New Routes to α-Arylated *N*-Boc Heterocycles

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Finally, my thanks to my family, Simon, Sallie and Judith in particular (and Pom!), for all they've done to help me get to this position now.

Author's Declaration

The research presented in this thesis is, to the best of my knowledge, original except where due reference has been made to other authors. This work has not previously been presented for an award at this, or any other, University.

Matthew Gill

Abbreviations

°C	Degrees Centigrade
3D	3-Dimensional
Å	Angstrom
$A_{1,3}$	Allylic strain
aq.	Aqueous
ax	axial
BCP	Bicyclo[1.1.1]pentyl
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
BTK	Bruton's tyrosine kinase
CCR3	C-C Chemokine Receptor Type 3
CDR	Catalytic Dynamic Resolution
cod	1,5-Cyclooctadiene
CPME	Cyclopentyl Methyl Ether
CSP-HPLC	Chiral Stationary Phase High Performance Liquid Chromatography
d	Doublet
dba	Dibenzylideneacetone
dec.	Decomposed
DEPT	Distortions Enhancement by Polarization Transfer
DFT	Density Functional Theory

DIPEA	*N*,*N*-Diisopropylethylamine
DKR	Dynamic Kinetic Resolution
DMAP	Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dppf	1,1'ferrocenediyl-bis(diphenylphosphine)
dr	Diastereomeric Ratio
dtbbpy	4,4′-Di-*tert*-butyl-2,2′-dipyridyl
dtbpf	1,1'-Bis(di-*tert*-butylphosphino)ferrocene
DTR	Dynamic Thermodynamic Resolution
E^+	Electrophile
eq	equatorial
eq.	Equivalents
er	Enantiomeric Ratio
ERK2	Mitogen-activated protein Kinase 1
es	Enantiospecificity
ESI	Electronspray Ionisation
evap.	Evaporated
FDA	Food and Drug Administration
FT-IR	Fourier Transform Infrared Spectroscopy
g	Gram(s)
G1	Generation 1
G2	Generation 2

G3	Generation 3
G4	Generation 4
GC	Gas Chromatography
h	Hour(s)
HAT	Hydrogen Atom Transfer
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
IC_{50}	Half-maximal Inhibitory Concentration
IR	Infra-red
J	Coupling constant in Hz
kg	Kilogram
LED	Light Emitting Diode
LUMO	Lowest-unoccupied molecular orbital
m	Multiplet
M	Molar
m	*meta*
m/z	Mass to charge ratio
M^+	Molecular ion
MeCN	Acetonitrile
mg	Milligrams
MHz	Megahertz
MIDA	*N*-Methyliminodiacetic acid
min	Minute
mL	Millilitre

mmol	Millimole
mol	Mole
mp	Melting point
MS	Molecular Sieves
MTBE	Methyl *tert*-butyl ether
n.d.	Not determined
NBS	*N*-Bromosuccinimide
n-BuLi	*n*-Butyllithium
neop	neopentyl
NK1	Neurokinin 1
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
NS5A	Nonstructural protein 5A
o	*ortho*
p	*para*
PDRA	Postdoctoral Research Associate
PEPPSI	Pyridine-Enhanced Precatalyst Preparation Stabilization + Initiation
pin	Pinacolato
q	Quartet
ReactIR	React Infra-red
RF	Retention factor
rt	Room Temperature
s	Singlet
s-BuLi	*sec*-Butyllithium

SMCC	Suzuki-Miyaura cross-coupling
S_NAr	Nucleophilic Aromatic Substitution
t	Triplet
t	*tert*
T3P	Propanephosphonic acid anhydride
t-AmylOH	2-Methylbutan-2-ol
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilane
TKR	Tropomyosin Receptor Kinase
TLC	Thin Layer Chromatography
TMEDA	*N*,*N*,*N*',*N*'-Tetramethylethylenediamine
TMO	2,2,5,5-Tetramethyltetrahydrofuran
TRIP	3,3'-Bis(2,4,6-triisopropylphenyl)-2,2'-binaphtholate
UV	Ultraviolet
UV-A	Ultraviolet A
W	Watt
δ	Chemical shift
µ	micro

1. Introduction

1.1 Use of α-Aryl Piperidines and Pyrrolidines in Biologically-Active Molecules

Nitrogen-containing heterocycles occur frequently in small molecule drugs and a study by Njardarson *et al.* of U.S. FDA approved unique small molecule drugs showed that 59% contained at least one nitrogen heterocycle.[1] The most frequently occurring nitrogen heterocycle is piperidine, whilst the fifth is pyrrolidine. In-depth analysis of the piperidine moieties found in this dataset showed that 58% of the small drug molecules that contained piperidine were 4-substituted, whilst 92% of pyrrolidine-containing drugs are substituted at the α-position. Therefore, there is a need to improve upon and develop methods that enable the α-arylation of pyrrolidine and 4-substituted piperidines and, in particular, to obtain methods that enable the cross-coupling of heteroaryl halides due to the prevalence of heteroaromatics in biologically-active molecules.

Examples of biologically-active molecules containing the α-aryl piperidine motif include **1**, an NK1 antagonist developed by chemists at Merck, and Ledipasvir (Figure 1.1). Harrison *et al.* originally reported the discovery of the NK1 antagonist **1**, which was further investigated by Xiao, Lavey and co-workers and shown to have good *in vitro* activity for the treatment of nausea associated with chemotheropy.[2,3,4] The molecule possess a 2,2-disubstituted piperidine ring, the alkyl substituent having been introduced *via* benzylic lithiation-trapping. Ledipasvir was developed by Gilead Sciences and is used, in combination with sofosbuvir, to treat hepatitis C.[5] Ledipasvir is an inhibitor of NS5A which, whilst the exact mode of action is not defined, prevents virus production. It contains both an α-aryl bridged piperidine and an α-arylpyrrolidine, highlighting the ubiquity of these motifs.

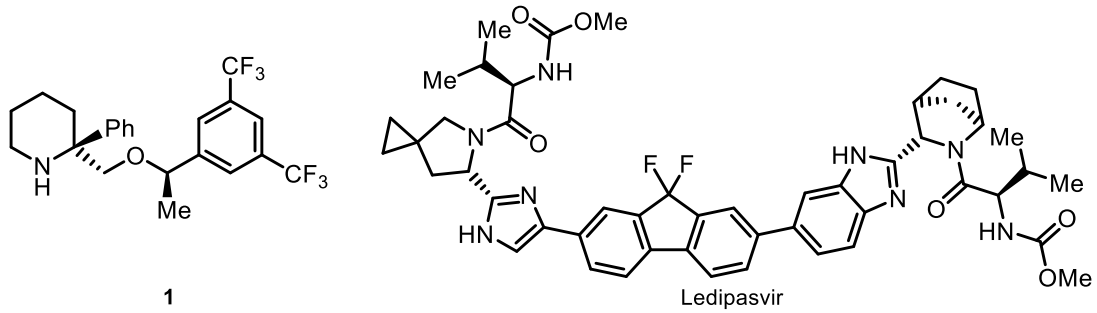


Figure 1.1: Structures of biologically-active compounds containing α-arylpiperidines

The α-arylpyrrolidine motif is present in several important biologically-active molecules (Figure 1.2). For example, it is present in Aticaparant, which was developed by Huang and co-workers at Eli Lilly to treat depression through its utility as a kappa opioid receptor antagonist.[6,7] The α-arylpyrrolidine motif is also present in Larotrectinib, a compound that was originally discovered by Array Biopharma and shown to have antitumor activity in patients with tropomyosin receptor kinase (TKR) fusion-positive tumours.[8,9] In 2018, Larotrectinib was approved as a first-in-class and highly selective TKR inhibitor. Developed by Acerta Pharma, Acalabrutinib is a Bruton's tyrosine kinase (BTK) inhibitor and is used to treat leukaemia; it has been approved for use in the U.S. and the E.U..[10] Inhibition of BTK leads to tumour cell death in leukaemia cells and is used to delay the progression of cancer. Acalabrutinib also possesses the α-arylpyrrolidine motif.

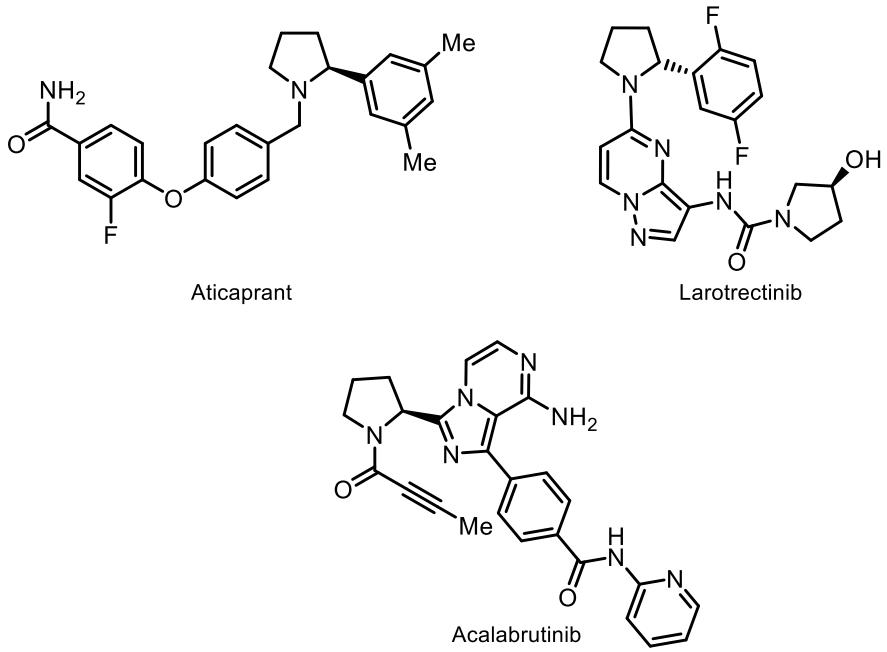
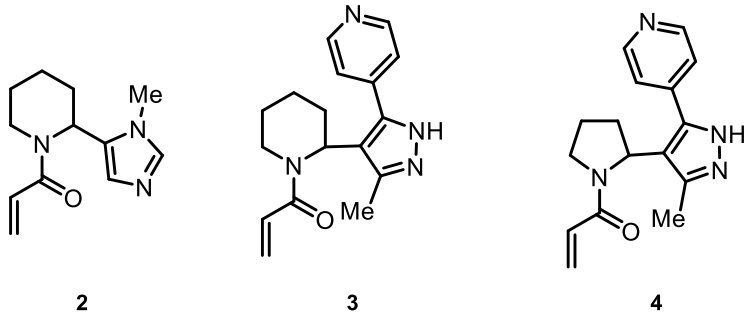


Figure 1.2: Structures of biologically-active compounds containing α-arylpyrrolidines

Recently, Denis, Cons and co-workers at Astex Pharmaceuticals reported the results of an electrophilic covalent fragment screen against extracellular signal-regulated kinase 2 (ERK2).[11] ERK2 is an important oncological target due to its role in cell proliferation. As part of a fragment-based drug discovery programme, a fragment screen with covalent fragments was carried out. From this, α-arylpiperidine **2** was shown to have good activity (Figure 1.3). This fragment was further developed. First, the aromatic group was modified to give α-arylpiperidine **3** and then it was improved further by

replacing the piperidine core with a pyrrolidine ring to give α-arylpyrrolidine **4**. The structural changes that gave α-arylpyrrolidine **4** were shown to increase the activity against ERK2; α-arylpyrrolidine **4** exhibited an IC_{50} of 7.8 μM.



2 **3** **4**

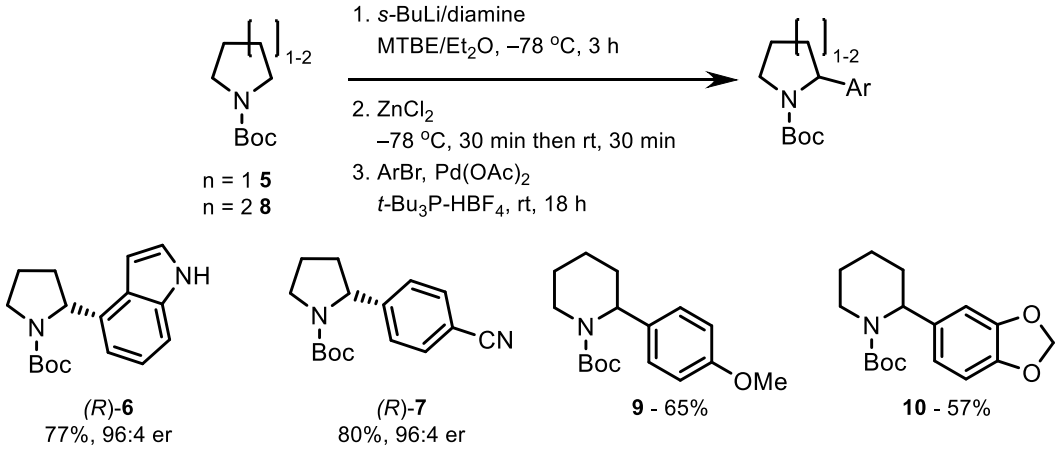
Figure 1.3: Covalent EKR2 fragment optimisation

Collectively, these selected examples demonstrate the widespread nature of the α-arylpiperidine and α-arylpyrrolidine motif in important pharmaceutical molecules and compounds in development. In 2009, Lovering and co-workers highlighted the importance of sp^3 centres in medicinal compounds, studying the fraction of sp^3 centres in all biologically-active molecules that had gone through medicinal development since 1980. It was reported that prospective drug candidates were more likely to succeed at each step if they possessed a greater fraction of sp^3 centres, indicated by higher proportions of these molecules making it to late-stage development and ultimately the market. Lovering and co-worker's report has since triggered renewed exploration of saturated systems and a shift in attention toward motifs with more 3D shape. This also highlights the importance of the development of methods for the functionalisation of piperidine and pyrrolidine, particularly *via* methods that deliver products with a high degree of stereoselectivity. These methods would enable medicinal chemists to synthesise molecules with greater chances of ultimately becoming commercial drugs.

1.2 Selected Overview of Approaches for the Synthesis of α-Aryl Piperidines and Pyrrolidines

There are numerous different methods for the arylation of saturated nitrogen heterocycles α to nitrogen and each method has different limitations and requirements. This overview covers selected examples of the main unique approaches that have been reported for the α-arylation of either pyrrolidine or piperidine in which the heterocycle is typically functionalised on the nitrogen.

One of the main approaches for the α-arylation of both pyrrolidines and piperidines is the lithiation-transmetallation-Negishi cross-coupling methodology developed by Campos *et al.*, examples of which are shown in Scheme 1.1.[12] This methodology makes use of a Boc group on nitrogen and C-H activation by lithiation with *s*-BuLi/diamine, which is directed by the carbonyl of the Boc group. The lithiated species is transmetallated to an organozinc intermediate and a palladium-catalysed Negishi cross-coupling reaction is then performed. Campos *et al.* developed this methodology for use on *N*-Boc-pyrrolidine **5** (for example, to give (*R*)-**6** and (*R*)-**7**) and it was subsequently adapted by Coldham and Leonori for the α-arylation of *N*-Boc-piperidine **8** (for example, to give **9** and **10**).[13] One particular advantage of this methodology is that the lithiation can be conducted asymmetrically through the use of a chiral diamine ligand in the lithiation step and stereochemistry is then retained through the procedure to afford α-arylpyrrolidines in high er. A disadvantage of this methodology is the use of a strong base and the limitations that this places on substituents already present in the pyrrolidine or piperidine ring. This methodology is discussed in detail in Chapter 2.



(*R*)-**6**
77%, 96:4 er

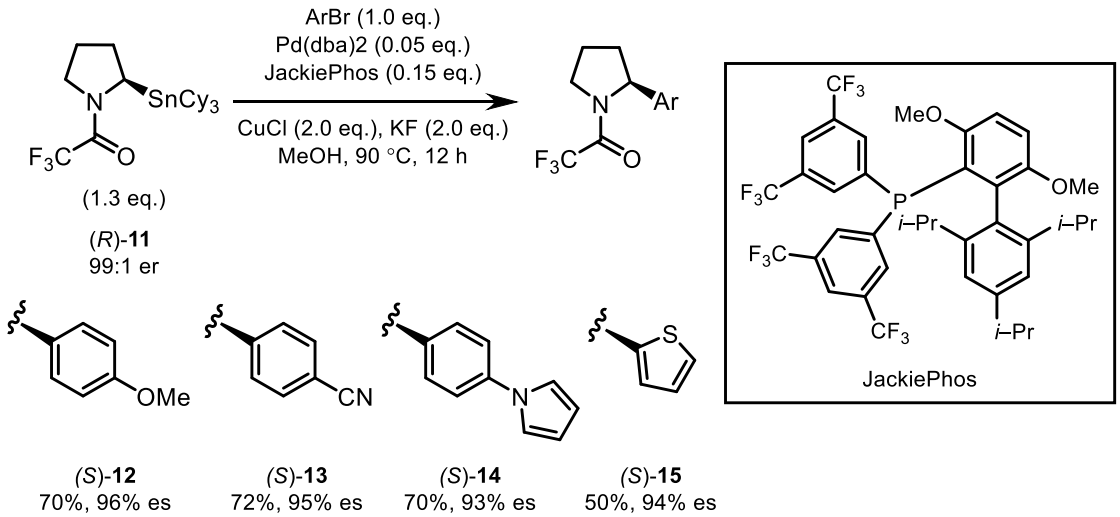
(*R*)-**7**
80%, 96:4 er

9 - 65%

10 - 57%

Scheme 1.1

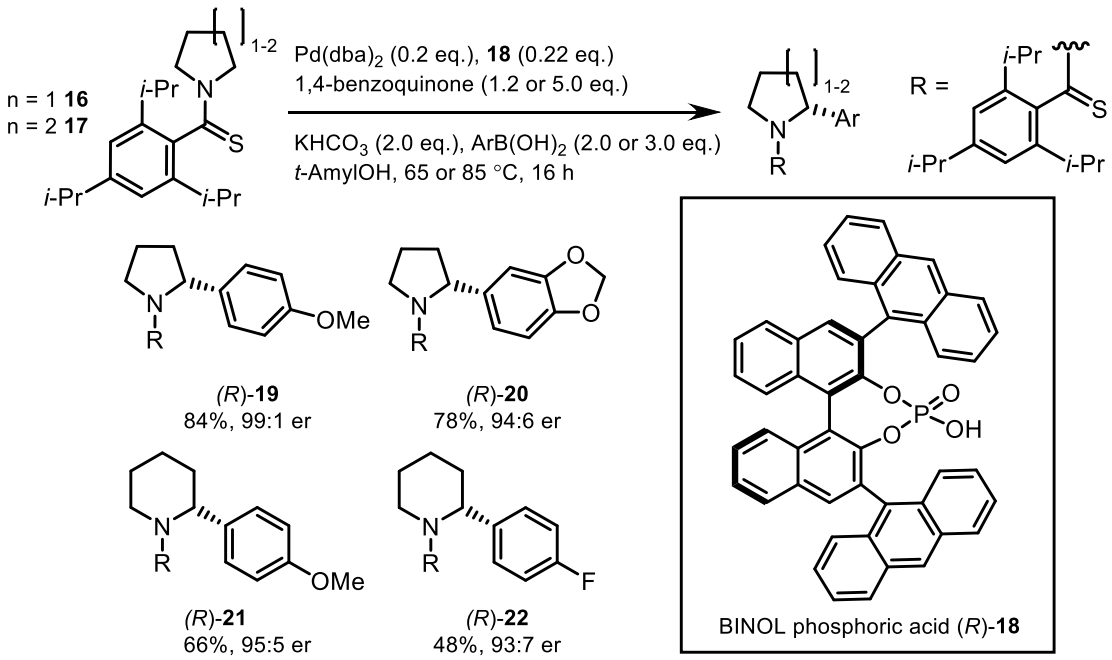
Biscoe *et al.* reported a method for the stereospecific Stille cross-coupling of enantioenriched α-stannyl-*N*-C(O)CF_3 pyrrolidine (*R*)-**11**.[14] The key step in the synthesis of α-stannyl-*N*-C(O)CF_3 pyrrolidine (*R*)-**11** used Ellman's auxiliary. After investigation, it was found that the C(O)CF_3 protecting group was superior to a Boc group and, in combination with JackiePhos, favoured the formation of the desired α-aryl-*N*-C(O)CF_3 pyrrolidines. A key feature of this methodology was the use of cyclohexyl groups instead of *n*-butyl groups in α-stannyl-*N*-C(O)CF_3pyrrolidine (*R*)-**11**. It was found that cyclohexyl groups underwent transmetallation less readily than *n*-butyl groups and thus the desired pyrrolidine group underwent the required transmetallation to palladium, reducing undesired side-products. Stille cross-coupling with $Pd(dba)_2$, JackiePhos, CuCl and KF in methanol at 90 °C gave α-arylpyrrolidines in high er. The reaction proceeded with high enantiospecificity (es) and examples are shown in Scheme 1.2. For example, the Stille cross-coupling of α-stannylpyrrolidine (*R*)-**11** (99:1 er) with 4-bromoanisole gave α-arylpyrrolidine (*S*)-**12** in 70% yield with 96% es. Key advantages of this methodology include the ability to synthesise enantioenriched α-arylpyrrolidines in good yield and from an isolatable and crystalline starting material. However, this methodology involved the use of toxic organotin reagents which make it less appealing for use in medicinal chemistry.



Scheme 1.2

Yu and co-workers have developed methodology for the enantioselective palladium-catalysed C-H α-arylation of pyrrolidine **16** and piperidine **17** using a thioamide directing group and BINOL phosphoric acid (*R*)-**18**.[15] The bulky

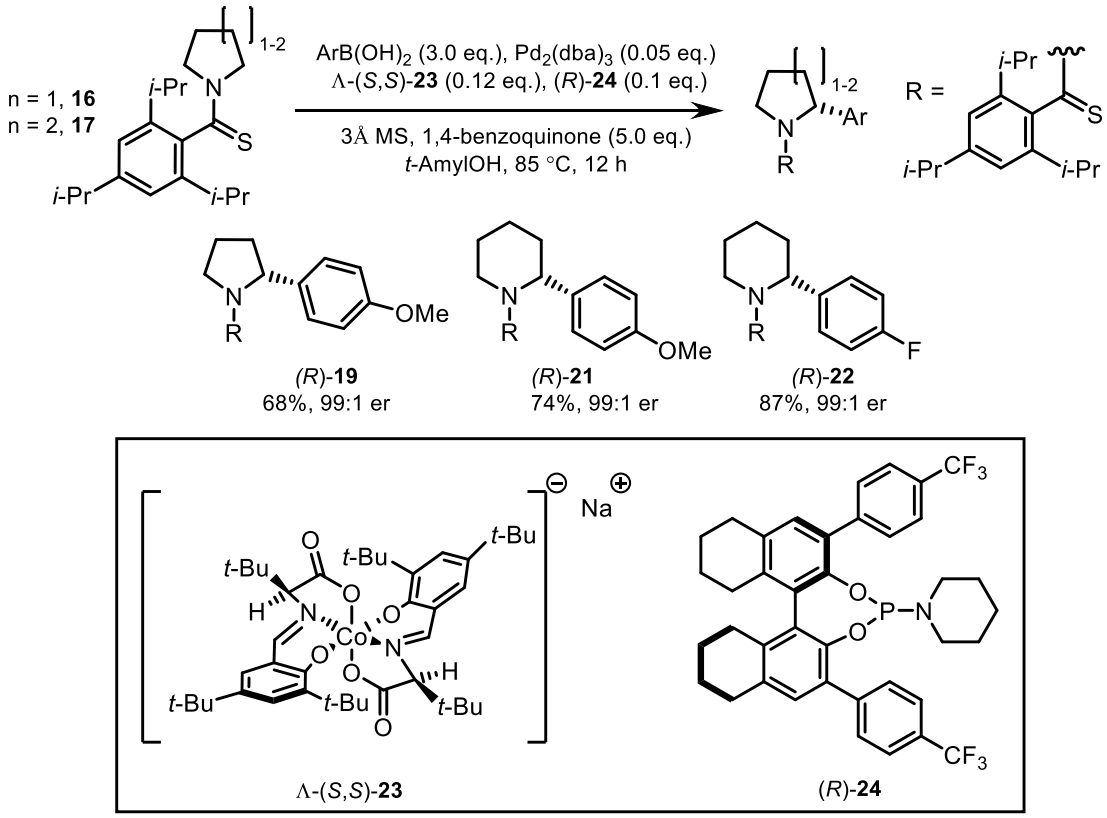
triisopropylbenzothioamide directing group gave the best reactivity and enantiocontrol. α-C-H functionalisation was achieved by reacting the substrates with $Pd_2(dba)_3$, BINOL phosphoric acid (*R*)-**18**, 1,4-benzoquinone and $KHCO_3$ in *t*-AmylOH at 65 °C for 16 hours. Under these conditions, good yields and enantioselectivities were achieved with pyrrolidine (Scheme 1.3). Increased equivalents of 1,4-benzoquinone (5.0) and arylboronic acid (3.0) were required for the α-arylation of piperidine as well as a reaction temperature of 85 °C. However, with these changes, α-aryl piperidines were also obtained in good yield and er. For example, the α-C-H arylation of piperidine **17** with 4-methoxyphenylboronic acid gave α-arylpiperidine (*R*)-**21** in 66% yield and 95:5 er. Yu and co-workers reported that the triisopropylbenzothioamide directing group could be removed, although harsh conditions were required ($NaBH_4$ and BCl_3). Nevertheless, the reaction possesses notable benefits including the ability to synthesise α-aryl heterocycles, piperidine in particular, in high er which is not otherwise easy to achieve. Also, the reaction proceeds by C-H activation without the requirement of a strong base. However, the disadvantages of the procedure include the necessity for directing group manipulation as well as the high equivalents of reagents required.



Scheme 1.3

The methodology of Yu and co-workers was subsequently developed further by Zhang, Gong and co-workers using the same thioamide directing group for the enantioselective α-arylation of pyrrolidines and piperidines.[16] Similar conditions were used for the cross-

coupling: 3.0 equivalents of arylboronic acid, $Pd_2(dba)_3$ and 1,4-benzoquinone in *t*-AmylOH at 85 °C for 12 hours. The differences were the use of 3Å molecular sieves (MS), chiral cobalt complex Λ-(*S*,*S*)-**23** and ligand (*R*)-**24**. With these conditions, thioamidepyrrolidine **16** and piperidine **17** could be cross-coupled with boronic acids in good yields and with excellent enantioselectivity. This work generally showed an improvement in the enantioselectivity compared to those reported by Yu and co-workers.[15] For example, cross-coupling with 4-methoxyphenylboronic acid gave α-arylpiperidine (*R*)-**21** in 74% yield and 99:1 er (Scheme 1.4). It should be noted that no examples of the cross-coupling of heteroarylboronic acids were included. Zhang, Gong and co-workers' adaptations included the addition of multiple additives and molecular sieves, as well as using three equivalents of boronic acid and a directing group, which renders the procedure less attractive. On the other hand, this work improved the enantioselectivity and demonstrated a good substrate scope.



Scheme 1.4

Doyle, MacMillan and co-workers reported that, with the combination of photocatalysed decarboxylation and nickel-catalysed cross-coupling, the α-arylation of α-carboxyl-*N*-Boc-pyrrolidine **25** could be accomplished with a wide range of aryl

halides.[17] The methodology relied on an interwoven catalytic cycle, involving iridium-catalysed decarboxylation to generate a pyrrolidine radical (Figure 1.4). Independently, the aryl halide would undergo oxidative addition to the nickel catalyst, which would then take up the pyrrolidine radical and undergo reductive elimination to afford an α-arylpyrrolidine. A single electron transfer would return the transition metals to their original oxidation levels ready to repeat the cycle. Doyle, MacMillan and co-workers used iridium photocatalyst **26** and $NiCl_2$•glyme along with dtbbpy and Cs_2CO_3 in DMF; the reaction was irradiated with two standard 26 W lights at rt for 72 hours. Aryl chlorides, bromides and iodides all worked well under the reaction conditions and examples are shown in Scheme 1.5.

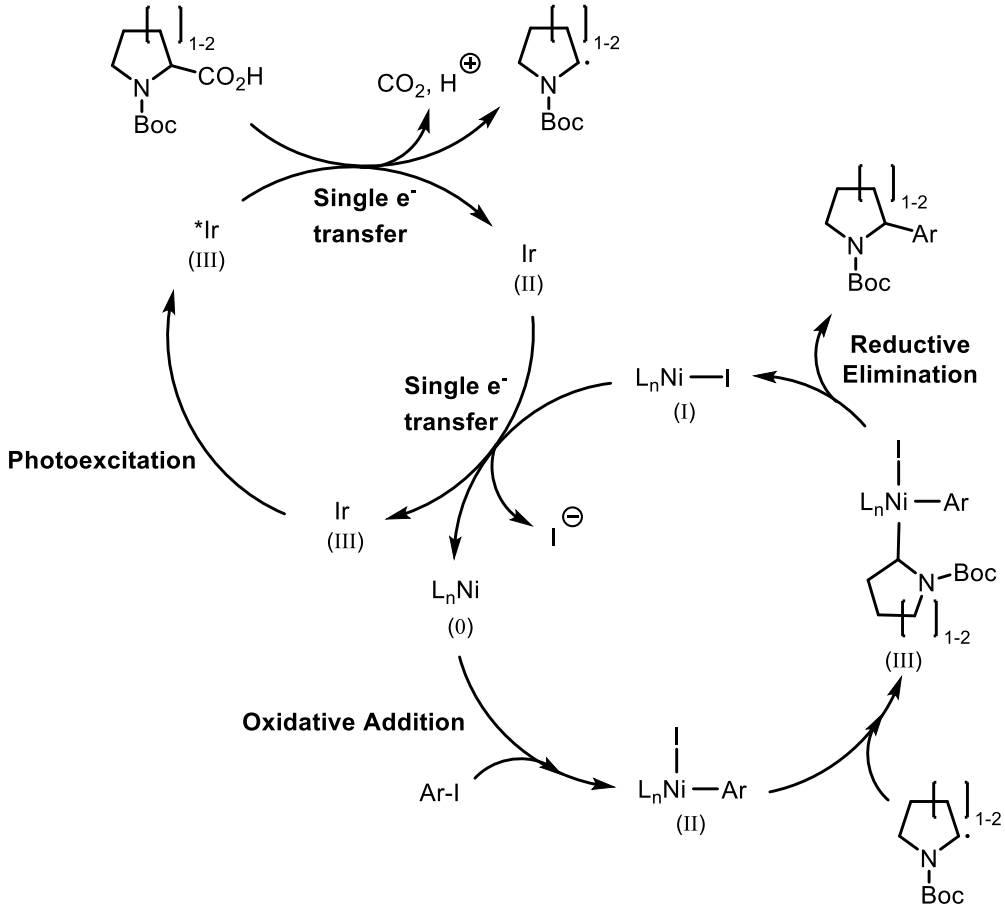
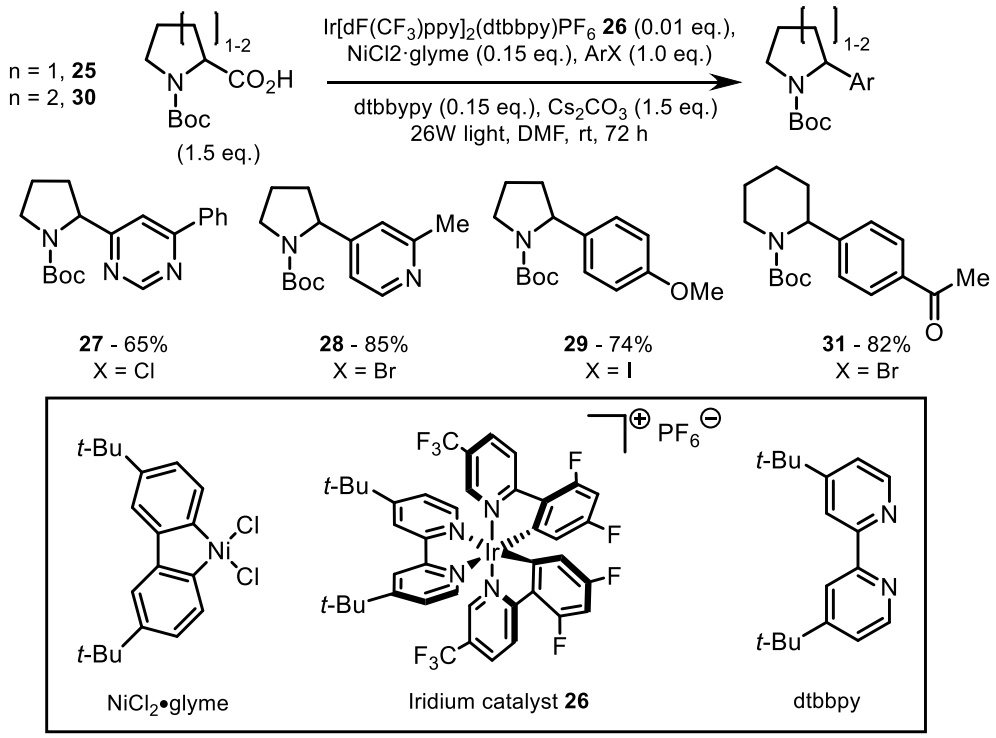


Figure 1.4 Catalytic cycle for the α-arylation of α-carboxyl-*N*-Boc-heterocycles

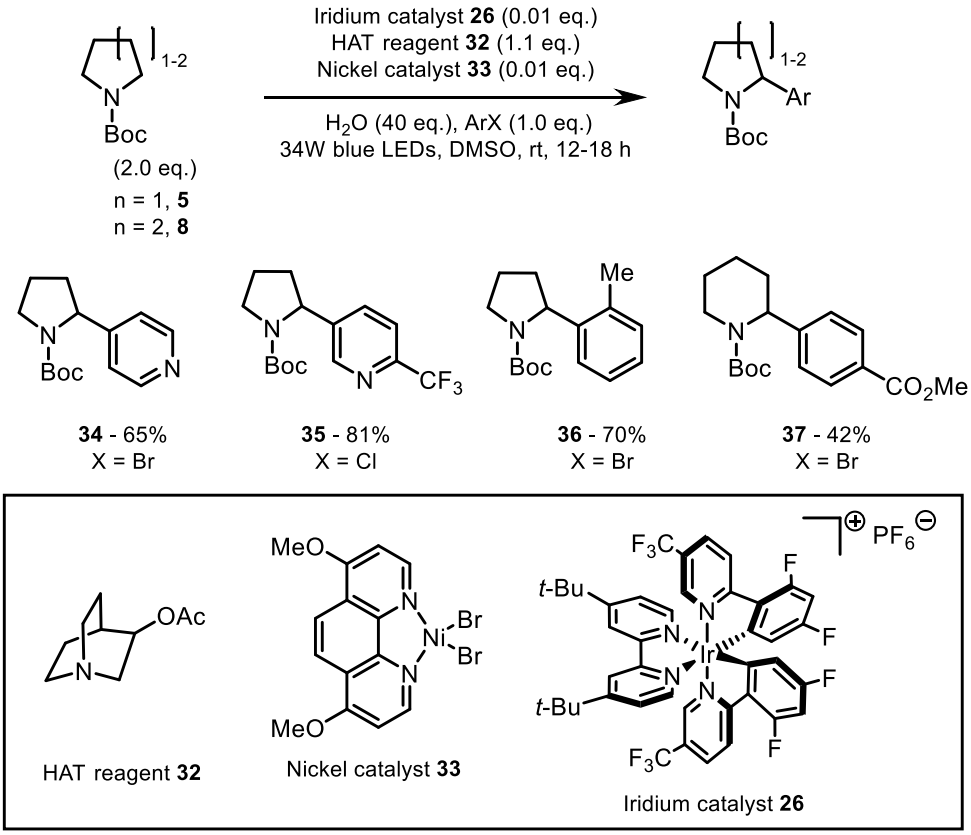


Scheme 1.5

The reaction tolerated the cross-coupling of heteroaryl halides such as 6-bromo-4-phenylpyrimidine which cross-coupled with α-carboxyl-*N*-Boc-pyrrolidine **25** to afford α-arylpyrrolidine **27** in 65% yield. An example of the α-arylation of α-carboxyl-*N*-Boc-piperidine **30** was also reported: cross-coupling with 4-bromoacetophenone gave α-arylpiperidine **31** in 82% yield. The ability to cross-couple heteroaryl halides in good yields is a highlight of this methodology. However, the reaction affords racemic α-arylpyrrolidines and piperidines.

Subsequently and independently, MacMillan *et al.* reported the α-arylation of unsubstituted *N*-Boc-pyrrolidine **5**.[18] The approach taken was to use the hydrogen atom transfer (HAT) reagent **32** to selectively abstract a hydrogen atom from the most electron-rich position on the pyrrolidine ring, the α-position, to generate a pyrrolidine radical. The HAT catalyst was activated by the excitation of iridium photocatalyst **26** which then underwent a single electron transfer with HAT reagent **32**. The pyrrolidine radical could then enter into a catalytic cycle with nickel catalyst **33** and undergo cross-coupling with an aryl bromide to afford α-arylpyrrolidines. Proton loss and single electron transfer from iridium to nickel closed the catalytic cycle. Using these three catalysts in DMSO at rt and with the application of blue LEDs, *N*-Boc-pyrrolidine **5** was

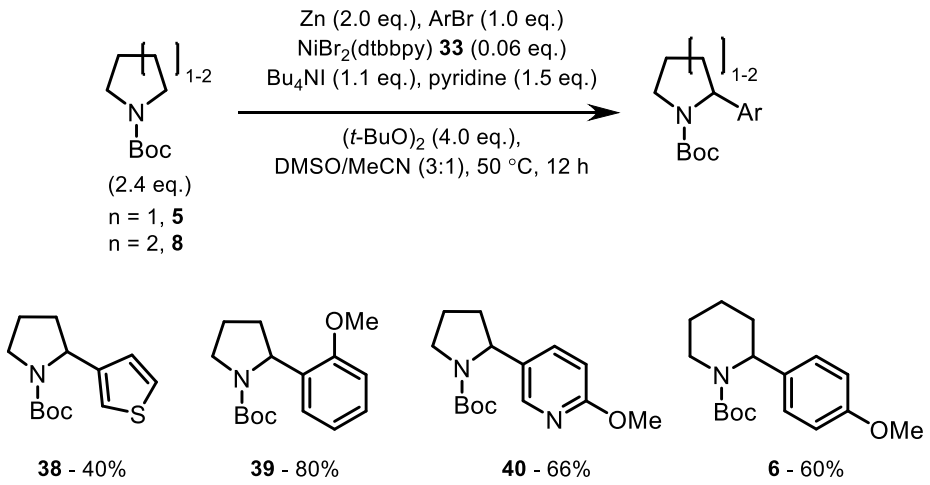
α-arylated with both aryl bromides and aryl chlorides in good yields (Scheme 1.6). A single example of the α-arylation of *N*-Boc-piperidine **8** was also disclosed. Heteroaryl halides, such as 4-bromopyridine, were shown to be competent cross-coupling partners. As an example, the cross-coupling of 4-bromopyridine was accomplished to afford α-arylpyrrolidine **34** in 65% yield. This method benefits from being able to functionalise unsubstituted nitrogen heterocycles in good yields and is an efficient way of generating racemic α-arylpyrrolidines and piperidines.



Scheme 1.6

Gong and co-workers reported an alternative nickel-catalysed α-arylation procedure that also used a HAT catalyst.[19] The reaction made use of elemental zinc as the external reductant and $(t\text{-BuO})_2$ as the oxidant. The proposed reaction mechanism involved the initial reduction of $(t\text{-BuO})_2$ by the nickel catalyst to form a *t*-BuO• radical, which could abstract a hydrogen from the pyrrolidine. The pyrrolidine radical could then be intercepted by the nickel catalyst and subsequent zinc reduction of the catalyst, oxidative addition with an aryl bromide and reductive elimination would then afford the α-arylpyrrolidine. The reaction was heated at 50 °C in a 3:1 mixture of DMSO and MeCN. Pyridine and Bu_4NI were used as additives to facilitate the reaction although,

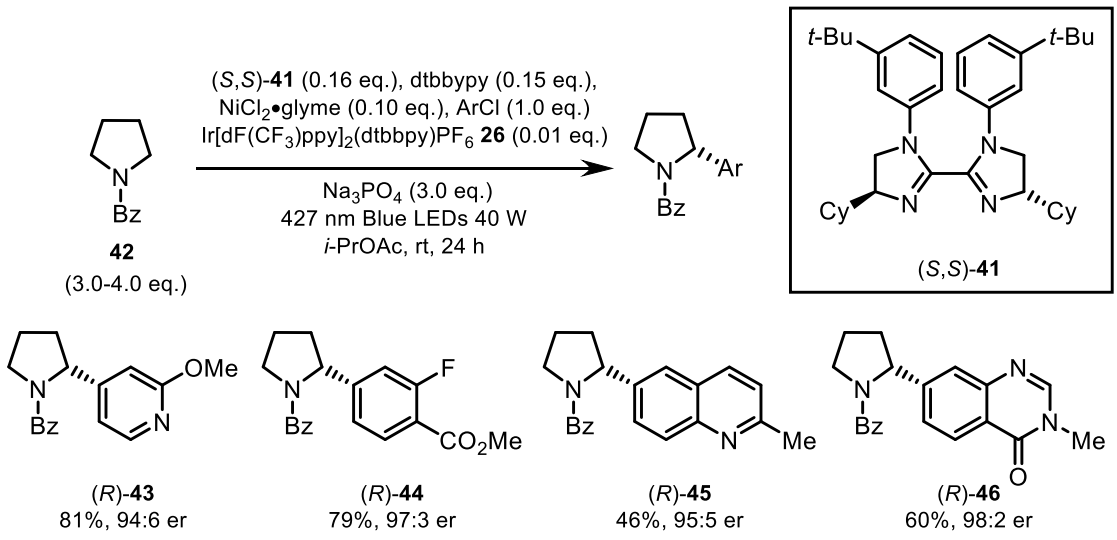
for the cross-coupling of electron-deficient aryl bromides, it was found that $FeCl_3$ was superior to Bu_4NI. With these conditions, a broad range of α-arylpyrrolidines were obtained (Scheme 1.7); for example, the cross-coupling of *N*-Boc-pyrrolidine **5** with 3-bromothiophene gave α-arylpyrrolidine **38** in 40% yield. Gong and co-workers also described the successful α-arylation of a range of other nitrogen-containing heterocycles including *N*-Boc-piperidine **8**, which cross-coupled with 4-bromoanisole to give α-aryl piperidine **9** in 60% yield. Overall, this methodology possessed the advantages of not requiring a pre-functionalised substrate and the ability to α-arylate a wide range of heterocycles in good yield. The methodology was also shown to be scalable, with a 10 g example being reported. However, due to the use of both oxidants and reductants in the reaction mixture, there were limitations on the tolerated functional groups.



Scheme 1.7

More recently, Huo *et al.* described a method for the enantioselective nickel-catalysed photoredox cross-coupling of nitrogen heterocycles.[20] This work built on the nickel-catalysed work of Doyle, MacMillan and co-workers and used iridium catalyst **26** and $NiCl_2$•glyme.[17] The initial steps of the reaction proceeded by a radical pathway; however, Huo *et al.* made use of chiral ligand (*S*,*S*)-**41** to induce stereochemistry during the reductive elimination step to afford enantioenriched α-arylpyrrolidines. The reaction was irradiated with 427 nm light in isopropylacetate at rt with Na_3PO_4 as the base and the nickel/iridium catalyst. Under these conditions, a broad scope was established that included the successful cross-coupling of heteroaryl chlorides (Scheme 3.8). Good yields and excellent enantioselectivities were observed. For example, the cross-coupling of *N*-Bz-pyrrolidine **42** with 4-chloro-2-methoxypyridine gave α-arylpyrrolidine (*R*)-**43**

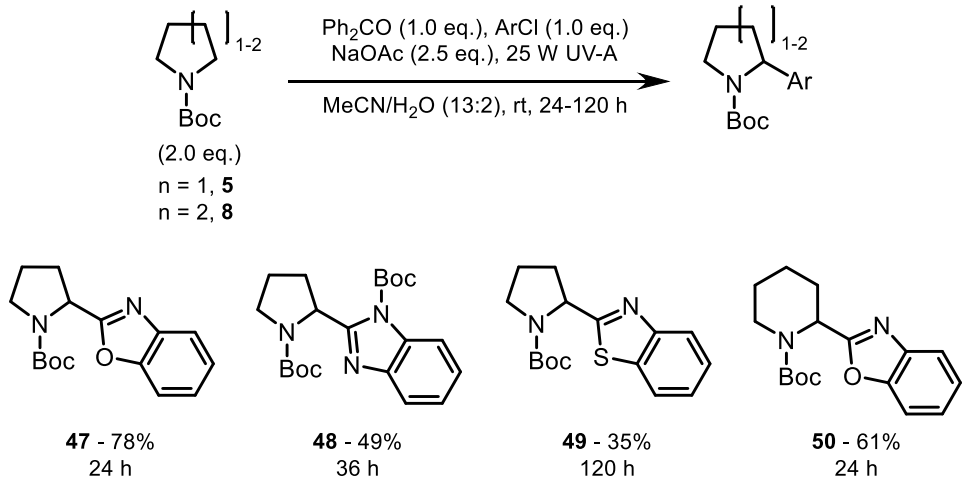
in 81% yield and 94:6 er. It was also reported that aryl bromides could be cross-coupled in comparable yields albeit in slightly lower ers. Two examples were reported of the cross-coupling of piperidines; both proceeded in good yield. In addition, Huo *et al.* described that the benzoyl group could be replaced with other groups, such as Boc or Cbz, although these gave either lower yield or enantioselectivity. This methodology possesses the significant benefit of providing enantioenriched α-aryl heterocycles in good yields without the need for a directing group or strong base. However, a disadvantage is the use of 3.0-4.0 equivalents of the nitrogen heterocycle, which would prove wasteful if the heterocycle was the more precious material.



Scheme 1.8

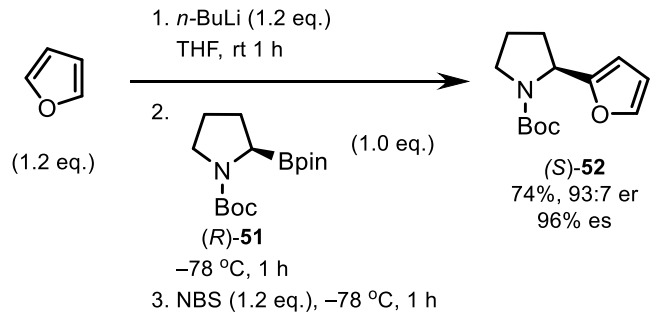
Opatz *et al.* reported the α-arylation of nitrogen heterocycles *via* a light induced and transition metal-free cross-coupling procedure.[21] This methodology makes use of a radical pathway where photoexcited benzophenone abstracts a hydrogen atom from the saturated heterocycle to generate an α-amino radical which can then undergo a radical cross-coupling with either 2-chlorobenzoxazole, 2-chloro-*N*-Boc-benzimidazole or 2-chlorobenzothiazole. HAT to the nitrogen atom of the heteroaromatic and elimination of HCl completes the catalytic cycle and affords α-aryl heterocycles. The reactions were performed with NaOAc in a 13:2 mixture of MeCN and water, conducted at rt and irradiated with two 25 W energy saving UV-A lamps for 24-120 h. Using this methodology, Optaz *et al.* successfully α-arylated *N*-Boc-pyrrolidine **5** and *N*-Boc-piperidine **8** in moderate to good yield (Scheme 1.9). For example, the cross-coupling of *N*-Boc-pyrrolidine **5** with 2-chlorobenzoxazole gave α-arylpyrrolidine **47** in 78% yield.

The reaction procedure was limited in scope, although it completely avoided the use of transition metals, was conducted under mild conditions and provided a method to cross-couple otherwise challenging heteroaromatics.



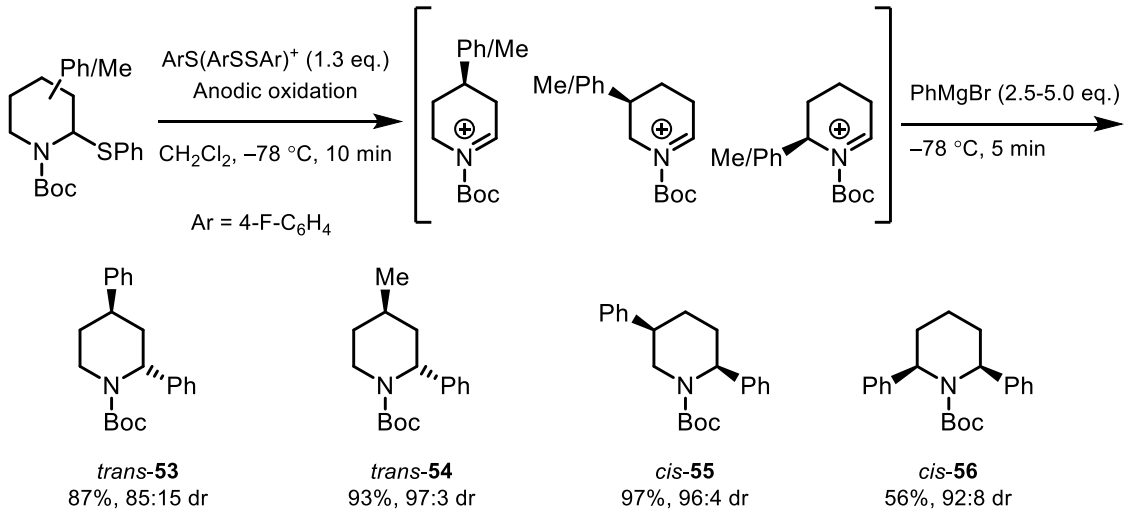
Scheme 1.9

Aggarwal, Leonori and Harvey *et al.* have reported a method for the α-alkylation of heteroaromatics using lithiation and organoboron methodology.[22] Placing the focus on the alkyl Bpin reagent, this methodology was used for the α-arylation of α-Bpin-*N*-Boc-pyrrolidine **51**. The reaction proceeds by the lithiation of heteroaromatics, such as furan, with *n*-BuLi followed by the addition of an alkyl Bpin to form a boronate intermediate and then subsequent addition of NBS to trigger a 1,2-migration of the C-B bond to from the desired C-C bond. The migration was shown to proceed with complete enantiospecificity and the er possessed by the alkyl Bpin reagent was transferred to the final product. Only a single example was reported of the effective α-arylation of a pyrrolidine or piperidine: reaction of α-Bpin-*N*-Boc-pyrrolidine (*R*)-**51** with lithiated furan gave α-arylpyrrolidine (*S*)-**52** in 74% yield and 96% (es) (Scheme 1.10). The methodology has clear advantages and limitations; being able to synthesise α-heteroaryl pyrrolidines in high er is particularly powerful as heteroaromatics are normally more challenging to cross-couple. However, the methodology is clearly limited by the range of heteroaromatics that can undergo the initial lithiation step.



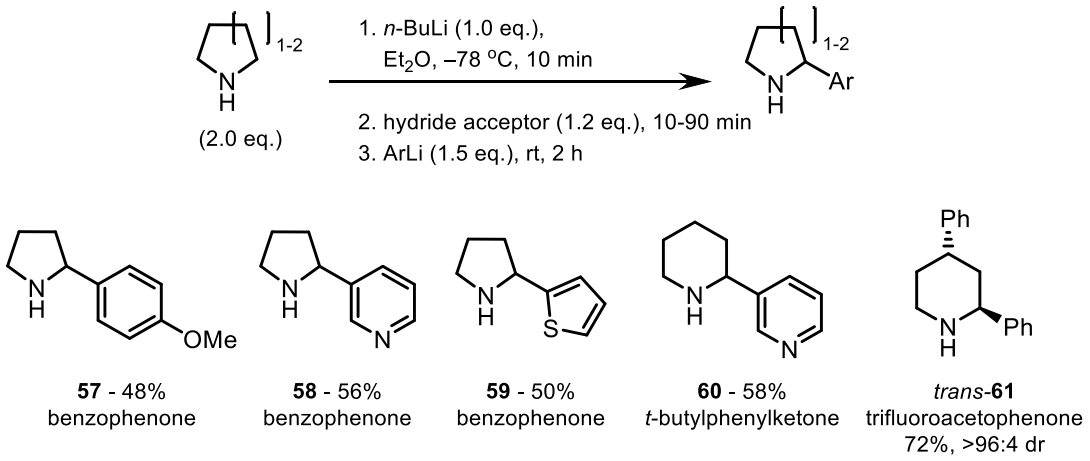
Scheme 1.10

Suga and co-workers developed a method for the α-arylation of substituted *N*-Boc-piperidines *via* the formation of an *N*-acyliminium ion which was subsequently reacted with nucleophiles.[23] α-Phenylsulfanyl piperidines were prepared by lithiation with *s*-BuLi/TMEDA and subsequent trapping with diphenyldisulfide. The piperidine *N*-acyliminium ions were then generated from low temperature electrolysis of these α-phenylsulfanylpiperidines with $ArS(ArSSAr)^+$ (Ar = 4-F-C_6H_4) in CH_2Cl_2. Treatment of the *N*-acyliminium ions with nucleophiles at –78 °C for 5 min then gave α-functionalised piperidines (Scheme 1.11). Suga and co-workers demonstrated that a range of nucleophiles could be used including PhMgBr, which gave α-aryl piperidines. For example, the reaction of the 4-phenyl-*N*-acyliminium ion, generated from α-phenylsulfanyl-4-phenylpiperidine, with PhMgBr gave 2,4-diphenylpiperidine *trans*-**53** in 87% yield and 85:15 dr. The reactions were reported to all be highly diastereoselective, the diastereoselectivity arising from the preferential direction of approach of the nucleophile to the *N*-acyliminium ion, which adopted a half-chair conformation. The methodology was limited by the use of electrochemistry and the nucleophile scope, although Suga and co-workers mainly explored non-aromatic nucleophiles. However, the methodology also gave access to 2,4-*trans*-disubstituted piperidines which are otherwise difficult to synthesise.



Scheme 1.11

A method for the α-arylation of nitrogen heterocycles *via* an imine intermediate was reported by Seidel and co-workers.[10] In this approach, pyrrolidine or piperidine was first lithiated with *n*-BuLi to remove the NH proton. Then, a hydride acceptor was added which generated the imine *in situ* and this could then be reacted with a nucleophile such as an aryllithium to afford α-aryl heterocycles. The lithiation step was conducted in Et_2O at –78 °C and this temperature was maintained during the addition of the hydride acceptor and the organolithium before the reaction was warmed to rt and stirred for 2 hours. Benzophenone, *t*-butylphenylketone or trifluoroacetophenone were used as the hydride acceptors depending on the substrate. The aryllithiums were prepared by halogen-lithium exchange of aryl bromides using *n*-BuLi. This methodology was used to α-arylate pyrrolidine, piperidine and other heterocycles with a variety of aromatic groups (Scheme 1.12). One example of particular note was the α-arylation of both pyrrolidine and piperidine with 3-lithiopyridine to afford α-arylpyrrolidine **58** in 56% yield and α-arylpiperidine **60** in 58% yield. Seidel and co-workers also noted that when 4-phenylpiperidine was cross-coupled with PhLi, the reaction was diastereoselective and gave 2,4-diphenylpiperidine *trans*-**61** in 72% yield with >96:4 dr. A key advantage of this methodology was that a directing group was not required on the heterocycle nitrogen, unlike all the other approaches covered in this section. Additionally, Seidel and co-worker's procedure did not require the use of transition metals. However, the methodology was restricted to the cross-coupling of aryl bromides that would readily form organolithiums and the functional group compatibility issues that that entailed.



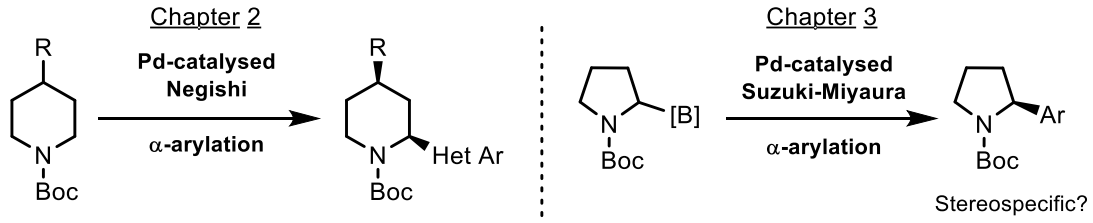
Scheme 1.12

To conclude, these examples cover a range of different methodologies for the α-arylation of piperidine and pyrrolidine using palladium catalysis, directing groups, photochemistry, HATs and lithiation. As highlighted throughout, there are advantages and disadvantages to each of the different methodologies. For example, although the photoredox and HAT methods of Doyle, MacMillan *et al.*, Gong and co-workers and Optaz *et al.* have wide scopes including heteroaryl halides, they afforded racemic products.[17,18,19,21] Conversely, the photocatalytic method of Huo *et al.* allows for the synthesis of α-aryl heterocycles with excellent enantioselectivity, but the method has its own issues such as the large excess (3.0-4.0 eq.) of heterocycles required for a good yield.[20] Other methods are limited in their scope or the use of strong bases or redox reagents. Thus, although multiple methods do exist for the α-arylation of piperidine and pyrrolidine, more methods and improvements to existing methodology are always beneficial. Increasing the variety of available methods would improve the number of tools in a medicinal chemist's toolkit and thus, ultimately, enable the more efficient and successful synthesis of pharmaceutically-relevant molecules.

1.3 Project Outline

In this thesis methods for the α-arylation of nitrogen heterocycles *via* palladium-catalysed cross-coupling were investigated. This chapter highlights the significance of nitrogen heterocycles, their prevalence in biologically-active molecules and thus the importance of methods for their α-arylation. The focus of this thesis was to establish methodology that would be particularly useful for medicinal chemists, methodology that would be: synthetically straightforward, easy to carry out and tolerable of the cross-coupling of nitrogen-containing heteroaryl halides, which are prevalent in biologically-active molecules. The secondary aim was to develop methodology that would be amenable to rapid screening for the use in structure activity relationship programmes.

The objective of Chapter 2 was to improve upon existing methodology for the α-arylation of 4-substituted-*N*-Boc-piperidine. There was only a single report of the α-arylation of a 4-substituted *N*-Boc-piperidine with a heteroaryl halide,[24] thus the aim of this work was to develop methodology compatible with the cross-coupling of heteroaryl halides. The diastereoselectivity and enantioselectivity of this reaction was also investigated with an aim to synthesising α-aryl-4-substituted-*N*-Boc-piperidines with both high diastereoselectivity and enantioselectivity (Scheme 1.13).

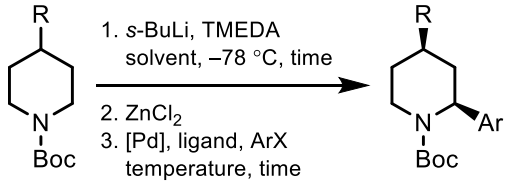


Scheme 1.13

The objective of Chapter 3 was to provide an alternative method for the α-arylation of pyrrolidine. As detailed in Chapter 1, whilst there exist a range of α-arylation procedures, one notably underexplored approach was that of the SMCC. There were only limited examples of the SMCC of α-boron pyrrolidines, those from one report were low yielding and the others were within a paper that has since been retracted.[25,26] This, therefore, represented an opportunity to fill a niche and provide an alternative method for the α-arylation of pyrrolidine with its own advantages. The stereospecificity of this reaction was also investigated with an aim to synthesising enantioenriched α-arylpyrrolidines (Scheme 1.13).

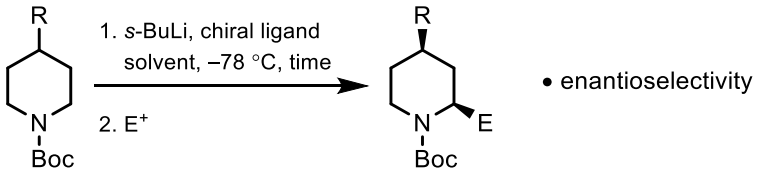
Chapter 2: α-Lithiation-Arylation and α-Lithiation-Functionalisation of *N*-Boc-piperidines

In the first part of this chapter (section 2.1), an overview is given of the existing methods for the α-arylation of substituted *N*-Boc-piperidines *via* Negishi cross-coupling. This covers key findings from multiple groups whose work underpins the field and gave rise to the current methodology. It also covers investigations into the asymmetric lithiation-functionalisation of substituted and unsubstituted *N*-Boc-piperidines. After setting out the planned approach and objectives in section 2.2, the α-arylation of 4-substituted *N*-Boc-piperidines *via* lithiation-transmetallation-Negishi cross-coupling is presented in section 2.3. The plan was to improve the existing *cis*-diastereoselective α-arylation methodology through solvent and reaction optimisation and to develop methodology for the successful cross-coupling of a wide range of aryl halides and heteroaryl halides in particular (Scheme 2.1).



Scheme 2.1

A study on the racemic and asymmetric α-lithiation-functionalisation of 4-substituted *N*-Boc-piperidines is presented in section 2.4. Here, the aim was to synthesise 2,4-disubstituted piperidines with high diastereo- and enantioselectivity (Scheme 2.2).



Scheme 2.2

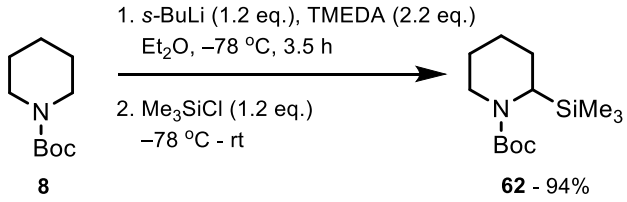
Finally, the further functionalisation of α-aryl-4-substituted *N*-Boc-piperidines would also be investigated (section 2.5). Here, a second α-lithiation-functionalisation and an intramolecular S_NAr reaction would be explored.

2.1 Overview of α-Lithiation-Functionalisation of *N*-Boc-piperidines

In 1989, Beak and Lee reported the ability of the *N*-Boc group to direct the lithiation of *N*-heterocycles to the α-position; subsequent trapping with electrophiles afforded α-functionalised *N*-heterocycles.[27] This discovery sparked interest in this area of research and, over the past 33 years, numerous groups have contributed to the field of α-lithiation-functionalisation of *N*-Boc heterocycles. This methodology is particularly attractive as it enables the activation and functionalisation of nominally unreactive C-H bonds and is also amenable to further functionalisation due to the ease of Boc group removal. This overview covers important developments in the field with a focus on piperidine and particularly on the α-arylation of *N*-Boc-piperidines.

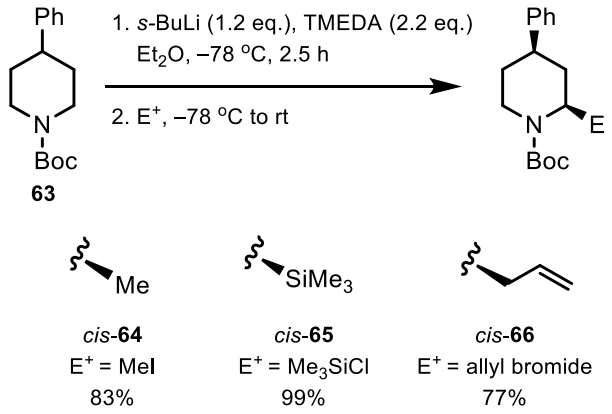
2.1.1 α-Lithiation-Trapping of Unsubstituted and Substituted *N*-Boc-piperidines

Beak and Lee reported that the α-lithiation-trapping of *N*-Boc heterocycles could be accomplished with *s*-BuLi/TMEDA in Et_2O at –78 °C for around 3.5 hours.[27] Subsequent addition of an electrophile gave α-substituted heterocycles. Among other heterocycles, the lithiation-trapping of *N*-Boc-piperidine **8** and 4-substituted *N*-Boc-piperidines were reported. For example, the α-lithiation of *N*-Boc-piperidine **8** and trapping with Me_3SiCl afforded α-silylpiperidine **62** in 94% yield.



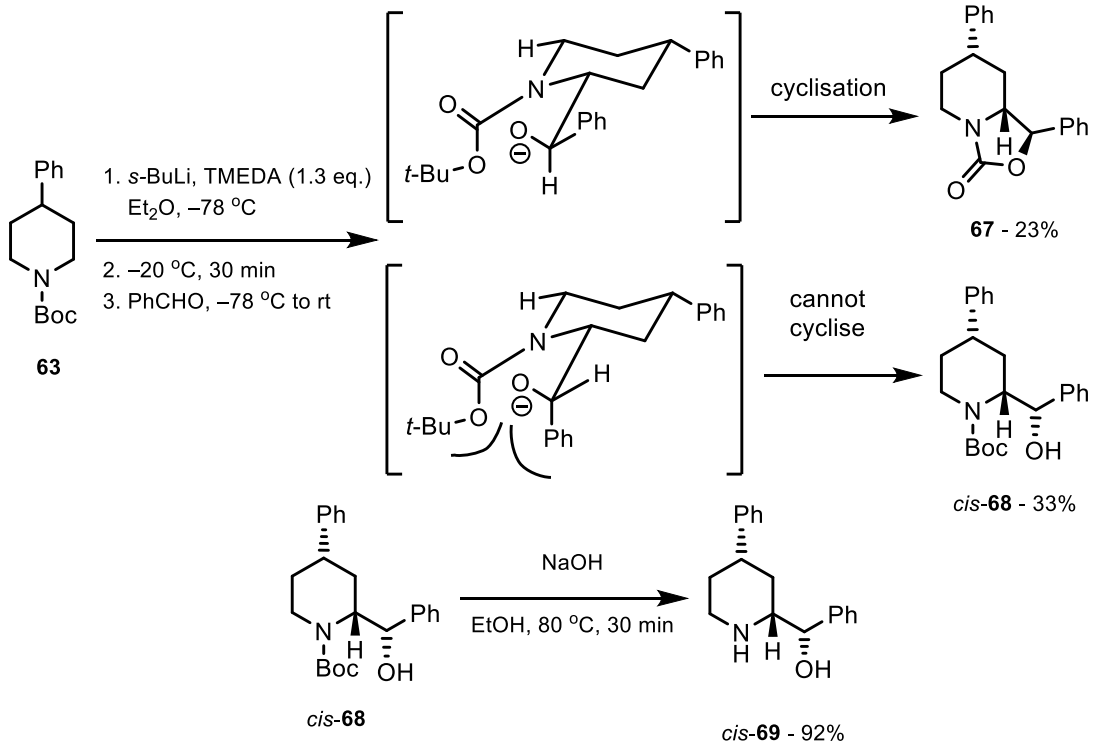
Scheme 2.3

The lithiation-trapping of 4-phenylpiperidine **63** with Me_3SiCl, methyliodide and allylbromide provided 2,4-disubstitutedpiperidines *cis*-**64**, *cis*-**65** and *cis*-**66** in 77-99% yield (Scheme 2.4). Although not initially reported, subsequent work from Beak and co-workers demonstrated that these reactions proceeded with *cis* diastereoselectivity.



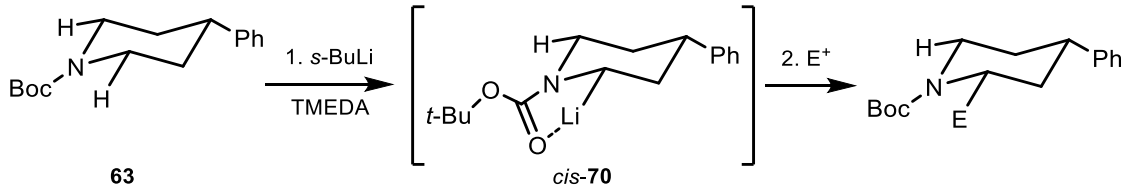
Scheme 2.4

In a subsequent paper, Beak and Lee further explored the lithiation-trapping of 4-phenyl-*N*-Boc-piperidine **63**.[28] Lithiation and trapping with benzaldehyde delivered the cyclised 2,4-disubstitutedpiperidine **67** and α-functionalised piperidine *cis*-**68** (Scheme 2.5). Reaction of the lithiated intermediate with benzaldehyde generated two diastereomeric alkoxides, one of which could cyclise through attack onto the Boc carbonyl to give the cyclised 2,4-disubstitutedpiperidine **67**. For the other diastereomeric alkoxide, there would be a steric clash between the phenyl group and the *tert*-butyl group when they aligned in such a way to enable cyclisation. This prevented cyclisation from occurring and hence α-functionalisedpiperidine *cis*-**68** was obtained. The stereochemistry of these functionalised piperidines was assigned by ^{1}H NMR spectroscopic analysis and by X-ray crystallography of 2,4-disubstitutedpiperidine *cis*-**69** generated by the removal of the Boc group. This provided the evidence for the *cis*-selectivity of the lithiation-trapping of 4-substituted piperidines.



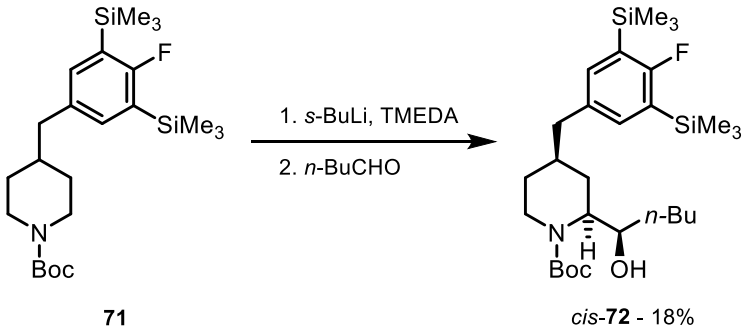
Scheme 2.5

Cis diastereoselectivity arises from preferential equatorial lithiation at the α-position and, as the lowest energy conformer has the 4-substitutent in an equatorial position, this results in lithiated intermediate *cis*-**70** (Scheme 2.6). The electrophilic substitution is then assumed to occur with retention of stereochemistry to preferentially afford a *cis*-2,4-disubstituted piperidine.[29]



Scheme 2.6

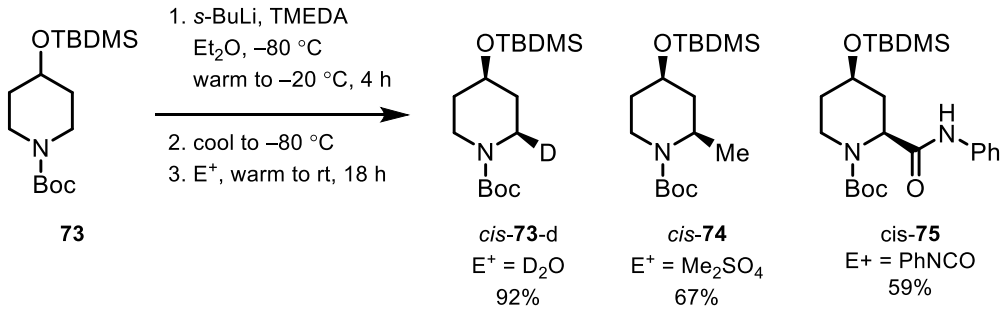
Beak and Lee's α-lithiation-trapping methodology was utilised by chemists at Bristol Myers Squibb during the synthesis of CCR3 antagonists for the treatment of asthma (Scheme 2.7).[30] Using lithiation with *s*-BuLi/TMEDA followed by trapping with butyraldehyde, the synthesis of 2,4-disubstituedpiperidine *cis*-**72** was achieved in 18% yield. It was reported that the silyl groups were necessary to prevent lithiation of the aromatic ring ortho to the fluorine atom.



71 *cis*-**72** - 18%

Scheme 2.7

Further examples of the synthesis of 2,4-disubstituted piperidines were described by Kantlehner *et al.* (Scheme 2.8).[31] The α-lithiation-functionalisation of 4-OTBDMS-*N*-Boc-piperidine **73** gave α-functionalised piperidines *cis*-**73**-d, *cis*-**74** and *cis*-**75** diastereoselectively. The reactions were conducted in Et_2O and the lithiation performed with *s*-BuLi/TMEDA at –20 °C for 4 h, the reaction was then cooled down to –80 °C prior to the addition of the electrophile. Of note, when 4-OTBDMS-piperidine **73** was lithiated and trapped with D_2O, piperidine *cis*-**73**-d was isolated in 92% yield, indicating near complete lithiation under these conditions. However, lower yields were obtained with dimethylsulfate (67%) and phenylisocyanate (59%). Despite the differences in lithiation procedure, Kantlehner and co-workers' results are in agreement with those published by Beak and Lee with the preferential formation of *cis*-2,4-disubstituted piperidines.[28]



73

cis-**73**-d
$E^+ = D_2O$
92%

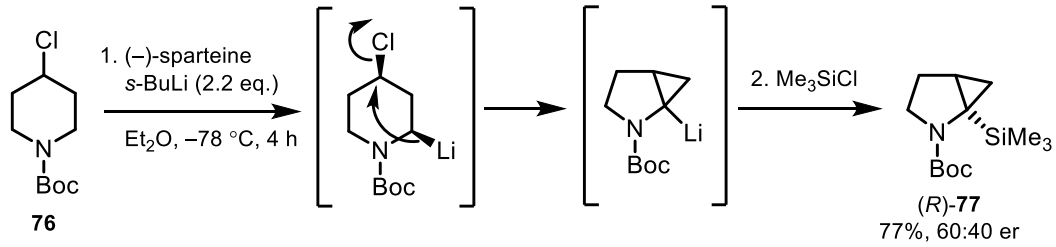
cis-**74**
$E^+ = Me_2SO_4$
67%

cis-**75**
E+ = PhNCO
59%

Scheme 2.8

Beak and Park reported that the lithiation of 4-chloropiperidine-*N*-Boc **76** with *s*-BuLi/(–)-sparteine in Et_2O at –78 °C gave α-silylpiperidine (*R*)-**77** in 77% yield and 60:40 er (Scheme 2.9).[32] Upon lithiation at the α-position, the lithiated piperidine underwent an intramolecular substitution reaction. Through the use of two equivalents

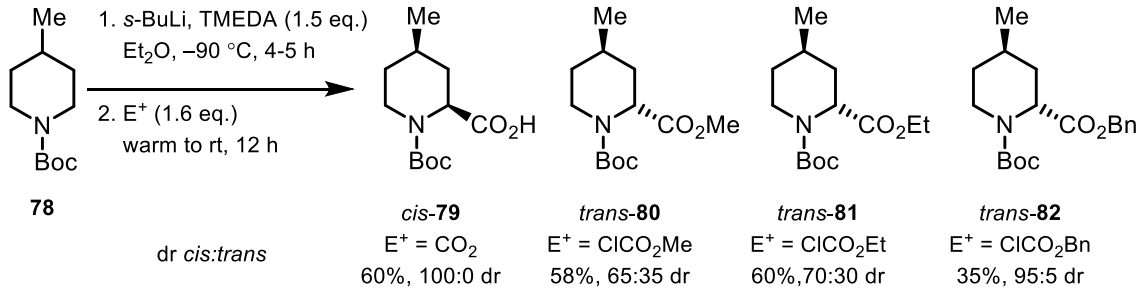
of *s*-BuLi, a second deprotonation occurred at the cyclopropyl α-position and subsequent trapping with Me_3SiCl afforded α-silylpiperidine (*R*)-**77**. This reaction was further developed by O'Brien *et al.* to enable the α-functionalisation of these [3.1.0] bicyclic systems in 99:1 er through the use of an asymmetric deprotonation and trapping with Andersen's sulfinate.[33] These reactions highlighted the importance of the choice of the group in the 4-position when carrying out lithiation reactions, as a substituent that could act as a leaving group could lead to an unwanted intramolecular reaction.



Scheme 2.9

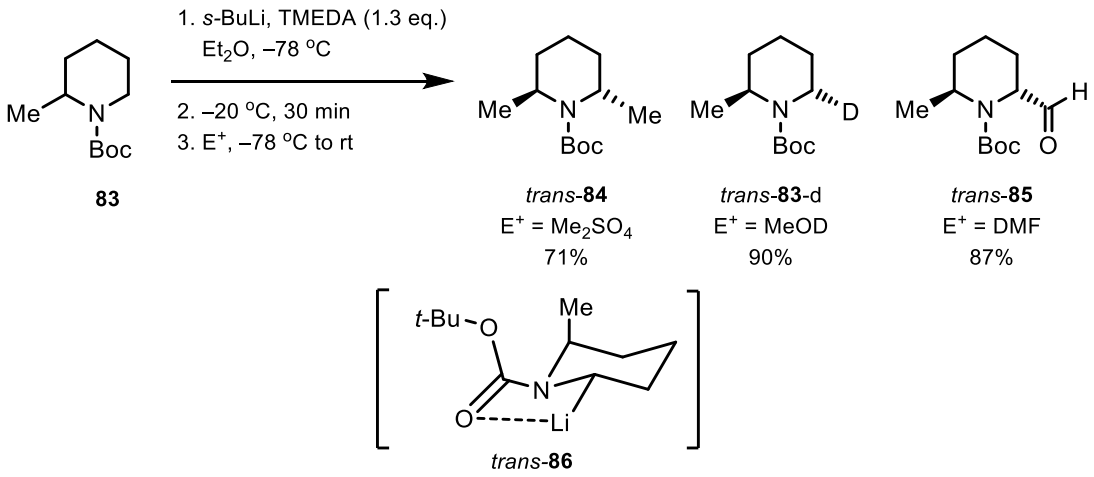
Investigations into the α-lithiation-functionalisation of 4-methyl-*N*-Boc-piperidine **78** were carried out by Cossy and Belotti.[34] This was the first report of exact diastereomeric ratios obtained from the lithiation-trapping of 4-substituted piperidines. Beak and Lee's previous work had assumed, or had sufficient evidence to surmise, that the products were entirely the *cis* diastereomer. Lithiation of 4-methylpiperidine **78** using *s*-BuLi/TMEDA in Et_2O at –90 °C and trapping with carbon dioxide gave α-functionalised piperidine *cis*-**79** exclusively in 60% yield (Scheme 2.10). Cossy and Belotti observed a peculiar feature when trapping with alkyl chloroformates, the *trans* diastereomers were the major products. Methylchloroformate afforded a 65:35 mixture of piperidines *trans*-**80** and *cis*-**80** (in 58% yield); ethylchloroformate gave a 70:30 mixture of piperidines *trans*-**81** and *cis*-**81** (in 60% yield) and benzylchloroformate yielded a 95:5 mixture of piperidines *trans*-**82** and *cis*-**82** (in 35% yield). A potential explanation for the unusual *trans* selectivity could be the epimerisation of the disubstituted piperidines. Whilst it is likely that the *cis* disubstituted piperidines are formed on trapping, these may then epimerise to the *trans* compound *via* enolate/enol formation, either in the reaction mixture, during work-up or upon purification by flash column chromatography. If the ester group was equatorial then there would be a steric clash with the Boc group, thus the *trans* compound would be likely to be more

thermodynamically stable as the methyl group could be equatorial whilst the ester group was axial.



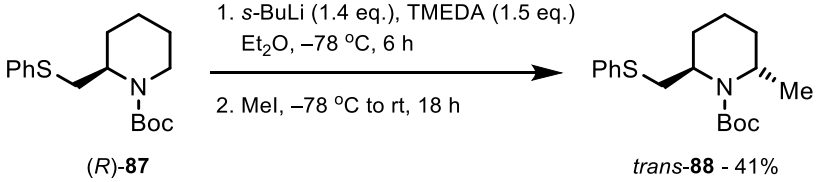
Scheme 2.10

In 1990, Beak and Lee reported the diastereoselective lithiation-trapping of 2-substituted *N*-Boc-piperidine.[28] The lithiation-trapping of 2-methylpiperidine **83** with dimethylsulfate gave 2,6-disubstitutedpiperidine *trans*-**84** in 71% yield (Scheme 2.11). This stereochemical outcome was due to the fact that the lowest energy conformer of 2-methylpiperidine **83** has the methyl group axial in order to avoid $A_{1,3}$-like interactions with the Boc group. Thus, lithiation generates the lithiated intermediate *trans*-**86** and subsequent trapping with electrophiles generates *trans*-2,6-disubstituted piperidines. *Trans* selectivity was also observed when trapping with MeOD and DMF, affording 2,6-disubstitutedpiperidines *trans*-**83**-d and *trans*-**85** in 90% and 87% yields respectively (Scheme 2.11).[35] In this work it was observed that, whilst aldehyde *trans*-**85** was the product of lithiation-trapping with DMF, during chromatography on silica gel it epimerised (presumably *via* enol formation) to afford aldehyde *cis*-**85** as the major isolated product. Aldehyde *cis*-**85** has both substituents axial to avoid $A_{1,3}$-strain with the Boc group and, whilst it will possess $A_{1,3}$ diaxial interactions between the substituents, these will be reduced by the sp^2 nature of the aldehyde group making the diaxial conformation preferable.



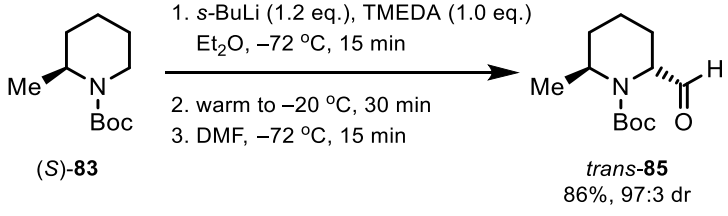
Scheme 2.11

Hart and Wu took advantage of the *trans* selectivity of the α-lithiation of 2-substituted piperidines during the total synthesis of (+)-Himbeline and (+)-Himbacine.[36] The lithiation-trapping of 2-substituted-*N*-Boc-piperidine (*R*)-**87** with methyliodide afforded 2,6-disubstitutedpiperidine *trans*-**88** in 41% yield with retention of the *R* stereocentre and introduction of a second stereogenic centre due to the aforementioned *trans* selectivity (Scheme 2.12).



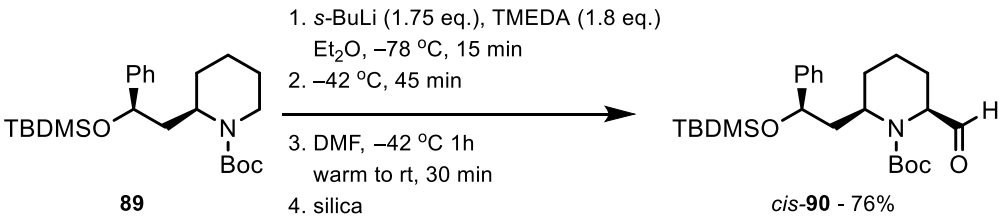
Scheme 2.12

Chackalamannil *et al.* published an alternative route to (+)-Himbeline and (+)-Himbacine that also utilised the lithiation-trapping of a 2-substituted piperidine.[37] 2-Methyl-*N*-Boc-piperidine (*S*)-**83** was lithiated and trapped with DMF and, in this work, epimerisation on purification was avoided and a 97:3 mixture of 2,6-disubstitutedpiperidines *cis*-**85** and *trans*-**85** was obtained in 86% yield (Scheme 2.13).



Scheme 2.13

The lithiation-trapping methodology of 2-substituted piperidines was also utilised by Stoltz and co-workers during the synthesis of (–)-Lobeline, (–)-Sedamine and (+)-Sedamine.[38] Lithiation-trapping of 2-substituted-*N*-Boc-piperidine **89** with DMF was carried out to afford 2,6-disubstitutedpiperidine *cis*-**90** in 76% yield (Scheme 2.14). Epimerisation of the aldehyde during flash column chromatography enabled the synthesis of the desired *cis* isomer as opposed to the expected *trans* isomer.

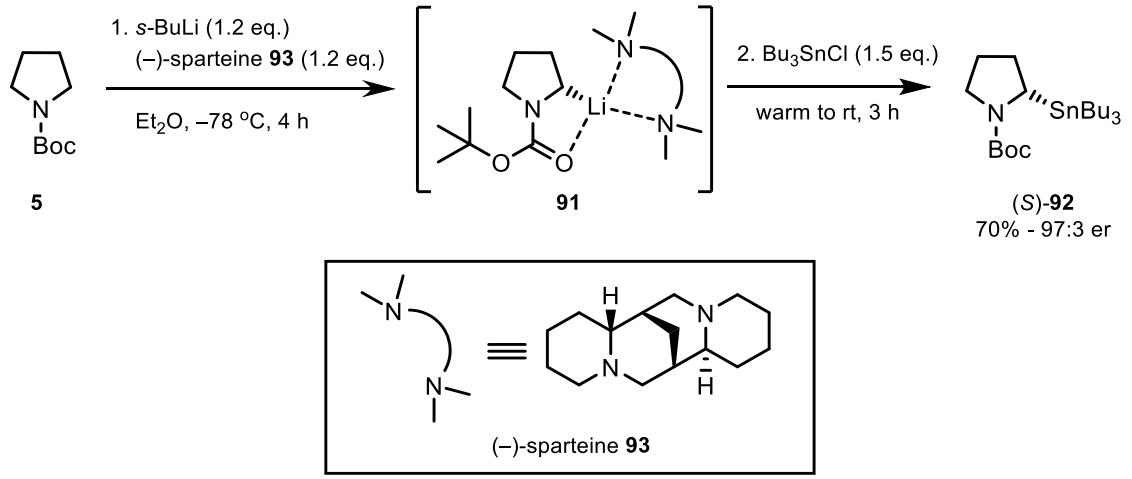


Scheme 2.14

Collectively, these examples demonstrate the utility of Beak and Lee's discovery and the ability to synthesise disubstituted piperidines with high diastereoselectivities, methodology that has been used both in natural product synthesis and within medicinal chemistry programmes. This also highlights the importance of this chemistry and the benefits that further developments would afford the scientific community.

2.1.2 Asymmetric α-Lithiation-Trapping of *N*-Boc-pyrrolidines and Piperidines

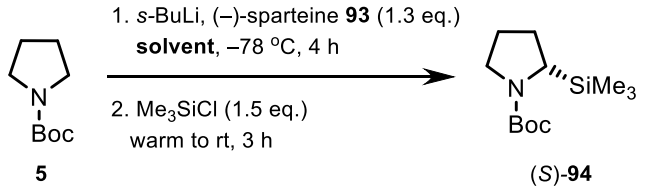
Beak and Kerrick demonstrated that the α-lithiation-functionalisation of *N*-Boc-pyrrolidine **5** could be conducted enantioselectively through the use of a chiral diamine instead of TMEDA.[39,40] The lithiation-trapping of pyrrolidine **5** with 1.2 equivalents of *s*-BuLi/(–)-sparteine **93** in Et_2O at –78°C gave α-functionalised pyrrolidines with high enantioselectivity (Scheme 2.15). For example, lithiation-trapping with Bu_3SnCl afforded α-stannylpyrrolidine (*S*)-**92** in 70% yield and 97:3 er. (–)-sparteine **93** and *s*-BuLi form a chiral complex which leads to asymmetric deprotonation of pyrrolidine **5** to form lithiated intermediate **91**.



Scheme 2.15

Beak *et al.* also performed the asymmetric lithiation-trapping of *N*-Boc-pyrrolidine **5** using (–)-sparteine **93** with Me_3SiCl in three other solvents besides Et_2O (Table 2.1).[40] Lithiation-functionalisation in Et_2O gave α-silyl (*S*)-**94** in 87% yield and 98:2 er, in line with the results with other electrophiles (entry 1). The use of MTBE gave a lower yield of α-silylpyrrolidine (*S*)-**94** (56%) but a comparable er (95:5) (entry 2). When the lithiation was conducted in pentane, a high yield of α-silylpyrrolidine (*S*)-**94** was observed (85%) but there was a significant decrease in the er compared to that obtained in Et_2O (83:17) (entry 3). Lithiation in THF gave a mixture of products and only a small amount of the desired α-silylpyrrolidine (*S*)-**94** (er not reported) (entry 4). Independently, Hoppe and co-workers reported that when the lithiation of 3-methylindene with *n*-BuLi/(–)-sparteine **93** was conducted in THF, the product obtained was racemic.[41] In contrast, when lithiation-trapping was conducted in Et_2O a 95:5 er was obtained. Hoppe and co-workers postulated that this was because THF had co-ordinated to the lithium, displacing (–)-sparteine **93**, thus the subsequent proton abstraction was not stereoselective and afforded a racemic product. In 2010, O'Brien, Hilmersson and Carbone showed, through ^{6}Li NMR spectroscopy, that 1.0 equivalent of (–)-sparteine **93** in THF did not form a chiral complex with *i*-PrLi and only THF-solvated *i*-PrLi was observed.[42] The *i*-PrLi/(–)-sparteine **93** complex was only observed with excess (≥3.0 eq.) (–)-sparteine **93** which explained why racemic lithiation was observed by Beak *et al.* and others when performing the lithiation of *N*-Boc heterocycles in THF with (–)-sparteine **93**, as the deprotonation would occur from the racemic *s*-BuLi/THF complex.[40,43]

Table 2.1: Solvent effect on the asymmetric lithiation-trapping of *N*-Boc-pyrrolidine **5**



5 (*S*)-**94**

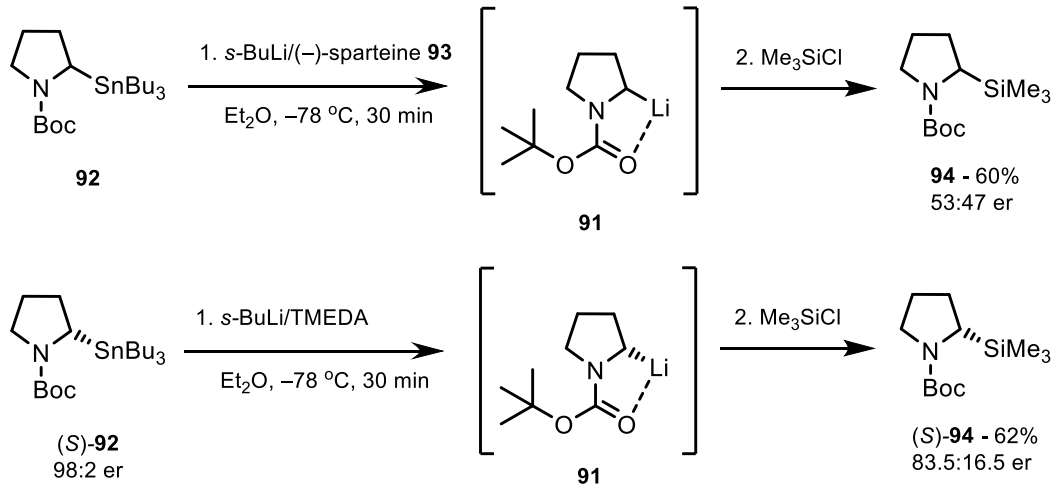
Entry	Solvent	Yield / %	er
1	Et_2O	87	98:2
2	MTBE	56	95:5
3	pentane[a]	85	83:17
4	THF	<10	-

a) –40 °C lithiation temperature

Overall, these results from Beak and co-workers showed that, whilst there was potential for the lithiation-trapping procedure to be conducted in alternative solvents, the original choice of Et_2O afforded the best results. Through the use of React IR, O'Brien, Campos and co-workers later reported that the lithiation of pyrrolidine **5** with *s*-BuLi/(–)-sparteine **93** in MTBE was complete in under an hour, as opposed to the 4 hour lithiation time first reported by Beak and co-workers.[44] Unpublished work from our group demonstrated that the lithiation of pyrrolidine **5** with *s*-BuLi/(–)-sparteine **93** in Et_2O was complete in 60 minutes.[45]

Beak and Kerrick demonstrated that the stereogenic centres of α-functionalised pyrrolidines were introduced *via* an asymmetric deprotonation pathway.[39] Two potential mechanisms were initially proposed. One was that (–)-sparteine **93** and *s*-BuLi formed a complex which effected the enantioselective deprotonation of *N*-Boc-pyrrolidine **5**. The alternative mechanism was an asymmetric substitution where racemic lithiation would occur followed by complexation of the chiral ligand which, together with a configurationally unstable organolithium, would lead to two possible diastereomeric transition states, one of which would trap preferentially to predominantly give one enantiomer. This second pathway was disproved through the lithiation of α-stannyl-*N*-Boc-pyrrolidine **92** and (*S*)-**92** (Scheme 2.16). Tin-lithium exchange was performed with *s*-BuLi on racemic α-stannylpyrrolidine **92** to give the lithiated intermediate **91** *in*

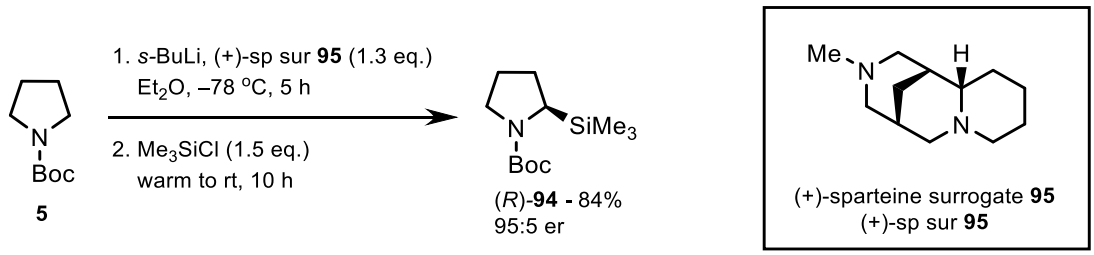
situ; this was then treated with (–)-sparteine **93** and subsequently trapped with Me_3SiCl to generate α-silylpyrrolidine **94** with 53:47 er, indicating that stereoinduction was not imparted after the deprotonation step. The lithiation-trapping of enantioenriched α-stannylpyrrolidine (*S*)-**92** with *s*-BuLi/TMEDA and Me_3SiCl afforded α-silylpyrrolidine (*S*)-**94** in 83.5:16.5 er. This indicated that there was a high degree of configurational stability to the lithiated intermediate **91** at –78 °C. O'Brien *et al.* later demonstrated that the asymmetric lithiation of *N*-Boc-piperidine **5** followed a similar pathway, i.e. the stereogenic centre was set up *via* asymmetric deprotonation as opposed to asymmetric substitution.[46]



Scheme 2.16

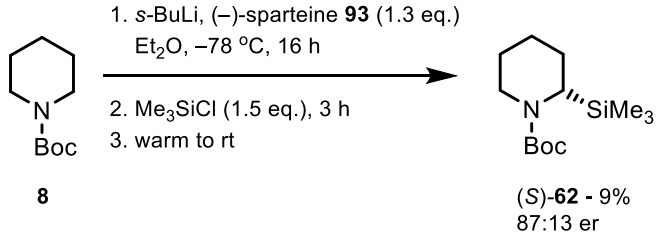
In 2002, the O'Brien group synthesised a (+)-sparteine surrogate **95** which was inspired by the lack of availability of (+)-sparteine **93** at the time.[47] Asymmetric lithiation of *N*-Boc-pyrrolidine **5** with *s*-BuLi/(+)-sparteine surrogate **95** in Et_2O at –78 °C and trapping with Me_3SiCl afforded α-silylpyrrolidine (*R*)-**94** in 84% yield and 95:5 er (Scheme 2.17). The work of O'Brien *et al.* provided access to the opposite enantiomer in comparable yield and er to that obtained with (–)-sparteine **93** (87%, 95:5 er). It should be noted that at the time of writing, for unknown reasons, (+)-sparteine **93** is now commercially available and (–)-sparteine **93** is not. Studies in our group demonstrated that the lithiation times of various heterocycles, including *N*-Boc-pyrrolidine **5** and *N*-Boc-piperidine **8**, with *s*-BuLi/(+)-sparteine surrogate **95** in Et_2O at –78 °C were shorter than those conducted with both TMEDA and (–)-sparteine **93**.[45] For example the lithiation of *N*-Boc-pyrrolidine in Et_2O at –78 °C was complete in 2 minutes with the

(+)-sparteine surrogate **95** compared to 5 minutes with TMEDA and 60 minutes with (–)-sparteine **93**.



Scheme 2.17

Beak and co-workers subsequently demonstrated that *s*-BuLi and (–)-sparteine **93** could be used to enantioselectively deprotonate *N*-Boc-piperidine **8**.[48] Lithiation of *N*-Boc-piperidine **8** in Et_2O with *s*-BuLi/(–)-sparteine **93** at –78 °C for 16 hours followed by trapping with Me_3SiCl gave α-silylpiperidine (*S*)-**62** in 9% yield and 87:13 er (Scheme 2.18). Through computational studies, it was reported that the low yield and long lithiation time required were due to a high activation energy for the deprotonation step. O'Brien *et al.* demonstrated by *in situ* reaction monitoring using React IR that after stirring piperidine **8** in Et_2O with *s*-BuLi/(–)-sparteine **93** at –78 °C for 6 hours, only around 10% of piperidine **8** had undergone lithiation.[46]

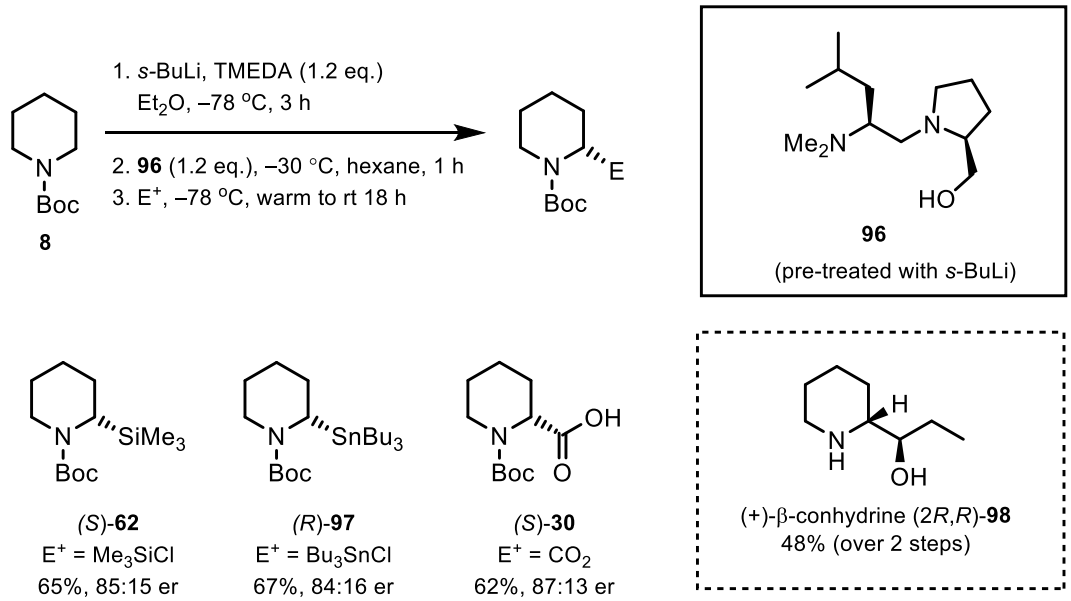


Scheme 2.18

Coldham *et al.* reported the use of dynamic resolution in an attempt to get around the poor enantioselectivities/yields obtained with the asymmetric deprotonation of *N*-Boc-piperidine **8**.[49] The process of dynamic thermodynamic resolution (DTR) involves a racemic lithiation of the substrate, warming the reaction mixture up to a point where it is configurationally unstable and treating it with a chiral ligand. The lithiated substrate forms a complex with the ligand and will preferentially favour one diastereomeric complex over the other. This sets up the stereogenic centre and thus the enantiomeric ratio. The reaction mixture is then cooled down to prevent further epimerisation and the

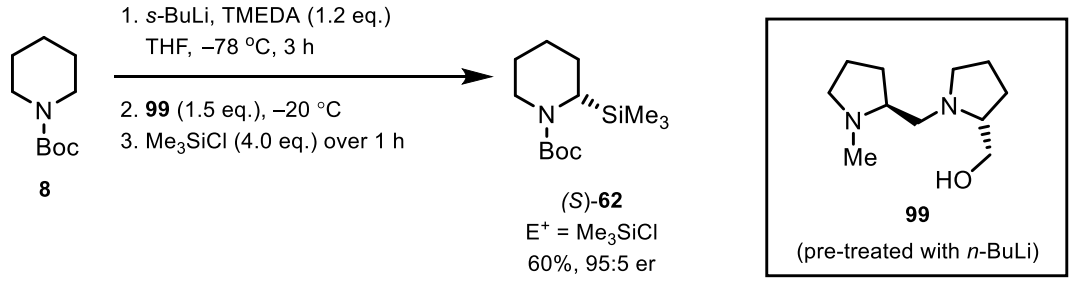
electrophile is added. In this way, the functionalised product will be obtained in an er matching the ratio of diastereomeric complexes. An alternative method is dynamic kinetic resolution (DKR); this approach relies on the rate of interconversion of the lithiated complexes being faster than the rate of trapping with the electrophile, so that the electrophile preferentially traps one complex to afford one enantiomeric product in excess. The difficulty with DKR is that the asymmetric induction achieved will change depending on the electrophile and how fast it traps, which can necessitate changing the temperature at which the trapping is conducted. This in turn means that there cannot be a general method for all electrophiles, unlike DTR which should yield a very similar enantioselectivity for all electrophiles.

Coldham *et al.* had initially reported the use of both DTR and DKR for the enantioselective α-functionalisation of *N*-Boc-pyrrolidine **8** and subsequently applied DTR for the successful α-functionalisation of *N*-Boc-piperidine **8** with a range of electrophiles.[50] Using ligand **96** (pre-treated with *s*-BuLi), the electrophile scope included Me_3SiCl which afforded α-silylpiperidine (*S*)-**62** in 65% yield and 85:15 er (Scheme 2.19). This was a comparable er but significantly higher yield to that obtained by Beak *et al.* (see Scheme 2.18), demonstrating the utility of this methodology. In one example, trapping with propionaldehyde gave a mixture of diastereomeric alcohols and the major diastereomer was used in the total synthesis of the naturally occurring alkaloid (+)-β-conhydrine (2*R*,*R*)-**98**.



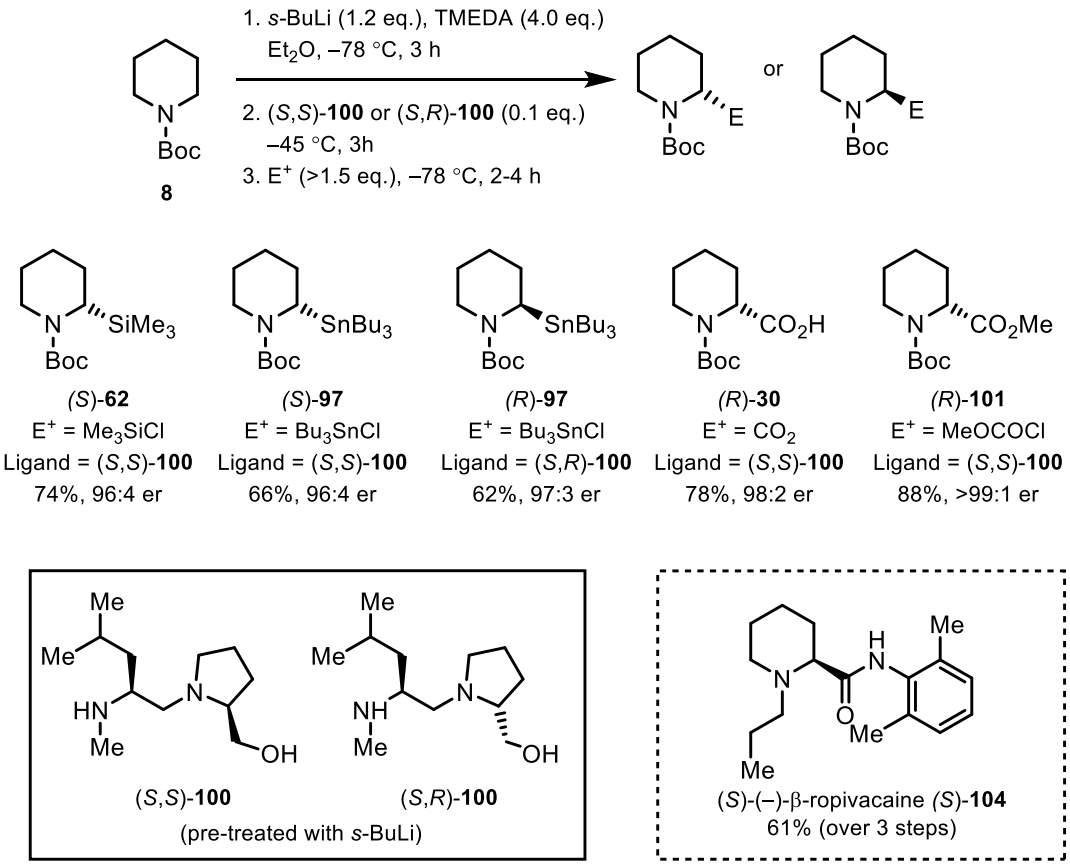
Scheme 2.19

Coldham *et al.* performed a DKR procedure on *N*-Boc-piperidine **8**.[49] In this case, the racemic lithiated species was generated in THF and then the lithium alkoxide ligand derived from **99** was added. Trapping with Me_3SiCl at –20 °C over 1 hour afforded α-silylpiperidine (*S*)-**62** in 62% yield and 95:5 er (Scheme 2.20). This was the only electrophile reported in this DKR procedure and highlights the key limitation of the DKR approach.



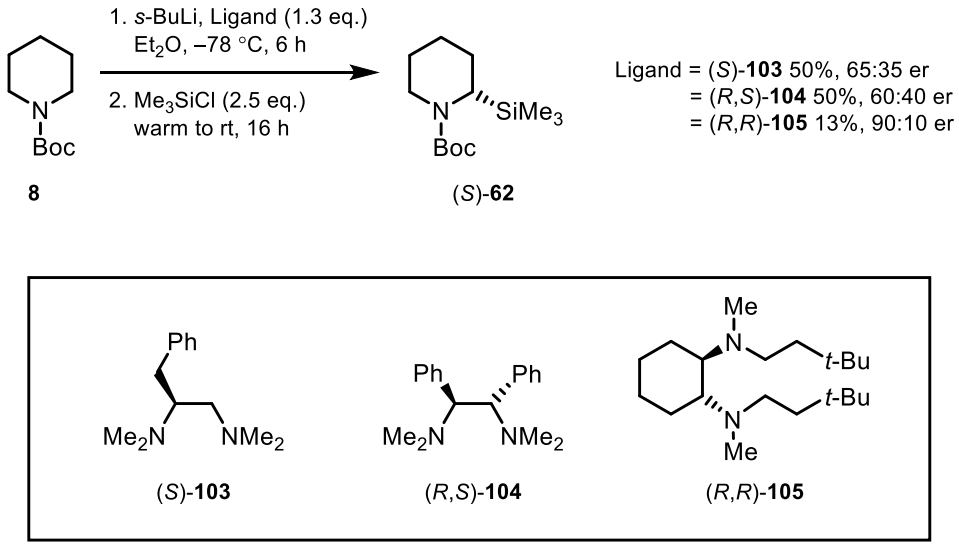
Scheme 2.20

Gawley and Beng built upon Coldham and co-worker's DKR procedure and, through the use of dilithiated ligands derived from amino alcohols (*S*,*S*)-**100** and (*S*,*R*)-**100**, accomplished the DKR of *N*-Boc-piperidine **8** with a range of electrophiles in ≥94:6 er (Scheme 2.21).[51] An advantage of this methodology was the use of a substoichiometric amount of the chiral ligand (0.1 equivalents) and, for this reason, the method was named a catalytic dynamic resolution (CDR). Using diastereomeric ligands (*S*,*S*)-**100** and (*S*,*R*)-**100**, the synthesis of α-stannylpiperidine **97** in both enantiomeric forms was carried out in excellent er. Other electrophiles were also shown to be compatible with this methodology, all affording α-functionalised piperidines in ≥94:6 er. This methodology was also used to synthesise six natural products and biologically-active compounds containing piperidine rings such as (*S*)-(–)-ropivacaine (Scheme 2.21).



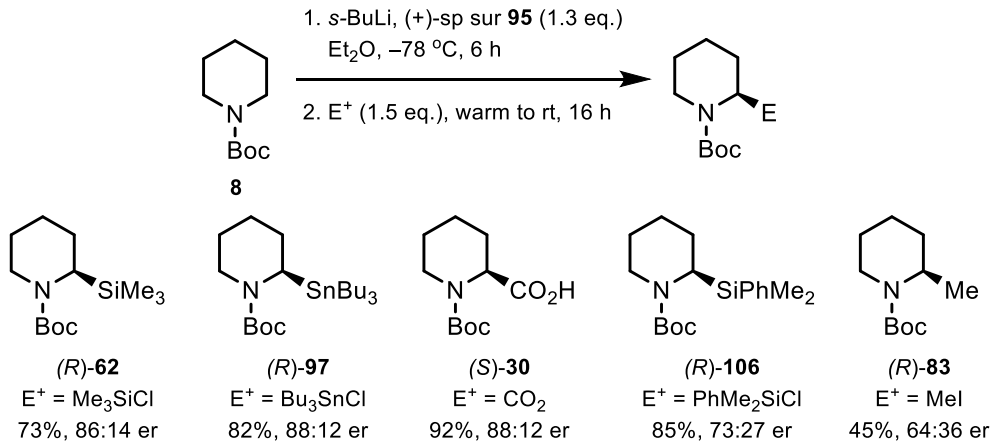
Scheme 2.21

O'Brien and Coldham *et al.* investigated alternative ligands for the asymmetric deprotonation of *N*-Boc-piperidine **8**.[52] 12 Chiral ligands were synthesised or acquired for use in the lithiation-trapping of piperidine **8** with either Me_3SiCl or $PhMe_2SiCl$. These reactions were conducted in Et_2O at –78 °C and piperidine **8** was treated with *s*-BuLi/ligand for 6 hours before addition of the electrophile (Scheme 2.22). Out of these 12 ligands, the only one to afford α-silylpiperidine (*S*)-**62** with an er greater than 70:30 was diamine (*R*,*R*)-**105**, initially introduced by Alexakis.[53] When used in the lithiation, diamine (*R*,*R*)-**105** afforded α-silyl piperidine (*S*)-**62** in 90:10 er but only 13% yield. The next best ligands, (*S*)-**103** and (*R*,*S*)-**104**, afforded α-silylpiperidine (*S*)-**62** in 50% yield in both cases but only modest er, 65:35 and 60:40 respectively.



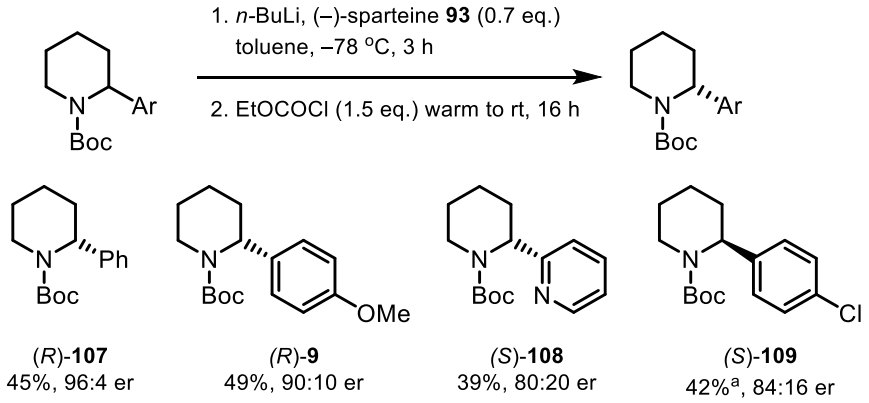
Scheme 2.22

Building upon their previous work O'Brien *et al.* applied the (+)-sparteine surrogate **95** to the lithiation-trapping of *N*-Boc-piperidine **8**.[46] The lithiation was conducted in Et_2O with *s*-BuLi/(+)-sparteine surrogate **95** with a lithiation time of 6 hours (Scheme 2.23). Under these conditions the synthesis of α-silylpiperidine (*R*)-**62** was accomplished in 73% yield and 86:14 er. This was a significantly higher yield than that obtained with (–)-sparteine **93** (see Scheme 2.18), but a lower er that that obtained by either dynamic resolution method (see Schemes 2.20 and 2.21). Other electrophiles were shown to give similar levels of success, for example, use of Bu_3SnCl afforded α-stannylpiperidine (*R*)-**97** in 82% yield and 88:12 er. However, it was observed that a lower yield and er was obtained when the electrophiles $PhMe_2SiCl$, dimethylsulfate, methyliodide and allylbromide were used. For example, with dimethylsulfate, α-methylpiperidine (*R*)-**83** was obtained in 45% yield and 60:40 er. This was shown to be due to slow trapping and configurational instability of the lithiated intermediate as it warmed up, resulting in degradation of the er and loss of yield. When tin-lithium exchange of enantioenriched α-stannylpiperidine (*R*)-**97** was performed in THF with *n*-BuLi followed by electrophilic trapping with dimethylsulfate, α-methylpiperidine (*R*)-**83** was obtained in good yield (54%) and high er (87:13).



Scheme 2.23

A classical resolution approach to enantioenriched α-aryl *N*-Boc-piperidines using lithiation-trapping has been described by Coldham *et al.*[54] This was performed by starting from a racemic α-aryl *N*-Boc-piperidine, lithiating with *n*-BuLi/(–)-sparteine **93** in toluene at –78 °C and then adding the electrophile at –78 °C and allowing the mixture to warm to rt. 0.7 Equivalents of *n*-BuLi/(–)-sparteine **93** were used, resulting in deliberate incomplete lithiation. Due to the presence of the chiral ligand one of the enantiomers would be lithiated preferentially over the other and subsequently trapped by the electrophile. Therefore, the α-aryl piperidine that was not lithiated would be enantioenriched when isolated as it could be separated from the functionalised piperidine. By nature of this procedure, the maximum yield that could be obtained would be ~50%, but Coldham demonstrated that it was a viable procedure on a range of α-aryl piperidines affording enantioenriched α-aryl piperidines (Scheme 2.24). Using (+)-sparteine surrogate **95**, the opposite enantiomer could be obtained.

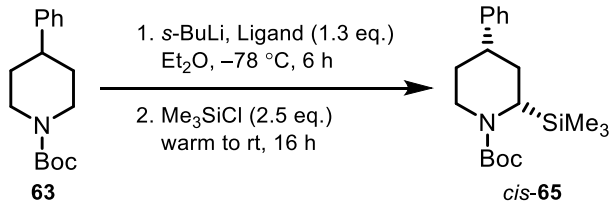


a) (+)-sparteine surrogate **95** used instead of (–)-sparteine **93**

Scheme 2.24

The first asymmetric deprotonation of a 4-substituted-*N*-Boc-piperidine was reported by O'Brien and Coldham *et al.*.[52] The α-lithiation-functionalisations of 4-phenyl-*N*-Boc-piperidine **63** and 4,4-(ethylenedioxy)-*N*-Boc-piperidine **110** were carried out using chiral ligands. The reactions were conducted in Et_2O and with a lithiation time of 6 hours before the addition of Me_3SiCl to give α-silyl piperidine *cis*-**65** or (*S*)-**111** (Tables 2.2 and 2.2).

Table 2.2: Asymmetric lithiation-trapping of 4-phenyl-*N*-Boc-pyrrolidine **63**

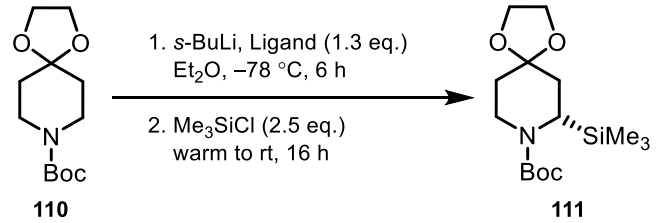


Entry	Ligand	Yield / %	er
1	(–)-sparteine **93**	6	78:22
2	(*S*)-**103**	68	58:42
3	(*R*,*S*)-**104**	24	56:44
4	(*R*,*R*)-**105**	48	87:13
5	(+)-sp surr **95**	89	30:70

The results of these investigations showed that only diamine (*R*,*R*)-**105** gave a degree of enantiocontrol approaching a synthetically useful value, affording *cis*-**65** in 48% yield and 87:13 er (Table 2.2 entry 4). However, when diamine (*R*,*R*)-**105** was used to effect the asymmetric lithiation of 4,4-(ethylenedioxy)-*N*-Boc-piperidine **110**, the resulting α-silylpiperidine (*R*)-**111** was only obtained in 53% yield and 53:47 er (Table 2.3 entry 4). Neither ligand (*S*)-**103** or (*R*,*S*)-**104** accomplished an er greater than 60:40 with either piperidine substrate. O'Brien and co-workers also applied the (+)-sparteine surrogate **95** to the asymmetric lithiation-trapping of 4-phenyl-*N*-Boc-piperidine **63**.[55] The use of this ligand gave α-silylpiperidine *cis*-**65** in 70:30 er and a significantly higher yield of 89% (Table 2.2 entry 5). The higher yield can be attributed to the greater reactivity of the *s*-BuLi/(+)-sparteine surrogate **95** complex compared to that of *s*-BuLi/(–)-sparteine **93**. These results demonstrated that whilst the enantioselective synthesis of 2,4-

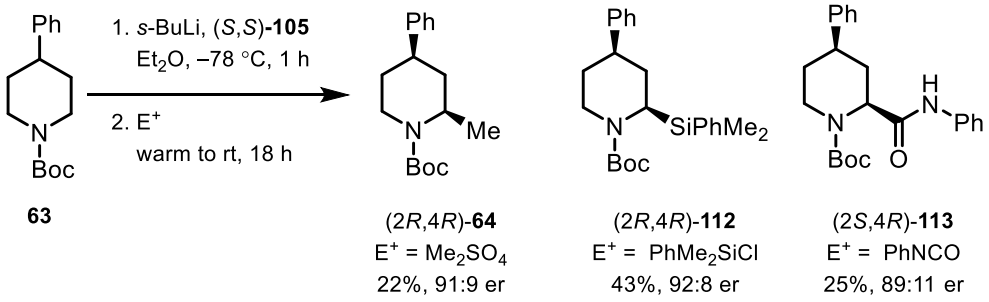
disubstituted piperidines *via* lithiation-trapping was possible, relatively low ers were obtained.

Table 2.3: Asymmetric lithiation-trapping of 4,4-(ethylenedioxy)-*N*-Boc-piperidine **110**



Entry	Ligand	Yield / %	er
1	(–)-sparteine **93**	0	-
2	(*S*)-**103**	47	60:40
3	(*R*,*S*)-**104**	6	60:40
4	(*R*,*R*)-**105**	53	47:53

Subsequently, O'Brien and co-workers reported the α-lithiation-functionalisation of 4-phenyl-*N*-Boc-piperidine **63** with further electrophiles.[55] These reactions were performed using the Alexakis diamine (*S*,*S*)-**105** as this ligand gave the highest er in the previous study (see Table 2.2). 2,4-Disubstituted piperidines *cis*-**64**, *cis*-**112** and *cis*-**113** were obtained in ~90:10 er, indicating the utility of the Alexakis diamine (*S*,*S*)-**105** (Scheme 2.25).



Scheme 2.25

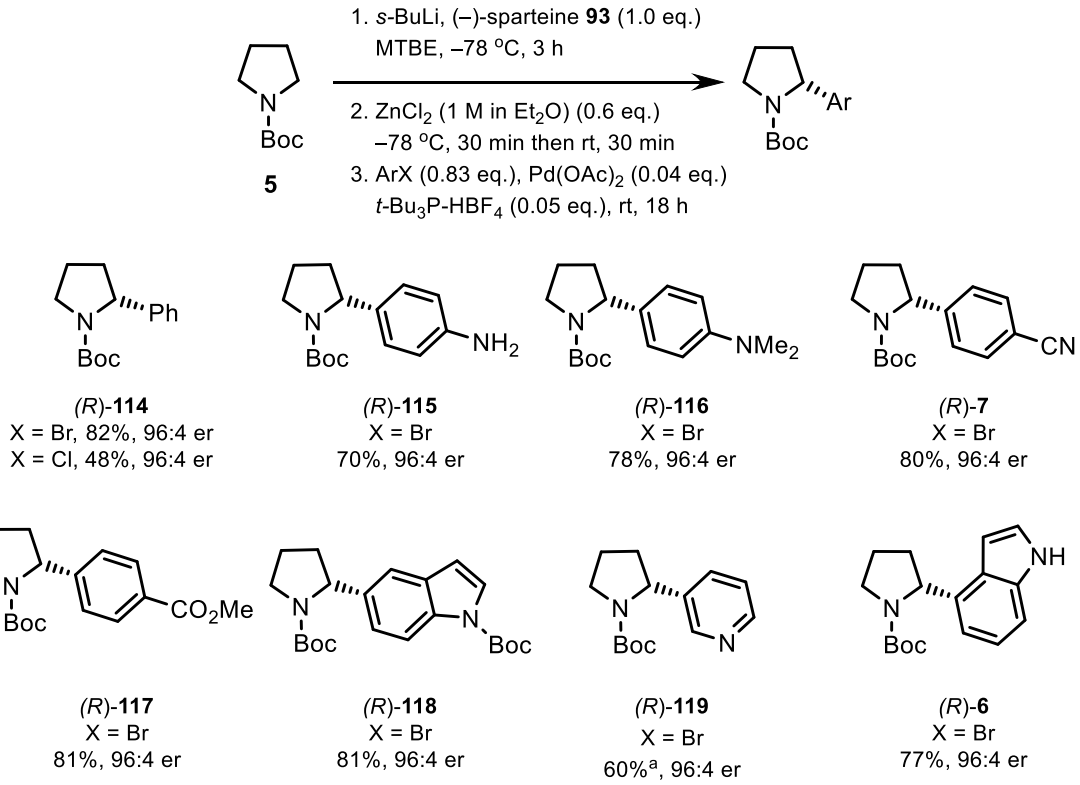
These reports have demonstrated that the asymmetric lithiation-trapping of substituted and unsubstituted *N*-Boc-piperidine is possible. However, the enantioselectivity achieved from the direct lithiation-trapping of *N*-Boc-piperidines is lower than that

when the method is applied to *N*-Boc-pyrrolidine **5**. Lithiation with *s*-BuLi/(–)-sparteine **93**, which, upon trapping gives α-functionalised *N*-Boc-pyrrolidines in good yield er, has been shown to be far less efficient with *N*-Boc-piperidine **8**. Instead, the ligand affording the highest degree of enantioselectivity is the Alexakis diamine (*S*,*S*)-**105** or (*R*,*R*)-**105**. Nevertheless, through the use of DTR and DKR, α-functionalised *N*-Boc-piperidines can be obtained with >95:5 er.

2.1.3 Racemic and Asymmetric α-Arylation of *N*-Boc-pyrrolidine and Piperidines *via* Negishi Cross-Coupling

As briefly covered in Chapter 1, chemists at Merck led by Campos expanded upon the utility of the *N*-Boc heterocycle α-functionalisation methodology by demonstrating that, instead of using an electrophile, the lithiated pyrrolidine could be transmetallated to an organozinc species using $ZnCl_2$. The organozinc species could then undergo a palladium-catalysed Negishi cross-coupling reaction, enabling the α-arylation of *N*-Boc-pyrrolidine.[12] Through the use of *s*-BuLi/(–)-sparteine **93**, the lithiation step was carried out enantioselectively and this asymmetric information was carried through the transmetallation to zinc, transmetallation to palladium and subsequent reductive elimination to give α-arylated pyrrolidines in ≥96:4 er with retention of stereochemistry (Scheme 2.26). During the investigation, it was reported that both RuPhos and QPhos gave comparable yields and enantioselectivities when utilised in the cross-coupling step, but, for reasons of cost, availability and practicality, *t*-Bu_3P-HBF_4 was selected. It was also observed that $Pd(OAc)_2$ provided a significantly faster rate of reaction compared to other palladium sources such as $PdCl_2$ and that both precatalysts $Pd(t\text{-}Bu_3P)_2$ and $[PdBr(t\text{-}Bu_3P)]_2$ gave lower conversions. Overall, this led to the use of *t*-Bu_3P-HBF_4 at 5 mol % and $Pd(OAc)_2$ at 4 mol %. As an example, asymmetric lithiation followed by transmetallation with 0.6 equivalents of $ZnCl_2$ gave an organozinc species which was cross-coupled with bromobenzene using $Pd(OAc_2)$ and *t*-Bu_3P-HBF_4 at rt to give α-phenylpyrrolidine (*R*)-**114** in 82% yield and 96:4 er. A selection of the aryl bromides reported to be compatible with this methodology are shown in Scheme 2.26; both electron-rich and electron-deficient aryl bromides were tolerated as well as heteroaromatics. Interestingly, the lithiation step was performed in MTBE not Et_2O, which may have been due to the higher flash point of MTBE, making it a safer solvent to work with whilst still possessing similar physical properties to Et_2O. It was

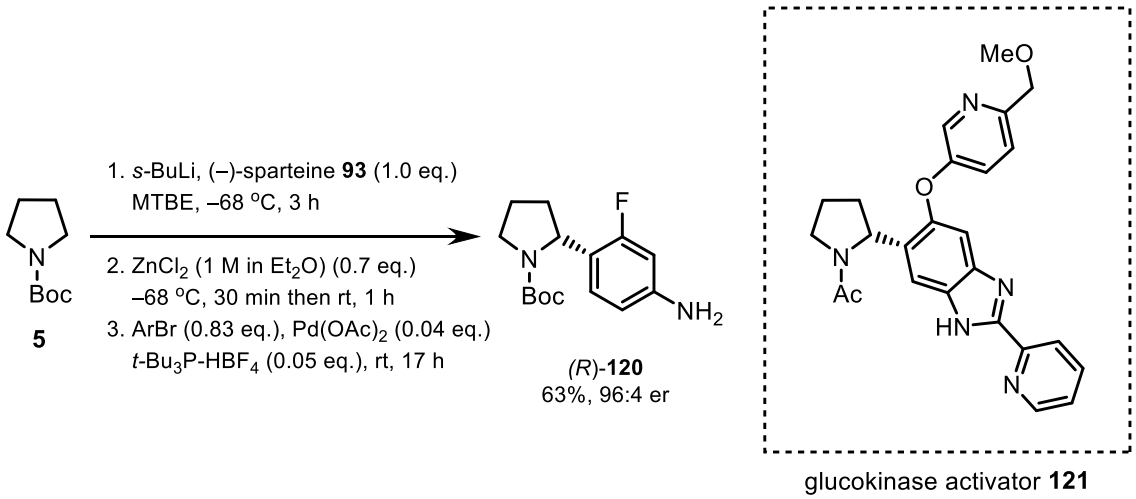
demonstrated that chlorobenzene could be used in the cross-coupling to give α-phenylpyrrolidine (*R*)-**114**, although with a lower yield (48%) compared to that achieved with bromobenzene (82%). The cross-coupling was attempted with PhOTs and PhOTf but, in both cases, no product was obtained. When 3-bromopyridine was cross-coupled, the Negishi reaction required an elevated temperature of 60 °C and with this change in conditions, α-pyridylpyrrolidine (*R*)-**119** was obtained in 60% yield and 96:4 er.



a) Cross-coupling conducted at 60 °C

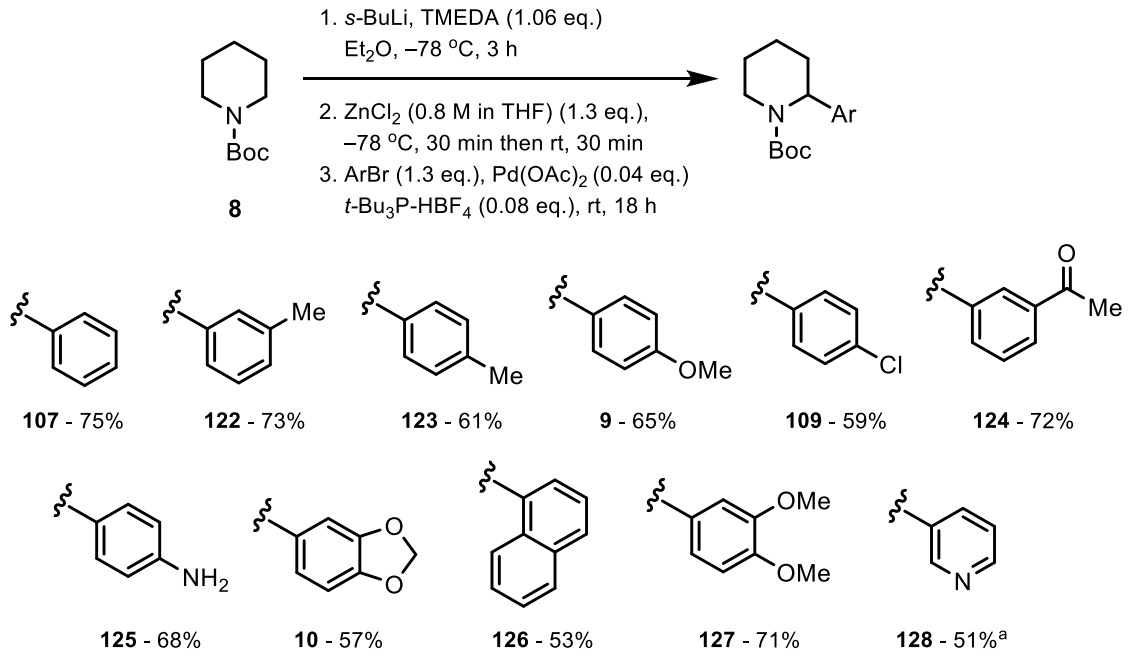
Scheme 2.26

The methodology was developed by the chemists at Merck in pursuit of glucokinase activator **121**, for which they performed the α-arylation of *N*-Boc-pyrrolidine **5** with 3-fluoro-4-bromophenylamine.[56] This reaction was performed on a large scale to deliver over 1 kg of α-arylpyrrolidine (*R*)-**121** in 63% yield and 96:4 er (Scheme 2.27).



