m, 1H, CH), 1.15–1.06 (m, 1H, CH), 0.99 (dd, $J = 5.5, 5.0$ Hz, 1H, CH), 0.91 (dd, $J = 8.5, 5.0$ Hz, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 155.1 (C=O), 147.8 (*ipso*-Ar), 144.0 (Ar), 128.8 (Ar), 126.0 (*ipso*-Ar), 125.8 (Ar), 120.2 (*ipso*-Ar), 100.2 (Ar), 79.4 (CMe_3), 43.5 (br, NCH_2), 36.7 (CH_2), 30.2 (CH_2), 28.5 (CMe_3), 26.3 (CHAr), 24.5 (C), 15.8 (CH_2CH); HRMS m/z calcd for $\text{C}_{19}\text{H}_{25}\text{N}_3\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 327.1947, found 327.1948 (–0.3 ppm error).

Lab book reference: ARG-3-103

3-(1-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-6-azaspiro[2.5]octan-6-yl)-3-oxopropanenitrile 164



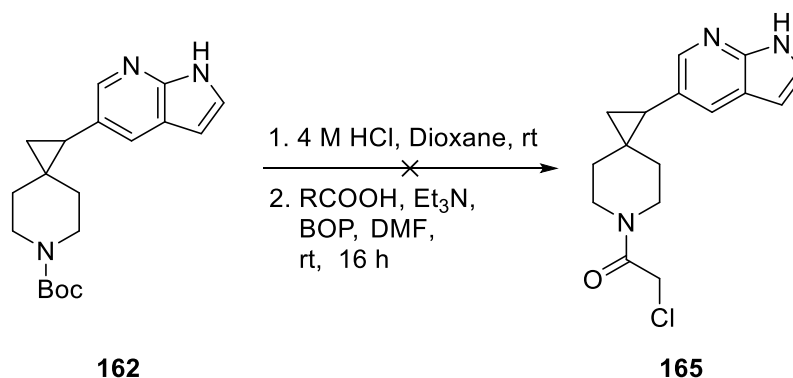
164

4 N HCl in dioxane (4 mL) was added to a stirred solution of arylated piperidine **162** (76 mg, 0.23 mmol, 1.0 eq) in dioxane L) at rt under Ar. The resulting mixture was stirred at rt for 1 h and the solvent was evaporated under reduced pressure to give the crude HCl salt. The crude HCl salt was dissolved in DMF (4.6 mL) and cyanoacetic acid (25 mg, 0.26 mmol, 1.1 eq) and Et_3N (0.13 mL, 0.92 mmol, 4.0 eq) were added under Ar. The resulting solution was cooled to 0 °C and BOP (150 mg, 0.34 mmol, 1.5 eq) was added and the solution was stirred at rt for 18 h. 1 M $\text{HCl}_{(\text{aq})}$ (15 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine (6×15 mL), dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 CH_2Cl_2 -acetone as eluent gave amide **164** (58 mg, 77%) as a white solid, mp 210–212 °C;

R_F (6:4 CH_2Cl_2 -acetone) 0.34; IR (ATR) 3212 (NH), 2921, 2258 (CN), 1650 (C=O), 1453, 740 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) (55:45 mixture of rotamers) δ 11.37 (s, 0.55H, NH), 11.32 (s, 0.45H NH), 8.24–8.10 (m, 1H, Ar), 7.73–7.60 (m, 1H, Ar), 7.43–7.29 (m, 1H, Ar), 6.48–6.18 (m, 1H, Ar), 3.74 (ddd, $J = 13.0, 7.0, 4.0$ Hz, 0.55H, NCH), 3.62–3.37 (m, 2.9H, NCH, CNCH), 3.36–3.33 (m, 1H, CNCH), 3.25 (ddd, $J = 12.5, 8.0, 4.0$ Hz, 0.54H, NCH), 3.17 – 3.02 (m, 1H, NCH), 2.07 (dd, $J = 8.0, 6.0$ Hz, 1H, CH), 1.69 (ddd, $J = 12.0, 8.0, 3.5$ Hz, 0.45H, CH), 1.62–1.41 (m, 1.55H, CH), 1.27–1.01 (m, 2H, CH), 0.96 (dd, $J = 6.0, 5.5$ Hz, 1H, CH), 0.92–0.85 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl_3) (rotamers) δ 160.2 (C=O), 160.1 (C=O), 147.8 (*ipso*-Ar), 143.85 (Ar), 143.81 (Ar), 137.9 (Ar), 129.1 (Ar), 128.8 (Ar), 128.7 (Ar), 128.3 (Ar), 126.0 (Ar), 125.9 (Ar), 125.5 (*ipso*-Ar), 125.3 (Ar), 120.2 (*ipso*-Ar), 114.3 (CN), 114.2 (CN), 100.3 (Ar), 46.6 (NCH_2), 46.1 (NCH_2), 42.8 (NCH_2), 42.3 (NCH_2), 36.8 (CH_2), 35.9 (CH_2), 30.5 (CH_2), 29.6 (CH_2), 26.3 (CHAr), 26.2 (CHAr), 25.2 (CNCH_2), 25.1 (CNCH_2), 24.1 (C), 24.0 (C), 15.8 (CH_2), 15.7 (CH_2); HRMS m/z calcd for $\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}$ ($\text{M} + \text{Na}$) $^+$ 317.1373, found 317.1770 (+0.8 ppm error).

Lab book reference ARG-3-112

Attempted synthesis of 1-(1-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-6-azaspiro[2.5]octan-6-yl)-2-chloroethan-1-one **165**

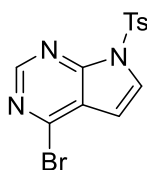


4 N HCl in dioxane (4 mL) was added to a stirred solution of arylated piperidine **162** (65 mg, 0.20 mmol, 1.0 eq) in dioxane (1 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h and the solvent was evaporated under reduced pressure to give the crude HCl salt. The crude HCl salt was dissolved in DMF (4.5 mL) and chloroacetic acid (21 mg, 0.22 mmol, 1.1 eq) and Et_3N (0.10 mL, 0.80 mmol, 4.0 eq) were added under Ar. The resulting solution was cooled to 0 °C and BOP (133 mg, 0.30 mmol, 1.5 eq) was added and the solution was stirred at rt for 18 h. 1 M $\text{HCl}_{(\text{aq})}$ (15 mL) was added and the two layers were separated.

The aqueous layer was extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine (6×15 mL), dried (MgSO_4) and evaporated under reduced pressure to give the crude product which contained (by ^1H NMR spectroscopy and HRMS) no chloramide **165**.

Lab book reference ARG-3-113

4-Bromo-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidine **167**

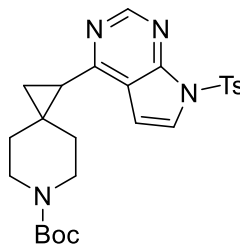


167

A solution of 4-bromo-7H-pyrrolo[2,3-d]pyrimidine **166** (1.0 g, 5.05 mmol, 1.0 eq) in THF (20 mL) was added dropwise to a stirred mixture of NaH (60% dispersion in paraffin liquid) (263 mg, 6.57 mmol, 1.3 eq) in THF (10 mL) at 0 °C under Ar. Then, a solution of TsCl (1.25 g, 6.57 mmol, 1.3 eq) in THF (20 mL) was added dropwise to the stirred mixture at 0 °C under Ar. The reaction was warmed to rt and stirred for 16 h. H_2O (30 mL) was added, and the product was extracted with EtOAc (3×50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 70:30 to 50:50 hexane–EtOAc as eluent gave 4-bromo-tosyl-pyrrolopyrimidine **167** (1.41 g, 79%) as a white solid, mp 148–151 °C, R_F (1:1 EtOAc–hexane) 0.60; IR (ATR) 1595, 1578, 1541, 1508, 1429, 1373, 1349, 1190, 1175, 1152, 1100, 1188, 1008, 905, 830, 813, 728, 702, 682, 658, 627, 534, 516 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.70 (s, 1H, Ar), 8.11–8.03 (m, 2H, Ts–Ar), 7.78 (d, $J = 4.0$ Hz, 1H, Ar), 7.35–7.28 (m, 2H, Ts–Ar), 6.63 (d, $J = 4.0$ Hz, 1H, Ar), 2.39 (s, 3H, Me); ^{13}C NMR (100.6 MHz, CDCl_3) 152.5 (Ar), 149.9 (*ipso*–Ar), 146.5 (*ipso*–Ar), 145.0 (*ipso*–Ar), 134.4 (*ipso*–Ar), 130.1 (Ts–Ar), 128.7 (Ts–Ar), 128.2 (Ar), 123.1 (*ipso*–Ar), 104.4 (Ar), 21.8 (Me); HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{10}\text{BrN}_3\text{O}_2\text{S}$ ($\text{M} + \text{Na}$) $^+$ 373.9569, found 373.9575 (–1.6 ppm error).

Lab Book Reference: ARG-3-085

tert*-Butyl 1-[7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-6-azaspiro[2.5]octane-6-carboxylate **168*



168

Using general procedure A, MIDA boronate **65** (366 mg, 1.0 mmol, 1.0 eq), Cs₂CO₃ (1.95 g, 6.0 mmol, 6.0 eq), 4-bromo-*N*-tosyl-diazaindole **167** (456 mg, 1.3 mmol, 1.3 eq), Pd(OAc)₂ (34 mg, 0.15 mmol, 0.15 eq) and PCy₃ (84 mg, 0.3 mmol, 0.30 eq) in toluene (20 mL) and H₂O (2 mL) gave the crude product. Purification by flash column chromatography on silica with 7:3 hexane-EtOAc as eluent gave arylated piperidine **168** (338 mg, 70%) as a white solid, mp 94–96 °C; *R*_F (7:3 hexane-EtOAc) 0.24; IR (ATR) 2926, 1686 (C=O), 1572, 1176, 1130, 680, 579 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.76 (s, 1H, Ar), 8.03 (d, *J* = 8.5 Hz, 2H, Ar), 7.62 (d, *J* = 4.0 Hz, 1H, Ar), 7.25 (d, *J* = 8.5 Hz, 2H, Ar), 6.66 (d, *J* = 4.0 Hz, 1H, Ar), 3.55–3.44 (m, 1H, NCH), 3.38 (ddd, *J* = 12.5, 7.0, 4.0 Hz, 1H, NCH), 3.19 (ddd, *J* = 13.0, 7.0, 4.0 Hz, 1H, NCH), 2.81 (ddd, *J* = 13.0, 8.0, 3.5 Hz, 1H, NCH), 2.33 (s, 3H, Me), 2.16 (dd, *J* = 8.0, 5.5 Hz, 1H, CHAr), 1.72 (dd, *J* = 5.5, 4.5 Hz, 1H, CH), 1.60–1.46 (m, 3H, CH), 1.41–1.30 (m, 10H, CMe₃, CH), 1.04 (dd, *J* = 8.0, 4.5 Hz, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.0 (C=O), 152.6 (Ar), 150.2 (*ipso*-Ar), 145.9 (*ipso*-Ar), 135.0 (*ipso*-Ar), 130.0 (Ar), 128.3 (Ar), 125.8 (Ar), 120.6 (*ipso*-Ar), 103.0 (Ar), 79.5 (CMe₃), 37.15 (NCH₂, only resolved in DEPT-135), 34.8 (CH₂), 31.0 (C), 28.5 (CMe₃), 28.0 (CH₂), 27.2 (CHAr), 21.8 (Me), 19.1 (CHCH₂) (1 x *ipso*-Ar resonance not resolved); HRMS (ESI) *m/z* calcd for C₂₅H₃₀N₄O₄S (M + Na)⁺ 505.1880, found 505.1889 (–1.9 ppm error).

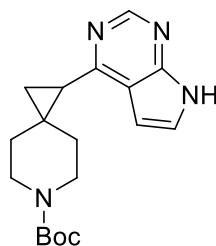
Lab book reference: ARG-3-121

Using general procedure B, MIDA boronate **65** (92 mg, 0.25 mmol, 1.0 eq), Cs₂CO₃ (244 mg, 0.75 mmol, 6.0 eq), 4-bromo-*N*-tosyl-diazaindole **167** (105 mg, 0.3 mmol, 1.2 eq), Pd(OAc)₂ (3 mg, 0.01 mmol, 0.05 eq) and PCy₃ (7 mg, 0.02 mmol, 0.1 eq) in toluene (5 mL) and H₂O (0.5 mL) gave the crude product. Purification by flash column chromatography on

silica with 7:3 hexane-EtOAc as eluent gave arylated piperidine **168** (62 mg, 52%) as a white solid. Spectroscopic data identical to those reported above.

Lab book reference: ARG-3-088

tert-Butyl 1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-6-azaspiro[2.5]octane-6-carboxylate
169

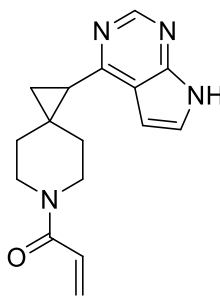


169

Cs₂CO₃ (470 mg, 1.44 mmol, 3.0 eq) was added to a stirred solution of arylated piperidine **168** (231 mg, 0.48 mmol, 1.0 eq) and pyrrolidine (0.16 mL, 1.91 mmol, 4.0 eq) in THF (5 mL) and MeOH (1.6 mL) and the resulting mixture was stirred at rt for 16 h. H₂O (15 mL) and EtOAc (15 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with 1 M HCl_(aq) (15 mL) and brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 2:3 hexane-EtOAc as eluent gave *N'*-H arylated piperidine **169** (121 mg, 77%) as a white solid, mp 156–158 °C; *R*_F (3:2 hexane-EtOAc) 0.11; IR (ATR) 3135 (NH), 2928, 1678, 1597 (C=O), 1423, 1239, 731 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 11.56 (s, 1H, NH), 8.75 (s, 1H, Ar), 7.34 (dd, *J* = 3.5, 2.0 Hz, 1H, Ar), 6.70–6.55 (m, 1H, Ar), 3.68–3.58 (m, 1H, NCH), 3.46 (ddd, *J* = 12.5, 8.0, 4.0 Hz, 1H, NCH), 3.30 (ddd, *J* = 13.0, 6.5, 4.0 Hz, 1H, NCH), 2.91–2.77 (m, 1H, NCH), 2.37 (dd, *J* = 8.0, 5.5 Hz, 1H, CHAr), 1.83 (dd, *J* = 5.5, 4.5 Hz, 1H, CH), 1.73 – 1.31 (m, 13H, CH, CMe₃), 1.10 (dd, *J* = 8.0, 4.5 Hz, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 161.0 (*ipso*-Ar), 155.0 (C=O), 150.8 (*ipso*-Ar), 150.5 (Ar), 124.9 (Ar), 118.9 (*ipso*-Ar), 99.8 (Ar), 79.5 (CMe₃), 43.6 (br, NCH₂), 37.2 (CH₂), 30.0 (C), 28.5 (CMe₃), 28.3 (CH₂), 27.5 (CHAr), 18.3 (CH₂); HRMS *m/z* calcd for C₁₈H₂₄N₄O₂ (M + H)⁺ 329.1972, found 329.1971 (+0.3 ppm error).

Lab book reference: ARG-3-125

1-(1-(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)-6-azaspiro[2.5]octan-6-yl)prop-2-en-1-one 152

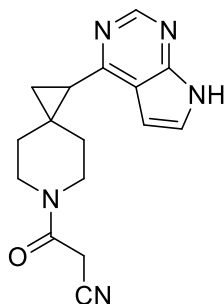


152

4 N HCl in dioxane (5 mL) was added to a stirred solution of arylated piperidine **169** (101 mg, 0.31 mmol, 1.0 eq) in dioxane (1 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h and the solvent was evaporated under reduced pressure to give the crude HCl salt. The crude HCl salt was suspended in DMF (2 mL) and Et₃N (0.21 mL, 1.55 mmol, 5.0 eq) were added under Ar. The resulting solution was cooled to 0 °C and acryloyl chloride (28 μ L, 0.33 mmol, 1.1 eq) was added and the solution was stirred at rt for 4 h. 1 M HCl_(aq) (15 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 $\times$ 15 mL). The combined organic extracts were washed with brine (6 $\times$ 15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 6:4 CH₂Cl₂-acetone as eluent gave acrylamide **152** (36 mg, 42%) as a white solid, mp 164–166 °C; *R*_F (6:4 CH₂Cl₂-acetone) 0.2; IR (ATR) 3134 (NH), 2852, 1563 (C=O), 1444, 722 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (60:40 mixture of rotamers) δ 11.89–11.58 (m, 1H, NH), 9.10–8.55 (m, 1H, Ar), 7.37–7.31 (m, 1H, Ar), 6.70–6.38 (m, 2H, =CHH'), 6.28–6.13 (m, 1H, =CHH'), 5.71–5.50 (m, 1H, =CH), 3.97–3.88 (m, 0.6H, NCH), 3.76–3.53 (m, 1.8H, NCH), 3.45–3.34 (m, 0.6H, NCH), 3.15–3.08 (m, 0.4H, NCH), 3.05–2.96 (m, 0.6H, NCH), 2.46–2.37 (m, 1H, CHAr), 1.88–1.83 (m, 1H, CH), 1.76–1.50 (m, 4H, CH), 1.17–1.10 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 211.0 (C=O), 165.7 (*ipso*-Ar), 160.5 (*ipso*-Ar), 160.3 (*ipso*-Ar), 150.8 (*ipso*-Ar), 150.4 (Ar), 127.9 (=CH), 127.5(=CH₂), 125.2 (Ar), 118.9 (*ipso*-Ar), 99.6 (Ar), 99.4 (Ar), 45.9 (NCH₂), 42.3 (NCH₂), 42.1 (NCH₂), 37.9 (CH₂), 36.8 (CH₂) 29.8 (C), 29.6 (C), 29.1 (CH₂), 28.0 (CH₂), 27.5 (CHAr), 18.4 (CHCH₂), 18.2 (CHCH₂); HRMS *m/z* calcd for C₁₆H₁₈N₄O (M + H)⁺ 283.1553, found 283.1557 (–1.2 ppm error).

Lab book reference ARG-3-120

3-Oxo-3-(1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-6-azaspiro[2.5]octan-6-yl)propanenitrile 154

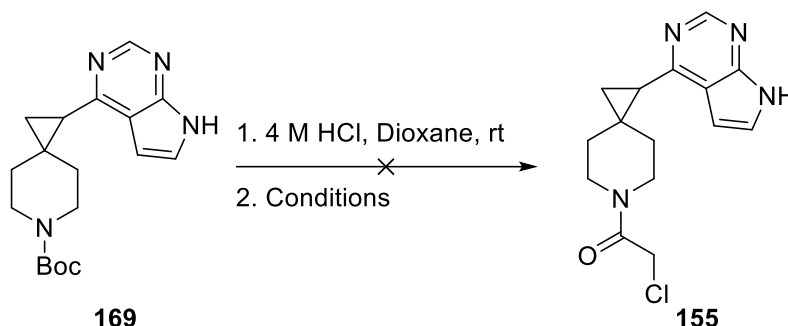


154

4 N HCl in dioxane (4 mL) was added to a stirred solution of arylated piperidine **169** (80 mg, 0.24 mmol, 1.0 eq) in dioxane (1 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h and the solvent was evaporated under reduced pressure to give the crude HCl salt. The crude HCl salt was dissolved in DMF (4.8 mL) and cyanoacetic acid (23 mg, 0.27 mmol, 1.1 eq) and Et₃N (0.13 mL, 0.96 mmol, 4.0 eq) were added under Ar. The resulting solution was cooled to 0 °C and BOP (150 mg, 0.34 mmol, 1.5 eq) was added and the solution was stirred at rt for 18 h. 1 M HCl_(aq) (15 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (6 × 15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 6:4 CH₂Cl₂-acetone as eluent gave amide **154** (46 mg, 66%) as a white solid, mp 210–212 °C; *R*_F (6:4 CH₂Cl₂-acetone) 0.20; IR (ATR) 3229 (NH), 2854, 2270 (CN), 1652 (C=O), 1454, 744 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) (60:40 mixture of rotamers) δ 11.97 (s, 1H, NH), 8.55 (s, 1H, Ar), 7.48–7.32 (m, 1H, Ar), 7.06–6.68 (m, 1H, Ar), 4.13–3.66 (m, 2.6H, CHCN, NCH), 3.51–3.37 (m, 1.8H, NCH), 3.18–2.97 (m, 0.6H, NCH), 2.80–2.32 (m, 2H, NCH, CHAr), 1.92–1.29 (m, 5H, CH), 1.06 (dd, *J* = 8.0, 4.0 Hz, 1H, CH); ¹³C NMR (100.6 MHz, DMSO-*d*₆) (rotamers) δ 161.78 (*ipso*-Ar), 159.8 (C=O), 150.9 (*ipso*-Ar), 150.8 (Ar), 150.7 (Ar), 126.4 (Ar), 122.6 (*ipso*-Ar), 118.5 (*ipso*-Ar), 116.8 (CN), 116.7 (CN), 99.5 (Ar), 46.2 (NCH₂), 45.9 (NCH₂), 42.4 (NCH₂), 42.1 (NCH₂), 36.9 (CH₂), 36.3 (CH₂), 29.6 (C), 28.6 (CH₂), 27.9 (CH₂), 26.7 (CHAr), 25.4 (CNCH₂), 25.3 (CNCH₂), 18.4 (CH₂), 18.3 (CH₂); HRMS *m/z* calcd for C₁₆H₁₇N₅O (M + H)⁺ 296.1506, found 296.0506 (–0.1 ppm error).

Lab book reference ARG-3-135

Attempted synthesis of 1-(1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-6-azaspiro[2.5]octan-6-yl)-2-chloroethan-1-one **155**



4 N HCl in dioxane (4 mL) was added to a stirred solution of arylated piperidine **169** (80 mg, 0.24 mmol, 1.0 eq) in dioxane (1 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h and the solvent was evaporated under reduced pressure to give the crude HCl salt. The crude HCl salt was dissolved in DMF (4.8 mL) and chloroacetic acid (23 mg, 0.27 mmol, 1.1 eq) and Et₃N (0.13 mL, 0.96 mmol, 4.0 eq) were added under Ar. The resulting solution was cooled to 0 °C and BOP (150 mg, 0.34 mmol, 1.5 eq) was added and the solution was stirred at rt for 18 h. 1 M HCl_(aq) (15 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (6 × 15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained (by ¹H NMR spectroscopy and HRMS) no chloramide **155**.

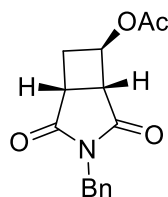
Lab book reference ARG-3-135

4 N HCl in dioxane (4 mL) was added to a stirred solution of arylated piperidine **169** (80 mg, 0.24 mmol, 1.0 eq) in dioxane (1 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h and the solvent was evaporated under reduced pressure to give the crude HCl salt. The crude HCl salt was dissolved in DMF (4.8 mL) and chloroacetic acid (23 mg, 0.27 mmol, 1.1 eq) and Et₃N (0.13 mL, 0.96 mmol, 4.0 eq) were added under Ar. The resulting solution was cooled to 0 °C and EDCI (53 mg, 0.34 mmol, 1.5 eq) and HOBT (46 mg, 0.34 mmol, 1.5 eq) were added and the solution was stirred at rt for 18 h. 1 M HCl_(aq) (15 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (6 × 15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained (by ¹H NMR spectroscopy and HRMS) no chloramide **155**.

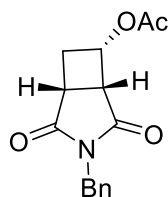
Lab book reference ARG-3-146

5.4 Experimental Procedures for Chapter 3

3-Benzyl-2,4-dioxo-3-azabicyclo[3.2.0]heptan-6-yl acetate *endo*-**218** and *exo*-**218**



exo-**218**



endo-**218**

Vinyl acetate (1.97 mL, 21.4 mmol, 1.0 eq) was added to a stirred solution of N-benzylmaleimide (4.0 g, 21.4 mmol, 1.0 eq) and benzophenone (389 mg, 2.1 mmol, 0.1 eq) in MeCN (430 mL), degassed by sparging with Ar for 30 min, at rt under Ar. The resulting mixture was stirred at rt and irradiated with a 365 nm LED lamp for 72 h under Ar and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 hexane-EtOAc as eluent gave imide *exo*-**218** (1.23 g, 21%) as a white solid, mp 74–76 °C (lit.,²⁴⁸ 79–80 °C); R_F (4:1 hexane-EtOAc) 0.17; IR (ATR) 1743 (C=O, ester), 1702 (C=O, imide), 1391, 1230, 1164 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.40–7.35 (m, 2H, Ar), 7.34–7.26 (m, 3H, Ar), 5.01–4.95 (m, 1H, OCH), 4.67 (s, 2H, CH_2Ar), 3.43 (dddd, $J = 7.5, 3.0, 1.0, 1.0$ Hz, 1H, C(O)CH), 3.31 (dddd, $J = 10.5, 7.5, 5.0, 0.5$ Hz, 1H, C(O)CH), 2.68–2.52 (m, 2H, CH), 2.08 (s, 3H, Me); ^{13}C NMR (100.6 MHz, CDCl_3) δ 178.1 (C=O, imide), 175.2 (C=O, imide), 169.8 (C=O, ester), 135.7 (*ipso*-Ar), 128.9 (Ar), 128.8 (Ar), 128.2 (Ar), 69.8 (OCH), 47.1 (CH), 42.8 (CH_2Ar), 34.5 (CH), 32.0 (CH_2), 20.9 (CH_3); HRMS m/z calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_4$ ($M + \text{Na}$)⁺ 296.0893, found 296.0898 (–1.6 ppm error), a 30:70 mixture (by ^1H NMR spectroscopy) of imides *exo*-**218** and *endo*-**218** (1.66 g, 28%) as a semi-solid and imide *endo*-**218** (2.6 g, 45%) as a white solid, mp 64–66 °C (lit.,²⁴⁸ 66–67 °C); IR (ATR) 1744 (C=O, ester), 1701 (C=O, imide), 1392, 1226, 1165 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.43–7.38 (m, 2H, Ar), 7.34–7.27 (m, 3H, Ar), 5.40–5.33 (m, 1H, OCH), 4.71 (s, 2H, CH_2Ar), 3.72–3.64 (m, 1H, C(O)CH), 3.15–2.97 (m, 2H, C(O)CH, CH), 2.23–2.16 (m, 1H, CH), 1.91 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ 178.4 (C=O, imide), 173.9 (C=O, imide), 169.7 (C=O, ester), 135.8 (*ipso*-Ar), 128.7 (Ar), 128.1 (Ar), 64.6 (OCH), 44.8 (CH), 42.7 (CH_2Ar), 33.4 (CH), 31.9 (CH_2), 20.6 (CH_3) (1 $\times$ Ar resonance not resolved); HRMS m/z calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_4$ ($M + \text{Na}$)⁺ 296.0893, found 296.0893 (+0.1 ppm error). Spectroscopic data consistent with those reported in the literature.²⁴⁸

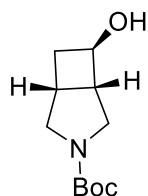
Note: Our work confirms that imides *exo*- and *endo*-**218** in Grygorenko's work are assigned the wrong way around.

Lab book reference: ARG-3-158

Vinyl acetate (14 mL, 100 mmol, 1.0 eq) was added to a stirred solution of N-benzylmaleimide (18.7 g, 100 mmol, 1.0 eq) and benzophenone (1.87 g, 10 mmol, 0.1 eq) in MeCN (2.0 L), degassed by sparging with Ar for 30 min, at rt under Ar. The resulting mixture was stirred at rt and irradiated with a 365 nm LED lamp for 72 h under Ar and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 hexane-EtOAc as eluent gave a 75:25 mixture of imides **218** (25.7 g, 94%) as a white solid semi-solid identical by (¹H NMR spectroscopy) to that described above.

Lab book reference: ARG-4-021

***tert*-Butyl 6-hydroxy-3-azabicyclo[3.2.0]heptane-3-carboxylate *exo*-170**



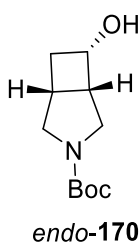
***exo*-170**

A solution of imide *exo*-**218** (1.41 g, 5.2 mmol, 1.0 eq) in THF (40 mL) was added to a stirred suspension of LiAlH₄ (587 mg, 15.5 mmol, 3.0 eq) in THF (15 mL) at 0 °C under Ar. The resulting mixture was stirred and heated at reflux for 16 h. The mixture was cooled to 0 °C and Et₂O (30 mL) was added followed by dropwise addition of H₂O (0.6 mL), 20% NaOH_(aq) (1.2 mL) and H₂O (0.6 mL) at 0 °C. The resulting mixture was stirred at rt for 1 h and MgSO₄ (5 g) was added. After stirring at rt for 30 min, the solids were removed by filtration through Celite[®] eluting with EtOAc (50 mL) and the filtrate evaporated under reduced pressure to give the crude *N*-Bn pyrrolidine. The crude *N*-Bn pyrrolidine was dissolved in MeOH (30 mL) and 20% Pd(OH)₂/C 50% wet (435 mg, 0.30 mmol, 0.06 eq) was added. The resulting suspension was evacuated and back-filled with Ar three times and

then with H₂ three times. The mixture was stirred under a balloon of H₂ (760 mmHg) at rt for 16 h. The solids were removed by filtration through Celite[®] eluting with MeOH (30 mL) and the filtrate evaporated under reduced pressure to give the crude *N*-H pyrrolidine. The crude *N*-H pyrrolidine was dissolved in THF (30 mL) and Boc₂O (1.65 g, 7.6 mmol, 1.46 eq) was added and the resulting mixture was stirred for 16 h at rt under Ar. EtOAc (30 mL) and H₂O (30 mL) were added and the layers separated. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (25 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:2 hexane-EtOAc as eluent gave *N*-Boc pyrrolidine *exo*-**170** (730 mg, 65%) as a colourless oil, *R*_F (3:2 hexane-EtOAc) 0.22; IR (ATR) 3406 (OH), 2974, 1671 (C=O), 1410, 1336, 1175, 869 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.10 (ddd, *J* = 7.0, 6.5, 4.0 Hz, 1H, OCH), 3.70–3.60 (m, 1H, NCH), 3.49–3.40 (m, 1H, NCH), 3.32 (dd, *J* = 11.5, 8.0 Hz, 1H, NCH), 3.17 (dd, *J* = 11.0, 6.5 Hz, 1H, NCH), 2.89–2.71 (m, 2H, CH), 2.15–2.09 (m, 2H, CH), 1.99 (br s, 1H, OH), 1.46 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.2 (C=O), 79.5 (OCMe₃), 71.2 (OCH), 52.0 (NCH₂), 50.6 (NCH₂), 36.1 (CH₂), 28.6 (CMe₃) (2 × CH resonances not resolved); HRMS *m/z* calcd for C₁₁H₁₉NO₃ (*M* + Na)⁺ 236.1257, found 236.1251 (+2.4 ppm error).

