Palladium-Catalysed sp^3-sp^2 Suzuki-Miyaura Cross-Coupling of Secondary Heterocyclic Boronates

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Abstract

Chapter 1 provides a rationale for the development of sp^3-sp^2 Suzuki-Miyaura cross-coupling (SMCC) methodology. An overview of the reported carbocyclic and heterocyclic alkyl-boron SMCC reactions is presented and methods to control the stereochemical pathway of transmetallation are discussed.

In **Chapter 2**, the synthesis and SMCC of racemic and enantioenriched 2-Bpin tetrahydrothiophene is described. A highly robust SMCC with 28 racemic examples (13-84%) and 10 enantioenriched examples (40-72%, 14-99% es) is developed, with the reactions proceeding predominantly with inversion of configuration.

In **Chapter 3**, the synthesis and SMCC of a series of 4-boryl *N*-R pyrrolidones is detailed. Reaction screening with 4-BF_3K N-PMP pyrrolidone improves the yield from 39% to 50%. A racemic scope of 17 examples (18-80%) is developed alongside a representative lactam deprotection scope of five examples (56-74%). The stereochemical pathway is shown to proceed with retention of configuration and an enantioenriched scope of six examples in high er is exhibited (14-60%, 96:4 to 97:3 er). Finally, the synthesis of (*R*,*R*)-Tetflupyrolimet is achieved in six steps with an overall yield of 21% using the newly developed sp^3-sp^2 SMCC methodology.

In **Chapter 4,** the SMCC of 3-BF_3K pyrrolidine is optimised using a combination of Design of Experiments and one-factor at a time screening approaches. The formation of an inseparable regioisomer is discovered and the cross-coupled products are consistently isolated as impure mixtures of 3- and 2-aryl pyrrolidines. Although no method is found to remove the regioisomer, the SMCC yield is rapidly optimised and a preliminary scope of 10 examples achieved (total yield 27-67%) with varying regioisomeric ratios.

In **Chapter 5**, the experimental and characterisation data for chapters 2-4 is presented.

In **Chapter 6**, the supporting references from in text citations are detailed.

Table of Contents

List of Figures v

List of Tables vii

Acknowledgements ix

Author's Declaration xi

List of Abbreviations xii

Chapter: 1 Introduction 1

1.1 Importance of sp^3 Character in Drug Design 1

1.2 Introduction to the Suzuki-Miyaura Cross-Coupling 4

1.3 Mechanistic Challenges in the sp^3-sp^2 Suzuki-Miyaura Cross-Coupling 6

1.4 Suzuki-Miyaura Cross-Coupling of Secondary Alkyl-Boron Compounds 14

1.5 Exploration and Control of the Stereochemical Outcome of sp^3-sp^2 Suzuki-Miyaura Cross-Couplings 26

1.6 Project Outline 42

Chapter: 2 Suzuki-Miyaura Cross-Coupling of 2-Bpin Tetrahydrothiophene 44

2.1 Introduction 44

2.1.1 Thiophenes and 2-Aryl Tetrahydrothiophenes in Drug Discovery 44

2.1.2 Synthetic Routes to Enantioenriched 2-Aryl Tetrahydrothiophenes 45

2.1.3 Background and Previous Work in the Group 48

2.2 Proposed Objectives 53

2.3 Synthesis of 2-Bpin Tetrahydrothiophene **110** 54

2.4 Exploration of the Chemical Space of the Suzuki-Miyaura Cross-Coupling Conditions 55

2.5 Racemic Scope of the Suzuki-Miyaura Cross-Coupling of 2-Bpin Tetrahydrothiophene 59

2.6 Synthesis of Enantioenriched 2-Bpin Tetrahydrothiophene 64

2.6.1 Benzylation of Cyclopentyl Hydroxylamine: Chemoselective Approaches 64

2.6.2 Benzylation of Cyclopentyl Hydroxylamine: Phthalimide Protection Strategy 67

2.6.3 Synthesis of (*R*,*R*)-BIDA from Benzyl Cyclopentyl (*R*,*R*)-136 72

2.7 Investigation of the Stereochemical Outcome of the Suzuki-Miyaura Cross-Coupling of Enantioenriched 2-Bpin Tetrahydrothiophene 75

2.7.1 Determination of Configuration of 2-Phenyl Tetrahydrothiophene (*S*)-116 75

2.7.2 Scope of the Suzuki-Miyaura Cross-Coupling of Enantioenriched 2-Bpin Tetrahydrothiophene 76

2.8 Conclusions and Future Work 89

Chapter: 3 Suzuki-Miyaura Cross-Couplings of 4-Boryl *N*-Substituted Pyrrolidones 92

3.1 Introduction 92

3.1.1 Pyrrolidones in Drug Discovery and Agrochemistry 92

3.1.2 Selected Overview of Synthetic Routes to 4-Aryl Pyrrolidones 94

3.2 Proposed Objectives 102

3.3 Initial Investigations into the Suzuki-Miyaura Cross-Coupling of 4-Boryl Pyrrolidones 103

3.3.1 Synthesis and Suzuki-Miyaura Cross-Coupling of 4-BF_3K *N*-*p*-Tolyl Pyrrolidone 103

3.3.2 Synthesis and Suzuki-Miyaura Cross-Coupling of a Series of 4-BF_3K *N*-R Pyrrolidones 105

3.3.3 Synthesis and Suzuki-Miyaura Cross-Coupling of *N*-PMP 4-Boryl Pyrrolidones 114

3.4 Optimisation of the Suzuki-Miyaura Cross-Coupling of 4-BF_3K *N*-PMP Pyrrolidone 118

3.4.1 Design of Experiment Screening 118

3.4.2 One Factor at a Time Screening 122

3.5 Scope of the Suzuki-Miyaura Cross-Coupling of 4-BF_3K *N*-PMP Pyrrolidone 134

3.6 Synthesis and Suzuki-Miyaura Cross-Coupling of 4-BF_3K *N*-PMP Piperidone 143

3.7 Investigation of the Stereochemical Outcome of the Suzuki-Miyaura Cross-Coupling of Enantioenriched 4-BF_3K *N*-PMP Pyrrolidone 148

3.7.1 Synthesis and Suzuki-Miyaura Cross-Coupling of Enantioenriched 4-BF_3K *N*-PMP Pyrrolidone 148

3.7.2 Enantioenriched Scope of the Suzuki-Miyaura Cross-Coupling of 4-BF_3K *N*-PMP Pyrrolidone 152

3.8 Application of a SMCC Reaction to the Synthesis of Tetflupyrolimet 154

3.9 Conclusions and Future Work 159

Chapter: 4 Suzuki-Miyaura Cross-Couplings of 3-Boryl Pyrrolidines 163

4.1 Introduction 163

4.1.1 3-Aryl Pyrrolidines in Drug Discovery and Agrochemistry 163

4.1.2 Selected Overview of Synthetic Routes to 3-Aryl Pyrrolidines 164

4.2 Proposed Objectives 173

4.3 Initial Investigations into the Suzuki-Miyaura Cross-Coupling of 3-BF_3K *N*-Boc Pyrrolidine 174

4.3.1 Synthesis of 3-BF_3K *N*-Boc Pyrrolidine 174

4.3.2 Initial Suzuki-Miyaura Cross-Coupling of 3-BF_3K *N*-Boc Pyrrolidine. 174

4.4 Optimisation of the Suzuki-Miyaura Cross-Coupling of 3-BF_3K *N*-Boc Pyrrolidine 178

4.5 Scope of the Suzuki-Miyaura Cross-Coupling of 3-BF_3K *N*-Boc Pyrrolidine 197

4.6 Conclusions and Future Work 199

Chapter: 5 Experimental 202

5.1 General Information 202

5.2 General Procedures 203

5.3 Analysis Methods 213

5.3.1 GC Analysis Methods 213

5.3.2 NMR Analysis Method 215

5.4 Experimental Procedures for Chapter 2 216

5.5 Experimental Procedures for Chapter 3 273
5.6 Experimental Procedures for Chapter 4 370
5.7 Crystallographic Data and Refinement Statistics 407
5.7.1 2-Phenyl tetrahydrothiophene (*S*)-163 407
5.7.2 Tetrahydrothiophene BBIDA (*R*,*R*,*S*)-134 412
5.7.3 BBIDA Pyrrolidone (*S*,*S*,*R*)-261 420
Chapter: 6 References 432

List of Figures

Figure 1.1: Structures of common boron motifs in sp^3-sp^2 SMCCs 11

Figure 1.2: Structures of optimised ligands 34

Figure 1.3: Proposed mechanism for axial shielding of stereoinvertive pathway 38

Figure 1.4: Structure of 2-Bpin tetrahydrothiophene investigated in Chapter 2 42

Figure 1.5: Structure of 4-boryl N-R pyrrolidones investigated in Chapter 3 43

Figure 1.6: Structure of 3-BF_3K N-Boc pyrrolidine investigated in Chapter 4 43

Figure 2.1: Examples of thiophene containing approved drugs 44

Figure 2.2: Examples of 2-aryl tetrahydrothiophenes in drug discovery 45

Figure 2.3: X-Ray crystal structure of BBIDA tetrahydrothiophene (*R*,*R*,*S*)-**134** 73

Figure 2.4: X-Ray crystal structure of 2-phenyl sulfone (*S*)-**163** 75

Figure 2.5: Proposed aryl bromides for SMCC with enantioenriched 2-Bpin tetrahydrothiophene 90

Figure 3.1: Structures of Levetiracetam and Brivaracetam 92

Figure 3.2: Structures of medicinally relevant 4-aryl pyrrolidones 93

Figure 3.3: Structure of Tetflupyrolimet 94

Figure 3.4: Structures of *N*-substituted pyrrolidones 106

Figure 3.5: Structures of ligands used in the 4-BF_3K *N*-PMP pyrrolidone **192** ligand screen 124

Figure 3.6: X-Ray crystal structure of (*S*,*S*,*R*)-**261** 151

Figure 3.7: Structure of Tetflupyrolimet 154

Figure 4.1: Structures of 3-aryl pyrrolidines in or previously enrolled in clinical trials 163

Figure 4.2: Structure of 3-aryl pyrrolidine **273** involved in agrochemical discovery 164

Figure 4.3: (a) ^{1}H NMR spectrum of 3-phenyl pyrrolidine **288**; (b) ^{1}H NMR spectrum of 2-phenyl pyrrolidine **124**; (c) ^{1}H NMR spectrum of SMCC product 75:25 mixture of 3- and 2-phenyl pyrrolidine **288** and **124** (signal at 3.75 corresponds to ISTD 1,3,5-trimethoxybenzene OMe peak) 176

Figure 4.4: Structures of the ligands screened in the SMCC of 3-BF_3K pyrrolidine **50** 190

Figure 5: Representative GC calibration curve for 4-phenyl *N*-PMP pyrrolidone **206** 213

Figure 6: Representative GC calibration curve for 4-BF_3K *N*-PMP pyrrolidone **206** 214

Figure 7: Representative GC calibration curve for 3-phenyl pyrrolidine **288** 215

Figure 8: Representative GC calibration curve for 3-phenyl pyrrolidine **288** and 2-phenyl pyrrolidine **124** 215

List of Tables

Table 1.1: Molander, Dreher et al.'s HTS of cyclopentyl BF_3K **19** with 2-chloroanisole using different solvents and ligands 16

Table 1.2: Biscoe, Sigman and coworkers aryl halide effects on stereochemical outcome 32

Table 1.3: Biscoe, Sigman and coworkers ligand electronic effects on stereochemical outcome 33

Table 2.1: Deviations to the standard SMCC conditions 57

Table 2.2: Effect of oxygen on the SMCC reaction of 2-Bpin tetrahydrothiophene . 62

Table 2.3: Optimisation of DMF benzylations of (*R*,*R*)-**161** 69

Table 2.4: Optimisation of benzylation using NaH and crown ethers in THF 71

Table 3.1: SMCC of 4-BF_3K *N*-R pyrrolidones with bromobenzene or chlorobenzene 112

Table 3.2: SMCCs of 4-Boryl N-PMP pyrrolidone with bromobenzene 117

Table 3.3: Evaluation of $Pd(OAc)_2$ and cataCXium A as an alternative catalytic system 119

Table 3.4: DOE full factorial design results 121

Table 3.5: Screening of the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with alternative ligands at 10 or 20 mol% (ligand) loading 123

Table 3.6: Screening of the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with different eq. of **192** and PhBr 126

Table 3.7: Screening of the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with alternative bases and additives 127

Table 3.8: Screening of the SMCC of 4-BF_3K N-PMP pyrrolidone **192** with different palladium sources 128

Table 3.9: Screening of the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with different eq. of water 129

Table 3.10: Screening of the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with various solvents and with CuI as additive 130

Table 3.11: Screening of the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with different eq. of Cs_2CO_3 131

Table 3.12: Screening of the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with different loadings of $Pd(OAc)_2$, concentrations of toluene and reaction times 132

Table 3.13: Isolated yields of the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with different mol% of $Pd(OAc)_2$ and cataCXium A 133

Table 3.14: Screening of the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with PhCl and PhI 141

Table 4.1: Validation of reaction scale – SMCC of 3-BF_3K pyrrolidine **50** with bromobenzene 179

Table 4.2: Validation of reaction set-up – SMCC of 3-BF_3K pyrrolidine **50** with bromobenzene 180

Table 4.3: DOE full factorial design results for 3-BF_3K pyrrolidine **50** with bromobenzene 181

Table 4.4: SMCC of 3-BF_3K pyrrolidine **50** with different cataCXium A : $Pd(OAc)_2$ ratio 185

Table 4.5: SMCC of 3-BF_3K pyrrolidine **50** with different eq. of bromobenzene .. 186

Table 4.6: Screening of the SMCC of 3-BF_3K pyrrolidine **50** with different ligands 188

Table 4.7: Screening of the SMCC of 3-BF_3K pyrrolidine **50** using different ratios of toluene : water while maintaining overall concentration 192

Table 4.8: Screening of the SMCC of 3-BF_3K pyrrolidine **50** using different concentrations of toluene while maintaining equivalents of water..... 192

Table 4.9: Screening of the SMCC of 3-BF_3K pyrrolidine **50** using different bases 194

Table 4.10: Screening of the SMCC of 3-BF_3K pyrrolidine **50** using different loadings of palladium maintaining the cataCXium A : palladium ratio..... 195

Table 4.11: Screening of the SMCC of 3-BF_3K pyrrolidine **50** using different aryl halides 196

Table 5.1: SMCC DOE screening of 3-BF_3K pyrrolidine using General Procedure K 378

Table 5.2: Screening of the SMCC of 3-BF_3K pyrrolidine **50** with different ligands using General Procedure L..... 385

Table 5.3: Screening of the SMCC of 3-BF_3K pyrrolidine **50** with different ligands using General Procedure L..... 386

Table 5.4: Screening of the SMCC of 3-BF_3K pyrrolidine **50** with different volumes of toluene and water using General Procedure M..... 389

Table 5.5: Screening of the SMCC of 3-BF_3K pyrrolidine **50** with different volumes of toluene using General Procedure M 390

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x

Author's Declaration

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

List of Abbreviations

°C	Degrees Centigrade
3D	3-Dimensional
aq.	Aqueous
BIDA	*N*-2-benzyloxycyclopentyl-iminodiacetic acid
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
BINOL	1,1′-Bi-2-naphthol
Boc	*tert*-Butoxycarbonyl
br	Broad
BCP	Bicyclo[1.1.1]pentyl
BTCAI	Benzyl 2,2,2-trichloroacetimidate
CAN	CericIV ammonium nitrate
CBS	Corey-Bakshi-Shibata
CEC	Cross-electrophile couplings
COD	1,5-cyclooctadiene
m-CPBA	*meta*-Chloroperoxybenzoic Acid
CPME	Cyclopentyl methyl ether
CSP-HPLC	Chiral Stationary Phase - High Performance Liquid Chromatography
d	Doublet
dba	Dibenzylideneacetone
DEPT	Distortions Enhancement by Polarization Transfer
DHODH	Dihydroorotate Dehydrogenase
DIPEA	*N*,*N*-Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	Dimethylaminopyridine
dme	1,2-Dimethoxyethane

DMEDA	*N,N′*-Dimethylethylenediamine
DMF	*N,N*-dimethylformamide
DMSO	Dimethylsulfoxide
DOE	Design of Experiments
dppf	1,1'ferrocenediyl-bis(diphenylphosphine)
dtbbpy	4,4′-Di-tert-butyl-2,2′-dipyridyl
dtbpf	1,1'-Bis(di-tert-butylphosphino)ferrocene
dr	Diastereomeric ratio
eq.	Equivalents
er	Enantiomeric ratio
ESI	Electrospray Ionisation
Et	Ether
FDA	The US Food and Drug Administration
FT-IR	Fourier Transform Infra-red Spectroscopy
g	Gram(s)
GABA	Gamma-aminobutyric acid
G2	Generation 2
G3	Generation 3
G4	Generation 4
GC	Gas Chromatography
GSK	GlaxoSmithKline
h	Hour(s)
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HTE	High-Throughput Experimentation
HTS	High-Throughput Screening
Hz	Hertz

IC-50	Half-maximal Inhibitory Concentration
IκB	Inhibitor of nuclear factor kappa-B
IKK-2	Inhibitor of nuclear factor kappa-B kinase subunit beta
IR	Infra-red
ISTD	Internal Standard
J	Coupling constant in Hz
kg	Kilogram
LDA	Lithium Diisopropylamine
LED	Light Emitting Diode
LUMO	Lowest-unnocupied molecular orbital
m	Multiplet
M	Molar
m	*meta*
M^+	Molecular ion
m/z	Mass to charge ratio
MC4R	Melanocortin-4 receptor
MDM2	Mouse Double Minute 2
Me	Methyl
mg	Milligrams
MHz	Megahertz
MIDA	*N*-Methyliminodiacetic acid
min	Minute
mL	Millilitre
mmol	Millimole
mol	Mole
mp	Melting Point
NBS	*N*-Bromosuccinimide

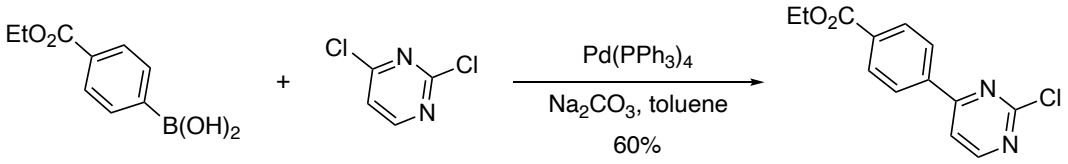
n-BuLi	*n*-Butyllithium
neop	Neopentyl
NHC	*N*-heterocyclic carbene
NLRP3	NLR family pyrin domain containing 3
NMP	*N*-Me pyrrolidone
NMR	Nuclear Magnetic Resonance
OFAT	One-Factor at a Time
o	*Ortho*
p	*Para*
PDB	Protein Data Bank
PEPPSI	Pyridine-enhanced precatalyst preparation stabilization and initiation
PI3K	Phosphoinositide 3-kinases
pin	Pinacolato
PMHS	Polymethylhydrosiloxane
q	Quartet
RE	Reductive Elimination
React-IR	React Infra-red
s	Singlet
SAR	Structure Activity Relationship
s-BuLi	*sec*-Butyllithium
SMCC	Suzuki-Miyaura cross-coupling
S_NAr	Nucleophilic Aromatic Substitution
SV2A	Synaptic vesicle glycoprotein 2A
t	Triplet
t	*tert*
T3P	Propanephosphonic acid anhydride
TBAF	Tetrabutylammonium fluoride

TBAI	Tetrabutylammoniumiodide
TBTU	2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TriBOT	2,4,6-tris(benzyloxy)-1,3,5-triazine
TS	Transition state
UV	Ultraviolet
δ	Chemical shift
μ	Micro

Chapter: 1 Introduction

1.1 Importance of sp^3 Character in Drug Design

A 2011 analysis of reaction type using the published output of the medicinal chemistry departments of GlaxoSmithKline, Pfizer and AstraZeneca as the dataset showed that the sp^2-sp^2 Suzuki-Miyaura cross-coupling (SMCC) reaction made up ~4.6% of all reactions, placing it amongst the top ten most used reactions in medicinal chemistry.[1] Further analysis by sub-type places the SMCC reaction as being responsible for 40.2% of all carbon-carbon bond forming reactions. The prevalence of the SMCC reaction in medicinal chemistry is due to several factors. The reaction operates under mild conditions often in any desired solvent,[2] it can display high chemoselectivity and regioselectivity, it is compatible with high-throughput experimentation (HTE) and the aryl coupling partners are both commercially ubiquitous and bench-stable.[3] A representative sp^2-sp^2 SMCC from the synthesis of Momelotinib, a GSK therapeutic for myelofibrosis-associated anaemia, is shown in Scheme 1.1.[4]



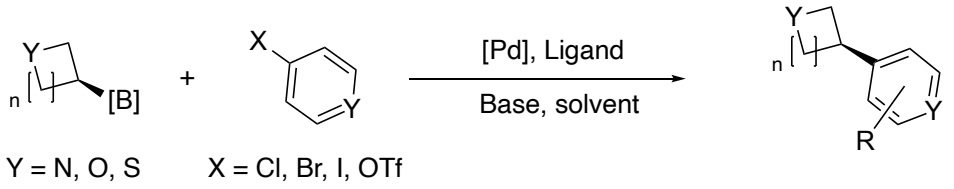
Scheme 1.1

The abundance of the SMCC reaction, especially in HTE, has been credited as a substantial component of the over-planarisation of drug-compound libraries.[1,5] In the early 2000s, the lack of diversity in hit molecules began to be addressed through increased efforts in diversity-oriented synthesis, which aimed to enhance the architectural complexity of compound libraries.[6] In 2009, Lovering *et al*. introduced the concept of Fsp^3 – the fraction of sp^3 hybridised carbons in a molecule – as a useful descriptor for three-dimensionality in drug candidates.[5] It was suggested that the complexity of a molecule can be encompassed by Fsp^3 and the binary presence of a stereogenic centre, and that this complexity directly correlated with success as compounds transition from discovery through clinical testing to drugs. This was extended in 2013 where it was suggested that Fsp^3 as a description of molecular complexity also correlated to reduced promiscuity and lower cytochrome P450

inhibition.[7] More recent reports have correlated increased 3D character in drugs with increased selectivity to the target resulting in decreased promiscuity and off-target effects. This was attributed to the fact that more complex 3D shapes have constrained molecular conformations making it less likely and more challenging for them to fit in unrelated off-target binding sites.[8] In 2020, Wei *et al*. demonstrated that the average Fsp^3 value increases from ~0.36 in a broad set of screening molecules up to ~0.47 in approved drugs,[9] adding support to the original claims by Lovering *et al*.[5] However, a recent 2025 report from Churcher, Murray and Newbold called the relation of high Fsp^3 character and clinical trial success rate into question.[10] Nevertheless, the dominance of sp^2 character in drug compounds remains evident in recent publications. For example, analysis of ligands found in the Protein Data Bank (PDB) and molecules from DrugBank by Cohen *et al*. revealed a persistent trend towards linearity and planarity,[11] indicating that the issue is just as prevalent today.

A comparative analysis of chemical reactions used in medicinal chemistry in 2014 and in 1984 revealed that none of today's most frequently employed synthetic methods had been discovered in the past 20 years, with only two, SMCC and Buchwald-Hartwig amination, originating in the late 1970s and 1990s, respectively.[12] New methodologies are needed to address the growing demand for molecular complexity, and new developments in the area of sp^3-sp^2 cross-couplings could be particularly useful. However, their adoption in industry will depend on meeting a range of forward-looking criteria. For example, the methodology must aim to be compatible with HTE for parallel screening and library synthesis, highly tolerant to a variety of functional groups, operationally uncomplicated, conform to green metrics and sustainability and proceed with stereoselectivity or, more correctly, with controllable stereochemical outcomes.[13–15] Some commonly used methods for performing sp^3-sp^2 cross-coupling reactions that are potentially compatible with these parameters include palladium-catalysed Negishi cross-couplings, nickel-catalysed cross-electrophile couplings, nickel/photoredox dual catalysis methods and the aforementioned SMCC reaction.[16,17] As discussed, SMCC is a widely prevalent and widely utilised reaction that already meets many of the forward-looking criteria required for industrial adoption. A variant enabling routine sp^3-sp^2 cross-couplings would therefore provide medicinal chemists with a novel yet familiar transformation to increase molecular complexity while remaining compatible with these important benchmarks (Scheme 1.2).[13] Moreover, in

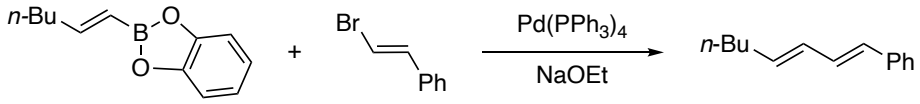
contrast to alternative approaches such as nickel/photoredox dual catalysis, the sp^3-sp^2 SMCC is inherently suited for a highly efficient transfer of stereochemistry (from an enantiopure alkyl-boron compound with a predefined configuration) without the need for a bespoke chiral catalyst, further underscoring its potential impact in medicinal chemistry.



Scheme 1.2

1.2 Introduction to the Suzuki-Miyaura Cross-Coupling

Suzuki and Miyaura first reported the sp^2-sp^2 Suzuki-Miyaura reaction in 1979, and Suzuki attained an equal share of the 2010 noble prize alongside Heck and Negishi for their contributions to palladium-catalysed cross-couplings in organic synthesis.[18] An example of one of the original sp^2-sp^2 SMCCs carried out by Suzuki and Miyaura in their initial report is shown in Scheme 1.3.[19] Since the discovery of the SMCC, many studies have been conducted investigating various combinations of base, solvent and catalyst for their effects on selectivity and yield of the cross-coupling reactions.[20] Several first row transition metals such as iron, copper and nickel have been investigated as catalysts for SMCC reactions due to their wider availability and high terrestrial abundance compared to palladium. However, palladium catalysts are still the most used and optimal choice in the majority of cross-coupling reactions.[3]



Scheme 1.3

A high proportion of research has been directed towards ligand design, and the understanding of the steric and electronic properties of ligands designed for palladium in the SMCC reactions.[21] Commonly used phosphine ligands are typically strongly electron-donating and sterically bulky such as tertiary tri-alkyl phosphines (PR_3) or the now common bi-aryl phosphine ligands developed by Buchwald *et al*.[22] The advantage of using bulky electron-rich ligands for SMCCs can be partly justified from fundamental sp^2-sp^2 SMCC research. This refers to electronic stabilisation of the Pd^{II} oxidative addition product and the promotion of reductive elimination *via* steric bulk.[22,23] However, arguments based on the formation of a more reactive mono-ligated palladium species should be discounted until a more thorough understanding of catalyst speciation for the system in question is obtained.[24] Design of well-defined palladium precatalysts has also seen a plethora of advancements since the discovery of the SMCC reaction in 1979. Major developments of dimeric Pd^{I} precatalysts were made by Schoenebeck *et al*.[25] Several generations of Pd^{II} palladacycles were developed by Buchwald *et al*. which are both air- and moisture-stable, generating the active Pd^0 species through reaction with base.[26] Precatalysts containing *N*-heterocyclic

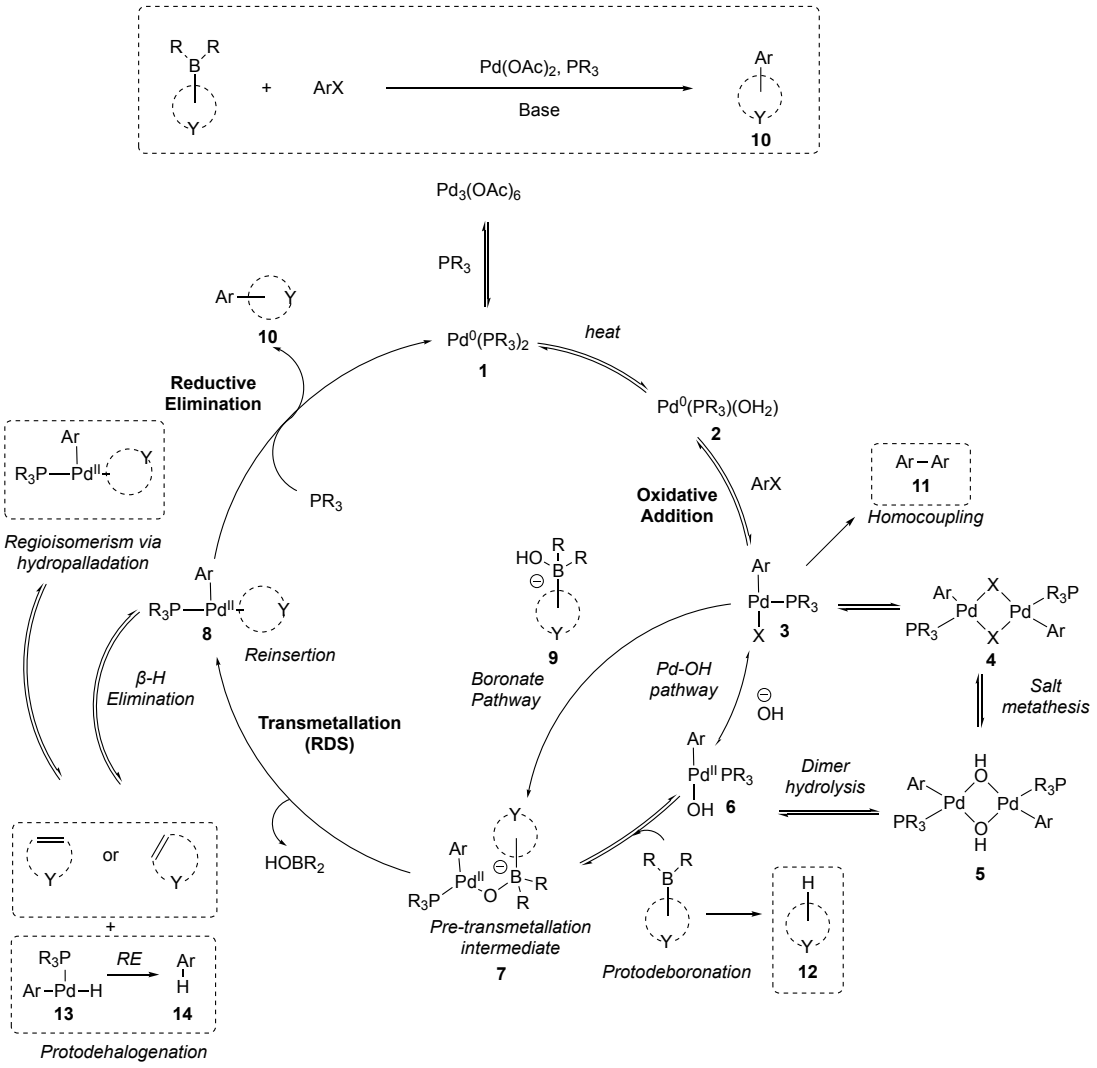
carbene (NHC) ligands have also been developed, with the PEPPSI class gaining more mainstream adoption.[3,27] The development of air- and moisture-stable precatalysts has been a great advantage to HTE. As precatalysts encompass both ligand and a Pd^0 precursor, there is no variation from palladium speciation that can occur between a separate precatalyst source and ligand. Therefore, for HTE, modern precatalysts not only reduce the number of components of the reaction but reduce overall variation between reactions. Overall, a vast increase in mechanistic understanding of sp^2-sp^2 SMCC since its conception has led to rapid and powerful advancements in the methodology.

1.3 Mechanistic Challenges in the sp^3-sp^2 Suzuki-Miyaura Cross-Coupling

The synthesis of sp^3-sp^2 carbon-carbon bonds by SMCC is intrinsically more challenging than the corresponding construction of sp^2-sp^2 carbon-carbon bonds. This is, in part, due to the increased challenge presented with *sec*-alkyl-borons. To understand these challenges, it is important to consider the catalytic cycle. Our proposed catalytic cycle is presented in Scheme 1.4, which also contains the prevalent side reactions. Our catalytic cycle is based on available evidence primarily taken from mechanistic studies of sp^2-sp^2 SMCC reactions. The SMCC reaction is proposed to follow a well-defined catalytic cycle of three steps: oxidative addition, transmetallation and reductive elimination. The first and last of these steps are common to all cross-coupling reactions and have been well studied both experimentally and computationally. However, transmetallation steps are unique to each cross-coupling as they differ in the type of nucleophile used. Moreover, experimental data is typically difficult to obtain for this step. As a result, even in the well-studied sp^2-sp^2 SMCC examples, transmetallation remains the least understood of the three key steps. In the far less explored sp^3-sp^2 SMCCs, this gap in understanding presents a significant barrier to further methodological development.

The first step of the catalytic cycle involves activation of a precatalyst, in this case demonstrated from $Pd_3(OAc)_6$ which, in solution, exists as a trimer in equilibrium with the corresponding dimeric and monomeric forms. In the presence of excess phosphine ligand, autoactivation *via* intramolecular reaction generates coordinatively unsaturated Pd^0 complex $Pd(PR_3)_2$ **1**, which is typically stabilised by organophosphine ligands or other additives in the reaction.[28,29] Following precatalyst activation, oxidative addition of $Pd(PR_3)_2$ **1**, likely *via* $Pd^0(PR_3)(OH_2)$ **2**, in the presence of an excess of aryl halide and sufficiently high temperature can form oxidative addition monomer **3** which could rapidly dimerise to form bridged halo dimer **4**. Under the basic conditions of the SMCC reaction, hydrolysis of bridged halo dimer **4** would form bridged hydroxy dimer **5** which is in equilibrium with palladium hydroxy monomer **6**. Oxidative addition of aryl iodides and bromides is often facile under SMCC conditions[3] and,

even with relatively inactivated bonds such as C-Cl for aryl chlorides, judicious choice of ligand can maintain an efficient oxidative addition step.[30] Complexation with the alkyl-boron will then form the relatively stable (depending on the nature of the alkyl-boron) pre-transmetallation intermediate **7**. Consequently, transmetallation, the proposed rate determining step,[31] occurs with loss of $HOBR_2$ to generate alkyl-Pd^{II}-aryl complex **8**. There is, however, some debate over whether transmetallation proceeds *via* the oxo-palladium pathway or the boronate pathways (both shown in Scheme 1.4). The pathways differ in the role of the base in SMCC. For example, in the boronate pathway, reaction between the neutral alkyl-boron and base forms nucleophilic tetrahedral boronate **9**. In contrast, in the oxo-palladium pathway, base interaction with oxidative addition monomer **3** or dimer **4** and ultimately results in formation of the more reactive palladium hydroxy monomer **6**. Computational work by Maseras *et al*.[32,33] proposed that the boronate pathway would be the most plausible. However, the main counter argument to this proposal came from kinetic studies performed by Hartwig *et al*.[34] which, under weakly basic conditions, showed that transmetallation proceeded from an alkoxo-Pd^{II} complex and a neutral alkyl-boron species. Various kinetic studies have supported Hartwig's oxo-palladium pathway such as the work from Amatore, Jutand and Le Duc.[35,36] However, recent experimental data from Lima *et al*.[37] investigating the role of the base, added support to the work of Maseras *et al*.[32] This work proposed that the transmetallation step was the rate determining step in the reaction thus supporting the hypothesis that the boronate pathway, as the faster pathway, is operative over the oxo-palladium pathway. Whichever of the two pathways is operative in a given system, it is followed by a rapid reductive elimination from alkyl-Pd^{II}-aryl complex **8** to generate cross-coupled product **10** and ideally regenerate $Pd(PR_3)_2$ **1**. However, it is also possible that agglomeration of palladium occurs over regeneration of the active catalyst resulting in the formation of palladium black.



Scheme 1.4

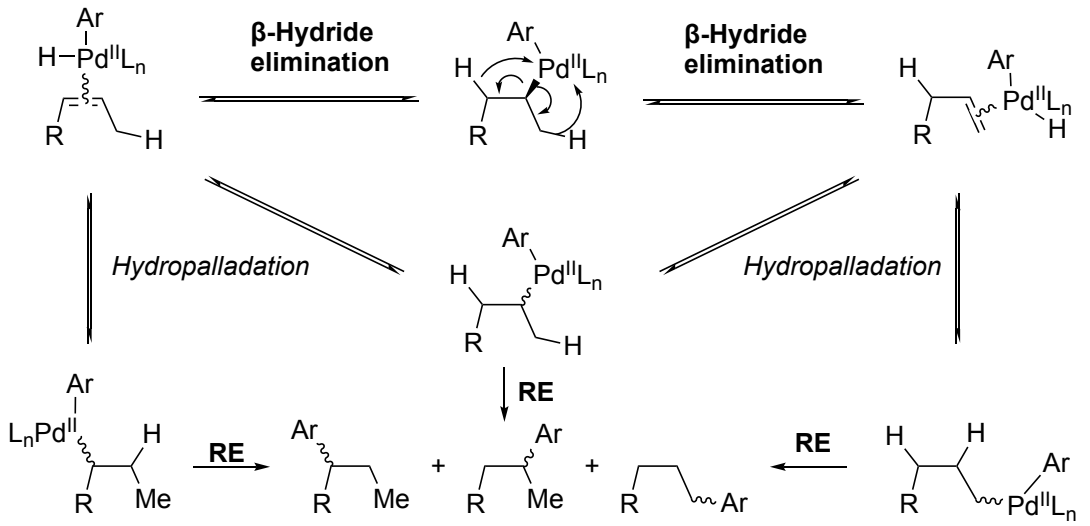
There are three main challenges with sp^3-sp^2 SMCC reactions, namely the slow rate of transmetallation, competitive rates of β-hydride elimination/reductive elimination leading to side-products, and control of the stereochemical outcome of the cross-coupling.

The slow rate of transmetallation is due to the use of more sterically hindered and less activated alkyl-boron compounds compared to typical aryl-borons used in sp^2-sp^2 SMCCs. Furthermore, if *sec*-alkyl-borons are used, the rate of transmetallation is significantly slower than their *n*-alkyl analogues further increasing the challenge of the cross-coupling. Overall, the slow transmetallation step is overcome by using higher temperatures than usual sp^2-sp^2 SMCC reaction conditions. For these reasons, transmetallation is proposed as the rate determining step for sp^3-sp^2 SMCCs.

The slow rate of transmetallation can lead to a build-up of oxidative addition complex **3** (or derivatives) as it waits to proceed through the transmetallation bottleneck. Accumulation of **3** can lead to generation of bi-aryl **11** through a degradative side reaction of aryl-aryl homocoupling (Scheme 1.4). Furthermore, a similar issue exists with the alkyl-boron nucleophile which also waits at the transmetallation bottleneck. The profile of the alkyl-boron nucleophile must be active enough to undergo transmetallation, but if it is too reactive it can decompose, with the most common pathway being protodeboronation, a reaction in which the boron substituent is replaced by a proton to form alkanes **12**.[38] Although less frequently observed, it is also possible for alkyl-alkyl homocoupling of the alkyl-boron compound to occur during SMCC reactions.[39]

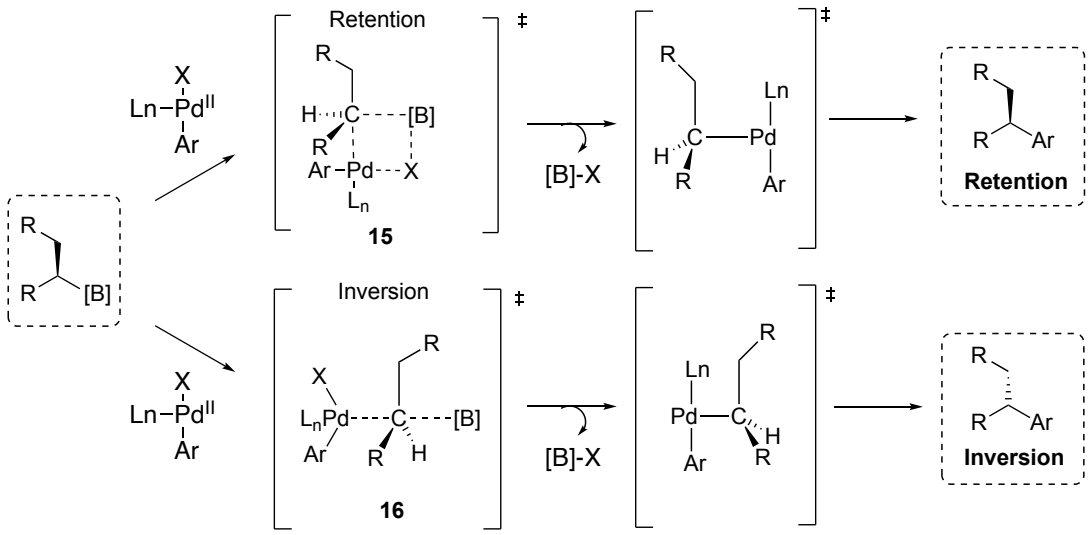
The rate of reductive elimination of alkyl-Pd^{II}-aryl **8** needs to outcompete the competitive rate of β-hydride elimination which generates alkene side-products. In some cases, β-hydride elimination can result in generation of regiosiomeric alkene side-products (Scheme 1.4). The regiosiomeric alkenes can undergo hydropalladation to give Pd^{II} intermediates, which, following reductive elimination, will give a mixture of regioisomeric cross-coupled products. β-Hydride elimination also generates aryl-Pd^{II}-H **13** which, *via* reductive elimination, can generate protodehalogenated side-product aryl **14**. Furthermore, the formation of regiosiomeric alkenes and reinsertion products can affect the stereochemical outcome of the product, leading to generation of cross-coupled products in variable enantiomeric ratio(s) (er).

The effect of β-hydride elimination/reinsertion on the stereochemical outcome of the product is shown in more detail in Scheme 1.5. Following transmetallation from a stereodefined alkyl-boron, the transmetallation product could undergo β-hydride elimination from either side of molecule to furnish regiosiomeric alkene side-products. Here, weak π-complexation of palladium and the alkene result in an equilibrium of free alkene and the alkene-palladium π-complex. Palladium can associate above or below the plane of the alkene, thus, following hydropalladation and reductive elimination the desired cross-coupled product and regiosiomeric side-products can be generated in variable ers.



Scheme 1.5

The sp^3-sp^2 SMCC can proceed *via* two stereospecific pathways which result in either retention or inversion of configuration at the carbon. However, it is possible that the SMCC transformation occurs *via* a mixture of the two. Thus, if the starting material is chiral and has a defined configuration, it is possible to generate cross-coupled products with variable ers. Based on experimental evidence in conjunction with the proposed mechanism for analogous Stille couplings, the mechanisms for the two sterospecific pathways have been proposed (Scheme 1.6).[40–42] Transmetallation is proposed to proceed *via* an S_E2 type mechanism which can be retentive or invertive. Retention is proposed to occur *via* **15** which contains a closed coplanar transition state. On the other hand, inversion is proposed to proceed through **16** with an axial approach of the palladium to the C-B bond. Several factors which can influence the pathway of transmetallation have been observed and are discussed in Section 2.7.10



Scheme 1.6

The challenges involved in sp^3-sp^2 SMCC reactions can be alleviated to some extent through the use of different alkyl-boron motifs. The core boron motifs often employed in sp^3-sp^2 SMCCs are $B(OH)_2$ (boronic acid), Bpin (pinacol boronate), BF_3K (potassium trifluoroborate) and BMIDA (methyliminodiacetic acid boronate), and their structures are shown in Figure 1.1.[39]

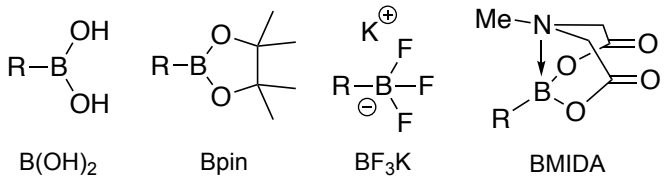
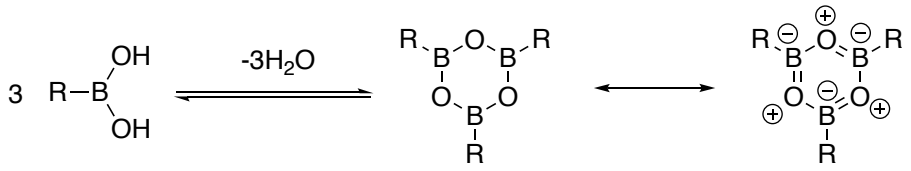


Figure 1.1: Structures of common boron motifs in sp^3-sp^2 SMCCs

Boronic acids are synthesised by a wide range of methods and are still commonly deployed in sp^2-sp^2 cross-couplings. Boronic acids can exist under an equilibrium with the partially aromatic trimeric anhydride boroxine, formed from an entropically favoured process by the association of three boronic acid molecules liberating three H_2O molecules (Scheme 1.7). This reduces the utility of boronic acids as exact stoichiometry becomes non-trivial and increases the complexity of the cross-coupling process. Boronic acids can also suffer from several side reactions such as oxidation, homocoupling and, as shown in Scheme 1.4, protodeboronation.



Scheme 1.7

One method for reducing undesired side reactions, such as those observed with boronic acids, is the use of masked boronic acids such as BF_3K salts developed primarily by Molander *et al*.[43] and BMIDA popularised by Burke *et al*.[44] Both contain sp^3 boron centres, and BMIDA derivatives achieve this *via* coordination of the Lewis basic amine. Both BF_3K salts and BMIDA derivatives are bench-stable, with efficient syntheses, but the MIDA boronates can be purified by chromatography unlike the BF_3K salts. The primary benefit of BF_3K salts in cross-coupling comes from the suppression of the detrimental side reactions observed with boronic acids. Under basic biphasic conditions, hydrolysis of BF_3K to boronic acid is slow resulting in a reduction in the maximum concentration of boronic acid present in the solution.[38] This, in combination with fluoride ions liberated during hydrolysis, reduce oxidative homocoupling and protodeboronation. In terms of transmetallation, BF_3K salts may transmetallate from a partially hydrolysed fluoro/hydroxy species. However, Lloyd-Jones *et al*. demonstrated that for sp^2-sp^2 transmetallation, catalytic turnover occurred primarily from the fully hydrolysed boronic acid.[45] This will, of course, depend on the conditions and the specific substrates.

Boronic esters, the most common being the Bpin derivative, are less reactive than boronic acids during transmetallation.[39] Inductive electron donation from carbon to oxygen increases lone pair donation of the pinacol oxygens into the empty boron p-orbital resulting in a less Lewis acidic boron. The benefits of boronates over boronic acids include an increased stability to column chromatography, solubility in apolar solvents and exclusive monomeric nature. The pathway for transmetallation with Bpin derivatives is currently unknown. Transmetallation may occur directly from the neutral Bpin with an $L_nPd^{II}(Ar)(OH)$ species or undergo complete/partial hydrolysis to a more reactive species (e.g. boronic acid, if complete hydrolysis occurs) which could proceed *via* either the oxo-palladium or boronate pathways. Moreover, the pathway and active

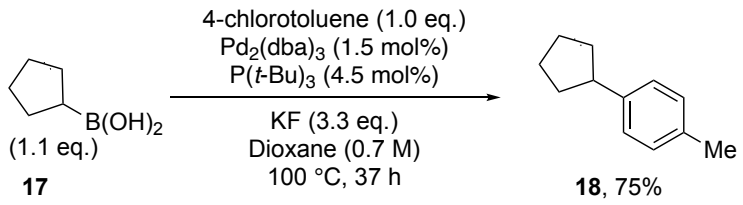
transmetallating species could be different depending on the reaction conditions and the alkyl-boron compound.

The mechanistic challenges in developing new sp^3-sp^2 SMCC reactions have been presented. These are primarily, the slow transmetallation step and the presence of a β-hydride elimination/reinsertion mechanism. Additionally, the stereochemical outcome would need to be controlled to access cross-coupled products in high enantiomeric ratio if starting from a chiral, enantiomerically enriched alkyl-boron compound.

1.4 Suzuki-Miyaura Cross-Coupling of Secondary Alkyl-Boron Compounds

The sp^3-sp^2 SMCC of acyclic alkyl-borons is now fairly-well precedented with many successful examples of cross-coupling under a variety of conditions.[17, 46–48] Relative to acyclic alkyl-borons, there are far fewer examples of sp^3-sp^2 SMCCs with cyclic alkyl-borons and even less on heterocyclic alkyl-borons. Thus, a select review of secondary carbocyclic alkyl-boron compounds in the SMCC will first be presented, followed by examples of the corresponding heterocycles. Due to the unique hybridisation status of the carbons in cyclopropanes, transmetallation is typically less of a challenge than in larger carbocyclic rings.[49] Moreover, due to geometrical requirements of the cyclopropyl ring, competing β-hydride elimination processes are not possible. For these reasons, the SMCC of 3-membered carbocyclic alkyl-borons will not be discussed and focus will be placed on four-, five- and six-membered rings. The SMCC of cyclopropyl-boron compounds for medicinal chemistry has been reviewed[50] and the O'Brien group has recently reported the development of a modular synthetic platform for fragment elaboration in 3D that utilised the reliable SMCC reactions of cyclopropyl BMIDA compounds.[51]

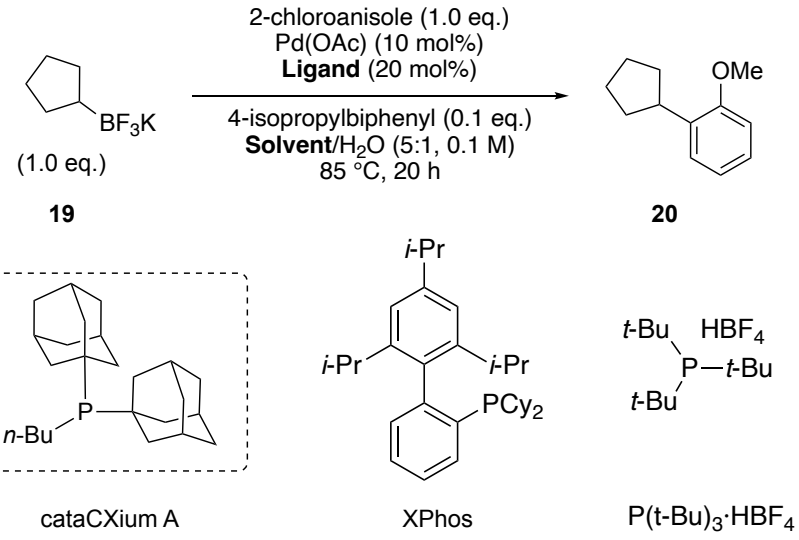
The earliest reported example of sp^3-sp^2 SMCCs with saturated carbocyclic alkyl-borons was demonstrated by Fu *et al.*[52] in 2000 whereby cross-coupling of cyclopentyl $B(OH)_2$ **17** with 4-chlorotoluene to give aryl cyclopentyl **18** was carried out in 75% yield (Scheme 1.8). The reaction used $Pd_2(dba)_3$ as precatalyst and bulky electron-rich P(*t*-Bu)$_3$ as ligand alongside KF as base in dioxane at 100 °C for 37 h. Fu *et al.* commented that the elevated temperature required compared to sp^2-sp^2 SMCCs was likely due to a slower rate of transmetallation using the sp^3 carbocyclic alkyl-boron.



Scheme 1.8

In 2008, Molander, Dreher *et al*., in collaboration with Merck, reported the first High-Throughput Screening (HTS) campaign of a sp^3 alkyl-boron in SMCC reactions, using cyclopentyl BF_3K salt **19** with 2-chloroanisole or 3-chloropyridine. A selection of the HTS results with 2-chloroanisole are detailed in Table 1.1.[53] In the screening campaign, 12 ligands and three different solvents (toluene, CPME and THF) were investigated. The results of the screening identified cataCXium A (PAd_2*n*-Bu), developed by Beller *et al*.,[54] to be a standout ligand in the set. For example, reaction of cyclopentyl BF_3K salt **19** with 2-chloroanisole using $Pd(OAc)_2$ and cataCXium A in toluene and water at 85 °C for 20 h gave aryl cyclopentane **20** in 106% HPLC yield (entry 1). The next best ligands were XPhos or P(*t*-Bu)$_3$•HBF_4, which, when used in the analogous SMCC reaction gave HPLC yields of **20** of 76% and 73% (entries 2 and 3). Clearly, the HPLC assay was overestimating the yields of **20** given the result with >100% yield (entry 1). However, indicatively, the results demonstrated that cataCXium A completely outperformed all other ligands in the set. Molander, Dreher *et al*. also found toluene to be the best solvent of the three investigated. For example, when the standard conditions were applied using cataCXium A and CPME with 2-chloroanisole, aryl cyclopentane **20** was obtained in a HPLC yield of 66% (entry 4). Similarly, use of THF gave **20** in only 30% HPLC yield (entry 5). The results of the HTS indicated that the combination of cataCXium A with $Pd(OAc)_2$ in toluene/water were the optimum conditions for the SMCC of cyclopentyl BFK salt **19**.

Table 1.1: Molander, Dreher et al.'s HTS of cyclopentyl BF_3K **19** with 2-chloroanisole using different solvents and ligands

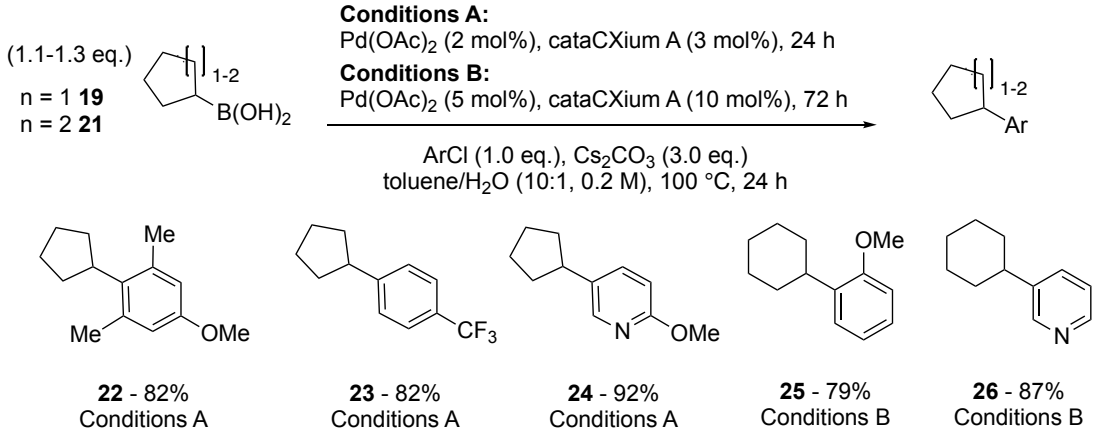


Entry	Ligand	Solvent	HPLC Yield / %[a]
1	cataCXium A	Toluene	106
2	XPhos	Toluene	76
3	P(*t*-Bu)$_3$•HBF$_4$	Toluene	73
4	cataCXium A	CPME	66
5	cataCXium A	THF	30

[a] Yield determined by HPLC using 4-isopropylbiphenyl as internal standard.

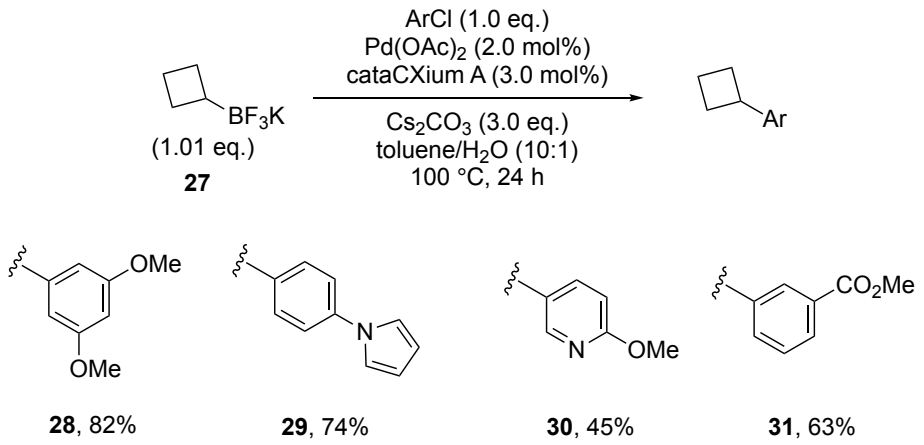
Following HTS and identification of optimised conditions, the generality of these conditions was then evaluated using a range of aryl chlorides with either of cyclopentyl BF_3K salt **19** or cyclohexyl BF_3K salt **21** (Scheme 1.9). Excellent yields were obtained across a range of aryl chlorides showing high functional group tolerance. For example, under conditions A with 2-chloro-5-methoxy-1,3-dimethylbenzene, aryl cyclopentane **22** was obtained in 82% yield tolerating both the significant steric bulk around the reaction centre and the electron-rich aromatic group. Similarly, high tolerance to electron-poor aromatics and heteroaromatics was demonstrated by the 82% and 92% yields obtained of aryl cyclopentanes **23** and **24** respectively. Significantly, the high yields observed in the SMCC of cyclopentyl BF_3K **19** were obtained using only 2 mol% $Pd(OAc)_2$ loading. More forcing conditions were required for successful cross-couplings of cyclohexyl BF_3K salt **21**. Specifically, increased palladium loading (10

mol%), increased reaction time and an increased excess of cyclohexyl BF_3K salt **21** (1.3 eq.) were required. With these modifications (conditions B), cyclohexyl BF_3K salt **21** was successfully cross-coupled with 3-chloropyridine in 87% yield to give aryl cyclohexane **26**. Although aryl bromides were tolerated, yields were lower than with aryl chlorides. Significantly, when aryl iodides were used, longer reaction times were required for the reaction to go to completion.



Scheme 1.9

Shortly thereafter, Molander and Gormisky published the application of their optimised conditions to cyclobutyl BF_3K salt **27** with four aryl chlorides.[55] Moderate to good yields of cross-coupled products were obtained. For example, reaction of cyclobutyl BF_3K salt **27** with 3,5-dimethoxybromobenzene under the optimised conditions gave aryl cyclobutane **28** in 82% yield (Scheme 1.10). Although the scope of cyclobutyl cross-couplings was limited to these four examples, it was reported that many reactions stalled before completion, leading to difficult purification and impure product mixtures. This suggests that while the conditions could generate a broader range of products, purification was the main limiting factor, highlighting an additional challenge involved in exploring sp^3-sp^2 SMCC reactions.

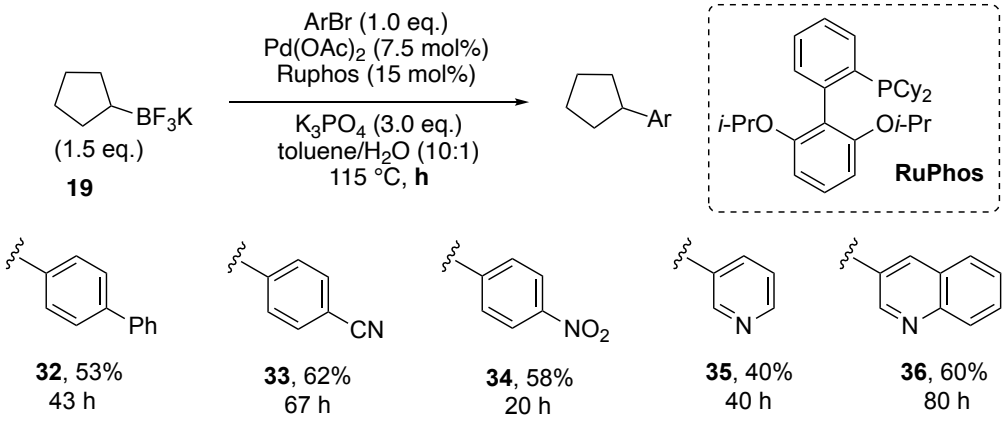


Scheme 1.10

The successful SMCC of four-, five- and six-membered carbocyclic BF_3K salts with aryl chlorides highlights the efficiency of the optimised conditions identified by Molander, Dreher *et al*.[53] The combination of cataCXium A and $Pd(OAc)_2$ was first employed by Beller *et al*.[54] in 2000 for the sp^2-sp^2 SMCC of aryl chlorides with aryl boronic acids. Beller *et al*. investigated a series of diamantylalkylphosphanes and found cataCXium A to exhibit exceptional reactivity. Using cataCXium A they were able to show excellent yields in the SMCC using just 0.005 mol% of $Pd(OAc)_2$. From the work of Molander, Dreher *et al.,* their optimised cataCXium A conditions for sp^3-sp^2 SMCCs have been replicated in numerous subsequent reports, many of which will be discussed herein. This emphasises the effectiveness of bulky electron rich ligands for sp^3-sp^2 cross-couplings. The benefits of bulky electron rich ligands in sp^3-sp^2 have been somewhat rationalised, however, the reasoning behind the enhanced activity of cataCXium A within this subclass of ligand remains unknown.

A concurrent investigation by van den Hoogenband *et al*.[56] identified RuPhos as a suitable ligand for the sp^3-sp^2 SMCC of cyclopentyl BF_3K salt **19** with aryl bromides. Their optimised conditions were an excess of cyclopentyl BF_3K salt **19**, $Pd(OAc)_2$, RuPhos and K_3PO_4 in toluene/water (10:1) at 115 °C for up to 80 h. Under these conditions, moderate to good yields were obtained with seven different aryl bromides. In some cases, it was found that increased reaction times were required to drive the reactions to completion. For example, using 4-bromobenzonitrile, aryl cyclopentyl **33** was obtained in a 62% yield after 67 h (Scheme 1.11). In contrast, with 4-bromonitrobenzene, aryl cyclopentane **34** (58%) was obtained in only 20 h.

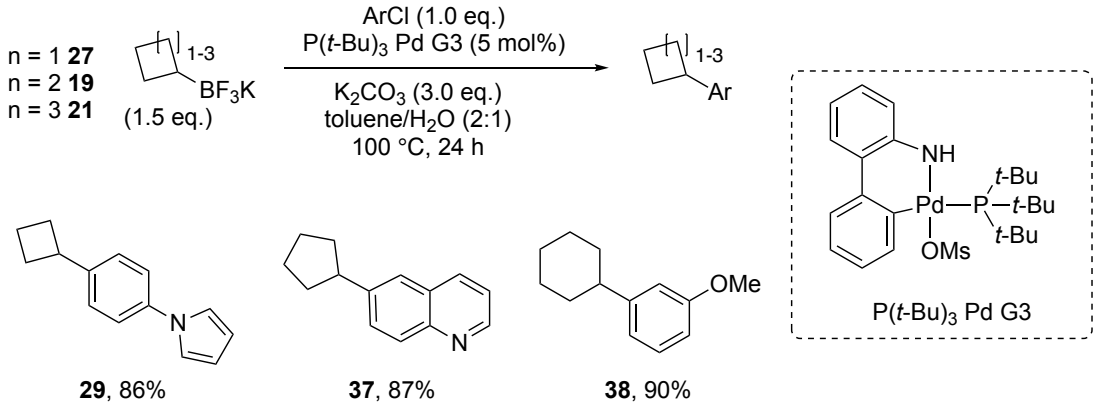
Interestingly, their use of RuPhos was driven by the identification of alkene side-products from β-hydride elimination when using less bulky phosphine ligands. It was also found that the reaction had a strong temperature dependence, such that the high reaction temperature was necessary for good conversion. However, an increase in β-hydride elimination and protodehalogenation side-products were observed at higher temperatures. This was exemplified by the reduced yields observed when the temperature was increased to 130 °C (xylene as solvent). As discussed, when β-hydride elimination is present there is also a possibility for alkene side-products to undergo hydropalladation which can generate regiosiomeric products, reducing the yield of the desired cross-coupled product. However, with unsubstituted carbocyclic alkyl-borons such as cyclopentyl BF_3K salt **19**, any reinsertion products will be undetectable as they give the same product. Thus, quantification of the alkene cannot indicate how prevalent the β-hydride elimination mechanism was in the van den Hoogenband study and how temperature affected the relative rates of β-hydride elimination and reductive elimination.



Scheme 1.11

The SMCC of a range of carbocyclic BF_3K salts was also investigated by Biscoe *et al*.[57] In this case, the SMCC of 4-6 membered carbocyclic BF_3K salts **27**, **19** and **21** was achieved using the Buchwald precatalyst P(*t*-Bu)$_3$ Pd G3, K_2CO_3 and aryl chlorides in 2:1 toluene/water at 100 °C for 24 h (Scheme 1.12). The use of third generation (G3) Buchwald precatalysts was first reported by Buchwald *et al*.[26] in 2013 and they are now in widespread use. This class of precatalysts are bench-stable, have high solution stability and break down into the active Pd^0 species easily *via* deprotonation and a subsequent reductive elimination process liberating carbazole as

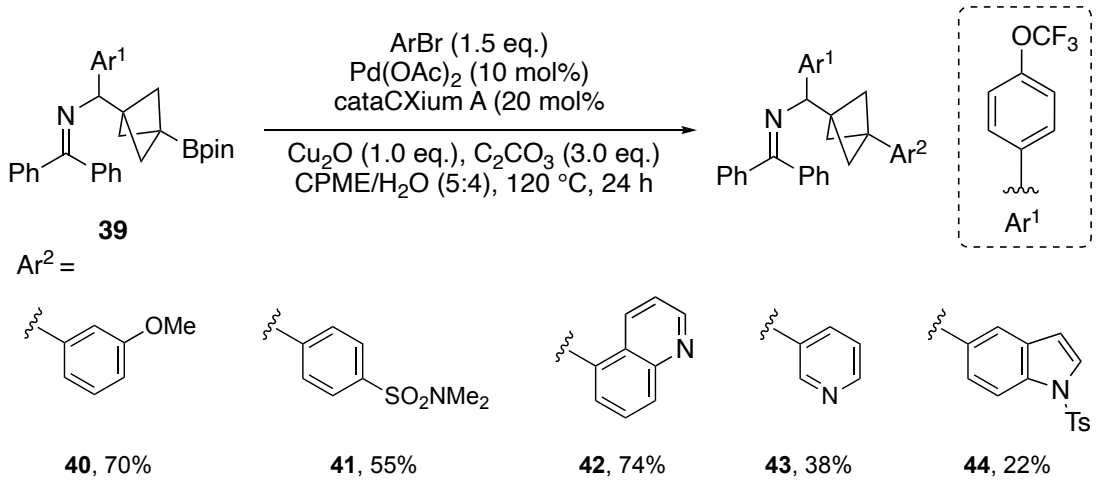
a side-product. Biscoe *et al*, showed that their conditions were transferable across each of the different sized carbocycles. For example, under the aforementioned conditions, cyclobutyl BF_3K **27** was reacted with 1-(4-bromophenyl)-1H-pyrrole to give aryl cyclobutane **29** in 86% yield (Scheme 1.12). Although the conditions used by Biscoe *et al*. are not identical to those used by Molander and Gormisky (see Scheme 1.10), they share many similarities. For example, both use $Pd(OAc)_2$, a carbonate base and toluene/water as solvent with a 100 °C reaction temperature for 24 h. Biscoe *et al*. achieved a slightly higher (86%) yield of aryl cyclobutane **29** than Molander and Gormisky (74%). However, the 74% yield of **29** achieved by Molander and Gormisky used only 2 mol% $Pd(OAc)_2$ and 3 mol% cataCXium A compared to the 5 mol% of P(*t*-Bu)$_3$ Pd G3 used by Biscoe *et al*. Although both employ bulky electron-rich ligands, the higher yield with cataCXium A underscores the unique ability of cataCXium A in sp^3-sp^2 SMCC reactions.



Scheme 1.12

CataCXium A was also found to be an efficient ligand for the SMCC of benzylamine bicyclo[1.1.1]pentyl (BCP) Bpins in a report by Walsh, Hughes *et al*.[58] Following extensive HTS, optimised conditions were found which consisted of excess aryl bromide, $Pd(OAc)_2$, cataCXium A, Cu_2O and Cs_2CO_3 in CPME/water at 120 °C for 24 h. Under these conditions, a wide range of aryl bromides were cross-coupled, and a selection are shown in Scheme 1.13. For example, using benzylamine BCP Bpin **39** and 3-bromoanisole, aryl benzylamine BCP **40** was obtained in 70% yield. Six heteroaryl bromides were successfully cross-coupled in a range of yields. For example, under optimised conditions with benzylamine BCP Bpin **39** and 5-bromoquinoline, aryl benzylamine BCP **42** was obtained in 74% yield. In contrast, when 5-bromo-*N*-

tosylindole was used, aryl benzylamine BCP **44** was obtained in only 22% yield. There are several interesting aspects to the optimised conditions which were identified through the HTS approach. During optimisation, a beneficial effect was observed with the inclusion of copper^{I} oxide. The additive was hypothesised to assist benzylamine BCP Bpin **39** during transmetallation, which due to the high steric bulk around the Bpin of **39**, was hypothesised to be particularly challenging. For similar reasons, the high temperature of 120 °C was also found to be important. Finally, the use of CPME/water as the solvent system was optimum. Given that the reported sp^3-sp^2 SMCCs described thus far have all reported the use of toluene, the CPME/water solvent system is somewhat surprising. However, the reported examples used alkyl BF_3K salts or $B(OH)_2$, and, as a result, there may be a significant relationship between the activation of alkyl Bpins in CPME/water that is beneficial for the cross-coupling.



Scheme 1.13

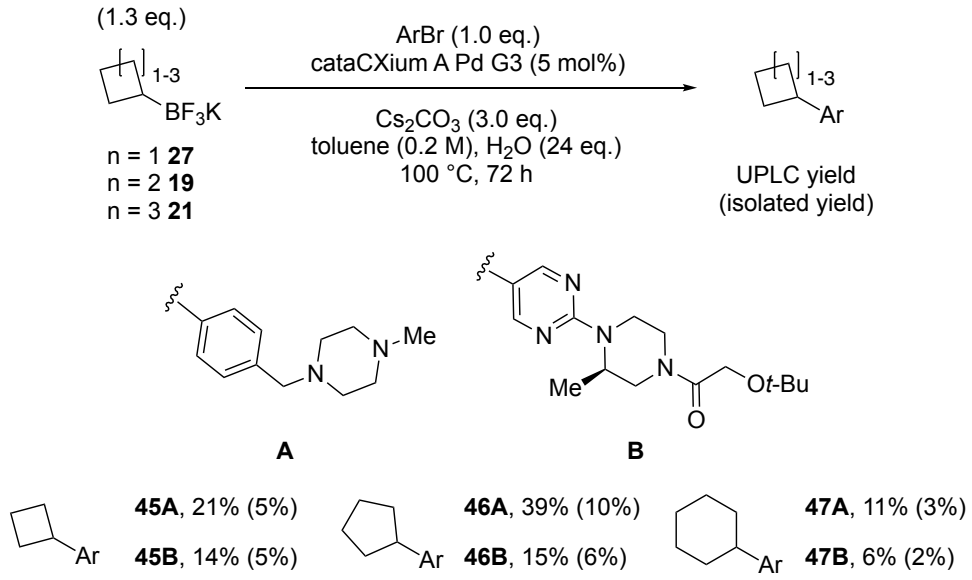
In 2020, Dombrowski, Gesmundo *et al.*[16] from AbbVie reported the comparison of a series of seven different sp^3-sp^2 cross-coupling methods using highly functionalised intermediates prevalent within medicinal chemistry. The methods included in the study were: Negishi cross-coupling, nickel/photoredox dual catalysis from alkyl BF_3K salts, decarboxylative couplings or cross-electrophile couplings (CEC), nickel-catalysed reductive CEC with alkyl bromides and SMCC using alkyl BF_3K salts or BMIDA boronates. The workflow was HTS with HPLC assay yields followed by reverse-phase HPLC purification to obtain isolated yields. Building blocks were selected which were desired in discovery project teams at AbbVie and, where possible, maximised electronic and steric diversity. This resulted in a broad range of building blocks that

included secondary, tertiary and benzylic groups as well as a variety of ring sizes. Similarly, the aryl bromides were selected as relevant examples of the challenging motifs present in library screening. Conditions were identified from a combination of publications and AbbVie's internal expertise. To minimise the number of experiments, only one or two reaction conditions were used per method. Nevertheless, for sp^3-sp^2 SMCC reactions of varied alkyl-borons, this work represents the most detailed investigation to date.

Given the HTS approach, it is unsurprising that the conditions used for SMCCs with BF_3K salts were strongly influenced by those reported by Molander, Dreher *et al*.[53] The conditions used by Dombrowksi, Gesmundo *et al*. were BF_3K salt, aryl bromide, cataCXium A Pd G3, Cs_2CO_3 in toluene/water at 100 °C for 72 h. Under these conditions, low to moderate HPLC yields and low isolated yields were obtained (Scheme 1.14). The highest yield obtained was SMCC of cyclopentyl BF_3K **19** with aryl bromide **A**, under the SMCC conditions aryl cyclopentane **46A** was obtained in 39% HPLC yield and 10% isolated yield. The 10% isolated yield underscores the challenge in isolating cross-coupled products in reactions that have not reached completion. Additionally, the 39% yield of aryl cyclopentane **46A** with such a challenging heteroaryl bromide is still a significant result. However, higher yielding SMCCs of cyclopentyl BF_3K **19** have been discussed previously (see Scheme 1.9 and Scheme 1.11),[52,53,56,57] many of which contained heteroaryl halides. However, it may be that the piperazine and piperazine/pyrimidine moieties are much more challenging coupling partners which resulted in the lower yields reported by Dombrowski, Gesmundo *et al*. Nevertheless, based on the SMCC results with cyclopentyl BF_3K **19**, these HTS results may not accurately reflect the current state of play for sp^3-sp^2 SMCC of carbocyclic alkyl-borons.

With cyclobutyl BF_3K **27** and aryl bromide **A**, aryl cyclobutane **45A** was obtained in 21% HPLC yield and 5% isolated yield. The low yield is surprising in relation to Molander and Gormisky's work where cross-coupling of cyclobutyl BF_3K **27** with a heteroaryl chloride was reported in high yield using a lower catalyst loading (see Scheme 1.10). Similarly, Biscoe *et al*., also showed success in the SMCC of cyclobutyl BF_3K **27** with a heteroaryl bromide using 5 mol% P(*t*-Bu)$_3$ Pd G3 (see Scheme 1.12). Therefore, it is not definitive whether the low yield obtained by Dombrowski,

Gesmundo *et al.* comes from subtle changes in reaction conditions, interaction from the Lewis basic piperazine nitrogens or reaction set-up/handling.

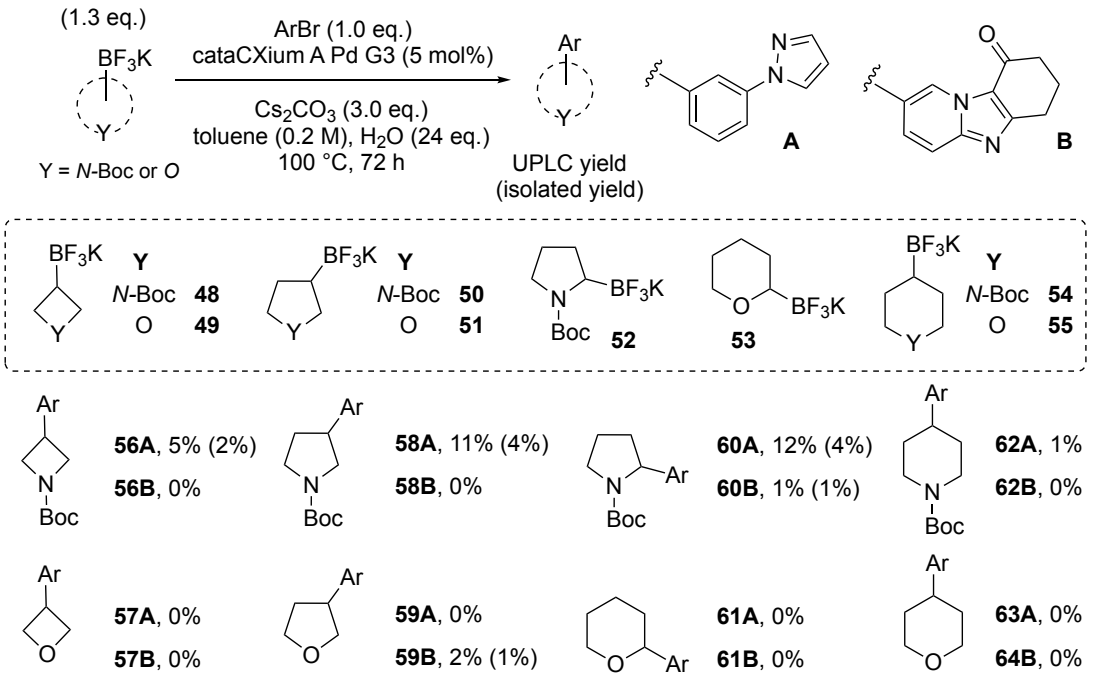


Scheme 1.14

A series of SMCC reactions using alkyl BMIDAs was explored with the same two aryl bromides. The conditions were: alkyl BMIDA (1.2 eq.), aryl bromide (1.0 eq.), SPhos Pd G3 (5 mol%), K_3PO_4 (7.5 eq.), dioxane (0.5 M) and H_2O (139 eq.). Under these conditions in any combination of aryl bromide and alkyl carbocycle, no conversion was observed. It is unclear where the lack of conversion would stem from. However, it is likely that it comes from either the use of SPhos or an incompatibility in the rate of hydrolysis of the BIMDA to $B(OH)_2$ resulting in a plethora of unproductive side reactions.

Dombrowski, Gesmundo *et al.*[16] also investigated a series of *N*- and *O*- heterocyclic BF_3K salts with two different heteroaryl bromides using the same conditions. The results are shown in Scheme 1.15. Given the disappointing results with carbocyclic MIDA boronates under the SMCC conditions, only heterocyclic BF_3K salts were evaluated in this study. Heterocyclic alkyl-borons are potentially more challenging to cross-couple due to the presence of potentially interfering heteroatoms. This can be seen reflected in the consistently low yields of cross-coupled products. For example, the highest cross-coupling yield was the SMCC of 2-BF_3K pyrrolidine **52** with aryl bromide **A** which gave 2-aryl pyrrolidine **60A** in 12% HPLC yield and 4% isolated

yield. With 3-BF_3K pyrrolidine **50** and aryl bromide **A**, 3-aryl pyrrolidine **58A** was obtained in a similar 11% HPLC yield and 4% isolated yield. With more complex aryl bromide **B**, only trace yields of cross-coupled products were obtained. For example, 3-BF_3K tetrahydrofuran **51** gave aryl tetrahydrofuran **59B** in 2% HPLC yield and 1% isolated yield. Overall, low yields were obtained with all *N*-heterocyclic BF_3K salts and even lower yields were obtained with *O*-heterocyclic BF_3K salts. This reflects the difficulty in carrying out SMCCs of heterocyclic boronates. Furthermore, it highlights the need for further development and understanding to access conditions which can cross-couple heterocyclic alkyl-borons in high yields and tolerate increased molecular complexity in line with the requirements of modern library synthesis.

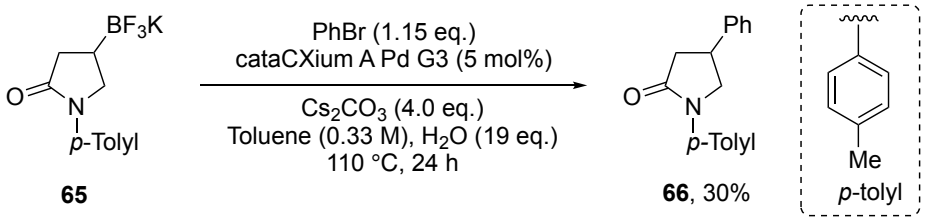


Scheme 1.15

Finally, in comparing the seven cross-coupling methods, it was found that the BF_3K SMCC showed good cross-coupling efficiency with primary alkyl groups regardless of functional groups. However, under the chosen conditions, performance of secondary alkyl BF_3K salts, especially cycloalkyl BF_3K salts, was very poor. The performance of secondary alkyl BF_3K salts in nickel/photoredox dual catalysis was suggested to present a good orthogonality for library synthesis. However, given the ability for the sp^3-sp^2 SMCC to access enantioenriched cross-coupled products, development of

conditions for high yielding SMCC of secondary alkyl-borons would be highly beneficial to medicinal chemistry applications.

Other than the detailed investigation from Dombrowski, Gesmundo *et al*.,[16] there are very few reports of sp^3-sp^2 SMCCs of heterocyclic alkyl-borons, almost exclusively in the patent literature. However, one key example was reported by Partridge *et al*.[59] using very similar conditions to those used by Dombrowski, Gesmundo *et al*. (see Scheme 1.15),[16] and Biscoe *et al* (see Scheme 1.12).[57] Partridge *et al.* reported the SMCC of 4-BF_3K *N*-*p*-tolyl pyrrolidone **65** with bromobenzene, cataCXium A Pd G3 and Cs_2CO_3 in toluene/H_2O (9:1) at 110 °C for 24 h. This gave 4-phenyl *N*-*p*-tolyl pyrrolidone **66** in 30% yield (Scheme 1.16). This is a relatively high yield for a sp^3-sp^2 SMCC reaction on a heterocyclic alkyl-boron considering that no optimisation was carried out.

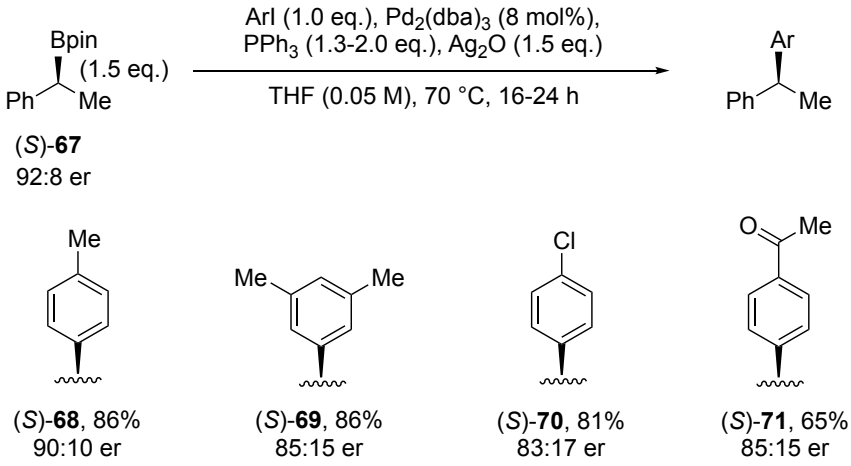


Scheme 1.16

Overall, the examples in this section demonstrate the challenges involved in developing new examples of sp^3-sp^2 SMCCs with carbocyclic and heterocyclic alkyl-borons. Collectively, the conditions used for challenging sp^3-sp^2 SMCCs broadly cover a similar chemical space. For example, most conditions use BF_3K salts, high temperatures, bulky electron-rich phosphine ligands either with $Pd(OAc)_2$ or using a Buchwald precatalyst, and a toluene/water solvent system. Particularly, the prevalence of cataCXium A stands out suggesting that, of the bulky electron-rich ligand class, cataCXium A is the most effective for enabling this type of cross-coupling reaction.

1.5 Exploration and Control of the Stereochemical Outcome of sp^3-sp^2 Suzuki-Miyaura Cross-Couplings

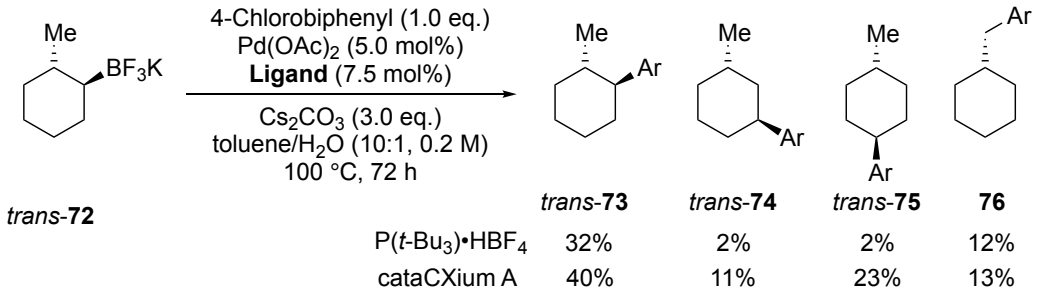
The stereochemical course of the SMCC of an acyclic secondary alkyl-boron was first reported by Crudden *et al.* in 2009.[47] The cross-coupling of methyl benzylic Bpin (*S*)-**67** was reported with a range of aryl iodides using $Pd_2(dba)_3$ with PPh_3 and Ag_2O in THF at 70 °C for 16-24 h. It was hypothesised that using Ag_2O as base would accelerate transmetallation which was postulated to be the rate limiting step.[31,60] The reaction proceeded with stereoretention and a range of cross-coupled products were obtained in high ers relative to the 92:8 er of methyl benzylic Bpin (*S*)-**67**. For example, SMCC of 1-iodo-3,5-dimethylbenzene and (*S*)-**67** gave aryl alkane (*S*)-**69** (85:15 er) in 86% yield (Scheme 1.17). Together with a subsequent report from Crudden and Aggarwal *et al.*,[61] it was proposed that the SMCC of both benzylic and allylic secondary alkyl-borons proceed with retention of configuration.



Scheme 1.17

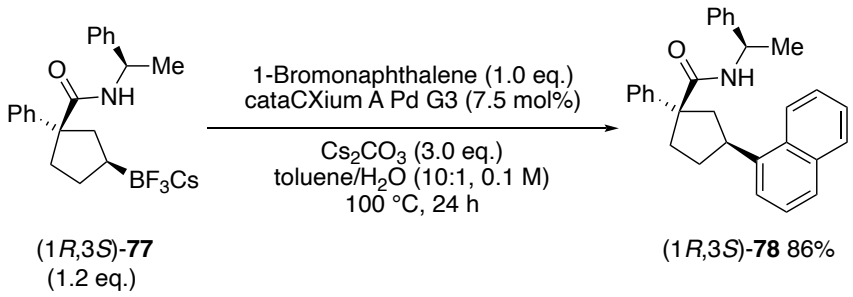
The first example of an investigation into the stereochemical outcome of a sp^3-sp^2 SMCC of a cyclic alkyl-boron compound was reported in 2008 by Molander, Dreher *et al*.[53] The SMCC of methyl cyclohexyl BF_3K *trans*-**72** was carried out in the presence of $Pd(OAc)_2$, bulky electron rich ligands P(*t*-Bu)$_3$ or cataCXium A and Cs_2CO_3 in a biphasic toluene/H_2O system at 100 °C for 72 hours (Scheme 1.18). Under these conditions, the stereoretention product methyl cyclohexyl aryl *trans*-**73** was obtained in 32% yield using P(*t*-Bu)$_3$•HB_4 and 40% yield using cataCXium A. However, with both ligands, *trans*-**73** was isolated as an impure mixture with regiosiomeric

byproducts *trans*-**74**, *trans*-**75** and **76**. These regiosiomeric products come from a β-hydride elimination/reinsertion (hydropalladation) mechanism (see Scheme 1.5) that was found to be stereospecific with the ratio of products dependent on the choice of ligand. Although cataCXium A gave a higher total isolated yield (80%) compared to P(*t*-Bu)$_3$•HB$_4$ (48%), much worse selectivity (for *trans*-**73**) was obtained. It is unknown whether it was primarily steric or electronic differences between the two ligands which accounted for the different product ratios. This experiment clearly displayed some of the major challenges in sp^3-sp^2 SMCCs, emphasising the potential issues with using unsymmetrical systems in future investigations.



Scheme 1.18

Another example of a cyclic alkyl-boron compound proceeding with a stereoretentive SMCC was reported by Takacs *et al*.[62] The SMCC used similar conditions to those reported by Molander, Dreher *et al*.,[53] namely cataCXium A Pd G3 and Cs_2CO_3 in toluene/water at 100 °C for 24 h (Scheme 1.19). As a representative example, under these conditions with cyclopentyl BF_3Cs (1*R*,3*S*)-**77** and 1-bromonaphthalene, aryl cyclopentyl (1*R*,3*S*)-**78** was obtained in 86% yield. No significant difference in the cross-coupling yields was reported when using either of BF_3K or BF_3Cs salts. Here, BF_3Cs salts were used as they were found to be easier to isolate. The stereochemical outcome of the SMCC was shown to proceed with retention of configuration and a further seven examples of the stereoretentive cross-coupling were reported using a variety of aryl chlorides and aryl bromides.



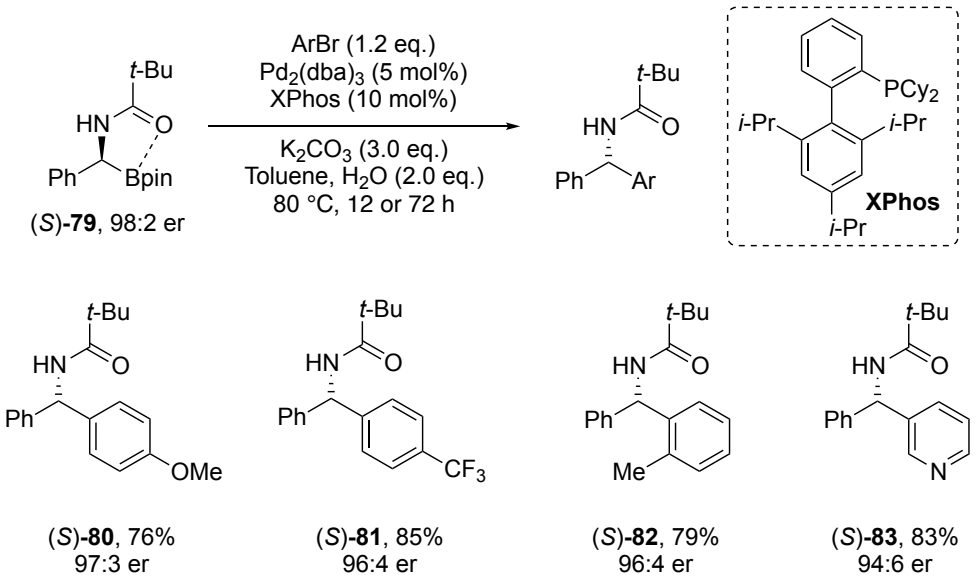
(1*R*,3*S*)-**77** (1.2 eq.)

(1*R*,3*S*)-**78** 86%

Scheme 1.19

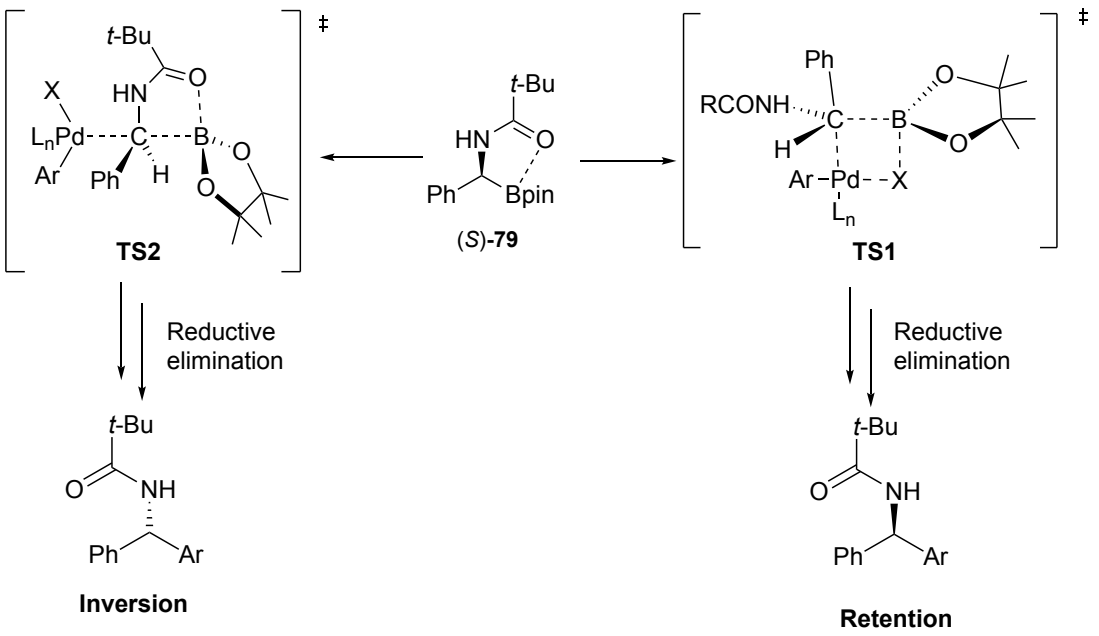
As discussed, the stereochemical outcome of transmetallation proceeds *via* competing stereodivergent pathways (retentive or invertive). It is possible for transmetallation to occur *via* a mixture of stereoretentive and stereoinvertive pathways resulting in cross-coupled products with variable ers. Such variability can also originate from competing β-hydride elimination/reinsertion pathways. There are several reported strategies to modulate or control the stereochemical outcome of the SMCC reaction. These include use of directing groups (amide,[42] ester[63]), ligand electronics,[40] ligand sterics,[41] and alkyl-boron sterics.[48]

In 2010, Suginome, Ohmura and Awano demonstrated the stereoinvertive SMCC of enantioenriched α-aminobenzyl Bpin (*S*)-**79**. The conditions used were an excess of the aryl bromide, $Pd_2(dba)_3$, XPhos, K_2CO_3 in toluene with a small amount of water at 80 °C for up to 72 h. Under these conditions, a diverse series of 11 aryl bromides was evaluated, and cross-coupled products were obtained in good to excellent yields and high ers of the stereoinvertive products. A representative selection of the aryl bromide scope is detailed in Scheme 1.20. For example, cross-coupling with electron-poor 4-bromobenzotrifluoride gave bi-aryl amine (*S*)-**81** in 85% yield and 96:4 er.



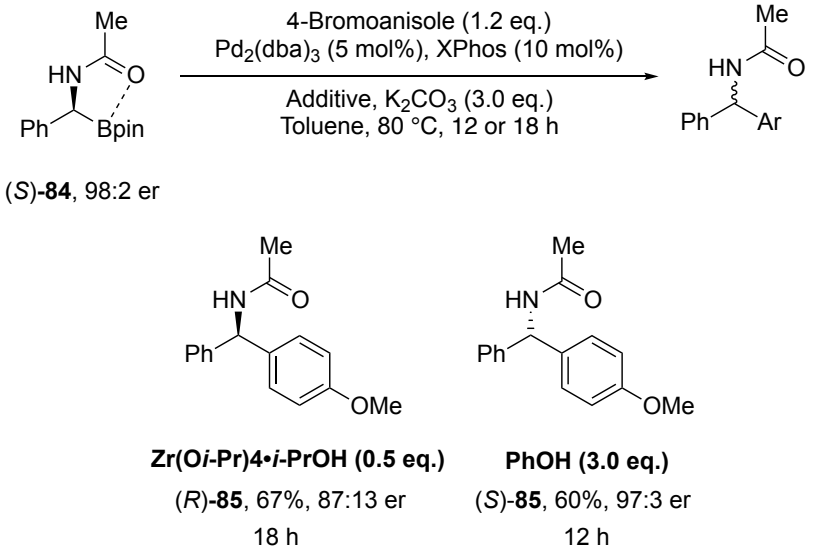
Scheme 1.20

Although no effect was observed between the electronic nature of the aryl bromide and stereochemical outcome, the steric nature of the amide group had an effect. Larger sterically demanding amide groups such as *t*-Bu increased the degree of observed inversion. In contrast, less sterically demanding groups such as methyl or ethyl displayed significantly less stereoinversion in the cross-coupled products. Based on these observations, Suginome, Ohmura and Awano proposed that the carbonyl oxygen of the amide group was coordinated to the boron (Scheme 1.21). The model is also based on the two proposed transmetallation mechanisms for retention and inversion (see Scheme 1.6). Without carbonyl coordination, a stereoretentive coplanar mechanism can occur as it is sterically favourable (TS1). However, occupation of the vacant boron p-orbital places the amide group and the boron in proximity, sterically disfavouring a boron side approach of the palladium. The axial backside approach is sterically much more accessible (TS2) when the carbonyl is coordinated to boron. Thus, when sterically bulky groups such as *t*-Bu are attached to the amide, TS2 (inversion) is even more favoured resulting in a greater degree of stereoinversion. The methodology has since been expanded by Ohmura and Suginome *et al.*[64] to successfully cross-couple α-amino alkyl Bpins, and the reactions were also shown to proceed with stereoinversion.



Scheme 1.21

Further work by Suginome *et al.* demonstrated the ability to control the stereochemical pathway of transmetallation by modulating the Lewis acid additive between PhOH (3.0 eq.) and Zr(O*i*-Pr)$_4$•*i*-PrOH (0.5 eq.) in the same class of α-amino aryl Bpin compounds.[42] The zirconium additive is proposed to undergo competitive coordination to the amide carbonyl, preventing intramolecular coordination of the oxygen lone pair into the boron p-orbital allowing the proposed retentive coplanar mechanism. Using $Pd_2(dba)_3$, XPhos, K_2CO_3 and Zr(O*i*-Pr)$_4$•*i*-PrOH in toluene at 80 °C, bi-aryl amine (*R*)-**85** (retentive product) was obtained in 63% yield and 86:14 er (Scheme 1.22). Alternatively, the phenol additive is proposed to coordinate to one of the oxygen's of pinacol, enhancing the intramolecular coordination and strengthening the O-B bond to favour the invertive mechanism. Using 3.0 equivalents of phenol, under equivalent conditions, bi-aryl amine (*S*)-**85** (invertive product) was obtained in 51% yield and 93:7 er.

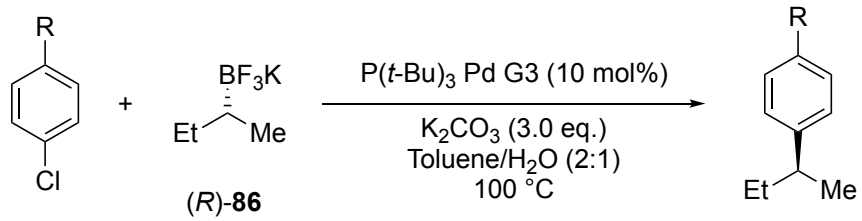


Scheme 1.22

In 2018, Sigman, Biscoe and coworkers conducted a detailed study into the effect of ligand sterics and electronics on the sp^3-sp^2 SMCC reaction of *sec*-acyclic BF_3K salts. The primary aim of the study was to design distinct ligands that respectively promoted stereoinvertive and stereoretentive cross-coupling reactions. To facilitate this, the initial ligand investigation established threshold values of steric and electronic phosphine descriptors for ligands which suppressed β-hydride elimination. Accordingly, subsequent investigation and ligand optimisation could reveal effects on the er of the cross-coupled product independently from β-hydride elimination/reinsertion processes. Thus, ligands and their parameters were investigated solely for their effect on the competing stereochemical pathways of transmetallation and how this related to the er of cross-coupled products.

Sigman, Biscoe and coworkers demonstrated that for cross-couplings of *sec*-butyl BF_3K (*R*)-**86** with aryl chlorides, the degree of observed stereoretention increased as the σ_{para} value of the *para* substituent of the aryl chloride increased (Table 1.2). The SMCC reaction of *sec*-butyl BF_3K (*R*)-**86** with 4-chloroanisole using P(*t*-Bu)$_3$ Pd G3 and K_2CO_3 in a toluene/water at 100 °C gave aryl *sec*-butane (*S*)-**87** in 96:4 er with inversion (entry 1). Changing the aryl chloride to ethyl 4-chlorobenzoate and 4-chlorobenzonitrile gave aryl *sec*-butane (*S*)-**89** and (*S*)-**91** in 79% ee and 67% ee respectively (entries 3 and 5), indicating that subtle electronic effects impact the mechanism and stereochemical outcome of transmetallation.

Table 1.2: Biscoe, Sigman and coworkers, aryl halide effects on stereochemical outcome

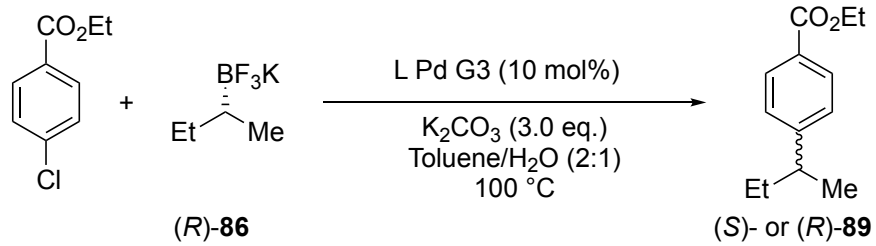


Entry	R	σ_{para}	er	Product
1	OMe	–0.27	96:4	(*S*)-**87**
2	CH_3	–0.17	91:9	(*S*)-**88**
3	CO_2Et	0.45	90:10	(*S*)-**89**
4	CF_3	0.54	86:14	(*S*)-**90**
5	CN	0.66	84:16	(*S*)-**91**

Additionally, Biscoe, Sigman and coworkers demonstrated the significant impact of ligand electronics on the stereochemical outcome of the SMCC reaction. When *sec*-butyl BF_3K (*R*)-**86** was reacted with ethyl 4-chlorobenzoate under the same conditions, using P(*t*-Bu)$_3$ Pd G3 as catalyst, the stereochemical outcome was largely stereoinvertive with aryl *sec*-butane (*S*)-**89** obtained in 90:10 er (Table 1.3, entry 1). The same reaction, carried out with cataCXium A Pd G3, gave aryl *sec*-butane **89** in 52:48 er (entry 2). These findings suggest that cataCXium A exerts minimal electronic influence on transmetallation and the rates of retentive and invertive transmetallation must be similar. This is noteworthy as cataCXium is, as shown in the previous section, one of the most prevalent ligands used for successful sp^3-sp^2 SMCC reactions. It also poses a potential concern: sp^3-sp^2 SMCCs optimised exclusively for yield rather than a combination of yield and stereofidelity may deliver high-yielding products which later prove to have poor stereochemical outcomes. Finally, using P(*o*-tolyl)$_3$ Pd G3 as catalyst, aryl *sec*-butane (*R*)-**89** was obtained in 83:17 er, primarily proceeding with retention of configuration (entry 3). Biscoe and Sigman suggested no simple correlation between ligand properties and stereochemical outcome. Therefore, they

progressed into ligand parameterisation and model generation to further interrogate the observed ligand effect on transmetallation.

Table 1.3: Biscoe, Sigman and coworkers ligand electronic effects on stereochemical outcome



(*R*)-**86** (*S*)- or (*R*)-**89**

Entry	L	er (*S*)-**89** : (*R*)-**89**
1	P(*t*-Bu)$_3$	10 : 90
2	PAd$_2$*n*-Bu	52 : 48
3	P(*o*-tolyl)$_3$	83 : 17

From ligand parameterisation, model generation and subsequent synthetic investigations it was shown that ligands must be sterically large enough to prevent unwanted β-hydride elimination. It was also found that σ-electron-rich phosphines promoted a stereoinvertive pathway and that electron-poor bi-aryl ligands promoted a stereoretentive pathway. Strong σ-donating ligands (electron-rich) were proposed to stabilise a two-coordinate cationic palladium complex favouring the stereoinvertive pathway. Alternatively, ligands which promoted π-backbonding may enhance coordination of the OH (π-donor ligand) to palladium and promote the stereoretentive pathway. This led to optimised ligands, synthesised as third generation (G3) Buchwald precatalysts: PAd$_3$ for stereoinversion and either of bis-CF$_3$PhXPhos or bis-CF$_3$PhSPhos for stereoretention (Figure 1.2).

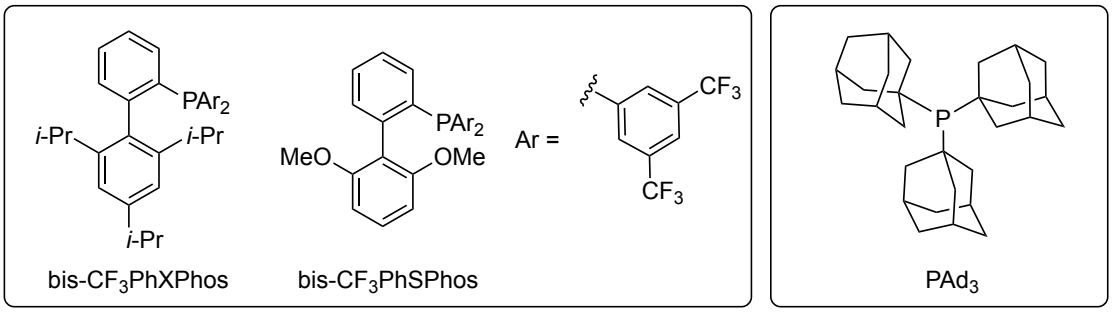
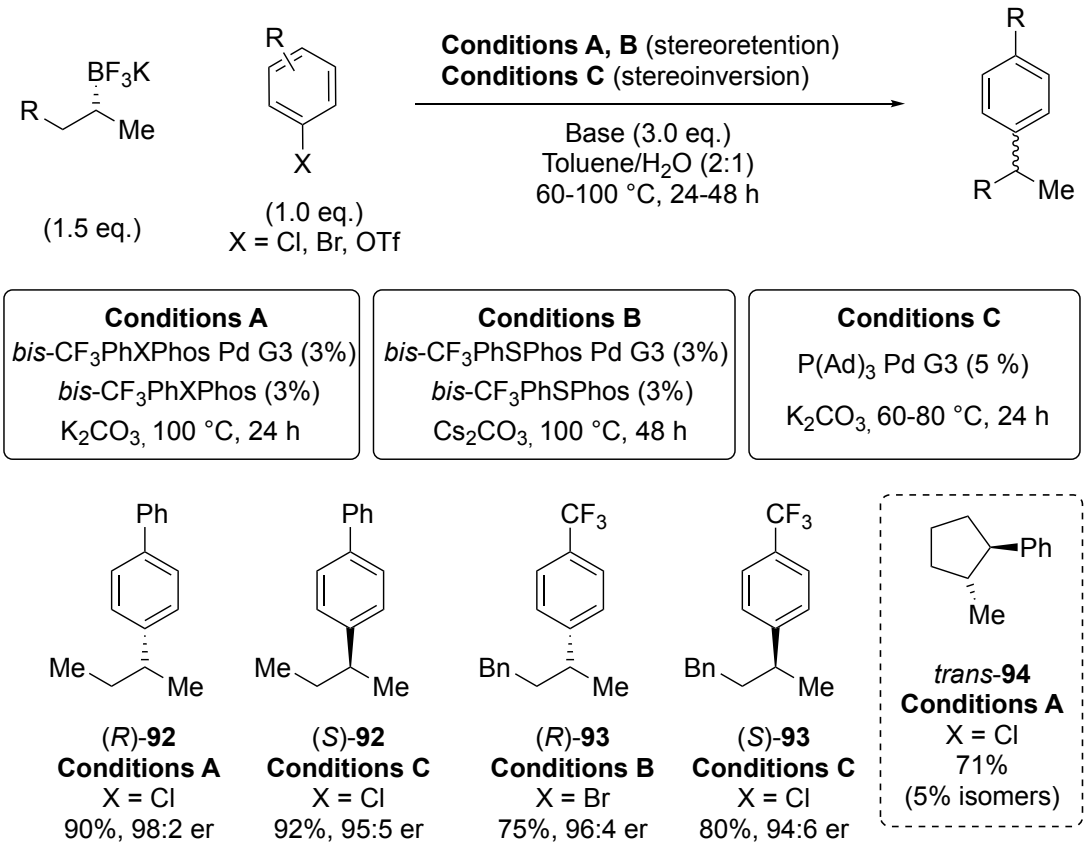


Figure 1.2: Structures of optimised ligands

With the ligands identified, a set of closely related yet not fully general conditions were identified for each ligand. All conditions employed a 2:1 toluene/water solvent system and 3 eq. of a carbonate base (K_2CO_3 or Cs_2CO_3). The alkyl BF_3K salt (≥97:3 er) was used in excess and reactions were heated in a range of 60-100 °C for 24-48 hours (Scheme 1.23). In conditions A and B, additional free ligand was included, possibly to saturate free sites on palladium thereby reducing undesired β-hydride elimination although this is not discussed in the original report.[65] Whilst these conditions are all similar, the lack of complete generality underscores the inherent sensitivity of sp^3-sp^2 SMCC reactions. Minor variations in halide identity, temperature, and water content within the substrate scope illustrate the complexity and challenge inherent in this area of synthetic chemistry. Both enantiomers of the arylated alkane compounds could be obtained in high er. For example, SMCC of (*R*)-*sec*-butyl BF_3K with 4-bromobenzotrifluoride under conditions B (bis-CF_3PhSPhos Pd G3, Cs_2CO_3, 100 °C, 48 h) gave aryl alkane (*R*)-**93** in 75% yield and with 96:4 er (stereoretentive pathway). The opposite enantiomer, aryl alkane (*S*)-**93** could be obtained by using conditions C ($P(Ad)_3$ Pd G3, K_2CO_3, 60 °C, 24 h) in 80% yield and 94:6 er (stereoinvertive pathway). Whilst a broad scope of acyclic aryl alkanes was developed, there was only one cyclic example included, and only with one set of conditions. When stereoretention conditions (conditions A) were used for the reaction between *trans*-1-BF_3K-2-methylcyclopentane and chlorobenzene, the reaction proceeded as expected with stereoretention, affording aryl cyclopentane *trans*-**94** in 71% yield alongside 5% of other isomers. The nature of these isomers was not reported and they could be regio- or stereoisomers which highlights the increased complexity observed when moving to a cyclic substrate. When the equivalent cross-coupling was carried out using stereoinvertive conditions C, inversion was not observed, and only a low yield of aryl

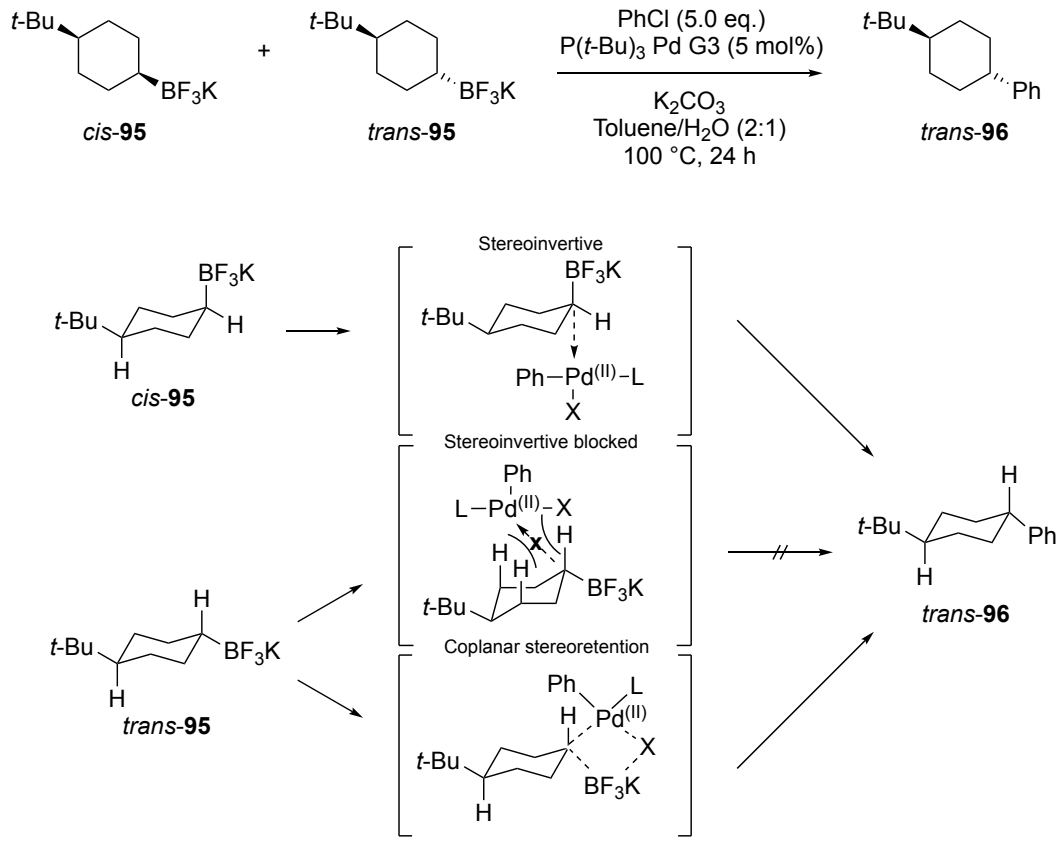
cyclopentane *trans*-**94** was obtained. Biscoe, Sigman *et al*. proposed that the low yield came from steric hindrance of the cyclopentyl framework, preventing approach of palladium to the σ^*_{C-B} orbital required for stereoinversion to take place.



Scheme 1.23

To further investigate the effects of steric hindrance on the stereochemical course of the SMCC, Biscoe *et al*. carried out the SMCC of a 5:1 diastereomeric mixture of *t*-Bu cyclohexyl BF_3K salts *cis*- and *trans*-**95** with chlorobenzene.[48] The conditions for the SMCC were P(*t*-Bu)$_3$ Pd G3 and K_2CO_3 in toluene/water at 100 °C for 24 h. Using a bulky electron rich ligand, based on the results from Biscoe, Sigman *et al*.,[40] stereoinversion would be expected. However, as observed with aryl cyclopentane *trans*-**94**, it is possible for steric effects of the compound to override steric control from the ligand (see Scheme 1.23). Thus, the experiment was designed with a *t*-Bu group in the 4-position relative to the BF_3K to conformationally lock the system without sterically interfering with the transmetallation step. The conformational lock was important because it held the BF_3K substituent in an axial position (in *cis*-**95**) and in an equatorial position (in *trans*-**95**). The kinetic profile of both *cis*- and *trans*-**95** was

monitored, alongside analysis of product mixtures, and this information would be used to inform on the stereochemical outcome of transmetallation. Consumption of BF_3K *cis*-**95** proceeded quickly, and with inversion, to generate *t*-Bu aryl cyclohexane *trans*-**96**. However, conversion of BF_3K *trans*-**95** proceeded much more slowly and, surprisingly, analysis of the product mixture indicated that *t*-Bu aryl cyclohexane *trans*-**96** was the sole product. Thus, both BF_3K *cis*- and *trans*-**95** were generating *t*-Bu aryl cyclohexane *trans*-**96** albeit with significantly different rates of reaction (Scheme 1.24).

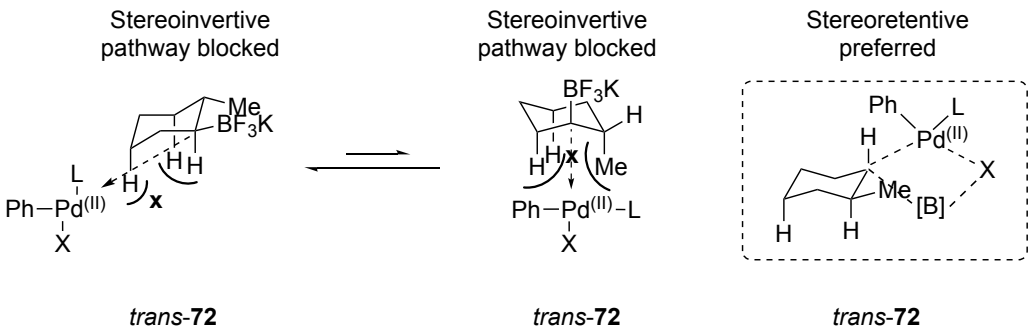


Scheme 1.24

Biscoe *et al*. rationalised the results through the steric hindrance presented by the cyclohexane ring. For example, BF_3K *cis*-**95** reacted through a stereoinvertive transmetallation mechanism, one which would be preferential when using a bulky electron rich ligand. For *cis*-**95**, the backside approach of palladium is sterically accessible resulting in a rapid kinetic profile to generate *trans*-**96**. In contrast, for BF_3K *trans*-**95**, the electronically favoured stereoinvertive pathway would be sterically disfavoured due to a steric clash with the adjacent 1,3-diaxial protons. Without the

presence of the conformationally locking *t*-Bu group, it would be possible to ring-flip and proceed with a less hindered stereoinvertive mechanism. However, the energy barrier to ring-flip is too high in this case and the only possible mechanism for transmetallation is to proceed *via* a coplanar stereoretentive mechanism, which is disfavoured by the bulky electron rich phosphine ligand. This results in a significantly slower kinetic profile to generate solely aryl *trans*-**96**.

The 2008 report from Molander, Dreher *et al*.[53] had demonstrated the stereoretentive SMCC of methyl cyclohexyl BF_3K *trans*-**72** with chlorobiphenyl using bulky electron rich ligands (see Scheme 1.18). Based on the work of Biscoe and Sigman *et al.*[40] SMCC using a bulky electron rich ligand should favour formation of the stereoinvertive product. Therefore, Biscoe *et al*.[48] used the results from Scheme 1.24 to rationalise the stereochemical outcome of the related methyl cyclohexyl BF_3K *trans*-**72** system reported by Molander, Dreher *et al*. (see Scheme 1.18). For methyl cyclohexyl BF_3K *trans*-**72**, the ring is not conformationally locked, but there will be a strong preference for the diequatorial conformation. In this diequatorial conformation, backside approach of the palladium to BF_3K *trans*-**72** would be sterically disfavoured by axial interactions. In the disfavoured diaxial conformation, backside approach to BF_3K *trans*-**72** would be disfavoured by the now also axial methyl group and the 1,3-diaxial protons. Instead, the coplanar stereoretention mechanism can proceed from the energetically favoured diequatorial conformation of *trans*-**72**. This resulted in the formation of solely the stereoretentive product, despite the use of a bulky electron rich ligand. Ultimately, Biscoe's study proved that it was possible to overcome the directing effects of ligand electronics through steric considerations of the substrate, and that conformational effects needs to be considered for SMCC reactions of cyclic alkyl-boron compounds.



Scheme 1.25

In 2019, Burke *et al.* proposed to use steric hindrance of the ligand to favour a stereoretentive pathway of the SMCC reaction. Ligands were designed with steric bulk along the axial position around palladium that would be required for the backside approach of palladium to the alkyl-boron species during the stereoinvertive transmetallation mechanism (Figure 1.3).[41] As a result, it would be energetically favourable for the stereoretentive mechanism to occur. In contrast to the stereoinversion mechanism, this proceeds in a coplanar transition state (see Scheme 1.6) which would be unimpeded by the steric bulk in the axial plane.

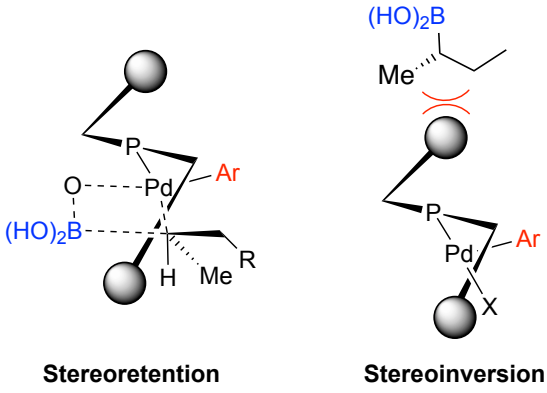
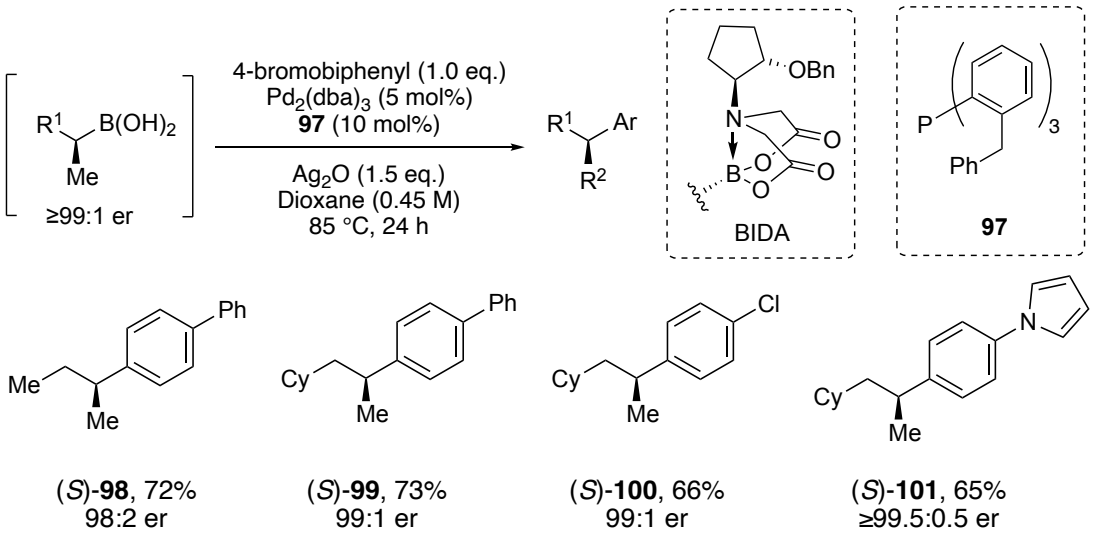


Figure 1.3: Proposed mechanism for axial shielding of stereoinvertive pathway

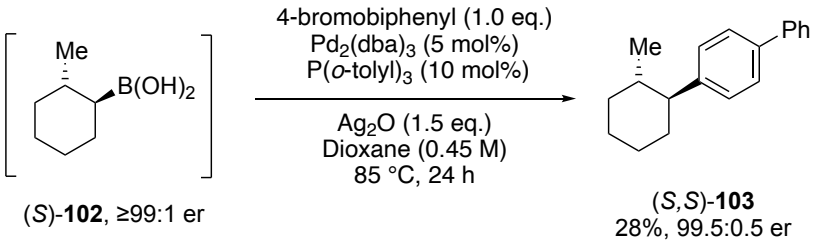
Following ligand optimisation studies, Burke *et al*. identified ligand **97** which exhibited high degrees of stereretention and minimised the generation of unproductive regioisomers from β-hydride elimination/reinsertion processes. Ligand **97** is a trivalent phosphine containing three *ortho*-benzyl aromatic groups. The vectors of the benzyl groups generate the required steric bulk in the axial plane. Using optimised ligand **97** with $Pd_2(dba)_3$ and Ag_2O in dioxane at 85 °C for 24 h, a range of alkyl boronic acids and aryl/viny bromides were investigated and a selection are shown in Scheme 1.26.