Scheme 2.27

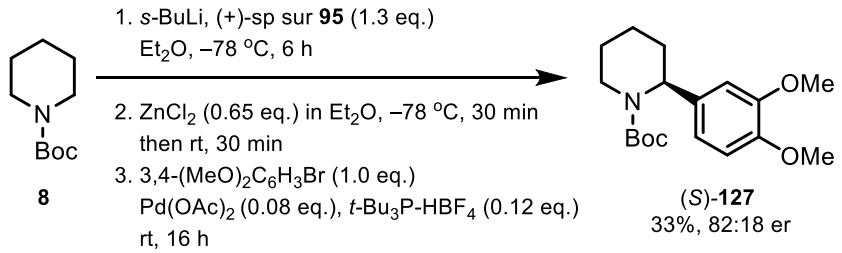
Campos *et al.*'s α-lithiation-arylation procedure was applied to *N*-Boc-piperidine **8** by Coldham and Leonori to generate α-aryl piperidines in good yields (Scheme 2.28).[13] The lithiation was performed racemically using *s*-BuLi/TMEDA in Et_2O followed by transmetallation with $ZnCl_2$ prior to Negishi cross-coupling with $Pd(OAc)_2$ and *t*-Bu_3P-HBF_4. Similar conditions to those reported by Campos *et al.* were used except that *N*-Boc-piperidine **8** was the limiting reagent (instead of the aryl halide) and the Pd:ligand ratio was increased to 1:2.[46] Electron-rich and deficient aryl bromides were tolerated in the cross-coupling and a single example of the coupling of a heteroaryl halide was reported, using 3-bromopyridine to afford α-pyridylpiperidine **128** in 51% yield. The pyridine cross-coupling step was conducted at 40 °C whereas the rest of the aryl bromides were successfully cross-coupled at rt. The effect of varying the halide was reported and successful cross-coupling was achieved with bromobenzene (75%) and iodobenzene (61%). However, only trace amounts of α-phenylpiperidine **107** were detected when chlorobenzene was cross-coupled. None of the desired α-aryl piperidine was observed when PPh_3 was used as a ligand although it was shown that PCy_3-HBF_4 was a viable alternative ligand; cross-coupling with bromobenzene gave α-phenylpiperidine **107** in 52% yield.



b) Cross-coupling conducted at 40 °C

Scheme 2.28

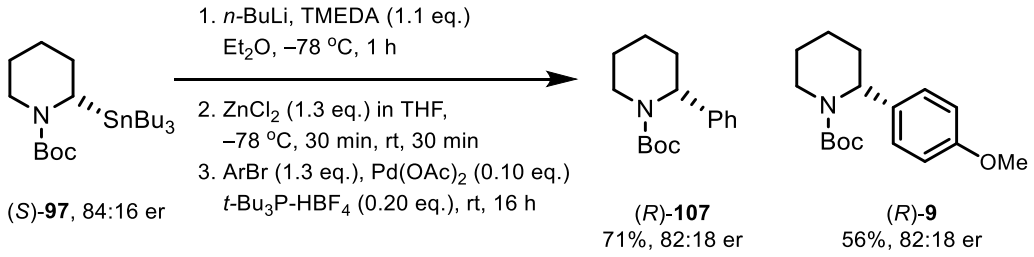
The O'Brien group subsequently reported that the α-arylation of *N*-Boc-piperidine **8** could be conducted enantioselectively through the use of *s*-BuLi/(+)-sparteine surrogate **95** in the lithiation step.[46] Using the same catalytic system as reported by Campos *et al.* (albeit with a higher catalyst loading), α-arylpiperidine (*S*)-**127** was formed in 33% yield and 82:18 er (Scheme 2.29). The er was slightly lower than those obtained by direct trappings with electrophiles such as CO_2, Bu_3SnCl and methylchloroformate (88:12 er, see Scheme 2.25). It is not clear why there was this discrepancy.



Scheme 2.29

Coldham *et al.* developed a method for the enantioselective α-arylation of *N*-Boc-piperidine **8** proceeding *via* enantioenriched α-stannylpiperidine (*S*)-**97**, which was

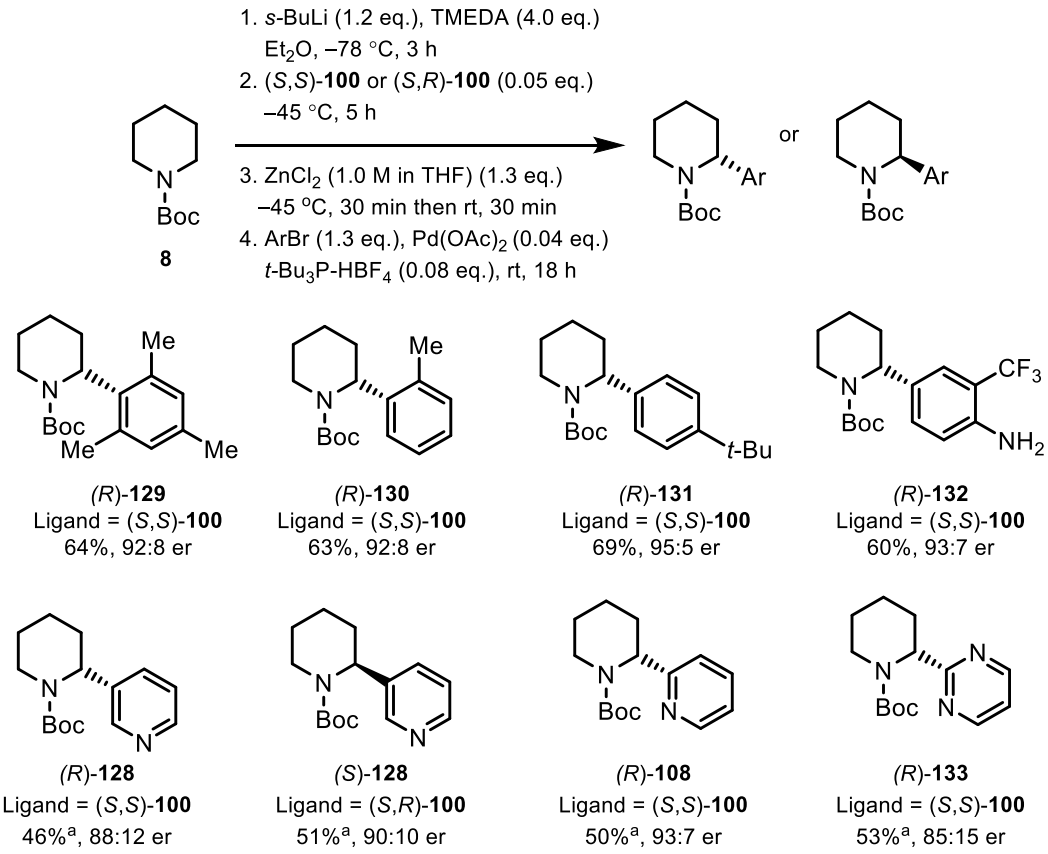
obtained through the DTR method in 84:16 er (see Scheme 2.19).[49] The lithiated intermediate was generated *via* tin-lithium exchange using *n*-BuLi/TMEDA in Et_2O at –78 °C for 1 hour. The transmetallation of lithium to zinc was carried out and the subsequent cross-coupling step was performed using $Pd(OAc)_2$ (10 mol%) and *t*-Bu_3P-HBF_4 (20 mol%). This α-arylation procedure was performed with bromobenzene and 4-bromoanisole to afford α-arylpiperidines (*R*)-**107** (71% yield, 82:18 er) and (*R*)-**9** (56% yield, 82:18 er) respectively (Scheme 2.30). This work demonstrated that there was retention of stereochemistry during tin-lithium exchange and subsequent cross-coupling.



Scheme: 2.30

Gawley and Beng expanded upon their previous research into the CDR of *N*-Boc-piperidine **8** by adapting their original method to accomplish the α-arylation of piperidine **8**, using the ligands (*S*,*S*)-**100** and (*S*,*R*)-**100** and through Negishi cross-coupling.[57,51] Et_2O was reported to be superior to MTBE, affording higher yields and superior enantioselectivities whilst decreasing the amount of ligand used in the resolution increased the er. The transmetallation to zinc was performed using 1.3 equivalents of $ZnCl_2$ in THF at –45 °C for 30 minutes, followed by warming the reaction mixture to rt and stirring for a further 30 minutes. The cross-coupling was then performed using the same conditions as originally reported by Coldham and Leonori.[13] The CDR-arylation procedure afforded a wide range of α-aryl piperidines in good yield (46-75%) and very good er; a selection of examples are shown in Scheme 2.31. Of note, the successful cross-coupling of sterically hindered mesitylbromide to afford α-arylpiperidine (*R*)-**129** was accomplished (64% yield, 92:8 er) alongside the cross-coupling of three nitrogen-containing heteroaryl halides: 2-bromopyridine, 3-bromopyridine and 2-bromopyrimidine. For the heteroaryl halides, the cross-coupling reactions were carried out at 60 °C, indicating the increased difficulty of cross-coupling these aryl bromides. Notably, the ers of the α-heteroaryl piperidines were lower than those of the other α-aryl piperidines. It was demonstrated that this was due to some

configurational instability of the organozinc intermediate at higher temperatures. With the exception of heteroaryl halides, Gawley and Beng's CDR method afforded α-aryl piperidines in superior ers compared to the asymmetric deprotonation method, a definite advantage of this methodology.



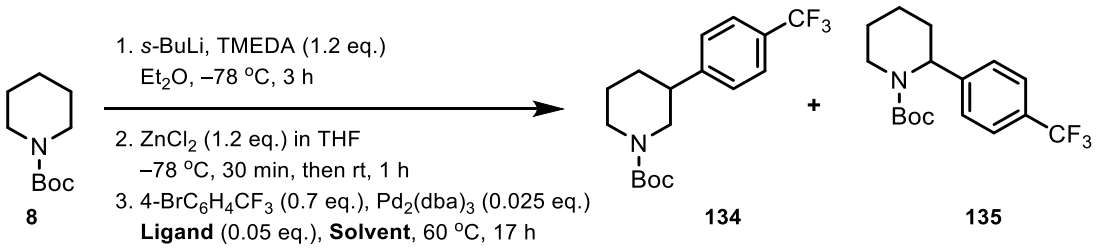
a) Cross-coupling conducted at 60 °C

Scheme: 2.31

Baudoin and co-workers demonstrated that it was possible to accomplish the β-arylation of *N*-Boc-piperidine **8** using a Negishi approach from an α-zincated piperidine (generated *via* α-lithiation-transmetallation).[58] This was achieved through the judicious choice of ligand in the cross-coupling step. Flexible biarylphosphine ligands favoured the β-arylated product whereas more rigid ligands gave the α-arylated product. The cross-coupling step used $Pd_2(dba)_3$ (2.5 mol%) and a solvent switch from Et_2O to toluene prior to the cross-coupling step (instead of conducting the whole procedure in a single solvent); the reactions were conducted in Schlenk tubes and the Et_2O was removed *in vacuo*. The catalyst, ligand and aryl halide were premixed in toluene and then added to the organozinc intermediate and the reaction was heated at 60 °C. This

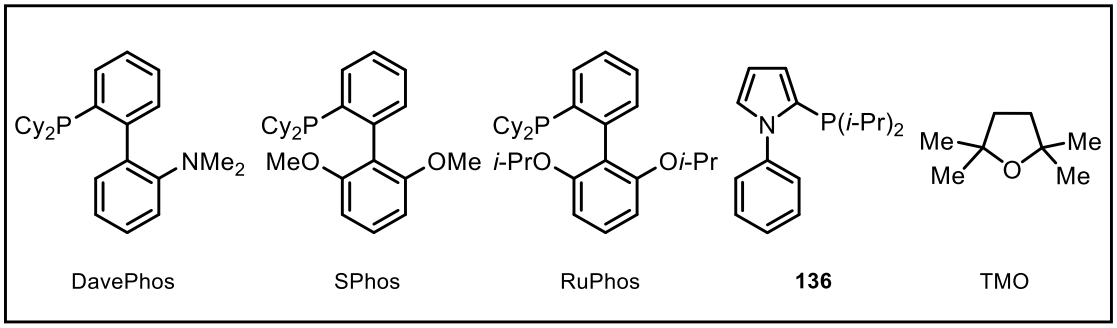
solvent switch enabled the cross-coupling step to be conducted at a higher temperature that would not otherwise be possible in Et_2O. The optimisation studies are summarised in Table 2.4. When cross-coupling was attempted using DavePhos (5 mol%) and a temperature of 60 °C, good yields of arylated piperidines **134** and **135** were obtained with toluene (68%, entry 1), THF (55%, entry 2), TMO (68%, entry 3), MTBE (62%) and mesitylene (54%). Under these conditions, only modest β selectivity was observed, in the range of 41:59 – 27:73. The effect of the ligand on selectivity was investigated whilst conducting the cross-coupling in toluene. Ligand studies showed that cross-coupling using DavePhos and RuPhos favoured the formation of α-arylpiperidine **135** (entries 1 and 6), whilst SPhos almost exclusively gave α-arylpiperidine **135** in high yield (78%, 94:6 ratio, entry 7). However, the use of **136** afforded a 91:9 mixture of β-arylpiperidine **134** and α-arylpiperidine **135** in 59% yield. Temperatures of 20-100 °C were investigated for the cross-coupling step and 60 °C was found to be optimal.

Table 2.4: Investigation of the α- and β-arylation of *N*-Boc-piperidine **8**



Entry	Ligand	Solvent	Yield / %[a]	**134**:**135**[b]
1	DavePhos	toluene	68	39:61
2	DavePhos	THF	55	41:59
3	DavePhos	TMO	68	29:71
4	DavePhos	MTBE	62	36:64
5	DavePhos	mesitylene	54	27:73
6	SPhos	toluene	78	6:94
7	RuPhos	toluene	65	10:90
8	**136**	toluene	59[c]	91:9

a) Combined yield of **134** and **135** unless otherwise stated; b) Ratio of **134** and **135** determined by ^{1}H NMR spectroscopic or GCMS analysis of crude product; c) Yield of isolated **134**



Supported by DFT studies, Baudoin *et al.* presented a mechanism for β-arylation (Figure 2.1). It was proposed that transmetallation from zinc to palladium occurred first to give **137**, followed by a ring-flip to the twist boat conformation **138** from which β-hydride elimination could occur to give **139**. There would then be rotation of the coordinated palladium followed by reinsertion to give **140** with the palladium now in the β position; this would be followed by a ring-flip back to a chair conformation to give **141**. Finally, reductive elimination would occur to give β-arylpiperidine **142**. In this proposed mechanism, the palladium stays coordinated to the same face of the piperidine ring throughout the process.

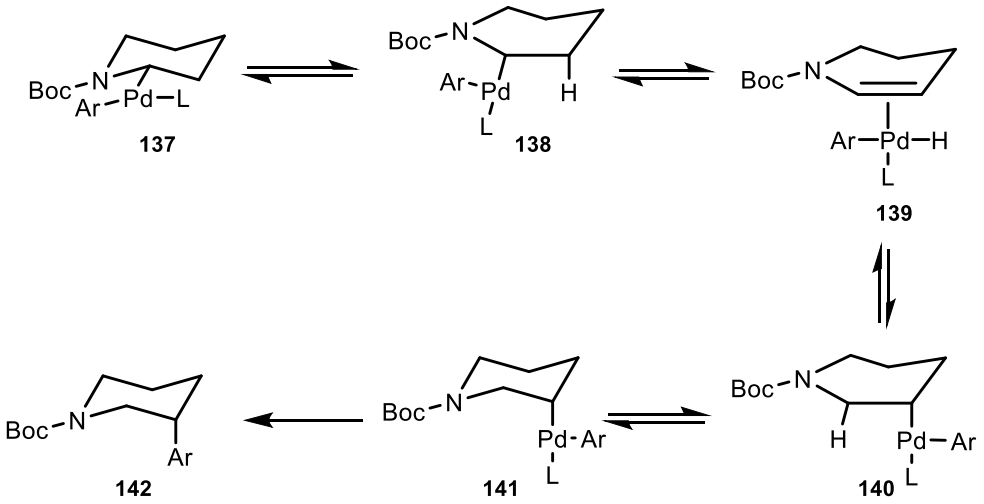
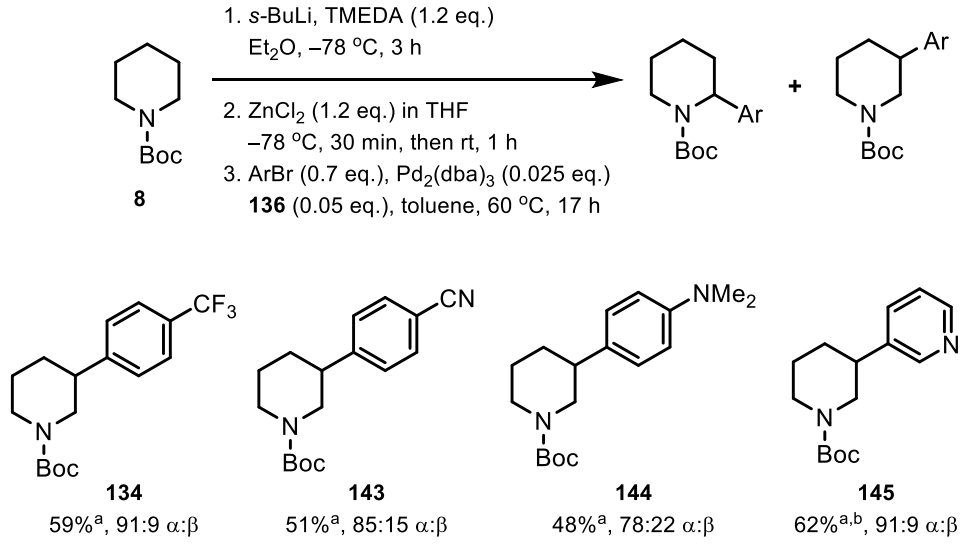


Figure 2.1: Proposed mechanism of β-arylation of *N*-Boc-piperidine **8**

Subsequently, the scope of the β-arylation was investigated using *N*-Boc-piperidine **8** and conducting the cross-coupling step in toluene. The cross-coupling of electron-rich, electron-deficient and 3-bromopyridine could all be successfully carried out, although in the case of 3-bromopyridine, the Negishi step required an elevated temperature of 80 °C. A selection of examples of β-aryl piperidines are shown in Scheme 2.32. Despite the

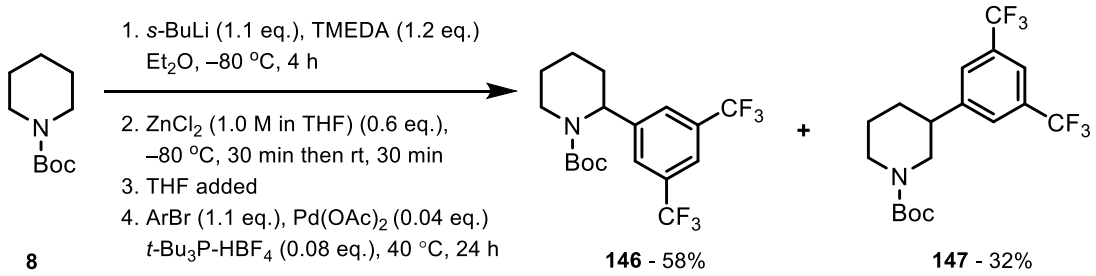
success with *N*-Boc-piperidine **8**, the β-arylation methodology was unsuccessful when applied to *N*-Boc-pyrrolidine **5**, *N*-Boc-azepane and *N*-Boc-azocane.



a) Isolated yield of β-aryl piperidine; b) Cross-coupling conducted at 80 °C

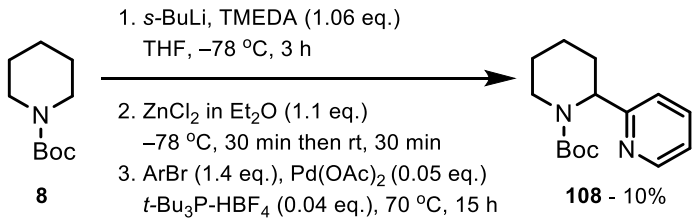
Scheme: 2.32

The β-arylation of *N*-Boc-piperidine **8** was subsequently observed by Beng and Fox.[59] It was reported that during the synthesis of α-arylpiperidine **146**, a 32% yield of β-arylpiperidine **147** was observed as a by-product (Scheme 2.33). Unlike Baudoin *et al.*'s methodology, Beng and Fox conducted the cross-coupling in THF and with *t*-Bu_3P-HBF_4.



Scheme: 2.33

Zhong and Tran *et al.* at Calibr reported the α-arylation of *N*-Boc-piperidine **8** in THF with 2-bromopyridine by lithiation in THF, transmetallation with $ZnCl_2$ and Negishi cross-coupling; this reaction afforded α-arylpiperidine **108** in 10% yield.[60] The advantage of conducting the lithiation in THF was that it avoided the need for a solvent switch prior to the cross-coupling step and, as THF has a higher boiling point than Et_2O, the Negishi step could be heated to 70 °C (Scheme 2.34).

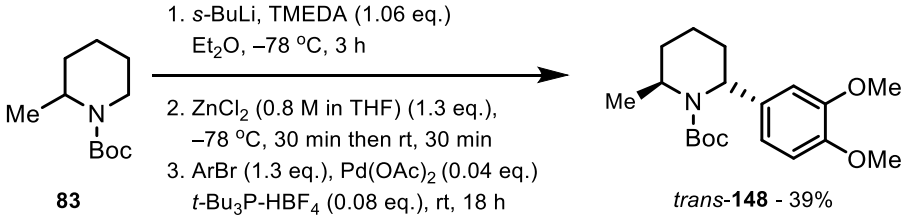


Scheme: 2.34

These reports have built upon the existing α-lithiation-functionalisation procedure and improved its utility by enabling the installation of aromatic groups. However, for *N*-Boc-piperidines, as with lithiation-trapping, the enantioselectivity of methods that proceed *via* direct lithiation-transmetallation cross-coupling have been shown to be lower than those obtained with *N*-Boc-pyrrolidines. Nevertheless, Beng and Gawley have shown that this is a problem that can be circumvented with CDR. A recurring trend throughout the existing reports is the challenge of cross-coupling nitrogen-containing heteroaryl halides; in almost all cases, they require higher temperatures to cross-couple relative to other aryl halides.

2.1.4 α-Arylation of Substituted *N*-Boc-piperidines *via* Negishi Cross-Coupling

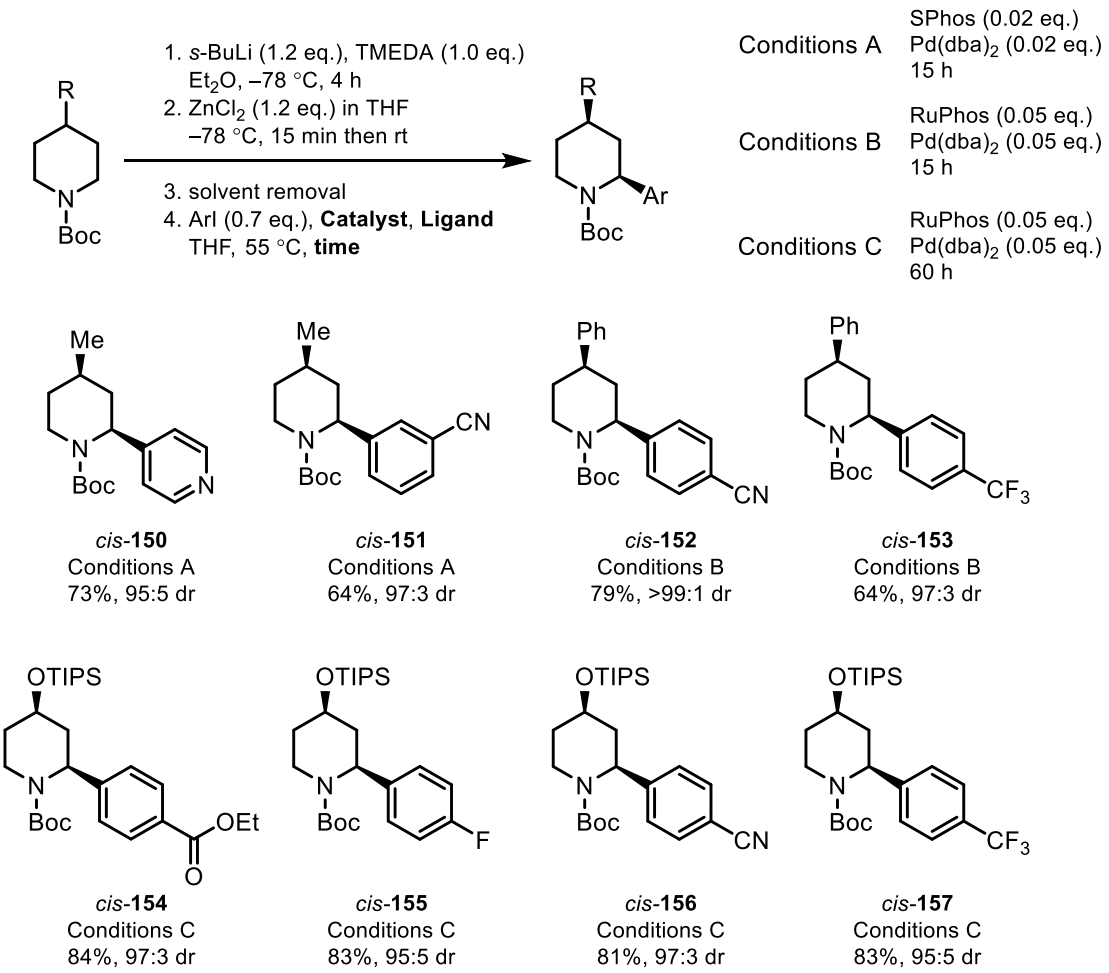
Coldham and Leonori reported the first α-arylation of a substituted piperidine, by performing the α-arylation of 2-methyl-*N*-Boc-piperidine **83** by lithiation-transmetallation-Negishi cross-coupling.[13] The Negishi step was performed using 4 mol% $Pd(OAc)_2$, 8 mol% *t*-BuP-HBF_4 at rt. 4-Bromo-1,2-dimethoxybenzene was cross-coupled to afford α-aryl-6-methylpiperidine *trans*-**148** in 39% yield (Scheme 2.35). The preferential formation of the *trans* diastereomer is consistent with the findings of Beak and Lee in direct electrophile trapping (see Scheme 2.11).[28]



Scheme: 2.35

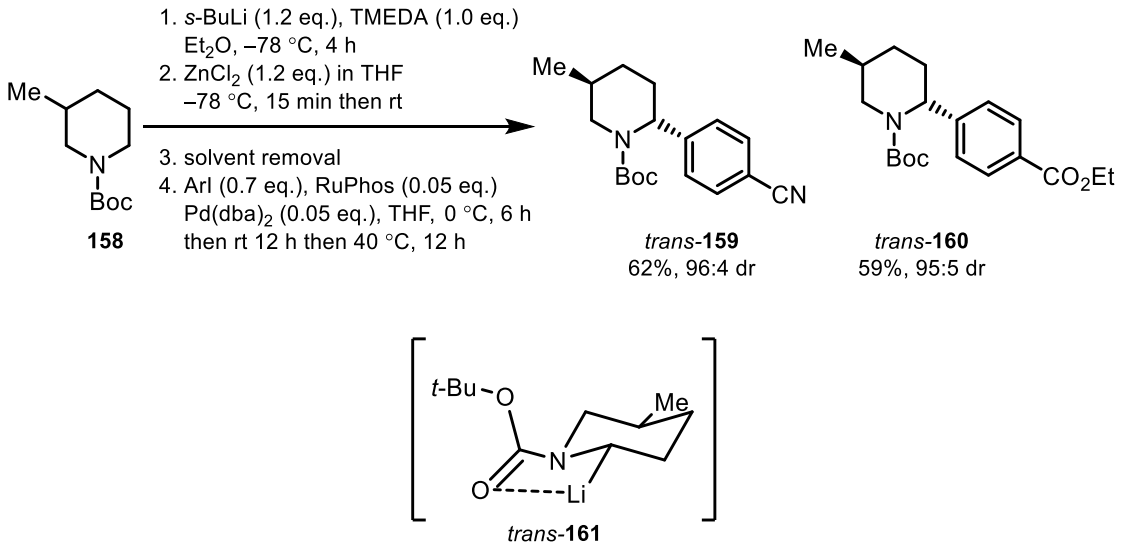
Knochel *et al.* provided the first report on the α-arylation of 4-substituted *N*-Boc-piperidines *via* lithiation, transmetallation and Negishi cross-coupling to afford 2,4-disubstituted piperidines.[24] After transmetallation, the lithiation solvent (Et_2O) was

removed *in vacuo* before performing the cross-coupling step with aryl iodides (as the limiting reagent) in THF at 55 °C using $Pd(dba)_2$ and either SPhos or RuPhos. This procedure successfully furnished a range of 4-methyl-, 4-phenyl- and 4-OTIPS-α-aryl piperidines in good yields with ≥95:5 *cis*-selectivity (Scheme 2.36). For example, cross-coupling the organozinc intermediate generated from 4-OTIPS-*N*-Boc-piperidine **149** with 4-iodobenzonitrile afforded α-arylpiperidine *cis*-**150** in 81% yield and 97:3 dr. A range of aryl iodides were successfully cross-coupled including those with both electron-rich and deficient groups. There was a single example of the cross-coupling of a heteroaryl iodide, 4-iodopyridine, which was coupled with the organozinc intermediate derived from 4-methyl-*N*-Boc-piperidine **78** in 73% yield and 95:5 dr. Using DFT calculations, it was shown that there was a preference for all the substituents of the organozinc species to sit equatorial, and it was postulated that this could contribute to the very high diastereoselectivity observed. The observed *cis*-selectivity and DFT calculations were in agreement with the findings of Beak and Lee for the preferential *cis*-selectivity during α-lithiation-functionalisation due to equatorial lithiation (see Scheme 2.4).[29] The *cis*-stereochemistry was definitively proven through two X-ray crystal structures, which also showed that the disubstituted products adopted a twist boat or a chair conformation.



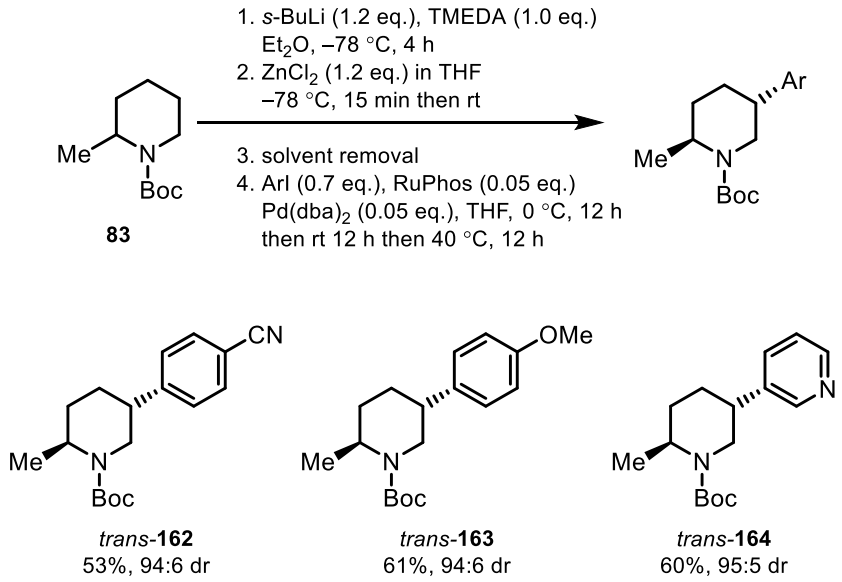
Scheme 2.36

Knochel *et al.* also reported the α-arylation of 3-methyl-*N*-Boc-piperidine **158**. The same lithiation-transmetallation cross-coupling procedure was performed using RuPhos and carrying out the cross-coupling step at 40 °C (Scheme 2.37). 4-Iodobenzonitrile and ethyl 4-iodobenzoate were cross-coupled to give *trans*-**159** in 62% yield and 96:4 dr and *trans*-**160** in 59% yield and 95:5 dr. The *trans* stereochemistry was the result of the substituent sitting equatorially and subsequent equatorial lithiation giving *trans*-**161**.



Scheme 2.37

Knochel *et al.* unintentionally performed the first β-arylation of *N*-Boc-piperidine **83**. The arylation of 2-methyl-*N*-Boc-piperidine **83** with RuPhos (5 mol%), $Pd(dba)_2$ (5 mol%) and heating to 40 °C in the cross-coupling step gave β-aryl-2-substituted piperidines, rather than 2,6-disubstituted piperidines (Scheme 2.38). The successful cross-coupling of a heteroaryl halide was accomplished; use of 3-iodopyridine afforded β-arylpiperidine *trans*-**163** in 60% yield and 95:5 dr. Knochel *et al.* proposed that the *trans* selectivity was due to palladium migration through β-hydride elimination where the palladium stayed coordinated on the same face of the piperidine ring before reinsertion occurred. Equatorial lithiation of 2-methylpiperidine **83** would afford the *trans* lithiated intermediate (see Scheme 2.11) and the *trans* stereochemistry would then be maintained during migration. Confirmation of this proposal has since been obtained by Baudoin and co-workers through their mechanistic studies of the β-arylation of *N*-Boc-piperidine **8** (see Scheme 2.32).[58] Knochel *et al.* also proposed that the use of a 1:1 ratio of ligand and catalyst favoured migration.

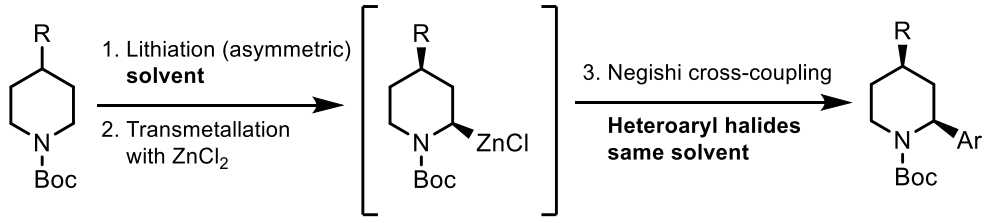


Scheme 2.38

The α-arylation of substituted *N*-Boc-piperidines has not been explored as thoroughly as that of unsubstituted *N*-Boc-piperidine **8**. However, pioneering work from Knochel *et al.* has shown that high diastereoselectivities can be obtained; a key part of this methodology is the solvent switch from Et_2O to toluene, allowing the cross-coupling step to be conducted at the higher temperatures required for good yields. Although the solvent switch is effective, it can certainly be considered to be a drawback of this procedure.

2.2 Proposed Approaches and Objectives

The aim of this work was to investigate the α-arylation of 4-substituted *N*-Boc-piperidines in detail. Although there are multiple reports of the synthesis of α-aryl *N*-Boc-piperidines *via* lithiation-transmetallation cross-coupling, the α-arylation of substituted *N*-Boc-piperidines *via* this methodology has not been covered in as much detail, with the only in-depth report coming from Knochel *et al.*.[24] Alternative α-arylation methods do exist, such as that reported by Suga and co-workers (see Scheme 1.11).[23] However, these methods are limited in scope by the availability of reagents, such as Grignard reagents. The desire was to deepen the understanding of this area with an aim of making the methodology more accessible for use by medicinal chemists. The key objectives toward this goal were: to remove the need for the solvent switch in the middle of the procedure, to expand the scope to incorporate heteroaryl halides and to investigate the asymmetric lithiation such that α-functionalised-4-substituted *N*-Boc-piperidines could be synthesised in both high diastereo- and enantioselectivity (Scheme 2.39).



Scheme 2.39

Broadly, the α-lithiation-functionalisation of *N*-Boc heterocycles has been conducted in Et_2O although there are noteworthy examples of other solvents being utilised either for lithiation or during the Negishi α-arylation step. For example, Beak *et al.* demonstrated that the lithiation of *N*-Boc-pyrrolidine **5** could be successfully conducted in Et_2O, MTBE and pentane.[40] The direct lithiation-trapping of *N*-Boc-piperidine **8** has only been conducted in Et_2O, although Coldham and co-workers have performed a DKR of piperidine **8** in THF and a DKR of α-aryl piperidines in toluene.[49,54] There are two examples of the lithiation-transmetallation cross-coupling being conducted in a solvent other than Et_2O, both instead using THF. O'Brien, Campos and Barker reported the α-arylation of pyrrolidine **5** in THF under diamine-free conditions.[43] However, these conditions were shown not to be applicable for the lithiation of *N*-Boc-piperidine **8**. The

whole α-arylation procedure has also been conducted in THF by Zhong, Tran and co-workers, albeit with a single low yielding result (see Scheme 2.34).[60] Other than these reports, there are no examples of a solvent, other than Et_2O, being used for both lithiation and cross-coupling. Finally, Knochel *et al.* have reported that the Negishi step in the α-arylation of substituted *N*-Boc-piperidines could be conducted in THF whilst Baudoin has reported that the cross-coupling of the organozinc intermediate derived from *N*-Boc-piperidine **8** could be conducted in toluene, THF, TMO, MTBE and mesitylene.[5824] Therefore, we set out to investigate the lithiation of 4-substituted piperidines in alternative solvents with an aim of identifying one that was suitable for both lithiation and cross-coupling. This would enable the entire process to be conducted in a single solvent, simplifying the procedure by removing the arduous solvent switch and thus making it more accessible and useful for medicinal chemists.

There is only a single example of the α-arylation of substituted *N*-Boc-piperidines with a nitrogen-containing heteroaryl halide (4-iodopyridine), reported by Knochel *et al.*, and the cross-coupling proceeded to give α-arylpiperidine *cis*-**143** in 73% yield at 55 °C (see Scheme 2.36).[24] There are a few results of the α-arylation of unsubstituted *N*-Boc-piperidine **8** with nitrogen-containing heteroaromatics. Coldham and Leonori reported a 51% yield when cross-coupling 3-bromopyridine at 40 °C (see Scheme 2.28).[13] Gawley and Beng have reported the cross-coupling of piperidine **8** at 60 °C in moderate yield with three heteroaryl halides using a CDR method (see Scheme 2.31).[57] Finally, there is a single example from Calibr involving the cross-coupling of 2-bromopyridine at 70 °C to afford α-arylpiperidine **108** in 10% yield (see Scheme 2.34).[60] All of these examples required elevated temperatures relative to those reported in the rest of their respective scope studies. This demonstrates that the cross-coupling of nitrogen-containing heteroaryl halides is both challenging and under-explored and, as a result, shall be a focus of this work.

Recently, Seidel and co-workers developed an alternative route to α-aryl piperidines going *via* an imine intermediate and a hydride transfer mechanism.[61] The synthesis of 2-(3-pyridyl)-piperidine was accomplished *via* this method in a 63% yield (see Scheme 1.12). Aside from this, there are four other reports of the α-arylation of *N*-Boc-piperidines with heteroaryl halides. Dieter and Li performed a palladium-catalysed cross-coupling using copper and antimony to install a thiophene ring.[62] Maruoka *et al.* performed a radical coupling of *N*-Boc-piperidine **8** to install a single heteroaromatic

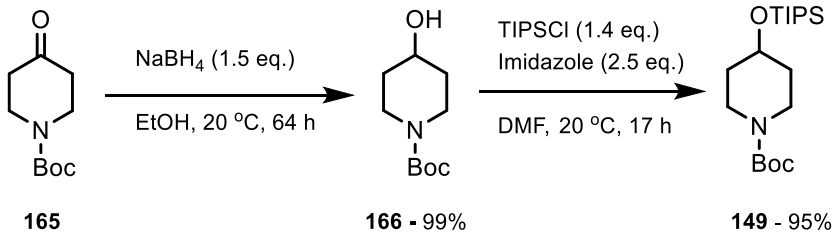
group.[63] Both Wang *et al.* and Kamijo and co-workers reported the use of photochemistry to install benzothiazole in the α position of *N*-Boc-piperidine **8** using iridium catalysts. Finally, Opatz, Lipp and Lahm reported a metal-free light-induced coupling of *N*-Boc-piperidine **8** with benzoxazole using sodium acetate and benzophenone.[64,65,21] As shown by these reports, there are limited examples of the α-arylation of *N*-Boc-piperidine **8** with heteroaryl halides and almost all only include a single example rather than an extensive scope. The coupling of heteroaromatics is of importance to medicinal chemists due to their ubiquitous nature in biologically-active compounds. Therefore, it would be beneficial for the scientific community for there to be methodology for the α-arylation of substituted *N*-Boc-piperidines that was widely applicable to heteroaryl halides and with a more substantial scope.

The enantioselective α-arylation of 4-substituted piperidines has not yet been investigated. Work by Beak *et al.* and Knochel and co-workers showed that α-lithiation-functionalisation and arylation both proceed with high diastereoselectivities.[28,24] O'Brien *et al.* and Coldham and co-workers have shown that 4-substituted *N*-Boc-piperidines can be α-functionalised with reasonable enantioselectivities (up to 92:8 er) using the Alexakis diamine (*S*,*S*)-**105** or (*R*,*R*)-**105**, although in only modest yield.[52,55] The asymmetric lithiation of substituted *N*-Boc-piperidines has only been conducted in Et_2O, although the asymmetric lithiation of *N*-Boc-pyrrolidine **5** has also been conducted in MTBE.[12] The asymmetric lithiation of piperidine **8** and 4-substituted piperidines in solvents other than Et_2O is essentially an unexplored field which shall be investigated prior to the exploration of the asymmetric α-arylation.

2.3 α-Arylation of 4-Substituted *N*-Boc-piperidines

2.3.1 Solvent Investigation for α-Lithiation-Functionalisation

4-OTIPS-*N*-Boc-piperidine **149** was chosen as the substrate to begin the investigations, due to it being one of the three 4-substituted *N*-Boc-piperidines investigated by Knochel *et al.*.[24] Piperidine **149** was synthesised in excellent yield from 1-Boc-4-piperidone **165** following a procedure from within the group.[66] Ketone reduction was carried out at room temperature using $NaBH_4$ for 64 hours to afford 4-hydroxy-*N*-Boc-piperidine **169** in 99% yield. Subsequent protection with TIPSCl in DMF afforded piperidine **149** in 95% yield (Scheme 2.40).



165 **166** - 99% **149** - 95%

Scheme 2.40

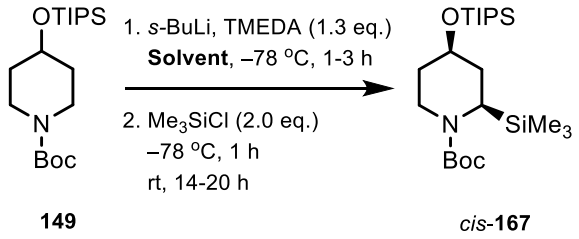
To achieve the first objective set out in section 2.2, an alternative solvent to Et_2O was required that would be compatible with both lithiation and the subsequent Negishi cross-coupling. As highlighted in section 2.1.3, the Negishi step typically requires elevated temperatures to achieve the successful cross-coupling of nitrogen-containing heteroaryl halides, hence the need to replace Et_2O as the solvent. Therefore, based on the temperature used in Knochel *et al.*'s work, solvents with boiling points greater than 55 °C were investigated.[24] The first step was to determine if these alternative solvents were compatible with α-lithiation-trapping using *s*-BuLi/TMEDA. Consequently, the lithiation-trapping of 4-OTIPS-*N*-Boc-piperidine **149** was conducted in MTBE, CPME, toluene, THF, 2-MeTHF and TMO as well as Et_2O for comparison; Me_3SiCl was used as an electrophile to provide easy comparison with existing published results.

Unpublished work from the O'Brien group has shown that the lithiation time of 4-OTIPS-*N*-Boc-piperidine **149** using *s*-BuLi/TMEDA is ~33 minutes in Et_2O at –78 °C.[66] This was determined through the use of React IR by monitoring the change in absorbance of the carbonyl stretching frequency in the Boc group. Uncomplexed piperidine **149** has a different frequency to that of the lithiated intermediate, allowing the reaction to be followed in real time by the decrease in intensity of one frequency and

the increase of the other. However, the exact time required for complete lithiation of piperidine **149** at –78 °C in other solvents is not known and would have required further React IR studies to determine. Unfortunately, the React IR equipment was not available at the time. Therefore, piperidine **149** was lithiated using *s*-BuLi/TMEDA at –78 °C for 1 hour in Et_2O, MTBE and CPME. As CPME and MTBE are ethereal solvents, it was assumed that they would behave similarly to Et_2O and thus it was presumed that the lithiation would be complete within 1 hour. The lithiation reactions conducted in toluene, THF, 2-MeTHF and TMO were all stirred for a conservative 3 hours at –78 °C to increase the chance of complete lithiation since there were no direct comparisons to existing reactions that could be made. After trapping with Me_3SiCl, the results shown in Table 2.5 were obtained.

Lithiation of 4-OTIPS-*N*-Boc-piperidine **149** was conducted in Et_2O with *s*-BuLi/TMEDA at –78 °C to afford α-silylpiperidine *cis*-**167** in 64% yield (entry 1). The reactions conducted in MTBE, THF and toluene also afforded good yields of α-silylpiperidine *cis*-**167** (74-77% entries 2, 4 and 9). These yields are comparable to those of α-aryl-4-substituted piperidines obtained by Knochel *et al.*, indicating that comparable levels of lithiation were accomplished.[24] It was noted that toluene from an Innovate Technology Inc. PS-MD-7 solvent dispenser afforded a higher yield than HPLC grade toluene freshly distilled over calcium hydride, potentially due to the unwanted introduction of oxygen during the distillation process. When the lithiation-functionalisation was conducted in toluene for 1 hour, α-silylpiperidine *cis*-**167** was obtained in a lower yield of 62% (entry 8), demonstrating the necessity for a longer lithiation time in toluene. Moderate yields of α-silylpiperidine *cis*-**167** were obtained in CPME (43%, entry 3) and TMO (57%, entry 6). The use of 2-MeTHF afforded no α-silylpiperidine *cis*-**167** (entry 5).

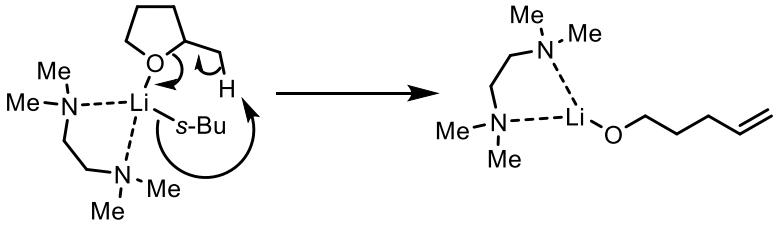
Table 2.5: Solvent effects on lithiation-functionalisation of 4-OTIPS-*N*-Boc-piperidine **149**, Me_3SiCl



Entry	Solvent	Time / h	Yield / %[a]
1	Et_2O	1	64
2	MTBE	1	74
3	CPME	1	43
4	THF	3	75
5	THF[b]	3	0
6	2-MeTHF	3	0
7	TMO	3	57
8	toluene	1	62
9	toluene	3	77

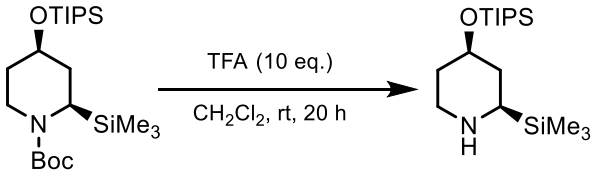
a) Yield after chromatography; b) Reaction carried out in the absence of TMEDA

A possible explanation for the lack of *cis*-**167** obtained from the reaction in 2-MeTHF is that the deprotonation of the 2-MeTHF methyl group could have occurred, consuming the *s*-BuLi before it could react with piperidine **149** (Scheme 2.41), as has previously been reported by the O'Brien group.[67] The extra steric hindrance around the oxygen in TMO may prevent coordination to *s*-BuLi and deprotonation of the methyl groups. The lithiation-trapping of piperidine **149** was attempted in THF without TMEDA based on previous findings in the O'Brien group on diamine-free lithiations using *s*-BuLi in THF.[43] However, none of the desired α-silylpiperidine *cis*-**167** was observed.



Scheme 2.41

The ^{1}H NMR spectrum of α-silylpiperidine *cis*-**167** was broad due to rotamers caused by the Boc group and it was not possible to determine the relative stereochemistry by *J* value analysis. Therefore, the exact diastereoselectivity of each reaction could not be obtained directly. As a result, the effect of the solvent on the diastereoselectivity was not investigated at this stage. However, the *cis*-stereochemistry of the sample of α-silyl piperidine *cis*-**167** obtained from the reaction in THF was assigned by Boc group removal. α-Silyl-*N*-Boc-piperidine *cis*-**167** was treated with TFA to afford α-silylpiperidine *cis*-**168** in 30% yield (Scheme 2.42). As anticipated, the ^{1}H NMR spectrum of α-silylpiperidine *cis*-**168** was well resolved and the splitting patterns were clearly defined. The dr of *cis*-**168**, and by extension *cis*-**167**, could therefore be determined from the ratio of the integrals of characteristic proton signals in the ^{1}H NMR of the crude reaction mixture.



cis-**167**

cis-**168**
30%, 97:3 dr

Scheme 2.42

The splitting patterns and *J* values of the protons in the 2- and 4-positions of α-silylpiperidine *cis*-**168** show that they both occupy axial positions (Figure 2.2). Proton H_B in the 4-position possesses two *J* values of 10.0 Hz and two of 4.5 Hz, these correspond to two $^{3}J_{ax\text{-}ax}$ interactions and two $^{3}J_{ax\text{-}eq}$ interactions respectively, indicating it occupies an axial position. Proton H_A in the 2-position possesses *J* values of 13.0 Hz and 2.0 Hz, which corresponds to a $^{3}J_{ax\text{-}ax}$ interaction and a $^{3}J_{ax\text{-}eq}$ interaction, showing that it is also axial. The axial proton H_C in the 3-position confirmed these assignments as it possesses the two corresponding $^{3}J_{ax\text{-}ax}$ coupling constants of 13.0 Hz and 10.0 Hz. Thus, the *cis*-stereochemistry of α-silylpiperidine *cis*-**168** could be assigned confidently and, by extension, the *cis*-stereochemistry of α-silyl-*N*-Boc-piperidine *cis*-**167**. On closer inspection, it was shown that α-silylpiperidine *cis*-**167** was obtained in a 97:3 dr as signals from the minor diastereomer, *trans*-**167**, could be seen in the ^{1}H NMR spectrum of the crude product.

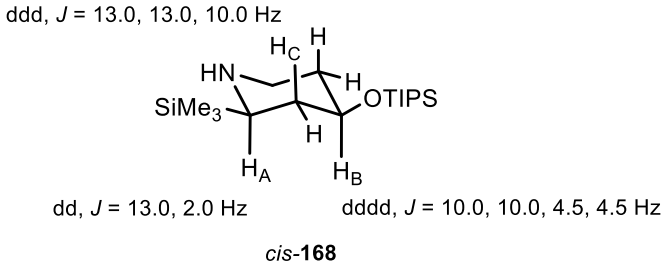
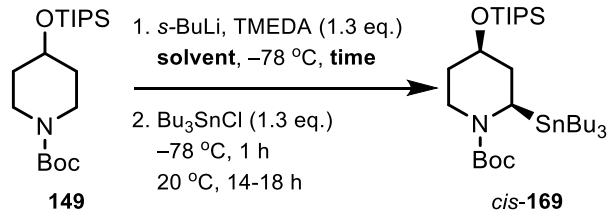


Figure 2.2: Conformational diagram of α-trimethylsilylpiperidine *cis*-**168**

Boc removal was also performed on α-silyl-*N*-Boc-piperidine *cis*-**167** obtained from the lithiation-functionalisation reaction conducted in toluene (Table 2.5, entry 9). This reaction afforded α-silylpiperidine *cis*-**168** in 29% yield and 97:3 dr, demonstrating that the reaction in toluene also gave the *cis* diastereomer as the major product and in excellent dr. These Boc removal reactions gave confidence that the lithiation-functionalisation in the other solvents would also be *cis*-selective.

Given the success that had been observed with the lithiation-functionalisation of piperidine **149** in toluene when trapping with Me_3SiCl, Et_2O and toluene were compared when trapping with Bu_3SnCl. Due to the results shown in Table 2.5, the lithiation in toluene was stirred at –78°C for 3 hours. α-Lithiation-functionalisation gave a 64% yield of α-stannylpiperidine *cis*-**169** in Et_2O and a 75% yield in toluene (Table 2.6). The diastereomeric ratio of these reactions could not be determined due to the broad peaks in the ^1H NMR spectrum of piperidine *cis*-**169**, which in turn was due to the nature of the stannyl group and rotamers caused by the Boc group.

Table 2.6: Solvent effects on lithiation-functionalisation of 4-OTIPS-*N*-Boc-piperidine **149**, Bu_3SnCl

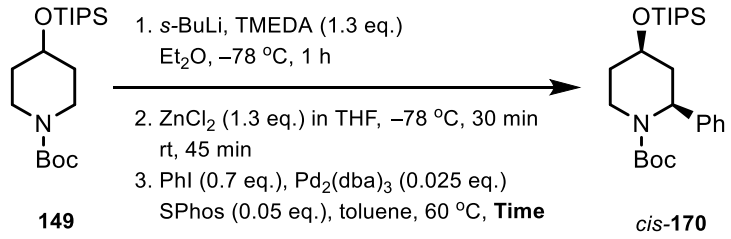


Entry	Solvent	Time / h	Yield / %[a]
1	Et_2O	1	64
2	toluene	3	75

a) Yield after chromatography

Prior to the investigation of the α-arylation procedure in alternative solvents, the solvent switch methodology reported by Baudoin *et al.* and Knochel and co-workers was attempted.[58,24] Two α-arylations of 4-OTIPS-*N*-Boc-piperidine **149** were performed to establish an understanding of both the cross-coupling step and the practicality issues with the existing solvent switch methodology. Transmetallation from the lithiated intermediate was achieved using a solution of freshly prepared flame-dried $ZnCl_2$ in THF. The Negishi step was conducted using $Pd_2(dba)_3$ (2.5 mol%) and SPhos (5 mol %) with iodobenzene. Based on the differing times of the cross-coupling step in the work of Baudoin *et al.* and Knochel and co-workers, two reactions were conducted in parallel, with the Negishi step being heated at 60 °C for 22 hours in one and 69 hours in the other. α-Phenylpiperidine **170** was obtained in comparable yield in both reactions, 50% from the reaction conducted for 69 hours (Table 2.7, entry 1) and 53% from that conducted for 22 hours (entry 2). α-Phenylpiperidine **170** was isolated as an inseparable mixture with the starting 4-OTIPS-*N*-Boc-piperidine **149** and, therefore, the yield was calculated from the ratio of **170** and **149** in the ^{1}H NMR spectrum of the product mixture after purification by chromatography.

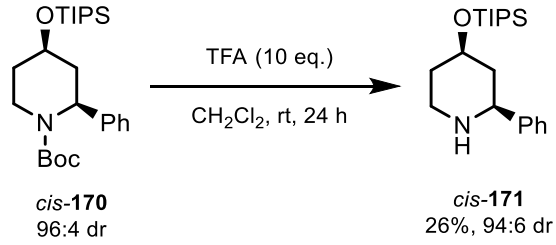
Table 2.7: α-Arylation of 4-OTIPS-*N*-Boc-piperidine **149** *via* solvent switch methodology



Entry	Time / h	Yield / %[a]	dr[b]
1	69	50	93:7
2	22	53	96:4

a) Product isolated as a mixture, yield determined from the ratio of **170** and **149** in the ^{1}H NMR spectrum after purification by chromatography; b) Ratio determined by ^{1}H NMR spectroscopy of the product mixture after chromatography

The dr of α-phenylpiperidine **170** was determined by the integration of the signal due to the benzylic NCH proton in the ^{1}H NMR spectrum. A detailed analysis of the ^{1}H spectrum and conformation of *cis*-α-aryl piperidines is presented in section 2.3.4. The dr was then confirmed by Boc removal from α-phenylpiperidine *cis*-**170** derived from the reaction conducted for 22 hours (Scheme 2.43). Stirring α-phenyl-*N*-Boc-piperidine *cis*-**170** with TFA for 24 hours afforded α-phenylpiperidine *cis*-**171** in 26% yield and 94:6 dr based on the ^{1}H NMR spectrum of the crude product.

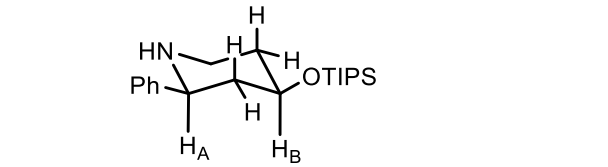


cis-**170**
96:4 dr

cis-**171**
26%, 94:6 dr

Scheme 2.43

Analysis of the splitting patterns in the ^{1}H NMR spectrum of α-phenylpiperidine **171** after purification by chromatography showed that the major product after Boc group removal was *cis*-**171** (Figure 2.3). Proton H_A at the 2-position had ^{3}J values of 11.5 and 2.5 Hz, corresponding to a $^{3}J_{ax\text{-}ax}$ interaction and a $^{3}J_{ax\text{-}eq}$ interaction respectively, showing that it was axial. Proton H_B at the 4-position had ^{3}J values of 10.5, 10.5, 4.5, and 4.5 Hz, corresponding to two $^{3}J_{ax\text{-}ax}$ interactions and two $^{3}J_{ax\text{-}eq}$ interactions, showing that it was also axial. This showed that the major product from the α-arylation reaction was *cis*-**170** as expected.



dd, *J* = 11.5, 2.5 Hz dddd, *J* = 10.5, 10.5, 4.5, 4.5 Hz

cis-**171**

Figure 2.3: Conformational diagram of 4-OTIPS-2-phenylpiperidine *cis*-**171**

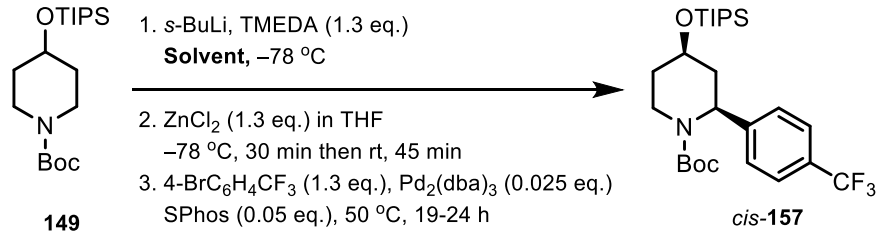
Boc removal also demonstrated that the peaks that had been observed in the ^{1}H NMR spectrum of α-phenyl-*N*-Boc-piperidine **170** were indeed due to the diastereomers and not caused by rotamers. Therefore, the diastereoselectivity of the Negishi cross-coupling reactions could be assigned by the integral ratios of the two benzylic NCH signals in the

^{1}H NMR spectrum of the product after chromatography. This method was applied to obtain the ratio of diastereomers of the α-arylation reactions in Table 2.7 and was also used for all subsequent α-arylation reactions. Thus, both of the α-arylation reactions in Table 2.7 proceeded with very high diastereoselectivities, in agreement with Knochel *et al.* (see Scheme 2.36).[24]

Using the information from the solvent screen, the α-arylation of 4-OTIPS-*N*-Boc-piperidine **149** was attempted using THF, MTBE and toluene since these solvents had shown good yields of α-silylpiperidine *cis*-**167**. It was desirable to use aryl bromides in the cross-coupling reaction due to their greater availability and lower cost compared to aryl iodides. Therefore, the conditions for the Negishi step from Baudoin *et. al*'s work were used since α-arylation of *N*-Boc-piperidine **149** with aryl bromides had been reported in that work.[58] As a result, the cross-coupling conditions selected used $Pd_2(dba)_3$ (0.025 equivalents) and SPhos (0.05 equivalents) and the reaction was heated to 50 °C. Based on the results shown in Table 2.8, a reaction time of 19-24 hours was selected, as comparable yields had been obtained when the Negishi step was heated for both 22 hours and 69 hours. Reactions were conducted with 4-bromobenzotrifluoride in excess (1.3 eq.) and also with the aryl halide as the limiting reagent (0.65 eq.). The results are presented in Table 2.8.

The α-arylation of *N*-Boc-piperidine **149** in MTBE gave a 24% yield of α-arylpiperidine *cis*-**157** in 93:7 dr (entry 1), compared to a 22% yield (99:1 dr) in THF (entry 2) and a 58% yield (91:9 dr) in toluene (entry 3). The reaction in toluene was repeated to afford α-arylpiperidine *cis*-**157** in 59% yield and 90:10 dr (entry 4), demonstrating the reproducibility of this result. The α-arylation was also carried out in toluene with the aryl bromide as the limiting reagent (0.65 eq.) and this gave α-arylpiperidine *cis*-**157** in 47% yield and 99:1 dr (entry 5), a yield that was ~10% lower than that achieved with excess aryl halide (entries 3 and 4). Unfortunately, α-arylpiperidine *cis*-**157** was isolated as an inseparable mixture with piperidine **149**. In addition, variable diastereoselectivities were observed in these reactions for reasons that are unclear.

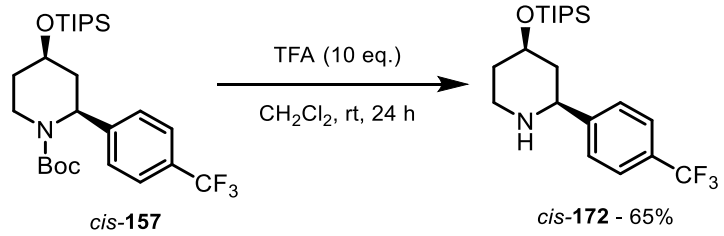
Table 2.8: α-Arylation of 4-OTIPS-*N*-Boc-piperidine **149** in different solvents



Entry	Solvent	Yield / %[a]	dr[b]
1	MTBE	24	93:7
2	THF	22	99:1
3	toluene	58	91:9
4	toluene	59	90:10
5	toluene	47[c]	99:1

a) Product isolated as a mixture, yield determined from the ratio of **157** and **149** in the ^{1}H NMR spectrum after purification by chromatography; b) Ratio determined by ^{1}H NMR spectroscopy of product after chromatography; c) 0.65 eq. of ArBr

To confirm that the major product was α-aryl-*N*-Boc-piperidine *cis*-**157**, Boc group removal was performed. The product from the first α-arylation reaction performed in toluene (Table 2.8, entry 3) was isolated in two separate fractions, one as a mixture of diastereomers along with piperidine **149** and the other as a single diastereomer mixed with piperidine **157**. Boc removal was performed with TFA on the mixture containing only the major diastereomer and piperidine **149** (Scheme 2.44). Analysis of the ^{1}H NMR spectrum showed that the major product was *cis*-**172** as expected. Due to literature precedent and the evidence from ^{1}H NMR spectroscopic analysis of piperidines *cis*-**168** and *cis*-**171** (see Figures 2.2 and 2.3), observation of the same pattern of signals due to benzylic NCH protons in the ^{1}H NMR spectra of other α-aryl piperidines led to the assumption of *cis*-stereochemistry.[24] The integration ratio between the peaks was used to assign the dr of other α-aryl piperidines.

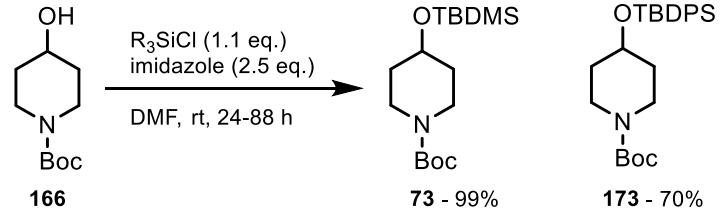


Scheme 2.44

The results shown in Tables 2.5 and 2.8 demonstrated the applicability of toluene as a solvent for both the α-lithiation-functionalisation and the α-arylation of 4-OTIPS-*N*-Boc-piperidine **149**. Therefore, toluene was used as the lithiation solvent in all future investigations.

2.3.2 Initial Studies of the α-Arylation of 4-Substituted *N*-Boc-piperidines

It had not been possible to isolate pure samples of α-aryl-4-OTIPS-*N*-Boc-piperidines due to separation issues during chromatography. To solve this problem, alternative silyl protecting groups were explored. 4-OTBDPS-*N*-Boc-piperidine **173** and 4-OTBDMS-*N*-Boc-piperidine **73** were synthesised in good yields following the procedure used to synthesise 4-OTIPS-*N*-Boc-piperidine **149** (Scheme 2.45).

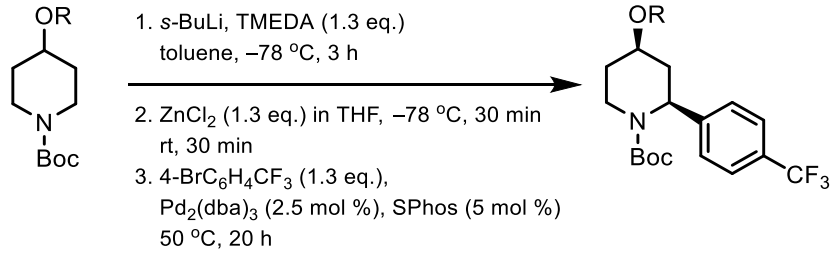


Scheme: 2.45

The α-lithiation-transmetallation cross-couplings of 4-OTBDMS-piperidine **73** and 4-OTBDPS-piperidine **173** were carried out in toluene. The lithiation was conducted using *s*-BuLi/TMEDA at –78 °C for 3 hours. 1.3 Equivalents of 4-bromobenzotrifluoride, $Pd_2(dba)_3$ (0.025 equivalents) and SPhos (0.05 equivalents) were used during the cross-coupling step, which was heated to 50 °C for 20 hours. The results are shown in Table 2.9, with those using 4-OTIPS-piperidine **149** included in entry 1. A moderate yield (51%, 96:4 dr) of α-aryl-piperidine *cis*-**174** was achieved for the α-arylation of 4-OTBDPS-piperidine **173** (entry 2). α-Arylation of 4-OTBDMS-

piperidine **73** gave a high yield (80%) of pure α-arylpiperidine *cis*-**175** in excellent dr (98:2) (entry 3). The α-arylation of 4-OTBDMS-piperidine **73** was also carried out with a commercial solution of $ZnCl_2$ in THF, which afforded α-arylpiperidine *cis*-**175** in 79% yield and 98:2 dr (entry 4). The comparable yield achieved with a commercial solution of $ZnCl_2$ demonstrated its viability as an alternative to freshly prepared flame-dried $ZnCl_2$. Fresh $Pd_2(dba)_3$ was prepared and recrystallised from $CHCl_3$ following a procedure published by Ishii *et al.*, and α-arylation performed with this palladium source.[68] Recrystallised $Pd_2(dba)_3$ did not afford any improvement over commercial $Pd_2(dba)_3$; α-arylpiperidine *cis*-**175** was obtained in 72% yield using recrystallised $Pd_2(dba)_3$ (entry 5). Therefore, for practicality and greater consistency, commercial $Pd_2(dba)_3$ was used in the subsequent reactions.

Table 2.9: α-Arylation of 4-Osilyl-*N*-Boc-piperidines in toluene



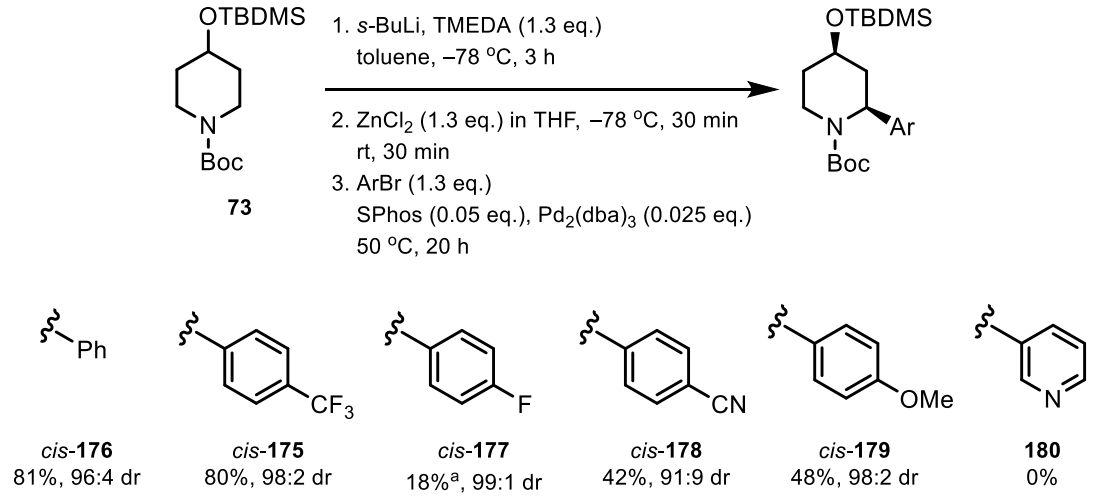
Entry	R	Yield / %[a]	dr[b]	Product
1	TIPS	58[c], 59[c]	91:9, 90:10	*cis*-**157**
2	TBDPS	51	96:4	*cis*-**174**
3	TBDMS	80	98:2	*cis*-**175**
4	TBDMS	79[d]	98:2	*cis*-**175**
5	TBDMS	72[e]	98:2	*cis*-**175**

a) Yield after chromatography; b) Ratio determined by ^{1}H NMR spectroscopy of product after chromatography; c) Ratio determined by ^{1}H NMR spectroscopy of the product mixture after chromatography; d) Commercial 0.7 M solution of $ZnCl_2$ in THF used; e) Freshly prepared and recrystallised $Pd_2(dba)_3$ used

Pleasingly, both α-arylpiperidine *cis*-**174** and α-arylpiperidine *cis*-**175** could be separated from the respective 4-Osilyl piperidine starting materials. Due to being a gum, 4-OTBDPS-piperidine **173** was harder to work with than 4-OTBDMS-piperidine **73**,

which is an oil. For this reason, and the fact that a higher yield was achieved with 4-OTBDMS-piperidine **73**, 4-OTBDMS-piperidine **73** was selected as the substrate for further investigation. We currently have no explanation for the improvement observed in diastereoselectivity in toluene on moving from 4-OTIPS-piperidine **149** to 4-OTBDMS-piperidine **73**.

The α-arylation of 4-OTBDMS-piperidine **73** was explored with other aryl halides (Scheme 2.46). The same cross-coupling conditions were used as in Table 2.9 (with 1.3 equivalents of the aryl halide) except that the organozinc reagent was prepared from flame-dried $ZnCl_2$ due to the reactions being conducted at the same time as those in Table 2.9. Cross-coupling with bromobenzene afforded α-phenylpiperidine *cis*-**176** in excellent yield (81%) and dr (96:4). α-Arylation with 4-fluorobromobenzene gave α-arylpiperidine *cis*-**177** in only 18% yield. The use of electron-deficient 4-bromobenzonitrile gave α-arylpiperidine *cis*-**178** in 42% yield and 91:9 dr, whereas electron-rich 4-bromoanisole gave a 48% yield of α-arylpiperidine *cis*-**179** in 98:2 dr. Disappointingly, these results did show substantial reductions in yield between bromobenzene and 4-substituted aryl bromides. Unfortunately, the cross-coupling of 3-bromopyridine gave none of the desired α-arylpiperidine *cis*-**180**.



cis-**176**	*cis*-**175**	*cis*-**177**	*cis*-**178**	*cis*-**179**	**180**
81%, 96:4 dr	80%, 98:2 dr	18%[a], 99:1 dr	42%, 91:9 dr	48%, 98:2 dr	0%

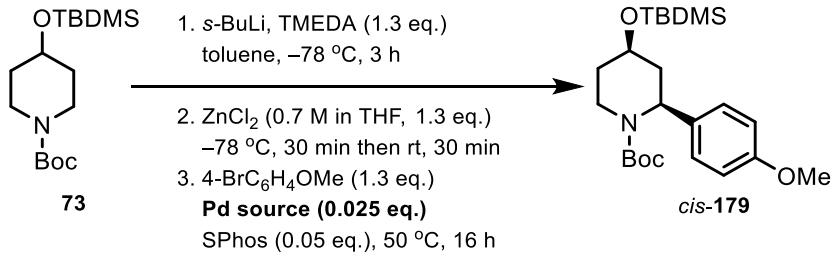
a) Product isolated as a mixture, yield determined from the ratio of **177** and **73** in the ^{1}H NMR spectrum after purification by chromatography

Scheme: 2.46

2.3.3 Optimisation of the Negishi Cross-Coupling Step

The results in Scheme 2.46 highlighted the need for further optimisation, particularly to enable the cross-coupling of nitrogen-containing heteroaryl halides such as 3-bromopyridine. To begin the optimisation process, the effect of the palladium source was explored. The research groups of Campos, Coldham and Gawley used $Pd(OAc)_2$ whereas those of Knochel and Baudoin used a Pd-dba complex (formulated as $Pd(dba)_2$ or $Pd_2(dba)_3$).[12,13,57,58,24] Therefore, the α-arylation of 4-OTBDMS-*N*-Boc-piperidine **73** was performed using $Pd_2(dba)_3$, $Pd(OAc)_2$ and $[Pd(allyl)Cl]_2$ and cross-coupling with 4-bromoanisole, which was chosen due to the ease of separation of the resulting α-arylpiperidine *cis*-**179** from 4-OTBDMS-piperidine **73** (Table 2.10). Performing the Negishi step with $Pd_2(dba)_3$ gave a 48% yield of α-arylpiperidine *cis*-**179** (entry 1) compared to a 5% yield with $Pd(OAc)_2$ (entry 2) and a 54% yield with $[Pd(allyl)Cl]_2$ (entry 3). The results of these reactions showed a preference for the use of $[Pd(allyl)Cl]_2$, which was used in subsequent investigations.

Table 2.10: Investigation into the effects of palladium source on α-arylation

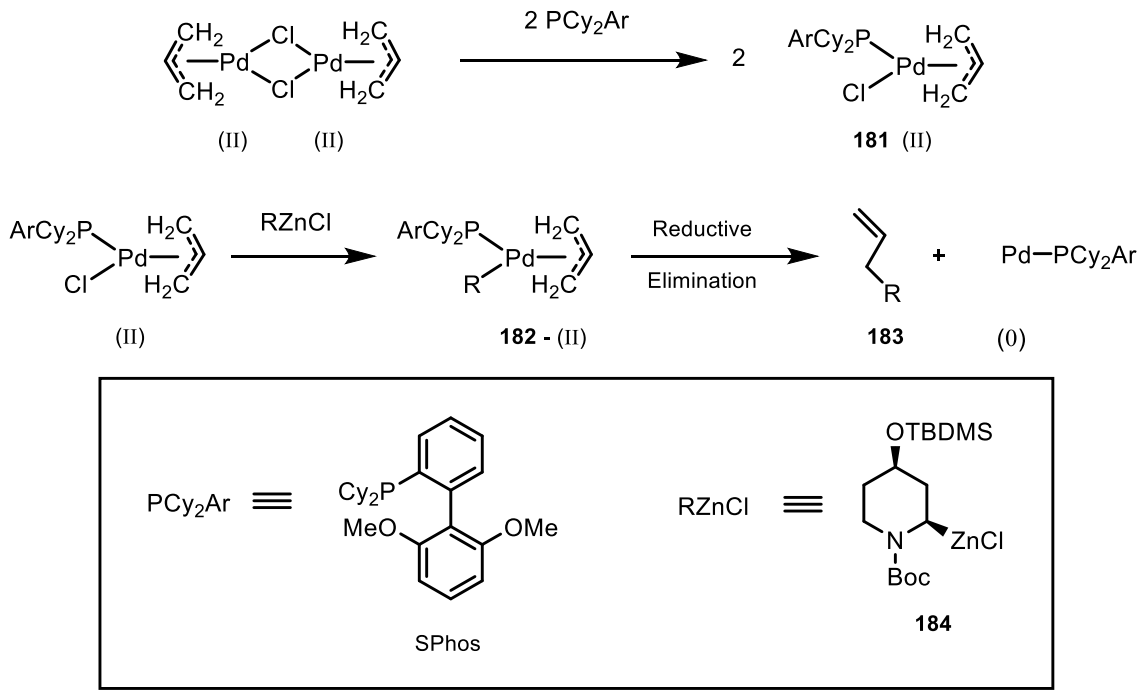


Entry	Pd Source	Yield / %[a]	dr[b]
1	$Pd_2(dba)_3$	48	99:1
2	$Pd(OAc)_2$	5	99:1
3	$[Pd(allyl)Cl]_2$	54	96:4

a) Yield after chromatography; b) Ratio determined by ^1H NMR spectroscopy of product after chromatography

It is important to consider the catalytic cycle and the mode of activation of the catalyst. $Pd_2(dba)_3$ exists as a Pd(0) species and can thus directly enter the catalytic cycle, undergoing ligand exchange and subsequent oxidative addition. Both $Pd(OAc)_2$ and

$[Pd(allyl)Cl]_2$ exist as Pd(II) species and first require reduction to Pd(0). Organ *et al.* report the development of a PEPPSI-*i*Pr precatalyst for Negishi cross-coupling in which the mode of activation is the loss of a sacrificial ligand followed by transmetallation with two equivalents of the organozinc reagent.[69] This is then followed by reductive elimination to afford the homocoupled product of the organozinc reagent and a Pd(0) species. A similar mode of activation is proposed for the α-arylation of piperidine **73** with $[Pd(allyl)Cl]_2$ (Scheme 2.47).

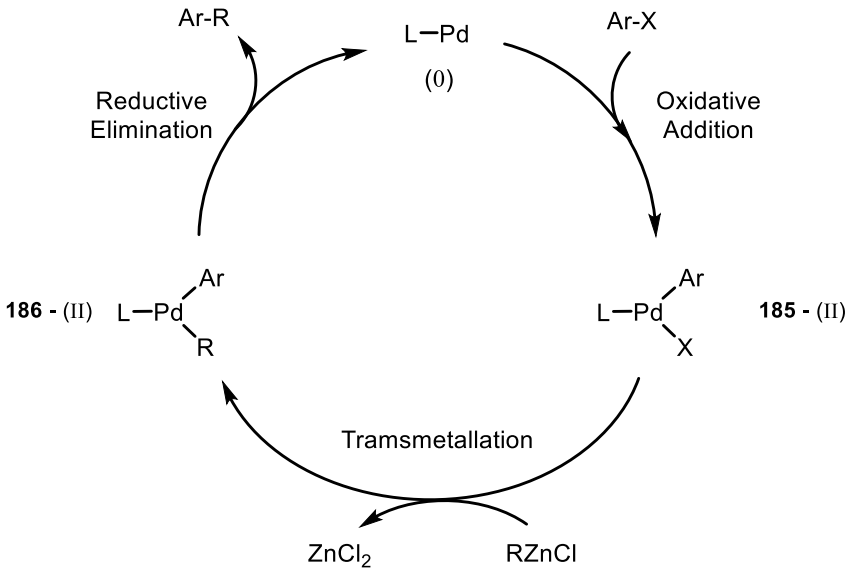


Scheme: 2.47

In the reaction set-up, SPhos, $[Pd(allyl)Cl]_2$ and the aryl halide are stirred in toluene at rt under Ar for 10 minutes. Therefore, the first step will likely be the addition of SPhos to the catalyst to generate allylpalladium(II) precatalyst **181**. An analogous precatalyst generation was performed by Colacot *et al.* in THF to generate Pd(allyl)(SPhos)Cl, which was subsequently isolated.[70] In the piperidine α-arylation procedure, precatalyst **181** was presumed to have been formed *in situ*. The solution of precatalyst **181** and aryl halide in toluene was then added to the solution containing the organozinc reagent. Based on the report of Organ and co-workers, it is presumed that transmetallation with one equivalent of organozinc intermediate **184** occurs to generate palladium intermediate **182**. This palladium intermediate can then undergo reductive elimination to afford the catalytically active Pd(0) species with SPhos bound and α-allylated

piperidine **183** as a by-product. This proposal is supported by the work of Nolan *et al.* where the reductive elimination of a *t*-butyl alkoxide and an allyl substituent ligated to palladium is proposed as the mechanism for reduction of Pd(II) to Pd(0).[71] This process consumes one equivalent of organozinc intermediate **184** for every equivalent of palladium. In the α-arylation procedure, 0.025 equivalents of $[Pd(allyl)Cl]_2$ is used, equating to 0.05 equivalents of palladium. Thus, the maximum yield of α-aryl piperidine could be as low as 95%, as 5% of the organozinc intermediate will have been consumed to generate the catalytically active Pd(0) species.

Once ligated Pd(0) has been generated, it can enter the catalytic cycle, first undergoing oxidative addition to generate palladium(II) intermediate **185** (Scheme 2.48). Transmetallation then occurs with the organozinc reagent to generate palladium(II) intermediate **186**, releasing $ZnCl_2$. Finally, reductive elimination affords the desired α-aryl piperidine and regenerates the palladium(0) catalyst.



Scheme: 2.48

Having determined the utility of $[Pd(allyl)Cl]_2$, the cross-coupling of 4-OTBDMS-*N*-Boc-piperidine **73** with 3-bromopyridine was targeted and an investigation conducted to identify a suitable catalytic system (Table 2.11). A wide range of ligands were tested (Figure 2.4), predominantly focusing on the Buchwald dialkylbiaryl phosphine "Phos" ligands, as the groups of Campos, Baudoin and Knochel had found success with the α-arylation of *N*-Boc heterocycles with RuPhos and SPhos in particular, but also with

QPhos and DavePhos.[12,58,24] In 1998, Buchwald and co-workers reported the use of the first dialkylbiarylphosphine ligand, DavePhos, for the amination and Suzuki-Miyaura cross-coupling (SMCC) of aryl chlorides.[72] Further Phos ligands were subsequently developed by Buchwald and co-workers, notably SPhos for SMCC reactions,[73] RuPhos for challenging biaryl Negishi cross-coupling reactions and CPhos in 2009.[74,75] Buchwald *et al.* identified CPhos as the best ligand for the cross-coupling of sp^3 hybridised isopropylzincbromide with aryl halides and proposed that it was a good ligand for forming sp^2-sp^3 C-C bonds *via* Negishi cross-coupling.

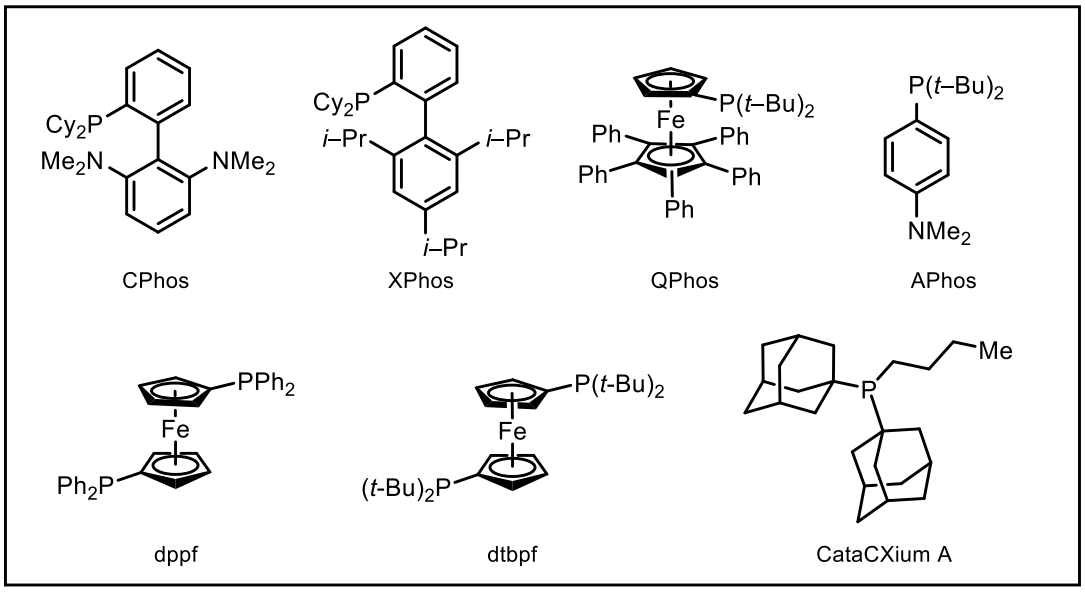
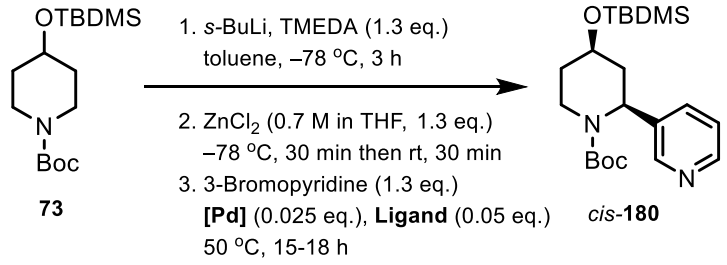


Figure 2.4: Ligands for Pd catalysed cross-coupling reactions

The organozinc intermediate **184** generated from piperidine **73** was cross-coupled with 3-bromopyridine using $[Pd(allyl)Cl]_2$ (2.5 mol%) and a ligand (5 mol%) in toluene at 50 °C. The only catalyst systems to afford isolable product were those using either RuPhos (entry 1) or CPhos (entry 2). The reaction with RuPhos afforded α-arylpiperidine *cis*-**180** in a higher yield (29%), albeit with a slightly lower dr (93:7), compared to that achieved when CPhos was used (18%, 98:2 dr). Surprisingly, with SPhos, only a trace amount of α-arylpiperidine *cis*-**180** was observed (entry 3). Trace product was observed by HRMS when the Buchwald Phos ligands XPhos (entry 4) and DavePhos (entry 5) were used as well as when $Pd(dppf)_2Cl_2$ was used (entry 10). Cross-coupling was also conducted with CPhos and $Pd_2(dba)_3$ to give a 7% yield of α-arylpiperidine *cis*-**180** as a single diastereomer (entry 14). This result further highlighted the improvement in yield

achieved on changing the palladium source from $Pd_2(dba)_3$ to $[Pd(allyl)Cl]_2$. In all the other reactions, no α-arylpiperidine *cis*-**180** was detected and only 4-OTBDMS-piperidine **73** starting material was observed in the ^1H NMR spectrum of the crude reaction mixture.

Table 2.11: Palladium source and ligand screen for α-arylation of 4-OTBDMS-*N*-Boc-piperidine **73** with 3-bromopyridine

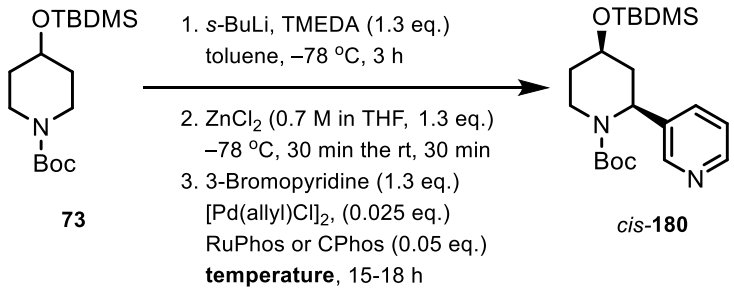


Entry	Pd Source	Ligand	Yield / %[a]	dr[b]
1	$[Pd(allyl)Cl]_2$	RuPhos	29	93:7
2	$[Pd(allyl)Cl]_2$	CPhos	18	98:2
3	$[Pd(allyl)Cl]_2$	SPhos	trace	-
4	$[Pd(allyl)Cl]_2$	XPhos	trace	-
5	$[Pd(allyl)Cl]_2$	DavePhos	trace	-
6	$[Pd(allyl)Cl]_2$	QPhos	-	-
7	$[Pd(allyl)Cl]_2$	cataCXium A	-	-
8	$[Pd(allyl)Cl]_2$	PCy_3	-	-
9	$Pd(PPh_3)_2Cl_2$	PPh_3	-	-
10	$Pd(dppf)Cl_2$	dppf	trace	-
11	$Pd(dtbpf)Cl_2$	dtbpf	-	-
12	$Pd(AmPhos)Cl_2$	APhos	-	-
13	$Pd_2(dba)_3$	SPhos	-	-
14	$Pd_2(dba)_3$	CPhos	7	100:0

a) Yield after chromatography; b) Ratio determined by ^1H NMR spectroscopy of product after chromatography

Having identified RuPhos and CPhos as promising ligands, the cross-coupling step was attempted at higher temperatures. The benefit of conducting the reaction in toluene was that the Negishi cross-coupling step could be heated up to 100 °C. The groups of Campos, Coldham, Gawley and Baudoin all found that the cross-coupling of heteroaryl halides required higher temperatures than the rest of the substrates in their respective scope studies to afford α-aryl piperidines in good yield, demonstrating the importance of temperature in the cross-coupling step.[12,13,57,58] The effect of temperature on the α-arylation of 4-OTBDMS-*N*-Boc-piperidine **73** is shown in Table 2.12. The cross-coupling step was performed with 3-bromopyridine, RuPhos or CPhos (5 mol%) and $[Pd(allyl)Cl]_2$ (2.5 mol%) in toluene. The use of CPhos afforded α-arylpiperidine *cis*-**180** in increasing yield associated with an increase in temperature, up to 42% at 100 °C (entries 2, 3 and 5). Similarly, with RuPhos, when the temperature was increased from 50 °C (entry 1) to 100 °C (entry 4), the yield of α-arylpiperidine *cis*-**180** increased from 29% to 54%.

Table 2.12: α-arylation of 4-OTBDMS-*N*-Boc-piperidine **73** at elevated temperatures

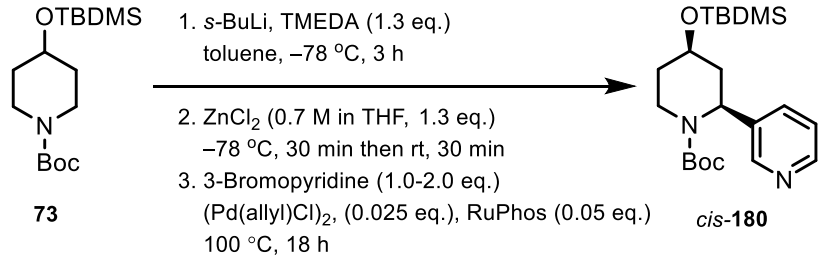


Entry	Temperature / °C	Ligand	Yield / %[a]	dr[b]
1	50	RuPhos	29	93:7
2	50	CPhos	18	98:2
3	80	CPhos	38	96:4
4	100	RuPhos	54	95:5
5	100	CPhos	42	95:5

a) Yield after chromatography; b) Ratio determined by ^{1}H NMR spectroscopy of product after chromatography

The best set of cross-coupling conditions thus far used $[Pd(allyl)Cl]_2$ and RuPhos heated at 100 °C. Next, the effect of the equivalents of aryl halide was investigated and the α-arylation was conducted with 1.0, 1.3, 1.5 and 2.0 equivalents of 3-bromopyridine (Table 2.13). The reaction set-up was improved by increasing the size of the round-bottomed flask and replacing the oil bath with a metal heating block to improve heat transfer from the heat source to the reaction mixture. With the changed set-up, the result previously obtained with 1.3 equivalents of 3-bromopyridine (54%) was improved and α-arylpiperidine *cis*-**180** was obtained in 62% yield. Given this success, this set-up was used for all subsequent reactions. When 1.0 equivalent of 3-bromopyridine was used, arylpiperidine *cis*-**180** was obtained in a lower yield (52%) (entry 1). In contrast, increasing the equivalents to 1.5 afforded α-arylpiperidine *cis*-**180** in 69% yield (entry 3). Further increasing the equivalents to 2.0 gave a 48% yield (entry 4).

Table 2.13: α-arylation of 4-OTBDMS-*N*-Boc-piperidine **73** with varied equivalents of 3-bromopyridine



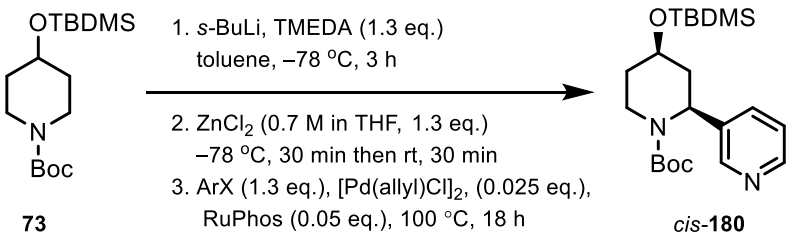
Entry	Equivalents	Yield / %[a]	dr[b]
1	1.0	52	97:3
2	1.3	62	96:4
3	1.5	69	96:4
4	2.0	48	95:5

a) Yield after chromatography; b) Ratio determined by ^{1}H NMR spectroscopy of product after chromatography

To examine the effect of changing the halide, the cross-coupling of 4-OTBDMS-*N*-Boc-piperidine **73** was carried out with 3-chloro-, 3-bromo- and 3-iodopyridine using 1.3 equivalents of aryl halide (Table 2.14). Cross-coupling with 3-chloropyridine afforded

α-arylpiperidine *cis*-**180** in 67% yield (entry 1) whereas the use of 3-iodopyridine only accomplished a 40% yield (entry 3). The yield with 3-chloropyridine was therefore higher than that achieved with 3-bromopyridine (62%), although lower than the result with 1.5 equivalents of 3-bromopyridine (69%, see Table 2.13, entry 3).

Table 2.14: α-arylation of 4-OTBDMS-*N*-Boc-piperidine **73** with 3-halopyridines



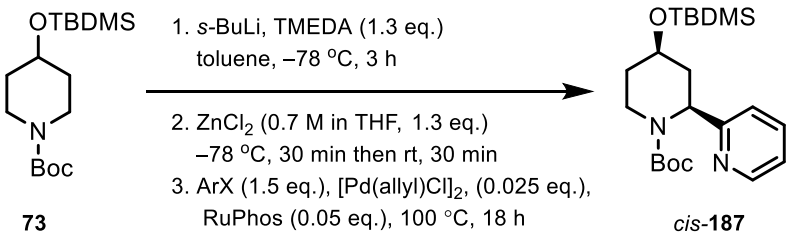
73 *cis*-**180**

Entry	X	Yield / %[a]	dr[b]
1	Cl	67	97:3
2	Br	62	96:4
3	I	40	97:3

a) Yield after chromatography; b) Ratio determined by ^{1}H NMR spectroscopy of product after chromatography

Due to the high yield of α-arylpiperidine *cis*-**180** achieved with 3-chloropyridine, an investigation was carried out with 2-halopyridine to provide another point of comparison. In light of the results shown in Table 2.14, these reactions were conducted with 1.5 equivalents of aryl halide (Table 2.15). α-Arylation of 4-OTBDMS-*N*-Boc-piperidine **73** with 2-bromopyridine afforded α-arylpiperidine *cis*-**187** in 26% yield and 99:1 dr (entry 2). Use of 2-chloropyridine gave a 23% yield of α-arylpiperidine *cis*-**187** (entry 1) whereas 2-iodopyridine gave a 19% yield (entry 3). Reassuringly, the results accomplished with the aryl bromide and the aryl chloride were comparable. Unfortunately, the yields of cross-coupled α-arylpiperidine *cis*-**187** obtained with 2-halopyridines were substantially lower than those with 3-halopyridines. Gawley and Beng reported comparable yields when using 2-bromopyridine and 3-bromopyridine in related cross-couplings,[57] although Tran and Zhong *et al.* reported only 10% yield when cross-coupling piperidine **8** with 2-bromopyridine.[60]

Table 2.15: α-arylation of 4-OTBDMS-*N*-Boc-piperidine **73** with 2-halopyridine

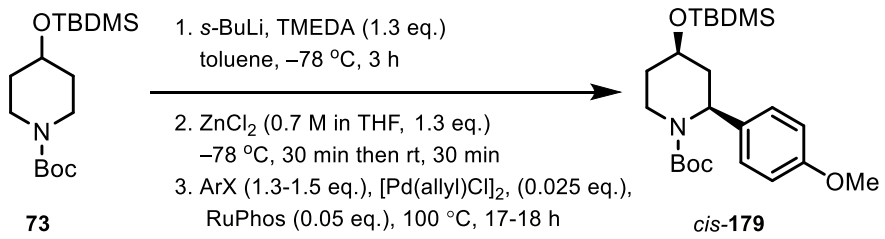


Entry	X	Yield / %[a]	dr[b]
1	Cl	23	>99:1
2	Br	26	99:1
3	I	19	97:3

a) Yield after chromatography; b) Ratio determined by ^{1}H NMR spectroscopy of product after chromatography

One final investigation was made into the effect on the cross-coupling of the choice of aryl halide (Table 2.16). When the α-arylation was performed with 4-bromoanisole using RuPhos and $[Pd(allyl)Cl]_2$, heating the reaction at 100 °C, a 72% yield of α-aryl piperidine *cis*-**179** was obtained (entry 1). This represented an improvement over the previous conditions using SPhos at 50 °C with $Pd_2(dba)_3$, where a 48% yield had been accomplished (see Scheme 2.46). By comparison, the cross-coupling of 4-chloroanisole gave a 62% yield of α-aryl piperidine *cis*-**179** (entry 2), lower than that with 4-bromoanisole although still high yielding. This further demonstrated the tolerance of the cross-coupling conditions for both aryl bromides and aryl chlorides. The α-arylation procedure was also carried out using 1.5 equivalents of 4-bromoanisole, which gave α-arylpiperidine *cis*-**179** in 78% yield and 96:4 dr (entry 3), highlighting a marginal improvement over the reaction conducted with 1.3 equivalents.

Table 2.16: α-arylation of 4-OTBDMS-*N*-Boc-piperidine **73** with 4-haloanisole



Entry	X	Equivalents	Yield / %[a]	dr[b]
1	Br	1.3	72	97:3
2	Cl	1.3	62	97:3
3	Br	1.5	78	96:4

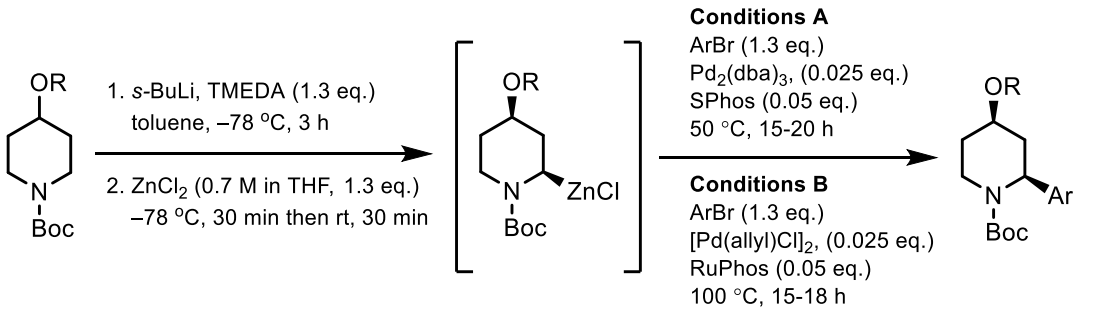
a) Yield after chromatography; b) Ratio determined by ^{1}H NMR spectroscopy of product after chromatography

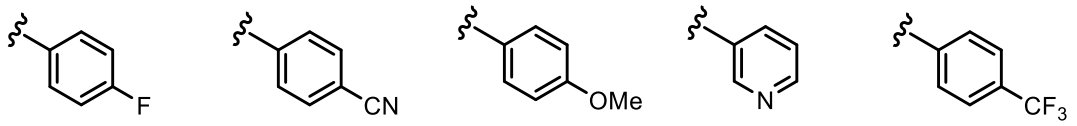
The results achieved with aryl chlorides and aryl bromides were comparable, although aryl bromides were selected for the investigation of the scope of the α-arylation procedure due to the marginally higher yields observed with them. Although lower yields were accomplished with aryl iodides, this was of less concern due to the greater commercial availability of aryl bromides and chlorides.

Based on our studies, the optimised Negishi cross-coupling conditions were: 1.5 equivalents of aryl bromide, 0.05 equivalents of RuPhos, 0.025 equivalents of $[Pd(allyl)Cl]_2$ (i.e. 0.05 equivalents of Pd) in toluene at 100 °C for 18 hours. The initial lithiation step was conducted in toluene using 1.3 equivalents of *s*-BuLi/TMEDA and stirred at –78 °C for 3 hours which was followed by transmetallation with 1.3 equivalents of a commercial solution of 0.7 M $ZnCl_2$ in THF.

Using these conditions, the scope of the α-arylation of 4-OTBDMS-*N*-Boc-piperidine **73** was investigated. First, the α-arylation reactions previously reported in Scheme 2.46 (Conditions A) were carried out under the optimised conditions (Conditions B) (Scheme 2.49). Reactions with 4-bromofluorobenzene, 4-bromobenzonitrile and 4-bromoanisole afforded α-arylpiperidines *cis*-**177**, *cis*-**178** and *cis*-**179** in good yields (61-78%). In each case, an improvement in yield was observed; the improvement for the reaction with 4-bromofluorobenzene was particularly pronounced, increasing from 18% to 65% yield.

The α-arylation of 4-OTBDPS-*N*-Boc-piperidine **173** with 4-bromobenzotrifluoride was also revisited and an increase in the yield of α-aryl piperidine *cis*-**174** from 51% to 67% was observed. This result highlighted the advantage of the TBDMS protecting group over TBDPS, as the result from this reaction was still lower than that achieved with TBDMS. The dr values obtained with the two sets of conditions remained broadly the same with the only noticeable difference being the change from 91:9 dr to 98:2 dr with 4-bromobenzonitrile. In conclusion, the optimised cross-coupling conditions afforded higher yields with a range of aryl bromides as well as 3-bromopyridine.





cis-**177**[a]	*cis*-**178**[a]	*cis*-**179**[a]	*cis*-**180**[a]	*cis*-**174**[b]
Conditions A	**Conditions A**	**Conditions A**	**Conditions A**	**Conditions A**
18%[c], 99:1 dr	50%, 91:9 dr	48%, 98:2 dr	0%	51%, 96:4 dr
Conditions B	**Conditions B**	**Conditions B**	**Conditions B**	**Conditions B**
65%, 96:4 dr	61%, 98:2 dr	78%[d], 96:4 dr	69%[d], 96:4 dr	67%, 98:2 dr

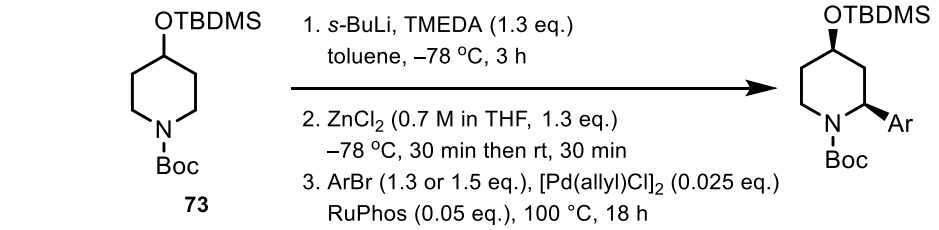
a) OTBDMS; b) OTBDPS; c) Product isolated as a mixture, yield determined from the ratio of **177** and **83** in the ^{1}H NMR spectrum after purification by chromatography; d) 1.5 equivalents of ArBr

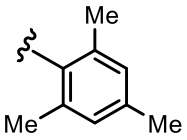
Scheme: 2.49

The optimised α-arylation procedure was then applied to a broader range of aryl bromides and heteroaryl bromides and a full scope was investigated (Scheme 2.50). Some of these reactions were conducted with 1.3 equivalents of aryl bromide due to being run at the same time as earlier reactions. Pleasingly, the coupling with sterically hindered 2-bromomesitylene afforded α-arylpiperidine *cis*-**188** in 32% yield and 98:2 dr. Although this yield is lower than other results, the aryl bromide possess two *ortho* groups giving it substantial steric hindrance and making it a challenging substrate to

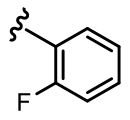
cross-couple. The cross-coupling of 3-fluoro-2-bromotoluene afforded only a trace amount of the desired α-arylpiperidine (detected by HRMS). As the cross-coupling reaction had been shown to tolerate high degrees of steric hindrance, it is proposed that the failure of this reaction was not solely due to steric effects. Support for this proposal came from the low yield obtained with 2-fluorobromobenzene (27% yield of α-aryl piperidine *cis*-**189**) compared to the significantly higher yield obtained with 4-fluorobromobenzene (65% yield of α-arylpiperidine *cis*-**177**). Likewise, there was a significant drop in yield when comparing 3-bromopyridine (69% yield of α-arylpiperidine *cis*-**180**) with 2-fluoro-3-bromopyridine (26% yield of α-arylpiperidine *cis*-**193**). Collectively, these results suggested the existence of a detrimental electronic effect when a fluorine atom was in the *ortho* position, which was not present when it was in the *para* position. Steric hindrance is evidently still important as the attempted cross-coupling of 1,2-dibromobenzene afforded only a trace amount of product, although this is perhaps not surprising due to the large size of the bromine atom.

Good yields and excellent diastereoselectivities were accomplished with a range of nitrogen-containing heteroaryl bromides. For example, the cross-coupling of 5-bromo-2-(trifluoromethyl)pyridine afforded α-arylpiperidine *cis*-**191** in 66% yield and 99:1 dr and 5-bromo-2-methoxypyrimidine gave α-arylpiperidine *cis*-**195** in 52% yield and 97:3 dr. The cross-coupling of 5-bromo-2-chloropyridine gave α-arylpiperidine *cis*-**192** selectively. No traces of the 2-pyridyl regioisomer were observed by HRMS, indicating that the bromine had reacted selectively over the chlorine. The reaction with 5-bromo-7-azaindole gave a much lower yield (13% of α-arylpiperidine *cis*-**198**) compared to that from the cross-coupling of other nitrogen-containing aryl halides. In all cases, excellent diastereoselectivity was observed (≥94:6 dr). However, no product was observed when cross-coupling reactions were attempted with 4-bromoacetanilide, 4-bromopyridin-2-ol, 2-bromopyrazine, 3-bromopyridine *N*-oxide and 4-bromopyrazole. The failure of 4-bromopyrazole to cross-couple was not surprising due to its nature as a challenging coupling partner.[76]

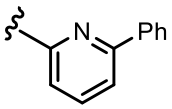




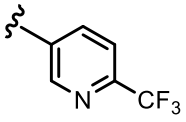
cis-**188**
32%[a], dr 98:2



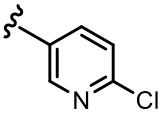
cis-**189**
27%, dr 96:4



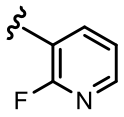
cis-**190**
60%, dr 94:6



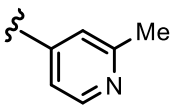
cis-**191**
66%, dr 99:1



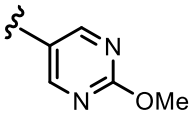
cis-**192**
43%, dr 98:2



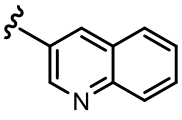
cis-**193**
26%[a], dr >99:1



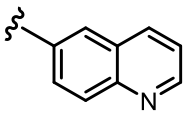
cis-**194**
67%, dr 97:3



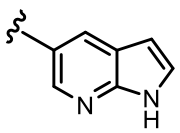
cis-**195**
52%[a], dr 97:3



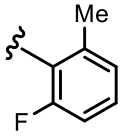
cis-**196**
66%, dr 98:2



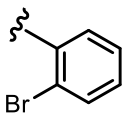
cis-**197**
67%[a], dr 96:4



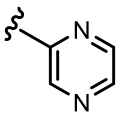
cis-**198**
13%[a], dr 96:4



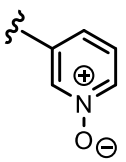
cis-**199**
trace



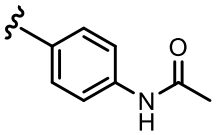
cis-**200**
trace



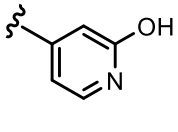
cis-**201**
-



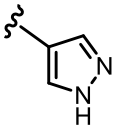
cis-**202**
-



cis-**203**
-[a]



cis-**204**
-[a]



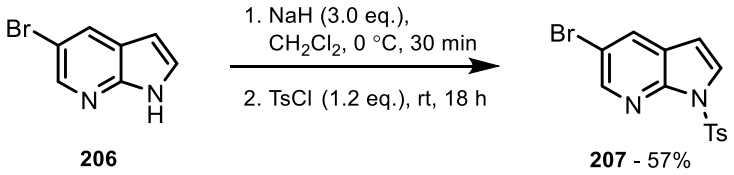
cis-**205**
-[a]

a) 1.3 equivalents of ArBr

Scheme: 2.50

Three of the unsuccessful cross-coupling reactions used aryl bromides that contained an acidic proton, either NH or OH, and the aryl bromide that gave the lowest yield (13%) in the scope was 5-bromoazaindole. To investigate whether the acidic proton was the cause of the problem, the cross-couplings of protected variants of these aryl bromides were conducted. First, 5-bromo-*N*-tosyl-7-azaindole **207** was prepared using an adapted

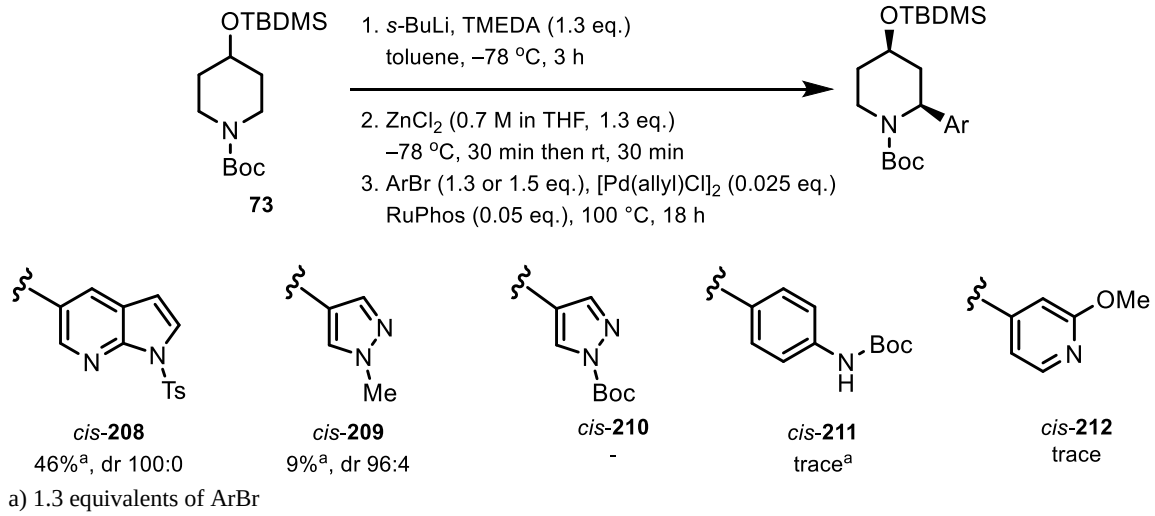
literature procedure from **206** in 57% yield using sodium hydride and then reaction with tosylchloride (Scheme 2.51).[77]



206 **207** - 57%

Scheme 2.51

The α-arylation of 4-OTBDMS-piperidine **73** was then performed using tosyl protected bromoazaindole **207** and other commercially available substrates including methyl and Boc protected 4-bromopyrazole (Scheme 2.52). Cross-coupling with tosyl-protected bromoazaindole afforded α-arylpiperidine *cis*-**208** in 46% yield, a significant improvement over the 13% yield obtained with the unprotected azaindole. The use of methyl protected pyrazole gave α-arylpiperidine *cis*-**209** in 9% yield and 96:4 dr, whereas the use of Boc protected pyrazole did not afford any α-arylated piperidine. Whilst disappointing, these reactions demonstrated that pyrazoles are still challenging cross-coupling partners in this procedure. When the α-arylation procedure was conducted with *N*-Boc-4-bromoaniline only a trace amount of product was observed by ^{1}H NMR spectroscopy and HRMS. This potentially suggested that the aniline required double protection to be a viable substrate in the cross-coupling reaction. Finally, 4-bromo-2-methoxypyridine was tested; surprisingly, only a trace amount of the desired product was observed, despite the previously successful cross-coupling of 2-methoxy-5-bromopyrimidine. Overall, these results broadly supported the theory that acidic protons interfered with the cross-coupling reaction and whilst a substantial improvement in yield was not observed with 4-bromopyrazoles, a useful increase was seen with tosyl protected azaindole **207**.



cis-**208**
46%[a], dr 100:0

cis-**209**
9%[a], dr 96:4

cis-**210**
-

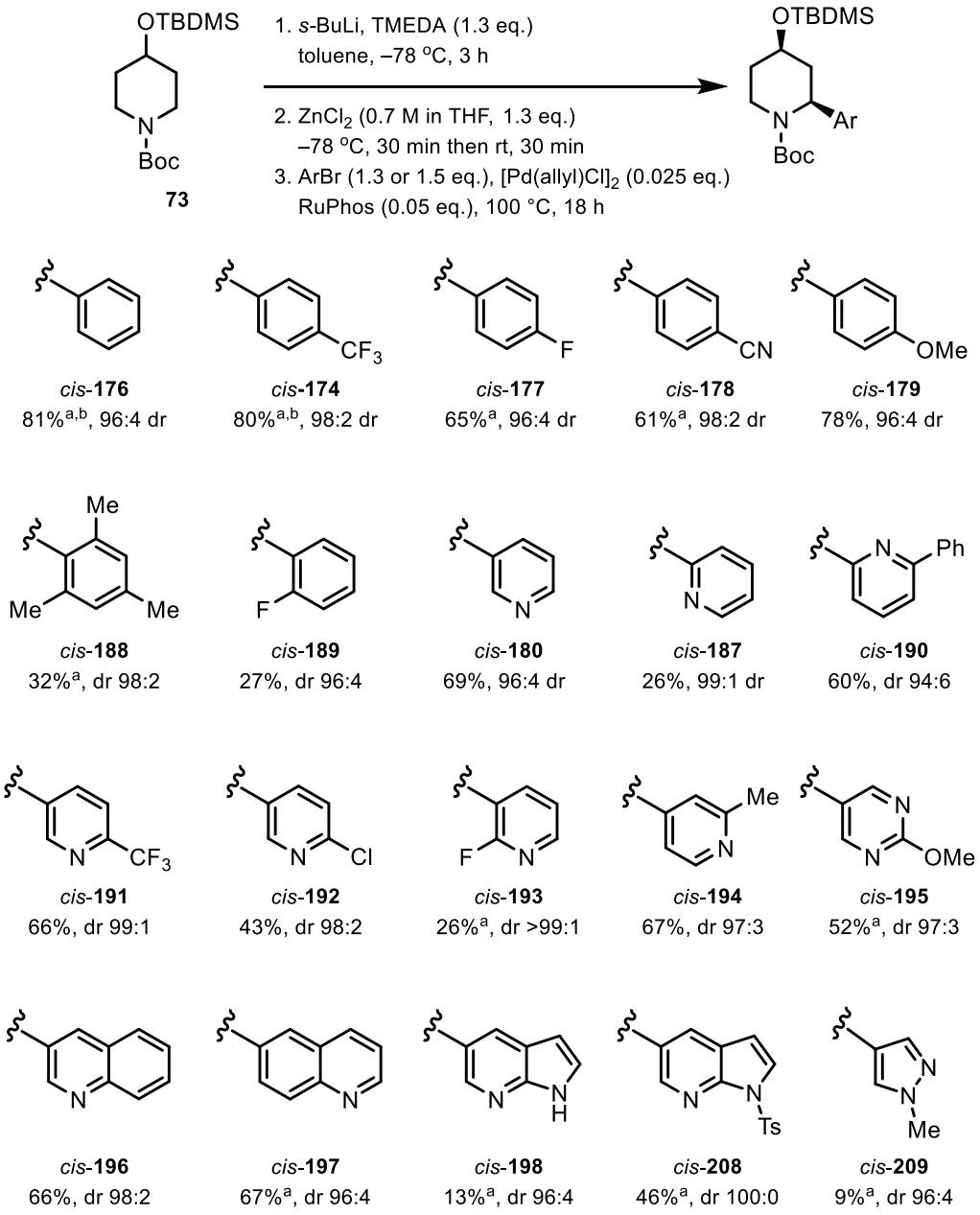
cis-**211**
trace[a]

cis-**212**
trace

a) 1.3 equivalents of ArBr

Scheme: 2.52

The full scope of the successful examples of the α-arylation of 4-OTBDMS-*N*-Boc-piperidine **73** is shown in Scheme 2.53. In each case, the highest yield achieved is reported along with the associated dr of the reaction. These results show that the α-arylation procedure can be applied to a wide range of aryl halides. The reaction tolerates electron-deficient aryl halides (*cis*-**174** and *cis*-**178**), electron-rich aryl halides (*cis*-**179**), sterically hindered aryl halides (*cis*-**188**) and a wide range of heteroaryl halides.



a) 1.3 equivalents of ArBr; b) 2.5 mol% $Pd_2(dba)_3$, 5.0 mol% SPhos, 50 °C

Scheme: 2.53

2.3.4 Conformation of 2,4-Disubstituted *N*-Boc-piperidines

In order to definitively prove the *cis*-stereochemistry of the α-aryl piperidines, an X-ray crystal structure of α-aryl 4-OTBDMS-piperidine *cis*-**175** was obtained which confirmed the expected *cis*-stereochemistry (Figure 2.5). However, interestingly, both the aryl group and OTBDMS group occupied axial positions in the solid-state.

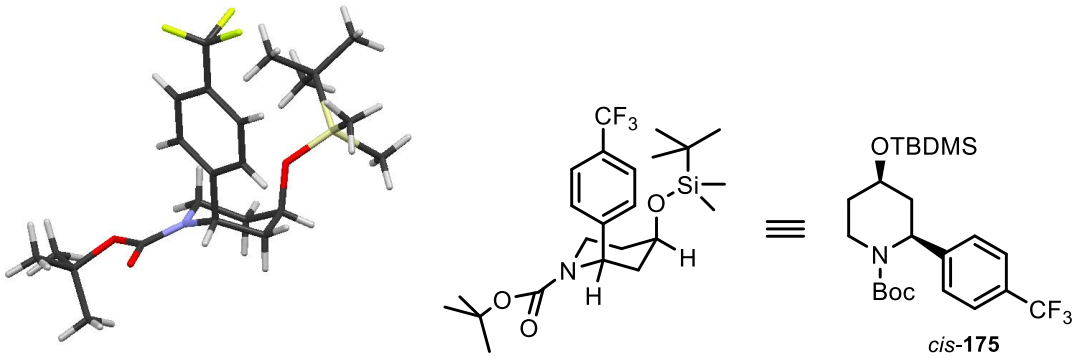


Figure 2.5: X-ray crystal structure of 4-OTBDMS-2-(4-(trifluoromethyl)phenyl)-*N*-Boc-piperidine **175**

To determine whether a similar diaxial conformation was observed in solution, ^{1}H NMR spectroscopy was used. In the ^{1}H NMR spectrum of piperidine *cis*-**175**, the benzylic NCH proton has *J* values of 7.5 Hz and 2.5 Hz which corresponds to a $^{3}J_{ax\text{-}eq}$ coupling to proton H_B and a $^{3}J_{eq\text{-}eq}$ coupling to proton H_C respectively (Figure 2.6). If the benzylic NCH proton had been axial, as was observed for the unprotected α-phenyl-4-OTIPS-piperidine *cis*-**171** (see Figure 2.3), then a larger $^{3}J_{ax\text{-}ax}$ coupling constant would have been expected. Proton H_B possesses a large ^{2}J coupling to H_C, the 7.5 Hz coupling to H_A and a coupling constant to proton H_D of only 3.0 Hz. This 3.0 Hz coupling can be assigned to a $^{3}J_{ax\text{-}eq}$ coupling as a $^{3}J_{ax\text{-}ax}$ coupling would be expected to be larger. In conclusion, the *J* value analysis demonstrated that both the aromatic group and the OTBDMS group are axial in solution and that the diaxial conformation in the X-ray crystal structure was not just a product of crystal packing.

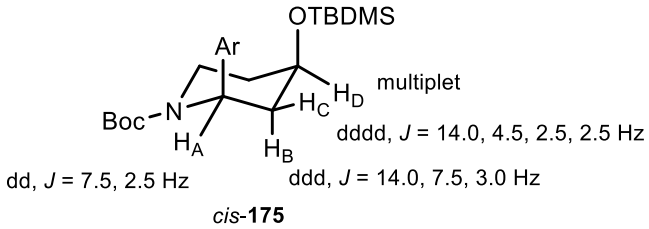


Figure 2.6: *J* value assignments of 4-OTBDMS-2-(4-(trifluoromethyl)phenyl)-*N*-Boc-piperidine *cis*-**175**

It is expected that, in unsubstituted α-aryl piperidine, the aryl group would occupy an axial position to avoid a steric clash with the Boc group (see Scheme 2.5).[28] However, the presence of the 4-OTBDMS group in α-aryl-4-OTBDMS-piperidine *cis*-**175** meant

that there would be a competing 1,3-diaxial interaction. The added steric strain could be predicted to make the diequatorial conformation lower in energy, or to make a boat or twist-boat conformation preferential. One potential explanation for α-aryl-4-OTBDMS-piperidine *cis*-**173** adopting the observed diaxial conformation is that there may be interactions between one of the lone pairs on the OTBDMS oxygen and the LUMO of the aromatic π-system. Such an interaction would stabilise the system and therefore make a diaxial conformation more favourable and accessible. Similar interactions have been reported by Sankararamakrishnan *et al.* between oxygen lone pairs in water atoms and the LUMO of aromatic rings in proteins.[78] Gamez, Reedijk and Mooibroek have examined X-ray crystal structures of compounds in the Cambridge Structure Database and concluded that these π-lone pair interactions are relatively common.[79]

As has been shown in Figure 2.3 with α-phenyl-4-OTIPS-piperidine **171**, when there is no Boc group present, the aromatic group and Osilyl group adopt a diequatorial conformation. It can therefore be concluded that the steric clash between the Boc group and the aromatic ring is more significant than any potential interaction between the oxygen lone pair and the LUMO of the aromatic π-system.

Three other X-ray crystal structures of α-aryl-4-OTBDMS-*N*-Boc-piperidines were obtained (Figures 2.7, 2.8 and 2.9). In all cases, the aryl group and OTBDMS group were *cis* and adopted a diaxial conformation. The same splitting patterns were observed in the ^{1}H NMR spectra for all of these compounds, as well as the rest of the α-aryl piperidines shown in Scheme 2.53, with only one exception.