Lab book reference: ARG-3-169

***tert*-Butyl 6-hydroxy-3-azabicyclo[3.2.0]heptane-3-carboxylate *endo*-218**



A solution of imide *endo*-**218** (2.6 g, 9.5 mmol, 1.0 eq) in THF (50 mL) was added to a stirred suspension of LiAlH₄ (1.1 g, 28.5 mmol, 3.0 eq) in THF (15 mL) at 0 °C under Ar. The resulting mixture was stirred and heated at reflux for 16 h. The mixture was cooled to 0 °C and Et₂O (35 mL) was added followed by dropwise addition of H₂O (1.1 mL), 20% NaOH_(aq) (2.2 mL) and H₂O (1.1 mL) at 0 °C. The resulting mixture was stirred at rt for 1 h and MgSO₄ (10 g) was added. After stirring at rt for 30 min the solids were removed by filtration through Celite[®] eluting with EtOAc (50 mL) and the filtrate evaporated under

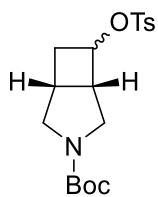
reduced pressure to give the crude *N*-Bn pyrrolidine. The crude *N*-Bn pyrrolidine was dissolved in MeOH (45 mL) and 20% Pd(OH)₂/C 50% wet (694 mg, 0.49 mmol, 0.05 eq) was added. The resulting suspension was evacuated and back-filled with Ar three times and then with H₂ three times. The mixture was stirred under a balloon of H₂ (760 mmHg) at rt for 16 h. The solids were removed by filtration through Celite® eluting with MeOH (35 mL) and the filtrate evaporated under reduced pressure to give the crude *N*-H pyrrolidine. The crude *N*-H pyrrolidine was dissolved in THF (45 mL) and Boc₂O (2.62 g, 12.0 mmol, 1.3 eq) was added and the resulting mixture was stirred for 16 h at rt under Ar. EtOAc (40 mL) and H₂O (40 mL) were added and the layers separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:2 hexane-EtOAc as eluent gave *N*-Boc pyrrolidine *endo*-**170** (1.46 g, 72%) as a semi-solid, *R*_F (3:2 hexane-EtOAc) 0.20; IR (ATR) 3406 (OH), 2974, 1671 (C=O), 1408, 1366, 1168, 1122, 876 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.24 (ddd, *J* = 8.0, 7.5, 7.5 Hz, 1H, OCH), 3.99 (dd, *J* = 12.5, 2.5 Hz, 1H, NCH), 3.43 (d, *J* = 11.5 Hz, 1H, NCH), 3.18 (dd, *J* = 12.5, 9.0 Hz, 1H, NCH), 3.10 (dd, *J* = 11.5, 5.5 Hz, 1H, NCH), 3.07–2.95 (m, 1H, CH), 2.62–2.53 (m, 1H, CH), 2.53–2.40 (m, 1H, CH), 2.30 (br s, 1H, OH), 1.62–1.54 (m, 1H, CH), 1.45 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.6 (C=O), 79.6 (OCMe₃), 62.8 (OCH), 52.0 (NCH₂), 45.0 (CH), 43.9 (NCH₂), 36.6 (CH₂), 30.2 (CH), 28.6 (CMe₃); HRMS *m/z* calcd for C₁₁H₁₉NO₃ (M + Na)⁺ 236.1257, found 236.1260 (–1.2 ppm error).

Lab book reference: ARG-3-168

NaBO₃•5H₂O (262 mg, 1.7 mmol, 5.0 eq) was added to a stirred solution of pinacol boronate *endo*-**279** (110 mg, 0.34 mmol, 1.0 eq) in THF (7 mL) and H₂O (7 mL), at rt under air. The resulting mixture was stirred at rt and for 6 h under air. EtOAc (15 mL) and H₂O (10 mL) were added and the layers separated. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:2 hexane-EtOAc as eluent gave *N*-Boc pyrrolidine *endo*-**170** (58 g, 82%) as a semi-solid identical by (¹H NMR spectroscopy) to that described above.

Lab book reference: ARG-4-089

tert*-Butyl 6-(tosyloxy)-3-azabicyclo[3.2.0]heptane-3-carboxylate **280*



280

TsCl (2.82 g, 14.8 mmol, 2.0 eq) was added to a stirred solution of a 70:30 mixture of pyrrolidines *endo*-**170** and *exo*-**170** (1.58 g, 7.4 mmol, 1.0 eq), DMAP (90 mg, 0.75 mg, 0.1 eq) and Et₃N (2.1 mL, 14.8 mmol, 2.0 eq) in CH₂Cl₂ (37 mL) at 0 °C under Ar. The resulting mixture was stirred at rt for 18 h under Ar. 1 M HCl_(aq) (20 mL) was added, and the two layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:1 hexane-EtOAc as eluent gave tosylates *endo*-**280** (1.23 g, 46%) as a white solid, *R*_F (6:4 hexane-EtOAc) 0.50; IR (ATR) 2976, 1601 (C=O), 1364, 1174, 854 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (60:40 mixture of rotamers) δ 7.86–7.72 (m, 2H, Ar), 7.40–7.28 (m, 2H, Ar), 4.92–4.69 (m, 1H, OCH), 3.90–3.81 (m, 1H, NCH), 3.50 (d, *J* = 11.5 Hz, 0.6H, NCH), 3.35 (d, *J* = 11.5 Hz, 0.4H, NCH), 3.18–2.97 (m, 3H, NCH, CH), 2.54–2.35 (m, 5H, CH, Me), 1.87 (s, 1H, CH), 1.50–1.40 (m, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.1 (C=O), 145.0 (*ipso*-Ar), 133.9 (*ipso*-Ar), 129.9 (Ar), 127.9 (Ar), 79.7 (OCMe₃), 51.3 (NCH₂), 44.7 (NCH₂), 34.8 (CH), 33.3 (CH₂), 28.5 (CMe₃), 27.8 (CH), 21.8 (Me) (1 × OCH resonance not resolved) and *exo*-**280** (413 mg, 15%) as a semi-solid, *R*_F (6:4 hexane-EtOAc) 0.49; IR (ATR) 2976, 1601 (C=O), 1364, 1174, 854 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.75–7.69 (m, 2H, Ar), 7.32–7.28 (m, 2H, Ar), 4.51 (dddd, *J* = 8.0, 4.0, 4.0, 2.0 Hz, 1H, OCH), 3.50 (d, *J* = 11.0 Hz, 1H, NCH), 3.42–3.32 (m, 1H, NCH), 3.21 (dd, *J* = 12.0, 8.0 Hz, 1H, NCH), 3.05–2.94 (m, 2H, NCH, CH), 2.88–2.78 (m, 1H, CH), 2.43–2.37 (m, 3H, Me), 2.35–2.26 (m, 1H, CH), 2.07–1.94 (m, 1H, CH), 1.42 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.0 (C=O), 145.1 (*ipso*-Ar), 133.7 (*ipso*-Ar), 130.0 (Ar), 127.9 (Ar), 79.8 (OCMe₃), 78.4 (OCH), 51.5 (NCH₂), 50.1 (NCH₂), 46.9 (CH), 33.3 (CH₂), 31.4 (CH), 28.5 (CMe₃), 21.7 (Me); HRMS *m/z* calcd for C₁₈H₂₅NO₅S (M + Na)⁺ 390.1346, found 390.1345

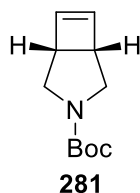
(+0.1 ppm error). Overall, this reaction gave a 70:30 mixture of tosylates *endo*-**280** and *exo*-**280** (1.65 g, 61%) as a semi-solid.

Lab book reference: ARG-4-005

TsCl (3.81 g, 20 mmol, 2.0 eq) was added to a stirred solution of a 75:25 mixture of pyrrolidines *endo*-**170** and *exo*-**170** (2.13 g, 10 mmol, 1.0 eq) and Et₃N (2.8 mL, 20 mmol, 2.0 eq) in CH₂Cl₂ (50 mL) at 0°C under Ar. The resulting mixture was stirred at rt for 18 h under Ar. 1 M HCl_(aq) (25 mL) was added, and the two layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 25 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:1 hexane-EtOAc as eluent gave a 75:25 mixture (by ¹H NMR spectroscopy) of tosylates *endo*-**280** and *exo*-**280** (3.01 g, 82%) as a semi-solid identical by (¹H NMR spectroscopy) to that described above.

Lab book reference: ARG-4-040

tert*-Butyl 3-azabicyclo[3.2.0]hept-6-ene-3-carboxylate **281*

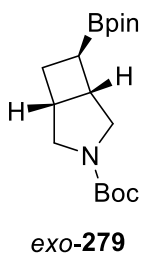


A solution containing a 70:30 mixture of tosylates *exo*-**280** and *endo*-**280** (500 mg, 1.36 mmol, 1.0 eq) in DMSO (3 mL) was added dropwise to a suspension of KO^t-Bu (458 mg, 4.08 mmol, 3.0 eq) in DMSO (9 mL) at rt under Ar and the resulting mixture was stirred and heated at 25 °C for 4 h. The solids were removed by filtration through silica eluting with 8:2 pentane-Et₂O (400 mL) and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 pentane-Et₂O as eluent gave cyclobutene **281** (90 mg, 40%) as a clear oil, *R*_F (9:1 pentane-Et₂O) 0.20; IR (ATR), 2973, 1692 (C=O), 1406, 1152, 1104, 882 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (50:50 mixture of rotamers) δ 5.98 (s, 2H, =CH), 3.69 (d, *J* = 12.0 Hz, 1H, NCH), 3.57 (d, *J* = 12.0 Hz, 1H, NCH), 3.26 (d, *J* = 6.0 Hz, 2H, CH), 2.85 (dd, *J* = 12.0, 6.0 Hz, 2H, NCH), 1.42 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 156.4 (C=O), 139.1 (=CH), 138.5

(=CH), 79.2 (OCMe₃), 47.0 (NCH₂), 46.8 (NCH₂), 46.2 (CH), 28.6 (CMe₃); HRMS *m/z* calcd for C₁₁H₁₇NO₂ (M + Na)⁺ 218.1151, found 218.1153 (−0.5 ppm error).

Lab book reference: ARG-4-011

***tert*-Butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.2.0]heptane-3-carboxylate *exo*-279**



A solution containing a 75:25 mixture of tosylates *exo*-280 and *endo*-280 (5.43 g, 1.36 mmol, 1.0 eq) in DMSO (20 mL) was added dropwise to a suspension of KO*t*-Bu (4.97 g, 44.3 mmol, 3.0 eq) in DMSO (15 mL) at rt under Ar and the resulting mixture was stirred and heated at 25 °C for 4 h. The solids were removed by filtration through silica eluting with 8:2 pentane-Et₂O (1 L) and the filtrate evaporated under reduced pressure to give the crude alkene. The crude alkene and MeOH (1.2 mL, 28.6 mmol, 2.0 eq) were dissolved THF (70 mL) and were subsequently added to a stirred solution of CuCl (141 mg, 1.43 mmol, 0.1 eq), Xantphos (910 mg, 1.57 mmol, 0.11 eq), B₂Pin₂ (4.0 g, 15.8 mmol, 1.1 eq) and KO*t*-Bu (803 mg, 7.16 mmol, 0.5 eq) in THF (35 mL) at rt under Ar. The resulting mixture was stirred at rt for 18 h. EtOAc (50 mL) and water (50 mL) were added and the layers separated. The aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave alkyl boronate *exo*-279 (1.71 g, 36%) as a colourless oil; *R*_F (8:2 hexane-EtOAc) 0.32; IR (ATR) 2976, 1697 (C=O), 1379, 1144, 853, 675 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) δ 3.55–3.34 (m, 2H, NCH), 3.19–3.08 (m, 2H, NCH), 2.82–2.71 (m, 2H, CH), 2.13–2.01 (m, 1H, CH), 1.73 (ddd, *J* = 12.0, 11.5, 3.5 Hz, 1H, CH), 1.57–1.47 (m, 1H, BCH), 1.38 (s, 9H, CMe₃), 1.20–1.10 (m, 12H, CMe₂); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 155.3 (C=O), 83.1 (OCMe₂), 79.0 (OCMe₃), 53.7 (NCH₂), 53.4 (NCH₂), 53.1 (NCH₂), 52.8 (NCH₂), 39.5 (CH), 38.6 (CH), 37.7 (CH), 36.7 (CH), 28.5 (CMe₃), 26.0

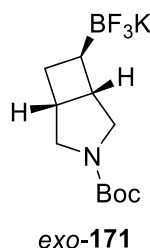
(CH₂), 24.7 (CMe₂), 20.3 (CHB); ¹¹B NMR (128 MHz, CDCl₃) δ 32.3; HRMS (ESI) *m/z* calcd for C₁₇H₃₀BNO₄ (M + Na)⁺ 346.2160 found 346.2162 (+0.4 ppm error).

Lab book reference ARG-4-072 & 4-073.

A solution of cyclobutene **281** (136 mg, 0.7 mmol, 1.0 eq) and MeOH (55 μL, 1.4 mmol, 2.0 eq) in THF (3.5 mL) was added to a stirred solution of CuCl (7 mg, 0.07 mmol, 0.1 eq), Xantphos (45 mg, 0.08 mmol, 0.11 eq), B₂Pin₂ (196 mg, 0.77 mmol, 1.1 eq) and KO^{*t*}-Bu (40 mg, 0.35 mmol, 0.5 eq) in THF (2.0 mL) at rt under Ar. The resulting mixture was stirred at rt for 18 h. EtOAc (10 mL) and water (10 mL) were added and the layers separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave alkyl boronate *exo*-**279** (145 mg, 64%) as a colourless oil identical by (¹H NMR spectroscopy) to that described above.

Lab book reference ARG-4-044.

Potassium (3-(*tert*-butoxycarbonyl)-3-azabicyclo[3.2.0]heptan-6-yl)trifluoroborate *exo*-171

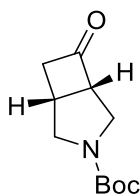


KHF₂ (1.5 mL of a 5.3 M aqueous solution, 6.0 eq) was added to a stirred solution of alkyl boronate *exo*-**279** (431 mg, 1.33 mmol, 1.0 eq) in MeOH (3 mL) at rt. The resulting mixture was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product as a white solid. The resulting residue was suspended in hot acetone (5 mL) and the solids were removed by filtration. The filtrate was evaporated under reduced pressure. Et₂O (20 mL) was added and the resulting mixture was stirred at rt for 1 h. The solids were collected by filtration and washed with cold Et₂O (2 × 5 mL) to give

trifluoroborate salt **exo-171** (271 mg, 67%) as a white solid, mp 138–140 °C; IR (ATR) 2971, 2864, 1672 (C=O), 1414, 1365, 1157, 929 cm⁻¹; ¹H NMR (400 MHz, (CD₃)₂SO) δ 3.38–3.29 (m, 1H, NCH), 3.27–3.21 (m, 1H, NCH), 3.17–3.04 (m, 2H, NCH), 2.64–2.54 (m, 1H, CH), 2.53–2.46 (m, 1H, resolved in HSQC), 1.82 (ddd, *J* = 11.0, 7.5, 7.5 Hz, 1H, CH), 1.40 (s, 9H, CMe₃), 1.38–1.28 (m, 1H, CH), 0.72 (s, 1H, BCH); ¹³C NMR (100.6 MHz, (CD₃)₂SO) (rotamers) δ 154.4 (C=O), 77.8 (OCMe₃), 54.3 (NCH₂), 53.5 (NCH₂), 53.3 (NCH₂), 36.8 (CH), 35.7 (CH), 28.3 (CMe₃), 26.5 (CH₂) (CBH resonance not resolved); ¹¹B NMR (128 MHz, (CD₃)₂SO) δ 3.90; ¹⁹F NMR (376 MHz, (CD₃)₂SO) δ –144.68; HRMS (ESI) *m/z* calcd for C₁₁H₁₈BF₃KNO₂ (M – K)[–] 264.1384 found 264.1388 (+2.2 ppm error).

Lab book reference ARG-4-118.

tert*-Butyl 6-oxo-3-azabicyclo[3.2.0]heptane-3-carboxylate **282*



282

(COCl)₂ (1.05 mL, 12 mmol, 1.2 eq) was added to a stirred solution of DMSO (1.5 mL, 20 mmol, 2.0 eq) in CH₂Cl₂ (50 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 30 min. Then, a solution of a 75:25 mixture of pyrrolidines **exo-170** and **endo-170** (2.13 g, 10 mmol, 1.0 eq) in CH₂Cl₂ (50 mL) was added at –78 °C under Ar. The resulting mixture was stirred at –78 °C for 1 h. Then Et₃N (5.6 mL, 40 mmol, 4.0 eq) was added dropwise at –78 °C under Ar and the resulting mixture stirred for 30 min at –78 °C under Ar. The mixture was then allowed to warm to rt and stirred for 18 h at rt under Ar. H₂O (50 mL) was added and the layers separated. The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried (MgSO₄), and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 hexane-EtOAc as eluent gave cyclobutanone **282** (1.91 g, 93%) as a colourless oil, *R*_F (3:2 hexane-EtOAc) 0.32; IR (ATR) 2977, 1783 (C=O, ketone), 1671 (C=O, Boc), 1393, 1166, 871 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.01–3.93 (m, 1H, NCH), 3.83–3.72 (m, 1H, NCH), 3.71–3.63 (m, 1H, C(O)CH), 3.42 (dd, *J* = 11.5, 6.5 Hz, 1H, NCH), 3.32 (ddd, *J* = 18.5, 9.0, 4.5 Hz, 1H,

C(O)CH), 3.27–3.17 (m, 1H, NCH), 3.10–3.01 (m, 1H, CH), 2.80 (ddd, $J = 18.5, 4.5, 3.0$ Hz, 1H, C(O)CH), 1.44 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 209.7 (C=O, ketone), 154.8 (C=O, Boc), 80.0 (OCMe₃), 63.7 (br, 2 $\times$ NCH₂), 52.7 (CH₂), 51.6 (CH), 48.0 (CH), 28.4 (CMe₃); HRMS m/z calcd for C₁₁H₁₇NO₃ (M + H)⁺ 234.1101, found 234.1098 (+1.2 ppm error).

Lab book reference: ARG-4-034

(COCl)₂ (103 μ L, 1.2 mmol, 1.2 eq) was added to a stirred solution of DMSO (142 μ L, 2.0 mmol, 2.0 eq) in CH₂Cl₂ (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 30 min. Then, a solution of a 75:25 mixture of pyrrolidines *exo*-**170** and *endo*-**170** (213 mg, 1.0 mmol, 1.0 eq) in CH₂Cl₂ (5 mL) was added at –78 °C under Ar. The resulting mixture was stirred at –78 °C for 1 h. Then Et₃N (560 μ L, 4.0 mmol, 4.0 eq) was added dropwise at –78 °C under Ar and the resulting mixture stirred for 30 min at –78 °C under Ar. The mixture was then allowed to warm to rt and stirred for 18 h at rt under Ar. H₂O (15 mL) was added and the layers separated. The aqueous layer was extracted with EtOAc (3 $\times$ 10 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO₄), and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 hexane-EtOAc as eluent gave cyclobutanone **282** (211 mg, 98%) as a colourless oil identical by (¹H NMR spectroscopy) to that described above.

Lab book reference: ARG-4-033

Dess-Martin periodinane (3.53 g, 8.33 mmol, 1.2 eq) was added to a stirred solution of a 70:30 mixture of pyrrolidines *exo*-**170** and *endo*-**170** (1.48 g, 6.94 mmol, 1.0 eq) in CH₂Cl₂ (40 mL) at rt under Ar. The resulting mixture was stirred at rt for 6 h. Saturated NaHCO_{3(aq)} (25 mL) was added and the mixture was stirred for 30 min. The layers were separated and the organic layer was washed with saturated Na₂S₂O_{3(aq)} (15 mL) and brine (25 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave cyclobutanone **282** (570 mg, 38%) as a colourless oil identical by (¹H NMR spectroscopy) to that described above.

Lab book reference: ARG-4-004

tert*-Butyl 6-(((trifluoromethyl)sulfonyl)oxy)-3-azabicyclo[3.2.0]hept-6-ene-3-carboxylate **283*

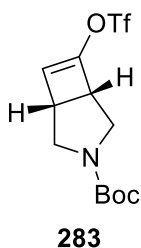


Table 3.1, Entry 6

KHMDS (47 mL of a 0.5 M solution in Toluene, 22.7 mmol, 1.6 eq) was added dropwise to a stirred solution of cyclobutanone **282** (3.00 g, 14.2 mmol, 1.0 eq) in THF (47 mL) at -78°C under Ar. The resulting solution was stirred at -78°C for 1 h. Then, a solution of Comins' reagent (8.91 g, 22.7 mmol, 1.6 eq) in THF (50 mL) was added and the resulting solution was stirred at -78°C for 10 min. Then, the solution was allowed to warm slowly to rt and stirred for 18 h. H_2O (50 mL) and Et_2O (50 mL) were added the layers separated. The aqueous layer was extracted with Et_2O (4×40 mL). The combined organic extracts were washed with 1 M $\text{NaOH}_{(\text{aq})}$ (50 mL) and brine (50 mL), dried (MgSO_4), and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 hexane- Et_2O as eluent gave vinyl triflate **283** (2.61 g, 53%) as a colourless oil, R_F (8:2 hexane- Et_2O) 0.20; IR (ATR) 2980, 1667 ($\text{C}=\text{O}$), 1423, 1209, 854, 607 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) (60:40 mixture of rotamers) δ 5.38 (s, 1H, $=\text{CH}$), 3.94–3.79 (m, 1H, NCH), 3.83 (d, $J = 12.0$ Hz, 0.6H, NCH), 3.72 (d, $J = 12.0$ Hz, 1H, NCH), 3.62–3.55 (m, 0.4H, NCH), 3.63–3.55 (m, 1H, NCH), 3.16–3.05 (m, 1H, CH), 2.89 (dd, $J = 12.0, 6.0$ Hz, 2H, NCH, CH), 1.42 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) (rotamers) δ 155.9 ($\text{C}=\text{O}$), 140.0 ($\text{OC}=\text{C}$), 139.6 ($\text{OC}=\text{C}$), 118.3 (q, $J = 319.7$ Hz, CF_3), 118.0 ($\text{OC}=\text{C}$), 117.4 ($\text{OC}=\text{C}$), 80.1 (OCMe_3), 51.0 (CH), 50.0 (CH), 45.5 (NCH), 44.8 (NCH), 44.0 (NCH), 43.4 (NCH), 39.1 (CH), 38.2 (CH), 28.4 (CMe_3); HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{16}\text{F}_3\text{NO}_5\text{S}$ ($\text{M} + \text{Na}$) $^{+}$ 266.0593 found 382.0338 (-2.1 ppm error).

Lab book reference: ARG-4-054

Table 3.1, Entry 1

NaHMDS (0.4 mL of a 2 M solution in THF, 0.80 mmol, 1.4 eq) was added dropwise to a stirred solution of cyclobutanone **282** (120 mg, 0.57 mmol, 1.0 eq) in THF (3.5 mL) at -78°C under Ar. The resulting solution was stirred at -78°C for 1 h. Then, a solution of Comins' reagent (312 mg, 0.80 mmol, 1.6 eq) in THF (4 mL) was added dropwise and the resulting solution was stirred at -78°C for 10 min. Then, the solution was allowed to warm slowly to rt and stirred for 18 h. H_2O (10 mL) and Et_2O (10 mL) were added the layers separated. The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic extracts were washed with 1 M $\text{NaOH}_{(\text{aq})}$ (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 8:2 hexane- Et_2O as eluent gave enol triflate **283** (73 mg, 41%) as a colourless oil identical by (^1H NMR spectroscopy) to that described above.

Lab book reference: ARG-4-026

Table 3.1, Entry 2

KHMDS (5.6 mL of a 0.5 M solution in Toluene, 2.80 mmol, 1.4 eq) was added dropwise to a stirred solution of cyclobutanone **282** (422 mg, 2.00 mmol, 1.0 eq) in THF (13 mL) at -78°C under Ar. The resulting solution was stirred at -78°C for 1 h. Then, a solution of Comins' reagent (1.09 g, 2.80 mmol, 1.4 eq) in THF (10 mL) was added dropwise and the resulting solution was stirred at -78°C for 10 min. Then, the solution was allowed to warm slowly to rt and stirred for 18 h. H_2O (20 mL) and Et_2O (20 mL) were added the layers separated. The aqueous layer was extracted with Et_2O (3×20 mL). The combined organic extracts were washed with 1 M $\text{NaOH}_{(\text{aq})}$ (30 mL) and brine (50 mL), dried (MgSO_4), and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 hexane- Et_2O as eluent gave enol triflate **283** (253 mg, 39%) as a colourless oil identical by (^1H NMR spectroscopy) to that described above.

Lab book reference: ARG-4-042

Table 3.1, Entry 3

LiHMDS (1.26 mL of a 1.0 M solution in THF, 1.26 mmol, 1.4 eq) was added dropwise to a stirred solution of cyclobutanone **282** (190 mg, 0.90 mmol, 1.0 eq) in THF (2.5 mL) at $-78\text{ }^{\circ}\text{C}$ under Ar. The resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. Then, a solution of Comins' reagent (495 mg, 1.26 mmol, 1.4 eq) in THF (10 mL) was added dropwise and the resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 10 min. Then, the solution was allowed to warm slowly to rt and stirred for 18 h. H_2O (15 mL) and Et_2O (15 mL) were added the layers separated. The aqueous layer was extracted with Et_2O ($3 \times 15\text{ mL}$). The combined organic extracts were washed with 1 M $\text{NaOH}_{(\text{aq})}$ (15 mL) and brine (25 mL), dried (MgSO_4), and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 hexane- Et_2O as eluent gave enol triflate **283** (70 mg, 23%) as a colourless oil identical by (^1H NMR spectroscopy) to that described above.

Lab book reference: ARG-4-036

Table 3.1, Entry 4

n-BuLi (0.19 mL of a 2.2 M solution in THF, 0.41 mmol, 1.4 eq) was added dropwise to a stirred solution of *i*-Pr₂NH (61 μL , 0.41 mmol, 1.4 eq) in THF (1 mL) at $-78\text{ }^{\circ}\text{C}$ under Ar. The resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 10 min and added dropwise to a stirred solution of cyclobutanone **282** (74 mg, 0.35 mmol, 1.0 eq) in THF (2.0 mL) at $-78\text{ }^{\circ}\text{C}$ under Ar. The resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. Then, a solution of Comins' reagent (161 mg, 0.41 mmol, 1.4 eq) in THF (2 mL) was added dropwise and the resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 10 min. Then, the solution was allowed to warm slowly to rt and stirred for 18 h. H_2O (15 mL) and Et_2O (15 mL) were added the layers separated. The aqueous layer was extracted with Et_2O ($3 \times 15\text{ mL}$). The combined organic extracts were washed with 1 M $\text{NaOH}_{(\text{aq})}$ (15 mL) and brine (25 mL), dried (MgSO_4), and evaporated under reduced pressure to give the crude product which contained (by ^1H NMR spectroscopy) $<10\%$ of vinyl triflate **283**.

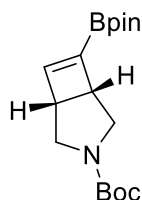
Lab book reference: ARG-4-041

Table 3.1, Entry 5

KHMDS (8.0 mL of a 0.5 M solution in Toluene, 4.00 mmol, 2.0 eq) was added dropwise to a stirred solution of cyclobutanone **282** (422 mg, 2.00 mmol, 1.0 eq) in THF (13 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, a solution of Comins' reagent (1.09 g, 2.80 mmol, 1.4 eq) in THF (10 mL) was added dropwise and the resulting solution was stirred at –78 °C for 10 min. Then, the solution was allowed to warm slowly to rt and stirred for 18 h. H₂O (20 mL) and Et₂O (20 mL) were added the layers separated. The aqueous layer was extracted with Et₂O (3 × 20 mL). The combined organic extracts were washed with 1 M NaOH_(aq) (30 mL) and brine (50 mL), dried (MgSO₄), and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 hexane-Et₂O as eluent gave enol triflate **283** (254 mg, 37%) as a colourless oil identical by (¹H NMR spectroscopy) to that described above.

Lab book reference: ARG-4-050

tert*-Butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.2.0]hept-6-ene-3-carboxylate **284*



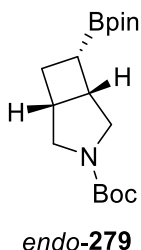
284

PdCl₂(dppf) (314 mg, 0.43 mmol, 0.06 eq), dppf (238 mg, 0.43 mmol, 0.06 eq), KOAc (2.10 g, 21.7 mmol, 3.0 eq) and B₂pin₂ (2.20 g, 8.66 mmol, 1.2 eq) were added to a stirred solution of vinyl triflate **283** (2.48 g, 7.22 mmol, 1.0 eq) in dioxane (50 mL) at rt under Ar. The resulting mixture was stirred and heated at 80 °C under Ar for 16 h. EtOAc (25 mL) and water (50 mL) were added and the layers separated. The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave vinyl Bpin **284** (1.52 g, 66%) as a colourless oil, *R_F* (8:2 hexane-EtOAc) 0.28; IR (ATR) 2977, 1669 (C=O), 1140, 852, 671 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (50:50 mixture of rotamers) δ

6.81–6.76 (m, 1H, =CH), 3.79–3.67 (m, 1.5H, NCH), 3.63–3.58 (m, 0.5H, NCH), 3.40–3.31 (m, 2H, NCH), 3.00–2.85 (m, 2H, CH), 1.44 (s, 9H, CMe₃), 1.27 (s, 12H, CMe₂); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 156.2 (C=O), 154.5 (=CH), 154.1 (=CH), 83.5 (OCMe₂), 83.4 (OCMe₂), 78.9 (OCMe₃), 47.6 (CH), 47.1 (NCH₂), 46.8 (CH), 46.7 (NCH₂), 46.6 (NCH₂), 46.0 (CH), 45.7 (NCH₂), 28.5 (CMe₃), 25.0 (CMe₂), 24.9 (CMe₂), 24.7 (CMe₂), 24.6 (CMe₂) (=CB bond resonance not resolved); ¹¹B NMR (128 MHz, CDCl₃) δ 25.7; HRMS (ESI) *m/z* calcd for C₁₇H₂₈BNO₄ (M + Na)⁺ 344.2004 found 344.2014 (–2.2 ppm error).

Lab book reference ARG-4-060.

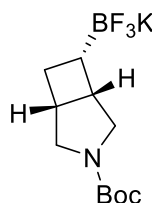
***tert*-Butyl (6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.2.0]heptane-3-carboxylate *endo*-279**



Vinyl boronate **284** (1.52 g, 4.73 mmol, 1.0 eq) was dissolved in EtOAc (25 mL). The reaction flask was evacuated and back-filled with Ar three times. Then, 10% Pd/C (503 mg, 0.47 mmol, 0.1 eq) was added. The reaction flask was evacuated and back-filled with H₂ five times. The resulting mixture was stirred under a balloon of H₂ (760 mmHg) at rt for 16 h. The solids were removed by filtration through a plug of Celite[®]. The filtrate was evaporated under reduced pressure to give alkyl boronate *endo*-279 (1.41 g, 92%) as a colourless oil. IR (ATR) 2973, 1693 (C=O), 1420, 1372, 1142, 854 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) δ 3.83–3.71 (m, 1H, NCH), 3.45 (m, 1H, NCH), 3.21–3.12 (m, 2H, NCH), 3.06 (ddd, *J* = 9.5, 8.0, 6.5 Hz, 1H, CH), 2.97 (ddd, *J* = 12.0, 7.0, 6.5 Hz, 1H, CH), 2.28 (dddd, *J* = 12.0, 11.0, 8.5, 1.5 Hz, 1H, CH), 2.10 (ddd, *J* = 11.0, 9.5, 9.0 Hz, 1H, BCH), 1.89–1.79 (m, 1H, CH), 1.46 (s, 9H, CMe₃), 1.26 (m, 12H, CMe₂); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 155.5 (C=O), 83.4 (OCMe₂), 79.0 (OCMe₃), 52.8 (NCH₂), 50.7 (NCH₂), 39.8 (CH), 39.0 (CH), 38.1 (CH), 37.3 (CH), 28.6 (CMe₃), 26.2 (CH₂), 25.1 (CMe₂), 25.0 (CMe₂) (CHB resonance not resolved); HRMS (ESI) *m/z* calcd for C₁₇H₃₀BNO₄ (M + Na)⁺ 346.2160 found 346.2171 (–2.2 ppm error).

Lab book reference ARG-4-064.

