Elaboration of FragLites *via* Suzuki-Miyaura Cross-Coupling of 3-D Bifunctional Cyclopropyl-Fused Building Blocks

Islam Mohamed Araar

MSc. by Research

University of York

Department of Chemistry

October 2023

Abstract

Fragment-based drug discovery is a common method for the discovery of lead compounds in medicinal chemistry groups both in academia and in the pharmaceutical industry. The research described in this thesis focuses on an investigation of Suzuki-Miyaura cross-coupling reactions using 3-D building block *exo*-**A** with FragLites or protected/masked FragLites. A comparison of cross-coupling results obtained between *exo*-**A** protected FragLites and their unprotected analogues are summarised below. This clearly demonstrates the efficacy of the protection strategy in facilitating efficient cross-coupling reactions. In addition, some examples of *N*-functionalisation (after Boc group removal) and deprotection reactions are also described.

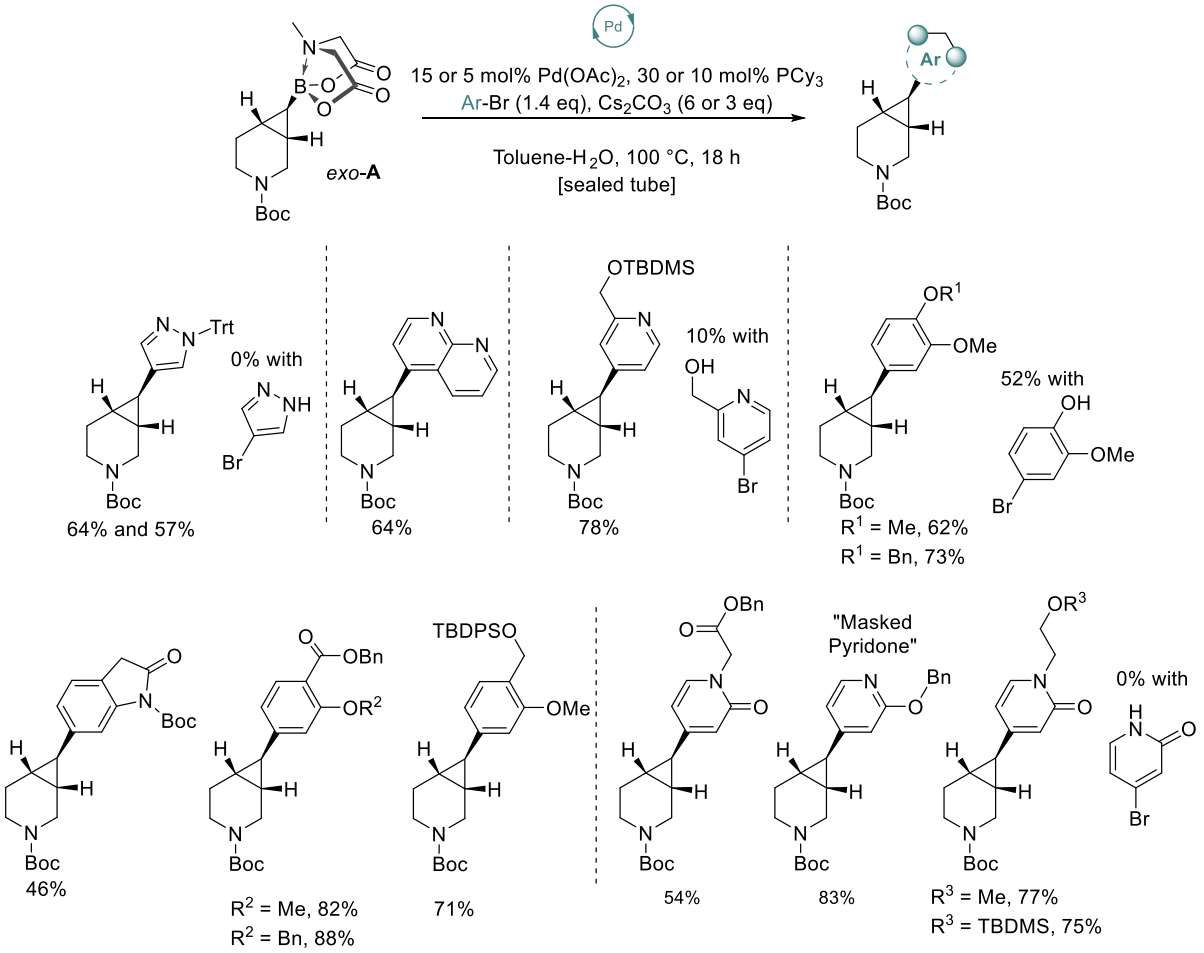


Table of Contents

Acknowledgements

First and foremost, I extend my gratitude to my supervisor Professor Peter O'Brien for granting me the opportunity to work on this project. His unwavering support, guidance, and mentorship have been vitally important, and I owe him a significant debt of gratitude. I appreciate the comprehensive research training he provided, characterised by enlightening discussions, consistent questioning, and constructive critique, which have resulted in the production of high-quality research and the refinement of my research skills and philosophy.

I wish to take the opportunity to thank the O'Brien group, most notably Stuart, Will, Lucy, Xinyu, Yuran, Andres, and Stephen, for fostering an unforgettable sense of community infused with joy and humour. This group truly comprises exceptionally talented individuals, and I am appreciative of the stimulating intellectual exchanges and assistance within the laboratory. Meeting all of you wonderful people has been an absolute pleasure.

I extend my thanks to the technical staff at the University of York, particularly Heather Fish, for overseeing an excellent NMR service. I must also acknowledge the contributions of current and past members of the O'Brien group to this project including Hanna, Andres, Yuran, Stephan, Will, Jake, James and Matt.

Lastly, I am grateful for the unwavering support of Leila and my close friends.

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.

Islam M. Araar

Abbreviations

3-D	Three-dimensional
Ac	Acetyl group
Aq	Aqueous
Ar	Aryl group
ATP	Adenosine triphosphate
Bcl-2	B-cell lymphoma 2
Bn	Benzyl group
Boc	*tert*-Butyloxycarbonyl
br	Broad
BuLi	Butyllithium
Cbz	Benzyloxycarbonyl
ClogP	Calculated logP
cm^{-1}	Wavenumber
COSY	2-D Correlated Spectroscopy
Cy	Cyclohexyl group
CSF-1R receptor	Colony stimulating factor 1 receptor
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide

DPP	Dipeptidyl peptidase
EDG	Electron donating group
Eq	Equivalent
ESI	Electron spray ionisation
Et	Ethyl group
EWG	Electron withdrawing group
FBDD	Fragment-based drug discovery
FDA	U.S. Food and Drug Administration
FGFR	Fibroblast growth factor receptor
h	Hour(s)
HRMS	High resolution mass spectrometry
HTS	High-throughput screening
Hz	Hertz
IC_{50}	The half maximal inhibitory concentration
in vitro	Outside the living organism
in vivo	Within the living organism
i-Pr	Isopropyl group
IR	Infrared spectroscopy
J	Coupling constant in Hz
KRAS-G12C	Kirsten rat sarcoma viral oncogene homolog - glycine to cysteine mutation

LG	Leaving group
M	Molar concentration
m-	Meta position on a phenyl ring
m/z	Mass to charge ratio
M^+	Molecular ion
Me	Methyl group
mg	Milligram(s)
MHz	Megahertz
MIDA	*N*-Methylimidodiacetic acid
min	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
MS	Mass spectrometry
MW	Molecular weight
n-	Unbranched (linear) chain
nM	Nanomolar concentration
NMR	Nuclear magnetic resonance spectroscopy
o-	Ortho position on a phenyl ring
p-	Para position on a phenyl ring
Pd/C	Palladium on carbon

Ph	Phenyl
pin	Pinacol
ppm	Parts per million
R_F	Retention factor
rt	Room temperature
sec	Secondary
S_N2	Substitution nucleophilic bimolecular
S_NAr	Nucleophilic aromatic substitution
T_3P	Propylphosphonic anhydride
tert	Tertiary
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilane
δ	Chemical shift in ppm
μ	Micro ($\times 10^{-6}$)
°C	Degrees Celsius

Chapter 1: Introduction

1.1 Fragment Based Drug Discovery

With up to several million compounds screened during drug development, the process from discovery to approval is a long and expensive endeavour, with high throughput screening and looking to natural products for inspiration being crucial in this process.[1] Fragment-based drug discovery (FBDD) is a method of drug discovery that uses small molecules, known as fragments, to identify potential binding sites on target proteins. These fragments are low in complexity, with a molecular weight typically less than 300 Daltons and they usually have a limited number of functional groups. A library of such fragments is screened against a protein in order to identify those which exhibit binding affinity (typically low binding affinity) and this then serves as a starting point for development into compounds with greater complexity and potency.[2] Optimisation is performed where refinements to the structure aim to reach a compromise between characteristics such as potency and selectivity meanwhile addressing physicochemical properties such as solubility, metabolic vulnerability or safety considerations, including possible unintended effects. [3] [4]

The advantages of FBDD to identify potential drug candidates rapidly in a relatively low-cost and low-risk manner has led to an increase in application of this drug discovery method in recent years.[5] To date, this approach has been used in the development of six drugs on the market (Figure 1.1). Vemurafenib, marketed as Zelboraf®, operates as a B-Raf kinase inhibitor and is prescribed for advanced-stage melanoma.[6] Two drugs originating from FBDD are employed in the treatment of non-small cell lung carcinoma: Pexidartinib (known commercially as Turalio®) acts as an inhibitor of the CSF-1R receptor, whereas Sotorasib (known as Lumakras®) targets the KRAS-G12C oncogene.[7] Erdafitinib (marketed as Balversa™), initially discovered by Astex Pharmaceuticals and the Northern Institute of Cancer Research, and subsequently developed by Janssen Pharmaceuticals, is used to treat metastatic urothelial cancer by inhibiting Fibroblast growth factor receptor (FGFR).[8] Venetoclax, approved by the FDA in 2016 and sold under the brand names Venclexta® and Venclyxto®, and functions by binding to Bcl-2, a protein which regulates apoptosis. This medicine is employed in the treatment of chronic lymphocytic leukemia, small lymphocytic lymphoma, or acute myeloid leukemia.[9] Asciminib (Scemblix®), on the other

hand, is utilised for chronic myeloid leukemia treatment by targeting the allosteric region of the BCR-ABL1, an oncogene prevalent in myeloid leukemia. [10]

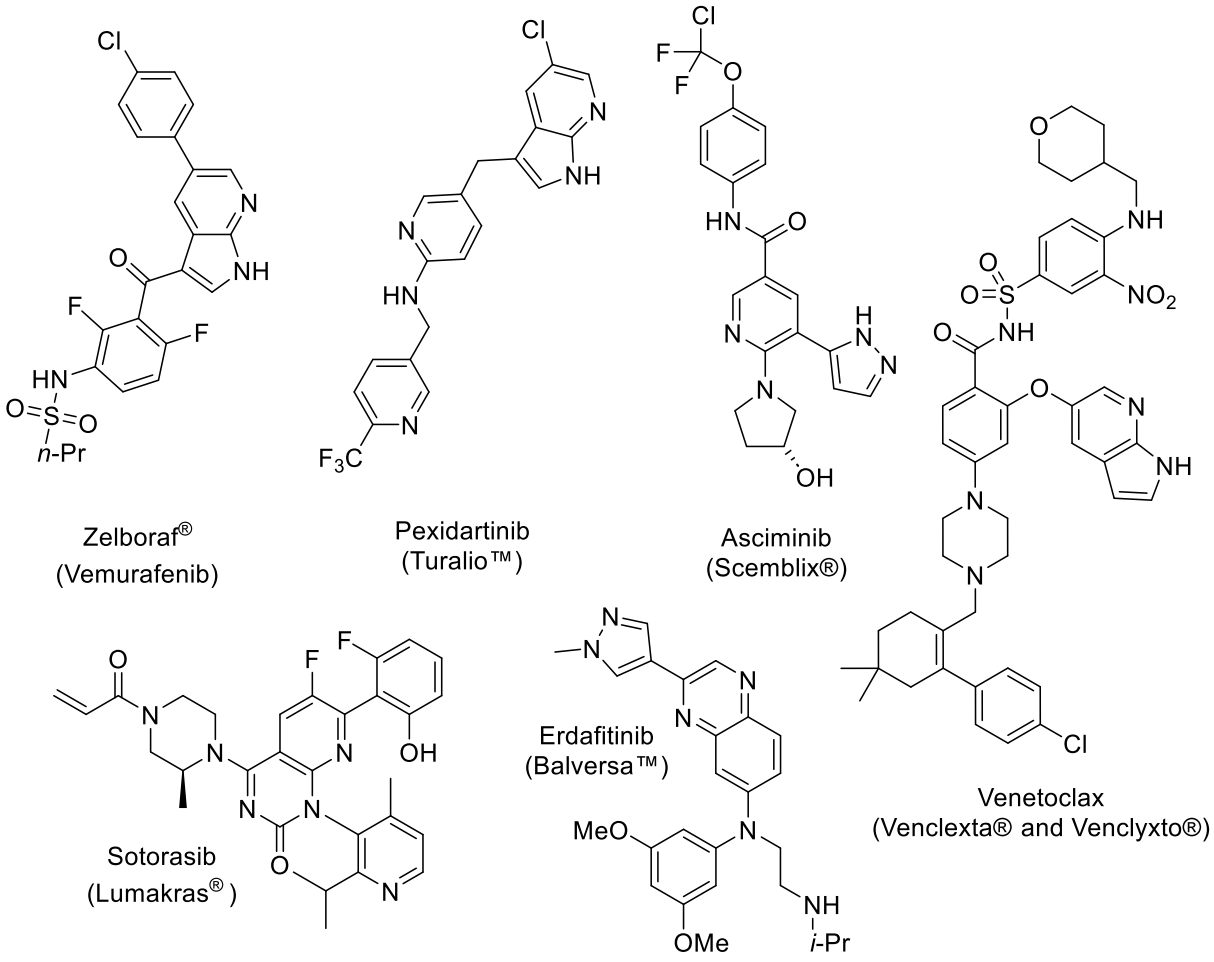


Figure 1.1. Drugs derived from FBDD.

FBDD has provided new opportunities for drug development by identifying binding sites on target proteins that were unknown previously. In the case of binding site identification, specific fragments have been developed with this intention in mind. For instance, FragLites are a collection of 31 fragments (further expanded to 33 fragments as of 2022[11]) which are designed with hydrogen-bond donors and/or acceptors to map protein binding sites.[12] In this process, X-ray crystallography is used to provide detailed information about the structure, location and orientation

of the bound FragLite (Figure 1.2). Through an iterative optimisation process, further structural modifications would be performed to increase binding affinity, specificity, or to improve pharmacokinetic properties, by adding/removing motifs or merging several fragments with linkers. These modified fragments would then be screened against the target protein, and those that show improved binding would be selected for further optimisation developing potent lead-like drug candidate. [2]

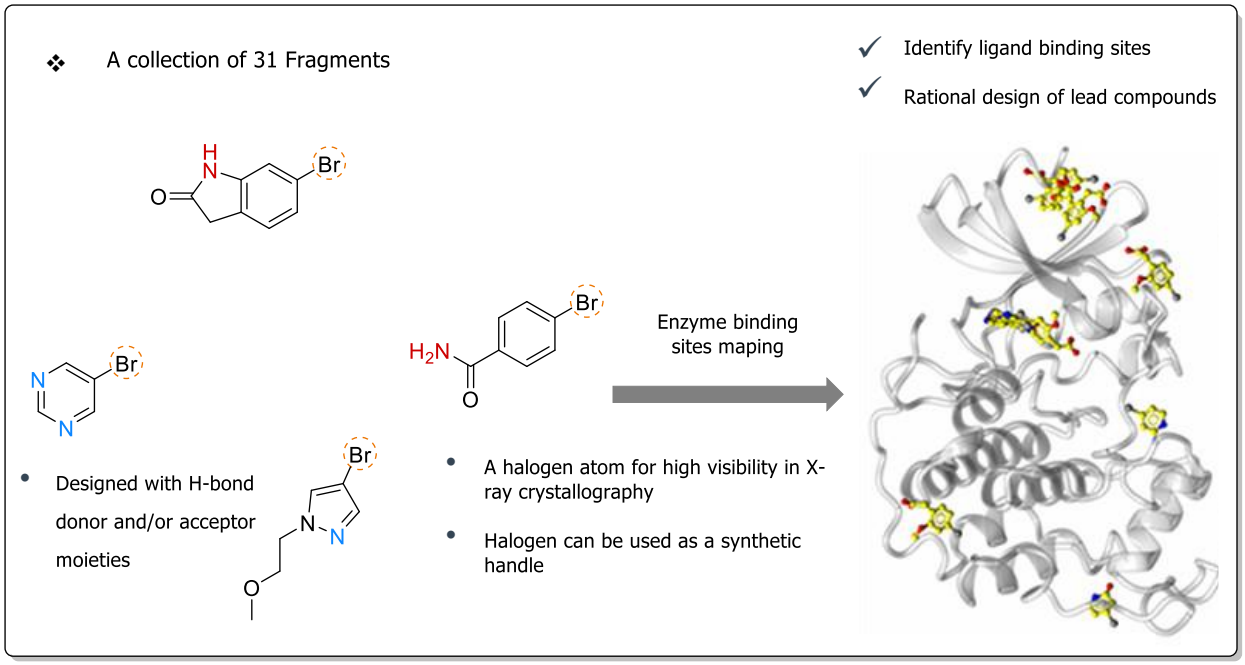


Figure 1.2. FragLites for binding site mapping

The library of FragLites include a range of structurally diverse molecules. This comprises of both heterocyclic and non-heterocyclic arenes which have been designed bearing pharmacophore doublets, namely combinations of hydrogen bond donors and acceptors motifs (Figure 1.3). In addition, a halogen tag is incorporated to enable greater visualisation of the small molecule by X-ray crystallography, and ultimately to identify the binding interaction of the FragLite with the protein. While it was not originally detailed by Waring *et al.*,[12] once a FragLite had been identified as a hit compound, the O'Brien group envisaged using the halogen tag as a synthetic handle for SMCC to grow the fragment into a more complex, lead-like compound.

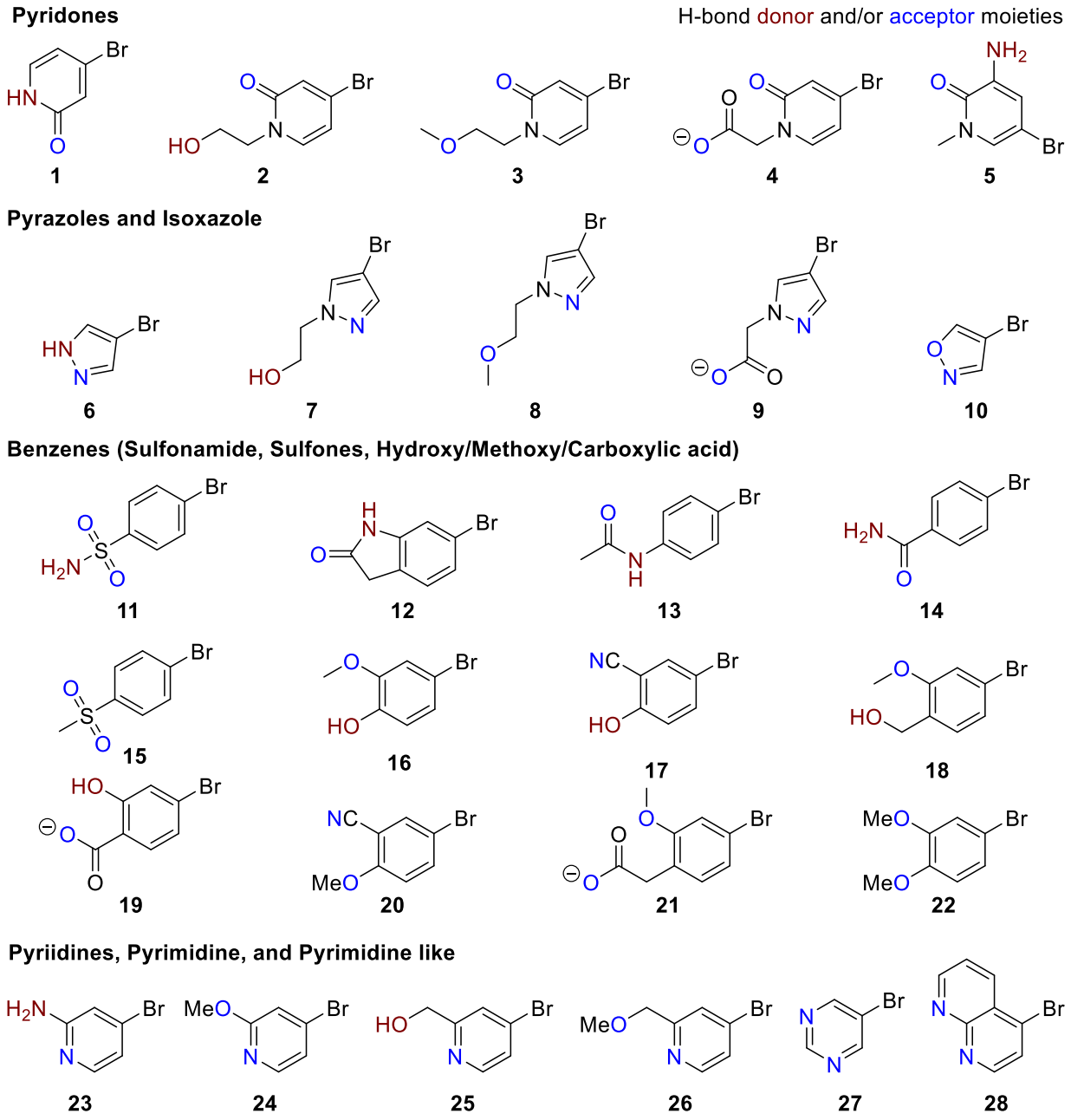


Figure 1.3. Collection of FragLites designed by Waring *et al.* [12]

Indeed, Waring *et al.* demonstrated the use FragLites to identify protein binding sites.[12] For instance, FragLites were screened against cyclin dependent kinase 2 (CDK2) (Figure 1.4). In this study, it was found that there were six distinct binding sites which were identified using FragLites including four previously unidentified allosteric sites. A binding event of particular interest were observed between FragLite **29** and CDK2, where direct interactions with the hinge region, as well

as binding to the ATP binding region. The carboxylate moiety of FragLite **30** made the critical interactions with the protein and it was decided to grow this fragment by merging with other fragments bound in the hinge region. For example, FragLite **29** was merged with **30** to form merged FragLite **31** which showed similar binding interactions to both FragLites in isolation (Figure 1.4).

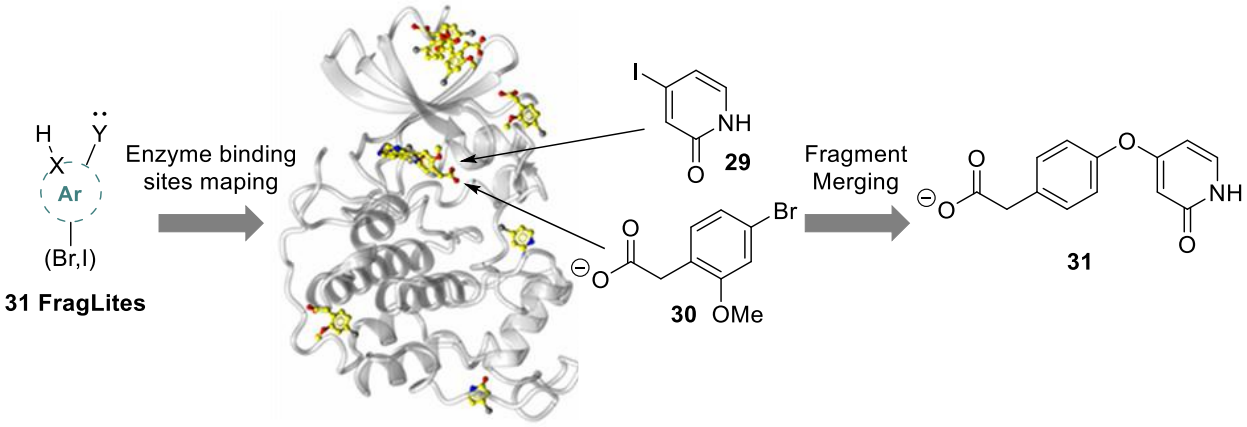


Figure 1.4. FragLites for binding site mapping

The growth of fragments in FBDD into lead-like compounds requires tools to generate modification with specific vectors for precise directional protein probing.[13] Significant investment in synthetic organic chemistry is required for the elaboration of the fragment, often requiring bespoke methodology. The process is time-consuming and may involve multiple steps, each of which can be challenging, with an added complexity when considering structural features such as stereoselective synthesis. As a result, the efficiency of the FBDD process is dependent on, and limited by, the available synthetic methodologies for fragment elaboration. [13]

1.2 Case Study: FBDD Development of Vemurafenib for Melanoma Therapy

Six medications currently available on the market have their origins from FBDD. The first of these to be developed was Vemurafenib (Zelboraf™), which resulted from a collaborative effort between Roche and Plexxikon. The project was initiated in 2006 and achieved FDA approval in 2011, for the treatment of late-stage melanoma, where the mechanism of action involves selective inhibition of a mutant form of B-Raf kinase. Treating patients with late-stage melanoma historically has posed challenges as the therapeutic options have been limited. The development of Vemurafenib stands as a significant milestone, not only in the treatment of late-stage melanoma but also in illustrating the efficacy of FBDD as an innovative approach to drug discovery.

The development of Vemurafenib first began with screening of 20,000 fragments ranging from 150 to 350 Daltons. Within these, a subset displayed an affinity for the mutated BRAF protein kinase. These were further investigative through crystallographic studies, where azaindole **32** was selected which was found to bind to the ATP binding region of BRAF protein kinase. Azaindole **33** served as a foundation for the synthesis of more complex analogues (Figure 1.5), whereby structural modifications were performed to achieve the desired properties, including optimising potency, selectivity and physicochemical properties.[14]

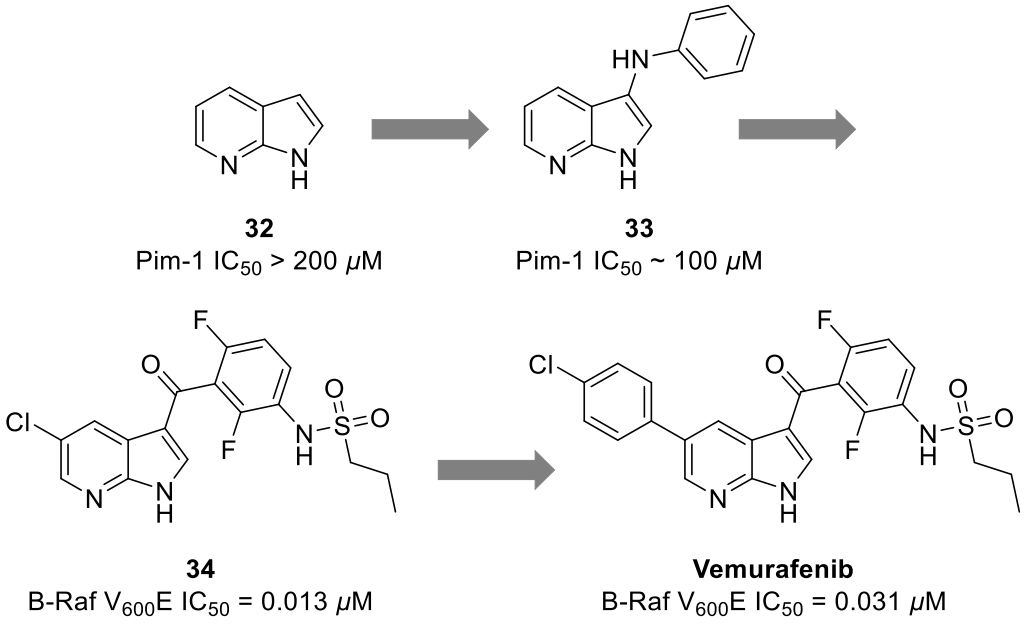


Figure 1.5. Development of Vemurafenib using FBDD.

The initial modifications centred on increasing the potency of the compound, which was achieved by the growth of the structure at C-3 of azaindole **32** with an aniline motif which gave azaindole **33**. However, this analogue, while potent, exhibited off-target inhibitory effects on other B-Raf kinases than the target, and therefore the development of a more selective compound was necessary. Several more analogues were generated, and ultimately azaindole **34** was chosen which showed superior specificity towards the target protein. Further structural modifications aimed to balance the previously described properties while modifying the physicochemical properties which gave the final azaindole Vemurafenib. The efficacy and safety of Vemurafenib was validated during clinical trials which led to approval by the FDA for therapeutic use.

1.3 Towards Three-dimensionality in FBDD: Use of York Building Blocks for Modular 3D Fragment Elaboration

The York 3-D bifunctional building blocks **35-43** (Figure 1.6) developed in the O'Brien group are a set of compounds that have been designed to be highly versatile as a tool for incorporating 3-dimensionality in FBDD, generating lead-like compounds quickly and efficiently. The building blocks are characterised by small, rigid scaffolds and the presence of two functional groups, one of which is a boron moiety used as a synthetic handle for attachment of a fragment and the other is a protected nitrogen for further functionalisation. The synthetic handle is bonded either to a fused or spiro cyclopropyl group – the conformationally strained nature of this group enables a defined attachment of fragments along specific three-dimensional vectors. These building blocks have been designed so that they have 3-D vectors which cover different areas of chemical space.

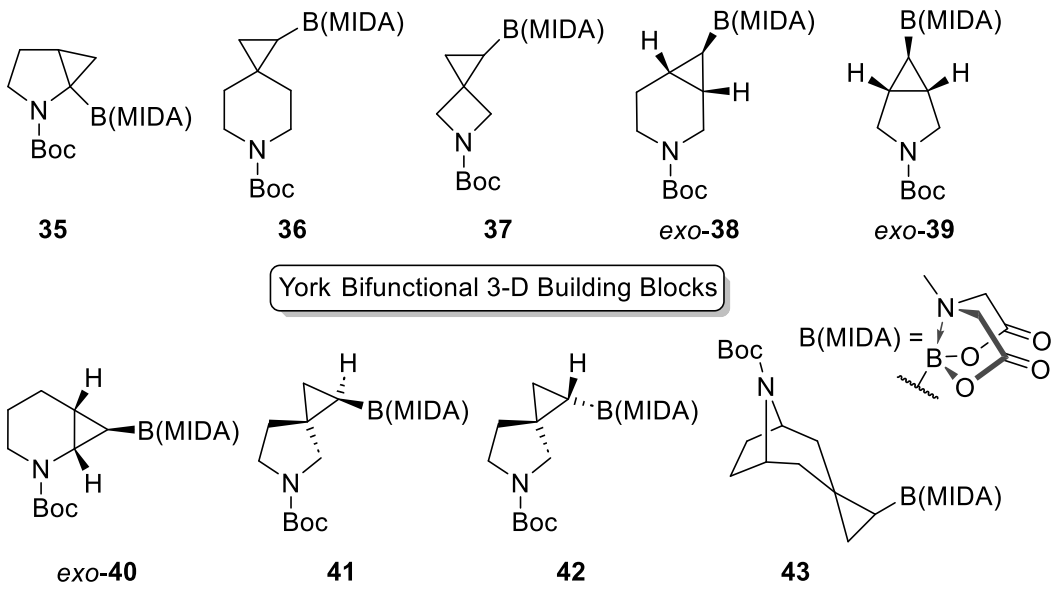
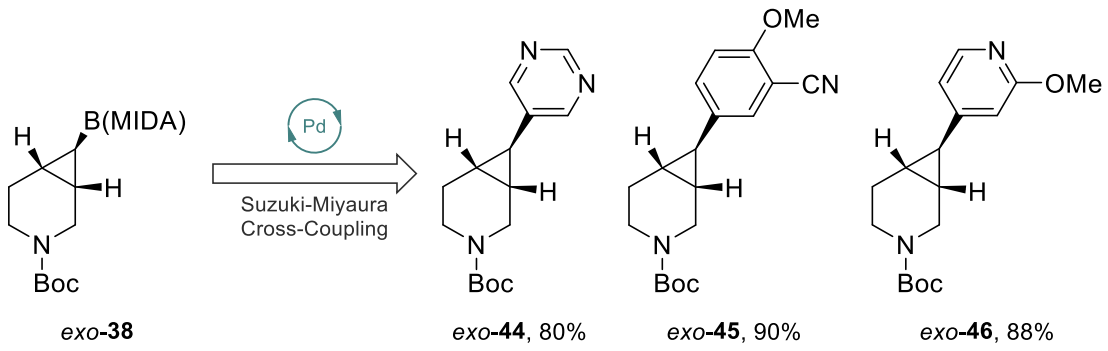


Figure 1.6 York 3-D bifunctional building blocks

The Suzuki–Miyaura cross-coupling (SMCC) reaction, first published in 1981, is a widely used reaction that allows for the efficient and selective formation of carbon-carbon bonds between an organoboron compound and a species with a halide or triflate.[15] A particular advantage of this reaction for FBDD lies in its ability to efficiently transform simple and small fragments, into complex, 3-D molecular frameworks. However, SMCC typically occurs between sp^2-sp^2 carbons, leading to the formation of potentially planar molecules. Transitioning to performing FBDD in

three-dimensions presents many difficulties. For instance, SMCC of sp^3 centres can lead to potential β-hydride elimination, necessitating the use of a specialised, electron-rich bulky ligand to facilitate such a reaction. In the case of cyclopropyl, and to a lesser extent, cyclobutyl sp^3 centres, there is a non-linear overlap of the sp^3 orbitals, resulting in an increased sp^2 character. This characteristic allows cyclopropyl boron reagents to readily undergo SMCC.

The work of the O'Brien group represents a significant contribution to FBDD by enabling vector growth to take place in 3-D. It is an ongoing endeavour within the O'Brien research group to carry out the cross-coupling of the York 3-D building blocks with aryl halides, with over 70 examples having been successfully demonstrated to date. Three examples with FragLites are shown in Scheme 1.1. Burke *et al.* first demonstrated the use of *N*-methyliminodiacetic acid (MIDA) boronates in 2008[16] and later extended it to cyclopropyl MIDA boronates.[17] There are several advantages of using MIDA boronates over their boronic acid counterparts, notably their remarkable stability during purification and their capacity for long-term storage. The MIDA boronates act as a masked form of the boronic acid, where under aqueous conditions, the MIDA boronate undergoes slow hydrolysis to yield the corresponding boronic acid.[18] During SMCC, the slow hydrolysis mechanism results in the generation of a low concentration of boronic acid to undergo cross-coupling, which at the same time reduces the instances of protodeborylation.

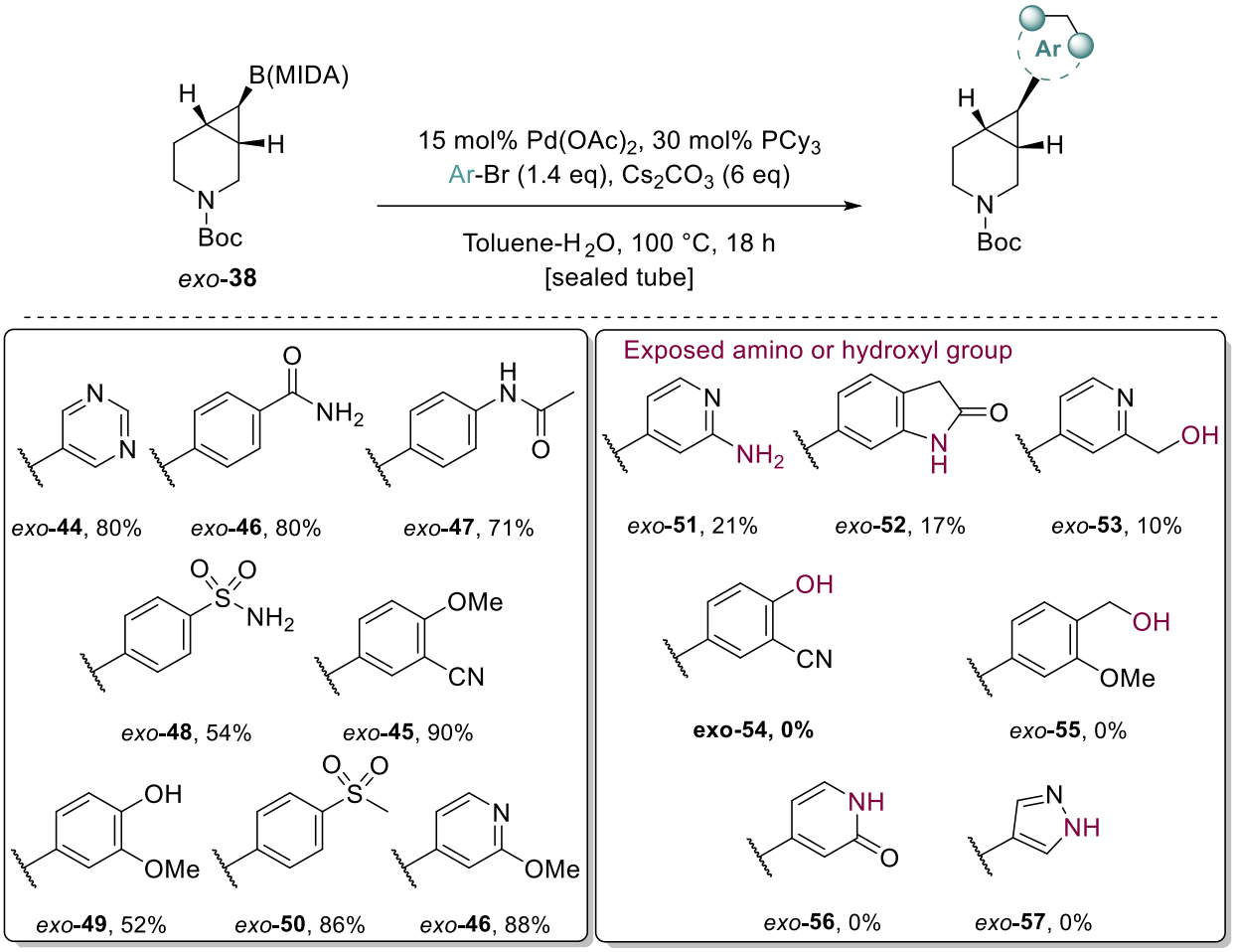


exo-**38** *exo*-**44**, 80% *exo*-**45**, 90% *exo*-**46**, 88%

Scheme 1.1 SMCC to synthesise 3-D lead-like compounds.

Studies conducted within the O'Brien group by Klein[19] and Gomez Angel[20] had focused on cross-coupling reactions utilising cyclopropyl building block *exo*-**4**. It was observed that a range of FragLites yielded excellent results with yields of cross-coupled products **10**-**17** ranging from 52-

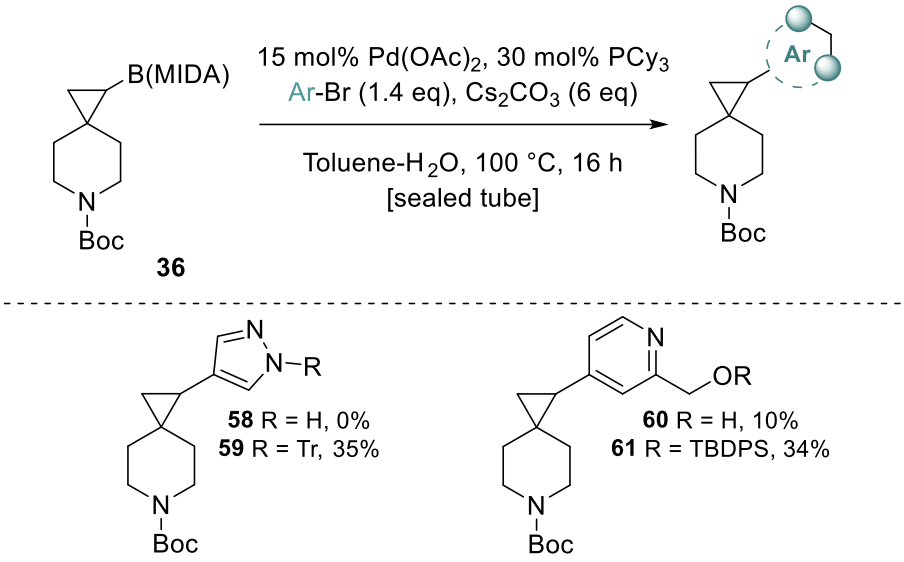
90%. However, certain FragLites exhibited poor yields or did not generate the desired product at all (for example, **18**-**24**) (Scheme 1.2). A correlation was established between these substrates, as it was found that many of them possessed exposed amino or hydroxyl groups, leading to the hypothesis that these functional groups may have an inhibitory effect on the cross-coupling reactions. As a means to resolve these issues, it was proposed to install protecting groups on the amino or hydroxyl groups prior to the coupling reactions.