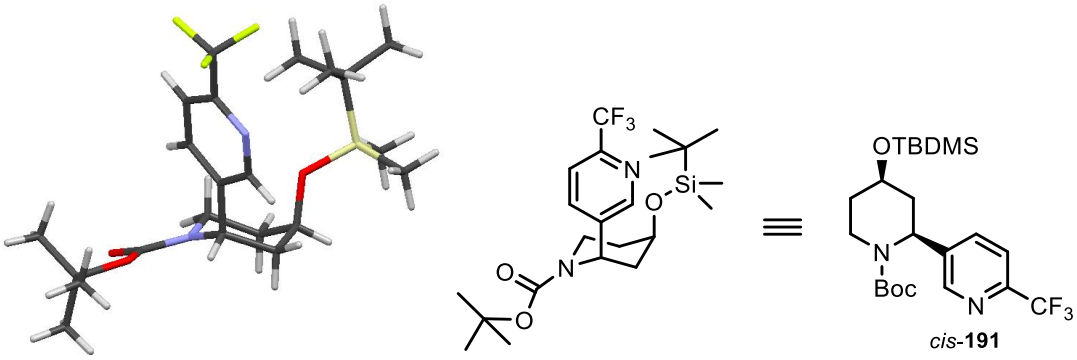


Figure 2.7: X-ray crystal structure crystal of 4-OTBDMS-2-[6-(trifluoromethyl)-3-pyridyl-*N*-Boc-piperidine **191**

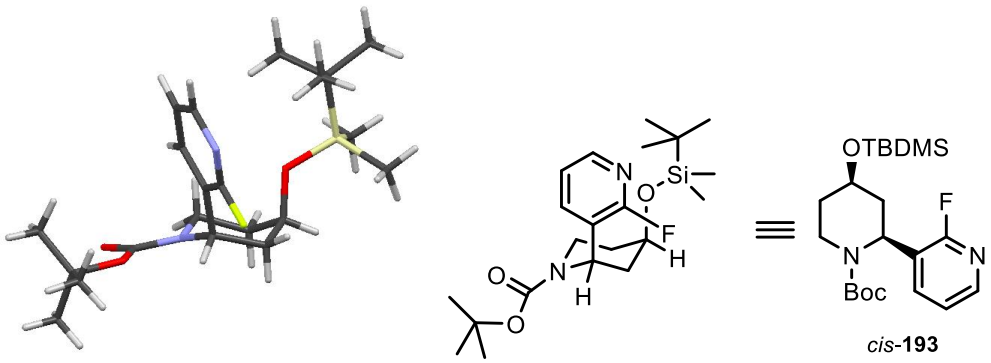


Figure 2.8: X-ray crystal structure crystal of 4-OTBDMS-2-(2-fluoro-3-pyridyl)-*N*-Boc-piperidine **193**

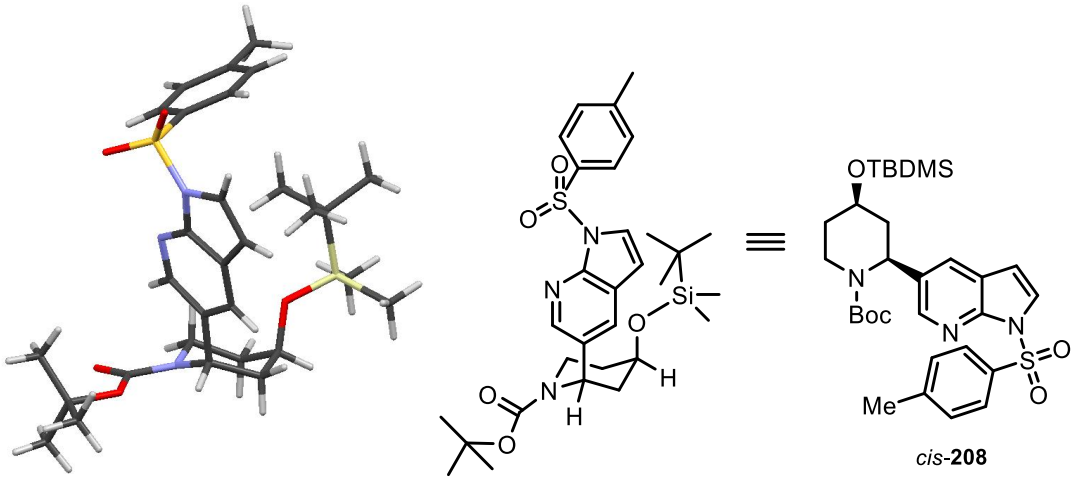


Figure 2.9: X-ray crystal structure of 4-OTBDMS-2-[1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-5-yl]-*N*-Boc-piperidine **208**

The only exception to the pattern of diaxial conformations was in the case of α-arylpiperidine *cis*-**188** which adopted a diequatorial conformation as shown by ^{1}H NMR spectroscopy. Presumably, the greater steric bulk imparted by the *ortho* methyl groups increased the energy penalty of the aryl group adopting an axial position and therefore forced it to adopt an equatorial conformation. Analysis of the *J* values of the protons in the 2- and 4-positions of α-arylpiperidine *cis*-**188** show that they both occupy axial or pseudo-axial positions (Figure 2.10). Proton H_A possesses *J* values of 13.5 and 4.5 Hz which correspond to a $^{3}J_{ax\text{-}ax}$ and a $^{3}J_{ax\text{-}eq}$ coupling. Proton H_B possesses *J* values of 10.5, 7.0, 5.5 and 5.5 Hz which could correspond to two $^{3}J_{ax\text{-}ax}$ couplings and two $^{3}J_{ax\text{-}eq}$ couplings. However, it is also possible that the piperidine ring adopts a twist boat conformation, which could explain the difference between the two $^{3}J_{ax\text{-}ax}$ couplings, as it would be expected that they would be similar if the molecule adopted a chair

conformation. Although it cannot be confirmed which conformation is adopted, it is clear that, in either case, the aryl and OTBDMS groups are equatorial or pseudo-equatorial.

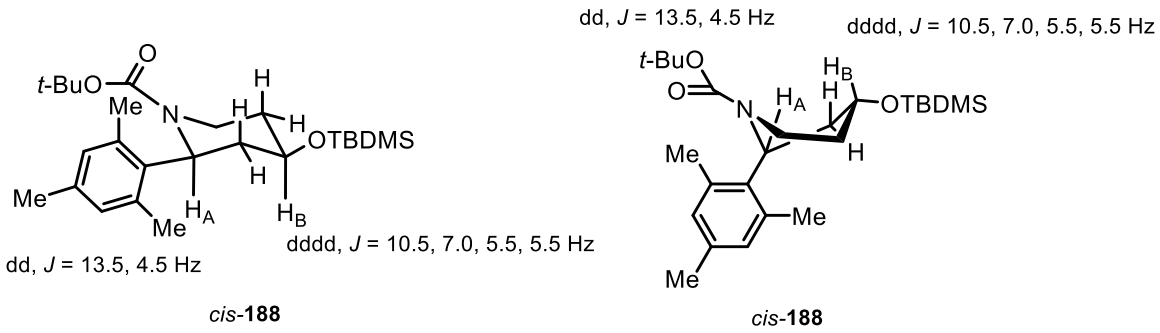


Figure 2.10: Potential conformational diagram of 4-OTBDMS-α-arylpiperidine *cis*-**188**

Knochel *et al.* reported two X-ray crystal structures obtained from the α-arylation of 4-substituted piperidines: α-aryl-4-phenylpiperidine *cis*-**148** which adopts a diequatorial conformation (Figure 2.11) and α-aryl-4-methylpiperidine *cis*-**147** which adopts a twist boat conformation with both substituents equatorial (Figure 2.12).[24] The twist-boat is a higher energy conformer relative to a chair, although it does allow both the 2-and 4-substituents to sit in pseudo-equatorial positions and avoid 1,3-diaxial interactions. The conformations of these compounds are different to the conformation adopted by all but one of the α-aryl-4-OTBDMS-piperidines. The compounds reported by Knochel and co-workers lack an oxygen atom in the 4-position, removing the possibility of a stabilising oxygen lone pair to aromatic LUMO interaction. Presumably, the steric repulsion of the 1,3-diaxial interaction has a larger effect than the α-aryl Boc interaction, resulting in the compounds adopting diequatorial conformations. The steric bulk of the group in the 4-position could also be affecting the conformation. Whilst the OTBDMS group is larger than a methyl or a phenyl group, the atom directly attached to the piperidine ring is oxygen which allows the large steric bulk of the silyl group to point away from the ring. Conversely, the methyl group in 4-methylpiperidine *cis*-**147** will have the largest steric bulk in the immediate vicinity of the piperidine ring, which would result in greater 1,3-diaxial interactions with the aromatic group if both groups were axial. The same would be true of the phenyl group, although to a slightly lesser extent due to the ability of the phenyl group to rotate and sit perpendicular to the ring. This could also explain the difference in conformations between 4-phenylpiperidine *cis*-**148** and 4-methylpiperidine *cis*-**147**.

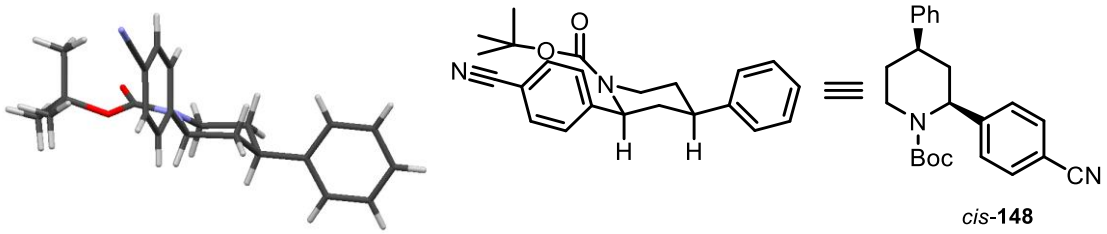


Figure 2.2 X-ray crystal structure of 2-(4-cyanophenyl)-4-phenyl-*N*-Boc-piperidine **148**

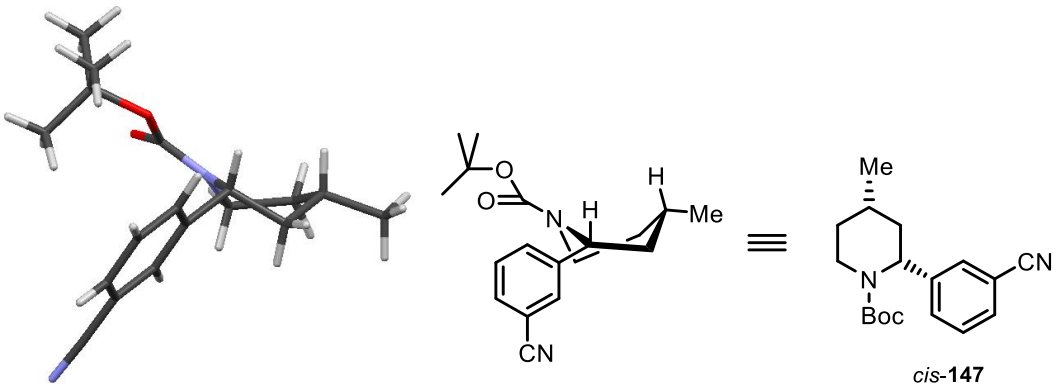


Figure 2.3 X-ray crystal structure of 2-(4-cyanophenyl)-4-methyl-*N*-Boc-piperidine **147**

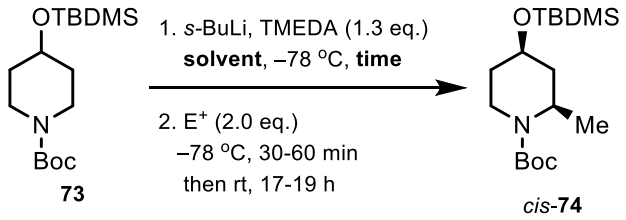
In conclusion, this overview of our results, together with those reported by Knochel *et al.*, indicates that the nature of the group in the 4-position directs the conformation adopted by α-aryl-4-substituted piperidines.[24] The α-aryl-4-OTBDMS piperidines synthesised in our work almost exclusively adopt a diaxial conformation with the lone exception of the highly sterically hindered mesitylene derived α-aryl-piperidine *cis*-**188**. The diaxial conformation could be made favourable by interaction from an oxygen lone pair and the LUMO of the aromatic π-system, the steric nature of the group in the 4-position, the presence of *ortho* groups on the α-aromatic ring or more likely a combination of all three effects.

2.4 α-Lithiation-Functionalisation of 4-Substituted-*N*-Boc-piperidines

2.4.1 Racemic α-Lithiation-Trapping of 4-Substituted-*N*-Boc-piperidines

As part of the development of the lithiation-transmetallation-Negishi cross-coupling of 4-substituted *N*-Boc-piperidines, the direct lithiation-trapping of 4-OTIPS-*N*-Boc-piperidine **149** in toluene had been investigated, trapping with Me_3SiCl (see Table 2.5). To broaden the scope of the lithiation-trapping in toluene, a wider range of electrophiles was briefly studied. Lithiation of 4-OTBDMS-*N*-Boc-piperidine **73** was conducted in toluene at –78 °C with *s*-BuLi/TMEDA and stirred for 3 hours. Then, 2 equivalents of the electrophile were added and the reaction was stirred for 30-60 minutes at –78 °C before being warmed to rt. Lithiation-trapping with methyliodide afforded α-methyl-4-OTBDMS-piperidine **74** in moderate yield (45%) and good dr (93:7) (Table 2.17, entry 1). The use of dimethylsulfate in Et_2O gave α-methyl-4-OTBDMS-piperidine **74** in good yield (66%) but low dr (83:17) (entry 2), whilst in toluene a high yield (72%) and good dr (92:8) were achieved (entry 3).

Table 2.17: α-Lithiation-functionalisation of 4-OTBDMS-*N*-Boc-piperidine **73**



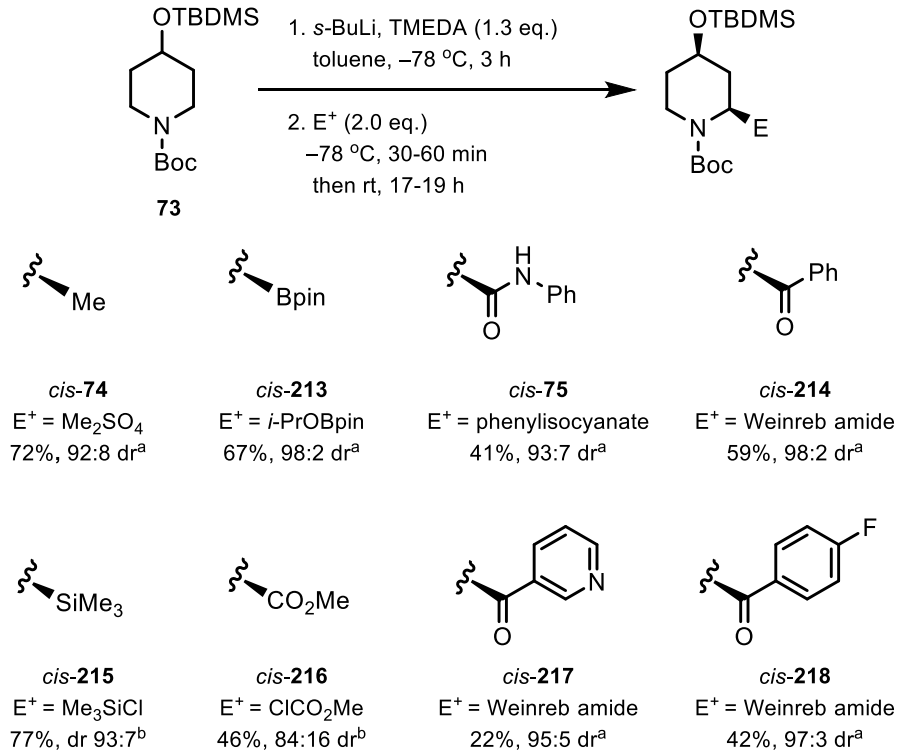
Entry	Solvent	Time / h	Electrophile	Yield[a] / %	dr[b]
1	toluene	3	MeI	45	93:7
2	Et_2O	1	Me_2SO_4	66	83:17
3	toluene	3	Me_2SO_4	72	92:8

a) Yield after chromatography; b) Ratio determined by ^{1}H NMR spectroscopy of product after chromatography

This demonstrated the competency of toluene as a solvent for the lithiation-trapping of piperidine **73**, affording α-methyl-4-OTBDMS-piperidine **74** in high yield and dr. In all cases, the dr was lower than that achieved in the α-arylation procedure, this could be due to the slow trapping of the lithiated piperidine by MeI and dimethylsulfate at low temperatures. Upon warming the solution during trapping, the trapping event can occur

at a temperature where the lithiated piperidine is configurationally unstable. A similar effect, albeit on er, has been observed by O'Brien, Campos, Coldham and co-workers in the trapping of enantioenriched lithiated *N*-Boc-piperidine (see Scheme 2.23).[46]

The α-lithiation-functionalisation of 4-OTBDMS-*N*-Boc-piperidine **73** in toluene was explored with other electrophiles, particularly those that possessed UV chromophores, which would be required for investigations into asymmetric lithiation and subsequent analysis by CSP-HPLC (Scheme 2.54). The use of *i*-PrOBpin afforded α-Bpin-piperidine *cis*-**213** in 67% yield and 98:2 dr. The trapping of piperidine **73** with phenylisocyanate gave α-functionalised piperidine *cis*-**75** in 41% yield and 93:7 dr. The use of 3-pyridyl Weinreb amide gave α-functionalised piperidine *cis*-**214** in only 17% yield but 99:1 dr. However, trapping with 4-fluorophenyl Weinreb amide gave α-functionalised piperidine *cis*-**218** in 42% yield and 97:3 dr. Lithiation-trapping with Me_3SiCl gave α-silylpiperidine *cis*-**215** in 73% and 93:7 dr. In this case, the dr was determined by Boc removal (using TFA) to afford the free amine, which sharpened the peaks in the ^1H NMR spectrum and enabled analysis. The yield of α-silylpiperidine *cis*-**215** was comparable to that achieved in the analogous reaction on 4-OTIPS-piperidine **149**, which gave a 77% yield of α-silylpiperidine *cis*-**167** (see Table 2.5). Trapping with methylchloroformate gave α-functionalised piperidine *cis*-**216** in 39% yield and 86:14 dr (determined by Boc removal). The dr was lower than those achieved with other electrophiles, which was assumed to be due to epimerisation. Low levels of *cis*-selectivity had been observed by Cossy and Belotti during the lithiation-trapping of 4-methyl-*N*-Boc-piperidine **78** with methylchloroformate (see Scheme 2.10).[34]

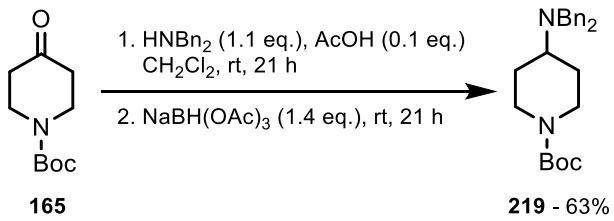


a) Ratio determined by ^{1}H NMR spectroscopy of product after chromatography; b) Ratio determined by ^{1}H NMR spectroscopy of crude mixture after Boc group removal with TFA

Scheme: 2.54

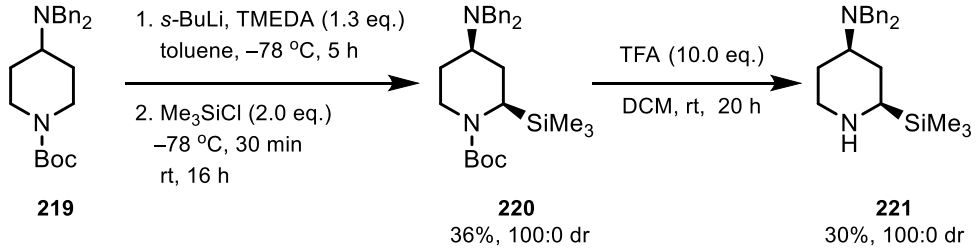
Overall, the yields obtained from these results were not particularly high, with the highest yields being achieved when trapping with Me_3SiCl (73%), dimethylsulfate (72%) and *i*-PrOBpin (67%). In general, good diastereoselectivity was observed (≥93:7), except with electrophiles that had the potential to trap slowly or to cause epimerisation *via* enolisation.

At this point, we also considered the investigation of the lithiation-trapping of other 4-substituted *N*-Boc-piperidines. With this in mind, it was planned to study 4-dibenzylamino-*N*-Boc-piperidine **219**. Thus, 4-dibenzylamino-*N*-Boc-piperidine **219** was synthesised in 63% yield from ketone **165** *via* reductive amination using dibenzylamine and sodium triacetoxyborohydride.[80]



Scheme: 2.55

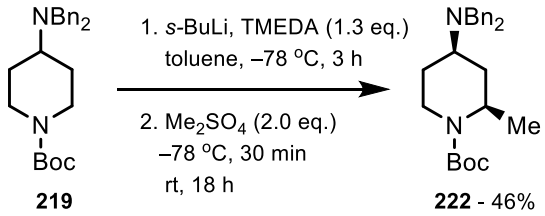
The lithiation-functionalisation of 4-dibenzylamino-*N*-Boc-piperidine **219** was investigated in toluene. Previous work in the group had demonstrated, through the use of ReactIR^{TM}, that 4-dimethylaminopiperidine **219** had a lithiation time of 94 minutes when carrying out the deprotonation using *s*-BuLi/TMEDA in Et_2O at –78 °C.[66] Based on earlier work, it was known that 4-OTIPS-*N*-Boc-piperidine **149** was slower to lithiate in toluene than in Et_2O and it was assumed that the same would be true with 4-dibenzylaminopiperidine **219**. Thus, lithiation was carried out with *s*-BuLi/TMEDA at –78 °C for 5 hours and the lithiated intermediate was trapped with Me_3SiCl. This afforded α-silyl-*N*-Boc-piperidine *cis*-**220** in 36% yield after chromatography (Scheme 2.56). The dr was determined by Boc removal (using TFA) to afford α-silylpiperidine *cis*-**221** on which ^{1}H NMR spectroscopic analysis could be performed. As before, the pattern of *J* values indicated that both the NBn_2 and $SiMe_3$ groups occupied equatorial positions.



219 **220** 36%, 100:0 dr **221** 30%, 100:0 dr

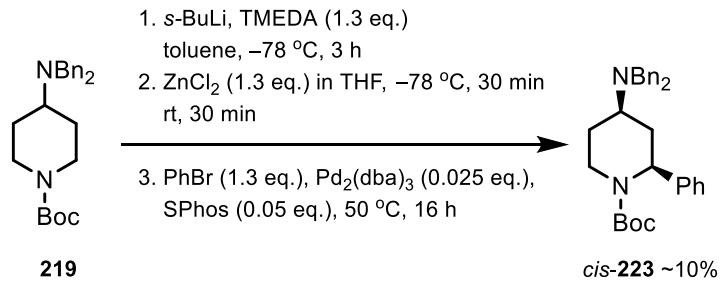
Scheme: 2.56

The lithiation-functionalisation of dibenzylaminopiperidine **219** was also performed with dimethylsulfate. Unfortunately, α-methyl-4-dibenzylaminopiperidine **222** was inseparable from piperidine *cis*-**219** and the product was isolated as a 50:50 mixture of the two compounds (from which a 46% yield of *cis*-**222** could be calculated) (Scheme 2.57). Whilst the ^{1}H and ^{13}C NMR spectra could be interpreted and the peaks from α-methylpiperidine *cis*-**222** identified by comparison with the spectra of piperidine **219**, the dr of the reaction could not be determined, due to the presence of broad peaks in the ^{1}H NMR spectrum. In this case, c*is*-stereochemistry was assumed, given the precedent in the reaction with Me_3SiCl.



Scheme: 2.57

With moderately promising lithiation results in hand, the α-arylation of dibenzylaminopiperidine **219** was attempted using the initial α-arylation conditions of SPhos (0.05 equivalents) and $Pd_2(dba)_3$ (0.025 equivalents) with heating at 50 °C. This reaction afforded an inseparable 80:20 mixture of the desired α-phenylpiperidine *cis*-**223** and piperidine **219** by ^{1}H NMR spectroscopy (Scheme 2.58). This equated to a yield of around 10% of α-phenylpiperidine *cis*-**223**. It is proposed that a higher yield could be achieved with the optimised conditions; however, this reaction was not revisited due to the inseparable nature of the product and starting material.



Scheme: 2.58

Overall, neither the α-lithiation-functionalisation or α-arylation of dibenzylaminopiperidine **219** gave comparable yields to those performed on 4-OTBDMS-*N*-Boc-piperidine **73**. As difficulties were encountered with the separation of dibenzylaminopiperidine **219** from the resulting α-functionalised and α-aryl piperidines, the lithiation-functionalisation of piperidine **219** was not investigated further.

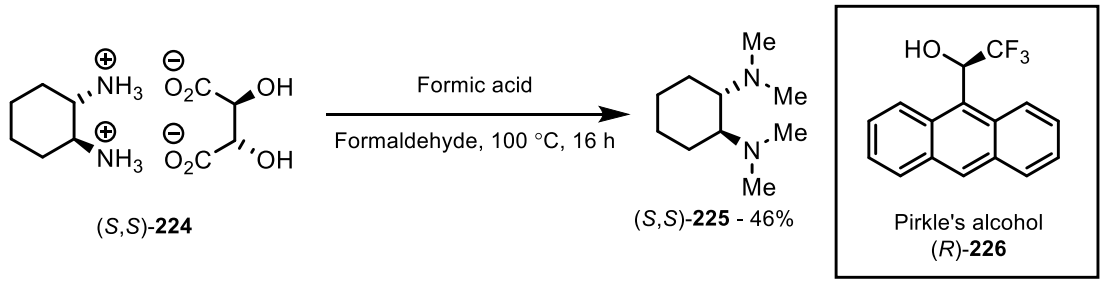
2.4.2 Asymmetric α-Lithiation-Trapping of 4-Substituted *N*-Boc-piperidines

O'Brien, Campos, Coldham and co-workers had demonstrated that asymmetric lithiation of *N*-Boc-piperidine **8** followed by transmetallation and cross-coupling can be used to deliver enantioenriched α-aryl piperidines (see Scheme 2.29).[46] Their work demonstrated that there was retention of stereochemical information during the

transmetallation and cross-coupling steps. Therefore, it was theorised that the same would be true with 4-substituted-*N*-Boc-piperidines, namely, that asymmetric lithiation during the lithiation and subsequent transmetallation and cross-coupling would lead to enantioenriched α-aryl piperidines. This would enable the synthesis of *cis*-α-aryl-4-substituted piperidines with both high diastereo- and enantioselectivity.

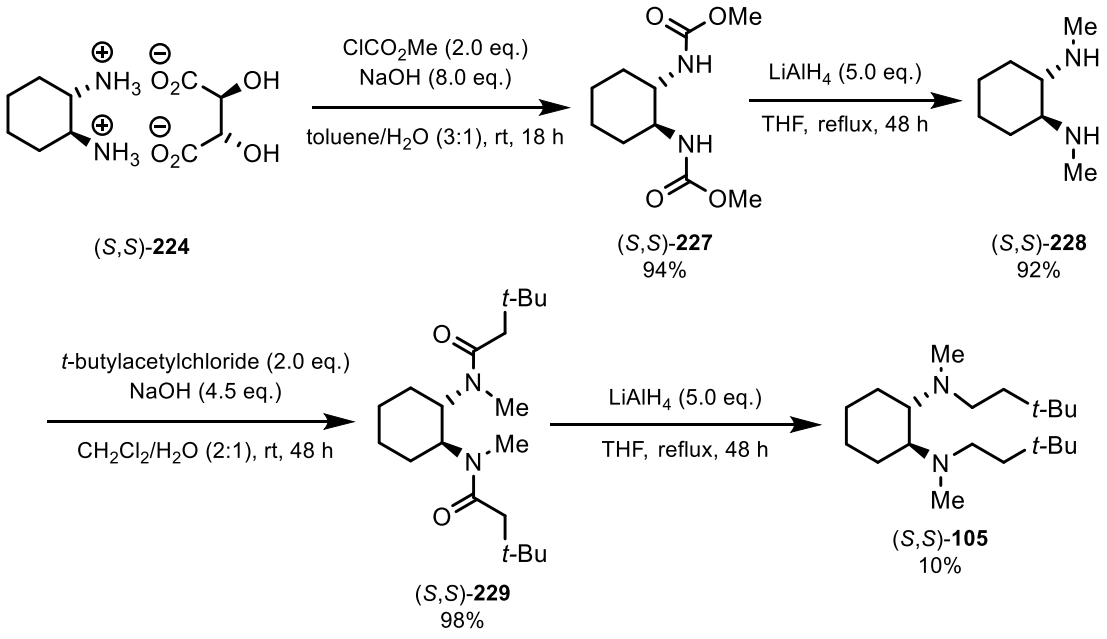
First, the asymmetric lithiation-trapping of 4-OTBDMS-*N*-Boc-piperidine **73** would be investigated as there are no reports of the asymmetric lithiation of any *N*-Boc heterocycle in toluene. Work by Coldham, O'Brien *et al.* had shown that diamines (*S*,*S*)-**105** (or (*R*,*R*)-**105**) gave the highest enantioselectivity when applied to 4-substituted-*N*-Boc-piperidines,[52] whereas the sparteine surrogate **95** gave the highest yield. For these reasons, these two ligands were targeted for synthesis and subsequent investigation.

The original synthesis of diamine (*S*,*S*)-**105** was reported by Alexakis and co-workers but a shorter and more efficient route was developed by O'Brien *et al.* [53,81] The first step was the resolution of (±)-*trans*-cyclohexane-1,2-diamine using tartaric acid. This step had already been carried out on a large scale by another member of the group and a substantial quantity of both resolved salts (*S*,*S*)-**224** and (*R*,*R*)-**224** were available. Alexakis diamine (*S*,*S*)-**105** was targeted as this would give the same sense of induction as the (+)-sparteine surrogate **95**. The er of the resolved salt (*S*,*S*)-**224** was determined by synthesising TMCDA (*S*,*S*)-**225** (Scheme 2.59) and carrying out ^{1}H NMR spectroscopic studies in the presence of 2,2,2-trifluoro-1-(9-anthryl)-ethanol (*R*)-**226** (also known as Pirkle's alcohol) as a chiral shift reagent.[82] Two separate samples of TMCDA (*S*,*S*)-**225** in $CDCl_3$ were prepared with a portion of (*R*)-**226** in one and (*S*)-**226** in the other. The ^{1}H NMR spectra could then be compared by examining the resonance due to the methyl protons, since the resulting complexes would be diastereomeric. Therefore, by comparing the two spectra, the presence and size of the peaks could be identified and from this, the er of the resolved salt determined. When this procedure was carried out, each ^{1}H NMR spectrum contained only one resonance (in a different position) for the methyl protons, indicating that TMCDA (*S*,*S*)-**225** and, by extension, the resolved salt (*S*,*S*)-**224**, was of >99:1 er.



Scheme 2.59

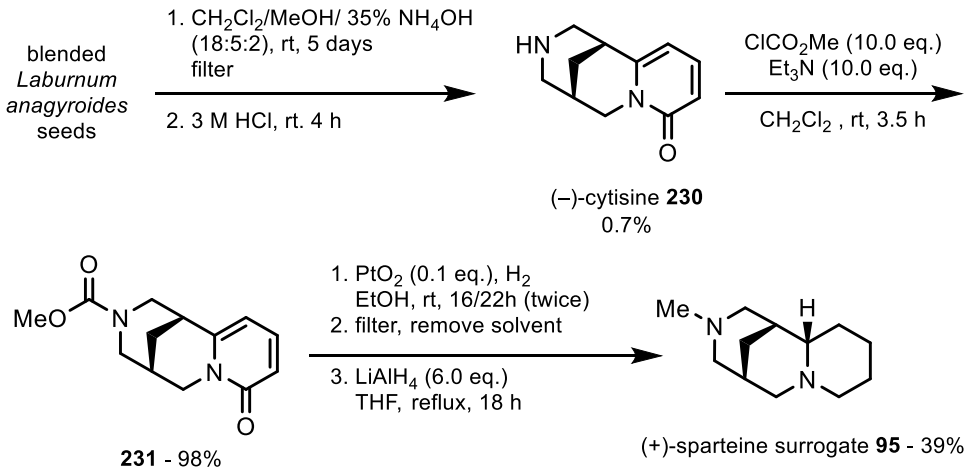
The synthetic route published by O'Brien *et al.* was followed (Scheme 2.60). The sequence involved the formation of bismethylcarbamate (*S*,*S*)-**227** from resolved salt (*S*,*S*)-**224** with 2 equivalents of methylchloroformate. The carbamate groups were then reduced to methylamines *via* a $LiAlH_4$ reduction in THF to afford dimethyldiamine (*S*,*S*)-**228** in 92% yield. Reaction of dimethylamine (*S*,*S*)-**228** with 2 equivalents of *t*-butylacetylchloride and sodium hydroxide at rt afforded dimethyldiamide (*S*,*S*)-**229** in 98% yield. Subsequent $LiAlH_4$ reduction gave the desired Alexakis diamine (*S*,*S*)-**105**. However, problems were encountered with the $LiAlH_4$ reductions and, since no purification was performed until a Kügelrohr distillation after the last step, this resulted in impurities being carried through. This was solved by the introduction of a 6 M $NaOH_{(aq)}$ wash after filtration through Celite®, which was implemented to aid the removal of aluminium-related by-products. However, purification difficulties resulted in the low 10% yield of diamine (*S*,*S*)-**105** in the final step.



Scheme 2.60

The synthesis of (+)-sparteine surrogate **95** was carried out following the procedure initially reported by O'Brien *et al.* and subsequently verified in *Organic Syntheses*.[47,83] The synthesis made use of the naturally occurring (–)-cytisine **230** which could be extracted from the seeds of *Laburnum anagyroides*, a procedure which itself had been reported by Lasne and co-workers.[84] The use of a naturally occurring alkaloid ensured that the starting material would be enantiopure and, as there was no change to the (–)-cytisine **230** core during the synthesis of (+)-sparteine surrogate **95**, it could safely be assumed that the resulting ligand would also be enantiopure.

Laburnum anagyroides seeds were blended and extracted with a mixture of CH_2Cl_2, MeOH and 35% aqueous ammonium hydroxide before being filtered and acidified with 3 M $HCl_{(aq)}$. The layers were separated and the aqueous layer was basified and extracted to afford (–)-cytisine **230** in 0.7% yield. Crude (–)-cytisine **230** was stirred at rt with methylchloroformate to afford methylcarbamate **231** in 98% yield. Methylcarbamate **231** was then hydrogenated over PtO_2 to reduce the pyridine on the *exo*-face. Subsequent reduction of the methylcarbamate with $LiAlH_4$ to an *N*-methyl group gave (+)-sparteine surrogate **95** in 39% yield (Scheme 2.61). Equipment difficulties were encountered during purification which resulted in the low yield; nevertheless, sufficient pure (+)-sparteine surrogate **95** was obtained for asymmetric lithiation investigations.



Scheme 2.61

The electrophile scope in Scheme 2.54 had demonstrated that the best lithiation-trapping yields were accomplished with Me_3SiCl, dimethylsulfate and *i*-PrOBpin; however, none of these electrophiles had strong UV chromophores. An electrophile that would impart a good choromophore upon the resulting α-functionalised piperidine was

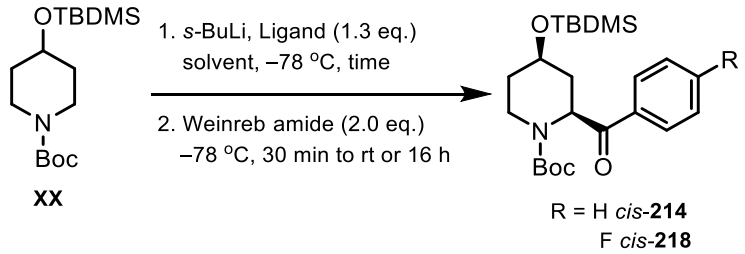
necessary to enable determination of the er by CSP-HPLC. Therefore, the electrophile of choice was phenyl Weinreb amide, as this had given a good 59% yield of α-functionalised piperidine *cis*-**214** in excellent 98:2 dr. However, it was subsequently determined that the resulting α-functionalised piperidine *cis*-**214** was not stable under ambient conditions upon storage. As a result, 4-fluoro-*N*-methoxy-*N*-methylbenzamide (4-fluorophenyl Weinreb amide) was also used as a comparable dr (97:3) had been observed with this electrophile and the yield of the resulting α-functionalised piperidine *cis*-**218** had only been slightly lower (42%).

Firth and O'Brien *et al.* have reported on the reactivity of a range of *s*-BuLi/diamines used in the lithiation of *N*-Boc heterocycles.[85,45,55] Collectively, these reports demonstrated that the *s*-BuLi/(+)-sparteine surrogate **95** complex was more reactive than *s*-BuLi/TMEDA and *s*-BuLi/Alexakis diamine (*S*,*S*)-**105**, both of which in turn were more reactive than *s*-BuLi/(–)-sparteine **93**. Although the relative reactivity of *s*-BuLi/diamine (*R*,*R*)-**105** and *s*-BuLi/TMEDA is not known, it is reasonable to assume that lithiation with *s*-BuLi/diamine (*R*,*R*)-**105** would be slower than with *s*-BuLi/TMEDA due to the greater steric bulk of the ligand. Firth had shown that in Et_2O at –78 °C the lithiation of 4-OTIPS-*N*-Boc-piperidine was complete in 30 minutes with *s*-BuLi/(+)-sparteine surrogate **95** and in 40 minutes with *s*-BuLi/TMEDA. In separate work, Beak and co-workers had shown that the lithiation of unsubstituted *N*-Boc-piperidine **8** with *s*-BuLi/(–)-sparteine **93** was very slow and low yielding.[48] In addition, as shown in Table 2.5, the lithiation of 4-OTIPS-*N*-Boc-piperidine **149** using *s*-BuLi/TMEDA is slower in toluene than in Et_2O. Taking all of this information together suggested that, for the asymmetric lithiation of 4-OTBDMS-*N*-Boc-piperidine **73** in toluene using *s*-BuLi/chiral diamines, long lithiation times (greater than 3 hours) would be required when using (+)-sparteine **93**, but 3 hours could be sufficient with the (+)-sparteine surrogate **95**. For the lithiation with diamine (*R*,*R*)-**105** in toluene, around 3 hours would likely be required but a longer lithiation time might be preferable to obtain complete lithiation.

Five lithiation-functionalisation reactions of 4-OTBDMS-*N*-Boc-piperidine **73** were carried out using the following general conditions (Table 2.18): 1.3 equivalents of *s*-BuLi/chiral diamine in Et_2O or toluene at –78 °C with a lithiation time of 1-7 hours before the addition of the Weinreb amide. Using *s*-BuLi/(+)-sparteine **93** in toluene with a 7 hour lithiation time, a 15% yield of α-ketopiperidine *cis*-**214** of 67:33 er (by CSP-

HPLC) was obtained (entry 4). For comparison, the analogous reaction in Et_2O was attempted under the same conditions and this afforded α-ketopiperidine *cis*-**214** in 74:26 er and 24% yield (entry 5). The enantioselectivity was very similar to that achieved by O'Brien *et al.* with 4-phenyl-*N*-Boc-piperidine **63** in Et_2O with (+)-sparteine **93** (78:22 er) (see Table 2.2).[55] Disappointingly, the initial result in toluene showed both lower yield and enantioselectivity than that achieved in Et_2O. Lithiation-trapping with *s*-BuLi/diamine (*S*,*S*)-**105** in toluene for 6 hours gave a meagre 7% yield of α-ketopiperidine *cis*-**214** in 76:24 er (entry 6). The same reaction was performed in Et_2O with a lithiation time of 1 hour and, encouragingly, a 27% yield of α-ketopiperidine *cis*-**214** was achieved in 83:17 er (entry 7). Unfortunately, given our long-term aim of performing one-pot lithiation-transmetallation-Negishi cross-coupling in toluene, it was shown that a higher er was accomplished when the lithiation was conducted in Et_2O. Lithiation-functionalisation of piperidine **73** using 4-fluorophenyl Weinreb amide with *s*-BuLi/(+)-sparteine surrogate **95** for 1 hour in Et_2O gave α-ketopiperidine *cis*-**218** in only 8% yield and 69:31 er (entry 8). The lithiation time was based on React IR studies from our group where it was reported that the lithiation of 4-OTIPS-*N*-Boc-piperidine **149** using *s*-BuLi/(+)-sparteine surrogate **95** in Et_2O at –78 °C was complete in 40 minutes.[45] The enantioselectivity achieved matched the analogous reaction conducted by O'Brien *et al.* on 4-phenyl-*N*-Boc-piperidine **63** with Me_3SiCl, where a 70:30 er was accomplished (see Scheme 2.25).[52] Due to the low enantioselectivity achieved in Et_2O, the analogous reaction in toluene was not attempted. For both α-ketopiperidines *cis*-**214** and *cis*-**218**, the sense of induction is assumed based on the extensive literature precedent and previous work with the same set of chiral diamine ligands.[52,55]

Table 2.18: Asymmetric lithiation-trapping of 4-OTBDMS-*N*-Boc-piperidine **73**



XX

R = H *cis*-**214**
F *cis*-**218**

Entry	Ligand	Solvent	Time / h	Product	Yield / %[a]	dr[b]	er[c]
1	TMEDA	toluene	3	*cis*-**214**	59	98:2	50:50
2	TMEDA	toluene	3	*cis*-**218**	42	97:3	50:50
3	TMEDA	Et_2O	1	*cis*-**218**	35	97:3	50:50
4	(+)-sparteine	toluene	7	*cis*-**214**	15	97:3	67:33
5	(+)-sparteine	Et_2O	7	*cis*-**214**	24	>99:1	74:26
6	(*S*,*S*)-**105**	toluene	6	*cis*-**214**	7	96:4	76:24
7	(*S*,*S*)-**105**	Et_2O	1	*cis*-**214**	27	>99:1	83:17
8	(+)-sp surr **95**	Et_2O	1	*cis*-**218**	8	>99:1	69:31

a) Yield after chromatography; b) dr determined by ^{1}H NMR spectroscopy of product after chromatography; c) er determined by CSP-HPLC, for *cis*-**214** R = H OD-H column 1 mL/min 90:10 hexane:*i*-PrOH, for *cis*-**218** R = F IC column 1 mL/min 99:1 hexane:*i*-PrOH

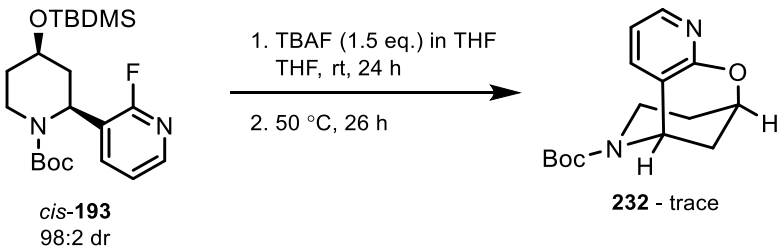
Overall, the asymmetric lithiation results were disappointing: the yields from all the asymmetric lithiation-trapping reactions were low (8-27%). However, in all cases, α-ketopiperidines *cis*-**214** (≥96:4 dr) and *cis*-**218** (>99:1 dr) were generated with high diastereoselectivity. Lithiation-functionalisation with both *s*-BuLi/(+)-sparteine **93** and *s*-BuLi/diamine (*S*,*S*)-**105** afforded α-ketopiperidine *cis*-**214** in higher er in Et_2O than in toluene. Therefore, despite the utility of toluene for the α-lithiation-arylation procedure, toluene appears to be inferior to Et_2O for the asymmetric lithiation of 4-OTBDMS-piperidine **73**. This was consistent with the findings of O'Brien, Coldham and co-workers where, during the asymmetric lithiation of 4-phenyl-*N*-Boc-piperidine **63**, the best enantioselectivity was achieved with *s*-BuLi/Alexakis diamine (*S*,*S*)-**105** in Et_2O (87:13 er) (see Table 2.2).[52] Modifications of the Alexakis diamine **105** have been investigated by McGlacken and co-workers, albeit with limited success and, due to this, further investigations of these ligands were not pursued.[86] Overall, for the asymmetric

lithiation to be synthetically useful, the er accomplished would need to be ≥ 90:10. As the er in toluene was lower than that in Et_2O, further investigations with the available ligands were not conducted and an asymmetric α-arylation was not attempted.

2.5 Further Functionalisations of 2,4-Disubstituted-*N*-Boc-piperidines

To demonstrate the utility of the 2,4-disubstituted α-aryl piperidines generated from the Negishi cross-coupling reactions, it was decided to briefly explore some functionalisation reactions on the α-aryl piperidines. Two aspects were envisioned: a cyclisation reaction between the aryl group and the hydroxyl group (after TBDMS removal) and a lithiation-trapping reaction at the benzylic position.

To start, the cyclisation reaction was explored. X-ray crystal structures and ^{1}H NMR spectroscopic analysis of α-aryl-4-OTBDMS-*N*-Boc-piperidines identified that the OTBDMS group and the aryl group adopted a diaxial conformation (see Figures 2.7 – 2.9). This inspired a brief investigation into whether the proximity of these groups could be utilised for the cyclisation reaction. It was theorised that, following removal of the TBDMS group, if a suitable group was present on the aromatic ring, cyclisation could occur from the alcohol onto the aromatic ring *via* an S_NAr reaction. To this aim, an α-arylation of 4-OTBDMS-piperidine **73** had been carried out with 3-bromo-2-fluoropyridine to afford α-arylpiperidine *cis*-**193**. This would give the opportunity for the hydroxyl group to attack the pyridine ring at the 2-position to give fused tricyclic piperidine **232**. The reaction was first attempted by reacting α-arylpiperidine *cis*-**193** with TBAF to effect the removal of the silyl protecting group and then heating to 50 °C to facilitate the S_NAr reaction. This reaction gave only a trace amount of the desired tricyclic piperidine **232** (detected by HRMS).



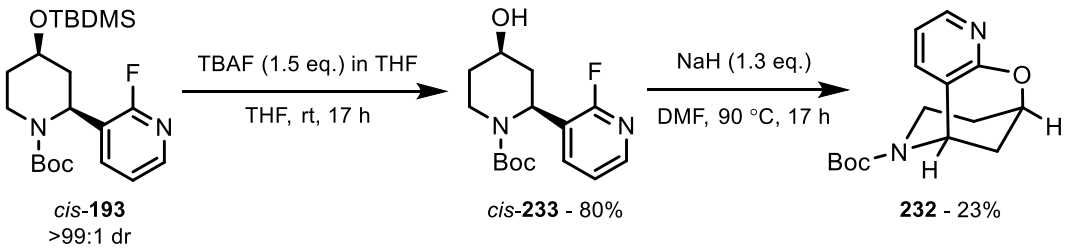
cis-**193**
98:2 dr

232 - trace

Scheme 2.62

An alternative two-step approach was therefore undertaken (Scheme 2.63). First, α-aryl piperidine *cis*-**193** was reacted with TBAF at rt to remove the TBDMS group, affording alcohol *cis*-**233** in 80% yield. Examination of the ^{1}H NMR spectrum of 4-hydoxypiperidine *cis*-**233** demonstrated that it still adopted a diaxial conformation. The cyclisation reaction was then attempted; deprotonation of the hydroxyl proton was

achieved using sodium hydride in DMF and the reaction was heated at 90 °C. Under these conditions, an intramolecular S_NAr reaction did occur and the desired tricyclic piperidine **232** was obtained in 23% yield.



cis-**193**
>99:1 dr

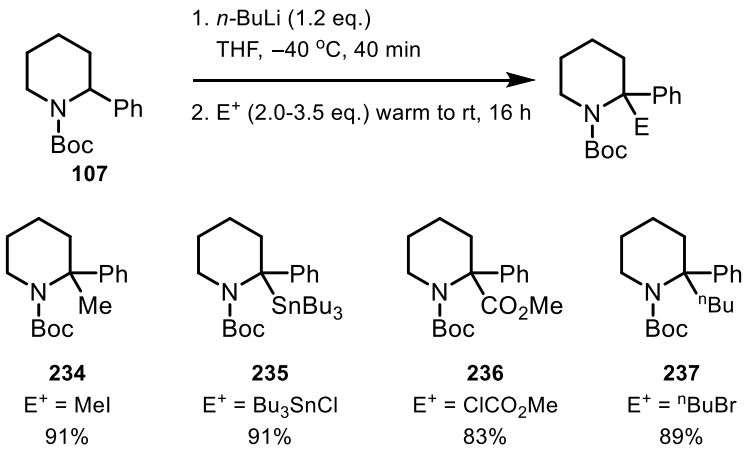
cis-**233** - 80%

232 - 23%

Scheme 2.63

Minimal amounts of unreacted α-arylpiperidine *cis*-**193** were present in the crude reaction mixture which suggested that other side reactions were occurring, potentially due to the elevated temperature. The low yield could have been due to these side reactions or simply the steric requirements of the reaction. Overall, this reaction gave a proof of concept that the diaxial conformation of the α-aryl-4-OTBDMS-piperidines could be exploited for further functionalisation to synthesise a molecule with a novel tricyclic core.

In 2012, Coldham, O'Brien and co-workers reported the lithiation-trapping of α-aryl-*N*-Boc-piperidines to give 2,2-disubstituted piperidines in good yield (≥75%) (Scheme 2.64).[87] For example, α-phenyl-*N*-Boc-piperidine **107** was lithiated with *n*-BuLi in THF at –40 °C and trapped with methyliodide to afford 2,2-disubstitutedpiperidine **234** in 91% yield.



107

234
E^+ = MeI
91%

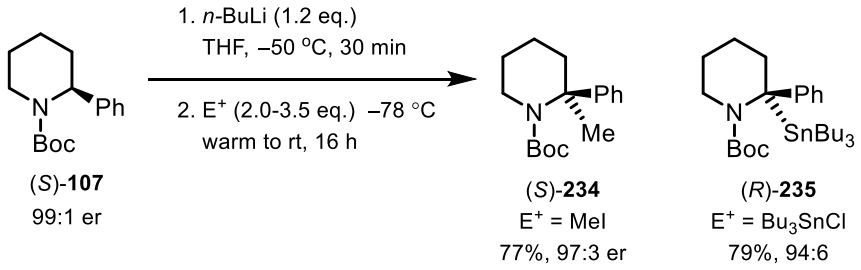
235
E^+ = Bu_3SnCl
91%

236
E^+ = $ClCO_2Me$
83%

237
E^+ = ^nBuBr
89%

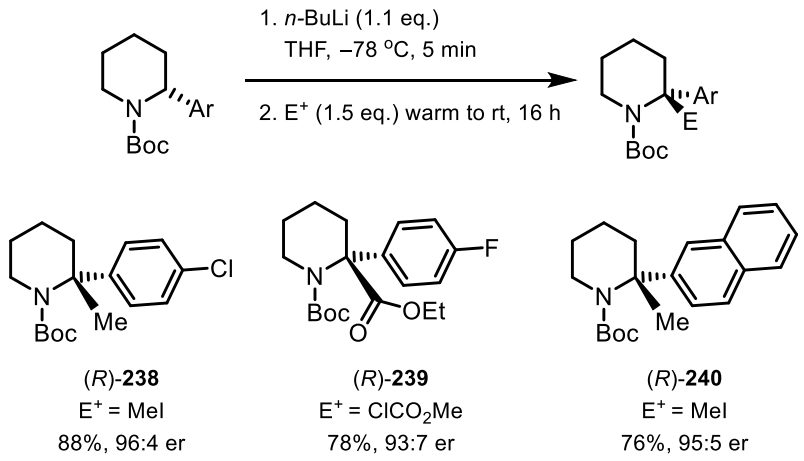
Scheme 2.64

Coldham, O'Brien and co-workers demonstrated that the lithiation-trapping of enantioenriched α-phenyl-*N*-Boc-piperidine (*S*)-**107** with *n*-BuLi in THF at –78 °C proceeded with retention of stereochemistry (Scheme 2.65).[87] Enantioenriched α-phenyl-*N*-Boc-piperidine (*S*)-**107** was prepared in 99:1 er *via* an asymmetric imine reduction reaction and subsequent recrystallisation. Lithiation of α-phenyl-*N*-Boc-piperidine (*S*)-**107** was carried out in THF with *n*-BuLi at –50 °C. Then, the reaction mixture was cooled to –78 °C and the electrophile was added. When the trapping was conducted with methyliodide, a 77% yield of 2,2-disubstitutedpiperidine (*S*)-**234** in 97:3 er was obtained, whereas trapping with Bu_3SnCl afforded 2,2-disubstitutedpiperidine (*S*)-**235** in 79% yield and 94:6 er. Both of these reactions proceeded with minimal reduction in er, demonstrating a retention of the original *S* stereocentre under these conditions.



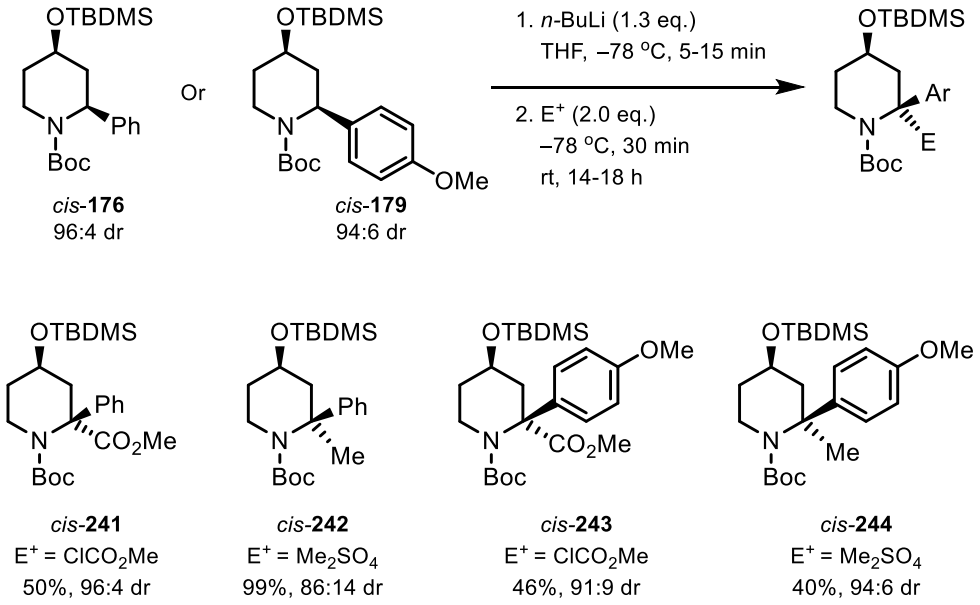
Scheme 2.65

Independently, and more recently, Coldham *et al.* reported the further functionalisation of enantioenriched α-aryl-*N*-Boc piperidines *via* benzylic lithiation using *n*-BuLi in THF at –78 °C and trapping to afford a range of 2,2-disubstituted piperidines (Scheme 2.67).[54] For example, lithiation-trapping of α-(4-chlorophenyl)piperidine was performed with *n*-BuLi in THF at –78 °C for 5 minutes and then trapping with methyliodide gave 2,2-disubstitutedpiperidine (*R*)-**238** in 88% yield and 96:4 er. As had been reported by Coldham, O'Brien and co-workers, the retention of stereochemistry was reported with no change in er during lithiation-trapping. Coldham *et al.*'s report demonstrated that other aryl groups could be used to facilitate the benzylic lithiation besides a phenyl group.



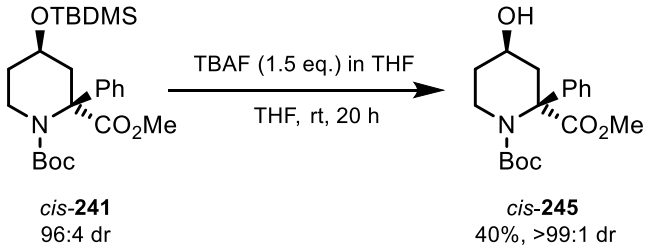
Scheme 2.67

Thus, based on this literature precedent, the further functionalisation of α-aryl piperidines using this methodology was explored. Benzylic lithiation was attempted on α-phenyl-4-OTBDMS-piperidine *cis*-**176** based on the procedure used by Coldham *et al.*.[54] α-Phenylpiperidine *cis*-**176** (96:4 dr) was lithiated using *n*-BuLi in THF at –78 °C for 5 min and then trapped with methylchloroformate to give trisubstituted piperidine *cis*-**241** in 50% yield and 96:4 dr (Scheme 2.68). For consistency, "*cis*" and "*trans*" in these trisubstituted piperidines refer to the relationship between the aromatic group and the OTBDMS group in the 4-position. The reaction clearly proceeded with complete retention of stereochemical information; initially, *cis*-**241** was assigned based on the previous precedent from the work of Coldham and O'Brien.[54] Lithiation-trapping of α-phenylpiperidine *cis*-**176** with dimethylsulfate gave trisubstitutedpiperidine *cis*-**242** in excellent yield (99%) but low dr (86:14). The erosion in dr was unexpected, although it should be highlighted that other trappings with dimethylsulfate can lead to lower dr, potentially due to slow trapping and configurational instability of the lithiated species as it warms up (see Scheme 2.23). The lithiation-trapping of α-arylpiperidine *cis*-**179** (94:6 dr) was also carried out; trapping with methylchloroformate and dimethylsulfate afforded trisubstitutedpiperidines *cis*-**243** (91:9 dr) and *cis*-**244** (94:6 dr) in 46% and 40% yields respectively (Scheme 2.68).



Scheme 2.68

The relative stereochemistry of the trisubstituted piperidines was initially assumed and could not be easily determined by ^{1}H NMR spectroscopy. Therefore, to confirm that the benzylic lithiation-trapping reaction occurred with the expected retention of configuration, attention turned to X-ray crystallography. The TBDMS group was removed from trisubstitutedpiperidine *cis*-**241** (96:4 dr) using TBAF to give trisubstituted 4-hydroxypiperidine *cis*-**245** in 40% yield and as a single diastereomer (Scheme 2.69).



Scheme 2.69

An X-ray crystal structure of trisubstituted 4-hydroxypiperidine *cis*-**245** was obtained which confirmed that the *cis*-stereochemistry of the starting material in the lithiation-trapping reaction had been retained (Figure 2.13). Interestingly, the hydroxyl group and the phenyl group adopted a diequatorial conformation. Due to rotamers, it was not possible to analyse the ^{1}H NMR spectrum to determine if the same conformation was

adopted in solution, nor if 4-OTBDMS-trisubstituted piperidine *cis*-**241** had adopted this conformation. However, the splitting pattern of the 4-OCH proton in the ^{1}H NMR spectrum of 2-methyl-trisubstitutedpiperidine *cis*-**245** suggested that it was axial and therefore that the OTBDMS and phenyl groups were equatorial.

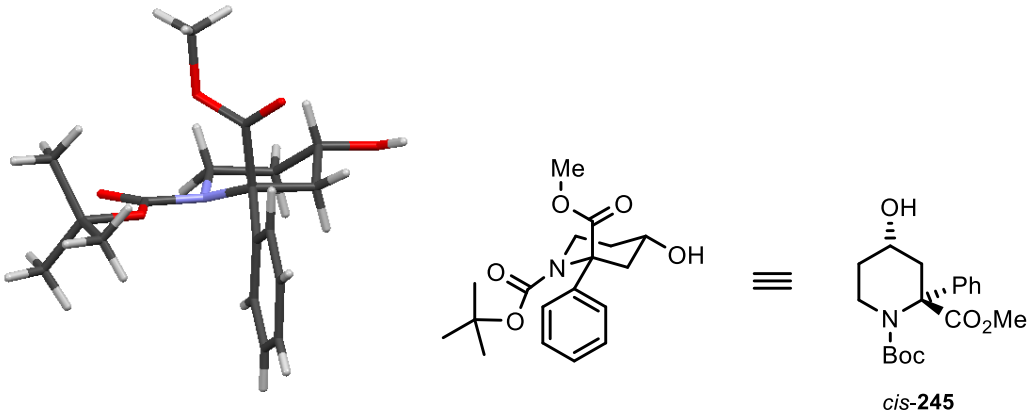


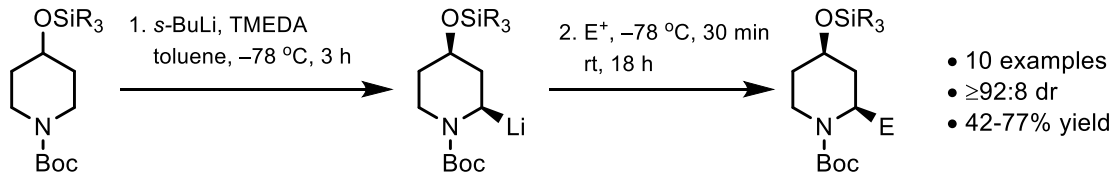
Figure 2.4: X-ray crystal structure of 2-(methoxycarbonyl)-2-methyl-4-hydroxy-*N*-Boc-piperidine *cis*-**245**

The lithiation-trapping reactions demonstrated that the benzylic position could be functionalised with minimal reduction in dr. Compared to the yields achieved by Coldham and co-workers on α-aryl piperidines (~80%), the yields were not particularly high although trisubstituted piperidine *cis*-**242** had been obtained in 99% yield. The reason for the large discrepancy in the yields was not clear. If all the reactions had afforded products with similar yields, it could have been possible that the reason was due to slow interconversion of the Boc rotamers on the timescale of the lithiation reaction. If this had been the case, then it could have been possible that only one rotamer was reacting, the one in which the carbonyl group was pointing towards the benzylic proton, resulting in incomplete lithiation and a maximum theoretical yield matching the ratio of rotamers. However, hindered rotation is evidently not the case as a 99% yield of trisubstituted piperidine *cis*-**242** was accomplished when α-phenyl-*N*-Boc-piperidine *cis*-**176** was lithiated and trapped with dimethylsulfate. In conclusion, without further investigation, the reason for the discrepancy in yields cannot be determined. Nevertheless, these reactions have demonstrated that the synthesis of fully substituted centres is possible with retention of *cis*-stereochemistry and the further functionalisation of α-aryl-4-OTBDMS-*N*-Boc-piperidines *via* lithiation-trapping is established.

2.6 Conclusions and Future Work

In summary, the procedure for the α-arylation of 4-Osilyl-*N*-Boc-piperidines has been significantly improved compared to previously reported procedure, making it both simpler to perform and effective when applied to nitrogen-containing heteroaryl halides. This has been made possible through the use of toluene for the lithiation of these substrates.

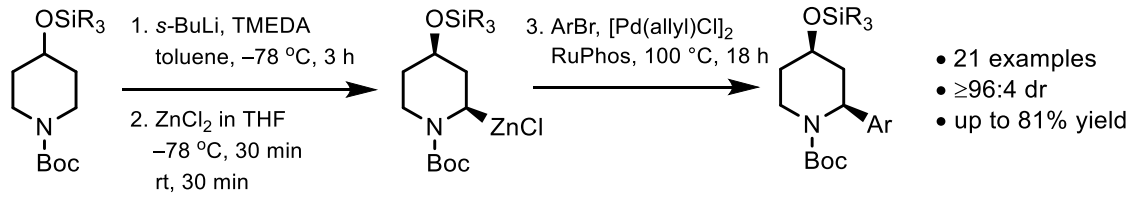
The work described herein shows that good yields of α-functionalised-4-Osilyl piperidines can be accomplished when the lithiation is conducted in toluene as opposed to the more commonly used Et_2O. The lithiation of 4-Osilyl-*N*-Boc-piperidine was conducted at –78 °C using 1.3 equivalents of *s*-BuLi/TMEDA for 3 hours followed by trapping with 2 equivalents of an electrophile. This gave α-functionalised-4-Osilyl piperidines in good yields (42-77%) and excellent *cis*-diastereoselectivities (≥92:8) in all cases bar one (Scheme 2.70).



Scheme 2.70

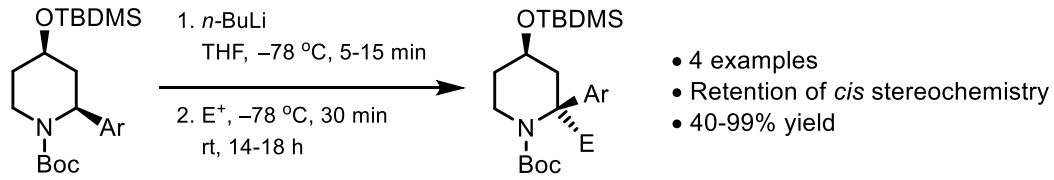
The true utility of the lithiation in toluene comes into play during the α-arylation procedure. The original methodology involved lithiation in Et_2O and a solvent switch to a higher boiling point solvent prior to Negishi cross-coupling, which could be avoided by performing the lithiation in toluene. This simplified the procedure from a practical point of view. The cross-coupling step was further optimised specifically to enable the cross-coupling of heteroaryl halides in good yield, by increasing the reaction temperature to 100 °C, changing the catalyst system to $[Pd(allyl)Cl]_2$ with RuPhos and increasing the equivalents of aryl halide to 1.5. The initial objective was met and 13 heteroaryl halides were successfully cross-coupled with a range of yields, although the majority were around 60%. Furthermore, it was demonstrated that aryl chlorides coupled in near comparable yields. Overall, 21 examples were obtained with yields of up to 81%; the majority of the lower yielding examples being those with fluorine atoms in the *ortho* position or high levels of steric hindrance (Scheme 2.71). Pleasingly, the high *cis*-diastereoselectivity observed during lithiation-functionalisation was maintained

in the α-arylation procedure and, in all cases bar one (where it was 94:6), the dr was ≥96:4. Proof of *cis*-selectivity was obtained through three X-ray crystal structures.



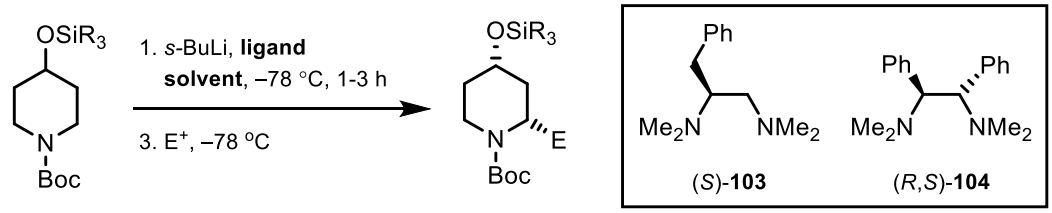
Scheme 2.71

It was also demonstrated that α-aryl-4-Osilyl piperidines could be further functionalised by lithiation-trapping with *n*-BuLi in THF at –78 °C. Lithiation occurred selectively at the benzylic position to afford 2,2,4-trisubstituted piperidines with retention of *cis*-stereochemistry (Scheme 2.72), which was demonstrated by an X-ray crystal structure.



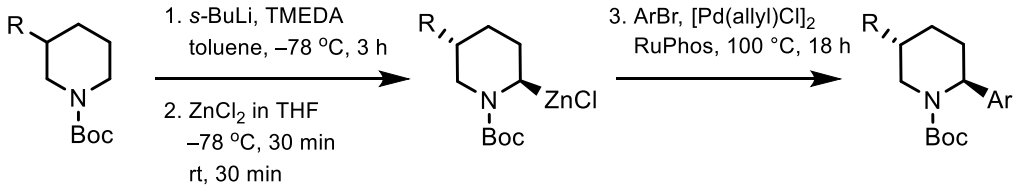
Scheme 2.72

Unfortunately, investigations into the asymmetric lithiation-functionalisation of 4-Osilyl piperidine were not very unsuccessful. The highest enantioselectivity achieved was 83:17 er using the Alexakis diamine (*S*,*S*)-**105**, a reaction that was performed in Et_2O whereas the analogous reaction in toluene only gave 76:24 er. This is certainly a field which could benefit from further work. One possibility would be to investigate the asymmetric lithiation in other solvents, for example, both MTBE and THF had shown promise during the lithiation-trapping of 4-OTIPS-*N*-Boc-piperidine **149** (see Table 2.5). Alternatively, other diamine ligands could be investigated, such as those used by O'Brien and Coldham *et al.* (Scheme 2.74).[52]



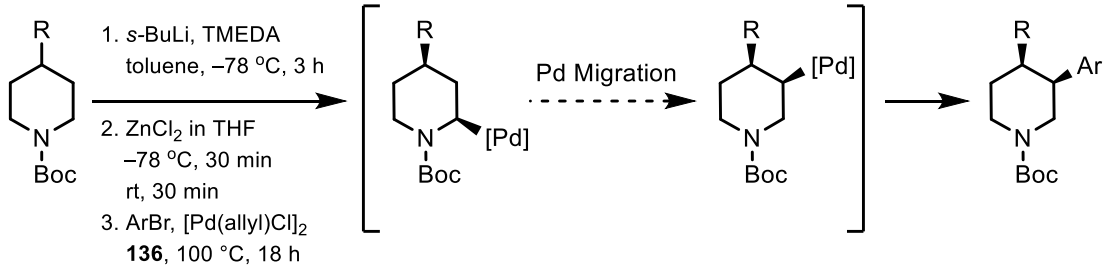
Scheme 2.73

Future work could also involve the α-arylation of 3-substituted-*N*-Boc-piperidines (Scheme 2.74). There are only two examples of this type of reaction, both performed by Knochel *et al.*, affording 2,5-*trans*-disubstituted piperidines in excellent diastereoselectivity.[24] Neither of the examples involved heteroaryl halides and both used a solvent switch. The α-arylation methodology developed here could be applied to these substrates to potentially improve both their scope and yield.



Scheme 2.74

Another possible avenue of research would be to utilise Baudoin and co-workers' β-arylation procedure with a 4-substituted piperidine (Scheme 2.75).[58] This could potentially afford 3,4-*cis*-disubstituted piperidines; the *cis*-stereochemistry would originate from the initial *cis*-selective lithiation, which would be followed by the elimination and reinsertion of the palladium on the same face. The choice of the group in the 4-position could be important for this work as the migration of the palladium may be hindered by a large group. Baudoin *et al.* report that flexible biaryl-phosphine ligands such as **136** favoured β-arylation and therefore ligands of this class could be investigated. By combining these findings with this research, it may be possible to cross-couple heteroaryl halides in good yields and without the need for the solvent switch, whilst also providing a new route to 3,4-disubstituted piperidines.

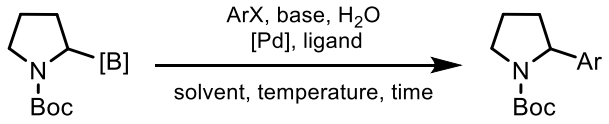


Scheme 2.75

Chapter 3: α-Arylation of α-Boryl pyrrolidines

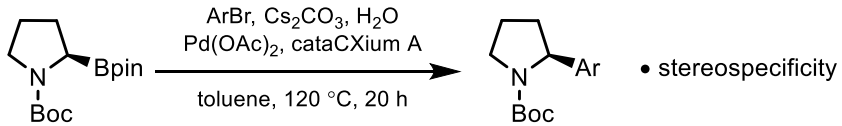
In the first part of this chapter (section 3.1), an overview of the Suzuki-Miyaura cross-coupling (SMCC) of sp^3 centred organoboron reagents with an α-amino substituent is provided. This covers the limited examples of the cross-coupling of these systems and details some closely related analogues, particularly those of cyclic systems. This overview also covers the stereochemistry of the SMCC of sp^3 organoboron compounds where the reaction has been shown to proceed with either stereoretention or stereoinversion; the factors that impart the reported stereochemical outcome are discussed. The aims and objectives of this work are set out in section 3.2.

The second part of the chapter (sections 3.3 and 3.4) details the synthesis of a range of α-boryl pyrrolidines with varied groups on the nitrogen and the SMCC reactions of these substrates. Section 3.5 focuses on the optimisation of the SMCC of α-Bpin-*N*-Boc-pyrrolidine **51** and other organoboron derivatives (Scheme 3.1). Using GC, a comprehensive screen of reaction conditions was carried out to identify conditions for the cross-coupling of α-Bpin-pyrrolidine **51** in good yield.



Scheme 3.1

In section 3.6, an investigation into the scope of the SMCC reaction is presented with a range of aryl chlorides and bromides, including heteroaryl halides. Finally, using enantioenriched α-Bpin-pyrrolidine (*R*)-**51**, results on the exploration of the stereospecificity of the SMCC reaction are described (Scheme 3.2).



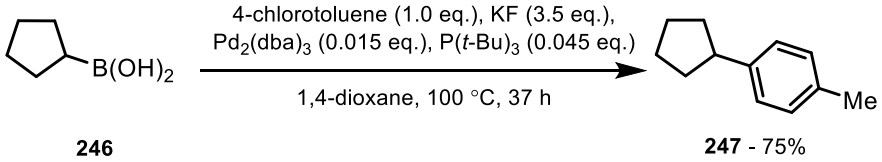
Scheme 3.2

3.1 Overview of sp^2-sp^3 Suzuki-Miyaura Cross-Coupling of Alkyl Organoboron Compounds

The palladium-catalysed Suzuki-Miyaura reaction was first reported by Suzuki and Miyaura in 1979 and, since then, a significant amount of research has been undertaken to expand upon the understanding and utility of the reaction.[88] It is the most commonly used reaction in the pharmaceutical industry for the synthesis of carbon-carbon bonds and, by 2017, over 4,000 articles had been published concerning or utilising it.[89] The Suzuki-Miyaura cross-coupling (SMCC) reaction is a proficient method for the synthesis of sp^2-sp^2 bonds and, more recently, attention has turned to the more challenging sp^2-sp^3 bond formation. This section shall give a brief overview of sp^2-sp^3 SMCC reactions, then will cover reports concerning stereoretentive and stereoinvertive sp^2-sp^3 SMCC reactions and, finally, will cover the SMCC of sp^3 centred organoboron compounds with an α-amino substituent.

3.1.1 Introduction to sp^2-sp^3 Suzuki-Miyaura Cross-Coupling of Secondary Alkyl Organoboron Compounds

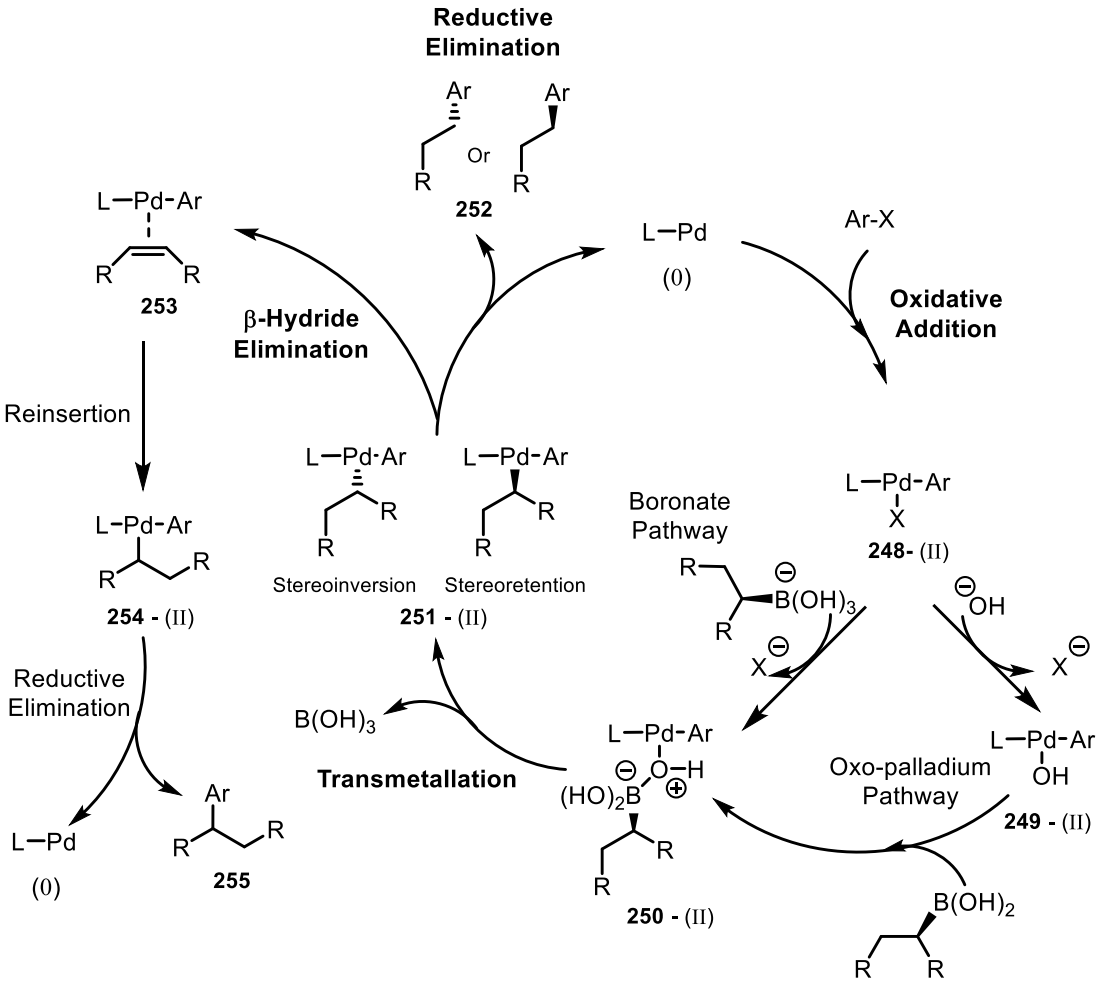
The synthesis of sp^2-sp^3 C-C bonds by SMCC is notably more challenging than the formation of sp^2-sp^2 bonds. This is partly due to the slower rate of transmetallation of the sterically hindered carbon-boron bond, which in turn is due to its sp^3 nature.[90] The first example of such a reaction came from Fu *et al.* in 2000 and involved the cross-coupling of 4-chlorotoluene with cyclopentylboronic acid **246** (Scheme 3.3).[91] The reaction was set up in a glove box using $Pd_2(dba)_3$ and P(*t*-Bu)$_3$ in a 1:3 ratio with KF in 1,4-dioxane and heated to 100 °C for 37 hours. These conditions afforded 1-cyclopentyl-4-methylbenzene **247** in 75% yield. Although this reaction was the only sp^2-sp^3 SMCC reported by Fu *et al.*, it demonstrated the feasibility of cross-coupling sp^3 centred organoboron reagents.



246 **247** - 75%

Scheme 3.3

To understand the challenges of sp^2-sp^3 SMCC reactions, it is important to consider the catalytic cycle (Scheme 3.4). The first step is the activation of the palladium catalyst, often the reduction of the palladium species to Pd(0), unless it is already Pd(0). After catalyst activation, the catalytic cycle of a SMCC reaction proceeds by the oxidative addition of the aryl halide to the Pd(0) species to generate Pd(II) intermediate **248**. There are then two potential pathways by which the transmetallation step can occur, the oxo-palladium pathway and the boronate pathway.



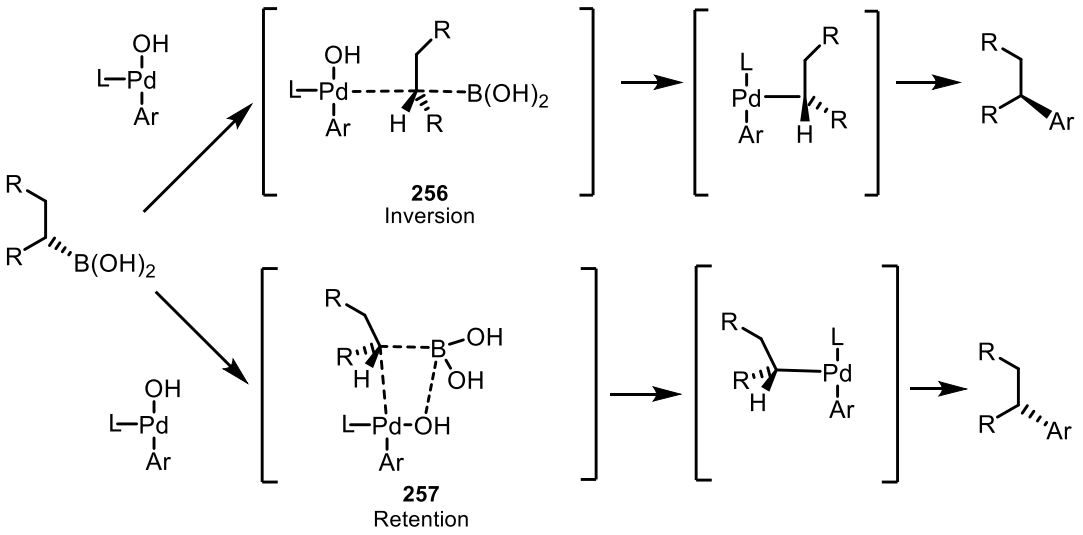
Scheme 3.4

It is widely accepted that the majority of SMCC reactions proceed *via* the oxo-palladium pathway, particularly in cases with weak bases.[92,93,94] In the oxo-palladium pathway, Pd(II) intermediate **248** undergoes halide exchange with base to generate hydroxyl Pd(II) intermediate **249** which then reacts with the organoboron reagent to give pre-transmetallation complex **250**. Alternatively, in the boronate pathway, the base instead reacts with the organoboron reagent to generate a boronate species which reacts

with Pd(II) intermediate **248** displacing the halogen and forming pre-transmetallation complex **250**. The common intermediate, pre-transmetallation complex **250**, then undergoes transmetallation to Pd(II) intermediate **251** which can reductively eliminate to afford the arylated product **252** and regenerate the Pd(0) catalyst.

However, there is the potential for off-path reactions to occur. Aside from the slow rate of transmetallation, the other key challenge with sp^2-sp^3 SMCC reactions is the presence of β-hydrogen atoms, as these can undergo β-hydride elimination with the palladium catalyst to afford unwanted unsaturated by-products, such as **253**. After β-hydride elimination has occurred, there is also the potential for the reinsertion of the catalyst to give Pd(II) intermediate **254** and reductive elimination to generate regioisomers of the arylated product, such as **255**. Alternatively, after reinsertion, a second β-hydride elimination can occur leading to migration of the double bond and potentially resulting in additional regioisomers.

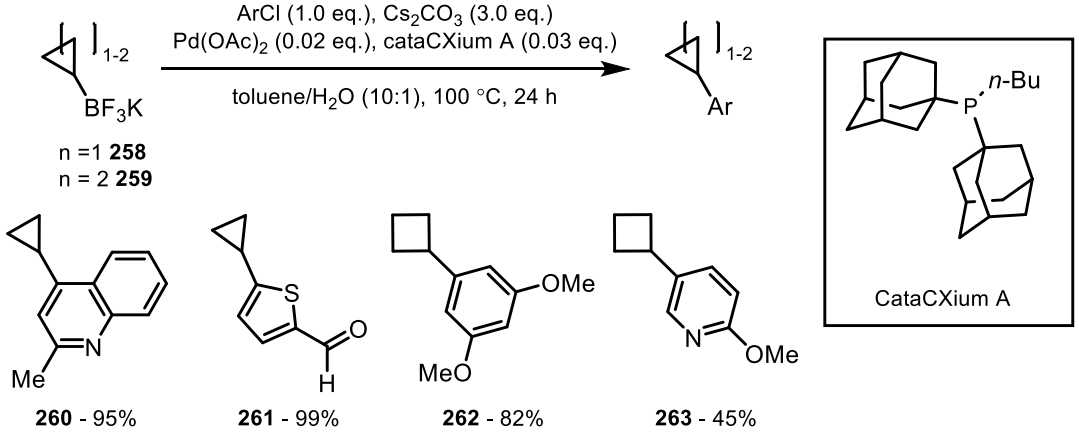
An additional complication for sp^2-sp^3 SMCC reactions occurs when the boron atom is attached to a stereogenic centre, as transmetallation to palladium can occur with either retention or inversion of the stereocentre. It is widely accepted that there are two pathways for the transmetallation of boron to palladium, a stereoretentive pathway and a stereoinvertive pathway.[90,95,96] These relate to the two potential modes of approach of the palladium catalyst during transmetallation: one from the opposite side to the boron atom *via* transition state **256** and the other from the same side *via* transition state **257** (Scheme 3.5). The factors that influence which pathway is preferred are discussed in sections 3.1.2 and 3.1.3.



Scheme 3.5

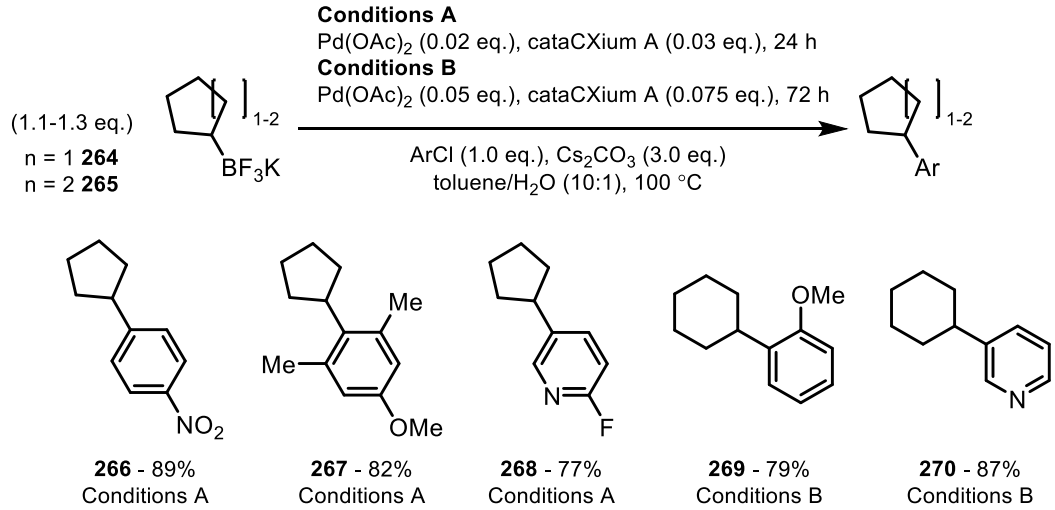
In summary, the necessity to consider stereoretentive and stereoinvertive pathways, the potential for various side-reactions to occur and the inherent challenge of transmetallation make the field of sp^2-sp^3 SMCC particularly challenging.

One of the early reports of sp^2-sp^3 SMCC reactions came from Molander and Gormisky where a successful method for the SMCC of cyclic sp^3 cyclopropyl-BF_3K **258** with a range of aryl chlorides and heteroaryl chlorides was reported.[97] It was determined that the use of XPhos as a ligand along with $Pd(OAc)_2$ was a successful combination for the cross-coupling of aryl chlorides. However, it was found that this selection of ligand and catalyst was not as fruitful when coupling heteroaryl halides and that the use of cataCXium A and $Pd(OAc)_2$ was superior. CataCXium A ($P(Ad)_2Bu$) was first reported by Beller *et al.* in 2000 and was shown to be a good ligand for the SMCC of aryl chlorides with arylboronic acids.[98] When cataCXium A was used in combination with $Pd(OAc)_2$, the catalytic complex was shown to possess very high turnover numbers.[98] Molander and Gormisky conducted the SMCC reaction in a 10:1 mixture of toluene-water with Cs_2CO_3 at 100 °C for 24 hours. With these conditions, a range of heteroaryl chlorides were cross-coupled in good yield (Scheme 3.6). For example, the SMCC of cyclopropyl-BF_3K **258** with 4-chloroquinaldine afforded arylcyclopropane **260** in 95% yield. These conditions also tolerated the cross-coupling of cyclobutyl-BF_3K **259** in good yields; for example, the SMCC of cyclobutyl-BF_3K **259** with 5-chloro-2-methoxypyridine gave arylcyclobutane **263** in 45% yield. Molander and Gormisky did note that the SMCC reaction with cyclobutyl-BF_3K **259** appeared to be substrate dependent as it was not successful with 1-chloro-4-methoxy-2,6-diemthylbenzene and 4-chlorobenzonitrile.



Scheme 3.6

At a similar time, Dreher, Molander and co-workers reported the SMCC of cyclopentyl-BF_3K **264** and cyclohexyl-BF_3K **265** with aryl chlorides and heteroaryl chlorides.[99] The SMCC conditions previously reported were utilised in these reactions: $Pd(OAc)_2$, cataCXium A and Cs_2CO_3 in a toluene-water mixture.[97] Under these conditions, cycloalkyl BF_3K salts were successfully coupled, although for the cross-coupling of cyclohexyl-BF_3K **265**, a higher catalyst loading was required along with a 72 hour reaction time and 1.3 equivalents of cyclohexyl-BF_3K **265** (Scheme 3.7). It was also noted that, although the cross-coupling of an aryl iodide was successful, the reaction took longer to go to completion; aryl bromides, on the other hand, cross-coupled with comparable, albeit slightly lower yields. For example, the SMCC of 4-bromonitrobenzene with cyclopentyl-BF_3K **264** gave arylcyclopentane **266** in 89% yield, compared to the yield of 89% obtained with 4-chloronitrobenzene.

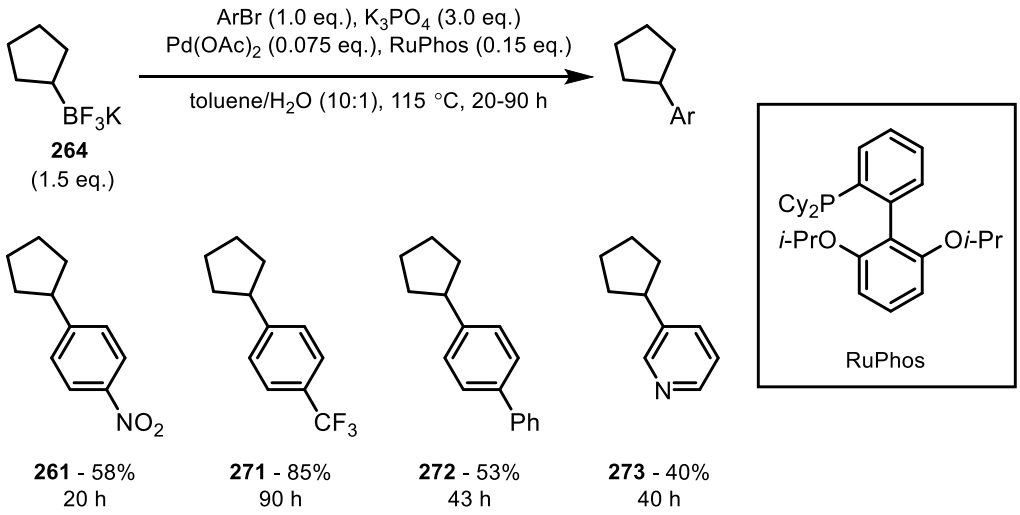


Scheme 3.7

These reports from Molander *et al.* represent the first detailed exploration into the SMCC of secondary sp^3 cyclic organoboron reagents. It should be noted that cyclopropylboron compounds are significantly easier to cross-couple than other sp^3 boron reagents due to the unique hybridisation of the atoms in the ring which helps facilitate SMCC reactions.[100,101] For example, Doucet *et al.* reported the SMCC of cyclopropylboronic acid with a large number of aryl bromides in good yield. However, under the same conditions, little success with the SMCC of cyclopentyl- or cyclohexylboronic acids was found.[102] The findings of these two reports from Molander

et al. are therefore not surprising; greater difficulty was encountered with 5- and 6-membered cycloalkyl BF_3K salts and more forcing conditions were required.

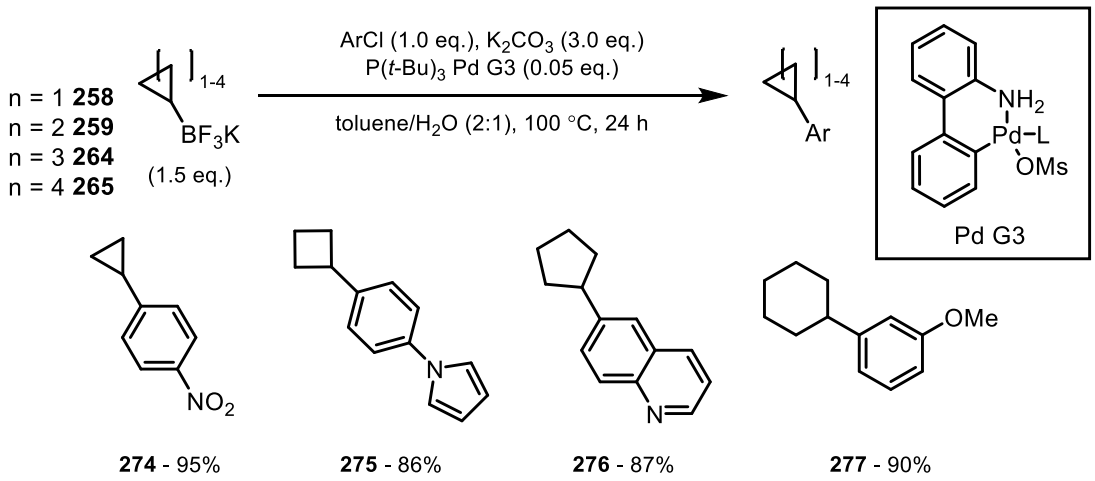
The cross-coupling of cyclopentyl-BF_3K **264** was also carried out by Hoogenband *et al.* using an electron-rich phosphine ligand.[101] Hoogenband *et al.* reported the use of $Pd(OAc)_2$ with RuPhos using K_3PO_4 in a 10:1 mixture of toluene-water at 115 °C. Under these conditions, cyclopentyl-BF_3K **264** was shown to competently cross-couple with aryl bromides although long reaction times were sometimes required (Scheme 3.8). For example, the SMCC of cyclopentyl-BF_3K **264** with 3-bromopyridine afforded arylcyclopentane **273** in 40% yield after 40 hours. It was also reported that the reaction possessed a strong temperature dependence and that the high temperature was necessary for good conversion. However, increasing the reaction temperature further to 130 °C in xylene lowered the conversion due to the generation of by-products.



Scheme 3.8

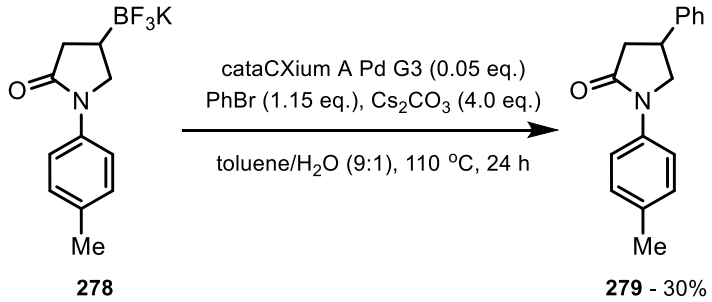
The SMCC of cycloalkyl BF_3K salts was also explored by Biscoe *et al.* in 2014.[103] In this report, the successful cross-coupling of a range of cycloalkyl BF_3K salts was described using the Buchwald precatalyst P(*t*-Bu)$_3$ Pd G3, K_2CO_3 and aryl chlorides in a 2:1 mixture of toluene-water at 100 °C for 24 hours (Scheme 3.9). It was demonstrated that all of the 3-6 membered cycloalkyl BF_3Ks could be cross-coupled with heteroaryl chlorides under these conditions. Although the SMCC reaction conditions were different to those used by Molander *et al.*, the precatalyst still possessed a bulky

electron-rich ligand and the reaction was similarly conducted in toluene at 100 °C using a carbonate base.



Scheme 3.9

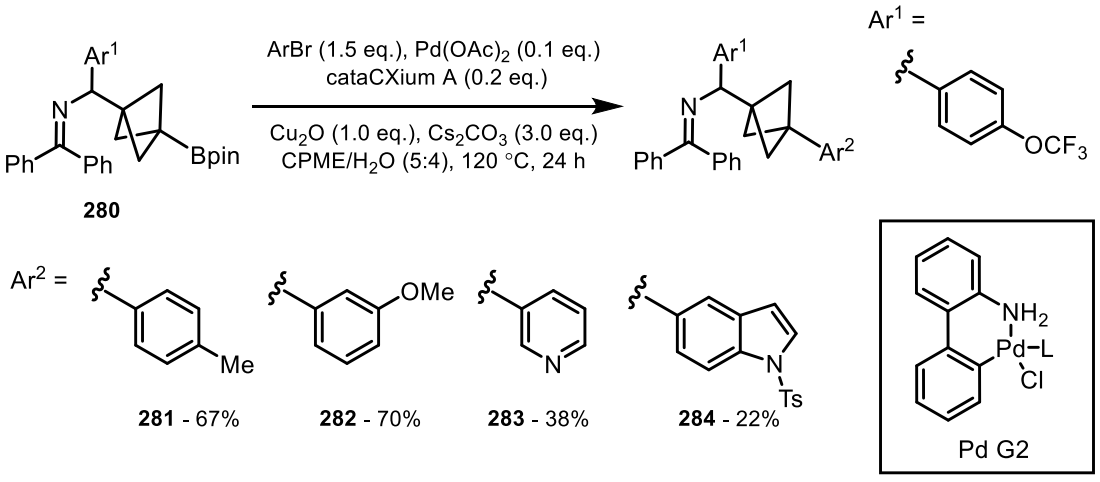
There are very limited examples of the SMCC of heterocycle-containing BF_3K salts. For example, Partridge *et al.* reported a single example of the SMCC of β-BF_3K-pyrrolidone **278** under similar conditions to those used for cycloalkyl BF_3K salts.[104] Having developed methodology for the copper-catalysed synthesis of β-Bpin-*N*-substituted pyrrolidones, Partridge *et al.* demonstrated that the corresponding β-BF_3K-*N*-*p*-tolylpyrrolidone **278** could undergo a SMCC reaction with bromobenzene. The cross-coupling reaction was achieved with the cataCXium A Pd G3 precatalyst and Cs_2CO_3 in a 9:1 mixture of toluene-water at 110 °C for 24 hours. With these conditions, β-BF_3K-pyrrolidone **278** was successfully cross-coupled with bromobenzene to give β-phenylpyrrolidone **279** in 30% yield (Scheme 3.10).



Scheme 3.10

During investigations into the SMCC of benzylamine bicycle[1.1.1]pentyl (BCP) Bpins, Walsh, Hughes and co-workers developed a novel set of SMCC conditions.[105] Having

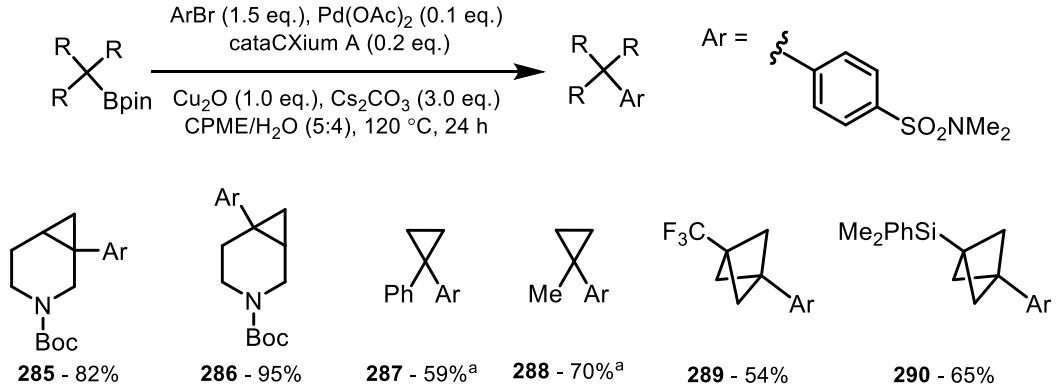
developed methodology for the synthesis of BCP Bpins, Walsh, Hughes and co-workers set out to obtain conditions for the SMCC of these substrates. Through extensive high throughput experimentation, cataCXium A was identified as the best ligand and the necessity of a reaction temperature of 120 °C was recognised. Further screening was then conducted with these two conditions identified and this led to the use of 3.0 equivalents of Cs_2CO_3 in a 5:4 mixture of CPME-water. It was found that increasing the concentration of the reaction to 0.4 M improved the yield and that the use of $Pd(OAc)_2$ instead of the cataCXium A Pd G2 precatalyst eliminated the generation of a co-eluting carbazole side product. Finally, it was hypothesised that the addition of copper(I) oxide would improve the reaction as it had been reported to assist transmetallation in sterically encumbered systems.[106] This proved to be the case and the final SMCC conditions were therefore: 1.5 equivalents of aryl bromide, 0.1 equivalents of $Pd(OAc)_2$, 0.2 equivalents of cataCXium A, 1.0 equivalent of copper(I) oxide and 3.0 equivalents of Cs_2CO_3 in a 5:4 mixture of toluene-water at 120 °C for 24 hours. With these conditions, benzylamine-BCP-Bpin **280** was cross-coupled with a range of aryl bromides and heteroaryl bromides in good yields. A sample of the substrate scope is shown in Scheme 3.11; for example, the cross-coupling of benzylamine-BCP-Bpin **283** with 3-bromopyridine gave aryl-BCP **283** in 38% yield.



Scheme 3.11

Although the SMCC reaction had been optimised for the cross-coupling of BCPs, Walsh, Hughes and co-workers then described its application to other tertiary alkyl Bpin compounds. These cross-coupling reactions were conducted with 4-bromo-*N*,*N*-dimethylbenzenesulfonamide and afforded arylated products in good yields. In particular, the SMCC of 1-Bpin-3-azabicyclo[4.1.0]heptane and 2-Bpin-3-

azabicyclo[4.1.0]heptane gave arylazabicyclo[4.1.0]heptanes **285** and **286** in 82% and 95% yields respectively (Scheme 3.12). These results demonstrated that, whilst not specifically designed for such, these conditions had the potential to enable the SMCC of highly sterically hindered sp^3 Bpin compounds.



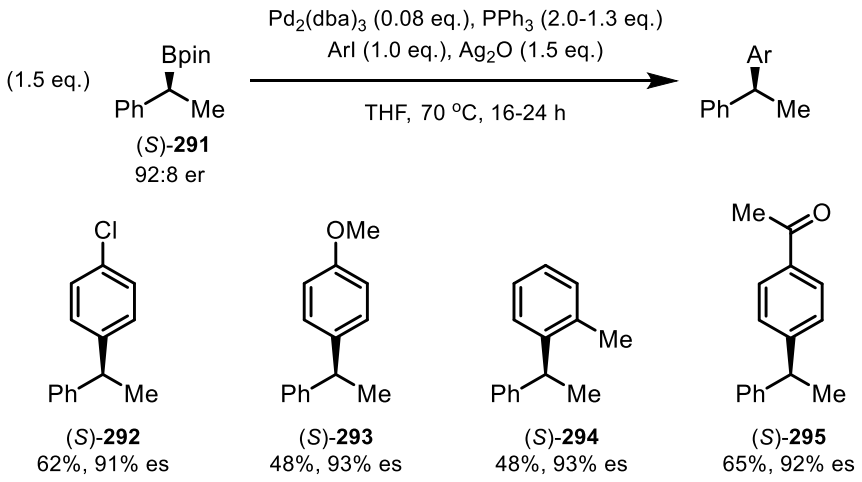
a) 1.5 eq. Alkyl Bpin, 1.0 eq. ArBr

Scheme 3.12

Collectively, these reports show some of the challenges of sp^2-sp^3 SMCC reactions and the reaction conditions that have been developed to overcome these issues. Broadly, the reactions conditions have involved the use of high temperature, carbonate bases and bulky electron-rich phosphine ligands along with $Pd(OAc)_2$. In particular, the results highlight the ability of cataCXium A to facilitate the SMCC of challenging and often sterically encumbered alkyl BF_3K salts and Bpin boronates.

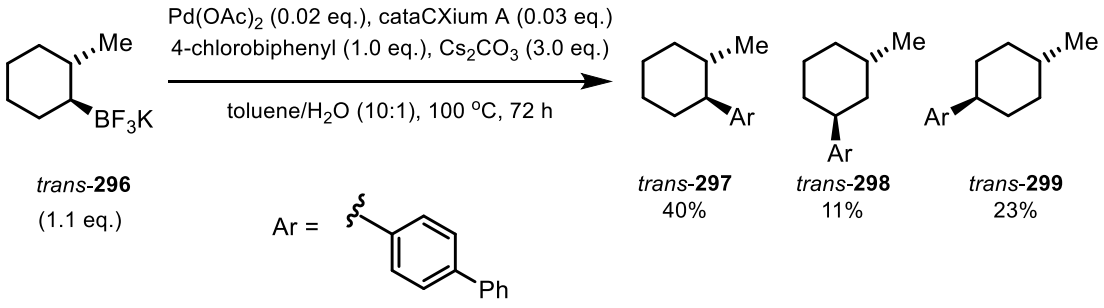
3.1.2 Stereoretentive and Stereoinvertive Suzuki-Miyaura Cross-Coupling of Secondary Alkyl Organoboron Compounds

The first example of a stereospecific SMCC of an acyclic secondary Bpin was reported by Crudden *et al.* in 2009.[107] In this reaction, enantioenriched α-methyl-benzylic-Bpin (*S*)-**291** (92:8 er) was cross-coupled with a range of aryl iodides using $Pd_2(dba)_3$ with PPh_3 and silver(I) oxide in THF and heated at 70 °C for 16-24 hours (Scheme 3.13). Based on a report from Kishi *et al.*, silver(I) oxide was added to the reaction to accelerate the, otherwise slow, transmetallation step.[108] All of the cross-coupling reactions were reported to proceed with high levels of enantiospecificity (es) and afforded biaryl compounds with retention of configuration. For example, the cross-coupling of benzylic-Bpin (*S*)-**291** with 4-chloroiodobenzene gave biaryl (*S*)-**292** in 62% yield and 91% es.



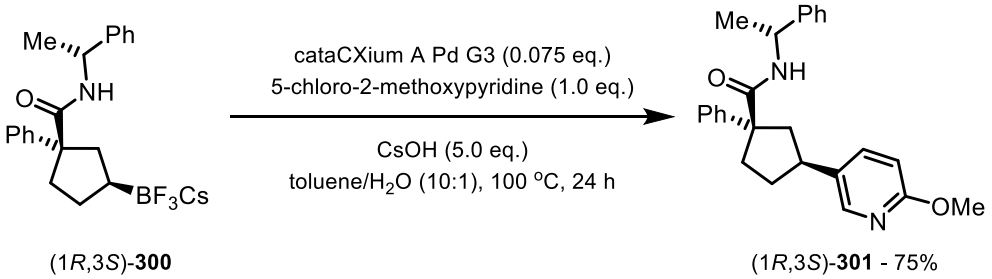
Scheme 3.13

The first example of a SMCC reaction on a cyclic alkylboron compound possessing stereochemical information was reported in 2008 by Molander, Dreher and co-workers.[99] The SMCC of BF_3K-cyclohexane *trans*-**296** with an aryl bromide was carried out using $Pd(OAc)_2$, cataCXium A and Cs_2CO_3 in a 10:1 mixture of toluene-water at 100 °C for 72 hours. Under these reaction conditions, arylcyclohexane *trans*-**297** was obtained in 40% yield as part of an inseparable mixture that also contained *trans*-**298** (11%) and *trans*-**299** (23%) (Scheme 3.14). Regioisomeric arylcyclohexanes *trans*-**298** and *trans*-**299** were formed as a result of β-hydride elimination and reinsertion of the palladium. Importantly, all of the isomers obtained possessed *trans*-stereochemistry due to the palladium staying coordinated to the same face of the cyclohexane ring. This showed that, in all cases, the transmetallation step from boron to palladium had occurred with retention of the original stereochemistry. The major product was 1-aryl-2-methylcyclohexane *trans*-**297** and the selectivity for this regioisomer was improved by using PPh*t*-Bu_2 instead of cataCXium A, albeit with a lower yield.



Scheme 3.14

A different example of the stereoretentive SMCC of a cyclic organoboron compound was provided by Takacs and co-workers.[109] Similar conditions were utilised to those reported by Molander, Dreher and co-workers, namely, using cataCXium A but as the 3rd generation Buchwald precatalyst and with CsOH as the base.[99] As a representative example, under these conditions, cyclopentyl-BF_3Cs (1*R*,3*S*)-**300** was cross-coupled with 5-chloro-2-methoxypyridine to provide arylcyclopentyl (1*R*,3*S*)-**301** in 75% yield; the reaction proceeded with retention of stereochemistry (Scheme 3.15). Takacs and co-workers reported a further seven examples of the stereoretentive SMCC reaction on cyclopentyl BF_3Cs compounds with both aryl bromides and chlorides.



(1*R*,3*S*)-**300** (1*R*,3*S*)-**301** - 75%

Scheme 3.15

Sigman, Biscoe and co-workers conducted a detailed study of the stereoretentive and stereoinvertive pathways of the sp^2-sp^3 SMCC reaction.[90] This was accomplished by carrying out modelling using ligand paramatisation followed by synthetic investigations. Their work demonstrated that judicious choice of the ligand enabled stereocontrol of the SMCC reaction when starting from an enantioenriched alkyl BF_3K compound. The computational and experimental studies led to the conclusion that electron-rich trialkylphosphine ligands promoted a stereoinvertive pathway and that electron-deficient triarylphosphine ligands promoted a stereoretentive pathway. In general, sterically bulky ligands suppressed β-hydride elimination. This led to the selection of the 3rd generation Buchwald precatalyst of $P(Ad)_3$ to facilitate stereoinvertive reactions whilst the 3rd generation precatalyst of either bis-CF_3PhXPhos or bis-CF_3PhSPhos were used for stereoretentive reactions (Figure 3.1).

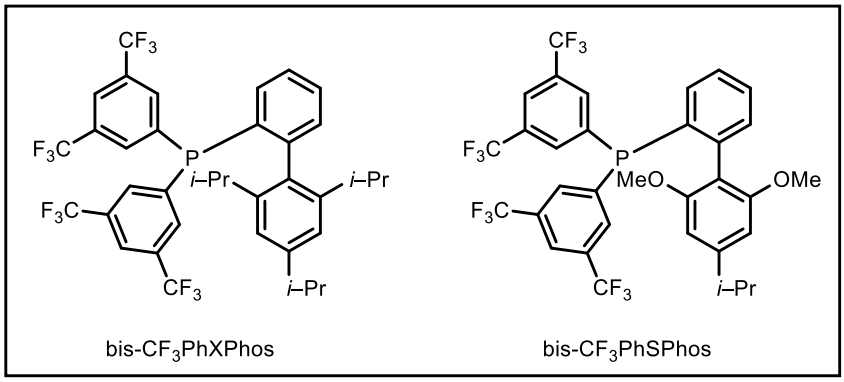
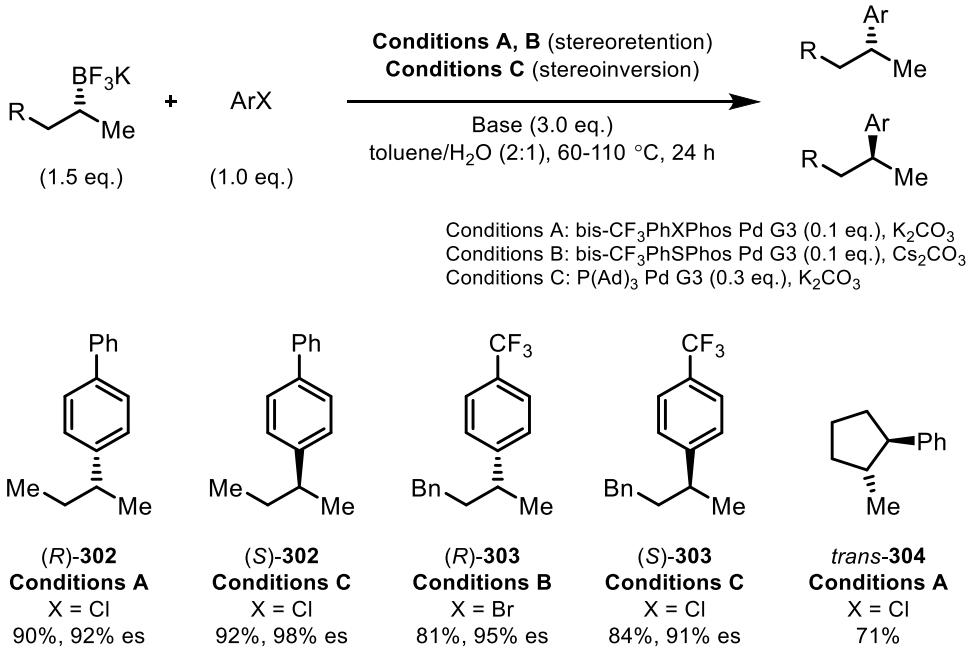


Figure 3.1: Electron-deficient triarylphosphine ligands

With the precatalysts selected, the SMCC reaction was optimised and three sets of conditions were identified, one per ligand; all three conditions used a 2:1 mixture of toluene-water and heating at 100-110 °C for 24 hours whilst using the alkyl BF_3K in excess. A sizeable scope was demonstrated starting from enantioenriched alkyl BF_3Ks (≥97:3 er). By changing the ligand, both enantiomers of arylated alkane compounds could be obtained in high ers (Scheme 3.16). For example, the SMCC reaction of (*R*)-*sec*-butyl-BF_3K under conditions A (bis-CF_3PhXPhos Pd G3, K_2CO_3, 100 °C) and 4-chlorobiphenyl gave arylalkane (*R*)-**302** in 90% yield and with 92% es (stereoinvertive pathway). The opposite enantiomer, arylalkane (*S*)-**302**, could be obtained by using conditions C ($P(Ad)_3$ Pd G3, K_2CO_3, 80 °C) in 92% yield and 98% es (stereoretentive pathway). When the SMCC procedure was applied to *trans*-1-BF_3K-2-methylcyclopentane, with conditions A, the reaction proceeded with retention of stereochemistry as expected, affording arylcyclopentyl *trans*-**304** in 71% yield. However, when the stereoinvertive conditions (conditions C) were applied, inversion was not observed; instead, only a low yield of arylcyclopentyl *trans*-**304** was obtained. Sigman, Biscoe and co-workers proposed that this was due to the cyclopentane ring sterically hindering the approach of the palladium from the back, thus preventing the stereoinvertive pathway.

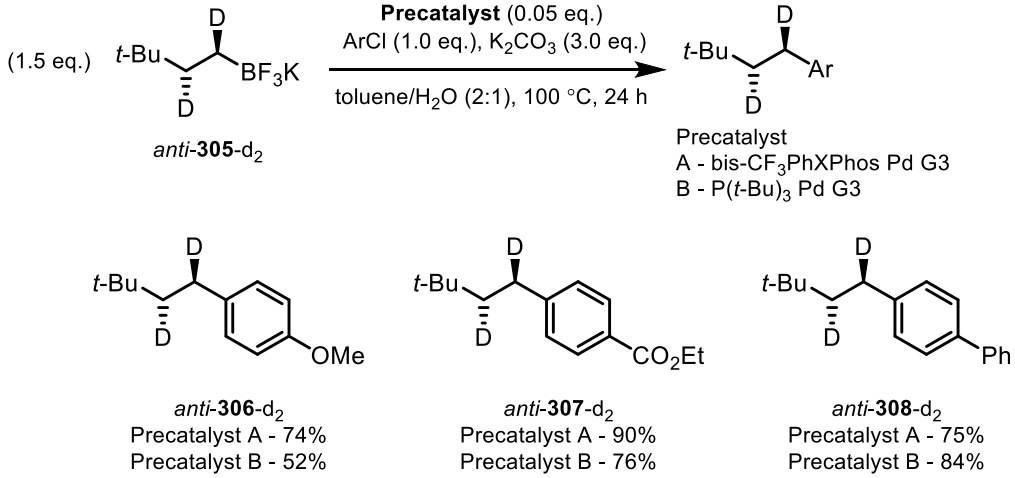


Scheme 3.16

In addition, it was proposed that the reason the stereoinvertive pathway was facilitated by electron-rich trialkylphosphine ligands was due to their strong σ-donating ability. The σ-donation was suggested to stabilise the palladium in the transition state of the stereoinvertive pathway, thus favouring it. Conversely, electron-deficient triarylphosphine ligands were proposed to facilitate the stereoretentive pathway as that transition state was better stabilised by ligands with π-back bonding ability. It was shown that both electron-rich and electron-deficient aryl halides could be cross-coupled without any effect on the enantiospecificity of the reaction. The report of bulky electron-rich phosphine ligands favouring inversion is in contrast to the result reported by Molander, Dreher and co-workers where the use of cataCXium A on BF_3K-cyclohexane *trans*-**296** gave arylcyclohexanes with retention of stereochemistry, although Biscoe *et al.* do propose a reason for this (see Schemes 3.14 and 3.19).[99,110] Overall, Sigman, Biscoe and co-workers demonstrated that the stereochemical outcome of the sp^2-sp^3 SMCC of alkylboron compounds could be controlled by the choice of ligand. In their examples, either enantiomer of the cross-coupled product could be selectively synthesised in high er by choosing either the ligand that favoured the stereoretentive pathway or the stereoinvertive pathway.

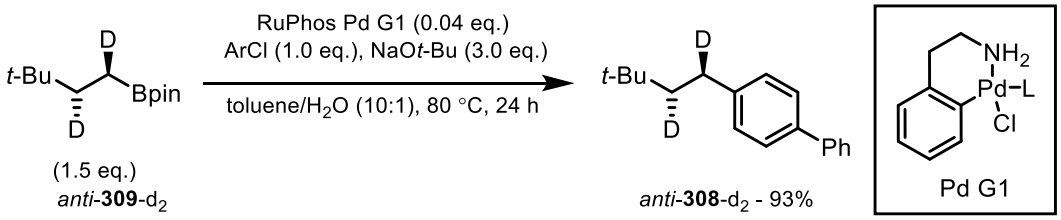
Further investigations from Biscoe *et al.* showed that primary alkyl BF_3K compounds exclusively underwent transmetallation *via* a stereoretentive pathway.[110] When SMCC

reactions of primary alkyl BF_3K compounds were conducted with the bulky and electron-rich 3rd generation precatalyst of P(*t*-Bu)$_3$ (Precatalyst B) under similar conditions to their previous work (conditions C in Scheme 3.16), only stereoretentive products were observed (Scheme 3.17). The same observation was made with bis-CF_3PhXPhos (Precatalyst A): high yields of the stereoretentive products were obtained. For example, the SMCC of dideuterated alkyl-BF_3K *anti*-**305**-d_2 with 4-chloroanisole gave arylalkane *anti*-**306**-d_2 in 74% yield with precatalyst A and 52% yield with precatalyst B; both precatalysts exclusively gave arylalkane *anti*-**306**-d_2.



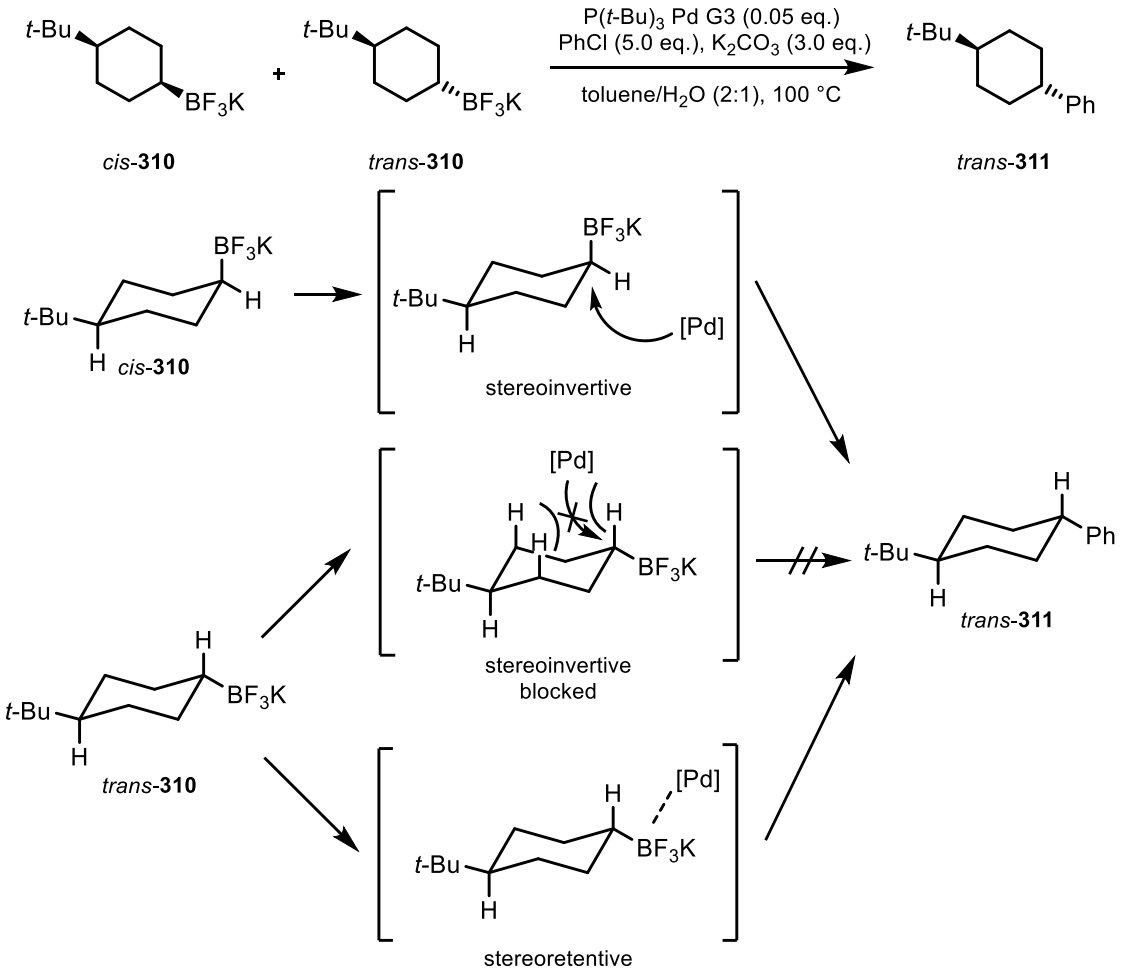
Scheme 3.17

It was noted that the Bpin analogue, alkyl-Bpin *anti*-**309**-d_2, required different SMCC conditions to undergo cross-coupling; no product was obtained using the conditions shown in Scheme 3.17. However, the use of the 1st generation RuPhos precatalyst and NaO*t*-Bu in 10:1 toluene-water at 80 °C enabled the SMCC of alkyl-Bpin *anti*-**309**-d_2. This gave arylalkane *anti*-**308**-d_2 in 93% yield with retention of the *anti*-stereochemistry (Scheme 3.18). From this and other experiments, Biscoe *et al.* concluded that primary alkylboron compounds were unaffected by the properties of the phosphine ligand or the electronics of the aryl halide and always reacted *via* a stereoretentive pathway.



Scheme 3.18

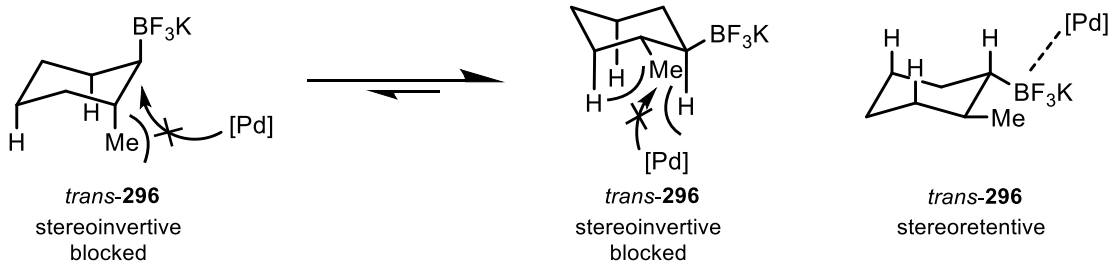
To further examine the effects of steric hindrance on these types of SMCC reactions, Biscoe *et al.* conducted the SMCC on a 5:1 mixture of diastereomeric 1-*tert*-butyl-4-BF_3K-cyclohexanes *cis*-**310** and *trans*-**310**.[110] The SMCC conditions used were: P(*t*-Bu)$_3$ Pd G3 with K_2CO_3, in a 2:1 mixture of toluene-water heated at 100 °C. Under these conditions, stereoinversion would be expected. The kinetics of the reaction were explored by monitoring the progress of each of BF_3K *cis*-**310** and *trans*-**310**. The results indicated the rapid consumption of BF_3K *cis*-**310** to afford 4-phenylcyclohexane *trans*-**311** and then the slower transformation of BF_3K *trans*-**310** which, interestingly, also gave 4-phenylcyclohexane *trans*-**311** (Scheme 3.19). Biscoe *et al.* proposed that this was due to the steric hindrance of the cyclohexane ring. The reaction of BF_3K *cis*-**310** was rapid due to the relatively unhindered approach of the palladium from the back and this gave 4-phenylcyclohexane *trans*-**311** *via* the stereoinvertive pathway. In the case of BF_3K *trans*-**310**, the backside approach was significantly more sterically hindered due to axial repulsion from the nearby 1,3-diaxial protons; in addition, ring-flipping to a conformation with a more reactive equatorial BF_3K was not possible due to the equatorial *tert*-butyl group locking the conformation. Therefore, the reaction of BF_3K *trans*-**310** proceeded significantly more slowly *via* the stereoretentive pathway, which was not the favoured pathway due to the bulky electron-rich phosphine ligand. Overall, this meant that both substrates reacted to give the 4-phenylcyclohexane *trans*-**311**.



Scheme 3.19

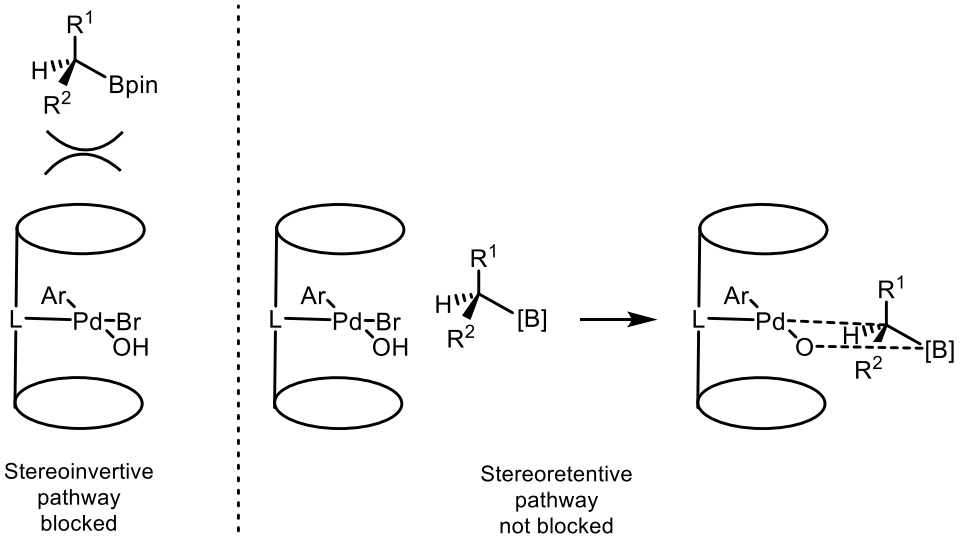
Biscoe *et al.* used the same reasoning to rationalise the observations of Molander, Dreher and co-workers, who had reported that the SMCC of BF_3K cyclohexane *trans*-**296** with 4-bromobiphenyl proceeded with retention of stereochemistry. The reaction was conducted in a 10:1 mixture of toluene-water with $Pd(OAc)_2$, cataCXium A and Cs_2CO_3 and heated at 100 °C for 72 hours (see Scheme 3.14).[99] In this example, the observation of stereoretention when a bulky electron-rich phosphine ligand was used can be explained by the fact that the stereoinvertive pathways from each of the chair conformations of *trans*-**296** were sterically blocked (Scheme 3.20). In the energetically favourable diequatorial conformation, backside attack onto BF_3K *trans*-**296** would be blocked by axial interactions; in the diaxial conformation, attack onto BF_3K *trans*-**296** would be blocked by the proximal methyl group which would now also be axial. Due to the preference for BF_3K *trans*-**296** to adopt the diequatorial conformation, the population of molecules in the diaxial conformation would be low and hence there would be less opportunity to overcome the diaxial methyl interaction to give

arylcyclohexane *cis*-**296**. Therefore, despite the use of a bulky electron-rich ligand, the reaction went *via* the stereoretentive pathway. One key aspect of Biscoe *et al.*'s study was that it highlighted that the effect of the ligand could be overridden by the steric considerations of the substrate, particularly in cyclic systems.