Potassium (3-(*tert*-butoxycarbonyl)-3-azabicyclo[3.2.0]heptan-6-yl)trifluoroborate
***endo*-171**

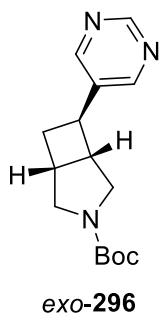


***endo*-171**

KHF₂ (5 mL of a 3.3 M aqueous solution, 5.0 eq) was added to a stirred solution of alkyl boronate *endo*-279 (700 mg, 2.16 mmol, 1.0 eq) in MeOH (5 mL) at rt. The resulting mixture was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product as a white solid. The resulting residue was suspended in hot acetone (5 mL) and the solids were removed by filtration. The filtrate was evaporated under reduced pressure. Et₂O (25 mL) was added and the resulting mixture was stirred at rt for 1 h. The solids were collected by filtration and washed with cold Et₂O (2 × 10 mL) to give trifluoroborate salt *endo*-171 (352 mg, 54%) as a white solid, mp 180-182 °C (decomposition); IR (ATR) 2945, 2851, 1676 (C=O), 1425, 1241, 1153, 901, 918 cm⁻¹; ¹H NMR (400 MHz, (CD₃)₂SO) δ 3.80 (dddd, *J* = 14.5, 11.0, 4.0 Hz, 1H, NCH), 3.14–2.99 (m, 3H, NCH), 2.83–2.71 (m, 1H, CH), 2.70–2.57 (m, 1H, CH), 1.84 (dddd, *J* = 11.0, 10.5, 8.0, 2.5 Hz, 1H, CH), 1.51 (ddd, *J* = 11.0, 10.5, 7.5 Hz, 1H, CH), 1.38 (s, 9H, CMe₃), 1.33–1.25 (m, 1H, BCH); ¹³C NMR (100.6 MHz, (CD₃)₂SO) (rotamers) δ 154.5 (C=O), 77.9 (OCMe₃), 52.7 (NCH₂), 52.5 (NCH₂), 49.5 (NCH₂), 38.4 (CH), 37.4 (CH) 28.8 (CMe₃), 27.8 (CH₂) (BCH resonance not resolved); ¹¹B NMR (128 MHz, (CD₃)₂SO) δ 2.92; ¹⁹F NMR (376 MHz, (CD₃)₂SO) δ –138.45; HRMS (ESI) *m/z* calcd for C₁₁H₁₈BF₃KNO₂ (*M* – K)[–] 264.1388 found 264.1388 (+0.7 ppm error).

Lab book reference ARG-4-074.

***tert*-Butyl 6-(pyrimidin-5-yl)-3-azabicyclo[3.2.0]heptane-3-carboxylate *exo*-296**



Using general procedure F, alcohol *exo*-170 (94 mg, 0.44 mmol, 1.75 eq), benzoxazolium salt **298** (185 mg, 0.40 mmol, 1.60 eq) and pyridine (32 μ L, 0.40 mmol, 1.60 eq) in anhydrous benzonitrile (2.5 mL) followed by 4,4'-di-*tert*-butyl-2,2'-bipyridine (3 mg, 0.012 mmol, 5.0 mol%), $\text{NiBr}_2 \cdot \text{dme}$ (4 mg, 0.012 mmol, 5.0 mol%), $[\text{Ir}(\text{dFCF}_3\text{ppy})_2(\text{dtbpy})]\text{PF}_6$ (4 mg, 0.0038 mmol, 1.5 mol%), quinuclidine (49 mg, 0.44 mmol, 1.75 eq) and 5-bromopyrimidine (40 mg, 0.25 mmol, 1.00 eq) in anhydrous DMA (2.5 mL), using 1 M $\text{HCl}_{(\text{aq})}$ (20 mL) and 15% $\text{CuSO}_{4(\text{aq})}$ (20 mL) in the work-up, gave the crude product. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc as eluent gave aryl cyclobutane *exo*-396 (43 mg, 65%) as a colourless oil, R_F (3:7 hexane-EtOAc) 0.24; IR (ATR) 2971, 1688 (C=O), 1390, 1233, 1151, 727 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.09 (s, 1H, Ar), 8.65 (s, 2H, Ar), 3.84–3.63 (m, 2H, NCH), 3.50–3.40 (m, 1H, NCH), 3.35–3.26 (m, 2H, NCH, CHAr), 3.07–2.98 (m, 2H, CH), 2.44–2.36 (m, 1H, CH), 2.33–2.24 (m, 1H, CH), 1.52 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) (rotamers) δ 156.9 (Ar), 155.3 (C=O), 155.2 (Ar), 137.9 (*ipso*-Ar), 79.7 (OCMe_3), 52.3 (br, NCH_2), 45.9 (CH), 45.3 (CH), 38.0 (CHAr), 34.8 (CH), 33.9 (CH), 31.7 (CH_2), 28.6 (CMe_3); HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_2$ ($\text{M} + \text{Na}$) $^+$ 298.1526 found 298.1534 (–2.8 ppm error).

Lab book reference ARG-4-087.

Using general procedure D, 4,4'-di-*tert*-butyl-2,2'-bipyridine (4 mg, 0.013 mmol, 5.0 mol%), $\text{NiCl}_2 \cdot \text{dme}$ (3 mg, 0.013 mmol, 5.0 mol%), alkyltrifluoroborate salt *exo*-171 (91 mg, 0.30 mmol, 1.2 eq), 5-bromopyrimidine (40 mg, 0.28 mmol, 1.0 eq), $[\text{Ir}(\text{dFCF}_3\text{ppy})_2(\text{dtbpy})]\text{PF}_6$ (7 mg, 0.0063 mmol, 2.5 mol%) and Cs_2CO_3 (123 mg, 0.38 mmol, 1.5 eq) in anhydrous 1,4-dioxane (5 mL) gave the crude product. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc as eluent gave aryl cyclobutane

exo-**296** (51 mg, 74%) as a colourless oil, identical (by ^1H NMR spectroscopy) to that described above.

Lab book reference ARG-4-084.

Using general procedure D, 4,4'-di-*tert*-butyl-2,2'-bipyridine (4 mg, 0.013 mmol, 5.0 mol%), $\text{NiCl}_2\cdot\text{dme}$ (3 mg, 0.013 mmol, 5.0 mol%), alkyltrifluoroborate salt *endo*-**171** (91 mg, 0.30 mmol, 1.2 eq), 5-bromopyrimidine (40 mg, 0.28 mmol, 1.0 eq), $[\text{Ir}(\text{dFCF}_3\text{ppy})_2(\text{dtbpy})]\text{PF}_6$ (7 mg, 0.0063 mmol, 2.5 mol%) and Cs_2CO_3 (123 mg, 0.38 mmol, 1.5 eq) in anhydrous 1,4-dioxane (5 mL) gave the crude product. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc gave aryl cyclobutane *exo*-**296** (18 mg, 19%) as a colourless oil, identical (by ^1H NMR spectroscopy) to that described above.

Lab book reference ARG-4-091.

Using general procedure E, 4,4'-di-*tert*-butyl-2,2'-bipyridine (4 mg, 0.013 mmol, 5 mol%), $\text{NiCl}_2\cdot\text{dme}$ (3 mg, 0.013 mmol, 5 mol%), alkylpinacolboronate *exo*-**279** (121 mg, 0.38 mmol, 1.5 eq), 5-bromopyrimidine (40 mg, 0.25 mmol, 1.0 eq), $[\text{Ir}(\text{dFCF}_3\text{ppy})_2(\text{dtbpy})]\text{PF}_6$ (4 mg, 0.0025 mmol, 1 mol%) and morpholine (33 μL , 0.38 mmol, 1.5 eq) in anhydrous DMF (5 mL) gave the crude product. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc as eluent gave aryl cyclobutane *exo*-**296** (40 mg, 59%) as a yellow solid, identical (by ^1H NMR spectroscopy) to that described above.

Lab book reference ARG-4-083.

Using general procedure E, 4,4'-di-*tert*-butyl-2,2'-bipyridine (4 mg, 0.013 mmol, 5 mol%), $\text{NiCl}_2\cdot\text{dme}$ (3 mg, 0.013 mmol, 5 mol%), alkylpinacolboronate *endo*-**279** (121 mg, 0.38 mmol, 1.5 eq), 5-bromopyrimidine (40 mg, 0.25 mmol, 1.0 eq), $[\text{Ir}(\text{dFCF}_3\text{ppy})_2(\text{dtbpy})]\text{PF}_6$ (4 mg, 0.0025 mmol, 1 mol%) and morpholine (33 μL , 0.38 mmol, 1.5 eq) in anhydrous DMF (5 mL) gave the crude product. Purification by flash column chromatography on silica with 1: hexane-EtOAc as eluent gave aryl cyclobutane *exo*-**296** (9 mg, 13%) as a yellow solid, identical (by ^1H NMR spectroscopy) to that described above.

Lab book reference ARG-4-090.

Using general procedure F, alcohol *exo*-**170** (94 mg, 0.44 mmol, 1.75 eq), benzoxazolium salt **297** (158 mg, 0.40 mmol, 1.60 eq) and pyridine (32 μ L, 0.40 mmol, 1.60 eq) in anhydrous MTBE (2.5 mL) followed by 4,4'-di-*tert*-butyl-2,2'-bipyridine (3 mg, 0.012 mmol, 5.0 mol%), NiBr₂•dme (4 mg, 0.012 mmol, 5.0 mol%), [Ir(dFCF₃ppy)₂(dtbpy)]PF₆ (4 mg, 0.0038 mmol, 1.5 mol%), quinuclidine (49 mg, 0.44 mmol, 1.75 eq) and 5-bromopyrimidine (40 mg, 0.25 mmol, 1.00 eq) in anhydrous DMA (2.5 mL), using 1 M HCl_(aq) (20 mL) and 15% CuSO_{4(aq)} (20 mL) in the work-up, gave the crude product. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc as eluent gave aryl cyclobutane *exo*-**296** (12 mg, 17%) as a colourless oil, identical (by ¹H NMR spectroscopy) to that described above.

Lab book reference ARG-4-081.

Using general procedure F, alcohol *endo*-**170** (94 mg, 0.44 mmol, 1.75 eq), benzoxazolium salt **298** (185 mg, 0.40 mmol, 1.60 eq) and pyridine (32 μ L, 0.40 mmol, 1.60 eq) in anhydrous benzotrifluoride (2.5 mL) followed by 4,4'-di-*tert*-butyl-2,2'-bipyridine (3 mg, 0.012 mmol, 5.0 mol%), NiBr₂•dme (4 mg, 0.012 mmol, 5.0 mol%), [Ir(dFCF₃ppy)₂(dtbpy)]PF₆ (4 mg, 0.0038 mmol, 1.5 mol%), quinuclidine (49 mg, 0.44 mmol, 1.75 eq) and 5-bromopyrimidine (40 mg, 0.25 mmol, 1.00 eq) in anhydrous DMA (2.5 mL), using 1 M HCl_(aq) (20 mL) and 15% CuSO_{4(aq)} (20 mL) in the work-up, gave the crude product. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc as eluent gave aryl cyclobutane *exo*-**296** (38 mg, 57%) as a colourless oil, identical (by ¹H NMR spectroscopy) to that described above.

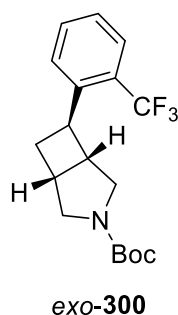
Lab book reference ARG-4-082.

Using general procedure G, alkyltrifluoroborate salt *exo*-**171** (91 mg, 0.30 mmol, 1.2 eq), 5-bromopyrimidine (40 mg, 0.25 mmol, 1.0 eq), Pd(OAc)₂ (6 mg, 0.025 mmol, 10 mol%), cataCXium A (18 mg, 0.05 mmol, 20 mol%) and Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq) in degassed toluene (1 mL) and degassed water (0.1 mL) gave the crude product. Purification

by flash column chromatography on silica with 1:1 hexane-EtOAc as eluent gave aryl cyclobutane *exo*-**296** (49 mg, 70%) as a colourless oil, identical (by ^1H NMR spectroscopy) to that described above.

Lab book reference ARG-4-085.

***tert*-Butyl 6-(2-(trifluoromethyl)phenyl)-3-azabicyclo[3.2.0]heptane-3-carboxylate *exo*-300**



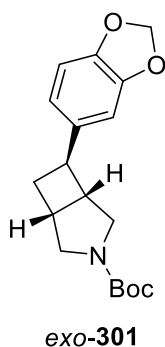
Using general procedure F, alcohol *exo*-**170** (94 mg, 0.44 mmol, 1.75 eq), benzoxazolium salt **298** (185 mg, 0.40 mmol, 1.60 eq) and pyridine (32 μL , 0.40 mmol, 1.60 eq) in anhydrous benzotrifluoride (2.5 mL) followed by 4,4'-di-*tert*-butyl-2,2'-bipyridine (3 mg, 0.012 mmol, 5.0 mol%), $\text{NiBr}_2 \cdot \text{dme}$ (4 mg, 0.012 mmol, 5.0 mol%), $[\text{Ir}(\text{dFCF}_3\text{ppy})_2(\text{dtbpy})]\text{PF}_6$ (4 mg, 0.0038 mmol, 1.5 mol%), quinuclidine (49 mg, 0.44 mmol, 1.75 eq) and 2-bromobenzotrifluoride (35 μL , 0.25 mmol, 1.00 eq) in anhydrous DMA (2.5 mL), using 1 M $\text{HCl}_{(\text{aq})}$ (10 mL) and 15% $\text{CuSO}_{4(\text{aq})}$ (10 mL) in the work-up, gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-Et₂O as eluent gave aryl cyclobutane *exo*-**300** (64 mg, 76%) as a colourless oil, R_F (8:2 hexane-Et₂O) 0.20; IR (ATR) 2975, 1690 (C=O), 1312, 1108, 765 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.67 (d, J = 8.0 Hz, 1H, Ar), 7.61–7.55 (m, 2H, Ar), 7.32–7.27 (m, 1H, Ar), 3.82–3.61 (m, 3H, NCH), 3.42–3.37 (m, 1H, CHAr), 3.34–3.09 (m, 1H, NCH), 3.04–2.95 (m, 2H, CH), 2.38–2.21 (m, 2H, CH), 1.51 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) (rotamers) δ 155.3 (C=O), 143.9 (*ipso*-Ar), 143.8 (*ipso*-Ar), 132.2 (Ar), 127.6 (br, Ar), 127.9 (q, J = 29.5 Hz, *ipso*-Ar), 126.5 (Ar), 126.1 (Ar), 125.7 (br, Ar), 124.5 (q, J = 274.0 Hz, CF_3), 79.5 (OCMe_3), 52.2 (br, NCH_2), 52.0 (CHAr), 46.7 (CH), 38.3 (CH), 34.5 (CH), 33.4 (CH), 33.3 (CH_2), 28.6 (CMe_3); HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{22}\text{F}_3\text{NO}_2$ ($\text{M} + \text{Na}$)⁺ 364.1495 found 364.1489 (1.5 ppm error).

Lab book reference ARG-4-106.

Using general procedure G, alkyltrifluoroborate salt *exo*-**171** (91 mg, 0.30 mmol, 1.2 eq), 2-bromobenzotrifluoride (35 μ L, 0.25 mmol, 1.0 eq), Pd(OAc)₂ (6 mg, 0.025 mmol, 10 mol%), cataCXium A (18 mg, 0.05 mmol, 20 mol%) and Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq) in degassed toluene (1 mL) and degassed water (0.1 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-Et₂O as eluent gave aryl cyclobutane *exo*-**300** (50 mg, 58%) as a colourless oil, identical (by ¹H NMR spectroscopy) to that described above.

Lab book reference ARG-4-123.

***tert*-Butyl 6-(benzo[d][1,3]dioxol-5-yl)-3-azabicyclo[3.2.0]heptane-3-carboxylate *exo*-301**



Using general procedure F, alcohol *exo*-**170** (94 mg, 0.44 mmol, 1.75 eq), benzoxazolium salt **298** (185 mg, 0.40 mmol, 1.60 eq) and pyridine (32 μ L, 0.40 mmol, 1.60 eq) in anhydrous benzotrifluoride (2.5 mL) followed by 4,4'-di-*tert*-butyl-2,2'-bipyridine (3 mg, 0.012 mmol, 5.0 mol%), NiBr₂•dme (4 mg, 0.012 mmol, 5.0 mol%), [Ir(dFCF₃ppy)₂(dtbpy)]PF₆ (4 mg, 0.0038 mmol, 1.5 mol%), quinuclidine (49 mg, 0.44 mmol, 1.75 eq) and 5-bromobenzo[d][1,3]dioxole (30 μ L, 0.25 mmol, 1.00 eq) in anhydrous DMA (2.5 mL), using 1 M HCl_(aq) (10 mL) and 15% CuSO_{4(aq)} (10 mL) in the work-up, gave the crude product. Purification by flash column chromatography on silica with 7:3 hexane-Et₂O as eluent gave aryl cyclobutane *exo*-**301** (87 mg, 74%) as a colourless oil, *R*_F (7:3 hexane-Et₂O) 0.18; IR (ATR) 2973, 1687 (C=O), 1366, 1163, 726, 585 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.76–6.71 (m, 2H, Ar), 6.64 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar), 5.91 (s, 2H,

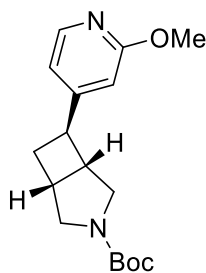
OCH₂), 3.77–3.55 (m, 2H, NCH), 3.48–3.37 (m, 1H, NCH), 3.26–3.18 (m, 2H, NCH, CHAr), 2.91–2.84 (m, 2H, CH), 2.32–2.21 (m, 1H, CH), 2.18–2.09 (m, 1H, CH), 1.48 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 155.5 (C=O), 147.8 (*ipso*-Ar), 145.8 (*ipso*-Ar), 143.8 (*ipso*-Ar), 139.4 (*ipso*-Ar), 119.3 (Ar), 108.2 (Ar), 106.9 (Ar), 100.9 (OCH₂O), 79.4 (OCMe₃), 52.5 (br, NCH₂), 46.9 (CH), 46.2 (CH), 42.7 (CHAr), 35.5 (CH), 34.5 (CH), 32.5 (CH₂), 28.6 (CMe₃); HRMS (ESI) *m/z* calcd for C₁₈H₂₃NO₄ (M + Na)⁺ 340.1519 found 340.1520 (–0.2 ppm error).

Lab book reference ARG-4-115.

Using general procedure G, alkyltrifluoroborate salt *exo*-**171** (91 mg, 0.30 mmol, 1.2 eq), 5-bromobenzo[*d*][1,3]dioxole (30 μL, 0.25 mmol, 1.0 eq), Pd(OAc)₂ (6 mg, 0.025 mmol, 10 mol%), cataCXium A (18 mg, 0.05 mmol, 20 mol%) and Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq) in degassed toluene (1 mL) and degassed water (0.1 mL) gave the crude product. Purification by flash column chromatography on silica with 7:3 hexane-Et₂O as eluent gave aryl cyclobutane *exo*-**301** (24 mg, 30%) as a pale-yellow oil, identical (by ¹H NMR spectroscopy) to that described above.

Lab book reference ARG-4-112.

***tert*-Butyl 6-(2-methoxypyridin-4-yl)-3-azabicyclo[3.2.0]heptane-3-carboxylate *exo*-302**



***exo*-302**

Using general procedure G, alcohol *exo*-**170** (94 mg, 0.44 mmol, 1.75 eq), benzoxazolium salt **298** (185 mg, 0.40 mmol, 1.60 eq) and pyridine (32 μ L, 0.40 mmol, 1.60 eq) in anhydrous benzotrifluoride (2.5 mL) followed by 4,4'-di-*tert*-butyl-2,2'-bipyridine (3 mg, 0.012 mmol, 5.0 mol%), NiBr₂•dme (4 mg, 0.012 mmol, 5.0 mol%), [Ir(dFCF₃ppy)₂(dtbpy)]PF₆ (4 mg, 0.0038 mmol, 1.5 mol%), quinuclidine (49 mg, 0.44 mmol, 1.75 eq) and 4-bromo-2-methoxypyridine (47 mg, 0.25 mmol, 1.00 eq) in anhydrous DMA (2.5 mL), using 1 M HCl_(aq) (10 mL) in the work-up, gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave aryl cyclobutane *exo*-**302** (51 mg, 67%) as a colourless oil, *R*_F (8:2 hexane-EtOAc) 0.20; IR (ATR) 2972, 1691 (C=O), 1609, 1390, 1156, 1039 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.08 (d, *J* = 5.5 Hz, 1H, Ar), 6.74 (dd, *J* = 5.5, 1.0 Hz, 1H, Ar), 6.59 (m, 1H, Ar), 3.93 (s, 3H, OMe), 3.80–3.57 (m, 2H, NCH), 3.47–3.36 (m, 1H, NCH), 3.31–3.19 (m, 2H, NCH, CHAr), 2.99–2.86 (m, 2H, CH), 2.38–2.27 (m, 1H, NCH), 2.23–2.13 (m, 1H, NCH), 1.50 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) (rotamers) δ 164.6 (*ipso*-Ar), 156.9 (*ipso*-Ar), 155.3 (C=O), 146.9 (Ar), 115.4 (Ar), 108.2 (Ar), 79.6 (OCMe₃), 53.4 (OMe), 52.5 (br, NCH₂), 45.8 (CH), 45.0 (CH), 41.8 (CHAr), 34.7 (CH), 33.8 (CH), 31.2 (CH₂) 28.6 (CMe₃); HRMS (ESI) *m/z* calcd for C₁₇H₂₄N₂O₃ (M + Na)⁺ 327.1679 found 327.1685 (–1.9 ppm error).

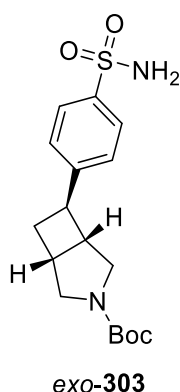
Lab book reference ARG-4-100.

Using general procedure G, alkyltrifluoroborate salt *exo*-**171** (91 mg, 0.30 mmol, 1.2 eq), 4-bromo-2-methoxypyridine (47 mg, 0.25 mmol, 1.0 eq), Pd(OAc)₂ (6 mg, 0.025 mmol, 10 mol%), cataCXium A (18 mg, 0.05 mmol, 20 mol%) and Cs₂CO₃ (244 mg, 0.75 mmol, 3.0

eq) in degassed toluene (1 mL) and degassed water (0.1 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave aryl cyclobutane *exo*-**302** (31 mg, 42%) as a colourless oil, identical (by ^1H NMR spectroscopy) to that described above.

Lab book reference ARG-4-109.

***tert*-Butyl 6-(4-sulfamoylphenyl)-3-azabicyclo[3.2.0]heptane-3-carboxylate *exo*-303**



Using general procedure F, alcohol *exo*-**170** (94 mg, 0.44 mmol, 1.75 eq), benzoxazolium salt **298** (185 mg, 0.40 mmol, 1.60 eq) and pyridine (32 μL , 0.40 mmol, 1.60 eq) in anhydrous benzotrifluoride (2.5 mL) followed by 4,4'-di-*tert*-butyl-2,2'-bipyridine (3 mg, 0.012 mmol, 5.0 mol%), $\text{NiBr}_2 \cdot \text{dme}$ (4 mg, 0.012 mmol, 5.0 mol%), $[\text{Ir}(\text{dFCF}_3\text{ppy})_2(\text{dtbpy})]\text{PF}_6$ (4 mg, 0.0038 mmol, 1.5 mol%), quinuclidine (49 mg, 0.44 mmol, 1.75 eq) and 4-bromobenzenesulfonamide (59 mg, 0.25 mmol, 1.00 eq) in anhydrous DMA (2.5 mL), using 1 M $\text{HCl}_{(\text{aq})}$ (10 mL) and 15% $\text{CuSO}_{4(\text{aq})}$ (10 mL) in the work-up, gave the crude product. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc as eluent gave aryl cyclobutane *exo*-**303** (31 mg, 35%) as a yellow semi-solid, R_F (4:6 hexane-EtOAc) 0.44; IR (ATR) 3249 (NH), 2973, 1669 (C=O), 1408, 1158, 579 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.90–7.86 (m, 2H, Ar), 7.39–7.34 (m, 2H, Ar), 5.14–5.10 (m, 2H, NH_2), 3.80–3.61 (m, 2H, NCH), 3.51–3.34 (m, 2H, NCH), 3.27 (dd, J = 11.0, 6.0 Hz, 1H, CHAr), 3.02–2.93 (m, 2H, CH), 2.40–2.31 (m, 1H, CH), 2.23 (dd, J = 10.5, 10.5 Hz, 1H, CH), 1.50 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) (rotamers) δ 155.4 (C=O), 150.7 (*ipso*-Ar), 139.8 (*ipso*-Ar), 127.2 (Ar), 126.8 (Ar), 79.7 (OCMe_3), 52.5 (br, NCH_2), 46.3 (CH), 45.7 (CH), 42.5 (CHAr), 34.7 (CH), 33.7 (CH), 32.0 (CH_2), 28.6 (CMe_3);

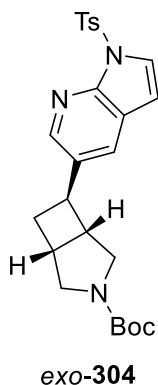
HRMS (ESI) m/z calcd for $C_{17}H_{24}N_2O_3$ ($M + Na$)⁺ 327.1679 found 327.1685 (−1.9 ppm error).

Lab book reference ARG-4-101.

Using general procedure G, alkyltrifluoroborate salt *exo*-**171** (91 mg, 0.30 mmol, 1.2 eq), 4-bromobenzenesulfonamide (59 mg, 0.25 mmol, 1.0 eq), $Pd(OAc)_2$ (6 mg, 0.025 mmol, 10 mol%), cataCXium A (18 mg, 0.05 mmol, 20 mol%) and Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq) in degassed toluene (1 mL) and degassed water (0.1 mL) gave the crude product. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc as eluent gave aryl cyclobutane *exo*-**303** (18 mg, 20%) as a colourless oil, identical (by ^1H NMR spectroscopy) to that described above.

Lab book reference ARG-4-123.

***tert*-Butyl 6-(1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-3-azabicyclo[3.2.0]heptane-3-carboxylate *exo*-304**



Using general procedure F, alcohol *exo*-**170** (94 mg, 0.44 mmol, 1.75 eq), benzoxazolium salt **298** (185 mg, 0.40 mmol, 1.60 eq) and pyridine (32 μ L, 0.40 mmol, 1.60 eq) in anhydrous benzotrifluoride (2.5 mL) followed by 4,4'-di-*tert*-butyl-2,2'-bipyridine (3 mg, 0.012 mmol, 5.0 mol%), $NiBr_2 \cdot dme$ (4 mg, 0.012 mmol, 5.0 mol%), $[Ir(dFCF_3ppy)_2(dtbbpy)]PF_6$ (4 mg, 0.0038 mmol, 1.5 mol%), quinuclidine (49 mg, 0.44 mmol, 1.75 eq) and *N*-Ts-Azaindole (87 mg, 0.25 mmol, 1.00 eq) in anhydrous DMA (2.5 mL), using 1 M $HCl_{(aq)}$ (10 mL) in the work-up, gave the crude product. Purification by flash column chromatography on silica with 7:3 hexane-EtOAc as eluent gave aryl cyclobutane

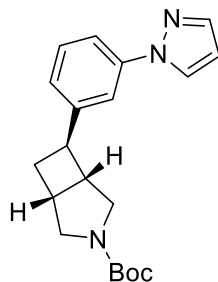
exo-**304** (46 mg, 40%) as a colourless oil, R_F (6:4 hexane-EtOAc) 0.32; IR (ATR) 2965, 1692 (C=O), 1392, 1122, 731 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.30 (d, J = 2.5 Hz, 1H, Ar), 8.08–8.05 (m, 2H, Ar), 7.72–7.68 (m, 2H, Ar), 7.29–7.25 (m, 2H, Ar), 6.55 (d, J = 2.5 Hz, 1H, Ar), 3.78–3.61 (m, 2H, NCH), 3.48–3.33 (m, 2H, NCH, CHAr), 3.25 (dd, J = 12.0, 5.5 Hz, 1H, NCH), 2.99–2.92 (m, 2H, CH), 2.39–2.30 (m, 4H, Me, CH), 2.28–2.19 (m, 1H, CH), 1.51 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) (rotamers) δ 155.4 (C=O), 146.2 (*ipso*-Ar), 145.2 (*ipso*-Ar), 144.1 (Ar), 135.9 (*ipso*-Ar), 135.6 (*ipso*-Ar), 129.7 (Ar), 128.1 (Ar), 127.1 (Ar), 126.9 (Ar), 122.9 (*ipso*-Ar), 105.2 (Ar), 79.6 (OCMe_3), 52.4 (br, NCH_2), 46.9 (CH), 46.1 (CH), 40.4 (CHAr), 34.7 (CH), 33.8 (CH), 32.6 (CH_2), 28.7 (CMe_3), 21.8 (Me); HRMS (ESI) m/z calcd for $\text{C}_{25}\text{H}_{30}\text{N}_3\text{O}_4\text{S}$ ($\text{M} + \text{Na}$) $^+$ 490.1771 found 490.1778 (–1.4 ppm error).

Lab book reference ARG-4-108.

Using general procedure G, alkyltrifluoroborate salt *exo*-**171** (91 mg, 0.30 mmol, 1.2 eq), *N*-Ts-Azaindole (87 mg, 0.25 mmol, 1.0 eq), $\text{Pd}(\text{OAc})_2$ (6 mg, 0.025 mmol, 10 mol%), cataCXium A (18 mg, 0.05 mmol, 20 mol%) and Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq) in degassed toluene (1 mL) and degassed water (0.1 mL) gave the crude product. Purification by flash column chromatography on silica with 7:3 hexane-EtOAc as eluent gave aryl cyclobutane *exo*-**304** (47 mg, 39%) as a pale-yellow oil, identical (by ^1H NMR spectroscopy) to that described above.

Lab book reference ARG-4-111.

***tert*-Butyl 6-(3-(1*H*-pyrazol-1-yl)phenyl)-3-azabicyclo[3.2.0]heptane-3-carboxylate**
***exo*-305**



***exo*-305**

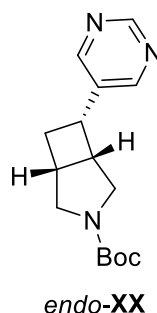
Using general procedure F, alcohol ***exo*-170** (94 mg, 0.44 mmol, 1.75 eq), benzoxazolium salt **298** (185 mg, 0.40 mmol, 1.60 eq) and pyridine (32 μ L, 0.40 mmol, 1.60 eq) in anhydrous benzotrifluoride (2.5 mL) followed by 4,4'-di-*tert*-butyl-2,2'-bipyridine (3 mg, 0.012 mmol, 5.0 mol%), $\text{NiBr}_2 \cdot \text{dme}$ (4 mg, 0.012 mmol, 5.0 mol%), $[\text{Ir}(\text{dFCF}_3\text{ppy})_2(\text{dtbpy})]\text{PF}_6$ (4 mg, 0.0038 mmol, 1.5 mol%), quinuclidine (49 mg, 0.44 mmol, 1.75 eq) and 1-(3-bromophenyl)-1*H*-pyrazole (56 mg, 0.25 mmol, 1.00 eq) in anhydrous DMA (2.5 mL), using 15% $\text{CuSO}_4(\text{aq})$ (10 mL) in the work-up, gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave aryl cyclobutane ***exo*-305** (45 mg, 54%) as a colourless oil, R_F (8:2 hexane-EtOAc) 0.22; IR (ATR) 2971, 1686 (C=O), 1391, 1155, 749 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.91 (d, J = 2.5 Hz, 1H, Ar), 7.71 (d, J = 1.5 Hz, 1H, Ar), 7.62–7.57 (m, 1H, Ar), 7.45 (d, J = 8.0 Hz, 1H, Ar), 7.36 (dd, J = 8.0, 7.5 Hz, 1H, Ar), 7.14 (d, J = 7.5 Hz, 1H, Ar), 6.45 (dd, J = 2.5, 1.5 Hz, 1H, Ar), 3.81–3.56 (m, 2H, NCH), 3.49–3.40 (m, 1H, NCH), 3.35 (ddd, J = 8.9, 8.5, 6.0 Hz, 1H, CHAr), 3.25 (dd, J = 11.5, 6.0 Hz, 1H, NCH), 3.05–2.89 (m, 2H, CH), 2.38 (ddd, J = 12.0, 8.5, 8.5 Hz, 1H, CH), 2.26–2.15 (m, 1H, CH), 1.49 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) (rotamers) δ 155.4 (C=O), 147.0 (*ipso*-Ar), 141.1 (Ar), 140.4 (*ipso*-Ar), 129.5 (Ar), 127.0 (Ar), 124.7 (Ar), 117.6 (Ar), 116.9 (Ar), 107.7 (Ar), 79.5 (OCMe_3), 52.6 (br, NCH_2), 46.5 (CH), 45.8 (CH), 42.7 (CHAr), 34.5 (CH), 33.6 (CH), 32.2 (CH_2), 28.7 (CMe_3); HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_2$ ($\text{M} + \text{Na}$) $^+$ 362.1839 found 362.1839 (0.0 ppm error).