Scheme 1.2. Suzuki-Miyaura cross-coupling reactions with FragLites

The results by Klein led the group to examine the functional groups of FragLites and to discern those that might present challenges during the SMCC. The trends showed that exposed amino or hydroxyl groups resulted in lower yields and therefore it was proposed that FragLites with these functionalities would require protection. This protection strategy was initially explored in previous work by Walder *et al.* for selected FragLites (Scheme 1.4).[21] Suzuki-Miyaura cross-coupling of

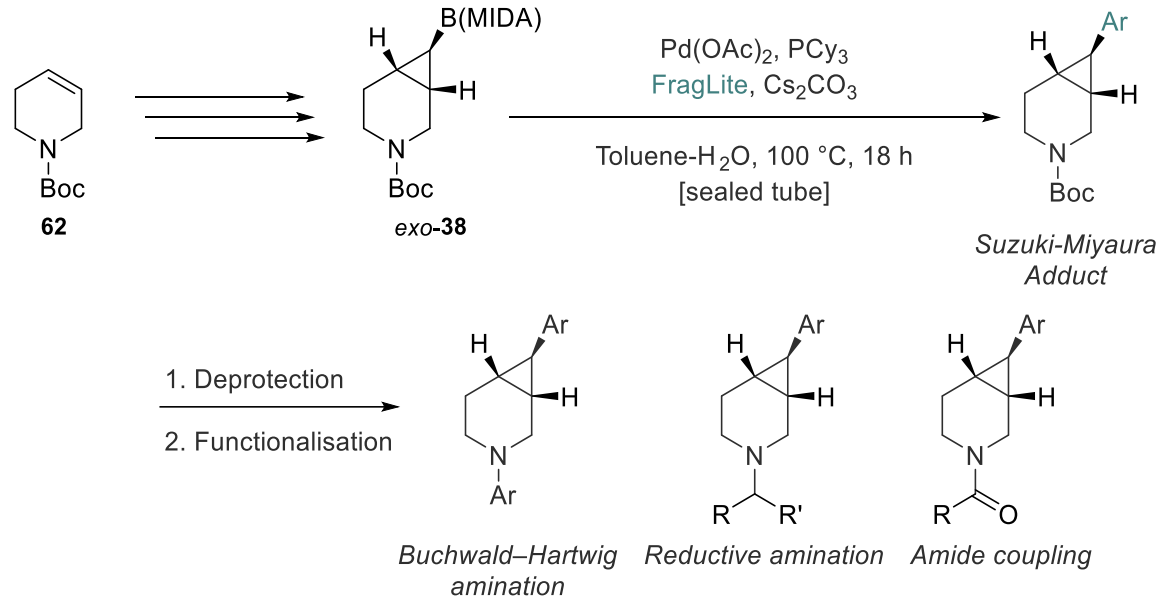
protected FragLites was performed with 4-spiro cyclopropyl piperidine B(MIDA) **36** which showed improved yields compared to the unprotected Fraglites. For example, it was shown that the protection strategy enabled cross-coupling of 4-spiro cyclopropyl piperidine B(MIDA) **36** to furnish trityl pyrazole **59** in improved yield compared to its unprotected counterpart. It was also shown that the strategy can be extending to silyl protecting groups to provide cross-coupled product **61**.



Scheme 1.3. SMCC of protected FragLites by Walder. [21]

1.4 Project Outline: Research Aims and Objectives

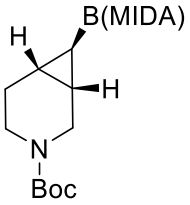
The genesis of FragLites by Waring *et al.* has provided an important tool in the field of medicinal chemistry and FBDD in particular. In anticipation of the integration of FragLites in upcoming drug discovery campaigns, it becomes vital to develop a methodology for their transformation into complex, medicinally relevant compounds. The purpose of the research described herein is to explore the scope of SMCC reactions of cyclopropyl piperidine B(MIDA) building block *exo*-**4** with FragLites to produce a set of structurally diverse compounds (Scheme 1.4). In order to do this, it was necessary to synthesise some of the FragLites as they are relatively expensive to purchase. In addition, the plan was to develop suitable protecting group strategies for some of the FragLites. A comparison can then be made between the protected and unprotected FragLite in the SMCC reactions. The results of our efforts in this area, together with the synthesis of 3-D building block *exo*-**4**, are presented in Chapter 2. Chapter 3 focuses on the studies of the SMCC reactions of 3-D building block *exo*-**4** with the protected and unprotected FragLites. In addition, our efforts on *N*-functionalisation and the removal of the protecting groups from the cross-coupled FragLites are also summarised in Chapter 3 (Scheme 1.4).



Scheme 1.4. Project outline

Chapter 2: Synthesis of 3-D Building Block, FragLites and Protected FragLites

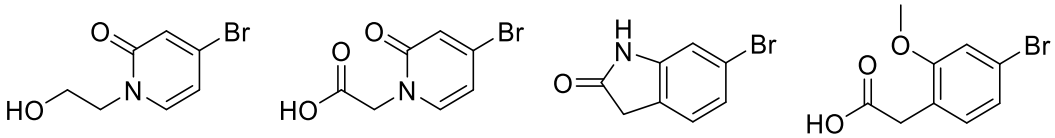
The initial objective involved construction of 3-D building block *exo*-**38** (Figure 2.1), using the synthesis developed by Klein,[19] a previous member of the O'Brien group. The results on the gram-scale synthesis of 3-D building block *exo*-**38** are summarised in Chapter 2.1.



exo-**38**

Figure 2.1 York 3-D bifunctional building block *exo*-**38**

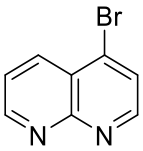
Chapter 2 also includes our efforts on the synthesis of FragLites and protected FragLites, including pyridones, pyrazoles, and substituted benzenes and pyridines. Many of the FragLites, by nature of their functional groups, did not work very well in SMCC reactions, and thus it was necessary to derivatise the FragLites with protected functional groups. The results are presented in Chapter 2.2 and selected examples of FragLites that required protection are shown in Figure 2.2.



2 **4** **12** **21**

Figure 2.2. Examples of FragLites needing protection.

Finally, in Chapter 2.3, the synthesis of naphthyridine FragLite **28** (Figure 2.3) is discussed. The synthesis of FragLite **28** proved challenging , and it was necessary to attempt several reaction conditions and perform optimisation to obtain the target compound.

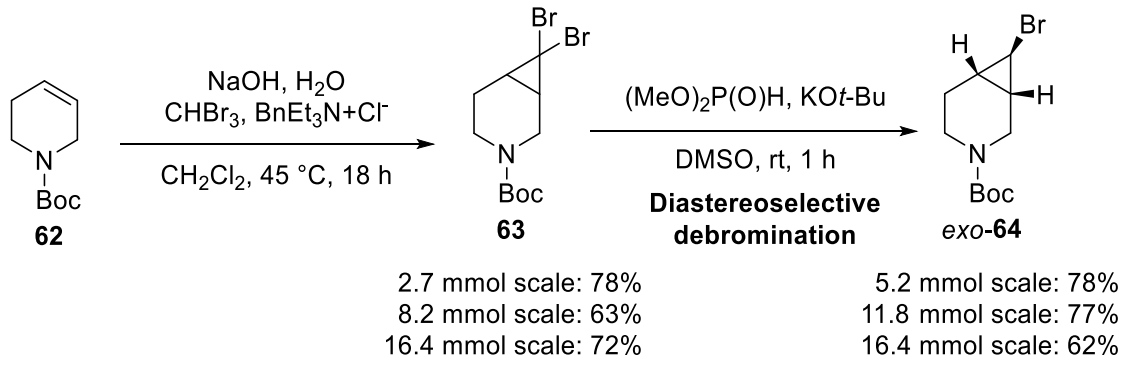


28

Figure 2.3. Naphthyridine FragLite **28**

2.1 Synthesis of a 3-Fused Cyclic Piperidine 3-D Building Block

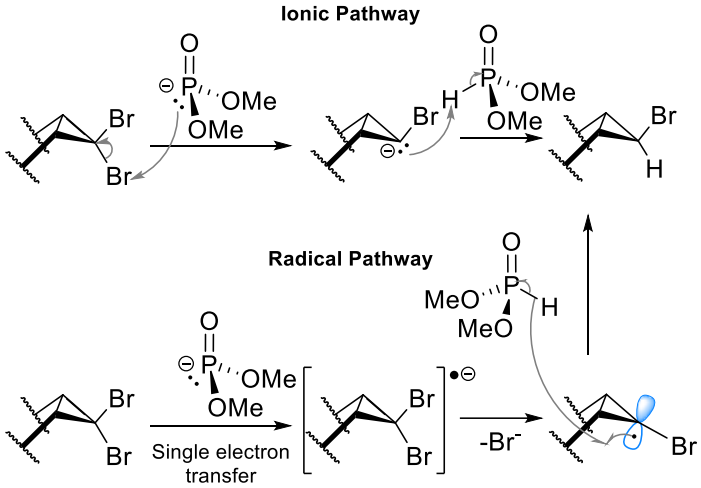
The starting point in this project was to synthesise 3-D building block *exo*-**38**. This was carried out using the route previously developed in the group by Klein.[19] The first two steps are shown in Scheme 2.1. First, dibromocyclopropanation of β,γ-unsaturated *N*-Boc protected piperidine **62** was performed using aqueous sodium hydroxide, bromoform and benzyltriethylammonium bromide at 45 °C for 18 h. This gave dibromocyclopropane **63** after purification by chromatography in 78% yield on a small scale (Scheme 2.1). In this reaction, a phase-transfer catalyst (benzyltriethylammonium bromide) is used to facilitate the transition of the hydroxide anion from the aqueous phase to the organic phase, thereby enabling the deprotonation of bromoform to proceed. Similar yields of 63% and 72% were obtained from larger-scale reactions. However, especially on larger scales, the work-up process was challenging due to the formation of black tar and emulsions. To separate the layers, a large amount of brine and agitation was used, followed by isolation of the organic phase and removal of insoluble solids *via* filtration.



Scheme 2.1. Synthesis of the dibromocyclopropane **63** and bromocyclopropane *exo*-**64**

The next step was debromination of dibromocyclopropane **63** which was performed by utilising methodology reported by Meijs and Doyle in 1985.[22] In their method, potassium *tert*-butoxide and dimethyl phosphite were used to carry out diastereoselective debromination *via* a proposed ionic mechanism, as discussed later. Dibromocyclopropane **63** was reacted with potassium *tert*-butoxide and dimethyl phosphite in DMSO at room temperature for 1 hour. After chromatography, monobromocyclopropane *exo*-**64** was obtained in 78% yield (Scheme 2.1). Upon scale-up to 11.8 mmol and 16.4 mmol, yields of *exo*-**64** of 62% and 77% were obtained respectively.

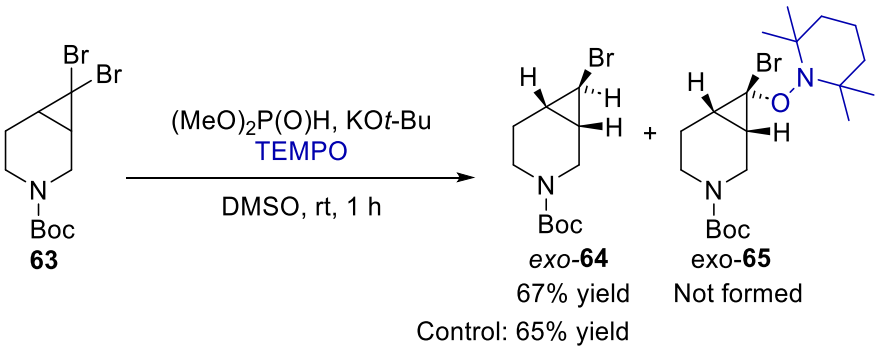
Meijs and Doyle proposed an ionic mechanism for the debromination reaction (Scheme 2.2). This would involve nucleophilic attack of the phosphite anion onto one of the bromine atoms to generate a cyclopropyl carbanion. The high diastereoselectivity can be explained in terms of thermodynamics, as having the cyclopropyl carbanion with the bromine atom in the *exo* position results in less steric hindrance. Subsequent irreversible protonation of the cyclopropyl carbanion would then lead to the formation of *exo*-**64**. This can be contrasted with a radical mechanism, where a single-electron could be transferred from the phosphite anion into the σ* orbital of the carbon-bromide bond of the dibromocyclopropane. Subsequent elimination of a bromide anion would form a sp^2-hybridised radical which could abstract a hydrogen atom from the dimethyl phosphite to give *exo*-**64** (Scheme 2.2).



Scheme 2.2. Plausible mechanisms for the debromination reaction

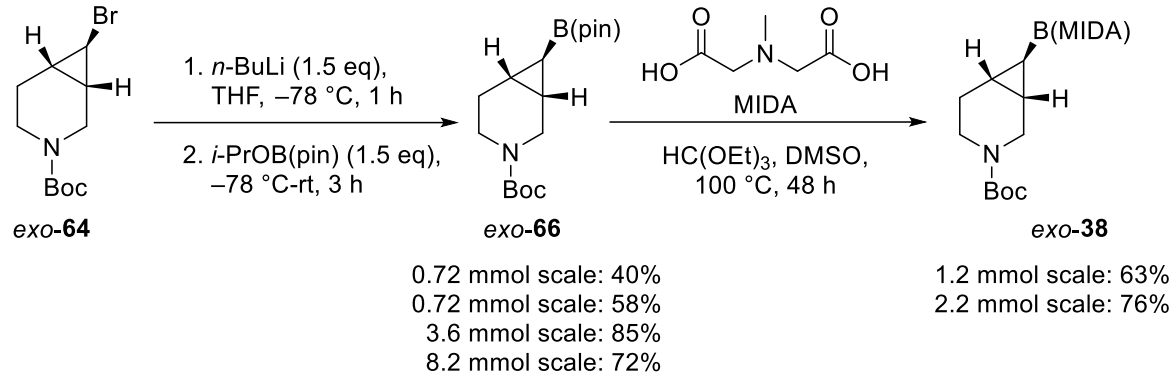
Mechanistic investigations by Meijs and Doyle found that the reaction proceeded in an oxygen atmosphere in the absence of light and also occurred in the presence of a radical scavenger. Such results led the authors to postulate that the reaction proceeded *via* an ionic pathway. We decided to perform an additional experiment to investigate the mechanism. It was envisioned that if the reaction proceeded *via* a radical pathway, it should be inhibited by the presence of a radical scavenger such as TEMPO. However, as shown in Scheme 2.3, despite the inclusion of TEMPO, debromination of **63** persisted to yield *exo*-**64** in 67% yield, comparable to that obtained under the standard conditions (65% yield). There was also no evidence for formation

of the TEMPO-trapped adduct *exo*-**28**. In light of this, the current evidence indicates that the reaction does indeed proceed *via* an ionic pathway, although further experiments would be required to prove the ionic pathway conclusively.



Scheme 2.3. Radical-trapping experiment

In the next step, bromocyclopropane *exo*-**64** was subjected to bromine-lithium exchange with *n*-butyllithium which was carried out at −78 °C for 1 hour. This was followed by trapping with *iso*-propoxypinacol boronate at –78 °C followed by reaction at room temperature for 3 hours. Following chromatography, cyclopropyl Bpin *exo*-**66** was obtained in 40% yield, with bromine-lithium exchange and trapping proceeding with stereoretention as previously established in the group (Scheme 2.4). Upon titration of the *n*-butyllithium, it was found that the concentration was lower than expected. With the proper concentration determined, the subsequent reactions resulted in higher yields on 0.7 mmol, 3.6 mmol and 8.2 mmol scale, with yields of 58%, 85%, and 72%, respectively. Finally, pinacol boronate *exo*-**66** was treated with MIDA and triethyl orthoformate in DMSO at 100 °C for 48 hours to provide the bench-stable cyclopropyl-B(MIDA) *exo*-**38** in good 63% and 76% yields (Scheme 2.4). For the small-scale reaction, it was found that purification of *exo*-**38** by recrystallisation did not provide the pure product, and chromatography was necessary.



exo-**64** *exo*-**66** *exo*-**38**

0.72 mmol scale: 40%
0.72 mmol scale: 58%
3.6 mmol scale: 85%
8.2 mmol scale: 72%

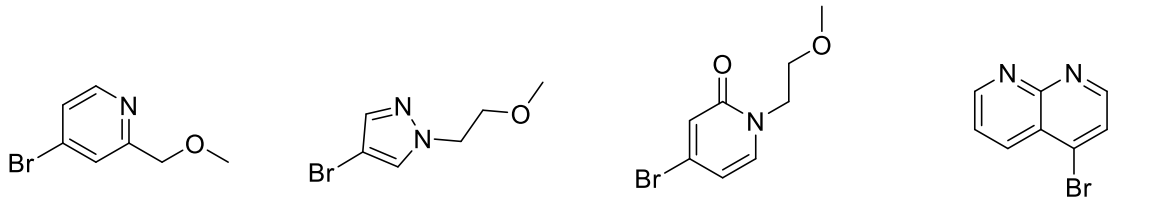
1.2 mmol scale: 63%
2.2 mmol scale: 76%

Scheme 2.4. Synthesis of the pinacol and MIDA boronates

In conclusion, the synthetic route was efficient in producing 3-D building block *exo*-**38** *via* a four-step process. It was possible to scale-up to gram-quantities with relative ease to generate enough material for the planned SMCC reactions.

2.2 Synthesis of FragLites and Protected FragLites

Many FragLites can be readily purchased from a commercial supplier in sufficient quantities and reasonable prices. However, certain FragLites are expensive and therefore it was decided to carry out their synthesis in house. As depicted in Figure 2.4, the expensive FragLites include bromo pyridine **26**, bromo pyrazole **8**, bromo pyridone **3**, and bromo naphthyridine **28**.



26 **8** **3** **28**

International Price for 250 mg: £600 - £800

International Price for 250 mg: £50 - £150

International Price for 250 mg: £150 - £400

International Price for 250 mg: £400 - £700

Figure 2.4. Expensive FragLites

Within the set of 31 FragLites, a subset has been discerned to possess functionalities that might present challenges during the SMCC. Precisely, fourteen FragLites, which are highlighted in Figure 2.5, contain one or more exposed amino and/or hydroxyl groups. These have been classified according to the central molecular framework, encompassing diverse structures including substituted benzenes, pyridones, and pyrazoles. For FragLites containing N-H functionalities, it was envisioned incorporating a range of different amino protecting groups such as trityl, Boc and tosyl groups. In the case of phenolic and carboxylic acid substituents, it was decided to use benzyl protecting groups, which can be readily cleaved *via* catalytic hydrogenolysis. Meanwhile, for FragLites with primary alcohols, silyl protective groups would be installed such as *tert*-butyldimethylsilyl (TBDMS) or the more sterically hindered *tert*-butyldiphenylsilyl (TBDPS). They can be deprotected using TBAF. Several factors needed to be considered prior to commencing the synthesis of protected FragLites. For example, it is necessary to consider the stability of the introduced protecting group to hydroxide at 100 °C since hydroxide will be generated during SMCC reactions due to the presence of caesium carbonate and water. Indeed, assessing the stability or otherwise of the planned protecting groups was a key part of this study.

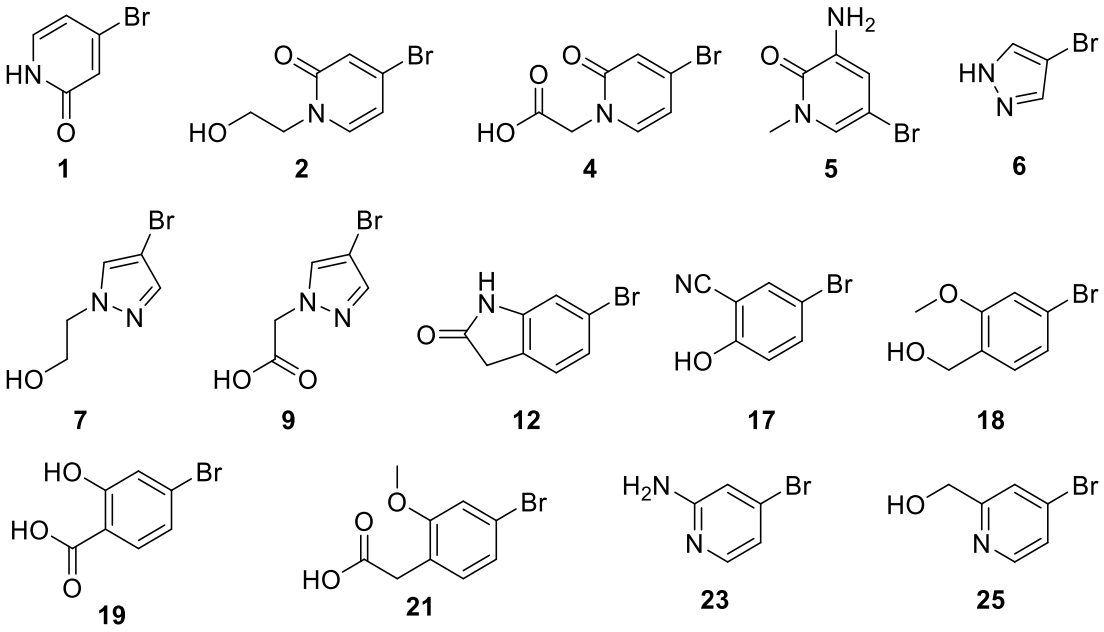


Figure 2.5. FragLites with exposed amino and/or hydroxyl group

2.2.1 Synthesis of Pyridone FragLites

The FragLites containing a pyridone structure, **1**-**4**, are shown in Figure 2.6. Three FragLites **2**-**4** involved substitution at the nitrogen atom. As a result, it was envisioned that these compounds could be synthesized by employing an *N*-alkylation approach starting from 4-bromopyridinone **1** and, where necessary, suitably protected alcohol or carboxylic acid groups.

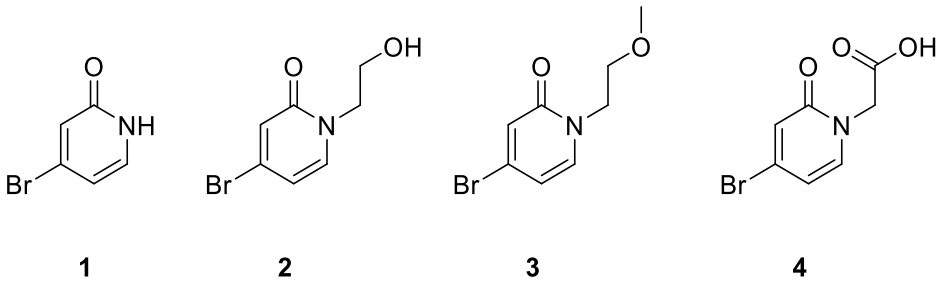
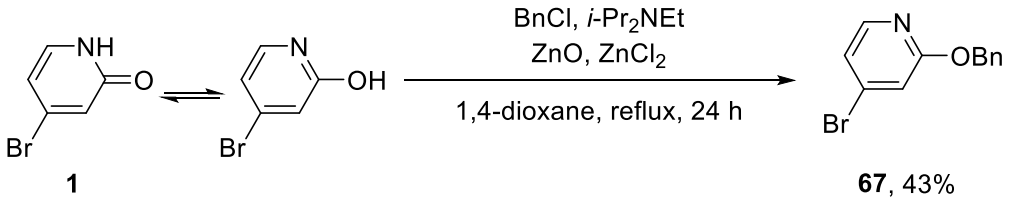


Figure 2.6. Pyridone FragLites needing synthesis and/or protection

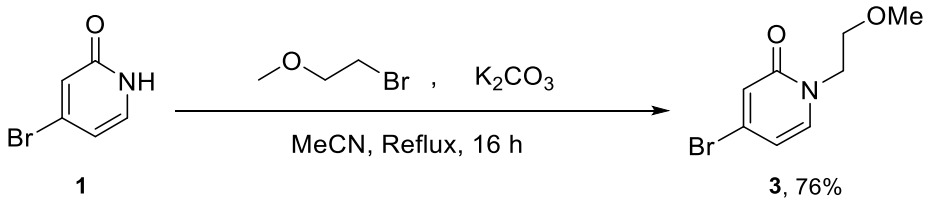
Although 4-bromopyridinone **1**, a FragLite itself, is commercially available, SMCC with the building block *exo*-**38**, as demonstrated by Klein, was completely unsuccessful (see Scheme 1.2). Consequently, a strategy involving a protective group was devised, with the aim of synthesising a masked pyridone. *O*-alkylated pyridines (such as **67**, Scheme 2.5) can be

considered as masked pyridines since, upon hydrogenolysis, the benzyl group is removed to reveal the pyridine tautomer. 4-Bromopyridinone **1**, which primarily exists in its pyridone tautomeric form, displays a higher propensity for *N*-alkylation rather than *O*-alkylation. Notwithstanding this inherent reactivity trend, a procedure outlined by Chen *et al.*[23] offered a viable methodology for selective *O*-alkylation. This unconventional approach was undertaken by a member of the O'Brien group, Butler, who employed 4-bromopyridinone **1** in reaction with benzyl chloride. The reaction was carried out in the presence of ZnO, $ZnCl_2$ and *i*-Pr_2NEt in dioxane under reflux for a duration of 24 hours. This protocol yielded *O*-alkylated bromopyridine **67** in an adequate 43% yield (Scheme 2.5).



Scheme 2.5. Masked pyridone **67** synthesis by Butler

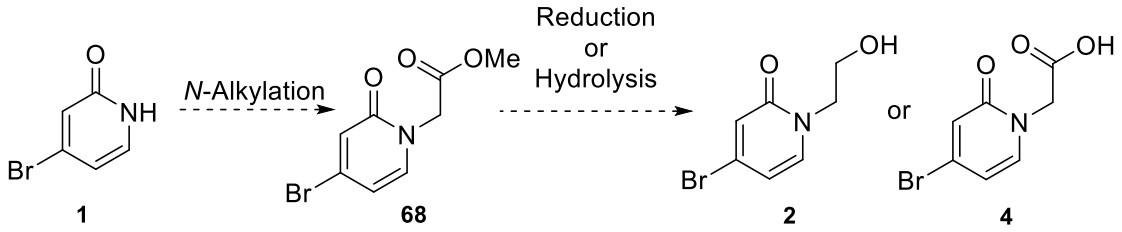
For FragLites **2-4**, a *N*-alkylation strategy was envisioned. The synthesis of *N*-substituted bromopyridine **3** has been reported.[12] Following the reported conditions, 4-bromopyridinone **1** was *N*-alkylated using potassium carbonate and 1-bromo-2-methoxyethane at reflux in acetonitrile for 16 hours. Alkylated bromopyridone **3** was isolated by chromatography in 86% yield (Scheme 2.6).



Scheme 2.6. Synthesis of pyridone FragLite **3**

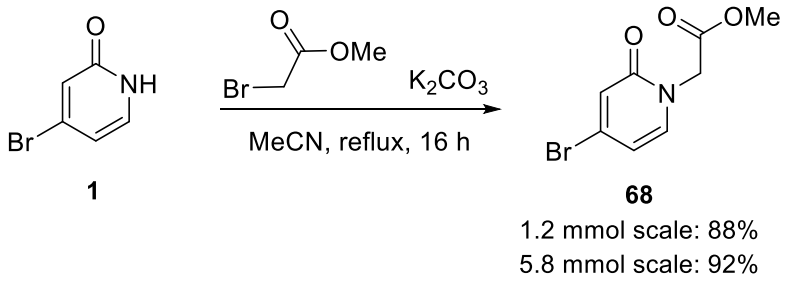
The initially planned strategy to synthesise pyridones **2** and **2** is shown in Scheme 2.7. It was envisioned that an intermediate methyl ester pyridone **68** could be synthesised, which could be converted by reduction or hydrolysis into pyridones **2** and **4** respectively. Both pyridones **2** and

4 are FragLites needed for SMCC reactions, although it is likely that the alcohol and carboxylic acid groups would be protected.



Scheme 2.7. Synthetic strategy to pyridones **2** and **4**

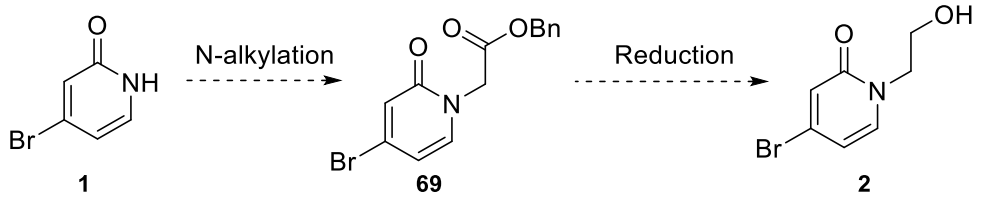
To this end, in a similar fashion used to synthesise pyridone **3**, *N*-alkylation was attempted with methyl 2-bromoacetate using the same procedure. Pleasingly, the reaction functioned well and provided pyridone **68** which was isolated after chromatography in 88% yield from a 1.2 mmol scale reaction (Scheme 2.8). Furthermore, having successfully synthesised pyridone **68** on a small scale, the decision was made to upscale the synthesis to enable further experimentation with the reduction to obtain the corresponding alcohol **2**. The synthesis of pyridone methyl ester **68** proceeded in 92% yield, providing an ample quantity for subsequent steps.



Scheme 2.8. Synthesis of bromo pyridone **68**

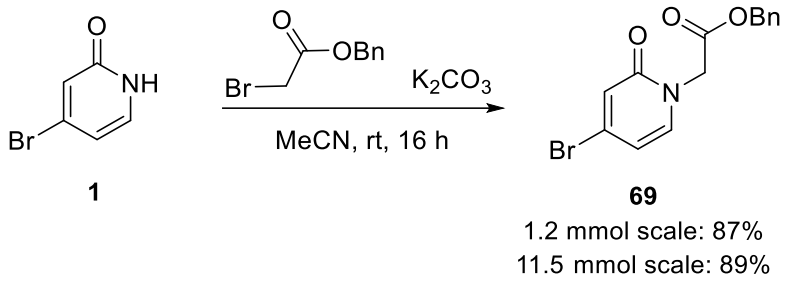
For the synthesis of pyridone acid **4**, in considering the synthetic plan, a key issue emerged regarding the hydrolysis of pyridone methyl ester **68** to pyridone acid **4**. Pyridones are inherently polar and the hydrolysis would result in a highly polar pyridone with an acid substituent, likely displaying substantial aqueous solubility. Given these complexities, an alternative strategy was explored to access pyridones **2** and **3**. In an analogous manner to the previous approach, it was proposed that *N*-alkylation could enable the synthesis of pyridone

benzyl ester **69**, a protected FragLite needed for SMCC reactions. Benzyl pyridone **69** could also be reduced to give ethyl alcohol **2** (Scheme 2.9).



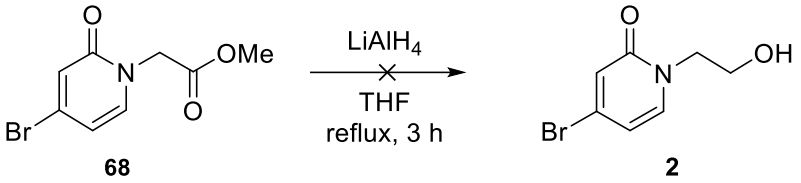
Scheme 2.9. Alternative synthetic strategy to pyridone **2**

Thus, following a literature procedure, [24] 4-bromopyridinone **1** was *N*-alkylated utilising potassium carbonate and benzyl 2-bromoacetate at room temperature in acetonitrile for 16 hours. After purification by chromatography, pyridone benzyl ester **69** was successfully obtained in 87% yield (Scheme 2.10). The synthesis was upscaled to 11.5 mmol, yielding the desired bromo pyridone **69** in 89% yield.

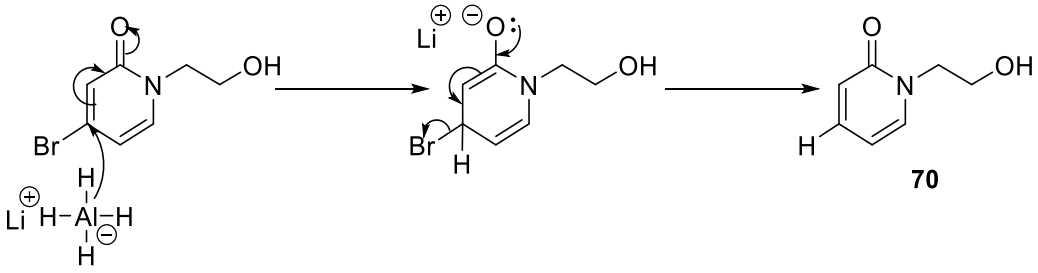


Scheme 2.10. Synthesis of bromo pyridone **69**

Having obtained pyridone methyl ester **68** and benzyl ester **69**, our attention turned to the reduction conditions to form pyridone ethyl alcohol **2**. To achieve this, pyridone methyl ester **68** was treated with $LiAlH_4$ in THF at 0 °C for 1 hour, followed by refluxing for 3 hours. Regrettably, these conditions did not yield the desired pyridone ethyl alcohol **2** (Scheme 2.11). Analysis of the ^1H NMR spectrum of the crude product indicated the absence of the target pyridine **2**. The ^1H NMR spectrum of the crude product led us to suspect that the 4-bromo group may also have been substituted. This transformation could occur through a 1,4-hydride addition and subsequent bromide elimination. A proposed mechanism is shown in Scheme 2.12.



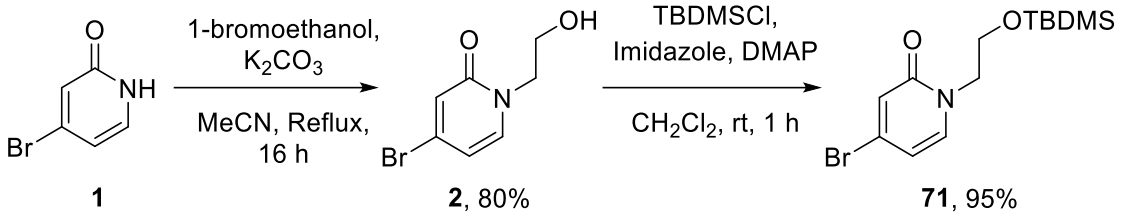
Scheme 2.11. Attempted reduction to obtain pyridone ethyl alcohol **2**



Scheme 2.12. Proposed mechanism for over-reduction of bromo pyridone **2**

Considering the potential for over-reduction, milder reduction conditions were explored. To this end, the reduction of pyridone methyl ester **68** was attempted using $LiAlH_4$ at 0 °C for 1 hour. In parallel, the conversion of pyridone benzyl ester was attempted with $LiBH_4$ at reflux for 3 h. In both attempts, there was no evidence for the formation of the desired pyridone ethyl alcohol **2**. The challenge probably lies in balancing the reduction conditions to obtain the desired product while preventing over-reduction.

To access pyridone ethyl alcohol, a different route was explored, namely a direct synthesis of pyridine ethyl alcohol **2** through *N*-alkylation of 4-bromopyridinone **1** with 1-bromoethanol. We had initial concerns that the nucleophilicity of the hydroxyl group would interfere with this process. However, using a literature protocol, [25] *N*-alkylation was carried out successfully using 4-bromopyridinone **1**, potassium carbonate and 1-bromoethanol at reflux in acetonitrile for 16 hours. This provided pyridone ethyl alcohol **2** in 80% yield following chromatography (Scheme 2.13). For the planned SMCC reaction, a TBDMS protected version was also prepared at this point. Thus, reaction of pyridone ethyl alcohol **2** with TBDMSCl, imidazole and DMAP in CH_2Cl_2 at room temperature for 1 hour gave, after chromatography, the TBDMS-protected pyridone **71** in 95% yield (Scheme 2.13).



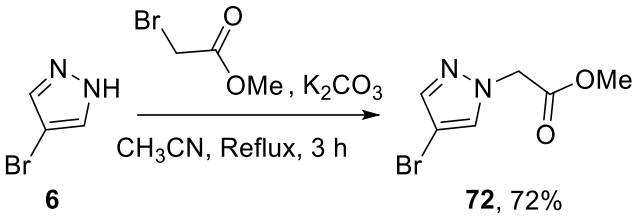
Scheme 2.13. Synthesis of pyridone ethyl alcohol **2** and TBDMS protection

In summary, the synthesis of pyridone FragLites and/or their protected derivatives was accomplished through different methodologies, encompassing *O*-alkylation, *N*-alkylation, or a combination of *N*-alkylation followed by hydroxyl protection. This enabled the generation of substantial quantities for SMCC reactions, and instilled confidence as we moved forward to synthesise the remaining FragLites.

2.2.2 Synthesis of Pyrazole FragLites

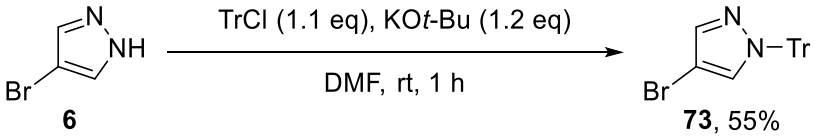
Four FragLites **6**-**9** contain the pyrazole core. Of these, bromopyrazole **9** needed to be synthesised. Although the remaining three could be purchased, it was decided that some would need to be protected prior to SMCC. Within the collaborative efforts of the O'Brien research group, the tasks concerning protection, cross-coupling, and diversification of bromopyrazoles **7** and **8** were assigned to Wang, a member of the group. The synthesis of FragLite **9** and a protected version of FragLite **6** are described in this section.

It was expected that commercially available bromopyrazole **6** could be transformed *via* *N*-alkylation into bromopyrazole **72**. The methodology employed was a procedure adapted from Anderson and Boger was employed *et al.*,[26] and was analogous to the procedure employed for the synthesis of *N*-alkylated pyridones (see Section 2.2.1). Thus, *N*-alkylation of bromopyrazole **6** was achieved with potassium carbonate and methyl 2-bromoacetate at reflux in acetonitrile for 16 hours. After chromatography, *N*-alkylated bromopyrazole **72** was isolated in 83% yield (Scheme 2.14). Further studies on this FragLite were transferred to Wang at this point.



Scheme 2.14. Synthesis of pyrazole FragLite **72**

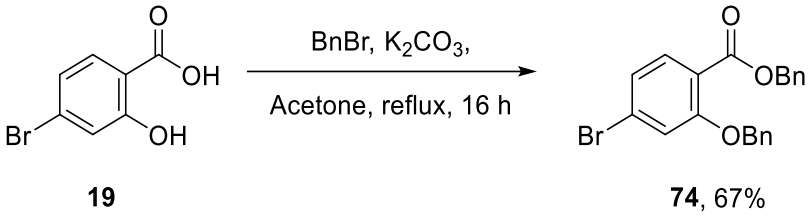
With bromopyrazole **6**, previous work from Klein had indicated that the implementation of N-H protection would be required to enable the SMCC to proceed satisfactorily. Trityl protection of bromopyrazole **6** was achieved using a procedure described by Anderson and Boger.[27] Bromopyrazole **6** was reacted with potassium *tert*-butoxide and trityl chloride in DMF for 1 hour at room temperature. After recrystallisation, pure trityl bromopyrazole **73** was obtained in 55% yield (Scheme 2.15).



Scheme 2.15. Synthesis of protected FragLite **73**

2.2.3 Synthesis of substituted benzenes and pyridines

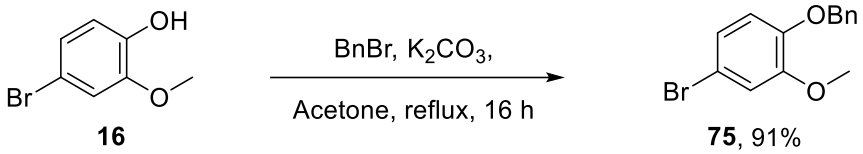
Several of the FragLites such as **12**, **16**, **17**, **18**, **19** and **21** feature substituted benzenes. Each of these compounds possesses distinctive functionalities, thus necessitating a unique protection strategy for individual cases. In situations where the aromatic ring bears phenolic and/or carboxylic acidic substituents directly attached to the aromatic ring, the choice was to utilise a benzyl ether as the protecting group(s). This endeavour was initiated by Parkin,[28] a member of the O'Brien group. Parkin successfully executed the benzyl protection of substituted benzenes **16**, **17** and **18**. For example, in one of Parkin's reactions, reaction of bromobenzene **19** with K_2CO_3 and benzyl bromide in acetone under reflux conditions for 16 hours yielded the desired doubly protected bromo benzene **74** in a satisfactory 67% yield (Scheme 2.16).



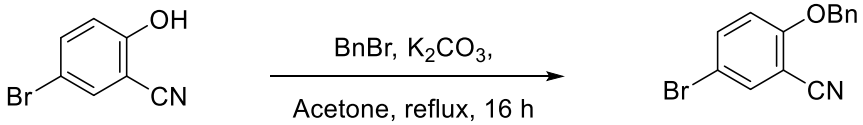
19 **74**, 67%

Scheme 2.16. Synthesis of protected FragLite **74** *via* benzyl protection by Parkin

Utilising identical conditions, the *O*-benzyl protection strategy was extended by Parkin to bromobenzene **16**, thus producing *O*-benzyl protected benzene **75** with a 91% yield. When applied to bromobenzene **17**, the conditions gave bromo benzene **76** in 49% yield (Scheme 2.17).



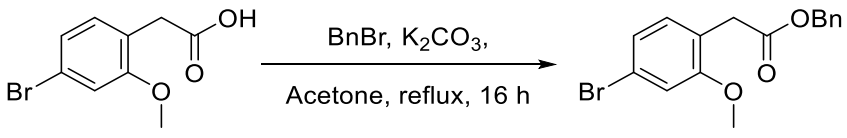
16 **75**, 91%



17 **76**, 49%

Scheme 2.17. Synthesis of benzyl protected FragLites **75** and **76** by Parkin

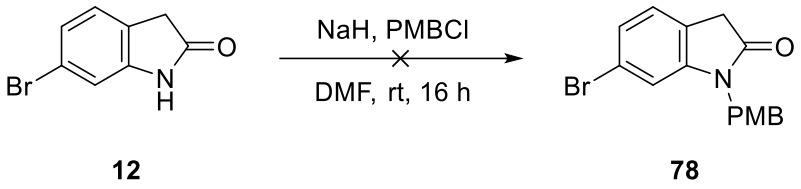
Encouraged by the positive outcomes achieved by Parkin, the established *O*-benzylation procedure was applied to the structurally related FragLite, bromobenzene **21**. Through the reaction of bromobenzene **21** with K_2CO_3 and benzyl bromide in acetone under reflux conditions for 16 hours, the desired product, benzyl protected benzene **77**, was afforded in 93% yield upon purification by chromatography (Scheme 2.18).