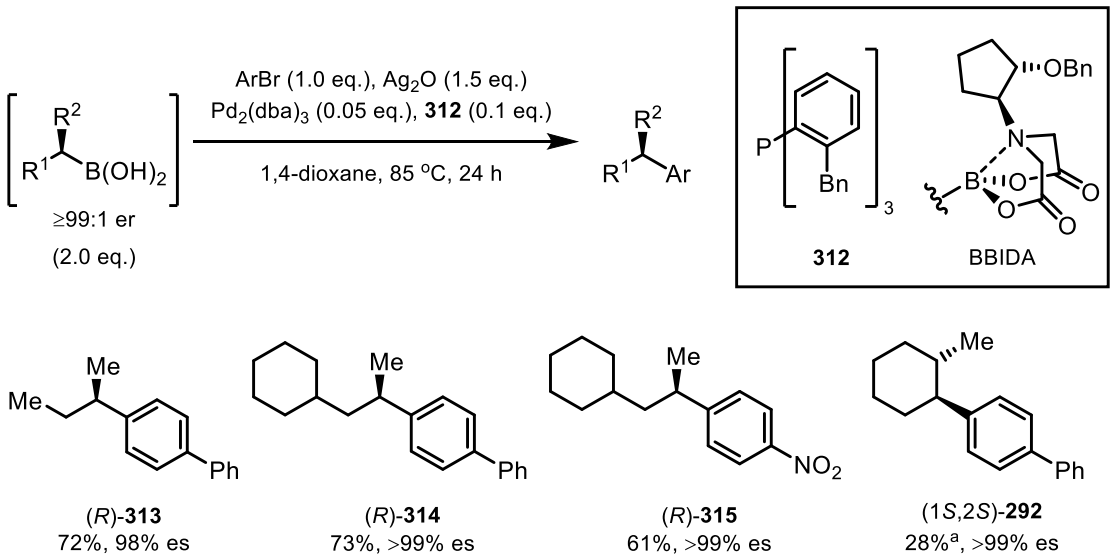
Scheme 3.20

Burke *et al.* reported an example of an sp^2-sp^3 stereoretentive SMCC reaction in which a sterically hindered phosphine ligand was used to block the stereoinvertive pathway.[95] Burke *et al.* proposed that, as the stereoinvertive pathway occurred by attack from the back, this pathway could be blocked through the use of a sterically bulky ligand (Scheme 3.21). Since the catalyst would need to approach the organoboron reagent on an open face, if the ligand possessed large groups above and below the plane of the palladium, the stereoinvertive attack would be disfavoured. Conversely, in the stereoretentive pathway, the catalyst would approach the organoboron reagent in the plane of the palladium, enabling the formation of the 4-membered transition state required for transmetallation (Scheme 3.21).



Scheme 3.21

After ligand optimisation studies, Burke *et al.* identified ligand **312** which gave excellent selectivity for the desired product over regioisomers, as well as near-perfect stereospecificity.[95] Using ligand **312**, the SMCC reactions of a range of alkylboronic acids were investigated and complete retention of stereochemistry was observed in all cases (Scheme 3.22). In each case, the enantioenriched alkylboronic acid was synthesised *in situ* from an alkyl BBIDA compound. BBIDA is a modification of the MIDA group and was used to enable separation of diastereomers. This enabled the synthesis of alkylboronic acids in >99:1 er. The SMCC conditions involved the use of silver(I) oxide with $Pd_2(dba)_3$ and the reactions were heated at 85 °C for 24 hours in 1,4-dioxane. Using these conditions and starting from enantioenriched boronic acids, a range of arylated alkanes were synthesised with high levels of enantiospecificity. For example, the synthesis of arylalkane (*R*)-**313** was accomplished in 72% yield and 98% enantiospecificity. Electron-rich and electron-deficient aryl bromides were tolerated in the reaction although aryl chlorides and triflates did not couple effectively. A key example was the SMCC of *trans*-2-methylcyclohexylboronic acid. The reaction proceeded in low yield using ligand **312**. However, using P(*o*-tol)$_3$ as the ligand instead, a 28% yield of arylcyclohexane (1*S*,2*S*)-**292** with >99% es and complete diastereoselectivity was obtained. It was also noted that no cyclohexane regioisomers were formed from β-hydride elimination and reinsertion.



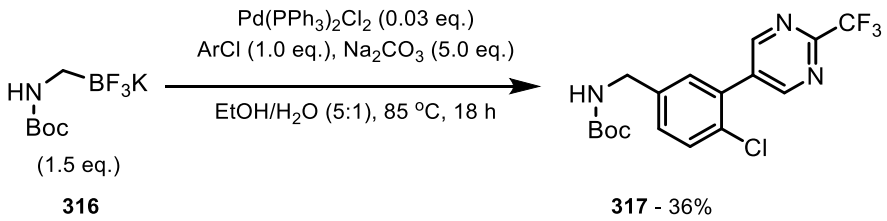
a) P(*o*-tol)$_3$ used

Scheme 3.22

Collectively, these examples show that both the choice of ligand and the structure of the organoboron reagent can have significant effects upon the stereochemical outcome of the SMCC reaction. Primary organoboron compounds afford cross-coupled products with the retention of stereochemistry.[110] However, for secondary organoboron compounds, the situation is more complicated. Careful choice of ligand can be used to selectively favour either the stereoinvertive or stereoretentive pathway and thus offer control of the stereochemical outcome.[90,95] However, in the case of cyclic compounds, steric hindrance caused by substituents or the ring itself can overturn ligand control.[90,95,110] The combination of these factors means that there is no simple set of rules that covers all substrates and, whilst trends can be predicted, each new substrate should be carefully considered.

3.1.3 Suzuki-Miyaura Cross-Coupling of Alkyl Organoborons α to Nitrogen

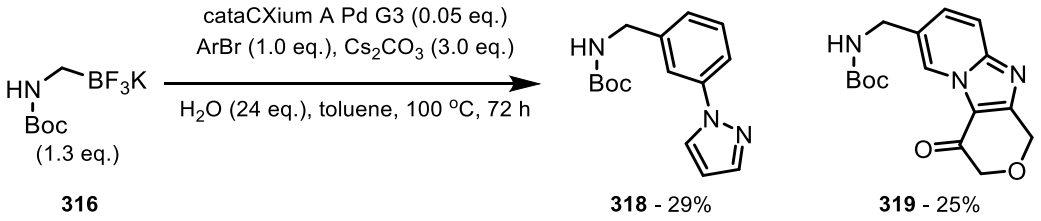
As is the case with primary sp^3 boron reagents, there are a greater number of examples of the SMCC of primary alkyl compounds possessing boron α to nitrogen than similar secondary compounds. This is to be expected as primary compounds will be less sterically hindered and thus the transmetallation will be step easier.[25,111] For example, the cross-coupling of *N*-Boc-aminomethyl-BF_3K **316** has also been performed by H. Chen, M. Volgraf and co-workers at Hoffmann-La Roche on a decagram scale (Scheme 3.23).[112] Excess of *N*-Boc-aminomethyl-BF_3K **316** (1.5 equivalents) was cross-coupled using $Pd(PPh_3)_2Cl_2$ (0.03 equivalents), Na_2CO_3 and 1,4-dichloro-2-[4-(trifluoromethyl)phenyl]benzene in a 5:1 mixture of ethanol-water at 85 °C for 18 hours. No comment was provided on the regioselectivity of the cross-coupling reaction, but it afforded arylaminomethyl-*N*-Boc **317** in 36% yield.



Scheme 3.23

Recently, Dombrowksi, Gesmundo and co-workers at AbbVie conducted an investigation into the sp^2-sp^3 SMCC of a range of alkyl building blocks with four medicinally-relevant, structurally complex aryl bromides using seven different

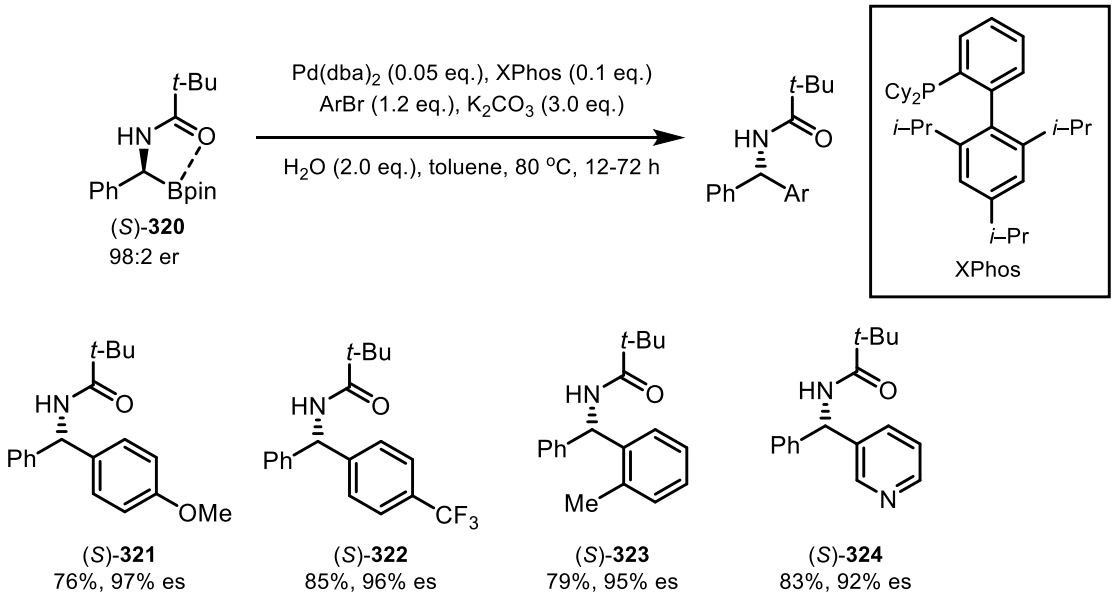
commonly used cross-coupling methodologies.[25] During the screening of cross-coupling methods, the arylation of *N*-Boc-aminomethyl-BF_3K **316** with two of these aryl bromides was carried out. These reactions were performed in toluene using the cataCXium A Pd G3 precatalyst with 3.0 equivalents of Cs_2CO_3 and 24 equivalents of water at 100 °C for 72 hours and afforded arylaminomethyl-*N*-Boc compounds **318** (29% yield) and **319** (25% yield) (Scheme 3.24).[25]



Scheme 3.24

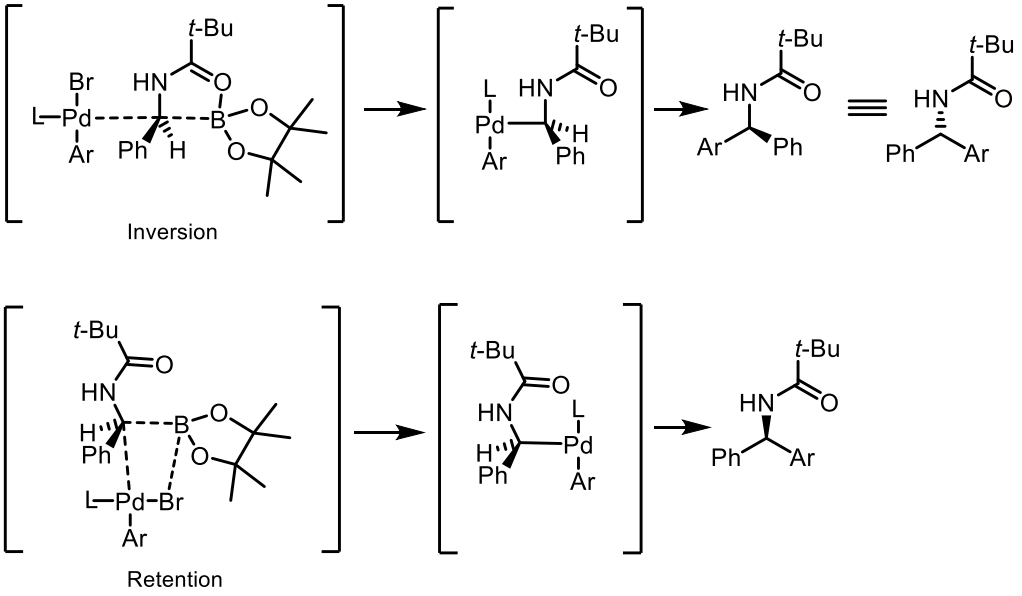
Dombrowksi, Gesmundo and co-workers' examples of the cross-coupling of *N*-Boc-aminomethyl-BF_3K **316** are not unique. Through the work of various groups, it has also been cross-coupled under multiple different conditions using: SPhos Pd G4 and K_2CO_3 in 1,4-dioxane in 11% yield, $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ and K_2CO_3 in 1,4-dioxane in 34% yield, $Pd(OAc)_2$ with cataCXium A and $Et_4N \bullet HBF_4$ in butan-1-ol in 92% yield, amongst other conditions.[113,114,115] The variety of conditions and catalysts used indicate that, whilst in most cases the yields are low, there exist multiple different methods for the SMCC of *N*-Boc-aminomethyl-BF_3K **316** and other primary alkylboron reagents.

Conversely, there are limited examples of the SMCC of secondary sp^3 boron compounds with an α nitrogen; the first report was from Ohmura, Awano and Suginome in 2010.[116] In this work, enantioenriched α-aminobenzyl-Bpin (*S*)-**320** was cross-coupled with aryl bromides using $Pd(dba)_2$, XPhos, K_2CO_3 and 2 equivalents of water. The SMCC reactions were typically heated at 80 °C in toluene for 12-18 hours, although the reaction with 3-bromopyridine was heated for 72 hours. It was shown that the reactions proceeded with inversion of stereochemistry and cross-coupled products were obtained with high enantiospecificity. A selection of examples from their scope studies are shown in Scheme 3.25. For example, cross-coupling with 4-bromoansiole gave biaryl (*S*)-**321** in 76% yield and 97% es. It was noted that the electronic nature of the aryl bromide did not affect the enantiospecificity and, broadly, similar enantiospecificities were observed with all aryl bromides. It was also reported that aryl chlorides gave yields comparable to those achieved with aryl bromides.



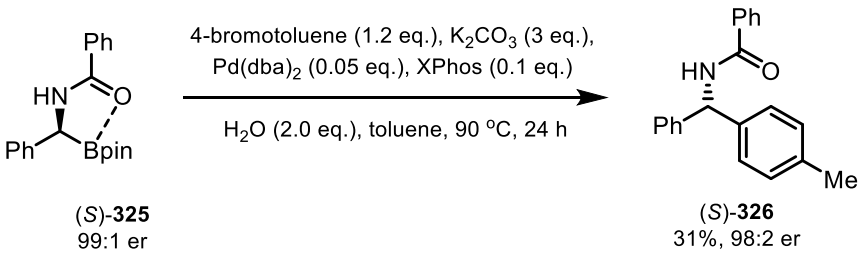
Scheme 3.25

Ohmura, Awano and Suginome reported that the nature of the acyl group had a large effect on the stereospecificity of the reaction; for example, the cross-coupling of an *N*-acetamide with 4-bromotoluene resulted in 59% es, favouring inversion.[96] However, with larger groups such as *N*-benzamide, the es increased to 89%, whilst use of *N*-pivalamide gave 97% es. Clearly, the amide group was influencing the stereochemical outcome. As described in section 3.1.1, there are two possible modes of approach for the palladium catalyst during transmetallation (see Scheme 3.5). It was proposed that during the SMCC reaction of α-aminobenzyl-Bpin (*S*)-**320** the carbonyl oxygen of the amide group coordinated to the boron (Scheme 3.26). As a result, the bulky *tert*-butyl group attached to the amide was in close proximity to the Bpin group. It was suggested that this prevented the approach of palladium from that side of the molecule, hence blocking transmetallation *via* the stereoretentive pathway. As a result, the stereoinvertive pathway was favoured during transmetallation.



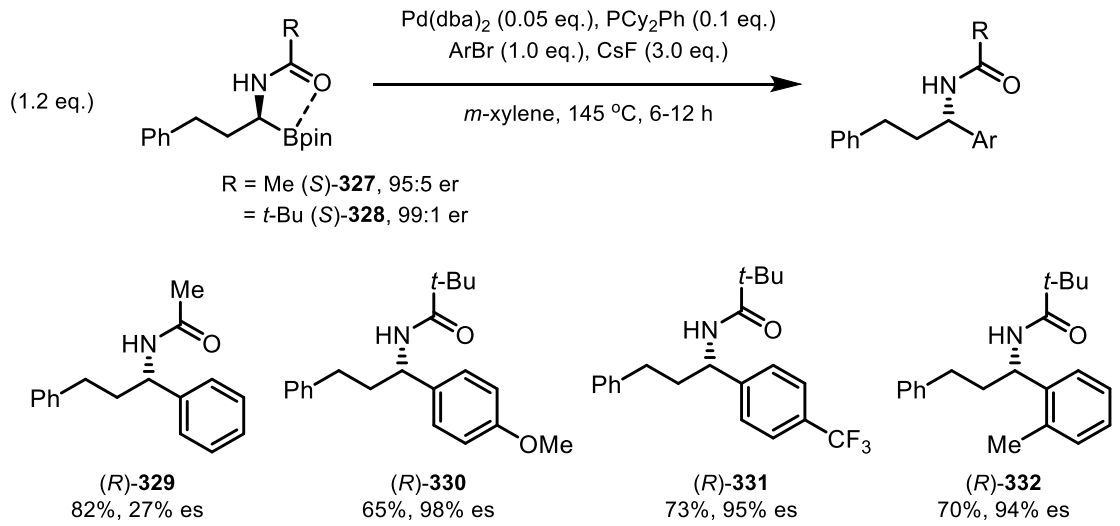
Scheme 3.26

During a study into the asymmetric rhodium-catalysed synthesis of α-amino Bpins, Sawamura *et al.* reported a few examples of the SMCC of enantioenriched secondary alkyl Bpins.[26] One of these examples was the SMCC of α-alkyl-Bpin (*S*)-**325** (99:1 er). The cross-coupling was conducted with 4-bromotoluene (1.2 equivalents) using $Pd(dba)_2$ (0.05 equivalents), XPhos (0.1 equivalents), K_2CO_3 (3.0 equivalents) with 2.0 equivalents of water and the reaction was heated in toluene at 90 °C for 24 hours. Under these conditions, the SMCC reaction afforded biaryl (*S*)-**326** in 31% yield and 98:2 er, the reaction having proceeded with inversion of stereochemistry (Scheme 3.27). Sawamura *et al.* did not provide an explanation for the stereochemical outcome, but the inversion of stereochemistry matched the reports of Ohmura, Suginome and co-workers.[96,116]



Scheme 3.27

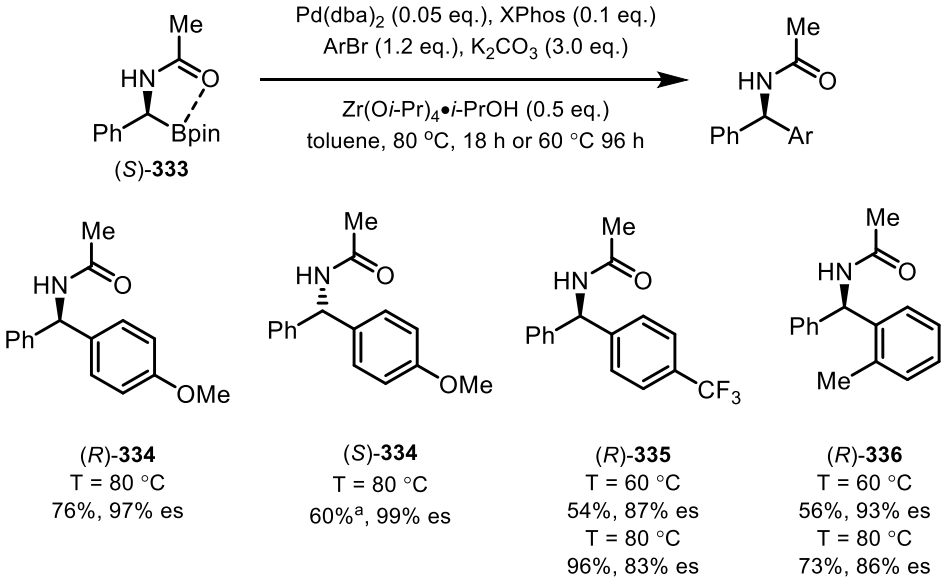
Further to the initial work on α-amino-benzylic Bpins, Ohmura, Suginome and co-workers reported the adaptation of their SMCC methodology to work with α-amino-alkyl Bpins.[96] However, none of the desired SMCC product was obtained when the conditions from Scheme 3.25 were applied to the cross-coupling of acetyl-α-amino-alkyl-Bpin (*S*)-**327**. Ohmura, Suginome and co-workers re-optimised the SMCC conditions and new conditions were developed for the cross-coupling of acetyl-α-amino-alkyl-Bpin (*S*)-**327** (95:5 er). These optimised conditions involved the use of PCy_2Ph, CsF and heating at 145 °C in *m*-xylene. The high temperature required highlighted the difficulty of this sp^2-sp^3 SMCC transformation. The optimised conditions were then applied to pivaloyl-α-amino-alkyl-Bpin (*S*)-**328** (99:1 er), which dramatically improved the enantiospecificity of the reaction (Scheme 3.28). Furthermore, matching previous findings, the SMCC proceeded with inversion of stereochemistry and it was proposed that a carbonyl-boron interaction was responsible for this selectivity (see Scheme 3.26).[116] With these optimised conditions, a scope study was carried out, and selected examples are shown in Scheme 3.28. For instance, the SMCC of pivaloyl-α-amino-alkyl-Bpin (*S*)-**328** with 4-bromoanisole gave arylalkane (*R*)-**330** in 65% yield with 98% es.



Scheme 3.28

Further work by Ohmura, Awano and Suginome demonstrated that the use of additives could be used to control the stereoselectivity of the SMCC reaction of enantioenriched α-amino-benzylic Bpins.[117] It was reported that the addition of 0.5 equivalents of Zr(O*i*-Pr)$_4$•*i*-PrOH reversed the original selectivity of the SMCC reaction so that it instead

proceeded by a stereoretentive pathway. The conditions used in this SMCC were $Pd(dba)_2$, XPhos, K_2CO_3, heated in toluene at 80 °C for 18 hours or at 60 °C for 96 hours and with the use of either a $Zr(O\textit{i}\text{-}Pr)_4$•*i*-PrOH additive for stereoretention or PhOH to favour stereoinversion (Scheme 3.29). For example, the SMCC of acetyl-α-aminobenzyl-Bpin (*R*)-**333** with 4-bromoanisole and the addition of $Zr(O\textit{i}\text{-}Pr)_4$•*i*-PrOH at 80 °C gave biaryl (*R*)-**334** in 76% yield and with 97% es, the reaction proceeding with retention of stereochemistry. If, instead of the use of $Zr(O\textit{i}\text{-}Pr)_4$•*i*-PrOH, 2.5 equivalents of phenol were added, the reaction proceeded with inversion of stereochemistry to give biaryl (*S*)-**334** in 60% yield and with 99% es. Conducting the SMCC reaction at 60 °C compared to 80 °C decreased the yield, but gave a higher es as was evidenced in the SMCCs of 4-bromobenzotrifluoride and 2-bromotoluene. However, the reactions conducted at 60 °C required a significantly longer reaction time of 96 hours.



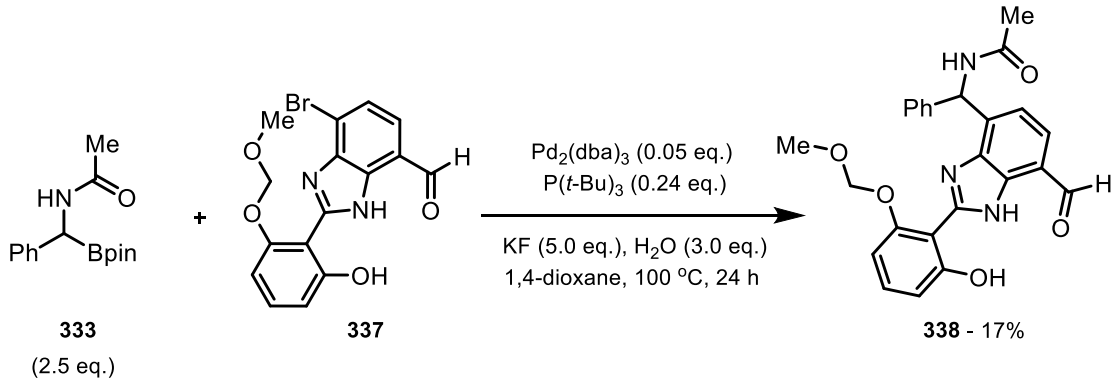
a) 2.5 eq. of PhOH instead of $Zr(O\textit{i}\text{-}Pr)_4$•*i*-PrOH

Scheme 3.29

Ohmura, Awano and Suginome proposed that the change in selectivity with $Zr(O\textit{i}\text{-}Pr)_4$•*i*-PrOH arose due to the disruption of the intramolecular coordination of the carbonyl oxygen to the boron atom, which had been proposed as the reason for the previously observed stereoinversion (see Scheme 3.26).[116] Competitive coordination of zirconium to the amide oxygen would prevent the intramolecular coordination as well as providing steric bulk around the back face of the molecule, thus favouring the

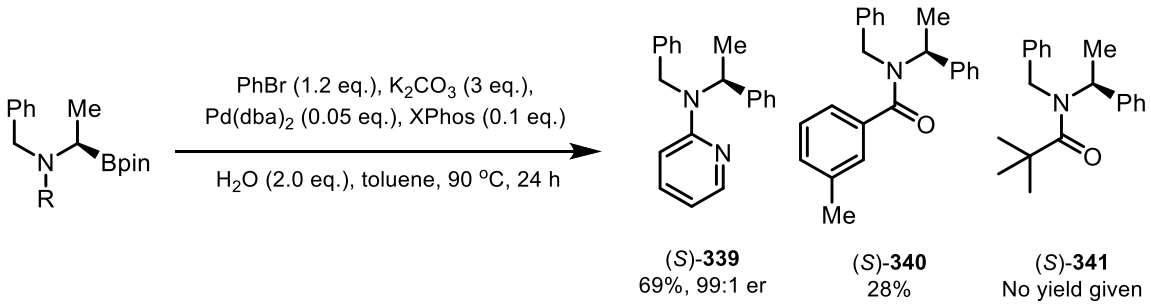
stereoretentive pathway. In conclusion, this report provided an excellent example of the stereocontrol of a SMCC by changing the additive used.

An alternative set of reaction conditions for the SMCC of acetyl α-aminobenzyl-Bpin **333** were reported by Park and Lee during the synthesis of a fluorophore designed to detect cyanide ions.[118] The synthesis of fluorophore **338** involved the SMCC of racemic acetyl-α-aminobenzyl-Bpin **333** with arylbromide **337**. The SMCC used $Pd_2(dba)_3$ (0.05 equivalents) with P(*t*-Bu)$_3$ (0.24 equivalents) and KF (5.0 equivalents) with 3 equivalents of water in 1,4-dioxane heated at 100 °C for 24 hours; this reaction gave fluorophore **338** in 17% yield (Scheme 3.30).



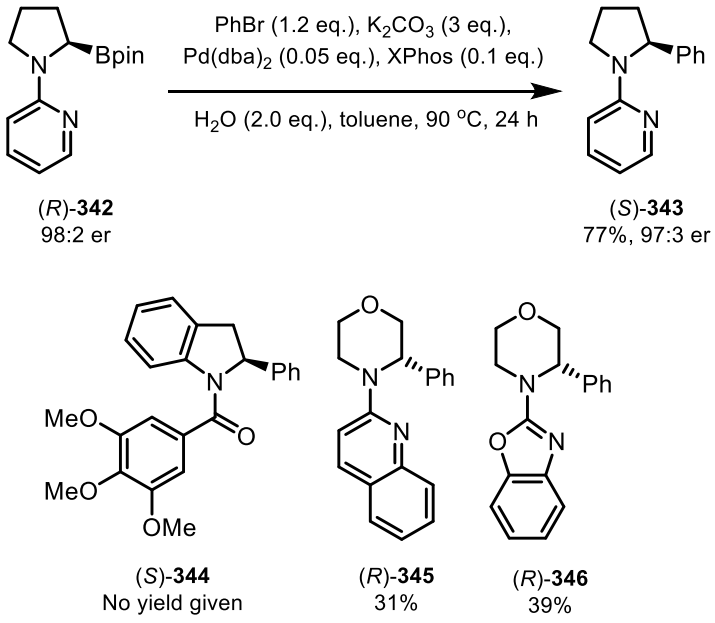
Scheme 3.30

Sawamura *et al.* also reported three more examples of the SMCC of enantioenriched secondary alkyl Bpins.[26] The structures of these compounds were similar to those initially investigated by Ohmura, Awano and Suginome; however, the amine/amide nitrogen was tertiary and possessed a benzyl group.[96,116] The SMCC reactions were conducted with the same conditions as previously reported ($Pd(dba)_2$, XPhos, K_2CO_3, 2.0 equivalents of water, in toluene at 90 °C for 24 hours). Under these conditions, (*R*)-*N*-benzyl-*N*-(1-Bpinethyl)pyridin-2-amine cross-coupled with bromobenzene to give aminobenzyl-α-aryl (*S*)-**339** in 69% yield and 99:1 er with retention of stereochemistry (Scheme 3.31). The er was not reported for either of the other SMCC reactions, although it was noted that both of the other reactions afforded arylated amides with retention of stereochemistry. These results contrast those of Ohmura, Awano and Suginome and no explanation of the stereochemistry is given. It is possible that the presence of the additional benzyl group on the nitrogen adds further steric hindrance and thus prevents backside attack and hence prevents the stereoinvertive pathway from occurring.



Scheme 3.31

In addition to the examples of the SMCC of acyclic alkyl organoborons α to nitrogen, there are just two reports of the SMCC of cyclic compounds. The first of these reports is from Sawamura *et al.* where, further to their acyclic examples, they described the α-arylation of four cyclic borylated compounds with an α nitrogen.[26] The key example was the α-arylation of α-Bpin-*N*-(2-pyridyl)pyrrolidine (*R*)-**342** (98:2 er) with bromobenzene (1.2 equivalents). The same conditions were used as previously noted, ($Pd(dba)_2$, XPhos, K_2CO_3, 2.0 equivalents of water, in toluene at 90 °C for 24 hours) and, under these conditions, the reaction was reported to afford α-phenylpyrrolidine (*S*)-**343** in 77% yield (97:3 er) with retention of stereochemistry (Scheme 3.32).

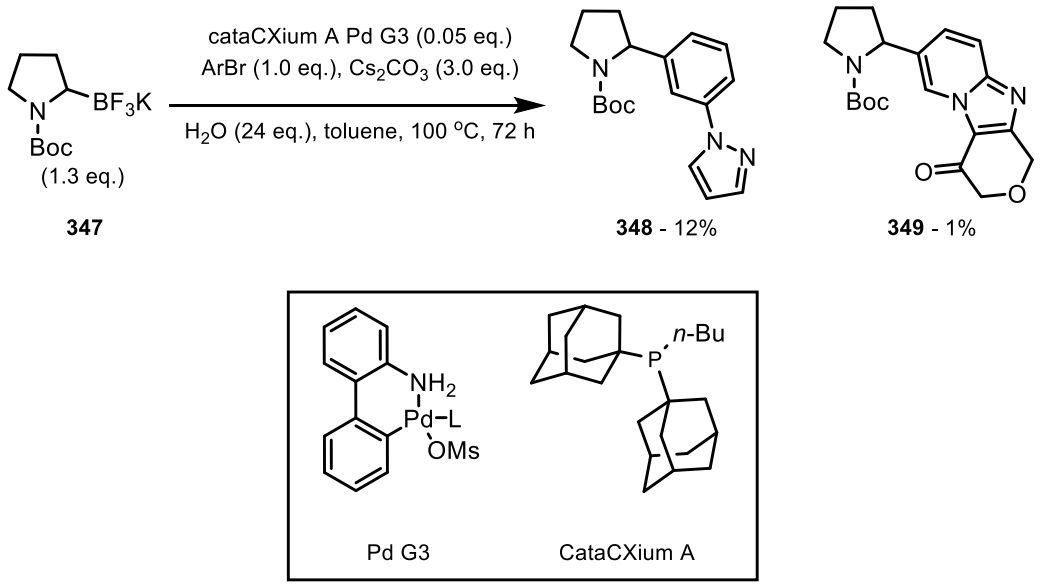


Scheme 3.32

The reason for the success of this SMCC reaction was not proposed by Sawamura *et al.*, although one potential explanation is the proximity of the pyridine nitrogen; the pyridine lone pair could be donating into the empty p orbital of the boron and thus

assisting with the otherwise challenging transmetallation step. Sawamura *et al.* reported that the same SMCC procedure could be conducted on an α-Bpin-indoline to afford (*S*)-**344** and on two α-Bpin *N*-functionalised morpholines to give (*S*)-**345** (31% yield) and (*S*)-**346** (39% yield) (Scheme 3.32). The er was not reported for the other SMCC reactions as these reactions had been performed to confirm absolute stereochemistry and only optical rotation data was provided. Nevertheless, it was shown that each of these reactions proceeded with retention of stereochemistry. Both of the substrates with aryl groups on the amine nitrogen atom possess a nitrogen atom in the 2-position of the aromatic ring, potentially giving support to the idea that the SMCC reaction is facilitated by the donation of lone pairs from the aryl group. For the substrate without an aryl group present on the nitrogen atom, there was an amide group and it is instead possible that the carbonyl group was donating electron density into the empty p orbital of the boron. However, it should be noted that the article in which Sawamura *et al.*'s SMCC work was published has since been retracted for the falsification of data, although it is unclear whether these SMCC reactions are specifically retracted.

The second report is that of Dombrowksi, Gesmundo and co-workers where, alongside the other medicinally-relevant fragments investigated, the SMCC of α-BF_3K-*N*-Boc-pyrrolidine **347** was described.[25] The same SMCC conditions were used as with *N*-Boc aminomethyl-BF_3K **316** (cataCXium A Pd G3 precatalyst, Cs_2CO_3, 24 equivalents of water in toluene at 100 °C for 72 hours). Under these conditions, the SMCC of α-BF_3K-*N*-Boc-pyrrolidine **347** gave α-arylpyrrolidines **348** in 12% yield and **349** in only 1% yield (Scheme 3.33). It should be noted that the cross-coupling of α-BF_3K-*N*-Boc-pyrrolidine **347** by nickel-catalysed photoredox chemistry gave α-arylpyrrolidine **347** in 40% yield. Although it was possible to obtain α-aryl-*N*-Boc-pyrrolidines, the reaction was clearly far from optimal.



Scheme 3.33

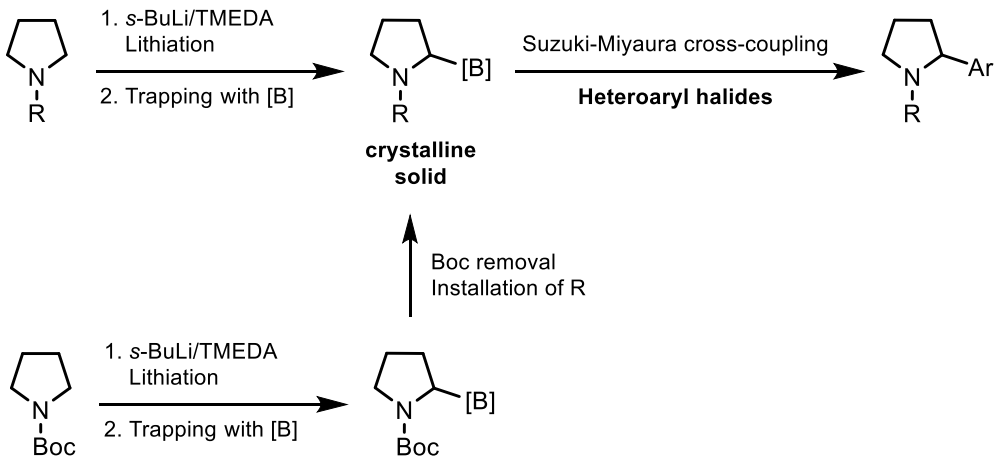
In summary, the work of Ohmura, Suginome and co-workers, Sawamura *et al.* and Dombrowksi, Gesmundo and co-workers represent the only examples of the palladium-catalysed SMCC of a secondary sp^3 boron reagent α to nitrogen.[26,25,116,117,118] There are then only two reports containing the SMCC of α-boryl pyrrolidines and no reports of the SMCC of α-boryl piperidines.[26,25] Although the cross-coupling of these substrates can be achieved with photocatalysis (see Chapter 1), the palladium-catalysed cross-coupling of α-boryl pyrrolidines and piperidines has not been investigated in detail.

3.2 Proposed Approaches and Objectives

The aim of this work was to investigate alternative methods for the α-arylation of *N*-substituted pyrrolidines *via* the SMCC of α-[B] pyrrolidines where [B] = Bpin, BF_3K or $B(OH)_2$. As outlined in section 1.1, a wide range of successful methods for the α-arylation of pyrrolidines exist, perhaps the most prominent amongst these is the lithiation-transmetallation-Negishi cross-coupling methodology of *N*-Boc-pyrrolidine developed by Campos *et al.*.[12] This methodology utilises lithiation with *s*-BuLi/(–)-sparteine followed by transmetallation with $ZnCl_2$ and subsequent palladium-catalysed cross-coupling to afford α-aryl-*N*-Boc-pyrrolidines (see Scheme 2.26). Due to the use of (–)-sparteine, the lithiation is asymmetric and affords products in high er although TMEDA can be used instead to afford racemic α-arylpyrrolidines. There are a range of other methods available for the α-arylation of pyrrolidines, most of which utilise photoredox catalysis, although both electrochemistry and imine formation have also been used; these were summarised in section 1.1. The most notable of these methodologies are the enantioselective nickel-catalysed photoredox cross-coupling reported by Huo *et al.*, particularly because of the lack of requirement of a directing group or prefunctionalisation.[119] Also important are the thioamide directed C-H activation cross-coupling initially reported by Yu and co-workers and subsequently developed by Zhang, Gong and co-workers.[16,15] These reactions are important due to their ability to afford enantioenriched α-arylpyrrolidines and are potentially the most powerful methods currently available to medicinal chemists.

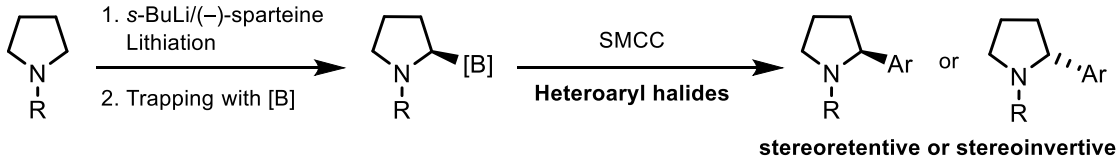
However, as outlined in section 3.1.3, there are only two reports of the SMCC of α-[B] pyrrolidines: two low yielding examples (≤12%) using α-BF_3K-*N*-Boc-pyrrolidine **347** described by Dombrowksi, Gesmundo and co-workers (see Scheme 3.33) and one example using α-Bpin-*N*-(2-pyridyl)pyrrolidine (*R*)-**342** reported by Sawamura *et al.* (see Scheme 3.32) (although, as previously noted, this manuscript has now been retracted for the falsification of data).[25,26] Therefore, the aim of this work was to improve upon these initial SMCC reports and to provide a synthetically simple, reliable and robust method for the α-arylation of pyrrolidine *via* a palladium-catalysed SMCC process (Scheme 3.34). Our plan was that the cross-coupling would be performed with aryl halides and bench-stable and ideally crystalline α-[B] pyrrolidines. This should deliver methodology that would be amenable to rapid screening with different conditions and/or aryl halides. Ideally, the reaction would be compatible with heteroaryl

halides which would allow for the easy screening of chemical space during medicinal chemistry programmes in industry or academia. For this methodology to be useful, a simple gram-scale route for the synthesis of the *N*-substituted-α-[B] pyrrolidines would be required. Thus, we planned to study routes to different *N*-substituted-α-[B] pyrrolidines either by direct borylation, by lithiation-trapping or through lithiation-trapping and protecting/directing group manipulation. After that, we planned to identify suitable reaction conditions for the SMCC reaction of these substrates.



Scheme 3.34

It was also desirable to be able to synthesise α-aryl pyrrolidines as single enantiomers as most of the existing α-arylation methods afford racemic products. Our approach to this was to perform an asymmetric lithiation-trapping of *N*-Boc-pyrrolidine **5** to afford enantioenriched α-[B] pyrrolidines and then investigate reaction conditions for stereoretentive or stereoinvertive SMCC reactions (Scheme 3.35).



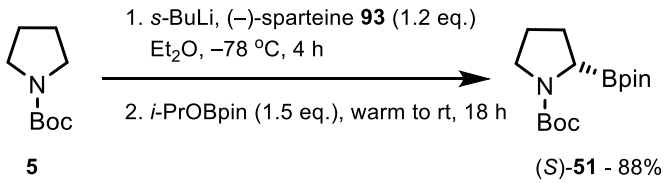
Scheme 3.35

3.3 Synthesis of α-Borylated Pyrrolidines and Piperidines

To investigate the sp^2-sp^3 SMCC reactions of α-borylated nitrogen heterocycles, a range of appropriate substrates was required. As well as exploring the pyrrolidine system, it was decided to include piperidines in our studies for comparison. The required α-borylated pyrrolidines and piperidines were synthesised either through lithiation-trapping and subsequent *N*-functionalisation or through direct borylation.

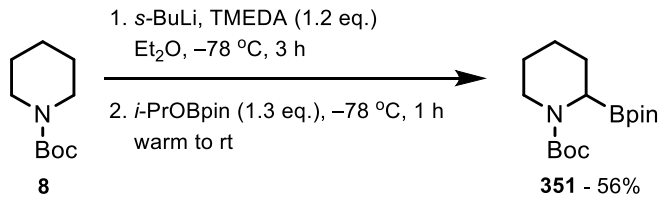
3.3.1 Synthesis of α-Borylated Pyrrolidines and Piperidines *via N*-Functionalisation

One of our approaches to the synthesis of α-borylated pyrrolidines and piperidines was lithiation-borylation of the corresponding *N*-Boc heterocycle followed by conversion of the *N*-Boc group into a range of different *N*-substituents. The lithiation-borylation reactions of *N*-Boc-pyrrolidine and piperidine are well precedented. For example, the synthesis of α-Bpin-*N*-Boc-pyrrolidine **51** was first performed by Whiting *et al.* during investigations into the synthesis of enantioenriched α-$B(OH)_2$-*N*-Boc-pyrrolidine **350**.[120] Lithiation of *N*-Boc-pyrrolidine **5** with *s*-BuLi/(–)-sparteine **93** in Et_2O at –78 °C for 4 hours followed by trapping with *i*-PrOBpin was reported to give enantioenriched α-Bpin-*N*-Boc-pyrrolidine (*S*)-**51** in 88% yield (Scheme 3.36). The er of α-Bpin-pyrrolidine (*S*)-**51** was not reported, although a similar approach with $B(Oi\text{-}Pr)_3$ and subsequent hydrolysis afforded α-$B(OH)_2$-pyrrolidine (*S*)-**350** in 95:5 er.



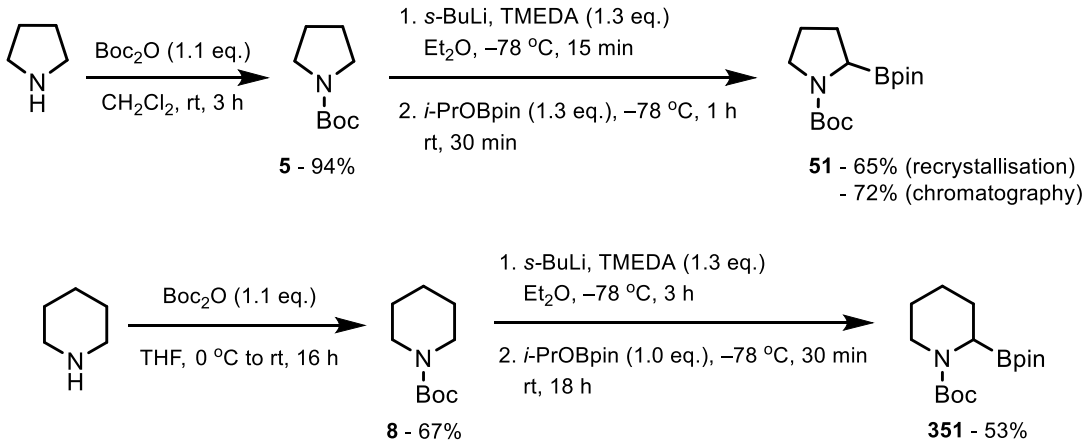
Scheme 3.36

The synthesis of the piperidine analogue, α-Bpin-*N*-Boc-piperidine **351**, was first reported by Aggarwal and co-workers.[121] Lithiation of piperidine **8** was performed with *s*-BuLi/TMEDA in Et_2O at –78 °C for 3 hours; the lithiated intermediate was then trapped with *i*-PrOBpin and upon acidic work-up afforded α-Bpin-piperidine **351** in 56% yield (Scheme 3.37).



Scheme 3.37

The synthesis of α-Bpin-pyrrolidine **51** and α-Bpin-piperidine **351** were conducted following the procedures of Whiting *et al.* and Aggarwal and co-workers. First, the *N*-Boc heterocycles **5** and **8** were readily prepared by reaction with Boc_2O (Scheme 3.38), then racemic lithiation-trapping reactions were carried out. Lithiation of *N*-Boc-pyrrolidine **5** and *N*-Boc-piperidine **8** were achieved using *s*-BuLi/TMEDA in Et_2O at –78 °C. Trapping the lithiated intermediates with *i*-PrOBpin afforded α-Bpin-pyrrolidine **51** and α-Bpin-piperidine **351** in 72% and 53% yields respectively after chromatography (Scheme 3.38). It was discovered that the purification of α-Bpin-pyrrolidine **51** could be simplified and that chromatography was not necessary. After aqueous work-up, the crude product could be dissolved in the minimum amount of boiling hexane and then allowed to slowly cool to rt. This afforded large quartz-like crystals of pure α-Bpin-pyrrolidine **51**. The melting point of α-Bpin-pyrrolidine **51** was determined to be 72-73 °C, so it was not clear if the purification was a result of recrystallisation, or simply the melting and solidifying of α-Bpin-pyrrolidine **51**. This improvement enabled α-Bpin-pyrrolidine **51** to be synthesised on a large scale without the need for chromatography and, in one example, over 8 g (65% yield) of α-Bpin-pyrrolidine **51** was produced.



Scheme 3.38

An X-ray crystal structure of α-Bpin-pyrrolidine **51** was obtained (Figure 3.2). This showed that in the solid state the carbonyl of the Boc group pointed toward the boron, which sat perpendicular to the carbonyl oxygen such that p orbital would align with the oxygen. However, the boron still appeared to possess sp^2 hybridisation, rather than sp^3, suggesting the oxygen was not fully co-ordinated. The x-ray crystal structure also highlighted the steric hindrance of the system.

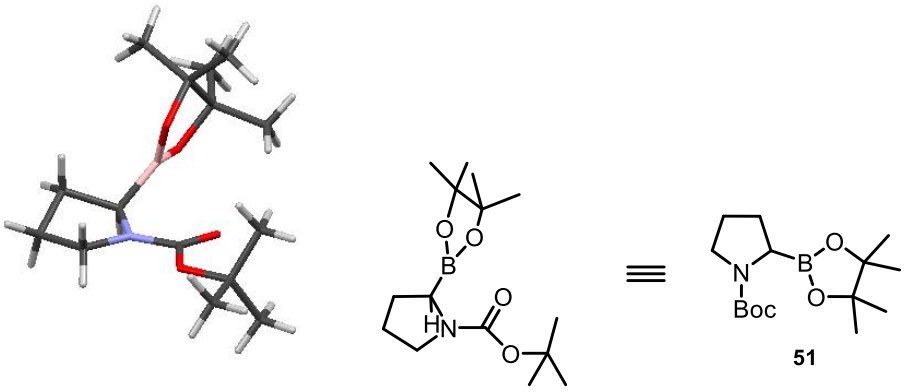
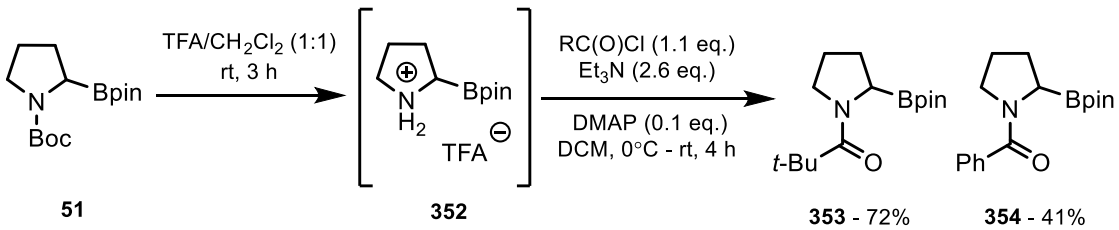


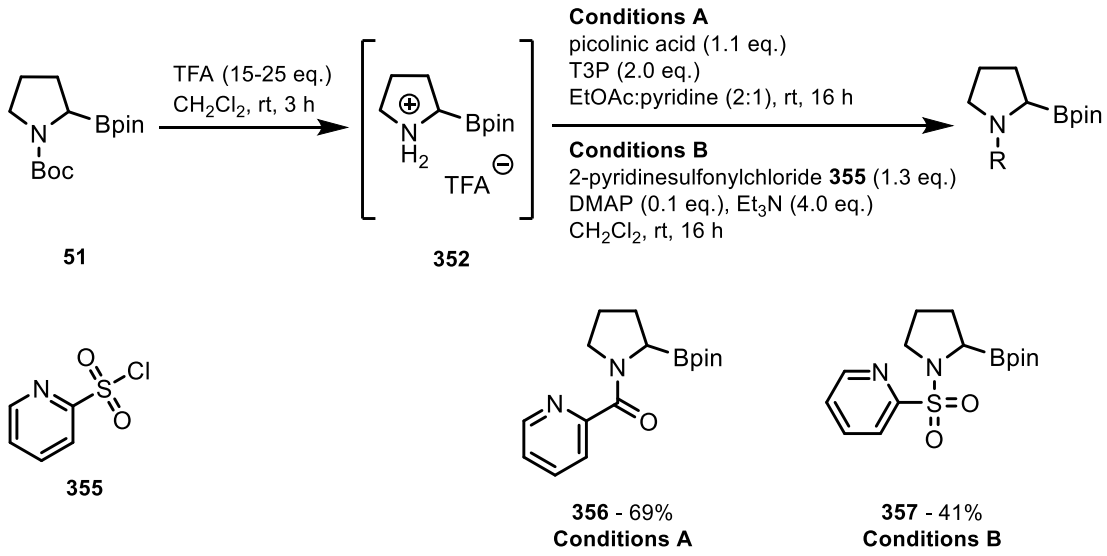
Figure 3.2: X-ray crystal structure of α-Bpin-*N*-Boc-pyrrolidine **51**

With good routes to α-Bpin-*N*-Boc-pyrrolidine **51** and piperidine **351** in hand, the synthesis of analogues with different *N*-substituents was explored. The quickest way to synthesise these compounds would be *via* Boc removal (with TFA) and *N*-functionalisation. This could be achieved in a one-pot process from material that was readily available and would avoid the need for complex or expensive catalysts or ligands. A previous member of the group had successfully synthesised α-Bpin-*N*-pivaloylpyrrolidine **353** and α-Bpin-*N*-benzoylpyrrolidine **354** *via* this methodology in 72% and 41% yields respectively (Scheme 3.39).[122]



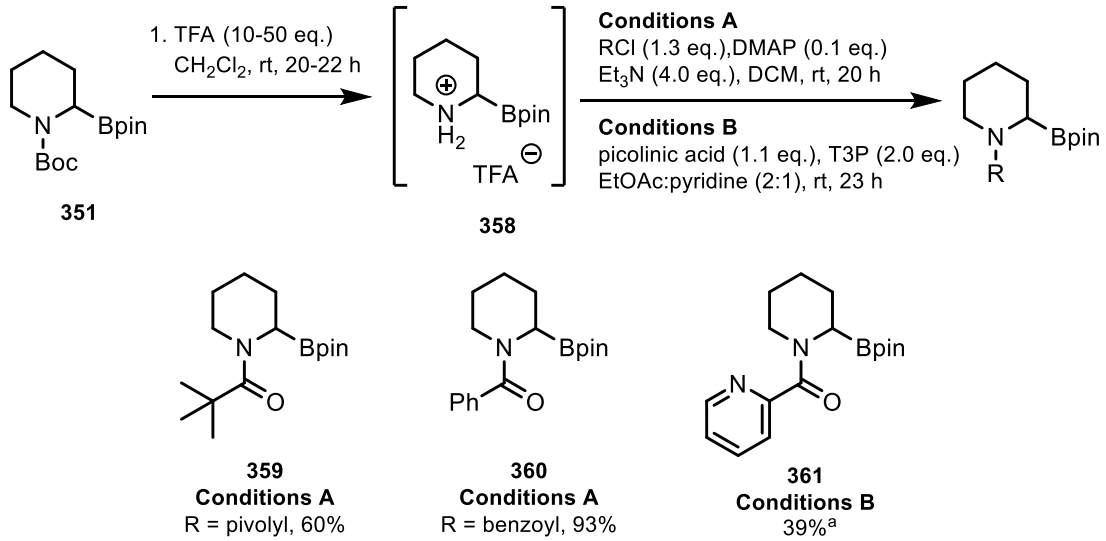
Scheme 3.39

Following the route used previously in the group, the synthesis of two further *N*-functionalised α-Bpin-pyrrolidines were conducted using Boc removal with TFA to give TFA salt **352** and subsequent *N*-functionalisation. To enable this, 2-pyridinesulfonyl chloride **355** was synthesised, following a literature procedure,[123] in 59% yield by stirring 2-thiopyridine with HCl and sodium hypochlorite in CH_2Cl_2 at 5 °C for 15 min. Without isolation, the α-Bpin TFA salt **352** was treated with picolinic acid and the amide coupling reagent T3P (conditions A) or with 2-pyridinesulfonyl chloride **355**, DMAP and Et_3N (conditions B). These reactions afforded α-Bpin-*N*-2-pyridinoylpyrrolidine **356** and α-Bpin-*N*-(pyridine-2-sulfonyl)pyrrolidine **357**, both in 40% yield (Scheme 3.40).



Scheme 3.40

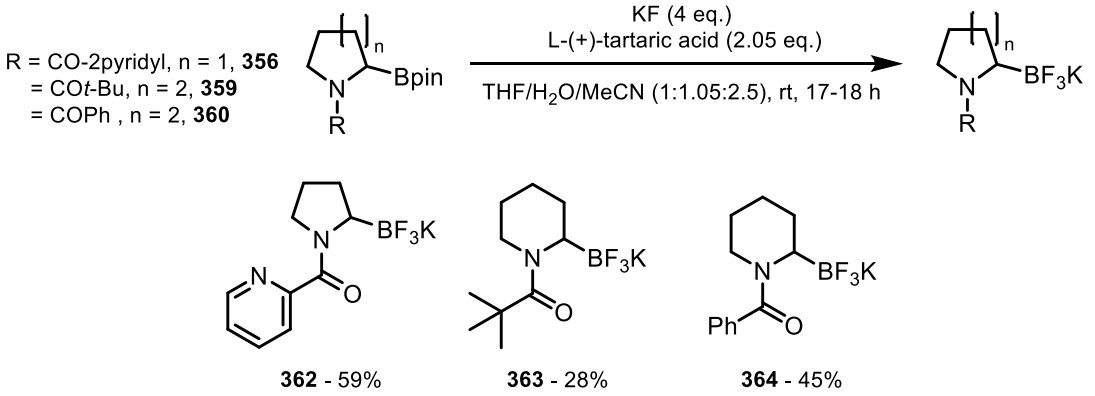
The same Boc removal-*N*-functionalisation strategy was applied to α-Bpin-*N*-Boc-piperidine **351** as a route to α-Bpin-*N*-functionalised piperidines. First, Boc removal was performed on α-Bpin-piperidine **351** using excess TFA to afford the α-Bpin-piperidine TFA salt **358** as a crude product. ^{1}H NMR spectroscopy confirmed the presence of the desired salt. Therefore, functionalisation with pivaloylchloride, benzoylchloride and picolinic acid were carried out to afford α-Bpin-*N*-pivaloylpiperidine **359** (60% yield), α-Bpin-*N*-benzoylpiperidine **360** (93% yield) and α-Bpin-*N*-2-pyridinoylpiperidine **361** (39% yield) (Scheme 3.41).



a) 89% pure by ^{1}H NMR spectroscopy

Scheme 3.41

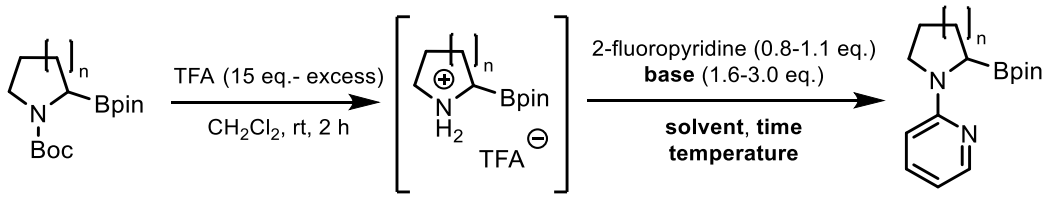
Having successfully synthesised *N*-functionalised α-Bpin-pyrrolidines and piperidines, portions of three of these compounds, pyrrolidine **356** and piperidines **359** and **360** were converted into BF_3K salts. Lloyd-Jones and Lennox reported that the use of tartaric acid and KF during BF_3K salt formation is a safer and more operationally simple method than previously existing methods that typically use KHF_2.[124] This is because isolation is easier and glassware etching is prevented. The conversion to BF_3K salts was effected using Lloyd-Jones and Lennox's methodology with 4 equivalents of KF and 2.05 equivalents of tartaric acid in a mixture of THF, water and methanol. The desired BF_3K salts α-BF_3K-*N*-2-pyridinoylpyrrolidine **362**, α-BF_3K-*N*-pivaloylpiperidine **363** and α-BF_3K-*N*-benzoylpiperidine **364** were successfully obtained in 59%, 28% and 45% yields respectively (Scheme 3.42).



Scheme 3.42

α-Bpin-*N*-(2-pyridyl)pyrrolidine **342** was one of the substrates that had been reported to successfully undergo a SMCC by Sawamura *et al.* (see Scheme 3.32) and had been synthesised *via* rhodium-catalysed borylation. To avoid the use of rhodium catalysis, the synthesis of α-Bpin-*N*-(2-pyridyl)pyrrolidine **342** by Boc removal (with TFA) and then treating with base and 2-fluoropyridine (in an effort to facilitate an S_NAr reaction) had previously been attempted by another member of the group (Table 3.1).[122] The reaction of pyrrolidine TFA salt **352** with *n*-BuLi had been attempted based on a similar procedure reported by Singaram *et al.* for the synthesis of *N*-(2-pyridyl)pyrrolidine **365** *via* an S_NAr reaction.[125] However, neither of those reactions were successful (entries 1 and 2). It was possible that the *n*-BuLi was adding to the boron rather than deprotonating the pyrrolidine TFA salt **352**, so we attempted the reaction with 2.5 equivalents of the more sterically hindered *s*-BuLi in Et_2O. Unfortunately, this reaction gave only traces of the desired *N*-(2-pyridyl)pyrrolidine **342** (detected by HRMS) (entry 3). The synthesis of α-Bpin-*N*-(2-pyridyl)piperidine **366** was also attempted *via* this methodology, using DIPEA as the base in DMF; however, this too was unsuccessful (entry 4).

Table 3.1: Attempted synthesis of α-Bpin *N*-(2-pyridyl)pyrrolidine **342** and piperidine **366** by S_NAr reactions



n = 1, **51**
n = 2, **351**

n = 1, **352**
n = 2, **358**

n = 1, **342**
n = 2, **366**

Entry	n	Base	Solvent	Time / h	Temperature / °C	Yield / %
1	1	Na_2CO_3	MeCN	1.5	150	-[a]
2	1	*n*-BuLi	THF	16	0 then rt	-[a]
3	1	*s*-BuLi	Et_2O	17	–78 then rt	trace
4	2	DIPEA	DMF	6	50	-

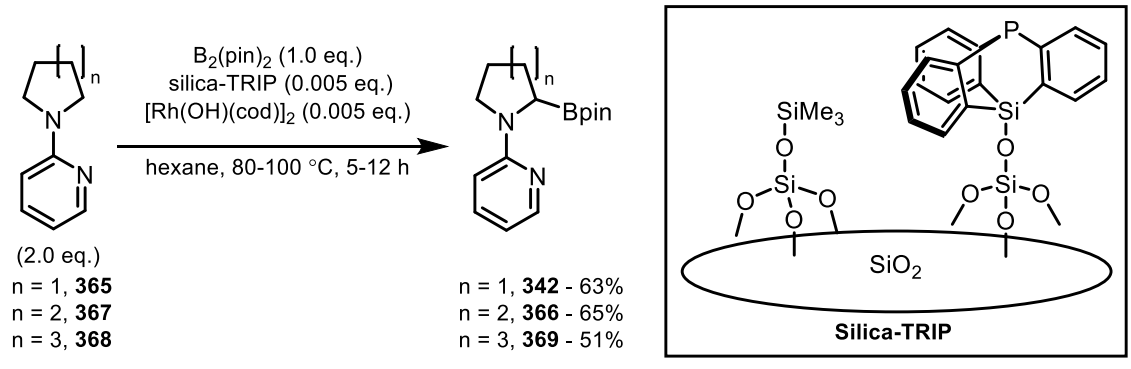
a) Reaction performed by another member of the group

In conclusion, through Boc removal with TFA and *N*-functionalisation, five Bpin *N*-substituted heterocycles were synthesised, two Bpin-pyrrolidines: *N*-2-pyridinoylpyrrolidine **355** and *N*-(pyridine-2-sulfonyl)pyrrolidine **356** along with three Bpin-piperidines: *N*-pivaloylpiperidine **359**, *N*-benzoylpiperidine **360** and *N*-2-pyridinoylpiperidine **361**. Using KF and tartaric acid, three of these substrates were converted into BF_3K *N*-substituted heterocycles: *N*-2-pyridinoylpyrrolidine **362**, *N*-pivaloylpiperidine **363** and *N*-benzoylpiperidine **364**.

3.3.2 Synthesis of α-borylated Pyrrolidines and Piperidines *via* Direct α-Borylation

Our efforts thus far had failed to achieve the synthesis of α-Bpin-*N*-(2-pyridyl)pyrrolidine **342** and piperidine **366**. Therefore, attention was turned to methods for the direct α-borylation of *N*-(2-pyridyl)pyrrolidine **365** and piperidine **367** using transition metal catalysis. A number of different approaches for achieving these types of direct α-borylation reactions have been reported and an overview is presented here.

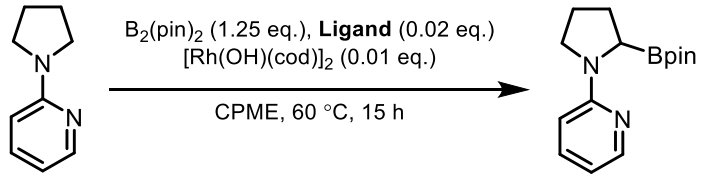
Sawamura and co-workers have reported several conditions for the rhodium-catalysed α-borylation of pyrrolidines and piperidines. The first report involved the use of an immobilised catalyst system using a 1:1 ratio of silica-TRIP and $[Rh(OH)(cod)]_2$ (0.5 mol%) with 1 equivalent of $B_2(pin)_2$ in hexane at temperatures between 80-100 °C.[126] This system was reported to be successful for the borylation α to nitrogen in a range of alkyl amides. However, it was also shown that the 2-pyridyl group directed and facilitated α-borylation to afford borylated compounds including α-Bpin-*N*-(2-pyridyl)pyrrolidine **342** (63% yield) and α-Bpin-*N*-(2-pyridyl)piperidine **366** (65% yield) (Scheme 3.43). It was found that immobilisation of the phosphine was critical to the success of this method; the use of free phosphine ligands such as PPh_3 and XPhos did not generate any of the desired products.



Scheme 3.43

A subsequent publication from Sawamura *et al.* (since retracted) described investigations into the enantioselective α-borylation of *N*-(2-pyridyl) compounds, including *N*-(2-pyridyl)pyrrolidine **365** and *N*-(2-pyridyl)piperidine **367**.[127] During the investigations, the borylation of *N*-(2-pyridyl)pyrrolidine **365** was reported using $B_2(pin)_2$, $[Rh(OH)(cod)]_2$ (0.01 equivalents) and several phosphine ligands (0.02 equivalents) in CPME at 60 °C (Table 3.2). The use of silica-TRIP ligand, P(*t*-Bu)$_3$ and P(*o*-tol)$_3$ afforded α-BPin-pyrrolidine **342** in near quantitative yield (entries 1-3) whereas the use of PCy_3 gave a 64% yield (entry 4) and the use of PPh_3 gave a 43% yield (entry 5).

Table 3.2: α-Borylation *N*-(2-pyridyl)pyrrolidine **342** by rhodium catalysis



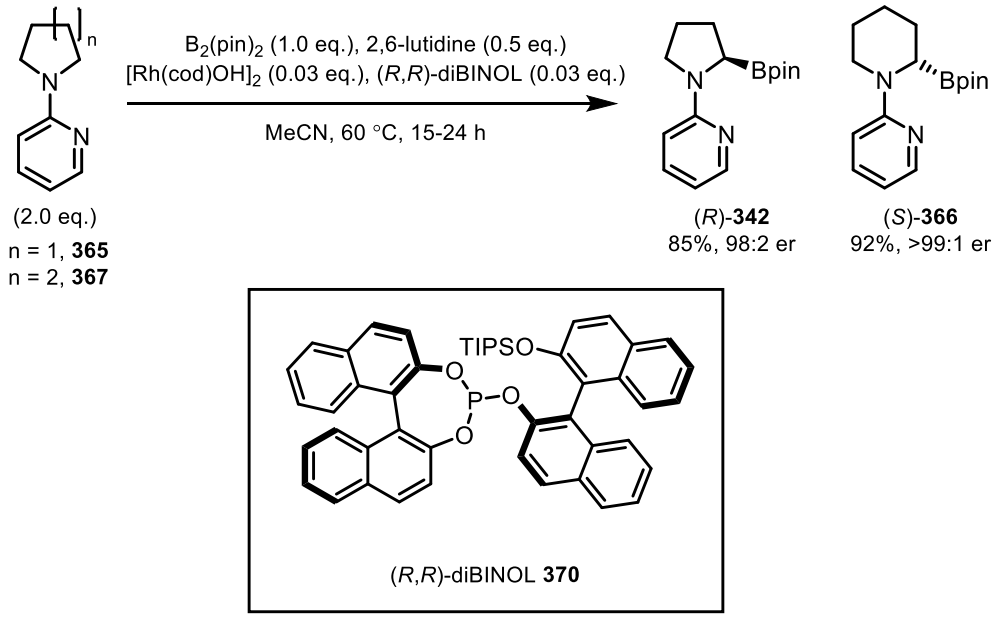
365 **342**

Entry	Ligand	Yield / %
1	Silica-TRIP[a]	99
2	P(*o*-tol)$_3$	99
3	P(*t*-Bu)$_3$	98
4	PCy_3	64
5	PPh_3	43
6	P(OPh)$_3$	0

a) 0.005 eq. Rh and 0.005 eq. ligand

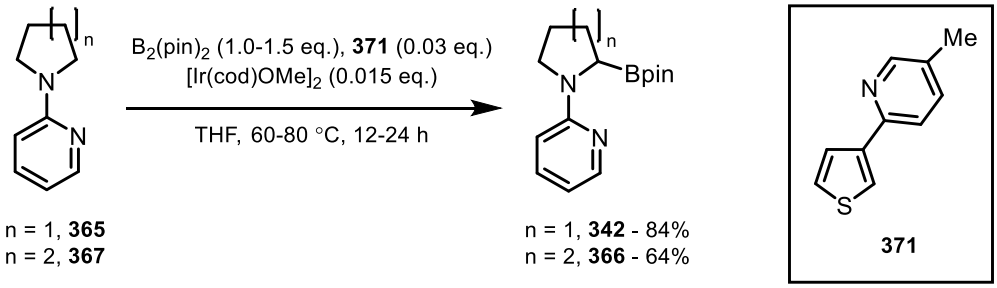
Sawamura *et. al.* went on to describe the asymmetric borylation of *N*-(2-pyridyl)pyrrolidine **365** and other nitrogen-containing compounds.[127,26] It was reported that the asymmetric borylation could be effectively achieved using diBINOL (*R*,*R*)-**370** as the ligand. Borylation of *N*-(2-pyridyl)pyrrolidine **365** with $B_2(pin)_2$, $[Rh(OH)(cod)]_2$ (0.03 eq.), diBINOL (*R*,*R*)-**370** (0.03 eq.) and 0.5 equivalents of 2,6-lutidine as an additive gave α-Bpin-*N*-(2-pyridyl)pyrrolidine (*R*)-**342** in 85% yield and 98:2 er (Scheme 3.44). The analogous reaction on *N*-(2-pyridyl)piperidine **367** gave α-Bpin-*N*-

(2-pyridyl)piperidine (*S*)-**366** in 92% yield and >99:1 er. The difference in the sense of stereoinduction was attributed to the substrate structure; these differences were also observed with the borylation of other substrates, although not in a predictable manner.



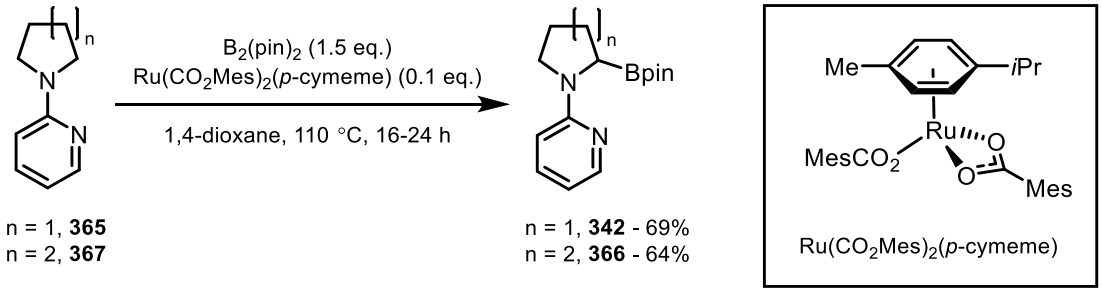
Scheme 3.44

An alternative method for the borylation of *N*-(2-pyridyl)pyrrolidine **365** and *N*-(2-pyridyl)piperidine **367** was reported by Chattopadhyay and co-workers.[128] It was stated that the use of novel thienyl ligand **371** (0.03 eq.) along with $[Ir(cod)OMe]_2$ (0.015 eq.) and $B_2(pin)_2$ in THF at 60-100 °C could affect the α-borylation of a wide range of compounds. Borylation selectively occurred α to nitrogen, α to directing groups or α to sulfur or oxygen atoms within heteroaromatics rings. When the borylation was attempted on substrates with two competing directing groups, very high selectivities were observed. The synthesis of α-Bpin-*N*-(2-pyridyl)pyrrolidine **342** (84% yield) and α-Bpin-*N*-(2-pyridyl)piperidine **366** (64% yield) were described within the studies of the scope of the reaction (Scheme 3.45).



Scheme 3.45

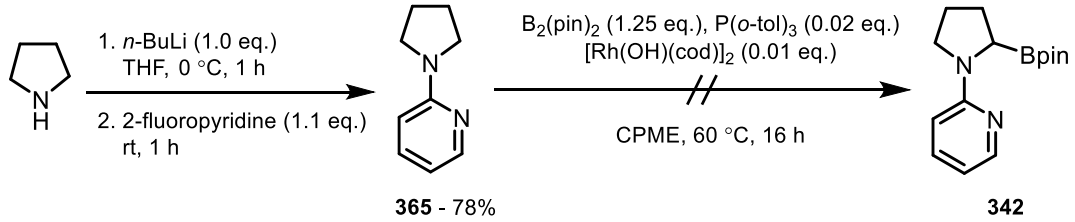
The borylation of *N*-(2-pyridyl)pyrrolidine **365** and *N*-(2-pyridyl)piperidine **367** has also been reported by Ackermann *et al.* using a ruthenium catalyst.[129] The borylation was achieved using $B_2(pin)_2$ and $Ru(CO_2Mes)_2$(*p*-cymene) in 1,4-dioxane at 110 °C. Using these conditions, α-Bpin-*N*-(2-pyridyl)pyrrolidine **342** was obtained in 69% yield and α-Bpin-*N*-(2-pyridyl)piperidine **366** in 64% yield (Scheme 3.46), alongside a range of other α-borylated nitrogen-containing compounds including 4-substituted piperidines. Ackermann and co-workers reported that the utility of the methodology lies in the lack of other additives and the lower cost of the ruthenium reagent compared to rhodium and iridium catalysts. However, with longer reaction times, diborylated by-products were observed which were reported to be challenging to separate from the desired mono-borylated product.



Scheme 3.46

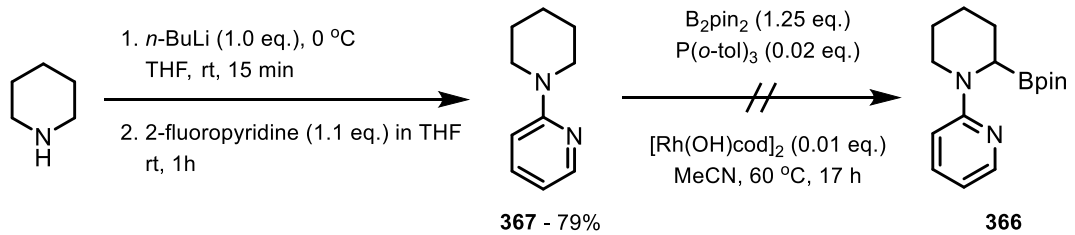
As highlighted in Table 3.1, it had not been possible to synthesise α-Bpin-*N*-(2-pyridyl)pyrrolidine **342** by Boc removal-*N*-functionalisation of α-Bpin-pyrrolidine **51**. Therefore, the borylation methodologies developed by Sawamura *et al.* and by Ackerman *et al.* were explored as alternative methods to synthesise α-Bpin-*N*-(2-pyridyl)pyrrolidine **342**.[127,129] To start, Sawamura *et al.*'s racemic borylation using $[Rh(OH)(cod)]_2$ in CPME was attempted on *N*-(2-pyridyl)pyrrolidine **365**. *N*-(2-pyridyl)pyrrolidine **365** was prepared following the procedure reported by a previous group member, which in turn was based on a procedure from Singaram and co-workers.[122,125] To achieve this, pyrrolidine was deprotonated using 1.0 equivalent of *n*-BuLi in THF at 0 °C and then the resulting lithium amine was reacted with 2-fluoropyridine at rt for 1 h.[122,125] This gave *N*-(2-pyridyl)pyrrolidine **365** in 78% yield (Scheme 3.47). Due to initial findings, care was taken during the preparation of reagents and the set-up of the reaction. Fresh CPME was used and was passed through alumina to remove any antioxidants and stabilisers; the CPME was also freeze-pump-thawed to

thoroughly degas the solvent. Newly acquired $[Rh(OH)(cod)]_2$ and P(*o*-tol)$_3$ were used; the $B_2(pin)_2$ was recrystallised from pentane and *N*-(2-pyridyl)pyrrolidine **365** was freshly distilled prior to use. With all these preparations made, the borylation of *N*-(2-pyridyl)pyrrolidine **365** was attempted following the procedure reported by Sawamura *et al.*, stirring and heating the reagents at 60 °C in CPME for 16 hours.[127] The reaction was unsuccessful. This reaction was also carried out with the addition of 0.65 equivalents of 2,6-lutidine since Sawamura and co-workers had included this additive when using diBINOL (*R*,*R*)-**370** as the ligand. However, this reaction was also unsuccessful. In both attempts, none of the desired α-Bpin-*N*-(2-pyridyl)pyrrolidine **342** was detected by ^{1}H NMR spectroscopy or HRMS.



Scheme 3.47

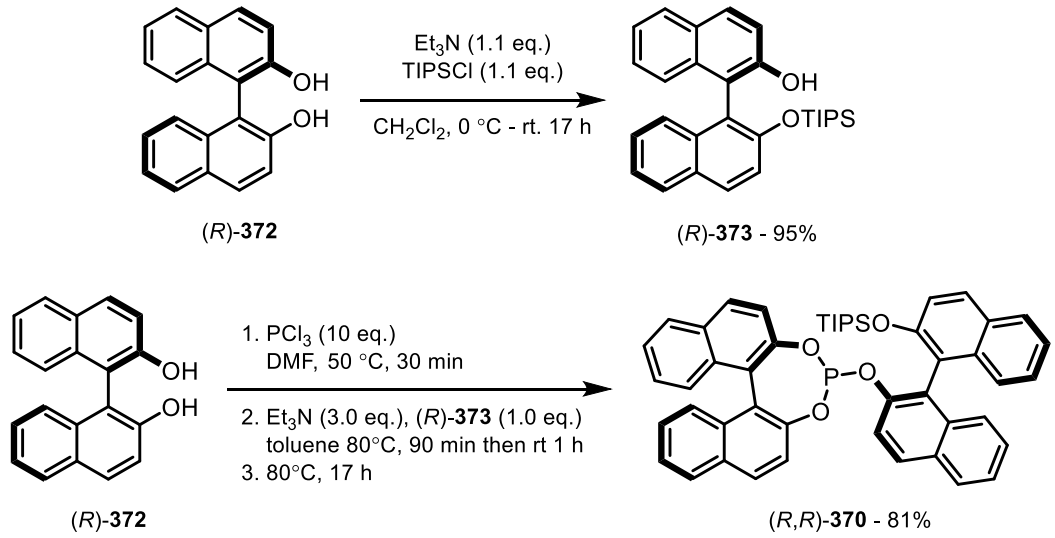
The racemic borylation procedure reported by Sawamura and co-workers was attempted on *N*-(2-pyridyl)piperidine **367**.[127] First, the synthesis of *N*-(2-pyridyl)piperidine **367** was accomplished in 79% yield through lithiation with *n*-BuLi (1.0 equivalent) in THF at 0 °C for 15 min, followed by the addition of 2-fluoropyridine to affect an S_NAr reaction (Scheme 3.48). Borylation was then attempted with $B_2(pin)_2$, $[Rh(OH)(cod)]_2$ and P(*o*-tol)$_3$ in MeCN at 60 °C for 17 hours. However, only trace amounts of α-Bpin-piperidine **366** were detected (by HRMS) and the reaction was not pursued further.



Scheme 3.48

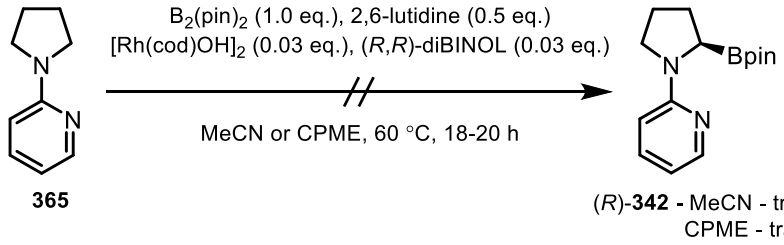
Next, Sawamura's asymmetric borylation procedure was investigated. For this, the ligand, diBINOL (*R*,*R*)-**370**, was synthesised according to the procedure published by Sawamura *et al.*.[26] TIPS protection of BINOL (*R*)-**372** was carried out with Et_3N and

TIPSCl in CH_2Cl_2 to afford BINOL monoTIPS (*R*)-**373** in 95% yield (Scheme 3.49). Reaction of BINOL (*R*)-**372** with PCl_3 in DMF at 50°C followed by addition of BINOL monoTIPS (*R*)-**373** with Et_3N and heating at 80 °C gave diBINOL (*R*,*R*)-**370** in 81% yield after purification by chromatography.



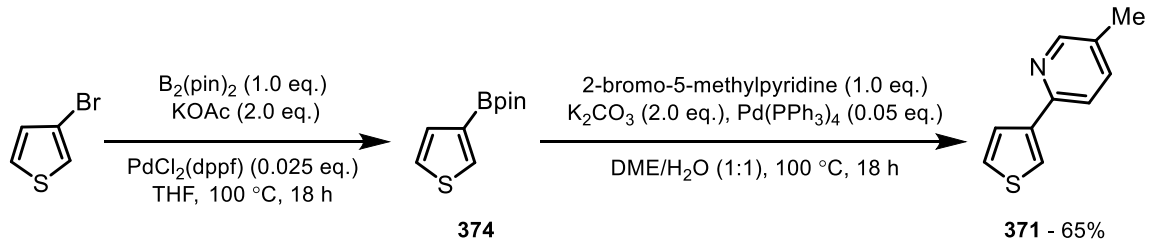
Scheme 3.49

With the ligand in hand, the borylation of *N*-(2-pyridyl)pyrrolidine **365** was attempted. *N*-(2-pyridyl)pyrrolidine **365** was reacted with $B_2(pin)_2$, 2,6-lutidine (0.5 eq.), $[Rh(OH)(cod)]_2$ (0.03 eq.) and diBINOL (*R*,*R*)-**370** (0.03 eq.) in MeCN at 60 °C for 20 h. Unfortunately, this afforded only trace amounts of α-Bpin-*N*-(2-pyridyl)pyrrolidine (Scheme 3.50). The reaction was also attempted in CPME as this was the solvent reported for the racemic borylation procedure. However, only trace amounts of α-Bpin-*N*-(2-pyridyl)pyrrolidine **342** were obtained. In both cases, the major component of the crude reaction mixture was the starting material, *N*-(2-pyridyl)pyrrolidine **365**.



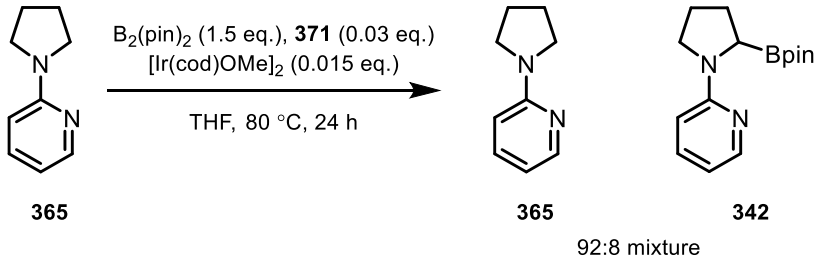
Scheme 3.50

Having not achieved success with the method described by Sawamura *et al.*, the approach to α-Bpin-*N*-(2-pyridyl)pyrrolidine **342** described by Chattopadhyay and co-workers was attempted. Thienyl ligand **371** was synthesised following the literature procedure.[128] The Miyaura borylation of 3-bromothiophene gave 3-Bpin-thiophene **374** and subsequent SMCC with 2-bromo-5-methylpyridine using $Pd(PPh_3)_4$ gave the desired thienyl ligand **371** in 65% yield over the two steps (Scheme 3.51).



Scheme 3.51

The iridium-catalysed borylation of *N*-(2-pyridyl)pyrrolidine **365** was then attempted using $B_2(pin)_2$, thienyl ligand **371** (0.03 eq.) and $[Ir(cod)OMe]_2$ (0.015 eq.) in THF at 80 °C for 24 hours. The reaction was set up in a glove box. In our hands, a 92:8 mixture of starting pyrrolidine **365** and α-Bpin-*N*-(2-pyridyl)pyrrolidine **342** was observed in the crude reaction mixture by ^{1}H NMR spectroscopy (Scheme 3.52). As a result, this approach was not pursued further.

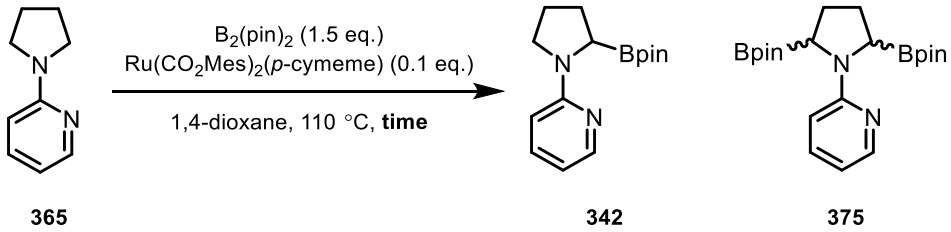


Scheme 3.52

Finally, the borylation methodology reported by Ackermann *et al.* was explored (Table 3.3).[129] Thus, *N*-(2-pyridyl)pyrrolidine **365** was reacted with $B_2(pin)_2$ and $Ru(CO_2Mes)_2$(*p*-cymene) (0.1 eq.) in 1,4-dioxane at 100 °C for 8 hours. This gave minimal amounts of α-Bpin-*N*-(2-pyridyl)pyrrolidine **342** after a challenging purification by chromatography on alumina. The product was only ~50% clean based on ^{1}H NMR spectroscopy which appeared to show the presence of pinacol contaminating the sample. Borylated products were identified in a 63:37 mixture of α-Bpin-pyrrolidine **342** (approximately 7% yield) and 2,5-diBpin-pyrrolidine **375** (approximately 4% yield)

(entry 1). The reaction was repeated with a longer reaction time of 16 hours but only trace amounts of α-Bpin-pyrrolidine **342** were obtained after purification (entry 2). The reaction was subsequently repeated by another member of the group and, in their hands, a 95:5 mixture of α-Bpin-pyrrolidine **342** (34% yield) and 2,5-diBpin-pyrrolidine **375** was obtained (entry 3).

Table 3.3: α-Borylation of *N*-(2-pyridyl)pyrrolidine **365** by ruthenium catalysis

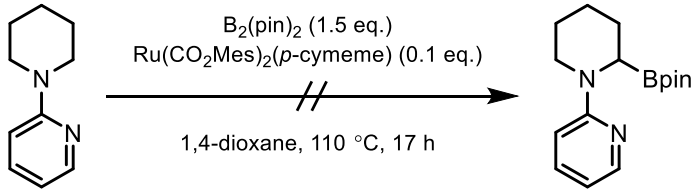


365 **342** **375**

Entry	Time / h	Yield / %
1	8	~7
2	16	trace
3	17	34[a]

a) Reaction performed by another member of the group

The ruthenium-catalysed α-borylation methodology developed by Ackermann *et al.* was applied to the borylation of *N*-(2-pyridyl)piperidine **367**, but without success (Scheme 3.53).[129] *N*-(2-pyridyl)piperidine **367** was reacted with $B_2(pin)_2$ and $Ru(CO_2Mes)_2$(*p*-cymene) in 1,4-dioxane at 110 °C for 17 hours. Regrettably, only trace amounts of the desired α-Bpin-*N*-(2-pyridyl)pyrrolidine **342** were detected (by HRMS) in the crude reaction mixture. Given the lack of success and difficulty of the borylation reactions, the synthesis of α-Bpin-piperidine **367** was not pursued any further.



367 **366**

Scheme 3.53

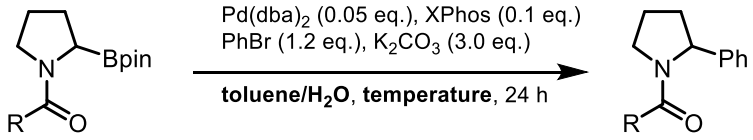
In conclusion, it was clear that the preparations of α-Bpin-*N*-(2-pyridyl)pyrrolidine **342** and α-Bpin-*N*-(2-pyridyl)piperidine **366** were challenging. It should now be noted that, since the attempts to perform the direct α-borylation by rhodium catalysis, the papers from Sawamura *et al.* in which these methods were published were retracted. However, even with alternative approaches, it had not been possible to prepare either compound as a pure sample or in high yield. Nevertheless, another member of the group did manage to obtain a 34% yield of mostly pure α-Bpin-*N*-(2-pyridyl)pyrrolidine **342** using ruthenium catalysis, although it was not an easily reproduced synthesis.

3.4 Initial Investigations of the Suzuki-Miyaura Cross-Coupling of α-Boryl pyrrolidines and Piperidines

3.4.1 Suzuki-Miyaura Cross-Coupling of α-Boryl pyrrolidines

Initial investigations into the SMCC of α-borylated pyrrolidines had been conducted by a previous group member using α-Bpin-*N*-Boc-pyrrolidine **51**, α-Bpin-*N*-pivaloylpyrrolidine **353** and α-Bpin-*N*-benzoylpyrrolidine **354** and the BF_3K analogues of these compounds.[122] The reactions conducted with the Bpin-pyrrolidines had been performed using conditions very similar to those reported by Sawamura *et al.*,[26] namely the use of $Pd(dba)_2$ (0.05 eq.), XPhos (0.1 eq.) and K_2CO_3 (3.0 eq.) at 90-100 °C in toluene-water with 1.2 equivalents of bromobenzene. The only difference in conditions was the use of different equivalents of water, compared to the 2.0 equivalents reported by Sawamura *et al.*. These previous results are shown in Table 3.4. The cross-coupling of both α-Bpin-*N*-Boc-pyrrolidine **51** (entry 1) and α-Bpin-*N*-benzoylpyrrolidine **354** (entry 3) gave none of the desired α-phenylpyrrolidines **114** and **377**. In contrast, the cross-coupling of α-Bpin-*N*-pivaloylpyrrolidine **353** gave trace amounts of α-phenylpyrrolidine **376** (entry 2).

Table 3.4: SMCC of α-Bpin-pyrrolidines previously carried out in the group

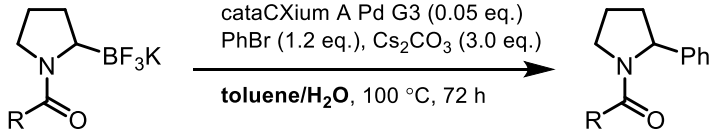


Entry	R	Product	toluene/H_2O	Temperature / °C	Yield / %
1	O*t*-Bu - **51**	**114**	1:1	90	-
2	*t*-Bu - **353**	**376**	2:1	100	trace
3	Ph - **354**	**377**	10 eq. H_2O	100	-

For the SMCC of the BF_3K analogues previously carried out in the group, the cross-coupling conditions reported by Dombrowski and Gesmundo *et al.* were utilised.[25] These conditions used cataCXium A Pd G3 precatalyst (0.05 eq.) and Cs_2CO_3 (3.0 eq.) in a 2:1 or 1:1 mixture of toluene-water at 100 °C. Two modifications were made to the conditions: the use of the pyrrolidine as the limiting reagent with 1.2 equivalents of

bromobenzene and a larger amount of water instead of 24 equivalents. Under these conditions, the cross-couplings of α-BF_3K-*N*-Boc-pyrrolidine **347**, α-BF_3K-*N*-pivaloylpyrrolidine **378** and α-BF_3K-*N*-benzoylpyrrolidine **379** were attempted (Table 3.5). In all cases, either none or trace amounts of α-arylated product were detected.

Table 3.5: SMCC of α-BF_3K pyrrolidines previously carried out in the group



Entry	R	Product	toluene/H_2O ratio	Yield / %
1	O*t*-Bu - **347**	**114**	1:1	-
2	*t*-Bu - **378**	**376**	2:1	trace
3	Ph - **379**	**377**	2:1	trace

With the four *N*-functionalised α-Bpin and BF_3K pyrrolidines in hand, the SMCC of these compounds was investigated building on the previous results in the group. The reaction conditions used were based on those of Sawamura and co-workers and those of Dombrowski and Gesmundo *et al.*.[2625] However, the conditions were altered to standardise them for easier comparison. The changes are highlighted in bold in Figure 3.3; the conditions derived from the work of Sawamura and co-workers will be referred to as the Bpin conditions, and those from Dombrowski and Gesmundo *et al.* as the BF_3K conditions.

Sawamura *et al.*
ArBr (1.2 eq.), $Pd(dba)_2$ (0.05 eq.)
XPhos (0.1 eq.), K_2CO_3 (3.0 eq.),
H_2O (2.0 eq.)
toluene, 90 °C, 24 h, 0.15 M

Dombrowski and Gesmundo *et al.*
ArBr (1.0 eq.), AlkylBF_3K (1.3 eq.)
cataCXium A Pd G3 (0.05 eq.)
Cs_2CO_3 (3.0 eq.), H_2O (24 eq.),
toluene, 100 °C, 72 h, 0.22 M

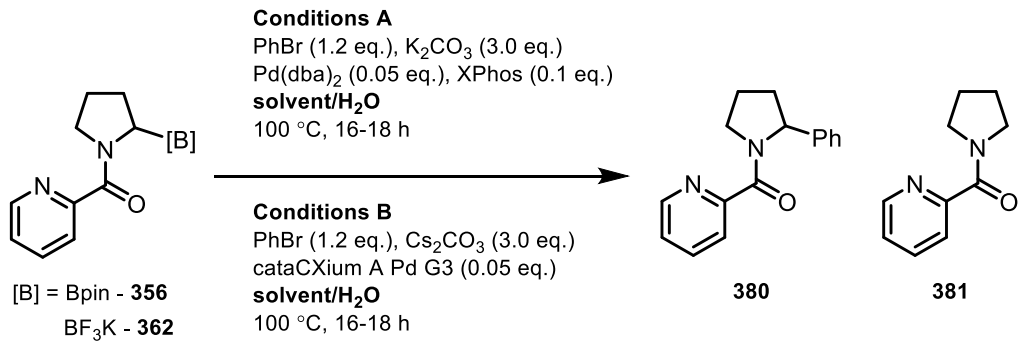
"Bpin" Conditions
ArBr (1.2 eq.), $Pd(dba)_2$ (0.05 eq.)
XPhos (0.1 eq.), K_2CO_3 (3.0 eq.),
H_2O (10 eq.)
toluene, **100 °C**, **18 h**, **0.20 M**

"BF_3K" Conditions
ArBr (1.2 eq.), AlkylBF_3K (1.0 eq.)
cataCXium A Pd G3 (0.05 eq.)
Cs_2CO_3 (3.0 eq.), H_2O (24 eq.),
toluene, 100 °C, **18 h**, **0.20 M**

Figure 3.3: Standardised SMCC conditions

First, the SMCC reactions of α-Bpin-*N*-2-pyridinoylpyrrolidine **356** and α-BF_3K-*N*-2-pyridinoylpyrrolidine **362** were investigated (Table 3.6). When the cross-coupling was conducted with the Bpin conditions ($Pd(dba)_2$/XPhos), only a trace amount of the desired α-phenylpyrrolidine **380** was detected, together with an 11% yield of the protodeborylated by-product *N*-2-pyridinoylpyrrolidine **381** after chromatography (entry 1). The mass balance was very low. However, it should be noted that purification of the reaction was challenging which may account for the low yield, as a large number of other unknown by-products were present in small quantities. No α-Bpin-*N*-pyridinoylpyrrolidine **356** starting material was isolated. Increasing (entry 2) and decreasing (entry 3) the equivalents of the water in the reaction did not afford any improvement, although more of the protodeborylated pyrrolidine **381** (43% yield) was isolated when 2.0 equivalents of water were used. The addition of silver(I) oxide to SMCC reactions has been reported by Crudden and co-workers to increase the rate of the transmetallation step.[107] However, in the case of this reaction the use of silver(I) oxide instead of K_2CO_3 did not afford any α-phenylpyrrolidine **380** (entry 4). Likewise, a ligand change to *t*-Bu_3P•HBF_4 did not give any α-phenylpyrrolidine **380** (entry 5). The use of the BF_3K conditions (cataCXium A Pd G3 precatalyst) did not result in successful cross-coupling reactions, both when applied to α-Bpin-pyrrolidine **356** (entry 6) and α-BF_3K-pyrrolidine **362** (entries 7 and 8). It had been proposed that the inclusion of a nitrogen atom in the *N*-group, using a pyridinoyl group, could assist the transmetallation step in the SMCC reaction by donating electron density to the boron. However, there was clearly no improvement in yield between the results with α-Bpin-*N*-2-pyridinoylpyrrolidine **356** and those with α-Bpin-*N*-benzoylpyrrolidine **379** previously performed in the group (see Table 3.5).

Table 3.6: Attempted SMCC of α-borylated-*N*-2-pyridinoylpyrrolidines **356** and **362**

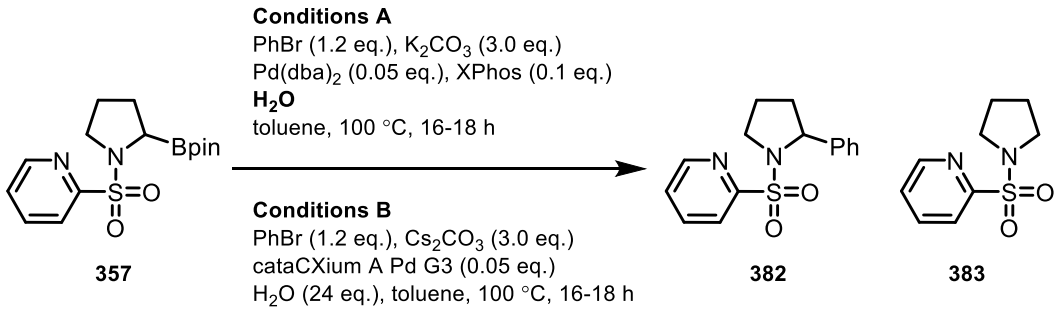


Entry	Pyrrolidine	Conditions	Toluene / Water	Yield **380** / %	Yield **381** / %[a]
1	**356**	A	10 eq. H_2O	trace	11
2	**356**	A	2:1 toluene-H_2O	-	
3	**356**	A	2 eq. H_2O	trace	43
4	**356**	A[b]	2:1 toluene-H_2O	-	
5	**356**	A[c]	2:1 toluene-H_2O	-	0
7	**356**	B	24 eq. H_2O	-	
8	**362**	B	24 eq. H_2O	-	
9	**362**	B	2:1 toluene-H_2O	trace	20

a) Yield after chromatography; b) Ag_2O instead of K_2CO_3; c) t-Bu 3 P•HBF 4 ligand used instead of XPhos

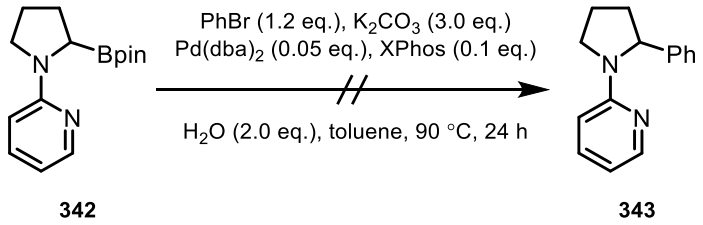
SMCC reactions with α-Bpin-*N*-(pyridine-2-sulfonyl)pyrrolidine **357** were investigated next (Table 3.7). Cross-coupling with the Bpin conditions did not afford any of the desired α-phenylpyrrolidine **382**, either with 10 equivalents of water (entry 1) or with 2:1 toluene-water (entry 2). Similarly, the use of the BF_3K conditions afforded only trace amounts of product, which could not be isolated (entry 3). In the reaction using cataCXium A (entry 3), none of the α-Bpin-pyrrolidine **357** starting material was isolated either.

Table 3.7: Attempted SMCC of α-Bpin-*N*-(pyridine-2-sulfonyl)pyrrolidine **357**



Entry	Conditions	Toluene / Water	Yield **382** / %	Yield **383** / %
1	A	10 eq. H_2O	-	
2	A	2:1 toluene-H_2O	-	
3	B	24 eq. H_2O	trace	0

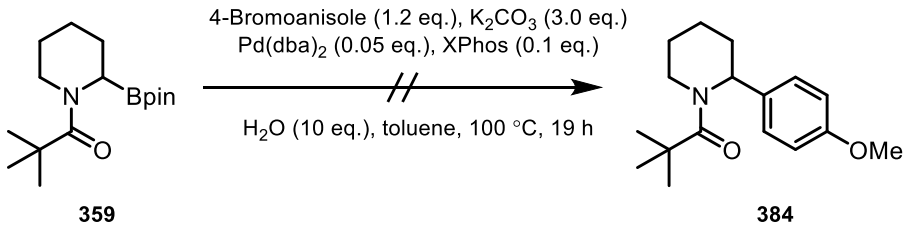
Finally, in an attempt to replicate the report of Sawamura *et al.*, the SMCC of α-Bpin-*N*-(2-pyridyl)pyrrolidine **342** was attempted by another group member.[26] The reaction was attempted using $Pd(dba)_2$ (0.05 eq.), XPhos (0.1 eq.) and K_2CO_3 (3.0 eq.) in toluene with 2.0 equivalents of water at 90 °C (Scheme 3.54). However, none of the desired α-phenylpyrrolidine **343** was detected by ^{1}H NMR spectroscopy.



Scheme 3.54

3.4.2 Attempted Suzuki-Miyaura Cross-Coupling of α-Boryl Piperidines

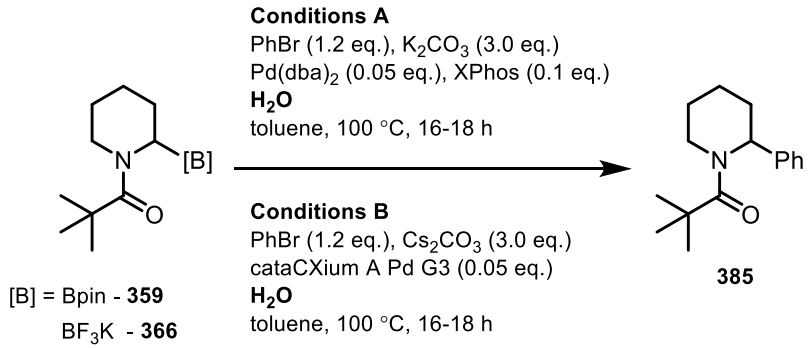
The SMCC reactions of the five *N*-functionalised α-borylated piperidines were also investigated. Initially, the SMCC of α-Bpin-*N*-pivaloylpiperidine **359** was conducted with 4-bromoanisole using the Bpin conditions ($Pd(dba)_2$/XPhos). This reaction did not afford any α-arylpiperidine **384** (Scheme 3.55). However, 90% of the α-Bpin-piperidine **359** starting material was recovered after chromatography on silica, indicating that there had not been protodeborylation or degradation of the Bpin reagent. Subsequent SMCC reactions were conducted with bromobenzene.



Scheme 3.55

The SMCC of α-Bpin-piperidine **359** was further investigated using both the Bpin and BF_3K conditions (cataCXium A Pd G3 precatalyst); however, in each case, there was no product detected by HRMS of the crude reaction mixture (Table 3.8, entries 1 and 2). Likewise, the cross-coupling of α-BF_3K-piperidine **366** was unsuccessful under the BF_3K conditions, both with 24 equivalents of water (entry 3) and 2:1 toluene-water (entry 4); none of the desired α-phenylpiperidine **385** was detected by either HRMS or ^1H NMR spectroscopy.

Table 3.8: Attempted SMCC of α-borylated-*N*-pivaloylpiperidine **359** and **366**

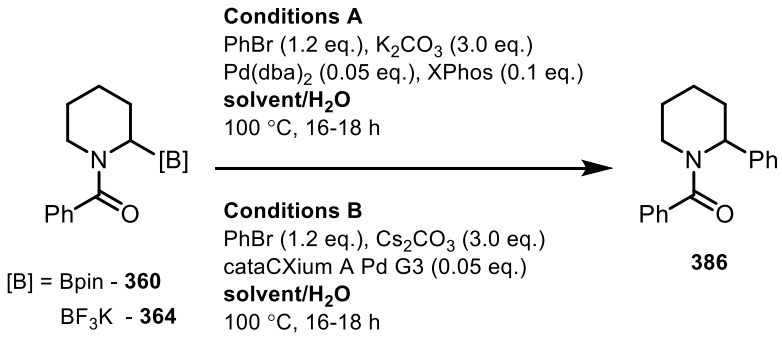


Entry	Piperidine	Conditions	Toluene / Water	Yield / %
1	**359**	A	10 eq. H_2O	-
2	**359**	B	24 eq. H_2O	-
3	**366**	B	24 eq. H_2O	-
4	**366**	B	2:1 toluene-H_2O	-

Next, the SMCC of α-Bpin-*N*-benzoylpiperidine **360** and α-BF_3K-*N*-benzoylpiperidine **364** were investigated (Table 3.9). The cross-coupling of α-Bpin-piperidine **360** was attempted using the Bpin conditions with 10 equivalents of water (entry 1) and in 2:1

toluene-water (entry 2) but neither were successful. The reaction with 10 equivalents of water was repeated with the addition of 1.0 equivalent of pyridine in an attempt to facilitate the transmetallation step. Unfortunately, this was unsuccessful and none of the desired α-phenylpiperidine **386** was obtained (entry 3). The SMCC of α-BF_3K-*N*-benzoylpiperidine **364** was similarly unsuccessful; neither the use of the BF_3K cross-coupling conditions in 1,4-dioxane (entry 4) nor those conditions in 2:1 toluene-water (entry 5) gave any α-phenylpiperidine **386**. Only the reaction conducted on α-Bpin-piperidine **360** under the Bpin conditions was purified by chromatography and, in this case, 72% of the α-Bpin-piperidine **360** starting material was recovered, indicating that there was limited, if any, transmetallation occurring and very little Bpin hydrolysis.

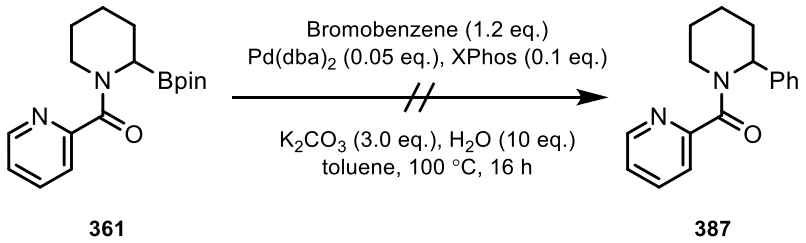
Table 3.9: Attempted SMCC of α-borylated-*N*-benzoylpiperidines **360** and **364**



Entry	Piperidine	Conditions	Solvent	Toluene / Water	Yield / %
1	**360**	A	toluene	10 eq. H_2O	-
2	**360**	A	toluene	2:1 toluene-H_2O	-
3	**360**	A[a]	toluene	10 eq. H_2O	-
4	**364**	B	1,4-dioxane	24 eq. H_2Osure	-
5	**364**	B	toluene	2:1 toluene-H_2O	-

a) 1.0 eq. of pyridine added

The SMCC of α-Bpin-*N*-(2-pyridinoyl)piperidine **361** was also investigated under the Bpin conditions, but with no success (Scheme 3.56). As was observed with the other α-borylated piperidines, there was no evidence of cross-coupling occurring and none of α-phenylpiperidine **387** was detected by either HRMS or ^{1}H NMR spectroscopy.

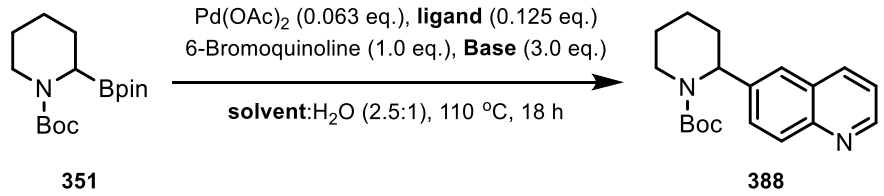


361 **387**

Scheme 3.56

With such little success with the SMCC reactions on α-borylated *N*-Boc-piperidines, we were fortunate that our industrial collaborators at Pfizer were in a position to carry out an extensive screen. This was carried out for the SMCC of α-Bpin-*N*-Boc-piperidine **351** with 6-bromoquinoline. The reactions were conducted on a 0.002 mmol scale at 0.02 M concentration. $Pd(OAc)_2$ (0.063 eq.) was used as the palladium source and the reactions were heated at 110 °C for 18 hours in a 5:2 solvent-water mixture. 12 Different ligands were investigated, along with five bases and four solvents with each combination being conducted (Table 3.10). Upon completion, the reactions were diluted with MeCN mixed and centrifuged before being analysed by LCMS. Analysis of all these reactions showed that the conversion to α-arylpiperidine **388** was <5% in all cases. The ligands which gave some conversion were PPh_3 and dppf. The solvent preference was 1,4-dioxane > MeCN > toluene > MeOH and the best base for the reaction was $NaHCO_3$ when the reaction was conducted in 1,4-dioxane and NaOH in the other solvents. α-Bpin-*N*-Boc-piperidine **351** was found to be stable under these conditions and was detected at the end of the reaction. This is a similar observation to the results of our SMCC reactions summarised in Tables 3.8 and 3.9.

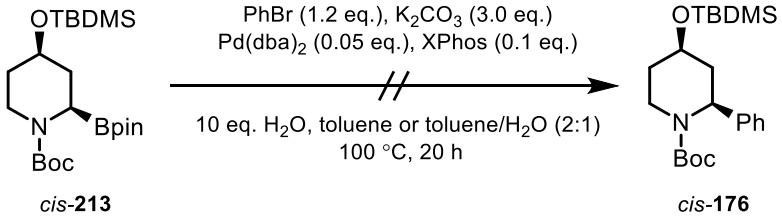
Table 3.10: Pfizer screen of the SMCC of α-Bpin-*N*-Boc-piperidine **351**



351 **388**

Ligands		Base	Solvent
None	AmPhos	NaOH	MeOH
P(*t*-Bu)$_3$	CyJohnPhos	$NaHCO_3$	MeCN
PPh_3	XPhos	CsF	THF
PCy_3	XantPhos	$K_2CO_{3(aq)}$	toluene
P(*o*-tol)$_3$	dtbpf	$K_2CO_{3(evap.)}$	
cataCXium A	dppf		

Finally, the SMCC of α-Bpin-4-OTBDMS-*N*-Boc-piperidine *cis*-**213** was attempted as this compound had been prepared in the lithiation-trapping reactions discussed in section 2.4.1 (see Scheme 2.54). The Bpin conditions were utilised with both 10 equivalents of water and in a 2:1 mixture of toluene-water; in each case, none of α-arylpiperidine *cis*-**176** was detected (Scheme 3.57).



cis-**213** *cis*-**176**

Scheme 3.57

Collectively, the results in sections 3.4.1 and 3.4.2 show the inherent challenges with the SMCC of α-Bpin and α-BF_3K-*N*-functionalised pyrrolidines and piperidines. Minimal, if any, product was detected from the reactions explored, with the best results being the conversions (<5 %) achieved by our collaborators at Pfizer. The challenge with the SMCC reactions on *N*-functionalised piperidines appeared to be transmetallation, as the α-borylated piperidine starting materials were still present in large quantities after the reactions, indicating that they had not entered the catalytic cycle. The same was not true with the SMCC of pyrrolidines, however, as the crude

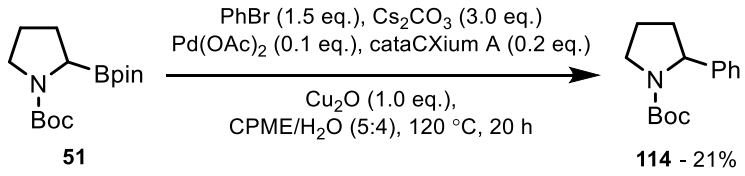
mixture contained a large amount of by-products in small quantities and it was not possible to precisely determine the difficulties being encountered there. Overall, the SMCC reactions with different groups on the nitrogen did not lead to success. In addition, another group member was unable to reproduce the SMCC of α-Bpin-*N*-(2-pyridyl)pyrrolidine **342** reported by Sawamura *et al.*.[26]

3.5 Optimisation of Suzuki-Miyaura Cross-Coupling of α-Bpin-*N*-Boc-pyrrolidine

3.5.1 $Pd(OAc)_2$/cataCXiumA for the Suzuki-Miyaura Cross-Coupling of α-Bpin-*N*-Boc-pyrrolidine

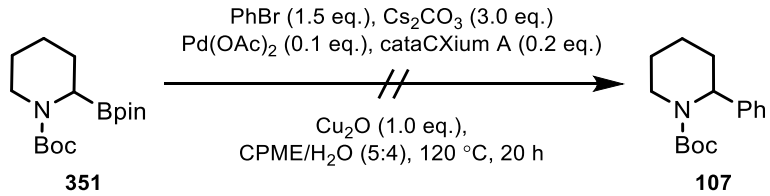
Due to the lack of success with *N*-functionalised pyrrolidines and piperidines, attention returned to the SMCC of α-borylated-*N*-Boc-pyrrolidines. This was partly due to the fact that Dombrowski and Gesmundo *et al.* had reported the successful cross-coupling of α-BF_3K-*N*-Boc-pyrrolidine **347** with 1-(3-bromophenyl)-1H-pyrazole to give α-arylpyrrolidine **348** in 12% yield (see Scheme 3.33).[25] In addition, traces of cross-coupled pyrrolidines had been detected by HRMS from some of the reactions described in sections 3.4.1.

As outlined in section 3.1.1, Walsh, Hughes and co-workers recently reported the SMCC of challenging and sterically hindered bicycle[1.1.1]pentylboronates and sterically hindered piperidines by using $Pd(OAc)_2$, cataCXium A and the addition of 1.0 equivalent of copper(I) oxide (see Schemes 3.11 and 3.12).[105] Due to the similarly challenging nature of the cross-coupling of α-Bpin-pyrrolidines, these conditions were applied to the cross coupling of α-Bpin-*N*-Boc-pyrrolidine **51** (Scheme 3.58). The SMCC was conducted with 1.5 equivalents of bromobenzene, 3.0 equivalents of Cs_2CO_3 with a $Pd(OAc)_2$ (0.1 equivalents) and cataCXium A (0.2 equivalents) catalytic system in a 5:4 mixture of CPME and water with 1.0 equivalent of copper(I) oxide as an additive at a 0.4 M reaction concentration. The reaction was heated at 120 °C for 20 hours and, excitingly, gave a 21% isolated yield of α-phenylpyrrolidine **114**.



Scheme 3.58

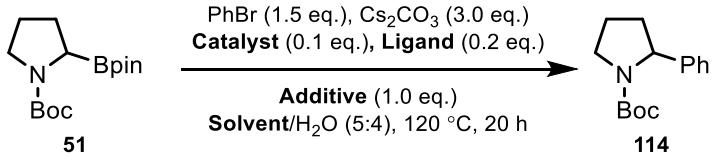
The Walsh reaction conditions were also applied to the SMCC of α-Bpin-*N*-Boc-piperidine **351**. Unfortunately, none of the desired α-phenylpiperidine **107** was detected by HRMS or ^1H NMR spectroscopy (Scheme 3.59).



Scheme 3.59

The result of the successful SMCC reaction with α-Bpin-pyrrolidine **51** was an important starting point for further investigations. Beginning with the conditions described by Walsh, Hughes and co-workers, optimisation of the SMCC of α-Bpin-pyrrolidine **51** with bromobenzene was explored (Table 3.11). The initially obtained 21% yield of α-phenylpyrrolidine **114** is shown in entry 1. Changing the solvent from CPME to toluene did not appreciably affect the reaction and a 23% yield of α-phenylpyrrolidine **114** was obtained (entry 2). Use of the cataCXium A Pd G3 precatalyst improved the yield to 27% (entry 3). Given that Walsh, Hughes and co-workers had highlighted the importance of copper(I) oxide in their SMCC reactions, it was perhaps surprising that removal of copper(I) oxide from the reaction actually improved the yield to 30% (entry 4). Increasing the reaction time to 63 hours did not improve the yield (30%, entry 5) compared to that after 20 hours reaction time. When the SMCC was conducted with cataCXium A Pd G3 in the absence of copper(I) oxide, α-phenylpyrrolidine **114** was obtained in 28% yield (entry 6), comparable to the 30% yield obtained with $Pd(OAc)_2$ and cataCXium A (entry 4). When the reaction was carried out in toluene with no copper(I) oxide present, a 32% yield of α-phenylpyrrolidine **114** was obtained (entry 7), comparable to the 30% yield obtained in CPME (entry 4), indicating that the two solvents could be used interchangeably. Finally, a SMCC reaction in the presence of silver(I) oxide resulted in no conversion to α-phenylpyrrolidine **114** (entry 8).

Table 3.11: Initial investigations of the SMCC of α-Bpin-*N*-Boc-pyrrolidine **51**



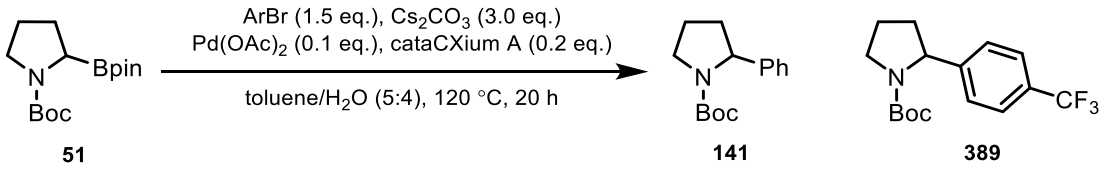
Entry	Catalyst/Ligand	Additive	Solvent	Time/ h	Yield / %[a]
1	$Pd(OAc)_2$, cataCXium A	Cu_2O	CPME	20	21
2	$Pd(OAc)_2$, cataCXium A	Cu_2O	toluene	20	23
3	cataCXium A Pd G3	Cu_2O	CPME	20	27
4	$Pd(OAc)_2$, cataCXium A	-	CPME	20	30
5	$Pd(OAc)_2$, cataCXium A	-	CPME	63	30
6	cataCXium A Pd G3	-	CPME	20	28
7	$Pd(OAc)_2$, cataCXium A	-	toluene	20	32
8	$Pd(OAc)_2$, cataCXium A	Ag_2O	toluene	20	-

a) Yield after chromatography

Overall, the learnings from these initial reactions resulted in the choice of toluene as a solvent, due to its greater availability and lower cost. It was decided not to use copper(I) oxide in future reactions and a reaction time of 20 hours was selected. These changes meant that the reaction conditions were in fact similar to other sp^2-sp^3 SMCC reactions, for example those reported by Dombrowski and Gesmundo *et al.*[25] (see Scheme 3.33) and Partridge *et al.* (see Scheme 3.10).[104] To proceed with optimisation, it was desirable to use an internal or external standard, which would enable rapid screening of reaction conditions by eliminating the need to purify each reaction. Therefore, the use of an external standard was first explored. Thus, 1,3,5-trimethoxybenzene was added to the reaction mixture prior to aqueous work-up. After work-up, an aliquot of the crude product was analysed by ^{1}H NMR spectroscopy. An NMR yield was determined by comparison of the integrations of the signals due to the benzylic NCH proton in α-arylpyrrolidines **114** and **389** and the signals due to the methoxy group and aromatic protons in 1,3,5-trimethoxybenzene. The results are summarised in Table 3.12. In the reaction conducted with bromobenzene, the NMR yield was determined to be 23% and, after purification by chromatography, a 24% isolated yield of α-phenylpyrrolidine **114**

was obtained (entry 1). When the SMCC was attempted with 4-bromobenzotrifluoride, a 40% NMR yield was obtained which precisely matched the 40% isolated yield of α-arylpyrrolidine **389** (entry 2). This reaction also demonstrated the successful cross-coupling of an electron-deficient aryl bromide. The SMCC reaction was then performed with 1,3,5-trimethoxybenzene as an internal standard; this reaction gave a 29% NMR yield compared to a 30% isolated yield (entry 3). Overall, this demonstrated that the presence of 1,3,5-trimethoxybenzene during the reaction did not negatively affect the yield and that it served as a suitable internal standard for determining the yield by ^{1}H NMR spectroscopy.

Table 3.12: Validation of external and internal standard for the SMCC of α-Bpin-*N*-Boc-pyrrolidine **51**

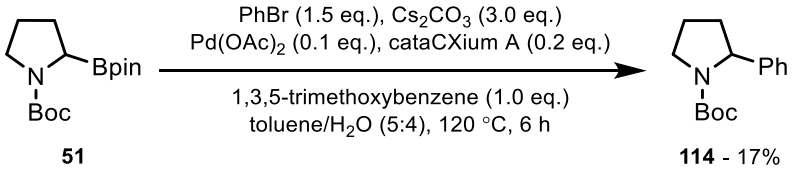


51 **141** **389**

Entry	ArBr	Product	Standard	NMR Yield / %[a]	Yield / %[b]
1	PhBr	**114**	External	23	24
2	4-Br$C_6H_4CF_3$	**389**	External	40	40
3	PhBr	**114**	Internal	29	30

a) Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an external or internal standard; b) Yield after chromatography

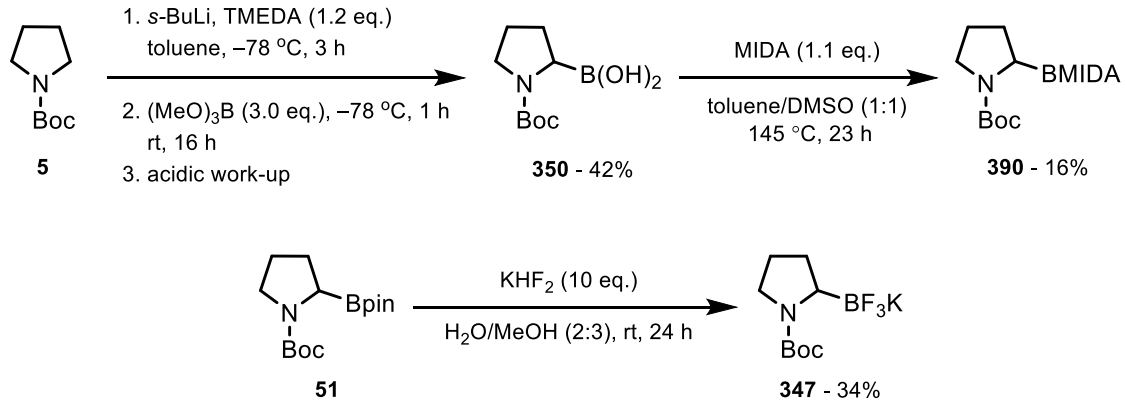
With the use of 1,3,5-trimethoxybenzene validated as an internal standard, the SMCC reaction with bromobenzene was carried out under the standard conditions with a reaction time of 6 hours. This reaction gave a 17% NMR yield (Scheme 3.60) which was significantly lower than that achieved with a 20 hour reaction time (32% isolated yield). As a result, a reaction time of 20 hours was used for future investigations.



51 **114** - 17%

Scheme 3.60

At this point, it was decided to examine the effect of changing the boron group. Indeed, Dombrowski and Gesmundo *et al.* had reported the SMCC of α-BF_3K-pyrrolidine **347** to give arylpyrrolidine **348** in 11% yield (see Scheme 3.33). First, a range of α-borylpyrrolidines were synthesised. α-$B(OH)_2$-pyrrolidine **350** was synthesised *via* lithiation-trapping of *N*-Boc-pyrrolidine **5**, based on a procedure reported by Whiting *et al.*. Thus, *N*-Boc-pyrrolidine **5** was lithiated with *s*-BuLi/TMEDA in Et_2O at –78 °C and the lithiated intermediate was then trapped with $B(OMe)_3$; an acidic work-up gave α-$B(OH)_2$-pyrrolidine **350** in 42% yield after chromatography (Scheme 3.61).[120] The synthesis of α-BMIDA-pyrrolidine **390** was accomplished by heating α-$B(OH)_2$-pyrrolidine **350** at reflux with a Dean-Stark condenser in toluene/DMSO with MIDA present. This procedure was based on the work of a previous group member, who in turn adapted it from a procedure reported by Gillis and Burke.[130,131] In this way, α-BMIDA-pyrrolidine **390** was obtained in 16% yield after chromatography (Scheme 3.61). Although the yield was low, enough material was obtained to perform a SMCC reaction. α-BF_3K-pyrrolidine **347** was synthesised in 34% yield from α-Bpin-pyrrolidine **51** by reacting with KHF_2 in a mixture of water and methanol using a procedure based on that reported by Molander *et al.*.[132] α-Bneop-pyrrolidine **391** was prepared by another member of the group following a procedure reported by Denmark and co-workers.[133]

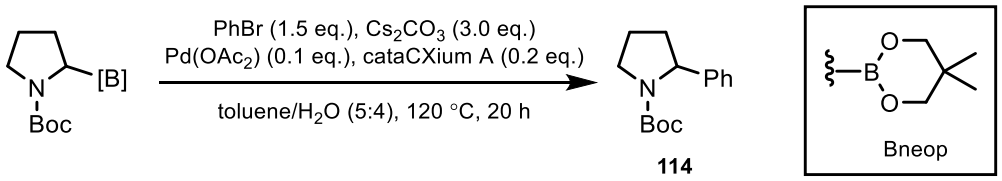


Scheme 3.61

With a selection of α-boryl pyrrolidines in hand, the SMCC reaction was attempted on each using the standard conditions and in the presence of 1,3,5-trimethoxybenzene as an internal standard (Table 3.13). In all cases, the yield was determined by ^{1}H NMR spectroscopy. None of the reactions gave an NMR yield of α-phenylpyrrolidine **114** higher than the 30% NMR yield (32% isolated yield) achieved with α-Bpin-pyrrolidine

51 (entry 1). The SMCC with α-$B(OH)_2$-pyrrolidine **350** was attempted at both 100 °C and 120 °C as the stability of the boronic acid at high temperatures was not known. However, in both cases, the NMR yield was <10% (entries 2 and 3). A similarly low yielding result (9% NMR yield) was obtained starting with α-BMIDA-pyrrolidine **390** (entry 4). Only trace amounts of α-phenylpyrrolidine **114** were detected by HRMS when the SMCC reaction was attempted with α-Bneop-pyrrolidine **391** (entry 5). The highest conversion was achieved with α-BF_3K-pyrrolidine **347**; an 11% NMR yield of α-phenylpyrrolidine **114** was obtained (entry 6). This investigation clearly demonstrated the utility of the Bpin group and, under these reaction conditions, its superiority to other α-boryl groups and was thus used for all further investigations.