Lab book reference ARG-4-107.

Using general procedure G, alkyltrifluoroborate salt *exo*-**171** (91 mg, 0.30 mmol, 1.2 eq), and 1-(3-bromophenyl)-1*H*-pyrazole (56 mg, 0.25 mmol, 1.00 eq), Pd(OAc)₂ (6 mg, 0.025 mmol, 10 mol%), cataCXium A (18 mg, 0.05 mmol, 20 mol%) and Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq) in degassed toluene (1 mL) and degassed water (0.1 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-Et₂O as eluent gave aryl cyclobutane *exo*-**305** (32 mg, 38%) as a colourless oil, identical (by ¹H NMR spectroscopy) to that described above.

Lab book reference ARG-4-124.

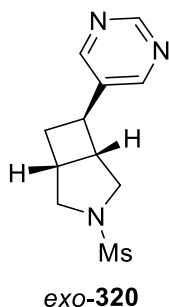
***tert*-Butyl 6-(pyrimidin-5-yl)-3-azabicyclo[3.2.0]heptane-3-carboxylate *endo*-296**



Using general procedure G, alkyltrifluoroborate salt *endo*-**171** (91 mg, 0.30 mmol, 1.2 eq), 5-bromopyrimidine (40 mg, 0.25 mmol, 1.0 eq), Pd(OAc)₂ (6 mg, 0.025 mmol, 10 mol%), cataCXium A (18 mg, 0.05 mmol, 20 mol%) and Cs₂CO₃ (244 mg, 0.75 mmol, 3.0 eq) in degassed toluene (1 mL) and degassed water (0.1 mL) gave the crude product. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc as eluent gave aryl cyclobutane *exo*-**296** (15 mg, 21%) as a colourless oil, *R*_F (3:7 hexane-EtOAc) 0.18; IR (ATR) 2974, 1687 (C=O), 1410, 1165, 729 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.07 (s, 1H, Ar), 8.49 (s, 2H, Ar), 3.75–3.46 (m, 2H, NCH, CHAr), 3.30–2.98 (m, 5H, NCH, CH), 2.65–2.52 (m, 1H, CH), 2.18–2.07 (m, 1H, CHAr), 1.38 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 156.9 (Ar), 156.4 (Ar), 154.8 (C=O), 134.1 (*ipso*-Ar), 79.8 (OCMe₃), 51.6 (br, NCH₂), 46.3 (CH₂), 42.8 (CH), 34.3 (CH), 33.4 (CHAr), 28.5 (CMe₃); HRMS (ESI) *m/z* calcd for C₁₅H₂₁N₃O₂ (M + Na)⁺ 298.1526 found 298.1533 (–2.5 ppm error).

Lab book reference ARG-4-087.

3-(Methylsulfonyl)-6-(pyrimidin-5-yl)-3-azabicyclo[3.2.0]heptane *exo*-320

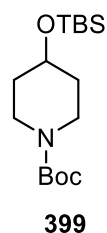


4 N HCl in dioxane (3.5 mL, 14.0 mmol, 70.0 eq) was added to a stirred solution of aryl cyclobutane *exo*-**296** (56 mg, 0.20 mmol, 1.00 eq) in CH₂Cl₂ (1.0 mL) at rt under Ar. The resulting mixture was stirred at rt under Ar for 2 h and the solvent was evaporated under reduced pressure to give the crude HCl salt. The crude HCl salt was suspended in CH₂Cl₂ (2 mL) and Et₃N (0.11 mL, 0.80 mmol, 4.0 eq) and MsCl (31 μ L, 0.40 mmol, 2.0 eq) were added at 0 °C under Ar. The resulting solution was stirred at rt for 18 h. CH₂Cl₂ (15 mL) and water (10 mL) were added and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (5 $\times$ 10 mL). The combined organic extracts were washed with 1 M HCl_(aq) (10 mL) and brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 6:4 CH₂Cl₂-EtOAc as eluent gave methanesulfonamide *exo*-**320** (35 mg, 71%) as a white-crystalline solid, mp 100–102 °C; *R*_F (6:4 CH₂Cl₂-EtOAc) 0.11; IR (ATR) 2926, 1561, 1413, 1326, 1145, 1019 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 9.10 (s, 1H, Ar), 8.67 (s, 2H, Ar), 3.71–3.60 (m, 2H, NCH), 3.44 (ddd, *J* = 8.5, 8.5, 4.3 Hz, 1H, CHAr), 3.21–3.11 (m, 4H, NCH, CH), 2.93 (s, 3H, Me), 2.46–2.37 (m, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 157.1 (Ar), 155.3 (Ar), 137.9 (*ipso*-Ar), 54.2 (NCH₂), 45.3 (CH), 37.3 (CHAr), 34.7 (CH), 34.3 (Me), 31.4 (CH₂); HRMS (ESI) *m/z* calcd for C₁₁H₁₅N₃O₂S (M + Na)⁺ 276.0777 found 276.0776 (+0.3 ppm error).

Lab book reference ARG-4-117.

5.5 Experimental Procedures for Chapter 4

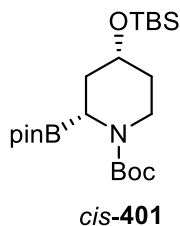
tert-Butyl 4-((*tert*-butyldimethylsilyl)oxy)piperidine-1-carboxylate **399**



A solution of 4-hydroxy-*N*-Boc piperidine **400** (8.05 g, 40 mmol, 1.0 eq), *tert*-butyldimethylsilyl chloride (7.84 g, 52 mmol, 1.3 eq) and imidazole (6.51 g, 100 mmol, 2.5 eq) in DMF (135 mL) under Ar was stirred at rt for 72 h. Saturated NaHCO_{3(aq)} (60 mL) and Et₂O (100 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (4 x 50 mL), and the combined organics were washed with brine (4 x 50 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 9:1 hexane-Et₂O as eluent gave 4-OTBS piperidine **399** (11.49 g, 92%) as a colourless oil, *R*_F (9:1 hexane-Et₂O) 0.20; IR (ATR) 2929, 1694 (C=O), 1419, 1231, 1172, 1101, 872, 833, 772 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.86 (tt, *J* = 7.0, 7.0, 3.5, 3.5 Hz, 1H, OCH), 3.61 (ddd, *J* = 12.5, 7.5, 3.5 Hz, 2H, NCH), 3.23 (ddd, *J* = 12.5, 7.0, 3.5 Hz, 2H, NCH), 1.72–1.63 (m, 2H, CH), 1.52–1.42 (m, 11H, CH, OCMe₃), 0.88 (s, 9H, SiCMe₃), 0.14–0.06 (m, 6H, SiMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.1 (C=O), 79.4 (OCMe₃), 67.4 (OCH), 40.3 (br, NCH₂), 34.4 (CH₂), 28.6 (OCMe₃), 25.9 (SiCMe₃), 18.2 (SiCMe₃), -4.59 (SiMe); HRMS (ESI) *m/z* calcd for C₁₆H₃₃NO₃Si (M + Na)⁺ 338.2122, found 338.2126 (−1.4 ppm error). Spectroscopic data consistent with those reported in the literature.³⁸⁵

Lab book reference: ARG-3-157

tert*-Butyl 4-[(*tert*-butyldimethylsilyl)oxy]-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine-1-carboxylate *cis*-**401*



s-BuLi (20 mL of a 1.31 M solution in hexane, 26.0 mmol, 1.3 eq) was added dropwise to a stirred solution of 4-OTBS-*N*-Boc piperidine **399** (6.3 g, 20.0 mmol, 1.0 eq) and TMEDA (3.8 mL, 26.0 mmol, 1.3 eq) in Et₂O (100 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. *i*-PrOBpin (4.84 g, 26.0 mmol, 1.3 eq) was added and the resulting solution was stirred at –78 °C for 1 h and then at rt for 18 h. 1 M HCl_(aq) (50 mL) and Et₂O (50 mL) were added, and the two layers were separated, and the aqueous layer was extracted with Et₂O (4 × 40 mL). The combined organics were dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained 2,4-disubstituted-piperidines **401** in 97:3 dr (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica using 75:25 hexane-Et₂O as eluent gave pinacol boronate *cis*-**401** (6.34 g, 72%) as a clear oil, *R*_F (4:1 hexane-Et₂O) 0.25; IR (ATR) 2930, 1609 (C=O), 1371, 1145, 1108, 872, 774 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) δ 3.77 (dd, *J* = 13.0, 5.0 Hz, 1H, NCH), 3.66 (ddd, *J* = 10.5, 10.5, 5.5 Hz, 1H, OCH), 2.80 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 1H, NCH), 2.39 (dd, *J* = 13.0, 3.0 Hz, 1H, NCHB), 1.79–1.70 (m, 2H, CH), 1.50 (s, 9H, OCMe₃), 1.45–1.31 (m, H, CH), 1.19 (s, 12H, CMe), 0.86 (s, 9H, SiCMe₃), 0.06–0.03 (m, 6H, SiMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 159.8 (C=O), 86.0 (OCMe₂), 80.2 (OCMe₃), 70.4 (OCH), 46.1 (BNCH, Only resolved in HSQC), 41.2 (br, NCH₂), 36.4 (CH₂), 34.6 (CH₂), 28.5 (OCMe₃), 25.9 (SiCMe₃), 25.2 (CMe), 24.9 (CMe), 18.1 (SiCMe₃), –4.3 (SiMe), –4.5 (SiMe); HRMS (ESI) *m/z* calcd for C₂₂H₄₄BNO₅Si (M + Na)⁺ 465.2974, found 464.2984 (–1.3 ppm error). Diagnostic signals for pinacol boronate *trans*-**401**: ¹H NMR (400 MHz, CDCl₃) δ 4.12–3.98 (m, 1H, OCH), 3.49–3.42 (m, 1H, NCH), 3.15 (ddd, *J* = 12.0, 5.0, 5.0 Hz, 1H, NCH).

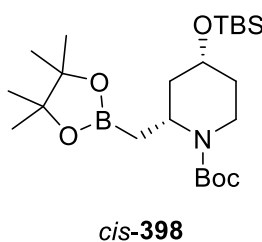
Lab book reference: ARG-4-130

s-BuLi (20 mL of a 1.31 M solution in hexane, 26.0 mmol, 1.3 eq) was added dropwise to a stirred solution of 4-OTBS-*N*-Boc piperidine **399** (6.3 g, 20.0 mmol, 1.0 eq) and TMEDA

(3.8 mL, 26.0 mmol, 1.3 eq) in toluene (100 mL) at $-78\text{ }^{\circ}\text{C}$ under Ar. The resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 3 h. *i*-PrOBpin (4.84 g, 26.0 mmol, 1.3 eq) was added and the resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h and then at rt for 18 h. 1 M HCl_(aq) (50 mL) and Et₂O (50 mL) were added, and the two layers were separated, and the aqueous layer was extracted with Et₂O (4 × 40 mL). The combined organics were dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained 2,4-disubstituted-piperidines **401** in 95:5 dr (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica using 75:25 hexane-Et₂O as eluent gave pinacol boronate *cis*-**401** (5.28 g, 60%) as a clear oil, identical (by ¹H and ¹³C NMR spectroscopy) to that described above.

Lab book reference: ARG-3-188

***tert*-Butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)piperidine-1-carboxylate *cis*-398**



s-BuLi (1.8 mL of a 1.1 M solution in hexane, 1.95 mmol, 1.3 eq) was added dropwise to a stirred solution of 4-OTBS-*N*-Boc piperidine **399** (479 mg, 1.5 mmol, 1.0 eq) and TMEDA (0.29 mL, 1.95 mmol, 1.3 eq) in Et₂O (7.5 mL) at $-78\text{ }^{\circ}\text{C}$ under Ar. The resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. A solution of BrCH₂Bpin (576 g, 1.95 mmol, 1.3 eq) in Et₂O (4 mL) was added and the resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h and then at rt for 18 h. Et₂O (10 mL), H₂O (10 mL) and sat. NH₄Cl_(aq) (10 mL) were added, and the two layers were separated, and the aqueous layer was extracted with Et₂O (3 × 15 mL). The combined organics were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained pinacol boronates **398** in 95:5 dr (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica using 19:1 to 4:1 hexane-Et₂O as eluent gave pinacol boronate *cis*-**398** (478 mg, 70%) as a clear oil, *R*_F (9:1 hexane-Et₂O) 0.15; IR (ATR) 2930, 1692 (C=O), 1364, 1145, 1053, 878, 774 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.35 (dddd, *J* = 11.5, 5.5, 4.5, 3.5 Hz, 1H, NCH), 4.05 (dddd, *J* = 3.5, 3.5, 3.5, 3.5 Hz, 1H, OCH), 3.76 (ddd, *J* = 13.0, 4.0, 4.0 Hz, 1H, NCH), 3.25 (ddd, *J*

= 13.0, 12.5, 3.5 Hz, 1H, NCH), 1.86 (dd, J = 15.5, 11.5 Hz, 1H, BCH), 1.80–1.66 (m, 2H, CH), 1.61–1.50 (m, 2H, CH), 1.44 (s, 9H, OCM₃), 1.21 (s, 12H, CMe), 1.00 (dd, J = 15.5, 4.5 Hz, 1H, BCH), 0.89 (s, 9H, SiCMe₃), 0.08 – -0.02 (m, 6H, SiMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.0 (C=O), 82.9 (OCMe₂), 79.0 (OCMe₃), 65.7 (OCH), 47.2 (NCH), 36.1 (CH₂), 33.7 (NCH₂), 33.3 (CH₂), 28.6 (OCMe₃), 26.0 (SiCMe₃), 25.0 (CMe₂), 24.9 (CMe₂), 18.1 (SiCMe₃), -4.87 (SiMe), -4.90 (SiMe) (CH₂B resonance not resolved); HRMS (ESI) m/z calcd for C₂₃H₄₆BNO₅Si (M + Na)⁺ 478.3131, found 478.3144 (-1.8 ppm error). Diagnostic signals for pinacol boronate *trans*-**398**: ¹H NMR (400 MHz, CDCl₃) δ 4.56 (m, 1H, OCH), 2.88–2.78 (m, 1H, NCH).

Lab book reference: ARG-4-001

Table 4.1, Entry 1

n-BuLi (0.32 mL of a 1.57 M solution in hexane, 0.51 mmol, 1.7 eq) was added dropwise to a stirred solution of pinacol boronate *cis*-**401** (132 mg, 0.30 mmol, 1.0 eq) and ClCH₂Br (78 mg, 0.6 mmol, 2.0 eq) in THF (1.5 mL) at -78 °C under Ar. The resulting solution was stirred at -78 °C for 1 h and then at 40 °C for 18 h. Et₂O (10 mL), H₂O (10 mL) and sat. NH₄Cl_(aq) (5 mL) were added, and the two layers were separated, and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organics were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 19:1 to 4:1 hexane-Et₂O as eluent gave piperidine **399** (40 mg, 42%) as a clear oil, pinacol boronate *cis*-**398** (14 mg, 10%) as a clear oil, identical (by ¹H and ¹³C NMR spectroscopy) to that described above and pinacol boronate *cis*-**401** (40 mg, 30%) as a clear oil.

Lab book reference: ARG-3-106

Table 4.1, Entry 2

n-BuLi (0.32 mL of a 1.57 M solution in hexane, 0.51 mmol, 1.7 eq) was added dropwise to a stirred solution of pinacol boronate *cis*-**401** (132 mg, 0.30 mmol, 1.0 eq) and ClCH₂Br (78 mg, 0.6 mmol, 2.0 eq) in THF (1.5 mL) at -78 °C under Ar. The resulting solution was stirred at -78 °C for 1 h and then at rt for 18 h. Et₂O (10 mL), H₂O (10 mL) and sat. NH₄Cl_(aq) (5

mL) were added, and the two layers were separated, and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organics were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 19:1 to 4:1 hexane-Et₂O as eluent gave piperidine **399** (7 mg, 7%) as a clear oil, pinacol boronate *cis*-**398** (62 mg, 46%) as a clear oil, identical (by ¹H and ¹³C NMR spectroscopy) to that described above and pinacol boronate *cis*-**401** (26 mg, 28%) as a clear oil.

Lab book reference: ARG-3-106

Table 4.1, Entry 3

n-BuLi (0.32 mL of a 1.57 M solution in hexane, 0.51 mmol, 1.7 eq) was added dropwise to a stirred solution of pinacol boronate *cis*-**401** (132 mg, 0.30 mmol, 1.0 eq), ClCH₂Br (78 mg, 0.6 mmol, 2.0 eq) and ZnCl₂ (1.1 mL of a 0.7 M solution in THF, 0.75 mmol, 2.5 eq) in THF (1.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h and then at rt for 18 h. Et₂O (10 mL), H₂O (10 mL) and sat. NH₄Cl_(aq) (5 mL) were added, and the two layers were separated, and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organics were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 19:1 to 4:1 hexane-Et₂O as eluent gave piperidine **300** (14 mg, 15%) as a clear oil, pinacol boronate *cis*-**398** (48 mg, 35%) as a clear oil, identical (by ¹H and ¹³C NMR spectroscopy) to that described above and pinacol boronate *cis*-**401** (42 mg, 32%) as a clear oil.

Lab book reference: ARG-3-107

Table 4.1, Entry 4

n-BuLi (0.23 mL of a 1.57 M solution in hexane, 0.35 mmol, 1.4 eq) was added dropwise to a stirred solution of pinacol boronate *cis*-**401** (110 mg, 0.25 mmol, 1.0 eq) and CH₂Br₂ (109 mg, 0.62 mmol, 2.5 eq) in THF (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h and then at rt for 18 h. Et₂O (10 mL), H₂O (10 mL) and sat. NH₄Cl_(aq) (5 mL) were added, and the two layers were separated, and the aqueous layer was extracted

with Et₂O (3 × 10 mL). The combined organics were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 19:1 to 4:1 hexane-Et₂O as eluent gave piperidine **399** (15 mg, 20%) as a clear oil, pinacol boronate *cis*-**398** (35 mg, 30%) as a clear oil, identical (by ¹H and ¹³C NMR spectroscopy) to that described above and pinacol boronate *cis*-**401** (32 mg, 29%) as a clear oil.

Lab book reference: ARG-3-099

Table 4.1, Entry 5

n-BuLi (1.75 mL of a 1.43 M solution in hexane, 2.5 mmol, 2.5 eq) was added dropwise to a stirred solution of pinacol boronate *cis*-**401** (442 mg, 1.0 mmol, 1.0 eq) and ClCH₂I (441 mg, 2.5 mmol, 2.5 eq) in THF (10 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h and then at rt for 18 h. Et₂O (20 mL), H₂O (10 mL) and sat. NH₄Cl_(aq) (10 mL) were added, and the two layers were separated, and the aqueous layer was extracted with Et₂O (3 × 15 mL). The combined organics were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 19:1 to 4:1 hexane-Et₂O as eluent gave piperidine **399** (6 mg, 2%) as a clear oil, pinacol boronate *cis*-**398** (291 mg, 63%) as a clear oil, identical (by ¹H and ¹³C NMR spectroscopy) to that described above and pinacol boronate *cis*-**401** (44 mg, 10%) as a clear oil.

Lab book reference: ARG-3-131

Table 4.1, Entry 6

n-BuLi (17.2 mL of a 1.37 M solution in hexane, 23.5 mmol, 2.5 eq) was added dropwise to a stirred solution of pinacol boronate *cis*-**401** (4.2 g, 9.38 mmol, 1.0 eq) and ClCH₂I (4.14 g, 23.5 mmol, 2.5 eq) in THF (90 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h and then at rt for 18 h. Et₂O (50 mL), H₂O (25 mL) and sat. NH₄Cl_(aq) (25 mL) were added, and the two layers were separated, and the aqueous layer was extracted with Et₂O (4 × 25 mL). The combined organics were washed with brine (50 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by

flash column chromatography on silica using 19:1 to 4:1 hexane-Et₂O as eluent gave pinacol boronate *cis*-**298** (3.75 g, 88%) as a clear oil, identical (by ¹H and ¹³C NMR spectroscopy) to that described above.

Lab book reference: ARG-4-010

Table 4.2, Entry 1

s-BuLi (0.94 mL of a 1.38 M solution in hexane, 1.30 mmol, 1.3 eq) was added dropwise to a stirred solution of 4-OTBS-*N*-Boc piperidine **399** (315 mg, 1.00 mmol, 1.0 eq) and TMEDA (0.19 mL, 1.30 mmol, 1.3 eq) in Et₂O (8 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. A solution of ZnCl₂ (2.7 mL of a 0.7 M solution in THF, 1.9 mmol, 1.9 eq) was added and the mixture stirred at –78 °C for 10 min then, ClCH₂Bpin (212 mg, 1.20 mmol, 1.2 eq) was added and the resulting solution was stirred at –78 °C for 1 h and then at rt for 18 h. Et₂O (10 mL), H₂O (10 mL) and sat. NH₄Cl_(aq) (10 mL) were added, and the two layers were separated, and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organics were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained traces of pinacol boronate *cis*-**398** (by HRMS).

Lab book reference: ARG-3-063

Table 4.2, Entry 2

s-BuLi (0.5 mL of a 1.25 M solution in hexane, 0.62 mmol, 1.2 eq) was added dropwise to a stirred solution of 4-OTBS-*N*-Boc piperidine **399** (158 mg, 0.50 mmol, 1.0 eq) and TMEDA (0.1 mL, 0.62 mmol, 1.2 eq) in Et₂O (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. A solution of ClCH₂Bpin (106 mg, 0.60 mmol, 1.2 eq) in Et₂O (2.5 mL) was added and the resulting solution was stirred at –78 °C for 1 h and then at rt for 18 h. Et₂O (10 mL), H₂O (10 mL) and sat. NH₄Cl_(aq) (5 mL) were added, and the two layers were separated, and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organics were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained pinacol boronates **398** in 93:7 dr (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica using

19:1 to 4:1 hexane-Et₂O as eluent gave pinacol boronate *cis*-**398** (20 mg, 9%, 93:7 dr) as a clear oil, identical (by ¹H and ¹³C NMR spectroscopy) to that described above.

Lab book reference: ARG-3-143

Table 4.2, Entry 3

s-BuLi (0.5 mL of a 1.25 M solution in hexane, 0.62 mmol, 1.2 eq) was added dropwise to a stirred solution of 4-OTBS-*N*-Boc piperidine **399** (158 mg, 0.50 mmol, 1.0 eq) and TMEDA (0.1 mL, 0.62 mmol, 1.2 eq) in Et₂O (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. A solution of ClCH₂Bpin (106 mg, 0.60 mmol, 1.2 eq) and MgBr₂ (115 mg, 0.62 mmol, 1.2 eq) in Et₂O (2.5 mL) was added and the resulting solution was stirred at –78 °C for 1 h and then at rt for 18 h. Et₂O (10 mL), H₂O (10 mL) and sat. NH₄Cl_(aq) (5 mL) were added, and the two layers were separated, and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organics were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained pinacol boronates **398** in 93:7 dr (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica using 19:1 to 4:1 hexane-Et₂O as eluent gave pinacol boronate *cis*-**398** (27 mg, 12%, 93:7 dr) as a clear oil, identical (by ¹H and ¹³C NMR spectroscopy) to that described above.

Lab book reference: ARG-3-143-2

Table 4.2, Entry 4

s-BuLi (0.5 mL of a 1.25 M solution in hexane, 0.62 mmol, 1.2 eq) was added dropwise to a stirred solution of 4-OTBS-*N*-Boc piperidine **399** (158 mg, 0.50 mmol, 1.0 eq) and TMEDA (0.1 mL, 0.62 mmol, 1.2 eq) in Et₂O (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. A solution of ClCH₂Bpin (106 mg, 0.60 mmol, 1.2 eq) in CHCl₃ (7.5 mL) was added and the resulting solution was stirred at –78 °C for 1 h and then at reflux for 18 h. CH₂Cl₂ (10 mL), H₂O (10 mL) and sat. NH₄Cl_(aq) (5 mL) were added, and the two layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organics were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained pinacol

boronates **398** in 93:7 dr (by ^1H NMR spectroscopy). Purification by flash column chromatography on silica using 19:1 to 4:1 hexane-Et₂O as eluent gave pinacol boronate *cis*-**398** (30 mg, 14%, 93:7 dr) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above.

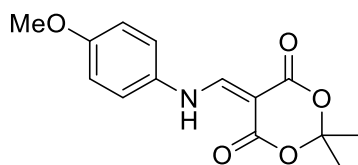
Lab book reference: ARG-3-154

Table 4.2, Entry 5

s-BuLi (0.5 mL of a 1.25 M solution in hexane, 0.62 mmol, 1.2 eq) was added dropwise to a stirred solution of 4-OTBS-*N*-Boc piperidine **399** (158 mg, 0.50 mmol, 1.0 eq) and TMEDA (0.1 mL, 0.62 mmol, 1.2 eq) in Et₂O (5 mL) at $-78\text{ }^\circ\text{C}$ under Ar. The resulting solution was stirred at $-78\text{ }^\circ\text{C}$ for 1 h. A solution of BrCH₂Bpin (106 mg, 0.60 mmol, 1.2 eq) in Et₂O (2.5 mL) was added and the resulting solution was stirred at $-78\text{ }^\circ\text{C}$ for 1 h and then at rt for 18 h. Et₂O (10 mL), H₂O (10 mL) and sat. NH₄Cl_(aq) (5 mL) were added, and the two layers were separated, and the aqueous layer was extracted with Et₂O ($3 \times 10\text{ mL}$). The combined organics were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained pinacol boronates **398** in 96:4 dr (by ^1H NMR spectroscopy). Purification by flash column chromatography on silica using 19:1 to 4:1 hexane-Et₂O as eluent gave pinacol boronate *cis*-**398** (103 mg, 45%, 96:4 dr) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above.

Lab book reference: ARG-3-144

5-(((4-Methoxyphenyl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione 404

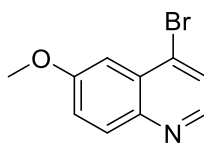


404

HC(OEt)₃ (4.25 mL, 50.8 mmol, 1.05 eq) was added to a stirred solution of *p*-anisidine (2.97 g, 48.2 mmol, 1.00 eq) and Meldrum's acid **403** (4.02 g, 55.8 mmol, 1.1 eq) in EtOH (25 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 4 h. After cooling down to rt, the solids were collected by filtration and washed with cold EtOH (25 mL) and cold Et₂O (10 mL) to give aniline **404** (11.4 g, 85%) as a white solid, mp 156-158 °C (lit.,³⁸⁶ 159-161 °C); IR (ATR) 3173 (NH), 1725 (C=O), 1681, 1626, 1453, 1418, 1269 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 11.22 (d, *J* = 14.5 Hz, 1H, NH), 8.53 (d, *J* = 14.5 Hz, 1H, =CH), 7.23–7.13 (m, 2H, Ar), 7.03–6.90 (m, 2H, Ar), 3.82 (s, 3H, OMe), 1.74 (s, 6H, Me); ¹³C NMR (100.6 MHz, CDCl₃) δ 165.9 (=CHN), 163.8 (C=O), 158.6 (C=O), 152.8 (*ipso*-Ar), 131.2 (=C), 119.7 (Ar), 115.3 (Ar), 105.2 (*ipso*-Ar), 86.6 (CO₂Me₂), 55.7 (OMe), 27.1 (Me); HRMS (ESI) *m/z* calcd for C₁₄H₁₅NO₅ (M + Na)⁺ 300.0842, found 300.0846 (–1.3 ppm error). Spectroscopic data consistent with those reported in the literature.²¹¹

Lab book reference: ARG-3-109

4-Bromo-6-methoxyquinoline 352



352

Aniline **404** (11.4 g, 41.1 mmol, 1.0 eq) was added portionwise to stirred Dowtherm A[®] (82 mL) at 255 °C (heating block temperature) over the course of 5 min. The resulting mixture was stirred at 255 °C for 20 min. After cooling to rt, Et₂O (40 mL) was added and the solids were collected by filtration and washed with cold Et₂O (100 mL) to give the crude hydroxyquinoline. The crude hydroxyquinoline was dissolved in DMF (38 mL) and PBr₃ (4.7 mL, 49.3 mmol, 1.2 eq) was added dropwise at rt under Ar. The resulting mixture was stirred at rt for 2 h and H₂O (100 mL) was added. The solids were collected by filtration and washed with cold H₂O (100 mL) and cold EtOH (15 mL) to give the crude product. Purification by flash column chromatography on silica using 4:1 hexane-Et₂O as eluent gave bromoquinoline **352** (4.89 g, 50%) as an off-white solid, mp 80-82 °C (lit.,³³⁷ 78-80 °C); *R*_F (9:1 hexane-Et₂O) 0.1; IR (ATR) 2962, 1618, 1495, 1230, 1027, 843, 659 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.52 (d, *J* = 4.5 Hz, 1H, Ar), 8.02–7.94 (m, 1H, Ar), 7.66 (d, *J* = 4.5 Hz, 1H, Ar), 7.46–7.36 (m, 2H, Ar), 3.98 (s, 3H, OMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 159.1 (*ipso*-Ar), 147.4 (Ar), 145.2 (*ipso*-Ar), 132.6 (*ipso*-Ar), 131.6 (Ar), 129.2 (*ipso*-Ar), 125.4 (Ar), 123.4 (Ar), 104.5 (Ar), 55.8 (OMe); HRMS (ESI) *m/z* calcd for C₁₀H₈⁷⁹BrNO (M + H)⁺ 237.9862, found 237.9860 (+0.6 ppm error). Spectroscopic data consistent with those reported in the literature.³³⁷

Lab book reference: ARG-4-009

***tert*-Butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-((6-methoxyquinolin-4-yl)methyl)piperidine-1-carboxylate *cis*-397**

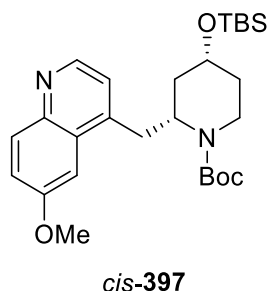


Table 4.3, Entry 6

A solution of Pd(OAc)₂ (33 mg, 0.15 mmol, 0.1 eq) and CataCXium A (104 mg, 0.29 mmol, 0.02 eq) in toluene (4.6 mL) was added to a solution of pinacol boronate *cis*-398 (863 mg, 1.89 mmol, 1.3 eq), Cs₂CO₃ (1.43 g, 4.38 mmol, 3.0 eq) and bromoquinoline **352** (347 mg, 1.46 mmol, 1.0 eq) in toluene (10 mL) at rt in a sealed tube under Ar. H₂O (1.46 mL), degassed by sparging with Ar for 30 min, was added and the resulting mixture was stirred and heated at 100 °C for 18 h under Ar. The solids were removed by filtration through Celite[®] and washed with EtOAc (25 mL). Water (15 mL) was added to the filtrate, the two layers were separated and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (25 mL), dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 9:1 to 7:3 hexane-EtOAc as eluent gave aryl piperidine *cis*-397 (660 mg, 93%) as a clear oil, *R*_F (7:3 hexane-EtOAc) 0.43; IR (ATR) 2965, 2935, 1678 (C=O), 1490, 1375, 1230, 1027, 854, 780, 643 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.62 (d, *J* = 4.5 Hz, 1H, Ar), 7.99 (d, *J* = 9.0 Hz, 1H, Ar), 7.79–7.25 (br m, 1H, Ar), 7.34 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar), 7.24–7.09 (m, 1H, Ar), 4.65–4.54 (m, 1H, OCH), 4.26–4.15 (m, 1H, NCH), 4.06–3.92 (m, 4H, OMe, NCH), 3.79–3.52 (m, 1H, CHAr), 3.52–3.14 (m, 2H, NCH, CHAr), 1.87–1.58 (m, 4H, CH₂), 1.53–0.56 (m, 18H, OMe₃, SiMe₃), 0.23–0.06 (m, 6H, SiMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 157.9 (*ipso*-Ar), 154.7 (C=O), 147.5 (Ar), 144.9 (*ipso*-Ar), 144.6 (*ipso*-Ar), 131.7 (Ar), 129.2 (*ipso*-Ar), 122.9 (Ar), 121.3 (Ar), 102.4 (Ar), 79.3 (OMe₃), 65.3 (OCH), 55.9 (OMe), 49.7 (NCH), 36.2 (NCH₂), 33.0 (CH₂), 28.0 (CH₂), 26.1 (OMe₃), 18.2 (CH₂), -4.5 (SiMe₃), -4.8 (SiMe) (1 × CMe₃ resonance not resolved); HRMS (ESI) *m/z* calcd for C₂₇H₄₂N₂O₄Si (M + H)⁺ 487.2987, found 487.2991 (–0.9 ppm error).