21 **77**, 93%

Scheme 2.18. Synthesis of benzyl protected FragLite **77**

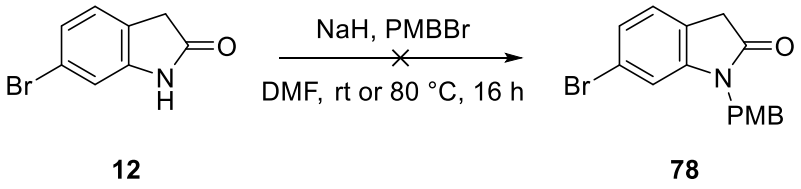
The protection of bromo oxindole **12** was initially envisioned by the application of a *p*-methoxybenzyl (PMB) group. This was due to the well-known cleavage of PMB ethers under conditions such as ceric ammonium nitrate. However, attempts at the synthesis of PMB-protected bromo oxindole **12** by Walder in the O'Brien group had previously been unsuccessful. To start, it was decided to replicate the reaction attempted by Walder. To achieve this, a modified procedure, inspired by PMB protection of dihydro-2(1H)-quinolinone by Winter *et al.*,[29] was employed. This involved the reaction of bromo oxindole **12** with 4-methoxybenzyl chloride and sodium hydride. Following work-up, analysis of the crude mixture by mass spectrometry and ^{1}H NMR spectroscopy revealed an absence of the desired product **78** (Scheme 2.19).



12 **78**

Scheme 2.19. Attempted syntheses of PMB protected oxindole **78**

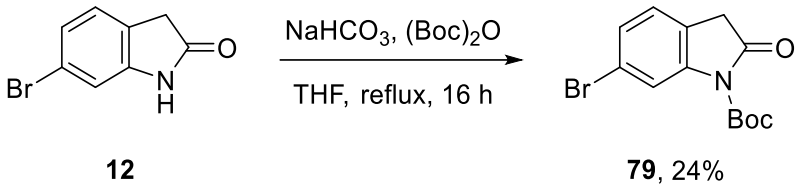
Cockerill and colleagues previously documented the PMB protection of an oxindole compound, although the reaction procedure was not supplied.[30] Therefore, a further modified procedure was explored by reacting bromo oxindole **12** with the presumably more reactive PMBBr rather than PMBCl. In this reaction, bromo oxindole **12** was subjected to deprotonation with sodium hydride in DMF and reaction with 4-methoxybenzyl bromide at room temperature for 16 hours. Despite these efforts, neither the ^{1}H NMR spectrum nor mass spectrometry revealed the presence of the protected oxindole **78** (Scheme 2.20). A final attempt at 80 °C for 16 hours was similarly unsuccessful.



12 **78**

Scheme 2.20. Attempted syntheses of PMB protected oxindole **78**

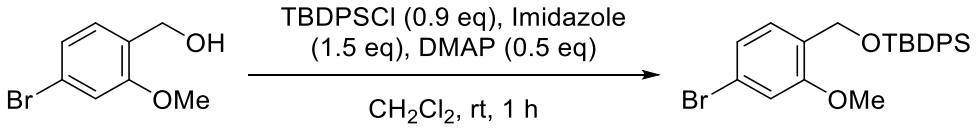
We had initially avoided Boc protection as we were concerned that a *N*-Boc group on an oxindole might be cleaved by nucleophilic attack of hydroxide in the SMCC reaction. However, it was decided to explore whether this was the case or not and so Boc-protected bromo oxindole **79** was targeted. Drawing upon conditions adapted from Kita *et al.*, [31] bromo oxindole **12** underwent reaction with sodium bicarbonate and di-*tert*-butyl dicarbonate in THF at reflux for 16 hours. Following chromatography, Boc-protected oxindole **79** was successfully isolated in 24% yield (Scheme 2.21).



12 **79**, 24%

Scheme 2.21. Synthesis of Boc-protected oxindole **79**

For FragLites containing primary alcohol groups, a strategy involving silyl protection seemed most appropriate (see Scheme 2.13 for a related example). In the specific case of hydroxymethyl methoxybenzene **18**, TBDPS protection was executed using a method detailed by Hamel *et al.*[32] This procedure entailed the utilization of TBDPSCl, imidazole and DMAP. These conditions, upon implementation, led to the successful generation of TBDPS-protected hydroxymethyl methoxybenzene **80** in 88% yield, following chromatography (Scheme 2.22). In this reaction, to aid purification of the product by chromatography, a deficiency of TBDPSCl (0.9 eq.) was used.

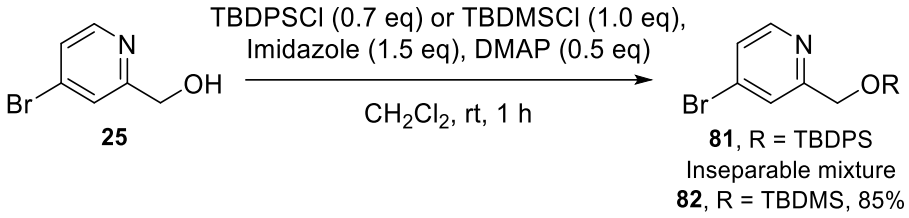


18 **80**, 88%

Scheme 2.22. Synthesis of protected FragLite **80**

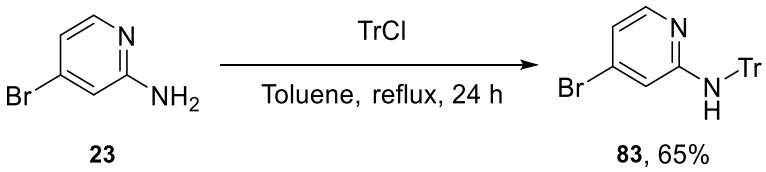
In a similar fashion, the same methodology was adopted for the TBDPS protection of hydroxymethyl pyridine **25**. However, on attempting to purify the TBDPS-hydroxymethyl pyridine **81** by chromatography, it was discovered that it was inseparable from silyl-containing

by-product(s). As an alternative, the hydroxyl group was protected with a TBDMS group using the same procedure. This gave TBDMS ether **82** in 85% yield after chromatography.



Scheme 2.23. Synthesis of protected FragLite **82**

Finally, a strategy was devised for protection of the N-H functionality observed in bromo aminopyridine **23**. Thus, trityl protection of bromoaminopyridine **23** was carried out using a method reported by Ganellin *et al.*[33] This entailed refluxing bromoaminopyridine **23** with trityl chloride in toluene for 24 hours. The reaction was successful, and the compound was isolated by chromatography. Trityl bromo aminopyridine **83** was obtained in 65% yield (Scheme 2.24).



Scheme 2.24. Synthesis of trityl protected FragLite **83**

To concluded, we have established synthetic pathways for the production of FragLites and their protected derivatives in sufficient quantities for forthcoming SMCC reactions.

2.3 Synthetic studies towards 4-Bromo-[1,8]-Naphthyridine

2.3.1 Background

Naphthyridines, alongside benzodiazines, are classified as diazanaphthalenes. This class features a naphthalene framework where two carbon atoms are replaced with nitrogen atoms. Naphthyridines, specifically, contain a single nitrogen atom within each ring, but none at the bridgehead positions. The naphthyridines consists of six distinct regioisomers, each named accordingly by the arrangement of the nitrogen atoms (Figure 2.7).[34]

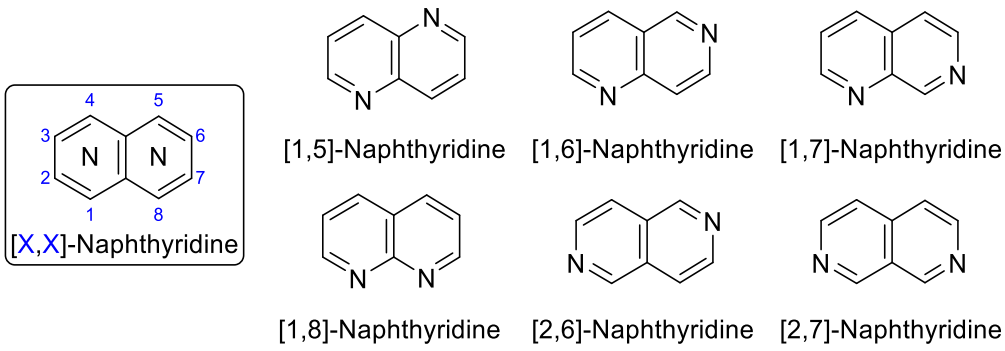
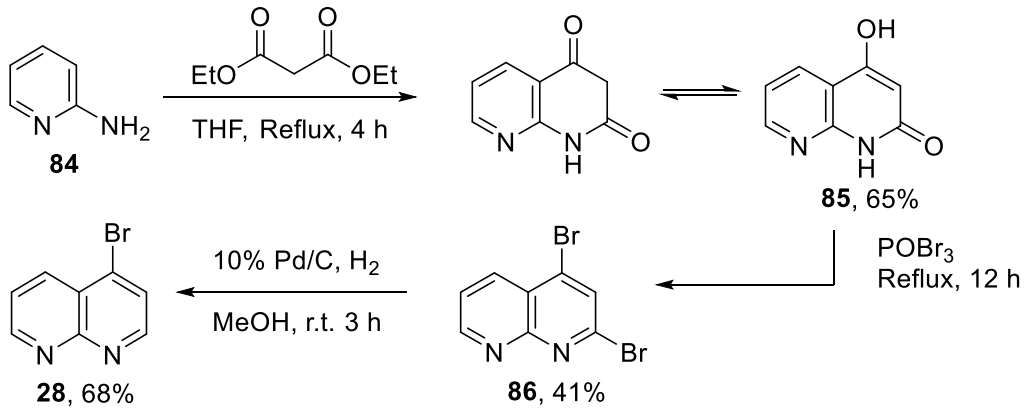


Figure 2.7. Structural classification of naphthyridines.

It was necessary to develop a methodology to produce sufficient quantities of the Fraglite, bromo naphthyridine **28**, for the planned SMCC reactions. Various methods have been reported for the synthesis of [1,8]-naphthyridine derivatives.[35-39] However, these methods commonly entail the synthesis of derivatives with substitution at the 2- and/or 3-position on the heterocycle, with reports featuring synthesis with substitution at the 4-position being less frequently reported.

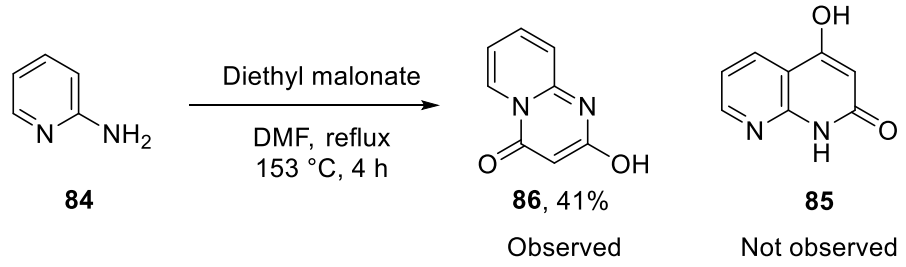
2.3.2. Exploration of Routes for the Synthesis of 4-Bromo-[1,8]-naphthyridine

The synthesis of bromo naphthyridine **28** using a three-step process was reported in a patent (Scheme 2.25).[37] The initial step involved the condensation of aminopyridine **84** with diethyl malonate in refluxing THF for 4 hours to give naphthyridone **85** in 65% yield. Subsequently, naphthyridone **85** was treated with phosphorus oxybromide to generate dibromo naphthyridine **86** (41% yield). Finally, selective debromination of the 2-bromo group was achieved *via* catalytic hydrogenation which gave bromo naphthyridine **28** in 68% yield.



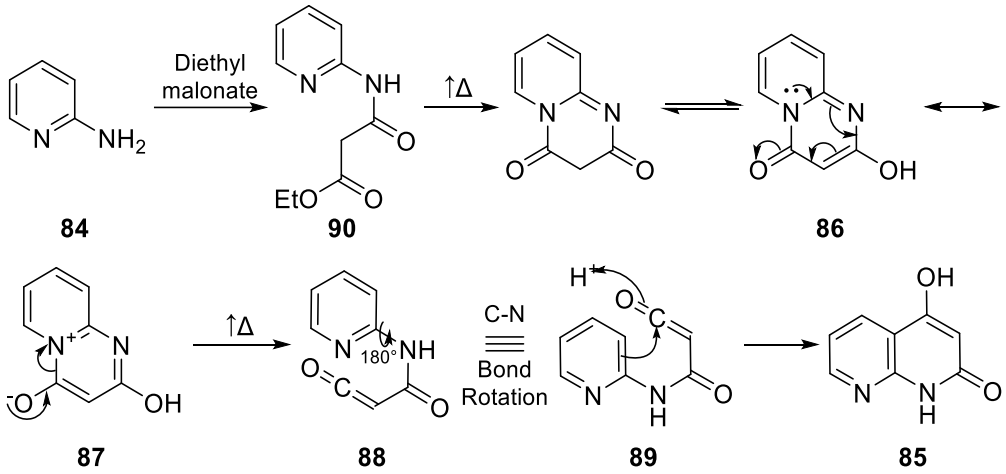
Scheme 2.25. Previous synthesis of bromo naphthyridine **28**[37]

In our hands, on attempting the initial condensation reaction between aminopyridine **84** and diethyl malonate, it was found that reaction in THF at reflux for 4 hours did not provide naphthyridone **85**. Instead, an amide formed but the ^{1}H NMR spectrum of the crude product suggested that it had not cyclised to give naphthyridone **85**. Therefore, the same reaction was carried out at a higher temperature in DMF at reflux and, intriguingly, the regioisomer pyrido[1,2-*a*]pyrimidin-4-one **86**, was obtained in 41% yield (Scheme 2.26). The formed pyrido[1,2-*a*]pyrimidin-4-one **86** is a regioisomer of the expected naphthyridone **85**. Evidence to assign pyrido[1,2-*a*]pyrimidin-4-one **86** as the product of this reaction came from the ^{1}H and ^{13}C NMR spectroscopy data. In the ^{1}H NMR spectrum, there were five aromatic CH signals, four of which were interconnected as shown by *J* values and ^{1}H-^{1}H COSY data. There were three quaternary carbons and five aromatic CH carbons in the ^{13}C NMR spectrum. To form pyrido[1,2-*a*]pyrimidin-4-one **86**, the pyridine nitrogen must have attacked the carbonyl group of the malonate after it had been attached to the amino group.



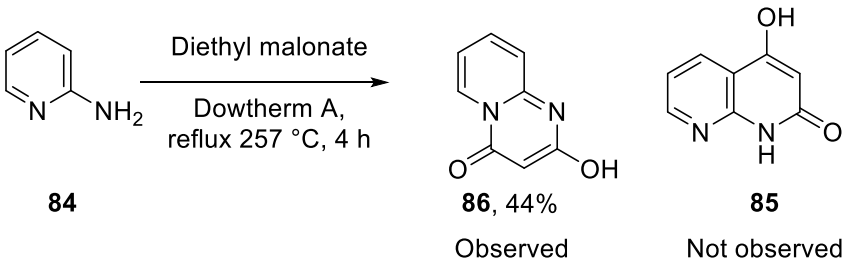
Scheme 2.26. Unexpected synthesis of pyrido[1,2-*a*]pyrimidin-4-one **86**

Upon further investigation of the literature, it was described that at very high temperatures, a thermal rearrangement of pyrido[1,2-*a*]pyrimidin-4-one **86** can occur to give the desired regioisomer, naphthyridone **85**. [40] [41] The proposed mechanism is shown in Scheme 2.27 and is supported by flash vacuum pyrolysis studies.[42] Resonance form **87** (of pyrido[1,2-*a*]pyrimidin-4-one **86**) can undergo cleavage of the C–N bond to give ketene **88**, which upon bond rotation, can cyclise onto the pyridine ring to give naphthyridone **89** after re-aromatisation. It is presumed that naphthyridone **85** is the thermodynamic product.



Scheme 2.27. Proposed mechanism for thermal rearrangement.

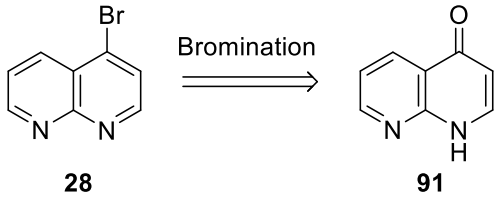
In light of this mechanistic knowledge, the reaction between aminopyridine **84** and diethyl malonate was attempted using a very high boiling point solvent, Dowtherm® A, which is a eutectic mixture of biphenyl and diphenyl ether. Upon heating aminopyridine **84** and diethyl malonate in Dowtherm® A at 257 °C for 4 hours and subsequent addition of diethyl ether, a solid was precipitated. ^{1}H NMR spectroscopic analysis of the solid revealed it to once again be pyrido[1,2-*a*]pyrimidin-4-one **86** which was formed in 44% yield (Scheme 2.28).



Scheme 2.28. Attempted synthesis of naphthyridone **85** *via* thermal rearrangement of pyrido[1,2-*a*]pyrimidin-4-one **86**

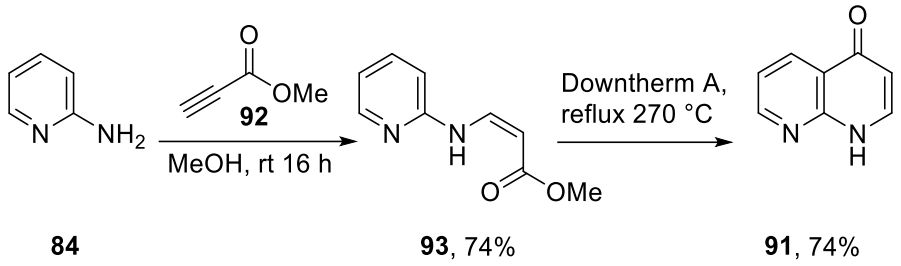
The reaction between aminopyridine **84** and diethyl malonate was attempted using various solvents including Toluene, Dioxane, DMF, and diphenyl ether. However, in all cases, the reactions gave pyrido[1,2-*a*]pyrimidin-4-one **86** rather than the desired naphthyridone **85**. Even repeating the conditions used in the original literature which described the thermal rearrangement,[41] the reaction between aminopyridine **84** and diethyl malonate in diphenyl ether gave pyrido[1,2-*a*]pyrimidin-4-one **86**. It is proposed that the information provided in the literature regarding the characterization might be erroneous. Further investigation and analysis are needed to clarify this discrepancy.

With several unsuccessful attempts at the synthesis of naphthyridone **85** from aminopyridine **84**, it was decided to explore a different approach to obtain the required bromo naphthyridine **28**. It was envisaged that bromo naphthyridine **28** could be synthesised *via* bromination of naphthyridone **91** using a precedented reaction [43] (Scheme 2.29). As a result, our next immediate target was naphthyridone **91**.



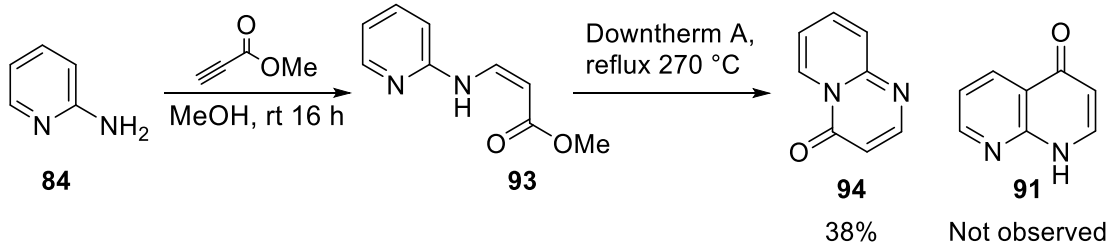
Scheme 2.29. Alternative synthetic strategy to access bromo naphthyridine **28**.

The synthesis of naphthyridone **91** from amino pyridine **84** was reported by Chary *et al. via* a two-step process. The initial step entailed the conjugate addition of aminopyridine **84** to methyl prop-2-ynoate **92** to form α,β-unsaturated ester **93** (74% yield). The subsequent ring-closure step was carried out by refluxing in Dowtherm® A at 257 °C for 1 hour which gave naphthyridone **91** in 74% yield (Scheme 2.30).



Scheme 2.30. Previous synthesis of naphthyridone **92**.[37]

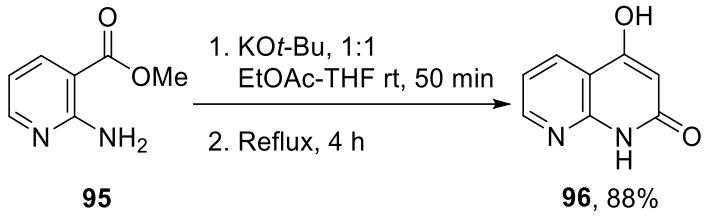
Performing these conditions, aminopyridine **84** was reacted with methyl prop-2-ynoate **92** in MeOH for 24 hours to furnish crude α,β-unsaturated ester **93** after evaporation of the solvent. Taken without purification to the following step, α,β-unsaturated ester **93** was dissolved in Dowtherm® A and heated to 257 °C for 1 hour. After cooling to room temperature, the product was precipitated by the addition of hexanes and collected. Analysis of the ^{1}H NMR spectrum indicated that the desired naphthyridone **91** did not form. Instead, the regioisomeric pyrido[1,2-*a*]pyrimidin-4-one **94** was obtained in high purity, without the need for further purification. Mechanistically, the pyridine nitrogen had cyclised onto the ester. The formation of pyrido[1,2-*a*]pyrimidin-4-one **94** was confirmed by the presence of four interconnected aryl CH signals and two coupled aryl CH signals in the ^{1}H NMR spectrum. Furthermore, the ^{13}C NMR spectrum showed six aryl CH signals and two quaternary carbon resonances.



Scheme 2.31. Attempted synthesis of naphthyridone **91**

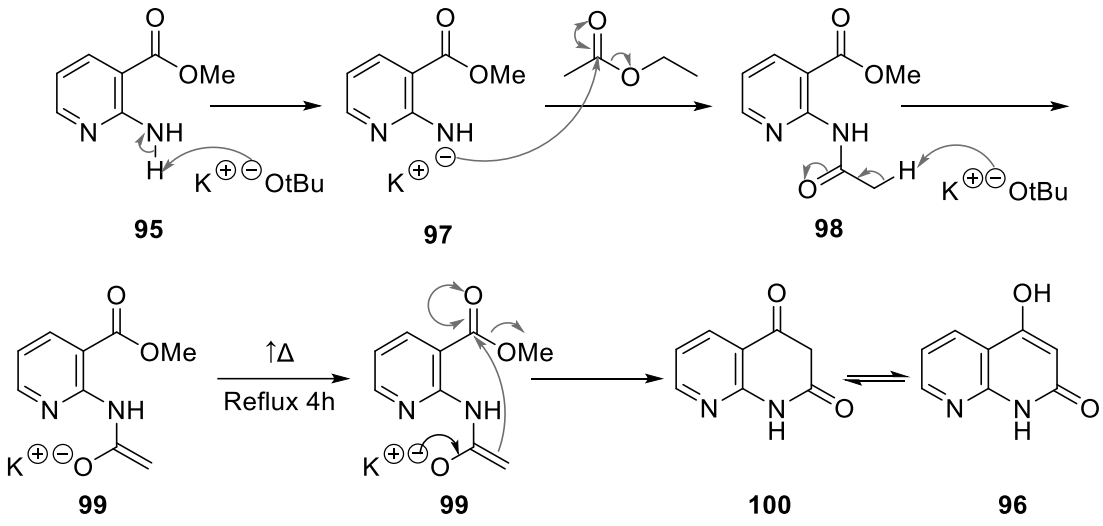
Disappointingly, our efforts thus far to synthesise the naphthyridine scaffold had been unsuccessful. Consequently, we had to shift to an alternative approach. A patent published by Agios Pharmaceuticals in 2012 reported a route to the naphthyridine skeleton *via* a different approach.[44] In this route, methyl 2-aminonicotinate **95** was reacted with KO*t*-Bu in EtOAc/THF (1:1) where EtOAc served both as a reagent and a solvent. The reaction components were mixed

at room temperature for 50 minutes and then heated at reflux for 4 hours. This gave naphthyridone **96** in a reported 88% yield (Scheme 2.32).



Scheme 2.32. Previous synthesis of naphthyridone **96** [44]

The reaction mechanism for this route to naphthyridone **96** is shown in Scheme 2.30. First, abstraction of an amino proton by KO*t*-Bu occurs to give an anion **97** that undergoes subsequent acetylation by nucleophilic substitution of EtOAc to form intermediate **98**. With excess KO*t*-Bu present, intermediate **98** would likely be spontaneously converted into enolate **99** *via* proton abstraction from the α carbon. Heating at reflux would then provide sufficient energy for the enolate to attack the carbonyl and substitute the methyl ester to form naphthyridone **100**, which exists in its preferred tautomeric form as naphthyridone **96**.

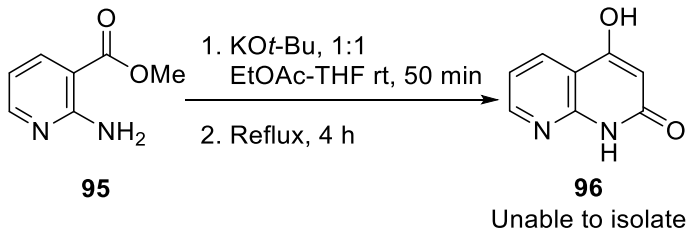


Scheme 2.33. Proposed mechanism for the synthesis of naphthyridone **96**

There is a notable difference in this approach to construct the naphthyridine scaffold compared to the two preceding methods (depicted in Schemes 2.25 and 2.30). Instead of elongating the

molecule from the amino nitrogen and subsequent ring closure from the aromatic ring to form the bicyclic system, this strategy begins with a precursor that already carries substitutions at carbon-3 of the amino pyridine **95**. By pursuing this direction, the strategy effectively circumvents the potential occurrence of the undesired formation of the regioisomeric pyrido[1,2-*a*]pyrimidin-4-one **86** *via* ring closure from occurring through the nitrogen rather from the aromatic ring.

The synthesis of napthyridone **96** from methyl 2-aminonicotinate **95** was attempted next. In our hands, methyl 2-aminonicotinate **95** was treated KO*t*-Bu in EtOAc at room temperature for 1 hour to give a brightly yellow-coloured solution. After this period, the reaction mixture was fitted with a condenser and refluxed for 4 hours which led to the emergence of a red precipitate. Encouragingly, as identified by mass specrometry, napthyridone **96** had formed. Further analysis of the crude product by ^{1}H NMR spectroscopy showed evidence for formation of napthyridone **96**, albeit with significant impurities, including inorganic salts which were not detected by ^{1}H NMR spectroscopy. Using the methodology outlined in the published procedure, we were unable to obtain a pure sample of naphthyridone **96**. Furthermore, attempting to purify the substance through conventional means by chromatography proved ineffective on many attempts (Scheme 2.34).

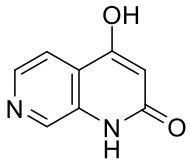


95 **96**
Unable to isolate

Scheme 2.34. Initial attempt to synthesise naphthyridone **96**

Upon further investigation of the literature, a method outlined in a 2012 patent by researchers at Cancer Research Technology Limited detailed the synthesis and purification of [1,7]-naphthyridone **101** (Figure 2.35),[45] structurally related to the targeted napthyridone **96**. In this procedure, following the synthesis, the solvent was evaporated to give the crude residue which was dissolved in water. Dilute $HCl_{(aq)}$ was added until a pH of 5-6 was reached and [1,7]-

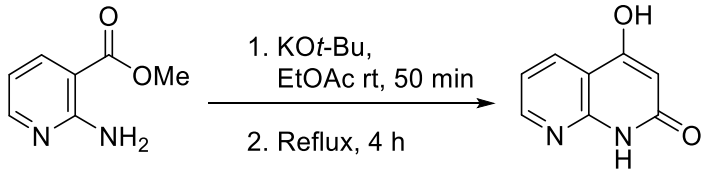
naphthyridone **101** crystallised from the solution and was collected by filtration. Based on this procedure, we decided to try and use this isolation procedure in the synthesis of naphthyridone **96**.



101

Scheme 2.35. Structure of [1,7]-Naphthyridine **101**

Thus, another synthesis of naphthyridone **96** was started from methyl 2-aminonicotinate **95** using KO*t*-Bu in EtOAc. When applying the new isolation approach, gratifyingly, it was observed that the desired naphthyridone **96** crystallised and could be collected with success. This gave naphthyridone **96** in 17% yield (Scheme 2.36).



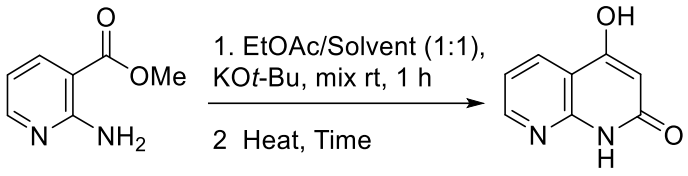
95 **96,** 17%

Scheme 2.36. Synthesise naphthyridone **96**

However, it is important to highlight that several challenges were encountered during the purification of naphthyridone **96**. Initially, during the filtration step using either a sintered funnel or filter paper with larger pore sizes, the solid had a tendency to pass through due to its fine particle nature. This issue was addressed by allowing the solid to settle and agglomerate prior to filtration and it was then collected using filter paper with smaller pore sizes. However, a considerable portion of the solid still managed to permeate through, leading to the requirement for several iterations of filtration. Furthermore, the filter paper quickly became obstructed, necessitating frequent replacement. A proposed improved strategy could encompass isolating the substance through centrifugation, followed by removal of the

supernatant by decantation. Adding to the complexity, when wet, the naphthyridone **96** was a viscous brown semi-solid, which posed difficulties in its manual transfer, as it adhered to any laboratory equipment it encountered. Consequently, to overcome this issue, naphthyridone **96** had to be gathered using several pieces of cotton wool. Ultimately, naphthyridone **96** was collected affixed to multiple filter papers and pieces of cotton wool. In attempting to dissolve naphthyridone **96**, it displayed insolubility in conventional organic solvents such as hexane, Et_2O, CH_2Cl_2, EtOAc, MeCN and acetone. However, it had slight solubility in methanol and moderate solubility in hot methanol. Consequently, several portions of hot methanol were employed to dissolve naphthyridone **96**, along with agitation to disintegrate the agglomerates that would otherwise not dissolve. Through this process, naphthyridone **96** was successfully dissolved and, after evaporation of the solvent, naphthyridone **96** was isolated. Moreover, it is worth noting that a substantial amount of methanol, ranging from 1 to 2 litres, was required to dissolve a modest amount of naphthyridone **96**. While this approach is effective, future enhancements to the procedure could involve utilizing a Soxhlet extractor to retrieve the substance from the filter papers and pieces of cotton wool. By employing this technique, a smaller quantity of solvent could be used, as opposed to using significant amounts of solvent to dissolve relatively minor quantities of naphthyridone **96**.

Following this initial success, the decision was taken to optimise some of the reaction parameters for the synthesis of naphthyridone **96**. The reaction was executed using consistent reagents and stoichiometric ratios while introducing variations in solvents and the temperature of the reaction. Specifically, the process involved reacting methyl 2-aminonicotinate **96** and KO*t*-Bu in a 1:1 mixture of EtOAc and the specified co-solvent. The reaction was mixed at room temperature for 1 hour and then subsequently refluxed for 4 hours. The precise experimental conditions and results are detailed in Table 2.1. As the results show, increasing the temperature for the second step led to improved yields. For example, using Dowtherm® A and heating at 200 °C, a 62% yield of naphthyridone **96** was obtained (entry 4).



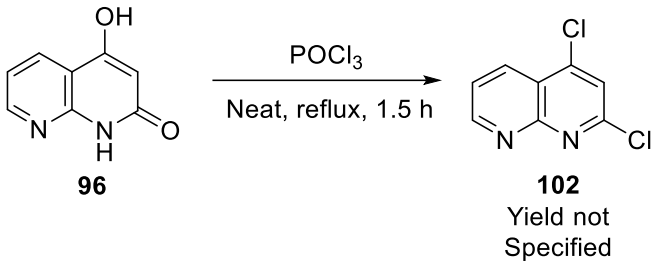
95 **96**

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	EtOAc	77.1	16	17
2	O-Xylene	144	16	33
3	O-Xylene	144	4	35
4	Dowtherm® A	200	4	62
5	Dowtherm® A	257	4	60

Table 2.1 Condition optimisation for synthesis for naphthyridone **96**

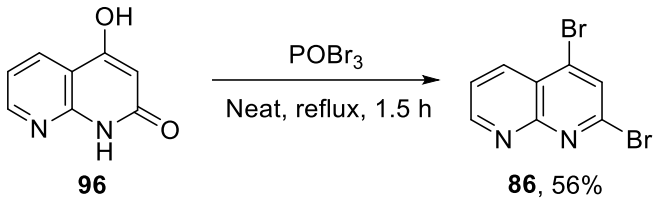
As a results of these experiments, the decision was reached to use Dowtherm® A as the co-solvent, subjected to a temperature of 200 °C for 4 hours. Confident in the optimised methodology, the subsequent course of action involved scaling up the synthesis of naphthyridone **96**. Employing a 1.3 mmol scale for the reaction, naphthyridone **96** was achieved in 60% yield (Table 2.1, entry 4). Continuation of the scale-up, commencing with an initial quantity of 12.4 mmol, yielded naphthyridone **96** in 44% yield. These endeavours yielded a substantial quantity of several grams of naphthyridone **96** which was an ample quantity for further reactions.

Having obtained naphthyridone **96**, the subsequent step involved its conversion into dibromo naphthyridine **86**. A literature search revealed that neat $POCl_3$ had been reported for the conversion of naphthyridone **96** into dichloro naphthyridine **102** without specification of the yield (Scheme 2.37.). [46] However, information regarding the conversion to dibromo naphthyridine **86** was uncertain. Although there are reports on this reaction, [47] the specific conditions such as reaction temperature, duration, and work-up procedure was not clearly outlined.



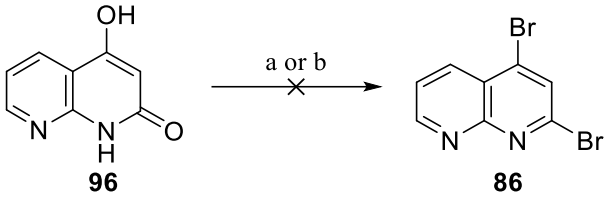
Scheme 2.37. Previous synthesis of dichloro naphthyridine **102**. [46]

Thus, a decision was made to conduct initial reactions on a small scale in an attempt to determine if naphthyridone **96** could indeed be transformed into dibromo naphthyridine **86**. The approach involved combining naphthyridone **96** (1.0 eq.) and $POBr_3$ (10 eq.). Subsequently, a condenser was attached, and the two solid components were mixed. The mixture was then cautiously heated until the $POBr_3$ melted and dissolved naphthyridone **96**. The temperature was then raised to 175 °C and maintained for 4 hours. Following work-up and chromatography, dibromo naphthyridine **86** was isolated in 56% yield (Scheme 2.38). The work-up methodology was adapted from a patent from researchers at Merck that focused on the synthesis of 2,4-dichloro naphthyridine **102**.



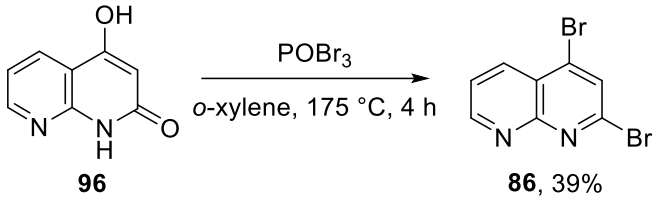
Scheme 2.38. Synthesis of dibromo naphthyridine **86**.

Since $POBr_3$ is a relatively expensive brominating reagent, there was a preference for exploring alternative reagents for the brominations. This led us to explore the desired conversion with PBr_3 or PBr_3 with catalytic DMF. However, these experiments failed to yield the desired dibromo naphthyridine **86** (Scheme 2.39).



Scheme 2.39. Attempted synthesis of dibromo naphthyridine **86**. Reagents and conditions: (a) PBr_3 (17.5 eq.), reflux, 1.5 h; (b) PBr_3 (17.5 eq.), DMF, rt, 3 h.

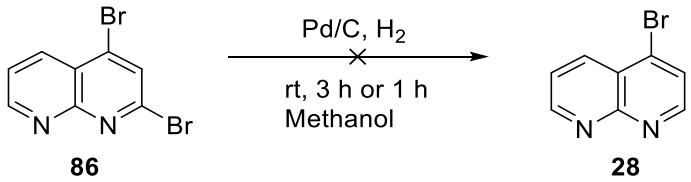
Thus, we continued using $POBr_3$ to prepare dibromo naphthyridine **86**. During upscaling of the synthesis of dibromo naphthyridine **86**, it was recognised that employing a substantial excess of 10.0 equivalents of $POBr_3$ would lead to significant usage of the reagent. This would result in cost-related concerns as well as potential safety issues. To address these considerations, the amount of $POBr_3$ was initially reduced to 2.0 equivalents and dibromo naphthyridine **86** was obtained in 54% yield. Furthermore, when attempting the reaction on a larger scale, the reaction components did not mix properly. To overcome this, the introduction of *o*-xylene was essential to effectively mix the suspended reaction components. In this instance, a scale of 3.9 mmol of naphthyridone **96** (1.0 eq.) and $POBr_3$ (3.0 eq.) were suspended in *o*-xylene and heated at 175 °C for 4 hours. Encouragingly, following chromatography, dibromo naphthyridine **86** was successfully isolated in 39% yield (Scheme 2.40).



Scheme 2.40. Synthesis of dibromo naphthyridine **86**.

After successfully developing a dependable and scalable method for synthesising dibromo naphthyridine **86**, the subsequent step involved debromination of the 2-bromo substituent to give bromo naphthyridine **28**. A patent described a method for selectively removing a halogen atom at the 2-position of dibromo naphthyridine **86** *via* catalytic hydrogenation with Pd/C.[37] Thus, we subjected dibromo naphthyridine **86** to catalytic hydrogenation, employing an excess of H_2 and Pd/C, at room temperature for 3 hours. Upon analysis of the ^{1}H NMR spectroscopic

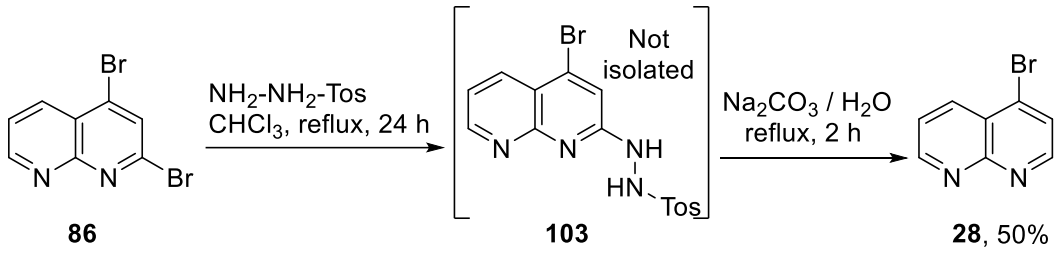
data, it was evident that the desired bromo naphthyridine **28** had not formed (Scheme 2.41). However, the ^{1}H NMR spectrum showed evidence of substrate degradation, potentially due to reduction not only of both bromides but also of the heterocycle itself. Similar transformations have been reported *via* catalytic hydrogenation with closely related naphthyridines.[48] We hypothesised that reducing the reaction time might prevent over-reduction. Unfortunately, conducting the reaction for 1 hour did not result in the formation of bromo naphthyridine **28**.



86 **28**

Scheme 2.41. Attempted synthesis of bromo naphthyridine **28** *via* catalytic hydrogenation.

An alternative methodology for the selective hydrodehalogenation in halogenated napthyridines was developed by Czuba *et al*.[47] In this method, one equivalent of tosyl hydrazine selectively underwent a nucleophilic aromatic substitution (S_NAr) reaction at the 2-position of dibromo naphthyridine **86**. This generated a tosyl hydrazine **103** which subsequently underwent base-catalysed decomposition to yield bromo naphthyridine **28** (Scheme 2.42).

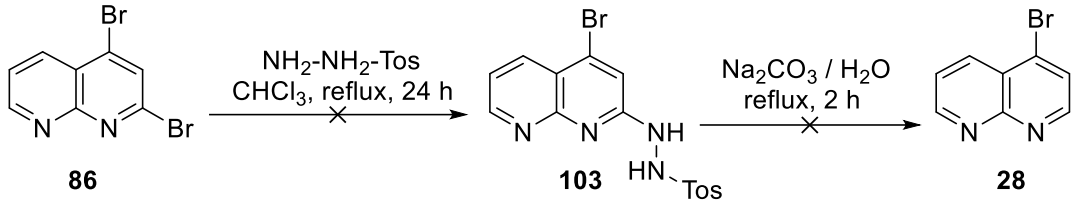


86 **103** **28**, 50%

Scheme 2.42. Synthesis of bromo naphthyridine **28** by Czuba and Woźniak [47]

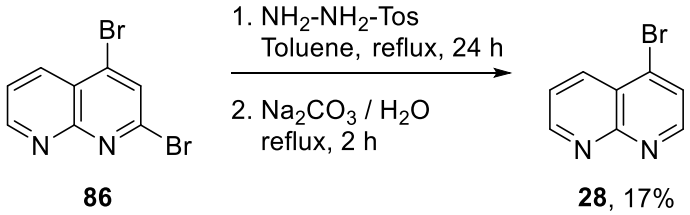
Accordingly, using this approach, dibromo naphthyridine **86** and tosyl hydrazine were refluxed in $CHCl_3$ for 24 hours. Unfortunately, the anticipated initial S_NAr reaction did not appear to have occured, as shown by the absence of the expected tosyl hydrazine **103** by mass spectrometry. Nevertheless, the base-catalysed thermal decomposition using Na_2CO_3 in water

was attempted. However, there was no evidence of the formation of the desired bromo naphthyridine **28** (Scheme 2.43).