The enantioenriched boronic acids were accessed through *in situ* hydrolysis of alkyl-borons that contained a chiral MIDA group. Moderate to excellent yields and excellent ers were obtained in a wide range of arylated alkanes. For example, aryl alkane (*S*)-**101** was obtained in 65% yield and ≥99.5:0.5 er. A range of electron-rich and electron-poor aryl bromides were well tolerated under the reaction conditions. However, the cross-coupling of only two heteroaryl bromides was reported.



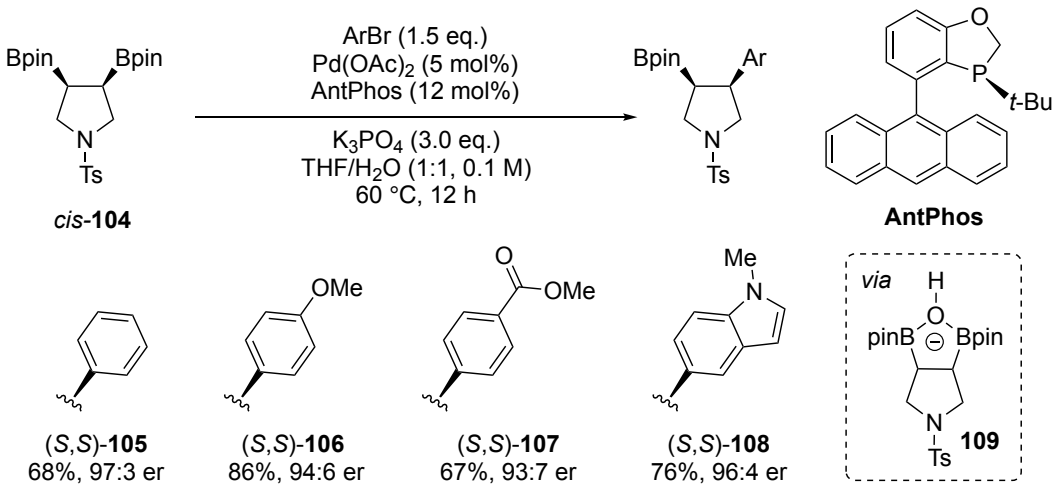
Scheme 1.26

In many of the aforementioned examples of stereochemical control in SMCC reactions, the translation of the approach to cyclic molecules often generated additional challenges. The axial shielding strategy was no exception. Burke *et al*. reported only one example of a SMCC on an enantioenriched cyclic alkyl-$B(OH)_2$ using P(*o*-tolyl)$_3$ as ligand (instead of ligand **97** which was optimised for acyclic substrates). Thus, with methyl cyclohexyl-$B(OH)_2$ *trans*-**102** (≥99:1 er) and 4-bromobiphenyl under standard conditions with P(*o*-tolyl)$_3$, the stereoretention product aryl methyl cyclohexane *trans*-**103** was obtained in 28% yield and 99.5:0.5 er (Scheme 1.27). In the acyclic substrates, P(*o*-tolyl)$_3$ was shown to offer a moderate degree of stereocontrol and moderate selectivity over regiosiomeric byproducts. Thus, it is somewhat surprising that it was found to work better than ligand **97** with the SMCC of methyl cyclohexyl-$B(OH)_2$ *trans*-**102**. This underscores the increased complexity when investigating the stereochemical outcome of transmetallation for cyclic alkyl-borons over acyclic alkyl-borons.



Scheme 1.27

Recently, Morken *et al*. reported an enantioselective SMCC of 3,4-Bpin *N*-tosyl pyrrolidine *cis*-**104** with aryl bromides. The chiral catalyst AntPhos was used to desymmetrise the *meso* compound and provide enantioenriched cross-coupled products containing various aryl substituents. The SMCC was carried out using an excess of the aryl bromide, $Pd(OAc)_2$ (5 mol%), AntPhos (12 mol%) and K_3PO_4 in THF/water (1:1, 0.1 M) at 60 °C for 12 h (Scheme 1.28). Under these conditions, a scope of four cross-coupled products was generated. The reaction demonstrated tolerance to electron-rich and electron-poor aromatics with 3-aryl Bpin *N*-Ts (*S*,*S*)-**106** (94:6 er) and (*S*,*S*)-**107** (93:7 er) obtained in 86% and 67% yields respectively. Significantly, the methodology also tolerated heteroaryl bromides. For example, reaction of 3,4-Bpin *N*-tosyl pyrrolidine *cis*-**104** with 5-bromo-1-methyl-1H-indole gave 3-aryl Bpin *N*-Ts (*S*,*S*)-**108** in 76% yield and 96:4 er. When the *N*-Ts group was replaced by a *N*-Cbz group the pyrrolidine was shown to perform well in the SMCC. The presence of a vicinal Bpin group is stated to increase the rate of the palladium-catalysed SMCC 50-fold. The rate increase was proposed to come from strained cyclic chelated diboronate complex **109** which was detected in ^{11}B NMR studies. The methodology from Morken *et al*. provides an efficient way to C3-arylate *N*-tosyl pyrrolidines containing vicinal Bpin groups. However, the requirement for the vicinal Bpin group is a limitation to the methodology. This underscores the requirement for a SMCC method which can access C3-arylated pyrrolidines without activation by a vicinal boronic ester.



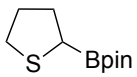
Scheme 1.28

Overall, based on the literature precedent, there are still many unknowns associated with the stereochemical outcome of the SMCC of cyclic alkyl-borons. Indeed, these examples highlight that aryl halide electronics, ligand electronics, ligand sterics and alkyl-boron sterics can all cumulatively act to influence the stereochemical pathway of transmetallation. The challenge of utilising ligand design to favour one stereochemical pathway over the other is increased by the desire to concurrently optimise for the reduction of regiosiomeric byproducts arising from β-hydride elimination/reinsertion pathways.

1.6 Project Outline

In this thesis, investigation of the SMCC of a range of racemic and enantioenriched heterocyclic alkyl-borons is described. The significant mechanistic aspects of sp^3-sp^2 SMCC examples that underpin much of this work have been discussed in the previous sections. Practitioners from the pharmaceutical industry have commented that sp^3-sp^2 carbon-carbon bond-forming methodology, compatible with library synthesis and able to stereoselectively synthesise complex 3D molecules, would be highly desirable.[13] To an extent, sp^3-sp^2 SMCC reactions can already deliver this for acyclic alkyl-borons and simple carbocyclic alkyl-borons. However, the analogous reaction with heterocyclic alkyl-borons remains vastly underdeveloped. Thus, the overall aim of this project was to enable new racemic and enantioenriched heterocyclic alkyl-borons in sp^3-sp^2 SMCC reactions, while simultaneously expanding our understanding of the process, ideally from a mechanistic standpoint. Our ultimate goal would be to establish a general set of reaction conditions applicable to a broad range of saturated heterocyclic alkyl-borons. However, if no general method was attainable, an alternative goal was to leverage our increased understanding of the SMCC to more efficiently enable cross-couplings of heterocyclic alkyl-borons.

In Chapter 2, further development of the SMCC with 2-Bpin tetrahydrothiophene **110** (Figure 1.4) is described, following on from some preliminary results that had been obtained by James Firth in the O'Brien group. The primary objectives were to expand the aryl bromide scope of the SMCC with racemic and enantioenriched 2-Bpin tetrahydrothiophene **110**, and to advance our understanding of this type of SMCC reaction.

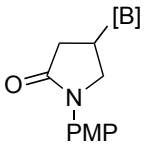


110

Figure 1.4: Structure of 2-Bpin tetrahydrothiophene investigated in Chapter 2

Development of the SMCC of 4-boryl pyrrolidones **111** (Figure 1.5) is presented in Chapter 3. To date, the only successful SMCC of a 4-boryl pyrrolidone was reported by Partridge *et al*. (see Scheme 1.16).[59] The objectives were to optimise the SMCC of 4-boryl pyrrolidones **111** and to explore the aryl halide scope in both racemic and

enantioenriched reactions, with the goal of delivering a SMCC reaction that was fit-for-purpose for use in medicinal chemistry programmes.



111

Figure 1.5: Structure of 4-boryl N-R pyrrolidones investigated in Chapter 3

Finally, in Chapter 4, the SMCC of 3-BF_3K pyrrolidine **50** (Figure 1.6) is described. It was hoped that application of a refined optimisation strategy from our increased understanding of the requirements for sp^3-sp^2 SMCCs, could guide an efficient optimisation of SMCC reactions with 3-BF_3K pyrrolidine **50**.

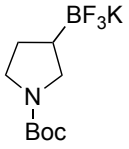


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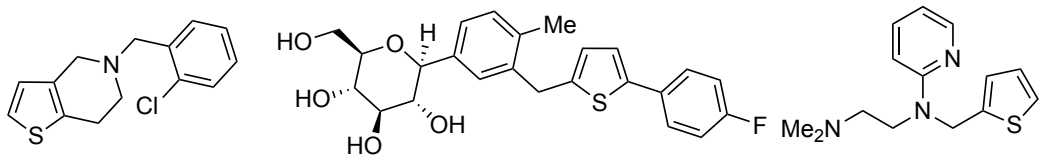
Figure 1.6: Structure of 3-BF_3K *N*-Boc pyrrolidine investigated in Chapter 4

Chapter: 2 Suzuki-Miyaura Cross-Coupling of 2-Bpin Tetrahydrothiophene

2.1 Introduction

2.1.1 Thiophenes and 2-Aryl Tetrahydrothiophenes in Drug Discovery

There have been many examples of drug molecules possessing the thiophene moiety. Examples include Ticlopidine (antiplatelet agent),[66] Canagliflozin (diabetes)[67] and Methapyrilene (antihistamine)[68] (Figure 2.1). Overall, there have been 26 drugs possessing a thiophene moiety that have been approved under different pharmacological classes.[68] With increasing developments in bioinformatics, thiophenes have seen increasing use in drug discovery. This is due to their role as a bioisostere of the phenyl ring, synthetic accessibility for modification, and additional hydrogen bonding available through the sulfur atom.[68]



Ticlopidine **Canagliflozin** **Methapyrilene**

Figure 2.1: Examples of thiophene containing approved drugs

In contrast, there are far fewer examples of the use of tetrahydrothiophenes in drug discovery. As discussed in Section 1.1, there is a growing emphasis on increasing sp^3 character in drug molecules. Therefore, the established value of thiophenes in medicinal chemistry highlights the potential of their saturated counterpart – tetrahydrothiophene. This is reflected in their success as hit molecules in both physical and virtual library screening. For example, 2-aryl tetrahydrothiophene **112** appeared as a hit molecule when screening for inhibitors of IKK-2, an IκB kinase involved in Rheumatoid arthritis (Figure 2.2).[69] Similarly, 2-aryl tetrahydrothiophene **113** was identified as an inhibitor of NLRP3 inflammasomes.[70] In particular, Picartamide is a 2-aryl tetrahydrothiophene which displayed significant promise as an antiulcer and gastric acid suppressant.[71] Although it is unclear why the development of Picartamide was discontinued, its serious consideration and potential as a commercial drug

compound highlights the importance of the 2-aryl tetrahydrothiophene class in medicinal chemistry.

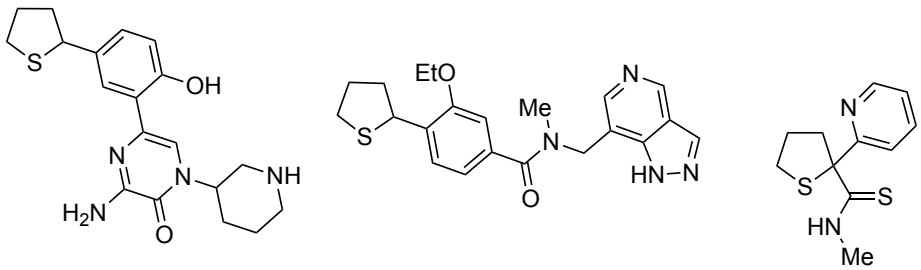


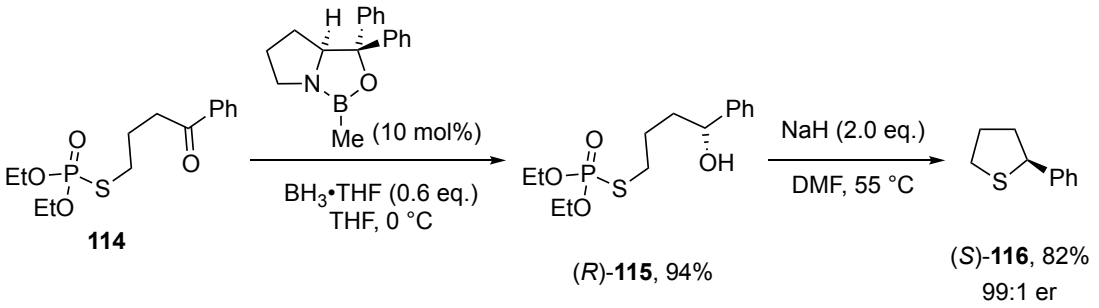
Figure 2.2: Examples of 2-aryl tetrahydrothiophenes in drug discovery

The adoption of tetrahydrothiophenes in medicinal chemistry, especially in tandem with virtual screening workflows, requires the continued development of new methodologies for the synthesis of functionalised tetrahydrothiophenes. The methodology must be amenable to synthesising a broad range of analogues for SAR studies and library synthesis. Currently, there are limited methodologies capable of efficiently synthesising broad series of enantioenriched 2-aryl tetrahydrothiophenes. In this chapter, we propose that the sp^3-sp^2 Suzuki-Miyaura cross-coupling could provide a suitable solution to this problem.

2.1.2 Synthetic Routes to Enantioenriched 2-Aryl Tetrahydrothiophenes

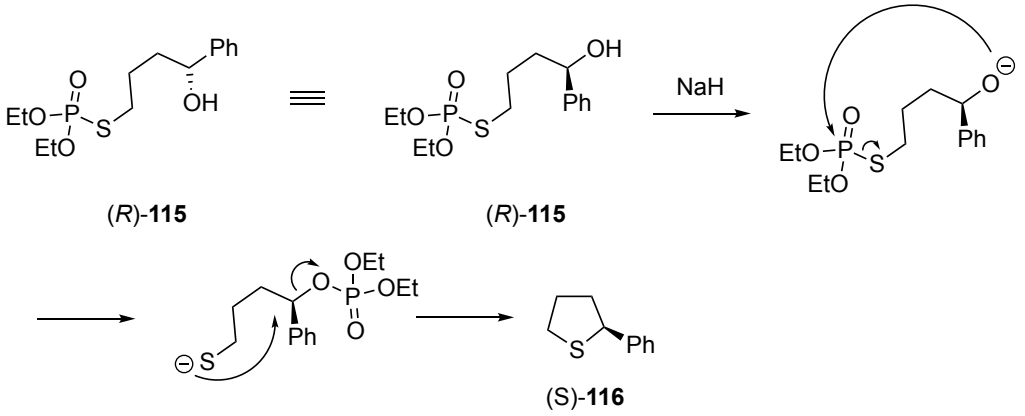
To the best of our knowledge, only two distinct methodologies have been reported for the synthesis of enantioenriched 2-aryl tetrahydrothiophenes. Generally, the most common method involves asymmetric reduction of an aryl ketone followed by S_N2-like cyclisation using a nucleophilic source of sulfur such as sodium sulfide or H_2S.[72] Wu and Robertson demonstrated the most comprehensive application of this methodology using phosphorothioic acids as a H_2S surrogate to generate 2-aryl tetrahyrothiophenes.[73] This is of particular merit as it circumvents the high toxicity of working with H_2S. An example of this strategy is shown in Scheme 2.1. Phenyl ketone **114** was reduced asymmetrically using a CBS reduction giving phenyl alcohol (*R*)-**115** in 94% yield. Due to issues of CSP-HPLC resolution of the chiral alcohol, the er was not measured until after the second C-S bond forming event. Cyclisation of phenyl

alcohol (*R*)-**115** was achieved under basic conditions using NaH in DMF. After stirring at 55 °C for 16 h, 2-phenyl tetrahydrothiophene (*S*)-**116** was obtained in 82% yield and 99:1 er.



Scheme 2.1

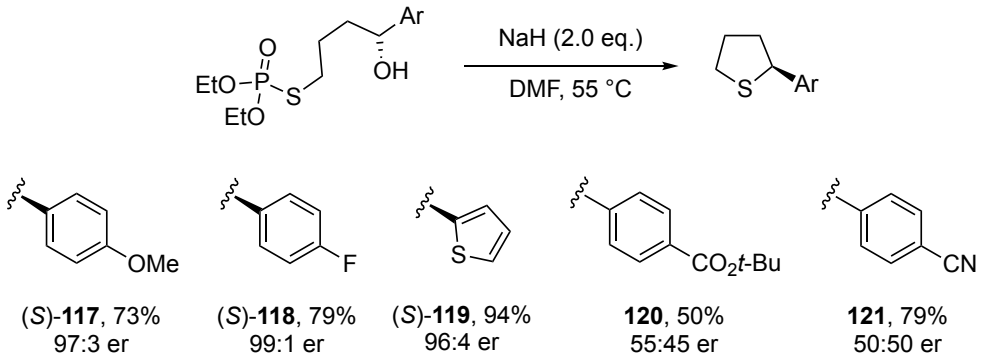
The reaction mechanism proceeds with deprotonation of alcohol (*R*)-**115** with NaH to form an alkoxide. Intramolecular attack of the phosphorothioate by the alkoxide displaces sulfur to form a thiolate anion. This is driven by the formation of a relatively strong P-O bond. Finally, a second intramolecular S_N2-like attack, this time with the thiolate anion attacking into the $\sigma^*_{C\text{-}O}$ orbital results in inversion of configuration and the formation of 2-phenyl tetrahydrothiophene (*S*)-**116** (Scheme 2.2).



Scheme 2.2

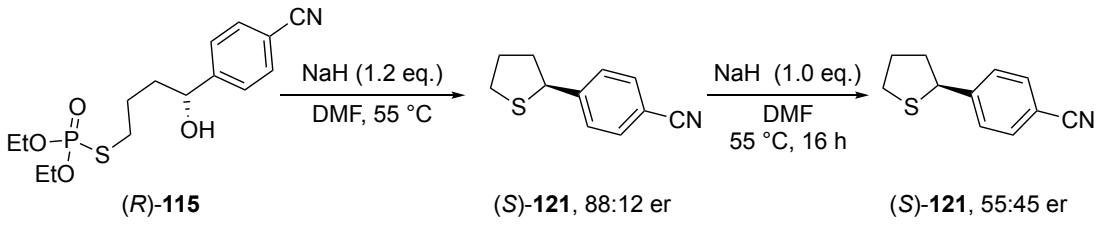
Wu and Robertson validated the methodology with 15 examples of 2-aryl tetrahydrothiophenes and a representative set of these are shown in Scheme 2.3. 4-Methoxy aryl tetrahydrothiophene (*S*)-**117** was obtained in 73% yield and 97:3 er. The methodology also tolerated heteroaromatics with 2-aryl tetrahydrothiophene (*S*)-**119** isolated in 94% yield and 96:4 er. When evaluating aromatic groups possessing an

electron-withdrawing *para* substituent, products with much lower ers were observed. For example, *tert*-butyl ester containing aryl tetrahydrothiophene **120** was obtained in 50% yield and 55:45 er. Similarly, nitrile containing aryl tetrahydrothiophene **121** was isolated in a 79% yield and 50:50 er.



Scheme 2.3

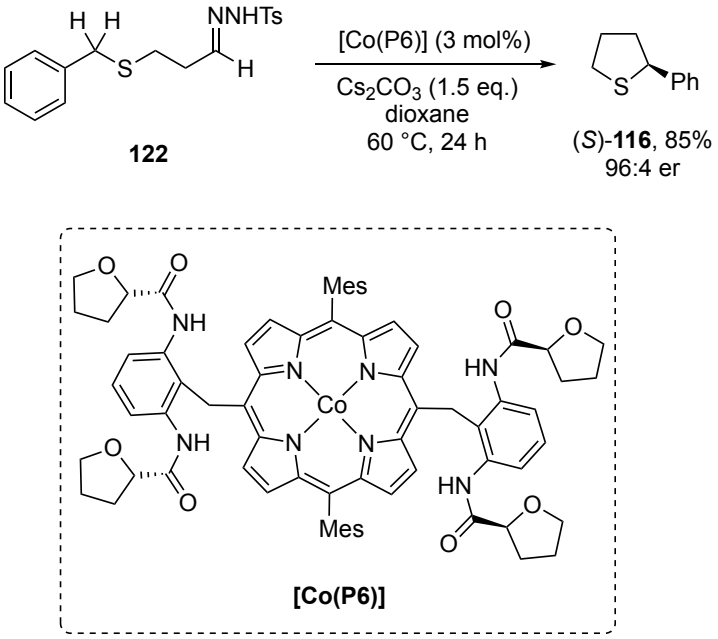
The low ers observed in **120** and **121** were attributed to epimerisation of the cyclised product, driven by increased acidity of the α-proton to sulfur. By reducing the equivalents of NaH (from 2.0 to 1.2), Wu and Robertson were able to obtain nitrile containing aryl tetrahydrothiophene (*S*)-**121** in 82% yield and 88:12 er (Scheme 2.4). Furthermore, reacting 2-aryl tetrahydrothiophene (*S*)-**121** of 88:12 er with one further equivalent of NaH in DMF gave aryl tetrahydrothiophene (*S*)-**121** in 55:45 er, confirming the epimerisation hypothesis.



Scheme 2.4

Zhang *et al*. demonstrated an enantioselective radical cyclisation approach to a 2-aryl tetrahydrothiophene using a chiral cobalt porphyrin catalyst.[74] Reaction of tosyl hydrazine **122** with the chiral cobalt porphyrin catalyst and Cs_2CO_3 in dioxane at 60 °C for 24 h gave phenyl tetrahydrothiophene (*S*)-**116** in 85% yield and 91% ee (Scheme 2.5). The mechanism proceeds with activation of tosyl hydrazone **122** by the cobalt^{II} complex forming a cobalt^{III} alkyl radical. This radical species then undergoes a 1,5-

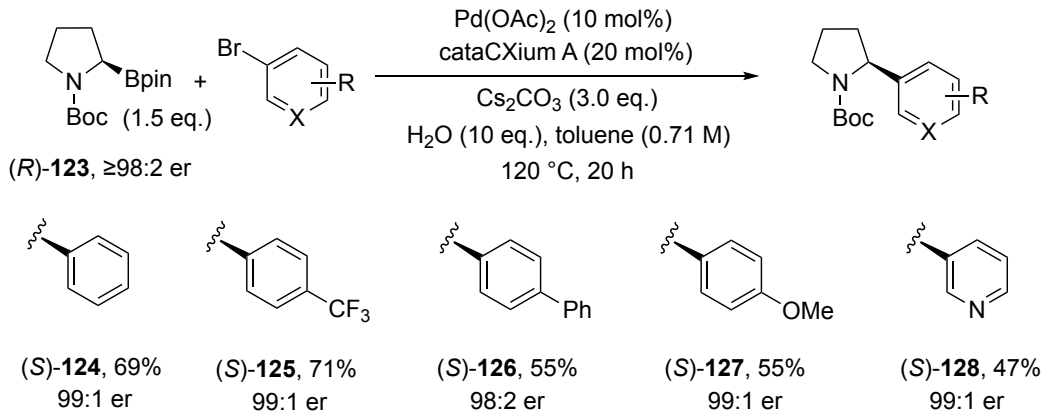
hydrogen atom abstraction followed by radical cyclisation, regenerating the cobalt^{II} catalyst and releasing the cyclised product. The asymmetric induction is controlled by the structurally rigid chiral porphyrin ligand. The work reported by Zhang *et al.* focused on *N*-heterocycles and their study included only this single instance of 2-aryl tetrahydrothiophene, underscoring the need for new synthetic methodology in this area.



Scheme 2.5

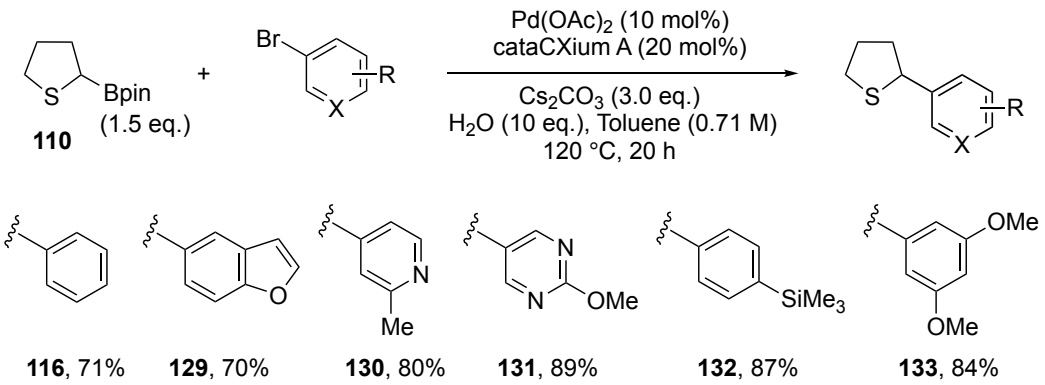
2.1.3 Background and Previous Work in the Group

In the O'Brien group, *via* extensive optimisation, conditions were identified for the cross-coupling of 2-Bpin pyrrolidine (*R*)-**123** with bromobenzene. The optimised conditions were 1.5 equivalents of 2-Bpin pyrrolidine (*R*)-**123**, 10 mol% loading of $Pd(OAc)_2$ with 20 mol% cataCXium A, Cs_2CO_3 (3.0 equivalents) and H_2O (10 equivalents) in toluene (0.7 M) at 120 °C for 20 h. Under these conditions, the SMCC reaction was shown to proceed stereospecifically with retention and 2-phenyl pyrrolidine (*S*)-**124** was obtained in 69% yield and 99:1 er (Scheme 2.6). A preliminary scope of seven enantioenriched examples was developed with yields of 47-71% and enantiomeric ratios of 98:2 to 99:1.[75]



Scheme 2.6

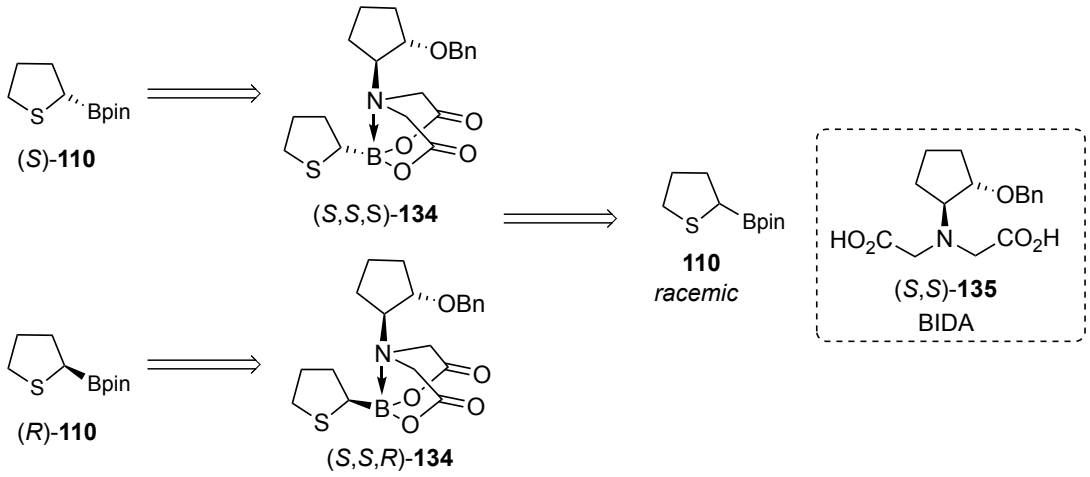
The developed cross-coupling conditions were adopted by James Firth in the O'Brien group for the SMCC of 2-Bpin tetrahydrothiophene **110**. Reacting 2-Bpin tetrahydrothiophene **110** under the optimised pyrrolidine SMCC conditions gave 2-phenyl tetrahydrothiophene **116** in 71% yield (Scheme 2.7). A preliminary scope of five additional examples performed similarly, with yields of 70-89% of aryl tetrahydrothiophenes **129-133** (Scheme 2.7). Typically, when SMCC conditions are transferred to a new saturated heterocyclic boronate system, the cross-coupling does not operate at a comparable level and optimisation is usually required. However, as the preliminary scope results with 2-Bpin tetrahydrothiophene **110** suggested, there was a generality observed with these conditions which may be due to a robustness of the 2-Bpin tetrahydrothiophene **110** system.



Scheme 2.7

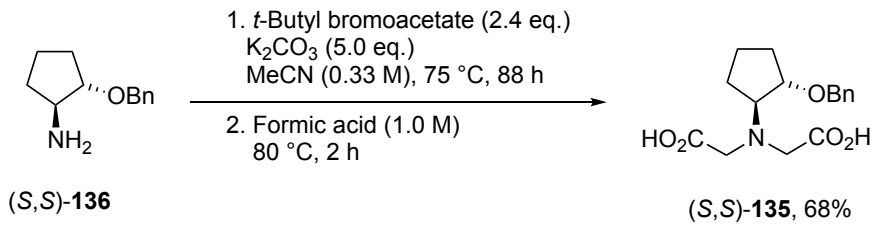
A preliminary route to enantioenriched 2-Bpin tetrahydrothiophene (*R*)- and (*S*)-**110** was also established by James Firth allowing investigation of the stereochemical

pathway of the reaction. As there was no simple asymmetric method to access enantioenriched 2-Bpin tetrahydrothiophene (*R*)- or (*S*)-**110**, they were accessed from diastereomeric chromatographic resolution using chiral MIDA analogues developed by Burke *et al*.[76] Originally, Burke used the chiral MIDA analogues in diastereoselective epoxidations of alkenylboronates. Here, they were used to generate a pair of chromatographically separable boronate diastereomers. Enantioenriched 2-Bpin tetrahydrothiophenes (*R*)- and (*S*)-**110** were accessed *via* simple ester exchange from single diastereomeric tetrahydrothiophenes (*S*,*S*,*S*)- and (*S*,*S*,*R*)-**134**. These, in turn, were accessed from racemic 2-Bpin tetrahydrothiophene *rac*-**110** and the chiral MIDA adduct, BIDA (*S*,*S*)-**135** (benzyl oxycyclopentyl amino diacetic acid), followed by subsequent chromatographic diastereomeric resolution (Scheme 2.8).



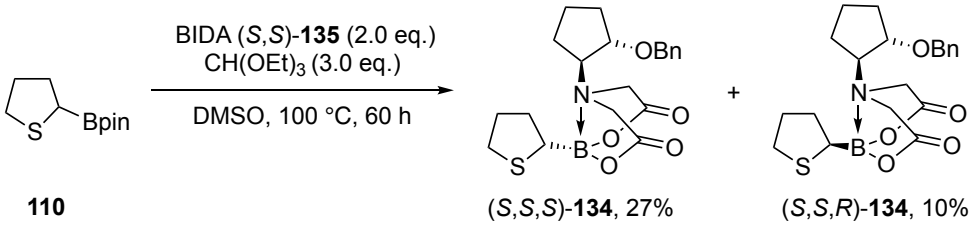
Scheme 2.8

Following the synthetic procedure established by Burke *et al*., the synthesis was carried out *via* a double *N*-alkylation of cyclopentyl amino Bn alcohol (*S*,*S*)-**136** using excess *tert*-butyl bromoacetate and K_2CO_3 in acetonitrile at 75 °C for 88 h. The *tert*-butyl ester was cleaved by stirring in formic acid at 80 °C for 2 h. Following removal of the formic acid and recrystallisation, BIDA (*S*,*S*)-**135** was obtained in 68% yield (Scheme 2.9).



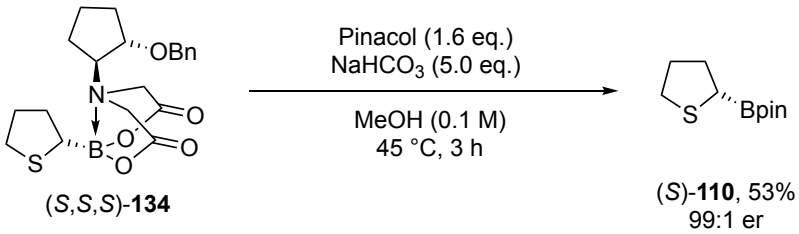
Scheme 2.9

On a small scale, 2-Bpin tetrahydrothiophene **110** was reacted with 2 equivalents of BIDA (*S*,*S*)-**135** and triethylorthoformate in DMSO at 100 °C for 48 h. Following chromatographic separation of the diastereomers, (*S*,*S*,*S*)-**134** was obtained in 27% yield and (*S*,*S*,*R*)-**134** was obtained in 10% yield (Scheme 2.10).



Scheme 2.10

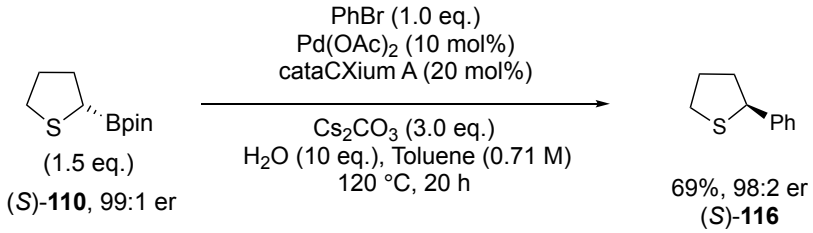
The BBIDA hydrolysis was carried out using conditions developed by Burke *et al*. in a separate report.[77] BBIDA tetrahydrothiophene (*S*,*S*,*S*)-**134**, excess $NaHCO_3$ and pinacol were stirred in methanol at 45 °C for 3 h. Following work-up and purification, 2-Bpin tetrahydrothiophene (*S*)-**110** was obtained in 53% yield and 99:1 er (Scheme 2.11).



Scheme 2.11

With access to enantioenriched 2-Bpin tetrahydrothiophene (*S*)-**110** of high er (99:1 er), it was reacted in an SMCC under the standard conditions with bromobenzene. Following purification, 2-phenyl tetrahydrothiophene (*S*)-**116** of 98:2 er was obtained

in a 69% yield (Scheme 2.12). The (*S*)-configuration was identified *via* comparison to a known $[\alpha]_D$ value.[73] In contrast to the SMCC reactions of 2-Bpin pyrrolidine (*R*)-**123** (see Scheme 2.6), the SMCC reaction of 2-Bpin tetrahydrothiophene (*S*)-**110** was shown to proceed with inversion of configuration.



Scheme 2.12

2.2 Proposed Objectives

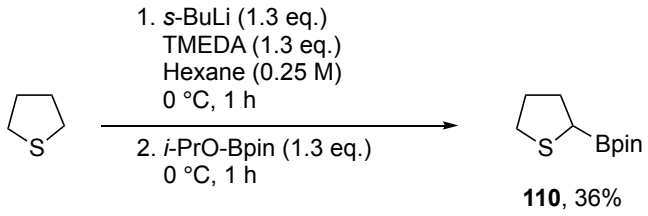
Following the preliminary study on the SMCC reactions of racemic and enantioenriched 2-Bpin tetrahydrothiophene **110**, the work described in this chapter had two primary objectives.

First, the plan was to expand the aryl bromide scope of the SMCC with racemic 2-Bpin tetrahydrothiophene **110**, as this had only been explored in a limited fashion during the initial investigation by James Firth. With high yields already obtained in six examples (70-89%), we also wanted to briefly explore the chemical space around the reaction conditions. The aim was to explore reducing some of the undesirable factors such as the high temperature (120 °C) and high catalytic loading (10 mol% $Pd(OAc)_2$ and 20 mol% cataCXium A).

Second, we particularly wished to further investigate the stereochemical outcome of the cross-coupling. To start, the plan was to confirm the stereoinvertive outcome, presumably due to a stereoinvertive transmetallation step predominating. Furthermore, we wanted to ascertain if the steroinvertive nature of the cross-coupling of 2-Bpin tetrahydrothiophene (*S*)-**110** was aryl bromide dependent. Given the protracted route to access enantioenriched material and the low-moderate yields obtained, the yields for the synthesis of 2-Bpin tetrahydrothiophene (*S*)-**110** required optimisation if the large quantities of material required were to be processed quickly and efficiently. Moreover, only 2-Bpin tetrahydrothiophene (*S*)-**110** was synthesised due to difficulty in separating BBIDA tetrahydrothiophene (*S*,*S*,*R*)-**134** from an unknown impurity. Therefore, a key issue was to optimise the synthesis of enantioenriched 2-Bpin tetrahydrothiophenes (*S*)-**110** and (*R*)-**110**. This would be a pivotal step towards expanding the enantioenriched scope and further investigating whether parameters such as ligand and aryl bromide effect the stereochemical outcome.

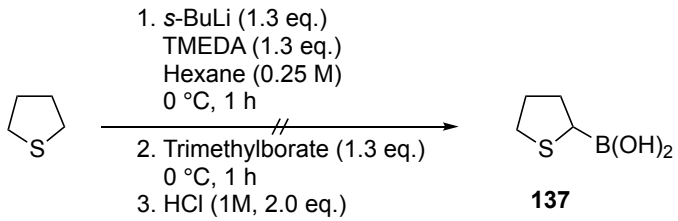
2.3 Synthesis of 2-Bpin Tetrahydrothiophene 110

The synthesis of 2-Bpin tetrahydrothiophene **110** was carried out using a lithiation-trapping reaction developed within the group.[78] *sec*-BuLi/TMEDA was used to lithiate tetrahydrothiophene in hexane at 0 °C for 1 h. Then, the resulting lithiated species was trapped with *i*-PrO-Bpin at 0 °C and allowed to react for 1 h. Following work-up and chromatography, 2-Bpin tetrahydrothiophene **110** was obtained in 36% yield on a 25 mmol scale (Scheme 2.13). Yields of **110** of up to 40% were obtained at a 17.5 mmol scale.



Scheme 2.13

2-Bpin tetrahydrothiophene **110** was challenging to isolate in high yields due to its degradation on silica during chromatography, which is exacerbated on larger scales, and to its observed reasonable volatility. Moreover, in previous work, it was determined that when trapping lithiated tetrahydrothiophene with electrophiles such as a Weinreb amide and chloro(dimethyl)phenylsilane, trapped products were obtained in 84% and 86% yields respectively.[78] This indicates that whilst degradation and volatility are contributing factors to the 25-40% yields of 2-Bpin tetrahydrothiophene **110**, the problem could also lie with the trapping of *i*-PrO-Bpin. Therefore, trimethylborate was employed as an alternative electrophile to circumvent this issue. The trapped trimethylborate would be hydrolysed to the boronic acid, which could, if desired, be converted easily into the pinacol ester. However, trapping with trimethylborate and acidic hydrolysis did not afford any of the desired tetrahydrothiophene boronic acid **137** (Scheme 2.14).



Scheme 2.14

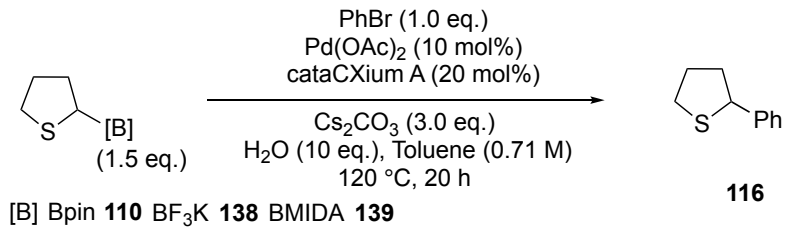
Given the focus of this work on the SMCC, further optimisation on the starting material synthesis was not pursued. The lithiation-trapping approach developed in the group was sufficient for producing the required material on a multi-gram scale which was adequate for the subsequent investigations.

2.4 Exploration of the Chemical Space of the Suzuki-Miyaura Cross-Coupling Conditions

As discussed, conditions for the SMCC of 2-Bpin tetrahydrothiophene **110** were transferred from 2-Bpin pyrrolidine **123**. As these systems are close analogues, we wanted to explore the chemical space around the cross-coupling with a series of targeted deviations to the standard conditions (Table 2.1). Firstly, a validation reaction was performed, cross-coupling 2-Bpin tetrahydrothiophene **110** with bromobenzene under the standard SMCC conditions employed by James Firth in the group (see Scheme 2.7). Gratifyingly, 2-phenyl tetrahydrothiophene **116** was obtained in 78% isolated yield, validating and, in fact, exceeding the original cross-coupling result (entry 1). Given the high yield with little to no optimisation, it was hypothesised that the high temperatures, typically thought to be required for transmetallation, may not be required for 2-Bpin tetrahydrothiophene **110**. Performing the standard cross-coupling at 100 °C gave 2-phenyl tetrahydrothiophene **116** in 34% yield (entry 2). This indicated that the SMCC still required high temperatures, presumably for the transmetallation step. When the palladium loading was halved to 5 mol% (maintaining the ligand to palladium ratio of 2:1), the cross-coupling was heavily affected with 2-phenyl tetrahydrothiophene **116** obtained in only 2% yield (entry 3). It was initially anticipated that the Lewis basic sulfur atom may result in palladium catalyst poisoning, resulting in minimal cross-coupled product. However, the high efficiency of 2-Bpin

tetrahydrothiophene **110** in the cross-coupling, suggested no significant incompatibility. Given the observed loss of yield at half palladium loading, it is possible that palladium poisoning is present but only significant when the palladium loading is reduced by half. However, there are numerous other factors which may cause a low yield of the cross-coupled product and, without more mechanistic evidence, this hypothesis cannot be proven definitively. Replacing $Pd(OAc)_2$ and cataCXium A with the Buchwald third generation precatalyst cataCXium A Pd G3 resulted in a 51% yield of 2-phenyl tetrahydrothiophene **116** (entry 4). The lower yield alongside the increased cost indicates that $Pd(OAc)_2$ and cataCXium A are a better catalytic system than the Buchwald precatalyst for this system. Replacing bromobenzene with chlorobenzene or iodobenzene resulted in yields of 2-phenyl tetrahydrothiophene **116** of 27% and 62% respectively (entries 5 and 6). The former result may indicate that a slower oxidative addition step hinders overall cross-coupling efficiency. In contrast, enhancing the rate of oxidative addition using iodobenzene's weaker C-I bond, while not improving yield, does not appear to compromise it either. Although a 62% yield of 2-phenyl tetrahydrothiophene **116** lies at the lower end of the expected range, it nonetheless represents an effective and functional cross-coupling reaction. An increased rate of oxidative addition may have been expected to promote aryl-aryl homocoupling due to an accumulation of the oxidative addition product prior to transmetallation.[79,80] However, given the high conversion observed, it may be that the transmetallation is sufficiently fast to combat this side reaction.

Table 2.1: Deviations to the standard SMCC conditions



Entry	Deviation	Yield / %[a]
1	none	78
2	100 °C	34
3	$Pd(OAc)_2$ (5 mol%), cataCXium A (10 mol%)	5
4	cataCXium A Pd G3 (10 mol%)	51
5	Chlorobenzene	27
6	Iodobenzene	62[b]
7	PAd_3 Pd G3 (10 mol%)	67
8	P*t*-Bu_3 Pd G4 (10 mol%)	16
9	SPhos Pd G3	2
10[d]	BF_3K (1.5 eq.)	35[c]
11[d]	BMIDA (1.5 eq.)	28[c]

[a] Yield after chromatography, [b] Average of two results (61% and 62%), [c] Conversion to 2-phenyl tetrahydrothiophene **116** determined by ^1H NMR using 1,3,5-trimethoxybenzene as in internal standard, [d] Reaction carried out by James Firth.

Modifying the ligand to $P(Ad)_3$ Pd G3, $P(t\text{-}Bu)_3$ Pd G4, or SPhos Pd G3 resulted in yields of 2-phenyl tetrahydrothiophene **116** of 67%, 16% and 2% respectively (entries 7-9). This indicates that compared to cataCXium A, increased steric bulk of the phosphine is tolerated but the reduced steric bulk of $P(t\text{-}Bu)_3$ Pd G4 results in significantly diminished yield. The poor performance of the biaryl phosphine SPhos suggests a potential incompatibility with this ligand class. Finally, the influence of the boronate type was assessed. Cross-coupling tetrahydrothiophene BF_3K **138** and BMIDA **139** resulted in yields of 2-phenyl tetrahydrothiophene **116** of 35% and 28% respectively (entries 10 and 11). These results indicate that under optimised conditions,

2-Bpin tetrahydrothiophene **110** is the most effective coupling partner. Due to a lack of synthetic feasibility, the tetrahydrothiophene boronic acid was not evaluated.

Establishing the kinetic profile of 2-Bpin tetrahydrothiophene **110** in the SMCC could give valuable insight into the mechanism. Unfortunately, attempts to generate accurate kinetic data of **110** were unsuccessful. Investigations within the O'Brien group with 2-Bpin pyrrolidine **123** using one-pot methods to access kinetic data such as ReactIR were ineffective due to palladium-black probe fouling, and complications in the biphasic toluene/water mixture. Unfortunately, exploration of individual reaction kinetics with 2-Bpin tetrahydrothiophene **110** and 4-fluorobromobenzene was also unproductive. The dataset contained too much variation between individual datapoints for accurate kinetic data to be generated. Thus, a new method to acquire accurate kinetic data is required. However, initial reaction kinetics suggested that reaction was complete within 30-60 min.

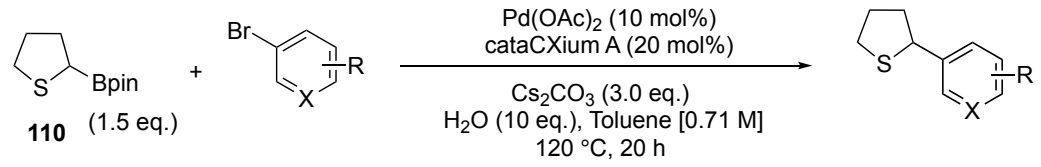
Overall, this focussed exploration of chemical space around the SMCC conditions revealed a surprising sensitivity to subtle variations, underscoring the value and significance of the optimised conditions.

2.5 Racemic Scope of the Suzuki-Miyaura Cross-Coupling of 2-Bpin Tetrahydrothiophene

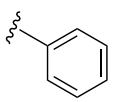
With confidence in the high efficiency of the original conditions, the racemic scope of 2-Bpin tetrahydrothiophene **110** was rapidly elaborated. The diverse set of cross-coupled products achieved is shown in Scheme 2.15. Firstly, it was immediately clear that the SMCC of 2-Bpin tetrahydrothiophene **110** exhibited an incredible robustness not observed with any other saturated heterocycle evaluated thus far. This allowed us to explore a broad range of diverse and challenging aryl bromides, including many that exhibited 0% yields with 2-Bpin pyrrolidine **123**. These include 4-bromobenzonitrile, 4-bromophenol, 4-bromoacetinilide, 2-bromopyridine and 2-bromothiophene.

The system exhibited good tolerance to electron donating groups, demonstrated by high yielding examples with aryl bromides such as 4-bromoanisole (63% of **140**) and 4-bromo-dimethylaniline (72% of **142**). However, there were still some aryl bromide dependent sensitivities observed. Based on the observed lower yield of phenol tetrahydrothiophene **141** (13%), the system exhibits sensitivity to acidic protons, which has been observed in other systems. Deprotonation of the phenol will be extensive in the 120 °C, basic (Cs_2CO_3) conditions and the presence of the phenolate anion may alter speciation of the palladium. Alternatively, the phenolate anion will have greater solubility in the water layer of the biphasic system which may interrupt the rate balance in the cross-coupling cycle. Ultimately, the exact mechanistic reason for the low yield with 4-bromophenol is unknown but the 63% yield of **140** on cross-coupling with 4-bromoanisole presents an alternative route (*via* deprotection) for the synthesis of the phenol compound.

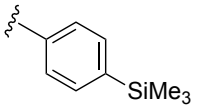
As well as electron donating groups, the SMCC tolerates electron withdrawing groups well with 4-bromonitrobenzene, 4-bromobenzonitrile and 4-bromobenzotrifluoride demonstrating high cross-coupling yields with 2-Bpin tetrahydrothiophene **110** (50% of **143**, 73% of **121** and 59% of **144**). Some sensitivity was observed with unsubstituted pyridines. 2-Pyridyl tetrahydrothiophenes **146** and **147** were obtained in 39% and 30% yields. When the pyridine nitrogen is more sterically hindered, higher cross-coupling yields are observed. For example, a high 80% yield of 2-aryl tetrahydrothiophene **130** was obtained when 2-methyl-4-bromopyridine was used in the reaction.



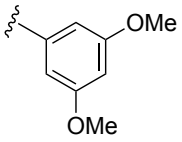
110



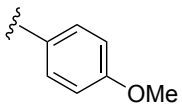
116, 78%



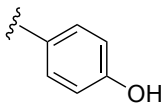
132, 87%[a]



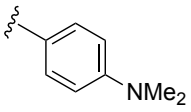
133, 84%[a]



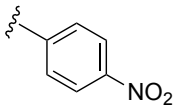
140, 63%



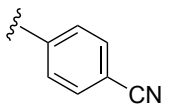
141, 16%



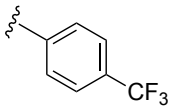
142, 72%



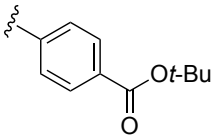
143, 50%[b]



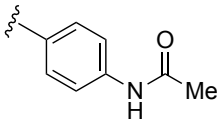
121, 73%



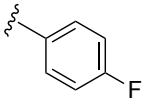
144, 59%



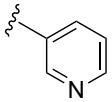
120, 44%



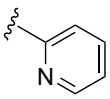
145, 75%



118, 80%



146, 39%



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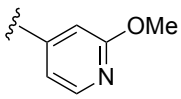
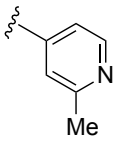


148, 73%



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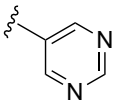
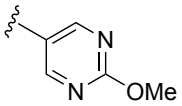
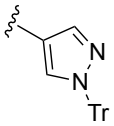


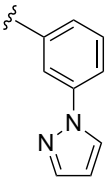
149, 65%



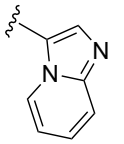
131, 89%[a]



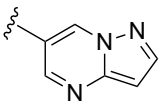
150, 70%



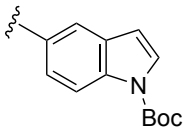
151, 73%



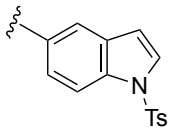
152, 76%



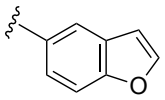
153, 44%



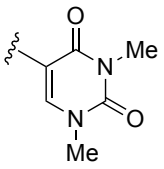
154, 40%



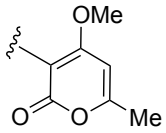
155, 79%



129, 70%[a]



156, 64%



157, 44%[c]

119, 62%[d]

[a] Reactions performed by James Firth in the O'Brien group, [b] Product isolated as a 93:7 mixture with protodehalogenated pyrone, [c] Conversion to 2-phenyl tetrahydrothiophene **116** determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as in internal standard, [d] Reaction performed by Stuart Smith in the Fairlamb and O'Brien groups.

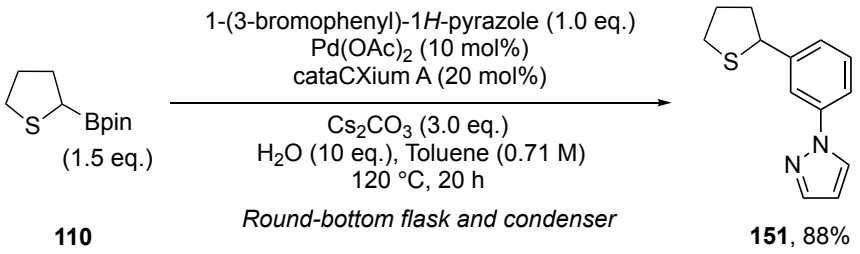
Scheme 2.15

High cross-coupling yields were obtained with a range of nitrogen and oxygen heterocyclic aryl bromides, highlighting the robustness and broad substrate tolerance of the method. Notably, the cross-coupling between 2-Bpin tetrahydrothiophene **110** and 1-(3-bromophenyl)-1H-pyrazole afforded 2-aryl tetrahydrothiophene **151** in 73% yield. This aryl bromide was previously employed by Dombrowski *et al*. in the 2020 AbbVie study (see Scheme 1.5), where poor yields were reported across a range of related heterocyclic boronates.

Cross-coupling of 5-bromo-*N*-Boc indole gave 2-aryl tetrahydrothiophene **154** in 40% yield. It was hypothesised that the moderate yield with 5-bromo *N*-Boc indole was due to removal of the Boc group under the harsh basic conditions, likely due to nucleophilic attack by hydroxide. To support this hypothesis, 5-bromo *N*-Ts indole was synthesised[81] and cross-coupled with 2-Bpin tetrahydrothiophene **110** to give *N*-Ts indole tetrahydrothiophene **155** in 79% yield. Finally, 2-aryl tetrahydrothiophene **157** was obtained in 44% yield. This result is mechanistically indicative of an efficient transmetallation. The aryl bromide, 3-Bromo-4-methoxy-6-methyl-2*H*-pyran-2-one, is extremely prone to protodehalogenation. In our systems, it has been used as a probe to both study protodehalogenation and, by inference, the relative rate of transmetallation of different systems. By cross-coupling to give **157** even in a 44% yield, transmetallation must occur unexpectedly quickly in order to outcompete protodehalogenation. Overall, the developed methodology demonstrated exceptional robustness and broad functional group tolerance, enabling moderate to excellent yields across a diverse array of aryl bromide coupling partners.

The cross-coupling examples of 2-Bpin tetrahydrothiophene **110** with aryl bromides shown in Scheme 2.15 were all carried out on a small scale (0.3 or 0.5 mmol) in sealed 7 mL screw cap vials. To expand the utility of this methodology, the reaction was scaled up and carried out in a round-bottom flask with condenser. On a 2.5 mmol scale in a round-bottom flask, SMCC of 2-Bpin tetrahydrothiophene **110** and 1-(3-bromophenyl)-1H-pyrazole under the standard conditions gave 2-aryl tetrahydrothiophene **151** (505 mg) in 88% yield (Scheme 2.16). Although originally designed for small scale synthesis to support early-stage hit identification, the methodologies adaptability to larger-scale reactions suggests potential in subsequent drug discovery stages where multigram syntheses are required. The increase in yield

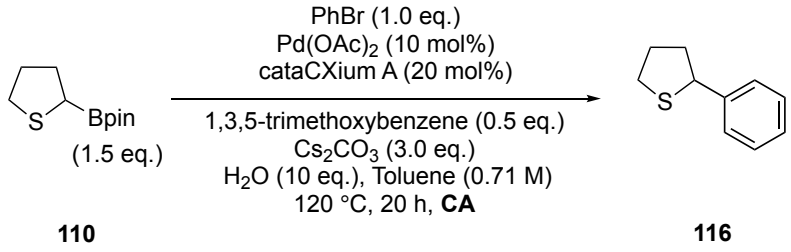
of **151** (88%) compared to the small scale (73%), may be due to decreased sensitivities to subtle variations in conditions. The inherent change in small amounts of oxygen or water between reactions will be less significant as the scale of the reaction increases.



Scheme 2.16

To evaluate the role of oxygen in the cross-coupling process, a series of reactions were carried out using 2-Bpin tetrahydrothiophene **110** and bromobenzene under the standard conditions, with incremental amounts of compressed air added. The results are shown in Table 2.2. No significant effect was observed with addition of compressed air up to 0.6 mL (entries 2-4) compared to the standard set-up (entry 1). Regarding the increased yield of 2-aryl tetrahydrothiophene **151** (see Scheme 2.16) on a larger scale, it is unlikely due to a decreased effect of sensitivity to oxygen on the large scale.

Table 2.2: Effect of oxygen on the SMCC reaction of 2-Bpin tetrahydrothiophene



Entry	Volume of compressed air (CA) / mL	NMR Yield / %[a]
1	0	86
2	0.2	84
3	0.4	85
4	0.6	83
5	Reaction carried out in CA	62

[a] Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as in internal standard.

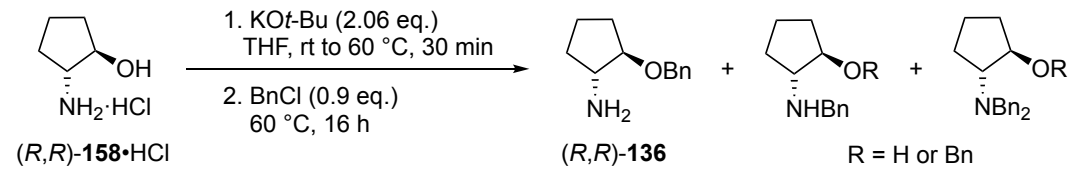
As no effect was observed with minor air exposure, a final experiment was carried out with the reaction carried out completely under aerobic conditions. In this case, the standard nitrogen purge step, used to exclude oxygen, was deliberately omitted. The reaction proceeded under ambient air, affording 2-phenyl tetrahydrothiophene **116** in 62% NMR yield (entry 5). Relative to the typical range of yields of 2-phenyl tetrahydrothiophene **116** obtained after chromatography, NMR yields appear to be reporting 10-20% higher. Thus, the 62% NMR yield indicates that while the reaction remains viable, the presence of substantial oxygen diminishes some efficiency. These findings underscore the importance of the nitrogen purge step while suggesting that minor oxygen exposure is unlikely to substantially affect the overall yield.

2.6 Synthesis of Enantioenriched 2-Bpin Tetrahydrothiophene

A key aim of this study was to further evaluate the stereochemical outcome of SMCC reactions with 2-Bpin tetrahydrothiophene (*S*)- or (*R*)-**110**. To achieve this, access to sufficient quantities of the enantioenriched 2-Bpin tetrahydrothiophenes (*S*)- and (*R*)-**110** was required. As outlined in Section 2.1.3, the route relied on diastereomeric resolution, the low yields of which meant that some further investigation of those steps would be needed. Moreover, the synthesis would usually start from cyclopentyl amino Bn alcohol (*S*,*S*)-**136** or (*R*,*R*)-**136** (see Scheme 2.9). However, due to commercial supply issues, the synthesis had to proceed from cyclopentyl hydroxylamine HCl salt (*R*,*R*)-**158•**HCl instead.

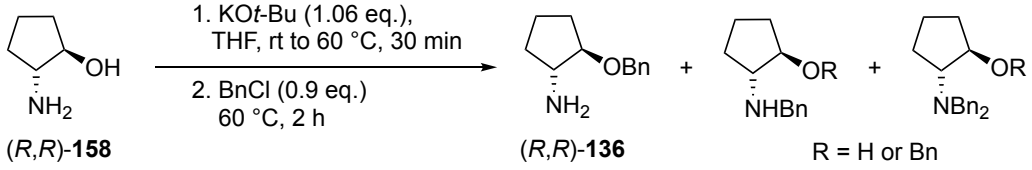
2.6.1 Benzylation of Cyclopentyl Hydroxylamine: Chemoselective Approaches

The first step of the proposed route would involve *O*-benzylation of cyclopentyl hydroxylamine HCl salt (*R*,*R*)-**158•**HCl to give benzyl ether (*R*,*R*)-**136**. However, benzyl protection of the cyclopentyl alcohol in the presence of the more nucleophilic amine group presented a chemoselectivity issue. A 2008 Novartis patent proposed a regioselective benzylation, harnessing the increased nucleophilicity of the alkoxide anion and the difference in acidity between the OH and the NH_2 protons.[82] The regioselective benzylation proceeded by initial deprotonation of the alcohol at 60 °C with KO*t*-Bu before addition of BnCl. Unfortunately, in our hands, the benzylation gave an unquantifiable mixture of the desired benzylated product (*R*,*R*)-**136** and the suspected *N*-Bn/*N*-Bn_2 products (with or without *O*-benzylation) as shown by ^{1}H NMR spectroscopy of the crude product (Scheme 2.17). The patent itself had not started from the HCl salt but the free amine. Therefore, to bring the conditions closer to that of the patent, an initial deprotonation of cyclopentyl hydroxylamine HCl salt (*R*,*R*)-**158•**HCl using *n*-BuLi was carried out, before continuing with the conditions from the patent. Unfortunately, no conversion to benzylcyclopentylamine (*R*,*R*)-**158•**HCl was obtained from this method.



Scheme 2.17

A second approach to starting from the free amine of cyclopentyl hydroxylamine HCl salt (*R*,*R*)-**158**•HCl involved extracting the amine with CH_2Cl_2 from a concentrated KOH solution. This was successful: 7.5g of HCl salt (*R*,*R*)-**158**•HCl gave 2.5g of the free amine (*R*,*R*)-**158**. In the Novartis patent, the reaction was carried out on a 30 g scale and the BnCl was added slowly. Therefore, in one last attempt, to align as much as possible with the reaction in the patent, benzylation was attempted on a 2.5 g scale and a syringe pump was used to slowly dose in the BnCl. Unfortunately, this also resulted in an unquantifiable mixture of *N*- and *O*-benzylated products (Scheme 2.18).

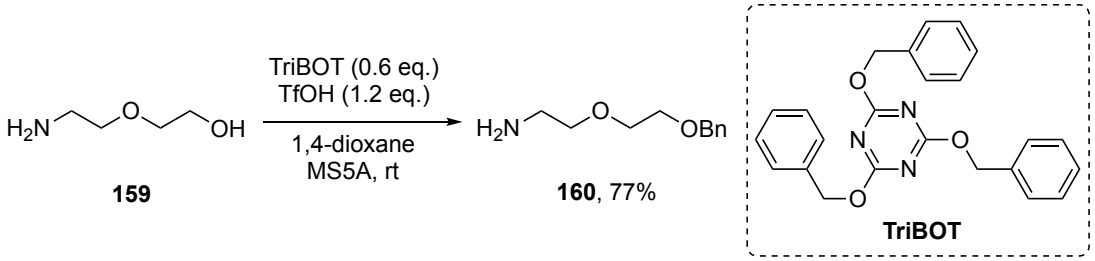


Scheme 2.18

Given challenges with chemoselectivity under basic conditions, it was hypothesised that employing an acidic benzylation strategy could be successful as these conditions would suppress the nucleophilicity of the amine nitrogen by forming an ammonium salt. This could allow selective benzylation of the alcohol in amino alcohol (*R*,*R*)-**158**. Benzyl 2,2,2-trichloroacetimidate (BTCAI) is a benzylating agent used under acidic conditions developed by Cramer *et al*.[83] in the 1950s and first used for benzylation by Bundle *et al*. in 1981.[83] In 2012, Kunishima *et al*. synthesised a trimeric form of BTCAI, named TriBOT, to overcome the practical limitations of BTCAI such as atom economy, cost and usability (it is a liquid). [84]

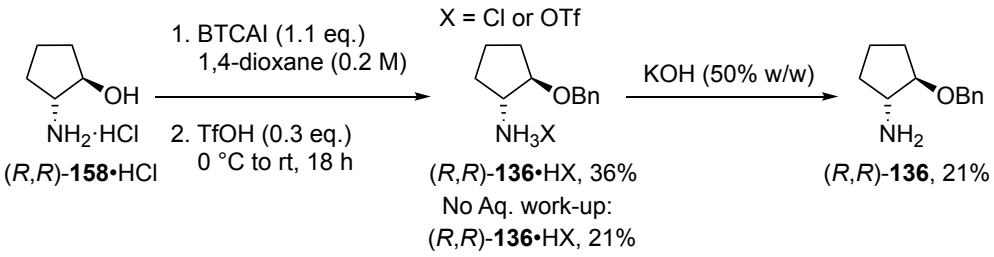
An example of the use of TriBOT in the chemoselective *O*-benzylation of an amino alcohol is shown in Scheme 2.19. The reaction proceeds with protonation of the more basic primary amine (stoichiometric) and of the pyridine nitrogen of TriBOT to activate it. The alcohol then attacks the protonated TriBOT in a nucleophilic

substitution reaction to form the corresponding benzyl ether. When amino alcohol **159** was reacted under these conditions, benzyl ether **160** was obtained in 77% yield (Scheme 2.19).



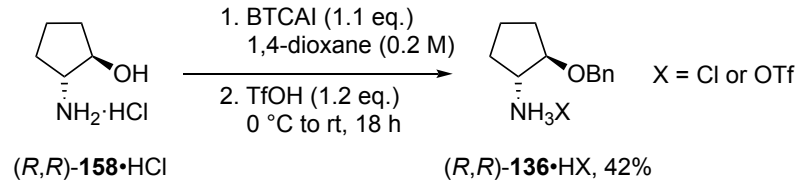
Scheme 2.19

TriBOT works *via* the same mechanism as BTCAI which is commercially available. Therefore, it was hypothesised that a chemoselective benzylation of cyclopentyl hydroxylamine HCl salt (*R*,*R*)-**158•**HCl could be achieved using BTCAI. In this case, the amine is already "protected" as a salt and so excess triflic acid should not be required. Thus, cyclopentyl hydroxylamine HCl salt (*R*,*R*)-**158•**HCl was stirred with BTCAI and dioxane before adding triflic acid at 0 °C. Following basic work-up and chromatography, the product isolated was in fact benzyl cyclopentyl hydroxylammonium salt (*R*,*R*)-**136**·HX in 36% yield (Scheme 2.20). Despite anticipating that the free amine benzylcyclopentylamine (*R*,*R*)-**136** would be obtained, given that a basic work-up had been used, the identity of an ammonium salt form was characterised based on the downfield shift of all alkyl peaks in the ^{1}H NMR spectrum and the presence of a broad singlet at 6.2 ppm integrating to 3 protons. It is noted that the reported 36% yield assumes that the ammonium salt is exclusively the hydrochloride salt and not at least partially comprised of the triflate salt. Employing the concentrated KOH and CH_2Cl_2 extraction protocol used previously gave benzylcyclopentylamine (*R*,*R*)-**136** in 21% yield (Scheme 2.20). To explore whether product was being lost in the aqueous basic work-up, the benzylation reaction was carried out moving straight to column of the ammonium salt without aqueous work-up. This resulted in a comparable 31% yield of cyclopentyl hydroxylammonium salt (*R*,*R*)-**136**·HX, suggesting that organic extraction in the basic work-up was not detrimental to the overall yield.



Scheme 2.20

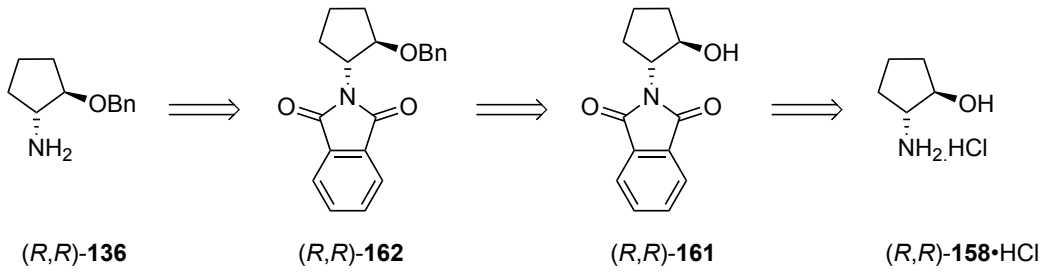
For comparison, the benzylation reaction was carried out using an excess of triflic acid resulting in a 42% yield of benzyl cyclopentyl hydroxylammonium salt (*R*,*R*)-**136**·HX (Scheme 2.21). This single step conversion was extremely promising. However, given the moderate 42% yield, the low recovery from extraction of the free amine and the inconsistency of working with the ammonium salt, this route was set aside. It would be interesting to explore the BBIDA formation from cyclopentyl hydroxylamine HCl salt (*R*,*R*)-**158**•HCl in the future.



Scheme 2.21

2.6.2 Benzylation of Cyclopentyl Hydroxylamine: Phthalimide Protection Strategy

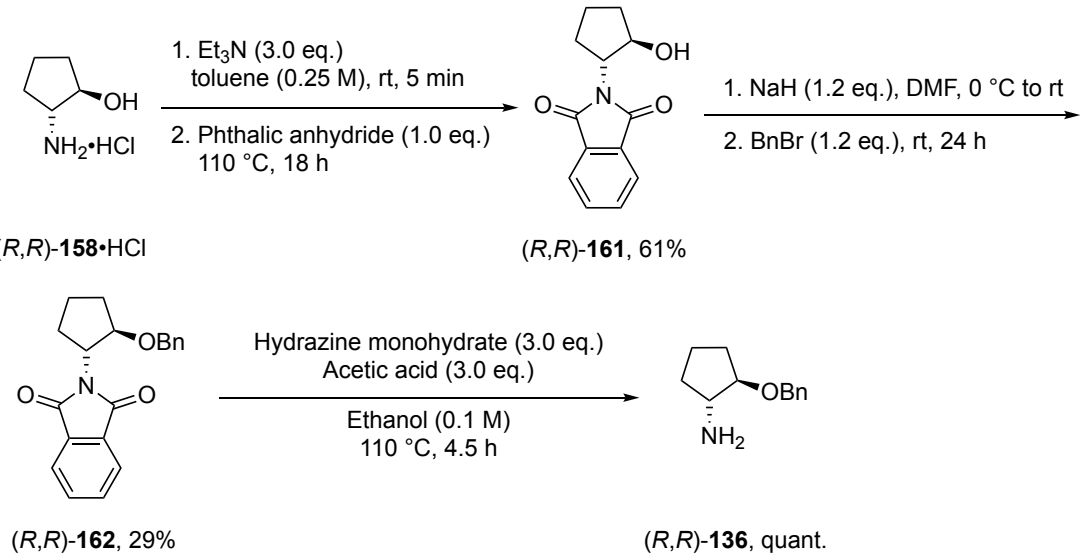
Based on the low yield of the free amine of (*R*,*R*)-**136** obtained *via* the acidic O-benzylation approach, the strategy was revised in favour of a longer, but more reliable, route involving phthalimide protection. This approach followed patent literature which described related methodology on cyclopentyl hydroxylamine (*R*,*S*)-**158**.[85] The retrosynthetic approach is outlined in Scheme 2.22. Phthalimide protection of amino alcohol (*R*,*R*)-**158**•HCl would give phthalimide (*R*,*R*)-**161** which would then allow *O*-benzylation without any issue of chemoselectivity. The resulting benzyl phthalimide (*R*,*R*)-**162** could then be deprotected to give the desired benzyl amino alcohol (*R*,*R*)-**136**.



(*R*,*R*)-**136** (*R*,*R*)-**162** (*R*,*R*)-**161** (*R*,*R*)-**158**•HCl

Scheme 2.22

Following the Novartis patent,[85] amino alcohol HCl salt (*R*,*R*)-**158**•HCl was stirred in toluene with triethylamine before adding phthalic anhydride and refluxing overnight. Following work-up and purification, pthahlimide (*R*,*R*)-**161** was isolated in 61% yield. Deprotonation with sodium hydride in DMF followed by alkylation with BnBr gave benzyl phthalimide (*R*,*R*)-**162** in 29% yield. Finally, amine deprotection using excess hydrazine monohydrate and acetic acid in ethanol gave quantitative conversion to benzyl amino alcohol (*R*,*R*)-**136** (Scheme 2.23).



(*R*,*R*)-**158**•HCl (*R*,*R*)-**161**, 61%

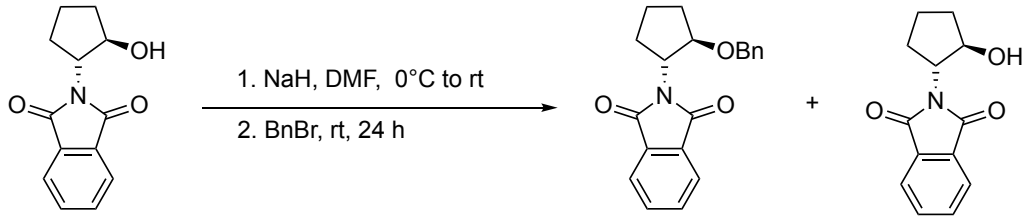
(*R*,*R*)-**162**, 29% (*R*,*R*)-**136**, quant.

Scheme 2.23

Although the synthetic route showed considerable promise, benzylation once again proved to be the problematic step. To address this key limitation, the benzylation reaction was carefully optimised around the patent conditions (Table 2.3). The primary issue identified was the persistence of unreacted starting material. Modifying the concentration of the reaction in DMF had no effect on the yield of benzyl phthalimide (*R*,*R*)-**162** and ~60% starting material was recovered in each case (entries 1 and 2).

Increasing the equivalents of sodium hydride from 1.2 to 2.0 eq. resulted in complete consumption of phthalimide (*R*,*R*)-**161** but was not accompanied with an increase in the yield of benzyl phthalimide (*R*,*R*)-**162** (entry 3). Similarly, increasing the equivalents of benzyl bromide and increasing the concentration in DMF had no positive effect on conversion to benzyl phthalimide (*R*,*R*)-**162** (entry 4). This suggested that the alkoxide generated by deprotonation of the alcohol by sodium hydride lacked sufficient nucleophilicity to efficiently alkylate benzyl bromide. Therefore, it was hypothesised that addition of tetrabutylammoniumiodide (TBAI) as a nucleophilic catalyst could enhance reactivity due to the *in situ* formation of benzyl iodide. This was confirmed experimentally. Addition of 10 mol% TBAI into the reaction increased the yield of benzyl phthalimide (*R*,*R*)-**162** to 50% on a small scale (entry 5). However, upon scale-up, benzyl phthalimide (*R*,*R*)-**162** was obtained in only 12% yield (entry 6), necessitating further optimisation.

Table 2.3: Optimisation of DMF benzylations of (*R*,*R*)-**161**



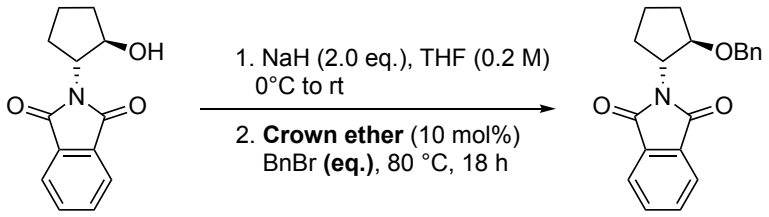
(*R*,*R*)-**161** (*R*,*R*)-**162** (*R*,*R*)-**161**

Entry	NaH / eq.	[DMF] / M	BnBr / eq.	Yield (*R*,*R*)-**162** / %[a]	Yield (*R*,*R*)-**161** / %[a]
1	1.2	0.2	1.2	25	61
2	1.2	2.16	1.2	25	58
3	2.0	0.2	1.2	29	0
4	2.0	0.5	2.0	22	0
5[b]	2.0	0.5	1.2	50	0
6[b,c]	2.0	0.5	1.2	12	0

[a] Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard, [b] Reaction included 10 mol% TBAI , [c] Reaction scaled up to 31 mmol

Based on work carried out by Lewis *et al*.,[86] the solvent was changed from DMF to THF with 18-crown-6 as an additive. DMF has a significantly higher dielectric constant than THF, which enables it to more effectively solvate cations such as Na^+. Consequently, in THF, the alkoxide generated from NaH remains more tightly ion-paired with sodium, reducing its nucleophilicity. The addition of 18-crown-6 overcomes this limitation by coordinating with the sodium cation and producing a "free" reactive anionic alkoxide. Accordingly, the hydroxyl group in phthalimide (*R*,*R*)-**161** was deprotonated using excess NaH in THF, followed by alkylation with excess benzyl bromide (5 equivalents) in the presence of 18-crown-6. After work-up and purification, benzyl phthalimide (*R*,*R*)-**162** was obtained in 81% yield (entry 1). On repetition, a slightly lower yield of 58% was observed, likely due to random variation, but still within an acceptable threshold. To improve the reaction's green chemistry metrics, a series of experiments were conducted to reduce the equivalents of benzyl bromide. The reaction remained efficient with 4 or 3 equivalents (entries 2 and 3), but a notable decrease in yield was observed using 2 equivalents (entry 4). To assess the necessity of the crown ether, the reaction was carried out in its absence, resulting in a significantly lower yield of (*R*,*R*)-**162** of 29% (entry 5). Given previous observations in DMF (see Table 2.3, entry 6) it was hypothesised that adding TBAI as a nucleophilic catalyst might improve conversion using only 2 equivalents of BnBr. However, with 10 mol% TBAI and 2 equivalents of BnBr, a 39% yield of (*R*,*R*)-**162** was observed (entry 6). Finally, as 15-crown-5 was hypothesised to be a better size-match to Na^+ than 18-crown-6, it was also tested. This substitution gave a slightly lower yield of (*R*,*R*)-**162** (51%, entry 7), indicating that while both crown ethers aid the reaction, 18-crown-6 remains marginally more effective. Thus, the optimised conditions for the benzylation of phthalimide (*R*,*R*)-**162** were those in Table 2.4 entry 3: NaH (2.0 eq.) in THF (0.2 M) with 18-crown-6 (10 mol%) and BnBr (3.0 eq.).

Table 2.4: Optimisation of benzylation using NaH and crown ethers in THF

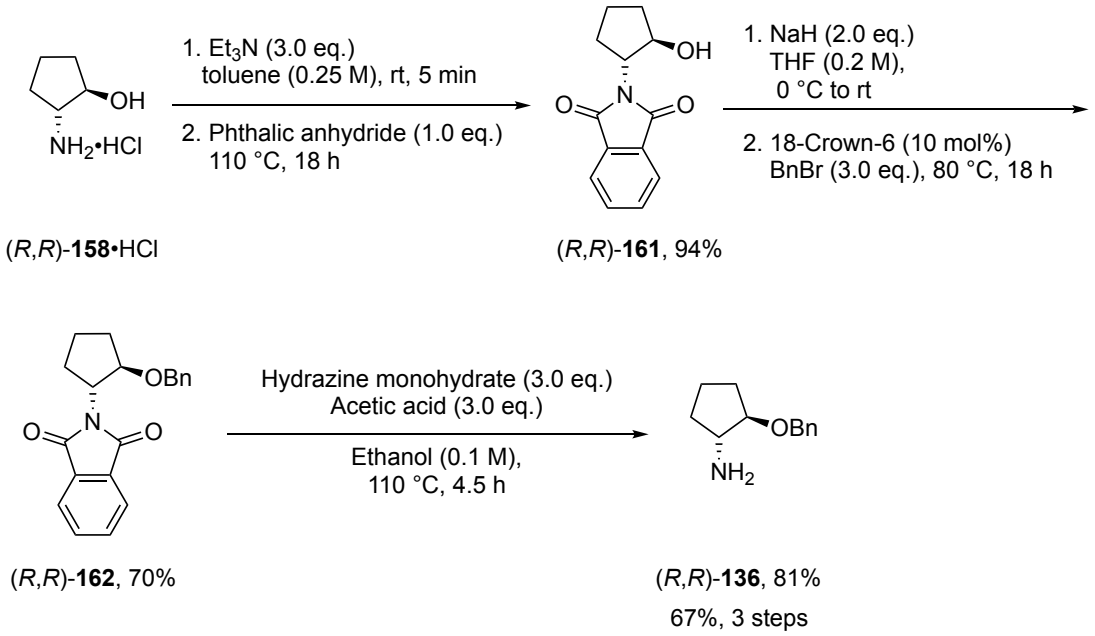


(*R*,*R*)-**161** (*R*,*R*)-**162**

Entry	BnBr / eq.	Crown ether	Yield / %[a]
1	5.0	18-crown-6	81%, 58%
2	4.0	18-crown-6	55%
3	3.0	18-crown-6	63%
4	2.0	18-crown-6	30%
5	5.0	None	29%[b]
6[c]	2.0	18-crown-6	39%
7	3.0	15-crown-5	51%

[a] Yield after chromatography, [b] Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard, [c] Reaction included 10 mol% TBAI

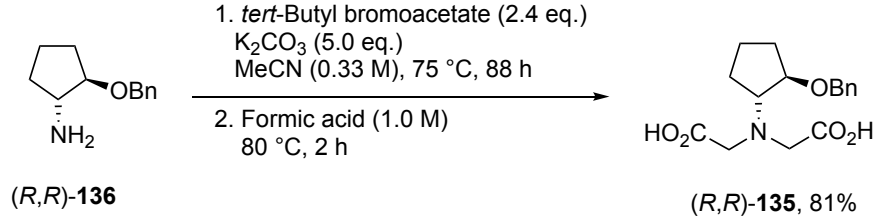
Following optimisation of the benzylation conditions, the synthesis was scaled up in a controlled and systematic manner to a 5 g scale, facilitating the rapid and efficient generation of material in the required preparative quantities. The phthalimide protection proceeded more efficiently on larger scale, with phthalimide (*R*,*R*)-**161** isolated in 94% yield without requiring chromatographic purification. Benzyl ether formation also proceeded more efficiently on larger scale and benzyl phthalimide (*R*,*R*)-**162** was obtained in 70% yield. Finally, although deprotection proceeded in a slightly lower yield on larger scale, the route afforded an overall 67% yield of benzyl amino alcohol (*R*,*R*)-**136** across the three-step sequence (Scheme 2.24). In this way, a 6.1 g batch of benzyl amino alcohol (*R*,*R*)-**136** was prepared.



Scheme 2.24

2.6.3 Synthesis of (*R*,*R*)-BIDA from Benzyl Cyclopentyl (*R*,*R*)-136

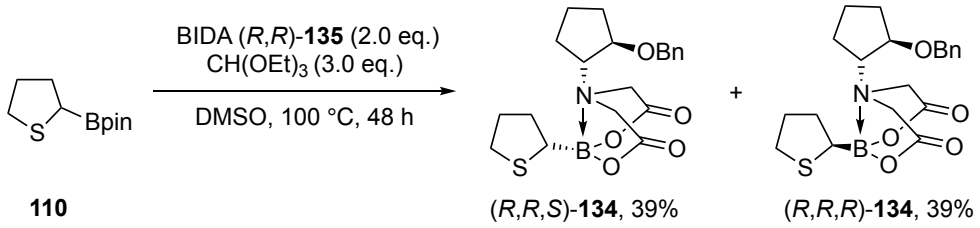
The generation of enantioenriched 2-Bpin tetrahydrothiophenes (*S*)-**110** and (*R*)-**110** then followed the steps previously carried out in the group by James Firth. Following the synthetic procedure established by Burke *et al.*,[76] described in Section 2.1.3, the synthesis proceeded with a double *N*-alkylation of benzyl amino alcohol (*R*,*R*)-**136** using excess *tert*-butyl bromoacetate and K_2CO_3 in acetonitrile at 75 °C for 88 h. Then, the *tert*-butyl esters were cleaved by stirring in formic acid at 80 °C for 2 h. Following removal of the formic acid and recrystallisation, BIDA (*R*,*R*)-**135** was obtained in 81% yield on an 8 g scale (Scheme 2.25), an improvement over the previous 68% yield for these two steps (see Scheme 2.9).



Scheme 2.25

Next, 2-Bpin tetrahydrothiophene *rac*-**110** was reacted with 2 equivalents of BIDA (*R*,*R*)-**135** and triethylorthoformate in DMSO at 100 °C for 48 h. Following separation

of the diastereomers, both BBIDA tetrahydrothiophenes (*R*,*R*,*S*)-**134** and (*R*,*R*,*R*)-**134** were obtained in 39% yield (Scheme 2.26). This is a significant improvement over the previous attempt within the O'Brien group (~20% yields). The configuration of BBIDA tetrahydrothiophene (*R*,*R*,*S*)-**134** was confirmed by X-ray crystallography (Figure 2.3).



Scheme 2.26

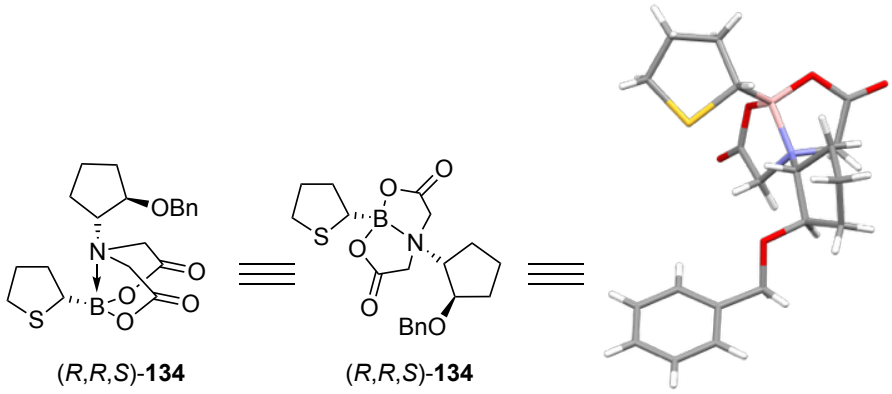
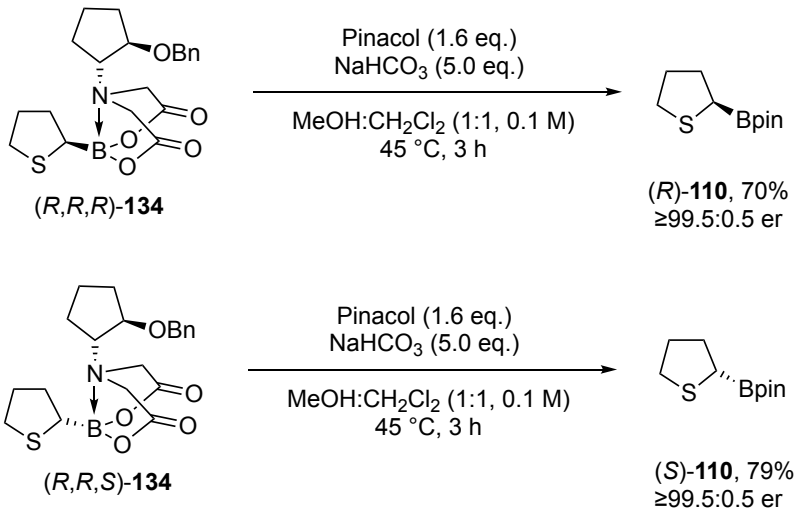


Figure 2.3: X-Ray crystal structure of BBIDA tetrahydrothiophene (*R*,*R*,*S*)-**134**

The conditions for the conversion of MIDA boronates into Bpin derivatives initially developed by Burke *et al.*[77] were explored as it was hypothesised that they would be suitable for use with BBIDA tetrahydrothiophenes (*R*,*R*,*S*)- and (*R*,*R*,*R*)-**134**. Thus, reacting BBIDA tetrahydrothiophenes (*R*,*R*,*S*)- and (*R*,*R*,*R*)-**134** separately with an excess of pinacol and $NaHCO_3$ in a 1:1 mixture of methanol-CH_2Cl_2 at 45 °C for 3 h gave, after work-up and purification, 2-Bpin tetrahydrothiophenes (*S*)- and (*R*)-**110** in 79% and 70% yield, respectively (Scheme 2.27). The CH_2Cl_2 cosolvent system was adopted due to the observed low solubility of BBIDA tetrahydrothiophene (*R*,*R*,*R*)-**134** in methanol.



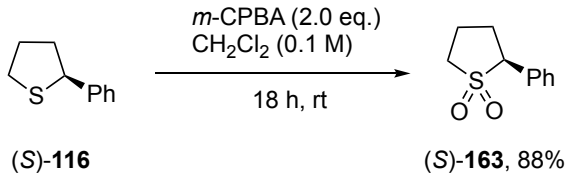
Scheme 2.27

A method was then developed for normal phase CSP-HPLC resolution of the two enantiomers of racemic 2-Bpin tetrahydrothiophene **110**. The enantioenriched 2-Bpin tetrahydrothiophenes (*S*)- and (*R*)-**110** were then analysed by CSP-HPLC and were shown to be of ≥99.5:0.5 er.

2.7 Investigation of the Stereochemical Outcome of the Suzuki-Miyaura Cross-Coupling of Enantioenriched 2-Bpin Tetrahydrothiophene

2.7.1 Determination of Configuration of 2-Phenyl Tetrahydrothiophene (*S*)-116

To further confirm the previous work performed on the stereochemical pathway of the SMCC (see Scheme 2.12), further stereochemical proof of the product was desired. The plan was to access a crystalline form of enantioenriched 2-phenyl tetrahydrothiophene (*S*)-**116** by converting it into the corresponding sulfone (*S*)-**163**. Thus, 2-phenyl tetrahydrothiophene (*S*)-**116** was reacted with *m*-CPBA in CH_2Cl_2 at rt for 18 h. Following work-up and chromatography, enantioenriched 2-phenyl sulfone (*S*)-**163** was obtained in 88% yield (Scheme 2.28).



(*S*)-**116** (*S*)-**163**, 88%

Scheme 2.28

A suitable crystal of (*S*)-**163** was grown and the absolute configuration was confirmed *via* X-ray crystallography (Figure 2.4).

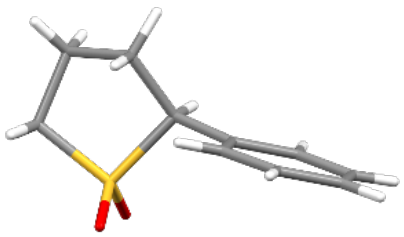


Figure 2.4: X-Ray crystal structure of 2-phenyl sulfone (*S*)-**163**

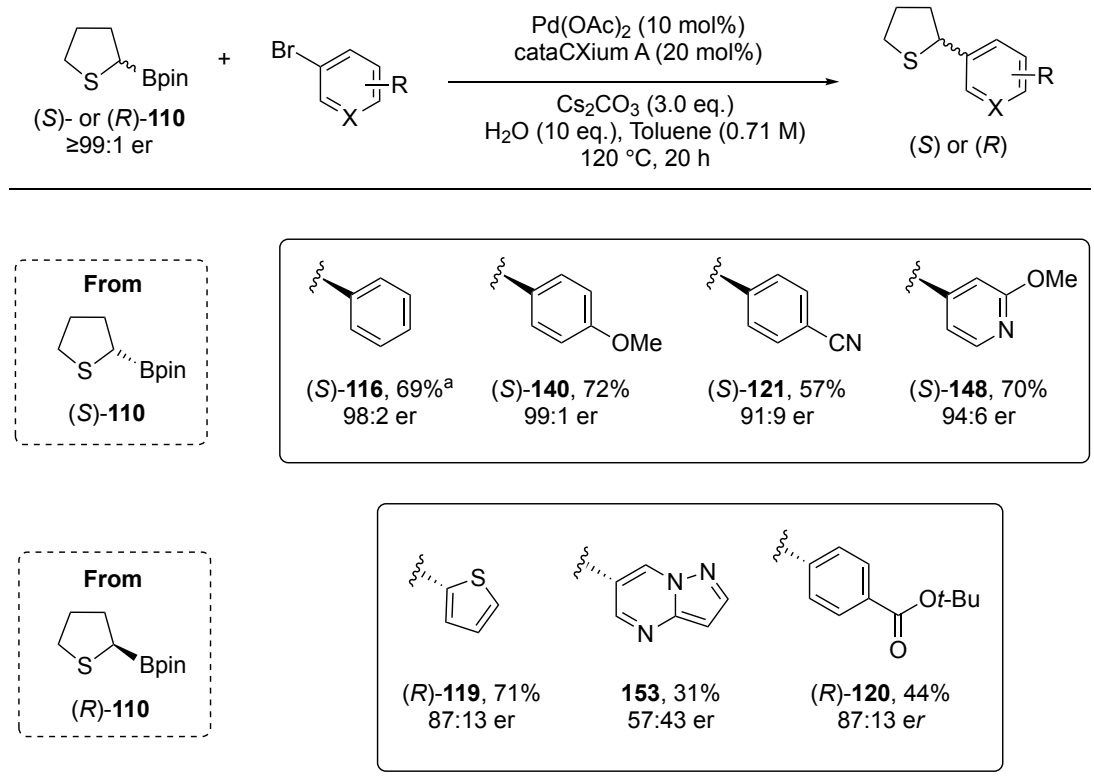
2.7.2 Scope of the Suzuki-Miyaura Cross-Coupling of Enantioenriched 2-Bpin Tetrahydrothiophene

With access to enantioenriched 2-Bpin tetrahydrothiophenes (*S*)- and (*R*)-**110** established, a carefully curated series of aryl bromides could be evaluated in the cross-coupling. To maximise experiments, the cross-couplings of 2-Bpin tetrahydrothiophene (*S*)- or (*R*)-**110** were performed on a 0.3 mmol scale (instead of the usual 0.5 mmol) and used 1.2 equivalents of **110** (instead of the 1.5 equivalents typically used). This was validated on racemic 2-Bpin tetrahydrothiophene **110** where phenyl tetrahydrothiophene **116** was obtained in 75% yield.

The original investigation by James Firth (see Section 2.1.3) had determined that the cross-coupling of 2-Bpin tetrahydrothiophene (*S*)-**110** (99:1 er) and bromobenzene gave the stereoinvertive product (2-phenyl tetrahydrothiophene (*S*)-**116**) in high (98:2) er. As discussed, the amount of 2-Bpin tetrahydrothiophene (*S*)- and (*R*)-**110** available was limited due to the protracted nature of the enantioenriched synthesis. Therefore, the initial aryl bromide scope was designed to investigate whether products in high er, *via* a stereoinvertive pathway, were obtained from the cross-couplings. Moreover, the stereochemical outcome of the transformation could be further validated by selecting aryl bromides which would give cross-coupled products with known optical rotations and configurations. Thus, 4-bromobenzonitrile, 4-bromoanisole, 2-bromothiophene and *tert*-butyl 4-bromobenzoate were chosen for this reason.[73] The initial seven examples of the enantioenriched scope, including the cross-coupling of bromobenzene by James Firth, are summarised in Scheme 2.29.

Cross-coupling of 2-Bpin tetrahydrothiophene (*S*)-**110** with 4-bromoanisole gave 2-aryl tetrahydrothiophene (*S*)-**140** in 72% yield and 99:1 er. Comparison to the literature $[\alpha]_D$ value confirmed that this was the stereoinvertive (*S*) product. However, when utilising more electron deficient aryl bromides, the cross-coupling proceeded with incomplete stereoinversion. For example, cross-coupling of 4-bromobenzonitrile with 2-Bpin tetrahydrothiophene (*S*)-**110** gave 2-aryl tetrahydrothiophene (*S*)-**121** in 57% yield and 91:9 er, proceeding primarily with stereoinversion. Similarly, using 4-bromobenzoate with 2-Bpin tetrahydrothiophene (*R*)-**110** gave aryl

tetrahydrothiophene (*R*)-**120** in 44% yield and 87:13 er. However, it was not only electron deficient aryl bromides which exhibited this effect. When 2-bromothiophene, which is not considered electron withdrawing, was cross-coupled with 2-Bpin tetrahydrothiophene (*R*)-**110**, 2-aryl tetrahydrothiophene (*R*)-**119** was obtained in 71% yield and 87:13 er. Similarly, using (*S*)-**110** with 2-methoxy-4-bromopyridine, aryl tetrahydrothiophene (*S*)-**148** was obtained in a 70% yield and 96:4 er. Moreover, using 6-bromopyrazolo[1,5-α]pyrimidine with (*R*)-**110**, 2-aryl tetrahydrothiophene **153** was obtained in 31% yield and 57:43 er.

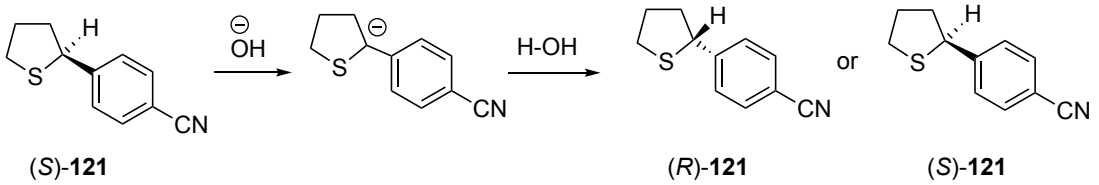


[a] Reaction performed by James Firth in the O'Brien group

Scheme 2.29

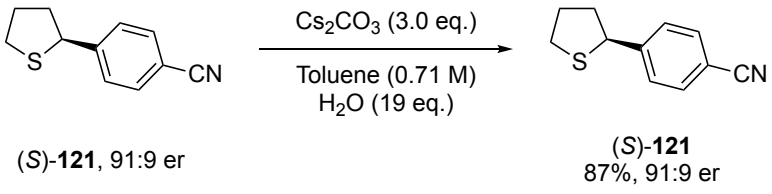
Three primary hypotheses emerged to rationalise the aryl-tetrahydrothiophenes with variable ers (i) partial epimerisation of the cross-coupled product; (ii) an unequal mixture of retentive and invertive transmetallation; (iii) a competitive β-hydride elimination reinsertion pathway. Using the cross-coupling results in Scheme 2.29 and additional experiments, the three hypotheses were investigated experimentally as much as was possible.

Taking 2-aryl tetrahydrothiophene (*S*)-**121** as an example, epimerisation would proceed *via* deprotonation of the tetrahydrothiophene α-proton. This would generate a carbanion which is likely to be planar and stabilised by conjugation with the *para*-nitrile group. Due to the low water concentration and excess base of the SMCC reaction, the conditions are highly basic and deprotonation of the α-proton would not be unexpected. The carbanion can then be re-protonated on either face, ultimately resulting in a mixture of 2-aryl tetrahydrothiophenes (*S*) and (*R*)-**121** (Scheme 2.30).



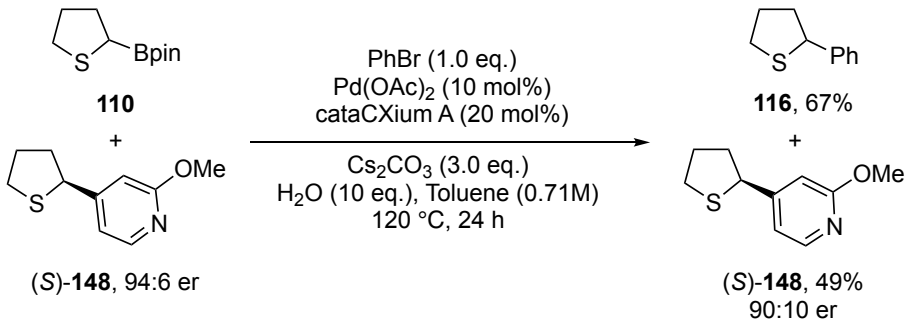
Scheme 2.30

Epimerisation of 2-aryl tetrahydrothiophene (*R*)-**121** had been previously demonstrated by Robertson *et al.*[73] By reacting 2-aryl tetrahydrothiophene (*R*)-**121** of 88:12 er with one equivalent of sodium hydride in DMF at 55 °C for 16 h, 2-aryl tetrahydrothiophene (*R*)-**121** 55:45 er was obtained (see Scheme 2.4). NaH is a much stronger base than the Cs_2CO_3 present in the SMCC conditions. Even under the highly concentrated conditions, Cs_2CO_3 may not be sufficiently basic to induce epimerisation. To test this experimentally, 2-aryl tetrahydrothiophene (*S*)-**121** of 91:9 er was stirred in Cs_2CO_3, toluene and water at 120 °C for 20 h to simulate the basic conditions of the SMCC reaction. Following work-up, 2-aryl tetrahydrothiophene (*S*)-**121** was recovered in 87% yield and 91:9 er (Scheme 2.31). Whilst this suggests that base alone does not induce epimerisation, the possibility remained that epimerisation may occur under the full SMCC conditions involving palladium catalysis.



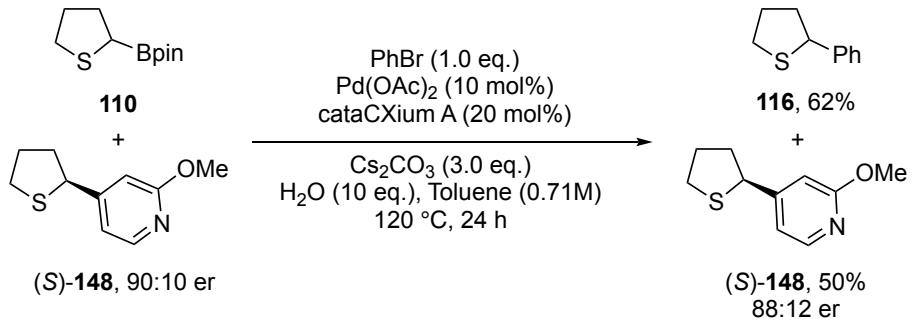
Scheme 2.31

To explore whether epimerisation might occur under the complete SMCC conditions, including the influence of any on-cycle generated palladium species, a control experiment was devised. Racemic 2-Bpin tetrahydrothiophene **110** was reacted under the typical SMCC conditions with bromobenzene and 2-aryl tetrahydrothiophene (*S*)-**148** of 94:6 er was included in this reaction mixture. Following work-up and chromatography, 2-phenyl tetrahydrothiophene **116** was obtained in 67% yield and 2-aryl tetrahydrothiophene (*S*)-**148** was recovered in 49% yield and 90:10 er (Scheme 2.31). The good yield of 2-phenyl tetrahydrothiophene **116** indicates that the reaction was not significantly inhibited. However, there was a small change in the er of 2-aryl tetrahydrothiophene (*S*)-**148** suggesting that some epimerisation can occur under full catalytic conditions. While the low recovery of (*S*)-**148** may suggest the presence of a degradation pathway, the consistently high yields observed in a variety of racemic cross-couplings, make it more likely that the loss is attributable to the reaction being carried out with a very small amount of (*S*)-**148**.



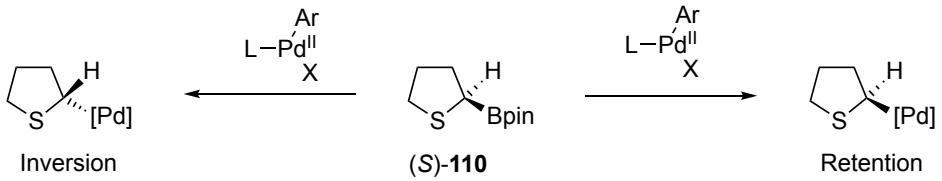
Scheme 2.32

To validate this result, 2-methoxypyridine tetrahydrothiophene (*S*)-**148** (90:10 er) was resubjected to the same SMCC reaction conditions. Following work-up and chromatography, 2-phenyl tetrahydrothiophene **110** was obtained in 62% yield and 2-methoxypyridine tetrahydrothiophene (*S*)-**148** was recovered in 50% yield and 88:12 er (Scheme 2.33). Although this represents a slight decrease from the original 90:10 er, the change is minimal and lies within the quantitation limits of the CSP-HPLC method. Thus, while small amounts of epimerisation cannot be entirely excluded, it is unlikely to be the primary contributor to the stereochemical erosion observed.



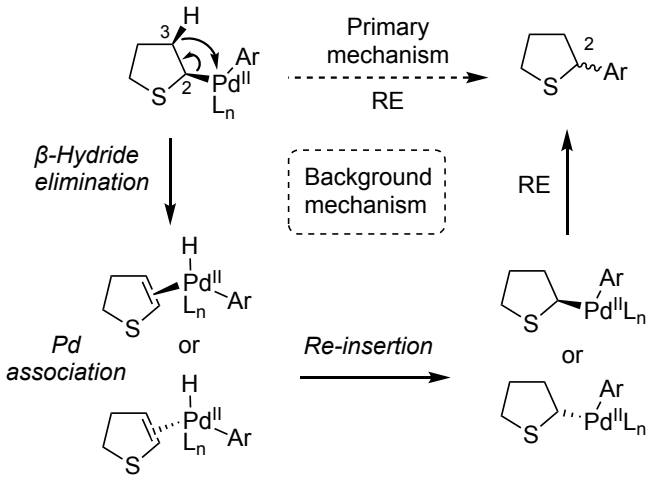
Scheme 2.33

With epimerisation ruled out as a significant factor in the stereochemical outcome, the remaining two hypotheses were considered, namely a mixture of retentive and invertive transmetallation and a β-hydride elimination reinsertion pathway. As shown in Section 1.3 (see Scheme 1.6), at the advent of transmetallation, 2-Bpin tetrahydrothiophene (*S*)- or (*R*)-**110** could undergo a mixture of retentive and invertive transmetallation mechanisms, ultimately resulting in a cross-coupled products with different ers, which could be aryl bromide dependent (Scheme 2.34).



Scheme 2.34

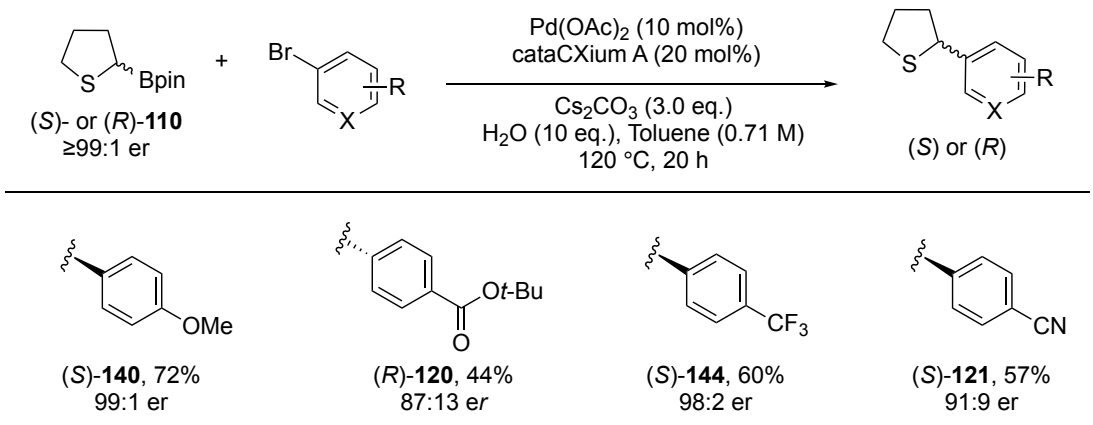
Alternatively, the epimerisation could take place after transmetallation. As discussed in Section 1.3, sp^3-sp^2 SMCC reactions can suffer from a detrimental side reaction of β-hydride elimination. This leads to alkene side products which can associate with the palladium aryl species and reinsert on either face, resulting in a mixture of enantiomeric pre-reductive elimination intermediates. When these undergo reductive elimination, a mixture of (*R*) and (*S*) 2-aryl tetrahydrothiophenes would be observed (Scheme 2.35).



Scheme 2.35

Considering the aryl bromide-dependent nature of the observed results, it is not possible to completely deconvolute the two factors. One possibility is that the steric/electronic properties of the aryl bromide bias transmetallation through a primarily stereoretentive or stereoinvertive pathway. Alternatively, these same features could influence the rates of β-hydride elimination and/or reductive elimination, ultimately affecting the er of the product. Regardless of the precise mechanism, whichever of the hypotheses is active, and because it is in fact challenging to devise experiments to distinguish between them, the empirical effect of the aryl bromide on stereochemical outcome can be investigated. As already noted, a very minor effect of epimerisation was observed for 2-aryl tetrahydrothiophene (*S*)-**148** (see Scheme 2.32). Thus, it remains plausible that the three proposed hypotheses all cumulatively contribute to the variation in ers observed, with their relative influence varying, depending on the aryl bromide employed. That said, the β-hydride elimination/reinsertion hypothesis lacks empirical evidence: neither alkene side products nor regiosiomeric 3-aryl tetrahydrothiophene products have been isolated or observed in ^{1}H NMR spectra of the crude products. Although volatility could explain why the alkene side products were never isolated, the lack of 3-aryl tetrahydrothiophene products is more telling. Therefore, whilst subsequent discussion could be applied to either of the two latter factors, the argument of a mixture of retentive and invertive transmetallation is favoured and will therefore be explored.

As discussed, previous work by Biscoe, Sigman and co-workers observed a correlation between aryl chloride electronics and stereochemical outcome (see Section 1.5, Table 1.2).[40] However, the trend was only explored in acyclic BF_3K systems. To determine whether the trend extended to 2-Bpin tetrahydrothiophene **110**, the outcomes of a representative set of cross-coupling reactions were examined. These included three of the already discussed reactions and one new example with *para*-trifluomethyl bromobenzene. The results are summarised in Scheme 2.36. Biscoe and Sigman observed a trend of increasing stereoretention with increasing electron withdrawing capacity of the *para* substituent of the phenyl group. Broadly, the trend is maintained with SMCC reactions of 2-Bpin tetrahydrothiophene **110**: complete stereoinversion was observed with electron-rich 4-bromoanisole and an increase in the degree of retention with electron withdrawing *para* substituents. However, a greater degree of retention was observed in 2-aryl tetrahydrothiophene (*R*)-**120** (87:13 er) than 2-aryl tetrahydrothiophene (*S*)-**121** (91:9 er), where the latter should react with more stereoretention given its superior electron withdrawing capability. Similarly, for trifluoromethyl containing 2-aryl tetrahydrothiophene (*S*)-**144**, an intermediate degree of retention would be expected, more than in 2-aryl tetrahydrothiophene (*R*)-**120** but less than 2-aryl tetrahydrothiophene (*S*)-**121**. However, 2-aryl tetrahydrothiophene (*S*)-**144** was obtained in 60% yield and 98:2 er, a completely stereoinvertive cross-coupling. These findings indicate that the stereochemical outcome cannot be attributed solely to the inductive effects of the aryl bromide, suggesting an increase in mechanistic complexity compared to the systems examined by Biscoe, Sigman and co-workers.



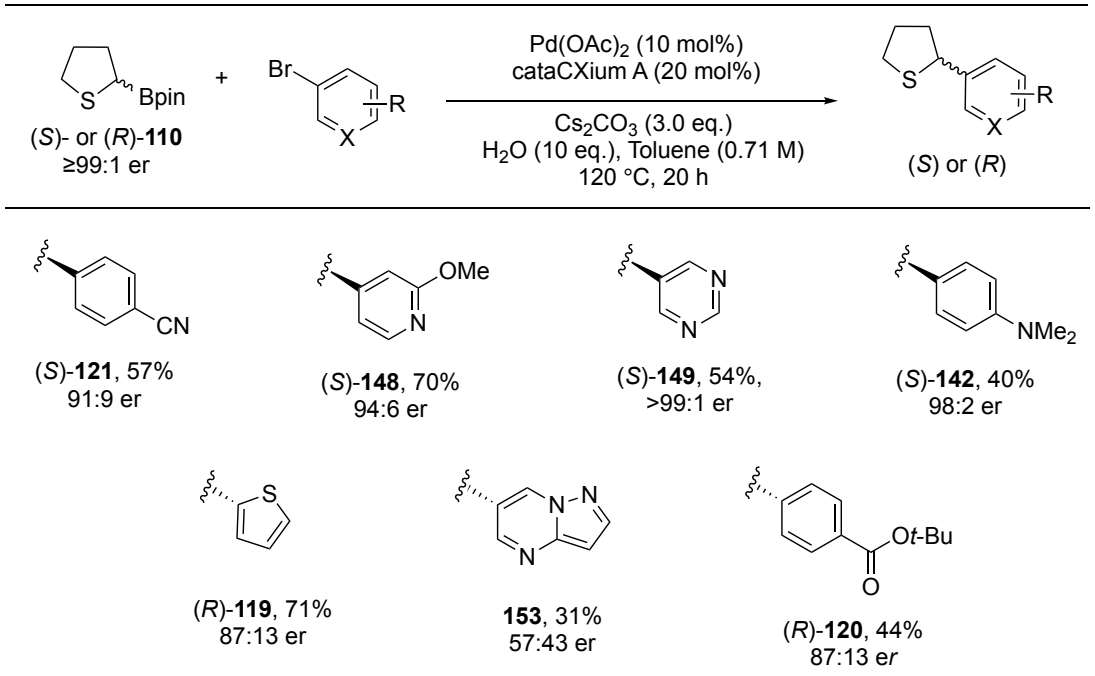
Scheme 2.36

With the electron donating/withdrawing capacity of the aryl bromide examined, attention was directed towards other properties of the aryl bromide. Cross-coupling of 2-Bpin tetrahydrothiophene (*S*)-**110** and 4-bromo-2-methoxypyridine gave (*S*)-**148** in 94:6 er (see Scheme 2.29). 2-Aryl tetrahydrothiophene (*S*)-**148** contains an electron deficient pyridine ring and an electron-donating 2-methoxy substituent. 4-Bromo-2-methoxypyridine is thus not strongly electron-rich or electron-poor overall, suggesting that electronic factors alone are unlikely to account for the observed stereochemical outcome. A closer look at the 2-aryl tetrahydrothiophenes with the highest levels of stereoretention suggests a correlation with the presence of a Lewis basic heteroatom. The results of seven examples, including two new ones, are collected in Scheme 2.37. Owing to the limited mechanistic understanding of the sp^3-sp^2 SMCC mechanism, the precise role of the heteroatom in influencing the stereochemical outcome remains unclear. As previously discussed, it is uncertain whether the Lewis basic groups on the aryl bromide direct the transmetallation pathway or modulate rates of β-hydride elimination/reductive elimination. However, before investigating whether these two processes could be distinguished, it was first examined whether the Lewis basicity of the aryl bromide played a causative role in the observed stereochemical outcomes.

The first experiment to explore this involved cross-coupling of 2-Bpin tetrahydrothiophene (*S*)-**110** with 5-bromopyrimidine. This resulted in 2-aryl tetrahydrothiophene (*S*)-**149** in 54% yield and >99:1 er. As 5-bromopyrimidine contains two Lewis basic nitrogen atoms, if Lewis basicity played a significant role, some degree of stereoretention would be expected, potentially more than observed in 2-aryl tetrahydrothiophene (*S*)-**148**. However, complete stereoinversion was observed. Whilst this may challenge the hypothesis, it is also plausible that due to the antagonistic electron withdrawing nature of the two nitrogen atoms in the pyrimidine ring, both nitrogen lone pairs are somewhat deactivated potentially modifying their influence on the stereochemical outcome.

To investigate the effect of Lewis basicity independent of the electron withdrawing capability of the system, an aryl bromide which is electron donating but contains a Lewis basic heteroatom was required. The electron donating nature, if aryl bromide electronics was an operable hypothesis, would favour stereoinversion. The Lewis basic groups, if Lewis basicity was an operable hypothesis, would promote some

stereoretention. 4-Bromo-*N*,*N*-dimethylaniline was chosen for this experiment and, following cross-coupling with 2-Bpin tetrahydrothiophene (*S*)-**110**, 2-aryl tetrahydrothiophene (*S*)-**142** was obtained in 40% yield and 98:2 er. With no amount of stereoretention observed, this could point towards the argument of aryl bromide electronics. However, it is more likely that the lone pair of the nitrogen is too delocalised into the aromatic ring system, preventing it from interfering with the SMCC cycle. Moreover, as discussed above, thiophene is not considered an electron deficient ring system but 2-aryl tetrahydrothiophene (*R*)-**119** was obtained in 87:13 er. This considerable amount of retention observed could be explained by the favourable interaction commonly observed between sulfur and palladium. Similarly, the surprising degree of stereoretention observed in 2-aryl tetrahydrothiophene **120**, which did not follow the trend of electronegativity may be explained by a cumulative effect between aryl bromide electronics and its Lewis basicity.

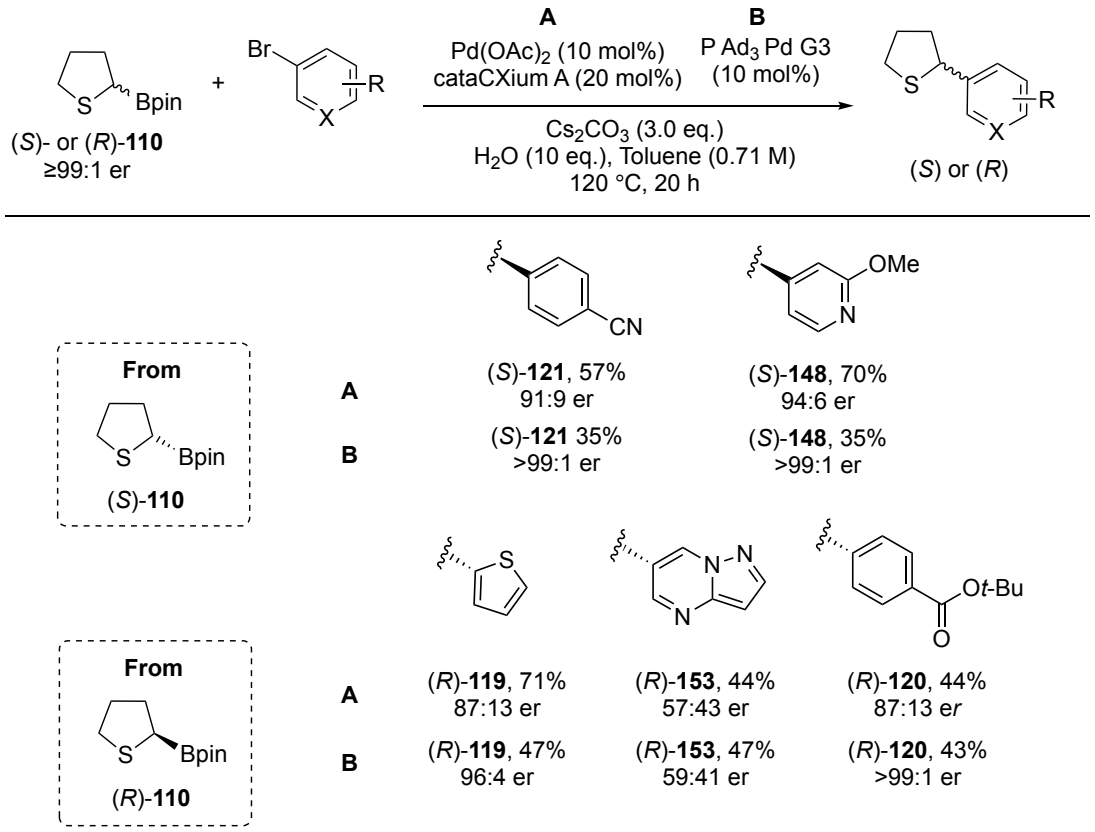


Scheme 2.37

Ultimately, after investigating the two most likely aryl bromide properties to affect the stereochemical outcome, no clear trends emerged. The heavily affected stereochemical outcome of 2-aryl tetrahydrothiophene **153** (57:43 er) remains unexplained by either of the hypotheses discussed above. As shown in Section 1.5 (see Table 1.3), Biscoe, Sigman *et al*. observed a similar level of stereoerosion for aryl *sec*-butyl **89** with

cataCXium A (52:48 er). This suggests that cataCXium A is a ligand which does not have a strong propensity to favour either of the two transmetallation pathways. Therefore, although cyclic systems are much more complex than their acyclic analogues, it may be possible to use the work of Biscoe, Sigman and co-workers to exploit ligand electronics in controlling the stereochemical outcome of the 2-Bpin tetrahydrothiophene **110** cross-coupling. The optimised ligands developed by Biscoe and Sigman were shown in Figure 1.2. The sterically bulky electron-rich triadamantyl phosphine (PAd_3) favoured inversion, whilst the electron deficient bespoke XPhos and SPhos analogues favoured retention.

As described in the chemical space exploration, reaction of 2-Bpin tetrahydrothiophene **110** with bromobenzene using PAd_3 Pd G3, maintaining all other parameters, gave 2-phenyl tetrahydrothiophene **116** in 67% yield (see Table 2.1, entry 7). Given the success of this racemic cross-coupling, SMCC reactions of 2-Bpin tetrahydrothiophene (*S*)- and (*R*)-**110** were carried out using $P(Ad)_3$ as the ligand together with aryl bromides whose cross-coupled products showed some degree of stereoretention. The intention was that the stereoretention pathway should be suppressed, in line with Biscoe and Sigman's observations, The results with five aryl bromides are shown in Scheme 2.38. Conditions A denote standard $Pd(OAc)_2$/cataCXium A conditions and conditions B use PAd_3 Pd G3. No significant change in er was observed when 2-aryl tetrahydrothiophene **153** was cross-coupled using PAd_3 Pd G3. Although this was disappointing, it highlights the rich complexity observed in the system. However, all remaining cross-coupled products were formed with an increase in stereoinversion under conditions B compared to the analogous reactions with conditions A. Under conditions B, 2-aryl tetrahydrothiophenes (*S*)-**121**, (*S*)-**148** and (*R*)-**120** were obtained with complete stereoinversion and 2-aryl tetrahydrothiophene (*R*)-**119** was obtained in 96:4 er, a considerable improvement over the 87:13 er with conditions A. In the case of the formation of 2-aryl tetrahydrothiophene **153**, the aryl bromide possesses an effect, whether it is Lewis basic heteroatom interference or something unconsidered, that exerts a greater impact than ligand electronics.