Table 3.13: SMCC of α-[B]-*N*-Boc-pyrrolidines



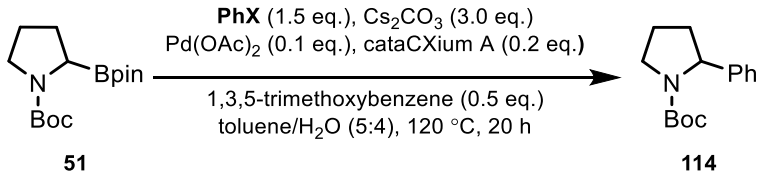
Entry	[B]	Pyrrolidine	Temperature / °C	Yield / %
1	Bpin	**51**	120	32[a]
2	$B(OH)_2$	**350**	100	5[b]
3	$B(OH)_2$	**350**	120	7[b]
4	BMIDA	**390**	120	9[b]
5	Bneop[c]	**391**	120	trace
6	BF_3K	**347**	120	11[b]

a) Yield after chromatography b) Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard; c) Substrate synthesised by another group member

Next, the effect of changing the halide in the aryl halide was investigated by conducting the SMCC reaction with chlorobenzene, iodobenzene and phenyltriflate (Table 3.14). Using chlorobenzene, encouragingly, a 55% NMR yield of α-phenylpyrrolidine **114** was obtained; after chromatography, this translated into a 58% isolated yield (entry 1). This represented a dramatic improvement in yield over the reaction with bromobenzene

(32% isolated yield, entry 2). The difference in yields between the NMR and isolated values may be due to inaccuracies in integrating the rather broad benzylic NCH signal in the ^{1}H NMR spectrum. Indeed, occasional differences between the NMR and isolated yields ultimately encouraged us to develop a more robust GC analytical method, as described in the section 3.5.2. Both the reactions with iodobenzene and phenyltriflate gave only a trace amount of α-phenylpyrrolidine **114** (by ^{1}H NMR spectroscopy) and were not further pursued (entries 3 and 4).

Table 3.14: SMCC of α-Bpin-*N*-Boc-pyrrolidine **51** with phenyl halides and triflate

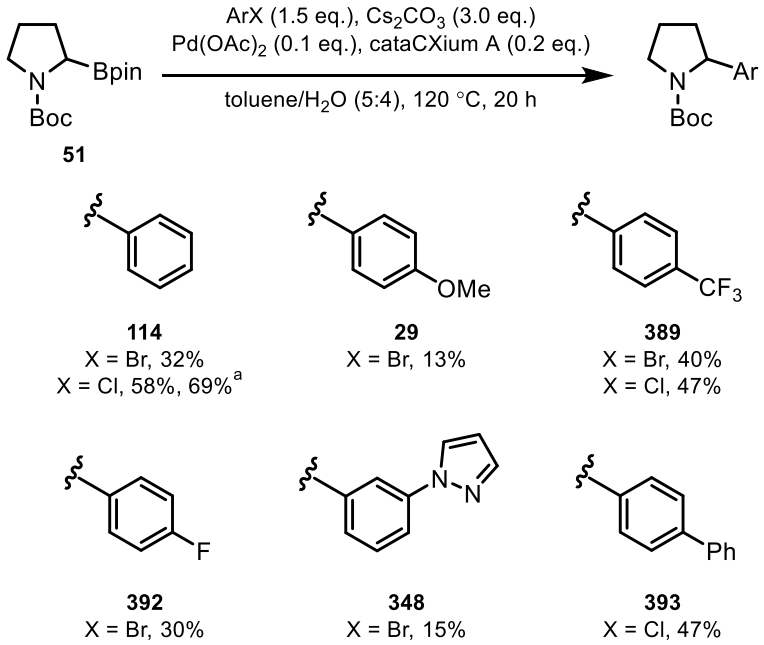


Entry	PhX	NMR Yield / %[a]	Yield / %[b]
1	PhCl	55	58
2	PhBr		32
3	PhI	trace	
4	PhOTf	trace	

a) Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as in internal standard; b) Yield after chromatography

Although the SMCC procedure with α-Bpin-pyrrolidine **51** was far from optimised, an early scope of the reaction was investigated with a few different aryl halides to determine the potential of the methodology. In all examples, the following conditions were used: $Pd(OAc)_2$ (0.1 equivalents), cataCXium A (0.2 equivalents) and Cs_2CO_3 (3.0 equivalents) in 5:4 toluene-water at 120 °C for 20 hours. First, the SMCC of two aryl bromides were investigated: the use of 4-bromoanisole gave α-arylpyrrolidine **29** in 13% yield and cross-coupling with 4-fluorobromobenzene afforded α-arylpyrrolidine **392** in 30% yield (Scheme 3.62). Having demonstrated that a higher yield could be achieved with chlorobenzene compared to bromobenzene (Table 3.14, entries 1 and 2), the SMCC of 4-chlorobenzotrifluoride was carried out. This SMCC reaction afforded a 47% yield of α-arylpyrrolidine **389**, compared to the 40% yield achieved with 4-bromobenzotrifluoride (Table 3.12, entry 2), demonstrating a preference for the cross

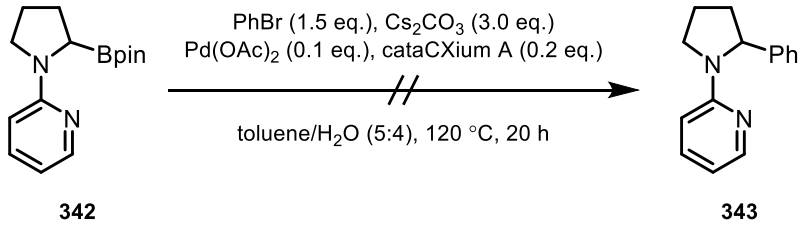
coupling of aryl chlorides. In light of this, the SMCC of 4-chlorobiphenyl was performed and this reaction gave α-arylpyrrolidine **393** in 47% yield. The SMCC conducted on α-BF_3K-pyrrolidine **347** by Dombrowski and Gesmundo *et al.* was attempted using the same aryl bromide but coupling with α-Bpin-pyrrolidine **51**; unfortunately the chlorine analogue was not available.[25] This reaction gave a 15% yield of α-arylpyrrolidine **348**, compared to the 12% achieved by Dombrowski and Gesmundo *et al.*. The highest yielding SMCC reaction, the cross-coupling of chlorobenzene, was then conducted with chlorobenzene as the limiting reagent and α-Bpin-pyrrolidine **51** in excess (1.5 equivalents). This SMCC reaction gave a 69% yield of α-phenylpyrrolidine **114**. However, the reaction was repeated several times and difficulties were encountered reproducing this result. Overall, this early investigation demonstrated that there was good potential for the scope of the SMCC reaction and that it was not restricted to electron-deficient or electron-rich substrates.



a) 1.0 equivalent of PhCl and 1.5 equivalent of α-Bpin-pyrrolidine **51** used

Scheme 3.62

With the new conditions in hand, the SMCC reaction of α-Bpin-*N*-(2-pyridyl)pyrrolidine **342** was revisited. The SMCC reaction with bromobenzene was attempted using these new conditions by another member of the group. However, none of the desired α-phenylpyrrolidine **114** was obtained (Scheme 3.63).



Scheme 3.63

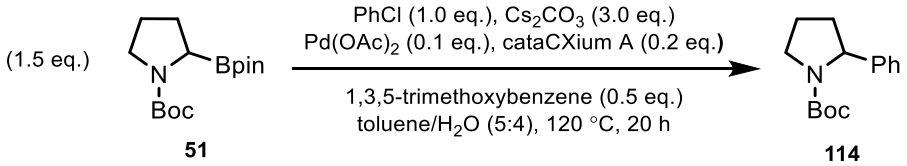
3.5.2 Gas Chromatography Screening for the Optimisation of the Suzuki-Miyaura Cross-Coupling of α-Bpin-*N*-Boc-pyrrolidine

At this stage, it was decided to develop a GC method for analysing the conversion to product. For this, a sample of the crude reaction mixture at the end of the reaction was taken from the toluene layer and diluted in MeCN before being filtered and analysed by GC. Another member of the group produced a calibration curve for α-phenylpyrrolidine **114** and the 1,3,5-trimethoxybenzene internal standard, so that the relative peak areas of each in the GC trace of the product could be used to determine the conversion (% GC yield). This method was validated using the SMCC with chlorobenzene (Table 3.14, entry 1). For this reaction, a 65% GC yield of α-phenylpyrrolidine **114** was determined. This compared well with the 55% NMR yield and 58% isolated yield. These results demonstrated the validity of the GC method.

Some issues were encountered with the reproducibility of the SMCC reaction. As highlighted previously, the SMCC with chlorobenzene had been giving variable yields. High yields, up to 69%, were accomplished but, on repetition of these reactions, yields as low as 33% were achieved. Issues were also encountered with the reaction set-up. Teflon screw cap vials had been used and some of the lids had been blowing off during the course of the reaction. It was suspected that differences in stirring speed and the hotplate used for the reaction were causing local variations that were resulting in large differences in the outcome of the reaction. Therefore, alongside another member of the group, the reaction set-up was standardised and reactions were carried out in duplicate side-by-side. The key features of the standardised set-up were as follows: the aryl halide was used as the limiting reagent, as the highest yield up to this point had been achieved with the aryl halide as the limiting reagent. The reactions were conducted at a 0.3 mmol scale in Teflon screw cap vials using 0.75 mL of solvent (0.42 mL of toluene and 0.33 mL of water) which corresponded to a 0.71 M concentration of aryl halide in toluene. The same hotplate was used for all of the reactions and it was set to the highest stirring

speed to ensure thorough mixing of the toluene and water layers. The dry reagents were added to the vial first, followed by purging with nitrogen for a minimum of 15 minutes then the subsequent addition of degassed water, aryl halide and degassed toluene. The vial was then immediately placed into a pre-heated aluminium block on a hotplate set at 120 °C. 1,3,5-Trimethoxybenzene (0.5 equivalents) was included as an internal standard and the reactions were analysed by GC. The reactions were performed in two sets of four (one set by another member of the group) and both sets gave high yields that were much more consistent than those that had previously been observed (Table 3.15). Across the eight reactions, an average GC yield of 61% was observed, ranging from 52-69%. This demonstrated that whilst the improved set-up was considerably more reliable, there was still a level of variability in the reaction. However, given the scale of the reaction and the challenging nature of this type of SMCC reaction, this level of variability was deemed to be acceptable.

Table 3.15: SMCC of α-Bpin-*N*-Boc-pyrrolidine **51** with chlorobenzene using an improved set-up



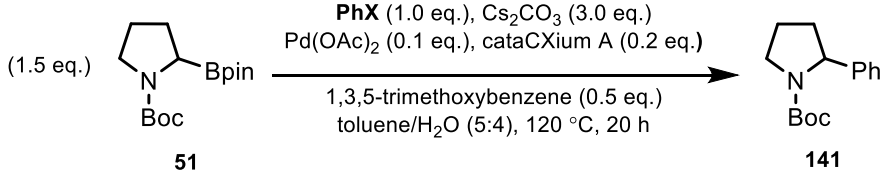
Entry	GC Yield / %[a]				Average Yield / %[a]
1	65	63	61[b]	58[b]	62
2	60	57	52[b]	69[b]	60

a) Yield determined by GC using 1,3,5-trimethoxybenzene as in internal standard; b) Reaction performed by another member of the group

Having demonstrated that the improved set-up gave reliable results, extensive screening of the SMCC reaction conditions commenced. The use of 1,3,5-trimethoxybenzene as an internal standard coupled with analysis by GC enabled the rapid exploration of a wide range of conditions as the reactions could be sampled directly without the need for an aqueous work-up or chromatography. Only key reactions, or those that gave high conversions by GC, were purified and isolated yields obtained. First, a re-investigation of the phenyl halide was carried out although, in this case, the phenyl halide was the

limiting reagent (Table 3.16). Similar results were observed to those using α-Bpin-pyrrolidine **51** as the limiting reagent (see Table 3.14). A higher isolated yield was accomplished with chlorobenzene (54%, 57% GC yield, entry 1) than with bromobenzene (46%, 50% GC yield, entry 2). However, it should be noted that the yield with bromobenzene was the highest obtained thus far with bromobenzene, highlighting the improvement of the new set-up. A 7% GC yield was observed with iodobenzene and a 6% GC yield with phenyltriflate, confirming that, under these conditions, chlorobenzene was the best coupling partner.

Table 3.16: Screening of the SMCC of α-Bpin-*N*-Boc-pyrrolidine **51** with alternative aryl halides and triflate



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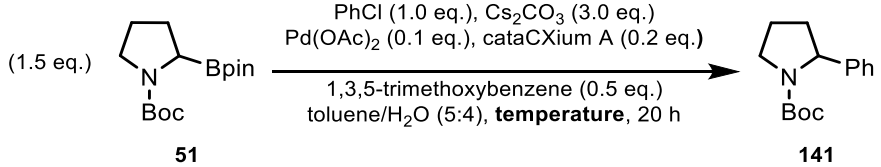
Entry	PhX	GC Yield / %[a]	Yield / %[b]
1	PhCl	57	54
2	PhBr	50	
3	PhI	7	
4	PhOTf	6	

a) Yield determined by GC using 1,3,5-trimethoxybenzene as in internal standard; b) Yield after chromatography

Following this study, the effects of varying the temperature were investigated with both bromobenzene and chlorobenzene. It was important to determine whether the high temperature of 120 °C was necessary. Therefore, the reaction was investigated at 100 °C and at 110 °C (Table 3.17). When the reaction was conducted at 100 °C with chlorobenzene, a 39% GC yield of α-phenylpyrrolidine **114** was obtained (entry 1) compared to a 40% GC yield with bromobenzene (entry 2). The reactions at 110 °C were conducted in triplicate: the reactions with chlorobenzene gave an average GC yield of 57% (entry 3) whereas those with bromobenzene gave an average GC yield of 47% (entry 4). These reactions showed that on decreasing the temperature, the yield dropped. The results with chlorobenzene were 61% yield at 120 °C, an average of a 57% yield at 110 °C and 39% yield at 100 °C. For the SMCC reactions with bromobenzene the same

trend was observed: 50% yield at 120 °C, an average of 47% yield at 110 °C and 40% yield at 100 °C. Although the reduction in yield between 120 °C and 110 °C was not significant, there was greater variability in the individual results obtained, particularly with bromobenzene where GC yields of 57%, 43% and 41% were observed. Overall, the yield decreased as the temperature decreased, demonstrating the necessity of the high temperature and, although similar results were obtained at 110 °C, it was decided that 120 °C would be used for further investigations.

Table 3.17: Screening of the SMCC of α-Bpin-*N*-Boc-pyrrolidine **51** with alternative temperatures



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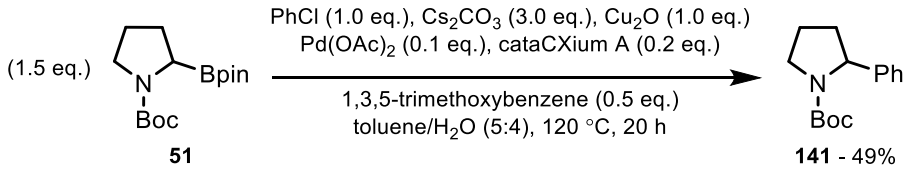
Entry	PhX	Temperature / °C	GC Yield / %[a]
1	PhCl	100	39
2	PhBr	100	40
3	PhCl	110	57[b]
4	PhBr	110	47[c]
5	PhCl	120	61[d]
6	PhBr	120	50

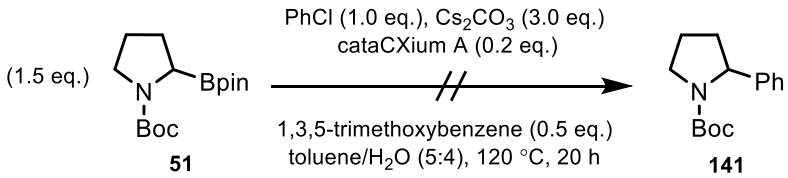
a) Yield determined by GC using 1,3,5-trimethoxybenzene as in internal standard; b) Average of 3 results: 66%, 53%, 53%; c) Average of 3 results: 41%, 57%, 43%; d) Average of 8 results, see Table 3.15

Next, the SMCC of α-Bpin-pyrrolidine **51** was attempted with the addition of 1.0 equivalent of copper(I) oxide as per the original conditions reported by Walsh, Hughes and co-workers.[105] This reaction gave a 49% GC yield of α-phenylpyrrolidine **114** (Scheme 3.64). This, compared to the 61% average GC yield obtained in the absence of copper(I) oxide, demonstrated that the addition of copper(I) oxide was in fact detrimental to the reaction. This is consistent with the previous findings presented in Table 3.11.



Scheme 3.64

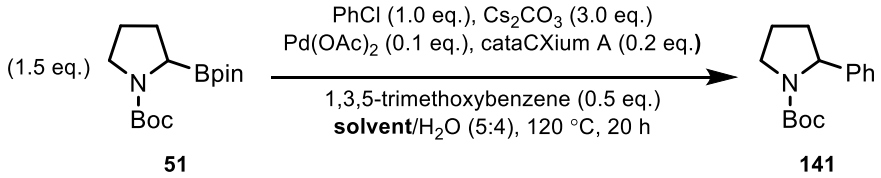
Before proceeding further, a control reaction was conducted in the absence of $Pd(OAc)_2$. Predictably, no α-phenylpyrrolidine **114** was observed by GC confirming that the reaction was indeed palladium-catalysed (Scheme 3.65).



Scheme 3.65

A solvent screen was conducted next. Here, it was of interest to investigate alternative solvents that could potentially allow the reaction to be carried out at lower temperatures since it had been demonstrated that, in toluene, the high temperature of 120 °C was required. Reactions in solvents with a boiling point above or close to 120 °C were conducted at this temperature and those with lower boiling points were conducted at temperatures matching their boiling points. All of the reactions were performed using the improved reaction set-up and conditions (Table 3.18). Unsurprisingly, the SMCC reaction conducted in xylene gave a 56% GC yield of α-phenylpyrrolidine **114** (entry 2) comparable to that obtained in toluene (61%, entry 1). Use of CPME (45%, entry 3), TMO (34%, entry 4) or MTBE (8%, entry 5) resulted in lower GC yields of α-phenylpyrrolidine **114**. The use of 1,4-dioxane, DMF and NMP all at 120 °C gave either trace amounts or none of α-phenylpyrrolidine **114** (entries 6-8) and all reactions conducted in solvents with a lower boiling point (MeCN, DME, THF, MeOH, entries 9-12) gave no cross-coupled product. Therefore, toluene remained the preferred solvent for the SMCC procedure under these conditions.

Table 3.18: Solvent screen of the SMCC of α-Bpin-*N*-Boc-pyrrolidine **51**



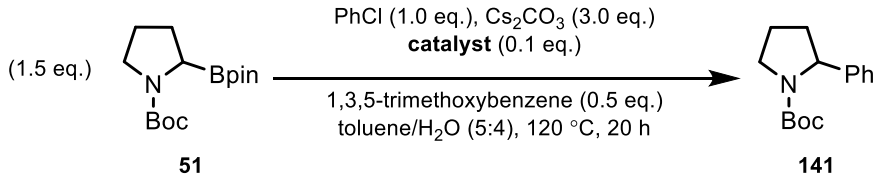
Entry	Solvent	Temperature / °C	GC Yield / %[a]
1	toluene	120	61[b]
2	xylene	120	56
3	CPME	120	45
4	TMO	120	34
5	MTBE	120	8
6	1,4-dioxane	120	1
7	DMF	120	-
8	NMP	120	-
9	MeCN	90	-
10	DME	90	-
11	THF	70	-
12	MeOH	70	-

a) Yield determined by GC using 1,3,5-trimethoxybenzene as in internal standard; b) Average of 8 results, see Table 3.15

Having determined that the reaction was best conducted in toluene at 120 °C, different catalysts and ligands were investigated. A screen was conducted of both precatalysts (0.1 equivalents) (Table 3.19) and of ligands (0.2 equivalents) with $Pd(OAc)_2$ (0.1 equivalents) (Table 3.20). Use of the cataCXium A Pd G3 precatalyst gave a 61% GC yield of α-phenylpyrrolidine **114** (Table 3.19, entry 1), matching the average GC yield (61%) obtained with $Pd(OAc)_2$/cataCXium A. This was an interesting observation as it demonstrated that the precatalyst was just as effective as the ligand with $Pd(OAc)_2$. With PCy_3 Pd G3, a 43% GC yield was achieved (entry 2). Due to the promising nature of this result, the reaction was carried out with bromobenzene instead of chlorobenzene but only a 16% GC yield was observed (entry 2). All other trialkyl- or triarylphosphine

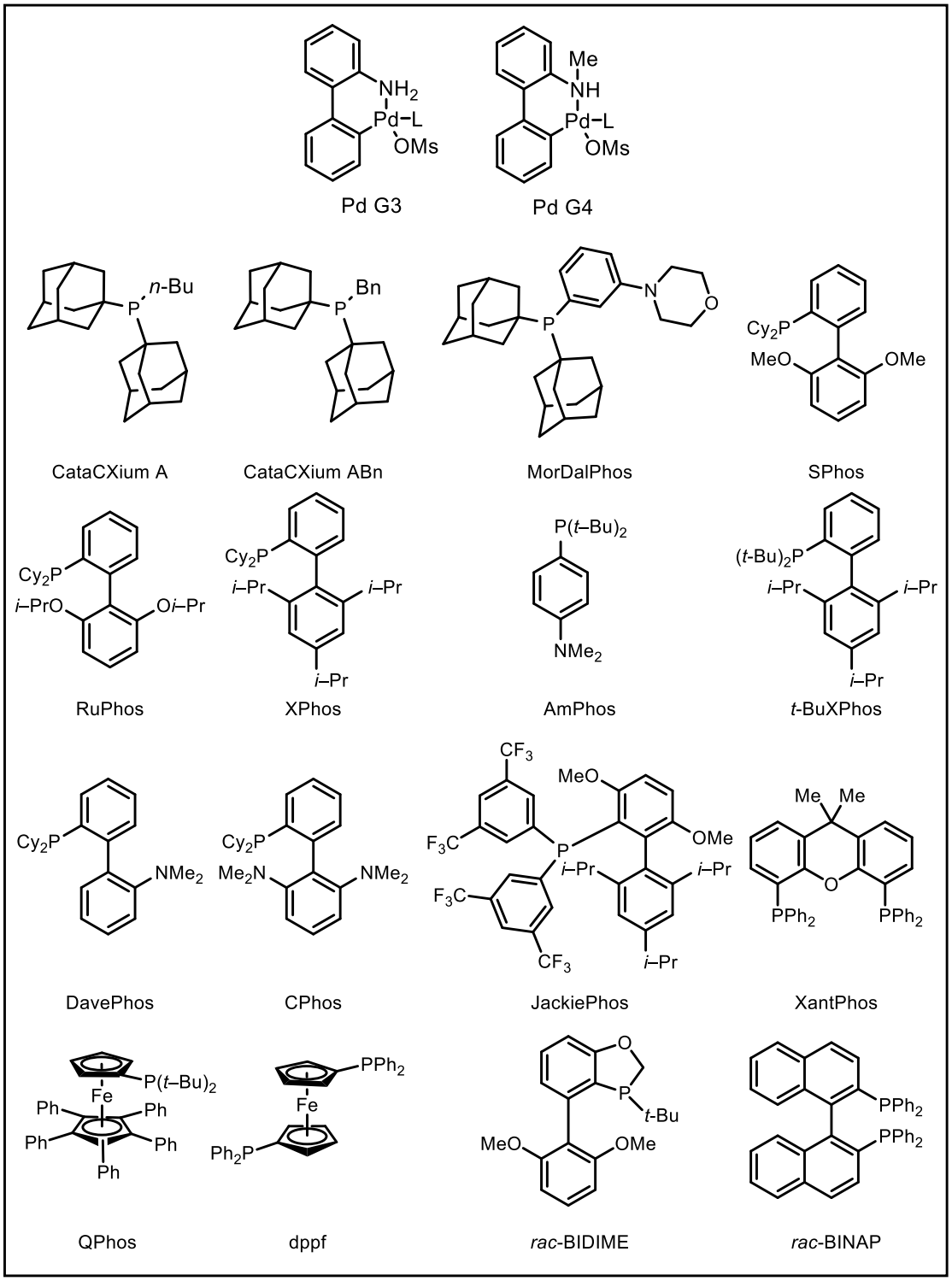
precatalysts gave yields ≤10% (entries 3-5), including $P(Ad)_3$ Pd G3, which is similar in structure to cataCXium A Pd G3. Minimal amounts of α-phenylpyrrolidine **114** were obtained when dppf Pd G3 was used (entry 6). Some conversion was accomplished with a selection of the Buchwald "Phos" type ligands, albeit in low GC yield: SPhos Pd G3 (27% GC yield, entry 7), RuPhos Pd G3 (25% GC yield, entry 8), XPhos Pd G3 (20% GC yield, entry 9) and AmPhos Pd G3 (19% GC yield, entry 10). However, no α-phenylpyrrolidine **114** was observed using *t*-BuXPhos Pd G3 (entry 11) or MorDalPhos Pd G3 (entry 12).

Table 3.19: Precatalyst screen of the SMCC of α-Bpin-*N*-Boc-pyrrolidine **51**



Entry	Precatalyst	GC Yield / %[a]
1	cataCXium A Pd G3	61
2	PCy_3 Pd G3	43 (16)[b]
3	$P(Ad)_3$ Pd G3	10[c]
4	P(*t*-Bu)$_3$ Pd G4	7
5	P(*o*-tol)$_3$ Pd G4	1
6	dppf Pd G3	2
7	SPhos Pd G3	27
8	RuPhos Pd G3	25
9	XPhos Pd G3	20
10	AmPhos Pd G3	19
11	*t*-BuXPhos Pd G3	-
12	MorDalPhos Pd G3	-

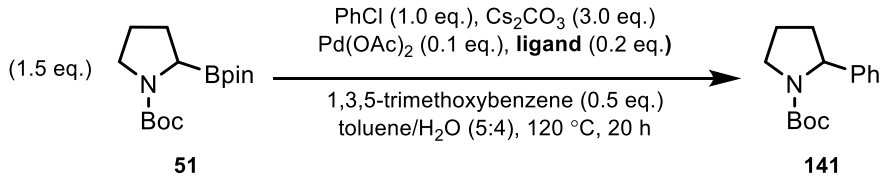
a) Yield determined by GC using 1,3,5-trimethoxybenzene as in internal standard; b) PhBr used instead of PhCl; c) Precatalyst synthesised by another group member



The ligand screen results are shown in Table 3.20. The use of cataCXium ABn with $Pd(OAc)_2$ was unsuccessful (entry 2). When the cross-coupling reaction was conducted with *rac*-BIDIME a 9% GC yield of α-phenylpyrrolidine **114** was obtained (entry 3). Minimal or no α-phenylpyrrolidine **114** was observed with the use of $P(Ad)_3$, PPh_3 or *rac*-BINAP as ligands (entries 4-6). As had been observed with precatalysts, the use of

"Phos" ligands afforded cross-coupled product, albeit in <20% GC yield. The highest GC yields were achieved with XantPhos (20%, entry 7) and DavePhos (11%, entry 8), whereas CPhos, QPhos and JackiePhos all met with minimal success (entries 9-11).

Table 3.20: Ligand screen of the SMCC of α-Bpin-*N*-Boc-pyrrolidine **51**



Entry	Ligand	GC Yield / %[a]	Entry	Ligand	GC Yield / %[a]
1	cataCXium A	61[b]	7	XantPhos	20
2	cataCXium ABn	-	8	DavePhos	11
3	*rac*-BIDIME	9	9	CPhos	7
4	$P(Ad)_3$	1[c]	10	QPhos	5
5	PPh_3	-	11	JackiePhos	1
6	*rac*-BINAP	-			

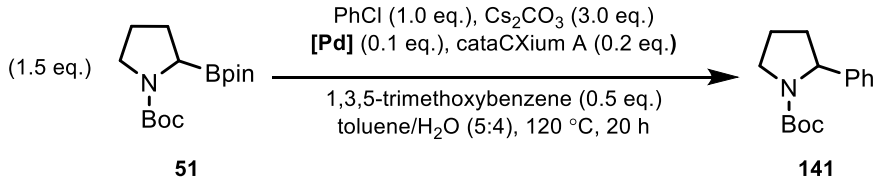
a) Yield determined by GC using 1,3,5-trimethoxybenzene as in internal standard; b) Average of 8 results, see Table 3.15; c) Ligand synthesised by another group member

The clear conclusion from the precatalyst and ligand screening was that cataCXium A was unique. Increasing the steric bulk of the precatalyst/ligand from $P(Ad)_2$*n*-Bu (cataCXium A) to $P(Ad)_3$ drastically reduced the reactivity and modifying the *n*-butyl chain to $P(Ad)_2$Bn (cataCXium ABn) or $P(Ad)_2$Ar (MorDalPhos) likewise prevented cross-coupling from occurring. Although the PCy_3 Pd G3 precatalyst gave a moderate GC yield of 43%, no other precatalyst or ligand gave >30% GC yield. For these reasons, further research was pursued with cataCXium A. The combination of cataCXium A and $Pd(OAc)_2$ was used instead of the cataCXium A Pd G3 precatalyst for cost reasons.

The palladium source was briefly investigated (Table 3.21) using 0.2 equivalents of cataCXium A and 0.1 equivalents of [Pd] (0.05 equivalents of the palladium dimers $[Pd(allyl)Cl]_2$ and $[Pd(p\text{-cinnamyl})Cl]_2$). The use of $[Pd(allyl)Cl]_2$ gave a 40% GC yield of α-phenylpyrrolidine **114** (entry 2) whereas $[Pd(p\text{-cinnamyl})Cl]_2$ gave a 15% GC yield (entry 3). Perhaps surprisingly, both $Pd_2(dba)_3$ and $PdCl_2$ gave minimal or no detectable

α-phenylpyrrolidine **114** (entries 4 and 5). It was clear that the originally utilised catalyst system, $Pd(OAc)_2$ and cataCXium A, was superior to the alternatives and was thus used for further investigations.

Table 3.21: Screening of the SMCC of α-Bpin-*N*-Boc-pyrrolidine **51** with alternative palladium sources



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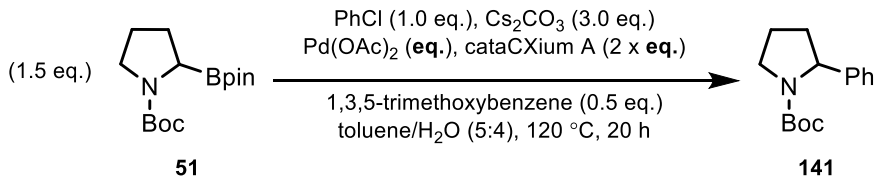
Entry	Pd Source	GC Yield / %[a]
1	$Pd(OAc)_2$	61[b]
2	$[Pd(allyl)Cl]_2$	40
3	$[Pd(p\text{-cinnamyl})Cl]_2$	15
4	$Pd_2(dba)_3$	5
5	$PdCl_2$	-

a) Yield determined by GC using 1,3,5-trimethoxybenzene as in internal standard; b) Average of 8 results, see Table 3.15

The use of 0.1 equivalents of $Pd(OAc)_2$ and 0.2 equivalents of cataCXium A were chosen based on the initial report from Walsh, Hughes and co-workers.[105] With the ultimate aim of seeing whether reduced palladium loadings could be tolerated, the equivalents of $Pd(OAc)_2$ and cataCXium A were investigated. The 2:1 ratio of palladium-ligand was maintained in these experiments (Table 3.22). Use of 0.15 equivalents of $Pd(OAc)_2$ (and therefore 0.3 equivalents of cataCXium A) resulted in an average GC yield of 58% of α-phenylpyrrolidine **114** (entry 4). However, it should be noted that the reaction was conducted twice with a large disparity in the yields (44% and 71%). Further increasing the $Pd(OAc)_2$ loading to 0.2 and 0.3 equivalents did not improve the yield (entries 5 and 6) and the results were broadly, within the natural variation of the reaction, the same as the result with 0.1 equivalents. However, decreasing the $Pd(OAc)_2$ loading did noticeably decrease the conversion, using 0.05 equivalents of $Pd(OAc)_2$ gave a 50% GC yield (entry 2) and 0.02 equivalents gave a

39% GC yield (entry 1). Overall, these results directed us to continue using 0.1 equivalents of $Pd(OAc)_2$ and 0.2 equivalents of cataCXium A.

Table 3.22: Screening of the SMCC of α-Bpin-*N*-Boc-pyrrolidine **51** varying the $Pd(OAc)_2$ loading



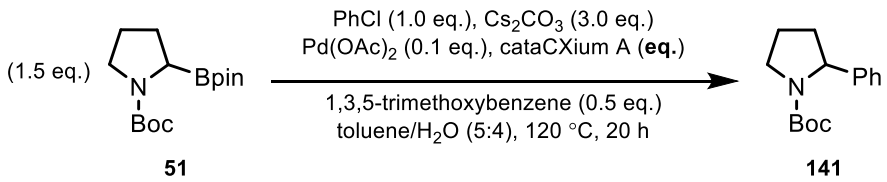
51 **141**

Entry	Eq. of Pd	GC Yield / %[a]
1	0.02	39
2	0.05	50
3	0.10[a]	61[b]
4	0.15	58[c]
5	0.20	58
6	0.30	56

a) Yield determined by GC using 1,3,5-trimethoxybenzene as in internal standard; b) Average of 8 results, see Table 3.15; c) Average of 2 results, 44% and 71%

The next variable explored was the catalyst:ligand ratio. For these experiments, 0.1 equivalents of $Pd(OAc)_2$ were used in all cases (Table 3.23). Increasing the amount of ligand relative to the $Pd(OAc)_2$ resulted in lower GC yields of α-phenylpyrrolidine **114**: a 1:3 ratio of Pd:ligand gave a 52% GC yield (entry 5) and a 1:4 ratio gave a 35% yield (entry 6). Reducing the amount of ligand relative to the palladium led to interesting results. When a 2:3 Pd:ligand ratio was used, a 73% GC yield of α-phenylpyrrolidine **114** was obtained, representing an increase compared to the standard conditions (1:2 Pd:ligand, 61% average GC yield, entry 3). Decreasing the amount of ligand further to a 1:1 ratio gave a 63% GC yield (60% when repeated) (entry 2). Further decreasing the ratio to 2:1 led to a lower GC yield of 44% (entry 1). The 73% GC yield of α-phenylpyrrolidine **114** obtained using a 2:3 Pd:ligand ratio represented the first improvement discovered from the GC screening. Despite the improvement, screening was continued using a 1:2 Pd:ligand ratio for comparison purposes and the 2:3 Pd:ligand ratio was subsequently revisited, as discussed later.

Table 3.23: Screening of the SMCC of α-Bpin-*N*-Boc-pyrrolidine **51** varying $Pd(OAc)_2$:ligand ratios



51 **141**

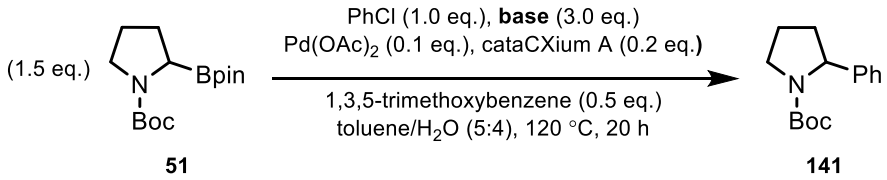
Entry	Eq. of Ligand	Pd:Ligand ratio	GC Yield / %[a]
1	0.05	2:1	44
2	0.10	1:1	62[b]
3	0.15	2:3	73
4	0.20	1:2	61[c]
5	0.30	1:3	52
6	0.40	1:4	35

a) Yield determined by GC using 1,3,5-trimethoxybenzene as in internal standard; b) Average of 2 results, 60% and 63%; c) Average of 8 results, see Table 3.15

The next variable that was investigated was the base. A large number of bases, all at 3.0 equivalents, were screened under the standard conditions (Table 3.24). The standout results from this screen were the use of K_3PO_4 which gave an average GC yield of 59% (entry 13) and Na_3PO_4 which gave a 55% GC yield (entry 14). In addition, K_2CO_3 gave a 47% GC yield (entry 2) and Na_2CO_3 a 33% GC yield (entry 3). Aside from these results, the only base to give α-phenylpyrrolidine **114** in a yield >10% was $KHCO_3$ which afforded an 11% yield of the cross-coupled product (entry 7). Perera, Sach and co-workers reported that, after extensive screening, Et_3N had been identified as an excellent base for sp^2-sp^2 cross-couplings using cataCXium A.[134] However, the use of Et_3N was unsuccessful in this reaction and no α-phenylpyrrolidine **114** was obtained (entry 10). The use of hydroxide and *tert*-butoxide bases resulted in all cases in yields <10% (entries 17-24). An interesting trend could be observed amidst the results: as the size of the cation in the base decreased, the yield decreased. For example, moving from Cs_2CO_3 to K_2CO_3 to Na_2CO_3, a decrease in yield was observed from 61% to 47% to 33%. Likewise, K_3PO_4 gave a slightly higher yield (59%) than Na_3PO_4 (55%). Due to the high initial result achieved with K_3PO_4 (74% GC yield, 54% isolated yield of α-phenylpyrrolidine **114**), the reaction was repeated twice more and then five times in

parallel. These results are shown in Table 3.25. The results in parentheses represent isolated yields (an average of 55%) and the overall average GC yield of the eight results was 59%. Although K_3PO_4 was clearly a viable alternative to Cs_2CO_3, it did not represent an improvement in the yield and none of the other bases screened led to results that were better than Cs_2CO_3.

Table 3.24: Base screen of the SMCC of α-Bpin-*N*-Boc-pyrrolidine **51**



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Entry	Base	GC Yield / %[a]	Entry	Base	GC Yield / %[a]
1	Cs_2CO_3	61[b]	13	K_3PO_4	59[c]
2	K_2CO_3	47	14	Na_3PO_4	44
3	Na_2CO_3	33	15	K_2HPO_4	1
4	$BaCO_3$	2	16	KH_2PO_4	1
5	Ag_2CO_3	1	17	NaOH	-
6	$NaHCO_3$	6	18	NaOAc	1
7	$KHCO_3$	11	19	KOH	2
8	CsF	3	20	KO*t*-Bu	1
9	KF	4	21	LiO*t*-Bu	1
10	Et_3N	-	22	Bu_4NOH	2
11	Et_4NI	-	23	$CsOH•H_2O$	9
12	Ag_2O	-	24	$LiOH•H_2O$	1

a) Yield determined by GC using 1,3,5-trimethoxybenzene as in internal standard; b) Average of 8 results, see Table 3.15; c) Average of 8 results, see Table 3.25

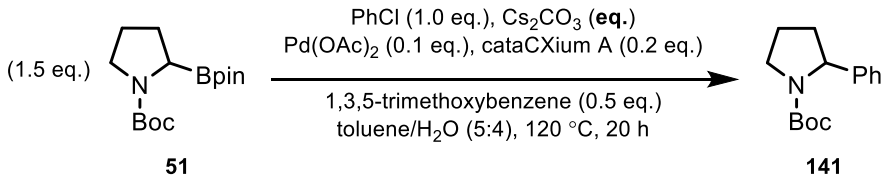
Table 3.25: SMCC of α-Bpin-*N*-Boc-pyrrolidine **51** with K_3PO_4

	GC Yield / %[a]				
Independent	74 (54)	63 (55)	33		
Parallel	65	62	60	58	55

a) Yield determined by GC using 1,3,5-trimethoxybenzene as in internal standard

Following on from the base screen, the next variable that was investigated was the equivalents of base used (Table 3.26). Increasing the amount of Cs_2CO_3 in the reaction to 5.0 equivalents gave a 69% GC yield of α-phenylpyrrolidine **114** (entry 6). Use of 2.0 equivalents of Cs_2CO_3 gave a 62% GC yield (entry 4) which was comparable to the 61% average GC yield obtained with 3 equivalents of base (entry 5). Further reducing the amount of Cs_2CO_3 essentially shut the reaction down (entries 1-3); for example, the use of 1.0 equivalent of Cs_2CO_3 gave only a 4% yield (entry 3). These results indicated that at least 2.0 equivalents of Cs_2CO_3 were required in the reaction and, whilst it did not increase the yield, there could be utility in reducing the equivalents of Cs_2CO_3 from an environmental impact perspective. The high GC yield obtained with 5.0 equivalents of Cs_2CO_3 (69%, entry 6) was unexpected although it should be highlighted that individual yields of 65% and 69% have also been obtained using 3.0 equivalents of Cs_2CO_3 (see Table 3.15). Therefore, it was decided to maintain the use of 3.0 equivalents of Cs_2CO_3.

Table 3.26: Screening of the SMCC of α-Bpin-*N*-Boc-pyrrolidine **51** with different equivalents of Cs_2CO_3



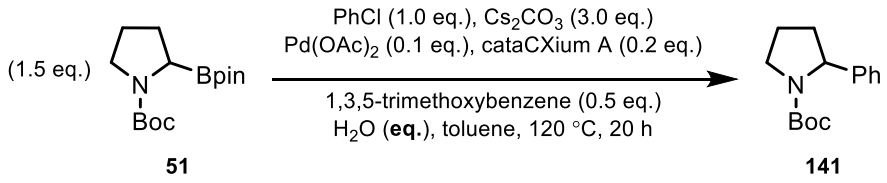
51 **141**

Entry	Eq.	GC Yield / %
1	0.2	1
2	0.5	2
3	1.0	4
4	2.0	62
5	3.0	61[a]
6	5.0	69

a) Yield determined by GC using 1,3,5-trimethoxybenzene as in internal standard; b) Average of 8 results, see Table 3.15

The final variable to be investigated was the equivalents of water used in the SMCC reaction of α-Bpin-*N*-Boc-pyrrolidine **51** and chlorobenzene (Table 3.27). Difficulties were encountered during this investigation as the reactions with low equivalents of water present often boiled dry and resulted in the conversion predicted by the GC not being accurate, potentially due to the degradation or loss of the internal standard once the reaction had boiled dry. Due to this, the reactions with 10 or fewer equivalents of water were worked-up and the product isolated in order to provide more meaningful results. However, it was felt that the GC yields from the reactions conducted with a 2:1 ratio of toluene-water or higher could be trusted. Increasing the amount of water present from the usual 5:4 toluene-water solvent mixture decreased the yield. For example, in 1:1 toluene-water (78 equivalents of water), a 53% GC yield was achieved (entry 8) and in 1:2 toluene-water (155 equivalents of water), only a 5% yield was obtained (entry 9). However, decreasing the amount of water in the reaction significantly increased the yield. Use of 2:1 toluene-water (39 equivalents of water, entry 6) gave an 80% GC yield and use of 8 or 10 equivalents of water gave 88% or 87% GC yields respectively (entries 4 and 5); upon work-up and chromatography, these reactions gave α-phenylpyrrolidine **114** in 77% and 75% yields respectively. The reaction with 10 equivalents of water was carried out three times and the results presented in entry 5 are the averages of these reactions. The recorded GC yields were 99%, 79% and 83% with associated isolated yields of 77%, 80% and 68% (entry 5). Further decreasing the equivalents of water to 2 or 5 equivalents lowered the isolated yield to 58 and 53% respectively (entries 2 and 3) and, when no water was added to the reaction, a 40% yield was achieved (entry 1). It is likely that the reaction was not completely water-free since anhydrous Cs_2CO_3 was not used. Overall, the reduction in the amount of water led to a significant and reproducible increase in the isolated yield (up to 80%) of α-phenylpyrrolidine **114**. Since this is a two-phase reaction mixture, it is likely that there is an optimum amount of water to allow the best mixing and transfer of the reagents between the aqueous and organic phases. These results suggest that 10 equivalents of water, which corresponds to a ~8:1 toluene-water solvent mixture, represents the optimum amount of water for the SMCC of α-Bpin-pyrrolidine **51** with chlorobenzene.

Table 3.27: Screening of the SMCC of α-Bpin-*N*-Boc-pyrrolidine **51** with different equivalents of water

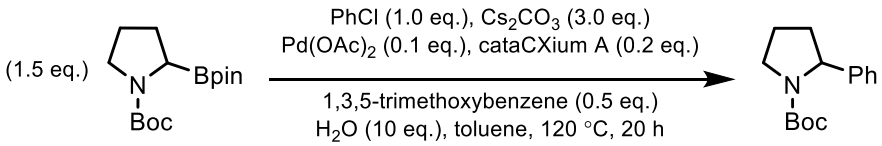


51 **141**

Entry	Eq. of H_2O	Toluene:H_2O ratio	GC Yield / %[a]	Yield / %[b]
1	0	-	54[c]	40
2	2	65:1	86	58
3	5	26:1	71	53
4	8	10:1	88	77
5	10	8:1	87[d]	75[d]
6	39	2:1	80	
7	61	5:4	61[e]	54
8	78	1:1	53	
9	155	1:2	5	

a) Yield determined by GC using 1,3,5-trimethoxybenzene as in internal standard; b) Yield after chromatography; c) Average of 2 results, 72% GC yield (40% isolated yield) and 36% GC yield; d) Average of 3 results, 99% GC yield (77% isolated yield), 79% GC yield (80% isolated yield), 83% GC yield (68% isolated yield); e) Average of 8 results, see Table 3.15

Due to the problems encountered with the reactions boiling dry when using low (<10.0) equivalents of water, the SMCC reaction was attempted with 10 equivalents of water and with twice the volume of solvent present, at half the overall reaction concentration i.e. 0.35 M rather than the standard 0.71 M. These 0.35 M reactions were conducted in triplicate and, pleasingly, the reactions did not boil dry. However, the reactions gave lower GC yields of 42%, 60% and 67% of α-phenylpyrrolidine **114**; the average GC yield afforded was 56% compared to the 87% achieved for the 0.71 M reactions. Subsequent reactions were therefore carried out under the 0.71 M concentration.



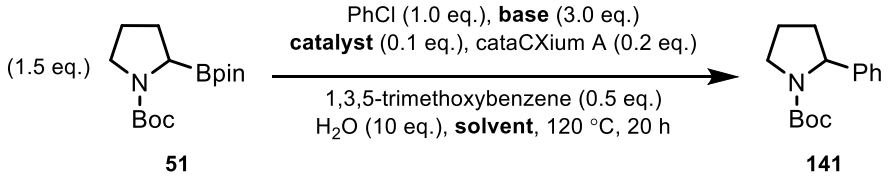
51 **141** - 56%[a]

a) Yield determined by GC using 1,3,5-trimethoxybenzene as in internal standard, average of 3 results

Scheme 3.66

At this point, it was felt that we were close to optimised reaction conditions. It was therefore decided to revisit a few of the variables already explored. The reactions were carried out at 0.71 M concentration and a selection of the best alternative bases (see Table 3.24) and precatalysts (see Table 3.19) were attempted with 10 equivalents of water (Table 3.28). For comparison, the 87% average GC yield of α-phenylpyrrolidine **114** obtained under the standard conditions with 10 equivalents of water is shown in entry 1. The use of K_3PO_4, whilst comparable to Cs_2CO_3 in 5:4 toluene-water (see Table 3.24, entry 13), gave only 51% GC yield with 10 equivalents of water (entry 2). Likewise, K_2CO_3 afforded a lower conversion (52%, entry 3). Minimal α-phenylpyrrolidine **114** was detected when the P(*t*-Bu)$_3$ Pd G4 precatalyst was used (entry 4). Use of the PCy_3 Pd G3 precatalyst gave a 61% GC yield (entry 5) which was an improvement over the analogous GC yield with in 5:4 toluene-water (43%, Table 3.19, entry 2). Finally, a standard reaction was also carried out in cumene and this gave a 58% GC yield (entry 6), demonstrating its potential utility as a solvent. None of these variables led to any improvements over the standard conditions with 10 equivalents of water.

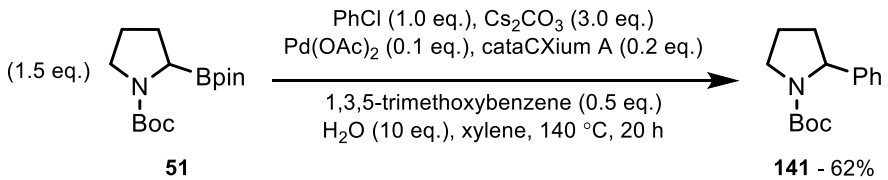
Table 3.28: SMCC reactions of α-Bpin-*N*-Boc-pyrrolidine **51** with 10 equivalents of water



Entry	Base	Pd Source	Ligand	Solvent	GC Yield / %[a]
1	Cs_2CO_3	$Pd(OAc)_2$	cataCXium A	toluene	87[b]
2	K_3PO_4	$Pd(OAc)_2$	cataCXium A	toluene	51
3	K_2CO_3[c]	$Pd(OAc)_2$	cataCXium A	toluene	52
4	Cs_2CO_3	P(*t*-Bu)$_3$ Pd G4	-	toluene	2
5	Cs_2CO_3	PCy_3 Pd G3	-	toluene	61
6	Cs_2CO_3	$Pd(OAc)_2$	cataCXium A	cumene	58

a) Yield determined by GC using 1,3,5-trimethoxybenzene as in internal standard; b) Average of 3 results, see Table 3.27; c) 4.6 eq. of base used

Xylene had given a comparable yield to toluene when a 5:4 xylene-water mixture was used (see Table 3.18, entry 2). Thus, a reaction was attempted in xylene with 10 equivalents of water at 140 °C, making use of the higher boiling point of xylene. The GC conversions were high (99% and 95%) but, frustratingly, these high GC conversions did not translate into an equally high isolated yield. A 62% yield of α-phenylpyrrolidine **114** was obtained after chromatography from the 99% GC yield reaction (Scheme 3.67). These reactions had not boiled dry but it is possible that the very high temperature had led to loss or destruction of some of the 1,3,5-trimethoxybenzene internal standard.

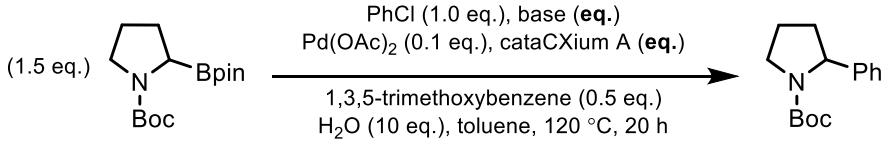


Scheme 3.67

The final investigation was conducted under the standard conditions with 10 equivalents of water and with a combination of 0.15 equivalents of ligand and 2.0 equivalents of base, since these had been shown to have potential in earlier studies (see Tables 3.23

and 3.26) (Table 3.29). The reactions were carried out in duplicate and in three combinations, with lower equivalents of base and ligand (entry 5), lower equivalents of base only (entries 3 and 4) and lower equivalents of ligand only (entry 2). The reaction with lower equivalents of both gave GC yields of 74% and 63% (69% average, entry 5) which was lower than that achieved with the standard 3.0 equivalents of base and 0.2 equivalents of cataCXium A (87%, entry 1). One of the reactions conducted with 2.0 equivalents of base and 0.2 equivalents of cataCXium A gave 85% GC yield and 62% isolated yield (entry 3), whilst the other gave a 73% GC yield (entry 4). Both the average GC yield for these reactions (79%) and the single isolated yield (62%) were lower than the averages achieved with the standard conditions. Finally, the reaction with 2.0 equivalents of base and 0.15 equivalents of cataCXium A gave 87% and 71% GC yields, an average of 79%, which was also lower than that achieved with the standard conditions (entry 5). Overall, none of the combinations of reduced equivalents of base or ligand gave an improvement in yield over 3.0 equivalents of base and 0.2 equivalents of ligand. Either the GC yields were lower, or, upon isolation and purification, the isolated yield was lower. Therefore, these alterations to the standard conditions were not pursued further.

Table 3.29: SMCC of α-Bpin-*N*-Boc-pyrrolidine **51** with 10 equivalents of water and reduced equivalents of base and ligand



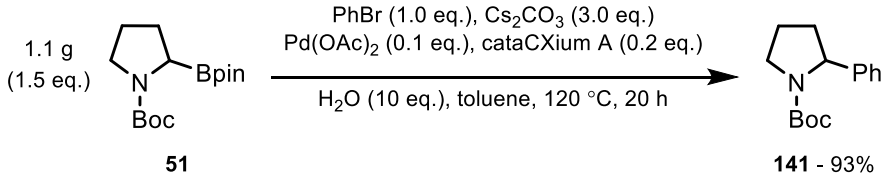
51 **141**

Entry	Base eq.	cataCXium A eq.	GC Yield / %[a]	Yield / %[b]
1	3.0	0.2	87[c]	75[c]
2	3.0	0.15	69[d]	
3	2.0	0.2	85	62
4	2.0	0.2	73	
5	2.0	0.15	79[e]	

a) Yield determined by GC using 1,3,5-trimethoxybenzene as in internal standard; b) Yield after chromatography; c) Average of 3 results, see Table 3.27; d) Average of 2 results, 74% and 63%; e) Average of 2 results, 87% and 71%

Thus, we arrived at the following final optimised conditions for the SMCC reaction of α-Bpin-pyrrolidine **51** with chlorobenzene to give α-phenylpyrrolidine **114**. The reaction used 1.0 equivalent of chlorobenzene, 1.5 equivalents of α-Bpin-pyrrolidine **51**, 3.0 equivalents of Cs_2CO_3, 0.1 equivalent of $Pd(OAc)_2$ and 0.2 equivalents of cataCXium A in toluene at 0.71 M concentration (relative to the chlorobenzene) with 10 equivalents of water and heated at 120 °C for 20 hours. The whole reaction was conducted under nitrogen in a sealed screw top Teflon vial. Using these conditions, isolated yields of α-phenylpyrrolidine **114** of 80%, 77% and 68% were obtained from three experiments run in parallel, an average isolated yield of 75%.

After the end of this work, the utility of these conditions was further demonstrated by another member of the group who performed the SMCC of α-Bpin-pyrrolidine **51** with chlorobenzene on a gram-scale. The optimised conditions were utilised with 1.1 g of α-Bpin-pyrrolidine **51** using 3.5 mL of toluene and 0.45 mL of water and the reaction was carried out in a 25 mL RBF under nitrogen with a reflux condenser attached. The SMCC reaction afforded α-phenylpyrrolidine **114** in 93% yield (0.58 g isolated) (Scheme 3.68).



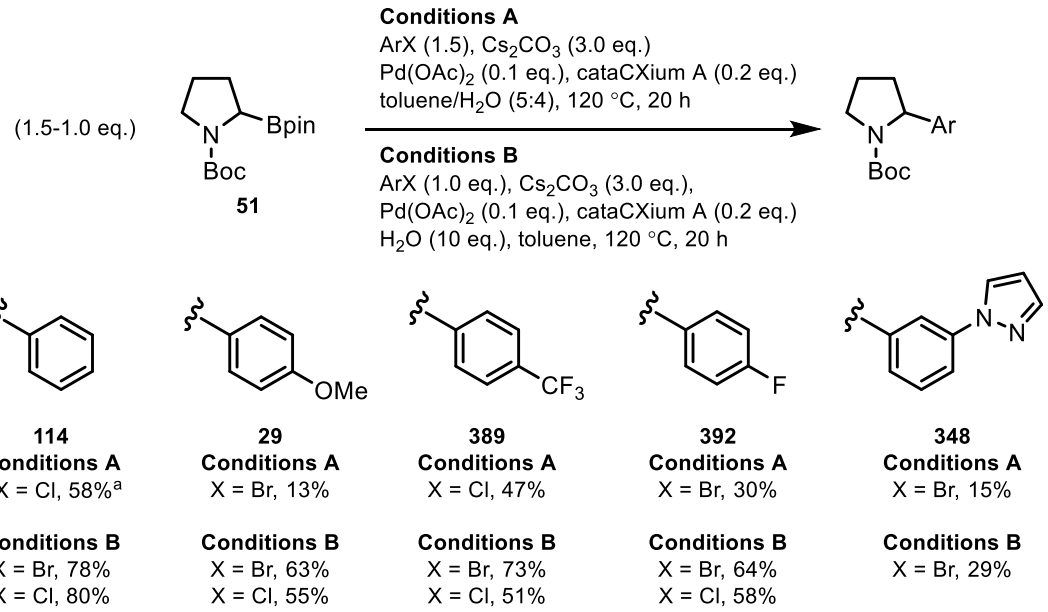
Scheme 3.68

This result demonstrated that the reaction could be scaled up and in fact afforded a higher yield when conducted on a larger scale. This may have been due to better mixing being achieved in a larger-scale set-up. In conclusion, the SMCC of α-Bpin-pyrrolidine **51** with chlorobenzene has been optimised and efficient conditions developed, with which α-phenylpyrrolidine **114** could be obtained in up to 93% yield.

3.6 Scope of Suzuki-Miyaura Cross-Coupling of α-Bpin-*N*-Boc-pyrrolidine

3.6.1 Racemic Suzuki-Miyaura Cross-Coupling of α-Bpin-*N*-Boc-pyrrolidine

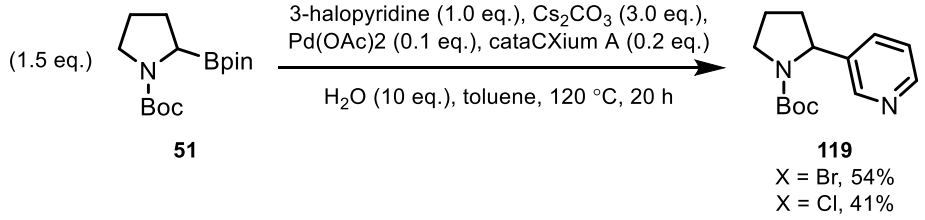
With optimised conditions for the SMCC reaction of α-Bpin-pyrrolidine **51** in hand, the scope of the aryl halide was explored. The aryl halides utilised in the initial scope investigation presented in section 3.51 (see Scheme 3.62) were used and the results are presented in Scheme 3.69. Conditions A used 1.5 equivalents of aryl halide, 5:4 toluene-water and the original reaction set-up. The newly optimised conditions, conditions B, used 1.5 equivalents of α-Bpin-pyrrolidine **51** (i.e. the aryl halide as the limiting reagent), 10 equivalents of water and the more robust reaction set-up developed for the GC screening. The cross-coupling reactions were conducted with both the aryl bromide and chloride in all four cases; unfortunately, 1-(3-chlorophenyl)-1*H*-pyrazole was not available. The yields quoted are all isolated yields after chromatography. Under conditions B, cross-coupling with bromobenzene gave a 78% yield of α-phenylpyrrolidine **114**, which compared well with the highest isolated yield of 80% using chlorobenzene. Cross-coupling with 4-bromoanisole afforded α-arylpyrrolidine **29** in 73% yield (conditions B), a dramatic improvement compared to the 13% achieved with the original conditions (conditions A). The use of 4-chloroanisole gave a 51% yield, notably lower than with 4-bromoanisole. With 4-bromobenzotrifluoride, a 63% yield of α-arylpyrrolidine **389** was obtained, an improvement on the original yield of 47% (conditions A). A 53% yield with 4-chlorobenzotrifluoride was obtained. Likewise, an improvement was seen in the synthesis of α-arylpyrrolidine **392** where a 64% yield was achieved with 4-fluorobromobenzene and conditions B, compared to 36% yield using conditions A. 4-Fluorochlorobenzene, by comparison, gave a 58% yield of α-arylpyrrolidine **392**. Finally, a 29% yield of α-arylpyrrolidine **348** was obtained when 1-(3-bromo-phenyl)-1H-pyrazole was cross-coupled using conditions B, essentially double that previously obtained using conditions A. Overall, these results showed a marked improvement in yield upon reducing the amount of water to 10 equivalents, changing the aryl halide to be the limiting reagent and improving the set-up (conditions B compared to conditions A). It also indicated that under the optimised conditions aryl bromides generally gave slightly higher yields than aryl chlorides, a reverse of the situation under conditions A (see Scheme 3.62).



a) 69% yield with 1.0 eq. of PhCl and 1.5 eq. of α-Bpin-pyrrolidine **51**

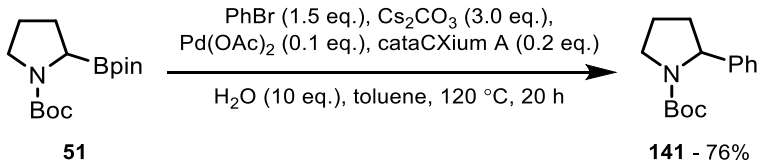
Scheme 3.69

The SMCC was then attempted using 3-bromopyridine and 3-chloropyridine as the coupling partners under the optimised conditions. When the cross-coupling was conducted with 3-chloropyridine, a 41% yield of α-arylpyrrolidine **119** was accomplished; the analogous reaction with 3-bromopyridine gave a 54% yield (Scheme 3.70). These results were consistent with the trend of slightly higher yields being obtained with the aryl bromide compared to the aryl chloride. Pleasingly, this reaction also demonstrated that heteroaryl halides could be cross-coupled.



Scheme 3.70

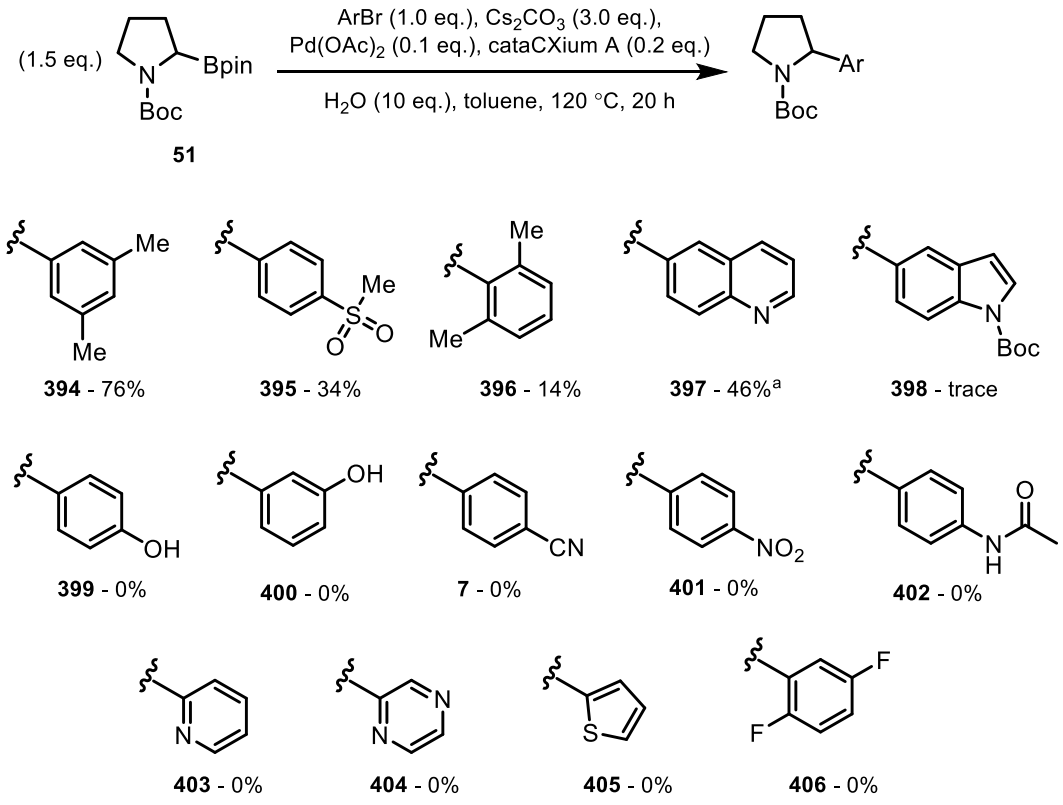
For comparison purposes, the SMCC reaction was also performed with α-Bpin-pyrrolidine **51** as the limiting reagent and 1.5 equivalents of bromobenzene using 10 equivalents of water. A 76% yield of α-phenylpyrrolidine **114** was obtained from this reaction (Scheme 3.71). Thus, it was demonstrated that comparably high (76-80%) yields could be achieved with either the aryl halide as the limiting reagent or α-Bpin-pyrrolidine **51** as the limiting reagent.



Scheme 3.71

As it had been demonstrated that aryl bromides made for slightly better coupling partners (in terms of yields), aryl bromides were used for the further exploration of the scope of the reaction. It was desirable to be able to cross-couple 1-bromo-3,5-dimethylbenzene since Aticaprant, a compound in the late stages of drug development, contains a pyrrolidine motif with a 3,5-dimethylbenzene group in the α-position (see Figure 1.2). Likewise, cross-coupling with 1-bromo-2,5-difluorobenzene would give the motif present in the anti-cancer drug Larotrectinib (see Figure 1.2) and, for this reason, it was included in the scope of aryl bromides. As well as these specific aryl bromides, a range of others with different electronic and structural features were cross-coupled with α-Bpin-pyrrolidine **51** to determine the scope of the reaction. The results obtained are summarised in Scheme 3.72. Pleasingly, when the SMCC reaction was attempted with 1-bromo-3,5-dimethylbenzene, a 76% yield of α-arylpyrrolidine **394** was achieved, demonstrating that the motif in Aticaprant could be synthesised *via* the SMCC methodology. The cross-coupling of 4-bromophenyl methyl sulfone gave α-arylpyrrolidine **395** in 34% yield whereas use of the highly sterically hindered 1-bromo-2,6-dimethylbenzene afforded α-arylpyrrolidine **396** in 14% yield. The yield of α-arylpyrrolidine **396** was significantly lower than that achieved with other aryl bromides, presumably due to the steric hindrance of the aryl bromide. 6-Bromoquinoline was cross-coupled to afford α-arylpyrrolidine **397** in 46% yield, further demonstrating that heteroaryl bromides were tolerated in the reaction. Due to issues arising from purification, the reaction was carried out with 6-bromoquinoline as the limiting reagent and 1.5 equivalents of α-Bpin-pyrrolidine **51**. In contrast, the cross-coupling of *N*-Boc-5-bromoindole afforded only trace amounts of α-arylpyrrolidine **398** by HRMS. Despite the successful cross-coupling of 4-bromoanisole (63% yield, see Scheme 3.69), the attempted SMCC with 4-bromophenol did not afford any of the desired α-arylpyrrolidine **399**; similarly, use of 3-bromophenol did not give α-arylpyrrolidine **400**. Likewise, no α-arylpyrrolidine **7** was obtained from the reaction with 4-bromobenzenecarbonitrile and the attempted SMCC reactions with 1-bromo-4-

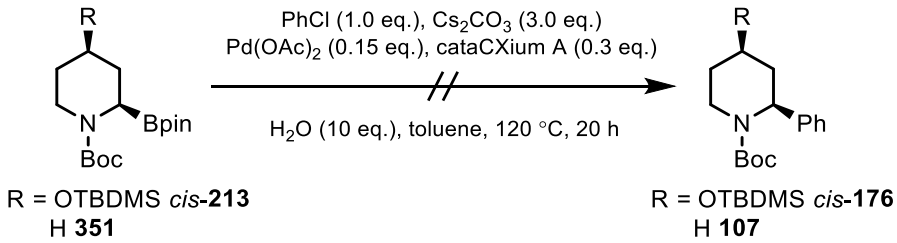
nitrobenzene, 4-bromoacetanilidine, 2-bromopyridine, 2-bromopyrazine and 2-bromothiophene were all unsuccessful. Unfortunately, when the cross-coupling was attempted with 1-bromo-2,5-difluorobenzene, the reaction was not successful, this may have been due to the presence of an *ortho* fluorine. The successful coupling of 1-bromo-2,6-dimethylbenzene suggested that the unsuccessful coupling of 1-bromo-2,5-difluorobenzene was not solely to do with sterics, as the SMCC reaction had been shown to tolerate two *ortho* methyl groups. It had been shown that, during the lithiation-trapping-Negishi cross-coupling α-arylation procedure, the α-arylation of 4-OTBDMS-*N*-Boc-piperidine **73** with 2-fluorobromobenzene gave a 27% yield of α-aryl piperidine *cis*-**189**, a low yield compared to the majority of results in the aryl halide scope (see Scheme 2.53). It had been proposed that the low yield in the Negishi α-arylation reaction had been due to the *ortho* fluorine which could suggest that *ortho* fluorine-containing aryl bromides are not good partners in palladium-catalysed cross-coupling reactions. In all SMCC reactions with no conversion, no cross-coupled product was detected by HRMS and ^{1}H NMR spectroscopy of the crude reaction mixture showed the presence of the α-Bpin-pyrrolidine **51** starting material.



a) 1.0 eq. pyrrolidine Bpin, 1.5 eq. ArBr

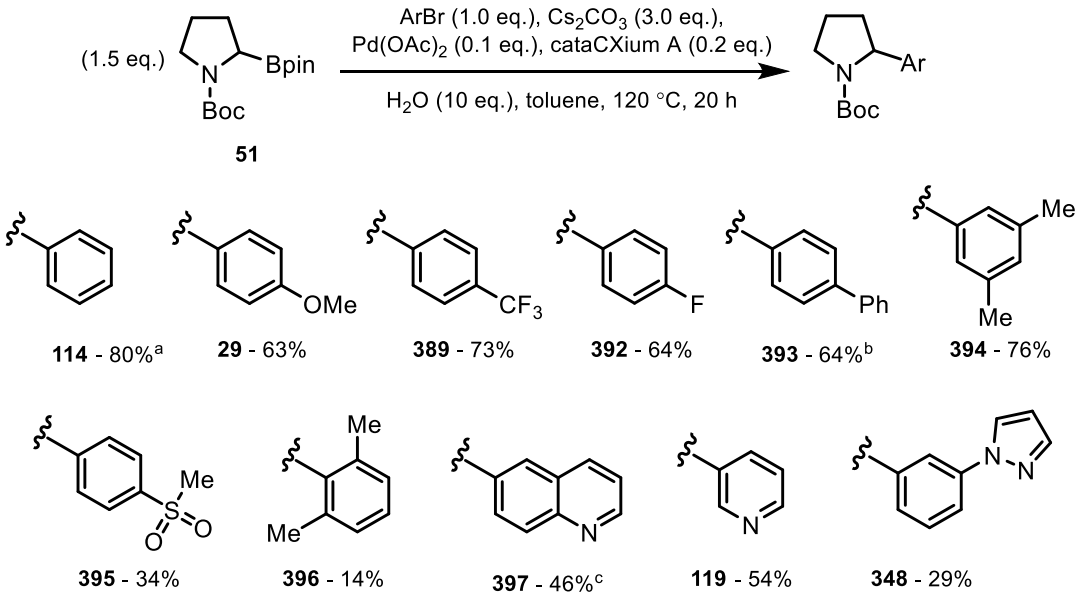
Scheme 3.72

Having obtained suitable conditions for the SMCC of α-Bpin-pyrrolidine **51**, the SMCC of α-Bpin-4-OTBDMS-*N*-Boc-piperidine *cis*-**213** was attempted as an example of a piperidine substrate. The optimised conditions were used; however, the reaction was unsuccessful and only trace amounts of α-arylpiperidine *cis*-**176** were detected by HRMS (Scheme 3.73). Another member of the group attempted the cross-coupling using the same conditions with α-Bpin-piperidine **351** and, similarly, no product was observed by HRMS or ^{1}H NMR spectroscopy. These results highlight the challenging nature of the SMCC of α-Bpin-piperidines.



Scheme 3.73

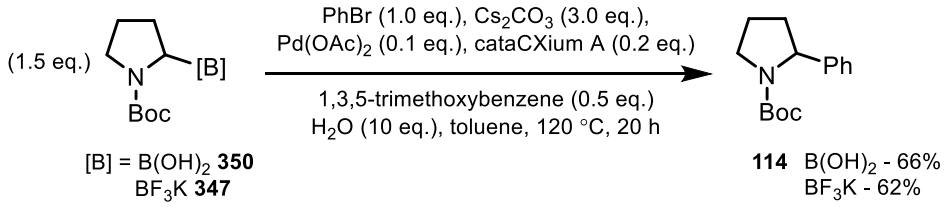
Our initial exploration of the scope of the SMCC reaction with α-Bpin-pyrrolidine **51** indicates that there are limitations. For example, although some heteroaryl halides could be cross-coupled, several could not be. In addition, as had been observed in the scope of the Negishi reaction, where the cross-coupling of 4-bromophenol and 4-bromopyrazole had been unsuccessful (see Scheme 2.50), it appears that coupling partners with acidic protons, such as 3-bromophenol and 4-bromoacetanilidine, were not tolerated. However, it was shown that a highly sterically hindered substrate, 1-bromo-2,6-dimethylbenzene, was tolerated, along with both electron withdrawing and electron donating groups. The full scope of the successful reactions are shown in Scheme 3.74.



a) PhCl used; b) 5:4 toluene-H_2O, 1.0 eq. pyrrolidine Bpin, 1.5 eq. ArCl; c) 1.0 eq. pyrrolidine Bpin, 1.5 eq. ArBr

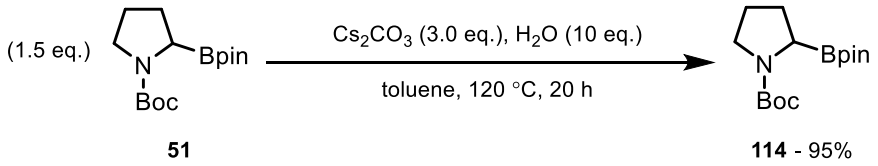
Scheme 3.74

Since the end of the project, the SMCC of α-$B(OH)_2$-*N*-Boc-pyrrolidine **350** and α-BF_3K-*N*-Boc-pyrrolidine **347** were revisited by another member of the group using the optimised conditions, critically with lower equivalents of water. The reactions were carried out with bromobenzene and, under these conditions, the SMCC of α-$B(OH)_2$-pyrrolidine **350** gave α-arylpyrrolidine **114** in 66% yield after chromatography whereas α-BF_3K-pyrrolidine **347** afforded a 62% yield (Scheme 3.75). These reactions demonstrated that, although the Bpin group was still the better coupling partner, good yields could be achieved with both the boronic acid and BF_3K salt. These results represented significant improvements on the results in section 3.5.1 where an 11% and 7% NMR yield were observed with the cross-coupling of α-BF_3K-pyrrolidine **347** and α-$B(OH)_2$-pyrrolidine **350** under slightly different conditions (see Table 3.13). It is possible that the increase in conversion was due to the lower equivalents of water used or the improved reaction set-up. Either way, the successful cross-couplings in >60% yield further demonstrated the utility of the optimised conditions and the methodology.



Scheme 3.75

The other group member also heated α-Bpin-pyrrolidine **51** at 120 °C in toluene with 10 equivalents of water and Cs_2CO_3 for 20 hours, mimicking the SMCC reaction conditions but in the absence of catalyst, ligand and aryl halide. The reaction was purified by chromatography and 95% of the α-Bpin-pyrrolidine **51** starting material was recovered. This demonstrated that hydrolysis to the boronic acid had not taken place and, hence, it can be proposed that Bpin hydrolysis did not occur prior to transmetallation in the SMCC, as, after stirring under the reaction conditions for 20 hours, the boronic acid was not observed. This, therefore, suggested that transmetallation was taking place directly from the BPin group or a boronate adduct of the Bpin group. The results with α-BF_3K-pyrrolidine **347** and α-$B(OH)_2$-pyrrolidine **350** demonstrated that the SMCC reaction could also proceed from the boronic acid and that at least two reaction pathways must be available.



51 **114** - 95%

Scheme 3.76

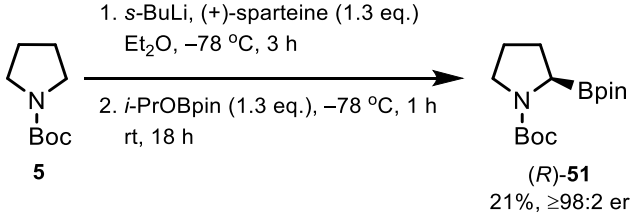
3.6.2 Investigation of the Stereospecificity of the Suzuki-Miyaura Cross-Coupling of Enantioenriched α-Bpin-*N*-Boc-pyrrolidine

The final stage of exploring the SMCC of α-Bpin-pyrrolidine **51** involved a study on the stereochemical outcome of the SMCC reaction with the aim of developing methodology that would be suitable for the synthesis of highly enantioenriched α-arylpyrrolidines. One particular advantage of the Suzuki-Miyaura methodology over the Negishi cross-coupling reaction previously developed by Campos *et al*. was that,[12] in principle, enantioenriched α-Bpin-pyrrolidine **51** could be prepared in a single large-scale lithiation reaction and then used in multiple SMCC reactions. In contrast, in the Negishi methodology, an asymmetric lithiation step would be needed before every cross-coupling reaction or the organozinc species would need to be split up into batches (as Campos *et al.* had reported). To explore the stereospecificity of the SMCC reaction, it would be necessary to synthesise enantioenriched α-Bpin-pyrrolidine **51** of known er and configuration. Then, carrying out the SMCC reaction with bromobenzene should give α-phenylpyrrolidine **114** and its optical rotation could be compared with the known

values in the literature to determine whether the reaction has proceeded with retention or inversion. In addition, the er of the α-phenylpyrrolidine **114** so-generated would report on the degree of stereospecificity of the SMCC reaction.

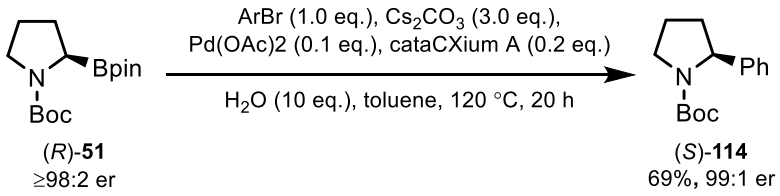
To this goal, the synthesis of enantioenriched α-Bpin-pyrrolidine (*R*)-**51** was required. This had been previously performed by Whiting *et al.* during their investigations into the synthesis of α-B(OH)$_2$-pyrrolidine (*S*)-**350**.[120] Whiting had prepared α-Bpin-pyrrolidine (*S*)-**51** in 88% yield *via* asymmetric lithiation-trapping with *s*-BuLi/(–)-sparteine **93** in Et_2O at –78 °C and α-B(OH)$_2$-pyrrolidine (*S*)-**350** by a similar method in 72% yield and 95:5 er (see Scheme 3.36). Whiting *et al.* definitively proved the stereochemistry of α-B(OH)$_2$-pyrrolidine (*S*)-**350** by transformation of the boronic acid into a hydrobenzoin ester from which an X-ray crystal structure was obtained. The sense of induction imparted by (–)-sparteine **93** during *N*-Boc heterocycle lithiation-trapping is well known and this was in agreement with the X-ray crystal structure determined by Whiting *et al.*.

Therefore, we performed the asymmetric lithiation-trapping of *N*-Boc-pyrrolidine **5** with *s*-BuLi/(+)-sparteine in Et_2O at –78 °C for 3 hours. The lithiated intermediate was trapped with *i*-PrOBPin to afford 1.2 g of α-Bpin-pyrrolidine (*R*)-**51** in 21% yield (Scheme 3.77); difficulties in purification accounted for the low yield. The product was recrystallised from hexane and several crops of crystals were obtained and the er of each batch was determined by CSP-HPLC. The reaction was assumed to give the opposite enantiomer, α-Bpin-pyrrolidine (*R*)-**51**, to that obtained by Whiting *et al.* as the opposite enantiomer of sparteine **93** had been used during the lithiation step. The absolute stereochemistry was confirmed by the $[\alpha]_D$ value (–58.4, c 1.0 in CH_2Cl_2) which had the opposite sense to the $[\alpha]_D$ of α-Bpin-pyrrolidine (*R*)-**51** obtained by Whiting *et al.* (+69.5, c 1.06 in CH_2Cl_2). Finally, the er was determined by CSP-HPLC, in comparison to a racemic sample, which showed that all the batches of α-Bpin-pyrrolidine (*R*)-**51** had been obtained in ≥98:2 er.



Scheme 3.77

The SMCC of α-Bpin-pyrrolidine (*R*)-**51** (≥98:2 er) was conducted with bromobenzene using the optimised conditions and α-phenylpyrrolidine (*S*)-**114** was obtained in 69% yield and 99:1 er (Scheme 3.78). The er was determined by CSP-HPLC with comparison to a racemic sample and comparison to data reported by O'Brien, Campos and co-workers who had reported the synthesis of an enantioenriched sample of α-phenylpyrrolidine (*R*)-**114** in 96:4 er.[44] O'Brien, Campos and co-workers reported $[\alpha]_D$ of +85.3 (*c* 1.0 in acetone). By comparison, the sample of α-phenylpyrrolidine (*S*)-**114** synthesised in this work had $[\alpha]_D$ of –84.3 (*c* 1.0 in acetone), the opposite sign in the optical rotation indicating that the major enantiomer was (*S*) as expected. O'Brien, Campos and co-workers reported a retention time of 12.2 min for the major (*R*)-enantiomer and 12.9 min for the minor (*S*)-enantiomer when using a chiralpak AD-H column (99:1 heptane-*i*-PrOH, 0.5 mL min^{-1}). The CSP-HPLC conditions used in this work, whilst not identical, (Chiralpak AD-H, 99.5:0.5 hexane:*i*-PrOH, 0.3 mL min^{-1}) were similar and, under these conditions, the (*R*)-enantiomer eluted first, matching the observations of O'Brien, Campos and co-workers. Therefore, we had confidence that the SMCC reaction had proceeded with retention of stereochemistry and had given α-phenylpyrrolidine (*R*)-**114** as the major product in 99:1 er.

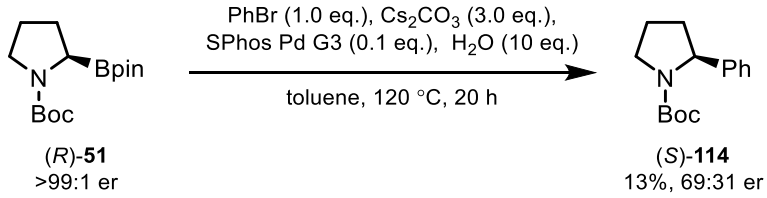


Scheme 3.78

This was an exciting result that clearly demonstrated that the SMCC reaction had proceeded with complete stereospecificity and retention of stereochemistry. Sigman, Biscoe and co-workers had reported that the use of bulky electron-rich alkyl phosphine ligands, such as $P(Ad)_3$, led to the favouring of the stereoinvertive pathway during transmetallation step (see Scheme 3.16).[90] However, Biscoe *et al.* went on to investigate the SMCC of cyclic alkylboronates and concluded that the ligand preference could be overridden by the steric considerations of the substrate, particularly in cyclic systems (see Schemes 3.19 and 3.20).[110] The closest published comparison to the SMCC of enantioenriched α-Bpin-pyrrolidine (*R*)-**51** is from Sawamura *et al.*, who reported that the α-arylation of α-Bpin-*N*-(2-pyridyl)pyrrolidine (*R*)-**342** proceeded with retention of

stereochemistry (see Scheme 3.32).[26] Therefore, whilst inversion of stereochemistry would have been expected based on the choice of ligand in this system (bulky electron-rich cataCXium A ligand), there is also precedent for the SMCC of cyclic boronates proceeding with the retention of stereochemistry. As covered in sections 3.1.2 and 3.1.3, the factors governing stereoselectivity in the SMCC of sp^3 alkylboronates are not straightforward. However, CSP-HPLC and $[\alpha]_D$ data clearly demonstrated that the reaction had proceeded with the retention of stereochemistry and complete enantiospecificity.

Next, the SMCC of enantioenriched α-Bpin-pyrrolidine (*R*)-**51** was conducted with SPhos Pd G3 to investigate if the ligand had any effect on the enantiospecificity of the reaction. This was inspired by the work of Sigman, Biscoe and co-workers who had reported that the choice of ligand during the SMCC of enantioenriched alkylboronates affected the stereochemical outcome (see Scheme 3.16).[90] The optimised conditions were utilised, albeit replacing $Pd(OAc)_2$/cataCXium A with SPhos Pd G3 (Scheme 3.79). Predictably, the yield of α-phenylpyrrolidine (*S*)-**114** was low, 13%, as SPhos had been shown to be an inferior ligand to cataCXium A (see Table 3.19, entry 7). However, α-phenylpyrrolidine (*S*)-**114** was obtained in 69:31 er, a clear erosion of stereochemical information. This example demonstrated that the ligand had a significant effect on the stereochemical outcome of the SMCC of enantioenriched α-Bpin-pyrrolidine (*R*)-**51** and highlighted the importance of the use of cataCXium A, which was both a good ligand for affecting the transformation and achieving stereospecificity.



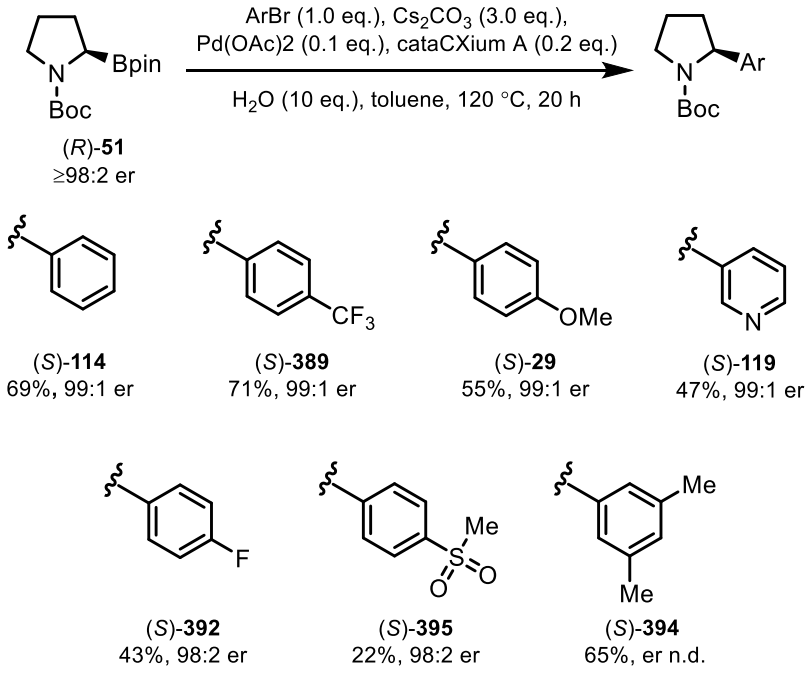
(*R*)-**51**
>99:1 er

(*S*)-**114**
13%, 69:31 er

Scheme 3.79

Further examples of the stereospecific nature of the SMCC were obtained with the synthesis of enantioenriched analogues of the substrates shown in Scheme 3.80. The cross-coupling of 4-bromobenzotrifluoride gave α-arylpyrrolidine (*S*)-**389** in 71% yield and 99:1 er. The use of 4-bromoanisole afforded α-arylpyrrolidine (*S*)-**29** in 55% yield and 99:1 er. α-Arylpyrrolidine (*S*)-**29** had $[\alpha]_D$ –89.7 (*c* 1.0 in acetone); for comparison, a sample of α-arylpyrrolidine (*R*)-**29** (96:4 er) synthesised by Denmark *et al.* had $[\alpha]_D$

+90.6 (*c* 0.5 in acetone), confirming that the (*S*)-enantiomer had been synthesised in this SMCC reaction.[135] The SMCC with 3-bromopyridine gave α-arylpyrrolidine (*S*)-**119** in 47% yield and 99:1 er; this result also represented a formal synthesis of (*S*)-nicotine since the conversion of the *N*-Boc group into an *N*-methyl group has previously been reported in our group.[44] The $[\alpha]_D$ of α-arylpyrrolidine (*S*)-**119** was –75.6 (*c* 1.0 in CH_2Cl_2), demonstrating the successful synthesis of the (*S*)-enantiomer since a sample of α-arylpyrrolidine (*R*)-**119** (98:2 er), previously prepared in our group, possessed $[\alpha]_D$ +80.0 (*c* 1.0 in CH_2Cl_2).[44] Alongside these examples of an electron-deficient, electron-rich and heteroaryl halide, further α-arylpyrrolidines were obtained in excellent ers: α-arylpyrrolidine (*S*)-**392** (43%, 98:2 er), α-arylpyrrolidine (*S*)-**395** (22%, 98:2 er) and α-arylpyrrolidine (*S*)-**394** (65%, the er could not be determined due to lack of separation on CSP-HPLC). However, the $[\alpha]_D$ value for α-arylpyrrolidine (*S*)-**394** was –88.5 (*c* 0.5 in acetone), indicating it was likely of high er and the opposite enantiomer to a sample of α-arylpyrrolidine (*R*)-**394** (96:4 er) prepared by Denmark *et al.* which possessed $[\alpha]_D$ +88.3 (*c* 0.5 in acetone).[135]

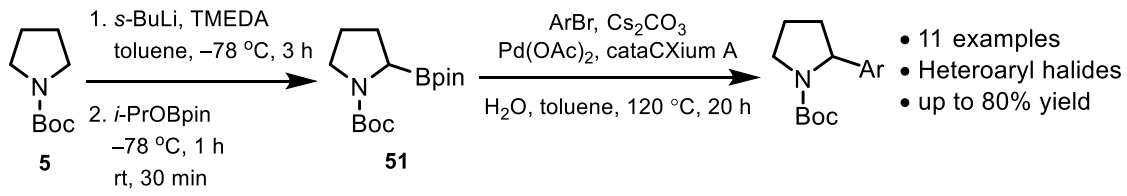


Scheme 3.80

3.7 Conclusions and Future Work

In summary, conditions have been developed for the sp^2-sp^3 SMCC of α-Bpin-*N*-Boc-pyrrolidine **51** with aryl bromides and chlorides. An initial hit was found by using conditions reported by Walsh, Hughes and co-workers which afforded α-arylpyrrolidine **114** in 21% yield and, through extensive screening, the yield of the reaction was increased up to 80%.[105] The key features of the reaction involved the use of cataCXium A, 10 equivalents of water and heating the reactions at 120 °C in toluene. As well as the developments to the SMCC reaction, a simple method for the recrystallisation of α-Bpin-pyrrolidine **51** enabled the starting material for the SMCC reaction to be synthesised on a large scale without the need for chromatography.

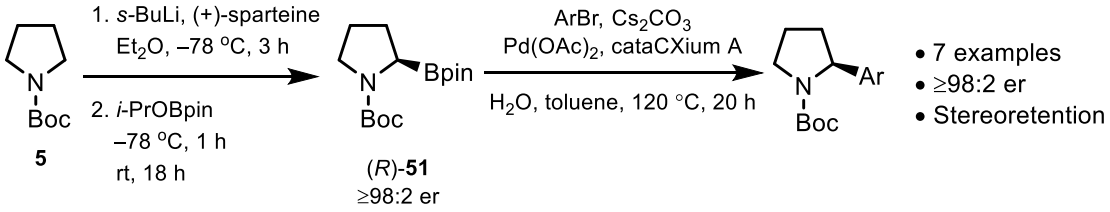
The optimised conditions for the SMCC of α-Bpin-pyrrolidine **51** used 0.1 equivalents of $Pd(OAc)_2$ with 0.2 equivalents of cataCXium A along with 3 equivalents of Cs_2CO_3 and 10 equivalents of water. The reaction was heated in toluene at 120 °C for 20 hours and it was shown that both aryl bromides and chlorides were tolerated and afforded α-arylpyrrolidines in good yields. It was also shown that either α-Bpin-pyrrolidine **51** or the aryl halide could be used in excess (1.5 equivalents) with no significant change in yield; the scope was conducted with α-Bpin-pyrrolidine **51** in excess. With these conditions, 11 aryl bromides were successfully cross-coupled in good yields (14-80%) with the low yielding examples being either a highly sterically hindered aryl bromide or a larger and more complex heteroaryl bromide. Some heteroaryl bromides were successfully cross-coupled, including the use of 3-bromopyridine in 54% yield.



Scheme 3.81

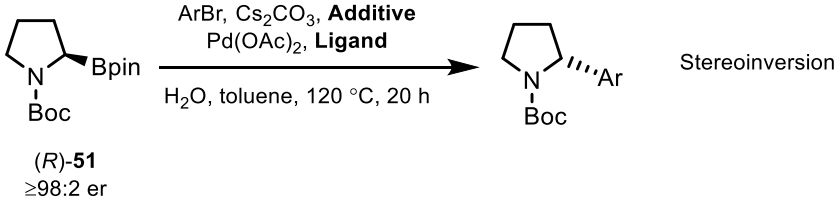
The utility of the methodology was further demonstrated with the SMCC of enantioenriched α-Bpin-pyrrolidine (*R*)-**51** (≥98:2 er) where it was shown that the reaction proceeded with complete stereospecificity and retention of stereochemistry. α-Bpin-pyrrolidine (*R*)-**51** could be synthesised by lithiation with *s*-BuLi and (+)-sparteine followed by trapping with *i*-PrOBpin. Subsequent recrystallisation of the crude product

afforded α-Bpin-pyrrolidine (*R*)-**51** in ≥98:2 er. SMCC of the resulting enantioenriched α-Bpin-pyrrolidine (*R*)-**51** under the same reaction conditions proceeded with complete enantiospecificity and gave α-arylpyrrolidines with retention of stereochemistry. Seven enantioenriched α-arylpyrrolidines were obtained, six with ≥98:2 er and one that could not be determined, but high selectivity was assumed.



Scheme 3.82

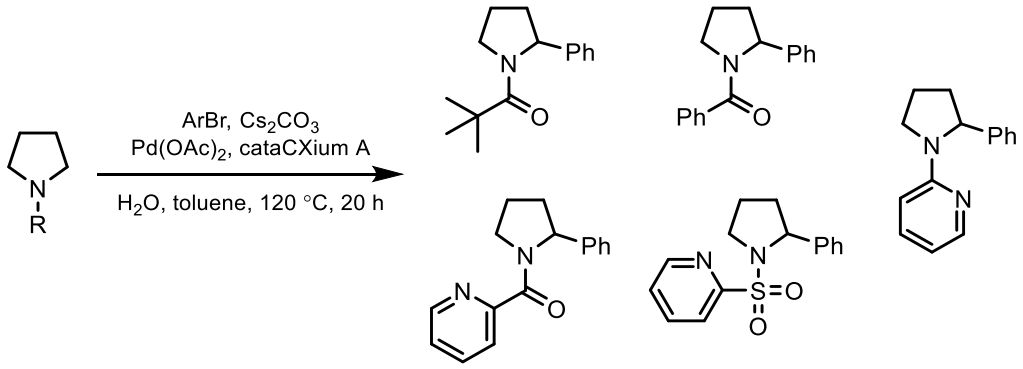
Other members of the group are continuing this work and investigating the cross-coupling of additional aryl bromides to expand the scope of the reaction. Other interesting future work could include further investigation into the factors determining the stereochemical outcome of the reaction and, specifically, to explore if it would be possible to favour the stereoinvertive pathway during transmetallation. As had been shown, the use of SPhos Pd G3 instead of cataCXium A/Pd(OAc)$_2$ reduced the enantiospecificity of the SMCC reaction (see Scheme 3.79). Potentially, complete inversion of stereochemistry could be obtained with further investigation. Ohmura, Awano and Suginome had reported that the stereochemical outcome of the SMCC reaction of enantioenriched α-amino-benzylic Bpins could be controlled by the addition of either phenol or Zr(O*i*-Pr)$_4$•*i*-PrOH (see Scheme 3.29).[117] The use of these additives in the SMCC of α-Bpin-pyrrolidine (*R*)-**51** and their effect on the stereochemistry of the reaction could be investigated (Scheme 3.83). Likewise, other biaryl phosphine ligands could be explored such as bis-CF$_3$PhSPhos or PCy$_3$.



Scheme 3.83

Unfortunately, the SMCC methodology developed for α-Bpin-pyrrolidine **51** could not be applied to the SMCC of α-Bpin-4-OTBDMS-piperidine *cis*-**213** or α-Bpin-*N*-Boc-piperidine **351**. Under the same optimised conditions, none of or trace amounts of the desired α-phenylpiperidines **176** and **107** were obtained. This, therefore, represents another area of potential future work. Further optimisation studies could be carried out to find conditions for the cross-coupling of piperidines, both with and without 4-substituents, potentially through the use of high temperatures and ligand design.

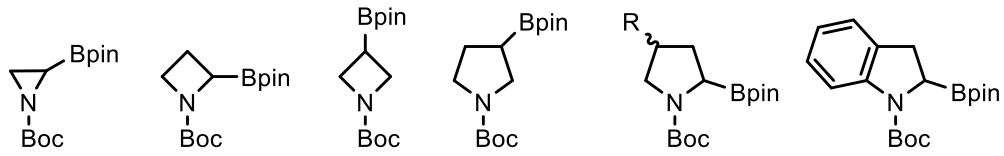
Another prospective field of work could be the re-investigation of the group on nitrogen (Scheme 3.84). Having obtained conditions for the successful SMCC of α-Bpin-*N*-Boc-pyrrolidine **51**, the SMCC of other *N*-functionalised pyrrolidines could be re-investigated with these conditions. Exploring the effect of different groups and their ability to facilitate the SMCC could provide useful mechanistic insights. Another member of the group has carried out some work to this effect obtaining a 29% NMR yield with the cross-coupling of α-Bpin-*N*-tosylpyrrolidine, a 35% NMR yield with α-Bpin-*N*-benzoylpyrrolidine and a 5% NMR yield with α-Bpin-*N*-pivaloylpyrrolidine. However, further work could be carried out, for example, the SMCC of α-Bpin-*N*-(2-pyridyl)pyrrolidine **342** could potentially be revisited with the optimised conditions.



Scheme 3.84

Finally, another potential avenue of research would be to investigate the SMCC of other *N*-Boc heterocycles (Scheme 3.85). For example, Bpin-*N*-Boc-aziridine **407**, α-Bpin-*N*-Boc-azetidine **408** or β-Bpin-*N*-Boc-azetidine **409**. The SMCC of β-Bpin-*N*-Boc-pyrrolidine **410** could be studied to determine if moving the Bpin group away from the Boc group prevented the reaction from occurring or if it was still activated enough to undergo transmetallation. Likewise, substitution of the pyrrolidine ring could also be investigated to determine if the presence of other substituents on the ring affected cross-

coupling or if the SMCC would proceed when the pyrrolidine ring was part of a larger ring system such as α-Bpin-*N*-Boc indoline **412**. The investigation of these substrates and similar ones could expand the methodology and determine its general applicability to other sp^2-sp^3 systems.



407 **408** **409** **410** **411** **412**

Scheme 3.85

Chapter 4: Experimental

4.1 General Information

All-non aqueous reactions were carried out under oxygen free Ar or N_2 using flame-dried glassware. Brine refers to a saturated solution. Water is deionised water. Alkyllithiums were titrated against *N*-benzylbenzamide before use. Electrophiles (methyliodide and dimethylsulfate) used in lithiation reactions were distilled over CaH_2 before use.

Flash column chromatography was carried out using Fluka Chemie GmbH silica (220-440 mesh). Thin layer chromatography was carried out using commercially available Merck F_{254} aluminium backed silica plates. Proton (400 MHz), carbon (100.6 MHz) and boron (128 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-d_6 (δ_H 2.50 ppm, central line of quintet) and d_6-DMSO (δ_C 39.5 ppm, central line of quintet). For samples recorded in CD_3CN, chemical shifts are quoted in parts per million relative to $CHCl_3$ (δ_H 1.94, central line of quintet). Carbon NMR spectra were recorded with broad band proton decoupling and assigned using DEPT experiments. Coupling constants (*J*) are quoted in Hertz. Melting points were carried out on a Gallenkamp melting point apparatus. Infrared spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer. Electrospray high and low resonance mass spectra were recorded at room temperature on a Bruker Daltronics microOTOF spectrometer. 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}. 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 Varian 430-GC with an Agilent J&W DB-5 30 m × 0.250 mm column using flame ionization detection.

4.2 General Procedures

General Procedure A: α-Lithiation-Trapping of 4-OTIPS-*N*-Boc-piperidine 149 with Me_3SiCl, 0.3 mmol scale

s-BuLi (0.30 mL of a 1.3 M solution in hexane, 0.39 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTIPS-*N*-Boc-piperidine **149** (108 mg, 0.30 mmol, 1.0 eq.) and TMEDA (0.058 mL, 0.39 mmol, 1.3 eq.) in solvent (1.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1-3 h. Me_3SiCl (0.076 mL, 0.60 mmol, 2.0 eq.) was added and the resulting solution was stirred at –78 °C for 1-2 h and then at rt for 14-21 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure B: α-Lithiation-Trapping of 4-Substituted *N*-Boc-piperidines, 0.5 mmol scale

s-BuLi (0.5 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-Osilyl-*N*-Boc-piperidine (0.5 mmol, 1.0 eq.) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. Electrophile (1.0 mmol, 2.0 eq.) was added and the resulting solution was stirred at –78 °C for 1-2 h and then at rt for 30 min-21 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure C: Negishi α-Arylation of 4-OTIPS-*N*-Boc-piperidine 149, 0.5 mmol scale

s-BuLi (0.5 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTIPS-*N*-Boc-piperidine **149** (178 mg, 0.50 mmol, 1.0 eq.) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in solvent (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1-3 h. A solution of $ZnCl_2$ (89 mg, 0.65

mmol, 1.3 eq.) in THF (1.0 mL) was added and the resulting solution was stirred at –78 °C for 30 min and then at rt for 30 min-2.5 h to give a solution of the organozinc species. In a separate flask, a solution of 4-bromobenzotrifluoride (0.33-0.65 mmol, 0.65-1.3 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $Pd_2(dba)_3$ (11.4 mg, 0.013 mmol, 0.025 eq.) in solvent (1.0-2.0 mL) was stirred at rt under Ar for 10 min. The solution of the organozinc species was added to the catalyst solution and the resulting solution was stirred and heated at 50 °C for 18-24 h. After being allowed to cool to rt, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure D: Optimised Negishi *α*-Arylation of 4-Substituted *N*-Boc-piperidines, 0.5 mmol scale

s-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-Osilyl-*N*-Boc-piperidine (158 mg, 0.50 mmol, 1.0 eq.) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. A solution of $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) was added and the resulting solution was stirred at –78 °C for 30 min-1 h and then at rt for 30 min-1 h to give a solution of the organozinc species. In a separate flask, a solution of aryl halide (0.65-0.75 mmol, 1.3-1.5 eq.), RuPhos (10.9 mg, 0.025 mmol, 0.05 eq.) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol, 0.025 eq.) in toluene (2.0-2.5 mL) was stirred at rt under Ar for 10 min. The catalyst solution was added to the solution of the organozinc species and the resulting solution was stirred and heated at 100 °C for 16-18 h. After being allowed to cool to rt, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure E: Initial Negishi α-Arylation of 4-Substituted-*N*-Boc-piperidines, 0.5 mmol scale

s-BuLi (0.5 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-Osilyl-*N*-Boc-piperidine (0.5 mmol, 1.0 eq.) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. A solution of $ZnCl_2$ (89 mg, 0.65 mmol, 1.3 eq.) in THF (0.65-1.0 mL) or a solution of $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) was added and the resulting solution was stirred at –78 °C for 30 min and then at rt for 30 min to give a solution of the organozinc species. In a separate flask, a solution of aryl halide (0.65 mmol, 1.3 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $Pd_2(dba)_3$ (11.4 mg, 0.013 mmol, 0.025 eq.) in toluene (1.0-2.0 mL) was stirred at rt under Ar for 10 min. The solution of the organozinc species was added to the catalyst solution and the resulting solution was stirred and heated at 50 °C for 17-20 h. After being allowed to cool to rt, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure F: Optimisation of Negishi α-Arylation of 4-OTBDMS-*N*-Boc-piperidine 73 with 3-Bromopyridine, 0.5 mmol scale

s-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol, 1.0 eq.) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. A solution of $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) was added and the resulting solution was stirred at –78 °C for 30 min-1 h and then at rt for 30 min-1 h to give a solution of the organozinc species. In a separate flask, a solution of 3-bromopyridine (0.50-1.0 mmol, 1.0-2.0 eq.), Ligand (0.025 mmol, 0.05 eq.) and catalyst (0.013 mmol, 0.025 eq.) in toluene (2.0-2.5 mL) was stirred at rt under Ar for 10 min. The catalyst solution was added to the solution of the organozinc species and the resulting solution was stirred and heated at 50-100 °C for 15-19. After being allowed to cool to rt, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were

separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure G: Optimised Suzuki-Miyaura α-Arylation of α-Bpin-*N*-Boc-pyrrolidine 51, 0.5 mmol scale liquid aryl halides

Aryl halide (0.50 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 3.0 eq.), cataCXium A (35.9 mg, 0.10 mmol, 0.2 eq.), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 0.1 eq.) and water (0.090 mL, 5.0 mmol, 10 eq.) in toluene (0.7 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure H: Optimised Suzuki-Miyaura α-Arylation of α-Bpin-*N*-Boc-pyrrolidine 51, 0.5 mmol scale solid aryl halides

A solution of aryl halide (0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 3.0 eq.), cataCXium A (35.9 mg, 0.10 mmol, 0.2 eq.), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 0.1 eq.) and water (0.090 mL, 5.0 mmol, 10 eq.) in toluene (0.7 mL) was stirred at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure I: Optimised Suzuki-Miyaura α-Arylation of α-Bpin-*N*-Boc-pyrrolidine 51, 0.3 mmol scale

Aryl halide (0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine (*R*)-**51** (134 mg, 0.45 mmol, 1.5 eq., ≥98:2 er), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.1 eq.) and water (0.054 mL, 3.0 mmol, 10 eq.) in toluene (0.7 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

GC Analysis Method

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 a Agilent J&W DB-5 30 m × 0.250 mm column. The oven temperature was programmed to 100 °C to 180 °C at 8 °C/min, then to 280 °C at 10°C/min. Hydrogen carrier gas was used.

All GC samples were in MeCN. Retention time:
1,3,5-trimethoxybenzene = 5.42 min
α-Bpin-*N*-Boc-pyrrolidine **51** = 8.87 min
α-phenyl-*N*-Boc-pyrrolidine **114** = 9.25 min

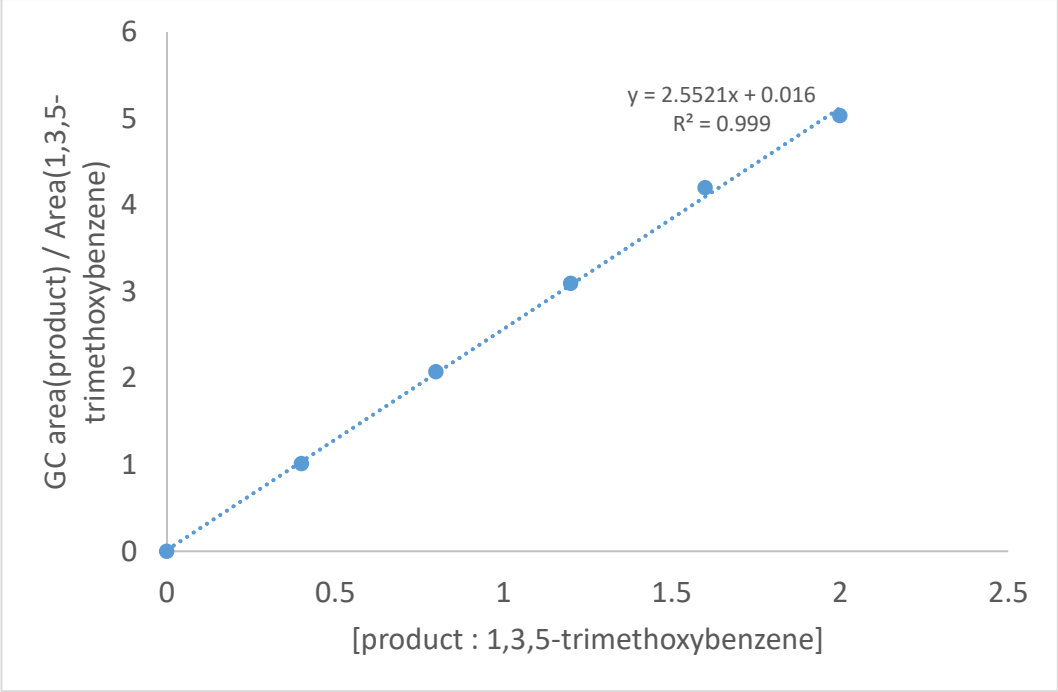


Figure 4.1: GC calibration curve for α-Bpin-*N*-Boc-pyrrolidine **51**

Line of best fit: y= 2.5521x + 0.016

R^2: 0.9990

Response factor: 2.540

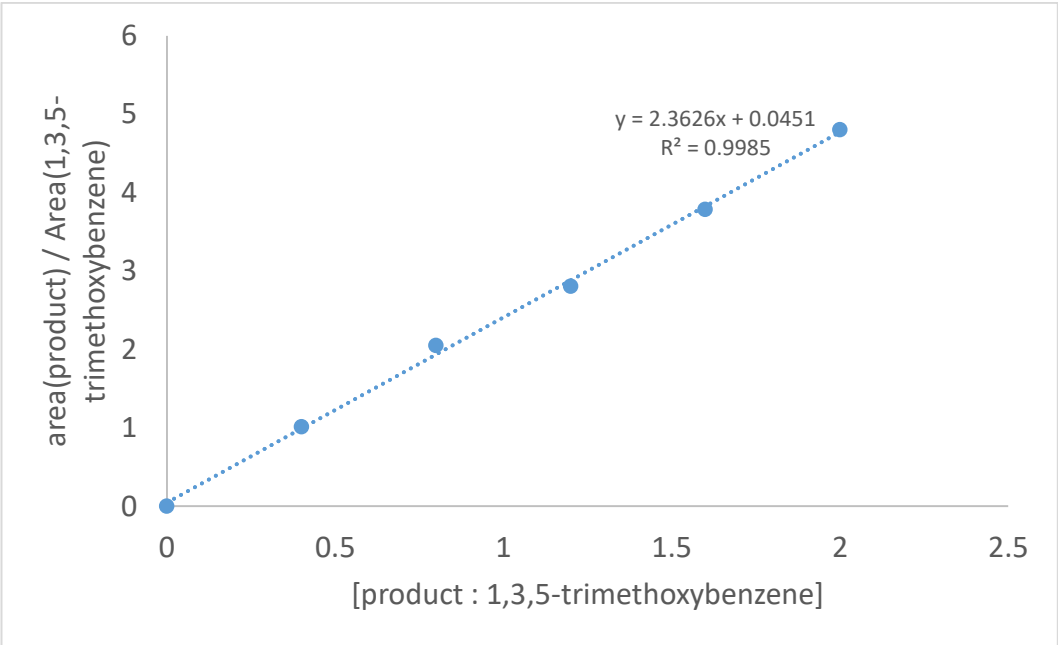


Figure 4.2: GC calibration curve for α-phenyl-*N*-Boc-pyrrolidine **114**

Line of best fit: y= 2.3626x + 0.0451

R^2: 0.9985

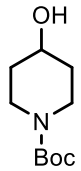
Response factor: 2.329

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 the benzylic NCH protons in α-aryl pyrrolidines (in the region δ 4.7-5.1) and the signals in 1,3,5-trimethoxybenzene (6.11 (s, 3H, Ar) and 3.78 (s, 9H, OMe)). 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.

4.3 Experimental Procedures Chapter 2

tert-Butyl-4-hydroxypiperidine-1-carboxylate 166

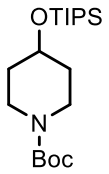


166

$NaBH_4$ (1.13 g, 30.0 mmol, 1.5 eq.) was added to a stirred solution of *N*-Boc-piperidin-4-one **165** (3.99 g, 20.0 mmol, 1.0 eq.) in EtOH (25 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 64 h. Then, the mixture was cooled to 0 °C and saturated $NH_4Cl_{(aq)}$ (40 mL) and EtOAc (100 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (2 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 4:1 CH_2Cl_2-acetone as eluent gave *N*-Boc-4-hydroxypiperidine **166** (3.99 g, 99%) as a colourless oil, R_F (4:1 CH_2Cl_2-acetone) 0.45; IR (ATR) 2975, 2933, 2866, 1691 (C=O), 1664, 1421, 1365, 1272, 1231, 1165, 1130, 1068, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.92-3.68 (m, 3H, NCH + OCH), 2.98 (ddd, J = 13.5, 10.0, 3.5 Hz, 2H, NCH), 3.49-3.33 (br s, 1H, OH), 1.86-1.73 (m, 2H, CH), 1.50-1.42 (m, 2H, CH), 1.41 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.9 (C=O), 79.7 (O*C*Me_3), 67.6 (OCH), 41.6 (NCH_2), 34.2 (CH_2), 28.5 (C*Me*$_3$); HRMS (ESI) *m/z* calcd for $C_{10}H_{19}NO_3$ $(M + Na)^+$ 224.1257, found 224.1257 (+0 ppm error). Spectroscopic data consistent with those reported in the literature.[136]

Lab book reference: **MTG-1-17**

tert-Butyl-4-{[tris(propan-2-yl)silyl]oxy}piperidine-1-carboxylate 149



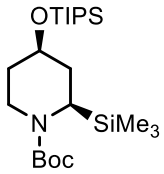
149

Triisopropylsilyl chloride (3.00 mL, 14 mmol, 1.4 eq.) was added dropwise to a stirred solution of 4-hydroxypiperidine **162** (2.01 g, 10 mmol, 1.0 eq.) and imidazole (1.70 g,

25 mmol, 2.5 eq.) in DMF (35 mL) at rt under Ar. The resulting solution was stirred at rt for 41 h. Saturated $NaHCO_{3(aq)}$ (30 mL) and Et_2O (30 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (4 × 30 mL) and the combined organics were washed with brine (4 × 30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 94:6 hexane-Et_2O as eluent gave 4-OTIPS-*N*-Boc-piperidine **149** (3.46 g, 95%) as a colourless oil, R_F (9:1 hexane-Et_2O) 0.30; IR (ATR) 2943, 2866, 1697 (C=O), 1420, 1231, 1173, 1110, 1046, 881 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.98 (tt, J = 6.5, 3.5 Hz, 1H, OCH), 3.66-3.53 (m, 2H, NCH), 3.37-3.21 (m, 2H, NCH), 1.78-1.65 (m, 2H, CH), 1.61-1.47 (m, 2H, CH), 1.45 (s, 9H, CMe_3), 1.11-1.00 (m, 21H, Si(*i*-Pr)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.0 (C=O), 79.3 (O*C*Me_3), 67.1 (OCH), 40.7 (NCH_2), 34.4 (CH_2), 28.5 (OC*Me*$_3$), 18.2 (SiCH*Me*), 12.3 (Si*C*HMe); HRMS (ESI) *m/z* calcd for $C_{19}H_{39}NO_3Si$ $(M + Na)^+$ 380.2591, found 380.2593 (–0.4 ppm error). ^1H NMR spectroscopic data consistent with those reported in the literature.[24]

Lab book reference: **MTG-1-48**

***tert*-Butyl-4-((triisopropylsilyl)oxy)-2-(trimethylsilyl)piperidine-1-carboxylate *cis*-167**



cis-**167**

Using General Procedure A, *s*-BuLi (0.32 mL of a 1.22 M solution in hexane, 0.39 mmol), 4-OTIPS-*N*-Boc-piperidine **149** (108 mg, 0.30 mmol) and TMEDA (0.058 mL, 0.39 mmol) in Et_2O (1.5 mL) for 1 h, Me_3SiCl (0.076 mL, 0.60 mmol) at –78 °C for 1 h and rt for 20 h. Purification by flash column chromatography on silica using 49:1 hexane-Et_2O as eluent gave 2,4-disubstituted piperidine *cis*-**167** (82 mg, 64%) as a colourless oil, R_F (99:1 hexane-Et_2O) 0.25; IR (ATR) 2943, 2867, 1691 (C=O), 1245, 1150, 1104, 880, 838, 826, 734, 677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.93 (br s, 1H, NCH), 3.83-3.55 (m, 1H, OCH), 2.82 (br s, 1H, NCH), 2.25 (br s, 1H, Me_3SiCHN),

1.89-1.80 (m, 2H, CH), 1.43 (s, 9H, CMe_3), 1.42-1.34 (m, 2H, CH), 1.10-1.00 (m, 21H, Si(*i*-Pr)$_3$), 0.07 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.0 (C=O), 79.1 (O*C*Me_3), 71.1 (OCH), 48.2 (Me_3SiCHN), 46.1 (NCH_2), 36.4 (CH_2), 36.1 (CH_2), 28.4 (C*Me*$_3$), 18.1 (SiCH*Me*), 12.4 (Si*C*HMe), –0.7 ($SiMe_3$); HRMS (ESI) *m/z* calcd for $C_{22}H_{47}NO_3Si_2$ $(M + Na)^+$ 452.2987, found 452.2985 (+0.4 ppm error).

Lab book reference: **MTG-1-43**

Using General Procedure A, *s*-BuLi (0.32 mL of a 1.22 M solution in hexane, 0.39 mmol), 4-OTIPS-*N*-Boc-piperidine **149** (107 mg, 0.30 mmol) and TMEDA (0.058 mL, 0.39 mmol) in MTBE (1.5 mL) for 1 h, Me_3SiCl (0.076 mL, 0.60 mmol) at –78 °C for 1 h and rt for 14 h. Purification by flash column chromatography on silica using 49:1 hexane-Et_2O as eluent gave 2,4-disubstituted piperidine *cis*-**167** (95 mg, 74%) as a colourless oil.

Lab book reference: **MTG-1-41**

Using General Procedure A, *s*-BuLi (0.35 mL of a 1.11 M solution in hexane, 0.39 mmol), 4-OTIPS-*N*-Boc-piperidine **149** (105 mg, 0.30 mmol) and TMEDA (0.058 mL, 0.39 mmol) in CPME (1.5 mL) for 1 h, Me_3SiCl (0.076 mL, 0.60 mmol) at –78 °C for 1 h and rt for 14 h. Purification by flash column chromatography on silica using 49:1 hexane-Et_2O as eluent gave 2,4-disubstituted piperidine *cis*-**167** (54 mg, 43%) as a colourless oil.

Lab book reference: **MTG-2-7**

Using General Procedure A, *s*-BuLi (0.32 mL of a 1.22 M solution in hexane, 0.39 mmol), 4-OTIPS-*N*-Boc-piperidine **149** (105 mg, 0.30 mmol) and TMEDA (0.058 mL, 0.39 mmol) in THF (1.5 mL) for 3 h, Me_3SiCl (0.076 mL, 0.60 mmol) at –78 °C for 1 h and rt for 16 h. Purification by flash column chromatography on silica using 49:1 hexane-Et_2O as eluent gave 2,4-disubstituted piperidines *cis*-**167** in 97:3 dr (based on ^1H NMR spectroscopy after Boc group removal) (95 mg, 75%) as a colourless oil.

Lab book reference: **MTG-1-42**

Using General Procedure A, *s*-BuLi (0.35 mL of a 1.11 M solution in hexane, 0.39 mmol), 4-OTIPS-*N*-Boc-piperidine **149** (105 mg, 0.30 mmol) and TMEDA (0.058 mL, 0.39 mmol) in TMO (1.5 mL) for 3 h, Me_3SiCl (0.076 mL, 0.60 mmol) at –78 °C for 1 h and rt for 20 h. Purification by flash column chromatography on silica using 49:1 hexane-Et_2O as eluent gave 2,4-disubstituted piperidine *cis*-**167** (72 mg, 57%) as a colourless oil, stereochemistry of major product assumed to be *cis* based on experiment **1-72**.

Lab book reference: **MTG-2-9**

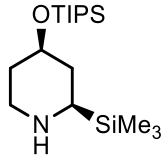
s-BuLi (0.59 mL of a 1.1 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTIPS-*N*-Boc-piperidine **149** (178 mg, 0.50 mmol, 1.0 eq.) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Me_3SiCl (0.127 mL, 1.0 mmol, 2.0 eq.) was added and the resulting solution was stirred at –78 °C for 1 h and then at rt for 21 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 49:1 hexane-Et_2O as eluent gave 2,4-disubstituted piperidine *cis*-**167** (133 mg, 62%) as a colourless oil.

Lab book reference: **MTG-8-16**

Using General Procedure B, *s*-BuLi (0.58 mL of a 1.12 M solution in hexane, 0.65 mmol), 4-OTIPS-*N*-Boc-piperidine **149** (178 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL) and Me_3SiCl (0.127 mL, 1.0 mmol) at –78 °C for 2 h and rt for 21 h. Purification by flash column chromatography on silica using 49:1 hexane-Et_2O as eluent gave 2,4-disubstituted piperidine *cis*-**167** (165 mg, 77%) as a colourless oil.

Lab book reference: **MTG-2-13**

4-((Triisopropylsilyl)oxy)-2-(trimethylsilyl)piperidine *cis*-168



cis-**168**

Trifluoroacetic acid (0.115 mL, 1.50 mmol, 10 eq.) was added dropwise to a stirred solution of 4-OTIPS-2-trimethylsilyl-*N*-Boc-piperidine *cis*-**167** (64 mg, 0.15 mmol, 1.0 eq.) in CH_2Cl_2 (2.5 mL) at rt under Ar. The resulting solution was stirred at rt for 24 h. Saturated $NaHCO_{3(aq)}$ (5 mL) and CH_2Cl_2 (5 mL) were added and the two layers were 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 which contained 2,4-disubstituted piperidines **168** in 97:3 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 4:1 EtOAc-MeOH as eluent gave 2,4-disubstituted piperidine *cis*-**168** (15 mg, 30%) as a yellow oil, R_F (90:34:1) EtOAc-MeOH-Et_3N) 0.50; IR (ATR) 2941, 2866, 1248, 1106, 1066, 882, 859, 832, 679 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (dddd, *J* = 10.0, 10.0, 4.5, 4.5 Hz, 1H, OCH), 3.20-3.10 (m, 1H, NCH), 2.56 (ddd, *J* = 12.5, 12.5, 2.5 Hz, 1H, NCH), 2.03 (dd, *J* = 13.0, 2.0 Hz, 1H, Me_3SiCHN), 1.91 (ddddd, *J* = 12.5, 4.5, 2.5, 2.5, 2.5 Hz, 1H, CH), 1.83 (dddd, *J* = 12.5, 4.5, 2.5, 2.0 Hz, 1H, CH), 1.38 (dddd, *J* = 12.5, 12.5, 10.0, 4.5 Hz, 1H, CH), 1.23 (ddd, *J* = 13.0, 12.5, 10.0 Hz, 1H, CH), 1.08.-1.02 (m, 21H, Si(*i*-Pr)$_3$), –0.02 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 71.4 (OCH), 48.0 (NCH_2), 46.8 (Me_3SiCHN), 38.1 (CH_2), 37.6 (CH_2), 18.2 (SiCH*Me*), 12.5 (Si*C*HMe), –3.9 ($SiMe_3$); HRMS (ESI) *m/z* calcd for $C_{17}H_{39}NOSi_2$ $(M + H)^+$ 330.2643, found 330.2633 (+3.0 ppm error). Diagnostic signals for *trans*-**168**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (ddd, *J* = 13.0, 12.5, 2.5 Hz, 1H, NCH), 2.13 (dd, *J* = 13.0, 2.0 Hz, 1H, Me_3SiCHN).

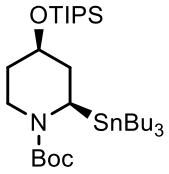
Lab book reference: **MTG-1-72**

Trifluoroacetic acid (0.291 mL, 3.80 mmol, 10 eq.) was added dropwise to a stirred solution of 4-OTIPS-2-trimethylsilyl-*N*-Boc-piperidine *cis*-**167** (163 mg, 0.38 mmol, 1.0 eq.) in CH_2Cl_2 (2.5 mL) at rt under Ar. The resulting solution was stirred at rt for 18 h. Saturated $NaHCO_{3(aq)}$ (5 mL) and CH_2Cl_2 (5 mL) were added and the two layers were

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 which contained 2,4-disubstituted piperidines **168** in 93:7 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 4:1 EtOAc-hexane as eluent gave 2,4-disubstituted piperidine *cis*-**168** (29 mg, 23%) and 2,4-disubstituted piperidines **168** in 86:14 dr (7 mg, 6%) as a colourless oil. Overall, this reaction gave a 97:3 mixture of 2,4-disubstituted piperidine *cis*-**168** and *trans*-**168** (36 mg, 29%).

Lab book reference: **MTG-2-51**

***tert*-Butyl-2-(tributylstannyl)-4-((triisopropylsilyl)oxy)piperidine-1-carboxylate *cis*-169**



cis-**169**

s-BuLi (2.93 mL of a 1.33 M solution in hexane, 3.9 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTIPS-*N*-Boc-piperidine **149** (1.073 g, 3.0 mmol, 1.0 eq.) and TMEDA (0.585 mL, 3.9 mmol, 1.3 eq.) in Et_2O (15 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Bu_3SnCl (1.058 mL, 3.9 mmol, 1.3 eq.) was added and the resulting solution was stirred at –78 °C for 1.5 h and then at rt for 18 h. Saturated $NH_4Cl_{(aq)}$ (15 mL) and Et_2O (15 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 30 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 199:1 hexane-Et_2O as eluent gave 2,4-disubstituted piperidine *cis*-**169** (1.24 g, 64%) as a colourless oil, R_F (199:1 hexane-Et_2O) 0.35; IR (ATR) 2923, 2867, 1671 (C=O), 1428, 1239, 1150, 1102, 881, 678 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19-4.04 (m, 1H, NCH), 3.69 (dddd, *J* = 10.5, 10.5, 4.5, 4.5 Hz, 1H, OCH), 2.81-2.67 (m, 1H, NCH), 2.57-2.38 (m, 1H, Bu_3SnCHN), 1.95 (dddd, *J* = 13.0, 4.5, 2.0, 2.0 Hz, 1H, CH), 1.85 (ddddd, *J* = 12.5, 4.5, 2.5, 2.5, 2.0 Hz, 1H, CH), 1.59-

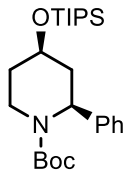
1.41 (m, 8H, CH, CH_2), 1.41 (s, 9H, CMe_3), 1.29 (qt, *J* = 7.0, 7.0, Hz, 6H, C*H*$_2$Me), 1.08-1.04 (m, 21H, Si(*i*-Pr)$_3$), 0.88 (t, *J* = 7.5 Hz, 9H), 0.83-0.69 (m, 6H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.1 (C=O), 79.4 (*C*Me_3), 72.1 (OCH), 45.9 (NCH_2), 43.5 (Bu_3SnCHN), 40.4 (CH_2), 36.3 (CH_2), 29.4 (CH_2), 28.4 (OC*Me*$_3$), 27.8 (CH_2), 18.2 (SiCH*Me*), 13.9 (Me), 12.4 (Si*C*HMe), 12.1 (CH_2); HRMS (ESI) *m/z* calcd for $C_{31}H_{65}NO_3SiSn$ $(M + H)^+$ 648.3834, found 648.3822 (–1.8 ppm error).