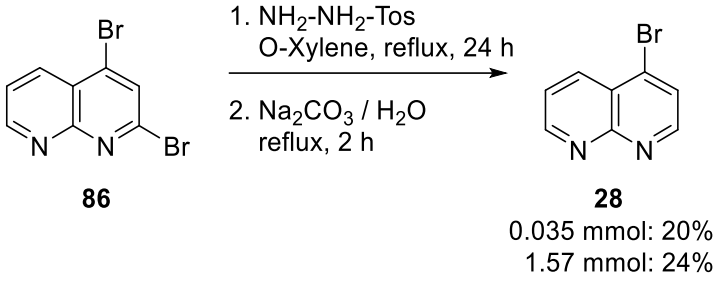
Scheme 2.43. Attempted synthesis of tosyl hydrazine **103** *via* S_NAr

Since it was expected that the initial S_NAr reaction had not occurred, a higher temperature for the reaction between dibromo naphthyridine **86** and tosyl hydrazine was explored. The reaction was therefore conducted in toluene. With analysis by mass spectrometry revealing the formation of tosyl hydrazine **103**. Subsequent reaction with Na_2CO_3 in water at reflux for 2 hours and work-up led to a crude product which contained the target bromo naphthyridine **28** by mass spectrometry. Purification by chromatography on silica was challenging – use of different solvent systems that gave R_F values of 0.3-0.4 led to impure product being isolated. In the end, use of EtOAc was used even though the R_F value in this solvent was only 0.15. Ultimately, pure bromo naphthyridine **28** was isolated in 17% yield (Scheme 2.44). It should be noted that significant decomposition of bromo naphthyridine **28** was observed during chromatography. Subsequent investigations may benefit from strategies such as deactivating silica with a base or employing alumina oxide as the stationary phase.



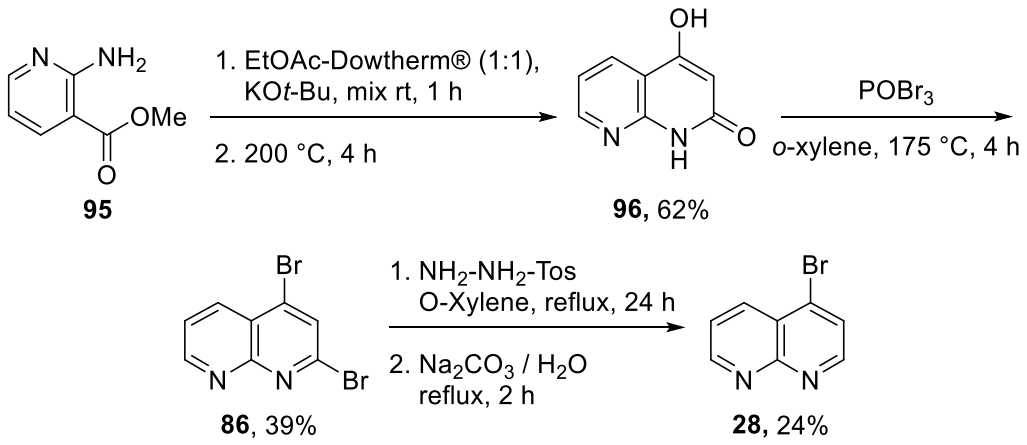
Scheme 2.44. Synthesis of bromo naphthyridine **28** *via* tosyl hydrazine

In an attempt to obtain a higher yield, a structurally similar solvent with a higher boiling point solvent than toluene was explored next. Thus, dibromo naphthyridine **86** (0.035 mmol scale) and tosyl hydrazine were reacted in *o*-xylene at reflux for 24 hours. Subsequent heating in an aqueous solution of Na_2CO_3 led to the formation of bromo naphthyridine **28** in 20% yield after purification by chromatography (Scheme 2.40). This procedure was scaled up to 1.57 mmol and bromo naphthyridine **28** was isolated in 24% yield (Scheme 2.40).



Scheme 2.45. Synthesis of bromo naphthyridine **28** *via* tosyl hydrazine.

To summarise, after exploring various methodologies and optimising the reactions, we successfully established a procedure for the synthesis of bromo naphthyridine **28**. The synthetic route is summarised in Scheme 2.46. The results of this synthetic campaign provided a sufficient quantity of bromo naphthyridine **28** for the planned SMCC reaction.

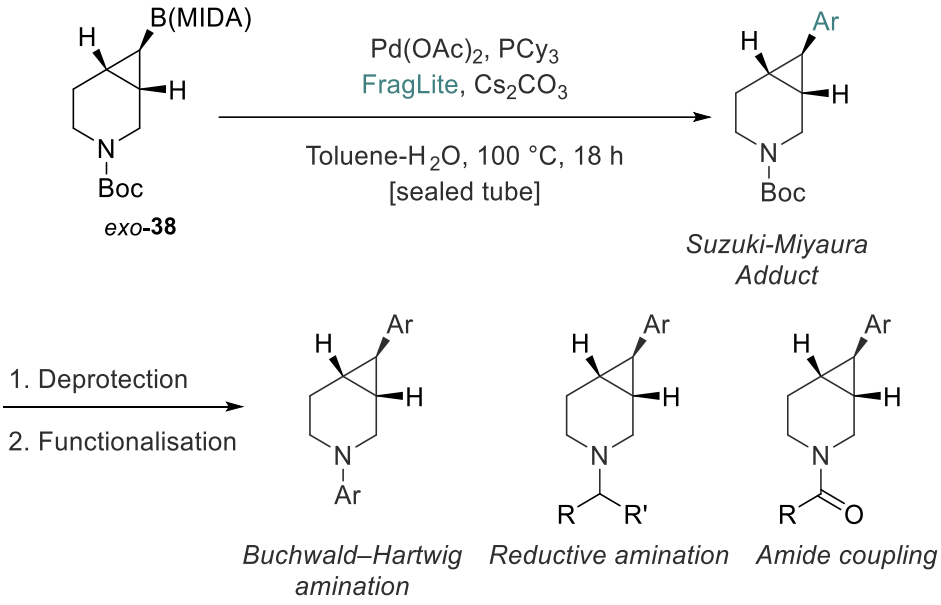


Scheme 2.46. Synthetic route to naphthyridine **28**.

Chapter 3: Suzuki-Miyaura Cross-Coupling and Diversification of FragLites and Protected FragLites

This chapter describes our efforts on Suzuki-Miyaura cross coupling (SMCC) of 3-D building block *exo*-**38** with FragLites and protected FragLites, together with initial investigations into the subsequent *N*-functionalisation and protecting group removal reactions. Chapter 3.1 describes a brief overview of SMCC reactions in relation to cyclopropyl boron reagents, followed by the progression towards the conditions which are used in this thesis for SMCC reactions with building block *exo*-**38** with aryl halides.

In Chapter 3.2, the prior work within the group regarding the SMCC of 3-D building block *exo*-**38** with aryl halides, encompassing a variety of aryl halides including the medicinally relevant FragLites. While certain FragLites were cross coupled in good yields, a considerable number posed challenges, necessitating the development of protected FragLites for SMCC reactions. The main body of new results are presented in Chapter 3.3 in which the SMCC reactions of BMIDA building block *exo*-**38** with the aryl bromides synthesised in Chapter 2 are reported (Scheme 3.1). The SMCC reactions were carried out with the protected FragLites, as well as the FragLites that were not available for purchase and had to be synthesised. Lastly, Chapter 3.4 provides an account of the deprotections of the protected FragLites and their diversification by *N*-functionalisation (Scheme 3.1).



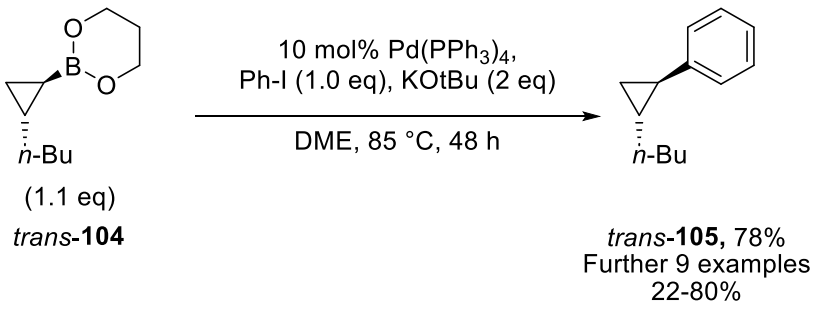
Scheme 3.1. Overview of SMCC and *N*-functionalisation

3.1 Brief overview of Suzuki-Miyaura Cross-Coupling of Cyclopropyl Boronates and Derivatives

The Suzuki-Miyaura cross-coupling (SMCC) reaction can rapidly construct complex molecular structures typically through the formation of a sp^2-sp^2 carbon-carbon bond from the reaction between an organoboron compound and an aryl or vinyl species with a halide or triflate group. [15] While SMCC of sp^3 centres can be difficult due in part to the potential for β-hydride elimination, cyclopropyl organoboron compounds present a unique exception owing to their sp^2 character thereby allowing sp^3-hybridised cyclopropyl borons to undergo SMCC reactions efficiently. Alongside boronic acids, SMCC can be achieved using boron reagents such as boronic esters, most commonly, pinicol boronate (Bpin) or BMIDA, or trifluoroborate (BF_3K) salts).[17]

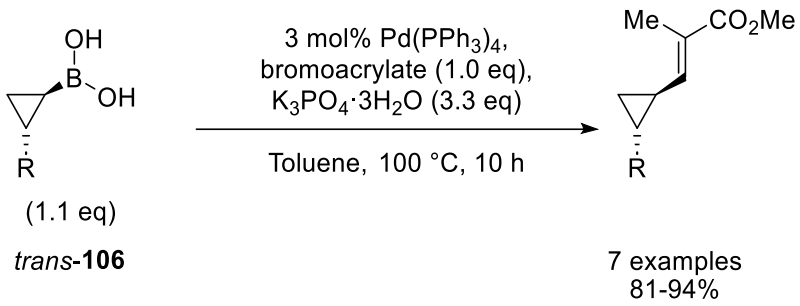
When comparing boronic acids to boronic esters, the general observation is reduced reactivity in the latter. This diminished reactivity is attributed to the non-bonding electron pairs of the boronic esters interacting with the vacant p orbital of the boron ($n_{oxygen} \rightarrow p_{boron}$), thus partially diminishing the Lewis acidity of the boron, which is crucial for SMCC reactions. Despite this reduction in reactivity, various boronic esters offer a degree of adjustability in reactivity for SMCC.

It was Marsden and Hildebrand in 1996 who developed the first SMCC strategy for cyclopropane, namely carbon-carbon bond formation between cyclopropyl boronates such as *trans*-**104** and various aryl halides with different electronic properties (Scheme 3.2).[49] This utilised the Pd^0 catalyst, $Pd(PPh_3)_4$ (10 mol%) and KO*t*-Bu (3.0 eq.) to cross-couple cyclopropyl boronic acid *trans*-**104** (1.1 eq.) with the aryl iodide (1.0 eq.) at 85 °C in DME for 48 hours. This methodology provided arylated cyclopropyl *trans*-**105** in 74% yield and a further nine 9 examples with cross-coupling occurring with retention of stereochemistry.



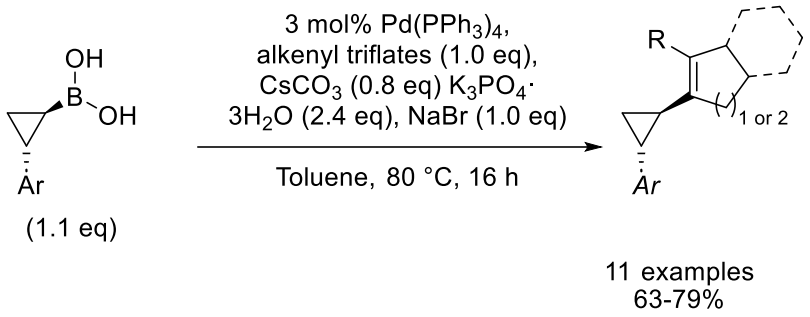
Scheme 3.2. First SMCC of cyclopropyl boronates by Marsden and Hildebrand[49]

In 1997, Deng *et al.* introduced a novel method for achieving stereocontrol in the synthesis of cyclopropyl-substituted α,β-unsaturated esters using Pd^0. [50] In this process, *trans*-substituted cyclopropylboronic acids *trans*-**106** were utilised in SMCC reactions with bromoacrylates, employing 3 mol% of $Pd(PPh_3)_4$ and $K_3PO_4 \bullet 3H_2O$ in toluene at 100 °C for 10 hours. This approach led to the forming cyclopropyl-substituted α,β-unsaturated esters in high yields (81-94%) (Scheme 3.3).



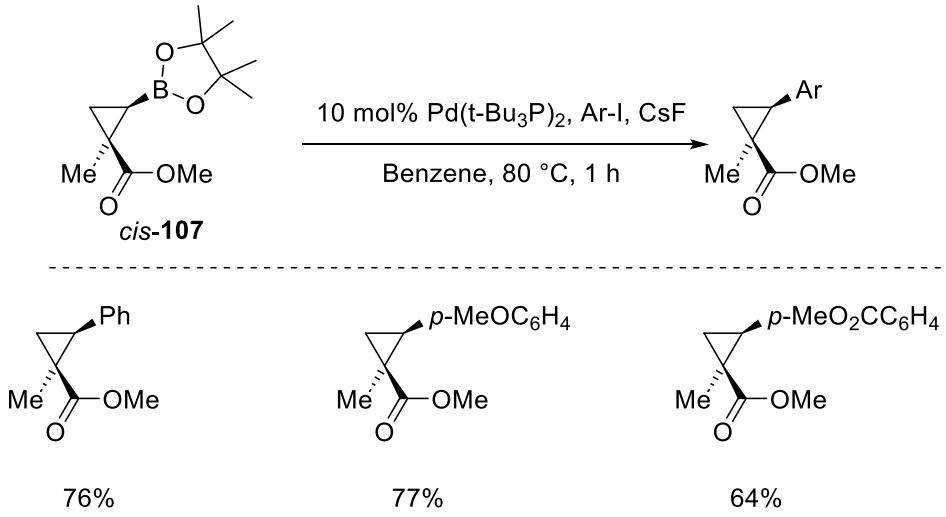
Scheme 3.3. Synthesis of cyclopropyl substituted α,β-unsaturated esters by Deng *et al.*[50]

Later, in 2000, Deng and Yao showcased the applicability of Pd^0 in SMCC reactions of *trans*-cyclopropylboronic acids and heteroaryl triflates with preservation of the *trans* configuration in the products.[51] Various reaction conditions were attempted, including changing the base, temperature, and solvent, ultimately identifying two main optimal conditions. When using 3 mol% $Pd(PPh_3)_4$, alkenyl triflates (1.0 eq), $K_3PO_4 \cdot 3H_2O$ (3.3 eq.) as the base and heating in toluene at 100 °C for 16 h, excellent yields up to 86% were attained for numerous substrates. However, it should be noted that this approach was not universally applicable, as certain alkenyl triflates lacking electron-withdrawing groups exhibited low or no yield. With an alternative set of conditions, more consitent yields ranging from 63-79% were obtained (Scheme 3.4). Specifically, these conditions involved the use of 3 mol% $Pd(PPh_3)_4$, alkenyl triflates (1.0 eq.) and a combination of $CsCO_3$ (0.8 eq.) and $K_3PO_4 \cdot 3H_2O$ (2.4 eq), along with 1 equivalent of NaBr. The reaction mixture was then heated in toluene at 80 °C for 16 hours.



Scheme 3.4. SMCC with heteroaryl triflates by Deng and Yao[51]

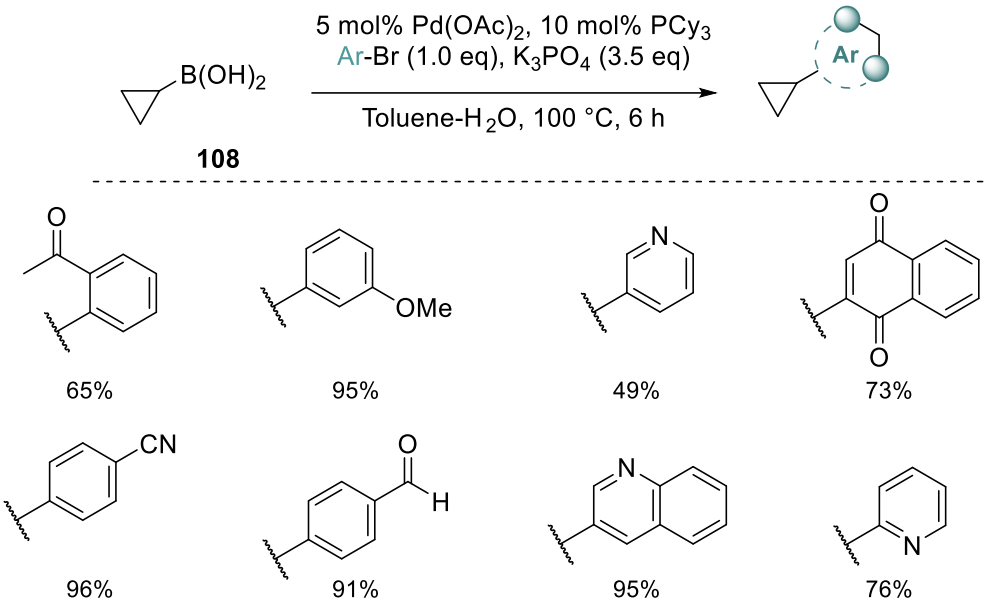
Similarly, Gevorgyan *et al.* presented a SMCC approach utilising substituted cyclopropyl Bpins such as *cis*-**107** rather than boronic acids.[52] Specifically, it was demonstrated that SMCC of cyclopropyl Bpin *cis*-**107** with Pd(*t*-$Bu_3P)_2$ and CsF as the base with several aryl and vinyl iodides gave yields ranging from good to excellent (64-85%) (Scheme 3.5).The reactions proceeded with retention of the *cis* stereochemistry.



Scheme 3.5. SMCC with cyclopropyl Bpin by Gevorgyan *et al.*[52]

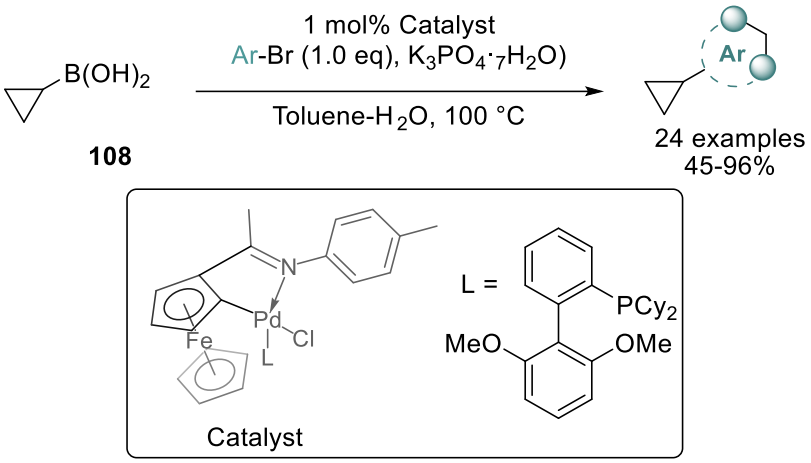
In 2002, Wallace and Chen were the first to document the SMCC of cyclopropyl boronic acid **108** which does not contain any substitution.[53] Examples were achieved with various aryl and heteroaryl halides. The SMCC reactions were accomplished using a catalytic system

comprising 5 mol% $Pd(OAc)_2$ and 10 mol% PCy_3 in a mixture of toluene and H_2O with K_3PO_4 (3.5 eq.) at 100 °C for 3 hours. Using such conditions resulted in yields of cross-coupled products ranging from 64-85%. Selected examples are shown in Scheme 3.6.



Scheme 3.6. SMCC of cyclopropyl boronic acid **108** by Wallace and Chen[53]

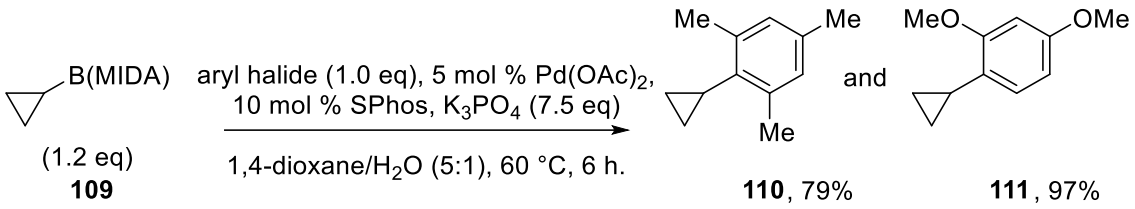
More recently, in 2012, Zhang and colleagues employed an efficient catalyst system for SMCC reactions with cyclopropylboronic acid **108**, which was compatible with a wide range of aryl and heteroaryl halides.[54] Specifically, an SPhos adduct of cyclopalladated ferrocenylimine was utilised. The results demonstrated the adaptability of SMCC to various functional groups under specific conditions, utilising 1 mol % of the catalyst and 3 equivalents of $K_3PO_4 \cdot 7H_2O$. The reaction involved the combination of cyclopropylboronic acid **108** and the aryl halide in a mixture of toluene and water, conducted at 100 °C for 3 hours, yielding a series of adducts with yields ranging from 45-96% (Scheme 3.7).



Scheme 3.7. SMCC of cyclopropyl boronic acid **108** by Zhang *et al.*[54]

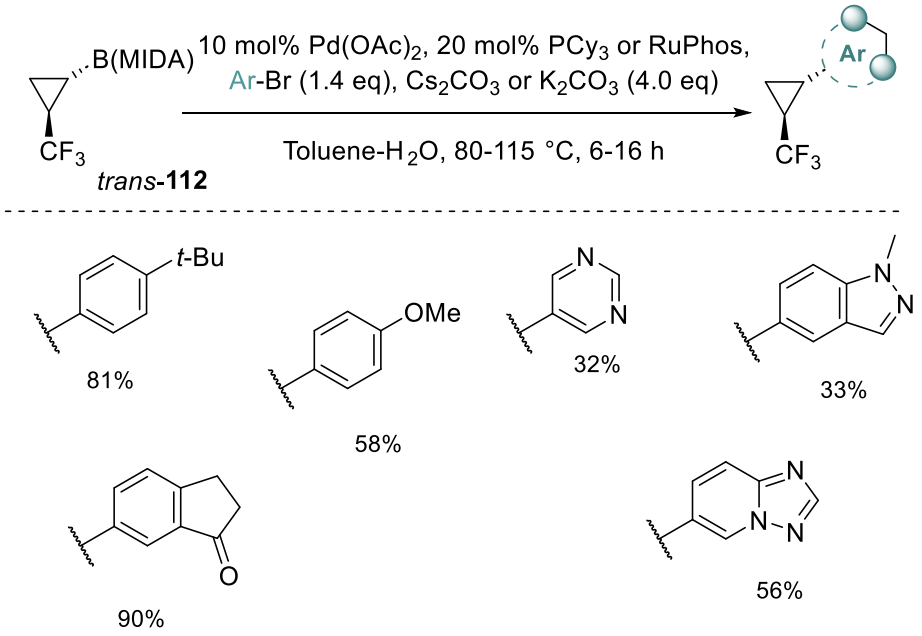
A significant difficulty associated with some cyclopropyl boronic acids and pinacol boronates is their challenging purification process due to instability on silica. Additionally, they can exhibit sensitivity to air, posing a significant challenge for long-term storage, particularly in the context of the described building blocks in this thesis. To address some of these issues, MIDA boronates were introduced by Burke *et al.* in 2008[16] and were later extended to cyclopropyl MIDA boronates. [17] MIDA boronates are known for their high bench stability which enables prolonged storage. It is proposed that the presence of a vacant p-orbital in boronic acids is crucial for transmetallation during SMCC, with the BMIDA group effectively masking the Lewis acidic boron. When compared, MIDA boronates exhibit remarkable resilience during purification and demonstrate a capacity for long-term storage. In stability assessments, after 15 days, boronic acids showed significant decomposition (31% remaining), whereas their BMIDA counterparts maintained exceptional stability over an extended period of 60 days, with minimal decomposition (95% remaining). The MIDA boronates function as a protected form of the boronic acid, undergoing gradual hydrolysis under aqueous conditions to yield the corresponding boronic acid.

Burke and colleagues demonstrated two instances of SMCC reactions involving cyclopropyl BMIDA **109**. This was achieved by employing 1.2 equivalents of MIDA boronate, 5 mol% $Pd(OAc)_2$, 10 mol% of SPhos and a substantial excess of K_3PO_4 (7.5 eq.) and heating in a mixture of dioxane and H_2O at 60 °C for 6 hours. As a result, aryl cyclopropanes **110** and **111** were obtained with yields of 79% and 97% respectively (Scheme 3.8).[17]



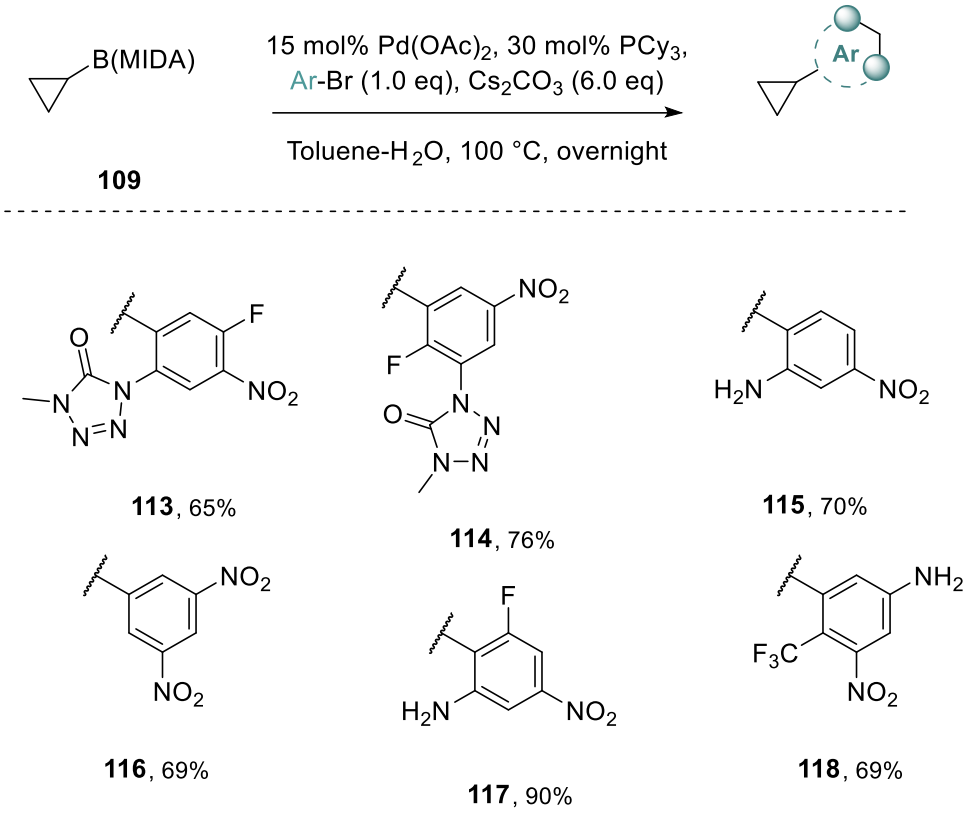
Scheme 3.8. SMCC of cyclopropyl MIDA **109** by Burke *et al.*[17]

In 2013, Duncton and Singh described conditions to prepare diastereomerically pure *trans*-(trifluoromethyl)cyclopropyl BMIDA *trans*-**112** and utilised this substrate in SMCC reactions with a Pd^{II} pre-catalytic system.[55] Examples included both aryl and heteroaryl bromides and resulted in the production of a series of compounds with potential significance in medicinal chemistry. These reactions employed 10 mol% of $Pd(OAc)_2$ along with 20 mol% of an electron-rich ligand such as RuPhos or PCy_3, and used 4 equivalents of Cs_2CO_3 or K_2CO_3. The reaction mixture was heated at 80–115 °C for 6–16 hours in a mixture of toluene and H_2O. In this way, a range of medically relevant compounds in yields ranging from 17-90% were obtained (Scheme 3.9).



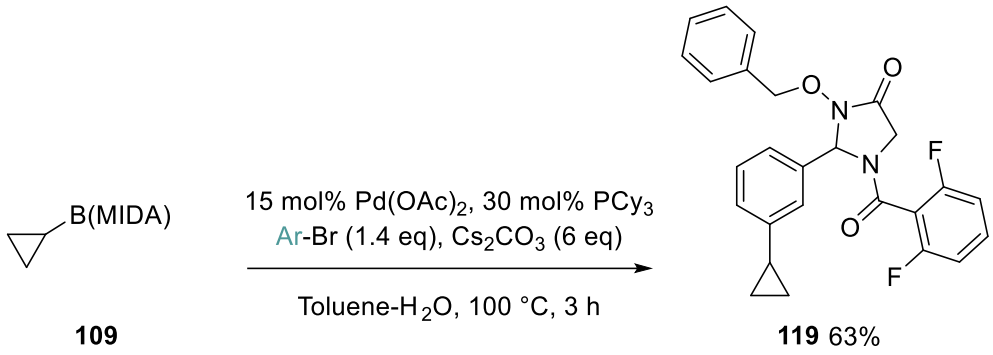
Scheme 3.9. SMCC of (trifluoromethyl)cyclopropyl BMIDA *trans*-**112** by Duncton and Singh[55]

Subsequently, Duncton and Singh applied their conditions to the synthesis of protein kinase C inhibitors. [56 57] Thus, cyclopropanes **113-118** were produced in 59-90% yields (Scheme 3.10). In these conditions established by Duncton and Singh, cyclopropyl MIDA **109** was reacted with the aryl halide using a higher catalyst loading of 15 mol% of $Pd(OAc)_2$, 30 mol% of PCy_3, and a substantial excess of Cs_2CO_3 (6.0 eq.) in a mixture of toluene and H_2O, heated at 100 °C overnight.



Scheme 3.10. Synthesis of protein kinase C inhibitors synthesised by Duncton and Singh[56,57]

Similarly, de Man and co-workers applied the same conditions, utilising the catalytic system consisting of $Pd(OAc)_2$ (15 mol%) and PCy_3 (30 mol%), to perform the cross-coupling of cyclopropyl MIDA boronate **109** with the aryl halide.[58] This reaction took place in a mixture of toluene and H_2O at 100 °C for 3 hours, resulting in the production of aryl cyclopropane **119** in 63% yield (Scheme 3.11).



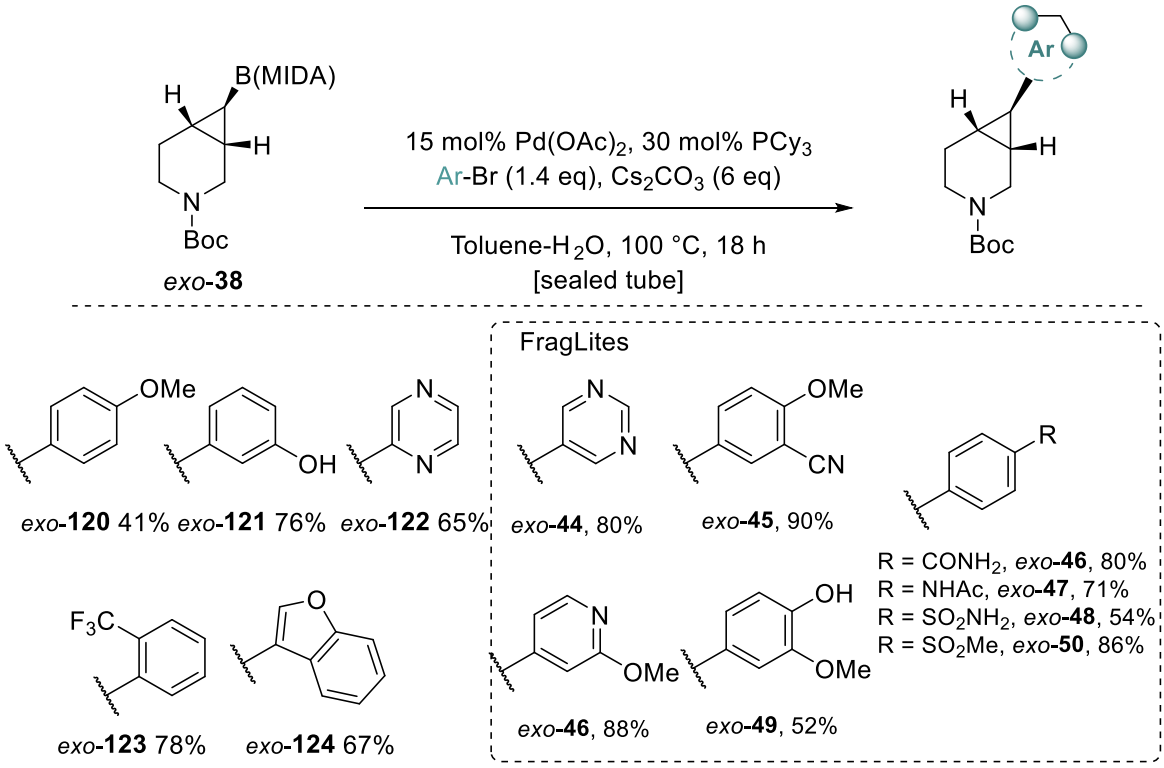
109 **119** 63%

Scheme 3.11. SMCC by de Man *et al.*[58]

In summary, the major developments in SMCC reactions of cyclopropyl boron reagents have been highlighted. In particular, for SMCC of cyclopropyl boron species with heterocyclic bromides, good outcomes were achieved by employing a Pd^{II} pre-atalytic system with the use of MIDA boronates. Typical conditions included $Pd(OAc)_2$, an electron-rich ligand such as PCy_3, a carbonate base, and the reactions were conducted at elevated temperatures ranging from 80-115 °C in a co-solvent system of toluene and water.

3.2 Overview of Suzuki-Miyaura Cross-Couplings of BMIDA Building Block *exo*-38

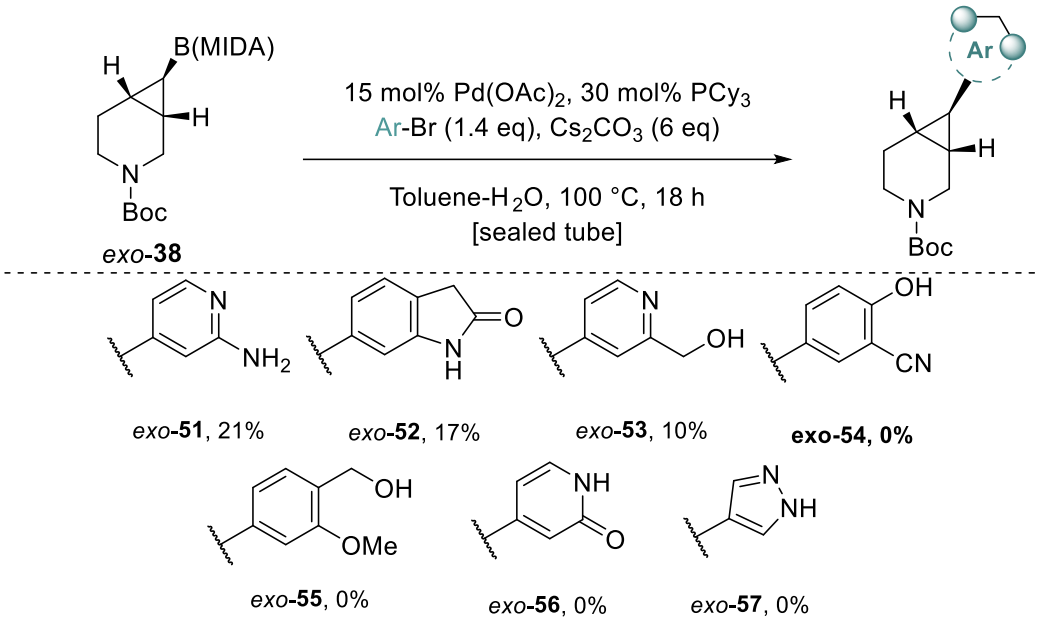
Within the group, the work on *exo*-**38** was initially carried out by Klein, who investigated the synthesis of *exo*-**38** and further used this building block in SMCC reactions with an array of aryl halides using 5 mol% and 15 mol% Pd catalyst loadings.[19] This work was continued by other members of the group with a wide range of aryl bromides.[20, 28] Some of the aryl halides investigated were not FragLites, but these cross-coupling results showcased that the reactions conditions were robust and there was great versatility with a diverse range of aryl and heteroaryl halides forming many cross-coupled products (Scheme 3.12). Klein also explored the cross-coupling of *exo*-**38** with FragLites to show that the conditions could be applied to synthesise a set of medicinally relevant compounds. Klein, along with Gomez Angel,[20] were able to successfully cross-couple many FragLites giving adducts *exo*-**44-49** and *exo*-**120-124** in yields ranging from 52-90% (Scheme 3.12).



Scheme 3.12. SMCC reactions by Klein and Gomez Angel with FragLites in excellent yields

However, Klein's work highlighted that there was instances were SMCC reactions of FragLites posed challenges. For instance, it was observed that poor yields or no yield at all could be achieved

in some cases (Scheme 3.13). From an analysis of the results, it was ascertained that the lower yields were generally obtained with functional groups that had exposed amino or hydroxyl functionalities.



Scheme 3.13 Low Yielding or Failed SMCC reactions with FragLites

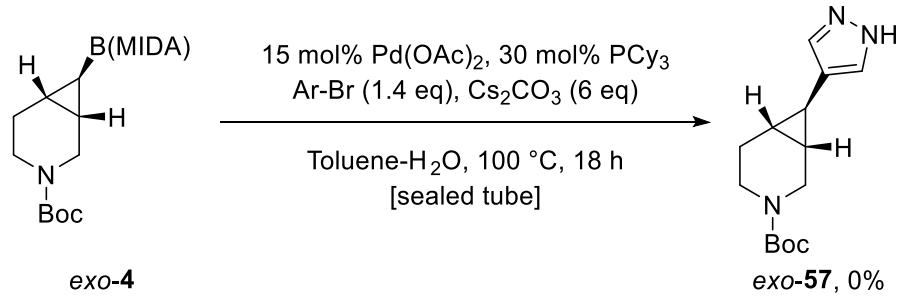
It was found that challenges arose in cases involving aryl bromides with reactive motifs, such as exposed hydroxyl or amino groups. Issues were also observed in cross-coupling of heterocyclic aryl bromides due to their distinct electronics compared to non-heterocyclic counterparts. However, arenes featuring exposed hydroxyl or amino groups, as well as heterocyclic arenes, are frequently found in drug-like molecules. Hence, it becomes crucial to establish and demonstrate a methodology for enabling SMCC in these cases. Walder first began the work of installing protecting groups on the amino or hydroxyl groups to mask the functionality and thus enabling the coupling reactions to proceed.[21] The work in the next section describes our efforts of continuing this work using the protected FragLites and the FragLites synthesised in Chapter 2.

3.3 Investigation into the Suzuki-Miyaura Cross-Coupling of BMIDA Building Block *exo*-38 with FragLites and Protected FragLites

Having prepared building block *exo*-**38** and the aryl bromides, we were now in a position to study the SMCC reactions. In particular, we could now investigate if the protection strategy could facilitate cross-coupling of FragLites with problematic motifs.

3.3.1 Suzuki-Miyaura Cross-Coupling of Bromo Pyrazoles, Pyridines, and Pyrimidine-like Compounds

Previous attempts to couple FragLites with exposed amino or hydroxyl groups showed poor yields (see Scheme 3.14). For unprotected bromopyrazole **6**, performing the SMCC reaction of building block *exo*-**38** with a high catalyst loading of $Pd(OAc)_2$ (15 mol%) and PCy_3 (30 mol%) and Cs_2CO_3 (6.0 eq.) yielded none of the desired cyclopropyl pyrazole *exo*-**57** (Scheme 3.14). This confirmed the result previously obtained by Klein.[19]

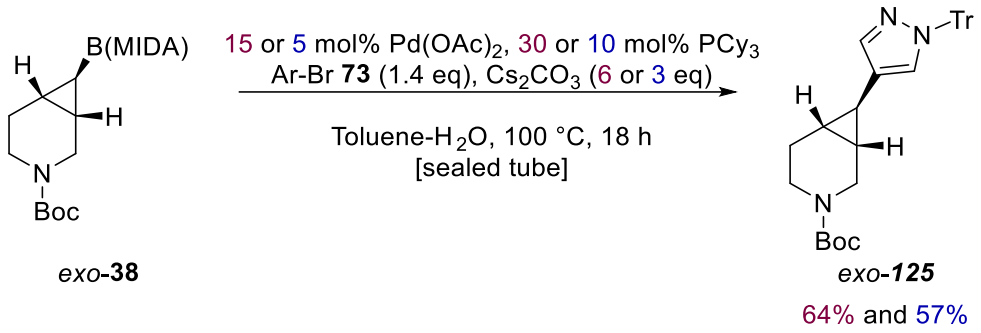


exo-**4** → *exo*-**57**, 0%

Scheme 3.14. SMCC of unprotected bromopyrazole **6**

In order to assess if the protection strategy for the pyrazole FragLite would lead to a successful SMCC reaction, SMCC of building block *exo*-**38** was performed with trityl pyrazole **76** using a high catalyst loading of $Pd(OAc)_2$ (15 mol%) and PCy_3 (30 mol%) and Cs_2CO_3 (6.0 eq.). Pleasingly, cyclopropyl pyrazole *exo*-**125** was obtained in 64% yield after chromatography (Scheme 3.15). Performing the reaction but with a lower catalyst loading of $Pd(OAc)_2$ (5 mol%), PCy_3 (10 mol%) and Cs_2CO_3 (3.0 eq.) gave cyclopropyl pyrazole *exo*-**125** in 57% yield. In recent work in the group, Wang carried out the cross-coupling with *N*-tosyl bromopyrazole and obtained the aryl cyclopropane in 76% yield using the 5 mol% $Pd(OAc)_2$ conditions.[59] The significant increase in yield between the protected and unprotected bromopyrazoles indicates

that the protection strategy can enable efficient SMCC reactions, and it held potential for cross-coupling other protected FragLites.