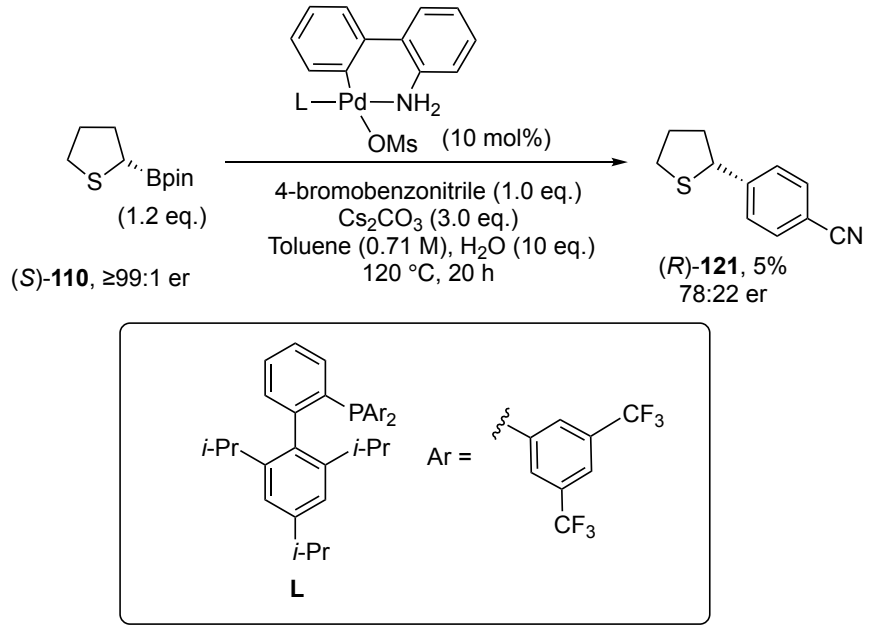


Scheme 2.38

We have established that there are a multitude of factors which affect the stereochemical outcome of SMCC reactions with 2-Bpin tetrahydrothiophene **110**. We have also found that there is no single factor which determines the stereochemical outcome and it may include a cumulative effect with factors we have not yet considered. However, we have, in the majority of cases, presented an approach to obtain high levels of stereoinversion. Whilst these datapoints do not allow a definitive conclusion regarding whether the improvement arises from enhanced stereoinvertive transmetallation or reduced β-hydride elimination with the bulkier ligand, the strategy nevertheless provides an elegant solution to the initially observed problem. Despite generally lower yields compared to reactions using cataCXium A, the approach demonstrates clear potential. Moreover, if a specific 2-aryl tetrahydrothiophene is desired, it is highly likely that optimising conditions for the specific aryl bromide with $P(Ad)_3$ Pd G3 could lead to improved yield.

Finally, it was hypothesised that SMCC reactions with 2-Bpin tetrahydrothiophene **110** could proceed *via* a stereoretentive pathway if the catalytic system was migrated

to Biscoe and Sigman's optimised ligands for stereoretention. For this, the the *bis*-CF_3PhXPhos derivative was chosen. Fortunately, the Buchwald third generation precatalyst of this ligand, *bis*-CF_3PhXPhos Pd G3, was available to us because Lucy Tomczyk from the O'Brien group had prepared a batch. The SMCC of 2-Bpin tetrahydrothiophene (*S*)-**110** with 4-bromobenzonitrile using *bis*-CF_3PhXPhos Pd G3 gave 2-aryl tetrahydrothiophene (*R*)-**121** in 5% yield and 78:22 er (Scheme 2.39). The yield and enantiomeric ratio, while not ideal, show promising potential as the major pathway is indeed the hoped-for stereoretention. This is the first example of using a SMCC to modulate between the two stereodivergent pathways of transmetallation for a heterocyclic boronate with an aryl bromide. This result also suggests that rather than reducing β-hydride elimination, modification of ligand electronics is the operable effect differentiating one transmetallation pathway over the other.



Scheme 2.39

Although the mechanism of the sp^3-sp^2 SMCC, whether *via* a mixture of inversion/retention or modulation of β-hydride elimination and reductive elimination, remains uncertain, observations from the dataset provide key insight into how the nature of the ligand and aryl bromide shape the stereochemical outcome of the SMCC of 2-Bpin tetrahydrothiophene **110**. Of the three factors discussed above – namely aryl bromide inductive withdrawal, aryl bromide Lewis basicity and ligand electronics – aryl bromide inductive withdrawal may at most play only a small role in the

stereochemical outcome of the cross-coupling. Whilst Biscoe, Sigman *et al.* could draw strong correlations between aryl chloride inductive withdrawal and stereochemical outcome. For 2-Bpin tetrahydrothiophene **110** too many inconsistencies were identified in this trend (see Scheme 2.36). This highlights the challenge presented by heterocyclic moieties when investigating sp^3-sp^2 SMCCs. As highlighted by Scheme 2.37, there is substantial evidence that Lewis basic heteroatom interference is a higher impact factor than inductive withdrawal. In most cases, it was shown that this can be outcompeted by increasing ligand electronics. However, our lack of complete understanding was highlighted by the surprisingly low er observed in the formation of 2-aryl tetrahydrothiophene **153** under either of the catalytic systems (see Scheme 2.38). Finally, the preliminary result using bis-CF_3PhXPhos with 2-Bpin tetrahydrothiophene (*S*)-**110** suggests a promising direction for future development.

2.8 Conclusions and Future Work

In summary, the racemic scope of SMCC reactions with 2-Bpin tetrahydrothiophene **110** was rapidly expanded and it displayed impressive robustness and tolerance in 28 successful examples. The methodology translated well to a round-bottom flask with the larger-scale SMCC reaction outperforming the small-scale reaction yield by 15%.

The stereoinvertive transmetallation was confirmed and synthesis of the enantioenriched 2-Bpin tetrahydrothiophenes (*R*)- and (*S*)-**110** was optimised with increased yields observed for each step. The enantioenriched scope was substantially expanded and an aryl halide dependent effect on the stereochemical outcome of the cross-coupled product was revealed. Although several hypotheses were investigated for this, no simple explanation was found. Fortunately, by employing PAd_3 Pd G3, the aryl bromide cross-couplings which displayed a reasonable degree of stereoretention could, in the majority of examples, be driven to complete stereoinversion. It is still unknown precisely how the steric or electronic parameters of PAd_3 Pd G3 influence the stereochemical outcome. It could be due to changing the rate of β-hydride elimination/reductive elimination, a change in the amount of retention/inversion during transmetallation or a mixture of the two.

Regarding future direction of the project, there are several areas where additional experimentation could provide significant understanding and developments. Due to issues with its synthesis, tetrahydrothiophene boronic acid was not evaluated in the SMCC. As both 2-BF_3K and 2-BMIDA tetrahydrothiophenes **138** and **139** were also evaluated in the cross-coupling, the SMCC of the respective boronic acid would complete the dataset.

To further explore role of the aryl bromide in the stereochemical outcome of the SMCC, a series of aryl bromides is proposed for investigation, and their respective cross-coupled products are shown in Figure 2.5. First, reaction of *tert*-butyl 2-(4-bromophenyl)acetate would evaluate aryl halide Lewis basicity independent of aryl halide inductive withdrawal. Use of 2-bromopyrrole and 2-bromofuran are also proposed. These ring systems are not electron deficient and contain Lewis basic *N* and *O* atoms. Therefore, if Lewis basicity is a causative parameter, some stereoretention would be expected. Following this, the enantioenriched SMCC should be explored

with 4-bromo *N*-trityl pyrazole. The pyrazole moiety is common to aryl tetrahydrothiophene **153**. Thus, analysis of the er from reaction with 4-bromo *N*-trityl pyrazole could inform on the unexpected observations in the observed er of aryl tetrahydrothiophene **153** with cataCXium A as ligand (57:43 er, see Scheme 2.29). Finally, ligand sterics should be evaluated to see if increased steric bulk around the carbon-bromide bond affects the stereochemical outcome and 2-bromo-1,3-dimethylbenzene is proposed to explore this.

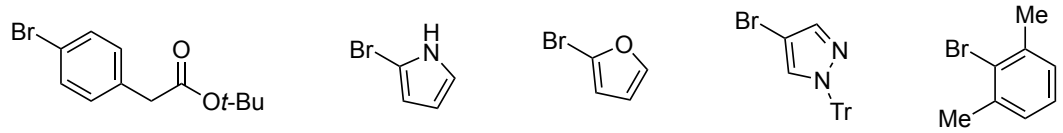


Figure 2.5: Proposed aryl bromides for SMCC with enantioenriched 2-Bpin tetrahydrothiophene

Ohmura, Awano and Suginome had reported that the stereochemical outcome of the SMCC reaction with enantioenriched α-amino-benzylic Bpins could be controlled by addition of either phenol or Zr(O*i*-Pr)$_4$•*i*-PrOH (see Scheme 1.22).[42] Exploration of these additives in the 2-Bpin tetrahydrothiophene **110** SMCC could offer supportive evidence on the role of the aryl bromide in influencing stereochemical outcome.

The SMCC of enantioenriched 2-Bpin tetrahydrothiophene (*R*)- or (*S*)-**110** with 6-bromopyrazolo[1,5-α]pyrimidine should be investigated further. A series of identical reactions should be carried out, quenching at several time points up to 60 min, measuring the stereochemical outcome. This could provide useful information on the origin of the observed stereoretention in the cross-coupled product.

To explore the promising initial result with *bis*-CF_3PhXPhos (see Scheme 2.39), optimisation of the cross-coupling yield under *bis*-CF_3PhXPhos catalytic conditions followed by further ligand design could result in increased stereoretention. Similarly, P(2-Bn-C_6H_4)$_3$ should be evaluated in the enantioenriched SMCC. Burke *et al.*[41] proposed this ligand favoured stereoretention through sterically disfavouring the axial pathway required for the stereoinvertive pathway (see Scheme 1.25). Thus, this represents another avenue to explore for controlling the stereochemical pathway of transmetallation for 2-Bpin tetrahydrothiophene **110**

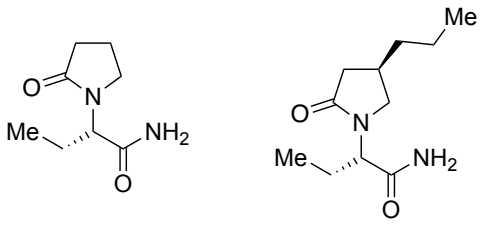
Ultimately, further investigation into the origin and cause of the aryl bromide effect on the SMCC of 2-Bpin tetrahydrothiophene (*R*)- or (*S*)-**110** could represent a significant breakthrough in sp^3-sp^2 SMCCs. It is hoped that further investigation into the mechanistic aspects of these observations, could unlock the ability to deliver either enantiomer of cross-coupled product. These understandings could then be applied to other heterocyclic boronate systems resulting in a general strategy for enantioenriched cross-couplings of a series of heterocyclic alkyl-borons.

Chapter: 3 Suzuki-Miyaura Cross-Couplings of 4-Boryl *N*-Substituted Pyrrolidones

3.1 Introduction

3.1.1 Pyrrolidones in Drug Discovery and Agrochemistry

Pyrrolidones are valuable scaffolds in drug discovery primarily due to their structural similarity to the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and their relevance in the design of cognition-enhancing (nootropic) agents.[87,88] Pyrrolidone-based drugs, such as racetams and some anticonvulsants, exert their effects primarily through modulation of neurotransmission. Racetams like piracetam, aniracetam, and oxiracetam enhance cognitive function through influencing glutamatergic and cholinergic systems, often benefiting synaptic plasticity and memory.[89] In contrast, antiepileptic agents such as Levetiracetam and Brivaracetam (Figure 3.1) target the SV2A protein on synaptic vesicles, regulating neurotransmitter release in the treatment of epilepsy.[90] Although their exact mechanisms vary, most pyrrolidone-based drugs act by subtly enhancing or modulating neurotransmitter signalling, rather than directly mimicking classical neurotransmitters such as GABA. Of the many investigated pyrrolidone drugs, only two are FDA approved - Levetiracetam (brand name Keppra) and Brivaracetam (brand name Briviact).[91]

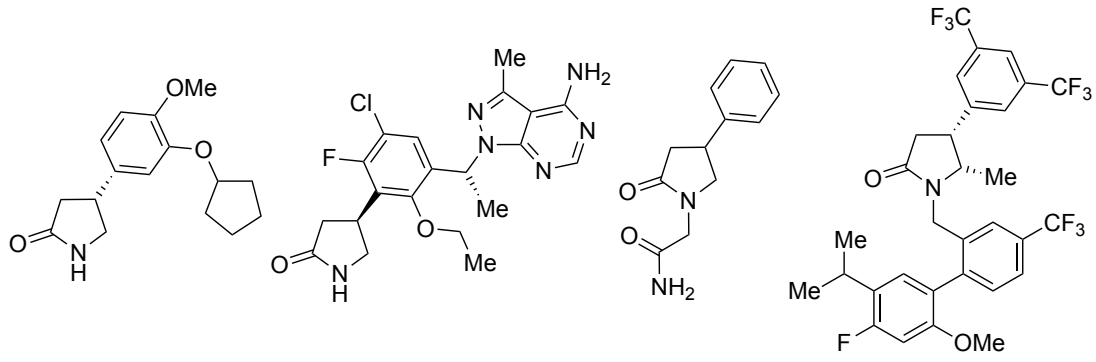


Levetiracetam **Brivaracetam**

Figure 3.1: Structures of Levetiracetam and Brivaracetam

Among medicinally relevant lactams, 4-aryl pyrrolidones are of particular interest as drug candidates. Although none have yet achieved regulatory approval, several 4-aryl pyrrolidones (Figure 3.2) have progressed through, or been discontinued from, various stages of clinical evaluation. For example, (*R*)-Rolipram, a selective phosphodiesterase-4 inhibitor, developed as an antidepressant, was eventually discontinued in phase II clinical trials due to a narrow therapeutic window with

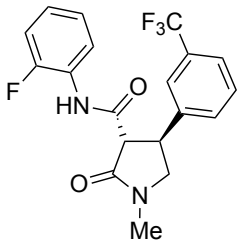
significant gastrointestinal side effects.[92] (*R*)-Rolipram has also gained interest in the treatment of various neurodegenerative diseases, demonstrating the privileged nature of the 4-aryl pyrrolidone scaffold, with its potential to treat high impact diseases such as Alzheimer's, where drug development has proven especially difficult.[93] Parsaclisib is a novel oral inhibitor of phosphatidylinositol 3-kinase delta (PI3Kδ) which has been in several phase II clinical trials for non-Hodgkin Lymphomas and a phase III study for autoimmune haemolytic anemia.[94] Fonturacetam is a Russian approved nootropic drug that operates in a similar mode of action to Piracetam.[95] Anacetrapib is a cholesteryl ester transfer protein inhibitor developed by Merck as a potential treatment for cardiovascular disease. Although Anacetrapib displayed a modest benefit during phase III clinical trials, regulatory approval was not sought by Merck.[96]



(*R*)-Rolipram **Parsaclisib** **Fonturacetam** **Anacetrapib**

Figure 3.2: Structures of medicinally relevant 4-aryl pyrrolidones

4-aryl pyrrolidones have also gained significant traction in agrochemical discovery. For example, Tetflupyrolimet (brand name Dodhylex^{TM}) (Figure 3.3) is the first herbicide with a new mode of action introduced in over 30 years.[97] The aryl pyrrolidone anilide motif represents a brand-new class of herbicides that inhibit dihydroorotate dehydrogenase (DHODH), responsible for the de novo pyrimidine biosynthetic pathway. The development of Tetflupyrolimet started with a high-volume screening approach which identified a 4-phenyl pyrrolidone as the lead compound. To progress the lead compound, a range of enantioenriched 4-aryl 3-anilide pyrrolidone analogues were synthesised, from which Tetflupyrolimet, with (*S*,*S*) configuration, was identified.



Tetflupyrolimet

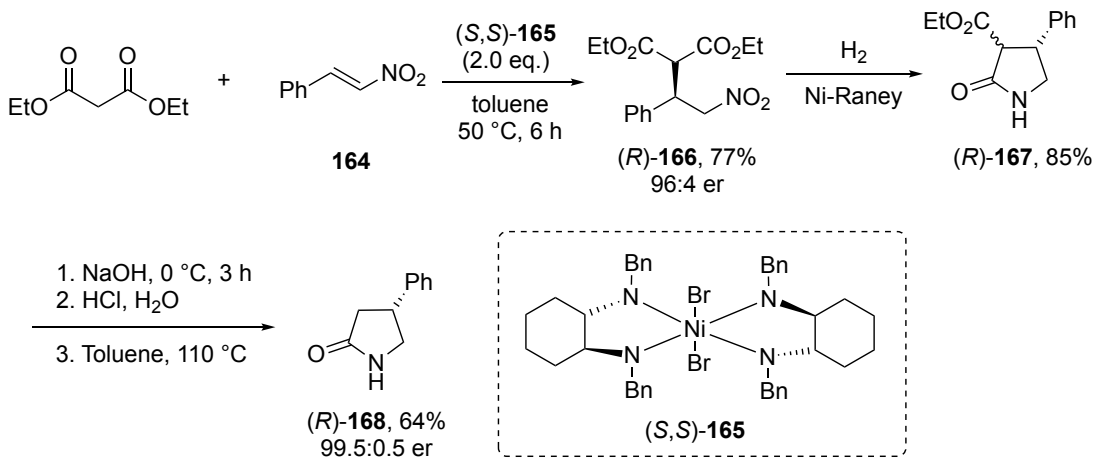
Figure 3.3: Structure of Tetflupyrolimet

3.1.2 Selected Overview of Synthetic Routes to 4-Aryl Pyrrolidones

As outlined in the previous section, 4-aryl pyrrolidones are increasingly recognised as valuable motifs for use in medicinal chemistry. However, synthetic strategies to access these compounds, especially in an enantioenriched manner, are relatively underdeveloped. Most reported methods offer only a limited aryl scope, predominantly yielding phenyl-substituted products. The lack of a general, versatile approach capable of rapidly delivering structurally diverse analogues remains a key obstacle in exploiting this scaffold for future therapeutic development. This selected overview mainly focuses on routes to enantioenriched 4-aryl pyrrolidones.

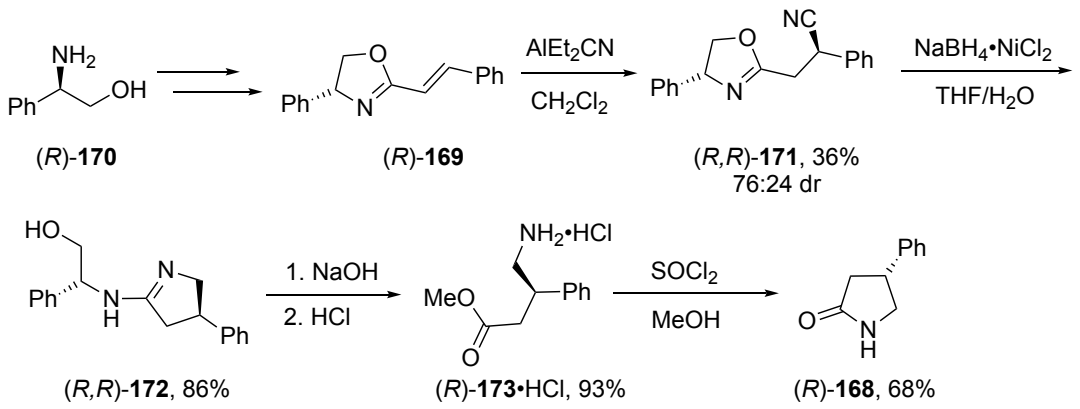
Classical syntheses of enantioenriched 4-aryl pyrrolidones typically involve installation of the aryl group to an acyclic precursor, followed by cyclisation to form the pyrrolidone. For example, this approach was reported by Reznikov *et al*., where a nickel catalysed asymmetric conjugate addition was used to generate the enantioenriched acyclic precursor. The reaction proceeded with conjugate addition of malonate to nitrostyrene **164** using two equivalents of the chiral nickel catalyst (*S*,*S*)-**165**. The conjugate addition product, phenyl malonate (*R*)-**166**, was obtained in 77% yield and 96:4 er (Scheme 3.1).[98] Subsequent reduction of phenyl malonate (*R*)-**166** using hydrogen with Raney nickel at high pressure reduced the nitro group to an amine which induced cyclisation to pyrrolidone ester (*R*)-**167** in 85% yield. Base mediated hydrolysis of (*R*)-**167** followed by decarboxylation of the intermediate carboxylic acid gave 4-phenyl *N*-H pyrrolidone (*R*)-**168** (99.5:0.5 er) in 64% yield. An advantage of this methodology is the synthesis of the unprotected pyrrolidone. This allows downstream *N*-functionalisation to proceed without any additional synthetic steps. However, as with many of these acyclic approaches, the aryl group is installed in the

first step. This increases the synthetic workload that would be required to generate a series of 4-aryl pyrrolidone analogues.



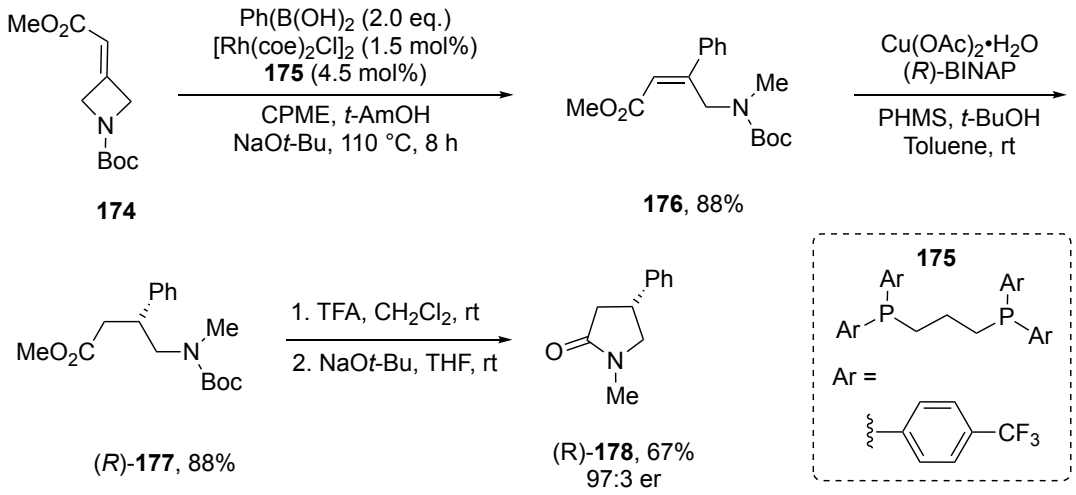
Scheme 3.1

Alternatively, Langlois *et al*. synthesised 4-phenyl *N*-H pyrrolidone (*R*)-**168** starting from α,β-unsaturated oxazoline **169** derived from phenylglycinol (*R*)-**170** (Scheme 3.2). Hydrocyanation of α,β-unsaturated oxazoline (*R*)-**169** with $AlEt_2CN$ gave nitrile oxazoline (*R*,*R*)-**171** in 36% yield and 76:24 dr. Subsequent chemoselective reduction of the nitrile functional group and cyclisation onto the oxazoline gave imino-aminal (*R*,*R*)-**172** in 86% yield. Based mediated hydrolysis of imino-aminal (*R*,*R*)-**172** with NaOH followed by addition of HCl gave amine HCl salt (*R*)-**173**•HCl in 93% yield. Finally, acidic cyclisation (HCl generated from $SOCl_2$ and methanol) gave 4-phenyl *N*-H pyrrolidone (*R*)-**168** in 68% yield. The final enantiomeric ratio was not given, although it was commented that analysis of the optical rotation indicated the absence of any epimerisation during the synthesis. This methodology takes advantage of the innate stereochemistry of a chiral pool reagent which removes the requirement for expensive or synthetically complex chiral catalysts. However, by this very feature, the synthetic approach does not lend itself well to the synthesis of a range of 4-aryl pyrrolidones



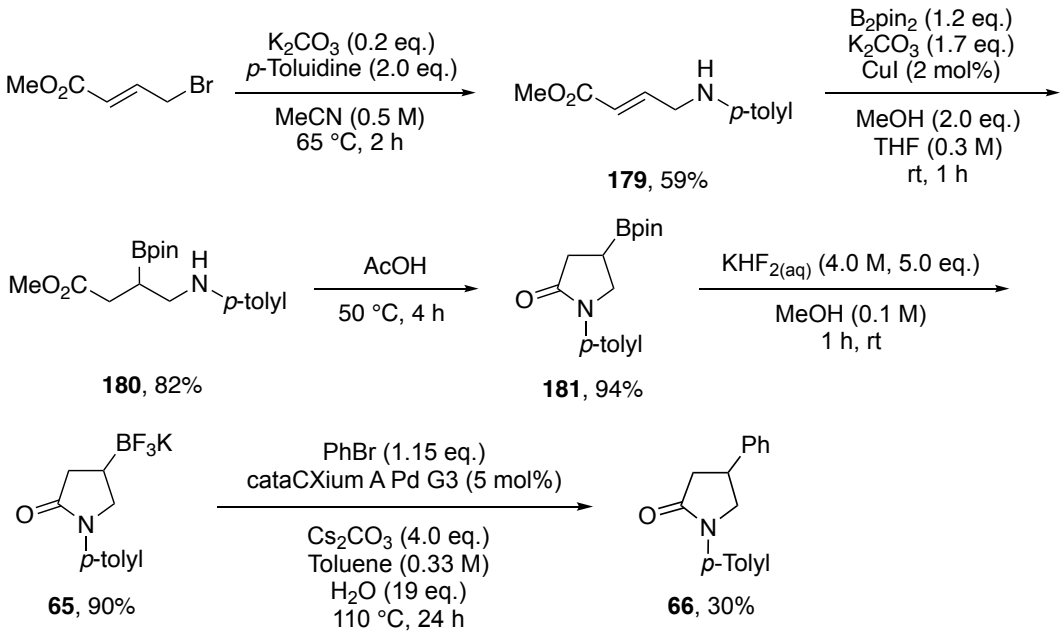
Scheme 3.2

Another common method to synthesise enantioenriched 4-aryl pyrrolidones is *via* asymmetric reduction. An example of this approach was demonstrated by Ouyang and Xie *et al*. (Scheme 3.3).[99] Rhodium catalysed addition of aryl boronic acids to 2-(azetidine-3-ylidene)acetate **174** led to conjugate addition and subsequent β-C bond cleavage of the azetidine to give an amine containing α,β unsaturated ester. This was reduced asymmetrically to furnish, after cyclisation, the enantioenriched 4-aryl pyrrolidone. The conjugate addition/β-C cleavage was carried out using excess $PhB(OH)_2$, $[Rh(coe)_2Cl]_2$ (1.5 mol%), ligand **175** (4.5 mol%) and NaO*t*-Bu in a CPME/*t*-AmOH solvent system at 110 °C for 8 h. Under these conditions, α,β-unsaturated aryl ester **176** was obtained in 88% yield. The asymmetric reduction was carried out using $Cu(OAc)_2•H_2O$, (*R*)-BINAP and PMHS in *t*-BuOH/toluene at rt and Boc amide (*R*)-**177** was obtained in 88% yield. Finally, removal of the Boc group with TFA and cyclisation with NaO*t*-Bu gave 4-phenyl *N*-methyl pyrrolidone (*R*)-**178** in 67% yield and 97:3 er. The conjugate addition methodology offers mild reaction conditions and a substantial scope of aromatic groups. However, these appear limited to carbocyclic aryl boronic acids, with very few examples of heteroaryl boronic acids demonstrated. It is worth noting that 4-aryl pyrrolidones can also be obtained through palladium catalysed carbonylative cyclisation, although, in contrast to the work of Ouyang and Xie *et al*., no subsequent asymmetric reduction was reported.[100]



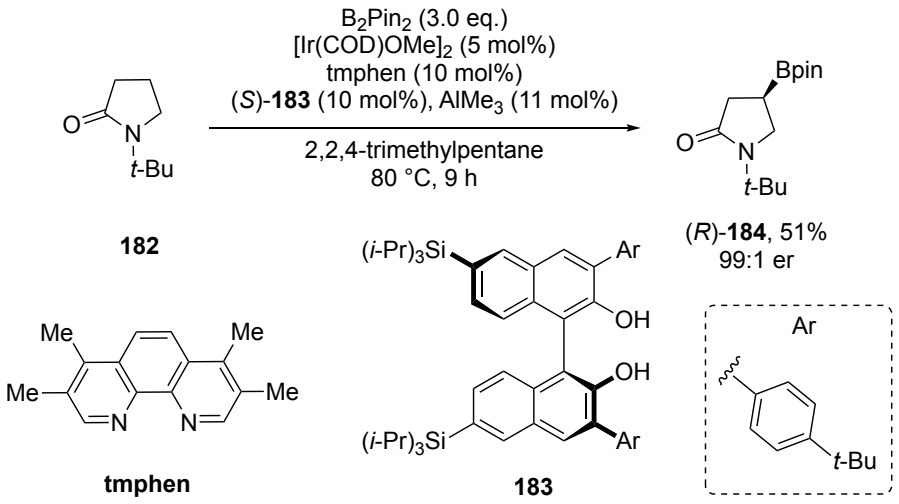
Scheme 3.3

In 2021, Partridge *et al*. demonstrated the racemic synthesis of a range of *N*-substituted 4-Bpin pyrrolidones. The Bpin was installed *via* addition of bis(pinacolato)diboron (B_2pin_2) to an acyclic enoate precursor. Under acidic conditions this could be cyclised to give the 4-Bpin pyrrolidone. To demonstrate the synthetic application of their 4-Bpin pyrrolidones, a single example of a sp^3-sp^2 SMCC of 4-BF_3K *N*-*p*-tolyl pyrrolidone **65** to give 4-phenyl *N*-*p*-tolyl pyrrolidone **66** was demonstrated. The forward synthesis is detailed in Scheme 3.4. Methyl 4-bromocrotonate was reacted with *p*-toluidine and K_2CO_3 in MeCN at 65 °C for 2 h to give amino acrylate **179** in 59% yield. Next, copper-catalyed conjugate addition of Bpin to amino acrylate **179** was carried out using B_2Pin_2, 2 mol% CuI, K_2CO_3 and MeOH in THF at rt for 1 h. Under these conditions the desired Bpin amino ester **180** was isolated in 82% yield. Acidic cyclisation of Bpin amino ester **180** in AcOH at 50 °C for 4 h gave 4-Bpin *N*-*p*-tolyl pyrrolidone **181** in 90% yield. Reaction of 4-Bpin *N*-*p*-tolyl pyrrolidone **181** with $KHF_{2(aq)}$ in MeOH gave 4-BF_3K *N*-*p*-tolyl pyrrolidone **65** in 90% yield. The SMCC conditions used an excess of bromobenzene, cataCXium A Pd G3 (5 mol%) and Cs_2CO_3 in toluene/water at 110 °C for 24 h. Reaction of BF_3K salt **65** under these conditions gave 4-phenyl *N*-*p*-tolyl pyrrolidone **66** in 30%. Given little to no optimisation had been carried out on these conditions, the 30% yield with a heterocyclic alkyl-boron was a significant feat. A synthetic route to enantioenriched (*S*)-4-Bpin *N*-phenyl pyrrolidone was reported, although no subsequent transformations of this material were described.



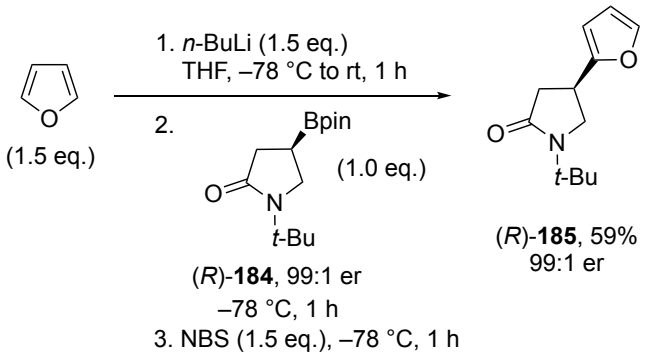
Scheme 3.4

Approaches to arylate directly from the pyrrolidone *via* C-H activation are less prevalent. For example, overall asymmetric arylation can be achieved in two steps *via* corresponding 4-boryl pyrrolidone. For the first step, Sakaki and Nakao *et al*. demonstrated a versatile iridium/aluminium cooperative strategy for the β-(Csp^3)-H borylation of pyrrolidines and pyrrolidones.[101] Following their established procedure, β-borylation of *N*-*t*-butyl pyrrolidone **182** was achieved using B_2pin_2, $[Ir(cod)OMe]_2$, tmphen, $AlMe_3$ and BINOL (*S*)-**183**. Heating the reagents in 2,2,4-trimethylpenate at 80 °C for 9 hours gave 4-Bpin *N*-*t*-butyl pyrrolidone (*R*)-**184** in 51% yield and 99:1 er (Scheme 3.5). The Lewis acidic aluminium cocatalyst directs the β-C-H borylation by the tris-boryl Ir^{III} species which undergoes oxidative addition with the C-H bond. The enantioselectivity comes *via* the *in situ* generated Lewis acidic-aluminium-based cocatalyst generated from $AlMe_3$ and BINOL (*S*)-**183**.



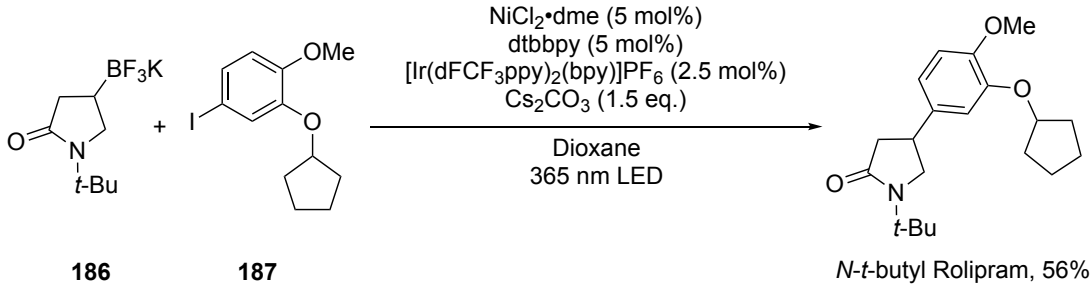
Scheme 3.5

Only one example of arylation of 4-Bpin *N*-*t*-butyl pyrrolidone (*R*)-**184** was demonstrated. This incorporated a furan group following a procedure from Aggarwal *et al.*[102] The reaction proceeded by lithiation of furan with *n*-BuLi in THF at –78 °C. Next, 4-Bpin *N*-*t*-butyl pyrrolidone (*R*)-**184** was added at –78 °C. Subsequent addition of excess NBS at –78 °C h gave 4-aryl *N*-*t*-butyl pyrrolidone (*R*)-**185** in 59% yield and 99:1 er (Scheme 3.6). The addition of NBS triggers a 1,2 migration of the C-B bond in the intermediate boronate (generated by addition of lithiated furan to the Bpin group) which generates 4-aryl *N*-*t*-butyl pyrrolidone (*R*)-**185** *via* a completely stereospecific mechanism. Although this methodology generates product in good yield and high er, the main limitation is that the methodology requires electron rich heteroaromatics that can be readily lithiated, which reduces its overall utility.



Scheme 3.6

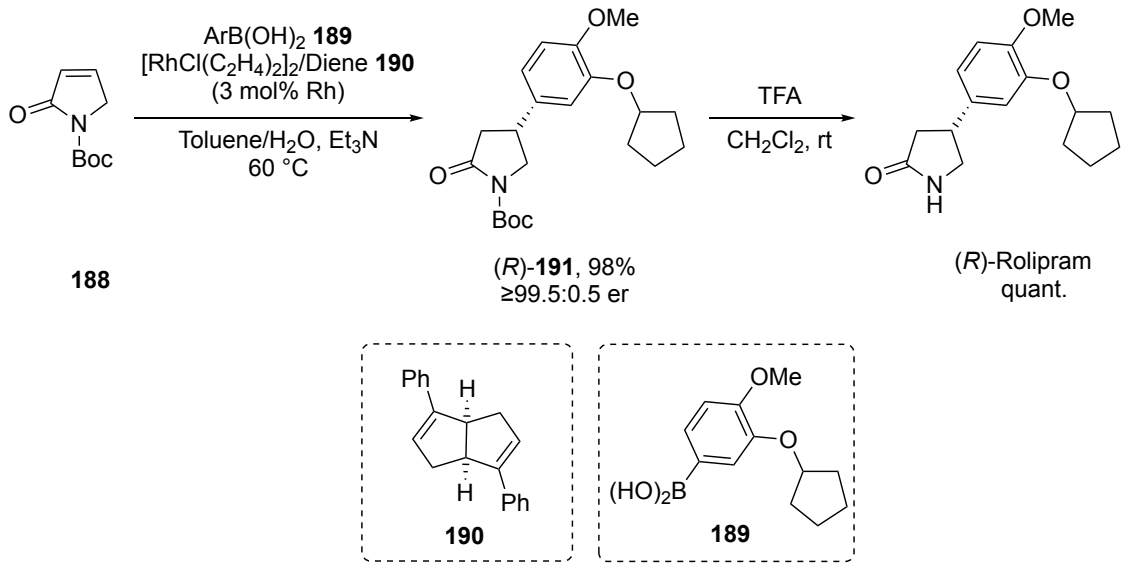
It is notable that Sakaki, Nakao *et al*. also reported an example of a nickel/iridium catalysed photoredox cross-coupling of 4-BF_3K *N*-*t*-butyl pyrrolidone **186** with various aryl bromides. Following a procedure from Molander *et al.,*[103] *N*-*t*-butyl BF_3K **186**, aryl iodide **187**, $NiCl_2$•dme, dtbbpy, Ir photocatalyst and Cs_2CO_3 were reacted in dioxane in the presence of two 365 nm LED lamps at rt for 24 hours. *N*-*t*-Butyl Rolipram was obtained in 56% yield (Scheme 3.7). The reaction proceeds *via* a planar radical and thus generating enantioenriched products using this approach would be challenging. However, it represents a promising methodology for the generation of libraries of racemic 4-aryl pyrrolidones. Interestingly, despite the fact that Sakaki, Nakao *et al*. had access to both *N*-*t*-butyl Bpin (*R*)-**184** and BF_3K **186**, no attempt at a sp^3-sp^2 SMCC was reported.



Scheme 3.7

Finally, a powerful methodology for the direct, enantioselective 4-arylation of α,β-unsaturated pyrrolidones was established by Feng and Lin *et al*.[104] The procedure was originally reported by Hayashi *et al*. for the rhodium catalysed asymmetric 1,4-addition of aryl boronic acids to the six-membered ring dihydropyridones.[105] Feng and Lin *et al*., adapted the methodology to generate a series of enantioenriched 4-aryl pyrrolidones in high yield and er. In particular, the asymmetric synthesis of (*R*)-Rolipram from α,β-unsaturated pyrrolidone **188** was described (Scheme 3.8). A conjugation addition reaction of $ArB(OH)_2$ **189** with α,β-unsaturated pyrrolidone **188** using $[RhCl(C_2H_4)]_2$, diene **190** and Et_3N in toluene/water at 60 °C gave *N*-Boc 4-aryl pyrrolidone (*R*)-**191** in 98% yield and ≥99.5:0.5 er with only 3 mol% catalytic loading of rhodium. Following subsequent Boc group removal of (*R*)-**191** with TFA, (*R*)-Rolipram was obtained in a quantitative yield. In addition, a scope with 12 different aryl boronic acids gave *N*-Boc 4-aryl pyrrolidones in yields of 56-99% and ers of ≥99:1. The ability to synthesise a range of analogues makes this approach compatible

with the requirements of modern medicinal chemistry. However, the analogues synthesised did not include any heteroaryl groups nor did they possess much molecular complexity. Moreover, although the loading is low, the high cost associated with use of rhodium makes it a less desirable catalyst.



Scheme 3.8

A range of the most relevant synthetic methods to access enantioenriched 4-aryl pyrrolidones has been presented. Although there are advantages and disadvantages associated with each piece of methodology, it is clear that none are able to provide ready access to a wide range of 4-aryl pyrrolidones which would be very useful for modern medicinal chemistry. Given the potential of this moiety in drug discovery, the development of new methods to synthesise 4-aryl pyrrolidones is of high importance to the field.

3.2 Proposed Objectives

The overall aim of the work described in this chapter was to investigate the synthesis of 4-aryl pyrrolidones *via* the Suzuki-Miyaura cross-coupling of 4-boryl *N*-R pyrrolidones. As outlined in the previous section, although there are several methods to access enantioenriched 4-aryl pyrrolidones, there are no reported methods able to efficiently synthesise a broad range of structurally diverse enantioenriched 4-aryl pyrrolidones. Therefore, we propose the sp^3-sp^2 SMCC approach as a synthetically simple, reliable and robust solution to this problem. The desire was to deepen our understanding of 4-boryl pyrrolidones in the SMCC reaction and to ultimately provide medicinal chemists with a new tool to access enantioenriched 4-aryl pyrrolidones. To achieve this, there were four objectives.

First, we wanted to develop the synthesis of racemic 4-boryl pyrrolidones with different *N*-substituents and a variety of different boron groups (Bpin, BF_3K, BMIDA, $B(OH)_2$). Synthesis would follow the precedent set by Partridge *et al*.,[59] focussing on *N*-substituents which could be readily removed. The series of 4-boryl *N*-R pyrrolidones would then be evaluated under the SMCC conditions established by Partridge *et al*. and the most promising 4-boryl *N*-R pyrrolidone would be selected.

The second and main objective was to optimise the SMCC with the selected 4-boryl *N*-R pyrrolidone and to develop the scope of the SMCC to explore the functional group tolerance and sensitivity in the cross-coupling.

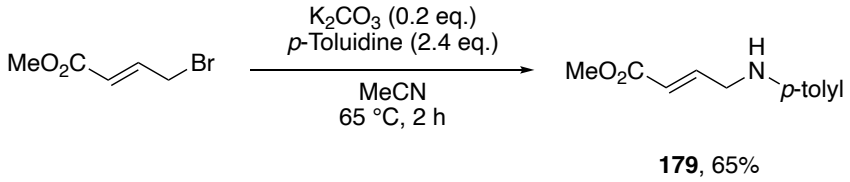
Third, the stereochemical outcome of the SMCC would be explored using an enantioenriched 4-boryl *N*-R pyrrolidone and several aryl halides to assess whether the reaction proceeds *via* stereoretention or stereoinversion.

Fourth, we desired to apply our methodology to a target synthesis and for this the agrochemical Tetflupyrolimet was selected. Successful application to a significant and real-world target would demonstrate the suitability of this methodology to future drug and agrochemical discovery projects.

3.3 Initial Investigations into the Suzuki-Miyaura Cross-Coupling of 4-Boryl Pyrrolidones

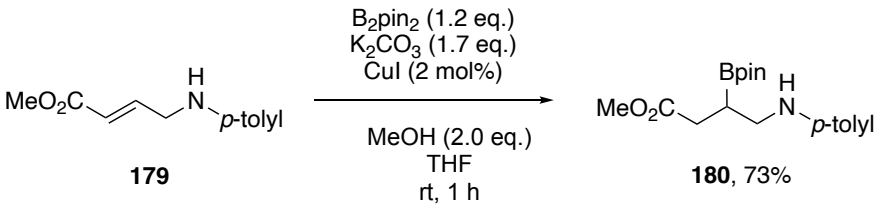
3.3.1 Synthesis and Suzuki-Miyaura Cross-Coupling of 4-BF_3K *N*-*p*-Tolyl Pyrrolidone

The starting point in the project was to validate the synthesis and SMCC reaction of 4-BF_3K *N*-*p*-tolyl pyrrolidone **65** reported by Partridge *et al.*[59] (See Scheme 1.16). For this, the synthesis of 4-BF_3K *N*-*p*-tolyl pyrrolidone **65** was required and we followed the route established by Partridge *et al.*[59] Thus, methyl 4-bromocrotonate was reacted with *p*-toluidine and K_2CO_3 in MeCN at 65 °C for 16 h. The literature work-up conditions were adapted to separate the excess *p*-toluidine from product using an acid-base extraction. Unfortunately, amino acrylate **179** and *p*-toluidine could not be separated using this approach and the similarity of their R_F values increased the challenge of the chromatographic separation. Despite this, amino acrylate **179** was isolated in 65% yield after chromatography (Scheme 3.9).



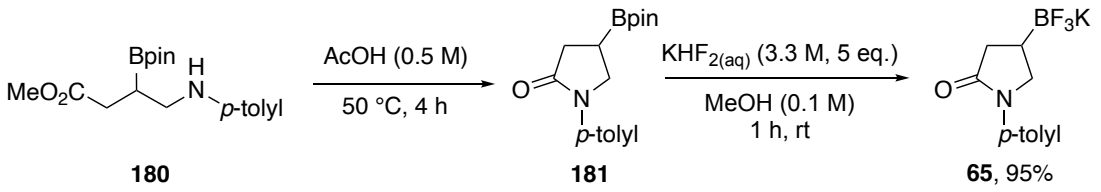
Scheme 3.9

The second step involved copper-catalysed conjugate addition of Bpin to amino acrylate **179**. The reaction was carried out using B_2pin_2, 2 mol% CuI, K_2CO_3 and MeOH in THF at rt for 1 h. It was found that a singular recrystallisation from *n*-hexane was not sufficient to remove remaining B_2pin_2 or a Bpin derivative (as determined by ^{11}B and ^{1}H NMR spectroscopy). Subjecting the material to a second recrystallisation from *n*-hexane gave the desired Bpin amino ester **180** in 73% yield (Scheme 3.10). The MeOH additive plays a key role in the efficiency of this reaction. A rate-limiting metathesis step between B_2Pin_2 and the formed organocopper reagent is bypassed by protonation of the copper enolate by the MeOH. This results in both the desired product and regeneration of the copper catalyst allowing efficient turnover.[106]



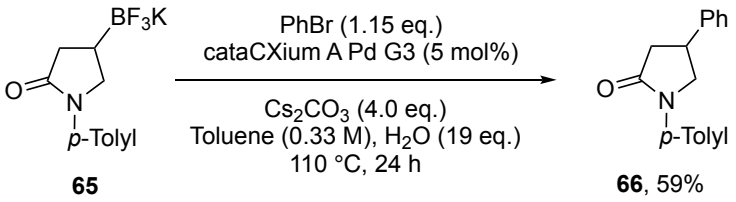
Scheme 3.10

Stirring Bpin amino ester **180** in acetic acid at 50 °C for 4 h achieved cyclisation to 4-Bpin *N*-*p*-tolyl pyrrolidone **181**. This was telescoped through to the next step without further purification since crude 4-Bpin *N*-*p*-tolyl pyrrolidone **181** showed good purity by ^{1}H NMR spectroscopy. Using an adapted procedure from Xu *et al.*,[107] $KHF_{2(aq)}$ and 4-Bpin *N*-*p*-tolyl pyrrolidone **181** were reacted in MeOH at rt for 1 h. To purify the BF_3K salt from the excess KHF_2 and organic impurities, the water and MeOH were first evaporated under reduced pressure. Then, separation of excess KHF_2 was achieved *via* trituration with a minimum volume of hot acetone. The acetone was removed under reduced pressure, and the crude residue was redissolved in Et_2O. Subsequent filtration of the precipitated solid liberated 4-BF_3K *N*-*p*-tolyl pyrrolidone **65** in 95% yield over the two steps (Scheme 3.11). The synthesis proceeded well with high yields achieved throughout the synthetic route, exactly as reported by Partridge *et al.*[59]



Scheme 3.11

With access to 4-BF_3K *N*-*p*-tolyl pyrrolidone **65**, the SMCC reaction reported by Partridge *et al.*,[59] was carried out. Following their protocol, on a 0.3 mmol scale, using 1.0 eq. of 4-BF_3K *N*-*p*-tolyl pyrrolidone **65**, 1.15 eq. bromobenzene, 5 mol% cataCXium A Pd G3 and 4.0 eq. of Cs_2CO_3 in toluene/water (9:1) at 110 °C for 24 h. The reaction was performed in a sealed vial under an atmosphere of N_2. Following work-up and chromatography, 4-phenyl *N*-*p*-tolyl pyrrolidone **66** was obtained in 59% yield (average of three examples: 60%, 60%, 57%) (Scheme 3.12). Pleasingly, our attempts were much higher yielding than that reported by Partridge *et al.* (30%).[59]



Scheme 3.12

The only differences between Partridge's cross-coupling reaction (see Scheme 1.16) and ours were the experimental set-up and the scale (Partridge's reaction was on a 1.0 mmol scale). We hypothesise that certain practical details in the experimental set-up can be significant to achieving reproducible and accurate yields in sp^3-sp^2 SMCC reactions. A full description of the experimental set up can be found in Chapter 5, but a brief description is included here for comparison with the set-up used by Partridge *et al*. In the O'Brien group sp^3-sp^2 SMCC reactions are carried out *via* addition of all solids to a 7 mL vial before purging the atmosphere with N_2 for 15 min. Then, the liquid aryl halide is added followed by degassed toluene and finally degassed water. The vial is then added to a pre-heated hotplate and stirred vigorously to ensure the biphasic solvent system is adequately mixed during reaction. Partridge *et al*. note that the solid components and bromobenzene were first added to a microwave vial, followed by addition of solvents. Argon was then bubbled through the mixture for 15 min. It is quite possible that the changed order of addition, the lack of degassed solvents and lack of preheating are the reasons for the lower yield observed in their SMCC reaction. Overall, our 59% yield of 4-phenyl *N*-*p*-tolyl pyrrolidone **66** was a significant and exciting initial result in the sp^3-sp^2 cross-couplings of 4-boryl pyrrolidones.

3.3.2 Synthesis and Suzuki-Miyaura Cross-Coupling of a Series of 4-BF_3K *N*-R Pyrrolidones

As outlined in section 3.2, a key aspect of our first objective was to replace the *p*-tolyl group on the nitrogen of 4-BF_3K pyrrolidone **65** to a readily removable protecting group. Protecting groups were chosen by three main criteria (i) structural similarity to

the *p*-tolyl group; (ii) compatibility to the lactam system; (iii) ease of deprotection. It was hypothesised that structural similarity to the *p*-tolyl group would minimise changes to the SMCC reaction. Any protecting groups which would form an imide functionality were deemed incompatible. Two such examples are Boc and Cbz protecting groups, as attack by nucleophiles (e.g. hydroxide) onto one of the imido carbonyl groups may present issues. PMP, as the closest structural analogue to a *p*-tolyl group, was the most logical choice. It should pose no incompatibility issues and there were several successful examples of PMP group removal reported on 4-aryl pyrrolidones.[108, 109, 110] Benzyl and PMB protecting groups should also possess no incompatibility with the lactam and there were reported examples of their removal on related 4-aryl pyrrlidones.[111,112] Therefore, 4-BF_3K *N*-PMP, *N*-Bn and *N*-PMB pyrrolidones **192-194** were selected for synthesis (Figure 3.4).

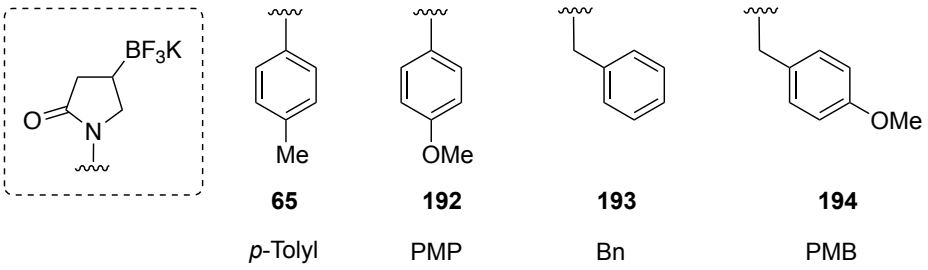
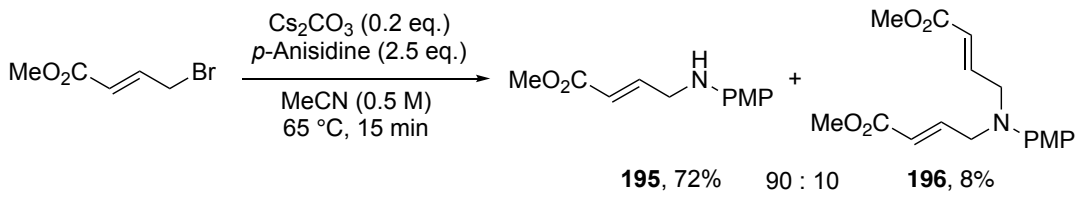


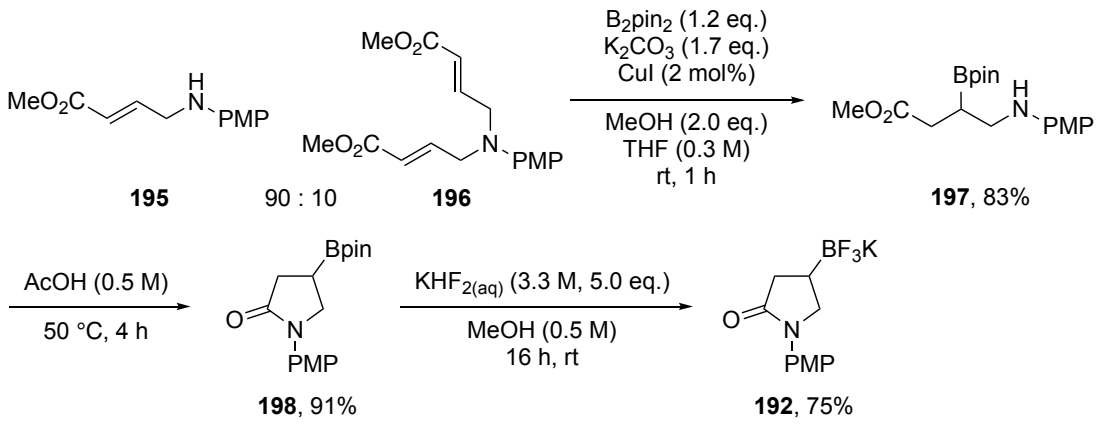
Figure 3.4: Structures of *N*-substituted pyrrolidones

The synthesis of 4-BF_3K *N*-PMP pyrrolidone **192** progressed *via* the same synthetic route established by Partridge *et al.*[59] However, compared to the synthesis of 4-BF_3K *N*-*p*-tolyl pyrrolidone **65**, a wider range of synthetic issues were encountered. Thus, using the same approach as with *p*-toluidine, a *N*-alkylation reaction between *p*-anisidine and methyl 4-bromocrotonate was used to prepare amine **195**. Reaction of *p*-anisidine and methyl 4-bromocrotonate in the presence of K_2CO_3 in MeCN at 65 ° for 1 h gave, after chromatography, a 90:10 inseparable mixture (by ^{1}H NMR spectroscopy) of mono-substituted amine **195** (72% yield) and di-substituted amine **196** (8% yield) (Scheme 3.13). In this case, the *N*-alkylation reaction progressed faster (only 15 min needed) than the equivalent *p*-toluidine reaction.



Scheme 3.13

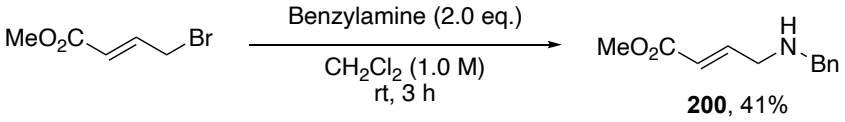
The 90:10 mixture of mono- and di-substituted amines **195** and **196** were taken on to the copper-catalysed borylation reaction. This proceeded uneventfully using the same protocol as with the *p*-tolyl substituent. Thus, after recrystallisation, Bpin amino ester **197** was isolated in 83% yield (Scheme 3.14). Fortunately, any impurities resulting from di-substituted amino acrylate **196** itself or from its reactions were removed during the recrystallisation stage. Bpin amino ester **197** was subjected to AcOH and, following work-up, 4-Bpin *N*-PMP pyrrolidone **198** was isolated in 91% yield without the need for further purification. Reacting 4-Bpin *N*-PMP pyrrolidone **198** with $KHF_{2(aq)}$ under the standard conditions gave, following work-up, 4-BF_3K *N*-PMP pyrrolidone **192** in 75% yield. Despite the increased challenges compared to the analogous *p*-tolyl synthetic route, the synthesis of 4-BF_3K *N*-PMP pyrrolidone **192** was proven to be scalable, with the synthesis carried out in up to a 100 mmol scale (of methyl 4-bromocrotonate).



Scheme 3.14

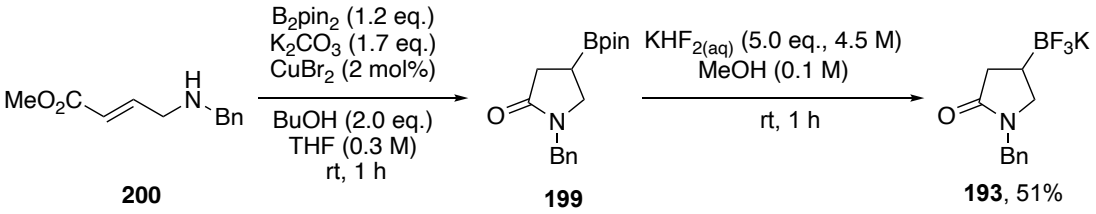
The synthesis of 4-Bpin *N*-Bn pyrrolidone **199** has also previously been reported by Partridge *et al.*[59] Following their approach, methyl 4-bromocrotonate and excess benzylamine were reacted in CH_2Cl_2 at rt for 3 h. Chromatographic separation was

uncomplicated in this case and the reaction gave *N*-Bn amino acrylate **200** in 41% yield (Scheme 3.15).



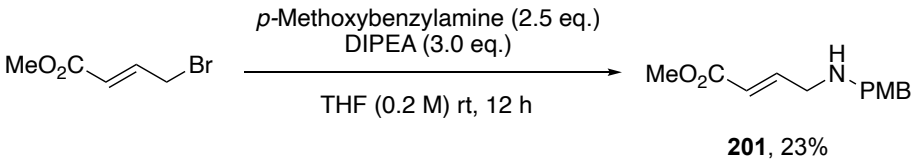
Scheme 3.15

The copper-catalysed conjugate addition of B_2Pin_2 followed a slightly modified procedure to that used for the prior two substrates. B_2pin_2, $CuBr_2$, and K_2CO_3 were stirred with *N*-Bn amine **200** in BuOH and THF at rt for 24 h. As reported by Partridge *et al*.,[44] following addition of B_2pin_2 across the double bond, the acyclic Bpin compound cyclised *in situ* completely, due to the more nucleophilic alkyl amine, giving crude 4-Bpin *N*-Bn pyrrolidone **199**. The crude material was dissolved in MeOH and reacted with $KHF_{2(aq)}$ without further purification resulting in 4-BF_3K *N*-Bn pyrrolidone **193** in 51% yield over the two steps (Scheme 3.16).



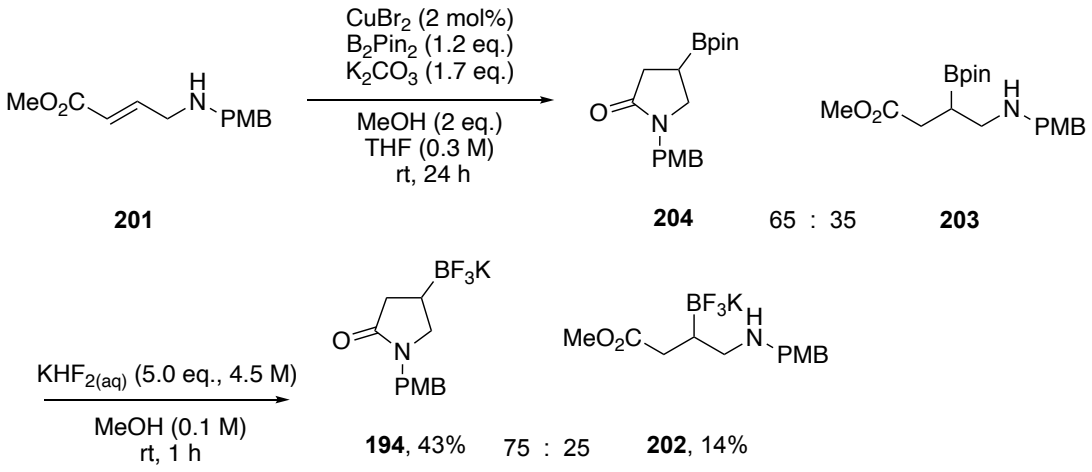
Scheme 3.16

The synthesis of 4-BF_3K *N*-PMB pyrrolidone **194** had not been previously reported. A synthetic procedure for the *N*-alkylation step was adapted from Wei *et al*., using an excess of paramethoxybenzylamine to disfavour formation of the di-substituted product.[113] Excess *p*-methoxybenzylamine was reacted with methyl 4-bromocrotonate and Hünig's base in THF at rt for 12 h. Unfortunately, the R_F values of *N*-PMB amine **201** and *p*-methoxybenzylamine were very similar and, after challenging chromatographic separation, *N*-PMB amine **201** was isolated in only 23% yield (Scheme 3.17).



Scheme 3.17

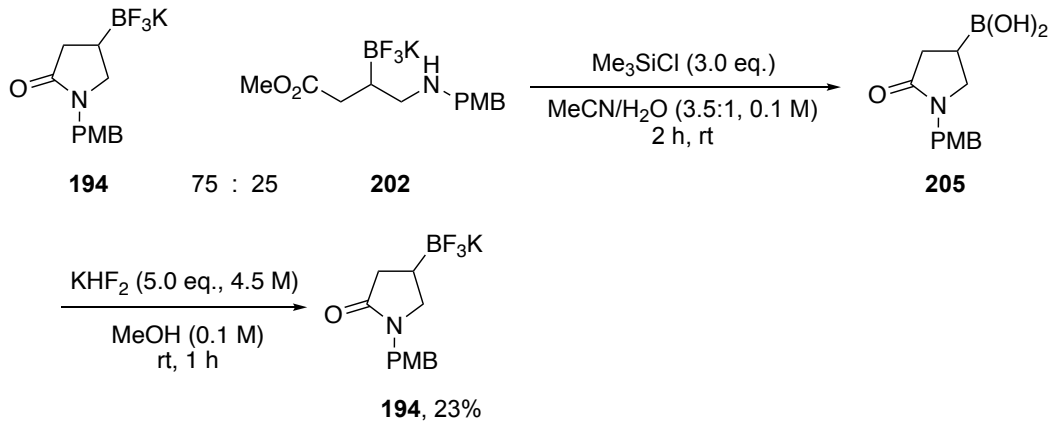
Slightly modifying the copper-catalysed borylation conditions used to prepare 4-Bpin *N*-Bn pyrrolidone **199**, B_2pin_2, $CuBr_2$, and K_2CO_3 were stirred with *N*-PMB amine **201** in MeOH (instead of BuOH) and THF at rt for 24 h. The crude material was dissolved in MeOH and reacted with $KHF_{2(aq)}$. Following work-up and analysis of the ^1H NMR spectroscopy and HRMS data, it was found that an inseparable 75:25 mixture of 4-BF_3K *N*-PMB pyrrolidone **194** (42% yield) and acyclic BF_3K **202** was obtained (Scheme 3.18). In this case, Bpin amino ester **203** had undergone incomplete cyclisation *in situ*. On close re-inspection of the ^1H NMR spectrum, a 65:35 ratio of 4-Bpin *N*-PMB pyrrolidone **204** and acyclic Bpin amino ester **203** had in fact been obtained from the copper-catalysed borylation reaction. Hence, on addition of $KHF_{2(aq)}$ both 4-BF_3K *N*-PMB pyrrolidone **194** and BF_3K amino ester **202** were produced in a similar ratio (Scheme 3.18).



Scheme 3.18

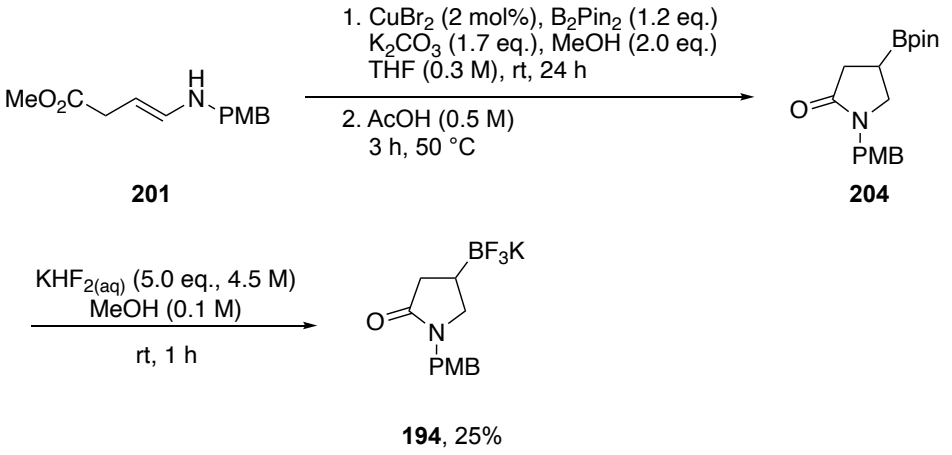
To access pure 4-BF_3K *N*-PMB pyrrolidone **194**, it was hypothesised that acidic conditions could be used to cyclise the 75:25 mixture of BF_3K salts **194** and **202**. However, since we suspected that hydrolysis of the BF_3K group to the corresponding $B(OH)_2$ group occur, it was envisaged that a subsequent treatment with $KHF_{2(aq)}$ would

generate the desired 4-BF_3K *N*-PMB pyrrolidone **194**. For the reaction conditions, we decided to use the *in situ* generation of HCl from $SOCl_2$ in MeCN-water.[114] Thus, the 75:25 mixture of BF_3K salts **194** and **202** were reacted with an aqueous solution of Me_3SiCl in MeCN at rt for 2 h. Crude $B(OH)_2$ pyrrolidone **205** was obtained with complete conversion (by ^{11}B NMR spectroscopy) and reacted immediately with $KHF_{2(aq)}$ to give 4-BF_3K *N*-PMB pyrrolidone **194** in 23% yield over the two steps (Scheme 3.19).



Scheme 3.19

Considering this information, the synthetic procedure was modified. Following addition of B_2pin_2 to amino acylate **201**, the resulting mixture of 4-Bpin *N*-PMB pyrrolidone **204** and acyclic Bpin amino ester **203** would be subjected to AcOH for 3 h. Following this modified procedure, complete cyclisation to 4-Bpin *N*-PMB pyrrolidone **201** was observed (by ^1H NMR spectroscopy). Then, reaction of 4-Bpin *N*-PMB pyrrolidone **204** with an aqueous solution of KHF_2 gave 4-BF_3K *N*-PMB pyrrolidone **194** in 25% yield over the three steps (Scheme 3.20).

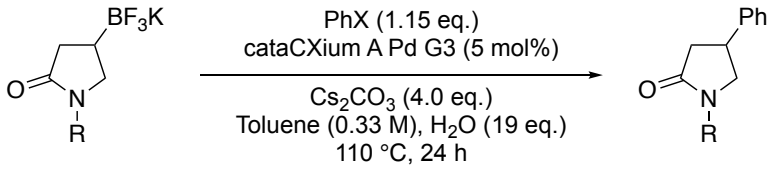


Scheme 3.20

With the series of 4-BF_3K *N*-R pyrrolidones in hand, the SMCC reaction was attempted on each using the standard conditions with bromobenzene (Table 3.1). The yields reported are isolated yields after chromatography. The reaction using 4-BF_3K *N*-*p*-tolyl pyrrolidone **65** (see Scheme 3.12) is presented in entry 1 for comparison. The SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** gave 4-phenyl *N*-PMP pyrrolidone **206** in 33% yield (entry 2). This was significantly lower than the equivalent *N*-*p*-tolyl reaction (entry 1), reflecting the sensitivity of this sp^3-sp^2 cross coupling to even a slight change in the *N*-substituent. This is especially interesting given the distal location of the *N*-group to the reactive boron handle in 4-BF_3K *N*-PMP pyrrolidone **192**. It was, however, somewhat frustrating as PMP is a readily removed *N*-R group. Reaction of 4-BF_3K *N*-Bn pyrrolidone **193** and 4-BF_3K *N*-PMB pyrrolidone **194** under the SMCC conditions with bromobenzene resulted in formation of phenyl pyrrolidones **207** (24% yield, entry 3) and **208** (41% yield, entry 4) respectively. As observed with *N*-PMP (entry 2), the *N*-Bn coupling yield was much lower than the original *N*-tolyl result (entry 1), although the yield of *N*-PMB pyrrolidone **208** was higher and closer to the original *N*-tolyl result. It is also relevant to note that the SMCC of 4-BF_3K *N*-Bn pyrrolidone **193** (entry 3) is an average of two reactions (26%, 21%) and shows good reproducibility for such a small scale. In other heterocyclic boronate systems within the group, potential aryl halide effects had been observed. Therefore, 4-BF_3K *N*-*p*-tolyl pyrrolidone **65** was reacted with 1.15 eq. chlorobenzene under the same conditions as for bromobenzene. Following work-up and chromatography, phenyl pyrrolidone **66** was obtained in a comparable 61% yield (entry 5). This suggested that under these

conditions, halide effects were likely not playing a significant role for this particular SMCC reaction.

Table 3.1: SMCC of 4-BF_3K *N*-R pyrrolidones with bromobenzene or chlorobenzene



Entry	R	Starting Material	Aryl Halide	Product	Yield / %[a]
1	*p*-tolyl	**65**	Ph–Br	**66**	59[b]
2	PMP	**192**	Ph–Br	**206**	33
3	Bn	**193**	Ph–Br	**207**	24[c]
4	PMB	**194**	Ph–Br	**208**	41
5	*p*-tolyl	**65**	Ph–Cl	**66**	61

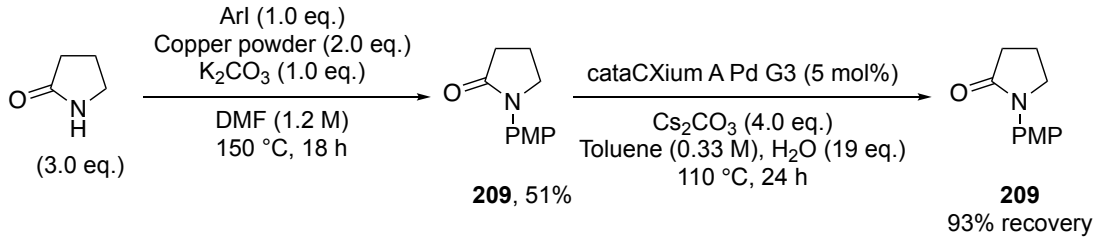
[a] Yield after chromatography; [b] Average of three results (57%, 60%, 60%); [c] Average of two results (26%, 21%).

It is not straightforward to interpret and explain the SMCC results with the different *N*-R groups, not least because we do not have an understanding of the mechanistic steps and catalyst speciation. The SMCC reaction is carried out in a biphasic reaction medium and the concentration of a reactant in the two phases is a complex equilibrium. As the *N*-R group will influence solubility of the pyrrolidone BF_3K salt, the concentration of reactants in both phases will differ, which could, at least in part, contribute to the observed variation in yield. Equally, the differences in electronics observed from varied *N*-R groups may result in detrimental interaction with certain on-cycle palladium species resulting in lower yields of cross-coupled products. However, at this moment in time, no satisfying answers can be given without further investigation.

To explain the difference in yields obtained with 4-BF_3K *N*-*p*-tolyl pyrrolidone **65** and 4-BF_3K *N*-PMP pyrrolidone **192**, we speculated that the *N*-PMP group may not be stable to the relatively harsh SMCC reaction conditions. To test this, we planned to react 4-BF_3K *N*-PMP pyrrolidone **192** under the reaction conditions without the aryl halide. However, the BF_3K substituent would likely hydrolyse to the boronic acid *in*

situ which could in turn not be easily recovered after reaction for quantification. Instead, it was decided to explore stability using the simpler *N*-PMP pyrrolidone **209**. The synthesis of *N*-PMP pyrrolidone **209**, reported by Procter *et al.*[115] in 2008, employed an Ullman condensation between 2-pyrrolidone and 4-iodoanisole. Thus, 2-pyrrolidone was stirred in DMF with copper powder, 4-iodoanisole, and K_2CO_3 at 150 °C for 18 h. After work-up and chromatography, *N*-PMP pyrrolidone **209** was obtained in 51% yield (Scheme 3.21).

N-PMP pyrrolidone **209** was reacted under the SMCC conditions without the presence of bromobenzene. After work-up and chromatography, *N*-PMP pyrrolidone **209** was recovered in 93% yield (Scheme 3.21). This clearly indicated that the *N*-PMP pyrrolidone scaffold was stable during the cross-coupling and that the low yield in the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** was likely not coming from its instability.

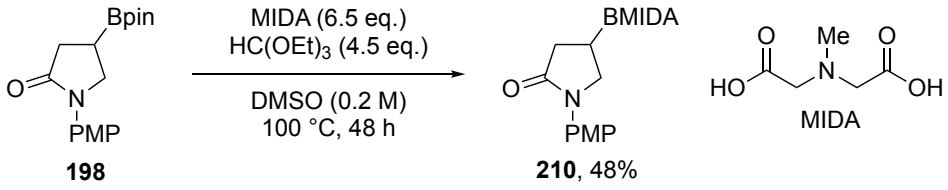


Scheme 3.21

A comprehensive investigation of optimisation and scope with all three readily deprotected *N*-R pyrrolidones was not feasible, and so we decided to instead select a single candidate for future work. It was clear that 4-BF_3K *N*-PMB pyrrolidone **194** performed best in the SMCC with the highest yield of **208** (41%, Table 3.1, entry 4). However, it also had the lowest yielding synthetic route (see Scheme 3.18 and Scheme 3.19). Optimisation of the synthetic route would be required and would take time away from investigating the SMCC reaction. The synthetic route for 4-BF_3K *N*-Bn pyrrolidone **193** was acceptable in terms of overall yield (see Scheme 3.16 and Scheme 3.17) but the lower yield of the SMCC reaction (24%, Table 3.1, entry 3) suggested it was not the ideal candidate. This left 4-BF_3K *N*-PMP pyrrolidone **192** which had a high yielding synthetic route (see Scheme 3.13 and Scheme 3.14) and an acceptable SMCC yield (33%, Table 3.1, entry 2) as a starting point. Therefore, 4-BF_3K *N*-PMP pyrrolidone **192** was selected and progressed into the next round of investigation.

3.3.3 Synthesis and Suzuki-Miyaura Cross-Coupling of *N*-PMP 4-Boryl Pyrrolidones

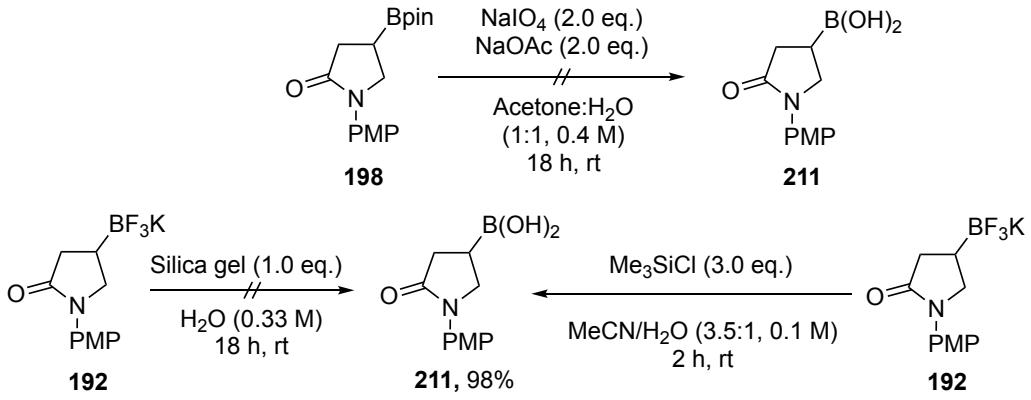
With 4-BF_3K *N*-PMP pyrrolidone **192** selected as our screening candidate, it was decided to investigate whether the BF_3K group was the optimal choice for the SMCC reactions. To this end, 4-Bpin *N*-PMP pyrrolidone **198**, 4-BMIDA *N*-PMP pyrrolidone **210** and 4-$B(OH)_2$ *N*-PMP pyrrolidone **211** were synthesised and reacted under SMCC conditions with bromobenzene. 4-Bpin *N*-PMP pyrrolidone **198** was the precursor to 4-BF_3K *N*-PMP pyrrolidone **192** and was therefore readily available. Similar to a BF_3K salt, BMIDA is a bench-stable boronic acid surrogate which hydrolyses to the active boronic acid species *in situ* and was popularised by Burke *et al*.[116] Using conditions adapted from Burke *et al*.,[117] 4-Bpin *N*-PMP pyrrolidone **198** was reacted with an excess of MIDA and triethylorthoformate in DMSO at 100 °C for 48 h. Following work-up and chromatography, crystalline BMIDA **210** was obtained in 48% yield (Scheme 3.22).



Scheme 3.22

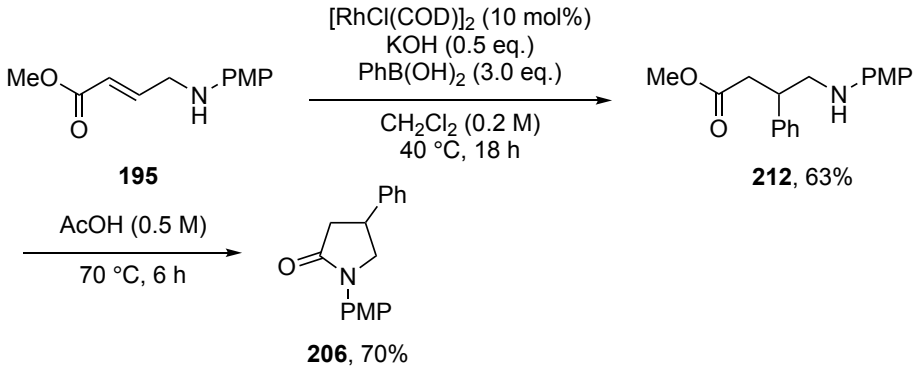
Accessing the boronic acid proved more troublesome. Initially, a hydrolysis method which had seen success within the group was attempted starting from 4-Bpin *N*-PMP pyrrolidone **198**.[118] 4-Bpin *N*-PMP Pyrrolidone **198** was reacted with sodium periodate and sodium acetate in an acetone-water mixture at rt for 18 h. Unfortunately, no conversion to 4-$B(OH)_2$ *N*-PMP pyrrolidone **211** was observed in the ^1H NMR spectrum of the crude product (Scheme 3.23). Next, a hydrolysis reaction reported by Molander *et al*.[119] starting from 4-BF_3K *N*-PMP pyrrolidone **192** was employed. BF_3K salt **192** and a stoichiometric quantity of silica gel were stirred in water at rt for 18 h. However, no conversion to 4-$B(OH)_2$ *N*-PMP pyrrolidone **211** was observed by ^1H NMR spectroscopy (Scheme 3.23). Finally, using conditions from Shen *et al*.,[114] 4-BF_3K *N*-PMP pyrrolidone **192** was reacted with excess Me_3SiCl in MeCN-water at rt for 2 h. Following work-up, high conversion was observed in the ^1H NMR spectrum

of the crude product and no further purification was required. This gave 4-$B(OH)_2$ *N*-PMP pyrrolidone **211** in 98% yield (Scheme 3.23).



Scheme 3.23

Before evaluating the series of 4-boryl *N*-PMP pyrrolidones under SMCC conditions, a GC method was developed to facilitate a higher throughput of experimentation. For this, an alternative synthetic method to access 4-phenyl *N*-PMP pyrrolidone **206** was used, namely a rhodium-catalysed Hayashi coupling reported by Liao *et al.*[120] for the conjugate addition of a phenyl group to amino acrylates. Thus, amino acrylate **195**, $[Rh(COD)Cl]_2$, KOH and phenylboronic acid were reacted in CH_2Cl_2 at 40 °C for 18 h. Following work-up and chromatography, arylated amino ester **212** was obtained in 63% yield. Subjecting arylated amino ester **212** to AcOH at 70 °C for 6 h gave 4-phenyl *N*-PMP pyrrolidone **206** in 70% yield post-purification (Scheme 3.24).



Scheme 3.24

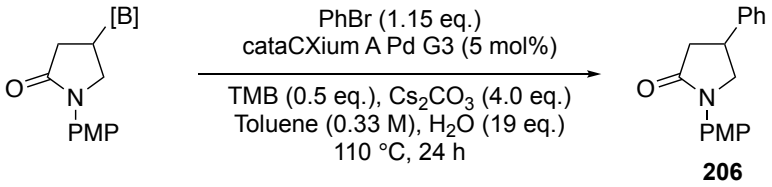
With the GC analyte in hand, a suitable analytical method was developed and the SMCC reactions of the 4-boryl *N*-PMP pyrrolidones with bromobenzene were carried

out. Furthermore, the SMCCs of 4-Bpin *N*-PMP pyrrolidone **198** and 4-BMIDA *N*-PMP pyrrolidone **210** were used to validate the GC method *via* comparison of GC yields *versus* isolated yields (Table 3.2).

With 4-BF_3K *N*-PMP pyrrolidone **192**, 4-phenyl *N*-PMP pyrrolidone **206** was isolated in 33% and 42% yields (entry 1). The average yield of 38% then acted as a benchmark for the PMP pyrrolidone system in this investigation. Lower isolated yields of **206** were obtained when cross-coupling 4-Bpin *N*-PMP pyrrolidone **198** (entry 2) and 4-BMIDA *N*-PMP pyrrolidone **210** (entry 3). It is possible that the equivalents of water used under these conditions are related to the higher yields with 4-BF_3K *N*-PMP pyrrolidone **192**. The amount of water in the system will influence the rate of hydrolysis for the different boryl groups as well as their solubility in the system. Different rates of hydrolysis would result in a different concentration of reactive boron species at any given time. As a result, the overall rates of oxidative addition and transmetallation could be affected. This may at least in part be responsible for the lower yields observed with 4-Bpin *N*-PMP pyrrolidone **198** and 4-BMIDA *N*-PMP pyrrolidone **210**. However, without mechanistic insight into the SMCC of the *N*-PMP pyrrolidone system under these conditions, the discussion is speculative. The results in entries 2 and 3 did indicate a good correlation between GC conversion and isolated yield. This served as sufficient data to validate the GC method for use in parameter screening. Of note, the SMCC of 4-$B(OH)_2$ *N*-PMP pyrrolidone **211** gave **206** in 38% yield (entry 4) equivalent to the results with 4-BF_3K *N*-PMP pyrrolidone **192** (entry 1). This suggests that the pyrrolidone system is not significantly susceptible to protodeboronation, a detrimental side reaction which is generally more prevalent when starting with boronic acids compared to trifluoroborate salts.[43]

The results in Table 3.2 indicated that screening should proceed with either 4-BF_3K *N*-PMP pyrrolidone **192** or 4-$B(OH)_2$ *N*-PMP pyrrolidone **211**. The optimal method to synthesise $B(OH)_2$ **211** proceeds from BF_3K **192**. Therefore, it was decided to continue using 4-BF_3K *N*-PMP pyrrolidone **192** as the system for subsequent parameter screening.

Table 3.2: SMCCs of 4-Boryl N-PMP pyrrolidone with bromobenzene



206

Entry	[B]	Starting material	GC Yield / %[a]	Isolated Yield / %[b]
1	BF_3K	**192**	-	33, 42
2	Bpin	**198**	7, 7	5, 5
3	BMIDA	**210**	25, 26	16
4	$B(OH)_2$	**211**	-	38

[a] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard; [b] Yield after chromatography.

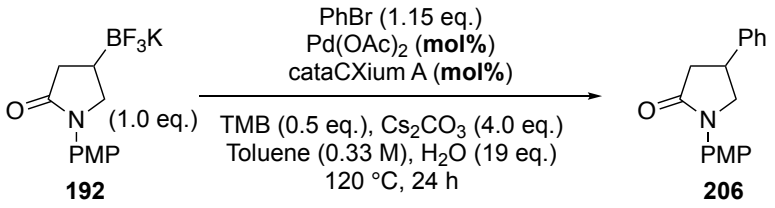
3.4 Optimisation of the Suzuki-Miyaura Cross-Coupling of 4-BF_3K *N*-PMP Pyrrolidone

3.4.1 Design of Experiment Screening

Previously in the group, optimisation of the SMCC reactions of saturated heterocyclic boronates has been carried out using a traditional One-Factor at a Time (OFAT) approach. This approach has led to successful optimisation campaigns such as the SMCC of 2-Bpin pyrrolidine **123** (see Scheme 2.6). However, the OFAT approach can be experimentally slow, wasteful and can not easily give insight into variable interactions. Therefore, to optimise the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192**, we decided to explore a Design of Experiments (DOE) methodology. This could maximise the exploration of multiple reaction parameters with the minimum number of experiments. Additionally, statistical analysis of the generated dataset could give valuable insight into interactions between factors and inform which factors are most pertinent to increasing the conversion/yield.

Before investigating a DOE approach to screening, a preliminary screen was carried out to investigate replacing cataCXium A Pd G3 with $Pd(OAc)_2$ and cataCXium A. This would allow control over the ligand : palladium ratio. Additionally, screening would utilise large quantities of catalyst, and thus changing to the cheaper combination of $Pd(OAc)_2$ and cataCXium A would greatly reduce the overall cost of the experiments. For these and subsequent experiments, the temperature of the reaction was increased from 110 °C to 120 °C in line with the conditions used for the SMCC reactions with 2-Bpin pyrrolidine **123** and others carried out in the group. SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** using $Pd(OAc)_2$ (5 mol%) and cataCXium A (10 mol%) at 120 °C gave 4-phenyl *N*-PMP pyrrolidone **206** in 22% yield (Table 3.3, entry 1). The moderate 22% yield of **206** suggested that cataCXium A Pd G3 was a better precatalyst for the reaction. However, when the same reaction was carried out using $Pd(OAc)_2$ (10 mol%) and cataCXium A (20 mol%), an improved yield of **206** of 38% was obtained (entry 2). This yield was comparable to that obtained using 5 mol% cataCXium A Pd G3 (22%, entry 1). Therefore, although it used increased palladium loading, overall, it was a cheaper catalytic system and subsequent screenings used $Pd(OAc)_2$ plus cataCXium A.

Table 3.3: Evaluation of $Pd(OAc)_2$ and cataCXium A as an alternative catalytic system



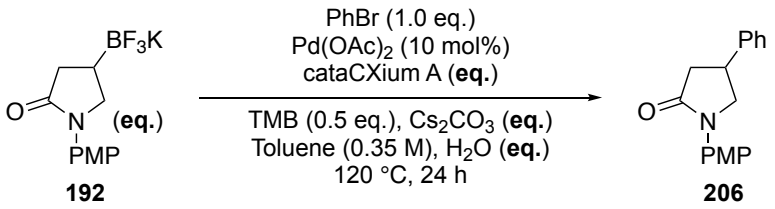
Entry	$Pd(OAc)_2$ / mol%	cataCXium A / mol%	Yield / %[a]
1	5	10	22[b]
2	10	20	38[c]

[a] Yield after chromatography, [b] Average of 2 results (21%, 22%), [c] Average of two results (37%, 38%).

To explore the potential of DOE in reaction screening at the University of York, a proof-of-concept study used MODDE software to create a full factorial design across two levels, for four factors, with three centre points. The response was designated as the GC yield of 4-phenyl *N*-PMP pyrrolidone **206**. The design had a power value of 94/100 indicating it had a high chance to detect a real effect and contain low false negatives. The L-optimality was 8.98 suggesting high predictive accuracy in the design space. The three centre points would help detect if the response was behaving non-linearly. The factors investigated in the design were: water eq. (10 or 50 eq.), ligand : palladium ratio (1:1 or 5:1 using 10 mol% $Pd(OAc)_2$), Cs_2CO_3 eq. (1.0 or 5.0 eq.) and BF_3K **192** : bromobenzene ratio (1:1 or 1.5:1). The screening would require large quantities of 4-BF_3K *N*-PMP pyrrolidone **192**; to alleviate this issue, the reactions were carried out on a 0.1 mmol scale (instead of 0.3 mmol which we had been using up to this point). To increase reproducibility and accuracy, an automated weighing robot was used to dispense all solids which were purged with N_2 prior to use. The reactions were to be carried out using multiple heating blocks on a single hotplate and no issues were observed with heating or stirring in different positions of the plate. All experiments were carried out in a random plate position to reduce bias from uncontrolled variation. The validation of scale, automated weighing and plate position was carried out on 3-BF_3K *N*-Boc pyrrolidine **50** and is detailed in Chapter 4 (see Section 4.4).

The results of the initial DOE campaign are shown in Table 3.4. The design centre points were three equivalent reactions which used 30 eq. of water, a ligand : palladium ratio of 3:1, 30 eq. of Cs_2CO_3 and 1.25 eq. of 4-BF_3K *N*-PMP pyrrolidone **192** (entries 17-19). GC yields of 4-phenyl *N*-PMP pyrrolidone **206** ranged from 23-39% indicating that there was more substantial inherent variation than expected from the validation reactions that had been conducted on 3-BF_3K *N*-Boc pyrrolidine **50**. Similarly, a GC yield of >100% was obtained (entry 2). This sample displayed a very low signal to noise ratio in the GC spectrum with significant baseline drift. When the reaction mixture was analysed by ^1H NMR spectroscopy, none of 4-phenyl *N*-PMP pyrrolidone **206** was detected which indicated that this was an anomalous result. Using 50 eq. of water, a ligand : palladium ratio of 1:1, 5.0 eq. of Cs_2CO_3 and 1.0 eq. of 4-BF_3K *N*-PMP pyrrolidone **192**, a 68% GC yield of 4-phenyl *N*-PMP pyrrolidone **206** was obtained (entry 6). To validate the yield, the reaction was purified by chromatography and 4-phenyl *N*-PMP pyrrolidone **206** was isolated in 38% yield. This indicated that there was a disparity between the GC yield and the yield after chromatography for the results of the DOE screen at 0.1 mmol scale. Therefore, the reaction in entry 6 was repeated on a 0.3 mmol scale. A GC yield of 38% and isolated yield of 37% of **206** were obtained (entry 20). This indicated that, despite validation with 3-BF_3K pyrrolidine **50** (see Section 4.4), reactions with BF_3K pyrrolidone **192** on a 0.1 mmol scale showed GC yields that were higher than the isolated yields after chromatography. However, the 37% and 38% isolated yields from repeat reactions showed the results to be reproducible (entries 6 and 20). Therefore, the conclusion was that the GC readout could be used indicatively, with reactions showing higher GC yields validated as singleton experiments. This still represented a significantly faster approach than using isolated yields for reaction parameter screening.

Table 3.4: DOE full factorial design results



Entry	Water / eq.	cataCXium A / mol%[a]	Cs_2CO_3 / eq.	**192** / eq.	GC Yield / %[b]
1	10	10	1	1	6
2	50	10	1	1	107
3	10	50	1	1	10
4	50	50	1	1	1
5	10	10	5	1	0
6	50	10	5	1	68 (38[c])
7	10	50	5	1	1
8	50	50	5	1	24
9	10	10	1	1.5	2
10	50	10	1	1.5	3
11	10	50	1	1.5	7
12	50	50	1	1.5	4
13	10	10	5	1.5	0
14	50	10	5	1.5	38
15	10	50	5	1.5	8
16	50	50	5	1.5	25
17	30	30	3	1.25	23
18	30	30	3	1.25	39
19	30	30	3	1.25	30
20[d]	50	10	5	1	38 (37[c])

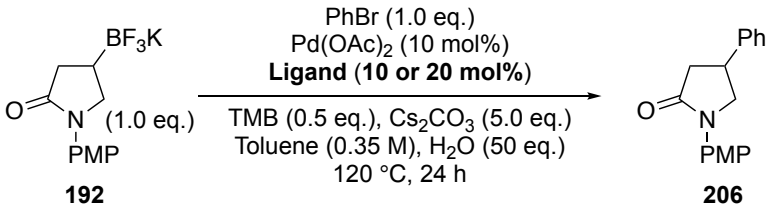
[a] 10 mol% corresponds to a 1:1 ligand : palladium ratio, 30 mol% corresponds to a 3:1 ligand : palladium ratio, 50% corresponds to a 5:1 ligand : palladium ratio; [b] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard; [c] Yield after chromatography; [d] Reaction carried out on a 0.3 mmol scale.

Unfortunately, in two experiments, zero values for the responses were observed (entries 5 and 13). This meant that the statistical methods used to extrapolate interactions between factors would not be operable. To gain more meaningful information from the DOE dataset, the experiment design would need to be restructured and repeated with new, more conservative factor levels which should give no responses with GC yields of zero. However, as there were no guarantees that this would be achieved with another single experimental run and the fact that the reactions would need to be carried out on the larger (0.3 mmol) scale (thus using up more 4-BF_3K *N*-PMP pyrrolidone **192**), a decision was made to return to the OFAT approach for further screening. Therefore, the best conditions from this dataset (entry 6) were taken and employed in a OFAT approach, with reactions carried out on a 0.3 mmol scale to reduce variation.

3.4.2 One Factor at a Time Screening

The best isolated yield from the DOE screening results was 38% (see Table 3.4, entry 6) which is equivalent to the highest yield obtained using the $Pd(OAc)_2$/cataXCium A version of the original SMCC conditions that were used for the *N*-R and *N*-boryl screening (see Table 3.3, entry 2). As both conditions were similar, the conditions from the DOE screen were used as the baseline for OFAT screening. The first individual factor investigated was the ligand. Based on the results in Table 3.4, a ligand : palladium ratio of 1:1 was identified as better than 5:1. However, the $Pd(OAc)_2$/cataXCium A conditions had used a 2:1 ligand : palladium ratio. Moreover, optimised conditions within the group, such as those used on 2-Bpin tetrahydrothiophene **110** (see Chapter 2) and 2-Bpin pyrrolidine **123** also operated with a 2:1 ligand : palladium ratio. Therefore, a screen was conducted with a series of ligands at both 1:1 and 2:1 ligand : palladium ratios and the results are shown in Table 3.5. In the results, 1:1 and 2:1 ligand : palladium ratios correspond to 10 mol% and 20 mol% cataCXium A loadings.

Table 3.5: Screening of the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with alternative ligands at 10 or 20 mol% (ligand) loading



Entry	Ligand	10 mol% ligand[a] GC yield / %[c]	20 mol% ligand[b] GC yield / %[c]
1	cataCXium A	-	44 (39[b])
2	APhos	21	45, (28[b])
3	PAd_3	11	6
4	RuPhos	8	21
5	XPhos	5	0
6	SPhos	2	11
7	JackiePhos	5	0
8	*t*-BuBrettPhos	0	0
9	BrettPhos	0	0
10	PCy_3	6	12
11	$P(t\text{-}Bu)_3 \bullet HBF_4$	3	4

[a] 10 mol% ligand corresponds to a 1:1 ligand : palladium ratio, [b] 20 mol% ligand corresponds to a 2:1 ligand : palladium ratio, [c] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard, [d] Yield after chromatography.

The structures of the selected ligands are shown in Figure 3.5. Use of 20 mol% cataCXium A loading gave a 44% GC yield of 4-phenyl *N*-PMP pyrrolidone **206** (entry 1). To validate this, the sample was worked-up and purified by chromatography to give a 39% yield of 4-phenyl *N*-PMP pyrrolidone **206**. Although the GC yield of **206** is lower than the 68% obtained in the DOE screen (see Table 3.4, entry 6), the isolated yield shows good concordance with the corresponding 38% isolated yield of 4-phenyl *N*-PMP pyrrolidone **206** with 10 mol% cataCXium A (see Table 3.4, entry 6). With APhos, a 45% GC yield of **206** was observed (entry 2). However, after chromatography, **206** was isolated in only 28% yield (entry 2). PAd_3 showed low GC

yields of **206** of 11% and 6% with 10 and 20 mol% PAd_3 respectively (entry 3). Significantly, a higher yield was obtained using 10 mol% ligand than 20 mol% ligand. However, with most ligands, a general trend was that a similar or better cross-coupling was observed when using 20 mol% ligand. Modest conversion to 4-phenyl *N*-PMP pyrrolidone **206** was accomplished with the Buchwald "Phos" type ligand RuPhos with a GC yield of 21% at 20 mol% ligand loading (entry 4). The remaining "Phos" type ligands (XPhos, SPhos, JackiePhos, *t*-BuBrettPhos, BrettPhos) displayed minimal conversion, with the best result, 20 mol% SPhos, being an 11% GC yield of **206** (entry 6). Given the shared trialkyl nature of PCy_3 and $P(t\text{-Bu})_3$ to cataCXium A, they were expected to outperform the "Phos" type ligands. However, this was not the case as maximum GC yields of 4-phenyl *N*-PMP pyrrolidone **206** of 12% and 4% were obtained with PCy_3 and $P(t\text{-Bu})_3$ (with 20 mol% ligand loading) (entries 10 and 11).

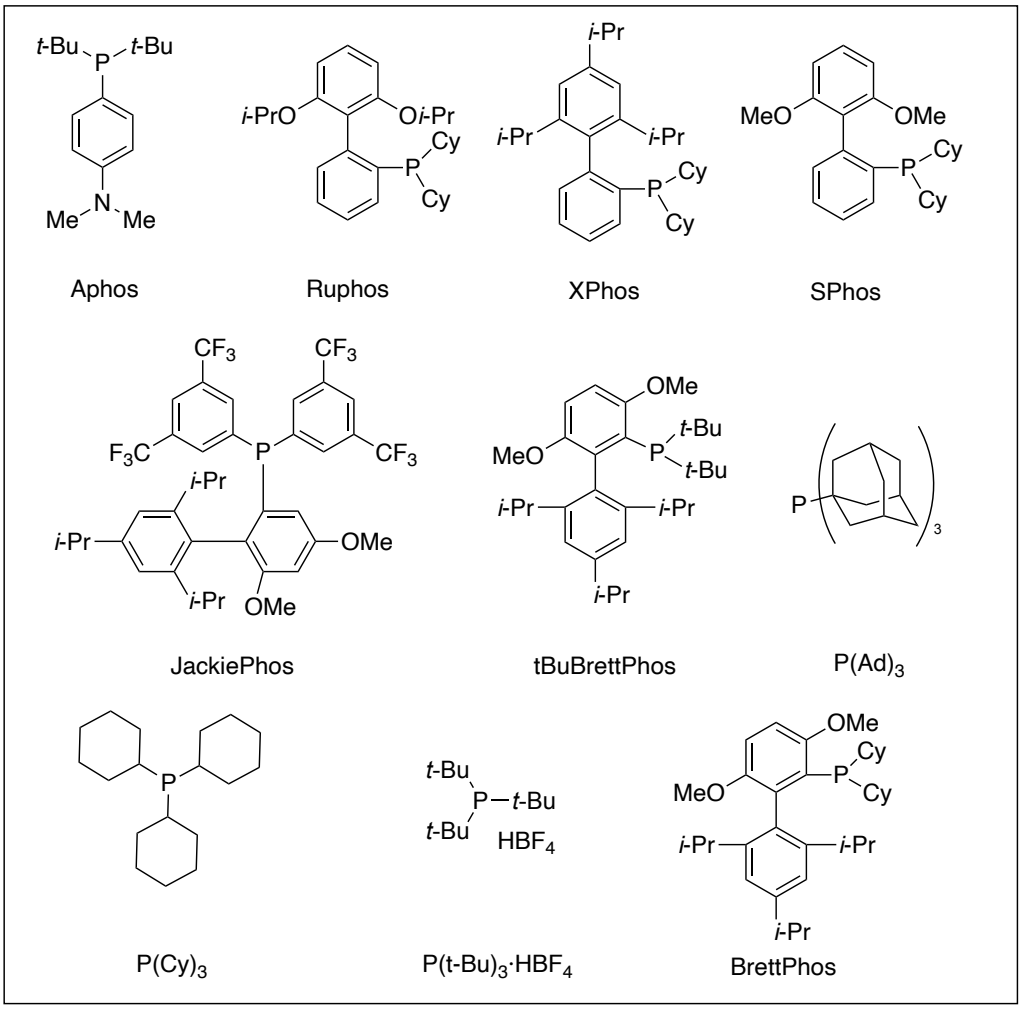
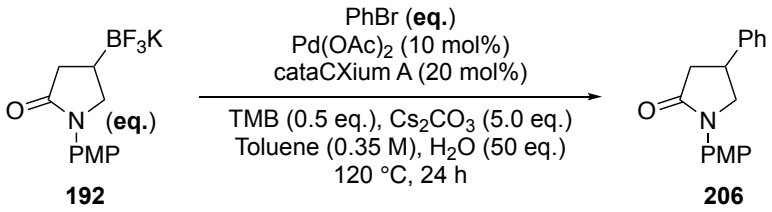


Figure 3.5: Structures of ligands in the 4-BF_3K *N*-PMP pyrrolidone **192** ligand screen

The results from the ligand screen clearly emphasised the unique effectiveness of cataCXium A in the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192**. However, the loading of cataCXium A in the reaction presented a less clear conclusion. Although there was no significant difference between the isolated yields of 4-phenyl *N*-PMP pyrrolidone **206** when using 10 mol% or 20 mol% cataCXium A, it was decided that reaction screening would continue with 20 mol% as the standard conditions. It was also hypothesised that this would maximise the chance to increase the yield of **206** in subsequent OFAT screening. If conditions were identified which improved the SMCC yield then there would be scope to investigate decreasing the cataCXium A loading.

Typically, an excess of the BF_3K salt is used in sp^3-sp^2 SMCCs. For example, the SMCCs from Dombrowski, Gesmundo *et al*.,[16] Biscoe, Sigman *et al*.[40] and Molander *et al*.[53] all use an excess of 1.0-1.5 eq. of the BF_3K salt. Ideally, the cross-coupling reaction would tolerate the use of just 1.0 equivalent of both reagents as this would conserve material and increase the atom economy of the reaction. Therefore, the equivalents of 4-BF_3K *N*-PMP pyrrolidone **192** and bromobenzene were investigated (Table 3.6). Using 1.25 or 1.5 eq. of either 4-BF_3K *N*-PMP pyrrolidone **192** or bromobenzene gave GC yields of 4-phenyl *N*-PMP pyrrolidone **206** of 38-44% (entries 1-4). Thus, with no significant effect observed between equivalents of starting material and GC yield of **206**, the combination of 1.5 eq. of bromobenzene and 1.0 eq. of 4-BF_3K *N*-PMP pyrrolidone **192** was proceeded to the next round of testing. This was due to the slightly higher yield observed under these conditions (44%, entry 2). Additionally, for this SMCC reaction, the BF_3K component is the more valuable material. However, results indicate that if the methodology was employed using a valuable aryl halide, it could likely be used as the limiting reagent, or in fact a 1:1 ratio of BF_3K **192** and aryl bromide.

Table 3.6: Screening of the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with different eq. of **192** and PhBr

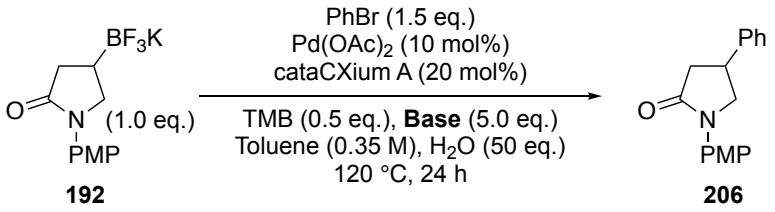


Entry	BF_3K **192** / eq.	PhBr / eq.	GC Yield / %[a]
1	1	1.25	41
2	1	1.5	44
3	1.25	1	38
4	1.5	1	43

[a] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard.

Next, the identity of the base was evaluated in the SMCC reaction. Using 5.0 eq. of base under the standard conditions, five bases were screened along with the combination of Cs_2CO_3 and 0.3 eq. of 18-crown-6 (Table 3.7). Standout results from the screen were K_3PO_4 which gave a GC yield of 4-phenyl *N*-PMP pyrrolidone **206** of 33% (entry 1). Interestingly, K_2CO_3 performed worse than Cs_2CO_3 with a GC yield of 22% (entry 2). A moderate GC yield of 19% of **206** was obtained using $CsOH.H_2O$ as base (entry 3) and no conversion to **206** was observed using KF or CsF as base (entries 4 and 5). Finally, the use of crown ethers to modify the solubility of both the potassium (from the BF_3K salt) and caesium (from the Cs_2CO_3 base) was investigated. Thus, 0.3 eq. of 18-crown-6 was added into the standard SMCC reaction conditions. A GC yield of 45% of 4-phenyl *N*-PMP pyrrolidone **206** was obtained showing no positive or negative impact on the reaction compared to current best GC yields obtained on a 0.3 mmol scale (44%, see Table 3.5, entry 1). In summary, although K_3PO_4 displayed the highest GC yield of **206** of the additional bases screened (33%, entry 1), none surpassed that of Cs_2CO_3 and, as a result, Cs_2CO_3 continued to be used as the base.

Table 3.7: Screening of the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with alternative bases and additives



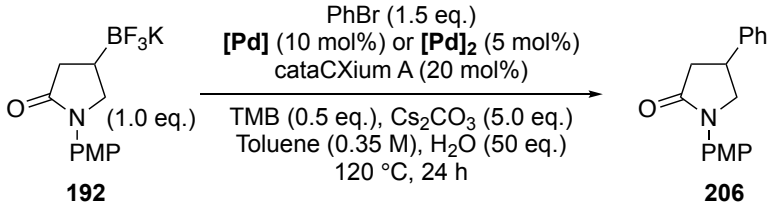
Entry	Base	GC Yield / %[a]
1	K_3PO_4	33
2	K_2CO_3	22
3	$CsOH.H_2O$	19
4	KF	0
5	CsF	0
6	Cs_2CO_3[b]	45

[a] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard, [b] Reaction contained 0.3 eq. of 18-crown-6

Our attention then turned to the precatalyst source. With some degree of confidence in the chosen base and ligand, it was hoped that exploring the chemical space of the palladium source could result in increased yield of 4-phenyl *N*-PMP pyrrolidone **206**. The reactions used 20 mol% of cataCXium A and 10 mol% of the palladium source; where the palladium source was a dimer, 5 mol% of the precatalyst was used (Table 3.8). When $[Pd(cinnamyl)Cl]_2$ dimer was used, a GC yield of 4-phenyl *N*-PMP pyrrolidone **206** of 27% was obtained (entry 1). Use of the Pd G3 dimer, a precursor in the synthesis of Buchwald's Pd G3 catalyst, gave **206** in 45% GC yield (entry 2). This was similar to yields obtained with $Pd(OAc)_2$. However, due to the cost disparity between the two palladium sources, $Pd(OAc)_2$ remained the best precatalyst source. Reaction using Pd_2dba_3 gave only an 8% yield of 4-phenyl *N*-PMP pyrrolidone **206** (entry 3). Related dimers, $[Pd(Me\text{-}allyl)Cl]_2$ and $[Pd(allyl)Cl]_2$, gave GC yields of **206** of 35% and 39% respectively (entries 4 and 5). Finally, based on a report by Bäckvall *et al*.,[121] $Pd(acac)_2$ was employed in the SMCC reaction. Unfortunately, 4-phenyl *N*-PMP pyrrolidone **206** was obtained in only 15% GC yield (entry 6). Based on the

results shown in Table 3.8, $Pd(OAc)_2$ was maintained as the best palladium source for its performance in the SMCC in combination with its low cost.

Table 3.8: Screening of the SMCC of 4-BF_3K N-PMP pyrrolidone **192** with different palladium sources

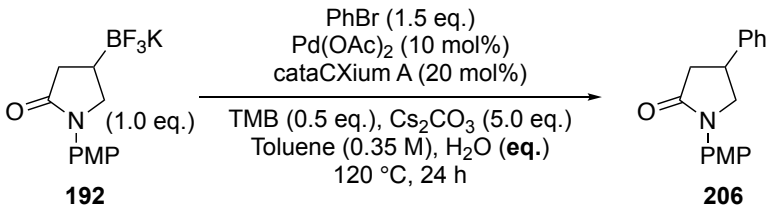


Entry	Precatalyst	GC Yield / %[a]
1	$[Pd(cinnamyl)Cl]_2$	27
2	Pd G3 dimer	45
3	$Pd_2(dba)_3$	8
4	$[Pd(Me\text{-}allyl)Cl]_2$	35
5	$[Pd(allyl)Cl]_2$	39
6	$Pd(acac)_2$	15

[a] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard

With little improvement made to the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192**, modifying the eq. of water in the cross-coupling was explored next. The eq. of water were observed to be a significant parameter during the optimisation of the SMCC of 2-Bpin pyrrolidine **123**.[75] The results of the SMCC reactions of 4-BF_3K *N*-PMP pyrrolidone **192** with varying eq. of water are shown in Table 3.9. At 10-50 eq. of water, yields of 4-phenyl *N*-PMP pyrrolidone **206** of 45-52% were obtained (entries 1-4). This indicated that there was no significant relationship between water content and GC yield of **206**. However, when 100 eq. of water was used, **206** was obtained in a slightly lower GC yield of 38%, suggesting that a large excess of water is detrimental to the reaction. As there was no significant effect observed between 10 and 50 eq. of water, screening was progressed using 20 eq. as this was similar to the original conditions (19 eq. of water) used by Partridge *et al*.[59]

Table 3.9: Screening of the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with different eq. of water



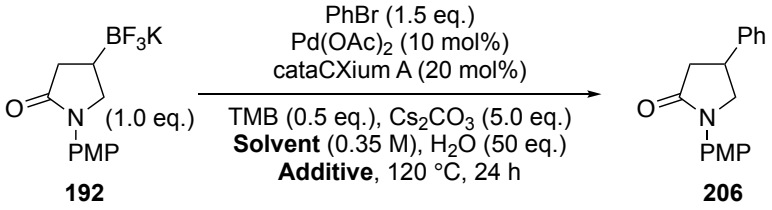
Entry	Water / eq.	GC Yield / %[a]
1	10	45
2	20	51
3	30	52
4	40	49
5	100	38

[a] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard

Concurrent to the investigation of water eq. in Table 3.9, the identity of the solvent was also briefly investigated using a small group of solvents. The results of the investigation are listed in Table 3.10. *t*-AmOH is considered a greener solvent than toluene and, compared to primary alcohol solvents such as methanol, the tertiary alcohol of *t*-AmOH was not expected to interfere with the cross-coupling reaction. Importantly, the solvent possesses a high boiling point (102 °C), pertinent for sp^2-sp^3 SMCC reactions which we have found generally require high temperature. Using *t*-AmOH in the SMCC gave 4-phenyl *N*-PMP pyrrolidone **206** in 35% GC yield (entry 1). Although this represents a lower yield than with toluene, it is significant as it offers an alternative that is less toxic and more environmentally friendly than toluene. As the SMCC reaction utilises a biphasic solvent mixture, it was hypothesised that reaction in DMSO may alleviate any issues of mixing with the bilayer. However, use of DMSO in the reaction gave 4-phenyl *N*-PMP pyrrolidone **206** in only 8% GC yield (entry 3). A solvent that would also allow a temperature above 120 °C was investigated. To this end, use of *o*-xylene at 140 °C gave 4-phenyl *N*-PMP pyrrolidone **206** in a GC yield of 41% (entry 3). This result was comparable to the standard conditions at 120 °C. Finally, it was hypothesised that a copper additive could assist transmetallation of the

boronic acid (formed after hydrolysis of the BF_3K salt).[58] Therefore, 6 mol% of copper^{I} iodide was included with the standard conditions. Under these modified conditions, 4-phenyl *N*-PMP pyrrolidone **206** was obtained in a GC yield of 29% (entry 4). No improvements over the standard conditions were identified from these experiments.

Table 3.10: Screening of the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with various solvents and with CuI as additive

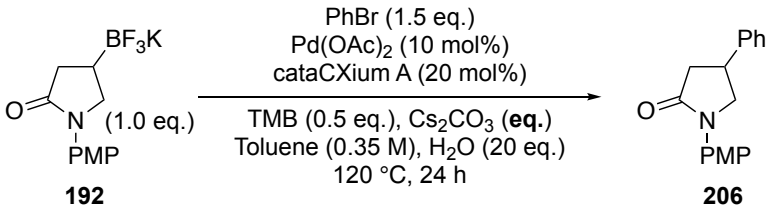


Entry	Solvent	GC Yield / %[a]
1	*t*-AmOH	35
2	DMSO	8
3	*o*-Xylene[b]	41[b]
4	Toluene[c]	29

[a] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard, [b] Temperature increased to 140 °C, [c] Reaction contained 6 mol% of CuI.

At this stage, the eq. of Cs_2CO_3 were investigated to evaluate whether the large excess (5.0 eq.) was necessary. With 4.0 eq. of Cs_2CO_3, a GC yield of 39% of 4-phenyl *N*-PMP pyrrolidone **206** was obtained (Table 3.11, entry 1), comparable to that of the result using 5.0 eq. Lower GC yields of 35% and 28% were obtained with 3.0 and 2.0 eq. of Cs_2CO_3 respectively (entries 2 and 3). Therefore, the standard conditions were modified to include the use of 4.0 eq. of Cs_2CO_3 going forward.

Table 3.11: Screening of the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with different eq. of Cs_2CO_3



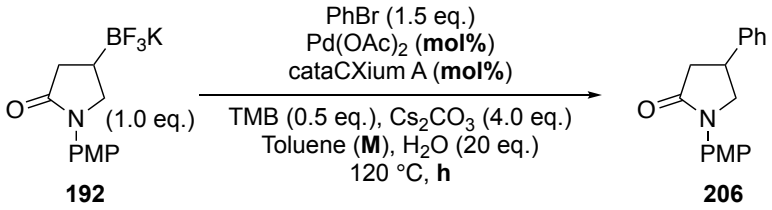
Entry	Cs_2CO_3 / eq.	GC Yield / %[a]
1	4	39
2	3	35
3	2	28

[a] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard

Simultaneously to the investigation of Cs_2CO_3 eq., three final parameters were investigated: higher loadings of $Pd(OAc)_2$ (maintaining the ligand : palladium ratio), changing the overall reaction concentration (maintaining the eq. of water) and shorter reaction times. The results are summarised in Table 3.12. Increasing the $Pd(OAc)_2$ loading to 15 and 20 mol% resulted in promising GC yields of 4-phenyl *N*-PMP pyrrolidone **206** of 48% and 45% respectively (entries 1 and 2). This suggested that a small increase in yield could be obtained moving to 15 mol% $Pd(OAc)_2$ but increasing beyond this would not result in further success. Reducing the reaction concentration in toluene to 0.1 M gave a much-diminished GC yield of **206** of 9% (entry 3). Gratifyingly, increasing the reaction concentration to 0.7 M in toluene gave a GC yield of 46% (entry 4). This was comparable to the yields observed using increasing loadings of palladium (entries 1 and 2). Therefore, it was hypothesised that combining the positive attributes observed from these changes (entries 1 and 4) could result in an increased cross-coupling yield of 4-phenyl *N*-PMP pyrrolidone **206** and the results of this is presented below. Finally, a brief exploration into the reaction timeframe was carried out, by quenching SMCC reactions under the standard conditions at 1, 3 and 7 h time points. After 1 h, none of product **206** was detected (entry 1). Quenching after 3 h gave a GC yield of **206** of 6% indicating that the reaction had started to generate **206** (entry 6). Finally, quenching after 7 h gave a GC yield of 34% (entry 7), indicating

that the reaction reaches its end-point in the 7-24 h period. To maintain consistency, SMCC reactions were continued to be carried out with the 24 h reaction time.

Table 3.12: Screening of the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with different loadings of $Pd(OAc)_2$, concentrations of toluene and reaction times



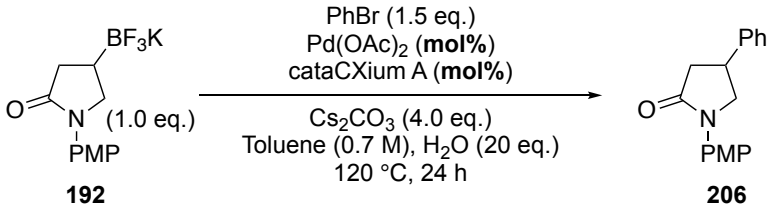
Entry	$Pd(OAc)_2$ / mol %	cataCXium A / mol %	[Toluene] / M	Time / h	GC Yield / %[a]
1	15	30	0.35	24	48
2	20	40	0.35	24	45
3	10	20	0.1	24	9
4	10	20	0.7	24	46
5	10	20	0.35	1	0
6	10	20	0.35	3	6
7	10	20	0.35	7	34

[a] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard

As highlighted above, the combination of increased palladium loading (15 mol%) and reaction concentration (0.7 M) was validated on a 0.5 mmol scale. Following work-up and chromatography, a 53% isolated yield of 4-phenyl *N*-PMP pyrrolidone **206** was obtained (Table 3.13, entry 1). This represented a significant increase over the previous highest isolated yield of 4-BF_3K *N*-PMP pyrrolidone **192** using $Pd(OAc)_2$ (39%, see Table 3.5, entry 1). The loading of 15 mol% $Pd(OAc)_2$ was considered to be particularly high. Therefore, before proceeding to a scope study at this loading, a reaction was carried out using 10 mol% $Pd(OAc)_2$ also at 0.7 M concentration. Under these conditions, an isolated yield of 50% of 4-phenyl *N*-PMP pyrrolidone **206** was obtained (entry 2), indicating that the use of increased palladium loading beyond 10 mol% was not required. Therefore, the final conditions for the SMCC of 4-BF_3K *N*-PMP pyrrolidone **206** were aryl bromide (1.5 eq.), $Pd(OAc)_2$ (10 mol%), cataCXium

A (20 mol%) and Cs_2CO_3 (4.0 eq.) in toluene (0.7 M) with water (20 eq.) at 120 °C for 24 h.

Table 3.13: Isolated yields of the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with different mol% of $Pd(OAc)_2$ and cataCXium A



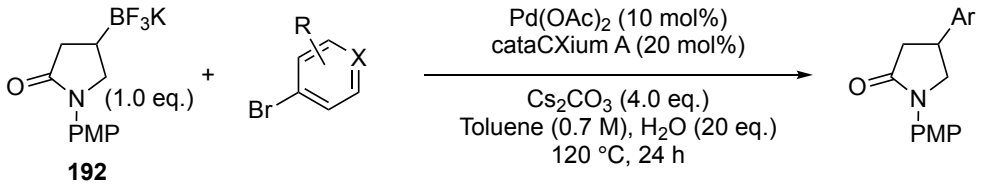
Entry	$Pd(OAc)_2$ / mol%	cataCXium A / mol%	Isolated Yield / %[a]
1	15	30	53
2	10	20	50

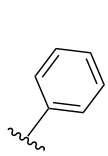
[a] Yield after chromatography.

3.5 Scope of the Suzuki-Miyaura Cross-Coupling of 4-BF_3K *N*-PMP Pyrrolidone

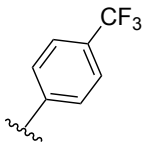
With optimised conditions for the SMCC reaction of 4-BF_3K *N*-PMP pyrrolidone **192** with bromobenzene in hand, attention switched to exploring the scope of aryl bromides. As shown in Scheme 3.25, 17 successful examples of SMCC reactions were carried out in yields ranging from 18-80%.

Good tolerance to aryl bromides bearing electron withdrawing groups was observed. For example, trifluoro methyl groups in the 3- or 4-position were tolerated with 4-aryl *N*-PMP pyrrolidones **213** and **215** obtained in 60% and 51% yields respectively. Carbocyclic aryl halides worked well overall with 4-aryl *N*-PMP pyrrolidone **216**, containing a 2-methyl substituent, obtained in a particularly high 80% yield. The scope revealed some sensitivity to electron-donating groups. For example, when 4-bromoanisole was cross-coupled, 4-aryl *N*-PMP pyrrolidone **221** was obtained in only 18% yield. With a 3-bromoanisole, 4-aryl pyrrolidone **222** was obtained in a significantly higher yield of 62%. This matches the hypothesis that increased electron density in the aromatic ring is detrimental to the yield of cross-coupled product. With the methoxy group in the 3-position of the aromatic ring, it cannot participate in resonance donation to the carbon that the bromide is attached to and, therefore, any detrimental effects from increased electron density do not apply. Although the system exhibited moderate sensitivity to heterocyclic aryl bromides, high yields of 62% and 74% were obtained for 4-aryl pyrrolidones **226** and **228**. With several aryl bromides low or no yield of cross-coupled product was observed. For example, the SMCC of 4-bromonitrobenzene or 4-bromo-dimethyl-isoxazole with 4-BF_3K *N*-PMP pyrrolidone **192** gave no detectable cross-coupled product by ^{1}H NMR spectroscopy or HRMS. With 4-bromo-2-methoxypyridine or 5-bromopyrimidine, cross-coupled products were detected (^{1}H NMR spectroscopy or HRMS) but purification was not successful.