Lab book reference: ARG-4-139

Table 4.3, Entry 1

A solution of Pd(dba)₂ (12 mg, 0.02 mmol, 0.1 eq) and dppf (11 mg, 0.02 mmol, 0.01 eq) in dioxane (1.0 mL) was added to a solution of pinacol boronate *cis*-**398** (90 mg, 0.20 mmol, 1.0 eq), CsOH·H₂O (134 mg, 0.80 mmol, 4.0 eq) and bromoquinoline **352** (71 mg, 0.30 mmol, 1.5 eq) in dioxane (0.5 mL) at rt in a sealed tube under Ar. H₂O (80 µL), degassed by sparging with Ar for 30 min, was added and the resulting mixture was stirred and heated at 100 °C for 18 h under Ar. The solids were removed by filtration through Celite® and washed with EtOAc (15 mL). Water (10 mL) was added to the filtrate, the two layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 9:1 to 7:3 hexane-EtOAc as eluent gave aryl piperidine *cis*-**397** (34 mg, 35%, ~90% pure) as a clear oil, identical (by ¹H and ¹³C NMR spectroscopy) to that described above.

Lab book reference: ARG-3-132

Table 4.3, Entry 2

A solution of PdCl₂(dppf) (12 mg, 0.02 mmol, 0.08 eq) in THF (1.5 mL) was added to a solution of pinacol boronate *cis*-**398** (90 mg, 0.20 mmol, 1.0 eq), K₂CO₃ (83 mg, 0.60 mmol, 3.0 eq), Ag₂O (69 mg, 0.30 mmol, 1.50 eq) and bromoquinoline **352** (71 mg, 0.30 mmol, 1.5 eq) in THF (0.5 mL) at rt in a sealed tube under Ar. H₂O (0.22 mL), degassed by sparging with Ar for 30 min, was added and the resulting mixture was stirred and heated at 100 °C for 18 h under Ar. The solids were removed by filtration through Celite® and washed with EtOAc (15 mL). Water (10 mL) was added to the filtrate, the two layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 9:1 to 7:3 hexane-EtOAc as eluent gave aryl piperidine *cis*-**397** (50 mg, 45%, ~90% pure) as a clear oil, identical (by ¹H and ¹³C NMR spectroscopy) to that described above.

Lab book reference: ARG-3-134

Table 4.3, Entry 3

A solution of Pd(OAc)₂ (5 mg, 0.02 mmol, 0.01 eq) and CataCXium A (15 mg, 0.04 mmol, 0.02 eq) in toluene (1.5 mL) was added to a solution of pinacol boronate *cis*-**398** (90 mg, 0.20 mmol, 1.0 eq), Cs₂CO₃ (195 mg, 0.60 mmol, 3.0 eq) and bromoquinoline **352** (71 mg, 0.30 mmol, 1.5 eq) in toluene (0.5 mL) at rt in a sealed tube under Ar. H₂O (0.2 mL), degassed by sparging with Ar for 30 min, was added and the resulting mixture was stirred and heated at 100 °C for 18 h under Ar. The solids were removed by filtration through Celite® and washed with EtOAc (15 mL). Water (10 mL) was added to the filtrate, the two layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 9:1 to 7:3 hexane-EtOAc as eluent gave aryl piperidine *cis*-**397** (52 mg, 55%, ~95% pure) as a clear oil, identical (by ¹H and ¹³C NMR spectroscopy) to that described above.

Lab book reference: ARG-3-133

Table 4.3, Entry 4

A solution of Pd(OAc)₂ (5 mg, 0.02 mmol, 0.01 eq) and CataCXium A (15 mg, 0.04 mmol, 0.02 eq) in dioxane (1.5 mL) was added to a solution of pinacol boronate *cis*-**398** (90 mg, 0.20 mmol, 1.0 eq), Cs₂CO₃ (195 mg, 0.60 mmol, 3.0 eq) and bromoquinoline **352** (71 mg, 0.30 mmol, 1.5 eq) in dioxane (0.5 mL) at rt in a sealed tube under Ar. H₂O (0.2 mL), degassed by sparging with Ar for 30 min, was added and the resulting mixture was stirred and heated at 100 °C for 18 h under Ar. The solids were removed by filtration through Celite® and washed with EtOAc (15 mL). Water (10 mL) was added to the filtrate, the two layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 9:1 to 7:3 hexane-EtOAc as eluent gave aryl piperidine *cis*-**397** (62 mg, 65%, ~90% pure) as a clear oil, identical (by ¹H and ¹³C NMR spectroscopy) to that described above.

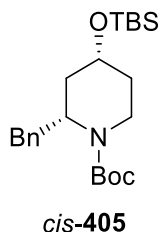
Lab book reference: ARG-3-133

Table 4.3, Entry 5

A solution of Pd(OAc)₂ (5 mg, 0.02 mmol, 0.1 eq) and CataCXium A (15 mg, 0.04 mmol, 0.02 eq) in toluene (1.5 mL) was added to a solution of pinacol boronate *cis*-**398** (114 mg, 0.25 mmol, 1.3 eq), Cs₂CO₃ (195 mg, 0.60 mmol, 3.0 eq) and bromoquinoline **352** (47 mg, 0.20 mmol, 1.0 eq) in toluene (1.0 mL) at rt in a sealed tube under Ar. H₂O (0.25 mL), degassed by sparging with Ar for 30 min, was added and the resulting mixture was stirred and heated at 100 °C for 18 h under Ar. The solids were removed by filtration through Celite® and washed with EtOAc (5 mL). Water (10 mL) was added to the filtrate, the two layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 9:1 to 7:3 hexane-EtOAc as eluent gave aryl piperidine *cis*-**397** (76 mg, 78%) as a clear oil, identical (by ¹H and ¹³C NMR spectroscopy) to that described above.

Lab book reference: ARG-3-163

***tert*-Butyl 2-benzyl-4-((*tert*-butyldimethylsilyl)oxy)piperidine-1-carboxylate *cis*-405**



s-BuLi (0.5 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq) was added dropwise to a stirred solution of 4-OTBS-*N*-Boc piperidine **399** (158 mg, 0.5 mmol, 1.0 eq) and TMEDA (0.1 mL, 0.65 mmol, 1.3 eq) in Et₂O (2.5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. ZnCl₂ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq) was added dropwise at −78 °C under Ar and the solution slowly warmed up to 0 °C and stirred at 0 °C for 10 min. The resulting solution was then cooled to −40 °C and a solution of CuCN•2LiCl (2 mL, of a 0.25 M solution, 1.0 mmol, 2.0 eq), prepared by addition of CuCN (45 mg, 0.5 mmol, 1.0 eq) to a stirred solution of LiCl (42 mg, 1.0 mmol, 2.0 eq) in THF (2 mL) at rt under Ar, was added dropwise at −40 °C under Ar. The resulting solution was stirred for 30 min at −40 °C under Ar and BnBr (119 μL, 1.0 mmol, 2.0 eq) was added and the resulting solution was stirred at −40 °C for 1 h and then at rt for 18 h under Ar. Et₂O

(10 mL), H₂O (10 mL) and sat. NH₄Cl_(aq) (10 mL) were added, and the two layers were separated, and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organics were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained benzylated piperidines **405** in 75:25 dr (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica using 19:1 to 9:1 hexane-Et₂O as eluent gave an impure mixture of benzylated piperidines *cis*-**405** (54 mg, <33%, 65:35 dr) as a clear oil. *R*_F (98:2 hexane-Et₂O) 0.14; ¹H NMR (400 MHz, CDCl₃) for major δ 7.30–7.11 (m, 5H, Ar), 4.54–4.43 (m, 1H, OCH), 4.18–4.07 (m, 1H, NCH), 4.05–3.94 (m, 2H, NCH), 3.90–3.81 (m, 1H, NCH), 3.02–2.88 (m, 1H, CHAr), 2.76–2.63 (m, 1H, CHAr), 1.86–1.60 (m, 4H, CH), 1.31 (s, 9H, OCM₃), 0.95–0.80 (m, 9H, SiCM₃), 0.10–0.00 (m, 6H, SiMe). Diagnostic signals for minor diastereomer δ 4.38–4.29 (m, 1H, OCH), 3.65–3.56 (m, 1H, NCH), 2.83 (dd, *J* = 13.5, 7.5 Hz, 1H, CHAr), 1.24 (s, 9H, CM₃) HRMS (ESI) *m/z* calcd for C₂₃H₃₉NO₃Si (M + Na)⁺ 428.2591, found 428.2599 (–1.7 ppm error).

Lab book reference: ARG-4-149

s-BuLi (0.5 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq) was added dropwise to a stirred solution of 4-OTBS-*N*-Boc piperidine **399** (158 mg, 0.5 mmol, 1.0 eq) and TMEDA (0.1 mL, 0.65 mmol, 1.3 eq) in Et₂O (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. BnCl (114 μL, 1.0 mmol, 2.0 eq) was added and the resulting solution was stirred at –78 °C for 1 h and then at rt for 18 h. Et₂O (10 mL), H₂O (10 mL) and sat. NH₄Cl_(aq) (10 mL) were added, and the two layers were separated, and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organics were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained only traces of piperidines **405** (by ¹H NMR spectroscopy and HRMS).

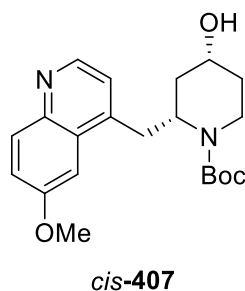
Lab book reference: ARG-4-135

s-BuLi (0.5 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq) was added dropwise to a stirred solution of 4-OTBS-*N*-Boc piperidine **399** (158 mg, 0.5 mmol, 1.0 eq) and TMEDA (0.1 mL, 0.65 mmol, 1.3 eq) in Et₂O (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. BnBr (119 μL, 1.0 mmol, 2.0 eq) was added and the resulting

solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h and then at rt for 18 h. Et_2O (10 mL), H_2O (10 mL) and sat. $\text{NH}_4\text{Cl}_{(\text{aq})}$ (10 mL) were added, and the two layers were separated, and the aqueous layer was extracted with Et_2O ($3 \times 10\text{ mL}$). The combined organics were washed with brine (15 mL), dried (MgSO_4) and evaporated under reduced pressure to give the crude product which contained benzylated piperidines **405** in 70:30 dr (by ^1H NMR spectroscopy). Purification by flash column chromatography on silica using 19:1 to 9:1 hexane- Et_2O as eluent gave an impure mixture of benzylated piperidines *cis*-**405** (44 mg, <22%, 60:40 dr) as a clear oil identical by (^1H NMR spectroscopy) to that described above.

Lab book reference: ARG-4-135

tert*-Butyl 4-hydroxy-2-((6-methoxyquinolin-4-yl)methyl)piperidine-1-carboxylate *cis*-**407*

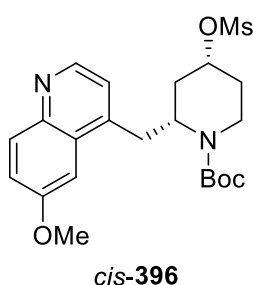


TBAF (4.27 mL of a 1 M solution in THF, 4.27 mmol, 1.3 eq) was added to a stirred solution of OTBS piperidine *cis*-**397** (1.6 g, 3.29 mmol, 1.00 eq) in THF (25 mL) at rt under Ar. The resulting solution was stirred at rt for 18 h and Et_2O (50 mL) and water (25 mL) were added. The layers were separated and the aqueous layer was extracted with Et_2O ($3 \times 25\text{ mL}$). 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 using 4:6 hexane-EtOAc as eluent gave hydroxy piperidine *cis*-**407** (1.16 g, 95%) as a white solid, mp $60\text{--}62\text{ }^{\circ}\text{C}$; R_F (1:1 hexane-EtOAc) 0.14; IR (ATR) $3249\text{ (OH)}, 2905, 1678\text{ (C=O)}, 1217, 1053, 728\text{ cm}^{-1}$; ^1H NMR (400 MHz, CDCl_3) δ 8.60 (d, $J = 4.5\text{ Hz}$, 1H, Ar), 7.99 (d, $J = 9.0\text{ Hz}$, 1H, Ar), 7.80–7.48 (br m, 1H), 7.34 (dd, $J = 9.0, 2.5\text{ Hz}$, 1H, Ar), 7.27 (d, $J = 4.5\text{ Hz}$, 1H, Ar), 4.59 (ddd, $J = 7.0, 7.0, 7.0\text{ Hz}$, 1H, NCH), 4.29–4.23 (m, 1H, OCH), 4.05–3.95 (m, 4H, OMe, NCH), 3.63–3.53 (m, 1H, NCH), 3.52–3.42 (m, 2H, CHAr), 2.32 (br s, 1H, OH), 1.84–1.64 (m, 4H, CH), 1.19 (br s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ 158.0 (*ipso*-Ar), 154.9 (C=O), 147.4 (Ar), 144.8 (*ipso*-Ar),

144.4 (*ipso*-Ar), 131.3 (Ar), 129.2 (*ipso*-Ar), 123.1 (Ar), 121.6 (Ar), 102.6 (Ar), 79.6 (OCMe₃), 64.5 (OCH), 55.9 (OMe), 49.6 (NCH), 35.7 (CH₂Ar), 33.7 (NCH₂), 32.8 (CH₂), 28.2 (CMe₃) (1 × CH₂ resonance not resolved); HRMS (ESI) *m/z* calcd for C₂₁H₂₈N₂O₄ (M + H)⁺ 373.2122, found 373.2121 (+0.3 ppm error).

Lab book reference: ARG-4-030

***tert*-Butyl 2-((6-methoxyquinolin-4-yl)methyl)-4-((methylsulfonyl)oxy)piperidine-1-carboxylate *cis*-396**



MsCl (0.37 mL, 4.81 mmol, 1.6 eq) was added to a solution of hydroxypiperidine *cis*-407 (1.12 g, 3.01 mmol, 1.0 eq) and Et₃N (0.67 mL, 4.81 mmol, 1.6 eq) in CH₂Cl₂ (20 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 18 h. 1 M HCl_(aq) (20 mL) was added, and the two layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 25 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc as eluent gave mesylate *cis*-396 (470 mg, 36%) as a white solid, mp 90-92 °C; *R*_F (1:1 hexane-EtOAc) 0.18; IR (ATR) 2924, 1682 (C=O), 1352, 1167, 907, 729, 530 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.68–8.56 (m, 1H, Ar), 7.99 (d, *J* = 9.0 Hz, 1H, Ar), 7.66–7.42 (m, 1H, Ar), 7.34 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar), 7.22–7.17 (m, 1H, Ar), 5.13–5.03 (m, 1H, OCH), 4.70 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 1H, NCH), 4.16–4.05 (m, 1H, NCH), 3.98 (s, 3H, OMe), 3.49–3.29 (m, 3H, NCH, CHAr), 3.08 (s, 3H, SO₂Me), 2.15–2.04 (m, 2H, CH), 1.93–1.78 (m, 2H, CH), 1.22 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 158.1 (*ipso*-Ar), 154.5 (C=O), 147.5 (Ar), 144.4 (*ipso*-Ar), 143.5 (*ipso*-Ar), 131.6 (Ar), 128.9 (*ipso*-Ar), 122.8 (Ar), 121.78 (Ar), 102.2 (Ar), 80.1 (OCMe₃), 76.4 (OCH), 55.9 (OMe), 48.6 (NCH), 38.7 (SO₂Me), 35.4 (CH₂Ar), 33.7 (NCH₂), 30.5 (CH₂), 29.8 (CH₂), 28.0 (CMe₃); HRMS *m/z* calcd for C₂₂H₃₀N₂O₆S (M + H)⁺ 451.1897, found 451.1898 (–0.2 ppm error).

Lab book reference: ARG-4-035

Diethyl 2-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)malonate **410**

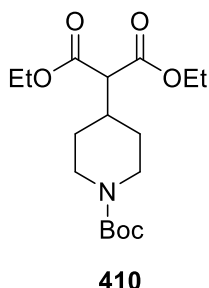


Table 4.4, Entry 7

Diethyl malonate (1.64 mL, 10.74 mmol, 3.0 eq) was added to a stirred solution of NaOt-Bu (1.03 g, 10.74 mmol, 3.0 eq) and 18-crown-6 (1.42 g, 5.37 mmol, 1.5 eq) in toluene (20 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 30 min. *tert*-Butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate **408** (1.0 g, 3.58 mmol, 1.0 eq) was added at 0 °C and the resulting mixture was stirred and heated at 100 °C for 18 h under Ar. H₂O (20 mL) was added, and the two layers separated. The aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 hexane-EtOAc as eluent gave diester **410** (1.05 g, 85%) as a clear oil, *R*_F (85:15 hexane-EtOAc) 0.18; ¹H NMR (400 MHz, CDCl₃) δ 4.15 (q, *J* = 7.0 Hz, 4H, OCH₂), 4.11–4.01 (m, 2H, NCH), 3.12 (d, *J* = 9.0 Hz, 1H, CHC(O)), 2.74–2.63 (m, 2H, NCH), 2.24–2.12 (m, 1H, CH), 1.69–1.60 (m, 2H, CH), 1.40 (s, 9H, CMe₃), 1.27–1.14 (m, 8H, Me, CH); HRMS *m/z* calcd for C₁₇H₂₉NO₆ (*M* + *H*)⁺ 344.2073, found 344.2071 (–0.5 ppm error).

Lab book reference: ARG-4-012

Table 4.4., Entry 1

Diethyl malonate (110 μL, 0.63 mmol, 1.75 eq) was added to a stirred solution of NaH (26 mg, 0.63 mmol, 1.75 eq) in dioxane (2 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 30 min. *tert*-Butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate **408**

(100 mg, 0.36 mmol, 1.0 eq) was added at 0 °C and the resulting mixture was heated and stirred at 85 °C for 18 h under Ar. H₂O (10 mL) was added, and the two layers separated. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 hexane-EtOAc as eluent gave diester **410** (37 mg, 30%) as a white solid identical (by ¹H NMR spectroscopy) to that described above.

Lab book reference: ARG-3-179

Table 4.4, Entry 2

Diethyl malonate (230 µL, 1.5 mmol, 3.0 eq) was added to a stirred solution of KO^{*t*}-Bu (168 mg, 1.5 mmol, 3.0 eq) in toluene (5 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 30 min. *tert*-Butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate **408** (140 mg, 0.5 mmol, 1.0 eq) was added at 0 °C and the resulting mixture was heated and stirred at 85 °C for 18 h under Ar. H₂O (10 mL) was added, and the two layers separated. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained (by ¹H NMR spectroscopy and HRMS) no diester **410**.

Lab book reference: ARG-3-180

Table 4.4 Entry 3

Diethyl malonate (230 µL, 1.5 mmol, 3.0 eq) was added to a stirred solution of NaO^{*t*}-Bu (145 mg, 1.5 mmol, 3.0 eq) in toluene (5 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 30 min. *tert*-Butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate **408** (140 mg, 0.5 mmol, 1.0 eq) was added at 0 °C and the resulting mixture was heated and stirred at 85 °C for 18 h under Ar. H₂O (10 mL) was added, and the two layers separated. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained (by ¹H NMR spectroscopy and HRMS) no diester **410**.

Lab book reference: ARG-4-002

Table 4.4, Entry 4

Diethyl malonate (230 μ L, 1.5 mmol, 3.0 eq) was added to a stirred solution of NaOt-Bu (145 mg, 1.5 mmol, 3.0 eq) and 18-crown-6 (66 mg, 0.25 mmol, 0.5 eq) in toluene (5 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 30 min. *tert*-Butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate **408** (140 mg, 0.5 mmol, 1.0 eq) was added at 0 °C and the resulting mixture was heated and stirred at 85 °C for 18 h under Ar. H₂O (10 mL) was added, and the two layers separated. The aqueous layer was extracted with EtOAc (3 $\times$ 15 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 hexane-EtOAc as eluent gave diester **410** (69 mg, 40%) as a white solid identical (by ¹H NMR spectroscopy) to that described above.

Lab book reference: ARG-4-003

Table 4.4, Entry 5

Diethyl malonate (230 μ L, 1.5 mmol, 3.0 eq) was added to a stirred solution of NaOt-Bu (145 mg, 1.5 mmol, 3.0 eq) and 18-crown-6 (132 mg, 0.50 mmol, 1.0 eq) in toluene (5 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 30 min. *tert*-Butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate **408** (140 mg, 0.5 mmol, 1.0 eq) was added at 0 °C and the resulting mixture was heated and stirred at 85 °C for 18 h under Ar. H₂O (10 mL) was added, and the two layers separated. The aqueous layer was extracted with EtOAc (3 $\times$ 15 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 hexane-EtOAc as eluent gave diester **410** (108 mg, 63%) as a white solid identical (by ¹H NMR spectroscopy) to that described above.

Lab book reference: ARG-4-003

Table 4.4, Entry 6

Diethyl malonate (230 μ L, 1.5 mmol, 3.0 eq) was added to a stirred solution of NaOt-Bu (145 mg, 1.5 mmol, 3.0 eq) and 18-crown-6 (198 mg, 0.75 mmol, 1.5 eq) in toluene (5 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 30 min. *tert*-Butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate **408** (140 mg, 0.5 mmol, 1.0 eq) was added at 0 °C and the resulting mixture was heated and stirred at 85 °C for 18 h under Ar. H₂O (10 mL) was added, and the two layers separated. The aqueous layer was extracted with EtOAc (3 $\times$ 15 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 hexane-EtOAc as eluent gave diester **410** (122 mg, 71%) as a white solid identical (by ¹H NMR spectroscopy) to that described above.

Lab book reference: ARG-4-003

Diethyl 2-(1-(*tert*-butoxycarbonyl)-2-((6-methoxyquinolin-4-yl)methyl)piperidin-4-yl)malonate *trans*-411, *tert*-butyl 6-((6-methoxyquinolin-4-yl)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate and *tert*-butyl 2-((6-methoxyquinolin-4-yl)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate **412**

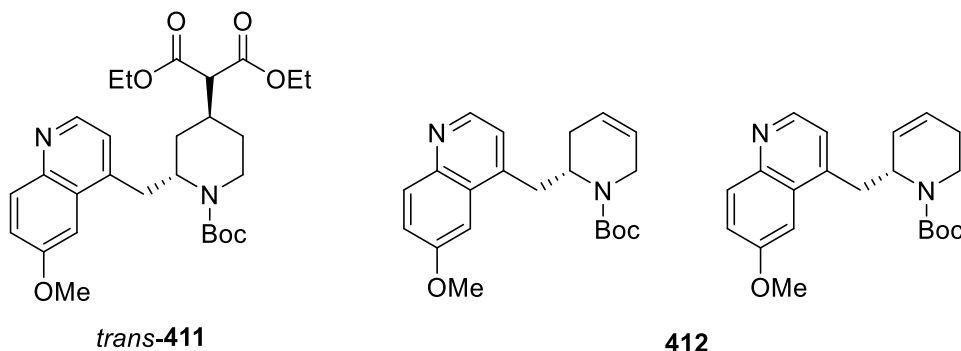


Table 4.5, Entry 2

Diethyl malonate (0.42 mL, 2.77 mmol, 3.0 eq) was added to a stirred solution of NaOt-Bu (266 mg, 2.77 mmol, 3.0 eq) and 18-crown-6 (366 mg, 1.39 mmol, 1.5 eq) in toluene (5 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 30 min. Piperidine mesylate *cis*-**396** (416 mg, 0.93 mmol, 1.0 eq) was added at 0 °C and the resulting mixture was stirred and heated at 90 °C for 18 h under Ar. EtOAc (15 mL) and H₂O (15 mL) was added, and the two layers separated. The aqueous layer was extracted with EtOAc (3 $\times$ 15 mL). The

combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:7 hexane-EtOAc as eluent gave a mixture of alkenes **412** (25 mg, 25%) as a clear oil and diester *trans*-**411** (339 mg, 71%) as a clear oil, *R*_F (4:6 hexane-EtOAc) 0.31; IR (ATR) 3249, 1678 (C=O), 1630, 1510, 1053, 728 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (60:40 mixture of rotamers) δ 8.63 (d, *J* = 4.5 Hz, 1H, Ar), 8.04–7.93 (m, 1H, Ar), 7.88–7.80 (m, 0.6H, Ar), 7.40–7.22 (m, 2H, Ar), 7.14–7.07 (m, 0.4H, Ar), 4.73–4.62 (m, 1H, NCH), 4.29–3.90 (m, 8H, C(O)CHH', OMe, NCH), 3.36–3.02 (m, 3H, CHAr, NCH), 2.72–2.58 (m, 1H, CHC(O)), 1.98–1.71 (m, 2H, CH), 1.57–1.39 (m, 6.4H, CH, CMe₃), 1.32–1.13 (m, 8H, CH₂Me, CH), 0.84 (s, 3.6H, CMe₃); ¹³C NMR (101 MHz, CDCl₃) (rotamers) δ 168.3 (C=O), 168.2 (C=O), 166.5 (C=O), 166.2 (C=O), 158.1 (*ipso*-Ar), 154.9 (C=O, Boc), 147.8 (Ar), 147.3 (Ar), 144.4 (*ipso*-Ar), 143.0 (*ipso*-Ar), 131.2 (Ar), 128.9 (*ipso*-Ar), 123.1 (Ar), 122.4 (Ar), 120.8 (Ar), 102.5 (Ar), 102.1 (Ar), 79.9 (CMe₃), 61.6 (OCH₂), 57.6 (OCH₂), 56.0 (OMe), 50.9 (NCH), 49.6 (NCH), 41.8 (CH₂Ar), 39.9 (NCH₂), 37.8 (NCH₂), 33.5 (CH₂Ar), 31.3 (CH), 31.0 (CH), 30.1 (CH₂), 29.7 (CH₂), 28.5 (CMe₃), 27.7 (CMe₃), 14.2 (CH₂Me), 14.1 (CH₂Me); HRMS *m/z* calcd for C₂₁H₂₉N₂O₄ (M + H)⁺ 373.2122, found 373.2121 (+0.3 ppm error). Diagnostic signals for alkenes **412**: ¹H NMR (400 MHz, CDCl₃). δ 8.67–8.61 (m, 1H, Ar), 8.07–7.88 (m, 1H, Ar), 7.37–7.32 (m, 1H, Ar), 7.16–7.10 (m, 1H, Ar), 5.98–5.76 (m, 1H, =CH), 5.75–5.21 (m, 1H, =CH), 4.84–4.71 (m, 1H, NCH).

Lab book reference: ARG-4-059

Table 4.5, Entry 1

Diethyl malonate (130 μL, 0.84 mmol, 3.0 eq) was added to a stirred solution of NaOt-Bu (81 mg, 0.84 mmol, 3.0 eq) and 18-crown-6 (111 mg, 0.43 mmol, 1.5 eq) in toluene (4 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 30 min. Piperidine mesylate *cis*-**396** (126 mg, 0.28 mmol, 1.0 eq) was added at 0 °C and the resulting mixture was stirred and heated at 100 °C for 18 h under Ar. EtOAc (10 mL) and H₂O (10 mL) was added, and the two layers separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:7 hexane-EtOAc as eluent gave a mixture of alkenes **412**

(25 mg, 25%), as a clear oil and diester *trans*-**411** (82 mg, 59%) as a clear oil. Characterisation identical (by ^1H NMR spectroscopy) to those described above.

Lab book reference: ARG-4-031

Table 4.5, Entry 3

Diethyl malonate (0.42 mL, 2.77 mmol, 3.0 eq) was added to a stirred solution of NaOt-Bu (266 mg, 2.77 mmol, 3.0 eq) and 18-crown-6 (366 mg, 1.39 mmol, 1.5 eq) in toluene (5 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 30 min. Piperidine mesylate *cis*-**396** (416 mg, 0.93 mmol, 1.0 eq) was added at 0 °C and the resulting mixture was stirred and heated at 80 °C for 18 h under Ar. EtOAc (15 mL) and H₂O (15 mL) was added, and the two layers separated. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:7 hexane-EtOAc as eluent gave a mixture of alkenes **412** (56 mg, 17%), as a clear oil and diester *trans*-**411** (292 mg, 61%) as a clear oil. Characterisation identical (by ^1H NMR spectroscopy) to those described above.

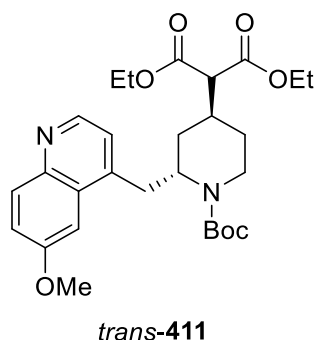
Lab book reference: ARG-4-059

Table 4.5, Entry 4

Diethyl malonate (130 μL , 0.84 mmol, 3.0 eq) was added to a stirred solution of NaOt-Bu (81 mg, 0.84 mmol, 3.0 eq) and 18-crown-6 (111 mg, 0.43 mmol, 1.5 eq) in toluene (4 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 30 min. Piperidine mesylate *cis*-**396** (126 mg, 0.28 mmol, 1.0 eq) was added at 0 °C and the resulting mixture was stirred and heated at 70 °C for 18 h under Ar. EtOAc (10 mL) and H₂O (10 mL) was added, and the two layers separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:7 hexane-EtOAc as eluent gave a mixture of alkenes **412** (38 mg, 12%), as a clear oil and diester *trans*-**411** (177 mg, 37%) as a clear oil. Characterisation identical (by ^1H NMR spectroscopy) to those described above.

Lab book reference: ARG-4-059

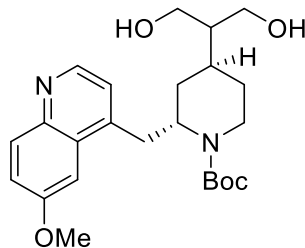
Diethyl 2-(1-(*tert*-butoxycarbonyl)-2-((6-methoxyquinolin-4-yl)methyl)piperidin-4-yl)malonate *trans*-411



MsCl (0.56 mL, 7.25 mmol, 1.4 eq) was added to a solution of hydroxypiperidine *cis*-407 (1.93 g, 5.18 mmol, 1.0 eq) and Et₃N (1.1 mL, 7.25 mmol, 1.4 eq) in CH₂Cl₂ (25 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 18 h. 1 M HCl_(aq) (20 mL) was added, and the two layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic extracts were washed with 2 M NaOH_(aq) (50 mL), brine (50 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude mesylate. Separately, diethyl malonate (2.44 mL, 15.5 mmol, 3.0 eq) was added to a stirred solution of NaOt-Bu (1.49 g, 15.5 mmol, 3.0 eq) and 18-crown-6 (2.05 g, 7.77 mmol, 1.5 eq) in toluene (25 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 30 min. The crude mesylation product (2.3 g) was added at 0 °C and the resulting mixture was stirred and heated at 90 °C for 18 h under Ar. EtOAc (25 mL) and H₂O (25 mL) was added, and the two layers separated. The aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:7 hexane-EtOAc as eluent diester *trans*-411 (2.05 g, 77%) as a clear oil, identical (by ¹H NMR spectroscopy) to that described above.