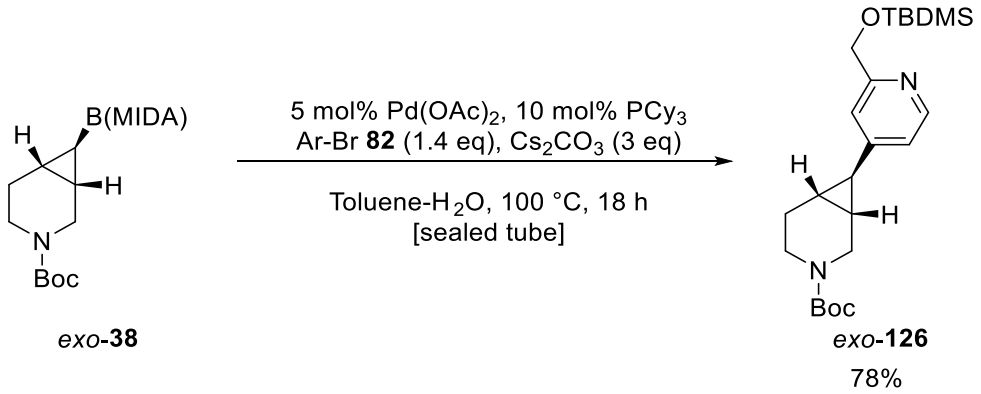


exo-**38** *exo*-***125***

64% and 57%

Scheme 3.15. SMCC of trityl protected bromo pyrazole **73**

Our investigations were extended to utilise TBDMS protected hydroxymethyl pyridine **82** as the coupling partner with *exo*-**38**. Initially, there was a concern that the TBDMS group might undergo cleavage due to the hydroxide produced under the basic SMCC conditions. However, as outlined in section 2.23, employing TBDPS protection led to the formation of an inseparable mixture in the synthesis of the FragLite itself (see Scheme 2.23.). Hence, it was necessary to synthesise TBDMS-protected pyridine **82** for use in the SMCC reaction. Despite our initial concerns, cross-coupling aryl halide **82** with a low catalyst loading of $Pd(OAc)_2$ (5 mol%), PCy_3 (10 mol%), and Cs_2CO_3 (3.0 eq.) led to the formation of cyclopropyl pyridine *exo*-**126** in 78% yield (Scheme 3.16). Notably, the adequate yield achieved suggests that the generation of hydroxide during the reaction did not cause cleavage of the TBDMS group on either the aryl bromide **82**, nor did it cleave the cross-coupled product *exo*-**126** post-coupling.

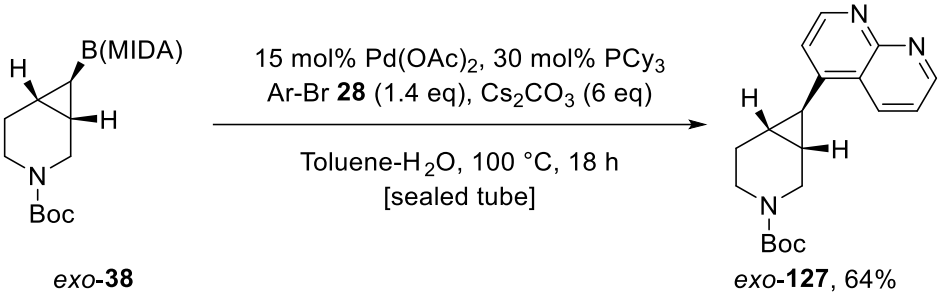


exo-**38** *exo*-**126**

78%

Scheme 3.16. SMCC of TBDMS-protected bromo pyridine **82**

Given the prior success in the O'Brien group in the cross-coupling of *exo*-**38** with 4-bromopyridine and 5-bromopyrimidine, there was a hope that cross-coupling of bromo naphthyridine **28** (which had been difficult to obtain, see Section 2.3) could be accomplished smoothly, without the need for nitrogen protective groups, such as the *N*-oxide moiety. However, due to the limited quantity of aryl bromide available, only one SMCC could be performed. Consequently, it was decided to conduct the cross-coupling with a high catalyst loading. SMCC between building block *exo*-**38** and naphthyridine **28** was performed using $Pd(OAc)_2$ (15 mol%), PCy_3 (30 mol%), and Cs_2CO_3 (6.0 eq.). Gratifyingly, this yielded arylated naphthyridine *exo*-**127** in 64% yield after chromatography (Scheme 3.17).

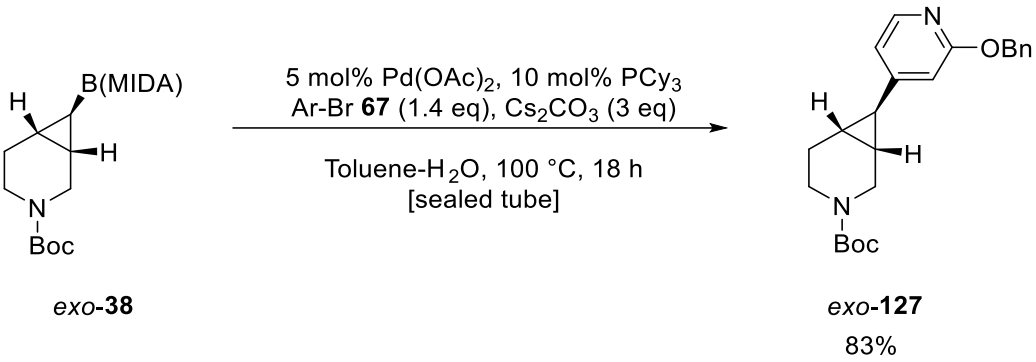


exo-**38** *exo*-**127**, 64%

Scheme 3.17. SMCC of bromo naphthyridine **28**

3.3.2 Suzuki-Miyaura Cross-Coupling of Pyridone-containing Heteroaryl Bromides

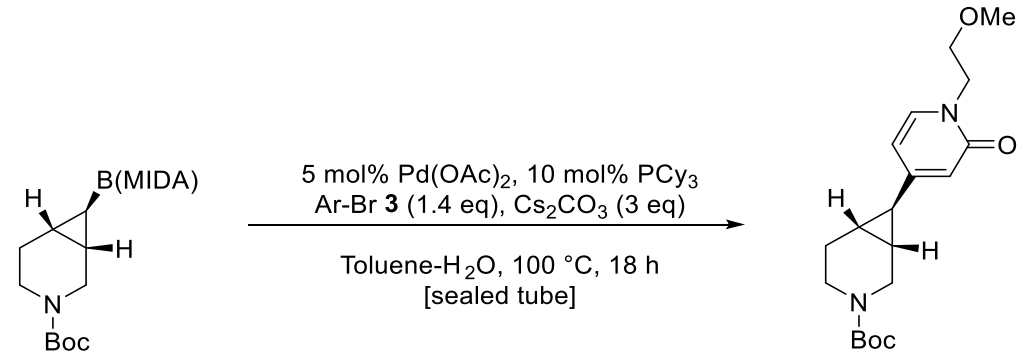
As shown in previous studies by Klein, cross-coupling of 4-bromopyridin-2(1H)-one **1** gave no product. We decide to investigate the approach to form *O*-benzyl pyridine **67** as a masked form of pyridone **1** which would be revealed by benzyl cleavage subsequent to cross-coupling. With *O*-benzyl pyridine **67** in hand, the cross-coupling was performed with standard conditions (5 mol% $Pd(OAc)_2$) which successfully furnished cyclopropyl pyridine *exo*-**127** in 83% yield after purification (Scheme 3.18).



exo-**38** *exo*-**127**
83%

Scheme 3.18. SMCC of masked pyridone **67**

With *N*-alkylated pyridones, our exploration began with bromo pyridone **3**. The SMCC reaction was performed between building block *exo*-**38** with bromopyridone **3** using $Pd(OAc)_2$ (5 mol%), PCy_3 (10 mol%) and Cs_2CO_3 (3.0 eq.) under the usual conditions. However, purification of pyridone *exo*-**128** proved difficult and the initially obtained product after chromatography was not completely pure. Following further purification by chromatography, pyridone *exo*-**128** was isolated in 77% yield (Scheme 3.19).

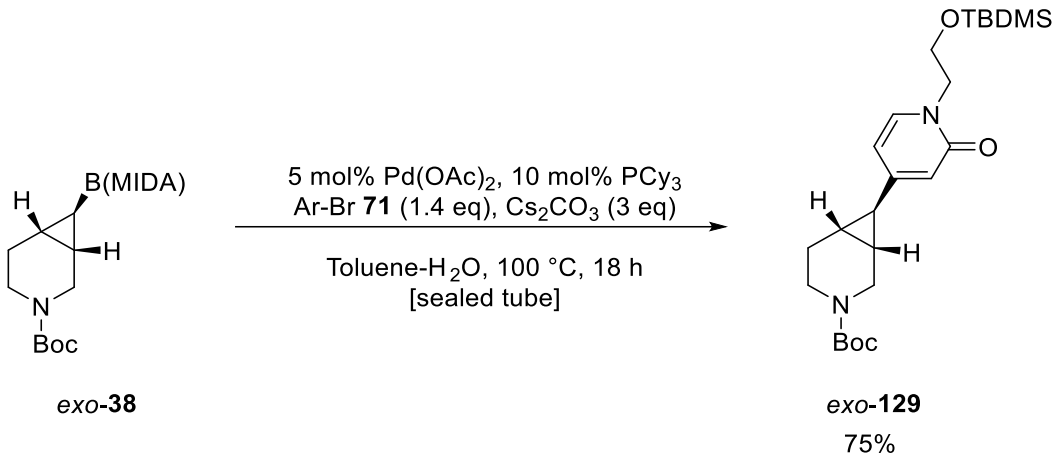


exo-**38** *exo*-**128**
77%

Scheme 3.19. SMCC of bromo pyridone **3** with *exo*-**38**

Following the success in achieving the cross-coupling of bromo pyridone **3**, we shifted our attention towards cross-coupling of the closely related TBDMS-protected pyridone **71**. Considering the stability of the installed silyl protecting group, we drew confidence from our earlier studies with pyridine **82**, which demonstrated that under the SMCC conditions, the TBDMS protected primary alcohol was stable under the cross-coupling conditions. With this in mind, we anticipated that the SMCC reaction of building block *exo*-**38** with pyridone **71**

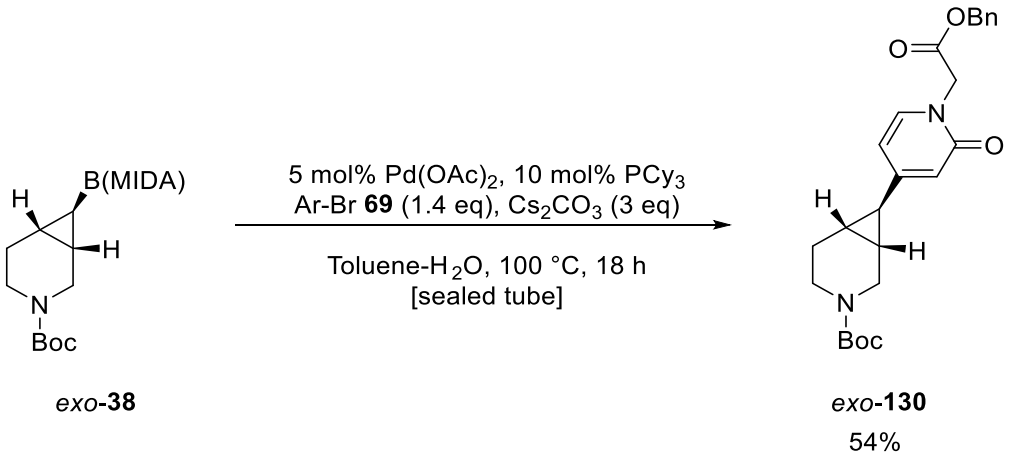
would proceed smoothly. Indeed, the experimental result provided the desired *exo*-**129** in 75% yield after purification by chromatography (Scheme 3.20).



exo-**38** *exo*-**129**
75%

Scheme 3.20. SMCC of TBDMS-protected bromo pyridone **71**

Next, we examined the cross-coupling between bromo pyridone **69** which contained a benzyl ester. The SMCC reaction between building block *exo*-**38** and bromo pyridone **69** was achievable with a catalyst loading of $Pd(OAc)_2$ (5 mol%), PCy_3 (10 mol%) and Cs_2CO_3 (3.0 eq.). Under these conditions, cyclopropyl pyridone *exo*-**130** was furnished in 54% yield after purifications by chromatography (Scheme 3.21). This outcome demonstrated that the benzyl ester was well-tolerated under the cross-coupling conditions, and ester hydrolysis did not occur. In contrast, although not explored specifically, it is expected that the unprotected FragLite **4** with a free carboxylic acid moiety would not be suitable for SMCC reactions.

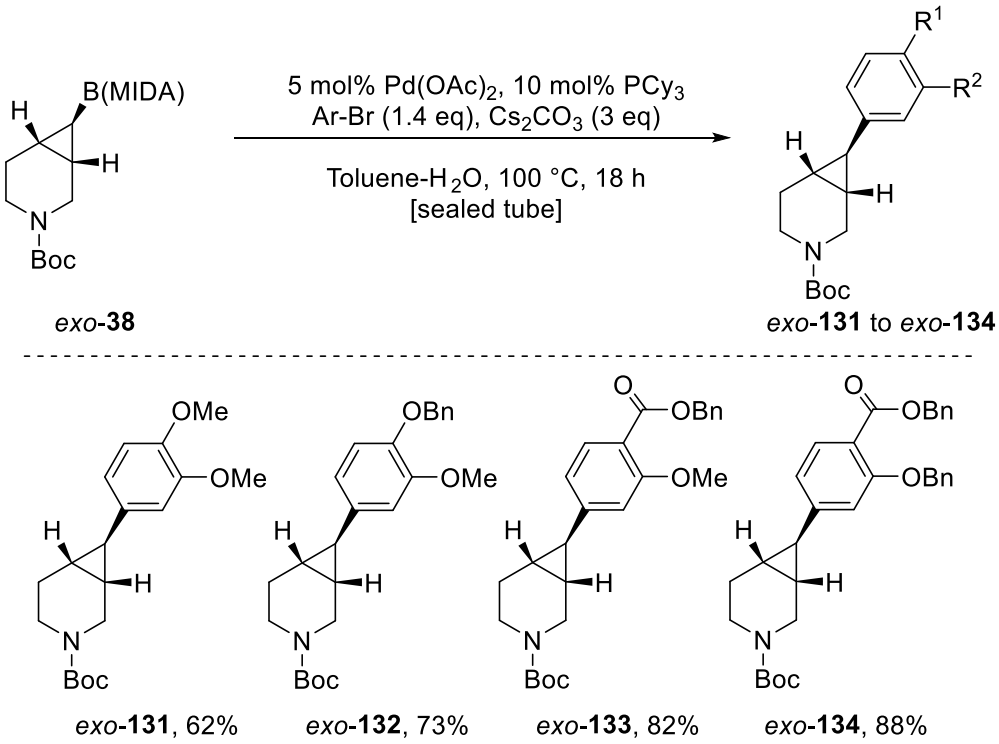


exo-**38** *exo*-**130**
54%

Scheme 3.21. SMCC of benzyl ester protected bromo pyridone **69** with *exo*-**130**

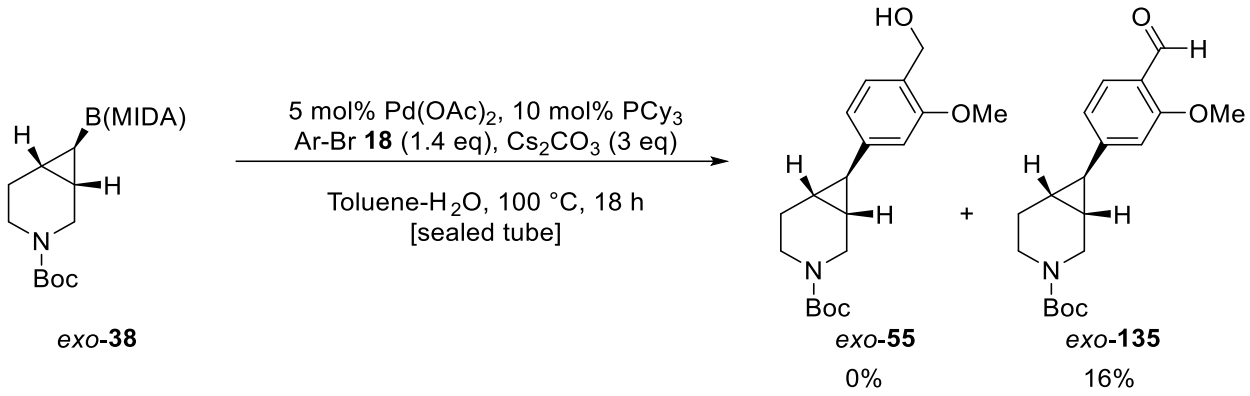
3.3.3 Suzuki-Miyaura Cross-Coupling of Substituted Bromobenzenes

Next, our focus shifted to non-heterocyclic aryl bromides. Our objective was to explore the SMCC scope of various FragLites featuring 1,2-disubstituted benzenes (see Figure 3.22). In these cases, different substitutions around the ring can have an impact on the outcome of the SMCC reactions. These aryl bromides featured various functional groups including electron-withdrawing (COOBn) and/or electron-donating (OMe, OBn, OH) motifs. We were pleased to find that in all attempts, SMCC reactions of *exo*-**38** with all 1,2-disubstituted bromo benzenes yielded excellent results, producing the cross-coupled products *exo*-**131**-**134** in the range of 62-88% yield (Scheme 3.22). This stands in contrast to earlier endeavours by Klein in cross-coupling of the unprotected aryl bromide **16** where, in this instance, the cross-coupled product *exo*-**49** was obtained in only 52% yield (see Scheme 1.2.). Interestingly, SMCC of 1,2 disubstituted benzenes to give *exo*-**131**-**134** (all of which lack the exposed hydroxyl group) surpassed Klein's result, even though the latter was conducted with a higher catalyst loading.



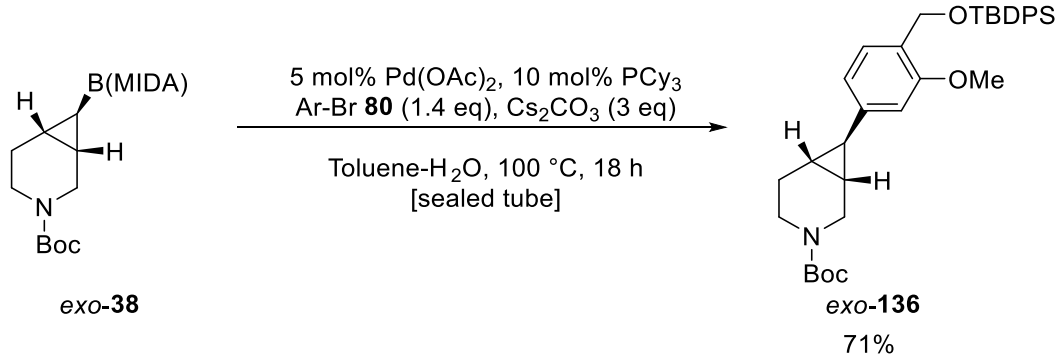
Scheme 3.22. SMCC of *exo*-**38** and 1,2-disubstituted bromo benzenes

4-Bromo-2-methoxybenzyl alcohol, FragLite **18**, proved to be troublesome SMCC substrate when previously attempted by Klein.[19] In this instance, it was observed that there was no conversion to the desired aryl cyclopropane *exo*-**55**. Instead, aldehyde-containing aryl cyclopropane **135** was isolated in 16% yield (Scheme 3.23), due to an oxidation of the alcohol into an aldehyde.



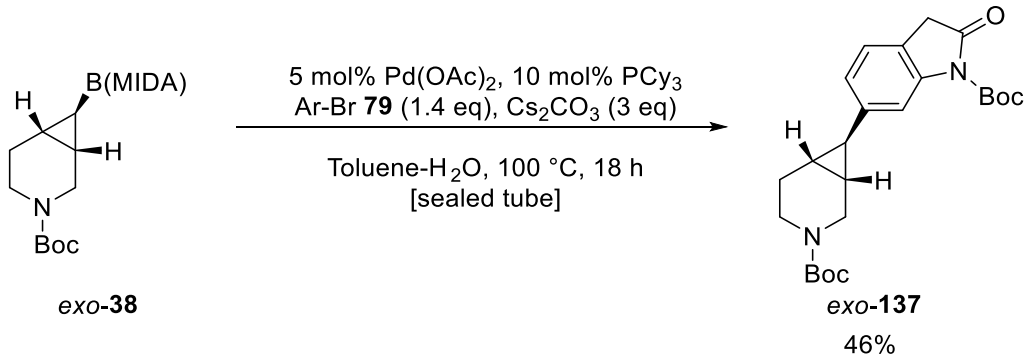
Scheme 3.23. Attempted SMCC of 4-bromo-2-methoxybenzyl alcohol by Klein

It was hoped that incorporation of a silyl protective group could facilitate the cross-coupling by removing the problematic hydroxyl group but also prevent formation of cross-coupled aldehyde *exo*-**135**. Indeed, performing a SMCC reaction with TBDPS-protected bromo benzene **80** proved successful, yielding the desired arylated cyclopropane *exo*-**136** in 71% yield (Scheme 3.24).



Scheme 3.24. SMCC of TBDMS-protected bromo benzene **80**

Finally, tackling the last FragLite with the benzene nucleus presented a unique case, namely bromo oxindole **12**, which is characterized by a cyclic amide structure, requiring masking of the N-H functionality. As detailed in section 2.2.3, we had shifted our strategy from a PMB protecting group towards use of Boc-protected bromo oxindole **79** despite concerns that the Boc moiety could be labile during the basic SMCC reaction conditions (due to hydroxide attack onto the Boc carbonyl group). There was a hope that the SMCC reaction kinetics could proceed at a rapid enough rate to yield a sufficient quantity of the cross-coupled product before Boc group removal became significant. In the event, the Boc group was not removed under the SMCC reaction conditions. Boc-protected bromo oxindole **79** was subjected to SMCC with building block *exo*-**38** under the standard low loading catalytic conditions. Pleasingly, arylated cyclopropane *exo*-**137** was isolated in 46% yield following chromatography (Scheme 3.25).



exo-**38**

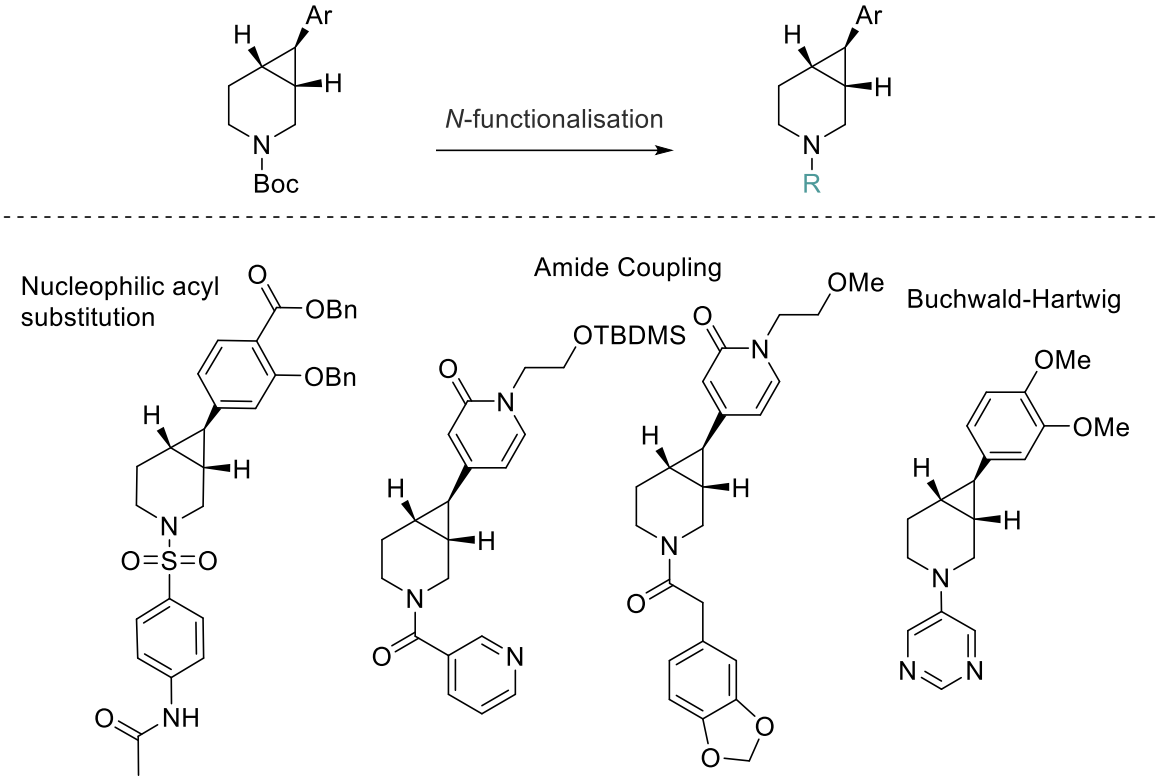
exo-**137**

46%

Scheme 3.25. SMCC of Boc-protected bromo oxindole **79**

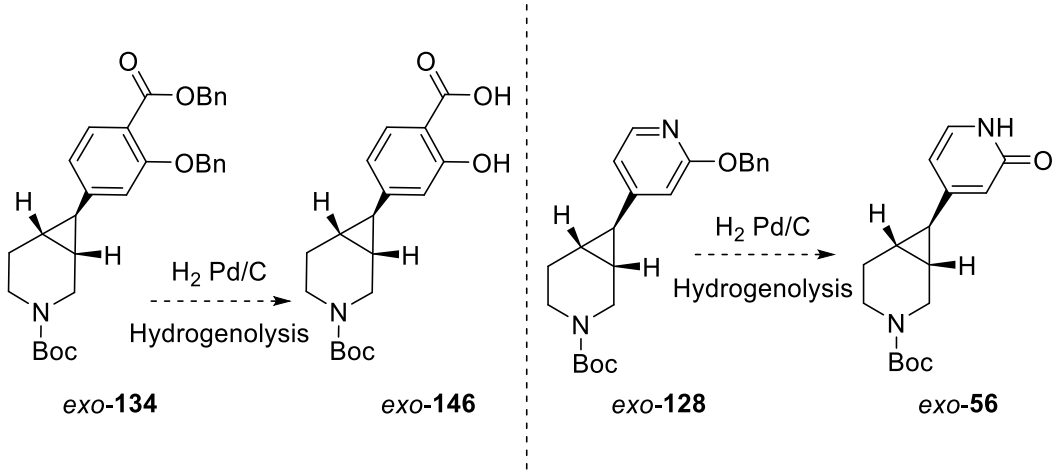
3.4. N-Functionalisation and FragLite Deprotection Studies

Having successfully cross-coupled a range of FragLites and protected FragLites, several SMCC reaction products were selected for subsequent *N*-functionalisation attempts. The selection was performed with the aim to incorporate a diverse collection of molecular structures. Furthermore, diversification of the cross-coupled FragLites employed a range of reactions, including nucleophilic acyl substitution, amide coupling and Buchward-Hartwig amination (Scheme 3.26).



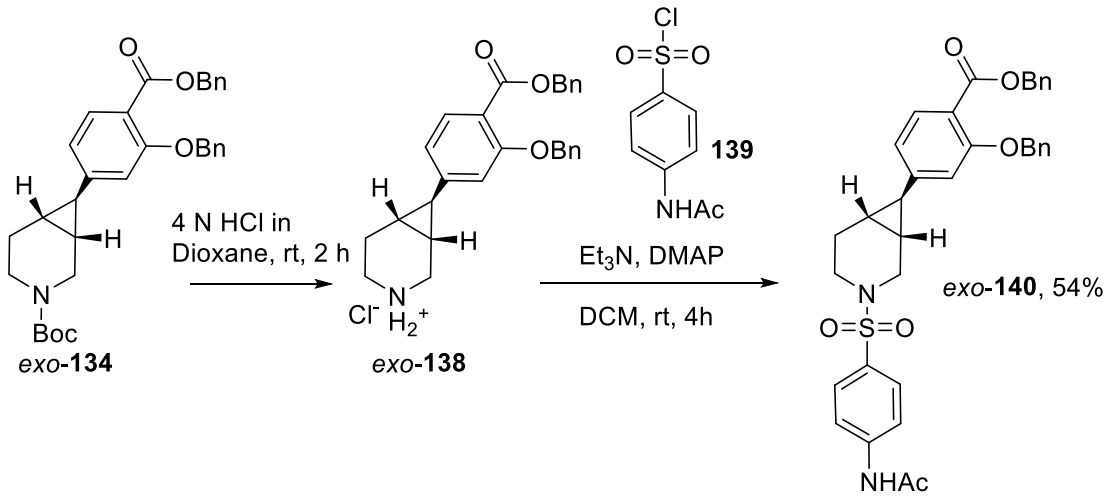
Scheme 3.26. Envisioned *N*-Functionalisations

Moreover, the decision was made to illustrate that deprotection of the benzyl group in two of the cross-coupled FragLites could be achieved. Firstly, benzyl group removal from *exo*-**134** was anticipated *via* catalytic hydrogenation (Scheme 3.27). For the *O*-benzyl pyridine *exo*-**128**, serving as a masked pyridone, it was similarly envisioned that catalytic hydrogenation would reveal pyridone *exo*-**56** (Scheme 3.27).



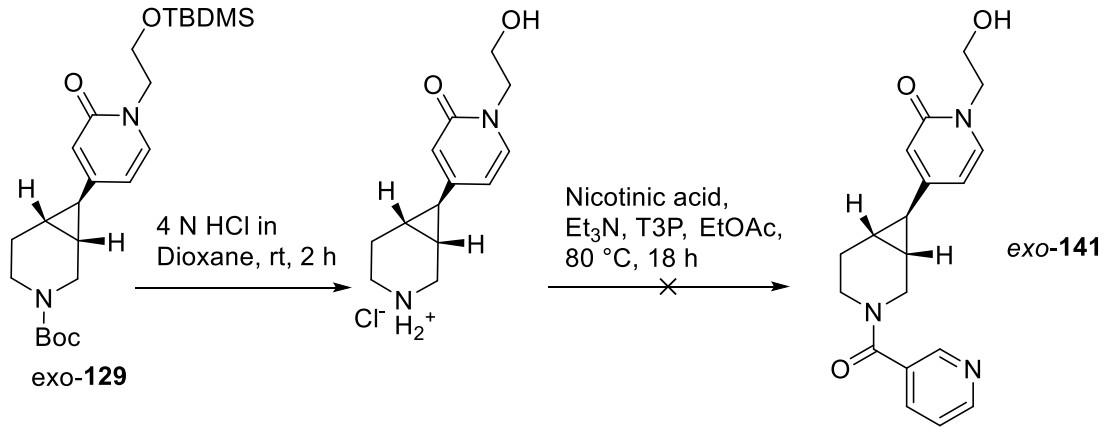
Scheme 3.27. Planned benzyl group removals

For the cross-coupled FragLite *exo*-**134**, it was determined that the amino group would be functionalised through nucleophilic acyl substitution. To accomplish this, removal of the Boc group of the arylated piperidine *exo*-**134** was carried out using 4 N HCl in dioxane at rt for 2 h. After evaporation of the solvent, the resulting hydrochloride salt *exo*-**138** (presumed) was obtained as a solid. This solid was suspended in CH_2Cl_2 and reacted with sulfonyl chloride **139** in the presence of DMAP and freshly distilled Et_3N at rt for 4 hours. Following work-up and chromatography, the *N*-functionalised benzene *exo*-**140** was obtained in a 54% yield (Scheme 3.28).



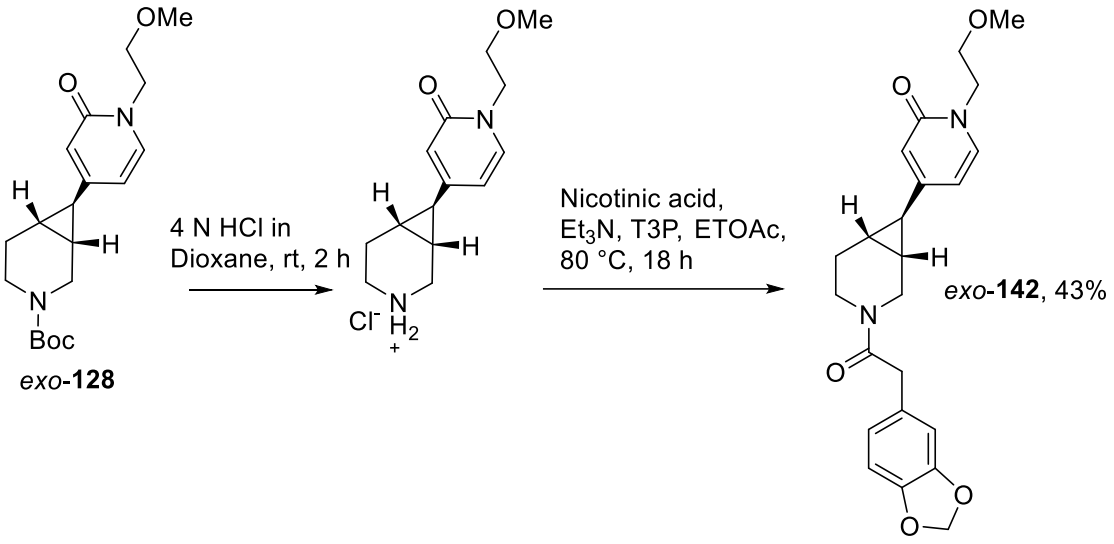
Scheme 3.28. *N*-Functionalisation of cross-coupled FragLite *exo*-**134**

Next, we decided to explore amide coupling reactions starting from arylated piperidines *exo*-**129** and *exo*-**128**. For this process, T3P was used as the coupling agent due to its ease of handling as a liquid solution and the water solubility of the by-products formed during the reaction. To this end, the Boc group in arylated piperidine *exo*-**129** was removed and then amidation of the crude HCl salt was attempted with nicotinic acid, Et_3N (4.0 eq.) and a 50% solution of T3P in EtOAc at 80 °C for 18 hours. Although the original procedure specified an acidic work-up, we decided on a neutral pH water work-up due to concerns that the pyridine nitrogen could become protonated and remain in the aqueous layer. Following chromatography, analysis using ^1H NMR spectroscopy suggested that the TBDMS group had been removed presumably in the first step (Boc group removal). However, despite attempted purification, we were unable to isolate a pure sample of the *N*-functionalised product *exo*-**141**. Nevertheless, there was reasonable evidence in the ^1H NMR spectrum and HRMS data confirmed that it had been formed.



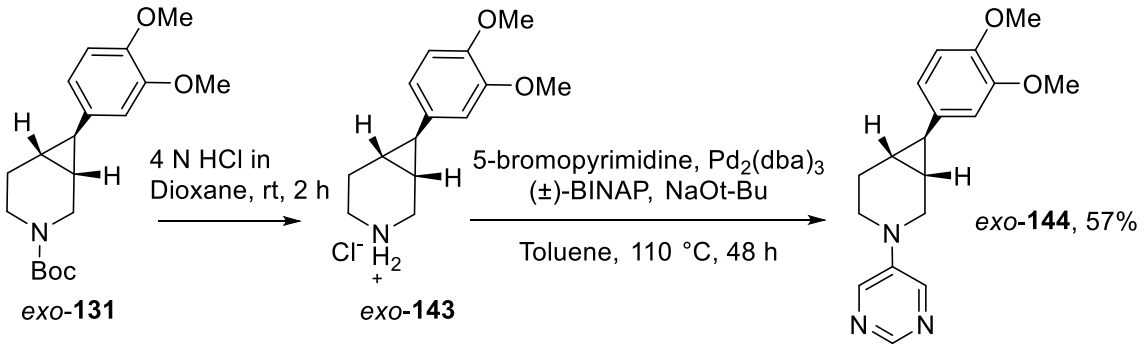
Scheme 3.29. Attempted *N*-Functionalisation of cross-coupled FragLite *exo*-**129**

Similarly, amide coupling was carried out with arylated piperidine *exo*-**128**. Upon treating arylated piperidine *exo*-**128** with 4 N HCl in dioxane, the resulting crude hydrochloride salt was subjected to amide coupling with 3-indoleacetic acid $Et_3N$and T3P. After work-up and chromatography, pure amide *exo*-**142** was obtained with in 43% yield (Scheme 3.30).



Scheme 3.30. *N*-Functionalisation of cross-coupled FragLite *exo*-**128**

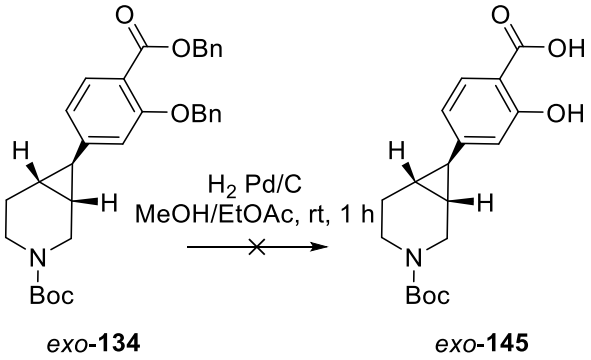
Next, it was decided to investigate Buchwald-Hartwig arylation, employing a modified protocol derived from the original procedure developed by Buchwald *et al.*[60] To begin, Boc group removal was achieved using 4 N HCl in dioxane, resulting in the formation of the crude hydrochloride salt *exo*-**143**. Buchwald-Hartwig arylation was then carried out by suspending the crude HCl salt in toluene, and reacting it with 5-bromopyrimidine, $Pd_2(dba)_3$, (±)-BINAP, and NaO*t*-Bu at 110 °C for 48 hours. After purification by chromatography, *N*-pyrimidinyl cyclopropane *exo*-**144** was isolated in 57% yield (Scheme 3.31).



Scheme 3.31. *N*-Functionalisation of cross-coupled FragLite *exo*-**131**

Finally, we also aimed to investigate conditions to remove the benzyl protecting group in cross-coupled FragLites *exo*-**134** and *exo*-**128**. The initial attempt to deprotect cross-coupled FragLite *exo*-**134** involved subjecting it to catalytic hydrogenation and catalytic Pd/C in MeOH/EtOAc

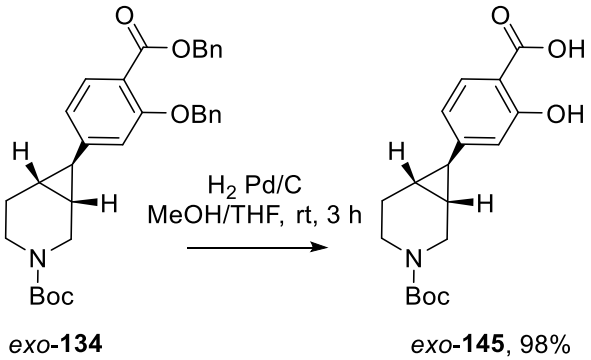
for 1 h. However, analysis by ^{1}H NMR spectroscopy revealed that acid *exo*-**145** had not formed (Scheme 3.32).



exo-**134** *exo*-**145**

Scheme 3.32. Attempted Benzyl group removal of cross coupled FragLite *exo*-**134**

After a brief literature search, Gunning *et al*. had reported benzyl group cleavage using catalytic hydrogenation on a structurally similar debenzylated salicylic acid. [61] These conditions were therefore employed on cross-coupled FragLite *exo*-**134**. This involved using an excess of hydrogen gas and Pd/C in MeOH/THF for 3 hours. Following filtration to remove the catalyst and solvent evaporation, gratifyingly, global deprotection had occurred. In this way, acid *exo*-**145** was obtained in 98% yield without the need for any purification (Scheme 3.33).