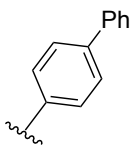




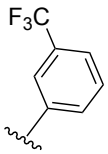
206, 50%



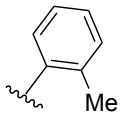
213, 60%



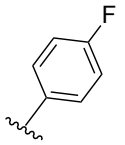
214, 44%



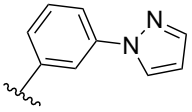
215, 51%



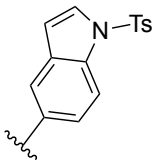
216, 80%



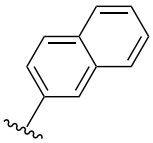
217, 50%



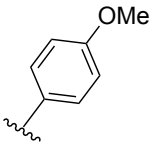
218, 34%



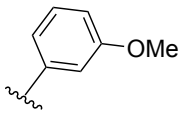
219, 23%



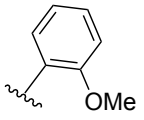
220, 41%



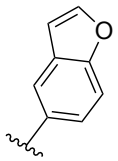
221, 18%



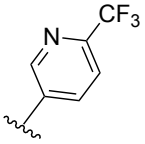
222, 62%



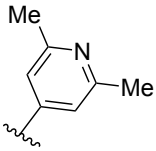
223, 32%[a]



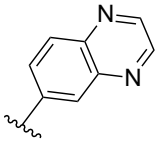
224, 10%



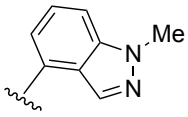
225, 33%[a]



226, 62%



227, 34%



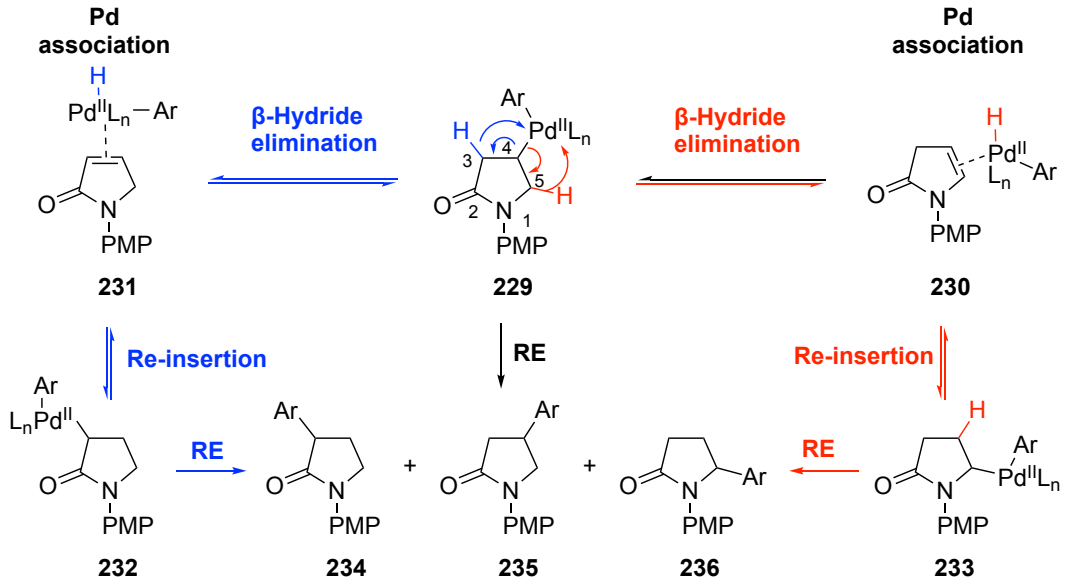
228, 74%[a]

[a] Isolated with or alongside regiosiomeric cross-coupled products

Scheme 3.25

During the development of the aryl bromide scope in the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192**, in three cases, regioisomeric 3- and 5-aryl pyrrolidone by-products were also formed together with the expected 4-aryl pyrrolidone products (which was always the major product). The three examples are highlighted in Scheme 3.25. The tendency for cyclic boronates to generate regiosiomeric by-products and the mechanism by which they can be formed during SMCC reactions has been briefly discussed previously (see Scheme 1.5) and is summarised in Scheme 3.26. Depending on the rate of relative rates of reductive elimination and β-hydride elimination, a β-

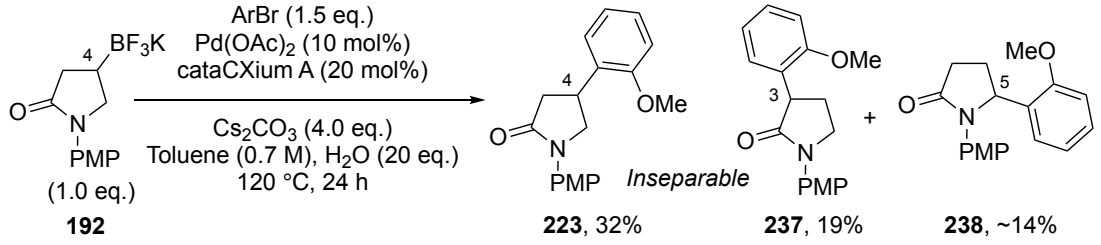
hydride elimination mechanism may be operative in the SMCC. For example, the transmetallation intermediate 4-Pd pyrrolidone **229** can undergo β-hydride elimination to give either of alkene pyrrolidones **230** and **231** potentially with the palladium still coordinated as shown. Alkene pyrrolidones **230** and **231** could reinsert, *via* hydropalladation, to place the palladium at the 4-position of the pyrrolidone regenerating 4-Pd pyrrolidone **229**. However, hydropalladation from **230** and **231** could also give 3-Pd pyrrolidone **232** and 5-Pd pyrrolidone **233**. Each of 3-, 4- and 5-Pd pyrrolidones **229**, **232** and **233** could undergo reductive elimination (labelled RE in Scheme 3.26) to generate the corresponding regiosiomeric aryl pyrrolidones **234**, **235** and **236**.



Scheme 3.26

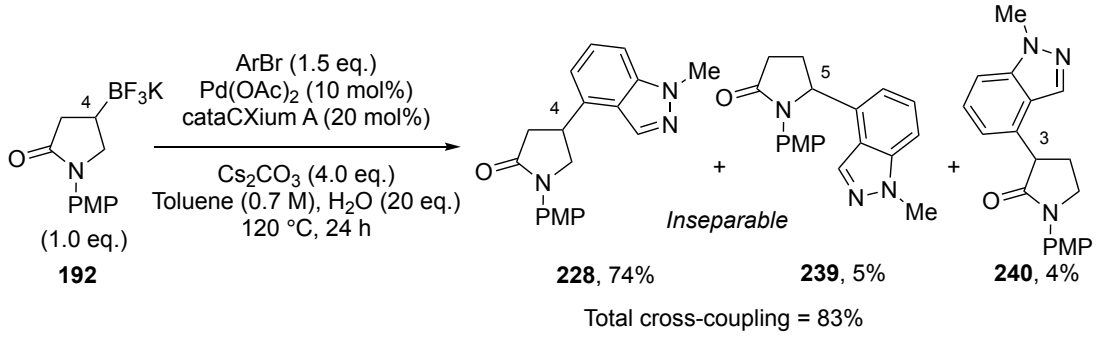
The formation of regioisomeric aryl pyrrolidone products was observed in the cross-coupling of 2-bromoanisole with 4-BF_3K *N*-PMP pyrrolidone **192**. Both 4- and 3-aryl *N*-PMP pyrrolidones **223** and **237** were isolated in 32% and 19% yields respectively as an inseparable mixture (Scheme 3.27). Additionally, 5-aryl pyrrolidone **238** was isolated with minor additional impurities in ~14% yield. The regiosiomeric pyrrolidones were identified using HRMS and ^{1}H NMR spectroscopy. 5-Aryl pyrrolidone **238** was easily identifiable from the ^{1}H NMR spectrum. There was a diagnostic doublet of doublets (dd, J = 7.5, 3.5 Hz) at 5.55 ppm with the chemical shift explained by the proximity of the 5-aryl proton to the pyrrolidone nitrogen. Additionally, 5-aryl *N*-PMP pyrrolidone **238** is a known compound[122] and comparison

of the ^{1}H NMR spectroscopic data with the literature values confirmed the assignment. 3-Aryl pyrrolidone **237** had analogous diagnostic doublet of doublets (J = 9.0, 9.0 Hz) at 4.07 ppm. Fortunately, this signal was resolved from either of the NCH or CHAr signals of 4-aryl pyrrolidone **223** which appeared at 4.15 and 3.92 ppm. Although 3-aryl *N*-PMP pyrrolidone **237** was not a known compound, the *N*-methyl analogue was reported previously[123] and these data were used to confirm the identification of 3-aryl pyrrolidone **237** in the mixture of 3- and 4-aryl pyrrolidones **237** and **238**. Overall, the total observed cross-coupling yield of aryl pyrrolidones **223**, **237** and **238** was ~65%, suggesting that a higher yield of 4-aryl pyrrolidone **223** could be obtained if the rate of reductive elimination could be increased relative to β-hydride elimination.



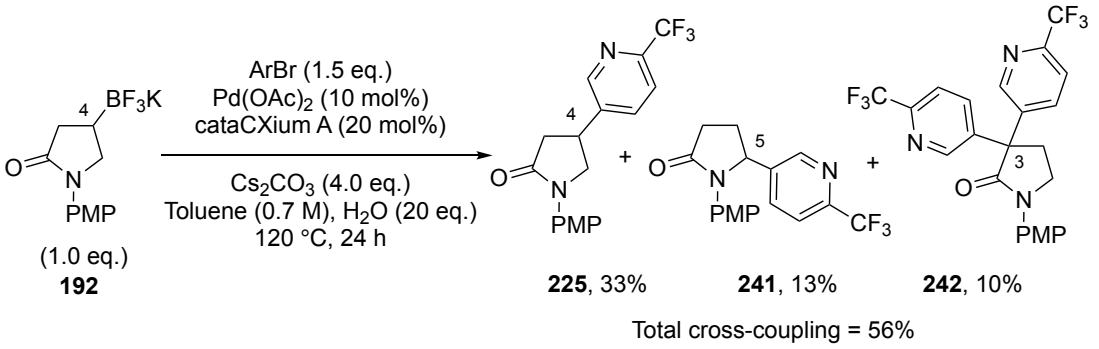
Scheme 3.27

Regioisomeric aryl pyrrolidones were also observed in the cross-coupling of 4-BF_3K *N*-PMP pyrrolidone **192** with 4-bromo-1-methyl-1*H*-indazole. In this case, an 89:6:5 mixture of 4-aryl pyrrolidone **228** (74%), 5-aryl pyrrolidone **239** (5%) and 3-aryl pyrrolidone **240** (4%) was isolated after chromatography (Scheme 3.28). Overall, this example demonstrated a highly efficient cross-coupling with an overall yield of 83% and only a very minor degree of regioisomers generated.



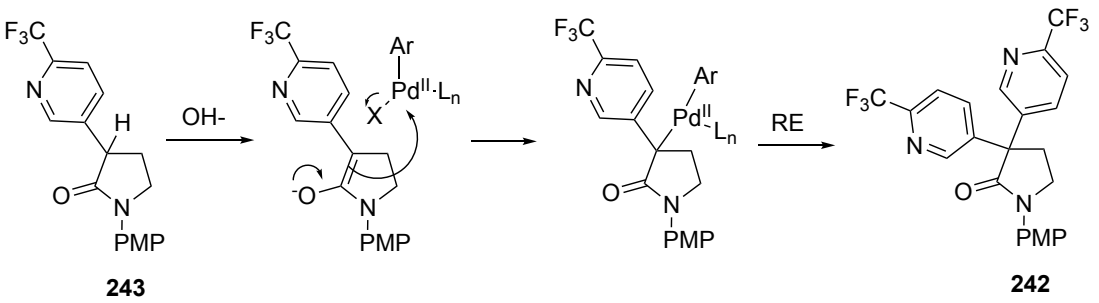
Scheme 3.28

Finally, regiosiomeric aryl pyrrolidones were also detected when 5-bromo-2-(trifluoromethyl)pyridine was employed in the cross-coupling. In this example, each of the three products of the reaction were separable by chromatography. Thus, 4-aryl pyrrolidone **225** and 5-aryl pyrrolidone **241** were isolated in 33% and 13% yields respectively. The 3-arylated pyrrolidone regioisomer was, however, not observed. Instead, 3,3-biarylated pyrrolidone **242** was obtained in 10% yield (Scheme 3.29).



Scheme 3.29

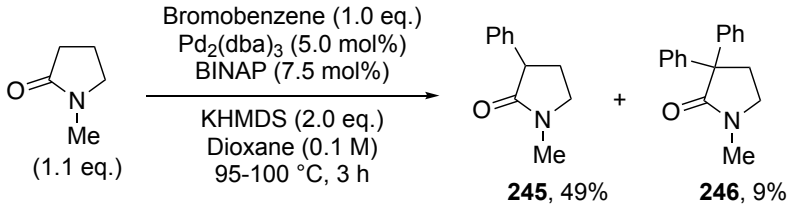
The proposed mechanism for the formation of 3,3-biaryl pyrrolidone **242** *via* palladium-catalysed enolate α-arylation is shown in Scheme 3.30. First, 3-aryl pyrrolidone **243** would be formed *via* the β-hydride elimination mechanism (see Scheme 3.26). Then, under the basic conditions of the SMCC reaction, deprotonation of 3-aryl pyrrolidone **243** would generate the corresponding enolate. Reaction of the enolate with the electrophilic palladium oxidative addition intermediate would furnish 3,3-biaryl pyrrolidone **242**.



Scheme 3.30

There are numerous reports of palladium-catalysed enolate α-arylation which add support to the hypothesis that it could be active under our SMCC conditions.[124–127] For example, the diastereoselective enolate α-arylation of 4-substituted cyclohexyl esters

was reported by Bercot and Caille *et al.*[126] in 2008, and several similarities can be drawn between their conditions and the optimised 4-BF_3K *N*-PMP pyrrolidone **192** SMCC conditions. For instance, the bulky electron-rich ligand P(*t*-Bu)$_3$ was used alongside aryl bromides and reactions were performed in toluene. Although, their reactions were carried out using a stronger base (LDA) than the carbonate base (Cs_2CO_3) used in the SMCC conditions. However, 3-aryl pyrrolidone **243** contains an electron-deficient pyridine with an additional electron-withdrawing CF_3 group which greatly increases the acidity of the α-proton. Additionally, considering the high temperature of the SMCC it is likely that enolate formation would be facile even with Cs_2CO_3. However, given the steric bulk of the geminal CF_3 pyridine aromatic group, it is somewhat surprising that complete conversion of 3-aryl pyrrolidone **243** to 3,3-biaryl pyrrolidone **242** was observed. However, Hartwig *et al.*[124] reported the formation of biphenyl *N*-Me pyrrolidone **244** as a side product in the palladium-catalysed enolate α-arylation of *N*-Me pyrrolidone (NMP) (Scheme 3.31). NMP was reacted with bromobenzene, $Pd_2(dba)_3$, BINAP, and KHMDS in dioxane at 95-100 °C for 3 h and a mixture of phenyl pyrrolidone **245** and biphenyl pyrrolidone **244** were obtained in 49% and 9% yields respectively. In just 3 h at 95-100 °C, roughly 15% of phenyl pyrrolidone **245** had undergone a second enolate α-arylation to form biaryl pyrrolidone **244**. Thus, at 120 °C for 24 h in the optimised SMCC conditions for 4-BF_3K *N*-PMP pyrrolidone **192** it would be expected that all of 3-aryl pyrrolidone **243** would undergo palladium-catalysed enolate α-arylation to 3,3-biphenyl pyrrolidone **242**.

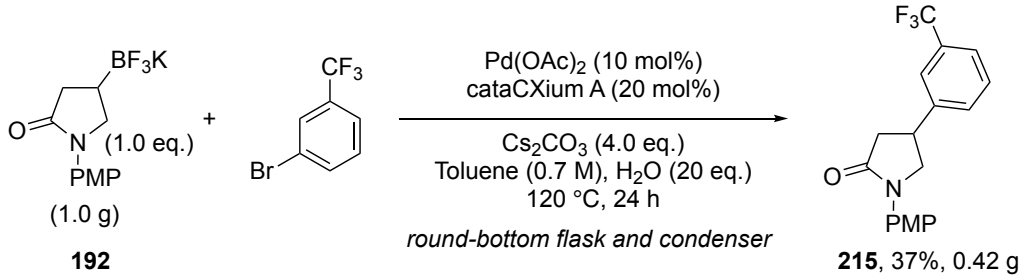


Scheme 3.31

Although the generation of regioisomeric aryl pyrrolidones diminishes the potential utility of the SMCC reactions of 4-BF_3K *N*-PMP pyrrolidone **192**, it was only observed with a small subset of aryl bromides (three out of 17 examples) and it was a minor pathway. There is no obvious trend linking the nature of the aryl bromide with the observed generation of regioisomeric products. Each aryl bromide possesses a Lewis

basic heteroatom, and it is possible that interaction with palladium during the catalytic cycle reduces the rate of reductive elimination relative to β-hydride elimination. Unlike with 2-bromoanisole, no regiosiomeric aryl pyrrolidone by-products were observed when cross-coupling 4- or 3-bromoanisole (see Scheme 3.25). This suggests that the position of the heteroatom in space is significant to its ability to promote reductive elimination. Despite the presence of regioisomers, the high overall conversions suggest that the transmetallation step was operating appropriately. Therefore, any subsequent rounds of reaction optimisation could focus on increasing the rate of reductive elimination relative to β-hydride elimination.

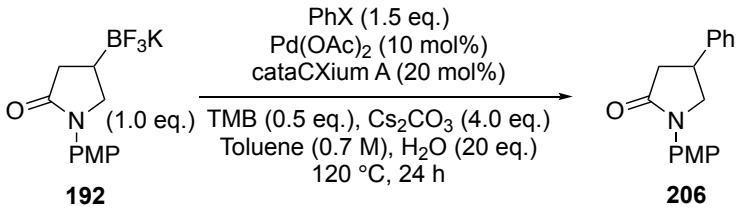
Next, the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with 3-bromobenzotrifluoride was scaled up. It would be useful evaluate if the methodology could be transferred to a round bottom flask and condenser set up. Under the optimised SMCC conditions, starting from 1 g (3.37 mmol) of 4-BF_3K *N*-PMP pyrrolidone **192**, 4-aryl *N*-PMP pyrrolidone **215** was isolated in 37% yield (0.42 g produced) after chromatography (Scheme 3.32). This is lower than the 51% yield of **215** obtained on a 0.3 mmol scale in the standard 7 mL sealed vial set-up (see Scheme 3.25). However, a satisfactory yield (37%) was obtained under the modified experimental set-up. Therefore, if a large-scale synthesis was required, optimisation of the experimental set-up may result in comparable yield to the small scale. For example, carrying out the larger scale reactions in a sealed vial rather than flask and condenser may increase the yield of **215** on a large scale.



Scheme 3.32

When 4-BF_3K *N*-*p*-tolyl pyrrolidone **65** was reacted with chlorobenzene, 4-phenyl *N*-*p*-tolyl pyrrolidone **66** was obtained in 61% yield (see Table 3.1, entry 5). The average yield of the analogous cross-coupling with bromobenzene was 59% (see Table 3.1, entry 1), thus no effect was observed between the nature of the halide in the SMCC with 4-BF_3K *N*-*p*-tolyl pyrrolidone **65**. Based on this result, when optimising the SMCC reaction of 4-BF_3K *N*-PMP pyrrolidone **192**, the identity of the halide in the cross-coupling partner was not investigated. However, following generation of the scope (*vide supra*) this was revisited and the results are highlighted in Table 3.14.

Table 3.14: Screening of the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with PhCl and PhI



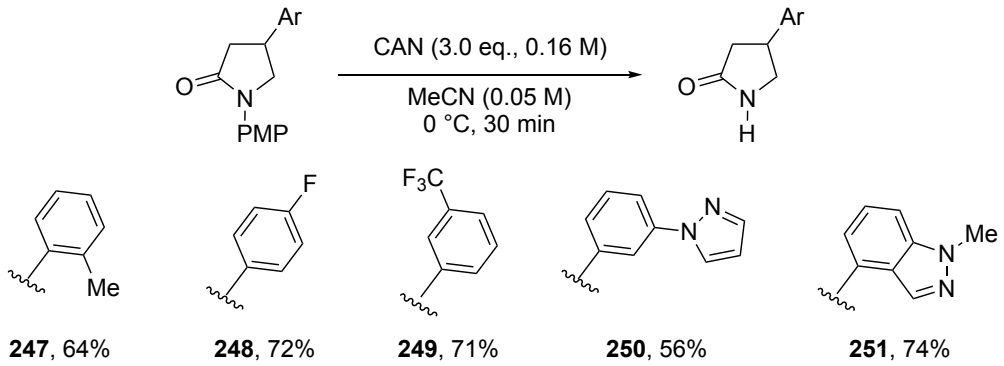
Entry	Aryl Halide	GC Yield / %[a]	Isolated Yield / %[b]
1	Chlorobenzene	-	65
2	Iodobenzene	9	-

[a] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard, [b] Yield after chromatography.

Cross-coupling of 4-BF_3K *N*-PMP pyrrolidone **192** under optimised conditions using chlorobenzene gave 4-phenyl *N*-PMP pyrrolidione **206** in an isolated yield of 65% (entry 1). Conversely, with iodobenzene, a GC yield of **206** of only 9% was observed and isolation was not pursued (entry 2). The improved yield with chlorobenzene does not follow the trend observed with 4-BF_3K *N*-*p*-tolyl pyrrolidone **55**. It is unknown whether this originates from the change of conditions, the change of *N*-R group or a mixture of the two. The results suggest that the scope would ideally have been explored using aryl chlorides and there is opportunity to explore the cross-coupling of aryl chlorides in the SMCC with 4-BF_3K *N*-PMP pyrrolidone **192**. However, the observed trend with aryl chlorides is based solely on SMCC reactions with bromo/chloro

benzene, and without further investigation it is unclear whether the beneficial effect of aryl chlorides would be consistent across a range of aromatic groups.

As outlined earlier in the chapter, the PMP group was selected as we anticipated that it would be relatively straightforward to reveal the N-H pyrrolidone. Therefore, it was important to demonstrate that deprotection of the PMP-protected lactam nitrogen could be achieved. Removal of the PMP group from pyrrolidones is well precedented and typically carried out using ceric^{IV} ammonium nitrate (CAN) to cleave the *N*-C bond *via* a single electron oxidative mechanism. The deprotection conditions were adapted from those reported by Morgan and Stoltz *et al.*[128] A representative set of diverse 4-aryl pyrrolidones were selected to probe for any incompatibilities with the deprotection methodology. Five examples of deprotection are shown in Scheme 3.33. CAN deprotection of 4-aryl *N*-PMP pyrrolidone **216** gave 4-aryl *N*-H pyrrolidone **247** in 64% yield. With 4-aryl *N*-PMP pyrrolidone **217**, deprotection proceeded more efficiently with a 72% yield of 4-aryl *N*-H pyrrolidone **248**. No issue was observed in the deprotection of electron deficient 4-aryl pyrrolidone **215**, with 4-aryl *N*-H pyrrolidone **249** isolated in 71% yield. Heteroaryl containing pyrrolidones were also tolerated well with 4-aryl *N*-H pyrrolidones **250** and **251** obtained in 56% and 74% yield respectively.



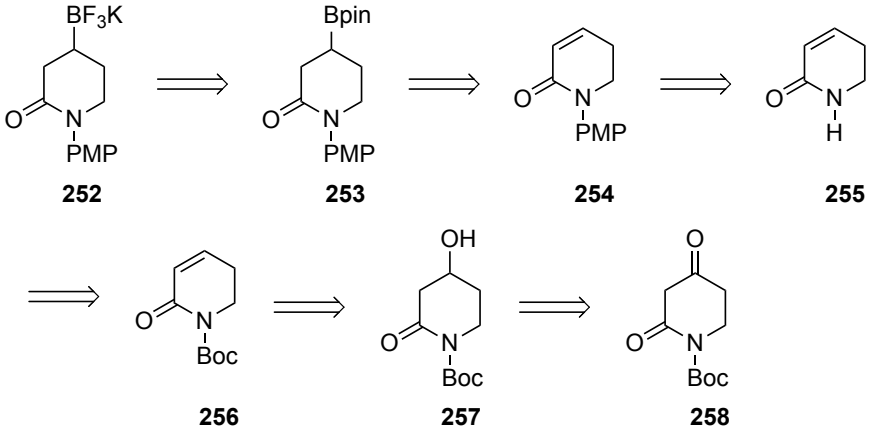
247, 64% **248**, 72% **249**, 71% **250**, 56% **251**, 74%

Scheme 3.33

3.6 Synthesis and Suzuki-Miyaura Cross-Coupling of 4-BF_3K *N*-PMP Piperidone

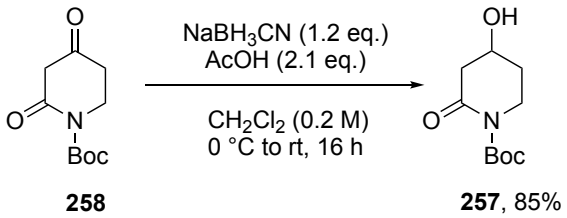
With the successful development of SMCC reactions with 4-BF_3K *N*-PMP pyrrolidone **192**, we wanted to evaluate whether the methodology could also be applied to similar lactam systems. To this end, the synthesis and SMCC of 4-BF_3K *N*-PMP piperidone **252** was explored.

The proposed retrosynthetic approach for the synthesis of 4-BF_3K *N*-PMP piperidone **252** is shown in Scheme 3.34. 4-BF_3K *N*-PMP piperidone **252** would be obtained from corresponding Bpin piperidone **253** which in turn would be prepared using the copper-catalysed conjugate addition of B_2pin_2 to the alkene in unsaturated *N*-PMP piperidone **254**. It was anticipated that *N*-arylation of unsaturated *N*-H lactam **255** to give unsaturated *N*-PMP piperidone **254** would be achieved using the copper-catalysed Ullman coupling. Unsaturated *N*-H lactam **255** would be accessible from unsaturated *N*-Boc lactam **256** where the alkene would be formed by elimination starting from hydroxy lactam **257**. Finally, hydroxy lactam **257** would be formed from keto lactam **258**. Although the overall proposed route was somewhat protracted, the initial three steps of reduction, elimination and Boc group removal were hypothesised to be simple and robust reactions that could be carried out easily to access *N*-H alkene **255** on a large scale. Additionally, this route would allow 4-BF_3K *N*-PMP piperidone **252** to be initially tested in the SMCC. If a hit was identified, the synthetic route could be subsequently optimised/modified.



Scheme 3.34

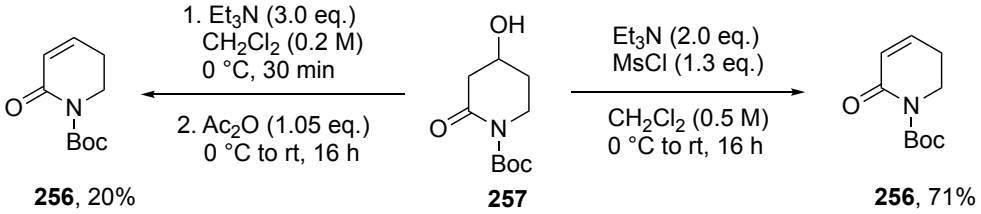
Initially, reduction of keto lactam **258** was carried out with $NaBH_4$. However, this resulted in ring opening of the lactam and no conversion to desired hydroxy lactam **257** was observed. Therefore, a milder reduction strategy was desired and use of $NaBH_3CN$ had been reported in a patent for this reaction.[129] Following the reported conditions, AcOH and $NaBH_3CN$ in CH_2Cl_2 gave hydroxy lactam **257** in 85% yield (Scheme 3.35).



258 **257**, 85%

Scheme 3.35

Following methodology from the same patent, elimination of the alcohol in hydroxy lactam **257** was attempted using Et_3N and Ac_2O. Following this procedure, unsaturated *N*-Boc lactam **256** was obtained in only 20% yield (Scheme 3.36). Analysis of the product mixture indicated large amounts of unreacted starting material **257** alongside a small amount of *O*-acylated starting material. It was hypothesised that a better leaving group could help facilitate the elimination. Based on conditions from Abe, Kaysser *et al.*[130] on a related 5-acyl keto hydroxy lactam, Ac_2O was replaced with MsCl. Under these conditions elimination was much more efficient and unsaturated *N*-Boc lactam **256** was isolated in 71% yield (Scheme 3.36).

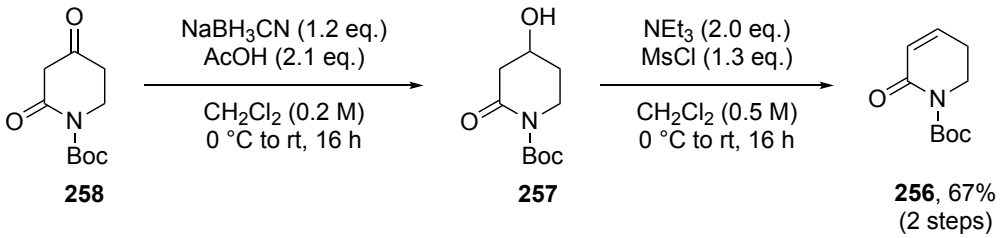


256, 20% **257** **256**, 71%

Scheme 3.36

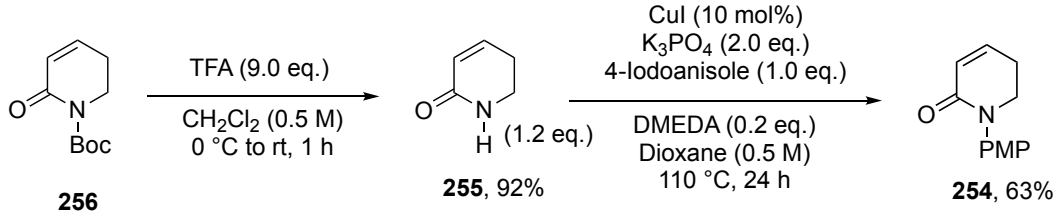
To increase efficiency of the synthesis, it was evaluated whether the chromatographic purification of hydroxy lactam **257** was necessary. Gratifyingly, when crude hydroxy lactam **257** was telescoped through to the elimination procedure, unsaturated *N*-Boc lactam **256** was obtained in a 67% yield over the 2 steps (Scheme 3.37). This was

carried out on an increased scale with 4 g of keto lactam **258** demonstrating the robust scalability of the initial steps of the route as originally planned in the retrosynthetic analysis.



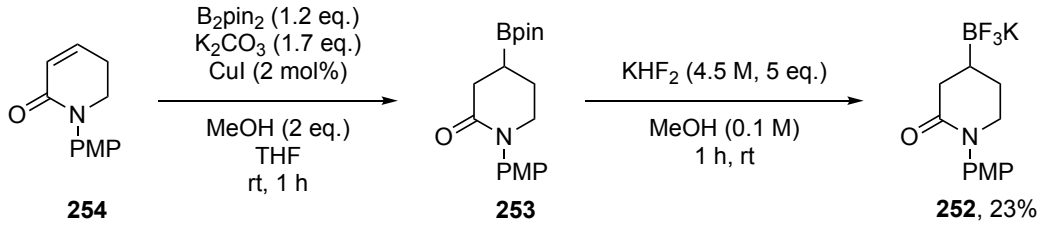
Scheme 3.37

Deprotection of the amine in unsaturated *N*-Boc lactam **256** under aqueous HCl or HCl/dioxane conditions resulted in minimal conversion to desired unsaturated *N*-H lactam **255**. There was evidence in the ^{1}H NMR spectrum of a new species which was neither remaining unsaturated *N*-Boc lactam **256** nor unsaturated *N*-H lactam **255**. Based on comparison of the NMR spectrum to hydroxy lactam **257** the lactam appeared to be 4-substituted. From the presence of a 1H multiplet at 3.72-3.64 ppm it was hypothesised that the chloride anion from HCl may have participated in conjugate addition to the electron deficient alkene. The chemical shift matched that of reported ^{1}H NMR spectra of structurally similar 4-Cl piperidones suggesting that the nucleophile was likely chloride rather than hydroxide.[131] Therefore, TFA was proposed for the deprotection as trifluoroacetate is not very nucleophilic, and this change worked well. Excess TFA was added to a solution of *N*-Boc alkene **256** and, following work-up, *N*-H alkene **255** was obtained in 92% yield (Scheme 3.38). Adapting conditions from *Jiang* et al.,[132] *N*-H alkene **255** was stirred in dioxane with CuI, K_3PO_4, 4-iodoanisole, and DMEDA at 110 °C for 24 h. After work-up and chromatography, *N*-PMP alkene **254** was obtained in 63% yield (Scheme 3.38).



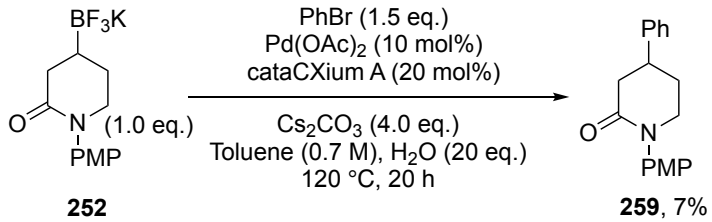
Scheme 3.38

Next, copper-catalysed borylation of unsaturated *N*-PMP piperidone **254** was explored. Therefore, the reaction was carried out with B_2pin_2, CuI, K_2CO_3 and MeOH in THF at rt for 1 h. By analysis of the ^1H NMR spectrum of the crude product, complete conversion of *N*-PMP alkene **254** was observed. 4-Bpin *N*-PMP piperidone **253** was then telescoped through to the next step without any further purification. Using the standard procedure, Bpin **253** and $KHF_{2(aq)}$ were reacted in MeOH at rt for 1 h. Unfortunately, the low solubility of 4-BF_3K *N*-PMP piperidone **252** in hot acetone created problems with isolation. The work-up procedure was modified to include additional trituration with hot MeCN. Under the modified procedure, BF_3K **252** was isolated in 23% yield (Scheme 3.39). This was enough material to evaluate the SMCC. However, this step would require optimisation if larger quantities were desired.



Scheme 3.39

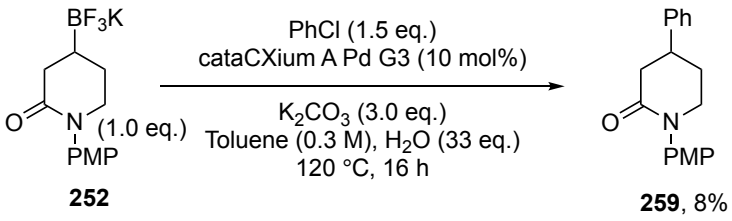
With a synthetic route to access 4-BF_3K *N*-PMP piperidone **252** developed, we could finally evaluate whether the conditions optimised for 4-BF_3K *N*-PMP pyrrolidone **192** could be applied to piperidone **252**. Therefore, under the optimised conditions, SMCC of 4-BF_3K *N*-PMP piperidone **252** and bromobenzene was carried out. Following work-up and purification, 4-phenyl *N*-PMP piperidone **259** was obtained in only 7% yield (Scheme 3.40).



Scheme 3.40

With minimal yield obtained of 4-phenyl *N*-PMP piperidone **259** under optimised pyrrolidone conditions. It was hypothesised that 4-BF_3K *N*-PMP piperidone **252** may

perform better in the cross-coupling under conditions developed within the group by Lucy Tomczyk for 4-BF_3K *N*-Boc piperidine.[133] The conditions were chlorobenzene (not bromobenzene), cataCXium A Pd G3 (10 mol%), K_2CO_3 (3.0 eq.) in toluene (0.3 M) with 33 eq. of water at 120 °C for 16 h. Under these conditions, 4-phenyl *N*-PMP piperidone **259** was obtained in only 8% yield (Scheme 3.41).



Scheme 3.41

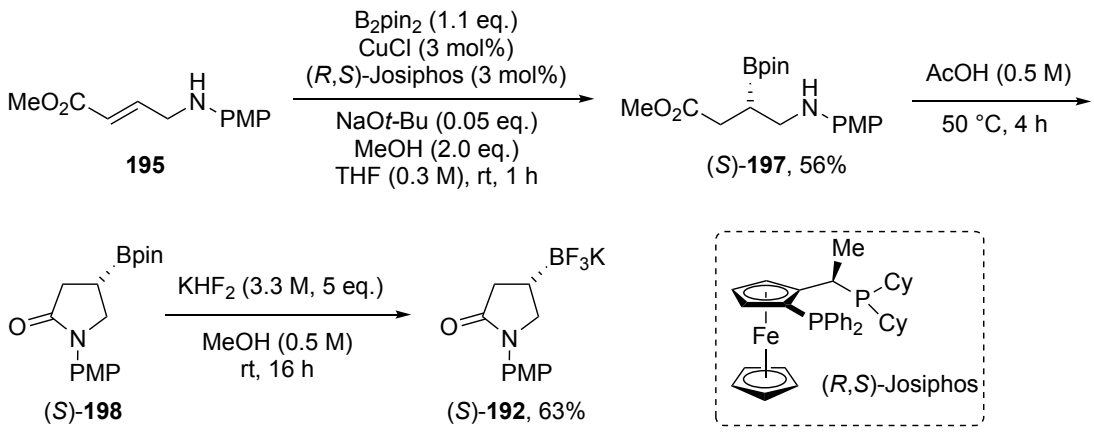
It was clear that neither sets of conditions were transferable directly to 4-BF_3K *N*-PMP piperidone **252**. The SMCC would require more rounds of screening to increase the yield. To facilitate this the BF_3K isolation would need to be improved. Similarly, if this heterocycle were to be investigated further a new shorter synthetic route would be desired. However, the cross-coupling results show that there is potential for this system to be optimised in a similar manner to 4-BF_3K *N*-PMP pyrrolidone **192**, should it be desired.

3.7 Investigation of the Stereochemical Outcome of the Suzuki-Miyaura Cross-Coupling of Enantioenriched 4-BF_3K *N*-PMP Pyrrolidone

3.7.1 Synthesis and Suzuki-Miyaura Cross-Coupling of Enantioenriched 4-BF_3K *N*-PMP Pyrrolidone

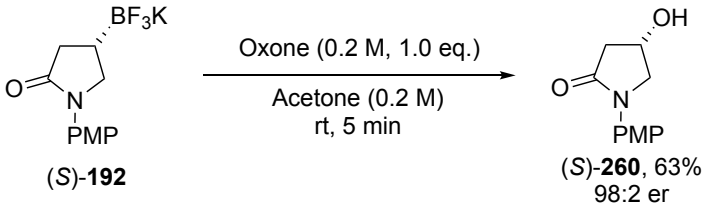
One question relevant to the development of the sp^3-sp^2 cross-coupling reactions discussed in Section 1.3 is stereochemistry. A key concept in this project is transforming pre-defined stereochemistry from substrate to product completely *via* a stereospecific pathway. To this end, 4-BF_3K *N*-PMP pyrrolidone **192** would be used to probe the stereochemical pathway of the SMCC reaction. Partridge *et al*.[59] had adapted known chemistry[134] in the use of (*R*,*S*)-Josiphos as a chiral ligand to induce enantioselectivity during the conjugate addition of B_2pin_2 and this enabled their preparation of enantioenriched (*S*)-4-Bpin *N*-Ph pyrrolidone (95:5 er). We planned to use the same asymmetric methodology to prepare enantioenriched 4-BF_3K *N*-PMP pyrrolidone (*S*)-**192** in high er and then to study the stereochemical outcome of its subsequent SMCC reaction with bromobenzene. Given the well-established sense of induction in the copper-catalysed asymmetric borylation using (*R*,*S*)-Josiphos, it was assumed that use of equivalent conditions in the addition of B_2pin_2 to *N*-PMP amino acrylate **195** would provide the (*S*)-enantiomer, 4-Bpin *N*-PMP amino ester (*S*)-**197**.

To this end, amino acrylate **195**, excess B_2pin_2, CuCl, NaO*t*Bu, MeOH and the chiral ligand (*R*,*S*)-Josiphos were stirred in THF at rt for 1 h. Following work-up and recrystallisation from *n*-hexane, the desired Bpin amino enoate (*S*)-**197** (assumed configuration) was obtained in 56% yield. The er of this compound was not assayed at this stage as the most important aspect for our planned SMCC study was the er of 4-BF_3K *N*-PMP pyrrolidone (*S*)-**192**. Following the standard cyclisation and BF_3K formation procedures used in the racemic route (see Scheme 3.14), 4-BF_3K *N*-PMP pyrrolidone (*S*)-**192** was obtained in 63% yield after purification (Scheme 3.42).



Scheme 3.42

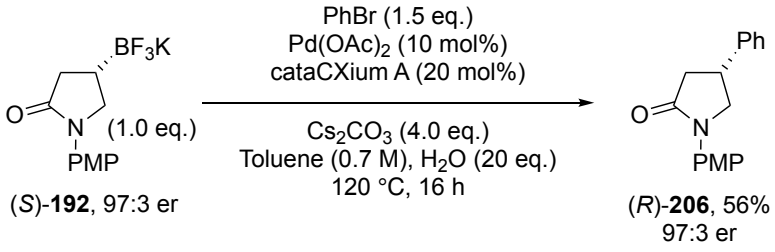
To ascertain the er of 4-BF_3K *N*-PMP pyrrolidone (*S*)-**192**, the plan was to oxidise it to the corresponding 4-hydroxy pyrrolidone (*S*)-**260** and measure its er by CSP-HPLC. Molander *et al.*[135] had reported the use of aqueous oxone solution in acetone for this type of transformation and, crucially, it had been demonstrated that this reaction proceeds with retention of configuration. Thus, 4-BF_3K *N*-PMP pyrrolidone (*S*)-**192** was reacted with an aqueous solution of oxone in acetone at rt for only 5 min. Following work-up and chromatographic separation, 4-hydroxy pyrrolidone (*S*)-**260** was isolated in 63% yield. Using CSP-HPLC, (*S*)-**260** was determined to be 97:3 er (Scheme 3.43).



Scheme 3.43

Finally, we were ready to explore the stereochemical pathway of the SMCC reaction of 4-BF_3K *N*-PMP pyrrolidone (*S*)-**192**. The reaction was carried out with bromobenzene under the optimised SMCC conditions. After chromatography, 4-phenyl *N*-PMP pyrrolidone (*R*)-**206** was obtained in 56% yield and 97:3 er by CSP-HPLC (Scheme 3.44). The (*R*) configuration was determined by comparing the optical rotation, $[\alpha]_D$ +9.8 (*c* 1.0 in $CHCl_3$), with that reported for the (*R*) enantiomer of 95:5 er, $[\alpha]_D$ +9.5 (*c* 1.0 in $CHCl_3$).[104] The optical rotation and CSP-HPLC result indicate

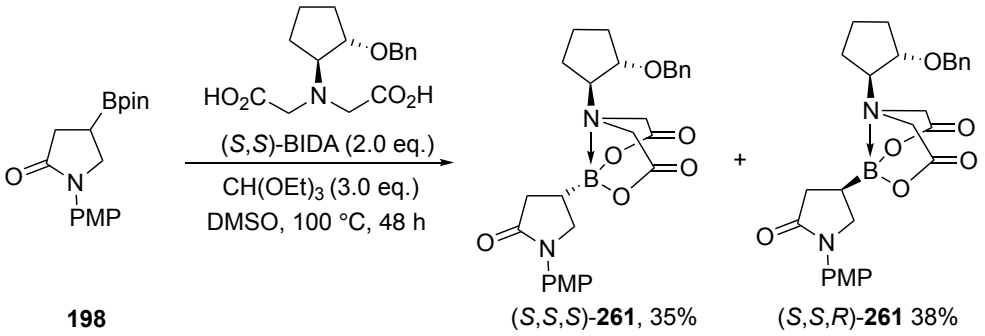
that this SMCC reaction proceeds with retention of configuration and with complete stereospecificity.



Scheme 3.44

In assessing this stereochemical outcome, we were confident in the assignment of the configuration of 4-phenyl *N*-PMP pyrrolidone (*R*)-**206** since it was based on comparison of an $[\alpha]_D$ value with that previously reported, which itself was assigned by comparison with known drug compounds (*R*)-(–)-baclofen and (*R*)-(–)-rolipram.[104] However, the assignment of the configuration of 4-BF_3K *N*-PMP pyrrolidone (*S*)-**192** was based on an assumed (albeit well precedented[59,134]) sense of induction in the asymmetric copper-catalysed B_2pin_2 addition reaction using (*R*,*S*)-Josiphos.

To address the assumption in the configuration of 4-BF_3K *N*-PMP pyrrolidone **192**, we planned to attach a group with defined stereochemistry to 4-Bpin *N*-PMP pyrrolidone **192** which would allow determination of the relative configuration *via* X-ray crystallography. Based on our previous work in the synthesis of enantioenriched tetrahydrothiophene 2-Bpin (*S*)- and (*R*)-**110** (see Scheme 2.26), Burke's chiral MIDA group, BIDA, was chosen. In this case, a batch of (*S*,*S*)-BIDA, which had been prepared by James Firth in the O'Brien group, was used. Thus, racemic 4-Bpin *N*-PMP pyrrolidone **198**, 2 eq. of (*S*,*S*)-BIDA and triethylorthoformate were reacted in DMSO at 100 °C for 48 h. Following work-up and chromatography, BBIDA pyrrolidones (*S*,*S*,*S*)-**261** and (*S*,*S*,*R*)-**261** were obtained in 35% and 38% yield respectively (Scheme 3.45). The identities of BBIDA pyrrolidones (*S*,*S*,*S*)-**261** and (*S*,*S*,*R*)-**261** were confirmed *via* X-ray crystallography of BBIDA pyrrolidone (*S*,*S*,*R*)-**261** (Figure 3.6).



Scheme 3.45

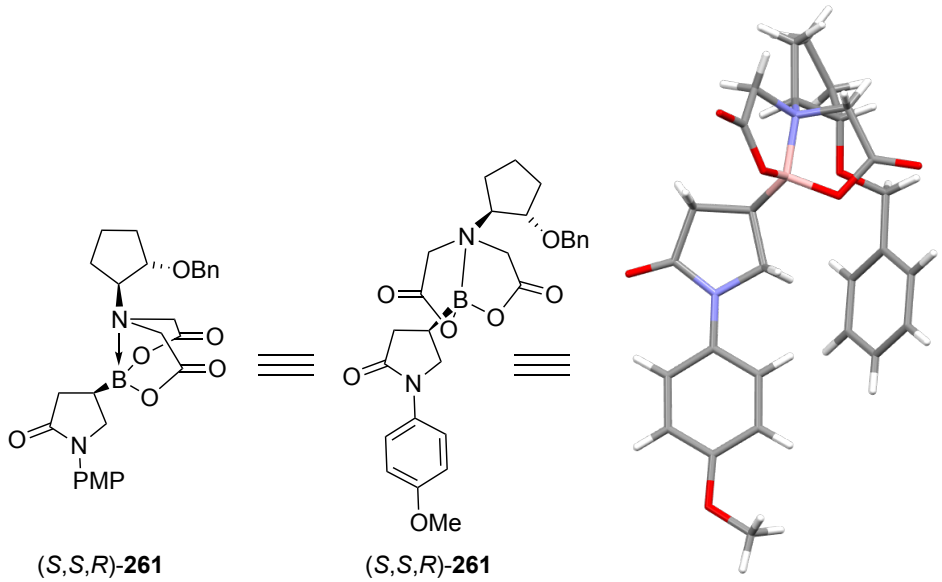
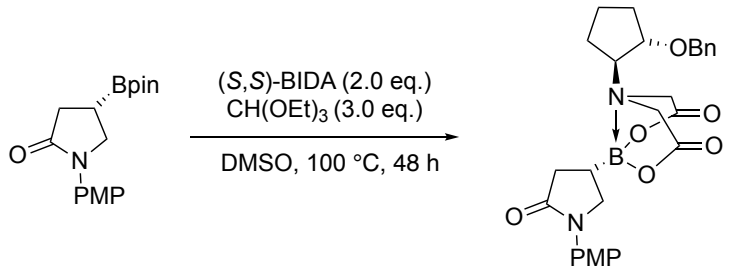


Figure 3.6: X-Ray crystal structure of (*S*,*S*,*R*)-**261**

Then, enantioenriched 4-Bpin *N*-PMP pyrrolidone (*S*)-**198** of 97:3 er (previously assumed configuration) was reacted with (*S*,*S*)-BIDA. With the identity of BIDA pyrrolidone (*S*,*S*,*R*)-**261** known, following purification, comparison of the ^{1}H and ^{13}C NMR spectra indicated that BIDA formation from enantioenriched (*S*)-**198** had yielded BBIDA pyrrolidone (*S*,*S*,*S*)-**261** in 78% yield (Scheme 3.46). This matches the precedent established by Yun and Lee[134] on the asymmetric copper-catalysed B_2pin_2 addition, as well as work reported by Partridge *et al.*[59] Therefore, we had confirmed that the SMCC reaction of 4-BF_3K *N*-PMP pyrrolidone, under our conditions, proceeded with retention of configuration.

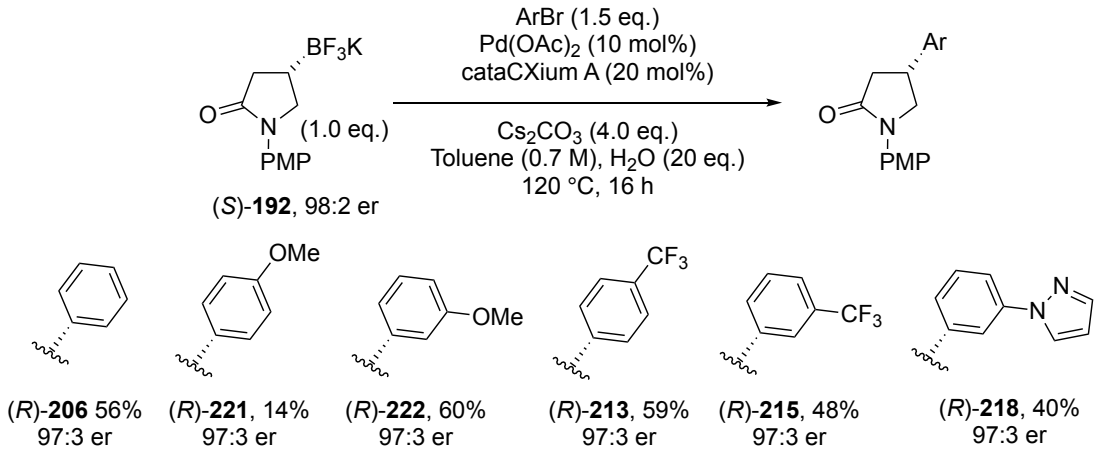


Assumed (*S*)-**198**, 97:3 er (*S*,*S*,*S*)-**261**, 78%

Scheme 3.46

3.7.2 Enantioenriched Scope of the Suzuki-Miyaura Cross-Coupling of 4-BF_3K *N*-PMP Pyrrolidone

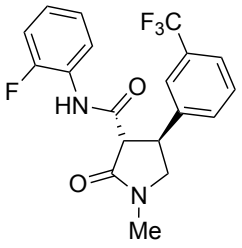
With the configuration of 4-BF_3K *N*-PMP pyrrolidone (*S*)-**192** confirmed, the stereochemical outcome of the SMCC was investigated for any aryl bromide dependent effects. A representative set of aryl bromides were selected for evaluation. The scope is presented in Scheme 3.47. Under the optimised SMCC conditions, reaction of 4-bromoanisole and 3-bromoanisole with 4-BF_3K *N*-PMP pyrrolidone (*S*)-**192** of 97:3 er gave 4-aryl pyrrolidones (*R*)-**221** (97:3 er) and (*R*)-**222** (97:3 er) in 14% and 60% yields respectively. The stereochemical assignment of both (*R*)-**221** and (*R*)-**222** was determined absolutely by comparison to the reported optical rotation values.[109] Gratifyingly, using electron deficient 4- or 3-bromobenzotrifluoride in the SMCC, aryl tetrahydrothiophenes (*R*)-**213** (97:3 er) and (*R*)-**215** (96:4 er) were obtained in 59% and 48% yields respectively. The 40% yield of 4-aryl pyrrolidone (*R*)-**218** of 97:3 er was significant as it demonstrates that heteroaryl-containing aryl bromides also react with retention of configuration in the SMCC. In contrast to the SMCC reactions of 2-Bpin tetrahydrothiophene **110** (see Section 2.7), in the representative set of pyrrolidone examples, complete stereoretention was observed with aryl bromides containing electron withdrawing groups or Lewis basic groups. These results suggest that the stereochemical outcome of the 4-BF_3K *N*-PMP pyrrolidone **192** SMCC was not sensitive to aryl bromide dependent effects.


ArBr (1.5 eq.)
Pd(OAc)2 (10 mol%)
cataCXium A (20 mol%)
Cs2CO3 (4.0 eq.)
Toluene (0.7 M), H2O (20 eq.)
120 °C, 16 h
BF3K
(1.0 eq.)
PMP
Ar
(S)-192, 98:2 er
OMe
CF3
(R)-206 56%
97:3 er
(R)-221, 14%
97:3 er
(R)-222, 60%
97:3 er
(R)-213, 59%
97:3 er
(R)-215, 48%
97:3 er
(R)-218, 40%
97:3 er

Scheme 3.47

3.8 Application of a SMCC Reaction to the Synthesis of Tetflupyrolimet

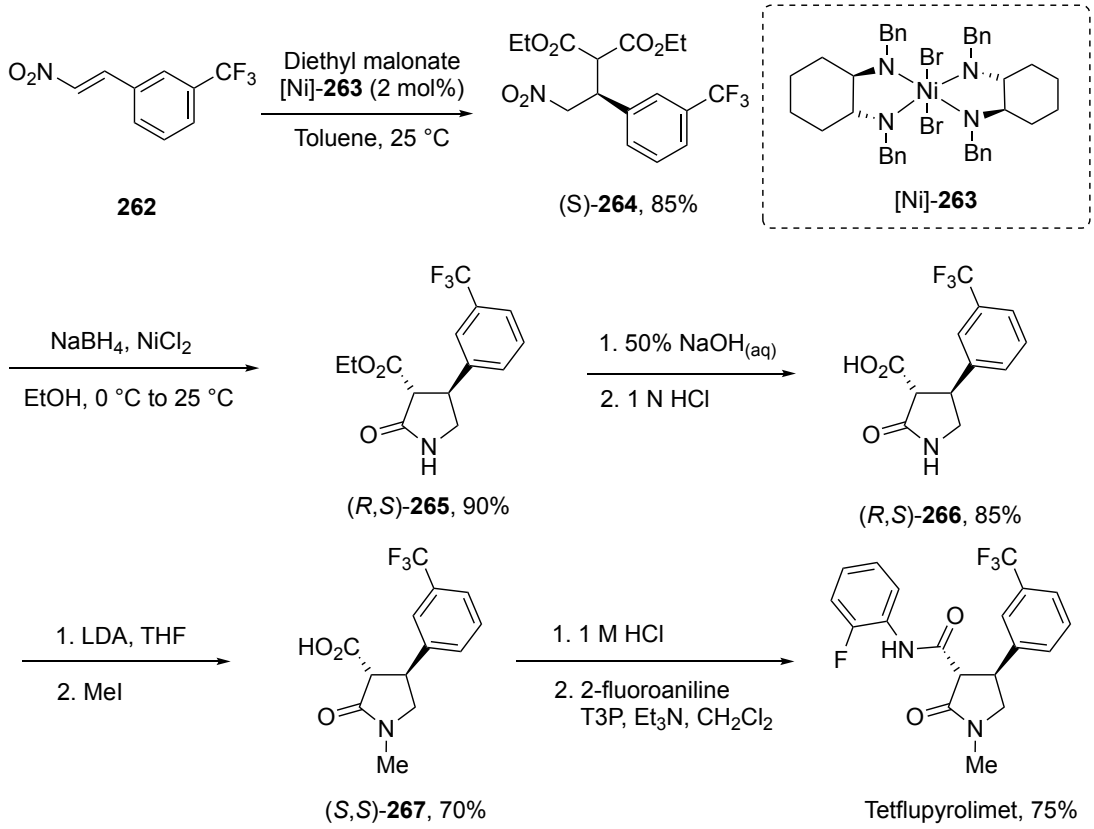
To showcase the practical utility of the sp^3-sp^2 SMCC methodology developed thus far in the chapter, a suitable synthetic target was selected to enable its evaluation in a real-world context. Tetflupyrolimet (brand name Dodhylex^{TM}) (Figure 3.7) is the first herbicide with a new mode of action introduced in over 30 years and currently appears in 188 patents.[97] The development of Tetflupyrolimet started with a high-volume screening approach which identified a 4-phenyl pyrrolidone as the lead compound. To progress the lead compound, a range of enantioenriched 4-aryl 3-anilide pyrrolidone analogues were synthesised, from which Tetflupyrolimet, with (*S*,*S*) configuration, was identified.



Tetflupyrolimet

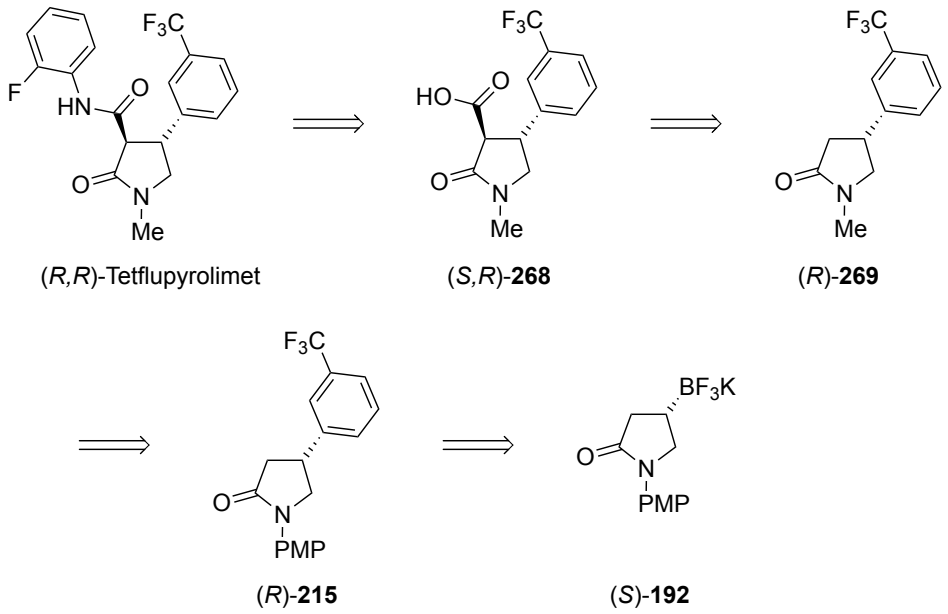
Figure 3.7: Structure of Tetflupyrolimet

The reported asymmetric synthesis of Tetflupyrolimet is summarised in Scheme 3.48. The synthesis started with Ni-catalysed Michael addition of diethylmalonate to nitro styrene **262**, using chiral catalyst **263** and methodology developed by Evans *et al*.,[136] which gave diester (*S*)-**264** in 85% yield. Next, reduction of the nitro group using $NaBH_4/NiCl_2$ formed an amine which cyclised onto one of the esters to give *trans*-pyrrolidone (*R*,*S*)-**265** in 90% yield. Base-mediated ester hydrolysis to *trans*-acid pyrrolidone (*R*,*S*)-**266** proceeded in 85% yield. Deprotonation with LDA and subsequent alkylation using methyl iodide afforded *trans*-acid methyl pyrrolidone (*S*,*S*)-**267** in 70% yield. The change in stereochemical designation (from *R*,*S* to *S*,*S*) was due to a change in chirality-rule substituent priorities which resulted from *N*-alkylation. Finally, amide coupling of acid (*S*,*S*)-**267** and 2-fluoroaniline using T3P gave Tetflupyrolimet in 75% yield with (*S*,*S*) configuration.



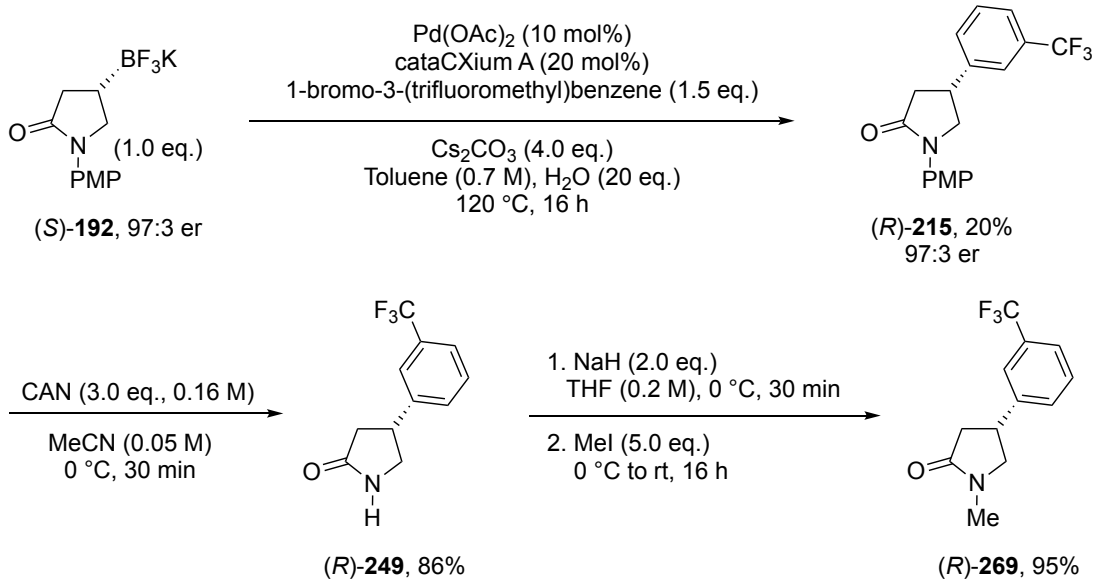
Scheme 3.48

Given that Tetflupyrolimet is a 4-aryl pyrrolidone, it was decided that its synthesis could be used to demonstrate the value of the sp^3-sp^2 disconnection and methodology that we had developed on 4-BF_3K *N*-PMP pyrrolidone **192**. As 4-BF_3K *N*-PMP pyrrolidone (*S*)-**192** had already been synthesised on a large scale, Tetflupyrolimet with (*R,R*) configuration was targeted. Our proposed retrosynthetic analysis is shown in Scheme 3.49. (*R*,*R*)-Tetflupyrolimet would be obtained *via* 4-aryl pyrrolidone acid (*S*,*R*)-**268**, which in turn could be prepared from Claisen condensation of *N*-Me pyrrolidone (*R*)-**269** and methyl chloroformate. *N*-Me Pyrrolidone (*R*)-**269** would be accessed through deprotection and subsequent methylation of 4-aryl *N*-PMP pyrrolidone (*R*)-**215**. Finally, pyrrolidone (*R*)-**215** would be obtained from the SMCC of 4-BF_3K *N*-PMP pyrrolidone (*S*)-**192** with 3-bromobenzotrifluoride.



Scheme 3.49

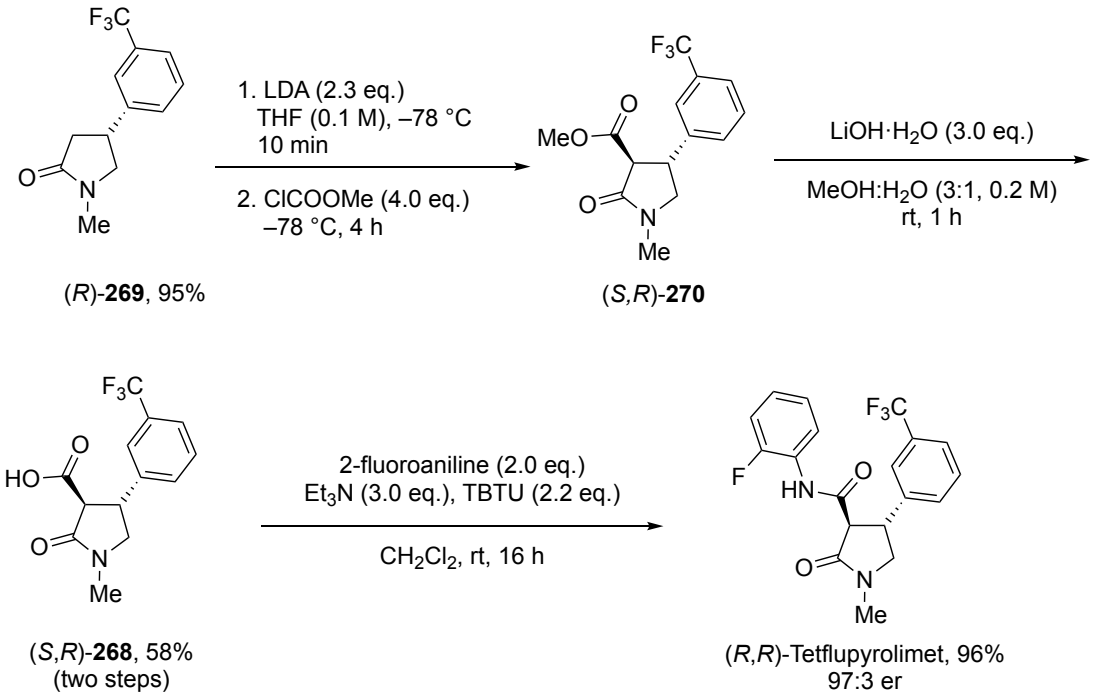
In order to develop our new synthesis of (*R*,*R*)-Tetflupyrolimet, a racemic and asymmetric synthesis were completed. This was to allow any steps to be optimised in the racemic series before completing the reactions with enantioenriched compounds, as well as providing a racemic reference for CSP-HPLC of the final product. The SMCC reaction between 4-BF_3K *N*-PMP pyrrolidone **192** and 1-bromo-3-(trifluoromethyl)benzene had already been carried out three times: small-scale racemic (0.5 mmol, 51% yield, see Scheme 3.25), small-scale enantioenriched (48% yield, see Scheme 3.47) and large-scale racemic (3.37 mmol, 37%, see Scheme 3.32). Frustratingly, the scale-up of the reaction with 4-BF_3K *N*-PMP pyrrolidone (*S*)-**192** was even lower yielding for unknown reasons. Thus, on a 3.37 mmol scale, under the optimised conditions SMCC reaction between 4-BF_3K *N*-PMP pyrrolidone (*S*)-**192** (97:3 er) and 1-bromo-3-(trifluoromethyl)benzene gave 4-aryl pyrrolidone (*R*)-**215** in only 20% yield and 97:3 er (Scheme 3.50). Nevertheless, sufficient material was obtained to proceed with the remainder of the synthesis. CAN deprotection of the lactam in *N*-PMP aryl pyrrolidone (*R*)-**215** proceeded to give 4-aryl *N*-H pyrrolidone (*R*)-**249** in 86% yield. Adapting methodology reported by Ortuño *et al*. for lactam *N*-methylation,[137] subsequent deprotonation with NaH in THF and alkylation using MeI gave 4-aryl *N*-Me pyrrolidone (*R*)-**269** in 95% yield (Scheme 3.50).



Scheme 3.50

To install the ester α to the amide carbonyl, conditions developed for a related 4-alkyl *N*-Boc pyrrolidone were adapted from Hanessian *et al.*[138] Thus, 4-aryl *N*-Me pyrrolidone (*R*)-**269** was treated with LDA at –78 °C to form the corresponding enolate which was acylated *via* addition of methyl chloroformate. Following work-up and purification, 4-aryl pyrrolidone ester (*R*)-**270** was obtained with a minor impurity. Two hypotheses were considered for the impurity (i) enolate formation of pyrrolidone ester (*S*,*R*)-**270** and reaction with methylchloroformate to give the corresponding diester; (ii) formation of the *cis*-diastereomer pyrrolidone ester (*R*,*R*)-**270** via sterically disfavoured acylation on the same face as the aromatic ring. The impurity's identity, however, could not be confirmed. Fortunately, subsequent base-mediated hydrolysis of the impure mixture with excess LiOH gave, after work-up, pure 4-aryl pyrrolidone acid (*S*,*R*)-**268** in 58% yield over these two steps. It was hypothesised that either of base-mediated decarboxylation of the pyrrolidone diester or epimerisation of the disfavoured *cis*-diastereomer pyrrolidone ester (*R*,*R*)-**270** resulted in the high purity of 4-aryl pyrrolidone acid (*S*,*R*)-**268** observed. During the racemic synthesis, 4-aryl pyrrolidone acid *rac*-**270** was obtained in a higher yield of 85% over these two steps. Finally, using conditions from Zhang *et al.*,[139] amide coupling of 4-aryl pyrrolidone acid (*S*,*R*)-**268** and 2-fluoroaniline was carried out using TBTU and (*R,R*)-Tetflupyrolimet was obtained in 96% yield with no diastereomeric impurities. Overall, taking the highest yields obtained for each step of the enantioenriched synthesis, (*R*,*R*)-

Tetflupyrolimet was synthesised in a yield of 21% over six steps. Finally, the er was determined by CSP-HPLC, in comparison to a racemic sample, which showed that (*R,R*)-Tetflupyrolimet had been obtained in 97:3 er. The (*R*,*R*) configuration was further confirmed by comparing the optical rotation, $[\alpha]_D$ –123.9 (*c* 1.0 in $CHCl_3$), with that reported for (*S*,*S*)-Tetflupyrolimet of 99:1 er, $[\alpha]_D$ +22.5 (*c* 0.9 in $CHCl_3$).[139]



Scheme 3.51

The synthesis of (*R*,*R*)-Tetflupyrolimet was successfully carried out using the novel sp^3-sp^2 SMCC methodology developed for 4-BF_3K *N*-PMP pyrrolidone (*S*)-**192**. This demonstrates an orthogonal approach to the synthetic route employed by Selby *et al*.,[97] which is more amenable to delivering a range of diverse 4-aryl Tetflupyrolimet analogues.

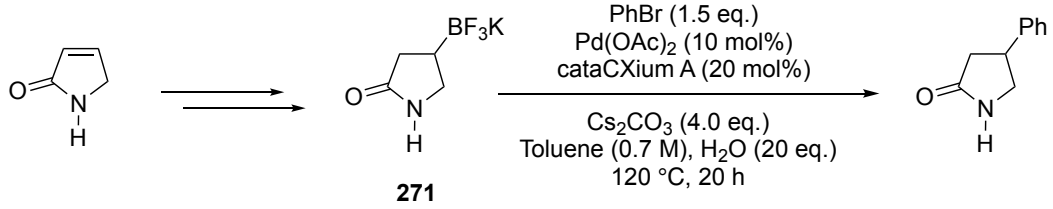
3.9 Conclusions and Future Work

In summary, conditions have been developed for the sp^2-sp^3 SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** with aryl bromides. Synthesis and evaluation of a series of 4-boryl *N*-R pyrrolidones in the SMCC led to the selection of 4-BF_3K *N*-PMP pyrrolidone **192** as the screening candidate. Unfortunately, the DOE screening approach was not successful in this investigation. However, subsequent rounds of OFAT optimisation resulted in an increased yield of 4-phenyl *N*-PMP pyrrolidone **206** from 39% to 50%. The screening revealed that no distinct alteration to the conditions made significant changes to the cross-coupling. For example, throughout screening no better reagent than any of $Pd(OAc)_2$, cataCXium A or Cs_2CO_3 (in toluene) were identified. The results suggest that micro adjustments to these "general conditions" result in increased cross-coupling yield of **206**, rather than, for example, the discovery of a better ligand or base. Increasing the reaction concentration to 0.7 M appeared to be a key modification. The reaction was also shown to be tolerant to small modulations in water content as well as tolerating the use of a 1:1 ratio of bromobenzene : BF_3K **192**.

The final optimised conditions for the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** used 10 mol% $Pd(OAc)_2$ with 20 mol% cataCXium A alongside 4.0 eq. of Cs_2CO_3 and an excess of 1.5 eq. of aryl bromide with 20 eq. of water and the reaction was heated in toluene at 120 °C for 20 h With these conditions, a diverse range of 4-aryl pyrrolidones was synthesised in 18-80% yields including successful cross-coupling of several heteroaryl halides. In the case of three aryl pyrrolidones (**223**, **225** and **228**), the presence of regioisomers was detected, highlighting that the nature of the aryl bromide can affect the relative rates of β-hydride elimination and reductive elimination. The cumulative yields of the 3- 4- and 5-aryl pyrrolidones highlights a very efficient cross-coupling reaction in several cases. Deprotection of the lactam in 4-aryl *N*-PMP pyrrolidones with CAN was evaluated with a select deprotection scope of five examples and yields of 56-74% were obtained. The optimised SMCC conditions were applied to 4-BF_3K *N*-PMP piperidone **252**. Unfortunately, the conditions were not directly transferable and only minimal conversion to product was observed.

The utility of the reaction was further demonstrated with the SMCC of enantioenriched 4-BF_3K *N*-PMP pyrrolidone (*S*)-**192**. Through generation of an enantioenriched aryl pyrrolidone scope of 6 examples, complete stereoretention was observed with no aryl halide effects on the stereochemical outcome. Applying the methodology to an agrochemical target, (*R*,*R*)-Tetflupyrolimet was synthesised in an overall yield of 21% over six steps. The application highlighted how the methodology could be efficiently employed to synthesise a range 4-aryl pyrrolidone analogues for testing in future investigations.

This work opens several directions for further development. Although there are many significant benefits to the methodology, which have been discussed throughout the chapter, the requirement for a nitrogen protecting group is a limitation. This was exemplified in the synthesis of (*R*,*R*)-Tetflupyrolimet which utilised deprotection and methylation following cross-coupling. Therefore, the synthesis of 4-BF_3K *N*-H pyrrolidone **271** could be explored, as well as its capability in the SMCC. 4-BF_3K *N*-H pyrrolidone **271** could be synthesised from the corresponding α,β-unsaturated pyrrolidone *via* conjugate addition of B_2pin_2 and subsequent BF_3K formation (Scheme 3.52). Evaluation of its ability in the cross-coupling with bromobenzene under optimised conditions could then be undertaken.

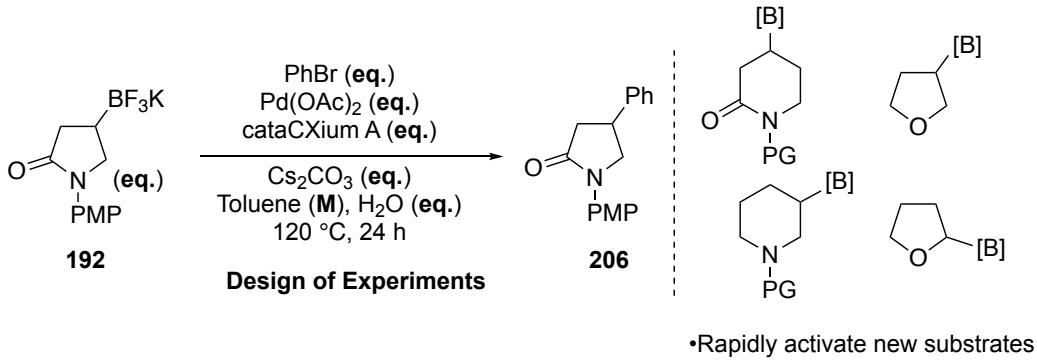


Scheme 3.52

Furthermore, the full of series of 4-BF_3K *N*-*p*-tolyl, -Bn and -PMB pyrrolidones **65**, **193** and **194** could be evaluated in the SMCC with bromobenzene under the optimised conditions. These BF_3K salts have already been synthesised or have synthetic methods that are already developed. Therefore, it would be a relatively straightforward way to expand the utility of the methodology.

Unfortunately, the DOE strategy was not successful in this study. Nevertheless, 4-BF_3K *N*-PMP pyrrolidone **192** remains a valuable case study for exploring a DOE strategy to investigate the sp^3-sp^2 SMCC of heterocyclic boronates. During OFAT optimisation, it was exceedingly difficult to find which parameters genuinely influenced the yield in any way, positive or negative. This could be achieved using the statistical analysis that comes with a DOE investigation.

Comparing the final optimised conditions for 4-BF_3K *N*-PMP pyrrolidone **192** to those used for 2-Bpin tetrahydrothiophene **110** or 2-Bpin pyrrolidine **123**, show that they are similar and only subtly different. Therefore, using 4-BF_3K *N*-PMP pyrrolidone **192** to develop the DOE set-up would allow us to rapidly activate new and similar heterocyclic boronates by using an optimised DOE screening approach. This approach would initially maintain the overall conditions such as $Pd(OAc)_2$, cataCXium A, Cs_2CO_3, toluene/water solvent system and investigate which of these factors (conditions) influence the yield of cross-coupled product. If the same factors were found to influence the yield in multiple different heterocyclic systems then a highly efficient and targeted optimisation would rapidly activate structurally similar heterocyclic boronates in the SMCC (Scheme 3.53). Furthermore, with multiple systems now operational, they could be used to validate the optimised DOE screening approach.



Scheme 3.53

Chapter: 4 Suzuki-Miyaura Cross-Couplings of 3-Boryl Pyrrolidines

4.1 Introduction

4.1.1 3-Aryl Pyrrolidines in Drug Discovery and Agrochemistry

Pyrrolidines represent privileged structures in drug discovery and 3-aryl pyrrolidines are prevalent in this regard. There are many drug candidates possessing the 3-aryl pyrrolidine motif currently or previously enrolled in clinical trials at various stages; a selection is shown in Figure 4.1.

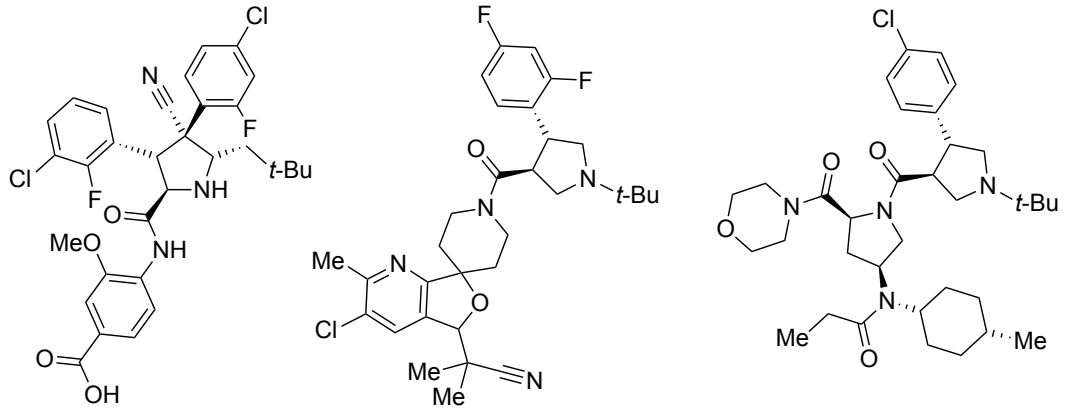
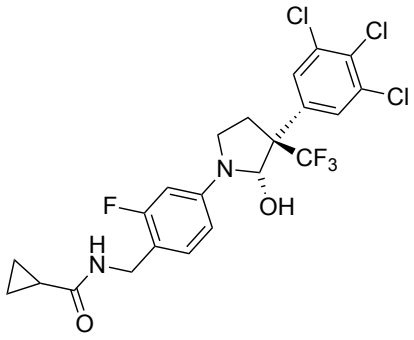


Figure 4.1: Structures of 3-aryl pyrrolidines in or previously enrolled in clinical trials

Idasanutlin is a second generation, orally available 3-aryl pyrrolidine which acts as a potent and selective MDM2 antagonist, designed to reactivate p53 tumour-suppressor signalling. Importantly, idasanutlin progressed into a Phase III study for relapsed or refractory acute myeloid leukemia.[140] Despite promising patient response rates, Roche halted further development. Similarly, Merck investigated a series of 3-aryl pyrrolidine melanocortin-4 receptor (MC4R) agonists for obesity and sexual dysfunction which led to their lead candidate MK-0493. Unfortunately, progression was halted after Phase II clinical trials as MK-0493 failed to significantly reduce body weight.[141] Recently, Bivamelagon was also investigated as a MC4R agonist.[142] Following positive Phase II results for hypothalamic obesity, Rhythm Pharmaceuticals are currently planning for Phase III evaluation. The plethora of late phase clinical trials

with 3-aryl pyrrolidine containing drug candidates demonstrates both their importance and relevance to drug discovery.

Alongside drug discovery, 3-aryl pyrrolidines have emerged as valuable scaffolds in agrochemical discovery, particularly as insecticidal and acaricidal agents. For example, 3-aryl pyrrolidine **272** has been repeatedly highlighted in recent patents for the control of animal pests including insects and mites (Figure 4.2).[143] 3-Aryl pyrrolidine **272** is the subject of extensive follow-on filings, particularly in mixture patents where it is combined with other pesticidal actives to achieve synergistic crop protection effects. This reflects sustained industrial interest and late-stage development, highlighting the privileged nature of the 3-aryl pyrrolidine scaffold.



272

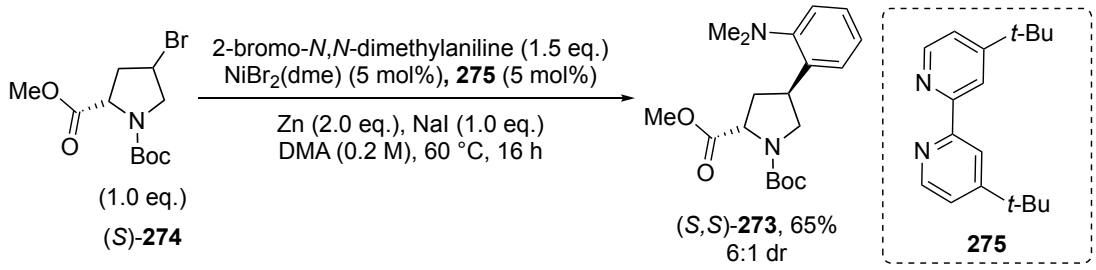
Figure 4.2: Structure of 3-aryl pyrrolidine **272** involved in agrochemical discovery

4.1.2 Selected Overview of Synthetic Routes to 3-Aryl Pyrrolidines

Given the importance of the 3-aryl pyrrolidine motif in drug and agrochemical discovery, it is not surprising that a wide range of routes have been developed for their synthesis. In this section, selected methods for the synthesis of 3-aryl pyrrolidine are presented, focusing on direct arylation of the pyrrolidine ring (functionalisation at the 3-position in different ways) rather than synthesis from acyclic precursors.

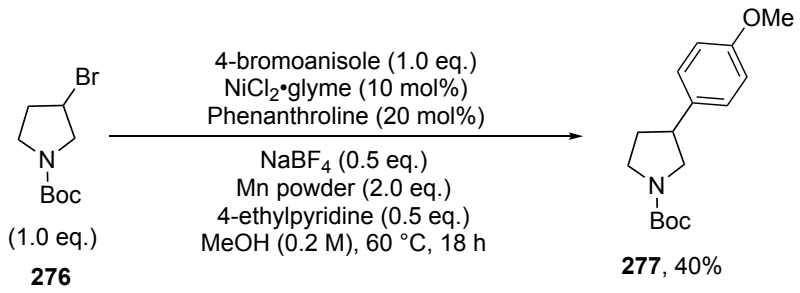
Weix *et al*. have published several reports on nickel-catalysed reductive cross-electrophile coupling of aryl halides with alkyl halides.[144–147] Using this approach, the synthesis of 3-aryl pyrrolidine (*S*,*S*)-**273** was recently reported (Scheme 4.1).[148] Two sets of conditions were developed using either cobalt or nickel as the catalyst; 3-aryl pyrrolidine (*S*,*S*)-**273** was synthesised using nickel catalytic conditions. Using

pyrrolidine ester (*S*)-**274**, 2-bromo-*N*,*N*-dimethylaniline, $NiBr_2$(dme), dtbbpy **275**, zinc and NaI in DMA at 60 °C for 16 h gave 3-aryl pyrrolidine (*S*,*S*)-**273** in 65% yield (6:1 dr). The methodology allows formation of sterically hindered sp^3-sp^2 bonds that are typically challenging to access with relatively mild conditions. The complementary choice of nickel or cobalt depending on structural features of the aryl halide further expands the utility of the reaction. However, the requirement for additional reductant in the form of zinc or manganese reduces the overall atom economy of the reaction. It is worth noting that Weix *et al*. also reported the synthesis of 3-aryl pyrrolidines using a related palladium and nickel reductive electrochemical approach.[149]



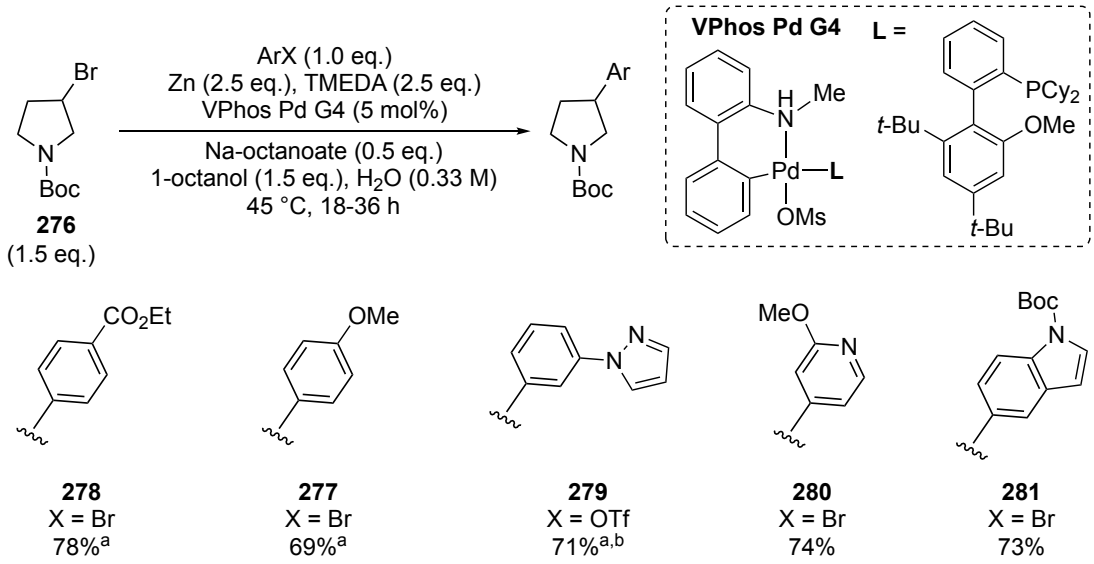
Scheme 4.1

The nickel catalysed cross-electrophile coupling of aryl halides with alkyl halides has also been utilised by Molander *et al*. on a range of saturated heterocyclic bromides,[150] including one example of arylation with 3-bromopyrrolidine **276**.[151] Reaction of 3-bromopyrrolidine **276**, 4-bromoanisole, $NiCl_2$•glyme, phenanthroline, $NaBF_4$, manganese powder and 4-ethylpyridine in methanol at 60 °C for 18 h gave 3-aryl pyrrolidine **277** in 40% yield (Scheme 4.2). The methodology supports a wide range of saturated heterocyclic bromides showing good functional group tolerance. However, there was only one reported example on a 3-substituted pyrrolidine in moderate yield.



Scheme 4.2

A series of 3-aryl pyrrolidines was synthesised by Buchwald *et al*. during the continued development of Lipshutz–Negishi reactions for the cross-coupling of alkyl bromides with aryl electrophiles.[152] The work was initially pioneered by Lipshutz *et al*. who developed the Negishi reactions in aqueous conditions with additional surfactant to generate micellular reaction conditions.[153] An advantage over the traditional Negishi cross-coupling methodology is the *in situ* generation of the organozinc intermediate which circumvents practical issues with the limited bench-top stability of organozincs. The reaction conditions were 3-bromopyrrolidine **276**, aryl halide, zinc, TMEDA, VPhos Pd G4 and sodium octanoate in a 1-octanol and water solvent system at 45 °C for 18-36 h. Under these conditions, an aryl halide scope of eight 3-aryl pyrrolidines was demonstrated in 67-78% yields; a representative set are shown in Scheme 4.3. Aryl bromides bearing electron-withdrawing substituents worked well, with 3-aryl pyrrolidine **278** obtained in 78% yield. Similarly, aryl bromides bearing electron-donating substituents were also well tolerated with 3-aryl pyrrolidine **277** formed in 69% yield. The system also presented very good tolerance to heterocyclic aryl halides such as 2-methoxy-4-bromopyridine which gave 3-aryl pyrrolidine **280** in 74% yield. Overall, this methodology represents an efficient, highly tolerant and mild cross-coupling approach for the synthesis of sp^3-sp^2 carbon-carbon bonds.

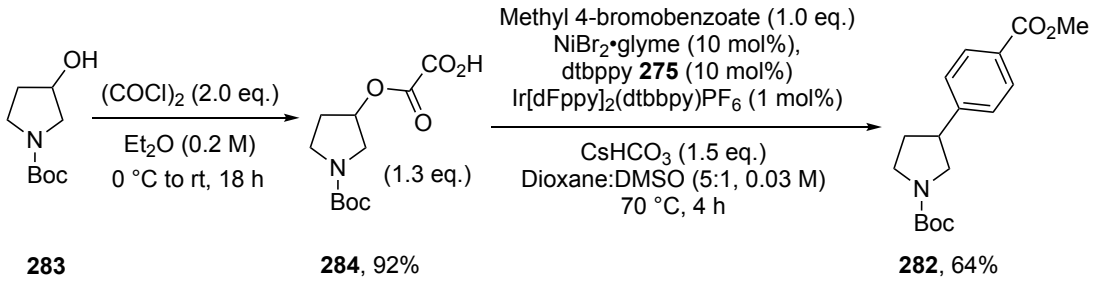


[a] Methyl octanoate (1.0 mmol) instead of 1-octanol [b] 55 °C instead of 45 °C

Scheme 4.3

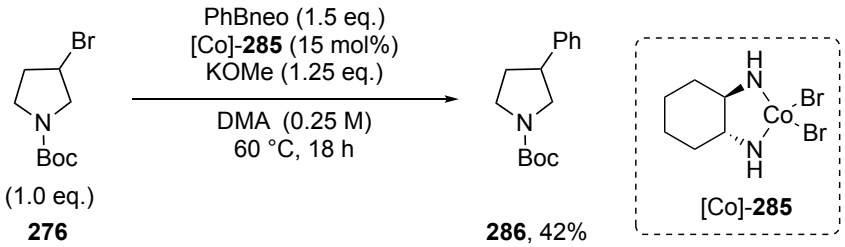
The synthesis of 3-aryl pyrrolidines using photoredox iridium-nickel dual catalysed cross-coupling has been demonstrated by Jiang and Liu *et al.* using an alkyl Bpin,[154] Hartwig *et al.,*[155] using methodology developed by Molander *et al.*[103] with an alkyl BF_3K salt, and Macmillan and coworkers using an oxalate.[156] Photoredox methodology represents a powerful approach for the synthesis of compounds containing sp^3-sp^2 carbon-carbon bonds. As a representative example of this type of approach, the synthesis of 3-aryl pyrrolidine **282** using MacMillan's oxalate strategy is shown in Scheme 4.4. The oxalates are derived from commercially available alcohols in a single step without purification. This was the key design feature of their methodology due to the plethora of commercially available saturated heterocyclic alcohols. Thus, 3-OH pyrrolidine **283** was first converted into 3-oxalate pyrrolidine **284** using oxalyl chloride in 92% yield. Then, an excess of 3-oxalate pyrrolidine **284** was subjected to photoredox cross-coupling with methyl 4-bromobenzoate, $NiBr_2$•glyme, dtbppy **275**, $Ir[dFppy]_2(dtbbpy)PF_6$ and $CsHCO_3$ in dioxane and DMSO at 70 °C for 4 h. Under these conditions, 3-aryl pyrrolidine **282** was obtained in 64% yield (Scheme 4.4). The methodology demonstrates a relatively mild and functional group tolerant way to access 3-aryl pyrrolidines, although the specific aryl bromide scope on 3-OH pyrrolidines was not described. Additionally, the methodology is further limited by its use of expensive iridium catalyst. Furthermore, the low atom

economy of photoredox reactions in general is highlighted in purification of the cross-coupled products which can be challenging due to the large number of components used in the reaction. Nevertheless, the photoredox methodology is still a valuable and efficient method for producing racemic 3-aryl pyrrolidines.



Scheme 4.4

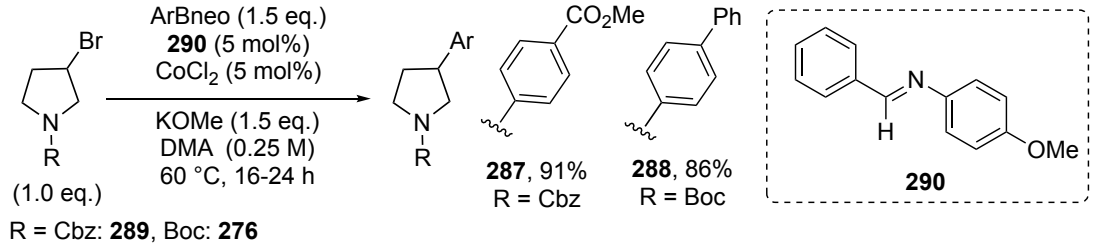
Chirik *et al*. have reported the synthesis of 3-aryl pyrrolidines using cobalt-[157,158] and iron- catalysed Suzuki-Miyaura cross-coupling reactions.[159] Alongside environmental and financial benefits of the methodology, Chirik *et al.* propose that the use of first row transition metals can mitigate observed challenges with competing β-hydride elimination from alkyl-Pd intermediates. In an example with cobalt catalysis, 3-bromopyrrolidine **276** was reacted with an excess of Bneo-benzene in the presence of cobalt complex **285** and KOMe in DMA at 60°C for 18 h. Under these conditions, 3-phenyl pyrrolidine **286** was isolated in 42% yield (Scheme 4.5).



Scheme 4.5

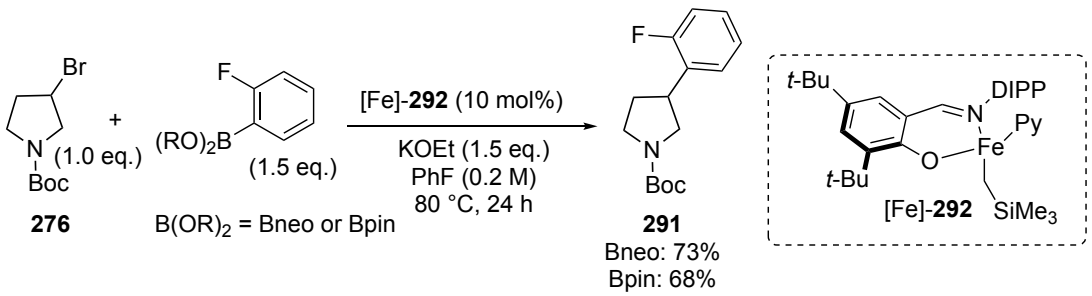
The high loading (15 mol%) of cobalt complex **285** was considered undesirable and a subsequent report detailed modified methodology replacing the diamine-type ligand with a phenoxy(imine)-type ligand. Under modified conditions, 3-aryl *N*-R pyrrolidines **287** and **288** were synthesised (Scheme 4.6). For example, using 3-bromo *N*-Cbz pyrrolidine **289**, methyl 4-Bneo-benzoate, phenoxy(imine) **290**, $CoCl_2$ and

KOMe in DMA at 60 °C for 16-24 h gave 3-aryl *N*-Cbz pyrrolidine **287** in 91% yield. This is a remarkably high yield for a sp^3-sp^2 cross-coupling of a saturated *N*-heterocycle using only 5 mol% catalyst. Under similar conditions using 3-bromo *N*-Boc pyrrolidine **276** with 4-Bneo-biphenyl gave 3-aryl *N*-Boc pyrrolidine **288** in 86% yield. Although only two examples with 3-bromopyrrolidines are described, there are numerous examples of cross-coupling with different saturated heterocyclic halides demonstrating the versatility of the methodology.



Scheme 4.6

Finally, Chirik *et al*. carried out the synthesis of 3-aryl pyrrolidine **291** using a four-coordinate phenoxy(imine) iron catalytic system **292** *via* a similar type of SMCC reaction. The methodology employed 3-bromopyrrolidine **276**, 2-Bneo-fluorobenzene or 2-Bpin-fluorobenzene, iron catalyst **292** and KOEt in fluorobenzene at 80 °C for 24 h. Under these conditions using 2-Bneo-fluorobenzene, 3-aryl pyrrolidine **291** was obtained in 73% yield (Scheme 4.7). When 2-Bpin-fluorobenzene was used, a similar yield of **291** of 68% was obtained. The general SMCC methodology developed by Chirik with cobalt and iron catalysts delivers high yielding examples. However, for the synthesis of 3-aryl pyrrolidines, both the cobalt- and iron-based approaches require broader evaluation of aryl boronic ester scope to fully establish their tolerance and limitations. Although the methodology shows high potential, until the compatibility of heteroaryl boronic esters is demonstrated, widespread adoption could remain limited.

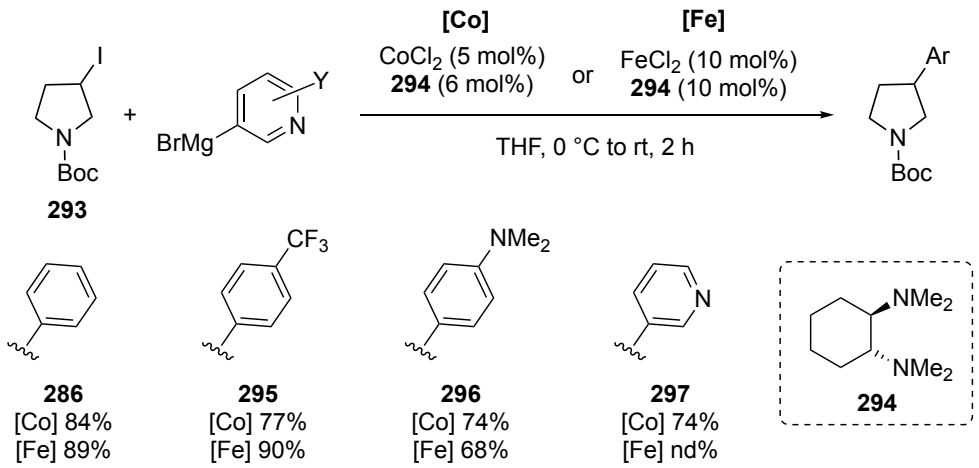


276 B(OR)$_2$ = Bneo or Bpin

291
Bneo: 73%
Bpin: 68%

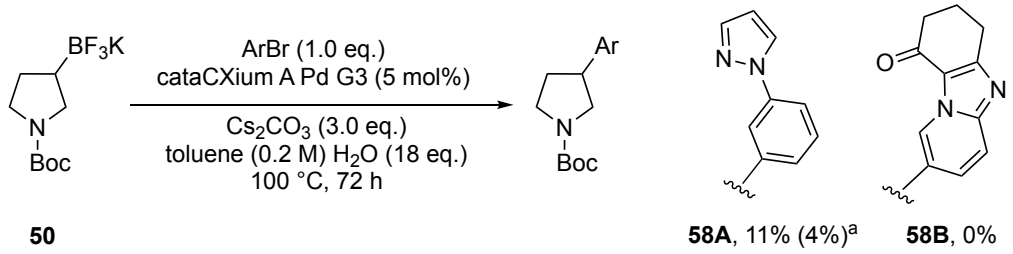
Scheme 4.7

Iron and cobalt catalysts were also utilised by Cossy *et al*. for the preparation of 3-aryl of pyrrolidines using Grignard reagents.[160] 3-Iodopyrrolidine **293** and freshly prepared aryl Grignard reagents were reacted with either $CoCl_2$ (5 mol%) and diamine **294** (6 mol%) or $FeCl_2$ (10 mol%) and diamine **294** (10 mol%) in THF at 0 °C to rt for 2 h. Under these conditions, eight aryl pyrrolidines were synthesised using both sets of catalytic conditions and a selection are shown in Scheme 4.8. For example, using (4-(trifluoromethyl)phenyl)magnesium bromide under cobalt catalytic conditions, a 77% yield of 3-aryl pyrrolidine **295** was obtained; using iron catalysis, a 90% yield of **295** was obtained. Both catalytic systems demonstrated tolerance to electron-poor Grignards. Similarly, electron-rich (4-(dimethylamino)phenyl)magnesium bromide worked well, with yields of 74% and 68% of **296** obtained using cobalt and iron catalysts respectively. Finally, pyridin-2-ylmagnesium bromide was successfully reacted to give 3-aryl pyrrolidine **297** in 74% yield under cobalt catalysis. This methodology demonstrates good tolerance to a range of steric and electronically diverse aryl Grignard reagents. However, the reactivity of the Grignard reagent may be an issue for molecules bearing incompatible functionality such as acidic protons or significantly electrophilic centres.



Scheme 4.8

Finally, there is one example of a palladium catalysed SMCC reaction with 3-BF_3K pyrrolidine **50** that was reported by Dombrowski, Gesmundo *et al*.[16] at AbbVie which was also discussed in Section 1.4 (see Scheme 1.15). The results of 3-BF_3K pyrrolidine **50** with their two selected aryl halides are shown in Scheme 4.9. The reaction conditions were an excess of BF_3K salt **50**, ArBr, cataCXium A Pd G3 and Cs_2CO_3 in toluene with water at 100 °C for 72 h. Under these conditions with 1-(3-bromophenyl)-1*H*-pyrazole, 3-aryl pyrrolidine **58A** was obtained in 11% HPLC yield and 4% isolated yield. However, when the more complex imidazole containing aryl bromide was used in the cross-coupling, no conversion to 3-aryl pyrrolidine **58B** was observed.

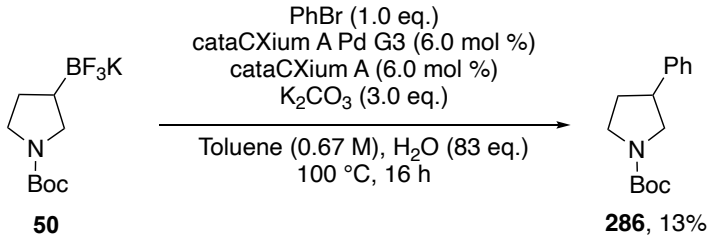


[a] Yield after chromatography given in brackets

Scheme 4.9

As a final example, a preliminary study on the SMCC of 3-BF_3K pyrrolidine **50** with bromobenzene was carried out by James Donald in the O'Brien group. In this case, reaction conditions were 6 mol% cataCXium A Pd G3 (with additional cataCXium A) and K_2CO_3 in toluene (0.67 M) with water (83 eq.) at 100 °C for 16 h. This gave 3-

phenyl pyrrolidine **286** 13% yield (Scheme 4.10). The isolation of 3-phenyl pyrrolidine **286** under similar conditions in an analogous yield to that reported by Dombrowski, Gesmundo *et al*., validated the initial hit with 3-BF_3K pyrrolidine **50**.



Scheme 4.10

In summary, although several methods have been reported for the synthesis of 3-aryl pyrrolidines, no high yielding palladium-catalysed sp^3-sp^2 SMCC methodology has been developed for this transformation. Dombrowski, Gesmundo *et al*. at AbbVie reported an initial hit using a palladium-catalysed SMCC (with cataXCium A as ligand), but did not pursue further optimisation.[16] In the O'Brien group, this hit was validated and this therefore presented an opportunity to apply our growing understanding of sp^3-sp^2 SMCC to the cross-coupling of 3-BF_3K pyrrolidine **50**.

4.2 Proposed Objectives

Following the very preliminary, initial investigation of the SMCC reaction with 3-BF_3K pyrrolidine **50** carried out by James Donald in the group, the work described in this chapter had three initial objectives.

First, we aimed to use a DOE screening approach to rapidly optimise the SMCC of 3-BF_3K pyrrolidine **50** with bromobenzene. Optimisation would use the common features of the conditions identified on related systems, namely 2-Bpin pyrrolidine **123** and 4-BF_3K *N*-PMP pyrrolidone **192**, such as a $Pd(OAc)_2$ and cataCXium A catalytic system, Cs_2CO_3 as base and a toluene/water solvent system. We were interested in the following primary factors: ratio of BF_3K salt **50** : PhBr, ratio of cataCXium A : $Pd(OAc)_2$, eq. of water, eq. of base and concentration of toluene. It was hoped that by subtle modification of these factors the cross-coupling could be efficiently enabled. Equally, it was hoped that this would serve as a case study proving the effectiveness of a highly designed screening criteria for the optimisation of similar saturated heterocyclic boronates in SMCC reactions.

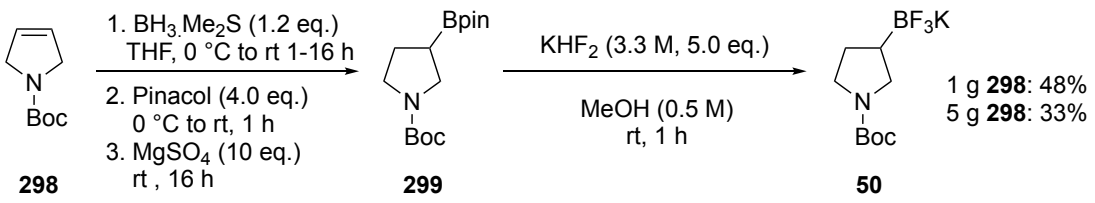
Second, following identification of appropriate SMCC conditions, a scope of aryl halides for the SMCC of racemic 3-aryl pyrrolidines would be developed. This would include structurally diverse aryl halides to probe the sensitivities of the SMCC of 3-BF_3K pyrrolidine **50**.

Third, if time permitted, the stereochemical outcome of the SMCC of enantioenriched 3-BF_3K pyrrolidine **50** with bromobenzene would be explored to determine if it proceeded with inversion or retention.

4.3 Initial Investigations into the Suzuki-Miyaura Cross-Coupling of 3-BF_3K *N*-Boc Pyrrolidine

4.3.1 Synthesis of 3-BF_3K *N*-Boc Pyrrolidine

Based on borylation work from Thomas *et al*.,[161] a two-step synthetic route to 3-BF_3K pyrrolidine **50** was carried out starting from *N*-Boc 3-pyrroline **298** (Scheme 4.11). Initial hydroboration using BH_3•THF resulted in incomplete consumption of *N*-Boc 3-pyrroline **298**. Therefore, the conditions were modified to use BH_3•Me_2S. Hydroboration of *N*-Boc 3-pyrroline **298** (1 g scale) with BH_3•Me_2S initially at 0 °C and then at rt for 1 h gave complete consumption of **298**. The organoboron intermediate was then converted into the pinacol ester using pinacol and $MgSO_4$. Following work-up, crude Bpin **299** was telescoped through to the next step without further purification. Conversion into 3-BF_3K pyrrolidine **50** (48% yield) was achieved using excess $KHF_{2(aq)}$ in methanol at rt for 24 h. Unfortunately, when the scale of the reaction was increased to 5 g of *N*-Boc 3-pyrroline **298**, a lower yield of 33% was achieved. Nevertheless, this gave enough material to facilitate investigation into the SMCC of 3-BF_3K pyrrolidine **50**, thus further optimisation was not explored.

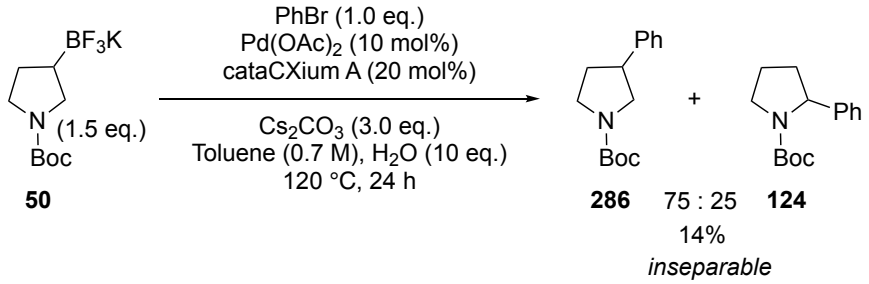


Scheme 4.11

4.3.2 Initial Suzuki-Miyaura Cross-Coupling of 3-BF_3K *N*-Boc Pyrrolidine

With access to 3-BF_3K pyrrolidine **50** established, SMCC with bromobenzene could now be investigated. Rather than simply repeating the initial result from James Donald in the O'Brien group (see Scheme 4.10), we decided to investigate the SMCC using the optimised conditions from 2-Bpin pyrrolidine **123** (see Scheme 2.6). Based on the relative similarity of the two molecules, it was hoped that there might be transferability of these conditions. Thus, on a 0.3 mmol scale, 3-BF_3K *N*-Boc pyrrolidine **50** was reacted with bromobenzene using 10 mol% $Pd(OAc)_2$, 20 mol% cataCXium A and 3.0 eq. of Cs_2CO_3 in toluene (0.7 M) with 10 eq. of water at 120 °C for 24 h (sealed vial

under N_2). After chromatography, a 14% yield of product was obtained. Upon careful analysis of the ^1H and ^{13}C NMR spectra of the product, it was found, to our surprise, that a 75:25 inseparable mixture of 3-phenyl pyrrolidine **286** and 2-phenyl pyrrolidine **128** (14% total yield) had been generated from this reaction (Scheme 4.12).



Scheme 4.12

The presence of 2-phenyl pyrrolidine **124** was confirmed by ^1H NMR spectroscopy. The signal for the C-H next to both nitrogen and the phenyl group in 2-phenyl pyrrolidine **124** is a characteristic set of two rotameric multiplets appearing as broad singlets (70:30 ratio of rotamers). The electron withdrawing effect of both the *N*-Boc nitrogen and the phenyl group places the signal downfield (~4.7-5.0 ppm) away from the NCH signals (3.0-4.0 ppm). This can be seen clearly in Figure 4.3 Part of the ^1H NMR spectrum of 3-phenyl pyrrolidine **286** is shown in Figure 4.3(a). Figure 4.3(b) shows the same region of the ^1H NMR spectrum of 2-phenyl pyrrolidine **124** with the characteristic pair of rotameric multiplets labelled H^a. The 75:25 mixture of 3-phenyl pyrrolidine **286** and 2-phenyl pyrrolidine **124** from the SMCC reaction is shown in Figure 4.3(c), note that the high intensity peak at 3.75 corresponds to the OMe peak of internal standard 1,3,5-trimethoxybenzene. Comparison of the overlapped spectra clearly confirms the identity of the two compounds.

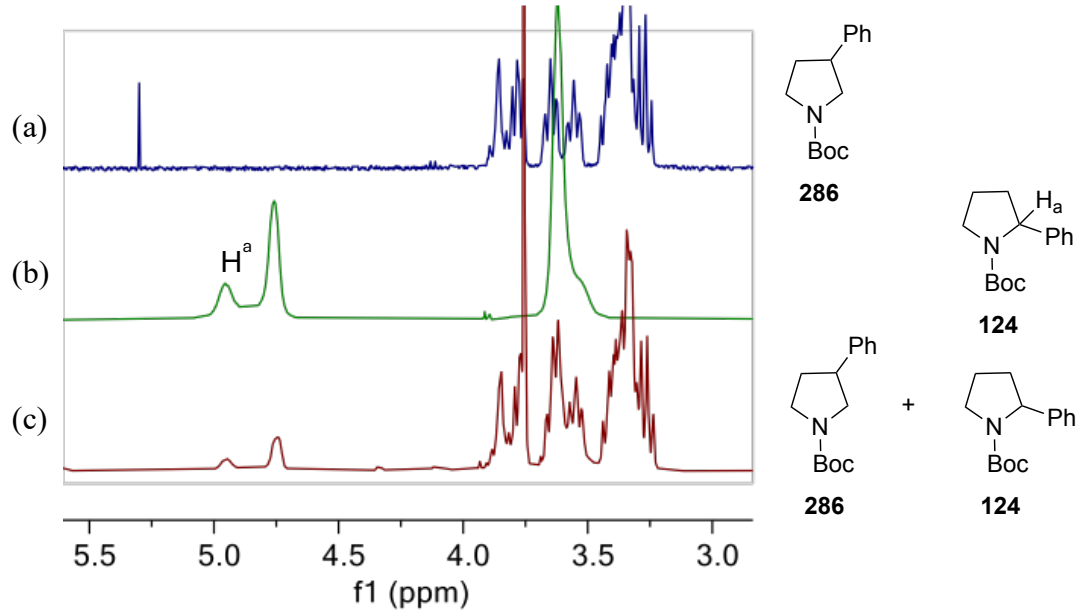
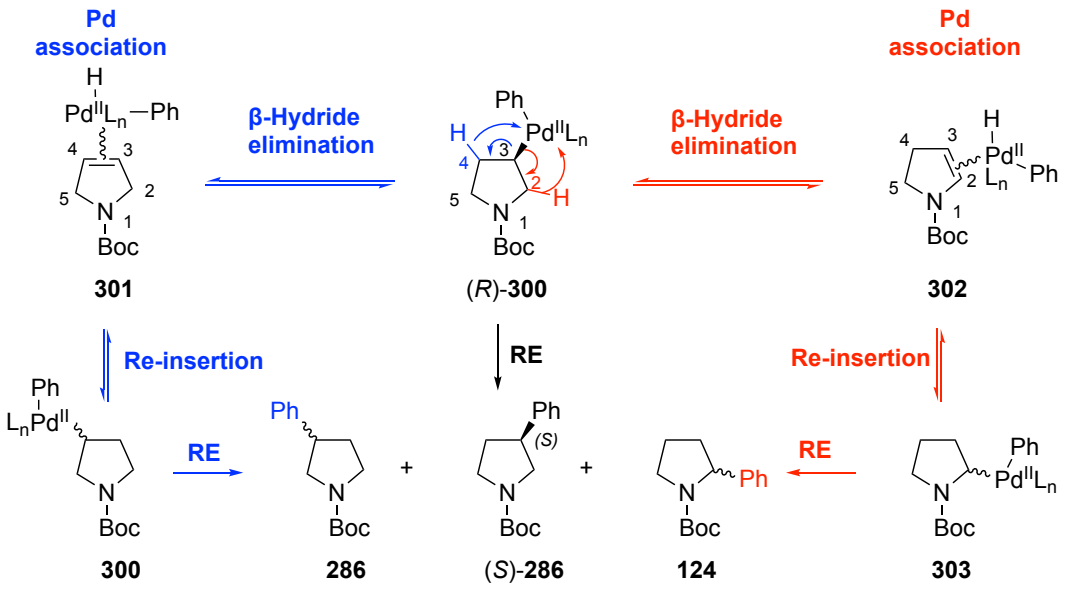


Figure 4.3: (a) ^{1}H NMR spectrum of 3-phenyl pyrrolidine **286**; (b) ^{1}H NMR spectrum of 2-phenyl pyrrolidine **124**; (c) ^{1}H NMR spectrum of SMCC product 75:25 mixture of 3- and 2-phenyl pyrrolidine **286** and **124** (signal at 3.75 corresponds to ISTD 1,3,5-trimethoxybenzene OMe peak)

The mechanism for the formation of 2-phenyl pyrrolidine **124** is analogous to the formation of 3- and 5-aryl *N*-PMP pyrrolidone (see Scheme 3.26) and is presented in Scheme 4.13. To aid discussion, the configuration of the transmetallation product 3-Pd pyrrolidine (*R*)-**300** is defined, and retentive cross-coupling is assumed. The significant difference between the two heterocycles lies in the symmetry of Pd-pyrroline 3,4-**301**. As with 4-BF_3K *N*-PMP pyrrolidone **192**, β-hydride elimination from transmetallation product 3-Pd pyrrolidine **300** can generate two regiosiomeric products – Pd-pyrrolines 2,3-**302** and 3,4-**301**. At this stage, the Pd-pyrrolines could dissociate from palladium to generate alkene byproducts. However, it is also possible for the Pd-pyrrolines to formally reinsert back into palladium (hydropalladation). In the case of Pd-pyrroline 3,4-**301**, the C3 and C4 positions are symmetry-related. This means that no matter which side of the alkene reinserts into palladium, the resulting palladium-intermediate will be chemically equivalent. However, this can have considerable effect on the stereochemical outcome of the cross-coupling.



Scheme 4.13

The effect of β-hydride elimination/reinsertion on the stereochemical outcome of the cross-coupling was discussed relating to 2-Bpin tetrahydrothiophene **110** with various aryl bromides (see Section 2.7). When Pd-pyrrolines 2,3-**302** or 3,4-**301** form, they can form *via* pyrroline association with the palladium on either face. Thus, when they hydropalladate back into palladium, a mixture of 3-Pd pyrrolidines (*R*)- and (*S*)-**300** and 2-Pd pyrrolidines (*R*)- and (*S*)-**303** would form. Moreover, even if the pyrroline stays on the same face of the palladium during the migration processes, it can still lead to formation of some of 3-phenyl pyrrolidine (*R*)-**286** which is the opposite configuration to that expected from the retentive SMCC shown in Scheme 4.13. For example, if Pd-pyrroline 3,4-**301** reinserts through C4 to palladium on the same face, following this through reductive elimination would generate 3-phenyl pyrrolidine (*R*)-**286**. Based on this analysis and the observation of regioisomeric 2-phenyl pyrrolidine **124** in the cross-coupling, it was concluded that the stereochemical outcome of the cross-coupling could not easily be investigated.

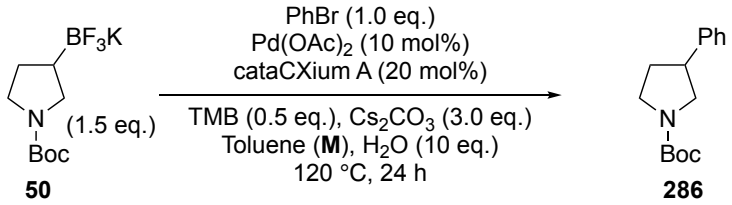
4.4 Optimisation of the Suzuki-Miyaura Cross-Coupling of 3-BF_3K *N*-Boc Pyrrolidine

In parallel to the development of the DOE approach with 4-BF_3K *N*-PMP pyrrolidone **192** (see 3.4.1), a DOE approach was also applied to 3-BF_3K pyrrolidine **50**. The aim was to identify the factors which influenced the yield of the cross-coupled product, 3-phenyl pyrrolidine **286**. At this initial stage of screening the presence of the undesired regioisomer was not yet realised. Therefore, GC yields were calculated for only 3-phenyl pyrrolidine **286**. Later, a GC calibration curve was created featuring both 3- and 2-phenyl pyrrolidines **286** and **124** allowing GC validation of their regiosiomeric ratio. However, applying this calibration curve to screening data retroactively would not generate accurate readings. Therefore, initially only the GC yield of 3-phenyl pyrrolidine **286** is reported. Fortunately, under our initial GC method, the GC signal for 3-phenyl pyrrolidine **286** was resolved from the GC signal for 2-phenyl pyrrolidine **124**. Thus, yields for 3-phenyl pyrrolidine were not inflated by signal overlap in the GC spectrum. Additionally, throughout screening, when cataCXium A was used as ligand, the regiosiomeric ratio of 3- and 2-phenyl pyrrolidines **286** and **124** were found to be consistently ~75:25 respectively. Therefore, the plan was to first use a DOE approach to try to improve the GC yield of 3-phenyl pyrrolidine **286**. Then, with GC analysis of 2-phenyl pyrrolidine **124** also enabled, a ligand screen (either with DOE or OFAT) would be used to identify ligands capable of disfavouring formation of the minor regioisomeric product, 2-phenyl pyrrolidine **124**.

Before proceeding to the DOE screening, validation of the reaction set-up, reaction scale and GC method was carried out to minimise variation between experimental runs. To accommodate the high volume of experiments planned in the optimisation campaign, reduction of the reaction scale was desired from 0.3 mmol to 0.1 mmol. The results of the SMCC of 3-BF_3K pyrrolidine **50** with bromobenzene at different reactions scales are shown in Table 4.1. Under standard conditions at 0.3 mmol scale (of bromobenzene), 3-phenyl pyrrolidine **286** was obtained in 11% GC yield (entry 1). This shows exemplary alignment to the isolated yield of 3-phenyl pyrrolidine (11%, see Scheme 4.12) validating the GC method. Reducing the scale of the reaction to 0.2 and 0.1 mmol gave GC yields of **286** of 23% and 1% respectively (entries 2 and 3). The higher yield on 0.2 mmol scale was an unexpected result. The low conversion on

the 0.1 mmol scale could be attributed to the high concentration of the reaction (0.7 M in toluene). The small amount of solvent is exacerbated as the scale of the reaction decreased and had clearly become detrimental to the reaction. Therefore, the reactions were repeated with a toluene concentration of 0.35 M. On a 0.3 mmol scale, 3-phenyl pyrrolidine **286** was obtained in 14% GC yield (entry 4). Gratifyingly, at 0.35 M toluene, on a 0.2 and 0.1 mmol scale, GC yields of **286** of 19% and 12% respectively were obtained (entries 5 and 6). These results all show good reproducibility suggesting that subsequent screening could be carried out on a 0.1 mmol scale with a 0.35 M concentration in toluene. Furthermore, it is proposed that the 23% GC yield of **286** obtained on 0.2 mmol scale at 0.7 M toluene concentration (entry 2) was likely an anomalous result.