Lab book reference: ARG-5-008

***tert*-Butyl 4-(1,3-dihydroxypropan-2-yl)-2-((6-methoxyquinolin-4-yl)methyl)piperidine-1-carboxylate *trans*-413**



***trans*-413**

DIBAL-H (15.3 mL of a 1 M solution in THF, 15.3 mmol, 4.3 eq) was added to a solution of diester *trans*-411 (1.83 g, 3.56 mmol, 1.0 eq) in THF (18 mL) at -78°C under Ar. The resulting solution was stirred at -78°C for 1 h and then at rt for 18 h. Sat. Rochelle's salt (25 mL) was added at rt under air and the resulting mixture stirred for 30 min. Et₂O (50 mL) and H₂O (25 mL) were added, and the two layers separated. The aqueous layer was extracted with Et₂O (4 $\times$ 30 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 96:4 CH₂Cl₂-MeOH as eluent gave diol *trans*-413 (1.0 g, 66%) as a white solid, mp 80-82 $^{\circ}\text{C}$; R_F (96:4 CH₂Cl₂-MeOH) 0.34; IR (ATR) 3356 (OH), 2932, 1676 (C=O), 1365, 1159, 830, 534 cm^{-1} ; ^1H NMR (400 MHz, CD₃OD) (55:45 mixture of rotamers) δ 8.56–8.45 (m, 1H, Ar), 7.93 (d, J = 9.0 Hz, 0.55H, Ar), 7.87 (d, J = 9.0 Hz, 0.45H, Ar), 7.80–7.76 (m, 0.45H, Ar), 7.41 (dd, J = 9.0, 2.5 Hz, 0.55H, Ar), 7.37–7.33 (m, 1H, Ar), 7.31 (d, J = 4.5 Hz, 0.45H, Ar), 7.19 (d, J = 4.5 Hz, 0.55H, Ar), 4.73–4.61 (m, 1H, NCH), 4.15–4.05 (m, 1H, NCH), 4.02 (s, 1.35H, OMe), 3.96 (s, 1.65H, OMe), 3.79–3.54 (m, 4H, OCH), 3.43 (dd, J = 12.5, 12.5 Hz, 0.55H, CHAr), 3.28–3.07 (m, 2.45H, CHAr, NCH), 2.23–2.10 (m, 1H, CH), 2.04–1.97 (m, 0.55H, CH), 1.89–1.77 (m, 1H, CH), 1.64–1.52 (m, 1H, CH), 1.47 (dd, J = 6.0, 6.0 Hz, 0.45H, CH), 1.40 (s, 4.05H, CMe₃), 1.30–1.10 (m, 2H, CH), 0.67 (s, 5.95H, CMe₃); ^{13}C NMR (100.6 MHz, CD₃OD) (rotamers) δ 159.7 (*ipso*-Ar), 159.6 (*ipso*-Ar), 156.4 (C=O), 155.9 (C=O), 148.0 (*ipso*-Ar), 147.7 (*ipso*-Ar), 147.2 (*ipso*-Ar), 146.4 (Ar), 144.6 (*ipso*-Ar), 131.3 (*ipso*-Ar), 130.9 (*ipso*-Ar), 130.6 (Ar), 130.3 (Ar), 124.1 (Ar), 123.8 (Ar), 123.0 (Ar), 103.4 (Ar), 103.3 (Ar), 80.8 (CMe₃), 80.3 (CMe₃), 61.5 (OCH₂), 61.47 (OCH₂), 61.4 (OCH₂), 56.4 (OMe), 56.2 (OMe), 53.0 (NCH), 51.6 (NCH), 41.4 (NCH₂), 39.3 (NCH₂), 35.2 (CH₂), 34.1 (CH₂Ar), 34.0 (CH₂Ar), 31.3 (CH₂), 30.7 (CH₂), 30.1 (CH), 29.4 (CH), 28.7 (CMe₃),

27.8(CMe₃); HRMS *m/z* calcd for C₂₄H₃₄N₂O₅ (M + H)⁺ 431.2540, found 431.2543 (−0.6 ppm error). The stereochemistry of diol *trans*-**413** was confirmed by X-ray crystallography.

Lab book reference: ARG-5-011

LiBH₄ (0.93 mL of a 4 M solution in THF, 3.73 mmol, 6.0 eq) was added to a solution of diester *trans*-**411** (320 mg, 0.62 mmol, 1.0 eq) in THF (12 mL) at 0 °C under Ar. The resulting solution was then stirred and heated at reflux for 18 h. After cooling to rt, Et₂O (15 mL) and H₂O (15 mL) were added, and the two layers separated. The aqueous layer was extracted with Et₂O (4 × 20 mL). The combined organic extracts were washed with brine (25 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 96:4 CH₂Cl₂-MeOH as eluent gave diol *trans*-**413** (120 mg, 45%) as a white solid, identical (by ¹H NMR spectroscopy) to that described above.

Lab book reference: ARG-4-160

tert*-Butyl 4-(1-acetoxy-3-hydroxypropan-2-yl)piperidine-1-carboxylate **418** and 2-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)propane-1,3-diyl diacetate **419*

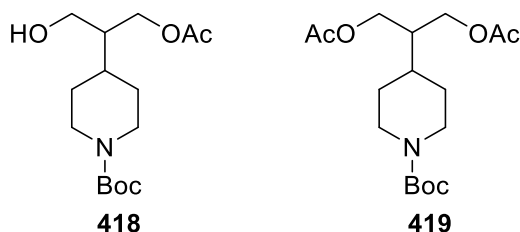


Table 4.6, Entry 7

PPL (120 mg of a 50 U/mg powder, 6000 U, 20000 U/mmol) was added to a suspension of diol **417** (78 g, 0.3 mmol, 1.0 eq) and 3 Å MS (200 mg) in vinyl acetate (3 mL, 0.1 mM) at 25 °C under Ar. The resulting solution was stirred and heated at 25 °C for 4 h and another portion of PPL (120 mg of a 50 U/mg powder, 6000 U, 20000 U/mmol) was added. The resulting suspension was stirred and heated at 25 °C for 4 h and another portion of PPL (120 mg of a 50 U/mg powder, 6000 U, 20000 U/mmol) was added. The total of PPL added was 360 mg, 18000 U, 60000 U/mmol. The resulting suspension was stirred and heated at 25 °C

for 10 h. The solids were removed by filtration through Celite[®] and washed with EtOAc (25 mL) and MeOH (25 mL). The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:9 hexane-EtOAc as eluent gave diacetate **419** (12 mg, 12%) as a white solid, R_F (2:8 hexane-EtOAc) 0.63; ^1H NMR (400 MHz, CDCl_3) δ 4.15–3.96 (m, 6H, OCH, NCH), 2.66–2.51 (m, 2H, NCH), 2.01–1.97 (m, 6H, Ac), 1.83–1.76 (m, 1H, CH), 1.65–1.57 (m, 2H, CH), 1.57–1.50 (m, 1H, CH), 1.39 (s, 9H, CMe_3), 1.24–1.12 (m, 2H, CH). And monoacetate **418** (58 mg, 64%) as a white solid, R_F (2:8 hexane-EtOAc) 0.32; ^1H NMR (400 MHz, CDCl_3) δ 4.25 (ddd, $J = 11.5, 4.0, 1.5$ Hz, 1H, OCH), 4.18–4.01 (m, 3H, OCH), 3.66 (ddd, $J = 11.5, 4.0, 1.5$ Hz, 1H, OCH), 3.57 (ddd, $J = 11.5, 6.0, 1.5$ Hz, 1H, NCH), 2.69–2.56 (m, 2H, NCH), 2.05 (s, 3H, Ac), 1.72–1.53 (m, 4H, CH, OH), 1.42 (s, 9H, CMe_3), 1.27–1.17 (m, 3H, CH); HRMS m/z calcd for $\text{C}_{15}\text{H}_{27}\text{NO}_5$ ($\text{M} + \text{Na}$)⁺ 324.1781, found 324.1783 (–0.6 ppm error). Spectroscopic data consistent with those reported in the literature.³⁸⁷

Lab book reference: ARG-4-183

Table 4.6, Entry 1

PPL (120 mg of a 50 U/mg powder, 6000 U, 20000 U/mmol) was added to a suspension of diol **417** (78 g, 0.3 mmol, 1.0 eq) and 3 Å MS (200 mg) in vinyl acetate (3 mL, 0.1 mM) at 25 °C under Ar. The resulting solution was stirred and heated at 25 °C for 24 h. The solids were removed by filtration through Celite[®] eluting with EtOAc (25 mL) and MeOH (25 mL). The solvent was then evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:9 hexane-EtOAc as eluent gave diacetate **419** (10 mg, 10%) as a white solid and monoacetate **418** (34 mg, 38%) as a white solid. Spectroscopic data consistent with those reported in the literature.³⁸⁷

Lab book reference: ARG-4-163

Table 4.6, Entry 2

PPL (120 mg of a 50 U/mg powder, 6000 U, 20000 U/mmol) was added to a suspension of diol **417** (78 g, 0.3 mmol, 1.0 eq) and 3 Å MS (200 mg) in vinyl acetate (3 mL, 0.1 mM) at 25 °C under Ar. The resulting solution was stirred and heated at 25 °C for 48 h. The solids

were removed by filtration through Celite[®] eluting with EtOAc (25 mL) and MeOH (25 mL). The solvent was then evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:9 hexane-EtOAc as eluent gave diacetate **419** (8 mg, 8%) as a white solid and monoacetate **418** (36 mg, 40%) as a white solid. Spectroscopic data consistent with those reported in the literature.³⁸⁷

Lab book reference: ARG-4-165

Table 4.6, Entry 3

PPL (120 mg of a 50 U/mg powder, 6000 U, 20000 U/mmol) was added to a suspension of diol **417** (78 g, 0.3 mmol, 1.0 eq) and 3 Å MS (200 mg) in vinyl acetate (3 mL, 0.1 mM) at 25 °C under Ar. The resulting solution was stirred and heated at 25 °C for 72 h. The solids were removed by filtration through Celite[®] eluting with EtOAc (25 mL) and MeOH (25 mL). The solvent was then evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:9 hexane-EtOAc as eluent gave diacetate **419** (8 mg, 8%) as a white solid and monoacetate **418** (40 mg, 44%) as a white solid. Spectroscopic data consistent with those reported in the literature.³⁸⁷

Lab book reference: ARG-4-165

Table 4.6, Entry 4

PPL (360 mg of a 50 U/mg powder, 18000 U, 20000 U/mmol) was added to a suspension of diol **417** (78 g, 0.3 mmol, 1.0 eq) and 3 Å MS (200 mg) in vinyl acetate (3 mL, 0.1 mM) at 25 °C under Ar. The resulting solution was stirred and heated at 25 °C for 4 h. The solids were removed by filtration through Celite[®] eluting with EtOAc (25 mL) and MeOH (25 mL). The solvent was then evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:9 hexane-EtOAc as eluent gave diacetate **419** (5 mg, 5%) as a white solid and monoacetate **418** (20 mg, 22%) as a white solid. Spectroscopic data consistent with those reported in the literature.³⁸⁷

Lab book reference: ARG-4-166

Table 4.6, Entry 5

PPL (120 mg of a 50 U/mg powder, 5850 U, 20000 U/mmol) was added to a suspension of diol **417** (78 g, 0.3 mmol, 1.0 eq) and 3 Å MS (200 mg) in EtOAc (3 mL, 0.1 mM) at 25 °C under Ar. The resulting solution was stirred and heated at 25 °C for 92 h. The solids were removed by filtration through Celite® eluting with EtOAc (25 mL) and MeOH (25 mL). The solvent was then evaporated under reduced pressure to give the crude product which contained (by ¹H NMR spectroscopy and HRMS) only trace diacetate **419**. Purification by flash column chromatography on silica with 1:9 hexane-EtOAc as eluent gave monoacetate **418** (30 mg, 33%) as a white solid. Spectroscopic data consistent with those reported in the literature.³⁸⁷

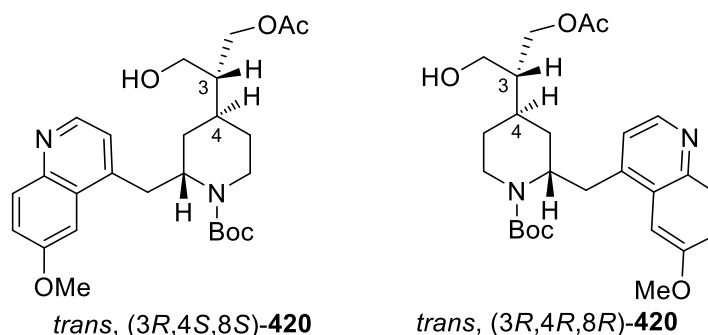
Lab book reference: ARG-4-168

Table 4.6, Entry 6

PPL (360 mg of a 50 U/mg powder, 18000 U, 20000 U/mmol) was added to a suspension of diol **417** (78 g, 0.3 mmol, 1.0 eq) and 3 Å MS (200 mg) in EtOAc (3 mL, 0.1 mM) at 25 °C under Ar. The resulting solution was stirred and heated at 25 °C for 24 h. The solids were removed by filtration through Celite® eluting with EtOAc (25 mL) and MeOH (25 mL). The solvent was then evaporated under reduced pressure to give the crude product which contained (by ¹H NMR spectroscopy and HRMS) only trace diacetate **419**. Purification by flash column chromatography on silica with 1:9 hexane-EtOAc as eluent gave monoacetate **418** (29 mg, 31%) as a white solid. Spectroscopic data consistent with those reported in the literature.³⁸⁷

Lab book reference: ARG-4-169

***tert*-Butyl (2*S*,4*S*)-4-((*R*)-1-acetoxy-3-hydroxypropan-2-yl)-2-((6-methoxyquinolin-4-yl)methyl)piperidine-1-carboxylate *trans*,(3*R*,4*S*,8*S*)-420 and *tert*-butyl (2*R*,4*R*)-4-((*R*)-1-acetoxy-3-hydroxypropan-2-yl)-2-((6-methoxyquinolin-4-yl)methyl)piperidine-1-carboxylate *trans*,(3*R*,4*R*,8*R*)-420**

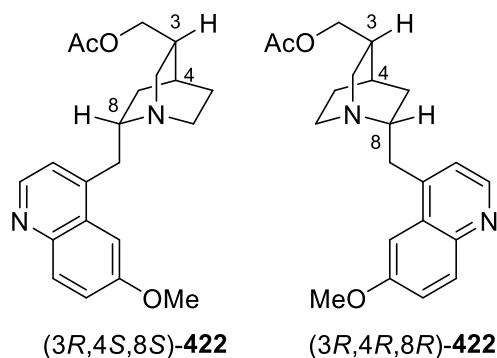


PPL (512 mg of a 50 U/mg powder, 25600 U, 20000 U/mmol) was added to a suspension of diol *trans*-**413** (550 mg, 1.28 mmol, 1.0 eq) and 3 Å MS (500 mg) in vinyl acetate (13 mL, 0.1 mM) and DMF (0.85 mL, 1.5 mM) at 25 °C under Ar. The resulting solution was stirred and heated at 25 °C for 4 h and another portion of PPL (512 mg of a 50 U/mg powder, 25600 U, 20000 U/mmol) was added. The resulting suspension was stirred and heated at 25 °C for 4 h and another portion of PPL (512 mg of a 50 U/mg powder, 25600 U, 20000 U/mmol) was added. The total PPL added was 1.54 g, 76800 U, 60000 U/mmol. The resulting suspension was stirred and heated at 25 °C for 10 h. The solids were removed by filtration through Celite® and washed with EtOAc (50 mL) and MeOH (50 mL). The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH₂Cl₂-MeOH as eluent gave a presumed 50:50 mixture of monoacetates (3*R*,4*S*,8*S*)- and (3*R*,4*R*,8*R*)-**420** (527 mg, 87%) as a clear oil, *R*_F (98:2 CH₂Cl₂-MeOH) 0.27; IR (ATR) 3342 (OH), 2946, 1736 (C=O, ester), 1680 (C=O, Boc), 1364, 1242, 1031, 855 cm⁻¹; ¹H NMR (400 MHz, Acetone-D₆) (60:40 mixture of rotamers) δ 8.63–8.57 (m, 1H, Ar), 8.01–7.91 (m, 1.6H, Ar), 7.50–7.47 (m, 0.4H, Ar), 7.42–7.34 (m, 1H, Ar), 7.31 (d, *J* = 4.5 Hz, 0.6H, Ar), 7.22 (d, *J* = 4.5 Hz, 0.4H, Ar), 4.81–4.67 (m, 1H, NCH), 4.24–4.13 (m, 2H, NCH, OCH), 4.11–4.03 (m, 2.8H, NCH, OMe), 3.99 (s, 1.2H, OMe), 3.81–3.52 (m, 2.6H, OCH), 3.51–3.12 (m, 3.4H, OCH, CHAr), 2.30–2.15 (m, 1H, OH), 2.04–1.98 (m, 3H, Ac), 1.92–1.79 (m, 1H, CH), 1.73–1.51 (m, 2H, CH), 1.47 (s, 5.4H, CMe₃), 1.39–1.14 (m, 2H, CH), 0.82–0.71 (m, 3.6H, CMe₃); ¹³C NMR (100.6 MHz, Acetone-D₆) (rotamers, diastereomers) δ 171.1 (C=O, ester), 158.6 (C=O, Boc), 158.57 (C=O, Boc), 155.5 (*ipso*-Ar), 154.3 (*ipso*-Ar), 148.0 (Ar), 147.8 (Ar), 145.2 (*ipso*-Ar), 145.1

(*ipso*-Ar), 144.2 (*ipso*-Ar), 132.1 (Ar), 131.8 (Ar), 129.7 (*ipso*-Ar), 129.5 (*ipso*-Ar), 123.6 (Ar), 123.4 (Ar), 123.2 (Ar), 122.6 (Ar), 121.6 (Ar), 103.1 (Ar), 103.0 (Ar), 79.7 (CMe₃), 78.5 (CMe₃), 63.4 (OCH₂), 63.1 (OCH₂), 63.0 (OCH₂), 60.1 (OCH₂), 60.0 (OCH₂), 59.8 (OCH₂), 59.7 (OCH₂), 56.0 (OMe), 55.9 (OMe), 52.1 (NCH), 50.7 (NCH), 50.6 (NCH), 45.7 (CH), 45.6 (CH), 45.4 (CH), 40.8 (NCH₂), 38.5 (NCH₂), 34.6 (CH₂Ar), 34.5 (CH₂Ar), 33.4 (CH₂Ar), 30.4 (CH₂), 30.2 (CH₂), 28.3 (CMe₃), 27.5 (CMe₃), 20.7 (Me); HRMS *m/z* calcd for C₂₆H₃₆N₂O₆ (M + Na)⁺ 495.2466, found 495.2460 (+1.2 ppm error).

Lab book reference: ARG-5-016

(3*R*,4*S*,6*S*)-6-((6-Methoxyquinolin-4-yl)methyl)quinuclidin-3-yl)methyl acetate
(3*R*,4*S*,8*S*)-422 and ((3*R*,4*R*,6*R*)-6-((6-methoxyquinolin-4-yl)methyl)quinuclidin-3-yl)methyl acetate (3*R*,4*R*,8*R*)-422

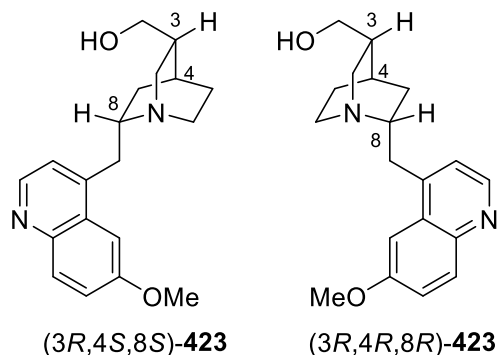


MsCl (57 μ L, 0.74 mmol, 1.5 eq) was added to a solution of a presumed 50:50 mixture of monoacetates (3*R*,4*S*,8*S*)- and (3*R*,4*R*,8*R*)-**420** (233 mg, 0.49 mmol, 1.0 eq) and Et₃N (0.10 mL, 0.74 mmol, 156 eq) in CH₂Cl₂ (3 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 18 h. 1 M HCl_(aq) (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 10 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 CH₂Cl₂-MeOH as eluent gave mesylates **421** (236 mg, 88%) as a white solid, ¹H NMR (400 MHz, CDCl₃) δ 8.64–8.55 (m, 1H, Ar), 8.02–7.90 (m, 1H, Ar), 7.79 (dd, *J* = 9.5, 2.5 Hz, 0.55H, Ar), 7.37–7.28 (m, 1H, Ar), 7.21–7.17 (m, 0.45H, Ar), 7.13–7.00 (m, 1H, Ar), 4.78–4.62 (m, 1H, NCH), 4.37–4.09 (m, 3.55H, NCH, OCH), 4.08–3.99 (m, 2.9H, OMe, OCH, NCH), 3.96–3.89 (m, 1.65H, OMe), 3.29–3.19 (m, 1H, CHAr), 3.16–2.90 (m, 4.9H, SO₂Me, CHAr, NCH), 2.07–2.01 (m, 3H, CO₂Me), 1.90–1.73 (m, 2.55H, CH), 1.61–1.48 (m, 1H, CH),

1.47–1.37 (m, 4.95H, CMe₃), 1.33–1.10 (m, 2.45H, CH), 0.81–0.71 (m, 4.05H, CMe₃). The mesylates (190 mg) were dissolved in CH₂Cl₂ (4 mL) and TFA (0.5 mL, 6.9 mmol, 20 eq) were added at rt under Ar. The resulting mixture was stirred at rt for 3 h and the solvent was evaporated under reduced pressure. Toluene (10 mL) was added, and the solvent evaporated under reduced pressure to give the crude TFA salt. The crude TFA salt was dissolved in DMF (7 mL). K₂CO₃ (525 mg, 7.25 mmol, 21 eq) was added and the resulting mixture was heated and stirred at 80 °C for 18 h. After cooling down to rt, EtOAc (25 mL) and H₂O (25 mL) were added and the two layers separated. The aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic extracts were washed with brine (5 × 15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 CH₂Cl₂-MeOH as eluent gave a 50:50 mixture of quinuclidines (3*R*,4*S*,8*S*)- and (3*R*,4*R*,8*R*)-**422** (90 mg, 73%, 64% over two steps) as a clear oil, *R*_F (9:1 CH₂Cl₂-MeOH) 0.21; IR (ATR) 2936, 1735 (C=O), 1508, 1241, 1030, 849 cm⁻¹; ¹H NMR (400 MHz, Acetone-D₆) δ 8.63–8.59 (m, 1H, Ar), 7.96–7.92 (m, 1H, Ar), 7.51–7.48 (m, 1H, Ar), 7.40–7.33 (m, 2H, Ar), 4.09–3.93 (m, 5H, OMe, OCH), 3.49–3.40 (m, 1H, CHAr), 3.37–3.25 (m, 2H, NCH, NCH), 3.19–3.01 (m, 2H, NCH, CHAr), 2.78–2.68 (m, 1H, NCH), 2.54–2.37 (m, 1H, NCH), 2.02–1.98 (m, 1H, CH) 1.97 (s, 1.5H, Me), 1.94 (s, 1.5H, Me), 1.91–1.69 (m, 3H, CH), 1.58–1.41 (m, 1H, CH), 1.33–1.24 (m, 1H, CH); ¹³C NMR (100.6 MHz, Acetone-D₆) δ 170.3 (C=O), 170.2 (C=O), 157.8 (*ipso*-Ar), 147.4 (Ar), 144.6 (*ipso*-Ar), 144.2 (*ipso*-Ar), 144.0 (*ipso*-Ar), 131.5 (Ar), 128.8 (*ipso*-Ar), 122.2 (*ipso*-Ar), 121.3 (Ar), 121.3 (Ar), 102.1 (Ar), 66.1 (OCH₂), 65.3 (OCH₂), 55.6 (OMe), 55.4 (OMe), 55.35 (NCH), 53.2 (NCH₂), 52.9 (NCH₂), 41.2 (NCH₂), 40.7 (NCH₂), 37.3 (CH₂Ar), 36.8 (CH₂Ar), 34.3 (CH₂), 34.28 (CH), 33.8 (CH), 27.6 (CH₂), 24.0 (CH), 23.8 (CH), 21.1 (CH), 19.92 (Me), 19.89 (Me); HRMS *m/z* calcd for C₂₁H₂₆N₂O₃ (M + H)⁺ 355.2016, found 355.2020 (–1.1 ppm error).

Lab book reference: ARG-5-005 & 5-020

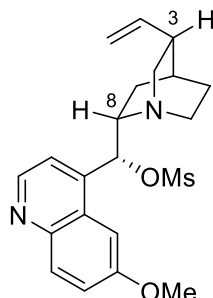
(3*R*,4*S*,6*S*)-6-((6-Methoxyquinolin-4-yl)methyl)quinuclidin-3-yl)methanol (3*R*,4*S*,8*S*)-423 and ((3*R*,4*R*,6*R*-6-((6-methoxyquinolin-4-yl)methyl)quinuclidin-3-yl)methanol (3*R*,4*R*,8*R*)-423



K₂CO₃ (66 mg, 0.48 mmol, 2.0 eq) was added to a solution of a 50:50 mixture of quinuclidine acetates (3*R*,4*S*,8*S*)- and (3*R*,4*R*,8*R*)-**422** (85 mg, 0.24 mmol, 1.0 eq) in MeOH (4 mL) at rt under air. The resulting solution was stirred at rt for 4 h. The solids were removed by filtration through Celite[®] and washed with EtOAc (25 mL) and MeOH (25 mL). The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 CH₂Cl₂-MeOH as eluent gave a presumed 50:50 mixture of quinuclidine alcohols (3*R*,4*S*,8*S*)- and (3*R*,4*R*,8*R*)-**423** (72 mg, 97%) as a clear oil, *R*_F (7:3 CH₂Cl₂-MeOH) 0.26; IR (ATR) 3291 (OH), 2932, 1509, 1242, 1029, 830 cm⁻¹; ¹H NMR (400 MHz, Acetone-D₆) δ 8.63–8.57 (m, 1H, Ar), 7.97–7.92 (m, 1H, Ar), 7.49–7.43 (m, 1H, Ar), 7.41–7.35 (m, 2H, Ar), 4.00–3.93 (m, 3H, OMe), 3.51 (m, 1H, OCH), 3.44–3.37 (m, 2H, OCH, CHAr), 3.29–2.99 (m, 4H, NCH, CHAr), 2.80–2.64 (m, 1H, NCH), 2.50–2.36 (m, 1H, NCH), 1.89–1.66 (m, 3H, CH), 1.61–1.39 (m, 2.5H, CH), 1.27–1.21 (m, 0.5H, CH); ¹³C NMR (100.6 MHz, Acetone-D₆) δ 158.92 (*ipso*-Ar), 158.9 (*ipso*-Ar), 148.05 (Ar), 148.0 (Ar), 145.5 (*ipso*-Ar), 145.3 (*ipso*-Ar), 144.9 (*ipso*-Ar), 131.8 (Ar), 129.8 (*ipso*-Ar), 123.12 (Ar), 123.1 (Ar), 122.6 (Ar), 102.8 (Ar), 102.79 (Ar), 64.9 (OCH₂), 64.1 (OCH₂), 56.4 (OMe), 56.2 (OMe), 56.14 (NCH), 56.11 (NCH), 54.5 (NCH₂), 54.2 (NCH₂), 42.2 (NCH₂), 41.8 (NCH₂), 38.7 (CH₂Ar), 38.5 (CH), 38.2 (CH₂Ar), 38.0 (CH), 35.3 (CH₂), 28.6 (CH₂), 24.3 (CH), 21.9 (CH₂); HRMS *m/z* calcd for C₁₉H₂₄N₂O₂ (M + H)⁺ 313.1911, found 313.1911 (–0.3 ppm error).

Lab book reference: ARG-5-044

**(R)-(6-Methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl
methanesulfonate (3R,4S,8S,9R)-424**

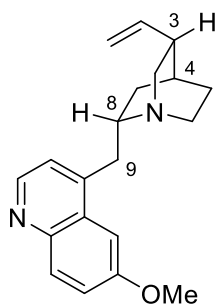


(3R,4S,8S,9R)-424

MsCl (5.4 mL, 69.35 mmol, 1.5 eq) was added to a solution of (–)-quinine (15 g, 46.2 mmol, 1.0 eq) and Et₃N (13 mL, 92.5 mmol, 2.0 eq) in CH₂Cl₂ (115 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 18 h. 1 M HCl_(aq) (100 mL) was added, and the two layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH₂Cl₂-MeOH as eluent gave mesylate (3R,4S,8S,9R)-**424** (12.6 g, 68%) as a white solid, mp (decomposition) 102–104 °C; *R*_F (95:5 CH₂Cl₂-MeOH) 0.31; IR (ATR) 2939, 1620, 1356, 1174, 915, 729, 524 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.80 (d, *J* = 4.5 Hz, 1H, Ar), 8.05 (d, *J* = 9.0 Hz, 1H, Ar), 7.47–7.33 (m, 3H, Ar), 6.45–5.93 (m, 1H, OCH), 5.83 (ddd, *J* = 17.5, 10.0, 7.5 Hz, 1H, =CH), 5.05–4.93 (m, 2H, =CH), 3.95 (s, 3H, OMe), 3.61–3.21 (m, 1H, NCH), 3.18–3.04 (m, 1H, NCH), 2.97 (dd, *J* = 14.0, 10.0 Hz, 1H, NCH), 2.68–2.49 (m, 5H, OMs, NCH), 2.30–2.23 (m, 1H, CH), 2.16–2.02 (m, 1H, CH), 1.97–1.87 (m, 1H, CH), 1.82–1.70 (m, 1H, CH), 1.70–1.61 (m, 1H, CH), 1.60–1.45 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 158.4 (*ipso*-Ar), 147.6 (Ar), 145.1 (*ipso*-Ar), 141.6 (=CH), 132.3 (Ar), 126.6 (*ipso*-Ar), 122.3 (Ar), 119.5 (br, Ar), 114.7 (=CH₂), 100.8 (br, Ar), 59.9 (br, NCH), 56.7 (NCH₂), 55.8 (OMe), 42.3 (br, NCH₂), 39.6 (CH), 39.3 (SO₂Me), 27.7 (CH₂), 27.4 (CH), 25.3 (br, CH₂) (1 × *ipso*-Ar resonance not resolved); HRMS *m/z* calcd for C₂₁H₂₇N₂O₄S (M + H)⁺ 403.1686, found 403.1694 (–1.0 ppm error). Spectroscopic data consistent with those reported in the literature.³⁷⁸

Lab book reference: ARG-5-019

(2*S*,4*S*,5*R*)-2-((6-Methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (3*R*,4*S*,8*S*)-322

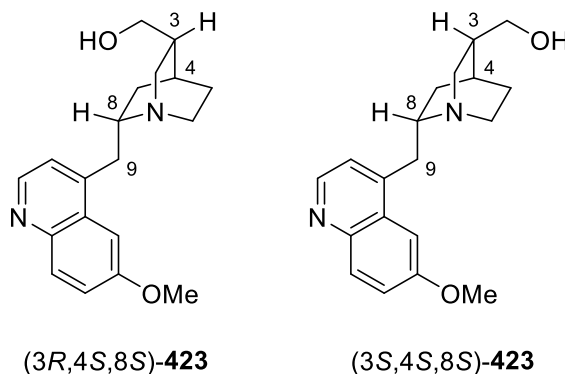


(3*R*,4*S*,8*S*)-322

Superhydride (6.21 mL of a 1 M solution in THF, 6.21 mmol, 2.5 eq) was added to a solution of mesyl quinine (3*R*,4*S*,8*S*,9*R*)-**424** (1 g, 2.48 mmol, 1.0 eq) in THF (15 mL) at -78°C under Ar. The resulting solution was stirred at -78°C for 1 h and then at rt for 18 h. EtOAc (25 mL) and H₂O (20 mL) were added, and the two layers separated. The aqueous layer was extracted with EtOAc (3 $\times$ 20 mL). The combined organic extracts were washed with brine (25 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 96:4 CH₂Cl₂-MeOH as eluent gave deoxyquinine (3*R*,4*S*,8*S*)-**322** (198 mg, 26%) as a clear oil, R_F (96:4 CH₂Cl₂-MeOH) 0.17; IR (ATR) 2933, 1620, 1508, 1228, 1030, 915, 848 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.67 (d, J = 4.5 Hz, 1H, Ar), 8.01 (d, J = 9.0 Hz, 1H, Ar), 7.37 (dd, J = 9.0, 2.5 Hz, 1H, Ar), 7.33 (d, J = 2.5 Hz, 1H, Ar), 7.23 (d, J = 4.5 Hz, 1H, Ar), 5.78 (ddd, J = 17.5, 10.5, 7.5 Hz, 1H, =CH), 5.05–4.95 (m, 2H, =CH₂), 3.97 (s, 3H, OMe), 3.58–3.48 (m, 1H, NCH), 3.35–3.23 (m, 3H, NCH, CHAr), 3.00 (dd, J = 13.5, 9.0 Hz, 1H, CHAr), 2.92–2.82 (m, 1H, NCH), 2.77 (d, J = 14.5 Hz, 1H, NCH), 2.40–2.30 (m, 1H, CH), 1.85–1.60 (m, 4H, CH), 1.28–1.22 (m, 1H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 157.9 (*ipso*-Ar), 147.5 (Ar), 144.5 (*ipso*-Ar), 143.3 (*ipso*-Ar), 141.2 (=CH), 131.7 (Ar), 128.7 (*ipso*-Ar), 122.0 (Ar), 121.6 (Ar), 114.8 (=CH₂), 101.7 (Ar), 55.9 (NCH₂), 55.88 (OMe), 55.6 (NCH), 41.0 (NCH₂), 39.2 (CH), 38.2 (CH₂Ar), 28.6 (CH₂), 27.8 (CH), 27.6 (CH₂); HRMS m/z calcd for C₂₀H₂₄N₂O (M + H)⁺ 309.1961, found 309.1967 (–1.0 ppm error). Spectroscopic data consistent with those reported in the literature.³³²

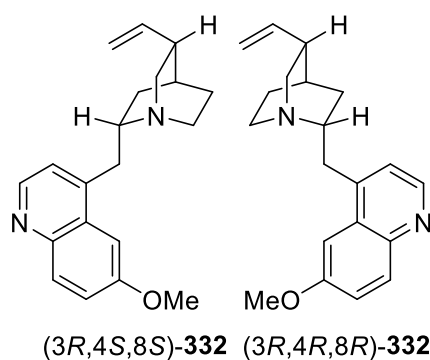
Lab book reference: ARG-5-017

(3R,4S,6S)-6-((6-Methoxyquinolin-4-yl)methyl)quinuclidin-3-yl)methanol (3R,4S,8S)-423 and ((3S,4S,6S-6-((6-methoxyquinolin-4-yl)methyl)quinuclidin-3-yl)methanol (3S,4S,8S)-423



$\text{K}_2\text{OsO}_4 \cdot \text{H}_2\text{O}$ (11 mg, 0.03 mmol, 0.1 eq) was added to a solution of deoxyquinine (3R,4S,8S)-**332** (93 mg, 0.30 mmol, 1.0 eq), $\text{K}_3[\text{Fe}(\text{CN})_6]$ (476 mg, 0.84 mmol, 2.8 eq) and K_2CO_3 (116 mg, 0.84 mmol, 2.8 eq) in *t*-BuOH (1 mL) and H_2O (1 mL) at 0 °C under air. The resulting solution was stirred at rt for 18 h. EtOAc (10 mL) and H_2O (10 mL) were added, and the two layers separated. The aqueous layer was extracted with EtOAc (3 $\times$ 10 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO_4) and evaporated under reduced pressure to give the crude product. The crude product and SiO_2 (420 mg, 2 g/mmol) were suspended in CH_2Cl_2 (0.5 mL) and the resulting mixture stirred at rt for 15 min. H_2O (0.5 mL) was added at rt and the resulting mixture stirred for 15 min at rt. NaIO_4 (58 mg, 0.27 mmol, 1.3 eq) was added at rt and the resulting mixture stirred at rt for 4 h. The solids were removed by filtration through Celite[®] and washed with EtOAc (25 mL). The filtrate was evaporated under reduced pressure to give the crude product (60 mg) as clear oil which contained a 50:50 mixture of diastereomeric aldehydes, diagnostic signals ^1H NMR (400 MHz, CD_2Cl_2) δ 9.72 (s, 1H, CHO), 9.68 (s, 1H, CHO). The crude product was then dissolved in MeOH (2 mL) and NaBH_4 (24 mg, 0.63 mmol, 3.0 eq) was added at 0 °C under Ar. The resulting mixture was stirred at rt for 16 h under Ar. EtOAc (10 mL) and H_2O (10 mL) were added, and the two layers separated. The aqueous layer was extracted with EtOAc (3 $\times$ 10 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 CH_2Cl_2 -MeOH as eluent gave a presumed 50:50 mixture of quinuclidine alcohols (3R,4S,8S)- and (3S,4S,8S)-**423** (27 mg, 46%) as a clear oil, identical (by ^1H NMR and ^{13}C spectroscopy) to that described above.