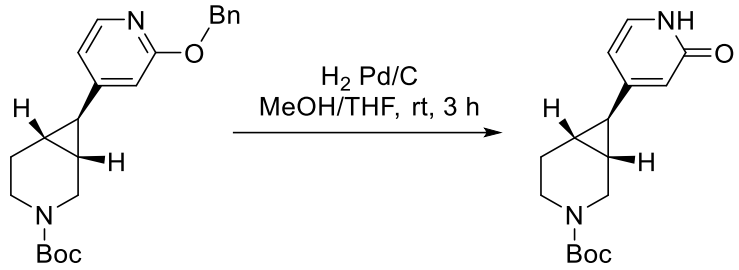


exo-**134** *exo*-**145**, 98%

Scheme 3.33. Global deprotection of cross-coupled FragLite *exo*-**134**

The hydrogenolysis conditions were then applied to masked pyridone *exo*-**128**. Catalytic hydrogenation of pyridone *exo*-**128** utilising an excess of H_2 and Pd/C for 3 hours at rt was thus carried out. This reaction was only conducted on a small scale (10 mg). There was reasonable

evidence to indicate that the benzyl group had been removed, based on the ^{1}H and ^{13}C NMR spectrum. Furthermore, the formation of pyridone *exo*-**146** was confirmed by HRMS data. However, the product formed was not pure and satisfactory full characterisation was not possible from this small-scale reaction. Clearly, this reaction should be replicated on a larger scale for validation.



exo-**128** *exo*-**146**

Scheme 3.34. Deprotection of cross coupled FragLite *exo*-**128**

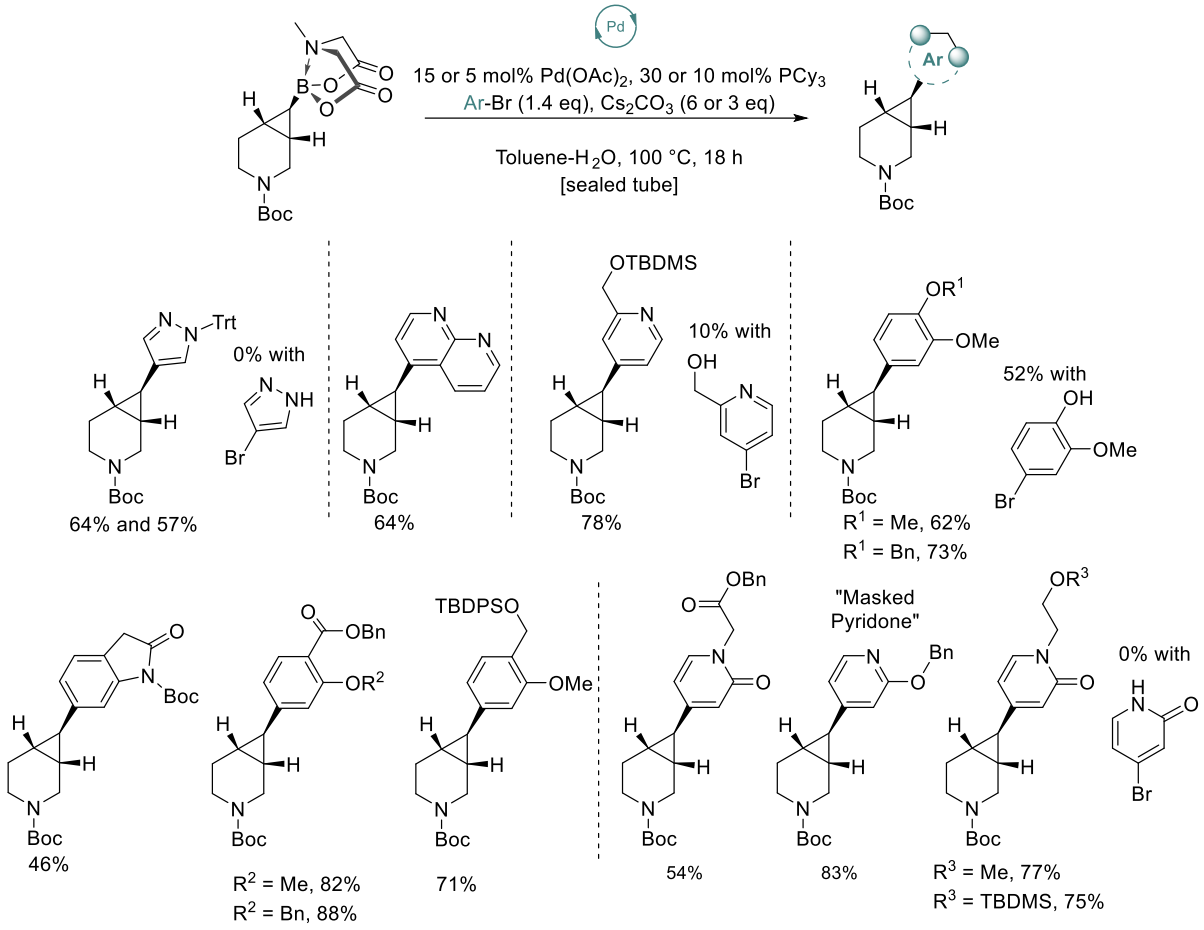
Chapter 4: Conclusions and Future Work

At the outset of our research endeavours, we accomplished the conversion of commercially available β,γ-unsaturated *N*-Boc protected piperidine **62** into the 3-D building block, cyclopropyl BMIDA *exo*-**38**.

Our report highlights the successful synthesis of FragLites, which were previously not obtainable at reasonable prices, achieved through the utilization of readily available precursors. This encompasses a range of structures, including **3, 8**, **26**, and **28**, all of which have been successfully prepared in satisfactory yields, while FragLites **6, 7, 8** and **24** have been the subject of research for other members of the O'Brien group. Despite numerous attempts employing procedures detailed in the literature for the synthesis of bromo naphthyridine **28**, most methods yielded regioisomeric compounds. Persistent efforts ultimately led to the development of a procedure that did yield the required naphthyridine scaffold. Through a series of optimized transformations, bromo naphthyridine **28** was synthesized in a sufficient yield.

Several FragLites presented or were anticipated to present challenges during SMCC due to their functional groups. To facilitate cross-coupling, it was necessary to mask these functionalities using a protection strategy. This was achieved through the careful selection of protection groups that could withstand the cross-coupling conditions. Depending on the functional groups, this involved protecting the FragLites with either an *O*-Benzyl, *O*-silyl, *N*-Boc, or *N*-trityl protection group(s). As a result, the developed methodology proved effective in generating sufficient quantities for SMCC of protected FragLites **69, 71, 73, 77, 79, 80**, and **82.**

The overarching objective of this thesis was to investigate SMCC using 3-D building blocks with FragLites. Elaboration was demonstrated with building blocks *exo*-**38** *via* SMCC with all the synthesized FragLites or their protected derivatives in satisfactory yields (Figure 4.1). This demonstrates the efficacy of the protection strategy in facilitating efficient SMCC reactions.



Scheme 4.1. Overview of cross-coupled FragLites

Furthermore, diversification was achieved through *N*-functionalization and deprotections. Initially, the removal of the Boc group, followed by functionalization of the piperidine nitrogen, led to the production of a series of structurally diverse, medically relevant compounds. Having demonstrated that the protection strategy facilitates efficient SMCC reactions, future work can includes employing orthogonal protection to optimise the strategy. This would provide greater control over substrate functionality for subsequent transformations, such as the orthogonal removal of the Boc group during *N*-functionalisation. An area of particular interest in this research involves exploring if it is possible to maintain respectable yields while further lowering the catalyst loading. Additionally, a comparative study between SMCC and alternative cross-coupling techniques, such as photoredox, could be explored. Moreover, there is ongoing research within the O'Brien group to develop a new generation of cyclobutyl building blocks with defined vectors to have a greater coverage of chemical space.

Finally, this work contributed to the broader objective of showcasing the methodology of the O'Brien group in FBDD, specifically applied to FragLites. It is conceivable that this approach could be extended to other sets of fragments, making it a valuable tool in drug discovery.

Chapter 5: Experimental

5.1. General Methods

All non-aqueous reactions were carried out under oxygen-free Ar or N_2 atmosphere using flame-dried glassware. Brine refers to a saturated $NaCl_{(aq)}$ solution. Water is distilled water. Flash column chromatography was carried out using Fluka Chemie GmbH silica (220-440 mesh). Thin layer chromatography was carried out using commercially available Merck F254 aluminium backed silica plates. Spots were visualised by UV and appropriate stains ($KMnO_4$ and Ninhydrin). Proton (400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument using an internal deuterium lock. For samples recorded in $CDCl_3$, chemical shifts are quoted in parts per million relative to $CHCl_3$ (δ_H 7.26) and $CDCl_3$ (δ_C 77.0, central line of triplet). For samples recorded in d_6-DMSO, chemical shifts are quoted in parts per million relative to DMSO (δ_H 2.50, central line of quintet) and d_6-DMSO (δ_C 39.5, central line of septet). Carbon NMR spectra were recorded with broad band proton decoupling and assigned using DEPT and HSQC experiments. Coupling constants (J) are quoted in Hertz. Melting points were carried out on a Gallenkamp melting point apparatus. Infrared spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer. Electrospray high and low resonance mass spectra were recorded at room temperature on a Bruker Daltronics microOTOF spectrometer.

5.2. General Procedures

General Procedure A: *N*-Alkylation of 4-bromopyridin-2(1H)-one

The alkyl bromide (2.40 mmol, 2.09 eq.) was added dropwise to a stirred solution of K_2CO_3 (996 mg, 7.21 mmol, 6.27 eq.) and 4-bromopyridin-2(1H)-one **1** (200 mg, 1.15 mmol, 1.0 eq.) in anhydrous MeCN (10 mL) at 0 °C under Ar. The resulting solution was stirred and heated at 80 °C for 16 h under Ar. After being allowed to cool to rt, the solids were removed by filtration and the solvent was evaporated under reduced pressure to give the crude product.

General Procedure B: Synthesis of 4-Hydroxy-[1,8]-naphthyridin-2(1H)-one 96

KO*t*Bu (370 mg, 3.30 mmol, 2.51 eq.) was added portionwise to a stirred solution of methyl 2-aminonicotinate **95** (200 mg, 1.31 mmol, 1.00 eq.) in EtOAc (8 mL) or 1:1 EtOAc-*o*-xylene (8 mL) or 1:1 EtOAc-Dowtherm® A (8 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h. Then, a reflux condenser (with water cooling as an air consdeneser was not sufficient to maintain the EtOAc in the reaction flask) was attached and the joints were sealed with PTFE tape. The reaction mixture was then gradually heated to the specified temperature in 30 °C increments over a 20 min duration while being stirred at a moderate speed to prevent any reaction mixture and/or red precipitate being splashed into the condenser. The resulting mixture was stirred and heated at the specified temperature for 4 h. After being allowed to cool to rt, the EtOAc (and EtOAc/*o*-xylene if co-solvent was used) was evaporated under reduced pressure to give the crude product (suspended in Dowtherm® A if the co-solvent was used). The crude product was dissolved in the minimum amount of H_2O (5 mL) and the solution was transferred to a separating funnel. Small portions of brine (5 mL) were required to aid separation of the emulsion. The two layers were separated and the organic layer was extracted with H_2O (6 × X 30 mL). The aqueoues layers were combined and the water was evaporated under reduced pressure. The residue was dissolved in a mimum amount of H_2O (5 mL) until all of the solids had dissolved. With vigorous stirring, the pH was adjusted to pH = 5-6 by the addition of 1 M $HCl_{(aq)}$ and solid precipitated to give an off-white suspension. The precipitated solid was allowed to settle and conglomerate before being collected by vacuum filtration using a filter paper with a small pore size. Subsequently, the fine

particle suspensions that passed through the filter paper were allowed to settle from the supernatant and were collected by filtration. The process was repeated until no additional solids were observed in the filtrate. The combined solids were washed with deionised water acidified with 1 M $HCl_{(aq)}$ (5 mL, pH = 5), dried by suction filtration and dissolved in hot MeOH with vigorous agitation using a stirring rod to break up the conglomerate. After everything had dissolved, the MeOH was evaporated under reduced pressure to give 4-hydroxy-[1,8]-naphthyridin-2(1H)-one **96** as a beige solid.

General Procedure C: Suzuki-Miyaura Cross-Coupling of Cyclopropyl MIDA Boronates (5 or 15 mol%) using liquid aryl bromides

Toluene and water were added to separate flasks and the solvents were each degassed by sparging with Ar for 20 min through a septum with an outlet. MIDA boronate (0.25 mmol, 1.0 eq.), $Pd(OAc)_2$ (2.8 mg, 0.01 mmol, 5 mol% or 8.4 mg, 0.03 mmol, 15 mol%), PCy_3 (7.0 mg, 0.02 mmol, 10 mol% or 21.0 mg, 0.06 mmol, 30 mol%) and Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 or 488 mg, 1.5 mmol, 6.0 eq.) were placed in a 15 mL ACE pressure tube. Then, a solution of the aryl bromide (0.35 mmol, 1.4 eq.) in degassed toluene (5 mL) was added and the vessel was sealed with a rubber septum and evacuated and refilled with Ar. Then, degassed water (0.5 mL) was added and the pressure tube was sealed with a screw plug. The pressure tube was placed in a heating block preheated to 100 °C and the solution was stirred and heated at 100 °C (stirrer block temperature) for 18 h under Ar. After being allowed to cool to rt, the solids were removed by filtration through Celite® and washed with EtOAc (5 mL) and H_2O (5 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

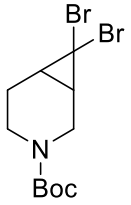
General Procedure D: Suzuki-Miyaura Cross-Coupling of Cyclopropyl MIDA Boronates (5 or 15 mol%) using solid aryl bromides

Toluene and water were added to separate flasks and the solvents were each degassed by sparging with Ar for 20 min through a septum with an outlet. MIDA boronate (0.25 mmol, 1.0 eq.), aryl bromide (0.35 mmol, 1.4 eq.), $Pd(OAc)_2$ (2.8 mg, 0.01 mmol, 5 mol% or 8.4 mg, 0.03 mmol, 15 mol%), PCy_3 (7.0 mg, 0.02 mmol, 10 mol% or 21.0 mg, 0.06 mmol, 30 mol%) and Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 or 488 mg, 1.5 mmol, 6.0 eq.) were placed in a 15 mL ACE pressure tube. Then, degassed water (0.5 mL) was added and the pressure tube was sealed with a screw plug. The pressure tube was placed in a heating block preheated to 100 °C and the solution was stirred and heated at 100 °C (stirrer block temperature) for 18 h under Ar. After being allowed to cool to rt, the solids were removed by filtration through Celite® and washed with EtOAc (5 mL) and H_2O (5 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

5.3. Experimental Procedures and Characterisation Data

5.3.1 Experimental for Chapter 2

tert-Butyl 7,7-dibromo-3-azabicyclo[4.1.0]heptane-3-carboxylate 63



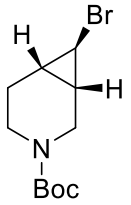
63

$CHBr_3$ (4.74 mL, 49.1 mmol, 3.0 eq.) and benzyltriethylammonium chloride (745.8 mg, 3.27 mmol, 0.2 eq.) were added to a stirred solution of *tert*-butyl 1,2,3,6-tetrahydropyridine1-carboxylate **62** (3.00 g, 16.4 mmol, 1.0 eq.) in CH_2Cl_2 (49.1 mL) at rt. Then, a solution of NaOH (38.6 g, 965.9 mmol, 39.0 eq.) in H_2O (30 mL) was added. The resulting solution was stirred and heated at 45 °C for 18 h. The mixture was then allowed to cool to rt. Then, H_2O (30 mL) was added and the solution was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$), decanted from the black sediment formed and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 1:1 hexane-Et_2O as eluent gave dibromocyclopropane **63** (4.18 g, 72%) as a yellow oil, R_F (1:1 hexane-Et_2O) 0.44; IR (ATR) 2975, 2928, 2864, 1689 (C=O), 1476, 1421 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 4.04 – 3.71 (m, 1.6H, NCH), 3.65 – 3.26 (m, 1.4H, NCH), 2.80 – 2.47 (m, 1H, NCH), 2.18 – 1.94 (m, 2H, CH), 1.90 – 1.72 (m, 1H, CH), 1.68 – 1.57 (m, 1H, CH), 1.42 – 1.39 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.4 (C=O), 79.8 ($OCMe_3$), 40.3 (br, NCH_2), 39.8 (br, NCH_2), 39.4 (br, NCH_2), 38.6 (NCH_2), 36.6 (CBr_2), 35.5 (CBr_2), 28.5 (CMe_3), 28.4 (CMe_3) , 26.7 (CH), 26.6 (CH), 25.9 (CH), 25.7 (CH), 20.9 (CH_2), 20.7

(CH_2); HRMS (ESI) *m/z* calcd for $C_{11}H_{17}{}^{79}Br_2NO_2$ ($^{79,79}M + Na)^+$ 375.9518, found 375.9518 (–0.1 ppm error).

Lab book reference: **IMA-6**

***tert*-Butyl-7-bromo-3-azabicyclo[4.1.0]heptane-3-carboxylate *exo*-64**



exo-**64**

Dimethyl phosphite (6.48 mL 70.7 mmol, 6 eq.) was added to a stirred solution of dibromocyclopropane **63** (4.18 g, 11.8 mmol, 1.0 eq.) in anhydrous DMSO (104 mL) at rt under Ar. Then, KO*t*-Bu (7.93 g, 70.7 mmol, 6.0 eq.) was added portionwise and the resulting solution was stirred at rt for 1 h. Saturated $Na_2CO_{3(aq)}$ (150 mL) and Et_2O (200 mL) were added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9.5:0.5 hexane-EtOAc as eluent gave bromocyclopropane *exo*-**64** (2.50 g, 77%) as a colourless oil, R_F (9.5:0.5 hexane-EtOAc) 0.20; IR (ATR) 2976, 2929, 2863, 1691 (C=O), 1448, 1420 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.98 (br d, *J* = 14.0 Hz, 1H, NCH), 3.57 – 3.19 (m, 2H, NCH), 2.91 – 2.71 (m, 1H, NCH), 2.58 (dd, *J* = 3.5, 3.5 Hz, 1H, CHBr), 1.99 – 1.88 (m, 1H, CH), 1.83 – 1.74 (m, 1H, CH), 1.55 – 1.50 (m, 1H, CH), 1.46-1.43 (m, 1H, CH), 1.43 (br s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.9 (C=O), 79.9 (O*C*Me_3), 41.5 (br, NCH_2), 40.7 (br, NCH_2), 28.5 (C*Me*$_3$), 23.1 (CHBr), 22.0 (CH_2), 21.1 (CH), 19.8 (CH); HRMS (ESI) *m/z* calcd for $C_{11}H_{18}{}^{79}BrNO_2$ ($^{79}M + Na)^+$ 298.0413, found 298.0411 (+0.5 ppm error).

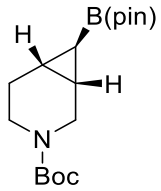
Lab book reference: **IMA-11**

Dimethyl phosphite (310 µL 3.38 mmol, 6.0 eq.) was added to a stirred solution of TEMPO (528 mg, 3.38 mmol, 6.0 eq.) and dibromocyclopropane **63** (200 mg, 0.563 mmol, 1.0 eq.) in anhydrous DMSO (5 mL) at rt under Ar. Then, KO*t*-Bu (379 mg, 3.38 mmol, 6.0 eq.) was added portionwise and the resulting solution was stirred at rt for 1 h. Saturated $Na_2CO_{3(aq)}$ (150 mL) and Et_2O (200 mL) were added. The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9.5:0.5 hexane-EtOAc as eluent gave bromocyclopropane *exo*-**64** (104 mg, 67%) as a colourless oil. Analytical data consistent with those stated in above.

Lab book reference: **IMA-34**

***tert*-Butyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo**

[4.1.0]heptane-3-carboxylate *exo*-66



exo-**66**

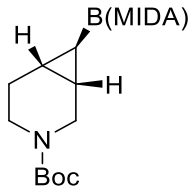
n-BuLi (3.96 mL of a 1.37 M solution in hexanes, 5.43 mmol, 1.5 eq.) was added dropwise to a stirred solution of bromocyclopropane *exo*-**64** (1.00 g, 3.62 mmol, 1.00 eq.) in THF (36.9 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, *i*-PrOBpin (1.11 mL,

5.43 mmol, 1.50 eq.) was added and the solution was allowed to warm to rt. The solution was stirred at rt for 3 h. Saturated $NH_4Cl_{(aq)}$ (40 mL) was added and the solution was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 hexane-Et_2O as eluent gave pinacol boronate *exo*-**66** (848 mg, 85%) as a pale yellow oil, R_F (7:3 hexane-Et_2O) 0.25; IR (ATR) 2959, 2926, 2855, 1696 (C=O), 1454, 1419 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.82 – 3.64 (m, 1H, NCH), 3.49 (dd, *J* = 13.5, 3.5 Hz, 1H, NCH), 3.38 – 3.15 (m, 1H, NCH), 2.93 (ddd, *J* = 13.5, 8.5, 5.5 Hz, 1H, NCH), 1.96 – 1.80 (m, 1H, CH), 1.75 – 1.58 (m, 1H, CH), 1.48 (s, 9H, CMe_3), 1.17 (s, 14H, Me and CH), –0.29 (dd, *J* = 5.5, 5.5 Hz, 1H, CHB); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.4 (C=O), 83.3 ($OCMe_2$), 79.5 ($OCMe_3$), 43.0 (br, NCH_2), 42.2 (br, NCH_2), 40.8 (br, NCH_2), 39.8 (br, NCH_2), 28.8 (CMe_3), 25.1 (Me), 25.0 (Me), 23.0 (CH_2), 17.0 (CH), 15.4 (CH), 5.2 (CHB); HRMS (ESI) *m/z* calcd for $C_{17}H_{30}BNO_4$ $(M + Na)^+$ 346.2160, found 346.2162 (+0.3 ppm error).

Lab book reference: **IMA-32**

***tert*-Butyl-7-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)-3-azabicyclo**

[4.1.0]heptane-3-carboxylate *exo*-38

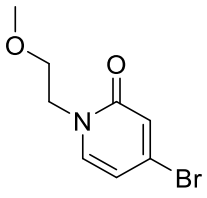


exo-**38**

$HC(OEt)_3$ (1.81 mL, 10.9 mmol, 4.50 eq.) and MIDA (2.31 g, 15.7 mmol, 6.50 eq.) were added to a stirred solution of pinacol boronate *exo*-**66** (781.0 mg, 2.41 mmol, 1.00 eq.) in anhydrous DMSO (14.1 mL) at rt. The resulting suspension was stirred and heated at 100 °C for 48 h. The reaction was then allowed to cool to rt, and saturated $NH_4Cl_{(aq)}$ (7 mL) was added. The mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 EtOAc-acetone as eluent gave MIDA boronate *exo*-**38** (659 mg, 77%) as a beige solid, mp 187.3-189.7 °C; R_F (8:2 EtOAc-acetone) 0.23; IR (ATR) 3005, 2964, 2929, 2860, 1759 (C=O, ester), 1677 (C=O, Boc), 1453, 1420 cm^{-1}; ^1H NMR (400 MHz, d_6-acetone) δ 4.18 (d, 1H, *J* = 1.5 Hz, 1H, MeNC*H*), 4.13 (d, 1H, *J* = 1.5 Hz, 1H, MeNC*H*), 4.10 – 4.05 (m, 1H, MeNC*H*), 4.01 – 3.97 (m, , 1H, MeNC*H*), 3.78 (br d, *J* = 13.5 Hz, 1H, NCH), 3.57 – 3.25 (m, 1H, NCH), 3.17 (s, 3H, NMe), 3.06 – 2.85 (m, 1H, NCH), 1.92 – 1.83 (m, 1H, CH), 1.72 – 1.61 (m, 1H, CH), 1.38 (s, 9H, CMe_3), 0.91 – 0.84 (m, 2H, CH), -0.44 (dd, *J* = 6.0, 6.0 Hz, 1H, CHB); ^{13}C NMR (100.6 MHz, d_6-acetone) (rotamers) δ 168.2 (C=O, ester), 168.1 (C=O, ester), 154.6 (C=O, Boc), 78.3 (O*C*Me_3), 62.1 ($MeNCH_2$), 62.1 ($MeNCH_2$), 46.3 (NMe), 46.3 (br, NCH_2), 42.8 (br, NCH_2), 42.0 (br, NCH_2), 40.7 (br, NCH_2), 30.3 (CHB), 29.6 (CMe_3), 29.4 (CMe_3), 29.3 (CMe_3), 29.3 (CMe_3), 29.1 (CMe_3), 29.1 (CMe_3), 28.9 (CMe_3), 28.7 (CMe_3), 28.5 (CMe_3), 23.7 (CH_2), 22.8 (CH_2), 13.5 (CH), 11.5 (CH); HRMS (ESI) *m/z* calcd for $C_{16}H_{25}BN_2O_6$ $(M + Na)^+$ 375.1698, found 375.1704 (−0.3 ppm error).

Lab book reference: **IMA-41**

4-Bromo-1-(2-methoxyethyl)pyridin-2(1H)-one 3

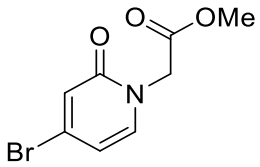


3

Using general procedure A, 1-bromo-2-methoxyethane (0.23 mL, 2.40 mmol, 2.09 eq.), K_2CO_3 (996 mg, 7.21 mmol, 6.27 eq.) and 4-bromopyridin-2(1H)-one **1** (200 mg, 1.15 mmol, 1.0 eq.) in anhydrous MeCN (10 mL) gave the crude product. Purification by flash column chromatography on silica with EtOAc as eluent gave alkylated pyridone **3** (202 mg, 76%) as a brown oil, R_F (EtOAc) 0.28; IR (ATR) 3073, 2894, 1647 (C=O), 1589, 1526, 1115, 1444 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 7.0 Hz, 1H, Ar), 6.81 (d, *J* = 3.0 Hz, 1H, Ar), 6.30 (dd, *J* = 7.0, 3.0 Hz, 1H, Ar), 4.07 (t, *J* = 5.0 Hz, OCH_2 or NCH_2), 3.63 (t, *J* = 5.0 Hz, 2H, OCH_2 or NCH_2), 3.31 (s, 3H, OMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.4 (C=O), 138.9 (Ar), 135.8 (*ipso*-Ar), 122.8 (Ar), 109.8 (Ar), 70.2 (OCH_2), 59.1 (OMe), 49.5 (br, NCH_2); HRMS (ESI) *m/z* calcd for $C_8H_{10}{}^{79}BrNO_2$ $(^{79}M + H)^+$ 231.9968, found 231.9968 (–0.3 ppm error), $(^{79}M + Na)^+$ 253.9787, found 253.9789 (–0.4 ppm error). Spectroscopic data consistent with those reported in the literature.[12]

Lab book reference **IMA-43**

Methyl 2-(4-bromo-2-oxopyridin-1(2H)-yl)acetate 68



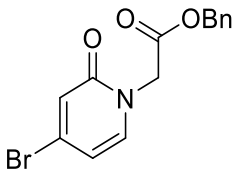
68

Using general procedure A, methyl 2-bromoacetate (1.03 mL, 10.9 mmol, 1.9 eq.), K_2CO_3 (4.98 g, 36.1 mmol, 6.27 eq.) and 4-bromo-1H-pyridin-2-one **1** (1.00 g, 5.75 mmol, 1.00 eq.) in anhydrous MeCN (52.2 mL) gave the crude product. Purification by flash column chromatography

on silica with 8.5:1.5 EtOAc-hexane as eluent gave *N*-alkylated pyridone **68** (1.31 g, 92%) as an off-white solid, mp 91.4 - 92.9 °C; R_F (8.5:1.5 EtOAc-hexane) 0.43; IR (ATR) 3076, 2954, 1751 (C=O, ester), 1654 (C=O, pyridone), 1589, 1526, 1438, 1409 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 7.5 Hz, 1H, Ar), 6.87 (d, *J* = 1.5 Hz, 1H, Ar), 6.37 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar), 4.61 (s, 2H, NCH_2), 3.80 (s, 3H, OMe);); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.8 (C=O, ester), 161.1(C=O, pyridone), 137.7 (Ar), 136.4 (ipso-Ar), 123.1 (Ar), 110.8 (Ar), 52.9 (OCH3), 50.0 (NCH2) HRMS (ESI) *m/z* calcd for $C_8H_8{}^{79}BrNO_3$ $(^{79}M + Na)^+$ 267.9580, found 267.9581 (+0.4 ppm error).

Lab book reference: **IMA-53**

Benzyl 2-(4-bromo-2-oxopyridin-1(2H)-yl)acetate 69



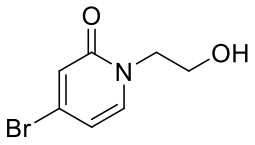
69

Using general procedure A, benzyl 2-bromoacetate (2.07 mL, 14.6 mmol, 1.27 eq.), K_2CO_3 (9.95 g, 72.1 mmol, 6.27 eq.) and 4-bromo-1H-pyridin-2-one **1** (2.00 g, 11.5 mmol, 1.00 eq.) in anhydrous MeCN (104 mL) gave the crude product. Purification by flash column chromatography on silica with 4:6 EtOAc-hexane as eluent gave *N*-alkylated pyridone **69** (3.30 g, 89%) as a white solid, mp 123.8 - 125.4 °C; R_F (4:6 EtOAc-hexane) 0.33; IR (ATR) 3073, 3033, 2955, 1750 (C=O, ester), 1654 (C=O, pyridone), 1589, 1526, 1498, 1456, 1408 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 5H, Ph), 7.06 (d, *J* = 7.5 Hz, 1H, Ar), 6.86 (d, *J* = 2.0 Hz, 1H, Ar), 6.36 (dd, *J* = 7.5, 2.0 Hz, 1H, Ar), 5.21 (s, 2H, OCH_2Ph), 4.63 (s, 2H, NCH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.3 (C=O, ester), 161.1 (C=O, pyridone), 137.6 (Ar), 136.4 (*ipso*-Ar), 135.0 (*ipso*-Ar), 128.8

(Ar), 128.7 (Ar), 128.6 (Ar), 123.2 (Ar), 110.7 (Ar), 67.8 (OCH_2Ph), 50.1 (br, NCH_2); HRMS (ESI) *m/z* calcd for $C_{14}H_{12}{}^{79}BrNO_3$ ($^{79}M + Na)^+$ 343.9893, found 343.9891 (+0.7 ppm error).

Lab book reference: **IMA-59**

4-Bromo-1-(2-hydroxyethyl)pyridin-2(1H)-one 2

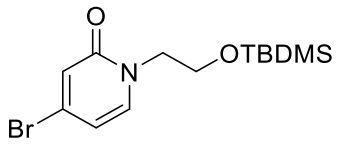


2

Using general procedure A, 2-bromoethanol (0.596 mL, 8.41 mmol, 2.09 eq.), K_2CO_3 (3.48 g, 25.2 mmol, 6.27 eq.) and 4-bromo-1H-pyridin-2-one **1** (699.5 mg, 4.02 mmol, 1.00 eq.) in anhydrous MeCN (36 mL) gave the crude product. Purification by flash column chromatography on silica with EtOAc as eluent gave *N*-alkylated pyridone **2** (699 mg, 80%) as a colourless oil which solidified upon standing to a white semi-solid, R_F (EtOAc) 0.22; IR (ATR) 2927, 1645 (C=O), 1575, 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 7.5 Hz, 1H, Ar), 6.86 – 6.80 (d, *J* = 2.0 Hz, Ar), 6.35 (dd, *J* = 7.5, 2.0 Hz, 1H, Ar), 4.12 – 4.04 (m, 2H, CH_2), 3.97 – 3.89 (m, 2H, CH_2), 2.72 (br s, OH, D_2O exchange); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.3 (C=O), 138.7 (Ar), 136.2 (*ipso*-Ar), 122.9 (Ar), 110.6 (Ar), 61.1 (CH_2), 52.8 (CH_2); HRMS (APCI) *m/z* calcd for $C_7H_8{}^{79}BrNO_2$ ($^{79}M)^+$ 217.981117, found 217.982416 (–5.0 ppm error).

Lab book reference: **IMA-82**

4-Bromo-1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)pyridin-2(1H)-one 71

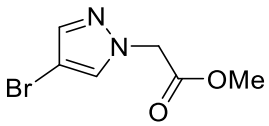


71

1H-imidazole (81 mg, 1.19 mmol, 1.3 eq.) was added to a stirred solution of 4-bromo-1-(2-hydroxyethyl)pyridin-2-one **2** (200 mg, 0.92 mmol, 1.00 eq.), DMAP (56 mg, 0.46 mmol, 0.5 eq.) and *tert*-butyl-chloro-dimethylsilane (178 mg, 1.19 mmol, 1.3 eq.) in dry CH_2Cl_2 (6.54 mL) at rt. The resulting solution was stirred at rt for 1 h. Then, CH_2Cl_2 (10 mL) and saturated NH_4Cl(aq) (10 mL) were added to the mixture and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:9 to 2:8 EtOAc-hexane as eluent gave *O*-silyl-protected pyridone **71** (290 mg, 95%) as a colourless oil, R_F (2:8 EtOAc-hexane) 0.26; IR (ATR) 3075, 2954, 2929, 2883, 2857, 1651 (C=O), 1591, 1526, 1471, 1464, 1425 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 7.5 Hz, 1H, Ar), 6.79 (d, *J* = 2.0 Hz, 1H, Ar), 6.28 (dd, *J* = 7.5, 2.0 Hz, 1H, Ar), 4.00 (t, *J* = 4.5 Hz, 2H, CH_2), 3.85 (t, *J* = 4.5 Hz, 2H, CH_2), 0.84 s, 9H, $SiCMe_3$), -0.06 (s, *J* = 5.8 Hz, 6H, $SiMe_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.4 (C=O), 139.4 (Ar), 135.7 (*ipso*-Ar), 122.7 (Ar), 109.3 (Ar), 60.7 (OCH_2Ph), 52.1 (br, NCH_2), 25.9 ($SiCMe_3$), 18.2 ($SiCMe_3$), –5.6 ($SiMe_2$); HRMS (ESI) *m/z* calcd for $C_{13}H_{22}{}^{79}BrNO_2Si$ ($^{79}M + Na)^+$ 354.0495, found 354.0500 (–1.0 ppm error).

Lab book reference: **IMA-84**

Methyl 2-(4-bromo-1H-pyrazol-1-yl)acetate 72

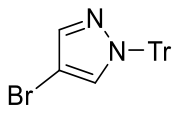


72

Methyl 2-bromoacetate (129 µL, 1.36 mmol, 1.00 eq.) was added dropwise to a stirred solution of K_2CO_3 (394.9 mg, 2.86 mmol, 2.10 eq.) and 4-bromo-1H-pyrazole **6** (200 mg, 1.36 mmol, 1.00 eq.) in anhydrous MeCN (10 mL) at 0 °C under Ar. The resulting solution was stirred and heated at reflux for 3 h under Ar. After being allowed to cool to rt, saturated $NH_4Cl_{(aq)}$ solution (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:7 EtOAc-hexane as eluent gave *N*-alkylated pyrazole **72** (215mg, 72%) as a yellow oil, R_F (3:7 EtOAc-hexane) 0.4; IR (ATR) 3132, 2955, 1747 (C=O), 1522, 1439, 1415 cm^{-1}; ^1H NMR (400 MHz, Acetone-d_6) δ 7.83 (s, 1H, Ar), 7.45 (s, 1H, Ar), 5.03 (s, 2H, NCH_2), 3.70 (s, 3H, OMe); ^{13}C NMR (100.6 MHz, Acetone-d_6) δ 167.7 (C=O), 139.9 (Ar), 130.9 (Ar), 93.1 (*ipso*-Ar), 52.9 (OMe), 52.0 (CH_2); HRMS (ESI) *m/z* calcd for $C_6H_7{}^{79}BrN_2O_2$ ($^{79}M + Na)^+$ 240.9583, found 240.9585 (–0.5 ppm error).

Lab book reference: **IMA-42**

4-Bromo-1-trityl-1H-pyrazole 73

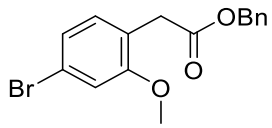


73

KO*t*Bu (1.38 g, 12.33 mmol, 1.2 eq.) and trityl chloride (3.15g, 11.30 mmol, 1.1.00 eq.) were added sequentially to a stirred suspension of 4-bromopyrazole **6** (1.51 g, 10.27 mmol, 1.0 eq.) in DMF (14.4 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 1 h. The reaction mixture was poured into EtOAc (50 mL) and H_2O (50 mL) and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were washed with saturated $NH_4Cl_{(aq)}$ (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a solid. The solid was dissolved in a minimum amount of EtOAc and warm hexane was added. The solution was allowed to cool slowly to rt and then cooled to 0 °C. The precipitated solid was collected by filtration to give bromopyrazole **73** (2.22 g, 55%) as a white solid, mp 178.2 – 180.5 °C (lit.,[26] 186 – 188 °C); IR (ATR) 3056, 2924, 1493, 1444, 1318, 939, 746, 698 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.64 (s, 1H, Ar), 7.47 (s, 1H, Ar), 7.40 – 7.33 (m, 9H, Ph), 7.17 – 7.11 (m, 6H, Ph); ^{13}C NMR (100.6 MHz, acetone-d_6) δ 143.9 (Ar), 140.7 (*ipso*-Ar), 133.3 (Ar), 131.4 (Ar), 128.9 (Ar), 128.7 (Ar), 93.1 (*ipso*-Ar), 80.3 (N*C*Ph_3); HRMS (ESI) *m/z* calcd for $C_{22}H_{17}{}^{79}BrN_2$ ($^{79}M + Na)^+$ 411.0467, found 411.0471 (–1.0 ppm error). Spectroscopic data consistent with those reported in the literature.[26]

Lab book reference: **IMA-15**

Benzyl 2-(4-bromo-2-methoxyphenyl)acetate 77



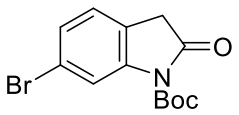
77

Benzyl bromide (0.29 mL, 2.45 mmol, 1.20 eq.) was added dropwise to a stirred solution of K_2CO_3 (338 mg, 2.45 mmol, 1.20 eq.) and 2-(4-bromo-2-methoxyphenyl)acetic acid **21** (500 mg, 2.04 mmol, 1.00 eq.) in acetone (10 mL) at rt under Ar. The resulting solution was stirred and heated

at reflux for 24 h under Ar. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give the crude product. H_2O (5 mL) was added and the solution was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with hexane to 0.5:9.5 EtOAc-hexane as eluent gave *O*-benzyl protected benzene **77** (639 mg, 93%) as a colourless oil, R_F (0.5:9.5 EtOAc-hexane) 0.34; IR (ATR) 2943, 1736 (C=O), 1594, 1456, 1445 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 5H, Ph), 7.06 – 7.01 (m, 2H, Ar), 6.98 (s, 1H, Ar), 5.14 (s, 2H, OCH_2Ph), 3.72 (s, 3H, OMe), 3.61 (s, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.2 (C=O), 158.2 (*ipso*-Ar), 136.1 (*ipso*-Ar), 132.1 (Ar), 128.6 (Ar), 128.3 (Ar), 123.6 (Ar), 122.2 (*ipso*-Ar), 121.8 (*ipso*-Ar), 114.2 (Ar), 66.5 (OCH_2Ph), 55.7 (OMe), 35.7 (CH_2); HRMS (ESI) *m/z* calcd for $C_{16}H_{15}{}^{79}BrO_3$ $(^{79}M + Na)^+$ 357.0097, found 357.0094 (+0.5 ppm error).

Lab book reference: **IMA-73**

tert-Butyl 6-bromo-2-oxoindoline-1-carboxylate 79



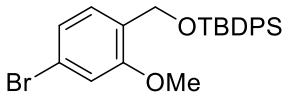
79

Di-*tert*-butyl dicarbonate (772 mg, 3.54 mmol, 1.5 eq.) was added to a stirred solution of $NaHCO_3$ (1.78 g, 21.2 mmol, 9.0 eq.) and 6-bromoindolin-2-one **12** (500 mg, 2.36 mmol, 1.00 eq.) in THF (25 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 16 h. After being allowed to cool to rt, the solids were removed by filtration and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:10 EtOAc-hexane as eluent gave *N*-Boc-protected oxindole **79** (174 mg, 24%) as a white

solid, mp 111.2 - 112.8 °C (lit.,[62] 95 - 97 °C); R_F (1:10 EtOAc-hexane) 0.32; IR (ATR) 3126, 2981, 2932, 1786 (C=O), 1770 (C=O), 1729 (C=O), 1664, 1607, 1586, 1477, 1420 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 2.0 Hz, 1H, Ar), 7.27 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar), 7.12 – 7.06 (m, 1H, Ar), 3.56 (s, 2H, CH_2), 1.63 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.5 (C=O, lactam), 149.1 (C=O, Boc), 142.1 (*ipso*-Ar), 127.3 (*ipso*-Ar), 125.5 (Ar), 122.1 (Ar), 121.7 (*ipso*-Ar), 118.7 (Ar), 85.0 (O*C*Me$_3$), 36.3 (CH_2), 28.1 (C*Me*$_3$); HRMS (ESI) *m/z* calcd for $C_{13}H_{14}{}^{79}BrNO_3$ ($^{79}M + Na)^+$ 334.0049, found 334.0050 (–2.9 ppm error).

Lab book reference: **IMA-102**

((4-Bromo-2-methoxybenzyl)oxy)(*tert*-butyl)diphenylsilane 80



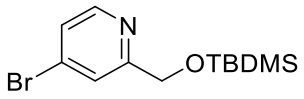
80

1H-imidazole (70.8 mg, 1.04 mmol, 1.5 eq.) was added to a stirred solution of (4-bromo-2-methoxyphenyl)methanol **18** (149.9 mg, 0.691 mmol, 1.00 eq.), DMAP (42.2 mg, 0.346 mmol, 0.5 eq.) and *tert*-butyl-chloro-diphenylsilane (0.196 mL, 0.622 mmol, 0.9 eq.) in dry CH_2Cl_2 (5 mL) at rt. The resulting solution was stirred at rt for 1 h. Then, CH_2Cl_2 (10 mL) and saturated NH_4Cl(aq) (10 mL) were added to the mixture and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:9 to 2:8 EtOAc-hexane as eluent gave *O*-silyl-protected benzene **80** (278 mg, 88%) as a colourless oil, R_F (1:9 EtOAc-hexane) 0.28; IR (ATR) 3071, 3049, 3000, 2958, 2931, 2893, 2857, 1594, 1487, 1472, 1462, 1444, 1428 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.76 (m, 4H, Ph), 7.69 – 7.65 (m, 1H, Ar), 7.54 – 7.41 (m, 6H, Ph), 7.24 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar), 7.00 (d, *J* = 2.0 Hz, 1H, Ar), 4.85 (s, 2H, OCH_2), 3.72 (s, 3H, OMe), 1.21 (s, 9H,

$SiCMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.6 (*ipso*-Ar), 135.6 (Ar), 133.6 (*ipso*-Ar), 129.8 (Ar), 128.0 (*ipso*-Ar), 127.8 (Ar), 123.5 (Ar), 128.8 (*ipso*-Ar), 113.2 (Ar), 60.7 (CH_2), 55.4 (OMe), 26.9 (Me_3), 19.4 (Si*C*Me_3); HRMS (APCI) *m/z* calcd for $C_{24}H_{27}{}^{79}BrO_2Si$ ($^{79}M)^+$ 455.1036, found 455.1034 (–0.1 ppm error).