Table 4.1: Validation of reaction scale – SMCC of 3-BF_3K pyrrolidine **50** with bromobenzene



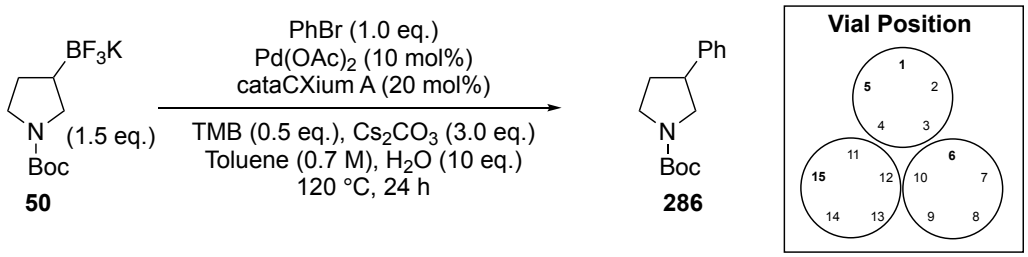
Entry	Reaction Scale / mmol	[Toluene] / M	GC Yield / %[a]
1	0.3	0.7	11
2	0.2	0.7	23
3	0.1	0.7	1
4	0.3	0.35	14
5	0.2	0.35	19
6	0.1	0.35	12

[a] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard

Next, the reaction set-up was validated. Typically, SMCC reactions were carried out using a single heating block on a hotplate which could hold up to five vials. To facilitate the increased throughput of reactions, the modified set-up would include three heating blocks on a single hotplate. The temperature was measured to be consistent across each heating block and equivalent to the standard single heating

block set-up. It was then determined whether variations in stirring or heating at different positions on the plate affected the yield. Therefore, a series of SMCC reactions with 3-BF_3K pyrrolidine **50** and bromobenzene (at 0.1 mmol scale) at various positions across the modified set-up was carried out (Table 4.2). For comparison, a validation SMCC was carried out on the standard single plate set-up to provide a benchmark GC yield of 3-phenyl pyrrolidine **286** of 11% (entry 1). Across four different plate positions (1, 5, 6 and 15), GC yields of **286** of 9-16% were obtained (entries 2-5). This demonstrated an acceptable level of variation of <10% in GC yield across equivalent reactions.

Table 4.2: Validation of reaction set-up – SMCC of 3-BF_3K pyrrolidine **50** with bromobenzene



Entry	Plate Position	GC Yield / %[a]
1	Standard single plate set-up	11
2	1	14
3	5	14
4	6	9
5	15	16

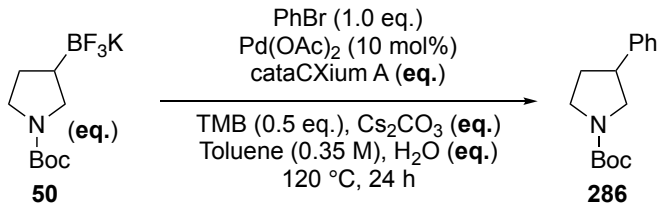
[a] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard

With the reaction set-up fully validated on a 0.1 mmol scale, the DOE full factorial design was implemented with the reactions also conducted on a 0.1 mmol scale . The design mirrored that used for 4-BF_3K *N*-PMP pyrrolidone **192**, with the only modification being the use of 100 eq. of water instead of 50 eq. (see Section 3.4.1). Thus, the factors investigated in the design were: water eq. (10 or 100 eq.), cataCXium A : $Pd(OAc)_2$ ratio (1:1 or 5:1 using 10 mol% $Pd(OAc)_2$), Cs_2CO_3 eq. (1.0 or 5.0 eq.)

and BF_3K **50** : bromobenzene ratio (1:1 or 1.5:1). The results of the DOE screen can be seen in Table 4.3.

Firstly, the results of the design's centre points (equivalent reactions) showed strong alignment, albeit with low GC yields of 3-phenyl pyrrolidine **286** of 4%, 6%, and 7% (entries 17-19). Unfortunately, two experiments gave 0% GC yield of **286** (entries 4 and 10). This was also the case with the DOE screen with 4-BF_3K *N*-PMP pyrrolidone **192**. For the reasons described in Section 3.4.1, the results could therefore not be investigated statistically to investigate factor interactions. However, useful information could still be gained from the results of the screen. Although most of the reactions gave <30% GC yields of 3-phenyl pyrrolidine **286**, three promising sets of conditions could be identified. When the reaction was carried out with 100 eq. of water, 1.0 equivalent of cataCXium A, 1.0 equivalent of Cs_2CO_3 and 1.0 equivalent of 3-BF_3K pyrrolidine **50**, a 54% GC yield of **286** was obtained (entry 2). Similarly, under those conditions with 10 eq. of water and 5.0 eq. of Cs_2CO_3, 3-phenyl pyrrolidine **286** was obtained in 57% GC yield (entry 5). With the conditions from entry 5 but using 100 eq. of water, a reduced yet still good 42% GC yield of **286** was obtained (entry 6).

Table 4.3: DOE full factorial design results for 3-BF_3K pyrrolidine **50** with bromobenzene

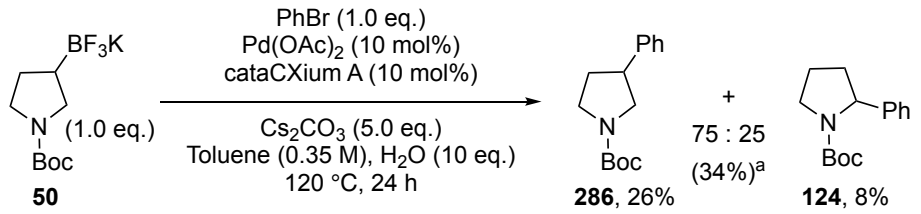


Entry	Water / eq.	Ligand / mol%[a]	Cs_2CO_3 / eq.	**50** / eq.	GC Yield / %[b]
1	10	10	1	1	9
2	100	10	1	1	54
3	10	50	1	1	1
4	100	50	1	1	0
5	10	10	5	1	57
6	100	10	5	1	42
7	10	50	5	1	11

Entry	Water / eq.	Ligand / mol%[a]	Cs_2CO_3 / eq.	**50** / eq.	GC Yield / %[b]
8	100	50	5	1	2
9	10	10	1	1.5	7
10	100	10	1	1.5	0
11	10	50	1	1.5	1
12	100	50	1	1.5	1
13	10	10	5	1.5	22
14	100	10	5	1.5	29
15	10	50	5	1.5	14
16	100	50	5	1.5	11
17	55	30	3	1.25	4
18	55	30	3	1.25	6
19	55	30	3	1.25	7

[a] 10 mol% corresponds to a 1:1 cataCXium A : $Pd(OAc)_2$ ratio, 30 mol% corresponds to a 3:1 cataCXium A : $Pd(OAc)_2$ ratio, 50% corresponds to a 5:1 cataCXium A : $Pd(OAc)_2$ ratio; [b] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard.

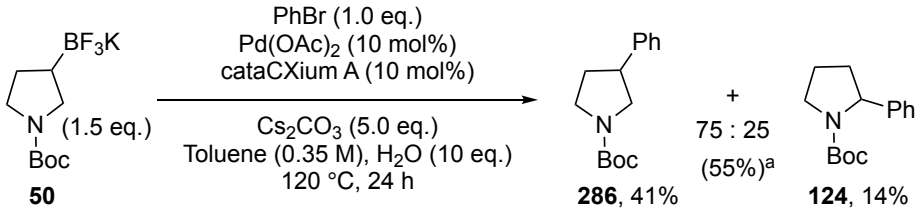
To validate the best set of conditions from the DOE screen (Table 4.3, entry 5), the experiment was repeated on a 0.3 mmol scale. Therefore, 3-BF_3K pyrrolidine **50** (1.0 eq.) was reacted with bromobenzene (1.0 eq.) in the presence of $Pd(OAc)_2$ (10 mol%), cataCXium A (10 mol%) and Cs_2CO_3 (5.0 eq.) in toluene (0.35 M) with 10 eq. of water at 120 °C for 24 h. Following work-up and chromatography, a 75:25 mixture of 3- and 2-phenyl pyrrolidines **286** and **124** was obtained in 34% isolated yield (26% yield of 3-phenyl pyrrolidine **286**) (Scheme 4.14). This was unexpectedly lower than the 57% GC yield of solely 3-phenyl pyrrolidine **286** obtained in the DOE screen (Table 4.3, entry 6).



[a] Yield in brackets represents combined yield of cross-coupled products in the mixture after chromatography

Scheme 4.14

With 4-BF_3K *N*-PMP pyrrolidone **192**, use of either BF_3K salt **192** or the aryl bromide as limiting reagent made little impact on the yield of cross-coupled product (see Table 3.6). However, as described previously, in most reported sp^3-sp^2 SMCC reactions, BF_3K salts were used as the excess reagent. Therefore, the reaction was repeated using 1.5 eq. of 3-BF_3K pyrrolidine **50**. Under these conditions, a 75:25 mixture of 3- and 2-phenyl pyrrolidines **286** and **124** was obtained in 55% yield after chromatography (41% of 3-phenyl pyrrolidine **286**) (Scheme 4.15). Surprisingly, this completely surpassed the GC yield of 22% obtained in the DOE screen under these conditions (Table 4.3, entry 13). This suggests that even though the reactions were validated on the 0.1 mmol scale, and in the new experimental set-up, we had potentially reduced reaction scale too ambitiously resulting in increased variation of the SMCC results. However, through the DOE screen we had, somewhat fortuitously, identified a set of conditions that significantly increased the isolated yield of 3-phenyl pyrrolidine **286**. Therefore, we could now prepare for the ligand screen, which aimed to explore any effects on the regioisomeric outcome of the reaction.



[a] Yield in brackets represents combined yield of cross-coupled products in mixture after chromatography

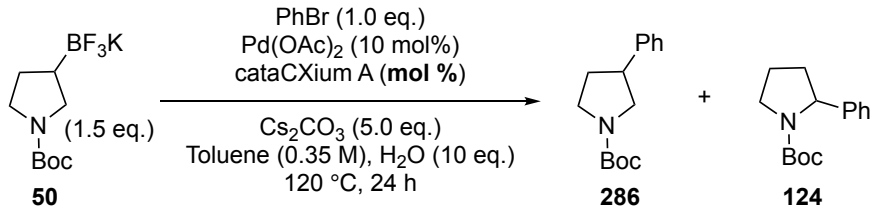
Scheme 4.15

Inspecting the newly discovered set of conditions, they were in fact very similar to the optimised conditions for SMCC reactions of 2-Bpin pyrrolidine **123** (see Scheme 2.6).

The significant difference being the use of a 1:1 cataCXium A : $Pd(OAc)_2$ ratio instead of 2:1 ratio. Indeed, the effectiveness of the 1:1 cataCXium A : $Pd(OAc)_2$ ratio in the new 3-BF_3K pyrrolidine **50** conditions was unexpected and warranted further consideration. In the O'Brien group, optimisation of a range of similar nitrogen heterocycles had found that a 2:1 ratio of cataCXium A : $Pd(OAc)_2$ was typically standard. Therefore, to evaluate if the improvement in yield was related to the 1:1 cataCXium A : $Pd(OAc)_2$ ratio, a series of SMCC reactions was carried out with 3-BF_3K pyrrolidine **50** and bromobenzene. The investigation used the new best conditions identified from the DOE screen and 10-50 mol% cataCXium A. The results are displayed in Table 4.4 with the result from Scheme 4.15 as entry 1.

When the reaction was carried out using 20 mol% cataCXium A, a 75:25 mixture of 3- and 2-phenyl pyrrolidines **286** and **124** was obtained in 37% isolated yield (entry 2). This is significantly higher than the 14% yield of **286** and **124** (75:25 ratio) obtained using 2:1 cataCXium A : $Pd(OAc)_2$ under the optimised 2-Bpin pyrrolidine **123** conditions (see Scheme 4.12). This suggests two things. First, the 1:1 cataCXium A : $Pd(OAc)_2$ ratio is significant. Second, the subtle differences between the new DOE derived conditions and the optimised 2-Bpin pyrrolidine **123** conditions do play a role in the increased yield of **286** and **124**. It is also significant that no meaningful change in the ratio of 3-phenyl pyrrolidine **286** : 2-phenyl pyrrolidine **124** was observed with any of the evaluated levels of ligand mol%. Use of 30 or 40 mol% of cataCXium A in the SMCC gave 3- and 2-phenyl pyrrolidines **286** and **124** (75:25 ratio) in 32% and 14% isolated yields respectively (entries 3 and 4). This shows a clear trend of increasing mol% of cataCXium A and diminished yield of **286** and **124** in the cross-coupling. Finally, with 50 mol% of cataCXium A an isolated yield of **286** and **124** (75:25 ratio) of 14% was observed (entry 5). This shows a plateau in the trend of decreasing yield of **286** and **124** with increasing mol% of cataCXium A. Overall, this investigation has demonstrated the effectiveness of the 1:1 cataCXium A : $Pd(OAc)_2$ ratio in the SMCC of 3-BF_3K pyrrolidine **50**. However, the improvement is not attributed solely to this modification. It is also likely that subtle changes to the reaction conditions (concentration, water eq., base eq.) have contributed to the increased reaction yield.

Table 4.4: SMCC of 3-BF_3K pyrrolidine **50** with different cataCXium A : $Pd(OAc)_2$ ratio

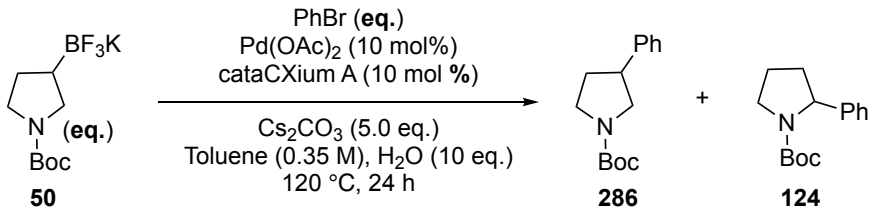


Entry	cataCXium A / mol%	cataCXium A : $Pd(OAc)_2$ ratio	Ratio **286** : **124**[a]	Isolated Yield **286** + **124** / %[b]
1	10	1:1	75:25	55
2	20	2:1	75:25	37
3	30	3:1	75:25	32
4	40	4:1	75:25	14
5	50	5:1	75:25	14

[a] Ratio determined by 1H NMR spectroscopy of product after chromatography; [b] Yield after chromatography.

Before further screening was explored, the relative eq. of 3-BF_3K pyrrolidine **50** and bromobenzene were evaluated in the cross-coupling (Table 4.5). We hoped to minimise the eq. of 3-BF_3K pyrrolidine **50** that would be used in the reaction and, ideally, a 1:1 ratio of 3-BF_3K pyrrolidine **50** and bromobenzene would be used as this would maximise the atom economy of the reaction. The result from Table 4.4 entry 1 is included as the first entry in Table 4.5. When an excess of 1.25 eq. of 3-BF_3K pyrrolidine **50** was used, a 70:30 mixture of 3- and 2-phenyl pyrrolidines **286** and **124** was obtained in 43% isolated yield (entry 2). Similarly, when a slight excess of bromobenzene (1.25 eq.) was used in the SMCC reaction, a 75:25 mixture of **286** and **124** was obtained in a 36% GC yield (entry 3). Although this result shows good alignment to the outcome using 1.25 eq. excess of BF_3K salt **50**, neither are close to the isolated yield obtained with 1.5 eq. excess of BF_3K salt **50** (75:25 ratio **286** to **124**, 55%, entry 1). Finally, when 1.5 eq. excess of bromobenzene was used, a 70:30 mixture of **286** and **124** was obtained in 26% yield (entry 4). Therefore, the reaction operates best with an excess of 1.5 eq. of 3-BF_3K pyrrolidine **50** and these conditions were maintained going forward.

Table 4.5: SMCC of 3-BF_3K pyrrolidine **50** with different eq. of bromobenzene



Entry	**50** / eq.	PhBr / eq.	Ratio **286** : **124**[a]	Yield **286** + **124** / %[b]
1	1.5	1.0	75:25	55
2	1.25	1.0	70:30	43
3[c]	1.0	1.25	75:25[d]	36[e]
4	1.0	1.5	70:30	26

[a] Ratio determined by ^{1}H NMR spectroscopy of product after chromatography; [b] Yield after chromatography, [c] Reaction also contained 0.5 eq. of 1,3,5 trimethoxybenzene as ISTD, [d] Ratio determined by GC using 1,3,5-trimethoxybenzene as internal standard, [e] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard.

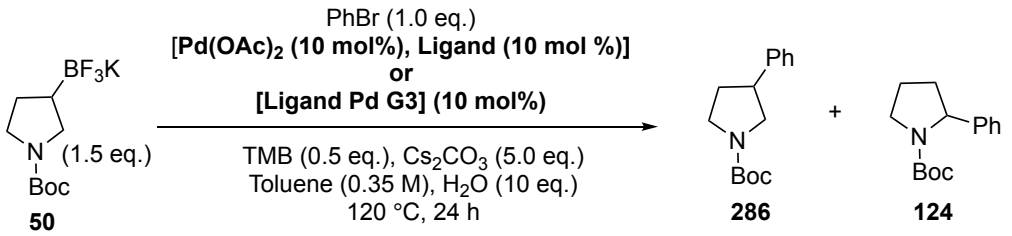
Following rapid success in optimisation of the cross-coupling yield of 3-phenyl pyrrolidine **286**, we wanted to explore the effect of ligands on the formation of the regioisomer, 2-phenyl pyrrolidine **124**. The aim of the investigation was to identify a ligand which would maintain the high cross-coupling yield of 3-phenyl pyrrolidine **286** but supress the formation of undesired 2-phenyl pyrrolidine **124**. Based on work by Biscoe, Sigman *et al.*[40] (see Section 1.5), we hypothesised that sterically bulky ligands should supress β-hydride elimination relative to reductive elimination therefore disfavouring the formation of 2-phenyl pyrrolidine **124**. Biscoe, Sigman *et al.* had used bespoke parameters to describe the steric properties of phosphine ligands. Using these parameters, we identified approximate threshold values associated with reduced β-hydride elimination. Since cataCXium A gave a 75:25 ratio of 3- and 2-phenyl pyrrolidines **286** and **124**, ligands with steric parameters comparable to or greater than cataCXium A were prioritised. Cross-referencing Biscoe and Sigman's ligands with these thresholds and commercial availability yielded the following set for evaluation in the SMCC: P(*t*-Bu)$_3$, XPhos, SPhos, P(*t*-Bu)Ph$_2$, RuPhos, CPhos, PCy_3 and PAd_3.

Many of the desired ligands were too expensive to access or required individual synthesis. Unfortunately, there was no scope in the project to synthesise ligands for this investigation. Several ligands were selected as commercially available substitutes: PCy_2Bp (Bp = biphenyl) and P(*t*-Bu)$_2$Bp to replace PCy_2(*t*-Bu) and P(*t*-Bu)$_2$Cy, *t*-BuXphos to replace PhXPhos. The remainder of the ligands in the screen were selected to cover an increased chemical space around the phosphine. By doing so, it was anticipated that other phosphine properties affecting the formation of 2-phenyl pyrrolidine **124** in the cross-coupling might be identified. Such findings could then inform the choice of ligands for any future screens.

The ligand screen was carried out using 0.1 mmol scale reactions with 24 different ligands and the results are shown in Table 4.6. Validation of the SMCC reaction with cataCXium A gave a 75:25 mixture of 3- and 2-phenyl pyrrolidines **286** and **124** in 48% GC yield (entry 1). There was no significant increase in yield when cataCXium A Pd G3 was used with **286** and **124** (75:25) obtained in 51% GC yield (entry 2). Surprisingly, using PCy_3 as ligand, a 25:75 ratio of **286** and **124** was obtained albeit in only 20% yield. Although PCy_3 is not as bulky as cataCXium A, it was unexpected that this ligand would give 2-phenyl pyrrolidine **124** as the major product. With RuPhos, a 75:25 ratio of **286** and **124** was obtained in 32% yield (entry 4). Similarly, moderate yields of 21-27% and 50:50 to 60:40 ratios of **286** and **124** were obtained with SPhos, APhos and *rac*-BIDIME (entries 5-7). Following the hypothesis, when P(Ad)$_3$ was used as ligand, 3- and 2-phenyl pyrrolidines **286** and **124** were isolated in 90:10 ratio but only 16% yield (entry 8). The agreement with the steric bulk hypothesis was gratifying but the low overall yield was not ideal. Furthermore, although the product ratio was greatly improved, 3-phenyl pyrrolidine **286** was still not the sole product generated. The remainder of the ligands all showed moderate to no conversion with varied and inconsequential product ratios (entries 9-24). The result with P(Ad)$_3$ would be much more useful if the cross-coupling yield of **286** was higher. Therefore, it was evaluated whether the yield of the cross-coupling could be elevated by increasing the temperature. This employed *o*-xylene as solvent and the reaction was carried at 140 °C using P(Ad)$_3$. Unfortunately, a detrimental effect was observed and only 4% of 3-phenyl pyrrolidine **286** was detected with none of 2-phenyl pyrrolidine **124** (entry 25). To validate this detrimental effect, the reaction was repeated using

cataCXium A as ligand. Under these conditions **286** and **124** were obtained in a 75:25 ratio in a diminished yield of 19% (entry 26), confirming the effect.

Table 4.6: Screening of the SMCC of 3-BF_3K pyrrolidine **50** with different ligands



Entry	Ligand	Ratio **286 : 124**[a]	GC Yield **286** / %[b]	GC Yield **124** / %[b]	Total GC Yield / %[b]
1	cataCXium A	75:25	38	10	48
2	cataCXium A Pd G3	75:25	39	12	51
3	PCy_3	25:75	6	14	20
4	RuPhos	75:25	24	8	32
5	SPhos	60:40	17	10	27
6	APhos	55:45	12	9	21
7	*rac*-BIDIME	50:50	11	11	22
8	$P(Ad)_3$	90:10	14	2	16
9	cataCXium ABn	-	0	0	0
10	AlPhos	-	0	0	0
11	XPhos	45:55	7	8	15
12	$P(t\text{-Bu})_3 \bullet HBF_4$	50:50	5	5	10
13	$P(t\text{-Bu})Ph_2$	44:54	9	10	19
14	cataCXium A PintB	50:50	1	1	2
15	JackiePhos	65:35	3	1	4
16	$P(Cy)_2Bp$	50:50	3	3	6
17	DavePhos	40:60	4	5	9
18	QPhos	50:50	6	6	12
19	Dppf	45:55	7	8	15
20	CPhos	50:50	5	4	9
21	$P(t\text{-Bu})_2Bp$	-	0	1	1

Entry	Ligand	Ratio **286 : 124**[a]	GC Yield **286** / %[b]	GC Yield **124** / %[b]	Total GC Yield / %[b]
22	*t*-BuBrettPhos	-	0	0	0
23	*t*-BuXPhos Pd G3	-	0	0	0
24	MorDalPhos Pd G3	-	1	0	1
25[c]	$P(Ad)_3$	–	4	0	4
26[c]	cataCXium A	75:25	15	4	19

[a] Ratio determined by GC using 1,3,5-trimethoxybenzene as internal standard, [b] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard, [c] Reaction ran in *o*-Xylene at 140 °C

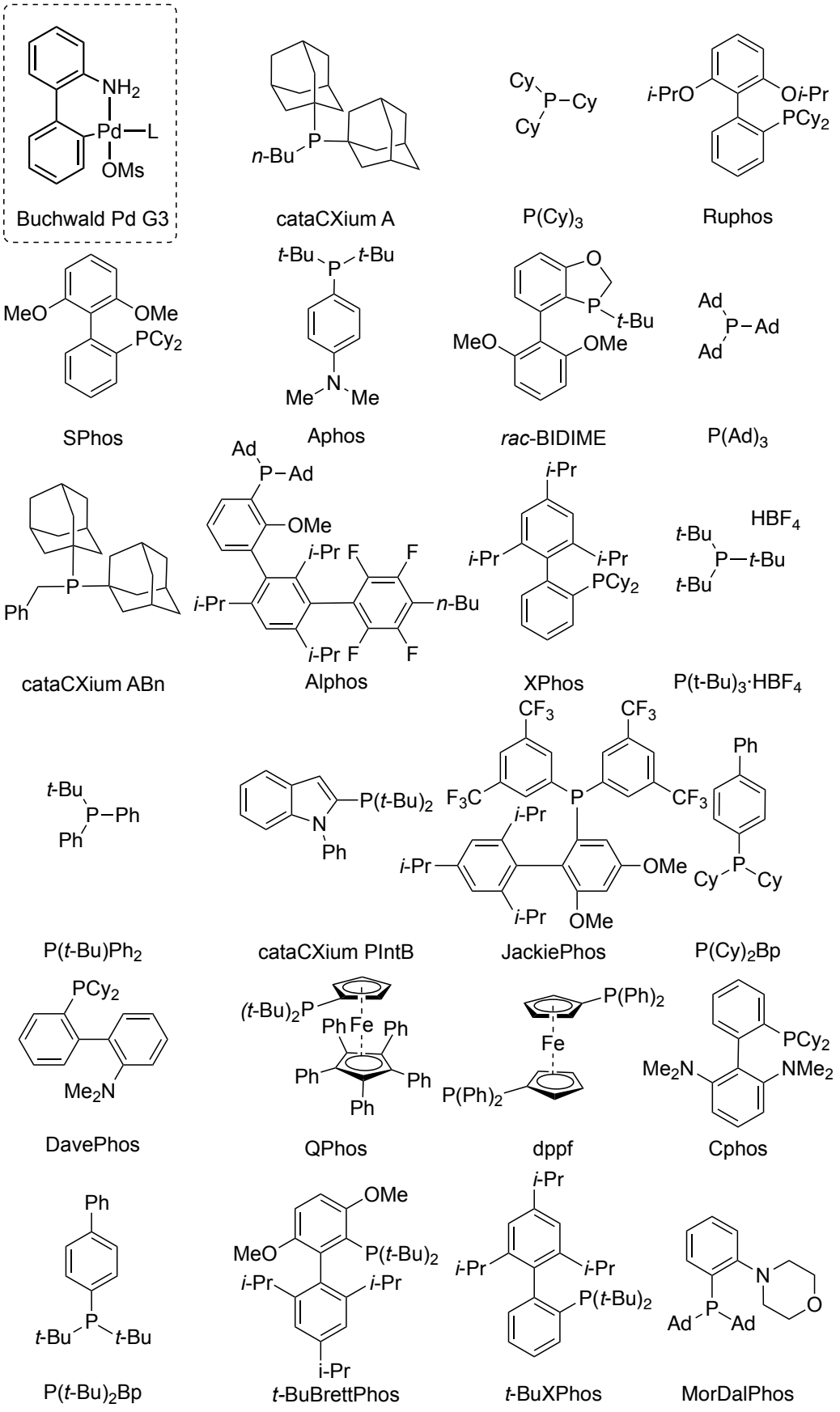
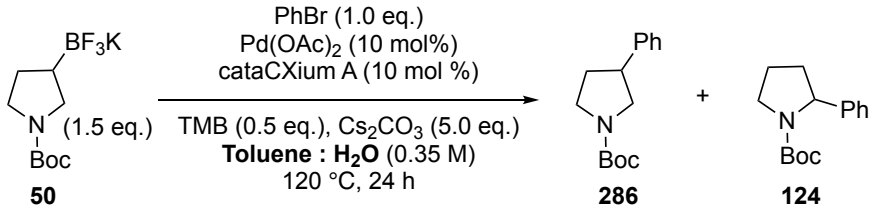


Figure 4.4: Structures of the ligands screened in the SMCC of 3-BF_3K pyrrolidine **50**

The results from the experiments shown in Table 4.6 suggest that $P(Ad)_3$ was the optimum ligand to favour reductive elimination over β-hydride elimination. However, with only a 16% overall yield of 3- and 2-phenyl pyrrolidines **286** and **124** (Table 4.6, entry 8), re-optimisation of the SMCC would be required. This was a significant step backwards, especially given the timeframe available for the study. Therefore, it was decided to proceed with cataCXium A as ligand, attempting to increase the overall yield of cross-coupled products **286** and **124** before evaluating the reaction sensitivity in an initial scope exploration.

Based on optimisation of a related *N*-heterocyclic boronate by Lucy Tomczyk within the group,[133] it was hypothesised that modifying the toluene : water ratio whilst maintaining the overall reaction concentration (0.35 M) could be worth exploring. The screening results are shown in Table 4.7, and, for comparison, the equivalents of water are also given. Using a 9:1 toluene : water ratio, a 70:30 ratio of 3- and 2-phenyl pyrrolidines **286** and **124** was obtained in 49% GC yield (entry 1). A similar GC yield of 41% of **286** and **124** (70:30) was obtained using a 7:1 toluene : water ratio (entry 2). Increasing the amount of water in the reaction with a 5:1 and 3:1 ratio of toluene and water resulted in lower GC yields of **286** and **124** of 23% and 31% respectively, both in 75:25 ratios (entries 3 and 4). Finally, using a 1:1 ratio of toluene : water gave a 70:30 ratio of **286** and **124** in 23% yield (entry 5). These results indicate that the reaction works best with a small amount of water, similar to the findings from the optimisation of 2-Bpin pyrrolidine **123**.[75]

Table 4.7: Screening of the SMCC of 3-BF_3K pyrrolidine **50** using different ratios of toluene : water while maintaining overall concentration

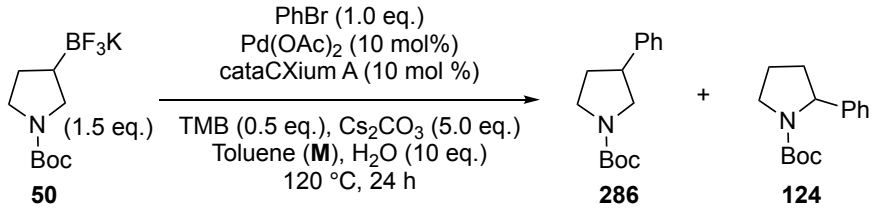


Entry	Ratio Toluene : Water	Water / eq.	Ratio **286 : 124**[a]	GC Yield **286** / %[b]	GC Yield **124** / %[b]	Total GC Yield / %[b]
1	9:1	16	70:30	38	11	49
2	7:1	20	70:30	32	9	41
3	5:1	26	75:25	18	5	23
4	3:1	40	75:25	24	7	31
5	1:1	79	70:30	18	5	23

[a] Ratio determined by GC using 1,3,5-trimethoxybenzene as internal standard, [b] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard.

Simultaneously, the solvent system was investigated by changing the concentration of toluene whilst maintaining 10 eq. of water (Table 4.8). When the reaction was carried out at 0.7 M in toluene, a 75:25 ratio of 3- and 2-phenyl pyrrolidines **286** and **124** was obtained in a 51% GC yield (entry 1). This reflected no significant difference over the current best GC yield obtained at 0.35 M of toluene (Table 4.5, entry 1). In contrast, running the reaction more dilute at 0.1 M in toluene gave a lower GC yield of 29% of **286** and **124** (75:25) (entry 3). Therefore, moving forward the concentration was maintained at 0.35 M in toluene with the equivalents of water set at 10.

Table 4.8: Screening of the SMCC of 3-BF_3K pyrrolidine **50** using different concentrations of toluene while maintaining equivalents of water

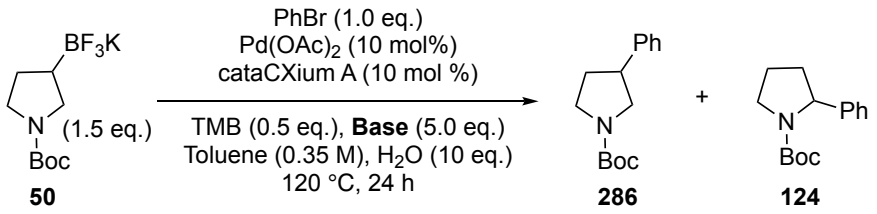


Entry	Ratio Toluene : Water	[Toluene] / M	Ratio **286 : 124**[a]	GC Yield **286** / %[b]	GC Yield **124** / %[b]	Total GC Yield / %[b]
1	8:1	0.7	75:25	40	11	51
2	56:1	0.1	75:25	22	7	29

[a] Ratio determined by GC using 1,3,5-trimethoxybenzene as internal standard, [b] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard.

Next, a small investigation into different bases was carried out. Here, common bases used in sp^3-sp^2 SMCC reactions were evaluated for their performance in the SMCC of 3-BF_3K pyrrolidine **50** with bromobenzene. Using K_2CO_3 instead of Cs_2CO_3 and standard conditions gave, surprisingly, only a 2% GC yield of 3-phenyl pyrrolidine **286**. A GC yield of 19% of **286** and **124** (60:40) was obtained with K_3PO_4 (entry 2). The change in product ratio from change in base was unexpected. This suggests alternative avenues of optimisation that could be used in future work to increase the amount of 3-phenyl pyrrolidine **286** formed. Finally, using CsOH as base, only a 2% GC yield of 3-phenyl pyrrolidine **286** was observed (entry 3). Overall, the results indicated that Cs_2CO_3 was still, by far, the optimum base for this SMCC. However, it is accepted that the scope of bases evaluated requires expansion to validate this claim.

Table 4.9: Screening of the SMCC of 3-BF_3K pyrrolidine **50** using different bases

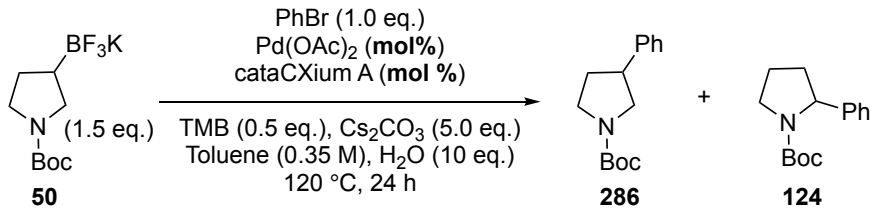


Entry	Base	Ratio **286 : 124**[a]	GC Yield **286** / %[b]	GC Yield **124** / %[b]	Total GC Yield / %[b]
1	K_2CO_3	–	2	0	2
2	K_3PO_4	60:40	11	8	19
3	CsOH	–	2	0	2

[a] Ratio determined by GC using 1,3,5-trimethoxybenzene as internal standard, [b] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard.

Next, the effect of increasing the palladium loading whilst maintaining the cataCXium A : $Pd(OAc)_2$ ratio was investigated. Concurrently, it represented an opportunity to evaluate whether the cross-coupling would proceed in similar yield and product ratios if the palladium loading was reduced. The results are shown in Table 4.10. A validation of standard conditions was first carried out, and 3- and 2-phenyl pyrrolidines **286** and **124** (75:25) were obtained in 46% yield (entry 1). When the palladium loading was reduced to 5 mol%, 3- and 2-phenyl pyrrolidines **286** and **124** (75:25) were obtained in 32% GC yield (entry 2). This result represents a substantial degree of conversion with a greatly reduced palladium loading which is somewhat surprising given the high sensitivity to subtle changes in conditions observed in the SMCC of 3-BF_3K pyrrolidine **50** thus far. Increasing the palladium loading to 15 mol% gave **286** and **124** (75:25) in 46% yield. This was not a significant difference to the 48% yield obtained with only 10 mol% palladium loading (Table 4.6, entry 1). Finally, further increase of the palladium loading to 20 mol% gave **286** and **124** (75:25) in 51% yield (entry 3). Therefore, conditions were maintained at 10 mol% palladium loading going forward.

Table 4.10: Screening of the SMCC of 3-BF_3K pyrrolidine **50** using different loadings of palladium maintaining the cataCXium A : palladium ratio

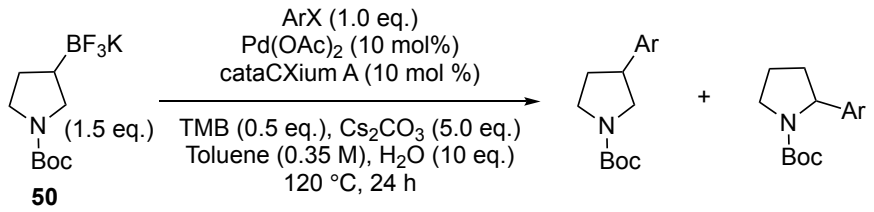


Entry	$Pd(OAc)_2$ / mol%	cataCXium A / mol%	Ratio **286 : 124**[a]	GC Yield **286** / %[b]	GC Yield **124** / %[b]	Total GC Yield / %[b]
1	5	5	75:25	24	8	32
2	15	15	75:25	35	11	46
3	20	20	75:25	39	12	51

[a] Ratio determined by GC using 1,3,5-trimethoxybenzene as internal standard, [b] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard.

Finally, we wanted to evaluate whether aryl bromides were the optimal cross-coupling partner. To ensure that the results were reliable, 3-bromo- and 3-chloroanisole were evaluated alongside chloro- and bromobenzene (Table 4.11). Currently, under our best conditions the highest isolated yield of 3- and 2-phenyl pyrrolidines **286** and **124** was 55% (Table 4.4, entry 1). Pleasingly, when chlorobenzene was used in the SMCC, an 80:20 ratio of 3-phenyl and 2-phenyl pyrrolidines **286** and **124** were obtained in 63% isolated yield (entry 1). In contrast, with iodobenzene, 3- and 2-phenyl pyrrolidines **286** and **124** (75:25) were obtained in 14% GC yield (entry 2). A similar higher yield with the aryl chloride was observed with 3-bromo- and 3-chloroanisole (entries 3 and 4). The results clearly suggested that aryl chlorides were preferred over aryl bromides or aryl iodides in the SMCC of 3-BF_3K pyrrolidine **50** and thus aryl chlorides were utilised when assessing the scope of the reaction. Therefore, the finalised conditions for the SMCC of 3-BF_3K pyrrolidine were: BF_3K salt **50** (1.5 eq.), aryl chloride (1.0 eq.), $Pd(OAc)_2$ (10 mol%), cataCXium A (10 mol%) and Cs_2CO_3 (5.0 eq.) in toluene (0.35 M) with water (10 eq.) at 120 °C for 24 h.

Table 4.11: Screening of the SMCC of 3-BF_3K pyrrolidine **50** using different aryl halides

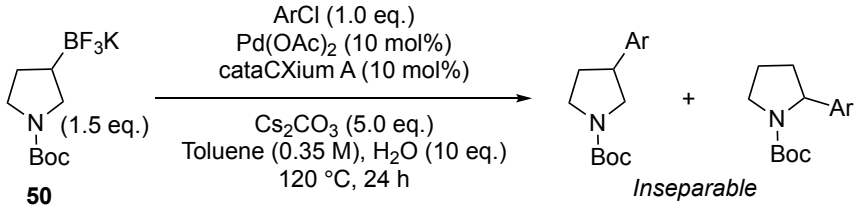


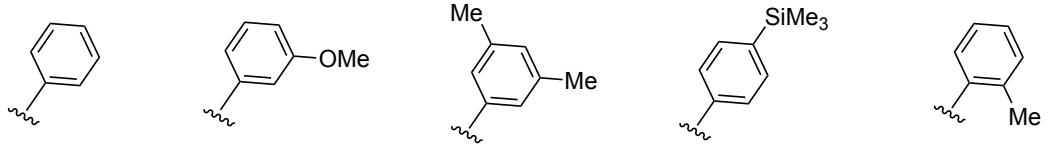
Entry	Aryl Halide	3-Aryl Product	2-Aryl Product	Ratio **3-aryl : 2-aryl**[a]	Yield / %[b]
1	Chlorobenzene	**286**	**124**	80:20	63
2	Iodobenzene	**286**	**124**	75:25[c]	14[d]
3	3-Bromoanisole	**304**	**305**	75:25	46
4	3-Chloroanisole	**304**	**305**	75:25	67

[a] Ratio determined by ^{1}H NMR spectroscopy of product after chromatography, [b] Yield after chromatography, [c] Ratio determined by GC using 1,3,5-trimethoxybenzene as internal standard, [d] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard.

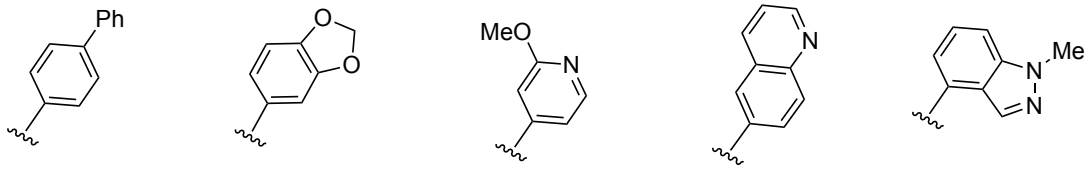
4.5 Scope of the Suzuki-Miyaura Cross-Coupling of 3-BF_3K *N*-Boc Pyrrolidine

With optimised conditions now developed, the scope of the SMCC of 3-BF_3K pyrrolidine **50** with aryl chlorides was explored. The full aryl chloride scope of the SMCC of 3-BF_3K pyrrolidine **50** is presented in Scheme 4.16. Ten successful examples of cross-coupling were carried out to give inseparable mixtures of 3- and 2-aryl pyrrolidines after chromatography. Generally, carbocyclic aryl chlorides were well tolerated. For example, SMCC of 3-BF_3K pyrrolidine **50** with 5-chloro-*m*-xylene gave an 85:15 mixture of 3- and 2-aryl pyrrolidines **306** and **307** in 36% yield. Similarly, with 2-chlorotoluene, **310** and **311** (75:25) were obtained in 48% yield.

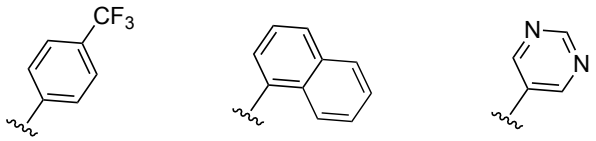




63%	67%	36%	42%	48%
286 + **124**	**304** + **305**	**306** + **307**	**308** + **309**	**310** + **311**
75 : 25	75 : 25	85 : 15	85 : 15	75 : 25



29%	27%	40%	49%[a]	41%
288 + **126**	**312** + **313**	**280** + **314**	**315** + **316**	**317** + **318**
75 : 25	55 : 45	40 : 60	55 : 45	55 : 45



<7%	0%	0%
319 + **125**	**320** + **321**	**322** + **323**

[a] 6-Bromoquinoline was used instead of 6-chloroquinoline

Scheme 4.16

Heteroaryl chlorides were less successful in the SMCC of 3-BF_3K pyrrolidine **50**. However, three successful examples were obtained. For example, SMCC of 2-chloro-4-methoxypyridine gave a 40:60 mixture of 3- and 2-aryl pyrrolidines **280** and **314** in 40% yield. Similarly, a 60:40 mixture of **317** and **318** were obtained in 41% yield using 4-chloro-1-methyl-1*H*-indazole. Finally, when 3-BF_3K pyrrolidine **50** and 6-chloroquinoline were reacted, neither 3-aryl pyrrolidine **315** nor 2-aryl pyrrolidine **316** were detected by ^1H NMR spectroscopy or HRMS analysis. The batch of 6-chloroquinoline had been validated in other SMCC reactions within the group showing that there was no issue with the aryl chloride. Therefore, to further investigate the cross-coupling, the reaction was repeated with 6-bromoquinoline. This afforded a 55:45 mixture of 3- and 2-aryl pyrrolidines **315** and **316** in 49% yield. Several reactions of 3-BF_3K pyrrolidine **50** and aryl chlorides showed no or only trace conversion to cross-coupled product (by ^1H NMR spectroscopy or HRMS). These included carbocyclic aryl chlorides such as chloronaphthalene and 4-chlorobenzotrifluoride and the heteroaryl chloride 5-chloropyrimidine (Scheme 4.16). Overall, compared to the scope of the SMCC with 2-Bpin tetrahydrothiophene **110** (see Scheme 2.15) or even 4-BF_3K *N*-PMP pyrrolidine **192** (see Scheme 3.25), the SMCC of 3-BF_3K pyrrolidine was found to be more sensitive to variations in the structure of the aryl chloride.

Four examples of aryl chlorides gave significant amounts of 2-aryl pyrrolidines (Scheme 4.16). These included 5-chloro-1,3-benzodioxole and three heteroaryl chlorides. With 5-chloro-1,3-benzodioxole, a 55:45 mixture of 3- and 2-aryl pyrrolidines **312** and **313** was obtained in 29% yield. Each of the SMCC reactions with 4-chloro-2-methoxypyridine, 4-chloro-1-methyl-1*H*-indazole and 6-bromoquinoline presented product ratios that included ≥40% of the 2-aryl pyrrolidines. Contrasting this to the carbocyclic cross-couplings, the proportion of 2-aryl pyrrolidines in the cross-coupled product mixture was never more than 25%. Furthermore, the cross-coupling yields of the heteroaryl chlorides are not insubstantial. Therefore, there is a trend of increasing β-hydride elimination with aryl chlorides containing Lewis basic heteroatoms. Although the mechanistic basis of this effect is unclear, the consistency of examples suggests the trend could be genuine.

4.6 Conclusions and Future Work

In summary, through investigation of the SMCC of 3-BF_3K pyrrolidine **50** with bromobenzene, the reaction yield was increased from 14% of a 75:25 ratio of 3- and 2-phenyl pyrrolidines **286** and **124** to 63% of **286** and **124** (75:25). The final optimised conditions were: 3-BF_3K pyrrolidine **50** (1.5 eq.), aryl chloride (1.0 eq.), $Pd(OAc)_2$ (10 mol%), cataCXium A (10 mol%), Cs_2CO_3 (5.0 eq.) in toluene (0.35 M) with water (10 eq.) at 120 °C for 24 h.

The optimisation of this SMCC was rapid and effective, significantly increasing the yield from the initial 14% yield following a relatively small number of optimisation experiments. This demonstrates how insights from the optimisation of 4-BF_3K *N*-PMP pyrrolidone **192** (see Section 3.4), and related systems in the group, can be applied to achieve substantial improvements in cross-coupling efficiency. It supports the concept of micro-optimisation around the "general conditions" proposed from the study on the SMCC of 4-BF_3K *N*-PMP pyrrolidone **192** (see Section 3.9). Even though high conversions in the SMCC reactions of 3-BF_3K pyrrolidine **50** were achieved in a short timeframe, the surrounding chemical space was only minimally explored, meaning that the current conditions are likely a local, rather than global, optimum. It is hoped that the development and application of further DOE-based statistical analysis could identify a more optimum set of conditions.

Of the 23 alternative ligands evaluated in the SMCC with 3-BF_3K pyrrolidine **50**, none could exclusively deliver 3-phenyl pyrrolidine **286**. However, a promising result with PAd_3 suggests a potential direction for future research. A workflow similar to that of Biscoe, Sigman *et al.*[40] could be applied. Using their bespoke steric and electronic descriptors, the design of diverse PAd_3 derivatives could be explored computationally and subsequently evaluated in the SMCC with 3-BF_3K pyrrolidine **50**. Concurrently, investigation of various SMCC parameters such as the nature and equivalents of base, could be conducted to determine their influence on the regioselectivity of this SMCC reaction. Ultimately, combining an optimised bespoke ligand with SMCC conditions disfavouring β-hydride elimination could enable complete formation 3-phenyl pyrrolidine **286**. If required, subsequent optimisation would furnish solely 3-phenyl pyrrolidine **286** in high yields.

A scope of ten 3-aryl pyrrolidines was developed, each isolated as inseparable mixtures of two regioisomers, including examples with heteroaryl chlorides. To further assess the sensitivities of 3-BF_3K pyrrolidine **50** in the cross-coupling, the scope should be expanded with a focus on medicinally relevant and structurally diverse heteroaryl chlorides.

Finally, the stereochemical pathway of transmetallation for 3-BF_3K pyrrolidine **50** should be explored. One strategy could be to first identify conditions that suppress the β-hydride/elimination process. Alternatively, it is possible that the major stereochemical pathway of transmetallation could still be inferred by simply analysing the er of the cross-coupled product. A high er of either enantiomer of the cross-coupled product would indicate the predominant (retentive or invertive) stereochemical pathway. If a moderate er of the stereoretentive enantiomer of 3-phenyl pyrrolidine **286** was observed, the major stereochemical pathway of transmetallation could still be inferred. However, if the major product was the stereoinvertive product, the interpretation becomes less straightforward. It would need to be assumed that stereoinversion arises from the transmetallation step itself, rather than from a β-hydride elimination/reinsertion pathway. If a low er of 3-phenyl pyrrolidine **286** was obtained, no information on the major stereochemical pathway of transmetallation would be gained. However, given the potential to discover valuable information about the stereochemical outcome of the SMCC, this investigation should be considered.

Chapter: 5 Experimental

5.1 General Information

All-non aqueous reactions were carried out under oxygen free Ar or N_2 using flame-dried glassware. Toluene, Et_2O, and THF were dried using Innovative Technologies solvent purification system using activated alumina. Alkyllithiums were titrated against *N*-benzylbenzamide before use. Brine refers to a saturated solution. Water is distilled water. TMEDA used in lithiations was distilled over CaH_2 before use.

Flash column chromatography was carried out using Supelco silica (220-440 mesh). Thin layer chromatography was carried out using commercially available Merck F_{254} aluminium backed silica plates. Proton (400 MHz), carbon (100.6 MHz), boron (128 MHz) and fluorine (375 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument using an internal deuterium lock. For samples recorded in $CDCl_3$, chemical shifts are quoted in parts per million relative to $CHCl_3$ (δ_H 7.26) and $CDCl_3$ (δ_C 77.0, central line of triplet). For samples recorded in d_6-DMSO, chemical shifts are quoted in parts per million relative to DMSO (δ_H 2.50, central line of quintet) and d_6-DMSO (δ_C 39.5, central line of septet). For samples recorded in d_6-acetone, chemical shifts are quoted in parts per million relative to acetone (δ_H 2.05, central line of quintet) and d_6-acetone (δ_C 29.8, central line of septet). Carbon NMR spectra were recorded with broad band proton decoupling and assigned using DEPT experiments. Coupling constants (*J*) are quoted in Hertz. Melting points were carried out on a Gallenkamp melting point apparatus. Infrared spectra were recorded on a Perkin Elmer UATR Two FT-IR spectrometer. Electrospray high and low resonance mass spectra were recorded at room temperature on a Bruker Daltronics microOTOF spectrometer. Chiral stationary phase HPLC was performed on an Agilent 1200 series instrument and a multiple wavelength, UV/Vis diode array detector. Gas chromatography was performed on a Thermo Scientific^{TM} TRACE_1300_1310 GC analyser with an Agilent J&W DB-5 30 m × 0.32 mm column with a 0.25 μm film thickness using flame ionization detection. Optical rotations were recorded at room temperature on a Jasco DIP-370 polarimeter (using sodium D line, 589 nm) and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^3 g^{-1}. Automated weighing was carried out using a Chemspeed Crystal Powderdose benchtop gravimetric solid dispensing unit.

5.2 General Procedures

General Procedure A: Suzuki-Miyaura cross-coupling of 2-Bpin tetrahydrothiophene 110 using liquid aryl halides

2-Bpin tetrahydrothiophene **110** (0.75 mmol, 1.5 eq.), $Pd(OAc)_2$ (11 mg, 50 µmol, 0.10 eq.), cataCXium A (36 mg, 100 µmol, 0.20 eq.) and Cs_2CO_3 (489 mg, 1.5 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and liquid aryl halide (0.5 mmol, 1.0 eq.), degassed toluene (0.70 mL, 0.71 M) and water (90 µL, 5.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure B: Suzuki-Miyaura cross-coupling of 2-Bpin tetrahydrothiophene 110 using solid aryl halides

2-Bpin tetrahydrothiophene **110** (0.75 mmol, 1.5 eq.), solid aryl halide (0.5 mmol, 1.0 eq.), $Pd(OAc)_2$ (11 mg, 50 µmol, 0.10 eq.), cataCXium A (36 mg, 100 µmol, 0.20 eq.) and Cs_2CO_3 (489 mg, 1.5 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and degassed toluene (0.70 mL, 0.71 M) and water (90 µL, 5.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the

combined organics were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure C: Suzuki-Miyaura cross-coupling of 2-Bpin tetrahydrothiophene (*S*)-or (*R*)-110 using liquid aryl halides

2-Bpin Tetrahydrothiophene (*S*)- or (*R*)-**110** (0.36 mmol, 1.2 eq., ≥99:1 er), $Pd(OAc)_2$ (7 mg, 30 µmol, 0.10 eq.), cataCXium A (22 mg, 60 µmol, 0.20 eq.) and Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and liquid aryl halide (0.3 mmol, 1.0 eq.), degassed toluene (0.42 mL, 0.71 M) and water (54 µL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure D: Suzuki-Miyaura coupling of 2-Bpin tetrahydrothiophene (*S*) or (*R*)-110 using solid aryl halides

2-Bpin Tetrahydrothiophene (*S*)- or (*R*)-**110** (0.36 mmol, 1.2 eq., ≥99:1 er), solid aryl halide (0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 0.10 eq.), cataCXium A (22 mg, 60 µmol, 0.20 eq.) and Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and degassed toluene (0.43 mL) and water (54 µL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After

being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure E: Sample work-up procedure for GC analysis of Suzuki-Miyaura cross-coupling reactions at a 0.2, 0.3 or 0.5 mmol scale

Completed reactions were allowed to cool to rt. Then, EtOAc (1 mL) and water (1 mL) were added to the vial. The vial was agitated and the layers separated. Using a needle, 0.1 mL of the organic (top) layer was transferred and EtOAc (0.9 mL) was added. Using a needle, 0.1 mL of the sample was then transferred *via* a syringe filter to an appropriate GC vial for analysis and topped up with EtOAc (0.9 mL).

General Procedure F: Sample work-up procedure for GC analysis of Suzuki-Miyaura cross-coupling reactions at a 0.1 mmol scale

Completed reactions were allowed to cool to rt. Then, EtOAc (1 mL) and water (1 mL) were added to the vial. The vial was agitated and the layers separated. Using a needle, 0.1 mL of the organic (top) layer was transferred and EtOAc (0.9 mL) was added. The sample was then transferred *via* a syringe filter to an appropriate GC vial for analysis.

General Procedure G: GC screening for the DOE optimisation of heterocyclic BF_3K salts

Heterocyclic BF_3K (0.10-0.15 mmol, 1.0-5.0 eq.), $Pd(OAc)_2$ (2.2 mg, 10 μmol, 0.10 eq.), cataCXium A (10-50 μmol, 0.1-0.5 eq.), Cs_2CO_3 (0.1-0.5 mmol, 1.0-5.0 eq.) and 1,3,5-trimethoxybenzene (0.05 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (11 μL, 0.1 mmol, 1.0 eq.), degassed toluene (0.29 mL) and water (1.0-

10.0 mmol, 10-100 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. The reaction was allowed to cool to rt. Then, EtOAc (1 mL) and water (1 mL) were added to the vial. The vial was agitated and the layers separated. Using a needle, 0.1 mL of the organic (top) layer was transferred and EtOAc (0.9 mL) was added. The sample was then transferred *via* a syringe filter to an appropriate GC vial for analysis. Where the yield after chromatography was also desired, water (10 mL) and EtOAc (10 mL) were added to the reaction vial and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 80:20 hexane-EtOAc as eluent gave the purified product.

General Procedure H: GC Screening of different ligands at 10 or 20 mol% loading for 4-BF_3K *N*-PMP Pyrrolidone 192

4-BF_3K *N*-PMP pyrrolidone **192** (0.1 mmol, 1.0 eq.), $Pd(OAc)_2$ (2.2 mg, 10 μmol, 0.10 eq.), ligand (10-20 μmol, 0.1-0.2 eq.), Cs_2CO_3 (163 mg, 0.5 mmol, 5.0 eq.) and 1,3,5-trimethoxybenzene (0.05 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (11 μL, 0.1 mmol, 1.0 eq.), degassed toluene (0.29 mL) and water (90 μL, 50 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. The reaction was allowed to cool to rt. Then, EtOAc (1 mL) and water (1 mL) were added to the vial. The vial was agitated and the layers separated. Using a needle, 0.1 mL of the organic (top) layer was transferred and EtOAc (0.9 mL) was added. The sample was then transferred *via* a syringe filter to an appropriate GC vial for analysis. Where the yield after chromatography was also desired, water (10 mL) and EtOAc (10 mL) were added to the reaction vial and the two layers were

separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 80:20 hexane-EtOAc as eluent gave the purified product.

General Procedure I: Optimised Suzuki-Miyaura cross-coupling of 4-BF_3K *N*-PMP pyrrolidone 192 using liquid aryl halides at a 0.5 mmol scale

4-BF_3K *N*-PMP pyrrolidone **192** (0.50 mmol, 1.0 eq.), $Pd(OAc)_2$ (11 mg, 50 μmol, 0.10 eq.), cataCXium A (36 mg, 100 μmol, 0.20 eq.) and Cs_2CO_3 (652 mg, 2.0 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and liquid aryl halide (0.75 mmol, 1.5 eq.), degassed toluene (0.70 mL, 0.71 M) and water (180 μL, 10.0 mmol, 20.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure J: Optimised Suzuki-Miyaura cross-coupling of 4-BF_3K *N*-PMP pyrrolidone 192 using solid aryl halides at a 0.5 mmol scale

4-BF_3K *N*-PMP pyrrolidone **192** (149 mg, 0.50 mmol, 1.5 eq.), solid aryl halide (0.75 mmol, 1.0 eq.), $Pd(OAc)_2$ (11 mg, 50 μmol, 0.10 eq.), cataCXium A (36 mg, 100 μmol, 0.20 eq.) and Cs_2CO_3 (652 mg, 2.0 mmol, 4.0 eq.) and were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and degassed toluene (0.70 mL, 0.71 M) and water (180 μL, 10.0 mmol, 20.0 eq.) were

added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure K: Optimised Suzuki-Miyaura cross-coupling of 4-BF_3K *N*-PMP pyrrolidone 192 using liquid aryl halides at a 0.3 mmol scale

4-BF_3K *N*-PMP pyrrolidone **192** (0.30 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 0.10 eq.), cataCXium A (22 mg, 60 μmol, 0.20 eq.) and Cs_2CO_3 (391 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and liquid aryl halide (0.45 mmol, 1.5 eq.), degassed toluene (0.42 mL, 0.71 M) and water (108 μL, 6.0 mmol, 20.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure L: Optimised Suzuki-Miyaura cross-coupling of 4-BF_3K *N*-PMP pyrrolidone 192 using solid aryl halides at a 0.3 mmol scale

4-BF_3K *N*-PMP pyrrolidone **192** (0.3 mmol, 1.0 eq.), solid aryl halide (0.45 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 0.10 eq.), cataCXium A (22 mg, 60 μmol, 0.20 eq.) and Cs_2CO_3 (389 mg, 1.2 mmol, 4.0 eq.) and were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the

headspace was purged with N_2 for 15 min. Then, the exit needle was removed and degassed toluene (0.42 mL) and water (108 μL, 6.0 mmol, 20.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure M: GC Screening of the SMCC of 3-BF_3K pyrrolidine 50 using different ligands at a 0.3 mmol scale (of bromobenzene)

3-BF_3K Pyrrolidine **50** (0.45 mmol, 1.5 eq.), [$Pd(OAc)_2$ (7 mg, 30 μmol, 0.10 eq.) and ligand (30 μmol, 0.3 eq.)] or [ligand Pd G3 (30 μmol, 0.3 eq.)] , Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and 1,3,5-trimethoxybenzene (0.15 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (31 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.86 mL) and water (54 μL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. The reaction was allowed to cool to rt. Then, EtOAc (1 mL) and water (1 mL) were added to the vial. The vial was agitated and the layers separated. Using a needle, 0.1 mL of the organic (top) layer was transferred and EtOAc (0.9 mL) was added. Using a needle, 0.1 mL of the sample was then transferred via a syringe filter to an appropriate GC vial for analysis and EtOAc (0.9 mL) was added and the vial analysed by GC using GC method B.

General Procedure N: GC Screening of the SMCC of 3-BF_3K pyrrolidine 50 using different ligands at a 0.1 mmol scale (of bromobenzene)

3-BF_3K Pyrrolidine **50** (0.10 mmol, 1.5 eq.), [$Pd(OAc)_2$ (2.2 mg, 10 μmol, 0.10 eq.) and ligand (10 μmol, 0.1 eq.)] or [ligand Pd G3 (10 μmol, 0.1 eq.)], Cs_2CO_3 (163 mg, 0.5 mmol, 5.0 eq.) and 1,3,5-trimethoxybenzene (0.05 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (11 μL, 0.1 mmol, 1.0 eq.), degassed toluene (0.29 mL) and water (18 μL, 1.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. The reaction was allowed to cool to rt. Then, EtOAc (1 mL) and water (1 mL) were added to the vial. The vial was agitated and the layers separated. Using a needle, 0.1 mL of the organic (top) layer was transferred and EtOAc (0.9 mL) was added. The sample was then transferred *via* a syringe filter to an appropriate GC vial for analysis using GC method B.

General Procedure O: GC Screening of the SMCC of 3-BF_3K pyrrolidine 50 using different volumes of toluene and water

3-BF_3K Pyrrolidine **50** (0.3 mmol, 1.5 eq.), $Pd(OAc)_2$ (4.5 mg, 20 μmol, 0.10 eq.) and cataCXium A (7 mg, 20 μmol, 0.1 eq.), Cs_2CO_3 (326 mg, 1.0 mmol, 5.0 eq.) and 1,3,5-trimethoxybenzene (0.1 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (21 μL, 0.2 mmol, 1.0 eq.), degassed toluene (0.29-2.0 mL) and water (36-290 μL, 3.0-81.0 mmol, 10.0-403 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. The reaction was allowed to cool to rt. Then, EtOAc (1 mL) and water (1 mL) were added to the vial. The vial was agitated and the

layers separated. Using a needle, 0.1 mL of the organic (top) layer was transferred and EtOAc (0.9 mL) was added. Using a needle, 0.1 mL of the sample was then transferred *via* a syringe filter to an appropriate GC vial for analysis and EtOAc (0.9 mL) was added and the vial analysed by GC using GC method B.

General Procedure P: Optimised Suzuki-Miyaura cross-coupling of 3-BF_3K pyrrolidine 50 using liquid aryl halides at a 0.3 mmol scale

3-BF_3K pyrrolidine **50** (0.30 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 0.10 eq.), cataCXium A (11 mg, 30 μmol, 0.10 eq.) and Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and liquid aryl halide (0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL, 0.35 M) and water (54 μL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure Q: Optimised Suzuki-Miyaura cross-coupling of 3-BF_3K pyrrolidine 50 using solid aryl halides at a 0.3 mmol scale

3-BF_3K pyrrolidine **50** (0.30 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 0.10 eq.), cataCXium A (11 mg, 30 μmol, 0.10 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and solid aryl halide (0.3 mmol, 1.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed, degassed toluene (0.86 mL, 0.35 M) and water (54 μL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was

placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

5.3 Analysis Methods

5.3.1 GC Analysis Methods

GC Method A:

Analysis was carried out by introducing the sample into the GC system by means of direct injection (1 µL by volume). A split dilution ratio of 5 was used. Injector temperature was 250 °C. The GC was equipped with an Agilent J&W DB-5 30 m × 0.32 mm column (0.25 µm film thickness). The oven temperature was programmed to 50 °C for 5 min then 50 °C to 280 °C at 16 °C / min and held at 280 °C for 5 min. Hydrogen carrier gas was used. All GC samples were in EtOAc.

Retention times:

1,3,5-trimethoxybenzene = 10.21 min

4-phenyl *N*-PMP pyrrolidone **206** = 31.56 min

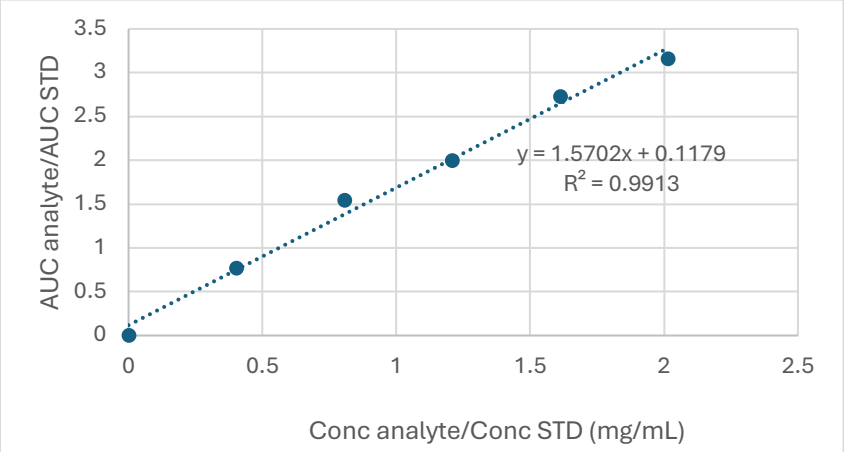


Figure 5: Representative GC calibration curve for 4-phenyl *N*-PMP pyrrolidone **206**

GC Method B:

Analysis was carried out by introducing the sample into the GC system by means of direct injection (1 µl by volume). Injector temperature was 250 °C. The GC was equipped with an Agilent J&W DB-5 30 m × 0.32 mm column (0.25 µm film thickness). The oven temperature was programmed to 50 to 150 °C at 8 °C / min, then to 280 at 4 °C / min then held at 280 °C for 5 min. Hydrogen carrier gas was used. All GC samples were in EtOAc.

Retention times:

1,3,5-trimethoxybenzene = 12.08 min

4-phenyl *N*-PMP pyrrolidone **206** = 21.5 min

2-phenyl pyrrolidine **124** = 14.27 min

3-phenyl pyrrolidine **286** = 15.22 min

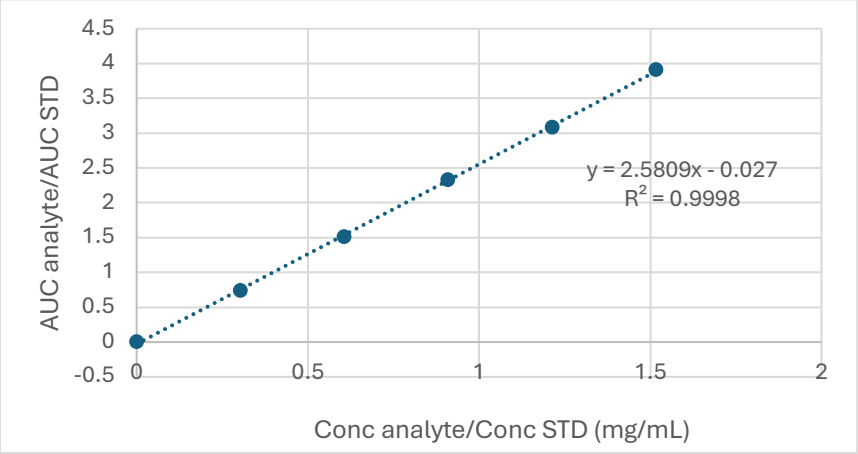


Figure 6: Representative GC calibration curve for 4-phenyl *N*-PMP pyrrolidone **206**

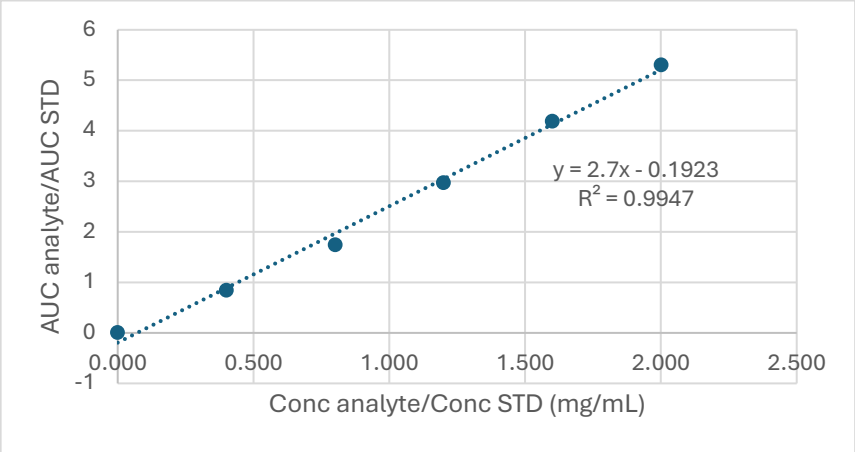


Figure 7: Representative GC calibration curve for 3-phenyl pyrrolidine **286**

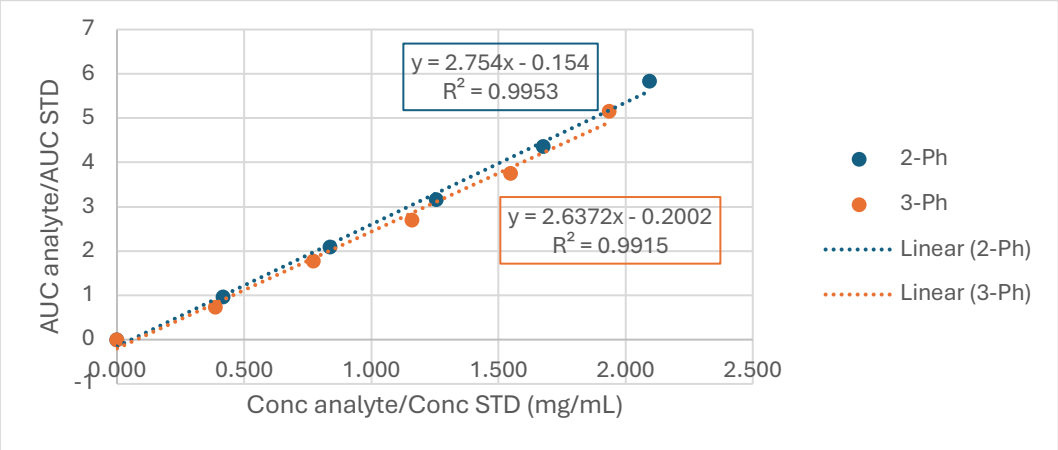


Figure 8: Representative GC calibration curve for 3-phenyl pyrrolidine **286** and 2-phenyl pyrrolidine **124**

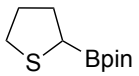
5.3.2 NMR Analysis Method

NMR yields were determined using the ^{1}H NMR (400 MHz, $CDCl_3$) of the crude reaction mixture and by comparison of the integration of clear, resolved diagnostic peaks in the respective compound and the signals in 1,3,5-trimethoxybenzene (6.11 (s, 3H, Ar) and 3.78 (s, 9H, OMe)). For SMCC reactions internal standard was added with solid reactants during reaction set up, for O-benzylation chemistry internal standard was added during work up post reaction unless stated otherwise. Internal standard was used at 0.3 or 0.5 equivalents. Having accounted for the equivalents and number of protons, the ratio between the two sets of the peaks was determined and an average

taken. This was then used to determine the conversion of the reaction and an NMR yield

5.4 Experimental Procedures for Chapter 2

4,4,5,5-Tetramethyl-2-(tetrahydrothiophen-2-yl)-1,3,2-dioxaborolane 110



110

sec-BuLi (29.5 mL of a 1.1 M solution in 92:8 cyclohexane-hexane, 32.5 mmol, 1.3 eq.) was added dropwise to a stirred solution of tetrahydrothiophene (2.20 mL, 25.0 mmol, 1.0 eq.) and TMEDA (4.80 mL, 32.5 mmol, 1.3 eq.) in hexane (100 mL) at 0 ˚C under Ar. The resulting solution was stirred at 0 ˚C for 1 h. Then, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.63 mL, 32.5 mmol, 1.3 eq.) was added, and the resulting solution was stirred at 0 ˚C for 1 h. The solution was allowed to warm to rt and saturated $NH_4Cl_{(aq)}$ (20 mL), water (100 mL) and Et_2O (30 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 93:7 hexane-Et_2O as eluent gave 2-Bpin tetrahydrothiophene **110** (1.90 g, 36%) as a colourless oil, R_F (93:7 hexane-Et_2O) 0.25; IR (ATR) 2977, 2933, 2861, 1407, 1370, 1324, 1305, 1263, 1247, 1214, 1166, 1140, 972, 851 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.95-2.76 (m, 2H, SCH), 2.61 (dd, J = 9.0, 6.0 Hz, 1H, SCH), 2.23-2.09 (m, 2H, CH), 1.87-1.71 (m, 2H, CH), 1.26 (s, 12H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 83.7 (O*C*Me_2), 33.5 (CH_2), 32.5 (CH_2), 32.4 (CH_2), 24.7 (C*Me*), 24.6 (C*Me*) (BCH resonance not resolved); ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.7; HRMS (APCI) *m/z* calcd for $C_{10}H_{19}BO_2S$ $(M + H)^+$ 215.1273, found 215.1273 (+0.2 ppm error).

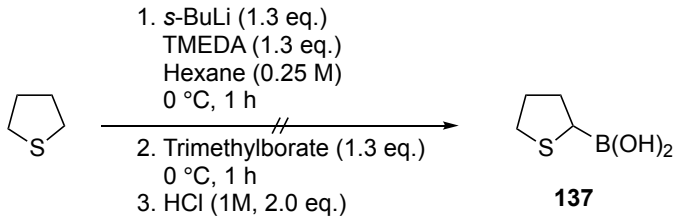
Lab book reference: **SMc3-73-7**

sec-BuLi (12.3 mL of a 1.3 M solution in 92:8 cyclohexane-hexane, 16.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of tetrahydrothiophene (1.1 mL, 12.5 mmol, 1.0 eq.) and TMEDA (2.43 mL, 16.3 mmol, 1.3 eq.) in hexane (50 mL) at 0 ˚C

under Ar. The resulting solution was stirred at 0 ˚C for 1 h. Then, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.3 mL, 16.3 mmol, 1.3 eq.) was added, and the resulting solution was stirred at 0 ˚C for 1 h. The solution was allowed to warm to rt and saturated $NH_4Cl_{(aq)}$ (20 mL), water (100 mL) and Et_2O (30 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 95:5 hexane-Et_2O as eluent gave 2-Bpin tetrahydrothiophene **110** (1.08 g, 40%) as a colourless oil.

Lab book reference: **SMc73-5**

Attempted synthesis of (tetrahydrothiophen-3-yl)-boronic acid 137

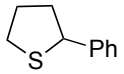


137

sec-BuLi (9.8 mL of a 1.3 M solution in 92:8 cyclohexane-hexane, 13 mmol, 1.3 eq.) was added dropwise to a stirred solution of tetrahydrothiophene (0.88 mL, 10.0 mmol, 1.0 eq.) and TMEDA (1.95 mL, 13 mmol, 1.3 eq.) in hexane (50 mL) at 0 ˚C under Ar. The resulting solution was stirred at 0 ˚C for 1 h. Then, trimethyl borate (1.45 mL, 13 mmol, 1.3 eq.) was added and the resulting solution was stirred at 0 °C for 1 h. Next, 1M $HCl_{(aq)}$ (20 mL) was added and the resulting solution was stirred at 0 ˚C for 1 h. CH_2Cl_2 (30 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give none of 2-$B(OH)_2$ tetrahydrothiophene **137** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **SMc3-93-1**

2-Phenyltetrahydrothiophene 116



116

Using General Procedure A, 2-Bpin tetrahydrothiophene **110** (162 mg, 0.75 mmol, 1.5 eq.) and bromobenzene (52 µL, 0.5 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 97.5:2.5 hexane-Et_2O as eluent gave 2-aryl tetrahydrothiophene **116** (64 mg, 78%) as a colourless oil, R_F (97.5:2.5 hexane-Et_2O) 0.37; IR (ATR) 2947, 2860, 1491, 1441, 1262, 1262, 759, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.38 (m, 2H, Ph), 7.37-7.27 (m, 2H, Ph), 7.27-7.19 (m, 1H, Ph), 4.52 (dd, *J* = 8.5, 6.0 Hz, 1H, SC*H*Ph), 3.22-3.11 (m, 1H, SCH), 3.02 (ddd, *J* = 10.5, 6.5, 4.0 Hz, 1H, SCH), 2.43-2.36 (m, 1H, CH), 2.33-2.24 (m, 1H, CH), 2.06-1.89 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.1 (*ipso*-Ph), 128.5 (Ph), 127.8 (Ph), 127.1 (Ph), 52.9 (SCH), 40.7 (CH_2), 33.6 (CH_2), 31.2 (CH_2); HRMS (APCI) *m/z* calcd for $C_{10}H_{12}S$ $(M + H)^+$ 165.0732, found 165.0726 (+3.2 ppm error). Spectroscopic data consistent with those reported in the literature.[73]

Lab book reference: **SMc3-74-1**

Experimental data for Table 2.1: Deviations to the standard SMCC conditions

2-Bpin tetrahydrothiophene **110** (159 mg, 0.75 mmol, 1.5 eq.), $Pd(OAc)_2$ (11 mg, 50 µmol, 0.10 eq.), cataCXium A (37 mg, 100 umol, 0.20 eq.) and Cs_2CO_3 (490 mg, 1.5 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (52 µL, 0.5 mmol, 1.0 eq.), degassed toluene (0.70 mL, 0.71 M) and water (90 µL, 5.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to **100 °C**. The mixture was stirred at 1000-1200 rpm and heated at 100 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two

layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using 97.5:2.5 hexane-Et_2O as eluent gave 2-aryl tetrahydrothiophene **116** (28 mg, 34%) as a colourless oil.

Lab book reference: **SMc3-84-1**

2-Bpin tetrahydrothiophene **110** (162 mg, 0.75 mmol, 1.5 eq.), $Pd(OAc)_2$ (5.3 mg, 24 μmol, 0.05 eq.), cataCXium A (17.7 mg, 50 umol, 0.1 eq.) and Cs_2CO_3 (490 mg, 1.5 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (52 μL, 0.5 mmol, 1.0 eq.), degassed toluene (0.70 mL, 0.71 M) and water (90 μL, 5.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using 97.5:2.5 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **116** (5 mg, 5%) as a colourless oil.

Lab book reference: **SMc3-83-1**

2-Bpin tetrahydrothiophene **110** (161 mg, 0.75 mmol, 1.5 eq.), cataCXium A Pd G3 (36 mg, 50 μmol, 0.10 eq.) and Cs_2CO_3 (490 mg, 1.5 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (52 μL, 0.5 mmol, 1.0 eq.), degassed toluene (0.70 mL, 0.71 M) and water (90 μL, 5.0 mmol, 10.0 eq.) were added under

N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using 97.5:2.5 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **116** (42 mg, 51%) as a colourless oil.

Lab book reference: **SMc3-88-1**

2-Bpin tetrahydrothiophene **110** (93 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 0.10 eq.), cataCXium A (22 mg, 60 μmol, 0.20 eq.) and Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and chlorobenzene (30 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.43 mL) and water (54 μL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using 99:1 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **116** (13 mg, 27%) as a colourless oil.

Lab book reference: **SMc4-221**

2-Bpin tetrahydrothiophene **110** (163 mg, 0.75 mmol, 1.5 eq.), $Pd(OAc)_2$ (11 mg, 50 μmol, 0.10 eq.), cataCXium A (36 mg, 100 μmol, 0.2 eq.) and Cs_2CO_3 (489 mg, 1.5

mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and iodobenzene (56 µL, 0.5 mmol, 1.0 eq.), degassed toluene (0.70 mL) and water (90 µL, 5.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using 97.5:2.5 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **116** (51 mg, 62%) as a colourless oil.

Lab book reference: **SMc3-118-1**

2-Bpin tetrahydrothiophene **110** (163 mg, 0.75 mmol, 1.5 eq.), $Pd(OAc)_2$ (11 mg, 50 µmol, 0.10 eq.), cataCXium A (36 mg, 100 µmol, 0.2 eq.) and Cs_2CO_3 (489 mg, 1.5 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and Iodobenzene (56 µL, 0.5 mmol, 1.0 eq.), degassed toluene (0.70 mL) and water (90 µL, 5.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using 97.5:2.5 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **116** (50 mg, 61%) as a colourless oil.

Lab book reference: **SMc3-118-2**

2-Bpin tetrahydrothiophene **110** (92 mg, 0.45 mmol, 1.5 eq.), P(Ad)$_3$ Pd G3 (24 mg, 30 μmol, 0.10 eq.) and Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (32 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.43 mL) and water (54 μL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using 97.5:2.5 hexane-Et_2O as eluent gave 2-Bpin tetrahydrothiophene **116** (33 mg, 67%) as a colourless oil.

Lab book reference: **SMc4-176-1**

2-Bpin tetrahydrothiophene **110** (94 mg, 0.45 mmol, 1.5 eq.), P(*t*-Bu)$_3$ Pd G3 (18 mg, 30 μmol, 0.1 eq.) and Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (32 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.43 mL) and water (54 μL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using 97.5:2.5 hexane-

Et_2O as eluent gave aryl tetrahydrothiophene **116** as a mixture with an unknown impurity. The impure mixture of aryl tetrahydrothiophene **116** was purified by flash column chromatography on silica using 99:1 hexane-Et_2O as eluent to give aryl tetrahydrothiophene **116** (8 mg, 16%) as a colourless oil.

Lab book reference: **SMc4-229**

2-Bpin Tetrahydrothiophene **110** (92 mg, 0.45 mmol, 1.5 eq.), SPhos Pd G3 (23 mg, 30 μmol, 0.1 eq.) and Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (32 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.43 mL, 0.71 M) and water (54 μL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using 199:1 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **116** (1 mg, 2%) as a colourless oil.

Lab book reference: **SMc4-230**

Experimental data for Table 2.2: Effect of oxygen on the SMCC reaction of 2-Bpin tetrahydrothiophene

2-Bpin Tetrahydrothiophene **110** (92 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 0.1 eq.) and cataCXium A (22 mg, 60 μmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for

15 min. Then, the exit needle was removed and bromobenzene (32 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.43 mL), water (54 μL, 3.0 mmol, 10.0 eq.), were added under N_2. The vial was removed from the nitrogen line (purge needle removed). the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, EtOAc (1 mL) and water (1 mL) were added to the vial. The vial was agitated and the layers separated. Using a needle, 0.1 mL of the organic (top) layer was transferred the solvent evaporated under a stream of compressed air and the sample was analysed by ^{1}H NMR (86% conversion to 2-phenyl tetrahydrothiophene **116**).

Lab book reference: **SMc6-450**

2-Bpin Tetrahydrothiophene **110** (92 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 0.1 eq.) and cataCXium A (22 mg, 60 μmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (32 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.43 mL), water (54 μL, 3.0 mmol, 10.0 eq.), were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and compressed air (0.2 mL) was added. the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, EtOAc (1 mL) and water (1 mL) were added to the vial. The vial was agitated and the layers separated. Using a needle, 0.1 mL of the organic (top) layer was transferred the solvent evaporated under a stream of compressed air and the sample was analysed by ^{1}H NMR (85% conversion to 2-phenyl tetrahydrothiophene **116**).

Lab book reference: **SMc6-449**

2-Bpin Tetrahydrothiophene **110** (92 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 0.1 eq.) and cataCXium A (22 mg, 60 μmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a

screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (32 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.43 mL), water (54 μL, 3.0 mmol, 10.0 eq.), were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and compressed air (0.4 mL) was added. the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, EtOAc (1 mL) and water (1 mL) were added to the vial. The vial was agitated and the layers separated. Using a needle, 0.1 mL of the organic (top) layer was transferred the solvent evaporated under a stream of compressed air and the sample was analysed by ^{1}H NMR (84% conversion to 2-phenyl tetrahydrothiophene **116**).

Lab book reference: **SMc6-448**

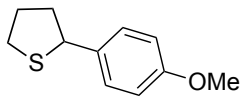
2-Bpin Tetrahydrothiophene **110** (92 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 0.1 eq.) and cataCXium A (22 mg, 60 μmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (32 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.43 mL), water (54 μL, 3.0 mmol, 10.0 eq.), were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and compressed air (0.6 mL) was added. the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, EtOAc (1 mL) and water (1 mL) were added to the vial. The vial was agitated and the layers separated. Using a needle, 0.1 mL of the organic (top) layer was transferred the solvent evaporated under a stream of compressed air and the sample was analysed by ^{1}H NMR (83% conversion to 2-phenyl tetrahydrothiophene **116**).

Lab book reference: **SMc6-447**

2-Bpin Tetrahydrothiophene **110** (92 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 0.1 eq.) and cataCXium A (22 mg, 60 μmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum. Then, the exit needle was removed and bromobenzene (32 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.43 mL), water (54 μL, 3.0 mmol, 10.0 eq.), were added under N_2. the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, EtOAc (1 mL) and water (1 mL) were added to the vial. The vial was agitated and the layers separated. Using a needle, 0.1 mL of the organic (top) layer was transferred the solvent evaporated under a stream of compressed air and the sample was analysed by ^{1}H NMR (62% conversion to 2-phenyl tetrahydrothiophene **116**).

Lab book reference: **SMc6-452**

2-(4-Methoxyphenyl)tetrahydrothiophene 140



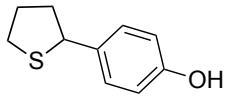
140

Using General Procedure A, 2-Bpin tetrahydrothiophene **110** (168 mg, 0.75 mmol, 1.5 eq.), and 4-bromoanisole (63 μL, 0.5 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 99:1 hexane-Et_2O to 97.5:2.5 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **140** (61 mg, 63%) as a yellow oil, R_F (9:1 hexane-Et_2O) 0.27; IR (ATR) 2947, 1610, 1510, 1247, 1035, 830 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.29 (m, 2H, Ar), 6.89-6.81 (m, 2H, Ar), 4.49 (dd, J = 8.5, 6.0 Hz, 1H, SC*H*Ar), 3.79 (s, 3H, OMe), 3.15 (ddd, J = 10.5, 8.5, 6.0 Hz, 1H, SCH), 3.00 (ddd, J = 10.5, 7.0, 4.0 Hz, 1H, SCH), 2.41-2.31 (m, 1H, CH), 2.31-2.22 (m, 1H, CH), 2.07-1.84 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.7 (*ipso*-Ar), 134.9 (*ipso*-Ar), 128.7 (Ar), 113.9 (Ar), 55.4 (OMe), 52.4 (SCH), 40.7 (CH_2), 33.5 (CH_2), 31.1 (CH_2); HRMS (ESI) *m/z* calcd for $C_{11}H_{14}OS$ $(M + H)^+$

195.0838, found 195.0831 (–3.6 ppm error). Spectroscopic data consistent with those reported in the literature.[23]

Lab book reference: **SMc3-123**

4-(Tetrahydrothiophen-2-yl)phenol 141

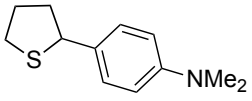


141

Using General Procedure B, 2-Bpin tetrahydrothiophene **110** (162 mg, 0.75 mmol, 1.5 eq.) and 4-bromophenol (88 mg, 0.5 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 93:7 hexane-Et_2O to 90:10 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **141** (12 mg, 16%) as a beige oil, R_F (80:20 hexane-Et_2O) 0.1; IR (ATR) 3327 (OH), 2928, 2858, 1611, 1596, 1511, 1440 (O-H), 1360, 1225 (OH), 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.25 (m, 2H, Ar), 6.81-6.74 (m, 2H, Ar), 4.85 (br s, 1H, OH) 4.47 (dd, J = 8.5, 6.0 Hz, 1H, SC*H*Ar), 3.19-3.09 (m, 1H, SCH), 3.04-2.95 (m, 1H, SCH), 2.40-2.31 (m, 1H, CH), 2.31-2.21 (m, 1H, CH), 2.04-1.83 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.6 (*ipso*-Ar), 135.1 (*ipso*-Ar), 128.9 (Ar), 115.3 (Ar), 52.3 (SCH), 40.7 (CH_2), 33.5 (CH_2), 31.1 (CH_2); HRMS (ESI) *m/z* calcd for $C_{10}H_{11}OS$ $(M + H)^+$ 179.0543, found 179.0536 (–3.9 ppm error).

Lab book reference: **SMc3-77-1**

***N*,*N*-Dimethyl-4-(tetrahydrothiophen-2-yl)aniline 142**



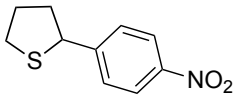
142

Using General Procedure B, 2-Bpin tetrahydrothiophene **110** (163 mg, 0.75 mmol, 1.5 eq.) and 4-bromo-*N*,*N*-dimethylaniline (100 mg, 0.5 mmol, 1.0 eq.) gave the crude

product. Purification by column chromatography on silica using 95:5 hexane-Et_2O eluent gave a mixture of aryl tetrahydrothiophene **142** and an unknown impurity. The impure mixture was purified by flash column chromatography on silica using 10:87:3 toluene-hexane-Et_2O as eluent to give aryl tetrahydrothiophene **142** (75 mg, 72%) as a pale yellow solid, mp 28-30 °C; R_F (10:87:3 toluene-hexane-Et_2O) 0.2; IR (ATR) 1612, 1512, 1441, 1346, 1163, 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.24 (m, 2H, Ar), 6.76-6.66 (m, 2H, Ar), 4.48 (dd, *J* = 9.0, 6.0 Hz, 1H, SC*H*Ar), 3.22-3.10 (m, 1H, SCH), 3.05-2.96 (m, 1H, SCH), 2.94 (s, 6H, Me), 2.41-2.22 (m, 2H, CH), 2.04-1.86 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 149.7 (*ipso*-Ar), 130.3 (*ipso*-Ar), 128.2 (Ar), 112.5 (Ar), 52.4 (SCH), 40.7 (NMe_2), 40.4 (CH_2), 33.3 (CH_2), 31.0 (CH_2); HRMS (ESI) *m/z* calcd for $C_{12}H_{17}NS$ $(M + H)^+$ 208.1154, found 208.1157 (–1.2 ppm error).

Lab book reference: **SMc5-246**

2-(4-Nitrophenyl)tetrahydrothiophene 143



143

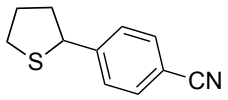
Using General Procedure B, 2-Bpin tetrahydrothiophene **110** (163 mg, 0.75 mmol, 1.5 eq.) and 1-bromo-4-nitrobenzene (101 mg, 0.5 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 197:3 hexane-Et_2O as eluent gave slightly impure aryl tetrahydrothiophene **143** (unknown impurity) (52 mg, 50% NMR yield using trimethoxybenzene as an external standard) as a yellow oil, R_F (90:10 hexane-Et_2O) 0.19; IR (ATR) 1597, 1518 (asymmetric NO_2), 1345 (symmetric NO_2), 967, 852 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) for **143**: δ 8.20-8.10 (m, 2H, Ar), 7.62-7.53 (m, 2H, Ar), 4.56 (dd, *J* = 8.5, 6.5 Hz, 1H, SC*H*Ar), 3.17 (ddd, *J* = 10.0, 8.5, 6.0 Hz, 1H, SCH), 3.04 (ddd, *J* = 10.0, 7.0, 4.0 Hz, 1H, SCH), 2.50-2.38 (m, 1H, CH), 2.33-2.21 (m, 1H, CH), 2.10-1.99 (m, 1H, CH), 1.96-1.85 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) for **143**: δ 151.2 (*ipso*-Ar), 147.0 (*ipso*-Ar), 128.7 (Ar), 123.7

(Ar), 52.0 (SCH), 40.7 (CH_2), 33.8 (CH_2), 31.2 (CH_2); HRMS (APCI positive) *m/z* calcd for $C_{10}H_{11}NO_2S$ $(M + H)^+$ 210.0583, found 210.0579 (+1.0 ppm error).

The NMR yield was determined by dissolving the slightly impure aryl tetrahydrothiophene **143** (obtained after the purification) in Et_2O (10 mL) and adding 1,3,5-trimethoxybenzene (42.5 mg, 0.25 mmol) as an external standard. The solution was evaporated under reduced pressure to give a sample which was analysed by ^1H NMR spectroscopy.

Lab book reference: **SMc3-91-1**

4-(Tetrahydrothiophen-2-yl)benzonitrile 121

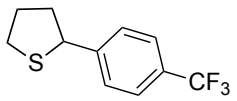


121

Using General Procedure B, 2-Bpin tetrahydrothiophene **110** (163 mg, 0.75 mmol, 1.5 eq.) and 4-bromobenzonitrile (91 mg, 0.5 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using hexane to 95:5 hexane-Et_2O to 90:10 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **121** (73 mg, 73%) as a dark orange oil, R_F (90:10 hexane-Et_2O) 0.14; IR (ATR) 2949, 2227 (C≡N), 1606, 1501, 1441 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59-7.53 (m, 2H, Ar), 7.53-7.46 (m, 2H, Ar), 4.49 (dd, *J* = 8.5, 6.5 Hz, 1H, SC*H*Ar), 3.14 (ddd, *J* = 10.5, 8.5, 6.5 Hz, 1H, SCH), 3.01 (ddd, *J* = 10.5, 7.0, 4.0 Hz, 1H, SCH), 2.45-2.34 (m, 1H, CH), 2.30-2.17 (m, 1H, CH), 2.06-1.93 (m, 1H, CH), 1.93-1.81 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) 149.0 (*ipso*-Ar), 132.3 (Ar), 128.6 (Ar), 119.0 (*ipso*-Ar or C≡N), 110.8 (*ipso*-Ar or C≡N), 52.3 (SCH), 40.6 (CH_2), 33.8 (CH_2), 31.2 (CH_2); HRMS (ESI) *m/z* calcd for $C_{11}H_{11}NS$ $(M + Na)^+$ 212.0504, found 212.0510 (–2.6 ppm error). Spectroscopic data consistent with those reported in the literature.[23]

Lab book reference: **SMc3-94-2**

3-(4-(Trifluoromethyl)phenyl)tetrahydrothiophene 144

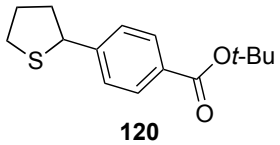


144

2-Bpin tetrahydrothiophene **110** (96 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 0.10 eq.), cataCXium A (22 mg, 60 μmol, 0.20 eq.) and Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and 1-bromo-4-(trifluoromethyl)-benzene (42 μL, 0.30 mmol, 1.0 eq.), degassed toluene (0.43 mL, 0.71 M) and water (54 μL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using 99:1 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **144** (29 mg, 59%) as a colourless oil, R_F (97.5:2.5 hexane-Et_2O) 0.37; IR (ATR) 1326 (C-F), 1164, 1122, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58-7.54 (m, 2H, Ar), 7.54-7.50 (m, 2H, Ar), 4.54 (dd, *J* = 8.5, 6.5 Hz, 1H, SC*H*Ar), 3.17 (ddd, *J* = 10.5, 8.5, 6.0 Hz, 1H, SCH), 3.06 (ddd, *J* = 10.5, 7.0, 4.0 Hz, 1H, SCH), 2.48-2.36 (m, 1H, CH), 2.33-2.21 (m, 1H, CH), 2.10-1.86 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 147.5 (*ipso*-Ar), 129.3 (q, *J* = 32 Hz, *ispo*-Ar), 128.2 (Ar), 125.5 (q, *J* = 4.0 Hz, Ar), 124.25 (q, *J* = 273 Hz, CF_3), 52.3 (SCH), 40.7 (CH_2), 33.8 (CH_2), 31.2 (CH_2); ^{19}F NMR (375 MHz, $CDCl_3$) δ -62.3; HRMS (EI) *m/z* calcd for $C_{11}H_{11}F_3S$ $(M + H)^+$ 232.05281, found 232.05305 (+1.1 ppm error). Spectroscopic data consistent with those reported in the literature.[162]

Lab book reference: **SMc5-238**

tert-Butyl 4-(tetrahydrothiophen-2-yl)benzoate 120

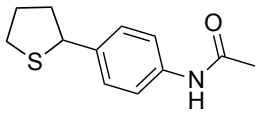


120

Using General Procedure A, 2-Bpin tetrahydrothiophene **110** (158 mg, 0.75 mmol, 1.5 eq.) and tert-butyl 4-bromobenzoate (98 μL, 0.5 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 95:5 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **120** (97 mg, 73%) as a yellow oil, R_F (90:10 hexane-Et_2O) 0.27; IR (ATR) 1709 (C=O), 1292, 1164, 1116, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96-7.88 (m, 2H, Ar), 7.49-7.41 (m, 2H, Ar), 4.53 (dd, *J* = 8.5, 6.0 Hz, 1H, SC*H*Ar), 3.15 (ddd, *J* = 10.5, 8.5, 6.0 Hz, 1H, SCH), 3.02 (ddd, *J* = 10.5, 7.0, 4.0 Hz, 1H, SCH), 2.45-2.34 (m, 1H, CH), 2.32-2.20 (m, 1H, CH), 2.10-1.84 (m, 2H, CH), 1.58 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.7 (C=O), 148.1 (*ipso*-Ar), 130.8 (*ipso*-Ar), 129.6 (Ar), 127.6 (Ar), 81.0 (O*C*Me_3), 52.5 (SCH), 40.6 (CH_2), 33.7 (CH_2), 31.2 (CH_2), 28.3 (C*Me*$_3$); HRMS (ESI) *m/z* calcd for $C_{15}H_{20}O_2S$ $(M + Na)^+$ 287.1076, found 287.1079 (–0.8 ppm error). Spectroscopic data consistent with those reported in the literature.[73]

Lab book reference: **SMc5-249**

_N_-(4-(Tetrahydrothiophen-2-yl)phenyl)acetamide 145



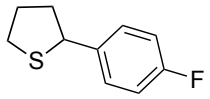
145

Using General Procedure B, 2-Bpin tetrahydrothiophene **110** (158 mg, 0.75 mmol, 1.5 eq.) and 4-bromoacetanilide (107 mg, 0.5 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 90:10 hexane-Et_2O to 60:40 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **145** (83 mg, 75%) as a yellow solid, mp 77-79 °C; R_F (Et_2O) 0.43; IR (ATR) 3300 (NH), 2929, 1664 (C=O), 1601, 1536, 1513, 1411, 1316 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.69 (s, 1H, NH),

7.45-7.38 (m, 2H, Ar), 7.36-7.30 (m, 2H, Ar), 4.47 (dd, *J* = 8.5, 6.0 Hz, 1H, SC*H*Ar), 3.19-3.08 (m, 1H, SCH), 3.04–2.94 (ddd, *J* = 10.5, 7.0, 4.0 Hz, 1H, SCH), 2.41-2.29 (m, 1H, CH), 2.29-2.18 (m, 1H, CH), 2.13 (s, 3H, Me), 2.04-1.81 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.7 (C=O), 138.9 (*ipso*-Ar), 136.8 (*ipso*-Ar), 128.2 (Ar), 120.1 (Ar), 52.4 (SCH), 40.6 (CH_2), 33.6 (CH_2), 31.1 (CH_2), 24.6 (Me); HRMS (ESI) *m/z* calcd for $C_{12}H_{15}NOS$ $(M + Na)^+$ 244.0767, found 244.0764 (–0.9 ppm error). Spectroscopic data consistent with those reported in the literature.[163]

Lab book reference: **SMc3-79-1**

2-(4-fluorophenyl)tetrahydrothiophene 118

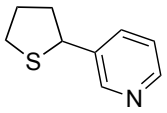


118

Using General Procedure A, 2-Bpin tetrahydrothiophene **110** (162 mg, 0.75 mmol, 1.5 eq.) and 4-fluorobromobenzene (55 μL, 0.5 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 97.5:2.5 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **118** (44 mg, 80%) as a yellow oil, R_F (97.5:2.5 hexane-Et_2O) 0.13; IR (ATR) 2928, 2856, 1602, 1508, 1224, 1157, 833 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.34 (m, 2H, Ar), 7.03-6.94 (m, 2H, Ar), 4.49 (dd, *J* = 9.0, 6.0, 1H, SC*H*Ar), 3.15 (ddd, *J* = 10.5, 9.0, 6.0, 1H, SCH), 3.01 (ddd, *J* = 10.5, 7.0, 4.0, 1H, SCH), 2.43-2.32 (m, 1H, CH), 2.32-2.20 (m, 1H, CH), 2.07-1.82 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.8 (d, *J* = 245.5 Hz, *ipso*-Ar), 138.6 (d, *J* = 3.5 Hz, *ipso*-Ar), 129.1 (d, *J* = 8.0 Hz, Ar), 115.1 (d, *J* = 21.0 Hz, Ar), 52.0 (SCH), 40.7 (CH_2), 33.4 (CH_2), 30.9 (CH_2); ^{19}F NMR (375 MHz, $CDCl_3$) δ -115.91 (tt, *J* = 8.50, 4.50 Hz); HRMS (APCI) *m/z* calcd for $C_{10}H_{11}FS$ $(M + H)^+$ 183.0638, found 183.0644 (–3.0 ppm error). Spectroscopic data consistent with those reported in the literature.[23]

Lab book reference: **SMc3-124**

3-(Tetrahydrothiophen-2-yl)pyridine 146

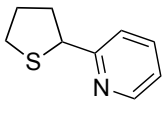


146

Using General Procedure A, 2-Bpin tetrahydrothiophene **110** (165 mg, 0.75 mmol, 1.5 eq.) and 3-bromopyridine (48 μL, 0.5 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 93:7 hexane-Et_2O to 90:10 hexane-Et_2O as eluent gave a mixture of aryl tetrahydrothiophene **146** and pinacol. Water (3 mL) was added and the impure mixture was evaporated under reduced pressure. The evaporate dissolve process was repeated twice more with water (2 x 3 mL) to give aryl tetrahydrothiophene **146** (32 mg, 39%) as a yellow oil, R_F (30:70 hexane-Et_2O) 0.15; IR (ATR) 2931, 2856, 1690, 1575, 1478, 1424, 1025, 804, 714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 2.0 Hz, 1H, Ar), 8.47 (dd, J = 5.0, 2.0 Hz, 1H, Ar), 7.78 (ddd, J = 8.0, 2.0, 2.0 Hz, 1H, Ar), 7.24 (dd, J = 8.0, 5.0 Hz, 1H, Ar), 4.51 (dd, J = 8.5, 6.0 Hz, 1H, SC*H*Ar), 3.17 (ddd, J = 10.5, 8.5, 6.0 Hz, 1H, SCH), 3.04 (ddd, J = 10.5, 7.0, 4.0 Hz, 1H, SCH), 2.49-2.37 (m, 1H, CH), 2.34-2.22 (m, 1H, CH), 2.09-1.98 (m, 1H, CH), 1.98-1.86 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 149.3 (Ar), 148.4 (Ar), 138.6 (*ipso*-Ar), 135.1 (Ar), 123.3 (Ar), 49.8 (SCH), 40.5 (CH_2), 33.6 (CH_2), 31.0 (CH_2); HRMS (ESI) *m/z* calcd for $C_9H_{11}NS$ $(M + H)^+$, found 166.0686 (–0.4 ppm error). Spectroscopic data consistent with those reported in the literature.[27]

Lab book reference: **SMc3-114-1**

2-(Tetrahydrothiophen-2-yl)pyridine 147



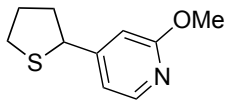
147

Using General Procedure A, 2-Bpin tetrahydrothiophene **110** (162 mg, 0.75 mmol, 1.5 eq.) and 2-bromopyridine (48 μL, 0.5 mmol, 1.0 eq.) gave the crude product.

Purification by flash column chromatography on silica using 50:50 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **147** (25 mg, 30%) as a yellow oil, R_F (50:50 hexane-Et_2O) 0.11; IR (ATR) 2925, 2854, 1697, 1582, 1455, 1125, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 8.28-8.52 (m, 1H, Ar), 7.59 (ddd, J = 7.5, 7.5, 2.0 Hz, 1H, Ar), 7.41 (d, J = 7.5 Hz, 1H, Ar), 7.10 (dd, J = 7.5, 5.0 Hz, 1H, Ar), 4.61 (dd, J = 7.0, 7.0 Hz, 1H, SC*H*Ar), 3.13 (ddd, J = 10.5, 8.0, 6.0 Hz, 1H, SCH), 2.99 (ddd, 10.5, 6.5, 5.0 Hz, 1H, SCH), 2.48-2.36 (m, 1H, CH), 2.32-2.09 (m, 2H, CH), 2.08-1.96 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.5 (*ipso*-Ar), 149.3 (Ar), 136.5 (Ar), 122.1 (Ar), 121.8 (Ar), 53.7 (SCH), 38.2 (CH_2), 33.7 (CH_2), 31.0 (CH_2); HRMS (ESI) *m/z* calcd for $C_9H_{11}NS$ $(M + H)^+$ 166.0685, found 166.0686 (–0.7 ppm error). Spectroscopic data consistent with those reported in the literature.[26]

Lab book reference: **SMc3-113-1**

2-Methoxy-4-(tetrahydrothiophen-2-yl)pyridine 148

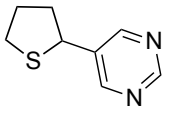


148

Using General Procedure B, 2-Bpin tetrahydrothiophene **110** (162 mg, 0.75 mmol, 1.5 eq.) and 4-bromo-2-methoxypyridine (96 mg, 0.5 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 93:7 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **148** (73 mg, 73%) as an orange oil, R_F (90:10 hexane-Et_2O) 0.11; IR (ATR) 2945, 2860, 1606, 1557, 1479, 1392, 1312, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 5.5 Hz, 1H, Ar), 6.88 (dd, J = 5.5, 1.5 Hz, 1H, Ar), 6.75 (d, J = 1.5 Hz, 1H, Ar), 4.36 (dd, J = 7.0, 7.0 Hz, 1H, SC*H*Ar), 3.89 (s, 3H, OMe), 3.08 (ddd, J = 10.0, 8.0, 6.5 Hz, 1H, SCH), 2.95 (ddd, J = 10.0, 6.5, 4.5 Hz, 1H, SCH), 2.39-2.28 (m, 1H, CH), 2.22-2.11 (m, 1H, CH), 2.03-1.79 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.6 (*ipso*-Ar), 155.4 (*ipso*-Ar), 146.8 (Ar), 116.3 (Ar), 109.6 (Ar), 53.5 (OMe), 51.3 (SCH), 39.7 (CH_2), 33.5 (CH_2), 30.9 (CH_2); HRMS (ESI) *m/z* calcd for $C_{10}H_{13}NOS$ $(M + H)^+$ 196.0791, found 196.0792 (–0.7 ppm error).

Lab book reference: **SMc3-81-1**

5-(Tetrahydrothiophen-2-yl)pyrimidine 149

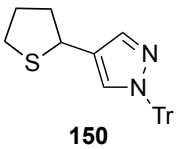


149

Using general procedure B, 2-Bpin tetrahydrothiophene **110** (159 mg, 0.75 mmol, 1.5 eq.) and 5-bromopyrimidine (80 mg, 0.5 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 80:20 hexane-Et_2O gave aryl tetrahydrothiophene **149** (73 mg, 65%) as a yellow oil, R_F (80:20 hexane-Et_2O) 0.21; IR (ATR) 2928, 2860, 1561, 1438, 1409, 1181, 1124, 727 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 9.07 (s, 1H, Ar), 8.76 (s, 2H, Ar), 4.44 (dd, *J* = 8.0, 6.5 Hz, 1H, SC*H*Ar), 3.17 (ddd, *J* = 10.0, 8.0, 6.5 Hz, 1H, SCH), 3.03 (ddd, *J* = 10.0, 8.5, 6.5 Hz, 1H, SCH), 2.50-2.39 (m, 1H, CH), 2.32-2.19 (m, 1H, CH), 2.11-1.98 (m, 1H, CH), 1.98-1.87 (m, 1H, CH); ^{13}C (100.6 MHz, $CDCl_3$) δ 157.6 (Ar), 156.4 (Ar), 136.8 (*ipso*-Ar), 47.4 (SCH), 40.3 (CH_2), 33.8 (CH_2), 31.1 (CH_2); HRMS (ESI) *m/z* calcd for $C_8H_{10}N_2S$ $(M + H)^+$ 167.0637, found 167.0635 (+1.7 ppm error).

Lab book reference: **SMc5-241**

4-(Tetrahydrothiophen-2-yl)-1-trityl-1*H*-pyrazole 150



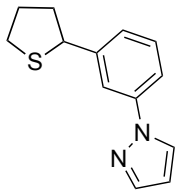
150

Using General Procedure B, 2-Bpin tetrahydrothiophene **110** (160 mg, 0.75 mmol, 1.5 eq.), and 4-bromo-1-(triphenylmethyl)-1H-pyrazole (194 mg, 0.5 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 80:20 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **150** (139 mg, 70%) as a yellow semi-solid, R_F (70:30 hexane-Et_2O) 0.23; IR (ATR) 2945, 1492, 1445, 1130, 875, 746, 700, 640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.62 (s, 1H, Ar), 7.30-7.21 (m, 10H, Ar), 7.18-7.09 (m, 6H, Ar), 4.40 (dd, *J* = 8.0, 6.0 Hz, 1H, SC*H*Ar), 3.03 (ddd, *J* = 10.0, 7.5, 7.5 Hz, 1H, SCH), 2.89 (ddd, *J* = 10.0, 6.5, 4.5 Hz, 1H, SCH), 2.30-2.20 (m, 1H, CH),

2.19-2.07 (m, 1H, CH), 1.97-1.82 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.3 (*ipso*-Ar), 138.4 (Ar), 130.5 (Ar), 130.1 (Ar), 127.69 (Ar), 127.66 (Ar), 122.6 (*ipso*-Ar), 78.5 (*C*Ph_3), 42.7 (SCH), 40.0 (CH_2), 33.0 (CH_2), 30.5 (CH_2); HRMS (ESI) *m/z* calcd for $C_{26}H_{24}N_2S$ $(M + K)^+$ 435.1292, found 435.1291 (+0.3 ppm error).

Lab book reference: **SMc3-119**

1-(3-(Tetrahydrothiophen-2-yl)phenyl)-1*H*-pyrazole 151



151

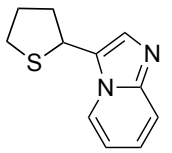
Using General Procedure B, 2-Bpin tetrahydrothiophene **110** (162 mg, 0.75 mmol, 1.5 eq.) and 1-(4-bromophenyl)-1H-pyrazole (112 mg, 0.5 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 93:7 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **151** (86 mg, 73%) as an amber oil, R_F (94:6 hexane-Et_2O) 0.10; IR (ATR) 2944, 2856, 1606, 1591, 1518, 1391, 1334, 1043 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.93 (d, *J* = 2.5 Hz, 1H, Ar), 7.80 (dd, *J* = 2.0, 2.0 Hz, 1H, Ar), 7.73 (d, *J* = 2.0, 1H, Ar), 7.52 (ddd, *J* = 7.5, 2.0, 2.0 Hz, 1H, Ar), 7.38 (dd, *J* = 7.5, 7.5 Hz, 1H, Ar), 7.34 (ddd, *J* = 7.5, 2.0, 2.0 Hz 1H, Ar), 6.46 (dd, *J* = 2.5, 2.0 1H, Ar), 4.57 (dd, *J* = 8.5, 6.0 Hz, 1H, SC*H*Ar), 3.24-3.09 (m, 1H, CH), 3.03 (m, 1H, CH), 2.49-2.37 (m, 1H, CH), 2.34-2.23 (m, 1H, CH), 2.11-1.91 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.0 (*ipso*-Ar), 141.1 (Ar), 140.3 (*ipso*-Ar), 129.5 (Ar), 127.0 (Ar), 125.9 (Ar), 118.8 (Ar), 117.9 (Ar), 107.6 (Ar), 52.6 (SCH), 40.7 (CH_2), 33.7 (CH_2), 31.1 (CH_2); HRMS (ESI) *m/z* calcd for $C_{13}H_{14}N_2S$ $(M + Na)^+$ 253.0770, found 253.0772 (–0.9 ppm error).

Lab book reference: **SMc3-78-1**

A 25 mL RBF was charged with 2-Bpin tetrahydrothiophene **110** (642 mg, 3.0 mmol, 1.2 eq.), $Pd(OAc)_2$ (56 mg, 10 mol%, 0.25 mmol), cataCXium® A (179 mg, 20 mol%, 0.50 mmol), Cs_2CO_3 (2.44 g, 7.5 mmol, 3.0 eq.). A condenser was added and the headspace was purged with N_2 for 15 min. Then, 1-(4-bromophenyl)-1H-pyrazole (558 mg, 2.5 mmol, 1.0 eq.), degassed toluene (3.6 mL) and degassed water (450 μL, 25 mmol, 10 eq.) were added under N_2. The flask was placed in a heating block preheated to 120 °C (heater block temperature) and the mixture was stirred vigorously and heated at 120 °C for 20 h. After being allowed to cool to rt, water (50 mL) and Et_2O (50 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 mL) and the combined organics were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 93:7 hexane:Et_2O as eluent gave aryl tetrahydrothiophene **151** (505 mg, 88%) as an amber oil.

Lab book reference: **SMc6-503**

3-(Tetrahydrothiophen-2-yl)imidazo[1,2-*a*]pyridine 152



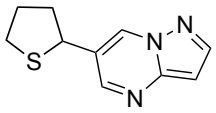
152

Using General Procedure B, 2-Bpin tetrahydrothiophene **110** (166 mg, 0.75 mmol, 1.5 eq.) and 3-bromoimidazo[1,2-a]pyridine (99 mg, 0.5 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using Et_2O to 90:10 Et_2O-CH_2Cl_2 as eluent gave a mixture of aryl tetrahydrothiophene **152** and pinacol. Water (5 mL) was added and the impure mixture was evaporated under reduced pressure. The evaporate dissolve process was repeated twice more with water (2 x 5 mL). Then, Toluene (5 mL) was added and the impure mixture was evaporated under reduced pressure. The toluene evaporation process was repeated twice more (2 x 5 mL) to give aryl tetrahydrothiophene **152** (78 mg, 76%) as an orange oil, R_F (Et_2O) 0.05; IR (ATR) 2928, 2858, 1634, 1499, 1499, 1440, 1305, 737 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$) δ 7.94 (d, *J* = 7.0 Hz, 1H, Ar), 7.50 (d, *J* = 9.0 Hz, 1H, Ar), 7.44 (s, 1H, Ar), 7.12-7.03 (m, 1H, Ar), 6.73 (dd, *J* = 7.0, 7.0 Hz, 1H, Ar), 4.66 (dd, *J* = 7.0, 7.0 Hz, 1H, SC*H*Ar), 3.06-2.91 (m, 2H, SCH), 2.38-2.15 (m, 3H, CH), 2.09-1.91 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.9 (*ipso*-Ar), 130.3 (Ar), 125.0 (*ipso*-Ar), 123.6 (Ar), 123.6 (Ar), 117.8 (Ar), 111.9 (Ar), 41.4 (SCH), 34.9 (CH_2), 32.60 (CH_2), 30.2 (CH_2); HRMS (ESI) *m/z* calculated for $C_{11}H_{12}N_2S$ $(M + H)^+$ 205.0794, found 205.0796 (-1.0 ppm error).081303

Lab book reference: **SMc3-121-1**

6-(Tetrahydrothiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine 153

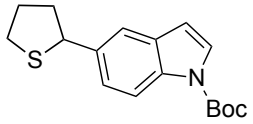


153

Using General Procedure B, 2-Bpin tetrahydrothiophene **110** (162 mg, 0.75 mmol, 1.5 eq.) and 6-bromopyrazolo[1,5-α]pyrimidine (99 mg, 0.5 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 90:10 hexane-Et_2O to 50:50 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **153** (45 mg, 44%) as a colourless oil, R_F (50:50 hexane-Et_2O) 0.16; IR (ATR) 2933, 2861, 1610, 1533, 1443, 1357, 1242, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.46 (d, *J* = 4.5 Hz, 1H, Ar), 8.15 (d, *J* = 2.5 Hz, 1H, Ar), 7.09 (d, *J* = 4.5 Hz, 1H, Ar), 6.73 (d, *J* = 2.5 Hz, 1H, Ar), 5.29 (dd, *J* = 7.5, 5.0 Hz, 1H, SC*H*Ar), 3.15-2.97 (m, 2H, SCH), 2.64-2.49 (m, 1H, SCH), 2.25-2.15 (m, 2H, CH), 2.15-2.05 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 150.6 (*ipso*-Ar), 149.2 (*ipso*-Ar), 149.1 (Ar), 144.4 (Ar), 105.1 (Ar), 97.2 (Ar), 45.4 (SCH), 35.2 (CH_2), 32.9 (CH_2), 30.5 (CH_2); HRMS (ESI) *m/z* calcd for $C_{10}H_{11}N_3S$ $(M + Na)^+$ 228.0566, found 228.0566 (–0.1 ppm error).

Lab book reference: **SMc3-98-1**

tert-Butyl 5-(tetrahydrothiophen-2-yl)-1*H*-indole-1-carboxylate 154

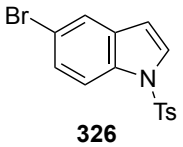


154

Using general procedure B, 2-Bpin tetrahydrothiophene **110** (163 mg, 0.75 mmol, 1.5 eq.) and *tert*-butyl 5-bromo-1-H-indole-1-carboxylate (148 mg, 0.5 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using hexane to 97:3 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **154** (60 mg, 40%) as a colourless oil, R_F (94:6 hexane-Et_2O) 0.29; IR (ATR) 1733 (C=O), 1469, 1372, 1352, 1257, 1161, 1130, 1081, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.5 Hz, 1H, Ar), 7.62 (d, J = 2.0 Hz, 1H, Ar), 7.58 (d, J = 3.5 Hz, 1H, Ar), 7.38 (dd, J = 8.5, 2.0 Hz, 1H, Ar), 6.53 (d, J = 3.5 Hz, 1H, Ar), 4.63 (dd, J = 8.5, 6.0 Hz, 1H, SC*H*Ar), 3.24-3.15 (m, 1H, SCH), 3.03 (ddd, J =10.0, 6.5, 3.5 Hz, 1H, SCH), 2.49-2.37 (m, 1H, CH), 2.36-2.23 (m, 1H, CH), 2.06-1.93 (m, 2H, CH), 1.67 (s, 9H, C*Me*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 149.8 (C=O), 137.3 (*ipso*-Ar), 134.4 (*ipso*-Ar), 130.7 (*ipso*-Ar), 126.4 (Ar), 124.1 (Ar), 119.8 (Ar), 115.1 (Ar), 107.3 (Ar), 83.7 (O*C*Me$_3$), 53.0 (SCH), 41.0 (CH_2), 33.6 (CH_2), 31.1 (CH_2), 28.3 (C*Me*$_3$); HRMS (ESI) *m/z* calcd for $C_{17}H_{21}NO_2S$ $(M + Na)^+$ 326.1185, found 326.1190 (–0.3 ppm error).

Lab book reference: **SMc3-80-2**

5-Bromo-1-tosyl-1*H*-indole 326



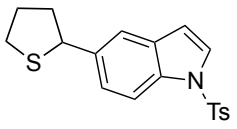
326

To a solution of 5-bromo-indole (1.48g, 7.5 mmol, 1.0 eq.) in MeCN (40 mL, 0.19 M) was added NaH (422 mg, 10.5 mmol, 1.4 eq.) at 0 °C under Ar and stirred for 10 min. TsCl (1.58g, 8.25 mmol, 1.1 eq.) was added and the resulting mixture was allowed to warm to rt and stirred at rt for 4 h. The reaction was quenched with NH_4Cl (100 mL), EtOAc (50 mL) was added and the two layers were separated. The aqueous layer was

extracted with EtOAc (3 x 20 mL) and the combined organics were washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 95:5 hexane-EtOAc gave *N*-Ts 5-bromoindole (1.5 g, 57%) as a white crystalline solid, R_F (9:1 hexane-EtOAc) 0.21; IR (ATR) 1596, 1440, 1373, 1195, 1170, 1130, 811, 763, 705, 666, 538 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 8.5 Hz, 1H, Ar), 7.77–7.71 (m, 2H, Ar), 7.65 (d, J = 2.0 Hz, 1H, Ar), 7.56 (d, J = 3.5 Hz, 1H, Ar), 7.39 (dd, J = 8.5, 2.0 Hz, 1H, Ar), 7.25-7.19 (m, 2H, Ar), 6.59 (d, J = 3.5 Hz, 1H, Ar), 2.34 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.4 (*ipso*-Ar), 135.1 (*ipso*-Ar), 133.7 (*ipso*-Ar), 132.6 (*ipso*-Ar), 130.1 (Ph), 127.7 (Ar), 127.5 (Ar), 126.9 (Ph), 124.1 (Ar), 116.9 (*ipso*-Ar), 115.0 (Ar), 108.4 (Ar), 21.7 (Me); HRMS (ESI) *m/z* calcd for $C_{15}H_{12}BrNO_2S$ $(M + K)^+$ 387.9404, found 387.9402 (–0.4 ppm error).