Lab book reference: **MTG-1-76**

s-BuLi (0.35 mL of a 1.11 M solution in hexane, 0.39 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTIPS-*N*-Boc-piperidine **149** (107 mg, 0.3 mmol, 1.0 eq.) and TMEDA (0.059 mL, 0.39 mmol, 1.3 eq.) in toluene (1.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. Bu_3SnCl (0.106 mL, 0.39 mmol, 1.3 eq.) was added and the resulting solution was stirred at –78 °C for 1 h and then at rt for 14 h. Saturated $NH_4Cl_{(aq)}$ (4 mL) and Et_2O (4 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 4 mL) and the combined organics were washed with brine (4 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on 90:10 silica-K_2CO_3 using 49:1 hexane-Et_2O as eluent gave 2,4-disubstituted piperidine *cis*-**169** (146 mg, 75%) as a colourless oil.

Lab book reference: **MTG-2-4**

tert-Butyl-2-phenyl-4-((_tert_-butyldimethylsilyl)oxy)-2-phenylpiperidine-1-carboxylate _cis_-170



cis-**170**

s-BuLi (0.53 mL of a 1.22 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTIPS-*N*-Boc-piperidine **149** (179 mg, 0.50 mmol, 1.0 eq.) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in Et_2O (2 mL) at –78 °C under

Ar. The resulting solution was stirred at –78 °C for 1 h. A solution of $ZnCl_2$ (89 mg, 0.65 mmol, 1.3 eq.) in THF (1.0 mL) was added and the resulting solution was stirred at –78 °C for 30 min and then at rt for 45 min. The solvent was evaporated under reduced pressure. In a separate flask, a solution of iodobenzene (0.039 mL, 0.35 mmol, 0.7 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $Pd_2(dba)_3$ (11.4 mg, 0.013 mmol, 0.025 eq.) in toluene (3 mL) was stirred at rt under Ar for 10 min. The catalyst solution was added to the zinc species. Toluene (2 mL) was added and the resulting solution was stirred and heated at 60 °C for 69 h. After being allowed to cool to rt, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpiperidines **170** in 93:7 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 24:1 hexane-Et_2O as eluent gave a 95:5 mixture of α-phenyl-piperidines **170** in 93:7 dr and 4-OTIPS-*N*-Boc-piperidine **149** (81 mg, i.e. 77 mg (50%) of α-phenyl-piperidines **170** and 4 mg (2%) of 4-OTIPS-*N*-Boc-piperidine **149**) as a colourless oil, R_F (9:1 hexane-Et_2O) 0.40; IR (ATR) 2943, 2866, 1697 (C=O), 1414, 1365, 1172, 1083, 1043 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.11 (m, 5H, Ph), 5.16 (dd, *J* = 7.0, 5.0 Hz, 1H, PhCHN), 4.22-4.17 (m, 1H, OCH), 4.01 (ddd, *J* = 13.0, 5.0, 2.5 Hz, 1H, NCH), 3.45 (ddd, *J* = 13.0, 12.5, 3.5 Hz, 1H, NCH), 2.30 (dddd, *J* = 14.0, 5.0, 5.0, 1.5 Hz, 1H, CH), 2.08 (ddd, *J* = 14.0, 7.0, 3.5 Hz, 1H, CH), 1.84 (dddd, *J* = 12.5, 12.5, 5.0, 5.0 Hz, 1H, CH), 1.69-1.62 (m, 1H, CH), 1.36 (s, 9H, $OCMe_3$), 0.94-0.86 (m, 21H, Si(*i*-Pr)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.7 (C=O), 143.3 (*ipso*-Ph), 128.1 (Ph), 125.9 (Ph), 125.6 (Ph), 79.7 (O*C*Me$_3$), 65.2 (OCH), 53.0 (PhCHN), 37.4 (CH_2), 36.1 (NCH_2), 33.4 (CH_2), 28.4 (OC*Me*$_3$), 18.0 (SiCH*Me*), 12.2 (Si*C*HMe); HRMS (ESI) *m/z* calcd for $C_{25}H_{43}NO_3Si$ (M + Na)$^+$ 456.2904, found 456.2909 (–1.0 ppm error). Diagnostic signals for *trans*-**170**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55-5.51 (m, 1H, PhCHN), 2.76 (ddd, *J* = 13.5, 13.5, 3.0 Hz, 1H, NCH), 2.55 (ddd, *J* = 16.0, 4.0, 2.5 Hz, 1H, CH).

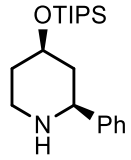
Lab book reference: **MTG-1-37**

s-BuLi (0.53 mL of a 1.22 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTIPS-*N*-Boc-piperidine **149** (179 mg, 0.50 mmol, 1.0 eq.) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in Et_2O (2 mL) at –78 °C under

Ar. The resulting solution was stirred at –78 °C for 1 h. A solution of $ZnCl_2$ (89 mg, 0.65 mmol, 1.3 eq.) in THF (1.0 mL) was added and the resulting solution was stirred at –78 °C for 30 min and then at rt for 1.5 h. The solvent was evaporated under reduced pressure. In a separate flask, a solution of iodobenzene (0.039 mL, 0.35 mmol, 0.7 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $Pd_2(dba)_3$ (11.4 mg, 0.013 mmol, 0.025 eq.) in toluene (3 mL) was stirred at rt under Ar for 10 min. The catalyst solution was added to the zinc species. Toluene (2 mL) was added and the resulting solution was stirred and heated at 60 °C for 22 h. After being allowed to cool to rt, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpiperidines **170** in 95:5 dr (by ^1H NMR spectroscopy). Purification by flash column chromatography on silica using 24:1 hexane-Et_2O as eluent gave an 84:16 mixture of α-phenyl-piperidines **170** in 96:4 dr and 4-OTIPS-*N*-Boc-piperidine **149** (93 mg, i.e. 80 mg (53%) of α-phenyl-piperidines **170** and 13 mg (7%) of 4-OTIPS-*N*-Boc-piperidine **149**) as a colourless oil.

Lab book reference: **MTG-1-39**

2-Phenyl-4-((triisopropylsilyl)oxy)piperidine *cis*-171



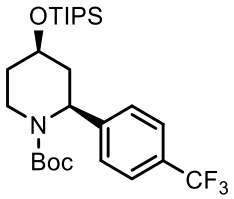
cis-**171**

Trifluoroacetic acid (0.115 mL, 1.50 mmol, 10 eq.) was added dropwise to a stirred solution of an 83:17 mixture of 4-OTIPS-2-phenyl-*N*-Boc-piperidine *cis*-**170** and 4-OTIPS-*N*-Boc-piperidine **149** (65 mg, i.e. 54 mg, 0.15 mmol, 1.0 eq. of 4-OTIPS-2-phenyl-*N*-Boc-piperidine *cis*-**170** and 11 mg of 4-OTIPS-*N*-Boc-piperidine **149**) in CH_2Cl_2 (2.5 mL) at rt under Ar. The resulting solution was stirred at rt for 24 h. Saturated $NaHCO_{3(aq)}$ (5 mL) and CH_2Cl_2 (5 mL) were added and the two layers were 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 which contained 2,4-disubstituted piperidines **171** in 94:6 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 4:1 hexane-Et_2O then 90:9:1 EtOAc-MeOH-$NH_4OH_{(aq)}$ then 40:9:1 EtOAc-MeOH-$NH_4OH_{(aq)}$ as eluent gave 2,4-disubstituted piperidine *cis*-**171** (13 mg, 26%) as a colourless oil, R_F (150:90:90:1 hexane-EtOAc-MeOH-Et_3N) 0.15; IR (ATR) 2941, 2865, 1118, 1096, 1069, 882, 757, 699, 680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.22 (m, 5H, Ph), 3.84 (dddd, *J* = 10.5, 10.5, 4.5, 4.5 Hz, 1H, OCH), 3.60 (dd, *J* = 11.5, 2.5 Hz, 1H, PhCHN), 3.20 (ddd, *J* = 12.0, 4.5, 2.5 Hz, 1H, NCH), 2.77 (ddd, *J* = 12.0, 12.0, 2.5 Hz, 1H, NCH), 2.08 (dddd, *J* = 12.5, 4.5, 2.5, 2.5 Hz, 1H, CH), 1.97 (ddddd, *J* = 12.0, 4.5, 2.5, 2.5, 2.5 Hz, 1H, CH), 1.76-1.69 (br s, 1H, NH), 1.63-1.50 (m, 2H, CH), 1.14-0.96 (m, 21H, Si(*i*-Pr)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.2 (*ipso*-Ph), 128.6 (Ph), 127.4 (Ph), 126.9 (Ph), 70.5 (OCH), 60.6 (Ph*C*HN), 45.3 (NCH_2), 44.6 (CH_2), 36.3 (CH_2), 18.2 (SiCH*Me*), 12.4 (Si*C*HMe); HRMS (ESI) *m/z* calcd for $C_{20}H_{35}NOSi$ $(M + H)^+$ 334.2561, found 334.2556 (+1.4 ppm error). Diagnostic signals for *trans*-**171**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36-4.31 (m, 1H, OCH), 4.22 (dd, *J* = 11.5, 3.0 Hz, 1H, PhCHN).

Lab book reference: **MTG-1-73**

tert-Butyl-2-(4-(trifluoromethyl)phenyl)-4-((triisopropylsilyl)oxy)piperidine-1-carboxylate _cis_-157



cis-**157**

Using General Procedure C, *s*-BuLi (0.49 mL of a 1.33 M solution in hexane, 0.65 mmol), 4-OTIPS-*N*-Boc-piperidine **149** (178 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in MTBE (2.5 mL), at –78 °C for 1 h, $ZnCl_2$ (89 mg, 0.65 mmol, 1.3 eq.) in THF (1.0 mL) at –78 °C for 30 min and rt for 2.5 h and 4-bromobenzotrifluoride (0.091 mL, 0.65 mmol, 1.3 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $Pd_2(dba)_3$ (11.4 mg, 0.013 mmol, 0.025 eq.) in MTBE (2 mL) for 18 h gave the crude product which contained α-arylpiperidines **157** in 95:5 dr (by ^{1}H NMR

spectroscopy). Purification by flash column chromatography on silica using 97:3 hexane-Et_2O, then 47:3 hexane-Et_2O as eluent gave a 27:73 mixture of α-arylpiperidines **157** in 94:6 dr and 4-OTIPS-*N*-Boc-piperidine **149** (173 mg, i.e. 59 mg (24%) of α-arylpiperidines **157** and 114 mg (64%) of 4-OTIPS-*N*-Boc-piperidine **149**) as a colourless oil, R_F (9:1 hexane-Et_2O) 0.35; IR (ATR) 2944, 2867, 1696 (C=O), 1327, 1164, 1125, 1082, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 2H, Ar), 7.30 (d, *J* = 8.0 Hz, 2H, Ar), 5.33-5.24 (m, 1H, ArCHN), 4.24-4.18 (m, 1H, OCH), 4.04 (ddd, *J* = 13.0, 5.0, 3.0 Hz, 1H, NCH), 3.43 (ddd, *J* = 13.0, 13.0, 3.5 Hz, 1H, NCH), 2.36 (dddd, *J* = 14.0, 4.5, 2.0, 2.0 Hz, 1H, CH), 2.11 (ddd, *J* = 14.0, 7.0, 3.0 Hz, 1H, CH), 1.79-1.72 (m, 1H, CH), 1.70-1.63 (m, 1H, CH), 1.39 (s, 9H, $OCMe_3$), 0.90-0.78 (m, 21H, Si(*i*-Pr)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.6 (C=O), 147.5 (*ipso*-Ar), 128.22 (q, *J* = 32.5 Hz, *ipso*-Ar), 125.9 (Ar), 125.14 (q, *J* = 3.5 Hz, Ar), 124.5 (q, *J* = 271.5 Hz, CF_3), 80.0 (O*C*Me_3), 64.8 (OCH), 52.1 (ArCHN), 37.0 (CH_2), 35.7 (NCH_2), 32.9 (CH_2), 28.4 (OC*Me*$_3$), 18.0 (SiCH*Me*), 17.9 (SiCH*Me*), 12.1 (Si*C*HMe_2); HRMS (ESI) *m/z* calcd for $C_{26}H_{42}F_3NO_3Si$ $(M + Na)^+$ 524.2778, found 524.2785 (–1.3 ppm error). Diagnostic signals for *trans*-**157**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 2H, Ar), 5.57-5.51 (m, 1H, ArCHN).

Lab book reference: **MTG-1-58**

Using General Procedure C, *s*-BuLi (0.49 mL of a 1.33 M solution in hexane, 0.65 mmol), 4-OTIPS-*N*-Boc-piperidine **149** (178 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in THF (2.5 mL), at –78 °C for 3 h, $ZnCl_2$ (89 mg, 0.65 mmol, 1.3 eq.) in THF (1.0 mL) at –78 °C for 30 min and rt for 30 min and 4-bromobenzotrifluoride (0.091 mL, 0.65 mmol, 1.3 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $Pd_2(dba)_3$ (11.4 mg, 0.013 mmol, 0.025 eq.) in THF (2 mL) for 22 h gave the crude product. Purification by flash column chromatography on silica using 97:3 hexane-Et_2O, then 47:3 hexane-Et_2O as eluent gave a 42:58 mixture of α-arylpiperidine *cis*-**157** and 4-OTIPS-*N*-Boc-piperidine **149** (111 mg, i.e. 56 mg (27%) of α-arylpiperidine *cis*-**157** and 55 mg (31%) of 4-OTIPS-*N*-Boc-piperidine **149**) as a colourless oil.

Lab book reference: **MTG-1-59**

Using General Procedure C, *s*-BuLi (0.49 mL of a 1.33 M solution in hexane, 0.65 mmol), 4-OTIPS-*N*-Boc-piperidine **149** (177 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), at –78 °C for 3 h, $ZnCl_2$ (89 mg, 0.65 mmol, 1.3 eq.) in THF (1.0 mL) at –78 °C for 30 min and rt for 30 min and 4-bromobenzotrifluoride (0.091 mL, 0.65 mmol, 1.3 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $Pd_2(dba)_3$ (11.4 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) for 24 h gave the crude product which contained α-arylpiperidines **157** in 91:9 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 97:3 hexane-Et_2O, then 47:3 hexane-Et_2O as eluent gave a 73:27 mixture of α-arylpiperidines **157** in 74:26 dr and 4-OTIPS-*N*-Boc-piperidine **149** (64 mg, i.e. 50 mg (20%) of α-arylpiperidines **157** and 14 mg (8%) of 4-OTIPS-*N*-Boc-piperidine **149**) as a colourless oil and a 88:12 mixture of α-arylpiperidine *cis*-**157** and 4-OTIPS-*N*-Boc-piperidine **149** (108 mg, i.e. 96 mg (38%) of α-arylpiperidine *cis*-**157** and 12 mg (7%) of 4-OTIPS-*N*-Boc-piperidine **149**) as a colourless oil. Overall, this reaction gave α-arylpiperidines **157** in 91:9 dr (146 mg, 58%).

Lab book reference: **MTG-1-60**

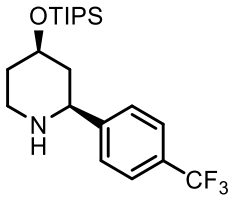
Using General Procedure C, *s*-BuLi (0.49 mL of a 1.33 M solution in hexane, 0.65 mmol), 4-OTIPS-*N*-Boc-piperidine **149** (177 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), at –78 °C for 3 h, $ZnCl_2$ (89 mg, 0.65 mmol, 1.3 eq.) in THF (1.0 mL) at –78 °C for 30 min and rt for 30 min and 4-bromobenzotrifluoride (0.091 mL, 0.65 mmol, 1.3 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $Pd_2(dba)_3$ (11.4 mg, 0.013 mmol, 0.025 eq.) in toluene (1 mL) for 20 h gave the crude product which contained α-arylpiperidines **157** in 90:10 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 97:3 hexane-Et_2O, then 47:3 hexane-Et_2O as eluent gave a 86:14 mixture of α-arylpiperidines **157** in 90:10 dr and 4-OTIPS-*N*-Boc-piperidine **149** (173 mg, i.e. 149 mg (59%) of α-arylpiperidines **157** and 24 mg (13%) of 4-OTIPS-*N*-Boc-piperidine **149**) as a colourless oil.

Lab book reference: **MTG-1-68**

Using General Procedure C, *s*-BuLi (0.53 mL of a 1.22 M solution in hexane, 0.65 mmol), 4-OTIPS-*N*-Boc-piperidine **149** (178 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), at –78 °C for 3 h, $ZnCl_2$ (89 mg, 0.65 mmol, 1.3 eq.) in THF (1.0 mL) at –78 °C for 30 min and rt for 1 h and 4-bromobenzotrifluoride (0.046 mL, 0.33 mmol, 0.65 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $Pd_2(dba)_3$ (11.4 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) for 23 h gave the crude product which contained α-arylpiperidines **157** in 99:1 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 97:3 hexane-Et_2O as eluent gave a 90:10 mixture of α-arylpiperidine *cis*-**157** and 4-OTIPS-*N*-Boc-piperidine **149** (83 mg, i.e. 77 mg (47%) of α-arylpiperidine *cis*-**157** and 6 mg (3%) of 4-OTIPS-*N*-Boc-piperidine **149**) as a colourless oil.

Lab book reference: **MTG-1-57**

2-(4-(Trifluoromethyl)phenyl)-4-((triisopropylsilyl)oxy)piperidine *cis*-172



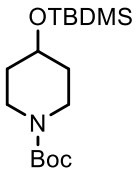
cis-**172**

Trifluoroacetic acid (0.115 mL, 1.50 mmol, 10 eq.) was added dropwise to a stirred solution of an 88:12 mixture of 4-OTIPS-2-(4-(trifluoromethyl)phenyl-*N*-Boc-piperidine *cis*-**157** and 4-OTIPS-*N*-Boc-piperidine **149** (84 mg, i.e. 74 mg, 0.15 mmol, 1.0 eq. of α-phenyl-*N*-Boc-piperidine *cis*-**157** and 10 mg of 4-OTIPS-*N*-Boc-piperidine **149**) in CH_2Cl_2 (2.5 mL) at rt under Ar. The resulting solution was stirred at rt for 23 h. Saturated $NaHCO_{3(aq)}$ (5 mL) and CH_2Cl_2 (5 mL) were added and the 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 (5 mL). The aqueous layer was extracted with CH_2Cl_2 (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 hexane then 90:9:1 EtOAc-MeOH-$NH_4OH_{(aq)}$ as eluent gave 2,4-disubstituted piperidine *cis*-**172** (39 mg, 65%) as a colourless oil, R_F

(150:90:90:1 hexane-EtOAc-MeOH-Et_3N) 0.30; IR (ATR) 2944, 2866, 1165, 1325, 1125, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 2H, Ar), 7.48 (d, *J* = 8.0 Hz, 2H, Ar), 3.84 (dddd, *J* = 10.5, 10.5, 4.5, 4.5 Hz, 1H, OCH), 3.67 (dd, *J* = 11.5, 2.5 Hz, 1H, ArCHN), 3.21 (ddd, *J* = 12.0, 4.5, 2.5 Hz, 1H, NCH), 2.77 (ddd, *J* = 12.5, 12.0, 2.5 Hz, 1H, NCH), 2.07 (dddd, *J* = 12.5, 4.5, 2.5, 2.5 Hz, 1H, CH), 1.98 (ddddd, *J* = 12.5, 4.5, 2.5, 2.5, 2.5 Hz, 1H, CH), 1.62 (br s, 1H, NH), 1.59-1.41 (m, 2H, CH), 1.08-0.99 (m, 21H, Si(*i*-Pr)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 148.3 (*ipso*-Ar), 129.6 (q, *J* = 32.5, Hz, *ipso*-Ar), 127.2 (Ar), 125.51 (q, *J* = 4.0 Hz, Ar), 124.3 (q, *J* = 272.0 Hz, CF_3), 70.3 (OCH), 60.2 (ArCHN), 45.2 (NCH_2), 44.8 (CH_2), 36.2 (CH_2), 18.2 (SiCH*Me*), 12.4 (Si*C*HMe_2); HRMS (ESI) *m/z* calcd for $C_{21}H_{34}F_3NOSi$ $(M + H)^+$ 402.2435, found 402.2429 (+1.4 ppm error).

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

tert-Butyl-4-((_tert_-butyldimethylsilyl)oxy)piperidine-1-carboxylate 73



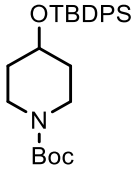
73

A solution of 4-hydroxy-*N*-Boc-piperidine **166** (2.01 g, 10 mmol, 1.0 eq.), *tert*-butyldimethylsilyl chloride (1.66 g, 11 mmol, 1.1 eq.) and imidazole (1.70 g, 25 mmol, 2.5 eq.) in DMF (35 mL) under Ar was stirred at rt for 88 h. Saturated $NaHCO_{3(aq)}$ (30 mL) and Et_2O (30 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (4 × 30 mL) and the combined organics were washed with brine (4 × 30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 9:1 hexane-Et_2O as eluent gave 4-OTBDMS-*N*-Boc-piperidine **73** (3.11 g, 99%) as a colourless oil, R_F (9:1 hexane-Et_2O) 0.20; IR (ATR) 2929, 2857, 1981, 1696 (C=O), 1173, 1102, 1044, 873, 834, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.86 (tt, *J* = 7.0, 3.5 Hz, 1H, OCH), 3.62 (ddd, *J* = 13.0, 7.5, 3.5 Hz, 2H, NCH), 3.24 (ddd, *J* = 13.0, 7.5, 3.5 Hz, 2H, NCH), 1.74-1.62 (m, 2H, CH), 1.52-1.46 (m, 2H, CH), 1.45 (s, 9H, CMe_3), 0.88 (s, 9H, $SiCMe_3$), 0.05 (s, 6H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.0

(C=O), 79.4 (O*C*Me$_3$), 67.3 (OCH), 40.7 (NCH$_2$), 34.4 (CH$_2$), 28.5 (C*Me*$_3$), 25.9 (SiC*Me*$_3$), 18.2 (Si*C*Me$_3$), –4.6 (SiMe); HRMS (ESI) *m/z* calcd for $C_{16}H_{33}NO_3Si$ (M + Na)$^+$ 338.2122, found 338.2117 (+1.4 ppm error). Spectroscopic data consistent with those reported in the literature.[31]

Lab book reference: **MTG-2-37**

tert-Butyl-4-((_tert_-butyldiphenylsilyl)oxy)piperidine-1-carboxylate 173

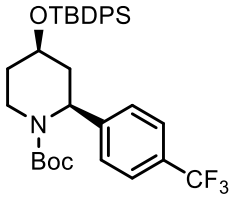


173

tert-Butyldiphenylsilyl chloride (0.572 mL, 2.2 mmol, 1.1 eq.) was added dropwise to a stirred solution of 4-hydroxy-piperidine **166** (403 mg, 2.0 mmol, 1.0 eq.) and imidazole (340 mg, 5.0 mmol, 2.5 eq.) in DMF (7 mL) at rt under Ar. The resulting solution was stirred at rt for 24 h. Saturated NaHCO$_{3(aq)}$ (6 mL) and Et$_2$O (6 mL) were added and the two layers were separated. The aqueous layer was extracted with Et$_2$O (4 x 6 mL) and the combined organics were washed with brine (4 x 6 mL), dried (MgSO$_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 19:1 hexane-Et$_2$O as eluent gave 4-OTBDPS-*N*-Boc-piperidine **173** (617 mg, 70%) as a colourless gum, R_F (9:1 hexane-Et$_2$O) 0.35; IR (ATR) 2931, 2858, 1696 (C=O), 1427, 1172, 1111, 702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.75-7.60 (m, 4H, Ph), 7.48-7.32 (m, 6H, Ph), 3.90 (tt, *J* = 7.0, 3.5 Hz, 1H, OCH), 3.70-3.56 (m, 2H, NCH), 3.25-3.12 (m, 2H, NCH), 1.64-1.48 (m, 4H, CH), 1.44 (s, 9H, CMe$_3$), 1.07 (s, 9H, SiCMe$_3$); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 155.0 (C=O), 135.8 (Ph), 134.3 (*ipso*-Ph), 129.8 (Ph), 127.7 (Ph), 79.4 (O*C*Me$_3$), 68.2 (OCH), 40.6 (NCH$_2$), 34.0 (CH$_2$), 28.5 (C*Me*$_3$), 27.1 (SiC*Me*$_3$), 19.3 (Si*C*Me$_3$); HRMS (ESI) *m/z* calcd for $C_{26}H_{37}NO_3Si$ (M + Na)$^+$ 462.2435, found 462.2429 (+1.3 ppm error).

Lab book reference: **MTG-2-11**

***tert*-Butyl-4-((*tert*-butyldiphenylsilyl)oxy)-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate *cis*-174**



cis-**174**

s-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTBDPS-*N*-Boc-piperidine **173** (220 mg, 0.5 mmol, 1.0 eq.) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. A solution of $ZnCl_2$ (89 mg, 0.65 mmol, 1.3 eq.) in THF (0.65 mL) was added and the resulting solution was stirred at –78 °C for 30 min and then at rt for 30 min. In a separate flask, a solution of 4-bromobenzotrifluoride (0.091 mL, 0.65 mmol, 1.3 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $Pd_2(dba)_3$ (11.4 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) was stirred at rt under Ar for 10 min. The solution of zinc species was added to the catalyst solution and the resulting solution was stirred and heated at 50 °C for 18 h. After being allowed to cool to rt, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-arylpiperidines **174** in 95:5 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 47:3 hexane-Et_2O as eluent gave α-arylpiperidines **174** in 56:44 dr (13 mg, 5%) as a colourless oil and a 98:2 mixture of α-arylpiperidine *cis*-**174** and 4-OTBDPS-*N*-Boc-piperidine **173** (138 mg, i.e. 136 mg (47%) of *cis*-**174** and 2 mg (1%) 4-OTBDPS-*N*-Boc-piperidine **173**) as a colourless oil, R_F (9:1 hexane-Et_2O) 0.20; IR (ATR) 2968, 2931, 2862, 1694 (C=O), 1327, 1165, 1124, 1074, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 2H, Ar), 7.52-7.27 (m, 12H, Ar), 5.38-5.26 (m, 1H, ArCHN), 4.21 (dddd, *J* = 3.5, 3.5, 3.0, 3.0 Hz, 1H, OCH), 4.03 (ddd, *J* = 13.0, 5.0, 2.5 Hz, 1H, NCH), 3.50 (ddd, *J* = 13.0, 12.5, 3.5, Hz, 1H, NCH), 2.39 (dddd, *J* = 14.5, 4.5, 3.0, 2.0 Hz, 1H, CH), 2.03 (ddd, *J* = 14.5, 7.0, 3.0 Hz, 1H, CH), 1.60-1.43 (m, 2H, CH), 1.41 (s, 9H, $OCMe_3$), 0.77 (s, 9H, $SiCMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.6 (C=O), 147.2 (*ipso*-Ar), 135.8 (Ar), 133.9 (*ipso*-Ar), 133.8 (*ipso*-Ar), 129.8 (Ar),

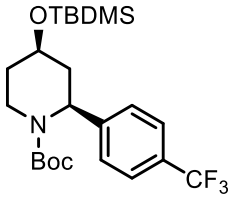
128.0 (q, *J* = 33.0 Hz, *ipso*-Ar), 127.6 (Ar), 125.9 (Ar), 125.4 (q, *J* = 3.5 Hz, Ar), 124.4 (q, *J* = 271.0 Hz, CF_3), 80.1 (O*C*Me$_3$), 65.6 (OCH), 51.8 (ArCHN), 36.2 (CH_2), 35.6 (NCH_2), 32.0 (CH_2), 28.4 (OC*Me*$_3$), 26.6 (SiC*Me*$_3$), 18.8 (Si*C*Me$_3$) (three Ar resonances not resolved); HRMS (ESI) *m/z* calcd for $C_{33}H_{40}F_3NO_3Si$ $(M + Na)^+$ 606.2622, found 606.2612 (+1.7 ppm error). Diagnostic signals for *trans*-**174**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (d, *J* = 8.0 Hz, 2H, Ar), 6.59 (d, *J* = 8.0 Hz, 2H, Ar), 5.47-5.35 (m, 1H, ArCHN). Overall, this reaction gave α-arylpiperidines **174** in 96:4 dr (150 mg, 51%).

Lab book reference: **MTG-2-19**

Using General Procedure D, *s*-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol), 4-OTBDPS-*N*-Boc-piperidine **173** (220 mg, 0.5 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 4-bromobenzotrifluoride (0.091 mL, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 15 h gave the crude product which contained α-arylpiperidines **174** in 95:5 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 9:1 hexane-Et_2O as eluent gave a 93:7 mixture of α-arylpiperidines **174** in 98:2 dr and 4-OTBDPS-*N*-Boc-piperidine **173** (209 mg, i.e. 196 mg (67%) of α-arylpiperidines **174** and 13 mg (5%) of 4-OTBDPS-*N*-Boc-piperidine **173**) as a colourless oil.

Lab book reference: **MTG-3-18**

***tert*-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate *cis*-175**



cis-**175**

s-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTBDMS-*N*-Boc-piperidine **73** (318 mg, 1.0 mmol, 1.0 eq.) and TMEDA (0.195 mL, 1.3 mmol, 1.3 eq.) in toluene (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. A solution of $ZnCl_2$ (177 mg, 1.3 mmol, 1.3 eq.) in THF (1.3 mL) was added and the resulting solution was stirred at –78 °C for 45 min and then at rt for 45 min. In a separate flask, a solution of 4-bromobenzotrifluoride (0.182 mL, 1.3 mmol, 1.3 eq.), SPhos (20.6 mg, 0.05 mmol, 0.05 eq.) and $Pd_2(dba)_3$ (22.8 mg, 0.025 mmol, 0.025 eq.) in toluene (4 mL) was stirred at rt under Ar for 10 min. The solution of zinc species was added to the catalyst solution and the resulting solution was stirred and heated at 50 °C for 19 h. After being allowed to cool to rt, saturated $NH_4Cl_{(aq)}$ (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 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 which contained α-arylpiperidines **175** in 98:2 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 97:3 hexane-Et_2O as eluent gave a 97:3 mixture of α-arylpiperidine *cis*-**175** and 4-OTBDMS-*N*-Boc-piperidine **73** (90 mg, i.e. 88 mg (19%) of α-arylpiperidine *cis*-**175** and 2 mg of 4-OTBDMS-*N*-Boc-piperidine **73**) as a white solid and α-arylpiperidines **175** in 98:2 dr (282 mg, 61%) as a white solid, R_F (9:1 hexane-Et_2O) 0.30; IR (ATR) 2954, 2929, 2885, 2858, 1693 (C=O), 1326, 1162, 1122, 1069, 1043, 876, 826, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.0 Hz, 2H, Ar), 7.28 (d, *J* = 8.0 Hz, 2H, Ar), 5.34-5.28 (m, 1H, ArCHN), 4.13-4.08 (m, 1H, OCH), 4.04 (ddd, *J* = 13.0, 5.0, 2.5 Hz, 1H, NCH), 3.38 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 1H, NCH), 2.29 (dddd, *J* = 14.0, 4.5, 2.5, 2.5 Hz, 1H, CH), 2.10 (ddd, *J* = 14.0, 7.0, 3.0 Hz, 1H, CH), 1.73 (dddd, *J* = 13.5, 13.0, 5.0, 3.0 Hz, 1H, CH), 1.56 (ddddd, *J* = 13.5, 5.5, 3.0, 2.5, 2.5 Hz, 1H, CH), 1.40 (s, 9H, $OCMe_3$), 0.54 (s, 9H, $SiCMe_3$), –0.12 (s, 3H, SiMe), –0.19 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.6 (C=O), 147.5 (*ipso*-Ar), 128.1 (q, *J* =

32.5 Hz, *ipso*-Ar), 125.8 (Ar), 125.14 (q, *J* = 4.0 Hz, Ar), 124.5 (q, *J* = 271.5 Hz, CF_3), 80.0 (O*C*Me$_3$), 64.6 (OCH), 51.9 (ArCHN), 36.8 (CH_2), 35.5 (NCH_2), 32.6 (CH_2), 28.4 (OC*Me*$_3$), 25.4 (SiC*Me*$_3$), 17.7 (Si*C*Me$_3$), –5.2 (SiMe) (one SiMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{23}H_{36}F_3NO_3Si$ $(M + Na)^+$ 482.2309, found 482.2304 (+0.9 ppm error). Diagnostic signals for *trans*-**175**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 2H, Ar), 7.32 (d, *J* = 8.0 Hz, 2H, Ar), 5.58-5.52 (m, 1H ArCHN). Overall this reaction gave α-arylpiperidines **175** in 98:2 dr (370 mg, 80%).

Lab book reference: **MTG-2-25**

Using General Procedure E, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (159 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 30 min and 4-bromobenzotrifluoride (0.091 mL, 0.65 mmol, 1.3 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $Pd_2(dba)_3$ (11.4 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) for 17 h gave the crude product which contained α-arylpiperidines **175** in 98:2 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 47:3 hexane-Et_2O as eluent gave a 97:3 mixture of α-arylpiperidine *cis*-**175** and 4-OTBDMS-*N*-Boc-piperidine **73** (118 mg, i.e. 115 mg (50%) of α-arylpiperidine *cis*-**175** and 3 mg (2%) of 4-OTBDMS-*N*-Boc-piperidine **73**) as a colourless oil and an 84:16 mixture of α-arylpiperidines **175** in 95:5 dr and 4-OTBDMS-*N*-Boc-piperidine **73** (74 mg, i.e. 66 mg (29%) of α-arylpiperidines **175** and 8 mg (5%) of 4-OTBDMS-*N*-Boc-piperidine **73**) as a colourless oil. Overall, this reaction gave α-arylpiperidines **175** in 96:4 dr (181 mg, 79%).

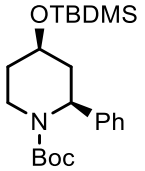
Lab book reference: **MTG-2-42**

s-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTBDMS-*N*-Boc-piperidine **73** (157 mg, 0.50 mmol, 1.0 eq.) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. A solution of $ZnCl_2$ (89 mg, 0.65 mmol, 1.3 eq.) in THF (0.65 mL) was added and the resulting solution was stirred at –78 °C for 30 min and then at rt for 30 min. In a separate flask, a solution of 4-

bromobenzotrifluoride (0.091 mL, 0.65 mmol, 1.3 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $Pd_2(dba)_3$•$CHCl_3$ (14.2 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) was stirred at rt under Ar for 10 min. The solution of zinc species was added to the catalyst solution and the resulting solution was stirred and heated at 50 °C for 18 h. After being allowed to cool to rt, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-arylpiperidines **175** in 95:5 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 47:3 hexane-Et_2O as eluent gave a 99:1 mixture of α-arylpiperidine *cis*-**175** and 4-OTBDMS-*N*-Boc-piperidine **73** (108 mg, i.e. 107 mg (46%) of α-arylpiperidine *cis*-**175** and 1 mg (1%) of 4-OTBDMS-*N*-Boc-piperidine **73**) as a colourless oil and a 96:4 mixture of α-arylpiperidines **175** in 84:16 dr and 4-OTBDMS-*N*-Boc-piperidine **73** (61 mg, i.e. 59 mg (26%) of α-arylpiperidines **175** and 2 mg (1%) of 4-OTBDMS-*N*-Boc-piperidine **73**) as a colourless oil. Overall, this reaction gave α-arylpiperidines **175** in 95:5 dr (166 mg, 72%).

Lab book reference: **MTG-2-30**

***tert*-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-phenylpiperidine-1-carboxylate *cis*-176**



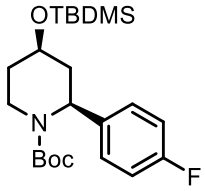
cis-**176**

s-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTBDMS-*N*-Boc-piperidine **73** (318 mg, 1.0 mmol, 1.0 eq.) and TMEDA (0.195 mL, 1.3 mmol, 1.3 eq.) in toluene (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. A solution of $ZnCl_2$ (177 mg, 1.3 mmol, 1.3 eq.) in THF (1.3 mL) was added and the resulting solution was stirred at –78 °C for 45 min and then at rt for 45 min to give a solution of the organozinc species. In a separate flask, a solution of bromobenzene (0.137 mL, 1.3 mmol, 1.3 eq.), SPhos (20.6 mg, 0.05 mmol, 0.05 eq.) and $Pd_2(dba)_3$ (22.8 mg, 0.025 mmol, 0.025 eq.) in toluene (4

mL) was stirred at rt under Ar for 10 min. The solution of the organozinc species was added to the catalyst solution and the resulting solution was stirred and heated at 50 °C for 19 h. After being allowed to cool to rt, saturated $NH_4Cl_{(aq)}$ (10 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 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 which contained α-phenylpiperidines **176** in 98:2 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 47:3 hexane-Et_2O as eluent gave a 95:5 mixture of α-phenylpiperidines **176** in 96:4 dr and 4-OTBDMS-*N*-Boc-piperidine **73** (330 mg, i.e. 317 mg (81%) of α-phenylpiperidines **176** and 13 mg of 4-OTBDMS-*N*-Boc-piperidine **73**) as a colourless oil, R_F (9:1 hexane-Et_2O) 0.25; IR (ATR) 2953, 2928, 2884, 2856, 1694 (C=O), 1171, 1079, 1042, 876, 835, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.08 (m, 5H, Ph), 5.19 (dd, *J* = 7.0, 4.0 Hz, 1H, PhCHN), 4.11-4.06 (m, 1H, OCH), 3.99 (ddd, *J* = 13.0, 5.0, 2.5 Hz, 1H, NCH), 3.39 (ddd, *J* = 13.0, 13.0, 3.5 Hz, 1H, NCH), 2.24 (dddd, *J* = 14.0, 5.0, 4.0, 1.5 Hz, 1H, CH), 2.04 (ddd, *J* = 14.0, 7.0, 3.0 Hz, 1H, CH), 1.77 (dddd, *J* = 13.0, 13.0, 5.0, 3.5 Hz, 1H, CH), 1.59-1.51 (m, 1H, CH), 1.36 (s, 9H, $OCMe_3$), 0.65-0.58 (s, 9H, $SiCMe_3$), –0.09 (s, 3H SiMe), –0.17 (s, 3H SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.8 (C=O), 143.2 (*ipso*-Ph), 128.1 (Ph), 125.8 (Ph), 125.6 (Ph), 79.7 (O*C*Me_3), 65.0 (OCH), 52.7 (PhNCH), 37.0 (CH_2), 35.8 (NCH_2), 33.0 (CH_2), 28.4 (OC*Me*$_3$), 25.6 (SiC*Me*$_3$), 17.9 (Si*C*Me_3), –5.0 (SiMe), –5.1 (SiMe); HRMS (ESI) *m/z* calcd for $C_{22}H_{37}NO_3Si$ $(M + Na)^+$ 414.2435, found 414.2432 (+0.7 ppm error). Diagnostic signals for *trans*-**176**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54-5.49 (m, 1H, PhCHN), 2.72 (ddd, *J* = 13.5, 13.5, 3.0 Hz, 1H, NCH), 2.48 (m, *J* = 13.2 Hz, 1H, CH).

Lab book reference: **MTG-2-26**

***tert*-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(4-fluorophenyl)piperidine-1-carboxylate *cis*-177**



cis-**177**

Using General Procedure E, *s*-BuLi (0.59 mL of a 1.1 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 40 min and 4-bromofluorobenzene (0.071 mL, 0.65 mmol, 1.3 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $Pd_2(dba)_3$ (11.4 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) for 19 h gave the crude product which contained α-arylpiperidines **17** in 99:1 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 19:1 hexane-Et_2O then 1:1 hexane-Et_2O as eluent gave a 54:46 mixture of α-arylpiperidines **177** in 99:1 dr and 4-OTBDMS-*N*-Boc-piperidine **73** (62 mg, i.e. 37 mg (18%) of α-arylpiperidines **177** and 25 mg of 4-OTBDMS-*N*-Boc-piperidine **73**) as a colourless oil, R_F (9:1 hexane-Et_2O) 0.30; IR (ATR) 2952, 2929, 2885, 2857, 1694 (C=O), 1172, 1078, 1044, 874, 834, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.10 (m, 2H, Ar), 6.97-6.88 (m, 2H, Ar), 5.18 (dd, *J* = 7.0, 3.5 Hz, 1H, NCHAr), 4.10-4.05 (m, 1H, OCH), 3.97 (ddd, *J* = 13.0, 5.0, 2.5 Hz, 1H, NCH), 3.34 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 1H, NCH), 2.20 (dddd, *J* = 14.0, 5.0, 3.5, 2.0 Hz, 1H, CH), 2.03 (ddd, *J* = 14.0, 7.0, 3.0 Hz, 1H, CH), 1.79-1.71 (m, 1H, CH), 1.57-1.52 (m, 1H, CH), 1.36 (s, 9H, $OCMe_3$), 0.62 (s, 9H, $SiCMe_3$), –0.10 (s, 3H SiMe), –0.16 (s, 3H SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.3 (d, *J* = 243.0 Hz, *ipso*-Ar), 155.6 (C=O), 138.9 (d, *J* = 3.0 Hz, *ipso*-Ar) 127.2 (d, *J* = 8.0 Hz, Ar), 114.8 (d, *J* = 21.5 Hz, Ar), 79.8 (O*C*Me$_3$), 64.8 (OCH), 52.0 (NCHAr), 36.9 (CH_2), 35.6 (NCH_2), 32.9 (CH_2), 28.4 (OC*Me*$_3$), 25.6 (SiC*Me*$_3$), 17.8 (Si*C*Me$_3$), –5.0 (SiMe), –5.1 (SiMe); HRMS (ESI) *m/z* calcd for $C_{22}H_{36}FNO_3Si$ $(M + Na)^+$ 432.2341, found 432.2343 (–0.6 ppm error). Diagnostic signals for *trans*-**177**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49-5.45 (m, 1H, NCHAr), 2.69 (ddd, *J* = 13.5, 13.5, 3.0 Hz, 1H, NCH).

Lab book reference: **MTG-2-46**

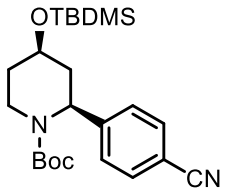
Using General Procedure D, *s*-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 40 min and 4-bromofluorobenzene (0.071 mL, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 18 h gave the crude product which contained α-arylpiperidines **177** in 97:3 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 49:1 hexane-Et_2O then 19:1 hexane-Et_2O as eluent gave a 94:6 mixture of α-arylpiperidines **177** in 96:4 dr and 4-OTBDMS-*N*-Boc-piperidine **73** (88 mg, i.e. 83 mg (43%) of α-arylpiperidines **177** and 5 mg of 4-OTBDMS-*N*-Boc-piperidine **73**) as a colourless oil and an 82:18 mixture of α-arylpiperidines **177** in 93:7 dr and 4-OTBDMS-*N*-Boc-piperidine **73** (60 mg, i.e. 53 mg (25%) of α-arylpiperidines **177** and 9 mg of 4-OTBDMS-*N*-Boc-piperidine **73**) as a colourless oil. Overall, this reaction gave α-arylpiperidines **177** in 96:4 dr (134 mg, 65%).

Lab book reference: **MTG-3-15**

Using General Procedure D, *s*-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (157 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 4-bromobenzonitrile (118 mg, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 15 h gave the crude product which contained α-arylpiperidines **177** in 95:5 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 4:1 hexane-Et_2O as eluent gave α-arylpiperidines **177** in 98:2 dr (126 mg, 61%) as a white solid.

Lab book reference: **MTG-3-17**

tert-Butyl-4-((_tert_-butyldimethylsilyl)oxy)-2-(4-cyanophenyl)piperidine-1-carboxylate _cis_-178

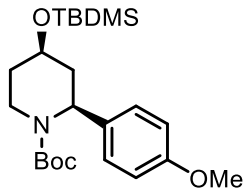


cis-**178**

Using General Procedure E, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (157 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 30 min and 4-bromobenzonitrile (118 mg, 0.65 mmol, 1.3 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $Pd_2(dba)_3$•$CHCl_3$ (14.2 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) for 18 h gave the crude product which contained α-arylpiperidines **178** in 88:12 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 4:1 hexane-Et_2O as eluent gave α-arylpiperidines **178** in 91:9 dr (88 mg, 42%) as a white solid, R_F (4:1 hexane-Et_2O) 0.15; IR (ATR) 2952, 2930, 2858, 2229 (C≡N), 1699 (C=O), 1365, 1257, 1171, 1082, 992, 869, 837, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.54 (m, 2H, Ar), 7.31-7.26 (m, 2H, Ar), 5.34-5.25 (m, 1H, ArCHN), 4.14-4.08 (m, 1H, OCH), 4.03 (ddd, *J* = 13.0, 5.0, 2.5z, 1H, NCH), 3.35 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 1H, NCH), 2.26 (dddd, *J* = 14.0, 4.0, 2.0, 2.0 Hz, 1H, CH), 2.10 (ddd, *J* = 14.0, 7.0, 3.0 Hz, 1H, CH), 1.72 (dddd, *J* = 13.0, 12.5, 5.0, 3.0 Hz, 1H, CH), 1.60-1.52 (m, 1H, CH), 1.39 (s, 9H, $OCMe_3$), 0.56 (s, 9H, $SiCMe_3$), –0.12 (s, 3H, SiMe), –0.20 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.5 (C=O), 149.4 (*ipso*-Ar), 132.1 (Ar), 126.4 (Ar), 119.3 (Ar*C*N), 109.5 (*ipso*-ArCN), 80.2 (O*C*Me$_3$), 64.5 (OCH), 52.0 (ArCHN), 36.7 (CH_2), 35.5 (NCH_2), 32.5 (CH_2), 28.4 (OC*Me*$_3$), 25.4 (SiC*Me*$_3$), 17.8 (Si*C*Me$_3$), –5.1 (SiMe), –5.1 (SiMe); HRMS (ESI) *m/z* calcd for $C_{23}H_{36}N_2O_3Si$ $(M + Na)^+$ 439.2387, found 439.2389 (–0.5 ppm error). Diagnostic signals for *trans*-**178**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82-5.77 (m, 1H, ArCHN), 1.47 (s. 9H, $OCMe_3$), 0.90 (s, 9H, Si*C*Me$_3$), 0.11 (s, 3H, SiMe), 0.10, (s, 3H, SiMe).

Lab book reference: **MTG-2-31**

tert-Butyl-4-((_tert_-butyldimethylsilyl)oxy)-2-(4-methoxyphenyl)piperidine-1-carboxylate _cis_-179



cis-**179**

Using General Procedure E, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (159 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (89 mg, 0.65 mmol, 1.3 eq.) in THF (0.65 mL) at –78 °C for 30 min and rt for 30 min and 4-bromoanisole (0.081 mL, 0.65 mmol, 1.3 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $Pd_2(dba)_3$ (11.4 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) for 17 h gave the crude product which α-arylpiperidines **179** in 96:4 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 97:3 hexane-Et_2O then 47:3 hexane-Et_2O as eluent gave α-arylpiperidines **179** in 98:2 dr (101 mg, 48%) as a colourless oil, R_F (4:1 hexane-Et_2O) 0.55; IR (ATR) 2952, 2928, 2856, 1691 (C=O), 1246, 1169, 1076, 1043, 833, 824, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.07 (m, 2H, Ar), 6.83-6.77 (m, 2H, Ar), 5.16 (dd, *J* = 7.0, 4.0 Hz, 1H, ArCHN), 4.08 (dddd, *J* = 5.0, 3.5, 3.5, 3.5 Hz, 1H, OCH), 4.01-3.93 (m, 1H, NCH), 3.76 (s, 3H, OMe), 3.36 (ddd, *J* = 13.0, 13.0, 3.5 Hz, 1H, NCH), 2.20 (dddd, *J* = 14.0, 5.0, 4.0, 1.5 Hz, 1H, CH), 2.02 (ddd, *J* = 14.0, 7.0, 3.5 Hz, 1H, CH), 1.78 (dddd, *J* = 13.0, 12.5, 5.0, 3.5 Hz, 1H, CH), 1.59-1.51 (m, 1H, CH), 1.38 (s, 9H, CMe_3), 0.65 (s, 9H, $SiCMe_3$), –0.07 (s, 3H SiMe), –0.12 (s, 3H SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.9 (*ipso*-Ar), 155.7 (C=O), 135.4 (*ipso*-Ar), 126.8 (Ar), 113.6 (Ar), 79.6 (O*C*Me_3), 65.0 (OCH), 55.4 (OMe), 52.2 (ArCHN), 36.9 (CH_2), 35.6 (NCH_2), 33.1 (CH_2), 28.5 (OC*Me*$_3$), 25.6 (SiC*Me*$_3$), 17.9 (Si*C*Me_3), –4.9 (SiMe), –5.0 (SiMe); HRMS (ESI) *m/z* calcd for $C_{23}H_{39}NO_4Si$ $(M + Na)^+$ 444.2541, found 444.2541 (–0.2 ppm error). Diagnostic signals for *trans*-**179**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88-6.84 (m, 2H, Ar), 5.49-5.44 (m, 1H, ArC*H*N), 3.78 (s, 3H, OMe), 0.03 (s, 3H, SiMe), 0.00 (s, 3H, SiMe).

Lab book reference: **MTG-2-39**

s-BuLi (0.59 mL of a 1.1 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTBDMS-*N*-Boc-piperidine **73** (160 mg, 0.51 mmol, 1.0 eq.) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. A solution of $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) was added and the resulting solution was stirred at –78 °C for 30 min and then at rt for 30 min. In a separate flask, a solution of 4-bromoanisole (0.081 mL, 0.65 mmol, 1.3 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $Pd(OAc)_2$ (5.9 mg, 0.025 mmol, 0.05 eq.) in toluene (2 mL) was stirred at rt under Ar for 10 min. The catalyst solution was added to the solution of zinc species and the resulting solution was stirred and heated at 50 °C for 16 h. After being allowed to cool to rt, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-arylpiperidines **179** in 99:1 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 19:1 hexane-Et_2O as eluent gave α-arylpiperidines **179** in 99:1 dr (11 mg, 5%) as a colourless oil.

Lab book reference: **MTG-2-49**

s-BuLi (0.51 mL of a 1.28 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.51 mmol, 1.0 eq.) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. A solution of $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) was added and the resulting solution was stirred at –78 °C for 30 min and then at rt for 40 min. In a separate flask, a solution of 4-bromoanisole (0.081 mL, 0.65 mmol, 1.3 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) was stirred at rt under Ar for 10 min. The catalyst solution was added to the solution of zinc species and the resulting solution was stirred and heated at 50 °C for 16 h. After being allowed to cool to rt, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-

arylpiperidines **179** in 94:6 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 19:1 hexane-Et_2O as eluent gave α-arylpiperidines **179** in 94:6 dr (114 mg, 54%) as a colourless oil.

Lab book reference: **MTG-2-50**

Using General Procedure D, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (160 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 1 h and 4-bromoanisole (0.081 mL, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2.5 mL) for 18 h gave the crude product which contained α-arylpiperidines **179** in 98:2 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 19:1 hexane-Et_2O as eluent gave α-arylpiperidines **179** in 97:3 dr (154 mg, 72%) as a colourless oil.

Lab book reference: **MTG-3-41**

Using General Procedure D, *s*-BuLi (0.59 mL of a 1.1 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (159 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 4-chloroanisole (0.080 mL, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2.5 mL) for 17 h gave the crude product which contained α-arylpiperidines **179** in 97:3 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 19:1 hexane-Et_2O then 9:1 hexane-Et_2O as eluent gave α-arylpiperidines **179** in 97:3 dr (143 mg, 62%) as a colourless oil.

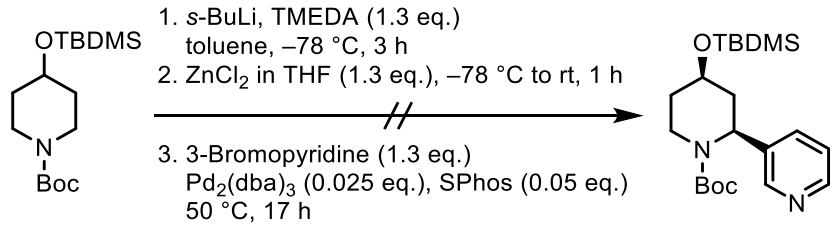
Lab book reference: **MTG-8-17**

Using General Procedure D, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 1 h and 4-bromoanisole (0.093 mL, 0.75 mmol,

1.5 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2.5 mL) for 18 h gave the crude product which contained α-arylpiperidines **179** in 96:4 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 97:3 hexane-Et_2O then 3:2 hexane-Et_2O as eluent gave α-arylpiperidines **179** in 96:4 dr (164 mg, 78%) as a colourless oil.

Lab book reference: **MTG-3-42**

Attempted synthesis of *tert*-butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(pyridin-3-yl)piperidine-1-carboxylate *cis*-180

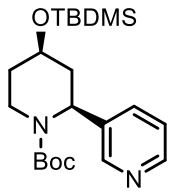


73 *cis*-**180**

Using General Procedure E, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (159 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (89 mg, 0.65 mmol, 1.3 eq.) in THF (0.65 mL) at –78 °C for 30 min and rt for 30 min and 3-bromopyridine (0.063 mL, 0.65 mmol, 1.3 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $Pd_2(dba)_3$ (11.4 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) for 17 h gave the crude product which contained none of α-arylpiperidine *cis*-**180** (by ^{1}H NMR spectroscopy).

Lab book reference: **MTG-2-40**

***tert*-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(pyridin-3-yl)piperidine-1-carboxylate *cis*-180**



cis-**180**

Using general procedure F, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (157 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 30 min and 3-bromopyridine (0.063 mL, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol, 0.05 eq.) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) for at 50 °C 17 h gave the crude product which contained α-arylpiperidines **180** in 95:5 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 4:1 hexane-EtOAc then 2:3 hexane-EtOAc as eluent gave α-arylpiperidines **180** in 97:3 dr (57 mg, 29%) as a colourless oil, R_F (7:3 hexane-EtOAc) 0.35; IR (ATR) 2953, 2929, 2884, 2857, 1693 (C=O), 1168, 1078, 1047, 875, 831, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50-8.43 (m, 1H, Ar), 8.39-8.33 (m, 1H, Ar), 7.50-7.45 (m, 1H, Ar), 7.16 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H, Ar), 5.32-5.26 (m, 1H, ArCHN), 4.13-4.07 (m, 1H, OCH), 3.99 (ddd, *J* = 13.0, 5.0, 2.5 Hz, 1H, NCH), 3.32 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 1H, NCH), 2.25 (dddd, *J* = 14.0, 4.5, 2.0, 2.0 Hz, 1H, CH), 2.06 (ddd, *J* = 14.0, 7.0, 3.0 Hz, 1H, CH), 1.71 (dddd, *J* = 13.0, 13.0, 5.0, 3.0 Hz, 1H, CH), 1.58-1.50 (m, 1H, CH), 1.36 (s, 9H, $OCMe_3$), 0.56 (s, 9H, $SiCMe_3$), –0.13 (s, 3H SiMe), –0.20 (s, 3H SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.5 (C=O), 147.8 (Ar), 147.1 (Ar), 138.5 (*ipso*-Ar), 133.2 (Ar), 123.0 (Ar), 80.1 (O*C*Me_3), 64.6 (OCH), 50.4 (ArNCH), 36.4 (CH_2), 35.4 (NCH_2), 32.6 (CH_2), 28.4 (OC*Me*$_3$), 25.6 (SiC*Me*$_3$), 17.8 (Si*C*Me_3), –5.0 (SiMe), –5.2 (SiMe); HRMS (ESI) *m/z* calcd for $C_{21}H_{37}N_2O_3Si$ $(M + H)^+$ 393.2568, found 393.2565 +0.7 ppm error). Diagnostic signals for *trans*-**180**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56-5.51 (m, 1H, ArCHN), 2.68 (ddd, *J* = 14.0, 13.5, 3.0 Hz, 1H, NCH), 1.83 (ddd, *J* = 13.5, 11.0, 6.0 Hz, 1H, CH), 0.00 (s, 3H, SiMe).

Lab book reference: **MTG-3-3**

Using general procedure F, *s*-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 30 min and 3-bromopyridine (0.063 mL, 0.65 mmol, 1.3 eq.), CPhos (10.9 mg, 0.025 mmol, 0.05 eq.) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) for at 50 °C 17 h gave the crude product which contained α-arylpiperidines **180** in 96:4 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 3:2 hexane-Et_2O as eluent gave α-arylpiperidines **180** in 98:2 dr (36 mg, 18%) as a colourless oil.

Lab book reference: **MTG-2-72**

Using general procedure F, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 30 min and 3-bromopyridine (0.063 mL, 0.65 mmol, 1.3 eq.), CPhos (10.9 mg, 0.025 mmol, 0.05 eq.) and $Pd_2(dba)_3$ (11.4 mg, 0.013 mmol, 0.025 eq.) in toluene (2.5 mL) for at 50 °C 18 h gave the crude product. Purification by flash column chromatography on silica using 9:1 hexane-EtOAc then 3:2 hexane-EtOAc as eluent gave α-arylpiperidine *cis*-**180** (13 mg, 7%) as a colourless oil.

Lab book reference: **MTG-7-68**

Using general procedure F, *s*-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 30 min and 3-bromopyridine (0.063 mL, 0.65 mmol, 1.3 eq.), CPhos (10.9 mg, 0.025 mmol, 0.05 eq.) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol, 0.025 eq.) in toluene (2.5 mL) for at 80 °C 15 h gave the crude product which contained α-arylpiperidines **180** in 88:12 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 4:1 hexane-EtOAc then 3:2 hexane-EtOAc as eluent gave α-arylpiperidines **180** in 96:4 dr (75 mg, 38%) as a colourless oil.

Lab book reference: **MTG-3-10**

Using general procedure F, *s*-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (157 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 30 min and 3-bromopyridine (0.063 mL, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol, 0.05 eq.) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) for at 100 °C 16 h gave the crude product which contained α-arylpiperidines **180** in 91:9 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 9:1 hexane-EtOAc then 3:2 hexane-EtOAc as eluent gave α-arylpiperidines **180** in 95:5 dr (105 mg, 54%) as a colourless oil.

Lab book reference: **MTG-3-11**

Using general procedure F, *s*-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (159 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 30 min and 3-bromopyridine (0.063 mL, 0.65 mmol, 1.3 eq.), CPhos (10.9 mg, 0.025 mmol, 0.05 eq.) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) for at 100 °C 16 h gave the crude product which contained α-arylpiperidines **180** in 94:6 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 9:1 hexane-EtOAc then 3:2 hexane-EtOAc as eluent gave α-arylpiperidines **180** in 95:5 dr (83 mg, 42%) as a colourless oil.

Lab book reference: **MTG-3-12**

Using general procedure F, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (157 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 30 min and 3-bromopyridine (0.048 mL, 0.50 mmol, 1.0 eq.), RuPhos (11.7 mg, 0.025 mmol, 0.05 eq.) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol, 0.025 eq.) in toluene (2.5 mL) for at 100 °C 18 h gave the crude product. Purification by flash column chromatography on silica using 9:1 hexane-

EtOAc then 4:1 hexane-EtOAc as eluent gave α-arylpiperidines **180** in 97:3 dr (102 mg, 52%) as a colourless oil.

Lab book reference: **MTG-3-35**

Using General Procedure D, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (157 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 3-bromopyridine (0.063 mL, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2.5 mL) for 18 h gave the crude product which contained α-arylpiperidines **180** in 97:3 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 9:1 hexane-EtOAc then 3:2 hexane-EtOAc as eluent gave α-arylpiperidines **180** in 96:4 dr (120 mg, 62%) as a colourless oil.

Lab book reference: **MTG-3-37**

Using general procedure F, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 30 min and 3-bromopyridine (0.072 mL, 0.75 mmol, 1.5 eq.), RuPhos (11.7 mg, 0.025 mmol, 0.05 eq.) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol, 0.025 eq.) in toluene (2.5 mL) for at 100 °C 18 h gave the crude product which contained α-arylpiperidines **180** in 95:5 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 9:1 hexane-EtOAc then 3:2 hexane-EtOAc as eluent gave α-arylpiperidines **180** in 96:4 dr (135 mg, 69%) as a colourless oil.

Lab book reference: **MTG-3-36**

Using general procedure F, *s*-BuLi (0.48 mL of a 1.35 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (157 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 30 min and 3-bromopyridine

(0.096 mL, 1.00 mmol, 2.0 eq.), RuPhos (11.7 mg, 0.025 mmol, 0.05 eq.) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) for at 100 °C 18 h gave the crude product which contained α-arylpiperidines **180** in 93:7 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 9:1 hexane-EtOAc then 3:2 hexane-EtOAc as eluent gave α-arylpiperidines **180** in 95:5 dr (94 mg, 48%) as a colourless oil.

Lab book reference: **MTG-3-27**

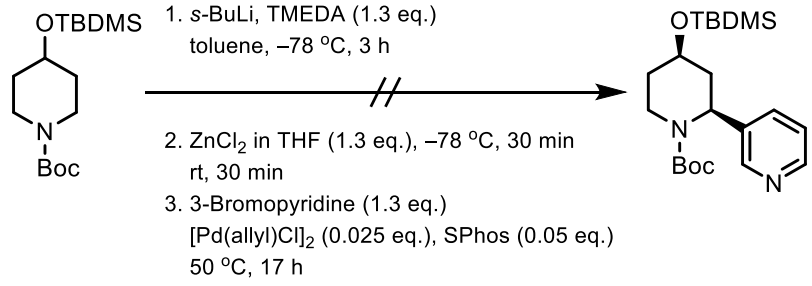
Using General Procedure D, *s*-BuLi (0.54 mL of a 1.21 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.5 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 1 h and rt for 30 min and 3-chloropyridine (0.062 mL, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2.5 mL) for 18 h gave the crude product which contained α-arylpiperidines **180** in 96:4 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 9:1 hexane-EtOAc then 3:2 hexane-EtOAc as eluent gave α-arylpiperidines **180** in 97:3 dr (132 mg, 67%) as a colourless oil.

Lab book reference: **MTG-3-71**

Using General Procedure D, *s*-BuLi (0.48 mL of a 1.35 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (160 mg, 0.5 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 3-iodopyridine (133 mg, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2.5 mL) for 18 h gave the crude product. Purification by flash column chromatography on silica using 9:1 hexane-EtOAc then 3:2 hexane-EtOAc as eluent gave α-arylpiperidines **180** in 97:3 dr (80 mg, 40%) as a colourless oil.

Lab book reference: **MTG-3-33**

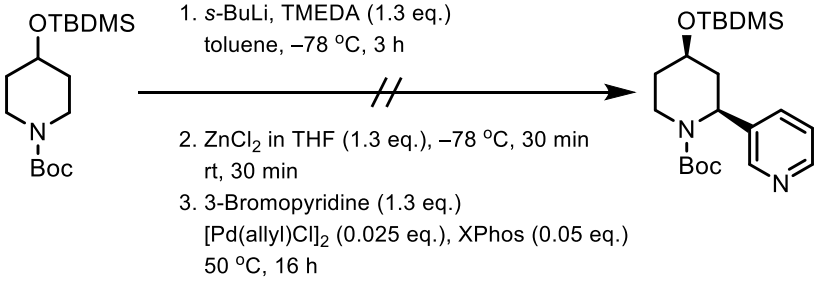
Attempted synthesis of *tert*-butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(pyridin-3-yl)piperidine-1-carboxylate *cis*-180



73 *cis*-**180**

Using general procedure F, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (157 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 30 min and 3-bromopyridine (0.063 mL, 0.65 mmol, 1.3 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol, 0.025 eq.) in toluene (2.5 mL) at 50 °C for 17 h gave the crude product which contained trace amounts of α-arylpiperidine **180** (by ^{1}H NMR spectroscopy and HRMS).

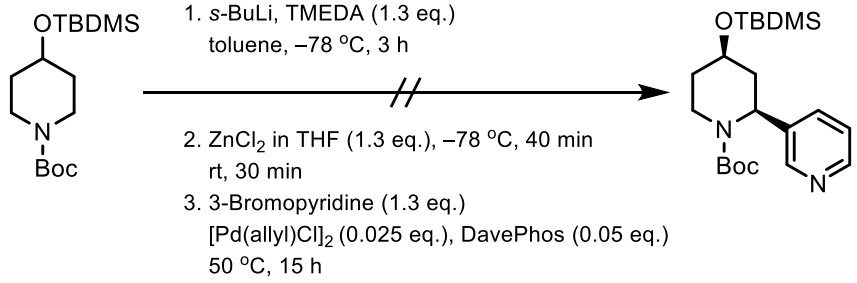
Lab book reference: **MTG-7-63**



73 *cis*-**180**

Using general procedure F, *s*-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 30 min and 3-bromopyridine (0.063 mL, 0.65 mmol, 1.3 eq.), XPhos (11.9 mg, 0.025 mmol, 0.05 eq.) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) at 50 °C for 16 h gave the crude product which contained none of α-arylpiperidine *cis*-**180** (by ^{1}H NMR spectroscopy).

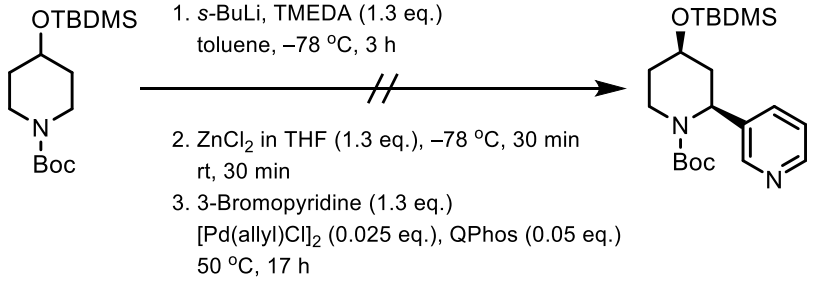
Lab book reference: **MTG-2-71**



73 *cis*-**180**

Using general procedure F, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 40 min and rt for 30 min and 3-bromopyridine (0.063 mL, 0.65 mmol, 1.3 eq.), DavePhos (9.8 mg, 0.025 mmol, 0.05 eq.) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) at 50 °C for 15 h gave the crude product which contained trace amounts of α-arylpiperidine *cis*-**180** (by ^{1}H NMR spectroscopy and HRMS).

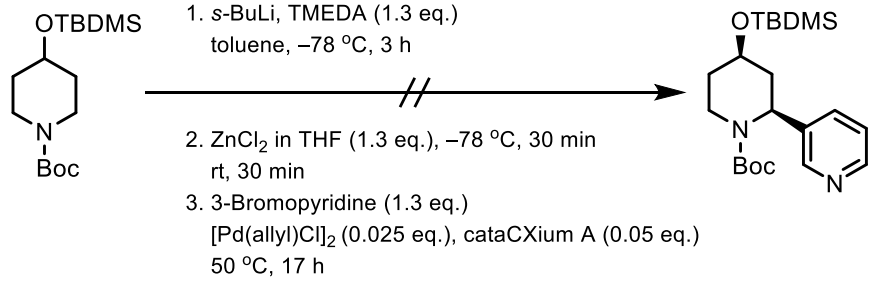
Lab book reference: **MTG-3-1**



73 *cis*-**180**

Using general procedure F, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (160 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 30 min and 3-bromopyridine (0.063 mL, 0.65 mmol, 1.3 eq.), QPhos (17.8 mg, 0.025 mmol, 0.05 eq.) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) at 50 °C for 17 h gave the crude product which contained none of α-arylpiperidine *cis*-**180** (by ^{1}H NMR spectroscopy and HRMS).

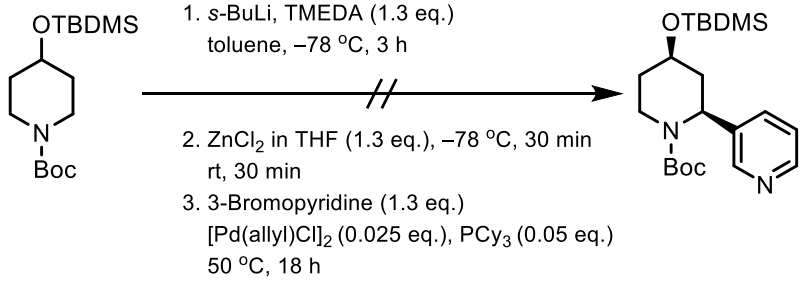
Lab book reference: **MTG-3-4**



73 *cis*-**180**

Using general procedure F, *s*-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 30 min and 3-bromopyridine (0.063 mL, 0.65 mmol, 1.3 eq.), cataCXium A (9.0 mg, 0.025 mmol, 0.05 eq.) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) at 50 °C for 17 h gave the crude product which contained none of α-arylpiperidine *cis*-**180** (by ^{1}H NMR spectroscopy and HRMS).

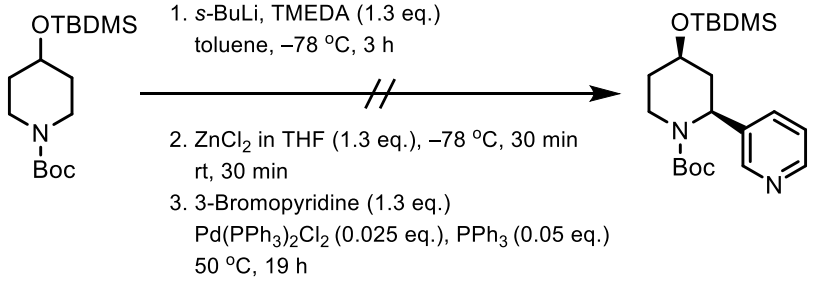
Lab book reference: **MTG-2-73**



73 *cis*-**180**

Using general procedure F, *s*-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (157 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 30 min and 3-bromopyridine (0.063 mL, 0.65 mmol, 1.3 eq.), PCy_3 (7.0 mg, 0.025 mmol, 0.05 eq.) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) at 50 °C for 19 h gave the crude product which contained none of α-arylpiperidine *cis*-**180** (by ^{1}H NMR spectroscopy and HRMS).

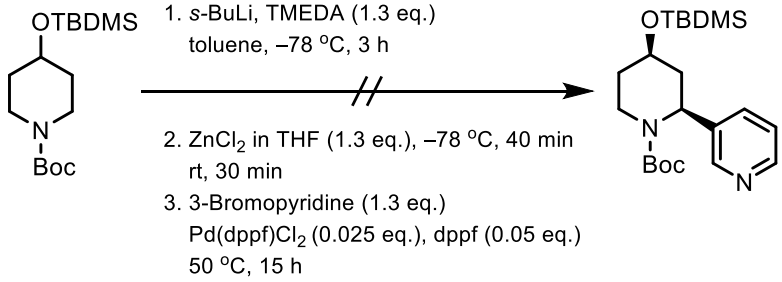
Lab book reference: **MTG-2-77**



73 *cis*-**180**

Using general procedure F, *s*-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (157 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 30 min and 3-bromopyridine (0.063 mL, 0.65 mmol, 1.3 eq.), PPh_3 (13.1 mg, 0.05 mmol, 0.10 eq.) and $Pd(PPh_3)_2Cl_2$ (17.5 mg, 0.025 mmol, 0.05 eq.) in toluene (2 mL) at 50 °C for 19 h gave the crude product which contained none of α-arylpiperidine *cis*-**180** (by ^{1}H NMR spectroscopy and HRMS).

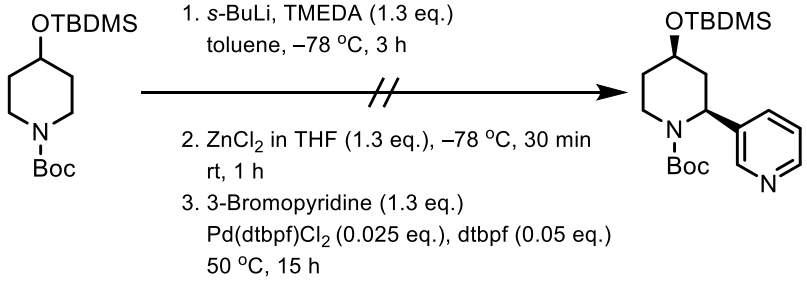
Lab book reference: **MTG-2-78**



73 *cis*-**180**

Using general procedure F, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (156 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 40 min and rt for 30 min and 3-bromopyridine (0.063 mL, 0.65 mmol, 1.3 eq.), dppf (13.9 mg, 0.025 mmol, 0.05 eq.) and $Pd(dppf)Cl_2$ (18.3 mg, 0.025 mmol, 0.05 eq.) in toluene (2 mL) at 50 °C for 15 h gave the crude product which contained trace amounts of α-arylpiperidine *cis*-**180** (by ^{1}H NMR spectroscopy and HRMS).

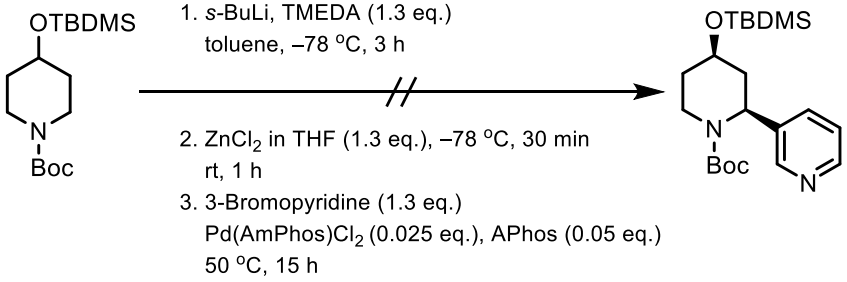
Lab book reference: **MTG-3-2**



73 *cis*-**180**

Using general procedure F, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 1 h and 3-bromopyridine (0.063 mL, 0.65 mmol, 1.3 eq.), dtbpf (11.9 mg, 0.025 mmol, 0.05 eq.) and Pd(dtbpf)Cl_2 (16.3 mg, 0.025 mmol, 0.05 eq.) in toluene (2 mL) at 50 °C for 15 h gave the crude product which contained none of α-arylpiperidine *cis*-**180** (by ^{1}H NMR spectroscopy).

Lab book reference: **MTG-3-8**

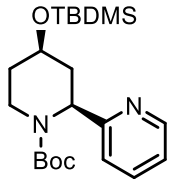


73 *cis*-**180**

Using general procedure F, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (157 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol, 1.3 eq.) at –78 °C for 30 min and rt for 1 h and 3-bromopyridine (0.063 mL, 0.65 mmol, 1.3 eq.), APhos (6.6 mg, 0.025 mmol, 0.05 eq.) and Pd(AmPhos)Cl_2 (17.7 mg, 0.025 mmol, 0.05 eq.) in toluene (2 mL) at 50 °C for 15 h gave the crude product which contained none of α-arylpiperidine *cis*-**180** (by ^{1}H NMR spectroscopy).

Lab book reference: **MTG-3-7**

***tert*-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(pyridin-2-yl)piperidine-1-carboxylate *cis*-187**



cis-**187**

Using General Procedure D, *s*-BuLi (0.54 mL of a 1.21 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (159 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 40 min and 2-chloropyridine (0.071 mL, 0.75 mmol, 1.5 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 18 h gave the crude product. Purification by flash column chromatography on silica using 9:1 hexane-EtOAc as eluent gave α-arylpiperidine *cis*-**187** (45 mg, 23%) as a colourless oil, R_F (4:1 hexane-EtOAc) 0.50; IR (ATR) 2954, 2928, 2885, 2856, 1694 (C=O), 1171, 1080, 1049, 878, 833, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H, Ar), 7.54 (ddd, *J* = 7.5, 7.5, 2.0 Hz, 1H, Ar), 7.09-7.04 (m, 1H, Ar) 7.04-6.98 (m, 1H, Ar), 5.27-5.19 (m, 1H, NCHAr), 4.09-3.98 (m, 2H, OCH and NCH), 3.44 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 1H, NCH), 2.69 (dddd, *J* = 14.0, 4.5, 2.0, 2.0 Hz, 1H, CH), 2.01 (ddd, *J* = 14.0, 7.5, 3.0 Hz, 1H, CH), 1.70 (dddd, *J* = 13.0, 13.0, 5.0, 2.5 Hz, 1H, CH), 1.59-1.50 (m, 1H, CH), 1.35 (s, 9H, $OCMe_3$), 0.52 (s, 9H, $SiCMe_3$), –0.16 (s, 3H SiMe), –0.29 (s, 3H SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.6 (*ipso*-Ar), 155.9 (C=O), 148.9 (Ar), 136.2 (Ar), 120.8 (Ar), 118.9 (Ar), 79.8 ($OCMe_3$), 64.6 (OCH), 53.9 (NCHAr), 35.7 (CH_2), 35.4 (NCH_2), 32.6 (CH_2), 28.4 ($OCMe_3$), 25.6 ($SiCMe_3$), 17.8 ($SiCMe_3$), –5.2 (SiMe), –5.3 (SiMe); HRMS (ESI) *m/z* calcd for $C_{21}H_{37}N_2O_3Si$ $(M + H)^+$ 393.2568, found 393.2576 (–2.1 ppm error).

Lab book reference: **MTG-3-32**

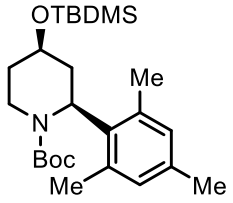
Using General Procedure D, *s*-BuLi (0.48 mL of a 1.35 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 2-bromopyridine (0.062 mL, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 18 h gave the crude product. Purification by flash column chromatography on silica using 9:1 hexane-EtOAc as eluent gave α-arylpiperidines **187** in 99:1 dr (55 mg, 28%) as a colourless oil. Diagnostic signals for *trans*-**187**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (s, 9H, $SiCMe_3$), 0.04-0.03 (m, 6H, SiMe).

Lab book reference: **MTG-3-28**

Using General Procedure D, *s*-BuLi (0.54 mL of a 1.21 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (159 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 1 h and rt for 30 min and 2-iodopyridine (0.080 mL, 0.75 mmol, 1.5 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 18 h gave the crude product. Purification by flash column chromatography on silica using 9:1 hexane-EtOAc then 7:3 hexane-EtOAc as eluent gave α-arylpiperidines **187** in 97:3 dr (38 mg, 19%) as a colourless oil.

Lab book reference: **MTG-3-65**

***tert*-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(2,4,6-trimethylphenyl)piperidine-1-carboxylate *cis*-188**

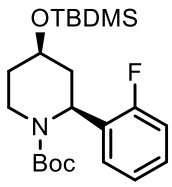


cis-**188**

Using General Procedure D, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 40 min and 2-bromomesitylene (0.115 mL, 0.75 mmol, 1.5 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 18 h gave the crude product. Purification by flash column chromatography on silica using 19:1 hexane-EtOAc as eluent gave a 66:34 mixture of α-arylpiperidine *cis*-**188** and 4-OTBDMS-*N*-Boc-piperidine **73** (91 mg, i.e. 70 mg (32%) of α-arylpiperidine *cis*-**188** and 21 mg of 4-OTBDMS-*N*-Boc-piperidine **73**) as a colourless oil, R_F (9:1 hexane-EtOAc) 0.45; IR (ATR) 2954, 2929, 2858, 1692 (C=O), 1364, 1173, 1081, 872, 834, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (s, 2H, Ar), 4.76 (dd, *J* = 13.5, 4.5 Hz, 1H, NCHAr), 3.98 (dddd, *J* = 10.5, 7.0, 5.5, 5.5 Hz, 1H, OCH), 3.76 (ddd, *J* = 14.0, 5.5, 5.5 Hz, 1H, NCH), 3.64 (ddd, *J* = 14.0, 10.0, 4.5 Hz, 1H, NCH), 2.29 (s, 6H, ArMe), 2.23 (s, 3H, ArMe), 2.20-2.09 (m, 1H, CH), 1.93 (ddd, *J* = 13.5, 13.5, 10.5 Hz, 1H, CH), 1.85-1.69 (m, 2H, CH and CH), 1.07 (s, 9H, $OCMe_3$), 0.87 (s, 9H, $SiCMe_3$), 0.06 (s, 3H SiMe), 0.04 (s, 3H SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.2 (C=O), 138.0 (*ipso*-Ar), 135.3 (*ipso*-Ar), 134.4 (*ipso*-Ar), 130.1 (Ar), 79.5 (O*C*Me_3), 67.0 (OCH), 53.0 (NCHAr), 39.4 (NCH_2), 36.8 (CH_2), 34.4 (CH_2), 27.9 (OC*Me*$_3$), 25.9 (SiC*Me*$_3$), 20.8 (ArMe), 20.6 (ArMe), 18.3 (Si*C*Me_3), –4.7 (SiMe), –4.7 (SiMe); HRMS (ESI) *m/z* calcd for $C_{25}H_{43}NO_3Si$ $(M + Na)^+$ 456.2904, found 456.2908 (–0.7 ppm error).

Lab book reference: **MTG-3-54**

tert-Butyl-4-[_tert_-butyl(dimethyl)silyl]oxy-2-(2-fluorophenyl)piperidine-1-carboxylate _cis_-189



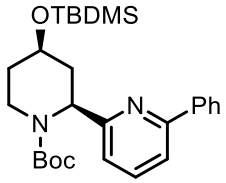
cis-**189**

Using General Procedure D, *s*-BuLi (0.59 mL of a 1.1 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (157 mg, 0.50 mmol) and TMEDA (0.097

mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 2-fluorobromobenzene (0.082 mL, 0.75 mmol, 1.5 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 18 h gave the crude product which contained α-arylpiperidines **189** in 93:7 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 13:7 hexane-CH_2Cl_2 then 1:1 hexane-CH_2Cl_2 as eluent gave α-arylpiperidines **189** in 97:3 dr (49 mg, 24%) as a colourless oil, R_F (1:1 hexane-CH_2Cl_2) 0.35; IR (ATR) 2958, 2928, 2891, 2862, 1694 (C=O), 1077, 1055, 878, 832, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, Ar), 7.14-7.09 (m, 1H, Ar), 7.02 (dd, *J* = 8.0, 7.5 Hz, 1H, Ar), 6.95 (dd, *J* = 11.0, 8.0 Hz, 1H, Ar), 5.34 (dd, *J* = 7.0, 4.0 Hz, 1H, ArCHN), 4.13-4.01 (m, 2H, NCH + OCH), 3.56 (ddd, *J* = 13.5, 13.0, 4.0 Hz, 1H, NCH), 2.23 (ddd, *J* = 14.0, 5.0, 4.0 Hz, 1H, CH), 2.03 (ddd, *J* = 14.0, 7.0, 3.0 Hz, 1H, CH), 1.82 (dddd, *J* = 13.0, 13.0, 5.5, 3.5 Hz, 1H, CH), 1.69-1.59 (m, 1H, CH), 1.32 (s, 9H, $OCMe_3$), 0.64 (s, 9H, $SiCMe_3$), –0.08 (s, 3H, SiMe), –0.21 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.0 (d, *J* = 244.0 Hz, *ipso*-Ar), 155.6 (C=O), 131.6 (d, *J* = 12.5 Hz, *ipso*-Ar), 127.5 (d, *J* = 8.5 Hz, Ar), 126.8 (d, *J* = 5.0 Hz, Ar), 123.9 (d, *J* = 3.0 Hz, Ar), 115.3 (d, *J* = 22.0 Hz, Ar), 79.8 (O*C*Me_3), 64.8 (OCH), 48.5 (ArCHN), 36.5 (CH_2), 36.5 (NCH_2), 32.8 (CH_2), 28.3 (OC*Me*$_3$), 25.6 (SiC*Me*$_3$), 17.9 (Si*C*Me_3), –5.1 (SiMe), –5.2 (SiMe); HRMS (ESI) *m/z* calcd for $C_{22}H_{36}FNO_3Si$ (M + Na)$^+$ 432.2341, found 432.2346 (–1.3 ppm error). Diagnostic signals for *trans*-**189**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61-5.57 (m, 1H, ArCHN), 1.46 (s, 9H, $OCMe_3$), 0.79 (s, 9H, $SiCMe_3$) and α-arylpiperidines **189** in 85:15 dr (7 mg, 3%) as a colourless oil. Overall, this reaction gave α-arylpiperidines **189** in 96:4 dr (56 mg, 27%).

Lab book reference: **MTG-8-20**

***tert*-Butyl-4-(*tert*-butyl(dimethyl)silyl)oxy-2-(6-phenyl-2-pyridyl)piperidine-1-carboxylate *cis*-190**

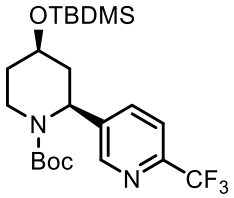


cis-**190**

Using General Procedure D, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (159 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 2-bromo-6-phenylpyridine (152 mg, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2.5 mL) for 16 h gave the crude product. Purification by flash column chromatography on silica using 24:1 hexane-EtOAc as eluent gave α-arylpiperidines **190** in 94:6 dr (141 mg, 60%) as a colourless oil, R_F (9:1 hexane-EtOAc) 0.40; IR (ATR) 2951, 2928, 2884, 2856, 1692 (C=O), 1170, 1087, 1069, 1046, 878, 832, 772, 761, 731, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04-7.98 (m, 2H, Ph), 7.63 (dd, *J* = 8.0, 8.0 Hz, 1H, Ar), 7.49 (d, *J* = 8.0 Hz, 1H, Ar), 7.46-7.40 (m, 2H, Ph), 7.39-7.33 (m, 1H, Ph), 7.03 (d, *J* = 8.0 Hz, 1H, Ar), 5.43-5.27 (m, 1H, ArCHN), 4.20-4.00 (m, 2H, OCH + NCH), 3.53 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 1H, NCH), 2.89 (dddd, *J* = 14.0, 4.0, 2.0, 2.0 Hz, 1H, CH), 2.08 (ddd, *J* =14.5, 7.5, 3.0 Hz, 1H, CH), 1.74 (dddd, *J* = 13.0, 13.0, 5.0, 2.5 Hz, 1H, CH), 1.64-1.54 (m, 1H, CH), 1.38 (s, 9H, $OCMe_3$), 0.48 (s, 9H, $SiCMe_3$), –0.15 (s, 3H SiMe), –0.31 (s, 3H SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.1 (*ipso*-Ar), 156.2 (C=O), 156.1 (*ipso*-Ar), 139.8 (*ipso*-Ph), 137.0 (Ar), 128.7 (Ph), 128.6 (Ph), 128.6 (Ph), 127.0 (Ph), 126.9 (Ph), 117.5 (Ar), 117.4 (Ar), 79.7 (O*C*Me_3), 64.6 (OCH), 54.0 (ArNCH), 35.8 (CH_2), 35.4 (NCH_2), 32.7 (CH_2), 28.5 (OC*Me*$_3$), 25.5 (SiC*Me*$_3$), 17.8 (Si*C*Me_3), –5.1 (SiMe), –5.3 (SiMe); HRMS (ESI) *m/z* calcd for $C_{27}H_{40}N_2O_3Si$ $(M + Na)^+$ 491.2700, found 491.2714 (–1.3 ppm error). Diagnostic signals for *trans*-**190**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.70-5.46 (m, 1H, ArCHN), 0.84 (s, 9H, $SiCMe_3$), 0.02 (SiMe), –0.03 (SiMe).

Lab book reference: **MTG-7-82**

***tert*-Butyl-4-(*tert*-butyl(dimethyl)silyl)oxy-2-(6-(trifluoromethyl)-3-pyridyl)piperidine-1-carboxylate *cis*-191**

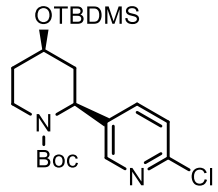


cis-**191**

Using General Procedure D, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (156 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 5-bromo-2-trifluoromethylpyridine (147 mg, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 17 h gave the crude product which contained α-arylpiperidines **191** in 97:3 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 9:1 hexane-EtOAc as eluent gave α-arylpiperidines **191** in 99:1 dr (150 mg, 66%) as a colourless crystalline solid, mp 92-94 °C; R_F (9:1 hexane-EtOAc) 0.30; IR (ATR) 2953, 2930, 2887, 2857, 1691 (C=O), 1339, 1168, 1136, 1087, 1044, 1027, 875, 829, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 2.0 Hz, 1H, Ar), 7.63 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar), 7.57 (d, *J* = 8.0 Hz, 1H, Ar), 5.45-5.36 (m, 1H, ArCHN), 4.16-4.09 (m, 1H, OCH), 4.03 (ddd, *J* = 13.5, 5.0, 2.5 Hz, 1H, NCH), 3.30 (ddd, *J* = 13.5, 13.0, 3.0 Hz, 1H, NCH), 2.30 (dddd, *J* = 14.5, 4.0, 2.0, 2.0 Hz, 1H, CH), 2.12 (ddd, *J* = 14.5, 7.0, 2.5 Hz, 1H, CH), 1.70 (dddd, *J* = 13.0, 13.0, 5.0, 2.5 Hz, 1H, CH), 1.61-1.51 (m, 1H, CH), 1.40 (s, 9H, $OCMe_3$), 0.51 (s, 9H, $SiCMe_3$), –0.14 (s, 3H SiMe), –0.20 (s, 3H SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.3 (C=O), 148.1 (Ar), 145.7 (q, *J* = 34.5 Hz, *ipso*-Ar), 142.1 (*ipso*-Ar), 134.2 (Ar), 120.4 (q, *J* = 274.0 Hz, CF_3), 119.9 (q, *J* = 3.0 Hz, Ar), 80.5 (O*C*Me$_3$), 64.4 (OCH), 50.0 (ArNCH), 36.4 (CH_2), 35.2 (NCH_2), 32.3 (CH_2), 28.4 (OC*Me*$_3$), 25.4 (SiC*Me*$_3$), 17.6 (Si*C*Me$_3$), –5.1 (SiMe), –5.2 (SiMe); HRMS (ESI) *m/z* calcd for $C_{22}H_{35}F_3N_2O_3Si$ $(M + Na)^+$ 483.2261, found 483.2277 (–3.2 ppm error). Diagnostic signals for *trans*-**191**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, *J* = 2.0 Hz, 1H, Ar), 8.09 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar), 7.84 (d, *J* = 8.0 Hz, 1H, Ar), –0.29 (SiMe), –0.35 (SiMe).

Lab book reference: **MTG-7-64**

***tert*-Butyl-4-(*tert*-butyl(dimethyl)silyl)oxy-2-(6-chloro-3-pyridyl)piperidine-1-carboxylate *cis*-192**

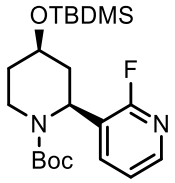


cis-**192**

Using General Procedure D, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (160 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 5-bromo-2-chloropyridine (125 mg, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2.5 mL) for 16 h gave the crude product which contained α-arylpiperidines **192** in 98:2 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 23:2 hexane-EtOAc as eluent gave α-arylpiperidines **192** in 98:2 dr (94 mg, 43%) as a colourless oil, R_F (9:1 hexane-EtOAc) 0.30; IR (ATR) 2953, 2929, 2884, 2857, 1691 (C=O), 1365, 1168, 1104, 1075, 1044, 875, 830, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 2.5 Hz, 1H, Ar), 7.46 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar), 7.19 (d, *J* = 8.5 Hz, 1H, Ar), 5.34-5.22 (m, 1H, ArCHN), 4.14-4.05 (m, 1H, OCH), 3.98 (ddd, *J* = 13.5, 5.0, 2.5 Hz, 1H, NCH), 3.26 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 1H, NCH), 2.20 (dddd, *J* = 14.5, 4.5, 2.5, 2.5 Hz, 1H, CH), 2.06 (ddd, *J* = 14.5, 7.0, 3.0 Hz, 1H, CH), 1.69 (dddd, *J* = 13.0, 13.0, 5.0, 2.5 Hz, 1H, CH), 1.59-1.49 (m, 1H, CH), 1.38 (s, 9H, $OCMe_3$), 0.58 (s, 9H, $SiCMe_3$), –0.12 (s, 3H SiMe), –0.17 (s, 3H SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.3 (C=O), 148.8 (*ipso*-Ar), 147.7 (Ar), 137.6 (*ipso*-Ar), 136.4 (Ar), 123.5 (Ar), 80.3 ($OCMe_3$), 64.5 (OCH), 49.8 (ArNCH), 36.3 (CH_2), 35.2 (NCH_2), 32.5 (CH_2), 28.4 ($OCMe_3$), 25.5 ($SiCMe_3$), 17.8 ($SiCMe_3$), –5.0 (SiMe), –5.2 (SiMe); HRMS (ESI) *m/z* calcd for $C_{21}H_{35}{}^{35}ClN_2O_3Si$ $(M + Na)^+$ 449.1998, found 449.2005 (–1.7 ppm error). Diagnostic signals for *trans*-**192**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50-5.41 (m, 1H, ArCHN), 0.83 (s, 9H, $SiCMe_3$), 0.05 (SiMe), –0.01 (SiMe).

Lab book reference: **MTG-7-83**

***tert*-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(2-fluoro-3-pyridyl)piperidine-1-carboxylate *cis*-193**

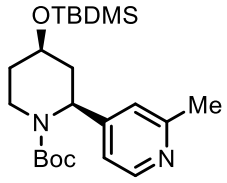


cis-**193**

Using General Procedure D, *s*-BuLi (0.50 mL of a 1.30 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 40 min and 3-bromo-2-fluoropyridine (0.076 mL, 0.75 mmol, 1.5 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 18 h gave the crude product which contained α-arylpiperidines **193** in 90:10 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 93:7 hexane-EtOAc as eluent gave a 98:2 mixture of α-arylpiperidines **193** in 98:2 dr (54 mg, 26%) as a colourless oil, R_F (4:1 hexane-Et_2O) 0.35; IR (ATR) 2952, 2930, 2890, 2857, 1698 (C=O), 1170, 1084, 1053, 1004, 878, 832, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (ddd, *J* = 5.0, 1.5, 1.5 Hz, 1H, Ar), 7.58-7.49 (m, 1H, Ar), 7.08 (ddd, *J* = 7.0, 5.0, 2.0 Hz, 1H, Ar), 5.35-5.28 (m, 1H, NCHAr), 4.12-4.00 (m, 2H, OCH and NCH), 3.45 (ddd, *J* = 13.0, 13.0, 3.5 Hz, 1H, NCH), 2.34-2.26 (m, 1H, CH), 2.00 (ddd, *J* = 14.0, 7.0, 2.5 Hz, 1H, CH), 1.73 (dddd, *J* = 13.0, 13.0, 5.0, 3.0, 1H, CH), 1.65-1.57 (m, 1H, CH), 1.32 (s, 9H, $OCMe_3$), 0.57 (s, 9H, $SiCMe_3$), -0.12 (s, 3H SiMe), -0.26 (s, 3H SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.5 (d, *J* = 237.5 Hz, *ipso*-Ar), 155.4 (C=O), 144.9 (d, *J* = 14.5 Hz, Ar), 137.3 (d, *J* = 5.5 Hz, Ar), 126.6 (d, *J* = 27.5 Hz, *ipso*-Ar), 121.4 (d, *J* = 4.0 Hz, Ar), 80.2 (O*C*Me_3), 64.4 (OCH), 47.9 (d, *J* = 4.5, NCHAr), 36.0 (NCH_2), 35.6 (d, *J* = 4.0, CH_2), 32.3 (CH_2), 28.3 (OC*Me*$_3$), 25.5 (SiC*Me*$_3$), 17.8 (Si*C*Me_3), –5.2 (SiMe), –5.3 (SiMe); HRMS (ESI) *m/z* calcd for $C_{21}H_{35}FN_2O_3Si$ $(M + Na)^+$ 433.2293, found 433.2293 (0.0 ppm error). Diagnostic signals for *trans*-**193**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26-5.21 (m, 1H, NCHAr), 0.88 (s, 9H, $SiCMe_3$).

Lab book reference: **MTG-3-55**

tert-Butyl-4-(_tert_-butyl(dimethyl)silyl)oxy-2-(2-methyl-4-pyridyl)piperidine-1-carboxylate _cis_-194

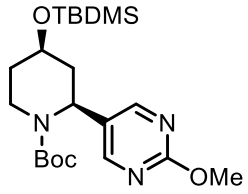


cis-**194**

Using General Procedure D, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 4-bromo-2-methylpyridine (0.077 mL, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2.5 mL) for 18 h gave the crude product which contained α-arylpiperidines **194** in 97:3 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 7:3 hexane-EtOAc as eluent gave α-arylpiperidines **194** in 97:3 dr (137 mg, 67%) as a colourless oil, R_F (4:1 hexane-EtOAc) 0.25; IR (ATR) 2954, 2929, 2885, 2857, 1696 (C=O), 1412, 1365, 1255, 1172, 1081, 1047, 835, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 5.0 Hz, 1H, Ar), 6.94 (s, 1H, Ar), 6.88 (d, *J* = 5.0 Hz, 1H, Ar), 5.25-5.14 (m, 1H, ArCHN), 4.13-4.07 (m, 1H, OCH), 4.07-3.97 (m, 1H, NCH), 3.36 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 1H, NCH), 2.50 (s, 3H, Me), 2.26 (dddd, *J* = 14.0, 4.5, 2.0, 2.0 Hz, 1H, CH), 2.07 (ddd, *J* = 14.0, 7.0, 2.5 Hz, 1H, CH), 1.70 (dddd, *J* = 13.0, 13.0, 5.0, 3.0 Hz, 1H, CH), 1.60-1.52 (m, 1H, CH), 1.40 (s, 9H, $OCMe_3$), 0.56 (s, 9H, $SiCMe_3$), –0.11 (s, 3H SiMe), –0.18 (s, 3H SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158 (*ipso*-Ar), 155.6 (C=O), 152.9 (*ipso*-Ar), 149.0 (Ar), 120.4 (Ar), 118.1 (Ar), 80.1 ($OCMe_3$), 64.5 (OCH), 51.3 (ArNCH), 36.3 (CH_2), 35.5 (NCH_2), 32.5 (CH_2), 28.4 ($OCMe_3$), 25.4 ($SiCMe_3$), 24.6 (Me), 17.7 ($SiCMe_3$), –5.1 (SiMe), –5.2 (SiMe); HRMS (ESI) *m/z* calcd for $C_{22}H_{38}N_2O_3Si$ $(M + Na)^+$ 429.2544, found 429.2540 (+0.9 ppm error). Diagnostic signals for *trans*-**194**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 5.5 Hz, 1H, Ar), 8.31 (d, *J* = 5.5 Hz, 1H, Ar), 5.48-5.43 (m, 1H, ArCHN), 0.04 (SiMe), 0.01 (SiMe).

Lab book reference: **MTG-7-75**

tert-Butyl-4-((_tert_-butyldimethylsilyl)oxy)-2-(2-methoxypyrimidin-5-yl)piperidine-1-carboxylate _cis_-195

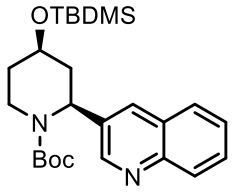


cis-**195**

Using General Procedure D, *s*-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 5-bromo-2-methoxypyrimidine (123 mg, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 18 h gave the crude product which contained α-arylpiperidines **195** in 95:5 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 17:3 hexane-EtOAc as eluent gave a 97:3 mixture of α-arylpiperidines **195** in 97:3 dr (110 mg, 52%) as a colourless oil, R_F (4:1 hexane-EtOAc) 0.25; IR (ATR) 2954, 2930, 2857, 1692 (C=O), 1472, 1408, 1391, 1322, 1167, 1080, 1049, 875, 834, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38-8.35 (m, 2H, Ar), 5.35-5.27 (m, 1H, ArCHN), 4.17-4.11 (m, 1H, OCH), 4.11-4.02 (m, 4H, NCH + OMe), 3.24 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 1H, NCH), 2.21 (dddd, *J* = 14.5, 4.0, 2.0, 2.0 Hz, 1H, CH), 2.06 (ddd, *J* = 14.5, 7.0, 3.0 Hz, 1H, CH), 1.77-1.65 (m, 1H, CH), 1.60-1.52 (m, 1H, CH), 1.42 (s, 9H, $OCMe_3$), 0.63 (s, 9H, $SiCMe_3$), –0.08 (s, 3H SiMe), –0.11 (s, 3H SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.4 (*ipso*-Ar), 157.2 (Ar), 155.3 (C=O), 128.9 (*ipso*-Ar), 80.4 (O*C*Me$_3$), 64.6 (OCH), 54.9 (OMe), 48.2 (ArCHN), 35.8 (CH_2), 35.0 (NCH_2), 32.6 (CH_2), 28.5 (O*C*Me$_3$), 25.6 (SiC*Me*$_3$), 17.9 (Si*C*Me$_3$), –4.4 (SiMe), –5.1 (SiMe); HRMS (ESI) *m/z* calcd for $C_{21}H_{37}N_3O_4Si$ $(M + Na)^+$ 446.2446, found 446.2454 (–1.9 ppm error). Diagnostic signals for *trans*-**195**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56-5.52 (m, 1H, ArCHN), 0.87 (s, 9H, $SiCMe_3$), 0.05 (s, 3H, SiMe), 0.03 (s, 3H, SiMe).

Lab book reference: **MTG-3-20**

***tert*-Butyl-4-(*tert*-butyl(dimethyl)silyl)oxy-2-(3-quinolyl)piperidine-1-carboxylate *cis*-196**

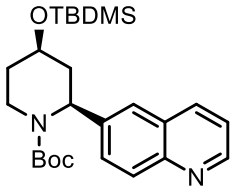


cis-**196**

Using General Procedure D, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 3-bromoquinoline (0.088 mL, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2.5 mL) for 18 h gave the crude product which contained α-arylpiperidines **196** in 98:2 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 9:1 hexane-EtOAc then 4:1 hexane-EtOAc as eluent gave α-arylpiperidines **196** in 98:2 dr (146 mg, 66%) as a colourless oil, R_F (4:1 hexane-EtOAc) 0.40; IR (ATR) 2953, 2928, 2884, 2856, 1690 (C=O), 1365, 1252, 1164, 1076, 1046, 870, 835, 774, 752, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 2.5 Hz, 1H, Ar), 8.04 (d, *J* = 8.5 Hz, 1H, Ar), 7.91-7.87 (m, 1H, Ar) 7.72 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar), 7.61 (ddd, *J* = 8.5, 6.5, 1.5 Hz, 1H, Ar), 7.50-7.43 (m, 1H, Ar), 5.52-5.44 (m, 1H, ArCHN), 4.18-4.11 (m, 1H, OCH), 4.07 (ddd, *J* = 13.0, 5.0, 2.5 Hz, 1H, NCH), 3.42 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 1H, NCH), 2.40 (dddd, *J* = 14.5, 4.5, 2.5, 2.5 Hz, 1H, CH), 2.15 (ddd, *J* = 14.5, 7.0, 3.0 Hz, 1H, CH), 1.75 (dddd, *J* = 13.0, 13.0, 5.0, 3.0 Hz, 1H, CH), 1.61-1.54 (m, 1H, CH), 1.37 (s, 9H, $OCMe_3$), 0.38 (s, 9H, $SiCMe_3$), –0.18 (s, 3H SiMe), –0.27 (s, 3H SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.5 (C=O), 149.5 (Ar), 146.5 (*ipso*-Ar), 135.9 (*ipso*-Ar), 131.9 (Ar), 128.8 (Ar), 128.8 (Ar), 128.0 (*ipso*-Ar), 127.6 (Ar), 126.6 (Ar), 80.2 ($OCMe_3$), 64.7 (OCH), 50.7 (ArCHN), 36.4 (CH_2), 35.4 (NCH_2), 32.6 (CH_2), 28.4 ($OCMe_3$), 25.3 ($SiCMe_3$), 17.6 ($SiCMe_3$), –4.5 (SiMe), –5.2 (SiMe); HRMS (ESI) *m/z* calcd for $C_{25}H_{38}N_2O_3Si$ $(M + Na)^+$ 465.2544, found 465.2567 (–5.0 ppm error). Diagnostic signals for *trans*-**196**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76-5.69 (m, 1H, ArC*H*N), 0.84 (s, 9H, $SiCMe_3$), 0.03 (s, 3H, SiMe), -0.01 (s, 3H, SiMe).

Lab book reference: **MTG-7-87**

***tert*-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(quinolin-6-yl)piperidine-1-carboxylate *cis*-197**

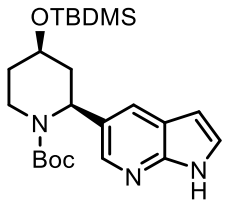


cis-**197**

Using General Procedure D, *s*-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (157 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 6-bromoquinoline (0.088 mL, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 18 h gave the crude product which contained α-arylpiperidines **197** in 96:4 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 4:1 hexane-EtOAc as eluent gave α-arylpiperidines **197** in 96:4 dr (149 mg, 67%) as a colourless oil, R_F (3:2 hexane-EtOAc) 0.50; IR (ATR) 2952, 2928, 2884, 2856, 1690 (C=O), 1169, 1075, 1046, 830, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 4.0 Hz, 1H, Ar), 8.04 (d, *J* = 8.5 Hz, 1H, Ar), 8.00 (d, *J* = 9.0 Hz, 1H, Ar) 7.57 (d, *J* = 9.0 Hz, 1H, Ar), 7.54 (s, 1H, Ar), 7.31 (dd, *J* = 8.5, 4.0 Hz, 1H, Ar), 5.39 (dd, *J* = 7.0, 3.0 Hz, 1H, ArCHN), 4.14-4.01 (m, 2H, OCH + NCH), 3.48 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 1H, NCH), 2.40-2.31 (m, 1H, CH), 2.12 (ddd, *J* = 14.0, 7.0, 3.0 Hz, 1H, CH), 1.82-1.69 (m, 1H, CH), 1.61-1.51 (m, 1H, CH), 1.35 (s, 9H, $OCMe_3$), 0.40-0.37 (m, 9H, $SiCMe_3$), –0.18 (s, 3H SiMe), –0.28 (s, 3H SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.8 (C=O), 149.7 (Ar), 147.2 (*ipso*-Ar), 141.8 (*ipso*-Ar), 135.9 (Ar), 129.2 (Ar), 128.4 (Ar), 128.2 (*ipso*-Ar), 123.3 (Ar), 121.1 (Ar), 79.9 ($OCMe_3$), 64.8 (OCH), 51.8 (ArCHN), 36.8 (CH_2), 35.7 (NCH_2), 32.8 (CH_2), 28.4 ($OCMe_3$), 25.3 ($SiCMe_3$), 17.7 ($SiCMe_3$), –5.1 (SiMe), –5.2 (SiMe); HRMS (ESI) *m/z* calcd for $C_{25}H_{38}N_2O_3Si$ $(M + Na)^+$ 465.2544, found 465.2555 (–2.3 ppm error). Diagnostic signals for *trans*-**197**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69-5.65 (m, 1H, ArC*H*N), 2.76 (ddd, *J* = 14.0, 13.5, 3.0 Hz, 1H, NCH), 0.02 (s, 3H, SiMe), –0.01 (s, 3H, SiMe).

Lab book reference: **MTG-3-21**

***tert*-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(1H-pyrrolo[2,3-b]pyridin-5-yl)piperidine-1-carboxylate *cis*-198**

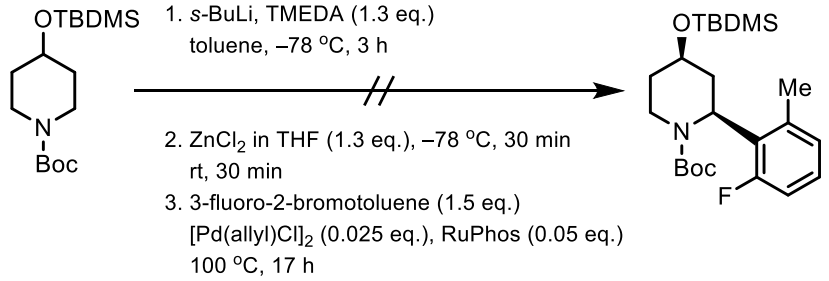


cis-**198**

Using General Procedure D, *s*-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (159 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 5-bromo-1H-pyrrolo[2,3-b]pyridine (128 mg, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 18 h gave the crude product. Purification by flash column chromatography on silica using 4:1 hexane-EtOAc then 3:2 hexane-EtOAc as eluent gave α-arylpiperidines **198** in 96:4 dr (29 mg, 13%) as a colourless oil, R_F (3:2 hexane-EtOAc) 0.25; IR (ATR) 3139, 2954, 2928, 2888, 2857, 1688 (C=O), 1252, 1168, 1076, 1045, 872, 833, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.35 (br s, 1H, NH), 8.25 (d, *J* = 2.0 Hz, 1H, Ar), 7.98 (d, *J* = 2.0 Hz, 1H, Ar), 7.37 (d, *J* = 3.5 Hz, 1H, Ar), 6.46 (d, *J* = 3.5 Hz, 1H, Ar), 5.44 (dd, *J* = 7.0, 3.0 Hz, 1H, ArCHN), 4.25-4.11 (m, 1H, OCH), 4.04 (ddd, *J* = 13.5, 5.0, 2.5 Hz, 1H, NCH), 3.41 (ddd, *J* = 13.5, 13.0, 3.0 Hz, 1H, NCH), 2.42-2.26 (m, 1H, CH), 2.15 (ddd, *J* = 14.0, 7.0, 3.0 Hz, 1H, CH), 1.81 (dddd, *J* = 13.0, 13.0, 5.0, 3.0 1H, CH), 1.66-1.53 (m, 1H, CH), 1.40 (s, 9H, $OCMe_3$), 0.55 (s, 9H, $SiCMe_3$), –0.09 (s, 3H SiMe), –0.15 (s, 3H SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.6 (C=O), 146.0 (*ipso*-Ar), 139.4 (Ar), 130.7 (*ipso*-Ar), 128.1 (Ar), 126.3 (Ar), 121.2 (*ipso*-Ar), 100.8 (*ipso*-Ar), 80.1 ($OCMe_3$), 64.9 (OCH), 51.1 (ArCHN), 36.8 (CH_2), 35.5 (NCH_2), 33.0 (CH_2), 28.5 ($OCMe_3$), 25.5 ($SiCMe_3$), 17.8 ($SiCMe_3$), –4.9 (SiMe), –5.1 (SiMe); HRMS (ESI) *m/z* calcd for $C_{23}H_{37}N_3O_3Si$ $(M + Na)^+$ 454.2496, found 454.2494 (+0.6 ppm error). Diagnostic signals for *trans*-**198**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.74-5.69 (m, 1H, ArCHN), 2.78 (ddd, *J* = 13.5, 13.5, 3.0 Hz, 1H, NCH), 0.87 (s, 9H, $SiCMe_3$).

Lab book reference: **MTG-3-22**

Attempted synthesis of *tert*-butyl-4-[*tert*-butyl(dimethyl)silyl]oxy-2-(2-fluoro-6-methyl-phenyl)piperidine-1-carboxylate *cis*-199

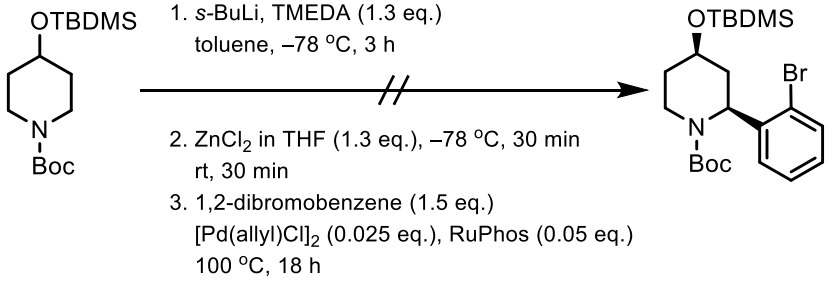


73 *cis*-**199**

Using General Procedure D, *s*-BuLi (0.59 mL of a 1.1 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (156 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 3-fluoro-2-bromotoluene (142 mg, 0.75 mmol, 1.5 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 17 h gave the crude product. Purification by flash column chromatography on silica using 23:2 hexane-EtOAc as eluent gave minimal α-arylpiperidine **199** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-8-18**

Attempted synthesis of *tert*-butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(2-bromophenyl)piperidine-1-carboxylate *cis*-200



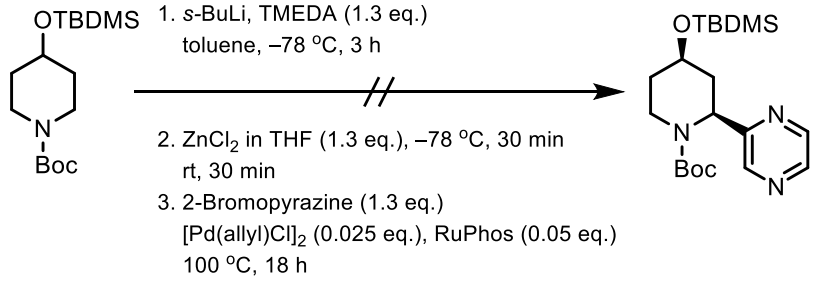
73 *cis*-**200**

Using General Procedure D, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 1,2-dibromobenzene (0.090 mL, 0.75 mmol, 1.5 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol)

in toluene (2 mL) for 18 h gave the crude product which contained trace amounts of α-arylpiperidine *cis*-**200** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-3-48**

Attempted synthesis of *tert*-butyl-4-(*tert*-butyl(dimethyl)silyl)oxy-2-pyrazin-2-yl-piperidine-1-carboxylate *cis*-201

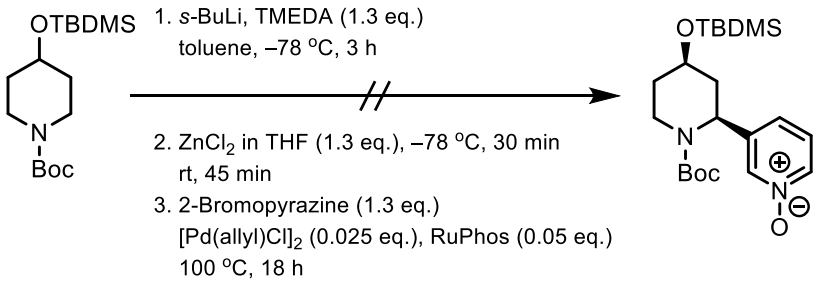


73 *cis*-**201**

Using General Procedure D, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 2-bromopyrazine (0.059 mL, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 18 h gave the crude product which contained none of α-arylpiperidine *cis*-**201** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-7-85**

Attempted synthesis of *tert*-Butyl-4-(*tert*-butyl(dimethyl)silyl)oxy-2-(pyridin-3-yl *N*-oxide)piperidine-1-carboxylate *cis*-202

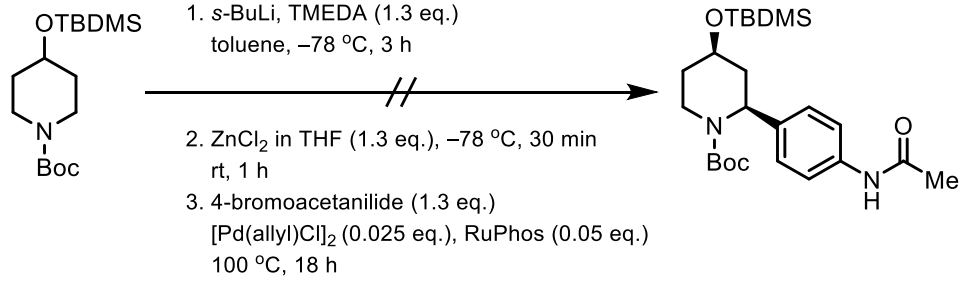


73 *cis*-**202**

Using General Procedure D, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (157 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 3-bromopyridine *N*-oxide (113 mg, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 18 h gave the crude product which contained none of α-arylpiperidine *cis*-**202** (by ^{1}H NMR spectroscopy).

Lab book reference: **MTG-7-86**

Attempted synthesis of *tert*-butyl-2-(4-acetamidophenyl)-4-((*tert*-butyldimethylsilyl)oxy)piperidine-1-carboxylate *cis*-203

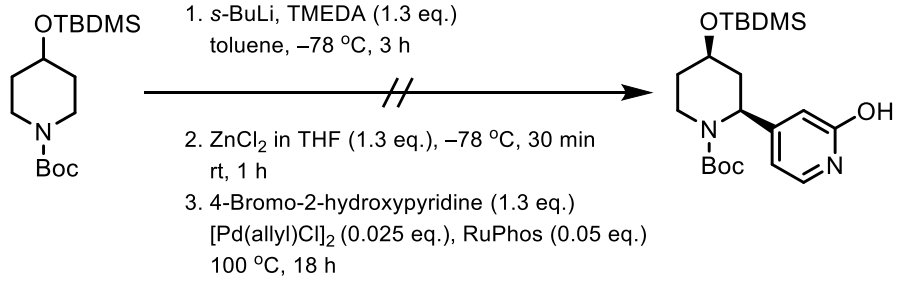


73 *cis*-**203**

Using General Procedure D, *s*-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (159 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 1 h and 4-bromoacetanilide (139 mg, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 18 h gave the crude product which contained none of α-arylpiperidine *cis*-**203** (by ^{1}H NMR spectroscopy).

Lab book reference: **MTG-3-24**

Attempted synthesis of *tert*-butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(2-hydroxypyridin-4-yl)piperidine-1-carboxylate *cis*-204

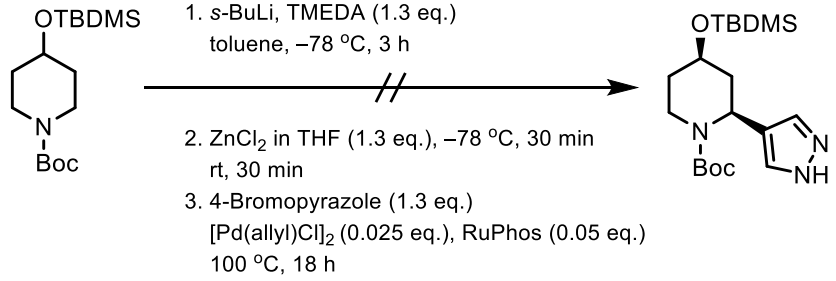


73 *cis*-**204**

Using General Procedure D, *s*-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (159 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 1 h and 4-bromo-2-hydroxypyridine (113 mg, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 18 h gave the crude product which contained none of α-arylpiperidine *cis*-**204** (by ^{1}H NMR spectroscopy).

Lab book reference: **MTG-3-25**

Attempted synthesis of *tert*-butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(1H-pyrazol-4-yl)piperidine-1-carboxylate *cis*-205



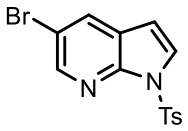
73 *cis*-**205**

Using General Procedure D, *s*-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (156 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 4-bromopyrazole (96 mg, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in

toluene (2 mL) for 18 h gave the crude product which contained none of α-arylpiperidine *cis*-**205** (by ^{1}H NMR spectroscopy).

Lab book reference: **MTG-3-23**

5-Bromo-1-tosyl-1*H*-pyrrolo[2,3-b]pyridine 207

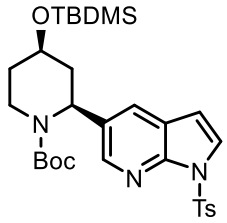


207

NaH (60% dispersion in mineral oil, 240 mg, 6.0 mmol, 3.0 eq.) was added to a stirred solution of 5-bromo-7-azaindole **202** (394 mg, 2.0 mmol, 1.0 eq.) and benzyltriethylammonium chloride (9 mg, 0.04 mmol, 0.02 eq.) in THF (20 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 30 min. Tosyl chloride (458 mg, 2.4 mmol, 1.2 eq) was added and the resulting solution was stirred at rt for 18 h. H_2O (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 (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 9:1 hexane-EtOAc as eluent gave 5-bromo-*N*-tosyl-7-azaindole **207** (400 mg, 57%) as a white solid, mp 139.3-140.5 °C (lit.,[137] 140-141 °C); R_F (9:1 hexane-Et_2O) 0.30; IR (ATR) 1373, 1191, 1170, 1152, 705, 668, 580, 537 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 2.5 Hz, 1H, Ar), 8.03 (d, *J* = 8.5 Hz, 2H, Ar), 7.94 (d, *J* = 2.5 Hz, 1H, Ar), 7.72 (d, *J* = 4.0 Hz, 1H, Ar), 7.26 (d, *J* = 8.5 Hz, 2H, Ar), 6.51 (d, *J* = 4.0 Hz, 1H, Ar), 2.36 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.6 (*ipso*-Ar), 145.6 (Ar), 145.5 (*ipso*-Ar), 135.1 (*ipso*-Ar), 131.8 (Ar), 129.8 (Ar), 128.2 (Ar), 128.0 (Ar), 124.5 (*ipso*-Ar), 115.3 (*ipso*-Ar), 104.6 (Ar), 21.8 (CH_3); HRMS (ESI) *m/z* calcd for $C_{14}H_{11}{}^{79}BrN_2O_2S$ $(M + Na)^+$ 372.9617, found 372.9616 (+0.1 ppm error). ^{1}H NMR spectroscopic data consistent with those reported in the literature.[137]

Lab book reference: **MTG-3-31**

***tert*-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(1-(*p*-tolylsulfonyl)pyrrolo[2,3-b]pyridin-5-yl)piperidine-1-carboxylate *cis*-208**



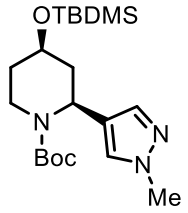
cis-**208**

s-BuLi (1.0 mL of a 1.30 M solution in hexane, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTBDMS-*N*-Boc-piperidine **73** (316 mg, 1.0 mmol, 1.0 eq.) and TMEDA (0.195 mL, 1.3 mmol, 1.3 eq.) in toluene (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. A solution of $ZnCl_2$ (1.86 mL of a 0.7 M solution in THF, 1.3 mmol, 1.3 eq.) was added and the resulting solution was stirred at –78 °C for 30 min and then at rt for 30 min. In a separate flask, a solution of *N*-Ts-5-bromo-7-azaindole (526 mg, 1.3 mmol, 1.3 eq.), RuPhos (23.4 mg, 0.05 mmol, 0.05 eq.) and $[Pd(allyl)Cl]_2$ (9.2 mg, 0.025 mmol, 0.025 eq.) in toluene (5 mL) was stirred at rt under Ar for 10 min. The catalyst solution was added to the solution of zinc species and the resulting solution was stirred and heated at 100 °C for 17 h. After being allowed to cool to rt, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 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 which contained α-arylpiperidine *cis*-**208** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 9:1 hexane-EtOAc then 4:1 hexane-EtOAc as eluent gave α-arylpiperidines **208** in 99:1 dr (271 mg, 46%) as a white solid, mp 127-129 °C, R_F (4:1 hexane-EtOAc) 0.30; IR (ATR) 2935, 2858, 1691 (C=O), 1377, 1169, 1077, 674, 585 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 2.0 Hz, 1H, Ar), 8.02 (d, *J* = 8.5 Hz, 2H, Ar), 7.68-7.66 (m, 1H, Ar), 7.66 (d, *J* = 4.0 Hz, 1H, Ar), 7.23 (d, *J* = 8.5 Hz, 2H, Ar), 6.50 (d, *J* = 4.0 Hz, 1H, Ar), 5.39 (dd, *J* = 7.0, 2.5 Hz, 1H, ArCHN), 4.11-4.06 (m, 1H, OCH), 4.01 (ddd, *J* = 13.0, 5.0, 2.5 Hz, 1H, NCH), 3.34 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 1H, NCH), 2.34 (s, 3H, Me), 2.25 (dddd, *J* = 14.0, 4.5, 2.5, 2.5 1H, CH), 2.09 (ddd, *J* = 14.0, 7.0, 3.0 Hz, 1H, CH), 1.72 (dddd, *J* = 13.0, 13.0, 5.0, 3.0 1H, CH), 1.57-1.49 (m, 1H, CH), 1.36 (s, 9H, $OCMe_3$), 0.30 (s, 9H, $SiCMe_3$), –0.19 (s, 3H SiMe), –0.33 (s, 3H SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.5 (C=O), 145.9 (*ipso*-Ar), 144.9 (*ipso*-Ar), 143.7 (Ar), 135.6

(*ipso*-Ar), 134.0 (*ipso*-Ar), 129.7 (Ar), 128.1 (Ar), 126.7 (Ar), 126.5 (Ar), 122.6 (*ipso*-Ar), 105.3 (*ipso*-Ar), 80.1 (O*C*Me$_3$), 64.6 (OCH), 50.5 (ArCHN), 36.8 (CH_2), 35.3 (NCH_2), 32.7 (CH_2), 28.4 (O*C*Me$_3$), 25.1 (SiC*Me*$_3$), 21.7 (Me), 17.5 (Si*C*Me$_3$), –5.1 (SiMe), –5.3 (SiMe); HRMS (ESI) *m/z* calcd for $C_{30}H_{43}N_3O_5Si$ $(M + Na)^+$ 608.2585, found 608.2593 (–1.3 ppm error).

Lab book reference: **MTG-7-84**

tert-Butyl-4-((_tert_-butyldimethylsilyl)oxy)-2-(1-methyl-1_H_-pyrazol-4-yl)piperidine-1-carboxylate _cis_-209



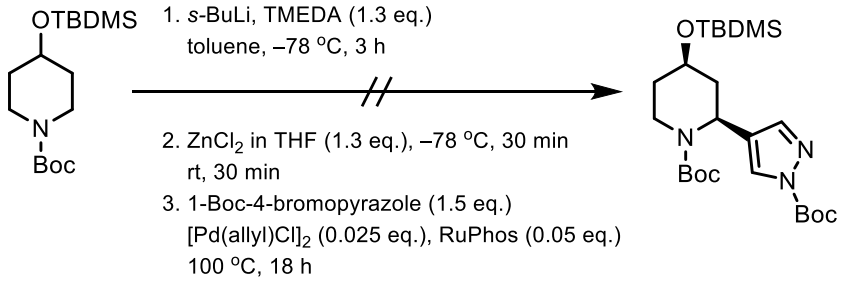
cis-**209**

Using General Procedure D, *s*-BuLi (0.48 mL of a 1.35 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (157 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 4-bromo-1-methyl-1*H*-pyrazole (0.067 mL, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 18 h gave the crude product. Purification by flash column chromatography on silica using 3:1 hexane-EtOAc as eluent gave crude product. Purification by flash column chromatography on silica using 4:1 hexane-EtOAc as eluent gave α-arylpiperidines **209** in 96:4 dr (19 mg, 9%) as a colourless oil, R_F (3:2 hexane-EtOAc) 0.45; IR (ATR) 2938, 2862, 1692 (C=O), 1413, 1364, 1170, 1082, 1049, 875, 836, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H, Ar), 7.32 (s, 1H, Ar), 5.28 (dd, *J* = 6.5, 3.0 Hz, 1H, ArCHN), 4.13 (dddd, *J* = 3.5, 3.5, 3.5, 3.5 Hz, 1H, OCH), 3.87-3.83 (m, 1H, NCH), 3.81 (s, 3H, NMe), 3.19 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 1H, NCH), 2.06-1.95 (m, 2H, CH + CH), 1.74-1.64 (m, 1H, CH), 1.61-1.54 (m, 1H, CH), 1.45 (s, 9H, OCMe$_3$), 0.78 (s, 9H, SiCMe$_3$), 0.02-–0.01 (m, 6H 2SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.1 (C=O), 138.4 (Ar), 128.8 (Ar), 123.6 (*ipso*-Ar), 79.7 (O*C*Me$_3$), 64.7 (OCH), 45.2 (ArCHN), 38.8 (NMe), 36.1 (CH_2), 34.2 (NCH_2), 33.2

(CH_2), 28.4 (O*C*Me$_3$), 25.8 (SiC*Me*$_3$), 18.1 (Si*C*Me$_3$), –4.8 (SiMe), –5.0 (SiMe); HRMS (ESI) *m/z* calcd for $C_{20}H_{37}N_3O_3Si$ $(M + Na)^+$ 418.2496, found 418.2496 (–0.1 ppm error). Diagnostic signals for *trans*-**209**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48-5.42 (m, 1H, ArC*H*N), 4.71-4.68 (m, 1H, OCH), 2.81-2.71 (m, 1H, NCH).