Lab book reference: **IMA-21**

4-Bromo-2-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridine 82

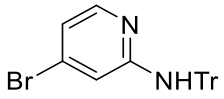


82

1H-imidazole (82 mg, 1.2 mmol, 1.5 eq.) was added to a stirred solution of (4-bromopyridin-2-yl)methanol **25** (150 mg, 0.80 mmol, 1.00 eq.), DMAP (49 mg, 0.40 mmol, 0.5 eq.) and *tert*-butyl-chloro-dimethylsilane (0.097 mL, 0.56 mmol, 1.0 eq.) in dry CH_2Cl_2 (5 mL) at rt. The resulting solution was stirred at rt for 1 h. Then, CH_2Cl_2 (10 mL) and saturated NH_4Cl(aq) (10 mL) were added to the mixture and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1.1:8.9 EtOAc-hexane as eluent gave *O*-silyl-protected pyridine **82** (206 mg, 85%) as a colourless oil, R_F (1.1:8.9 EtOAc-hexane) 0.35; IR (ATR) 2954, 2928, 2858, 1729, 1572, 1558, 1463 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 5.0 Hz, 1H, Ar), 7.67 (br s, 1H, Ar), 7.32 (dd, *J* = 5.0, 2.0 Hz, 1H, Ar), 4.80 (s, 2H, OCH_2), 0.96 (s, 9H, $SiCMe_3$), 0.12 (s, 6H, $SiMe_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.1 (*ipso*-Ar), 149.5 (Ar), 133.9 (Ar), 125.3 (Ar), 123.7 (Ar), 65.6 (CH_2), 26.0 (Si*C*Me_3), 18.1(Si*C*Me_3), -5.3 ($SiMe_2$). HRMS (ESI) *m/z* calcd for $C_{12}H_{20}{}^{79}BrNOSi$ ($^{79}M + H)^+$ 302.0570, found 302.0580 (–4.4 ppm error).

Lab book reference: **IMA-27**

4-Bromo-*N*-tritylpyridin-2-amine 83

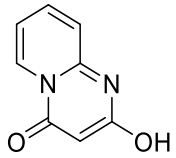


83

Trityl chloride (354 mg, 1.27 mmol, 1.10 eq.) was added to a stirred solution of 4-bromopyridin-2-amine **23** (1.51 g, 10.27 mmol, 1.0 eq.) in toluene (14.4 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 24 h. After being allowed to cool to rt, the solids were removed by filtration and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 2:8 to 4:6 Et_2O-hexane as eluent gave *N*-trityl-protected aminopyridine **83** (312 mg, 65%) as an off-white solid, mp 121.9 - 123.7 °C; R_F (4:6 Et_2O-hexane) 0.43; IR (ATR) 3058, 3032, 2973, 1660, 1579, 1490, 1448 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.00 (br s, 1H, NH), 7.85 (d, *J* = 6.5 Hz, 1H, Ar), 7.34 – 7.12 (m, 15H, Ph) , 6.89 (d, *J* = 6.5 Hz, 1H, Ar), 6.54 (s, 1H, Ar); HRMS (APCI) *m/z* calcd for $C_{24}H_{19}{}^{79}BrN_2$ $(^{79}M)^+$ 415.0804, found 415.0796 (+2.1 ppm error).

Lab book reference: **IMA-28**

2-Hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one 86



86

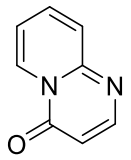
Diethyl malonate (0.356 mL, 2.34 mmol, 1.10 eq.) was added dropwise to a stirred solution of 2-aminopyridine **84** (200 mg, 2.13 mmol, 1.00 eq.) in Dowtherm A® (5 mL) at rt under Ar. The resulting mixture was stirred and heated at 275 °C (heating block temperature) for 4 h. After being allowed to cool to rt, Et_2O (50 mL) was added, and the precipitated solid was collected by filtration and washed with cold Et_2O (5 mL) give 2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one **86** (153 mg, 44%) as a light brown solid, mp 309.2-310.6 °C (lit.,[63] 312.4 (dec.)); IR (ATR) 3095, 1687 (C=O), 1609, 1583, 1518, 1481 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 8.87 (d, *J* = 7.0 Hz, 1H, Ar), 8.10 (dd, *J* = 8.5, 8.5 Hz, 1H, Ar), 7.43 (d, *J* = 8.5 Hz, 1H, Ar), 7.36 (dd, *J* = 7.0, 7.0 Hz, 1H, Ar), 5.17 (s, 1H, Ar); ^{13}C NMR (100.6 MHz, D_2O) δ 178.2 (C=O or *ipso*-Ar), 177.8 (C=O or *ipso*-Ar), 158.8 (*ipso*-Ar), 143.8 (Ar), 129.5 (Ar), 115.4 (Ar), 83.0 (Ar); HRMS (ESI) *m/z* calcd for $C_8H_6N_2O_2$ $(M + Na)^+$ 185.0321, found 185.0323 (+1.8 ppm error).

Lab book reference: **IMA-47**

Diethyl malonate (0.356 mL, 2.34 mmol, 1.10 eq.) was added dropwise to a stirred solution of 2-aminopyridine **84** (200 mg, 2.13 mmol, 1.00 eq.) in DMF (5 mL) at rt under Ar. The resulting mixture was stirred and heated at reflux for 4 h. After being allowed to cool to rt, Et_2O (50 mL) was added, and the precipitated solid was collected by filtration and washed with cold Et_2O (5 mL) give 2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one **86** (141 mg, 41%) as a light brown solid.

Lab book reference: **IMA-38**

4H-Pyrido[1,2-a]pyrimidin-4-one 91

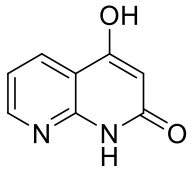


91

Methyl prop-2-ynoate (0.284 mL, 3.19 mmol, 1.50 eq.) was added dropwise to a stirred solution of 2-aminopyridine **84** (200 mg, 2.13 mmol, 1.00 eq.) in dry MeOH (5 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The solvent was evaporated under reduced pressure to give crude methyl 3-(pyridin-2-ylamino)acrylate as a bright red solid. The crude methyl 3-(pyridin-2-ylamino)acrylate was dissolved in Dowtherm A® (5 mL) and the resulting mixture was stirred and heated at 275 °C (heating block temperature) for 1 h. After being allowed to cools to rt, the mixture was poured into hexane (100 mL). The precipitated solid was collected by filtration and washed with hexane (3 x 5 mL) to give 4H-pyrido[1,2-a]pyrimidin-4-one **91** (117 mg, 38%) as a dark brown solid, mp 245.9 - 247.2 °Cx; IR (ATR) 3066, 3026, 1641 (C=O), 1595, 1579, 1544, 1450 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (d, *J* = 7.5 Hz, 1H, Ar), 8.18 (d, *J* = 7.5 Hz, 1H, Ar), 7.68 (dd, *J* = 9.0 Hz, 1.5 Hz, 1H, Ar), 7.14 (d, *J* = 9.0 Hz, 1H, Ar), 6.96 (dd, *J* = 7.0, 1.5 Hz, 1H, Ar), 6.41 (d, *J* = 7.5 Hz, 1H, Ar); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 168.0 (C=O or *ipso*-Ar), 152.0 (C=O or *ipso*-Ar), 140.2 (Ar), 137.4 (Ar), 134.8 (Ar), 123.4 (Ar), 116.2 (Ar), 113.2 (Ar); HRMS (ESI) *m/z* calcd for $C_8H_6N_2O$ $(M + Na)^+$ 169.0372, found 169.0372 (–0.9 ppm error).

Lab book reference: **IMA-49**

4-Hydroxy-[1,8]-naphthyridin-2(1H)-one 96



96

Using general procedure B, KO*t*Bu (370 mg, 1.31 mmol, 2.51 eq.) and methyl 2-aminonicotinate **95** (200 mg, 1.31 mmol, 1.00 eq.) in 1:1 EtOAc- Dowtherm® A (8 mL) at 200 °C for 4 h gave 4-hydroxy-[1,8]-naphthyridin-2(1H)-one **96** (132 mg, 62%) as a beige solid, mp 352 °C (dec.) (lit.,[64] 300 °C); IR (ATR) 3240 (br, OH), 2920, 2851, 1611 (C=O), 1561, 1401 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (br s, 1H, OH), 8.24 (dd, *J* = 4.5, 2.0 Hz, 1H, Ar), 8.06 (dd, *J* = 7.5, 2.0 Hz, 1H, Ar), 6.94 (dd, *J* = 7.5, 4.5 Hz, 1H, Ar), 4.97 (s, 1H, Ar); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 173.2 (*ipso*-Ar or C=O), 169.4 (*ipso*-Ar or C=O), 166.0 (*ipso*-Ar or C=O), 151.4 (*ipso*-Ar or C=O), 149.9 (Ar), 132.9 (Ar), 117.0 (Ar), 115.6 (*ipso*-Ar), 96.3 (Ar) (we believe that there is one extra resonance due to a hydroxy pyridine tautomeric form); HRMS (ESI) *m/z* calcd for $C_8H_6N_2O_2$ $(M + Na)^+$ 185.0321, found 185.0326 (–2.9 ppm error).

Lab book reference: **IMA-92**

Using general procedure B, KO*t*Bu (370 mg, 3.30 mmol, 2.51 eq.) and methyl 2-aminonicotinate **95** (200 mg, 1.31 mmol, 1.00 eq.) in 1:1 EtOAc-*o*-xylene (8 mL) at 144 °C for 16 h gave 4-hydroxy-[1,8]-naphthyridin-2(1H)-one **96** (75 mg, 35%) as a beige solid.

Lab book reference: **IMA-86**

Using general procedure B, KO*t*Bu (370 mg, 3.30 mmol, 2.51 eq.) and methyl 2-aminonicotinate **95** (200 mg, 1.31 mmol, 1.00 eq.) in 1:1 EtOAc-*o*-xylene (8 mL) at 144 °C for 4 h gave 4-hydroxy-[1,8]-naphthyridin-2(1H)-one **96** (70 mg, 33%) as a beige solid.

Lab book reference: **IMA-88**

Using general procedure B, KO*t*Bu (370 mg, 3.30 mmol, 2.51 eq.) and methyl 2-aminonicotinate **95** (200 mg, 1.31 mmol, 1.00 eq.) in EtOAc (8 mL) at 77 °C for 4 h gave 4-hydroxy-[1,8]-naphthyridin-2(1H)-one **96** (36 mg, 17%) as a beige solid.

Lab book reference: **IMA-90**

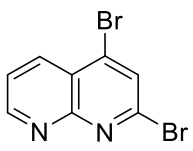
Using general procedure B, KO*t*Bu (370 mg, 3.30 mmol, 2.51 eq.) and methyl 2-aminonicotinate **95** (200 mg, 1.31 mmol, 1.00 eq.) in 1:1 EtOAc- Dowtherm® A (8 mL) at 280 °C (heating block temperature) for 4 h gave 4-hydroxy-[1,8]-naphthyridin-2(1H)-one **96** (128 mg, 60%) as a beige solid.

Lab book reference: **IMA-93**

Using general procedure B, KO*t*Bu (3.48 g, 31.0 mmol, 2.51 eq.) and methyl 2-aminonicotinate **95** (1.88 g, 12.36 mmol, 1.00 eq.) in 1:1 EtOAc- Dowtherm® A (76 mL) at 200 °C for 4 h gave the crude product. Purification by recrystallisation from hot EtOH gave 4-hydroxy-[1,8]-naphthyridin-2(1H)-one **96** (874 mg, 44%) as a beige solid.

Lab book reference: **IMA-96**

2,4-Dibromo-[1,8]-naphthyridine 86



86

4-Hydroxy-[1,8]-naphthyridin-2(1H)-one **96** (47 mg, 0.29 mmol, 1.00 eq.) and $POBr_3$ (833 mg, 2.91 mmol, 10.00 eq.) were added to a Schlenk tube shaped cylindrical glass vessel. With stirring, the solids were slowly heated to 70 °C until all of the $POBr_3$ had melted and a solution was obtained. The resulting solution was stirred and heated at 175 °C for 2 h. After being allowed to cool to rt, the reaction mixture was cooled to 0 °C and saturated $NaHCO_{3(aq)}$ solution (10 mL) was added slowly and dropwise with vigorous stirring (Caution, exotherm and release of HBr fumes!). The reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 0.5:9.5 acetone-CH_2Cl_2 as eluent gave dibromo naphthyridine **86** (47 mg, 56%) as a white solid, mp 126.1 - 127.4 °C (lit.,[47] 134 - 135 °C); R_F (0.5:9.5, acetone-CH_2Cl_2) 0.31; IR (ATR) 3097, 3061, 3035, 1595, 1569, 1544, 1472 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.13 (dd, *J* = 4.0, 2.0 Hz, 1H, Ar), 8.54 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar), 7.94 (s, 1H, Ar), 7.62 (dd, *J* = 8.5, 4.0 Hz, 1H, Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.7 (*ipso*-Ar), 155.2 (Ar), 144.6 (*ipso*-Ar), 136.6 (Ar), 135.1 (*ipso*-Ar), 130.2 (Ar), 123.6 (Ar), 122.3 (*ipso*-Ar); HRMS (ESI) *m/z* calcd for $C_8H_4{}^{79}Br_2N_2$ ($^{79,79}M + Na)^+$ 308.8633, found 308.8631 (–0.3 ppm error).

Lab book reference: **IMA-87**

4-Hydroxy-[1,8]-naphthyridin-2(1H)-one **96** (31 mg, 0.19 mmol, 1.00 eq.) and $POBr_3$ (545 mg, 1.90 mmol, 10.0 eq.) were added to a Schlenk tube shaped cylindrical glass vessel fitted with a side-arm. With stirring, the solids were slowly heated to 70 °C until all of the $POBr_3$ had melted and a solution was obtained. The resulting solution was stirred and heated at 175 °C for 2 h. After being allowed to cool to rt, the reaction mixture was cooled to 0 °C and saturated $NaHCO_{3(aq)}$ solution (10 mL) was added slowly and dropwise with vigorous stirring (Caution, exotherm and release of HBr fumes!). The reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica

with 0.5:9.5 acetone-CH_2Cl_2 as eluent gave dibromo naphthyridine **86** (25 mg, 45%) as a white solid.

Lab book reference: **IMA-98**

4-Hydroxy-[1,8]-naphthyridin-2(1H)-one **96** (150 mg, 0.93 mmol, 1.00 eq.) and $POBr_3$ (2.65 g, 9.25 mmol, 10.00 eq.) were added to a Schlenk tube shaped cylindrical glass vessel fitted with a side-arm. With stirring, the solids were slowly heated to 70 °C until all of the $POBr_3$ had melted and a solution was obtained. The resulting solution was stirred and heated at 175 °C for 4 h. After being allowed to cool to rt, the reaction mixture was cooled to 0 °C and saturated $NaHCO_{3(aq)}$ solution (50 mL) was added slowly and dropwise with vigorous stirring (Caution, exotherm and release of HBr fumes!). The reaction mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 0.5:9.5 acetone-CH_2Cl_2 as eluent gave dibromo naphthyridine **86** (145 mg, 54%) as a white solid.

Lab book reference: **IMA-99**

$POBr_3$ (351 mg, 2.82 mmol, 3.00 eq.) was added to a stirred suspension of 4-hydroxy-[1,8]-naphthyridin-2(1H)-one **96** (636 mg, 3.93 mmol, 1.00 eq.) in *o*-xylene (5 mL) at rt in a Schlenk tube shaped cylindrical glass vessel fitted with a side-arm. The resulting solution was stirred and heated at 175 °C for 4 h. After being allowed to cool to rt, the reaction mixture was cooled to 0 °C and saturated $NaHCO_{3(aq)}$ solution (120 mL) was added slowly and dropwise with vigorous stirring (Caution, exotherm and release of HBr fumes!). The reaction mixture was extracted with EtOAc (3 × 120 mL). The combined organic layers were washed with brine (120 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 0.5:9.5 acetone-CH_2Cl_2 as eluent gave dibromo naphthyridine **86** (444 mg, 39%) as a white solid.

Lab book reference: **IMA-108**

4-Bromo-[1,8]-naphthyridine 28

28

Tosyl hydrazine (292 mg, 1.57 mmol, 1.00 eq.) was added to a stirred solution of dibromo naphthyridine **86** (451 mg, 1.57 mmol, 1.00 eq.) in *o*-xylene (15 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 24 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give a residue. The residue was dissolved in $Na_2CO_{3(aq)}$ (13.3 mL of a 0.377 M solution in H_2O, 5.02 mmol, 3.2 eq.). Then, the resulting solution was stirred and heated at reflux for 2 h. After being allowed to cool to rt, $CHCl_3$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with $CHCl_3$ (5 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc as eluent gave bromo naphthyridine **28** (79 mg, 24%) as a purple oil, R_F (EtOAc) 0.15; IR (ATR) 3036, 2926, 1669, 1586, 1546, 1478, 1461, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.15 (dd, *J* = 4.5, 2.0 Hz, 1H, Ar), 8.92 (d, *J* = 4.5 Hz, 1H, Ar), 8.56 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar), 7.78 (d, *J* = 4.5 Hz, 1H, Ar), 7.60 (dd, *J* = 8.5, 4.5 Hz, 1H, Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.5 (Ar), 154.6 (Ar), 153.2 (Ar), 136.5 (Ar), 134.4 (*ipso*-Ar), 126.0 (Ar), 123.4 (Ar), 123.3 (Ar); HRMS (ESI) *m/z* calcd for $C_8H_5{}^{79}BrN_2$ ($^{79}M + Na)^+$ 230.9528, found 230.9528 (–3.1 ppm error).

Lab book reference: **IMA-112**

Tosyl hydrazine (7 mg, 0.037 mmol, 1.05 eq.) was added to a stirred solution of dibromo naphthyridine **86** (10 mg, 0.035 mmol, 1.00 eq.) in $CHCl_3$ (5 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 24 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give a residue. The residue was dissolved in $Na_2CO_{3(aq)}$ (5 mL of a 0.377 M solution in H_2O, 1.89 mmol, 54.0 eq.). Then, the resulting solution was stirred and heated at reflux for 2 h. After being allowed to cool to rt, $CHCl_3$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with $CHCl_3$ (5 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. None of the desired product was observed in the ^1H NMR spectrum of the crude product.

Lab book reference: **IMA-109**

Tosyl hydrazine (7 mg, 0.037 mmol, 1.05 eq.) was added to a stirred solution of dibromo naphthyridine **86** (10 mg, 0.035 mmol, 1.00 eq.) in toluene (5 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 24 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give a residue. The residue was dissolved in $Na_2CO_{3(aq)}$ (5 mL of a 0.377 M solution in H_2O, 1.89 mmol, 54.0 eq.). Then, the resulting solution was stirred and heated at reflux for 2 h. After being allowed to cool to rt, $CHCl_3$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with $CHCl_3$ (5 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc as eluent gave bromo naphthyridine **28** (2.3 mg, 17%) as a purple oil.

Lab book reference: **IMA-110**

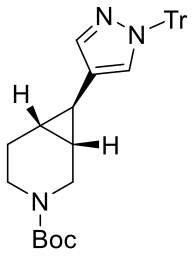
Tosyl hydrazine (7 mg, 0.037 mmol, 1.05 eq.) was added to a stirred solution of dibromo naphthyridine **86** (10 mg, 0.035 mmol, 1.00 eq.) in *o*-xylene (5 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 24 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give a residue. The residue was dissolved in $Na_2CO_{3(aq)}$ (5

mL of a 0.377 M solution in H_2O, 1.89 mmol, 54.0 eq.). Then, the resulting solution was stirred and heated at reflux for 2 h. After being allowed to cool to rt, $CHCl_3$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with $CHCl_3$ (5 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc as eluent gave bromo naphthyridine **28** (9.2 mg, 20%) as a purple oil.

Lab book reference: **IMA-111**

5.3.2 Experimental for Chapter 3

***tert*-Butyl 7-(1-trityl-1H-pyrazol-4-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate *exo*-125**



exo-**125**

Using general procedure D, MIDA boronate *exo*-**38** (88 mg, 0.25 mmol, 1.0 eq.), Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq.), aryl bromide **73** (136.3 mg, 0.35 mmol, 1.4 eq.), $Pd(OAc)_2$ (2.8 mg, 0.01 mmol, 0.05 eq.) and PCy_3 (7.0 mg, 0.02 mmol, 0.10 eq.) in toluene (5 mL) and H_2O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 3:7 EtOAc-hexane as eluent gave arylated piperidine *exo*-**125** (81.3 mg, 64%) as a colourless oil which solidified upon standing to a white solid, mp 153.9 - 154.7 °C; R_F (3:7 EtOAc-hexane) 0.45; IR (ATR) 3059, 2927, 2856, 2246, 1688 (C=O), 1598, 1542, 1492, 1477, 1466, 1446, 1421 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H, Ar), 7.33 – 7.27 (m, 9H, Ar), 7.21 – 7.08 (m, 7H, Ar), 4.01 – 3.73 (m, 1H, NCH), 3.55 (dd, J = 13.5, 4.5 Hz, 1H, NCH), 3.46 – 3.26 (br m, 1H, NCH), 3.13 – 2.88 (br m, 1H, NCH), 2.04 – 1.92 (m, 1H, CH), 1.78 (br s, 1H, CH), 1.46 (s, 10H, CMe_3, C*H*Ar), 1.31 – 1.11

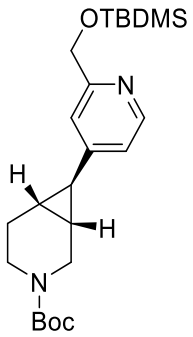
(m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.2 (C=O), 143.5 (*ipso*-Ar), 137.4 (Ar), 130.2 (Ar), 127.9 (Ar), 127.8 (Ar), 127.7 (Ar), 122.1 (*ipso*-Ar), 79.5 (N*C*Ph$_3$), 78.5 (O*C*Me$_3$), 41.2 (br, NCH_2), 39.7 (br, NCH_2), 28.6 (C*Me*$_3$), 22.9 (CH), 20.5 (CH_2), 17.7 (CH) (CH resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{33}H_{35}N_3O_2$ $(M + Na)^+$ 528.2621, found 528.2636 (–2.6 ppm error).

Lab book reference: **IMA-20**

Using general procedure D, MIDA boronate *exo*-**38** (88 mg, 0.25 mmol, 1.0 eq.), Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq.), aryl bromide **73** (136.3 mg, 0.35 mmol, 1.4 eq.), $Pd(OAc)_2$ (2.8 mg, 0.01 mmol, 0.05 eq.) and PCy_3 (7.0 mg, 0.02 mmol, 0.10 eq.) in toluene (5 mL) and H_2O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 3:7 EtOAc-hexane as eluent gave arylated piperidine *exo*-**125** (72 mg, 57%) as a colourless oil which solidified upon standing to a white solid.

Lab book reference: **IMA-22**

tert-Butyl 7-(2-(((_tert_-butyldimethylsilyl)oxy)methyl)pyridin-4-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate _exo_-128

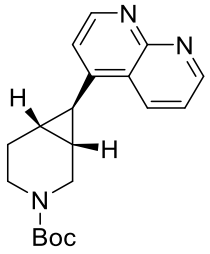


exo-**128**

Using general procedure C, MIDA boronate *exo*-**38** (88 mg, 0.25 mmol, 1.0 eq.), Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq.), aryl bromide **82** (105.8 mg, 0.35 mmol, 1.4 eq.), $Pd(OAc)_2$ (2.8 mg, 0.01 mmol, 0.05 eq.) and PCy_3 (7.0 mg, 0.02 mmol, 0.10 eq.) in toluene (5 mL) and H_2O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 1:9 to 4:6 EtOAc-hexane as eluent gave arylated piperidine *exo*-**128** (81.3 mg, 78%) as a golden oil, R_F (4:6 EtOAc-

hexane) 0.37; IR (ATR) 2954, 2928, 2857, 1968, 1697 (C=O), 1605, 1557, 1463, 1421 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 5.0 Hz, 1H, Ar), 7.14 – 7.10 (s, 1H, Ar), 6.75 (d, *J* = 5.0 Hz, 1H, Ar), 4.78 (s, 2H, OCH_2), 3.99 (d, *J* = 13.5 Hz, 1H, NCH), 3.57 (d, *J* = 13.5 Hz, 1H, NCH), 3.55 – 3.35 (br m, 1H, NCH), 3.10 – 2.90 (m, 1H, NCH), 2.09 – 1.98 (m, 1H, CH), 1.95 – 1.79 (m, 1H, CH), 1.65 – 1.61 (dd, *J* = 4.5, 4.5 Hz, 1H, CHAr), 1.60 – 1.59 (m, 2H, CH), 1.48 (s, 9H, CMe_3), 0.97 (s, 9H, $SiCMe_3$), 0.12 (s, 6H, $SiMe_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.1 (*ipso*-Ar), 155.1 (C=O), 153.3 (*ipso*-Ar), 148.4 (Ar), 118.8 (Ar), 116.6 (Ar), 79.7 ($OCMe_3$), 66.0 (OCH_2), 42.4 (NCH_2), 38.8 (NCH_2), 28.5 (CMe_3), 26.0 ($SiCMe_3$), 23.4 (CH), 21.7 (CH_2), 18.5 ($SiCMe_3$), –5.3 ($SiMe_2$), –5.6 ($SiMe_2$) (two CH resonances not resolved); HRMS (ESI) *m/z* calcd for $C_{23}H_{38}N_2O_3Si$ $(M + H)^+$ 419.2724, found 419.2736 (–3.0 ppm error).
Lab book reference: **IMA-76**

***tert*-Butyl 7-([1,8]-naphthyridin-4-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate *exo*-127**

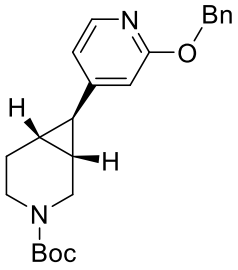


exo-**127**

Using general procedure C, MIDA boronate *exo*-**38** (88 mg, 0.25 mmol, 1.0 eq.), Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq.), aryl bromide **28** (73.2 mg, 0.35 mmol, 1.4 eq.), $Pd(OAc)_2$ (2.8 mg, 0.01 mmol, 0.05 eq.) and PCy_3 (7.0 mg, 0.02 mmol, 0.10 eq.) in toluene (5 mL) and H_2O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 3:7 acetone-toluene gave impure product. Purification by flash column chromatography on silica with 5:5 acetone-CH_2Cl_2 and then 3:7 acetone-toluene as eluent gave impure product. Purification by flash column chromatography on silica with 5:5 acetone-CH_2Cl_2 as eluent gave arylated piperidine *exo*-**127** (53.8 mg, 64%) as a dark red oil, R_F (5:5 acetone-CH_2Cl_2) 0.31; IR (ATR) 2974, 2926, 2857, 1686 (C=O), 1602, 1592, 1560, 1501, 1466, 1449, 1421 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.11 (dd, *J* = 4.0, 2.0 Hz, 1H, Ar), 8.96 (d, *J* = 4.5 Hz, 1H, Ar), 8.56 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar), 7.52 (dd,

J = 8.5, 4.0 Hz, 1H, Ar), 7.03 (d, *J* = 4.5 Hz, 1H, Ar), 4.42 – 4.10 (br m, 1H, NCH), 3.83 – 3.61 (br m, 1H, NCH), 3.61 – 3.36 (br m, 1H, NCH), 3.03 – 2.91 (br m, 1H, NCH), 2.15 (dd, *J* = 5.0, 5.0 Hz, 1H, CHAr), 2.12 – 2.05 (m, 1H, CH), 2.03 – 1.90 (br m, 1H, CH), 1.70 – 1.64 (m, 1H, CH), 1.49 (s, 9H, CMe_3), 1.47 – 1.43 (m, 1H, CH), 1.27 – 1.20 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.2 (*ipso*-Ar), 155.0 (C=O, Boc), 153.5 (Ar), 153.4 (Ar), 150.7 (*ipso*-Ar), 133.6 (Ar), 123.2 (*ipso*-Ar), 121.9 (Ar), 117.5 (Ar), 80.0 (O*C*Me_3), 43.5 (br, NCH_2), 41.3 (br, NCH_2), 29.8 (CH_2), 28.6 (C*Me*$_3$), 23.4 (CH), 22.0 (CH) (one CH resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{19}H_{23}N_3O_2$ $(M + Na)^+$ 348.1682, found 348.1690 (–3.6 ppm error).
Lab book reference: **IMA-113**

***tert*-Butyl 7-(2-(benzyloxy)pyridin-4-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate *exo*-127**



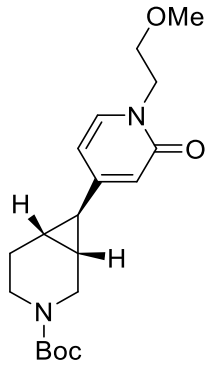
exo-**127**

Using general procedure C, MIDA boronate *exo*-**38** (88 mg, 0.25 mmol, 1.0 eq.), Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq.), aryl bromide **67** (92.4 mg, 0.35 mmol, 1.4 eq.), $Pd(OAc)_2$ (2.8 mg, 0.01 mmol, 0.05 eq.) and PCy_3 (7.0 mg, 0.02 mmol, 0.10 eq.) in toluene (5 mL) and H_2O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 2.2:7.8 EtOAc-hexane as eluent gave arylated piperidine *exo*-**127** (78.9 mg, 83%) as a colourless oil, R_F (2.2:7.8 EtOAc-hexane) 0.3; IR (ATR) 2975, 2929, 2858, 1688 (C=O), 1609, 1554, 1478, 1417 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 5.0 Hz, 1H, Ar), 7.46 – 7.26 (m, 5H, Ar), 6.52 (d, *J* = 5.0 Hz, 1H, Ar), 6.40 (s, 1H, Ar), 5.33 (s, 2H, OCH_2Ph), 3.95 (d, *J* = 14.0 Hz, 1H, NCH), 3.56 (dd, *J* = 14.0, 4.5 Hz, 1H, NCH), 3.41 – 3.31 (br m, 1H, NCH), 3.09 – 2.84 (br m, 1H, NCH), 2.07 – 1.95 (m, 1H, CH), 1.92 – 1.76 (br m, 1H, CH), 1.57 (dd, *J* = 4.5, 4.5 Hz, 1H, CHAr), 1.47 (s, 9H, CMe_3), 1.45 – 1.35 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.0 (*ipso*-Ar), 155.5 (C=O), 155.2 (*ipso*-Ar), 146.5 (Ar), 137.5 (*ipso*-Ar), 128.5 (Ar), 128.0 (Ar), 127.9 (Ar), 114.9 (Ar), 107.2 (Ar),

79.8 (O*C*Me$_3$), 67.6 (O*C*H$_2$Ph), 42.2 (br, NCH$_2$), 40.0 (br, NCH$_2$), 29.8 (CH$_2$), 28.6 (C*Me*$_3$), 26.9 (CH), 23.1 (CH), 21.4 (CH); HRMS (ESI) *m/z* calcd for $C_{23}H_{28}N_2O_3$ $(M + H)^+$ 381.2173, found 381.2178 (–2.2 ppm error).

Lab book reference: **IMA-61**

***tert*-Butyl 7-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-4-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate *exo*-128**

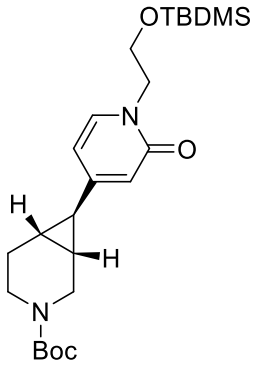


exo-**128**

Using general procedure C, MIDA boronate *exo*-**38** (88 mg, 0.25 mmol, 1.0 eq.), Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq.), aryl bromide **3** (81.2 mg, 0.35 mmol, 1.4 eq.), $Pd(OAc)_2$ (2.8 mg, 0.01 mmol, 0.05 eq.) and PCy_3 (7.0 mg, 0.02 mmol, 0.10 eq.) in toluene (5 mL) and H_2O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 1:9 MeOH-EtOAc as eluent gave impure product. Purification by flash column chromatography on silica with with 3:7 acetone-CH_2Cl_2 as eluent gave arylated piperidine *exo*-**128** (67.1 mg, 77%) as a light yellow oil, R_F (1:9 MeOH-EtOAc) 0.31; IR (ATR) 2925, 2856, 1687 (C=O, Boc), 1655 (C=O, pyridone), 1583, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 7.0 Hz, 1H, Ar), 6.08 (s, 1H, Ar), 5.74 (d, *J* = 7.0 Hz, 1H, Ar), 3.99 (t, *J* = 5.0 Hz, 2H, CH_2), 3.88 (d, *J* = 14.0 Hz, 1H, NCH), 3.57 (t, *J* = 5.0, 2H, CH_2), 3.51 – 3.28 (m, 2H, NCH), 3.24 (s, 3H, OMe), 2.98 – 2.79 (m, 1H, NCH), 2.00 – 1.88 (m, 1H, CH), 1.74 (br s, 1H, CH), 1.44-1.33 (br m 3H, CH, CHAr,), 1.39 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.4 (C=O, pyridone), 156.7 (*ipso*-Ar), 155.1 (C=O, Boc), 138.2 (Ar), 114.2 (Ar), 104.6 (Ar), 79.7 (O*C*Me_3), 70.5 (OCH_2), 59.0 (OMe), 49.2 (NCH_2), 41.4 (NCH_2), 39.9 (NCH_2), 29.7 (CH_2), 29.4 (CH), 28.5 (C*Me*$_3$), 26.9 (CH), 22.7 (CH), 21.1 (CH); HRMS (ESI) *m/z* calcd for $C_{19}H_{28}N_2O_4$ $(M + Na)^+$ 371.1941, found 371.1955 (–3.6 ppm error).

Lab book reference: **IMA-70**

***tert*-Butyl 7-(1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-oxo-1,2-dihydropyridin-4-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate *exo*-129**

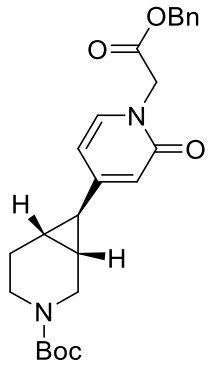


exo-**129**

Using general procedure C, MIDA boronate *exo*-**38** (88 mg, 0.25 mmol, 1.0 eq.), Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq.), aryl bromide **71** (116.3 mg, 0.35 mmol, 1.4 eq.), $Pd(OAc)_2$ (2.8 mg, 0.01 mmol, 0.05 eq.) and PCy_3 (7.0 mg, 0.02 mmol, 0.10 eq.) in toluene (5 mL) and H_2O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 EtOAc-hexane as eluent gave arylated piperidine *exo*-**129** (84.1 mg, 75%) as a colourless oil, R_F (9:1 EtOAc-hexane) 0.35; IR (ATR) 2927, 2856, 1697 (C=O, Boc), 1661 (C=O, pyridine), 1597, 1530, 1464, 1421 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 7.0 Hz, 1H, Ar), 6.07 (s, 1H, Ar), 5.73 (d, *J* = 7.0 Hz, 1H, Ar), 3.93 (t, *J* = 5.0 Hz, 2H, CH_2), 3.95 – 3.84 (br m, 1H, NCH), 3.78 (t, *J* = 5.0 Hz, 2H, CH_2), 3.46 (dd, *J* = 13.5, 4.5 Hz, 1H, NCH), 3.44 – 3.26 (br m, 1H, NCH), 2.96 – 2.84 (br m, 1H, NCH), 2.01 – 1.88 (m, 1H, CH), 1.84– 1.71 (br m, 2H, CH), 1.69 – 1.48 (m 1H, CH), 1.37 (s, 9H, CMe_3), 1.37 – 1.29 (m, 2H, CH, CHAr), 0.78 (s, 9H, $SiCMe_3$), –0.13 (s, 6H, $SiMe_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.5 (C=O, pyridone), 156.7 (*ipso*-Ar), 155.1 (C=O, Boc), 138.7 (Ar), 114.1 (Ar), 104.2 (Ar), 79.8 (O*C*Me_3), 61.1 (OCH_2), 51.9 (NCH_2), 39.7 (NCH_2), 37.5 (NCH_2), 32.0 (CH_2), 30.1 (CH_2), 29.8 (CH), 28.6 (OC*Me*$_3$), 25.9 (SiC*Me*$_3$), 22.7 (CH), 21.0 (CH), 18.2 (Si*C*Me_3), –5.6 ($SiMe_2$); HRMS (ESI) *m/z* calcd for $C_{24}H_{40}N_2O_4Si$ $(M + Na)^+$ 471.265, found 471.2656 (–1.5 ppm error).

Lab book reference: **IMA-85**

***tert*-Butyl 7-(1-(2-(benzyloxy)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-4-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate *exo*-130**

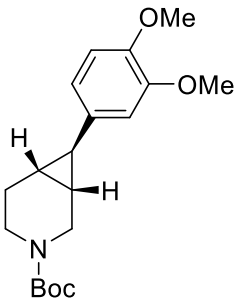


exo-**130**

Using general procedure D, MIDA boronate *exo*-**38** (88 mg, 0.25 mmol, 1.0 eq.), Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq.), aryl bromide **69** (112.8 mg, 0.35 mmol, 1.4 eq.), $Pd(OAc)_2$ (2.8 mg, 0.01 mmol, 0.05 eq.) and PCy_3 (7.0 mg, 0.02 mmol, 0.10 eq.) in toluene (5 mL) and H_2O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 EtOAc-hexane as eluent gave arylated piperidine *exo*-**130** (59.6 mg, 54%) as a light yellow solid, mp 104.6 - 105.3 °C; R_F (8:2 EtOAc-hexane) 0.28; IR (ATR) 2975, 2931, 2859, 1750 (C=O, ester), 1660 (C=O), 1592, 1530, 1477, 1455, 1416 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H, Ar), 7.05 (d, *J* = 7.0 Hz, 1H, Ar), 6.17 (s, 1H, Ar), 5.85 (d, *J* = 7.0 Hz, 1H, Ar), 5.18 (s, 2H, OCH_2Ph), 4.62 (s, 2H, NCH_2), 3.94 (d, *J* = 14.0 Hz, 1H, NCH), 3.50 (dd, *J* = 14.0, 4.5 Hz, 1H, NCH), 3.61 – 3.36 (m, 1H, NCH), 3.01 – 2.87 (br m, 1H, NCH), 2.06 – 1.93 (m, 1H, CH), 1.90 – 1. 54 (br m, 2H, CH), 1.48 – 1.44 (m, 11H, CMe_3, CH), 1.36 – 1.16 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.9 (C=O, ester), 162.3 (C=O, pyridone), 157.5 (*ipso*-Ar), 155.1 (C=O, Boc), 137.0 (Ar), 135.2 (*ipso*-Ar), 128.7 (Ar), 128.6 (Ar), 128.5 (Ar), 114.4 (Ar), 79.8 ($OCMe_3$), 67.6 (OCH_2), 50.0 (NCH_2), 42.2 (NCH_2), 40.9 (NCH_2), 28.6 (CMe_3), 27.1 (CH), 22.9 (CH), 21.3 (CH) (Ar and CH_2 resonances not resolved); HRMS (ESI) *m/z* calcd for $C_{25}H_{30}N_2O_5$ $(M + Na)^+$ 461.2047, found 461.2053 (–2.6 ppm error).

Lab book reference: **IMA-60**

***tert*-Butyl 7-(3,4-dimethoxyphenyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate *exo*-131**

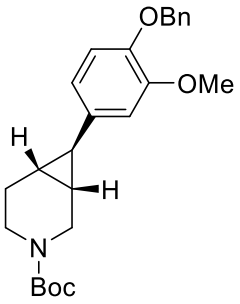


exo-**131**

Using general procedure C, MIDA boronate *exo*-**38** (88 mg, 0.25 mmol, 1.0 eq.), Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq.), aryl bromide **22** (76 mg, 0.35 mmol, 1.4 eq.), $Pd(OAc)_2$ (2.8 mg, 0.01 mmol, 0.05 eq.) and PCy_3 (7.0 mg, 0.02 mmol, 0.10 eq.) in toluene (5 mL) and H_2O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 1:9 to 2:8 EtOAc-hexane as eluent gave arylated piperidine *exo*-**131** (51.8 mg, 62%) as a yellow oil, R_F (2:8 EtOAc-hexane) 0.13; IR (ATR) 2932, 2857, 1688 (C=O), 1588, 1517, 1465, 1420 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.0 Hz, 1H, Ar), 6.58 – 6.51 (m, 2H, Ar), 3.98 – 3.88 (br m, 1H, NCH), 3.86 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.62 – 3.53 (br m, 1H, NCH), 3.47 – 3.43 (br m, 1H, NCH), 3.06 – 2.95 (br m, 1H, NCH), 2.08 – 1.95 (m, 1H, CH), 1.93 – 1.74 (br m, 1H, CH), 1.61 (dd, *J* = 5.0, 5.0 Hz, 1H, CHAr), 1.47 (s, 9H, CMe_3), 1.40 – 1.22 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.3 (C=O), 149.0 (*ipso*-Ar), 147.2 (*ipso*-Ar), 135.5 (*ipso*-Ar), 117.2 (Ar), 111.5 (Ar), 109.5 (Ar), 79.5 (O*C*Me_3), 56.1 (OMe), 55.9 (OMe), 42.6 (br, NCH_2), 41.0 (br, NCH_2), 28.6 (C*Me*$_3$), 27.2 (CH), 21.3 (CH), 19.1 (br, CH) (one CH_2 resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{19}H_{27}NO_4$ $(M + Na)^+$ 356.1832, found 356.1843 (–3.7 ppm error).