Lab book reference: **SMc3-96-1**

5-(Tetrahydrothiophen-2-yl)-1-tosyl-1H-indole 155



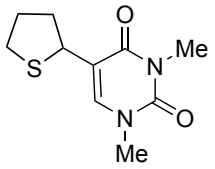
155

Using General Procedure B, 2-Bpin tetrahydrothiophene **110** (162 mg, 0.75 mmol, 1.5 eq.) and 5-bromo-1-(4-methylbenzenesulfonyl)-1H-indole (175 mg, 0.5 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 20:80 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **155** (143 mg, 79%) as an amber oil**,** R_F (70:30 hexane-Et_2O) 0.22; IR (ATR) 2928, 1458, 1371 (S=O), 1173, 1128, 996 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.5 Hz, 1H, Ar), 7.79-7.70 (m, 2H, Ar), 7.56 (d, J = 2.0 Hz, 1H, Ar), 7.53 (d, J = 3.5 Hz, 1H, Ar), 7.36 (dd, J = 8.5, 2.0 Hz, 1H, Ar), 7.17 (d, J = 8 Hz, 2H, Ar), 6.59 (d, J = 3.5 Hz, 1H, Ar), 4.56 (dd, J = 8.5, 6.0 Hz, 1H, SC*H*Ar), 3.20-3.09 (m, 1H, SCH), 2.99 (ddd, J = 10.5, 6.5, 4.0 Hz, 1H, SCH), 2.42-2.31 (m, 1H, CH), 2.28 (s, 3H, Me), 2.27-2.20 (m, 1H, CH), 2.00-1.85 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.1 (*ipso*-Ar), 138.2 (*ipso*-Ar), 135.3 (*ipso*-Ar), 134.0 (*ipso*-Ar), 130.9 (*ipso*-Ar), 130.0 (Ar), 126.9 (Ar),

126.8 (Ar), 124.6 (Ar), 120.3 (Ar), 113.5 (Ar), 109.1 (Ar), 52.9 (SCH), 40.9 (CH_2), 33.7 (CH_2), 31.2 (CH_2), 21.6 (Me); HRMS (ESI) *m/z* calcd for $C_{19}H_{19}NO_2S_2$ $(M + Na)^+$ 380.0749, found 380.0756 (–1.7 ppm error).

Lab book reference: **SMc3-97-1**

1,3-Dimethyl-5-(tetrahydrothiophen-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione 156

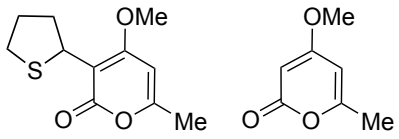


156

Using General Procedure B, 2-Bpin tetrahydrothiophene **110** (162 mg, 0.75 mmol, 1.5 eq.) and 5-bromo-1,3-dimethyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (110 mg, 0.5 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 20:80 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **156** (72 mg, 64%) as an orange oil, R_F (20:80 hexane-Et_2O) 0.2; IR (ATR) 2946, 2860, 1697 (C=O), 1653 (C=O), 1632, 1445, 1342, 1229 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H, C=C*H*), 4.46 (dd, *J* = 6.5, 6.0 Hz, 1H, SC*H*Ar), 3.36 (s, 3H, NMe), 3.29 (s, 3H, NMe), 2.95 (ddd, *J* = 10.0, 6.5, 6.5 Hz, 1H, SCH), 2.83 (ddd, *J* = 10.0, 6.5, 6.5 Hz, 1H, SCH), 2.31-2.19 (m, 1H, CH), 2.03-1.84 (m, 2H, CH), 1.82-1.70 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.0 (C=O), 151.6 (C=O), 140.7 (C=*CH*), 115.1 (*C*=CH), 44.4 (SCH), 37.4 (NMe), 37.2 (CH_2), 32.6 (CH_2), 29.9 (CH_2), 28.1 (NMe); HRMS (ESI) *m/z* calcd for $C_{10}H_{14}N_2O_2S$ $(M + H)^+$ 227.0849, found 227.0851 (–0.8 ppm error).

Lab book reference: **SMc3-82-1**

4-Methoxy-6-methyl-3-(tetrahydrothiophen-2-yl)-2*H*-pyran-2-one 157 and 4-methoxy-6-methyl-2*H*-pyran-2-one 327

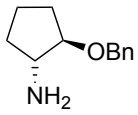


157 **327**

Using General Procedure B, 2-Bpin tetrahydrothiophene **110** (162 mg, 0.75 mmol, 1.5 eq.) and 3-bromo-4-methoxy-6-methyl-2H-pyran-2-one (109 mg, 0.5 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 90:10 hexane-Et_2O as eluent gave a 93:7 mixture of aryl tetrahydrothiophene **157** and pyrone **327** (20 mg, 41% of **157**) as an orange solid, mp 102-104 °C; R_F (90:10 hexane-Et_2O) 0.16; IR (ATR) 2935 (C-H), 1704 (C=O), 1551, 1464, 1387, 1253, 1128, 1019, 793; Diagnostic ^{1}H NMR signals for **327**:[164] 5.76 (s, 1H, Ar), 5.38 (s, 1H, Ar), 3.77 (s, OMe, 3H), 2.19 (s, Me, 3H); ^{1}H NMR signals for **157**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (s, 1H, Ar), 4.88 (dd, *J* = 8.5, 7.0, 1H, SC*H*Ar), 3.86 (s, 3H, OMe), 3.20-3.11 (m, 1H, SCH), 2.94-2.86 (m, 1H, SCH), 2.45-2.30 (m, 2H, CH), 2.23 (s, 3H, Me), 2.13-1.95 (m, 1H, CH), 1.92-1.78 (m, 1H, CH); ^{13}C NMR signals for **157**: ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.7 (C=O or *ipso*-Ar), 163.1 (C=O or *ipso*-Ar), 162.4 (C=O or *ipso*-Ar), 104.9 (*ipso*-Ar), 95.0 (Ar), 56.5 (OMe), 41.2 (SC*H*Ar), 34.2 (CH_2), 33.0 (CH_2), 32.9 (CH_2), 20.5 (Me); HRMS (ESI) *m/z* calcd for $C_{11}H_{14}O_3S$ $(M + Na)^+$ 249.0556, found 249.0556 (+0.3 ppm error).

Lab book reference: **SMc6-525**

2-(benzyloxy)cyclopentan-1-amine (*R*,*R*)-136



(*R*,*R*)-**136**

BTCAI (0.2 mL, 1.1 mmol, 1.1 eq.) and TfOH (26 μL, 0.3 mmol, 0.3 eq.) were added to a stirred solution of cyclopentyl hydroxylamine (*R*,*R*)-**158•**HCl (138 mg, 1.0 mmol, 1.0 eq.) in dioxane (5 mL, 0.2 M) at 0 °C. The resulting solution was allowed to warm to rt and stirred at rt for 18 h. $NaHCO_{3(aq)}$ (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 CH_2Cl_2:MeOH as eluent gave cyclopentyl hydroxylammonium salt (*R*,*R*)-**136**·HX (83 mg, 36%, assumed hydrochloride salt). Cyclopentyl hydroxylammonium salt (*R*,*R*)-**136**·HX was partitioned with $KOH_{(aq)}$ (15 mL) and CH_2Cl_2 (15 mL) and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 x CH_2Cl_2) and the combined organics were dried (Na_2SO_4) and evaporated under reduced pressure to give cyclopentyl hydroxylamine (*R*,*R*)-**136** (40 mg, 21%) as an orange oil, IR (ATR) 2956, 1454, 1098, 736.670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.23 (m, 5H, Ph), 4.57 (d, *J* = 12.0 Hz, 1H, OC*H*Ph), 4.48 (d, *J* = 12.0 Hz, 1H, OC*H*Ph), 3.55 (ddd, *J* = 6.5, 5.5, 5.5 Hz, 1H, OCH), 3.26 (ddd, *J* = 7.5, 7.5, 5.0 Hz, 1H, NCH), 2.06-1.90 (m, 2H, CH), 1.86 (br s, 2H, NH_2), 1.80-1.56 (m, 3H, CH), 1.39-1.20 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.8 (*ipso*-Ar), 128.5 (Ar), 127.8 (Ar), 127.7 (Ar), 87.9 (OCH), 71.6 (O*C*H_2Ph), 58.0 (NCH), 32.3 (CH_2), 29.7 (CH_2), 20.7 (CH_2); HRMS (ESI) *m/z* calcd for $C_{12}H_{17}NO$ $(M + H)^+$ 192.1383, found 192.1385 (-1.3 ppm error); $[\alpha]_D$ -56.9 (c 1.0 in $CHCl_3$).

Lab book reference: **SMc3-156**

Acetic acid (0.06 mL, 1.1 mmol, 3.0 eq.) and hydrazine monohydrate (0.05 mL, 1.1 mmol, 3.0 eq.) were added to a stirred solution of amino cyclopentyl benzyl ether (*R*,*R*)-**162** (114 mg, 0.35 mmol, 1.0 eq.) in EtOH (3.5 mL, 0.1 M). The resulting

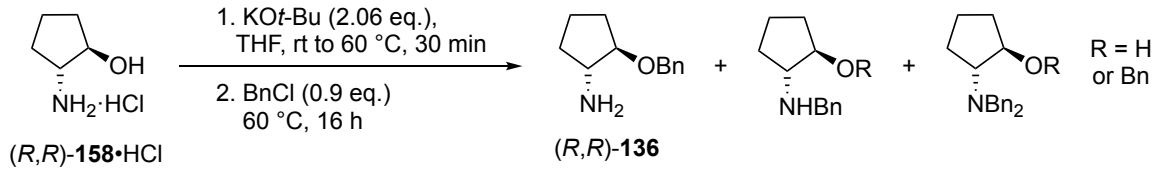
mixture was heated to 110 °C and stirred at 110 °C for 4 h. After being allowed to cool to rt, the reaction mixture was filtered and the filtrate evaporated under reduced pressure. The crude residue was re-dissolved in EtOAc (10 mL) then 1M HCl (10 mL) was added and the two layers separated. The organic layer was extracted with 1 M HCl (3 x 10 mL) and the combined aqueous layers were neutralised with solid $NaHCO_3$. EtOAc (10 mL) was added and the two layers separated, the aqueous layer was then extracted with EtOAc (3 x 10 mL), dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give benzyl amino alcohol (*R*,*R*)-**136** as a colourless oil.

Lab book reference: S**Mc4-167**

Acetic acid (6.3 mL, 109 mmol, 3.0 eq.) and hydrazine monohydrate (5.3 mL, 109 mmol, 3.0 eq.) were added to a stirred solution of amino cyclopentyl benzyl ether (*R*,*R*)-**162** (11.7 g, 36.4 mmol, 1.0 eq.) in EtOH (364 mL, 0.1 M). The resulting mixture was heated to 110 °C and stirred at 110 °C for 4 h. After being allowed to cool to rt, the reaction mixture was filtered and the filtrate evaporated under reduced pressure. The crude residue was re-dissolved in EtOAc (150 mL) then 1M HCl (150 mL) was added and the two layers separated. The organic layer was extracted with 1 M HCl (3 x 150 mL) and the combined aqueous layers were neutralised with solid $NaHCO_3$. EtOAc (100 mL) was added and the two layers separated, the aqueous layer was then extracted with EtOAc (3 x 100 mL), dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give benzyl amino alcohol (*R*,*R*)-**136** as a colourless oil (6.1 g, 88% yield).

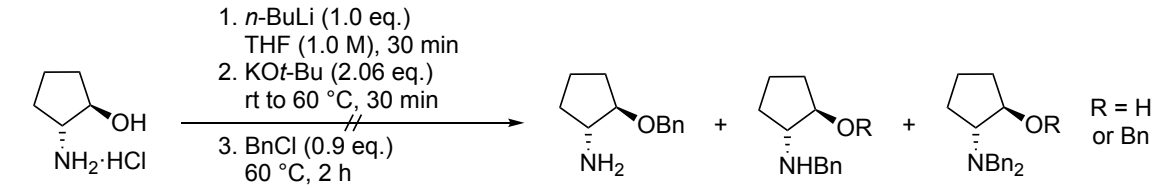
Lab book reference: **SMc4-215**

Attempted syntheses of benzyl amino alcohol (*R*,*R*)-136



KO*t*-Bu (693 mg, 6.18 mmol, 2.06 eq.) was dissolved in THF (3mL) and the resulting mixture was heated to 60 °C. Then, a solution of cyclopentyl hydroxylamine HCl salt (*R*,*R*)-**158**•HCl (414 mg, 3.0 mmol, 1.0 eq.) in THF (3 mL) was added dropwise over 10 min and the resulting solution stirred at 60 °C for 30 min. Then, BnCl (0.31 mL, 2.7 mmol, 0.9 eq.) was added dropwise and the resulting solution was stirred at 60 °C for 16 h. Water (15 mL) and EtOAc (15 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organics were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with silica using 90:10 CH_2Cl_2:MeOH as eluent gave benzylcyclopentylamine (*R*,*R*)-**136** as an unquantifiable mixture with suspected *N*-Bn/*N*-Bn_2 cyclopentylamine impurities (by ^{1}H NMR and HRMS).

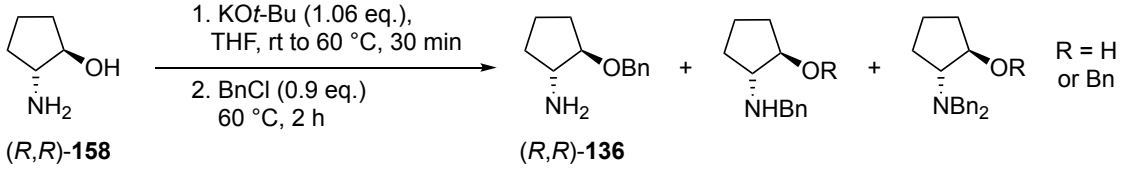
Lab book reference: **SMc3-99-1**



n-BuLi (1.9 mL of a 1.6 M solution in hexanes, 3.0 mmol, 1.3 eq.) was added dropwise to a stirred solution of cyclopentyl hydroxylamine HCl salt (*R*,*R*)-**158**•HCl (414 mg, 3.0 mmol, 1.0 eq.) in THF (3 mL) at 0 °C and the resulting solution was allowed to warm to rt and stirred at rt for 30 mins. KO*t*-Bu (693 mg, 6.18 mmol, 2.06 eq.) added and the resulting mixture was heated to 60 °C and stirred at 60 °C for 30 min. Then, BnCl (0.31 mL, 2.7 mmol, 0.9 eq.) was added dropwise and the resulting solution was stirred at 60 °C for 16 h. Water (15 mL) and EtOAc (15 mL) were added and the two

layers were separated. The aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organics were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the none of benzylcyclopentylamine (*R*,*R*)-**136** (by ^1H NMR and HRMS)

Lab book reference: **SMc3-129**

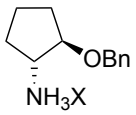


(*R*,*R*)-**158** (*R*,*R*)-**136**

KO*t*-Bu (2.65 g, 23.6 mmol, 1.03 eq.) was dissolved in THF (20 mL) and the resulting mixture was heated to 60 °C. Then, a solution of cyclopentyl hydroxylamine (*R*,*R*)-**158** (2.32 g, 23 mmol, 1.0 eq.) in THF (20 mL) was added dropwise over 30 min using a syringe pump and the resulting solution stirred at 60 °C for 30 min. Then, BnCl (2.4 mL, 20.6 mmol, 0.9 eq.) was added dropwise and the resulting solution was stirred at 60 °C for 16 h. Water (15 mL) and EtOAc (15 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organics were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to gave trace conversion to benzylcyclopentylamine (*R*,*R*)-**136** (by ^1H NMR and HRMS)

Lab book reference: **SMc3-134**

2-(Benzyloxy)cyclopentan-1-ammonium (*R*,*R*)-136•HX



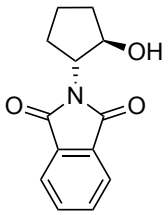
(*R*,*R*)-**136•**HX

BTCAI (0.37 mL, 1.1 mmol, 1.1 eq.) and TfOH (0.11 mL, 1.2 mmol, 1.2 eq.) were added to a stirred solution of cyclopentyl hydroxylamine (*R*,*R*)-**158•**HCl (138 mg, 1.0

mmol, 1.0 eq.) in dioxane (5 mL, 0.2 M) at 0 °C. The resulting solution was allowed to warm to rt and stirred at rt for 18 h. $NaHCO_{3(aq)}$ (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (5 x 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 CH_2Cl_2:MeOH as eluent gave cyclopentyl hydroxylammonium salt (*R*,*R*)-**136**·HX (97 mg, 42%, assumed hydrochloride salt) as an orange solid, R_F (90:10 CH_2Cl_2:MeOH) 0.14; mp; IR (ATR) 3302, 2956, 1454, 1098, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.15 (m, 5H, Ar), 6.30 (br s, 3H, NH_3), 4.39 (s, 2H, OCH), 3.82 (ddd, *J* = 6.0, 6.0, 1H, OCH), 3.31 (ddd, *J* = 7.5, 7.0, 7.0 Hz, 1H, NCH), 2.00-1.84 (m, 2H, CH), 1.70-1.58 (m, 2H, CH), 1.58-1.43 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.9 (*ipso*-Ar), 128.6 (Ar), 128.0 (Ar), 83.6 (OCH), 72.0 (OCH_2), 57.7 (NCH), 29.5 (CH_2), 28.3 (CH_2), 20.6 (CH_2), (one Ar resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{12}H_{18}NO$ $(M)^+$ 192.1383, found 192.1385 (–2.2 ppm error).

Lab book reference: **SMc3-166**

2-Hydroxycyclopentyl)isoindoline-1,3-dione (*R*,*R*)-161



(*R*,*R*)-**161**

Et_3N (15.2 mL, 109 mmol, 3.0 eq.) was added dropwise to a stirred solution of (1*R*,2*R*)-2-aminocyclopentan-1-ol hydrochloride (5.0 g, 36 mmol, 1.0 eq.) in toluene (125 mL, 0.25 M) at rt and stirred for 10 min. Then, phthalic anhydride (5.38 g, 36 mmol, 1.0 eq.) was added, and the resulting solution heated to 110 °C (heater block temperature) and stirred at 110 °C for 16 h. The solution was allowed to cool to rt, then water (100 mL) and EtOAc (50 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics

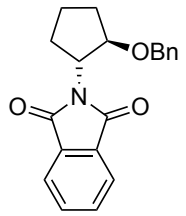
were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give phthalimide (*R*,*R*)-**161** (4.93 g, 94%) as a white solid, 102-104 °C (lit.,[165] 106-108 °C); R_F (50:50 hexane-EtOAc) 0.31; IR (ATR) 3419 (O-H), 1702 (C=O), 1380, 1078, 907, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87-7.77 (m, 2H, Ar), 7.75-7.66 (m, 2H, Ar), 4.80-4.68 (m, 1H, CH), 4.37 (ddd, *J* = 9.5, 9.5, 7.0 Hz, 1H, CH), 2.27-1.97 (m, 3H, CH, OH), 1.96-1.75 (m, 3H, CH), 1.72-1.59 (m, 1H, CH); ^{13}C (100.6 MHz, $CDCl_3$) δ 168.8, (C=O), 134.0 (Ar), 132.0 (*ipso*-Ar), 123.2 (Ar), 75.0 (OCH), 59.3 (NCH), 32.3 (CH_2), 27.2 (CH_2), 21.1 (CH_2); HRMS (ESI) *m/z* calcd for $C_{13}H_{13}NO_3$ $(M + Na)^+$ 254.0788, found 254.0791 (–1.1 ppm error); $[\alpha]_D$ -48.96 (*c* 1.0 in $CHCl_3$). [lit.,[165] $[\alpha]_D$ -32.5 (*c* 1.0 in $CHCl_3$ for (*R*,*R*)-**161** of 99% ee).

Lab book reference: **SMc4-173-4**

Et_3N (1.53 mL, 11 mmol, 3.0 eq.) was added dropwise to a stirred solution of (1*R*,2*R*)-2-aminocyclopentan-1-ol hydrochloride (500 mg, 3.6 mmol, 1.0 eq.) in toluene (15 mL, 0.25 M) at rt and stirred for 10 min. Then, phthalic anhydride (541 mg, 3.6 mmol, 1.0 eq.) was added, and the resulting solution heated to 130 °C (heater block temperature) and stirred at 130 °C for 16 h. The solution was allowed to cool to rt, then water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 60:40 hexane-EtOAc as eluent gave *N*-phthalyl alcohol (*R*,*R*)-**161** (519 mg, 61%) as a white solid.

Lab book reference: **SMc4-151**

2-(Benzyloxy)cyclopentyl)isoindoline-1,3-dione (*R*,*R*)-162



(*R*,*R*)-**162**

A solution of phthalyl alcohol (*R*,*R*)-**161** (12.3 g, 53 mmol, 1.0 eq.) in dry THF (106 mL, 0.5 M) was added dropwise to a stirred suspension of NaH (60 wt% in mineral oil, 4.26 g, 106 mmol, 2.0 eq.) and 18-Crown-6 (1.4 g, 5.2 mmol, 0.1 eq.) in dry THF (106 mL, 0.5 M) at 0 °C *via* cannula transfer. The suspension was allowed to warm to rt and stirred at rt for 1 h. Then, BnBr (19 mL, 159 mmol, 3.0 eq.) was added and the suspension heated to 80 °C. The suspension was stirred and heated at 80 °C for 18 h. After being allowed to cool to rt, the reaction mixture was cooled to 0 °C and quenched with water (200 mL). EtOAc (100 mL) was added and the two layers separated. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave amino cyclopentyl benzyl ether (*R*,*R*)-**162** (11.9 g, 70%) as a pale gold oil, R_F (90:10 hexane:EtOAc) 0.22; IR (ATR) 2959 (C-H), 1707 (C=O), 1387, 1069, 719; 1H NMR (400 MHz, $CDCl_3$) δ 7.84-7.77 (m, 2H, Ar), 7.75-7.67 (m, 2H, Ar), 7.25-7.08 (m, 5H, Ph), 4.61 (ddd, *J* = 9.5, 9.0, 6.0 Hz, 1H, OCH), 4.52-4.40 (m, 3H, CH), 2.25-2.13 (m, 1H, CH), 2.09-1.99 (m, 2H, CH), 1.98-1.72 (m, 3H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) 168.3 (C=O), 138.6 (*ipso*-Ar), 133.9 (Ar), 132.1 (*ispo*-Ar), 128.3 (Ph), 127.6 (Ph), 127.4 (Ph), 123.2 (Ar), 82.2 (CH), 71.5 (CH_2), 57.0 (CH), 31.5 (CH_2), 28.3 (CH_2), 22.5 (CH_2); HRMS (ESI) *m/z* calcd for $C_{20}H_{19}NNaO_3$ $(M + Na)^+$ 344.1257, found 344.1255 (+0.5 error); $[\alpha]_D$ -37.9 (c 1.0 in $CHCl_3$).

Lab book reference: **SMc4-213**

Experimental data for Table 2.3: Optimisation of DMF benzylations of (*R*,*R*)-161

NaH (60 wt% in mineral oil, 94 mg, 2.3 mmol, 1.2 eq.) was added to a solution of phthalyl alcohol (*R*,*R*)-**161** (440 mg, 1.9 mmol, 1.0 eq.) in DMF (9.5 mL, 0.2 M) at 0 °C. The suspension was allowed to warm to rt and stirred at rt for 1 h. Then, BnBr (0.27 mL, 2.3 mmol, 1.2 eq.) was added and the suspension stirred at rt for 24 h. The reaction mixture was cooled to 0 °C and quenched with water (20 mL). EtOAc (20 mL) was added and the two layers separated. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organics were washed with brine (5 x 20 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave amino cyclopentyl benzyl ether (*R*,*R*)-**162** (153 mg, 25%) as a pale gold oil and *N*-phthalyl alcohol (*R*,*R*)-**161** (268 mg, 61%) as a white solid.

Lab book reference: **SMc4-152-1**

NaH (60 wt% in mineral oil, 46 mg, 1.15 mmol, 1.2 eq.) was added to a solution of phthalyl alcohol (*R*,*R*)-**161** (267 mg, 1.15 mmol, 1.0 eq.) in DMF (0.5 mL, 2.16 M) at 0 °C. The suspension was allowed to warm to rt and stirred at rt for 30 min. Then, BnBr (0.15 mL, 1.15 mmol, 1.2 eq.) was added and the suspension stirred at rt for 24 h. The reaction mixture was quenched with water (10 mL). EtOAc (10 mL) was added and the two layers separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were washed with brine (5 x 10 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave amino cyclopentyl benzyl ether (*R*,*R*)-**162** (93 mg, 25%) as a pale gold oil and *N*-phthalyl alcohol (*R*,*R*)-**161** (154 mg, 58%) as a white solid.

Lab book reference: **SMc4-152-2**

NaH (60 wt% in mineral oil, 80 mg, 2.0 mmol, 2.0 eq.) was added to a solution of phthalyl alcohol (*R*,*R*)-**161** (231 mg, 1.0 mmol, 1.0 eq.) in DMF (5 mL, 0.2 M) at 0

°C. The suspension was allowed to warm to rt and stirred at rt for 30 min. Then, BnBr (0.14 mL, 1.2 mmol, 1.2 eq.) was added and the suspension stirred at rt for 24 h. The reaction mixture was quenched with water (10 mL). EtOAc (10 mL) was added and the two layers separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were washed with brine (5 x 10 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave amino cyclopentyl benzyl ether (*R*,*R*)-**162** (92 mg, 29%) as a pale gold oil.

Lab book reference: **SMc4-160**

NaH (60 wt% in mineral oil, 40 mg, 1.0 mmol, 2.0 eq.) was added to a solution of phthalyl alcohol (*R*,*R*)-**161** (116 mg, 0.5 mmol, 1.0 eq.) in DMF (1 mL, 0.5 M) at 0 °C. The suspension was allowed to warm to rt and stirred at rt for 30 min. Then, BnBr (0.12 mL, 1.0 mmol, 2.0 eq.) was added and the suspension stirred at rt for 24 h. The reaction mixture was quenched with water (10 mL). EtOAc (10 mL) was added and the two layers separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were washed with brine (5 x 10 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave amino cyclopentyl benzyl ether (*R*,*R*)-**162** (36 mg, 22%) as a pale gold oil.

Lab book reference: **SMc4-163**

NaH (60 wt% in mineral oil, 40 mg, 1.0 mmol, 2.0 eq.) was added to a solution of phthalyl alcohol (*R*,*R*)-**161** (116 mg, 0.5 mmol, 1.0 eq.) in DMF (1 mL, 0.5 M) at 0 °C. The suspension was allowed to warm to rt and stirred at rt for 30 min. Then, BnBr (0.07 mL, 0.6 mmol, 1.2 eq.) and TBAI (19 mg, 0.05 mmol, 0.1 eq.) were added and the suspension stirred at rt for 24 h. The reaction mixture was quenched with water (10 mL). EtOAc (10 mL) was added and the two layers separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were washed with brine (5 x 10 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 99:1

hexane-EtOAc to 90:10 hexane-EtOAc as eluent gave amino cyclopentyl benzyl ether (*R*,*R*)-**162** (80 mg, 50%) as a pale gold oil.

Lab book reference: **SMc4-164**

NaH (60 wt% in mineral oil, 2.5 g, 1.0 mmol, 2.0 eq.) was added to a solution of phthalyl alcohol (*R*,*R*)-**161** (7.25 g, 31.4 mmol, 1.0 eq.) in DMF (65 mL, 0.5 M) at 0 °C. The suspension was allowed to warm to rt and stirred at rt for 30 min. Then, BnBr (4.5 mL, 37.6 mmol, 1.2 eq.) and TBAI (1.16 g, 3.14 mmol, 0.1 eq.) were added and the suspension stirred at rt for 24 h. The reaction mixture was quenched with water (100 mL). EtOAc (100 mL) was added and the two layers separated. The aqueous layer was extracted with EtOAc (2 x 100 mL) and the combined organics were washed with brine (2 x 100 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 99:1 hexane-EtOAc to 90:10 hexane-EtOAc as eluent gave amino cyclopentyl benzyl ether (*R*,*R*)-**162** (1.18 g, 13%) as a pale gold oil.

Lab book reference: **SMc4-174**

Experimental data for Table 2.4: Optimisation of benzylation using NaH and crown ethers in THF

NaH (60 wt% in mineral oil, 40 mg, 1.0 mmol, 2.0 eq.) was added to a solution of phthalyl alcohol (*R*,*R*)-**161** (116 mg, 0.5 mmol, 1.0 eq.) in THF (2.5 mL, 0.2 M) at 0 °C. The suspension was allowed to warm to rt and stirred at rt for 1 h. Then, BnBr (0.24 mL, 2.5 mmol, 5.0 eq.) and 18-crown-6 (14 mg, 0.05 mmol, 0.1 eq.) were added and the resulting mixture heated to 80 °C and stirred at 80 °C for 18 h. The reaction mixture was quenched with NH_4Cl (10 mL). CH_2Cl_2 (10 mL) was added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave amino cyclopentyl benzyl ether (*R*,*R*)-**162** (130 mg, 81%) as a pale gold oil.

Lab book reference: **SMc4-180**

NaH (60 wt% in mineral oil, 80 mg, 2.0 mmol, 2.0 eq.) was added to a solution of phthalyl alcohol (*R*,*R*)-**161** (231 mg, 1.0 mmol, 1.0 eq.) in THF (5 mL, 0.2 M) at 0 °C. The suspension was allowed to warm to rt and stirred at rt for 1 h. Then, BnBr (0.6 mL, 5.0 mmol, 5.0 eq.) and 18-crown-6 (28 mg, 0.1 mmol, 0.1 eq.) were added and the resulting mixture heated to 80 °C and stirred at 80 °C for 18 h. The reaction mixture was quenched with NH_4Cl (10 mL). CH_2Cl_2 (10 mL) was added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave amino cyclopentyl benzyl ether (*R*,*R*)-**162** (198 mg, 58%) as a pale gold oil.

Lab book reference: **SMc4-197**

NaH (60 wt% in mineral oil, 80 mg, 2.0 mmol, 2.0 eq.) was added to a solution of phthalyl alcohol (*R*,*R*)-**161** (231 mg, 1.0 mmol, 1.0 eq.) in THF (5 mL, 0.2 M) at 0 °C. The suspension was allowed to warm to rt and stirred at rt for 1 h. Then, BnBr (0.48 mL, 4.0 mmol, 4.0 eq.) and 18-crown-6 (28 mg, 0.1 mmol, 0.1 eq.) were added and the resulting mixture heated to 80 °C and stirred at 80 °C for 18 h. The reaction mixture was quenched with NH_4Cl (10 mL). CH_2Cl_2 (10 mL) was added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave amino cyclopentyl benzyl ether (*R*,*R*)-**162** (177 mg, 55%) as a pale gold oil.

Lab book reference: **SMc4-196**

NaH (60 wt% in mineral oil, 80 mg, 2.0 mmol, 2.0 eq.) was added to a solution of phthalyl alcohol (*R*,*R*)-**161** (231 mg, 1.0 mmol, 1.0 eq.) in THF (5 mL, 0.2 M) at 0 °C. The suspension was allowed to warm to rt and stirred at rt for 1 h. Then, BnBr (0.36 mL, 3.0 mmol, 3.0 eq.) and 18-crown-6 (28 mg, 0.1 mmol, 0.1 eq.) were added and the resulting mixture heated to 80 °C and stirred at 80 °C for 18 h. The reaction mixture was quenched with NH_4Cl (10 mL). CH_2Cl_2 (10 mL) was added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave amino cyclopentyl benzyl ether (*R*,*R*)-**162** (201 mg, 63%) as a pale gold oil.

Lab book reference: **SMc4-195**

NaH (60 wt% in mineral oil, 40 mg, 1.0 mmol, 2.0 eq.) was added to a solution of phthalyl alcohol (*R*,*R*)-**161** (117 mg, 0.5 mmol, 1.0 eq.) in THF (2.5 mL, 0.2 M) at 0 °C. The suspension was allowed to warm to rt and stirred at rt for 1 h. Then, BnBr (0.12 mL, 2.0 mmol, 2.0 eq.) and 18-crown-6 (14 mg, 0.05 mmol, 0.1 eq.) were added and the resulting mixture heated to 80 °C and stirred at 80 °C for 18 h. The reaction mixture was quenched with NH_4Cl (10 mL). CH_2Cl_2 (10 mL) was added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave amino cyclopentyl benzyl ether (*R*,*R*)-**162** (48 mg, 30%) as a pale gold oil.

Lab book reference: **SMc4-190**

NaH (60 wt% in mineral oil, 40 mg, 1.0 mmol, 2.0 eq.) was added to a solution of phthalyl alcohol (*R*,*R*)-**161** (116 mg, 0.5 mmol, 1.0 eq.) in THF (2.5 mL, 0.2 M) at 0 °C. The suspension was allowed to warm to rt and stirred at rt for 1 h. Then, BnBr (0.24 mL, 2.5 mmol, 5.0 eq.) was added and the resulting mixture heated to 80 °C and

stirred at 80 °C for 18 h. The reaction mixture was quenched with NH_4Cl (10 mL). CH_2Cl_2 (10 mL) was added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product which contained amino cyclopentyl benzyl ether (*R*,*R*)-**162** (29% NMR yield).

Lab book reference: **SMc4-187**

NaH (60 wt% in mineral oil, 80 mg, 2.0 mmol, 2.0 eq.) was added to a solution of phthalyl alcohol (*R*,*R*)-**161** (231 mg, 1.0 mmol, 1.0 eq.) in THF (5 mL, 0.2 M) at 0 °C. The suspension was allowed to warm to rt and stirred at rt for 1 h. Then, BnBr (0.24 mL, 2.0 mmol, 2.0 eq.), 18-crown-6 (25 mg, 0.1 mmol, 0.1 eq.) and TBAI (37 mg, 0.1 mmol, 0.1 eq.) were added and the resulting mixture heated to 80 °C and stirred at 80 °C for 18 h. The reaction mixture was quenched with NH_4Cl (10 mL). CH_2Cl_2 (10 mL) was added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave amino cyclopentyl benzyl ether (*R*,*R*)-**162** (127 mg, 39%) as a pale gold oil.

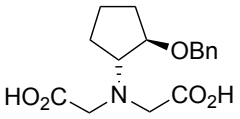
Lab book reference: **SMc4-194**

NaH (60 wt% in mineral oil, 40 mg, 1.0 mmol, 2.0 eq.) was added to a solution of phthalyl alcohol (*R*,*R*)-**161** (116 mg, 0.5 mmol, 1.0 eq.) in THF (2.5 mL, 0.2 M) at 0 °C. The suspension was allowed to warm to rt and stirred at rt for 1 h. Then, BnBr (0.36 mL, 1.5 mmol, 3.0 eq.) and 15-crown-5 (10 μL, 0.05 mmol, 0.1 eq.) were added and the resulting mixture heated to 80 °C and stirred at 80 °C for 18 h. The reaction mixture was quenched with NH_4Cl (10 mL). CH_2Cl_2 (10 mL) was added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on

silica using 90:10 hexane-EtOAc as eluent gave amino cyclopentyl benzyl ether (*R*,*R*)-**162** (82 mg, 51%) as a pale gold oil.

Lab book reference: **SMc4-200**

2-[(Carboxymethyl)[2-phenoxycyclopentyl]amino]acetic acid (*R*,*R*)-135



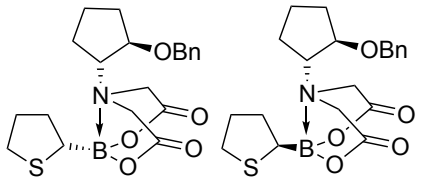
(*R*,*R*)-**135**

tert-Butyl bromoacetate (14.8 mL, 100 mmol, 2.4 eq.) was added dropwise to a stirred mixture of (1*R*,2*R*)-(–)-2-benzyloxycyclopentylamine **136** (8.0 g, 42 mmol, 1.0 eq.) and K_2CO_3 (29 g, 209 mmol, 5.0 eq.) in MeCN (127 mL, 0.33 M) at 0 °C. The mixture was heated to 70 °C and stirred and heated at 70 °C (heater block temperature) for 40 h. After being allowed to cool to rt, the solids were removed by filtration through Celite® and washed with EtOAc (250 mL). The filtrate was evaporated under reduced pressure then re-dissolved in formic acid (42 mL) and the resulting mixture heated at 85 °C (heater block temperature) and stirred at 85 °C for 2 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure. EtOH (200 mL) was added and the resulting mixture was heated to 100 °C and stirred at 100 °C (heater block temperature) for 5 min. The mixture was allowed to cool slowly to rt, then it was cooled to 0 °C. The precipitated solid was collected by filtration, washed with cold EtOH (20 mL) and dried under reduced pressure to give diacid (*R*,*R*)-**135** (10.4 g, 81%) as a white solid, mp 162-164 °C; IR (ATR) 3406 (OH), 2968, 2508, 1729 (C=O), 1630, 1393, 1239, 1099, 867, 742, 700 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.34-7.18 (m, 5H, Ph), 4.41 (d, *J* = 11.5 Hz, 1H, OC*H*Ph), 4.33 (d, *J* = 11.5 Hz, 1H, OC*H*Ph), 3.78-3.69 (m, 1H, OCH), 3.50 (d, *J* = 17.5 Hz, 2H, NCH), 3.45 (d, *J* = 17.5 Hz, 2H, NCH), 3.20 (ddd, *J* = 9.0, 7.0, 5.5 Hz, 1H, NCH), 1.89-1.68 (m, 2H, CH), 1.60-1.43 (m, 3H, CH), 1.39-1.25 (m, 1H, CH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 173.1 (C=O), 138.6 (*ipso*-Ph), 128.2 (Ph), 127.7 (Ph), 127.3 (Ph), 83.0 (OCH), 70.4 (O*C*H_2Ph), 68.2 (NCH), 53.6 (NCH_2), 29.8 (CH_2), 28.5 (CH_2), 20.9 (CH_2); HRMS (ESI) *m/z* calcd for $C_{16}H_{21}NO_5$ $(M - H)^-$ 306.1347, found 306.1356 (+0.8 ppm error);

$[\alpha]_D$ +72.0 (*c* 1.0 in MeOH). Spectroscopic data consistent with those reported in the literature.[76]

Lab book reference: **SMc4-217-1**

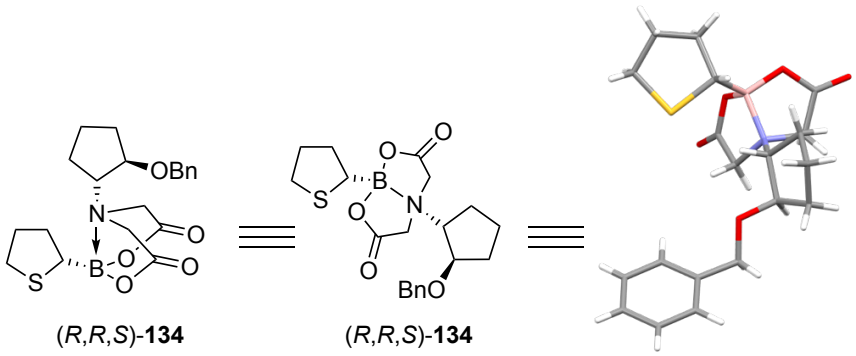
6-((1*R*,2*R*)-2-(Benzyloxy)cyclopentyl)-2-((*S*)-tetrahydrothiophen-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (*R*,*R*,*S*)-134 and 6-((1*R*,2*R*)-2-(Benzyloxy)cyclopentyl)-2-((*R*)-tetrahydrothiophen-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (*R*,*R*,*R*)-134



(*R*,*R*,*S*)-**134** (*R*,*R*,*R*)-**134**

Triethylorthoformate (3.4 mL, 20.4 mmol, 3.0 eq.) was added to a stirred solution of 2-Bpin tetrahydrothiophene **110** (1.5 g, 6.8 mmol, 1.0 eq.) and diacid (*R*,*R*)-**135** (4.03 g, 13.6 mmol, 2.0 eq.) in anhydrous DMSO (27 mL, 0.25 M) under N_2. The resulting mixture was stirred and heated at 100 °C (heater block temperature) for 72 h. After being allowed to cool to rt, water (100 mL) and EtOAc (100 mL) were added and the two layers separated. The aqueous layer was extracted with EtOAc (3 × 50 mL) and 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 using hexane to 40:60 hexane-EtOAc as eluent gave impure tetrahydrothiophene BBIDA (*R*,*R*,*S*)-**134**, R_F (40:60 hexane-EtOAc) 0.40 and tetrahydrothiophene BBIDA (*R*,*R*,*R*)-**134** (1.07 g, 39%) as a white solid, mp 76-78 °C; R_F (40:60 hexane-EtOAc) 0.15; IR (ATR) 2948, 1763 (C=O), 1440, 1292, 1107, 1021, 960, 910, 856, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.27 (m, 5H, Ph), 4.54 (d, *J* = 11.0 Hz, 1H, OC*H*Ph), 4.40 (d, *J* = 11.0 Hz, 1H, OC*H*Ph), 4.04-3.95 (m, 2H, NCH or OCH), 3.90-3.78 (m, 2H, NCH), 3.65 (d, *J* = 16.0 Hz, 1H, NCH), 3.58 (d, *J* = 17.0 Hz, 1H, NCH), 2.92-2.70 (m, 3H, CH), 2.30-2.07 (m, 3H, CH), 1.96-1.76 (m, 4H, CH), 1.74-1.49 (m, 3H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.3 (C=O), 167.1 (C=O), 136.8 (*ipso*-Ph), 128.7 (Ph), 128.3 (Ph), 79.4 (OCH), 73.6 (NCH), 72.3

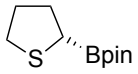
(O*C*H$_2$Ph), 60.4 (NCH$_2$), 57.2 (NCH$_2$), 33.7 (CH$_2$), 33.2 (CH$_2$), 32.0 (CH$_2$), 30.6 (CH$_2$), 27.4 (CH$_2$), 21.2 (CH$_2$), (SCHB and one Ph resonances not resolved); ^{11}B NMR (128 MHz, CDCl$_3$) δ 12.0; HRMS (ESI) *m/z* calcd for $C_{20}H_{26}BNO_5S$ (M + Na)$^+$ 426.1517, found 426.1523 (–0.6 ppm error); $[\alpha]_D$ +52.56 (*c* 1.0 in CHCl$_3$). The impure tetrahydrothiophene BBIDA (*R*,*R*,*S*)-**134** was purified by flash column chromatography on silica using 97:3 CH$_2$Cl$_2$:acetone as eluent to give tetrahydrothiophene BBIDA (*R*,*R*,*S*)-**134** (1.07 g, 39%) as a white solid, mp 180-182 °C; R_F (60:40 hexane-EtOAc) 0.4; IR (ATR), 2950, 1765 (C=O), 1291, 1024 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.44-7.26 (m, 5H, Ph), 4.64 (d, *J* = 11.5 Hz, 1H, OC*H*Ph), 4.41-4.30 (m, 2H, OC*H*Ph, NCH), 3.90 (ddd, *J* = 6.5, 6.5, 6.5 Hz, 1H, NCH or OCH), 3.76 (ddd, *J* = 8.5, 8.5, 7.0 Hz, 1H, NCH or OCH), 3.65 (d, *J* = 17.0 Hz, 1H, NCH), 3.50 (d, *J* = 16.5 Hz, 1H, NCH), 3.40 (d, *J* = 17.0 Hz, 1H, NCH), 2.95–2.85 (m, 1H, CH), 2.84-2.73 (m, 1H, CH), 2.55 (dd, *J* = 10.0, 6.0 Hz, 1H, CH), 2.32-2.11 (m, 3H, CH), 2.10-1.97 (m, 1H, CH), 1.89-1.62 (m, 5H, CH), 1.51-1.36 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 168.8 (C=O), 167.5 (C=O), 136.5 (*ipso*-Ph), 128.9 (Ph), 128.6 (Ph), 128.3 (Ph), 79.0 (OCH), 72.7 (NCH), 71.8 (O*C*H$_2$Ph), 61.9 (NCH$_2$), 55.7 (NCH$_2$), 33.8 (CH$_2$), 33.7 (CH$_2$), 32.0 (CH$_2$), 29.3 (CH$_2$), 26.2 (CH$_2$), 21.2 (CH$_2$) (SCHB resonance not resolved); ^{11}B NMR (128 MHz, CDCl$_3$) δ 11.9; HRMS (ESI) *m/z* calcd for $C_{20}H_{26}BNO_5S$ (M + Na)$^+$ 426.1517, found 426.1520 (+0.1 ppm error); $[\alpha]_D$ –15.46 (*c* 1.0 in CHCl$_3$). The structure of tetrahydrothiophene BBIDA (*R*,*R*,*S*)-**134** was determined by X-ray crystallography.



(*R*,*R*,*S*)-**134** (*R*,*R*,*S*)-**134**

Lab book reference: **SMc4-220-1**

(*S*)-4,4,5,5-Tetramethyl-2-(tetrahydrothiophen-2-yl)-1,3,2-dioxaborolane (*S*)-110

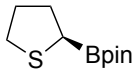


(*S*)-**110**

$NaHCO_3$ (1.05 g, 12.6 mmol, 5.0 eq.) was added to a stirred solution of tetrahydrothiophene BBIDA (*R*,*R*,*S*)-**134** (1.01 g, 2.51 mmol, 1.0 eq.) and pinacol (481 mg, 4.02 mmol, 1.6 eq.) in MeOH (7 mL) and CH_2Cl_2 (7 mL). The resulting mixture was stirred and heated at 45 °C for 3 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure. Then, water (20 mL) and CH_2Cl_2 (15 mL) were added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organics 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 using 95:5 pentane-Et_2O as eluent gave 2-Bpin tetrahydrothiophene (*S*)-**110** (424 mg, 79%, ≥99.5:0.5 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –44.5 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel IA (99.5:0.5 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**110** 8.6 min, (*S*)-**110** 10.4 min.

Lab book reference: **SMc3-111**

(*R*)-4,4,5,5-Tetramethyl-2-(tetrahydrothiophen-2-yl)-1,3,2-dioxaborolane (*R*)-110



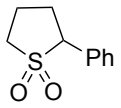
(*R*)-**110**

$NaHCO_3$ (972 mg, 11.5 mmol, 5.0 eq.) was added to a stirred solution of tetrahydrothiophene BBIDA (*R*,*R*,*R*)-**134** (926 mg, 2.3 mmol, 1.0 eq.) and pinacol (436 mg, 3.68 mmol, 1.6 eq.) in MeOH (7 mL) and CH_2Cl_2 (7 mL). The resulting mixture was stirred and heated at 45 °C for 3 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure. Then, water (20 mL) and CH_2Cl_2 (15 mL) were added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organics 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 using 95:5 pentane-Et_2O as

eluent gave 2-Bpin tetrahydrothiophene (*R*)-**110** (345 mg, 70%, ≥99.5:0.5 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +38.5 (c 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel IA (99.5:0.5 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**110** 8.4 min, (*S*)-**110** 10.2 min.

Lab book reference: **SMc3-112**

2-Phenyltetrahydrothiophene 1,1-dioxide 163

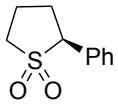


163

A solution of phenyl tetrahydrothiophene **116** (13 mg, 0.08 mmol, 1.0 eq.) in CH_2Cl_2 (1 mL, 0.8 M) was added to a stirred solution of *m*-CPBA (99 mg of assumed 70% purity, 0.4 mmol, 5.0 eq.) in CH_2Cl_2 (0.7 mL) at rt. The resulting solution was stirred at rt for 5 h. Then, $Na_2SO_{4(aq)}$ (20% (w/w), 5 mL) and CH_2Cl_2 (5 mL) were added and the two layers were separated. The organic layer was washed with saturated $NaHCO_{3(aq)}$ (5 mL) and brine (2 x 5 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 50:50 hexane-Et_2O as eluent gave phenyl sulfone **163** (7 mg, 41%) as a white solid, R_F (50:50 hexane-Et_2O) 0.1; IR (ATR) 2950, 1302, 1124, 765, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.34 (m, 5H, Ph), 4.17 (dd, J = 12.0, 7.0 Hz, 1H, SCH), 3.31 (ddd, J = 13.0, 9.0, 3.0 Hz, 1H, SCH), 3.17 (dd, J = 13.0, 9.0, 9.0 Hz, 1H, SCH), 2.64-2.32 (m, 3H, CH), 2.31-2.15 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 130.4 (*ipso*-Ph), 129.3 (Ph), 129.2 (Ph), 129.0 (Ph), 66.9 (SCH), 50.7 (CH_2), 28.9 (CH_2), 19.9 (CH_2); HRMS (APCI) *m/z* calcd for $C_{10}H_{12}O_2S$ $(M + Na)^+$ 219.0450, found 219.0451 (–0.5 ppm error); Spectroscopic data consistent with those reported in the literature.[28]

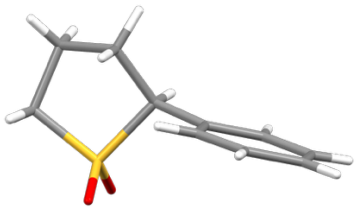
Lab book reference: **SMc3-104-2**

(*S*)-2-Phenyltetrahydrothiophene 1,1-dioxide (*S*)-163



(*S*)-**163**

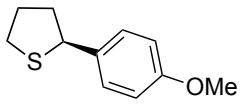
A solution of phenyl tetrahydrothiophene (*S*)-**116** (21 mg, 0.13 mmol, 1.0 eq.) in CH_2Cl_2 (0.6 mL) was added to a stirred solution of *m*-CPBA (160 mg of assumed 70% purity, 0.65 mmol, 5.0 eq.) in CH_2Cl_2 (0.7 mL) at rt. The resulting solution was stirred at rt for 60 h. Then, $Na_2SO_{4(aq)}$ (20% (w/w), 10 mL) and CH_2Cl_2 (15 mL) were added and the two layers were separated. The organic layer was washed with saturated $NaHCO_{3(aq)}$ (10 mL) and brine (2 x 10 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 50:50 hexane-Et_2O as eluent gave phenyl sulfone (*S*)-**163** (22 mg, 88%) as a white solid, $[\alpha]_D$ –20.96 (*c* 1.0 in CH_2Cl_2) [lit.,[28] $[\alpha]_D$ –24.7 (*c* 0.58 in $CHCl_3$) for (*S*)-**163** of 97:3 er); The structure of phenyl sulfone **163** was determined by X-ray crystallography. Spectroscopic data consistent with those reported in the literature.[28]



(*S*)-**163**

Lab book reference: **SMc3-107**

2-(4-methoxyphenyl)tetrahydrothiophene (*S*)-140

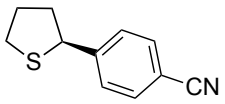


(*S*)-**140**

Using General Procedure C, 2-Bpin tetrahydrothiophene (*S*)-**110** (79 mg, 0.36 mmol, 1.2 eq., ≥99.5:0.5 er by CSP-HPLC) and 4-bromoanisole (38 μL, 0.3 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 90:10 hexane-Et_2O as eluent gave aryl tetrahydrothiophene (*S*)-**140** (42 mg, 72%, 99:1 er by CSP-HPLC) as a yellow oil, $[\alpha]_D$ +31.5 (*c* 1.0 in CH_2Cl_2) [lit.,[73] $[\alpha]_D$ +32.6 (*c* 0.95 in CH_2Cl_2) for (*S*)-**140** of 95:5 er]; CSP-HPLC: CHIRALPAK® OD-H (99:1 hexane-*i*-PrOH, 1.0 mL min-1) (R)-**140** 12.10 min, (S)-**140** 13.68 min.

Lab book reference: **SMc3-115-1**

4-(Tetrahydrothiophen-2-yl)benzonitrile (*S*)-121



(*S*)-**121**

Using General Procedure D, 2-Bpin tetrahydrothiophene (*S*)-**110** (79 mg, 0.36 mmol, 1.2 eq., ≥99.5:0.5 er) and 4-bromobenzonitrile (55 mg, 0.3 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using hexane to 95:5 hexane-Et_2O to 90:10 hexane-Et_2O as eluent gave aryl tetrahydrothiophene (*S*)-**121** (32 mg, 57%, 91:9 er by CSP-HPLC) as a dark orange oil, $[\alpha]_D$ +59.7 (*c* 1.0 in CH_2Cl_2) [lit.,[73] $[\alpha]_D$ +45.6 (*c* 1.4 in CH_2Cl_2) for (*S*)-**121** of 91:9 er]; CSP-HPLC: Chiracel IC (99:1 hexane-*i*-PrOH), 1.0 mL min^{-1}) (*S*)-**121** 29.5 min, (*R*)-**121** 34.2 min.

Lab book reference: **SMc3-117**

4-(Tetrahydrothiophen-2-yl)benzonitrile (*S*)-121

4-aryl tetrahydrothiophene (*S*)-**110** (15 mg, 0.08 mmol, 1.0 eq., 91:9 er) and Cs_2CO_3 (77 mg, 0.24 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, degassed toluene (0.22 mL) and degassed water (54 μL, 3.0 mmol, 37.4 eq.) were added under N_2. The vial was placed in a heating block preheated to 120 °C and the mixture was stirred at 1000-1200 rpm and heated at 120 °C (stirrer block temperature) for 20 h. After being allowed to cool to rt, Et_2O (10 mL) and water (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give aryl tetrahydrothiophene (*S*)-**121** (13 mg, 87%, 91:9 er by CSP-HPLC) as a dark orange oil, CSP-HPLC: Chiracel IC (99:1 hexane-*i*-PrOH), 1.0 mL min^{-1}) (*S*)-**121** 29.3 min, (*R*)-**121** 34.2 min.

Lab book reference: **SMc3-117E**

2-Bpin Tetrahydrothiophene (*S*)-**110** (79 mg, 0.36 mmol, 1.2 eq., ≥99.5:0.5 er), 4-bromobenzonitrile (55 mg, 0.3 mmol, 1.0 eq.), $P(Ad)_3$ Pd G3 (24 mg, 30 μmol, 0.1 eq.) and Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and degassed toluene (0.43 mL) and water (54 μL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using hexane to 95:5 hexane-Et_2O to 90:10 hexane-Et_2O as eluent gave aryl tetrahydrothiophene (*S*)-**121** (20 mg, 35%, 99:1 er by CSP-HPLC) as a dark orange oil, $[\alpha]_D$ +55.67 (*c* 1.0 in CH_2Cl_2) [lit.,[73] $[\alpha]_D$ +45.6 (*c* 1.4 in CH_2Cl_2)

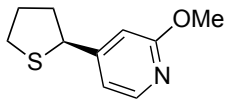
for (*S*)-**121** of 91:9 er]; CSP-HPLC: Chiracel IC (99:1 hexane-*i*-PrOH), 1.0 mL min^{-1}) (*S*)-**121** 34.6 min, (*R*)-**121** 40.44 min.

Lab book reference: **SMc4-227**

2-Bpin tetrahydrothiophene (*S*)-**110** (72 mg, 0.34 mmol, 1.1 eq.), 4-bromobenzonitrile (55 mg, 0.30 mmol, 1.0 eq.), bis(3,5-bis(trifluoromethyl)phenyl)(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphane Pd G3 (33 mg, 30 μmol, 0.1 eq.) and Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and degassed toluene (0.43 mL) and water (54 μL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using 90:10 hexane-Et_2O as eluent gave an impure mixture of aryl tetrahydrothiophene (*R*)-**121** and carbazole. Purification of the impure mixture of aryl tetrahydrothiophene **121** and carbazole by flash column chromatography on silica using 1:1 hexane-toluene as eluent gave aryl tetrahydrothiophene (*R*)-**121** (3 mg, 5%, 78:22 er by CSP-HPLC) as a dark orange oil, $[\alpha]_D$ -18.3 (*c* 0.2 in CH_2Cl_2); CSP-HPLC Chiracel IC (99:1 hexane-*i*-PrOH), 1.0 mL min^{-1}) (*S*)-**121** 32.5 min, (*R*)-**121** 37.0 min.

Lab book reference: **SMc5-259**

2-Methoxy-4-(tetrahydrothiophen-2-yl)pyridine (*S*)-148



(*S*)-**148**

Using General Procedure D, 2-Bpin tetrahydrothiophene (*S*)-**110** (79 mg, 0.36 mmol, 1.2 eq., ≥99.5:0.5 er) and 4-bromo-2-methoxypyridine (57 mg, 0.3 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 90:10 hexane-Et_2O as eluent gave aryl tetrahydrothiophene (*S*)-**148** (41 mg, 70%, 94:6 er by CSP-HPLC) as an orange oil, $[\alpha]_D$ +32.0 (*c* 1.0 in CH_2Cl_2); CSP-HPLC: Chiracel IC (99:1 hexane-*i*-PrOH), 1.0 mL min^{-1}) (*S*)-**148** 15.0 min, (*R*)-**148** 16.5 min.

Lab book reference: **SMc3-116**

2-Bpin Tetrahydrothiophene **110** (163 mg, 0.75 mmol, 1.5 eq.), $Pd(OAc)_2$ (11 mg, 50 μmol, 0.10 eq.), cataCXium A (36 mg, 100 μmol, 0.2 eq.) and Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (53 μL, 0.5 mmol, 1.0 eq.), and aryl tetrahydrothiophene (*S*)-**148** (41 mg, 0.21 mmol, 94:6 er by CSP-HPLC) as a solution in degassed toluene (0.70 mL), and water (90 μL, 5.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using 99:1 hexane-Et_2O to 90:10 hexane-Et_2O as eluent gave phenyl tetrahydrothiophene **116** (55 mg, 67%) as a colourless oil and aryl tetrahydrothiophene (*S*)-**148** (20 mg, 49%, 91:9 er by CSP-HPLC) as an orange oil,

CSP-HPLC: Chiracel IC (99:1 hexane-*i*-PrOH), 1.0 mL min^{-1}) (*S*)-**148** 14.7 min, (*R*)-**148** 16.1 min.

Lab book reference: **SMc3-128**

2-Bpin Tetrahydrothiophene **110** (163 mg, 0.75 mmol, 1.5 eq.), $Pd(OAc)_2$ (11 mg, 50 μmol, 0.10 eq.), cataCXium A (36 mg, 100 μmol, 0.2 eq.) and Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (53 μL, 0.5 mmol, 1.0 eq.), and aryl tetrahydrothiophene (*S*)-**148** (20 mg, 0.11 mmol, 90:10 er by CSP-HPLC) as a solution in degassed toluene (0.70 mL), and water (90 μL, 5.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using 99:1 hexane-Et_2O to 90:10 hexane-Et_2O as eluent gave 2-phenyl tetrahydrothiophene **116** (51 mg, 62%) as a colourless oil and aryl tetrahydrothiophene (*S*)-**148** (10 mg, 50%, 88:12 er by CSP-HPLC) as an orange oil, CSP-HPLC: Chiracel IC (99:1 hexane-*i*-PrOH), 1.0 mL min^{-1}) (*S*)-**148** 15.0 min, (*R*)-**148** 16.4 min.

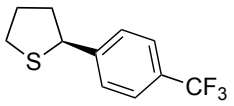
Lab book reference: **SMc3-135**

2-Bpin tetrahydrothiophene (*S*)-**110** (79 mg, 0.36 mmol, 1.2 eq., ≥99.5:0.5 er), 4-bromo-2-methoxypyridine (57 mg, 0.3 mmol, 1.0 eq.), $P(Ad)_3$ Pd G3 (24 mg, 30 μmol, 0.1 eq.) and Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and

degassed toluene (0.43 mL) and water (54 μL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using 96:4 hexane-Et_2O as eluent gave an impure mixture of aryl tetrahydrothiophene (*S*)-**148** and pinacol. Water (5 mL) was added and the impure mixture was evaporated under reduced pressure. The dissolve evaporation process was repeated twice more (2 x 5 mL) to give aryl tetrahydrothiophene (*S*)-**148** (20 mg, 34%, ≥99.5:0.5 er by CSP-HPLC) as an orange oil. $[\alpha]_D$ +47.5 (*c* 0.5 in CH_2Cl_2); CSP-HPLC: Chiracel IC (99:1 hexane-*i*-PrOH), 1.0 mL min^{-1}) (*S*)-**148** 17.8 min, (*R*)-**148** 20.9 min.

Lab book reference: **SMc5-237**

2-(4-(Trifluoromethyl)phenyl)tetrahydrothiophene-(*S*)-144

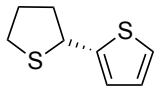


(*S*)-**144**

Using General Procedure C, 2-Bpin tetrahydrothiophene (*S*)-**110** (76 mg, 0.36 mmol, 1.2 eq., ≥99.5:0.5 er) and 1-bromo-4-(trifluoromethyl)-benzene (42 μL, 0.30 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 99:1 hexane-Et_2O as eluent gave aryl tetrahydrothiophene (*S*)-**144** (42 mg, 60%, 98:2 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ -11.2 (*c* 0.3 in CH_2Cl_2); CSP-HPLC CHIRALPAK® IG (99.9:0.1 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**144** 11.1 min, (*S*)-**144** 12.5 min.

Lab book reference: **SMc5-236**

2-(Tetrahydrothiophen-2-yl)thiophene (*R*)-119



(*R*)-**119**

Using General Procedure C, 2-Bpin tetrahydrothiophene (*R*)-**110** (82 mg, 0.36 mmol, 1.2 eq., ≥99.5:0.5 er) and 2-bromothiophene (29 μL, 0.30 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 98.5:1.5 pentane-Et_2O as eluent gave aryl tetrahydrothiophene (*R*)-**119** (30 mg, 59%, 87:13 er by CSP HPLC) as a pale yellow oil, $[\alpha]_D$ –18.8 (*c* 1.0 in CH_2Cl_2) [lit.,[73] $[\alpha]_D$ +12.0 (*c* 0.89 in CH_2Cl_2 for (*S*)-**119** of 96:4 er); CSP-HPLC: CHIRALPAK® IG (99.5:0.5 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**119** 13.3 min, (*S*)-**119** 15.3 min.

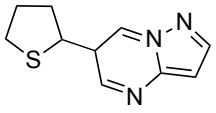
Lab book reference: **SMc3-126-1**

2-Bpin tetrahydrothiophene (*R*)-**110** (79 mg, 0.36 mmol, 1.2 eq., ≥99.5:0.5 er), $P(Ad)_3$ Pd G3 (24 mg, 30 μmol, 0.1 eq.) and Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and 2-bromothiophene (29 μL, 0.30 mmol, 1.0 eq.), degassed toluene (0.43 mL) and water (54 μL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined rganics 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 using 399:1 hexane:Et_2O as eluent gave aryl tetrahydrothiophene (*R*)-**119** (24 mg, 47%) as a pale yellow oil. $[\alpha]_D$ -40.28 (*c* 1.0 in CH_2Cl_2 [lit.,[73] $[\alpha]_D$ +12.0 (*c* 0.89

in CH_2Cl_2 for (*S*)-**119** of 96:4 er); CSP-HPLC CHIRALPAK® IG (99.5:0.5 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**119** 12.8 min, (*S*)-**119** 15.2 min.

Lab book reference: **SMc4-232**

6-(Tetrahydrothiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine 153



153

Using General Procedure D, 2-Bpin tetrahydrothiophene (*R)*-**110** (80 mg, 0.37 mmol, 1.2 eq., ≥99.5:0.5 er) and 6-bromopyrazolo[1,5-a]pyrimidine (59 mg, 0.30 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 50:50 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **153** (19 mg, 31%, 57:43 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +0.90 (*c* 1.0 in CH_2Cl_2); CSP-HPLC (*R*) or (*S*)-**153** 20.2 min, (*R*) or (*S*)-**153** 33.5 min.

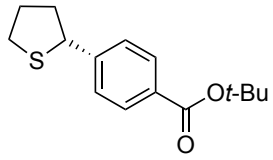
Lab book reference: **SMc4-226-1**

2-Bpin Tetrahydrothiophene (*R*)-**110** (79 mg, 0.36 mmol, 1.2 eq., ≥99.5:0.5 er), 6-bromopyrazolo[1,5-a]pyrimidine (60 mg, 0.3 mmol, 1.0 eq.), $P(Ad)_3$ Pd G3 (24 mg, 30 μmol, 0.1 eq.) and Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and degassed toluene (0.43 mL) and water (54 μL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using 50:50 hexane-Et_2O as eluent gave aryl tetrahydrothiophene **153** (21 mg, 34%, 59:41 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ + 0.28 (*c* 1.0 in CH_2Cl_2); CSP-HPLC (*R*) or (*S*)-**153** 17.8 min, (*R*) or (*S*)-**153** 29.0 min.

Lab book reference: **SMc6-234**

***tert*-butyl 4-(tetrahydrothiophen-2-yl)benzoate (*R*)-120**



(*R*)-**120**

Using General Procedure C, 2-Bpin tetrahydrothiophene (*R*)-**110** (79 mg, 0.36 mmol, 1.2 eq., ≥99.5:0.5 er) and tert-butyl 4-bromobenzoate (59 µL, 0.3 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 97:3 hexane-Et_2O as eluent gave aryl tetrahydrothiophene (*R*)-**120** (35 mg, 44%, 87:13 er by CSP-HPLC) as a yellow oil, $[\alpha]_D$ -30.4 (*c* 1.0 in CH_2Cl_2); CSP-HPLC CHIRALPAK® IC (99:1 hexane:*i*PrOH 1.0 mL min^{-1}) (*R*)-**120** 10.7 min, (*S*)-**120** 12.1 min.

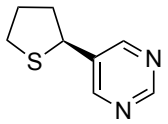
Lab book reference: **SMc5-251**

2-Bpin tetrahydrothiophene (*R*)-**110** (79 mg, 0.36 mmol, 1.2 eq., ≥99.5:0.5 er), tert-butyl 4-bromobenzoate (59 µL, 0.3 mmol, 1.0 eq.), $P(Ad)_3$ Pd G3 (24 mg, 30 µmol, 0.1 eq.) and Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and degassed toluene (0.43 mL) and water (54 µL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being

allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using 95:5 hexane-Et_2O as eluent gave aryl tetrahydrothiophene (*R*)-**120** (34 mg, 43%, ≥99:1 er by CSP-HPLC) as a yellow oil, $[\alpha]_D$ -33.1 (*c* 1.0 in CH_2Cl_2); CSP-HPLC CHIRALPAK® IC (99:1 hexane:*i*PrOH 1.0 mL min^{-1}) (*R*)-**120** 10.7 min, (*S*)-**120** 12.1 min.

Lab book reference: **SMc5-252**

5-(Tetrahydrothiophen-2-yl)pyrimidine (*S*)-149

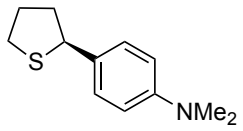


(*S*)-**149**

Using General Procedure D, 2-Bpin tetrahydrothiophene (*S*)-**110** (75 mg, 0.36 mmol, 1.2 eq., ≥99.5:0.5 er), and 5-bromopyrimidine (48 mg, 0.3 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 80:20 hexane-Et_2O as eluent gave aryl tetrahydrothiophene (*S*)-**149** (27 mg, 54%, >99:1 er by CSP-HPLC) as an orange oil, $[\alpha]_D$ –14.5 (*c* 1.0 in CH_2Cl_2); CSP-HPLC CHIRALPAK® IC (95:5 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**149** 37.5 min, (*R*)-**149** 40.7 min.

Lab book reference: **SMc5-247**

_N_,_N_-Dimethyl-4-(tetrahydrothiophen-2-yl)aniline (_S_)-142



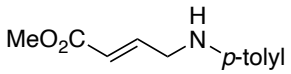
(*S*)-**142**

Using General Procedure D, 2-Bpin tetrahydrothiophene (*S*)-**110** (76 mg, 0.36 mmol, 1.2 eq., ≥99.5:0.5 er by CSP-HPLC) and 4-Bromo-*N*,*N*-dimethylaniline (60 mg, 0.3 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 10:87:3 toluene-hexane-Et_2O as eluent gave aryl tetrahydrothiophene (*S*)-**142** (35 mg, 40%, 98:2 er by CSP-HPLC) as a pale yellow solid, $[\alpha]_D$ +44.76 (*c* 1.0 in CH_2Cl_2); CSP-HPLC CHIRALPAK® IC (95:5 hexane-*i*PrOH 1.0 mL min^{-1}) (*R*)-**142** 8.24 min, (*S*)-**142** 12.05 min.

Lab book reference: **SMc5-248**

5.5 Experimental Procedures for Chapter 3

(*E*)-Methyl 4-(*p*-tolylamino)but-2-enoate (*E*)-179

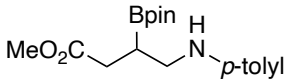


179

Methyl 4-bromocrotonate (2.94 mL, 25 mmol, 1.0 eq.) was added to a stirred mixture of *p*-toluidine (6.43 g, 60 mmol, 2.4 eq.) and K_2CO_3 (690 mg, 5.0 mmol, 0.1 eq.) in MeCN (50 mL) at rt. The resulting mixture was stirred and heated at 65 °C (heater block temperature) for 2 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure. Water (30 mL) and EtOAc (30 mL) were added and the two layers separated. The aqueous layer was extracted with EtOAc (3 x 30 mL) and 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 80:20 hexane-EtOAc as eluent gave monosubstituted amine (*E*)-**179** (3.35 g, 65%) as an amber solid. mp 48-50 °C (lit.,[6] 51-53 °C (CH_2Cl_2)); R_F (60:40 hexane-EtOAc) 0.57; IR (ATR) 3395 (NH), 1720 (C=O), 1521, 1276, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (dt, *J* = 16.0, 5.0 Hz, 1H, CH_2CH=CH), 7.02-6.99 (m, 2H, Ar), 6.55-6.50 (m, 2H, Ar), 6.06 (dt, *J* = 16.0, 2.0 Hz, 1H, CH_2CH=C*H*), 3.95-3.89 (dd, *J* = 4.5, 2.0 Hz, 2H, CH_2CH=CH), 3.82 (br s, 1H, NH) 3.73 (s, 3H, OMe), 2.25 (s, 3H, Ar*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.9 (C=O), 146.3 (CH_2CH=CH), 145.1 (*ipso*-Ar), 129.9 (Ar), 127.3 (*ipso*-Ar), 121.3 (CH_2CH=*CH*), 113.1 (Ar), 51.6 (OMe), 45.2 (CH_2), 20.4 (Ar*Me*); HRMS (ESI) *m/z* calcd for $C_{12}H_{15}NO_2$ $(M + Na)^+$ 228.0989, found 228.0995 (+2.5 ppm error). Spectroscopic data consistent with those reported in the literature.[59]

Lab book reference: **SMc61**

Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(*p*-tolylamino)butanoate 180

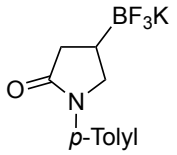


180

B_2Pin_2 (5.1 g, 19.6 mmol, 1.2 eq.), CuI (63 mg, 0.33 mmol, 2 mol%) and K_2CO_3 4.0 g, 27.8 mmol, 1.7 eq.) were added to a flame-dried flask at rt under Ar. THF (25 mL) was added and the resulting mixture was stirred at rt for 10 min. Then, a solution of enoate (*E*)-**179** (3.35 g, 16.3 mmol, 1.0 eq.) in THF (30 mL) was added followed by the addition of dry MeOH (13 mL, 2.0 eq.). The resulting mixture was stirred at rt for 1 h. The solids were removed by filtration through a plug of Celite® and the solvent was evaporated under reduced pressure to give the crude product. Purification by recrystallisation (x2) from *n*-hexane gave Bpin ester **180** (4.0 g, 73%) as a white solid, mp 67-70 °C (lit.,[6] 99-102 °C (CH_2Cl_2)); IR (ATR) 3386 (NH), 2977, 1733 (C=O), 1515, 1388, 1305, 1142, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.01-6.93 (m, 2H, Ar), 6.57-6.49 (m, 2H, Ar), 3.81 (br s, 1H, NH), 3.66 (s, 3H, OMe), 3.22 (dd, *J* = 12.0, 7.5 Hz, 1H, NCH), 3.15 (dd, *J* = 12.0, 7.5 Hz, 1H, NCH) 2.57 (dd, *J* = 17.0, 7.0 Hz, 1H, CHCO), 2.51 (dd, *J* = 17.0, 6.0 Hz, 1H, CHCO), 2.23 (s, 3H, Ar*Me*), 1.69 (dddd, *J* = 7.0, 7.0, 7.0, 6.0 Hz, 1H, BCH), 1.24 (s, 12H, C*Me*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.4 (C=O), 146.3 (*ipso*-Ar), 129.8 (Ar), 126.4 (*ipso*-Ar), 113.2 (Ar), 83.7 (O*C*Me$_2$), 51.7 (OMe), 45.2 (NCH_2), 33.7 (*C*H_2CO), 24.89 (CMe), 24.86 (CMe), 20.5 (Ar*Me*) (BCH resonance not resolved); ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.01; HRMS (ESI) *m/z* calcd for $C_{18}H_{28}BNO_4$ $(M + H)^+$ 334.2184, found 334.2194 (–1.9 ppm error). Spectroscopic data consistent with those reported in the literature.[59]

Lab book reference: **SMc62**

Potassium(1-(4-tolyl))-4-trifluoroboratepyrrolidin-2-one 65

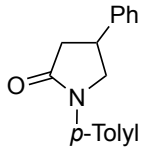


65

A solution of Bpin ester **180** (3.9 g, 11.9 mmol, 1.0 eq.) in AcOH (24 mL) was stirred and heated at 50 °C (heater block temperature) for 4 h. After being allowed to cool to rt, saturated $Na_2CO_{3(aq)}$ (50 mL) was added. Then, CH_2Cl_2 (30 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give crude Bpin lactam as an off-white solid. The crude product was dissolved in MeOH (20 mL) and saturated $KHF_{2(aq)}$ (3.3 M, 18 mL, 5.0 eq.) was added. The resulting mixture was stirred at rt for 1 h, then the solvent was evaporated under reduced pressure. The residue was dissolved in the minimum amount of hot acetone and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give a white solid. Et_2O (150 mL) was added and the resulting mixture was stirred at rt for 3 h. The solids were collected by filtration to give trifluoroborate salt **65** (3.3 g, 95%) as a white solid, mp 208-212 °C (lit.,[6] 140 °C (acetone)); IR (ATR) 1671 (C=O), 1515, 1399, 1269, 1098, 954, 818 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ 7.55-7.47 (m, 2H, Ar), 7.15-7.08 (m, 2H, Ar), 3.60-3.49 (m, 2H, NCH), 2.25 (s, 3H, Ar*Me*), 2.18 (d, J = 10.0 Hz, 2H, CH_2CO), 1.15-1.02 (m, 1H, BCH); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 176.5 (C=O), 138.1 (*ipso*-Ar), 132.0 (*ipso*-Ar), 128.9 (Ar), 118.9 (Ar), 52.2 (NCH_2), 36.4 (CH_2CO), 20.4 (Ar*Me*), (BCH resonance not resolved); ^{11}B NMR (128 MHz, d_6-DMSO) δ 3.28; ^{19}F NMR (375 MHz, d_6-DMSO) δ –144.2; HRMS (ESI) *m/z* calcd for $C_{11}H_{12}BF_3NO$ M^- 242.097, found 242.0967 (+1.8 ppm error). Spectroscopic data consistent with those reported in the literature.[59]

Lab book reference: **SMc63-1**

4-Phenyl-1-(*p*-tolyl)pyrrolidin-2-one 66



66

4-BF_3K *N*-*p*-tolyl pyrrolidone **65** (84 mg, 0.3 mmol, 1.0 eq.), cataCXium A Pd G3 (11 mg, 15 μmol, 0.05 eq.) and Cs_2CO_3 (390 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (36 μL, 0.35 mmol, 1.15 eq.), degassed toluene (0.90 mL) and water (100 μL, 5.7 mmol, 19.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 110 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 80:20 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **66** (46 mg, 60%) as a pale yellow/white solid, R_F (80:20 hexane-EtOAc) 0.14; mp 87-90 °C (lit.,[59] 95-87 °C (CH_2Cl_2)); IR (ATR) 1690, 1513, 1390, 1220, 815, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.47 (m, 2H, Ar), 7.42-7.33 (m, 2H, Ar), 7.33-7.26 (m, 3H, Ar), 7.23-7.16 (m, 2H, Ar), 4.18 (dd, *J* = 9.5, 8.0 Hz, 1H, NCH), 3.88 (dd, *J* = 9.5, 7.5 Hz, 1H, NCH) 3.70 (dddd, *J* = 8.5, 8.5, 8.0, 7.5 Hz, 1H, C*H*Ph), 3.02 (dd, *J* = 17.0, 8.5 Hz, 1H, CH), 2.80 (dd, *J* = 17.0, 8.5 Hz, 1H, CH) 2.34 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.9 (C=O), 141.9 (*ipso*-Ar), 136.7 (*ipso*-Ar), 134.5 (*ipso*-Ar), 129.6 (Ar), 129.1 (Ar), 127.4 (Ar), 126.9 (Ar), 120.2 (Ar), 55.9 (NCH_2), 40.4 (CH_2), 37.3 (*C*HPh), 21.0 (Me); HRMS (ESI) *m/z* calcd for $C_{17}H_{17}NO$ $(M + Na)^+$ 274.1202, found 274.1210 (+2.7 ppm error). Spectroscopic data consistent with those reported in the literature.[59]

Lab book reference **SMc21Br**

4-BF_3K *N*-*p*-tolyl pyrrolidone **65** (84 mg, 0.3 mmol, 1.0 eq.), cataCXium A Pd G3 (11 mg, 15 μmol, 0.05 eq.) and Cs_2CO_3 (390 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (36 μL, 0.35 mmol, 1.15 eq.), degassed toluene (0.90 mL) and water (100 μL, 5.7 mmol, 19.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 110 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 80:20 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **66** (46 mg, 60%) as a pale yellow/white solid.

Lab book reference: **SMc26**

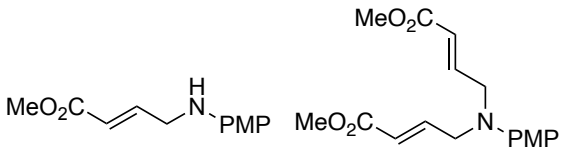
4-BF_3K *N*-*p*-tolyl pyrrolidone **65** (84 mg, 0.3 mmol, 1.0 eq.), cataCXium A Pd G3 (11 mg, 15 μmol, 0.05 eq.) and Cs_2CO_3 (390 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (36 μL, 0.35 mmol, 1.15 eq.), degassed toluene (0.90 mL) and water (100 μL, 5.7 mmol, 19.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 110 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 7:3 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **66** (43 mg, 57%) as a pale yellow/white solid.

Lab book reference: **SMc34-1**

4-BF_3K *N*-*p*-tolyl pyrrolidone **65** (84 mg, 0.3 mmol, 1.0 eq.), cataCXium A Pd G3 (11 mg, 15 μmol, 0.05 eq.) and Cs_2CO_3 (390 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and chlorobenzene (35 μL, 0.35 mmol, 1.15 eq.), degassed toluene (0.90 mL) and water (100 μL, 5.7 mmol, 19.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 110 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 8:2 hexane-EtOAc as eluent gave 4-phenyl *N*-*p*-tolyl pyrrolidone **66** (46 mg, 61%) as a pale yellow/white solid.

Lab book reference: **SMc26Cl**

Methyl 4-(4-methoxyphenyl)but-2-enoate (*E*) 195 and dimethyl 4,4'-((4-methoxyphenyl)azanediyl)(2E,2'E)-bis(but-2-enoate) 196



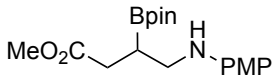
195 **196**

Methyl 4-bromocrotonate (11.8 mL, 100 mmol, 1.0 eq.) was added to *p*-anisidine (31 g, 250 mmol, 2.5 eq.) and K_2CO_3 (2.8 g, 20 mmol, 0.2 eq.) in MeCN (200 mL) at 65 °C (heater block temperature). The resulting mixture was stirred for 1 h, cooled to room temperature and solvent evaporated under reduced pressure. Water (100 mL) and

EtOAc (100 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 100 mL) and 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 70:15:15 hexane-EtOAc-toluene as eluent gave a 90:10 mixture (by ^1H NMR spectroscopy) of monosubstituted amine (*E*)-**195** and disubstituted amine (*E*)-**196** (18.5 g, i.e. 15.9 g (72%) of (*E*)-**195** and 2.6 g (8%) of (*E*)-**196**) as an amber oil, R_F (70:30 hexane-EtOAc) 0.31 for (E)-**195** and 0.24 for (E)-**196**; IR (ATR) 3389 (NH), 1713 (C=O), 1511, 1232, 1170, 1034, 819 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) for (*E*)-**195** δ 7.04 (dt, *J* = 16.0, 5.0 Hz, 1H, CH_2CH=CH), 6.99-6.91 (m, 2H, Ar), 6.85-6.73 (m, 2H, Ar), 6.05 (dt, *J* = 16.0, 2.0 Hz, 2H, CH_2CH=C*H*), 3.91 (dd, *J* = 5.0, 2.0 Hz, 2H, C*H*$_2$CH=CH), 3.74 (s, 3H, OMe), 3.73 (s, 3H, OMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) for (*E*)-**195** δ 166.9 (C=O), 152.5 (*ipso*-Ar), 145.3 (CH_2*C*H=CH), 141.5 (*ipso*-Ar), 121.4 (CH_2CH=*C*H), 115.0 (Ar), 114.5 (Ar), 55.8 (OMe), 51.7 (OMe), 45.8 (CH_2); HRMS (ESI) *m/z* calcd for $C_{12}H_{15}NO_3$ $(M + Na)^+$ 244.0944, found 244.0942 (–0.2 ppm error). Diagnostic signal for disubstituted amine (*E*)-**196**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.94 (dt, *J* = 16.0, 2.0 Hz, 4H, CH_2CH=C*H*); Spectroscopic data for monosubstituted amine (*E*)-**195** consistent with those reported in the literature.[59]

Lab book reference: **SMc420-1**

Methyl 4-((4-methoxyphenyl)amino)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate 197



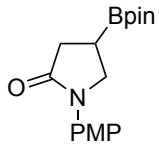
197

B_2pin_2 (18 g, 71 mmol, 1.2 eq.), CuI (225 mg, 1.18 mmol, 0.02 eq.) and K_2CO_3 (13.9 g, 100 mmol, 1.7 eq.) were added to a flamed dried flask at rt under Ar. THF (160 mL) was added and the mixture was stirred at rt for 10 min. Then, a 90:10 mixture of PMP enoate (E)-**195** and (E)-**196** (13.2 g, i.e. 11.9 g, 54 mmol of (*E*)-**195** and 1.3 g, 4 mmol of (*E*)-**196**) in THF (40 mL) was added followed by the addition of MeOH (4.8 mL). The resulting mixture was stirred at rt for 1 h. The solids were removed by filtration

through a plug of Celite® and the solvent was evaporated under reduced pressure to give the crude product. Purification by recrystallisation from *n*-hexane to give *B*pin ester **197** (15.6 g, 83%) as a white solid, mp 74-76 °C (lit.,[6] 84-85 °C (*n*-hexane)); IR (ATR) 3386 (NH), 2978, 1732 (C=O), 1513, 1235, 1142, 821 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78-6.74 (m, 2H, Ar), 6.59-6.54 (m, 2H, Ar), 3.74 (s, 3H, OMe), 3.68 (br s, 1H, NH), 3.66 (s, 3H, ArO*Me*), 3.20 (dd, *J* = 12.0, 7.5 Hz, 1H, NCH), 3.13 (dd, *J* = 12.0, 7.0 Hz, 1H, NCH), 2.59 (dd, *J* = 16.5, 7.5 Hz, 1H, CH), 2.54 (dd, *J* = 16.5, 6.5 Hz, 1H, CH), 1.69 (dddd, *J* = 7.5, 7.5, 7.0, 6.5 Hz, 1H, BCH), 1.24 (s, 12H, CMe_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.4 (C=O), 152.1 (*ipso*-Ar), 142.9 (*ipso*-Ar), 115.0 (Ar), 114.4 (Ar), 83.7 (O*C*Me_2), 55.9 (ArO*Me*), 51.7 (OMe), 45.2 (NCH_2), 33.7 (*C*H_2CO), 24.89 (C*Me*), 24.86 (C*Me*), 20.5 (BCH); ^{11}B NMR (128 MHz, d_6-DMSO) δ 33.3; HRMS (ESI) *m/z* calculated for $C_{18}H_{28}BNO_5$ $(M + H)^+$ 350.2133, found 350.2140 (-0.8 ppm error). Spectroscopic data consistent with those reported in the literature.[6]

Lab book reference: **SMc6-424**

1-(4-Methoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-2-one 198



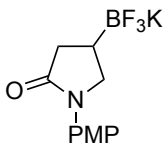
198

A solution of Bpin ester **197** (7.3 g, 21 mmol, 1.0 eq.) was dissolved in AcOH (42 mL, 0.5 M solution) at 50 °C (heater block temperature) and stirred for 4 h. After being allowed to cool to rt, the solution was basified to pH 8 using solid $NaHCO_3$. Then, CH_2Cl_2 (50 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organics were dried ($MgSO_4$) and solvent evaporated under reduced pressure to give 4-Bpin *N*-PMP pyrrolidone **198** (6 g, 91%) as a brown solid, mp 90-92 °C; IR (ATR) 2978, 1691 (C=O), 1513, 1389, 1327, 1247, 1034, 830 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.45 (m, 2H, Ar), 6.92-6.85 (m, 2H, Ar), 3.92-3.83 (dd, 2H, NCH), 3.79 (s, 3H, OMe), 2.67 (dd, *J* = 17.0,

10.0 Hz, 1H, CH), 2.58 (dd, *J* = 17.0, 10.5 Hz, 1H, CH), 1.95 (dddd, *J* = 10.5, 10.0, 9.5, 9.5 Hz, 1H, BCH), 1.27 (s, 12H, C*Me*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.2 (C=O), 156.6 (*ipso*-Ar), 132.8 (*ipso*-Ar), 122.0 (Ar), 114.1 (Ar), 84.1 (O*C*Me$_2$), 55.6 (OMe), 51.1 (NCH_2), 34.7 (CH_2), 24.9 (C*Me*) (BCH resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{17}H_{24}BNO_4$ $(M + H)^+$ 318.1874, found 318.1871 (–0.7 ppm error); spectroscopic data consistent with those reported in the literature.[59]

Lab book reference: **SMc5-331**

1-(4-Methoxyphenyl)-4-(trifluoro-λ^4-boraneyl)pyrrolidin-2-one, potassium salt 192

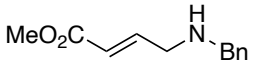


192

4-Bpin *N*-PMP pyrrolidone **198** (6g, 18.9 mmol, 1.0 eq.) was dissolved in MeOH (38 mL) and saturated $KHF_{2(aq)}$ (3.3 M, 29 mL, 5.0 eq.) was added. The resulting mixture was stirred for 1 h and then the solvent was evaporated under reduced pressure. The residue was dissolved in the minimum amount of hot acetone and the solids were removed by filtration. The residue was dissolved in the minimum amount of hot acetone and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give a brown solid. Et_2O (150 mL) was added and the resulting mixture was stirred at rt for 1 h. The solids were collected by filtration to give 4-BF_3K *N*-PMP pyrrolidone **192** (4.2 g, 75%) as an off white solid, mp 238-240 ºC; IR (ATR) 1692 (C=O), 1513, 1390, 1248, 1143 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO) *δ* 7.54 (m, 2H, Ar), 6.88 (m, 2H, Ar), 3.72 (s, 3H, OMe), 3.59-3.48 (m, 2H, NCH), 2.18 (d, *J* = 10.0 Hz, 2H, CH), 1.16-1.01 (m, 1H, BCH); ^{13}C NMR (100.6 MHz, d_6-DMSO) *δ* 176.1 (C=O), 155.1 (*ipso*-Ar), 133.9 (*ipso*-Ar), 120.5 (Ar), 113.64 (Ar), 55.2 (OMe), 52.4 (NCH_2), 36.2 (*C*H_2), (BCH resonance not resolved); ^{11}B NMR (128 MHz, d_6-DMSO) δ 3.33; ^{19}F NMR (375 MHz, d_6-DMSO) δ –144.15; HRMS (ESI) *m/z* calculated for $C_{11}H_{12}BF_3NO_2$ $(M)^-$ 258.0919, found 258.0918 (-0.9 ppm error).

Lab book reference: **SMc6-431**

Methyl (E)-4-(benzylamino)but-2-enoate 200

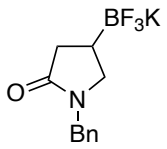


200

Methyl 4-bromocrotonate (1.2 mL, 10.0 mmol, 1.0 eq.) was added to a stirred solution of benzylamine (2.2 mL, 20 mmol, 2.0 eq.) in CH_2Cl_2 (10 mL) at rt. The resulting mixture was stirred at rt for 3 h. Saturated $NaHCO_{3(aq)}$ (30 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 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 80:20 to 60:40 hexane-EtOAc as eluent gave benzyl amino enoate **200** (837 mg, 41%) as an orange oil, R_F (60:40 hexane-EtOAc) 0.11; IR (ATR) 2950, 2916, 1719 (C=O), 1435, 1269, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.20 (m, 5H, Ar), 7.01 (dt, J = 16.0, 5.5 Hz, 1H, CH_2CH=CH), 6.02 (dt, J = 16.0, 2.0 Hz, 1H, CH_2CH=C*H*), 3.79 (s, 2H, NCH_2Ph), 3.73 (s, 3H, OMe), 3.41 (dd, J = 5.5, 2.0 Hz, 2H, CH_2CH=CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.0 (C=O), 147.1 (CH_2CH=CH), 139.9 (*ipso*-Ar), 128.6 (Ar), 128.2 (Ar), 127.3 (Ar), 121.3 (CH_2CH=*C*H), 53.3 (NCH_2Ph), 51.6 (OMe), 49.6 (CH_2CH=CH); HRMS (ESI) *m/z* calculated for $C_{12}H_{16}NO_2$ $(M + H)^+$ 206.1176, found 206.1180 (–2.2 ppm error). Spectroscopic data consistent with those reported in the literature.[59]

Lab book reference: **SMc42-1**

Potassium(1-benzyl)-4-trifluoroboratepyrrolidin-2-one 193

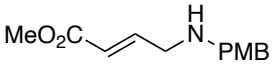


193

B_2Pin_2 (1.01 g, 3.97 mmol, 1.2 eq.), $CuBr_2$ (15 mg, 0.07 mmol, 0.02 eq.) and K_2CO_3 (915 mg, 6.62 mmol, 2.0 eq.) were added to THF (10 mL) at rt. The mixture was stirred at rt for 1 h then a solution of Bn enoate ester **200** (778 mg, 3.31 mmol, 1.0 eq.) in THF (7 mL) and BuOH (0.60 mL) was added. The reaction mixture was stirred at rt for 24 h, then brine was added (40 mL) and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a dark green solid. The crude product was dissolved in MeOH (33 mL) and saturated $KHF_{2(aq)}$ (1.3 g in 4.1 mL H_2O) was added. The resulting mixture was stirred at rt for 1 h and then the solvent was evaporated under reduced pressure. The residue was dissolved in the minimum amount of hot acetone and the solids were removed by filtration. The filtrate was evaporated under reduced pressure then Et_2O (150 mL) was added and the resulting mixture stirred at rt for 1 h. The solids were collected by filtration to give trifluoroborate salt **193** (476 mg, 51%) as an off white powder, mp 202-204 ºC; IR (ATR) 1651, 1625, 1451, 1249, 972, 698 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ 7.38-7.29 (m, 2H, Ar), 7.27-7.21 (m, 1H, Ar), 7.21-7.13 (m, 2H, Ar), 4.31-4.27 (m, 2H, NC*H*Ph), 3.09-2.94 (m, 2H, NCH), 2.10-2.02 (m, 1H, CH), 2.02-1.94 (m, 1H, CH), 1.03-0.89 (m, 1H, BCH); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 176.6 (C=O), 137.8 (*ipso*-Ar), 128.5 (Ar), 127.6 (Ar), 127.0 (Ar), 50.1 (NCH_2), 45.6 (N*C*H_2Ph), 34.3 (*C*H_2), 26.0 (BCH); ^{11}B NMR (128 MHz, d_6-DMSO) δ 2.92; ^{19}F NMR (375 MHz, d_6-DMSO) δ –144.21; HRMS (ESI) *m/z* calculated for $C_{11}H_{12}BF_3NO$ $(M)^-$ 242.0970, found 242.0974 (-1.0 ppm error).

Lab book reference **SMc43-1**

(E)-Methyl 4-(*p*-methoxybenzyl amino)but-2-enoate 201

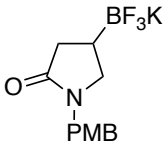


201

Methyl 4-bromocrotonate (1.2 mL, 10.0 mmol, 1.0 eq.) was added to a stirred mixture of 4-methoxybenzylamine (3.3 mL, 25.0 mmol, 2.5 eq.) and Hünig's base (5.2 mL, 30.0 mmol, 3.0 eq.) in MeCN (50 mL) at rt. The resulting mixture was stirred and heated at 65 °C (heater block temperature) for 2 h. After being allowed to cool to rt the solvent was evaporated under reduced pressure. The residue was dissolved in Et_2O (40 mL) and the organic layer was extracted with 2M $HCl_{(aq)}$ (3 x 30 mL). Combined aqueous phases were neutralised with solid Na_2CO_3 and basified with 1M NaOH (5 mL). Et_2O (50 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 CH_2Cl_2-(90:10 MeOH-35% $NH_4OH_{(aq)}$) as eluent gave PMB enoate ester **201** (567 mg, 23%) as a yellow oil, R_F (90:10 CH_2Cl_2-(90:10 MeOH-35% $NH_4OH_{(aq)}$)) 0.22; IR (ATR) 1721 (C=O), 1511, 1246, 1172, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.21 (m, 2H, Ar), 7.01 (dt, J = 16.0, 5.5 Hz, 1H, CH_2CH=CH), 6.90-6.84 (m, 2H, Ar), 6.02 (dt, J = 16.0, 2.0 Hz, 1H, CH_2CH=C*H*), 3.79 (s, 3H, OMe), 3.73 (s, 5H, OMe, NCH_2Ar), 3.41 (dd, J = 5.5, 2.0 Hz, CH_2CH=CH), 1.42 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.0 (C=O), 158.9 (*ipso*-Ar), 147.2 (CH_2CH=CH), 132.0 (*ipso*-Ar), 129.4 (Ar), 121.2 (CH_2CH=*CH*), 113.9 (Ar), 55.4 (OMe), 52.8 (NCH_2Ar), 51.6 (OMe), 49.5 (CH_2CH=CH); HRMS (ESI) *m/z* calcd for $C_{12}H_{13}NO_2$ $(M + Na)^+$ 226.0838, found 226.0840 (–0.9 ppm error).

Lab book reference **SMc41-4**

Potassium(1-(4-methoxybenzyl))-4-trifluoroboratepyrrolidin-2-one 194



194

B_2pin_2 (482 mg, 1.88 mmol, 1.2 eq.), $CuBr_2$ (7.4 mg, 0.03 mmol, 0.02 eq.) and K_2CO_3 (423 mg, 3.14 mmol, 2.0 eq.) were added to THF (5 mL) at rt. The mixture was stirred at rt for 10 minutes then a solution of PMB enoate ester **201** (369 mg, 1.57 mmol, 1.0 eq.) in THF (2 mL) and MeOH (0.18 mL) was added. The reaction mixture was stirred at rt for 24 h, then brine was added (20 mL) and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a dark green solid. Saturated $KHF_{2(aq)}$ (1.07 g in 3.4 mL H_2O) was added to a stirred solution of the crude material in MeOH (27 mL) at rt. The resulting mixture was stirred for 1 h and then the solvent was evaporated under reduced pressure. The residue was dissolved in the minimum amount of hot acetone and the solids were removed by filtration. The filtrate was evaporated under reduced pressure then Et_2O (75 mL) was added and the resulting mixture stirred at rt for 1 h. The solids were collected by filtration to give the crude product as a white powder which contained a 75:25 mixture (by ^1H NMR spectroscopy) of trifluoroborate salt **194** and acyclic trifluoroborate salt **202**. Me_3SiCl (0.347 mL, 2.73 mmol, 3.0 eq.) was added to a stirred solution of the crude product in MeCN (9.1 mL) and H_2O (2.7 mL) at rt. The resulting mixture was stirred for 2 h at rt then the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (15 mL). Then, H_2O (10 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude boronic acid. A saturated solution of KHF_2 (376 mg) in H_2O (1.1 mL) was added to a stirred solution of the crude boronic acid in MeOH (10 mL) at rt. The resulting mixture was stirred at rt for 1 h and then the solvent was evaporated under reduced pressure. The residue was dissolved in the minimum amount of hot acetone and the solids were removed by filtration. The filtrate was evaporated under reduced pressure. Et_2O (150 mL) was added and the resulting mixture was stirred at rt for 1 h.

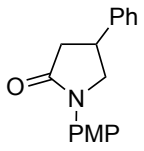
The solids were collected by filtration to give 4-BF_3K *N*-PMB pyrrolidone **194** (102 mg, 23%) as an off-white powder, mp 238-240 ºC; IR (ATR) 1651 (C=O), 1514, 1246, 1088 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ 7.11 (d, J = 8.0 Hz, 2H, Ar), 6.88 (d, J = 8.0 Hz, 2H, Ar), 4.23 (d, J = 14.5 Hz, 1H, NC*H*Ar), 4.18 (d, J = 14.5 Hz, 1H, NC*H*Ar), 3.73 (s, 3H, OMe), 3.03-2.89 (m, 2H, NCH), 2.07-1.90 (m, 2H, CH), 1.13-0.76 (m, 1H, BCH); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 176.9 (C=O), 158.8 (*ipso*-Ar), 130.2 (*ipso*-Ar), 129.5 (Ar), 114.3 (Ar), 55.5 (OMe), 50.4 (N*C*H_2CH), 45.5 (N*C*H_2Ar), 34.9 (CH_2) (BCH resonance not resolved); ^{11}B NMR (128 MHz, d_6-DMSO) δ 3.16; ^{19}F NMR (375 MHz, d_6-DMSO) δ –144.15; HRMS (ESI) *m/z* calcd for $C_{12}H_{14}BF_3NO_2$ M^- 272.1075, found 272.1076 (+0.5 ppm error).

Lab book reference: **SMc46-1/SMc47-1**

B_2Pin_2 (437 mg, 1.72 mmol, 1.2 eq.), $CuBr_2$ (7 mg, 0.03 mmol, 0.02 eq.) and K_2CO_3 (390 mg, 2.86 mmol, 2.0 eq.) were added to THF (5 mL) at rt. The mixture was stirred at rt for 10 minutes then a solution of PMB enoate ester **201** (337 mg, 1.43 mmol, 1.0 eq.) in THF (2 mL) and MeOH (0.12 mL) was added. The reaction mixture was stirred at rt for 24 h, then brine was added (20 mL) and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a dark green solid. The crude material was dissolved in AcOH (3 mL, 0.5 M solution) at 50 °C (heater block temperature) and stirred for 3 h. After being allowed to cool to rt, water (10 mL) was added and the solution was basified to pH 8 using solid $NaHCO_3$. Then, CH_2Cl_2 (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organics were dried ($MgSO_4$) and solvent evaporated under reduced pressure to give. Saturated $KHF_{2(aq)}$ (537 mg in 1.7 mL H_2O) was added to a stirred solution of the crude material in MeOH (13.5 mL) at rt. The resulting mixture was stirred for 1 h and then the solvent was evaporated under reduced pressure. The residue was dissolved in the minimum amount of hot acetone and the solids were removed by filtration. The filtrate was evaporated under reduced pressure then Et_2O (75 mL) was added and the resulting mixture stirred at rt for 1 h. The solids were collected by filtration to give 4-BF_3K *N*-PMB pyrrolidone **194** (178 mg, 25%) as an off-white powder.

Lab book reference: **SMc46-3/52-1**

1-(4-Methoxyphenyl)-4-phenylpyrrolidin-2-one 206



206

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), cataCXium A Pd G3 (11 mg, 15 μmol, 5 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (36 μL, 0.35 mmol, 1.15 eq.), degassed toluene (0.42 mL) and water (0.1 mL, 5.7 mmol, 19.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 110 °C. The mixture was stirred at 1000-1200 rpm and heated at 110 °C (heater block temperature) for 24 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 80:20 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **206** (26 mg, 33%) as a brown solid, R_F (80:20 hexane-EtOAc) 0.12; mp 73-76 ºC (lit.,[8] mp 92.5-95 °C (EtOAc/petroleum ether)); IR (ATR) 1682 (C=O), 1508, 1294, 1231, 1031, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54-7.46 (m, 2H, Ar), 7.39-3.32 (m, 2H, Ar), 7.31-7.25 (m, 3H, Ar), 6.94-6.86 (m, 2H, Ar), 4.13 (dd, J = 9.0, 8.5 Hz, 1H, NCH), 3.85 (dd, J = 9.0, 7.5 Hz, 1H, NCH), 2.94 (s, 3H, OMe), 3.68 (dddd, J = 8.5, 8.5, 8.0, 7.5, 1H, CHPh), 2.99 (dd, J = 17.0, 8.5 Hz, 1H, CHCO), 2.77 (dd, J = 17.0, 8.5 Hz, 1H, CHCO); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8 (C=O), 156.8 (*ipso*-Ar), 141.9 (*ipso*-Ar), 132.4 (*ipso*-Ar), 129.1 (Ar), 127.4 (Ar), 126.9 (Ar), 122.0 (Ar), 114.2 (Ar), 56.2 (NCH_2), 55.6 (OMe), 40.2 (CH_2CO), 37.3 (*C*HPh); HRMS (ESI) *m/z* calcd for

$C_{17}H_{17}NO_2$ $(M + Na)^+$ 290.1151, found 290.1145 (–2.4 ppm error). Spectroscopic data consistent with those reported in the literature.[9]

Lab book reference: **SMc33-3**

Experimental data for Scheme 3.24:

A solution of *N*-PMP Ph ester **212** (93 mg, 0.31 mmol, 1.0 eq.) was dissolved in AcOH (0.65 mL, 0.5 M solution) at 50 °C (heater block temperature) and stirred for 4 h. After being allowed to cool to rt, the solution was basified to pH 8 using solid $NaHCO_3$. Then, CH_2Cl_2 (510mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organics were dried ($MgSO_4$) and solvent evaporated under reduced pressure to give 4-Ph *N*-PMP pyrrolidone **206** (59 mg, 70%) as a brown solid.

Lab book reference: **SMc65-1**

Experimental data for Table 3.2: SMCCs of 4-Boryl N-PMP pyrrolidone with bromobenzene

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), cataCXium A Pd G3 (11 mg, 15 μmol, 5 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (36 μL, 0.35 mmol, 1.15 eq.), degassed toluene (0.42 mL) and water (0.1 mL, 5.7 mmol, 19.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 110 °C. The mixture was stirred at 1000-1200 rpm and heated at 110 °C (heater block temperature) for 24 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 80:20

hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **206** (27 mg, 34%) as a brown solid.

Lab book reference: **SMc33-3**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), cataCXium A Pd G3 (11 mg, 15 μmol, 5 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (36 μL, 0.35 mmol, 1.15 eq.), degassed toluene (0.42 mL) and water (0.1 mL, 5.7 mmol, 19.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 110 °C. The mixture was stirred at 1000-1200 rpm and heated at 110 °C (heater block temperature) for 24 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 80:20 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **206** (34 mg, 42%) as a brown solid.

Lab book reference: **SMc33-4**

4-Bpin *N*-PMP pyrrolidone **192** (95 mg, 0.3 mmol, 1.0 eq.), cataCXium A Pd G3 (11 mg, 15 μmol, 5 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (36 μL, 0.35 mmol, 1.15 eq.), degassed toluene (0.42 mL) and water (0.1 mL, 5.7 mmol, 19.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 110 °C. The mixture was stirred at 1000-1200 rpm and heated at 110 °C (heater block temperature) for 24 h. After being allowed to cool to rt the

reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method A, 7% conversion to 4-phenyl *N*-PMP pyrrolidone **206**). Water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 80:20 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **206** (4 mg, 5%) as a brown solid.

Lab book reference: **SMc57-1**

4-Bpin *N*-PMP pyrrolidone **198** (95 mg, 0.3 mmol, 1.0 eq.), cataCXium A Pd G3 (11 mg, 15 μmol, 5 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (36 μL, 0.35 mmol, 1.15 eq.), degassed toluene (0.42 mL) and water (0.1 mL, 5.7 mmol, 19.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 110 °C. The mixture was stirred at 1000-1200 rpm and heated at 110 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method A, 7% conversion to 4-phenyl *N*-PMP pyrrolidone **206**). Water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 80:20 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **206** (4 mg, 5%) as a brown solid.

Lab book reference: **SMc57-2**

4-BMIDA *N*-PMP pyrrolidone **210** (97 mg, 0.3 mmol, 1.0 eq.), cataCXium A Pd G3 (11 mg, 15 μmol, 5 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a

PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (34 μL, 0.35 mmol, 1.15 eq.), degassed toluene (0.42 mL) and water (0.1 mL, 5.7 mmol, 19.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 110 °C. The mixture was stirred at 1000-1200 rpm and heated at 110 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method A, 25% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc58-1**

4-BMIDA *N*-PMP pyrrolidone **210** (97 mg, 0.3 mmol, 1.0 eq.), cataCXium A Pd G3 (11 mg, 15 μmol, 5 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (34 μL, 0.35 mmol, 1.15 eq.), degassed toluene (0.42 mL) and water (0.1 mL, 5.7 mmol, 19.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 110 °C. The mixture was stirred at 1000-1200 rpm and heated at 110 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method A, 26% conversion to 4-phenyl *N*-PMP pyrrolidone **206**). Water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 80:20 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **206** (13 mg, 16%) as a brown solid.

Lab book reference: **SMc58-2**

4-$B(OH)_2$ *N*-PMP pyrrolidone **211** (71 mg, 0.3 mmol, 1.0 eq.), cataCXium A Pd G3 (11 mg, 15 μmol, 5 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (36 μL, 0.35 mmol, 1.15 eq.), degassed toluene (0.42 mL) and water (0.1 mL, 5.7 mmol, 19.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 110 °C. The mixture was stirred at 1000-1200 rpm and heated at 110 °C (heater block temperature) for 24 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 80:20 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **206** (30 mg, 38%) as a brown solid.

Lab book reference: **SMc76-1**

Experimental data for Table 3.3: Evaluation of Pd(OAc)2 and cataCXium A as an alternative catalytic system

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (3.5 mg, 15 μmol, 5 mol%), cataCXium A (11 mg, 30 μmol, 10 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (36 μL, 0.35 mmol, 1.15 eq.), degassed toluene (0.42 mL) and water (0.1 mL, 5.7 mmol, 19.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 70:30 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **206** (18 mg, 22%) as a brown solid.

Lab book reference: **SMc60-1**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (3.5 mg, 15 μmol, 5 mol%), cataCXium A (11 mg, 30 μmol, 10 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (36 μL, 0.35 mmol, 1.15 eq.), degassed toluene (0.42 mL) and water (0.1 mL, 5.7 mmol, 19.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 65:35 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **206** (17 mg, 21%) as a brown solid.

Lab book reference: **SMc33-6**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 10 mol%.) and Cs_2CO_3 (391 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (36 μL, 0.35 mmol, 1.15 eq.), degassed toluene (0.42 mL) and water (0.1 mL, 5.7 mmol, 19.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at

1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 65:35 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **206** (30 mg, 37%) as a brown solid.

Lab book reference: **SMc3-85-1**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (36 μL, 0.35 mmol, 1.15 eq.), degassed toluene (0.42 mL) and water (0.1 mL, 5.7 mmol, 19.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 65:35 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **206** (31 mg, 38%) as a brown solid.

Lab book reference: **SMc3-86-1**

Experimental data for Table 3.4: DOE full factorial design results

Table 5.1: SMCC DOE screening of 4-BF_3K *N*-PMP pyrrolidone **192** using General Procedure G

Experiment number[a]	Water / μL	$Pd(OAc)_2$ / mg	cataCXium A / mg	Cs_2CO_3 / mg	**192** / mg	TMB / mg	Conversion of **206** / %[b]
1	18	2.6	3.6	33	31.8	7.6	6
2	90	2.2	3.5	32.1	31.8	7.8	107
3	18	2.2	18.2	32.2	31.6	7.7	10
4	90	2.4	17.9	32.3	31.3	7.5	1
5	18	2.2	3.6	162.8	31.4	8.1	0
6	90	2.2	3.5	162.9	31.4	7.6	68 (38)[c]
7	18	2.2	17.9	162.7	31.3	8.5	1
8	90	2.2	17.9	162.5	31.4	8.1	24
9	18	2.2	3.5	32.1	47.2	7.9	2
10	90	2.2	3.5	32.3	47.4	7.6	3
11	18	2.3	17.9	32.3	48	7.6	7

Experiment number[a]	Water / µL	$Pd(OAc)_2$ / mg	cataCXium A / mg	Cs_2CO_3 / mg	**192** / mg	TMB / mg	Conversion of **206** / %[b]
12	90	2.4	17.9	32.5	47.1	7.7	4
13	18	2.3	3.5	162.6	47.3	7.6	0
14	90	2.3	3.6	162.6	47.7	7.6	38
15	18	2.3	17.9	162.6	47.1	7.7	8
16	90	2.2	18.2	162.6	47.6	8.3	25
17	54	2.3	10.7	97.4	39.2	7.5	23
18	54	2.3	10.8	97.5	39.2	7.5	39
19	54	2.6	10.7	97.4	39.3	7.9	30

[a] Lab book reference is in the form of "$4BF_3K$_NPMP_Pyrrolidone_DOE1_**Experiment number***" where experiment number corresponds to the value in the respective cell; [b] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard; [c] Yield after chromatography

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 0.1 mmol, 10 mol%), cataCXium A (11 mg, 10 μmol, 10 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (18.2 mg, 0.11 mmol, 0.36 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (32 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.86 mL) and water (0.27 mL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt, the reaction was sampled using General Procedure F and the reaction was analysed by GC (GC Method B, 38% conversion to 4-phenyl *N*-PMP pyrrolidone **206**). Water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 80:20 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **206** (30 mg, 37%) as a brown solid.

Lab book reference: **SMc5-337-2**

Experimental data for Table 3.5: Screening of the SMCC of 4-BF3K *N-PMP* pyrrolidone 192 with alternative ligands at 10 or 20 mol% (ligand) loading

Table 5.2: SMCC screening of 4-BF_3K *N*-PMP pyrrolidone **192** using General Procedure H

Experiment number[a]	Ligand	Ligand / mg	Ligand / μmol	$Pd(OAc)_2$ / mg	Cs_2CO_3 / mg	BF_3K salt **192** / mg	TMB / mg	Conversion of **206** / %[b]
1	APhos	6.5	10	2.3	162.6	30.1	7.4	21
2	APhos	13	20	2.2	162.6	29.3	7.4	45
3	PAd_3	4.4	10	2.2	162.7	29.3	7.6	11
4	PAd_3	8.8	20	2.2	162.5	29.3	8.2	6
5	RuPhos	4.7	10	2.2	162.5	29.6	7.6	8
6	RuPhos	9.4	20	2.4	162.5	29.4	7.4	21
7	XPhos	4.8	10	2.3	162.7	29.4	8.2	5
8	XPhos	9.8	20	2.2	162.7	29.4	7.8	0
9	SPhos	4.1	10	2.3	162.6	29.6	7.8	2

Experiment number[a]	Ligand	Ligand / mg	Ligand / µmol	$Pd(OAc)_2$ / mg	Cs_2CO_3 / mg	BF_3K salt **192** / mg	TMB / mg	Conversion of **206** / %[b]
10	SPhos	8.5	20	2.2	162.6	29.3	7.9	11
11	JackiePhos	8	10	2.2	162.5	29.3	7.4	5
12	JackiePhos	16	20	2.3	162.5	29.3	7.8	0
13	*t*-BuBrettPhos	5	10	2.3	162.5	29.3	7.6	0
14	*t*-BuBrettPhos	9.8	20	2.3	162.6	29.6	7.9	0
15	BrettPhos	5.5	10	2.2	162.6	29.5	7.6	0
16	BrettPhos	10.7	20	2.2	162.6	29.6	7.5	0
17	PCy_3	3	10	2.3	162.6	29.3	8.4	6
18	PCy_3	5.8	20	2.2	162.5	29.6	8.2	12
19	$P(t\text{-Bu})_3 \bullet HBF_4$	2.8	10	2.2	162.7	29.3	7.9	3
20	$P(t\text{-Bu})_3 \bullet HBF_4$	5.8	20	2.6	162.5	29.3	8.3	4

[a] $4BF_3K$_NPMP_Pyrrolidone_LigandScreen_**Experiment number**" where experiment number corresponds to the value in the respective cell; [b] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard;

Experimental data for Table 3.5, entry 1 (isolated yield)

4-BF_3K *N*-PMP pyrrolidone **192** (30 mg, 0.1 mmol, 1.0 eq.), $Pd(OAc)_2$ (2.3 mg, 10 μmol, 10 mol%), cataCXium A (7 mg, 20 μmol, 20 mol%), Cs_2CO_3 (165 mg, 0.5 mmol, 5.0 eq.) and TMB (8.4 mg, 0.05 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (11 μL, 0.1 mmol, 1.0 eq.), degassed toluene (0.29 mL) and water (90 μL, 50 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure F and the reaction was analysed by GC (GC Method B, 44% conversion to 4-phenyl *N*-PMP pyrrolidone **206**). Water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 80:20 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **206** (10 mg, 39%) as a brown solid.

Lab book reference: **SMc5-338-2**

Experimental data for Table 3.5, entry 2 (isolated yield)

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), APhos (38 mg, 60 μmol, 20 mol%) and Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (32 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.86 mL) and water (0.27 mL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-

1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 80:20 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **206** (22 mg, 28%) as a brown solid.

Lab book reference: **SMc5-360**

Experimental data for Table 3.6: Screening of the SMCC of 4-BF3K *N-PMP* pyrrolidone 192 with different eq. of 192 and PhBr

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (25.3 mg, 0.15 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (40 μL, 0.38 mmol, 1.25 eq.), degassed toluene (0.86 mL) and water (0.27 mL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 41% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc5-361**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (23.9 mg, 0.15 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the

headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (0.27 mL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 44% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc5-362**

4-BF_3K *N*-PMP pyrrolidone **192** (111 mg, 0.38 mmol, 1.25 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (25.7 mg, 0.15 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (36 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.86 mL) and water (0.27 mL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 38% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc5-363**

4-BF_3K *N*-PMP pyrrolidone **192** (134 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (26.0 mg, 0.15 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (36 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.86 mL) and water

(0.27 mL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 43% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc5-364**

Experimental data for Table 3.7: Screening of the SMCC of 4-BF3K *N-PMP* pyrrolidone 192 with alternative bases and additives

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 10 mol%), cataCXium A (22 mg, 60 µmol, 20 mol%), K_3PO_4 (318 mg, 1.5 mmol, 5.0 eq.) and TMB (17.5 mg, 0.10 mmol, 0.35 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 µL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (0.27 mL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 33% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc5-366**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 10 mol%), cataCXium A (22 mg, 60 µmol, 20 mol%), K_2CO_3 (207 mg, 1.5 mmol, 5.0 eq.) and TMB (25.6 mg, 0.15 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 µL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water

(0.27 mL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 22% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc5-367**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), $CsOH•H_2O$ (225 mg, 1.5 mmol, 5.0 eq.) and TMB (26.3 mg, 0.15 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (0.27 mL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 19% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc5-368**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), KF (87 mg, 1.5 mmol, 5.0 eq.) and TMB (24.0 mg, 0.14 mmol, 0.48 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (0.27 mL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block

preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 0% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc5-369**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 10 mol%), cataCXium A (22 mg, 60 µmol, 20 mol%), CsF (228 mg, 1.5 mmol, 5.0 eq.) and TMB (27.6 mg, 0.16 mmol, 0.52 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 µL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (0.27 mL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 0% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc5-370**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 10 mol%), cataCXium A (22 mg, 60 µmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.), 18-Crown-6 (24 mg, 0.09 mmol, 0.3 eq.) and TMB (26.7 mg, 0.15 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 µL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (0.27 mL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to

cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 45% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc5-371**

Experimental data for Table 3.8: Screening of the SMCC of 4-BF3K N-PMP pyrrolidone 192 with different palladium sources

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $[Pd(cinnamyl)Cl]_2$ (15.5 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (27.3 mg, 0.16 mmol, 0.52 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (0.27 mL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 27% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc5-372**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), (2'-Amino-1,1'-biphenyl-2-yl)methanesulfonatopalladium(II) dimer (Pd G3 dimer) (22 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (27.3 mg, 0.16 mmol, 0.52 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (0.27 mL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature)

for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 45% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc5-373**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), Pd_2dba_3 (17 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (25.8 mg, 0.15 mmol, 0.50 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (0.27 mL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 8% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc5-374**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $[Pd(Me\text{-}allyl)Cl]_2$ (12 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (25.3 mg, 0.15 mmol, 0.50 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (0.27 mL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the

reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 35% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc5-375**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $[Pd(allyl)Cl]_2$ (11 mg, 30 µmol, 10 mol%), cataCXium A (22 mg, 60 µmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (24.0 mg, 0.15 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 µL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (0.27 mL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 39% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc5-376**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(acac)_2$ (15 mg, 30 µmol, 10 mol%), cataCXium A (22 mg, 60 µmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (25.3 mg, 0.15 mmol, 0.50 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 µL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (0.27 mL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 15% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc5-377**

Experimental data for Table 3.9: Screening of the SMCC of 4-BF3K *N-PMP* pyrrolidone 192 with different eq. of water

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (27.2 mg, 0.16 mmol, 0.52 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (54 μL, 3 mmol, 10 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 45% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-378**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (22.0 mg, 0.13 mmol, 0.44 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (108 μL, 6 mmol, 20 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 51% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-379**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (27.6 mg, 0.16 mmol, 0.52 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (162 μL, 9 mmol, 30 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 52% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-380**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (26.2 mg, 0.15 mmol, 0.50 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (216 μL, 12 mmol, 40 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 49% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-381**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (23.4 mg, 0.14 mmol, 0.49 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (540 μL, 30 mmol, 100 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 38% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-382**

Experimental data for Table 3.10: Screening of the SMCC of 4-BF3K *N-PMP* pyrrolidone 192 with various solvents and with CuI as additive

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (23.6 mg, 0.14 mmol, 0.49 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed *t*-AmOH (0.86 mL) and water (270 μL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 35% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-383**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 10 mol%), cataCXium A (22 mg, 60 µmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (29.1 mg, 0.17 mmol, 0.58 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 µL, 0.45 mmol, 1.5 eq.), degassed DMSO (0.86 mL) and water (270 µL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 8% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-384**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 10 mol%), cataCXium A (22 mg, 60 µmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (26.0 mg, 0.15 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 µL, 0.45 mmol, 1.5 eq.), degassed *o*-xylene (0.86 mL) and water (270 µL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 140 °C. The mixture was stirred at 1000-1200 rpm and heated at 140 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 41% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-385**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 10 mol%), cataCXium A (22 mg, 60 µmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0

eq.), CuI (6 mg, 30 μmol, 10 mol%) and TMB (26.0 mg, 0.15 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (270 μL, 15 mmol, 50 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 29% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-386**

Experimental data for Table 3.11: Screening of the SMCC of 4-BF3K *N-PMP* pyrrolidone 192 with different eq. of Cs2CO3

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (389 mg, 1.2 mmol, 5.0 eq.) and TMB (25.6 mg, 0.15 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (108 μL, 6 mmol, 20 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 39% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-398**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 10 mol%), cataCXium A (22 mg, 60 µmol, 20 mol%), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) and TMB (27.5 mg, 0.16 mmol, 0.52 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 µL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (108 µL, 6 mmol, 20 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 35% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-399**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 10 mol%), cataCXium A (22 mg, 60 µmol, 20 mol%), Cs_2CO_3 (195 mg, 0.6 mmol, 2.0 eq.) and TMB (26.0 mg, 0.15 mmol, 0.50 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 µL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (108 µL, 6 mmol, 20 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 28% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-400**

Experimental data for Table 3.12: Screening of the SMCC of 4-BF3K *N-PMP* pyrrolidone 192 with different loadings of $Pd(OAc)_2$, concentrations of toluene and reaction times

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (10 mg, 45 μmol, 15 mol%), cataCXium A (32 mg, 90 μmol, 30 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (27.5 mg, 0.16 mmol, 0.52 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (108 μL, 6 mmol, 20 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 48% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-396**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (14 mg, 60 μmol, 20 mol%), cataCXium A (44 mg, 120 μmol, 40 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (23.0 mg, 0.13 mmol, 0.46 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (108 μL, 6 mmol, 20 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 45% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-397**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (26.3 mg, 0.15 mmol, 0.50 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (3.0 mL) and water (108 μL, 6 mmol, 20 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 9% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-403**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (23.9 mg, 0.14 mmol, 0.48 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.43 mL) and water (108 μL, 6 mmol, 20 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 46% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-402**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (20.6 mg, 0.12 mmol, 0.40 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (108 μL, 6 mmol, 20 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 1 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 0% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-393**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and TMB (24.5 mg, 0.15 mmol, 0.50 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (108 μL, 6 mmol, 20 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 3 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 6% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-394**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0

eq.) and TMB (23 mg, 0.14 mmol, 0.46 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL) and water (108 μL, 6 mmol, 20 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 7 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 34% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-395**

4-BF_3K *N*-PMP pyrrolidone **192** (149 mg, 0.5 mmol, 1.0 eq.), $Pd(OAc)_2$ (17 mg, 75 μmol, 15 mol%), cataCXium A (54 mg, 150 μmol, 30 mol%) and Cs_2CO_3 (652 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (79 μL, 0.75 mmol, 1.5 eq.), degassed toluene (0.70 mL) and water (180 μL, 10 mmol, 20 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 80:20 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **206** (71 mg, 53%) as a brown solid.