Lab book reference: **MTG-3-34**

Attempted synthesis of *tert*-butyl-2-(1-*tert*-butoxycarbonylpyrazol-4-yl)-4-[*tert*-butyl(dimethyl)silyl]oxy-piperidine-1-carboxylate *cis*-210

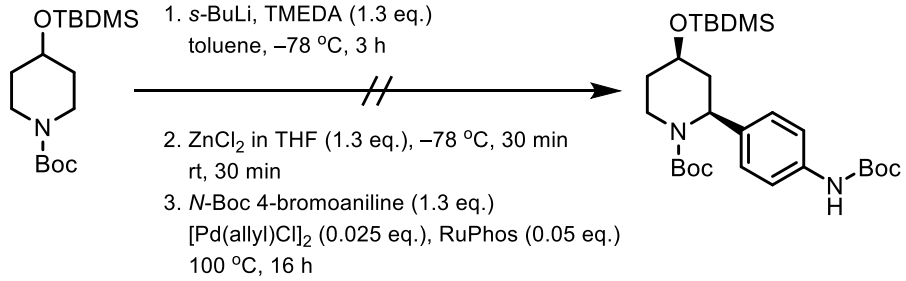


73 *cis*-**210**

Using General Procedure D, *s*-BuLi (0.59 mL of a 1.1 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (157 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 1-Boc-4-bromopyrazole (185 mg, 0.75 mmol, 1.5 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 18 h gave the crude product which contained none of α-arylpyrrolidine *cis*-**210** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-8-21**

Attempted synthesis of *tert*-butyl-2-[4-(*tert*-butoxycarbonylamino)phenyl]-4-[*tert*-butyl(dimethyl)silyl]oxy-piperidine-1-carboxylate *cis*-211

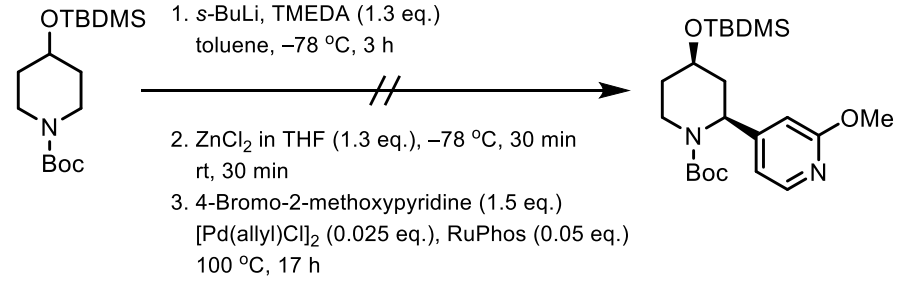


73 *cis*-**211**

Using General Procedure D, *s*-BuLi (0.59 mL of a 1.1 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (159 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and *N*-Boc 4-bormoaniline (177 mg, 0.65 mmol, 1.3 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 16 h gave the crude product. Purification by flash column chromatography on silica using 17:3 hexane-EtOAc as eluent gave the crude product which contained trace amounts of α-arylpiperidine **211** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-8-15**

Attempted synthesis of *tert*-butyl-4-[*tert*-butyl(dimethyl)silyl]oxy-2-(2-methoxy-4-pyridyl)piperidine-1-carboxylate *cis*-212



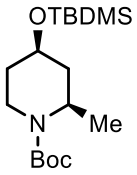
73 *cis*-**212**

Using General Procedure D, *s*-BuLi (0.59 mL of a 1.1 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (156 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL), $ZnCl_2$ (0.93 mL of a 0.7 M solution in THF, 0.65 mmol) at –78 °C for 30 min and rt for 30 min and 4-bromo-2-methoxypyridine (142

mg, 0.75 mmol, 1.5 eq.), RuPhos (11.7 mg, 0.025 mmol) and $[Pd(allyl)Cl]_2$ (4.6 mg, 0.013 mmol) in toluene (2 mL) for 18 h gave the crude product which contained trace amounts of α-arylpiperidine **212** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-8-19**

***tert*-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-methylpiperidine-1-carboxylate *cis*-74**



cis-**74**

s-BuLi (0.5 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTBDMS-*N*-Boc-piperidine **73** (159 mg, 0.50 mmol, 1.0 eq.) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. Methyliodide (0.040 mL, 0.65 mmol, 1.3 eq.) was added and the resulting solution was stirred at –78 °C for 1 h and then at rt for 19 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained 2,4-disubstituted piperidines **74** in 93:7 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 9:1 hexane-Et_2O as eluent gave a 93:7 mixture of 2,4-disubstituted piperidines **74** in 93:7 dr and 4-OTBDMS-*N*-Boc-piperidine **73** (80 mg, i.e. 75 mg (45%) of 2,4-disubstituted piperidines **74** and 5 mg (3%) of 4-OTBDMS-*N*-Boc-piperidine **73**) as a colourless oil, R_F (19:1 hexane-Et_2O) 0.25; IR (ATR) 2955, 2930, 2886, 2858, 1692 (C=O), 1173, 1072, 1054, 834, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (dddd, *J* = 7.0, 7.0, 6.5, 6.5 Hz, 1H, OCH), 4.09-4.02 (m, 1H, MeCHN), 3.82-3.73 (m, 1H, NCH), 3.22 (ddd, *J* = 12.5, 12.5, 4.5 Hz, 1H, NCH), 1.73 (ddd, *J* = 14.0, 6.5, 3.0 Hz, 1H, CH), 1.60-1.49 (m, 3H, CH), 1.44-1.43 (m, 9H, C*Me*$_3$), 1.31-1.25 (d, *J* = 7.0 Hz, 3H, *Me*CHN), 0.89-0.85 (m, 9H, SiC*Me*$_3$), 0.04-0.01 (m, 6H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.1 (C=O), 79.1 (O*C*Me$_3$), 65.2 (MeN*C*H), 45.7 (OCH), 36.8 (CH_2), 33.3 (NCH_2), 33.1 (CH_2), 28.6 (OC*Me*$_3$), 25.8 (SiC*Me*$_3$), 19.2 (*Me*CHN),

18.0 (Si*C*Me_3), –4.9 (SiMe), –5.0 (SiMe); HRMS (ESI) *m/z* calcd for $C_{17}H_{35}NO_3Si$ (M + Na)$^+$ 352.2278, found 352.2275 (+0.9 ppm error). Diagnostic signals for *trans*-**74**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48-4.38 (m, 1H, OCH), 2.88-2.78 (m, 1H, NCH), 1.13-1.08 (d, *J* = 7.0 Hz, 3H, *Me*CHN). Spectroscopic data consistent with those reported in the literature.[31]

Lab book reference: **MTG-2-43**

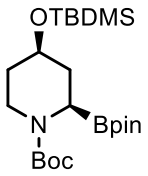
s-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTBDMS-*N*-Boc-piperidine **73** (156 mg, 0.50 mmol, 1.0 eq.) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in Et_2O (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Dimethylsulfate (0.095 mL, 1.00 mmol, 2.0 eq.) was added and the resulting solution was stirred at –78 °C for 30 min and then at rt for 18 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained 2,4-disubstituted piperidines **74** in 81:19 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 9:1 hexane-Et_2O as eluent gave a 94:6 mixture of 2,4-disubstituted piperidines **74** in 83:17 dr and 4-OTBDMS-*N*-Boc-piperidine **73** (113 mg, i.e. 107 mg (66%) of 2,4-disubstituted piperidines **74** and 6 mg (3%) of 4-OTBDMS-*N*-Boc-piperidine **73**) as a colourless oil.

Lab book reference: **MTG-2-69**

Using General Procedure B, *s*-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (157 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL) and dimethylsulfate (0.095 mL, 1.00 mmol) at –78 °C for 30 min and rt for 18 h. Purification by flash column chromatography on silica using 9:1 hexane-Et_2O as eluent gave an 89:11 mixture of 2,4-disubstituted piperidines **74** in a 92:8 dr and 4-OTBDMS-*N*-Boc-piperidine **73** (132 mg, i.e. 118 mg (72%) of 2,4-disubstituted piperidines **74** and 14 mg of 4-OTBDMS-*N*-Boc-piperidine **73**) as a colourless oil.

Lab book reference: **MTG-2-68**

***tert*-Butyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((*tert*-butyldimethylsilyl)oxy) piperidine-1-carboxylate *cis*-213**

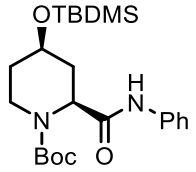


cis-**213**

s-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTBDMS-*N*-Boc-piperidine **73** (316 mg, 1.0 mmol, 1.0 eq.) and TMEDA (0.194 mL, 1.3 mmol, 1.3 eq.) in toluene (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. *i*-PrOB(pin) (0.266 mL, 1.3 mmol, 1.3 eq.) was added and the resulting solution was stirred at –78 °C for 2.5 h and then at rt for 22 h. 1 M $HCl_{(aq)}$ (15 mL) and Et_2O (5 mL) were added and the two layers were separated. The organic layer was washed with brine (3 × 5 mL) and the combined aqueous layers were extracted with Et_2O (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained 2,4-disubstituted piperidines **213** in 94:6 dr (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 7:3 hexane-Et_2O as eluent gave 2,4-disubstituted piperidines **213** in 76:24 dr (44 mg, 10%) as a colourless oil and 2,4-disubstituted piperidine *cis*-**213** (253 mg, 57%) as a colourless oil, R_F (4:1 hexane-Et_2O) 0.25; IR (ATR) 2930, 2857, 1609 (C=O), 1371, 1252, 1145, 1108, 872, 836, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80-3.73 (m, 1H, NCH), 3.66 (dddd, *J* = 11.0, 11.0, 4.0, 4.0 Hz, 1H, OCH), 2.79 (ddd, *J* = 13.5, 13.5, 3.0 Hz, 1H, NCH), 2.39 (dd, *J* = 13.0, 3.0 Hz, 1H, BCHN), 1.78-1.70 (m, 2H, CH), 1.49 (s, 9H, CMe_3), 1.48-1.31 (m, 2H, CH), 1.18 (s, 12H, CMe), 0.85 (s, 9H, $SiCMe_3$), 0.04 (s, 3H, SiMe), 0.04 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.8 (C=O), 86.0 (O*C*Me_2), 80.2 (O*C*Me_3), 70.4 (OCH), 46.1 (BNCH)*, 41.2 (NCH_2), 36.4 (CH_2), 34.6 (CH_2), 28.5 (OC*Me*$_3$), 25.9 (SiC*Me*$_3$), 25.2 (C*Me*), 24.9 (C*Me*), 18.1 (Si*C*Me_3), –4.3 (SiMe), –4.5 (SiMe); HRMS (ESI) *m/z* calcd for $C_{22}H_{44}BNO_5Si$ $(M + Na)^+$ 464.2974, found 464.2972 (+1.4 ppm error). Diagnostic signals for *trans*-**213**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10-4.05 (m, 1H, CHO), 3.49 (ddd, *J* = 12.5, 5.0, 2.5 Hz, 1H, NCH), 3.19 (ddd, *J* = 12.5, 11.0, 5.0 Hz, 1H, NCH), 0.86 (s, 9H, $SiCMe_3$). *Peak obtained from HMQC, no detectable signal in ^{13}C NMR spectrum.[138] Overall, this reaction gave 2,4-disubstituted piperidines **213** in 96:4 dr (297 mg, 67%).

Lab book reference: **MTG-2-38**

***tert*-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(phenylcarbamoyl)piperidine-1-carboxylate *cis*-75**

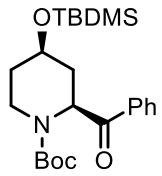


cis-**75**

Using General Procedure B, *s*-BuLi (0.50 mL of a 1.30 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (159 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL) and phenylisocyanate (0.109 mL, 1.00 mmol) at –78 °C for 30 min and rt for 18 h. Purification by flash column chromatography on silica using 9:1 hexane-EtOAc as eluent gave 2,4-disubstituted piperidines **75** in 93:7 dr (90 mg, 41%) as a colourless oil, R_F (9:1 hexane-EtOAc) 0.25; IR (ATR) 3324, 2953, 2929, 2889, 2857, 1695 (C=O), 1667 (C=O), 1441, 1250, 1169, 1087, 1079, 1054, 877, 833, 774, 752, 731, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (br s, 1H, NH), 7.50 (d, *J* = 8.0 Hz, 2H, Ph), 7.27 (dd, *J* = 8.0, 7.5 Hz, 2H, Ph), 7.06 (t, *J* = 7.5 Hz, 1H, Ph), 4.82-4.63 (m, 1H, OCCHN), 4.12-4.06 (m, 1H, OCH), 4.07-3.96 (m, 1H, NCH), 3.41 (ddd, *J* = 13.0, 12.0, 4.5, Hz, 1H, NCH), 2.56 (dddd, *J* = 14.0, 4.0, 2.0, 2.0 Hz, 1H, CH), 1.79 (ddd, *J* = 14.0, 7.5, 2.5 Hz, 1H, CH), 1.66-1.55 (m, 2H, CH + CH), 1.45 (s, 9H, $OCMe_3$), 0.72 (s, 9H, $SiCMe_3$), –0.03 (s, 3H, SiMe), –0.04 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.4 (PhHNC=O), 155.5 (C=O), 138.0 (*ipso*-Ph), 128.9 (Ph), 124.1 (Ph), 119.7 (Ph), 81.1 ($OCMe_3$), 63.9 (OCH), 53.5 (OCCHN), 36.2 (NCH_2), 32.9 (CH_2), 32.4 (CH_2), 28.4 ($OCMe_3$), 25.8 ($SiCMe_3$), 18.1 ($SiCMe_3$), –5.0 (SiMe), –5.1 (SiMe); HRMS (ESI) *m/z* calcd for $C_{23}H_{38}N_2O_4Si$ $(M + Na)^+$ 457.2493, found 457.2500 (–1.4 ppm error). Diagnostic signals for *trans*-**75**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.16-7.10 (m, 1H, Ph), 2.30-2.19 (m, 2H, CH + CH), 0.05 (s, 3H, SiMe). Spectroscopic data consistent with those reported in the literature.[31]

Lab book reference: **MTG-4-2**

***tert*-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-benzoylpiperidine-1-carboxylate *cis*-214**

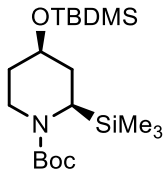


cis-**214**

Using General Procedure B, *s*-BuLi (0.56 mL of a 1.17 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL) and *N*-methoxy-*N*-methylbenzamide (0.152 mL, 1.0 mmol) at –78 °C for 30 min and rt for 30 min. Purification by flash column chromatography on silica using 93:7 hexane-EtOAc as eluent gave 2,4-disubstituted piperidines **214** in 98:2 dr (124 mg, 59%) as a colourless oil, R_F (4:1 hexane-Et_2O) 0.30; IR (ATR) 2953, 2929, 2892, 2857, 1702 (C=O), 1687 (C=O), 1170, 1087, 1052, 878, 832, 773, 693 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 8.26-8.18 (m, 2H, Ar), 7.97-7.90 (m, 1H, Ar), 7.89-7.81 (m, 2H, Ar), 5.69 (dd, *J* = 6.0, 4.5 Hz, 1H, OCCHN), 4.44-4.38 (m, 1H, OCH), 4.11-4.02 (m, 1H, NCH), 3.96-3.86 (m, 1H, NCH), 2.53-2.48 (m, 2H, 2 x CH), 2.09-1.98 (m, 1H, CH), 1.95-1.84 (m, 1H, CH), 1.71 (s, 9H, $OCMe_3$), 1.11 (s, 9H, $SiCMe_3$), 0.32-0.28 (m, 3H, SiMe), 0.18-0.14 (m, 3H, SiMe); ^{13}C NMR (100.6 MHz, DMSO-d_6, 100 °C) δ 197.4 (PhC=O), 154.6 (C=O), 135.2 (*ipso*-Ar), 131.9 (Ar), 127.8 (Ar), 127.5 (Ar), 78.6 (O*C*Me_3), 64.1 (OCH), 54.9 (OCCHN), 36.5 (NCH_2), 34.1 (CH_2), 31.4 (CH_2), 27.5 (OC*Me*$_3$), 25.1 (SiC*Me*$_3$), 17.1 (Si*C*Me_3), –5.6 (SiMe), –5.8 (SiMe); HRMS (ESI) *m/z* calcd for $C_{23}H_{37}NO_4Si$ $(M + Na)^+$ 442.2384, found 442.2384 (0.0 ppm error). Diagnostic signals for *trans*-**214**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.90-5.83 (m, 1H, ArC*H*N), 4.61-4.55 (m, 1H, OCH).

Lab book reference: **MTG-3-84**

***tert*-Butyl-4-(*tert*-butyl(dimethyl)silyl)oxy-2-trimethylsilylpiperidine-1-carboxylate *cis*-215**

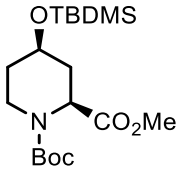


cis-**215**

Using General Procedure B, *s*-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL) and Me_3SiCl (0.127 mL, 1.00 mmol) at –78 °C for 30 min and rt for 17 h. Purification by flash column chromatography on silica using hexane then 49:1 hexane-Et_2O then 24:1 hexane-Et_2O as eluent gave 2,4-disubstituted piperidines **215** in 93:7 dr (based on ^{1}H NMR spectroscopy after Boc group removal) (142 mg, 73%) as a colourless oil, R_F (49:1 hexane-Et_2O) 0.45; IR (ATR) 2953, 2931, 2896, 2857, 1690 (C=O), 1245, 1151, 1099, 1085, 834, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09-3.38 (m, 2H, OCH + NCH), 3.37-2.77 (m, 1H, NCH), 2.77-2.03 (m, 1H, SiNCH), 1.85-1.64 (m, 2H, CH + CH), 1.59-1.20 (m, 2H, CH + CH), 1.41 (s, 9H, $OCMe_3$), 0.87 (s, 9H, $SiCMe_3$), 0.22–—0.012 (m, 15H, 5 x SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.1 (C=O), 79.1 (O*C*Me_3), 70.6 (OCH), 47.6 (SiNCH), 45.2 (NCH_2), 35.6 (2 × CH_2), 28.5 (OC*Me*$_3$), 26.0 (SiC*Me*$_3$), 18.4 (Si*C*Me_3), –0.7 (3 × SiMe), –4.5 (SiMe), –4.6 (SiMe); HRMS (ESI) *m/z* calcd for $C_{19}H_{41}NO_3Si_2$ $(M + Na)^+$ 410.2517, found 410.2517 (0.0 ppm error).

Lab book reference: **MTG-7-130**

***tert*-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-methylpiperidine-1,2-dicarboxylate *cis*-216**

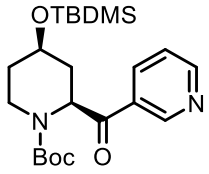


cis-**216**

Using General Procedure B, *s*-BuLi (0.51 mL of a 1.28 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (159 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL) and methylchloroformate (0.077 mL, 1.0 mmol) at –78 °C for 30 min and rt for 16 h. Purification by flash column chromatography on silica using 9:1 hexane-Et_2O then 4:1 hexane-Et_2O as eluent gave 2,4-disubstituted piperidines **216** in 84:16 dr (based on ^{1}H NMR spectroscopy after Boc group removal) (85 mg, 46%) as a colourless oil, R_F (4:1 hexane-Et_2O) 0.35; IR (ATR) 2952, 2930, 2890, 2857, 1753 (C=O), 1698 (C=O), 1170, 1054, 1053, 1004, 879, 832, 774 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 4.58-4.49 (m, 1H, OCCHN), 4.12-4.05 (m, 1H, OCH), 3.73-3.66 (m, 1H, NCH), 3.63 (s, 3H, OMe), 3.31 (ddd, *J* = 12.5, 12.5, 3.0 Hz, 1H, NCH), 2.23-2.14 (m, 1H, CH), 1.90 (ddd, *J* = 14.0, 7.0, 2.5 Hz, 1H, CH), 1.64-1.51 (m, 2H, 2 × CH), 1.40 (s, 9H, $OCMe_3$), 0.86 (s, 9H, $SiCMe_3$), 0.04-0.00 (m, 6H, 2 × SiMe); ^{13}C NMR (100.6 MHz, DMSO-d_6, 100 °C) δ 172.7 (C=O, CO_2Me), 156.1 (C=O), 80.0 (O*C*Me_3), 64.0 (OCH), 51.9 (OMe), 50.4 (OCCHN), 36.2 (NCH_2), 33.9 (CH_2), 32.3 (CH_2), 28.4 (OC*Me*$_3$), 25.9 (SiC*Me*$_3$), 18.2 (Si*C*Me_3), –4.9 (SiMe), –5.1 (SiMe); HRMS (ESI) *m/z* calcd for $C_{18}H_{35}NO_5Si$ $(M + Na)^+$ 396.2177, found 396.2173 (+0.9 ppm error). Diagnostic signals for *trans*-**216**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81-4.76 (m, 1H, OCCHN), 0.88 (s, 9H, $SiCMe_3$). Diagnostic signals for *trans*-**216**: ^{13}C NMR (100.6 MHz, DMSO-d_6, 100 °C) 172.3 (C=O, CO_2Me), 155.8 (C=O), 80.4 (O*C*Me_3), 63.8 (OCH), 51.6 (OCCHN), 35.2 (NCH_2), 33.9 (CH_2), 32.0 (CH_2), 28.4 (OC*Me*$_3$), 25.8 (SiC*Me*$_3$), –4.7 (SiMe).

Lab book reference: **MTG-2-55**

***tert*-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(pyridine-3-carbonyl)piperidine-1-carboxylate *cis*-217**

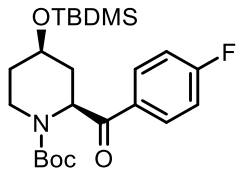


cis-**217**

Using General Procedure B, *s*-BuLi (0.50 mL of a 1.30 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (160 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL) and *N*-methoxy-*N*-methylpyridine-3-carboxamide (0.166 mg, 1.00 mmol) at –78 °C for 30 min and rt for 18 h. Purification by flash column chromatography on silica using 3:1 hexane-EtOAc then 3:2 hexane-EtOAc as eluent gave 2,4-disubstituted piperidine *cis*-**217** (11 mg, 5%) as a colourless oil and 2,4-disubstituted piperidines **217** in 93:7 dr (36 mg, 17%) as a colourless oil, R_F (4:1 hexane-EtOAc) 0.15; IR (ATR) 2931, 2898, 2858, 1695 (C=O), 1690 (C=O), 1379, 1365, 1254, 1171, 1088, 1052, 878, 835, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.11 (d, *J* = 2.0 Hz, 1H, Ar), 8.81-8.67 (m, 1H, Ar), 8.29-8.11 (m, 1H, Ar), 7.45-7.30 (m, 1H, Ar), 5.71-5.31 (m, 1H, OCCHN), 4.06-3.78 (m, 2H, OCH + NCH), 3.15-2.75 (m, 1H, NCH), 2.31-2.04 (m, 1H, CH), 1.85-1.63 (m, 2H, CH), 1.48-1.34 (m, 1H, CH), 1.41 (s, 9H, $OCMe_3$), 0.83 (s, 9H, $SiCMe_3$), 0.02-–0.07 (m, 6H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 199.2 (ArC=O), 155.3 (C=O), 153.5 (Ar), 149.7 (Ar), 135.7 (Ar), 131.1 (*ipso*-Ar), 123.5 (Ar), 81.0 (O*C*Me_3), 65.7 (OCH), 57.0 (OC*C*HN), 41.3 (NCH_2), 34.8 (CH_2), 34.2 (CH_2), 28.3 (OC*Me*$_3$), 25.9 (SiC*Me*$_3$), 18.1 (Si*C*Me_3), –4.7 (SiMe), –4.7 (SiMe); HRMS (ESI) *m/z* calcd for $C_{22}H_{36}N_2O_4Si$ $(M + Na)^+$ 443.2337, found 443.2343 (–1.4 ppm error). Diagnostic signals for *trans*-**217**: ^1H NMR (400 MHz, $CDCl_3$) δ 2.85 (ddd, *J* = 13.5, 13.0, 3.0 Hz, 1H, NCH), 0.86 (s, 9H, $SiCMe_3$), 0.05 (s, 6H, SiMe). Overall, this reaction gave 2,4-disubstituted piperidines **217** in 95:5 dr (47 mg, 22%).

Lab book reference: **MTG-4-12**

***tert*-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(4-fluorobenzoyl)piperidine-1-carboxylate *cis*-218**



cis-**218**

Using General Procedure B, *s*-BuLi (0.50 mL of a 1.30 M solution in hexane, 0.65 mmol), 4-OTBDMS-*N*-Boc-piperidine **73** (156 mg, 0.50 mmol) and TMEDA (0.097 mL, 0.65 mmol) in toluene (2.5 mL) and 4-fluoro-*N*-methoxy-*N*-methylbenzamide (0.183 mg, 1.00 mmol) at –78 °C for 30 min and rt for 19 h. Purification by flash column chromatography on silica using 23:2 hexane-EtOAc then 7:3 hexane-EtOAc as eluent gave 2,4-disubstituted piperidines **218** in 97:3 dr (92 mg, 42%) as a colourless oil, R_F (47:3 hexane-EtOAc) 0.30; IR (ATR) 2956, 2930, 2896, 2857, 1702 (C=O), 1690 (C=O), 1379, 1230, 1212, 1172, 1157, 1086, 1052, 1034, 878, 834, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88-7.82 (m, 2H, Ar), 7.14-6.98 (m, 2H, Ar), 5.33-5.07 (m, 1H, OCCHN), 3.99 (dddd, *J* = 3.0, 3.0, 3.0, 3.0 Hz, 1H, OCH), 3.89-3.72 (m, 1H, NCH), 3.70-3.49 (m, 1H, NCH), 2.40-2.15 (m, 1H, CH), 2.09 (ddd, *J* = 14.0, 7.0, 3.0 Hz, 1H, CH), 1.20-1.51 (m, 2H, CH + CH), 1.50-1.19 (m, 9H, $OCMe_3$), 0.69 (s, 9H, $SiCMe_3$), –0.11 (s, 3H, SiMe), –0.28 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 196.7 (ArC=O), 165.3 (d, *J* = 254.0 Hz, *ipso*-Ar), 156.3 (C=O), 132.1 (d, *J* = 3.0 Hz, *ipso*-Ar), 131.1 (br, Ar), 115.5 (d, *J* = 21.5 Hz, Ar), 80.1 (O*C*Me_3), 64.5 (OCH), 54.7 (OC*C*HN), 37.0 (NCH_2), 35.1 (CH_2), 32.2 (CH_2), 28.4 (OC*Me*$_3$), 25.7 (SiC*Me*$_3$), 18.1 (Si*C*Me_3), –5.0 (SiMe), –5.2 (SiMe); HRMS (ESI) *m/z* calcd for $C_{23}H_{36}FNO_4Si$ $(M + Na)^+$ 460.2290, found 460.2294 (–1.0 ppm error). Diagnostic signals for *trans*-**218**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.60 (m, 2H, Ar), 1.75 (s, 9H, $OCMe_3$), 0.85 (s, 9H, $SiCMe_3$).

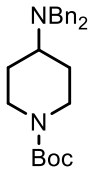
Lab book reference: **MTG-4-13**

s-BuLi (0.50 mL of a 1.30 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTBDMS-*N*-Boc-piperidine **73** (160 mg, 0.50 mmol, 1.0 eq.) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in freshly distilled Et_2O (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. 4-Fluoro-*N*-

methoxy-*N*-methylbenzamide (0.183 mg, 1.00 mmol, 2.0 eq.) was added and the resulting solution was stirred at –78 °C for 30 min and then at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 19:1 hexane-EtOAc then 7:3 hexane-EtOAc as eluent gave 2,4-disubstituted piperidines **218** in 97:3 dr (76 mg, 35%) as a colourless oil.

Lab book reference: **MTG-4-45**

***tert*-Butyl-4-(dibenzylamino)piperidine-1-carboxylate 219**



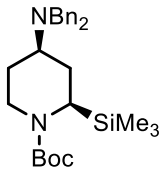
219

Acetic acid (0.029 mL, 0.5 mmol, 0.1 eq.) and dibenzylamine (1.06 mL, 5.5 mmol, 1.1 eq.) were added to a stirred solution of *N*-Boc-piperidin-4-one **165** (996 mg, 5.0 mmol, 1.0 eq.) in CH_2Cl_2 (25 mL) under Ar. The resulting solution was stirred at rt for 21 h then sodium triacetoxyborohydride (1.48 g, 7.0 mmol, 1.4 eq.) was added and the resulting mixture stirred at rt for 21 h. CH_2Cl_2 (50 mL) and H_2O (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 washed with $NaHCO_{3(aq)}$ (50 mL), H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 900:90:9:1 hexane-EtOAc-MeOH-Et_3N as eluent gave crude product. Purification by flash column chromatography on silica using 19:1 hexane-EtOAc as eluent gave 4-dibenzylamino-*N*-Boc-piperidine **219** (1.21 g, 63%) as a white solid, mp 124-125 °C; R_F (9:1 hexane-Et_2O) 0.20; IR (ATR) 3027, 2975, 2931, 2853, 2801, 1689, 1423, 1365, 1237, 1174, 1149, 737, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.17 (m, 10H, Ph), 4.37-3.90 (m, 2H, NCH), 3.62 (s, 4H, $PhNCH_2$), 2.64 (tt, J = 12.0, 3.5 Hz, 1H, Bn_2NCH), 2.59-

2.45 (m, 2H, NCH_2), 1.86-1.70 (m, 2H, CH + CH), 1.60-1.46 (m, 2H, CH + CH), 1.43 (s, 9H, $OCMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.9 (C=O), 140.7 (*ipso*-Ph), 128.5 (Ph), 128.3 (Ph), 126.8 (Ph), 79.5 (O*C*Me_3), 56.4 (Bn_2NCH), 53.9 ($PhNCH_2$), 43.8 (NCH_2), 28.5 (OC*Me*$_3$), 27.6 (CH_2); HRMS (ESI) *m/z* calcd for $C_{24}H_{32}N_2O_2$ $(M + H)^+$ 381.2537, found 381.2530 (1.8 ppm error). Spectroscopic data consistent with those reported in the literature.[139]

Lab book reference: **MTG-2-76**

***tert*-Butyl-4-(bis(cyclohexylmethyl)amino)-2-trimethylsilyl-piperidine-1-carboxylate *cis*-220**



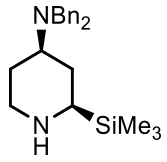
cis-**220**

s-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-NBn_2-*N*-Boc-piperidine **219** (190 mg, 0.50 mmol, 1.0 eq.) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. Me_3SiCl (0.127 mL, 1.0 mmol, 2.0 eq.) was added and the resulting solution was stirred at –78 °C for 30 min and then at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 19:1 hexane-EtOAc as eluent gave crude product. Purification by flash column chromatography on silica using 24:1 hexane-EtOAc as eluent gave 2,4-disubstituted piperidine *cis*-**220** (86 mg, 36%) as a white solid, R_F (49:1 hexane-Et_2O) 0.15; IR (ATR) 3027, 2980, 2939, 2803, 1685 (C=O), 1243, 1156, 838, 733, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.21 (m, 10H, Ph), 4.10-3.94 (m, 1H, NCH), 3.70 (d, *J* = 14.0 Hz, 2H, PhNCH), 3.65 (d, *J* = 14.0 Hz, 2H, PhNCH), 2.84-2.65 (m, 2H, NCH + Bn_2NCH), 2.23-2.04 (m, 1H, SiNCH), 1.90-1.75 (m, 2H, CH + CH), 1.64-1.48 (m, 2H, CH + CH), 1.46 (s, 9H, $OCMe_3$), 0.11 (s, 9H, $SiMe_3$); ^{13}C NMR

(100.6 MHz, $CDCl_3$) δ 155.2 (C=O), 140.8 (*ipso*-Ph), 128.5 (Ph), 128.3 (Ph), 126.9 (Ph), 79.2 (O*C*Me$_3$), 58.0 (Bn_2NCH), 54.0 ($PhNCH_2$), 50.0 (SiNCH), 47.6 (NCH_2), 28.9 (CH_2), 28.6 (OC*Me*$_3$), 27.8 (CH_2), –0.6 ($SiMe_3$); HRMS (ESI) *m/z* calcd for $C_{27}H_{40}N_2O_2Si$ $(M + H)^+$ 453.2932, found 453.2932 (–0.1 ppm error).

Lab book reference: **MTG-3-5**

4-(Bis(cyclohexylmethyl)amino)-2-trimethylsilyl-piperidine *cis*-221

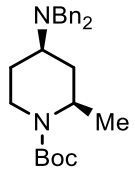


cis-**221**

Trifluoroacetic acid (0.129 mL, 1.68 mmol, 10 eq.) was added dropwise to a stirred solution of 4-dibenzylamino-2-trimethylsilyl-*N*-Boc-piperidine *cis*-**220** (76 mg, 0.17 mmol, 1.0 eq.) in CH_2Cl_2 (2.5 mL) at rt under Ar. The resulting solution was stirred at rt for 27 h. Saturated $NaHCO_{3(aq)}$ (5 mL) and CH_2Cl_2 (5 mL) were added and the two layers were 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 which contained only 2,4-disubstituted piperidine *cis*-**221** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica using 9:1 EtOAc-MeOH as eluent gave 2,4-disubstituted piperidine *cis*-**221** (18 mg, 30%) as a yellow oil, R_F (9:1 EtOAc-MeOH) 0.50; IR (ATR) 3085, 3062, 3026, 2929, 2799, 1247, 852, 833, 741, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.14 (m, 10H, Ph), 3.68 (d, *J* = 14.0 Hz, 2H, PhNCH), 3.64 (d, *J* = 14.0 Hz, 2H, PhNCH), 3.20 (ddd, *J* = 12.0, 4.0, 2.5 Hz, 1H, NCH), 2.60 (dddd, *J* = 12.0, 12.0, 4.0, 4.0 Hz, 1H, Bn_2NCH), 2.50 (ddd, *J* = 12.0, 12.0, 2.5 Hz, 1H, NCH), 2.19-1.92 (m, 1H, NH), 1.95 (dd, *J* = 12.5, 2.5 Hz, 1H, SiNCH), 1.90-1.82 (m, 1H, CH), 1.75 (dddd, *J* = 12.5, 4.0, 2.5, 2.5 Hz, 1H, CH), 1.56 (dddd, 12.0, 12.0, 12.0, 4.0 Hz, 1H, CH), 1.36 (ddd, *J* = 12.5, 12.5, 12.0 Hz, 1H, CH), 0.02 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.0 (*ipso*-Ph), 128.5 (Ph), 128.2 (Ph), 126.7 (Ph), 57.8 (Bn_2NCH), 53.9 ($PhNCH_2$), 48.9 (NCH_2), 47.9 (SiNCH), 29.8 (CH_2), 29.0 (CH_2), –3.8 ($SiMe_3$); HRMS (ESI) *m/z* calcd for $C_{22}H_{33}N_2Si$ $(M + H)^+$ 353.2408, found 353.2406 (+0.4 ppm error).

Lab book reference: **MTG-3-101**

***tert*-Butyl-4-(dibenzylamino)-2-methylpiperidine-1-carboxylate *cis*-222**

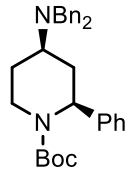


cis-**222**

s-BuLi (0.51 mL of a 1.27 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-dibenzylamino-*N*-Boc-piperidine **219** (190 mg, 0.50 mmol, 1.0 eq.) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. Dimethylsulfate (0.095 mL, 1.00 mmol, 2.0 eq.) was added and the resulting solution was stirred at –78 °C for 30 min and then at rt for 18 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 9:1 hexane-EtOAc as eluent gave a 50:50 mixture of 2,4-disubstituted piperidine **222** and 4-dibenzylamino-*N*-Boc-piperidine **219** (176 mg, i.e. 90 mg (46%) of 2,4-disubstituted piperidine **222**, 86 mg (45%) of 4-dibenzylamino-*N*-Boc-piperidine **219**) as a white solid, R_F (9:1 hexane-EtOAc) 0.25; IR (ATR) 3027, 2974, 2932, 2802, 1687 (C=O), 1409, 1364, 1238, 1174, 1149, 731, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.19 (m, 10H, Ph), 3.77-3.69 (m, 2H, NCH + MeNCH), 3.69-3.56 (m, 4H, $PhNCH_2$), 3.13 (ddd, *J* = 14.0, 10.5, 6.0 Hz, 1H, NCH), 2.86 (dddd, *J* = 12.0, 8.5, 4.0, 4.0 Hz, 1H, Bn_2NCH), 2.05-1.87 (m, 2H, CH + CH), 1.68-1.52 (m, 2H, CH + CH), 1.48 (s, 9H, $OCMe_3$), 1.23 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.3 (C=O), 140.4 (*ipso*-Ph), 128.5 (Ph), 128.4 (Ph), 126.9 (Ph), 79.5 ($OCMe_3$), 54.0 ($PhNCH_2$), 52.6 (Bn_2NCH), 49.7 (NCHMe), 38.0 (NCH_2), 31.6 (CH_2), 28.6 ($OCMe_3$), 25.7 (CH_2), 20.6 (Me); HRMS (ESI) *m/z* calcd for $C_{25}H_{34}N_2O_2$ $(M + Na)^+$ 417.2512, found 417.2510 (+0.6 ppm error).

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

***tert*-Butyl-4-(bis(cyclohexylmethyl)amino)-2-phenyl-piperidine-1-carboxylate *cis*-223**

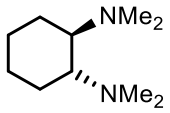


cis-**223**

s-BuLi (0.50 mL of a 1.3 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-NBn_2-*N*-Boc-piperidine **219** (189 mg, 0.50 mmol, 1.0 eq.) and TMEDA (0.097 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. In a separate flask, a solution of bromobenzene (0.068 mL, 0.65 mmol, 1.3 eq.), SPhos (10.3 mg, 0.025 mmol, 0.05 eq.) and $Pd_2(dba)_3$ (11.4 mg, 0.013 mmol, 0.025 eq.) in toluene (2 mL) was stirred at rt under Ar for 10 min. The catalyst solution was added to the solution of zinc species and the resulting solution was stirred and heated at 50 °C for 16 h. After being allowed to cool to rt, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 9:1 hexane-EtOAc as eluent gave a 20:80 mixture of α-arylpiperidine *cis*-**223** and 4-NBn_2-*N*-Boc-piperidine **219** (97 mg, i.e. 22 mg (10%) of α-arylpiperidine *cis*-**223** and 75 mg (39%) of 4-NBn_2-*N*-Boc-piperidine **219**) as a white solid. Diagnostic signals for *cis*-**223**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.56 (dd, *J* = 12.0, 5.5 Hz, 1H, ArNCH), 3.39 (ddd, *J* = 14.0, 11.5, 5.5 Hz, 1H, NCH), 3.11-2.99 (m, 1H, NCH), 2.16-2.05 (m, 2H, CH + CH), 1.17 (s, 9H, $OCMe_3$); HRMS (ESI) *m/z* calcd for $C_{30}H_{37}N_2O_2$ $(M + H)^+$ 457.2850, found 257.2841 (+1.8 ppm error).

Lab book reference: **MTG-3-6**

(1*S*,2*S*)-N^1,N^1,N^2,N^2-Tetramethylcyclohexane-1,2-diamine ((*S*,*S*)-TMCDA) 225

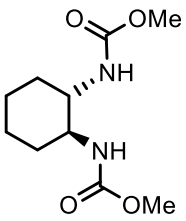


(*S*,*S*)-**225**

Formic acid (0.755 mL, 2.0 mmol, 1.0 eq.) was added to a stirred solution of *trans*-1,2 diaminocyclohexane salt **224** (529 mg, 2.0 mmol, 1.0 eq.) in 37% (w/w) formaldehyde$_{(aq)}$ (1.49 mL, 2.0 mmol, 1.0 eq.). The resulting solution was stirred and heated at 100 °C for 16 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure. Then 2 M NaOH$_{(aq)}$ (5 mL) and $CHCl_3$ (10 mL) were added and the two layers were separated. The aqueous layer was extracted with $CHCl_3$ (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by Kügelrohr distillation gave (*S*,*S*)-TMCDA **225** (156 mg, 46%) as a colourless oil, R_F (1:1 EtOAc-MeOH) 0.05; IR (ATR) 2960, 2919, 2856, 1661, 1635, 1264, 1094, 1023, 797 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45-2.31 (m, 2H, NCH), 2.26 (s, 12H, NMe_2), 1.87-1.63 (m, 4H, CH + CH), 1.19-1.00 (m, 4H, CH + CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 63.9 (NCH), 40.2 (NMe_2), 25.7 (CH_2), 22.9 (CH_2); HRMS (ESI) *m/z* calcd for $C_{10}H_{22}N_2$ $(M + H)^+$ 171.1856, found 171.1857 (–0.6 ppm error). Spectroscopic data consistent with those reported in the literature.[140]

Lab book reference: **MTG-3-47**

((1*S*,2*S*)-2-Methoxycarbonylaminocyclohexyl)carbamic acid methyl ester (*S*,*S*)-227



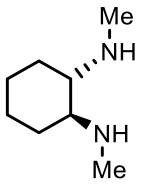
(*S*,*S*)-**227**

A solution of NaOH (3.20 g, 80 mmol, 8.0 eq.) in water (5 mL) and methylchloroformate (1.62 mL, 21 mmol, 2.1 eq.) were simultaneously added to a stirred suspension of cyclohexane diamine (*S*,*S*)-**224** (2.64 g, 10 mmol, 1.0 eq.) in toluene (15 mL) at 0 °C under air. This led to the formation of a gel-like precipitate. The

resulting mixture was stirred at rt for 48 h. Then CH_2Cl_2 (15 mL) was added and the solids were removed by filtration and washed with CH_2Cl_2 (2 x 8 mL). Water (8 mL) was added to the filtrate and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL) and the combined organics dried (K_2CO_3) and evaporated under reduced pressure to give the crude carbamate (*S*,*S*)-**227** (1.63 g) as a white solid. Purification by flash column chromatography on silica using EtOAc as eluent gave carbamate (*S*,*S*)-**227** (358 mg, 16%) as a white solid, R_F (7:3 hexane-EtOAc) 0.15; IR (ATR) 3321 (NH), 2929, 2857, 1684 (C=O), 1533, 1321, 1283, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.20-4.60 (m, 2H, 2 x NH), 3.64 (s, 6H, 2 x Me), 3.40-3.10 (m, 2H, 2 x NCH), 2.15-1.98 (m, 2H, 2 x NHCHC*H*), 1.83-1.64 (m, 2H, 2 x CH), 1.39-1.10 (m, 4H, 2 x CH + 2 x NHCHC*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.5 (C=O), 55.5 (NCH), 52.2 (Me), 32.9 (NHCH*CH*$_2$), 24.8 (CH_2); HRMS (ESI) *m/z* calcd for $C_{10}H_{18}N_2O_4$ $(M + Na)^+$ 253.1159, found 253.1163 (–1.6 ppm error). Spectroscopic data consistent with those reported in the literature.[81]

Lab book reference: **MTG-3-83**

(1*S*,2*S*)-*N*^{1},*N*^{2}-Dimethylcyclohexane-1,2-diamine (*S*,*S*)-228



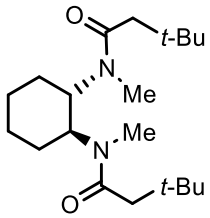
(*S*,*S*)-**228**

A solution of the crude carbamate **227** (4.70 g, max. 20.4 mmol, 1.0 eq.) in THF (65 mL) was added dropwise to a stirred solution of $LiAlH_4$ (3.87 g, 102 mmol, 5.0 eq.) in THF (33 mL) at 0 °C under Ar. The resulting solution was stirred and heated at reflux for 40 h. The solution was cooled to 0 °C and Et_2O (20 mL) was added, followed by addition of Na_2SO_4•$10H_2O$ (19.3 g) and Et_2O (40 mL). The resulting mixture was then stirred at rt for 3 h. The solids were removed by filtration through a pad of Celite® and were washed with 24:1 CH_2Cl_2-MeOH (2 x 25 mL) and evaporated under reduced pressure. EtOAc (80 mL) and 6 M $NaOH_{(aq)}$ (80 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 80 mL) and the combined organics were dried (K_2CO_3) and evaporated under reduced pressure to give

crude diamine (*S*,*S*)-**228** (1.87 g, max. 64%) as a crystalline solid. The crude product was used in the next step without further purification (≥95% purity by ^{1}H NMR spectroscopy), ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 6H, 2 x Me), 2.14-2.06 (m, 2H, 2 x NCH), 2.05-1.96 (m, 2H, 2 x NHCHC*H*), 1.78-1.66 (m, 2H, 2 x NHCHC*H*), 1.43 (br s, 2H, 2 x NH), 1.29-1.14 (m, 2H, 2 x CH), 1.01-0.87 (m, 2H, 2 x CH). Spectroscopic data consistent with those reported in the literature.[81]

Lab book reference: **MTG-3-98**

(1*S*,2*S*)-*N*^{1},*N*^{2}-Dimethyl-*N*^{1},*N*^{2}-bis(3,3-dimethylbutanoyl)cyclohexane-1,2-diamine (*S*,*S*)-229

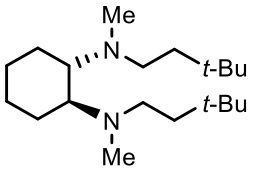


(*S*,*S*)-**229**

A solution of *t*-butylacetyl chloride (3.83 mL, 27.6 mmol, 2.1 eq.) in CH_2Cl_2 (6 mL) was added dropwise to a stirred biphasic mixture of crude diamine (*S*,*S*)-**228** (1.87 g, max. 13.1 mmol) in CH_2Cl_2 (15 mL) and NaOH (2.41 g, 60.3 mmol, 4.6 eq.) in water (7.5 mL) at 0 °C under air. The resulting mixture was stirred at rt for 52 h. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were dried (K_2CO_3) and evaporated under reduced pressure to give the bis-amide (*S*,*S*)-**229** (4.36 g, 98% crude yield) as a white solid. The crude product was used in the next step without further purification (≥95% purity by ^{1}H NMR spectroscopy), R_F (7:3 hexane-EtOAc) 0.30; IR (ATR) 2956, 2933, 2865, 1640 (C=O), 1626, 1480, 1403 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75-4.65 (m, 2H, NCH), 2.80 (s, 6H, 2 x NMe), 2.21 (d, *J* = 14.0 Hz, 2H, 2 x NCOCH), 2.12 (d, *J* = 14.0 Hz, 2H, 2 x NCOCH), 1.78-1.62 (m, 4H, 2 x CH + 2 x NHCHC*H*), 1.50 (dddd, *J* = 12.0, 9.0, 9.0, 3.5 Hz, 2H, 2 x NCHC*H*), 1.42-1.26 (m, 2H, CH), 1.00 (s, 18H, 2 x CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.1 (C=O), 51.7 (NCH), 45.5 (NCO*C*H_2), 31.5 (*C*Me_3), 31.0 (NMe), 30.1 (C*Me*$_3$), 29.6 (NCH*C*H_2), 25.2 (CH_2CH_2); HRMS (ESI) *m/z* calcd for $C_{20}H_{38}N_2O_2$ $(M + Na)^+$ 361.2825, found 361.2832 (–1.7 ppm error).

Lab book reference: **MTG-3-99**

(1*S*,2*S*)-N^1,N^2-Dimethyl-N^1,N^2-bis(3,3-dimethylbutyl)cyclohexane-1,2-diamine (*S*,*S*)-105

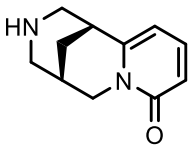


(*S*,*S*)-**105**

A solution of the bis-amide (*S*,*S*)-**229** (2.73 g, max. 8.1 mmol, 1.0 eq.) in THF (15 mL) was added dropwise to a stirred solution of $LiAlH_4$ (1.53 g, 40.3 mmol, 5.0 eq.) in THF (15 mL) at 0 °C under Ar. The resulting solution was stirred and heated at reflux for 40 h. The solution was cooled to 0 °C and Et_2O (13 mL) was added, followed by addition of Na_2SO_4•$10H_2O$ (7.7 g). The resulting mixture was then stirred at rt for 3 h. The solids were removed by filtration through a pad of Celite® and were washed with 24:1 CH_2Cl_2-MeOH (25 mL) and evaporated under reduced pressure. Purification by Kügelrohr distillation under reduced pressure gave diamine (*S*,*S*)-**105** (256 mg, approximately 95% pure with unknown impurities, 10%) as a colourless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56-2.35 (m, 6H, 2 x NCH + 2 x NCH_2), 2.24 (s, 6H, 2 x NMe), 1.81-1.66 (m, 4H, 2 x NCHC*H*), 1.42-1.33 (m, 4H, 2 x C$H_2$$CMe_3$), 1.22-1.05 (m, 4H, 4 x CH), 0.89 (s, 18H, 2 x CMe_3). Spectroscopic data consistent with those reported in the literature.[81]

Lab book reference: **MTG-3-93**

(-)-Cytisine 230



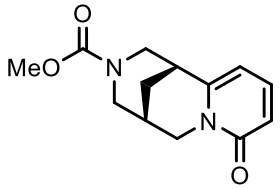
230

Laburnum anagyroides seeds (600 g) were ground in a blender in batches for 8-10 sec. The ground seeds were stirred with CH_2Cl_2 (900 mL), MeOH (255 mL) and 35% $NH_4OH_{(aq)}$ (96 mL) for 5 days. The solids were removed by filtration and washed with CH_2Cl_2 (2.5 L) until the filtrate was colourless. To the filtrate, 3 M $HCl_{(aq)}$ (600 mL) was added and the mixture was stirred for 4 h. The mixture was allowed to separate for

8 days then the layers were separated. The aqueous layer was basified with 35% $NH_4OH_{(aq)}$ (~100 mL) to pH 8-9 and stirred for 2 h. The aqueous layer was extracted with CH_2Cl_2 (3 x 500 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product (4.33 g, 0.69% by mass) as a yellow-brown solid. The crude product was used in the next step without further purification (95% purity by ^{1}H NMR spectroscopy), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 9.0, 7.0 Hz, 1H, Ar), 6.44 (dd, *J* = 9.0, 1.5 Hz, 1H, Ar), 5.99 (dd, *J* = 7.0, 1.5 Hz, 1H, Ar), 4.12 (d, *J* = 15.5 Hz, 1H, NCH), 3.89 (dd, *J* = 15.5, 6.5 Hz, 1H, NCH), 3.12 (dd, *J* = 12.5 2.5 Hz, 1H, NCH), 3.06 (dd, *J* = 12.5, 2.5 Hz, 1H, NCH), 3.04-2.97 (m, 2H, NCH_2), 2.93-2.88 (m, 1H, CH), 2.37-2.31 (m, 1H, CH), 2.30-2.11 (m, 1H, NH), 2.00-1.91 (m, 2H, CH). Spectroscopic data consistent with those reported in the literature.[141]

Lab book reference: **MTG-4-24**

(1*R*,5*S*)-*N*-Methoxycarbonyl-1,2,3,4,5,6-hexahydro-1,5-methanopyrido-[1,2-a][1,5]diazocin-8-one 231



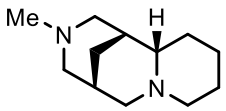
231

Methylchloroformate (3.86 mL, 50.0 mmol) was added dropwise over 10 min to a stirred solution of (-)-cytisine **230** (951 mg, 5.0 mmol) and Et_3N (6.97 mL, 50.0 mmol) in CH_2Cl_2 (30 mL) at 0 ºC under Ar. The resulting solution was stirred at rt for 3.5 h. The solvent was evaporated under reduced pressure and EtOAc (15 mL) was added to the residue. The solids were removed by filtration and the filtrate was evaporated under reduced pressure. Purification by flash column chromatography on silica using 24:1 CH_2Cl_2-MeOH as eluent gave pyridone **231** (1.22 g, 98%) as an orange gum, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 9.0, 7.0 Hz, 1H, Ar), 6.44 (d, *J* = 9.0 Hz, 1H, Ar), 6.05 (d, *J* = 7.0 Hz, 1H, Ar), 4.40-4.00 (m, 2H, NCH), 4.13 (d, *J* = 15.5 Hz, 1H, NCH), 3.86 (dd, *J* = 15.5, 6.5 Hz, 1H, NCH), 3.63-3.45 (m, 3H, OMe), 3.18-2.93 (m, 3H, NCH

+ CH), 2.54-2.36 (m, 1H, CH), 2.05-1.88 (m, 2H, CH). Spectroscopic data consistent with those reported in the literature.[142]

Lab book reference: **MTG-3-97**

3-Methyldecahydro-1,5-methanopyrido[1,2-a][1,5]diazocine (+)-95



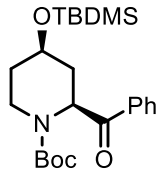
(+)-**95**

A suspension of pyridone **231** (559 mg, 2.25 mmol) and platinum(IV) oxide (51 mg, 0.23 mmol) in EtOH (15 mL) was stirred at rt under a H_2 atmosphere (H_2 balloon) for 16 h. The solids were removed by filtration through Celite® and the filter cake was washed with 9:1 CH_2Cl_2-MeOH (50 mL). The filtrate was evaporated under reduced pressure to give the crude product, ^{1}H NMR spectroscopy showed residual pyridone **231** present. A suspension of crude product and platinum(IV) oxide (51 mg, 0.23 mmol) in EtOH (15 mL) was stirred at rt under a H_2 atmosphere (H_2 balloon) for 22 h. The solids were removed by filtration through Celite® and the filter cake was washed with 9:1 CH_2Cl_2-MeOH (50 mL). The filtrate was evaporated under reduced pressure to give the crude product as a white solid. To this crude product in THF (15 mL) under Ar was added $LiAlH_4$ (512 mg, 13.5 mmol), the resulting suspension was heated at reflux for 18 h. After cooling to 0 ºC, Et_2O (15 mL) was added followed by the dropwise addition of saturated $Na_2SO_{4(aq)}$ until effervescence ceased. The solids were removed by filtration through Celite® and the filter cake was washed with 9:1 EtOAc-MeOH (50 mL). Roughly three quarters of the solvent was removed under reduced pressure. Then 2 M $NaOH_{(aq)}$ (20 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 dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by Kügelrohr distillation (180 ºC, 3 mbar) gave diamine (+)-**95** (172 mg, 39%) as a colourless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.06-2.72 (m, 4H, NCH), 2.30-2.18 (m, 1H, NCH), 2.18-2.04 (m, 1H, NCH), 2.13 (s, 3H, NMe), 2.03-1.39 (m, 11H, 2 x CH + 3 x NCH + 3 x CH_2), 1.37-1.18 (m, 2H, CH + CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 66.6 (NCH), 60.6 (NCH_2), 60.6 (NCH_2), 57.8 (NCH_2), 56.5 (NCH_2), 47.6 (NMe), 35.3 (CH), 34.1 (CH_2),

31.0 (CH_2), 30.8 (CH), 25.8 (CH_2), 25.3 (CH_2). Spectroscopic data consistent with those reported in the literature.[83]

Lab book reference: **MTG-4-22**

(2*S*,4*R*)-*tert*-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-benzoylpiperidine-1-carboxylate *cis*-214



(2*S*,4*R*)-**214**

s-BuLi (0.56 mL of a 1.17 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol, 1.0 eq.) and (+)-sparteine (0.149 mL, 0.65 mmol, 1.3 eq.) in toluene (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 7 h. *N*-methoxy-*N*-methylbenzamide (0.152 mL, 1.0 mmol, 2.0 eq.) was added and the resulting solution was stirred at –78 °C for 1 h and then at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 23:2 hexane-EtOAc as eluent gave 2,4-disubstituted piperidines **214** in 97:3 dr (31 mg, 15%, 67:33 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralpak AD-H (90:10: *i*-PrOH, 1.0 mL min^{-1}) (2*R*,4*S*)-**214** 4.2 min, (2*S*,4*R*)-**214** 8.9 min.

Lab book reference: **MTG-3-90**

s-BuLi (0.56 mL of a 1.17 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTBDMS-*N*-Boc-piperidine **73** (159 mg, 0.50 mmol, 1.0 eq.) and (+)-sparteine (0.149 mL, 0.65 mmol, 1.3 eq.) in Et_2O (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 7 h. *N*-methoxy-*N*-methylbenzamide (0.152 mL, 1.0 mmol, 2.0 eq.) was added and the resulting solution

was stirred at –78 °C for 1 h and then at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 19:1 hexane-EtOAc then 9:1 hexane-EtOAc as eluent gave 2,4-disubstituted piperidine (2*S*,4*R*)-*cis*-**214** (50 mg, 24%, 74:26 er by CSP-HPLC) as a colourless oil.

Lab book reference: **MTG-3-89**

s-BuLi (0.33 mL of a 1.37 M solution in hexane, 0.46 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTBDMS-*N*-Boc-piperidine **73** (110 mg, 0.35 mmol, 1.0 eq.) and diamine ligand (*R*,*R*)-**105** (141 mg, 95% purity by ^{1}H NMR, 0.46 mmol, 1.3 eq.) in toluene (1.75 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 6 h. *N*-methoxy-*N*-methylbenzamide (0.107 mL, 0.70 mmol, 2.0 eq.) in toluene (0.35 mL) was added and the resulting solution was stirred at –78 °C for 30 min and then at rt for 18 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 19:1 hexane-EtOAc as eluent gave a 96:4 mixture of 2,4-disubstituted piperidines **214** in 96:4 dr and 4-OTBDMS-*N*-Boc-piperidine **73** (11 mg, i.e. 10.6 mg, (7%), 76:24 er by CSP-HPLC of 4-disubstituted piperidine **214** and 0.4 mg of 4-OTBDMS-*N*-Boc-piperidine **73**) as a colourless oil.

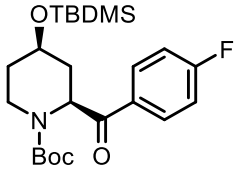
Lab book reference: **MTG-4-95**

s-BuLi (0.50 mL of a 1.29 M solution in hexane, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTBDMS-*N*-Boc-piperidine **73** (158 mg, 0.50 mmol, 1.0 eq.) and diamine ligand (*S*,*S*)-**105** (224 mg, 90% purity by ^{1}H NMR spectroscopy, 0.65 mmol, 1.3 eq.) in Et_2O (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. *N*-methoxy-*N*-methylbenzamide (0.152 mL, 1.0 mmol, 2.0 eq.) was added and the resulting solution was stirred at –78 °C for 30 min and then warmed to rt. Saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were

separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 93:7 hexane-EtOAc then 9:1 hexane-EtOAc as eluent gave 2,4-disubstituted piperidine (2*S*,4*R*)-*cis*-**214** (56 mg, 27%, 83:17 er by CSP-HPLC) as a colourless oil.

Lab book reference: **MTG-3-96**

(2*S*,4*R*)-*tert*-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(4-fluorobenzoyl)piperidine-1-carboxylate *cis*-218

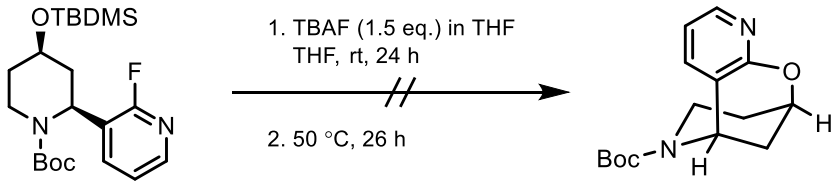


(2*S*,4*R*)-**218**

s-BuLi (0.33 mL of a 1.30 M solution in hexane, 0.43 mmol, 1.3 eq.) was added dropwise to a stirred solution of 4-OTBDMS-*N*-Boc-piperidine **73** (105 mg, 0.33 mmol, 1.0 eq.) and diamine (+)-**95** (84 mg, 0.43 mmol, 1.3 eq.) in Et_2O (1.65 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. 4-Fluoro-*N*-methoxy-*N*-methylbenzamide (0.122 mg, 0.67 mmol, 2.0 eq.) was added and the resulting solution was stirred at –78 °C for 30 min and then at rt for 17 h. Saturated $NH_4Cl_{(aq)}$ (4 mL) and Et_2O (4 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 4 mL) and the combined organics were washed with brine (4 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 19:1 hexane-EtOAc then 7:3 hexane-EtOAc as eluent gave 2,4-disubstituted piperidine (2*S*,4*R*)-*cis*-**218** (11 mg, 8%, 69:31 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralpak AD-H (90:10: *i*-PrOH, 1.0 mL min^{-1}) (2*R*,4*S*)-**218** 9.3 min, (2*S*,4*R*)-**218** 10.7 min.

Lab book reference: **MTG-4-21**

Attempted synthesis of *tert*-butyl-8-oxa-6,12-diazatricyclo[7.3.1.02,7]trideca-2(7),3,5-triene-12-carboxylate 232

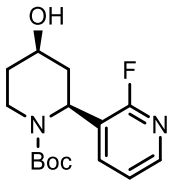


cis-**193** **232**

TBAF (0.11 mL of a 1.00 M solution in THF, 0.11 mmol, 1.5 eq.) was added to a stirred solution of α-arylpiperidines *cis*-**193** (31 mg, 0.07 mmol, 1.0 eq., 98:2 dr) in THF (1 mL) under Ar. The resulting solution was stirred at rt for 24 h. THF (2 mL) was added and the resulting solution was stirred at 50 °C for 26 h. After being allowed to cool to rt, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product, which contained trace amounts of piperidine **232** (by HRMS).

Lab book reference: **MTG-3-64**

***tert*-Butyl-2-(2-fluoro-3-pyridyl)-4-hydroxypiperidine-1-carboxylate *cis*-233**



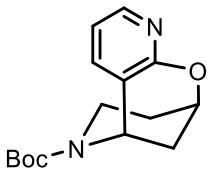
cis-**233**

TBAF (2.06 mL of a 1.00 M solution in THF, 2.06 mmol, 1.5 eq.) was added to a stirred solution of α-arylpiperidine *cis*-**193** (564 mg, 1.37 mmol, 1.0 eq., 98:2 dr) in THF (7 mL) under Ar. The resulting solution was stirred at rt for 17 h. Saturated $NH_4Cl_{(aq)}$ (15 mL) and Et_2O (15 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 15 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 1:1 hexane-EtOAc then EtOAc as eluent gave α-arylpiperidine *cis*-**233** (325 mg, 80%) as a white solid, mp 123-124 °C; R_F

(3:7 hexane-EtOAc) 0.45; IR (ATR) 3418, 2975, 2936, 2888, 1692 (C=O), 1684, 1433, 1404, 1367, 1247, 1166, 1062 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.95 (m, 1H, Ar), 7.64 (ddd, *J* = 10.0, 7.0, 2.0 Hz, 1H, Ar), 7.11 (ddd, *J* = 7.0, 5.0, 2.0 Hz, 1H, Ar), 5.26 (dd, *J* = 7.0, 4.5 Hz, 1H, ArCHN), 4.21-4.14 (m, 1H, OCH), 4.04 (ddd, *J* = 13.5, 5.5, 3.0 Hz, 1H, NCH), 3.49 (ddd, *J* = 13.5, 12.0, 4.0 Hz, 1H, NCH), 2.26 (ddd, *J* = 14.5, 4.5, 4.5 Hz, 1H, CH), 2.13 (ddd, *J* = 14.5, 7.0, 3.0 Hz, 1H, CH), 1.90 (dddd, *J* = 14.0, 12.0, 5.5, 4.0 1H, CH), 1.77-1.66 (m, 2H, CH + OH), 1.31 (s, 9H, $OCMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.4 (d, *J* = 238.0 Hz, *ipso*-Ar), 155.3 (C=O), 145.3 (d, *J* = 15.0 Hz, Ar), 137.5 (d, *J* = 5.0 Hz, Ar), 126.4 (d, *J* = 27.5 Hz, *ipso*-Ar), 121.5 (d, *J* = 4.0 Hz, Ar), 80.4 ($OCMe_3$), 64.2 (OCH), 48.2 (d, *J* =4.0 Hz, ArCHN), 36.5 (NCH_2), 35.8 (d, *J* = 3.5 Hz, CH_2), 31.7 (CH_2), 28.3 ($OCMe_3$); HRMS (ESI) *m/z* calcd for $C_{15}H_{21}FN_2O_3$ $(M + Na)^+$ 319.1428, found 319.1425 (+1.1 ppm error).

Lab book reference: **MTG-3-69**

***tert*-Butyl-8-oxa-6,12-diazatricyclo[7.3.1.02,7]trideca-2(7),3,5-triene-12-carboxylate 232**



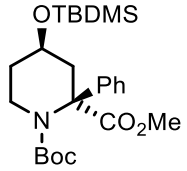
232

A solution of NaH (16 mg of 60% wt in mineral oil, 0.39 mmol, 1.3 eq.) and (2-fluoro-3-pyridyl)-4-hydroxy-*N*-Boc-piperidine *cis*-**233** (89 mg, 0.30 mmol, 1.0 eq.) in DMF (1.5 mL) was stirred and heated at 90 °C for 17 h under Ar. After being allowed to cool to rt, saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (4 x 5 mL) and the combined organics were washed with brine (4 x 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 3:1 hexane-EtOAc as eluent gave 2,4-cyclised piperidine **232** (19 mg, 23%) as a colourless oil, R_F (3:2 hexane-EtOAc) 0.30; IR (ATR) 2973, 2937, 2871, 1688 (C=O), 1435, 1393, 1364, 1166, 1061, 978, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 5.0, 2.0 Hz, 1H, Ar), 7.65-7.38 (m, 1H, Ar), 6.84 (dd,

J = 7.5, 5.0 Hz, 1H, Ar), 5.48-5.19 (m, 1H, ArCHN), 4.92-4.83 (m, 1H, OCH), 3.98-3.74 (m, 1H, NCH), 2.80-2.55 (m, 1H, NCH), 2.19-1.95 (m, 3H, CH), 1.86-1.77 (m, 1H, CH), 1.63-1.32 (m, 9H, $OCMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers - 17 of 26 signals were observed) δ 162.2 (*ipso*-Ar), 155.0 (C=O), 148.9 (Ar), 148.7 (Ar), 138.8 (Ar), 138.1 (Ar), 135.2 (*ipso*-Ar), 117.3 (Ar), 80.4 ($OCMe_3$), 69.9 (OCH), 46.7 (ArCHN), 45.5 (ArCHN), 36.4 (NCH_2), 35.3 (CH_2), 31.5 (CH_2), 28.8 ($OCMe_3$), 28.5 ($OCMe_3$); HRMS (ESI) *m/z* calcd for $C_{15}H_{20}N_2O_3$ $(M + H)^+$ 277.1547, found 277.1551 (–1.6 ppm error).

Lab book reference: **MTG-3-72**

1-(*tert*-Butyl)-2-methyl-4-((*tert*-butyldimethylsilyl)oxy)-2-phenylpiperidine-1,2-dicarboxylate *cis*-241



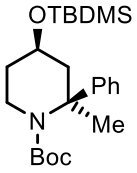
cis-**241**

n-BuLi (0.23 mL of a 1.48 M solution in hexane, 0.34 mmol, 1.4 eq.) was added dropwise to a stirred solution of a 95:5 mixture of α-arylpiperidines **176** in 96:4 dr and 4-OTBDMS-*N*-Boc-piperidine **73** (101 mg, i.e. 96 mg, 0.24 mmol, 1.0 eq. of α-arylpiperidines **176** and 5 mg of 4-OTBDMS-*N*-Boc-piperidine **73** in THF (1 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 5 min. Methylchloroformate (0.03 mL, 0.34 mmol, 1.4 eq.) was added and the resulting solution was stirred at –78 °C for 30 min then at rt for 18 h. Saturated $NH_4Cl_{(aq)}$ (3 mL) and Et_2O (3 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 3 mL) and the combined organics were washed with brine (3 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 9:1 hexane-Et_2O as eluent gave 2,2,4-trisubstituted-*N*-Boc-piperidine *cis*-**241** (57 mg, 50%) as a colourless oil, R_F (4:1 hexane-Et_2O) 0.35; IR (ATR) 2952, 2930, 2890, 2858, 1746 (C=O, CO_2Me), 1698 (C=O, Boc), 1365, 1253, 1172, 1119, 1090, 836, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.14 (m, 5H, Ph), 3.89 (ddd, 1H, *J* = 13.5, 7.0, 4.5 Hz, NCH), 3.83-3.73 (m, 1H, OCH), 3.78 (s, 3H, OMe), 3.43 (ddd, 1H, *J* = 13.5, 9.0, 4.0 Hz, NCH), 2.45 (ddd, 1H, *J*

= 13.5, 4.0, 1.5 Hz, CH), 2.05-1.92 (m, 2H, CH), 1.66-1.55 (m, 1H, CH), 1.12 (s, 9H, $OCMe_3$), 0.75 (s, 9H, $SiCMe_3$), –0.03 (s, 3H, SiMe), –0.07 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.6 (C=O, CO_2Me), 156.4 (C=O, Boc), 142.9 (*ipso*-Ph), 127.8 (Ph), 126.5 (Ph), 125.8 (Ph), 80.4 (O*C*Me_3), 68.4 (Ph*C*N), 65.8 (OCH), 52.4 (OMe), 47.0 (CH_2), 41.3 (NCH_2), 33.6 (CH_2), 27.9 (C*Me*$_3$), 25.8 (SiC*Me*$_3$), 18.1 (Si*C*Me_3), –4.8 (SiMe), –4.9 (SiMe); HRMS (ESI) *m/z* calcd for $C_{24}H_{39}NO_5Si$ $(M + Na)^+$ 472.2490, found 472.2483 (+1.4 ppm error).

Lab book reference: **MTG-2-34**

tert-Butyl-4-((_tert_-butyldimethylsilyl)oxy)-2-methyl-2-phenylpiperidine-1-carboxylate _cis_-242



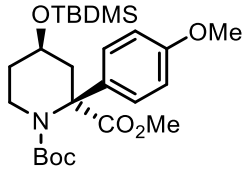
cis-**242**

n-BuLi (2.0 mL of a 2.08 M solution in hexane, 4.21 mmol, 1.3 eq.) was added dropwise to a stirred solution of an 87:13 mixture of α-arylpiperidines **176** in 96:4 dr and 4-OTBDMS-*N*-Boc-piperidine **73** (1.27 g, i.e. 1.09 g, 2.72 mmol, 1.0 eq. of α-arylpiperidines **176** and 141 mg of 4-OTBDMS-*N*-Boc-piperidine **73**, 0.45 mmol, 0.13 eq.) in THF (16 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 15 min. Dimethylsulfate (0.614 mL, 6.48 mmol, 2.0 eq.) was added and the resulting solution was stirred at –78 °C for 30 min then at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (30 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 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 97:3 hexane-EtOAc as eluent gave an 89:11 mixture of 2,2,4-trisubstituted piperidines **242** in 96:4 dr and 4-OTBDMS-*N*-Boc-piperidine **73** (1.25 g, i.e. 1.13 g, 99% of 2,2,4-trisubstituted piperidines **242** and 116 mg of 4-OTBDMS-*N*-Boc-piperidine **73**) as a white solid, R_F (9:1 hexane-EtOAc) 0.45; IR (ATR) 2953, 2929, 2891, 2857, 1688 (C=O), 1387, 1364, 1254, 1168, 1093, 866, 834, 775, 760, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.23 (m, 4H, Ph), 7.19-7.11 (m, 1H, Ph), 4.01 (ddd, *J* = 13.5, 7.0,

4.5 Hz, 1H, NCH), 3.93 (dddd, *J* = 10.5, 7.5, 5.5, 5.0 Hz, 1H, OCH), 3.45 (ddd, *J* = 13.5, 9.5, 4.0 Hz, 1H, NCH), 2.11-2.02 (m, 1H, CH), 1.88-1.79 (m, 1H, CH), 1.73 (ddd, *J* = 13.5, 5.0, 1.5 Hz, 1H, CH), 1.68 (s, 3H, NCMe), 1.67-1.61 (m, 1H, CH), 1.01 (s, 9H, $OCMe_3$), 0.83 (s, 9H, $SiCMe_3$), 0.04 (s, 3H SiMe), 0.00 (s, 3H SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.1 (C=O), 150.9 (*ipso*-Ph), 128.1 (Ph), 125.7 (Ph), 124.2 (Ph), 79.7 (O*C*Me_3), 65.9 (OCH), 60.0 (PhN*C*Me), 51.9 (CH_2), 41.1 (NCH_2), 34.7 (CH_2), 28.0 (OC*Me*$_3$), 25.9 (SiC*Me*$_3$), 21.5 (C*Me*), 18.2 (Si*C*Me_3), –4.6 (SiMe); HRMS (ESI) *m/z* calcd for $C_{23}H_{39}NO_3Si$ $(M + Na)^+$ 428.2591, found 428.2593 (–0.5 ppm error). Diagnostic signals for *trans*-**242**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.61 (s, 9H, $SiCMe_3$) –0.03 (s, 3H, SiMe), –0.05 (s, 3H, SiMe).

Lab book reference: **MTG-3-56**

1-(*tert*-Butyl)-2-methyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(4-methoxyphenyl)piperidine-1,2-dicarboxylate *cis*-243



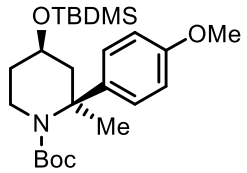
cis-**243**

n-BuLi (0.26 mL of a 2.08 M solution in hexane, 0.54 mmol, 1.3 eq.) was added dropwise to a stirred solution of α-arylpiperidines **179** in 96:4 dr (174 mg, 0.41 mmol, 1.0 eq.) in THF (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 15 min. Methylchloroformate (0.035 mL, 0.45 mmol, 1.1 eq.) was added and the resulting solution was stirred at –78 °C for 30 min then at rt for 14 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 23:2 hexane-EtOAc as eluent gave crude product. Purification by flash column chromatography on silica using 17:3 hexane-Et_2O as eluent gave 2,2,4-trisubstituted piperidines **243** in 91:9 dr (91 mg, 46%) as a white solid, R_F (9:1 hexane-EtOAc) 0.25; IR (ATR) 2952, 2932, 2857, 1744 (C=O, CO_2Me), 1695 (C=O, Boc), 1248, 1171, 1109, 1088, 830, 774, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.16 (m, 2H, Ar), 6.82-

6.76 (m, 2H, Ar), 3.86-3.76 (m, 2H, OCH + NCH), 3.76 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.50 (ddd, *J* = 13.0, 8.0, 4.5 Hz, 1H, NCH), 2.41 (ddd, *J* = 14.0, 4.0, 1.5 Hz, 1H, CH), 2.05-1.90 (m, 2H, CH + CH), 1.58 (dddd, *J* = 12.5, 8.0, 8.0, 4.0 Hz, 1H, CH), 1.17 (s, 9H, CMe_3), 0.73 (s, 9H, $SiCMe_3$), –0.04 (s, 3H SiMe), –0.08 (s, 3H SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.0 (C=O, CO_2Me), 158.2 (*ipso*-Ar), 156.3 (C=O, Boc), 134.7 (*ipso*-Ar), 127.1 (Ar), 113.1 (Ar), 80.4 ($OCMe_3$), 67.6 (ArCN), 65.6 (OCH), 55.4 (OMe), 52.4 (OMe), 46.5 (CH_2), 40.8 (NCH_2), 33.4 (CH_2), 28.0 ($OCMe_3$), 25.8 ($SiCMe_3$), 18.1 ($SiCMe_3$), –4.8 (SiMe), –4.9 (SiMe); HRMS (ESI) *m/z* calcd for $C_{25}H_{41}NO_6Si$ $(M + Na)^+$ 502.2595, found 502.2600 (–1.0 ppm error). Diagnostic signals for *trans*-**243**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08 (ddd, *J* = 13.5, 13.0, 3.5 Hz, NCH), 1.29 (s, 9H, $OCMe_3$), 0.81 (s, 9H, $SiCMe_3$).

Lab book reference: **MTG-3-50**

tert-Butyl-4-((_tert_-butyldimethylsilyl)oxy)-2-(4-methoxyphenyl)-2-methylpiperidine-1-carboxylate _cis_-244



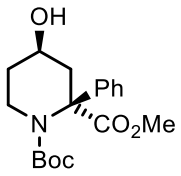
cis-**244**

n-BuLi (1.0 mL of a 2.08 M solution in hexane, 2.08 mmol, 1.3 eq.) was added dropwise to a stirred solution of α-arylpiperidines **179** in 94:6 dr (676 mg, 1.60 mmol, 1.0 eq.) in THF (8 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 15 min. Dimethylsulfate (0.303 mL, 3.21 mmol, 2.0 eq.) was added and the resulting solution was stirred at –78 °C for 30 min then at rt for 18 h. 2 M $NaOH_{(aq)}$ (15 mL) and Et_2O (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organics were washed with brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 9:1 hexane-Et_2O as eluent gave an 86:14 mixture of 2,2,4-trisubstituted piperidines **244** in 94:6 dr and α-arylpiperidine *cis*-**179** (319 mg, i.e. 276 mg (40%) of 2,2,4-trisubstituted piperidines **244** and 44 mg of α-arylpiperidine *cis*-**179**) as a colourless oil, R_F (9:1 hexane-Et_2O)

0.30; IR (ATR) 2954, 2930, 2857, 2892, 1687 (C=O), 1512, 1389, 1364, 1249, 1173, 1096, 832, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 9.0 Hz, 2H, Ar), 6.81 (d, *J* = 9.0 Hz, 2H, Ar), 4.02-3.89 (m, 2H, NCH + OCH), 3.78 (s, 3H, OMe), 3.45 (ddd, *J* = 13.5, 9.5, 4.0 Hz, 1H, NCH), 2.10-2.01 (m, 1H, CH), 1.82 (dd, *J* = 13.5, 10.5 Hz, 1H, CH), 1.74-1.68 (m, 1H, CH), 1.67-1.61 (m, 4H, CH*Me* + CH), 1.05 (s, 9H, CMe_3), 0.83 (s, 9H, $SiCMe_3$), 0.03 (s, 3H SiMe), 0.00 (s, 3H SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.6 (*ipso*-Ar), 156.1 (C=O), 143.2 (*ipso*-Ar), 125.3 (Ar), 113.3 (Ar), 79.6 ($OCMe_3$), 65.9 (OCH), 59.6 (ArMe*C*N), 55.4 (OMe), 52.0 (CH_2), 41.1 (NCH_2), 34.7 (CH_2), 28.1 ($OCMe_3$), 25.9 ($SiCMe_3$), 21.8 (C*Me*), 18.2 ($SiCMe_3$), –4.6 (SiMe); HRMS (ESI) *m/z* calcd for $C_{24}H_{41}NO_4Si$ $(M + Na)^+$ 458.2697, found 458.2698 (–0.2 ppm error). Diagnostic signals for *trans*-**244**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65-2.58 (m, 1H, CH), 3.80 (s, 3H, OMe), 0.87 (s, 9H, $SiCMe_3$).

Lab book reference: **MTG-3-59**

1-(*tert*-Butyl)-4-hydroxy-2-methyl-2-phenylpiperidine-1,2-dicarboxylate *cis*-245



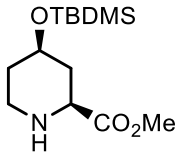
cis-**245**

TBAF (0.32 mL of a 1.00 M solution in THF, 0.32 mmol, 1.5 eq.) was added to a stirred solution of 2,2,4-trisubstituted-piperidine *cis*-**241** (94 mg, 0.21 mmol, 1.0 eq.) in THF (1 mL) under Ar. The resulting solution was stirred at rt for 20 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 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 7:3 hexane-EtOAc then 1:1 hexane-EtOAc as eluent gave 2,2,4-trisubstituted-piperidine *cis*-**245** (28 mg, 40%) as a white solid, mp 114-117 °C; R_F (3:2 hexane-EtOAc) 0.25; IR (ATR) 3429, 2976, 2948, 2874, 1738 (C=O), 1694 (C=O), 1672, 1392, 1366, 1348, 1257, 1228, 1163, 1075, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.27 (m, 4H, Ph), 7.25-7.19 (m, 1H, Ph), 3.93-3.82 (m, 2H, OCH + NCH), 3.77 (s, 3H, OMe), 3.49 (ddd, *J* = 13.5, 9.0, 4.0 Hz, 1H, NCH), 2.57

(ddd, *J* = 13.5, 4.0, 1.0 Hz, 1H, CH), 2.17-2.02 (m, 2H, CH + CH), 1.66-1.55 (m, 1H, CH), 1.45 (s, 1H, OH), 1.17 (s, 9H, $OCMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.5 (C=O, CO_2Me), 156.2 (C=O, Boc), 142.4 (*ipso*-Ph), 128.1 (Ph), 127.0 (Ph), 126.1 (Ph), 80.7 (O*C*Me_3), 67.6 (PhN*C*), 65.1 (OCH), 52.6 (OMe), 45.8 (CH_2), 40.7 (NCH_2), 32.8 (CH_2), 27.9 (OC*Me*$_3$); HRMS (ESI) *m/z* calcd for $C_{18}H_{25}NO_5$ $(M + Na)^+$ 358.1625, found 358.1619 (+1.8 ppm error).

Lab book reference: **MTG-4-44**

4-((*tert*-Butyldimethylsilyl)oxy)-2-methylpiperidine-2-carboxylate *cis*-413



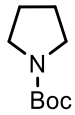
cis-**413**

Trifluoroacetic acid (0.072 mL, 0.94 mmol, 10 eq.) was added dropwise to a stirred solution of 2,4-disubstituted-*N*-Boc-piperidine *cis*-**216** (35 mg, 0.09 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) at rt under Ar. The resulting solution was stirred at rt for 23 h. Saturated $NaHCO_{3(aq)}$ (5 mL) and CH_2Cl_2 (5 mL) were added and the two layers were 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 which contained an 84:16 mixture of 2,4-disubstituted-piperidines *cis*-**413** and *trans*-**413** (by ^1H NMR spectroscopy). Diagnostic signals for *cis*-**413**: ^1H NMR (400 MHz, $CDCl_3$) δ 3.41 (dd, *J* = 10.5, 3.5 Hz, 1H, C(OOME)NCH), 3.21 (ddd, *J* = 13.0, 4.0, 4.0 Hz, 1H, NCH), 2.64 (ddd, *J* = 13.0, 11.0, 3.0 Hz, 1H, NCH), 0.87 (s, 9H, $SiCMe_3$), 0.05 (s, 6H SiMe). Diagnostic signals for *trans*-**413**: ^1H NMR (400 MHz, $CDCl_3$) 2.94 (ddd, *J* = 12.0, 4.0, 4.0 Hz, 1H, NCH), 0.90 (s, 9H, $SiCMe_3$), 0.09 (s, 6H SiMe).

Lab book reference: **MTG-3-115**

4.4 Experimental Procedures Chapter 3

tert-Butylpyrrolidine-1-carboxylate 5

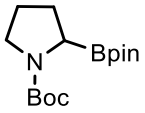


5

Pyrrolidine (1.97 mL, 24 mmol, 1.2 eq.) was added to a stirred solution of di-*tert*-butyl dicarbonate (4.37 g, 20 mmol, 1.0 eq.) in CH_2Cl_2 (50 mL) at rt under air. The resulting solution was stirred at rt for 3 h. 1 M $HCl_{(aq)}$ (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 organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 9:1 hexane-EtOAc as eluent gave *N*-Boc-pyrrolidine **5** (3.21 g, 94%) as a colourless oil, R_F (9:1 hexane-EtOAc) 0.25; IR (ATR) 2939, 2874, 1695 (C=O), 1398, 1365, 1167, 1128, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.36-3.21 (m, 4H, NCH_2), 1.88-1.76 (m, 4H, CH_2), 1.45 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers - 7 of 10 signals were observed) δ 154.8 (C=O), 79.0 (O*C*Me_3), 46.0 (NCH_2), 45.7 (NCH_2), 28.6 (CH_2), 25.8 (CH_2), 25.1 (CH_2); HRMS (ESI) *m/z* calcd for $C_9H_{17}NO_2$ $(M + Na)^+$ 194.1151, found 194.1155 (–1.8 ppm error). Spectroscopic data consistent with those reported in the literature.[143]

Lab book reference: **MTG-5-22**

tert-Butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidine-1-carboxylate 51



51

s-BuLi (9.42 mL of a 1.37 M solution in hexane, 12.9 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc-pyrrolidine **5** (1.69 g, 9.9 mmol, 1.0 eq.) and TMEDA (1.93 mL, 12.9 mmol, 1.3 eq.) in Et_2O (50 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 15 min. *i*-PrOB(pin) (2.63 mL, 12.9 mmol, 1.3 eq.) was added and the resulting solution was stirred at –78 °C for 1 h and then at rt

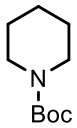
for 17 h. 1 M $HCl_{(aq)}$ (100 mL) and Et_2O (100 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 100 mL) and the combined organics were washed with brine (100 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 17:3 hexane-EtOAc as eluent gave α-Bpin-pyrrolidine **51** (2.10 g, 72%) as a white solid, mp 72-73 °C; R_F (4:1 hexane-EtOAc) 0.5; IR (ATR) 2976, 2935, 2872, 1686, 1412, 1388, 1367, 1335, 1144 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.44-2.88 (m, 3H, BNCH + NCH), 2.04-1.60 (m, 4H, CH), 1.43 (s, 9H, CMe_3), 1.26 (s, 6H, CMe), 1.23 (s, 6H, CMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.1 (C=O), 83.5 (O*C*Me_2), 79.1 (O*C*Me_3), 46.0 (NCH_2), 43.9* (BNCH), 28.6 (C*Me*$_3$), 27.9 (CH_2), 27.3 (CH_2), 25.1 (C*Me*), 24.5 (C*Me*); HRMS (ESI) *m/z* calcd for $C_{15}H_{28}BNO_4$ $(M + Na)^+$ 320.2004, found 320.2005 (+0.4 ppm error). Spectroscopic data consistent with those reported in the literature.[120] *Peak obtained from HMQC, no detectable signal in ^{13}C NMR spectrum.[138]

Lab book reference: **MTG-5-21**

s-BuLi (35.5 mL of a 1.27 M solution in hexane, 45.1 mmol and 10.4 mL of a 1.17 M solution in hexane, 12.1 mmol, 57.2 mmol overall, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc-pyrrolidine **5** (7.53 g, 44.0 mmol, 1.0 eq.) in THF (200 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. *i*-PrOBpin (11.7 mL, 57.2 mmol, 1.3 eq.) was added and the resulting solution was stirred at –78 °C for 30 min and then at rt for 13 h. 1 M $HCl_{(aq)}$ (200 mL) and Et_2O (200 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 200 mL) and the combined organics were washed with brine (200 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by recrystallisation from hot hexane (5 mL) to afford a colourless crystalline solid which was washed with cold hexane (50 mL) and dried under reduced pressure to give α-Bpin-pyrrolidine **51** (5.63 g, 43%) as a colourless crystalline solid. On standing solid crystallised out of the filtrate, which was washed with cold hexane (50 mL) and dried under reduced pressure to give α-Bpin-pyrrolidine **51** (2.81 g, 22%) as a colourless crystalline solid. Overall, this reaction gave α-Bpin-pyrrolidine **51** (8.44 g, 65%).

Lab book reference: **MTG-7-1**

***tert*-Butyl piperidine-1-carboxylate 8**

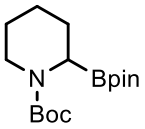


8

Di-*tert*-butyl dicarbonate (4.80 g, 22 mmol, 1.1 eq.) was dissolved in THF (10 mL) at 0 °C and piperidine (1.98 mL, 20 mmol, 1.0 eq.) was added and the resulting solution was stirred at rt for 16 h. Et_2O (20 mL) and saturated $NaHCO_{3(aq)}$ (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organics were washed with brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 97:3 hexane-Et_2O then 4:1 hexane-Et_2O as eluent gave *N*-Boc-piperidine **8** (2.49 g, 67%) as a colourless oil, R_F (9:1 hexane-Et_2O) 0.50; IR (ATR) 2975, 2934, 2855, 1688 (C=O), 1417, 1364, 1268, 1257, 1237, 1175, 1144, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.46-3.23 (m, 4H, NCH_2), 1.61-1.52 (m, 2H, CH_2), 1.52-1.46 (m, 4H, CH_2), 1.41 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.0 (C=O), 79.1 (O*C*Me_3), 44.6 (NCH_2), 28.5 (C*Me*$_3$), 25.8 (CH_2), 24.5 (CH_2); HRMS (ESI) *m/z* calcd for $C_{10}H_{19}NO_2$ $(M + Na)^+$ 208.1308, found 208.1307 (+0.3 ppm error). Spectroscopic data consistent with those reported in the literature.[144]

Lab book reference: **MTG-4-41**

***tert*-Butyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine-1-carboxylate 351**



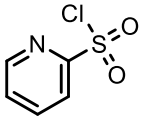
351

s-BuLi (12.7 mL of a 1.37 M solution in hexane, 17.4 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc-piperidine **8** (2.49 g, 13.4 mmol, 1.0 eq.) and TMEDA (2.62 mL, 17.4 mmol, 1.3 eq.) in Et_2O (67 mL) at –78 °C under Ar. The

resulting solution was stirred at –78 °C for 3 h. Distilled *i*-PrOB(pin) (2.74 mL, 13.4 mmol, 1.0 eq.) in Et_2O (2 mL) was added and the resulting solution was stirred at –78 °C for 30 min and then at rt for 18 h. 1 M $HCl_{(aq)}$ (60 mL) and Et_2O (60 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 60 mL) and the combined organics were washed with brine (60 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 4:1 hexane-EtOAc as eluent gave α-Bpin-piperidine **351** (2.22 g, 53%) as a colourless oil, R_F (4:1 hexane-EtOAc) 0.25; IR (ATR) 2972, 2933, 2855, 1610 (C=O), 1528, 1308, 1370, 1160, 1133 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.76-3.69 (m, 1H, NCH), 2.71 (ddd, *J* = 12.5, 12.5, 3.5 Hz, 1H, NCH), 2.33 (dd, *J* = 12.5, 3.5 Hz, 1H, BNCH), 1.85-1.77 (m, 1H, CH), 1.71-1.58 (m, 2H, CH), 1.50 (s, 9H, CMe_3), 1.48-1.39 (m, 1H, CH), 1.39-1.23 (m, 2H, CH), 1.18 (s, 12H, C*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.8 (C=O), 85.8 (O*C*Me_2), 80.0 (O*C*Me_3), 48.1* (BNCH), 42.5 (NCH_2), 28.5 (C*Me*$_3$), 26.6 (CH_2), 25.2 (C*Me*), 25.0 (CH_2), 24.6 (CH_2); HRMS (ESI) *m/z* calcd for $C_{16}H_{30}BNO_4$ $(M + Na)^+$ 334.2160, found 334.2165 (–0.6 ppm error). Spectroscopic data mostly consistent with those reported in the literature.[121] *Peak obtained from HMQC, no detectable signal in ^{13}C NMR spectrum.[138]

Lab book reference: **MTG-4-49**

Pyridine-2-sulfonyl chloride 355



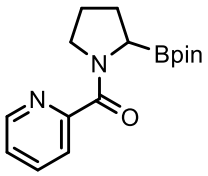
355

A 5% wt solution of $NaOCl_{(aq)}$ (69 mL) was added dropwise over 15 min to a vigorously stirred solution of 2-mercaptopyridine (667 mg, 6.0 mmol, 1.0 eq.) and 12 M $HCl_{(aq)}$ (4.1 mL) in CH_2Cl_2 (30 mL) and water (12.5 mL) at 0 °C under air. The resulting solution was stirred at 0 °C for 15 min. The two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were washed with $NaHCO_{3(aq)}$ (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give pyridine-2-sulfonyl chloride **355** (817 mg, 77%) as a pale yellow oil, R_F (4:1 hexane-EtOAc) 0.25; IR (ATR) 3092, 1581, 1428, 1377, 1186, 573, 553 cm^{-1}; ^1H

NMR (400 MHz, $CDCl_3$) δ 8.85-8.30 (m, 1H, Ar), 8.13-8.09 (m, 1H, Ar), 8.05 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H, Ar), 7.68 (ddd, *J* = 7.5, 4.5, 1.5 Hz, 1H, Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.3 (*ipso*-Ar), 150.8 (Ar), 139.1 (Ar), 129.2 (Ar), 122.0 (Ar); HRMS (ESI) *m/z* calcd for $C_5H_4{}^{35}ClNO_2S$ $(M + Na)^+$ 199.9543, found 199.9542 (+0.8 ppm error). The crude product was used in the next step without further purification (>95% purity by ^1H NMR spectroscopy). Spectroscopic data consistent with those reported in the literature.[145]

Lab book reference: **MTG-4-97**

2-Pyridyl-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-yl]methanone 356



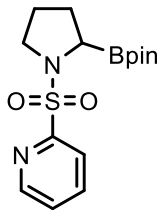
356

Trifluoroacetic acid (5.25 mL, 68.6 mmol, 15 eq.) was added to a stirred solution of α-Bpin-*N*-Boc-pyrrolidine **51** (1.36 g, 4.57 mmol, 1.0 eq.) in CH_2Cl_2 (22.5 mL) at rt under air. The resulting solution was stirred at rt for 3 h. The solvent was evaporated under reduced pressure and the crude product azeotroped with toluene (3 x 45 mL). The solvent was evaporated under reduced pressure to give a colourless oil. The oil and picolinic acid (619 mg, 5.03 mmol, 1.1 eq.) were dissolved in EtOAc (15 mL) and pyridine (7.5 mL) under air. 1-Propanephosphonic anhydride (50% in toluene, 3.38 mL, 9.1 mmol, 2.0 eq.) was added and the resulting solution was stirred at rt for 16 h. 1 M $HCl_{(aq)}$ (45 mL) and EtOAc (45 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 45 mL) and the combined organic layers were washed with brine (45 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 9:1 EtOAc-MeOH as eluent gave α-Bpin-pyrrolidine **356** (996 mg, 69%) as a white solid, mp 158-160 °C; R_F (9:1 EtOAc-MeOH) 0.15; IR (ATR) 3061, 3028, 2939, 1621 (C=O), 1445, 1409, 749, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.08 (dd, *J* = 5.5, 1.5 Hz, 1H, Ar), 8.47 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar), 8.16 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H, Ar),

7.68 (ddd, *J* = 7.5, 5.5, 1.5 Hz, 1H, Ar), 3.82-3.72 (m, 1H, NCH), 3.66-3.53 (m, 1H, NCH), 2.82 (dd, *J* = 11.5, 5.5 Hz, 1H, BNCH), 2.17-1.94 (m, 3H, CH), 1.77-1.61 (m, 1H, CH), 1.25 (s, 6H, CMe), 1.05 (s, 6H, CMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.9 (C=O), 148.4 (*ipso*-Ar), 141.9 (Ar), 141.8 (Ar), 126.4 (Ar), 126.1 (Ar), 80.6 (O*C*Me$_2$), 47.7 (NCH_2), 30.0 (CH_2), 27.2 (C*Me*), 25.9 (C*Me*), 24.4 (CH_2), (BNCH resonance not resolved);[138] HRMS (ESI) *m/z* calcd for $C_{16}H_{23}BN_2O_3$ $(M + Na)^+$ 325.1694, found 325.1696 (+0.2 ppm error).

Lab book reference: **MTG-5-2**

2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-yl]sulfonylpyridine 357



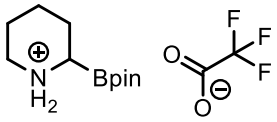
357

Trifluoroacetic acid (2.16 mL, 28.2 mmol, 15 eq.) was added to a stirred solution of α-Bpin-*N*-Boc-pyrrolidine **51** (559 mg, 1.88 mmol, 1.0 eq.) in CH_2Cl_2 (9.5 mL) at rt under air. The resulting solution was stirred at rt for 3 h. The solvent was evaporated under reduced pressure and the crude product azeotroped with toluene (3 x 20 mL). The solvent was evaporated under reduced pressure to give a colourless oil. The oil was dissolved in CH_2Cl_2 (9.5 mL). Then, DMAP (23 mg, 0.19 mmol, 0.1 eq.) and Et_3N (1.05 mL, 7.5 mmol, 4.0 eq.) were added followed by 2-pyridinesulfonyl chloride (434 mg, 2.4 mmol, 1.3 eq.). The resulting solution was stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (20 mL) and CH_2Cl_2 (20 mL) were added and the two layers were separated. The organic layer was washed with H_2O (20 mL) and 1 M $HCl_{(aq)}$ (20 mL). Then, saturated $NaHCO_{3(aq)}$ (20 mL) was added to the organic layer and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (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 7:3 hexane-EtOAc as eluent gave α-Bpin-piperidine **357** (259 mg, 41%) as a white solid, mp 158-

160 °C; R_F (3:2 hexane-EtOAc) 0.20; IR (ATR) 2977, 2890, 1389, 1340, 1170, 1145, 1121, 601, 575 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (dd, *J* = 4.5, 1.5 Hz, 1H, Ar), 7.94 (d, *J* = 7.5 Hz, 1H, Ar), 7.85 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H, Ar), 7.44 (dd, *J* = 7.5, 4.5 Hz, 1H, Ar), 3.61 (ddd, *J* = 10.0, 8.5, 4.0 Hz, 1H, NCH), 3.51 (ddd, *J* = 10.0, 8.0, 6.5 Hz, 1H, NCH), 3.12 (dd, *J* = 9.5, 7.0 Hz, 1H, BNCH), 2.00-1.88 (m, 2H, CH), 1.88-1.76 (m, 1H, CH), 1.73-1.59 (m, 1H, CH), 1.27 (s, 12H, CMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.9 (*ipso*-Ar), 150.0 (Ar), 137.7 (Ar), 126.4 (Ar), 123.3 (Ar), 84.1 (O*C*Me_2), 49.4 (NCH_2), 46.5* (BNCH), 29.0 (CH_2), 26.8 (CH_2), 24.8 (C*Me*), 24.6 (C*Me*); HRMS (ESI) *m/z* calcd for $C_{15}H_{23}BN_2O_4S$ $(M + Na)^+$ 361.1364, found 361.1367 (–0.2 ppm error). *Peak obtained from HMQC, no detectable signal in ^{13}C NMR spectrum.[138]

Lab book reference: **MTG-5-8**

2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)piperidin-1-ium;2,2,2-trifluoroacetate 358

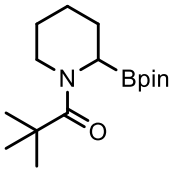


358

Trifluoroacetic acid (1.5 mL, 19.6 mmol, 118 eq.) was added to a stirred solution of α-Bpin-*N*-Boc-piperidine **51** (52 mg, 0.17 mmol, 1.0 eq.) in CH_2Cl_2 (1.5 mL) at rt under air. The resulting solution was stirred at rt for 18 h. The solvent was evaporated under reduced pressure and the crude product azeotroped with toluene (3 x 3 mL). The solvent was evaporated under reduced pressure to give the crude product. Desired product detected by ^1H NMR spectroscopy and HRMS. Diagnostic signals for **358**: ^1H NMR (400 MHz, CD_3CN) δ 3.34-3.22 (m, 1H, NCH), 3.02-2.67 (m, 2H, NCH), 1.59-1.21 (m, 12H, CMe); HRMS (ESI) *m/z* calcd for $C_{11}H_{23}BNO_2$ M^+ 212.1816, found 212.1820 (–0.7 ppm error).

Lab book reference: **MTG-4-39**

2,2-Dimethyl-1-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-piperidyl]propan-1-one 359

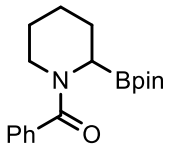


359

Trifluoroacetic acid (13.6 mL, 178 mmol, 25 eq.) was added to a stirred solution of α-Bpin-*N*-Boc-piperidine **351** (2.22 g, 7.1 mmol, 1.0 eq.) in CH_2Cl_2 (27 mL) at rt under air. The resulting solution was stirred at rt for 21 h. The solvent was evaporated under reduced pressure and the crude product azeotroped with toluene (3 x 30 mL). The solvent was evaporated under reduced pressure to give a white solid. The solid was dissolved in CH_2Cl_2 (35 mL). Then, DMAP (87 mg, 0.07 mmol, 0.1 eq.) and Et_3N (4.0 mL, 28.5 mmol, 4.0 eq.) were added followed by the dropwise addition of pivaloylchloride (1.14 mL, 9.3 mmol, 1.3 eq.). The resulting solution was stirred at rt for 17 h. Saturated $NH_4Cl_{(aq)}$ (70 mL) and CH_2Cl_2 (70 mL) were added and the two layers were separated. The organic layer was washed sequentially with H_2O (70 mL) and 1 M $HCl_{(aq)}$ (70 mL) then saturated $NaHCO_{3(aq)}$ (70 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 70 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 α-Bpin-piperidine **359** (1.26 g, 60%) as a white solid, mp 133-134 °C; R_F (EtOAc) 0.40; IR (ATR) 2968, 2933, 2859, 1568 (C=O), 1251, 1186, 1160, 1119, 1099, 1002 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.12-4.04 (m, 1H, NCH), 3.08 (ddd, *J* = 12.5, 12.5, 3.0 Hz, 1H, NCH), 2.31 (dd, *J* = 12.5, 3.5 Hz, 1H, BNCH), 1.84 (ddddd, *J* = 9.0, 3.0, 3.0, 3.0, 3.0 Hz 1H, CH), 1.77-1.65 (m, 2H, CH), 1.55-1.32 (m, 3H, CH), 1.28 (s, 9H, CMe_3), 1.24-0.96 (m, 12H, CMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 178.9 (C=O), 79.5 (O*C*Me_2), 47.2 (NCH_2), 35.5 (*C*Me_3), 27.4 (C*Me*$_3$), 27.4 (CH_2), 27.4 (C*Me*), 26.1 (CH_2), 25.0 (BNCH), 24.7 (CH_2); HRMS (ESI) *m/z* calcd for $C_{16}H_{30}BNO_3$ $(M + Na)^+$ 318.2211, found 318.2213 (+0.4 ppm error).

Lab book reference: **MTG-4-60**

Phenyl-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-piperidyl]methanone 360

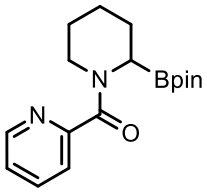


360

Trifluoroacetic acid (5.83 mL, 76 mmol, 50 eq.) was added to a stirred solution of α-Bpin-*N*-Boc-piperidine **351** (474 mg, 1.52 mmol, 1.0 eq.) in CH_2Cl_2 (7.5 mL) at rt under air. The resulting solution was stirred at rt for 22 h. The solvent was evaporated under reduced pressure and the residue was azeotroped with toluene (3 x 15 mL) to give the crude TFA salt as a white solid. The crude TFA salt was dissolved in CH_2Cl_2 (15 mL). Then, DMAP (19 mg, 0.15 mmol, 0.1 eq.) and Et_3N (0.85 mL, 6.1 mmol, 4.0 eq.) were added followed by the dropwise addition of benzoylchloride (0.23 mL, 2.0 mmol, 1.3 eq.). The resulting solution was stirred at rt for 20 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the two layers were separated. The organic layer was washed with H_2O (10 mL) and 1 M $HCl_{(aq)}$ (10 mL). Then, saturated $NaHCO_{3(aq)}$ (10 mL) was added to the organic layer and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (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 α-Bpin-piperidine **360** (444 mg, 93%) as a colourless gum, R_F (EtOAc) 0.55; IR (ATR) 2968, 2935, 2861, 2219, 1592 (C=O), 1570, 1472, 1295, 1188, 1157, 1133, 1114, 1099, 994, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53-7.36 (m, 5H, Ph), 4.00-3.85 (m, 1H, NCH), 3.16 (ddd, *J* = 12.5, 12.5, 3.5 Hz, 1H, NCH), 2.54 (dd, *J* = 13.0, 4.0 Hz, 1H, BNCH), 1.94-1.77 (m, 2H, CH), 1.73-1.55 (m, 2H, CH), 1.52-1.31 (m, 2H, CH), 1.24-1.13 (m, 12H, CMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.7 (C=O), 131.9 (Ph), 128.7 (Ph), 128.7 (Ph), 127.7 (*ipso*-Ph), 79.9 (O*C*Me_2), 46.9 (NCH_2), 27.0 (CH_2), 26.2 (CH_2), 25.4 (BNCH), 25.1 (C*Me*), 24.5 (CH_2); HRMS (ESI) *m/z* calcd for $C_{18}H_{26}BNO_3$ $(M + Na)^+$ 338.1898, found 338.1896 (+1.7 ppm error).

Lab book reference: **MTG-4-50**

2-Pyridyl-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-piperidyl]methanone 361

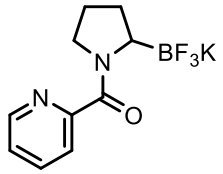


361

Trifluoroacetic acid (2.32 mL, 30.3 mmol, 10 eq.) was added to a stirred solution of α-Bpin-*N*-Boc-piperidine **351** (944 mg, 3.03 mmol, 1.0 eq.) in CH_2Cl_2 (15 mL) at rt under air. The resulting solution was stirred at rt for 21 h. The solvent was evaporated under reduced pressure and the crude product azeotroped with toluene (3 x 30 mL). The solvent was evaporated under reduced pressure to give a white solid. The solid and picolinic acid (441 mg, 3.34 mmol, 1.1 eq.) were dissolved in EtOAc (10.2 mL) and pyridine (4.8 mL) under air. 1-Propanephosphonic anhydride (50% in toluene, 2.25 mL, 6.07 mmol, 2.0 eq.) was added and the resulting solution was stirred at rt for 23 h. 1 M $HCl_{(aq)}$ (15 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 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 EtOAc as eluent gave crude product. Purification by flash column chromatography on silica using 10:9:1 hexane-EtOAc-MeOH as eluent gave α-Bpin-piperidine **361** (338 mg, 90% pure with unknown impurities by ^{1}H NMR spectroscopy, 39%) as a white solid, mp 128-129 °C; R_F (EtOAc) 0.25; IR (ATR) 2969, 2934, 2857, 1606 (C=O), 1566, 1158, 1139, 1117, 996 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (dd, *J* = 5.0, 1.5 Hz, 1H, Ar), 8.06 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar), 7.82 (ddd, *J* = 8.0, 8.0, 1.5 Hz, 1H, Ar), 7.40 (ddd, *J* = 8.0, 5.0, 1.5 Hz, 1H, Ar), 5.34-5.20 (m, 1H, NCH), 3.17 (ddd, *J* = 13.0, 12.5, 3.5 Hz, 1H, NCH), 2.59 (dd, *J* = 13.0, 3.5 Hz, 1H, BNCH), 1.91-1.61 (m, 4H, CH), 1.58-1.42 (m, 2H, CH), 1.21 (m, 12H, CMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.8 (C=O), 148.5 (Ar), 147.5 (*ipso*-Ar), 137.1 (Ar), 127.2 (Ar), 126.4 (Ar), 79.9 (O*C*Me$_2$), 52.6* (BNCH), 47.2 (NCH_2), 27.5 (CH_2), 26.3 (CH_2), 25.4 (C*Me$_2$*), 25.1 (C*Me*), 24.7 (CH_2); HRMS (ESI) *m/z* calcd for $C_{17}H_{25}BN_2O_3$ $(M + Na)^+$ 339.1850, found 339.1847 (+1.9 ppm error). *Peak obtained from HMQC, no detectable signal in ^{13}C NMR spectrum.[138]

Lab book reference: **MTG-4-84**

2-Pyridyl-[2-(potassium trifluoroborate)pyrrolidin-1-yl]methanone 362

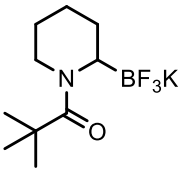


362

α-Bpin-pyrrolidine **51** (316 mg, 1.0 mmol, 1.0 eq.), KF (232 mg, 4.0 mmol, 4.0 eq.) and L-(+)-tartaric acid (308 mg, 2.05 mmol, 2.05 eq.) were dissolved in THF (2 mL), water (2.1 mL) and MeCN (5 mL) under air. The resulting solution was stirred at rt for 18 h. The solids were removed by filtration and washed with MeCN (20 mL). The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 3:7 hexane-EtOAc then EtOAc as eluent gave α-BF_3K-pyrrolidine **362** (167 mg, 59%) as a white solid, mp 154-155 °C; R_F (EtOAc) 0.35; IR (ATR) 3091, 2967, 2876, 1659 (C=O), 1611, 1574, 1433, 1127, 1105, 1088, 1066, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.81 (dd, *J* = 5.5, 1.5 Hz, 1H, Ar), 8.58 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar), 8.32 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H, Ar), 7.84 (ddd, *J* = 7.5, 5.5, 1.5 Hz, 1H, Ar), 3.81-3.70 (m, 1H, NCH), 3.68-3.55 (m, 1H, NCH), 3.01-2.79 (m, 1H, BNCH), 2.35-2.08 (m, 2H, CH), 1.99 (dddd, *J* = 12.0, 12.0, 12.0, 7.0 Hz, 1H, CH), 1.90-1.73 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.9 (C=O), 146.9 (*ipso*-Ar), 143.5 (Ar), 141.1 (Ar), 141.0 (Ar), 127.5 (Ar), 126.9 (Ar), 47.4 (NCH_2), 27.9 (CH_2), 24.8 (CH_2) (BNCH resonance not resolved);[138] HRMS (ESI) *m/z* calcd for $C_{10}H_{11}BF_2N_2O$ $(M - F + Na)^+$ 247.0825, found 247.0828 (–0.6 ppm error).

Lab book reference: **MTG-5-13**

2,2-Dimethyl-1-[2-(potassium trifluoroborate)-1-piperidyl]propan-1-one 363



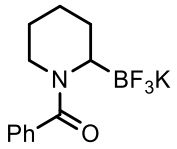
363

α-Bpin-piperidine **359** (443 mg, 1.5 mmol, 1.0 eq.), KF (349 mg, 6.0 mmol, 4.0 eq.) and L-(+)-tartaric acid (462 mg, 3.08 mmol, 2.05 eq.) were dissolved in THF (1.5 mL),

water (1.6 mL) and MeCN (3.8 mL) under air. The resulting solution was stirred at rt for 17 h. The solids were removed by filtration and washed with MeCN (50 mL). The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 4:1 hexane-EtOAc as eluent gave α-BF_3K-piperidine **363** (117 mg, 28%) as a white solid, mp 128-129 °C; R_F (7:3 hexane-EtOAc) 0.35; IR (ATR) 2994, 2942, 2864, 1584 (C=O), 1115, 1001, 906, 725, 648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.25-4.06 (m, 1H, NCH), 3.19 (ddd, *J* = 12.5, 12.5, 3.5 Hz, 1H, NCH), 2.57-2.37 (m, 1H, BNCH), 1.94-1.75 (m, 3H, CH), 1.52-1.39 (m, 3H, CH), 1.34 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 180.0 (C=O), 54.1 (br, BNCH), 47.5 (NCH_2), 35.7 (*C*Me_3), 27.4 (C*Me*$_3$), 26.8 (CH_2), 26.1 (CH_2), 24.0 (CH_2); HRMS (ESI) *m/z* calcd for $C_{10}H_{18}BF_2NO$ $(M - F + Na)^+$ 240.1342, found 240.1343 (+0.4 ppm error) and recovered α-Bpin-piperidine **363** (280 mg, 63%) as a white solid.

Lab book reference: **MTG-4-62**

Phenyl-[2-(potassium trifluoroborate)-1-piperidyl]methanone 364



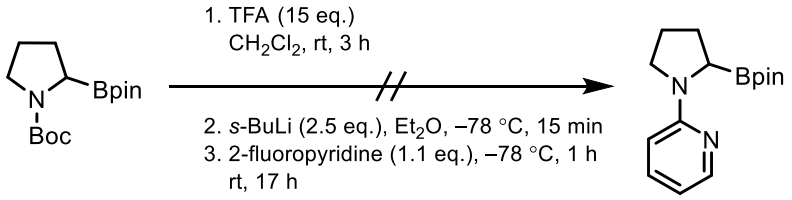
364

α-Bpin-piperidine **360** (268 mg, 0.85 mmol, 1.0 eq.), KF (198 mg, 3.40 mmol, 4.0 eq.) and L-(+)-tartaric acid (262 mg, 1.74 mmol, 2.05 eq.) were dissolved in THF (1.3 mL), water (1.4 mL) and MeCN (3.4 mL) under air. The resulting mixture was stirred at rt for 20 h. The solids were removed by filtration and washed with MeCN (20 mL). The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 7:3 hexane-EtOAc as eluent gave α-BF_3K-piperidine **364** (112 mg, 45%) as a white solid, mp 128-130 °C; R_F (7:3 hexane-EtOAc) 0.40; IR (ATR) 2936, 2859, 1612, 1598 (C=O), 1462, 1297, 1137, 1111, 994, 796, 719, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68-7.44 (m, 5H, Ph), 4.14-4.02 (m, 1H, NCH), 3.31 (ddd, *J* = 12.5, 12.5, 3.5 Hz, 1H, NCH), 2.81-2.64 (m, 1H, BNCH), 2.04-1.74 (m, 3H, CH), 1.70-1.41 (m, 3H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.0 (C=O), 133.1 (Ph), 129.0 (Ph), 128.9 (Ph), 125.8 (*ipso*-Ph), 47.2 (NCH_2), 26.4 (CH_2),

26.2 (CH_2), 23.7 (CH_2), (BNCH resonance not resolved);[138] HRMS (ESI) *m/z* calcd for $C_{12}H_{14}BF_3NO$ $(M)^-$ 256.1115, found 256.1115 (+1.1 ppm error).

Lab book reference: **MTG-4-57**

Attempted synthesis of 2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-yl]pyridine 342

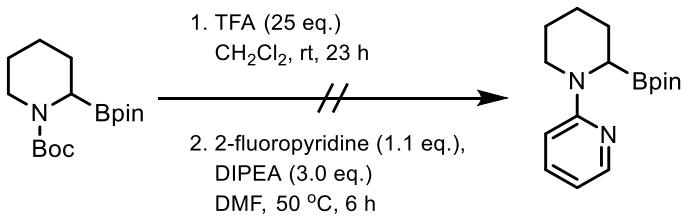


51 **342**

Trifluoroacetic acid (1.15 mL, 15 mmol, 15 eq.) was added to a stirred solution of α-Bpin-*N*-Boc-pyrrolidine **51** (297 mg, 1.0 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL) at rt under air. The resulting solution was stirred at rt for 3 h. The solvent was evaporated under reduced pressure and the crude product azeotroped with toluene (3 x 5 mL). The solvent was evaporated under reduced pressure to give a colourless oil. The oil was dissolved in Et_2O (5 mL) at –78 °C under Ar and *s*-BuLi (1.89 mL of a 1.32 M solution in hexane, 2.5 mmol, 2.5 eq.) was added. The resulting solution was stirred at –78 °C for 15 min. 2-Fluoropyridine (0.095 mL, 1.1 mmol, 1.1 eq.) was added and the resulting solution was stirred at –78 °C for 1 h and then at rt for 17 h. 1 M $HCl_{(aq)}$ (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained trace amounts of α-Bpin-pyrrolidine **342** (by HRMS).

Lab book reference: **MTG-5-35**

Attempted synthesis of 2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-piperidyl]pyridine 366

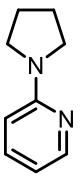


351 **366**

Trifluoroacetic acid (0.96 mL, 12.5 mmol, 25 eq.) was added to a stirred solution of α-Bpin-*N*-Boc-piperidine **351** (156 mg, 5.0 mmol, 1.0 eq.) in CH_2Cl_2 (2.5 mL) at rt under air. The resulting solution was stirred at rt for 19 h. The solvent was evaporated under reduced pressure and the crude product azeotroped with toluene (3 x 5 mL). The solvent was evaporated under reduced pressure to give a white solid. The solid was dissolved in DMF (2.5 mL) and DIPEA (0.261 mL, 1.5 mmol, 3.0 eq.) and 2-fluoropyridine (0.047 mL, 0.55 mmol, 1.1 eq.) were added. The resulting solution was stirred and heated at 50 °C for 6 h. Saturated $NaHCO_{3(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 x 5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of α-Bpin-piperidine **366** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-4-75**

2-Pyrrolidin-1-ylpyridine 365



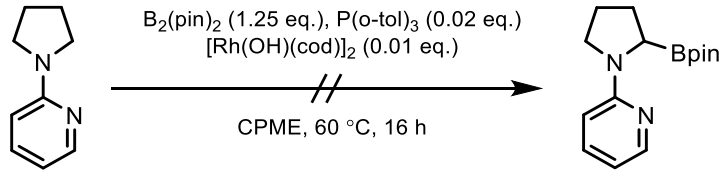
365

n-BuLi (8.7 mL of a 2.3 M solution in hexane, 20 mmol, 1.0 eq.) was added dropwise to a stirred solution of pyrrolidine (1.64 mL, 20 mmol, 1.0 eq.) in THF (16 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 15 min. Then, a solution of degassed 2-fluoropyridine (1.89 mL, 22 mmol, 1.1 eq.) in THF (4 mL) was added dropwise and the resulting solution was stirred at rt for 1 h. Water (20 mL) was added

and the two layers were separated. The aqueous layer was extracted with 1:1 THF-Et_2O (3 x 80 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 4:1 hexane-EtOAc as eluent gave pyrrolidine **365** (2.31 g, 78%) as a colourless oil, R_F (4:1 hexane-EtOAc) 0.40; IR (ATR) 2967, 2851, 1594, 1496, 1479, 1460, 1440, 1384, 1299, 992, 766, 732, 467 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14-8.10 (m, 1H, Ar), 7.38 (ddd, *J* = 8.5, 7.0, 2.0 Hz, 1H, Ar), 6.47 (dd, *J* = 7.0, 5.0 Hz, 1H, Ar), 6.31 (d, *J* = 8.5 Hz, 1H, Ar), 3.48-3.34 (m, 4H, NCH_2), 2.02-1.91 (m, 4H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.4 (*ipso*-Ar), 148.3 (Ar), 137.0 (Ar), 111.1 (Ar), 106.5 (Ar), 46.7 (NCH_2), 25.6 (CH_2); HRMS (ESI) *m/z* calcd for $C_9H_{12}N_2$ $(M + H)^+$ 149.1073, found 149.1072 (+0.9 ppm error). Spectroscopic data consistent with those reported in the literature.[146]

Lab book reference: **MTG-5-44**

Attempted synthesis of 2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-yl]pyridine 342

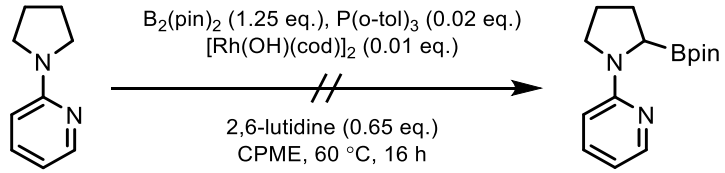


365 **342**

P(*o*-tol)$_3$ (6.1 mg, 0.02 mmol, 0.02 eq.) and $B_2(pin)_2$ (317 mg, 1.25 mmol, 1.25 eq.) were dissolved in degassed CPME (3 mL) at rt under Ar. Then, a solution of $[Rh(OH)(cod)]_2$ (4.6 mg, 0.01 mmol, 0.01 eq.) in CPME (3 mL) was added and the resulting solution was stirred at rt for 2 min. Then, pyrrolidine **365** (162 mg, 1.0 mmol, 1.0 eq.) was added. The resulting solution was stirred at 60 °C for 16 h. After being allowed to cool to rt, the solids were removed by filtration and the filtrate was evaporated under reduced pressure to give the crude product which contained none of α-Bpin-pyrrolidine **342** (by ^1H NMR spectroscopy and HRMS).

Lab book reference: **MTG-5-28**

Attempted synthesis of 2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-yl]pyridine 342

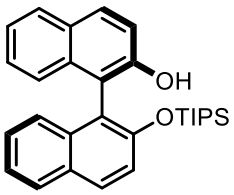


365 **342**

P(*o*-tol)$_3$ (6.1 mg, 0.02 mmol, 0.02 eq.) and $B_2(pin)_2$ (317 mg, 1.25 mmol, 1.25 eq.) were dissolved in degassed CPME (3 mL) at rt under Ar. Then, a solution of $[Rh(OH)(cod)]_2$ (4.6 mg, 0.01 mmol, 0.01 eq.) in CPME (3 mL) was added and the resulting solution was stirred at rt for 2 min. Then, 2,6-lutidine (0.076 mL, 0.65 mmol, 0.65 eq.) and pyrrolidine **365** (162 mg, 1.0 mmol, 1.0 eq.) were added. The resulting solution was stirred at 60 °C for 16 h. After being allowed to cool to rt, the solids were removed by filtration and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 9:1 hexane-EtOAc then 4:1 hexane-EtOAc as eluent gave none of α-Bpin-pyrrolidine **342** (by ^{1}H NMR spectroscopy and HRMS) and recovered pyrrolidine **365** (115 mg, 36%) as a colourless oil.

Lab book reference: **MTG-5-29**

(*R*)-1-(2-Triisopropylsilyoxy-1-naphthyl)naphthalen-2-ol (*R*)-373



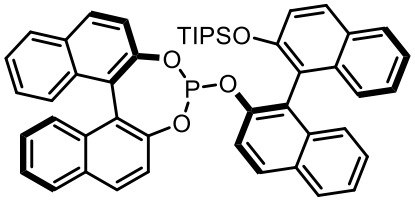
(*R*)-**373**

Triethylamine (0.77 mL, 5.5 mmol, 1.1 eq.) and triisopropylsilyl chloride (1.18 mL, 5.5 mmol, 1.1 eq.) were added to a stirred solution of (*R*)-BINOL **372** (1.43 g, 5.0 mmol, 1.0 eq.) in CH_2Cl_2 (25 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 17 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organics were

washed with brine (25 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 4:1 hexane-CH_2Cl_2 as eluent gave (*R*)-BINOL mono-TIPS (*R*)-**373** (2.17 g, 95%) as a colourless gum, R_F (9:1 hexane-EtOAc) 0.40; IR (ATR) 3541 (OH), 3443 (OH), 2944, 2892, 2866, 1000, 810, 746, 684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 9.0 Hz, 1H, Ar), 7.78-7.85 (m, 2H, Ar), 7.83 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar), 7.39-7.23 (m, 6H, Ar), 7.20 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H, Ar), 7.11 (dd, *J* = 9.0, 1.0 Hz, 1H, Ar), 4.99 (s, 1H, OH), 1.11-0.95 (m, 3H, SiCH), 0.82 (d, *J* = 7.5 Hz, 9H, SiCMe), 0.76 (d, *J* = 7.5 Hz, 9H, SiCMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.8 (*ipso*-Ar), 151.4 (*ipso*-Ar), 134.5 (*ipso*-Ar), 133.9 (*ipso*-Ar), 130.7 (Ar), 129.7 (Ar), 129.4 (*ipso*-Ar), 129.3 (*ipso*-Ar), 128.2 (Ar), 128.0 (Ar), 127.2 (Ar), 126.2 (Ar), 125.3 (Ar), 125.2 (Ar), 124.1 (Ar), 123.2 (Ar), 120.6 (Ar), 117.5 (Ar), 117.2 (*ipso*-Ar), 115.8 (*ipso*-Ar), 17.7 (SiC*Me*), 17.7 (SiCH*Me*), 12.9 (Si*C*HMe); HRMS (ESI) *m/z* calcd for $C_{29}H_{34}O_2Si$ $(M + Na)^+$ 465.2220, found 465.2217 (+0.8 ppm error).