(2*S*,4*S*,5*R*)-2-((6-Methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (3*R*,4*S*,8*S*)-332
and (2*R*,4*R*,5*R*)-2-((6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (3*R*,4*R*,8*R*)-332

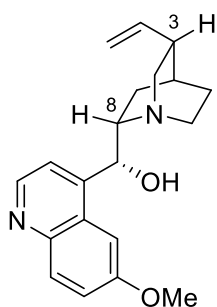


(COCl)₂ (20 μ L, 0.23 mmol, 1.2 eq) was added to a stirred solution of DMSO (27 μ L, 0.38 mmol, 2.0 eq) in CH₂Cl₂ (2 mL) at –78 $^{\circ}$ C under Ar. The resulting solution was stirred at –78 $^{\circ}$ C for 30 min. Then, a solution of a presumed 50:50 mixture of quinuclidine alcohols (3*R*,4*S*,8*S*)- and (3*R*,4*R*,8*R*)-**423** (60 mg, 0.19 mmol, 1.0 eq) in CH₂Cl₂ (2 mL) was added at –78 $^{\circ}$ C under Ar. The resulting mixture was stirred at –78 $^{\circ}$ C for 1 h. Then, Et₃N (0.1 mL, 0.76 mmol, 4.0 eq) was added dropwise at –78 $^{\circ}$ C under Ar and the resulting mixture stirred for 30 min at –78 $^{\circ}$ C under Ar. The mixture was then allowed to warm to rt and stirred for 18 h at rt under Ar. H₂O (10 mL) and CH₂Cl₂ (10 mL) were added and the two layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO₄), and evaporated under reduced pressure to give the crude product as a clear oil, diagnostic signals ¹H NMR (400 MHz, CD₂Cl₂) δ 9.72 (s, 1H, CHO), 9.68 (s, 1H, CHO). The crude product and PPh₃MeBr (136 mg, 0.38 mmol, 2.0 eq) were then dissolved in THF (2 mL) under Ar and *t*-BuOK (42 mg, 0.38 mmol, 2.0 eq) was added at 0 $^{\circ}$ C under Ar. The resulting mixture was stirred at rt for 4 h under Ar. H₂O (10 mL) and EtOAc (10 mL) were added and the two layers separated. The aqueous layer was extracted with EtOAc (3 $\times$ 10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO₄), and evaporated under reduced pressure to give the crude product which contained (by ¹H NMR spectroscopy and HRMS) a mixture of vinyl quinuclidines (3*R*,4*S*,8*S*)- and (3*R*,4*R*,8*R*)-**332**. Attempted purification by flash column

chromatography on silica with 96:4 CH₂Cl₂-MeOH as eluent failed to give vinyl quinuclidines (3*R*,4*S*,8*S*)- and (3*R*,4*R*,8*R*)-**332**.

Lab book reference: ARG-5-045

(*R*)-(6-Methoxyquinolin-4-yl)((2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanol (-)-Quinine



(-)-Quinine

t-BuOK (272 mg, 2.43 mmol, 5.0 eq) was added to a stirred solution of deoxyquinine (3*R*,4*S*,8*S*)-**332** (150 mg, 0.49 mmol, 1.0 eq) in DMSO (8 mL) and *t*-BuOH (2 mL) 0 °C under Ar. The resulting mixture was evacuated and back-filled with Ar three times and then with O₂ three times. The mixture was stirred under a balloon of O₂ (760 mmHg) at rt for 2 h. The flask was evacuated and back-filled with Ar three times and H₂O (20 mL) and EtOAc (20 mL) were added and the two layers separated. The aqueous layer was extracted with EtOAc (4 × 15 mL). The combined organic extracts were washed with brine (3 × 25 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 85:15 CH₂Cl₂-MeOH as eluent gave (-)-quinine (78 mg, 48%) as a white solid, mp 168-170 °C (lit.³³⁷, 172-175 °C); *R*_F (85:15 CH₂Cl₂-MeOH) 0.22; IR (ATR) 3106 (OH), 2935, 1621, 1509, 1241, 731 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.43 (d, *J* = 4.5 Hz, 1H, Ar), 7.88 (d, *J* = 9.0 Hz, 1H, Ar), 7.44 (d, *J* = 4.5 Hz, 1H, Ar), 7.27–7.19 (m, 2H, Ar), 5.72 (ddd, *J* = 17.0, 10.5, 7.5 Hz, 1H, =CH), 5.51–5.45 (m, 1H, OCH), 5.24 (s, 1H, OH), 4.97–4.85 (m, 2H, =CH₂), 3.89 (s, 3H, OMe), 3.44 (dddd, *J* = 12.5, 5.0, 2.0 Hz, 1H, NCH), 3.13–2.96 (m, 2H, NCH, NCH), 2.66–2.55 (m, 2H, NCH), 2.28–2.19 (m, 1H, CH), 1.81–1.67 (m, 3H, CH), 1.55–1.40 (m, 2H, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 157.7 (*ipso*-Ar), 148.4 (*ipso*-Ar), 147.4 (Ar), 144.1 (*ipso*-Ar), 142.1 (=CH), 131.3 (Ar), 126.7 (*ipso*-Ar), 121.5 (Ar), 118.6 (Ar), 114.4 (=CH₂), 101.5 (Ar), 72.0

(OCH), 60.1 (NCH), 57.2 (NCH₂), 55.8 (OMe), 43.3 (NCH₂), 40.1 (CH), 28.0 (CH), 27.8 (CH₂), 21.9 (CH₂); HRMS *m/z* calcd for C₂₀H₂₄N₂O₂ (M + H)⁺ 325.1911, found 325.1915 (−1.5 ppm error). Spectroscopic data consistent with those reported in the literature.³³⁷

Lab book reference: ARG-5-028

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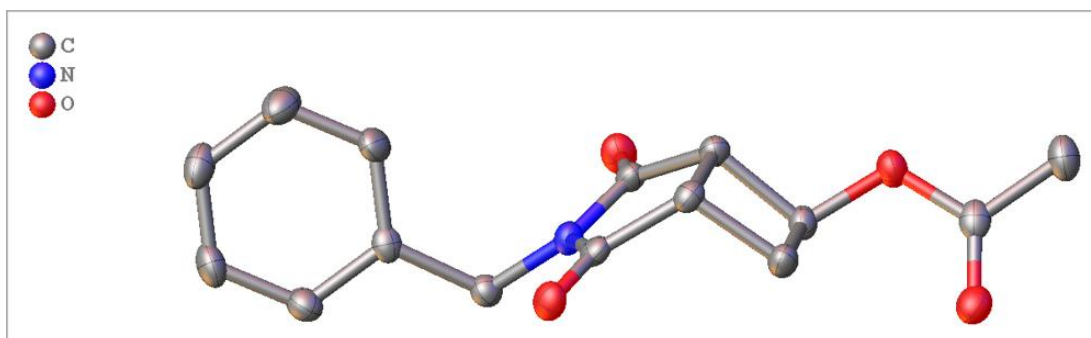
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Annexes

Annex I: Crystallographic Data and Refinement Statistics

exo-218



Data collected, solved and refined by Adrian C Whitwood

Table 1 Crystal data and structure refinement for paob23002.

Identification code	paob23002
Empirical formula	C ₁₅ H ₁₅ NO ₄
Formula weight	273.28
Temperature/K	110.00(10)
Crystal system	orthorhombic
Space group	Pna2 ₁
a/Å	14.1157(2)
b/Å	15.6018(3)
c/Å	5.93300(12)
α/°	90
β/°	90
γ/°	90
Volume/Å ³	1306.63(4)
Z	4
ρ _{calc} /g/cm ³	1.389
μ/mm ⁻¹	0.841
F(000)	576.0
Crystal size/mm ³	0.397 × 0.043 × 0.021
Radiation	Cu Kα (λ = 1.54184)
2θ range for data collection/°	8.448 to 134.146
Index ranges	-16 ≤ h ≤ 14, -18 ≤ k ≤ 15, -7 ≤ l ≤ 7
Reflections collected	8646
Independent reflections	2258 [R _{int} = 0.0350, R _{sigma} = 0.0312]
Data/restraints/parameters	2258/1/241
Goodness-of-fit on F ²	1.061
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0289, wR ₂ = 0.0738
Final R indexes [all data]	R ₁ = 0.0305, wR ₂ = 0.0747
Largest diff. peak/hole / e Å ⁻³	0.14/-0.14

Flack parameter -0.07(11)

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for paob23002. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij} tensor.

Atom	x	y	z	U_{eq}
C1	5755.2(15)	3382.9(15)	3956(4)	20.6(5)
C2	6482.0(16)	4071.2(16)	3458(4)	22.0(5)
C3	7499.1(15)	3825.8(14)	4240(4)	22.3(5)
C4	7466.5(16)	4525.6(16)	6057(5)	24.0(5)
C5	6415.7(15)	4708.1(15)	5425(4)	21.0(5)
C6	5702.5(14)	4320.5(14)	7007(4)	20.0(5)
C7	9078.3(17)	3980.6(14)	3056(5)	24.4(5)
C8	9716.2(19)	4134.3(19)	1089(5)	32.9(6)
C9	4753.2(16)	2967.8(14)	7278(4)	21.9(5)
C10	3710.3(15)	3192.1(14)	7161(4)	20.8(5)
C11	3311.6(17)	3616.4(16)	5353(5)	27.9(6)
C12	2343.6(18)	3766.8(18)	5274(6)	35.1(6)
C13	1764.4(17)	3491.7(16)	7021(5)	31.8(6)
C14	2153.7(18)	3061.5(17)	8826(5)	31.3(6)
C15	3124.1(17)	2917.8(15)	8911(5)	27.1(5)
N1	5380.1(12)	3557.9(12)	6061(4)	20.4(4)
O1	5546.3(11)	2774.1(11)	2814(3)	28.8(4)
O2	8160.1(11)	3961.5(11)	2437(3)	26.1(4)
O3	9327.2(12)	3895.8(11)	4992(3)	29.3(4)
O4	5446.3(11)	4587.0(10)	8822(3)	26.3(4)

Table 3 Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for paob23002. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^{*}b^{*}U_{12}+\dots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	16.8(10)	27.6(11)	17.4(11)	-0.5(11)	-1.7(9)	1.3(9)
C2	19.7(11)	27.8(12)	18.4(12)	-0.2(10)	-0.9(9)	-1.4(9)
C3	17.9(11)	23.8(11)	25.3(13)	2.5(10)	2.4(10)	-0.9(9)
C4	18.4(11)	31.7(13)	22.0(13)	-0.6(10)	-0.5(10)	-1.1(10)
C5	18.1(10)	20.4(11)	24.5(13)	0.3(9)	-2.5(10)	0.7(8)
C6	16.4(9)	21.6(11)	21.9(12)	-0.6(9)	-3.0(9)	4.2(8)
C7	22.0(12)	17.8(11)	33.5(15)	-0.8(10)	3.9(11)	0.3(9)
C8	25.1(13)	34.5(15)	39.1(17)	-1.3(13)	8.5(12)	-3.4(11)
C9	21.9(11)	21.8(11)	21.9(12)	1.3(10)	1.0(10)	-1.7(9)
C10	20.4(10)	17.0(10)	24.9(13)	-3.0(9)	3.3(10)	-3.2(8)
C11	23.6(11)	32.7(13)	27.3(14)	8.2(11)	1.5(11)	-6.4(10)

Table 3 Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for paob23002. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\dots]$.

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
C12	27.6(13)	34.9(13)	43.0(17)	12.1(13)	-5.9(13)	-1.4(11)
C13	19.3(11)	27.3(12)	49.0(17)	0.8(12)	1.1(12)	-2.4(10)
C14	25.8(12)	34.3(13)	33.6(16)	0.0(12)	11.8(12)	-2.7(10)
C15	28.9(13)	28.1(12)	24.3(14)	4.3(11)	2.3(11)	0.2(10)
N1	17.1(8)	21.5(9)	22.5(10)	-1.3(8)	0.3(8)	-0.3(7)
O1	27.9(9)	32.9(10)	25.6(9)	-6.6(8)	1.3(7)	-6.1(7)
O2	21.9(8)	32.0(9)	24.3(9)	-1.8(7)	3.6(7)	-2.4(7)
O3	25.0(9)	28.5(9)	34.4(11)	2.5(8)	-0.7(8)	1.3(7)
O4	22.4(8)	29.8(8)	26.7(10)	-6.1(8)	2.4(7)	3.0(6)

Table 4 Bond Lengths for paob23002.

Atom Atom	Length/ $\text{\AA}$	Atom Atom	Length/ $\text{\AA}$
C1 C2	1.514(3)	C7 C8	1.493(4)
C1 N1	1.383(3)	C7 O2	1.347(3)
C1 O1	1.204(3)	C7 O3	1.209(3)
C2 C3	1.556(3)	C9 C10	1.515(3)
C2 C5	1.535(3)	C9 N1	1.467(3)
C3 C4	1.535(3)	C10 C11	1.381(4)
C3 O2	1.435(3)	C10 C15	1.395(3)
C4 C5	1.556(3)	C11 C12	1.387(4)
C5 C6	1.503(3)	C12 C13	1.388(4)
C6 N1	1.392(3)	C13 C14	1.378(4)
C6 O4	1.210(3)	C14 C15	1.389(4)

Table 5 Bond Angles for paob23002.

Atom Atom Atom	Angle/ $^\circ$	Atom Atom Atom	Angle/ $^\circ$
N1 C1 C2	107.18(19)	O2 C7 C8	111.8(2)
O1 C1 C2	128.0(2)	O3 C7 C8	125.8(2)
O1 C1 N1	124.8(2)	O3 C7 O2	122.4(2)
C1 C2 C3	113.1(2)	N1 C9 C10	114.75(19)
C1 C2 C5	105.63(19)	C11 C10 C9	122.9(2)
C5 C2 C3	89.37(17)	C11 C10 C15	118.9(2)
C4 C3 C2	90.38(17)	C15 C10 C9	118.1(2)
O2 C3 C2	110.0(2)	C10 C11 C12	120.6(2)
O2 C3 C4	115.97(19)	C11 C12 C13	120.2(3)
C3 C4 C5	89.41(18)	C14 C13 C12	119.7(2)
C2 C5 C4	90.37(18)	C13 C14 C15	120.0(2)
C6 C5 C2	104.77(19)	C14 C15 C10	120.6(2)
C6 C5 C4	114.5(2)	C1 N1 C6	114.05(19)
N1 C6 C5	108.1(2)	C1 N1 C9	123.45(19)

Table 5 Bond Angles for paob23002.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O4	C6	C5	128.2(2)	C6	N1	C9	122.3(2)
O4	C6	N1	123.7(2)	C7	O2	C3	115.20(19)

Table 6 Torsion Angles for paob23002.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C1	C2	C3	C4	-112.0(2)	C9	C10	C11	C12	176.6(2)
C1	C2	C3	O2	130.1(2)	C9	C10	C15	C14	-176.2(2)
C1	C2	C5	C4	119.0(2)	C10	C9	N1	C1	-101.1(3)
C1	C2	C5	C6	3.5(2)	C10	C9	N1	C6	83.6(3)
C2	C1	N1	C6	4.8(3)	C10	C11	C12	C13	0.1(4)
C2	C1	N1	C9	-170.8(2)	C11	C10	C15	C14	0.6(4)
C2	C3	C4	C5	5.18(18)	C11	C12	C13	C14	-0.6(4)
C2	C3	O2	C7	164.02(18)	C12	C13	C14	C15	1.1(4)
C2	C5	C6	N1	-0.9(2)	C13	C14	C15	C10	-1.2(4)
C2	C5	C6	O4	177.5(2)	C15	C10	C11	C12	-0.1(4)
C3	C2	C5	C4	5.18(18)	N1	C1	C2	C3	91.1(2)
C3	C2	C5	C6	-110.31(18)	N1	C1	C2	C5	-5.0(2)
C3	C4	C5	C2	-5.25(19)	N1	C9	C10	C11	29.4(3)
C3	C4	C5	C6	101.2(2)	N1	C9	C10	C15	-153.9(2)
C4	C3	O2	C7	63.4(3)	O1	C1	C2	C3	-86.7(3)
C4	C5	C6	N1	-98.2(2)	O1	C1	C2	C5	177.2(2)
C4	C5	C6	O4	80.1(3)	O1	C1	N1	C6	-177.3(2)
C5	C2	C3	C4	-5.25(19)	O1	C1	N1	C9	7.0(3)
C5	C2	C3	O2	-123.17(19)	O2	C3	C4	C5	117.7(2)
C5	C6	N1	C1	-2.5(2)	O3	C7	O2	C3	-0.5(3)
C5	C6	N1	C9	173.21(19)	O4	C6	N1	C1	179.0(2)
C8	C7	O2	C3	-179.3(2)	O4	C6	N1	C9	-5.2(3)

Table 7 Hydrogen Atom Coordinates ($\text{\AA} \times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for paob23002.

Atom	x	y	z	U(eq)
H2	6431(17)	4252(17)	1890(50)	20(6)
H3	7548(18)	3245(17)	4830(50)	21(6)
H4A	7951(16)	5014(16)	5710(50)	15(6)
H4B	7560(20)	4340(20)	7560(70)	39(8)
H5	6261(17)	5289(18)	5090(50)	20(6)
H8A	9970(30)	4680(20)	1150(70)	58(11)
H8B	10320(30)	3850(20)	1220(80)	62(12)
H8C	9420(30)	3930(30)	-300(100)	80(14)
H9A	4970(20)	2940(18)	8800(60)	28(7)
H9B	4848(16)	2412(17)	6480(40)	14(6)
H11	3690(20)	3795(18)	4240(60)	29(8)

Table 7 Hydrogen Atom Coordinates ($\text{\AA} \times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for paob23002.

Atom	x	y	z	U(eq)
H12	2110(20)	4030(20)	3940(70)	48(9)
H13	1120(20)	3611(17)	6870(50)	25(7)
H14	1770(20)	2900(20)	9990(70)	47(9)
H15	3370(20)	2644(19)	10190(60)	37(8)

paob23002

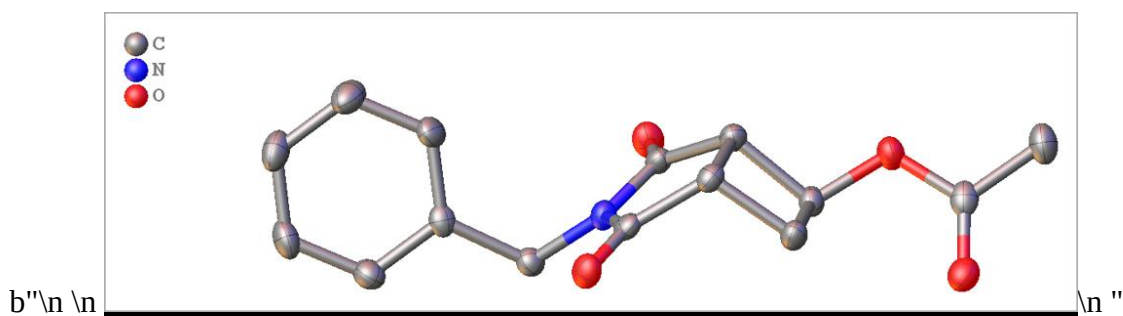
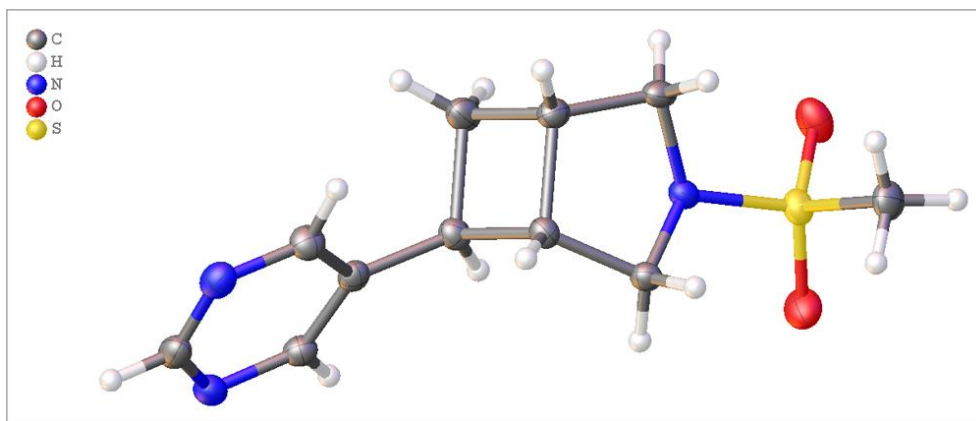


Table 1 Crystal data and structure refinement for paob23002.

Identification code	paob23002
Empirical formula	$\text{C}_{15}\text{H}_{15}\text{NO}_4$
Formula weight	273.28
Temperature/K	110.00(10)
Crystal system	orthorhombic
Space group	$\text{Pna}2_1$
a/ $\text{\AA}$	14.1157(2)
b/ $\text{\AA}$	15.6018(3)
c/ $\text{\AA}$	5.93300(12)
$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	90
Volume/ $\text{\AA}^3$	1306.63(4)
Z	4
$\rho_{\text{calc}}/\text{g cm}^{-3}$	1.389
μ/mm^{-1}	0.841
F(000)	576.0
Crystal size/ mm^3	$0.397 \times 0.043 \times 0.021$
Radiation	$\text{Cu K}\alpha$ ($\lambda = 1.54184$)
2θ range for data collection/ $^\circ$	8.448 to 134.146
Index ranges	$-16 \leq h \leq 14, -18 \leq k \leq 15, -7 \leq l \leq 7$
Reflections collected	8646
Independent reflections	2258 [$R_{\text{int}} = 0.0350, R_{\text{sigma}} = 0.0312$]
Data/restraints/parameters	2258/1/241
Goodness-of-fit on F^2	1.061

Final R indexes [$I \geq 2\sigma(I)$] $R_1 = 0.0289$, $wR_2 = 0.0738$
Final R indexes [all data] $R_1 = 0.0305$, $wR_2 = 0.0747$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$ 0.14/-0.14
Flack parameter -0.07(11)

exo-320



Data collected, solved and refined by Adrian C Whitwood

Table 1 Crystal data and structure refinement for paob23007.

Identification code	paob23007
Empirical formula	C ₁₁ H ₁₅ N ₃ O ₂ S
Formula weight	253.32
Temperature/K	110.05(10)
Crystal system	orthorhombic
Space group	Pca2 ₁
a/Å	19.25705(13)
b/Å	5.59305(4)
c/Å	10.89590(8)
α/°	90
β/°	90
γ/°	90
Volume/Å ³	1173.549(15)
Z	4
ρ _{calc} /cm ³	1.434
μ/mm ⁻¹	2.419
F(000)	536.0
Crystal size/mm ³	0.23 × 0.159 × 0.107
Radiation	Cu Kα (λ = 1.54184)
2θ range for data collection/°	9.184 to 134.018
Index ranges	-23 ≤ h ≤ 22, -6 ≤ k ≤ 6, -13 ≤ l ≤ 12
Reflections collected	10033
Independent reflections	2071 [R _{int} = 0.0209, R _{sigma} = 0.0152]
Data/restraints/parameters	2071/1/215
Goodness-of-fit on F ²	1.032
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0201, wR ₂ = 0.0530
Final R indexes [all data]	R ₁ = 0.0202, wR ₂ = 0.0531
Largest diff. peak/hole / e Å ⁻³	0.17/-0.20
Flack parameter	-0.009(5)

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for paob23007. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	x	y	z	U(eq)
C1	4388.1 (9)	4056 (4)	4761.3 (19)	18.3 (4)
C2	3833.8 (10)	5404 (4)	5468.8 (18)	17.7 (4)
C3	3546.9 (11)	4095 (4)	6632.8 (19)	19.3 (4)
C4	2846.2 (11)	3686 (4)	5941 (2)	25.1 (5)
C5	3136.2 (10)	4922 (4)	4782 (2)	20.4 (4)
C6	3317.6 (10)	3288 (4)	3720 (2)	20.2 (4)
C7	3512.2 (10)	5548 (4)	7787.4 (19)	18.3 (4)
C8	3786.7 (10)	4760 (4)	8887 (2)	19.6 (4)
C9	3464.7 (11)	8181 (4)	9830 (2)	23.5 (4)
C10	3206.6 (10)	7804 (4)	7826 (2)	22.3 (4)
C11	4643.8 (12)	2206 (4)	1914 (2)	24.8 (5)
N1	3977.7 (8)	2159 (3)	4140.3 (15)	17.4 (4)
N2	3179.3 (9)	9133 (3)	8842.1 (19)	24.1 (4)
N3	3766.6 (9)	6038 (4)	9924.3 (16)	22.7 (4)
O1	3880.1 (9)	-1272 (3)	2739.1 (15)	29.0 (4)
O2	4991.4 (8)	-422 (3)	3781.3 (17)	28.8 (4)
S1	4378.2 (2)	426.0 (8)	3172.7 (5)	19.81 (15)

Table 3 Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for paob23007. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[\text{h}^2\text{a}^{*2}\text{U}_{11}+2\text{hka}^*\text{b}^*\text{U}_{12}+\dots]$.

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
C1	16.8 (10)	20.0 (10)	18.1 (10)	-0.4 (9)	-1.6 (8)	-2.0 (7)
C2	19.4 (10)	17.5 (10)	16.3 (11)	0.0 (7)	-0.4 (8)	-1.6 (7)
C3	21.2 (10)	19.8 (10)	16.8 (10)	1.7 (8)	-0.5 (7)	-2.8 (8)
C4	21.7 (10)	33.7 (12)	20.0 (11)	1.3 (9)	0.5 (8)	-8.0 (9)
C5	17.2 (10)	24.6 (10)	19.4 (11)	2.3 (8)	-0.4 (7)	-0.8 (8)
C6	16.1 (9)	26.8 (10)	17.5 (9)	3.6 (10)	-3.1 (8)	-2.6 (8)
C7	16.1 (9)	19.2 (10)	19.8 (10)	1.2 (8)	1.9 (7)	-2.5 (7)
C8	17.3 (9)	18.9 (10)	22.6 (11)	1.1 (9)	-0.7 (8)	-0.7 (7)
C9	19.4 (10)	26.3 (11)	24.9 (11)	-7.6 (9)	1.1 (8)	-3.0 (8)
C10	23.7 (10)	21.8 (10)	21.5 (11)	3.8 (8)	-0.7 (8)	0.4 (8)
C11	27.2 (12)	29.1 (11)	18.2 (10)	3.7 (9)	4.3 (9)	-2.0 (9)
N1	17.8 (7)	18.9 (8)	15.4 (8)	0.1 (6)	-1.6 (7)	-1.9 (7)
N2	22.1 (8)	20.7 (8)	29.6 (10)	-2.6 (8)	2.3 (8)	-1.1 (7)
N3	19.8 (8)	27.7 (9)	20.5 (9)	-2.4 (7)	-1.9 (7)	-1.4 (7)
O1	40.3 (9)	23.1 (8)	23.5 (7)	-3.5 (6)	1.0 (7)	-7.4 (6)

Table 3 Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for paob23007. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\dots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O2	30.6 (8)	27.7 (9)	28.2 (8)	-0.5 (8)	-0.1 (7)	10.0 (6)
S1	25.4 (2)	17.5 (2)	16.6 (2)	1.0 (2)	1.20 (19)	0.63 (17)

Table 4 Bond Lengths for paob23007.

Atom Atom	Length/ $\text{\AA}$	Atom Atom	Length/ $\text{\AA}$
C1 C2	1.517 (3)	C7 C10	1.393 (3)
C1 N1	1.486 (3)	C8 N3	1.338 (3)
C2 C3	1.565 (3)	C9 N2	1.321 (3)
C2 C5	1.561 (3)	C9 N3	1.336 (3)
C3 C4	1.562 (3)	C10 N2	1.334 (3)
C3 C7	1.499 (3)	C11 S1	1.770 (2)
C4 C5	1.544 (3)	N1 S1	1.6266 (17)
C5 C6	1.515 (3)	O1 S1	1.4301 (16)
C6 N1	1.491 (3)	O2 S1	1.4350 (17)
C7 C8	1.381 (3)		

Table 5 Bond Angles for paob23007.