Lab book reference: **SMc6-408**

4-BF_3K *N*-PMP pyrrolidone **192** (149 mg, 0.5 mmol, 1.0 eq.), $Pd(OAc)_2$ (11 mg, 50 μmol, 10 mol%), cataCXium A (36 mg, 100 μmol, 20 mol%) and Cs_2CO_3 (652 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (79 μL, 0.75 mmol, 1.5 eq.), degassed toluene (0.70 mL) and water (180 μL, 10 mmol, 20 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 80:20 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **206** (66 mg, 50%) as a brown solid.

Lab book reference: **SMc6-407**

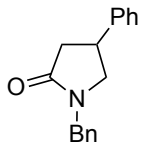
4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (391 mg, 1.2 mmol, 4.0 eq.) and TMB (22.4 mg, 0.13 mmol, 0.43 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and iodobenzene (50 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.42 mL) and water (108 μL, 6 mmol, 20 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt, the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 9% conversion to 4-phenyl *N*-PMP pyrrolidone **206**).

Lab book reference: **SMc6-488**

4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%), Cs_2CO_3 (391 mg, 1.2 mmol, 4.0 eq.) and TMB (27.8 mg, 0.17 mmol, 0.55 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and chlorobenzene (46 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.42 mL) and water (108 μL, 6 mmol, 20 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 24 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 75:25 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **206** (52 mg, 63%) as a brown solid.

Lab book reference: **SMc6-475**

1-(4-Benzyl)-4-phenylpyrrolidin-2-one 207



207

4-BF_3K *N*-Bn pyrrolidone **193** (84 mg, 0.3 mmol, 1.0 eq.), cataCXium A Pd G3 (11 mg, 15 μmol, 0.05 eq.) and Cs_2CO_3 (394 mg, 1.2 mmol, 4.0 eq.) were placed in a 7mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (36 μL, 0.35 mmol, 1.15 eq.), degassed toluene (0.90 mL) and water (0.1 mL, 5.7 mmol, 19.0 eq.) were added under N_2. The vial was removed

from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 110 °C. The mixture was stirred at 1000-1200 rpm and heated at 110 °C (heater block temperature) for 24 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 60:40 hexane-EtOAc as eluent gave 4-phenyl *N*-Bn pyrrolidone **207** (20 mg, 26%) as a brown solid, R_F (60:40 hexane-EtOAc) 0.19; mp 58-62 ºC; IR (ATR) 1688, 1667, 1494, 1248, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.26 (m, 8H, Ar), 7.24-7.19 (m, 2H, Ar), 4.57 (d, J = 14.5 Hz, 1H, NC*H*Ar), 4.47 (d, J = 14.5 Hz, 1H, NC*H*Ar), 3.63 (dd, J = 9.5, 8.0 Hz, 1H, NCH), 3.56 (dddd, J = 9.0, 8.5, 8.0, 7.0 Hz, 1H, C*H*Ph), 3.28 (dd, J = 9.5, 7.0 Hz, 1H, NCH), 2.89 (dd, J = 17.0, 9.0 Hz, 1H, CH), 2.63 (dd, J = 17.0, 8.5, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.9 (C=O), 142.4 (*ipso*-Ar), 136.4 (*ipso*-Ar), 129.0 (Ar), 128.9 (Ar), 128.4 (Ar), 127.8 (Ar), 127.2 (Ar), 126.9 (Ar), 53.9 (NCH_2), 46.8 (N*C*H_2Ph), 39.0 (CH_2), 37.3 (*C*HPh); HRMS (ESI) *m/z* calculated for $C_{17}H_{17}NO$ $(M + Na)^+$ 274.1202, found 274.1204 (-0.6 ppm error). Spectroscopic data consistent with those reported in the literature.[166]

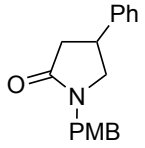
Lab book reference: **SMc44-2**

4-BF_3K *N*-Bn pyrrolidone **193** (84 mg, 0.3 mmol, 1.0 eq.), cataCXium A Pd G3 (11 mg, 15 μmol, 0.05 eq.) and Cs_2CO_3 (394 mg, 1.2 mmol, 4.0 eq.) were placed in a 7mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (36 μL, 0.35 mmol, 1.15 eq.), degassed toluene (0.90 mL) and water (0.1 mL, 5.7 mmol, 19.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 110 °C. The mixture was stirred at 1000-1200 rpm and heated at 110 °C (heater block temperature) for 24 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 60:40 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone **207** (16 mg, 21%) as a brown solid.

Lab book reference: **SMc44-1**

1-(4-Methoxybenzyl)-4-phenylpyrrolidin-2-one 208



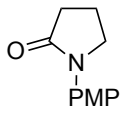
208

4-BF_3K *N*-PMB Pyrrolidone **194** (69.6 mg, 0.23 mmol, 1.0 eq.), cataCXium A Pd G3 (8.4 mg, 12 μmol, 0.05 eq.) and Cs_2CO_3 (300 mg, 0.92 mmol, 4.0 eq.) were placed in a 7mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (28 μL, 0.26 mmol, 1.15 eq.), degassed toluene (0.70 mL) and water (80 μL, 4.4 mmol, 19.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 110 °C. The mixture was stirred at 1000-1200 rpm and heated at 110 °C (heater block temperature) for 24 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 60:40 hexane-EtOAc as eluent gave 4-phenyl *N*-PMB pyrrolidone **208** (26 mg, 41%) as a brown oil, R_F (60:40 hexane-EtOAc) 0.12; IR (ATR) 1672 (C=O), 1512, 1243 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.19 (m, 7H, Ar), 6.89-6.81 (m, 2H, Ar), 4.48 (d, J = 14.5 Hz, 1H, NC*H*Ph), 4.40 (d, J = 14.5 Hz, 1H, NC*H*Ph), 3.78 (s, 3H, OMe), 3.66-3.56 (m, 1H, NCH), 3.51 (m, 1H, C*H*Ph), 3.24 (dd, J = 9.5, 7.0 Hz, 1H, NCH), 2.86 (dd, J = 17.0, 9.0 Hz, 1H, CH), 2.59 (dd, J = 17.0, 8.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.7 (C=O), 159.2 (*ipso*-Ar), 142.4 (*ipso*-Ar), 129.7 (Ar), 128.9 (Ar), 128.5 (*ipso*-Ar), 127.1 (Ar), 126.8 (Ar),

114.2 (Ar), 55.4 (OMe), 53.8 (NCH_2), 46.1 (N*C*H_2Ph), 39.1 (CH_2), 37.3 (*C*HPh); HRMS (ESI) *m/z* calculated for $C_{18}H_{19}NNaO_2$ $(M + Na)^+$ 302.1308, found 304.1308 (-0.1 ppm error).

Lab book reference **SMc48-1**

1-(4-methoxyphenyl)pyrrolidin-2-one 209



209

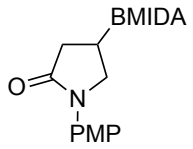
2-Pyrrolidone (0.68 mL, 9.00 mmol, 3.0 eq.) was added to a stirred suspension of copper powder (380 mg, 5.98 mmol, 2.0 eq.), K_2CO_3 (434 mg, 3.14 mmol, 1.1 eq.) and 1-iodo-4-methoxybenzene (702 mg, 3.00 mmol, 1.0 eq.) in DMF (3.5 mL, 0.86 M) at rt. The flask was sealed and purged under N_2 for 15 min, then stirred at 150 °C (heater block temperature) for 18 h. After being allowed to cool to rt, the crude mixture was filtered through a plug of silica. H_2O (30 mL) was added and two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organics were washed with brine (5 x 30 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 20:80 hexane-EtOAc as eluent gave *N*-PMP pyrrolidone **209** (292 mg, 51%) as a white crystalline solid, mp 104-106 ºC (lit.,[167] mp 89.5–91 °C (EtOH)); R_F (20:80 hexane-EtOAc) 0.33; IR (ATR) 1678 (C=O), 1508, 1224, 1030, 828 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52-7.44 (m, 2H, Ar), 6.93-6.85 (m, 2H, Ar), 3.81 (t, J = 7.0 Hz, 2H, NCH_2), 3.79 (s, 3H, OMe), 2.58 (t, J = 8.0 Hz, 2H, CH_2), 2.14 (tt, J = 8.0, 7.0 Hz, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.1 (C=O), 156.7 (*ipso*-Ar), 132.7 (*ipso*-Ar), 121.9 (Ar), 114.1 (Ar), 55.6 (OMe), 49.3 (NCH_2), 32.6 (CH_2), 18.1 (*C*H_2); HRMS (ESI) *m/z* calculated for $C_{11}H_{13}NO_2$ $(M + Na)^+$ 214.0838, found 214.0838 (+0.1 ppm error). Spectroscopic data consistent with those reported in the literature.[167]

Lab book reference: **SMc36-1**

N-PMP pyrrolidone **209** (89 mg, 0.3 mmol, 1.0 eq.), cataCXium A Pd G3 (11 mg, 15 μmol, 15 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and degassed toluene (0.42 mL) and water (0.1 mL, 5.7 mmol, 19.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 110 °C. The mixture was stirred at 1000-1200 rpm and heated at 110 °C (heater block temperature) for 24 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 80:20 hexane-EtOAc as eluent recovered *N*-PMP pyrrolidone **209** (74 mg, 93%) as a brown solid.

Lab book reference: **SMc39-1**

2-[1-(4-Methoxyphenyl)-5-oxopyrrolidin-3-yl]-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione 210



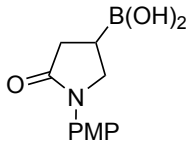
210

Triethylorthoformate (1.18 mL, 7.11 mmol, 4.5 eq.) was added to a stirred solution of 4-Bpin *N*-PMP pyrrolidone **198** (500 mg, 1.58 mmol, 1.0 eq.) and MIDA (1.5 g, 10.27 mmol, 6.0 eq.) in anhydrous DMSO (8 mL) under N_2. The resulting mixture was stirred and heated at 100 °C for 60 h. After being allowed to cool to rt, NH_4Cl (20 mL) and EtOAc (20 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with brine (3 x 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 60:40 CH_2Cl_2-acetone as eluent gave 4-BMIDA *N*-PMP pyrrolidone **210** (263 mg, 48%) as

a white solid, R_F (60:40 CH_2Cl_2-acetone) 0.1; IR (ATR) 1763, 1676, 1513, 1295, 1247, 1030 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.69-7.60 (m, 2H, Ar), 6.95-6.86 (m, 2H, Ar), 4.33 (dd, J = 17.0, 2.0 Hz, 2H, NCH), 4.15 (dd, J = 17.0, 9.5 Hz, 2H, NCH), 3.95-3.73 (m, 5H, NCH, OMe), 3.25 (s, 3H, NMe), 2.52 (dd, J = 16.5, 9.5 Hz, 1H, CHCO), 2.40 (dd, J = 16.5, 11.5 Hz, 1H, CHCO), 2.03-1.91 (m, 1H, BCH);^{13}C NMR (100.6 MHz, acetone-d_6) δ 173.6 (C=O, lactam), 167.9 (C=O, ester), 167.8 (C=O, ester), 156.1 (*ipso*-Ar), 133.7 (*ipso*-Ar), 120.9 (Ar), 113.7 (Ar), 62.4 (NCH_2), 54.8 (OMe), 51.0 (NCH_2), 46.1 (NMe), 34.9 (CH_2) (BCH resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{16}H_{19}BN_2O_6$ $(M + Na)^+$ 369.1228, found 369.1230 (+0.5 ppm error).

Lab book reference: **SMc56-1**

(1-(4-Methoxyphenyl)-5-oxopyrrolidin-3-yl)boronic acid 11

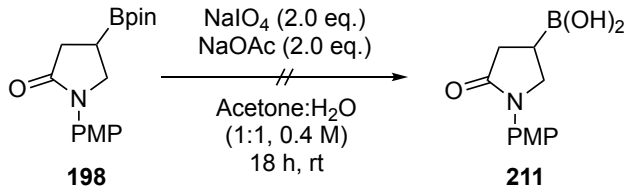


211

TMSCl (0.64 mL, 2.78 mmol, 3.0 eq.) was added to a stirred solution of 4-BF_3K *N*-PMP pyrrolidone **192** in 3.2:1 MeCN-H_2O (11.8 mL, 0.08 M) at rt. The resulting solution was stirred at rt for 18 h. Saturated $NaHCO_{3(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were dried ($MgSO_4$), and evaporated under reduced pressure to give 4-B(OH_2) *N*-PMP pyrrolidone **211** (215 mg, 98%) as a white solid, IR (ATR) 3334, 1659, 1512, 1247, 1031, 829 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ ^1H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 2H, OH), 7.56-7.48 (m, 2H, Ar), 6.99-6.88 (m, 2H, Ar), 3.76 (d, J = 9.0 Hz, 2H, NCH), 3.73 (s, 3H, OMe), 2.43 (d, J = 10.0 Hz, 2H, CH), 1.73 (dddd, J = 10.0, 10.0, 9.0, 9.0 Hz, 1H, BCH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 174.0 (C=O), 155.6 (*ipso*-Ar), 133.1 (*ipso*-Ar), 121.0 (Ar), 113.8 (Ar), 55.2 (OMe), 51.0 (NCH_2), 35.2 (CH_2), 18.3 (BCH); ^{11}B NMR (128 MHz, DMSO-d_6) δ 31.1; HRMS (ESI) *m/z* calcd for $C_{11}H_{14}BNO_4$ $(M + Na)^+$ 258.0908, found 258.0909 (+0.4 ppm error).

Lab book reference: **SMc72-1**

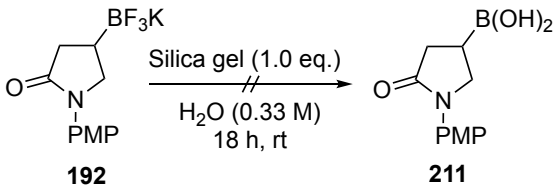
Attempted synthesis of 4-B(OH)$_2$ *N*-PMP pyrrolidone 211



4-Bpin *N*-PMP pyrrolidone **198** (1 g, 3.15 mmol, 1.0 eq.), $NaIO_4$ (1.35 g, 6.3 mmol, 2.0 eq.) and NaOAc (486 mg, 6.3 mmol, 2.0 eq.) were dissolved in acetone (7.8 mL) and water (7.8 mL) at rt. The resulting solution was stirred at rt for 18 h. The solids were removed by filtration and the filtrate was evaporated under reduced pressure. The residue was dissolved in Et_2O (20 mL), water was added and the two layers were separated. The aqueous layer was extracted with Et_2O (4 x 20 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give none of 4-B(OH)$_2$ *N*-PMP pyrrolidone **211** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **SMc70-1**

Attempted synthesis of 4-B(OH)$_2$ *N*-PMP pyrrolidone 211

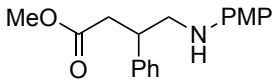


4-BF_3K *N*-PMP pyrrolidone **192** (256 mg, 0.86 mmol, 1.0 eq.) and silica gel (55 mg, 0.86 mmol, 1.0 eq.) were stirred in water (26 mL, 0.33 M) at rt for 18 h. Then, the reaction mixture was filtered through Celite®. EtOAc (15 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced

pressure to give none of 4-$B(OH)_2$ *N*-PMP pyrrolidone **211** (by ^1H NMR spectroscopy and HRMS).

Lab book reference: **SMc71**

methyl 4-((4-methoxyphenyl)amino)-3-phenylbutanoate 212

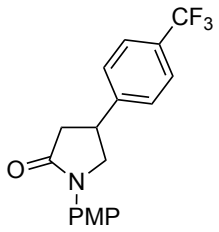


212

monosubstituted amine (*E*)-**195** (117 mg, 0.49 mmol, 1.0 eq.), $[RhCl(COD)]_2$ (25 mg, 0.05 mmol, 0.1 eq.) and $PhB(OH)_2$ (182 mg, 1.49 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicon septum and the headspace purged with N_2 for 15 min. Then, degassed KOH (0.1 M, 0.25 mL, 0.5 eq.) and degassed CH_2Cl_2 (2.5 mL) were added under N_2. The vial was placed in a heating block preheated to 40 °C and the mixture was heated and stirred at 40 °C (stirrer block temperature) for 18 h. After being allowed to cool to rt, the mixture was passed through a plug of silica eluting with EtOAc and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave *N*-PMP Ph ester **212** (93 mg, 63%) as an orange oil, R_F (90:10 hexane-EtOAc) 0.1; IR (ATR) 3396, 2950, 2832, 1732 (C=O), 1513, 1237, 1165, 1036, 820, 701, 524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.30 (m, 2H, Ar), 7.25-7.14 (m, 3H, Ar), 6.80-6.73 (m, 2H, Ar), 6.59-6.51 (m, 2H, Ar), 3.74 (s, 3H, OMe), 3.61 (s, 3H, OMe), 3.51-3.32 (m, 3H, NH, NCH), 3.30-3.18 (m, 1H, C*H*Ph), 2.79 (dd, *J* = 15.5, 7.5 Hz, 1H, CH), 2.67 (dd, *J* = 15.5, 7.0 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.8 (C=O), 152.3 (*ipso*-Ar), 142.1 (*ipso*-Ar), 141.8 (*ipso*-Ar), 128.9 (Ar), 127.7 (Ar), 127.2 (Ar), 115.0 (Ar), 114.5 (Ar), 55.9 (OMe), 51.8 (OMe), 50.2 (NCH_2), 41.4 (CHPh), 38.9 (CH_2); HRMS (ESI) *m/z* calcd for $C_{18}H_{21}NO_3$ $(M + Na)^+$ 322.1414, found 322.1417 (-1.0 ppm error).

Lab book reference: **SMc64-1**

1-(4-methoxyphenyl)-4-(4-(trifluoromethyl)phenyl)pyrrolidin-2-one 213

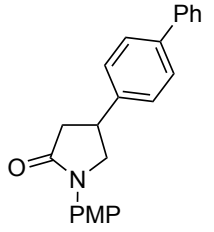


213

Using General Procedure I, 4-BF_3K *N*-PMP pyrrolidone **192** (149 mg, 0.5 mmol, 1.0 eq.) and 4-bromobenzotrifluoride (105 μL, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using 70:30 hexane-EtOAc as eluent gave 4-aryl *N*-PMP pyrrolidone **213** (101 mg, 60%) as a pale brown solid, R_F (70:30 hexane-EtOAc) 0.13; mp 95-97 °C; IR (ATR) 1675 (C=O), 1515, 1328, 1165, 1119, 824, 730 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 2H, Ar), 7.54-7.46 (m, 2H, Ar), 7.42 (d, *J* = 8.0 Hz, 2H, Ar), 6.96-6.88 (m, 2H, Ar), 4.20 (dd, *J* = 9.5, 8.0 Hz, 1H, NCH), 3.86 (dd, *J* = 9.5, 7.0 Hz, 1H, NCH), 3.82-3.79 (s, 3H, OMe), 3.79-3.71 (m, 1H, CHAr), 3.05 (dd, *J* = 17.0, 9.0 Hz, 1H, CH), 2.78 (dd, *J* = 17.0, 8.0 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.2 (C=O), 157.0 (*ipso*-Ar), 146.1 (*ipso*-Ar), 132.03 (*ipso*-Ar), 129.8 (q, *J* = 32 Hz, *ipso*-Ar), 127.3 (Ar), 126.1 (q, *J* = 4.0 Hz, Ar), 124.5 (q, *J* = 272.0 Hz, CF_3), 122.1 (Ar), 114.3 (Ar), 55.9 (NCH_2), 55.6 (OMe), 40.0 (CH_2), 37.2 (CHAr); ^{19}F (375 MHz, $CDCl_3$) δ –62.4; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NO_2$ $(M + K)^+$ 320.1047, found 320.1055 (–1.6 ppm error).

Lab book reference: **SMc6-413**

4-([1,1'-biphenyl]-4-yl)-1-(4-methoxyphenyl)pyrrolidin-2-one 214

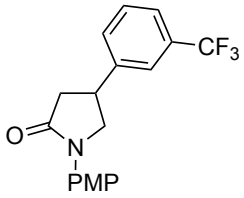


214

Using General Procedure J, 4-BF_3K *N*-PMP pyrrolidone **192** (149 mg, 0.5 mmol, 1.0 eq.) and 4-bromobiphenyl (175 mg, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using 75:25 hexane-EtOAc as eluent gave 4-aryl *N*-PMP pyrrolidone **214** as a brown solid, R_F (75:25 hexane-EtOAc) 0.14; mp 125-128 °C; IR (ATR) 1694 (C=O), 1513, 1464, 1264, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.57 (m, 4H, Ar), 7.56-7.51 (m, 2H, Ar), 7.49-7.43 (m, 2H, Ar), 7.41-7.33 (m, 3H, Ar), 6.98-6.90 (m, 2H, Ar), 4.19 (dd, *J* = 9.5, 8.5 Hz, 1H, NCH), 3.91 (dd, *J* = 9.5, 8.0 Hz, 1H, NCH), 3.81 (s, 3H, OMe), 3.75 (dddd, *J* = 8.5, 8.5, 8.5, 8.0 Hz, 1H, CHAr), 3.05 (dd, *J* = 17.0, 8.5, 1H, CH), 2.83 (dd, *J* = 17.0, 8.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.7 (C=O), 156.8 (*ipso*-Ar), 140.9 (*ipso*-Ar), 140.6 (*ipso*-Ar), 140.4 (*ipso*-Ar), 132.4 (*ipso*-Ar), 129.0 (Ar), 127.8 (Ar), 127.5 (Ar), 127.4 (Ar), 127.2 (Ar), 122.0 (Ar), 114.3 (Ar), 56.2 (NCH_2), 55.6 (OMe), 40.3 (CH_2), 37.1 (CHAr); HRMS (ESI) *m/z* calcd for $C_{23}H_{21}NO_2$ $(M + Na)^+$ 366.1464, found 366.1468 (–1.9 ppm error);

Lab book reference: **SMc6-423**

1-(4-Methoxyphenyl)-4-(3-(trifluoromethyl)phenyl)pyrrolidin-2-one 215



215

Using General Procedure I, 4-BF_3K *N*-PMP pyrrolidone **192** (149 mg, 0.5 mmol, 1.0 eq.) and 3-bromobenzotrifluoride (105 μL, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using 70:30 hexane-EtOAc as eluent gave 4-aryl *N*-PMP pyrrolidone **215** (84 mg, 51%) as a brown solid, R_F (70:30 hexane-EtOAc) 0.1; mp 111-114 °C; IR (ATR) 1678 (C=O), 1514, 1329, 1134, 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.46 (m, 6H, Ar), 6.95-6.89 (m, 2H, Ar), 4.20 (dd, *J* = 9.5, 8.0 Hz, 1H, NCH), 3.86 (dd, *J* = 9.5, 7.5 Hz, 1H, NCH), 3.82-3.72 (m, 4H, OMe, CHAr), 3.04 (dd, *J* = 17.0, 8.5 Hz, 1H, CH), 2.77 (dd, *J* = 17.0, 8.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.2 (C=O), 157.0 (*ipso*-Ar), 142.9 (*ipso*-

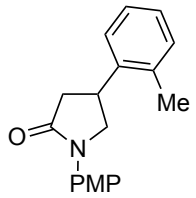
Ar), 132.1 (*ipso*-Ar), 131.3 (q, J = 32.0 Hz, *ipso*-Ar), 130.2 (Ar), 129.7 (Ar), 124.33 (q, J = 3.5 Hz, Ar), 123.9 (q, J = 272.0 Hz, CF_3), 123.4 (q, J = 4.0 Hz, Ar), 122.1 (Ar), 114.3 (Ar), 55.9 (NCH_2), 55.6 (OMe), 40.0 (CH_2), 37.2 (CHAr); ^{19}F NMR (375 MHz, $CDCl_3$) δ -62.49; HRMS (ESI) *m/z* calcd for $C_{18}H_{16}F_3NO_2$ $(M + K)^+$ 374.0765, found 374.0766 (–0.4 ppm error);

Lab book reference: **SMc6-434**

4-BF_3K *N*-PMP pyrrolidone **192** (1.0 g, 3.37 mmol, 1.0 eq.), $Pd(OAc)_2$ (76 mg, 0.34 mmol, 0.10 eq.), cataCXium A (240 mg, 0.67 mmol, 0.20 eq.) and Cs_2CO_3 (4.4 g, 13.5 mmol, 4.0 eq.) were placed in flame dried round bottom flask. The flask was purged with N_2 for 15 min. Then, the exit needle was removed and 3-bromobenzotrifluoride (0.7 mL, 5.1 mmol, 1.5 eq.), degassed toluene (4.8 mL) and water (1.2 mL, 67.4 mmol, 20.0 eq.) were added under N_2. The flask was fitted with a reflux condenser and the mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h under N_2. After being allowed to cool to rt, water (30 mL) and EtOAc (30 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organics were washed with brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 70:30 hexane-EtOAc as eluent gave 4-aryl *N*-PMP pyrrolidone **215** (420 mg, 37%) as a brown solid.

Lab book reference: **SMc6-464**

1-(4-Methoxyphenyl)-4-(*o*-tolyl)pyrrolidin-2-one 216

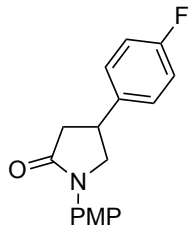


216

Using General Procedure I, 4-BF_3K *N*-PMP pyrrolidone **192** (149 mg, 0.5 mmol, 1.0 eq.) and 2-bromotoluene (90 μL, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using 70:30 hexane-EtOAc as eluent gave 4-aryl *N*-PMP pyrrolidone **216** (113 mg, 80%) as a brown oil. R_F (70:30 hexane-EtOAc) 0.16; IR (ATR) 1692 (C=O), 1512, 1463, 1396, 1248, 1180, 829, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.49 (m, 2H, Ar), 7.31 (d, *J* = 7.5 Hz, 1H, Ar), 7.25-7.14 (m, 3H, Ar), 6.95-6.88 (m, 2H, Ar), 4.16 (dd, *J* = 9.5, 7.5Hz, 1H, NCH), 3.91 (dddd, *J* = 8.0, 8.0, 7.5, 6.5 Hz, 1H, CHAr), 3.84 (dd, *J* = 9.5, 6.5 Hz, 1H, NCH), 3.81 (s, 3H, OMe), 3.00 (dd, *J* = 17.0, 8.0 Hz, 1H, CH), 2.76 (dd, *J* = 17.0, 8.0 Hz, 1H, CH), 2.39 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.9 (C=O), 156.8 (*ipso*-Ar), 140.1 (*ipso*-Ar), 135.9 (*ipso*-Ar), 132.4 (*ipso*-Ar), 130.9 (Ar), 127.2 (Ar), 126.9 (Ar), 125.2 (Ar), 122.0 (Ar), 114.3 (Ar), 55.6 (OMe), 55.5 (NCH_2), 39.7 (CH_2), 33.2 (CHAr), 19.9 (Me); HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NO_2$ $(M + K)^+$ 320.1047, found 320.1055 (–1.6 ppm error);

Lab book reference: **SMc6-417**

4-(4-fluorophenyl)-1-(4-methoxyphenyl)pyrrolidin-2-one 217



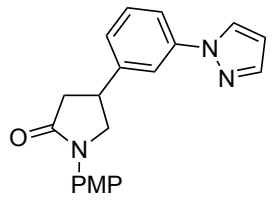
217

Using general procedure I, 4-BF_3K *N*-PMP pyrrolidone **192** (149 mg, 0.5 mmol, 1.0 eq.) and 1-bromo-fluorobenzene (82 μL, 0.75 mmol, 1.5 eq.) gave the crude product.

Purification by flash column chromatography on silica using 60:40 hexane-EtOAc as eluent gave 4-aryl *N*-PMP pyrrolidone **217** (71 mg, 50%) as a red-brown solid, R_F (60:40 hexane-EtOAc) 0.18; mp 88-90 ° C; IR (ATR) 1693 (C=O), 1512, 1265, 832, 733 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.46 (m, 2H, Ar), 7.32-7.21 (m, 2H, Ar), 7.11-7.00 (m, 2H, Ar), 6.96-6.87 (m, 2H, Ar), 4.15 (dd, *J* = 9.5, 8.0 Hz, 1H, NCH), 3.86-3.78 (m, 4H, OMe, NCH), 3.68 (dddd, *J* = 8.5, 8.5, 8.0, 8.0 Hz, 1H), 3.00 (dd, *J* = 17.0, 9.0 Hz, 1H, CH), 2.73 (dd, *J* = 17.0, 8.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.6 (C=O), 162.0 (d, *J* = 246.0 Hz, *ipso*-Ar), 156.9 (*ipso*-Ar), 137.7 (d, *J* = 3.0 Hz, *ipso*-Ar), 132.3 (*ipso*-Ar), 128.4 (d, *J* = 7.5 Hz, Ar), 122.0 (Ar), 116.0 (d, *J* = 21.5 Hz, Ar), 114.3 (Ar), 56.1 (NCH_2), 55.6 (OMe), 40.3 (CH_2), 36.7 (CHAr); ^{19}F (375 MHz, $CDCl_3$) δ –115.14 (tt, *J* = 8.0, 3.0 Hz); HRMS (ESI) *m/z* calcd for $C_{17}H_{16}FNO_2$ 324.0797 $(M + K)^+$ found 324.0794 (+0.5 ppm error);

Lab book reference: **SMc6-419**

4-(3-(1*H*-Pyrazol-1-yl)phenyl)-1-(4-methoxyphenyl)pyrrolidin-2-one 218



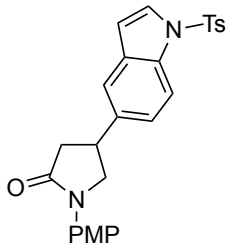
218

Using general procedure L, 4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.) and 1-(3-bromophenyl)-1*H*-pyrazole (96 mg, 0.45 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using 80:20 toluene-EtOAc gave 4-aryl *N*-PMP pyrrolidone **218** (34 mg, 34%) as an orange oil, R_F (80:20 toluene-EtOAc) 0.14; IR (ATR) 1700 (C=O), 1511, 1450, 1170, 853 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 2.5 Hz, 1H, Ar), 7.75-7.70 (m, 2H, Ar), 7.58-7.52 (m, 1H, Ar), 7.52-7.48 (m, 2H, Ar), 7.43 (dd, *J* = 8.0, 8.0 Hz, 1H, Ar), 7.24-7.19 (m, 1H, Ar), 6.94-6.87 (m, 2H, Ar), 6.48 (dd, *J* = 2.0, 2.0 Hz, 1H, Ar), 4.17 (dd, *J* = 10.0, 8.0 Hz, 1H, NCH), 3.91 (dd, *J* = 10.0, 7.5 Hz, 1H, NCH), 3.81-3.70 (m, 4H, OMe, CHAr), 3.03 (dd, *J* = 17.0, 9.0 Hz, 1H, CH), 2.81 (dd, *J* = 17.0, 9.0 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.4 (C=O), 156.8 (*ipso*-Ar), 143.6 (*ipso*-Ar), 141.4

(Ar), 140.7 (*ipso*-Ar), 132.3 (*ipso*-Ar), 130.2 (Ar), 126.9 (Ar), 124.7 (Ar), 122.0 (Ar), 118.2 (Ar), 117.8 (Ar), 114.2 (Ar), 108.0 (Ar), 56.0 (NCH_2), 55.6 (OMe), 40.1 (CH_2), 37.3 (CHAr); HRMS (ESI) calcd for $C_{20}H_{19}N_3O_2$ $(M + H)^+$ 344.1550, found 344.1550 (+0.1 ppm error);

Lab book reference: **SMc6-439**

1-(4-Methoxyphenyl)-4-(1-tosyl-1*H*-indol-5-yl)pyrrolidin-2-one 219

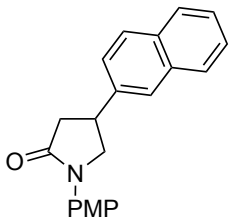


219

Using general procedure L, 4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.) and 5-bromo-1-tosyl-1*H*-indole (158 mg, 0.45 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using 80:20 hexane-EtOAc as eluent gave 4-aryl *N*-PMP pyrrolidone **219** (32 mg, 23%) as a brown semi solid, R_F (80:20 hexane-EtOAc) 0.18; IR (ATR) 1692 (C=O), 1513, 1463, 1377, 1264, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.5 Hz, 1H, Ar), 7.79-7.74 (m, 2H, Ar), 7.57 (d, *J* = 3.5 Hz, 1H, Ar), 7.54-7.48 (m, 2H, Ar), 7.44 (d, *J* = 2.0 Hz, 1H, Ar), 7.25-7.20 (m, 3H, Ar), 6.93-6.88 (m, 2H, Ar), 6.63 (d, *J* = 3.5 Hz, 1H, Ar), 4.15 (dd, *J* = 9.5, 8.0 Hz, 1H, NCH), 3.85 (dd, *J* = 9.5, 7.0 Hz, 1H, NCH), 3.82-3.70 (m, 4H, OMe, CHAr), 3.01 (dd, *J* = 17.0, 9.0 Hz, 1H, CH), 2.77 (dd, *J* = 17.0, 8.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.8 (C=O), 156.8 (*ipso*-Ar), 145.2 (*ipso*-Ar), 137.1 (*ipso*-Ar), 135.3 (*ipso*-Ar), 134.0 (*ipso*-Ar), 132.4 (*ipso*-Ar), 131.3 (*ipso*-Ar), 130.1 (Ar), 127.1 (Ar), 126.9 (Ar), 123.6 (Ar), 121.9 (Ar), 119.4 (Ar), 114.2 (Ar), 114.1 (Ar), 108.9 (Ar), 56.5 (NCH_2), 55.6 (OMe), 40.5 (CHAr), 37.2 (CH_2), 21.7 (Me); HRMS (APCI) *m/z* calcd for $C_{26}H_{24}N_2O_4S$ $(M + H)^+$ 461.1530, found 461.1545 (–1.7 ppm error).

Lab book reference **SMc6-440**

1-(4-Methoxyphenyl)-4-(naphthalen-2-yl)pyrrolidin-2-one 220

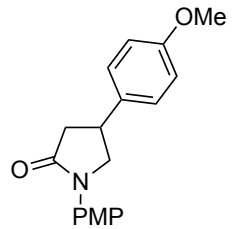


220

Using general procedure I, 4-BF_3K *N*-PMP Pyrrolidone **192** (149 mg, 0.5 mmol, 1.0 eq.) and 2-bromonaphthalene (155 mg, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using 80:20 hexane-EtOAc as eluent gave 4-aryl *N*-PMP pyrrolidone **220** (65 mg, 41%) as an orange/brown solid, R_F (80:20 hexane-EtOAc) 0.23; mp 98-100 °C; IR (ATR) 1692 (C=O), 1513, 1265, 1036, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89-7.80 (m, 3H, Ar), 7.73 (s, 1H, Ar), 7.58-7.52 (m, 2H, Ar), 7.52-7.47 (m, 2H, Ar), 7.42 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar), 6.96-6.90 (m, 2H, Ar), 4.23 (dd, *J* = 9.5, 8.0 Hz, 1H, NCH), 3.96 (dd, *J* = 9.5, 7.5 Hz, 1H, NCH), 3.91-3.78 (m, 4H, OMe, CHAr), 3.09 (dd, *J* = 17.0, 9.0 Hz, 1H, CH), 2.90 (dd, *J* = 17.0, 8.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.8 (C=O), 156.8 (*ipso*-Ar), 139.2 (*ipso*-Ar), 133.5 (*ipso*-Ar), 132.6 (*ispo*-Ar), 132.4 (*ipso*-Ar), 129.0 (Ar), 127.79 (Ar), 127.77 (Ar), 126.6 (Ar), 126.1 (Ar), 125.5 (Ar), 124.9 (Ar), 122.0 (Ar), 114.2 (Ar), 56.1 (NCH_2), 55.6 (OMe), 40.2 (CH_2), 37.4 (CHAr); HRMS (ESI) *m/z* calcd for $C_{21}H_{19}NO_2$ $(M + K)^+$ 356.1047, found 356.1037 (+0.6 ppm error).

Lab book reference: **SMc6-438**

1,4-bis(4-Methoxyphenyl)pyrrolidin-2-one 221

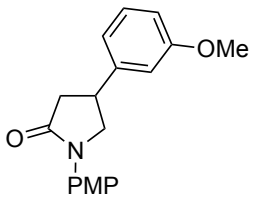


221

Using General Procedure I, 4-BF_3K *N*-PMP Pyrrolidone **192** (149 mg, 0.5 mmol, 1.0 eq.) and 4-bromoanisole (94 µL, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using 70:30 hexane-EtOAc as eluent gave 4-aryl *N*-PMP pyrrolidone (16 mg, 18%) as a brown solid, R_F (70:30 hexane-EtOAc) 0.12; mp 68-70 °C (lit.,[109] mp 105-110 °C); IR (ATR) 1694 (C=O), 1513, 1328, 1248, 1128, 1035 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54-7.48 (m, 2H, Ar), 7.24-7.19 (m, 2H, Ar), 6.94-6.87 (m, 4H, Ar), 4.12 (dd, *J* = 9.5, 8.0 Hz, 1H, NCH), 3.86-3.78 (m, 7H, OMe, OMe, NCH), 3.64 (dddd, *J* = 9.5, 9.0, 8.5, 8.5 Hz, 1H, CHAr), 2.98 (dd, *J* = 17.0, 8.5 Hz, 1H, CH), 2.74 (dd, *J* = 17.0, 8.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.9 (C=O), 158.9 (*ipso*-Ar), 156.8 (*ipso*-Ar), 133.9 (*ipso*-Ar), 132.5 (*ipso*-Ar), 127.9 (Ar), 122.0 (Ar), 114.4 (Ar), 114.2 (Ar), 56.5 (NCH_2), 55.6 (OMe), 55.5 (OMe), 40.4 (CH_2), 36.7 (CHAr); HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NO_3$ $(M + H)^+$ 298.1438, found 298.1443 (–0.2 ppm error). Spectroscopic data consistent with those reported in the literature.[109]

Lab book reference: **SMc6-416**

4-(3-methoxyphenyl)-1-(4-methoxyphenyl)pyrrolidin-2-one 222



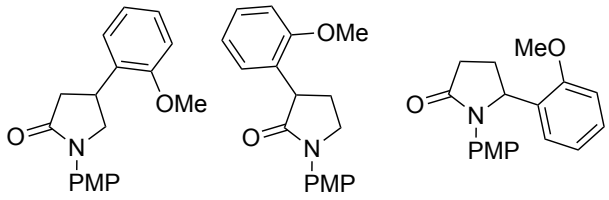
222

Using General Procedure K, 4-BF_3K *N*-PMP Pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.) and 4-bromoanisole (57 µL, 0.45 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using 70:30 hexane-EtOAc as eluent gave 4-aryl *N*-PMP pyrrolidone **222** (55 mg, 62%) as a brown solid, R_F (70:30 hexane-EtOAc) 0.14; mp 74-76 °C IR (ATR) 1696 (C=O), 1513, 1328, 1245, 1123 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.46 (m, 2H, Ar), 7.31-7.23 (m, 1H, Ar), 6.96-6.86 (m, 3H, Ar), 6.85-6.79 (m, 2H, Ar), 4.13 (dd, *J* = 9.5, 8.0 Hz, 1H, NCH), 3.85 (dd, *J* = 9.5, 7.5 Hz, 1H, NCH), 3.81 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.66 (dddd,

J = 9.0, 9.0, 8.0, 7.5 Hz, 1H, CHAr), 2.99 (dd, *J* = 17.0, 9.0 Hz, 1H, CH), 2.77 (dd, *J* = 17.0, 9.0 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.7 (C=O), 160.1 (*ipso*-Ar), 156.8 (*ipso*-Ar), 143.5 (*ipso*-Ar), 132.4 (*ipso*-Ar), 130.1 (Ar), 122.0 (Ar), 119.1 (Ar), 114.2 (Ar), 113.0 (Ar), 112.3 (Ar), 56.1 (NCH_2), 55.6 (OMe), 55.4 (OMe), 40.1 (CH_2), 37.3 (CHAr); HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NO_3$ $(M + H)^+$ 298.1438, found 298.1444 (–0.2 ppm error). Spectroscopic data consistent with those reported in the literature.[168]

Lab book reference: **SMc6-477**

4-(2-methoxyphenyl)-1-(4-methoxyphenyl)pyrrolidin-2-one 223 and 3-(2-methoxyphenyl)-1-(4-methoxyphenyl)pyrrolidin-2-one 237



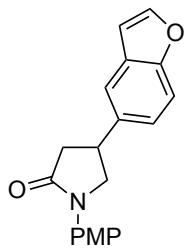
223 **237** **238**

Using General Procedure I, 4-BF_3K *N*-PMP pyrrolidone **192** (149 mg, 0.5 mmol, 1.0 eq.) and 2-bromoanisole (93 μL, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using 60:30:10 hexane-EtOAc-toluene as eluent gave an impure mixture (by ^{1}H NMR spectroscopy) of 5-aryl pyrrolidone **238** and an unknown impurity (24 mg, <14% of **238**), and a 70:30 mixture (by ^{1}H NMR spectroscopy) of 4-aryl pyrrolidone **192** and 3-aryl pyrrolidone **237** (69 mg i.e 48 mg (32%) of **223**; 21 mg (14%) of **237**) as a brown oil, R_F (60:30:10 hexane-EtOAc-toluene) 0.21; IR (ATR) 1686 (C=O), 1510, 1394, 1241, 1027, 828, 752 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) (70:30 mixture of 4-aryl pyrrolidone **223** and 3-aryl pyrrolidone **237**) δ 7.61-7.56 (m, 0.6H, Ar), 7.54-7.48 (m, 1.4H, Ar), 7.30-7.17 (m, 2H, Ar), 6.98-6.86 (m, 4H, Ar), 4.13 (dd, *J* = 8.0, 8.0 Hz, 0.7H, NCH), 4.07 (dd, *J* = 9.0, 9.0 Hz, 0.3H, CHAr), 3.92 (dddd, *J* = 8.0, 8.0, 8.0, 8.0 Hz, 0.7H, CHAr), 3.81 (m, 7.3H, OMe, NCH), 2.93 (dd, *J* = 17.0, 9.0 Hz, 0.7H, CH), 2.87 (dd, *J* = 17.0, 8.5 Hz, 0.7H, CH), 2.59-2.48 (m, 0.3H, CH), 2.24-2.12 (m, 0.3H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.4 (C=O), 173.4 (C=O), 157.5 (*ipso*-Ar), 156.7 (*ipso*-Ar), 156.6 (*ipso*-

Ar), 133.3 (*ipso*-Ar), 132.7 (*ipso*-Ar), 129.8 (Ar), 129.6 (*ipso*-Ar), 128.5 (*ipso*-Ar), 128.4 (Ar), 128.3 (Ar), 127.5 (Ar), 122.0 (Ar), 121.7 (Ar), 121.0 (Ar), 120.9 (Ar), 114.19 (Ar), 114.16 (Ar), 111.2 (Ar), 110.8 (Ar), 55.7 (OMe), 55.6 (OMe), 55.4 (OMe), 54.9 ($NCH_{2[4\text{-}Ar]}$), 47.5 ($NCH_{2[3\text{-}Ar]}$), 45.6 ($CHAr_{[3\text{-}Ar]}$), 38.5 ($CH_{2[4\text{-}Ar]}$), 32.3 ($CHAr_{[4\text{-}Ar]}$), 26.8 ($CH_{2[3\text{-}Ar]}$), (one *ipso*-Ar and one OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NO_3$ $(M + H)^+$ 298.1438, found 298.1443 (–0.2 ppm error); Spectroscopic data for 4-aryl pyrrolidone **223** consistent with those reported in the literature.[168]

Lab book reference: **SMc6-409**

4-(Benzofuran-5-yl)-1-(4-methoxyphenyl)pyrrolidin-2-one 224

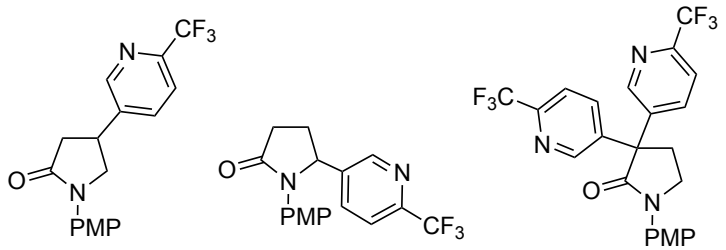


224

Using General Procedure G, 4-BF_3K *N*-PMP pyrrolidone **192** (149 mg, 0.5 mmol, 1.0 eq.) and 5-bromobenzofuran (94 μL, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using 60:40 hexane-EtOAc as eluent gave 4-aryl *N*-PMP pyrrolidone **224** (15 mg, 10%) as a brown oil, R_F (60:40 hexane-EtOAc) 0.18; IR (ATR) 1693 (C=O), 1513, 1464, 1378, 1264, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 2.0 Hz, 1H, Ar), 7.56-7.47 (m, 4H, Ar), 7.22 (dd, *J* = 8.5, 2.0, 1H, Ar), 6.95-6.88 (m, 2H, Ar), 6.75 (d, *J* = 2.0 Hz, 1H, Ar), 4.19 (dd, *J* = 9.5, 8.0 Hz, 1H, NCH), 3.89 (dd, *J* = 9.5, 7.5 Hz, 1H, NCH), 3.85-3.74 (m, 4H, CHAr, OMe), 3.05 (dd, *J* = 17.0, 8.5 Hz, 1H, CH), 2.82 (dd, *J* = 17.0, 8.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.9 (C=O), 156.8 (*ipso*-Ar), 154.2 (*ipso*-Ar), 145.9 (Ar), 136.5 (*ipso*-Ar), 132.4 (*ipso*-Ar), 128.0 (*ipso*-Ar), 123.2 (Ar), 122.0 (Ar), 119.2 (Ar), 114.2 (Ar), 111.9 (Ar), 106.6 (Ar), 56.7 (NCH_2), 55.6 (OMe), 40.7 (CH_2), 37.3 (CHAr); HRMS (ESI) *m/z* calcd for $C_{19}H_{17}NO_3$ $(M + Na)^+$ 330.1101, found 330.1108 (–1.9 ppm error).

Lab book reference: **SMc6-418**

1-(4-Methoxyphenyl)-4-(6-(trifluoromethyl)pyridin-3-yl)pyrrolidin-2-one 225, 1-(4-methoxyphenyl)-5-(6-(trifluoromethyl)pyridin-3-yl)pyrrolidin-2-one 241 and 1-(4-methoxyphenyl)-3,3-bis(6-(trifluoromethyl)pyridin-3-yl)pyrrolidin-2-one 242



Using General Procedure J, 4-BF_3K *N*-PMP pyrrolidone **192** (149 mg, 0.5 mmol, 1.0 eq.) and 5-bromo-2-(trifluoromethyl)pyridine (169 mg, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using 70:30 hexane-EtOAc to 30:70 hexane-EtOAc as eluent gave:

4-aryl *N*-PMP pyrrolidone **225** (56 mg, 33%) as a yellow solid, R_F (70:30 hexane-EtOAc) 0.1; mp 125-128 °C; IR (ATR) 1694 (C=O), 1513, 1458, 1378, 1264, 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 2.0 Hz, 1H, Ar), 7.81 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar), 7.69 (d, *J* = 8.0 Hz, 1H, Ar), 7.52-7.42 (m, 2H, Ar), 6.95-6.85 (m, 2H, Ar), 4.29-4.17 (m, 1H, NCH), 3.88-3.75 (m, 5H, NCH, OMe, CHAr), 3.07 (dd, *J* = 17.0, 8.5 Hz, 1H, CH), 2.73 (dd, *J* = 17.0, 8.0 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.5 (C=O), 157.1 (*ipso*-Ar), 149.1 (Ar), 147.5 (q, *J* = 35.0 Hz, *ipso*-Ar), 141.0 (*ipso*-Ar), 135.5 (Ar), 131.8 (*ipso*-Ar), 122.1 (Ar), 121.5 (q, *J* = 273.0 Hz, CF_3), 120.8 (q, *J* = 2.5 Hz, Ar), 114.3 (Ar), 55.6 (OMe), 55.4 (NCH_2), 39.6 (CH_2), 34.8 (CHAr); ^{19}F NMR (375 MHz, $CDCl_3$) δ –67.8; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}F_3N_2O_2$ $(M + Na)^+$ 359.0978, found 359.0985 (–0.1 ppm error);

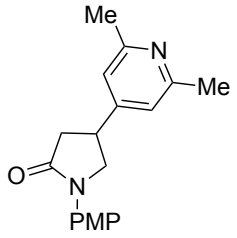
5-aryl *N*-PMP pyrrolidone **241** (22 mg, 13%) as an orange semi solid, R_F (70:30 hexane-EtOAc) 0.05; IR 1694 (C=O), 1512, 1455, 1264, 1034, 896 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 2.0 Hz, 1H, Ar), 7.69 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar), 7.61 (d, *J* = 8.0 Hz, 1H, Ar), 7.24-7.18 (m, 2H, Ar), 6.83-6.77 (m, 2H, Ar), 5.34 (dd, *J*

= 7.5, 5.5, 1H, CHAr), 3.72 (s, 3H, OMe), 2.80-2.62 (m, 3H, CH), 2.07-1.92 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.3 (C=O), 157.3 (*ipso*-Ar), 148.4 (Ar), 147.8 (q, *J* = 35.0 Hz, *ipso*-Ar), 140.3 (*ipso*-Ar), 135.0 (Ar), 129.9 (*ipso*-Ar), 124.3 (Ar), 122.6 (q, *J* = 272 Hz, CF_3), 120.7 (q, *J* = 3.5 Hz, Ar), 114.3 (Ar), 61.40 (CHAr), 55.3 (OMe), 30.8 (CH_2), 28.8 (CH_2); ^{19}F NMR (375 MHz, $CDCl_3$) δ –67.8; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}F_3N_2O_2$ $(M + K)^+$ 375.0731, found 375.0717 (–0.8 ppm error);

3-di-aryl *N*-PMP pyrrolidone **242** (25 mg, 10%) as an orange oil, R_F (70:30 hexane-EtOAc) 0.23; IR (ATR) 1694 (C=O), 1513, 1486, 1264, 1181, 1036, 830 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 2.0 Hz, 2H, Ar), 7.96 (dd, *J* = 8.0, 2.0 Hz, 2H, Ar), 7.68 (d, *J* = 8.0 Hz, 2H, Ar), 7.54-7.47 (m, 2H, Ar), 6.96-6.90 (m, 2H, Ar), 3.89 (dd, *J* = 6.5, 6.5 Hz, 2H, CH), 3.81 (s, 3H, OMe), 3.02 (dd, *J* = 6.5, 6.5 Hz, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.7 (C=O), 157.5 (*ipso*-Ar), 148.8 (Ar), 147.5 (q, *J* = 35.0 Hz, *ipso*-Ar), 139.9 (*ipso*-Ar), 137.3 (Ar), 131.4 (*ipso*-Ar), 122.5 (q, *J* = 274.0 Hz, CF_3), 122.0 (Ar), 120.5 (q, *J* = 3.0 Hz, Ar), 114.3 (Ar), 55.5 (OMe), 55.1 (CAr), 45.5 (CH_2), 32.7 (CH_2); ^{19}F NMR (375 MHz, $CDCl_3$) δ –67.8 ;HRMS (ESI) *m/z* calcd for $C_{23}H_{17}F_6N_3O_2$ $(M + Na)^+$ 504.1117, found 504.1122 (–2.4 ppm error).

Lab book reference: **SMc6-422**

4-(2,6-Dimethylpyridin-4-yl)-1-(4-methoxyphenyl)pyrrolidin-2-one 226



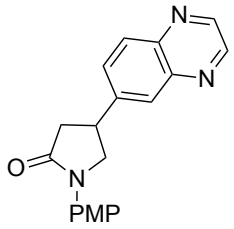
226

Using General Procedure J, 4-BF_3K *N*-PMP pyrrolidone **192** (149 mg, 0.5 mmol, 1.0 eq.) and 4-bromo-2,6-dimethylpyridine (139 mg, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using EtOAc as eluent gave 4-aryl *N*-PMP pyrrolidone **226** (92 mg, 62%) as a white solid, R_F (EtOAc) 0.1; mp 104-106 °C; IR (ATR) 1695 (C=O), 1513, 1265, 1034, 830 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.43 (m, 2H, Ar), 6.90-6.82 (m, 4H, Ar), 4.11 (dd, *J* = 10.0, 8.0

Hz, 1H, NCH), 3.82-3.72 (m, 4H, NCH, OMe), 3.55 (dddd, *J* = 8.0, 8.0, 8.0, 8.0 Hz, 1H, CHAr), 2.94 (dd, *J* = 17.5, 9.5 Hz, 1H, CH), 2.68 (dd, *J* = 17.5, 8.0 Hz, 1H, CH), 2.49 (s, 6H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.1 (C=O), 158.4 (*ipso*-Ar), 156.8 (*ipso*-Ar), 151.4 (*ipso*-Ar), 132.0 (*ipso*-Ar), 121.9 (Ar), 118.6 (Ar), 114.1 (Ar), 55.5 (OMe), 55.1 (NCH_2), 39.2 (CH_2), 36.3 (CHAr), 24.4 (Me); HRMS (ESI) calcd for $C_{18}H_{20}N_2O_2$ $(M + H)^+$ 297.1598, found 297.1596 (+0.2 ppm error).

Lab book reference: **SMc6-421**

1-(4-methoxyphenyl)-4-(quinoxalin-6-yl)pyrrolidin-2-one 227

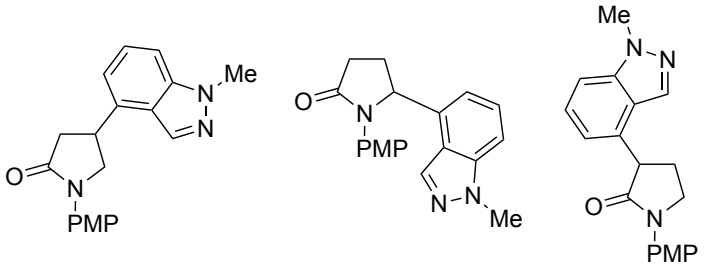


227

Using general procedure K, 4-BF_3K *N*-PMP pyrrolidone **192** (89 mg, 0.3 mmol, 1.0 eq.) and 6-bromoquinoxaline (94 mg, 0.45 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using 60:40 EtOAc-toluene as eluent gave an impure mixture of 4-aryl *N*-PMP pyrrolidone **227** and unknown impurities. Purification by flash column chromatography on silica using 50:50 EtOAc-toluene gave 4-aryl *N*-PMP pyrrolidone **227** (33 mg, 34%) as a yellow solid, R_F (60:40 EtOAc-toluene) 0.1; mp 55-57 °C; IR (ATR) 1694 (C=O), 1513, 1462, 1378, 1264, 895 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88-8.84 (m, *J* = 2.0 Hz, 2H, Ar), 8.13 (d, *J* = 8.5 Hz, 1H, Ar), 8.01 (d, *J* = 2.0 Hz, 1H, Ar), 7.73 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar), 7.57-7.49 (m, 2H, Ar), 6.96-6.89 (m, 2H, Ar), 4.36-4.23 (m, 1H, NCH), 4.06-3.92 (m, 2H, NCH, CHAr), 3.80 (s, 3H, OMe), 3.14 (dd, *J* = 17.0, 8.5 Hz, 1H, CH), 2.89 (dd, *J* = 17.0, 8.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.2 (C=O), 157.0 (*ipso*-Ar), 145.6 (Ar), 145.2 (Ar), 144.2 (*ipso*-Ar), 143.1 (*ipso*-Ar), 142.3 (*ipso*-Ar), 132.1 (*ipso*-Ar), 130.5 (Ar), 129.3 (Ar), 127.1 (Ar), 122.1 (Ar), 114.3 (Ar), 55.7 (NCH_2), 55.6 (OMe), 40.0 (CH_2), 37.3 (CHAr); HRMS (ESI) *m/z* calcd for $C_{19}H_{17}N_3O_2$ $(M + K)^+$ 358.0952, found 358.0953 (–1.0 ppm error).

Lab book reference: **SMc6-441**

1-(4-Methoxyphenyl)-4-(1-methyl-1H-indazol-4-yl)pyrrolidin-2-one 228, 1-(4-methoxyphenyl)-3-(1-methyl-1H-indazol-4-yl)pyrrolidin-2-one 239 and 1-(4-methoxyphenyl)-5-(1-methyl-1H-indazol-4-yl)pyrrolidin-2-one 240



228 **239** **240**

Using General Procedure K, *N*-PMP pyrrolidone BF_3K **192** (89 mg, 0.3 mmol, 1.0 eq.) and 4-bromo-1-methyl-1*H*-indazole (95 mg, 0.45 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using 50:50 hexane-EtOAc as eluent gave a 92:8 mixture (by ^{1}H NMR spectroscopy) of 4-Ar pyrrolidone **228** and 3-Ar pyrrolidone **240** (49 mg, 51%) as a dark orange oil, R_F (50:50 hexane-EtOAc) 0.1; IR (ATR) 2921, 2851, 1692 (C=O), 1513, 1463, 1248, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) for **228**: δ 8.00 (s, 1H, Ar), 7.53-7.47 (m, 2H, Ar), 7.38-7.28 (m, 2H, Ar), 7.04 (dd, *J* = 6.5, 1.5 Hz, 1H, Ar), 6.94-6.85 (m, 2H, Ar), 4.25 (dd, *J* = 9.5, 8.0 Hz, 1H, NCH), 4.14-3.96 (m, 5H, NCH, NMe, CHAr), 3.77 (s, 3H, OMe), 3.08 (dd, *J* = 17.0, 9.0 Hz, 1H, CH), 2.94 (dd, *J* = 17.0, 8.0 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) for **228**: δ 172.6 (C=O), 156.8 (*ipso*-Ar), 140.3 (*ipso*-Ar), 135.2 (*ipso*-Ar), 132.3 (*ipso*-Ar), 130.7 (Ar), 126.6 (Ar), 122.7 (*ipso*-Ar), 122.0 (Ar), 117.6 (Ar), 114.2 (Ar), 108.3 (Ar), 55.5 (OMe), 55.3 (NCH_2), 39.3 (CH_2), 35.8 (NMe), 35.1 (*C*HAr); HRMS (ESI) *m/z* calcd for $C_{19}H_{19}N_3O_2$ $(M + K)^+$ 360.1109, found 360.1106 (–0.3 ppm error); and an 85:15 mixture of 4-Ar pyrrolidone **228** and 5-Ar pyrrolidone **239** (31 mg, 32%) as a dark orange oil, R_F (50:50 hexane-EtOAc) 0.08; IR (ATR) 2922, 2853, 1692 (C=O), 1512, 1463, 1248, 1033, 788 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{19}H_{19}N_3O_2$ $(M + Na)^+$ 344.1369, found 344.1382 (–2.7 ppm error).

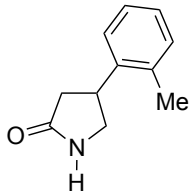
Diagnostic signals for 5-Ar pyrrolidone **239**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75-6.68 (m, 2H, Ar), 5.57 (dd, *J* = 7.5, 5.0 Hz, 1H, CHAr).

Diagnostic signals for 3-Ar pyrrolidone **240**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.59 (m, 2H, Ar), 2.77-2.66 (m, 1H, CH), 2.45-2.34 (m, 1H, CH).

The total yield was 83% (71 mg) i.e. 74% of 4-Ar pyrrolidone **228**; 4% of 3-Ar pyrrolidone **240**, 5% of 5-Ar pyrrolidone **239**.

Lab book reference: **SMc6-442**

4-(*o*-Tolyl)pyrrolidin-2-one 247

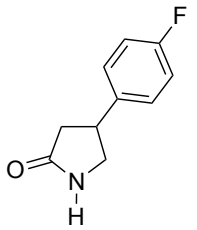


247

Cerium^{IV} ammonium nitrate (8 mL of a 0.08 M solution in water, 0.66 mmol, 3.0 eq.) was added to a stirred solution of 4-Ar *N*-PMP pyrrolidone **216** (59 mg, 0.22 mmol, 1.0 eq.) in MeCN (4.4 mL, 0.05 M) at 0 °C. The resulting solution was stirred at 0 °C for 30 min. After being allowed to warm to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using EtOAc as eluent gave 4-aryl *N*-H pyrrolidone (25 mg, 64%) as a white solid, R_F (EtOAc) 0.1; mp 85-87 °C (lit.,[169] 106-109°C); IR (ATR) 3194 (N-H), 1683 (C=O), 1489, 1380, 1263, 1079, 763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 1H, Ar), 7.25-7.1 (m, 3H, Ar), 6.73 (s, 1H, NH), 3.89 (dddd, *J* = 8.0, 8.0, 8.0, 6.5 Hz, 1H, CHAr), 3.75 (dd, *J* = 9.5, 8.0 Hz, 1H, NCH), 3.39 (dd, *J* = 9.5, 6.5 Hz, 1H, NCH), 2.71 (dd, *J* = 17.0, 8.0 Hz, 1H, CH), 2.46 (dd, *J* = 17.0, 8.0 Hz, 1H, CH), 2.33 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 178.1 (C=O), 140.4 (*ipso*-Ar), 135.7 (*ipso*-Ar), 130.8 (Ar), 127.0 (Ar), 126.8 (Ar), 125.4 (Ar), 49.0 (NCH_2), 37.6 (CH_2), 36.1 (CHAr), 19.8 (Me); HRMS (ESI) *m/z* calcd for $C_{11}H_{13}NO$ 214.0629, found 214.0627 (–0.7 ppm error); Spectroscopic data consistent with those reported in the literature.[169]

Lab book reference: **SMc6-455-2**

4-(4-Fluorophenyl)pyrrolidin-2-one 248

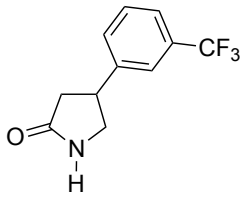


248

Cerium^{IV} ammonium nitrate (2.6 mL of a 0.08 M solution in water, 0.21 mmol, 3.0 eq.) was added to a stirred solution of 4-Ar *N*-PMP pyrrolidone **217** (19 mg, 0.07 mmol, 1.0 eq.) in MeCN (1.4 mL, 0.05 M) at 0 °C. The resulting solution was stirred at 0 °C for 30 min. After being allowed to warm to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using EtOAc as eluent gave 4-Ar *N*-H pyrrolidone **248** (9 mg, 72%) as an orange solid, R_F (EtOAc) 0.1; mp 62-64 ºC (lit.,[169] mp 95-97 °C); IR (ATR) 3233 (N-H), 1694 (C=O), 1513, 1328, 1224, 1100, 1052, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.19 (m, 2H, Ar), 7.07-6.99 (m, 2H, Ar), 6.23 (br s, 1H, NH), 3.78 (dd, J = 9.0, 8.5 Hz, 1H, NCH), 3.68 (dddd, J = 9.0, 8.5, 8.5, 7.0 Hz, 1H, CHAr), 3.38 (dd, J = 9.5, 7.0 Hz, 1H, NCH), 2.73 (dd, J = 17.0, 9.0 Hz, 1H, CH), 2.46 (dd, J = 17.0, 8.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.5 (C=O), 162.0 (d, J = 246.0 Hz, *ipso*-Ar), 137.9 (d, J = 3.5 Hz, *ipso*-Ar), 128.4 (d, J = 8.0 Hz, Ar), 115.9 (d, J = 21.5 Hz, Ar), 49.7 (NCH_2), 39.8 (CHAr), 38.10 (CH_2); ^{19}F NMR (175 MHz, $CDCl_3$) δ –115.38 (tt, J = 9.0, 5.0 Hz); HRMS (ESI) *m/z* calculated for $C_{10}H_{10}FNO$ $(M + K)^+$ 218.0378, found 218.0369 (+1.3 ppm error). Spectroscopic data consistent with those reported in the literature.[169]

Lab book reference: **SMc6-465-2**

4-(3-(trifluoromethyl)phenyl)pyrrolidin-2-one 249

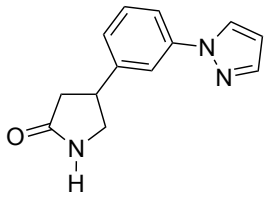


249

Cerium^{IV} ammonium nitrate (5.6 mL of a 0.08 M solution in water, 0.45 mmol, 3.0 eq.) was added to a stirred solution of 4-Ar *N*-PMP pyrrolidone **215** (50 mg, 0.15 mmol, 1.0 eq.) in MeCN (3 mL, 0.05 M) at 0 °C. The resulting solution was stirred at 0 °C for 30 min. After being allowed to warm to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using EtOAc as eluent gave 4-aryl *N*-H pyrrolidone **249** (25 mg, 71%) as a brown solid, R_F (EtOAc) 0.1; mp 48-50 °C; IR (ATR) 3230 (N-H), 1692 (C=O), 1326, 1119, 1074, 803 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.43 (m, 4H, Ar), 7.01 (br s, 1H, NH), 3.85 (ddd, *J* = 9.5, 8.0 Hz, 1H, NCH), 3.77 (dddd, *J* = 8.5, 8.5, 8.5, 6.5 Hz, 1H, CHAr), 3.45 (dd, *J* = 9.5, 6.5, 1H, NCH), 2.79 (dd, *J* = 17.0, 8.5 Hz, 1H, CH), 2.51 (dd, *J* = 17.0, 8.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.5 (C=O), 143.3 (*ipso*-Ar), 131.3 (q, *J* = 31.5 Hz, *ipso*-Ar), 130.2 (Ar), 129.6 (Ar), 124.2 (q, *J* = 4.0 Hz, Ar), 124.1 (q, *J* = 273.0, CF_3), 123.8 (q, *J* = 4.0 Hz, Ar), 49.5 (NCH_2), 40.2 (CHAr), 38.0 (CH_2); ^{19}F (375 MHz, $CDCl_3$) δ –62.6; HRMS (ESI) *m/z* calcd for $C_{11}H_{10}F_3NO$ $(M + H)^+$ 230.0787 found 2301.0787 (+0.2 ppm error); Spectroscopic data consistent with those reported in the literature.[170]

Lab book reference: **SMc6-468**

4-(3-(1*H*-pyrazol-1-yl)phenyl)pyrrolidin-2-one 250

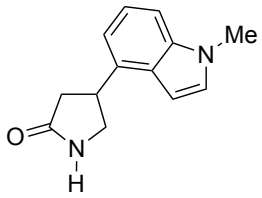


250

Cerium^{IV} ammonium nitrate (3.75 mL of a 0.08 M solution in water, 0.30 mmol, 3.0 eq.) was added to a stirred solution of 4-Ar *N*-PMP pyrrolidone **218** (35 mg, 0.1 mmol, 1.0 eq.) in MeCN (2 mL, 0.05 M) at 0 °C. The resulting solution was stirred at 0 °C for 30 min. After being allowed to warm to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 95:5 CH_2Cl_2-MeOH as eluent gave 4-aryl *N*-H pyrrolidone **250** (13 mg, 56%) as an orange oil, R_F (95:5 CH_2Cl_2-MeOH) 0.13; IR (ATR) 3251 (N-H), 2923 (C-H), 1683 (C=O), 1394, 1048, 925 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 2.0 Hz, 1H, Ar), 7.70 (d, *J* = 2.0 Hz, 1H, Ar), 7.64 (dd, *J* = 2.0, 2.0 Hz, 1H, Ar), 7.50 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, Ar), 7.40 (dd, *J* = 8.0, 8.0 Hz, 1H, Ar), 7.16 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, Ar), 6.72 (s, 1H, NH), 6.45 (dd, *J* = 2.0, 2.0 Hz, 1H, Ar), 3.87-3.66 (m, 2H, NCH, CHAr), 3.45 (dd, *J* = 9.0, 6.5 Hz, 1H, NCH), 2.75 (dd, *J* = 17.0, 8.5 Hz, 1H, CH), 2.53 (dd, *J* = 17.0, 8.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.6 (C=O), 144.0 (*ipso*-Ar), 141.3 (*ipso*-Ar), 140.7 (Ar), 130.1 (Ar), 126.9 (Ar), 124.8 (Ar), 118.2 (Ar), 117.8 (Ar), 107.9 (Ar), 49.5 (NCH_2), 40.4 (CHAr), 38.0 (CH_2); HRMS (ESI) *m/z* calcd for $C_{13}H_{13}N_3O$ $(M + H)^+$ 228.1131, found 228.1132 (–0.1 ppm error);

Lab book reference: **SMc6-473**

4-(1-methyl-1*H*-indazol-4-yl)pyrrolidin-2-one 251

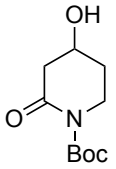


251

Cerium^{IV} ammonium nitrate (3.4 mL of a 0.08 M solution in water, 0.27 mmol, 3.0 eq.) was added to a stirred solution of 4-Ar *N*-PMP pyrrolidone **228** (30 mg, 0.09 mmol, 1.0 eq.) in MeCN (1.8 mL, 0.05 M) at 0 °C. The resulting solution was stirred at 0 °C for 30 min. After being allowed to warm to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 95:5 CH_2Cl_2-MeOH as eluent gave 4-aryl *N*-H pyrrolidone **251** (11 mg, 74%) as a brown solid, R_F (95:5 CH_2Cl_2-MeOH) 0.14; mp 112-114 °C; IR (ATR) 3250 (N-H), 2924 (C-H), 1682 (C=O), 1438, 1264, 1161, 1045, 987 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H, Ar), 7.40-7.28 (m, 2H, Ar), 7.03 (d, *J* = 6.5 Hz, 1H, Ar), 6.64 (br s, 1H, NH), 4.16-4.04 (m, 4H, NMe, CHAr), 3.90 (dd, *J* = 9.5, 8.5 Hz, 1H, NCH), 3.61 (dd, *J* = 9.5, 7.0 Hz, 1H, NCH), 2.84 (dd, *J* = 17.0, 9.0 Hz, 1H, CH), 2.71 (dd, *J* = 17.0, 8.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.6 (C=O), 140.4 (*ipso*-Ar), 135.5 (*ipso*-Ar), 130.8 (Ar), 126.6 (Ar), 122.7 (*ipso*-Ar), 117.8 (Ar), 108.2 (Ar), 48.7 (NCH_2), 38.4 (CHAr), 37.2 (CH_2), 35.9 (NMe); HRMS (ESI) *m/z* calcd for $C_{12}H_{13}N_3O$ $(M + H)^+$ 216.1131, found 216.1133 (–0.2 ppm error).

Lab book reference: **SMc6-482**

tert-Butyl 4-hydroxy-2-oxopiperidine-1-carboxylate 257



257

AcOH (0.24 mL, 4.2 mmol, 2.1 eq.) was added to a stirred solution of $NaBH_3CN$ (174 mg, 2.76 mmol, 1.2 eq.) in CH_2Cl_2 (0.2 M) at 0 °C under Ar. Then, *tert*-butyl 2,4-dioxopiperidine-1-carboxylate (498 mg, 2.3 mmol, 1.0 eq.) was added portion-wise under a stream of Ar at 0 °C and the resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, the mixture was cooled to 0 °C and H_2O (30 mL) and CH_2Cl_2 (30 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 40:60 hexane-EtOAc as eluent gave hydroxy lactam (420 mg, 85%) **257** as a colourless oil, R_F (30:70 hexane-EtOAc) 0.21; IR (ATR) 3439, 1762 (C=O), 1715 (C=O), 1293, 1149 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.25-4.15 (m, 1H, OCH), 3.82 (ddd, J = 12.0, 7.0, 5.0 Hz, 1H, NCH), 3.55 (ddd, J = 12.0, 7.0, 5.0 Hz, 1H, NCH), 2.73 (ddd, J = 17.5, 5.0, 1.5 Hz, 1H, CH), 2.52 (ddd, J = 17.5, 6.0, 1.5 Hz, 1H, CH), 2.08-1.96 (m, 1H, CH), 1.93-1.78 (m, 1H, CH), 1.49 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.0 (C=O), 152.4 (C=O), 83.3 (O*C*Me_3), 64.2 (OCH), 43.8 (NCH_2), 42.2 (CH_2), 30.9 (CH_2), 28.1 (C*Me*$_3$); HRMS (ESI) *m/z* calcd for $C_{10}H_{17}NO_4$ $(M + Na)^+$ 238.1050, found 238.1051 (–1.1 ppm error).[171]

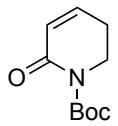
Lab book reference: **SMc5-299-1**

$NaBH_4$ (17.5 mg, 0.46 mmol, 2.0 eq.) was added to a mixture of CH_2Cl_2:AcOH (14.4 mL, 9:1, 0.016 M) at at 0 °C under Ar. Then, *tert*-butyl 2,4-dioxopiperidine-1-carboxylate (50 mg, 0.23 mmol, 1.0 eq.) was added portion-wise under a stream of Ar to and the resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, the mixture was cooled to 0 °C and H_2O (30 mL) and CH_2Cl_2 (30 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30

mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 30:70 hexane-EtOAc as eluent gave hydroxy lactam (25 mg, 51%) **257** as a colourless oil.

Lab book reference: **SMc5-298-1**

tert-Butyl 6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate 256



256

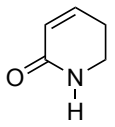
MsCl (0.11 mL, 1.43 mmol, 1.3 eq.) was added to a stirred solution of hydroxy lactam **257** (230 mg, 1.1 mmol, 1.0 eq.) and Et_3N (0.31 mL, 2.2 mmol, 2.0 eq.) in CH_2Cl_2 (2.2 mL, 0.5 M) at 0 °C and the resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then $NaHCO_{3(aq)}$ (30 mL) and CH_2Cl_2 (30 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 80:20 hexane-EtOAc as eluent gave unsaturated *N*-Boc lactam **256** (155 mg, 71%) as a colourless oil, R_F (80:20 hexane-EtOAc) 0.12; IR (ATR) 1764 (C=O), 1711 (C=O), 1369, 1314, 1134, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (dt, *J* = 10.0, 4.0 Hz, 1H, CH=C*H*CH_2), 5.95 (dt, *J* = 10.0, 2.0 Hz, 1H, C*H*=$CHCH_2$), 3.85 (t, *J* = 6.5 Hz, 2H, NCH_2), 2.40 (tdd, J = 6.5, 4.0, 2.0 Hz, 2H, CH=CHCH_2), 1.54 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.8 (C=O), 152.6 (C=O), 143.4 (CH=*C*HCH_2), 126.3 (*C*H=$CHCH_2$), 82.9 (O*C*Me_3), 43.5 (NCH_2), 28.1 (CMe_3), 24.7 (CH=CH*C*H_2); HRMS (ESI) *m/z* calcd for $C_{10}H_{15}NO_3$ $(M + Na)^+$ 220.0944, found 220.0937 (+2.4 ppm error); Spectroscopic data consistent with those reported in the literature.[171]

Lab book reference: **SMc5-301-1**

AcOH (2.25 mL, 39.4 mmol, 2.1 eq.) was added to a stirred solution of $NaBH_3CN$ (1.4 g, 22.5 mmol, 1.2 eq.) in CH_2Cl_2 (94 mL, 0.2 M) at 0 °C under Ar. Then, *tert*-butyl 2,4-dioxopiperidine-1-carboxylate (4 g, 18.8 mmol, 1.0 eq.) was added portion-wise under a stream of Ar at 0 °C and the resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, the mixture was cooled to 0 °C and H_2O (50 mL) and CH_2Cl_2 (50 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give crude hydroxy lactam **257**. Crude hydroxy lactam **257** was dissolved in CH_2Cl_2 (40 mL, 0.5 M) and MsCl (2.1 mL, 26.5 mmol, 1.3 eq.) and Et_3N (5.6 mL, 40.7 mmol, 2.0 eq.) were added in at 0 °C and the resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then $NaHCO_{3(aq)}$ (50 mL) and CH_2Cl_2 (50 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 80:20 hexane-EtOAc as eluent gave unsaturated *N*-Boc lactam **256** (2.5 g, 67%) as a colourless oil.

Lab book reference: **SMc5-301-2**

5,6-Dihydropyridin-2(1*H*)-one 255



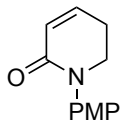
255

Trifluoroacetic acid (3.5 mL, 45.6 mmol, 9.0 eq.) was added to a stirred solution of unsaturated *N*-Boc lactam **256** (1 g, 5.1 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL, 0.5 M) at 0 °C for 20 min. The solvent was evaporated under reduced pressure and toluene (20 mL) was added and the solvent evaporated under reduced pressure. The dissolve evaporate cycle was repeated with toluene (5 x 20 mL). $NaHCO_3$ (20 mL) and CH_2Cl_2:MeOH (10:1, 30 mL) were added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2:MeOH (10:1, 5 x 30 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give unsaturated *N*-H

lactam **255** (895 mg, 95%) as a white solid, mp 41-43 °C (lit.,[173] 61-62 °C); IR (ATR) 3352 (N-H), 2943, 1693 (C=O), 1554 (C=C), 1474, 1003, 874 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.65 (dt, *J* = 10.0, 4.0 Hz, 1H, CH=C*H*CH_2), 6.11 (br s, 1H, NH), 5.91 (dtd, *J* = 10.0, 2.0, 2.0 Hz, 1H, C*H*=$CHCH_2$), 3.43 (td, *J* = 7.0, 2.0 Hz, 2H, NCH_2), 2.41-2.30 (m, 2H, CH=CHC*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.4 (C=O), 141.5 (CH=*C*HCH_2), 124.8 (*C*H=$CHCH_2$), 39.7 (NCH_2), 23.9 (CH=CH*C*H_2); HRMS (ESI) *m/z* calcd for C_5H_7NO $(M + Na)^+$ 120.042, found 120.0418 (+ 1.6 ppm error); Spectroscopic data consistent with those reported in the literature.[173]

Lab book reference: **SMc5-328-1**

1-(4-methoxyphenyl)-5,6-dihydropyridin-2(1*H*)-one 254



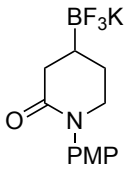
254

Unsaturated *N*-H lactam **255** (35 mg, 0.36 mmol, 1.2 eq.) was added to a stirred suspension of copper(I) iodide (6 mg, 0.03 mmol, 10 mol%), K_2CO_3 (127 mg, 0.6 mmol, 2.0 eq.) and 4-iodoanisole (70 mg, 0.3 mmol, 1.0 eq.) in dioxane (1 mL, 0.3 M) at rt. The flask was sealed and purged under N_2 for 15 min, then stirred at 110 °C (heater block temperature) for 24 h. After being allowed to cool to rt, H_2O (10 mL) and CH_2Cl_2 (10 mL) were added and two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 x 10 mL) and the combined organics were washed with brine (10 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 50:50 hexane-EtOAc as eluent gave unsaturated *N*-PMP piperidone **254** (39 mg, 63%) as a white crystalline solid, R_F (50:50 hexane-EtOAc) 0.14; mp 65-67 °C (lit.,[174] 93 °C); IR (ATR) 2936, 1668 (C=O), 1511, 1442, 1322, 1297, 1241, 1145, 1033, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23-7.17 (m, 2H, Ar), 6.95-6.84 (m, 2H, Ar), 6.66 (dt, *J* = 9.5, 4.0 Hz, 1H, CH=C*H*CH_2), 6.04 (dt, *J* = 9.5, 2.0 Hz, 1H, (C*H*=$CHCH_2$), 3.81-3.74 (m, 5H, OMe, NCH_2), 2.53-2.45 (m, 2H, CH=CHC*H*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.5 (C=O), 157.7 (*ipso*-Ar), 140.2 (CH=*CH*CH_2),

135.7 (*ipso*-Ar), 126.6 (Ar), 126.1 (*CH*=CHCH$_2$), 114.3 (Ar), 55.5 (OMe), 49.0 (NCH$_2$), 24.7 (CH$_2$); HRMS (ESI) *m/z* calcd for $C_{12}H_{13}NO_2$ $(M + K)^+$ 242.0578, found 242.0576 (+ 0.5 ppm error); Spectroscopic data consistent with those reported in the literature.[174]

Lab book reference: **SMc5-334-1**

1-(4-methoxyphenyl)-4-(trifluoro-^{4}-boraneyl)piperidin-2-one, potassium salt 254



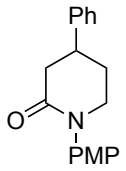
252

B_2pin_2 (1.3 g, 5.1 mmol, 1.2 eq.), CuI (16 mg, 0.09 mmol, 2 mol%) and K_2CO_3 (1 g, 7.2 mmol, 2.0 eq.) were added to THF (7 mL) at rt. The mixture was stirred at rt for 10 minutes. Then a solution of unsaturated *N*-PMP piperidone **254** (862 mg, 4.24 mmol, 1.0 eq.) in THF (7 mL) and MeOH (0.34 mL) was added and the reaction mixture was stirred at rt for 24 h. Then, brine (20 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried ($MgSO_4$), and evaporated under reduced pressure to give the crude product. Saturated $KHF_{2(aq)}$ (3.3 M, 6.4 mL, 5.0 eq.) was added to a stirred solution of the crude material in MeOH (8.5 mL) at rt. The resulting mixture was stirred at rt for 1 h, then the solvent was evaporated under reduced pressure. The residue was dissolved in the minimum amount of hot acetone and the solids were removed by filtration. The process was repeated using the minimum amount of hot acetonitrile and the solids were removed by filtration. The filtrate was evaporated under reduced pressure then Et_2O (75 mL) was added and the resulting mixture stirred at rt for 1 h. The solids were collected by filtration to give 4-BF_3K *N*-PMP piperidone **252** (300 mg, 23%) as a white solid, mp 195 °C (dec.); IR (ATR) 1601 (C=O), 1510, 1242, 1101, 966, 829 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) 7.14-7.08 (m, 2H, Ar), 6.91-6.84 (m, 2H, Ar), 3.73 (s, 3H, OMe), 3.48-3.41 (m, 2H, NCH), 2.10 (ddd, *J* = 17.5, 5.5, 2.0 Hz, 1H, CH), 1.99 (dd, *J* = 17.5, 11.5 Hz, 1H, CH), 1.76-1.65 (m, 1H,

CH), 1.55-1.40 (m, 1H, CH), 0.67-0.51 (m, 1H, BCH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 171.9 (C=O), 156.9 (*ipso*-Ar), 137.4 (*ipso*-Ar), 127.4 (Ar), 113.8 (Ar), 55.2 (OMe), 53.1 (NCH_2), 35.9 (CH_2), 25.9 (CH_2), BCH resonance not resolved; ^{11}B NMR (128 MHz, DMSO-d_6) δ 2.91; ^{19}F NMR (375 MHz, DMSO-d_6) δ –145.4; HRMS (ESI) m/z calcd for $C_{12}H_{14}BF_3NO_2$ $(M–K)^-$ 272.107, found 272.1076 (+ 2.2 ppm error);

Lab book reference: **SMc6-460**

1-(4-methoxyphenyl)-4-phenylpiperidin-2-one 259



259

4-BF_3K *N*-PMP piperidone **252** (93 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 0.10 eq.), cataCXium A (22 mg, 60 µmol, 0.20 eq.) and Cs_2CO_3 (391 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (48 µL, 0.45 mmol, 1.5 eq.), degassed toluene (0.42 mL) and water (108 µL, 6.0 mmol, 20.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 50:50 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP piperidone **259** (6 mg, 7%) as a white solid, R_F (50:50 hexane-EtOAc) 0.1; IR (ATR) 2933, 1643 (C=O), 1508, 1244, 1026, 831, 762, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.34 (m, 2H, Ph), 7.31-7.25 (m, 3H, Ph), 7.22-7.16 (m, 2H, Ar), 6.95-6.91 (m, 2H, Ar), 3.81 (s, 3H, OMe), 3.80-3.70 (m, 1H, NCH), 3.62 (ddd, *J* = 12.5, 5.5, 3.5 Hz, 1H, NCH), 3.27 (dddd, *J* = 11.0, 11.0, 5.5, 3.5 Hz, 1H, CHAr), 2.89 (ddd, *J* = 17.5,

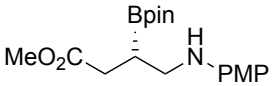
5.5, 2.0 Hz, 1H, CH), 2.70 (dd, *J* = 17.5, 11.0 Hz, 1H, CH), 2.29-2.20 (m, 1H, CH), 2.20-2.08 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.7 (C=O), 158.4 (*ipso*-Ar), 143.5 (*ipso*-Ph), 136.0 (*ipso*-Ar), 128.9 (Ph), 127.5 (Ar), 127.0 (Ph), 126.7 (Ph), 114.7 (Ar), 55.6 (OMe), 51.1 (NCH_2), 39.9 (CH_2), 38.9 (CHPh), 30.8 (CH_2); HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NO_2$ $(M + K)^+$ 320.1047, found 320.1049 (–1.2 ppm error); Spectroscopic data consistent with those reported in the literature.[175]

Lab book reference: **SMc6-461**

4-BF_3K *N*-PMP piperidone **252** (93 mg, 0.3 mmol, 1.0 eq.), cataCXium A Pd G3 (22 mg, 30 μmol, 10 mol%) and K_2CO_3 (124 mg, 0.9 mmol, 3.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and chlorobenzene (46 μL, 0.45 mmol, 1.5 eq.), degassed toluene (1.0 mL) and water (180 μL, 9.9 mmol, 33.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 using 50:50 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP piperidone **259** (7 mg, 8%) as a white solid.

Lab book reference: **SMc6-462**

Methyl (*S*)-4-((4-methoxyphenyl)amino)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (*S*)-197

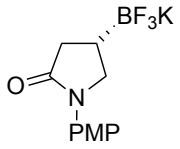


(*S*)-**197**

B_2pin_2 (6 g, 23.5 mmol, 1.2 eq.), CuCl (64 mg, 0.64 mmol, 0.03 eq.), NaO^{t}Bu (93 mg, 0.96 mmol, 0.05 eq.) and (*R*,*S*)-Josiphos (410 mg, 0.64 mmol, 0.03 eq.) were added to a flame-dried flask at rt under Ar. THF (35 mL) was added and the resulting mixture was stirred at rt for 30 min. Then, a solution of enoate **195** (4.73 g, 21.4 mmol, 1.0 eq.) in THF (35 mL) was added followed by the addition of MeOH (1.7 mL). The resulting mixture was stirred at rt for 1 h. The solids were removed by filtration through a plug of Celite® and the solvent was evaporated under reduced pressure to give the crude product. Purification by recrystallisation from *n*-hexane gave Bpin ester (*S*)-**197** (4.2 g, 56%) as a white solid, $[\alpha]_D$ +8.93 (*c* 1.0 in $CHCl_3$).

Lab book reference **SMc30-5**

Potassium(1-(4-methoxyphenyl))-4-(*S*)-trifluoroboratepyrrolidin-2-one (*S*)-192



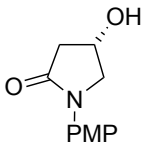
(*S*)-**192**

A solution of (*S*)-Bpin ester (*S*)-**197** (4.1 g, 11.7 mmol, 1.0 eq.) was dissolved in AcOH (23 mL, 0.5 M solution) at 50 °C (heater block temperature) and stirred for 4 h. After being allowed to cool to rt, $Na_2CO_{3(aq)}$ (30 mL) was added. Then, CH_2Cl_2 (30 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organics were dried ($MgSO_4$) and solvent evaporated under reduced pressure to give the crude material. The crude product was dissolved in MeOH (23 mL) and saturated $KHF_{2(aq)}$ (3.3 M, 18 mL, 5.0 eq.) was added. The resulting mixture was stirred for 1 h at rt and then the solvent was evaporated under reduced pressure. The residue was dissolved in the minimum amount of hot acetone

and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give a white solid. Et_2O (150 mL) was added, and the resulting mixture was stirred at rt for 1 h. The solids were collected by filtration to 4-BF_3K *N*-PMP pyrrolidone (*S*)-**192** (2.2 g, 63%) as a white solid, $[\alpha]_D$ –21.95 (*c* 1.0 in Acetone).

Lab book reference: **SMc31-5**

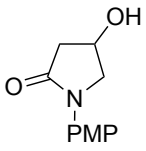
4-Hydroxy-1-(4-methoxyphenyl)pyrrolidine-2-one (*S*)-260



(*S*)-**260**

A solution of $oxone_{(aq)}$ (0.2 M, 0.50 mL, 1.0 eq.) was added to a stirred solution of (*S*)-trifluoroborate salt (*S*)-**192** (30 mg, 0.1 mmol, 1.0 eq.) in acetone (0.5 mL, 0.2 M) at rt. The resulting mixture was stirred at rt for 3 min. Then, 2 M $HCl_{(aq)}$ (0.3 mL) and H_2O (0.5 mL) were added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and 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 30:70 hexane-EtOAc as eluent gave 4-OH *N*-PMP pyrrolidone (*S*)-**260** (13 mg, 63%, 98:2 er by CSP-HPLC) as an orange solid, mp 140-144 ºC; R_F (3:7 hexane-EtOAc) 0.23; IR (ATR) 3314 (OH), 2923, 1651 (C=O), 1512, 1239, 1035, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.51-7.43 (m, 2H, Ar), 6.94-6.84 (m, 2H, Ar), 4.65-4.59 (m, 1H, OCH), 4.48 (d, *J* = 4.0 Hz, 1H, OH), 4.10 (dd, *J* = 10.5, 5.5 Hz, 1H, NCH), 3.78 (s, 3H, Ome), 3.68 (dd, *J* = 10.5, 2.5 Hz, 1H, NCH), 2.90 (dd, *J* =17.0, 6.0 Hz, 1H, CH), 2.37 (dd, *J* = 17.5, 2.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.7 (C=O), 157.0 (*ipso*-Ar), 134.3 (*ipso*-Ar), 121.8 (Ar), 114.5 (Ar), 64.3 (OCH), 58.3 (NCH_2), 55.6 (OMe), 43.0 (CH_2); HRMS (ESI) *m/z* calculated for $C_{11}H_{12}NO_3$ $(M + H)^+$ 208.0968, found 208.0967 (+0.6 ppm error), $[\alpha]_D$ +8.57 (*c* 0.38 in $CHCl_3$); CSP-HPLC: CHIRALPAK® IC (70:30 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**260** 15.15 min, (*S*)-**260** 18.28 min.

Lab book reference: **SMc6-454**

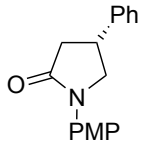


260

A solution of oxone$_{(aq)}$ (0.2 M, 0.50 mL, 1.0 eq.) was added to a stirred solution of *rac*-4-BF_3K *N*-PMP pyrrolidone **192** (30 mg, 0.1 mmol, 1.0 eq.) in acetone (0.5 mL, 0.2 M) at rt. The resulting mixture was stirred at rt for 3 min. Then, 2 M $HCl_{(aq)}$ (0.3 mL) and H_2O (0.5 mL) were added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The residue was passed through a plug of silica topped with activated charcoal eluted with CH_2Cl_2 then MeOH to give hydroxy pyrrolidone **260** (16 mg, 77%) as an orange solid.

Lab book reference: **SMc49-1**

(*R*)-1-(4-methoxyphenyl)-4-phenylpyrrolidin-2-one (*R*)-206



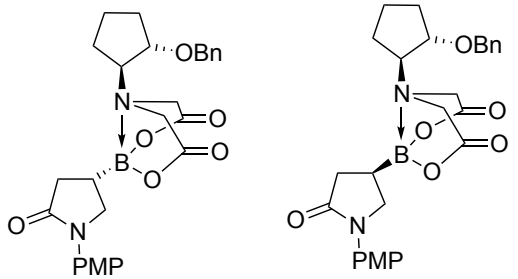
(*S*)-**206**

4-BF_3K *N*-PMP pyrrolidone (*S*)-**192** (89 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 10 mol%), cataCXium A (22 mg, 60 μmol, 20 mol%) and Cs_2CO_3 (391 mg, 1.2 mmol, 4.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and liquid bromobenzene (47 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.42 mL) and water (108 μL, 6.0 mmol, 20.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added

and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics 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 80:20 hexane-EtOAc as eluent gave 4-phenyl *N*-PMP pyrrolidone (*R*)-**206** (50 mg, 56%, 97:3 er by CSP-HPLC) as a white solid. $[\alpha]_D$ +9.8 (*c* 0.6 in $CHCl_3$) (lit.,[104] $[\alpha]_D$ + 9.5 (c 1.0 in $CHCl_3$) for (*R*)-**206** of 95:5 er); CSP-HPLC: CHIRALPAK® IB (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**206** 29.0 min, (*R*)-**206** 31.2 min.

Lab book reference: **SMc6-474**

(6-[(1*S*,2*S*)-2-(Benzyloxy)cyclopentyl]-2-[(3*S*)-1-(4-methoxyphenyl)-5-oxopyrrolidin-3-yl]-1,3,6,2-dioxazaborocane-4,8-dione) (*S*,*S*,*S*)-261 and (6-[(1S,2*S*)-2-(benzyloxy)cyclopentyl]-2-[(3*R*)-1-(4 methoxyphenyl)-5-oxopyrrolidin-3-yl]-1,3,6,2-dioxazaborocane-4,8-dione) (*S*,*S*,*R*)-261



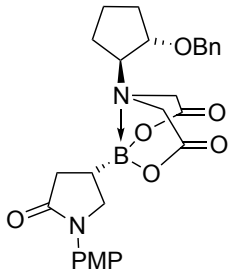
(*S*,*S*,*S*)-**261** (*S*,*S*,*R*)-**261**

Triethylorthoformate (264 μL, 1.59 mmol, 3.0 eq.) was added to a stirred solution of 4-Bpin *N*-PMP pyrrolidone *rac*-**198** (167 mg, 0.53 mmol, 1.0 eq.) and (*S*,*S*)-BIDA (326 mg, 1.06 mmol, 2.0 eq.) in anhydrous DMSO (2.6 mL) under N_2. The resulting mixture was stirred and heated at 100 °C for 60 h. After being allowed to cool to rt, NH_4Cl (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 50:50 hexane-EtOAc to 20:80 hexane-EtOAc to EtOAc as eluent gave pyrrolidone BBIDA (*S*,*S*,*S*)-**261** (101 mg, 38%) as a white solid, mp 200-202; R_F (20:80 hexane-EtOAc) 0.13; IR (ATR) 2955, 1762, 1680, 1512, 1293, 1246, 1125, 1028, 832, 702

cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.40 (m, 2H, Ar), 7.37-7.24 (m, 5H, Ph), 6.87-6.81 (m, 2H, Ar), 4.55 (d, *J* = 11.5 Hz, 1H, OC*H*Ph), 4.37 (d, *J* = 11.5 Hz, 1H, OC*H*Ph), 4.02-3.91 (m, 2H, NCH, OCH), 3.85 (dd, *J* = 10.0, 10.0 Hz, 1H, ArNC*H*), 3.81-3.65 (m, 7H, NCH, OMe, ArNC*H*), 3.46 (ddd, *J* = 8.5, 8.5, 6.5 Hz, 1H, NC*H*CHO), 2.46 (dd, *J* = 16.0, 9.0 Hz, 1H, CHCO), 2.32 (dd, *J* = 16.0, 12.0 Hz, 1H, CHCO), 2.21-2.09 (m, 1H, CH), 2.09-1.97 (m, 1H, CH), 1.89-1.75 (m, 2H, BCH, CH), 1.75-1.64 (m, 2H, CH), 1.56-1.43 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 173.7 (C=O, lactam), 168.9 (C=O, ester), 167.1 (C=O, ester), 156.7 (*ipso*-Ar), 136.6 (*ipso*-Ph), 132.6 (*ipso*-Ar), 128.9 (Ph), 128.6 (Ph), 128.2 (Ph), 122.0 (Ar), 114.1 (Ar), 79.6 (OCH), 73.4 (NCH), 72.0 (O*C*H_2Ph), 60.6 (NCH_2), 55.9 (NCH_2), 55.5 (OMe), 51.6 (NCH_2), 34.7 (*C*H_2CO), 29.7 (CH_2), 26.5 (CH_2), 21.6 (CH_2), 19.8 (BCH); ^{11}B (128 MHz, $CDCl_3$) 12.58; HRMS (ESI) *m/z* calcd for $C_{27}H_{31}BN_2O_7$ $(M + Na)^+$ 529.2117, found 529.2123 (–0.3 ppm error); $[\alpha]_D$ +16.92 (*c* 1.0 in CH_2Cl_2) and BIDA pyrrolidone (*S*,*S*,*R*)-**261** (93 mg, 35%) as a white solid, mp 102-104; R_F (20:80 hexane-EtOAc) 0.05; IR (ATR) 2926, 1761, 1678, 1511, 1290, 1245, 1106, 1026, 830, 733, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.36 (m, 2H, Ar), 7.36-7.22 (m, 5H, Ph), 6.90-6.80 (m, 2H, Ar), 4.54 (d, *J* = 11.0 Hz, 1H, OC*H*Ph), 4.35 (d, *J* = 11.0 Hz, 1H, OC*H*Ph), 4.00-3.91 (m, 2H, NCH, OCH), 3.82-3.59 (m, 8H, NCH, OMe, ArNC*H*), 3.49 (ddd, *J* = 8.5, 8.5, 6.5 Hz, 1H, NC*H*CHO), 2.58-2.40 (m, 2H, CHCO), 2.21-2.08 (m, 1H, CH), 2.08-1.96 (m, 1H, CH), 1.93-1.65 (m, 4H, BCH, CH), 1.56-1.43 (m, 1H, CH); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 174.2 (C=O, lactam), 168.3 (C=O, ester), 167.3 (C=O, ester), 156.7 (*ipso*-Ar), 136.5 (*ipso*-Ph), 132.5 (*ipso*-Ar), 128.9 (Ph), 128.6 (Ph), 128.2 (Ph), 122.2 (Ar), 114.1 (Ar), 79.7 (OCH), 73.2 (NCH), 72.2 (O*C*H_2Ph), 59.3 (NCH_2), 56.9 (NCH_2), 55.5 (OMe), 51.6 (NCH_2), 35.1 (CH_2CO), 29.9 (CH_2), 26.8 (CH_2), 21.5 (CH_2), 19.4 (BCH); ^{11}B (128 MHz, $CDCl_3$) 11.56; HRMS (ESI) *m/z* calcd for $C_{27}H_{31}BN_2O_7$ $(M + K)^+$ 545.1856, found 545.1865 (–0.7 ppm error); $[\alpha]_D$ –3.14 (*c* 1.0 in CH_2Cl_2).

Lab book reference: **SMc67-1**

(6-[(1S,2*S*)-2-(Benzyloxy)cyclopentyl]-2-[(3*S*)-1-(4 methoxyphenyl)-5-oxopyrrolidin-3-yl]-1,3,6,2-dioxazaborocane-4,8-dione) (*S*,*S*,*S*)-261

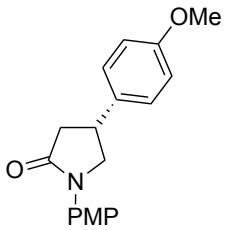


(*S*,*S*,*S*)-**261**

Triethylorthoformate (200 μL, 1.2 mmol, 3.0 eq.) was added to a stirred solution of 4-Bpin *N*-PMP pyrrolidone (*S*)-**198** (126 mg, 0.40 mmol, 1.0 eq.) and (*S*,*S*)-BIDA (268 mg, 0.77 mmol, 2.2 eq.) in anhydrous DMSO (2.0 mL) under N_2. The resulting mixture was stirred and heated at 100 °C for 60 h. After being allowed to cool to rt, NH_4Cl (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 50:50 hexane-EtOAc to 20:80 hexane-EtOAc as eluent gave substituted pyrrolidone (*S*,*S*,*S*)-**206** (158 mg, 78%) as a white solid.

Lab book reference: **SMc66-1**

(*R*)-1,4-bis(4-Methoxyphenyl)pyrrolidin-2-one (*R*)-221



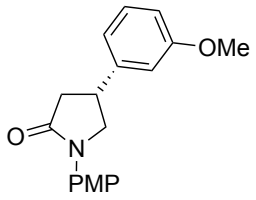
(*R*)-**221**

Using general procedure K, 4-BF_3K N-PMP (*R*)-**192** (89 mg, 0.3 mmol, 1.0 eq., 98:2 er by CSP-HPLC) and 4-bromoanisole (56 μL, 0.45 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using 70:30 hexane-

EtOAc as eluent gave 4-aryl *N*-PMP pyrrolidone (*R*)-**221** (13 mg, 14%, 97:3 er by CSP-HPLC) as a brown solid, $[\alpha]_D$ +39.13 (*c* 0.5 in $CHCl_3$) (lit.,[109] $[\alpha]_D$ +9.8 (*c* 0.61 in $CHCl_3$) for (*R*)-**221** of 99:1 er); CSP-HPLC: CHIRALPAK® IA (80:20 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**221** 22.6 min, (*R*)-**221** 34.7 min.

Lab book reference: **SMc6-458**

4-(3-Methoxyphenyl)-1-(4-methoxyphenyl)pyrrolidin-2-one (*R*)-222

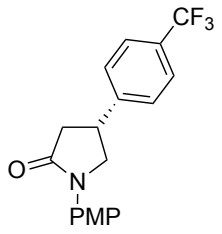


(*R*)-**222**

Using general procedure K, 4-BF_3K *N*-PMP Pyrrolidone (*S*)-**192** (89 mg, 0.3 mmol, 1.0 eq., 98:2 er by CSP-HPLC) and 3-bromoanisole (57 μL, 0.45 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using 70:30 hexane-EtOAc as eluent gave 4-aryl *N*-PMP pyrrolidone (*R*)-**222** (53 mg, 60%, 97:3 er by CSP-HPLC) as a brown solid. $[\alpha]_D$ +9.73 (*c* 1.0 in $CHCl_3$) (lit.,[168] $[\alpha]_D$ –6.29 (*c* 0.8 in $CHCl_3$) for (*S*)-**222** of 84:16 er); CSP-HPLC: CHIRALPAK® IA (80:20 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**222**17.5 min, (*R*)-**222** 22.6 min.

Lab book reference: **SMc6-478**

1-(4-methoxyphenyl)-4-(4-(trifluoromethyl)phenyl)pyrrolidin-2-one (*R*)-213

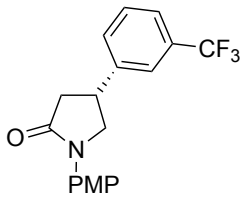


(*R*)-**213**

Using general procedure K, 4-BF_3K *N*-PMP Pyrrolidone (*S*)-**192** (89 mg, 0.3 mmol, 1.0 eq., 98:2 er by CSP-HPLC) and 1-bromo-4-(trifluoromethyl)benzene (101 μL, 0.45 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using 70:30 hexane-EtOAc as eluent gave 4-aryl *N*-PMP pyrrolidone (*R*)-**213** (53 mg, 59%, 97:3 er by CSP-HPLC) as a brown solid. $[\alpha]_D$ +17.1 (*c* 0.3 in $CHCl_3$); CSP-HPLC: CHIRALPAK® ADH (80:20 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**213** 14.9 min, (*R*)-**213** 21.2 min.

Lab book reference: **SMc6-471**

1-(4-Methoxyphenyl)-4-(3-(trifluoromethyl)phenyl)pyrrolidin-2-one (*R*)-215



(*R*)-**215**

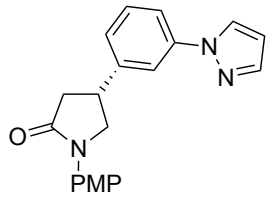
Using general procedure K, 4-BF_3K *N*-PMP Pyrrolidone (*S*)-**192** (89 mg, 0.3 mmol, 1.0 eq., 98:2 er by CSP-HPLC) and 1-bromo-3-(trifluoromethyl)benzene (101 μL, 0.45 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using 70:30 hexane-EtOAc as eluent gave 4-aryl *N*-PMP pyrrolidone (*R*)-**215** (48 mg, 48%, 97:3 er by CSP-HPLC) as a brown solid. $[\alpha]_D$ +7.15 (*c* 1.0, $CHCl_3$); CSP-HPLC: CHIRALPAK® IC (80:20 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**215** 29.7 min, (*R*)-**215** 33.8 min.

Lab book reference: **SMc6-519**

4-BF_3K *N*-PMP pyrrolidone (*S*)-**192** (1.0 g, 3.37 mmol, 1.0 eq.), $Pd(OAc)_2$ (76 mg, 0.34 mmol, 0.10 eq.), cataCXium A (240 mg, 0.67 mmol, 0.20 eq.) and Cs_2CO_3 (4.4 g, 13.5 mmol, 4.0 eq.) were placed in flame dried round bottom flask. The flask was purged with N_2 for 15 min. Then, the exit needle was removed and 3-bromobenzotrifluoride (0.7 mL, 5.1 mmol, 1.5 eq.), degassed toluene (4.8 mL) and water (1.2 mL, 67.4 mmol, 20.0 eq.) were added under N_2. The flask was fitted with a reflux condenser and the mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h under N_2. After being allowed to cool to rt, water (30 mL) and EtOAc (30 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organics were washed with brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 70:30 hexane-EtOAc as eluent gave 4-aryl *N*-PMP pyrrolidone **215** (225 mg, 20%, 98:2 er by CSP-HPLC) as a brown solid, $[\alpha]_D$ +7.25 (*c* 1.0, $CHCl_3$).

Lab book reference: **SMc6-513**

4-(3-(1*H*-Pyrazol-1-yl)phenyl)-1-(4-methoxyphenyl)pyrrolidin-2-one (*R*)-218

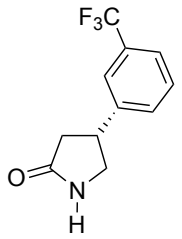


(*R*)-**218**

Using general procedure L, 4-BF_3K *N*-PMP pyrrolidone (*S*)-**192** (89 mg, 0.3 mmol, 1.0 eq., 98:2 er by CSP-HPLC) and 1-(3-bromophenyl)-1*H*-pyrazole (96 mg, 0.45 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica using 65:35 hexane-EtOAc gave 4-aryl *N*-PMP pyrrolidone (*R*)-**218** (40 mg, 40%, 97:3 er by CSP-HPLC) as an orange oil; $[\alpha]_D$ +7.35 (*c* 1.0 in $CHCl_3$); CSP-HPLC: CHIRALPAK® IG (75:25 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**218** 69.7 min, (*R*)-**218** 74.1 min.

Lab book reference: **SMc6-470**

4-(3-(trifluoromethyl)phenyl)pyrrolidin-2-one (*R*)-249

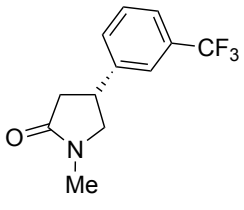


(*R*)-**249**

Cerium^{IV} ammonium nitrate (11 mL of a 0.16 M solution in water, 1.83 mmol, 3.0 eq.) was added to a stirred solution of 4-aryl *N*-PMP pyrrolidone (*R*)-**215** (198 mg, 0.61 mmol, 1.0 eq.) in MeCN (12 mL, 0.05 M) at 0 °C. The resulting solution was stirred at 0 °C for 30 min. After being allowed to warm to rt, water (20 mL) and EtOAc (20 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using EtOAc as eluent gave 4-aryl *N*-H pyrrolidone (*R*)-**249** (120 mg, 86%) as a brown solid, $[\alpha]_D$ –24.17 (*c* 1.0, $CHCl_3$).

Lab book reference: **SMc6-514**

1-Methyl-4-(3-(trifluoromethyl)phenyl)pyrrolidin-2-one (*R*)-269



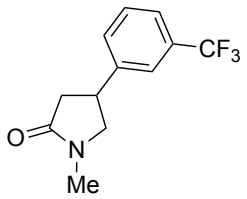
(*R*)-**269**

A solution of 4-aryl *N*-H pyrrolidone (*R*)-**249** (102 mg, 0.45 mmol, 1.0 eq.) in dry THF (2.25 mL, 0.2 M) was added dropwise to a stirred suspension of NaH (60 wt% in mineral oil, 36 mg, 0.9 mmol, 2.0 eq.) at 0 °C and stirred at 0 °C for 30 min. Then,

MeI (0.14 mL, 2.25 mmol, 5.0 eq.) was added at 0 °C and the suspension was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was quenched with brine (10 mL) and EtOAc (10 mL) was added and the two layers separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a mixture of the crude product and mineral oil. The crude product was dissolved in acetonitrile (10 mL), hexane (10 mL) was added and the two layers separated. The acetonitrile layer was extracted with hexane (3 x 10 mL) and the acetonitrile was evaporated under reduced pressure to give 4-aryl *N*-Me pyrrolidone (*R*)-**269** (104 mg, 95%) as a colourless oil, IR (ATR) 1692 (C=O), 1500, 1121, 805, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56-7.38 (m, 4H, Ar), 3.79 (dd, *J* = 10.0, 8.5 Hz, 1H, NCH), 3.64 (dddd, *J* = 8.5, 8.5, 8.5, 7.0 Hz, 1H, CHAr), 3.42 (dd, *J* = 10.0, 7.0 Hz, 1H, NCH), 2.92 (s, 3H, NMe), 2.85 (dd, *J* = 17.0, 8.5 Hz, 1H, CH), 2.53 (dd, *J* = 17.0, 8.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.5 (C=O), 143.6 (*ipso*-Ar), 131.3 (q, *J* = 32.0 Hz, *ipso*-Ar), 130.2 (Ar), 129.6 (Ar), 124.1 (q, *J* = 4.0 Hz, Ar), 124.1 (q, *J* = 272.0 Hz, CF_3), 123.80 (q, *J* = 4.0 Hz, Ar), 56.5 (NCH_2), 38.8 (CH_2), 37.1 (CHAr), 29.8 (NMe); HRMS (ESI) *m/z* calcd for $C_{12}H_{12}F_3NO$ $(M + Na)^+$ 266.0763, found 266.0755 (+ 2.1 ppm error); $[\alpha]_D$ – 27.91 (*c* 1.0, $CHCl_3$). Spectroscopic data consistent with those reported in the literature.[170]

Lab book reference: **SMc6-515**

1-methyl-4-(3-(trifluoromethyl)phenyl)pyrrolidin-2-one 269



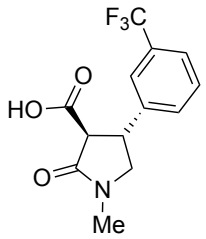
269

A solution of 4-aryl *N*-H pyrrolidone **249** (145 mg, 0.63 mmol, 1.0 eq.) in dry THF (3.5 mL, 0.2 M) was added dropwise to a stirred suspension of NaH (60 wt% in mineral oil, 51 mg, 1.27 mmol, 2.0 eq.) at 0 °C and stirred at 0 °C for 30 min. Then, MeI (0.2 mL, 3.16 mmol, 5.0 eq.) was added at 0 °C and the suspension was allowed to warm

to rt and stirred at rt for 16 h. The reaction mixture was quenched with brine (10 mL) and EtOAc (10 mL) was added and the two layers separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a mixture of the crude product and mineral oil. The crude product was dissolved in acetonitrile (10 mL) and hexane (10 mL) was added and the two layers separated. The acetonitrile layer was extracted with hexane (3 x 10 mL) and the acetonitrile was evaporated under reduced pressure to give 4-aryl *N*-Me pyrrolidone **269** (140 mg, 92%) as a colourless oil.

Lab book reference: **SMc6-511**

1-Methyl-2-oxo-4-(3-(trifluoromethyl)phenyl)pyrrolidine-3-carboxylic acid (*S*,*R*)-268



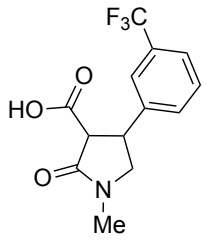
(*S*,*R*)-**268**

n-BuLi (0.52 mL of a 1.6 M solution in hexanes, 0.83 mmol, 2.3 eq.) was added to a stirred solution of diisopropylamine (0.13 mL, 0.92 mmol, 2.53 eq.) in THF (4 mL, 0.1 M) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 2 min. Then, 4-aryl *N*-Me pyrrolidone (*R*)-**269** (88 mg, 0.36 mmol, 1.0 eq.) was added and the resulting solution was stirred at –78 °C for 10 min. Then, trimethylchloroformate (0.11 mL, 1.44 mmol, 4.0 eq.) was added and the resulting solution was stirred at –78 °C for 4 h. The solution was allowed to warm to rt and the reaction was quenched with saturated $NH_4Cl_{(aq)}$ (1 mL). Water (10 mL) and CH_2Cl_2 (10 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 x 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 40:60 hexane-EtOAc as eluent gave 4-aryl pyrrolidone ester (*S*,*R*)-**270** as

a mixture with unknown impurities. The impure mixture of 4-aryl pyrrolidone ester (*S*,*R*)-**270** was dissolved in MeOH (0.9 mL) and water (0.3 mL). LiOH•H_2O (31 mg, 0.72 mmol, 3.0 eq.) was added and the resulting solution was stirred at rt for 1 h. Then, the reaction mixture was adjusted to pH 1 by addition of 1 M HCl (2 mL), water (10 mL) and EtOAc (10 mL) were added and the two layers separated. The aqueous layer was extracted with EtOAc (5 x 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give 4-aryl pyrrolidone acid (*S*,*R*)-**268** (60 mg, 58%) as a white solid, mp 90-92 °C (lit.,[176] 93.1 °C); IR (ATR) 2931, 1732 (C=O acid), 1670 (C=O amide), 1497, 1328, 1261, 1122 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.75 (s, 1H, Ar), 7.71-7.56 (m, 3H, Ar), 3.94 (ddd, *J* = 10.0, 9.5, 9.0 Hz, 1H, CHAr), 3.73 (dd, *J* = 9.0, 9.0 Hz, 1H, NCH), 3.64 (d, *J* = 10.0 Hz, 1H, CH), 3.39 (dd, *J* = 9.5, 9.5 Hz, 1H, NCH), 2.80 (s, 3H, NMe); ^{13}C NMR (100.6 MHz, $(CD_3)_2SO$) δ 170.9 (C=O), 168.7 (C=O), 141.6 (*ipso*-Ar), 131.7 (Ar), 129.8 (Ar), 129.4 (q, *J* = 32.0 Hz, *ipso*-Ar), 125.5 (q, *J* = 273.0, CF_3), 124.16 (q, *J* = 4.0, Ar), 124.0 (q, *J* = 4.0, Ar), 55.3 (CH), 53.4 (NCH_2), 41.7 (CHAr), 29.38 (NMe); HRMS ESI *m/z* calcd for $C_{13}H_{11}F_3NO_3$ $(M - H)^-$ 242.0798, found 242.0793 (+ 1.2 ppm error), $[\alpha]_D$ –29.9 (*c* 1.0, $CHCl_3$). Spectroscopic data consistent with 1-Methyl-2-oxo-4-(3-(trifluoromethyl)phenyl)pyrrolidine-3-carboxylic acid (3*S*,4*S*)-**268** reported in the literature.[176]

Lab book reference: **SMc6-522**

1-Methyl-2-oxo-4-(3-(trifluoromethyl)phenyl)pyrrolidine-3-carboxylic acid 268



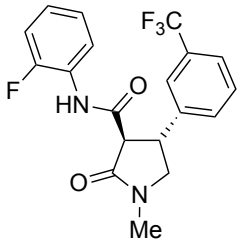
268

n-BuLi (0.56 mL of a 1.6 M solution in hexanes, 0.89 mmol, 2.3 eq.) was added to a stirred solution of Diisopropylamine (0.14 mL, 0.99 mmol, 2.53 eq.) in THF (4 mL, 0.1 M) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 2 min. Then, 4-aryl *N*-Me pyrrolidone **269** (94 mg, 0.39 mmol, 1.0 eq.) was added and the

resulting solution was stirred at –78 °C for 10 min. Then, trimethylchloroformate (0.12 mL, 1.56 mmol, 4.0 eq.) was added and the resulting solution was stirred at –78 °C for 4 h. The solution was allowed to warm to rt and the reaction was quenched with saturated $NH_4Cl_{(aq)}$ (1 mL). Water (10 mL) and CH_2Cl_2 (10 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 x 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 40:60 hexane-EtOAc as eluent gave 4-aryl pyrrolidone ester **270** as a mixture with unknown impurities. The impure mixture of 4-aryl pyrrolidone ester **270** was dissolved in MeOH (1.35 mL) and water (0.45 mL). LiOH•H_2O (45 mg, 1.07 mmol, 3.0 eq.) was added and the resulting solution was stirred at rt for 1 h. Then, the reaction mixture was adjusted to pH 1 by addition of 1 M HCl (2 mL) and water (10 mL) and EtOAc (10 mL) were added and the two layers separated. The aqueous layer was extracted with EtOAc (5 x 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give 4-aryl pyrrolidone acid **268** (95 mg, 85%).

Lab book reference: **SMc6-521**

(3*R*,4*R*)-*N*-(2-fluorophenyl)-1-methyl-2-oxo-4-(3-(trifluoromethyl)phenyl)pyrrolidine-3-carboxamide (*R*,*R*)-Tetflupyrolimet



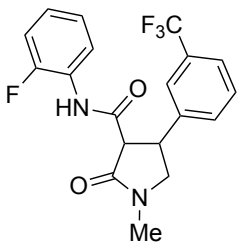
(*R*,*R*)-Tetflupyrolimet

Et_3N (58 µL, 0.42 mmol, 3.0 eq.) was added dropwise to a stirred solution of 4-aryl pyrrolidone acid (*R*,*R*)-**268** (43 mg, 0.14 mmol, 1.0 eq.) in CH_2Cl_2 (1.2 mL, 0.1 M) at rt. Then, 2-Fluoroaniline (27 µL, 0.28 mmol, 2.0 eq.) was added and the resulting solution stirred at rt for 16 h. Water (5 mL) and CH_2Cl_2 (5 mL) were added and two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organics 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 using 60:40 hexane-EtOAc as eluent gave (*R*,*R*)-Tetflupyrolimet (51 mg, 96%, 97:3 er by CSP-HPLC) as a white crystalline solid, R_F (60:40 hexane-EtOAc) 0.1; mp 125-127 (lit., for (*S*,*S*)-Tetflupyrolimet,[139] 116-120 °C; IR (ATR) 1703 (C=O), 1693 (C=O), 1512, 1490, 1328, 1203 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H, NH), 8.26-8.17 (m, 1H, Ar), 7.64-7.44 (m, 4H, Ar), 7.12-6.96 (m, 3H, Ar), 4.17 (ddd, *J* = 9.5, 9.5, 9.0 Hz, 1H, CHAr), 3.80 (dd, *J* = 9.5, 9.5 Hz, 1H, NCH), 3.64 (d, *J* = 9.0 Hz, 1H, CH), 3.45 (dd, *J* = 10.0, 8.0 Hz, 1H, NCH), 3.00 (s, 3H, NMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.5 (C=O), 165.2 (C=O), 152.9 (d, *J* = 245.0 Hz, *ipso*-Ar), 142.6 (*ipso*-Ar), 131.4 (q, *J* = 32.5 Hz, *ipso*-Ar), 131.3 (Ar), 129.6 (Ar), 126.2 (d, *J* = 10.5 Hz, *ipso*-Ar), 124.5 (d, *J* = 7.5 Hz, Ar), 124.4 (d, *J* = 3.5 Hz, Ar), 124.3 (q, *J* = 3.5 Hz, Ar), 124.2 (q, *J* = 4.0 Hz, Ar), 124.1 (q, *J* = 273.0, CF_3), 121.8 (Ar), 115.1 (d, *J* = 19.0, Ar), 54.7 (NCH_2), 54.7 (CH), 39.1 (CHAr), 30.3 (NMe); ^{19}F (375 MHz, $CDCl_3$) δ -62.4, -129.5; HRMS (ESI) *m/z* calcd for $C_{19}H_{16}F_4N_2O_2$ $(M + H)^+$ 381.1121, found 381.1223 (–0.5 ppm error); $[\alpha]_D$ –123.89 (*c* 1.0, $CHCl_3$) [lit.,[139] $[\alpha]_D$ +22.5 (c 0.9 in $CHCl_3$), for (*S*,*S*)-Tetflupyrolimet, 99:1 er]; CSP-HPLC: CHIRALPAK® ADH (70:30 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*R,R*)-Tetflupyrolimet 5.95 min, (*S,S*)-Tetflupyrolimet 7.70 min. Spectroscopic data consistent with (*S*,*S*)-Tetflupyrolimet reported in the literature.[139]

Lab book reference: **SMc6-524**

_N_-(2-Fluorophenyl)-1-methyl-2-oxo-4-(3-(trifluoromethyl)phenyl)pyrrolidine-3-carboxamide *rac*-Tetflupyrolimet



rac-Tetflupyrolimet

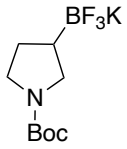
Et_3N (40 µL, 0.3 mmol, 3.0 eq.) was added dropwise to a stirred solution of 4-aryl pyrrolidone acid *rac*-**268** (29 mg, 0.1 mmol, 1.0 eq.) in CH_2Cl_2 (1 mL, 0.1 M) at rt. Then, 2-Fluoroaniline (19 µL, 0.2 mmol, 2.0 eq.) was added and the resulting solution

stirred at rt for 16 h. Water (5 mL) and CH_2Cl_2 (5 mL) were added and two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organics 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 using 70:30 hexane-EtOAc as eluent gave *rac*-Tetflupyrolimet (38 mg, 87%) as a white crystalline solid.