Lab book reference: **IMA-71**

***tert*-Butyl 7-(4-(benzyloxy)-3-methoxyphenyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate *exo*-132**

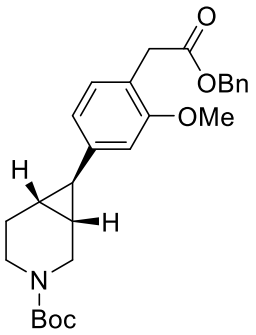


exo-**132**

Using general procedure D, MIDA boronate *exo*-**38** (88 mg, 0.25 mmol, 1.0 eq.), Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq.), aryl bromide **75** (102.6 mg, 0.35 mmol, 1.4 eq.), $Pd(OAc)_2$ (2.8 mg, 0.01 mmol, 0.05 eq.) and PCy_3 (7.0 mg, 0.02 mmol, 0.10 eq.) in toluene (5 mL) and H_2O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 1:9 to 2:8 EtOAc-hexane as eluent gave arylated piperidine *exo*-**132** (75 mg, 73%) as an orange solid, mp 107.8 - 109.2 °C; R_F (2:8 EtOAc-hexane) 0.27; IR (ATR) 2927, 2857, 1687 (C=O), 1588, 1514, 1453, 1419 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.25 (m, 5H, Ar), 6.76 (d, *J* = 8.5 Hz, 1H, Ar), 6.58 (br s, 1H, Ar), 6.46 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar), 5.09 (s, 2H, OCH_2Ph), 3.93 (d, *J* = 13.0 Hz, 1H, NCH), 3.86 (s, 3H, OMe), 3.57 (dd, *J* = 13.0, 5.0 Hz, 1H, NCH), 3.52 – 3.36 (br m, 1H, NCH), 3.00 (ddd, *J* = 14.0, 9.0, 5.0 Hz, 1H, NCH), 2.07 – 1.94 (m, 1H, CH), 1.83 (br m, 1H, CH), 1.59 (dd, *J* = 5.0, 5.0 Hz, 1H, CHAr), 1.47 (s, 9H, CMe_3), 1.43 – 1.30 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 155.3 (C=O), 149.8 (*ipso*-Ar), 146.3 (*ipso*-Ar), 137.5 (*ipso*-Ar), 136.3 (*ipso*-Ar), 128.7 (Ar), 127.8 (Ar), 127.4 (Ar), 117.2 (Ar), 114.7 (Ar), 110.0 (Ar), 79.5 ($OCMe_3$), 71.5 (OCH_2), 71.4 (OCH_2), 56.1 (OMe), 42.5(br, NCH_2), 41.0 (br, NCH_2), 29.8 (CH), 28.6 (CMe_3), 27.2 (CH), 22.8 (CH), 21.4 (CH), 19.9 (CH); HRMS (ESI) *m/z* calcd for $C_{25}H_{31}NO_4$ $(M + Na)^+$ 432.2145, found 432.2157 (–2.8 ppm error).

Lab book reference: **IMA-66**

tert-Butyl 7-(4-(2-(benzyloxy)-2-oxoethyl)-3-methoxyphenyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate *exo*-133

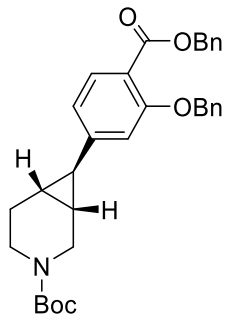


exo-**133**

Using general procedure D, MIDA boronate *exo*-**38** (88 mg, 0.25 mmol, 1.0 eq.), Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq.), aryl bromide **77** (117.3 mg, 0.35 mmol, 1.4 eq.), $Pd(OAc)_2$ (2.8 mg, 0.01 mmol, 0.05 eq.) and PCy_3 (7.0 mg, 0.02 mmol, 0.10 eq.) in toluene (5 mL) and H_2O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 1:9 to 2:8 EtOAc-hexane as eluent gave arylated piperidine *exo*-**133** (90 mg, 82%) as a light yellow oil, R_F (2:8 EtOAc-hexane) 0.13; IR (ATR) 2928, 2856, 1739 (C=O, ester), 1691 (C=O, Boc), 1615, 1581, 1514, 1498, 1455, 1421 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 5H, Ar), 7.04 (d, J = 8.0 Hz, 1H, Ar), 6.57 – 6.46 (m, 2H, Ar), 5.12 (s, 2H, OCH_2), 3.92 (d, J = 13.5 Hz, 1H, NCH), 3.72 (s, 3H, OMe), 3.63 – 3.34 (br m, 4H, NCH, CH), 3.07 – 2.95 (br m, 1H, NCH), 2.08 – 1.96 (m, 1H, CH), 1.91 – 1.76 (m, 1H, CH), 1.63 (dd, J = 5.0, 5.0 Hz, 1H, CHAr), 1.47 (s, 9H, CMe_3), 1.42-1.32 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.9 (C=O, ester), 157.6 (*ipso*-Ar), 155.3 (C=O, Boc), 143.8 (*ipso*-Ar), 136.4 (*ipso*-Ar), 131.5 (Ar), 131.0 (Ar), 130.8 (Ar), 128.6 (Ar), 128.5 (Ar), 128.3 (Ar), 128.2 (Ar), 128.1 (Ar), 120.2 (Ar), 117.1 (Ar), 108.3 (Ar), 79.6 ($OCMe_3$), 66.3 (OCH_2Ph), 55.4 (OMe), 42.5 (br, NCH_2), 40.0 (br, NCH_2), 35.8 (CH_2), 29.0 (CH), 28.6 (CMe_3), 21.9 (CHAr), 23.8 (CH) (one CH_2 resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{26}H_{31}NO_5$ $(M + Na)^+$ 460.2094, found 460.2086 (+6.1 ppm error).

Lab book reference: **IMA-75**

***tert*-Butyl 7-(3-(benzyloxy)-4-((benzyloxy)carbonyl)phenyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate *exo*-134**

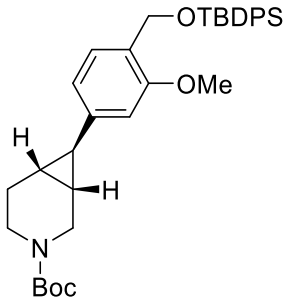


exo-**134**

Using general procedure C, MIDA boronate *exo*-**38** (88 mg, 0.25 mmol, 1.0 eq.), Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq.), aryl bromide **74** (144 mg, 0.35 mmol, 1.4 eq.), $Pd(OAc)_2$ (2.8 mg, 0.01 mmol, 0.05 eq.) and PCy_3 (7.0 mg, 0.02 mmol, 0.10 eq.) in toluene (5 mL) and H_2O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 1:9 to 2:8 EtOAc-hexane as eluent gave arylated piperidine *exo*-**134** (113.3 mg, 88%) as a colourless oil, R_F (2:8 EtOAc-hexane) 0.23; IR (ATR) 2928, 2856, 1722 (C=O, ester), 1690 (C=O, Boc), 1608, 1569, 1499, 1454, 1420 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.5 Hz, 1H, Ar), 7.48 – 7.41 (m, 2H, Ar), 7.42 – 7.25 (m, 8H, Ar), 6.66 (br s, 1H, Ar), 6.57 (d, *J* = 8.5 Hz, 1H, Ar), 5.32 (s, 2H OCH_2Ph), 5.14 (s, 2H, OCH_2Ph), 3.94 (br d, *J* = 13.5 Hz, 1H, NCH), 3.56 (dd, *J* = 14.0 Hz, 5.0 Hz, 1H, NCH), 3.51 – 3.38 (br m, 1H, NCH), 3.03 (ddd, *J* = 14.0, 9.0, 5.5 Hz, 1H, NCH), 2.08 – 1.96 (m, 1H, CH), 1.90 – 1.76 (br m, 1H, CH), 1.64 (dd, *J* = 4.5, 4.5 Hz, 1H, CHAr), 1.47 (s, 9H, CMe_3), 1.47 – 1.30 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.1 (C=O, ester), 158.8 (*ipso*-Ar), 155.2 (C=O, Boc), 150.0 (*ipso*-Ar), 136.8 (*ipso*-Ar), 136.4 (*ipso*-Ar), 132.5 (*ipso*-Ar), 128.6 (Ar), 128.6 (Ar), 128.2 (Ar), 128.1 (Ar), 127.9 (Ar), 127.2 (Ar), 117.5 (Ar), 117.2 (Ar), 79.7 ($OCMe_3$), 70.8 (OCH_2Ph), 66.6 (OCH_2Ph), 42.1 (br, NCH_2), 41.2 (br, NCH_2), 28.6 (CMe_3), 22.9 (*C*HAr) (one Ar, CH_2 and 2 x CH resonances not resolved); HRMS (ESI) *m/z* calcd for $C_{32}H_{35}NO_5$ $(M + Na)^+$ 536.2407, found 536.2423 (–3.0 ppm error).

Lab book reference **IMA-67**

***tert*-Butyl 7-(4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-methoxyphenyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate *exo*-136**

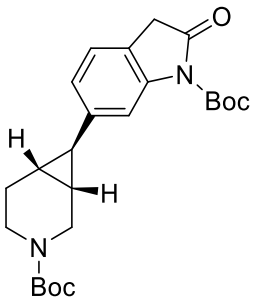


exo-**136**

Using general procedure D, MIDA boronate *exo*-**38** (88 mg, 0.25 mmol, 1.0 eq.), Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq.), aryl bromide **80** (159.4 mg, 0.35 mmol, 1.4 eq.), $Pd(OAc)_2$ (2.8 mg, 0.01 mmol, 0.05 eq.) and PCy_3 (7.0 mg, 0.02 mmol, 0.10 eq.) in toluene (5 mL) and H_2O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 0.5:9.5 to 2:8 EtOAc-hexane as eluent gave arylated piperidine *exo*-**136** (102.1 mg, 71%) as a yellow oil, R_F (2:8 EtOAc-hexane) 0.42; IR (ATR) 3071, 3049, 3001, 2959, 2931, 2857, 2247, 1979, 1892, 1690 (C=O), 1614, 1582, 1510, 1464, 1426 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.68 (m, 4H, Ph), 7.54 (d, *J* = 8.0 Hz, 1H, Ar), 7.46 – 7.33 (m, 6H, Ph), 6.65 (d, *J* = 8.0 Hz, 1H, Ar), 6.50 (s, 1H, Ar), 4.78 (s, 1H, OCH_2), 3.96 (d, *J* = 13.5 Hz, 1H, NCH), 3.65 (s, 3H, OMe), 3.61 (dd, *J* = 13.5, 4.5 Hz, 1H, NCH), 3.56 – 3.36 (br m, 1H, NCH), 3.10 – 2.98 (br m, 1H, NCH), 2.11 – 1.99 (m, 1H, CH), 1.97 – 1.75 (m, 1H, CH), 1.69 (dd, *J* = 4.5, 4.5 Hz, 1H, CHAr), 1.49 (s, 9H, CMe_3), 1.46 – 1.38 (m, 2H, CH), 1.10 (s, 9H, $SiCMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.2 (*ipso*-Ar), 155.3 (C=O, Boc), 142.8 (*ipso*-Ar), 135.7 (Ar), 133.9 (*ipso*-Ar), 129.7 (Ar), 127.8 (Ar), 126.94 (Ar), 126.89 (*ipso*-Ar), 116.9 (Ar), 79.6 (O*C*Me_3), 60.9 (OCH_2), 55.1 (OMe), 41.8 (br, NCH_2), 40.0 (br, NCH_2), 28.6 (C*Me*$_3$), 27.0 (SiC*Me*$_3$), 23.1 (CH), 21.9 (CHAr), 19.5 (Si*C*Me_3) (Ar, CH and CH_2 resonances not resolved); HRMS (ESI) *m/z* calcd for $C_{35}H_{45}NO_4Si$ $(M + Na)^+$ 594.301, found 594.3044 (–3.5 ppm error).

Lab book reference: **IMA-77**

***tert*-Butyl 6-(3-(*tert*-butoxycarbonyl)-3-azabicyclo[4.1.0]heptan-7-yl)-2-oxoindoline-1-carboxylate *exo*-137**

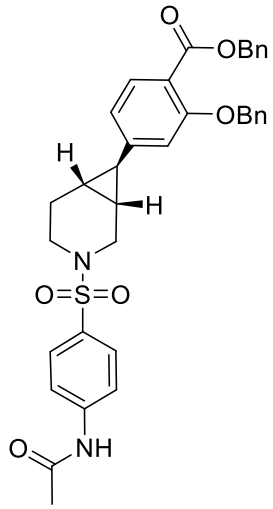


exo-**137**

Using general procedure C, MIDA boronate *exo*-**38** (88 mg, 0.25 mmol, 1.0 eq.), Cs_2CO_3 (244 mg, 0.75 mmol, 3.0 eq.), aryl bromide **79** (109.3 mg, 0.35 mmol, 1.4 eq.), $Pd(OAc)_2$ (2.8 mg, 0.01 mmol, 0.05 eq.) and PCy_3 (7.0 mg, 0.02 mmol, 0.10 eq.) in toluene (5 mL) and H_2O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 1:9 EtOAc-toluene as eluent gave arylated piperidine *exo*-**137** (49.1 mg, 46%) as a red oil, R_F (1:9 EtOAc-toluene) 0.3; IR (ATR) 2978, 2931, 2863, 2252, 1967, 1794 (C=O), 1766 (C=O), 1726 (C=O), 1687 (C=O, Boc), 1619, 1592, 1476, 1442, 1424 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (br s, 1H, Ar), 7.08 (d, *J* = 8.0 Hz, 1H, Ar), 6.79 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar), 3.92 (d, *J* = 14.0 Hz, 1H, NCH), 3.60 – 3.54 (m, 3H, NCH, CHC(O)), 3.52 – 3.32 (br m, 1H, NCH), 3.06 – 2.95 (br m, 1H, NCH), 2.08 – 1.96 (m, 1H, CH), 1.90 – 1.79 (m, 1H, CH), 1.67 (dd, *J* = 4.5, 4.5 Hz, 1H, CHAr), 1.57 (s, 9H, CMe_3), 1.47 (s, 9H, CMe_3), 1.42 – 1.35 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.5 (C=O, lactam), 155.2 (C=O, Boc), 149.4 (C=O, Boc), 143.4 (*ipso*-Ar), 141.3 (*ipso*-Ar), 124.0 (*ipso*-Ar), 121.7 (Ar), 120.3 (Ar), 112.2 (Ar), 84.4 ($OCMe_3$), 79.6 ($OCMe_3$), 42.5 (br, NCH_2), 41.7 (br, NCH_2), 36.4 ($CH_2C(O)$), 28.6 (CMe_3), 28.2 (CMe_3), 27.8 (CH_2), 22.0 (CHAr), 20.6 (CH) (one CH resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{24}H_{32}N_2O_5$ $(M + Na)^+$ 451.2203, found 451.2216 (–2.4 ppm error).

Lab book reference: **IMA-103**

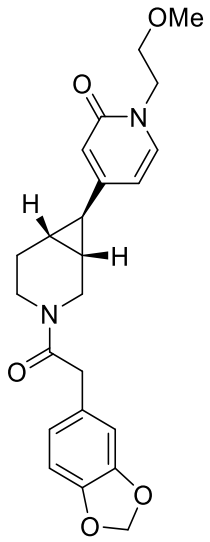
Benzyl 4-(3-((4-acetamidophenyl)sulfonyl)-3-azabicyclo[4.1.0]heptan-7-yl)-2-(benzyloxy)benzoate *exo*-140



exo-**140**

4 N HCl in dioxane (4 mL) was added to a stirred solution of arylated piperidine *exo*-**134** (43.6 mg, 0.085 mmol, 1.00 eq.) in dioxane (1 mL) at rt under Ar. The resulting solution was stirred at rt for 2 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 (5 mL) and DMAP (5 mg, 0.04 mmol, 0.5 eq.) and Et_3N (59 µL, 0.42 mmol, 5.0 eq.) were added under Ar. The resulting solution was cooled to 0 °C and 4-acetamidobenzenesulfonyl chloride (25 mg, 0.11 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 CH_2Cl_2 (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 7:3 EtOAc-hexane as eluent gave sulfonamide *exo*-**140** (28 mg, 54%) as an orange oil, R_F (7:3 EtOAc-hexane) 0.36; IR (ATR) 3066, 3034, 2926, 2854, 1727 (C=O, ester), 1601, 1586, 1498, 1488, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (br s, 1H, NH), 7.79 – 7.61 (m, 5H, Ar), 7.45 – 7.23 (m, 10H, Ar), 6.68 (s, 1H, Ar), 6.55 – 6.45 (m, 1H, Ar), 5.30 (s, 2H, OCH_2), 5.11 (s, 2H, OCH_2), 3.69 (m, 2H, NCH), 3.34 – 3.24 (m, 1H, NCH), 3.03 – 2.93 (m, 1H, NCH), 2.49 – 2.28 (m, 1H, CH), 2.18 (s, 3H, Me), 2.15 – 2.06 (m, 1H, CH), 2.06 – 1.90 (m, 2H, CH), 1.89 – 1.84 (dd, *J* = 5.0, 5.0 Hz, 1H, CHAr); HRMS (ESI) *m/z* calcd for $C_{35}H_{34}N_2O_6S$ $(M + Na)^+$ 633.2041, found 633.2030 (–2.0 ppm error). Lab book reference: **IMA-115**

4-(3-(2-(Benzo[d][1,3]dioxol-5-yl)acetyl)-3-azabicyclo[4.1.0]heptan-7-yl)-1-(2-methoxyethyl)pyridin-2(1H)-one *exo* 142

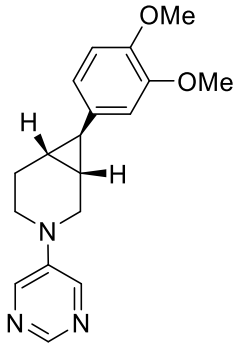


exo-**142**

4 N HCl in dioxane (4 mL) was added to a stirred solution of arylated piperidine *exo*-**128** (50 mg, 0.144 mmol, 1 eq.) in dioxane (1 mL) at rt under Ar. The resulting solution was stirred at rt for 2 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 3,4-(methylenedioxy)phenylacetic acid (28 mg, 0.16 mmol, 1.1 eq.) and Et_3N (80 µL, 0.57 mmol, 4.0 eq.) were added under Ar. The resulting solution was cooled to 0 °C and a 50% solution of T_3P in EtOAc (0.15 mL, 0.29 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. The solution was washed with H_2O (10 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 to 9:1 EtOAc-MeOH as eluent gave amide *exo*-**142** (25.1 mg, 43%) as a light yellow oil, R_F (9:1 EtOAc-MeOH) 0.22; IR (ATR) 2926, 2857, 1654 (C=O), 1581, 1530, 1503, 1491, 1444 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.17 (d, *J* = 7.0 Hz, 0.5H), 7.15 (d, *J* = 7.0 Hz, 0.5H), 6.79 – 6.72 (m, 2H, Ar), 6.72 – 6.63 (m, 1H, Ar), 6.06 (d, *J* = 2.0 Hz, 0.5H, Ar), 5.98 – 5.92 (m, 2.5H, OCH_2O, Ar), 5.78 (dd, *J* =

7.0, 2.0 Hz, 0.5H, Ar), 5.61 (dd, *J* = 7.0, 2.0 Hz, 0.5H, Ar), 4.31 (d, *J* = 14.0 Hz, 0.5H, NCH), 4.12 – 3.85 (m, 2H, OCH_2), 3.92 (d, *J* = 14.0 Hz, 0.5H, NCH), 3.66 – 3.53 (m, 4H, NCH, NCH_2), 3.52 – 3.37 (m, 1H, NCH), 3.23 (s, 3H, OMe), 2.86 – 2.75 (m, 0.5H, CH), 2.07 – 1.86 (m, 1H, CH), 1.84 – 1.71 (m, 0.5H, CH), 1.55 – 1.34 (m, 1H, CH), 1.38 – 1.25 (m, 1H, CH), 1.10 (dd, *J* = 5.0, 5.0 Hz, 1H, CHAr); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) 170.3 (C=O, amide), 170.0 (C=O, amide), 162.4 (C=O, pyridone), 156.3 (*ipso*-Ar), 156.0 (*ipso*-Ar), 148.1 (*ipso*-Ar), 148.1 (*ipso*-Ar), 146.7 (*ipso*-Ar), 146.6 (*ipso*-Ar), 138.2 (Ar), 128.6 (*ipso*-Ar), 128.6 (*ipso*-Ar), 121.8 (Ar), 121.8 (Ar), 114.2 (Ar), 114.0 (Ar), 109.21 (Ar), 109.17 (Ar), 108.6 (Ar), 108.5 (Ar), 104.8 (Ar), 104.4 (Ar), 101.3 (OCH_2O), 101.2 (OCH_2O), 70.5 (OCH_2), 59.1 (OMe), 49.3 (NCH_2), 44.2 ($CH_2C(O)$), 42.8 (NCH_2), 41.1 (NCH_2), 41.0 (NCH_2), 40.2 (NCH_2), 39.2 ($CH_2C(O)$), 26.9 (CH_2), 26.6 (CH_2), 23.4 (CH), 22.7 (CHAr), 22.6 (CHAr), 22.4 (CH), 20.8 (CH), 20.6 (CH); HRMS (ESI) *m/z* calcd for $C_{23}H_{26}N_2O_5$ $(M + Na)^+$ 433.1742, found 433.1734 (–1.8 ppm error).
Lab book reference: **IMA-117**

7-(3,4-Dimethoxyphenyl)-3-(pyrimidin-5-yl)-3-azabicyclo[4.1.0]heptane *exo*-144



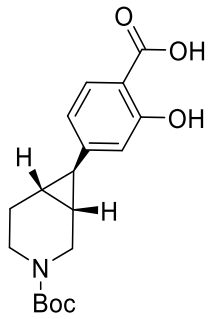
exo-**144**

4 N HCl in dioxane (4 mL) was added to a stirred solution of arylated piperidine *exo*-**131** (38.6 mg, 0.116 mmol, 1.00 eq.) in dioxane (1 mL) at rt under Ar. The resulting solution was stirred at rt for 2 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 5-bromopyrimidine (20.3 mg, 0.13 mmol,

1.1 eq), $Pd_2(dba)_3$ (11 mg, 0.012 mmol, 0.1 eq), (±)-BINAP (11 mg, 0.17 mmol, 0.15 eq.) and NaO*t*-Bu (28 mg, 0.29 mmol, 2.5 eq.) were added under Ar and the resulting solution 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 1:9 to 3:6 EtOAc-hexane as eluent gave aminopyrimidine *exo*-**144** (20.4 mg, 57%) as a light-yellow oil, R_F (3:6 EtOAc- hexane) 0.3; IR (ATR) 2923, 2853, 1684, 1608, 1588, 1568, 1549, 1517, 1441 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H, Ar), 8.27 (s, 2H, Ar), 6.75 (d, *J* = 8.0 Hz, 1H, Ar), 6.59 – 6.51 (m, 2H, Ar), 3.85 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.73 – 3.57 (m, 2H, NCH), 3.35 – 3.25 (m, 1H, NCH), 3.17 – 3.07 (m, 1H, NCH), 2.18 – 2.13 (m, 1H, CH), 2.10 – 1.99 (m, 1H, CH), 1.85 – 1.79 (dd, *J* = 5.0, 5.0 Hz, 1H, CHAr), 1.72 – 1.62 (m, 1H, CH), 1.45 – 1.41 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 149.0 (Ar), 148.2 (*ipso*-Ar), 147.3 (*ipso*-Ar), 143.9 (*ipso*-Ar), 142.1 (Ar), 134.9 (*ipso*-Ar), 117.1 (Ar), 111.5 (Ar), 109.5 (Ar), 56.1 (OMe), 55.9 (OMe), 44.7 (NCH_2), 43.9 (NCH_2), 29.8 (CH_2), 26.4 (CH), 22.7 (CHAr), 21.4 (CH); HRMS (ESI) *m/z* calcd for $C_{18}H_{21}N_3O_2$ $(M + Na)^+$ 334.1531, found 334.1526 (–2.9 ppm error).

Lab book reference: **IMA-118**

4-(3-(*tert*-Butoxycarbonyl)-3-azabicyclo[4.1.0]heptan-7-yl)-2-hydroxybenzoic acid *exo* 145



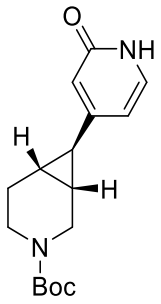
exo-**145**

Arylated piperidine *exo*-**134** (105.6 mg, 0.21 mmol, 1.0 eq.) was dissolved in MeOH/THF (3 mL/ 2 mL). The reaction flask was evacuated and back-filled with Ar three times. Then, 10% Pd/C (10 mg, 0.09 mmol, 1.2 eq.) was added. The reaction flask was evacuated and back-filled with H_2 five

times *via* a three-way valve. The resulting solution was stirred under a balloon of H_2 at rt for 3 h. The solids were removed by filtration through a plug of Celite®. The filtrate was evaporated under reduced pressure to give acid *exo*-**145** (68 mg, 98%) as a clear oil, IR (ATR) 3007, 2976, 2926, 2858, 1668 (C=O), 1618, 1574, 1536, 1501, 1478, 1424 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.01 – 9.67 (br s, 2H, OH), 7.74 – 7.70 (br m, 1H, Ar), 6.55 – 6.49 (m, 2H, Ar), 3.96 (br d, *J* = 14.0 Hz, 1H, NCH), 3.59 – 3.51 (m, 2H, NCH), 3.02 – 2.97 (br m, 1H, NCH), 2.08 – 1.96 (br m, 1H, CH), 1.94 – 1.75 (br m, 2H, CH), 1.61 (dd, *J* = 4.5, 4.5 Hz, 1H, CHAr), 1.47 (s, 9H, CMe_3), 1.46 – 1.41 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.0 (C=O, carboxylic acid), 162.2 (*ipso*-Ar), 155.5 (C=O, Boc), 153.2 (*ipso*-Ar), 130.8 (Ar), 117.1 (Ar), 113.4 (*ipso*-Ar), 109.3 (Ar), 80.2 (O*C*Me_3), 41.7 (br, NCH_2), 40.1 (br, NCH_2), 29.8 (CH), 28.6 (C*Me*$_3$), 28.0 (CH_2), 23.1 (*C*HAr), 21.6 (CH); HRMS (ESI) *m/z* calcd for $C_{18}H_{23}NO_5$ $(M + Na)^+$ 356.1476, found 356.1468 (–4.7 ppm error).

Lab book reference: **IMA-121**

tert-Butyl 7-(2-oxo-1,2-dihydropyridin-4-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate _exo_ 147



exo-**147**

Arylated piperidine *exo*-**128** (30 mg, 0.079 mmol, 1.0 eq.) was dissolved in MeOH/THF (3 mL/ 2 mL). The reaction flask was evacuated and back-filled with Ar three times. Then, 10% Pd/C (10 mg, 0.09 mmol, 1.2 eq.) was added. The reaction flask was evacuated and back-filled with H_2 five times *via* a three-way valve. The resulting solution was stirred under a balloon of H_2 at rt for 3 h. The solids were removed by filtration through a plug of Celite®. The filtrate was evaporated

under reduced pressure to give pyridone *exo*-**147** (11 mg) as a white solid. This product was not completely pure but there was evidence that the pyridine functionality had been obtained. Diagnostic signals for pyridone *exo*-**147**: IR (ATR) 1691 (C=O, pyridone), 1652 (C=O, Boc) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 7.0 Hz, 1H, Ar), 6.13 (s, 1H, Ar), 5.89 (d, *J* = 7.0 Hz, 1H, Ar), 3.95 (d, *J* = 13.0 Hz, 1H, NCH), 3.58-3.40 (m, 1H, NCH), 3.52 (d, *J* = 13.0 Hz, 1H, NCH), 3.03 – 2.87 (br m, 1H, NCH), 1.46 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.9 (C=O, pyridone), 158.9 (*ipso*-Ar), 155.1 (C=O, Boc), 133.6 (Ar), 114.2 (Ar), 105.7 (Ar), 79.9 ($OCMe_3$); HRMS (ESI) *m/z* calcd for $C_{16}H_{22}N_2O_3$ $(M + Na)^+$ 313.1533, found 313.1523 (–3.7 ppm error).

Lab book reference: **IMA-120**

Chapter 6: References

1. S. Kraljevic, P. J. Stambrook and K. Pavelic, *EMBO Rep.*, 2004, **5**, 837-842.
2. Q. Li, *Front. Mol. Biosci.*, 2020, **7**, 180.
3. M. Bon, A. Bilsland, J. Bower and K. McAulay, *Mol. Oncol.*, 2022, **16**, 3761-3777.
4. J. P. Hughes, S. Rees, S. B. Kalindjian and K. L. Philpott, *Br. J. Pharmacol.*, 2011, **162**, 1239-1249.
5. B. C. Doak, R. S. Norton and M. J. Scanlon, *Pharmacol. Ther.*, 2016, **167**, 28-37.
6. G. Bollag, P. Hirth, J. Tsai, J. Zhang, P. N. Ibrahim, H. Cho, W. Spevak, C. Zhang, Y. Zhang, G. Habets, E. A. Burton, B. Wong, G. Tsang, B. L. West, B. Powell, R. Shellooe, A. Marimuthu, H. Nguyen, K. Y. Zhang, D. R. Artis, J. Schlessinger, F. Su, B. Higgins, R. Iyer, K. D'Andrea, A. Koehler, M. Stumm, P. S. Lin, R. J. Lee, J. Grippo, I. Puzanov, K. B. Kim, A. Ribas, G. A. McArthur, J. A. Sosman, P. B. Chapman, K. T. Flaherty, X. Xu, K. L. Nathanson and K. Nolop, *Nature*, 2010, **467**, 596-599.
7. W. D. Tap, Z. A. Wainberg, S. P. Anthony, P. N. Ibrahim, C. Zhang, J. H. Healey, B. Chmielowski, A. P. Staddon, A. L. Cohn, G. I. Shapiro, V. L. Keedy, A. S. Singh, I. Puzanov, E. L. Kwak, A. J. Wagner, D. D. Von Hoff, G. J. Weiss, R. K. Ramanathan, J. Zhang, G. Habets, Y. Zhang, E. A. Burton, G. Visor, L. Sanftner, P. Severson, H. Nguyen, M. J. Kim, A. Marimuthu, G. Tsang, R. Shellooe, C. Gee, B. L. West, P. Hirth, K. Nolop, M. van de Rijn, H. H. Hsu, C. Peterfy, P. S. Lin, S. Tong-Starksen and G. Bollag, *N Engl J Med*, 2015, **373**, 428-437.
8. C. W. Murray, D. R. Newell and P. Angibaud, *MedChemComm*, 2019, **10**, 1509-1511.
9. Y.-Y. Ku, V. S. Chan, A. Christesen, T. Grieme, M. Mulhern, Y.-M. Pu and M. D. Wendt, *J. Org. Chem.*, 2019, **84**, 4814-4829.
10. J. Schoepfer, W. Jahnke, G. Berellini, S. Buonamici, S. Cotesta, S. W. Cowan-Jacob, S. Dodd, P. Drueckes, D. Fabbro, T. Gabriel, J.-M. Groell, R. M. Grotzfeld, A. Q. Hassan, C. Henry, V. Iyer, D. Jones, F. Lombardo, A. Loo, P. W. Manley, X. Pellé, G. Rummel, B. Salem, M. Warmuth, A. A. Wylie, T. Zoller, A. L. Marzinzik and P. Furet, *J. Med. Chem.*, 2018, **61**, 8120-8135.
11. G. Davison, M. P. Martin, S. Turberville, S. Dormen, R. Heath, A. B. Heptinstall, M. Lawson, D. C. Miller, Y. M. Ng, J. N. Sanderson, I. Hope, D. J. Wood, C. Cano, J. A. Endicott, I. R. Hardcastle, M. E. M. Noble and M. J. Waring, *J Med Chem*, 2022, **65**, 15416-15432.
12. D. J. Wood, J. D. Lopez-Fernandez, L. E. Knight, I. Al-Khawaldeh, C. Gai, S. Lin, M. P. Martin, D. C. Miller, C. Cano, J. A. Endicott, I. R. Hardcastle, M. E. M. Noble and M. J. Waring, *J. Med. Chem.*, 2019, **62**, 3741-3752.
13. C. W. Murray and D. C. Rees, *Angew. Chem. Int. Ed. Engl.*, 2016, **55**, 488-492.
14. P. N. Mortenson, V. Berdini and M. O'Reilly, in *Methods Enzymol.*, ed. K. M. Shokat, Academic Press, 2014, vol. 548, pp. 69-92.
15. D. Blakemore, *ChemMedChem*, 2016, vol. 1, pp. 1-69.
16. E. P. Gillis and M. D. Burke, *J. Am. Chem. Soc.*, 2008, **130**, 14084-14085.
17. D. M. Knapp, E. P. Gillis and M. D. Burke, *J. Am. Chem. Soc.*, 2009, **131**, 6961-6963.
18. J. A. Gonzalez, O. M. Ogba, G. F. Morehouse, N. Rosson, K. N. Houk, A. G. Leach, P. H. Cheong, M. D. Burke and G. C. Lloyd-Jones, *Nat. Chem*, 2016, **8**, 1067-1075.
19. H. Klein, *Univ. of York, Dept. of Chem.*, 2022.

20. A. R. G. Angel, *Univ. of York, Dept. of Chem.*, 2021.
21. J. Walder, *Univ. of York, Dept. of Chem.*, 2022.
22. G. F. Meijs and I. R. Doyle, *J. Org. Chem.*, 1985, **50**, 3713-3716.
23. Q. Zhou, F. Du, X. Liang, W. Liu, T. Fang and G. Chen, *Journal*, 2018, **23**.
24. W. J. Begley, G. Lowe, A. K. Cheetham and J. M. Newsam, *J. Chem. Soc., Perkin trans. 1*, 1981, DOI: 10.1039/P19810002620, 2620-2624.
25. T. L. May-Dracka, F. Gao, B. T. Hopkins, X. Hronowski, T. Chen, J. V. Chodaparambil, C. M. Metrick, M. Cullivan, I. Enyedy, M. Kaliszczak, M. W. Kankel, I. Marx, M. A. Michell-Robinson, P. Murugan, P. R. Kumar, M. Rooney, E. Schuman, A. Sen, T. Wang, T. Ye and E. A. Peterson, *ACS Med. Chem. Lett.*, 2022, **13**, 665-673.
26. E. D. Anderson and D. L. Boger, *J. Am. Chem. Soc.*, 2011, **133**, 12285-12292.
27. E. D. Anderson and D. L. Boger, *J. Am. Chem. Soc.*, 2011, **133**, 12285-12292.
28. M. Parkin, *Univ. of York, Dept. of Chem.*, 2023.
29. D. K. Winter, A. Drouin, J. Lessard and C. Spino, *J. Org. Chem.*, 2010, **75**, 2610-2618.
30. G. S. Cockerill, R. M. Angell, A. Bedernjak, I. Chuckowree, I. Fraser, J. Gascon-Simorte, M. S. A. Gilman, J. A. D. Good, R. Harland, S. M. Johnson, J. H. Ludes-Meyers, E. Littler, J. Lumley, G. Lunn, N. Mathews, J. S. McLellan, M. Paradowski, M. E. Peeples, C. Scott, D. Tait, G. Taylor, M. Thom, E. Thomas, C. Villalonga Barber, S. E. Ward, D. Watterson, G. Williams, P. Young and K. Powell, *J. Med. Chem.*, 2021, **64**, 3658-3676.
31. S. Akai, T. Tsujino, T. Naka, K. Tanimoto and Y. Kita, *Tetrahedron Lett.*, 2001, **42**, 7315-7317.
32. P. Hamel, D. Riendeau, C. Brideau, C. C. Chan, S. Desmarais, D. Delorme, D. Dubé, Y. Ducharme, D. Ethier, E. Grimm, J. P. Falgueyret, J. Guay, T. R. Jones, E. Kwong, M. McAuliffe, C. S. McFarlane, H. Piechuta, M. Roumi, P. Tagari, R. N. Young and Y. Girard, *J Med Chem*, 1997, **40**, 2866-2875.
33. P. A. Zunszain, M. M. Shah, Z. Miscony, M. Javadzadeh-Tabatabaie, D. G. Haylett and C. R. Ganellin, *Archiv der Pharmazie*, 2002, **335**, 159-166.
34. G. Chabowska, E. Barg and A. Wójcicka, *Molecules*, 2021, **26**, 4324
35. E. C. Anderson, H. F. Sneddon and C. J. Hayes, *RSC Green Chem.* , 2019, **21**, 3050-3058.
36. S. S. Choudhury, S. Jena, D. K. Sahoo, S. Shekh, R. K. Kar, A. Dhakad, K. H. Gowd and H. S. Biswal, *ACS Omega*, 2021, **6**, 19304-19313.
37. CN107226813A, 2017.
38. W. W. Paudler and T. J. Kress, *J. Org. Chem*, 1967, **32**, 832-833.
39. B. Sakram, P. Madhu, B. Sonyanaik, S. Rambabu, D. Ravi and A. Kurumanna, *Russ. J. Gen. Chem.*, 2018, **88**, 1224-1227.
40. P. L. Ferrarini, C. Mori, M. Badawneh, V. Calderone, L. Calzolari, T. Loffredo, E.Martinotti and G. Saccomanni, *European J. Med. Chem.*, 1998, **33**, 383-397.
41. M. Abass and A. S. Mayas, *Heteroat. Chem.*, 2007, **18**, 19-27.
42. A. Fiksdahl, C. Plug and C. Wentrup, *J. Chem. Soc., Perkin trans.*, 2000, DOI: 10.1039/B003662P.
43. A. Narender, E. Laxminarayana and M. Thirumala Chary, *J. Chil. Chem. Soc.*, 2009, **54**.
44. WO2012171337, 2012.
45. WO2021084264, 2021.
46. US2013102603A1, 2013.
47. W. Czuba and M. WoŹNiak, *Synthesis*, 1974, **1974**, 809-810.
48. EP1226138A1, 2004.

49. J. P. Hildebrand and S. P. Marsden, *Synlett*, 1996, **1996**, 893-894.
50. S.-M. Zhou, Y.-L. Yan and M.-Z. Deng, *Synlett*, 1998, **1998**, 198-200.
51. M.-L. Yao and M.-Z. Deng, *Tetrahedron Lett.*, 2000, **41**, 9083-9087.
52. M. Rubina, M. Rubin and V. Gevorgyan, *J. Am. Chem. Soc.*, 2003, **125**, 7198-7199.
53. D. J. Wallace and C.-y. Chen, *Tetrahedron Lett.*, 2002, **43**, 6987-6990.
54. M. Zhang, X. Cui, X. Chen, L. Wang, J. Li, Y. Wu, L. Hou and Y. Wu, *Tetrahedron*, 2012, **68**, 900-905.
55. M. A. J. Duncton and R. Singh, *Org Lett*, 2013, **15**, 4284-4287.
56. WO2013152198A1, 2011.
57. WO 2012/012619, 2012.
58. Y. Grobben, J. de Man, A. M. van Doornmalen, M. Muller, N. Willemsen-Seegers, D. Vu-Pham, W. R. Mulder, M. B. W. Prinsen, J. de Wit, J. G. Sterrenburg, F. van Cauter, J. E. den Ouden, A. M. van Altena, L. F. Massuger, J. C. M. Uitdehaag, R. C. Buijsman and G. J. R. Zaman, *Front. immunol*, 2020, **11**, 609490.
59. Y. Wang, *Univ. of York, Dept. of Chem.*, 2023.
60. J. P. Wolfe and S. L. Buchwald, *Tetrahedron Lett.*, 1997, **38**, 6359-6362.
61. B. D. G. Page, S. Fletcher, P. Yue, Z. Li, X. Zhang, S. Sharmeen, A. Datti, J. L. Wrana, S. Trudel, A. D. Schimmer, J. Turkson and P. T. Gunning, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 5605-5609.
62. J. R. Frost, S. M. Huber, S. Breitenlechner, C. Bannwarth and T. Bach, *Angew. Chem., Int. Ed. Engl.*, 2015, **54**, 691-695.
63. A. F. Stepan, M. M. Claffey, M. R. Reese, G. Balan, G. Barreiro, J. Barricklow, M. J. Bohanon, B. P. Boscoe, G. D. Cappon, L. K. Chenard, J. Cianfrogna, L. Chen, K. J. Coffman, S. E. Drozda, J. R. Dunetz, S. Ghosh, X. Hou, C. Houle, K. Karki, J. T. Lazzaro, J. Y. Mancuso, J. M. Marcek, E. L. Miller, M. A. Moen, S. O'Neil, I. Sakurada, M. Skaddan, V. Parikh, D. L. Smith, P. Trapa, J. B. Tuttle, P. R. Verhoest, D. P. Walker, A. Won, A. S. Wright, J. Whritenour, K. Zasadny, M. M. Zaleska, L. Zhang and C. L. Shaffer, *J. Med. Chem.*, 2017, **60**, 7764-7780.
64. EP1426374A1, 2004.