Atom Atom Atom	Angle/ $^\circ$	Atom Atom Atom	Angle/ $^\circ$
N1 C1 C2	102.25 (14)	N3 C8 C7	123.44 (19)
C1 C2 C3	115.31 (16)	N2 C9 N3	127.2 (2)
C1 C2 C5	106.02 (16)	N2 C10 C7	123.1 (2)
C5 C2 C3	90.21 (15)	C1 N1 C6	106.90 (16)
C4 C3 C2	88.99 (15)	C1 N1 S1	117.93 (12)
C7 C3 C2	116.23 (16)	C6 N1 S1	117.22 (14)
C7 C3 C4	116.47 (18)	C9 N2 C10	115.82 (18)
C5 C4 C3	90.95 (15)	C9 N3 C8	115.28 (19)
C4 C5 C2	89.81 (16)	N1 S1 C11	107.71 (10)
C6 C5 C2	105.78 (15)	O1 S1 C11	108.14 (11)
C6 C5 C4	115.97 (18)	O1 S1 N1	106.97 (9)
N1 C6 C5	102.56 (16)	O1 S1 O2	119.01 (10)
C8 C7 C3	122.52 (18)	O2 S1 C11	107.83 (11)
C8 C7 C10	115.11 (19)	O2 S1 N1	106.71 (9)
C10 C7 C3	122.37 (19)		

Table 6 Torsion Angles for paob23007.

A B C D	Angle/ $^\circ$	A B C D	Angle/ $^\circ$
C1 C2 C3 C4	109.20 (19)	C4 C3 C7 C8	127.8 (2)
C1 C2 C3 C7	131.57 (18)	C4 C3 C7 C10	-52.9 (3)

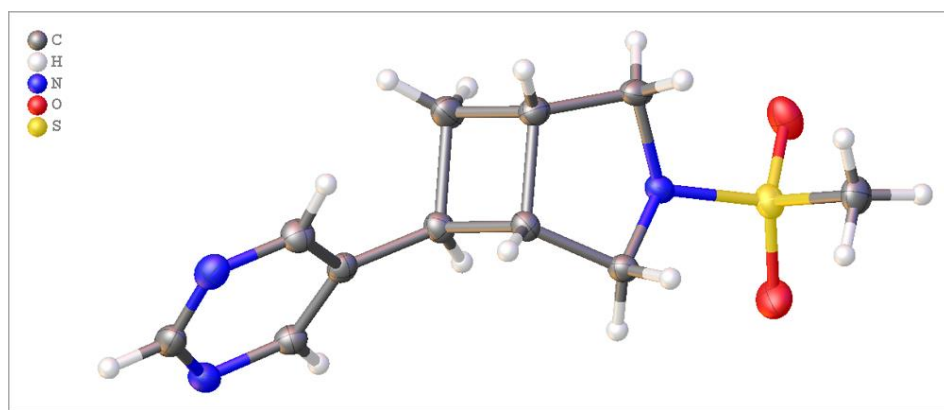
Table 6 Torsion Angles for paob23007.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C1	C2	C5	C4	117.81 (17)	C4	C5	C6	N1	-75.0 (2)
C1	C2	C5	C6	0.8 (2)	C5	C2	C3	C4	-1.31 (16)
C1	N1	S1	C11	-65.81 (17)	C5	C2	C3	C7	120.55 (18)
C1	N1	S1	O1	178.14 (15)	C5	C6	N1	C1	-39.7 (2)
C1	N1	S1	O2	49.75 (17)	C5	C6	N1	S1	174.64 (13)
C2	C1	N1	C6	40.1 (2)	C6	N1	S1	C11	64.19 (17)
C2	C1	N1	S1	174.66 (13)	C6	N1	S1	O1	-51.86 (17)
C2	C3	C4	C5	1.33 (17)	C6	N1	S1	O2	179.75 (14)
C2	C3	C7	C8	129.30 (19)	C7	C3	C4	C5	120.35 (18)
C2	C3	C7	C10	50.0 (3)	C7	C8	N3	C9	-0.7 (3)
C2	C5	C6	N1	22.7 (2)	C7	C10	N2	C9	0.2 (3)
C3	C2	C5	C4	1.33 (17)	C8	C7	C10	N2	0.3 (3)
C3	C2	C5	C6	115.68 (17)	C10	C7	C8	N3	0.0 (3)
C3	C4	C5	C2	-1.33 (17)	N1	C1	C2	C3	74.0 (2)
C3	C4	C5	C6	106.17 (18)	N1	C1	C2	C5	-24.1 (2)
C3	C7	C8	N3	179.39 (19)	N2	C9	N3	C8	1.2 (3)
C3	C7	C10	N2	179.13 (18)	N3	C9	N2	C10	-1.0 (3)

Table 7 Hydrogen Atom Coordinates ($\text{\AA} \times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for paob23007.

Atom	x	y	z	U(eq)
H1A	4619 (12)	5120 (50)	4140 (20)	17 (6)
H1B	4744 (14)	3310 (50)	5270 (20)	24 (6)
H2	3960 (12)	7050 (40)	5600 (20)	15 (5)
H3	3811 (13)	2610 (50)	6760 (20)	23 (6)
H4A	2726 (14)	1930 (50)	5810 (30)	31 (7)
H4B	2465 (17)	4560 (40)	6330 (30)	28 (6)
H5	2866 (13)	6360 (50)	4480 (30)	26 (6)
H6A	2979 (13)	2100 (50)	3590 (20)	22 (6)
H6B	3404 (12)	4290 (40)	2990 (20)	17 (6)
H8	3999 (12)	3220 (50)	8900 (20)	21 (6)
H9	3451 (13)	9120 (40)	10570 (30)	21 (6)
H10	2984 (13)	8440 (50)	7130 (20)	26 (6)
H11A	4263 (14)	3050 (50)	1630 (30)	22 (6)
H11B	4999 (15)	3220 (50)	2260 (30)	35 (7)
H11C	4833 (15)	1200 (50)	1290 (30)	33 (7)

paob23007



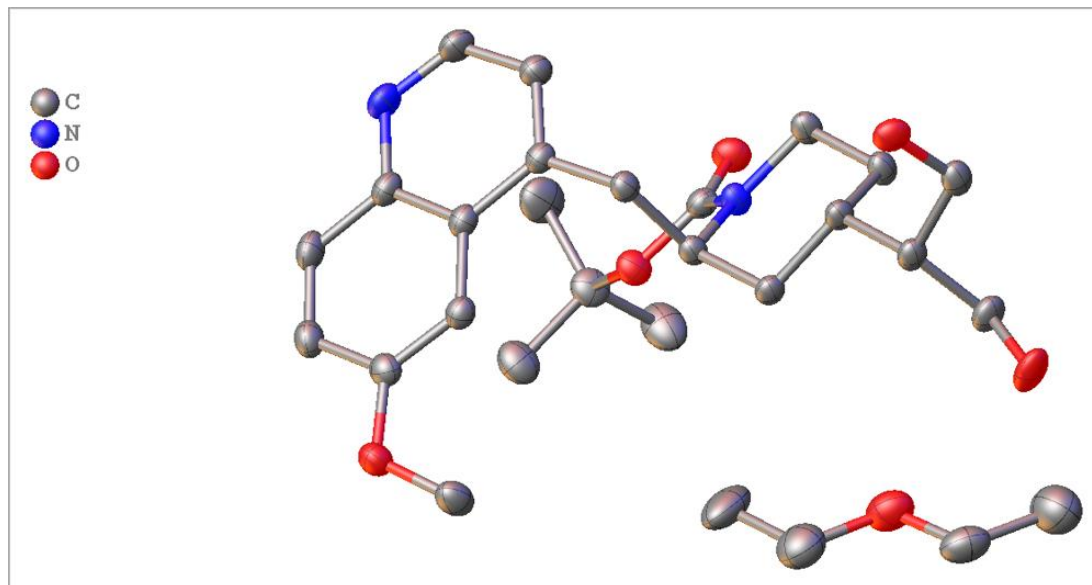
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Table 1 Crystal data and structure refinement for paob23007.

Identification code	paob23007
Empirical formula	C ₁₁ H ₁₅ N ₃ O ₂ S
Formula weight	253.32
Temperature/K	110.05(10)
Crystal system	orthorhombic
Space group	Pca2 ₁
a/Å	19.25705(13)
b/Å	5.59305(4)
c/Å	10.89590(8)
α/°	90
β/°	90
γ/°	90
Volume/Å ³	1173.549(15)
Z	4
ρ _{calc} /cm ³	1.434
μ/mm ⁻¹	2.419
F(000)	536.0
Crystal size/mm ³	0.23 × 0.159 × 0.107
Radiation	Cu Kα (λ = 1.54184)
2θ range for data collection/°	9.184 to 134.018
Index ranges	-23 ≤ h ≤ 22, -6 ≤ k ≤ 6, -13 ≤ l ≤ 12
Reflections collected	10033
Independent reflections	2071 [R _{int} = 0.0209, R _{sigma} = 0.0152]
Data/restraints/parameters	2071/1/215
Goodness-of-fit on F ²	1.032
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0201, wR ₂ = 0.0530
Final R indexes [all data]	R ₁ = 0.0202, wR ₂ = 0.0531
Largest diff. peak/hole / e Å ⁻³	0.17/-0.20
Flack parameter	-0.009(5)

trans-413



Data collected, solved and refined by Adrian C Whitwood

Refinement Special Details

The asymmetric unit contained a diethyl ether disordered about the inversion centre with an occupancy of 0.5 per asymmetric unit.

Table 1 Crystal data and structure refinement for paob23010.

Identification code	paob23010
Empirical formula	C ₂₆ H ₃₉ N ₂ O _{5.5}
Formula weight	467.59
Temperature/K	110.00(10)
Crystal system	monoclinic
Space group	P2 ₁ /c
a/Å	12.4129(4)
b/Å	11.5226(4)
c/Å	18.1200(5)
α/°	90
β/°	93.845(3)
γ/°	90
Volume/Å ³	2585.87(15)
Z	4
ρ _{calc} /cm ³	1.201
μ/mm ⁻¹	0.678
F(000)	1012.0
Crystal size/mm ³	0.15 × 0.09 × 0.05
Radiation	Cu Kα (λ = 1.54184)
2θ range for data collection/°	7.138 to 134.152
Index ranges	-14 ≤ h ≤ 14, -6 ≤ k ≤ 13, -21 ≤ l ≤ 19
Reflections collected	18535

Independent reflections	4615 [$R_{\text{int}} = 0.0451$, $R_{\text{sigma}} = 0.0396$]
Data/restraints/parameters	4615/9/463
Goodness-of-fit on F^2	1.039
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0422$, $wR_2 = 0.1126$
Final R indexes [all data]	$R_1 = 0.0502$, $wR_2 = 0.1182$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.26/-0.24

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for paob23010. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	x	y	z	$U(\text{eq})$
C1	1718.3 (11)	4417.0 (12)	2413.4 (7)	22.4 (3)
C2	2862.3 (13)	3018.9 (12)	3103.1 (7)	24.6 (3)
C3	2916.6 (13)	2655.6 (12)	3917.1 (7)	24.8 (3)
C4	3511.8 (12)	3550.0 (11)	4414.7 (7)	21.9 (3)
C5	2958.0 (12)	4724.5 (12)	4292.8 (7)	22.0 (3)
C6	2914.1 (11)	5108.2 (11)	3480.0 (7)	20.7 (3)
C7	4050.2 (11)	5423.7 (12)	3244.2 (7)	21.8 (3)
C8	4024.8 (11)	5976.9 (12)	2492.0 (7)	21.4 (3)
C9	4252.8 (12)	5337.3 (13)	1881.8 (7)	25.8 (3)
C10	4214.3 (13)	5863.3 (13)	1182.2 (8)	29.9 (3)
C11	3707.0 (11)	7615.8 (13)	1653.3 (7)	24.7 (3)
C12	3405.5 (12)	8789.7 (13)	1531.0 (8)	28.8 (3)
C13	3151.0 (12)	9486.8 (13)	2098.4 (8)	28.1 (3)
C14	3191.8 (11)	9035.2 (12)	2830.9 (7)	24.4 (3)
C15	3477.7 (11)	7910.6 (12)	2973.8 (7)	22.7 (3)
C16	3738.5 (11)	7165.7 (12)	2385.9 (7)	21.9 (3)
C17	3621.6 (12)	3214.9 (12)	5239.9 (7)	23.3 (3)
C18	2571.7 (13)	2800.9 (14)	5540.0 (7)	28.9 (3)
C19	4505.9 (13)	2322.4 (12)	5407.5 (7)	26.2 (3)
C20	642.4 (12)	5972.8 (14)	1798.5 (8)	30.5 (3)
C21	605.3 (16)	7260.5 (15)	1973.7 (10)	38.2 (4)
C22	1050.0 (18)	5777.3 (18)	1036.2 (9)	44.9 (4)
C23	-440.1 (15)	5412.6 (17)	1894.8 (12)	45.6 (4)
C24	2829.3 (16)	9388.0 (15)	4083.8 (9)	34.5 (4)
N1	2415.3 (10)	4191.7 (10)	3006.1 (6)	22.4 (3)
N2	3959.3 (11)	6956.7 (11)	1060.4 (6)	29.9 (3)
O1	1440.7 (8)	5544.3 (9)	2377.3 (5)	26.1 (2)
O2	1369.8 (8)	3678.6 (9)	1973.5 (5)	28.2 (2)
O3	2929.4 (9)	9822.0 (9)	3355.5 (6)	29.4 (2)
O4	2679.7 (10)	2887.1 (10)	6325.2 (5)	37.7 (3)
O5	5552.5 (8)	2764.1 (9)	5308.3 (5)	27.7 (2)
C25	270 (10)	6458 (10)	4197 (5)	59 (3)

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for paob23010. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij} tensor.

Atom	x	y	z	U_{eq}
C26	342 (3)	6084 (4)	5007 (2)	52.2 (9)
C27	28 (3)	4475 (4)	5768.5 (19)	43.8 (8)
C28	-441 (13)	3250 (10)	5730 (7)	61 (3)
O6	-20 (50)	4890 (30)	5020 (20)	45 (2)

Table 3 Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for paob23010. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\dots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	24.7 (7)	25.0 (7)	17.8 (6)	0.2 (5)	4.3 (5)	-0.4 (6)
C2	37.0 (9)	20.3 (7)	16.5 (6)	-1.8 (5)	1.3 (6)	0.0 (6)
C3	38.0 (9)	19.2 (7)	17.2 (6)	1.5 (5)	2.2 (5)	-0.1 (6)
C4	31.3 (8)	20.7 (7)	13.9 (6)	0.6 (5)	3.8 (5)	0.6 (6)
C5	30.4 (8)	21.4 (7)	14.5 (6)	-0.6 (5)	4.9 (5)	-0.2 (6)
C6	29.1 (7)	17.9 (6)	15.2 (6)	-0.3 (5)	1.7 (5)	1.2 (5)
C7	28.6 (7)	19.9 (7)	17.0 (6)	1.4 (5)	1.6 (5)	1.7 (6)
C8	22.9 (7)	23.8 (7)	17.9 (6)	1.1 (5)	3.0 (5)	-1.1 (5)
C9	31.6 (8)	25.5 (7)	20.7 (6)	0.5 (5)	5.4 (5)	2.3 (6)
C10	39.4 (9)	32.2 (8)	19.0 (7)	0.0 (6)	9.2 (6)	2.4 (6)
C11	27.8 (7)	28.2 (7)	18.5 (6)	3.4 (5)	4.9 (5)	-1.5 (6)
C12	32.6 (8)	29.8 (8)	24.3 (7)	10.1 (6)	3.8 (6)	-2.1 (6)
C13	31.5 (8)	23.3 (7)	29.5 (7)	6.6 (6)	2.7 (6)	-0.2 (6)
C14	24.7 (7)	22.5 (7)	26.3 (7)	-0.6 (5)	2.5 (5)	-1.4 (5)
C15	24.9 (7)	23.8 (7)	19.3 (6)	1.6 (5)	2.3 (5)	-1.7 (5)
C16	23.0 (7)	24.5 (7)	18.3 (6)	2.7 (5)	2.5 (5)	-1.7 (5)
C17	33.8 (8)	22.3 (7)	14.0 (6)	-0.6 (5)	4.1 (5)	-2.3 (6)
C18	39.1 (9)	32.3 (8)	15.8 (6)	1.6 (6)	7.0 (6)	-3.6 (7)
C19	40.3 (9)	22.7 (7)	15.5 (6)	1.1 (5)	2.2 (5)	-1.0 (6)
C20	29.4 (8)	34.0 (8)	27.1 (7)	3.1 (6)	-6.0 (6)	5.5 (6)
C21	37.8 (10)	34.0 (9)	41.6 (9)	3.3 (7)	-6.2 (7)	5.6 (7)
C22	62.7 (13)	47.7 (11)	23.6 (8)	4.8 (7)	-3.1 (7)	7.8 (9)
C23	30.9 (9)	40.6 (11)	64.0 (12)	2.5 (9)	-6.0 (8)	2.3 (8)
C24	51.2 (10)	27.2 (8)	25.5 (7)	-2.0 (6)	4.6 (7)	6.6 (8)
N1	31.3 (6)	20.1 (6)	15.6 (5)	-0.1 (4)	0.0 (4)	0.4 (5)
N2	38.4 (7)	34.0 (7)	18.2 (6)	3.4 (5)	8.3 (5)	0.1 (6)
O1	29.9 (5)	26.3 (5)	21.5 (5)	1.1 (4)	-3.4 (4)	3.2 (4)
O2	33.1 (6)	29.7 (5)	21.4 (5)	-5.0 (4)	-1.1 (4)	0.8 (4)
O3	37.9 (6)	22.2 (5)	28.7 (5)	-0.9 (4)	5.2 (4)	2.7 (4)
O4	56.2 (8)	42.1 (7)	16.3 (5)	-2.1 (4)	12.3 (5)	-15.9 (6)
O5	34.5 (6)	32.8 (6)	15.9 (5)	-3.5 (4)	2.8 (4)	1.6 (4)
C25	50 (5)	78 (7)	53 (4)	21 (4)	28 (3)	20 (5)

Table 3 Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for paob23010. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\dots]$.

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
C26	46 (2)	59 (3)	53 (2)	1.6 (19)	12.1 (17)	2.1 (19)
C27	43 (2)	57 (3)	31.9 (17)	-6.5 (17)	7.9 (14)	7.4 (19)
C28	62 (5)	54 (4)	68 (4)	-5 (3)	12 (3)	-1 (3)
O6	49 (3)	52 (8)	34 (3)	-8 (4)	8.5 (19)	-2 (8)

Table 4 Bond Lengths for paob23010.

Atom	Atom	Length/ $\text{\AA}$	Atom	Atom	Length/ $\text{\AA}$
C1	N1	1.3582 (18)	C12	C13	1.358 (2)
C1	O1	1.3443 (17)	C13	C14	1.423 (2)
C1	O2	1.2248 (17)	C14	C15	1.364 (2)
C2	C3	1.5304 (17)	C14	O3	1.3686 (17)
C2	N1	1.4670 (18)	C15	C16	1.4221 (19)
C3	C4	1.5269 (19)	C17	C18	1.522 (2)
C4	C5	1.5272 (19)	C17	C19	1.520 (2)
C4	C17	1.5416 (17)	C18	O4	1.4235 (16)
C5	C6	1.5352 (17)	C19	O5	1.4178 (19)
C6	C7	1.544 (2)	C20	C21	1.519 (2)
C6	N1	1.4713 (17)	C20	C22	1.519 (2)
C7	C8	1.5031 (17)	C20	C23	1.511 (2)
C8	C9	1.3739 (19)	C20	O1	1.4786 (17)
C8	C16	1.4249 (19)	C24	O3	1.4245 (18)
C9	C10	1.4031 (19)	C25	C26	1.525 (8)
C10	N2	1.314 (2)	C26	O6	1.45 (3)
C11	C12	1.417 (2)	C27	C28	1.527 (8)
C11	C16	1.4233 (18)	C27	O6	1.44 (3)
C11	N2	1.3689 (18)			

Table 5 Bond Angles for paob23010.

Atom	Atom	Atom	Angle/ $^\circ$	Atom	Atom	Atom	Angle/ $^\circ$
O1	C1	N1	111.77 (11)	O3	C14	C13	114.22 (12)
O2	C1	N1	124.07 (13)	C14	C15	C16	120.05 (12)
O2	C1	O1	124.15 (12)	C11	C16	C8	117.84 (12)
N1	C2	C3	111.06 (11)	C15	C16	C8	123.12 (12)
C4	C3	C2	111.89 (11)	C15	C16	C11	119.04 (12)
C3	C4	C5	108.51 (11)	C18	C17	C4	113.76 (12)
C3	C4	C17	114.30 (11)	C19	C17	C4	112.27 (11)
C5	C4	C17	111.83 (10)	C19	C17	C18	109.92 (12)
C4	C5	C6	112.37 (10)	O4	C18	C17	108.04 (12)
C5	C6	C7	111.04 (11)	O5	C19	C17	112.79 (11)
N1	C6	C5	109.86 (11)	C21	C20	C22	110.58 (14)

Table 5 Bond Angles for paob23010.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
N1	C6	C7	111.34 (10)	C23	C20	C21	110.70 (15)
C8	C7	C6	112.75 (11)	C23	C20	C22	113.24 (15)
C9	C8	C7	120.61 (12)	O1	C20	C21	101.90 (12)
C9	C8	C16	118.04 (12)	O1	C20	C22	110.31 (13)
C16	C8	C7	121.32 (11)	O1	C20	C23	109.52 (13)
C8	C9	C10	119.93 (13)	C1	N1	C2	119.12 (11)
N2	C10	C9	124.00 (13)	C1	N1	C6	123.04 (11)
C12	C11	C16	118.95 (12)	C2	N1	C6	116.76 (11)
N2	C11	C12	118.61 (12)	C10	N2	C11	117.73 (12)
N2	C11	C16	122.44 (13)	C1	O1	C20	120.97 (11)
C13	C12	C11	121.23 (13)	C14	O3	C24	116.77 (11)
C12	C13	C14	119.60 (13)	O6	C26	C25	106.3 (16)
C15	C14	C13	121.12 (13)	O6	C27	C28	105.9 (17)
C15	C14	O3	124.66 (12)	C27	O6	C26	109 (3)

Table 6 Hydrogen Bonds for paob23010.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O4	H4A	O2 ¹	0.89 (2)	1.86 (2)	2.7449 (15)	172 (2)
O5	H5	N2 ²	0.85 (2)	1.91 (2)	2.7541 (15)	175 (2)

¹+X,1/2-Y,1/2+Z; ²1-X,-1/2+Y,1/2-Z

Table 7 Torsion Angles for paob23010.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C2	C3	C4	C5	56.13 (15)	C12	C13	C14	C15	-0.3 (2)
C2	C3	C4	C17	178.31 (12)	C12	C13	C14	O3	179.36 (13)
C3	C2	N1	C1	139.95 (13)	C13	C14	C15	C16	-0.2 (2)
C3	C2	N1	C6	51.60 (16)	C13	C14	O3	C24	172.69 (14)
C3	C4	C5	C6	-57.00 (15)	C14	C15	C16	C8	178.83 (13)
C3	C4	C17	C18	-47.98 (16)	C14	C15	C16	C11	0.7 (2)
C3	C4	C17	C19	77.65 (15)	C15	C14	O3	C24	-7.7 (2)
C4	C5	C6	C7	-69.77 (15)	C16	C8	C9	C10	0.9 (2)
C4	C5	C6	N1	53.84 (15)	C16	C11	C12	C13	0.2 (2)
C4	C17	C18	O4	161.14 (12)	C16	C11	N2	C10	1.5 (2)
C4	C17	C19	O5	66.70 (15)	C17	C4	C5	C6	176.01 (11)
C5	C4	C17	C18	75.81 (15)	C18	C17	C19	O5	165.61 (11)

Table 7 Torsion Angles for paob23010.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C5	C4	C17	C19	158.56 (12)	C19	C17	C18	O4	71.99 (15)
C5	C6	C7	C8	171.15 (11)	C21	C20	O1	C1	179.45 (12)
C5	C6	N1	C1	140.47 (13)	C22	C20	O1	C1	-62.00 (18)
C5	C6	N1	C2	-51.57 (15)	C23	C20	O1	C1	63.29 (17)
C6	C7	C8	C9	100.21 (15)	N1	C1	O1	C20	176.65 (11)
C6	C7	C8	C16	78.17 (16)	N1	C2	C3	C4	-53.03 (16)
C7	C6	N1	C1	-96.10 (15)	N1	C6	C7	C8	66.10 (14)
C7	C6	N1	C2	71.86 (14)	N2	C11	C12	C13	179.72 (14)
C7	C8	C9	C10	179.31 (13)	N2	C11	C16	C8	-1.2 (2)
C7	C8	C16	C11	178.43 (12)	N2	C11	C16	C15	179.23 (13)
C7	C8	C16	C15	1.1 (2)	O1	C1	N1	C2	175.81 (11)
C8	C9	C10	N2	-0.6 (2)	O1	C1	N1	C6	-8.12 (18)
C9	C8	C16	C11	0.0 (2)	O2	C1	N1	C2	5.5 (2)
C9	C8	C16	C15	179.49 (13)	O2	C1	N1	C6	173.16 (12)
C9	C10	N2	C11	-0.6 (2)	O2	C1	O1	C20	2.1 (2)
C11	C12	C13	C14	0.3 (2)	O3	C14	C15	C16	179.82 (13)
C12	C11	C16	C8	178.86 (13)	C25	C26	O6	C27	180 (3)
C12	C11	C16	C15	-0.7 (2)	C28	C27	O6	C26	176 (3)
C12	C11	N2	C10	178.55 (14)					

Table 8 Hydrogen Atom Coordinates ($\text{\AA} \times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for paob23010.

Atom	x	y	z	U(eq)
H2A	3610 (13)	3000 (13)	2929 (8)	20 (4)
H2B	2421 (14)	2488 (14)	2793 (9)	26 (4)
H3A	2155 (14)	2553 (15)	4058 (9)	28 (4)
H3B	3261 (14)	1915 (16)	3960 (9)	28 (4)
H4	4263 (14)	3638 (13)	4261 (9)	22 (4)
H5A	2204 (13)	4687 (13)	4441 (9)	21 (4)
H5B	3347 (14)	5323 (15)	4589 (9)	25 (4)
H6	2441 (12)	5778 (13)	3419 (8)	18 (4)
H7A	4499 (13)	4738 (14)	3237 (8)	19 (4)
H7B	4407 (13)	5974 (14)	3620 (9)	25 (4)
H9	4456 (13)	4515 (15)	1931 (9)	27 (4)
H10	4391 (15)	5408 (16)	754 (10)	35 (5)

Table 8 Hydrogen Atom Coordinates ($\text{\AA}\times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2\times 10^3$) for paob23010.

Atom	x	y	z	U(eq)
H12	3372 (14)	9077 (15)	1026 (10)	32 (4)
H13	2938 (14)	10284 (16)	2011 (10)	31 (4)
H15	3546 (13)	7643 (14)	3478 (9)	25 (4)
H17	3835 (12)	3935 (14)	5519 (8)	16 (3)
H18A	2422 (13)	1965 (15)	5390 (9)	22 (4)
H18B	1955 (14)	3289 (15)	5350 (9)	28 (4)
H19A	4385 (13)	1630 (15)	5106 (9)	26 (4)
H19B	4503 (13)	2072 (14)	5920 (10)	26 (4)
H21A	1319 (16)	7633 (16)	1942 (10)	39 (5)
H21B	358 (16)	7386 (17)	2474 (12)	46 (5)
H21C	84 (19)	7661 (19)	1609 (13)	58 (6)
H22A	1800 (20)	6150 (20)	1014 (13)	61 (6)
H22B	1065 (19)	4900 (20)	899 (14)	65 (7)
H22C	530 (20)	6160 (20)	670 (15)	73 (7)
H23A	-432 (16)	4607 (19)	1794 (11)	43 (5)
H23B	-981 (19)	5807 (18)	1578 (12)	52 (6)
H23C	-630 (20)	5510 (20)	2419 (15)	63 (7)
H24A	2300 (17)	8760 (19)	4088 (11)	43 (5)
H24B	3521 (18)	9076 (18)	4305 (11)	46 (5)
H24C	2575 (15)	10070 (18)	4360 (11)	42 (5)
H4A	2221 (18)	2375 (18)	6494 (12)	50 (6)
H5	5736 (16)	2547 (17)	4885 (13)	45 (5)
H25A	751.15	5973.45	3920.49	89
H25B	486.67	7272.7	4162.77	89
H25C	-474.48	6367.04	3989.15	89
H26A	1094.84	6145.41	5221.1	63
H26B	-123.79	6580.94	5297.65	63
H27A	-401.1	4979.77	6079.37	53
H27B	784.07	4460.66	5980.84	53
H28A	-11.58	2764.54	5416.29	91
H28B	-1188.92	3280.01	5520.35	91
H28C	-423.35	2918.28	6228.79	91

Table 9 Atomic Occupancy for paob23010.

Atom	Occupancy	Atom	Occupancy	Atom	Occupancy
C25	0.5	H25A	0.5	H25B	0.5
H25C	0.5	C26	0.5	H26A	0.5
H26B	0.5	C27	0.5	H27A	0.5
H27B	0.5	C28	0.5	H28A	0.5
H28B	0.5	H28C	0.5	O6	0.5

paob23010

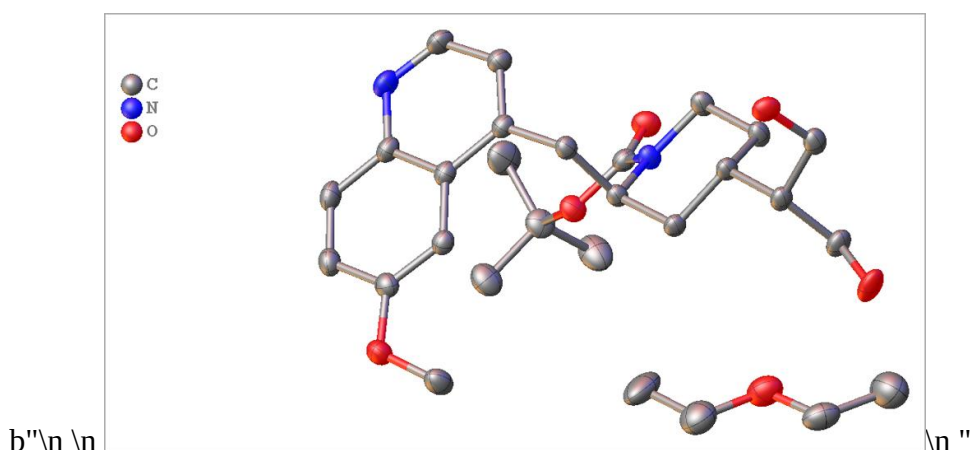


Table 1 Crystal data and structure refinement for paob23010.

Identification code	paob23010
Empirical formula	C ₂₆ H ₃₉ N ₂ O _{5.5}
Formula weight	467.59
Temperature/K	110.00(10)
Crystal system	monoclinic
Space group	P2 ₁ /c
a/Å	12.4129(4)
b/Å	11.5226(4)
c/Å	18.1200(5)
α/°	90
β/°	93.845(3)
γ/°	90
Volume/Å ³	2585.87(15)
Z	4
ρ _{calc} /cm ³	1.201
μ/mm ⁻¹	0.678
F(000)	1012.0
Crystal size/mm ³	0.15 × 0.09 × 0.05
Radiation	Cu Kα (λ = 1.54184)
2θ range for data collection/°	7.138 to 134.152
Index ranges	-14 ≤ h ≤ 14, -6 ≤ k ≤ 13, -21 ≤ l ≤ 19
Reflections collected	18535
Independent reflections	4615 [R _{int} = 0.0451, R _{sigma} = 0.0396]
Data/restraints/parameters	4615/9/463
Goodness-of-fit on F ²	1.039
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0422, wR ₂ = 0.1126
Final R indexes [all data]	R ₁ = 0.0502, wR ₂ = 0.1182
Largest diff. peak/hole / e Å ⁻³	0.26/-0.24