Lab book reference: **SMc6-520**

5.6 Experimental Procedures for Chapter 4

Potassium(1-tert-butoxycarbonylpyrrolidin-3-yl)-trifluoroborate 50



50

BH_3•Me_2S (3.6 mL of a 2M solution in THF, 7.1 mmol, 1.2 eq.) was added to a stirred solution of *N*-Boc 3-pyrroline (1 g, 5.9 mmol, 1.0 eq.) in THF (15 mL) in a flame-dried round-bottomed flask at 0 °C under N_2. The resulting solution was allowed to warm to rt and stirred at rt for 1 h. Then, the mixture was cooled to 0 °C and a solution of pinacol (2.8 g, 24 mmol, 4.0 eq.) in THF (5 mL) was added. After being allowed to warm to rt, the mixture was stirred at rt for 1 h. Then, $MgSO_4$ (7 g, 59 mmol, 10.0 eq.) was added and the mixture was stirred at rt for 16 h. A solution of saturated $NH_4Cl_{(aq)}$/H_2O (2:1, 30 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The crude product was dissolved in MeOH (12 mL) and saturated $KHF_{2(aq)}$ (3.3 M, 29.5 mmol, 5.0 eq.) was added. The resulting mixture was stirred at rt for 1 h and then the solvent was evaporated under reduced pressure. Then, the crude product was dissolved in the minimum amount of hot acetone and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give a white solid. Pentane-Et_2O (2:1, 50 mL) was added and the resulting mixture was stirred at rt for 1 h. The solids were collected by filtration to give 3-BF_3K pyrrolidine **50** (790 mg, 48%) as a white solid, mp 198-201 °C (lit.,[3] 195-199 °C); IR (ATR) 1686 (C=O), 1420, 1281, 1118, 935; ^{1}H NMR (400 MHz, d_6-DMSO) δ 3.22 (dd, J = 9.0, 9.0 Hz, 1H, NCH), 3.17-3.09 (m, 1H, NCH), 2.97-2.87 (m, 1H, NCH), 2.87-2.75 (m, 1H, NCH), 1.66-1.55 (m, 1H, CH), 1.51-1.41 (m, 1H, CH), 1.37 (s, 9H, $OCMe_3$), 0.77 (br s, 1H, BCH); ^{13}C NMR (101 MHz, d_6-DMSO) (rotamers) δ 153.8 (C=O), 153.7 (C=O), 77.15 ($OCMe_3$), 77.10 ($OCMe_3$), 49.9 (NCH_2), 49.5 (NCH_2), 47.4 (NCH_2), 47.2 (NCH_2), 28.7 (CH_2), 28.4 (CMe_3), 27.9 (CH_2) (BCH resonance not resolved); δ ^{11}B NMR (128 MHz, d_6-DMSO) δ 3.04; ^{19}F NMR (375 MHz, DMSO-d_6) –142.3; HRMS (ESI) *m/z* calcd for

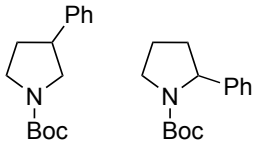
$C_9H_{16}BF_3NO_2$ M^- 238.1232, found 238.1232 (+0.4 ppm error). Spectroscopic data consistent with those reported in the literature.[4]

Lab book reference: **SMc6-303-1**

BH_3•Me_2S (18 mL of a 2M solution in THF, 35.4 mmol, 1.2 eq.) was added to a stirred solution of *N*-Boc 3-pyrroline (5 g, 29.5 mmol, 1.0 eq.) in THF (70 mL, 0.3 M) in a flame-dried round-bottomed flask at 0 °C under N_2. The resulting solution was allowed to warm to rt and stirred at rt for 1 h. Then, the mixture was cooled to 0 °C and a solution of pinacol (14 g, 118 mmol, 4.0 eq.) in THF (30 mL) was added. After being allowed to warm to rt, the mixture was stirred at rt for 1 h. Then, $MgSO_4$ (36 g, 300 mmol, 10.0 eq.) was added and the mixture was stirred at rt for 16 h. A solution of saturated $NH_4Cl_{(aq)}$/H_2O (2:1, 120 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. The crude product was dissolved in MeOH (60 mL) and saturated $KHF_{2(aq)}$ (3.3 M, 148 mmol, 5.0 eq.) was added. The resulting mixture was stirred at rt for 1 h and then the solvent was evaporated under reduced pressure. Then, the crude product was dissolved in the minimum amount of hot acetone and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give a white solid. Pentane-Et_2O (2:1, 150 mL) was added and the resulting mixture was stirred at rt for 1 h. The solids were collected by filtration to give 3-BF_3K pyrrolidine **50** (2.6 g, 33%) as a white solid.

Lab book reference: **SMc5-305-1**

tert-Butyl 3-phenylpyrrolidine-1-carboxylate 286 and _tert_-butyl 2-phenylpyrrolidine-1-carboxylate 124



286 **124**

3-BF_3K Pyrrolidine **50** (208 mg, 0.75 mmol, 1.5 eq.), $Pd(OAc)_2$ (11 mg, 50 μmol, 0.10 eq.), cataCXium A (36 mg, 100 μmol, 0.20 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 3.0 eq.) and 1,3,5-trimethoxybenzene (42 mg, 0.25 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (52 μL, 0.5 mmol, 1.0 eq.), degassed toluene (0.70 mL) and water (90 μL, 5.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using hexane to 80:10:10 hexane-EtOAc-toluene as eluent gave a 75:25 mixture (by ^1H NMR spectroscopy) of 3-phenyl pyrrolidine **286** and 2-phenyl pyrrolidine **124** (17 mg i.e. 13 mg (11%) of **286**; 4 mg (3%) of **124**) as a colourless oil, R_F (70:30 hexane-EtOAc) 0.14; IR (ATR) 1694 (C=O), 1403, 1165, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (75:25 mixture of 3-phenyl pyrrolidine **286** and 2-phenyl pyrrolidine **124**; 50:50 mixture of rotamers for 3-phenyl pyrrolidine **286**; 70:30 mixture of rotamers for 2-Ar pyrrolidine **124**) δ ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.11 (m, 5H, Ph), 5.04-4.87 (m, 0.08H, CHAr), 4.83-4.65 (m, 0.17H, CHAr), 3.90-3.73 (m, 0.75H, NCH), 3.69-3.49 (m, 1.25H, NCH), 3.47-3.21 (m, 2.25H, NCH), 2.39-2.19 (m, 1H, CH), 2.05-1.77 (m, 1.5H, CH), 1.53-1.39 (m, 7.5H), 1.17 (s, 1.5H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.6 (C=O), 145.2 (*ipso*-$Ar_{[2\text{-}Ar]}$), 141.5 (*ipso*-Ar), 128.7 (Ar), 128.4 (Ar), 128.2 (Ar), 127.2 (Ar), 126.9 (Ar), 126.8 (Ar), 126.6 (Ar), 125.6 (Ar), 79.3 ($OCMe_3$), 52.7 (NCH_2), 51.9 (NCH_2), 47.4 ($NCH_{2[2\text{-}Ar]}$), 47.2 ($NCH_{2[2\text{-}Ar]}$), 46.1 (NCH_2), 45.7 (NCH_2), 44.4 (CHAr), 43.5 (CHAr), 36.1 ($CH_{2[2\text{-}Ar]}$), 33.5 (CH_2), 32.6 (CH_2), 28.7 (CMe_3), 28.2 ($CMe_{3[2\text{-}Ar]}$), 23.5 ($CH_{2[2\text{-}Ar]}$), 23.3 ($CH_{2[2\text{-}Ar]}$); HRMS (ESI) *m/z* calcd for $C_{15}H_{21}NO_2$ $(M + H)^+$ 248.1645, found 248.1642 (+1.2 ppm error). Spectroscopic data for 3-phenyl pyrrolidine **286** consistent with those reported in the literature.[160] Spectroscopic data for 2-phenyl pyrrolidine **124** consistent with those reported in the literature.[177]

Lab book reference: **SMc5-309**

Experimental data for Table 4.1: Validation of reaction scale – SMCC of 3-BF3K pyrrolidine 50 with bromobenzene

3-BF_3K Pyrrolidine **50** (83 mg, 0.3 mmol, 1.5 eq.), $Pd(OAc)_2$ (4.5 mg, 20 µmol, 0.10 eq.), cataCXium A (14 mg, 40 µmol, 0.20 eq.), Cs_2CO_3 (196 mg, 0.6 mmol, 3.0 eq.) and 1,3,5-trimethoxybenzene (18 mg, 0.1 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (21 µL, 0.2 mmol, 1.0 eq.), degassed toluene (0.29 mL) and water (36 µL, 2.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 23% conversion to 3-phenyl pyrrolidine **286**).

Lab book reference: **SMc5-322**

3-BF_3K Pyrrolidine **50** (42 mg, 0.15 mmol, 1.5 eq.), $Pd(OAc)_2$ (2.2 mg, 10 µmol, 0.10 eq.), cataCXium A (7 mg, 20 µmol, 0.20 eq.), Cs_2CO_3 (98 mg, 0.3 mmol, 3.0 eq.) and 1,3,5-trimethoxybenzene (10.4 mg, 0.05 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (11 µL, 0.1 mmol, 1.0 eq.), degassed toluene (0.14 mL) and water (18 µL, 1.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 1% conversion to 3-phenyl pyrrolidine **286**).

Lab book reference: **SMc5-323**

3-BF_3K Pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 0.10 eq.), cataCXium A (22 mg, 60 µmol, 0.20 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) and 1,3,5-trimethoxybenzene (28.1 mg, 0.17 mmol, 0.51 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (31 µL, 0.3 mmol, 1.0 eq.), degassed toluene (0.86 mL) and water (54 µL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 14% conversion to 3-phenyl pyrrolidine **286**).

Lab book reference: **SMc5-325**

3-BF_3K Pyrrolidine **50** (83 mg, 0.3 mmol, 1.5 eq.), $Pd(OAc)_2$ (4.5 mg, 20 µmol, 0.10 eq.), cataCXium A (14 mg, 40 µmol, 0.20 eq.), Cs_2CO_3 (196 mg, 0.6 mmol, 3.0 eq.) and 1,3,5-trimethoxybenzene (18 mg, 0.1 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (21 µL, 0.2 mmol, 1.0 eq.), degassed toluene (0.57 mL) and water (36 µL, 2.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 19% conversion to 3-phenyl pyrrolidine **286**).

Lab book reference: **SMc5-326**

3-BF_3K Pyrrolidine **50** (42 mg, 0.15 mmol, 1.5 eq.), $Pd(OAc)_2$ (2.2 mg, 10 µmol, 0.10 eq.), cataCXium A (7 mg, 20 µmol, 0.20 eq.), Cs_2CO_3 (98 mg, 0.3 mmol, 3.0 eq.) and 1,3,5-trimethoxybenzene (10.7 mg, 0.05 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum

and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (11 μL, 0.1 mmol, 1.0 eq.), degassed toluene (0.29 mL) and water (18 μL, 1.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 12% conversion to 3-phenyl pyrrolidine **286**).

Lab book reference: **SMc5-327**

Experimental data for Table 4.2: Validation of reaction set-up – SMCC of 3-BF3K pyrrolidine 50 with bromobenzene

3-BF_3K Pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 0.10 eq.), cataCXium A (22 mg, 60 μmol, 0.20 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) and 1,3,5-trimethoxybenzene (26.2 mg, 0.15 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (31 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.42 mL) and water (54 μL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 11% conversion to 3-phenyl pyrrolidine **286**).

Lab book reference: **SMc5-318-5**

3-BF_3K Pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 0.10 eq.), cataCXium A (22 mg, 60 μmol, 0.20 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) and 1,3,5-trimethoxybenzene (26.2 mg, 0.15 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (31 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.42 mL)

and water (54 µL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 14% conversion to 3-phenyl pyrrolidine **286**).

Lab book reference: **SMc5-318-1**

3-BF_3K Pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 0.10 eq.), cataCXium A (22 mg, 60 µmol, 0.20 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) and 1,3,5-trimethoxybenzene (24.2 mg, 0.14 mmol, 0.48 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (31 µL, 0.3 mmol, 1.0 eq.), degassed toluene (0.42 mL) and water (54 µL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 14% conversion to 3-phenyl pyrrolidine **286**).

Lab book reference: **SMc5-318-2**

3-BF_3K Pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 0.10 eq.), cataCXium A (22 mg, 60 µmol, 0.20 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) and 1,3,5-trimethoxybenzene (25.8 mg, 0.15 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (31 µL, 0.3 mmol, 1.0 eq.), degassed toluene (0.42 mL) and water (54 µL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating

block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 9% conversion to 3-phenyl pyrrolidine **286**).

Lab book reference: **SMc5-318-3**

3-BF_3K Pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 0.10 eq.), cataCXium A (22 mg, 60 μmol, 0.20 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) and 1,3,5-trimethoxybenzene (25.9 mg, 0.15 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (31 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.42 mL) and water (54 μL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 16% conversion to 3-phenyl pyrrolidine **286**).

Lab book reference: **SMc5-318-4**

Experimental data for Table 4.3: DOE full factorial design results for 3-BF3K pyrrolidine 50 with bromobenzene

Table 5.3: SMCC DOE screening of 3-BF_3K pyrrolidine **50** using General Procedure G

Experiment number[a]	Water / μL	$Pd(OAc)_2$ / mg	cataCXium A / mg	Cs_2CO_3 / mg	**50** / mg	TMB / mg	Conversion of **286** / %[b]
1	18	2.5	3.6	32.3	27.4	7.9	9
2	180	2.4	3.6	32.6	27.4	7.7	54
3	18	2.2	18	32.2	27.3	7.8	1
4	180	2.3	18	32.2	27.3	8.1	0
5	18	2.4	3.6	162.6	27.3	7.7	57
6	180	2.3	3.6	162.5	27.5	7.7	42
7	18	2.2	18	162.7	27.6	7.7	11
8	180	2.3	18	162.5	27.4	8	2
9	18	2.3	3.6	32.7	41.1	7.5	7
10	180	2.2	3.6	32.2	41.3	8	0
11	18	2.3	18	32.1	41.1	7.7	1

Experiment number[a]	Water / µL	$Pd(OAc)_2$ / mg	cataCXium A / mg	Cs_2CO_3 / mg	**50** / mg	TMB / mg	Conversion of **286** / %[b]
12	180	2.4	18	32.9	41.1	8.1	1
13	18	2.2	3.6	162.6	41.2	7.7	22
14	180	2.3	3.6	162.9	41.5	7.9	29
15	18	2.3	18	162.8	41.2	7.9	14
16	180	2.3	18	162.6	41.1	7.7	11
17	100	2.4	11	97.8	34.3	7.8	4
18	100	2.2	11	97.7	34.3	7.5	6
19	100	2.2	11	97.5	34.2	7.7	7

[a] Lab book reference is in the form of "20241008_interactions2_3BF_3KNBocPyrrolidine_**Experiment number**" where experiment number corresponds to the value in the respective cell; [b] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard;

3-BF_3K Pyrrolidine **50** (83 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 0.10 eq.), cataCXium A (11 mg, 30 µmol, 0.10 eq.) and Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (32 µL, 0.3 mmol, 1.0 eq.), degassed toluene (0.86 mL, 0.35 M) and water (54 µL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using hexane to 80:10:10 hexane-EtOAc-toluene as eluent gave a 75:25 mixture (by ^1H NMR spectroscopy) of 3-phenyl pyrrolidine **286** and 2-phenyl pyrrolidine **124** (25 mg i.e. 19 mg (26%) of **286**; 6 mg (8%) of **124**) as a colourless oil.

Lab book reference: **SMc5-335**

3-BF_3K Pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 0.10 eq.), cataCXium A (11 mg, 30 µmol, 0.10 eq.) and Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (32 µL, 0.3 mmol, 1.0 eq.), degassed toluene (0.86 mL, 0.35 M) and water (54 µL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using hexane to 80:10:10 hexane-EtOAc-toluene as eluent gave a 75:25 mixture (by ^{1}H NMR spectroscopy) of 3-phenyl pyrrolidine **286** and 2-phenyl pyrrolidine **124** (41 mg i.e. 29 mg (41%) of **286**; 12 mg (14%) of **124**) as a colourless oil.

Lab book reference: **SMc5-336**

Experimental data for Table 4.4: SMCC of 3-BF3K pyrrolidine 50 with different cataCXium A : $Pd(OAc)_2$ ratio

3-BF_3K Pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 0.10 eq.), cataCXium A (22 mg, 60 μmol, 0.20 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and 1,3,5-trimethoxybenzene (29 mg, 0.17 mmol, 0.57 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (32 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.86 mL, 0.35 M) and water (54 μL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using hexane to 80:10:10 hexane-EtOAc-toluene as eluent gave a 75:25 mixture (by ^{1}H NMR spectroscopy) of 3-phenyl pyrrolidine **286** and 2-phenyl pyrrolidine **124** (27 mg i.e. 20 mg (27%) of **286**; 7 mg (10%) of **124**) as a colourless oil.

Lab book reference: **SMc5-347**

3-BF_3K Pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 μmol, 0.10 eq.), cataCXium A (32 mg, 90 μmol, 0.30 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.)

and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (32 µL, 0.3 mmol, 1.0 eq.), degassed toluene (0.86 mL, 0.35 M) and water (54 µL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using hexane to 80:10:10 hexane-EtOAc-toluene as eluent gave a 75:25 mixture (by ^1H NMR spectroscopy) of 3-phenyl pyrrolidine **286** and 2-phenyl pyrrolidine **124** (24 mg i.e. 17 mg (24%) of **286**; 6 mg (8%) of **124**) as a colourless oil.

Lab book reference: **SMc5-348**

3-BF_3K Pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 0.10 eq.), cataCXium A (43 mg, 120 µmol, 0.40 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and 1,3,5-trimethoxybenzene (27.5 mg, 0.16 mmol, 0.54 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (32 µL, 0.3 mmol, 1.0 eq.), degassed toluene (0.86 mL, 0.35 M) and water (54 µL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using hexane to 80:10:10 hexane-EtOAc-toluene as eluent gave a 75:25 mixture (by ^1H

NMR spectroscopy) of 3-phenyl pyrrolidine **286** and 2-phenyl pyrrolidine **124** (13 mg i.e. 7 mg (10%) of **286**; 3 mg (4%) of **124**) as a colourless oil.

Lab book reference: **SMc5-349**

3-BF_3K Pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 0.10 eq.), cataCXium A (54 mg, 150 µmol, 0.50 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and 1,3,5-trimethoxybenzene (30 mg, 0.18mmol, 0.6 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (32 µL, 0.3 mmol, 1.0 eq.), degassed toluene (0.86 mL, 0.35 M) and water (54 µL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using hexane to 80:10:10 hexane-EtOAc-toluene as eluent gave a 75:25 mixture (by ^1H NMR spectroscopy) of 3-phenyl pyrrolidine **286** and 2-phenyl pyrrolidine **124** (13 mg i.e. 7 mg (10%) of **286**; 3 mg (4%) of **124**) as a colourless oil.

Lab book reference: **SMc5-350**

Experimental data for Table 4.5: SMCC of 3-BF3K pyrrolidine 50 with different eq. of bromobenzene

3-BF_3K Pyrrolidine **50** (104 mg, 0.45 mmol, 1.25 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 0.10 eq.), cataCXium A (11 mg, 30 µmol, 0.10 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and 1,3,5-trimethoxybenzene (25.9 mg, 0.15 mmol, 0.5) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum

and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (32 µL, 0.3 mmol, 1.0 eq.), degassed toluene (0.86 mL, 0.35 M) and water (54 µL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using 95:5 hexane-EtOAc as eluent gave a 70:30 mixture (by ^1H NMR spectroscopy) of 3-phenyl pyrrolidine **286** and 2-phenyl pyrrolidine **124** (32 mg i.e. 22 mg (30%) of **286**; 10 mg (13%) of **124**) as a colourless oil.

Lab book reference: **SMc6-485**

3-BF_3K Pyrrolidine **50** (28 mg, 0.10 mmol, 1.0 eq.), $Pd(OAc)_2$ (2.3 mg, 10 µmol, 0.10 eq.), cataCXium A (3.5 mg, 10 µmol, 0.10 eq.), Cs_2CO_3 (163 mg, 0.5 mmol, 5.0 eq.) and 1,3,5-trimethoxybenzene (10.2 mg, 0.05 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (14 µL, 0.125 mmol, 1.25 eq.), degassed toluene (0.29 mL) and water (18 µL, 1.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure F and the reaction was analysed by GC (GC Method B, 28% conversion to 3-phenyl pyrrolidine **286**, 8% to 2-phenyl pyrrolidine **124**).

Lab book reference: **SMc5-390**

3-BF_3K Pyrrolidine **50** (88 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 0.10 eq.), cataCXium A (11 mg, 30 µmol, 0.10 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.)

and 1,3,5-trimethoxybenzene (25.9 mg, 0.15 mmol, 0.5) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (47 μL, 0.45 mmol, 1.5 eq.), degassed toluene (0.86 mL, 0.35 M) and water (54 μL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using hexane to 80:10:10 hexane-EtOAc-toluene as gave a 70:30 mixture (by ^{1}H NMR spectroscopy) of 3-phenyl pyrrolidine **286** and 2-phenyl pyrrolidine **124** (18 mg i.e. 13 mg (18%) of **286**; 5 mg (8%) of **124**) as a colourless oil.

Lab book reference: **SMc6-480**

Experimental data for Table 4.6: Screening of the SMCC of 3-BF3K pyrrolidine 50 with different ligands

Table 5.4: Screening of the SMCC of 3-BF_3K pyrrolidine **50** with different ligands using General Procedure M

Lab book reference	Ligand or Pd G3 precatalyst	Ligand / mg	TMB / mg	Conversion Of **286**/ %[a]	Conversion of **124**/ %[a]
SMc5-353	PAd_3	13	28	5	5
SMc5-354	P(*t*-Bu)$_3$.HBF_4	9	26	12	9
SMc5-355	APhos	8	28	12	9
SMc5-356	cataCXium A Pd G3	22	25	39	12

[a] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard;

Table 5.5: Screening of the SMCC of 3-BF_3K pyrrolidine **50** with different ligands using General Procedure N

Experiment number[a]	Ligand or Pd G3 precatalyst	Ligand / mg	$Pd(OAc)_2$ / mg	Cs_2CO_3 / mg	BF_3K salt **50** / mg	TMB / mg	Conversion of **286**/ %[b]	Conversion of **124**/ %[b]
1	cataCXium ABn	3.9	2.2	162.9	41.6	7.9	0	0
2	AlPhos	8.2	2.4	162.8	41.3	8.1	0	0
3	XPhos	4.8	2.2	162.6	41.1	7.9	7	8
4	SPhos	4.1	2.3	162.5	41.3	7.5	17	10
5	P(*t*-Bu)Ph_2	2.4	2.5	162.6	41.1	7.6	9	10
6	RuPhos	4.7	2.2	162.5	41.1	7.6	24	8
7	cataCXium A PintB	3.4	2.2	162.6	41.1	8	1	1
8	JackiePhos	8.0	2.4	162.6	41.1	7.7	3	1
9	cataCXium A	3.6	2.2	162.6	41.2	7.5	38	10
10	$P(Cy)_2$Biphenyl	3.5	2.3	162.6	41.3	8.4	3	3
11	DavePhos	3.9	2.3	162.6	41.2	7.6	4	5
12	Qphos	7.4	2.3	162.6	41.6	7.6	6	6
13	dppf	5.8	2.3	162.9	41.3	7.4	7	8

Experiment number[a]	Ligand or Pd G3 precatalyst	Ligand / mg	$Pd(OAc)_2$ / mg	Cs_2CO_3 / mg	BF_3K salt **50** / mg	TMB / mg	Conversion of **286**/ %[b]	Conversion of **124**/ %[b]
14	*rac*-BIDIME	3.3	2.3	162.7	41.1	7.5	11	11
15	CPhos	4.4	2.3	162.8	41.1	7.4	5	4
16	P(*t*-Bu)$_2$Biphenyl	3.0	2.3	162.6	41.2	7.7	0	1
17	*t*-BuBrettPhos	4.8	2.3	162.5	41.5	7.5	0	0
18	$P(Cy)_3$	2.8	2.3	162.6	41.3	7.5	6	14
19	*t*-BuXPhos Pd G3	7.9	2.3	162.7	42.6	7.9	0	0
20	MorDalPhos Pd G3	8.3	2.3	162.5	41.4	8	1	0

[a] Lab book reference is in the form of "3BF_3Kpyrrolidine_ligandscreen_**Experiment number***" where experiment number corresponds to the value in the respective cell; [b] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard;

3-BF_3K Pyrrolidine **50** (83 mg, 0.3 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 0.10 eq.), PAd_3 (13 mg, 30 µmol, 0.10 eq.) and Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (32 µL, 0.3 mmol, 1.0 eq.), degassed *o*-xylene (0.86 mL, 0.35 M) and water (54 µL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 140 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 4% conversion to 3-phenyl pyrrolidine **286**, 0% to 2-phenyl pyrrolidine **124**).

Lab book reference: **SMc6-504**

3-BF_3K Pyrrolidine **50** (55.4 mg, 0.2 mmol, 1.0 eq.), $Pd(OAc)_2$ (4.5 mg, 20 µmol, 0.10 eq.), cataCXium A (7 mg, 20 µmol, 0.10 eq.), Cs_2CO_3 (325.8 mg, 1.0 mmol, 5.0 eq.) and 1,3,5-trimethoxybenzene (16.1 mg, 0.1 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (21 µL, 0.3 mmol, 1.0 eq.), degassed *o*-xylene (0.57 mL, 0.35 M) and water (36 µL, 2.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 140 °C. The mixture was stirred at 1000-1200 rpm and heated at 140 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 15% conversion to 3-phenyl pyrrolidine **286**, 4% to 2-phenyl pyrrolidine **124**).

Lab book reference: **3-BF_3K_pyrrolidine_misc_7**

Experimental data for Table 4.7: Screening of the SMCC of 3-BF3K pyrrolidine 50 using different ratios of toluene : water while maintaining overall concentration

Table 5.6: Screening of the SMCC of 3-BF_3K pyrrolidine **50** with different volumes of toluene and water using General Procedure O

Lab book reference	Toluene / mL	Water / μL	$Pd(OAc)_2$ / mg	cataCXium A / mg	Cs_2CO_3 / mg	TMB / mg	Conversion of **286**/ %[a]	Conversion of **124**/ %[a]
3-pyrrolidine-misc-2	0.51	60	4.5	7.2	325.7	16.7	11	49
3-pyrrolidine-misc-3	0.50	70	4.4	7.3	325.7	16	9	41
3-pyrrolidine-misc-4	0.48	100	4.9	7.1	326	16.1	5	23
3-pyrrolidine-misc-5	0.43	140	4.4	7.1	325.6	16.1	7	31
3-pyrrolidine-misc-6	0.29	290	4.6	7.2	325.5	16.1	5	23

[a] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard;

Experimental data for: .

Table 4.8: Screening of the SMCC of 3-BF3K pyrrolidine 50 using different concentrations of toluene while maintaining equivalents of water

Table 5.7: Screening of the SMCC of 3-BF_3K pyrrolidine **50** with different volumes of toluene using General Procedure O

Lab book reference	Toluene / mL	Water / µL	$Pd(OAc)_2$ / mg	cataCXium A / mg	Cs_2CO_3 / mg	TMB / mg	Conversion of **286**/ %[a]	Conversion of **124**/ %[a]
3-pyrrolidine-misc-1	0.57	36	4.5	7.2	326	16.7	11	51
3-pyrrolidine-misc-11	2.0	36	4.4	7.1	326	15.9	7	29

[a] Yield determined by GC using 1,3,5-trimethoxybenzene as internal standard;

Experimental data for Table 4.9: Screening of the SMCC of 3-BF3K pyrrolidine 50 using different bases

3-BF_3K Pyrrolidine **50** (55.4 mg, 0.2 mmol, 1.0 eq.), $Pd(OAc)_2$ (4.5 mg, 20 μmol, 0.1 eq.), cataCXium A (7 mg, 20 μmol, 0.1 eq.), K_2CO_3 (138 mg, 1.0 mmol, 5.0 eq.) and 1,3,5-trimethoxybenzene (16.8 mg, 0.1 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (21 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.57 mL, 0.35 M) and water (36 μL, 2.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 140 °C. The mixture was stirred at 1000-1200 rpm and heated at 140 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 2% conversion to 3-phenyl pyrrolidine **286**, 0% to 2-phenyl pyrrolidine **124**).

Lab book reference: **3-pyrrolidine-misc-12**

3-BF_3K Pyrrolidine **50** (55.4 mg, 0.2 mmol, 1.0 eq.), $Pd(OAc)_2$ (4.5 mg, 20 μmol, 0.1 eq.), cataCXium A (7 mg, 20 μmol, 0.1 eq.), K_3PO_4 (212.3 mg, 1.0 mmol, 5.0 eq.) and 1,3,5-trimethoxybenzene (16.8 mg, 0.1 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (21 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.57 mL, 0.35 M) and water (36 μL, 2.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 140 °C. The mixture was stirred at 1000-1200 rpm and heated at 140 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 11% conversion to 3-phenyl pyrrolidine **286**, 8% to 2-phenyl pyrrolidine **124**).

Lab book reference: **3-pyrrolidine-misc-13**

3-BF_3K Pyrrolidine **50** (55.4 mg, 0.2 mmol, 1.0 eq.), $Pd(OAc)_2$ (4.5 mg, 20 µmol, 0.1 eq.), cataCXium A (7 mg, 20 µmol, 0.1 eq.), K_3PO_4 (168 mg, 1.0 mmol, 5.0 eq.) and 1,3,5-trimethoxybenzene (16.8 mg, 0.1 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (21 µL, 0.3 mmol, 1.0 eq.), degassed toluene (0.57 mL, 0.35 M) and water (36 µL, 2.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 140 °C. The mixture was stirred at 1000-1200 rpm and heated at 140 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 2% conversion to 3-phenyl pyrrolidine **286**, 0% to 2-phenyl pyrrolidine **124**).

Lab book reference: **3-pyrrolidine-misc-14**

Experimental data for Table 4.10: Screening of the SMCC of 3-BF3K pyrrolidine 50 using different loadings of palladium maintaining the cataCXium A : palladium ratio

3-BF_3K Pyrrolidine **50** (55.4 mg, 0.2 mmol, 1.0 eq.), $Pd(OAc)_2$ (2.25 mg, 10 µmol, 0.05 eq.), cataCXium A (3.6 mg, 10 µmol, 0.05 eq.), Cs_2CO_3 (325.8 mg, 1.0 mmol, 5.0 eq.) and 1,3,5-trimethoxybenzene (16.8 mg, 0.1 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (21 µL, 0.3 mmol, 1.0 eq.), degassed toluene (0.57 mL, 0.35 M) and water (36 µL, 2.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 140 °C. The mixture was stirred at 1000-1200 rpm and heated at 140 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by

GC (GC Method B, 24% conversion to 3-phenyl pyrrolidine **286**, 8% to 2-phenyl pyrrolidine **124**).

Lab book reference: **3-pyrrolidine-misc-15**

3-BF_3K Pyrrolidine **50** (55.4 mg, 0.2 mmol, 1.0 eq.), $Pd(OAc)_2$ (7 mg, 25 μmol, 0.25 eq.), cataCXium A (11 mg, 25 μmol, 0.25 eq.), Cs_2CO_3 (325.8 mg, 1.0 mmol, 5.0 eq.) and 1,3,5-trimethoxybenzene (16.8 mg, 0.1 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (21 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.57 mL, 0.35 M) and water (36 μL, 2.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 140 °C. The mixture was stirred at 1000-1200 rpm and heated at 140 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 35% conversion to 3-phenyl pyrrolidine **286**, 11% to 2-phenyl pyrrolidine **124**).

Lab book reference: **3-pyrrolidine-misc-16**

3-BF_3K Pyrrolidine **50** (55.4 mg, 0.2 mmol, 1.0 eq.), $Pd(OAc)_2$ (9 mg, 40 μmol, 0.40 eq.), cataCXium A (14 mg, 40 μmol, 0.40 eq.), Cs_2CO_3 (325.8 mg, 1.0 mmol, 5.0 eq.) and 1,3,5-trimethoxybenzene (16.8 mg, 0.1 mmol, 0.5 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and bromobenzene (21 μL, 0.3 mmol, 1.0 eq.), degassed toluene (0.57 mL, 0.35 M) and water (36 μL, 2.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 140 °C. The mixture was stirred at 1000-1200 rpm and heated at 140 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC

(GC Method B, 39% conversion to 3-phenyl pyrrolidine **286**, 12% to 2-phenyl pyrrolidine **124**).

Lab book reference: **3-pyrrolidine-misc-17**

Experimental data for Table 4.11: Screening of the SMCC of 3-BF3K pyrrolidine 50 using different aryl halides

3-BF_3K Pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 0.10 eq.), cataCXium A (11 mg, 30 µmol, 0.10 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and 1,3,5-trimethoxybenzene (22.9 mg, 0.14 mmol, 0.45 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and chlorobenzene (31 µL, 0.3 mmol, 1.0 eq.), degassed toluene (0.86 mL, 0.35 M) and water (54 µL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics 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 using hexane to 95:5 hexane-EtOAc as eluent gave a 80:20 mixture (by ^1H NMR spectroscopy) of 3-phenyl pyrrolidine **286** and 2-phenyl pyrrolidine **214** (46 mg i.e. 36 mg (49%) of **286**; 14 mg (14%) of **214**) as a colourless oil.

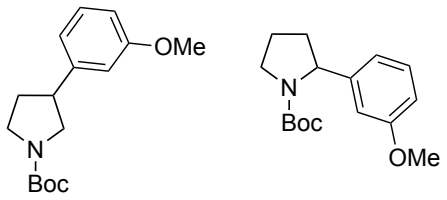
Lab book reference: **SMc6-484**

3-BF_3K Pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 0.10 eq.), cataCXium A (11 mg, 30 µmol, 0.50 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and 1,3,5-trimethoxybenzene (22.4 mg, 0.14 mmol, 0.45 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone

septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and iodobenzene (50 µL, 0.3 mmol, 1.0 eq.), degassed toluene (0.86 mL, 0.35 M) and water (54 µL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt the reaction was sampled using General Procedure E and the reaction was analysed by GC (GC Method B, 10% conversion to 3-phenyl pyrrolidine **286**, 4% to 2-phenyl pyrrolidine **124**).

Lab book reference: **SMc6-488**

tert-Butyl 3-(3-methoxyphenyl)pyrrolidine-1-carboxylate 304 and _tert_-butyl 2-(3-methoxyphenyl)pyrrolidine-1 carboxylate 305



304 **305**

3-BF_3K Pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 30 µmol, 0.10 eq.), cataCXium A (11 mg, 30 µmol, 0.10 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.) and 1,3,5-trimethoxybenzene (27.6 mg, 0.16 mmol, 0.55 eq.) were placed in a 7 mL screw cap vial. The vial was then sealed with a screw top cap with a PTFE/silicone septum and the headspace was purged with N_2 for 15 min. Then, the exit needle was removed and 2-bromoanisole (32 µL, 0.3 mmol, 1.0 eq.), degassed toluene (0.86 mL, 0.35 M) and water (54 µL, 3.0 mmol, 10.0 eq.) were added under N_2. The vial was removed from the nitrogen line (purge needle removed) and the vial was placed in a heating block preheated to 120 °C. The mixture was stirred at 1000-1200 rpm and heated at 120 °C (heater block temperature) for 20 h. After being allowed to cool to rt, water (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to

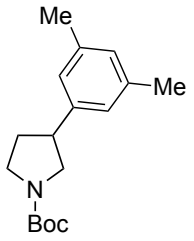
give the crude product. Purification by flash column chromatography on silica using 185:15 hexane-EtOAc as eluent gave a 75:25 mixture (by ^{1}H NMR spectroscopy) of 3-aryl pyrrolidine **304** and 2-aryl pyrrolidine **305** (38 mg i.e. 29 mg (46%) of **304**; 9 mg (11%) of **305**) as a yellow oil, R_F (185:15 hexane-EtOAc) 0.12; IR (ATR) 1691 (C=O), 1397, 1165, 1120, 1046, 876, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (75:25 mixture of 3-aryl pyrrolidine **304** and 2-aryl pyrrolidine **305**; 65:35 mixture of rotamers for 2-aryl pyrrolidine **305**) δ 7.25-7.14 (m, 1H, Ar), 6.85 (d, *J* = 7.5 Hz, 0.75H, Ar), 6.80-6.68 (m, 2.25H, Ar), 4.97-4.87 (m, 0.09H, CHAr), 4.81-4.66 (m, 0.16H, CHAr), 3.87-3.72 (m, 3.75H, OMe, NCH), 3.70-3.45 (m, 1.25H, NCH), 3.45-3.12 (m, 2.25H, NCH, CHAr), 2.33-2.17 (m, 1H, CH), 2.04-1.75 (m, 1.5H, CH), 1.51-1.42 (m, 7.5H, C*Me*$_3$), 1.27-1.13 (m, 1.5H, C*Me*$_3$); ^{13}C NMR (400 MHz, $CDCl_3$) (rotamers) δ 159.8 (C=O), 159.7 (C=O), 154.6 (*ipso*-Ar), 147.0 (*ipso*-Ar), 143.2 (*ipso*-Ar), 129.6 (Ar), 129.2 (Ar), 119.5 (Ar), 118.0 (Ar), 113.3 (Ar), 113.1 (Ar), 112.0 (Ar), 111.8 (Ar), 111.7 (Ar), 111.3 (Ar), 79.3 (O*C*Me$_3$), 61.4 (*C*HAr$_{[2\text{-}Ar]}$), 55.2 (OMe), 52.6 (NCH_2), 51.8 (NCH_2), 47.2 ($NCH_{2[2\text{-}Ar]}$), 46.0 (NCH_2), 45.7 (NCH_2), 44.3 (CHAr$_{[3\text{-}Ar]}$), 43.4 (CHAr$_{[3\text{-}Ar]}$), 36.0 (CH_2), 33.4 (CH_2), 32.5 (CH_2), 28.6 (C*Me*$_3$), 28.3 (C*Me*$_3$), 23.5 ($CH_{2[2\text{-}Ar]}$), 23.3 ($CH_{2[2\text{-}Ar]}$); HRMS (ESI) *m/z* calcd for $C_{16}H_{24}NO_3$ $(M + Na)^+$ 278.1751, found 278.1754 (–0.5 ppm error). Spectroscopic data for 3-aryl pyrrolidine **304** consistent with those reported in the literature.[160] Spectroscopic data for 2-aryl pyrrolidine **305** consistent with those reported in the literature.[177]

Lab book reference: **SMc6-486**

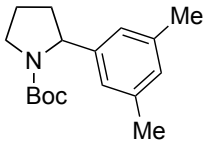
Using General Procedure P, 3-BF_3K pyrrolidine (125 mg, 0.45 mmol, 1.5 eq.) and 2-chloroanisole (37 μL, 0.3 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 185:15 hexane-EtOAc as eluent gave a 75:25 mixture (by ^{1}H NMR spectroscopy) of 3-aryl pyrrolidine **304** and 2-aryl pyrrolidine **305** (56 mg i.e. 42 mg (50%) of **304**; 14 mg (17%) of **305**) as a yellow oil

Lab book reference: **SMc6-487**

tert-Butyl 3-(3,5-dimethylphenyl)pyrrolidine-1-carboxylate 306 and tert-Butyl 2-(3,5-dimethylphenyl)pyrrolidine-1-carboxylate 307



306

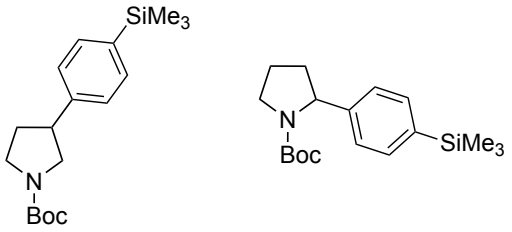


307

Using General Procedure P, 3-BF_3K pyrrolidine (125 mg, 0.45 mmol, 1.5 eq.) and 5-chloro-*m*-xylene (41 μL, 0.3 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 97:3 hexane-EtOAc as eluent gave an 85:15 mixture (by ^{1}H NMR spectroscopy) of 3-aryl pyrrolidine **306** and 2-aryl pyrrolidine **307** (30 mg i.e. 25 mg (30%) of **306**; 5 mg (6%) of **307**) as an orange oil, R_F (97:3 hexane-EtOAc) 0.1; IR (ATR) 1694 (C=O), 1606, 1400, 1166, 1129, 885 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (85:15 mixture of 3-aryl pyrrolidine **306** and 2-aryl pyrrolidine **307**; 65:35 mixture of rotamers for 2-aryl pyrrolidine **307**) δ 6.88 (s, 0.85H, Ar), 6.85 (s, 1.7H, Ar), 6.83 (s, 0.15H, Ar), 6.76 (s, 0.3H, Ar), 4.87 (m, 0.05H, CHAr), 4.68 (m, 0.1H, CHAr), 3.87-3.70 (m, 0.85H, NCH), 3.69-3.49 (m, 1.15H, NCH), 3.45-3.18 (m, 2.55H, NCH, CHAr), 2.31 (s, 5.1H, Me), 2.29 (s, 0.9H, Me), 2.27-2.16 (m, 1H, CH), 2.04-1.90 (m, 0.85H, CH), 1.90-1.75 (m, 0.45H, CH), 1.54-1.41 (m, 8.1H, CMe_3), 1.19 (s, 0.9H, CMe_3); ^{13}C NMR ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.5 (C=O), 141.41 (*ipso*-Ar), 141.35 (*ipso*-Ar), 138.1 (*ipso*-Ar), 128.40 (Ar), 128.35 (Ar), 124.9 (Ar), 123.4 ($Ar_{[2\text{-}Ar]}$) 79.1 (O*C*Me_3), 52.7 (NCH_2), 51.8 (NCH_2), 46.0 (NCH_2), 45.7 (NCH_2), 44.2 (CHAr), 43.3 (CHAr), 33.5 (CH_2), 32.5 (CH_2), 28.6 (C*Me*$_3$), 28.2 (C*Me*$_{3[2\text{-}Ar]}$), 21.3 (Me); HRMS (ESI) *m/z* calcd for $C_{17}H_{25}NO_2$ $(M + Na)^+$ 298.1783, found 298.1783 (–1.8 ppm error); Spectroscopic data for 2-aryl pyrrolidone **307** consistent with those reported in the literature.[178]

Lab book reference: **SMc6-494**

tert-Butyl 3-(4-(trimethylsilyl)phenyl)pyrrolidine-1-carboxylate 308 and _tert_-butyl 2-(4-(trimethylsilyl)phenyl)pyrrolidine-1-carboxylate 309

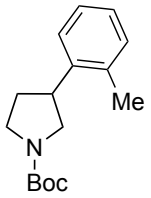


308 **309**

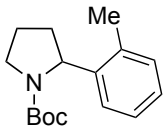
Using General Procedure P, 3-BF_3K pyrrolidine (125 mg, 0.45 mmol, 1.5 eq.) and (4-chlorophenyl)trimethylsilane (56 μL, 0.3 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 95:5 hexane-EtOAc as eluent gave an 85:15 mixture (by ^{1}H NMR spectroscopy) of 3-aryl pyrrolidine **308** and 2-aryl pyrrolidine **309** (40 mg i.e. 34 mg (36%) of **308**; 6 mg (6%) of **309**) as a colourless oil, R_F (90:10 hexane-EtOAc) 0.2; IR (ATR) 1698, 1398, 1176, 1135, 840 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (85:15 mixture of 3-aryl pyrrolidine **308** and 2-aryl pyrrolidine **309**; 50:50 mixture of rotamers for 3-aryl pyrrolidine **308**; 65:35 mixture of rotamers for 2-aryl pyrrolidine **309**) δ 7.51-7.45 (m, 1.7H Ar), 7.46-7.41 (m, 0.3H, Ar) 7.26-7.20 (m, 1.7H, Ar), 7.16 (m, 0.3H, Ar), 5.00-4.89 (m, 0.05H, CHAr), 4.82-4.68 (m, 0.1H, CHAr), 3.90-3.80 (dd, J = 9.0, 7.0 Hz, 0.43H, NCH), 3.76 (dd, J = 10.0, 7.0 Hz, 0.42H, NCH), 3.71-3.48 (m, 1.15H, NCH), 3.47-3.22 (m, 2.55H, NCH, CHAr), 2.38-2.18 (m, 1H, CH), 1.98 (dddd, J = 10.0, 10.0, 10.0, 10.0 Hz, 0.85H, CH), 1.91-1.75 (m, 0.45H, CH), 1.51-1.43 (m, 8.1H, CMe_3), 1.17 (s, 0.9H, CMe_3), 0.25 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.7 (C=O), 142.2 (*ipso*-Ar), 138.9 (*ipso*-Ar), 138.8 (*ipso*-Ar) 133.8 (Ar), 133.2 (Ar), 126.7 (Ar), 125.1 (Ar), 124.8 (Ar), 79.3 (O*C*Me$_3$), 61.4 (CHAr$_{[2\text{-Ar}]}$), 60.7 (CHAr$_{[2\text{-Ar}]}$), 52.8 (NCH$_{2[3\text{-Ar}]}$), 51.8 (NCH$_{2[3\text{-Ar}]}$) 47.4 (NCH_2), 47.2 (NCH_2), 46.1 (NCH_2), 45.8 (NCH_2), 44.4 (CHAr$_{[3\text{-Ar}]}$), 43.5 (CHAr$_{[3\text{-Ar}]}$), 36.0 (CH_2), 33.5 (CH_2), 32.5 (CH_2), 28.7 (C*Me*$_3$), 28.3 (C*Me*$_3$), 23.6 ($CH_{2[2\text{-Ar}]}$), 23.3 ($CH_{2[2\text{-Ar}]}$), –0.94 ($SiMe_3$), –1.0 ($SiMe_3$); 1 *ipso*-Ar$_{[3\text{-Ar}]}$ carbon resonance not resolved; HRMS (ESI) *m/z* calcd for $C_{18}H_{29}NO_2Si$ $(M + Na)^+$ 342.186, found 342.1859 (–0.4 ppm error); Spectroscopic data for 2-aryl pyrrolidone **309** consistent with those reported in the literature.[179]

Lab book reference: **SMc6-501**

tert-Butyl 3-(_o_-tolyl)pyrrolidine-1-carboxylate 310 and _tert_-butyl 2-(_o_-tolyl)pyrrolidine-1-carboxylate 311



310

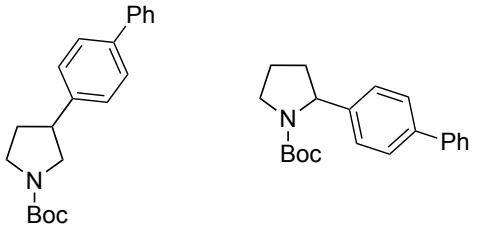


311

Using General Procedure P, 3-BF_3K pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.) and 1-chloro-2-methylbenzene (35 μL, 0.3 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 97:3 hexane-EtOAc as eluent gave an 75:25 mixture (by ^{1}H NMR spectroscopy) of 3-aryl pyrrolidine **310** and 2-aryl pyrrolidine **311** (38 mg i.e. 29 mg (36%) of **310**; 9 mg (12%) of **311**) as a colourless oil; IR (ATR) 1694 (C=O), 1397, 1365, 1165, 1124, 879, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (75:25 mixture of 3-aryl pyrrolidine **310** and 2-aryl pyrrolidine **311**; 50:50 mixture of rotamers for 3-aryl pyrrolidine **310**; 65:35 mixture of rotamers for 2-aryl pyrrolidine **311**) δ 7.25-6.99 (m, 4H, Ar), 5.17-5.10 (m, 0.08H, CHAr), 4.96 (dd, J = 8.0, 4.5 Hz, 0.17H, CHAr), 3.86-3.21 (m, 4.25H, NCH, CHAr), 2.37 (s, 2.25H, Me), 2.35-2.31 (m, 1H, Me, CH), 2.26-2.14 (m, 0.75H, CH), 2.06-1.92 (m, 0.75H, CH), 1.91-1.80 (m, 0.5H, CH), 1.79-1.62 (m, 0.25H, CH), 1.53-1.44 (m, 7.5H, CMe_3), 1.15 (m, 1.5H, CMe_3; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.6 (C=O), 154.5 (C=O), 143.4 (*ipso*-Ar), 139.7 (*ipso*-Ar), 136.2 (*ipso*-Ar), 136.1 (*ipso*-Ar), 133.9 (*ipso*-Ar), 130.6 (Ar), 130.1 (Ar), 126.6 (Ar), 126.5 (Ar), 126.4 (Ar), 126.0 (Ar), 125.4 (Ar), 124.6 (Ar), 79.3 (O*C*Me_3), 79.1 (O*C*Me_3), 58.2 ($CHAr_{[2\text{-}Ar]}$), 52.0 (NCH_2), 51.4 (NCH_2), 47.5 (NCH_2), 47.2 (NCH_2), 45.7 (NCH_2), 45.5 (NCH_2), 40.2 ($CHAr_{[3\text{-}Ar]}$), 39.5 ($CHAr_{[3\text{-}Ar]}$), 34.3 (CH_2), 33.0 (CH_2), 32.5 (CH_2), 31.8 (CH_2), 28.7 (CMe_3), 28.2 (CMe_3), 19.9 ($Me_{[3\text{-}Ar]}$), 19.4 ($Me_{[2\text{-}Ar]}$); HRMS (ESI) *m/z* calcd for MH+ $C_{16}H_{23}NO_2$ $(M + H)^+$ 262.1802, found 262.1807 (+0.1 ppm error). Spectroscopic data for 3-aryl pyrrolidine **310** consistent with those reported in the literature.[160] Spectroscopic data for 2-aryl pyrrolidine **311** consistent with those reported in the literature.[177]

Lab book reference: **SMc6-499**

tert-Butyl 3-([1,1'-biphenyl]-4-yl)pyrrolidine-1-carboxylate 288 and _tert_-butyl 2-([1,1'-biphenyl]-4-yl)pyrrolidine-1-carboxylate 126

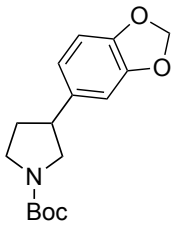


288 **126**

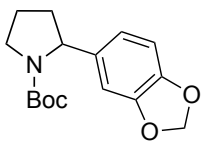
Using General Procedure Q, 3-BF_3K pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.) and 4-chloro-1,1'-biphenyl (57 mg, 0.3 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 94:6 hexane-EtOAc as eluent gave a 75:25 mixture (by ^{1}H NMR spectroscopy) of 3-aryl pyrrolidine **288** and 2-aryl pyrrolidine **126** (28 mg i.e. 21 mg (22%) of **288**; 7 mg (7%) of **126**) as an orange oil, R_F (90:10 hexane-EtOAc) 0.12; IR (ATR) 2974, 2876, 1693 (C=O), 1487, 1399, 1166, 1123, 880 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) (75:25 mixture of 3-aryl pyrrolidine **288** and 2-aryl pyrrolidine **126**; 50:50 mixture of rotamers for 3-aryl pyrrolidine **288**; 65:35 mixture of rotamers for 2-aryl pyrrolidine **126**) δ 7.63-7.50 (m, 4H, Ar), 7.47-7.38 (m, 2H, Ar), 7.38-7.27 (m, 2.5H, Ar), 7.26-7.19 (m, 0.5H, Ar), 5.07-4.93 (m, 0.08H, CHAr), 4.88-4.74 (m, 0.17H, CHAr), 3.93-3.85 (m, 0.375H, NCH), 3.81 (dd, 10.5, 7.0 Hz, 0.375H, NCH), 3.74-3.50 (m, 1.25H, NCH), 3.49-3.25 (m, 2.25H, NCH, CHAr), 2.45-2.22 (m, 1H, CH), 2.09-1.95 (m, 0.75H, CH), 1.96-1.80 (m, 0.75H, CH), 1.53-1.44 (m, 7.5H, CMe_3), 1.20 (s, 1.5H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.7 (C=O), 140.9 (*ipso*-Ar), 140.6 (*ipso*-Ar), 139.9 (*ipso*-Ar), 139.8 (*ipso*-Ar), 128.9 (Ar), 128.8 (Ar), 128.3 (Ar), 127.6 (Ar), 127.4 (Ar), 127.3 (Ar), 127.1 (Ar), 126.9 (Ar), 126.7 (Ar), 126.5 (Ar), 126.1 (Ar), 79.4 (O*C*Me$_3$), 61.2 (CHAr$_{[2\text{-}Ar]}$), 52.8 (NCH_2), 51.9 (NCH_2), 46.1 (NCH_2), 45.8 (NCH_2), 44.1 (CHAr$_{[3\text{-}Ar]}$), 43.2 (CHAr$_{[3\text{-}Ar]}$), 36.1 (CH_2), 33.6 (CH_2), 32.6 (CH_2), 28.7 (C*Me*$_3$), 28.3 (C*Me*$_3$), 23.6 (CH_2), 23.4 (CH_2); HRMS (ESI) *m/z* calcd for $C_{21}H_{25}NO_2$ $(M + Na)^+$ 346.1777, found 346.1779 (–0.1 ppm error). Spectroscopic data for 3-aryl pyrrolidine **288** consistent with those reported in the literature.[158] Spectroscopic data for 2-aryl pyrrolidine **126** consistent with those reported in the literature.[180]

Lab book reference: **SMc6-498**

tert-Butyl 3-(benzo[_d_][1,3]dioxol-5-yl)pyrrolidine-1-carboxylate 314 _tert_-butyl 2-(benzo[_d_][1,3]dioxol-5-yl)pyrrolidine-1-carboxylate 315



312

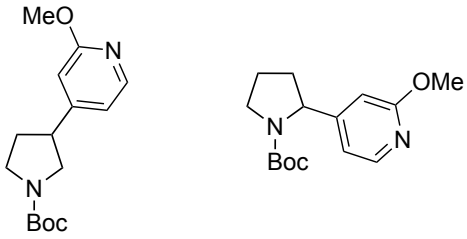


313

Using General Procedure P, 3-BF_3K pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.) and 5-chlorobenzo[*d*][1,3]dioxole (35 μL, 0.3 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc to 95:5 toluene:Et2O as eluent gave a 55:45 mixture (by ^{1}H NMR spectroscopy) of 3-aryl pyrrolidine **312** and 2-aryl pyrrolidine **313** (25 mg i.e. 13 mg (15%) of **312**; 12 mg (14%) of **313**) as a yellow oil, R_F (95:5 toluene:Et_2O) 0.15; IR (ATR) 2926, 1690 (C=O), 1403, 1265, 1167, 1127 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of 3-aryl pyrrolidine **312** and 2-aryl pyrrolidine **313**; 50:50 mixture of rotamers for 3-aryl pyrrolidine **312**; 65:35 mixture of rotamers for 2-aryl pyrrolidine **313**) δ 6.80-6.58 (m, 3H, Ar), 5.95-5.87 (m, 2H, OCH), 4.92-4.79 (m, 0.17H, NCH), 4.74-4.61 (m, 0.28H, CHAr), 3.86-3.76 (m, 0.27H, NCH), 3.76-3.69 (m, 0.28H, NCH), 3.67-3.43 (m, 1.45H, NCH), 3.43-3.07 (m, 1.65H, NCH, CHAr), 2.34-2.14 (m, 1H, CH), 1.98-1.72 (m, 1.9H, CH), 1.50-1.40 (m, 6.3H, CMe_3), 1.23 (s, 2.7H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.6 (C=O), 147.9 (*ipso*-Ar), 147.7 (*ipso*-Ar), 146.4 (*ipso*-Ar), 146.1 (*ipso*-Ar), 135.4 (*ipso*-Ar), 120.2 (Ar), 118.6 (Ar), 108.4 (Ar), 107.9 (Ar), 107.5 (Ar), 106.2 (Ar), 101.1 (OCH_2), 101.0 (OCH_2), 79.3 (O*C*Me_3), 61.2 ($CHAr_{[2\text{-}Ar]}$), 60.6 ($CHAr_{[2\text{-}Ar]}$), 52.8 (NCH_2), 52.1 (NCH_2), 47.4 (NCH_2), 47.1 (NCH_2), 46.0 (NCH_2), 45.7 (NCH_2), 44.2 ($CHAr_{[3\text{-}Ar]}$), 43.3 ($CHAr_{[3\text{-}Ar]}$), 36.2 (CH_2), 35.2 (CH_2), 33.6 (CH_2), 32.8 (CH_2), 28.7 (CMe_3), 28.4 (CMe_3), 23.6 (CH_2), 23.2 (CH_2); HRMS (ESI) *m/z* calcd for $C_{16}H_{21}NO_4$ $(M + Na)^+$ 314.1363, found 314.1357 (+1 ppm error). Spectroscopic data for 3-aryl pyrrolidone **313** consistent with those reported in the literature.[181]

Lab book reference: **SMc6-502**

tert-Butyl 3-(2-methoxypyridin-4-yl)pyrrolidine-1-carboxylate 280 and _tert_-butyl 2-(2-methoxypyridin-4-yl)pyrrolidine-1-carboxylate 314

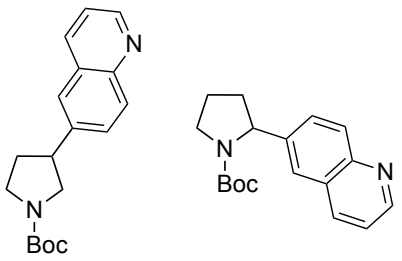


280 **314**

Using General Procedure Q, 3-BF_3K pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.) and 4-chloro-2-methoxypyridine (43 mg, 0.3 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 85:15 hexane-EtOAc as eluent gave a 40:60 mixture (by ^{1}H NMR spectroscopy) of 3-aryl pyrrolidine **280** and 2-aryl pyrrolidine **314** (33 mg i.e. 13 mg (16%) of **280**; 20 mg (24%) of **314**) as a colourless oil, R_F (90:10 hexane-EtOAc) 0.05; IR (ATR) 2975, 1697 (C=O), 1611, 1562, 1397, 1164, 1118, 1044 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (40:60 mixture of 3-aryl pyrrolidine **280** and 2-aryl pyrrolidine **314**; 50:50 mixture of rotamers for 3-aryl pyrrolidine **280**; 65:35 mixture of rotamers for 2-aryl pyrrolidine **314**) δ 8.11-8.0 (m, 1H, Ar), 6.72 (d, J = 5.5 Hz, 0.4H, Ar), 6.68 (d, J = 5.5 Hz, 0.6H, Ar), 6.58 (s, 0.4H, Ar), 6.53 (s, 0.6H, Ar), 4.89-4.81 (m, 0.23H, CHAr), 4.68 (dd, J = 8.0, 4.0 Hz, 0.37H, CHAr), 3.91 (s, 3H, OMe), 3.85-3.78 (m, 0.2H, NCH), 3.78-3.71 (m, 0.2H, NCH), 3.63-3.21 (m, 2.8H, NCH, CHAr), 2.39-2.18 (m, 1H, CH), 1.98-1.89 (m, 0.4H, CH), 1.88-1.63 (m, 1.8H, CH), 1.50-1.41 (m, 5.4H, CMe_3), 1.21 (s, 3.6H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.7 (C=O), 164.6 (C=O), 157.1 (*ipso*-Ar), 156.1 (*ipso*-Ar), 154.5 (*ipso*-Ar), 154.4 (*ipso*-Ar), 153.5 (*ipso*-Ar), 147.1 (Ar), 146.9 (Ar), 146.8 (Ar), 115.9 (Ar), 114.5 (Ar), 114.4 (Ar), 109.2 (Ar), 107.5 (Ar), 79.8 (O*C*Me_3), 79.6 (O*C*Me_3), 60.5 ($CHAr_{[2\text{-}Ar]}$), 59.9 ($CHAr_{[2\text{-}Ar]}$), 53.5 (OMe), 51.6 (NCH_2), 51.0 (NCH_2), 47.4 (NCH_2), 47.1 (NCH_2), 45.8 (NCH_2), 45.5 (NCH_2), 43.5 ($CHAr_{[3\text{-}Ar]}$), 42.6 ($CHAr_{[3\text{-}Ar]}$), 40.6 (NCH_2), 36.6 (CH_2), 35.4 (CH_2), 34.2 (CH_2), 32.6 (CH_2), 31.7 (CH_2), 28.6 (C*Me*$_3$), 28.3 (C*Me*$_3$), 23.7 (CH_2), 23.3 (CH_2); HRMS (ESI) *m/z* calcd for $C_{15}H_{22}N_2O_3$ $(M + Na)^+$ 301.1523, found 301.1525 (–1 ppm error). Spectroscopic data for 3-aryl pyrrolidine **280** consistent with those reported in the literature.[152] Spectroscopic data for 2-aryl pyrrolidine **314** consistent with those reported in the literature.[177]

Lab book reference: **SMc6-500**

tert-Butyl 3-(quinolin-6-yl)pyrrolidine-1-carboxylate 315 and _tert_-butyl 2-(quinolin-7-yl)pyrrolidine-1-carboxylate 316



315 **316**

Using General Procedure Q, 3-BF_3K pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.) and 6-bromoquinoline (41 μL, 0.3 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 70:30 hexane-EtOAc to 50:50 hexane-EtOAc gave impure product. Purification by flash column chromatography on silica using 60:30:10 hexane-EtOAc-toluene as eluent gave a 55:45 mixture (by ^{1}H NMR spectroscopy) of 3-aryl pyrrolidine **315** and 2-aryl pyrrolidine **316** (43 mg i.e. 24 mg (27%) of **315**; 20 mg (22%) of **316**) as a colourless oil, R_F (60:40 hexane-EtOAc) 0.16; IR (ATR) 2973, 2926, 1690 (C=O), 1392, 1165, 1121, 825 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of 3-aryl pyrrolidine **315** and 2-aryl pyrrolidine **316**; 50:50 mixture of rotamers for 3-aryl pyrrolidine **315**; 65:35 mixture of rotamers for 2-aryl pyrrolidine **316**) δ 8.91-8.80 (m, 1H, Ar), 8.12-8.06 (m, 2H, Ar), 7.65-7.57 (m, 1.1H, Ar), 7.57-7.51 (m, 0.9H, Ar), 7.41-7.34 (m, 1H, Ar), 5.16-5.03 (m, 0.15H, CHAr), 4.99-4.91 (m, 0.3H, CHAr), 3.92 (dd, J = 9.5, 6.5 Hz, 0.28H, NCH), 3.85 (dd, J = 10.5, 7.5 Hz, 0.27H, NCH), 3.75-3.31 (m, 3.1H, NCH, CHAr), 2.44-2.27 (m, 1H, CH), 2.13-2.00 (m, 0.55H, CH), 1.96-1.82 (m, 1.35H, CH), 1.51-1.43 (m, 6.3H, CMe_3), 1.11 (s, 2.7H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.7 (C=O), 154.6 (C=O), 150.2 (Ar), 150.0 (Ar), 147.5 (*ipso*-Ar), 147.4 (*ipso*-Ar), 143.5 (*ipso*-Ar), 140.0 (*ipso*-Ar), 135.9 (Ar), 129.8 (Ar), 129.5 (Ar), 129.4 (Ar), 128.3 (Ar), 127.9 (Ar), 125.2 (Ar), 123.6 (Ar), 121.4 (Ar), 79.5 (O*C*Me$_3$), 61.3 (CHAr$_{[2\text{-}Ar]}$), 60.9 (CHAr$_{[2\text{-}Ar]}$), 52.5 (CH_2), 51.7 (CH_2), 47.6 (CH_2), 47.3 (CH_2), 46.0 (CH_2), 45.7 (CH_2), 44.3 (CHAr$_{[3\text{-}Ar]}$), 43.3 (CHAr$_{[3\text{-}Ar]}$), 35.9 (CH_2), 33.4 (CH_2), 32.5 (CH_2), 28.6 (CMe_3), 28.2 (CMe_3), 23.7

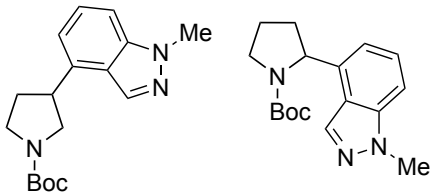
(CH_2), 23.3 (CH_2); HRMS (ESI) *m/z* calcd for $C_{18}H_{22}N_2O_2$ 321.1573, found 321.1581 (+0.7 ppm error). Spectroscopic data for 2-Ar pyrrolidine **316** consistent with those reported by another group member.[133]

Lab book reference: **SMc5-346**

Using General Procedure Q, 3-BF_3K pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.) and 6-chloroquinoline (49 mg, 0.3 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 70:30 hexane-EtOAc to 50:50 hexane-EtOAc gave impure product. Purification by flash column chromatography on silica using 60:30:10 hexane-EtOAc-toluene as eluent gave a none of 3-aryl pyrrolidine **315** (by ^{1}H NMR or HRMS).

Lab book reference: **SMc6-507**

tert-Butyl 3-(1-methyl-1*H*-indazol-4-yl)pyrrolidine-1-carboxylate 317 and _tert_-butyl 2-(1-methyl-1*H*-indazol-4-yl)pyrrolidine-1-carboxylate 318



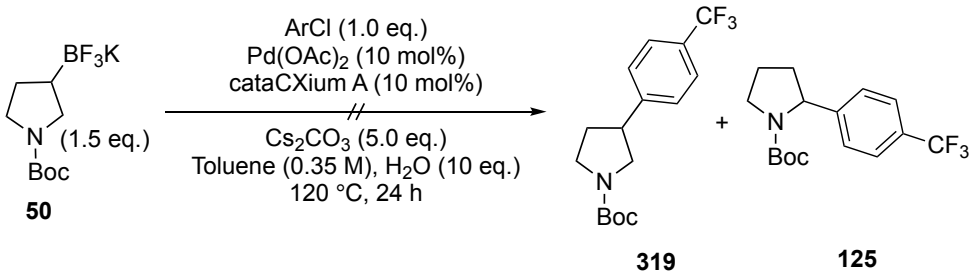
317 **318**

Using General Procedure Q, 3-BF_3K pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.) and 4-chloro-1-methyl-1*H*-indazole (50 mg, 0.3 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 80:20 hexane-EtOAc to 70:30 hexane-EtOAc as eluent gave a 55:45 mixture (by ^{1}H NMR spectroscopy) of 3-aryl pyrrolidine **317** and 2-aryl pyrrolidine **318** (37 mg i.e. 21 mg (24%) of **317**; 16 mg (17%) of **318**) as a colourless oil, R_F (70:30 hexane-EtOAc) 0.15; IR (ATR) 2925, 1696 (C=O), 1400, 1254 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of 3-aryl pyrrolidine **317** and 2-aryl pyrrolidine **318**; 50:50 mixture of rotamers for 3-aryl pyrrolidine **317**; 60:40 mixture of rotamers for 2-aryl pyrrolidine **318**) δ 8.04 (s, 0.55H,

Ar), 7.97 (s, 0.45H, Ar), 7.38-7.21 (m, 2H, Ar), 7.00 (d, *J* = 7.0 Hz, 0.55H, Ar), 6.91 (d, *J* = 7.0 Hz, 0.45H, Ar), 5.39-5.30 (m, 0.18H, CHAr), 5.24-5.13 (m, 1H, 0.27H, CHAr), 4.08 (m, 3H, NMe), 3.96 (dd, *J* = 10.5, 7.5, 0.27H, NCH), 3.92-3.84 (m, 0.28H, NCH), 3.84-3.64 (m, 1.45H, NCH), 3.64-3.39 (m, 1.65H, NCH, CHAr), 2.46-2.29 (m, 1H, CH), 2.26-2.11 (m, 0.55H, CH), 1.98-1.80 (m, 1.35H, CH), 1.59-1.41 (m, 6.3H, C*Me*$_3$), 1.07 (s, 2.7H, C*Me*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (rotamers) δ 154.6 (C=O), 140.3 (*ipso*-Ar), 140.1 (*ipso*-Ar), 138.5 (*ipso*-Ar), 135.2 (*ipso*-Ar), 131.2 (Ar), 130.9 (Ar), 126.6 (Ar), 126.4 (Ar), 126.2 (Ar), 123.4 (*ipso*-Ar), 121.4 (*ipso*-Ar), 117.4 (Ar), 116.6 (Ar), 116.5, (Ar), 107.7 (Ar), 107.5 (Ar), 107.3 (Ar), 79.4 (O*C*Me$_3$), 79.3 (O*C*Me$_3$), 59.7 (CHAr$_{[2\text{-}Ar]}$), 59.4 (CHAr$_{[2\text{-}Ar]}$), 51.9 (NCH_2), 51.2 (NCH_2), 47.4 (NCH_2), 47.0 (NCH_2), 45.9 (NCH_2), 45.6 (NCH_2), 42.1 (CHAr$_{[3\text{-}Ar]}$), 41.3 (CHAr$_{[3\text{-}Ar]}$), 35.7 (NMe), 35.2 (CH_2), 34.3 (CH_2), 32.7 (CH_2), 31.8 (CH_2), 28.6 (C*Me*$_3$), 28.2 (C*Me*$_3$), 24.0 (CH_2), 23.6 (CH_2); HRMS (ESI) *m/z* cald for $C_{17}H_{23}N_2O_2$ $(M + Na)^+$ 324.1682, found 324.1689 (–2.7 ppm error).

Lab book reference: **SMc6-496**

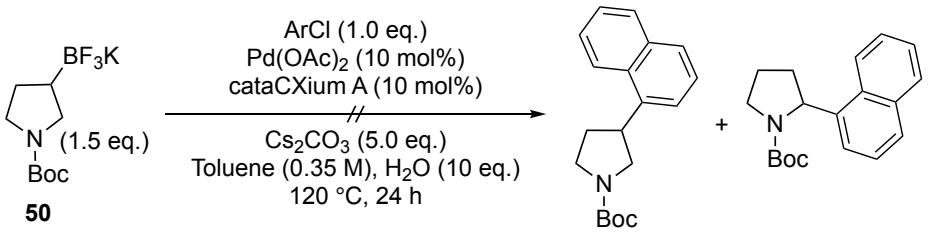
Attempted synthesis of *tert*-butyl 3-(4-(trifluoromethyl)phenyl)pyrrolidine-1-carboxylate 319 and *tert*-butyl 2-(4-(trifluoromethyl)phenyl)pyrrolidine-1-carboxylate 125



Using general procedure O, 3-BF_3K Pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.) and 4-chlorobenzotrifluoride (40 μL, 0.3 mmol, 1.0 eq.) gave the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave an unquantifiable mixture of 3-aryl pyrrolidine **319**, 2-aryl pyrrolidine **125** and an unknown impurity.

Lab book reference: **SMc6-493**

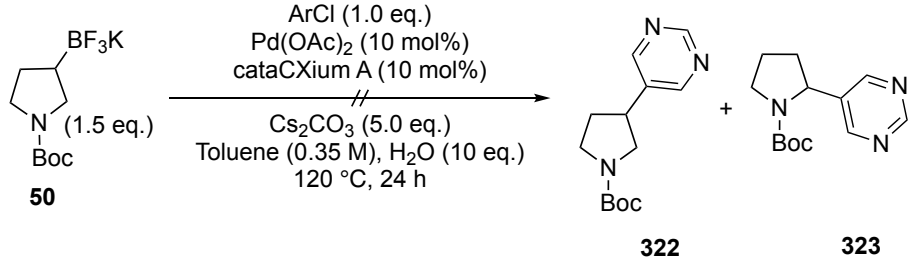
Attempted synthesis of *tert*-butyl 3-(naphthalen-1-yl)pyrrolidine-1-carboxylate 320 and *tert*-butyl 2-(naphthalen-1-yl)pyrrolidine-1-carboxylate 321



Using General Procedure O, 3-BF_3K Pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.) and 1-chloronaphthalene (41 μL, 0.3 mmol, 1.0 eq.) gave the crude product which contained none of 3-aryl pyrrolidine **320** or 2-aryl pyrrolidine **321** (by ^{1}H NMR spectroscopy or HRMS).

Lab book reference: **SMc6-495**

Attempted synthesis of *tert*-butyl 3-(pyrimidin-5-yl)pyrrolidine-1-carboxylate 322 and *tert*-butyl 2-(pyrimidin-5-yl)pyrrolidine-1-carboxylate 323



Using General Procedure P, 3-BF_3K pyrrolidine **50** (125 mg, 0.45 mmol, 1.5 eq.) and 5-chloropyrimidine (35 mg, 0.3 mmol, 1.0 eq.) gave the crude product which contained trace amounts of 3-aryl pyrrolidine **322** or 2-aryl pyrrolidine **323** (by HRMS).

Lab book reference: **SMc6-507**

5.7 Crystallographic Data and Refinement Statistics

5.7.1 2-Phenyl tetrahydrothiophene (*S*)-163

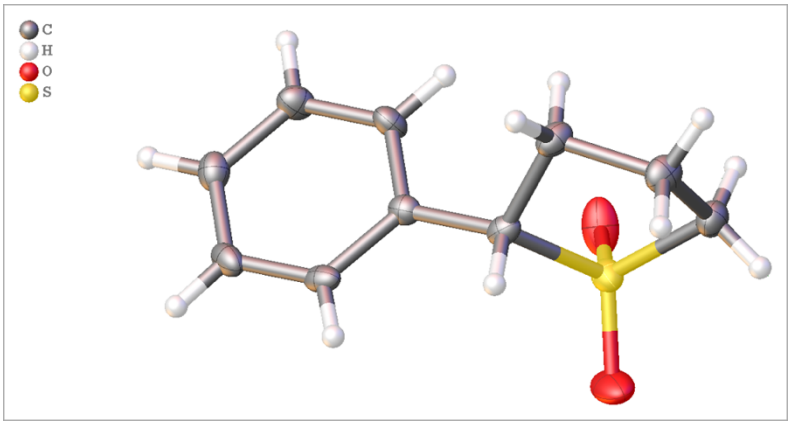


Table 5.8: Crystal data and structure refinement for (*S*)-**163**

Identification code	(*S*)-**163**
Empirical formula	$C_{10}H_{12}O_2S$
Formula weight	196.26
Temperature/K	110.00(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	5.71308(6)
b/Å	10.71883(12)
c/Å	15.32229(16)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	938.300(17)
Z	4
ρ_{calc}g/cm^3	1.389
μ/mm^{-1}	2.765

F(000)	416.0
Crystal size/mm^3	0.251 × 0.103 × 0.031
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	10.072 to 134.126
Index ranges	-6 ≤ h ≤ 5, -12 ≤ k ≤ 12, -18 ≤ l ≤ 18
Reflections collected	9651
Independent reflections	1680 [R_{int} = 0.0324, R_{sigma} = 0.0193]
Data/restraints/parameters	1680/0/167
Goodness-of-fit on F^2	1.101
Final R indexes [I>=2σ (I)]	R_1 = 0.0209, wR_2 = 0.0546
Final R indexes [all data]	R_1 = 0.0212, wR_2 = 0.0550
Largest diff. peak/hole / e Å^{-3}	0.21/-0.19
Flack parameter	-0.007(8)

Data collected, solved and refined by Adrian C Whitwood

Table 5.9: Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for (*S*)-**163**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor

Atom	*x*	*y*	*z*	U(eq)
C1	2751(4)	7473(2)	996.7(14)	22.5(4)
C2	1930(4)	8573.6(19)	1548.3(14)	24.2(4)
C3	1949(4)	8139.5(19)	2499.4(13)	22.1(4)
C4	4350(3)	7554.5(17)	2656.7(12)	17.8(4)
C5	4672(3)	6811.0(16)	3478.7(12)	17.1(4)
C6	2986(4)	5969.9(18)	3773.7(13)	20.4(4)
C7	3271(4)	5352.9(19)	4559.2(14)	22.9(4)

Atom	*x*	*y*	*z*	U(eq)
C8	5270(4)	5540.7(18)	5059.7(12)	22.5(4)
C9	6973(4)	6362(2)	4765.6(13)	22.6(5)
C10	6674(3)	6993.4(19)	3982.6(13)	19.9(4)
O1	3978(3)	5380.5(13)	1790.7(10)	34.9(4)
O2	7164(3)	6810(2)	1358.3(11)	41.3(5)
S1	4800.1(8)	6638.1(4)	1668.3(3)	19.95(16)

Table 5.10: Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for (*S*)-**163**. The Anisotropic displacement factor exponent takes the form:
$2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	25.6(11)	23.2(10)	18.8(10)	1.9(8)	0.4(8)	1.9(9)
C2	28.0(11)	19.8(10)	24.9(10)	5.1(8)	1.5(8)	4.5(8)
C3	25.9(10)	18.9(10)	21.5(10)	1.5(8)	5.8(8)	4.1(9)
C4	20.3(10)	14.3(8)	18.7(9)	-3.9(7)	3.9(7)	-3.1(8)
C5	17.2(9)	14.5(8)	19.4(9)	-4.1(7)	0.5(7)	-0.4(7)
C6	16.0(10)	19.8(10)	25.4(10)	1.1(8)	-4.9(8)	-0.8(8)
C7	21.8(10)	19.2(10)	27.7(10)	3.1(8)	-0.4(8)	-2.8(8)
C8	28.2(11)	20.4(9)	19.0(9)	-2.1(7)	-2.3(9)	4.2(9)
C9	17.6(9)	28.1(12)	22.0(10)	-10.5(8)	-3.8(8)	2.3(8)
C10	15.8(9)	21.3(9)	22.6(10)	-8.9(8)	4.3(8)	-2.6(8)
O1	58.2(11)	16.5(7)	29.9(8)	-4.0(6)	-13.2(8)	4.4(7)
O2	21.2(8)	70.1(13)	32.6(8)	-18.1(9)	5.0(7)	7.4(8)
S1	19.7(2)	20.6(2)	19.5(2)	-5.28(17)	-0.78(19)	3.77(17)

Table 5.11: Bond Lengths for (*S*)-**163**

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C2	1.525(3)	C5	C10	1.394(3)
C1	S1	1.797(2)	C6	C7	1.383(3)
C2	C3	1.530(3)	C7	C8	1.390(3)
C3	C4	1.527(3)	C8	C9	1.387(3)
C4	C5	1.502(3)	C9	C10	1.388(3)
C4	S1	1.8233(19)	O1	S1	1.4397(16)
C5	C6	1.395(3)	O2	S1	1.4434(16)

Table 5.12: Bond Angles for (*S*)-**163**

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C2	C1	S1	105.57(14)	C6	C7	C8	120.5(2)
C1	C2	C3	106.89(16)	C9	C8	C7	119.26(19)
C4	C3	C2	106.35(16)	C8	C9	C10	120.27(19)
C3	C4	S1	102.53(13)	C9	C10	C5	120.75(19)
C5	C4	C3	117.42(16)	C1	S1	C4	96.62(10)
C5	C4	S1	113.16(13)	O1	S1	C1	109.19(10)
C6	C5	C4	122.00(16)	O1	S1	C4	110.50(9)
C10	C5	C4	119.40(17)	O1	S1	O2	117.85(11)
C10	C5	C6	118.55(18)	O2	S1	C1	110.94(11)
C7	C6	C5	120.67(19)	O2	S1	C4	109.68(9)

Table 5.13: Torsion Angles for (*S*)-**163**

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C1	C2	C3	C4	50.2(2)	C5	C4	S1	C1	148.56(14)

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C2	C1	S1	C4	6.18(16)	C5	C4	S1	O1	35.19(16)
C2	C1	S1	O1	120.62(16)	C5	C4	S1	O2	-96.38(16)
C2	C1	S1	O2	-107.86(16)	C5	C6	C7	C8	-1.4(3)
C2	C3	C4	C5	-167.48(16)	C6	C5	C10	C9	-0.7(3)
C2	C3	C4	S1	-42.79(18)	C6	C7	C8	C9	0.5(3)
C3	C4	C5	C6	43.3(3)	C7	C8	C9	C10	0.4(3)
C3	C4	C5	C10	-134.36(19)	C8	C9	C10	C5	-0.3(3)
C3	C4	S1	C1	21.10(15)	C10	C5	C6	C7	1.5(3)
C3	C4	S1	O1	-92.27(14)	S1	C1	C2	C3	-32.3(2)
C3	C4	S1	O2	136.16(14)	S1	C4	C5	C6	-75.9(2)
C4	C5	C6	C7	-176.19(18)	S1	C4	C5	C10	106.44(17)
C4	C5	C10	C9	177.08(17)					

Table 5.14: Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for (*S*)-**163**.

Atom	*x*	*y*	*z*	U(eq)
H1A	3470(50)	7680(20)	499(19)	29(7)
H1B	1570(50)	6900(30)	910(17)	30(7)
H2A	440(50)	8790(20)	1380(16)	27(6)
H2B	2980(50)	9290(30)	1474(18)	36(7)
H3A	780(40)	7530(20)	2575(16)	25(6)
H3B	1700(50)	8850(30)	2887(18)	32(7)
H4	5490(40)	8150(20)	2625(15)	19(5)
H6	1640(40)	5840(20)	3442(16)	22(6)
H7	2090(50)	4800(20)	4756(16)	25(6)
H8	5470(40)	5110(20)	5606(16)	21(6)

Atom	*x*	*y*	*z*	U(eq)
H9	8290(50)	6530(30)	5075(17)	34(7)
H10	7760(40)	7590(20)	3778(16)	23(6)

5.7.2 Tetrahydrothiophene BBIDA (*R*,*R*,*S*)-134

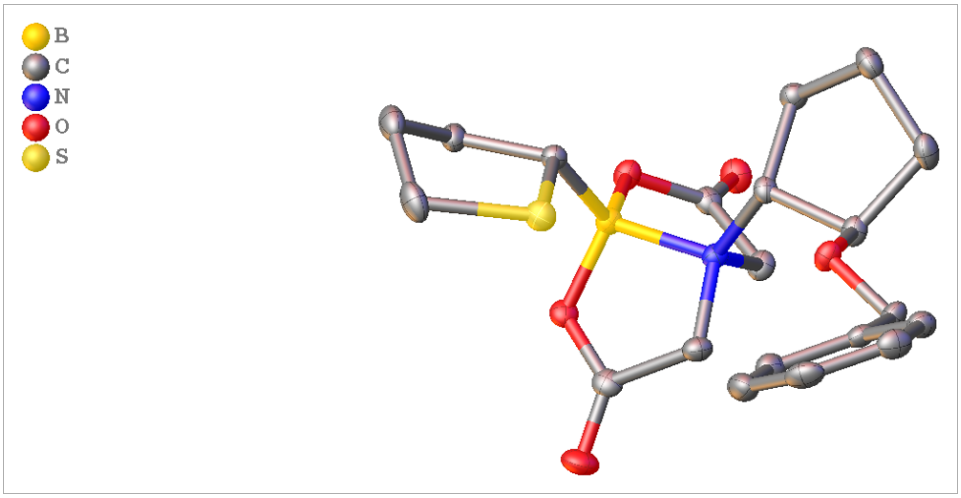


Table 5.15: Crystal data and structure refinement for (*R*,*R*,*S*)-**134**

Identification code	(*R*,*R*,*S*)-**134**
Empirical formula	$C_{20}H_{26}BNO_5S$
Formula weight	403.29
Temperature/K	110.00(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	6.60047(6)
b/Å	15.68859(13)
c/Å	18.79994(18)
α/°	90
β/°	90

γ/°	90
Volume/Å^3	1946.77(3)
Z	4
ρ_{calc}g/cm^3	1.376
μ/mm^{-1}	1.750
F(000)	856.0
Crystal size/mm^3	0.295 × 0.101 × 0.042
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.34 to 134.128
Index ranges	-7 ≤ h ≤ 7, -18 ≤ k ≤ 17, -22 ≤ l ≤ 22
Reflections collected	19213
Independent reflections	3479 [R_{int} = 0.0283, R_{sigma} = 0.0183]
Data/restraints/parameters	3479/0/357
Goodness-of-fit on F^2	1.033
Final R indexes [I>=2σ (I)]	R_1 = 0.0227, wR_2 = 0.0574
Final R indexes [all data]	R_1 = 0.0233, wR_2 = 0.0578
Largest diff. peak/hole / e Å^{-3}	0.22/-0.20
Flack parameter	0.002(5)

Data collected, solved and refined by Adrian C Whitwood

Table 5.16: Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for (*R,R,S*)-134. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor

Atom	*x*	*y*	*z*	U(eq)
B00S	1750(3)	5742.7(13)	6293.5(12)	14.5(4)
C1	6347(3)	6980.0(14)	5467.4(13)	26.3(5)

Atom	*x*	*y*	*z*	U(eq)
C2	5770(4)	6348.8(14)	4893.9(12)	24.8(4)
C3	3745(3)	5959.4(13)	5121.8(11)	18.3(4)
C4	3895(3)	5700.5(11)	5909.7(10)	14.4(4)
C5	971(3)	7014.6(12)	6899.6(11)	18.0(4)
C6	1850(3)	6434.1(13)	7473.2(11)	17.7(4)
C7	-930(3)	4816.7(12)	6535.7(10)	16.2(4)
C8	-362(3)	5191.1(13)	7254.2(11)	17.1(4)
C9	3378(3)	4973.0(12)	7422.4(10)	13.8(4)
C10	3209(3)	4044.8(12)	7181.0(11)	17.0(4)
C11	4564(3)	3591.0(13)	7721.4(11)	21.3(4)
C12	3960(4)	4006.7(13)	8421.6(11)	22.4(4)
C13	3611(3)	4953.7(13)	8239.5(10)	16.2(4)
C14	5467(3)	5722.5(14)	9120.3(10)	19.4(4)
C15	7354(3)	6242.7(12)	9223.1(10)	16.4(4)
C16	8711(3)	6033.0(13)	9760.5(11)	18.8(4)
C17	10437(3)	6519.9(14)	9877.7(11)	22.6(4)
C18	10820(4)	7222.6(13)	9456.1(12)	23.5(4)
C19	9477(4)	7440.6(13)	8920.5(12)	23.7(4)
C20	7752(3)	6954.1(13)	8805.5(11)	20.9(4)
N1	1717(2)	5557.7(10)	7162.3(8)	13.7(3)
O1	863(2)	6611.8(8)	6282.8(7)	16.8(3)
O2	452(2)	7739.8(9)	6998.7(8)	26.5(3)
O3	306(2)	5103.8(9)	6029.2(7)	16.6(3)
O4	-2299(2)	4325.7(9)	6440.3(8)	21.0(3)
O5	5329(2)	5481.5(9)	8388.8(7)	16.5(3)
S1	5705.4(7)	6459.6(3)	6305.1(3)	19.13(12)

Table 5.17: Anisotropic Displacement Parameters ($Å^2×10^3$) for (*R*,*R*,*S*)-**134**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
B00S	12.8(9)	16.7(10)	13.9(9)	-0.9(9)	-2.4(8)	-1.1(8)
C1	21.6(11)	24.4(11)	33.0(12)	12.3(9)	-1.2(9)	-5.2(9)
C2	22.1(11)	25.7(10)	26.7(11)	9.8(9)	6.8(9)	1.7(9)
C3	19.0(11)	19.0(9)	17.0(10)	3.3(8)	1.6(8)	2.6(8)
C4	13.5(9)	14.5(8)	15.2(9)	-0.6(7)	-0.9(7)	-0.3(7)
C5	11.1(9)	20.1(10)	22.9(10)	-0.2(8)	0.4(8)	1.1(8)
C6	16.8(10)	18.1(9)	18.1(9)	-3.4(8)	-0.1(8)	2.6(8)
C7	11.0(9)	17.7(9)	19.7(9)	2.1(7)	-1.1(7)	1.6(8)
C8	10.4(9)	22.8(10)	18.1(10)	1.3(8)	0.0(8)	-0.1(8)
C9	10.2(8)	16.4(9)	14.8(9)	2.5(7)	-0.9(7)	0.3(8)
C10	17.0(10)	16.8(9)	17.2(10)	-0.9(8)	0.2(8)	-0.7(8)
C11	21.3(11)	17.5(9)	25.0(10)	5.8(8)	0.2(8)	0.4(9)
C12	26.2(12)	21.8(10)	19.2(10)	6.3(8)	-4.7(9)	-4.3(9)
C13	12.4(9)	20.7(10)	15.4(9)	1.3(8)	-1.2(7)	-2.5(8)
C14	18.3(10)	27.6(10)	12.4(9)	-0.9(8)	0.2(8)	-1.3(9)
C15	16.1(9)	18.7(9)	14.3(9)	-4.9(7)	0.7(8)	2.2(8)
C16	21.0(11)	18.5(9)	16.8(10)	-1.8(8)	-1.7(8)	2.2(8)
C17	20.5(10)	26.7(11)	20.7(10)	-5.4(9)	-5.4(8)	2.9(9)
C18	20.4(10)	21.6(10)	28.6(11)	-11.8(9)	2.1(9)	-3.9(9)
C19	28.6(11)	16.8(9)	25.7(11)	-0.5(8)	5.4(10)	0.1(9)
C20	22.4(10)	21.3(10)	19.0(10)	0.1(8)	-2.7(9)	3.7(8)
N1	10.9(8)	15.9(8)	14.4(8)	-1.3(6)	-0.5(6)	0.4(6)
O1	12.4(6)	18.9(6)	19.0(6)	1.2(5)	-0.7(6)	2.6(5)
O2	28.4(8)	18.8(7)	32.2(8)	-2.8(6)	-0.5(7)	8.5(6)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O3	13.0(6)	21.6(7)	15.2(6)	-0.3(5)	-1.4(5)	-3.2(5)
O4	15.0(7)	23.5(7)	24.5(7)	1.6(6)	-2.1(6)	-4.8(6)
O5	14.6(7)	21.5(7)	13.4(6)	-1.4(5)	-1.3(5)	-4.2(5)
S1	14.6(2)	19.8(2)	23.0(2)	-0.35(19)	-0.92(19)	-3.45(18)

Table 5.18: Bond Lengths for (*R*,*R*,*S*)-**134**

Atom	Atom	Length/Å	Atom	Atom	Length/Å
B00S	C4	1.591(3)	C8	N1	1.498(2)
B00S	N1	1.659(3)	C9	C10	1.529(3)
B00S	O1	1.484(2)	C9	C13	1.544(3)
B00S	O3	1.469(2)	C9	N1	1.511(2)
C1	C2	1.513(3)	C10	C11	1.530(3)
C1	S1	1.824(2)	C11	C12	1.522(3)
C2	C3	1.531(3)	C12	C13	1.542(3)
C3	C4	1.539(3)	C13	O5	1.432(2)
C4	S1	1.8435(18)	C14	C15	1.502(3)
C5	C6	1.526(3)	C14	O5	1.429(2)
C5	O1	1.323(2)	C15	C16	1.390(3)
C5	O2	1.203(3)	C15	C20	1.390(3)
C6	N1	1.497(2)	C16	C17	1.389(3)
C7	C8	1.520(3)	C17	C18	1.381(3)
C7	O3	1.332(2)	C18	C19	1.385(3)
C7	O4	1.201(2)	C19	C20	1.387(3)

Table 5.19: Bond Angles for (*R*,*R*,*S*)-**134**

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C4	B00S	N1	116.81(15)	C12	C11	C10	102.81(17)
O1	B00S	C4	112.53(16)	C11	C12	C13	105.07(16)
O1	B00S	N1	99.72(14)	C12	C13	C9	104.75(16)
O3	B00S	C4	113.29(16)	O5	C13	C9	105.22(15)
O3	B00S	N1	101.83(14)	O5	C13	C12	113.28(16)
O3	B00S	O1	111.50(15)	O5	C14	C15	108.69(16)
C2	C1	S1	105.31(14)	C16	C15	C14	119.98(18)
C1	C2	C3	106.35(18)	C20	C15	C14	121.37(18)
C2	C3	C4	108.57(16)	C20	C15	C16	118.61(19)
B00S	C4	S1	111.54(13)	C17	C16	C15	120.92(19)
C3	C4	B00S	111.61(16)	C18	C17	C16	119.9(2)
C3	C4	S1	105.03(13)	C17	C18	C19	119.8(2)
O1	C5	C6	110.79(16)	C18	C19	C20	120.2(2)
O2	C5	C6	124.30(19)	C19	C20	C15	120.60(19)
O2	C5	O1	124.91(19)	C6	N1	B00S	102.88(14)
N1	C6	C5	104.48(16)	C6	N1	C8	111.20(15)
O3	C7	C8	110.71(16)	C6	N1	C9	112.88(14)
O4	C7	C8	124.47(18)	C8	N1	B00S	101.12(14)
O4	C7	O3	124.82(18)	C8	N1	C9	113.22(14)
N1	C8	C7	105.76(16)	C9	N1	B00S	114.54(14)
C10	C9	C13	106.48(15)	C5	O1	B00S	113.94(15)
N1	C9	C10	115.42(15)	C7	O3	B00S	112.70(15)
N1	C9	C13	113.97(16)	C14	O5	C13	113.07(14)
C9	C10	C11	101.74(16)	C1	S1	C4	95.25(10)

Table 5.20: Torsion Angles for (*R*,*R*,*S*)-**134**

A	B	C	D	Angle/°	A	B	C	D	Angle/°
B00S	C4	S1	C1	-126.13(15)	C15	C14	O5	C13	177.81(15)
C1	C2	C3	C4	-47.1(2)	C15	C16	C17	C18	-0.1(3)
C2	C1	S1	C4	-20.84(16)	C16	C15	C20	C19	0.4(3)
C2	C3	C4	B00S	150.94(16)	C16	C17	C18	C19	0.3(3)
C2	C3	C4	S1	29.92(18)	C17	C18	C19	C20	-0.2(3)
C3	C4	S1	C1	-5.07(15)	C18	C19	C20	C15	-0.2(3)
C4	B00S	N1	C6	94.12(18)	C20	C15	C16	C17	-0.3(3)
C4	B00S	N1	C8	-150.86(16)	N1	B00S	C4	C3	-175.05(15)
C4	B00S	N1	C9	-28.8(2)	N1	B00S	C4	S1	-57.90(19)
C4	B00S	O1	C5	-104.69(19)	N1	B00S	O1	C5	19.82(19)
C4	B00S	O3	C7	146.02(16)	N1	B00S	O3	C7	19.73(19)
C5	C6	N1	B00S	25.66(18)	N1	C9	C10	C11	-160.73(16)
C5	C6	N1	C8	-81.85(18)	N1	C9	C13	C12	138.52(16)
C5	C6	N1	C9	149.64(16)	N1	C9	C13	O5	-101.80(17)
C6	C5	O1	B00S	-4.4(2)	O1	B00S	C4	C3	-60.6(2)
C7	C8	N1	B00S	24.91(17)	O1	B00S	C4	S1	56.59(18)
C7	C8	N1	C6	133.57(16)	O1	B00S	N1	C6	-27.36(16)
C7	C8	N1	C9	-98.10(18)	O1	B00S	N1	C8	87.66(15)
C8	C7	O3	B00S	-4.4(2)	O1	B00S	N1	C9	-150.24(14)
C9	C10	C11	C12	43.67(19)	O1	B00S	O3	C7	-85.81(19)
C9	C13	O5	C14	164.53(16)	O1	C5	C6	N1	-15.3(2)
C10	C9	C13	C12	10.1(2)	O2	C5	C6	N1	164.80(19)
C10	C9	C13	O5	129.77(16)	O2	C5	O1	B00S	175.54(19)
C10	C9	N1	B00S	-68.4(2)	O3	B00S	C4	C3	67.1(2)
C10	C9	N1	C6	174.33(16)	O3	B00S	C4	S1	-175.79(13)
C10	C9	N1	C8	46.9(2)	O3	B00S	N1	C6	-141.93(14)

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C10	C11	C12	C13	-38.1(2)	O3	B00S	N1	C8	-26.91(17)
C11	C12	C13	C9	17.2(2)	O3	B00S	N1	C9	95.19(17)
C11	C12	C13	O5	-96.93(19)	O3	B00S	O1	C5	126.74(17)
C12	C13	O5	C14	-81.6(2)	O3	C7	C8	N1	-15.1(2)
C13	C9	C10	C11	-33.16(19)	O4	C7	C8	N1	164.56(18)
C13	C9	N1	B00S	167.91(15)	O4	C7	O3	B00S	176.02(18)
C13	C9	N1	C6	50.6(2)	O5	C14	C15	C16	-129.12(18)
C13	C9	N1	C8	-76.8(2)	O5	C14	C15	C20	53.1(2)
C14	C15	C16	C17	-178.17(18)	S1	C1	C2	C3	41.1(2)
C14	C15	C20	C19	178.27(18)					

Table 5.21: Hydrogen Atom Coordinates ($Å \times 10^4$) and Isotropic Displacement Parameters ($Å^2 \times 10^3$) for (*R*,*R*,*S*)-**134**

Atom	*x*	*y*	*z*	U(eq)
H1A	7790(40)	7100(15)	5485(13)	21(6)
H1B	5480(40)	7492(18)	5433(14)	32(7)
H2A	6820(40)	5925(15)	4870(12)	13(5)
H2B	5690(50)	6623(17)	4410(15)	35(7)
H3A	2720(40)	6390(16)	5059(12)	16(5)
H3B	3380(40)	5457(16)	4837(14)	25(6)
H4	4600(40)	5142(15)	5954(12)	18(6)
H6A	1120(40)	6488(15)	7923(13)	18(6)
H6B	3300(40)	6579(15)	7544(13)	19(6)
H8A	-420(40)	4785(15)	7628(13)	18(6)
H8B	-1240(40)	5671(15)	7358(12)	17(6)
H9	4600(40)	5211(14)	7247(11)	10(5)

Atom	*x*	*y*	*z*	U(eq)
H10A	1890(40)	3844(15)	7243(12)	18(6)
H10B	3640(40)	3962(14)	6707(13)	15(6)
H11A	5980(40)	3696(17)	7608(14)	28(6)
H11B	4280(40)	2972(16)	7746(12)	20(6)
H12A	2700(40)	3758(15)	8606(13)	22(6)
H12B	4930(50)	3970(19)	8795(16)	40(8)
H13	2430(40)	5189(14)	8492(12)	17(6)
H14A	4240(40)	6054(14)	9239(12)	16(5)
H14B	5520(40)	5261(15)	9431(13)	18(6)
H16	8390(40)	5551(16)	10070(13)	22(6)
H17	11300(40)	6394(16)	10246(14)	23(6)
H18	11990(50)	7549(18)	9529(15)	37(8)
H19	9690(40)	7895(17)	8642(14)	24(6)
H20	6860(40)	7104(17)	8460(15)	30(7)

5.7.3 BBIDA Pyrrolidone (*S*,*S*,*R*)-261

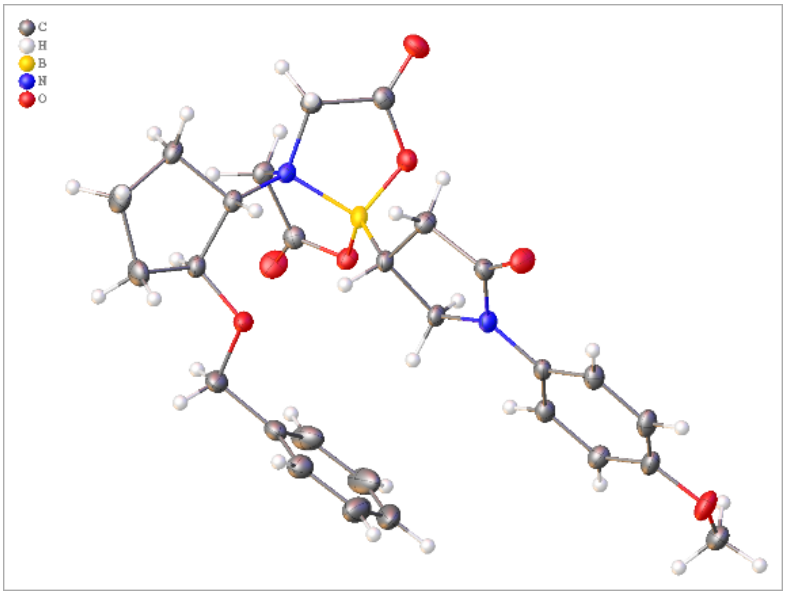


Table 5.22: Crystal data and structure refinement for (*S*,*S*,*R*)-**261**

Identification code	(*S*,*S*,*R*)-**261**
Empirical formula	$C_{27}H_{31}BN_2O_7$
Formula weight	506.35
Temperature/K	109.90(14)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.11296(3)
b/Å	13.28782(5)
c/Å	26.23360(11)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2479.487(17)
Z	4
ρ_{calc}g/cm^3	1.356
μ/mm^{-1}	0.801
F(000)	1072.0
Crystal size/mm^3	0.315 × 0.235 × 0.193
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.458 to 154.078
Index ranges	$-8 \leq h \leq 8$, $-16 \leq k \leq 16$, $-33 \leq l \leq 33$
Reflections collected	90379
Independent reflections	5188 [R_{int} = 0.0666, R_{sigma} = 0.0170]
Data/restraints/parameters	5188/0/335
Goodness-of-fit on F^2	1.069

Final R indexes [I>=2σ (I)]	R_1 = 0.0290, wR_2 = 0.0750
Final R indexes [all data]	R_1 = 0.0292, wR_2 = 0.0753
Largest diff. peak/hole / e Å^{-3}	0.15/-0.18
Flack parameter	0.02(4)

Data collected, solved and refined by Theo Tanner.

Diffraction special details:

'The crystals were found during screening to be twinned. The full data collection was carried out using the "Complete data for twins" collection strategy to ensure full data coverage'

Refine special details:

'The sample was twinned, but the major component (BASF ~0.8) was retained as hklf4, and the data for the minor component (BASF ~0.2, hlkf5) was discarded.'

Table 5.23: Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for (*S*,*S*,*R*)-**261**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O7	5259.1(17)	8115.6(8)	3702.5(4)	20.9(2)
O4	5777.8(16)	5999.6(8)	2333.0(4)	20.3(2)
O3	3615.4(15)	6736.6(8)	2932.5(4)	18.8(2)
O1	10029.9(17)	4076.9(9)	3499.8(5)	26.9(3)
O6	7287.8(18)	6032.9(9)	1582.6(4)	26.3(3)
O5	1299.7(16)	7835.4(10)	2787.2(5)	27.8(3)

Atom	*x*	*y*	*z*	U(eq)
O2	4328.0(19)	1078.5(9)	4674.4(5)	31.0(3)
N2	6205.9(17)	7724.2(9)	2584.8(5)	15.0(2)
N1	6953.3(19)	4525.3(9)	3679.6(5)	17.5(3)
C12	6859(2)	6427.8(12)	1978.0(6)	20.0(3)
C5	6308(2)	3660.3(11)	3945.5(6)	17.8(3)
C3	8682(2)	4641.7(12)	3455.5(6)	19.3(3)
C14	2901(2)	7557.4(12)	2729.7(6)	19.4(3)
C16	7124(2)	8448.4(11)	2953.6(6)	16.7(3)
C10	4390(2)	3579.5(12)	4061.8(6)	19.9(3)
C17	5849(2)	8884.3(11)	3366.2(6)	18.6(3)
C15	4341(2)	8094.4(12)	2401.1(6)	18.3(3)
C20	7939(2)	9391.6(11)	2704.8(6)	20.8(3)
C13	7486(2)	7463.4(11)	2149.8(6)	18.8(3)
C6	7512(2)	2876.1(12)	4091.6(6)	22.1(3)
C2	8631(2)	5580.2(12)	3127.4(6)	20.4(3)
C1	6806(2)	6129.9(11)	3268.6(6)	17.4(3)
C8	4882(3)	1948.8(12)	4442.2(6)	23.0(3)
C22	3102(3)	7494.0(13)	4305.3(6)	24.3(3)
C9	3682(2)	2731.4(12)	4306.8(6)	22.6(3)
C7	6791(3)	2037.5(12)	4336.6(7)	24.4(3)
C19	8356(3)	10075.6(13)	3163.4(7)	28.3(4)
C4	5612(2)	5309.2(11)	3528.5(6)	17.7(3)
C23	4171(3)	7055.6(14)	4689.2(7)	29.0(4)
C21	3799(3)	8425.3(13)	4042.0(7)	25.6(4)
C11	2357(3)	880.7(13)	4705.1(7)	29.4(4)
C18	7096(3)	9698.7(13)	3602.1(7)	26.5(4)
C27	1436(3)	7040.7(17)	4157.5(7)	35.8(4)

Atom	*x*	*y*	*z*	U(eq)
C24	3570(3)	6168.5(16)	4918.9(8)	39.4(5)
C25	1912(4)	5716.5(15)	4767.4(9)	44.8(6)
B1	5621(2)	6604.2(12)	2809.2(7)	16.9(3)
C26	838(4)	6153.6(18)	4387.3(8)	46.3(6)

Table 5.24: Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for (*S*,*S*,*R*)-**261**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O7	24.2(6)	16.2(5)	22.2(5)	0.9(4)	6.7(5)	2.4(4)
O4	21.6(6)	17.8(5)	21.5(5)	-2.1(4)	0.8(4)	-1.6(4)
O3	14.4(5)	18.7(5)	23.2(5)	2.6(4)	0.7(4)	-0.7(4)
O1	22.3(6)	25.8(6)	32.6(6)	5.7(5)	4.6(5)	9.1(5)
O6	28.5(6)	28.6(6)	21.9(5)	-4.9(5)	1.8(5)	4.9(5)
O5	13.8(5)	32.0(6)	37.5(7)	4.6(5)	1.3(5)	3.1(5)
O2	33.8(7)	18.9(6)	40.4(7)	10.2(5)	1.2(6)	-2.6(5)
N2	12.4(6)	14.4(5)	18.2(6)	2.2(4)	0.2(5)	1.7(5)
N1	17.9(6)	14.4(6)	20.0(6)	0.9(5)	0.0(5)	2.4(5)
C12	17.5(7)	20.5(7)	22.0(7)	0.1(6)	-1.8(6)	3.7(6)
C5	22.4(7)	13.6(6)	17.4(7)	-0.8(5)	-1.0(6)	0.0(6)
C3	21.1(7)	17.0(7)	19.9(7)	-1.4(6)	0.6(6)	2.3(6)
C14	15.8(7)	20.4(7)	22.1(7)	-1.1(6)	-1.9(6)	-1.1(6)
C16	14.3(6)	14.6(7)	21.2(7)	0.9(5)	-0.8(6)	-0.2(6)
C10	21.7(8)	16.8(7)	21.2(7)	0.7(6)	-1.0(6)	2.1(6)
C17	19.1(7)	14.5(7)	22.3(7)	0.6(6)	0.9(6)	0.0(6)
C15	14.1(7)	18.8(7)	22.0(7)	3.1(5)	-1.8(6)	2.1(6)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C20	18.9(7)	16.2(7)	27.3(8)	3.2(6)	1.9(6)	-1.6(6)
C13	17.6(7)	19.5(7)	19.5(7)	0.5(5)	3.9(6)	0.5(6)
C6	22.5(8)	18.0(7)	25.7(7)	0.6(6)	-2.2(6)	2.7(6)
C2	17.1(7)	19.9(7)	24.1(7)	2.9(6)	2.6(6)	2.0(6)
C1	17.6(7)	13.6(7)	21.2(7)	0.6(5)	1.5(6)	1.1(6)
C8	31.2(9)	14.9(7)	23.0(7)	2.0(6)	-0.5(6)	-2.6(7)
C22	28.8(8)	22.4(8)	21.6(7)	-3.8(6)	7.5(7)	-0.6(7)
C9	23.0(8)	20.6(7)	24.2(7)	2.5(6)	0.5(6)	-1.4(6)
C7	28.1(8)	16.3(7)	29.0(8)	2.7(6)	-5.4(7)	2.5(6)
C19	29.0(9)	21.8(8)	34.1(9)	-0.8(7)	-2.5(7)	-9.2(7)
C4	18.3(7)	13.0(6)	21.7(7)	2.3(6)	1.0(6)	2.8(6)
C23	29.6(9)	29.2(8)	28.1(8)	0.9(7)	6.1(7)	2.6(7)
C21	28.8(9)	21.5(7)	26.3(8)	-0.6(6)	9.7(7)	3.7(7)
C11	36.7(10)	21.4(8)	30.1(8)	2.5(7)	6.2(8)	-5.7(7)
C18	29.0(9)	21.7(7)	29.0(8)	-6.7(6)	0.3(7)	-5.2(7)
C27	38.0(10)	45.0(11)	24.3(8)	-3.5(8)	2.0(8)	-12.4(9)
C24	49.0(12)	33.5(10)	35.8(10)	9.2(8)	13.6(9)	10.3(9)
C25	65.9(15)	24.2(9)	44.2(11)	-2.0(8)	28.7(11)	-8.8(10)
B1	15.2(8)	12.1(7)	23.3(8)	-0.4(6)	0.9(7)	-1.2(6)
C26	57.3(14)	46.7(12)	34.9(10)	-12.2(9)	13.6(10)	-29.1(11)

Table 5.25: Bond Lengths for (*S*,*S*,*R*)-**261**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O7	C17	1.4133(18)	C3	C2	1.516(2)
O7	C21	1.4288(19)	C14	C15	1.517(2)
O4	C12	1.335(2)	C16	C17	1.527(2)

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O4	B1	1.4896(19)	C16	C20	1.527(2)
O3	C14	1.3157(19)	C10	C9	1.392(2)
O3	B1	1.473(2)	C17	C18	1.530(2)
O1	C3	1.223(2)	C20	C19	1.537(2)
O6	C12	1.202(2)	C6	C7	1.385(2)
O5	C14	1.207(2)	C2	C1	1.535(2)
O2	C8	1.365(2)	C1	C4	1.541(2)
O2	C11	1.429(2)	C1	B1	1.600(2)
N2	C16	1.5129(19)	C8	C9	1.391(2)
N2	C15	1.4949(18)	C8	C7	1.391(3)
N2	C13	1.5004(19)	C22	C23	1.390(3)
N2	B1	1.654(2)	C22	C21	1.501(2)
N1	C5	1.4207(19)	C22	C27	1.385(3)
N1	C3	1.372(2)	C19	C18	1.542(2)
N1	C4	1.4671(19)	C23	C24	1.391(3)
C12	C13	1.515(2)	C27	C26	1.391(3)
C5	C10	1.402(2)	C24	C25	1.382(4)
C5	C6	1.402(2)	C25	C26	1.384(4)

Table 5.26: Bond Angles for (*S*,*S*,*R*)-**261**

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C17	O7	C21	113.37(12)	N2	C15	C14	105.14(12)
C12	O4	B1	113.47(12)	C16	C20	C19	102.95(13)
C14	O3	B1	112.60(12)	N2	C13	C12	104.92(12)
C8	O2	C11	117.65(14)	C7	C6	C5	119.91(15)
C16	N2	B1	116.96(11)	C3	C2	C1	105.94(13)

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C15	N2	C16	112.34(11)	C2	C1	C4	103.65(12)
C15	N2	C13	111.68(11)	C2	C1	B1	116.83(13)
C15	N2	B1	100.80(11)	C4	C1	B1	108.76(12)
C13	N2	C16	111.80(11)	O2	C8	C9	124.77(16)
C13	N2	B1	102.45(11)	O2	C8	C7	116.25(15)
C5	N1	C4	119.79(13)	C7	C8	C9	118.98(15)
C3	N1	C5	126.25(13)	C23	C22	C21	119.89(16)
C3	N1	C4	112.77(12)	C27	C22	C23	119.25(17)
O4	C12	C13	110.44(13)	C27	C22	C21	120.81(17)
O6	C12	O4	124.19(15)	C8	C9	C10	120.10(16)
O6	C12	C13	125.36(15)	C6	C7	C8	121.48(15)
C10	C5	N1	118.90(14)	C20	C19	C18	106.25(13)
C10	C5	C6	118.55(14)	N1	C4	C1	105.29(12)
C6	C5	N1	122.55(14)	C22	C23	C24	120.06(19)
O1	C3	N1	126.36(15)	O7	C21	C22	106.82(13)
O1	C3	C2	125.27(15)	C17	C18	C19	105.37(13)
N1	C3	C2	108.35(13)	C22	C27	C26	120.6(2)
O3	C14	C15	111.03(13)	C25	C24	C23	120.4(2)
O5	C14	O3	124.61(15)	C24	C25	C26	119.73(19)
O5	C14	C15	124.34(15)	O4	B1	N2	99.67(11)
N2	C16	C17	115.99(12)	O4	B1	C1	112.31(12)
N2	C16	C20	114.36(12)	O3	B1	O4	108.74(12)
C17	C16	C20	102.55(12)	O3	B1	N2	102.39(11)
C9	C10	C5	120.97(15)	O3	B1	C1	113.06(13)
O7	C17	C16	110.16(12)	C1	B1	N2	119.34(12)
O7	C17	C18	115.52(13)	C25	C26	C27	120.0(2)
C16	C17	C18	102.14(13)				

Table 5.27: Torsion Angles for (*S*,*S*,*R*)-**261**

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O7	C17	C18	C19	150.69(14)	C20	C16	C17	O7	-168.38(12)
O4	C12	C13	N2	-15.74(16)	C20	C16	C17	C18	-45.12(15)
O3	C14	C15	N2	-21.22(17)	C20	C19	C18	C17	-5.80(19)
O1	C3	C2	C1	-170.16(16)	C13	N2	C16	C17	171.24(12)
O6	C12	C13	N2	165.29(16)	C13	N2	C16	C20	52.15(16)
O5	C14	C15	N2	160.38(16)	C13	N2	C15	C14	135.22(13)
O2	C8	C9	C10	-178.71(15)	C13	N2	B1	O4	-28.71(13)
O2	C8	C7	C6	178.52(15)	C13	N2	B1	O3	-140.50(12)
N2	C16	C17	O7	66.26(16)	C13	N2	B1	C1	93.80(15)
N2	C16	C17	C18	-170.48(12)	C6	C5	C10	C9	-1.4(2)
N2	C16	C20	C19	167.83(13)	C2	C1	C4	N1	19.26(15)
N1	C5	C10	C9	177.87(14)	C2	C1	B1	O4	32.81(18)
N1	C5	C6	C7	-178.04(15)	C2	C1	B1	O3	156.33(13)
N1	C3	C2	C1	11.47(17)	C2	C1	B1	N2	-83.22(17)
C12	O4	B1	O3	127.78(13)	C22	C23	C24	C25	0.1(3)
C12	O4	B1	N2	21.07(15)	C22	C27	C26	C25	0.0(3)
C12	O4	B1	C1	-106.32(14)	C9	C8	C7	C6	-1.3(3)
C5	N1	C3	O1	-9.6(3)	C7	C8	C9	C10	1.1(2)
C5	N1	C3	C2	168.71(14)	C4	N1	C5	C10	-0.5(2)
C5	N1	C4	C1	178.28(13)	C4	N1	C5	C6	178.72(14)
C5	C10	C9	C8	0.3(2)	C4	N1	C3	O1	-177.10(16)
C5	C6	C7	C8	0.1(3)	C4	N1	C3	C2	1.25(17)
C3	N1	C5	C10	-167.17(15)	C4	C1	B1	O4	-84.01(15)
C3	N1	C5	C6	12.1(2)	C4	C1	B1	O3	39.51(16)

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C3	N1	C4	C1	-13.36(16)	C4	C1	B1	N2	159.96(12)
C3	C2	C1	C4	-18.68(16)	C23	C22	C21	O7	75.30(19)
C3	C2	C1	B1	-138.27(13)	C23	C22	C27	C26	-0.4(3)
C14	O3	B1	O4	-90.88(14)	C23	C24	C25	C26	-0.5(3)
C14	O3	B1	N2	13.96(15)	C21	O7	C17	C16	-169.27(13)
C14	O3	B1	C1	143.65(13)	C21	O7	C17	C18	75.67(18)
C16	N2	C15	C14	-98.24(14)	C21	C22	C23	C24	-177.22(16)
C16	N2	C13	C12	152.99(12)	C21	C22	C27	C26	177.15(18)
C16	N2	B1	O4	-151.33(12)	C11	O2	C8	C9	10.9(2)
C16	N2	B1	O3	96.88(14)	C11	O2	C8	C7	-168.91(16)
C16	N2	B1	C1	-28.82(18)	C27	C22	C23	C24	0.3(3)
C16	C17	C18	C19	31.12(17)	C27	C22	C21	O7	-102.22(19)
C16	C20	C19	C18	-21.80(18)	C24	C25	C26	C27	0.4(3)
C10	C5	C6	C7	1.2(2)	B1	O4	C12	O6	174.07(15)
C17	O7	C21	C22	170.27(14)	B1	O4	C12	C13	-4.91(17)
C17	C16	C20	C19	41.41(16)	B1	O3	C14	O5	-178.26(16)
C15	N2	C16	C17	44.76(16)	B1	O3	C14	C15	3.34(17)
C15	N2	C16	C20	-74.33(15)	B1	N2	C16	C17	-71.11(16)
C15	N2	C13	C12	-80.17(14)	B1	N2	C16	C20	169.80(13)
C15	N2	B1	O4	86.58(12)	B1	N2	C15	C14	27.04(14)
C15	N2	B1	O3	-25.20(13)	B1	N2	C13	C12	26.94(14)
C15	N2	B1	C1	-150.90(13)	B1	C1	C4	N1	144.22(12)

Table 5.28: Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for (*S*,*S*,*R*)-**261**

Atom	*x*	*y*	*z*	U(eq)
H16	8176.61	8084.84	3126.69	20
H10	3561.76	4111.52	3972.01	24
H17	4724.76	9204.03	3204.3	22
H15A	4157.45	7926.39	2036.79	22
H15B	4240.39	8832.76	2443.49	22
H20A	7018.5	9707.48	2471.38	25
H20B	9101.43	9234.58	2513.06	25
H13A	8813.29	7450.79	2263	23
H13B	7355.71	7957.78	1869.7	23
H6	8820.15	2920.04	4022.56	26
H2A	8633.49	5399.27	2761.32	24
H2B	9736.06	6011.33	3198	24
H1	7096.07	6669.88	3522.15	21
H9	2378.37	2686.77	4381.75	27
H7	7618.51	1510.91	4434.65	29
H19A	8060.48	10784.92	3080.34	34
H19B	9699.15	10029.64	3259.81	34
H4A	4954.13	5584.23	3830.46	21
H4B	4665.69	5035.91	3288.86	21
H23	5312.87	7362.03	4794.9	35
H21A	2765.55	8749.72	3850.01	31
H21B	4291.97	8912.2	4294.48	31
H11A	1818.22	873.82	4361.31	44
H11B	1747.48	1407.31	4907.89	44
H11C	2152.71	225.36	4867.31	44

Atom	*x*	*y*	*z*	U(eq)
H18A	7869.13	9415.98	3881.38	32
H18B	6322.36	10254.96	3739.77	32
H27	694.56	7338.49	3896.8	43
H24	4303.47	5871.7	5181.44	47
H25	1511.3	5108.16	4923.52	54
H26	-306.78	5847.81	4283.48	56

Experimental

Single crystals of $C_{27}H_{31}BN_2O_7$ **[**(*S*,*S*,*R*)-**261]** were **[]**. A suitable crystal was selected and **[]** on a **SuperNova, Dual, Cu at home/near, HyPix** diffractometer. The crystal was kept at 109.90(14) K during data collection. Using Olex2 [1], the structure was solved with the SHELXT [2] structure solution program using Intrinsic Phasing and refined with the SHELXL [3] refinement package using Least Squares minimisation.

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Crystal structure determination of [(*S*,*S*,*R*)-261]

Crystal Data for $C_{27}H_{31}BN_2O_7$ (*M* =506.35 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 7.11296(3) Å, *b* = 13.28782(5) Å, *c* = 26.23360(11) Å, *V* = 2479.487(17) Å^3, *Z* = 4, *T* = 109.90(14) K, μ(Cu Kα) = 0.801 mm^{-1}, *Dcalc* = 1.356 g/cm^3, 90379 reflections measured (7.458° ≤ 2Θ ≤ 154.078°), 5188 unique (R_{int} = 0.0666, R_{sigma} = 0.0170) which were used in all calculations. The final R_1 was 0.0290 (I > 2σ(I)) and wR_2 was 0.0753 (all data).

Refinement model description

Number of restraints - 0, number of constraints - unknown.

Details:

```
1. Fixed Uiso
 At 1.2 times of:
  All C(H) groups, All C(H,H) groups
 At 1.5 times of:
  All C(H,H,H) groups
2.a Ternary CH refined with riding coordinates:
 C16(H16), C17(H17), C1(H1)
2.b Secondary CH2 refined with riding coordinates:
 C15(H15A,H15B), C20(H20A,H20B), C13(H13A,H13B), C2(H2A,H2B),
C19(H19A,H19B),
 C4(H4A,H4B), C21(H21A,H21B), C18(H18A,H18B)
2.c Aromatic/amide H refined with riding coordinates:
 C10(H10), C6(H6), C9(H9), C7(H7), C23(H23), C27(H27), C24(H24), C25(H25),
 C26(H26)
2.d Idealised Me refined as rotating group:
 C11(H11A,H11B,H11C)
```

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