Lab book reference: **MTG-5-60**

[1-[2-(12,14-dioxa-13-phosphapentacyclo[13.8.0.02,11.03,8.018,23]tricosa-1(15),2(11),3,5,7,9,16,18,20,22-decaen-13-yloxy)-1-naphthyl]-2-naphthyl]oxy-triisopropyl-silane (*R*,*R*)-370



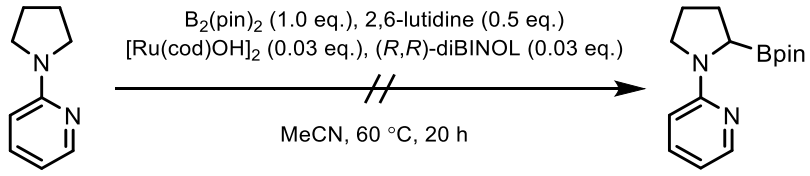
(*R*,*R*)-**370**

Phosphorus trichloride (3.49 mL, 40 mmol, 10 eq.) and DMF (8 μL, 0.1 mmol, 0.025 eq.) were added to (*R*)-BINOL (1.15 g, 4 mmol, 1.0 eq.) at rt under Ar. The resulting solution was stirred at 50 °C for 30 min. After being allowed to cool to rt, the solvent and excess phosphorus trichloride were evaporated under reduced pressure and the solid azeotroped with toluene (8 mL) to give a white solid. The white solid was dissolved in toluene (20 mL) followed by the addition of triethylamine (1.67 mL, 12 mmol, 3.0 eq.) and a solution of (*R*)-BINOL mono-TIPS (*R*)-**373** (1.77 g, 4 mmol, 1.0 eq.) in toluene (10 mL) at 0 °C. The resulting solution was allowed to warm to rt and then stirred and

heated at 80 °C for 90 min. After being allowed to cool to rt, the solution was stirred at rt for 1 h. The reaction had not gone to completion and was therefore stirred and heated at 80 °C for 17 h. After being allowed to cool to rt, the solids were removed by filtration through a pad of Celite® and were washed with EtOAc (20 mL). The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica using 9:1 hexane-EtOAc as eluent gave crude product. Purification by flash chromatography on silica using 93:7 hexane-acetone as eluent gave crude product. Purification by flash chromatography on silica using 97:3 hexane-EtOAc as eluent gave (*R*,*R*)-diBINOL monophosphite (*R*,*R*)-**370** (2.46 g, 81%) as a white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.0 Hz, 1H, Ar), 8.01-7.80 (m, 6H, Ar), 7.67 (d, *J* = 9.0 Hz, 1H, Ar), 7.58 (d, *J* = 9.0 Hz, 1H, Ar), 7.48-7.15 (m, 14H, Ar), 6.38 (d, *J* = 8.5 Hz, 1H, Ar), 1.07-0.93 (m, 3H, SiCH), 0.90-0.50 (m, 18H, SiCMe); HRMS (ESI) *m/z* calcd for $C_{49}H_{45}O_4PSi$ $(M + Na)^+$ 779.2717, found 779.2733 (–2.1 ppm error). Spectroscopic data consistent with those reported in the literature.[26]

Lab book reference: **MTG-5-50**

Attempted synthesis of 2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-yl]pyridine 342

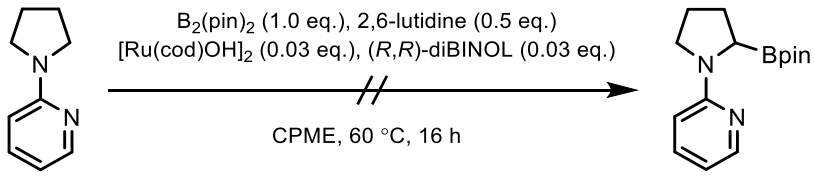


365 **342**

diBINOL monophosphite (*R*,*R*)-**370** (11.4 mg, 0.015 mmol, 0.03 eq.) and $B_2(pin)_2$ (127 mg, 0.50 mmol, 1.0 eq.) were dissolved in degassed MeCN (1.5 mL) at rt under Ar. Then, a solution of $[Rh(OH)(cod)]_2$ (3.4 mg, 0.0075 mmol, 0.015 eq., 0.015 mmol Rh) in MeCN (1 mL) was added and the resulting solution was stirred at rt for 2 min. Then, pyrrolidine **365** (0.14 mL, 0.50 mmol, 1.0 eq.) and 2,6-lutidine (0.029 mL, 0.25 mmol, 0.50 eq.) were added. The resulting solution was stirred at 60 °C for 20 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give the crude product which contained none of α-Bpin-pyrrolidine **342** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-5-52**

Attempted synthesis of 2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-yl]pyridine 342

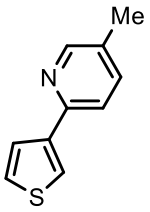


365 **342**

diBINOL monophosphite (*R*,*R*)-**370** (11.4 mg, 0.015 mmol, 0.03 eq.) and $B_2(pin)_2$ (127 mg, 0.50 mmol, 1.0 eq.) were dissolved in degassed CPME (1.5 mL) at rt under Ar. Then, a solution of $[Rh(OH)(cod)]_2$ (3.4 mg, 0.0075 mmol, 0.015 eq., 0.015 mmol Rh) in CPME (1 mL) was added and the resulting solution was stirred at rt for 2 min. Then, pyrrolidine **365** (0.14 mL, 0.50 mmol, 1.0 eq.) and 2,6-lutidine (0.029 mL, 0.25 mmol, 0.50 eq.) were added. The resulting solution was stirred at 60 °C for 16 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give the crude product which contained trace amounts of α-Bpin-pyrrolidine **342** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-5-54**

5-Methyl-2-(3-thienyl)pyridine 371



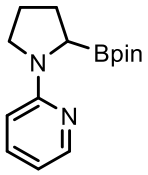
371

3-Bromothiophene (0.47 mL, 5.0 mmol, 1.0 eq.) was added to $B_2(pin)_2$ (1.27 g, 5.0 mmol, 1.0 eq.), KOAc (980 mg, 10.0 mmol, 2.0 eq.) and $PdCl_2$•dppf (92 mg, 0.125 mmol, 0.025 eq.), the reagents were then dissolved in THF (25 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred at 100 °C for 16 h. After being allowed to cool to rt, the solids were evaporated by filtration through a pad of Celite® and were washed with EtOAc (25 mL). The filtrate was evaporated under

reduced pressure to give the crude 3-Bpin-thiophene **374** (≥95% purity by ^{1}H NMR spectroscopy)as a dark brown solid. The crude 3-Bpin-thiophene **374** (5.0 mmol assumed, 1.0 eq.), 2-bromo-5-methylpyridine (860 mg, 5.0 mmol, 1.0 eq.), K_2CO_3 (1.38 g, 10 mmol, 2.0 eq.) and $Pd(PPh_3)_4$ (289 mg, 0.25 mmol, 0.05 eq.) were dissolved in DME (20 mL) and water (20 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 19 h. After being allowed to cool to rt, water (25 mL) and EtOAc (25 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 washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica using 19:1 hexane-EtOAc as eluent gave 5-methyl-2-(3-thienyl)pyridine **371** (571 mg, 65%) as an off-white solid, mp 41-42 °C; R_F (47:3 hexane-EtOAc) 0.15; IR (ATR) 3094, 2995, 2924, 1473, 789, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H, Ar), 7.84 (dd, *J* = 3.0, 1.5 Hz, 1H, Ar), 7.63 (dd, *J* = 5.0, 1.5 Hz, 1H, Ar), 7.53-7.47 (m, 2H, Ar), 7.37 (dd, *J* = 5.0, 3.0 Hz, 1H, Ar), 2.33 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 151.0 (*ipso*-Ar), 150.0 (Ar), 142.2 (*ipso*-Ar), 137.4 (Ar), 131.4 (*ipso*-Ar), 126.3 (Ar), 126.3 (Ar), 122.9 (Ar), 120.0 (Ar), 18.3 (Me); HRMS (ESI) *m/z* calcd for $C_{10}H_9NS$ $(M + H)^+$ 176.0528, found 176.0528 (0.0 ppm error). Spectroscopic data consistent with those reported in the literature.[128]

Lab book reference: **MTG-5-55** and **MTG-5-56**

2-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-yl]pyridine 342



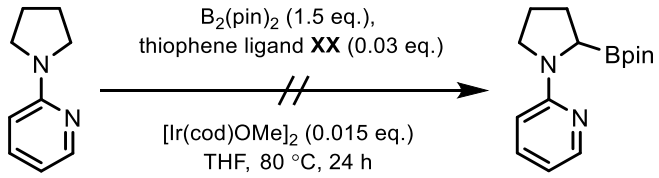
342

Pyrrolidine **365** (74 mg, 0.5 mmol, 1.0 eq.), $Ru(O_2CMes)_2$(*p*-cymene) (28 mg, 0.05 mmol, 0.1 eq.) and $B_2(pin)_2$ (191 mg, 0.75 mmol, 1.5 eq.) were dissolved in degassed 1,4-dioxane (2 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 110 °C for 8 h. After being allowed to cool

to rt, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on neutral aluminium oxide using 19:1 hexane-EtOAc then 9:1 hexane-EtOAc then 4:1 hexane-EtOAc as eluent gave a 63:37 mixture of α-Bpin-pyrrolidine **342** and 2,5-diBpin-pyrrolidine **375** (31 mg, approximately 50% pure with unknown impurities by ^{1}H NMR spectroscopy, i.e. 10 mg (7%) of α-Bpin-pyrrolidine **342** and 6 mg (4%) of 2,5-diBpin-pyrrolidine **375**) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 6.0, 1.5 Hz, 1H, Ar), 7.49 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Ar), 6.52 (ddd, *J* = 7.0, 6.0, 1.0 Hz, 1H, Ar), 6.41 (dd, *J* = 8.5, 1.0 Hz, 1H, Ar), 3.52-3.40 (m, 1H), 3.15-3.03 (m, 1H), 2.76 (ddd, *J* = 12.0, 6.0, 2.5 Hz, 1H), 2.14-2.03 (m, 1H), 2.03-1.90 (m, 1H), 1.87-1.74 (m, 1H), 1.55-1.40 (m, 1H), 1.26-1.22 (m, 12H, CMe); HRMS (ESI) *m/z* calcd for $C_{15}H_{24}BN_2O_2$ $(M + H)^+$ 275.1925, found 275.1932 (–1.5 ppm error). Diagnostic signals for **375**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 1.0 Hz, 1H, Ar), 7.78 (d, *J* = 8.5, 1.5 Hz, 1H, Ar), 6.35 (d, *J* = 8.5, 1.0 Hz, 1H, Ar), 1.29-1.26 (m, 12H, CMe).

Lab book reference: **MTG-5-45**

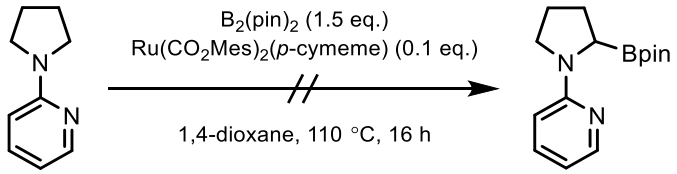
Attempted synthesis of 2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-yl]pyridine 342



365 **342**

In a glove box, $B_2(pin)_2$ (381 mg, 1.5 mmol, 1.5 eq.), thiophene ligand **371** (5.3 mg, 0.03 mmol, 0.03 eq.) and $[Ir(cod)OMe]_2$ (10.1 mg, 0.015 mmol, 0.015 eq.) were added to a pressure tube. The tube was sealed with a suba seal and removed from the glove box. THF (5 mL) was added and the resulting solution was stirred at rt for 2 min. Then, pyrrolidine **365** (0.139 mL, 1.0 mmol, 1.0 eq.) was added and the pressure tube sealed. The resulting solution was stirred and heated at 80 °C for 24 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give the crude product which contained a 92:8 mixture of pyrrolidine **365** and α-Bpin-pyrrolidine **342** (by ^{1}H NMR spectroscopy).

Lab book reference: **MTG-5-58**

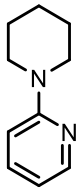


365 **342**

Pyrrolidine **365** (74 mg, 0.5 mmol, 1.0 eq.), $Ru(O_2CMes)_2$(*p*-cymene) (28 mg, 0.05 mmol, 0.1 eq.) and $B_2(pin)_2$ (191 mg, 0.75 mmol, 1.5 eq.) were dissolved in degassed 1,4-dioxane (2 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 110 °C for 16 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on neutral aluminium oxide using 19:1 hexane-EtOAc then 9:1 hexane-EtOAc then 4:1 hexane-EtOAc as eluent gave trace amounts of α-Bpin-pyrrolidine **342** (<1 mg) (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-5-47**

2-(1-Piperidyl)pyridine 367



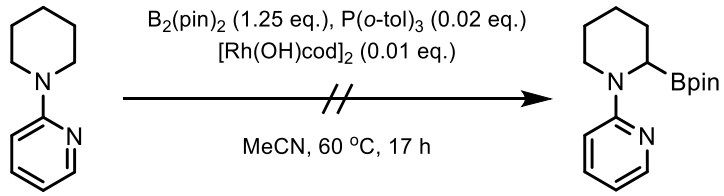
367

n-BuLi (3.14 mL of a 1.59 M solution in hexane, 5.0 mmol, 1.0 eq.) was added dropwise to a stirred solution of piperidine (0.50 mL, 5.0 mmol, 1.0 eq.) in THF (4.0 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 15 min. Then, a solution of 2-fluoropyridine (0.47 mL, 5.5 mmol, 1.1 eq.) in THF (3 mL) was added dropwise and the resulting solution was stirred at rt for 1 h. Water (5 mL) was added and the two layers were separated. The aqueous layer was extracted with 1:1 THF-Et_2O (4 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 19:1 hexane-EtOAc as eluent gave piperidine **367** (643 mg, 79%) as a colourless oil, R_F (19:1 hexane-EtOAc) 0.25; IR (ATR) 3005, 2931,

2852, 1594, 1482, 1437, 1310, 1245, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 5.0, 2.0 Hz, 1H, Ar), 7.43 (ddd, *J* = 8.5, 7.0, 2.0 Hz, 1H, Ar), 6.64 (d, *J* = 8.5 Hz, 1H, Ar), 6.54 (dd, *J* = 7.0, 5.0 Hz, 1H, Ar), 3.58-3.45 (m, 4H, NCH_2), 1.69-1.57 (m, 6H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.8 (*ipso*-Ar), 148.0 (Ar), 137.4 (Ar), 112.5 (Ar), 107.2 (Ar), 46.4 (NCH_2), 25.6 (CH_2), 24.8 (CH_2); HRMS (ESI) *m/z* calcd for $C_{10}H_{14}N_2$ $(M + H)^+$ 163.1230, found 163.1232 (–1.6 ppm error). Spectroscopic data consistent with those reported in the literature.[147]

Lab book reference: **MTG-4-78**

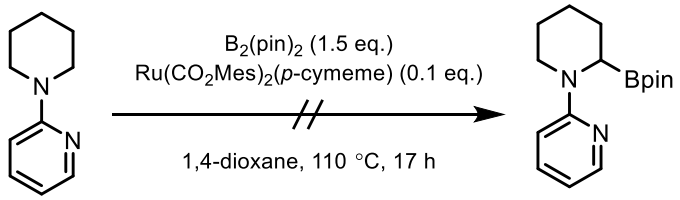
Attempted synthesis of 2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-piperidyl]pyridine 366



367 **366**

B_2pin_2 (159 mg, 0.63 mmol, 1.25 eq.), P(*o*-tol)$_3$ and piperidine **367** (81 mg, 0.50 mmol, 1.0 eq.) were dissolved in MeCN (1.5 mL) in a pressure tube at rt under Ar. In a separate flask, $[Rh(OH)cod]_2$ (2.3 mg, 0.01 mmol, 0.02 eq.) was dissolved in MeCN (1.0 mL) at rt under Ar. The catalyst solution was added to the pressure tube and the tube was sealed and the resulting solution was stirred and heated at 60 °C for 17 h. After being allowed to cool to rt, the solids were removed by filtration and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 19:1 hexane:EtOAc as eluent gave none of α-Bpin-piperidine **366** (by ^{1}H NMR spectroscopy and HRMS) and piperidine **367** (61 mg, 75%) as a colourless oil.

Lab book reference: **MTG-4-85**

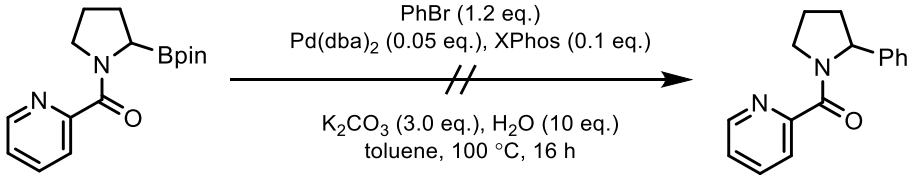


367 **366**

Piperidine **367** (81 mg, 0.5 mmol, 1.0 eq.), $Ru(O_2CMes)_2$(*p*-cymene) (28 mg, 0.05 mmol, 0.1 eq.) and B_2pin_2 (191 mg, 0.5 mmol, 1.5 eq.) were dissolved in degassed 1,4-dioxane (2 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 110 °C for 17 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give the crude product which contained trace amounts of α-Bpin-piperidine **366** (<1 mg) (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-5-57**

Attempted synthesis of (2-phenylpyrrolidin-1-yl)-(2-pyridyl)methanone 380

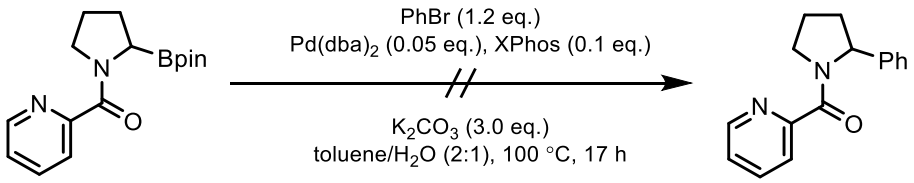


356 **380**

Bromobenzene (0.025 mL, 0.24 mmol, 1.2 eq.) was added to a stirred solution of α-Bpin-piperidine **356** (60 mg, 0.20 mmol, 1.0 eq.), $Pd(dba)_2$ (5.8 mg, 0.01 mmol, 0.05 eq.), XPhos (9.5 mg, 0.02 mmol, 0.1 eq.), K_2CO_3 (83 mg, 0.60 mmol, 3.0 eq.) and water (0.036 mL, 2.0 mmol, 10.0 eq.) in toluene (1 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 16 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 1:1 hexane:EtOAc then EtOAc as eluent gave trace

amounts of α-phenylpyrrolidine **380** (<1 mg) and 2-pyridyl(pyrrolidin-1-yl)methanone **356** (4 mg, 11%) as a colourless oil.

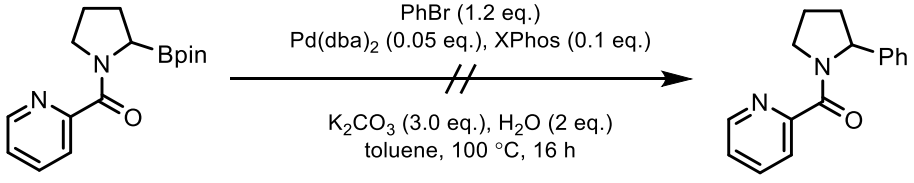
Lab book reference: **MTG-5-5**



356 **380**

Bromobenzene (0.012 mL, 0.11 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-piperidine **356** (32 mg, 0.11 mmol, 1.0 eq.), $Pd(dba)_2$ (2.7 mg, 0.005 mmol, 0.045 eq.), XPhos (4.5 mg, 0.009 mmol, 0.09 eq.), K_2CO_3 (39 mg, 0.28 mmol, 2.54 eq.) in toluene (0.5 mL) and water (0.25 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 17 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of α-phenylpyrrolidine **380** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-5-1**

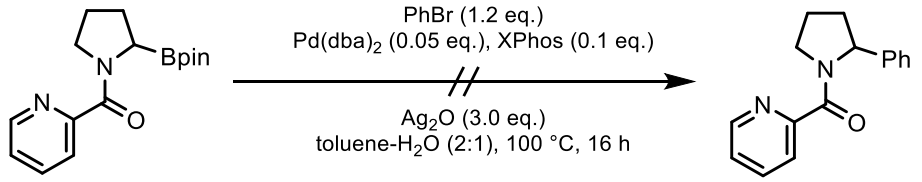


356 **380**

Bromobenzene (0.025 mL, 0.24 mmol, 1.2 eq.) was added to a stirred solution of α-Bpin-piperidine **356** (60 mg, 0.20 mmol, 1.0 eq.), $Pd(dba)_2$ (5.8 mg, 0.01 mmol, 0.05 eq.), XPhos (9.5 mg, 0.02 mmol, 0.1 eq.), K_2CO_3 (83 mg, 0.60 mmol, 3.0 eq.) and water (0.007 mL, 0.4 mmol, 2.0 eq.) in toluene (1 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 16 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two

layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), 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 trace amounts of α-phenylpyrrolidine **380** (<1 mg) and 2-pyridyl(pyrrolidin-1-yl)methanone **356** (15 mg, 43%) as a colourless oil, ^{1}H NMR for **356** (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.5 Hz, 1H, Ar), 7.86-7.74 (m, 2H, Ar), 7.33 (ddd, *J* = 7.0, 4.5, 2.0 Hz, 1H, Ar), 3.69 (ddd, *J* = 18.5, 6.5, 6.5 Hz, 4H, NCH_2), 1.98-1.85 (m, 4H, CH_2).

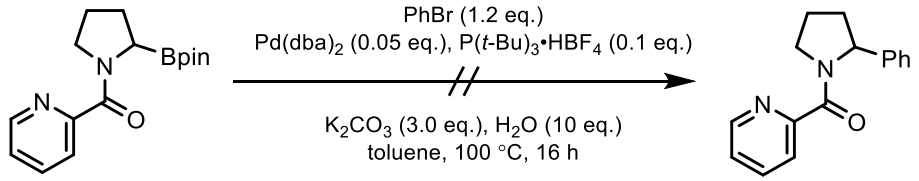
Lab book reference: **MTG-5-9**



356 **380**

Bromobenzene (0.023 mL, 0.22 mmol, 1.2 eq.) was added to a stirred solution of α-Bpin-piperidine **356** (54 mg, 0.17 mmol, 1.0 eq.), XPhos (8.6 mg, 0.018 mmol, 0.1 eq.), $Pd(dba)_2$ (5.2 mg, 0.009 mmol, 0.05 eq.) and Ag_2O (125 mg, 0.54 mmol, 3.0 eq.) in toluene (0.9 mL) and water (0.45 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 16 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of α-phenylpyrrolidine **380** (by ^{1}H NMR spectroscopy and HRMS).

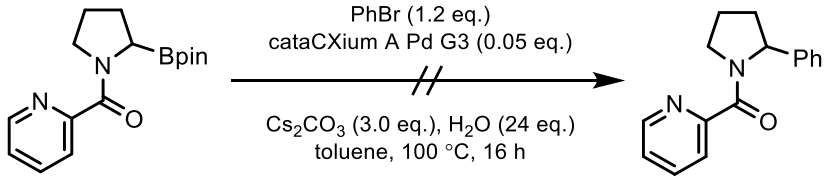
Lab book reference: **MTG-5-34**



356 **380**

Bromobenzene (0.025 mL, 0.24 mmol, 1.2 eq.) was added to a stirred solution of α-Bpin-piperidine **356** (60 mg, 0.20 mmol, 1.0 eq.), $Pd(dba)_2$ (5.8 mg, 0.01 mmol, 0.05 eq.), P(*t*-Bu)$_3$•HBF_4 (5.8 mg, 0.02 mmol, 0.1 eq.) and K_2CO_3 (83 mg, 0.60 mmol, 3.0 eq.) in toluene (1 mL) and water (0.5 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 16 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 1:1 hexane:EtOAc then EtOAc as eluent gave none of α-arylpyrrolidine **380** (by ^{1}H NMR spectroscopy and HRMS).

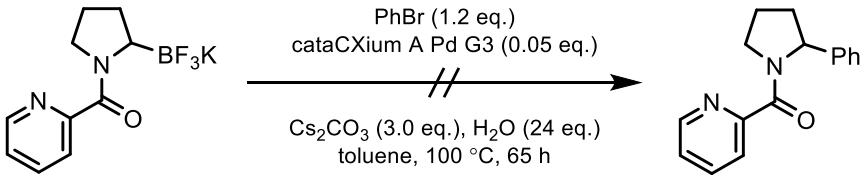
Lab book reference: **MTG-5-7**



356 **380**

Bromobenzene (0.025 mL, 0.24 mmol, 1.2 eq.) was added to a stirred solution of α-Bpin-piperidine **356** (60 mg, 0.20 mmol, 1.0 eq.), cataCXium A Pd G3 (7.3 mg, 0.01 mmol, 0.05 eq.), Cs_2CO_3 (196 mg, 0.60 mmol, 3.0 eq.) and water (0.087 mL, 4.8 mmol, 24.0 eq.) in toluene (1 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 16 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of α-phenylpyrrolidine **380** (by ^{1}H NMR spectroscopy and HRMS).

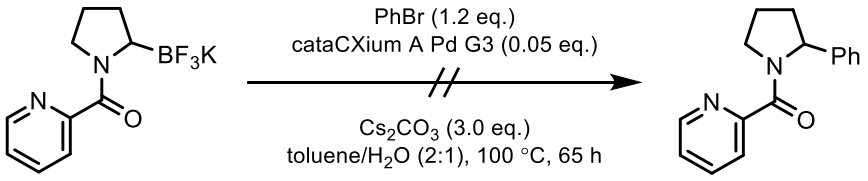
Lab book reference: **MTG-5-6**



362 **380**

Bromobenzene (0.027 mL, 0.26 mmol, 1.2 eq.) was added to a stirred solution of α-BF_3K-pyrrolidine **362** (60 mg, 0.21 mmol, 1.0 eq.), cataCXium A Pd G3 (7.8 mg, 0.011 mmol, 0.05 eq.), Cs_2CO_3 (208 mg, 0.64 mmol, 3.0 eq.) and water (0.092 mL, 5.1 mmol, 24.0 eq.) in toluene (1.05 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 65 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of α-phenylpyrrolidine **380** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-5-19**

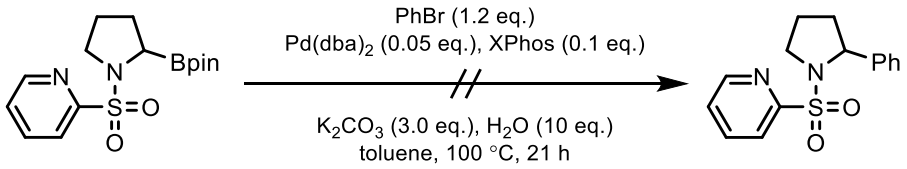


362 **380**

Bromobenzene (0.033 mL, 0.31 mmol, 1.2 eq.) was added to a stirred solution of α-BF_3K-pyrrolidine **362** (73 mg, 0.26 mmol, 1.0 eq.), cataCXium A Pd G3 (9.5 mg, 0.013 mmol, 0.05 eq.) and Cs_2CO_3 (254 mg, 0.78 mmol, 3.0 eq.) in toluene (1.3 mL) and water (0.65 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 65 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), 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 trace amounts of α-phenylpyrrolidine **380** (<1 mg) and 2-pyridyl(pyrrolidin-1-yl)methanone **362** (9 mg, 20%) as a colourless oil.

Lab book reference: **MTG-5-20**

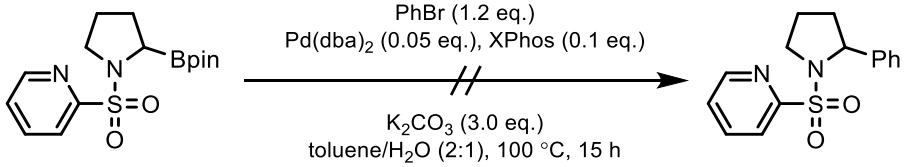
Attempted synthesis of 2-(2-phenylpyrrolidin-1-yl)sulfonylpyridine 382



357 **382**

Bromobenzene (0.025 mL, 0.24 mmol, 1.2 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **357** (68 mg, 0.20 mmol, 1.0 eq.), $Pd(dba)_2$ (5.8 mg, 0.01 mmol, 0.05 eq.), XPhos (9.5 mg, 0.02 mmol, 0.1 eq.), K_2CO_3 (83 mg, 0.60 mmol, 3.0 eq.) and water (0.036 mL, 2.0 mmol, 10.0 eq.) in toluene (1 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 21 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of α-phenylpyrrolidine **382** (by ^{1}H NMR spectroscopy and HRMS).

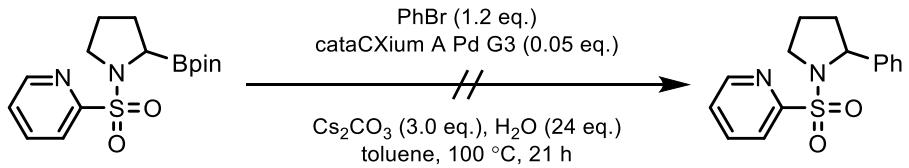
Lab book reference: **MTG-5-11**



357 **382**

Bromobenzene (0.015 mL, 0.14 mmol, 1.2 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **357** (39 mg, 0.12 mmol, 1.0 eq.), $Pd(dba)_2$ (3.3 mg, 0.006 mmol, 0.05 eq.), XPhos (5.5 mg, 0.012 mmol, 0.1 eq.) and K_2CO_3 (48 mg, 0.35 mmol, 3.0 eq.) in toluene (0.6 mL) and water (0.3 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 15 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of α-phenylpyrrolidine **382** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-5-4**

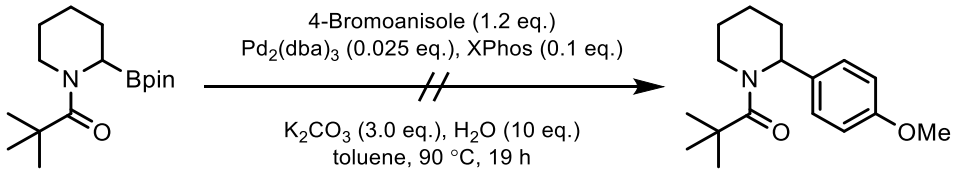


357 **382**

Bromobenzene (0.025 mL, 0.24 mmol, 1.2 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **357** (68 mg, 0.20 mmol, 1.0 eq.), cataCXium A Pd G3 (7.3 mg, 0.01 mmol, 0.05 eq.), Cs_2CO_3 (196 mg, 0.60 mmol, 3.0 eq.) and water (0.087 mL, 4.8 mmol, 24.0 eq.) in toluene (1 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 21 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained trace amounts of α-phenylpiperidine **382**. Purification by flash column chromatography on silica using 3:2 hexane:EtOAc then EtOAc as eluent gave none of α-phenylpyrrolidine **382** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-5-12**

Attempted synthesis of 1-[2-(4-methoxyphenyl)-1-piperidyl]-2,2-dimethyl-propan-1-one 384



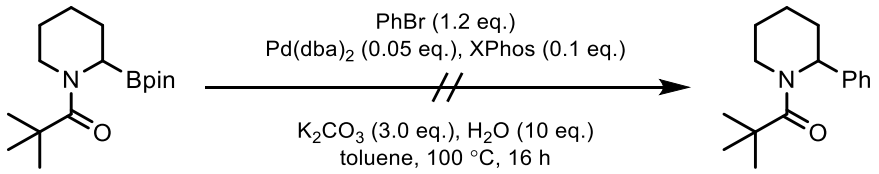
359 **373**

4-Bromoanisole (0.064 mL, 0.51 mmol, 1.2 eq.), $Pd_2(dba)_3$ (10 mg, 0.01 mmol, 0.025 eq.), XPhos (20 mg, 0.04 mmol, 0.1 eq.), K_2CO_3 (175 mg, 1.27 mmol, 3.0 eq.) and water (0.076 mL, 4.23 mmol, 10.0 eq.) were added to a stirred solution of α-Bpin-piperidine **359** (125 mg, 0.42 mmol, 1.0 eq.) in toluene (2.1 mL) at rt. The resulting solution was stirred and heated at 90 °C for 19 h. After being allowed to cool to rt,

water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using EtOAc gave none of α-arylpiperidine **373** (by ^{1}H NMR spectroscopy and HRMS) and α-Bpin-piperidine **359** (113 mg, 90%) as a white solid.

Lab book reference: **MTG-4-48**

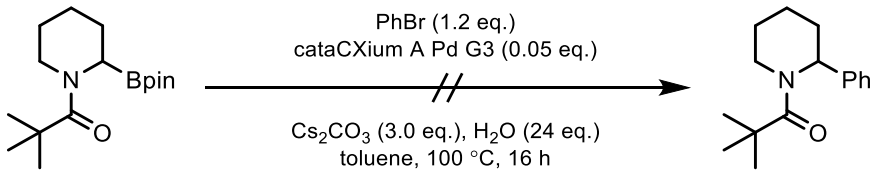
Attempted synthesis of 2,2-dimethyl-1-(2-phenyl-1-piperidyl)propan-1-one 385



359 **385**

A solution of bromobenzene (0.024 mL, 0.23 mmol, 1.2 eq.), $Pd(dba)_2$ (5.5 mg, 0.01 mmol, 0.05 eq.) and XPhos (9.1 mg, 0.02 mmol, 0.1 eq.) in toluene (1 mL) was added to a stirred solution of α-Bpin-piperidine **359** (56 mg, 0.19 mmol, 1.0 eq.), K_2CO_3 (79 mg, 0.57 mmol, 3.0 eq.) and water (0.034 mL, 1.9 mmol, 10.0 eq.) in toluene (1 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 16 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of α-arylpiperidine **385** (by ^{1}H NMR spectroscopy and HRMS).

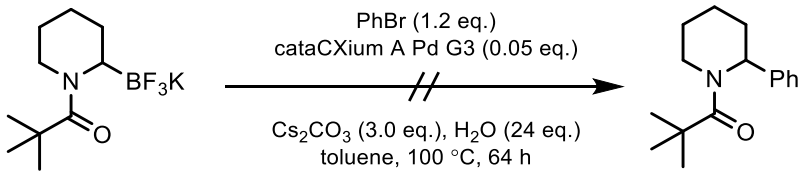
Lab book reference: **MTG-4-52**



359 **385**

A solution of bromobenzene (0.024 mL, 0.23 mmol, 1.2 eq.) and cataCXium A Pd G3 (6.9 mg, 0.01 mmol, 0.05 eq.) in toluene (1 mL) was added to a stirred solution of α-Bpin-piperidine **359** (56 mg, 0.19 mmol, 1.0 eq.), Cs_2CO_3 (186 mg, 0.57 mmol, 3.0 eq.) and water (0.082 mL, 4.6 mmol, 24 eq.) in toluene (1 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 16 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of α-arylpiperidine **385** (by ^{1}H NMR spectroscopy and HRMS).

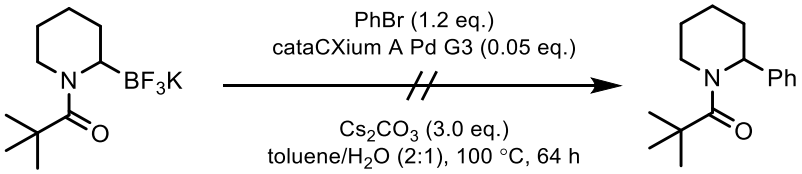
Lab book reference: **MTG-4-53**



363 **385**

Bromobenzene (0.014 mL, 0.13 mmol, 1.2 eq.) was added to a stirred solution of α-BF_3K-piperidine **363** (30 mg, 0.11 mmol, 1.0 eq.), cataCXium A Pd G3 (4.0 mg, 0.006 mmol, 0.05 eq.), Cs_2CO_3 (201 mg, 0.62 mmol, 3.0 eq.) and water (0.048 mL, 2.6 mmol, 24 eq.) in toluene (0.55 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 64 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of α-arylpiperidine **385** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-4-64**

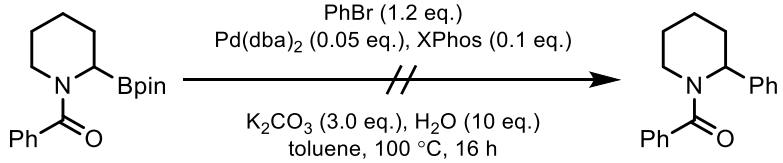


363 **385**

Bromobenzene (0.018 mL, 0.17 mmol, 1.2 eq.) was added to a stirred solution of α-BF_3K-piperidine **363** (38 mg, 0.14 mmol, 1.0 eq.), cataCXium A Pd G3 (5.1 mg, 0.007 mmol, 0.05 eq.), Cs_2CO_3 (254 mg, 0.78 mmol, 3.0 eq.) and in toluene (0.70 mL) and water (0.35 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 64 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 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of α-arylpiperidine **385** (by ^1H NMR spectroscopy and HRMS).

Lab book reference: **MTG-4-65**

Attempted synthesis of phenyl-(2-phenyl-1-piperidyl)methanone 386

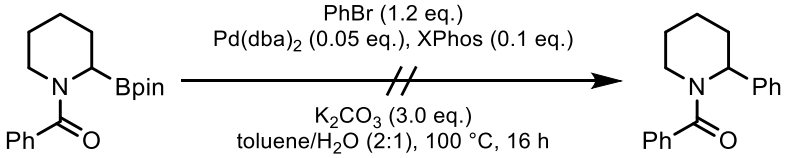


360 **386**

A solution of bromobenzene (0.025 mL, 0.24 mmol, 1.2 eq.), $Pd(dba)_2$ (5.8 mg, 0.01 mmol, 0.05 eq.) and XPhos (9.5 mg, 0.02 mmol, 0.1 eq.) in toluene (1 mL) was added to a stirred solution of α-Bpin-piperidine **360** (63 mg, 0.20 mmol, 1.0 eq.), K_2CO_3 (83 mg, 0.60 mmol, 3.0 eq.) and water (0.036 mL, 2.0 mmol, 10.0 eq.) in toluene (1 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 16 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which

contained none of α-arylpiperidine **386** (by ^{1}H NMR spectroscopy and HRMS). Purification by flash column chromatography on silica using EtOAc as eluent gave recovered α-Bpin-piperidine **360** (49 mg, 78%) as a white solid.

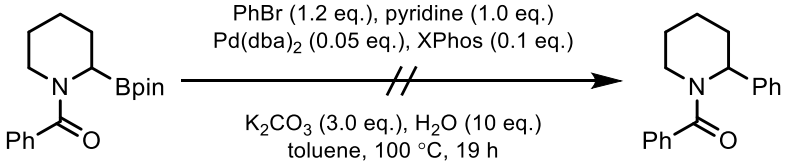
Lab book reference: **MTG-4-54**



360 **386**

A solution of bromobenzene (0.025 mL, 0.24 mmol, 1.2 eq.), $Pd(dba)_2$ (5.8 mg, 0.01 mmol, 0.05 eq.) and XPhos (9.5 mg, 0.02 mmol, 0.1 eq.) in toluene (1 mL) was added to a stirred solution of α-Bpin-piperidine **360** (63 mg, 0.20 mmol, 1.0 eq.) and K_2CO_3 (83 mg, 0.60 mmol, 3.0 eq.) in toluene (1 mL) and water (1 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 16 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of α-arylpiperidine **386** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-4-55**

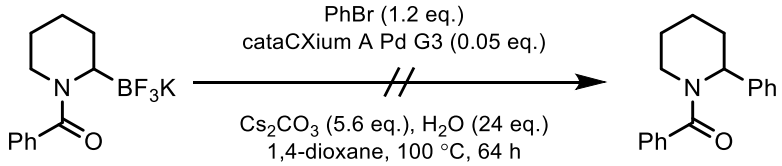


360 **386**

A solution of bromobenzene (0.025 mL, 0.24 mmol, 1.2 eq.), $Pd(dba)_2$ (5.8 mg, 0.01 mmol, 0.05 eq.) and XPhos (9.5 mg, 0.02 mmol, 0.1 eq.) in toluene (1 mL) was added to a stirred solution of α-Bpin-piperidine **360** (63 mg, 0.20 mmol, 1.0 eq.), pyridine (0.016 mL, 0.20 mmol, 1.0 eq.) and K_2CO_3 (83 mg, 0.60 mmol, 3.0 eq.) in toluene (1 mL) and water (1 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 19 h. After being allowed to cool

to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of α-arylpiperidine **386** (by ^1H NMR spectroscopy and HRMS).

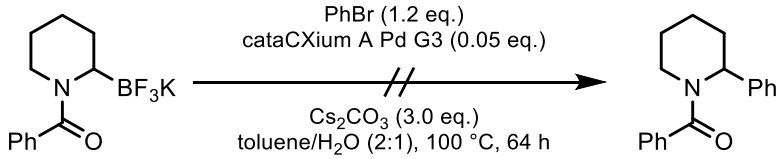
Lab book reference: **MTG-4-56**



360 **386**

A solution of cataCXium A Pd G3 (3.7 mg, 0.004 mmol, 0.05 eq.) in 1,4-dioxane (1 mL) was added to a stirred solution of α-BF_3K-piperidine **360** (30 mg, 0.10 mmol, 1.0 eq.), Cs_2CO_3 (182 mg, 0.56 mmol, 5.6 eq.) and water (0.045 mL, 2.4 mmol, 24 eq.) in 1,4-dioxane (1 mL) at rt under Ar in a pressure tube followed by the addition of bromobenzene (0.013 mL, 0.12 mmol, 1.2 eq.). The tube was sealed and the resulting solution was stirred and heated at 100 °C for 64 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of α-arylpiperidine **386** (by ^1H NMR spectroscopy and HRMS).

Lab book reference: **MTG-4-58**

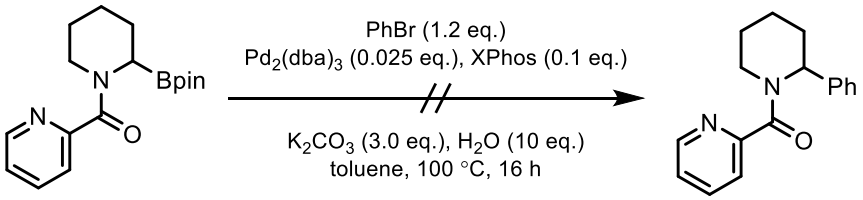


364 **386**

A solution of cataCXium A Pd G3 (6.8 mg, 0.01 mmol, 0.05 eq.) in toluene (1 mL) was added to a stirred solution of α-BF_3K-piperidine **364** (55 mg, 0.19 mmol, 1.0 eq.) and Cs_2CO_3 (182 mg, 0.56 mmol, 3.0 eq.) in toluene (1 mL) and water (1 mL) at rt under Ar in a pressure tube followed by the addition of bromobenzene (0.024 mL, 0.22 mmol, 1.2 eq.). The tube was sealed and the resulting solution was stirred and heated at 100 °C for 64 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of α-arylpiperidine **386** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-4-59**

Attempted synthesis of (2-phenyl-1-piperidyl)-(2-pyridyl)methanone 387



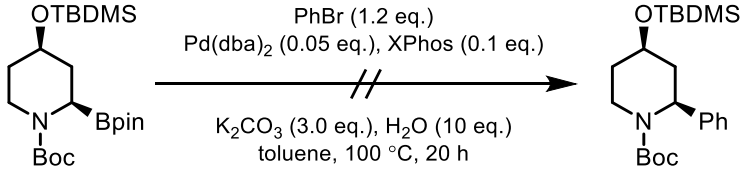
361 **387**

Bromobenzene (0.019 mL, 0.18 mmol, 1.2 eq.) was added to a stirred solution of α-Bpin-piperidine **361** (49 mg, 0.15 mmol, 1.0 eq., 89% purity), $Pd_2(dba)_3$ (4.4 mg, 0.008 mmol, 0.025 eq.), XPhos (7.3 mg, 0.015 mmol, 0.1 eq.), K_2CO_3 (64 mg, 0.46 mmol, 3.0 eq.) and water (0.028 mL, 1.54 mmol, 10.0 eq.) in toluene (1.5 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 16 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and

evaporated under reduced pressure to give the crude product which contained none of α-arylpiperidine **387** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-4-86**

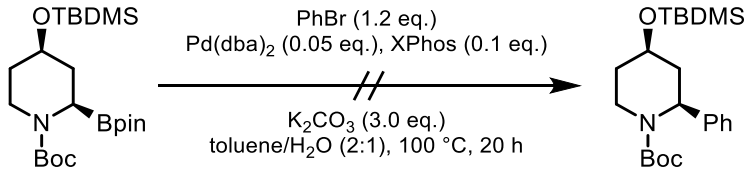
Attempted synthesis of *tert*-Butyl-4-((*tert*-butyldiphenylsilyl)oxy)-2-phenyl-piperidine-1-carboxylate cis-176



cis-**213** *cis*-**176**

Bromobenzene (0.038 mL, 0.36 mmol, 1.2 eq.) was added to a stirred solution of α-Bpin-4-OTBDMS-piperidine *cis*-**213** (133 mg, 0.30 mmol, 1.0 eq.), K_2CO_3 (125 mg, 0.90 mmol, 3.0 eq.), $Pd(dba)_2$ (8.7 mg, 0.015 mmol, 0.05 eq.), XPhos (14.3 mg, 0.030 mmol, 0.1 eq.) and water (0.054 mL, 3.0 mmol, 10.0 eq.) in toluene (1.5 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 20 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 17:3 hexane:EtOAc as eluent gave none of α-arylpiperidine *cis*-**176** (by ^{1}H NMR spectroscopy and HRMS) and α-Bpin-4-OTBDMS-piperidine *cis*-**213** (84 mg, 63%) as a white solid.

Lab book reference: **MTG-4-67**

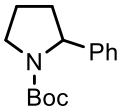


cis-**213** *cis*-**176**

Bromobenzene (0.038 mL, 0.36 mmol, 1.2 eq.) was added to a stirred solution of α-Bpin-4-OTBDMS-piperidine *cis*-**213** (133 mg, 0.30 mmol, 1.0 eq.), K_2CO_3 (125 mg, 0.90 mmol, 3.0 eq.), $Pd(dba)_2$ (8.7 mg, 0.015 mmol, 0.05 eq.) and XPhos (14.3 mg, 0.030 mmol, 0.1 eq.) in toluene (1.5 mL) and water (0.75 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 100 °C for 20 h. After being allowed to cool to rt, water (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of α-arylpiperidine *cis*-**176** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-4-68**

***tert*-Butyl-2-phenylpyrrolidine-1-carboxylate 114**



114

Bromobenzene (0.158 mL, 1.5 mmol, 1.5 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (297 mg, 1.0 mmol, 1.0 eq.), cataCXium A (71.7 mg, 0.20 mmol, 0.2 eq.), Cs_2CO_3 (978 mg, 3.0 mmol, 3.0 eq.), copper(I) oxide (143 mg, 1.0 mmol, 1.0 eq.) and $Pd(OAc)_2$ (22.5 mg, 0.10 mmol, 0.1 eq.) in CPME (2.5 mL) and water (2.0 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C 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 199:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (51 mg, 21%) as a pale yellow

oil, R_F (99:1 CH_2Cl_2-EtOAc) 0.50; IR (ATR) 2974, 2931, 2876, 1686 (C=O), 1389, 1365, 1157, 1112, 749, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.42-7.23 (m, 2H, Ph), 7.23-7.03 (m, 3H, Ph), 5.07-4.85 (m, 0.3H, PhNCH), 4.85-4.60 (m, 0.7H, PhNCH), 3.95-3.22 (m, 2H, NCH_2), 2.57-2.11 (m, 1H, CH), 2.10-1.57 (m, 3H, CH), 1.44 (s, 2.7H, CMe_3), 1.16 (s, 6.3H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers - 19 of 22 signals were observed) δ 154.5 (C=O), 145.5 (*ipso*-Ph), 144.2 (*ipso*-Ph), 128.4 (Ph), 128.2 (Ph), 126.6 (Ph), 125.4 (Ph), 125.2 (Ph), 79.3 ($OCMe_3$), 61.4 (NCH), 60.7 (NCH), 47.7 (NCH_2), 47.4 (NCH_2), 36.1 (CH_2), 34.9 (CH_2), 28.6 (CMe_3), 28.2 (CMe_3), 23.5 (CH_2), 23.3 (CH_2); HRMS (ESI) *m/z* calcd for $C_{15}H_{21}NO_2$ $(M + Na)^+$ 270.1464, found 270.1460 (+1.6 ppm error). Spectroscopic data consistent with those reported in the literature.[12]

Lab book reference: **MTG-5-61**

Bromobenzene (0.079 mL, 0.75 mmol, 1.5 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (149 mg, 0.50 mmol, 1.0 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 3.0 eq.), copper(I) oxide (72 mg, 0.50 mmol, 1.0 eq.) and cataCXium A Pd G3 (36.4 mg, 0.05 mmol, 0.1 eq.) in CPME (1.25 mL) and water (1.0 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 199:1 CH_2Cl_2-EtOAc as eluent gave α-phenylpyrrolidine **114** (33 mg, 27%) as a pale yellow oil.

Lab book reference: **MTG-5-63**

Bromobenzene (0.079 mL, 0.75 mmol, 1.5 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (149 mg, 0.50 mmol, 1.0 eq.), cataCXium A (35.9 mg, 0.10 mmol, 0.2 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 3.0 eq.) and $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 0.1 eq.) in CPME (1.25 mL) and water (1.0 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After

being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 199:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (37 mg, 30%) as a pale yellow oil.

Lab book reference: **MTG-5-62**

Bromobenzene (0.079 mL, 0.75 mmol, 1.5 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (149 mg, 0.50 mmol, 1.0 eq.), cataCXium A (35.9 mg, 0.10 mmol, 0.2 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 3.0 eq.) and $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 0.1 eq.) in CPME (1.25 mL) and water (1.0 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 63 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 199:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (37 mg, 30%) as a colourless oil.

Lab book reference: **MTG-5-68**

Bromobenzene (0.079 mL, 0.75 mmol, 1.5 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (149 mg, 0.50 mmol, 1.0 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 3.0 eq.) and cataCXium A Pd G3 (36.4 mg, 0.05 mmol, 0.1 eq.) in CPME (1.25 mL) and water (1.0 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using

199:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (35 mg, 28%) as a pale yellow oil.

Lab book reference: **MTG-5-66**

Bromobenzene (0.079 mL, 0.75 mmol, 1.5 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (149 mg, 0.50 mmol, 1.0 eq.), cataCXium A (35.9 mg, 0.10 mmol, 0.2 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 3.0 eq.) and $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 0.1 eq.) in toluene (1.25 mL) and water (1.0 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 199:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (40 mg, 32%) as a pale yellow oil.

Lab book reference: **MTG-5-67**

4-Bromobenzene (0.049 mL, 0.45 mmol, 1.5 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (89 mg, 0.30 mmol, 1.0 eq.), Cs_2CO_3 (293 mg, 0.90 mmol, 3.0 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.) and $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.1 eq.) in toluene (0.75 mL) and water (0.6 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL) and dried ($MgSO_4$). 1,3,5-Trimethoxybenzene (25 mg, 0.15 mmol, 0.5 eq.) was added as an external standard and the solution was evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (23% NMR yield). Purification by flash column chromatography on silica using 199:1 CH_2Cl_2-EtOAc as eluent gave α-phenylpyrrolidine **114** (18 mg, 24%) as a colourless oil.

Lab book reference: **MTG-5-85**

Bromobenzene (0.047 mL, 0.45 mmol, 1.5 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (89 mg, 0.30 mmol, 1.0 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.75 mL) and water (0.6 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (29% NMR yield). Purification by flash column chromatography on silica using 199:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (22 mg, 30%) as a colourless oil.

Lab book reference: **MTG-6-8**

Bromobenzene (0.047 mL, 0.45 mmol, 1.5 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (89 mg, 0.30 mmol, 1.0 eq.), Cs_2CO_3 (293 mg, 0.90 mmol, 3.0 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.) and $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.1 eq.) in toluene (0.75 mL) and water (0.6 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 6 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL) and dried ($MgSO_4$). 1,3,5-Trimethoxybenzene (50.5 mg, 0.30 mmol, 1.0 eq.) was added as an external standard and the solution was evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (17% NMR yield).

Lab book reference: **MTG-5-92**

Bromobenzene (0.047 mL, 0.45 mmol, 1.5 eq.) was added to a stirred solution of α-$B(OH)_2$ pyrrolidine **350** (65 mg, 0.30 mmol, 1.0 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.1 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.75 mL) and water (0.60 mL) at rt under Ar in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (5% NMR yield).

Lab book reference: **MTG-6-20**

Bromobenzene (0.041 mL, 0.39 mmol, 1.5 eq.) was added to a stirred solution of α-$B(OH)_2$ pyrrolidine **350** (57 mg, 0.26 mmol, 1.0 eq.), cataCXium A (18.9 mg, 0.053 mmol, 0.2 eq.), Cs_2CO_3 (257 mg, 0.79 mmol, 3.0 eq.), $Pd(OAc)_2$ (5.4 mg, 0.026 mmol, 0.15 eq.) and 1,3,5-trimethoxybenzene (22.1 mg, 0.13 mmol, 0.5 eq.) as an internal standard in toluene (0.75 mL) and water (0.6 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (7% NMR yield).

Lab book reference: **MTG-6-16**

Bromobenzene (0.020 mL, 0.19 mmol, 1.5 eq.) was added to a stirred solution of α-BMIDA pyrrolidine **390** (41.0 mg, 0.13 mmol, 1.0 eq.), cataCXium A (9.0 mg, 0.025 mmol, 0.2 eq.), Cs_2CO_3 (123 mg, 0.38 mmol, 3.0 eq.), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (10.6 mg, 0.063 mmol, 0.5 eq.) as an internal standard in toluene (0.33 mL) and water (0.26 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 20 h.

After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (9% NMR yield).

Lab book reference: **MTG-6-28**

Bromobenzene (0.047 mL, 0.45 mmol, 1.5 eq.) was added to a stirred solution of α-BF_3K pyrrolidine **347** (83 mg, 0.30 mmol, 1.0 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.1 eq.), and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.75 mL) and water (0.60 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (11% NMR yield).

Lab book reference: **MTG-6-33**

Chlorobenzene (0.046 mL, 0.45 mmol, 1.5 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (89 mg, 0.30 mmol, 1.0 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.1 eq.), and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.75 mL) and water (0.60 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (55% NMR yield) and α-Bpin-pyrrolidine **51** (45% NMR yield). Purification by

flash column chromatography on silica using 199:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (43 mg, 58%) as a colourless oil.

Lab book reference: **MTG-6-40**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.75 mL) and water (0.6 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (66% NMR yield). Purification by flash column chromatography on silica using 199:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (51 mg, 69%) as a colourless oil.

Lab book reference: **MTG-6-43**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (65% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-6-100**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (63% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-6-101**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (60% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-6-102**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (57% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-6-103**

Bromobenzene (0.032 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (50% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-6-116**

Iodobenzene (0.034 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (7% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-6-117**

Phenyltriflate (0.049 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (6% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-6-118**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), Cu_2O (42.9 mg, 0.30 mmol, 1.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (49% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-74**

Table 3.17: Screening of the SMCC of α-Bpin-*N*-Boc-pyrrolidine 51 with alternative temperatures

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 100 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (39% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-6-129**

Bromobenzene (0.032 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 100 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (40% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-6-130**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 110 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (66% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-6-124**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 110 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (53% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-6-126**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 110 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (53% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-2**

Bromobenzene (0.032 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 110 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (41% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-6-125**

Bromobenzene (0.032 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 110 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (57% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-6-127**

Bromobenzene (0.032 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 110 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (43% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-3**

Table 3.18: Solvent screen of the SMCC of α-Bpin-*N*-Boc-pyrrolidine 51

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in xylene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (56% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-50**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in CPME (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (45% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-48**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in TMO (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (34% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-49**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in MTBE (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (8% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-51**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in 1,4-dioxane (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (1% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-52**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in DMF (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (0.4% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-137**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in NMP (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (0% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-66**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in MeCN (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 90 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (0% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-53**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in DME (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 90 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (0% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-54**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in THF (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 70 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (0% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-60**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in MeOH (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 70 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (0% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-61**

Table 3.19: Precatalyst screen of the SMCC of α-Bpin-*N*-Boc-pyrrolidine 51

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), cataCXium A Pd G3 (21.8 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (61% conversion to α-phenylpyrrolidine **114**). Water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous

layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (57% NMR yield). Purification by flash column chromatography on silica using 399:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (42 mg, 57%) as a colourless oil.

Lab book reference: **MTG-7-8**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), PCy_3P Pd G3 (19.5 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (43% conversion to α-phenylpyrrolidine **114**). Water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (44% NMR yield). Purification by flash column chromatography on silica using 399:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (24 mg, 32%) as a colourless oil.

Lab book reference: **MTG-7-20**

Bromobenzene (0.032 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), PCy_3P Pd G3 (19.5 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (16% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-21**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), PAd_3 Pd G3 (24.2 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (10% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-67**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), *t*-Bu_3PPd G4 (17.6 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (7% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-18**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), *o*-tol_3P Pd G2 (18.4 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (1% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-19**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), dppf Pd G3 (27.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (2% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-23**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), SPhos Pd G3 (23.4 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (27% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-7**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), RuPhos Pd G3 (25.1 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (25% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-5**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), XPhos Pd G3 (25.4 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg,

0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (20% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-6**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), AmPhos Pd G3 (19.1 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (19% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-22**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), *t*-BuXPhos Pd G3 (23.8 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (0% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-4**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), MorDalPhos Pd G3 (25.0 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was

stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (0.2% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-11**

Table 3.20: Ligand screen of the SMCC of α-Bpin-*N*-Boc-pyrrolidine 51

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium ABn (23.6 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (0% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-90**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), *rac*-BI-DIME (19.8 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.90 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (9% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-158**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), $P(Ad)_3$ (26.2 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in

toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (1% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-6-104**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), PPh_3 (15.7 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (0% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-24**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), BINAP (37.4 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (0% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-15**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), XantPhos (34.7 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in

toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (20% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-131**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), DavePhos (23.6 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (11% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-16**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), CPhos (26.2 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (7% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-13**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), QPhos (42.6 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in

toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (5% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-14**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), JackiePhos (47.8 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (1% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-10**

Table 3.21: Screening of the SMCC of α-Bpin-*N*-Boc-pyrrolidine 51 with alternative palladium sources

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $[Pd(allyl)Cl]_2$ (5.5 mg, 0.015 mmol, 0.05 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (40% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-92**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), [Pd(*p*-cinnamyl)Cl]$_2$ (7.8 mg, 0.015 mmol, 0.05 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (15% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-94**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd_2(dba)_3$ (13.7 mg, 0.015 mmol, 0.05 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (5% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-91**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $PdCl_2$ (5.3 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (0% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-93**

Table 3.22: Screening of the SMCC of α-Bpin-*N*-Boc-pyrrolidine 51 varying the $Pd(OAc)_2$ loading

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (4.3 mg, 0.012 mmol, 0.04 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (1.3 mg, 0.006 mmol, 0.02 eq.), water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) at rt under air in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (39% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-108**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (10.8 mg, 0.03 mmol, 0.1 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 0.05 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under air in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (50% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-109**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (32.3 mg, 0.09 mmol, 0.3 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (10.1 mg, 0.045 mmol, 0.15 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under air in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (44% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-111**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (32.3 mg, 0.09 mmol, 0.3 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (10.1 mg, 0.045 mmol, 0.15 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (71% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-132**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (43.0 mg, 0.12 mmol, 0.4 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (13.5 mg, 0.06 mmol, 0.2 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under air in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (58% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-112**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (64.5 mg, 0.18 mmol, 0.6 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (20.2 mg, 0.09 mmol, 0.3 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under air in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (56% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-113**

Table 3.23: Screening of the SMCC of α-Bpin-*N*-Boc-pyrrolidine 51 varying $Pd(OAc)_2$:ligand ratios

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (5.4 mg, 0.015 mmol, 0.05 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under air in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (44% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-95**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (10.8 mg, 0.03 mmol, 0.1 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under air in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (60% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-96**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (10.8 mg, 0.03 mmol, 0.1 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (63% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-135**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (16.1 mg, 0.045 mmol, 0.15 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (73% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-136**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (32.3 mg, 0.09 mmol, 0.3 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under air in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (52% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-97**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (43.0 mg, 0.12 mmol, 0.4 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under air in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (35% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-98**

Table 3.24: Base screen of the SMCC of α-Bpin-*N*-Boc-pyrrolidine 51

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), K_2CO_3 (124 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (47% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-31**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Na_2CO_3 (95 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (33% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-25**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), $BaCO_3$ (178 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (2% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-72**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Ag_2CO_3 (248 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (1% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-41**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), $NaHCO_3$ (76 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (6% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-27**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), $KHCO_3$ (90 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (11% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-33**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), CsF (137 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (3% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-36**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), KF (52 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (4% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-42**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) and Et_3N (0.125 mL, 0.9 mmol, 3.0 eq.) were added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (0% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-30**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Et_4NI (231 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (0% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-43**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Ag_2O (209 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (0% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-40**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), K_3PO_4 (191 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (74% conversion to α-phenylpyrrolidine **114**). Water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated

under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (70% NMR yield). Purification by flash column chromatography on silica using 399:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (40 mg, 54%) as a colourless oil.

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

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), K_3PO_4 (191 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (63% conversion to α-phenylpyrrolidine **114**). Water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (68% NMR yield). Purification by flash column chromatography on silica using 399:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (41 mg, 55%) as a colourless oil.

Lab book reference: **MTG-7-32**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), K_3PO_4 (191 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (33% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-59**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), K_3PO_4 (191 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (65% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-81**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), K_3PO_4 (191 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (62% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-78**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), K_3PO_4 (191 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (60% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-79**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), K_3PO_4 (191 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (58% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-77**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), K_3PO_4 (191 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (55% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-80**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Na_3PO_4 (148 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (44% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-57**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), K_2HPO_4 (157 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (1% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-55**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), KH_2PO_4 (122 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (1% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-56**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), NaOH (36 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (0.4% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-26**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), NaOAc (74 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (1% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-28**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), KOH (50 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (2% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-29**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), KO*t*-Bu (101 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (1% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-37**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), LiO*t*-Bu (72 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (1% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-34**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) and Bu_4NOH (0.58 mL of a 1.54 M solution in H_2O, 0.9 mmol, 3.0 eq.) were added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (2% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-35**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), $CsOH•H_2O$ (151 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (9% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-38**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), $LiOH•H_2O$ (38 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (1% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-39**

Table 3.26: Screening of the SMCC of α-Bpin-*N*-Boc-pyrrolidine 51 with different equivalents of Cs_2CO_3

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (20 mg, 0.06 mmol, 0.2 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (1% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-114**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (49 mg, 0.15 mmol, 0.5 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (2% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-115**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (98 mg, 0.30 mmol, 1.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (4% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-116**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (195 mg, 0.60 mmol, 2.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (62% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-117**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 5.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (69% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-118**

Table 3.27: Screening of the SMCC of α-Bpin-*N*-Boc-pyrrolidine 51 with different equivalents of water

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (72% conversion to α-phenylpyrrolidine **114**). Water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (76% NMR yield). Purification by flash column chromatography on silica using 199:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (30 mg, 40%) as a colourless oil.

Lab book reference: **MTG-7-100**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (36% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-128**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.011 mL, 0.60 mmol, 2 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) at rt under N_2 in a pressure vial.

The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (86% conversion to α-phenylpyrrolidine **114**). Water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (84% NMR yield). Purification by flash column chromatography on silica using 199:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (43 mg, 58%) as a colourless oil.

Lab book reference: **MTG-7-101**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.027 mL, 1.5 mmol, 5 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (71% conversion to α-phenylpyrrolidine **114**). Water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (71% NMR yield). Purification by flash column chromatography on silica using 199:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (39 mg, 53%) as an orange oil.

Lab book reference: **MTG-7-129**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.042 mL, 2.4 mmol, 8 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol,

0.5 eq.) as an internal standard in toluene (0.42 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (88% conversion to α-phenylpyrrolidine **114**). Water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (92% NMR yield). Purification by flash column chromatography on silica using 199:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (57 mg, 77%) as a colourless oil.

Lab book reference: **MTG-7-103**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (99% conversion to α-phenylpyrrolidine **114**). Water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (88% NMR yield). Purification by flash column chromatography on silica using 199:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (57 mg, 77%) as a colourless oil.

Lab book reference: **MTG-7-102**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (79% conversion to α-phenylpyrrolidine **114**). Water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (91% NMR yield). Purification by flash column chromatography on silica using 199:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (59 mg, 80%) as a colourless oil.

Lab book reference: **MTG-7-119**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (83% conversion to α-phenylpyrrolidine **114**). Water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (79% NMR yield). Purification by flash column chromatography on silica using 199:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (50 mg, 68%) as a colourless oil.

Lab book reference: **MTG-7-120**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.21 mL, 39 eq.) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (80% conversion to α-phenylpyrrolidine **114**). Water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (84% NMR yield). Purification by flash column chromatography on silica using 199:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (28 mg, 38%) as a colourless oil.

Lab book reference: **MTG-7-104**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.42 mL, 78 eq.) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (53% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-106**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.84 mL, 155 eq.) at rt under N_2 in a pressure vial. The

vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (5% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-107**

Further Optimisation Reactions

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.84 mL) at rt under air in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (67% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-122**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.84 mL) at rt under air in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (60% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-123**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol,

0.5 eq.) as an internal standard in toluene (0.84 mL) at rt under air in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (42% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-121**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), K_3PO_4 (191 mg, 0.9 mmol, 3.0 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (51% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-134**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), K_2CO_3 (191 mg, 1.38 mmol, 4.6 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (52% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-139**

Bromobenzene (0.053 mL, 0.50 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 3.0 eq.), P*t*-Bu_3Pd G4 (29.3 mg, 0.05 mmol, 0.10 eq.), water (0.09 mL, 5.0 mmol, 10 eq.) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred

and heated at 120 °C for 20 h. After being allowed to cool to rt 1,3,5-trimethoxybenzene (50.5 mg, 0.30 mmol, 1.0 eq.) was added as an external standard, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (2% NMR yield).

Lab book reference: **MTG-7-181**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), PCy_3Pd G3 (19.5 mg, 0.03 mmol, 0.10 eq.), water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (61% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-133**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in cumene (0.42 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (58% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-127**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in xylene (0.42 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 140 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (99% conversion to α-phenylpyrrolidine **114**). Water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (80% NMR yield). Purification by flash column chromatography on silica using 199:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (46 mg, 62%) as a colourless oil.

Lab book reference: **MTG-7-148**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in xylene (0.42 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 140 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (95% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-149**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (16.1 mg, 0.045 mmol, 0.15 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) at rt under N_2 in a pressure

vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (74% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-142**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (16.1 mg, 0.045 mmol, 0.15 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (63% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-143**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (16.1 mg, 0.045 mmol, 0.15 eq.), Cs_2CO_3 (195 mg, 0.6 mmol, 2.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (85% conversion to α-phenylpyrrolidine **114**). Water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-phenylpyrrolidine **114** (89% NMR yield). Purification by flash column chromatography on silica using 199:1 CH_2Cl_2:EtOAc then 99:1 CH_2Cl_2:EtOAc as eluent gave α-phenylpyrrolidine **114** (46 mg, 62%) as a colourless oil.

Lab book reference: **MTG-7-144**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (16.1 mg, 0.045 mmol, 0.15 eq.), Cs_2CO_3 (195 mg, 0.6 mmol, 2.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (73% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-145**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (195 mg, 0.6 mmol, 2.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (87% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-147**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (195 mg, 0.6 mmol, 2.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.10 eq.), water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (71% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-146**

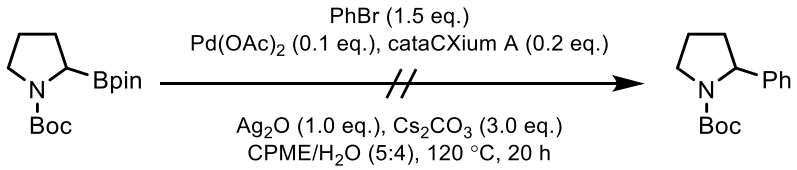
Using general procedure G, bromobenzene (0.053 mL, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product. Purification by flash column chromatography on silica using 199:1 CH_2Cl_2-EtOAc as eluent gave α-phenylpyrrolidine **114** (97 mg, 78%) as a colourless oil.

Lab book reference: **MTG-7-155**

Bromobenzene (0.079 mL, 0.75 mmol, 1.5 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (149 mg, 0.50 mmol, 1.0 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 3.0 eq.), cataCXium A (35.9 mg, 0.10 mmol, 0.2 eq.), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 0.1 eq.) and water (0.090 mL, 5.0 mmol, 10 eq.) in toluene (0.7 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 199:1 CH_2Cl_2-EtOAc as eluent gave α-phenylpyrrolidine **114** (94 mg, 76%) as a colourless oil.

Lab book reference: **MTG-7-179**

Attempted synthesis of *tert*-butyl-2-phenylpyrrolidine-1-carboxylate 114

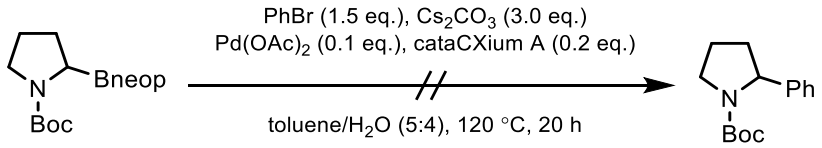


51 **114**

Bromobenzene (0.079 mL, 0.75 mmol, 1.5 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (149 mg, 0.50 mmol, 1.0 eq.), cataCXium A (35.9 mg, 0.10 mmol, 0.2 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 3.0 eq.), silver(I) oxide (116 mg, 0.50 mmol, 1.0 eq.) and $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 0.1 eq.) in toluene (1.25 mL) and water (1.0 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution

was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained trace amounts of α-phenylpyrrolidine **114** (by ^{1}H NMR spectroscopy and HRMS).

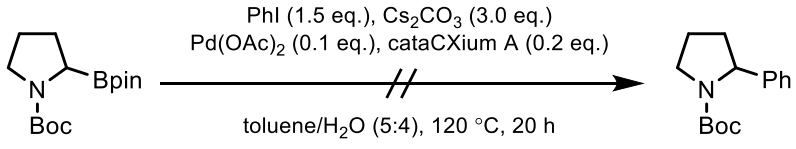
Lab book reference: **MTG-5-70**



391 **114**

Bromobenzene (0.047 mL, 0.45 mmol, 1.5 eq.) was added to a stirred solution of α-Bneop pyrrolidine **391** (85 mg, 0.30 mmol, 1.0 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.1 eq.), and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.75 mL) and water (0.6 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained trace amounts of α-phenylpyrrolidine **114** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-6-54**

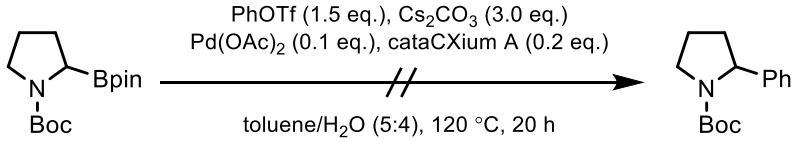


51 **114**

Iodobenzene (0.050 mL, 0.45 mmol, 1.5 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (89 mg, 0.30 mmol, 1.0 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.1 eq.), and

1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.75 mL) and water (0.60 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained trace amounts of α-phenylpyrrolidine **114** (by ^{1}H NMR spectroscopy) and α-Bpin-pyrrolidine **51** (54% NMR yield).

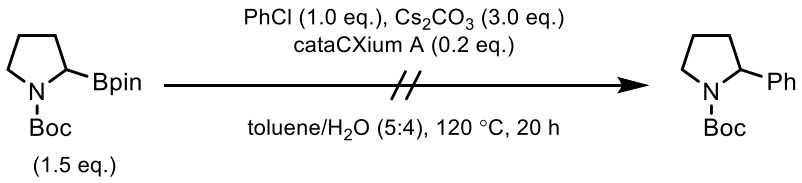
Lab book reference: **MTG-6-38**



51 **114**

Phenyl trifluoromethanesulfonate (0.073 mL, 0.45 mmol, 1.5 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (89 mg, 0.30 mmol, 1.0 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.1 eq.), and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.75 mL) and water (0.6 mL) at rt under Ar in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of α-phenylpyrrolidine **114** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-6-60**

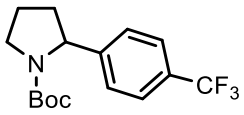


51 **114**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (134 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) and water (0.33 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, the reaction mixture was analysed by GC (0% conversion to α-phenylpyrrolidine **114**).

Lab book reference: **MTG-7-45**

***tert*-Butyl-2-[4-(trifluoromethyl)phenyl]pyrrolidine-1-carboxylate 389**



389

Using general procedure G, 4-bromobenzotrifluoride (0.070 mL, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product. Purification by flash column chromatography on silica using 199:1 CH_2Cl_2-EtOAc as eluent gave α-arylpyrrolidine **389** (116 mg, 73%) as an orange oil, R_F (199:1 CH_2Cl_2-EtOAc) 0.70; IR (ATR) 2977, 2934, 2880, 1693 (C=O), 1390, 1366, 1323, 1158, 1111, 1066, 1016, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.53 (d, *J* = 8.0 Hz, 2H, Ar), 7.26 (d, *J* = 8.0 Hz, 2H, Ar), 5.12-4.89 (m, 0.4H, ArNCH), 4.89-4.67 (m, 0.6H, ArNCH), 3.74-3.44 (m, 2H, NCH_2), 2.44-2.21 (m, 1H, CH), 1.92-1.71 (m, 3H, CH), 1.43 (s, 3.6H, CMe_3), 1.16 (s, 5.4H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers - 20 of 24 signals were observed) δ 154.5 (C=O), 149.4 (*ipso*-Ar), 148.5 (*ipso*-Ar), 129.0 (q, *J* = 32.0 Hz, *ipso*-Ar), 125.9 (Ar), 125.8 (Ar), 125.5 (Ar), 125.2 (Ar), 124.4 (q, *J* = 272.0 Hz, CF_3) 79.7 ($OCMe_3$), 61.1 (NCH), 60.6 (NCH), 47.5 (NCH_2), 47.2 (NCH_2), 36.0 (CH_2), 34.9 (CH_2), 28.5 (CMe_3), 28.2 (CMe_3), 23.6 (CH_2), 23.3 (CH_2); HRMS

(ESI) *m/z* calcd for $C_{16}H_{20}F_3NO_2$ $(M + Na)^+$ 338.1338, found 338.1338 (+0.0 ppm error). Spectroscopic data consistent with those reported in the literature.[19]

Lab book reference: **MTG-7-152**

4-Bromobenzotrifluoride (0.105 mL, 0.75 mmol, 1.5 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (149 mg, 0.50 mmol, 1.0 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 3.0 eq.), cataCXium A (35.9 mg, 0.10 mmol, 0.2 eq.) and $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 0.1 eq.) in toluene (1.25 mL) and water (1.0 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL) and dried ($MgSO_4$). 1,3,5-Trimethoxybenzene (84 mg, 0.50 mmol, 1.0 eq.) was added as an external standard and the solution was evaporated under reduced pressure to give the crude product which contained α-arylpyrrolidine **389** (40% NMR yield). Purification by flash column chromatography on silica using 199:1 CH_2Cl_2-EtOAc as eluent gave α-arylpyrrolidine **389** (62 mg, approximately 97% pure with unknown impurities, 40%) as a colourless oil.

Lab book reference: **MTG-5-83**

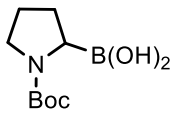
4-Chlorobenzotrifluoride (0.060 mL, 0.45 mmol, 1.5 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (89 mg, 0.30 mmol, 1.0 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.) and $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.1 eq.) in toluene (0.75 mL) and water (0.6 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-arylpyrrolidine **389** (57% NMR yield). Purification by flash column chromatography on silica using 199:1 CH_2Cl_2-EtOAc as eluent gave α-arylpyrrolidine **389** (45 mg, approximately 95% pure with unknown impurities, 47%) as a colourless oil.

Lab book reference: **MTG-6-41**

Using general procedure G, 4-chlorobenzotrifluoride (0.067 mL, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product. Purification by flash column chromatography on silica using 199:1 CH_2Cl_2-EtOAc as eluent gave α-arylpyrrolidine **389** (80 mg, approximately 98% pure with unknown impurities, 51%) as a colourless oil.

Lab book reference: **MTG-7-153**

(1-*tert*-Butoxycarbonylpyrrolidin-2-yl)boronic acid 350



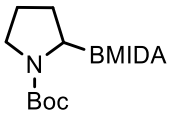
350

s-BuLi (18.3 mL of a 1.31 M solution in hexane, 24 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc-pyrrolidine **5** (3.42 g, 20 mmol, 1.0 eq.) and TMEDA (3.60 mL, 24 mmol, 1.2 eq.) in toluene (50 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. $B(OMe)_3$ (6.69 mL, 60 mmol, 3.0 eq.) was added and the resulting solution was stirred at –78 °C for 1 h and then at rt for 16 h. 2 M $NaOH_{(aq)}$ (100 mL) was added and the resulting solution was stirred at rt for 30 min. Toluene (100 mL) was added and the two layers were separated. The aqueous layer was acidified to pH 2 with 2 M $HCl_{(aq)}$ and then extracted with EtOAc (3 x 100 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure. The resulting solid was dissolved in EtOAc (4 mL) and heptane (20 mL) and stirred at rt for 72 h. The resulting white precipitate was collected by filtration and washed sequentially with cold heptane (20 mL) and cold Et_2O (10 mL) to afford α-$B(OH)_2$-pyrrolidine **350** (781 mg, 18%) as a white solid. The filtrate was evaporated under reduced pressure and the resulting solid was dissolved in EtOAc (4 mL) and heptane (20 mL) and stirred at rt for 20 h. The resulting white precipitate was collected by filtration and washed sequentially with cold heptane (20 mL) and cold Et_2O (10 mL) to afford α-$B(OH)_2$-pyrrolidine **350** (791 mg, 19%) as a white solid. The filtrate was evaporated under reduced pressure and the resulting solid was dissolved in EtOAc (4 mL) and heptane

(20 mL) and stirred at rt for 20 h. The resulting white precipitate was collected by filtration and washed sequentially with cold heptane (15 mL) and cold Et_2O (5 mL) to afford α-$B(OH)_2$-pyrrolidine **350** (235 mg, 5%) as a white solid, mp 300 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) (80:20 mixture of rotamers) δ 3.40 (ddd, *J* = 11.0, 8.5, 2.5 Hz, 1H, NCH), 3.21 (ddd, *J* = 11.0, 10.5, 7.0 Hz, 1H, NCH), 2.91 (dd, *J* = 11.0, 6.5 Hz, 1H, BNCH), 2.05 (dddd, *J* = 12.5, 6.5, 6.5, 2.5 Hz, 1H, CH), 2.00-1.90 (m, 1H, CH), 1.87-1.74 (m, 1H, CH), 1.68 (dddd, *J* = 11.5, 11.5, 5.5, 5.5 Hz, 1H, CH), 1.42 (s, 1.8H, CMe_3), 1.41 (s, 7.2H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers - 13 of 14 signals were observed) δ 156.4 (C=O), 156.1 (C=O), 81.8 (O*C*Me_3), 81.1 (O*C*Me_3), 47.5 (NCHB), 46.6 (NCH_2), 46.3 (NCH_2), 28.5 (CH_2), 27.8 (C*Me*$_3$), 27.8 (CH_2), 27.7 (C*Me*$_3$), 26.5 (CH_2), 25.8 (CH_2); HRMS (ESI) *m/z* calcd for $C_9H_{18}BNO_4$ $(M + Na)^+$ 238.1221, found 238.1225 (–0.9 ppm error). Overall this reaction gave α-$B(OH)_2$-pyrrolidine **350** (1.81 g, 42%) as a white solid. Spectroscopic data consistent with those reported in the literature.[120]

Lab book reference: **MTG-6-23**

tert-Butyl-2-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)pyrrolidine-1-carboxylate 390



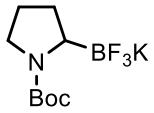
390

MIDA (647 g, 4.4 mmol, 1.1 eq.) was added to a stirred solution of α-$B(OH)_2$-pyrrolidine **350** (460 mg, 4.0 mmol, 1.0 eq.) in DMSO (20 mL) and toluene (20 mL) at rt under Ar. The resulting solution was stirred and heated at 145 °C for 23 h. After being allowed to cool to rt, water (40 mL) and EtOAc (40 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 40 mL) and the combined organic layers were washed sequentially with water (40 mL) and brine (40 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 using 90:10 CH_2Cl_2-acetone as eluent gave α-BMIDA-pyrrolidine **390** (210 mg, 16%) as a white solid, mp 204-205 °C; R_F (9:1 CH_2Cl_2-Acetone) 0.45; IR (ATR) 2975, 2930,

2878, 1760 (C=O, ester), 1673 (C=O, Boc), 1415, 1340, 1116, 1052, 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43 (d, *J* = 15.5 Hz, 1H, N*C*HCO), 3.77 (d, *J* = 16.5 Hz, 1H, N*C*HCO), 3.73 (d, *J* = 16.5 Hz, 1H, N*C*HCO), 3.65 (d, *J* = 15.5 Hz, 1H, N*C*HCO), 3.44-3.34 (m, 2H, BNCH + NCH), 3.32 (s, 3H, NMe), 3.25 (ddd, *J* = 11.0, 7.5, 5.5 Hz, 1H, NCH), 2.15-2.05 (m, 1H, CH), 2.04-1.93 (m, 1H, CH), 1.93-1.83 (m, 1H, CH), 1.79-1.69 (m, 1H, CH), 1.41 (s, 9H CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.0 (NCH_2*C*=O), 167.2 (NCH_2*C*=O), 155.7 (C=O, Boc), 79.2 (O*C*Me_3), 63.9 (N*C*H_2C=O), 61.6 (N*C*H_2C=O), 47.5 (NCH_2), 45.6 (NMe) 29.1 (CH_2), 28.6 (OC*Me*$_3$), 25.3 (CH_2), (NCHB resonance not resolved);[138] HRMS (ESI) *m/z* calcd for $C_{14}H_{23}BN_2O_6$ $(M + Na)^+$ 349.1541, found 349.1538 (+1.7 ppm error).

Lab book reference: **MTG-6-22**

(1-*tert*-Butoxycarbonylpyrrolidin-2-yl)-potassium trifluoroborate 347



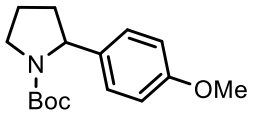
347

KHF_2 (1.56 g, 20 mmol, 10 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (594 mg, 2.0 mmol, 1.0 eq.) in water (4.4 mL) and MeOH (7.0 mL) at rt under air. The resulting solution was stirred at rt for 24 h. The solvent was evaporated under reduced pressure and the resulting solid was washed with hot acetone (40 mL). The filtrate was evaporated under reduced pressure to give a white solid which was washed with a 2:1 mixture of pentane-Et_2O (30 mL) and dried under vacuum to give crude product. The crude product was washed with a 2:1 mixture of heptane-Et_2O (90 mL) and dried under vacuum to give crude product. The crude product was stirred in Et_2O (30 mL) at rt for 1 h. The solid was collected by filtration and dried under vacuum to give crude product. The crude product was stirred in Et_2O (30 mL) at rt for 2 h. The solid was collected by filtration and dried under vacuum to give α-BF_3K-pyrrolidine **347** (186 mg, 34%) as a white solid, mp 137–138 °C; IR (ATR) 2973, 2873, 1676 (C=O), 1412, 1364, 1173, 1107, 1057, 975, 945, 922, 890, 861, 767 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.25–3.11 (m, 1H, NCH), 3.02 (br s, 1H, NCH), 2.86–2.73 (m, 1H, NCH), 1.86–1.71 (m, 1H, CH), 1.71–1.61 (m, 1H, CH), 1.61–1.46 (m, 2H, CH), 1.35 (s, 9H, CMe_3); ^{13}C NMR

(101 MHz, DMSO-d_6) (rotamers - 10 of 14 signals were observed) δ 154.4 (C=O), 153.7 (C=O), 76.5 (O*C*Me$_3$), 76.0 (O*C*Me$_3$), 46.3 (NCH$_2$), 45.9 (NCH$_2$), 28.5 (C*Me*$_3$), 27.2 (CH$_2$), 24.7 (CH$_2$), 24.1 (CH$_2$), (NCHB resonance not resolved);[138] ^{11}B NMR (128 MHz, DMSO-d_6): 2.52; HRMS (ESI) *m/z* calcd for $C_9H_{16}BF_3NO_2$ $(M)^-$ 238.1221, found 238.1222 (+0.4 ppm error).

Lab book reference: **MTG-6-30**

***tert*-Butyl-2-(4-methoxyphenyl)pyrrolidine-1-carboxylate 29**



29

Using general procedure G, 4-chloroanisole (0.061 mL, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), Pd(OAc)$_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product. Purification by flash column chromatography on silica using 49:1 CH_2Cl_2-EtOAc as eluent gave α-arylpyrrolidine **29** (76 mg, 55%) as a colourless oil, R_F (49:1 CH_2Cl_2-EtOAc) 0.45; IR (ATR) 2973, 2928, 2876, 1691 (C=O), 1513, 1390, 1364, 1246, 1160, 1111, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 7.07 (d, *J* = 8.5 Hz, 2H, Ar), 6.82 (d, *J* = 8.5 Hz, 2H, Ar), 5.11-4.49 (m, 1H, ArNCH), 3.77 (s, 3H, OMe), 3.67-3.42 (m, 2H, NCH$_2$), 2.36-2.14 (m, 1H, CH), 1.97-1.71 (m, 3H, CH), 1.44 (s, 3H, CMe$_3$), 1.19 (s, 6H, CMe$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers - 20 of 24 signals were observed) δ 158.3 (*ipso*-Ar), 154.7 (C=O), 137.4 (*ipso*-Ar), 128.1 (Ar), 126.7 (Ar), 114.0 (Ar), 113.8 (Ar), 113.5 (Ar), 79.2 (O*C*Me$_3$), 60.8 (ArNCH), 60.2 (ArNCH), 55.3 (OMe), 47.3 (NCH$_2$), 47.1 (NCH$_2$), 36.1 (CH$_2$), 34.9 (CH$_2$), 28.6 (C*Me*$_3$), 28.3 (C*Me*$_3$), 23.5 (CH$_2$), 23.2 (CH$_2$); HRMS (ESI) *m/z* calcd for $C_{16}H_{23}NO_3$ $(M + Na)^+$ 300.1570, found 300.1568 (+0.6 ppm error). Spectroscopic data consistent with those reported in the literature.[19]

Lab book reference: **MTG-7-157**

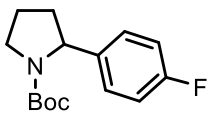
4-Bromoanisole (0.094 mL, 0.75 mmol, 1.5 eq.) was added to a stirred solution of α-Bpin-pyrrolidine-**51** (149 mg, 0.50 mmol, 1.0 eq.), cataCXium A (35.9 mg, 0.10 mmol, 0.2 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 3.0 eq.) and $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 0.1 eq.) in toluene (1.25 mL) and water (1.0 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 99:1 CH_2Cl_2:EtOAc then 197:3 CH_2Cl_2:EtOAc then 24:1 CH_2Cl_2:EtOAc as eluent gave α-arylpyrrolidine **29** (18 mg, approximately 90% pure with unknown impurities, 13%) as a colourless oil.

Lab book reference: **MTG-5-77**

Using general procedure G, 4-bromoanisole (0.063 mL, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product. Purification by flash column chromatography on silica using 99:1 CH_2Cl_2-EtOAc as eluent gave α-arylpyrrolidine **29** (88 mg, 63%) as a colourless oil.

Lab book reference: **MTG-7-156**

***tert*-Butyl-2-(4-fluorophenyl)pyrrolidine-1-carboxylate 392**



392

1-Bromo-4-fluorobenzene (0.049 mL, 0.45 mmol, 1.5 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (89 mg, 0.30 mmol, 1.0 eq.), Cs_2CO_3 (293 mg, 0.90 mmol, 3.0 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.) and $Pd(OAc)_2$ (6.7 mg,

0.03 mmol, 0.1 eq.) in toluene (0.75 mL) and water (0.6 mL) at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL) and dried ($MgSO_4$). 1,3,5-trimethoxybenzene (25 mg, 0.15 mmol, 0.5 eq.) was added as an external standard and the solution was evaporated under reduced pressure to give the crude product which contained α-arylpyrrolidine **392** (42% NMR yield). Purification by flash column chromatography on silica using 199:1 CH_2Cl_2-EtOAc as eluent gave α-arylpyrrolidine **392** (24 mg, 30%) as a colourless oil, ^{1}H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 7.12 (dd, *J* = 8.5, 5.5 Hz, 2H, Ar), 7.01-6.94 (m, 2H, Ar), 5.02-4.63 (m, 1H, ArNCH), 3.75-3.42 (m, 2H, NCH_2), 2.45-2.16 (m, 1H, CH), 2.01-1.71 (m, 3H, CH), 1.45 (s, 3H, CMe_3), 1.19 (s, 6H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers - 12 of 22 signals were observed) δ 161.6 (d, *J* = 246.0 Hz, *ipso*-Ar), 154.6 (C=O), 127.0 (d, *J* = 6.0 Hz, Ar), 115.0 (d, *J* = 21.5 Hz), 141.0 (*ipso*-Ar), 79.4 (O*C*Me_3), 60.8 (ArNCH), 47.2 (NCH_2), 36.2 (CH_2), 28.6 (C*Me*$_3$), 28.3 (C*Me*$_3$), 23.2 (CH_2); HRMS (ESI) *m/z* calcd for $C_{15}H_{20}FNO_2$ $(M + Na)^+$ 288.1370, found 288.1368 (+0.8 ppm error). Spectroscopic data consistent with those reported in the literature.[12]

Lab book reference: **MTG-5-86**

Using general procedure G, 1-bromo-4-fluorobenzene (0.055 mL, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product. Purification by flash column chromatography on silica using 199:1 CH_2Cl_2-EtOAc as eluent gave α-arylpyrrolidine **392** (85 mg, 64%) as a white solid.

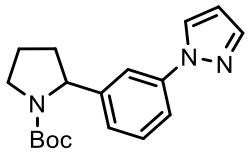
Lab book reference: **MTG-7-150**

Using general procedure G, 1-chloro-4-fluorobenzene (0.053 mL, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product. Purification by flash column

chromatography on silica using 199:1 CH_2Cl_2-EtOAc as eluent gave α-arylpyrrolidine **392** (77 mg, 58%) as a white solid.

Lab book reference: **MTG-7-151**

***tert*-Butyl-2-(3-pyrazol-1-ylphenyl)pyrrolidine-1-carboxylate 348**



348

A solution of 1-(3-bromophenyl)-1-H-pyrazole (167 mg, 0.75 mmol, 1.5 eq.), α-Bpin-pyrrolidine **51** (149 mg, 0.50 mmol, 1.0 eq.), cataCXium A (35.9 mg, 0.10 mmol, 0.2 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 3.0 eq.) and $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 0.1 eq.) in toluene (1.25 mL) and water (1.0 mL) was stirred at rt under Ar in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 17:3 hexane-EtOAc as eluent gave impure product. Purification by flash column chromatography on silica using 97:3 CH_2Cl_2-EtOAc then 19:1 CH_2Cl_2-EtOAc as eluent gave α-arylpyrrolidine **348** (24 mg, 15%) as a colourless oil, R_F (24:1 CH_2Cl_2-EtOAc) 0.25; IR (ATR) 2974, 2931, 2876, 1686 (C=O), 1389, 1365, 1157, 1112, 749, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 7.95-7.82 (m, 1H, Ar), 7.75-7.66 (m, 1H, Ar), 7.57-7.44 (m, 2H, Ar), 7.36 (dd, *J* = 8.0, 8.0 Hz, 1H Ar), 7.08 (d, *J* = 8.0 Hz, 1H, Ar), 6.50-6.38 (m, 1H, Ar), 5.07-4.89 (m, 0.35H, ArNCH), 4.89-4.71 (m, 0.65H, ArNCH), 3.71-3.45 (m, 2H, NCH_2), 2.43-2.23 (m, 1H, CH), 2.00-1.78 (m, 3H, CH), 1.44 (s, 3H, CMe_3), 1.18 (s, 6H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers - 24 of 32 signals were observed) δ 154.7 (C=O), 147.1 (*ipso*-Ar), 146.0 (*ipso*-Ar), 141.1 (Ar), 140.3 (Ar), 129.5 (Ar), 129.3 (Ar), 126.8 (Ar), 123.6 (Ar), 117.7 (Ar), 117.4 (Ar), 116.6 (Ar), 107.7 (Ar), 79.5 (O*C*Me_3), 61.3 (ArNCH), 60.7 (ArNCH), 47.5 (NCH_2), 47.2 (NCH_2), 36.1 (CH_2), 34.9 (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 $C_{18}H_{23}N_3O_2$

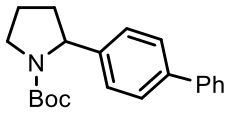
$(M + Na)^+$ 336.1682, found 336.1687 (–1.5 ppm error). Spectroscopic data similar to those reported in d_6-DMSO in the literature.[25]

Lab book reference: **MTG-5-69**

A solution of 1-(3-bromophenyl)-1-H-pyrazole, α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 3.0 eq.), cataCXium A (35.9 mg, 0.10 mmol, 0.2 eq.), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 0.1 eq.) and water (0.090 mL, 5.0 mmol, 10 eq.) in toluene (0.7 mL) was stirred at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 19:1 CH_2Cl_2-EtOAc as eluent gave crude product. Purification by flash column chromatography on silica using 4:1 hexane-EtOAc as eluent gave crude product. Purification by flash column chromatography on silica using 24:1 CH_2Cl_2-EtOAc as eluent gave α-arylpyrrolidine **348** (46 mg, 29%) as a colourless oil.

Lab book reference: **MTG-7-159**

***tert*-Butyl-2-(4-phenylphenyl)pyrrolidine-1-carboxylate 393**



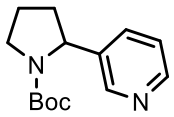
393

A solution of 4-chlorobiphenyl (85 mg, 0.45 mmol, 1.5 eq.), α-Bpin-pyrrolidine **51** (89 mg, 0.30 mmol, 1.0 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.) and $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.1 eq.) in toluene (0.75 mL) and water (0.6 mL) was stirred at rt under Ar in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5

mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained α-arylpyrrolidine **393** (57% NMR yield). Purification by flash column chromatography on silica using 399:1 CH_2Cl_2-EtOAc as eluent gave α-arylpyrrolidine **393** (46 mg, 47%) as a colourless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.57 (m, 2H, Ph), 7.55 (d, *J* = 8.0 Hz, 2H, Ar), 7.44 (dd, *J* = 7.5, 7.5 Hz, 2H, Ph), 7.34 (t, *J* = 7.5 Hz, 1H, Ph), 7.25 (d, *J* = 8.0 Hz, 2H, Ar), 5.12-4.71 (m, 1H, ArNCH), 3.75-3.45 (m, 2H, NCH_2), 2.45-2.19 (m, 1H, CH), 2.06-1.82 (m, 3H, CH), 1.62-1.13 (m, 9H, CMe_3). Spectroscopic data consistent with those reported in the literature.[148]

Lab book reference: **MTG-6-73**

***tert*-Butyl-2-(3-pyridyl)pyrrolidine-1-carboxylate 119**



119

Using general procedure G, 3-bromopyridine (0.048 mL, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product. Purification by flash column chromatography on silica using 99:1 CH_2Cl_2-EtOAc as eluent gave crude product. Purification by flash column chromatography on silica using 1:1 hexane-EtOAc as eluent gave α-arylpyrrolidine **119** (67 mg, 54%) as a colourless oil, R_F (3:2 hexane-EtOAc) 0.20; IR (ATR) 2974, 2935, 2877, 1688 (C=O), 1388, 1364, 1157, 1113, 715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 8.48-8.34 (m, 2H, Ar), 7.44 (d, *J* = 8.0 Hz, 1H, Ar), 7.18 (dd, *J* = 8.0, 5.0 Hz, 1H, Ar), 5.01-4.60 (m, 1H, ArNCH), 3.68-3.36 (m, 2H, NCH_2), 2.41-2.18 (m, 1H, CH), 1.95-1.67 (m, 3H, CH), 1.41 (s, 3H, CMe_3), 1.16 (s, 6H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers - 21 of 24 signals were observed) δ 154.5 (C=O), 154.4 (C=O), 148.1 (Ar), 147.9 (Ar), 147.3 (*ipso*-Ar), 140.5 (*ipso*-Ar), 139.5 (*ipso*-Ar), 133.5 (Ar), 133.1 (Ar), 123.3 (Ar), 79.7 (O*C*Me_3), 59.2 (ArNCH), 58.9 (ArNCH), 47.3 (NCH_2), 47.2 (NCH_2), 36.0 (CH_2), 34.7

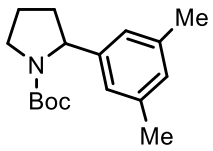
(CH_2), 28.5 (C*Me*$_3$), 28.2 (C*Me*$_3$), 23.6 (CH_2), 23.4 (CH_2); HRMS (ESI) *m/z* calcd for $C_{14}H_{20}N_2O_2$ $(M + Na)^+$ 271.1417, found 271.1417 (0.0 ppm error). Spectroscopic data consistent with those reported in the literature.[19]

Lab book reference: **MTG-7-154**

Using general procedure G, 3-chloropyridine (0.029 mL, 0.30 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product. Purification by flash column chromatography on silica using 24:1 CH_2Cl_2-EtOAc then 1:1 CH_2Cl_2-EtOAc as eluent gave crude product. Purification by flash column chromatography on silica using 2:3 EtOAc-hexane as eluent gave α-arylpyrrolidine **119** (30 mg, 41%) as a colourless oil.

Lab book reference: **MTG-7-124**

***tert*-Butyl-2-(3,5-dimethylphenyl)pyrrolidine-1-carboxylate 394**



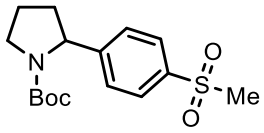
394

Using general procedure G, 5-bromo-*m*-xylene (0.068 mL, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product. Purification by flash column chromatography on silica using 24:1 CH_2Cl_2-EtOAc then 1:1 CH_2Cl_2-EtOAc as eluent gave crude product. Purification by flash column chromatography on silica using 99:1 CH_2Cl_2-EtOAc as eluent α-arylpyrrolidine **394** (105 mg, 76%) as an off-white solid, mp 55-56 °C; R_F (99:1 CH_2Cl_2-EtOAc) 0.55; IR (ATR) 2973, 2927, 2875, 1693 (C=O), 1391, 1365, 1163, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 6.83 (s, 1H, Ar), 6.76 (s, 2H, Ar), 4.95-4.60 (m, 1H, ArNCH), 3.69-3.44 (m, 2H, NCH_2), 2.37-2.19 (m, 1H, CH), 2.28 (s, 6H, Me), 1.98-1.72 (m, 3H, CH), 1.45 (s, 3H, CMe_3), 1.17 (s, 6H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers - 13 of 24 signals were observed) δ 154.8 (C=O), 145.1 (*ipso*-Ar), 137.6 (*ipso*-Ar), 128.1 (Ar), 123.5 (Ar),

79.2 (O*C*Me$_3$), 61.3 (ArNCH), 47.1 (NCH$_2$), 36.0 (CH$_2$), 28.6 (C*Me$_3$*), 28.2 (C*Me$_3$*), 23.3 (CH$_2$), 21.4 (Me); HRMS (ESI) *m/z* calcd for $C_{17}H_{25}NO_2$ $(M + Na)^+$ 298.1777, found 298.1782 (–1.4 ppm error). Spectroscopic data consistent with those reported in the literature.[135]

Lab book reference: **MTG-7-177**

***tert*-Butyl-2-(4-methylsulfonylphenyl)pyrrolidine-1-carboxylate 395**

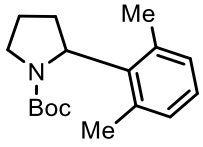


395

Using general procedure H, 4-bromophneyl methyl sulfone (118 mg, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), Pd(OAc)$_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product. Purification by flash column chromatography on silica using 24:1 CH_2Cl_2-EtOAc then 1:1 CH_2Cl_2-EtOAc as eluent gave crude product. Purification by flash column chromatography on silica using 199:1 CH_2Cl_2-EtOAc then 19:1 CH_2Cl_2-EtOAc as eluent gave crude product. Purification by flash column chromatography on silica using 17:3 hexane-EtOAc then 3:2 hexane-EtOAc as eluent gave α-arylpyrrolidine **395** (54 mg, 34%) as an off-white solid, mp 103-105 °C (lit.,[12] 101 °C); R_F (3:2 hexane-EtOAc) 0.20; IR (ATR) 2975, 2931, 2883, 1687 (C=O), 1390, 1366, 1307, 1145, 1117, 767, 542, 533 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 7.86 (d, *J* = 8.5 Hz, 2H, Ar), 7.35 (d, *J* = 8.5 Hz, 2H, Ar), 5.13-4.62 (m, 1H, ArNCH), 3.75-3.46 (m, 2H, NCH$_2$), 3.02 (s, 3H, SMe), 2.50-2.20 (m, 1H, CH), 1.97-1.67 (m, 3H, CH), 1.43 (s, 4.1H, CMe$_3$), 1.16 (s, 4.9H, CMe$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers - 17 of 24 signals were observed) δ 155.0 (C=O), 151.9 (*ipso*-Ar), 150.9 (*ipso*-Ar), 138.9 (*ipso*-Ar), 127.6 (Ar), 126.5 (Ar), 79.9 (O*C*Me$_3$), 61.1 (ArNCH), 60.7 (ArNCH), 47.4 (NCH$_2$), 44.7 (SMe), 35.9 (CH$_2$), 34.9 (CH$_2$), 28.6 (C*Me$_3$*), 28.3 (C*Me$_3$*), 23.6 (CH$_2$), 23.3 (CH$_2$); HRMS (ESI) *m/z* calcd for $C_{16}H_{23}NO_4S$ $(M + Na)^+$ 348.1240, found 348.1242 (–0.5 ppm error). Spectroscopic data consistent with those reported in the literature.[12]

Lab book reference: **MTG-7-167**

***tert*-Butyl-2-(2,6-dimethylphenyl)pyrrolidine-1-carboxylate 396**

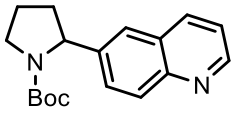


396

Using general procedure G, 2-bromo-*m*-xylene (0.067 mL, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product. Purification by flash column chromatography on silica using 24:1 CH_2Cl_2-EtOAc then 1:1 CH_2Cl_2-EtOAc as eluent gave crude product. Purification by flash column chromatography on silica using 199:1 CH_2Cl_2-EtOAc as eluent gave crude product. Purification by flash column chromatography on silica using 24:1 hexane-EtOAc as eluent gave α-arylpyrrolidine **51** (19 mg, 14%) as a colourless oil, R_F (99:1 CH_2Cl_2-EtOAc) 0.45; IR (ATR) 2971, 2927, 2873, 1688 (C=O), 1397, 1364, 1160, 1118, 768, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (85:15 mixture of rotamers) δ 7.07-6.89 (m, 3H, Ar), 5.27-4.96 (m, 1H, ArNCH), 3.93-3.64 (m, 1H, NCH), 3.53-3.32 (m, 1H, NCH), 2.37-2.17 (m, 1H, CH), 2.31 (s, 6H, Me), 2.11-1.79 (m, 3H, CH), 1.41 (s, 1.4H, CMe_3), 1.06 (s, 7.6H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers - 13 of 24 signals were observed) δ 154.6 (C=O), 139.6 (*ipso*-Ar), 134.9 (*ipso*-Ar), 129.6 (Ar), 126.2 (Ar), 79.0 (O*C*Me_3), 58.1 (ArNCH), 46.8 (NCH_2), 32.2 (CH_2), 28.6 (C*Me*$_3$), 28.0 (C*Me*$_3$), 25.0 (CH_2), 20.7 (Me); HRMS (ESI) *m/z* calcd for $C_{17}H_{25}NO_2$ $(M + Na)^+$ 298.1777, found 298.1780 (–0.9 ppm error).

Lab book reference: **MTG-7-162**

***tert*-Butyl-2-(6-quinolyl)pyrrolidine-1-carboxylate 397**

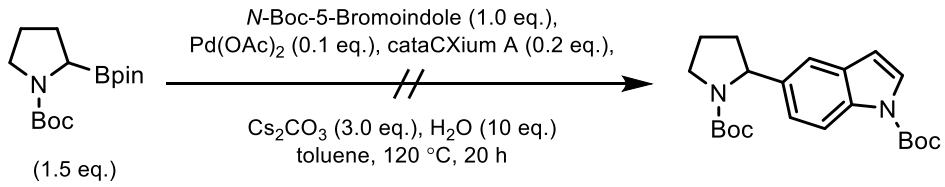


397

6-Bromoquinoline (0.101 mL, 0.75 mmol, 1.5 eq.) was added to a stirred solution of α-Bpin-pyrrolidine **51** (149 mg, 0.50 mmol, 1.0 eq.), Cs_2CO_3 (489 mg, 1.5 mmol, 3.0 eq.), cataCXium A (35.9 mg, 0.10 mmol, 0.2 eq.), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 0.1 eq.) and water (0.090 mL, 5.0 mmol, 10 eq.) in toluene (0.7 mL) at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 4:1 CH_2Cl_2-EtOAc as eluent gave crude product. Purification by flash column chromatography on silica using 9:1 CH_2Cl_2-acetone as eluent gave crude product. Purification by flash column chromatography on silica using 2:3 hexane-EtOAc as eluent gave α-arylpyrrolidine **397** (68 mg, 46%) as a colourless oil, R_F (1:1 hexane-EtOAc) 0.50; IR (ATR) 2974, 2927, 2875, 1687 (C=O), 1386, 1364, 1162, 1109, 834, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 8.90-8.76 (m, 1H, Ar), 8.13-7.98 (m, 2H, Ar), 7.59-7.45 (m, 2H, Ar), 7.43-7.29 (m, 1H, Ar), 5.19-4.79 (m, 1H, ArNCH), 3.76-3.49 (m, 2H, NCH), 2.43-2.16 (m, 1H, CH), 1.98-1.68 (m, 3H, CH), 1.43 (s, 3H, CMe_3), 1.10 (s, 6H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers - 25 of 32 signals were observed) δ 154.7 (C=O), 150.1 (Ar), 147.6 (*ipso*-Ar), 143.4 (*ipso*-Ar), 142.6 (*ipso*-Ar), 136.1 (Ar), 135.9 (Ar), 129.8 (Ar), 129.6 (Ar), 128.1 (Ar), 127.9 (Ar), 123.6 (Ar), 121.4 (Ar), 121.2 (Ar), 79.5 (O*C*Me_3), 61.3 (ArNCH), 60.8 (ArNCH), 47.6 (NCH_2), 47.3 (NCH_2), 35.9 (CH_2), 34.7 (CH_2), 28.6 (C*Me*$_3$), 28.2 (C*Me*$_3$), 23.8 (CH_2), 23.3 (CH_2); HRMS (ESI) *m/z* calcd for $C_{18}H_{22}N_2O_2$ $(M + Na)^+$ 321.1573, found 321.1575 (–0.5 ppm error).

Lab book reference: **MTG-7-183**

Attempted synthesis of *tert*-butyl-5-(1-*tert*-butoxycarbonylpyrrolidin-2-yl)indole-1-carboxylate 398

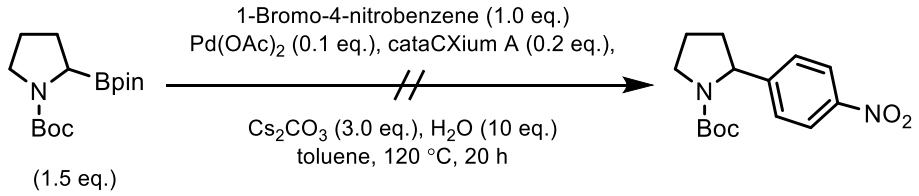


51 **398**

Using general procedure H, *N*-Boc-5-bromoindole (148 mg, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product. Purification by flash column chromatography on silica using 24:1 CH_2Cl_2-EtOAc then 1:1 CH_2Cl_2-EtOAc as eluent gave crude product which contained α-arylpyrrolidine **398** (by ^{1}H NMR spectroscopy and HRMS). Purification by flash column chromatography on silica using 4:1 hexane-EtOAc then 3:2 hexane-EtOAc as eluent gave trace amounts of α-arylpyrrolidine **398**.

Lab book reference: **MTG-8-1**

Attempted synthesis of *tert*-butyl-2-(4-nitrophenyl)pyrrolidine-1-carboxylate 401

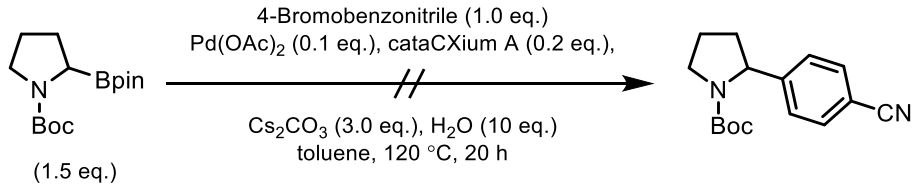


51 **401**

Using general procedure H, 1-bromo-4-nitrobenzene (101 mg, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product which contained none of α-arylpyrrolidine **401** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-7-166**

Attempted synthesis of *tert*-butyl-2-(4-cyanophenyl)pyrrolidine-1-carboxylate 7

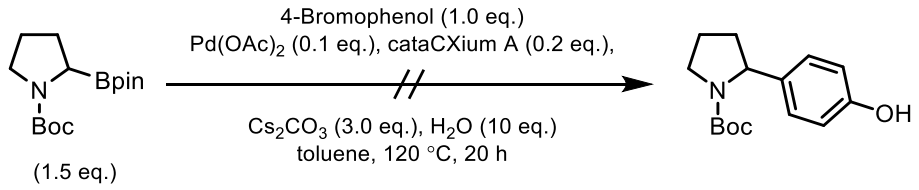


51 **7**

Using general procedure H, 4-bromobenzonitrile (91 mg, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product which contained none of α-arylpyrrolidine **7** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-7-169**

Attempted synthesis of *tert*-butyl-2-(4-hydroxyphenyl)pyrrolidine-1-carboxylate 399

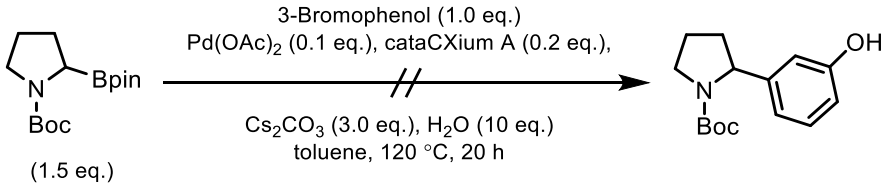


51 **399**

Using general procedure H, 4-bromophenol (87 mg, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product which contained none of α-arylpyrrolidine **399** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-7-168**

Attempted synthesis of *tert*-butyl-2-(3-hydroxyphenyl)pyrrolidine-1-carboxylate 400

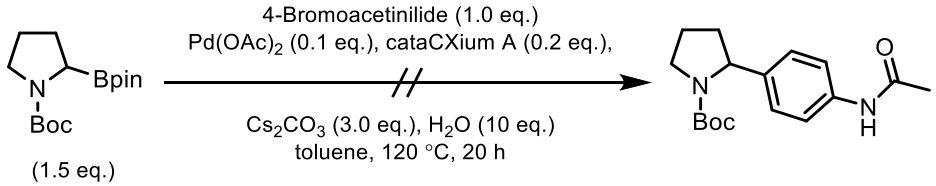


51 **400**

Using general procedure G, 3-bromophenol (0.053 mL, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product which contained none of α-arylpyrrolidine **400** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-7-165**

Attempted synthesis of *tert*-butyl-2-(4-acetamidophenyl)pyrrolidine-1-carboxylate 402

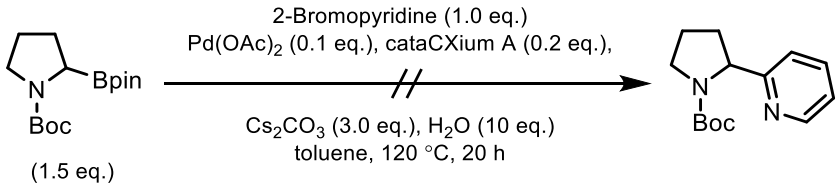


51 **402**

Using general procedure H, 4-bromoacetinilide (107 mg, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product which contained none of α-arylpyrrolidine **402** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-7-164**

Attempted synthesis of *tert*-butyl-2-(2-pyridyl)pyrrolidine-1-carboxylate 403

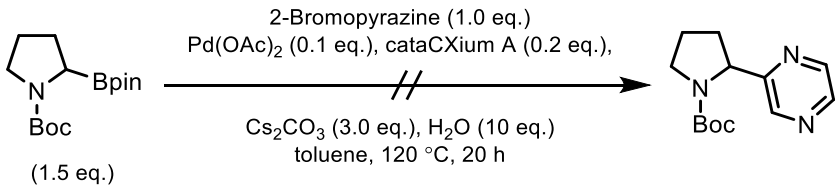


51 **403**

Using general procedure G, 2-bromopyridine (0.048 mL, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product which contained none of α-arylpyrrolidine **403** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-7-171**

Attempted synthesis of *tert*-butyl-2-(pyrazin-2-yl)pyrrolidine-1-carboxylate 404

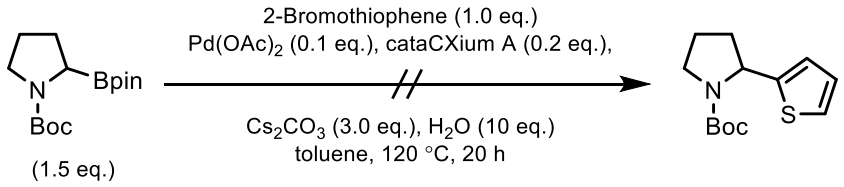


51 **404**

Using general procedure G, 2-bromopyrazine (0.045 mL, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product which contained none of α-arylpyrrolidine **404** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-7-173**

Attempted synthesis of *tert*-butyl-2-(2-thienyl)pyrrolidine-1-carboxylate 405

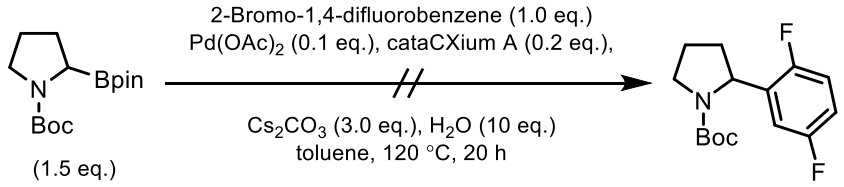


51 **405**

Using general procedure G, 2-bromothiophene (0.048 mL, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product which contained none of α-arylpyrrolidine **405** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-7-172**

Attempted synthesis of *tert*-butyl-2-(2,5-difluorophenyl)pyrrolidine-1-carboxylate 406

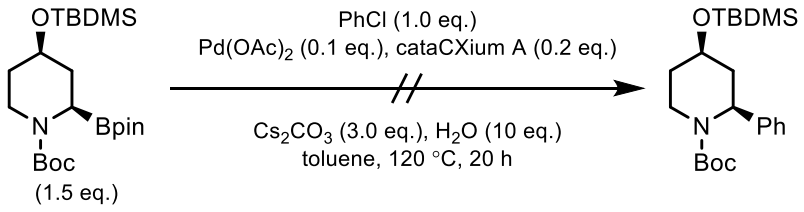


51 **406**

Using general procedure G, 2-bromo-1,4-difluorobenzene (0.056 mL, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine **51** (223 mg, 0.75 mmol, 1.5 eq.), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product which contained α-arylpyrrolidine **406** (by ^{1}H NMR spectroscopy and HRMS). Purification by flash column chromatography on silica using 99:1 CH_2Cl_2-EtOAc then 97:3 CH_2Cl_2-EtOAc then 9:1 CH_2Cl_2-EtOAc as eluent gave none of α-arylpyrrolidine **406** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-7-174**

Attempted synthesis of *tert*-Butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-phenylpiperidine-1-carboxylate *cis*-176

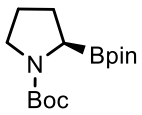


cis-**213** *cis*-**176**

Chlorobenzene (0.031 mL, 0.30 mmol, 1.0 eq.) was added to a stirred solution of α-Bpin-4-OTBDMS-piperidine *cis*-**213** (199 mg, 0.45 mmol, 1.5 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.1 eq.) water (0.054 mL, 3.0 mmol, 10 eq.) and 1,3,5-trimethoxybenzene (25.2 mg, 0.15 mmol, 0.5 eq.) as an internal standard in toluene (0.42 mL) at rt under N_2 in a pressure tube. The tube was sealed and the resulting solution was stirred and heated at 120 °C for 20 h. After being allowed to cool to rt, water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained trace amounts of α-arylpiperidine *cis*-**176** (by ^{1}H NMR spectroscopy and HRMS).

Lab book reference: **MTG-7-140**

(*R*)-*tert*-Butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidine-1-carboxylate (*R*)-51



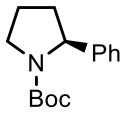
(*R*)-**51**

s-BuLi (18.8 mL of a 1.27 M solution in hexane, 23.9 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc-pyrrolidine **5** (3.14 g, 18.4 mmol, 1.0 eq.) and (+)-sparteine (5.49 mL, 23.9 mmol, 1.3 eq.) in Et_2O (90 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C 3 h. *i*-PrOB(pin) (4.87 mL, 23.9 mmol, 1.3 eq.) was added and the resulting solution was stirred at –78 °C for 1 h and then at rt for 18 h. 1 M $HCl_{(aq)}$ (200 mL) and Et_2O (200 mL) were added and the two layers were

separated. The aqueous layer was extracted with Et_2O (3 x 200 mL) and the combined organics were washed with brine (200 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 49:1 hexane:EtOAc then 19:1 hexane:EtOAc as eluent gave crude product. Purification by recrystallisation from hot hexane (3 mL) gave a colourless crystalline solid which was washed with cold hexane (20 mL) and dried under reduced pressure to give α-Bpin-pyrrolidine (*R*)-**51** (497 mg, 9%, 98:2 er by CSP-HPLC) as a colourless crystalline solid. On standing, solid crystallised out of the filtrate, which was washed with cold hexane (20 mL) and dried under reduced pressure to give α-Bpin-pyrrolidine (*R*)-**51** (369 mg, 7%, 99:1 er by CSP-HPLC) as a colourless crystalline solid. On standing, solid crystallised out of the filtrate, which was washed with cold hexane (20 mL) and dried under reduced pressure to give α-Bpin-pyrrolidine (*R*)-**51** (279 mg, 5%, >99:1 er by CSP-HPLC) as a colourless crystalline solid, $[\alpha]_D$ –58.4 (*c* 1.0 in CH_2Cl_2) (lit.,[120] $[\alpha]_D$ +69.5 (*c* 1.06 in CH_2Cl_2) for (*R*)-**51**); CSP-HPLC: Chiralpak AD-H (99:1 hexane:*i*-PrOH, 0.3 mL min^{-1}) (*S*)-**51** 17.8 min, (*R*)-**51** 19.7 min. Overall, this reaction gave α-Bpin-pyrrolidine (*R*)-**51** (1.15 g, 21%, ≥98:2 er by CSP-HPLC) as a colourless crystalline solid.

Lab book reference: **MTG-8-4**

(*S*)-*tert*-Butyl-2-phenylpyrrolidine-1-carboxylate (*S*)-114



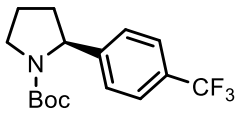
(*S*)-**114**

Using general procedure G, bromobenzene (0.053 mL, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine (*R*)-**51** (223 mg, 0.75 mmol, 1.5 eq., >99:1 er), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product. Purification by flash column chromatography on silica using 199:1 CH_2Cl_2:EtOAc as eluent gave α-arylpyrrolidine (*S*)-**114** (85 mg, 69%, 99:1 er by CSP-HPLC) as a white solid, $[\alpha]_D$ –84.3 (*c* 1.0 in acetone) (lit.,[44] $[\alpha]_D$ +85.3 (*c* 1.0 in acetone) for (*R*)-**114** of 96:4 er); CSP-HPLC:

Chiralpak AD-H (99.5:0.5 hexane:*i*-PrOH, 0.3 mL min^{-1}) (*R*)-**114** 28.8 min, (*S*)-**114** 31.4 min.

Lab book reference: **MTG-8-13**

(*S*)-*tert*-Butyl-2-[4-(trifluoromethyl)phenyl]pyrrolidine-1-carboxylate (*S*)-389

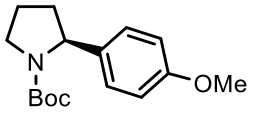


(*S*)-**389**

Using general procedure I, 4-bromobenzotrifluoride (0.042 mL, 0.30 mmol, 1.0 eq.), α-Bpin-pyrrolidine (*R*)-**51** (134 mg, 0.45 mmol, 1.5 eq., >99:1 er), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.1 eq.) and water (0.054 mL, 3.0 mmol, 10 eq.) in toluene (0.7 mL) gave the crude product. Purification by flash column chromatography on silica using 199:1 CH_2Cl_2-EtOAc as eluent gave α-arylpyrrolidine (*S*)-**389** (67 mg, 71%, 99:1 er by CSP-HPLC) as a white solid, mp 57-58 °C; $[\alpha]_D$ –70.0 (*c* 1.0 in acetone); CSP-HPLC: Chiralpak AD-H (99.5:0.5 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**389** 12.8 min, (*S*)-**389** 21.2 min.

Lab book reference: **MTG-8-7**

(*S*)-*tert*-Butyl-2-(4-methoxyphenyl)pyrrolidine-1-carboxylate (*S*)-29

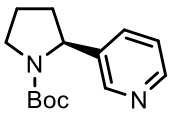


(*S*)-**29**

Using general procedure G, 4-bromoanisole (0.063 mL, 0.50 mmol, 1.0 eq.), α-Bpin-pyrrolidine (*R*)-**51** (223 mg, 0.75 mmol, 1.5 eq., 99:1 er), Cs_2CO_3 (489 mg, 1.5 mmol), cataCXium A (35.9 mg, 0.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and water (0.090 mL, 5.0 mmol) in toluene (0.7 mL) gave the crude product. Purification by flash column chromatography on silica using 49:1 CH_2Cl_2:EtOAc as eluent gave α-arylpyrrolidine (*S*)-**29** (80 mg, 55%, 99:1 er by CSP-HPLC) as a colourless oil; $[\alpha]_D$ –89.7 (*c* 1.0 in acetone) (lit.,[135] $[\alpha]_D$ +90.6 (*c* 0.5 in acetone) for (*R*)-**29** of 96:4 er); CSP-HPLC: Chiralpak AD-H (99:1 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**29** 20.2 min, (*S*)-**29** 22.8 min.

Lab book reference: **MTG-8-14**

(*S*)- *tert*-Butyl-2-(3-pyridyl)pyrrolidine-1-carboxylate (*S*)-119

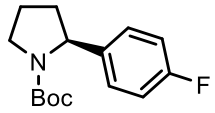


(*S*)-**119**

Using general procedure I, 3-bromopyridine (0.029 mL, 0.30 mmol, 1.0 eq.), α-Bpin-pyrrolidine (*R*)-**51** (134 mg, 0.45 mmol, 1.5 eq., >99:1 er), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.1 eq.) and water (0.054 mL, 3.0 mmol, 10 eq.) in toluene (0.7 mL) gave the crude product. Purification by flash column chromatography on silica using 1:1 CH_2Cl_2-EtOAc as eluent gave crude product. Purification by flash column chromatography on silica using 1:1 hexane-EtOAc as eluent gave α-arylpyrrolidine (*S*)-**119** (35 mg, 47%, 99:1 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –75.6 (*c* 1.0 in CH_2Cl_2) (lit.,[44] $[\alpha]_D$ +80.0 (*c* 1.0 in CH_2Cl_2) for (*R*)-**119** of 98:2 er); CSP-HPLC: Chiralpak AD-H (90:10 hexane:*i*-PrOH, 0.7 mL min^{-1}) (*S*)-**119** 17.5 min, (*R*)-**119** 23.4 min.

Lab book reference: **MTG-8-8**

(*S*)-*tert*-Butyl-2-(4-fluorophenyl)pyrrolidine-1-carboxylate (*S*)-392

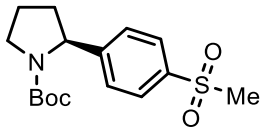


(*S*)-**392**

Using general procedure I, 4-fluorobenzene (0.033 mL, 0.30 mmol, 1.0 eq.), α-Bpin-pyrrolidine (*R*)-**51** (134 mg, 0.45 mmol, 1.5 eq., 98:2 er), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.1 eq.) and water (0.054 mL, 3.0 mmol, 10 eq.) in toluene (0.7 mL) gave the crude product. Purification by flash column chromatography on silica using 199:1 CH_2Cl_2-EtOAc as eluent α-arylpyrrolidine (*S*)-**392** (34 mg, 43%, 98:2 er by CSP-HPLC) as a white solid, mp 67-69 °C; $[\alpha]_D$ –70.4 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralpak AD-H (99:1 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**392** 11.6 min, (*S*)-**392** 13.7 min.

Lab book reference: **MTG-8-11**

(*S*)-*tert*-Butyl-2-(4-methylsulfonylphenyl)pyrrolidine-1-carboxylate (*S*)-395



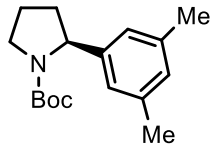
(*S*)-**395**

A solution of α-Bpin-pyrrolidine (*R*)-**51** (134 mg, 0.45 mmol, 1.5 eq., 98:2 er), 4-bromophenyl methyl sulfone (71 mg, 0.30 mmol, 1.0 eq.), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.1 eq.) and water (0.054 mL, 3.0 mmol, 10 eq.) in toluene (0.42 mL) was stirred at rt under N_2 in a pressure vial. The vial was sealed and the resulting solution was stirred at 120 °C for 20 h. After being allowed to cool to rt water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 19:1 CH_2Cl_2-EtOAc as eluent gave crude product. Purification by flash column chromatography on silica using 3:2 hexane-EtOAc as eluent gave α-arylpyrrolidine (*S*)-**395** (22 mg, 22%, 98:2 er by CSP-HPLC) as

a colourless oil, $[\alpha]_D$ –80.0 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralpak AD-H (90:10 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**395** 18.1 min, (*S*)-**395** 21.1 min.

Lab book reference: **MTG-8-10**

(*S*)-*tert*-Butyl-2-(3,5-dimethylphenyl)pyrrolidine-1-carboxylate (*S*)-394



(*S*)-**394**

Using general procedure I, 5-bromo-*m*-xylene (0.041 mL, 0.30 mmol, 1.0 eq.), α-Bpin-pyrrolidine (*R*)-**51** (134 mg, 0.45 mmol, 1.5 eq., >99:1 er), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 eq.), cataCXium A (21.5 mg, 0.06 mmol, 0.2 eq.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.1 eq.) and water (0.054 mL, 3.0 mmol, 10 eq.) in toluene (0.7 mL) gave the crude product. Purification by flash column chromatography on silica using 99:1 CH_2Cl_2-EtOAc as eluent α-arylpyrrolidine (*S*)-**394** (54 mg, 65%, er n.d.) as a colourless oil, $[\alpha]_D$ –88.5 (*c* 0.5 in acetone) (lit.,[135] $[\alpha]_D$ +88.3 (*c* 0.5 in acetone) for (*R*)-**394** of 96:4 er).

Lab book reference: **MTG-8-12**

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